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Applying the conformational bias of amides to the synthesis of triarylmethanes, difluoromethyl arenes and medium-sized rings

Applying the conformational bias of amides to the synthesis of triarylmethanes, difluoromethyl arenes and medium-sized rings

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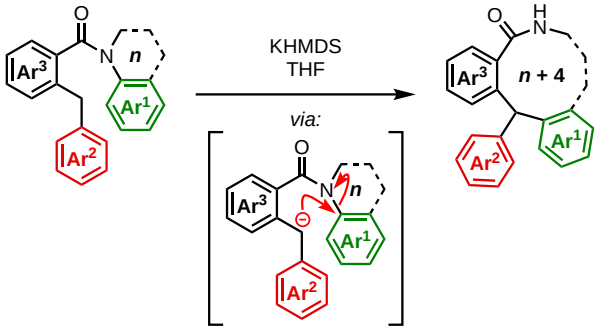
Abstract

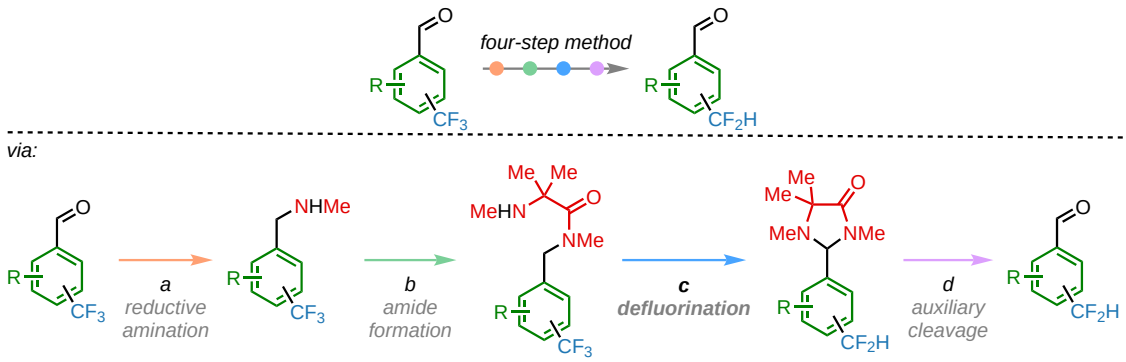
Chapter 1 — Triarylmethanes by the Truce–Smiles rearrangement of benzanilides

The triarylmethane (TRAM) motif can be found embedded within the structures of compounds with applications across diverse fields, rendering methods to construct TRAMs of significant value. In Chapter 1, we present a new approach to TRAM synthesis, employing the intramolecular nucleophilic aromatic substitution, or Truce–Smiles rearrangement, of readily accessible 2-benzylbenzanilide precursors. In contrast to classical rearrangements of this kind, the reaction succeeds without electronic activation of the arene that serves as electrophile, with rate acceleration instead provided by the conformational preference of an amide tether within the substrate. Access to TRAM products of varied structure was achieved, with the methodology allowing for independent modification of each of the three aromatic rings. It was demonstrated that the amide function of the reaction products can be removed or used as a functional handle in further transformations. Mechanistic investigation by in situ infrared spectroscopy, a deuterium exchange study and Hammett analysis suggest the reaction proceeds through a partially concerted aryl migration. In addition, a ring-expanding version of the rearrangement provided access to novel TRAM-containing medium ring lactams. On account of the broad tolerance of steric and electronic parameters tolerated for each of the three (hetero)aromatic rings, this methodology is expected to be an attractive approach to TRAM derivatives that are important within various areas of science.



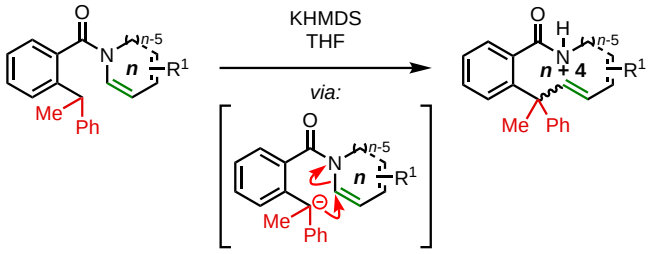
Chapter 2 — Difluoromethyl arenes by the monodefluorination of trifluoromethyl arenes

As a consequence of being an unusual hydrogen bond donor, and a potential bioisostere for a range of functionalities, the difluoromethyl group has attracted much interest amongst designers of pharmaceutical and crop protection agents. In addition, it has emerged as an appealing substitute for the trifluoromethyl group, whose inclusion in industrial products is thought to be having unforeseen negative impacts on the environment. Hence, the defluorination of trifluoromethylated precursors to valuable difluoromethylated products is an intriguing prospect. In Chapter 2, we describe the realisation of this transformation by designing a four-step protocol that employs an amide-based auxiliary to selectively delete one fluorine atom from the CF_3 group of widely available trifluoromethylated benzaldehydes. Diversely substituted CF_2H-containing products could be obtained, including building blocks relevant to medicinal and agrochemical discovery, which highlights the utility and practicality of the method for industrial application. The defluorination of other polyfluoroalkyl groups could also be effected by the method. By probing the defluorination reaction using in situ infrared spectroscopy, and deuterium studies that allowed for measurement of a primary kinetic isotope effect, a viable mechanism was proposed, which includes loss of fluoride by a rate-limiting elimination reaction. We anticipate this is a timely discovery of a highly applicable entry into CF_2H-functionalised arenes that allows for direct replacement of trifluoromethylated intermediates within industrial settings.



Chapter 3 — Medium-sized rings by the migratory ring expansion of alkenes

Owing to their characteristic conformational properties, medium-sized rings are favourable scaffolds for exploration within drug and agrochemical discovery. However, these conformational properties are often a double-edged sword, precluding medium ring formation by the cyclisation of an acyclic precursor. This remains a considerable barrier to the inclusion of medium-sized rings in screening libraries or novel compound designs. The strategy of ring expansion has recently been fruitful for unlocking methods that access medium ring products. In Chapter 3, we describe investigations into employing a ring expansion strategy towards the synthesis of medium-sized rings by the conformationally-enhanced migration of alkenes. This is both an enticing and ambitious endeavour, which could offer a route to enlarged cyclic frameworks with diverse structure. An amide linkage between a 1-phenylethyl anion-stabilising group and a migrating alkene provided the conformational bias to promote vinyl transfer, generating sterically congested olefin products. Although reactivity was unfortunately limited to this specific system, some degree of structural variation was attainable through a carbolithiation–vinyl migration cascade of a related amide-containing substrate. Significantly, the availability of common-sized heterocycles could be leveraged to rapidly access ring expansion precursors from pyridine. Furthermore, progress has been made towards elucidating the mechanism of unactivated vinyl migration processes by identification of a candidate system for a kinetic isotope effect study.



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Author's declaration

I declare that the work in this dissertation was carried out in accordance with the requirements of the University's *Regulations and Code of Practice for Research Degree Programmes* and that it has not been submitted for any other academic award. Except where indicated by specific reference in the text, the work is the candidate's own work. Work done in collaboration with, or with the assistance of, others, is indicated as such. Any views expressed in the dissertation are those of the author.

SIGNED: Mehul H. Jesani DATE: 13/09/2023

Contents

Abbreviations

18-c-6	18-crown-6
2D	two-dimensional
4 CzIPN	1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene
Ac	acetyl
acac	acetylacetonate
Aib	α-aminoisobutyric acid
AIBN	2,2′-azobis(2-methylpropionitrile)
APCI	atmospheric pressure chemical ionisation
Ar	aryl
ATR	attenuated total reflection
BDE	bond dissociation enthalpy
BINOL	1,1′-bi-2-naphthol
BMEA	bis(2-methoxyethyl)amine
Bn	benzyl
Boc	*tert*-butoxycarbonyl
bpy	2,2′-bipyridine
br	broad
BSc	Bachelor of Science
Bu	butyl
Bz	benzoyl
ca.	circa
calcd	calculated
CFL	compact fluorescent lamp
COPD	chronic obstructive pulmonary disease
COSY	correlation spectroscopy
CPME	cyclopentyl methyl ether
DAST	*N*,*N*-diethylaminosulfur trifluoride
DBB	4,4′-di-*tert*-butylbiphenyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
DFT	density functional theory
DIBAL-H	diisobutylaluminium hydride
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMEDA	*N*,*N*′-dimethylethylenediamine

DMF	*N*,*N*-dimethylformamide
DMPU	*N*,*N*′-dimethylpropyleneurea
dppf	1,1′-ferrocenediyl-bis(diphenylphosphine)
dppo	1,8-bis(diphenylphosphino)octane
dr	diastereomeric ratio
E	electrophile
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EDG	electron-donating group
ee	enantiomeric excess
eq	equilibrium
eq.	equivalent
er	enantiomeric ratio
es	enantiospecificity
ESI	electrospray ionisation
Et	ethyl
EWG	electron-withdrawing group
FDA	United States Food and Drug Administration
Fmoc	9-fluorenylmethoxycarbonyl
gem	geminal
Hal	(pseudo)halide
HMBC	heteronuclear multiple-bond correlation spectroscopy
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoramide
HOBt	1-hydroxybenzotriazole
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single-quantum correlation spectroscopy
i	iso
IPA	isopropyl alcohol
IR	infrared
LDA	lithium diisopropylamide
LDEA	lithium diethylamide
m	*meta*
maj	major
max	maximum
Me	methyl
m.p.	melting point
MS	mass spectrometry
MS	molecular sieves
MSci	Master in Science
MTBE	*tert*-butyl methyl ether
µw	microwave
n	normal

Naph	naphthyl
NBS	*N*-bromosuccinimide
NCA	*N*-carboxyanhydride
NMM	4-methylmorpholine
NMO	4-methylmorpholine *N*-oxide
NMP	1-methyl-2-pyrrolidinone
NMR	nuclear magentic resonance
NS	nonstructural
Nu	nucleophile
o	*ortho*
p	*para*
pet. ether	petroleum ether 40–60 °C
PFAS	per- and polyfluoroalkyl substances
Ph	phenyl
phen	1,10-phenanthroline
PMP	1,2,2,6,6-pentamethylpiperidine
Pr	propyl
Py	pyridine
qu	quantitative
quant.	quantitative
R	substituent
RDS	rate-determining step
R_f	retention factor
rot.	rotamer
r.t.	room temperature
s	secondary
S_NAr	nucleophilic aromatic substitution
S_NV	nucleophilic vinylic substitution
t	tertiary
TBDPS	*tert*-butyldiphenylsilyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMEDA	*N*,*N*,*N*′,*N*′-tetramethylethylenediamine
TMP	2,2,6,6-tetramethylpiperidine
TMS	trimethylsilyl
TRAM	triarylmethane
Ts	*para*-toluenesulfonyl
UV	ultraviolet

1 Triarylmethanes by the Truce–Smiles rearrangement of benzanilides

Part of the work presented in this chapter has been published:

Abrams, R.; Jesani, M. H.; Browning, A.; Clayden, J. *Angew. Chem. Int. Ed.* **2021**, *60*, 11272–11277

1.1 Introduction

1.1.1 Importance of TRAMs

Triarylmethanes (TRAMs) are a class of molecule in which three aromatic rings are bound to the same central carbon atom. The motif is present in a wide range of valuable substances (Figure 1.1), including natural products,[1,2] compounds with therapeutic effects,[3–5] agrochemical agents,[6] building blocks in material chemistry,[7] ligand scaffolds,[8,9] and dyes,[10,11] which has opened potential applications as fluorescent probes,[12] photoredox catalysts,[13] and within organic LEDs.[14]

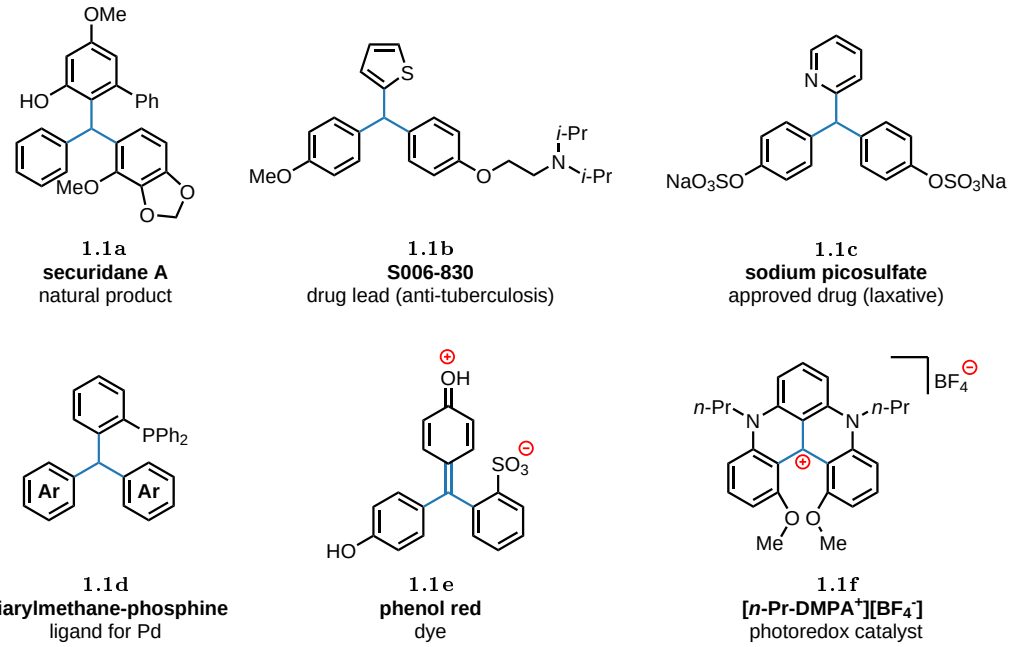


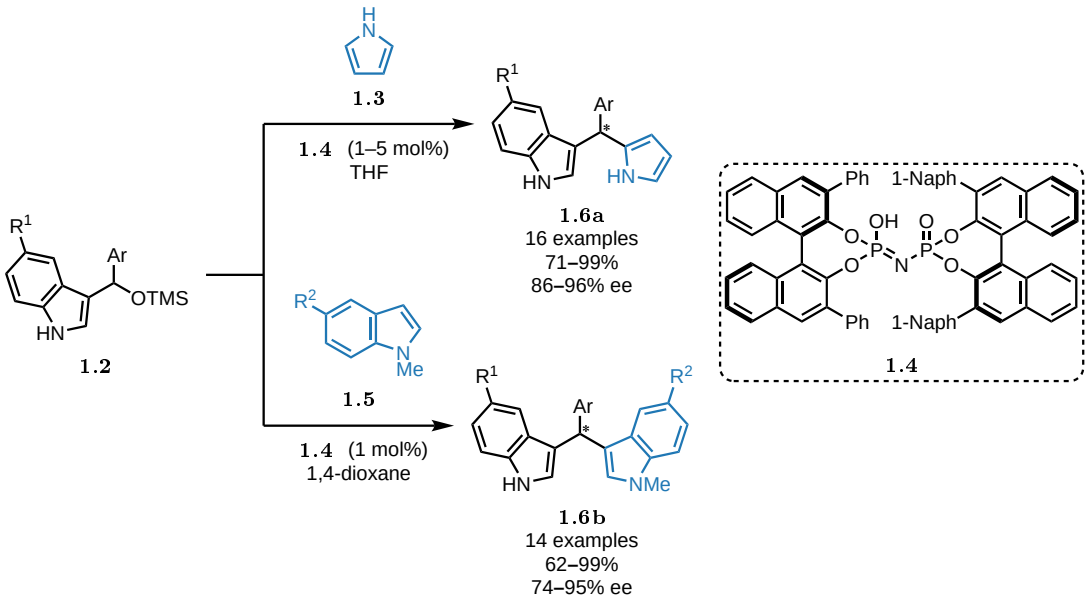
Figure 1.1: The TRAM moiety is embedded in molecules associated with diverse areas of chemistry.

1.1.2 Synthesis of TRAMs

Since TRAM derivatives feature so broadly across chemistry, with pertinence to both science and wider society, their preparation has been of significant interest to the synthetic community. The development of methods towards TRAMs has been reviewed extensively,[15–19] and some examples of the most valuable approaches are briefly summarised here.

1.1.2.1 Friedel–Crafts alkylation

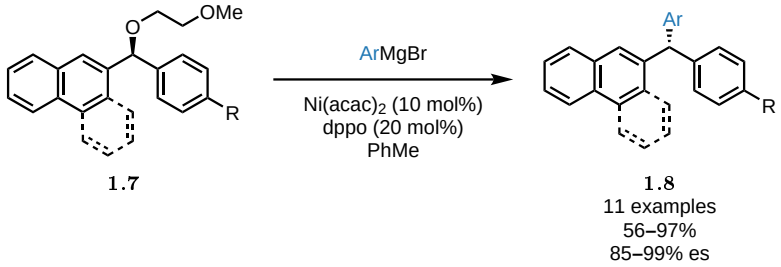
Amongst the most widely used methods to prepare TRAMs is the Friedel–Crafts reaction, mediated by Lewis or Brønsted acids.[17] By using chiral acids, there is potential to render the process asymmetric. This was explored by Zhang and co-workers in their synthesis of heteroaryl-bearing TRAMs,[20] which have demonstrated promising biological activity.[21] An imidophosphoric acid **1.4** was employed as a chiral Brønsted acid catalyst in the Friedel–Crafts alkylation of pyrroles **1.3** and indoles **1.5** with TMS-protected 3-indolylarylmethanols **1.2** (Scheme 1.1). The researchers provided a broad substrate scope, reporting generally high yields and enantioselectivities for the two classes of TRAM products **1.6a** and **1.6b**. It is unsurprising that only the reactions of electron-rich heterocycles **1.3** and **1.5** were presented: the Friedel–Crafts reaction is usually limited to nucleophilic arenes. In addition, as with all electrophilic aromatic substitution processes, regioisomeric products would likely arise from reactions employing alternate aromatic systems that possess multiple sites with comparable nucleophilicity.



Scheme 1.1: The enantioselective preparation of TRAMs **1.6** by Friedel–Crafts alkylation employing chiral catalyst **1.4**.

1.1.2.2 Cross-coupling reactions

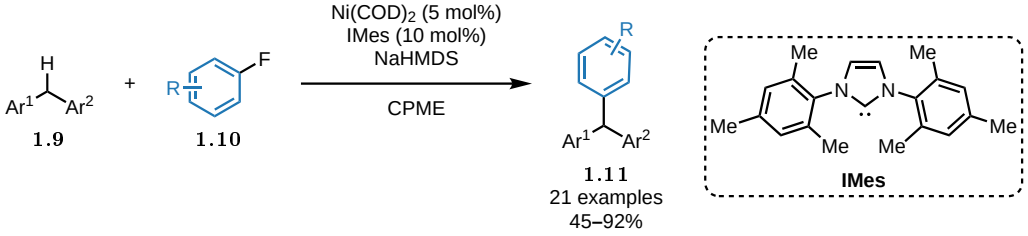
Cross-coupling reactions can facilitate the same disconnection as the Friedel–Crafts approach, whilst overcoming the associated constraints. However, the arene partner must be pre-functionalised with a reactive handle to participate in cross-coupling. In one contribution, researchers developed a nickel-catalysed Kumada-type cross-coupling of enantioenriched diarylmethanol derivatives **1.7**, which were readily prepared by the asymmetric arylation of aldehydes (Scheme 1.2).[22] The chelating methoxyethyl group was designed to coordinate to magnesium ions, accelerating oxidative addition of the benzylic C–O bond. The reaction has to be prepared in a glovebox and has a somewhat limited functional group tolerance, but the chiral TRAMs **1.8** were isolable in good yields with impressive enantiospecificities (85–99%). The overall coupling of **1.7** proceeds with inversion at the chiral centre, explained by a stereochemically invertive oxidative addition step, with a retentive reductive elimination.



Scheme 1.2: A nickel-catalysed cross-coupling of chiral diarylmethanol derivatives **1.7** with Grignard reagents can yield enantioenriched TRAMs **1.8**.

1.1.2.3 Benzylic C(sp^3)–H arylation

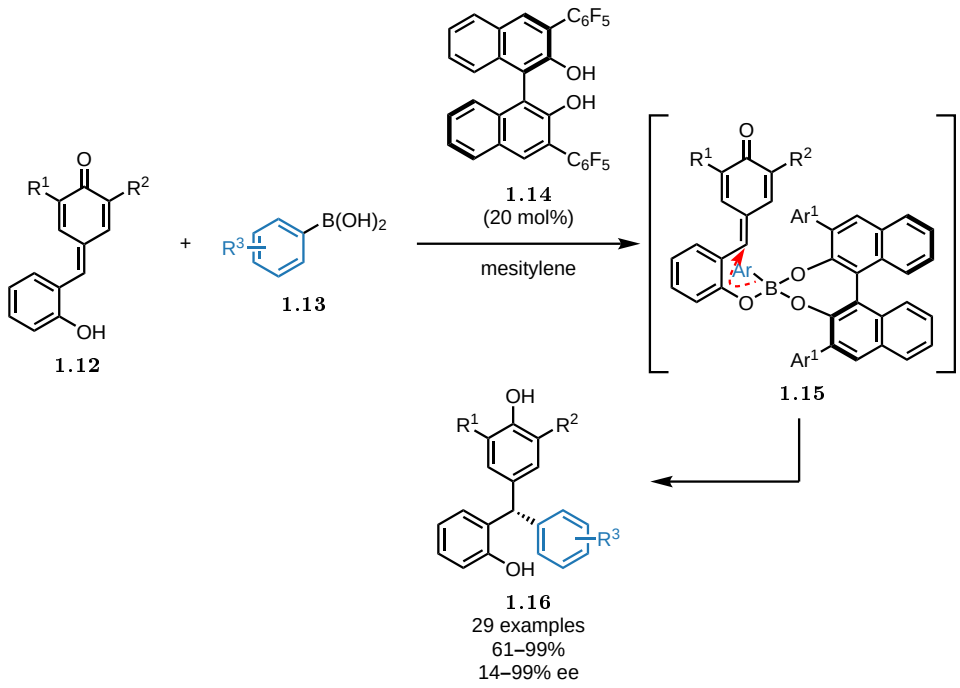
Alternative starting materials can be used to synthesise TRAMs: unfunctionalised diarylmethane derivatives can undergo direct arylation of a benzylic C(sp^3)–H bond. The Walsh group developed a deprotonative cross-coupling method of diarylmethanes **1.9** under nickel catalysis (Scheme 1.3).[23] The catalytic cycle involves oxidative addition of Ni^0 to **1.10**, transmetallation of the benzylic anion of **1.9**, and reductive elimination to provide **1.11**. Although this approach is attractive in terms of the ease of accessing diversely substituted TRAMs, once again, glovebox techniques are necessary with this nickel catalyst system.



Scheme 1.3: Walsh's method to synthesise TRAMs **1.11** by the benzylic C(sp^3)–H arylation of diarylmethanes **1.9**.

1.1.2.4 Addition to quinone methides

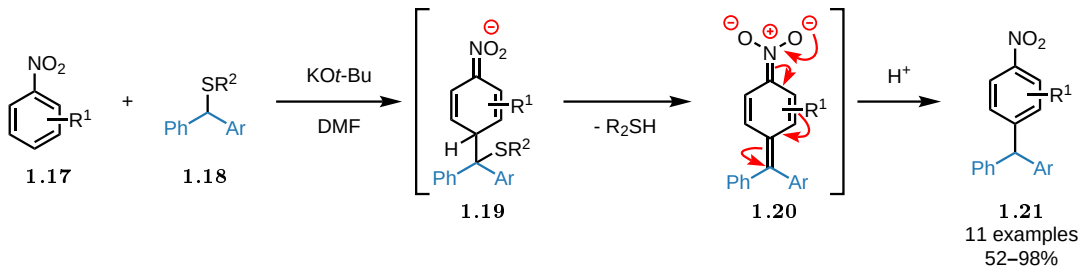
The 1,6-addition of arylboronic acids **1.13** to *para*-quinone methides **1.12** opened an innovative route to generate TRAM products **1.16** (Scheme 1.4).[24] The *ortho*-hydroxy substituent of the salicylaldehyde-derived substrate **1.12** serves as a directing group for a chiral BINOL-type organocatalyst **1.14**. This enables generation of intermediate **1.15**, which is key for the enantioselective conjugate addition of the arene. This is an elegant design, although the structural features required of the substrates — namely, the *para*-quinone methide and the directing group — limits the range of TRAM structures that can be accessed. Nevertheless, for a diverse range of examples, the reaction proceeds in excellent yield (≥80% for all but two examples) with high enantioselectivity (26 products were formed with at least 85% ee).



Scheme 1.4: The asymmetric organocatalytic 1,6-addition of arylboronic acids **1.13** to *para*-quinone methides **1.12** provides chiral TRAMs **1.16**.

1.1.2.5 S_NAr of activated aryl electrophiles

The nucleophilic attack of a diarylmethane carbanion on an aryl electrophile is a simple, direct and modular route to TRAMs, though reports of such S_NAr reactivity are particularly rare. Where this has been successful, only arene substrates **1.17** activated with the one of the strongest EWGs, the nitro group, could undergo attack by the carbanions of benzhydryl sulfides **1.18** in a vicarious nucleophilic substitution reaction (Scheme 1.5).[25] Since the carbon nucleophile bears a thiolate leaving group, after nucleophilic attack forms intermediate **1.19**, an elimination can occur to give **1.20**. Rearomatisation and protonation upon aqueous work up generates TRAMs **1.21** in moderate to excellent yields. Employing a sterically demanding pronucleophile **1.18** disfavoured attack *ortho* to the nitro group, exclusively giving rise to *para*-substituted products **1.21**.

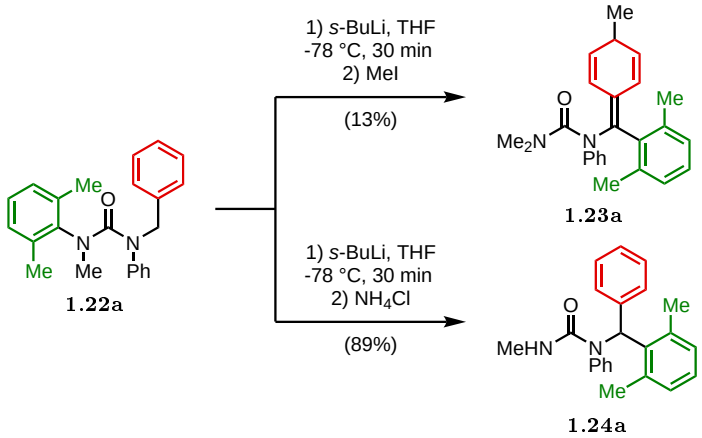


Scheme 1.5: A vicarious nucleophilic substitution process is an attractive route to TRAMs **1.21**, but a nitro EWG is necessary to activate the aryl electrophile **1.17**. R^2 = 4-chlorophenyl.

1.2 Background

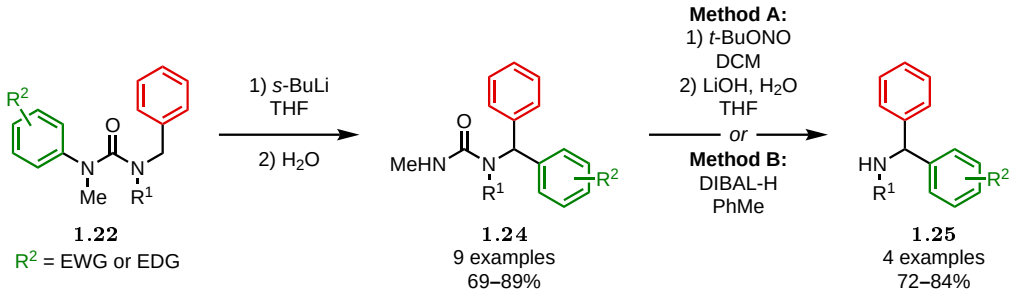
1.2.1 Intramolecular aryl migration: reaction discovery

While aiming to investigate the regioselectivity for the deprotonation of *N*-aryl ureas, the Clayden group discovered a novel stereospecific intramolecular aryl transfer reaction.[26] It was found that, after treatment of *N*-benzyl-*N*′-aryl urea **1.22a** with *s*-BuLi and MeI, the unstable compound **1.23a** could be isolated in low yield, in which the 2,6-dimethylphenyl group had remarkably migrated from the nitrogen of the urea to the benzylic carbon (Scheme 1.6). Replacement of MeI with an aqueous quench provided rearranged product **1.24a** in excellent yield.



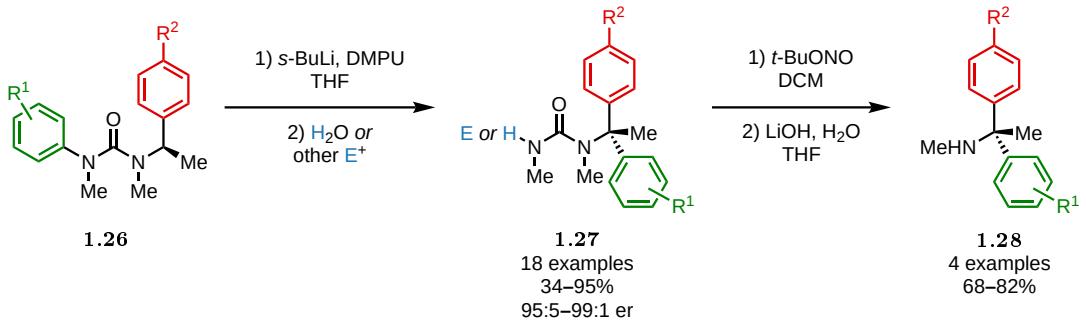
Scheme 1.6: The aryl migration of a lithiated urea.

The intramolecular N→C aryl migration process, or Truce–Smiles rearrangement, of ureas **1.22** to products **1.24** was demonstrated to be general and high yielding for different migrating rings, irrespective of their steric or electronic nature (Scheme 1.7). The substitution patterns of the migrated arenes in the rearranged products **1.24** were identical to those in the reaction substrates **1.22**. This is consistent with a formal *ipso* S_NAr of the urea nitrogen by the benzylic carbon centre. The rearrangement products **1.24** are derivatives of diarylmethylamines; cleavage of the urea group of **1.24** was achieved by either an *N*-nitrosation–hydrolysis sequence, or by reduction with DIBAL-H, to access diarylmethylamines **1.25**.



Scheme 1.7: The scope of the discovered aryl transfer reaction of lithiated ureas included electron-rich and electron-poor migrating rings.

When identical reaction conditions were used, the researchers also found that α-methylbenzylureas **1.26** could undergo rearrangement — although the reaction was considerably slower, with significant quantities of substrate **1.26** remaining after 2 h at −78 °C. Attempts to improve conversion by either increasing the reaction temperature or lengthening the reaction time led to the formation of olefinic products, arising from elimination of the urea moiety. Solvents that can coordinate to lithium are commonly employed to increase organolithium reactivity,[27] with DMPU, TMEDA and HMPA being amongst the most used. Upon addition of DMPU, much greater conversions could be attained, and ureas **1.27** could be isolated in generally good yields (Scheme 1.8). Once again, both electron-rich and electron-deficient rings could undergo migration, although migrations of fluorinated rings were found to be susceptible to decomposition. The chiral products **1.27** could be isolated with very little erosion of enantiomeric purity, providing evidence that the aryl transfer occurred through an organolithium intermediate that is configurationally stable under the reaction conditions. Once again, cleavage of the urea group of **1.27** was accomplished via *N*-nitrosation, and provided access to chiral α,α-diarylethylamines **1.28**.



1.26

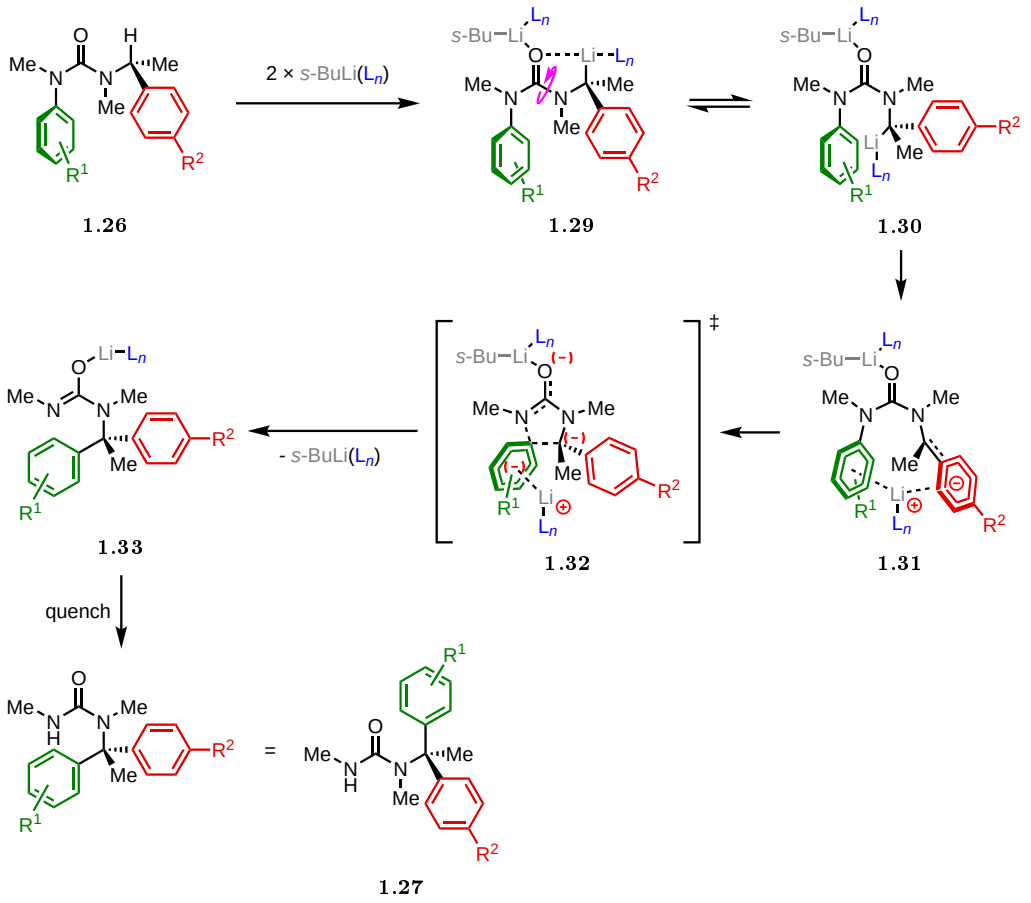
1.27
18 examples
34–95%
95:5–99:1 er

1.28
4 examples
68–82%

Scheme 1.8: Rearrangements of α-methylbenzylureas **1.26** can be used to prepare α,α-diarylethylamines **1.28**.

In addition to the synthetic value of the arylated products accessible by these transformations, the rearrangement is highly intriguing from a mechanistic perspective. Although the rearrangement can be viewed as an overall S_NAr process, it was remarkable that the reaction was shown to proceed without the usually required electronic activation of the ring that assumes the role of electrophile in the S_NAr reaction. Hence, greater mechanistic understanding was sought, with DFT analysis proving most illuminating, revealing the important role of solvated Li^+ ions to the mechanism of the reaction (Scheme 1.9).[28] After benzylic lithiation of α-methylbenzylurea **1.26** to **1.29**, a bond rotation accesses the reactive conformation **1.30**, wherein both aryl groups are *trans* to the C=O, thus holding the lithiated centre in close proximity to the migrating arene. Migration of the solvated Li^+ to a position sandwiched between the two aryl rings in **1.31** enables a stereoretentive N→C aryl translocation to occur to **1.33** via a spirocyclic transition state **1.32**. It is thought that the sandwiched cation helps to stabilise the negative charge accumulating on the migrating ring, significantly lowering the energy barrier for the migration. This mechanistic model provides a basis for the requirement of excess organolithium base, since it favours the disruption of the intramolecular O···Li interaction in **1.29** that occurs on bond

rotation to **1.30** by coordination of the organolithium base to the urea carbonyl. This coordination also has the effect of stabilising the developing negative charge on the urea oxygen in the transition state **1.32**. Moreover, this mechanistic hypothesis helps to understand the role of coordinating solvents, like THF and DMPU, which can solvate Li^+, thus promoting formation of **1.30** from **1.29**, and stabilising **1.31**. In accordance to this mechanistic picture, no evidence for a dearomatised Meisenheimer intermediate between **1.31** and **1.33** could be collected through in situ NMR and IR spectroscopy studies, with the exception of where the migrating group was 1-naphthyl.[28] Despite the textbook mechanism for traditional S_NAr reactions being a stepwise addition–elimination sequence through a discrete Meisenheimer intermediate, this has recently been called into question, with a concerted, or partially concerted, pathway now thought to be operative in many S_NAr processes.[29–31]



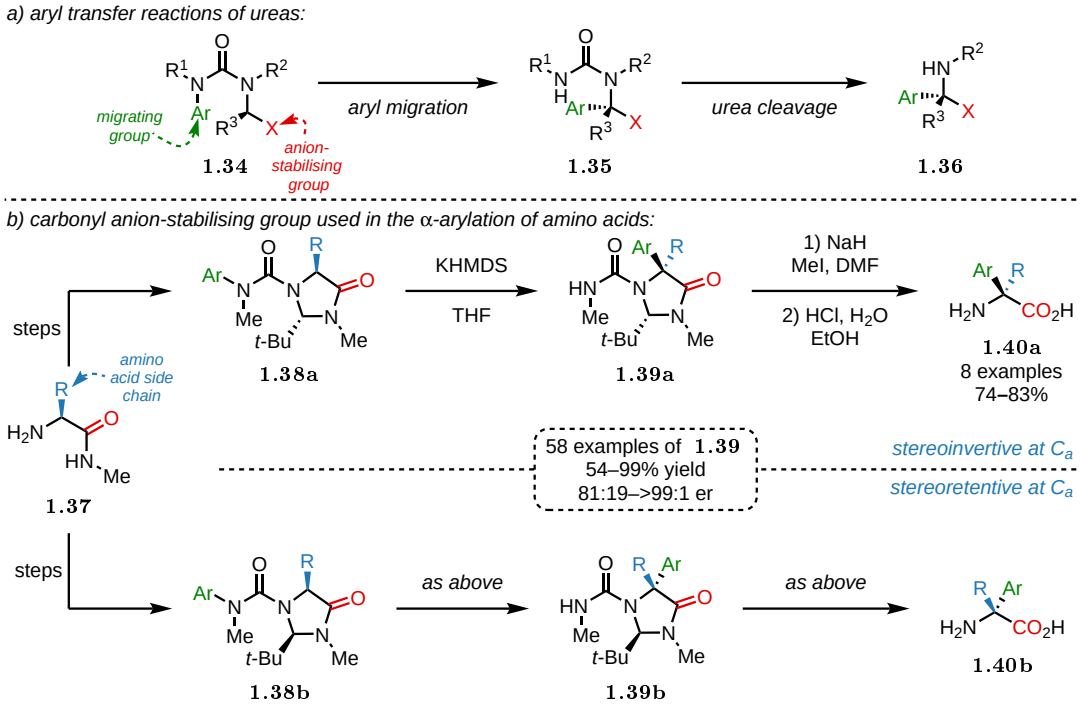
Scheme 1.9: The mechanism for the stereoretentive aryl migration of α-methylbenzylureas **1.26**.

1.2.2 Exploration of urea substrates

Following the discovery of the intramolecular aryl migration of ureas with arenes as anion-stabilising groups, a series of investigations found that analogous rearrangement was feasible with other functionalities to stabilise the anion of the substrate, including heteroarenes,[32] allyl chains,[33,34] nitriles,[35,36] and

carbonyls[36–39] (Scheme 1.10a). In each case, substrates **1.34** bearing electron-poor and electron-rich migrating rings could undergo rearrangement to **1.35**, which, following urea cleavage, provided routes to a range of valuable arylated amine products **1.36**.

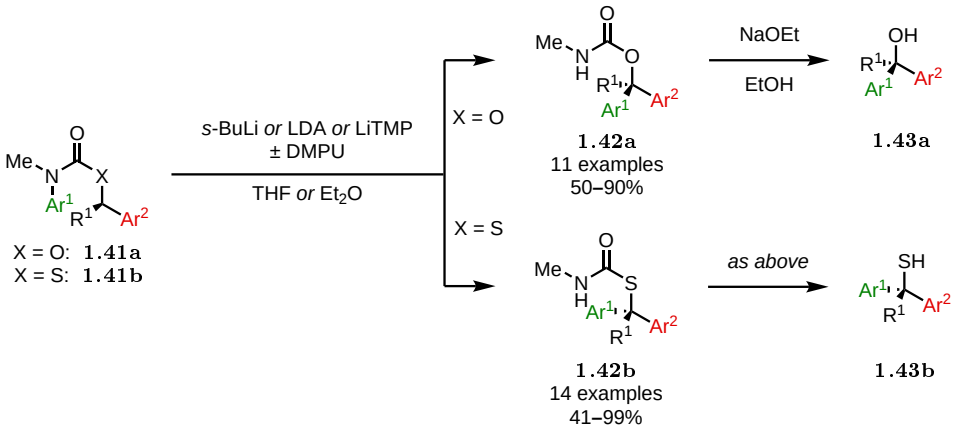
In a particularly noteworthy contribution, the arylation of ureas with a carbonyl anion-stabilising group provided a route to α-arylated amino acids. Whereas there are a range of established methods for the racemic and asymmetric α-alkylation of amino acids, introduction of α-aryl substituents is a markedly greater challenge.[40,41] It was envisaged that the arylation of ureas with a carbonyl anion-stabilising group could enable an asymmetric α-arylation methodology for quaternary amino acid synthesis (Scheme 1.10b).[42] The readily available methylamide derivatives of enantiopure α-amino acids **1.37** could be used to diastereoselectively form an imidazolidinone bearing a urea, with either an *anti*- (**1.38a**) or a *syn*-relationship (**1.38b**) between the stereocentres on the heterocycle. Based on the principle of the self-regeneration of stereocentres,[43] the stereocentre generated during imidazolidinone formation directs the diastereoselective aryl transfer upon KHMDS addition, with the migrating group attaching onto the face opposite to the bulky *t*-Bu group, giving either **1.39a** or **1.39b**. Subsequent hydrolysis completed a highly general, practical and scalable method to prepare either enantiomer of α-arylated amino acids **1.40a** (stereoinverted) or **1.40b** (stereoretained) from a single precursor **1.37**. Once again, this approach was successful irrespective of the electronics of the migrating arene, and mechanistic study by in situ IR spectroscopy and Hammett analysis suggests the rearrangement proceeds without generation of a Meisenheimer intermediate.[29–31]



Scheme 1.10: The intramolecular N→C aryl migration of ureas **1.34**.

1.2.3 Non-urea tethers

The Clayden group has shown that intramolecular aryl transfer, which can form α-arylated tertiary amines from *N*-aryl ureas, is successful with other linkages: carbamates[44] and thiocarbamates[45] can undergo similar α-arylation, giving rise to tertiary alcohol and thiol products, respectively. Lithiation of *N*-aryl-*O*-benzylic carbamates **1.41a** and *N*-aryl-*S*-benzylic thiocarbamates **1.41b** induces N→C aryl migration, leading to arylated carbamates **1.42a** or thiocarbamates **1.42b** (Scheme 1.11). Nucleophilic cleavage of the (thio)carbamate group reveals the α-tertiary alcohol **1.43a** or thiol **1.43b** products. As with urea-tethered substrates, the aryl transfer of thio(carbamates) was found to be stereospecific. However, carbamate-containing substrates were observed to rearrange with stereoinversion, and thiocarbamates with stereoretention. By in situ IR spectroscopy and detailed computational studies,[46,47] this stereodivergence could be rationalised through decisive, but subtle, differences in the role of Li^+ counterions in the reaction pathways.

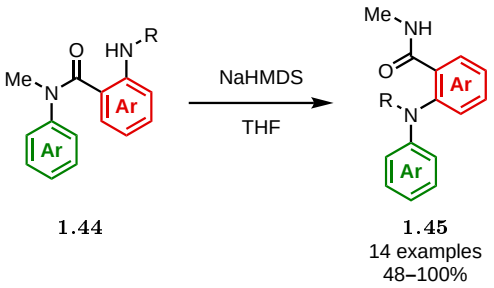


Scheme 1.11: The stereospecific 1,4-aryl transfer reactions of (thio)carbamates **1.41** can provide access to chiral α-tertiary alcohols **1.43a** and thiols **1.43b**.

Most recently, efforts within the Clayden laboratory have discovered that amides are suitable tethers for intramolecular aryl migrations, potentially providing new approaches to a range of hindered products. In 2017, the N→N aryl transfer of *N*-aryl anthranilamides **1.44** was reported, and demonstrated access to diarylamines **1.45** (Scheme 1.12).[48] This Smiles rearrangement could be readily induced by treatment of **1.44** with NaHMDS, and proceeded in good to excellent yields for the translocation of electron-deficient and electron-rich arenes. While the high levels of steric hindrance around the C–N bond in more substituted diarylamines is often problematic for formation by cross-coupling methods,[49] this 1,5-aryl migration approach proved notably general for the synthesis of even the most sterically demanding diarylamine products **1.45**.

1.2.4 Importance of conformation

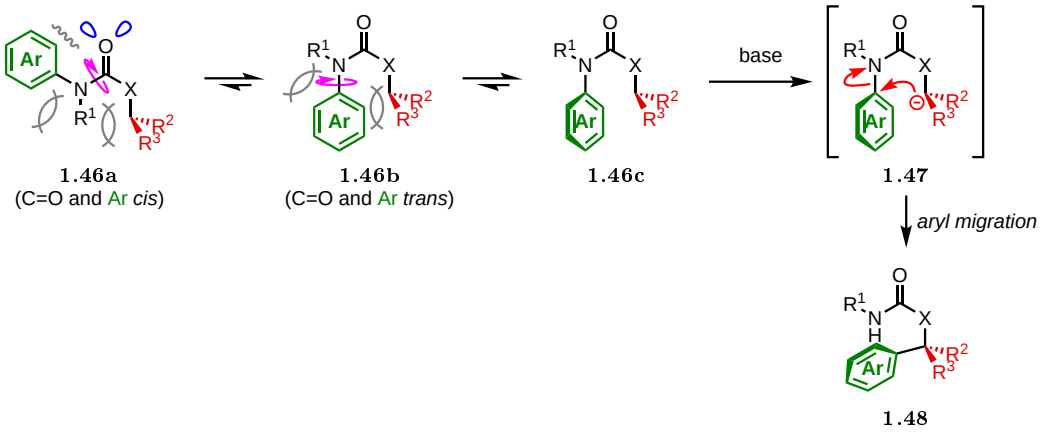
Overall, since the Clayden group's initial discovery in 2007, the remarkable generality for intramolecular aryl migration has been established, with ureas, carbamates, thiocarbamates, and, with recent work, amides all found to be



1.44 **1.45**
14 examples
48–100%

Scheme 1.12: The Smiles rearrangement of *N*-aryl anthranilamides **1.44** can form hindered diarylamines **1.45**.

suitable linkages. In addition, it is a significant observation that such S_NAr processes occur without requiring electronic activation of the ring that assumes the role of electrophile. The broad success of the Clayden laboratory's aryl migration chemistry can be attributed to the conformational acceleration of reactivity that is provided by the tether, which disposes the nucleophilic centre and the electrophilic arene to be close in space. *N*-Alkyl anilides **1.46**, which are embedded in the tethers of aryl migration substrates, can adopt a conformation with the carbonyl and aromatic group either *cis* (**1.46a**) or *trans* (**1.46b**) to one another (Scheme 1.13). The energetics of the system are dictated by multiple factors, including minimising steric clashes, retaining $n_N \rightarrow \pi^*_{C=O}$ delocalisation, avoiding unfavourable n_O-π electronic interactions, and maximising favourable π-π electronic interactions.[50] Repulsion between the oxygen lone pairs and the π-system of the aromatic ring favours the *trans* conformer **1.46b**. There is even greater preference for conformer **1.46b**, if the nucleophilic centre is bound to a π-system that can stack with the arene. Further relief of steric clash is achievable by the aromatic ring twisting to be orthogonal to the carbonyl in **1.46c**. This strong conformational bias of *N*-alkylanilides **1.46** to adopt reactive conformation **1.46c** is crucial in accelerating aryl transfer reactions, with the *N*-aryl ring pre-organised for migration by occupying a position close in space to the nucleophilic site generated upon addition of base.



1.46a (C=O and Ar *cis*) **1.46b** (C=O and Ar *trans*) **1.46c** **1.47**

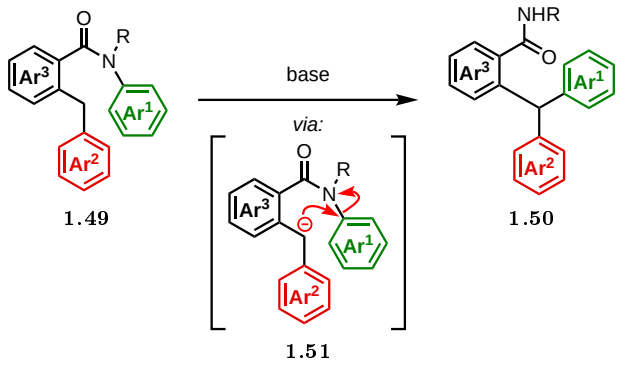
1.48

Scheme 1.13: The conformational bias of *N*-alkyl anilides **1.46** leads to acceleration of intramolecular aryl migration processes.

1.3 Results and discussion

1.3.1 Project aims

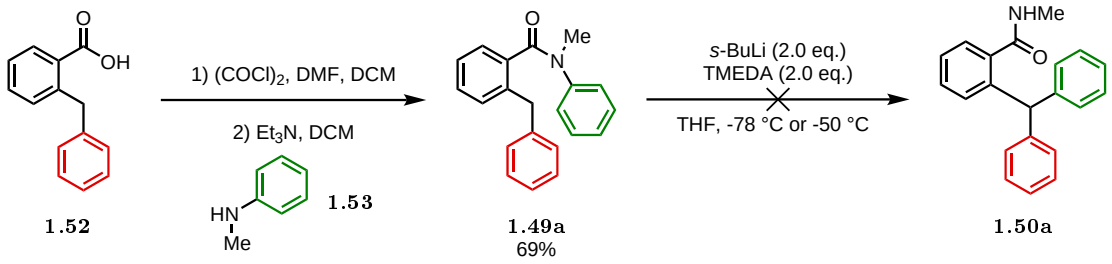
The conformationally-accelerated intramolecular arylation reactions of ureas, (thio)carbamates and amides developed by the Clayden group have provided routes to a range of valuable products, such as α-tertiary amines, alcohols and thiols, quaternary α-amino acids, and hindered diarylamines (see Section 1.2). Given TRAMs are a privileged motif within chemistry, and the ability of the group's aryl migration chemistry to access hindered moieties, we wanted to target the construction of TRAMs by an intramolecular N→C aryl migration of readily accessible 2-benzylbenzamide precursors **1.49** (Scheme 1.14). We believed that upon treatment of **1.49** with base, a conformationally-enhanced Truce–Smiles rearrangement would occur via anion **1.51**, providing the TRAM product **1.50** after quench. If realised, this transformation would represent a straightforward approach to TRAM synthesis, without the need for Brønsted or Lewis acids, or transition metals. In addition, this methodology would offer the ability to independently vary each of the three aromatic rings to access diverse TRAM-containing targets.



Scheme 1.14: The proposed Truce–Smiles rearrangement 2-benzylbenzamides **1.49** to form TRAMs **1.50**.

1.3.2 Reaction discovery and optimisation

To investigate the feasibility of the proposed TRAM synthesis, 2-benzylbenzamide **1.49a** was prepared from commercially available starting materials, 2-benzylbenzoic acid **1.52** and *N*-methylaniline **1.53** (Scheme 1.15). For initial attempts at initiating the aryl transfer, *s*-BuLi was employed as the base, with TMEDA used as a co-solvent, since it can coordinate to lithium and increase organolithium reactivity.[27] However, performing the reaction at −78 °C only led to recovery of starting material **1.49a**. To encourage reactivity, the reaction was then performed at the higher temperature of −50 °C. This led to significant decomposition, with no sign of formation of product **1.50a** upon analysis of the reaction mixture by ^{1}H NMR.

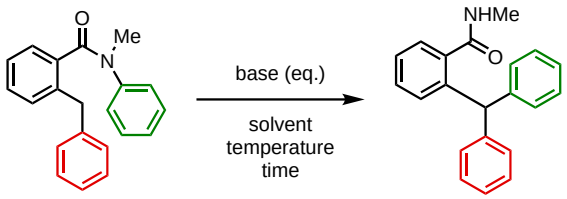


Scheme 1.15: Initial attempts to effect the aryl migration of **1.49a** upon treatment of *s*-BuLi were unsuccessful.*

Following this, the use of a milder base was investigated so that the reaction could be carried out at elevated temperatures (Table 1.1). The base chosen was NaHMDS, since it had successfully induced intramolecular S_NAr reactivity in related systems examined by the Clayden group.[51] Although no reactivity was observed at low temperatures (Table 1.1, entries 1, 2), we were pleased to observe the formation of a small amount of product **1.50a** at ambient temperature (Table 1.1, entry 3). Upon increasing the temperature, improved yields of TRAM product **1.50a** could be attained (Table 1.1, entries 4–6). Following a base screen, KHMDS was found to be the optimal base (Table 1.1, Entries 7–9); addition of 18-crown-6, a ligand with high affinity for potassium cations, did not provide any improvement (Table 1.1, Entry 10). THF and Et_2O were identified as the best solvents (Table 1.1, entries 9, 11–14). Decreased stoichiometry of base (Table 1.1, entries 15, 16), or further elevation of the reaction temperature (Table 1.1, entries 17, 18) led to slightly diminished yields. Following these optimisation experiments, performing the reaction under the conditions outlined in Table 1.1, entry 9, led to a high spectroscopic yield of **1.50a** (81%), and a good isolated yield of 67% on a 0.2 mmol scale (Table 1.1, entry 19).

*Substrate synthesis and aryl migration attempt performed by Alex Browning.

Table 1.1: Optimisation study of the Truce–Smiles rearrangement of **1.49a** to **1.50a**; reactions were conducted on a 0.1 mmol scale.*



1.49a **1.50a**

Entry	Base (eq.)	Solvent	T / °C	t / h	Yield / %[a]
1	NaHMDS (2.0)	THF	−50	16	0
2	NaHMDS (2.0)	THF	0	16	0
3	NaHMDS (2.0)	THF	20	16	<5
4	NaHMDS (2.0)	THF	40	16	12
5	NaHMDS (2.0)	THF	60	16	49
6	NaHMDS (2.0)	THF	100	1	62
7	NaHMDS (2.0)	THF	100	1	(73)
8	LiHMDS (2.0)	THF	100	1	(62)
9	**KHMDS (2.0)**	**THF**	**100**	**1**	**(81)**
10	KHMDS (2.0)[b]	THF	100	1	(54)
11	KHMDS (2.0)	1,4-dioxane	100	1	(27)
12	KHMDS (2.0)	MTBE	100	1	(30)
13	KHMDS (2.0)	Et_2O	100	1	(80)
14	KHMDS (2.0)	PhMe	100	1	(39)
15	KHMDS (1.5)	THF	100	1	(72)
16	KHMDS (1.1)	THF	100	1	(70)
17	KHMDS (2.0)	THF	120	1	(69)
18	KHMDS (2.0)	THF	140	1	(75)
19[c]	**KHMDS (2.0)**	**THF**	**100**	**1**	**67**

[a]Isolated yield; yield determined by ^{1}H NMR in parentheses, using 1,3,5-trimethoxybenzene as an internal standard. [b]With 18-crown-6 (2.0 eq.). [c]0.2 mmol scale.

1.3.3 Scope

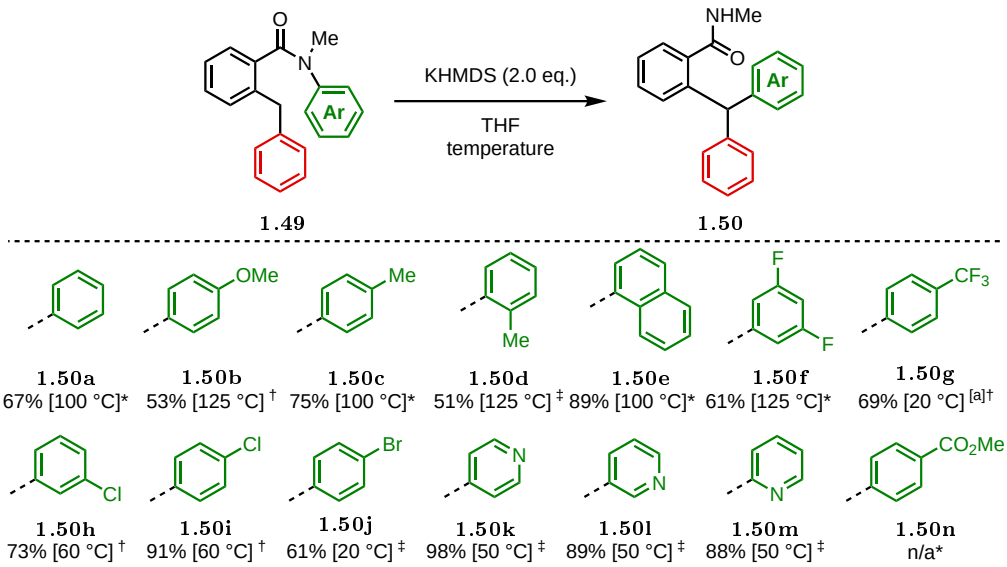
With an optimised set of conditions in hand, we then looked to apply the transformation to a range of substrates to assess the scope of the methodology.

1.3.3.1 Variation of the migrating aryl ring

In an analogous manner to the initial substrate **1.49a** (Scheme 1.15), 2-benzylbenzamides **1.49** bearing migrating arenes with diverse steric and electronic characteristics were prepared, and the N→C aryl transfer induced with addition of KHMDS (Scheme 1.16). Consistent with other intramolecular arylations reported by the Clayden group (see Section 1.2), the acceleration of rate provided by the preferred conformation of the amide tether allowed for unactivated (**1.50a**) and even deactivated, electron-rich (**1.50b** and **1.50c**) arenes to be competent migratory groups. Similarly, sterically encumbered migrating groups

*Optimisation study performed by Alex Browning.

could be transferred (**1.50d** and **1.50e**). Halogenated rings also underwent rearrangement in moderate to excellent yields (**1.50f**–**1.50j**), although chlorinated and brominated migratory groups demanded reduced reaction temperatures to prevent protodehalogenation. Pleasingly, heteroarenes were also found to migrate: 4-, 3- and 2-substituted pyridines were all incorporated into their TRAM products in high yield (**1.50k**–**1.50m**). A substrate bearing a migrating arene functionalised with a methyl ester substituent (**1.50n**) did undergo rearrangement, but not to a single product. The crude reaction mixture contained two TRAM species: one with a methyl ester, and one in which the ester had been cleaved to the carboxylic acid. Purification to separate these compounds was not attempted.



Scheme 1.16: Scope of migrating groups for the intramolecular aryl shift of 2-benzylbenzamides **1.49**. [a]LiHMDS used instead of KHMDS.

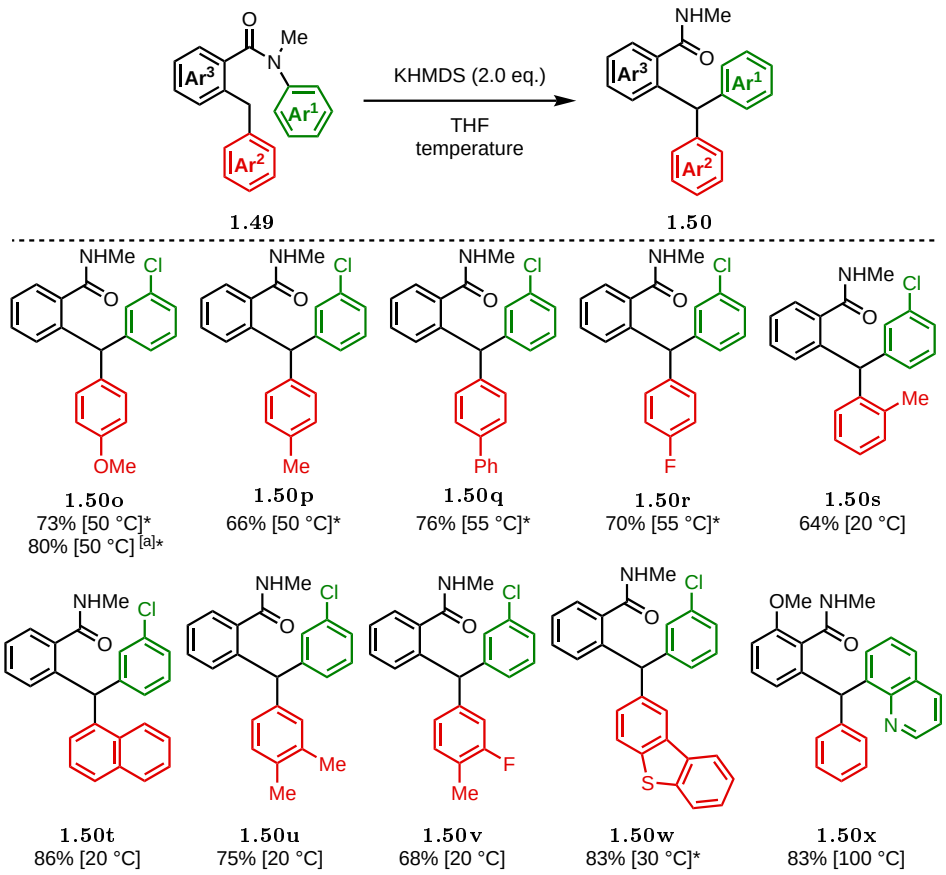
1.3.3.2 Variation of the other aryl rings

The benzylic ring serves as an anion-stabilising group, and the sensitivity of the methodology to variation of this group was investigated (Scheme 1.17). A range of functionalities were discovered to be well-tolerated, namely methoxy, methyl, phenyl and fluoro substituents (**1.50o**–**1.50r**), with the transformation performing well on gram-scale to give **1.50o** without loss of yield. Impressively, more hindered *ortho*-tolyl (**1.50s**) and 1-naphthyl (**1.50t**) anion-stabilising groups did not preclude rearrangement, and TRAMs with multiply-substituted benzylic rings (**1.50u**–**1.50w**) were formed in good yield. Moreover, substitution on the benzamide ring was not detrimental: even with substitution *ortho* to the amide, a position with significant steric implications,[52] rearrangement to generate **1.50x** proceeded smoothly.

*Substrate synthesis and aryl migration performed by Alex Browning.

†Substrate synthesis performed by Alex Browning and aryl migration performed by Roman Abrams.

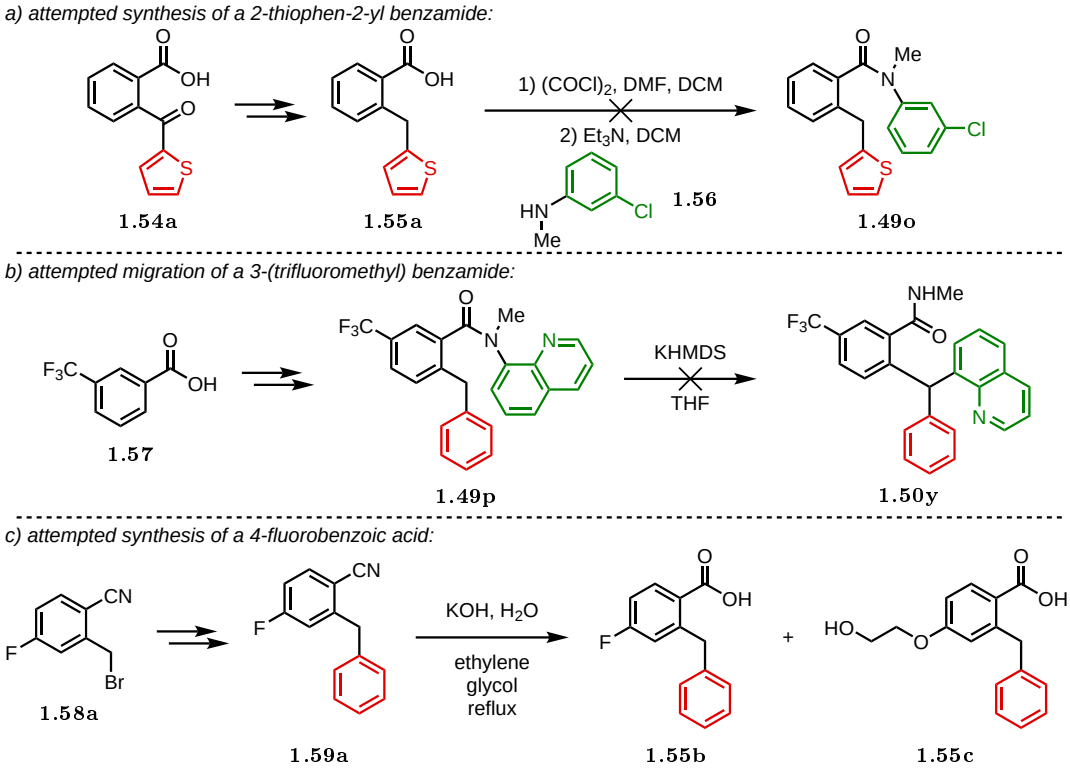
‡Substrate synthesis and aryl migration performed by Roman Abrams.



Scheme 1.17: Scope of benzylic aryl groups for the Truce–Smiles rearrangement of 2-benzylbenzamides **1.49**. [a]3.7 mmol scale.

There were instances in which the attempted variation of the benzylic and benzamide rings was not successful. Reduction of commercial keto acid **1.54a** yielded **1.55a**, following which amide formation was attempted under the standard conditions (Scheme 1.18a). This proved unsuccessful, with decomposition observed upon reaction with $(COCl)_2$, presumably due to acylation of the nucleophilic thiophene ring. 3-(Trifluoromethyl)benzamide substrate **1.49p** was successfully synthesised, but upon addition of KHMDS to initiate Truce–Smiles rearrangement, TRAM product **1.50y** could not be isolated (Scheme 1.18b). The insoluble material formed during the reaction and the broad NMR spectra of the crude reaction mixture suggested that polymerisation had occurred, despite trialling the reaction at different temperatures. Hydrolysis of a benzonitrile provided the requisite benzoic acid towards TRAM **1.50t**, and the same conditions were applied to fluoro-substituted benzonitrile (Scheme 1.18c). Unfortunately, this gave rise to a mixture of desired product **1.55b** and the side-product **1.55c**, arising from substitution of fluoride by a molecule of solvent, ethylene glycol. We recognised that acid **1.55c** could still provide a viable substrate for the methodology: protection of the primary alcohol by *O*-benzylation was attempted, but unfortunately formed multiple products, and so was not pursued any further.

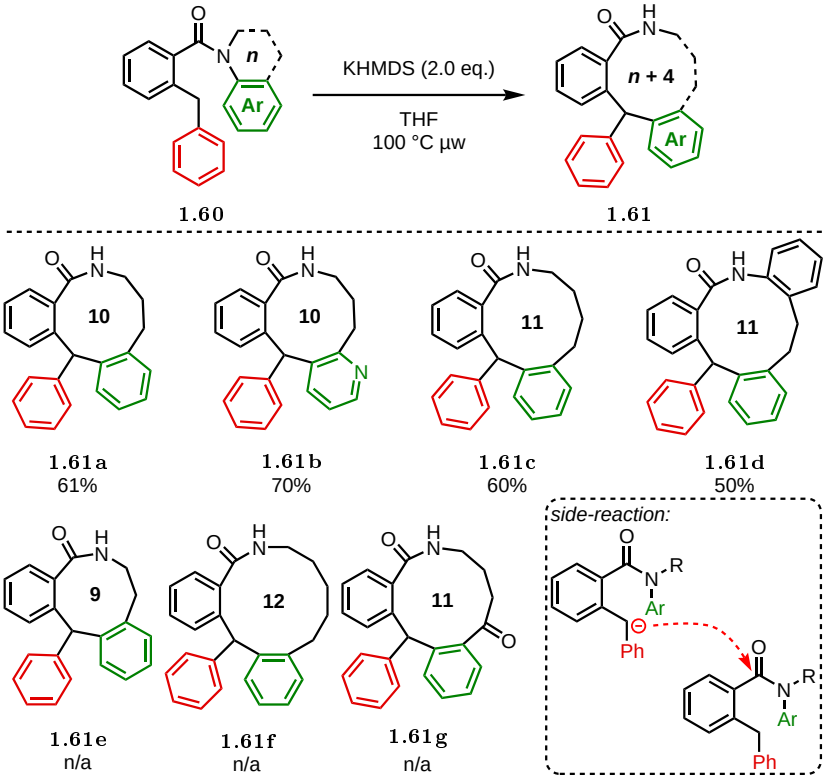
*Substrate synthesis and aryl migration performed by Roman Abrams.



Scheme 1.18: Unsuccessful attempts to prepare, or conduct rearrangements of, substrates with different benzylic and benzamide rings.

1.3.3.3 Ring expansions

Given the Clayden group's interest in ring-expanding arylation reactions (see Section 3.2.1), starting materials **1.60** were synthesised in which the migrating ring was incorporated into a heterocycle (Scheme 1.19). We expected that the n-membered heterocycles could be transformed into medium ring lactams **1.61** of size $n + 4$. Pleasingly, a tetrahydroquinoline could be successfully ring-expanded to ten-membered lactam (**1.61a**), with a tetrahydronaphthyridine also found to be reactive, forming **1.61b** in good yield. Similarly, seven-membered heterocycles, including a dihydrodibenzazepine, could undergo reaction to eleven-membered TRAMs (**1.61c** and **1.61d**). Under the same conditions, an indoline-containing substrate underwent full conversion. However, as well as ca. 20% yield of the desired 9-membered lactam product **1.61e**, significant quantities of indoline could be isolated. This suggested operation of a competing reaction, namely the intermolecular attack of the benzylic anion on the amide of a second molecule of substrate. The expansion of an eight-membered heterocyclic precursor was sluggish, with incomplete conversion despite prolonged heating. Once again, ca. 20% of the ring-expanded product **1.61f** was formed, but the reaction profile was messy, likely due to the slow kinetics of the desired reaction necessitating the mixture to be held at elevated temperature for several hours. Finally, attempts to construct **1.61g** were unsuccessful, with significant decomposition observed at 100 °C. Hence, the reaction temperature was lowered, but similar results were obtained at 60 °C. It is thought the likely pathway for decomposition involves nucleophilic attack of the benzylic anion at the reactive ketone function.

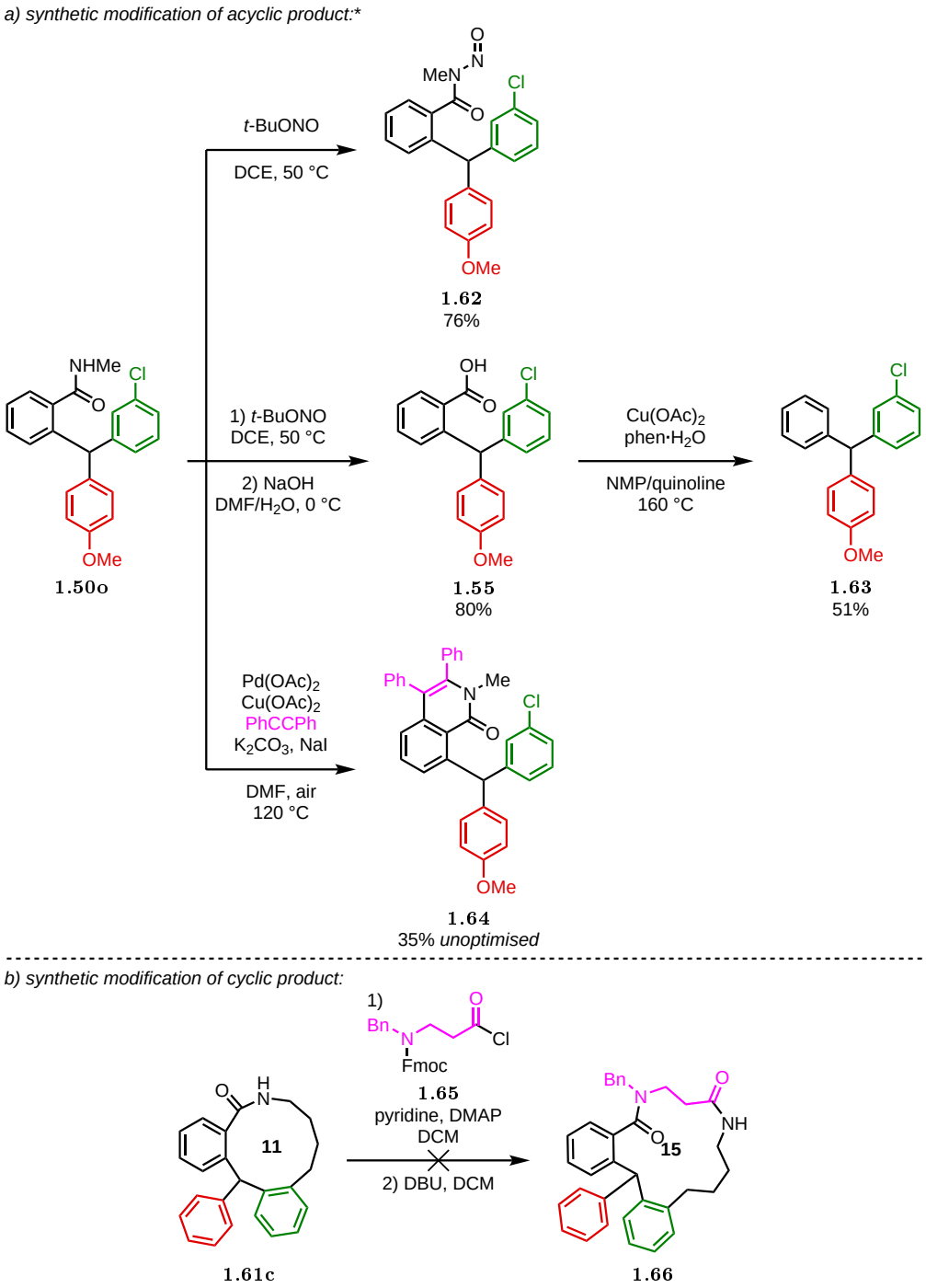


Scheme 1.19: Scope of the ring-expanding aryl migration to generate medium ring TRAMs **1.61**.

1.3.4 Product functionalisation

Following Truce–Smiles rearrangement, the reaction products bear an amide substituent, which can serve as a synthetic handle for further transformation, or be removed completely (Scheme 1.20a). The carbonyl of amide **1.50o** could be rendered an activated electrophile by *N*-nitrosation (**1.62**). Indeed, in one pot, the amide in **1.50o** was transformed to its parent carboxylic acid **1.55** in high yield. Decarboxylation of **1.55** delivered the "traceless" TRAM **1.63**. Alternatively, the amide could be used as a functional handle in a constructive sense; this was exemplified through an unoptimised metal-catalysed cyclisation to construct the isoquinolone heterocycle of **1.64**.

A second opportunity to make use of the amide functionality was investigated: eleven-membered lactam **1.61c** was submitted to Unsworth's SuRE reaction conditions (see Section 3.1.3.2) in the attempt to insert the amino acid chain of **1.65** into the ring framework (Scheme 1.20b).[53] After the reaction, only starting material **1.61c** was recovered in 59% yield, as well as dibenzofulvene, the byproduct of Fmoc cleavage, with no sign of the fifteen-membered macrocycle **1.66**. Although the ring expansion of eleven-membered lactams did feature in the published scope of the methodology, no benzannulated medium ring lactams appear to have been trialled.

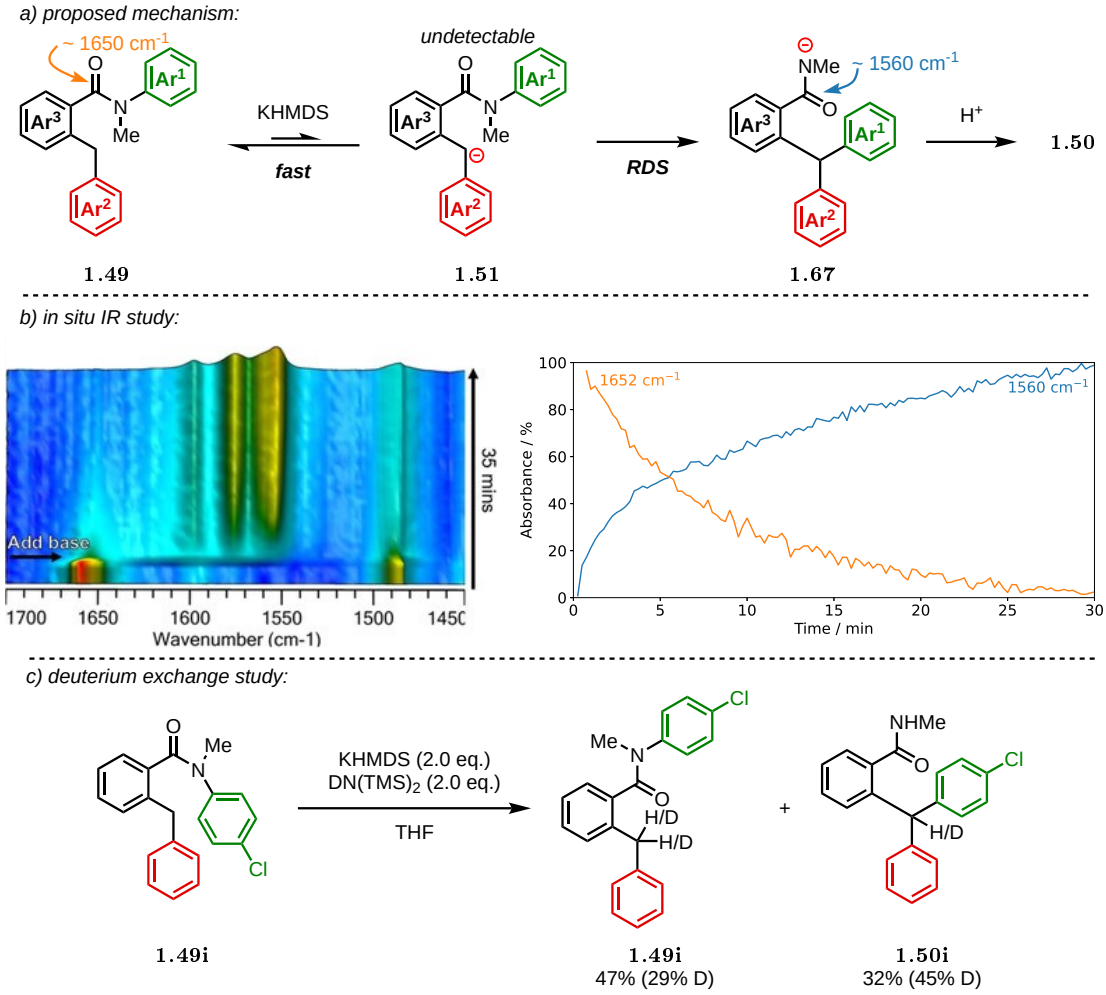


Scheme 1.20: Transforming the secondary amide function in the Truce–Smiles rearrangement products can produce various TRAM derivatives.

*Synthetic modifications of acyclic product performed by Roman Abrams.

1.3.5 Mechanistic study

The mechanism proposed for the Truce–Smiles rearrangement of 2-benzylbenzamides **1.49** to TRAM products **1.50** is outlined in Scheme 1.21a. The substrate **1.49** is deprotonated at the doubly benzylic position by KHMDS. The DMSO pK_a of HMDS (26)[54] is lower than that of diarylmethane (33.5–28)[54], which suggests the equilibrium between diarylmethane-containing substrate **1.49** and its anion **1.51** likely favours the protonated form **1.49** — with the caveat that the negative charge in **1.51** is additionally stabilised by delocalisation into the amide group. Under the reaction conditions, however, **1.51** can perform the irreversible intramolecular aryl migration, leading to further deprotonation of **1.49** such that after quench, the rearranged product TRAM **1.50** is generated in synthetically useful yields.

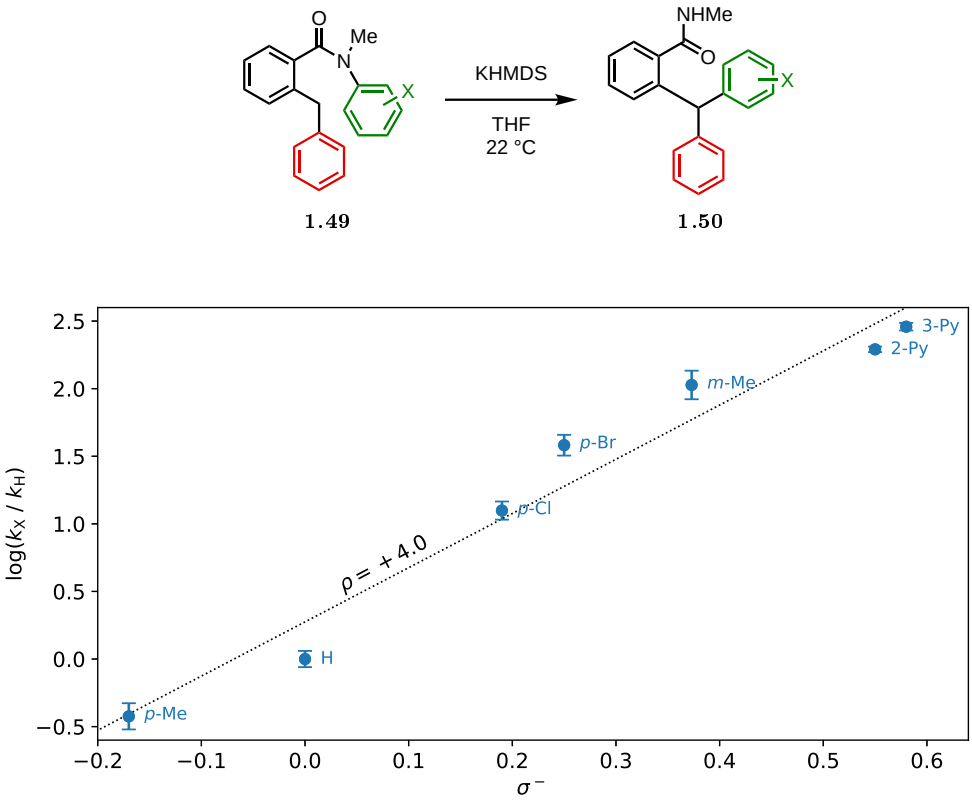


Scheme 1.21: Probing the aryl migration of **1.49i** by in situ IR spectroscopy and a deuterium exchange study provided evidence to support a mechanistic proposal.*

*Mechanistic study performed by Roman Abrams.

To gain support for this mechanistic proposal, we probed the reaction using in situ IR spectroscopy. Upon treatment with KHMDS, the intensity of the carbonyl absorption of amide **1.49i** (1652 cm^{-1}) gradually reduced, with a second absorption beginning to appear at 1560 cm^{-1} (Scheme 1.21b). This absorption was confirmed to correspond to the amidate anion **1.67i** by comparison to an authentic sample of anion, generated by separately treating TRAM **1.50i** with KHMDS. A carbonyl absorption for substrate anion **1.51i** could not be detected. This observation was consistent with one of two mechanistic scenarios: either deprotonation at the benzylic carbon of **1.49** was rate-limiting, or the aryl migration was rate-limiting and occurring from a concentration of anion **1.51** that was below the limit of detection. In order to distinguish between these two scenarios, the Truce–Smiles rearrangement of **1.49i** was performed in the presence of deuterated HMDS, and quenched prior to complete conversion (Scheme 1.21c). The incorporation of deuterium at the benzylic position of the recovered starting material **1.49i** suggested that deprotonation of the substrate is fast and reversible, with the aryl migration as the rate-determining step.

Classical S_NAr reactions require the arene to be activated by electron-withdrawing substituents.[55] In contrast, a key feature of the transformation we developed was that the electronic properties of the migrating ring did not exert a strong influence over the reaction success: electron-poor, electron-neutral and even electron-rich arenes were all observed to be competent migratory groups (see Scheme 1.16). To examine the role of the electronic effects of the migrating ring, the rearrangement was carried out on differently substituted *N*-aryl 2-benzylbenzamides, and the formation of the product anion monitored using in situ IR spectroscopy. Using this data, a Hammett plot could be constructed (Scheme 1.22). A value of + 4.0 for ρ points towards a significant accumulation of negative charge on the migrating ring during the reaction, although the magnitude of ρ is no longer thought to be indicative of whether an S_NAr proceeds through a stepwise or concerted mechanism.[56] Since a better fit was achievable with σ^- instead of σ values, it is thought some conjugation is possible between the substituents on the migrating ring and the developing negative charge, consistent with the build-up of negative charge on the migrating arene. Moreover, the strong correlation between the Hammett substituent constant σ^- and the reaction rate provides a rationale for the observation that the rearrangement of substrates with more electron-deficient migrating groups could be performed at lower temperatures. However, it is unusual that migrating arenes with diverse electronic characteristics can all undergo productive S_NAr. We believe this is due to the rate acceleration provided by the substrate conformation.

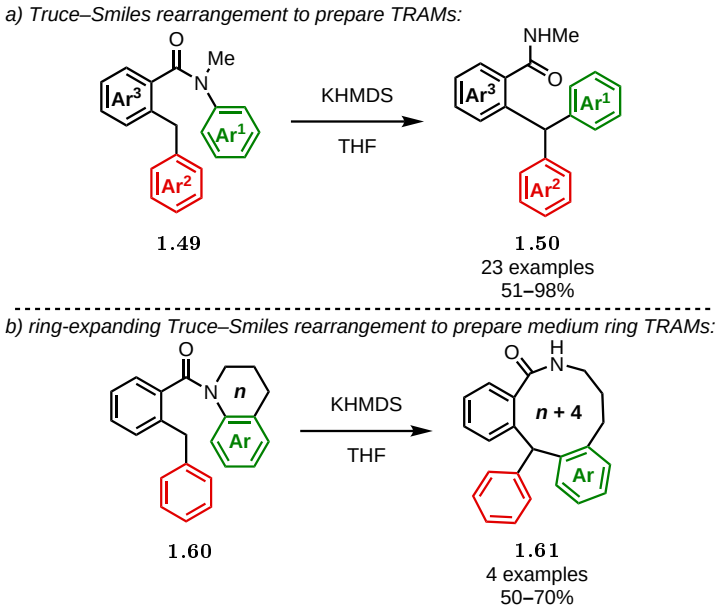


Scheme 1.22: Hammett analysis for the Truce–Smiles rearrangement of *N*-aryl 2-benzylbenzamides **1.49** to TRAMs **1.50**.*

*Hammett study performed by Roman Abrams.

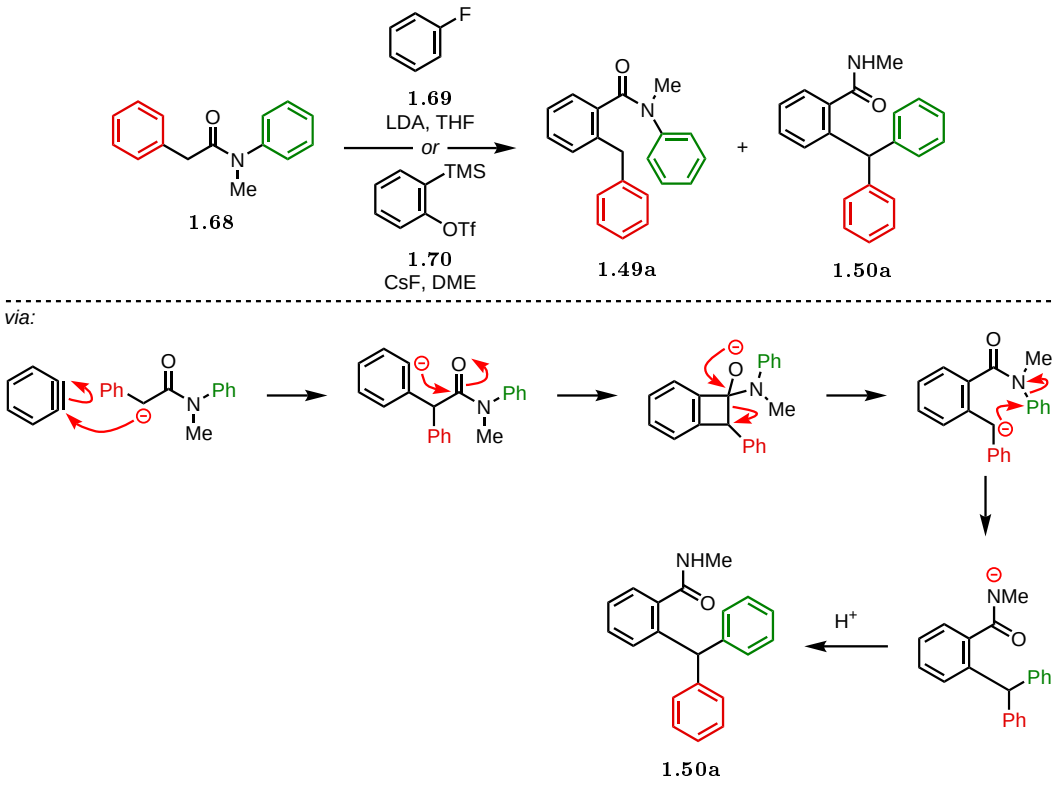
1.4 Conclusion

TRAMs are important synthetic targets because of their applications across a broad range of fields. Despite multiple routes being available for their preparation, new methods continue to be sought after, in order to equip synthetic chemists with different options to access TRAM-containing compounds. In this chapter, the development an operationally simple, transition metal-free methodology for the construction of TRAMs **1.50** was described, in which the Truce–Smiles rearrangement of easily accessed 2-benzylbenzamides **1.49** was employed (Scheme 1.23a). The reaction is successful for substrates with a variety of steric and electronic properties across all three aromatic rings. Most noteworthy is that the arene that assumes the role of electrophile need not activated with electron-withdrawing substituents. In lieu of this usually indispensable source of rate acceleration, the S_NAr process is accelerated through the conformational bias imposed by the amide tether in the substrate, and so electron-neutral and even electron-rich rings are rendered adept migratory groups. Following the transformation, it was demonstrated that the residual amide functionality in the products can be removed, or used as a synthetic handle to broaden the scope of TRAM derivatives accessible by this method. Investigations into the reaction mechanism through in situ IR spectroscopy, a deuterium exchange study and Hammett analysis are consistent with a partially concerted aryl transfer. In addition, novel TRAM-containing medium ring lactams **1.61** can be formed by a ring-expanding arylation reaction of heterocycle-containing substrates **1.60** (Scheme 1.23b). Overall, the broad scope of steric and electronic characteristics tolerated for each of the three (hetero)arenes suggest that this methodology should represent a valuable addition to the synthetic chemistry toolbox, providing access to TRAM derivatives that are key targets in a wide range of settings.



Scheme 1.23: The Truce–Smiles rearrangement of 2-benzylbenzamides **1.49** gave TRAM products **1.50**, with a ring expansive version generating medium-sized rings **1.61** from substrates **1.60** that contain a benzo-fused heterocycle.

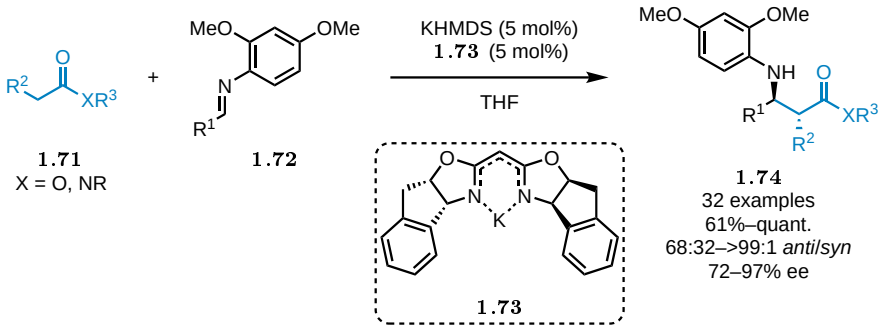
In the pursuit of alternative means of synthesising substrates for the methodology, we were inspired by literature reports for the insertion of arynes into C–C bonds.[57,58] We envisaged that benzyne, either generated by treatment of fluorobenzene **1.69** with base,[57] or precursor **1.70** in the presence of fluoride,[58] could be intercepted by the enolate of phenylacetamide **1.68** (Scheme 1.24). After cyclisation, ring-opening of the cyclobutane, and quench upon work up, we expected formation of **1.49a**. Very little reactivity was observed when benzyne precursor **1.70** was employed, likely as the concentration of the enolised form of amide **1.68** was too low to productively engage with benzyne. Reactions using fluorobenzene **1.69** for aryne generation also suffered with low levels of conversion, with no sign of diarylmethane **1.49a** in the crude reaction mixture by ^{1}H NMR. However, to our surprise, in addition to observing unconverted starting material **1.68**, approximately 20% of the rearranged product **1.50a** was formed. Presumably this arises from benzylic lithation of the generated **1.49a**, with subsequent Truce–Smiles rearrangement. Despite the limited conversion, further optimisation studies based on this intriguing preliminary result could open a new and simple avenue for the preparation of TRAMs.



Scheme 1.24: Attempted preparation of **1.49a** by insertion of benzyne into the C–C bond of phenylacetamide **1.68**.

General methods for the enantioselective preparation of TRAMs continues to be an active area of research.[59] Given the generality of the methodology developed, an asymmetric variant of the reaction could be an interesting route to enantioenriched TRAM derivatives. Recent work within the Clayden group has successfully utilised chiral lithium amide bases in enantioselective transformations,[60,61] although reactions employing chiral bases with other alkali metal counterions have not yet been explored. Kobayashi and co-workers have

recently developed an asymmetric Mannich reaction mediated by a chirally-modified potassium amide base (Scheme 1.25).[62] The researchers found that reaction between KHMDS and a chiral bis(oxazoline) gives a potassium salt **1.73**, which can complex with a molecule of KHMDS to generate a chiral potassium base. This was then able to enantioselectively deprotonate amides and esters **1.71**. Attack of the potassium enolates on imines **1.72** proceeded with high diastereoselectivity, forming Mannich adducts **1.74** with good levels of enantioselectivity (>80% ee in all but two cases). This work provides encouragement for the development of asymmetric versions of reactions that use non-lithium amide bases, like the Truce–Smiles rearrangement presented in this chapter.



Scheme 1.25: Kobayashi and co-workers developed an asymmetric Mannich reaction using a chiral potassium salt **1.73** in concert with KHMDS.

2 Difluoromethyl arenes by the monodefluorination of trifluoromethyl arenes

2.1 Introduction

2.1.1 Importance and properties of fluorine in medicinal and agrochemistry

It was not until the 1950s that fluorine was first introduced into a drug molecule: the 9α-fluorinated derivative of hydrocortisone, known as fludrocortisone **2.1a**, was found to have an impressive ten-fold improved glucocorticoid activity compared to the parent steroid (Figure 2.1).[63] Since then, fluorine has grown to assume a privileged role within the discovery of pharmaceuticals and agrochemicals — a recent estimate suggests around 20% of marketed drugs and 50% of modern crop protection products contain fluorine.[64]

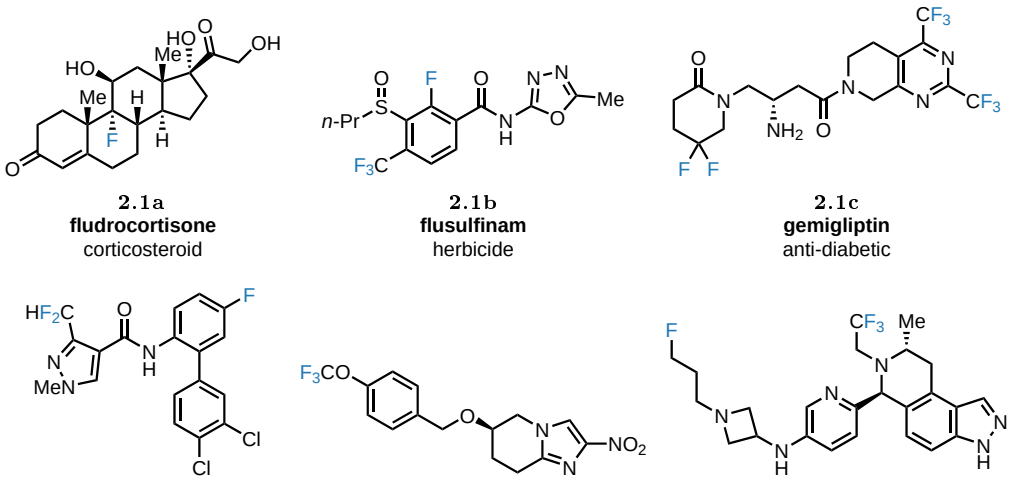


Figure 2.1: Some examples of pharmaceutical and agrochemical agents **2.1** that bear at least one fluorine atom.

The increasing popularity of including fluorine within pharmaceuticals and agrochemicals stems from fluorine's unique properties. The van der Waals radius of fluorine (1.47 Å) is similar to that of hydrogen (1.20 Å), and so replacement of a hydrogen atom by fluorine is usually a conservative change in terms of steric impact.[65] However, fluorine's high electronegativity (3.98 on Pauling's scale, compared to 2.20 for H and 2.55 for C) causes C–F bonds to be highly polarised.[66] Thus, fluorination can impact the stereoelectronic properties of molecules, as well as the pK_a of neighbouring functional groups.[66,67] In addition,

the significant ionic character of the C–F bond serves to increase the bond dissociation enthalpy (BDE) to give the strongest bond in organic chemistry (441 kJ mol^{-1} for C–F, compared to 413 kJ mol^{-1} for C–H).[67] Hence, C–F bonds are often more resistant to oxidative metabolism than C–H bonds, offering a means to modulate pharmacokinetic properties.[68]

Unfortunately, the high stability of C–F bonds can lead to unwanted consequences, arising from organofluorine molecules, notably per- and polyfluoroalkyl substances (PFAS), being resistant to chemical and biological degradation in the environment.[69,70] Fluorinated long-chains are persistent pollutants that can bioaccumulate in and be toxic to animal and humans,[71,72] and low-boiling fluorinated molecules are potent greenhouse gases that can have long lifetimes in the atmosphere.[73] More pertinent to drug and agrochemical settings is that the degradation of a compound containing an inert perfluoroalkylated motif often occurs by modification at non-fluorinated regions or at the functionality bound to the fluorinated moiety, which can generate perfluoroalkylated substances.[74] One such product that has recently been brought into the spotlight is trifluoroacetic acid (TFA), which is highly water-soluble, unreactive, and has no known degradation pathways in aqueous environments.[75,76] This renders TFA a highly persistent contaminant of water systems, and although current concentrations are not thought to be toxic,[77] the longer-term risk to animals and humans remains under scrutiny.[78] Given the trifluoromethyl (CF_3) group is a popular substituent in drug compounds[79,80] and agrochemical agents,[81] it is worrying that the common fate of CF_3-containing compounds is to release TFA into the environment.[78,82,83]

As fluorine-containing substances are being used increasingly frequently and are finding ever-broader ranges of application, the environmental burden and toxicological risk of these "forever chemicals" is growing.[69,82] Hence, finding methods for their degradation by defluorination is an active area of research.[84,85] Moreover, in anticipation of potential future regulation around perfluoroalkyl-containing substances,[86] designers of drugs and agrochemicals are beginning to phase out the CF_3 group, seeking a non-perfluorinated alternative. A potentially suitable replacement could be the difluoromethyl (CF_2H) group — with the fluoromethyl (CH_2F) group another possibility.

2.1.2 The difluoromethyl group

The difluoromethyl (CF_2H) group has been gaining significant interest within medicinal and agrochemical research.[80,81] In addition to the properties shared with other fluorine-containing substituents (see Section 2.1.1), the weakly acidic hydrogen can serve as a hydrogen bond donor.[87–89] Thus, the CF_2H group can act as a versatile bioisostere for different hydrogen-bonding functionalities like alcohols, thiols and amines, as well as being able to replace methyl groups by virtue of their similar steric properties.[88–90] In addition, depending on the attached functionality, the introduction of a CF_2H group impacts a range of factors that contribute to the overall lipophilicity of a molecule, allowing for modulation of a property that is highly important to drug and agrochemical design.[89,90]

In an illustrative example of the hydrogen bond-donating ability of the CF_2H group, inpyrfluxam **2.2b**, a CF_2H-containing fungicide, demonstrated approximately two- to five-fold improved activity over the CF_3-substituted analogue **2.2a** across multiple applications (Figure 2.2a).[91] This may be attributable to the greater structural rigidity of **2.2b**, achieved through formation of an intramolecular hydrogen bond ($CF_2-H\cdots O=C$).[87,92]

During a computationally-driven campaign to discover a non-nucleophilic mimic of cysteine-based peptidic lead **2.3a**, which is a potent inhibitor of hepatitis C virus NS3 protease (K_i = 40 nM), the CF_2H-bearing molecule **2.3b** (K_i = 30 nM) was designed (Figure 2.2b).[93] The researchers identified the likeness, in terms of size and electrostatic properties, of the thiol group of **2.3a** and the CF_2H group of **2.3b**, which manifested in similar potencies.[92] Notably, the C=O of Lys_{136} of the protein engaged in a key hydrogen bonding interaction to the S−H of lead compound **2.3a**, and this could be successfully conserved in the mimic **2.3b** by the CF_2-H function acting as a hydrogen bond donor.

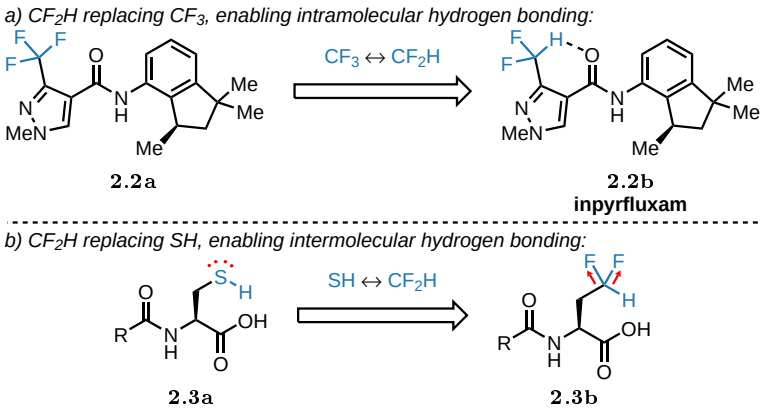


Figure 2.2: The CF_2H moiety can act as a lipophilic hydrogen bond donor, which can offer opportunities within pharmaceutical and agrochemical discovery.

2.1.3 Synthesis of difluoromethyl-containing compounds

In light of their increasing importance to the pharmaceutical and crop protection industries, methods to prepare CF_2H-functionalised molecules — especially difluoromethylated arenes, $ArCF_2H$ — are in demand.[94–102] With the varied objectives and requirements at different stages at drug and agrochemical development,[103,104] it is attractive to have complementary synthetic routes that might offer distinct selectivities, make use of different reagents, or require alternative starting materials. Hence, the selected approaches to $ArCF_2H$ synthesis discussed in this section are categorised by the disconnection they target.

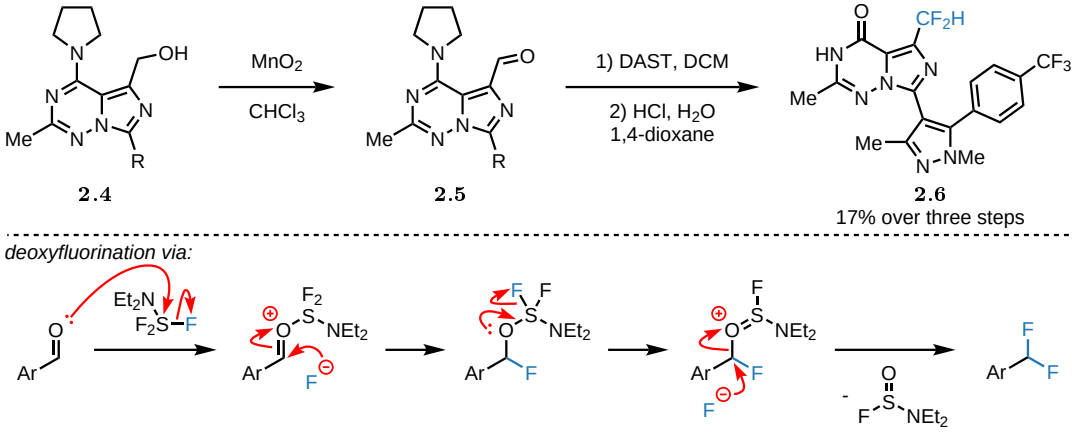
2.1.3.1 C−F bond formation

Deoxyfluorination

The replacement of the carbonyl oxygen of an aldehyde with fluorine was amongst the earliest and most widely used approaches to introduce a CF_2H moiety, often achieved by the highly toxic gas, SF_4.[105] To improve ease of

handling, N–SF_3 reagents were investigated as alternatives, and *N*,*N*-diethylaminosulfur trifluoride (DAST) emerged as a popular replacement to SF_4.[106] Other deoxyfluorination reagents have also been developed, including Deoxo-Fluor,[107] Fluolead[108] and Py-Fluor.[109] However, the drawbacks of DAST and these alternative reagents include some sensitivity to moisture, limited functional group tolerance, varying degrees of thermal stability, and high cost that may restrict scalability.[94,101,109,110] The introduction of XtalFluor-E and XtalFluor-M, bench-stable crystalline solids with improved stability to heat, has addressed some of these limitations.[111] However, the uptake of these reagents is impeded by safety concerns, since activation with HF is required, usually achieved by employing $Et_3N \cdot 3\,HF$. Therefore, researchers continue to pursue novel reagents that may facilitate safe, practical and cost-effective deoxyfluorination reactions.[112]

Although the cost and potential explosivity of DAST likely prohibit application on a process scale,[109] it is used in discovery settings to access fluorinated products. In one such case, researchers at Pfizer reported a method for the late-stage diversification of lead compounds by incubation with liver microsomes.[113] As part of this study, nine lead phosphodiesterase-2 inhibitors were selected as substrates for biotransformation, and compound **2.6** featured a CF_2H-substituted heterocyclic core (Scheme 2.1). The CF_2H functionality was successfully installed by deoxyfluorination of aldehyde **2.5**, followed by hydrolytic removal of pyrrolidine to reveal imidazotriazinone **2.6**.



Scheme 2.1: The deoxyfluorination of aldehyde **2.5** was used to generate difluoromethylated lead compound **2.6** as a candidate for late-stage diversification.

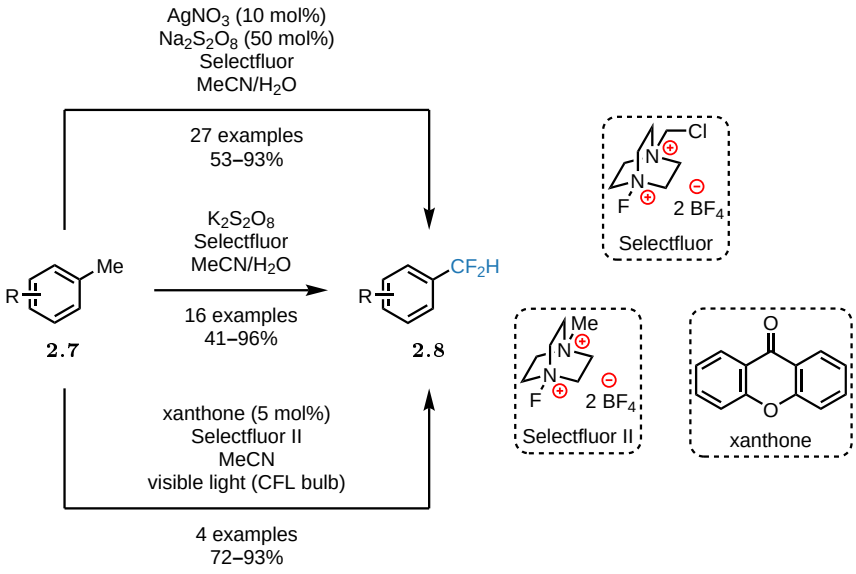
C–H fluorination

While deoxyfluorination can be viewed as a nucleophilic fluorination reaction, a valuable route to CF_2H-derivatised compounds is the fluorination of C–H bonds using electrophilic fluorine sources. Modern reagents for this, such as Selectfluor, often contain a N–F bond. Tang and co-workers employed Selectfluor as the fluorine source in their silver-catalysed method for the double benzylic C–H fluorination of toluene derivatives **2.7** to synthesise CF_2H-substituted arenes **2.8** (Scheme 2.2, top).[114] The mechanistic proposal for the reaction begins with oxidation of Ag^{I} to Ag^{II} by sodium persulfate. The benzylic C–H bond can be subsequently oxidised by Ag^{II} to form a benzylic radical, which is trapped by Selectfluor to achieve monofluorination. The process can then repeat to yield the difluoromethylated products **2.8**, which are formed in generally good yields. Some

formation of **2.8** was observed in the absence of silver salts, potentially indicative that persulfate can directly oxidise benzylic C–H bonds.

Indeed, methodology developed by Yi and co-workers revealed the same overall transformation could be effected under transition metal-free conditions, attaining similar yields of product **2.8**, if a greater stoichiometry of persulfate was employed (Scheme 2.2, middle).[115] However, in both reports, further C–H fluorination of the CF_2H-containing product **2.8** was possible, requiring alteration of the reaction conditions to prevent this for certain substrates. Moreover, the use of a stoichiometric oxidant seemingly restricted the range of tolerated aryl substituents, with electron-rich arenes absent from both of the published scopes.

In the C–H fluorination protocol from Chen and co-workers, an external oxidant was not required (Scheme 2.2, bottom).[116] The researchers envisioned access to the requisite benzylic radical via abstraction of a hydrogen atom from **2.7** by a photoexcited molecule of xanthone, which served as a photocatalyst. Although access to only a modest number of CF_2H-containing products **2.8** was demonstrated, circumventing the need for an exogenous oxidant could be a productive approach for unlocking the C–H fluorination of electron-rich toluene derivatives.



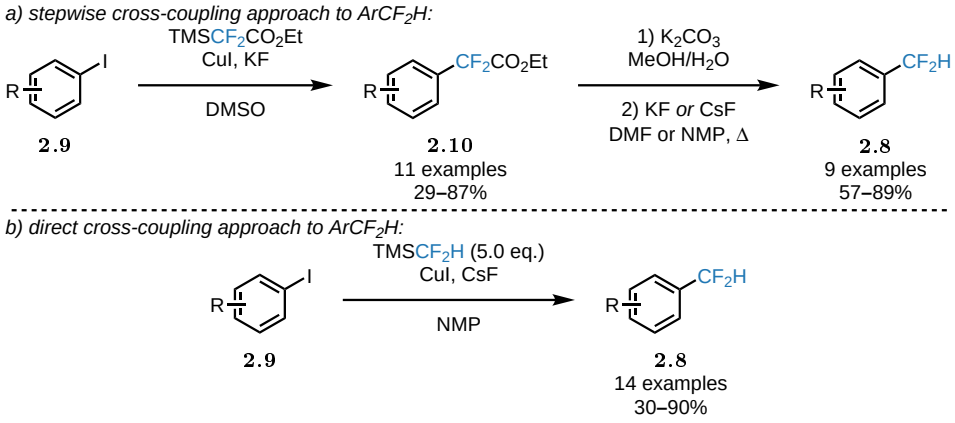
Scheme 2.2: Access to CF_2H-bearing arenes **2.8** by the difluorination of benzylic C–H bonds of toluene derivatives **2.7**.

2.1.3.2 C–C bond formation

Since the report that copper could mediate the perfluoroalkylation of aryl halides in the 1960s,[117] the development of methods for the trifluoromethylation of aryl halides has been extensive.[118] By contrast, progress in realising copper-mediated difluoromethylations has been much slower, stifled by the reduced thermal stability of $CuCF_2H$ complexes compared to their trifluoromethylated counterparts.[119] In 2011, Amii and co-workers devised a stepwise approach to overcome this problem:[120] aryl iodides **2.9** were cross-coupled with α-silyldifluoroacetate, and the coupled products **2.10** subjected to hydrolysis and

thermal decarboxylation to generate CF_2H-substituted arenes **2.8** (Scheme 2.3a). This represented the first general cross-coupling method of aryl halides to produce CF_2H-functionalised arenes, although coupled products **2.10** containing electron-rich arenes were not found to undergo decarboxylation. The mechanism for the coupling step is thought to involve fluoride-assisted transmetallation of the organosilane to Cu^I, oxidative addition of the aryl iodide **2.9**, and reductive elimination to yield the coupled product **2.10**.

Shortly after, Hartwig and co-workers reported their procedure for the first direct copper-mediated difluoromethylation of aryl iodides **2.9** to **2.8** (Scheme 2.3b).[119] The researchers proposed their use of superstoichiometric quantities of $TMSCF_2H$ allowed for formation of $[Cu(CF_2H)_2]^-$, which can serve as a more stable source of $CuCF_2H$. While the method tolerated different functional groups and worked well for electron-rich aryl iodides **2.9**, the coupling of electron-deficient aryl iodides was unsuccessful on account of suffering protodehalogenation. Moreover, ketone- or aldehyde-containing substrates underwent attack at the carbonyl group. By replacing the CF_2H source, $TMSCF_2H$, with Bu_3SnCF_2H, Prakash and co-workers were able to develop a difluoromethylation protocol compatible with electron-poor aryl iodides, including those with ketone or aldehyde functions.[121] Other research groups have since also made contributions to offer improved methods for the copper-mediated difluoromethylation of aryl electrophiles.[122–124]

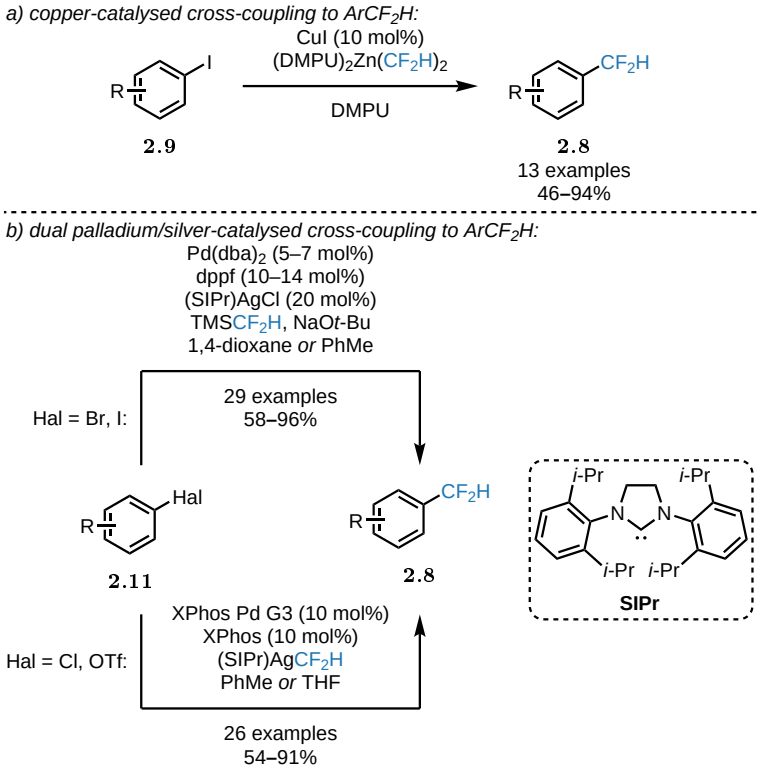


Scheme 2.3: Formation of CF_2H-functionalised arenes **2.8** by the copper-mediated cross-coupling of aryl iodides **2.9**.

Following the advent of difluoromethylation reactions that were stoichiometric in copper, the development of catalytic cross-coupling processes was pursued. In the first difluoromethylation catalysed by copper, Mikami and co-workers demonstrated the cross-coupling of aryl iodides **2.9** with readily prepared (difluoromethyl)zinc reagent $(DMPU)_2Zn(CF_2H)_2$ in the presence of a catalytic amount of CuI (Scheme 2.4a).[125] The transmetallation from the organozinc reagent to copper was proposed to generate the same organocuprate $[Cu(CF_2H)_2]^-$ that Hartwig and co-workers believed could act as a stable reservoir of $CuCF_2H$ (*vide supra*). A range of aryl iodides **2.9** with electron-withdrawing substituents were shown to undergo difluoromethylation in moderate to high yield, though more electron-rich aryl iodides performed less well, since the slower oxidative addition rendered decomposition pathways of $CuCF_2H$ competitive. Notably, this

limitation was addressed by an alternative system reported by Sanford and co-workers.[124] The researchers proposed that, in their system, the stabilisation of copper, provided by an *N*-heterocyclic carbene ligand, allowed for the increased reaction temperature needed for oxidative addition of electron-rich substrates.

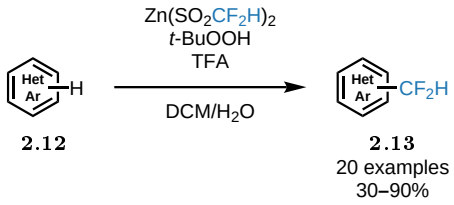
Drawing inspiration from the Sonogashira cross-coupling reaction — in which the desired coupling is effected by a Pd^0/Pd^{II} catalytic system, and a redox-neutral Cu^I co-catalyst system is involved in rate-determining transmetallation[126] — Shen and co-workers designed a palladium-catalysed cross-coupling with a silver co-catalyst, which could accomplish the cross-coupling of aryl bromides and iodides **2.11** with $TMSCF_2H$ (Scheme 2.4b, top).[127] An impressive range of diversely substituted arene substrates, including medicinally relevant molecules, could undergo cross-coupling in good yields. The same research group then published an extension of this reaction that could couple aryl chlorides and triflates **2.11** with stoichiometric pre-formed $(SIPr)AgCF_2H$ (Scheme 2.4b, bottom); once again, the reaction performed well on a considerably broad range of substrates.[128] Building on these seminal contributions, many catalytic cross-coupling methods for the difluoromethylation of aryl (pseudo)halides began to populate the literature; some selected examples include palladium-catalysed Negishi[129] and Hiyama[130] couplings, nickel-catalysed Negishi couplings,[131] and iron-catalysed Kumada couplings.[132]



Scheme 2.4: The preparation of difluoromethylated arenes **2.8** by the catalytic cross-coupling of aryl (pseudo)halides.

Although powerful, the cross-coupling methods described so far in this section require a pre-functionalised aryl coupling partner. A more attractive approach is the direct functionalisation of a $C(sp^2)–H$ bond with a difluoromethyl precursor. A diverse range of methods for this exist, usually relying on the generation of the

difluoromethyl radical.[94–101] This nucleophilic radical can engage in Minisci-type reactions: Baran and co-workers reported the first general protocol for this, in which they developed sulfinate salt $Zn(SO_2CF_2H)_2$ as a bench-stable precursor to $^{\bullet}CF_2H$.[133] This allowed for the C–H difluoromethylation of both electron-rich and electron-poor heterocycles in a method that displayed high functional group tolerance (Scheme 2.5). In cases that the substrate had multiple sites of potential reactivity, moderate to good selectivity for the most electron-deficient site was observed. Since this initial report, other radical-based C–H difluoromethylation methodologies have been published that generate $^{\bullet}CF_2H$ by other means.[134–138]



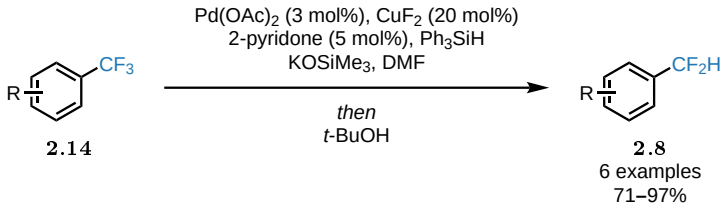
Scheme 2.5: Baran's method for the C(sp^2)–H difluoromethylation of heteroarenes **2.12** using a zinc sulfinate radical precursor.

As summarised in this section, there have been many significant advances in the last decade or so, which have led to the reaction with a difluoromethylating reagent becoming the most popular way of introducing a CF_2H group into a molecule.[94–101]

2.1.3.3 C–F bond cleavage

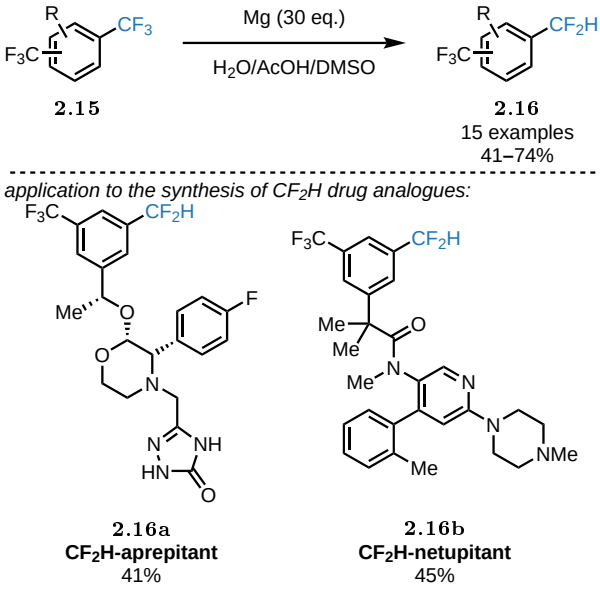
Resulting from long-standing demand from the pharmaceutical and agrochemical industries,[79–81] numerous CF_3-substituted aromatic building blocks with diverse structure can be readily purchased. Therefore, trifluoromethylated arenes are an attractive starting point for accessing difluoromethylated arenes, which have strikingly limited commercial availability.[139–142] However, there is a large thermodynamic cost to breaking a C–F bond on account of a very high BDE (see Section 2.1.1). In addition, the BDE of a C–F bond decreases with a decreasing number of fluorine substituents on the carbon atom.[143] Thus, following one defluorination, successive defluorination events become increasingly easier, rendering the controlled monohydrodefluorination of $ArCF_3$ precursors to $ArCF_2H$ products a highly challenging feat.

During a study from 1991 by Périchon and co-workers, which investigated the samarium-catalysed electrochemical reduction of carbon–halogen bonds, the researchers found that the attempted reduction of $PhCF_3$ gave a mixture of mono- and didefluorinated compounds, as well as some coupled products.[144] Few details regarding the mechanism of this remarkable finding were offered. It was not until over twenty years later that one of the first synthetically useful procedures for the selective monodefluorination of CF_3-subtituted arenes was published by Lalic and co-workers.[145] Treatment of trifluoromethylated arene substrates **2.14** with catalytic $Pd(OAc)_2$ and CuF_2, in the presence of reductant Ph_3SiH and base $KOSiMe_3$, and quenching with *t*-BuOH, led to selectively monodefluorinated products **2.8** (Scheme 2.6). Despite a limited scope, the examples presented were formed in a notably high yield. The additive, 2-pyridone, was found to prevent exhaustive defluorination of substrates **2.14** to their toluene derivatives.



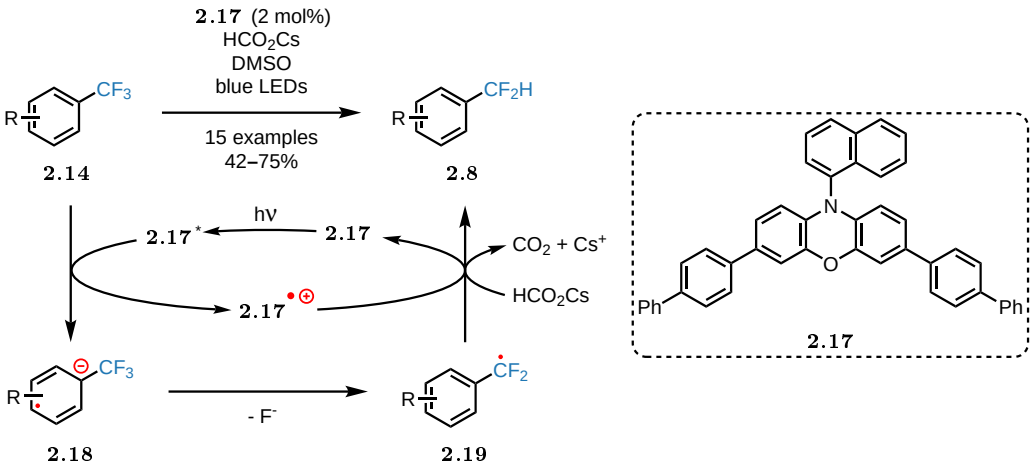
Scheme 2.6: The selective monoreduction of CF_3-containing substrates **2.14** to difluoromethylated products **2.8** under palladium and copper catalysis by Lalic.

In the transition metal-free selective monodefluorination developed by Prakash and co-workers, reduction was accomplished using magnesium metal in the presence of AcOH.[146] Bis(trifluoromethyl)arenes **2.15** bearing various substituents could be transformed to the desired CF_2H-containing products **2.16** in moderate to good yields (Scheme 2.7). The methodology was also successfully applied to access **2.16a** and **2.16b**, CF_2H-analogues of anti-sickness drugs. However, depending on the substrate, the selectivity margin to over-reduced $ArCH_2F$ or $ArCH_3$ products varied widely, with substrates bearing strong EWGs often over-reducing, or forming complex reaction mixtures. Moreover, the use of this reductant system confined the scope to only bis(trifluoromethyl)arenes — less activated substrates with a single CF_3 group did not undergo reaction.



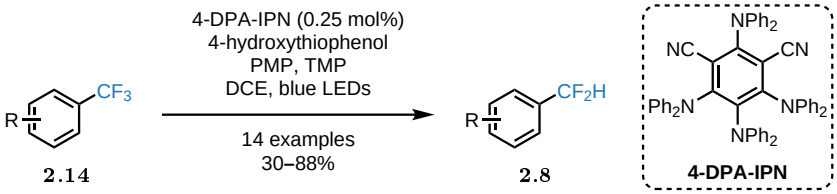
Scheme 2.7: Prakash's defluorination of bis(trifluoromethyl)arenes **2.15** with magnesium metal, and its use to provide CF_2H analogues of pharmaceutical agents.

The photocatalytic methodology of Jui and co-workers was able to overcome some of the limitations of Prakash's magnesium-mediated defluorination.[147] An arene substrate bearing a CF_3 group **2.14** could be reduced to radical anion **2.18** using organic photoredox catalyst **2.17** (Scheme 2.8). Mesolytic cleavage of a C–F bond generated the difluorobenzylic radical **2.19**, and hydrogen atom transfer with HCO_2Cs yielded difluoromethylated product **2.8**. A similar method from Shang and co-workers has also been recently published,[148] but in both reports, most of the successful examples have EDGs on the aromatic ring.



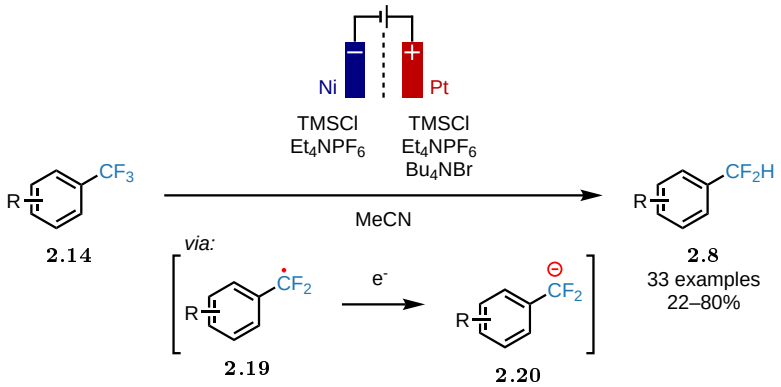
Scheme 2.8: Jui's photoredox approach to the hydrodefluorination of trifluoromethyl arenes **2.14** to CF_2H-substituted products **2.8**.

Complementary to Jui's and Shang's methods, Gouverneur and co-workers developed an organophotoredox reaction that can achieve hydrodefluorination of electron-deficient $ArCF_3$ substrates.[149] In particular, nitrile-containing substrates performed well, with good yields and selectivity for monodefluorinated products **2.8** (Scheme 2.9). However, substrates containing other EWGs, including esters and sulfonamides, were generally lower yielding and/or less selective. Nevertheless, the protocol is highly useful, as demonstrated by the defluorination of six different biologically relevant CF_3-substituted compounds to their CF_2H analogues.



Scheme 2.9: The defluorination of electron-poor CF_3-containing arenes **2.14** by photoredox catalysis was developed by the group of Gouverneur.

Recently, the Lennox lab published a defluorination methodology that exhibits remarkable generality with regards to the electronics of the arene substrate $ArCF_3$.[150] By performing the reduction electrochemically, the researchers were able to apply the deeply reducing potentials required for hydrodefluorination, including for substrates that are inaccessible to chemical reductants or photoredox catalysts. Thus, electron-rich, electron-neutral and electron-deficient substrates **2.14** bearing diverse functional groups could all undergo hydrodefluorination to difluoromethylated arene products **2.8** (Scheme 2.10). In most cases, this approach compared favourably to the previously reported protocols from Prakash, Jui, Shang and Gouverneur (*vide supra*) during benchmarking studies. Mechanistic studies point towards formation of the difluorobenzylic radical **2.19** as accessed by the photoredox method, followed by a second reduction event to difluorobenzylic anion **2.20**, which is protonated by the reaction solvent, MeCN.

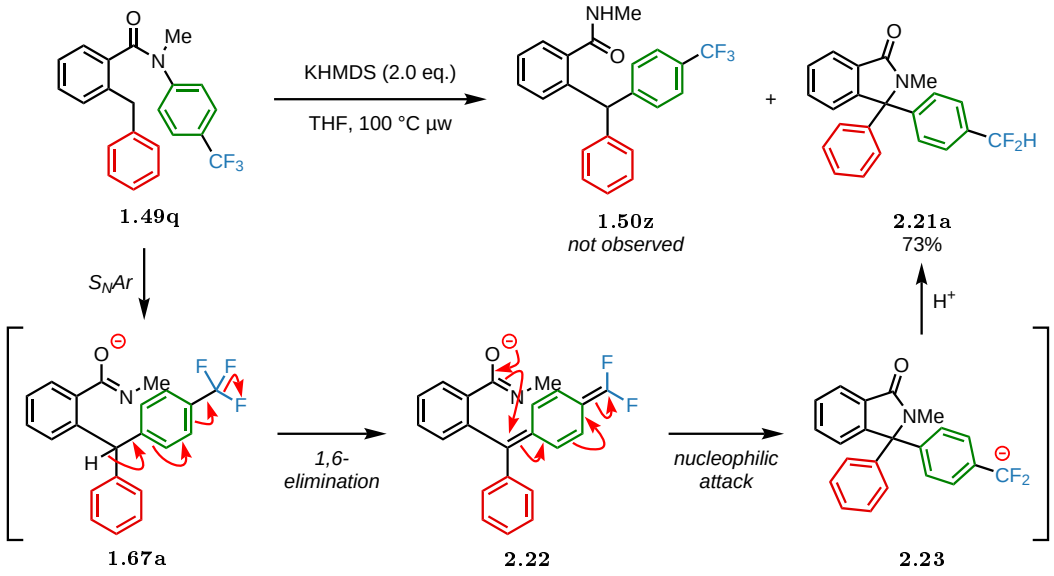


Scheme 2.10: The electrochemical defluorination of trifluoromethylated arenes **2.14** by Lennox and co-workers.

2.2 Background

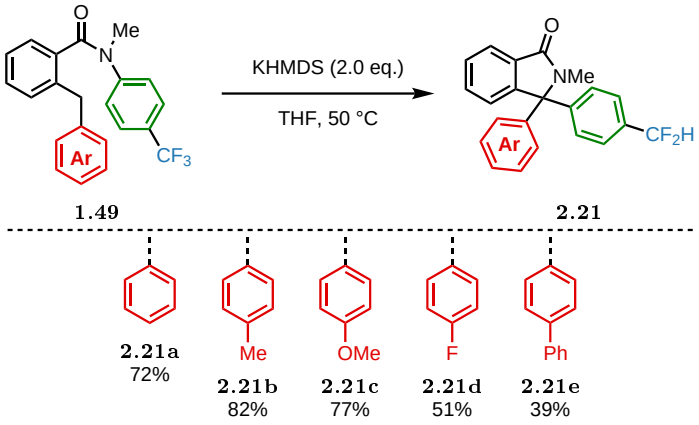
2.2.1 Initial defluorination reaction discovery

The Clayden group's interest in the synthesis of CF_2H-functionalised compounds can be traced back to Alex Browning's MSci project. The scope of migrating rings was being evaluated for the Truce–Smiles rearrangement of 2-benzylbenzamides **1.49** to TRAM products **1.50** (see Section 1.3.3.1).[151] Substrate **1.49q**, with a 4-(trifluoromethyl)phenyl migrating ring, was submitted to the standard conditions for aryl migration (Scheme 2.11). Unexpectedly, the ^{1}H NMR data for the reaction product could not be assigned to the rearranged compound **1.50z**, whose triarylmethyl proton should give a singlet at ca. 6 ppm. Instead, a triplet at 6.68 ppm was observed, with a very large coupling constant (J = 56.3 Hz). The product structure was elucidated as CF_2H-containing isoindolinone **2.21a**, which produced the distinctive triplet in the ^{1}H NMR spectrum by the difluoromethyl proton coupling to two adjacent fluorine atoms. In light of the growing interest in the CF_2H group (see Section 2.1.2), the generation of a CF_2H-containing product from a CF_3-substituted starting material was intriguing. The formation of **2.21a** was hypothesised to arise via the product of the desired aryl transfer **1.67a** undergoing a 1,6-elimination to give dearomatised intermediate **2.22**. Capture by the pendant amidate nucleophile, and subsequent protonation of **2.23**, would lead to the isoindolinone **2.21a**.



Scheme 2.11: Treatment of **1.49q** with KHMDS led to the unexpected formation of CF_2H-functionalised compound **2.21a**, rather than expected TRAM product **1.50z**.

It was then explored whether this tandem aryl migration–defluorination could be applied to other substrates with a 4-(trifluoromethyl)phenyl migrating ring, but with different substituents on the benzyl ring. An initial series of 2-benzylbenzamides **1.49** were prepared and treated with KHMDS (Scheme 2.12). Pleasingly, under slightly modified reaction conditions, it was found that the cascade was successful in each case, providing CF_2H-containing isoindolinones **2.21** in moderate to good yields.



Scheme 2.12: Initial scope for the sequential aryl migration–defluorination reaction of CF_3-substituted 2-benzylbenzamides **1.49** to produce CF_2H-functionalised isoindolinones **2.21**.*

2.2.2 Generalising the defluorination reaction

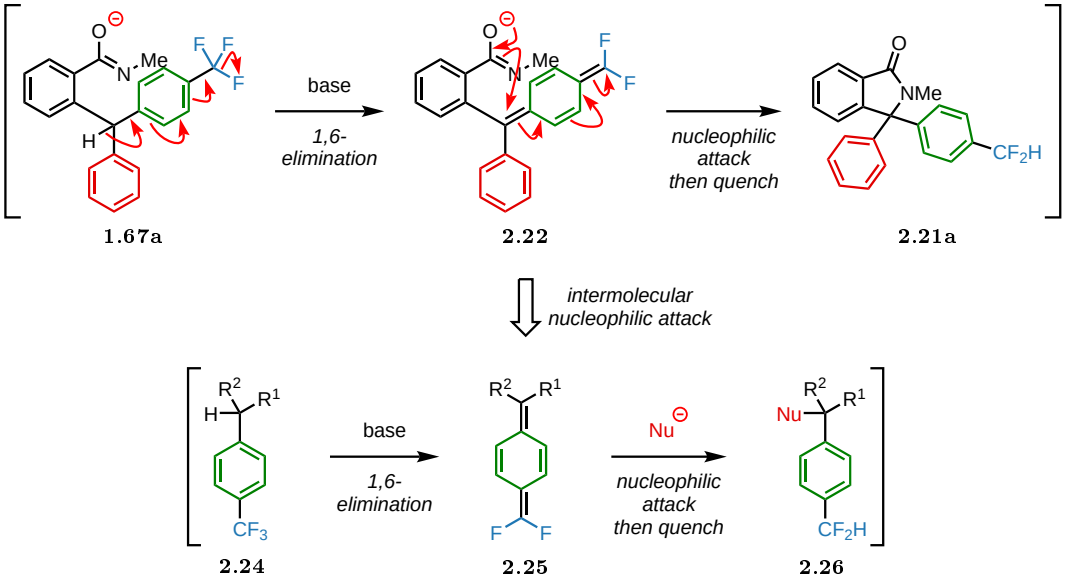
Although an interesting reaction, it was recognised that the cascade process described in Section 2.2.1 was limited in terms of the diversity of the product structures that could be accessed. A more worthwhile pursuit was a general method to access aromatic products with a CF_2H substituent. Investigations into this were initiated through Alex White's BSc project, the findings of which are summarised here.[152]

2.2.2.1 Intermolecular nucleophilic attack

It was hoped that the 1,6-elimination–nucleophilic attack cascade of **1.67a** to **2.21a** could be replicated to establish a more general entry into CF_2H arenes (Scheme 2.13). It was envisioned that (4-trifluoromethyl)benzyl compounds **2.24** could be treated with base to initiate elimination to difluoro-*para*-quinodimethanes **2.25**. While similar structures are known to be susceptible to polymerisation,[153,154] it was anticipated that **2.25** could be instead intercepted by a nucleophile, as achieved in Section 2.2.1. Thus, intermolecular attack of a nucleophile, and subsequent quench, would yield the desired difluoromethylated arene products **2.26**.

The initially designed substrate was **2.24a**, and it was proposed that LDA could function both as a base to induce the elimination, and as a nucleophile to trap the dearomatised intermediate (Scheme 2.14). Analysis of the crude reaction by NMR spectroscopy did not indicate formation of CF_2H-containing **2.26a**. Rather, there were two carbonyl signals in the ^{13}C NMR spectrum, which led to dicarbonyl compound **2.27** being determined as the major product. This was confirmed by comparison with literature characterisation data for **2.27**. Although LDA had successfully acted as both a base and a nucleophile, the nucleophilic attack had occurred at the fluorinated end of difluoro-*para*-quinodimethane **2.25a**, rather than at the benzylic position. The resulting anion **2.28** could then attack adventitious O_2 to produce **2.29**, which could be finally hydrolysed to stable

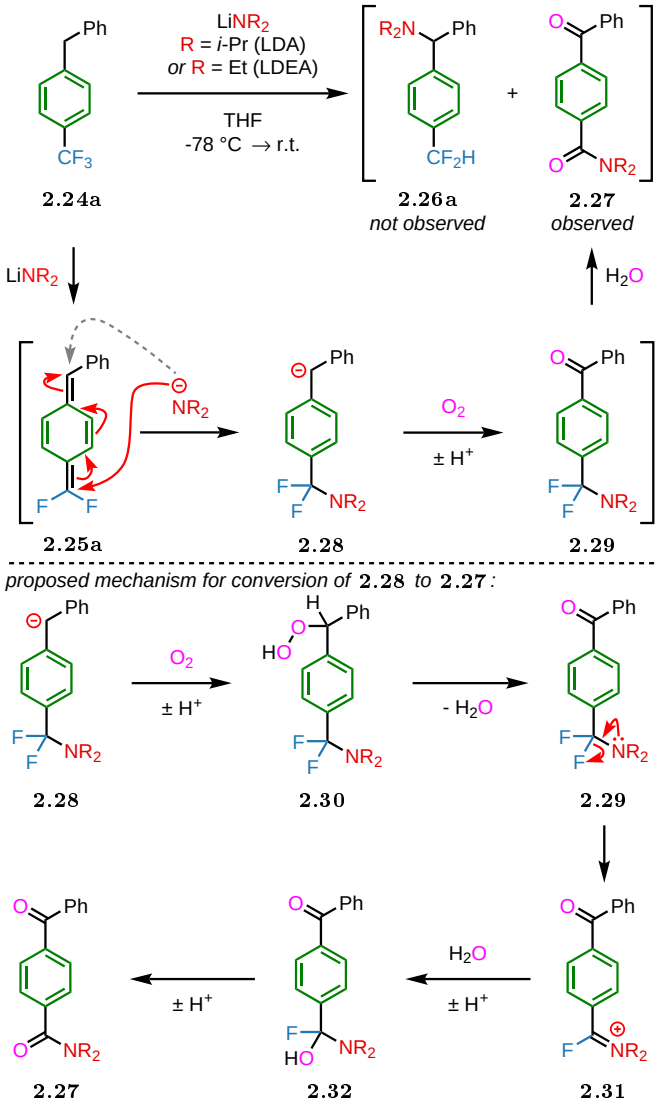
*Substrate synthesis and tandem aryl migration–defluorination performed by Roman Abrams.



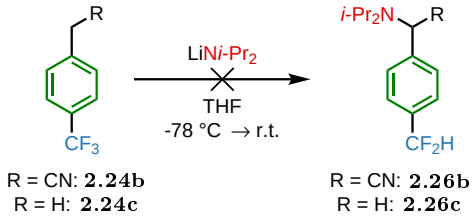
Scheme 2.13: Proposed route to defluorinated products **2.26** by the intermolecular nucleophilic attack on intermediate **2.25**.

compound **2.27**. In the attempt to bias the reaction away from the formation of **2.27**, the procedure was repeated with degassed solvent. And in the event that the steric hindrance of LDA was the origin of the undesired attack at the fluorinated terminus of **2.25a**, LDEA was employed as the base/nucleophile. Unfortunately, this did not productively affect the reaction outcome.

Alternative substrates for defluorination were considered: a nitrile group is much less bulky than the phenyl group of **2.24a**, and could better stabilise an adjacent anion. Hence, **2.24b** was treated with LDA, but this was only found to lead to decomposition (Scheme 2.15). Following this, toluene derivative **2.24c** was submitted to the same conditions. As observed by Schlosser when **2.24c** was treated with the *n*-BuLi/KO*t*-Bu superbase,[153] the material underwent polymerisation, as evidenced by the streaking observed on TLC, poor solubility upon work up, and the broad signals in the ^{1}H NMR spectrum of the crude reaction mixture.



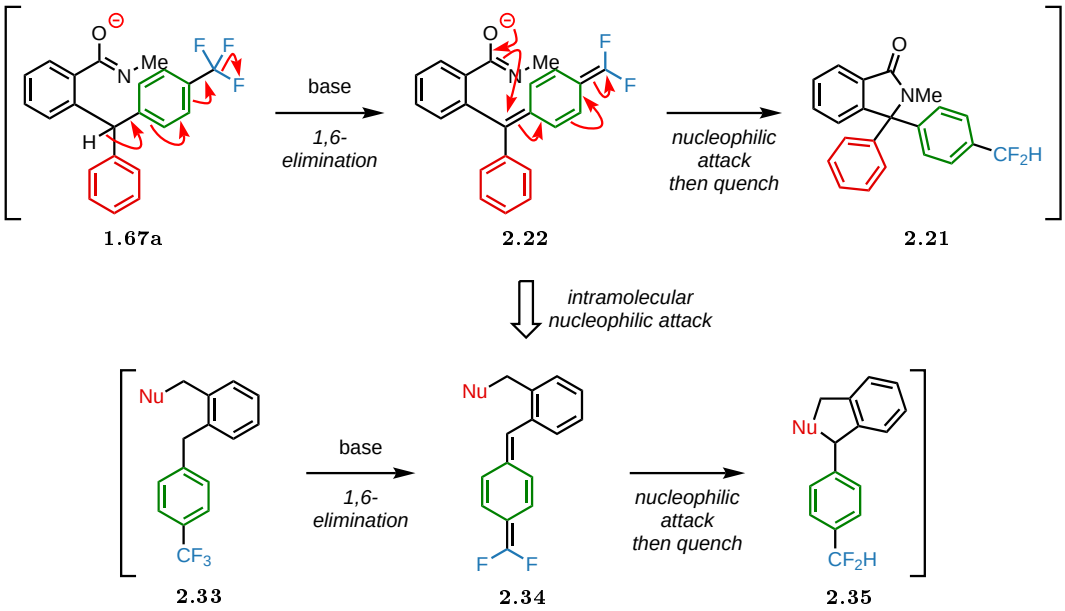
Scheme 2.14: The attempted defluorination–nucleophilic capture of **2.24a** to **2.26a** using lithium amides as bases and nucleophiles led to the formation of dicarbonyl compounds **2.27**.



Scheme 2.15: Upon treatment with LDA, neither nitrile compound **2.24b** nor toluene derivative **2.24c** were found to undergo productive reaction to give defluorinated compounds **2.26**.

2.2.2.2 Intramolecular nucleophilic attack

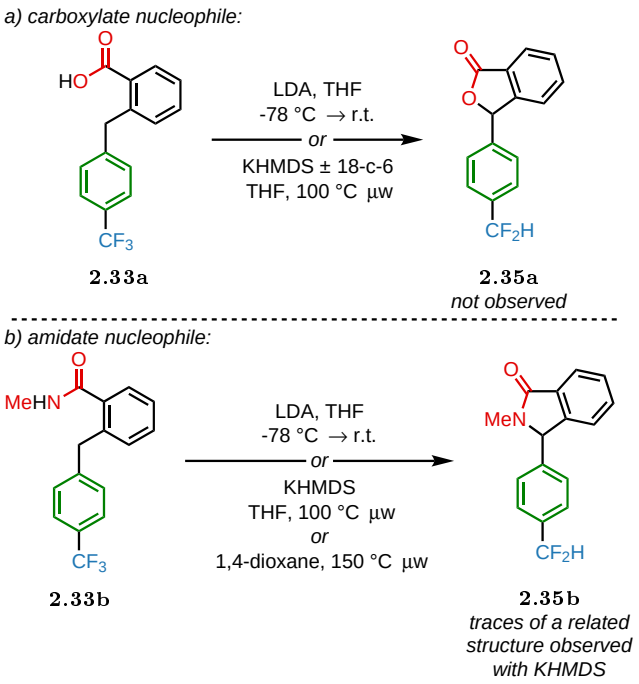
Whilst polymerisation was observed to outcompete nucleophilic attack in the attempted defluorination of **2.24c** (see Scheme 2.15), the intramolecular nucleophilic trapping was successful in the originally discovered reaction (Scheme 2.16). Thus, efforts then focused on finding a substrate **2.33** that had a suitable intramolecular nucleophile that would allow for isolable CF_2H-containing products **2.35**.



Scheme 2.16: The intended defluorination of **2.33** via the intramolecular attack of a tethered nucleophile on intermediate **2.34**.

Substrate **2.33a** was prepared, and featured a carboxylic acid that could serve to trap the dearomatised intermediate formed after 1,6-elimination (Scheme 2.17a). However, neither treatment with LDA nor KHMDS provided access to defluorinated lactone **2.35a**, with polymerisation observed in each attempt.

Since the originally successful system (see Section 2.2.1) made use of an amide nucleophile, benzamide **2.33b** was synthesised, but treatment with LDA caused polymerisation (Scheme 2.17b). Although no reaction product could be isolated cleanly when KHMDS was employed as the base, with polymerisation being the major fate of substrate **2.33b**, encouragingly, the ^{1}H and ^{19}F NMR spectra of the partially purified material indicated traces of a CF_2H-containing product. Repeating the reaction in 1,4-dioxane, a more coordinating solvent than THF, allowed the reaction temperature to be raised further. Theoretically, this could disfavour the intermolecular polymerisation reaction, due to the loss of entropy when many monomer molecules combine to form macromolecules. In addition, the dilution of the reaction was increased to discourage intermolecular polymerisation. Despite these changes, polymerisation proved unavoidable, which hampered purification attempts. Once again, the characteristic NMR signals for a CF_2H-functionalised compound were observed, but the lack of a signal for a benzylic proton excluded **2.35b** from being the structure of the product. Unfortunately, the limited quantity of material and incomplete purification prevented the elucidation of the defluorinated product structure. Nevertheless, the formation of a CF_2H-containing molecule was a promising result.



Scheme 2.17: While both **2.33a** and **2.33b** mostly formed polymerised products when subjected to base, traces of a CF_2H-containing product were observable after treatment of **2.33b** with KHMDS.

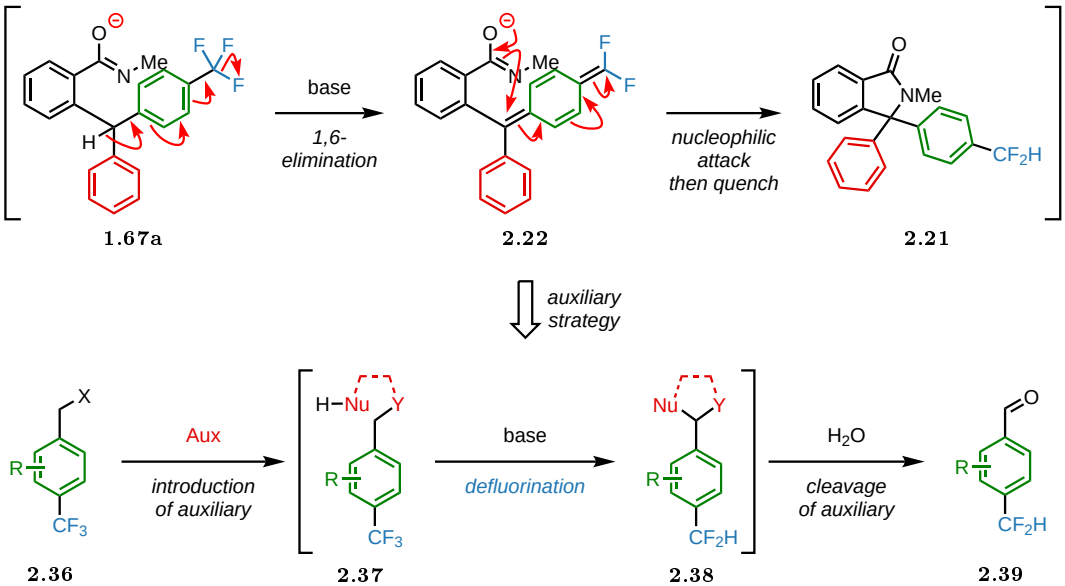
2.3 Results and discussion

2.3.1 Project aims

The growing importance of the CF_2H group to the pharmaceutical and crop protection industries (see Section 2.1.2) has prompted the search for methods to access CF_2H-functionalised molecules, with routes to aromatic CF_2H groups particularly valuable (see Section 2.1.3). An attractive approach is the monodefluorination of widely available CF_3 arene precursors (see Section 2.1.3.3). Thus, following the work outlined in Section 2.2.2, we wanted to continue the development of a methodology that could remove a fluorine atom from aromatic CF_3 groups, and provide access to valuable difluoromethylated arenes.

The plan for the project is summarised in Scheme 2.18. A suitable auxiliary would be appended to readily available trifluoromethylated benzyl precursors **2.36**. This would allow for hydrodefluorination of the CF_3 group of **2.37** to form **2.38**, by an elimination–cyclisation sequence analogous to that of **1.67a**. Hydrolytic cleavage of the auxiliary would culminate in a new entry into CF_2H-containing products **2.39**. In a modification of the reaction designs pursued previously (see Scheme 2.16), **2.37** features heteroatom Y that has been introduced between the CF_3-containing benzyl group and the tethered nucleophile. This is to enable removal of the auxiliary, so as to reveal the final difluoromethylated products **2.39**.

Compared to methods from the literature (see Section 2.1.3.3), this approach to reduce a CF_3 group to a CF_2H group is conceptually distinct: the transformation of **2.37** to **2.38** constitutes the intramolecular transfer of oxidation from one C–F bond to the benzylic centre. In addition, at a time where alternatives to CF_3 groups are sought after (see Section 2.1.1), this strategy is particularly appealing, since it would facilitate the straightforward replacement of trifluoromethylated intermediates with their difluoromethylated counterparts, without needing to significantly modify established synthetic routes.

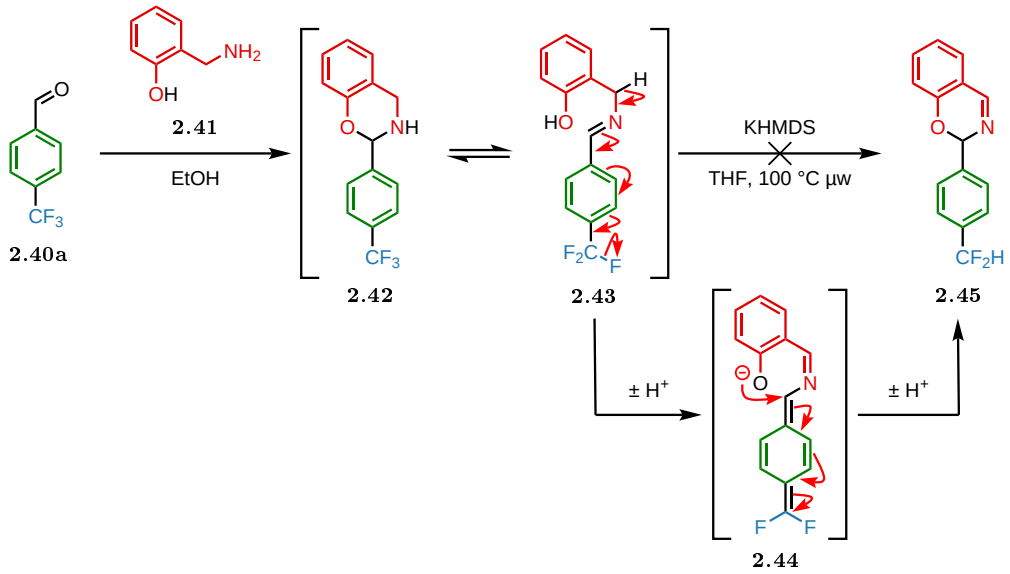


Scheme 2.18: The proposed auxiliary-based strategy for the defluorination of trifluoromethylated arenes **2.36** to difluoromethylated products **2.39**.

2.3.2 Finding a suitable auxiliary

2.3.2.1 Initial auxiliary designs

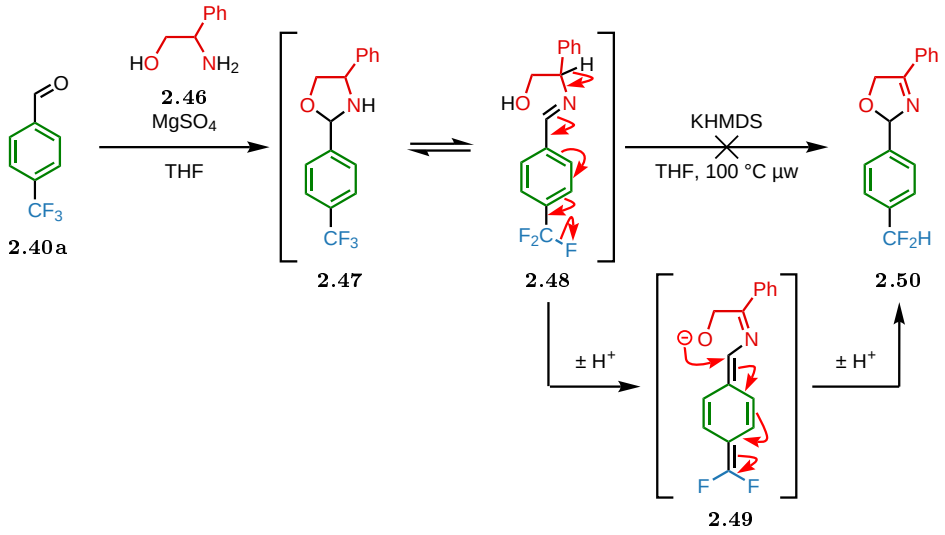
The first auxiliary concept drew inspiration from the mechanisms of reactions catalysed by pyridoxal phosphate-dependent enzymes.[155] It was thought that condensation of CF_3 benzaldehyde **2.40a** with salicylamine **2.41** would provide **2.42**, which is in equilibrium with its ring-opened form **2.43** (Scheme 2.19). Treatment with base could trigger elimination to **2.44**, with cyclisation forming the six-membered ring of **2.45**. However, under the reaction conditions previously used (see Scheme 2.11), ^{19}F NMR analysis revealed the presence of many CF_3-containing species, with virtually no CF_2H formation.



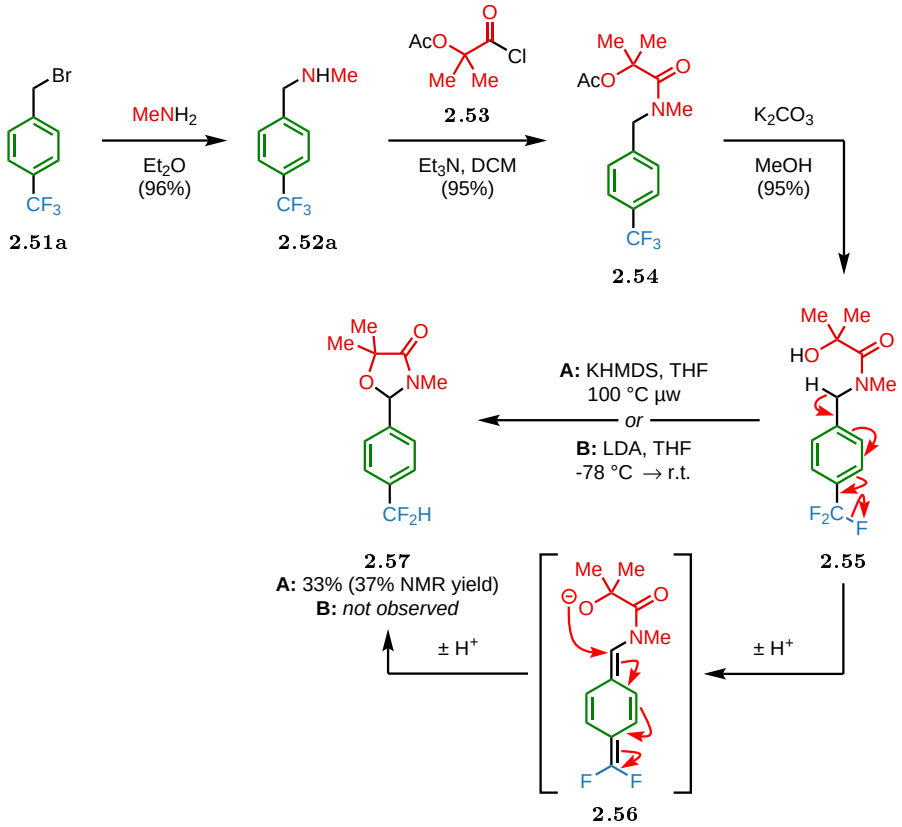
Scheme 2.19: An auxiliary derived from salicylamine **2.41** did not allow for the intended difluoromethylated compound **2.45** to be generated.

This first design required cyclisation of a six-membered ring to trap the dearomatised intermediate **2.44**, but we had previously only detected CF_2H-containing products upon cyclising to five-membered rings (see Sections 2.2.1 and 2.2.2.2). Hence, a design was conceived using 2-phenylglycinol **2.46**, targeting formation of five-membered product **2.50** (Scheme 2.20). Reaction with KHMDS resulted in a complex mixture of CF_3, CF_2H and CH_2F species, which, although intractable, provided optimism that the defluorination of aromatic CF_3 groups by an auxiliary approach was possible.

The two reactions described above targeted a 1,8-elimination, but the key precedent made use of a 1,6-elimination (see Section 2.2.1). Therefore, after some time sketching new designs, **2.55** was selected for synthesis (Scheme 2.21). We hoped subjection to base would initiate 1,6-elimination to dearomatised intermediate **2.56**, with cyclisation forming five-membered ring product **2.57**. We were delighted that, after treating **2.55** with KHMDS, ^{19}F NMR analysis revealed formation of a CF_2H-containing product in 37% yield, with **2.57** isolated in 33% yield. The remainder of the mass balance was attributed to polymerisation. Trialling LDA as the base led to a messy reaction with poor conversion, though ^{19}F NMR indicated trace amounts of a CF_2H-containing species.



Scheme 2.20: Attempted defluorination using **2.46** as the auxiliary generated a mixture of CF_3-, CF_2H-, and CH_2F-containing products.



Scheme 2.21: The defluorination of α-hydroxyisobutyramide **2.55** with KHMDS allowed for the isolation of CF_2H-functionalised product **2.57** in 33% yield.

2.3.2.2 Optimising the auxiliary

Having successfully found an auxiliary that allowed for the first CF_2H-containing product to be isolated since those described in Section 2.2.1, we then sought to optimise the design of α-hydroxyisobutyramide **2.55** to improve the yield of defluorinated product. Table 2.1 summarises the auxiliary designs that were evaluated for comparison to **2.55**, which was fully consumed after subjection to KHMDS, and provided a 37% NMR yield of the desired product, alongside significant decomposition and/or polymerisation.

Removal of the *gem*-dimethyl group gave system **2.60**, the attempted reaction of which was sluggish and only formed trace amounts of product. Thus, we proposed two possible benefits provided by the *gem*-dimethyl group. Either it could favour nucleophilic capture by providing the Thorpe–Ingold effect,[156] or it could prevent enolisation of the carbonyl, which could conceivably lead to undesired side-products. Similarly, replacement of the amide linkage with an ester was also detrimental: **2.61** was not found to form any product under the same reaction conditions. A somewhat distinct design was also proposed, which had neither a *gem*-dimethyl nor an amide linkage. The reaction of urea **2.62** formed an intractable mixture of products, some of which were CF_2H-containing.

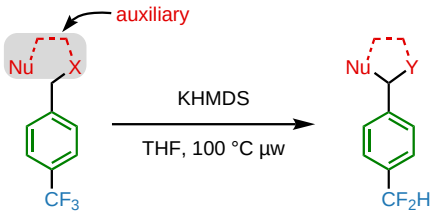
We hypothesised that the fluoride generated by 1,6-elimination could be trapped by silicon. Hence, this could trigger the "self-deprotection" of the TMS group of the auxiliary **2.63**, thus revealing the alcohol functionality required for cyclisation. However, this did not prove fruitful, with exposure to KHMDS only leading to polymerisation and decomposition. Sulfur is an archetypal soft nucleophile, so could be ideal for the proposed nucleophilic attack at carbon that traps the dearomatised difluoro-*para*-quinodimethane intermediate. But design **2.64**, with a neutral sulfur-centred nucleophile, was also unsuccessful.

Since amines are more nucleophilic than their alcohol counterparts, we wanted to assess primary amine-containing substrate **2.65**, which featured an auxiliary based on the non-proteinogenic amino acid, α-aminoisobutyric acid (Aib). Promisingly, full conversion was seen after reaction with KHMDS, with a markedly cleaner reaction profile than obtained with previous auxiliary designs. After chromatography, the desired CF_2H product was isolated in 24% yield, but purification was complicated by formation of another fluorinated compound. Interestingly, a CH_2F-containing product could also be isolated in 15% yield; further details of the reaction of **2.65** are provided in Section 2.3.7.

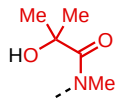
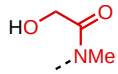
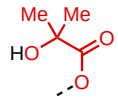
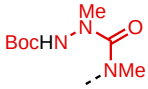
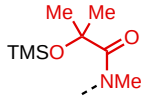
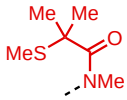
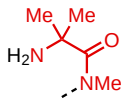
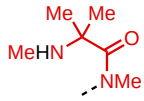
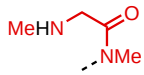
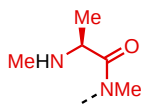
Significant progress was made when a secondary amine nucleophile was employed: after the reaction of **2.66a**, analysis by NMR revealed complete consumption of substrate, with the defluorinated product generated in high yield (88%). Encouragingly, no other side-products were formed in meaningful quantities with this auxiliary design. Purification led to isolation of the CF_2H-containing product in a much improved yield of 66%.

Motivated by this exciting result, further modifications were explored. Once again, removal of the *gem*-dimethyl group was not advantageous: following treatment with KHMDS, glycine derivative **2.67** was mostly returned unchanged, with some decomposition and polymerisation observed. An auxiliary based on L-alanine was also considered, which featured just a single methyl group α to the carbonyl. While attempted defluorination of **2.68** led to complete consumption of starting material, a complex mixture of CF_3 and CF_2H species resulted.

Table 2.1: Testing different auxiliary designs for the defluorination of **2.58** to difluoromethylated product **2.59**.



2.58 **2.59**

Cmpd	Auxiliary	Reaction outcome		
		Full conversion?	Yield / %	Comment
2.55		✓	33 (37)[a]	some decomposition/ polymerisation
2.60		✗	trace	some decomp./ polym.
2.61		✗	-	some decomp./ polym.
2.62[b]		✗	trace	some decomp./ polym.
2.63		✗	-	severe decomp./ polym.
2.64		✗	-	severe decomp./ polym.
2.65		✓	24[c]	trace decomp./ polym.
2.66a		✓	66 (88)[a]	-
2.67		✗	-	some decomp./ polym.
2.68		✓	trace	some decomp./ polym.

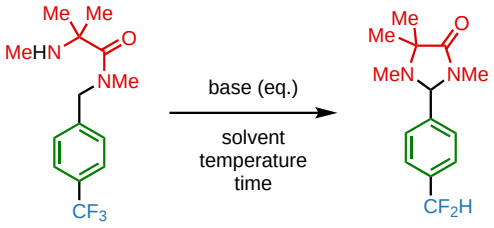
[a]Yield determined by ^{19}F NMR using fluorobenzene or hexafluorobenzene as an internal standard. [b]Defluorination reaction attempted at room temperature. [c]$ArCH_2F$ product also isolated in 15% yield.

2.3.3 Optimisation of reaction conditions

After evaluating different auxiliaries, the defluorination reaction of the standout auxiliary design **2.66a** was selected for optimisation (Table 2.2). Remarkably, it was found that substrate **2.66a** underwent spot-to-spot conversion to **2.69a** at room temperature (Table 2.2, Entry 2), with formation of product **2.69a** complete after just 10 min (Table 2.2, Entry 3). While NaHMDS performed reasonably well (Table 2.2, Entry 4), bases with Li counterions were less competent (Table 2.2, Entries 5, 6). Addition of 18-crown-6 was also found to be slightly detrimental (Table 2.2, Entry 7). Replacing THF as the reaction solvent had only a small negative impact, if an ethereal solvent was selected (Table 2.2, Entries 8–12). Employing a decreased stoichiometry of base was observed to diminish yield (Table 2.2, Entries 13, 14). Following these optimisation experiments, carrying out the reaction under the conditions stated in Table 2.2, Entry 3, led to essentially quantitative formation **2.69a** by NMR spectroscopy, with an excellent isolated yield of 96% on a 1.0 mmol scale (Table 2.2, Entry 15).

It is of note that, under the conditions of Table 2.2, Entry 2, substrate **2.55**, bearing the alternative α-hydroxy auxiliary, underwent full conversion, with a 49% NMR yield of defluorinated product **2.57**.

Table 2.2: Optimisation study for the defluorination of **2.66a** to **2.69a**; reactions were conducted on a 0.1 mmol scale.



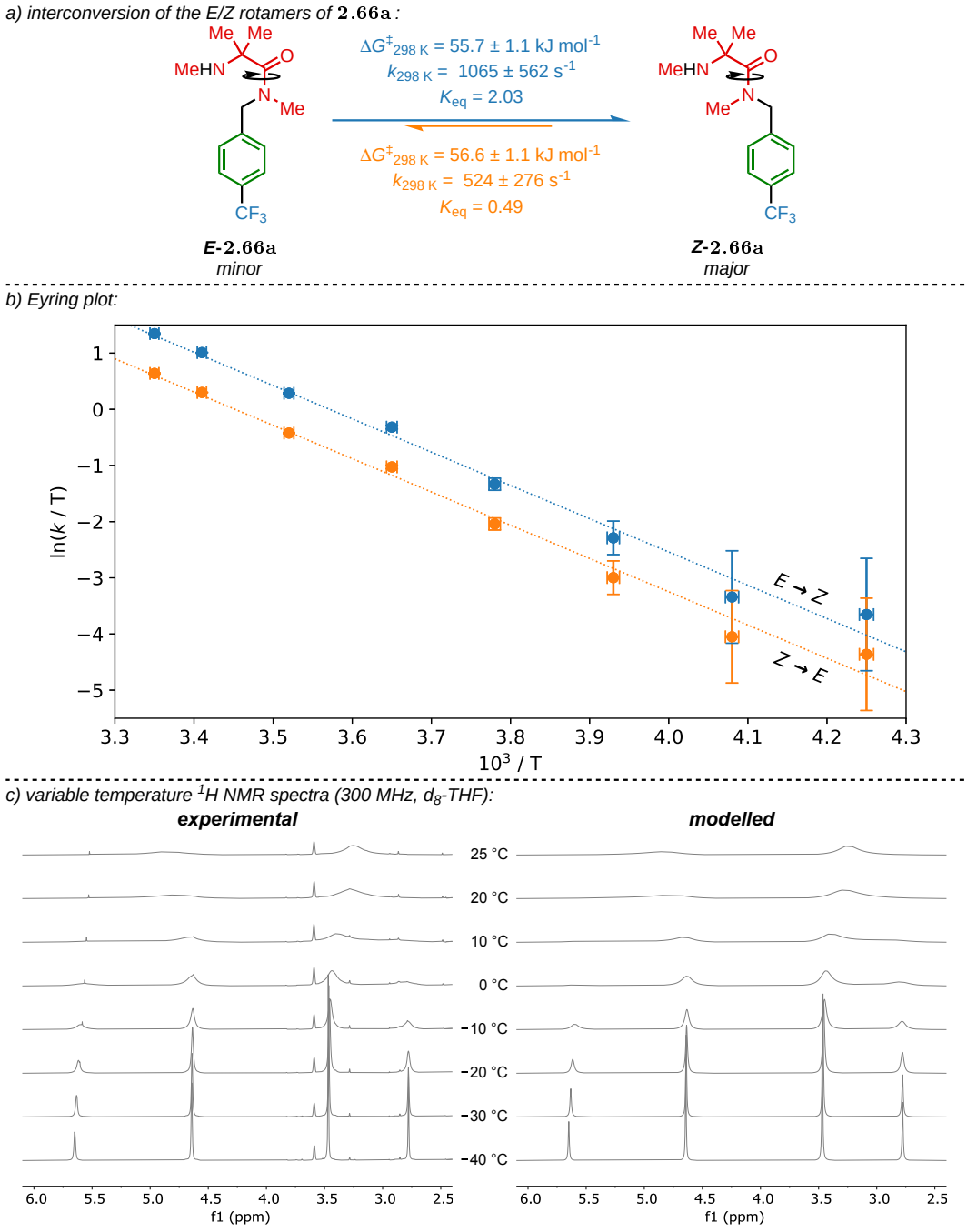
2.66a **2.69a**

Entry	Base (eq.)	Solvent	T / °C	t / min	Yield / %[a]
1[b]	KHMDS (2.0)	THF	100	60	(88) 66
2[b]	KHMDS (2.0)	THF	r.t.	15	(quant.) 93
3	**KHMDS (2.0)**	**THF**	**r.t.**	**10**	**(99)**
4	NaHMDS (2.0)	THF	r.t.	10	(89)
5	LiHMDS (2.0)	THF	r.t.	10	(59)
6	LDA (2.0)	THF	r.t.	10	(18)
7	KHMDS (2.0)[c]	THF	r.t.	10	(83)
8	KHMDS (2.0)	2-MeTHF	r.t.	10	(91)
9	KHMDS (2.0)	1,4-dioxane	r.t.	10	(84)
10	KHMDS (2.0)	MTBE	r.t.	10	(83)
11	KHMDS (2.0)	Et_2O	r.t.	10	(81)
12	KHMDS (2.0)	PhMe	r.t.	10	(67)
13	KHMDS (1.0)	THF	r.t.	10	(83)
14	KHMDS (0.5)	THF	r.t.	10	(53)
15[d]	**KHMDS (2.0)**	**THF**	**r.t.**	**10**	**96**

[a]Isolated yield; yield determined by ^{19}F NMR in parentheses, using hexafluorobenzene or 3-(trifluoromethyl)benzoic acid as an internal standard. [b]0.2 mmol scale. [c]With 18-crown-6 (2.2 eq.). [d]1.0 mmol scale.

2.3.4 Understanding the dynamics of amide conformation

The substrate of the defluorination reaction **2.66a** is a ca. 1:2 mixture of E/Z isomers about the amide C–N bond (Scheme 2.22a). The putative stereochemical assignment of the rotamers of the tertiary alkylamide **2.66a** is based on the expected upfield shift of the protons of the benzylic CH_2 group or the amide CH_3 group, when *cis* to the carbonyl.[157] This assignment might be as intuitively expected, with the preferred Z conformation placing the bulkier benzylic group away from the *gem*-dimethyl group. Although E-**2.66a** is the minor conformer, it is also likely the reactive conformer, since the secondary amine nucleophile is in position to attack the benzylic position of the dearomatised intermediate after elimination.



Scheme 2.22: Probing the interconversion of the E/Z rotamers of **2.66a**.

To gain an understanding of the interconversion of the amide rotamers, Eyring analysis was carried out for the processes *E*-**2.66a** → *Z*-**2.66a** and *Z*-**2.66a** → *E*-**2.66a** (Scheme 2.22b). Thus, ^{1}H NMR spectra were recorded at varying temperatures (Scheme 2.22c, left). Then the lineshapes for the signals arising from the benzylic CH_2 group and the amide CH_3 group were modelled to estimate the interconversion rate constant at each temperature (Scheme 2.22c, right). The Eyring analysis revealed the two isomers interconvert on the millisecond timescale at 25 °C. Moreover, this investigation might shed light on why the *gem*-dimethyl group is so crucial to the auxiliary design (see Section 2.3.2.2). If the amide isomerisation is relatively slow, the dearomatised intermediate generated from the major *Z* conformer could be susceptible to polymerisation.[153,154] The steric hindrance of the *gem*-dimethyl group of the Aib-based auxiliary increases the rate of *E*/*Z* isomerisation,[158] and therefore may allow for the desired nucleophilic trapping from an *E*-configured amide, before any unwanted polymerisation can occur. While the Clayden group has employed Aib in foldamer chemistry to induce helical turns,[159] the conformational properties are leveraged here to control reactivity, rather than structure.

2.3.5 Developing a strategy towards difluoromethyl arenes from trifluoromethyl arenes

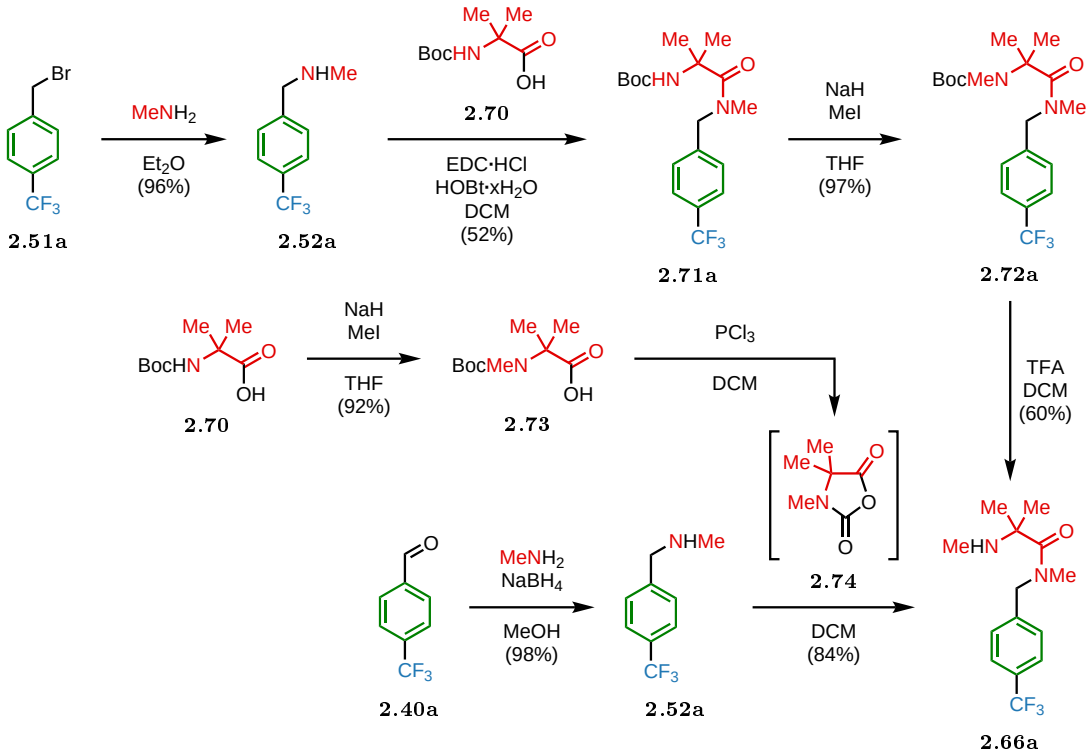
With an auxiliary identified that enabled the removal of a fluorine atom from an aromatic CF_3 group in high yield (see Section 2.3.3), and having gained some understanding of the conformational dynamics of the amide tether (see Section 2.3.4), our attention then turned towards incorporating the defluorination reaction into a practical method for converting trifluoromethylated arene precursors into their difluoromethylated counterparts.

2.3.5.1 Substrate synthesis

The initial route used to introduce the auxiliary onto a CF_3-containing arene substrate began with substitution of 4-(trifluoromethyl)benzyl bromide **2.51a** with $MeNH_2$, requiring a large excess of amine to prevent overalkylation (Scheme 2.23). This was followed by an amide coupling with Boc-protected Aib **2.70**. Subsequent *N*-methylation of the carbamate **2.71a** and deprotection of the Boc group delivered the target compound **2.66a**.

We recognised that this synthetic sequence was unideal, since the CF_3 starting material had to be taken through four steps before the key defluorination reaction. Therefore, we targeted a more convergent synthesis, and we were aware that hydrolytic cleavage of the auxiliary from **2.66a** would likely return 4-(difluoromethyl)benzaldehyde **2.39a** as product (see Section 2.3.5.2). Hence, if our synthesis began with a CF_3-substituted benzaldehyde, the overall transformation of our method would be the hydrodefluorination of CF_3-substituted benzaldehydes. With the carbonyl group being one of the most versatile synthetic handles in organic chemistry, an attractive prospect was a methodology applicable to aldehyde-containing substrates, with the aldehyde function still part of the defluorinated products.

In an improved synthetic approach, the methylation of Boc-Aib-OH **2.70** was performed prior to cyclisation to *N*-carboxyanhydride (NCA) **2.74**, which can act as an activated carboxylic acid (Scheme 2.23). By making use of the Boc group to form NCA **2.74**, the deprotection step could be avoided. Amine **2.52a** could be readily formed by reductive amination of 4-(trifluoromethyl)benzaldehyde **2.40a** with $MeNH_2$, and acylation with **2.74** achieved formation of the desired substrate **2.66a**. This redesigned route was much more amenable for application to a range of CF_3-containing substrates, with two steps from CF_3 precursor **2.40a** to the defluorination substrate **2.66a**, and only a single chromatographic purification required at the end of the sequence.



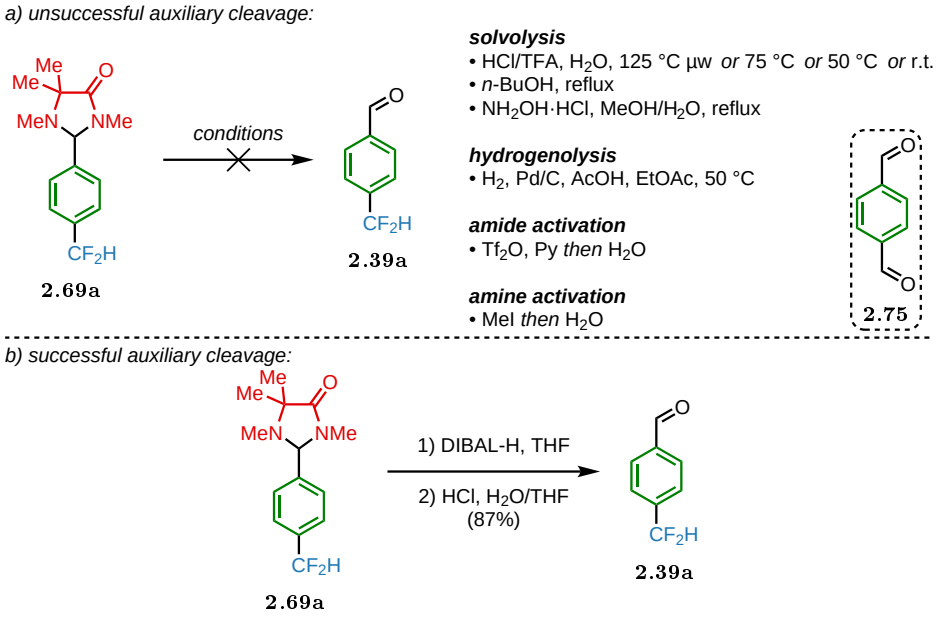
Scheme 2.23: Two different synthetic routes to the defluorination substrate **2.66a**.

2.3.5.2 Auxiliary cleavage

We then sought a protocol to cleave the auxiliary from defluorinated product **2.69a**, and initially, the hydrolysis of the amide group under acidic conditions was attempted (Scheme 2.24a). Heating **2.69a** with a mixture of aqueous HCl and TFA at 125 °C led to full conversion. But the desired compound **2.39a** was only a minor constituent of the reaction mixture (ca. 5%), with dialdehyde **2.75** the major product, arising from the unwanted hydrolysis of the CF_2H function. Lowering the reaction temperature led to sluggish consumption of starting material **2.69a**, with prolonged reaction times continuing to provide mixtures that contained over-hydrolysed side-product **2.75**. Other solvolysis attempts with alcohol- or amine-based nucleophiles led to no conversion, with the same outcome after the attempted hydrogenolysis over Pd/C. As an alternative, activation–hydrolysis sequences were conceived to enable auxiliary removal in the absence of strong

acids, thus avoiding hydrolysis of the CF_2H group. Neither activation of the amide with Tf_2O, nor activation of the amine by methylation, were found to be successful, with solely unreacted **2.69a** observed after these cleavage attempts.

A breakthrough for removing the auxiliary came from reduction of the amide function of **2.69a** with DIBAL-H, followed by hydrolysis of the resulting aminal under mild conditions with dilute aqueous HCl (Scheme 2.24b). The desired product, 4-(difluoromethyl)benzaldehyde **2.39a**, was pleasingly formed in 87% yield. This significant result represented a new entry into a difluoromethylated aromatic product from a trifluoromethylated precursor.



Scheme 2.24: Finding conditions to cleave the auxiliary from the product of defluorination **2.69a** to produce 4-(difluoromethyl)benzaldehyde **2.39a**.

2.3.6 Scope

Having established a four-step method to achieve overall transformation of 4-(trifluoromethyl)benzaldehyde **2.40a** to its difluoromethylated equivalent **2.39a**, we were pleased that other CF_3-bearing aromatic aldehydes **2.40** could serve as competent substrates (Scheme 2.25). The defluorination of rings with a *para*-CF_3 group proceeded to give difluoromethylated products **2.39** in very good yields, including those substituted with halogens (**2.39b**–**2.39d**) and other heteroatoms (**2.39e** and **2.39f**). When applied to 2,4-bis(trifluoromethyl)benzaldehyde **2.40g**, only defluorination of the *para*-CF_3 group was observed, providing product **2.39g**. Despite requiring heating to achieve a more remote 1,10-elimination, CF_2H-functionalised biphenyl **2.39h** could also be accessed in a good overall yield.

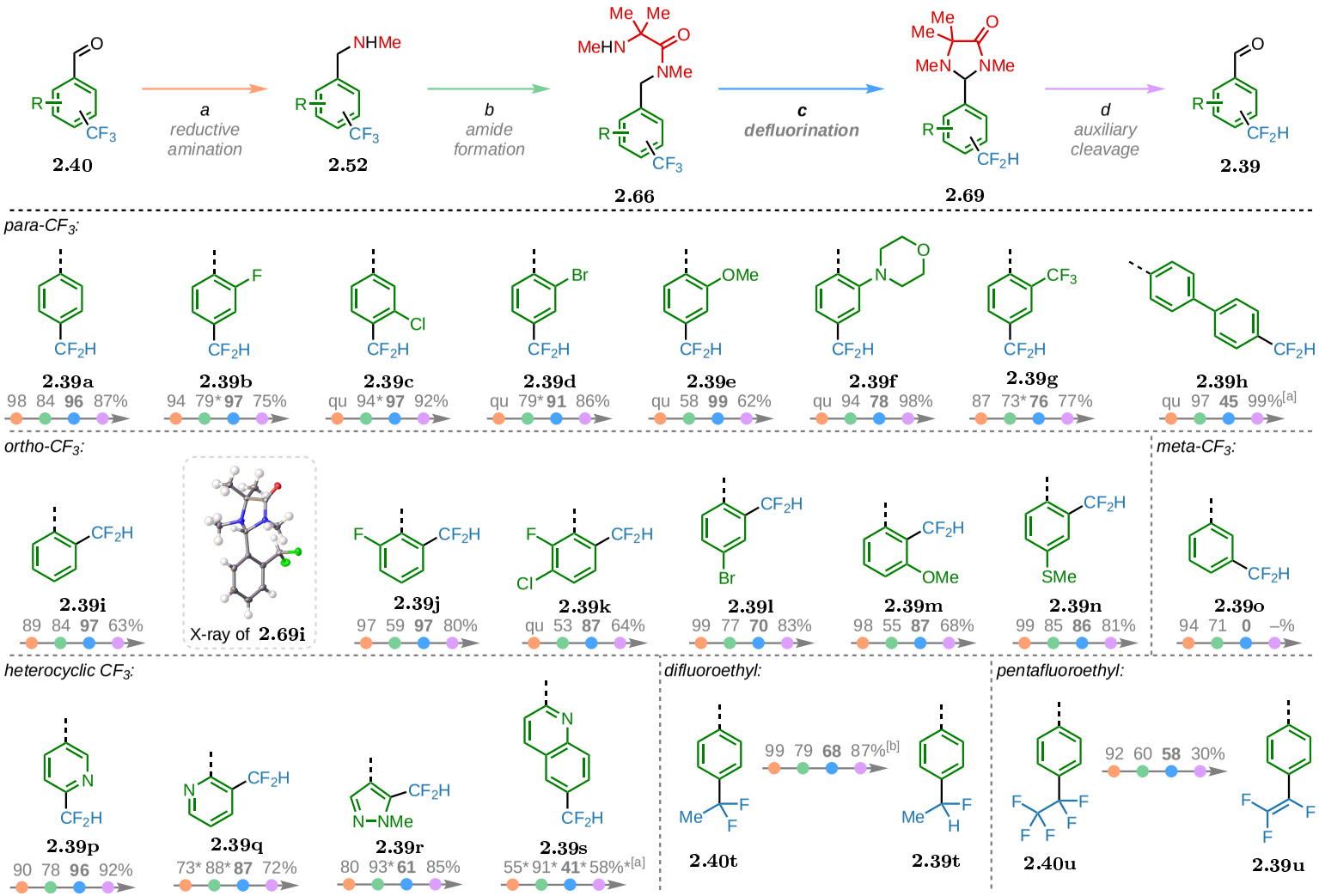
In addition, the methodology could be employed to modify *ortho*-CF_3 groups, with defluorination now proceeding through a 1,4-elimination. A range of difluoromethylated products with various substituents (**2.39i**–**2.39n**) could be obtained. The x-ray crystal structure of **2.69i** exemplified the hydrogen bonding capability of the CF_2H group (see Section 2.1.2). An interaction was revealed

between the CF_2H group and the amine nitrogen atom ($CF_2H\cdots N$ distance 2.40 Å, which is comparable to reported values)[88].

As expected, substrate **2.40o** with a *meta*-CF_3 group did not undergo defluorination by this methodology, on account of the 1,n relationship required between the aldehyde and the CF_3 group, where n is even. If product **2.39o** was desired, one could envision access through decarbonylation of compound **2.39d**, followed by formylation of the aryl bromide via an organolithium or Grignard reagent.

Heterocycles with CF_3 substituents were also viable substrates: 1,6-elimination provided 2-(difluoromethyl)pyridine **2.39p**, 1,4-elimination could be achieved to access **2.39q** and **2.39r**, and 1,8-elimination produced difluoroquinoline **2.39s**.

Besides substrates bearing CF_3 groups, a fluorine could be removed from other polyfluoroalkyl motifs, with the 1,1-difluoroethyl group of precursor **2.40t** transformed to monofluoroethylated product **2.39t**. When the methodology was applied to pentafluoroethyl substrate **2.40u**, the defluorination reaction was followed by a subsequent 1,2-elimination of HF. Thus, the final product of the four-step method was **2.39u**, in which a molecule of F_2 had been formally extruded from the perfluoroalkyl chain of **2.40u**.



Scheme 2.25: Scope of the methodology for the transformation of trifluoromethylated benzaldehydes **2.40** into their difluoromethylated counterparts **2.39** using an auxiliary strategy. qu = quantitative. a) $MeNH_2$, $NaBH_4$, MeOH; b) NCA (**2.74**), DCM *or* PhMe; c) KHMDS, THF; d) DIBAL-H, THF *then* HCl, H_2O/THF. [a]Defluorination performed at 100 °C under microwave irradiation. [b]Auxiliary cleavage performed with $LiAlH_4$ instead of DIBAL-H.

*Reaction performed by Maria Schwarz.

2.3.6.1 Application towards bioactive targets and analogues

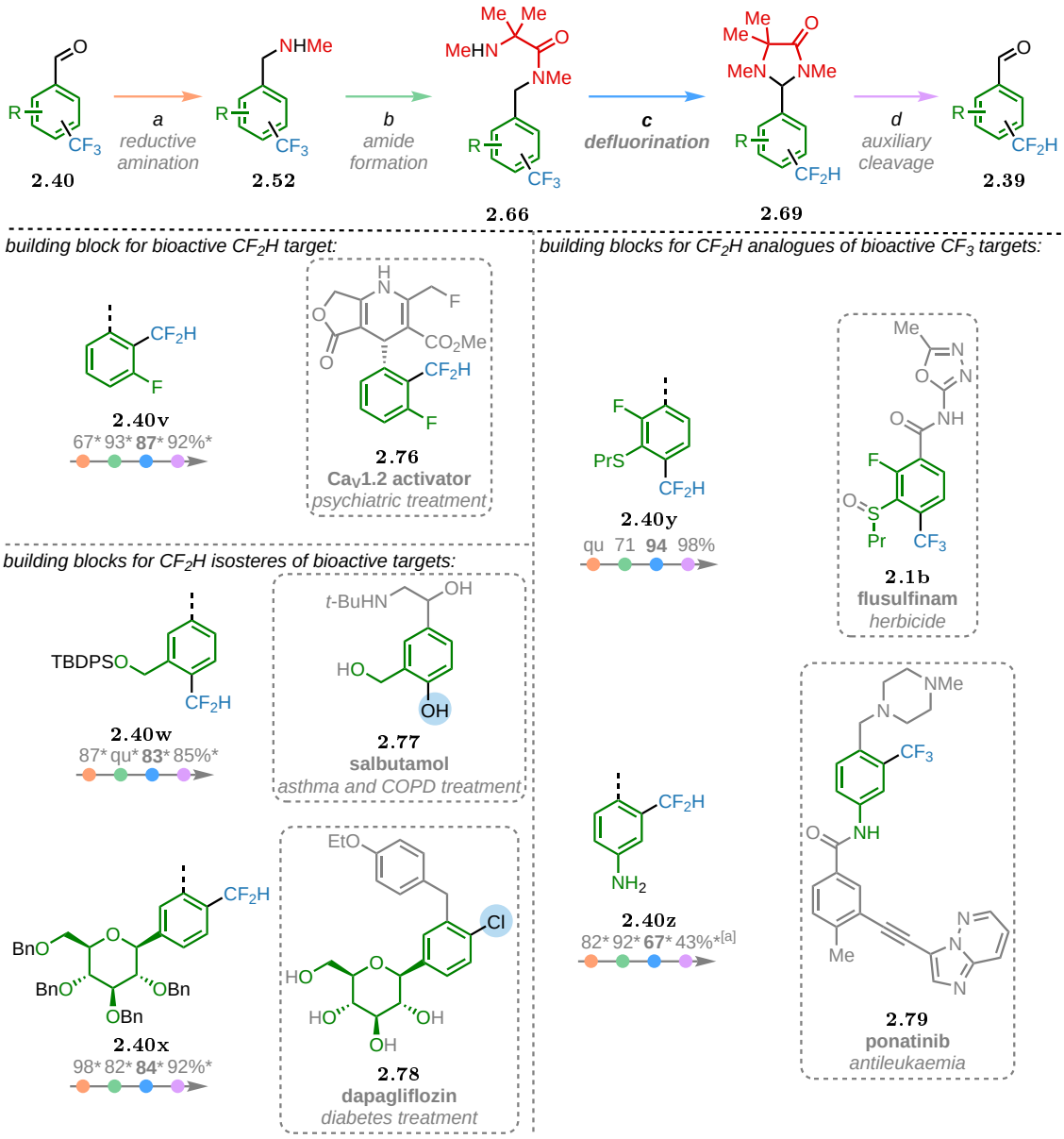
Given the relevance of the CF_2H group to pharmaceutical and agrochemical research (see Section 2.1.2), we then looked to demonstrate the practicality and utility of the method towards the synthesis of bioactive target molecules (Scheme 2.26). Our method could generate difluoromethylated product **2.39v**, a known intermediate in the preparation of a CF_2H-containing calcium channel activator **2.76** discovered by Novartis.[160] Building blocks **2.39w** and **2.39x** feature a CF_2H group that can serve as an isostere for the phenolic hydroxyl group of salbutamol **2.77**, or the chloro substituent of dapagliflozin **2.78**. This could open new avenues for generating analogues of these two FDA-approved therapeutics. Moreover, as industry seeks alternatives to the CF_3 group (see Section 2.1.1), **2.39y** and **2.39z** represent attractive precursors to the difluoromethylated analogues of the herbicide, flusulfinam **2.1b**, and the oncology drug, ponatinib **2.79**.

2.3.6.2 Unsuccessful examples

There were examples of substrates whose synthesis or defluorination was not found to be successful (Scheme 2.27). The attempted installation of the auxiliary onto amine **2.52y**, which has a 2-nitro substituent, by acylation with NCA **2.74** led to complete decomposition, with many CF_3-containing species formed. Unfortunately, reductive amination of pyrimidine **2.40z** with $MeNH_2$ was also not achieved. The ^{1}H NMR spectrum of the crude reaction mixture was complex, with no aromatic C−H signals, perhaps indicative of direct nucleophilic attack occurring at the ring.

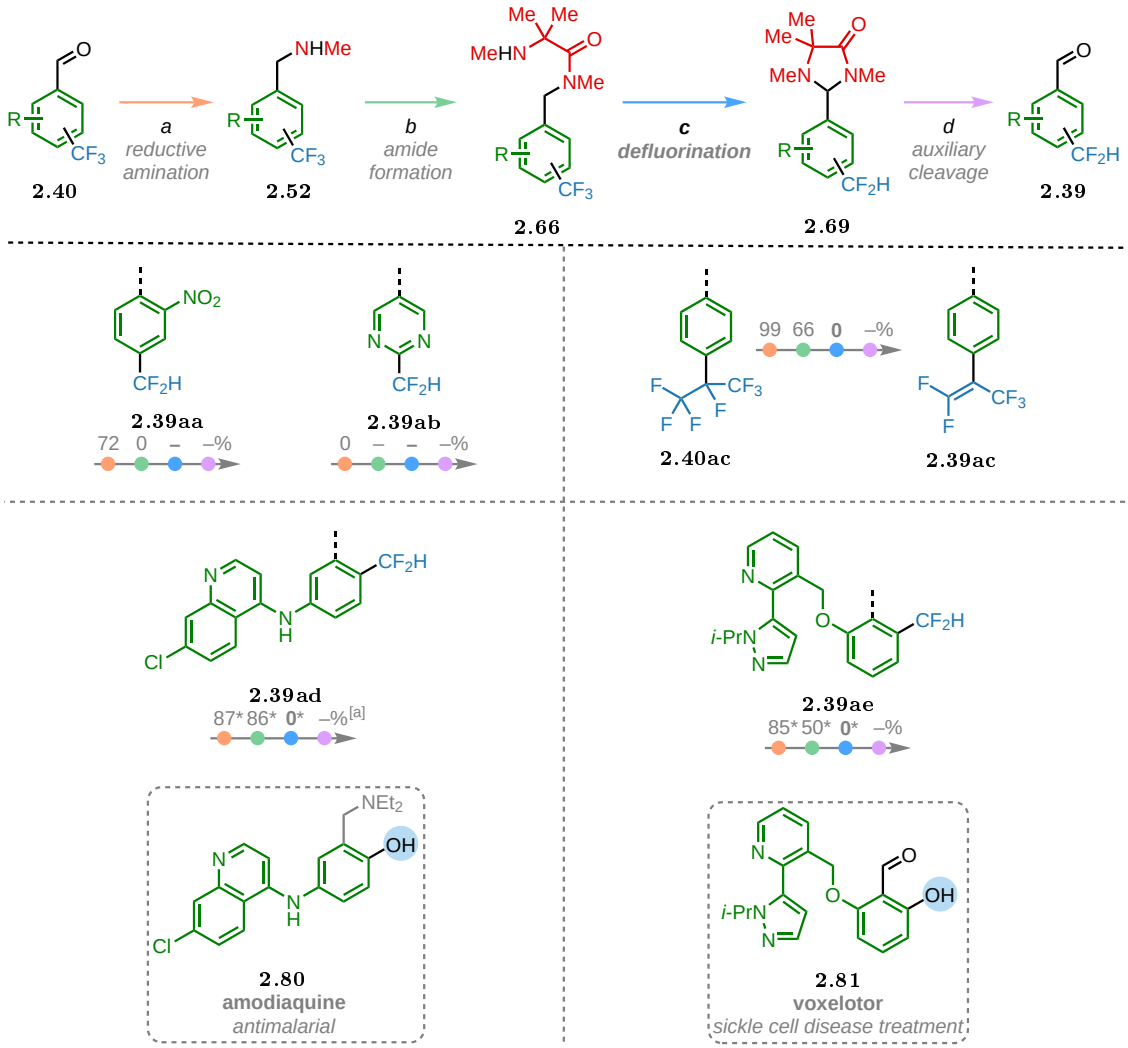
The defluorination of the perfluoroisopropyl group of **2.40ac** was investigated, which, like pentafluoroethyl substrate **2.40u**, ought to undergo 1,2-elimination after the defluorination. While there were hints of product formation, conversion was very slow, and so this reaction was not pursued any further.

In our attempts to showcase the usefulness of the method to prepare pharmaceutically useful CF_2H-containing products, we pursued compound **2.39ad**. By employing a CF_2H group for the bioisosteric replacement of a hydroxyl group, analogue synthesis of the antimalarial compound, amodiaquine **2.80**, could be considered. However, the defluorination reaction proved messy and sluggish, even upon microwave irradiation. Our attention then turned to another drug, voxelotor **2.81**, which also contains a candidate hydroxyl group for isosteric replacement with a CF_2H function. Unfortunately, treatment of **2.66ae** with KHMDS did not effect defluorination on route to target aldehyde **2.39ae**, but was only found to cleave the benzylic ether linkage.



Scheme 2.26: Application of the methodology to access difluoromethylated building blocks of relevance to medicinal and agrochemistry. qu = quantitative. a) $MeNH_2$, $NaBH_4$, MeOH; b) NCA (**2.74**), DCM *or* PhMe; c) KHMDS, THF; d) DIBAL-H, THF *then* HCl, H_2O/THF. [a]Starting from 4-(diallylamino)-2-(trifluoromethyl)benzaldehyde, with the yield for defluorination reported after deprotection of the allyl groups with [Pd].

*Reaction performed by Maria Schwarz.



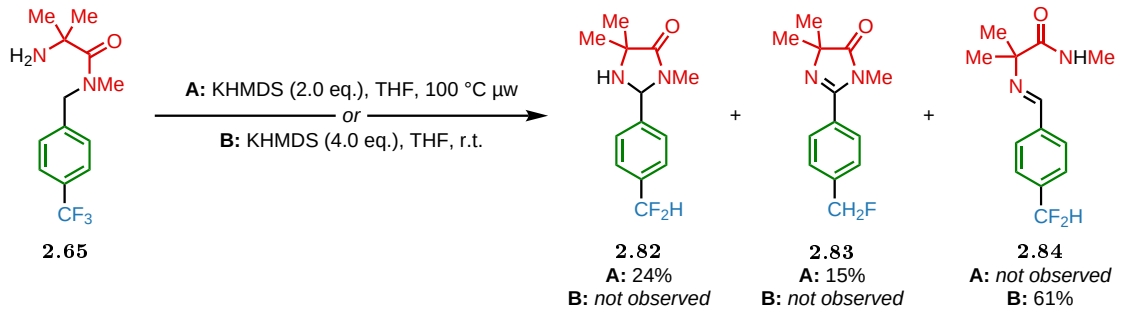
Scheme 2.27: Instances of unsuccessful substrate preparation or defluorination attempts. a) $MeNH_2$, $NaBH_4$, MeOH; b) NCA (**2.74**), DCM *or* PhMe; c) KHMDS, THF; d) DIBAL-H, THF *then* HCl, H_2O/THF. [a]Starting from 5-(allyl(7-chloroquinolin-4-yl)amino)-2-(trifluoromethyl)benzaldehyde.

2.3.7 Didefluorination

Following the development of a powerful method for the removal of one fluorine atom from aromatic CF_3 groups (see Section 2.3.6), our attention then turned towards the goal of being able to eject two fluorine atoms to generate CH_2F products. Given the attempted monodefluorination of **2.65**, bearing an auxiliary with primary amine nucleophile, gave rise to a mixture of CF_2H- and CH_2F-containing products (Scheme 2.28), we wondered whether the selective generation of CH_2F products could be achieved. Thus, the stoichiometry of KHMDS was increased, but this only led to isolation of a different CF_2H-containing compound **2.84**.

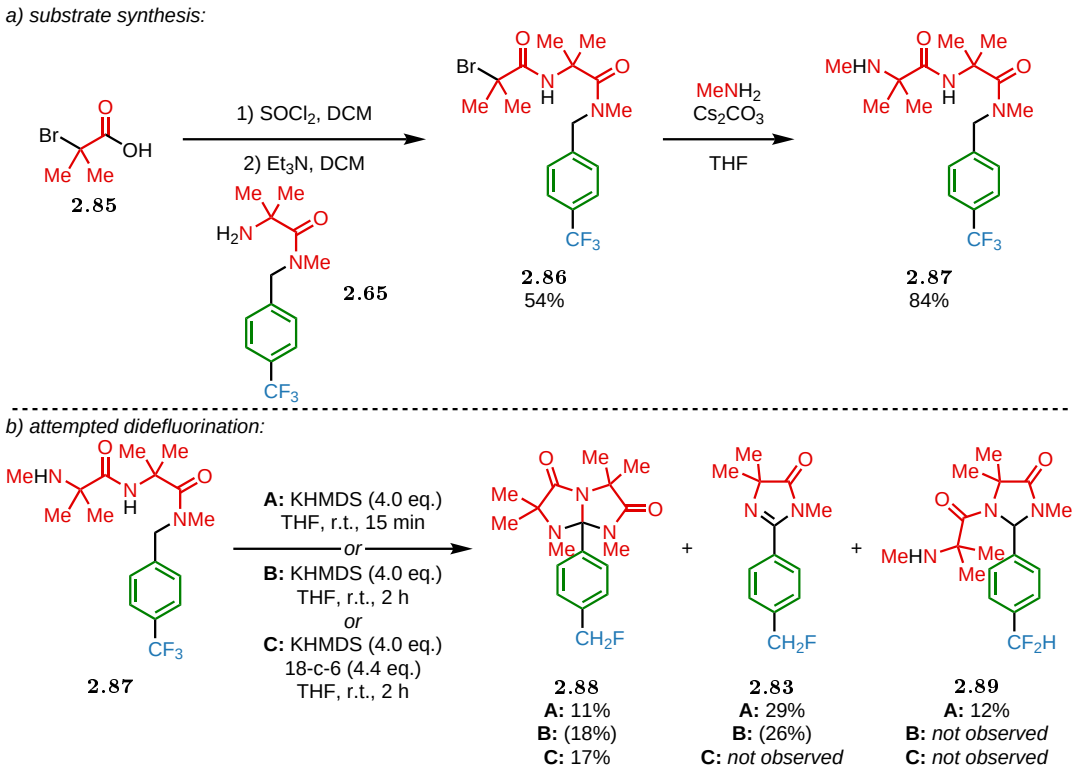
We next considered whether the auxiliary could be altered to favour formation of CH_2F-functionalised products. In light of the efficiency and generality of the Aib-based auxiliary for monodefluorination (see Section 2.3.6), we thought to

*Reaction performed by Maria Schwarz.



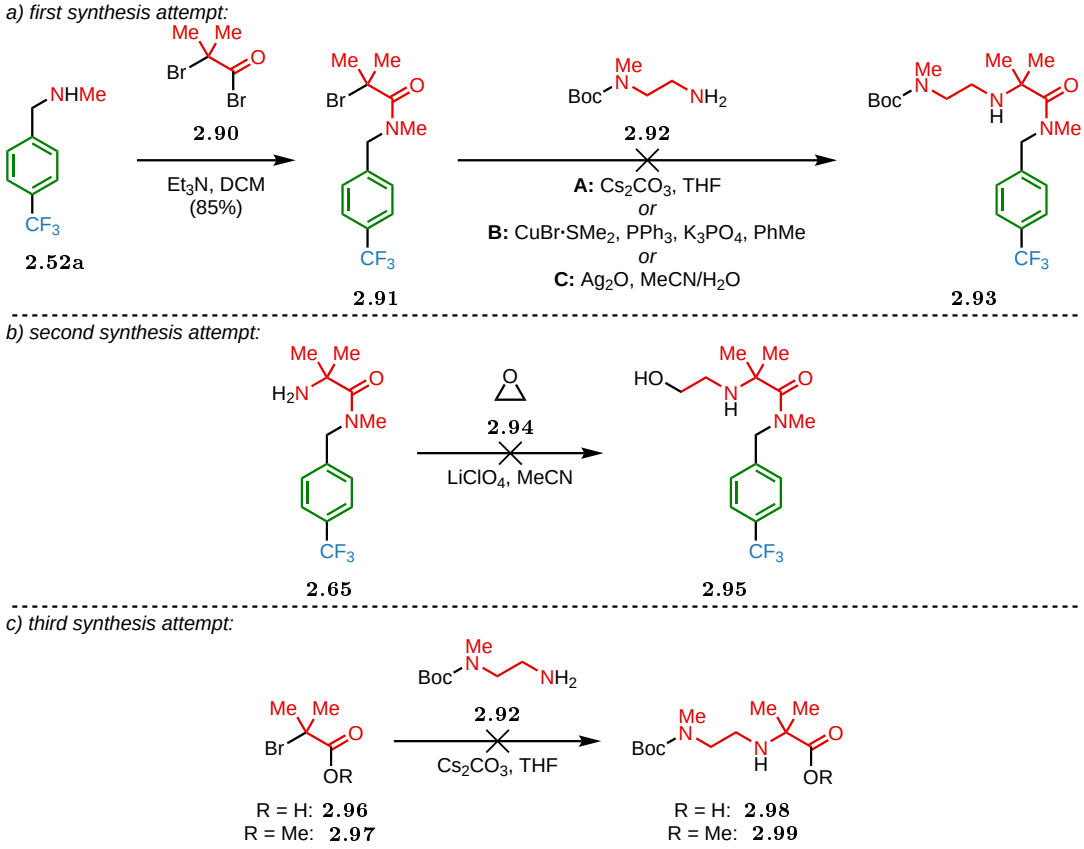
Scheme 2.28: Attempted double defluorination of the aromatic CF_3 group of **2.65**.

evaluate an Aib dimer auxiliary for didefluorination. Thus, substrate **2.87** was prepared in two steps from **2.65** (Scheme 2.29a). Upon addition of KHMDS, rapid and complete consumption of **2.87** was observed, and three products could be isolated: the intended benzylic fluoride **2.88**, compound **2.83** in which the auxiliary had been partially cleaved, and the singly defluorinated CF_2H product **2.89** (Scheme 2.29b). Despite a poor mass balance, this encouraging result prompted further investigation. It was thought that monodefluorinated compound **2.89** could be an intermediate towards the desired CH_2F products, and thus the reaction time was increased. While this exclusively led to CH_2F-containing products, the mass balance remained poor due to decomposition and polymerisation. When 18-crown-6 was added to the reaction, it was promising that only one CH_2F product was formed, but the isolated yield of **2.88** was still low.



Scheme 2.29: Investigating an auxiliary based on an Aib dimer for the didefluorination of **2.87**. Yield determined by ^{19}F NMR analysis in parentheses, using hexafluorobenzene as an internal standard.

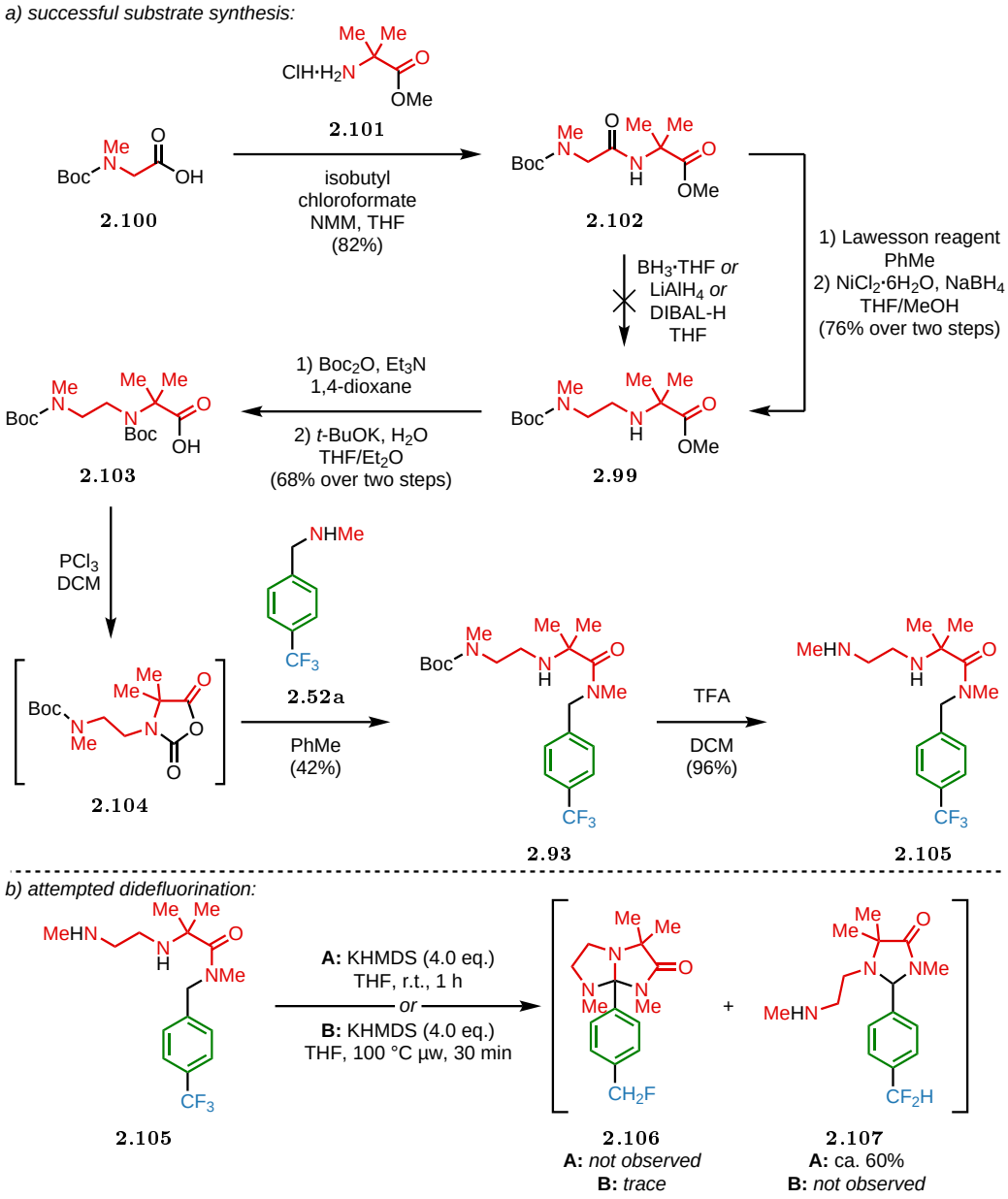
We recognised that the first nucleophilic capture of auxiliary design **2.87** required attack with an amide nitrogen. If this was outcompeted by polymerisation and/or decomposition, a poor mass balance would result. This motivated us to replace the amide with a more nucleophilic amine function. In addition, we sought to reduce the steric hindrance of the second nucleophilic attack by removing the *gem*-dimethyl group. The initial route for substrate preparation involved substitution of alkyl bromide **2.91** with primary amine **2.92**,[161–163] but this was unsuccessful and returned only starting material, or the product of elimination of HBr from **2.91** under conditions **A** (Scheme 2.30a). Switching the nucleophilic and electrophilic handles around was also unfruitful: the reaction of hindered amine **2.65** and epoxide **2.94** did not go to completion, and the product **2.95** could not be isolated from the reaction mixture (Scheme 2.30b).[164] In a different approach, we looked to pre-form the auxiliary, before introducing the CF_3-containing moiety. Unfortunately, attempted substitution of α-bromo carbonyl compounds **2.96** or **2.97** with amine **2.92** only led to recovery of starting material (Scheme 2.30c).[161]



Scheme 2.30: Three unsuccessful attempts at preparing a substrate for double defluorination that had an improved auxiliary design.

Since construction of the auxiliary by alkylation of amines was proving challenging, we turned to amide formation because it is a reliable reaction of amines. Indeed, an amide coupling enabled assembly of the skeleton of the auxiliary, with **2.102** straightforwardly accessed (Scheme 2.31a). However, the subsequent step would be a challenging selective reduction of the amide carbonyl of **2.102** in the presence of other reducible carbonyl functionalities. While attempted reduction with $BH_3 \cdot THF$ was sluggish,[165] hydride reducing agents

returned intractable mixtures of multiple species. We then considered a two-step approach, involving thioamide formation[166] and subsequent reduction. A range of reducing agents were trialled, though no product formation was observed with $BH_3 \cdot SMe_2$,[167] $Fe(CO)_5/KOH$,[168] or Meerwein's salt/$NaBH_4$.[169] Pleasingly, desulfurisation by Raney nickel was effective,[170] but the amine product **2.99** was found to be easier to isolate in good yield after employing nickel boride as the reducing agent. Finally, protecting group manipulations and attachment of the auxiliary to CF_3-substituted amine **2.52a** provided the desired substrate **2.105**.



Scheme 2.31: Trialling a redesigned auxiliary for the double defluorination of **2.105**.*

*Substrate synthesis performed in collaboration with Maria Schwarz; attempted defluorination performed by Maria Schwarz.

However, when the double defluorination of **2.105** was tested, the second nucleophilic capture could not be triggered at room temperature, with predominant formation of the monodefluorinated compound **2.107** (Scheme 2.31b). Nevertheless, we were encouraged by the improvement in mass balance. With the aim of driving conversion to the desired compound **2.106**, the reaction temperature was increased, but this unfortunately led to mostly decomposition.

2.3.8 Mechanistic study

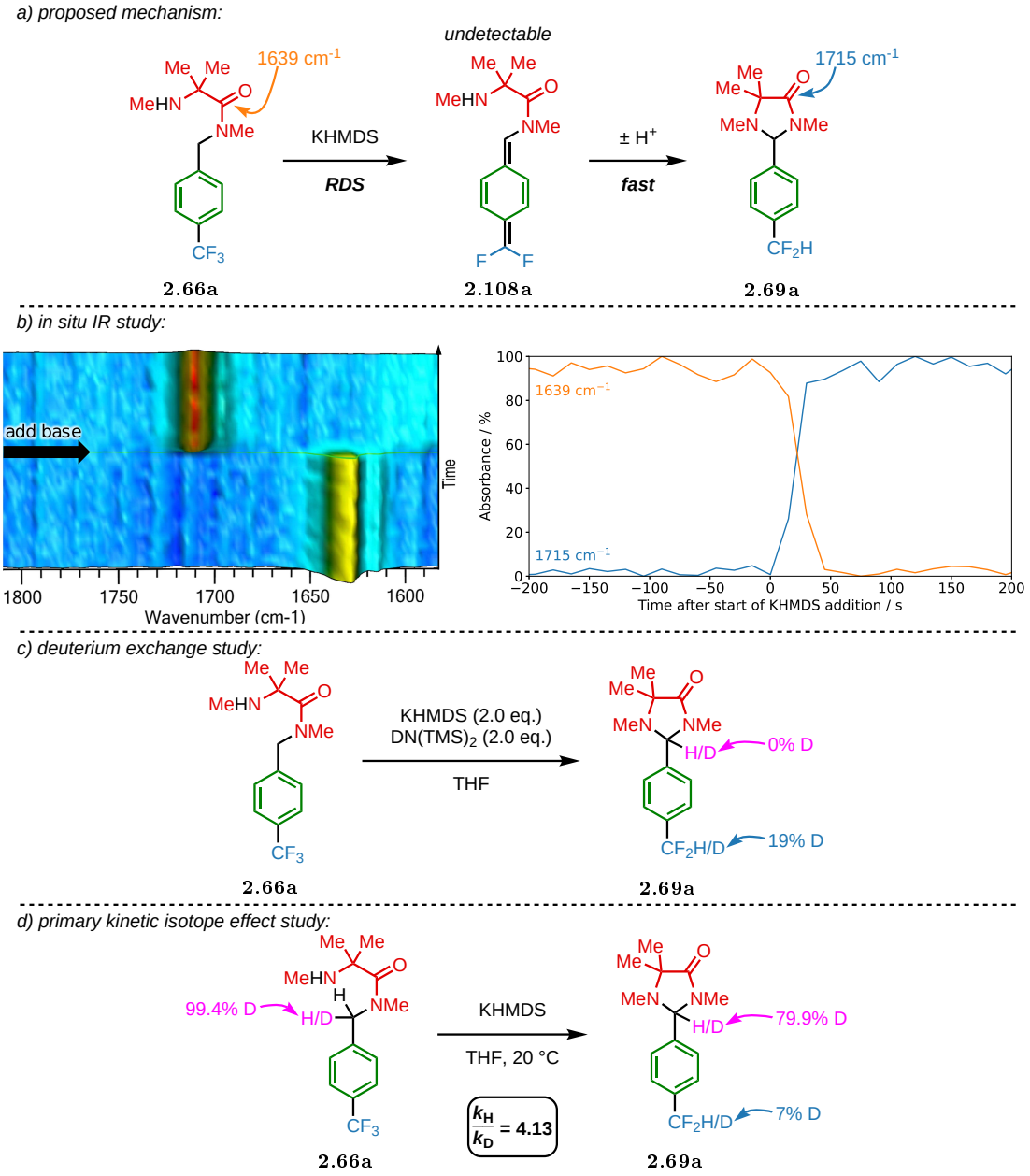
Besides providing a route into valuable difluoromethylated products, the elimination of a molecule of HF from a CF_3-containing aromatic compound is an unusual transformation, and so we wanted to study the mechanism of defluorination. A mechanistic proposal for the reaction of substrate **2.66a** to CF_2H product **2.69a** is outlined in Scheme 2.32a. Briefly, the elimination reaction of **2.66a** is triggered by KHMDS to form the dearomatised difluoro-*para*-quinodimethane intermediate **2.108a**. A subsequent cyclisation by nucleophilic attack of the pendant amine function leads to the difluoromethylated product **2.69a**. Given the relatively low pK_a of HMDS (26 in THF)[171], it is expected that the cyclisation of **2.108a** likely occurs with the neutral secondary amine acting as a nucleophile (c.f. the pK_a of diisopropylamine is 36 in THF)[171].

The reaction of **2.66a** was first examined by in situ IR spectroscopy, with a scan taken at 15 s intervals. From a THF solution of the substrate **2.66a**, a strong signal at 1639 cm^{-1} was seen due to the amide carbonyl (Scheme 2.32b). Upon addition of KHMDS, the intensity of this signal rapidly decayed, with concomitant formation of another band at 1715 cm^{-1} for the amide carbonyl of product **2.69a**. Remarkably, the transformation of starting material **2.66a** to product **2.69a** was found to be virtually instantaneous. No additional absorptions could be observed for either the proposed difluoro-*para*-quinodimethane intermediate **2.108a**, or any anions of the starting material or product. This is consistent with either rate-limiting elimination to **2.108a**, or the deprotonation of substrate **2.66a** being rapid and reversible, before a rate-determining nucleophilic capture.

Evidence that the elimination is the rate-determining step was gained by carrying out the reaction in the presence of deuterated HMDS (Scheme 2.32c). No deuterium was incorporated in the benzylic position of the product **2.69a**. If deprotonation was reversible, some deuterium incorporation would be expected at this position. Thus, the elimination proceeds through either an E2 or an irreversible $E1_{cB}$ mechanism, depending on whether the loss of fluoride is concerted with deprotonation (E2), or follows deprotonation ($E1_{cB}$). A small amount of deuterium was incorporated within the difluoromethyl group (19% D). This suggests that the final protonation step is performed by the HMDS generated in situ. Indeed, quenching the reaction with d_4-MeOD led to no deuterium incorporation at any position of the product **2.69a**.

Since deprotonation is involved in the rate-determining step, it should exhibit a significant primary kinetic isotope effect. With the aim of measuring this effect, substrate **2.66a** was prepared with one deuterium incorporated at the benzylic position (99.4% D), and subjected to the standard conditions for defluorination (Scheme 2.32d). This scenario represents an intramolecular competition experiment between breaking a benzylic C–H bond or benzylic C–D bond. Since

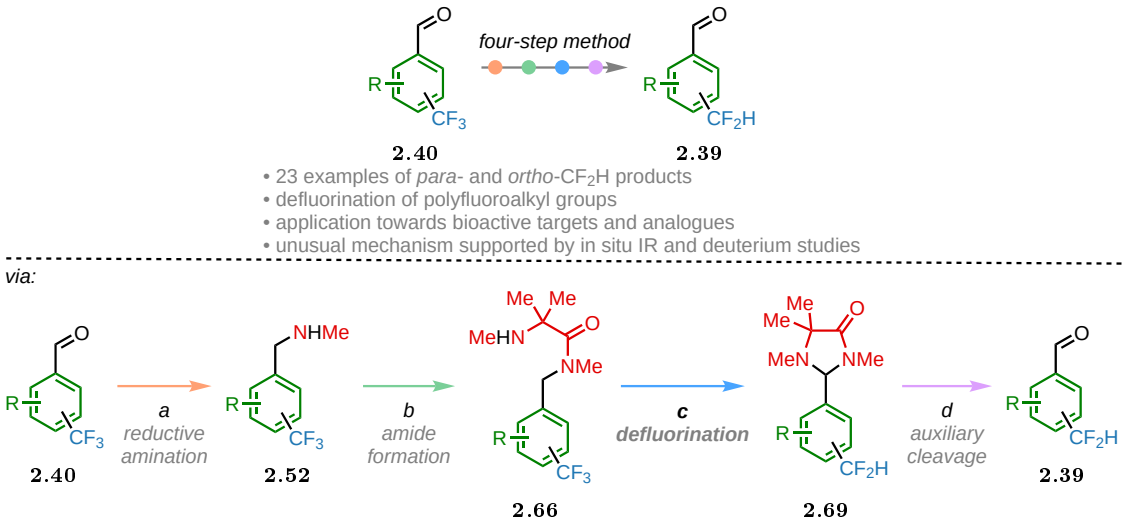
C−H bonds are weaker than C−D bonds on account of different zero-point energies, the C−H bond ought to be broken in preference to the C−D bond. The product was formed with 79.9% D at the benzylic position, meaning there was a considerable preference for C−H bond cleavage. From the extents of isotopic incorporation of the starting material **2.66a** and product **2.69a**, the kinetic isotope effect was calculated as $k_H/k_D = 4.13$ at 20 °C, which is consistent with the elimination being rate-limiting. Once again, a small amount of deuterium was also incorporated within the difluoromethyl group (7% D), by virtue of the proton of the CF_2H being derived from the HMDS formed during the reaction. A second role for HMDS could be revealed by ^{19}F NMR analysis of some crude reaction mixtures. The observation of a signal for Me_3SiF suggested that HMDS serves to trap fluoride as it leaves,[172] although this volatile by-product was only detectable if NMR analysis was performed directly on a quenched reaction mixture.



Scheme 2.32: The proposed mechanism for the defluorination of **2.66a** was supported by in situ IR spectroscopy and deuterium studies.

2.4 Conclusion

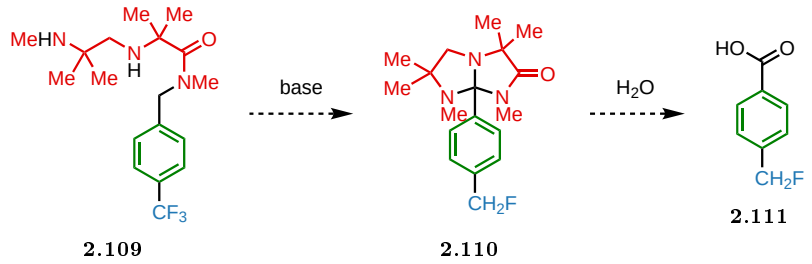
Researchers involved in modern drug and agrochemical design are looking to benefit from the unique properties offered by the CF_2H group, and thus methods to prepare difluoromethylated molecules are highly sought after. In addition, the environmental concerns around the CF_3 group have triggered the pursuit of alternatives, with the CF_2H group emerging as an attractive candidate. Therefore, the hydrodefluorination of widely available trifluoromethylated precursors is an appealing approach to difluoromethylated products. This chapter describes the successful development of a novel methodology to synthesise difluoromethylated aromatic compounds by the monodefluorination of trifluoromethylated arenes. We have employed an auxiliary strategy to selectively remove one fluorine atom from aromatic CF_3 groups of aldehyde starting materials **2.40** to form their CF_2H-containing equivalents **2.39** (Scheme 2.33). A range of variously functionalised difluoromethylated aldehyde products **2.39** could be accessed through the four-step method, including building blocks relevant to medicinal and agrochemistry. The defluorination of other polyfluoroalkylated substrates could also be performed, and the mechanism of the unusual transformation of **2.66** to **2.69** was investigated by in situ IR spectroscopy and deuterium studies. Overall, we expect this methodology to represent a useful entry into CF_2H-functionalised arenes, on account of the availability of trifluoromethylated precursors **2.40**, the broad diversity of accessible difluoromethylated products **2.39**, and the practicality of the method in allowing for direct replacement of trifluoromethylated intermediates within established synthetic routes.



Scheme 2.33: The defluorination of CF_3-containing aromatic aldehydes **2.40** to their CF_2H-functionalised counterparts **2.39** by an auxiliary strategy.

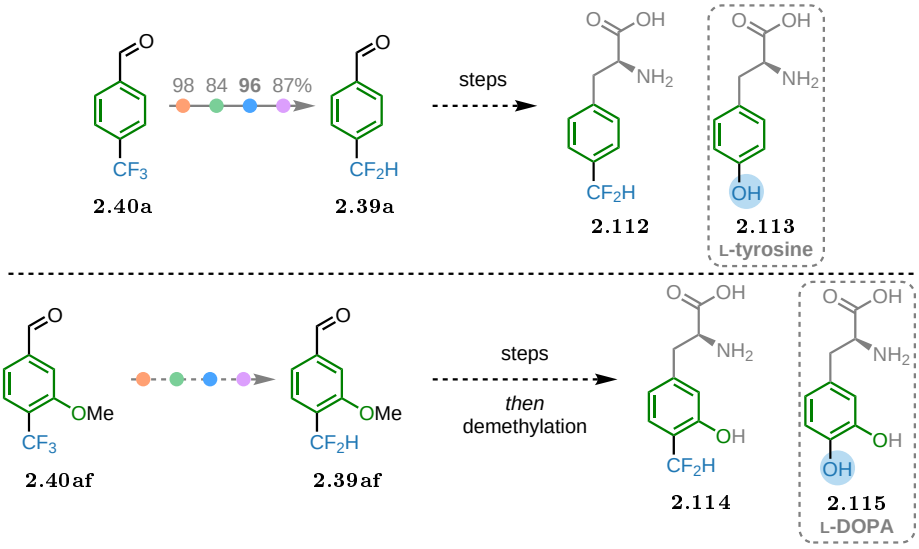
Although extension to a general method for the removal of two fluorine atoms from CF_3 groups could not yet be realised, the initial studies outlined in Section 2.3.7 suggest that this goal may be achievable. A possible improvement on the auxiliaries evaluated thus far is shown in Scheme 2.34. With the apparent importance of *gem*-dimethyl group of the auxiliary employed for monodefluorination (see Section 2.3.3), perhaps **2.109** would be more likely to perform the two successive cyclisations onto a

difluoro-*para*-quinodimethane intermediate to produce the intended benzylic fluoride **2.110**. If viable, it is anticipated that the orthoamide-type motif of **2.110** could be hydrolysed to the parent benzoic acid **2.111**.



Scheme 2.34: The double defluorination of **2.109**, and subsequent hydrolysis, could provide a route into benzylic fluoride product **2.111**.

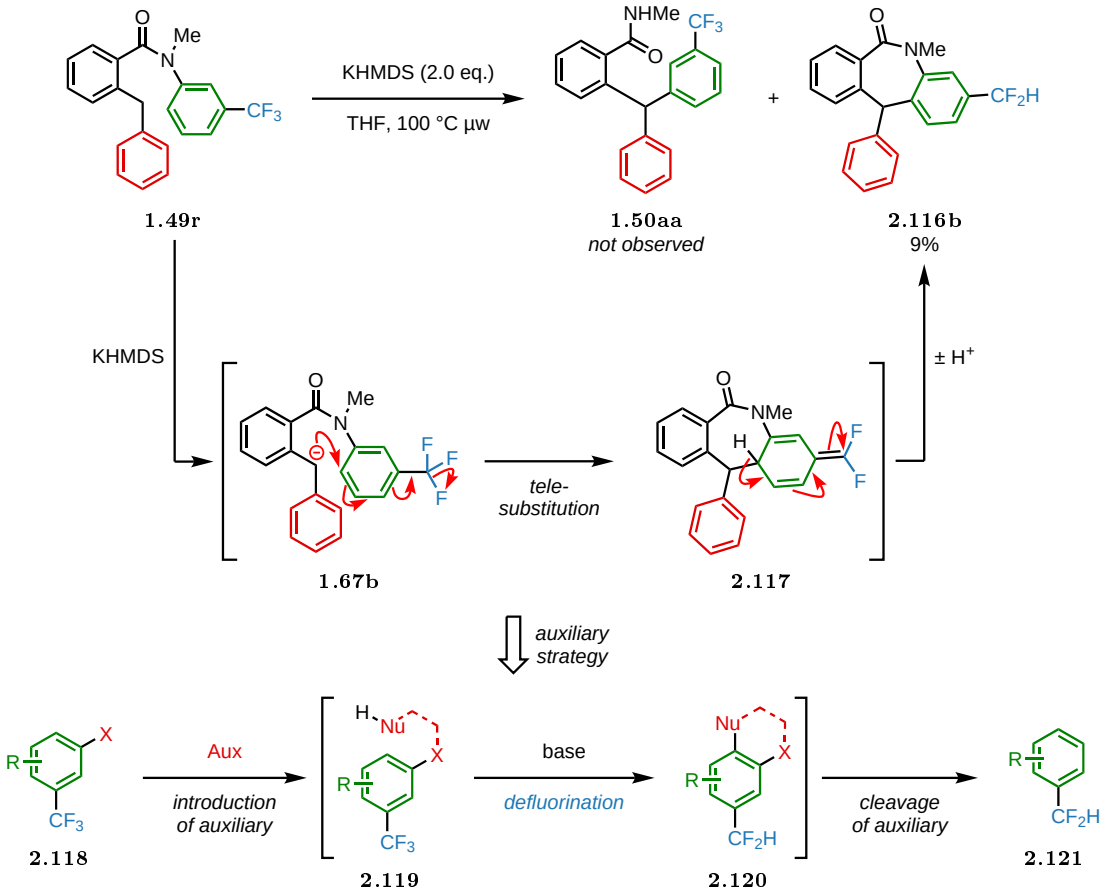
In an effort to further showcase the utility of the developed transformation, we would like to target the preparation of the CF_2H analogues of the amino acid, L-tyrosine **2.113**, and the dopamine precursor, L-DOPA **2.115** (Scheme 2.35). The summer project of undergraduate student, Finlay Evans, is concerned with executing the synthesis of **2.112** and **2.114**. While the preparation of **2.40a**, aldehyde precursor to L-tyrosine **2.113**, was part of the original scope, the methodology has not previously been applied to **2.40af**. If viable, it is anticipated that the aldehyde functions of **2.39a** and **2.39af** could be elaborated towards the difluoro-amino acids **2.112** and **2.114** with suitable two-carbon reagents.



Scheme 2.35: The proposed synthesis of CF_2H-analogues of L-tyrosine **2.113** and L-DOPA **2.115** using the developed methodology.

In addition to the CF_2H-bearing isoindolinone **2.21a** (see Section 2.2.1), MSci student, Alex Browning, observed formation of a second difluoromethylated compound while exploring the aryl migrations of 2-benzylbenzamides.[151] Following treatment of *meta*-CF_3 substrate **1.49r** with KHMDS, rather than the expected product **1.50aa**, compound **2.116b** could be isolated, albeit in low yield (Scheme 2.36). It was proposed that formation of **2.116b** proceeded through

tele-substitution of fluoride via attack of the benzylic anion **1.67b** to give **2.117**. Rearomatisation upon proton transfer then would form CF_2H-containing product **2.116b**. No further exploration of this reaction was carried out, but despite the low isolated yield of **2.116b**, adaptation and optimisation of such a transformation could enable a new defluorination reaction mode. Trifluoromethylated precursors **2.118** could be functionalised with an auxiliary to give defluorination substrates **2.119**. An analogous *tele*-substitution with the nucleophile built into the auxiliary would lead to products **2.120**. Finally, cleavage of the auxiliary would provide the parent CF_2H-functionalised arenes **2.121**. If such a methodology could be developed, it would broaden the range of accessible difluoromethylated aromatic products.



Scheme 2.36: Subjecting **1.49r** to KHMDS did not provide the anticipated aryl migration product **1.50aa**, but instead formed CF_2H-containing compound **2.116b**; such a *tele*-substitution process could inspire a novel auxiliary-based approach to CF_2H-bearing arenes **2.121**.

3 Medium-sized rings by the migratory ring expansion of alkenes

3.1 Introduction

3.1.1 Importance and structure of medium rings

Since the beginning of civilisation, humans have used the products of Nature for treating disease.[173–175] A selection of bioactive natural products containing a medium-sized ring (eight–twelve atoms) are shown in Figure 3.1. They exhibit diverse biological activity, provoking interest amongst practitioners of medicinal and agrochemistry.[176,177]

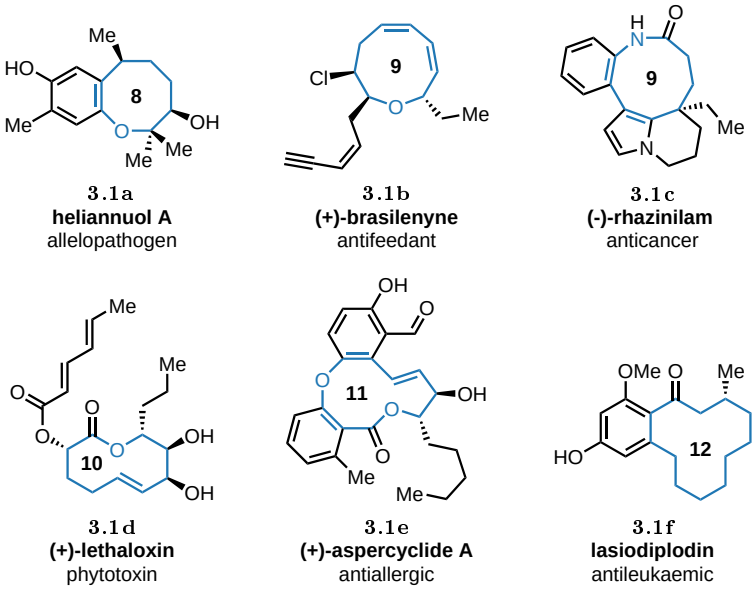


Figure 3.1: Some examples of natural products **3.1** containing a medium ring scaffold with varied biological activities.

Medium ring compounds are characterised by the conformational constraint imposed by the cyclic structure.[178,179] Restriction of a ligand's conformation can lower the entropy cost upon binding to a biological target, translating into improved binding affinity compared to less rigid analogues.[180–182] Yet, medium-sized rings tend to have several conformations with low barriers for interconversion (*vide infra*), providing a specific degree of flexibility to these molecules, which can be beneficial for accessing and fitting into the binding pocket.[183–185] In addition, medium ring scaffolds offer the opportunity to incorporate three-dimensional structure into drug designs. Not only can this impart improvements to physicochemical properties like lipophilicity, solubility and metabolic stability, it also enables the controlled presentation of functional groups into different vectors of a three-dimensional binding pocket.[177,180,186,187]

Despite such promise, medium rings remain underrepresented in screening libraries, novel compounds designs, and marketed bioactive agents.[188–190] The synthetic challenge of constructing medium rings is a fundamental reason for this.[177,191–193] Although the unique conformational features of a medium-sized ring may confer attractive biological properties, formation of such a ring from an acyclic precursor is enthalpically and entropically disfavoured.[194–196]

The overall energy barrier of a chemical reaction, $\Delta G^{\ddagger}$, is a composite of the enthalpy of activation $\Delta H^{\ddagger}$ and the entropy of activation $\Delta S^{\ddagger}$.[197] By considering the structural changes on going from the reactants to the transition state, we can understand why medium ring formation is challenging in terms of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$.[198] For the cyclisation of an acyclic precursor, $\Delta S^{\ddagger}$ expresses how easily an ordered transition state can be formed that resembles the medium ring product. It is dependent on how many rotational degrees of freedom the molecule has — the longer the chain, the lower the probability of the two reacting ends coming together. Thus, cyclisations to form larger rings become increasingly disfavoured on entropic grounds. The energy required to overcome the strain and repulsive forces in bringing together two reactive centres of a bifunctional molecule is encapsulated in $\Delta H^{\ddagger}$. The relationship between $\Delta H^{\ddagger}$ and ring size is complex. The net ring strain in differently-sized rings (Figure 3.2) is contributed to by the three main sources of strain:[178,179,199]

1. steric strain: the van der Waals repulsion of atoms close together in space.
2. torsional strain: arising from eclipsing bonds, which leads to repulsion between bonding pairs of electrons and the loss of stabilising hyperconjugation interactions.
3. angle strain: caused by the deviation of bond angles from their ideal values.

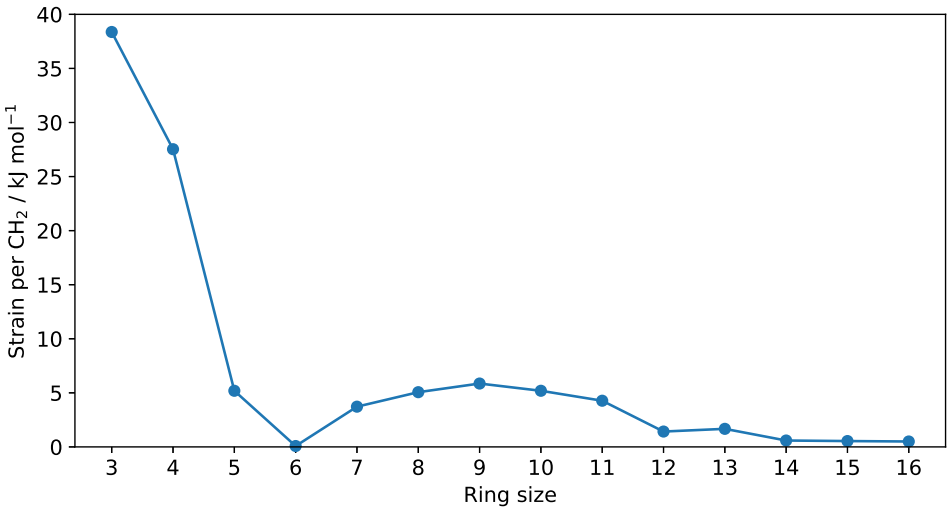


Figure 3.2: Ring strain of cycloalkanes of different sizes.[199]

In small (three to four-membered) rings, bond angle distortion contributes majorly to the large overall ring strain, with torsional strain playing a secondary role. Even in the preferred puckered conformation of cyclobutane, the C–H bonds remain partially eclipsed. Therefore, cyclisation reactions to form small, strained rings have a high $\Delta H^{\ddagger}$, but with only a short chain of bonds between the reacting centres, the $\Delta S^{\ddagger}$ parameter remains small.

Five–seven membered rings are significantly less strained. In the preferred conformations of these cycloalkanes, destabilising eclipsing interactions are minimised, and there is very little angle strain. In addition, the increase in the number of degrees of rotational freedom is not too large. Therefore, these common rings are the most synthetically accessible of all, with both activation parameters $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ being generally favourable.

Although the contributions of torsional and angle strain remain small, a specific type of steric strain, known as transannular strain, affects medium ring compounds. In minimising torsional and angle strains, the preferred conformations of medium rings often position substituents to point into one another across the ring. This can be readily visualised in the ten-membered ring of cyclodecane (Figure 3.3). In the compromise to avoid eclipsing interactions, minimise distortion of bond angles, and reduce transannular interactions, rather than having a single lowest energy conformation, it is common for medium-sized rings to be able to adopt multiple conformations with low energy barriers for interconversion.[183,184] The unfavourable $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ contributions to $\Delta G^{\ddagger}$ mean that cyclisations to form medium rings are often highly challenging.

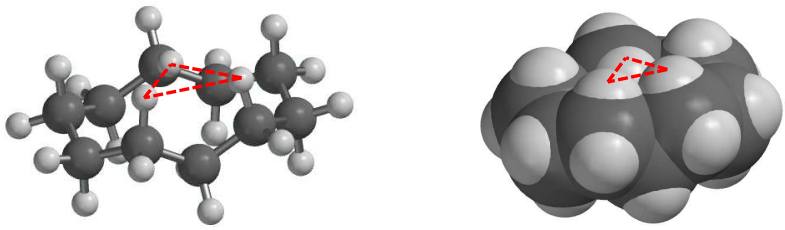


Figure 3.3: A low energy conformation of cyclodecane in ball-and-stick and space-filling representations; transannular C−H interactions are highlighted in red.

For even larger ring sizes, the overall strain is reduced, since the ring is able to adopt conformations that begin to approximate an acyclic compound. Thus, although more difficult than cyclisation to form three to seven-membered rings, macrocyclisations are often feasible, even against the backdrop of escalating numbers of rotational degrees of freedom in the acyclic precursors.

The combined effect of the disfavourable enthalpic and entropic factors hindering medium ring-forming cyclisations has biased drug and agrochemical discovery efforts away from designs that contain medium rings. If this synthetic challenge could be overcome by the development of general and efficient methods for preparing medium ring compounds, it is expected that such scaffolds would be more widely incorporated into compound designs, due to the favourable biological properties conferred by the rigid and three-dimensional cyclic framework.

3.1.2 Synthesis of medium rings: ring formation

Although the preparation of medium rings by ring closure of an acyclic precursor is challenging, this strategy is successful in cases where the thermodynamic costs of constructing the medium-sized ring can be offset by the distinct features of the ring-forming reaction employed. The methods presented here are amongst the most popular for accessing medium rings by head-to-tail cyclisation.

3.1.2.1 Lactonisation and lactamisation

Lactones and lactams feature in many bioactive natural products of varying ring size, which has motivated significant efforts to develop robust methods for forging these linkages. A number of these methodologies have been successful for forming medium rings.[176] In important work by Illuminati and co-workers, the kinetics for the cyclisation of ω-bromoalkanoic acids **3.2** to their corresponding lactones **3.3** were investigated.[200] The rate constants for these end-to-end cyclisations are shown in Figure 3.4. This data suggests that access to three- to seven-, and thirteen-membered lactones and larger is feasible from their corresponding ω-bromoalkanoic acids. However, the analogous cyclisations to medium-sized lactones are sluggish, and may suffer from competing intermolecular reactivity giving rise to oligomeric products. Ruggli[201] and Ziegler[202] introduced the idea of making use of high dilution conditions to reduce the rate of intermolecular reactions by decreasing the frequency of intermolecular collisions, thereby favouring the desired intramolecular reaction over the undesired intermolecular process. However, even under high dilutions conditions, accessing medium-sized lactones by such direct ring closure remains a challenge.

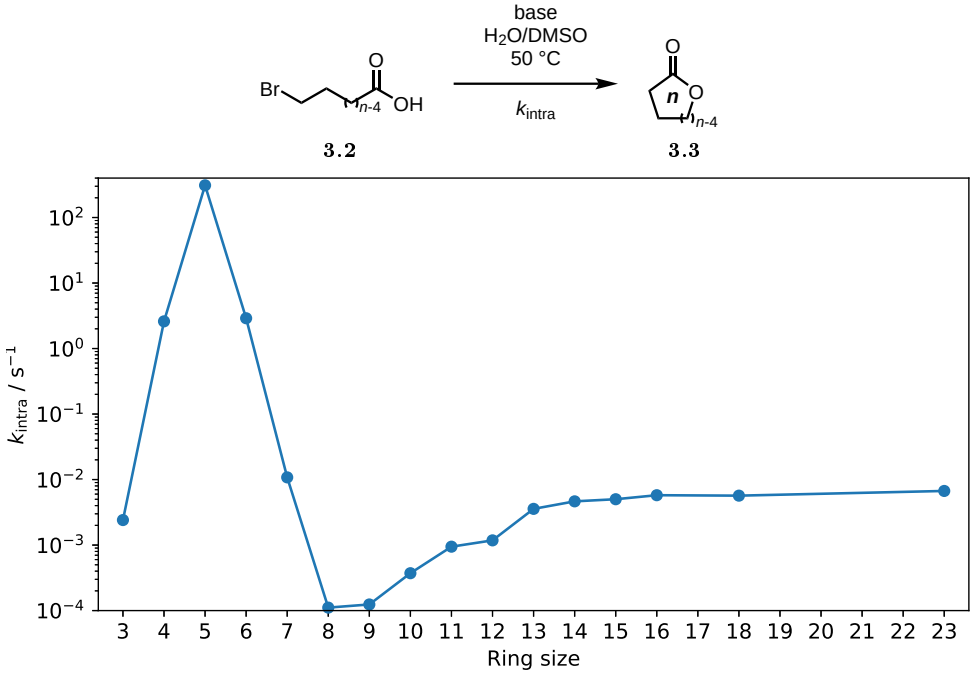
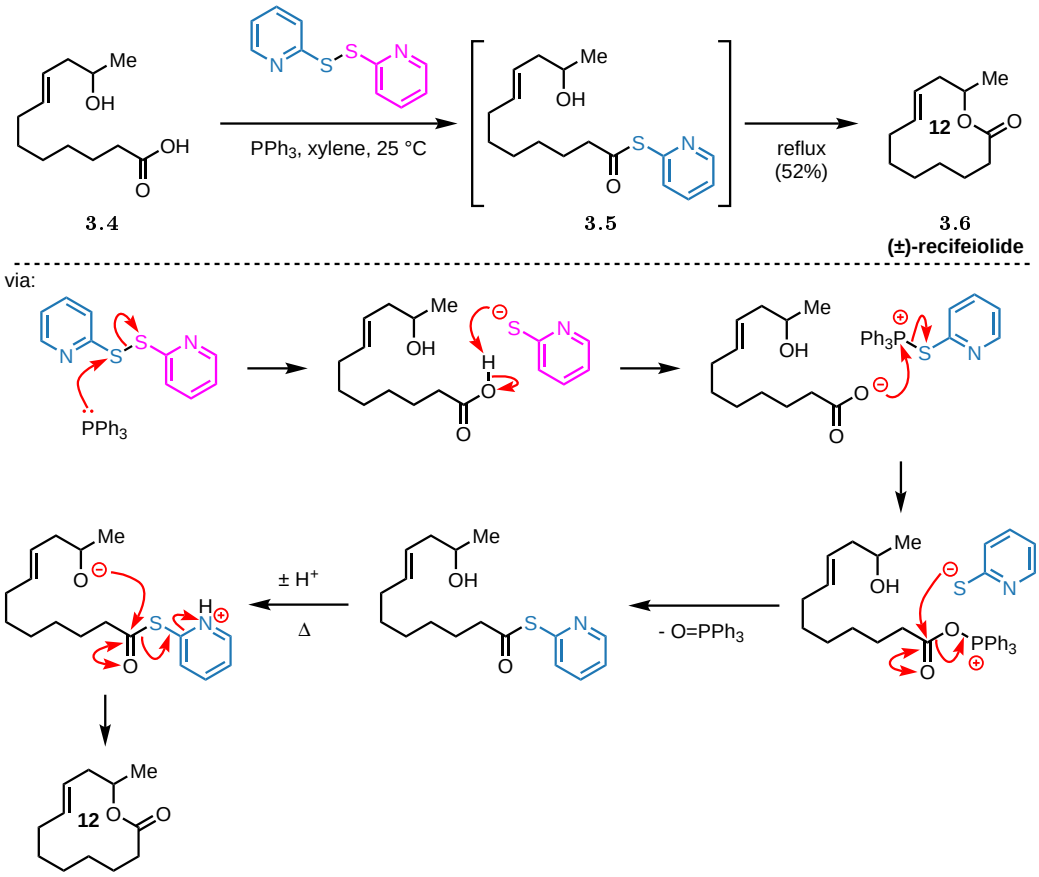


Figure 3.4: Rates of formation for lactones **3.3** from ω-bromoalkanoic acids **3.2** in 99% aqueous DMSO at 50 °C.[200]

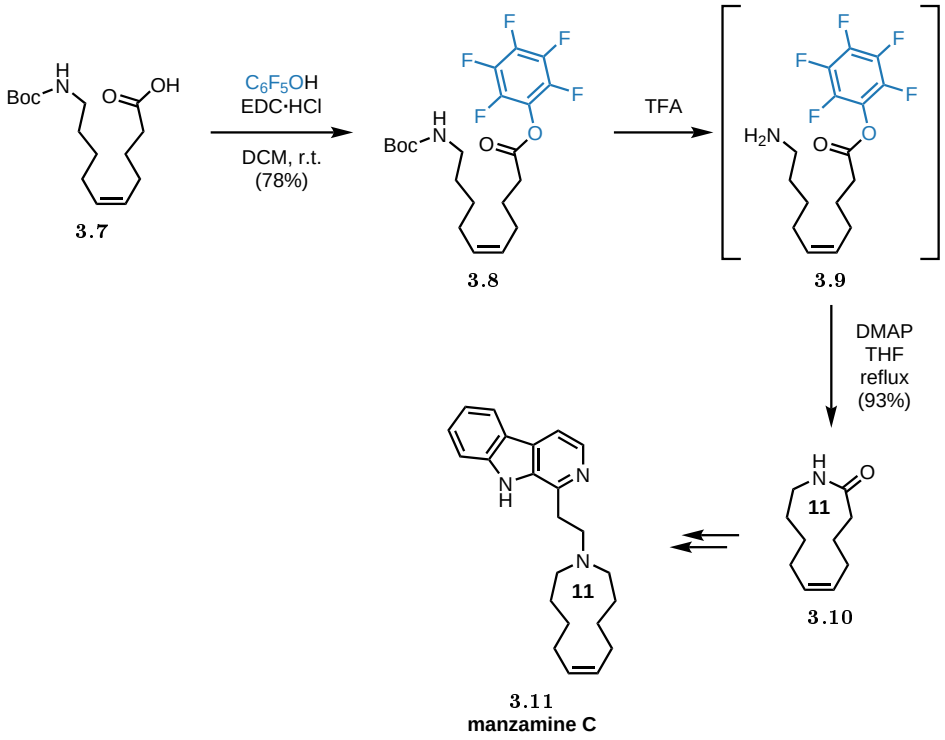
A common tactic to improve lactonisations of hydroxy acids involves activation of the carboxylic acid to promote the intramolecular attack of the hydroxyl group.[203,204] Thioesters are key intermediates in the biosynthetic lactonisation of macrolides.[205] Corey and Nicolaou were the first to report a lactonisation protocol based on a thioester as an activated carboxylic acid.[206] The Corey–Nicolaou lactonisation has been successfully applied in numerous total syntheses, including by Corey's group for the racemic synthesis of (±)-recifeiolide **3.6** (Scheme 3.1).[207] The mechanism involves initial formation of an *S*-pyridyl ester **3.5** from hydroxy acid **3.4** via a Mukaiyama oxidation–reduction condensation.[208] Upon heating,

proton transfer generates a zwitterionic intermediate that can undergo an electrostatically-promoted lactonisation to yield the natural product **3.6**. Since the initial report, protocols with improved reagents[209,210] or metal additives[211] have been developed.



Scheme 3.1: The total synthesis of (±)-recifeiolide **3.6** employing a Corey–Nicolaou lactonisation.

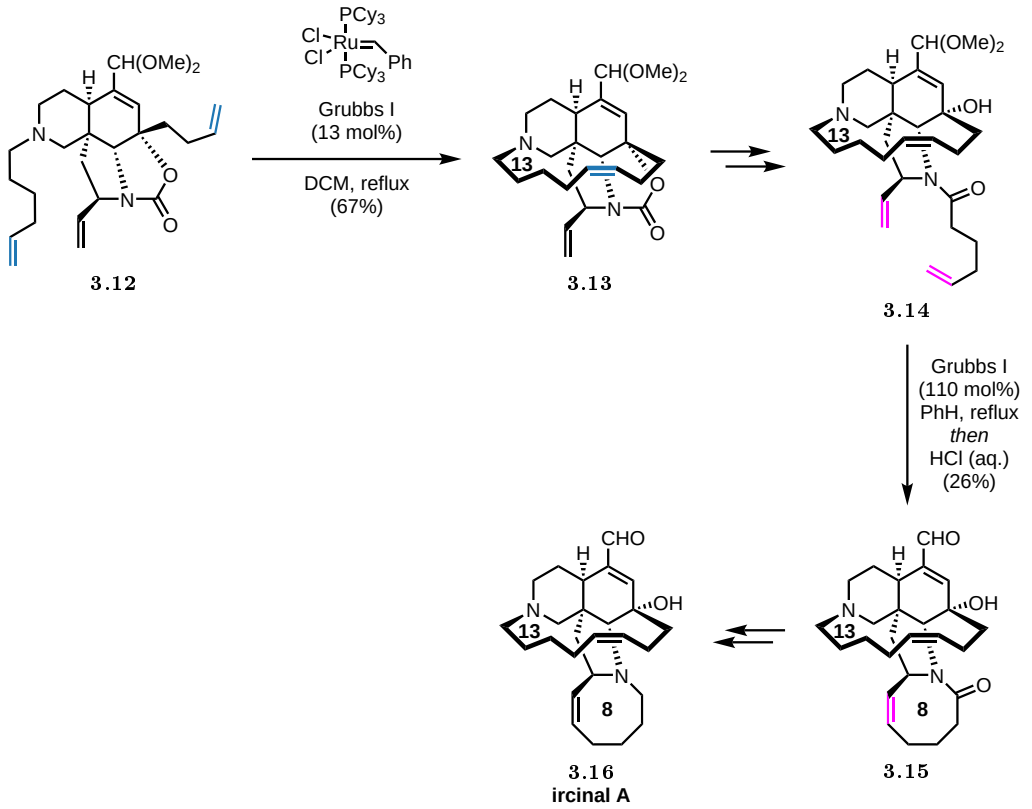
Despite the ubiquity of amide linkages in proteins, macrolactam scaffolds appear to be less prevalent in natural products than macrolactones.[212] Direct lactamisation of ω-amino acids is often unsuccessful, and once again, activation of the carboxylic acid is usually required.[213] The reagents popularly used for intermolecular peptide couplings are often suitable for mediating macrolactamisations. In one representative example, the eleven-membered ring of the alkaloid, manzamine C **3.11**, was constructed from ω-amino acid derivative **3.7**, using a pentafluorophenyl ester as an activated acyl group (Scheme 3.2).[214] After removal of the Boc protecting group of **3.8**, addition of **3.9** to a highly dilute, refluxing solution of DMAP in THF provided the desired lactam **3.10** in high yield. The *Z*-configured alkene in the lactamisation substrate **3.9** likely serves to bring the reactive centres into proximity, contributing to the high yield attained for this otherwise challenging lactamisation.



Scheme 3.2: A pentafluorophenyl ester peptide coupling strategy was employed by Gerlach to construct the medium-sized ring of manzamine C **3.11**.

3.1.2.2 Ring-closing metathesis

The generality of ring-closing metathesis for the construction of cyclic scaffolds of different sizes has enabled many natural product syntheses.[176,215–218] Although generation of a more stabilised olefin in the product may contribute in certain cases, the entropic favourability of releasing ethylene, or another volatile olefin, is the primary driving force for ring formation.[216–220] One example from natural product synthesis that highlights the flexibility of ring-closing metathesis to construct different-sized cyclic frameworks is Martin's approach to ircinal A **3.16** (Scheme 3.3),[221] a member of the manzamine family of alkaloids, which have been shown to demonstrate diverse biological activities.[222] Treatment of diene **3.12** with a catalytic amount of ruthenium complex, Grubbs I, in a dilute solution of refluxing DCM constructed the thirteen-membered ring of **3.13** in good yield, with the *N*-allyl group left unaffected. A second ring-closing metathesis was envisioned to form the eight-membered lactam **3.15**. The researchers found that this medium ring cyclisation required stoichiometric quantities of Grubbs I and greater thermal activation. Following reflux in benzene, and an acidic work up to cleave the acetal protecting group, **3.15** could be isolated in a modest 26% yield. The stark contrast in the ease of formation for the large- and medium-sized rings illustrates the challenge in medium ring-forming reactions, even for the most coveted of cyclisation methods.



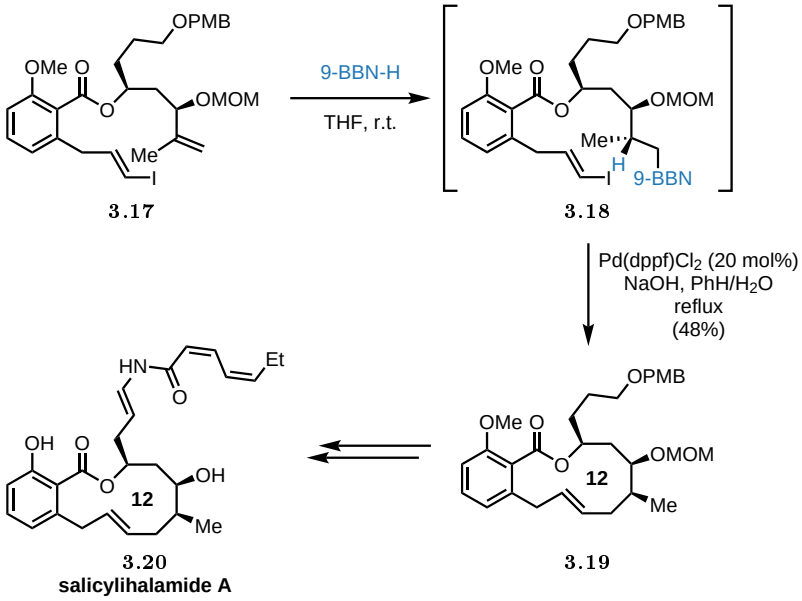
Scheme 3.3: Martin's total synthesis of ircinal A **3.16** made use of the versatility of ring-closing metathesis to form two different-sized rings.

3.1.2.3 Transition metal-catalysed cross-coupling

Cross-coupling reactions, particularly those catalysed by palladium, have uniquely enriched the modern organic chemist's reaction toolbox.[223] Intramolecular variants of powerful C–C, C–O or C–N bond-forming methods for cross-coupling have been successfully employed to construct medium rings.[176,215,220] By forging a C–C bond, a cross-coupling reaction was able to build the cyclic core of the benzolactone natural product, salicylihalamide A **3.20**, which was first isolated from a marine sponge and is a potent cytotoxin.[224] The researchers targeted an alternative cyclisation strategy to other literature reports, opting for a hydroboration/Suzuki–Miyaura coupling sequence of **3.17** that successfully formed twelve-membered lactone **3.19** (Scheme 3.4).[225] Notably, the cross-coupling was carried out under high dilution conditions to suppress competing intermolecular reactivity.

3.1.3 Synthesis of medium rings: ring expansion

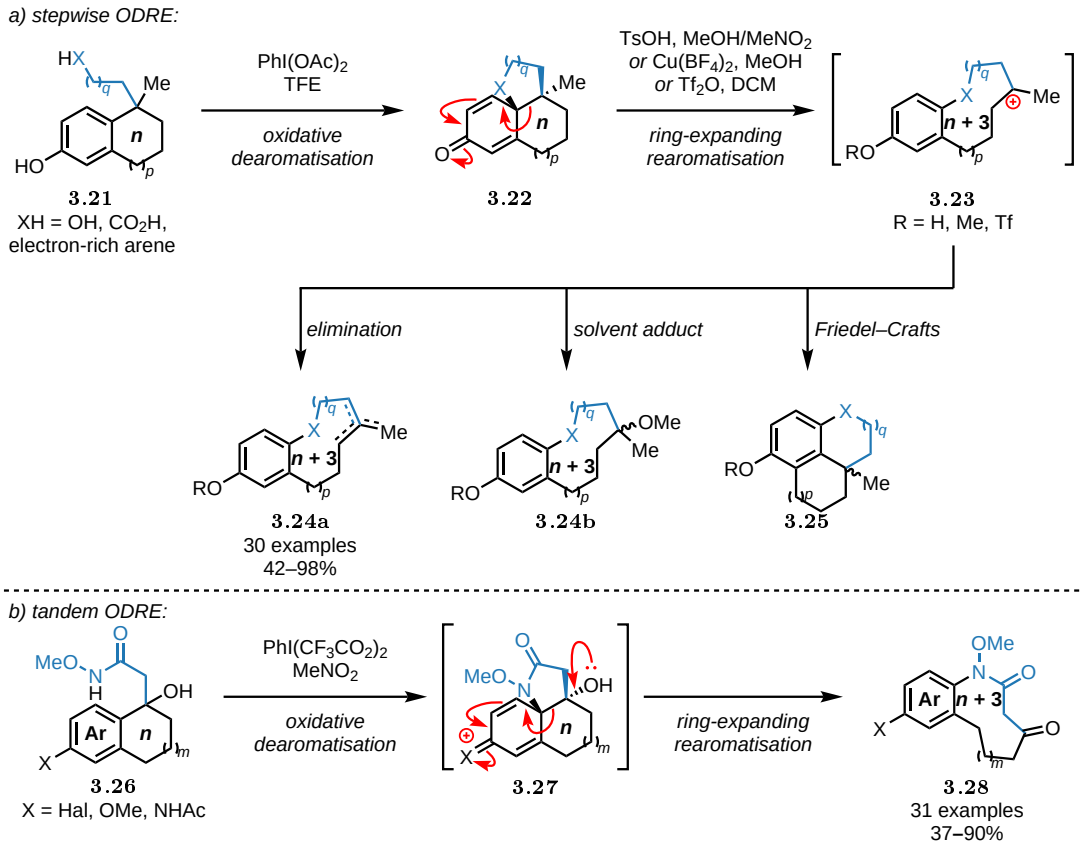
Ring expansion has become a popular strategy to access challenging medium ring products: it avoids the disfavoured medium-sized transition state structures that afflict ring formation reactions, and offers the opportunity to exploit the synthetic availability of smaller rings.[177,193,226] However, conversion of a smaller ring to a medium ring is, in itself, often thermodynamically disfavoured. For a successful ring-expanding process, this energy penalty must be negated in some way to render the overall process exergonic.



Scheme 3.4: A hydroboration/Suzuki–Miyaura coupling sequence constructed the twelve-membered lactone of salicylihalamide A **3.20**.

3.1.3.1 Ring expansion driven by aromatisation

One way in which the thermodynamic costs of ring enlargement can be offset is by pairing the expansion with the gain of aromaticity. Such a tactic is thought to be used by Nature: the proposed biosyntheses of a variety of medium ring natural products proceed by oxidative dearomatisation of an arene, followed by an aromatisation-driven ring expansion.[227–232] This inspired Tan and co-workers to target a biomimetic oxidative dearomatisation–ring-expanding rearomatisation (ODRE) sequence to access a library of diverse benzannulated medium rings.[190] A series of phenols fused to five- to eight-membered carbocycles **3.21** were oxidatively dearomatised by a hypervalent iodine reagent to form cyclohexadienones **3.22** (Scheme 3.5a). The key ring-expanding rearomatisation process was then induced by activation of the carbonyl group with a Brønsted acid, a Lewis acid, or a sulfonic anhydride. Elimination reactions of **3.23** gave rise to desired medium ring scaffolds **3.24**, but this stepwise process suffered from two limitations. Firstly, the substrate scope was restricted to phenolic substrates **3.21**. Secondly, there was potential for mixture of products to form by virtue of the different possible fates for carbocation **3.23**: alternative elimination events could give rise to multiple olefin regioisomers **3.24a**, adducts **3.24b** could form by nucleophilic attack of solvent molecules, or the carbocation could act as the electrophile in transannular Friedel–Crafts alkylations (with a subsequent 1,2-alkyl shift) leading to non-medium ring products **3.25**. To address these shortcomings, the researchers reported a redesigned ODRE process.[233] In this improved system, the electron flow was reversed: an electron-rich (hetero)arene in **3.26** could attack an oxidatively-generated electrophilic side chain (Scheme 3.5b). The subsequent ring-expanding rearomatisation of **3.27** gave eight- to eleven-membered benzannulated lactam products **3.28** with diverse aryl substitution.

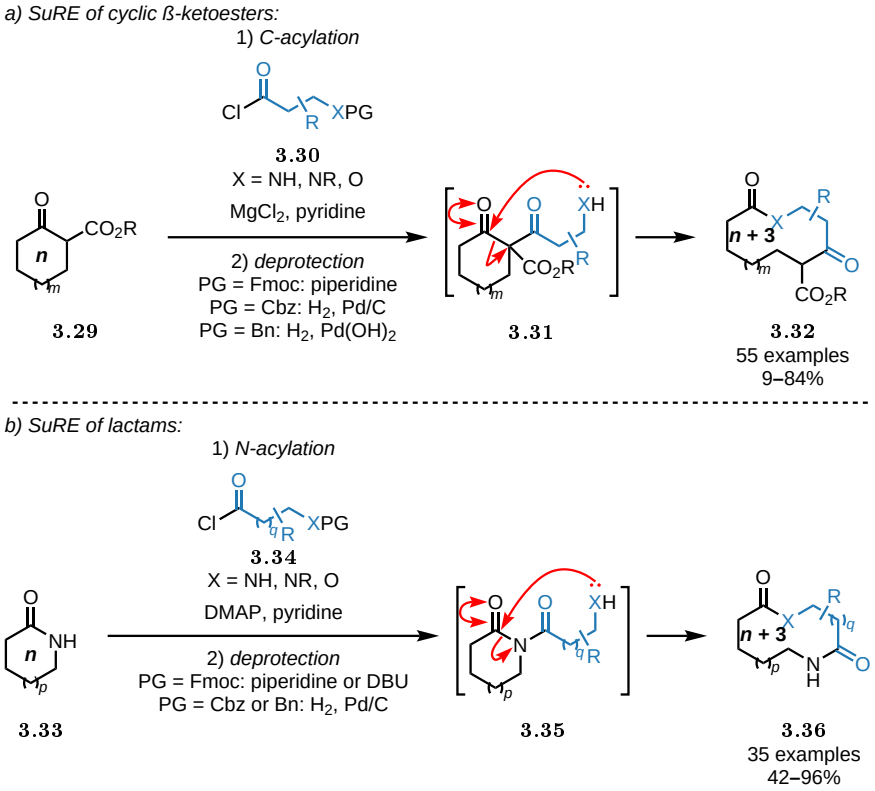


Scheme 3.5: Tan's development of biomimetic oxidative dearomatisation–ring-expanding rearomatisation (ODRE) processes.

3.1.3.2 Ring expansion driven by formation of strong bonds

The chemical energy inherent in reactive functional groups of substrate molecules can be used to promote ring expansion through transformation into more thermodynamically stable species.[177] Designers of new ring expansion processes have often found the favourable formation of strong amide linkages to be particularly suitable for this.[234] Building on important work from Hesse,[235–237] the Unsworth group has pioneered the synthesis of medium-sized and macrocyclic rings based on iterative insertions of acyclic units into an initial cyclic scaffold, primarily driven by amide formation. In the first demonstration of this successive ring expansion (SuRE) concept, cyclic β-ketoesters **3.29** could undergo *C*-acylation with amino acid-derived electrophiles **3.30**, followed by deprotection to induce production of ring-expanded lactams **3.32** (Scheme 3.6a).[238,239] The methodology was also applicable to lactone synthesis by insertion of a hydroxy acid unit. Fundamental to the success of the SuRE protocol is that after each iteration, the key reactive functionality, the β-ketoester, is available for further reaction, so that the macrocycle can be "grown" by repeated insertions. Impressively, between one and three iterations could generate eight- to 24-membered macrocycles. However, this reaction design was based on β-ketoesters, a motif whose metabolic instability limits the utility of the reaction products in biological settings. In addition, the reported yields were usually moderate (50–60%), with only β-amino acid-derived linear fragments **3.30** found to be reliable for insertion. Thus, an improved SuRE

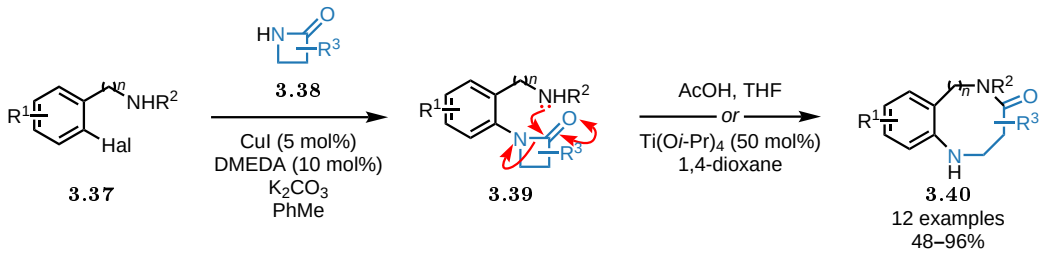
reaction mode was published in 2017 that enabled sequential ring expansions of lactams **3.33** (Scheme 3.6b).[53] Notably, this reaction system was found to be higher yielding, boasted an improved substrate scope, and no longer relied on reactive β-ketoesters. The only functional groups in the ring-expanded products **3.36** are amide or ester linkages, opening potential application as cyclic peptide mimics.[240] A range of linear units **3.34** based on α- and β-amino acids, and hydroxy acids were found to be competent in this ring enlargement protocol. Further systems have been developed that continue to underscore the versatility of the SuRE concept to access different-sized cyclic products, such as for the iterative generation of macrocyclic lactones.[241]



Scheme 3.6: The successive ring expansion (SuRE) concept enables sequential incorporation of linear fragments into cyclic scaffolds.

3.1.3.3 Ring expansion driven by relief of ring strain

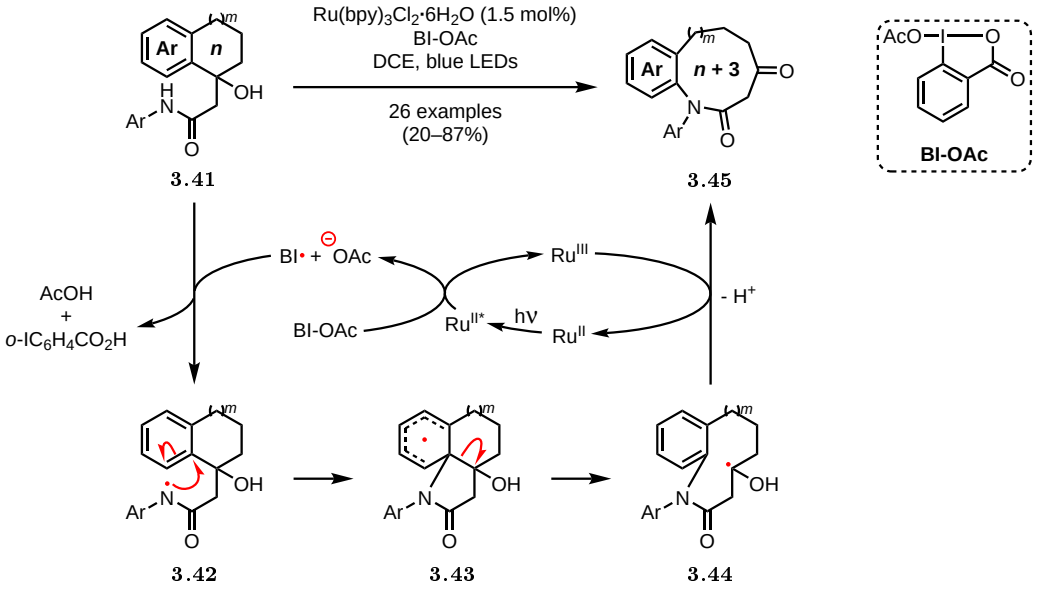
The unique level of ring strain characteristic of small (three- and four-membered) rings (see Figure 3.2) can serve as an energy reservoir for enabling powerful strain-release methodologies.[242–247] A copper-catalysed methodology for the *N*-arylation of amides was developed by Buchwald and co-workers,[248,249] and was employed to generate intermediates **3.39** by the cross-coupling of aryl bromides or iodides **3.37** with β-lactams **3.38** (Scheme 3.7).[250] While spontaneous in a small number of cases, the intramolecular transamidation of **3.39** was then initiated by treatment with a Brønsted or Lewis acid, culminating in a simple protocol to prepare ring-expanded nitrogen heterocycles **3.40**.



Scheme 3.7: The strain of small rings can be exploited in a ring-expansion to generate medium ring nitrogen heterocycles **3.40**.

3.1.3.4 Ring expansion driven by radical stability

Ring expansion reactions involving free radicals can be driven by formation of the most thermodynamically stable radical.[251,252] Over the last twenty years, methods involving transition metals,[253,254] photochemistry,[255,256] or electrochemistry[257,258] have been discovered that can generate open-shell species under milder, safer and greener conditions, and with greater control and selectivity than ever before.[259–261] Several contributions from Liu and co-workers have highlighted the potential of ring expansive radical processes to access medium rings.[262–264] One impressive report from 2018 targeted medium-sized lactams through a radical aryl migration process under photoredox catalysis (Scheme 3.8).[265] Readily available substrates **3.41** were treated with a ruthenium photocatalyst and a hypervalent iodine reagent, under irradiation from blue LEDs, to successfully access eight- to eleven-membered products **3.45**. The researchers' proposed mechanism involved oxidative quenching of the photoexcited species $Ru(bpy)_3^{2+*}$ by BI−OAc. Subsequent oxidation of the substrate **3.41** forms amidyl radical **3.42**, which can perform a stepwise *ipso*-substitution via **3.43** to form a more stable radical species **3.44**. Oxidation by $Ru(bpy)_3^{3+}$ closes the photocatalytic cycle and generates medium lactam product **3.45**. One limitation of this work was that highly electron-rich (hetero)aryl groups were poorly tolerated under the strongly oxidising reaction conditions. Within two years of this report, two research groups independently published electrochemical variants for the same overall transformation that could address this shortcoming.[266,267]



Scheme 3.8: Liu's photocatalytic approach to medium-sized lactams **3.45**.

3.2 Background

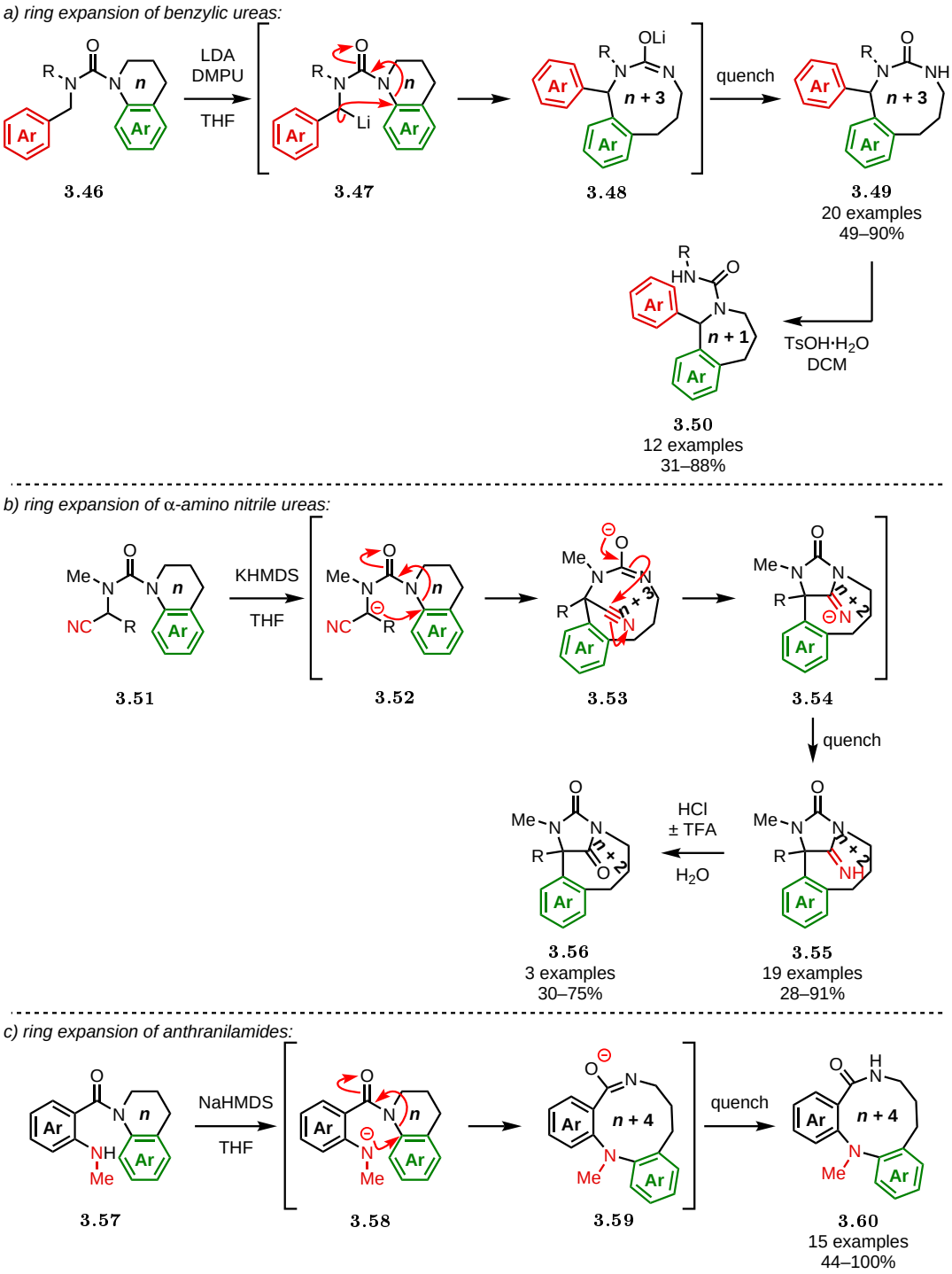
3.2.1 Ring-expanding aryl migration

With the conformationally-enhanced intramolecular migration of arenes an established reactivity mode for *N*-alkyl anilides (see Section 1.2), in recent years, the Clayden group has investigated the ring expansion of benzo-fused *N*-heterocycles by aryl transfer reactions. This research programme has resulted in methods that take readily available heterocyclic precursors and generate highly valuable medium ring products with potentially promising biological activity, but are otherwise challenging to access (see Section 3.1). These transformations are complementary to the ring-expanding methodologies presented in Section 3.1.3, in that the driving force is the stabilisation of charge: treatment of a substrate with base generates a reactive anion, which undergoes rearrangement to a more stable anion.

In 2016, the Clayden laboratory published their first migratory ring expansion method, which formed medium ring heterocycles from benzylic ureas.[268] Upon deprotonation of benzylic urea **3.46** with LDA in the presence of DMPU, nucleophilic attack on the benzo-fused heterocycle generated the comparatively stabilised urea anion **3.48** (Scheme 3.9a). This $n \rightarrow n + 3$ ring expansion provided access to a range of eight- to twelve-membered medium-sized ring products **3.49** in generally good yields. In accordance with other aryl migration methods from the Clayden group, the transformation was remarkably tolerant of migrating rings with diverse electronic parameters and sterically challenging substitution patterns. It was subsequently reported that the ring-expanded products **3.49** could be used to prepare tetrahydroisoquinoline or tetrahydrobenzazepine derivatives **3.50** by an acid-mediated ring contraction.[269]

In related work that featured a nitrile anion-stabilising group **3.51**, eight- to ten-membered iminohydantoin-bridged medium rings **3.55** were constructed by a two atom ring expansion of *N*-heterocycles (Scheme 3.9b).[270] As in the report of the acyclic version of this arylation,[36] the anion **3.53** generated after Truce–Smiles rearrangement of **3.52** was observed to spontaneously cyclise to iminohydantoin anion **3.54** by nucleophilic attack onto the nitrile group. Acidic hydrolysis of ring-expanded products **3.55** yielded hydantoins **3.56**.

Building on previous work employing an amide tether to enforce the reactive conformation (see Section 1.2.3), an $n \rightarrow n + 4$ ring expansion of readily accessible five- to eight-membered heterocyclic anthranilamides **3.57** generated medium ring dibenzodiazepine analogues **3.60** in good yields (Scheme 3.9c).[51] The reaction was initiated by addition of NaHMDS to **3.57** forming high-energy *N*-anion **3.58**, which acted as a nucleophile in the *ipso*-substitution of the amide nitrogen, giving rise to amidate anion **3.59**, stabilised by delocalisation. Compared to the non-ring expansive aryl migration,[48] the ring-expanding variant required heating to higher temperatures ($\geq$100 °C under microwave irradiation) to achieve complete conversion, perhaps indicative of the greater activation barrier owing to strain of the medium-sized lactam products **3.60**.

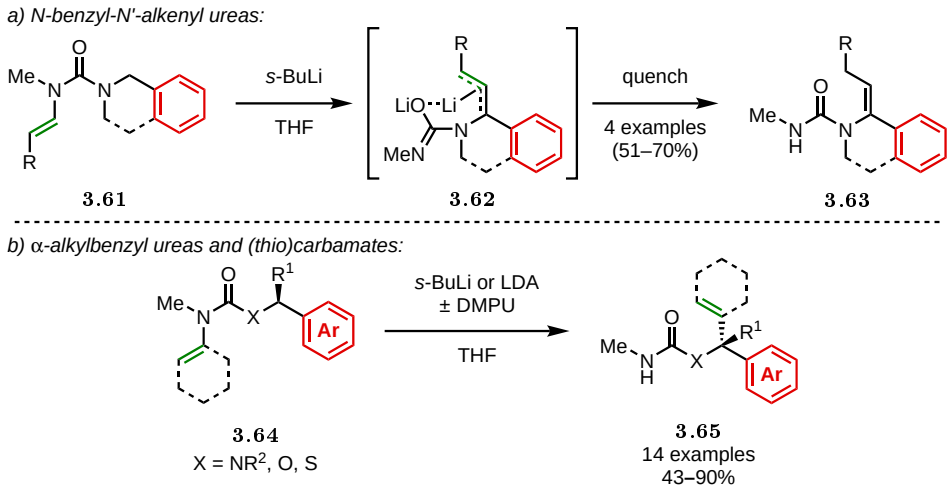


Scheme 3.9: The Clayden group has used the stabilisation of charge as a driving force in the migratory ring expansions of arenes to generate medium rings.

3.2.2 Intramolecular alkenyl migration

Given the success of intramolecular aryl transfer of lithiated *N′*-aryl ureas and (thio)carbamates, even for highly electron-rich rings (see Section 1.2), the Clayden group looked to investigate the feasibility of the migration of unactivated alkenyl groups. A successful vinyl transfer would represent a nucleophilic vinylic substitution, S_NV,[271–273] a process that, like S_NAr, is rare on unactivated substrates. Pleasingly, it was found that, following treatment of *N*-benzyl-*N′*-alkenyl ureas **3.61** with *s*-BuLi, rearranged products **3.63** could be isolated as single *Z*-configured isomers (Scheme 3.10a).[274] Formation of **3.63** presumably arises from benzylic lithiation and migration of the vinyl group, followed by a second benzylic deprotonation to give *Z*-configured allyllithium species **3.62**. Reprotonation at the γ-position upon quench generates **3.63**.

Replacement of one of the benzylic protons with an alkyl group removes the possibility of a second deprotonation. Thus, α-alkylbenzylureas and (thio)carbamates **3.64** could form rearranged products **3.65** that bear a vinylic quaternary stereocentre (Scheme 3.10b).[274] It was found that the reactivity of the hindered organolithium could be increased by the addition of DMPU. As in aryl transfer processes, these vinyl migrations occurred with high stereoselectivity, proceeding via a configurationally stable benzyllithium species. Related work has shown benzomorpholines can been employed as masked vinyl groups for the vinylation of lithiated benzylic ureas and carbamates.[275]

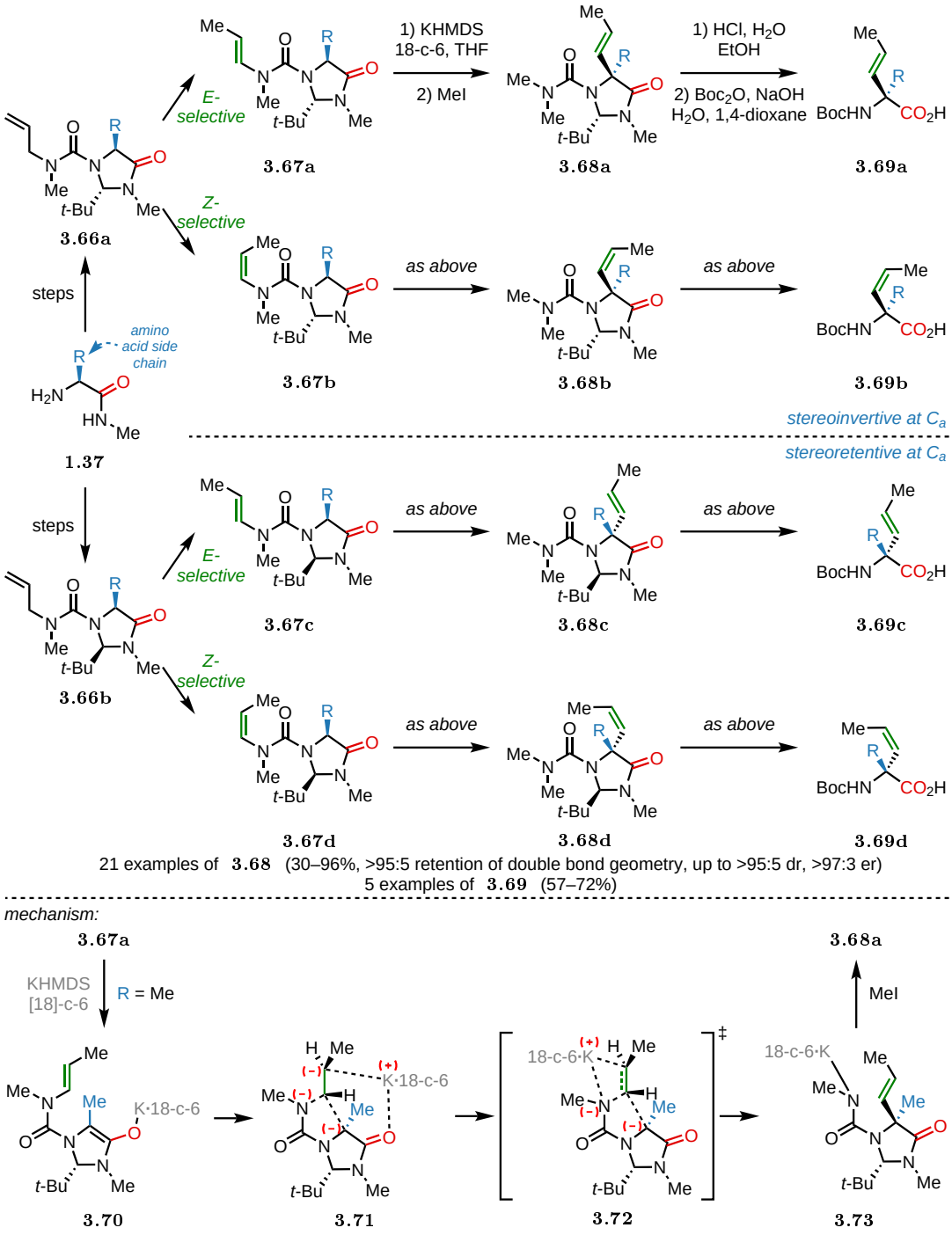


Scheme 3.10: The intramolecular alkenyl migration of urea and (thio)carbamates.

The preparation of quaternary α-alkenyl amino acid derivatives could be achieved by application of a nitrile anion-stabilising group.[276] Although the products were racemic, the rearrangement proceeded with retention of double bond geometry, providing access to *E*- and *Z*-alkenyl amino acids. This laid the foundation for working towards using a carbonyl anion-stabilising group to target synthesis of enantiopure *E*- and *Z*-alkenyl α-amino acids. Once again, the principle of self-regeneration of stereocentres proved fruitful (see Section 1.2.2). The methylamide derivative of naturally-occurring α-amino acids **1.37** could be used to diastereoselectively form the *anti*- (**3.66a**) and *syn*- (**3.66b**) *N′*-allyl-ureidoimidazolidinones (Scheme 3.11, top).[277] Isomerisation of the *N′*-allyl group

to either *E*- (**3.67a** and **3.67c**) or *Z*- (**3.67b** and **3.67d**) alkenyl ureas could be achieved, culminating in the synthesis of four stereoisomers of **3.67**. Treatment with KHMDS and 18-crown-6 was found to initiate N→C vinyl transfer on the opposite face to the *t*-Bu group, proceeding with retention of the olefin geometry. A quench with MeI formed **3.68**, and hydrolysis and Boc protection culminated in synthesis of α-alkenyl amino acids **3.69** with stereocontrol with respect to both absolute configuration and olefin geometry.

Mechanistically, these transfers of electron-rich olefins arguably present even more intrigue than the transfer of arenes. Vinyl migration processes share some commonalities with their aryl counterparts: no intermediate is observable by in situ IR studies,[276] with current understanding, supported by DFT calculations,[274,277] invoking a crucial role for the metal counterion in enabling a partially concerted reaction. The anion **3.70** generated upon treatment of **3.67a** (R = Me) with KHMDS and 18-crown-6 is stabilised by coordination between oxygen and a [$K^+ \cdot$ 18-crown-6] counterion (Scheme 3.11, bottom). Interaction between the counterion and the β-carbon of the olefin allows for carbometallation to **3.71**, following which, antarafacial O→N migration of the counterion enables transfer of the vinyl group, with *syn*-elimination via **3.72** to **3.73**, in which the alkene geometry has been preserved.

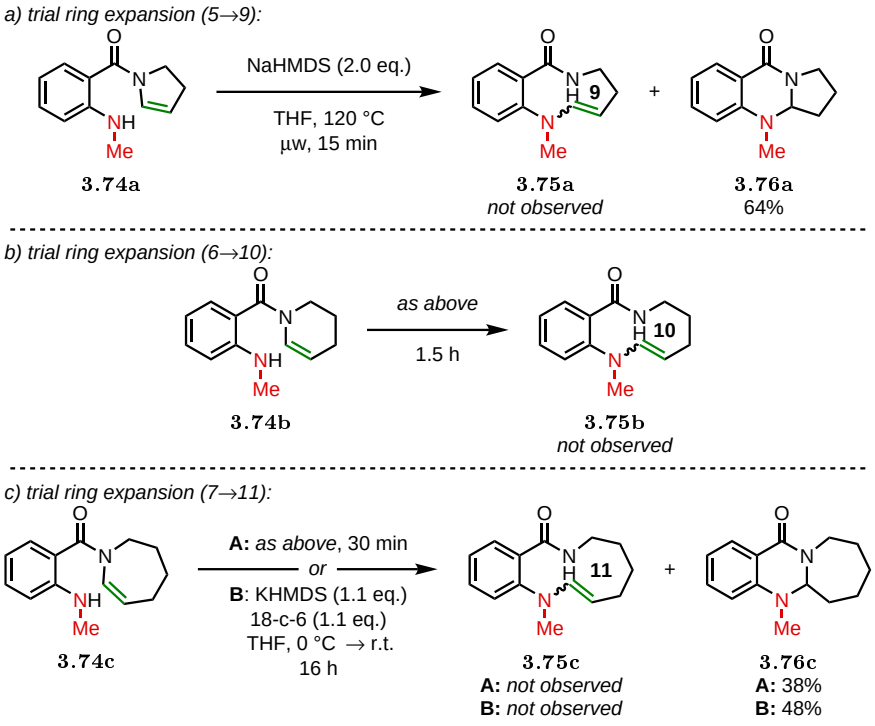


Scheme 3.11: The principle of self-regeneration of stereocentres in the alkenylation of α-amino acids, proceeding through a partially concerted vinyl transfer.

3.2.3 Ring-expanding alkenyl migration

Given the Clayden group's success in adapting established arylation processes (see Section 1.2) for ring expansion (see Section 3.2.1), preliminary investigations into ring-expanding alkenylations were conducted by MSci student, Madeline Townley.[278] Inspired by the ring expansive aryl rearrangement of heterocyclic anthranilamides (see Scheme 3.9c), five-, six- and seven-membered substrates **3.74** for analogous alkenyl migration were prepared (Scheme 3.12). Treatment of five-membered substrate **3.74a** with NaHMDS under microwave irradiation did not form medium ring lactam **3.75a** (Scheme 3.12a). Instead, the product of hydroamination of the alkene, **3.76a**, could be isolated. Under the same conditions, low conversion of six-membered homologue **3.74b** was observed after 1.5 h (Scheme 3.12b). Analysis by ^{1}H NMR spectroscopy indicated some decomposition was occurring through cleavage of the amide bond. The attempted ring expansion of seven-membered substrate **3.74c** was also accompanied with significant amounts of decomposition, although considerable amounts of hydroamination product **3.76c** was obtained (Scheme 3.12c). It was hoped that alternative reactions conditions, based on those published by the Clayden group for alkenyl migrations (see Scheme 3.11), could bias reactivity towards the desired ring-expanded lactam **3.75c**. Although the reaction proceeded more cleanly using KHMDS in conjugation with 18-crown-6 at room temperature, only tricyclic compound **3.76c** was isolated.

Despite these initial studies not demonstrating access to ring-expanded products **3.75**, we were intrigued by the formation of hydroamination products **3.76**. It was hoped that any insights gained about their formation pathway could guide efforts to design a reaction system capable of generating medium rings.



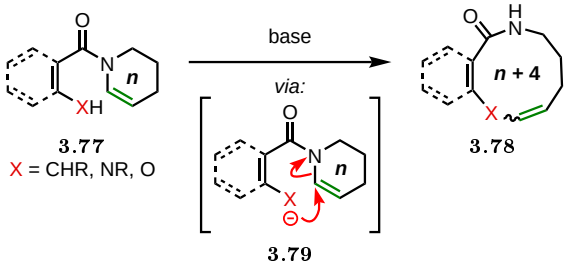
Scheme 3.12: Trial ring expansion of anthranilamides **3.74** was met with competitive hydroamination to **3.76** and/or decomposition.

3.3 Results and discussion

3.3.1 Project aims

Medium-sized rings are important targets for medicinal and agrochemistry because of their appealing potential bioactivity, but their synthesis remains a persistent challenge that demands the generation of novel methods (see Section 3.1). The goal of this project was to achieve medium ring preparation by bringing together the Clayden group's interests in ring expansion (see Section 3.2.1) and conformationally-accelerated alkenyl migration (see Section 3.2.2). If building on the initial findings summarised in Section 3.2.3 successfully led to the development of novel methodology, the library of accessible medium-sized cyclic scaffolds would be greatly enriched.

It was anticipated that precursors **3.77** containing unsaturated heterocycles could engage in a conformationally-enabled vinyl migration, resulting in "heterocyclic inflation" to medium ring lactams **3.78** (Scheme 3.13). This would be a highly attractive route to medium-sized rings, since the broad availability of common-sized nitrogen heterocycles could be exploited. In particular, pyridine could serve as an exciting starting material for ring expansion by leveraging intermediate pyridinium species that possess diverse reactivity. One could envisage benzamide and acrylamide derivatives with carbon or heteroatom nucleophiles as viable substrate families for study. The reaction products **3.78** would retain the double bond that can serve as a synthetic handle for further elaboration, which would highlight the value of ring-expanded heterocycles **3.78** to drug and agrochemical discovery. The migration of unactivated alkenes is a highly unusual transformation (see Section 3.2.2), and so further mechanistic investigation could develop our understanding of such processes. We hoped to identify a candidate reaction system for a kinetic isotope effect study, which could provide insight into the concertedness of conformationally-enhanced vinylations.



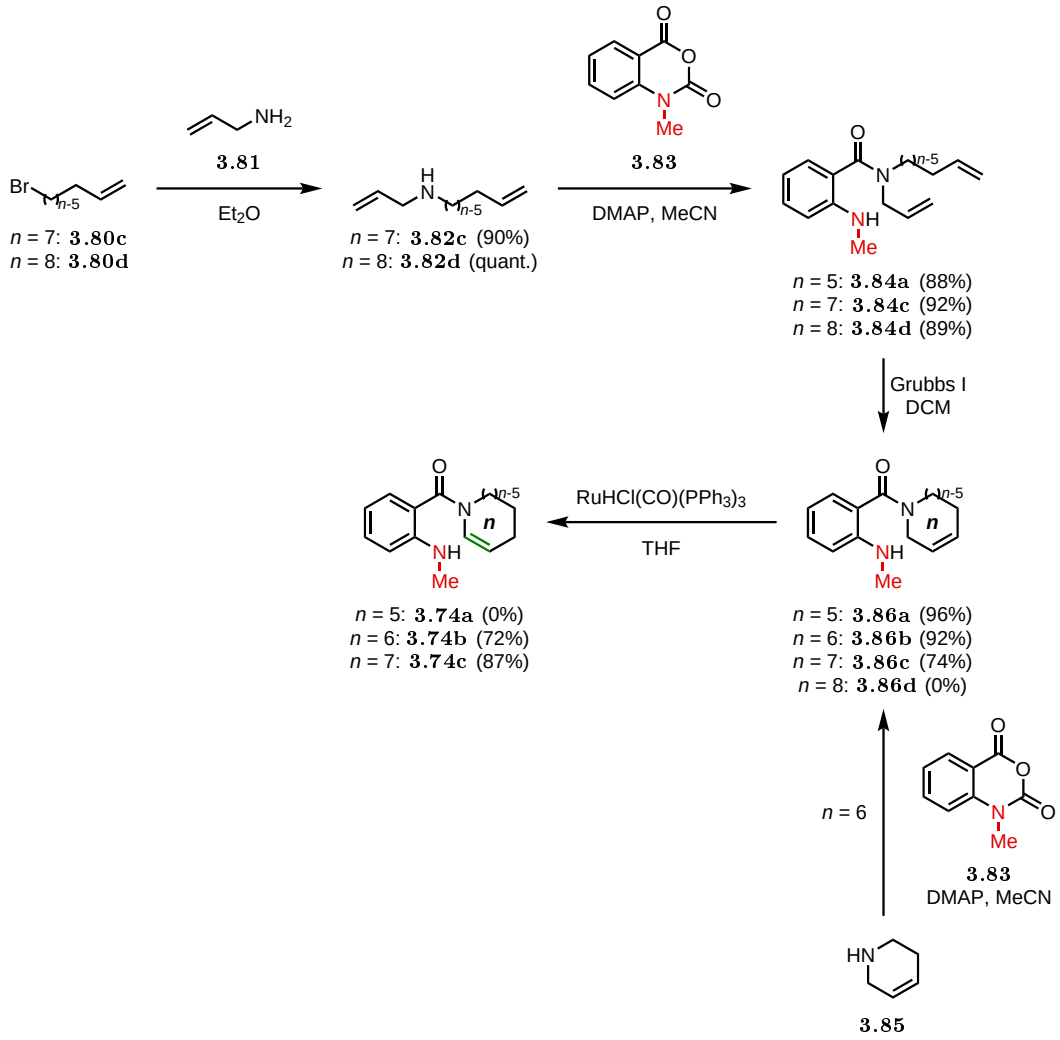
Scheme 3.13: The proposed migratory ring expansion of alkenes to form medium-sized products **3.78**.

3.3.2 Examining prospective substrate families

3.3.2.1 Anthranilamide series

Initial efforts focused on continuing the work towards the ring-expanding vinyl migrations of anthranilamides (see Section 3.2.3). After minor modification of the initial route, substrates **3.74** were prepared (Scheme 3.14). The general strategy

involved amide formation with *N*-methylisatoic anhydride **3.83**, ring-closing metathesis to form the heterocycle, and isomerisation of the alkene from the allylic position in **3.86** to the vinylic position in **3.74**. Due to the versatility of ring-closing metathesis, the synthetic sequence was amenable for accessing substrates of different ring size, depending on the amine used in the coupling step. Diallylamine **3.82a**, the precursor for a five-membered heterocycle, is commercially available, and coupling of tetrahydropyridine **3.85** avoided the need for the ring closure step, directly providing **3.86b**. Unsaturated amines **3.82c** and **3.82d**, which would enable the construction of seven- and eight-membered rings respectively, were readily prepared by alkylation of allylamine **3.81** with the appropriate ω-bromoalkenes **3.80c** and **3.80d**.

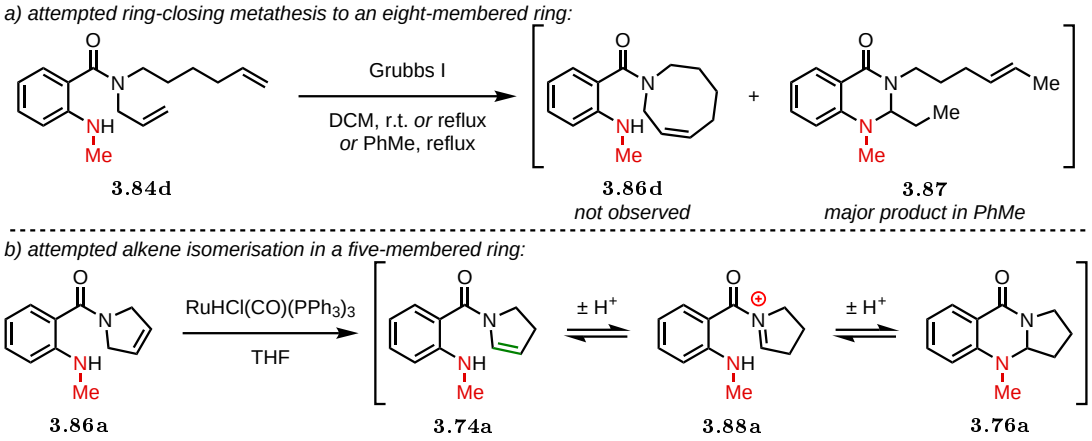


Scheme 3.14: Synthesis of anthranilamide substrates **3.74** for the ring expansive N→N vinyl migration.

Ring-closing metathesis of **3.84d** to form the eight-membered ring of **3.86d** proved problematic. Under the standard conditions, with 5 mol% of Grubbs I in DCM at room temperature, essentially no consumption of starting material **3.84d** was observed after 2 d (Scheme 3.15a). Overnight heating at reflux also proved ineffective. After a solvent exchange to PhMe, addition of a further portion of Grubbs I catalyst, and prolonged reflux over 4 d, ^{1}H NMR analysis indicated

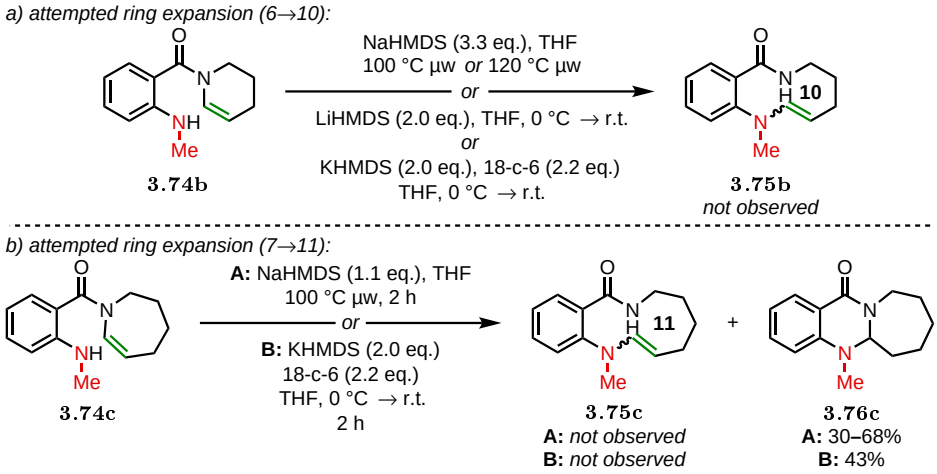
significant consumption of **3.84d**. However, as well as some decomposition, the major product species was putatively assigned structure **3.87**. Given the reluctance of **3.84d** to undergo ring closure to **3.86d**, further synthetic effort towards eight-membered substrate **3.74d** was paused — although these results demonstrated that end-to-end cyclisations to construct medium-sized rings are challenging, and pursuit of methods for their preparation is worthwhile.

As previously observed,[278] the attempted isomerisation of **3.86a** to **3.74a** formed a mixture of desired compound **3.74a** and hydroamination product **3.76a** (Scheme 3.15b). Isolation of **3.74a** had been reported to be achieved on one occasion,[278] but in our hands, purification attempts were unsuccessful, with suggestion that the interconversion of **3.74a** and **3.76a** was promoted by silica. At this point, pursuit of **3.74a** was stopped, in order to trial the ring expansion of the six- and seven-membered substrates **3.74b** and **3.74c** that were in hand.



Scheme 3.15: The preparation of 5- and 8-membered vinyl migration substrates was unsuccessful.

Six-membered substrate **3.74b** was treated with NaHMDS (1.1 eq.) and heated to 100 °C in the microwave (Scheme 3.16a). No conversion was observed after 1 h, nor after attempting to encourage the reaction by adding a further portion of NaHMDS (2.2 eq.) with continued heating for several hours. Increasing the reaction temperature to 120 °C, employing LiHMDS, or using KHMDS in concert with 18-crown-6 were all similarly ineffective. Interestingly, the behaviour of seven-membered substrate **3.74c** was found to be quite different: promisingly, complete consumption of **3.74c** could be achieved by treatment with NaHMDS at 100 °C under microwave irradiation for 2 h, or with KHMDS in the presence of 18-crown-6 at room temperature after 2 h (Scheme 3.16b). But in both cases, following column chromatography on silica, only hydroaminated product **3.76c** could be obtained in moderate yields, as observed previously (see Scheme 3.12).



Scheme 3.16: Attempts to induce ring expansion of anthranilamides **3.74b** and **3.74c** did not provide isolable medium rings **3.75b** and **3.75c**.

Closer inspection of the crude reaction mixture from Scheme 3.16b, conditions **A**, by ^{1}H NMR spectroscopy revealed significant differences between the reaction mixture and the material isolated after chromatography. The signals for the enamine protons H_{13} (5.05 ppm) and H_{14} (6.34 ppm) of substrate **3.74c** are shown in Figure 3.5, top. In the spectrum for crude reaction mixture (Figure 3.5, middle), which promisingly indicated the desired compound **3.75c** was the major product, H_{13} had slightly shifted to 5.07 ppm and H_{14} was significantly displaced to 5.67 ppm. The coupling constant $J_{H_{13}-H_{14}}$ between the two enamine protons from the crude reaction mixture was measured as 7.5 Hz. The magnitude of this coupling constant is consistent with a *Z*-configured double bond, arising from alkenyl migration proceeding with retention of the olefin geometry. This assignment of the double bond geometry was supported by comparison of coupling constants in related substructures from the literature, for which products with both *Z* ($J \approx 8$ Hz) and *E* ($J \approx 14$ Hz) geometries have been reported.[279,280] However, after column chromatography on silica, no olefinic protons could be observed. Instead, there was a signal for aliphatic H_{14}, with a chemical shift consistent with having the two adjacent nitrogen atoms in the assigned structure of the hydroaminated product **3.76c** (Figure 3.5, bottom). This side-product presumably arises via enamine–iminium tautomerisation of **3.75c** on silica, followed by transannular cyclisation. Attempts to isolate the ring-expanded product **3.75c** by chromatography using a basified eluent system, or on alumina rather than silica, also only led to tricyclic compound **3.76c** being obtained.

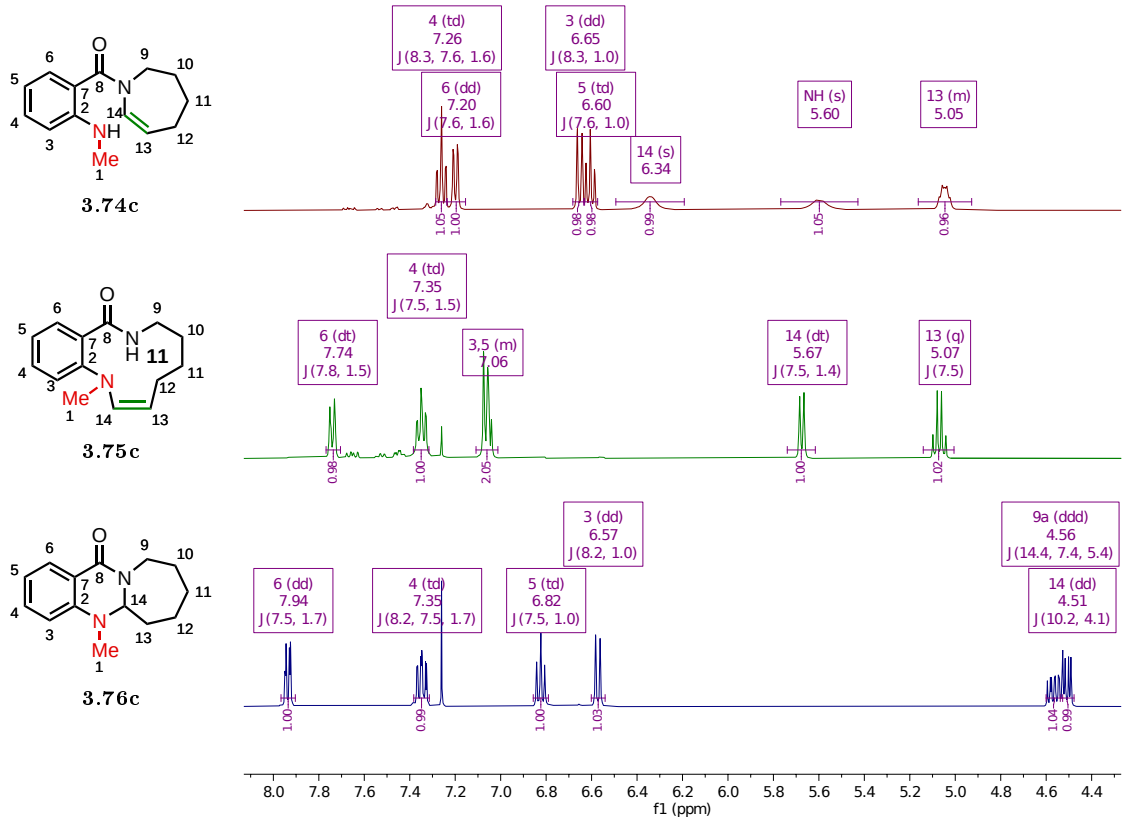
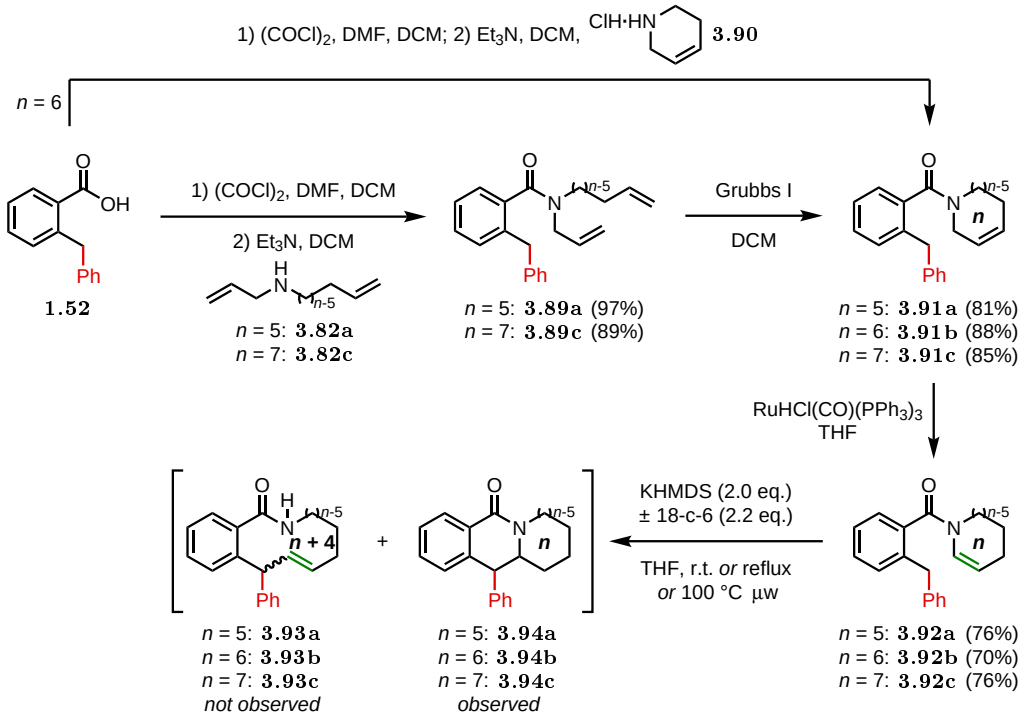


Figure 3.5: Selected portions of ^{1}H NMR spectra (400 MHz, $CDCl_3$) — top: isolated **3.74c**; middle: crude reaction mixture from Scheme 3.16b, conditions **A**, containing primarily **3.75c**; bottom: **3.76c** by column chromatography on silica.

3.3.2.2 2-Benzylbenzamide series

With a view to exclude the possibility of the hydroamination seen with the anthranilamide series (see Section 3.3.2.1), we considered substrates in which the nucleophile was a carbanion, rather than an anionic nitrogen. It was also hoped that this would provide a greater driving force for ring expansion, since the vinyl transfer would involve going from a higher energy C-anion to a resonance-stabilised amidate anion. As for the anthranilamides (see Scheme 3.14), a synthetic sequence involving amide formation, ring-closing metathesis and alkene isomerisation, provided 2-benzylbenzamide substrates **3.92** in good yields (Scheme 3.17). Pleasingly, in contrast to five-membered anthranilamide **3.74a**, 2-benzylbenzamide **3.92a** could now be prepared straightforwardly.

With five-, six- and seven-membered 2-benzylbenzamides **3.92** in hand, their ring expansion was attempted. For all three ring sizes, we were surprised to find that treatment with KHMDS led to formation of hydroalkylated products **3.94** as the only identifiable species, accompanied with significant decomposition at all temperatures trialled (room temperature, at reflux, or under microwave irradiation at 100 °C), and either in the presence or absence of 18-crown-6 (Scheme 3.17). In contrast to the analogous tricyclic hydroaminated compounds **3.94** derived from anthranilamides **3.74** (see Scheme 3.16), the tricyclic hydroalkylated products **3.94** were now present in the crude ring expansion reaction mixtures of **3.92**, rather than being generated from the desired medium ring lactams **3.93** during purification.

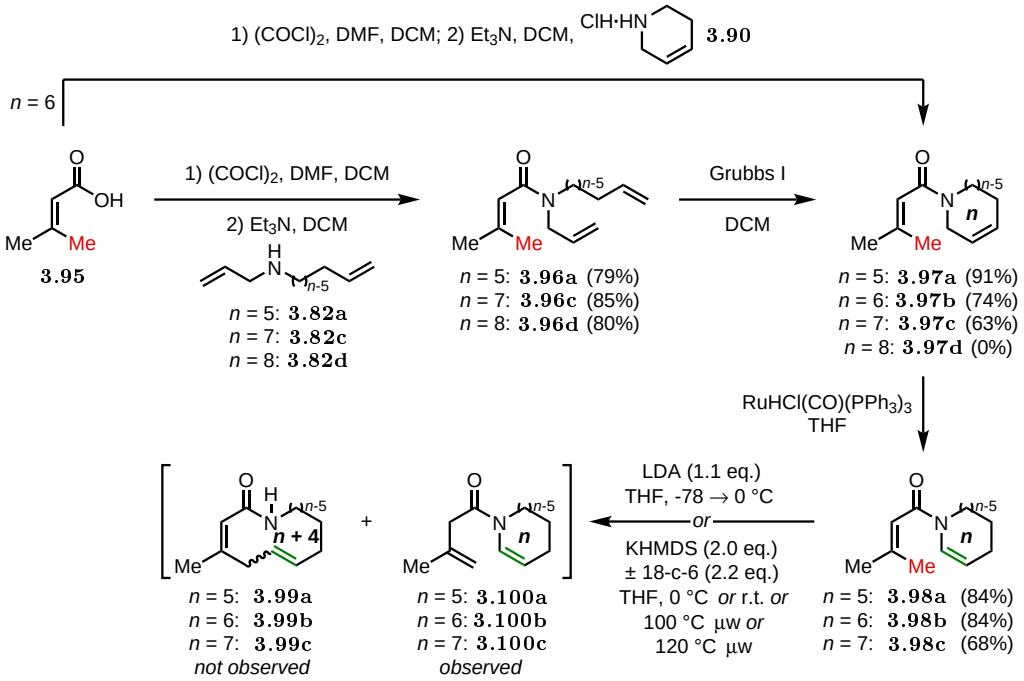


Scheme 3.17: 2-Benzylbenzamide substrates **3.92** were made to explore ring expansive N→C vinyl transfer, but treatment with KHMDS formed tricyclic compounds **3.94**, products of hydroalkylation of the alkene.

3.3.2.3 3,3-Dimethylacrylamide series

Exploration of a structurally distinct class of substrates — based on acrylamides, rather than benzamides — was commenced. Successful ring expansion would generate non-benzannulated medium rings, broadening the scope of potentially bioactive medium-sized scaffolds that could be constructed. In addition, replacement of the benzamide would likely have a profound impact on the reactivity of the substrates with respect to tricyclic compound formation. We initially targeted 3,3-dimethylacrylamides **3.98**, access to which was accomplished in an analogy to 2-benzylbenzamide substrates **3.92** (see Scheme 3.17), starting with commercially available 3,3-dimethylacrylic acid **3.95** (Scheme 3.18). Pleasingly, the ring-closing metathesis and alkene isomerisation steps remained chemoselective in all cases, with no interference caused by the double bond in the acrylamide backbone. Ring-closing metathesis, once again, failed to construct an eight-membered ring: there was no formation of any **3.97d**, even after a solvent swap to PhMe and lengthy reaction period at an elevated temperature of 80 °C.

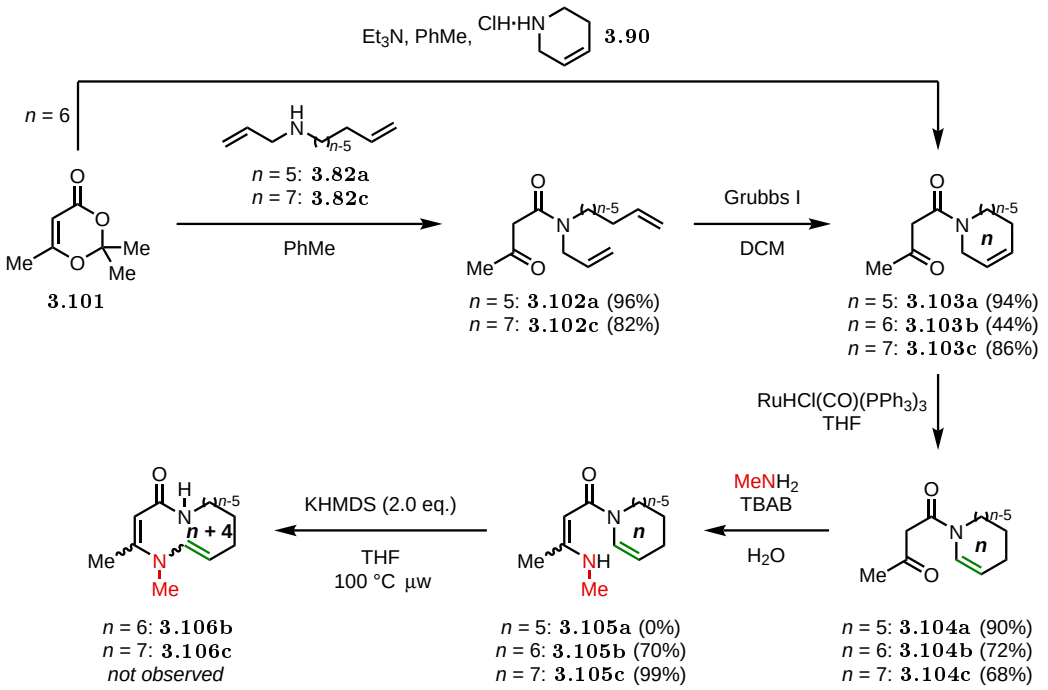
We attempted to ring-expand 3,3-dimethylacrylamides **3.98** with KHMDS or LDA, a stronger base that may be needed to deprotonate this less activated substrate. Unfortunately, analysis of the crude reaction mixtures by ^{1}H NMR revealed that, in each case, the only change was some of the starting material **3.98** had undergone isomerisation to β,γ-unsaturated amide **3.100** (Scheme 3.18). This indicated both bases were proficient at deprotonating the substrate **3.98**, but neither initiated vinyl transfer to **3.99**. Unfortunately, no change to the reaction outcome could be effected by employing 18-crown-6 in concert with KHMDS.



Scheme 3.18: 3,3-Dimethylacrylamide substrates **3.98** were prepared, but ring expansion attempts only led to recovery of starting material **3.98** and isomerised starting material **3.100**.

3.3.2.4 β-Aminocrotonamide series

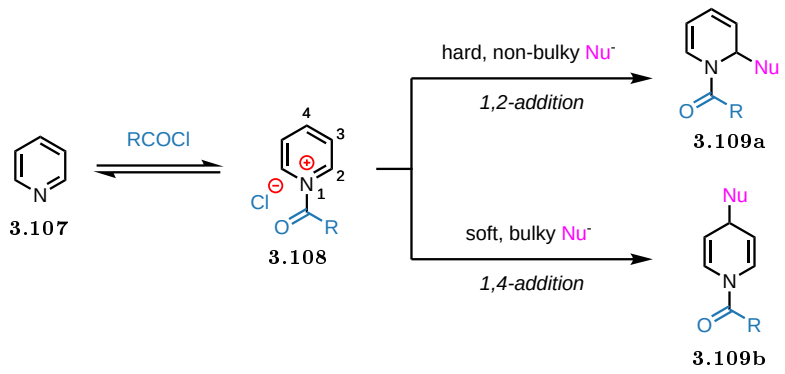
Another series of substrates based on the acrylamide structure was conceived: the ring expansion of β-aminocrotonamides **3.105** would involve an N→N vinyl transfer. To investigate the possibility for such reactivity, a synthesis of β-aminocrotonamides **3.105** was executed, and began with formation of β-ketoamides **3.102** in good yields with the acetoacetylating agent, diketene acetone adduct **3.101** (Scheme 3.19). As demonstrated for previous classes of substrates (*vide supra*), ring-closing metathesis and alkene isomerisation constructed the heterocycle of **3.104**, although chromatographic removal of the ruthenium catalysts, particularly after the isomerisation step, proved challenging for this substrate class. The nucleophilic methylamino group of **3.105** was then left to be introduced at the end of the synthesis in a condensation reaction. Although five-membered β-ketoamide **3.104a** was found to decompose during the reaction, six- and seven-membered congeners **3.104b** and **3.104c** were smoothly converted to their corresponding β-aminocrotonamides **3.105** as single geometric isomers, with an undetermined geometry of the acyclic double bond. However, attempted ring expansion by subjection to KHMDS did not lead to any observable change.



Scheme 3.19: β-Aminocrotonamides **3.105** were synthesised, but attempted N→N vinylation only led to recovery of starting material.

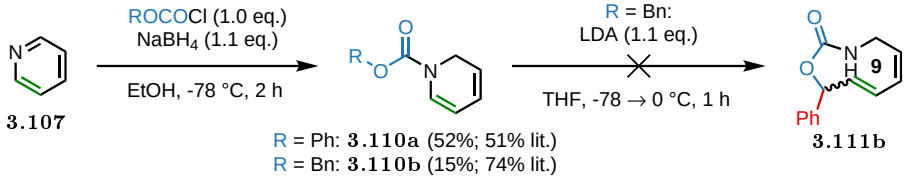
3.3.3 Studies into the ring expansion of pyridine

A key advantage of medium ring synthesis by a ring expansion strategy is the opportunity to exploit the broad availability of common-sized rings. Pyridine is a particularly attractive starting point, with *N*-activated pyridinium salts susceptible to both nucleophilic and electrophilic attack on the ring to give dearomatised products.[281,282] It is well-established that the regioselectivity for nucleophilic attack on *N*-acylpyridiniums **3.108** is determined primarily by the steric demands and hardness/softness of the nucleophile (Scheme 3.20). Hard, non-bulky nucleophiles tend to attack at the 2-position to give 1,2-dihydropyridines **3.109a**, while soft, bulky nucleophiles favour 1,4-addition to **3.109b**. It was envisioned that the *N*-vinyl motif of dearomatised structures **3.109** could partake in alkenyl migration to enable the ring expansion of pyridine.



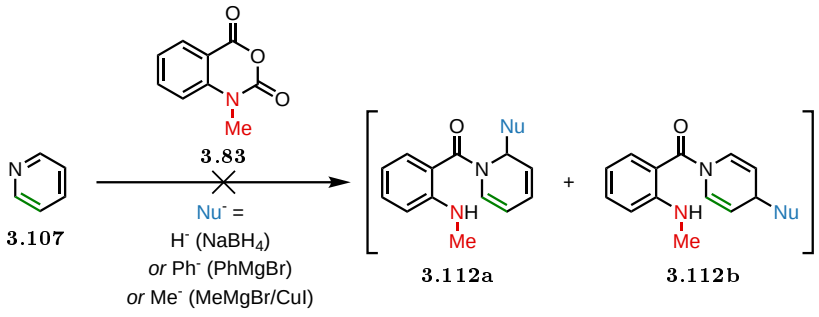
Scheme 3.20: *N*-Acylpyridinium salts **3.108** are activated for dearomatising nucleophilic addition to the ring.

Initial experiments attempted to recapitulate the 1,2-reduction of pyridine **3.107** after activation with a chloroformate, which was reported to proceed in moderate to good yield.[283] In the event, dearomatisation to form **3.110a** proceeded smoothly, but the yield of **3.110b** was significantly lower than reported in the literature due to stability issues (Scheme 3.21). Nevertheless, both reactions were found to proceed with complete regioselectivity, with no hydride attack at the 4-position of the pyridine. We postulated that treatment of **3.110b** with base could induce alkenyl migration to the benzylic centre to give ring-expanded product **3.111b**, with the phenyl ring serving as an anion-stabilising group. Unfortunately, subjection to LDA led to decomposition through cleavage of the carbamate linkage. Despite this, the successful activation of pyridine, and subsequent nucleophilic attack, motivated further exploration into the heterocyclic inflation of pyridine.



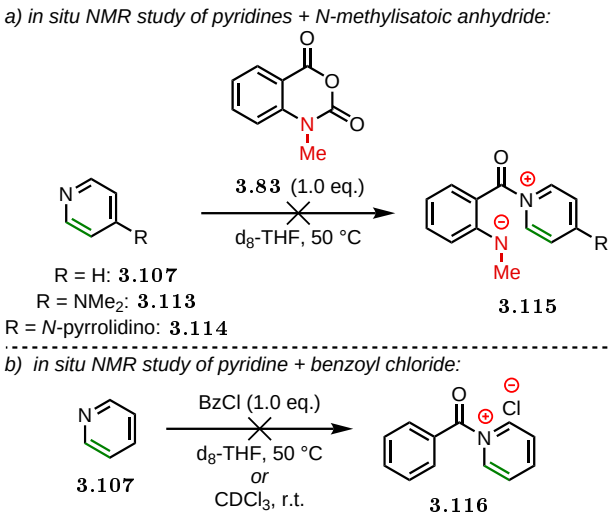
Scheme 3.21: Pyridine **3.107** can be activated with chloroformates and reduced with $NaBH_4$ to give carbamate products **3.110**.

In parallel to the ring expansion studies of anthranilamides (see Section 3.3.2.1), investigations were undertaken to establish whether *N*-methylisatoic anhydride **3.83** could serve to activate pyridine **3.107** towards nucleophilic attack (Scheme 3.22). However, dihydropyridine products **3.112** were not generated upon mixing pyridine **3.107**, *N*-methylisatoic anhydride **3.83**, and a nucleophile ($NaBH_4$, a Grignard reagent, or an organocopper reagent), with products of direct nucleophilic attack on anhydride **3.83** observed in each case.



Scheme 3.22: Attempts to activate pyridine **3.107** to nucleophilic attack by acylation with anhydride **3.83** were unsuccessful.

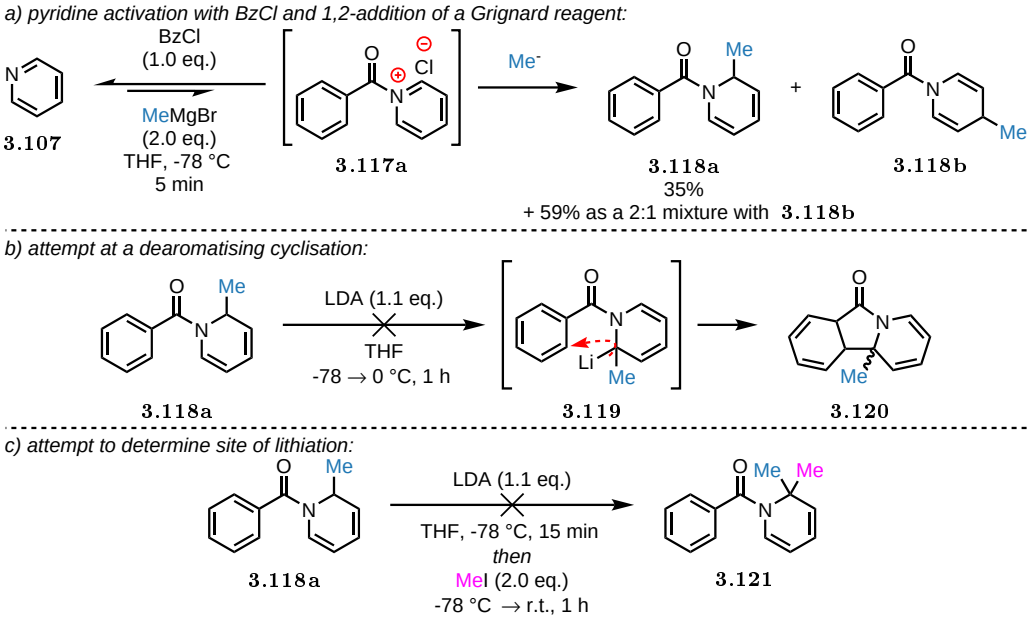
This prompted the in situ ^{1}H NMR study of mixtures of anhydride **3.83** and pyridine **3.107** — and some more nucleophilic pyridine derivatives, **3.113** and **3.114**. To our surprise, no change was observed upon heating to 50 °C in d_8-THF (Scheme 3.23a). Similarly, no formation of pyridinium salt **3.116** was observed when BzCl was employed as the electrophilic partner (Scheme 3.23b), a reagent known to be able to activate pyridine towards nucleophilic attack.[284]



Scheme 3.23: No formation of *N*-acylpyridinium formation could be observed by in situ ^{1}H NMR spectroscopy studies.

Having not seen any evidence of *N*-acylpyridinium formation by in situ NMR spectroscopy, the literature reaction between pyridine **3.107**, BzCl and a Grignard reagent was performed.[284] Interestingly, dihydropyridine products **3.118** were generated in high yield, with conversion found to be complete after just 5 min at −78 °C (Scheme 3.24a). As described in the literature, 1,2-dihydropyridine **3.118a** was the major product, with an approximate 4:1 ratio to the minor regioisomeric 1,4-dihydropyridine **3.118b**. Essentially no competing Grignard addition to the reactive electrophile BzCl was observed. Thus, the reaction between pyridine **3.107** and BzCl must be exceptionally fast. In addition, given that no formation of an intermediate *N*-acylpyridinium species **3.117a** could be observed by in situ NMR spectroscopy (see Scheme 3.23), this suggested that there is a rapid equilibrium between the reagents and the *N*-acylpyridinium salt **3.117a**, which is heavily biased towards the reagents. The reaction would then be driven to completion by the irreversible attack of the Grignard reagent on **3.117a**.

The Clayden group has an interest in dearomatising reactions, especially those featuring the attack of organolithiums onto aromatic systems.[60] Having already dearomatised the pyridine ring, we wondered whether the benzamide ring could also undergo dearomatisation. As such, 1,2-dihydropyridine **3.118a** was treated with LDA, with the hope of initiating a dearomatising cyclisation of organolithium **3.119** to form **3.120** (Scheme 3.24b). However, only starting material **3.118a** could be recovered. Repeating the reaction, and quenching the deep blue-coloured reaction with MeI, in order to confirm the position of lithiation was α to nitrogen, unfortunately led to decomposition (Scheme 3.24c). Nevertheless, these results demonstrated that 1,2-dihydropyridines could be rapidly accessed by reactions of acid chlorides with pyridines and a Grignard reagent, and it was envisioned that such dearomatisations could provide expedient entry to vinyl migration substrates.

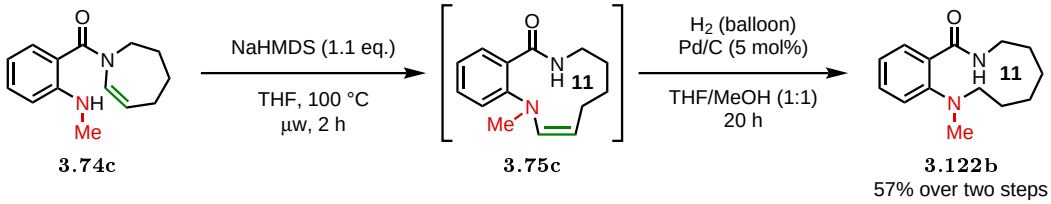


Scheme 3.24: Activation of pyridine **3.107** with BzCl allowed for nucleophilic addition of a Grignard reagent onto the ring.

3.3.4 Finding a direction to pursue

3.3.4.1 Anthranilamide series

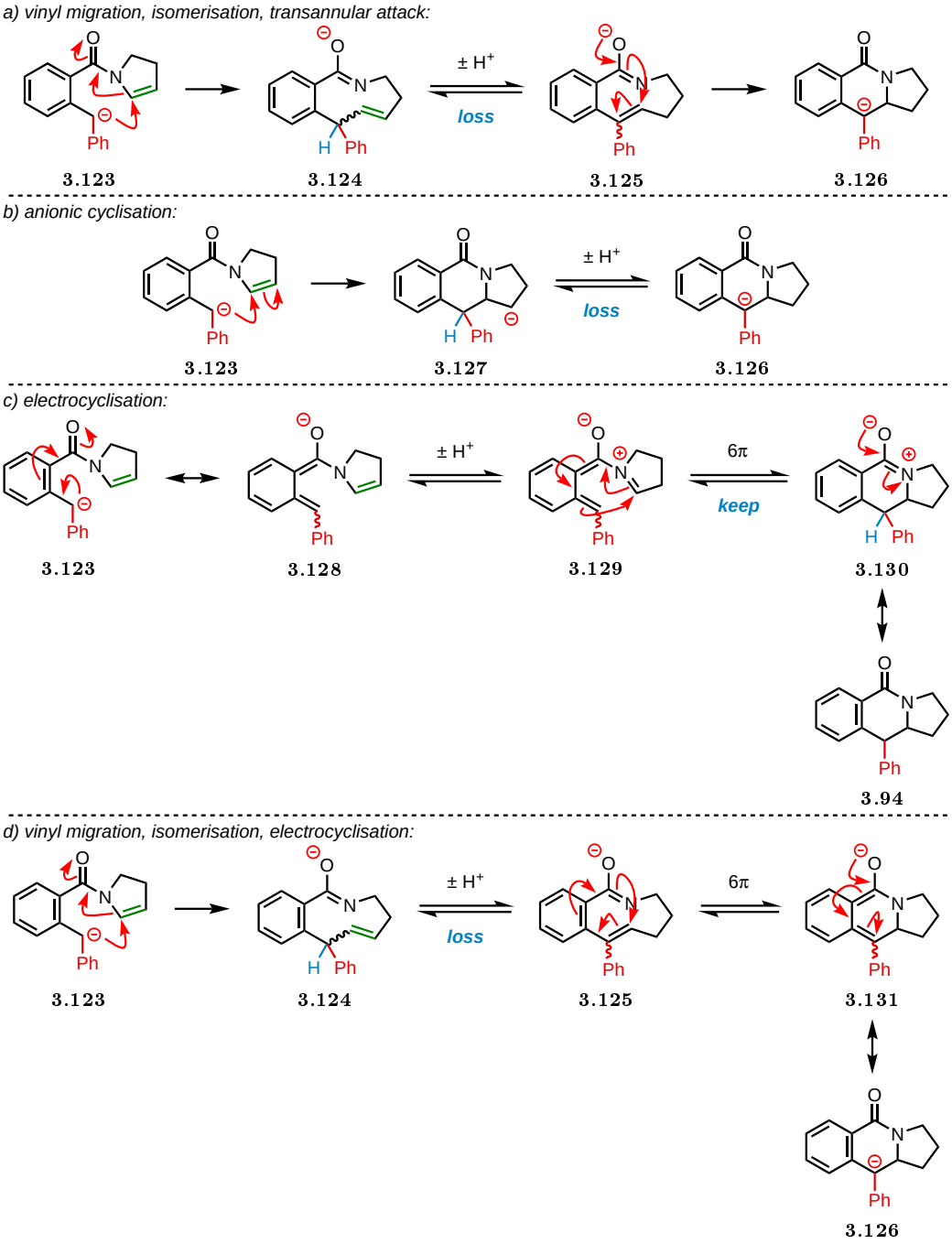
Despite promising reactivity seen for anthranilamide **3.74c** (see Section 3.3.2.1), it was unclear what the next steps should be, due to the difficulties with isolation of the ring-expanded product **3.75c**, and the transformation being successful for just a single ring size. However, the seven-membered anthranilamide **3.74c** could be ring-expanded to **3.75c**, and immediately hydrogenated to avoid hydroamination, enabling isolation of the reduced eleven-membered lactam **3.75c** in an unoptimised yield of 57% over two steps (Scheme 3.25). This served to demonstrate that ring-expanding vinyl migration was a viable route to medium-sized rings.



Scheme 3.25: Hydrogenation of crude **3.75c** could avoid hydroamination and allow for isolation of reduced medium ring product **3.122b**.

3.3.4.2 2-Benzylbenzamide series

We were intrigued that 2-benzylbenzamide substrates with different-sized rings all displayed similar reactivity, albeit to form undesired hydroalkylated products (see Section 3.3.2.2). Hence, efforts focused on redirecting reactivity towards ring expansion. Some potential mechanisms were considered to potentially establish how tricyclic compounds **3.94** could form from substrate anion **3.123** (Scheme 3.26).



Scheme 3.26: Some plausible mechanisms for the hydroalkylation of 2-benzylamide substrates **3.92**, illustrated for a five-membered ring substrate.

(a) the successful vinyl migration to amidate anion **3.124** could be followed by the likely favourable isomerisation of the double bond into conjugation with the two aromatic rings — reminiscent of the enamine–iminium tautomerisation that afflicted the anthranilamide series — and a transannular ring closure of **3.125** would lead to stabilised anion **3.126**.

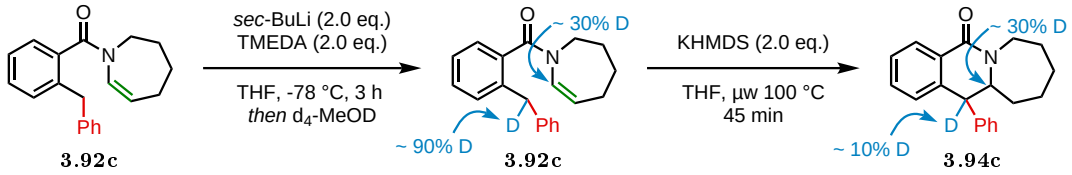
(b) rather than vinyl migration, an alternative could be the anionic cyclisation onto the alkene to form the unstabilised anion **3.127**; this may look unlikely, but rapid isomerisation to the more stabilised anion **3.126** would be expected.

(c) as opposed to an ionic mechanism, a third potential pathway could involve an electrocyclic ring closure; the starting material anion could be drawn as resonance form **3.128**, then the enamide could be protonated at the β-carbon — either by the HMDS generated during the initial deprotonation of the substrate, or from another molecule of protonated substrate — and a 6π electrocyclisation would produce **3.130**, a resonance structure of the hydroalkylation product **3.94**.

(d) a fourth conceivable mechanism could entail vinyl migration and isomerisation of the olefin to amidate anion **3.125**, which could undergo 6π electrocyclisation to **3.131**, a resonance form of **3.126**.

Notably, pathways (a) and (d) both involve the isomerisation of the alkene in product anion **3.124** into conjugation with the two arenes to give **3.125**. This is accompanied by loss of the proton at the benzylic position, highlighted in blue. Similarly, pathway (b) features loss of this benzylic proton. Thus, if this blue proton could be labelled, insight into the mechanism of hydroalkylation may be gained.

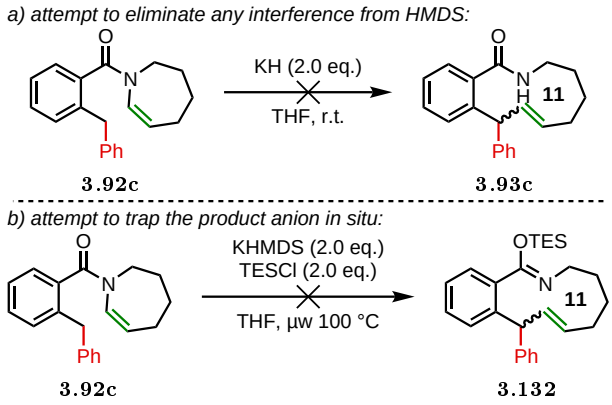
The benzylic position of seven-membered substrate **3.92c** was labelled with deuterium by forming an anion under conditions that did not lead to hydroalkylation, and quenching with a deuteron source: treatment of **3.92c** with *sec*-BuLi at −78 °C, and then adding d_4-MeOD led to approximately 90% incorporation of the isotopic label (Scheme 3.27). In addition, ca. 30% D at the α-position of the enamide was also observed, likely from γ-deprotonation, followed by α-reprotonation by d_4-MeOD in the quench; the incorporation of deuterium at this position would be inconsequential for the mechanistic study. Upon submission of the labelled substrate **3.92c** to the vinyl migration conditions, the hydroalkylation product **3.94** was isolated, and most of the isotopic label had been lost, with only around 10% D incorporation. Therefore, this investigation provided evidence to support the proposal that the isomerisation of the double bond in the product anion generated during the reaction, and subsequent transannular ring closure, was the pathway by which the desired ring-expanded compounds formed the unwanted hydroalkylated products **3.94**.



Scheme 3.27: The loss of the isotopic label during the reaction of deuterated **3.92c** to form hydroalkylated product **3.94c** supported the idea that the isomerisation of the double bond after vinyl migration drives formation of the tricyclic compounds from the products of ring expansion.

With some knowledge of how the target ring expansion products may form undesired tricyclic products by onward reactivity, we considered that HMDS, generated as the reaction proceeds, could be facilitating isomerisation by acting as a proton shuttle. Hence, a hydride base was tested, since it should deprotonate the substrate, but the conjugate acid, H_2 gas, would not act as a proton source. However, employing KH as the base, to retain the K^+ counterion, and stirring with **3.92c** at room temperature overnight simply led to recovery of starting material (Scheme 3.28a).

In a similar sense, the possibility of trapping the anion of the ring-expanded product in situ, immediately after its formation, was explored: silylating agents have an affinity for oxygen atoms on account of the strong Si−O bond,[285] and so we hoped that addition of TESCl to the reaction mixture could silylate the amidate anion to give **3.132**, which would presumably hydrolyse to **3.93c** upon work up, and thereby serve to prevent onward reaction of the product anion to the hydroalkylated product. In the event, a high degree of decomposition was observed, with no signs that the either the ring expansion or silicon trap was successful under these conditions (Scheme 3.28b).



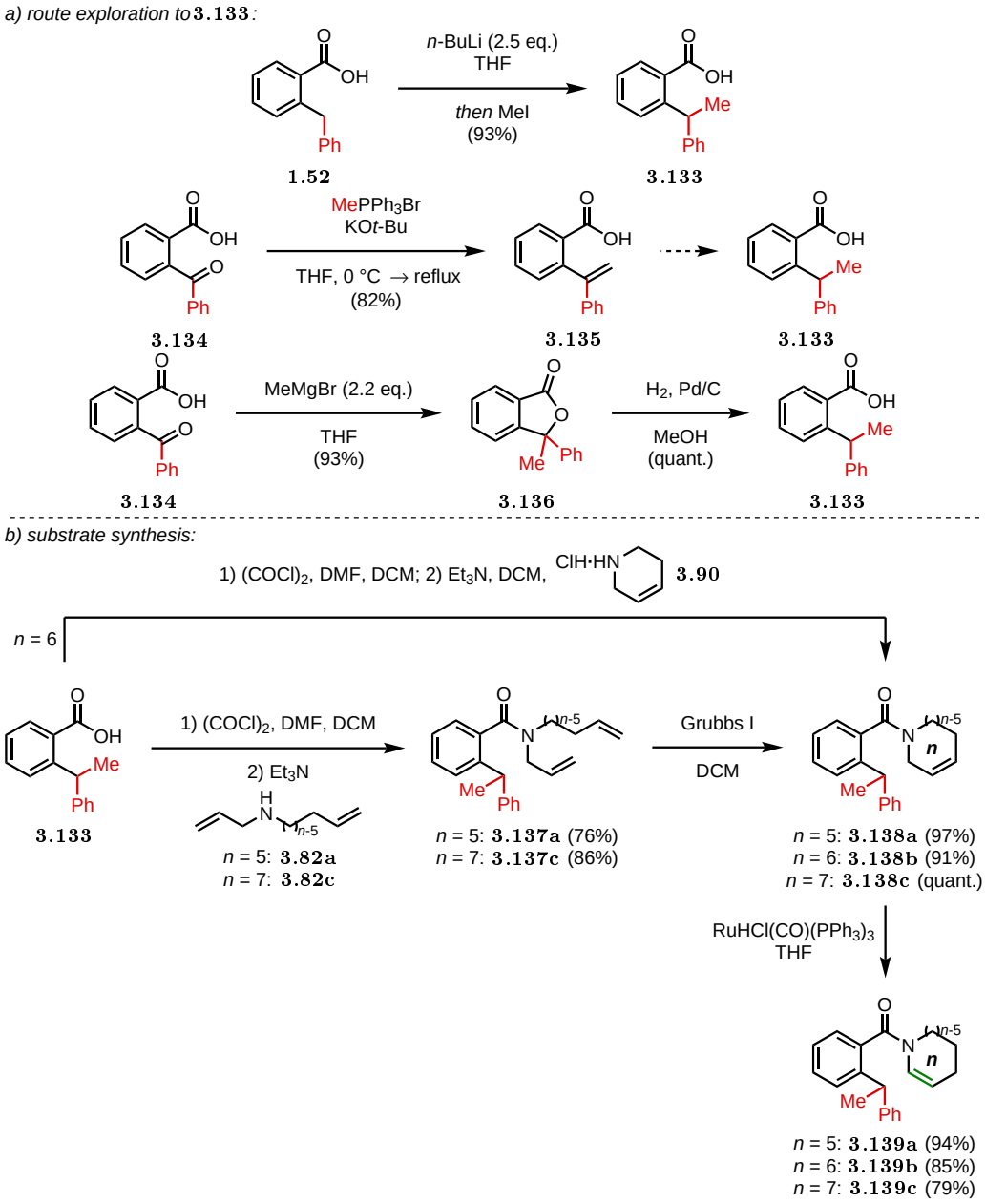
Scheme 3.28: Neither avoiding hydroalkylation by replacing KHMDS with KH, nor attempting to trap the ring expansion product by silylation, performed as intended.

3.3.4.3 2-(1-Phenylethyl)benzamide series

Introduction of a third substituent at the benzylic position of the 2-benzylbenzamide substrates **3.92** would remove the possibility of alkene isomerisation after the vinyl transfer step. However, we were aware this modification might preclude alkenyl transfer, on account of increased steric hindrance at the nucleophilic centre. Conversely, if this tactic were successful, the migration would enable assembly of sterically congested alkene products that bear a new all-carbon quaternary centre.

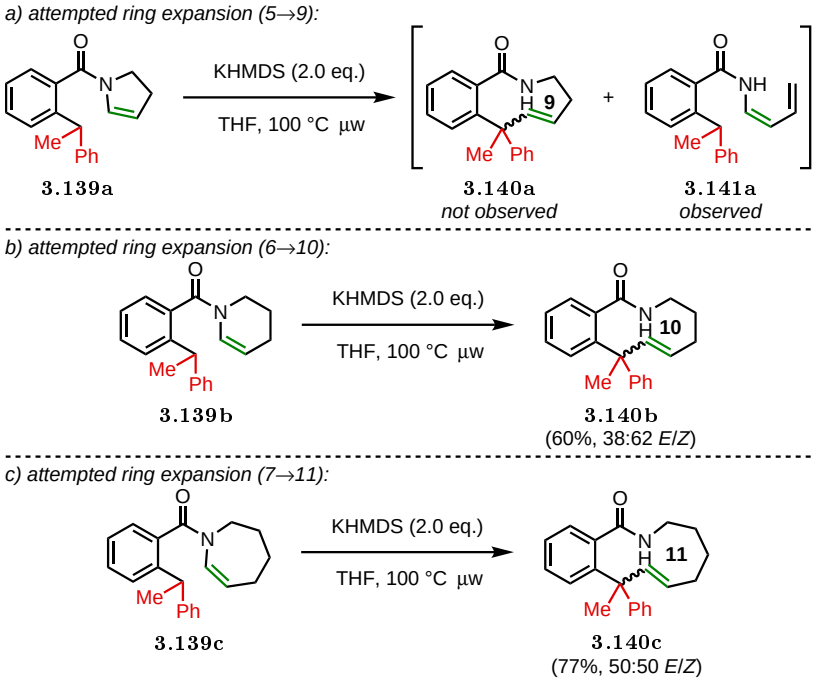
We targeted replacement of one of the benzylic protons by a methyl group, and three different routes to the required carboxylic acid starting material **3.133** were evaluated (Scheme 3.29a). A single step synthesis by benzylic methylation of 2-benzylbenzoic acid **1.52** seemed straightforward, but was susceptible to variation in isolated yield. This was because chromatographic purification of the product **3.133** was challenging: the poor separation from any remaining starting material was exacerbated by the carboxylic acid functionality causing tailing on the column.

A second approach was the Wittig reaction of 2-benzoylbenzoic acid **3.134** to **3.135**, which would be followed by reduction of the olefin. Although reported to proceed at room temperature,[286] in our hands, the methylenation required heating to reflux in THF to achieve acceptable conversion, and similar chromatography issues were encountered as in the direct methylation route. The most reliable, practical and scalable synthesis was found to be the Grignard addition to keto acid **3.134** to produce lactone **3.136**, an intermediate that was much easier to isolate in high purity by chromatography, followed by hydrogenolysis to the desired carboxylic acid **3.133**. With an optimal route to **3.133** established, substrates **3.139** could be accessed by amide formation, ring-closing metathesis and alkene isomerisation (Scheme 3.29b).



Scheme 3.29: Investigations into making 2-(1-phenylethyl)benzoic acid **3.133**, and elaboration to substrates **3.139** for ring-expanding vinyl migration.

With 2-(1-phenylethyl)benzamide substrates **3.139** in hand, they were submitted to ring expansion conditions (Scheme 3.30). Five-membered homologue **3.139a** did not lead to the intended product **3.140a**, but ring-opened compound **3.141a** was formed (Scheme 3.30a). This could derive from γ-deprotonation of the enamide and expulsion of the amidate anion as a leaving group. In contrast, we were delighted to find that the six-membered 2-(1-phenylethyl)benzamide **3.139b** underwent vinyl migration to the ten-membered lactam **3.140b** in a respectable yield (Scheme 3.30b). The reaction yielded both *E*- and *Z*-configured products, which could be separated by column chromatography, with a slight preference for formation of the *Z*-product observed. Similarly, seven-membered congener **3.139c** returned medium ring **3.140c** in good yield, with equimolar amounts of *E*- and *Z*-isomers formed (Scheme 3.30c).



Scheme 3.30: Although the vinyl transfer reaction of five-membered substrate **3.139a** was unsuccessful, the six-membered **3.139b** and seven-membered **3.139c** substrates underwent ring expansion by vinyl migration to give corresponding medium-sized lactams **3.140b** and **3.140c** as a mixture of *E*- and *Z*-isomers.

In contrast to the stereoretentive migration of *N*-vinyl ureas previously reported by the Clayden group (see Scheme 3.11), it was intriguing that mixtures of alkene isomers were produced in the reaction of *N*-vinyl amides **3.139**. This may give clues as to the mechanism of this remarkable transformation, and further mechanistic investigation is required. At this point, it is worth noting that separately resubjecting each isomer of **3.140c** to the ring expansion conditions did not lead to any observable isomerisation of the double bond geometry. This suggested that the olefin geometry was established during the vinyl transfer, and the reaction products **3.140b** and **3.140c** were not subject to any post-migratory isomerisation, which one could envisage may be promoted by transannular interaction of the amidate anion with the alkene.

3.3.5 Exploring and expanding the utility of the reaction

We were pleased that medium ring lactams could be prepared and isolated by ring-expanding vinyl migration of 2-(1-phenylethyl)benzamides **3.139**. However, we wanted to explore avenues to broaden the applicability of the vinyl transfer reaction towards generating valuable ring-expanded products with diverse structures (Figure 3.6). Four key areas of the substrate were identified for investigation:

1. Migrating group: other than simple six- and seven-membered rings, could vinyl transfer occur with non-cyclic alkenes, and could the broad availability of heterocycles, like pyridine, be exploited to access ring expansion substrates?
2. Anion-stabilising group: what is the scope for employing a wider variety of substituents here?
3. Backbone scaffold: can this aromatic ring be replaced with a simple alkene to deliver non-benzannulated products?
4. Tether: the amide tether is thought to be crucial to the reactivity, but can other linkages also enforce the conformation required for the vinyl shift?

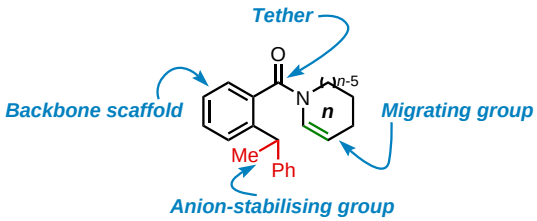


Figure 3.6: Areas for exploration to establish and develop the utility of the ring-expanding vinyl migrations of 2-(1-phenylethyl)benzamides.

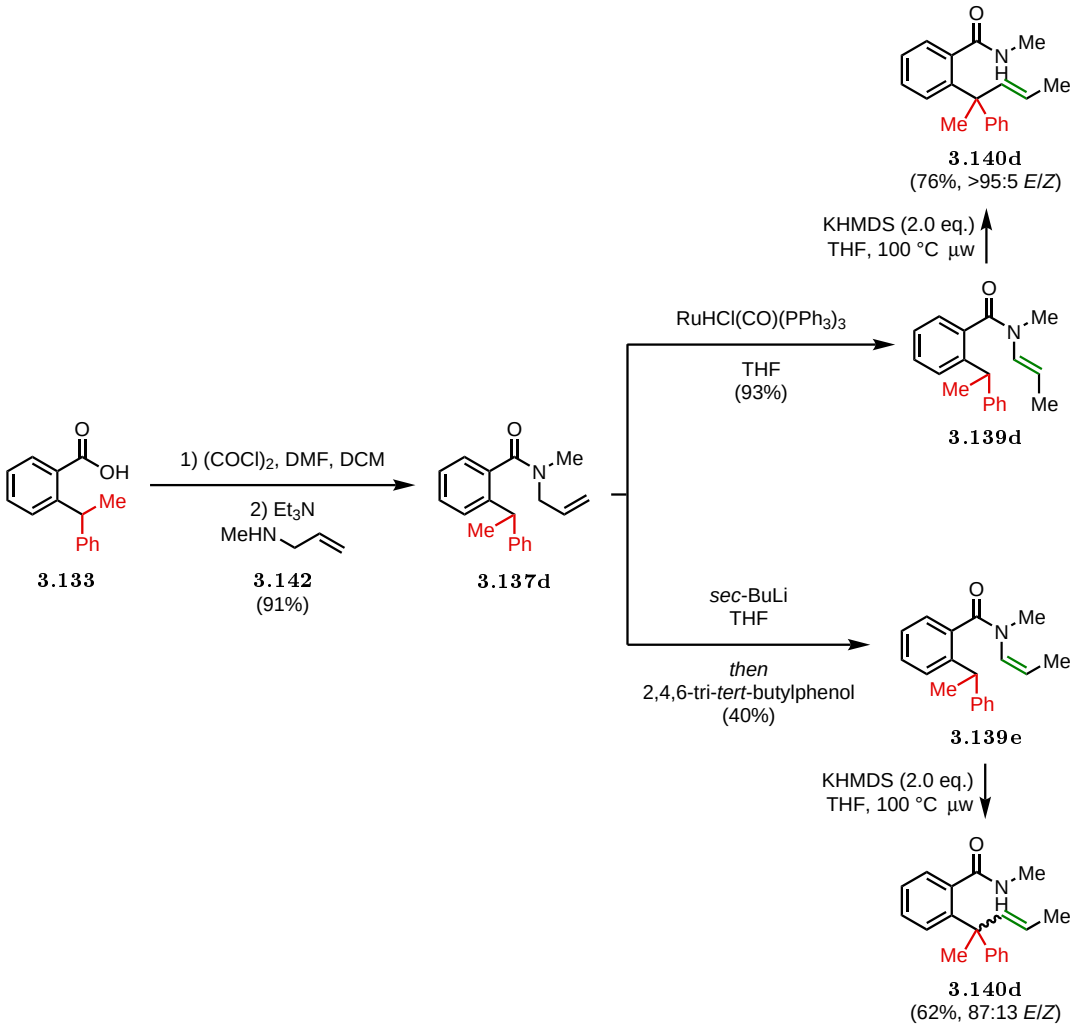
3.3.5.1 Changing the migrating group

Non-ring expansive vinyl migrations

Since the vinylation of 2-(1-phenylethyl)benzamides generates hindered alkene-containing products, the migration of olefins not part of a heterocycle may also be of interest. In addition, with the alkene no longer incorporated into a ring, both *E*- and *Z*-configured substrates could be independently synthesised, the rearrangement of which could give rise to different selectivities for the double bond geometry of the migration products.

The synthesis of both the *E*-configured **3.139d** and *Z*-configured **3.139e** substrates was pursued (Scheme 3.31). Amide coupling was followed by isomerisation of the allyl group to a vinyl group. The Ru catalyst system yielded exclusively the *E*-configured vinyl amide **3.139d**,[287] whereas α-deprotonation by *sec*-BuLi and γ-reprotonation with 2,4,6-tri-*tert*-butylphenol, a bulky proton source, gave a separable mixture of the *Z*-configured substrate **3.139e** and recoverable starting material **3.137d**.[276] Employing LDA as the base instead of *sec*-BuLi gave comparable results.

Then, the vinyl shifts were tested, and pleasingly, KHMDS prompted alkenyl migration of *E*-configured substrate **3.139d** to **3.140d** with complete retention of the alkene geometry (Scheme 3.31). Under identical conditions, the substrate with a *Z*-configured double bond **3.139e** underwent migration to **3.140d** as an inseparable mixture of *E*- and *Z*-products in a 87:13 ratio. Both migration of **3.139d** and **3.139e** yielded **3.140d** with an *E*-configured alkene as the major product. This may be explained by vinyl transfer proceeding, at least partially, by an addition–elimination mechanism, in which the double bond geometry of the substrate would be lost.

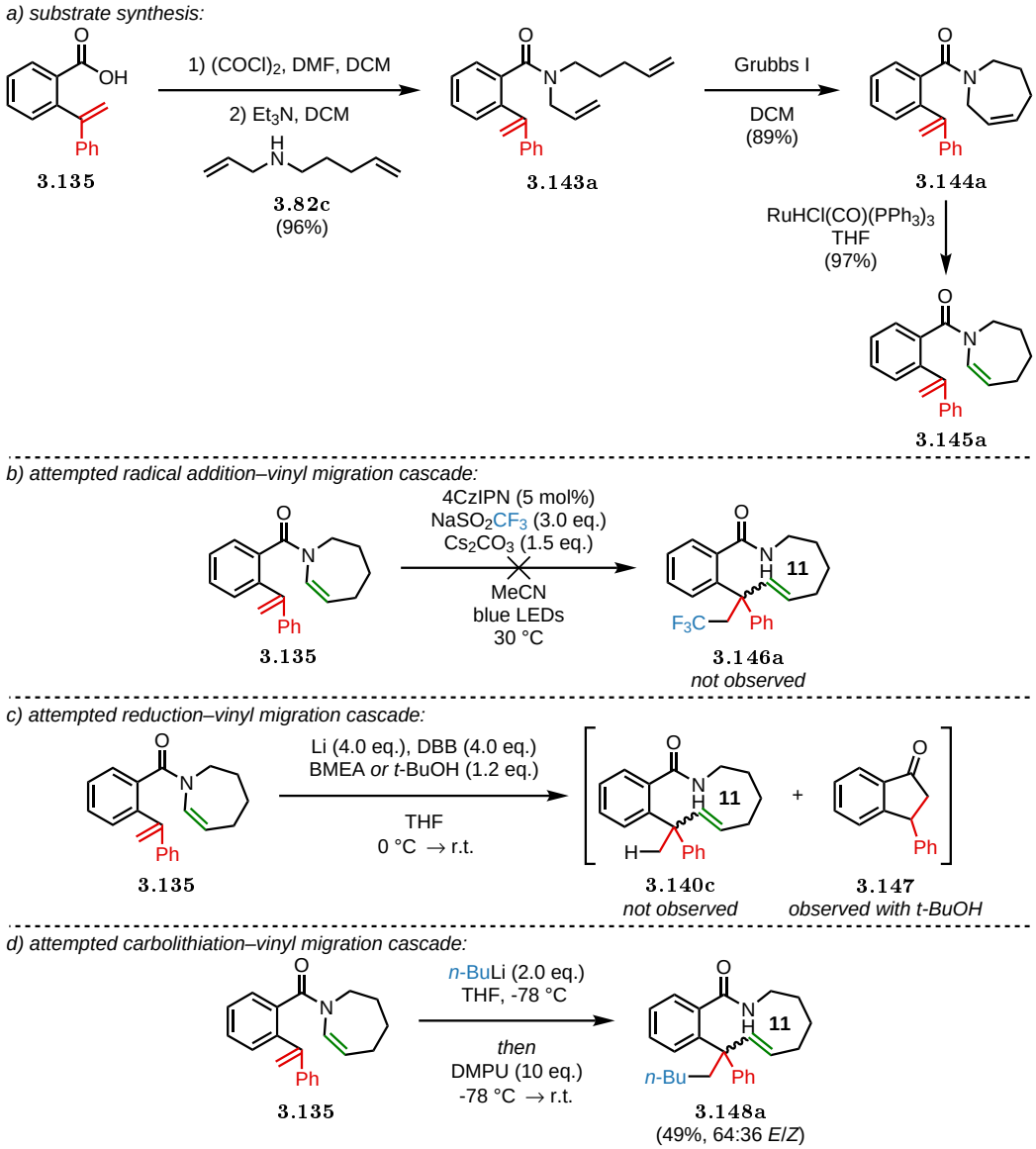


Scheme 3.31: Preparation of acyclic 2-(1-phenylethyl)benzamides **3.139d** and **3.139e**, and successful non-ring expansive alkenyl migration to sterically congested alkenylated product **3.140d**.

2-(1-Phenylvinyl)benzamide series

2-(1-Phenylvinyl)benzoic acid **3.135** had been previously prepared (see Scheme 3.29a), and we wanted to investigate whether attack on the terminal olefin could be followed by a spontaneous vinyl migration. Hence, seven-membered substrate **3.145a** was synthesised (Scheme 3.32a), and submitted to photoredox conditions that had been previously employed by the Clayden group for the radical addition–aryl migration of *N*-vinyl ureas (Scheme 3.32b).[288] Unfortunately, a

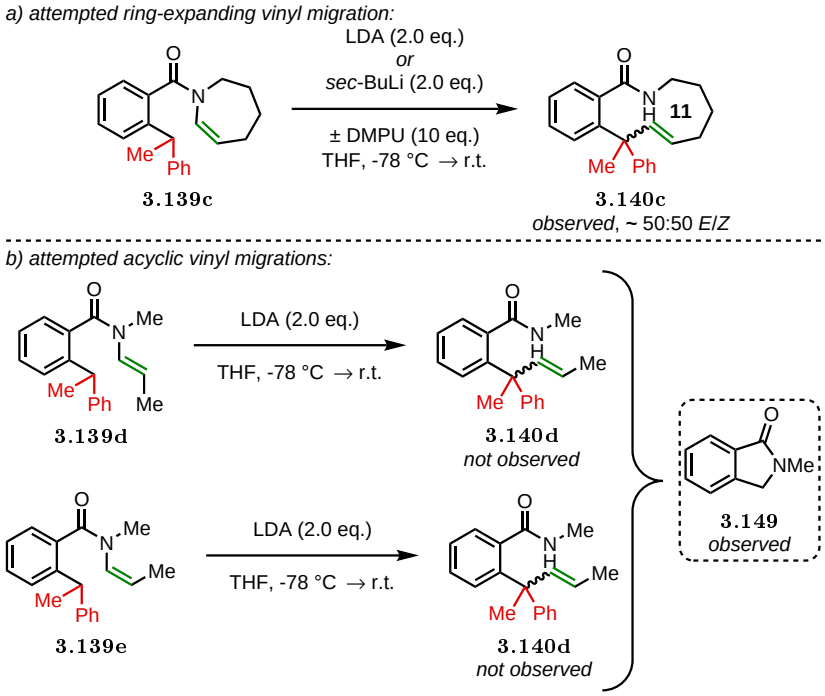
mixture of many compounds resulted, none of which were able to be characterised, with no evidence that the desired eleven-membered lactam **3.146a** was formed. Attempts to initiate vinyl migration by reduction using LiDBB and a proton source, BMEA, were also unsuccessful (Scheme 3.32c).[289] Trialling a more acidic proton source, *t*-BuOH, led to formation of ketone **3.147**, likely arising from reduction of the 1-phenylvinyl motif to an anion at the terminal position, followed by intramolecular attack on the carbonyl. However, we were pleased to discover that treating **3.145a** with *n*-BuLi at −78 °C, then adding DMPU and warming to room temperature, afforded **3.148a** in a 49% yield as a separable mixture of *E*- and *Z*-isomers (Scheme 3.32d). This carbolithiation–vinyl migration cascade, therefore, offered potential access to a variety of medium-sized products bearing alkyl groups other than just methyl.



Scheme 3.32: The seven-membered 2-(1-phenylvinyl)benzamide **3.145a** was prepared, and cascade reactions attempted that involved attack at the terminal olefin and subsequent alkenyl translocation.

Exploring Li bases

Having discovered that the organolithium generated by carbolithiation underwent vinyl migration (see Scheme 3.32d), the application of stronger bases with a Li counterion for vinyl migration were investigated. This would likely reduce the reaction temperature required, and may lead to changes in geometry selectivity of alkenyl transfer. Both LDA and *sec*-BuLi were competent for the ring-expanding vinyl migration of seven-membered substrate **3.139c** (Scheme 3.33); the addition of a THF solution of **3.139c** to the base was carried out at −78 °C, and the reaction mixtures stirred at room temperature overnight, after which complete starting material consumption was seen. However, both the isolated yields and ratios of isomers for **3.140c** were similar to the reactions carried out with KHMDS and microwave irradiation. Addition of an excess of DMPU to the reactions with either Li base gave similar results. Interestingly, both the acyclic substrates **3.139d** and **3.139e** did not undergo vinyl migration when LDA was employed as the base. The reaction mixtures were messy and there were signs of an intermolecular acyl shift occurring. Curiously, 2-methylisoindolin-1-one **3.149** was the only identifiable product from the reactions of the acyclic substrates; the pathway for its formation is not immediately obvious.

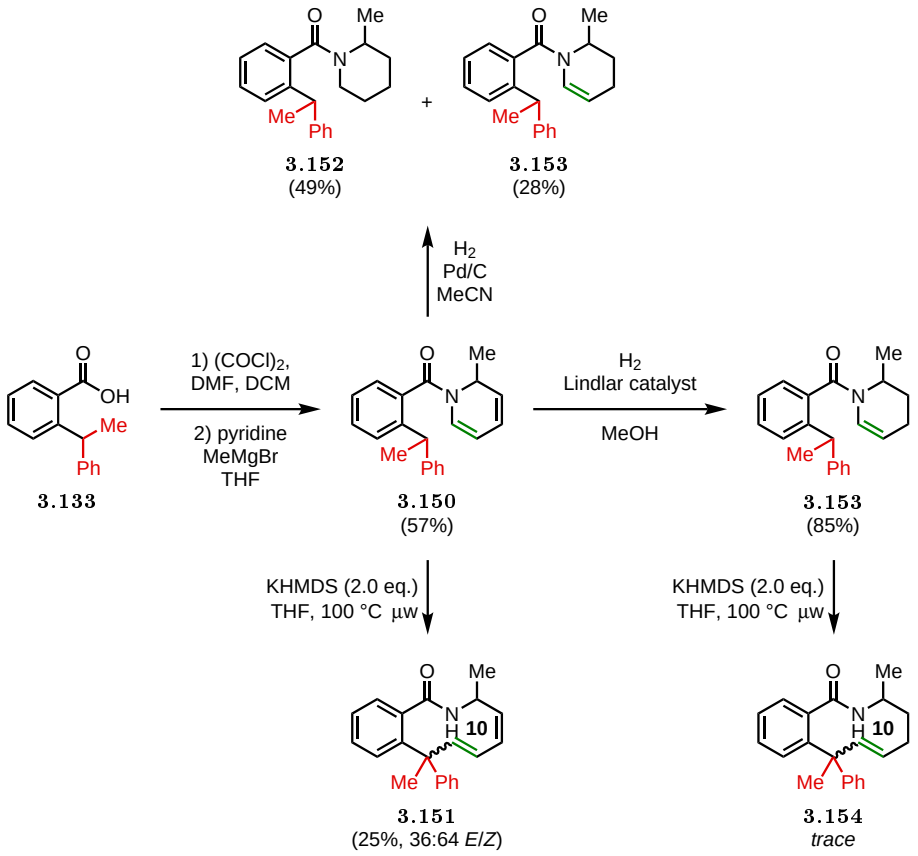


Scheme 3.33: Attempts to use Li bases for the vinyl migrations of 2-(1-phenylethyl)benzamides **3.139**.

Ring expansion of pyridine

We hoped to make use of common-sized heterocycles, like pyridine, to rapidly generate ring expansion substrates, building on the work from Section 3.3.3. Accordingly, we found the acyl chloride of acid **3.133** could be reacted with pyridine and MeMgBr to give 1,2-dihydropyridine **3.150**.[284] No formation of the 1,4-addition product was observed. Pleasingly, dihydropyridine **3.150** could undergo ring expansion, in a previously unexplored migration of a diene, to give ten-membered lactam **3.151** as a separable mixture of *E*- and *Z*-isomers, albeit in

a messy reaction with a relatively low yield of **3.151**. Employing Pd/C in trial hydrogenations of **3.150**, with the aim of selective reduction of the dienamide $C_\gamma = C_\delta$ bond often led to over-reduction to the fully saturated piperidine product **3.152**, with poor yields of the desired tetrahydropyridine **3.153**.[290] But it was discovered that Lindlar's catalyst enabled selective reduction to provide **3.153** in high yield.[291] However, after attempting to effect ring expansion with KHMDS, only trace amounts of **3.154** could be isolated. Despite a cleaner reaction profile than diene **3.150**, the conversion of this substrate was markedly slower, and so a longer reaction time may be required to produce **3.154** in synthetically useful yields.

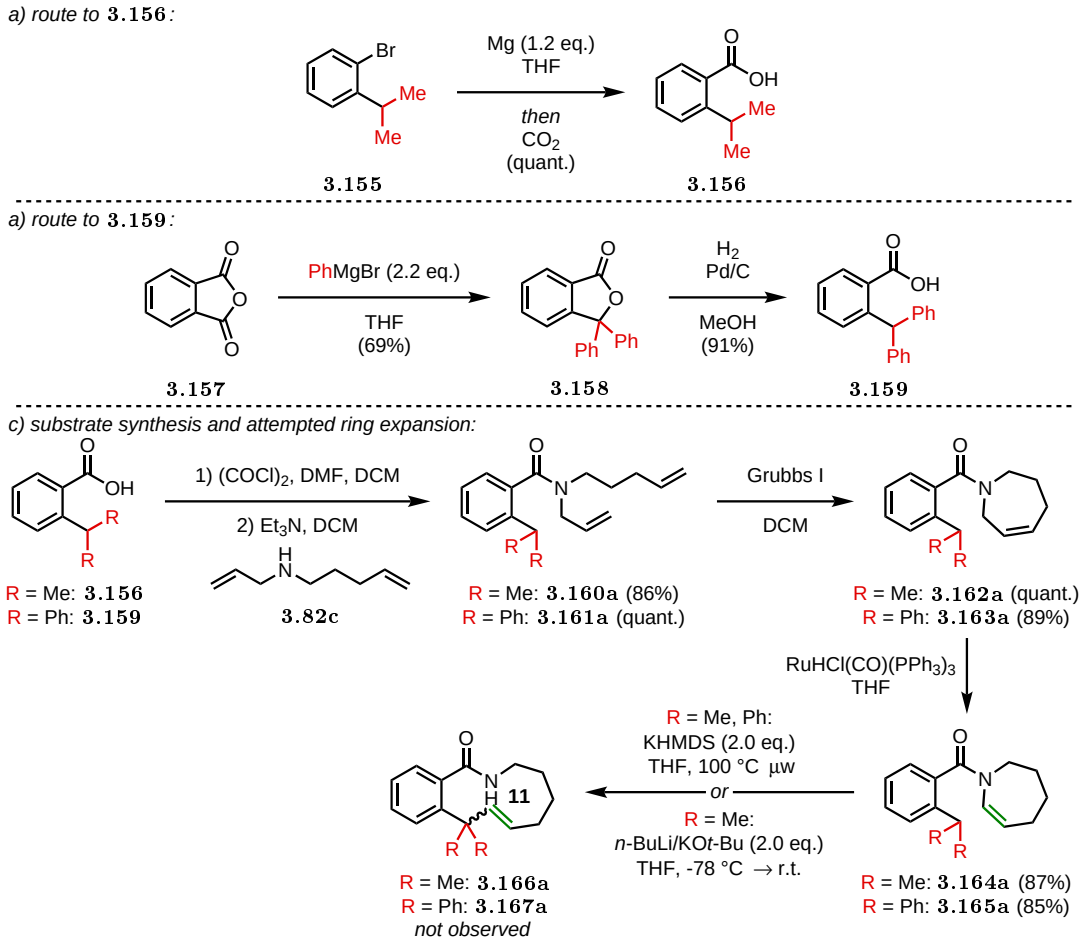


Scheme 3.34: Pyridine can be exploited to rapidly access 2-(1-phenylethyl)benzamide substrates **3.150** and **3.153** for application in ring expansive alkenyl migration reactions.

3.3.5.2 Changing the anion-stabilising group

In an effort to diversify the medium ring-containing products that could be accessed, we considered other anion-stabilising groups aside from 2-(1-phenylethyl). Benzoic acids substituted at the 2-position with either an isopropyl group **3.156** (Scheme 3.35a) or a benzhydryl group **3.159** (Scheme 3.35b) were readily prepared, and then elaborated to seven-membered substrates **3.164a** and **3.165a** to investigate the viability of these anion-stabilising groups in ring-expanding alkenylations (Scheme 3.35b).

Unfortunately, both 2-isopropylbenzamide **3.164a** and 2-benzhydrylbenzamide **3.165a** were found to decompose when treated with KHMDS (Scheme 3.35c). In either case, there was no evidence of successful ring expansion. In the event that the less acidic substrate **3.164a** required a stronger base to induce migration, the ring expansion was trialled with *n*-BuLi/KO*t*-Bu superbase,[292] but similarly led to decomposition. These results suggested that the 2-(1-phenylethyl) moiety may offer a balance of anion stabilisation and steric bulk, with neither the less stabilising, less hindered 2-isopropyl group of **3.164a**, nor the more stabilising, more hindered 2-benzhydryl motif in **3.165a**, proving fruitful for supporting vinyl migration.

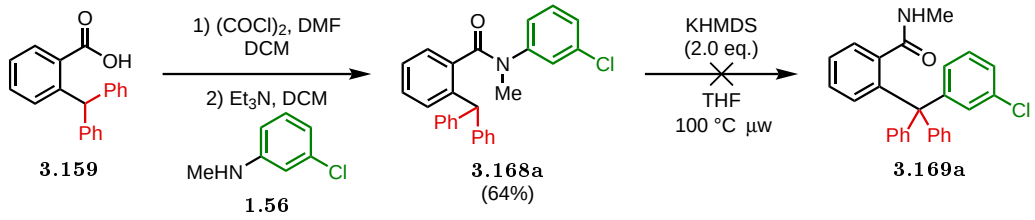


Scheme 3.35: Synthetic route to and attempted vinylation of 2-isopropylbenzamide **3.164a** and 2-benzhydrylbenzamide **3.165a**.

Aryl migration

Since the aryl migration to 2-benzylbenzamides to form triarylmethanes has precedent within the Clayden group (see Chapter 1),[293] it was expected that 2-benzhydrylbenzamide **3.168a** may undergo aryl migration to form highly hindered tetraarylmethane **3.169a** (Scheme 3.36). Promisingly, the starting material **3.168a** underwent conversion to one major product upon heating with base. However, the product NMR spectra were not consistent with structure **3.169a**. The exact structure of the reaction product could not be confirmed, despite analysis by NMR, IR and MS. The lack of a C=O or N–H bond, but the presence of an N–Me bond, an isotopic pattern by MS consistent with a

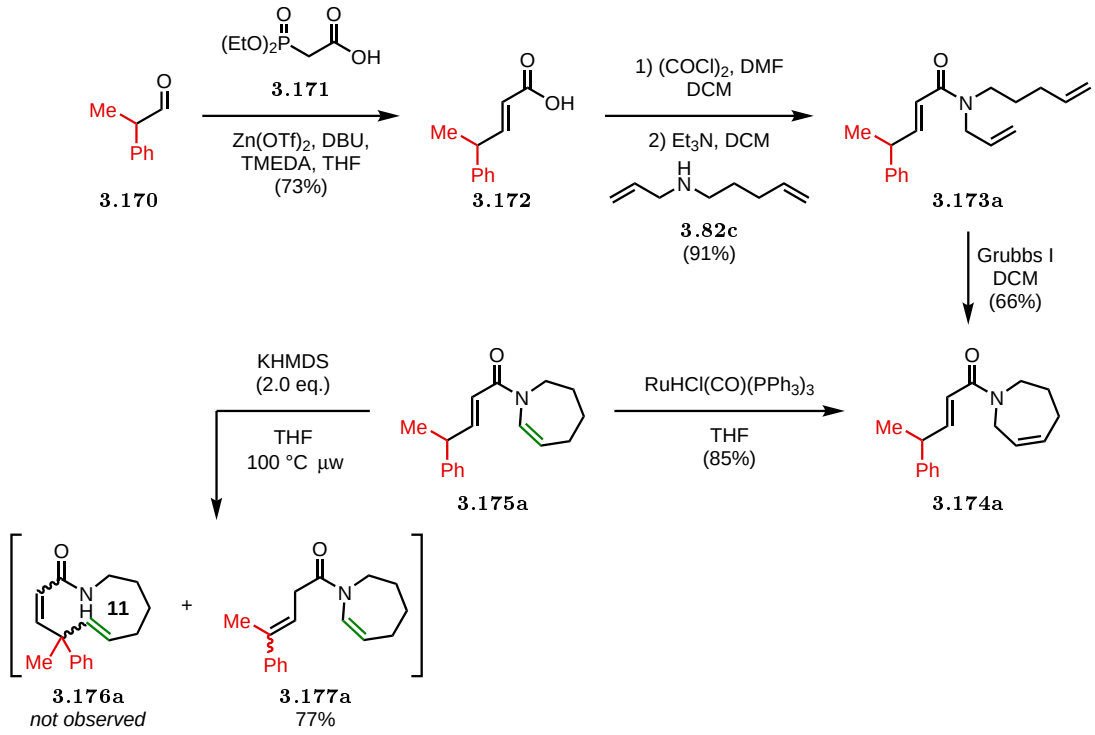
monochlorinated compound, and a major monoisotopic mass of 407 (the major monoisotopic mass of **3.168a** is 411), all point towards a reaction in which an aromatic ring is attacked. Since the desired product could not observed, this aryl transfer reaction was not investigated further.



Scheme 3.36: Attempted preparation of tetraarylmethane **3.169a**.

3.3.5.3 Changing the backbone scaffold

The next substrate modification pursued was replacement of the backbone aromatic ring with a simple alkene, in order to explore access to non-benzannulated products. Substrate preparation commenced with a Zn-promoted Horner–Wadsworth–Emmons reaction of 2-phenylpropionaldehyde **3.170** and commercially available diethylphosphonoacetic acid **3.171**, which selectively produced α,β-unsaturated acid **3.172** with an *E*-configured double bond (Scheme 3.37).[294] Amide coupling with **3.82c**, ring-closing metathesis, and alkene isomerisation yielded the acrylamide substrate **3.175a**.



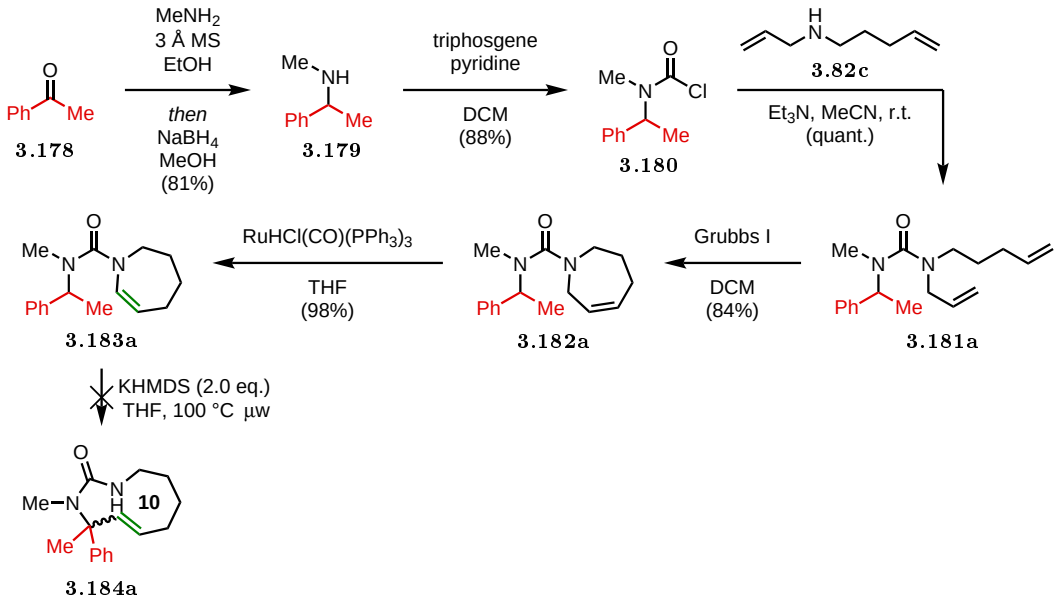
Scheme 3.37: Synthesis of acrylamide substrate **3.175a** and attempted ring-expanding vinylation to **3.176a**.

It was hoped that, upon deprotonation at the γ-position to the carbonyl, rotation about the $C_\alpha - C_\beta$ bond would be possible, which would place the deprotonated C_γ in close proximity to the migrating alkene. Whilst submitting substrate **3.175a** to ring expansion conditions resulted in one main product (Scheme 3.37), upon NMR analysis, it was clear that this was not the desired compound **3.176a**. There ought to be four olefin signals in ^{1}H NMR spectrum of **3.176a**, but there were only three for the major product, which was deduced to be the isomerised starting material **3.177a**, arising from α-reprotonation; similar reactivity was seen with the 3,3-dimethylacrylamide series (see Section 3.3.2.3).

3.3.5.4 Changing the tether

As well as amides, the Clayden group have found that migration chemistry is compatible with urea, carbamate and thiocarbamate tethers (see Section 1.2). Ongoing work within the group has demonstrated that *N*-vinyl ureas are competent in alkenyl migrations.[295] If the ring-expanding vinyl transfer with a 2-(1-phenylethyl) anion-stabilising group could be translated to ureas, it would facilitate preparation of medium-sized urea products.

Seven-membered urea substrate **3.183a** could be traced back to acetophenone **3.178** (Scheme 3.38). Reductive amination with $MeNH_2$ was followed by formation of urea **3.181a** via carbamoyl chloride **3.180**. The seven-membered ring was constructed by ring-closing metathesis, and the olefin isomerised to deliver substrate **3.183a**. Upon heating with KHMDS, complete consumption of **3.183a** was observed to give two main products. However, after isolation and analysis by NMR, neither compound gave rise to the signals expected for the olefin-containing ten-membered urea product **3.184a**, and their structures could not be determined.



Scheme 3.38: Preparation of urea-tethered substrate **3.183a** and unsuccessful ring-expanding alkenyl translocation.

3.3.6 Towards a mechanistic study

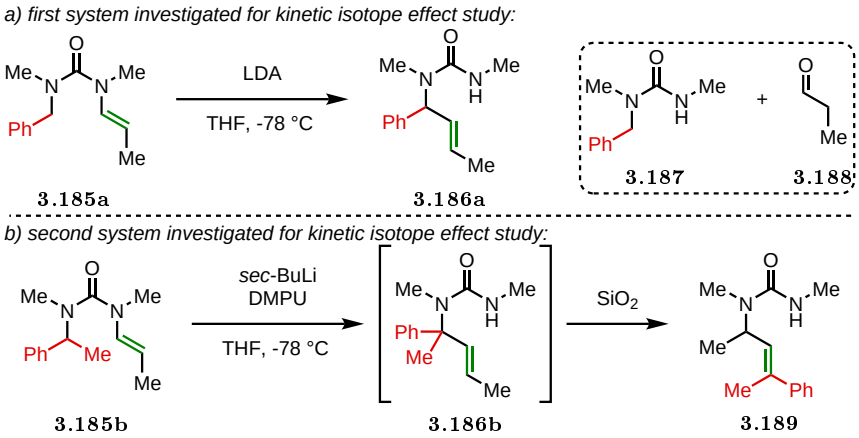
Having spent considerable effort exploring avenues to improve the utility of vinylations of 2-(1-phenylethyl)benzamides (see Section 3.3.5), aside from being able to access valuable medium ring scaffolds, we had hoped to gain some insight into the mechanism of these highly unusual nucleophilic substitution reactions of unactivated alkenes. In particular, we thought kinetic isotope effect experiments may help to clarify whether the S_NV proceeds through a stepwise addition–elimination process, a concerted vinylation, or something in between. To avoid the challenges with selective isotopic labelling of each position of the vinyl group, we hoped to measure the kinetic isotope effect at the natural isotopic abundance of ^{13}C.[296] This would represent an intermolecular competition between reactions of ^{12}C- and ^{13}C-containing substrate molecules.

To carry out such a study,* we required an appropriate reaction system that involved clean conversion of substrate to product in an isothermal reaction, with accurate, reproducible control over the level of conversion. In addition, since the analysis would be performed on either the recovered starting material or the isolated product, the substrate and product should be separable from one another. With quantitative NMR serving as the analytical method, the spectra ought not to be complicated by rotamers or overlapping signals.

Given the vinyl migration of amide-tethered substrates described in this chapter did not satisfy these requirements, we considered the vinylation of urea **3.185a**, which had been previously carried out within the Clayden group (Scheme 3.39a).[295] Although the migration reaction was clean, and suitable for analysis by NMR, essentially full conversion was observed after just a few minutes at −78 °C, which prevented controlling the conversion by quenching the reaction before completion. Reducing the stoichiometry of LDA did provide a means to control the conversion, however, under these conditions, side-products derived from C−N bond cleavage **3.187** and **3.188** were found to form.

An alternative alkenyl migration reaction was interrogated (Scheme 3.39b).[274] The reaction of **3.185b** was clean, however, product **3.186b** is unstable with respect to rearrangement to **3.189** on silica. Although this would preclude a product-based analysis, the NMR spectra of the starting material are uncomplicated by rotamers. In $CDCl_3$, some decomposition could be observed, but this was solved by recording NMR spectra in d_8-PhMe. Since *sec*-BuLi is sold as solution in cyclohexane, a solvent that has a melting point of ca. 7 °C,[297] for the addition of base at −78 °C, the commercial *sec*-BuLi/cyclohexane solution required dilution in THF. Once again, conversion could be controlled by altering the stoichiometry of base, although this proved challenging to do reproducibly, with varying conversion levels obtained in replicate experiments ran side-by-side. This was discerned to be due inconsistencies in the dropwise addition of a specific volume of *sec*-BuLi/cyclohexane/THF solution at −78 °C under inert atmosphere. This addition was performed using standard inert atmosphere techniques, but could not be done reliably, without significant warming and/or exposure to moisture. Given these practical difficulties, further mechanistic investigation was paused.

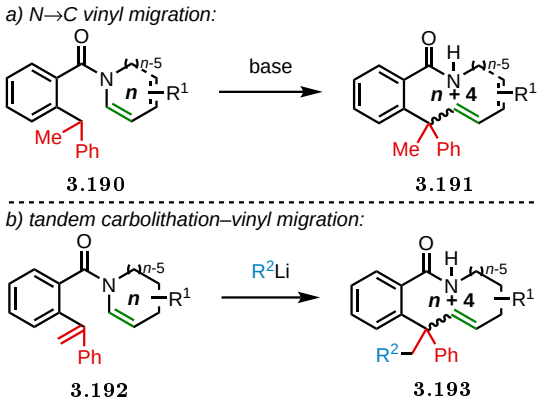
*Work towards a kinetic isotope effect study was performed under the guidance of Eugene E. Kwan, Merck.



Scheme 3.39: Two systems were examined as candidates for a kinetic isotope effect study of conformationally-enhanced S_NV reactions.

3.4 Conclusion

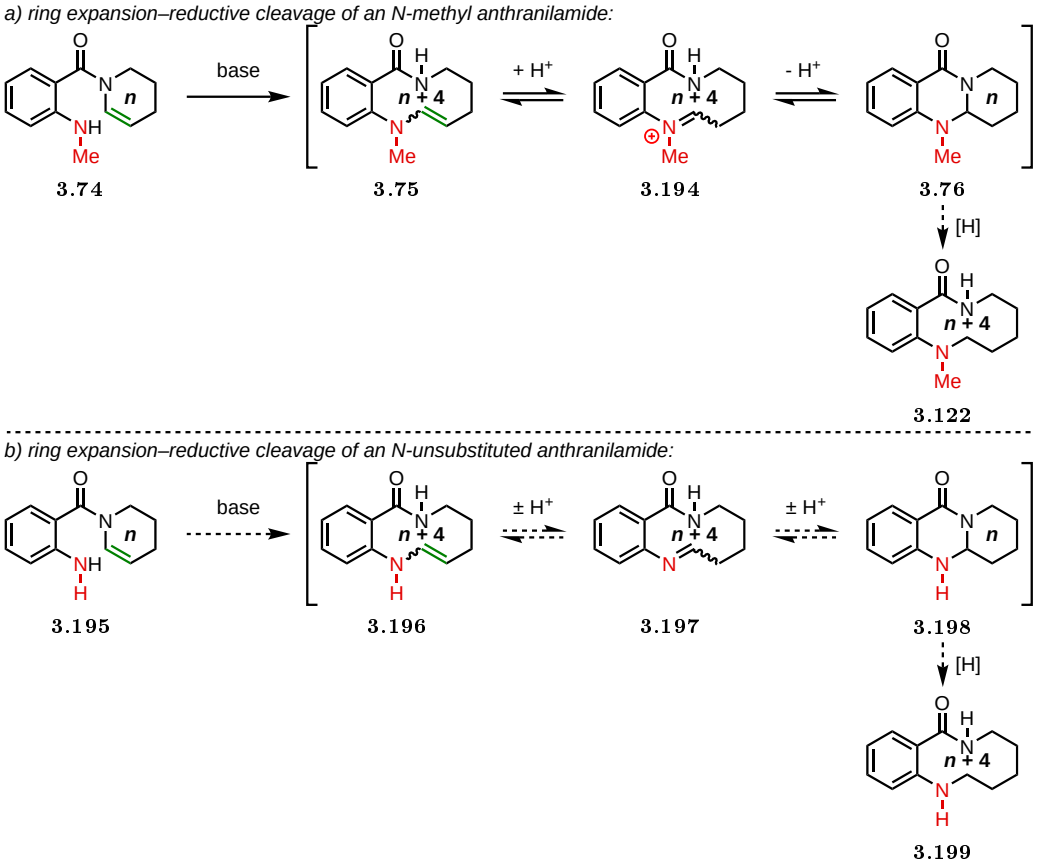
Medium ring-containing compounds have the potential to offer properties that are favourable in the pursuit of new pharmaceuticals and agrochemicals, which continues to motivate efforts to identify solutions to their challenging synthesis. The strategy of ring expansion has demonstrated promise to overcome the barriers that limit the application of end-to-end cyclisation methods. This chapter examines the construction of medium-sized rings by the migratory ring expansion of alkenes, an ambitious but highly attractive approach that would offer the opportunity to access enlarged cyclic frameworks with diverse structure. The discovered transformation was found to be successful for 2-(1-phenylethyl) benzamides **3.190**, capable of forming sterically congested alkene products **3.191** (Scheme 3.40a). The methodology allows for migration of either cyclic or acyclic olefins, including structures derived expediently by the dearomatisation of pyridine. However, the reaction is unfortunately restricted by requiring the substrate to feature an amide tether, the backbone aromatic, and an aryl/alkyl anion-stabilising group. Although some structural variation can be achieved by a carbolithiation–vinyl migration cascade of 2-(1-phenylvinyl) benzamides **3.192** (Scheme 3.40b), overall, access to only a limited range of products was achievable by vinylation of amide substrates.



Scheme 3.40: 2-(1-Phenylethyl)benzamides **3.190** are competent substrates for vinyl migration, and 2-(1-phenylvinyl)benzamides **3.192** can participate in a carbolithiation–vinyl migration cascade.

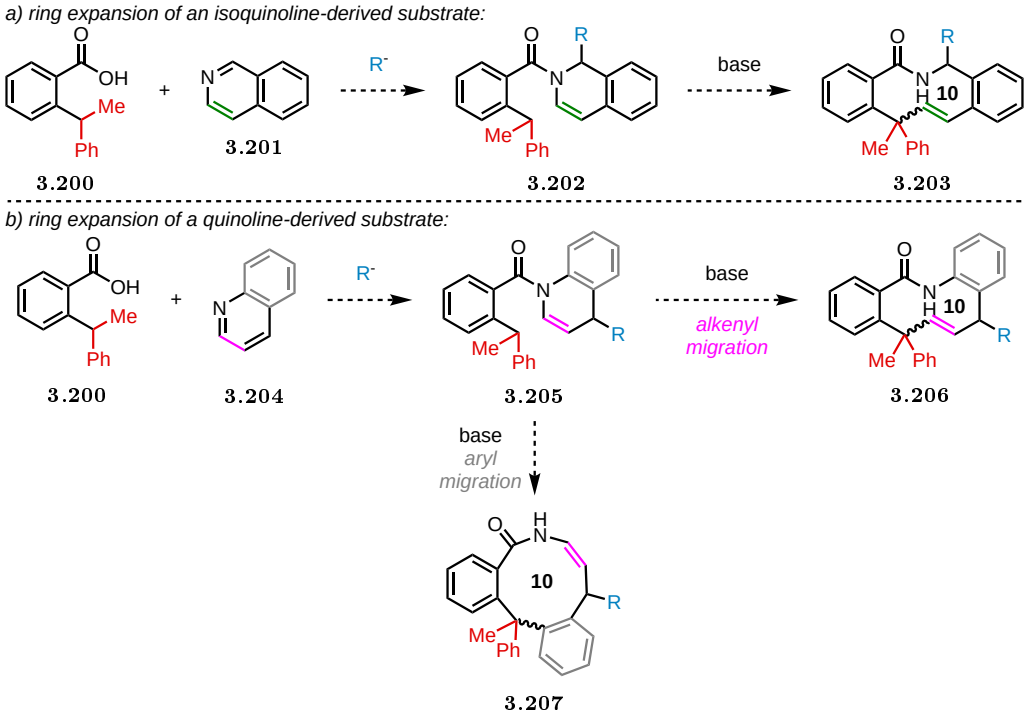
In the study of the anthranilamide substrate series, hydroalkylation to **3.76** was thought to occur by the tautomerisation of ring-expanded enamine **3.75** to iminium **3.194**, followed by transannular cyclisation (Scheme 3.41a). Hydrogenolytic cleavage of tricyclic product **3.76** to **3.122** was unsuccessful, but using hydride reducing agents was never tried. A recent publication from Kostyuk and co-workers employed the reductive cleavage of aminal-type bicycles with $NaBH_3CN$ to give medium ring products.[298] This suggests that, under such conditions, substrates similar to **3.74** could be transformed to medium-sized products **3.122**, although such reductive methods would lead to ring-enlarged scaffolds with eradication of the olefin. In addition, the use of a primary amine nucleophile was never explored (Scheme 3.41b). If the ring-expanding vinyl transfer of **3.195** to **3.196** was possible, tautomerisation could yield an imine **3.197**, rather than the iminium **3.194** derived

from **3.75**. This difference would likely impact the formation of tricyclic product **3.198**, and investigation of this may provide for a more general approach to ring-expanded products **3.199**.



Scheme 3.41: The ring-expanding vinylation of anthranilamides **3.74** and **3.195** could be followed by reductive cleavage to medium-sized lactams **3.122** and **3.199**.

Perhaps the most notable finding was that pyridine could be readily dearomatised to deliver ring expansion substrates. Other aromatic heterocycles could feasibly undergo analogous reactivity to broaden the scope of accessible ring-expanded products. One could envisage the 1,2-addition to isoquinoline **3.201** to form **3.202**, a viable precursor to doubly benzo-fused medium ring lactam **3.203** (Scheme 3.42a). An interesting substrate for ring expansion would be **3.205**, potentially accessible via nucleophilic attack at the 4-position of quinoline **3.204** (Scheme 3.42b). Now, both ring-expanding arylation and alkenylation are possible, and it would be intriguing to probe whether generation of **3.206** or **3.207** would be favoured. Given that the kinetics of aryl migration are highly dependent on the electronics of the migrating ring (see Scheme 1.22), judicious selection of substituents on the carbocyclic ring of quinoline **3.204** could conceivably allow for promoting or impeding aryl migration as desired.



Scheme 3.42: Aromatic heterocycles, other than pyridine, may be employed to generate substrates that are susceptible for inflation to medium-sized lactam products.

The mechanism of conformationally-enhanced S_NV reactions of unactivated alkenes continues to be of interest. Although a potentially suitable reaction system for study has been identified (see Section 3.3.6), the key challenge remains reproducibly achieving a target conversion of the reaction. The major difficulty is the addition of a specific volume of base at cryogenic temperatures under an inert atmosphere. Performing a cannula transfer of a pre-cooled solution of base into the substrate solution could be the basis of a fix to this problem. An alternative avenue to explore might be experimenting with addition of substrate solution to the pre-cooled base solution, with expulsion of the substrate solution down the inside wall of a reaction vessel submerged in a cooling bath, so as to cool the substrate before it mixes with the base. If these adjustments were not able to reliably achieve a specific level of conversion, trialling other less reactive bases could eliminate the reproducibly errors that affect carrying out the study with *sec*-BuLi.

Experimental

General information

All reactions were performed under a dry nitrogen atmosphere using standard Schlenk techniques in flame-dried glassware, unless otherwise stated. Air- and/or moisture-sensitive liquids and solutions were transferred via syringe into the reaction vessels through rubber septa. Anhydrous DCM, Et_2O, MeCN, PhMe and THF were dried on an Anhydrous Engineering alumina column drying system before use. All reagents were purchased at the highest commercial quality, and used as received, with the following exceptions: 18-crown-6 was recrystallised from MeCN; diisopropylamine was distilled from KOH; DMPU was distilled from CaH_2; Et_3N was stored over KOH; NBS was recrystallised from H_2O.

Chromatography: Flash chromatography was performed on an automated Biotage Isolera Spektra Four on pre-packed silica gel Biotage Sfär Duo columns, or on VWR silica gel (40–63 µm).

m.p.: Melting points, expressed in °C, were measured on a Stuart SMP30 melting point apparatus, and are uncorrected.

R_f: Analytical thin-layer chromatography was performed on aluminium-backed silica plates (0.20 mm, 60 F_{254}). Visualisation of the developed chromatogram was achieved by UV fluorescence (254 nm), and/or chemical staining with potassium permanganate solution, bromocresol green solution, 'Seebach' solution, or iodine.

$[\alpha]_D^T$: Optical rotations, expressed in °/cm^2/g, were measured on a Bellingham and Stanley ADP220 polarimeter using a cell with a pathlength of 2.5 cm in the solvent specified, at temperature T, expressed in °C, at concentration c, expressed in g/100 mL.

NMR: NMR spectra were recorded on a Bruker Avance (400 or 500 MHz), Jeol ECS (300 or 400 MHz), Jeol ECZ (400 MHz) or Varian VNMR (400, 500 or 600 MHz) spectrometer. ^{1}H chemical shifts are reported in parts per million (ppm), quoted to the nearest 0.01 ppm, relative to residual solvent: $CDCl_3$ (7.26 ppm), DMSO-d_6 (2.50 ppm). ^{13}C chemical shifts are reported in parts per million (ppm), quoted to the nearest 0.1 ppm, relative to residual solvent: $CDCl_3$ (77.2 ppm), DMSO-d_6 (39.5 ppm). ^{19}F chemical shifts are reported in parts per million (ppm), quoted to the nearest 0.1 ppm, relative to hexafluorobenzene (−164.9 ppm) as an internal standard. Spin-spin coupling constants (J) are reported in Hz, and multiplicities are reported according to the following convention: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, sept = septet, m = multiplet, br = broad, or some combination thereof. 2D NMR experiments (COSY, HSQC and HMBC) were used, where necessary, to assign NMR spectra.

IR: IR spectra were recorded from compounds in a solution applied as films on a Perkin Elmer Spectrum One FT-IR spectrometer (iD5 diamond ATR sampling accessory). Only strong and selected absorptions (ν_{max} expressed in cm^{-1}) are reported.

HRMS: High resolution mass spectra were recorded by the technical staff at the University of Bristol on a Bruker Daltronics micrOTOF II (ESI), Waters Synapt G2S (ESI), Thermo Scientific Orbitrap Elite (ESI, APCI) or Thermo Scientific QExactive (EI) mass spectrometer, with only molecular ions of interest ($[M+H]^+$, $[M+Na]^+$, $[M-H]^+$, or M^+) reported. The isotope of each element with the highest natural abundance was used to calculate m/z values, unless otherwise stated.

X-ray crystallography: Crystals for x-ray crystallography were grown by slow evaporation and analysed by the technical staff at the University of Bristol on a Bruker D8 Venture single-crystal x-ray diffractometer.

In situ IR spectroscopy: Spectra were recorded on a Mettler Toledo ReactIR 15 spectrometer equipped with a DST series AgX Fiber Conduit with an integrated DiComp probe, under a dry nitrogen atmosphere in anhydrous THF.

General procedures

General procedure 1 (GP1): Reduction of benzylic ketones and alcohols by hydrogenation

By the method of Song and co-workers[299] with modifications, in air, the ketone or alcohol (1.0 eq.) and AcOH (2.0 eq.) were dissolved in EtOAc (0.3 M with respect to the ketone or alcohol), Pd/C (10 wt%, 0.05 eq.) added, and the reaction mixture stirred at 50 °C under H_2 (1 atm, balloon) for the specified amount of time. The reaction mixture was filtered through Celite, eluting with EtOAc, and concentrated *in vacuo* to yield the desired compound without further purification.

General procedure 2 (GP2): Amide formation via acid chloride

The carboxylic acid (1.0 eq.) was dissolved in anhydrous DCM (0.5 M), a few drops of anhydrous DMF added, and the reaction mixture cooled to 0 °C. Oxalyl chloride (2 M in DCM, 1.2 eq.) was added dropwise (note: effervescence), the reaction mixture warmed to room temperature, stirred for the specified amount of time, and concentrated *in vacuo* to yield the crude acid chloride, which was used without further purification.

For general amines: the amine (1.2 eq.) and Et_3N (2.0 eq.) were dissolved in anhydrous DCM (0.5 M with respect to the amine), a solution of the crude acid chloride (0.5 M in anhydrous DCM) added dropwise, and the reaction mixture stirred at room temperature for the specified amount of time. The reaction mixture was diluted with DCM, washed sequentially with aqueous HCl (1 M), aqueous NaOH (1 M) and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The crude residue was purified by flash column chromatography to yield the desired compound.

For tethered anilines: the tethered aniline (1.2 eq.) and Et_3N (2.0 eq.) were dissolved in anhydrous PhMe (0.5 M with respect to the tethered aniline), a solution of the crude acid chloride (0.5 M in anhydrous PhMe) added dropwise, and the reaction mixture stirred at 80 °C for the specified amount of time. The reaction mixture was concentrated *in vacuo*, diluted with DCM, washed sequentially with aqueous HCl (1 M), aqueous NaOH (1 M) and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The crude residue was purified by flash column chromatography to yield the desired compound.

General procedure 3 (GP3): Triarylmethane synthesis by Truce–Smiles rearrangement

In a microwave vial, the 2-arylbenzamide (1.0 eq.) was dissolved in anhydrous THF (0.08 M), and the reaction mixture degassed by bubbling N_2 through the solution for 5 min. KHMDS (1 M in THF, 2.0 eq.) was added, the vial sealed, and the reaction mixture stirred at the specified temperature (if 60 °C or below: performed thermally; if above 60 °C: performed under microwave irradiation) for the specified amount of time. The reaction mixture was quenched by the addition of saturated aqueous NH_4Cl, diluted with H_2O, extracted three times with EtOAc, and the combined organic extracts concentrated *in vacuo*. The crude residue was purified by flash column chromatography to yield the desired compound.

General procedure 4 (GP4): Suzuki–Miyaura coupling of 2-(bromomethyl)benzonitriles

By the method of Chiba and co-workers,[300] the 2-(bromomethyl)benzonitrile (1.0 eq.), the boronic acid (1.5 eq.), $Pd(OAc)_2$ (0.01 eq.), PPh_3 (0.02 eq.) and K_3PO_4 (4.0 eq.) were suspended in anhydrous PhMe (0.33 M with respect to the 2-(bromomethyl)benzonitrile). The reaction mixture was stirred at 80 °C for the specified amount of time, diluted with H_2O, and extracted three times with Et_2O. The combined organic extracts were washed sequentially with H_2O, aqueous NaOH (1 M) and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The crude residue was purified by flash column chromatography to yield the desired compound.

General procedure 5 (GP5): Auxiliary-assisted $C(sp^3)$–H benzylation

By the method of Daugulis and co-workers,[301] $Pd(OAc)_2$ (0.05 eq.), the 8-aminoquinolinyl benzamide (1.0 eq.), K_2CO_3 (2.5 eq.), pivalic acid (0.20 eq.) and BnBr (3.0 eq.) were dissolved in anhydrous *tert*-amyl alcohol (2.64 M with respect to the 8-aminoquinolinyl benzamide). The reaction mixture was stirred at 110 °C for the specified amount of time, and diluted with EtOAc and H_2O. The aqueous layer was extracted three times with EtOAc, the combined organic extracts dried ($MgSO_4$), and concentrated *in vacuo*. The crude residue was purified by flash column chromatography to yield the desired compound.

General procedure 6 (GP6): *N*-Methylation of amides

By the method of Wencel-Delord and co-workers,[302] NaH (60% dispersion in mineral oil, 2.05 eq.) was suspended in anhydrous DMF (0.42 M), cooled to 0 °C, and a solution of the amide (0.2 M in anhydrous DMF, 1.0 eq.) added dropwise. The reaction mixture was warmed to room temperature, stirred for 3 h, and MeI (1.3 eq.) added dropwise. The reaction mixture was stirred for 1 h, diluted with DCM, washed three times with H_2O, dried (Na_2SO_4), and concentrated *in vacuo*. The crude residue was purified by flash column chromatography to yield the desired compound.

General procedure 7 (GP7): Reductive amination of aldehydes with methylamine

By the method of Charrier and co-workers[303] with modifications, the aldehyde (1.0 eq.) was dissolved in MeOH (0.6 M), $MeNH_2$ (33 wt% in EtOH, 1.2 eq.) added, the reaction mixture stirred at room temperature for 1.5 h, and cooled to 0 °C. $NaBH_4$ (1.5 eq.) was added portionwise (note: effervescence), the reaction mixture warmed to room temperature, stirred for the specified amount of time, quenched by the addition of aqueous NaOH (1 M), and extracted with EtOAc. The organic extract was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to yield the desired compound without further purification.

General procedure 8 (GP8): Carbamoyl chloride synthesis

By the method of Clayden and co-workers[39] with modifications, triphosgene (0.46 eq.) was dissolved in anhydrous DCM (0.7 M with respect to the amine), cooled to 0 °C, and pyridine (1.5 eq.) added dropwise. The reaction mixture was stirred at 0 °C for 5 min, and the amine (1.0 eq.) added dropwise. The reaction mixture was stirred at 0 °C for 5 min, warmed to room temperature, and stirred

for the specified amount of time. The reaction mixture was cooled to 0 °C, quenched by the slow addition of aqueous HCl (1 M) (note: effervescence), and extracted three times with DCM. The combined organic extracts were washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and concentrated *in vacuo* to yield the desired compound without further purification.

General procedure 9 (GP9): Urea synthesis from a carbamoyl chloride

By the method of Clayden and co-workers[268] with modifications, the carbamoyl chloride (1.0 eq.) was dissolved in anhydrous MeCN (0.4 M), and Et_3N (2.0 eq.) and the amine (1.2 eq.) added. The reaction mixture was stirred at room temperature for the specified amount of time, diluted with saturated aqueous $NaHCO_3$, and extracted three times with DCM. The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The crude residue was purified by flash column chromatography to yield the desired compound.

General procedure 10 (GP10): Amide coupling between a Boc-protected amino acid and an *N*-methylbenzylamine

By the method of Yamaki and co-workers[304] with modifications, the *N*-methylbenzylamine (1.0 eq.) was dissolved in anhydrous DCM (0.5 M), the Boc-protected amino acid (1.05 eq.), EDC hydrochloride (1.1 eq.) and 1-hydroxybenzotriazole hydrate (1.1 eq.) added, and the reaction mixture stirred at room temperature for the specified amount of time. The reaction mixture was diluted with $CHCl_3$, washed sequentially with H_2O, aqueous HCl (1 M) and saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and concentrated *in vacuo*. The crude residue was purified by flash column chromatography to yield the desired compound.

General procedure 11 (GP11): Boc deprotection

By the method of Blass and co-workers[305] with modifications, the Boc-protected amine (1.0 eq.) was dissolved in anhydrous DCM (0.35 M), TFA (12.4 eq.) added, the reaction mixture stirred at room temperature for the specified amount of time, quenched by the dropwise addition of saturated aqueous $NaHCO_3$ (note: effervescence), and adjusted to pH 12 with aqueous KOH (3.5 M). The aqueous layer was extracted two times with DCM, the combined organic extracts dried ($MgSO_4$), and concentrated *in vacuo*. Where required, the crude residue was purified by flash column chromatography to yield the desired compound.

General procedure 12 (GP12): *N*-Methylation of carbamates

The carbamate (1.0 eq.) was dissolved in anhydrous THF (0.12 M), cooled to 0 °C, and NaH (60% dispersion in mineral oil, 2.2 eq.) and MeI (7.3 eq.) added. The reaction mixture was warmed to room temperature, stirred for the specified amount of time, diluted with H_2O (note: effervescence), and extracted with DCM. The organic extract was washed two times with H_2O, dried (Na_2SO_4), and concentrated *in vacuo*. Where required, the crude residue was purified by flash column chromatography to yield the desired compound.

General procedure 13 (GP13): Amide formation with *N*-carboxyanhydride

The *N*-carboxyanhydride (1.5 eq.) was dissolved in anhydrous DCM (1 M), and a solution of the amine (1 M in anhydrous DCM, 1.0 eq.) added dropwise. The reaction mixture was stirred at room temperature for the specified amount of time, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography to yield the desired compound.

General procedure 14 (GP14): Defluorination of fluoroalkyl arenes

The fluoroalkyl arene (1.0 eq.) was dissolved in anhydrous THF (0.1 M), KHMDS (1 M in THF, 2.0 eq.) added dropwise, and the reaction mixture stirred at room temperature for 10 min. The reaction mixture was quenched by the addition of saturated aqueous NH_4Cl, diluted with H_2O, and extracted three times with DCM. The combined organic extracts were dried ($MgSO_4$), and concentrated *in vacuo*. The crude residue was purified by flash column chromatography to yield the desired compound.

General procedure 15 (GP15): Imidazolidinone reduction–hydrolysis

The imidazolidinone (1.0 eq.) was dissolved in anhydrous THF (0.36 M), DIBAL-H (1.0 M in heptane, 2.2 eq.) added dropwise, and the reaction mixture stirred at room temperature for 2 h. The reaction mixture was diluted with Et_2O, cooled to 0 °C, and quenched by the dropwise addition of aqueous NaOH (1 M, 0.3 eq. with respect to DIBAL-H). The reaction mixture was warmed to room temperature, stirred for 15 min, $MgSO_4$ added, stirred for 15 min, filtered, eluting with Et_2O, and concentrated *in vacuo*.

The residue was dissolved in 1:1 aqueous HCl (1 M)/THF (0.18 M), warmed to room temperature, stirred for 30 min, and the reaction mixture extracted three times with DCM. The combined organic extracts were dried ($MgSO_4$), and concentrated *in vacuo* to yield the desired compound without further purification.

General procedure 16 (GP16): Secondary *N*-allyl amine synthesis by alkylation

By the method of Bowman and co-workers,[306] allylamine (10.0 eq.) was dissolved in anhydrous Et_2O (17.5 M), and a solution of the alkyl bromide (1.75 M in anhydrous Et_2O, 1.0 eq.) added. The reaction mixture was stirred at 36 °C for the specified amount of time, poured onto saturated aqueous K_2CO_3, adjusted to pH 14 with aqueous NaOH (1 M), and extracted two times with Et_2O. The combined organic extracts were dried ($MgSO_4$), and concentrated *in vacuo* to yield the desired compound without further purification.

General procedure 17 (GP17): Amide formation with *N*-methylisatoic anhydride

By the method of Zhang and co-workers,[307] *N*-methylisatoic anhydride (1.0 eq.) was dissolved in anhydrous MeCN (0.5 M), cooled to 0 °C, and DMAP (0.1 eq.) and the amine (1.1 eq.) added. The reaction mixture was stirred at 0 °C for 2 h, warmed to room temperature, and stirred for the specified amount of time. H_2O was added, and the reaction mixture extracted three times with EtOAc. The combined organic extracts were washed sequentially five times with H_2O, and brine, dried (Na_2SO_4), and concentrated *in vacuo*. Where required, the crude

residue was purified by flash column chromatography to yield the desired compound.

General procedure 18 (GP18): Ring-closing metathesis of amides and ureas

By the method of Clayden and co-workers,[287] the amide or urea (1.0 eq.) was dissolved in anhydrous DCM (0.05 M), Grubbs' first generation catalyst (0.05 eq.) added, the reaction mixture stirred at room temperature for the specified amount of time, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography to yield the desired compound.

General procedure 19 (GP19): Double bond isomerisation of allylic amides and ureas

By the method of Clayden and co-workers,[287] the allylic amide or urea (1.0 eq.) was dissolved in anhydrous THF (0.1 M), carbonylchlorohydridotris-(triphenylphosphine)ruthenium(II) (0.1 eq.) added, the reaction mixture stirred at reflux for the specified amount of time, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography to yield the desired compound.

General procedure 20 (GP20): Amide formation with diketene acetone adduct

By the method of Studer and co-workers,[308] the amine (1.0 eq.) was dissolved in anhydrous PhMe (0.25 M), and diketene acetone adduct (1.5 eq.) added dropwise. The reaction mixture was stirred at room temperature for 15 min, then stirred at reflux for the specified amount of time, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography to yield the desired compound.

General procedure 21 (GP21): β-Methylaminocrotonamide formation from 3-oxobutanamides

By the method of Dong and co-workers[309] with modifications, the 3-oxobutanamide (1.0 eq.) and TBAB (0.05 eq.) were suspended in H_2O (0.5 M with respect to the 3-oxobutanamide), and $MeNH_2$ (33 wt% in EtOH, 1.0 eq.) added. The reaction mixture was stirred at room temperature for the specified amount of time, and extracted with EtOAc. The organic extract was washed sequentially three times with H_2O, and brine, dried ($MgSO_4$), and concentrated *in vacuo* to yield the desired compound without further purification.

General procedure 22 (GP22): Attack of an *N*-acylpyridinium by $NaBH_4$

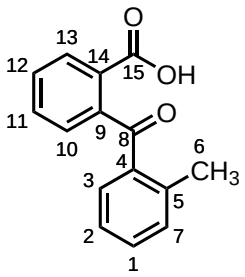
By the method of Sundberg and co-workers[283] with modifications, $NaBH_4$ (1.1 eq.) and pyridine (1.0 eq.) were suspended in anhydrous EtOH (2.5 M with respect to pyridine), and cooled to −78 °C. The chloroformate (1.0 eq.) was added dropwise over 1 h using a syringe pump, and the reaction mixture stirred at −78 °C for 2 h. H_2O was added dropwise (note: effervescence), and the reaction mixture extracted three times with Et_2O. The combined organic extracts were dried ($MgSO_4$), and concentrated *in vacuo*. The crude residue was purified by flash column chromatography to yield the desired compound.

General procedure 23 (GP23): Attack of an *N*-acylpyridinium by MeMgBr

By the method of Pineschi and co-workers[284] with modifications, pyridine (1.0 eq.) was dissolved in anhydrous THF (0.66 M), the acid chloride (1.0 eq.) added, the reaction mixture cooled to −78 °C, and MeMgBr (3.0 M in Et_2O, 2.0 eq.) added dropwise over 5 min. The reaction mixture was quenched by the dropwise addition of saturated aqueous NH_4Cl, diluted with H_2O, and extracted three times with Et_2O. The combined organic extracts were dried ($MgSO_4$), and concentrated *in vacuo*. The crude residue was purified by flash column chromatography to yield the desired compound.

Chapter 1 experimental procedures

2-(2-Methylbenzoyl)benzoic acid (1.54b)

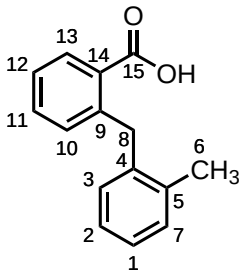


By the method of Song and co-workers,[299] Mg turnings (306 mg, 12.6 mmol, 1.26 eq.) and iodine (76 mg, 0.30 mmol, 0.03 eq.) were stirred at room temperature, and a solution of 2-bromotoluene (240 µL, 2.00 mmol, 0.2 eq.) in anhydrous THF (12 mL) added dropwise. The reaction mixture was stirred at reflux for 5 min, and a solution of 2-bromotoluene (1.2 mL, 10.0 mmol, 1.0 eq.) in anhydrous THF (10 mL) added dropwise. The reaction mixture was stirred at reflux for 1 h, and cooled to room temperature to yield the crude Grignard solution that was used without further purification.

A solution of phthalic anhydride (1.48 g, 10.0 mmol, 1.0 eq.) in anhydrous THF (5.0 mL) was cooled to 0 °C, and the crude Grignard solution added dropwise. The reaction mixture was stirred at room temperature for 2 h, cooled to 0 °C, quenched by the addition of aqueous HCl (20 mL, 1 M), and extracted with EtOAc (3 × 20 mL). The combined organic extracts were concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2; gradient elution: 2–10% MeOH in DCM) to yield the title compound as a white solid (1.38 g, 48%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.02 (1H, br s, O*H*), 8.01 (1H, dd, *J* 7.6, 1.4, H_{13}), 7.65 (1H, td, *J* 7.6, 1.4, H_{12}), 7.55 (1H, td, *J* 7.6, 1.4, H_{11}), 7.43 (1H, dd, *J* 7.6, 1.4, H_{10}), 7.35 (1H, td, *J* 7.4, 1.6, H_1), 7.28–7.23 (1H, m, H_7), 7.15 (1H, dd, *J* 7.8, 1.6, H_3), 7.12–7.06 (1H, m, H_2), 2.62 (3H, s, H_6). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 198.8 (C_8), 171.7 (C_{15}), 143.8 (C_9), 140.3 (C_4), 136.7 (C_5), 133.1 (C_{12}), 132.0 (C_7), 132.0 (C_1), 131.5 (C_3), 130.8 (C_{13}), 129.8 (C_{11}), 128.4 (C_{10}), 128.4 (C_{14}), 125.3 (C_2), 21.3 (C_6). Data consistent with literature.[310]

2-(2-Methylbenzyl)benzoic acid (1.55d)

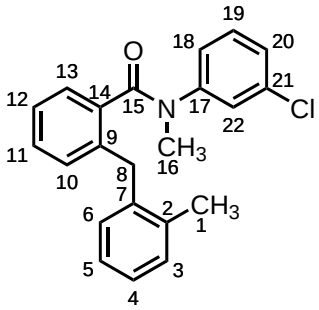


By the method of Miller and co-workers[311] with modifications, in air, 2-(2-methylbenzoyl)benzoic acid (**1.54b**) (1.34 g, 5.58 mmol, 1.0 eq.) was dissolved in aqueous NaOH (35 mL, 10 wt%), and zinc dust (2.44 g, 37.3 mmol, 6.7 eq.) and $CuSO_4 \cdot 5\,H_2O$ (28 mg, 0.11 mmol, 0.02 eq.) added. The reaction mixture was stirred at reflux for 73 h, the liquid decanted from the solid residue, and the solid residue washed sequentially with H_2O and aqueous HCl (0.5 M). The combined aqueous solutions were adjusted to pH 1 with aqueous HCl (6 M), cooled to 0 °C, and filtered, washing with H_2O. The solid was dissolved in DCM, filtered through a plug of SiO_2, eluting with DCM, and concentrated *in vacuo*. NMR analysis revealed the crude material was a mixture of 2-(hydroxy(*o*-tolyl)methyl)benzoic acid and 2-(2-methylbenzyl)benzoic acid in an approximate 10:1 ratio.

By **GP1**, the crude material was used, and stirred for 26 h to yield the title compound as a white solid without further purification (784 mg, 62%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.60 (1H, s, O*H*), 8.13 (1H, dd, *J* 7.6, 1.6, H_{13}), 7.45 (1H, td, *J* 7.6, 1.6, H_{11}), 7.33 (1H, td, *J* 7.6, 1.2, H_{12}), 7.23–7.11 (3H, m, H_1, H_2, H_7), 7.01 (1H, dd, *J* 7.6, 1.2, H_{10}), 6.96 (1H, dd, *J* 7.1, 1.8, H_3), 4.46 (2H, s, H_8), 2.26 (3H, s, H_6). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.4 (C_{15}), 143.3 (C_9), 138.8 (C_4), 136.9 (C_5), 133.2 (C_{11}), 131.9 (C_{13}), 130.8 (C_{10}), 130.3 (C_7), 129.8 (C_3), 128.6 (C_{14}), 126.5 (C_2), 126.3 (C_{12}), 126.2 (C_1), 37.5 (C_8), 19.7 (C_6). Data consistent with literature.[311]

N-(3-Chlorophenyl)-*N*-methyl-2-(2-methylbenzyl)benzamide (1.49s)

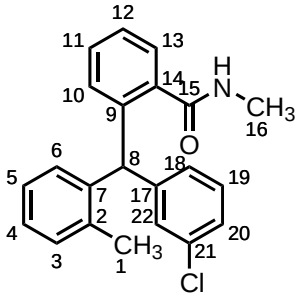


By **GP2**, the acid chloride of carboxylic acid 2-(2-methylbenzyl)benzoic acid (**1.55d**) (784 mg, 3.46 mmol) was made by stirring with oxalyl chloride for 21 h. *N*-Methyl-3-chloroaniline (510 µL, 4.16 mmol) was used as the general amine that was stirred with the acid chloride intermediate for 24 h, and purified by flash column chromatography (SiO_2; gradient elution: 12–100% Et_2O in pet. ether) to yield the title compound as a red gum (1.05 g, 87%).

$\boldsymbol{R_f}$ = 0.39 (50% Et_2O in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33–6.85 (10H, m, 10 × H_{Ar}), 6.85–6.60 (2H, m, 2 × H_{Ar}), 4.10 (2H, s, H_8), 3.68–2.67 (3H, m, H_{16}), 2.23 (3H, s, H_1). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.7 (C_{15}), 145.1 (C_{17}), 137.9 (C_9), 137.8 (C_7), 137.2 (C_2), 136.0 (C_{14}), 134.5 (C_{21}), 130.8 (C_{Ar}), 130.6 (C_3), 130.2 (C_{Ar}), 129.9 (C_{Ar}), 129.1 (C_{Ar}), 128.1 (C_{Ar}), 126.9 (C_{Ar}), 126.8 (2 × C_{Ar}), 126.1 (C_4), 125.7 (C_{Ar}), 124.8 (C_{Ar}), 37.5 (C_{16}), 36.9 (C_8), 20.0 (C_1).

IR (film, $CDCl_3$) ν_{max} = 3064 (C−H), 3020 (C−H), 2925 (C−H), 1646 (C=O), 1590, 1477, 1358, 779, 744, 734, 694 cm^{-1}. **HRMS** (ESI^+) m/z calcd for $C_{22}H_{20}ClNNaO$ $[M+Na]^+$ 372.1126, found 372.1125.

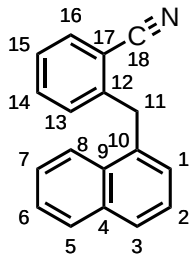
2-((3-Chlorophenyl)(*o*-tolyl)methyl)-*N*-methylbenzamide (1.50ab)



By **GP3**, *N*-(3-chlorophenyl)-*N*-methyl-2-(2-methylbenzyl)benzamide (**1.49s**) (70 mg, 0.20 mmol) was used as the 2-arylbenzamide that was stirred at room temperature for 2 h, and purified by flash column chromatography (SiO_2; gradient elution: 12–100% Et_2O in pet. ether) to yield the title compound as a yellow solid (45 mg, 64%).

m.p. = 150–152 °C (DCM). $\boldsymbol{R_f}$ = 0.12 (50% Et_2O in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35 (1H, dd, J 7.4, 1.6, H_{13}), 7.30 (1H, td, J 7.4, 1.6, H_{11}), 7.24 (1H, td, J 7.4, 1.6, H_{12}), 7.22–7.18 (2H, m, H_{19}, H_{20}), 7.18–7.12 (2H, m, H_3, H_5), 7.09 (1H, td, J 7.3, 2.1, H_4), 7.06–7.03 (1H, m, H_{22}), 7.00–6.94 (1H, m, H_{18}), 6.88 (1H, dd, J 7.4, 1.6, H_{10}), 6.76 (1H, dd, J 7.5, 2.1, H_6), 6.22 (1H, s, H_8), 5.19 (1H, br q, J 4.8, NH), 2.64 (3H, d, J 4.8, H_{16}), 2.21 (3H, s, H_1). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.7 (C_{15}), 144.9 (C_{17}), 141.2 (C_7), 140.9 (C_9), 137.5 (C_{14}), 137.3 (C_2), 134.5 (C_{21}), 130.8 (C_3), 130.1 (C_{10}), 129.8 (C_{22}), 129.8 (C_{11}), 129.7 (C_{19}), 129.1 (C_6), 128.2 (C_{18}), 127.3 (C_{13}), 126.9 (C_5), 126.8 (C_{20}), 126.8 (C_{12}), 126.0 (C_4), 49.2 (C_8), 26.5 (C_{16}), 19.9 (C_1). **IR** (film, $CDCl_3$) ν_{max} = 3301 (N−H, br), 3064 (C−H), 2928 (C−H), 1635 (C=O), 1594, 1570, 1532, 1474, 908, 730, 687 cm^{-1}. **HRMS** (ESI^+) m/z calcd for $C_{22}H_{20}ClNNaO$ $[M+Na]^+$ 372.1126, found 372.1127.

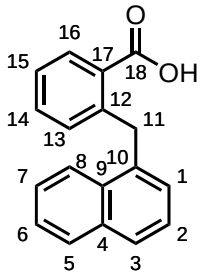
2-(Naphthalen-1-ylmethyl)benzonitrile (1.59b)



By **GP4**, 2-(bromomethyl)benzonitrile (980 mg, 5.00 mmol) was used as 2-(bromomethyl)benzonitrile and 1-naphthaleneboronic acid (1.29 g, 7.50 mmol) was used as the boronic acid that were stirred for 20 h, and purified by flash column chromatography (SiO_2; gradient elution: 7–60% Et_2O in pet. ether) to yield the title compound as a yellow oil (1.10 g, 90%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94–7.87 (2H, m, H_8, H_{Ar}), 7.83 (1H, dd, J 8.3, 1.1, H_{Ar}), 7.72 (1H, dd, J 7.6, 1.5, H_{16}), 7.54–7.43 (3H, m, H_{17}, 2 × H_{Ar}), 7.38 (1H, td, J 7.7, 1.5, H_{14}), 7.32–7.27 (2H, m, H_{15}, H_{Ar}), 7.01 (1H, d, J 7.7, H_{13}), 4.69 (2H, s, H_{11}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.5 (C_{12}), 134.4 (C_{10}), 134.1 (C_4), 133.0 (C_{14}), 132.9 (C_{16}), 132.0 (C_9), 129.7 (C_{13}), 128.9 (C_{Ar}), 128.0 (C_{Ar}), 127.8 (C_{Ar}), 126.9 (C_{Ar}), 126.5 (C_{Ar}), 125.9 (C_{Ar}), 125.7 (C_{Ar}), 124.0 (C_8), 118.2 (C_{18}), 112.6 (C_{17}), 37.2 (C_{11}). Data consistent with literature.[300]

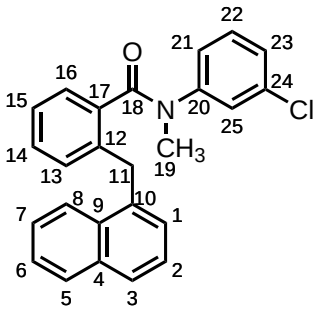
2-(Naphthalen-1-ylmethyl)benzoic acid (1.55e)



By the method of Westkaemper and co-workers[312] with modifications, in air, 2-(naphthalen-1-ylmethyl)benzonitrile (**1.59b**) (1.04 g, 4.27 mmol, 1.0 eq.), KOH (1.75 g, 31.2 mmol, 7.3 eq.) and H_2O (650 µL, 36.1 mmol, 8.4 eq.) were dissolved in ethylene glycol (9.1 mL). The reaction mixture was stirred at reflux for 1.5 h, diluted with H_2O (25 mL), washed with DCM (2 × 25 mL), adjusted to pH 1 with aqueous HCl (6 M), and extracted with DCM (3 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$), and concentrated *in vacuo* to yield the title compound as a white solid without further purification (682 mg, 61%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.64 (1H, br s, OH), 8.15 (1H, dd, J 7.5, 1.6, H_{16}), 7.96–7.91 (1H, m, H_8), 7.90–7.86 (1H, m, H_5), 7.78 (1H, dd, J 8.2, 1.2, H_3), 7.51–7.42 (2H, m, H_6, H_7), 7.42 (1H, dd, J 8.2, 7.0, H_2), 7.36 (1H, td, J 7.5, 1.6, H_{14}), 7.31 (1H, td, J 7.5, 1.6, H_{15}), 7.18 (1H, dd, J 7.0, 1.2, H_1), 6.96 (1H, dd, J 7.5, 1.6, H_{13}), 4.93 (2H, s, H_{11}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.4 (C_{18}), 143.4 (C_{12}), 136.5 (C_{10}), 134.0 (C_4), 133.2 (C_{14}), 132.4 (C_9), 131.8 (C_{16}), 131.1 (C_{13}), 128.8 (C_5), 128.5 (C_{17}), 127.5 (C_1), 127.3 (C_3), 126.4 (C_{15}), 126.2 (C_7), 125.7 (C_2, C_6), 124.4 (C_8), 37.0 (C_{11}). Data consistent with literature.[313]

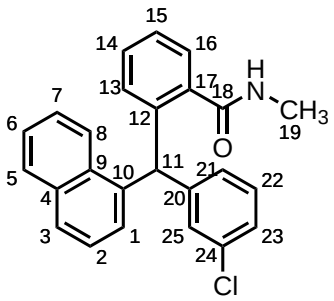
N-(3-Chlorophenyl)-*N*-methyl-2-(naphthalen-1-ylmethyl)benzamide (1.49t)



By **GP2**, the acid chloride of carboxylic acid 2-(naphthalen-1-ylmethyl)benzoic acid (**1.55e**) (680 mg, 2.59 mmol) was made by stirring with oxalyl chloride for 2 h. *N*-Methyl-3-chloroaniline (380 µL, 3.10 mmol) was used as the general amine that was stirred with the acid chloride intermediate for 21 h, and purified by flash column chromatography (SiO_2; gradient elution: 7–60% Et_2O in pet. ether) to yield the title compound as an orange gum (936 mg, 94%).

$\boldsymbol{R_f}$ = 0.17 (30% Et_2O in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.94 (1H, d, *J* 7.5, H_{Ar}), 7.89–7.83 (1H, m, H_8), 7.77 (1H, d, *J* 8.2, H_{Ar}), 7.51–7.33 (3H, m, 3 × H_{Ar}), 7.31 (1H, dd, *J* 7.1, 1.2, H_{13}), 7.28–7.17 (1H, m, H_{Ar}), 7.15–6.84 (6H, m, H_{21}, 5 × H_{Ar}), 6.77–6.54 (1H, m, H_{Ar}), 4.54 (2H, s, H_{11}), 3.77–2.91 (3H, m, H_{19}). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.9 (C_{18}), 144.9 (C_{20}), 138.0 (C_{12}), 135.9 (C_{17}), 135.5 (C_{10}), 134.5 (C_{24}), 134.0 (C_4), 132.4 (C_9), 130.2 (C_1), 129.9 (C_{Ar}), 129.3 (C_{Ar}), 128.8 (C_8), 128.3 (C_{13}), 128.0 (C_{Ar}), 127.5 (C_{Ar}), 126.9 (C_{Ar}), 126.8 (C_{Ar}), 126.3 (C_{Ar}), 125.8 (2 × C_{Ar}), 125.6 (C_{Ar}), 124.9 (C_{Ar}), 124.5 (C_{Ar}), 36.2 (C_{11}), 32.0 (C_{19}). **IR** (film, $CDCl_3$) ν_{max} = 3063 (C–H), 2924 (C–H), 1647 (C=O), 1591, 1478, 1360, 790, 776, 733, 695 cm^{-1}. **HRMS** (ESI$^+$) *m*/*z* calcd for $C_{25}H_{20}ClNNaO$ $[M+Na]^+$ 408.1126, found 408.1131.

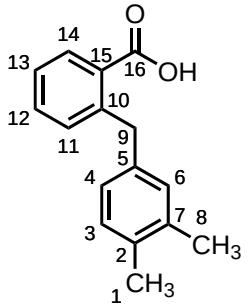
2-((3-Chlorophenyl)(naphthalen-1-yl)methyl)-*N*-methylbenzamide (1.50ac)



By **GP3**, *N*-(3-chlorophenyl)-*N*-methyl-2-(naphthalen-1-ylmethyl)benzamide (**1.49t**) (77 mg, 0.20 mmol) was used as 2-arylbenzamide that was stirred at room temperature for 2 h, and purified by flash column chromatography (SiO_2; gradient elution: 12–100% Et_2O in pet. ether) to yield the title compound as a yellow solid (66 mg, 86%).

m.p. = 196–198 °C (DCM). $\boldsymbol{R_f}$ = 0.16 (50% Et_2O in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.13–8.07 (1H, m, H_8), 7.87–7.82 (1H, m, H_5), 7.77 (1H, d, J 8.2, H_3), 7.48–7.41 (2H, m, H_6, H_7), 7.41–7.33 (2H, m, H_2, H_{16}), 7.29–7.22 (2H, m, H_{14}, H_{15}), 7.22–7.17 (2H, m, H_{22}, H_{23}), 7.12–7.09 (1H, m, H_{25}), 7.02 (1H, td, J 4.6, 1.7, H_{21}), 6.95 (1H, d, J 7.2, H_1), 6.93–6.89 (1H, m, H_{13}), 6.88 (1H, s, H_{11}), 5.24 (1H, br q, J 4.9, NH), 2.56 (3H, d, J 4.9, H_{19}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.7 (C_{18}), 145.5 (C_{20}), 140.9 (C_{12}), 139.0 (C_{10}), 137.2 (C_{17}), 134.5 (C_{24}), 134.1 (C_4), 131.9 (C_9), 130.2 (C_{13}), 129.9 (C_{14}, C_{25}), 129.8 (C_{22}), 128.6 (C_5), 128.3 (C_{21}), 127.9 (C_3), 127.4 (C_1), 127.4 (C_{16}), 126.9 (C_{15}), 126.9 (C_{23}), 126.8 (C_6), 126.0 (C_7), 125.1 (C_2), 124.6 (C_8), 48.7 (C_{11}), 26.5 (C_{19}). **IR** (film, $CDCl_3$) ν_{max} = 3300 (N–H, br), 3061 (C–H), 2935 (C–H), 1634 (C=O), 1594, 1571, 1532, 1474, 907, 790, 778, 730, 696 cm^{-1}. **HRMS** (ESI$^+$) m/z calcd for $C_{25}H_{21}ClNO$ $[M+H]^+$ 386.1306, found 386.1308.

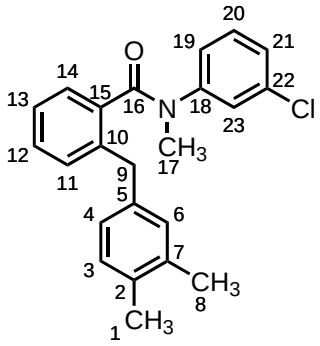
2-(3,4-Dimethylbenzyl)benzoic acid (1.55f)



By **GP1**, 2-(3,4-dimethylbenzoyl)benzoic acid (1.27 g, 4.99 mmol) was used as the ketone that was stirred for 24 h to yield the title compound as a white solid without further purification (1.15 g, 96%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.91 (1H, br s, OH), 8.09 (1H, dd, J 7.7, 1.3, H_{14}), 7.49 (1H, td, J 7.7, 1.3, H_{12}), 7.33 (1H, td, J 7.7, 1.3, H_{13}), 7.25 (1H, dd, J 7.7, 1.3, H_{11}), 7.06 (1H, d, J 7.6, H_3), 6.98 (1H, d, J 2.0, H_6), 6.92 (1H, dd, J 7.6, 2.0, H_4), 4.42 (2H, s, H_9), 2.24 (3H, s, H_1), 2.23 (3H, s, H_8). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.4 (C_{16}), 144.0 (C_{10}), 138.2 (C_7), 136.6 (C_2), 134.2 (C_5), 133.1 (C_{12}), 131.8 (C_{14}), 131.8 (C_{11}), 130.6 (C_6), 129.8 (C_3), 128.6 (C_{15}), 126.6 (C_4), 126.3 (C_3), 39.2 (C_9), 19.9 (C_8), 19.4 (C_1). Data consistent with literature.[314]

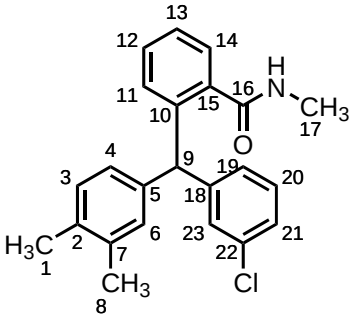
N-(3-Chlorophenyl)-2-(3,4-dimethylbenzyl)-*N*-methylbenzamide (1.49u)



By **GP2**, the acid chloride of carboxylic acid 2-(3,4-dimethylbenzyl)benzoic acid (**1.55f**) (1.12 g, 4.66 mmol) was made by stirring with oxalyl chloride for 2.5 h. *N*-Methyl-3-chloroaniline (500 µL, 4.08 mmol, 0.88 eq.) was used as the general amine that was stirred with the acid chloride intermediate for 3.5 h, and purified by flash column chromatography (SiO_2; gradient elution: 12–100% Et_2O in pet. ether) to yield the title compound as an orange gum (1.03 g, 69%).

$\boldsymbol{R_f}$ = 0.38 (50% Et_2O in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.30–6.87 (9H, m, 9 × H_{Ar}), 6.83–6.20 (2H, m, 2 × H_{Ar}), 4.07 (2H, s, H_9), 3.77–2.55 (3H, m, H_{17}), 2.23 (6H, s, H_1, H_8). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.6 (C_{16}), 145.2 (C_{18}), 139.6 (C_5), 137.6 (C_{10}), 136.7 (C_2), 135.5 (C_{15}), 134.6 (C_7), 134.3 (C_{22}), 130.8 (C_3), 130.5 (C_{Ar}), 129.8 (C_6), 129.8 (C_{Ar}), 129.2 (C_{Ar}), 128.1 (C_{Ar}), 126.9 (C_4, C_{Ar}), 126.8 (C_{Ar}), 125.5 (C_{Ar}), 125.0 (C_{Ar}), 38.7 (C_9), 37.5 (C_{17}), 19.8 (C_8), 19.4 (C_1). **IR** (film, $CDCl_3$) ν_{max} = 3063 (C–H), 2921 (C–H), 1645 (C=O), 1590, 1476, 1357, 771, 729, 694 cm^{-1}. **HRMS** (ESI$^+$) *m/z* calcd for $C_{23}H_{22}ClNNaO$ $[M+Na]^+$ 386.1282, found 386.1293.

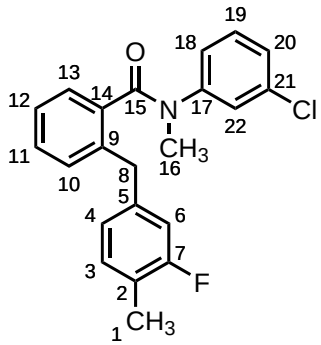
2-((3-Chlorophenyl)(3,4-dimethylphenyl)methyl)-*N*-methylbenzamide (1.50ad)



By **GP3**, *N*-(3-chlorophenyl)-2-(3,4-dimethylbenzyl)-*N*-methylbenzamide (**1.49u**) (73 mg, 0.20 mmol) was used as the 2-arylbenzamide that was stirred at room temperature for 2 h, and purified by flash column chromatography (SiO_2; gradient elution: 12–100% Et_2O in pet. ether) to yield the title compound as an off-white solid (55 mg, 75%).

m.p. = 57–58 °C (DCM). $\boldsymbol{R_f}$ = 0.12 (50% Et_2O in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.30–7.21 (2H, m, H_{19}, H_{Ar}), 7.20–7.14 (1H, m, H_{20}), 7.13–7.08 (2H, m, H_{21}, H_{23}), 7.02–6.91 (4H, m, H_3, 3 × H_{Ar}), 6.82 (1H, d, *J* 2.0, H_6), 6.72 (1H, dd, *J* 7.7, 2.0, H_4), 5.93 (1H, s, H_9), 5.25 (1H, br q, *J* 4.9, NH), 2.65 (3H, d, *J* 4.9, H_{17}), 2.16 (3H, s, H_1), 2.13 (3H, s, H_8). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.8 (C_{16}), 146.0 (C_{18}), 141.2 (C_{10}), 140.0 (C_5), 137.5 (C_{15}), 136.8 (C_7), 135.1 (C_2), 134.3 (C_{22}), 130.9 (C_6), 130.3 (C_{Ar}), 129.8 (C_3), 129.8 (C_{Ar}), 129.6 (C_{21}, C_{Ar}), 128.0 (C_{Ar}), 127.2 (C_{19}), 126.9 (C_4), 126.7 (C_{20}), 126.6 (C_{23}), 51.9 (C_9), 26.5 (C_{17}), 19.9 (C_8), 19.5 (C_1). **IR** (film, $CDCl_3$) ν_{max} = 3294 (N–H, br), 2923 (C–H), 2855 (C–H), 1635 (C=O), 1594, 1569, 1532, 1473, 908, 731, 687 cm^{-1}. **HRMS** (ESI$^+$) *m*/*z* calcd for $C_{23}H_{22}ClNNaO$ $[M+Na]^+$ 386.1282, found 386.1301.

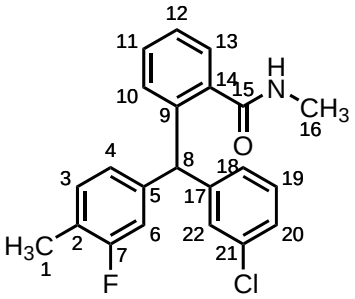
N-(3-Chlorophenyl)-2-(3-fluoro-4-methylbenzyl)-*N*-methylbenzamide (1.49v)



By **GP2**, the acid chloride of carboxylic acid 2-(3-fluoro-4-methylbenzyl)benzoic acid (989 mg, 4.05 mmol) was made by stirring with oxalyl chloride for 15 h, with addition of a second portion of oxalyl chloride (2.4 mL, 2 M in DCM, 4.80 mmol, 1.2 eq.), and stirring for a further 5.5 h. *N*-Methyl-3-chloroaniline (600 µL, 4.90 mmol) was used as the general amine that was stirred with the acid chloride intermediate for 3.5 h, and purified by flash column chromatography (SiO_2; gradient elution: 7–60% Et_2O in pet. ether) to yield the title compound as a red oil (1.04 g, 70%).

$\boldsymbol{R_f}$ = 0.19 (30% Et_2O in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.24–6.82 (9H, m, 9 × H_{Ar}), 6.82–6.22 (2H, m, 2 × H_{Ar}), 4.05 (2H, s, H_8), 3.40 (3H, m, H_{16}), 2.23 (3H, d, *J* 2.1, H_1). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.6 (C_{15}), 160.2 (d, *J* 243.5, C_7), 145.1 (C_{17}), 139.1 (C_9), 135.6 (d, *J* 3.7, C_5), 135.5 (C_{14}), 134.4 (C_{21}), 132.5 (d, *J* 5.0, C_3), 130.5 (C_{Ar}), 129.9 (C_{Ar}), 129.4 (C_{Ar}), 128.2 (C_{Ar}), 128.2 (C_{Ar}), 126.9 (C_{Ar}), 126.8 (C_{Ar}), 125.8 (C_{Ar}), 124.9 (d, *J* 17.2, C_2), 124.8 (C_{Ar}), 115.0 (d, *J* 22.2, C_6), 38.3 (C_8), 37.5 (C_{16}), 14.6 (d, *J* 3.5, C_1). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −121.0 (1F, br s, F_7). **IR** (film, $CDCl_3$) ν_{max} = 3066 (C–H), 2925 (C–H), 1644 (C=O), 1590, 1501, 1357, 1119, 908, 773, 729, 694 cm^{-1}. **HRMS** (ESI$^+$) *m*/*z* calcd for $C_{22}H_{19}ClFNNaO$ $[M+Na]^+$ 390.1031, found 390.1039.

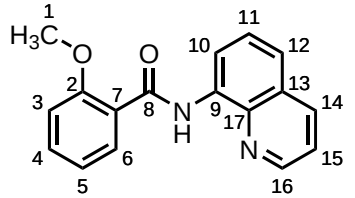
2-((3-Chlorophenyl)(3-fluoro-4-methylphenyl)methyl)-*N*-methylbenzamide (1.50ae)



By **GP3**, *N*-(3-chlorophenyl)-2-(3-fluoro-4-methylbenzyl)-*N*-methylbenzamide (**1.49v**) (74 mg, 0.20 mmol) was used as the 2-arylbenzamide that was stirred at room temperature for 1 h, and purified by flash column chromatography (SiO_2; gradient elution: 12–100% Et_2O in pet. ether) to yield the title compound as a yellow solid (50 mg, 68%).

m.p. = 103–105 °C (DCM). $\boldsymbol{R_f}$ = 0.11 (50% Et_2O in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36–7.29 (2H, m, 2 × H_{Ar}), 7.27–7.16 (3H, m, 3 × H_{Ar}), 7.07–7.04 (1H, m, H_{Ar}), 7.01–6.95 (2H, m, 2 × H_{Ar}), 6.95–6.91 (1H, m, H_3), 6.89 (1H, dd, *J* 9.1, 2.4, H_6), 6.83 (1H, ddd, *J* 8.1, 5.0, 2.4, H_4), 6.08 (1H, s, H_8), 5.39 (1H, br s, NH), 2.73 (3H, d, *J* 4.8, H_{16}), 2.20 (3H, d, *J* 2.1, H_1). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.7 (C_{15}), 160.2 (d, *J* 244.3, C_7), 145.6 (C_{17}), 141.2 (C_9), 138.1 (d, *J* 3.7, C_5), 137.3 (C_{14}), 134.4 (C_{21}), 132.6 (d, *J* 5.2, C_3), 130.2 (C_{Ar}), 129.9 (C_{Ar}), 129.7 (C_{Ar}), 129.5 (C_{Ar}), 128.3 (d, *J* 7.9, C_4), 127.9 (C_{Ar}), 127.2 (C_{Ar}), 126.8 (C_{Ar}), 126.8 (C_{Ar}), 124.9 (d, *J* 17.4, C_2), 115.0 (d, *J* 22.2, C_6), 51.3 (C_8), 26.6 (C_{16}), 14.7 (d, *J* 3.4, C_1). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −120.5 (1F, dddq, *J* 9.1, 7.1, 5.0, 2.1, F_7). **IR** (film, $CDCl_3$) ν_{max} = 3293 (N−H, br), 2960 (C−H), 2929 (C−H), 1634 (C=O), 1594, 1532, 1499, 1473, 1120, 908, 729, 686 cm^{-1}. **HRMS** (ESI^+) *m*/*z* calcd for $C_{22}H_{19}ClFNNaO$ $[M+Na]^+$ 390.1031, found 390.1039.

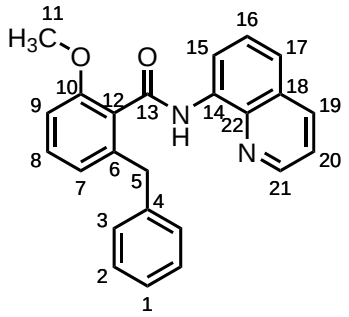
2-Methoxy-*N*-(quinolin-8-yl)benzamide (1.75a)



By **GP2**, the acid chloride of carboxylic acid 2-methoxybenzoic acid (1.52 g, 10.0 mmol) was made by stirring with oxalyl chloride for 23 h. 8-Aminoquinoline (1.73 g, 12.0 mmol) was used as the general amine that was stirred with the acid chloride intermediate for 25 h, and purified by flash column chromatography (SiO_2; gradient elution: 7–60% EtOAc in pet. ether) to yield the title compound as a tan solid (2.48 g, 89%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.32 (1H, s, NH), 9.04 (1H, dd, J 7.8, 1.4, H_{10}), 8.84 (1H, dd, J 4.2, 1.7, H_{16}), 8.36 (1H, dd, J 7.8, 1.8, H_6), 8.13 (1H, dd, J 8.3, 1.7, H_{14}), 7.57 (1H, t, J 7.8, H_{11}), 7.53–7.45 (2H, m, H_4, H_{12}), 7.42 (1H, dd, J 8.3, 4.2, H_{15}), 7.13 (1H, ddd, J 7.8, 7.3, 1.0, H_5), 7.05 (1H, dd, J 8.4, 1.0, H_3), 4.16 (3H, s, H_1). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.7 (C_8), 157.8 (C_2), 148.3 (C_{16}), 139.3 (C_{17}), 136.3 (C_{14}), 135.8 (C_9), 133.2 (C_4), 132.4 (C_6), 128.2 (C_{13}), 127.6 (C_{11}), 122.4 (C_7), 121.6 (C_{12}), 121.5 (C_{15}), 121.3 (C_5), 117.5 (C_{10}), 111.7 (C_3), 56.2 (C_1). Data consistent with literature.[315]

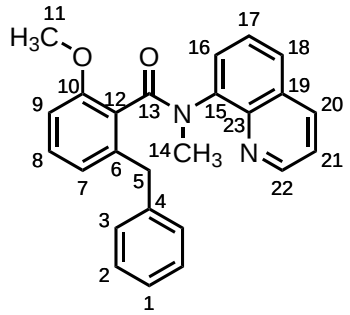
2-Benzyl-6-methoxy-*N*-(quinolin-8-yl)benzamide (1.76a)



By **GP5**, 2-methoxy-*N*-(quinolin-8-yl)benzamide (**1.75a**) (206 mg, 0.74 mmol) was used as the 8-aminoquinolinyl benzamide that was stirred for 22 h, and purified by flash column chromatography (SiO_2; gradient elution: 0–1.2% EtOAc in PhMe) to yield the title compound as a pale yellow solid (168 mg, 62%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.00 (1H, s, NH), 8.99 (1H, dd, J 7.6, 1.5, H_{15}), 8.70 (1H, dd, J 4.2, 1.7, H_{21}), 8.15 (1H, dd, J 8.3, 1.7, H_{19}), 7.59 (1H, dd, J 8.3, 7.6, H_{16}), 7.53 (1H, dd, J 8.3, 1.5, H_{17}), 7.42 (1H, dd, J 8.3, 4.2, H_{20}), 7.31 (1H, t, J 8.0, H_8), 7.23–7.18 (2H, m, H_2), 7.16–7.09 (2H, m, H_3), 7.07–7.00 (1H, m, H_1), 6.87 (1H, d, J 8.0, H_9), 6.84 (1H, d, J 8.0, H_7), 4.14 (2H, s, H_5), 3.85 (3H, s, H_{11}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.4 (C_{13}), 156.6 (C_{10}), 148.1 (C_{21}), 140.6 (C_6), 140.5 (C_4), 138.6 (C_{22}), 136.3 (C_{19}), 134.8 (C_{14}), 130.4 (C_8), 129.3 (C_2), 128.4 (C_3), 128.1 (C_{18}), 127.6 (C_{16}), 127.3 (C_{12}), 126.1 (C_1), 122.7 (C_7), 121.8 (C_{17}), 121.6 (C_{20}), 116.9 (C_{15}), 109.2 (C_9), 56.0 (C_{11}), 39.0 (C_5). Data consistent with literature.[301]

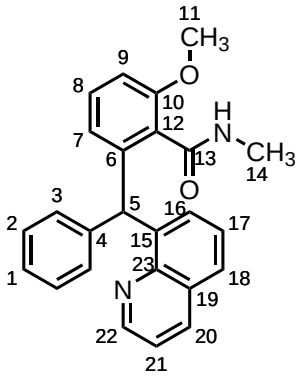
2-Benzyl-6-methoxy-*N*-methyl-*N*-(quinolin-8-yl)benzamide (1.49w)



By **GP6**, 2-benzyl-6-methoxy-*N*-(quinolin-8-yl)benzamide (**1.76a**) (283 mg, 0.77 mmol) was used as the amide, and purified by flash column chromatography (SiO_2; gradient elution: 7–60% EtOAc in pet. ether) to yield the title compound as a yellow gum (237 mg, 81%).

***R*$_f$** = 0.17 (30% EtOAc in pet. ether). **^{1}H NMR** (500 MHz, $CDCl_3$, mixture of rotamers A:B:C in an approximate 55:25:20 ratio) δ 9.11–9.04 (1H^C, d, *J* 3.1, H_{22}), 8.88 (1H^B, br s, H_{22}), 8.77 (1H^A, dd, *J* 4.3, 1.7, H_{22}), 8.21 (1H^B, d, *J* 8.2, H_{20}), 8.13–8.04 (1H^A + 1H^C, m, $H_{20}{}^A$, $H_{20}{}^C$), 7.87–7.81 (1H^B + 1H^C, m, H_{Ar}), 7.76 (1H^A, dd, *J* 7.3, 1.4, H_{Ar}), 7.66 (1H^A, dd, *J* 8.1, 1.5, H_{Ar}), 7.63 (1H^C, d, *J* 7.7, $H_{Ar}{}^C$), 7.52 (1H^C, d, *J* 8.2, $H_{Ar}{}^C$), 7.49–7.39 (3H^B + 2H^C, m, $H_{21}{}^B$, $H_{21}{}^C$, H_{Ar}), 7.38–7.27 (2H^A + 3H^B + 2H^C, m, $H_{21}{}^A$, H_{Ar}), 7.27–7.23 (1H^C, m, H_{Ar}), 7.23–7.18 (2H^B, m, H_{Ar}), 7.08–7.01 (3H^A, m, H_1, H_3), 6.98 (1H^B, t, *J* 8.0, H_{Ar}), 6.91 (1H^C, t, *J* 7.8, H_{Ar}), 6.87–6.81 (1H^A + 1H^B + 1H^C, m, $H_9{}^C$, H_{Ar}), 6.77 (1H^C, d, *J* 7.6, H_{Ar}), 6.62–6.57 (2H^A, m, H_2), 6.55 (1H^A, d, *J* 8.3, H_9), 6.15–6.08 (1H^A + 1H^B + 1H^C, m, $H_9{}^B$, H_{Ar}), 4.44 (1H^B, d, *J* 15.4, H_{5a}), 4.44 (1H^C, d, *J* 14.5, H_{5a}), 4.31 (1H^B, d, *J* 15.4, H_{5b}), 4.11 (1H^C, d, *J* 14.5, H_{5b}), 4.05 (1H^A, d, *J* 16.2, H_{5a}), 3.96 (3H^B, s, H_{11}), 3.93 (3H^A, s, H_{11}), 3.80 (1H^A, d, *J* 16.2, H_{5b}), 3.70 (3H^C, s, H_{14}), 3.70 (3H^A, s, H_{14}), 3.31 (3H^B, s, H_{14}), 2.61 (3H^C, s, H_{11}). **^{13}C NMR** (101 MHz, $CDCl_3$, mixture of rotamers A:B:C in an approximate 55:25:20 ratio) δ 169.9 ($C_{13}{}^B$), 169.2 ($C_{13}{}^A$), 168.5 ($C_{13}{}^C$), 155.7 ($C_{10}{}^B$), 155.5 ($C_{10}{}^A$), 155.1 ($C_{10}{}^C$), 150.3 ($C_{22}{}^A$, $C_{22}{}^B$), 149.8 ($C_{22}{}^C$), 144.4 ($C_{15}{}^B$), 144.1 ($C_{15}{}^A$, $C_{15}{}^C$), 141.0 ($C_4{}^C$), 140.7 ($C_{23}{}^A$, $C_{23}{}^B$), 140.5 ($C_4{}^A$), 140.4 ($C_{23}{}^C$), 140.3 ($C_4{}^B$), 140.3 ($C_6{}^C$), 140.0 ($C_6{}^B$), 139.5 ($C_6{}^A$), 136.4 ($C_{20}{}^C$), 136.2 ($C_{20}{}^B$), 136.0 ($C_{20}{}^A$), 129.7 ($C_2{}^C$), 129.7 ($C_2{}^B$), 129.6 ($C_{Ar}{}^C$), 129.6 ($C_{Ar}{}^B$), 129.4 ($C_{Ar}{}^B$), 129.4 ($C_{Ar}{}^C$), 129.2 ($C_2{}^A$, $C_{19}{}^A$), 128.9 ($C_{Ar}{}^A$), 128.8 ($C_{19}{}^B$), 128.5 ($C_3{}^C$), 128.4 ($C_3{}^B$), 128.1 ($C_{Ar}{}^A$), 128.0 ($C_3{}^A$, $C_{Ar}{}^B$), 127.9 ($C_{Ar}{}^B$), 127.8 ($C_{Ar}{}^A$), 127.2 ($C_{12}{}^B$), 127.2 ($C_{Ar}{}^C$), 126.6 ($C_{12}{}^A$), 126.4 ($C_{Ar}{}^C$), 126.3 ($C_{19}{}^C$), 126.0 ($C_{Ar}{}^B$), 125.9 ($C_{Ar}{}^A$), 125.6 ($C_1{}^A$), 125.5 ($C_{12}{}^C$), 125.3 ($C_{Ar}{}^C$), 122.4 ($C_{Ar}{}^B$), 122.2 ($C_{Ar}{}^C$), 121.6 ($C_{Ar}{}^A$), 121.5 ($C_{21}{}^A$), 121.5 ($C_{21}{}^B$), 121.0 ($C_{21}{}^C$), 108.4 ($C_9{}^C$), 107.7 ($C_9{}^A$), 107.7 ($C_9{}^B$), 56.0 ($C_{11}{}^B$), 55.6 ($C_{11}{}^A$), 53.8 ($C_{11}{}^C$), 39.7 ($C_{14}{}^B$), 39.4 ($C_5{}^C$), 38.4 ($C_5{}^B$), 38.1 ($C_5{}^A$), 37.4 ($C_{14}{}^C$), 37.3 ($C_{14}{}^A$). **IR** (film, $CDCl_3$) ν_{max} = 3060 (C–H), 3028 (C–H), 2933 (C–H), 1642 (C=O), 1596, 1581, 1496, 1469, 1390, 1261, 1067, 732 cm^{-1}. **HRMS** (ESI$^+$) *m*/*z* calcd for $C_{25}H_{22}N_2NaO_2$ $[M+Na]^+$ 405.1573, found 405.1581.

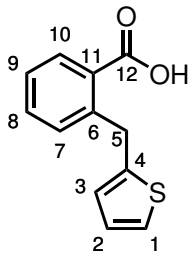
2-Methoxy-*N*-methyl-6-(phenyl(quinolin-8-yl)methyl)benzamide (1.50x)



By **GP3**, 2-benzyl-6-methoxy-*N*-methyl-*N*-(quinolin-8-yl)benzamide (**1.49w**) (76 mg, 0.20 mmol) was used as the 2-arylbenzamide that was stirred at 100 °C for 1 h, and purified by flash column chromatography (SiO_2; gradient elution: 12–100% EtOAc in pet. ether) to yield the title compound as a yellow solid (63 mg, 83%).

m.p. = 203–205 °C (DCM). $\boldsymbol{R_f}$ = 0.41 (100% EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.81 (1H, dd, *J* 4.2, 1.8, H_{22}), 8.16 (1H, dd, *J* 8.2, 1.8, H_{20}), 8.02 (1H, br q, *J* 4.9, N*H*), 7.72 (1H, dd, *J* 8.1, 1.2, H_{16}), 7.47 (1H, dd, *J* 8.1, 7.0, H_{17}), 7.38 (1H, dd, *J* 8.2, 4.2, H_{21}), 7.34 (1H, dd, *J* 7.0, 1.2, H_{18}), 7.29–7.09 (6H, m, H_{Ar}), 6.92 (1H, s, H_5), 6.75 (1H, dd, *J* 8.4, 0.9, H_9), 6.60 (1H, dd, *J* 8.0, 0.9, H_7), 3.83 (3H, s, H_{11}), 2.93 (3H, d, *J* 4.9, H_{14}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.6 (C_{13}), 156.9 (C_{10}), 149.3 (C_{22}), 146.2 (C_{23}), 143.0 (C_{15}), 142.4 (C_4), 141.1 (C_6), 137.6 (C_{20}), 130.5 (C_{18}), 129.8 (C_2), 129.2 (C_8), 128.7 (C_{19}), 128.4 (C_3), 127.6 (C_{12}), 127.0 (C_{16}), 126.5 (C_1), 126.4 (C_{17}), 121.9 (C_7), 121.1 (C_{21}), 109.1 (C_9), 55.9 (C_{11}), 48.1 (C_5), 26.5 (C_{14}). **IR** (film, $CDCl_3$) ν_{max} = 3259 (N–H, br), 3061 (C–H), 2934 (C–H), 1659 (C=O), 1597, 1580, 1495, 1467, 1262, 1066, 909, 726, 699 cm^{-1}. **HRMS** (ESI$^+$) *m*/*z* calcd for $C_{25}H_{23}N_2O_2$ $[M+H]^+$ 383.1754, found 383.1752.

2-(Thiophen-2-ylmethyl)benzoic acid (1.55a)



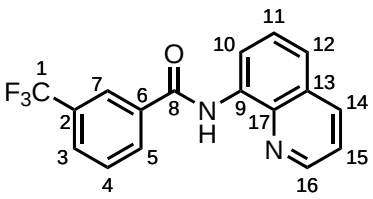
By the method of Prinz and co-workers[316] with modifications, in air, 2-(2-thienylcarbonyl)benzoic acid (2.16 g, 9.30 mmol, 1.0 eq.), zinc dust (7.54 g, 115 mmol, 12.4 eq.) and $CuSO_4 \cdot 5H_2O$ (319 mg, 1.30 mmol, 0.14 eq.) were suspended in aqueous NH_4OH (62 mL, 35 wt%), and the reaction mixture stirred at reflux for 45 h, with portions of aqueous NH_4OH (3 × 5 mL, 35 wt%) added

over this period. While hot, the liquid was decanted from the solid residue, and the solid residue washed with H_2O. The combined aqueous solutions were cooled to 0 °C, adjusted to pH 1 with aqueous HCl (37 wt%), extracted with EtOAc (3 × 50 mL), and concentrated *in vacuo*. NMR analysis revealed the crude material was a mixture of 3-(thiophen-2-yl)isobenzofuran-1(3*H*)-one and 2-(thiophen-2-ylmethyl) benzoic acid in an approximate 5:1 ratio.

By the method of Hong and co-workers[317], in air, the crude material was dissolved in AcOH (5.0 mL), Pd/C (990 mg, 10 wt%, 0.93 mmol, 0.10 eq.) added, and the reaction mixture stirred at 90 °C under H_2 (1 atm, balloon) for 3.5 d. The reaction mixture was filtered through Celite, eluting with EtOAc, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2; gradient elution: 7–60% EtOAc in pet. ether) to yield the title compound as a white solid (797 mg, 39%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.68 (1H, br s, O*H*), 8.11 (1H, dd, *J* 8.1, 1.5, H_{10}), 7.52 (1H, td, *J* 7.5, 1.5, H_8), 7.39–7.32 (2H, m, H_7, H_9), 7.14 (1H, dd, *J* 5.2, 1.2, H_1), 6.92 (1H, dd, *J* 5.2, 3.5, H_2), 6.84–6.81 (1H, m, H_3), 4.66 (2H, s, H_5). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.2 (C_{12}), 143.6 (C_4), 143.3 (C_6), 133.5 (C_8), 132.0 (C_{10}), 131.5 (C_7), 128.0 (C_{11}), 126.9 (C_9), 126.8 (C_2), 125.6 (C_3), 124.1 (C_1), 34.2 (C_5). Data consistent with literature.[317]

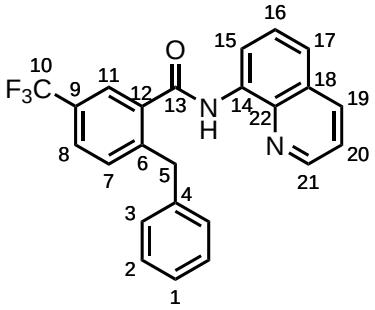
N-(Quinolin-8-yl)-3-(trifluoromethyl)benzamide (1.75b)



By **GP2**, the acid chloride of carboxylic acid 3-trifluoromethyl)benzoic acid (951 mg, 5.00 mmol) was made by stirring with oxalyl chloride for 23 h. 8-Aminoquinoline (1.73 g, 12.0 mmol) was used as the general amine that was stirred with the acid chloride intermediate for 24 h, and purified by flash column chromatography (SiO_2; gradient elution: 12–100% Et_2O in pet. ether) to yield the title compound as a pale yellow solid (1.29 g, 82%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.77 (1H, s, N*H*), 8.91 (1H, dd, *J* 7.1, 1.8, H_{10}), 8.86 (1H, dd, *J* 4.2, 1.7, H_{16}), 8.35 (1H, s, H_7), 8.24 (1H, d, *J* 7.7, H_5), 8.19 (1H, dd, *J* 8.3, 1.7, H_{14}), 7.84 (1H, d, *J* 7.7, H_3), 7.68 (1H, t, *J* 7.7, H_4), 7.64–7.54 (2H, m, H_{11}, H_{12}), 7.49 (1H, dd, *J* 8.3, 4.2, H_{15}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.0 (C_8), 148.6 (C_{16}), 138.8 (C_{17}), 136.6 (C_{14}), 136.1 (C_9), 134.2 (C_6), 131.6 (q, *J* 32.9, C_2), 130.4 (C_5), 129.5 (C_4), 128.5 (q, *J* 3.6, C_3), 128.1 (C_{13}), 127.6 (C_{11}), 124.7 (q, *J* 3.8, C_7), 123.9 (q, *J* 272.7, C_1), 122.3 (C_{12}), 121.9 (C_{15}), 116.9 (C_{10}). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −62.7 (3F, s, F_1). Data consistent with literature.[301]

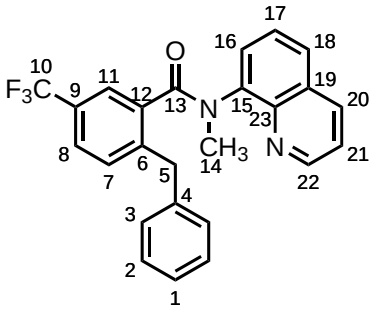
2-Benzyl-*N*-(quinolin-8-yl)-5-(trifluoromethyl)benzamide (1.76b)



By **GP5**, *N*-(quinolin-8-yl)-3-(trifluoromethyl)benzamide (**1.75b**) (234 mg, 0.74 mmol) was used as the 8-aminoquinolinyl benzamide that was stirred for 21 h, and purified by flash column chromatography (SiO_2; gradient elution: 2–20% EtOAc in pet. ether) to yield the title compound as an off-white solid (228 mg, 76%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.12 (1H, s, N*H*), 8.90 (1H, dd, *J* 6.8, 2.2, H_{15}), 8.74 (1H, dd, *J* 4.2, 1.7, H_{21}), 8.19 (1H, dd, *J* 8.3, 1.7, H_{19}), 7.92 (1H, d, *J* 2.0, H_{11}), 7.66 (1H, dd, *J* 8.0, 2.0, H_8), 7.63–7.56 (2H, m, H_{16}, H_{17}), 7.46 (1H, dd, *J* 8.3, 4.2, H_{20}), 7.39 (1H, d, *J* 8.0, H_7), 7.24–7.15 (4H, m, H_2, H_3), 7.15–7.07 (1H, m, H_1), 4.36 (2H, s, H_5). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.9 (C_{13}), 148.9 (C_{21}), 143.9 (q, *J* 1.3, C_6), 139.6 (C_4), 138.6 (C_{22}), 137.6 (C_{12}), 136.5 (C_{19}), 134.4 (C_{14}), 131.6 (C_7), 129.3 (C_2), 129.0 (q, *J* 32.9, C_9), 128.7 (C_3), 128.1 (C_{18}), 127.5 (C_6), 127.1 (q, *J* 3.6, C_8), 126.5 (C_1), 124.3 (q, *J* 3.8, C_{11}), 124.0 (q, *J* 272.2, C_{10}), 122.4 (C_{17}), 121.9 (C_{20}), 117.0 (C_{15}), 38.9 (C_5). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −62.4 (3F, s, F_1). Data consistent with literature.[301]

2-Benzyl-*N*-methyl-*N*-(quinolin-8-yl)-5-(trifluoromethyl)benzamide (1.49p)

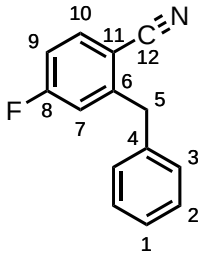


By **GP6**, 2-benzyl-*N*-(quinolin-8-yl)-5-(trifluoromethyl)benzamide (**1.76b**) (371 mg, 0.91 mmol) was used as the amide, and purified by flash column chromatography (SiO_2; gradient elution: 7–60% EtOAc in pet. ether) to yield the title compound as a yellow gum (271 mg, 71%).

***R*$_f$** = 0.29 (30% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.03–8.95 (1H, m, H_{22}), 8.09 (1H, d, *J* 8.3, H_{20}), 7.61 (1H, d, *J* 8.3, H_{Ar}), 7.43 (1H, dd, *J*

8.3, 4.2, H_{21}), 7.39–7.21 (4H, m, H_3, 2 × H_{Ar}), 7.21–7.10 (4H, m, H_2, 2 × H_{Ar}), 7.10–6.89 (1H, m, H_{Ar}), 6.54 (1H, br s, H_{Ar}), 4.52–4.04 (2H, m, H_5), 3.67– 3.06 (3H, m, H_{14}). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.0 (C_{13}), 151.0 (C_{22}), 144.2 (C_{23}), 143.0 (C_4), 141.0 (C_{15}), 139.7 (C_6), 137.0 (C_{12}), 136.4 (C_{20}), 130.3 (C_{Ar}), 129.8 (C_2), 129.3 (C_{19}), 129.0 (C_{Ar}), 128.7 (C_3), 128.4 (C_{Ar}), 127.2 (q, J 32.4, C_9), 126.6 (C_{Ar}), 126.2 (C_{Ar}), 125.3 (C_{Ar}), 124.5 (C_{Ar}), 123.6 (q, J 272.4, C_{10}), 121.9 (C_{21}), 38.9 (C_5), 37.6 (C_{14}). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −63.2 (3F, s, F_1). **IR** (film, $CDCl_3$) ν_{max} = 3062 (C−H), 3029 (C−H), 2927 (C−H), 1647 (C=O), 1615, 1495, 1372, 1330, 1320, 1164, 1122, 1079, 794, 730 cm^{-1}. **HRMS** (ESI$^+$) m/z calcd for $C_{25}H_{20}F_3N_2O$ $[M+H]^+$ 421.1522, found 421.1517.

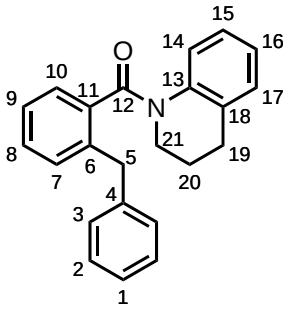
2-Benzyl-4-fluorobenzonitrile (1.59a)



By **GP4**, 2-(bromomethyl)-4-fluorobenzonitrile (2.14 g, 10.0 mmol) was used as the 2-(bromomethyl)benzonitrile and phenylboronic acid (1.83 g, 15.0 mmol) was used as the boronic acid that were stirred for 22 h, and purified by flash column chromatography (SiO_2; gradient elution: 3–25% Et_2O in pet. ether) to yield the title compound as a colourless oil (1.50 g, 71%).

***R*$_f$** = 0.63 (30% Et_2O in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.67 (1H, dd, J 8.6, 5.6, H_{10}), 7.39–7.33 (2H, m, H_2), 7.32–7.28 (1H, m, H_1), 7.28–7.23 (2H, m, H_3), 7.03 (1H, ddd, J 8.6, 7.9, 2.6, H_9), 6.97 (1H, dd, J 9.4, 2.6, H_7), 4.22 (2H, s, H_5). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.1 (d, J 256.3, C_8), 148.6 (d, J 8.7, C_6), 138.0 (C_4), 135.3 (d, J 9.6, C_{10}), 129.1 (C_3), 129.0 (C_2), 127.2 (C_1), 117.6 (C_{12}), 117.5 (d, J 22.8, C_7), 114.7 (d, J 22.8, C_9), 108.7 (d, J 3.3, C_{11}), 40.2 (d, J 1.6, C_5). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −102.6 (1F, ddd, J 9.4, 7.9, 5.6, F_8). **IR** (film, $CDCl_3$) ν_{max} = 3088 (C−H), 3065 (C−H), 3031 (C−H), 2226 (C−N), 1608, 1583, 1489, 1451, 1275, 1242, 963, 827, 697, 686, 562 cm^{-1}. **HRMS** (ESI$^+$) m/z calcd for $C_{14}H_{10}FNNa$ $[M+H]^+$ 234.0689, found 234.0682.

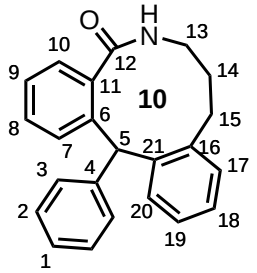
(2-Benzylphenyl)(3,4-dihydroquinolin-1(2*H*)-yl)methanone (1.60a)



By **GP2**, the acid chloride of carboxylic acid 2-benzylbenzoic acid (1.06 g, 5.00 mmol) was made by stirring with oxalyl chloride for 24 h. 1,2,3,4-Tetrahydroquinoline (750 µL, 5.97 mmol) was used as the tethered aniline that was stirred with the acid chloride intermediate for 20 h, and purified by flash column chromatography (SiO_2; gradient elution: 12–100% Et_2O in pet. ether) to yield the title compound as a yellow oil that solidified upon standing (1.22 g, 74%).

m.p. = 76–77 °C (DCM). $\boldsymbol{R_f}$ = 0.38 (50% Et_2O in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.48–7.23 (4H, m, 4 × H_{Ar}), 7.23–7.14 (5H, m, 5 × H_{Ar}), 7.13 (1H, d, J 7.8, H_{17}), 7.10–6.78 (2H, m, 2 × H_{Ar}), 6.78–5.45 (1H, m, H_{Ar}), 4.08 (2H, s, H_5), 3.77 (2H, br s, H_{21}), 2.80 (2H, t, J 6.8, H_{19}), 2.22–1.54 (2H, m, H_{20}). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.3 (C_{12}), 140.1 (C_4), 138.6 (C_6), 138.4 (C_{11}), 136.8 (C_{13}), 130.5 (C_{Ar}), 129.4 (C_2), 129.3 (C_{Ar}), 128.7 (C_{17}), 128.5 (C_3), 127.6 (C_{18}), 126.3 (C_{Ar}), 126.2 (C_{Ar}), 125.8 (C_{Ar}), 124.8 (C_{Ar}), 124.7 (C_{Ar}), 43.7 (C_{21}), 38.8 (C_5), 27.0 (C_{19}), 23.8 (C_{20}). **IR** (film, $CDCl_3$) ν_{max} = 3025 (C–H), 2942 (C–H), 1638 (C=O), 1600, 1579, 1490, 1377, 1350, 758, 739, 699 cm^{-1}. **HRMS** (ESI$^+$) m/z calcd for $C_{23}H_{21}NNaO$ $[M+Na]^+$ 350.1515, found 350.1528.

14-Phenyl-7,8,9,14-tetrahydrodibenzo[*c*,*f*]azecin-5(6*H*)-one (1.61a)

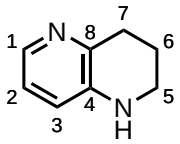


By **GP3**, (2-benzylphenyl)(3,4-dihydroquinolin-1(2*H*)-yl)methanone (**1.60a**) (262 mg, 0.80 mmol) was used as the 2-arylbenzamide that was stirred at 100 °C for 2 h, and purified by flash column chromatography (SiO_2; gradient elution: 7–60% EtOAc in pet. ether) to yield the title compound as an off-white solid (160 mg, 61%).

m.p. = 245–247 °C (DCM). $\boldsymbol{R_f}$ = 0.11 (30% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers in an approximate 65:35 ratio) δ 7.69 (1H^{min}, d,

J 8.0, H_{Ar}), 7.62–7.56 (1H$^{\mathrm{min}}$, m, H_{Ar}), 7.44–7.11 (11H$^{\mathrm{maj}}$ + 9H$^{\mathrm{min}}$, m, 11 × $H_{\mathrm{Ar}}{}^{\mathrm{maj}}$, 9 × $H_{\mathrm{Ar}}{}^{\mathrm{min}}$), 7.06–7.01 (2H$^{\mathrm{maj}}$, m, H_2), 7.00–6.95 (2H$^{\mathrm{min}}$, m, H_2), 6.78 (1H$^{\mathrm{min}}$, d, J 11.5, NH), 6.09 (1H$^{\mathrm{maj}}$, s, H_5), 5.86 (1H$^{\mathrm{min}}$, s, H_5), 5.35 (1H$^{\mathrm{maj}}$, d, J 9.4, NH), 4.30 (1H$^{\mathrm{maj}}$, dddd, J 13.6, 12.6, 9.4, 5.6, $H_{13\mathrm{a}}$), 3.29–3.18 (1H$^{\mathrm{maj}}$ + 1H$^{\mathrm{min}}$, m, $H_{13\mathrm{b}}{}^{\mathrm{maj}}$, $H_{15\mathrm{a}}{}^{\mathrm{min}}$), 3.08 (1H$^{\mathrm{min}}$, dt, J 13.8, 3.3, $H_{13\mathrm{a}}$), 2.97–2.80 (2H$^{\mathrm{maj}}$ + 1H$^{\mathrm{min}}$, m, $H_{15}{}^{\mathrm{maj}}$, $H_{13\mathrm{b}}{}^{\mathrm{min}}$), 2.57 (1H$^{\mathrm{min}}$, dt, J 14.1, 3.8, $H_{15\mathrm{b}}$), 2.36 (1H$^{\mathrm{maj}}$, dddt, J 15.2, 7.6, 5.6, 1.9, $H_{14\mathrm{a}}$), 2.09–1.99 (1H$^{\mathrm{min}}$, m, $H_{14\mathrm{a}}$), 1.99–1.86 (1H$^{\mathrm{min}}$, m, $H_{14\mathrm{b}}$), 1.63 (1H$^{\mathrm{min}}$, ddt, J 16.8, 10.8, 2.8, $H_{14\mathrm{b}}$). **^{13}C NMR** (101 MHz, $CDCl_3$, mixture of rotamers in an approximate 65:35 ratio) δ 174.3 ($C_{12}{}^{\mathrm{min}}$), 170.8 ($C_{12}{}^{\mathrm{maj}}$), 145.0 ($C_4{}^{\mathrm{min}}$), 143.1 ($C_4{}^{\mathrm{maj}}$), 142.8 ($C_{21}{}^{\mathrm{maj}}$), 142.4 ($C_{21}{}^{\mathrm{min}}$), 142.2 ($C_{11}{}^{\mathrm{maj}}$), 140.2 ($C_{16}{}^{\mathrm{min}}$), 139.8 ($C_{11}{}^{\mathrm{min}}$), 139.4 ($C_{16}{}^{\mathrm{maj}}$), 138.5 ($C_6{}^{\mathrm{maj}}$), 136.9 ($C_6{}^{\mathrm{min}}$), 131.3 ($C_{17}{}^{\mathrm{maj}}$), 130.7 ($C_{17}{}^{\mathrm{min}}$), 130.6 ($C_{\mathrm{Ar}}{}^{\mathrm{maj}}$), 130.0 ($C_{\mathrm{Ar}}{}^{\mathrm{maj}}$, $C_{\mathrm{Ar}}{}^{\mathrm{min}}$), 129.8 ($C_{\mathrm{Ar}}{}^{\mathrm{maj}}$), 129.8 ($C_{\mathrm{Ar}}{}^{\mathrm{min}}$), 129.4 ($C_2{}^{\mathrm{maj}}$), 129.1 ($C_2{}^{\mathrm{min}}$), 128.2 ($C_3{}^{\mathrm{maj}}$), 128.1 ($C_3{}^{\mathrm{min}}$), 127.4 ($C_{\mathrm{Ar}}{}^{\mathrm{maj}}$, $C_{\mathrm{Ar}}{}^{\mathrm{min}}$), 127.2 ($C_{\mathrm{Ar}}{}^{\mathrm{min}}$), 126.9 ($C_{\mathrm{Ar}}{}^{\mathrm{min}}$), 126.9 ($C_{\mathrm{Ar}}{}^{\mathrm{maj}}$), 126.6 ($C_{\mathrm{Ar}}{}^{\mathrm{maj}}$), 126.6 ($C_{\mathrm{Ar}}{}^{\mathrm{min}}$), 126.4 ($C_{\mathrm{Ar}}{}^{\mathrm{maj}}$), 126.3 ($C_{\mathrm{Ar}}{}^{\mathrm{maj}}$), 126.0 ($C_{\mathrm{Ar}}{}^{\mathrm{min}}$), 48.3 ($C_5{}^{\mathrm{maj}}$), 47.4 ($C_5{}^{\mathrm{min}}$), 41.3 ($C_{13}{}^{\mathrm{maj}}$), 41.0 ($C_{13}{}^{\mathrm{min}}$), 32.5 ($C_{14}{}^{\mathrm{min}}$), 30.1 ($C_{14}{}^{\mathrm{maj}}$), 29.1 ($C_{15}{}^{\mathrm{maj}}$), 27.7 ($C_{15}{}^{\mathrm{min}}$). **IR** (film, $CDCl_3$) ν_{max} = 3195 (N–H, br), 3060 (C–H), 3024 (C–H), 2936 (C–H), 1648 (C=O), 1599, 1493, 1445, 1033, 909, 774, 725, 698, 612 cm^{-1}. **HRMS** (ESI$^+$) m/z calcd for $C_{23}H_{22}NNaO$ [M+Na]$^+$ 350.1515, found 350.1515.

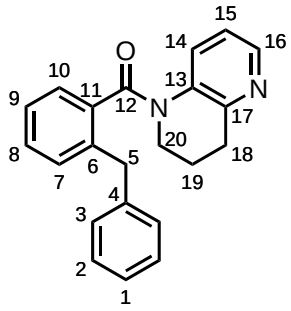
1,2,3,4-Tetrahydro-1,5-naphthyridine (1.77a)



By the method of Song and co-workers[314] with modifications, 1,5-naphthyridine (260 mg, 2.00 mmol, 1.0 eq.), bis(pinacolato)diboron (1.52 g, 5.99 mmol, 3.0 eq.) and $Pd(OAc)_2$ (45 mg, 0.10 mmol, 0.10 eq.) were suspended in H_2O (20 mL) that had been degassed by bubbling N_2 through the liquid for 30 min. The reaction mixture was stirred at room temperature for 14 h, and extracted with EtOAc (3 × 25 mL). The combined organic extracts were washed sequentially with aqueous NaOH (3 × 25 mL, 2 M) and brine (25 mL), and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2; gradient elution: 10–80% EtOAc in pet. ether) to yield the title compound as a yellow solid (127 mg, 47%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (1H, dd, J 4.7, 1.5, H_1), 6.85 (1H, dd, J 8.0, 4.7, H_2), 6.69 (1H, dd, J 8.0, 1.5, H_3), 3.87 (1H, br s, NH), 3.27 (2H, dd, J 5.5, 4.2, H_5), 2.91 (2H, t, J 6.5, H_7), 2.00 (2H, tdd, J 6.5, 5.5, 4.2, H_6). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.8 (C_8), 141.1 (C_4), 137.9 (C_1), 122.0 (C_2), 120.3 (C_3), 41.6 (C_5), 30.4 (C_7), 21.8 (C_6). Data consistent with literature.[318]

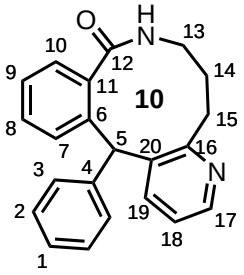
(2-Benzylphenyl)(3,4-dihydro-1,5-naphthyridin-1(2*H*)-yl)methanone (1.60b)



By **GP2**, the acid chloride of carboxylic acid 2-benzylbenzoic acid (395 mg, 1.86 mmol) was made by stirring with oxalyl chloride for 22 h. 1,2,3,4-tetrahydro-1,5-naphthyridine (**1.77a**) (250 mg, 1.86 mmol, 1.0 eq.) was used as the tethered aniline that was stirred with the acid chloride intermediate for 23 h, and pyrified by flash column chromatography (SiO_2; gradient elution: 12–100% Et_2O in pet. ether) to yield the title compound as a yellow oil that solidified upon standing (380 mg, 62%).

m.p. = 101–103 °C (DCM). $\boldsymbol{R_f}$ = 0.15 (50% Et_2O in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.24 (1H, br s, H_{16}), 7.32 (1H, t, J 7.4, H_{Ar}), 7.28–7.06 (9H, m, 9 × H_{Ar}), 7.05–6.80 (1H, m, H_{14}), 4.07 (2H, br s, H_5), 3.87–3.12 (2H, m, H_{20}), 2.92 (2H, br s, H_{18}), 1.88 (1H, br s, H_{19a}), 1.66 (1H, br s, H_{19b}). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.4 (C_{12}), 149.7 (C_{17}), 145.1 (C_{16}), 139.8 (C_4), 138.6 (C_{13}), 136.1 (C_6), 134.7 (C_{11}), 131.5 (C_{Ar}), 130.9 (C_{Ar}), 129.6 (C_{Ar}), 129.2 (C_2), 128.5 (C_3), 126.9 (C_{Ar}), 126.4 (C_{Ar}), 126.3 (C_{Ar}), 120.8 (C_{14}), 38.9 (C_{20}), 38.9 (C_5), 30.1 (C_{18}), 22.7 (C_{19}). **IR** (film, $CDCl_3$) ν_{max} = 3061 (C–H), 3026 (C–H), 2935 (C–H), 1644 (C=O), 1581, 1450, 1369, 1344, 908, 726, 698, 640 cm^{-1}. **HRMS** (ESI$^+$) m/z calcd for $C_{22}H_{20}N_2NaO$ $[M+Na]^+$ 351.1468, found 351.1462.

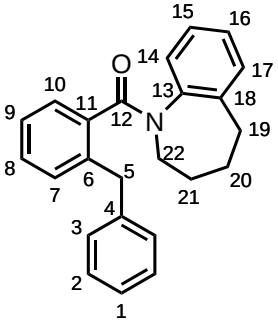
14-Phenyl-5,7,8,14-tetrahydrobenzo[*c*]pyrido[3,2-*f*]azecin-9(6*H*)-one (1.61b)



By **GP3**, (2-benzylphenyl)(3,4-dihydro-1,5-naphthyridin-1(2*H*)-yl)methanone (**1.60b**) (263 mg, 0.80 mmol) was used as the 2-arylbenzamide that was stirred at 100 °C for 2 h, and purified by flash column chromatography (SiO_2; gradient elution: 0–10% MeOH in EtOAc) to yield the title compound as a pale orange solid (185 mg, 70%).

m.p. = 222–224 °C (DCM). $\boldsymbol{R_f}$ = 0.25 (10% MeOH in EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers in an approximate 65:35 ratio) δ 8.50 (1H^{maj}, dd, *J* 4.6, 1.7, H_{17}), 8.48 (1H^{min}, dd, *J* 4.6, 1.7, H_{17}), 7.88 (1H^{min}, dd, *J* 8.0, 1.7, H_{19}), 7.71 (1H^{maj}, dd, *J* 8.0, 1.7, H_{19}), 7.54–7.49 (1H^{min}, m, H_{10}), 7.41–7.18 (7H^{maj} + 6H^{min}, m, H_{Ar}), 7.18–7.14 (1H^{min}, m, H_{18}), 7.11 (1H^{maj}, dd, *J* 8.0, 4.6, H_{18}), 7.04–6.99 (2H^{maj}, m, H_{Ar}), 6.99–6.94 (2H^{min}, m. H_{Ar}), 6.51 (1H^{min}, d, *J* 11.7, N*H*), 6.08 (1H^{maj}, s, H_5), 5.86 (1H^{min}, s, H_5), 5.19 (1H^{maj}, d, *J* 10.0, N*H*), 4.41–4.28 (1H^{maj}, m, H_{13a}), 3.47 (1H^{min}, td, *J* 13.0, 3.1, H_{15a}), 3.20 (1H^{maj}, ddt, *J* 13.7, 5.7, 1.7, H_{13b}), 3.16–3.08 (1H^{maj} + 1H^{min}, m, $H_{15a}{}^{maj}$, $H_{13a}{}^{min}$), 2.95 (1H^{maj}, ddd, *J* 14.1, 7.9, 1.9, H_{15b}), 2.88–2.73 (2H^{min}, m, $H_{13b,\ 15b}$), 2.36–2.17 (2H^{maj}, m, H_{14}), 2.12–1.93 (2H^{min}, m, H_{14}). **^{13}C NMR** (101 MHz, $CDCl_3$, mixture of rotamers in an approximate 65:35 ratio) δ 173.9 ($C_{12}{}^{min}$), 170.5 ($C_{12}{}^{maj}$), 161.6 ($C_{16}{}^{maj}$), 159.1 ($C_{16}{}^{min}$), 148.5 ($C_{17}{}^{min}$), 148.3 ($C_{17}{}^{maj}$), 143.8 ($C_4{}^{min}$), 142.0 ($C_4{}^{maj}$), 141.4 ($C_6{}^{maj}$), 139.1 ($C_6{}^{min}$), 138.9 ($C_{11}{}^{maj}$), 138.5 ($C_{19}{}^{maj}$), 138.2 ($C_{20}{}^{min}$), 137.8 ($C_{19}{}^{min}$), 136.9 ($C_{11}{}^{min}$), 135.5 ($C_{20}{}^{maj}$), 129.9 ($C_{Ar}{}^{min}$), 129.8 ($C_{Ar}{}^{maj}$), 129.3 ($C_2{}^{min}$), 129.2 ($C_2{}^{maj}$, $C_{10}{}^{min}$), 129.0 ($C_{Ar}{}^{maj}$), 128.4 ($C_3{}^{maj}$), 128.3 ($C_3{}^{min}$), 127.7 ($C_{Ar}{}^{min}$), 127.2 ($C_{Ar}{}^{maj}$), 126.9 ($C_{Ar}{}^{min}$), 126.8 ($C_{Ar}{}^{maj}$), 126.5 ($C_{Ar}{}^{min}$), 126.2 ($C_{Ar}{}^{maj}$), 122.0 ($C_{18}{}^{min}$), 121.3 ($C_{18}{}^{maj}$), 48.0 ($C_5{}^{maj}$), 47.4 ($C_5{}^{min}$), 41.5 ($C_{13}{}^{min}$), 40.6 ($C_{13}{}^{maj}$), 31.3 ($C_{15}{}^{maj}$), 30.7 ($C_{14}{}^{min}$), 30.2 ($C_{15}{}^{min}$), 28.4 ($C_{14}{}^{maj}$). **IR** (film, $CDCl_3$) ν_{max} = 3264 (N–H, br), 3061 (C–H), 2934 (C–H), 1646 (C=O), 1601, 1538, 1444, 1432, 727, 699 cm^{-1}. **HRMS** (ESI$^+$) *m*/*z* calcd for $C_{22}H_{20}N_2NaO$ [M+Na]$^+$ 351.1468, found 351.1476.

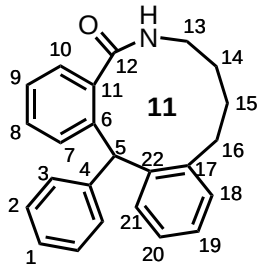
(2-Benzylphenyl)(2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-1-yl)methanone (1.60c)



By **GP2**, the acid chloride of carboxylic acid 2-benzylbenzoic acid (1.06 g, 5.00 mmol) was made by stirring with oxalyl chloride for 16 h. 2,3,4,5-Tetrahydro-1*H*-benzo[*b*]azepine (883 mg, 6.00 mmol) was used as the tethered aniline that was stirred with the acid chloride intermediate for 4.5 h, and purified by flash column chromatography (SiO_2; gradient elution: 7–60% Et_2O in pet. ether) to yield the title compound as a white solid (1.41 g, 82%).

m.p. = 107–109 °C (DCM). $\boldsymbol{R_f}$ = 0.25 (30% Et_2O in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46–7.17 (5H, m, H_2, H_3, H_{Ar}), 7.14–7.06 (3H, m, H_{14}, 2 × H_{Ar}), 6.97 (1H, td, *J* 7.6, 1.4, H_{15}), 6.84 (1H, td, *J* 7.4, 1.7, H_{Ar}), 6.75–6.70 (1H, m, H_{Ar}), 6.70 (1H, td, *J* 7.6, 1.4, H_{16}), 5.87 (1H, br d, *J* 7.6, H_{17}), 4.98 (1H, br d, *J* 12.9, H_{22a}), 4.41 (1H, d, *J* 14.7, H_{5a}), 4.06 (1H, d, *J* 14.7, H_{5b}), 3.00 (1H, br t, *J* 12.9, H_{19a}), 2.87–2.77 (1H, m, H_{19b}), 2.72 (1H, br t, *J* 12.9, H_{22b}), 2.15–1.98 (2H, m, H_{20a}, H_{21a}), 1.98–1.89 (1H, m, H_{21b}), 1.46 (1H, br q, *J* 12.9, H_{20b}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.3 (C_{12}), 143.3 (C_{13}), 140.6 (C_4), 139.2 (C_6, C_{18}), 136.3 (C_{11}), 130.3 (C_{Ar}), 129.9 (C_{Ar}), 129.7 (C_2), 128.8 (C_{14}), 128.5 (C_3), 127.8 (C_{17}), 127.1 (C_{15}), 126.8 (C_{16}, C_{Ar}), 126.4 (C_{Ar}), 125.3 (C_{Ar}), 47.5 (C_{22}), 39.2 (C_5), 35.2 (C_{19}), 29.5 (C_{21}), 26.6 (C_{20}). **IR** (film, $CDCl_3$) ν_{max} = 3060 (C–H), 3025 (C–H), 2931 (C–H), 2852 (C–H), 1638 (C=O), 1598, 1578, 1492, 1388, 1311, 737, 699 cm^{-1}. **HRMS** (ESI$^+$) *m*/*z* calcd for $C_{24}H_{23}NNaO$ $[M+Na]^+$ 364.1672, found 364.1676.

15-Phenyl-6,7,8,9,10,15-hexahydro-5*H*-dibenzo[*c*,*f*][1]azacycloundecin-5-one (1.61c)

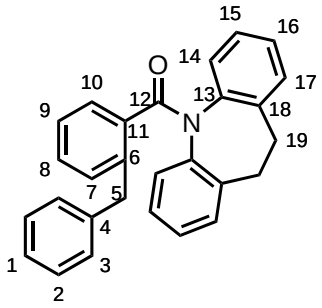


By **GP3**, (2-benzylphenyl)(2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-1-yl) methanone (**1.60c**) (273 mg, 0.80 mmol) was used the 2-arylbenzamide that was stirred at 100 °C for 2 h, and purified by flash column chromatography (SiO_2; gradient elution: 7–60% EtOAc in pet. ether) to yield the title compound as an off-white solid (165 mg, 60%).

m.p. = 222–224 °C (DCM). $\boldsymbol{R_f}$ = 0.21 (30% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46 (1H, dd, *J* 7.5, 1.6, H_{10}), 7.36–7.16 (9H, m, 9 × H_{Ar}), 7.05 (1H, dd, *J* 7.7, 1.4, H_{Ar}), 7.01–6.96 (2H, m, H_2), 6.10 (1H, s, H_5), 5.16 (1H, d, *J* 8.8, N*H*), 3.91 (1H, dddd, *J* 13.5, 10.9, 8.8, 2.4, H_{13a}), 3.02 (1H, ddd, *J* 15.0, 9.1, 5.0, H_{16a}), 2.79 (1H, ddt, *J* 13.5, 6.4, 2.4, H_{13b}), 2.61 (1H, dt, *J* 15.0, 6.0, H_{16b}), 2.18–1.99 (2H, m, H_{15}), 1.82 (1H, ddt, *J* 17.9, 10.1, 3.7, 2.4, H_{14a}), 1.49 (1H, dddd, *J* 17.9, 10.9, 6.4, 3.1, H_{14b}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.0 (C_{12}),

142.5 (C_{quat}), 141.5 (C_{11}), 140.8 (C_{22}), 139.5 (C_{17}), 137.9 (C_{quat}), 130.7 (C_{Ar}), 130.6 (C_{Ar}), 130.2 (C_{Ar}), 129.7 (C_{Ar}), 129.5 (C_2), 128.3 (C_3), 128.2 (C_{10}), 127.1 (C_{Ar}), 126.9 (C_{Ar}), 126.6 (C_{Ar}), 126.5 (C_{Ar}), 48.9 (C_5), 40.2 (C_{13}), 29.1 (C_{16}), 27.5 (C_{15}), 25.6 (C_{14}). **IR** (film, $CDCl_3$) ν_{max} = 3284 (N–H, br), 2923 (C–H), 2855 (C–H), 1633 (C=O), 1599, 1524, 1446, 908, 757, 728, 699, 612 cm^{-1}. **HRMS** (ESI^+) m/z calcd for $C_{24}H_{23}NNaO$ $[M+Na]^+$ 364.1672, found 364.1660.

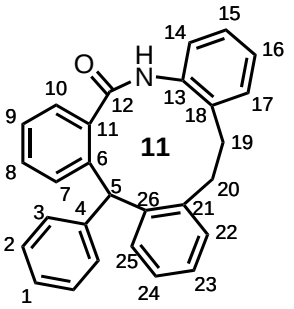
(2-Benzylphenyl)(10,11-dihydro-5*H*-dibenzo[*b*,*f*]azepin-5-yl)methanone (1.60d)



By **GP2**, the acid chloride of carboxylic acid 2-benzylbenzoic acid (1.06 g, 5.00 mmol) was made by stirring with oxalyl chloride for 16 h. 10,11-Dihydro-5*H*-dibenzo[*b*,*f*]azepine (1.17 g, 6.00 mmol) was used as the tethered aniline that was stirred with the acid chloride intermediate for 11 d, and purified by flash column chromatography (SiO_2; gradient elution: 0–25% Et_2O in pet. ether) to yield the title compound as a cream solid (1.11 g, 57%).

m.p. = 170–172 °C (DCM). $\boldsymbol{R_f}$ = 0.21 (30% Et_2O in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48 (1H, d, J 7.8, H_{Ar}), 7.42–7.34 (4H, m, H_2, H_3), 7.34–7.23 (4H, m, 4 × H_{Ar}), 7.21–7.13 (2H, m, 2 × H_{Ar}), 7.10–6.89 (4H, m, 4 × H_{Ar}), 6.68 (1H, t, J 7.4, H_{16a}), 6.09 (1H, d, J 7.9, H_{Ar}), 4.57 (1H, d, J 15.0, H_{5a}), 4.19 (1H, d, J 15.0, H_{5b}), 3.70–3.51 (2H, m, H_{19a}), 3.02–2.83 (2H, m, H_{19b}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.9 (C_{12}), 141.5 (C_{quat}), 141.3 (C_{quat}), 140.5 (C_4), 139.7 (C_{quat}), 136.0 (C_{quat}), 135.7 (C_{quat}), 135.3 (C_{quat}), 130.7 (C_{Ar}), 130.3 (C_{Ar}), 129.9 (C_2, C_{Ar}), 129.1 (C_{Ar}), 128.6 (C_3), 128.3 (C_{Ar}), 128.2 (C_{Ar}), 128.0 (C_{Ar}), 127.5 (2 × C_{Ar}), 127.1 (C_{Ar}), 126.5 (2 × C_{Ar}), 125.4 (C_{Ar}), 39.2 (C_5), 31.5 (C_{19a}), 30.4 (C_{19b}). **IR** (film, $CDCl_3$) ν_{max} = 3061 (C–H), 3025 (C–H), 2922 (C–H), 2858 (C–H), 1651 (C=O), 1601, 1574, 1489, 1339, 738 cm^{-1}. **HRMS** (ESI^+) m/z calcd for $C_{28}H_{23}NNaO$ $[M+Na]^+$ 412.1672, found 412.1677.

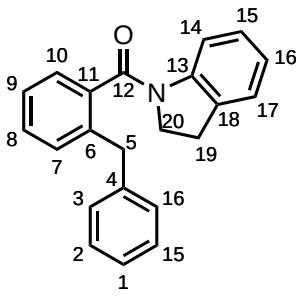
11-Phenyl-5,11,16,17-tetrahydro-6*H*-tribenzo[*b*,*f*,*i*][1]azacycloundecin-6-one (1.61d)



By **GP3**, (2-benzylphenyl)(10,11-dihydro-5*H*-dibenzo[*b*,*f*]azepin-5-yl) methanone (**1.60d**) (312 mg, 0.80 mmol) was used as the 2-arylbenzamide that was stirred at 100 °C for 2 h, and purified by flash column chromatography (SiO_2; gradient elution: 7–60% EtOAc in pet. ether) to yield the title compound as a yellow solid (157 mg, 50%).

m.p. = 102 °C (decomposition) (DCM). $\boldsymbol{R_f}$ = 0.21 (20% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.53 (1H, d, *J* 7.0, H_{Ar}), 7.39–7.00 (13H, m, 13 × H_{Ar}), 6.94 (1H, d, *J* 7.7, H_{Ar}), 6.89 (1H, t, *J* 7.7, H_{14}), 6.62 (1H, d, *J* 7.7, H_{16}), 6.31 (1H, s, H_5), 5.99 (1H, s, N*H*), 3.89 (1H, td, *J* 13.8, 6.5, H_{19a}), 3.22 (1H, dd, *J* 13.8, 6.5, H_{20a}), 2.91 (1H, dd, *J* 13.8, 6.5, H_{19b}), 2.71 (1H, td, *J* 13.8, 6.5, H_{20b}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.7 (C_{12}), 143.5 (C_4), 141.7 (C_{quat}), 141.1 (C_{quat}), 138.1 (C_{quat}), 137.9 (C_{quat}), 137.3 (C_{quat}), 135.5 (C_{quat}), 132.7 (C_{16}), 131.1 (C_{Ar}), 130.2 (C_{Ar}), 129.9 (C_2), 129.8 (C_{Ar}), 128.9 (C_{Ar}), 128.6 (C_3), 128.2 (C_{Ar}), 127.9 (C_{Ar}), 127.5 (C_{Ar}), 127.1 (2 × C_{Ar}), 127.0 (C_{Ar}), 126.9 (C_{Ar}), 126.3 (C_{14}), 49.6 (C_5), 35.6 (C_{20}), 32.1 (C_{19}). **IR** (film, $CDCl_3$) ν_{max} = 3289 (N–H, br), 2859 (C–H), 1649 (C=O), 1600, 1520, 1494, 1450, 909, 753, 731, 700 cm^{-1}. **HRMS** (ESI^+) *m*/*z* calcd for $C_{28}H_{23}NNaO$ $[M+Na]^+$ 412.1672, found 412.1666.

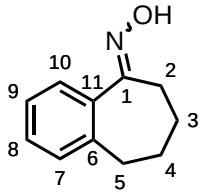
(2-Benzylphenyl)(indolin-1-yl)methanone (1.60e)



By **GP2**, the acid chloride of carboxylic acid 2-benzylbenzoic acid (1.06 g, 5.00 mmol) was made by stirring with oxalyl chloride for 22 h. Indoline (670 µL, 5.98 mmol) was used as the tethered aniline that was stirred with the acid chloride intermediate for 23 h, and purified by flash column chromatography (SiO_2; gradient elution: 5–100% Et_2O in pet. ether) to yield the title compound as a yellow oil that solidified upon standing (1.22 g, 78%).

m.p. = 84–86 °C (DCM). $\boldsymbol{R_f}$ = 0.45 (50% Et_2O in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers in an approximate 70:30 ratio) δ 8.35 (1H^{maj}, d, *J* 7.5, H_{14}), 7.44–7.03 (12H^{maj} + 10H^{min}, m, H_{Ar}), 6.87 (1H^{min}, t, *J* 7.5, H_{16}), 6.73 (1H^{min}, t, *J* 7.5, H_{15}), 5.56 (1H^{min}, d, *J* 7.5, H_{14}), 4.38–3.90 (2H^{maj} + 2H^{min}, m, H_{20}), 4.01–3.95 (2H^{min}, m, H_5), 3.71–2.44 (2H^{maj}, m, H_5), 3.21–2.93 (2H^{min}, m, H_{19}), 2.71 (2H^{maj}, br s, H_{19}). **^{13}C NMR** (126 MHz, $CDCl_3$, mixture of rotamers in an approximate 65:35 ratio) δ 169.0 ($C_{12}{}^{maj}$), 168.3 ($C_{12}{}^{min}$), 142.5 ($C_{13}{}^{maj}$), 141.3 ($C_{13}{}^{min}$), 140.0 ($C_4{}^{maj}$), 139.5 ($C_4{}^{min}$), 138.4 ($C_6{}^{min}$), 138.1 ($C_6{}^{maj}$), 137.7 ($C_{11}{}^{maj}$), 136.9 ($C_{11}{}^{min}$), 133.2 ($C_{18}{}^{min}$), 132.1 ($C_{18}{}^{maj}$), 130.7 ($C_{Ar}{}^{maj}$, $C_{Ar}{}^{min}$), 130.0 ($C_{Ar}{}^{min}$), 129.4 ($C_2{}^{maj}$, $C_2{}^{min}$, 2 × $C_{Ar}{}^{min}$), 128.3 ($C_3{}^{maj}$, $C_3{}^{min}$, $C_{Ar}{}^{min}$), 127.5 ($C_{15}{}^{maj}$), 127.0 ($C_{Ar}{}^{maj}$), 126.9 ($C_{15}{}^{min}$), 126.6 ($C_{Ar}{}^{maj}$), 126.2 ($C_{Ar}{}^{min}$), 126.2 ($C_{Ar}{}^{maj}$), 126.0 ($C_{Ar}{}^{maj}$), 125.5 ($C_{17}{}^{min}$), 124.6 ($C_{17}{}^{maj}$), 124.3 ($C_{16}{}^{maj}$), 123.3 ($C_{16}{}^{min}$), 117.7 ($C_{14}{}^{maj}$), 114.2 ($C_{14}{}^{min}$), 50.1 ($C_5{}^{maj}$), 47.9 ($C_{20}{}^{min}$), 39.3 ($C_{20}{}^{maj}$), 39.0 ($C_5{}^{min}$), 27.9 ($C_{19}{}^{maj}$), 26.7 ($C_{19}{}^{min}$). **IR** (film, $CDCl_3$) ν_{max} = 3061 (C–H), 3027 (C–H), 1644 (C=O), 1596, 1482, 1463, 1396, 757, 742, 699 cm^{-1}. **HRMS** (ESI$^+$) *m*/*z* calcd for $C_{22}H_{19}NNaO$ $[M+Na]^+$ 336.1359, found 336.1349.

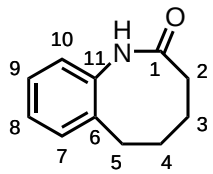
6,7,8,9-Tetrahydro-5*H*-benzo[7]annulen-5-one oxime (1.78a)



By the method of Spring and co-workers[319] with modifications, in air, 1-benzosuberone (1.1 mL, 7.35 mmol, 1.0 eq.), hydroxylamine hydrochloride (973 mg, 14.0 mmol, 1.9 eq.) and pyridine (1.1 mL, 13.6 mmol, 1.9 eq.) were dissolved in EtOH (35 mL), stirred at reflux for 20 h, and concentrated *in vacuo*. The residue was diluted with H_2O (50 mL) and extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$), and concentrated *in vacuo* to yield the title compound as a white solid without further purification (1.28 g, 99%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (1H, br s, O*H*), 7.42 (1H, dd, *J* 7.4, 1.5, H_{10}), 7.31 (1H, td, *J* 7.4, 1.5, H_8), 7.24 (1H, td, *J* 7.4, 1.5, H_9), 7.14 (1H, dd, *J* 7.4, 1.5, H_7), 2.80–2.71 (4H, m, H_2, H_5), 1.79 (2H, quint, *J* 6.4, H_4), 1.65 (2H, quint, *J* 6.4, H_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.9 (C_1), 139.6 (C_{11}), 136.2 (C_6), 129.4 (C_8), 129.0 (C_7), 127.5 (C_9), 126.7 (C_{10}), 32.0 (C_5), 26.2 (CH_2), 26.1 (CH_2), 21.7 (C_3). Data consistent with literature.[319]

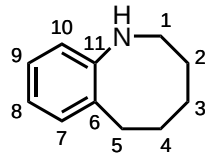
3,4,5,6-Tetrahydrobenzo[*b*]azocin-2(1*H*)-one (1.79a)



By the method of Zanger and co-workers[320] with modifications, in air, polyphosphoric acid (1.31 g, 13.4 mmol, 2.0 eq.) was stirred at 115 °C, and 6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-one oxime (**1.78a**) (1.16 g, 6.62 mmol, 1.0 eq.) added. The reaction mixture was stirred at 130 °C for 10 min, and cooled slowly to room temperature. Ice was added portionwise, the reaction mixture stirred for 2 h, and diluted with saturated aqueous $NaHCO_3$ (20 mL). The reaction mixture was extracted with DCM (20 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2; gradient elution: 17–100% EtOAc in pet. ether) to yield the title compound a pale orange solid (384 mg, 33%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (1H, s, N*H*), 7.29–7.17 (3H, m, H_7, H_8, H_9), 7.09 (1H, dd, *J* 7.5, 1.6, H_{10}), 2.68 (2H, br s, H_5), 2.38–1.41 (6H, m, H_2, H_3, H_4). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.3 (C_1), 139.9 (C_{11}), 136.1 (C_6), 131.0 (C_{Ar}), 127.8 (C_{Ar}), 127.1 (C_{Ar}), 125.3 (C_{10}), 32.6 (C_2), 31.3 (C_5), 29.7 (C_4), 24.9 (C_3). Data consistent with literature.[321]

1,2,3,4,5,6-Hexahydrobenzo[*b*]azocine (1.77b)

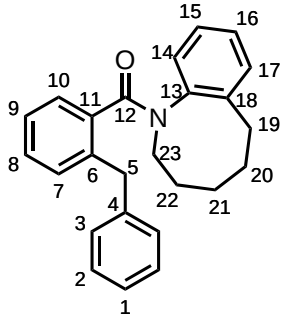


By the method of Zanger and co-workers[320] with modifications, $LiAlH_4$ (248 mg, 6.53 mmol, 3.0 eq.) was suspended in anhydrous Et_2O (10.9 mL), and a solution of 3,4,5,6-tetrahydrobenzo[*b*]azocin-2(1*H*)-one (**1.79a**) (382 mg, 2.18 mmol, 1.0 eq.) in THF (5.1 mL) added dropwise. The reaction mixture was stirred at reflux for 20 h, and quenched by the sequential dropwise addition of H_2O (1 mL), aqueous NaOH (1 mL, 2 M) and H_2O (3 mL). The reaction mixture was stirred at room temperature for 1 h, and filtered, eluting with Et_2O. The filtrate was concentrated *in vacuo*, diluted with DCM (20 mL), and washed with brine (20 mL). The aqueous layer was extracted with DCM (2 × 20 mL), the combined organic extracts dried ($MgSO_4$), and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2; gradient elution: 17–100% EtOAc in pet. ether) to yield the title compound a yellow oil (115 mg, 33%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (1H, td, *J* 7.6, 1.6, H_9), 7.07 (1H, dd, *J* 7.6, 1.6, H_7), 6.94 (1H, td, *J* 7.6, 1.3, H_8), 6.90 (1H, dd, *J* 7.6, 1.3, H_{10}), 3.26–3.17

(2H, m, H_1), 3.19 (1H, br s, NH), 2.88–2.83 (2H, m, H_5), 1.77–1.70 (2H, m, H_4), 1.60–1.48 (4H, m, H_2, H_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.7 (C_{11}), 135.1 (C_6), 130.5 (C_7), 127.3 (C_9), 122.9 (C_{10}), 122.8 (C_8), 51.5 (C_1), 32.1 (C_5), 31.4 (C_4), 28.8 (C_2), 25.4 (C_3). Data consistent with literature.[322]

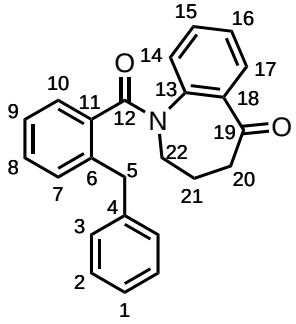
(2-Benzylphenyl)(3,4,5,6-tetrahydrobenzo[*b*]azocin-1(2*H*)-yl)methanone (1.60f)



By **GP2**, the acid chloride of carboxylic acid 2-benzylbenzoic acid (151 mg, 0.71 mmol) was made by stirring with oxalyl chloride for 22 h. 3,4,5,6-Tetrahydrobenzo[*b*]azocin-2(1*H*)-one (**1.77b**) (115 mg, 0.71 mmol, 1.0 eq.) was used as the tethered aniline that was stirred with the acid chloride intermediate for 23 h, and purified by flash column chromatography (SiO_2; gradient elution: 12–100% Et_2O in pet. ether) to yield the title compound as an off-white gum (197 mg, 78%).

***R*$_f$** = 0.37 (50% Et_2O in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers in an approximate 60:40 ratio) δ 7.45 (1H^{min}, dd, J 6.6, 2.2, H_{Ar}), 7.39–7.19 (8H^{maj} + 8H^{min}, m, 8 × H_{Ar}), 7.10–6.96 (3H^{maj} + 3H^{min}, m, 3 × H_{Ar}), 6.93–6.83 (1H^{maj} + 1H^{min}, m, H_{Ar}), 6.30 (1H^{maj}, d, J 7.8, H_{16}), 4.99 (1H^{maj}, ddd, J 13.5, 7.7, 3.0, H_{23a}), 4.32 (1H^{maj}, d, J 15.1, H_{5a}), 4.27–4.11 (2H^{min}, m, H_5), 4.07 (1H^{maj}, d, J 15.1, H_{5b}), 3.50 (2H^{min}, br s, H_{21}), 2.97 (1H^{maj}, td, J 13.0, 4.1, H_{21a}), 2.87 (1H^{maj}, ddd, J 13.5, 8.7, 2.6, H_{23b}), 2.75 (2H^{maj}, br s, H_{19}), 2.63 (1H^{maj}, dt, J 13.0, 4.1, H_{21b}), 1.98–1.86 (1H^{maj}, m, H_{19b}), 1.86–1.77 (1H^{min}, m, H_{22a}), 1.74–1.63 (1H^{maj}, m, H_{20a}), 1.60–1.47 (2H^{maj} + 2H^{min}, m, $H_{22}{}^{maj}$, $H_{19}{}^{min}$, $H_{22b}{}^{min}$), 1.36–1.23 (1H^{maj} + 1H^{min}, m, $H_{20b}{}^{maj}$, $H_{20}{}^{min}$). **^{13}C NMR** (126 MHz, $CDCl_3$, mixture of rotamers in an approximate 60:40 ratio) δ 171.0 ($C_{12}{}^{min}$), 170.5 ($C_{12}{}^{maj}$), 141.5 ($C_{13}{}^{maj}$, $C_{13}{}^{min}$), 141.1 ($C_{18}{}^{maj}$, $C_{18}{}^{min}$), 140.7 ($C_4{}^{maj}$, $C_4{}^{min}$), 140.1 ($C_{Ar}{}^{min}$), 138.5 ($C_6{}^{maj}$, $C_6{}^{min}$), 136.4 ($C_{11}{}^{maj}$, $C_{11}{}^{min}$), 130.8 ($C_{Ar}{}^{min}$), 130.2 ($C_{Ar}{}^{maj}$), 130.1 ($C_{Ar}{}^{min}$), 129.7 ($C_2{}^{min}$), 129.7 ($C_2{}^{maj}$), 129.4 (2 × $C_{Ar}{}^{min}$), 129.0 ($C_{Ar}{}^{min}$), 128.6 ($C_{Ar}{}^{min}$), 128.6 (2 × $C_{Ar}{}^{maj}$), 128.4 ($C_3{}^{maj}$), 128.4 ($C_3{}^{min}$), 128.2 ($C_{Ar}{}^{maj}$), 127.9 ($C_{Ar}{}^{min}$), 127.2 ($C_{Ar}{}^{min}$), 127.2 ($C_{Ar}{}^{maj}$), 126.5 ($C_{Ar}{}^{min}$), 126.4 ($C_{Ar}{}^{maj}$), 126.4 ($C_{Ar}{}^{maj}$), 126.3 ($C_{Ar}{}^{maj}$), 125.1 ($C_{Ar}{}^{maj}$), 53.6 ($C_{23}{}^{min}$), 51.4 ($C_{23}{}^{maj}$), 39.2 ($C_5{}^{maj}$), 38.9 ($C_5{}^{min}$), 31.6 ($C_{21}{}^{min}$), 31.2 ($C_{19}{}^{maj}$, $C_{19}{}^{min}$), 30.9 ($C_{21}{}^{maj}$), 27.2 ($CH_2{}^{min}$), 26.4 ($C_{20}{}^{maj}$), 26.3 ($C_{22}{}^{maj}$), 26.0 ($CH_2{}^{min}$). **IR** (film, $CDCl_3$) ν_{max} = 2924 (C–H), 2852 (C–H), 1637 (C=O), 1599, 1492, 1451, 1395, 1305, 730, 699 cm^{-1}. **HRMS** (ESI$^+$) m/z calcd for $C_{25}H_{26}NO$ [M+H]$^+$ 356.2009, found 356.2013.

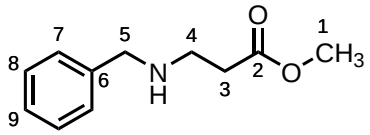
1-(2-Benzylbenzoyl)-1,2,3,4-tetrahydro-5*H*-benzo[*b*]azepin-5-one (1.60g)



By **GP2**, the acid chloride of carboxylic acid 2-benzylbenzoic acid (354 mg, 1.67 mmol) was made by stirring with oxalyl chloride for 16 h. 1,2,3,4-Tetrahydro-benzo[*b*]azepin-5-one (322 mg, 2.00 mmol) was used as the tethered aniline that was stirred with the acid chloride intermediate for 11 d, and purified by flash column chromatography (SiO_2; gradient elution: 7–100% Et_2O in pet. ether) to yield the title compound as a yellow solid (563 mg, 95%).

m.p. = 97–99 °C (DCM). $\boldsymbol{R_f}$**:** 0.27 (50% Et_2O in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.72 (1H, d, *J* 7.8, H_{10}), 7.29 (4H, br d, *J* 7.4, H_2, H_3), 7.23–7.16 (2H, m, H_1, H_8), 7.16–7.07 (2H, m, H_9, H_{17}), 6.93 (1H, t, *J* 7.6, H_{15}), 6.84 (1H, t, *J* 7.6, H_{16}), 6.64 (1H, d, *J* 5.6, H_7), 5.74 (1H, d, *J* 7.6, H_{14}), 4.21 (2H, s, H_5), 3.44 (1H, br s, H_{22a}), 2.86 (2H, t, *J* 6.2, H_{20}), 2.15 (2H, br s, H_{21}), 1.75 (1H, br s, H_{22b}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 202.3 (C_{19}), 170.5 (C_{12}), 141.9 (C_6), 140.3 (C_4), 139.8 (C_{13}), 135.4 (C_{11}), 134.8 (C_{18}), 132.8 (C_{15}), 130.8 (C_8), 129.7 (C_2), 129.5 (C_9), 129.2 (C_{10}), 128.6 (C_3), 128.4 (C_{14}), 127.9 (C_7), 127.3 (C_{17}), 126.5 (C_1), 125.7 (C_{16}), 46.5 (C_{22}), 40.3 (C_{20}), 39.2 (C_5), 22.4 (C_{21}). **IR** (film, $CDCl_3$) ν_{max} = 3062 (C–H), 3026 (C–H), 2934 (C–H), 2876 (C–H), 1681 (C=O), 1644 (C=O), 1596, 1571, 1480, 1381, 1319, 731, 699 cm^{-1}. **HRMS** (ESI^+) *m*/*z* calcd for $C_{24}H_{21}NNaO_2$ $[M+Na]^+$ 378.1464, found 378.1478.

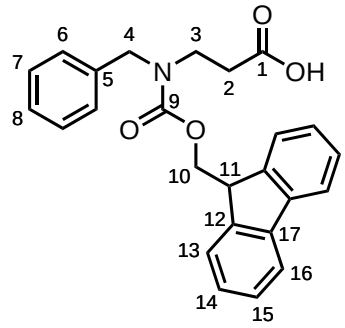
Methyl 3-(benzylamino)propanoate (1.80)



By the method of Oguri and co-workers,[323] in a microwave vial, benzylamine (1.9 mL, 17.4 mmol, 1.0 eq.) and methyl acrylate (1.7 mL, 18.9 mmol, 1.1 eq.) were dissolved in MeOH (5.0 mL). The vial was sealed, the reaction mixture stirred at 65 °C under microwave irradiation for 10 min, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2; gradient elution: 2–10% MeOH in EtOAc) to yield the title compound as a colourless oil (2.55 g, 76%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.19 (5H, m, H_7, H_8, H_9), 3.79 (2H, s, H_5), 3.66 (3H, s, H_1), 2.89 (2H, t, J 6.5, H_4), 2.53 (2H, t, J 6.5, H_3), 1.74 (1H, s, NH). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.3 (C_2), 140.2 (C_6), 128.5 (C_8), 128.2 (C_7), 127.1 (C_9), 53.8 (C_5), 51.7 (C_1), 44.5 (C_4), 34.6 (C_1). Data consistent with literature.[324]

3-((((9*H*-Fluoren-9-yl)methoxy)carbonyl)(benzyl)amino)propanoic acid (1.65)

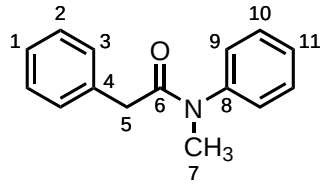


By the method of Unsworth and co-workers[53] with modifications, methyl 3-(benzylamino)propanoate (**1.80**) (2.53 g, 13.1 mmol, 1.0 eq.) was dissolved in THF (30 mL), aqueous NaOH (30 mL, 1 M) added, and the reaction mixture stirred at room temperature for 2 h. AcOH (1.5 mL, 26.2 mmol, 2.0 eq.) was added, and the reaction mixture concentrated *in vacuo*. The residue was dissolved in H_2O (45 mL), 1,4-dioxane (65 mL) and aqueous Na_2CO_3 (50 mL, 10%) added, and the reaction mixture cooled to 0 °C. A solution of 9-fluorenylmethoxycarbonyl chloride (3.73 g, 14.4 mmol, 1.1 eq.) in 1,4-dioxane (11 mL) was added dropwise, the reaction mixture warmed to room temperature, and stirred for 23 h. The reaction mixture was quenched by the addition of H_2O (150 mL), washed with EtOAc (2 × 150 mL), adjusted to pH 2 with aqueous HCl (1 M), and extracted with EtOAc (3 × 25 mL). The combined organic extracts were washed sequentially with HCl (5 × 100 mL, 1 M) and brine (25 mL), dried ($MgSO_4$), and concentrated *in vacuo* to yield the title compound as a yellow gum without further purification (4.81 g, 91%).

^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers in an approximate 50:50 ratio) δ 8.73 (1H, br s, OH, both rot.), 7.80–7.70 (2H, m, H_{13}, both rot.), 7.64–7.56 (1H, m, H_{16}), 7.46 (1H, d, J 7.5, H_{16}), 7.41–7.34 (2H, m, 2 × H_{Ar}, both rot.), 7.33–7.20 (5H, m, 5 × H_{Ar}, both rot.), 7.14 (2H, d, J 7.1, H_{Ar}), 7.08–7.01 (1H, m, H_{Ar}), 4.66 (1H, d, J 5.4, H_{10}), 4.54 (1H, d, J 6.1, H_{10}), 4.45 (1H, s, H_4), 4.40 (1H, s, H_4), 4.29–4.19 (1H, m, H_{11}, both rot.), 3.53 (1H, t, J 6.7, H_3), 3.23 (1H, t, J 7.2, H_3), 2.61 (1H, t, J 6.7, H_2), 2.17 (1H, t, J 7.2, H_2). **^{13}C NMR** (126 MHz, $CDCl_3$, mixture of rotamers in an approximate 50:50 ratio) δ 177.3 (C_1), 177.2 (C_1), 156.5 (C_9), 156.3 (C_9), 144.0 (C_{12}, both rot.), 141.5 (C_{17}), 141.5 (C_{17}), 137.5 (C_5, both rot.), 128.8 (C_7), 128.8 (C_7), 127.9 (C_6), 127.8 (C_6, C_{14}), 127.6 (C_8, both rot.), 127.3 (C_{14}), 127.2 (C_{15}), 127.2 (C_{15}), 125.0 (C_{16}), 124.8 (C_{16}), 120.1 (C_{13}, both

rot.), 67.6 (C_{10}), 67.2 (C_{10}), 51.3 (C_4), 51.2 (C_4), 47.6 (C_{11}), 47.4 (C_{11}), 43.4 (C_3), 42.2 (C_3), 32.9 (C_2, both rot.). Data consistent with literature.[53]

N-Methyl-*N*,2-diphenylacetamide (1.68)

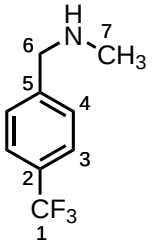


By **GP2**, *N*-methylaniline (1.3 mL, 12.0 mmol) was used as the general amine that was stirred with phenylacetyl chloride (1.3 mL, 9.83 mmol) for 17 h, and purified by flash column chromatography (SiO_2; gradient elution: 7–60% EtOAc in pet. ether) to yield the title compound as a yellow oil (1.81 g, 82%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.32 (3H, m, H_{10}, H_{11}), 7.30–7.16 (3H, m, H_1, H_2), 7.14–7.10 (2H, m, H_9), 7.06 (2H, d, J 7.2, H_3), 3.46 (2H, s, H_5), 3.28 (3H, s, H_7). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.1 (C_6), 144.1 (C_8), 135.5 (C_4), 129.8 (C_{10}), 129.1 (C_3), 128.4 (C_2), 128.0 (C_{11}), 127.7 (C_9), 126.6 (C_1), 41.0 (C_5), 37.7 (C_7). Data consistent with literature.[325]

Chapter 2 experimental procedures

N-Methyl-1-(4-(trifluoromethyl)phenyl)methanamine (2.52a)

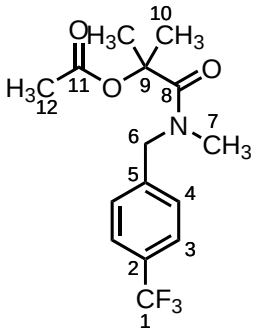


Method 1: A solution of 4-(trifluoromethyl)benzyl bromide (2.72 g, 11.4 mmol, 1.0 eq.) in anhydrous Et_2O (4.5 mL) was added dropwise to $MeNH_2$ (28.3 mL, 33 wt% in EtOH, 227 mmol, 20.0 eq.). The reaction mixture was stirred at room temperature for 21 h, and concentrated *in vacuo*. The residue was diluted with EtOAc (50 mL), washed with saturated aqueous $NaHCO_3$ (50 mL), dried ($MgSO_4$), and concentrated *in vacuo* to yield the title compound as a pale orange oil without further purification (2.07 g, 96%).

Method 2: By **GP7**, 4-(trifluoromethyl)benzaldehyde (4.7 mL, 34.4 mmol) was used as the aldehyde that was stirred for 30 min to yield the title compound as a colourless oil (6.35 g, 98%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (2H, d, *J* 8.0, H_3), 7.44 (2H, d, *J* 8.0, H_4), 3.81 (2H, s, H_6), 2.45 (3H, s, H_7), 1.69 (1H, s, N*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.2 (C_5), 129.4 (q, *J* 32.4, C_2), 128.5 (C_4), 125.4 (q, *J* 3.8, C_3), 124.4 (q, *J* 271.9, C_1), 55.5 (C_6), 36.0 (C_7). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −65.6 (3F, s, F_1). Data consistent with literature.[326]

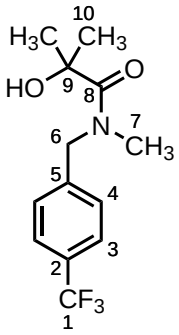
2-Methyl-1-(methyl(4-(trifluoromethyl)benzyl)amino)-1-oxopropan-2-yl acetate (2.54)



By **GP2**, *N*-methyl-1-(4-(trifluoromethyl)phenyl)methanamine (**2.52a**) (726 mg, 3.84 mmol, 1.0 eq.) was used as the general amine that was stirred with α-acetoxyisobutyryl chloride (550 µL, 3.80 mmol) for 17 h, and purified by flash column chromatography (SiO_2; gradient elution: 7–30% EtOAc in pet. ether) to yield the title compound as a colourless oil (1.14 g, 95%).

$\boldsymbol{R_f}$ = 0.28 (30% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.56 (2H, d, *J* 7.9, H_3), 7.34 (2H, d, *J* 7.9, H_4), 4.89–4.49 (2H, m, H_6), 2.97 (3H, br s, H_7), 2.09–1.98 (3H, m, H_{12}), 1.63 (6H, s, H_{10}). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.9 (C_8), 169.4 (C_{11}), 141.5 (C_5), 129.6 (q, *J* 32.2, C_2), 128.1 (C_3), 125.6 (C_4), 124.3 (q, *J* 272.0, C_1), 80.9 (C_9), 52.5 (C_6), 35.0 (C_7), 25.4 (C_{10}), 21.2 (C_{12}). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −65.7 (3F, s, F_1). **IR** (film, $CDCl_3$) ν_{max} = 2996 (C−H), 2941 (C−H), 1739 (C=O), 1642 (C=O), 1324, 1248, 1161, 1143, 1120, 1110, 1095, 1066, 1017 cm^{-1}. **HRMS** (ESI^+) *m/z* calcd for $C_{15}H_{18}F_3NNaO_3$ $[M+Na]^+$ 340.1136, found 340.1150.

2-Hydroxy-*N*,2-dimethyl-*N*-(4-(trifluoromethyl)benzyl)propanamide (2.55)



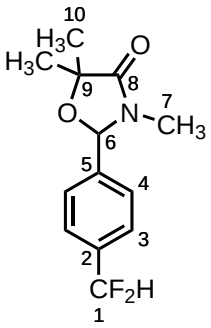
Method 1: By the method of Procopiou and co-workers[327] with modifications, 2-methyl-1-(methyl(4-(trifluoromethyl)benzyl)amino)-1-oxopropan-2-yl acetate (**2.54**) (1.07 g, 3.37 mmol, 1.0 eq.) and K_2CO_3 (1.39 g, 10.1 mmol, 3.0 eq.) were dissolved in MeOH (84 mL), the reaction mixture stirred at room temperature for 18 h, and concentrated *in vacuo*. The residue was diluted with H_2O (50 mL), and extracted with EtOAc (3 × 25 mL). The combined organic extracts were washed with brine (25 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2; gradient elution: 12–40% EtOAc in pet. ether) to yield the title compound as a pale yellow oil (883 mg, 95%).

Method 2: By **GP2**, *N*-methyl-1-(4-(trifluoromethyl)phenyl)methanamine (**2.52a**) (1.18 g, 6.24 mmol, 1.0 eq.) was used as the general amine that was stirred with α-acetoxyisobutyryl chloride (900 µL, 6.33 mmol) for 69 h to yield the crude amide, which was used without further purification.

By the method of Procopiou and co-workers[327] with modifications, the crude amide and K_2CO_3 (2.59 g, 18.7 mmol, 3.0 eq.) were dissolved in MeOH (156 mL), the reaction mixture stirred at room temperature for 21 h, and concentrated *in vacuo*. The residue was diluted with H_2O (50 mL), and extracted with EtOAc (3 × 25 mL). The combined organic extracts were washed with brine (25 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2; gradient elution: 12–40% EtOAc in pet. ether) to yield the title compound as a pale yellow oil (1.61 g, 96%).

$\boldsymbol{R_f}$ = 0.29 (50% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.58 (2H, d, *J* 8.0, H_3), 7.31 (2H, d, *J* 8.0, H_4), 4.70 (2H, br s, H_6), 4.17 (1H, br s, O*H*), 3.06 (3H, br s, H_7), 1.52 (6H, s, H_{10}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.8 (C_8), 141.1 (q, *J* 1.3, C_5), 129.9 (q, *J* 32.6, C_2), 127.8 (C_4), 125.8 (q, *J* 3.8, C_3), 124.1 (q, *J* 272.0, C_1), 72.3 (C_9), 53.2 (C_6), 36.5 (C_7), 27.7 (C_{10}). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −65.7 (3F, s, F_1). **IR** (film, $CDCl_3$) ν_{max} = 3389 (O−H, br), 2981 (C−H), 2936 (C−H), 1616 (C=O), 1323, 1162, 1120, 1109, 1066, 1018, 732 cm^{-1}. **HRMS** (ESI^+) *m*/*z* calcd for $C_{13}H_{17}F_3NO_2$ $[M+H]^+$ 276.1211, found 276.1215.

2-(4-(Difluoromethyl)phenyl)-3,5,5-trimethyloxazolidin-4-one (2.57)

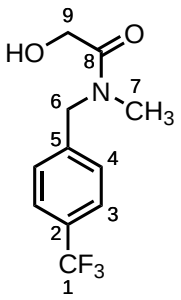


2-Hydroxy-*N*,2-dimethyl-*N*-(4-(trifluoromethyl)benzyl)propanamide (**2.55**) (55 mg, 0.20 mmol, 1.0 eq.) was dissolved in anhydrous THF (2.0 mL), KHMDS (400 µL, 1 M in THF, 0.40 mmol, 2.0 eq.) added dropwise, the reaction mixture stirred at room temperature for 15 min, and quenched by the addition of saturated aqueous NH_4Cl (2 mL). The reaction mixture was diluted with H_2O (2 mL), and extracted with 3:1 $CHCl_3$/IPA (3 × 5 mL). The combined organic extracts were dried ($MgSO_4$), and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2; gradient elution: 12–60% EtOAc in pet. ether) to yield the title compound as a yellow oil (20 mg, 38%).

$\boldsymbol{R_f}$ = 0.34 (50% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.59 (2H, d, *J* 8.0, H_3), 7.48 (2H, d, *J* 8.0, H_4), 6.67 (1H, t, *J* 56.3, H_1), 5.81 (1H, s, H_6), 2.63 (3H, s, H_7), 1.54 (3H, s, H_{10a}), 1.44 (3H, s, H_{10b}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.6 (C_8), 139.6 (t, *J* 1.8, C_5), 136.4 (t, *J* 22.6, C_2), 128.0 (C_4), 126.4 (t, *J* 6.0, C_3), 114.3 (t, *J* 239.4, C_1), 89.6 (C_6), 80.3 (C_9), 26.8 (C_7), 25.5 (C_{10a}), 23.4 (C_{10b}). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −114.4 (2F, d, *J* 56.3, F_1). **IR** (film, $CDCl_3$) ν_{max} = 2980 (C−H), 2933 (C−H), 1711 (C=O), 1436, 1404, 1073, 1031

cm^{-1}. **HRMS** (ESI^+) m/z calcd for $C_{13}H_{16}F_2NO_2$ $[M+H]^+$ 256.1149, found 256.1160.

2-Hydroxy-*N*-methyl-*N*-(4-(trifluoromethyl)benzyl)acetamide (2.60)

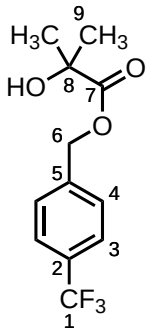


By the method of Procter and co-workers[328] with modifications, *N*-methyl-1-(4-(trifluoromethyl)phenyl)methanamine (**2.52a**) (1.00 g, 5.29 mmol, 1.0 eq.) was dissolved in anhydrous DCM (26 mL). Acetoxyacetic acid (749 mg, 6.34 mmol, 1.2 eq.), EDC hydrochloride (1.22 g, 6.36 mmol, 1.2 eq.) and 1-hydroxybenzotriazole hydrate (143 mg, 1.06 mmol, 0.2 eq.) were added, the reaction mixture stirred at room temperature for 18 h, washed with aqueous HCl (3 × 25 mL, 1 M), dried (Na_2SO_4), and concentrated *in vacuo* to yield the crude amide, which was used without further purification.

The crude amide and K_2CO_3 (2.92 g, 21.1 mmol, 3.0 eq.) were dissolved in MeOH (21 mL), H_2O (10 mL) added, the reaction mixture stirred at room temperature for 23 h, and concentrated *in vacuo* to remove MeOH. The residue was diluted with H_2O (25 mL), and extracted with EtOAc (3 × 25 mL). The combined organic extracts were dried (Na_2SO_4), and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2; gradient elution: 25–100% EtOAc in pet. ether) to yield the title compound as a colourless oil (893 mg, 68%).

$\boldsymbol{R_f}$ = 0.41 (EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers in an approximate 75:25 ratio) δ 7.62 ($2H^{min}$, d, J 8.0, H_3), 7.57 ($2H^{maj}$, d, J 8.0, H_3), 7.34 ($2H^{maj}$, d, J 8.0, H_4), 7.26 ($2H^{min}$, d, J 8.0, H_4), 4.67 ($2H^{maj}$, s, H_6), 4.40 ($2H^{min}$, s, H_6), 4.21 ($2H^{maj}$, s, H_9), 4.20 ($2H^{min}$, s, H_9), 3.56 ($1H^{maj}$, s, OH), 3.56 ($1H^{min}$, s, OH), 3.00 ($3H^{min}$, s, H_7), 2.81 ($3H^{maj}$, s, H_7). **^{13}C NMR** (101 MHz, $CDCl_3$, mixture of rotamers in an approximate 75:25 ratio) δ 172.2 ($C_8{}^{maj}$), 172.2 ($C_8{}^{min}$), 140.5 ($C_5{}^{maj}$), 139.6 ($C_5{}^{min}$), 130.5 (q, J 32.6, $C_2{}^{min}$), 130.1 (q, J 32.6, $C_2{}^{maj}$), 128.3 ($C_4{}^{maj}$), 126.9 ($C_4{}^{min}$), 126.2 (q, J 3.8, $C_3{}^{min}$), 125.8 (q, J 3.8, $C_3{}^{maj}$), 124.1 (q, J 272.0, $C_1{}^{maj}$), 124.0 (q, J 272.0, $C_1{}^{min}$), 60.1 ($C_9{}^{maj}$), 59.9 ($C_9{}^{min}$), 51.2 ($C_6{}^{maj}$), 51.0 ($C_6{}^{min}$), 34.1 ($C_7{}^{min}$), 32.7 ($C_7{}^{maj}$). **^{19}F NMR** (377 MHz, $CDCl_3$, mixture of rotamers in an approximate 75:25 ratio) δ −65.8 ($3F^{maj}$, s, F_1), −65.8 ($3F^{min}$, s, F_1). **IR** (film, $CDCl_3$) ν_{max} = 3420 (O–H, br), 2932 (C–H), 1648 (C=O), 1620, 1322, 1161, 1108, 1064, 1018, 820 cm^{-1}. **HRMS** (ESI^+) m/z calcd for $C_{11}H_{13}F_3NO_2$ $[M+H]^+$ 248.0893, found 248.0896.

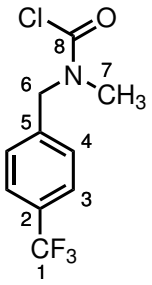
4-(Trifluoromethyl)benzyl 2-hydroxy-2-methylpropanoate (2.61)



By the method of Kobayashi and co-workers[329] with modifications, α-hydroxyisobutyric acid (521 mg, 5.00 mmol, 1.0 eq.), 4-(trifluoromethyl)benzyl bromide (1.20 g, 5.02 mmol, 1.0 eq.), $NaHCO_3$ (420 mg, 5.00 mmol, 1.0 eq.) and TBAI (1.85 g, 5.01 mmol, 1.0 eq.) were suspended in DCM (10 mL). H_2O (10 mL) was added, the reaction mixture stirred at room temperature for 7 d, and concentrated *in vacuo* to remove DCM. The residue was extracted with Et_2O (25 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2; isocratic elution: 40% Et_2O in pet. ether) to yield the title compound as a pale orange oil (949 mg, 72%).

$\boldsymbol{R_f}$ = 0.24 (40% Et_2O in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.63 (2H, d, *J* 8.0, H_3), 7.46 (2H, d, *J* 8.0, H_4), 5.24 (2H, s, H_6), 3.09 (1H, s, O*H*), 1.46 (6H, s, H_9). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.2 (C_7), 139.5 (q, *J* 1.1, C_5), 130.8 (q, *J* 32.6, C_2), 128.1 (C_4), 125.8 (q, *J* 3.8, C_3), 124.1 (q, *J* 272.2, C_1), 72.2 (C_8), 66.4 (C_6), 27.3 (C_9). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −65.9 (3F, s, F_1). **IR** (film, $CDCl_3$) ν_{max} = 3465 (O−H, br), 2984 (C−H), 2939 (C−H), 1733 (C=O), 1323, 1267, 1160, 1121, 1111, 1065, 1020, 976, 823 cm^{-1}. **HRMS** (APCI$^+$) *m*/*z* calcd for $C_{12}H_{14}F_3O_3$ $[M+H]^+$ 263.0890, found 263.0897.

Methyl(4-(trifluoromethyl)benzyl)carbamic chloride (2.122)

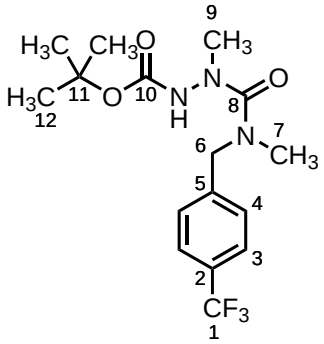


By **GP8**, *N*-methyl-1-(4-(trifluoromethyl)phenyl)methanamine (**2.52a**) (1.51 g, 8.00 mmol) was used as the amine that was stirred at room temperature for 21 h to yield the title compound as a brown oil (1.61 g, 80%).

$\boldsymbol{R_f}$ = 0.65 (30% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers in an approximate 60:40 ratio) δ 7.64 ($2H^{min}$, d, *J* 8.2, H_3), 7.62 ($2H^{maj}$,

d, J 8.2, H_3), 7.39 (2H^{maj}, d, J 8.2, H_4), 7.38 (2H^{min}, d, J 8.2, H_4), 4.77 (2H^{min}, s, H_6), 4.63 (2H^{maj}, s, H_6), 3.10 (3H^{maj}, s, H_7), 3.02 (3H^{min}, s, H_7). **^{13}C NMR** (101 MHz, $CDCl_3$, mixture of rotamers in an approximate 60:40 ratio) δ 150.7 ($C_8{}^{maj}$), 149.5 ($C_8{}^{min}$), 139.6 ($C_5{}^{maj}$), 139.5 ($C_5{}^{min}$), 130.5 (q, J 32.6, $C_2{}^{maj}$, $C_2{}^{min}$), 128.3 ($C_4{}^{maj}$), 127.4 ($C_4{}^{min}$), 126.1 (q, J 4.1, $C_3{}^{maj}$), 125.9 (q, J 4.1, $C_3{}^{min}$), 124.1 (q, J 272.3, $C_1{}^{maj}$, $C_1{}^{min}$), 56.0 ($C_6{}^{min}$), 54.0 ($C_6{}^{maj}$), 38.2 ($C_7{}^{maj}$), 36.7 ($C_7{}^{min}$). **^{19}F NMR** (377 MHz, $CDCl_3$, mixture of rotamers in an approximate 60:40 ratio) δ −65.7 (3F^{min}, s, F_1). −65.7 (3F^{maj}, s, F_1). **IR** (film, $CDCl_3$) ν_{max} = 2942 (C−H), 1728 (C=O), 1322, 1162, 1109, 1064, 1017, 818, 666 cm^{-1}. **HRMS** (EI$^+$) m/z calcd for $C_{10}H_9ClF_3NO$ M$^+$ 251.0319, found 251.0318.

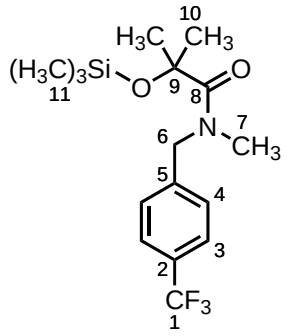
tert-Butyl 2-methyl-2-(methyl(4-(trifluoromethyl)benzyl)carbamoyl) hydrazine-1-carboxylate (2.62)



By **GP9**, methyl(4-(trifluoromethyl)benzyl)carbamic chloride (**2.122**) (1.38 g, 5.48 mmol) was used as the carbamoyl chloride and 1-Boc-2-methylhydrazine (800 mg, 5.47 mmol, 1.0 eq.) was used as the amine that were stirred for 22 h, and purified by flash column chromatography (SiO_2; gradient elution: 12–100% EtOAc in pet. ether) to yield the title compound as a pale yellow gum that solidified upon standing (1.25 g, 63%).

m.p. = 155–156 °C ($CHCl_3$). $\boldsymbol{R_f}$ = 0.41 (50% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.55 (2H, d, J 8.0, H_3), 7.36 (2H, d, J 8.0, H_4), 6.65 (1H, s, NH), 4.49 (2H, s, H_6), 3.01 (3H, s, H_9), 2.82 (3H, s, H_7), 1.37 (9H, s, H_{12}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.2 (C_8), 154.6 (C_{10}), 142.0 (q, J 1.4, C_5), 129.6 (q, J 32.3, C_8), 127.8 (C_4), 125.5 (q, J 3.8, C_3), 124.3 (q, J 271.9, C_1), 81.5 (C_{11}), 53.7 (C_6), 39.7 (C_9), 36.4 (C_7), 28.2 (C_{12}). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −65.6 (3F, s, F_1). **IR** (film, $CDCl_3$) ν_{max} = 3261 (N−H, br), 2980 (C−H), 2931 (C−H), 1717 (C=O), 1640 (C=O), 1323, 1159, 1114, 1066, 1018, 731 cm^{-1}. **HRMS** (ESI$^+$) m/z calcd for $C_{16}H_{22}F_3N_3NaO_3$ [M+H]$^+$ 384.1505, found 348.1505.

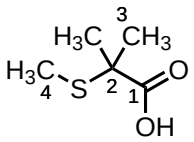
_N_,2-Dimethyl-_N_-(4-(trifluoromethyl)benzyl)-2-((trimethylsilyl)oxy) propanamide (2.63)



By the method of Paterson and co-workers[330] with modifications, 2-hydroxy-_N_,2-dimethyl-_N_-(4-(trifluoromethyl)benzyl)propanamide (**2.55**) (330 mg, 1.20 mmol, 1.0 eq.) was dissolved in anhydrous DCM (8.6 mL). Et_3N (420 µL, 3.01 mmol, 2.5 eq.) was added, TMSCl (300 µL, 2.36 mmol, 2.0 eq.) added dropwise, the reaction mixture stirred at room temperature for 66 h, and quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL). The aqueous layer was extracted with DCM (3 × 10 mL), the combined organic extracts dried (Na_2SO_4), and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2; gradient elution: 7–30% Et_2O in pet. ether) to yield the title compound as a pale yellow oil (417 mg, quant.).

$\boldsymbol{R_f}$ = 0.21 (21% Et_2O in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers A/B/C in an approximate 60:30:10 ratio) δ 7.59 ($2H^{rot.\ B}$, d, J 8.0, H_3) 7.57 ($2H^{rot.\ A}$ + $2H^{rot.\ C}$, d, J 8.0, H_3), 7.34 ($2H^{rot.\ A}$ + $2H^{rot.\ C}$, d, J 8.0, H_3), 7.30 ($2H^{rot.\ B}$, d, J 8.0, H_3), 5.05 ($2H^{rot.\ B}$ + $2H^{rot.\ C}$, s, H_6), 4.58 ($2H^{rot.\ A}$, s, H_6), 3.23 ($3H^{rot.\ A}$ + $3H^{rot.\ C}$, s, H_7), 2.82 ($3H^{rot.\ B}$, s, H_7), 1.53 ($6H^{rot.\ A}$ + $6H^{rot.\ B}$ + $6H^{rot.\ C}$, s, H_{10}), 0.11 ($9H^{rot.\ A}$ + $9H^{rot.\ C}$, s, H_{11}), 0.00 ($9H^{rot.\ B}$, s, H_{11}). **^{13}C NMR** (126 MHz, $CDCl_3$, mixture of rotamers A/B/C in an approximate 60:30:10 ratio) δ 176.8 ($C_8{}^{rot.\ C}$), 175.7 ($C_8{}^{rot.\ B}$), 175.1 ($C_8{}^{rot.\ A}$), 142.2 ($C_5{}^{rot.\ B}$), 141.9 ($C_5{}^{rot.\ A}$), 141.1 ($C_5{}^{rot.\ C}$), 130.0 (q, J 32.4, $C_2{}^{rot.\ C}$), 129.6 (q, J 32.4 $C_2{}^{rot.\ A}$, $C_2{}^{rot.\ B}$), 128.3 ($C_4{}^{rot.\ A}$, $C_4{}^{rot.\ C}$), 127.1 ($C_4{}^{rot.\ B}$), 125.9 (q, J 3.8, $C_3{}^{rot.\ C}$), 125.6 (q, J 3.8, $C_3{}^{rot.\ A}$, $C_3{}^{rot.\ B}$), 124.3 (q, J 271.9, $C_1{}^{rot.\ A}$, $C_1{}^{rot.\ B}$), 123.1 (q, J 271.9, $C_1{}^{rot.\ C}$), 77.9 ($C_9{}^{rot.\ A}$, $C_9{}^{rot.\ B}$), 72.1 ($C_9{}^{rot.\ C}$), 53.7 ($C_6{}^{rot.\ B}$), 53.2 ($C_6{}^{rot.\ C}$), 52.6 ($C_6{}^{rot.\ A}$), 36.6 ($C_7{}^{rot.\ A}$), 35.4 ($C_7{}^{rot.\ B}$, $C_7{}^{rot.\ C}$), 29.4 ($C_{10}{}^{rot.\ B}$), 29.1 ($C_{10}{}^{rot.\ A}$), 27.7 ($C_{10}{}^{rot.\ C}$), 2.0 ($C_{11}{}^{rot.\ C}$), 2.0 ($C_{11}{}^{rot.\ A}$, $C_{11}{}^{rot.\ B}$). **^{19}F NMR** (377 MHz, $CDCl_3$, mixture of rotamers A/B/C in an approximate 60:30:10 ratio) δ −65.6 ($3F^{rot.\ B}$, s, F_1), −65.6 ($3F^{rot.\ A}$ + $3F^{rot.\ C}$, s, F_1). **IR** (film, $CDCl_3$) ν_{max} = 2959 (C–H), 1638 (C=O), 1620, 1396, 1323, 1253, 1163, 1123, 1110, 1066, 1096, 1030, 1019, 893, 839, 818, 753 cm^{-1}. **HRMS** (ESI^+) m/z calcd for $C_{16}H_{25}F_3NO_2Si$ $[M+H]^+$ 348.1607, found 348.1620.

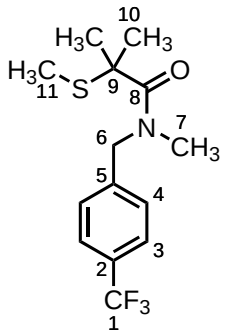
2-Methyl-2-(methylthio)propanoic acid (2.123)



By the method of Jacobson and co-workers[331] with modifications, diisopropylamine (6.2 mL, 44.2 mmol, 1.1 eq.) was dissolved in anhydrous THF (50 mL), cooled to −78 °C, and *n*-BuLi (16.0 mL, 2.5 M in hexanes, 40.0 mmol, 1.0 eq.) added dropwise. Methyl isobutyrate (4.6 mL, 40.1 mmol, 1.0 eq.) was added dropwise over 10 min, and the reaction mixture stirred at −78 °C for 30 min. Dimethyl disulfide (3.5 mL, 47.7 mmol, 1.2 eq.) was added, the reaction mixture was stirred at −78 °C for 10 min, warmed to 0 °C, and stirred for 40 min. H_2O (8.3 mL) and NaOH (2.24 g, 56.0 mmol, 1.4 eq.) were added, the reaction mixture stirred at room temperature for 15 h, and concentrated *in vacuo* to remove THF and hexanes. The residue was adjusted to pH 1 with aqueous HCl (3 M), and extracted with Et_2O (3 × 50 mL). The combined organic extracts were concentrated *in vacuo*. The crude residue was purified by bulb-to-bulb distillation (151 °C at 94 mbar) to yield the title compound as a white solid (4.33 g, 81%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.36 (1H, br s, O*H*), 2.16 (3H, s, H_4), 1.52 (6H, s, H_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 180.3 (C_1), 46.1 (C_2), 24.8 (C_3), 13.2 (C_4). Data consistent with literature.[332]

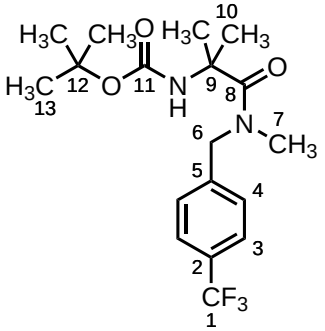
***N*,2-Dimethyl-2-(methylthio)-*N*-(4-(trifluoromethyl)benzyl) propanamide (2.64)**



By **GP2**, the acid chloride of 2-methyl-2-(methylthio)propanoic acid (**2.123**) (497 mg, 3.70 mmol) was made by stirring with oxalyl chloride for 2.5 h. *N*-Methyl-1-(4-(trifluoromethyl)phenyl)methanamine (**2.52a**) (701 mg, 3.71 mmol, 1.0 eq.) was used as the general amine that was stirred with the acid chloride intermediate for 15 h, and purified by flash column chromatography (SiO_2; isocratic elution: 30% Et_2O in pet. ether) to yield the title compound as a yellow oil (950 mg, 84%).

$\boldsymbol{R_f}$ = 0.21 (30% Et_2O in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51 (2H, d, *J* 8.0, H_3), 7.27 (2H, d, *J* 8.0, H_4), 4.72 (2H, br s, H_6), 3.14 (3H, br s, H_7), 1.98 (3H, s, H_{11}), 1.50 (6H, s, H_{10}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.1 (C_8), 142.0 (C_5), 129.6 (q, *J* 32.4, C_2), 127.7 (C_4), 125.7 (q, *J* 3.8, C_3), 124.2 (q, *J* 272.0, C_1), 53.6 (C_6), 47.4 (C_9), 37.1 (C_7), 27.4 (C_{10}), 12.8 (C_{11}). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −65.7 (3F, s, F_1). **IR** (film, $CDCl_3$) ν_{max} = 2975 (C−H), 2923 (C−H), 1627, 1619, 1393, 1322, 1161, 1120, 1108, 1089, 1065, 1018, 818 cm^{-1}. **HRMS** (ESI$^+$) *m*/*z* calcd for $C_{14}H_{19}F_3NOS$ $[M+H]^+$ 306.1139, found 306.1136.

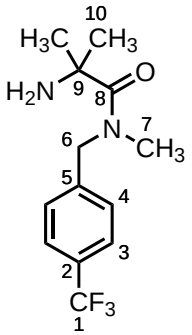
tert-Butyl (2-methyl-1-(methyl(4-(trifluoromethyl)benzyl)amino)-1-oxopropan-2-yl)carbamate (2.71a)



By **GP10**, *N*-methyl-1-(4-(trifluoromethyl)phenyl)methanamine (**2.52a**) (946 mg, 5.00 mmol) was used as the *N*-methylbenzylamine and α-(Boc-amino) isobutyric acid (1.07 g, 5.26 mmol) was used as the Boc-protected amino acid that were stirred for 73 h, and purified by flash column chromatography (SiO_2; gradient elution: 7–50% EtOAc in pet. ether) to yield the title compound as a white solid (978 mg, 52%).

m.p. = 56–60 °C ($CHCl_3$). $\boldsymbol{R_f}$ = 0.34 (40% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.55 (2H, d, *J* 8.0, H_3), 7.40 (2H, d, *J* 8.0, H_4), 4.93 (1H, s, NH), 4.72 (2H, s, H_6), 3.05 (3H, s, H_7), 1.55 (6H, s, H_{10}), 1.40 (9H, s, H_{13}). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 173.2 (C_8), 154.0 (C_{11}), 141.8 (C_5), 129.5 (q, *J* 32.7, C_2), 128.1 (C_4), 125.6 (C_3), 124.3 (q, *J* 271.9, C_1), 79.9 (C_{12}), 56.9 (C_9), 53.1 (C_6), 36.0 (C_7), 28.4 (C_{13}), 26.4 (C_{10}). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −65.6 (3F, s, F_1). **IR** (film, $CDCl_3$) ν_{max} = 3313 (N−H, br), 2981 (C−H), 2934 (C−H), 1699 (C=O), 1620 (C=O), 1324, 1160, 1123, 1110, 1066 cm^{-1}. **HRMS** (ESI$^+$) *m*/*z* calcd for $C_{18}H_{26}F_3N_2NaO_3$ $[M+H]^+$ 375.1709, found 375.1703.

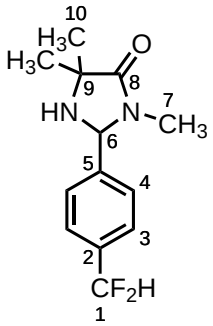
2-Amino-*N*,2-dimethyl-*N*-(4-(trifluoromethyl)benzyl)propanamide (2.65)



By **GP11**, *tert*-butyl (2-methyl-1-(methyl(4-(trifluoromethyl)benzyl)amino)-1-oxopropan-2-yl)carbamate (**2.71a**) (2.75 g, 7.35 mmol) was used as the Boc-protected amine that was stirred for 3 h to yield the title compound as a pale orange oil without further purification (1.88 g, 93%).

$\boldsymbol{R_f}$ = 0.14 (EtOAc + 1% Et_3N). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.56 (2H, d, *J* 8.0, H_3), 7.30 (2H, d, *J* 8.0, H_4), 4.82 (2H, br s, H_6), 3.10 (3H, br s, H_7), 1.77 (2H, s, N*H*), 1.44 (6H, s, H_{10}), **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.8 (C_8), 142.0 (C_5), 129.6 (q, *J* 32.3, C_2), 127.6 (C_4), 125.7 (q, *J* 3.8, C_3), 124.2 (q, *J* 272.0, C_1), 56.0 (C_9), 53.4 (C_6), 36.7 (C_7), 29.5 (C_{10}). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −65.7 (3F, s, F_1). **IR** (film, $CDCl_3$) ν_{max} = 3357 (N−H, br), 3291 (N−H, br), 2972 (C−H), 2928 (C−H), 1618 (C=O), 1322, 1161, 1118, 1109, 1065, 1017, 816 cm^{-1}. **HRMS** (ESI$^+$) *m*/*z* calcd for $C_{13}H_{18}F_3N_2O$ $[M+H]^+$ 275.1366, found 275.1368.

2-(4-(Difluoromethyl)phenyl)-3,5,5-trimethylimidazolidin-4-one (2.82)

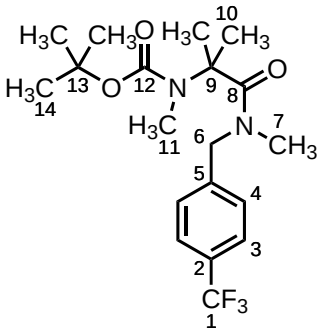


In a microwave vial, 2-amino-*N*,2-dimethyl-*N*-(4-(trifluoromethyl)benzyl) propanamide (**2.65**) (55 mg, 0.20 mmol, 1.0 eq.) was dissolved in anhydrous THF (2.0 mL), and KHMDS (400 µL, 1 M in THF, 0.40 mmol, 2.0 eq.) added dropwise. The vial was sealed, the reaction mixture stirred at 100 °C under microwave irradiation for 1 h, quenched by the addition of MeOH (5 mL), and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2; gradient elution: 12–100% EtOAc in pet. ether) to yield the title compound as a yellow oil (12 mg, 24%). (Note: 2-(4-(fluoromethyl)phenyl)-3,5,5-trimethyl-3,5-dihydro-4*H*-imidazol-4-one (**2.83**) was also isolated as a yellow oil (7 mg, 15%).)

2.82:
$\boldsymbol{R_f}$ = 0.23 (EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.58 (2H, d, *J* 8.0, H_3), 7.45 (2H, d, *J* 8.0, H_4), 6.66 (1H, t, *J* 56.3, H_1), 5.29 (1H, s, H_6), 2.65 (3H, s, H_7), 2.14 (1H, br s, N*H*), 1.42 (3H, s, H_{10a}), 1.32 (3H, s, H_{10b}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 178.3 (C_8), 141.4 (C_5), 135.8 (t, *J* 22.6, C_2), 127.7 (C_4), 126.7 (t, *J* 6.0, C_3), 114.3 (t, *J* 239.1, C_1), 75.5 (C_6), 59.7 (C_9), 27.8 (C_7), 26.2 (C_{10a}), 24.9 (C_{10b}). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −114.2 (2F, d, *J* 56.3, F_1). **IR** (film, $CDCl_3$) ν_{max} = 3316 (N−H, br), 2971 (C−H), 2929 (C−H), 1694 (C=O), 1434, 1399, 1229, 1070, 1023 cm^{-1}. **HRMS** (ESI$^+$) *m*/*z* calcd for $C_{13}H_{17}F_2N_2O$ $[M+H]^+$ 255.1303, found 255.1310.

2.83:
$\boldsymbol{R_f}$ = 0.43 (EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.69 (2H, d, *J* 8.0, H_4), 7.51 (2H, d, *J* 8.0, H_3), 5.46 (2H, d, *J* 47.3, H_1), 3.15 (3H, s, H_7), 1.43 (6H, s, H_{10}). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 186.6 (C_8), 160.9 (C_6), 139.7 (d, *J* 17.5, C_2), 129.6 (C_5), 128.7 (C_4), 127.4 (d, *J* 6.5, C_3), 83.8 (d, *J* 168.5, C_1), 67.7 (C_9), 29.0 (C_7), 24.2 (C_{10}). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −214.8 (1F, t, *J* 47.3, F_1). **IR** (film, $CDCl_3$) ν_{max} = 2975 (C−H), 2929 (C−H), 1723 (C=O), 1624, 1608, 1429, 1378, 1362, 1324, 1048, 1037, 1015 cm^{-1}. **HRMS** (ESI$^+$) *m*/*z* calcd for $C_{13}H_{16}FN_2O$ $[M+H]^+$ 235.1241, found 235.1246.

tert-Butyl methyl(2-methyl-1-(methyl(4-(trifluoromethyl)benzyl) amino)-1-oxopropan-2-yl)carbamate (2.72a)

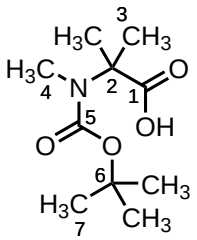


By **GP12**, *tert*-butyl (2-methyl-1-(methyl(4-(trifluoromethyl)benzyl) amino)-1-oxopropan-2-yl)carbamate (**2.71a**) (2.07 g, 5.53 mmol) was used as the carbamate that was stirred at room temperature for 19 h to yield the title compound as a yellow oil without further purification (2.09 g, 97%).

$\boldsymbol{R_f}$ = 0.29 (30% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.52 (2H, d, *J* 7.9, H_3), 7.39 (2H, d, *J* 7.9, H_4), 4.63 (2H, s, H_6), 2.89 (3H, s, H_7), 2.85 (3H, s, H_{11}), 1.45 (6H, s, H_{10}), 1.40 (9H, s, H_{14}). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 174.2 (C_8), 155.0 (C_{12}), 142.1 (C_5), 129.4 (q, *J* 32.3, C_2), 128.3 (C_4), 125.4 (C_3), 123.9 (q, *J* 271.9, C_1), 80.6 (C_{13}), 61.4 (C_9), 52.5 (C_6), 35.3 (C_7), 29.1 (C_{11}), 28.3 (C_{14}), 24.2 (C_{10}). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −65.5 (3F, s, F_1). **IR** (film, $CDCl_3$) ν_{max} = 2980 (C−H), 2927 (C−H), 1690 (C=O), 1644 (C=O), 1362, 1323,

1162, 1121, 1110, 1087, 1066 cm^{-1}. **HRMS** (ESI^+) m/z calcd for $C_{19}H_{27}F_3N_2NaO_3$ $[M+Na]^+$ 411.1875, found 411.1872.

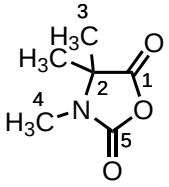
2-((*tert*-Butoxycarbonyl)(methyl)amino)-2-methylpropanoic acid (2.73)



By the method of Fehrentz and co-workers[333] with modifications, α-(Boc-amino)isobutyric acid (12.12 g, 59.6 mmol, 1.0 eq.) was dissolved in anhydrous THF (119 mL), cooled to 0 °C, and NaH (7.56 g, 60% dispersion in mineral oil, 189 mmol, 3.2 eq.) added portionwise (note: effervescence). MeI (30.6 mL, 492 mmol, 8.3 eq.) was added, the reaction mixture stirred at room temperature for 18 h, diluted with H_2O (250 mL) (note: effervescence), washed with Et_2O (250 mL), adjusted to pH 1 with aqueous HCl (3 M), and extracted with EtOAc (250 mL). The organic extract was washed sequentially with aqueous $Na_2S_2O_3$ (250 mL, 1 M), aqueous $KHSO_4$ (250 mL, 1 M) and brine (250 mL), dried (Na_2SO_4), and concentrated *in vacuo* to yield the title compound as a white solid without further purification (11.89 g, 92%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.27 (1H, br s, O*H*), 2.90 (3H, s, H_4), 1.45 (6H, s, H_3), 1.42 (9H, s, H_7). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 181.4 (C_1), 155.3 (C_5), 81.2 (C_6), 60.4 (C_2), 29.6 (C_4), 28.4 (C_7), 24.1 (C_3). Data consistent with literature.[333]

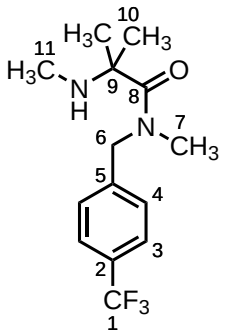
3,4,4-Trimethyloxazolidine-2,5-dione (2.74)



By the method of Bode and co-workers[334] with modifications, 2-((*tert*-butoxycarbonyl)(methyl)amino)-2-methylpropanoic acid (**2.73**) (2.10 g, 9.67 mmol, 1.0 eq.) was dissolved in anhydrous DCM (48 mL), cooled to 0 °C, and PCl_3 (930 µL, 10.6 mmol, 1.1 eq.) added. The reaction mixture was warmed to room temperature, stirred for 3 h, filtered, eluting with DCM, and concentrated *in vacuo* to yield the title compound as a white solid without further purification (1.38 g, quant.).

m.p. = 56–57 °C (DCM). $\boldsymbol{R_f}$ = 0.21 (30% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.91 (3H, s, H_4), 1.50 (6H, s, H_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.7 (C_1), 151.0 (C_5), 62.0 (C_2), 25.7 (C_4), 22.5 (C_3). **IR** (film, DCM) ν_{max} = 2987 (C–H), 1841 (C=O), 1769 (C=O), 1387, 1284, 1171, 961, 757, 733, 550 cm^{-1}. **HRMS** (APCI$^+$) m/z calcd for $C_6H_{10}NO_3$ $[M+H]^+$ 144.0655, found 144.0658.

N,2-Dimethyl-2-(methylamino)-*N*-(4-(trifluoromethyl)benzyl) propanamide (2.66a)

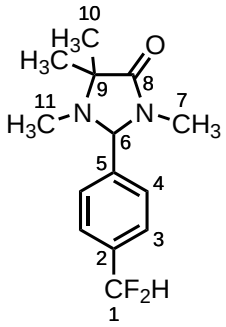


Method 1: By **GP11**, *tert*-butyl methyl(2-methyl-1-(methyl(4-(trifluoromethyl)benzyl)amino)-1-oxopropan-2-yl)carbamate (**2.72a**) (1.99 g, 5.12 mmol) was used as the Boc-protected amine that was stirred for 3.5 h, and purified by flash column chromatography (SiO_2; gradient elution: 20–75% acetone in pet. ether) to yield the title compound as a pale yellow oil (886 mg, 60%).

Method 2: By **GP13**, 3,4,4-trimethyloxazolidine-2,5-dione (**2.74**) (220 mg, 1.54 mmol, 1.0 eq.) was used as the *N*-carboxyanhydride and *N*-methyl-1-(4-(trifluoromethyl)phenyl)methanamine (**2.52a**) (291 mg, 1.54 mmol) was used as the amine that were stirred at room temperature for 17 h, and purified by flash column chromatography (SiO_2; gradient elution: 0–5% MeOH in DCM) to yield the title compound as a pale yellow oil (370 mg, 84%).

$\boldsymbol{R_f}$ = 0.17 (acetone). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.57 (2H, d, J 8.0, H_3), 7.31 (2H, d, J 8.0, H_4), 4.80 (2H, br s, H_6), 3.23 (3H, br s, H_7), 2.30 (3H, s, H_{11}), 1.39 (6H, s, H_{10}), 1.24 (1H, br s, NH). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.2 (C_8), 142.4 (C_5), 129.5 (q, J 32.3, C_2), 127.7 (C_4), 125.6 (q, J 3.8, C_3), 124.3 (q, J 271.9, C_1), 61.1 (C_9), 53.2 (C_6), 36.0 (C_7), 30.4 (C_{11}), 26.4 (C_{10}). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −65.6 (3F, s, F_1). **IR** (film, $CDCl_3$) ν_{max} = 3319 (N–H, br), 2926 (C–H), 2856 (C–H), 1629 (C=O), 1391, 1323, 1161, 1121, 1108, 1065, 1018 cm^{-1}. **HRMS** (ESI$^+$) m/z calcd for $C_{14}H_{20}F_3N_2O$ $[M+H]^+$ 289.1522, found 289.1529.

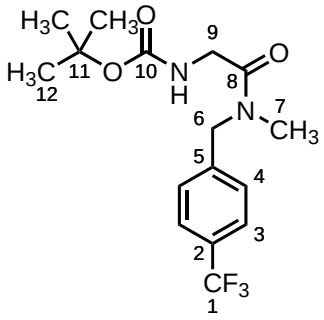
2-(4-(Difluoromethyl)phenyl)-1,3,5,5-tetramethylimidazolidin-4-one (2.69a)



By **GP14**, *N*,2-dimethyl-2-(methylamino)-*N*-(4-(trifluoromethyl)benzyl) propanamide (**2.66a**) (288 mg, 1.00 mmol) was used as the fluoroalkyl arene, and purified by flash column chromatography (SiO_2; gradient elution: 12–100% EtOAc in pet. ether) to yield the title compound as a pale yellow oil (257 mg, 96%).

$\boldsymbol{R_f}$ = 0.38 (50% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51 (2H, d, *J* 8.0, H_3), 7.46 (2H, d, *J* 8.0, H_4), 6.63 (1H, t, *J* 56.4, H_1), 4.59 (1H, s, H_6), 2.49 (3H, s, H_7), 2.11 (3H, s, H_{11}), 1.32 (3H, s, H_{10a}), 1.12 (3H, s, H_{10b}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.3 (C_8), 140.6 (t, *J* 2.0, C_5), 135.6 (t, *J* 22.4, C_2), 129.0 (C_4), 126.0 (t, *J* 6.0, C_3), 114.4 (t, *J* 238.9, C_1), 81.2 (C_6), 61.5 (C_9), 30.4 (C_{11}), 26.9 (C_7), 24.1 (C_{10a}), 16.7 (C_{10b}). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −114.1 (2F, d, *J* 56.4, F_1). **IR** (film, $CDCl_3$) ν_{max} = 2973 (C–H), 2800 (C–H), 1701 (C=O), 1435, 1400, 1299, 1219, 1072, 1022 cm^{-1}. **HRMS** (ESI^+) *m/z* calcd for $C_{14}H_{19}F_2N_2O$ $[M+H]^+$ 269.1460, found 269.1464.

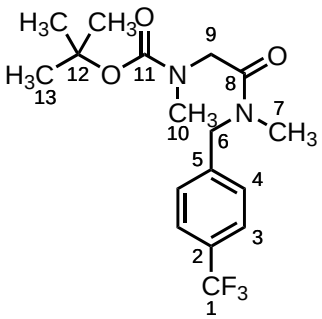
***tert*-Butyl (2-(methyl(4-(trifluoromethyl)benzyl)amino)-2-oxoethyl) carbamate (2.124)**



By **GP10**, *N*-methyl-1-(4-(trifluoromethyl)phenyl)methanamine (**2.52a**) (420 mg, 2.22 mmol) was used as the *N*-methylbenzylamine and Boc-glycine (408 mg, 2.32 mmol) was used as the Boc-protected amino acid that were stirred 16 h, and purified by flash column chromatography (SiO_2; gradient elution: 5–50% EtOAc in pet. ether) to yield the title compound as a pale yellow gum (289 mg, 38%).

$\boldsymbol{R_f}$ = 0.35 (50% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers in an approximate 75:25 ratio) δ 7.62 ($2H^{min}$, d, *J* 8.0, H_3), 7.57 ($2H^{maj}$, d, *J* 8.0, H_3), 7.33 ($2H^{maj}$, d, *J* 8.0, H_4), 7.27 ($2H^{min}$, d, *J* 8.0, H_4), 5.52 ($1H^{both\ rot.}$, br s, N*H*), 4.64 ($2H^{maj}$, s, H_6), 4.52 ($2H^{min}$, s, H_6), 4.01 ($2H^{maj}$, s, H_9), 3.99 ($2H^{min}$, s, H_9), 2.97 ($3H^{min}$, s, H_7), 2.90 ($3H^{maj}$, s, H_7), 1.45 ($9H^{maj}$, s, H_{12}), 1.42 ($9H^{min}$, s, H_{12}). **^{13}C NMR** (101 MHz, $CDCl_3$, mixture of rotamers in an approximate 75:25 ratio) δ 169.0 ($C_8{}^{maj}$), 169.0 ($C_8{}^{min}$), 156.0 ($C_{10}{}^{maj}$), 155.9 ($C_{10}{}^{min}$), 140.8 ($C_5{}^{maj}$), 139.9 ($C_5{}^{min}$), 130.1 (q, *J* 32.7, $C_2{}^{both\ rot.}$), 128.3 ($C_4{}^{maj}$), 126.8 ($C_4{}^{min}$), 126.2 (q, *J* 3.8, $C_3{}^{min}$), 125.8 (q, *J* 3.8, $C_3{}^{maj}$), 124.1 (q, *J* 272.0, $C_1{}^{maj}$), 124.0 (q, *J* 272.0, $C_1{}^{min}$), 79.9 ($C_{11}{}^{both\ rot.}$), 52.0 ($C_6{}^{min}$), 51.1 ($C_6{}^{maj}$), 42.5 ($C_9{}^{maj}$), 42.4 ($C_9{}^{min}$), 34.3 ($C_7{}^{min}$), 33.9 ($C_7{}^{maj}$), 28.4 ($C_{12}{}^{maj}$), 28.4 ($C_{12}{}^{min}$). **^{19}F NMR** (377 MHz, $CDCl_3$, mixture of rotamers in an approximate 75:25 ratio) δ −65.7 ($3F^{maj}$, s, F_1), −65.8 ($3F^{min}$, s, F_1). **IR** (film, $CDCl_3$) ν_{max} = 3332 (N−H, br), 2978 (C−H), 2932 (C−H), 1708 (C=O), 1651 (C=O), 1485, 1416, 1367, 1323, 1160, 1119, 1066, 1051, 1018, 733 cm^{-1}. **HRMS** (ESI^+) *m*/*z* calcd for $C_{16}H_{22}F_3N_2O_3$ $[M+H]^+$ 347.1577, found 347.1573.

tert-Butyl methyl(2-(methyl(4-(trifluoromethyl)benzyl)amino)-2-oxoethyl)carbamate (2.125)

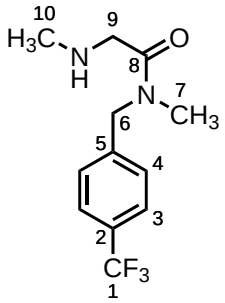


By **GP12**, *tert*-butyl (2-(methyl(4-(trifluoromethyl)benzyl)amino)-2-oxoethyl) carbamate (**2.124**) (280 mg, 0.81 mmol) was used as the carbamate that stirred for 20 h, and purified by flash column chromatography (SiO_2; gradient elution: 7–50% EtOAc in pet. ether) to yield the title compound as a yellow gum (257 mg, 88%).

$\boldsymbol{R_f}$ = 0.18 (50% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers A/B/C/D in an approximate 45:25:20:10 ratio) δ 7.60 ($2H^{rot.\ C}$ + $2H^{rot.\ D}$, d, *J* 8.0, H_3), 7.55 ($2H^{rot.\ A}$ + $2H^{rot.\ B}$, d, *J* 8.0, H_3), 7.35 ($2H^{rot.\ B}$, d, *J* 8.0, H_4), 7.34 ($2H^{rot.\ A}$, d, *J* 8.0, H_4), 7.28 ($2H^{rot.\ C}$ + $2H^{rot.\ D}$, d, *J* 8.0, H_4), 4.61 ($2H^{rot.\ A}$ + $2H^{rot.\ B}$, s, H_6), 4.58 ($2H^{rot.\ C}$, s, H_6), 4.52 ($2H^{rot.\ D}$, s, H_6), 4.08 ($2H^{rot.\ A}$, s, H_9), 4.07 ($2H^{rot.\ C}$, s, H_9), 4.00 ($2H^{rot.\ B}$ + $2H^{rot.\ D}$, s, H_9), 2.97–2.88 ($6H^{rot.\ A}$ + $6H^{rot.\ B}$ + $6H^{rot.\ C}$ + $6H^{rot.\ D}$, m, H_7, H_{10}), 1.46 ($9H^{rot.\ B}$ + $9H^{rot.\ C}$, s, H_{13}), 1.39 ($9H^{rot.\ D}$, s, H_{13}), 1.38 ($9H^{rot.\ A}$, s, H_{13}). **^{13}C NMR** (151 MHz, $CDCl_3$, mixture of rotamers A/B/C/D in an approximate 45:25:20:10 ratio) δ 169.3 ($C_8{}^{rot.\ C}$), 169.1 ($C_8{}^{rot.\ A}$), 168.9 ($C_8{}^{rot.\ B}$), 168.8 ($C_8{}^{rot.\ D}$), 156.4 ($C_{11}{}^{rot.\ A}$), 156.2 ($C_{11}{}^{rot.\ C}$), 155.7 ($C_{11}{}^{rot.\ B}$), 155.6 ($C_{11}{}^{rot.\ D}$), 141.3 ($C_5{}^{rot.\ B}$), 141.3 ($C_5{}^{rot.\ A}$), 140.7 ($C_5{}^{rot.\ C}$), 140.5 ($C_5{}^{rot.\ D}$), 130.8–129.3 (m, $C_2{}^{rot.\ A}$, $C_2{}^{rot.\ B}$, $C_2{}^{rot.\ C}$,

C_2[rot. D]), 128.4 (C_4[rot. B]), 128.3 (C_4[rot. A]), 126.7 (C_5[rot. C]), 126.6 (C_5[rot. D]), 126.1 (C_3[rot. D]), 126.0 (q, J 3.8, C_3[rot. C]), 125.7 (q, J 3.8, C_3[rot. A], C_3[rot. B]), 123.3 (q, J 272.0, C_1[rot. A]), 123.3 (q, J 272.0, C_1[rot. B]), 123.2 (q, J 272.0, C_1[rot. C]), 123.1 (q, J 272.0, C_1[rot. D]), 80.1 (C_{12}[rot. A], C_{12}[rot. B]), 79.9 (C_{12}[rot. C], C_{12}[rot. D]), 52.4 (C_6[rot. C]), 52.1 (C_6[rot. D]), 51.1 (C_6[rot. B]), 51.0 (C_6[rot. A]), 50.9 (C_9[rot. B]), 50.8 (C_9[rot. B]), 50.3 (C_9[rot. C]), 50.3 (C_9[rot. A]), 35.9 (C_{10}[rot. A]), 35.8 (C_{10}[rot. B]), 35.7 (C_{10}[rot. D]), 35.6 (C_{10}[rot. C]), 34.4 (C_7[rot. D]), 34.2 (C_{10}[rot. A], C_{10}[rot. B]), 34.1 (C_{10}[rot. C]), 28.4 (C_{13}[rot. B], C_{13}[rot. D]), 28.3 (C_{13}[rot. A], C_{13}[rot. C]). **^{19}F NMR** (377 MHz, $CDCl_3$, mixture of rotamers A/B/C/D in an approximate 45:25:20:10 ratio) δ −65.6 (3F[rot. A], s, F_1), −65.6 (3F[rot. B], s, F_1), −65.7 (3F[rot. C], s, F_1), −65.7 (3F[rot. D], s, F_1). **IR** (film, $CDCl_3$) ν_{max} = 2977 (C−H), 2932 (C−H), 1693 (C=O), 1661 (C=O), 1391, 1323, 1247, 1151, 1114, 1066, 1018, 885, 820, 732 cm^{-1}. **HRMS** (ESI$^+$) m/z calcd for $C_{17}H_{24}F_3N_2O_3$ $[M+H]^+$ 361.1734, found 361.1721.

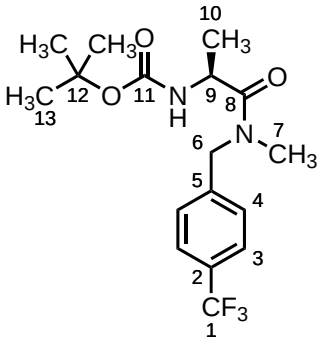
N-Methyl-2-(methylamino)-*N*-(4-(trifluoromethyl)benzyl)acetamide (2.67)



By **GP11**, *tert*-butyl methyl(2-(methyl(4-(trifluoromethyl)benzyl)amino)-2-oxoethyl)carbamate (**2.125**) (270 mg, 0.75 mmol) was used as the Boc-protected amine that was stirred for 3 h, and purified by flash column chromatography (SiO_2; gradient elution: 1–10% MeOH in DCM) to yield the title compound as a yellow oil (119 mg, 61%).

***R*$_f$** = 0.09 (10% MeOH in DCM). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers in an approximate 70:30 ratio) δ 7.55 (2H[min], d, J 8.0, H_3), 7.50 (2H[maj], d, J 8.0, H_3), 7.28 (2H[maj], d, J 8.0, H_4), 7.23 (2H[min], d, J 8.0, H_4), 4.59 (2H[maj], s, H_6), 4.49 (2H[min], s, H_6), 3.39 (2H[maj], s, H_9), 3.34 (2H[min], s, H_9), 2.91 (3H[min], s, H_7), 2.84 (3H[maj], s, H_7), 2.41 (3H[maj], s, H_{10}), 2.35 (3H[min], s, H_{10}), 1.91 (1H[both rot.], br s, NH). **^{13}C NMR** (101 MHz, $CDCl_3$, mixture of rotamers in an approximate 70:30 ratio) δ 171.4 (C_8[min]), 171.3 (C_8[maj]), 141.3 (C_5[maj]), 140.6 (C_5[min]), 130.0 (q, J 32.7, C_2[min]), 129.6 (q, J 32.4, C_2[maj]), 128.2 (C_4[maj]), 126.6 (C_4[min]), 125.9 (q, J 3.8, C_3[min]), 125.5 (q, J 3.8, C_3[maj]), 124.1 (q, J 272.0, C_1[maj]), 123.9 (q, J 272.0, C_1[min]), 52.4 (C_9[maj]), 52.3 (C_9[min]), 51.9 (C_6[min]), 50.7 (C_6[maj]), 36.5 (C_{10}[maj]), 36.5 (C_{10}[min]), 33.9 (C_7[min]), 33.8 (C_7[maj]). **^{19}F NMR** (377 MHz, $CDCl_3$, mixture of rotamers in an approximate 70:30 ratio) δ −65.5 (3F[maj], s, F_1), −65.6 (3F[min], s, F_1). **IR** (film, $CDCl_3$) ν_{max} = 3334 (N−H, br), 2937 (C−H), 2794 (C−H), 1646 (C=O), 1403, 1323, 1192, 1110, 1065, 1018, 819, 729 cm^{-1}. **HRMS** (ESI$^+$) m/z calcd for $C_{12}H_{16}F_3N_2O$ $[M+H]^+$ 261.1209, found 261.1197.

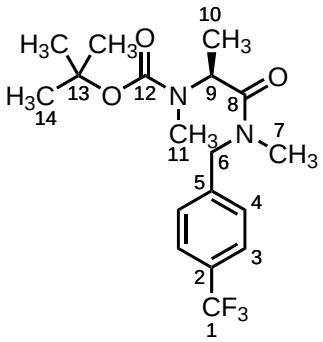
tert-Butyl (_S_)-(1-(methyl(4-(trifluoromethyl)benzyl)amino)-1-oxopropan-2-yl)carbamate (2.126)



By **GP10**, *N*-methyl-1-(4-(trifluoromethyl)phenyl)methanamine (**2.52a**) (420 mg, 2.22 mmol) was used as the *N*-methylbenzylamine and Boc-L-alanine (408 mg, 2.32 mmol) was used as the Boc-protected amino acid that were stirred for 16 h, and purified by flash column chromatography (SiO_2; gradient elution: 5–50% EtOAc in pet. ether) to yield the title compound as a pale yellow gum (598 mg, 75%).

$\boldsymbol{R_f}$ = 0.50 (50% EtOAc in pet. ether). $\boldsymbol{[\alpha]_D^{21.5}}$ (*c* 1.00, DCM): +8.0°. **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers in an approximate 75:25 ratio) δ 7.61 (2H^{min}, d, *J* 8.0, H_3), 7.57 (2H^{maj}, d, *J* 8.0, H_3), 7.31 (2H$^{both\ rot.}$, d, *J* 8.0, H_4), 5.48 (1H^{maj}, br d, *J* 7.5, N*H*), 5.40 (1H^{min} br d, *J* 7.5, N*H*), 4.72–4.64 (1H$^{both\ rot.}$, m, H_9), 4.67 (2H^{min}, s, H_6), 4.63 (2H^{maj}, s, H_6), 3.00 (3H^{maj}, s, H_7), 2.92 (3H^{min}, s, H_7), 1.44 (9H^{maj}, s, H_{13}), 1.39 (9H^{min}, s, H_{13}), 1.34 (3H^{maj}, d, *J* 6.8, H_{10}), 1.28 (3H^{min}, d, *J* 6.8, H_{10}). **^{13}C NMR** (101 MHz, $CDCl_3$, mixture of rotamers in an approximate 75:25 ratio) δ 173.6 ($C_8{}^{min}$), 173.5 ($C_8{}^{maj}$), 155.4 ($C_{11}{}^{maj}$), 155.2 ($C_{11}{}^{min}$), 141.0 (q, *J* 1.2, $C_5{}^{maj}$), 140.4 (q, *J* 1.2, $C_5{}^{min}$), 130.0 (q, *J* 32.5, $C_2{}^{both\ rot.}$), 128.1 ($C_4{}^{maj}$), 127.1 ($C_4{}^{min}$), 126.1 (q, *J* 3.8, $C_3{}^{min}$), 125.8 (q, *J* 3.8, $C_3{}^{maj}$), 124.2 (q, *J* 272.0, $C_1{}^{maj}$), 124.1 (q, *J* 272.0, $C_1{}^{min}$), 79.8 ($C_{12}{}^{both\ rot.}$), 52.8 ($C_6{}^{min}$), 51.1 ($C_6{}^{maj}$), 46.5 ($C_9{}^{maj}$), 46.3 ($C_9{}^{min}$), 34.9 ($C_7{}^{maj}$), 34.2 ($C_7{}^{min}$), 28.5 ($C_{13}{}^{maj}$), 28.4 ($C_{13}{}^{min}$), 19.6 ($C_{10}{}^{min}$), 18.9 ($C_{10}{}^{maj}$). **^{19}F NMR** (377 MHz, $CDCl_3$, mixture of rotamers in an approximate 75:25 ratio) δ −65.7 (3F^{maj}, s, F_1), −65.7 (3F^{min}, s, F_1). **IR** (film, $CDCl_3$) ν_{max} = 3316 (N−H, br), 2980 (C−H), 2934 (C−H), 1702 (C=O), 1644 (C=O), 1487, 1415, 1367, 1323, 1161, 1121, 1110, 1065, 1018, 921, 863, 819, 733 cm^{-1}. **HRMS** (ESI$^+$) *m*/*z* calcd for $C_{17}H_{24}F_3N_2O_3$ $[M+H]^+$ 361.1734, found 361.1730.

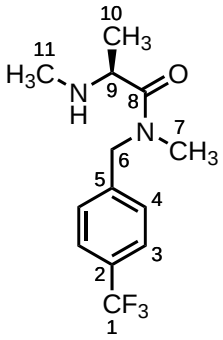
tert-Butyl (_S_)-methyl(1-(methyl(4-(trifluoromethyl)benzyl)amino)-1-oxopropan-2-yl)carbamate (2.127)



By **GP12**, _tert_-butyl (_S_)-(1-(methyl(4-(trifluoromethyl)benzyl)amino)-1-oxopropan-2-yl)carbamate (**2.126**) (573 mg, 1.59 mmol) was used as the carbamate that was stirred for 20 h, and purified by flash column chromatography (SiO_2; gradient elution: 7–50% EtOAc in pet. ether) to yield the title compound as a pale yellow gum (416 mg, 70%).

$\boldsymbol{R_f}$ = 0.59 (50% EtOAc in pet. ether). $\boldsymbol{[\alpha]_D^{21.3}}$ (_c_ 1.00, DCM): +8.0°. **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers A/B/C/D in an approximate 45:25:20:10 ratio) δ 7.58 (2H$^{\text{rot. B}}$, d, _J_ 8.0, H_3), 7.55 (2H$^{\text{rot. A}}$ + 2H$^{\text{rot. C}}$ + 2H$^{\text{rot. D}}$, d, _J_ 8.0, H_3), 7.34 (2H$^{\text{rot. C}}$, d, _J_ 8.0, H_4), 7.33 (2H$^{\text{rot. A}}$, d, _J_ 8.0, H_4), 7.21 (2H$^{\text{rot. B}}$ + 2H$^{\text{rot. D}}$, d, _J_ 8.0, H_4), 5.20 (1H$^{\text{rot. B}}$, q, _J_ 6.9, H_9), 5.13 (1H$^{\text{rot. A}}$, q, _J_ 6.9, H_9), 4.92–4.62 (2H$^{\text{rot. B}}$ + 1H$^{\text{rot. C}}$ +, 3H$^{\text{rot. D}}$, m, $H_6$$^{\text{rot. B}}$, $H_6$$^{\text{rot. D}}$, $H_9$$^{\text{rot. C}}$, $H_9$$^{\text{rot. D}}$), 4.62–4.40 (2H$^{\text{rot. A}}$ + 2H$^{\text{rot. C}}$, m, H_6), 2.96 (3H$^{\text{rot. A}}$ + 3H$^{\text{rot. C}}$, s, H_7), 2.90 (3H$^{\text{rot. B}}$ + 3H$^{\text{rot. D}}$, s, H_7), 2.76 (3H$^{\text{rot. A}}$ + 3H$^{\text{rot. B}}$, s, H_{11}), 2.72 (3H$^{\text{rot. C}}$ + 3H$^{\text{rot. D}}$, s, H_{11}), 1.44 (9H$^{\text{rot. A}}$, s, H_{14}), 1.43 (9H$^{\text{rot. C}}$, s, H_{14}), 1.31 (3H$^{\text{rot. A}}$, 3H$^{\text{rot. C}}$, 3H$^{\text{rot. D}}$, d, _J_ 6.9, H_{10}), 1.30 (9H$^{\text{rot. D}}$, s, H_{14}), 1.27 (3H$^{\text{rot. B}}$, d, _J_ 6.9, H_{10}), 1.23 (9H$^{\text{rot. B}}$, s, H_{14}). **^{13}C NMR** (151 MHz, $CDCl_3$, mixture of rotamers A/B/C/D in an approximate 45:25:20:10 ratio) δ 172.2 ($C_8$$^{\text{rot. A}}$), 172.1 ($C_8$$^{\text{rot. B}}$), 171.6 ($C_8$$^{\text{rot. C}}$), 171.2 ($C_8$$^{\text{rot. D}}$), 155.6 ($C_{12}$$^{\text{rot. A}}$), 155.2 ($C_{12}$$^{\text{rot. B}}$), 154.8 ($C_{12}$$^{\text{rot. C}}$), 154.4 ($C_{12}$$^{\text{rot. D}}$), 141.5 ($C_5$$^{\text{rot. A}}$), 141.4 ($C_5$$^{\text{rot. B}}$, $C_5$$^{\text{rot. C}}$), 140.8 ($C_5$$^{\text{rot. D}}$), 129.8 (q, _J_ 32.2, $C_2$$^{\text{rot. B}}$, $C_5$$^{\text{rot. D}}$), 129.8 (q, _J_ 32.2, $C_2$$^{\text{rot. A}}$, $C_2$$^{\text{rot. C}}$), 128.5 ($C_4$$^{\text{rot. C}}$), 128.2 ($C_4$$^{\text{rot. A}}$), 126.7 ($C_4$$^{\text{rot. B}}$, $C_4$$^{\text{rot. D}}$), 126.1 ($C_3$$^{\text{rot. D}}$), 125.8 (q, _J_ 3.8, $C_3$$^{\text{rot. B}}$), 125.7 (q, _J_ 3.8, $C_3$$^{\text{rot. A}}$, $C_3$$^{\text{rot. C}}$), 124.2 (q, _J_ 271.8, $C_1$$^{\text{rot. A}}$, $C_1$$^{\text{rot. D}}$), 124.1 (q, _J_ 271.8, $C_1$$^{\text{rot. B}}$, $C_1$$^{\text{rot. C}}$), 80.6 ($C_{13}$$^{\text{rot. D}}$), 80.5 ($C_{13}$$^{\text{rot. C}}$), 80.2 ($C_{13}$$^{\text{rot. A}}$), 80.2 ($C_{13}$$^{\text{rot. B}}$), 52.6 ($C_6$$^{\text{rot. B}}$), 52.3 ($C_6$$^{\text{rot. D}}$), 52.1 ($C_9$$^{\text{rot. C}}$), 51.7 ($C_9$$^{\text{rot. D}}$), 51.3 ($C_6$$^{\text{rot. A}}$, $C_6$$^{\text{rot. C}}$), 50.6 ($C_9$$^{\text{rot. A}}$), 49.8 ($C_9$$^{\text{rot. B}}$), 34.8 ($C_7$$^{\text{rot. A}}$), 34.5 ($C_7$$^{\text{rot. C}}$), 34.2 ($C_7$$^{\text{rot. B}}$, $C_7$$^{\text{rot. D}}$), 29.5 ($C_{11}$$^{\text{rot. A}}$), 29.3 ($C_{11}$$^{\text{rot. B}}$), 29.2 ($C_{11}$$^{\text{rot. C}}$), 29.1 ($C_{11}$$^{\text{rot. D}}$), 28.5 ($C_{14}$$^{\text{rot. C}}$), 28.4 ($C_{14}$$^{\text{rot. A}}$), 28.3 ($C_{14}$$^{\text{rot. D}}$), 28.1 ($C_{14}$$^{\text{rot. B}}$), 15.1 ($C_{10}$$^{\text{rot. D}}$), 14.9 ($C_{10}$$^{\text{rot. C}}$), 14.9 ($C_{10}$$^{\text{rot. B}}$), 14.7 ($C_{10}$$^{\text{rot. A}}$). **^{19}F NMR** (377 MHz, $CDCl_3$, mixture of rotamers A/B/C/D in an approximate 45:25:20:10 ratio) δ −65.6 (3F$^{\text{rot. A}}$, s, F_1), −65.7 (3F$^{\text{rot. C}}$, s, F_1), −65.7 (3F$^{\text{rot. B}}$ + 3F$^{\text{rot. D}}$, s, F_1). **IR** (film, $CDCl_3$) ν_{max} = 2979 (C–H), 2935 (C–H), 1686 (C=O), 1655 (C=O), 1389, 1368, 1325, 1158, 1124, 1067, 1018 cm^{-1}. **HRMS** (ESI$^+$) _m/z_ calcd for $C_{18}H_{25}F_3NNa_2O_3$ $[M+Na]^+$ 397.1709, found 397.1694.

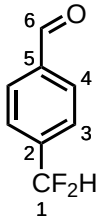
(*S*)-*N*-Methyl-2-(methylamino)-*N*-(4-(trifluoromethyl)benzyl) propanamide (2.68)



By **GP11**, *tert*-butyl (*S*)-methyl(1-(methyl(4-(trifluoromethyl)benzyl)amino)-1-oxopropan-2-yl)carbamate (**2.127**) (404 mg, 1.08 mmol) was used as the Boc-protected amine that was stirred for 3 h, and purified by flash column chromatography (SiO_2; gradient elution: 1–10% MeOH in DCM) to yield the title compound as a pale yellow oil (259 mg, 88%).

$\boldsymbol{R_f}$ = 0.21 (10% MeOH in DCM). $\boldsymbol{[\alpha]_D^{19.2}}$ (*c* 1.43, DCM): −30.8°. **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers in an approximate 75:25 ratio) δ 7.57 (2H^{min}, d, *J* 8.0, H_3), 7.51 (2H^{maj}, d, *J* 8.0, H_3), 7.28 (2H^{maj}, d, *J* 8.0, H_4), 7.25 (2H^{min}, d, *J* 8.0, H_4), 4.67 (1H^{min}, d, *J* 17.2, H_{6a}), 4.65 (1H^{maj}, d, *J* 15.0, H_{6a}), 4.59 (1H^{maj}, d, *J* 15.0, H_{6b}), 4.48 (1H^{min}, *J* 17.2, H_{6b}), 3.48 (1H^{maj}, q, *J* 6.8, H_9), 3.36 (1H^{min}, q, *J* 6.8, H_9), 2.93 (3H^{min}, s, H_7), 2.92 (3H^{maj}, s, H_7), 2.29 (3H^{maj}, s, H_{11}), 2.22 (3H^{min}, s, H_{11}), 1.87 (1H$^{both\ rot.}$, br s, N*H*), 1.20 (3H^{maj}, d, *J* 6.8, H_{10}), 1.17 (3H^{min}, d, *J* 6.8, H_{10}). **^{13}C NMR** (101 MHz, $CDCl_3$, mixture of rotamers in an approximate 75:25 ratio) δ 175.8 ($C_8{}^{min}$), 175.6 ($C_8{}^{maj}$), 141.4 (q, *J* 1.5, $C_5{}^{maj}$), 140.8 (q, *J* 1.5, $C_5{}^{min}$), 130.1 (q, *J* 32.6, $C_2{}^{min}$), 129.7 (q, *J* 32.4, $C_2{}^{maj}$), 128.1 ($C_4{}^{maj}$), 126.6 ($C_4{}^{min}$), 125.9 (q, *J* 3.8, $C_3{}^{min}$), 125.6 (q, *J* 3.8, $C_3{}^{maj}$), 124.1 (q, *J* 271.9, $C_1{}^{maj}$), 124.0 (q, *J* 271.9, $C_1{}^{min}$), 55.3 ($C_9{}^{min}$), 55.2 ($C_9{}^{maj}$), 52.3 ($C_6{}^{min}$), 50.9 ($C_6{}^{maj}$), 34.8 ($C_{11}{}^{maj}$), 34.8 ($C_{11}{}^{min}$), 34.5 ($C_7{}^{maj}$), 34.2 ($C_7{}^{min}$), 19.4 ($C_{10}{}^{min}$), 18.9 ($C_{10}{}^{maj}$). **^{19}F NMR** (377 MHz, $CDCl_3$, mixture of rotamers in an approximate 75:25 ratio) δ −65.6 (3F^{maj}, s, F_1), −65.6 (3F^{min}, s, F_1). **IR** (film, $CDCl_3$) ν_{max} = 3315 (N−H, br), 2975 (C−H), 2939 (C−H), 1638 (C=O), 1406, 1323, 1162, 1110, 1065, 1017, 817, 730 cm^{-1}. **HRMS** (ESI$^+$) *m*/*z* calcd for $C_{13}H_{18}F_3N_2O$ $[M+H]^+$ 275.1366, found 275.1353.

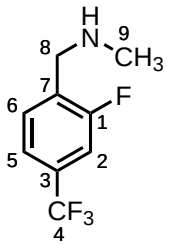
4-(Difluoromethyl)benzaldehyde (2.39a)



By **GP15**, 2-(4-(difluoromethyl)phenyl)-1,3,5,5-tetramethylimidazolidin-4-one (**2.69a**) (99 mg, 0.37 mmol) was used as the imidazolidinone to yield the title compound as a yellow oil (51 mg, 87%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.08 (1H, s, H_6), 7.98 (2H, d, J 7.9, H_4), 7.69 (2H, d, J 7.9, H_3), 6.71 (1H, t, J 56.0, H_1). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 191.6 (C_6), 139.9 (t, J 22.4, C_2), 138.1 (t, J 1.7, C_5), 130.1 (C_4), 126.5 (t, J 6.1, C_3), 113.9 (t, J 240.2, C_1). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −115.7 (2F, d, J 56.0, F_1). Data consistent with literature.[121]

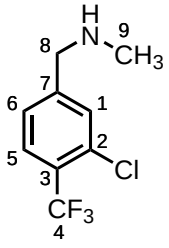
1-(2-Fluoro-4-(trifluoromethyl)phenyl)-*N*-methylmethanamine (2.52b)



By **GP7**, 2-fluoro-4-(trifluoromethyl)benzaldehyde (750 µL, 5.50 mmol) was used as the aldehyde that was stirred for 20 h to yield the title compound as a colourless oil (1.08 g, 94%).

***R*$_f$** = 0.28 (5% MeOH in DCM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47 (1H, td, J 8.0, 7.1, 1.0, H_6), 7.36 (1H, dd, J 8.0, 1.7, H_5), 7.27 (1H, dd, J 9.8, 1.7, H_2), 3.82 (2H, s, H_8), 2.43 (3H, s, H_9), 1.40 (1H, s, NH). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.8 (d, J 247.9, C_1), 131.5 (dq, J 15.2, 1.4, C_7), 131.1 (qd, J 33.2, 7.9, C_3), 130.9 (d, J 5.3, C_6), 123.5 (qd, J 272.0, 2.6, C_4), 121.0 (quint, J 3.8, C_5), 112.8 (dq, J 25.5, 3.9, C_2), 48.9 (d, J 2.9, C_8), 35.9 (C_9). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −65.7 (3F, s, F_4), −120.1 (1F, dd, J 9.9, 7.2, F_1). **IR** (film, $CDCl_3$) ν_{max} = 3306 (N−H, br), 2942 (C−H), 2853 (C−H), 2800 (C−H), 1429, 1327, 1167, 1123, 1102, 1064, 906, 878, 832, 744 cm^{-1}. **HRMS** (ESI$^+$) m/z calcd for $C_9H_{10}F_4N$ $[M+H]^+$ 208.0744, found 208.0740.

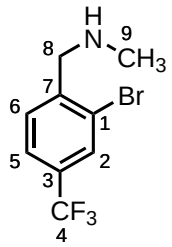
1-(3-Chloro-4-(trifluoromethyl)phenyl)-*N*-methylmethanamine (2.52c)



By **GP7**, 3-chloro-4-(trifluoromethyl)benzaldehyde (3.2 mL, 21.8 mmol) was used as the aldehyde that was stirred for 3.5 h to yield the title compound as a colourless oil (4.89 g, quant.).

$\boldsymbol{R_f}$ = 0.16 (5% MeOH in DCM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.61 (1H, d, *J* 8.0, H_5), 7.48 (1H, s, H_1), 7.29 (1H, d, *J* 8.0, H_6), 3.76 (2H, s, H_8), 2.43 (3H, s, H_9), 1.55 (1H, s, N*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.3 (C_7), 132.4 (q, *J* 1.9, C_2), 130.9 (C_1), 127.6 (q, *J* 5.2, C_5), 127.0 (q, *J* 31.3, C_3), 126.2 (C_6), 123.1 (q, *J* 272.7, C_4), 54.9 (C_8), 36.1 (C_9). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −65.3 (3F, s, F_4). **IR** (film, $CDCl_3$) ν_{max} = 3310 (N−H, br), 2851 (C−H), 2796 (C−H), 1609, 1403, 1312, 1174, 1124, 1100, 1027, 828 cm^{-1}. **HRMS** (ESI^+) *m*/*z* calcd for $C_9H_{10}ClF_3N$ $[M+H]^+$ 224.0448, found 224.0447.

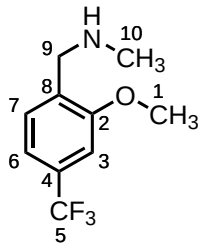
1-(2-Bromo-4-(trifluoromethyl)phenyl)-*N*-methylmethanamine (2.52d)



By **GP7**, 2-bromo-4-(trifluoromethyl)benzaldehyde (1.1 mL, 7.29 mmol) was used as the aldehyde that was stirred for 25 h to yield the title compound as a pale yellow oil (1.97 g, quant.).

$\boldsymbol{R_f}$ = 0.36 (5% MeOH in DCM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.80 (1H, s, H_2), 7.56–7.51 (2H, m, H_5, H_6) 3.86 (2H, s, H_8), 2.46 (3H, s, H_9), 1.56 (1H, s, N*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.4 (q, *J* 1.0, C_7), 130.9 (q, *J* 33.0, C_3), 130.2 (C_6), 129.8 (q, *J* 3.9, C_2), 124.3 (q, *J* 3.7, C_5), 124.0 (C_1), 123.3 (q, *J* 272.5, C_4), 55.4 (C_8), 36.0 (C_9). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −65.7 (3F, s, F_4). **IR** (film, $CDCl_3$) ν_{max} = 3301 (N−H, br), 2851 (C−H), 2797 (C−H), 1395, 1318, 1270, 1168, 1123, 1077, 1040, 830, 680 cm^{-1}. **HRMS** (ESI^+) *m*/*z* calcd for $C_9H_{10}BrF_3N$ $[M+H]^+$ 267.9943, found 267.9945.

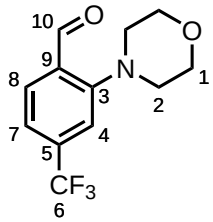
1-(2-Methoxy-4-(trifluoromethyl)phenyl)-*N*-methylmethanamine (2.52e)



By **GP7**, 2-methoxy-4-(trifluoromethyl)benzaldehyde (1.07 g, 5.24 mmol) was used as the aldehyde that was stirred for 20 h to yield the title compound as a colourless oil (1.15 g, quant.).

$\boldsymbol{R_f}$ = 0.12 (5% MeOH in DCM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33 (1H, d, *J* 7.7, H_7), 7.17 (1H, dd, *J* 7.7, 1.6, H_6), 7.04 (1H, d, *J* 1.6, H_3), 3.86 (3H, s, H_1), 3.76 (2H, s, H_9), 2.40 (3H, s, H_{10}), 1.75 (1H, s, N*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.7 (C_2), 132.4 (q, *J* 1.3, C_8), 130.5 (q, *J* 32.3, C_4), 129.9 (C_7), 124.2 (q, *J* 272.2, C_5), 117.3 (q, *J* 4.0, C_6), 106.9 (q, *J* 3.7, C_3), 55.5 (C_1), 50.8 (C_9), 35.9 (C_{10}). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −65.5 (3F, s, F_5). **IR** (film, $CDCl_3$) ν_{max} = 3310 (N−H, br), 2942 (C−H), 2847 (C−H), 2797 (C−H), 1415, 1325, 1238, 1162, 1114, 1077, 1032, 891, 858, 739 cm^{-1}. **HRMS** (ESI$^+$) *m*/*z* calcd for $C_{10}H_{12}F_3NO$ $[M+H]^+$ 220.0944, found 220.0939.

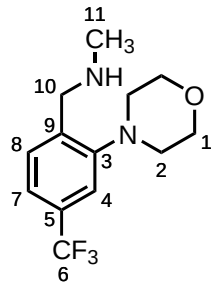
2-Morpholino-4-(trifluoromethyl)benzaldehyde (2.40f)



By the method of Grice and co-workers[335] with modifications, K_2CO_3 (7.30 g, 52.8 mmol, 3.0 eq.), 2-fluoro-4-(trifluoromethyl)benzaldehyde (2.4 mL, 17.6 mmol, 1.0 eq.) and morpholine (4.6 mL, 52.8 mmol, 3.0 eq.) were suspended in anhydrous DMSO (34 mL). The reaction mixture was stirred at 80 °C for 21 h, quenched by the addition of H_2O (50 mL), and extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with brine (100 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2; gradient elution: 7–15% Et_2O in pet. ether) to yield the title compound as a yellow oil that solidified upon standing (1.47 g, 32%).

m.p. = 60–61 °C ($CHCl_3$). $\boldsymbol{R_f}$ = 0.31 (30% Et_2O in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.32 (1H, s, H_{10}), 7.89 (1H, d, *J* 8.0, H_8), 7.37 (1H, d, *J* 8.0, H_7), 7.33 (1H, s, H_4), 3.91 (4H, dd, *J* 5.8, 3.4, H_1), 3.12 (4H, dd, *J* 5.8, 3.4, H_2). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 190.1 (C_{10}), 155.3 (C_3), 136.2 (q, *J* 32.4, C_5), 131.1 (C_8), 130.9 (C_9), 123.6 (q, *J* 273.1, C_6), 119.4 (q, *J* 3.8, C_7), 115.9 (q, *J* 3.8, C_4), 66.9 (C_1), 54.1 (C_2). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −66.4 (3F, s, F_6). **IR** (film, $CDCl_3$) ν_{max} = 2964 (C−H), 2851 (C−H), 1690 (C=O), 1499, 1425, 1343, 1309, 1295, 1167, 1115, 1074, 1051, 956, 878, 867, 833, 734 cm^{-1}. **HRMS** (EI$^+$) *m*/*z* calcd for $C_{12}H_{12}F_3NO_2$ $[M]^+$ 259.0815, found 259.0818.

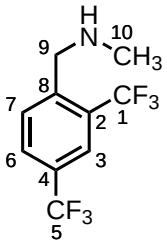
N-Methyl-1-(2-morpholino-4-(trifluoromethyl)phenyl)methanamine (2.52f)



By **GP7**, 2-morpholino-4-(trifluoromethyl)benzaldehyde (**2.40f**) (1.39 g, 5.36 mmol) was used as the aldehyde that was stirred for 15 h to yield the title compound as a yellow oil (1.49 g, quant.).

$\boldsymbol{R_f}$ = 0.16 (5% MeOH in DCM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.49 (1H, d, *J* 8.0, H_8), 7.33 (1H, dd, *J* 8.0, 1.8, H_7), 7.29 (1H, d, *J* 1.8, H_4), 3.87–3.82 (4H, m, H_1), 3.82 (2H, s, H_{10}), 2.98–2.92 (4H, m, H_2), 2.45 (3H, s, H_{11}), 1.85 (1H, br s, N*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 151.7 (C_3), 138.9 (C_9), 130.2 (q, *J* 32.0, C_5), 130.1 (C_8), 124.2 (q, *J* 272.2, C_6), 120.7 (q, *J* 3.8, C_7), 116.6 (q, *J* 3.6, C_4), 67.4 (C_1), 53.0 (C_2), 51.5 (C_{10}), 36.4 (C_{11}). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −65.5 (3F, s, F_6). **IR** (film, $CDCl_3$) ν_{max} = 3316 (N−H, br), 2961 (C−H), 2853 (C−H), 1421, 1336, 1310, 1296, 1162, 1111, 1078, 1051, 953, 732 cm^{-1}. **HRMS** (ESI$^+$) *m*/*z* calcd for $C_{13}H_{18}F_3N_2O$ $[M+H]^+$ 275.1371, found 275.1370.

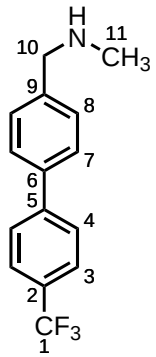
1-(2,4-Bis(trifluoromethyl)phenyl)-*N*-methylmethanamine (2.52g)



By **GP7**, 2,4-bis(trifluoromethyl)benzaldehyde (1.0 mL, 6.11 mmol) was used as the aldehyde that was stirred for 1.5 h to yield the title compound as a pale yellow oil (1.37 g, 87%).

$\boldsymbol{R_f}$ = 0.22 (5% MeOH in DCM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.88 (1H, d, *J* 1.8, H_3), 7.86 (1H, d, *J* 8.3, H_7), 7.78 (1H, dd, *J* 8.3, 1.8, H_6), 3.97 (2H, s, H_9), 2.48 (3H, s, H_{10}), 1.32 (1H, s, N*H*). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 143.5 (qq, *J* 1.2, C_8), 130.7 (C_7), 129.6 (q, *J* 33.4, C_4), 129.1 (q, *J* 31.3, C_2), 128.8 (qq, *J* 3.6, 1.0, C_6), 123.9 (q, *J* 274.1, C_5), 123.6 (q, *J* 272.1, C_1), 123.2 (qq, *J* 6.0, 3.9, C_3), 51.5 (q, *J* 2.4, C_9), 36.3 (C_{10}). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −63.3 (3F, s, F_1). −65.9 (3F, s, F_5). **IR** (film, $CDCl_3$) ν_{max} = 3310 (N−H, br), 2856 (C−H), 2802 (C−H), 1344, 1274, 1168, 1117, 1082, 1055, 911, 844, 670 cm^{-1}. **HRMS** (ESI$^+$) *m*/*z* calcd for $C_{10}H_{10}F_6N$ $[M+H]^+$ 258.0712, found 258.0705.

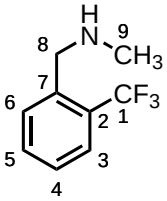
N-Methyl-1-(4′-(trifluoromethyl)-[1,1′-biphenyl]-4-yl)methanamine (2.52h)



By **GP7**, 4′-trifluoromethylbiphenyl-4-carbaldehyde (2.00 g, 7.99 mmol) was used as the aldehyde (with the modification of THF (equal volume as MeOH) added to the reaction mixture to aid solubilisation of the aldehyde) that was stirred for 15 h to yield the title compound as a white solid (2.18 g, quant.).

m.p. = 115–116 °C ($CHCl_3$). $\boldsymbol{R_f}$ = 0.05 (5% MeOH in DCM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.71–7.66 (4H, m, H_3, H_4), 7.57 (2H, d, J 7.8, H_7), 7.43 (2H, d, J 7.8, H_8), 3.82 (2H, s, H_{10}), 2.50 (3H, s, H_{11}), 1.77 (1H, s, NH). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.6 (C_5), 140.3 (C_9), 138.6 (C_6), 129.4 (q, J 32.4, C_2), 128.9 (C_8), 127.4 (C_4, C_7), 125.8 (q, J 3.9, C_3), 124.4 (q, J 271.9, C_1), 55.7 (C_{10}), 36.1 (C_{11}). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −65.5 (3F, s, F_1). **IR** (film, $CDCl_3$) ν_{max} = 3334 (N−H, br), 2940 (C−H), 2797 (C−H), 1616, 1324, 1165, 1122, 1110, 1070, 907, 812, 728 cm^{-1}. **HRMS** (ESI$^+$) m/z calcd for $C_{15}H_{15}NF_3$ $[M+H]^+$ 266.1157, found 266.1159.

N-Methyl-1-(2-(trifluoromethyl)phenyl)methanamine (2.52i)

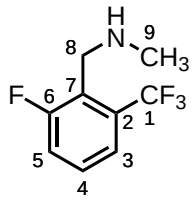


By **GP7**, 2-(trifluoromethyl)benzaldehyde (3.0 mL, 22.8 mmol) was used as the aldehyde that was stirred for 2.5 h to yield the title compound as a pale yellow oil (3.85 g, 89%).

$\boldsymbol{R_f}$ = 0.20 (5% MeOH in DCM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.63 (1H, d, J 7.6, H_3), 7.61 (1H, d, J 7.6, H_6), 7.52 (1H, t, J 7.6, H_5), 7.34 (1H, t, J 7.6, H_4), 3.91 (2H, s, H_8), 2.48 (3H, s, H_9), 1.50 (1H, s, NH). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.9 (q, J 1.6, C_7), 132.0 (C_5), 130.5 (C_6), 128.4 (q, J 30.2, C_2), 127.0 (C_4), 126.0 (q, J 5.8, C_3), 124.7 (q, J 274.0, C_1), 52.1 (q, J 2.1, C_8), 36.3 (C_9). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −62.6 (3F, s, F_1). **IR** (film, $CDCl_3$) ν_{max} = 3318

(N–H, br), 2940 (C–H), 2852 (C–H), 2798 (C–H), 1453, 1312, 1168, 1116, 1100, 1059, 1037, 768, 654 cm^{-1}. **HRMS** (ESI^+) m/z calcd for $C_9H_{11}F_3N$ $[M+H]^+$ 190.0838, found 190.0841.

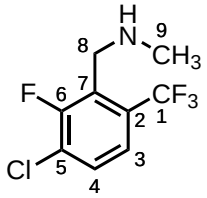
1-(2-Fluoro-6-(trifluoromethyl)phenyl)-*N*-methylmethanamine (2.52j)



By **GP7**, 2-fluoro-6-(trifluoromethyl)benzaldehyde (640 µL, 4.77 mmol) was used as the aldehyde that was stirred for 1.5 h to yield the title compound as a colourless oil (954 mg, 97%).

R_f = 0.61 (5% MeOH in DCM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 (1H, d, J 7.8, H_3), 7.34 (1H, tdd, J 7.8, 5.5, H_4), 7.25 (1H, ddd, J 9.8, 7.8, H_5), 3.91 (2H, s, H_8), 2.44 (3H, s, H_9), 1.41 (1H, s, NH). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.4 (d, J 247.2, C_6), 131.0 (qd, J 30.6, 4.8, C_2), 129.0 (d, J 9.2, C_4), 126.6 (dq, J 17.9, 1.5, C_7), 123.9 (qd, J 274.2, 3.9, C_1), 121.9 (qd, J 5.7, 3.5, C_3), 119.4 (d, J 23.4, C_5), 45.3 (dq, J 4.0, 2.0, C_8), 36.0 (C_9). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −61.7 (3F, s, F_1), −118.0 (1F, dd, J 9.8, 5.5, F_6). **IR** (film, $CDCl_3$) ν_{max} = 3334 (N–H, br), 2945 (C–H), 2854 (C–H), 2799 (C–H), 1465, 1313, 1247, 1166, 1153, 1119, 1071, 876, 799, 744, 722 cm^{-1}. **HRMS** (ESI^+) m/z calcd for $C_9H_{10}F_4N$ $[M+H]^+$ 208.0744, found 208.0740.

1-(3-Chloro-2-fluoro-6-(trifluoromethyl)phenyl)-*N*-methylmethanamine (2.52k)

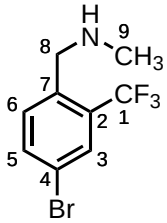


By **GP7**, 3-chloro-2-fluoro-6-(trifluoromethyl)benzaldehyde (570 µL, 3.85 mmol) was used as the aldehyde that was stirred for 1.5 h to yield the title compound as a pale yellow oil (959 mg, quant.).

R_f = 0.74 (5% MeOH in DCM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48–7.34 (2H, m, H_3, H_4), 3.93 (2H, s, H_8), 2.45 (3H, s, H_9), 1.60 (1H, br s, NH). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.8 (d, J 249.2, C_6), 129.5 (C_4), 129.3 (qd, J 31.1, 3.7, C_2), 128.3 (d, J 18.7, C_5), 125.7 (d, J 20.0, C_7), 123.6 (qd, J 274.1, 3.1, C_1), 122.3

(qd, J 5.8, 4.6, C_3), 45.6 (dq, J 3.9, 2.1, C_8), 36.0 (C_9). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −61.8 (3F, s, F_1), −118.9 (1F, d, J 5.6, F_5). **IR** (film, $CDCl_3$) ν_{max} = 3330 (N−H, br), 2946 (C−H), 2855 (C−H), 2799 (C−H), 1431, 1316, 1162, 1121, 1101, 990, 977, 821, 740, 647, 566, 464 cm^{-1}. **HRMS** (ESI$^+$) m/z calcd for $C_9H_9ClF_4N$ $[M+H]^+$ 242.0354, found 242.0350.

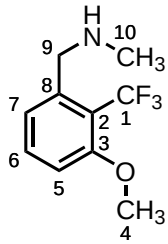
1-(4-Bromo-2-(trifluoromethyl)phenyl)-*N*-methylmethanamine (2.52l)



By **GP7**, 4-bromo-2-(trifluoromethyl)benzaldehyde (1.03 g, 4.07 mmol) was used as the aldehyde that was stirred for 30 min to yield the title compound as a pale orange oil (1.08 g, 99%).

$\boldsymbol{R_f}$ = 0.59 (5% MeOH in DCM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.75 (1H, d, J 2.1, H_3), 7.63 (1H, dd, J 8.3, 2.1, H_5), 7.52 (1H, d, J 8.3, H_6), 3.85 (2H, s, H_8), 2.45 (3H, s, H_9), 1.74 (1H, br s, NH). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.9 (C_7), 135.0 (C_5), 132.0 (C_6), 130.1 (q, J 30.7, C_2), 129.1 (q, J 6.1, C_3), 123.6 (q, J 274.4, C_1), 120.7 (C_4), 51.4 (q, J 2.3, C_8), 36.2 (C_9). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −63.1 (3F, s, F_1). **IR** (film, $CDCl_3$) ν_{max} = 3323 (N−H, br), 2854 (C−H), 2797 (C−H), 1405, 1301, 1273, 1166, 1118, 1050, 890, 824, 678, 668 cm^{-1}. **HRMS** (ESI$^+$) m/z calcd for $C_9H_{10}BrF_3N$ $[M+H]^+$ 267.9943, found 267.9944.

1-(3-Methoxy-2-(trifluoromethyl)phenyl)-*N*-methylmethanamine (2.52m)

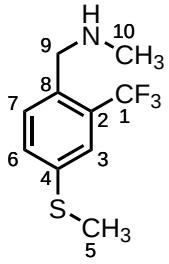


By **GP7**, 3-methoxy-2-(trifluoromethyl)benzaldehyde (1.04 g, 5.09 mmol) was used as the aldehyde that was stirred for 30 min to yield the title compound as a colourless oil (1.10 g, 98%).

$\boldsymbol{R_f}$ = 0.09 (5% MeOH in DCM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41 (1H, dd, J 8.4, 7.5, H_6), 7.08 (1H, d, J 7.5, H_7), 6.93 (1H, d, J 8.4, H_5), 3.89 (2H, q, J 2.2,

H_9), 3.87 (3H, s, H_5), 2.44 (3H, s, H_{10}), 1.45 (1H, s, NH). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.0 (q, J 2.1, C_3), 140.6 (C_8), 132.5 (C_6), 125.1 (q, J 275.6, C_1), 123.2 (C_7), 117.1 (q, J 29.3, C_2), 111.6 (C_5), 56.5 (C_4), 54.0 (q, J 4.4, C_9), 36.1 (C_{10}). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −57.9 (3F, q, J 2.2, F_1). **IR** (film, $CDCl_3$) ν_{max} = 3298 (N−H, br), 2942 (C−H), 2845 (C−H), 2796 (C−H), 1586, 1473, 1439, 1290, 1266, 1110, 1062, 1035, 784, 750 cm^{-1}. **HRMS** (ESI$^+$) m/z calcd for $C_{10}H_{13}F_3NO$ $[M+H]^+$ 220.0944, found 220.0937.

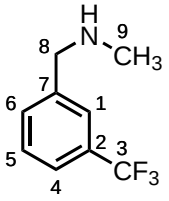
N-Methyl-1-(4-(methylthio)-2-(trifluoromethyl)phenyl)methanamine (2.52n)



By **GP7**, 4-(methylthio)-2-(trifluoromethyl)benzaldehyde (954 mg), 4.33 mmol) was used as the aldehyde that was stirred for 30 min to yield the title compound as a pale yellow oil (1.01 g, 99%).

***R*$_f$** = 0.12 (5% MeOH in DCM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51 (1H, d, J 8.2, H_7), 7.49 (1H, d, J 2.1, H_3), 7.37 (1H, dd, J 8.2, 2.1, H_6), 3.85 (2H, s, H_9), 2.49 (3H, s, H_5), 2.46 (3H, s, H_{10}), 1.80 (1H, br s, NH). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.0 (C_4), 135.3 (C_8), 131.1 (C_7), 129.7 (q, J 1.2, C_6), 129.0 (q, J 30.2, C_2), 124.4 (q, J 274.2, C_1), 123.9 (q, J 6.0, C_3), 51.7 (q, J 2.1, C_9), 36.2 (C_{10}), 15.8 (C_5). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −62.8 (3F, s, F_1). **IR** (film, $CDCl_3$) ν_{max} = 3311 (N−H, br), 2924 (C−H), 2851 (C−H), 2796 (C−H), 1305, 1114, 1050, 826 cm^{-1}. **HRMS** (ESI$^+$) m/z calcd for $C_{10}H_{13}F_3NS$ $[M+H]^+$ 236.0715, found 236.0710.

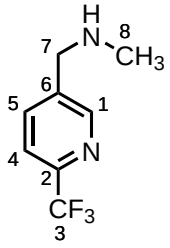
N-Methyl-1-(3-(trifluoromethyl)phenyl)methanamine (2.52o)



By **GP7**, 3-(trifluoromethyl)benzaldehyde (1.0 mL, 7.47 mmol) was used as the aldehyde that was stirred for 20 h to yield the title compound as a pale orange oil (1.33 g, 94%).

$\boldsymbol{R_f}$ = 0.14 (5% MeOH in DCM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.59 (1H, s, H_1), 7.49 (2H, d, J 7.7, H_4, H_6), 7.41 (1H, t, J 7.7, H_5), 3.79 (2H, s, H_8), 2.44 (3H, s, H_{10}), 1.67 (1H, s, NH). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.2 (C_7), 131.6 (q, J 1.1, C_6), 130.8 (q, J 32.1, C_2), 128.9 (C_5), 124.9 (q, J 3.8, C_1), 124.3 (q, J 272.3, C_3), 123.9 (q, J 3.8, C_4), 55.6 (C_8), 36.0 (C_{10}). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −65.6 (3F, s, F_3). **IR** (film, $CDCl_3$) ν_{max} = 3298 (N−H, br), 2850 (C−H), 2796 (C−H), 1325, 1161, 1117, 1092, 1072, 797, 701, 660 cm^{-1}. **HRMS** (ESI$^+$) m/z calcd for $C_9H_{11}F_3N$ $[M+H]^+$ 190.0838, found 190.0837.

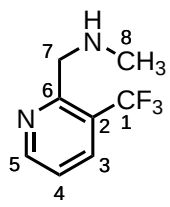
N-Methyl-1-(6-(trifluoromethyl)pyridin-3-yl)methanamine (2.52p)



By **GP7**, 6-(trifluoromethyl)nicotinaldehyde (1.01 g, 5.77 mmol) was used as the aldehyde that was stirred for 2.5 h to yield the title compound as a yellow oil (985 mg, 90%).

$\boldsymbol{R_f}$ = 0.17 (5% MeOH in DCM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.62 (1H, d, J 2.1, H_1), 7.83 (1H, dd, J 8.0, 2.1, H_5), 7.60 (1H, d, J 8.0, H_4), 3.81 (2H, s, H_7), 2.41 (3H, s, H_8), 1.49 (1H, s, NH). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.9 (C_1), 147.0 (q, J 34.6, C_2), 139.1 (q, J 1.1, C_6), 137.0 (C_5), 121.7 (q, J 273.8, C_3), 120.2 (q, J 2.8, C_4), 52.8 (C_7), 36.1 (C_8). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −70.8 (3F, s, F_3). **IR** (film, $CDCl_3$) ν_{max} = 3312 (N−H, br), 2853 (C−H), 2796 (C−H), 1333, 1173, 1126, 1083, 1028, 852, 831, 635, 591 cm^{-1}. **HRMS** (ESI$^+$) m/z calcd for $C_8H_{10}F_3N_2$ $[M+H]^+$ 191.0791, found 191.0786.

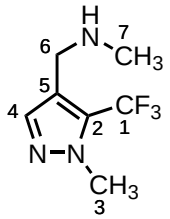
N-Methyl-1-(3-(trifluoromethyl)pyridin-2-yl)methanamine (2.52q)



By **GP7**, 3-(trifluoromethyl)pyridine-2-carboxaldehyde (981 mg), 5.60 mmol) was used as the aldehyde that was stirred for 30 min to yield the title compound as a yellow–brown oil (544 mg, 50%).

$\boldsymbol{R_f}$ = 0.04 (5% MeOH in DCM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.73 (1H, d, *J* 5.0, H_5), 7.90 (1H, d, *J* 8.0, H_3), 7.28 (1H, dd, *J* 8.0, 5.0, H_4), 4.00 (2H, s, H_7), 2.46 (3H, s, H_8), 2.30 (1H, br s, N*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.2 (C_6), 152.1 (C_5), 133.9 (q, *J* 5.3, C_3), 124.6 (q, *J* 32.1, C_2), 124.0 (q, *J* 273.2, C_1), 121.5 (C_4), 53.4 (q, *J* 2.5, C_7), 36.2 (C_8). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −64.0 (3F, s, F_1). **IR** (film, $CDCl_3$) ν_{max} = 3334 (N−H, br), 2942 (C−H), 2854 (C−H), 2796 (C−H), 1592, 1578, 1437, 1317, 1118, 1075, 1033, 812, 779, 738 cm^{-1}. **HRMS** (ESI$^+$) *m/z* calcd for $C_8H_{10}F_3N_2$ $[M+H]^+$ 191.0791, found 191.0786.

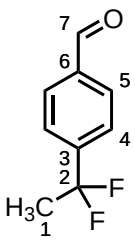
N-Methyl-1-(1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-4-yl) methanamine (2.52r)



By **GP7**, 1-methyl-5-(trifluoromethyl)-1*H*-pyrazole-4-carbaldehyde (1.08 g, 6.06 mmol) was used as the aldehyde that was stirred for 2.5 h to yield the title compound as a pale yellow oil (935 mg, 80%).

$\boldsymbol{R_f}$ = 0.12 (5% MeOH in DCM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42 (1H, s, H_4), 3.93 (3H, s, H_3), 3.67 (2H, s, H_6), 2.39 (3H, s, H_7), 1.28 (1H, s, N*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.9 (C_4), 128.2 (q, *J* 38.0, C_2), 122.3 (q, *J* 1.2, C_5), 121.0 (q, *J* 269.3, C_1), 44.8 (q, *J* 1.7, C_6), 38.6 (q, *J* 2.3, C_3), 35.9 (C_7). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −61.1 (3F, s, F_1). **IR** (film, $CDCl_3$) ν_{max} = 3319 (N−H, br), 2955 (C−H), 2852 (C−H), 2798 (C−H), 1164, 1113, 1083, 1050, 1003 cm^{-1}. **HRMS** (ESI$^+$) *m/z* calcd for $C_7H_{11}F_3N_3$ $[M+H]^+$ 194.0900, found 194.0895.

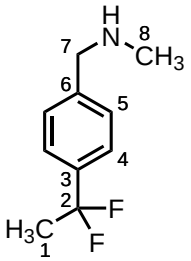
4-(1,1-Difluoroethyl)benzaldehyde (2.40t)



By the method of Mykhailiuk and co-workers[336] with modifications, 1-bromo-4-(1,1-difluoroethyl)benzene (1.5 mL, 10.1 mmol, 1.0 eq.), was dissolved in anhydrous THF (31 mL), and cooled to −78 °C. *n*-BuLi (5.3 mL, 2.09 M in hexanes, 11.1 mmol, 1.1 eq.) was added dropwise, and the reaction mixture stirred at −78 °C for 1 h. Anhydrous DMF (1.6 mL, 20.7 mmol, 2.0 eq.) was added dropwise, the reaction mixture slowly warmed to room temperature, quenched by the addition of aqueous HCl (50 mL, 3 M), and extracted with Et_2O (50 mL). The organic extract was washed with brine (50 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2; gradient elution: 0–40% DCM in pet. ether) to yield the title compound as a colourless oil (1.51 g, 87%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.06 (1H, s, H_7), 7.94 (2H, d, J 8.0, H_5), 7.67 (2H, d, J 8.0, H_4), 1.93 (3H, t, J 18.2, H_1). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 191.6 (C_7), 143.9 (t, J 26.7, C_3), 137.4 (t, J 1.6, C_6), 130.0 (C_5), 125.6 (t, J 6.0, C_4), 121.3 (t, J 240.0, C_2), 26.0 (t, J 29.4, C_1). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −92.0 (2F, q, J 18.2, F_2). Data consistent with literature.[336]

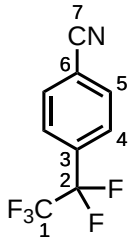
1-(4-(1,1-Difluoroethyl)phenyl)-*N*-methylmethanamine (2.52t)



By **GP7**, 4-(1,1-difluoroethyl)benzaldehyde (**2.40t**) (1.74 g, 10.2 mmol) was used as the aldehyde that was stirred for 30 min to yield the title compound as a colourless oil (1.88 g, 99%).

***R*$_f$** = 0.06 (5% MeOH in DCM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 (2H, d, J 8.0, H_4), 7.36 (2H, d, J 8.0, H_5), 3.76 (2H, s, H_7), 2.44 (3H, s, H_8), 1.90 (3H, t, J 18.1, H_1), 1.52 (1H, s, NH). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.0 (t, J 1.8, C_6), 136.9 (t, J 26.6, C_3), 128.2 (C_5), 124.8 (t, J 5.9, C_4), 121.9 (t, J 238.6, C_2), 55.6 (C_7), 36.1 (C_8), 26.0 (t, J 30.0, C_1). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −90.1 (2F, q, J 18.1, F_2). **IR** (film, $CDCl_3$) ν_{max} = 3311 (N−H, br), 3003 (C−H), 2849 (C−H), 2793 (C−H), 1384, 1171, 1129, 1104, 1088, 914, 844, 816, 611, 578 cm^{-1}. **HRMS** (ESI$^+$) m/z calcd for $C_{10}H_{14}F_2N$ $[M+H]^+$ 186.1089, found 186.1083.

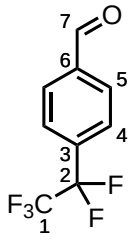
4-(Perfluoroethyl)benzonitrile (2.128)



By the method of Hannam and co-workers[337] with modifications, 4-bromobenzonitrile (4.03 g, 22.1 mmol, 1.0 eq.), sodium pentafluoropropionate (10.71 g, 57.6 mmol, 2.6 eq.) and CuI (10.96 g, 57.5 mmol, 2.6 eq.) were suspended in anhydrous DMF (53 mL). The reaction mixture was stirred at reflux for 71 h, and diluted with H_2O (100 mL) and Et_2O (100 mL). Kieselguhr was added, the reaction mixture stirred for 5 min, and filtered, eluting with Et_2O. The aqueous layer was extracted with Et_2O (100 mL), the combined organic extracts washed sequentially with H_2O (100 mL) and aqueous NH_4OH (25 mL, 28 wt%), dried ($MgSO_4$), and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2; gradient elution: 0–10% DCM in pet. ether) to yield the title compound as a pale yellow oil (2.96 g, 60%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (2H, d, *J* 8.2, H_5), 7.74 (2H, d, *J* 8.2, H_4). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 133.2 (t, *J* 24.4, C_3), 132.7 (C_5), 127.6 (tq, *J* 6.2, 1.0, C_4), 118.8 (qt, *J* 286.1, 38.4, C_1), 117.5 (C_7), 116.4 (t, *J* 1.8, C_6), 112.7 (tq, *J* 255.1, 38.7, C_2). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −87.6 (3F, t, *J* 1.9, F_1), −118.8 (2F, q, *J* 1.9, F_2). Data consistent with literature.[338]

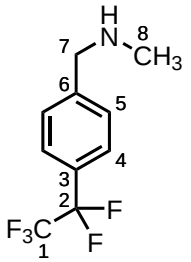
4-(Perfluoroethyl)benzaldehyde (2.40u)



By the method of Hannam and co-workers[337] with modifications, 4-(perfluoroethyl)benzonitrile (**2.128**) (1.23 g, 5.56 mmol, 1.0 eq.) was dissolved in anhydrous PhMe (27.8 mL), and cooled to −30 °C. DIBAL-H (5.6 mL, 1.0 M in heptane, 5.60 mmol, 1.0 eq.) was added dropwise, and the reaction mixture stirred at −30 °C for 1.5 h. The reaction mixture was quenched by the dropwise addition of aqueous HCl (30 mL, 1 M), stirred at room temperature for 5 min, and extracted with DCM (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$), and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2; isocratic elution: 10% DCM in pet. ether) to yield the title compound as a pale yellow oil (826 mg, 66%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.11 (1H, s, H_7), 8.02 (2H, d, J 8.1, H_5), 7.79 (2H, d, J 8.1, H_4). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 191.1 (C_7), 138.8 (C_6), 134.1 (t, J 23.9, C_3), 129.8 (C_5), 127.4 (t, J 6.3, C_4), 118.8 (qt, J 286.1, 38.5, C_1), 112.9 (tq, J 254.5, 38.5, C_2). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −87.6 (3F, t, J 1.9, F_1), −118.4 (2F, q, J 1.9, F_2). Data consistent with literature.[339]

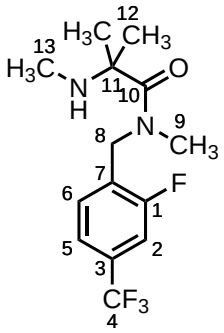
N-Methyl-1-(4-(perfluoroethyl)phenyl)methanamine (2.52u)



By **GP7**, 4-(perfluoroethyl)benzaldehyde (**2.40u**) (1.18 g, 5.26 mmol) was used as the aldehyde that was stirred for 4 h to yield the title compound as a pale yellow oil (1.16 g, 92%).

***R*$_f$** = 0.04 (5% MeOH in DCM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48 (2H, d, J 8.1, H_4), 7.38 (2H, d, J 8.1, H_5), 3.74 (2H, s, H_7), 2.38 (3H, s, H_8), 1.35 (1H, br s, NH). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.7 (t, J 1.8, C_6), 128.4 (C_5), 127.5 (t, J 24.0, C_3), 126.6 (t, J 6.4, C_4), 119.3 (qt, J 285.7, 39.4, C_1), 113.6 (tq, J 253.9, 38.2, C_2), 55.6 (C_7), 36.2 (C_8). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −87.9 (3F, t, J 2.0, F_1), −117.7 (2F, q, J 2.0, F_2). **IR** (film, $CDCl_3$) ν_{max} = 3302 (N−H, br), 2853 (C−H), 2798 (C−H), 1340, 1287, 1198, 1144, 1091, 972 cm^{-1}. **HRMS** (ESI$^+$) m/z calcd for $C_{10}H_{11}F_5N$ $[M+H]^+$ 240.0806, found 240.0802.

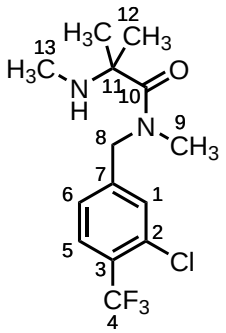
N-(2-Fluoro-4-(trifluoromethyl)benzyl)-*N*,2-dimethyl-2-(methylamino) propanamide (2.66b)



By **GP13**, with 3,4,4-trimethyloxazolidine-2,5-dione (**2.74**) (667 mg, 4.66 mmol, 1.0 eq.) used as the *N*-carboxyanhydride and 1-(2-fluoro-4-(trifluoromethyl) phenyl)-*N*-methylmethanamine (**2.52b**) (966 mg, 4.66 mmol) used as the amine that were stirred for 16 h, and purified by flash column chromatography (SiO_2; isocratic elution: 8% acetone + 1% Et_3N in DCM + 1% Et_3N) to yield the title compound as a colourless oil (724 mg, 51%).

$\boldsymbol{R_f}$ = 0.13 (3% MeOH + 1% Et_3N in DCM + 1% Et_3N). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38–7.30 (2H, m, H_5, H_6), 7.27 (1H, d, *J* 9.8, H_2), 4.77 (2H, br s, H_8), 3.29 (3H, br s, H_9), 2.36 (3H, s, H_{13}), 1.35 (6H, s, H_{12}), 0.90 (1H, br s, N*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.5 (C_{10}), 160.5 (d, *J* 248.3, C_1), 131.1 (qd, *J* 33.2, 8.4, C_3), 130.0 (C_6), 129.5 (d, *J* 15.7, C_7), 123.4 (qd, *J* 272.2, 2.8, C_4), 121.2 (quint, *J* 3.8, C_5), 112.8 (dq, *J* 25.1, 3.8, C_2), 61.0 (C_{11}), 47.0 (C_8), 36.4 (C_9), 30.3 (C_{13}), 26.3 (C_{12}). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −65.7 (3F, s, F_4), −119.6 (1F, d, *J* 9.8, F_1). **IR** (film, $CDCl_3$) ν_{max} = 3320 (N−H, br), 2978 (C−H), 2937 (C−H), 1630 (C=O), 1426, 1327, 1167, 1116, 1095, 1065, 906, 877, 743 cm^{-1}. **HRMS** (ESI$^+$) *m*/*z* calcd for $C_{14}H_{19}F_4N_2O$ $[M+H]^+$ 307.1428, found 307.1430.

N-(3-Chloro-4-(trifluoromethyl)benzyl)-*N*,2-dimethyl-2-(methylamino) propanamide (2.66c)

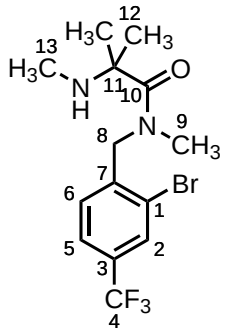


By **GP13**, 3,4,4-trimethyloxazolidine-2,5-dione (**2.74**) (597 mg, 4.66 mmol) was used as the *N*-carboxyanhydride and 1-(3-chloro-4-(trifluoromethyl) phenyl)-*N*-methylmethanamine (**2.52c**) (932 mg, 4.17 mmol) was used as the amine that were stirred for 16 h, and purified by flash column chromatography (SiO_2; isocratic elution: 8% acetone + 1% Et_3N in DCM + 1% Et_3N) to yield the title compound as a colourless oil that solidified upon standing (536 mg, 40%).

m.p. = 69–70 °C ($CHCl_3$). $\boldsymbol{R_f}$ = 0.11 (3% MeOH + 1% Et_3N in DCM + 1% Et_3N). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.60 (1H, d, *J* 8.1, H_5), 7.32 (1H, s, H_1), 7.17 (1H, d, *J* 8.1, H_6), 4.68 (2H, br s, H_8), 3.27 (3H, br s, H_9), 2.28 (3H, s, H_{13}), 1.36 (6H, s, H_{12}), 0.88 (1H, br s, N*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.3 (C_{10}), 144.3 (C_7), 132.6 (q, *J* 2.1, C_2), 130.1 (C_1), 127.8 (q, *J* 5.2, C_5), 127.1 (q, *J* 31.5, C_3), 125.5 (C_6), 122.9 (q, *J* 272.8, C_4), 61.0 (C_{11}), 52.7 (C_8), 36.2 (C_9), 30.4 (C_{13}), 26.3 (C_{12}). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −65.4 (3F, s, F_4). **IR** (film, $CDCl_3$) ν_{max} = 3320 (N−H, br), 2977 (C−H), 2934 (C−H), 1627 (C=O),

1610, 1388, 1312, 1173, 1127, 1099, 1027 cm^{-1}. **HRMS** (ESI^+) m/z calcd for $C_{14}H_{19}ClF_3N_2O$ $[M+H]^+$ 323.1133, found 323.1138.

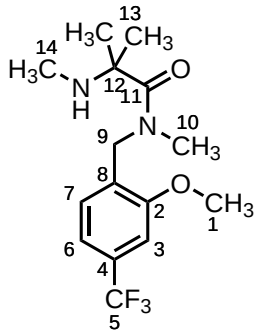
N-(2-Bromo-4-(trifluoromethyl)benzyl)-*N*,2-dimethyl-2-(methylamino) propanamide (2.66d)



By **GP13**, 3,4,4-trimethyloxazolidine-2,5-dione (**2.74**) (667 mg, 4.66 mmol) was used as the *N*-carboxyanhydride and 1-(2-bromo-4-(trifluoromethyl) phenyl)-*N*-methylmethanamine (**2.52d**) (1.71 g, 6.38 mmol) was used as the amine that were stirred for 52 h (with the modifications of PhMe instead of DCM, and stirring at 80 °C), and purified by flash column chromatography (SiO_2; gradient elution: 0–3% acetone + 1% Et_3N in DCM + 1% Et_3N) to yield the title compound as a colourless oil (995 mg, 42%).

$\boldsymbol{R_f}$ = 0.61 (80% acetone + 1% Et_3N in DCM + 1% Et_3N). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.79 (1H, d, J 1.8, H_2), 7.52 (1H, dd, J 8.1, 1.8, H_5), 7.21 (1H, d, J 8.1, H_6), 5.30 (2H, br s, H_8), 3.34 (3H, br s, H_9), 2.30 (3H, s, H_{13}), 1.37 (6H, s, H_{12}), 0.91 (1H, br s, NH). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.6 (C_{10}), 141.5 (C_7), 130.8 (q, J 33.0, C_3), 129.9 (q, J 3.8, C_2), 128.0 (C_6), 124.5 (q, J 3.7, C_5), 123.2 (q, J 272.5, C_4), 123.2 (C_1), 61.0 (C_{11}), 53.8 (C_8), 36.7 (C_9), 30.5 (C_{13}), 26.3 (C_{12}). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −65.7 (3F, s, F_4). **IR** (film, $CDCl_3$) ν_{max} = 3321 (N−H, br), 2977 (C−H), 2934 (C−H), 1632 (C=O), 1387, 1318, 1169, 1124, 1096, 1078, 1039, 835, 687 cm^{-1}. **HRMS** (ESI^+) m/z calcd for $C_{14}H_{19}BrF_3N_2O$ $[M+H]^+$ 367.0627, found 367.0622.

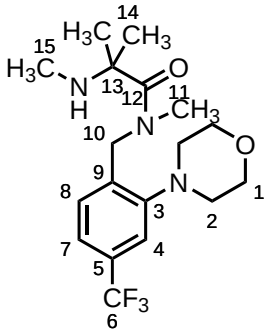
***N*-(2-Methoxy-4-(trifluoromethyl)benzyl)-*N*,2-dimethyl-2-(methylamino)propanamide (2.66e)**



By **GP13**, 3,4,4-trimethyloxazolidine-2,5-dione (**2.74**) (692 mg, 4.84 mmol, 1.0 eq.) was used as the *N*-carboxyanhydride and 1-(2-methoxy-4-(trifluoromethyl) phenyl)-*N*-methylmethanamine (**2.52e**) (1.06 g, 4.84 mmol) was used as the amine that were stirred for 16 h, and purified by flash column chromatography (SiO_2; isocratic elution: 8% acetone + 1% Et_3N in DCM + 1% Et_3N) to yield the title compound as a colourless oil (895 mg, 58%).

$\boldsymbol{R_f}$ = 0.07 (3% MeOH + 1% Et_3N in DCM + 1% Et_3N). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.19–7.13 (2H, m, H_6, H_7), 7.27 (1H, s, H_3), 4.82 (2H, br s, H_9), 3.85 (3H, s, H_1), 3.19 (3H, br s, H_{10}), 2.28 (3H, s, H_{14}), 1.34 (6H, s, H_{13}), 0.93 (1H, br s, NH). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.4 (C_{11}), 157.3 (C_2), 130.4 (C_8), 130.2 (q, J 32.1, C_4), 127.7 (C_7), 124.2 (q, J 272.1, C_5), 117.5 (q, J 4.0, C_6), 106.9 (q, J 3.7, C_3), 60.9 (C_{12}), 55.5 (C_1), 48.3 (C_9), 36.4 (C_{10}), 30.4 (C_{14}), 26.4 (C_{13}). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −65.4 (3F, s, F_5). **IR** (film, $CDCl_3$) ν_{max} = 3318 (N−H, br), 2972 (C−H), 2940 (C−H), 1626 (C=O), 1416, 1327, 1239, 1165, 1117, 1097, 1078, 1031, 890, 858, 739 cm^{-1}. **HRMS** (ESI$^+$) m/z calcd for $C_{15}H_{22}F_3N_2O_2$ $[M+H]^+$ 319.1628, found 319.1631.

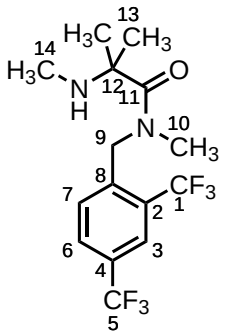
***N*,2-Dimethyl-2-(methylamino)-*N*-(2-morpholino-4-(trifluoromethyl) benzyl)propanamide (2.66f)**



By **GP13**, 3,4,4-trimethyloxazolidine-2,5-dione (**2.74**) (1.10 g, 7.75 mmol) was used as the *N*-carboxyanhydride and *N*-methyl-1-(2-morpholino-4-(trifluoromethyl)phenyl)methanamine (**2.52f**) (1.41 g, 5.14 mmol) was used as the amine that were stirred for 21 h, and purified by flash column chromatography (SiO_2; gradient elution: 0–5% acetone + 1% Et_3N in DCM + 1% Et_3N) to yield the title compound as a pale yellow oil that solidified upon standing (1.81 g, 94%).

m.p. = 113–114 °C ($CHCl_3$). $\boldsymbol{R_f}$ = 0.55 (80% acetone + 1% Et_3N in DCM + 1% Et_3N). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31 (1H, dd, *J* 8.3, 1.8, H_7), 7.29 (1H, d, *J* 1.8, H_4), 7.18 (1H, d, *J* 8.0, H_8), 5.79–4.44 (1H, br m, H_{10}), 3.89–3.78 (4H, m, H_1), 3.29 (3H, br s, H_{11}), 2.96–2.85 (4H, m, H_2), 2.32 (3H, s, H_{15}), 1.38 (6H, s, H_{14}), 1.07 (1H, br s, N*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.5 (C_{12}), 151.4 (C_3), 136.7 (C_9), 129.9 (q, *J* 32.2, C_5), 127.4 (C_8), 124.2 (q, *J* 272.3, C_6), 120.9 (q, *J* 3.8, C_7), 116.5 (q, *J* 3.6, C_4), 67.2 (C_1), 61.0 (C_{13}), 52.8 (C_2), 48.6 (C_{10}), 36.4 (C_{11}), 30.5 (C_{15}), 26.4 (C_{14}). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −65.4 (3F, s, F_6). **IR** (film, $CDCl_3$) ν_{max} = 3323 (N−H, br), 2967 (C−H), 2857 (C−H), 1625 (C=O), 1421, 1336, 1310, 1165, 1114, 1079, 955, 921, 909, 728 cm^{-1}. **HRMS** (ESI$^+$) *m*/*z* calcd for $C_{18}H_{27}F_3N_3O_2$ $[M+H]^+$ 374.2055, found 374.2048.

N-(2,4-Bis(trifluoromethyl)benzyl)-*N*,2-dimethyl-2-(methylamino) propanamide (2.66g)

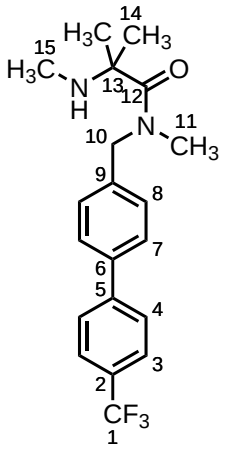


By **GP13**, 3,4,4-trimethyloxazolidine-2,5-dione (**2.74**) (870 mg, 6.12 mmol) was used as the *N*-carboxyanhydride and 1-(2,4-bis(trifluoromethyl)phenyl)-*N*-methylmethanamine (**2.52g**) (1.32 g, 5.13 mmol) was used as the amine that were stirred for 50 h (with the modifications of PhMe instead of DCM, and stirring at 80 °C), and purified by flash column chromatography (SiO_2; gradient elution: 0–2% acetone + 1% Et_3N in DCM + 1% Et_3N), with further purification by bulb-to-bulb distillation (160 °C at 100 mbar) to remove remaining 1-(2,4-bis(trifluoromethyl)phenyl)-*N*-methylmethanamine (**2.52g**) to yield the title compound as a pale yellow oil (661 mg, 36%).

$\boldsymbol{R_f}$ = 0.70 (80% acetone + 1% Et_3N in DCM + 1% Et_3N). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers in an approximate 75:25 ratio) δ 7.89 ($1H^{both\ rot.}$, d, *J* 1.9, H_3), 7.76 ($1H^{both\ rot.}$, dd, *J* 8.2, 1.9, H_6), 7.40 ($1H^{both\ rot.}$, d, *J* 8.2, H_7), 5.54 ($2H^{min}$, br s, H_9), 4.88 ($2H^{maj}$, br s, H_9), 3.36 ($3H^{both\ rot.}$, br s, H_{10}), 2.32 ($3H^{both\ rot.}$, s, H_{14}), 1.39 ($6H^{both\ rot.}$, s, H_{13}), 0.94 ($1H^{both\ rot.}$, br s, N*H*). **^{13}C**

NMR (126 MHz, $CDCl_3$) δ 175.8 (C_{11}), 141.6 (C_8), 129.6 (q, J 33.5, C_2), 129.0 (q, J 3.7, C_6), 128.2 (C_7), 123.7 (q, J 274.2, CF_3), 123.5 (q, J 272.2, CF_3), 123.4 (C_3), 123.1 (C_4), 61.0 (C_{12}), 49.8 (C_9), 36.6 (C_{10}), 30.5 (C_{14}), 26.3 (C_{13}). **^{19}F NMR** (377 MHz, $CDCl_3$, mixture of rotamers in an approximate 75:25 ratio) δ −63.5 ($3F^{maj}$, br s, F_1), −64.3 ($3F^{min}$, br s, F_1), −65.9 ($3F^{both\ rot.}$, br s, F_5). **IR** (film, $CDCl_3$) ν_{max} = 3323 (N−H, br), 2979 (C−H), 1628 (C=O), 1345, 1301, 1275, 1172, 1121, 1097, 1084, 1055, 910, 856, 732, 671 cm^{-1}. **HRMS** (ESI^+) m/z calcd for $C_{15}H_{19}F_6N_2O$ $[M+H]^+$ 357.1396, found 357.1398.

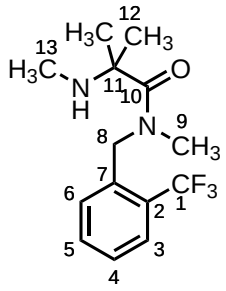
N,2-Dimethyl-2-(methylamino)-*N*-((4′-(trifluoromethyl)-[1,1′-biphenyl]-4-yl)methyl)propanamide (2.66h)



By **GP13**, 3,4,4-trimethyloxazolidine-2,5-dione (**2.74**) (1.65 g, 11.5 mmol) was used as the *N*-carboxyanhydride and *N*-methyl-1-(4′-(trifluoromethyl)-[1,1′-biphenyl]-4-yl)methanamine (**2.52h**) (2.04 g, 7.69 mmol) was used as the amine that were stirred for 21 h, and purified by flash column chromatography (SiO_2; gradient elution: 0–3% acetone + 1% Et_3N in DCM + 1% Et_3N) to yield the title compound as a colourless oil (2.71 g, 97%).

R_f = 0.55 (80% acetone + 1% Et_3N in DCM + 1% Et_3N). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.67 (4H, s, H_3, H_4), 7.55 (2H, d, J 8.0, H_7), 7.32 (2H, d, J 8.0, H_8), 4.84 (2H, br s, H_{10}), 3.25 (3H, br s, H_{11}), 2.33 (3H, s, H_{15}), 1.42 (6H, s, H_{14}), 1.08 (1H, br s, NH). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.2 (C_{12}), 144.4 (C_5), 138.6 (C_6), 138.4 (C_9), 129.4 (q, J 32.6, C_2), 128.2 (C_8), 127.5 (C_7), 127.4 (C_4), 125.8 (q, J 3.7, C_3), 124.4 (q, J 271.9, C_1), 61.0 (C_{13}), 53.1 (C_{10}), 35.9 (C_{11}), 30.5 (C_{15}), 26.5 (C_{14}). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −65.5 (3F, s, F_6). **IR** (film, $CDCl_3$) ν_{max} = 3323 (N−H, br), 2977 (C−H), 1617 (C=O), 1393, 1323, 1165, 1121, 1110, 1070, 908, 810, 728 cm^{-1}. **HRMS** (ESI^+) m/z calcd for $C_{20}H_{24}F_3N_2O$ $[M+H]^+$ 365.1841, found 365.1837.

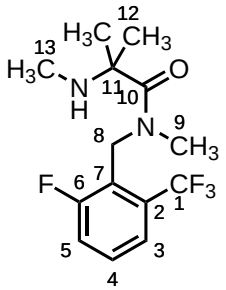
N,2-Dimethyl-2-(methylamino)-*N*-(2-(trifluoromethyl)benzyl) propanamide (2.66i)



By **GP13**, 3,4,4-trimethyloxazolidine-2,5-dione (**2.74**) (2.15 g, 15.0 mmol) was used as the *N*-carboxyanhydride and *N*-methyl-1-(2-(trifluoromethyl)phenyl) methanamine (**2.52i**) (1.89 g, 10.0 mmol) was used as the amine that were stirred for 23 h, and purified by flash column chromatography (SiO_2; gradient elution: 0–2% acetone + 1% Et_3N in DCM + 1% Et_3N) to yield the title compound as a pale yellow oil (2.42 g, 84%).

$\boldsymbol{R_f}$ = 0.26 (acetone). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers in an approximate 65:35 ratio) δ 7.63 ($1H^{\text{both rot.}}$, d, *J* 7.9, H_3), 7.49 ($1H^{\text{both rot.}}$, t, *J* 7.9, H_5), 7.31 ($1H^{\text{both rot.}}$, t, *J* 7.9, H_4), 7.25 ($1H^{\text{both rot.}}$, d, *J* 7.9, H_6), 5.38 ($2H^{\text{min}}$, br s, H_8), 4.87 ($2H^{\text{maj}}$, br s, H_8), 3.25 ($3H^{\text{both rot.}}$, br s, H_9), 2.31 ($3H^{\text{both rot.}}$, s, H_{13}), 1.38 ($6H^{\text{both rot.}}$, s, H_{12}), 1.04 ($1H^{\text{both rot.}}$, br s, N*H*). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 175.7 (C_{10}), 138.9 (q, *J* 1.6, C_7), 137.0 (C_2), 132.2 (C_5), 127.5 (C_6), 126.9 (C_4), 126.1 (q, *J* 5.7, C_3), 124.5 (q, *J* 273.9, C_1), 61.0 (C_{11}), 49.7 (C_8), 36.3 (C_9), 30.5 (C_{13}), 26.4 (C_{12}). **^{19}F NMR** (377 MHz, $CDCl_3$, mixture of rotamers in an approximate 65:35 ratio) δ −62.9 ($3F^{\text{maj}}$, br s, F_1), −63.8 ($3F^{\text{min}}$, br s, F_1). **IR** (film, $CDCl_3$) ν_{max} = 3320 (N−H, br), 2976 (C−H), 2801 (C−H), 1630 (C=O), 1311, 1158, 1106, 1059, 1038, 767, 656 cm^{-1}. **HRMS** (ESI^+) *m*/*z* calcd for $C_{14}H_{20}F_3N_2O$ $[M+H]^+$ 289.1522, found 289.1524.

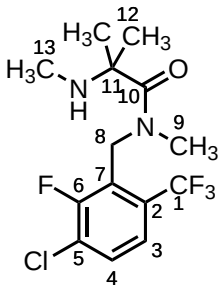
N-(2-Fluoro-6-(trifluoromethyl)benzyl)-*N*,2-dimethyl-2-(methylamino) propanamide (2.66j)



By **GP13**, 3,4,4-trimethyloxazolidine-2,5-dione (**2.74**) (1.08 g, 7.55 mmol) was used as the *N*-carboxyanhydride and 1-(2-fluoro-6-(trifluoromethyl)phenyl)-*N*-methylmethanamine (**2.52j**) (1.04 g, 5.02 mmol) was used as the amine that were stirred for 68 h (with the modifications of PhMe instead of DCM, and stirring at 80 °C), and purified by flash column chromatography (SiO_2; gradient elution: 0–6% acetone + 1% Et_3N in DCM + 1% Et_3N), with further purification by bulb-to-bulb distillation (160 °C at 100 mbar) to remove remaining 1-(2-fluoro-6-(trifluoromethyl)phenyl)-*N*-methylmethanamine (**2.52j**) to yield the title compound as a yellow solid (902 mg, 59%).

m.p. = 76–77 °C ($CHCl_3$). $\boldsymbol{R_f}$ = 0.58 (80% acetone + 1% Et_3N in DCM + 1% Et_3N). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48 (1H, d, *J* 7.9, H_3), 7.38 (1H, ddd, *J* 8.5, 7.9, 5.1, H_4), 7.24 (1H, dd, *J* 9.9, 8.5, H_5), 4.97 (2H, br s, H_8), 3.15 (3H, br s, H_9), 2.28 (3H, s, H_{13}), 1.37 (6H, s, H_{12}), 1.04 (1H, br s, N*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.7 (C_{10}), 162.4 (d, *J* 250.5, C_6), 131.6 (q, *J* 32.1, C_2), 129.4 (d, *J* 9.2, C_4), 123.8 (dq, *J* 15.8, 1.5, C_7), 123.7 (qd, *J* 274.4, 3.8, C_1), 122.0 (qd, *J* 5.8, 3.6, C_3), 119.7 (d, *J* 23.2, C_5), 61.1 (C_{11}), 43.3 (C_8), 34.3 (C_9), 30.2 (C_{13}), 26.2 (C_{12}). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −61.5 (3F, s, F_1), −115.1 (1F, dd, *J* 9.9, 5.1, F_6). **IR** (film, $CDCl_3$) ν_{max} = 3320 (N−H, br), 2977 (C−H), 2936 (C−H), 1630 (C=O), 1462, 1388, 1314, 1249, 1166, 1117, 1092, 1075, 988, 944, 798, 755, 724 cm^{-1}. **HRMS** (ESI^+) *m*/*z* calcd for $C_{14}H_{19}F_4N_2O$ $[M+H]^+$ 307.1428, found 307.1420.

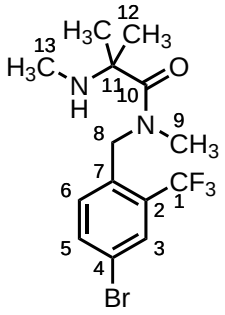
N-(3-Chloro-2-fluoro-6-(trifluoromethyl)benzyl)-*N*,2-dimethyl-2-(methylamino)propanamide (2.66k)



By **GP13**, 3,4,4-trimethyloxazolidine-2,5-dione (**2.74**) (533 mg, 3.73 mmol) was used as the *N*-carboxyanhydride and 1-(3-chloro-2-fluoro-6-(trifluoromethyl)phenyl)-*N*-methylmethanamine (**2.52k**) (600 mg, 2.48 mmol) was used as the amine that were stirred for 21 h (with the modifications of PhMe instead of DCM, and stirring at 80 °C), and purified by flash column chromatography (SiO_2; gradient elution: 0–1% acetone + 1% Et_3N in DCM + 1% Et_3N), with further purification by bulb-to-bulb distillation (170 °C at 100 mbar) to remove remaining 1-(3-chloro-2-fluoro-6-(trifluoromethyl)phenyl)-*N*-methylmethanamine (**2.52k**) to yield the title compound as a pale yellow oil that solidified upon standing (449 mg, 53%).

m.p. = 74–75 °C ($CHCl_3$). $\boldsymbol{R_f}$ = 0.55 (80% acetone + 1% Et_3N in DCM + 1% Et_3N). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48–7.40 (2H, m, H_3, H_4), 4.97 (2H, br s, H_8), 3.20 (3H, br s, H_9), 2.29 (3H, s, H_{13}), 1.38 (6H, s, H_{12}), 1.01 (1H, br s, NH). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 174.8 (C_{10}), 157.8 (d, J 252.9, C_6), 129.8 (C_4), 129.8 (qd, J 31.1, 2.4, C_2), 126.1 (d, J 19.0, C_5), 125.8 (dq, J 15.6, 1.5, C_7), 123.3 (qd, J 274.2, 3.2, C_1), 122.3 (qd, J 6.0, 4.6, C_3), 61.1 (C_{11}), 43.8 (C_8), 34.7 (C_9), 30.2 (C_{13}), 26.2 (C_{12}). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −61.7 (3F, s, F_1), −116.3 (1F, s, F_6). **IR** (film, $CDCl_3$) ν_{max} = 3322 (N−H, br), 2978 (C−H), 1632 (C=O), 1431, 1388, 1316, 1169, 1127, 1110, 1092, 992, 947, 822, 739, 647, 461 cm^{-1}. **HRMS** (ESI$^+$) m/z calcd for $C_{14}H_{18}ClF_4N_2O$ $[M+H]^+$ 341.1038, found 341.1034.

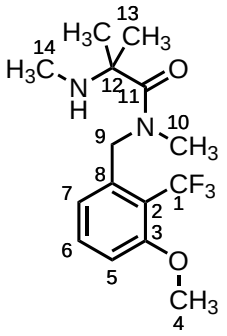
N-(4-Bromo-2-(trifluoromethyl)benzyl)-*N*,2-dimethyl-2-(methylamino) propanamide (2.66l)



By **GP13**, 3,4,4-trimethyloxazolidine-2,5-dione (**2.74**) (513 mg, 3.58 mmol) was used as the *N*-carboxyanhydride and 1-(4-bromo-2-(trifluoromethyl) phenyl)-*N*-methylmethanamine (**2.52l**) (640 mg, 2.39 mmol) was used as the amine that were stirred for 68 h (with the modifications of PhMe instead of DCM, and stirring at 80 °C), and purified by flash column chromatography (SiO_2; gradient elution: 0–4% acetone + 1% Et_3N in DCM + 1% Et_3N) to yield the title compound as a colourless oil (674 mg, 77%).

$\boldsymbol{R_f}$ = 0.48 (80% acetone + 1% Et_3N in DCM + 1% Et_3N). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers in an approximate 65:35 ratio) δ 7.76 (1H$^{\text{both rot.}}$, d, J 2.1, H_3), 7.61 (1H$^{\text{both rot.}}$, dd, J 8.4, 2.1, H_5), 7.14 (1H$^{\text{both rot.}}$, d, J 8.4, H_6), 5.37 (2H$^{\text{min}}$, br s, H_8), 4.79 (2H$^{\text{maj}}$, br s, H_8), 3.28 (3H$^{\text{both rot.}}$, br s, H_9), 2.30 (3H$^{\text{both rot.}}$, s, H_{13}), 1.37 (6H$^{\text{both rot.}}$, s, H_{12}), 0.88 (1H$^{\text{both rot.}}$, br s, NH). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.7 (C_{10}), 136.3 (C_2), 135.3 (C_5), 129.5 (C_7), 129.4 (C_6), 129.2 (q, J 6.0, C_3), 123.5 (q, J 274.5, C_1), 120.5 (C_4), 61.0 (C_{11}), 49.5 (C_8), 36.4 (C_9), 30.5 (C_{13}), 26.3 (C_{12}). **^{19}F NMR** (377 MHz, $CDCl_3$, mixture of rotamers in an approximate 65:35 ratio) δ −63.2 (3F$^{\text{maj}}$, br s, F_1), −64.1 (3F$^{\text{min}}$, br s, F_1). **IR** (film, $CDCl_3$) ν_{max} = 3321 (N−H, br), 2977 (C−H), 2937 (C−H), 1630 (C=O), 1484, 1392, 1302, 1163, 1121, 1095, 1049, 827, 730, 673 cm^{-1}. **HRMS** (ESI$^+$) m/z calcd for $C_{14}H_{19}BrF_3N_2O$ $[M+H]^+$ 367.0627, found 367.0617.

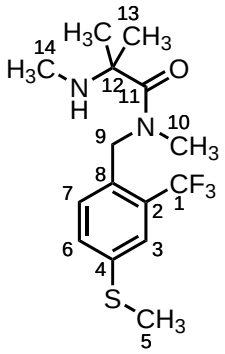
***N*-(3-Methoxy-2-(trifluoromethyl)benzyl)-*N*,2-dimethyl-2-(methylamino)propanamide (2.66m)**



By **GP13**, 3,4,4-trimethyloxazolidine-2,5-dione (**2.74**) (989 mg, 6.91 mmol) was used as the *N*-carboxyanhydride and 1-(3-methoxy-2-(trifluoromethyl) phenyl)-*N*-methylmethanamine (**2.52m**) (1.01 g, 4.61 mmol) was used as the amine that were stirred for 26 h (with the modifications of PhMe instead of DCM, and stirring at 80 °C), and purified by flash column chromatography (SiO_2; gradient elution: 0–3% acetone + 1% Et_3N in DCM + 1% Et_3N), with further purification by bulb-to-bulb distillation (170 °C at 100 mbar) to remove remaining 1-(3-methoxy-2-(trifluoromethyl)phenyl)- *N*-methylmethanamine (**2.52m**) to yield the title compound as a colourless oil that solidified upon standing (814 mg, 55%).

m.p. = 104–105 °C ($CHCl_3$). $\boldsymbol{R_f}$ = 0.47 (80% acetone + 1% Et_3N in DCM + 1% Et_3N). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers in an approximate 60:40 ratio) δ 7.40 ($1H^{\text{both rot.}}$, dd, *J* 8.3, 7.9, H_6), 6.90 ($1H^{\text{both rot.}}$, d, *J* 8.3, H_5), 6.76 ($1H^{\text{both rot.}}$, d, *J* 7.9, H_7), 5.45 ($2H^{\text{min}}$, br s, H_9), 4.81 ($2H^{\text{maj}}$, br s, H_9), 3.85 ($3H^{\text{both rot.}}$, s, H_4), 3.32 ($3H^{\text{maj}}$, s, H_{10}), 3.11 ($3H^{\text{min}}$, s, H_{10}), 2.30 ($3H^{\text{both rot.}}$, s, H_{14}), 1.35 ($6H^{\text{both rot.}}$, s, H_{13}), 1.20 ($1H^{\text{both rot.}}$, br s, N*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.6 (C_{11}), 159.0 (q, *J* 1.8, C_3), 138.7 (C_8), 132.7 (C_6), 125.1 (q, *J* 275.8, C_1), 118.9 (C_7), 116.6 (C_2), 111.2 (C_5), 60.9 (C_{12}), 56.4 (C_4), 51.4 (C_9), 36.7 (C_{10}), 30.4 (C_{14}), 26.3 (C_{13}). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −56.9 (3F, s, F_1). **IR** (film, $CDCl_3$) ν_{max} = 3320 (N−H, br), 2976 (C−H), 2940 (C−H), 2802 (C−H), 1627 (C=O), 1587, 1476, 1291, 1267, 1118, 1097, 1064, 1036, 783, 748, 729 cm^{-1}. **HRMS** (ESI^+) *m*/*z* calcd for $C_{15}H_{22}F_3N_2O_2$ $[M+H]^+$ 319.1628, found 319.1630.

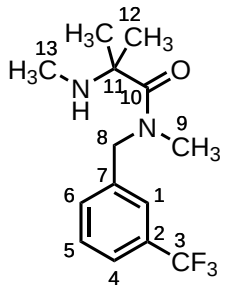
N,2-Dimethyl-2-(methylamino)-*N*-(4-(methylthio)-2-(trifluoromethyl) benzyl)propanamide (2.66n)



By **GP13**, 3,4,4-trimethyloxazolidine-2,5-dione (**2.74**) (870 mg, 6.12 mmol) was used as the *N*-carboxyanhydride and *N*-methyl-1-(4-(methylthio)-2-(trifluoromethyl)phenyl)methanamine (**2.52n**) (960 mg, 4.08 mmol) was used as the amine that were stirred at room temperature for 22 h, and purified by flash column chromatography (SiO_2; gradient elution: 0–6% acetone + 1% Et_3N in DCM + 1% Et_3N) to yield the title compound as a pale yellow oil (1.16 g, 85%).

$\boldsymbol{R_f}$ = 0.53 (80% acetone + 1% Et_3N in DCM + 1% Et_3N). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers in an approximate 65:35 ratio) δ 7.50 ($1H^{\text{both rot.}}$, d, *J* 2.1, H_3), 7.36 ($1H^{\text{both rot.}}$, dd, *J* 8.2, 2.1, H_6), 7.18 ($1H^{\text{both rot.}}$, d, *J* 8.2, H_7), 5.32 ($2H^{\text{maj}}$, br s, H_9), 4.82 ($2H^{\text{min}}$, br s, H_9), 3.24 ($3H^{\text{both rot.}}$, s, H_{10}), 2.49 ($3H^{\text{both rot.}}$, s, H_5), 2.31 ($3H^{\text{both rot.}}$, s, H_{14}), 1.38 ($6H^{\text{both rot.}}$, s, H_{13}), 0.94 ($1H^{\text{both rot.}}$, br s, N*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.7 (C_{11}), 138.0 (C_4), 133.6 (C_8), 131.0 (C_2), 129.9 (C_6), 128.3 (C_7), 124.2 (q, *J* 274.2, C_1), 124.0 (q, *J* 5.9, C_3), 61.0 (C_9), 49.4 (C_{12}), 36.3 (C_{10}), 30.5 (C_{14}), 26.4 (C_{13}), 15.8 (C_5). **^{19}F NMR** (377 MHz, $CDCl_3$, mixture of rotamers in an approximate 65:35 ratio) δ −63.0 ($3F^{\text{maj}}$, br s, F_1), −63.9 ($3F^{\text{min}}$, br s, F_1). **IR** (film, $CDCl_3$) ν_{max} = 3320 (N−H, br), 2977 (C−H), 2925 (C−H), 1631 (C=O), 1306, 1161, 1118, 1097, 1051, 844, 682 cm^{-1}. **HRMS** (ESI^+) *m*/*z* calcd for $C_{15}H_{22}F_3N_2OS$ $[M+H]^+$ 335.1399, found 335.1388.

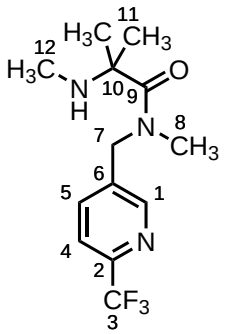
N,2-Dimethyl-2-(methylamino)-*N*-(3-(trifluoromethyl)benzyl) propanamide (2.66o)



By **GP13**, 3,4,4-trimethyloxazolidine-2,5-dione (**2.74**) (938 mg, 6.55 mmol, 1.0 eq.) was used as the *N*-carboxyanhydride and *N*-methyl-1-(3-(trifluoromethyl) phenyl)methanamine (**2.52o**) (1.24 g, 6.55 mmol) was used as the amine that were stirred for 16 h, and purified by flash column chromatography (SiO_2; isocratic elution: 10% acetone + 1% Et_3N in DCM + 1% Et_3N) to yield the title compound as a pale yellow oil (1.34 g, 71%).

$\boldsymbol{R_f}$ = 0.47 (80% acetone + 1% Et_3N in DCM + 1% Et_3N). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.49–7.46 (1H, m, H_4), 7.43 (1H, s, H_1), 7.42–7.35 (2H, m, H_5, H_6), 4.78 (2H, br s, H_8), 3.22 (3H, br s, H_9), 2.28 (3H, s, H_{13}), 1.37 (6H, s, H_{12}), 0.88 (1H, br s, NH). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.2 (C_{10}), 139.3 (C_7), 131.0 (q, J 32.4, C_2), 130.8 (C_6), 129.1 (C_5), 124.2 (q, J 272.2, C_3), 124.1 (C_1), 124.0 (q, J 3.8, C_4), 61.0 (C_{11}), 53.0 (C_8), 35.9 (C_9), 30.4 (C_{13}), 26.4 (C_{12}). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −65.7 (3F, s, F_3). **IR** (film, $CDCl_3$) ν_{max} = 3319 (N−H, br), 2977 (C−H), 2933 (C−H), 1626 (C=O), 1391, 1327, 1162, 1121, 1093, 1073, 796, 702, 659 cm^{-1}. **HRMS** (ESI$^+$) m/z calcd for $C_{14}H_{20}F_3N_2O$ $[M+H]^+$ 289.1522, found 289.1525.

N,2-Dimethyl-2-(methylamino)-*N*-((6-(trifluoromethyl)pyridin-3-yl) methyl)propanamide (2.66p)

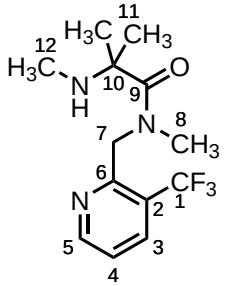


By **GP13**, 3,4,4-trimethyloxazolidine-2,5-dione (**2.74**) (1.03 g, 7.16 mmol) was used as the *N*-carboxyanhydride and *N*-methyl-1-(6-(trifluoromethyl) pyridin-3-yl)methanamine (**2.52p**) (908 mg, 4.77 mmol) was used as the amine that were stirred for 23 h, and purified by flash column chromatography (SiO_2; isocratic elution: DCM + 1% Et_3N) to yield the title compound as a yellow oil (1.08 g, 78%).

$\boldsymbol{R_f}$ = 0.38 (80% acetone + 1% Et_3N in DCM + 1% Et_3N). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.54 (1H, d, J 0.8, H_1), 7.71 (1H, d, J 8.1, H_4), 7.60 (1H, dd, J 8.1, 0.8, H_5), 4.70 (2H, br s, H_7), 3.31 (3H, br s, H_8), 2.24 (3H, s, H_{12}), 1.33 (6H, s, H_{11}), 0.93 (1H, br s, NH). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.4 (C_9), 149.2 (C_1), 147.1 (q, J 34.8, C_2), 137.3 (C_6), 136.6 (C_4), 121.6 (q, J 274.0, C_3), 120.4 (q, J 2.8, C_5), 60.9 (C_{10}), 50.9 (C_7), 36.2 (C_8), 30.3 (C_{12}), 26.2 (C_{11}). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −70.8 (3F, s, F_3). **IR** (film, $CDCl_3$) ν_{max} = 3320 (N−H, br), 2979 (C−H), 2934 (C−H), 1626 (C=O), 1388, 1333, 1172, 1129, 1083, 1028, 830, 757,

732 cm^{-1}. **HRMS** (ESI^+) m/z calcd for $C_{13}H_{19}F_3N_3O$ $[M+H]^+$ 290.1475, found 290.1469.

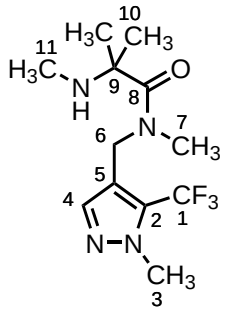
N,2-Dimethyl-2-(methylamino)-*N*-((3-(trifluoromethyl)pyridin-2-yl) methyl)propanamide (2.66q)



By **GP13**, 3,4,4-trimethyloxazolidine-2,5-dione (**2.74**) (549 mg, 3.84 mmol) was used as the *N*-carboxyanhydride and *N*-methyl-1-(3-(trifluoromethyl) pyridin-2-yl)methanamine (**2.52q**) (505 mg, 2.57 mmol) was used as the amine that were stirred for 27 h, and purified by flash column chromatography (SiO_2; gradient elution: 0–5% acetone + 1% Et_3N in DCM + 1% Et_3N) to yield the title compound as an orange oil (351 mg, 47%).

$\boldsymbol{R_f}$ = 0.42 (80% acetone + 1% Et_3N in DCM + 1% Et_3N). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers in an approximate 65:35 ratio) δ 8.65 ($1H^{both\ rot.}$, d, J 4.6, H_5), 7.88 ($1H^{both\ rot.}$, d, J 7.8, H_3), 7.24 ($1H^{both\ rot.}$, dd, J 7.8, 4.6, H_4), 5.68 ($2H^{min}$, br s, H_7), 4.82 ($2H^{maj}$, br s, H_7), 3.54 ($3H^{maj}$, br s, H_8), 2.94 ($3H^{min}$, br s, H_8), 2.37 ($1H^{both\ rot.}$, br s, H_{12}), 1.37 ($6H^{both\ rot.}$, s, H_{11}), 0.94 ($1H^{both\ rot.}$, br s, NH). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.5 (C_9), 156.0 (C_6), 152.1 (C_5), 133.9 (q, J 5.4, C_3), 124.3 (C_2), 124.0 (q, J 273.3, C_1), 121.3 (C_4), 60.9 (C_{10}), 52.4 (q, J 3.3, C_7), 37.9 (C_8), 30.3 (C_{12}), 26.4 (C_{11}). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −64.6 (3F, s, F_1). **IR** (film, $CDCl_3$) ν_{max} = 3317 (N−H, br), 2977 (C−H), 2932 (C−H), 1629 (C=O), 1317, 1157, 1116, 1075, 1033, 812, 732 cm^{-1}. **HRMS** (ESI^+) m/z calcd for $C_{13}H_{19}F_3N_3O$ $[M+H]^+$ 290.1475, found 290.1466.

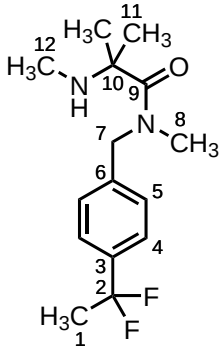
N,2-Dimethyl-*N*-((1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-4-yl) methyl)-2-(methylamino)propanamide (2.66r)



By **GP13**, 3,4,4-trimethyloxazolidine-2,5-dione (**2.74**) (959 mg, 6.70 mmol was used as the *N*-carboxyanhydride and *N*-methyl-1-(1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-4-yl)methanamine (**2.52r**) (863 mg, 4.47 mmol) was used as the amine that were stirred for 16 h, and purified by flash column chromatography (SiO_2; gradient elution: 0–2% acetone + 1% Et_3N in DCM + 1% Et_3N) to yield the title compound as a pale yellow oil (520 mg, 40%).

$\boldsymbol{R_f}$ = 0.41 (80% acetone + 1% Et_3N in DCM + 1% Et_3N). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31 (1H, s, H_4), 4.62 (2H, br s, H_6), 3.91 (3H, s, H_3), 3.22 (3H, br s, H_7), 2.22 (3H, s, H_{11}), 1.31 (6H, s, H_{10}), 0.91 (1H, br s, NH). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.9 (C_8), 138.5 (C_2), 120.9 (q, J 269.3, C_1), 120.5 (C_5), 60.8 (C_9), 43.3 (C_6), 38.6 (q, J 2.3, C_3), 35.7 (C_7), 30.3 (C_{11}), 26.2 (C_{10}). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −60.8 (3F, s, F_1). **IR** (film, $CDCl_3$) ν_{max} = 3319 (N−H, br), 2957 (C−H), 1628 (C=O), 1490, 1391, 1359, 1273, 1163, 1118, 1094, 1056, 1004 cm^{-1}. **HRMS** (ESI$^+$) m/z calcd for $C_{12}H_{20}F_3N_4O$ $[M+H]^+$ 293.1584, found 293.1579.

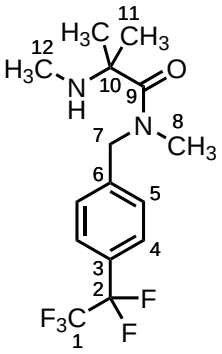
N-(4-(1,1-Difluoroethyl)benzyl)-*N*,2-dimethyl-2-(methylamino) propanamide (2.66t)



By **GP13**, 3,4,4-trimethyloxazolidine-2,5-dione (**2.74**) (1.96 g, 13.8 mmol) was used as the *N*-carboxyanhydride and 1-(4-(1,1-difluoroethyl)phenyl)-*N*-methylmethanamine (**2.52t**) (1.70 g, 9.18 mmol) was used as the amine that were stirred for 21 h, and purified by flash column chromatography (SiO_2; gradient elution: 0–3% acetone + 1% Et_3N in DCM + 1% Et_3N) to yield the title compound as a colourless oil (2.06 g, 79%).

$\boldsymbol{R_f}$ = 0.43 (80% acetone + 1% Et_3N in DCM + 1% Et_3N). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 (2H, d, J 8.0, H_4), 7.26 (2H, d, J 8.0, H_5), 4.81 (2H, br s, H_7), 3.20 (3H, br s, H_8), 2.31 (3H, s, H_{12}), 1.90 (3H, t, J 18.1, H_1), 1.39 (6H, s, H_{11}), 0.94 (1H, br s, NH). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.2 (C_9), 140.0 (C_6), 137.1 (t, J 26.7, C_3), 127.6 (C_5), 125.0 (t, J 5.9, C_4), 121.9 (t, J 238.7, C_2), 61.0 (C_{10}), 53.1 (C_7), 35.9 (C_8), 30.5 (C_{12}), 26.5 (C_{11}), 26.0 (t, J 30.1, C_1). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −90.2 (1F, q, J 18.1, F_{2a}), −90.2 (1F, q, J 18.1, F_{2b}). **IR** (film, $CDCl_3$) ν_{max} = 3317 (N−H, br), 2977 (C−H), 2933 (C−H), 1626 (C=O), 1387, 1295, 1171, 1108, 1088, 915, 815, 697, 573 cm^{-1}. **HRMS** (ESI$^+$) m/z calcd for $C_{15}H_{23}F_2N_2O$ $[M+H]^+$ 285.1773, found 285.1763.

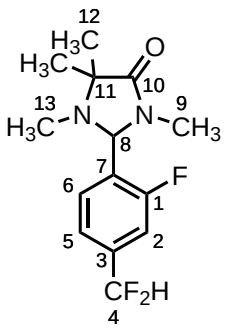
N,2-Dimethyl-2-(methylamino)-*N*-(4-(perfluoroethyl)benzyl) propanamide (2.66u)



By **GP13**, 3,4,4-trimethyloxazolidine-2,5-dione (**2.74**) (978 mg, 6.88 mmol) as the *N*-carboxyanhydride and *N*-methyl-1-(4-(perfluoroethyl)phenyl)methanamine (**2.52u**) (1.10 g, 4.60 mmol) as the amine that were stirred at room temperature for 25 h, and purified by flash column chromatography (SiO_2; gradient elution: 0–5% acetone + 1% Et_3N in DCM + 1% Et_3N) to yield the title compound as a pale yellow oil (929 mg, 60%).

$\boldsymbol{R_f}$ = 0.54 (80% acetone + 1% Et_3N in DCM + 1% Et_3N). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.53 (2H, d, *J* 8.1, H_4), 7.32 (2H, d, *J* 8.1, H_5), 4.79 (2H, br s, H_7), 3.25 (3H, br s, H_8), 2.29 (3H, s, H_{12}), 1.38 (6H, s, H_{11}), 1.05 (1H, br s, N*H*). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 175.3 (C_9), 142.6 (C_6), 127.6 (C_5), 127.5 (t, *J* 24.0, C_3), 126.8 (t, *J* 6.2, C_4), 119.2 (qt, *J* 285.8, 39.6, C_1), 113.5 (tq, *J* 253.5, 38.2, C_2), 61.0 (C_{10}), 53.1 (C_7), 36.1 (C_8), 30.4 (C_{12}), 26.4 (C_{11}). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −87.8 (3F, t, *J* 2.1, F_1), −117.6 (2F, q, *J* 2.1, F_2). **IR** (film, $CDCl_3$) ν_{max} = 3319 (N−H, br), 2978 (C−H), 2934 (C−H), 1628 (C=O), 1391, 1287, 1199, 1145, 1091, 972, 814, 749, 732 cm^{-1}. **HRMS** (ESI^+) *m*/*z* calcd for $C_{15}H_{20}F_5N_2O$ $[M+H]^+$ 339.1490, found 339.1493.

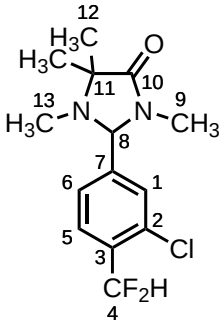
2-(4-(Difluoromethyl)-2-fluorophenyl)-1,3,5,5-tetramethylimidazolidin-4-one (2.69b)



By **GP14**, *N*-(2-fluoro-4-(trifluoromethyl)benzyl)-*N*,2-dimethyl-2-(methylamino)propanamide (**2.66b**) (306 mg, 1.00 mmol) was used as the fluoroalkyl arene, and purified by flash column chromatography (SiO_2; gradient elution: 12–70% EtOAc in pet. ether) to yield the title compound as a yellow oil (276 mg, 97%).

$\boldsymbol{R_f}$ = 0.52 (50% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.58 (1H, dd, *J* 8.1, 7.0, H_6), 7.33 (1H, dd, *J* 8.1, 1.6, H_5), 7.23 (1H, dd, *J* 10.3, 1.6, H_2), 6.62 (1H, t, *J* 56.1, H_4), 5.12 (1H, s, H_8), 2.58 (3H, s, H_9), 2.17 (3H, s, H_{13}), 1.32 (3H, s, H_{12a}), 1.15 (3H, s, H_{12b}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.3 (C_{10}), 162.3 (d, *J* 250.2, C_1), 137.3 (td, *J* 23.0, 7.8, C_3), 130.4 (d, *J* 3.7, C_6), 127.4 (dt, *J* 10.5, 1.8, C_7), 122.2 (td, *J* 6.1, 3.5, C_5), 113.4 (td, *J* 239.9, 2.0, C_4), 113.0 (dt, *J* 24.2, 6.2, C_2), 73.2 (d, *J* 3.4, C_8), 61.6 (C_{11}), 30.6 (C_{13}), 26.7 (C_9), 24.1 (C_{12a}), 17.0 (C_{12b}). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −114.9 (2F, d, *J* 56.1, F_4), −123.2 (1F, dd, *J* 10.3, 7.0, F_1). **IR** (film, $CDCl_3$) ν_{max} = 2973 (C−H), 2802 (C−H), 1700 (C=O), 1434, 1400, 1376, 1301, 1281, 1158, 1138, 1073, 1031, 879, 855, 833, 821, 788, 762, 749, 534 cm^{-1}. **HRMS** (ESI^+) *m*/*z* calcd for $C_{14}H_{18}F_3N_2O$ $[M+H]^+$ 287.1366, found 283.1367.

2-(3-Chloro-4-(difluoromethyl)phenyl)-1,3,5,5-tetramethylimidazolidin-4-one (2.69c)

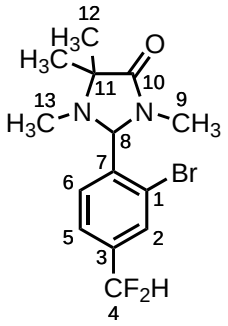


By **GP14**, *N*-(3-chloro-4-(trifluoromethyl)benzyl)-*N*,2-dimethyl-2-(methylamino)propanamide (**2.66c**) (323 mg, 1.00 mmol) was used as the fluoroalkyl arene, and purified by flash column chromatography (SiO_2; gradient elution: 12–70% EtOAc in pet. ether) to yield the title compound as a yellow oil (294 mg, 97%).

$\boldsymbol{R_f}$ = 0.39 (50% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.67 (1H, d, *J* 7.9, H_5), 7.46 (1H, d, *J* 1.6, H_1), 7.39 (1H, dd, *J* 7.9, 1.6, H_6), 6.93 (1H, t, *J* 54.8, H_4), 4.57 (1H, s, H_8), 2.52 (3H, s, H_9), 2.14 (3H, s, H_{13}), 1.33 (3H, s, H_{12a}), 1.13 (3H, s, H_{12b}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.3 (C_{10}), 142.8 (t, *J* 2.0, C_7), 133.3 (t, *J* 6.1, C_2), 132.9 (t, *J* 23.2, C_3), 129.9 (C_1), 127.5 (C_6), 127.3 (t, *J* 6.0, C_5), 111.9 (t, *J* 238.3, C_4), 80.7 (C_8), 61.6 (C_{11}), 30.5 (C_{13}), 27.0 (C_9), 24.1 (C_{12a}), 16.9 (C_{12b}). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −118.4 (2F, d, *J* 54.8, F_4). **IR** (film, $CDCl_3$) ν_{max} = 2972 (C−H), 2798 (C−H), 1702 (C=O), 1432, 1417,

1398, 1377, 1291, 1138, 1090, 1075, 1047, 1034, 857, 834, 813, 551 cm^{-1}. **HRMS** (ESI^+) m/z calcd for $C_{14}H_{18}ClF_2N_2O$ $[M+H]^+$ 303.1070, found 303.1075.

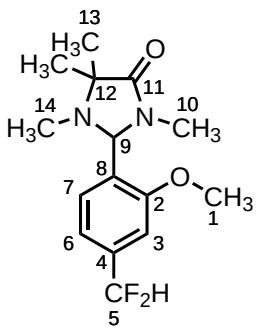
2-(2-Bromo-4-(difluoromethyl)phenyl)-1,3,5,5-tetramethylimidazolidin-4-one (2.69d)



By **GP14**, *N*-(2-bromo-4-(trifluoromethyl)benzyl)-*N*,2-dimethyl-2-(methylamino)propanamide (**2.66d**) (367 mg, 1.00 mmol) was used as the fluoroalkyl arene, and purified by flash column chromatography (SiO_2; gradient elution: 12–90% EtOAc in pet. ether) to yield the title compound as an orange oil (314 mg, 91%).

$\boldsymbol{R_f}$ = 0.43 (50% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.72 (1H, s, H_2), 7.62 (1H, d, J 8.1, H_6), 7.50 (1H, d, J 8.1, H_5), 6.62 (1H, t, J 56.1, H_4), 5.31 (1H, s, H_8), 2.57 (3H, s, H_9), 2.17 (3H, s, H_{13}), 1.35 (3H, s, H_{12a}), 1.18 (3H, s, H_{12b}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.3 (C_{10}), 139.2 (C_7), 136.9 (t, J 22.8, C_3), 130.9 (C_6), 123.0 (t, J 6.2, C_2), 125.7 (C_1), 125.6 (t, J 4.4, C_5), 113.4 (t, J 240.3, C_1), 78.4 (C_8), 61.7 (C_{11}), 30.6 (C_{13}), 26.9 (C_9), 24.2 (C_{12a}), 17.2 (C_{12b}). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −115.1 (2F, d, J 56.1, F_4). **IR** (film, $CDCl_3$) ν_{max} = 2971 (C–H), 2799 (C–H), 1701 (C=O), 1431, 1398, 1360, 1298, 1212, 1073, 1031, 1011, 852, 811, 732, 688, 549, 449 cm^{-1}. **HRMS** (ESI^+) m/z calcd for $C_{14}H_{18}BrF_2N_2O$ $[M+H]^+$ 347.0565, found 347.0555.

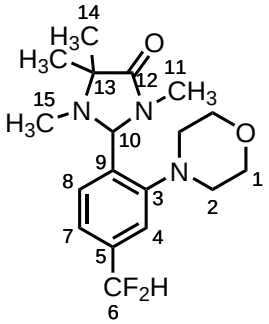
2-(4-(Difluoromethyl)-2-methoxyphenyl)-1,3,5,5-tetramethyl imidazolidin-4-one (2.69e)



By **GP14**, *N*-(2-methoxy-4-(trifluoromethyl)benzyl)-*N*,2-dimethyl-2-(methylamino)propanamide (**2.66e**) (318 mg, 1.00 mmol) was used as the fluoroalkyl arene, and purified by flash column chromatography (SiO_2; gradient elution: 12–70% EtOAc in pet. ether) to yield the title compound as a pale yellow oil (294 mg, 99%).

$\boldsymbol{R_f}$ = 0.56 (50% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.54 (1H, d, *J* 7.9, H_7), 7.10 (1H, dd, *J* 7.9, 1.6, H_6), 7.04 (1H, d, *J* 1.6, H_3), 6.61 (1H, t, *J* 56.4, H_5), 5.26 (1H, s, H_9), 3.87 (3H, s, H_1), 2.53 (3H, s, H_{10}), 2.12 (3H, s, H_{14}), 1.31 (3H, s, H_{13a}), 1.13 (3H, s, H_{13b}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.3 (C_{11}), 159.2 (C_2), 136.2 (t, *J* 22.2, C_4), 129.6 (C_7), 128.1 (t, *J* 2.1, C_8), 118.6 (t, *J* 6.4, C_6), 114.4 (t, *J* 239.2, C_5), 107.5 (t, *J* 5.9, C_3), 72.9 (C_9), 61.5 (C_{12}), 55.7 (C_1), 30.6 (C_{14}), 26.6 (C_{10}), 24.1 (C_{13a}), 16.9 (C_{13b}). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −113.9 (2F, d, *J* 56.4, F_5). **IR** (film, $CDCl_3$) ν_{max} = 2970 (C−H), 2848 (C−H), 2800 (C−H), 1697 (C=O), 1460, 1432, 1401, 1377, 1305, 1286, 1259, 1164, 1073, 1028, 862, 853, 749, 553 cm^{-1}. **HRMS** (ESI$^+$) *m*/*z* calcd for $C_{15}H_{21}F_2N_2O_2$ $[M+H]^+$ 299.1566, found 299.1567.

2-(4-(Difluoromethyl)-2-morpholinophenyl)-1,3,5,5-tetramethyl imidazolidin-4-one (2.69f)

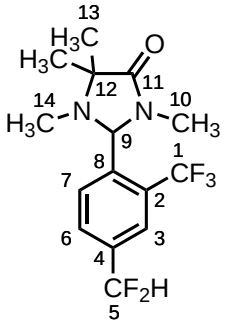


By **GP14**, *N*,2-dimethyl-2-(methylamino)-*N*-(2-morpholino-4-(trifluoromethyl) benzyl)propanamide (**2.66f**) (373 mg, 1.00 mmol) was used as the fluoroalkyl arene, and purified by flash column chromatography (SiO_2; gradient elution: 12–80% EtOAc in pet. ether) to yield the title compound as an orange solid (274 mg, 78%).

m.p. = 177–178 °C ($CHCl_3$). $\boldsymbol{R_f}$ = 0.29 (50% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.59 (1H, d, *J* 8.2, H_8), 7.36 (1H, s, H_4), 7.33 (1H, d, *J* 8.2, H_7), 6.63 (1H, t, *J* 56.4, H_6), 5.44 (1H, s, H_{10}), 3.84 (4H, t, *J* 4.6, H_1), 3.00–2.84 (4H, m, H_2), 2.53 (3H, s, H_{11}), 2.15 (3H, s, H_{15}), 1.35 (3H, s, H_{14a}), 1.17 (3H, s, H_{14b}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.4 (C_{12}), 153.8 (C_3), 136.2 (C_9), 136.1 (t, *J* 22.2, C_5), 129.9 (C_8), 123.2 (C_7), 118.3 (d, *J* 5.9, C_4), 114.4 (t, *J* 239.4, C_6), 73.7 (C_{10}), 67.3 (C_1), 61.6 (C_{13}), 54.0 (C_2), 30.8 (C_{15}), 26.9 (C_{11}), 24.2 (C_{14a}), 16.8 (C_{14b}). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −114.2 (2F, d, *J* 56.4, F_6). **IR** (film, $CDCl_3$) ν_{max} = 2968 (C−H), 2852 (C−H), 1696 (C=O), 1432, 1399,

1374, 1270, 1114, 1071, 1024, 732 cm^{-1}. **HRMS** (ESI^+) m/z calcd for $C_{18}H_{25}F_2N_3NaO_2$ $[M+Na]^+$ 376.1813, found 376.1818.

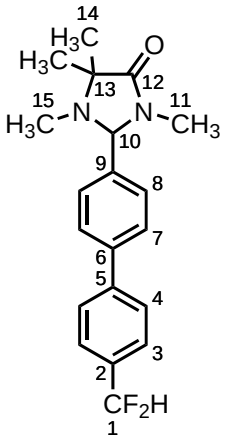
2-(4-(Difluoromethyl)-2-(trifluoromethyl)phenyl)-1,3,5,5-tetramethyl imidazolidin-4-one (2.69g)



By **GP14**, *N*-(2,4-bis(trifluoromethyl)benzyl)-*N*,2-dimethyl-2-(methylamino) propanamide (**2.66g**) (356 mg, 1.00 mmol) was used as the fluoroalkyl arene, and purified by flash column chromatography (SiO_2; gradient elution: 12–70% EtOAc in pet. ether) to yield the title compound as a pale yellow oil that solidified upon standing (257 mg, 76%).

m.p. = 103–104 °C ($CHCl_3$). $\boldsymbol{R_f}$ = 0.57 (50% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.88 (1H, d, J 8.2, H_7), 7.82 (1H, s, H_3), 7.76 (1H, d, J 8.2, H_6), 6.71 (1H, t, J 56.0, H_5), 5.15 (1H, q, J 2.0, H_9), 2.49 (3H, s, H_{10}), 2.13 (3H, s, H_{14}), 1.37 (3H, s, H_{13a}), 1.18 (3H, s, H_{13b}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.4 (C_{11}), 140.9 (C_8), 135.7 (t, J 23.1, C_4), 131.3 (C_7), 131.0 (q, J 31.0, C_2), 129.9 (t, J 5.7, C_6), 123.8 (q, J 274.8, C_1), 122.6 (q, J 6.1, C_3), 113.5 (t, J 240.2, C_5), 75.0 (C_9), 61.7 (C_{12}), 30.4 (C_{14}), 26.8 (C_{10}), 24.1 (C_{13a}), 17.0 (C_{13b}). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −59.1 (3F, d, J 2.0, F_1), −115.2 (2F, d, J 56.0, F_5). **IR** (film, $CDCl_3$) ν_{max} = 2974 (C−H), 2805 (C−H), 1705 (C=O), 1399, 1318, 1267, 1212, 1164, 1121, 1075, 1056, 1034, 1010, 860, 818, 547 cm^{-1}. **HRMS** (ESI^+) m/z calcd for $C_{15}H_{18}F_5N_2O$ $[M+H]^+$ 337.1334, found 337.1337.

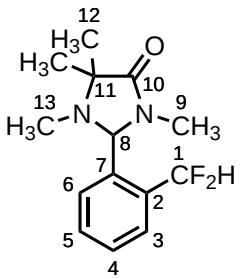
2-(4′-(Difluoromethyl)-[1,1′-biphenyl]-4-yl)-1,3,5,5-tetramethyl imidazolidin-4-one (2.69h)



By **GP14**, *N*,2-dimethyl-2-(methylamino)-*N*-((4′-(trifluoromethyl)-[1,1′-biphenyl]-4-yl)methyl)propanamide (**2.66h**) (364 mg, 1.00 mmol) was used as the fluoroalkyl arene (with modification of stirring at 100 °C under microwave irradiation for 1 h), and purified by flash column chromatography (SiO_2; gradient elution: 7–30% EtOAc in pet. ether) to yield the title compound as a pale yellow gum (155 mg, 45%).

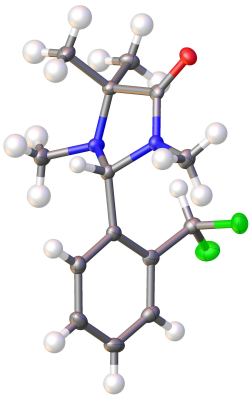
$\boldsymbol{R_f}$ = 0.36 (50% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.68 (2H, d, *J* 8.4, H_4), 7.62 (2H, d, *J* 8.1, H_7), 7.59 (2H, d, *J* 8.4, H_3), 7.48 (2H, d, *J* 8.1, H_8), 6.70 (1H, t, *J* 56.5, H_1), 4.64 (1H, s, H_{10}), 2.59 (3H, s, H_{11}), 2.20 (3H, s, H_{15}), 1.38 (3H, s, H_{14a}), 1.18 (3H, s, H_{14b}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.5 (C_{12}), 143.1 (t, *J* 2.1, C_5), 141.5 (C_6), 137.5 (C_9), 133.6 (t, *J* 22.4, C_2), 129.2 (C_8), 127.6 (C_7), 127.6 (C_4), 126.2 (t, *J* 6.0, C_3), 114.8 (t, *J* 238.6, C_1), 81.4 (C_{10}), 61.7 (C_{13}), 30.6 (C_{15}), 27.1 (C_{11}), 24.3 (C_{14a}), 16.8 (C_{14b}). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −113.6 (2F, d, *J* 56.5, F_1). **IR** (film, $CDCl_3$) ν_{max} = 2971 (C−H), 2929 (C−H), 2797 (C−H), 1697 (C=O), 1432, 1400, 1293, 1218, 1136, 1071, 1021, 1006, 910, 840, 809, 729, 650, 548, 528 cm^{-1}. **HRMS** (ESI^+) *m*/*z* calcd for $C_{20}H_{23}F_2N_2O$ $[M+H]^+$ 345.1773, found 345.1761.

2-(2-(Difluoromethyl)phenyl)-1,3,5,5-tetramethylimidazolidin-4-one (2.69i)



By **GP14**, *N*,2-dimethyl-2-(methylamino)-*N*-(2-(trifluoromethyl)benzyl) propanamide (**2.66i**) (288 mg, 1.00 mmol) was used as the fluoroalkyl arene, and purified by flash column chromatography (SiO_2; gradient elution: 12–80% EtOAc in pet. ether) to yield the title compound as a pale yellow solid (259 mg, 97%). Crystals for x-ray crystallography were grown from a solution of the title compound in DCM.

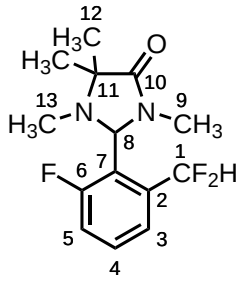
m.p. = 93–94 °C ($CHCl_3$). $\boldsymbol{R_f}$ = 0.49 (50% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.69 (1H, d, *J* 7.5, H_3), 7.67–7.53 (3H, m, H_4, H_5, H_6), 7.46 (1H, t, *J* 54.8, H_1), 5.09 (1H, s, H_8), 2.39 (3H, s, H_9), 2.07 (3H, s, H_{13}), 1.24 (3H, s, H_{12a}), 1.07 (3H, s, H_{12b}). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 174.9 (C_{10}), 135.9 (C_7), 133.7 (t, *J* 21.6, C_2), 131.4 (C_4), 129.7 (C_5, C_6), 126.1 (C_3), 113.1 (t, *J* 237.7, C_1), 74.5 (C_8), 60.8 (C_{11}), 30.2 (C_{13}), 26.4 (C_9), 23.4 (C_{12a}), 16.1 (C_{12b}). **^{19}F NMR** (283 MHz, $CDCl_3$, −40 °C, mixture of rotamers in an approximate 60:40 ratio) δ −100.9 (dd, *J* 301.1, 54.6, $F_{1a}{}^{maj}$), −102.9 (dd, *J* 301.1, 54.5, $F_{1b}{}^{maj}$), −107.3 (dd, *J* 303.4, 56.4, $F_{1a}{}^{min}$), −114.9 (dd, *J* 303.4, 54.8, $F_{1b}{}^{min}$). **IR** (film, $CDCl_3$) ν_{max} = 2972 (C–H), 2801 (C–H), 1699 (C=O), 1458, 1432, 1400, 1289, 1213, 1119, 1075, 1056, 1020, 867, 839, 824, 763, 750, 547 cm^{-1}. **HRMS** (ESI^+) *m*/*z* calcd for $C_{14}H_{19}F_2N_2O$ $[M+H]^+$ 269.1460, found 269.1461. **X-ray crystallography:**



Empirical formula	$C_{14}H_{18}F_2N_2O$
Formula weight	268.30
Temperature/K	100(2)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	7.9913(7)
b/Å	24.383(2)
c/Å	7.8184(6)
α/°	90
β/°	116.266(3)
γ/°	90
Volume/Å^3	1366.1(2)
Z	4
ρ_{calc}g/cm^3	1.304
μ/mm^{-1}	0.102
F(000)	568.0

Crystal size/mm^3	0.396 × 0.326 × 0.271
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	5.684 to 52.804
Index ranges	$-9 \leq h \leq 9$, $-30 \leq k \leq 30$, $-8 \leq l \leq 9$
Reflections collected	41350
Independent reflections	2788 [R_{int} = 0.0612, R_{sigma} = 0.0285]
Data/restraints/parameters	2788/0/176
Goodness-of-fit on F^2	1.192
Final R indexes [I>=2σ (I)]	R_1 = 0.0564, wR_2 = 0.1299
Final R indexes [all data]	R_1 = 0.0675, wR_2 = 0.1336
Largest diff. peak/hole /e Å^{-3}	0.32/−0.24

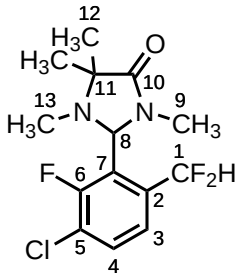
2-(2-(Difluoromethyl)-6-fluorophenyl)-1,3,5,5-tetramethylimidazolidin-4-one (2.69j)



By **GP14**, *N*-(2-fluoro-6-(trifluoromethyl)benzyl)-*N*,2-dimethyl-2-(methylamino)propanamide (**2.66j**) (306 mg, 1.00 mmol) was used as the fluoroalkyl arene, and purified by flash column chromatography (SiO_2; gradient elution: 12–30% EtOAc in pet. ether) to yield the title compound as a yellow oil (278 mg, 97%).

$\boldsymbol{R_f}$ = 0.54 (50% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.73–7.47 (3H, m, H_3, H_4, H_5), 7.47 (1H, t, *J* 55.0, H_1), 5.36 (1H, s, H_8), 2.49 (3H, s, H_9), 2.13 (3H, s, H_{13}), 1.21 (3H, s, H_{12a}), 1.08 (3H, s, H_{12b}). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 175.7 (C_{10}), 162.6 (d, *J* 249.3, C_6), 137.1 (t, *J* 19.9, C_2), 131.4 (d, *J* 9.5, C_4), 123.0 (t, *J* 8.4, C_3), 121.4 (C_7), 117.7 (d, *J* 21.4, C_5), 109.5 (t, *J* 237.4, C_1), 72.2 (C_8), 61.5 (C_{11}), 30.5 (C_{13}), 26.7 (C_9), 22.9 (C_{12a}), 15.8 (C_{12b}). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −111.1 (1F, dd, *J* 305.2, 56.0, F_{1a}), −117.4 (1F, dd, *J* 305.2, 56.0, F_{1b}), −121.1 (1F, s, F_6). **IR** (film, $CDCl_3$) ν_{max} = 2974 (C−H), 2799 (C−H), 1704 (C=O), 1464, 1403, 1298, 1283, 1256, 1241, 1100, 1068, 1027, 806, 789, 767, 749, 731, 560, 548, 527 cm^{-1}. **HRMS** (ESI$^+$) *m*/*z* calcd for $C_{14}H_{18}F_3N_2O$ $[M+H]^+$ 287.1366, found 283.1372.

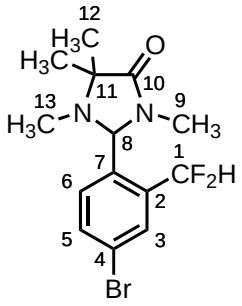
2-(3-Chloro-6-(difluoromethyl)-2-fluorophenyl)-1,3,5,5-tetramethyl imidazolidin-4-one (2.69k)



By **GP14**, *N*-(3-chloro-2-fluoro-6-(trifluoromethyl)benzyl)-*N*,2-dimethyl-2-(methylamino)propanamide (**2.66k**) (341 mg, 1.00 mmol) was used as the fluoroalkyl arene, and purified by flash column chromatography (SiO_2; gradient elution: 12–100% EtOAc in pet. ether) to yield the title compound as an orange oil (278 mg, 87%).

$\boldsymbol{R_f}$ = 0.65 (50% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.85 (1H, t, *J* 7.8, H_4), 7.60 (1H, br s, H_3), 7.45 (1H, t, *J* 54.7, H_1), 5.38 (1H, s, H_8), 2.51 (3H, s, H_9), 2.15 (3H, s, H_{13}), 1.20 (3H, s, H_{12a}), 1.08 (3H, s, H_{12b}). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 175.7 (C_{10}), 157.9 (d, *J* 251.8, C_6), 135.4 (C_2), 131.9 (C_4), 123.9 (C_7), 123.4 (C_3, C_5), 109.0 (t, *J* 237.7, C_1), 72.6 (C_8), 61.6 (C_{11}), 30.6 (C_{13}), 26.9 (C_9), 22.9 (C_{12a}), 16.0 (C_{12b}). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −111.4 (1F, dd, *J* 305.5, 55.4, F_{1a}), −117.6 (2F, dd, *J* 305.5, 55.4, F_{1b}), −122.5 (1F, s, F_6). **IR** (film, $CDCl_3$) ν_{max} = 2974 (C−H), 2803 (C−H), 1705 (C=O), 1438, 1400, 1298, 1283, 1261, 1137, 1094, 1075, 1031, 968, 910, 831, 803, 730, 702, 645, 568, 548 cm^{-1}. **HRMS** (ESI^+) *m*/*z* calcd for $C_{14}H_{17}ClF_3N_2O$ $[M+H]^+$ 321.0976, found 321.0980.

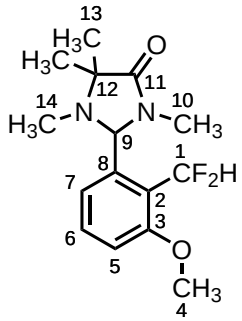
2-(4-Bromo-2-(difluoromethyl)phenyl)-1,3,5,5-tetramethylimidazolidin-4-one (2.69l)



By **GP14**, *N*-(4-bromo-2-(trifluoromethyl)benzyl)-*N*,2-dimethyl-2-(methylamino)propanamide (**2.66l**) (367 mg, 1.00 mmol) was used as the fluoroalkyl arene, and purified by flash column chromatography (SiO_2; gradient elution: 12–30% EtOAc in pet. ether) to yield the title compound as an orange gum (244 mg, 70%).

R_f = 0.44 (50% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.84 (1H, s, H_3), 7.83–7.80 (1H, m, H_5), 7.56 (1H, d, J 9.0, H_6), 7.43 (1H, t, J 54.4, H_1), 5.10 (1H, s, H_8), 2.39 (3H, s, H_9), 2.07 (3H, s, H_{13}), 1.23 (3H, s, H_{12a}), 1.06 (3H, s, H_{12b}). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 174.9 (C_{10}), 135.8 (t, J 22.0, C_2), 135.7 (C_7), 134.5 (C_5), 132.3 (C_6), 128.8 (C_3), 122.7 (C_4), 112.3 (t, J 244.5, C_1), 74.2 (C_8), 60.8 (C_{11}), 30.1 (C_{13}), 26.3 (C_9), 23.4 (C_{12a}), 16.3 (C_{12b}). **^{19}F NMR** (377 MHz, DMSO-d_6, mixture of rotamers in an approximate 70:30 ratio) δ −106.3–−113.2 (m, $F_{1a}{}^{maj}$, $F_{1b}{}^{maj}$, $F_{1a}{}^{min}$), −116.2 (br s, $F_{1b}{}^{min}$). **IR** (film, $CDCl_3$) ν_{max} = 2973 (C–H), 2801 (C–H), 1698 (C=O), 1432, 1398, 1291, 1210, 1133, 1096, 1074, 1056, 1028, 879, 853, 833, 816, 731, 547, 496, 468 cm^{-1}. **HRMS** (ESI$^+$) m/z calcd for $C_{14}H_{18}BrF_2N_2O$ $[M+H]^+$ 347.0565, found 347.0575.

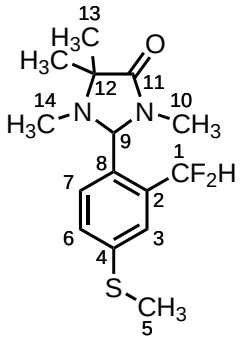
2-(2-(Difluoromethyl)-3-methoxyphenyl)-1,3,5,5-tetramethylimidazolidin-4-one (2.69m)



By **GP14**, *N*-(3-methoxy-2-(trifluoromethyl)benzyl)-*N*,2-dimethyl-2-(methylamino)propanamide (**2.66m**) (318 mg, 1.00 mmol) was used as the fluoroalkyl arene, and purified by flash column chromatography (SiO_2; gradient elution: 12–40% EtOAc in pet. ether) to yield the title compound as a yellow oil (260 mg, 87%).

R_f = 0.50 (50% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers in an approximate 50:50 ratio) δ 7.44 ($1H^{both\ rot.}$, t, J 8.2, H_6), 7.34 ($1H^{both\ rot.}$, t, J 54.5, H_1), 7.28 ($1H^{both\ rot.}$, d, J 8.2, H_7), 6.91 ($1H^{both\ rot.}$, d, J 8.2, H_5), 5.36 ($1H^{both\ rot.}$, s, H_9), 3.86 ($3H^{both\ rot.}$, s, H_4), 2.50 ($3H^{both\ rot.}$, s, H_{10}), 2.14 ($3H^{one\ rot.}$, s, H_{14}), 2.14 ($3H^{one\ rot.}$, s, H_{14}), 1.34 ($3H^{both\ rot.}$, s, H_{13a}), 1.14 ($3H^{both\ rot.}$, s, H_{13b}). **^{13}C NMR** (101 MHz, $CDCl_3$, mixture of rotamers in an approximate 50:50 ratio) δ 176.4 ($C_{11}{}^{both\ rot.}$), 157.0 (t, J 5.3, $C_3{}^{both\ rot.}$), 140.6 ($C_8{}^{both\ rot.}$), 132.5 ($C_6{}^{both\ rot.}$), 122.8 (t, J 22.0, $C_2{}^{both\ rot.}$), 121.8 ($C_7{}^{both\ rot.}$), 112.0 (t, J 234.2, $C_1{}^{both\ rot.}$), 111.2 ($C_5{}^{both\ rot.}$), 74.9 ($C_9{}^{both\ rot.}$), 61.6 ($C_{12}{}^{both\ rot.}$), 56.1 ($C_4{}^{both\ rot.}$), 30.5 ($C_{14}{}^{one\ rot.}$), 30.5 ($C_{14}{}^{one\ rot.}$), 26.8 ($C_{10}{}^{one\ rot.}$), 26.8 ($C_{10}{}^{one\ rot.}$), 24.1 ($C_{13a}{}^{both\ rot.}$), 16.9 ($C_{13b}{}^{both\ rot.}$). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −107.4 (1F, dd, J 310.8, 54.5, F_{1a}), −108.8 (1F, dd, J 310.8, 54.5, F_{1b}). **IR** (film, $CDCl_3$) ν_{max} = 2972 (C–H), 2946 (C–H), 2803 (C–H), 1696 (C=O), 1475, 1396, 1265, 1050, 1013, 908, 838, 727, 646, 546 cm^{-1}. **HRMS** (ESI$^+$) m/z calcd for $C_{15}H_{21}F_2N_2O_2$ $[M+H]^+$ 299.1566, found 299.1558.

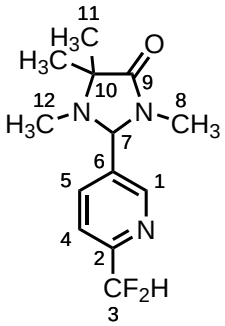
2-(2-(Difluoromethyl)-4-(methylthio)phenyl)-1,3,5,5-tetramethyl imidazolidin-4-one (2.69n)



By **GP14**, *N*,2-dimethyl-2-(methylamino)-*N*-(4-(methylthio)-2-(trifluoromethyl)benzyl)propanamide (**2.66n**) (334 mg, 1.00 mmol) was used as the fluoroalkyl arene, and purified by flash column chromatography (SiO_2; gradient elution: 12–70% EtOAc in pet. ether) to yield the title compound as an orange oil (271 mg, 86%).

$\boldsymbol{R_f}$ = 0.36 (50% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.55–7.45 (3H, m, H_3, H_6, H_7), 7.40 (1H, t, J 54.8, H_1), 5.06 (1H, s, H_9), 2.39 (3H, s, H_{10}), 2.07 (3H, s, H_{14}), 1.23 (3H, s, H_{13a}), 1.06 (3H, s, H_{13b}). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 174.9 (C_{11}), 140.6 (C_4), 134.2 (t, J 21.5, C_2), 132.0 (C_8), 130.4 (C_6), 128.1 (C_7), 122.6 (C_3), 113.5 (C_1), 74.0 (C_{12}), 60.8 (C_9), 30.1 (C_{14}), 26.3 (C_{10}), 23.4 (C_{13a}), 16.1 (C_{13b}), 14.1 (C_5). **^{19}F NMR** (377 MHz, DMSO-d_6, mixture of rotamers in an approximate 70:30 ratio) δ −106.1–−111.2 (m, ${F_{1a}}^{maj}$, ${F_{1b}}^{maj}$, ${F_{1a}}^{min}$), −116.2 (br s, ${F_{1b}}^{min}$). **IR** (film, $CDCl_3$) ν_{max} = 2973 (C–H), 2927 (C–H), 1697 (C=O), 1431, 1398, 1290, 1202, 1102, 1074, 1051, 1022, 851, 730, 546 cm^{-1}. **HRMS** (ESI$^+$) m/z calcd for $C_{15}H_{21}F_2N_2OS$ $[M+H]^+$ 315.1337, found 315.1331.

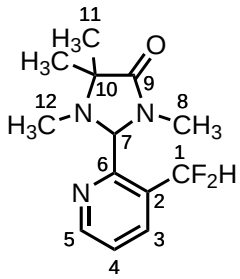
2-(6-(Difluoromethyl)pyridin-3-yl)-1,3,5,5-tetramethylimidazolidin-4-one (2.69p)



By **GP14**, *N*,2-dimethyl-2-(methylamino)-*N*-((6-(trifluoromethyl)pyridin-3-yl)methyl)propanamide (**2.66p**) (289 mg, 1.00 mmol) was used as the fluoroalkyl arene, and purified by flash column chromatography (SiO_2; gradient elution: 12–80% EtOAc in pet. ether) to yield the title compound as a yellow oil (233 mg, 86%).

$\boldsymbol{R_f}$ = 0.24 (50% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.61 (1H, d, *J* 2.0, H_1), 7.88 (1H, dd, *J* 8.0, 2.0, H_5), 7.66 (1H, d, *J* 8.0, H_4), 6.63 (1H, t, *J* 55.4, H_3), 4.67 (1H, s, H_7), 2.53 (3H, s, H_8), 2.13 (3H, s, H_{12}), 1.32 (3H, s, H_{11a}), 1.13 (3H, s, H_{11b}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.3 (C_9), 154.3 (t, *J* 25.9, C_2), 150.1 (C_1), 137.6 (C_5), 135.7 (t, *J* 1.7, C_6), 120.5 (t, *J* 2.9, C_4), 113.7 (t, *J* 240.7, C_3), 79.0 (C_7), 61.6 (C_{10}), 30.5 (C_{12}), 27.0 (C_8), 24.1 (C_{11a}), 16.9 (C_{11b}). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −118.9 (2F, d, *J* 55.4, F_3). **IR** (film, $CDCl_3$) ν_{max} = 2974 (C−H), 2798 (C−H), 1699 (C=O), 1399, 1373, 1290, 1076, 1041, 729, 547 cm^{-1}. **HRMS** (ESI^+) *m*/*z* calcd for $C_{13}H_{18}F_2N_3O$ $[M+H]^+$ 270.1412, found 270.1497.

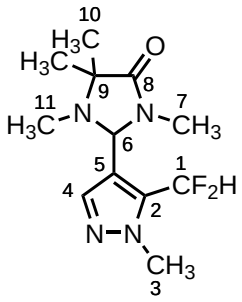
2-(3-(Difluoromethyl)pyridin-2-yl)-1,3,5,5-tetramethylimidazolidin-4-one (2.69q)



By **GP14**, *N*,2-dimethyl-2-(methylamino)-*N*-((3-(trifluoromethyl)pyridin-2-yl)methyl)propanamide (**2.66q**) (289 mg, 1.00 mmol) was used as the fluoroalkyl arene, and purified by flash column chromatography (SiO_2; gradient elution: 12–100% EtOAc in pet. ether) to yield the title compound as an orange oil (233 mg, 87%).

$\boldsymbol{R_f}$ = 0.14 (50% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.66 (1H, d, *J* 4.8, H_5), 8.09 (1H, d, *J* 7.9, H_3), 7.46 (1H, dd, *J* 7.9, 4.8, H_4), 7.45 (1H, t, *J* 55.3, H_1), 4.98 (1H, s, H_7), 2.56 (3H, s, H_8), 2.16 (3H, s, H_{12}), 1.33 (3H, s, H_{11a}), 1.12 (3H, s, H_{11b}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.9 (C_9), 154.2 (t, *J* 5.5, C_6), 150.8 (t, *J* 2.0, C_5), 135.5 (dd, *J* 7.3, 4.8, C_3), 131.2 (t, *J* 23.4, C_2), 124.7 (C_4), 109.6 (dd, *J* 238.8, 236.7, C_1), 84.4 (C_7), 61.6 (C_{10}), 30.7 (C_{12}), 27.0 (C_8), 23.0 (C_{11a}), 16.3 (C_{11b}). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −112.5 (dd, *J* 306.7, 55.3, F_{1a}), −118.5 (dd, *J* 306.7, 55.3, F_{1b}). **IR** (film, $CDCl_3$) ν_{max} = 2973 (C−H), 2801 (C−H), 1705 (C=O), 1398, 1298, 1283, 1074, 1050, 1027, 874, 663, 638, 547 cm^{-1}. **HRMS** (ESI^+) *m*/*z* calcd for $C_{13}H_{18}F_2N_3O$ $[M+H]^+$ 270.1412, found 270.1409.

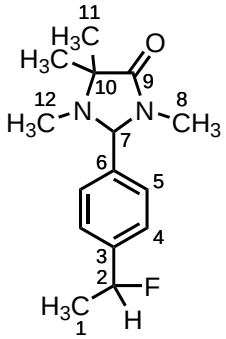
2-(5-(Difluoromethyl)-1-methyl-1*H*-pyrazol-4-yl)-1,3,5,5-tetramethyl imidazolidin-4-one (2.69r)



By **GP14**, *N*,2-dimethyl-*N*-((1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-4-yl) methyl)-2-(methylamino)propanamide (**2.66r**) (292 mg, 1.00 mmol) was used as the fluoroalkyl arene, and purified by flash column chromatography (SiO_2; gradient elution: 12–80% EtOAc in pet. ether) to yield the title compound as a pale yellow solid (165 mg, 61%).

m.p. = 97–98 °C ($CHCl_3$). $\boldsymbol{R_f}$ = 0.18 (50% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46 (1H, s, H_4), 7.02 (1H, dd, *J* 53.6, 52.7, H_1), 4.70 (1H, s, H_6), 3.99 (3H, s, H_3), 2.56 (3H, s, H_7), 2.15 (3H, s, H_{11}), 1.27 (3H, s, H_{10a}), 1.05 (3H, s, H_{10b}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.8 (C_8), 139.7 (C_4), 133.4 (t, *J* 23.7, C_2), 119.2 (t, *J* 4.9, C_5), 107.6 (t, *J* 235.5, C_1), 73.3 (C_6), 61.3 (C_9), 39.0 (t, *J* 2.6, C_3), 30.5 (C_{11}), 26.8 (C_7), 23.6 (C_{10a}), 15.6 (C_{10b}). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −116.6 (1F, dd, *J* 313.4, 53.6, F_{1a}), −118.0 (1F, dd, *J* 313.4, 52.7, F_{1b}). **IR** (film, $CDCl_3$) ν_{max} = 2968 (C–H), 1699 (C=O), 1402, 1285, 1213, 1094, 1058, 1020, 850, 560, 547 cm^{-1}. **HRMS** (ESI^+) *m*/*z* calcd for $C_{12}H_{19}F_2N_4O$ $[M+H]^+$ 273.1521, found 273.1517.

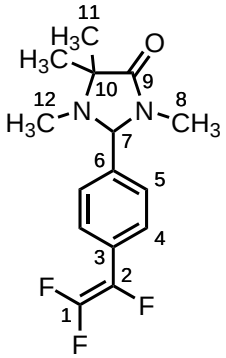
2-(4-(1-Fluoroethyl)phenyl)-1,3,5,5-tetramethylimidazolidin-4-one (2.69t)



By **GP14**, *N*-(4-(1,1-difluoroethyl)benzyl)-*N*,2-dimethyl-2-(methylamino) propanamide (**2.66t**) (284 mg, 1.00 mmol) was used as the fluoroalkyl arene, and purified by flash column chromatography (SiO_2; gradient elution: 12–70% EtOAc in pet. ether) to yield the title compound as a yellow-orange oil (144 mg, 68%).

$\boldsymbol{R_f}$ = 0.34 (50% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of enantiomeric diastereomers in an approximate 50:50 ratio) δ 7.39 (2H, d, J 8.4, $H_5$$^{\text{both pairs}}$), 7.36 (2H, d, J 8.4, $H_4$$^{\text{both pairs}}$), 5.63 (1H, dq, J 47.6, 6.4, $H_2$$^{\text{both pairs}}$), 4.58 (1H, s, $H_7$$^{\text{both pairs}}$), 2.52 (3H, s, $H_8$$^{\text{both pairs}}$), 2.14 (3H, s, $H_{12}$$^{\text{both pairs}}$), 1.64 (3H, dd, J 23.9, 6.4, $H_1$$^{\text{both pairs}}$), 1.34 (3H, s, $H_{11a}$$^{\text{both pairs}}$), 1.14 (3H, s, $H_{11b}$$^{\text{both pairs}}$). **^{13}C NMR** (101 MHz, $CDCl_3$, mixture of enantiomeric diastereomers in an approximate 50:50 ratio) δ 176.5 ($C_9$$^{\text{both pairs}}$), 143.0 (d, J 2.2, $C_3$$^{\text{one pair}}$), 142.8 (d, J 2.2, $C_3$$^{\text{one pair}}$), 137.8 (d, J 1.8, $C_6$$^{\text{one pair}}$), 137.8 (d, J 1.8, $C_6$$^{\text{one pair}}$), 128.8 ($C_5$$^{\text{both pairs}}$), 125.6 (d, J 6.8, $C_4$$^{\text{one pair}}$), 125.6 (d, J 6.8, $C_4$$^{\text{one pair}}$), 90.7 (d, J 167.9, $C_2$$^{\text{one pair}}$), 90.7 (d, J 167.9, $C_2$$^{\text{one pair}}$), 81.4 ($C_7$$^{\text{both pairs}}$), 61.6 ($C_{10}$$^{\text{both pairs}}$), 30.5 ($C_{12}$$^{\text{both pairs}}$), 27.0 ($C_8$$^{\text{both pairs}}$), 24.2 ($C_{11a}$$^{\text{both pairs}}$), 23.0 (d, J 25.0, $C_1$$^{\text{both pairs}}$), 16.7 ($C_{11b}$$^{\text{both pairs}}$). **^{19}F NMR** (377 MHz, $CDCl_3$, mixture of enantiomeric diastereomers in an approximate 50:50 ratio) δ −170.6 (1F, dq, J 47.6, 23.9, $F_2$$^{\text{one pair}}$), −170.8 (1F, dq, J 47.6, 23.9, $F_2$$^{\text{one pair}}$). **IR** (film, $CDCl_3$) ν_{max} = 2976 (C−H), 2930 (C−H), 2797 (C−H), 1700 (C=O), 1432, 1398, 1294, 1070, 1006, 859, 843, 817, 545 cm^{-1}. **HRMS** (ESI$^+$) m/z calcd for $C_{15}H_{22}FN_2O$ $[M+H]^+$ 265.1711, found 265.1708.

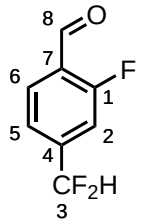
1,3,5,5-Tetramethyl-2-(4-(1,2,2-trifluorovinyl)phenyl)imidazolidin-4-one (2.69u)



By **GP14**, *N*,2-dimethyl-2-(methylamino)-*N*-(4-(perfluoroethyl)benzyl) propanamide (**2.66u**) (338 mg, 1.00 mmol) was used as the fluoroalkyl arene, and purified by flash column chromatography (SiO_2; gradient elution: 12–100% EtOAc in pet. ether) to yield the title compound as a yellow oil (172 mg, 58%).

$\boldsymbol{R_f}$ = 0.45 (50% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.49 (2H, d, J 8.2, H_4), 7.45 (2H, d, J 8.2, H_5), 4.59 (1H, s, H_7), 2.53 (3H, s, H_8), 2.15 (3H, s, H_{12}), 1.34 (3H, s, H_{11a}), 1.14 (3H, s, H_{11b}). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 176.4 (C_9), 154.0 (ddd, J 291.5, 283.5, 49.6, C_1), 138.6 (t, J 2.1, C_6), 129.0 (d, J 1.2, C_5), 128.6 (dd, J 22.1, 6.8, C_3), 128.5 (ddd, J 226.7, 45.1, 19.8, C_2), 124.8 (ddd, J 7.3, 6.0, 4.0, C_4), 81.2 (C_7), 61.6 (C_{10}), 30.5 (C_{12}), 27.0 (C_8), 24.2 (C_{11a}), 16.8 (C_{11b}). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −102.0 (dd, J 69.0, 32.8, $F_{1\,cis\text{ to }F_2}$), −116.8 (dd, J 109.3, 69.0, F_2), −180.0 (dd, J 109.3, 32.8, $F_{1\,trans\text{ to }F_2}$). **IR** (film, $CDCl_3$) ν_{max} = 2972 (C−H), 2798 (C−H), 1756 (FC=CF_2), 1703 (C=O), 1398, 1286, 1148, 1111, 1074, 983, 859, 841, 816, 508 cm^{-1}. **HRMS** (ESI$^+$) m/z calcd for $C_{15}H_{18}F_3N_2O$ $[M+H]^+$ 299.1366, found 299.1361.

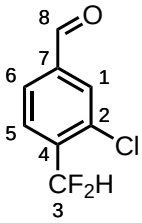
4-(Difluoromethyl)-2-fluorobenzaldehyde (2.39b)



By **GP15**, 2-(4-(difluoromethyl)-2-fluorophenyl)-1,3,5,5-tetramethylimidazolidin-4-one (**2.69b**) (105 mg, 0.37 mmol) was used as the imidazolidinone to yield the title compound as a yellow-green oil (48 mg, 75%).

$\boldsymbol{R_f}$ = 0.69 (30% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.38 (1H, s, H_8), 7.96 (1H, dd, J 8.0, 6.7, H_6), 7.41 (1H, d, J 8.0, H_5), 7.35 (1H, d, J 10.3, H_2), 6.67 (1H, t, J 55.8, H_4). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 186.5 (d, J 6.5, C_8), 164.5 (d, J 260.2, C_1), 142.1 (td, J 23.1, 8.3, C_3), 129.6 (d, J 2.2, C_6), 125.7 (dt, J 8.5, 1.7, C_7), 122.0 (td, J 6.1, 3.9, C_5), 114.3 (dt, J 22.8, 6.2, C_2), 113.0 (td, J 241.1, 2.0, C_4). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −116.5 (2F, d, J 55.8, F_4), −123.3 (1F, dd, J 10.3, 6.7, F_1). **IR** (film, $CDCl_3$) ν_{max} = 2872 (C−H), 1697 (C=O), 1628, 1435, 1371, 1194, 1159, 1076, 1036, 883, 840, 808, 775 cm^{-1}. **HRMS** (EI$^+$) m/z calcd for $C_8H_4F_3O$ $[M-H]^+$ 173.0209, found 173.0206.

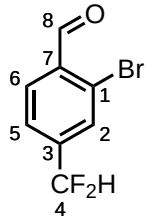
3-Chloro-4-(difluoromethyl)benzaldehyde (2.39c)



By **GP15**, 2-(3-chloro-4-(difluoromethyl)phenyl)-1,3,5,5-tetramethylimidazolidin-4-one (**2.69c**) (111 mg, 0.35 mmol) was used as the imidazolidinone to yield the title compound as a yellow oil (64 mg, 92%).

$\boldsymbol{R_f}$ = 0.70 (30% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.01 (1H, s, H_8), 7.92 (1H, s, H_1), 7.87 (1H, d, J 8.0, H_6), 7.84 (1H, d, J 8.0, H_5), 6.97 (1H, t, J 54.4, H_4). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 190.1 (C_8), 139.1 (t, J 1.9, C_7), 137.0 (t, J 23.2, C_3), 134.0 (t, J 6.0, C_2), 130.6 (C_1), 128.3 (C_6), 127.9 (t, J 6.2, C_5), 111.5 (t, J 239.5, C_4). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −119.5 (2F, d, J 54.4, F_4). **IR** (film, $CDCl_3$) ν_{max} = 2848 (C−H), 1702 (C=O), 1571, 1368, 1184, 1090, 1037, 847, 808, 699 cm^{-1}. **HRMS** (EI$^+$) m/z calcd for $C_8H_4ClF_2O$ $[M-H]^+$ 188.9913, found 188.9912.

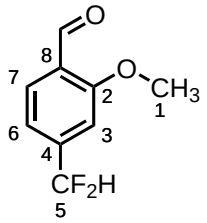
2-Bromo-4-(difluoromethyl)benzaldehyde (2.39d)



By **GP15**, 2-(2-bromo-4-(difluoromethyl)phenyl)-1,3,5,5-tetramethylimidazolidin-4-one (**2.69d**) (162 mg, 0.47 mmol) was used as the imidazolidinone to yield the title compound as an orange-brown oil (94 mg, 86%).

$\boldsymbol{R_f}$ = 0.71 (30% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.38 (1H, s, H_8), 7.99 (1H, d, J 8.0, H_6), 7.81 (1H, s, H_2), 7.57 (1H, d, J 8.0, H_5), 6.66 (1H, t, J 55.6, H_4). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 191.1 (C_8), 140.9 (t, J 22.9, C_3), 135.2 (t, J 1.7, C_7), 131.3 (t, J 6.3, C_2), 130.4 (C_6), 127.1 (C_1), 125.3 (t, J 6.0, C_5), 112.9 (t, J 241.4, C_4). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −116.5 (2F, d, J 55.6, F_4). **IR** (film, $CDCl_3$) ν_{max} = 2860 (C−H), 1695 (C=O), 1608, 1364, 1266, 1200, 1077, 1036, 838, 794 cm^{-1}. **HRMS** (EI$^+$) m/z calcd for $C_8H_4BrF_2O$ $[M-H]^+$ 232.9408, found 232.9406.

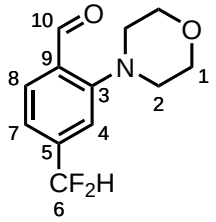
4-(Difluoromethyl)-2-methoxybenzaldehyde (2.39e)



By **GP15**, 2-(4-(difluoromethyl)-2-methoxyphenyl)-1,3,5,5-tetramethylimidazolidin-4-one (**2.69e**) (133 mg, 0.45 mmol) was used as the imidazolidinone to yield the title compound as an orange oil (52 mg, 62%).

$\boldsymbol{R_f}$ = 0.61 (30% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.47 (1H, s, H_9), 7.88 (1H, d, J 8.1, H_7), 7.16–7.11 (2H, m, H_3, H_6), 6.64 (1H, t, J 56.1, H_5), 3.97 (3H, s, H_1). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 189.2 (C_9), 161.9 (C_2), 141.3 (t, J 22.3, C_4), 129.2 (C_7), 126.4 (t, J 1.9, C_8), 118.0 (t, J 6.2, C_6), 113.9 (t, J 240.5, C_5), 108.9 (t, J 6.1, C_3), 56.0 (C_1). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −115.8 (2F, d, J 56.1, F_5). **IR** (film, $CDCl_3$) ν_{max} = 2949 (C−H), 2868 (C−H), 1684 (C=O), 1616, 1464, 1423, 1395, 1376, 1285, 1261, 1195, 1169, 1073, 1024, 810 cm^{-1}. **HRMS** (EI$^+$) m/z calcd for $C_9H_8F_2O_2$ $[M]^+$ 186.0487, found 186.0484.

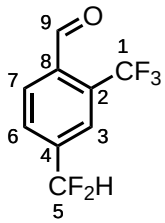
4-(Difluoromethyl)-2-morpholinobenzaldehyde (2.39f)



By **GP15**, 2-(4-(difluoromethyl)-2-morpholinophenyl)-1,3,5,5-tetramethylimidazolidin-4-one (**2.69f**) (190 mg, 0.54 mmol) was used as the imidazolidinone (with the modification of adjusting the reaction mixture to pH 7 with aqueous NaOH (1 M) before extraction) to yield the title compound as a yellow-orange oil (127 mg, 98%).

$\boldsymbol{R_f}$ = 0.42 (30% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.32 (1H, s, H_{10}), 7.87 (1H, d, J 7.9, H_8), 7.25 (1H, d, J 7.9, H_7), 7.24 (1H, s, H_4), 6.64 (1H, t, J 56.1, H_6), 3.93–3.86 (4H, m, H_1), 3.14–3.08 (4H, m, H_2). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 190.5 (C_{10}), 155.5 (C_3), 140.4 (t, J 22.2, C_5), 131.0 (C_8), 130.2 (t, J 1.9, C_9), 119.9 (t, J 6.1, C_7), 116.0 (t, J 6.0, C_4), 114.0 (t, J 240.3, C_6), 66.9 (C_1), 54.2 (C_2). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −115.7 (2F, d, J 56.1, F_6). **IR** (film, $CDCl_3$) ν_{max} = 2962 (C−H), 2916 (C−H), 2851 (C−H), 1686 (C=O), 1612, 1493, 1438, 1372, 1282, 1256, 1240, 1194, 1114, 1071, 1027, 971, 891, 831, 809 cm^{-1}. **HRMS** (EI$^+$) m/z calcd for $C_{12}H_{13}F_2NO_2$ $[M]^+$ 241.0909, found 241.0911.

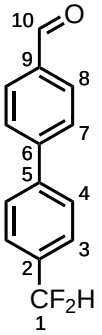
4-(Difluoromethyl)-2-(trifluoromethyl)benzaldehyde (2.39g)



By **GP15**, 2-(4-(difluoromethyl)-2-(trifluoromethyl)phenyl)-1,3,5,5-tetramethylimidazolidin-4-one (**2.69g**) (148 mg, 0.44 mmol) was used as the imidazolidinone to yield the title compound as a yellow oil (76 mg, 77%).

$\boldsymbol{R_f}$ = 0.76 (30% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.42 (1H, q, J 2.0, H_9), 8.22 (1H, d, J 8.0, H_7), 7.93 (1H, s, H_3), 7.86 (1H, d, J 8.0, H_6), 6.75 (1H, t, J 55.6, H_5). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 188.1 (q, J 2.9, C_9), 139.5 (t, J 23.2, C_4), 135.5 (C_8), 131.8 (q, J 33.3, C_2), 129.9 (C_6), 129.7 (tq, J 5.9, 1.2, C_7), 123.8 (sext, J 5.9, C_3), 123.4 (q, J 274.6. C_1), 113.1 (t, J 241.2, C_5). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −59.0 (3F, d, J 2.0, F_1), −116.5 (2F, d, J 55.6, F_5). **IR** (film, $CDCl_3$) ν_{max} = 2918 (C−H), 1704 (C=O), 1316, 1276, 1213, 1170, 1124, 1081, 1055, 1041, 910, 851, 803, 772, 663 cm^{-1}. **HRMS** (EI$^+$) m/z calcd for $C_9H_4F_5O$ $[M-H]^+$ 223.0177, found 223.0171.

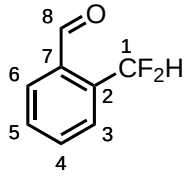
4′-(Difluoromethyl)-[1,1′-biphenyl]-4-carbaldehyde (2.39h)



By **GP15**, 2-(4′-(difluoromethyl)-[1,1′-biphenyl]-4-yl)-1,3,5,5-tetramethyl imidazolidin-4-one (**2.69h**) (79 mg, 0.23 mmol) was used as the imidazolidinone to yield the title compound as a pale yellow solid (53 mg, 99%).

m.p. = 83–84 °C ($CHCl_3$). $\boldsymbol{R_f}$ = 0.61 (30% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.07 (1H, s, H_{10}), 7.97 (2H, d, J 8.0, H_8), 7.76 (2H, d, J 8.0, H_7), 7.71 (2H, d, J 8.0, H_4), 7.63 (2H, d, J 8.0, H_3), 6.71 (1H, t, J 56.4, H_1). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 191.9 (C_{10}), 146.1 (C_6), 142.3 (t, J 2.1, C_5), 135.8 (C_9), 134.5 (t, J 22.6, C_2), 130.5 (C_8), 128.0 (C_7), 127.8 (C_4), 126.4 (t, J 6.0, C_3), 114.6 (t, J 238.9, C_1). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −114.1 (2F, d, J 56.4, F_1). **IR** (film, $CDCl_3$) ν_{max} = 2961 (C−H), 2926 (C−H), 2851 (C−H), 1699 (C=O), 1605, 1377, 1212, 1171, 1073, 1026, 907, 813, 756, 729, 660 cm^{-1}. **HRMS** (EI^+) m/z calcd for $C_{14}H_9F_2O$ $[M-H]^+$ 231.0616, found 231.0612.

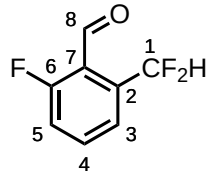
2-(Difluoromethyl)benzaldehyde (2.39i)



By **GP15**, 2-(2-(difluoromethyl)phenyl)-1,3,5,5-tetramethylimidazolidin-4-one (**2.69i**) (125 mg, 0.47 mmol) was used as the imidazolidinone to yield the title compound as a red oil (46 mg, 63%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.18 (1H, s, H_8), 7.93 (1H, d, J 7.0, H_6), 7.81 (1H, d, J 7.0, H_3), 7.76–7.65 (2H, m, H_4, H_5), 7.43 (1H, t, J 54.9, H_1). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 191.9 (C_8), 134.7 (t, J 22.5, C_2), 134.2 (C_4), 133.7 (t, J 4.0, C_7), 133.6 (C_6), 131.2 (t, J 1.9, C_5), 126.6 (t, J 8.1, C_3), 112.2 (t, J 238.2, C_1). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −114.8 (2F, d, J 54.9, F_1). Data consistent with literature.[121]

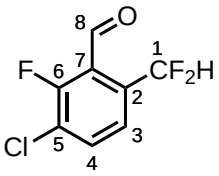
2-(Difluoromethyl)-6-fluorobenzaldehyde (2.39j)



By **GP15**, 2-(2-(difluoromethyl)-6-fluorophenyl)-1,3,5,5-tetramethylimidazolidin-4-one (**2.69j**) (119 mg, 0.42 mmol) was used as the imidazolidinone to yield the title compound as a brown oil (58 mg, 80%).

$\boldsymbol{R_f}$ = 0.73 (30% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.49 (1H, s, H_8), 7.71 (1H, td, J 8.0, 4.8, H_4), 7.66 (1H, d, J 8.0, H_3), 7.46 (1H, t, J 54.7, H_1), 7.34 (1H, dd, J 9.9, 8.0, H_5). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 187.9 (d, J 11.0, C_8), 165.8 (d, J 259.1, C_6), 136.3 (d, J 10.1, C_4), 136.3 (t, J 23.0, C_2), 122.2 (td, J 8.6, 3.7, C_3), 121.7 (d, J 7.1, C_7), 119.1 (dt, J 21.6, 1.8, C_5), 110.8 (td, J 238.7, 3.3, C_1). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −117.3 (dd, J 54.7, 2.2, F_6), −122.6 (ddt, J 9.9, 4.8, 2.2, F_1). **IR** (film, $CDCl_3$) ν_{max} = 2892 (C−H), 1698 (C=O), 1613, 1583, 1480, 1456, 1367, 1256, 1245, 1193, 1160, 1106, 1070, 1033, 958, 821, 779, 593, 516 cm^{-1}. **HRMS** (EI^+) m/z calcd for $C_8H_5F_3O$ $[M]^+$ 174.0287, found 174.0283.

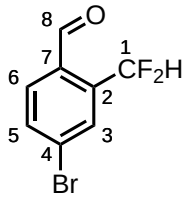
3-Chloro-6-(difluoromethyl)-2-fluorobenzaldehyde (2.39k)



By **GP15**, 2-(3-chloro-6-(difluoromethyl)-2-fluorophenyl)-1,3,5,5-tetramethylimidazolidin-4-one (**2.69k**) (185 mg, 0.58 mmol) was used as the imidazolidinone to yield the title compound as a brown oil (77 mg, 64%).

$\boldsymbol{R_f}$ = 0.78 (30% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.46 (1H, s, H_8), 7.76 (1H, dd, J 8.4, 7.2, H_4), 7.61 (1H, d, J 8.4, H_3), 7.40 (1H, t, J 54.8, H_1). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 187.0 (d, J 10.4, C_8), 161.2 (d, J 260.9, C_6), 136.3 (d, J 1.3, C_4), 134.5 (t, J 23.4, C_2), 125.2 (dt, J 18.0, 2.1, C_7), 122.9 (dt, J 7.4, 4.6, C_5), 122.6 (td, J 8.6, 4.8, C_3), 110.4 (td, J 239.1, 2.9, C_1). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −117.3 (2F, d, J 54.8, F_1), −124.4 (1F, d, J 7.2, F_6). **IR** (film, $CDCl_3$) ν_{max} = 2895 (C−H), 1699 (C=O), 1572, 1483, 1430, 1407, 1259, 1191, 1144, 1103, 1038, 843, 796, 740, 533 cm^{-1}. **HRMS** (EI^+) m/z calcd for $C_8H_4ClF_3O$ $[M]^+$ 207.9897, found 207.9893.

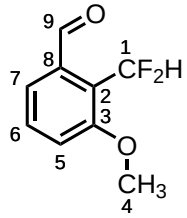
4-Bromo-2-(difluoromethyl)benzaldehyde (2.39l)



By **GP15**, 2-(4-bromo-2-(difluoromethyl)phenyl)-1,3,5,5-tetramethylimidazolidin-4-one (**2.69l**) (105 mg, 0.30 mmol) was used as the imidazolidinone to yield the title compound as a brown oil (59 mg, 83%).

$\boldsymbol{R_f}$ = 0.63 (30% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.12 (1H, s, H_8), 7.95 (1H, d, J 1.8, H_3), 7.84 (1H, dd, J 8.2, 1.8, H_5), 7.79 (1H, d, J 8.2, H_6), 7.38 (1H, t, J 54.7, H_1). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 190.6 (C_8), 136.2 (t, J 22.9, C_2), 134.8 (C_6), 134.5 (t, J 1.8, C_5), 132.4 (t, J 3.9, C_7), 130.2 (t, J 8.6, C_3), 129.6 (C_4), 111.2 (t, J 239.7, C_1). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −115.5 (2F, d, J 54.7, F_1). **IR** (film, $CDCl_3$) ν_{max} = 2852 (C−H), 2748 (C−H), 1698 (C=O), 1590, 1569, 1370, 1204, 1134, 1204, 1090, 1034, 884, 827, 506, 459 cm^{-1}. **HRMS** (EI^+) m/z calcd for $C_8H_5BrF_2O$ $[M]^+$ 233.9486, found 233.9484.

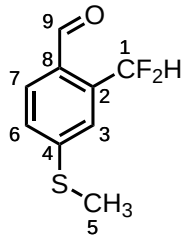
2-(Difluoromethyl)-3-methoxybenzaldehyde (2.39m)



By **GP15**, 2-(2-(difluoromethyl)-3-methoxyphenyl)-1,3,5,5-tetramethylimidazolidin-4-one (**2.69m**) (185 mg, 0.62 mmol) was used as the imidazolidinone to yield the title compound as a dark blue oil (78 mg, 68%).

$\boldsymbol{R_f}$ = 0.51 (30% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.53 (1H, t, J 2.4, H_9), 7.63 (1H, d, J 7.7, H_7), 7.54 (1H dd, J 8.3, 7.7, H_6), 7.37 (1H, t, J 54.4, H_1), 7.18 (1H, d, J 8.3, H_5), 3.91 (3H, s, H_4). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 191.05 (t, J 4.4, C_9), 157.8 (t, J 6.8, C_3), 136.4 (C_8), 132.4 (t, J 1.2, C_6), 123.3 (t, J 23.6, C_2), 120.8 (t, J 1.7, C_7), 116.4 (C_5), 111.6 (t, J 235.5, C_1), 56.4 (C_4). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −107.5 (2F, dd, J 54.4, 2.4, F_1). **IR** (film, $CDCl_3$) ν_{max} = 2908 (C−H), 2850 (C−H), 1700 (C=O), 1599, 1473, 1394, 1267, 1244, 1197, 1049, 1015, 839, 794, 774, 744, 650, 546 cm^{-1}. **HRMS** (EI^+) m/z calcd for $C_9H_8F_2O_2$ $[M]^+$ 186.0487, found 186.0484.

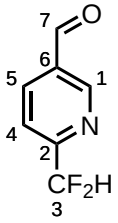
2-(Difluoromethyl)-4-(methylthio)benzaldehyde (2.39n)



By **GP15**, 2-(2-(difluoromethyl)-4-(methylthio)phenyl)-1,3,5,5-tetramethylimidazolidin-4-one (**2.69n**) (193 mg, 0.61 mmol) was used as the imidazolidinone to yield the title compound as a dark green oil (100 mg, 81%).

$\boldsymbol{R_f}$ = 0.55 (30% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.04 (1H, s, H_9), 7.79 (1H, d, J 8.1, H_7), 7.58 (1H, s, H_3), 7.43 (1H, d, J 8.1, H_6), 7.42 (1H, t, J 54.9, H_1), 2.56 (3H, s, H_5). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 190.8 (C_9), 148.5 (C_4), 134.9 (t, J 22.3, C_2), 134.1 (C_7), 129.8 (t, J 3.9, C_8), 126.7 (t, J 1.8, C_6), 122.8 (t, J 8.5, C_3), 111.8 (t, J 238.9, C_1), 14.7 (C_5). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −115.9 (2F, d, J 54.9, F_1). **IR** (film, $CDCl_3$) ν_{max} = 2924 (C−H), 2848 (C−H), 2747 (C−H), 1691 (C=O), 1592, 1559, 1371, 1222, 1208, 1199, 1096, 1030, 894, 832, 820 cm^{-1}. **HRMS** (EI$^+$) m/z calcd for $C_9H_7F_2OS$ $[M-H]^+$ 201.0180, found 201.0177.

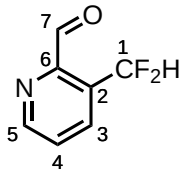
6-(Difluoromethyl)nicotinaldehyde (2.39p)



By **GP15**, 2-(6-(difluoromethyl)pyridin-3-yl)-1,3,5,5-tetramethylimidazolidin-4-one (**2.69p**) (98 mg, 0.36 mmol) was used as the imidazolidinone (with the modification of adjusting the reaction mixture to pH 7 with aqueous NaOH (1 M) before extraction) to yield the title compound as a yellow-orange oil (52 mg, 92%).

$\boldsymbol{R_f}$ = 0.48 (30% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.16 (1H, s, H_7), 9.09 (1H, d, J 2.1, H_1), 8.31 (1H, dd, J 8.1, 2.1, H_5), 7.80 (1H, d, J 8.1, H_4), 6.67 (1H, t, J 55.0, H_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 190.0 (C_7), 157.4 (t, J 25.9, C_2), 151.5 (C_1), 137.6 (C_5), 132.6 (C_6), 120.7 (t, J 3.7, C_4), 113.3 (t, J 241.5, C_3). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −119.9 (2F, d, J 55.0, F_3). **IR** (film, $CDCl_3$) ν_{max} = 2853 (C−H), 1706 (C=O), 1598, 1369, 1236, 1087, 1040, 1024, 845, 809 cm^{-1}. **HRMS** (EI$^+$) m/z calcd for $C_7H_4F_2NO$ $[M-H]^+$ 156.0255, found 156.0254.

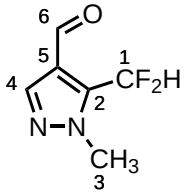
3-(Difluoromethyl)picolinaldehyde (2.39q)



By **GP15**, 2-(3-(difluoromethyl)pyridin-2-yl)-1,3,5,5-tetramethylimidazolidin-4-one (**2.69q**) (162 mg, 0.60 mmol) was used as the imidazolidinone (with the modification of adjusting the reaction mixture to pH 7 with aqueous NaOH (1 M) before extraction) to yield the title compound as a yellow oil (68 mg, 72%).

$\boldsymbol{R_f}$ = 0.41 (30% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.13 (1H, s, H_7), 8.91 (1H, d, J 4.7, H_5), 8.20 (1H, d, J 8.0, H_3), 7.64 (1H, dd, J 8.0, 4.7, H_4), 7.59 (1H, t, J 54.7, H_1). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 194.3 (C_7), 151.8 (t, J 2.0, C_5), 149.4 (t, J 5.2, C_6), 134.6 (t, J 7.2, C_3), 130.8 (t, J 23.6, C_2), 127.5 (C_4), 110.2 (t, J 238.8, C_1). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −118.3 (2F, d, J 54.7, F_1). **IR** (film, $CDCl_3$) ν_{max} = 2923 (C−H), 2850 (C−H), 1711 (C=O), 1587, 1576, 1365, 1225, 1174, 1130, 1034, 874, 838, 796, 746, 670, 641 cm^{-1}. **HRMS** (EI$^+$) m/z calcd for $C_7H_5F_2NO$ $[M]^+$ 157.0334, found 157.0332.

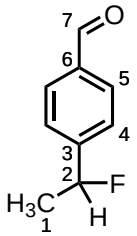
5-(Difluoromethyl)-1-methyl-1*H*-pyrazole-4-carbaldehyde (2.39r)



By **GP15**, 2-(5-(difluoromethyl)-1-methyl-1*H*-pyrazol-4-yl)-1,3,5,5-tetramethylimidazolidin-4-one (**2.69r**) (75 mg, 0.28 mmol) was used as the imidazolidinone (with the modification of adjusting the reaction mixture to pH 7 with aqueous NaOH (1 M) before extraction) to yield the title compound as a pale yellow oil (37 mg, 85%).

$\boldsymbol{R_f}$ = 0.40 (30% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.91 (1H, s, H_6), 7.90 (1H, s, H_4), 7.35 (1H, t, J 52.7, H_1) 4.07 (3H, s, H_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 184.7 (C_6), 141.7 (C_4), 136.0 (t, J 24.2, C_2), 122.8 (t, J 4.4, C_5), 107.5 (t, J 236.8, C_1), 39.2 (t, J 2.7, C_3). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −118.8 (2F, d, J 52.7, F_1). **IR** (film, $CDCl_3$) ν_{max} = 2959 (C−H), 2916 (C−H), 2851 (C−H), 1679 (C=O), 1556, 1495, 1356, 1101, 1065, 1032, 844, 817, 762, 653 cm^{-1}. **HRMS** (EI$^+$) m/z calcd for $C_6H_5F_2N_2O$ $[M-H]^+$ 159.0364, found 159.0365.

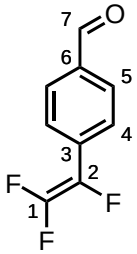
4-(1-Fluoroethyl)benzaldehyde (2.39t)



By **GP15**, 2-(4-(1-fluoroethyl)phenyl)-1,3,5,5-tetramethylimidazolidin-4-one (**2.69t**) (51 mg, 0.19 mmol) was used as the imidazolidinone (with the modification of $LiAlH_4$ (1.0 M in THF) instead of DIBAL-H (1.0 M in heptane)) to yield the title compound as a pale orange oil (26 mg, 87%).

$\boldsymbol{R_f}$ = 0.61 (30% EtOAc in pet. ether). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.02 (1H, s, H_7), 7.89 (2H, d, J 8.0, H_5), 7.50 (2H, d, J 8.0, H_4), 5.69 (1H, dq, J 47.9, 6.5, H_2), 1.65 (3H, dd, J 24.0, 6.5, H_4). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 191.9 (C_7), 148.3 (d, J 19.5, C_3), 136.3 (d, J 1.6, C_6), 130.1 (C_5), 125.6 (d, J 7.5, C_4), 90.3 (d, J 170.4, C_2), 23.1 (d, J 24.6, C_1). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −175.1 (dq, J 47.9, 24.0, F_2. **IR** (film, $CDCl_3$) ν_{max} = 2985 (C−H), 2932 (C−H), 2830 (C−H), 2738 (C−H), 1700 (C=O), 1612, 1306, 1209, 1169, 1069, 1007, 887, 827, 746, 542 cm^{-1}. **HRMS** (EI^+) m/z calcd for C_9H_8FO $[M-H]^+$ 151.0554, found 151.0552.

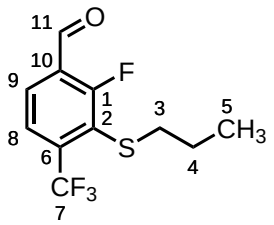
4-(1,2,2-Trifluorovinyl)benzaldehyde (2.39u)



By **GP15**, 1,3,5,5-tetramethyl-2-(4-(1,2,2-trifluorovinyl)phenyl) imidazolidin-4-one (**2.69u**) (100 mg, 0.34 mmol) was used as the imidazolidinone to yield the title compound as a red oil (19 mg, 30%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.03 (1H, s, H_7), 7.94 (2H, d, J 8.2, H_5), 7.64 (2H, d, J 8.2, H_4). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 191.4 (C_7), 154.5 (ddd, J 294.3, 286.6, 49.0, C_1), 136.2 (t, J 2.1, C_6), 133.1 (dd, J 21.7, 7.3, C_3), 130.1 (d, J 1.4, C_5), 128.3 (ddd, J 227.8, 44.6, 20.6, C_2), 124.8 (ddd, J 8.0, 6.3, 4.1, C_4). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −98.5 (dd, J 60.0, 33.3, $F_{1\,cis\text{ to }F_2}$), −113.3 (dd, J 108.4, 60.0, F_2), −180.5 (dd, J 108.4, 33.3, $F_{1\,trans\text{ to }F_2}$). Data consistent with literature.[340]

2-Fluoro-3-(propylthio)-4-(trifluoromethyl)benzaldehyde (2.40y)

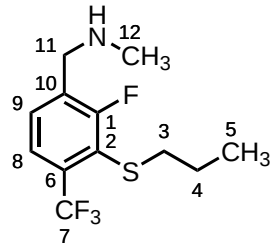


By the method of Lian and co-workers[341] with modifications, 2,3-difluorobenzotrifluoride (2.91 g, 16.0 mmol, 1.0 eq.) and NaOH (704 mg, 17.6 mmol, 1.1 eq.) were suspended in anhydrous DMF (30 mL), and the reaction mixture cooled to 0 °C. 1-Propanethiol (1.5 mL, 16.6 mmol, 1.05 eq.) was added dropwise, the reaction mixture stirred at 0 °C for 1.5 h, and diluted with EtOAc (50 mL). The reaction mixture was washed sequentially with H_2O (30 mL) and brine (3 × 50 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2; gradient elution: 0–5% DCM in pet. ether) to yield a colourless oil (3.47 g). NMR analysis revealed the product was a mixture of 2-fluoro-6-(trifluoromethyl)phenyl)(propyl)sulfane and 2-fluoro-3-(trifluoromethyl) phenyl)(propyl)sulfane) in an approximate 10:1 ratio.

By the method of Lian and co-workers[341] with modifications, the product mixture (3.37 g, 14.1 mmol, 1.0 eq.) was dissolved in anhydrous THF (33 mL), and cooled to −78 °C. *n*-BuLi (6.8 mL, 2.51 M in hexanes, 17.0 mmol, 1.2 eq.) was added dropwise, and the reaction mixture stirred at −78 °C for 30 min. Anhydrous DMF (2.2 mL, 28.4 mmol, 2.0 eq.) was added dropwise, the reaction mixture slowly warmed to room temperature, quenched by the addition of aqueous HCl (50 mL, 3 M), and extracted with Et_2O (50 mL). The organic extract was washed with brine (50 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2; gradient elution: 0–10% DCM in pet. ether) to yield the title compound as a pale yellow oil (3.27 g, 79%).

$\boldsymbol{R_f}$ = 0.24 (20% DCM in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.40 (1H, s, H_{11}), 7.88 (1H, dd, *J* 8.2, 6.5, H_9), 7.62 (1H, d, *J* 8.2, H_8), 2.94 (2H, t, *J* 7.3, H_3), 1.61 (2H, sext, *J* 7.3, H_4), 1.00 (3H, t, *J* 7.3, H_5). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 186.3 (d, *J* 6.7, C_{11}), 165.5 (d, *J* 257.0, C_1), 139.9 (qd, *J* 30.1, 2.5, C_6), 128.1 (d, *J* 3.0, C_9), 126.6 (d, *J* 11.5, C_{10}), 125.1 (d, *J* 21.2, C_2), 122.7 (qd, *J* 5.6, 4.3, C_8), 122.6 (qd, *J* 274.8, 3.3, C_7), 37.8 (d, *J* 5.7, C_3), 23.2 (C_4), 13.3 (C_5). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −63.5 (3F, s, F_7), −115.3 (1F, d, *J* 6.5, F_1). **IR** (film, $CDCl_3$) ν_{max} = 2968 (C−H), 2936 (C−H), 2876 (C−H), 1699 (C=O), 1414, 1393, 1313, 1248, 1164, 1139, 1109, 917, 833, 752, 651, 542 cm^{-1}. **HRMS** (EI$^+$) *m*/*z* calcd for $C_{11}H_{10}F_4OS$ $[M]^+$ 266.0383, found 266.0380.

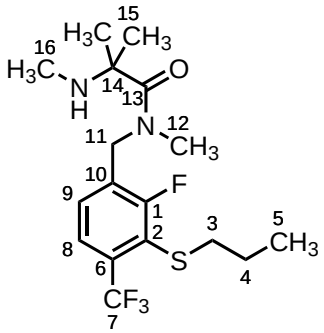
1-(2-Fluoro-3-(propylthio)-4-(trifluoromethyl)phenyl)-*N*-methyl methanamine (2.52y)



By **GP7**, 2-fluoro-3-(propylthio)-4-(trifluoromethyl)benzaldehyde (**2.40y**) (3.23 g, 12.1 mmol) was used as the aldehyde that was stirred for 30 min to yield the title compound as a colourless oil (3.41 g, quant.).

***R*$_f$** = 0.33 (5% MeOH in DCM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 (1H, d, *J* 8.2, H_8), 7.39 (1H, dd, *J* 8.2, 6.5, H_9), 3.83 (2H, s, H_{11}), 2.86 (2H, t, *J* 7.3, H_3), 2.44 (3H, s, H_{12}), 1.56 (2H, sext, *J* 7.3, H_4), 1.37 (1H, s, N*H*), 0.96 (3H, t, *J* 7.3, H_5). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.2 (d, *J* 245.8, C_1), 133.5 (qd, *J* 29.5, 1.5, C_6), 131.9 (d, *J* 18.2, C_{10}), 129.5 (d, *J* 5.9, C_9), 123.3 (qd, *J* 273.7, 3.5, C_7), 122.4 (q, *J* 1.0, C_2), 122.1 (qd, *J* 5.7, 4.0, C_8), 49.2 (d, *J* 3.2, C_{11}), 37.7 (d, *J* 5.5, C_3), 36.1 (C_{12}), 23.1 (C_4), 13.3 (C_5). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −62.6 (3F, s, F_7), −111.9 (1F, d, *J* 6.5, F_1). **IR** (film, $CDCl_3$) ν_{max} = 3314 (N−H, br), 2967 (C−H), 2936 (C−H), 2875 (C−H), 2797 (C−H), 1408, 1313, 1156, 1132, 1107, 907, 828, 747, 648 cm^{-1}. **HRMS** (ESI$^+$) *m*/*z* calcd for $C_{12}H_{16}F_4NS$ $[M+H]^+$ 282.0934, found 282.0929.

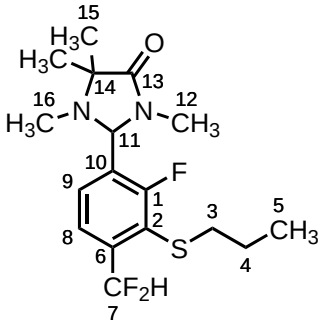
***N*-(2-Fluoro-3-(propylthio)-4-(trifluoromethyl)benzyl)-*N*,2-dimethyl-2-(methylamino)propanamide (2.66y)**



By **GP13**, 3,4,4-trimethyloxazolidine-2,5-dione (**2.74**) (1.08 g, 7.55 mmol) was used as the *N*-carboxyanhydride and 1-(2-fluoro-3-(propylthio)-4-(trifluoromethyl)phenyl)-*N*-methylmethanamine (**2.52y**) (1.41 g, 5.01 mmol) was used as the amine that were stirred for 70 h (with the modifications of PhMe instead of DCM, and stirring at 80 °C), and purified by flash column chromatography (SiO_2; gradient elution: 0–2% acetone + 1% Et_3N in DCM + 1% Et_3N) to yield the title compound as a pale yellow oil (1.36 g, 71%).

R_f = 0.33 (80% acetone + 1% Et_3N in DCM + 1% Et_3N). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 (1H, d, *J* 8.1, H_8), 7.23 (1H, dd, *J* 8.1, 6.9, H_9), 4.73 (2H, br s, H_{11}), 3.34 (3H, br s, H_{12}), 2.85 (2H, t, *J* 7.4, H_3), 2.28 (3H, s, H_{16}), 1.56 (2H, sext, *J* 7.4, H_4), 1.36 (6H, s, H_{15}), 0.96 (3H, t, *J* 7.4, H_5), 0.89 (1H, br s, N*H*). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 175.5 (C_{13}), 161.9 (d, *J* 245.9, C_1), 133.5 (q, *J* 29.9, C_6), 129.9 (C_{10}), 128.8 (C_9), 123.2 (qd, *J* 273.6, 3.2, C_7), 122.5 (d, *J* 22.3, C_2), 122.3 (q, *J* 5.6, C_8), 61.0 (C_{14}), 47.5 (C_{11}), 37.6 (d, *J* 5.4, C_3), 36.6 (C_{12}), 30.4 (C_{16}), 26.3 (C_{15}), 23.1 (C_4), 13.3 (C_5). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −62.6 (3F, s, F_7), −111.2 (1F, d, *J* 6.9, F_1). **IR** (film, $CDCl_3$) ν_{max} = 3321 (N−H, br), 2968 (C−H), 2935 (C−H), 1631 (C=O), 1409, 1390, 1314, 1189, 1158, 1135, 1111, 1096, 909, 827, 731, 646 cm^{-1}. **HRMS** (ESI$^+$) *m*/*z* calcd for $C_{17}H_{25}F_4N_2OS$ $[M+H]^+$ 381.1618, found 381.1605.

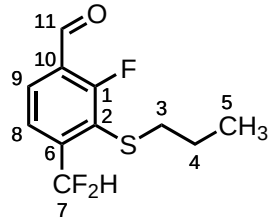
2-(4-(Difluoromethyl)-2-fluoro-3-(propylthio)phenyl)-1,3,5,5-tetramethyl imidazolidin-4-one (2.69y)



By **GP14**, *N*-(2-fluoro-3-(propylthio)-4-(trifluoromethyl)benzyl)-*N*,2-dimethyl-2-(methylamino)propanamide (**2.66y**) (380 mg, 1.00 mmol) was used as the fluoroalkyl arene, and purified by flash column chromatography (SiO_2; gradient elution: 12–30% EtOAc in pet. ether) to yield the title compound as an orange oil (337 mg, 94%).

R_f = 0.62 (50% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.55 (1H, dd, *J* 8.2, 6.2, H_9), 7.51 (1H, d, *J* 8.2, H_8), 7.16 (1H, t, *J* 55.1, H_7), 5.12 (1H, s, H_{11}), 2.82 (2H, t, *J* 7.3, H_3), 2.58 (3H, s, H_{12}), 2.17 (3H, s, H_{16}), 1.53 (2H, sext, *J* 7.3, H_4), 1.32 (3H, s, H_{15a}), 1.15 (3H, s, H_{15b}), 0.95 (3H, t, *J* 7.3, H_5). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 176.2 (C_{13}), 162.6 (d, *J* 248.3, C_1), 139.5 (td, *J* 23.0, 1.8, C_6), 129.8 (d, *J* 4.2, C_9), 127.5 (d, *J* 12.6, C_{10}), 122.1 (td, *J* 5.9, 4.4, C_8), 122.0 (d, *J* 6.2, C_2), 112.1 (td, *J* 238.3, 4.5, C_7), 73.6 (C_{11}), 61.5 (C_{14}), 37.8 (d, *J* 4.2, C_3), 30.6 (C_{16}), 26.7 (C_{12}), 24.0 (C_{15a}), 23.0 (C_4), 17.1 (C_{15b}), 13.2 (C_5). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −115.3 (d, *J* 54.1, F_{7a}), −115.4 (d, *J* 54.1, F_{7b}), −117.1 (br s, F_1). **IR** (film, $CDCl_3$) ν_{max} = 2967 (C−H), 2933 (C−H), 2874 (C−H), 1708 (C=O), 1431, 1418, 1398, 1364, 1299, 1256, 1138, 1105, 1075, 1032, 953, 852, 798, 552 cm^{-1}. **HRMS** (ESI$^+$) *m*/*z* calcd for $C_{17}H_{24}F_3N_2OS$ $[M+H]^+$ 361.1556, found 361.1546.

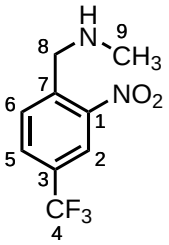
4-(Difluoromethyl)-2-fluoro-3-(propylthio)benzaldehyde (2.39y)



By **GP15**, 2-(4-(difluoromethyl)-2-fluoro-3-(propylthio)phenyl)-1,3,5,5-tetramethylimidazolidin-4-one (**2.69y**) (140 mg, 0.39 mmol) was used as the imidazolidinone to yield the title compound as an orange oil (95 mg, 98%).

$\boldsymbol{R_f}$ = 0.78 (30% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.37 (1H, s, H_{11}), 7.89 (1H, dd, J 8.2, 6.5, H_9), 7.58 (1H, d, J 8.2, H_8), 7.19 (1H, t, J 54.8, H_7), 2.87 (2H, t, J 7.3, H_3), 1.57 (2H, sext, J 7.3, H_4), 0.98 (3H, t, J 7.3, H_5). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 186.5 (d, J 6.7, C_{11}), 165.0 (d, J 257.7, C_1), 144.3 (td, J 22.8, 2.4, C_6), 128.7 (d, J 2.6, C_9), 125.7 (dt, J 10.4, 1.8, C_{10}), 123.8 (dt, J 20.3, 6.2, C_2), 122.0 (td, J 6.2, 4.5, C_8), 111.8 (td, J 239.4, 4.5, C_7), 37.8 (d, J 4.2, C_3), 23.2 (C_4), 13.2 (C_5). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −116.4 (2F, d, J 54.8, F_1), −117.5 (1F, d, J 6.5, F_7). **IR** (film, $CDCl_3$) ν_{max} = 2977 (C−H), 2934 (C−H), 2875 (C−H), 1696 (C=O), 1419, 1394, 1363, 1245, 1106, 1036, 953, 841, 794, 553 cm^{-1}. **HRMS** (EI$^+$) m/z calcd for $C_{11}H_{11}F_3OS$ $[M]^+$ 248.0477, found 248.0473.

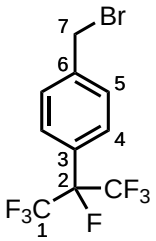
***N*-Methyl-1-(2-nitro-4-(trifluoromethyl)phenyl)methanamine (2.52aa)**



By **GP7**, 2-nitro-4-(trifluoromethyl)benzaldehyde (1.02 g, 4.65 mmol) was used as the aldehyde that was stirred for 1.5 h to yield the title compound as a yellow oil (789 mg, 72%).

$\boldsymbol{R_f}$ = 0.34 (5% MeOH in DCM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.20 (1H, d, J 1.8, H_2), 7.86 (1H, d, J 8.3, H_6), 7.83 (1H, dd, J 8.3, 1.8, H_5), 4.07 (2H, s, H_8), 2.45 (3H, s, H_9), 1.61 (1H, s, NH). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.1 (C_1), 139.9 (C_7), 131.8 (C_6), 130.7 (q, J 34.2, C_3), 129.5 (q, J 3.5, C_5), 123.0 (q, J 272.4, C_4), 122.1 (q, J 4.0, C_2), 52.5 (C_8), 36.3 (C_9). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −65.9 (3F, s, F_4). **IR** (film, $CDCl_3$) ν_{max} = 3338 (N−H, br), 2855 (C−H), 2799 (C−H), 1537 (N=O), 1321 (N=O), 1173, 1125, 1085 cm^{-1}. **HRMS** (ESI$^+$) m/z calcd for $C_9H_{10}F_3N_2O_2$ $[M+H]^+$ 235.0689, found 235.0684.

1-(Bromomethyl)-4-(perfluoropropan-2-yl)benzene (2.129)

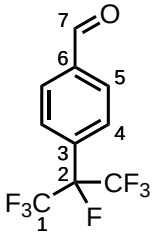


By the method of Ge and co-workers[342] with modifications, 4-(heptafluoroisopropyl)toluene (2.95 g, 11.3 mmol, 1.0 eq.), NBS (3.03 g, 17.0 mmol, 1.5 eq.) and AIBN (93 mg, 0.57 mmol, 0.05 eq.) were dissolved in anhydrous MeCN (11.3 mL), and the reaction mixture stirred at reflux for 21 h. Hexane (100 mL) was added, the reaction mixture filtered, eluting with hexane, and concentrated *in vacuo*.

By the method of Deng and co-workers[343] with modifications, the crude residue was dissolved in anhydrous THF (22.7 mL), cooled to 0 °C, and diethyl phosphite (5.8 mL, 45.0 mmol, 4.0 eq.) and DIPEA (7.9 mL, 45.4 mmol, 4.0 eq.) added. The reaction mixture was stirred at room temperature for 27 h, poured onto ice-cold H_2O (50 mL), and extracted with Et_2O (3 × 50 mL). The combined organic extracts were washed sequentially with aqueous HCl (100 mL, 1 M) and brine (100 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2; isocratic elution: pet. ether) to yield the title compound as a colourless oil (2.77 g, 72%).

$\boldsymbol{R_f}$ = 0.69 (10% DCM in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.60 (2H, d, *J* 8.4, H_4), 7.53 (2H, d, *J* 8.4, H_5), 4.50 (2H, s, H_7). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.0 (d, *J* 1.2, C_6), 129.6 (d, *J* 2.3, C_5), 126.9 (d, *J* 20.7, C_3), 126.4 (dsept, *J* 9.4, 1.4, C_4), 120.7 (qd, *J* 287.2, 27.5, C_1), 91.5 (dsept, *J* 202.4, 32.7, C_2), 31.8 (C_7). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −78.7 (6F, d, *J* 7.2, F_1), −185.5 (1F, sept, *J* 7.2, F_2). **IR** (film, $CDCl_3$) ν_{max} = 2973 (C−H), 1308, 1281, 1207, 1193, 1166, 1094, 982, 952, 754, 708, 612 cm^{-1}. **HRMS** (EI$^+$) *m*/*z* calcd for $C_{10}H_5BrF_7$ $[M-H]^+$ 336.9457, found 336.9449.

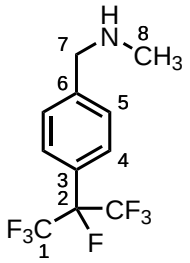
4-(Perfluoropropan-2-yl)benzaldehyde (2.40ac)



By the method of Togo and co-workers[344] with modifications, 1-(bromomethyl)-4-(perfluoropropan-2-yl)benzene (**2.129**) (2.70 g, 7.96 mmol, 1.0 eq.) and NMO (3.73 g, 31.8 mmol, 4.0 eq.) were suspended in anhydrous THF (40 mL). The reaction mixture was stirred at reflux for 18 h, diluted with H_2O (50 mL), and extracted with Et_2O (3 × 50 mL). The combined organic extracts were dried (Na_2SO_4), and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2; isocratic elution: 10% DCM in pet. ether) to yield the title compound as a colourless oil (1.65 g, 75%).

$\boldsymbol{R_f}$ = 0.19 (10% DCM in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.10 (1H, s, H_7), 8.02 (2H, d, J 8.2, H_5), 7.81 (2H, d, J 8.2, H_4). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 191.1 (C_7), 138.3 (d, J 0.8, C_6), 132.5 (d, J 20.5, C_3), 130.0 (d, J 2.4, C_5), 126.7 (dsept, J 10.8, 1.5, C_4), 120.5 (qd, J 287.4, 27.9, C_1), 91.5 (dsept, J 203.0, 32.9, C_2). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −78.4 (6F, d, J 7.2, F_1), −185.2 (1F, sept, J 7.2, F_2). Data consistent with literature.[345]

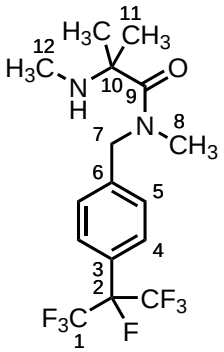
N-Methyl-1-(4-(perfluoropropan-2-yl)phenyl)methanamine (2.52ac)



By **GP7**, 4-(perfluoropropan-2-yl)benzaldehyde (**2.40ac**) (1.89 g, 6.89 mmol) was used as the aldehyde that was stirred for 30 min to yield the title compound as a colourless oil (1.98 g, 99%).

$\boldsymbol{R_f}$ = 0.11 (5% MeOH in DCM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.56 (2H, d, J 8.2, H_4), 7.45 (2H, d, J 8.2, H_5), 3.80 (2H, s, H_7), 2.46 (3H, s, H_8), 1.58 (1H, s, NH). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.6 (C_6), 128.6 (d, J 2.2, C_5), 125.9 (dsept, J 10.6, 1.5, C_4), 125.5 (d, J 20.5, C_3), 120.8 (qd, J 287.0, 28.2, C_1), 91.7 (dsept, J 201.5, 33.0, C_2), 55.5 (C_7), 36.2 (C_8). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −78.8 (6F, d, J 7.2, F_1), −185.4 (1F, sept, J 7.2, F_2). **IR** (film, $CDCl_3$) ν_{max} = 3283 (N−H, br), 2853 (C−H), 2798 (C−H), 1307, 1280, 1206, 1166, 1097, 981, 952, 731, 708 cm^{-1}. **HRMS** (ESI$^+$) m/z calcd for $C_{11}H_{11}F_7N$ $[M+H]^+$ 290.0774, found 290.0765.

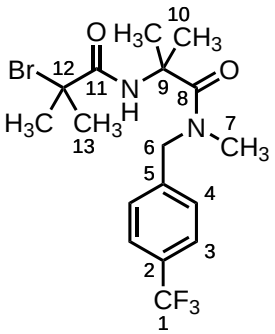
N,2-Dimethyl-2-(methylamino)-*N*-(4-(perfluoropropan-2-yl)benzyl) propanamide (2.66ac)



By **GP13**, 3,4,4-trimethyloxazolidine-2,5-dione (**2.74**) (1.34 g, 9.39 mmol) was used as the *N*-carboxyanhydride and *N*-methyl-1-(4-(perfluoropropan-2-yl)phenyl) methanamine (**2.52ac**) (1.81 g, 6.26 mmol) was used as the amine that were stirred at room temperature for 27 h, and purified by flash column chromatography (SiO_2; gradient elution: 0–2% acetone + 1% Et_3N in DCM + 1% Et_3N), with further purification by bulb-to-bulb distillation (160 °C at 100 mbar) to remove remaining *N*-methyl-1-(4-(perfluoropropan-2-yl)phenyl)methanamine (**2.52ac**) to yield the title compound as a yellow oil (1.54 g, 66%).

$\boldsymbol{R_f}$ = 0.47 (80% acetone + 1% Et_3N in DCM + 1% Et_3N). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.53 (2H, d, *J* 8.2, H_4), 7.30 (2H, d, *J* 8.2, H_5), 4.78 (2H, br s, H_7), 3.23 (3H, br s, H_8), 2.29 (3H, s, H_{12}), 1.37 (6H, s, H_{11}), 1.13 (1H, br s, N*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.2 (C_9), 141.6 (C_6), 127.7 (C_5), 126.0 (d, *J* 10.3, C_4), 125.5 (d, *J* 20.6, C_3), 120.7 (qd, *J* 286.6, 28.1, C_1), 91.5 (dsept, *J* 201.5, 33.0, C_2), 61.0 (C_{10}), 53.0 (C_7), 36.1 (C_8), 30.3 (C_{12}), 26.3 (C_{11}). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −78.7 (6F, d, *J* 7.3, F_1), −185.3 (1F, sept, *J* 7.3, F_2). **IR** (film, $CDCl_3$) ν_{max} = 3320 (N−H, br), 2978 (C−H), 2934 (C−H), 1627 (C=O), 1392, 1303, 1278, 1208, 1166, 1098, 982, 952, 729, 711 cm^{-1}. **HRMS** (ESI^+) *m/z* calcd for $C_{16}H_{20}F_7N_2O$ $[M+H]^+$ 389.1458, found 389.1439.

2-(2-Bromo-2-methylpropanamido)-*N*,2-dimethyl-*N*-(4-(trifluoromethyl) benzyl)propanamide (2.86)

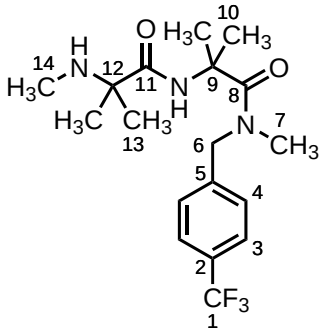


2-Bromo-2-methylpropionic acid (256 mg, 1.53 mmol, 1.0 eq.) was dissolved in anhydrous DCM (6.1 mL), and $SOCl_2$ (670 µL, 9.19 mmol, 6.0 eq.) added dropwise. The reaction mixture was stirred at reflux for 4 h, and concentrated *in vacuo* to yield the crude acid chloride, which was used without further purification.

By **GP2**, 2-amino-*N*,2-dimethyl-*N*-(4-(trifluoromethyl)benzylpropanamide (**2.65**) (420 mg, 1.53 mmol, 1.0 eq.) was used as the general amine that was stirred with the crude acid chloride for 65 h, and purified by flash column chromatography (SiO_2; gradient elution: 12–50% EtOAc in pet. ether) to yield the title compound as a white solid (352 mg, 54%).

m.p. = 124–125 °C ($CHCl_3$). $\boldsymbol{R_f}$ = 0.38 (50% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.57 (2H, d, *J* 8.0, H_3), 7.51 (1H, s, N*H*), 7.36 (2H, d, *J* 8.0, H_4), 4.70 (2H, s, H_6), 3.02 (3H, s, H_7), 1.91 (6H, s, H_{13}), 1.66 (6H, s, H_{10}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.9 (C_8), 170.5 (C_{11}), 141.3 (C_5), 129.8 (q, *J* 32.5, C_2), 127.9 (C_4), 125.7 (q, *J* 3.8, C_3), 124.2 (q, *J* 272.0, C_1), 62.5 (C_{12}), 57.5 (C_9), 53.1 (C_6), 36.3 (C_7), 32.4 (C_{13}), 25.0 (C_{10}). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −65.6 (3F, s, F_1). **IR** (film, $CDCl_3$) ν_{max} = 3322 (N−H, br), 2987 (C−H), 2933 (C−H), 1667 (C=O), 1629 (C=O), 1508, 1419, 1325, 1163, 1109, 1067, 1018, 934, 818 cm^{-1}. **HRMS** (ESI^+) *m*/*z* calcd for $C_{17}H_{23}BrF_3N_2O_2$ $[M+H]^+$ 423.0890, found 423.0889.

N,2-Dimethyl-2-(2-methyl-2-(methylamino)propanamido)-*N*-(4-(trifluoromethyl)benzyl)propanamide (2.87)

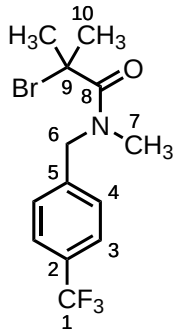


By the method of Bartolozzi and co-workers[161] with modifications, 2-(2-bromo-2-methylpropanamido)-*N*,2-dimethyl-*N*-(4-(trifluoromethyl)benzyl)propanamide (**2.86**) (1.16 g, 2.74 mmol, 1.0 eq.), Cs_2CO_3 (1.79 g, 5.49 mmol, 2.0 eq.) were suspended in anhydrous THF (23 mL). $MeNH_2$ (27.4 mL, 2.0 M in THF, 54.8 mmol, 20.0 eq.) was added dropwise, and the reaction mixture stirred at 65 °C in a sealed tube for 17 h. The reaction mixture was diluted with EtOAc (100 mL), washed with brine (100 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2; gradient elution: 0–9% MeOH in DCM to yield the title compound as a yellow solid (861 mg, 84%).

$\boldsymbol{R_f}$ = 0.09 (5% MeOH in DCM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.85 (1H, s, NH_{amide}), 7.55 (2H, d, *J* 8.0, H_3), 7.36 (2H, d, *J* 8.0, H_4), 4.69 (2H, s, H_6), 2.98 (3H, s, H_7), 2.26 (3H, s, H_{14}), 1.58 (6H, s, H_{10}), 1.48 (1H, br s, NH_{amine}), 1.24

(6H, s, H_{13}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.8 (C_{11}), 173.3 (C_8), 141.7 (C_5), 129.5 (q, J 32.7, C_2), 127.9 (C_4), 125.6 (q, J 4.0, C_3), 124.3 (q, J 272.0, C_1), 59.2 (C_{12}), 56.4 (C_9), 52.9 (C_6), 36.0 (C_7), 30.2 (C_{14}), 25.9 (C_{10}), 24.9 (C_{13}). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −65.6 (3F, s, F_1). **IR** (film, $CDCl_3$) ν_{max} = 3326 (N−H, br), 2981 (C−H), 2933 (C−H), 1632 (C=O), 1496, 1397, 1324, 1168, 1121, 1111, 1095, 1066, 1018, 911, 819, 730, 645, 602 cm^{-1}. **HRMS** (ESI$^+$) m/z calcd for $C_{18}H_{27}F_3N_3O_2$ $[M+H]^+$ 374.2050, found 374.2042.

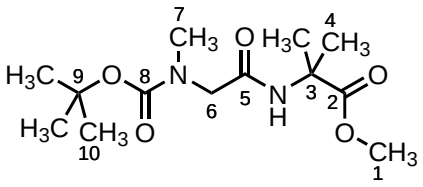
2-Bromo-*N*,2-dimethyl-*N*-(4-(trifluoromethyl)benzyl)propanamide (2.91)



By **GP2**, with the modification of an acid bromide instead of an acid chloride, *N*-methyl-1-(4-(trifluoromethyl)phenyl)methanamine (**2.52a**) (1.57 g, 8.30 mmol, 1.0 eq.) was used as the general amine that was stirred with α-bromoisobutyryl bromide (1.0 mL, 8.09 mmol) for 22 h, and purified by flash column chromatography (SiO_2; gradient elution: 5–15% EtOAc in pet. ether) to yield the title compound as a white solid (2.33 g, 85%).

m.p. = 70–71 °C ($CHCl_3$). $\boldsymbol{R_f}$ = 0.53 (30% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.59 (2H, d, J 8.0, H_3), 7.34 (2H, d, J 8.0, H_4), 4.76 (2H, br s, H_6), 3.19 (3H, br s, H_7), 2.01 (6H, s, H_{10}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.8 (C_8), 141.2 (C_5), 129.8 (q, J 32.6, C_2), 127.6 (C_4), 125.8 (q, J 3.8, C_3), 124.2 (q, J 272.0, C_1), 56.9 (C_9), 53.5 (C_6), 37.6 (C_7), 32.6 (C_{10}). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −65.6 (3F, s, F_1). **IR** (film, $CDCl_3$) ν_{max} = 2979 (C−H), 2933 (C−H), 1635 (C=O), 1396, 1322, 1161, 1108, 1090, 1065, 1018, 936, 817 cm^{-1}. **HRMS** (ESI$^+$) m/z calcd for $C_{13}H_{16}BrF_3NO$ $[M+H]^+$ 338.0362, found 338.0354.

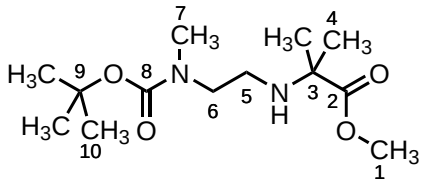
Methyl 2-(2-((*tert*-butoxycarbonyl)(methyl)amino)acetamido)-2-methyl propanoate (2.102)



By the method of Clayden and co-workers[346] with modifications, Boc-sarcosine (2.91 g, 15.4 mmol, 1.0 eq.) and NMM (5.2 mL, 47.2 mmol, 3.05 eq.) were dissolved in anhydrous THF (96 mL), and cooled to −10 °C. Isobutyl chloroformate (2.0 mL, 15.4 mmol, 1.0 eq.) was added dropwise, and the reaction mixture stirred at −10 °C for 15 min. Methyl α-aminoisobutyrate hydrochloride (4.74 g, 30.9 mmol, 2.0 eq.) was added, the reaction mixture stirred at room temperature for 16 h, and concentrated *in vacuo*. The residue was diluted with EtOAc (200 mL), washed sequentially with aqueous $KHSO_4$ (3 × 25 mL, 1 M), saturated aqueous $NaHCO_3$ (3 × 25 mL) and brine (25 mL), dried ($MgSO_4$), concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2; gradient elution: 12–60% EtOAc in pet. ether) to yield the title compound as a colourless gum that solidified upon standing (3.62 g, 82%).

m.p. = 99–100 °C ($CHCl_3$). $\boldsymbol{R_f}$ = 0.19 (50% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers in an approximate 50:50 ratio) δ 6.76 (1H$^{\text{one rot.}}$, br s, N*H*), 6.46 (1H$^{\text{one rot.}}$, br s, N*H*), 3.77 (2H$^{\text{both rot.}}$, s, H_6), 3.71 (3H$^{\text{both rot.}}$, s, H_1), 2.92 (3H$^{\text{both rot.}}$, s, H_7), 1.52 (6H$^{\text{both rot.}}$, s, H_4), 1.45 (9H$^{\text{both rot.}}$, s, H_{10}). **^{13}C NMR** (151 MHz, $CDCl_3$, mixture of rotamers in an approximate 50:50 ratio) δ 174.9 ($C_2$$^{\text{both rot.}}$), 168.9 ($C_5$$^{\text{both rot.}}$), 156.6 ($C_8$$^{\text{one rot.}}$), 155.4 ($C_8$$^{\text{one rot.}}$), 80.8 ($C_9$$^{\text{both rot.}}$), 56.5 ($C_3$$^{\text{both rot.}}$), 53.5 ($C_6$$^{\text{both rot.}}$), 52.7 ($C_1$$^{\text{both rot.}}$), 35.7 ($C_7$$^{\text{both rot.}}$), 28.4 ($C_{10}$$^{\text{both rot.}}$), 24.8 ($C_4$$^{\text{both rot.}}$). **IR** (film, $CDCl_3$) ν_{max} = 3312 (N−H, br), 2980 (C−H), 1742 (C=O), 1665 (C=O), 1453, 1391, 1366, 1287, 1245, 1146, 877, 731 cm^{-1}. **HRMS** (ESI$^+$) *m/z* calcd for $C_{13}H_{25}N_2O_5$ $[M+H]^+$ 289.1758, found 289.1744.

Methyl 2-((2-((*tert*-butoxycarbonyl)(methyl)amino)ethyl)amino)-2-methylpropanoate (2.99)



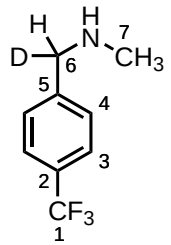
By the method of Sawada and co-workers[166] with modifications, methyl 2-(2-((*tert*-butoxycarbonyl)amino)acetamido)-2-methylpropanoate (**2.102**) (2.70 g, 9.36 mmol, 1.0 eq.) and Lawesson reagent (2.27 g, 5.61 mmol, 0.60 eq.) were dissolved in anhydrous PhMe (47 mL), stirred at reflux for 1 h, and concentrated *in vacuo* to yield the crude thioamide, which was used without further purification.

By the method of Guziec Jr. and co-workers[347] with modifications, the crude thioamide and $NiCl_2 \cdot 6H_2O$ (17.81 g, 74.9 mmol, 8.0 eq.) were dissolved in 1:1 THF/MeOH (94 mL), cooled to 0 °C, and $NaBH_4$ (8.50 g, 225 mmol, 24.0 eq.) added portionwise. The reaction mixture was stirred at room temperature for 20 h, filtered through Celite, eluting with MeOH, and concentrated *in vacuo*. The crude residue was dissolved in EtOAc (100 mL), washed sequentially with aqueous NaOH (100 mL, 1 M) and brine (100 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2; gradient

elution: 25–100% EtOAc in pet. ether) to yield the title compound as a colourless oil (1.94 g, 76%).

$\boldsymbol{R_f}$ = 0.38 (EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.67 (3H, s, H_1), 3.27 (2H, t, J 6.4, H_6), 2.83 (3H, s, H_7), 2.59 (2H, t, J 6.4, H_5), 1.97 (1 H, br s, NH), 1.43 (9H, s, H_{10}), 1.27 (6H, s, H_4). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 177.3 (C_2), 156.0 (C_8), 79.6 (C_9), 59.1 (C_3), 52.0 (C_1), 49.6 (C_6), 42.6 (C_5), 34.8 (C_7), 28.5 (C_{10}), 25.4 (C_4). **IR** (film, $CDCl_3$) ν_{max} = 3335 (N−H, br), 2976 (C−H), 2932 (C−H), 1731 (C=O), 1692 (C=O), 1456, 1392, 1365, 1258, 1218, 1137, 874, 771 cm^{-1}. **HRMS** (ESI$^+$) m/z calcd for $C_{13}H_{27}N_2O_4$ $[M+H]^+$ 275.1965, found 275.1952.

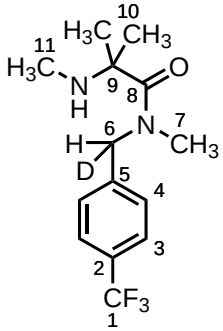
N-Methyl-1-(4-(trifluoromethyl)phenyl)methan-*d*-amine (2.130)



By **GP7**, 4-(trifluoromethyl)benzaldehyde (2.7 mL, 19.8 mmol) was used as the aldehyde (with the modification of $NaBD_4$ instead of $NaBH_4$) that was stirred for 2 h to yield the title compound as a colourless oil (1.28 g, 92%, 99.3% D).

$\boldsymbol{R_f}$ = 0.05 (5% MeOH in DCM). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.57 (2H, d, J 8.0, H_3), 7.43 (2H, d, J 8.0, H_4), 3.78 (1H, 1:1:1 t, J 2.1, H_6), 2.44 (3H, s, H_7), 1.36 (1H, s, NH). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.4 (C_5), 129.4 (q, J 32.3, C_2), 128.4 (C_4), 125.4 (q, J 3.8, C_3), 124.4 (q, J 271.8, C_1), 55.2 (1:1:1 t, J 20.5, C_6), 36.1 (C_7). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −65.5 (3F, s, F_1). **IR** (film, $CDCl_3$) ν_{max} = 3302 (N−H, br), 2939 (C−H), 2851 (C−H), 2795 (C−H), 1322, 1160, 1116, 1105, 1065, 1018, 813 cm^{-1}. **HRMS** (ESI$^+$) m/z calcd for $C_9H_{10}DNF_3$ $[M+H]^+$ 190.0838, found 190.0834.

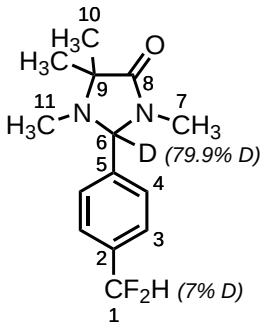
N,2-Dimethyl-2-(methylamino)-*N*-((4-(trifluoromethyl)phenyl)methyl-*d*)propanamide (2.131)



By **GP13**, 3,4,4-trimethyloxazolidine-2,5-dione (**2.74**) (1.38 g, 9.62 mmol) was used as the *N*-carboxyanhydride and *N*-methyl-1-(4-(trifluoromethyl)phenyl) methan-*d*-amine (**2.130**) (1.22 g, 6.41 mmol) was used as the amine that were stirred for 24 h, and purified by flash column chromatography (SiO_2; gradient elution: 0–2% acetone + 1% Et_3N in DCM + 1% Et_3N) to yield the title compound as a colourless oil (763 mg, 41%, 99.4% D).

$\boldsymbol{R_f}$ = 0.45 (80% acetone + 1% Et_3N in DCM + 1% Et_3N). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.56 (2H, d, *J* 8.0, H_3), 7.31 (2H, d, *J* 8.0, H_4), 4.76 (1H, br s, H_6), 3.23 (3H, br s, H_7), 2.29 (3H, s, H_{11}), 1.38 (6H, s, H_{10}), 0.89 (1H, br s, N*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.3 (C_8), 142.4 (C_5), 129.5 (q, *J* 32.3, C_2), 127.8 (C_4), 125.6 (q, *J* 3.8, C_3), 122.9 (q, *J* 271.9, C_1), 61.0 (C_9), 52.9 (1:1:1 t, *J* 21.3, C_6), 36.0 (C_7), 30.4 (C_{11}), 26.4 (C_{10}). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −65.6 (3F, s, F_1). **IR** (film, $CDCl_3$) ν_{max} = 3319 (N−H, br), 2978 (C−H), 2835 (C−H), 1620 (C=O), 1389, 1323, 1161, 1120, 1107, 1065, 1017 cm^{-1}. **HRMS** (ESI$^+$) *m*/*z* calcd for $C_{14}H_{19}DF_3N_2O$ $[M+H]^+$ 290.1585, found 290.1588.

2-(4-(Difluoromethyl)phenyl)-1,3,5,5-tetramethylimidazolidin-4-one-2-*d* (2.132)



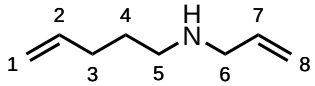
By **GP14**, *N*,2-dimethyl-2-(methylamino)-*N*-((4-(trifluoromethyl)phenyl) methyl-*d*)propanamide (**2.131**) (58 mg, 0.20 mmol) was used as the fluoroalkyl arene, and purified by flash column chromatography (SiO_2; gradient elution: 12–100% EtOAc in pet. ether) to yield the title compound as a pale yellow oil (54 mg, 99%, 79.9% D at C_6 (with approximately 7% D at C_1)).

$\boldsymbol{R_f}$ = 0.30 (50% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.53 (2H, d, *J* 8.0, H_3), 7.48 (2H, d, *J* 8.0, H_4), 6.65 (0.93H, t, *J* 56.4, H_1), 4.61 (0.20H, s, H_6), 2.52 (3H, s, H_7), 2.14 (3H, s, H_{11}), 1.34 (3H, s, H_{10a}), 1.14 (3H, s, H_{10b}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.5 ($C_{8,\text{ deuterated}}$), 176.4 ($C_{8,\text{ non-deuterated}}$), 140.7 (t, *J* 2.1, $C_{5,\text{ non-deuterated}}$), 140.7 (t, *J* 2.1, $C_{5,\text{ deuterated}}$), 135.7 (t, *J* 22.4, $C_{2,\text{ deuterated}}$, $C_{2,\text{ non-deuterated}}$), 129.1 ($C_{4,\text{ non-deuterated}}$), 129.0 ($C_{4,\text{ deuterated}}$), 126.1 (t, *J* 6.0, $C_{3,\text{ deuterated}}$, $C_{3,\text{ non-deuterated}}$), 114.5 (t, *J* 239.0, $C_{1,\text{ deuterated}}$, $C_{1,\text{ non-deuterated}}$), 81.3 ($C_{6,\text{ non-deuterated}}$), 80.8 (1:1:1 t, *J* 22.2, $C_{6,\text{ deuterated}}$), 61.6 ($C_{9,\text{ deuterated}}$, $C_{9,\text{non-deuterated}}$), 30.5 ($C_{11,\text{ non-deuterated}}$), 30.5 ($C_{11,\text{ deuterated}}$), 27.0 ($C_{7,\text{ deuterated}}$, $C_{7,\text{ non-deuterated}}$), 24.2 ($C_{10a,\text{ deuterated}}$, $C_{10a,\text{ non-deuterated}}$), 16.9 ($C_{10b,\text{ deuterated}}$), 16.8 ($C_{10b,\text{ non-deuterated}}$). **^{19}F NMR** (377 MHz, $CDCl_3$) δ −114.0 (1.86F, d, *J* 56.4, F_1),

−114.7 (0.14F, 1:1:1 t, J 8.6, F_1). **IR** (film, $CDCl_3$) ν_{max} = 2972 (C−H), 2799 (C−H), 1697 (C=O), 1428, 1400, 1396, 1283, 1218, 1072, 1056, 1017, 836, 545 cm^{-1}. **HRMS** (ESI^+) m/z calcd for $C_{14}H_{18}DF_2N_2O$ $[M+H]^+$ 270.1523, found 270.1525.

Chapter 3 experimental procedures

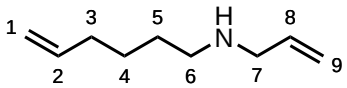
N-Allylpent-4-en-1-amine (3.82c)



By **GP16**, 5-bromo-1-pentene (3.1 mL, 26.2 mmol) was used as the alkyl bromide that was stirred for 49 h to yield the title compound as a yellow oil (2.95 g, 90%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 (1H, ddt, *J* 17.1, 10.2, 6.0, H_7), 5.79 (1H, ddt, *J* 17.1, 10.2, 6.7, H_2), 5.14 (1H, dq, *J* 17.1, 1.6, H_{8cis}), 5.05 (1H, ddt, *J* 10.2, 2.1, 1.3, H_{8trans}), 4.99 (1H, ddt, *J* 17.1, 2.1, 1.6, H_{1cis}), 4.92 (1H, ddt, *J* 10.2, 2.1, 1.3, H_{1trans}), 3.21 (2H, ddd, *J* 6.0, 1.6, 1.3, H_6), 2.62–2.56 (2H, m, H_5), 2.12–2.02 (2H, m, H_3), 1.56 (2H, quint, *J* 7.4, H_4), 1.18 (1H, br s, N*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.5 (C_7), 137.1 (C_2), 115.8 (C_8), 114.7 (C_1), 52.6 (C_6), 48.9 (C_5), 31.6 (C_3), 29.4 (C_4). Data consistent with literature.[348]

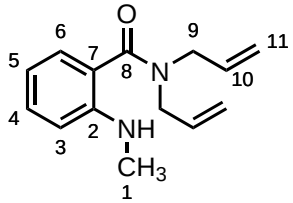
N-Allylhex-5-en-1-amine (3.82d)



By **GP16**, 6-bromo-1-hexene (1.8 mL, 13.4 mmol) was used as the alkyl bromide that was stirred for 45 h to yield the title compound as a yellow oil (1.89 g, quant.).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.91 (1H, ddt, *J* 17.2, 10.3, 6.1, H_8), 5.80 (1H, ddt, *J* 16.9, 10.2, 6.9, H_2), 5.17 (1H, dq, *J* 17.2, 1.4, H_{9cis}), 5.08 (1H, dq, *J* 10.3, 1.4, H_{9trans}), 5.00 (1H, dq, *J* 16.9, 1.4, H_{1cis}), 4.94 (1H, dq, *J* 10.2, 1.4, H_{1trans}), 3.25 (2H, dt, *J* 6.1, 1.4, H_7), 2.61 (2H, dd, *J* 7.7, 6.5, H_6), 2.06 (2H, tdd, *J* 6.9, 5.3, 1.4, H_3), 1.56–1.47 (2H, m, H_5), 1.47–1.37 (2H, m, H_4), 1.30 (1H, br s, N*H*). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.9 (C_2), 137.1 (C_8), 115.9 (C_9), 114.6 (C_1), 52.7 (C_7), 49.4 (C_6), 33.8 (C_3), 29.7 (C_5), 26.8 (C_4). Data consistent with literature.[348]

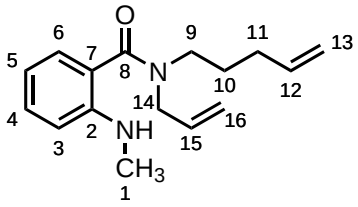
N,*N*-Diallyl-2-(methylamino)benzamide (3.84a)



By **GP17**, diallylamine (1.4 mL, 11.3 mmol) was used as the amine that was stirred for 21 h, and purified by flash column chromatography (SiO_2; gradient elution: 7–60% EtOAc in pet. ether) to yield the title compound as a yellow oil (2.02 g, 88%).

$\boldsymbol{R_f}$ = 0.56 (30% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.25 (1H, ddd, *J* 8.3, 7.5, 1.6, H_4), 7.12 (1H, dd, *J* 7.5, 1.6, H_6), 6.66 (1H, dd, *J* 8.3, 1.0, H_3), 6.62 (1H, td, *J* 7.5, 1.0, H_5), 5.81 (2H, ddt, *J* 16.1, 10.5, 5.5, H_{10}), 5.22 (2H, dq, *J* 10.5, 1.4, $H_{11\,trans}$), 5.17 (2H, dq, *J* 16.1, 1.6, $H_{11\,cis}$), 5.13 (1H, br s, N*H*), 3.99 (4H, br s, H_9), 2.80 (3H, s, H_1). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.7 (C_8), 147.8 (C_2), 133.2 (C_{10}), 131.0 (C_4), 127.1 (C_6), 119.7 (C_7), 117.7 (C_{11}), 115.6 (C_5), 111.0 (C_3), 49.5 (C_9), 30.3 (C_1). **IR** (film, $CDCl_3$) ν_{max} = 3390 (N–H, br), 3079 (C–H), 2982 (C–H), 2916 (C–H), 2813 (C–H), 1622 (C=O), 1597, 1579, 1514, 1458, 1406, 1316, 1242, 924, 749 cm^{-1}. **HRMS** (ESI^+) *m*/*z* calcd for $C_{14}H_{19}N_2O$ $[M+H]^+$ 231.1492, found 231.1499.

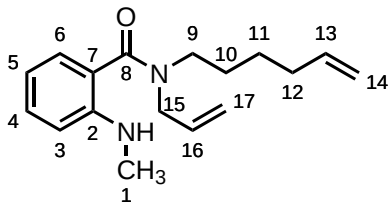
N-Allyl-2-(methylamino)-*N*-(pent-4-en-1-yl)benzamide (3.84c)



By **GP17**, *N*-allylpent-4-en-1-amine (**3.82c**) (2.92 g, 23.3 mmol) was used as the amine that was stirred for 19 h, and purified by flash column chromatography (SiO_2; gradient elution: 7–60% EtOAc in pet. ether) to yield the title compound as a yellow liquid (5.03 g, 92%).

$\boldsymbol{R_f}$ = 0.65 (30% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.25 (1H, ddd, *J* 8.5, 7.4, 1.6, H_4), 7.07 (1H, dd, *J* 7.4, 1.6, H_6), 6.66 (1H, dd, *J* 8.5, 1.1, H_3), 6.64 (1H, td, *J* 7.4, 1.1, H_5), 5.99–5.51 (2H, m, H_{12}, H_{15}), 5.24–5.15 (2H, m, H_{16}), 5.07–4.82 (3H, m, H_{13}, N*H*), 3.98 (2H, br s, H_{14}), 3.38 (2H, br s, H_9), 2.80 (3H, s, H_1), 2.02 (2H, br s, H_{11}), 1.69 (2H, quint, *J* 7.7, H_{10}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.6 (C_8), 147.6 (C_2), 137.7 (C_{15}), 133.7 (C_{12}), 130.8 (C_4), 127.0 (C_6), 120.4 (C_7), 117.6 (C_{16}), 115.7 (C_5), 115.2 (C_{13}), 111.0 (C_3), 50.4 (C_{14}), 45.9 (C_9), 31.1 (C_{11}), 30.4 (C_1), 27.0 (C_{10}). **IR** (film, $CDCl_3$) ν_{max} = 3392 (N–H, br), 2926 (C–H), 1623 (C=O), 1598, 1581, 1515, 1460, 1413, 1316, 1243, 749 cm^{-1}. **HRMS** (ESI^+) *m*/*z* calcd for $C_{16}H_{23}N_2O$ $[M+H]^+$ 259.1805, found 259.1802.

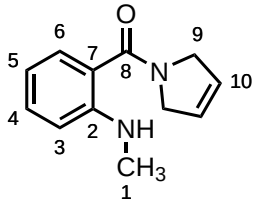
N-Allyl-*N*-(hex-5-en-1-yl)-2-(methylamino)benzamide (3.84d)



By **GP17**, *N*-allylhex-5-en-1-amine (**3.82d**) (1.85 g, 13.3 mmol) was used as the amine that was stirred for 19 h, and purified by flash column chromatography (SiO_2; gradient elution: 7–60% EtOAc in pet. ether) yield the title compound as a pale yellow oil (2.97 g, 89%).

$\boldsymbol{R_f}$ = 0.49 (30% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.28–7.20 (1H, m, H_4), 7.07 (1H, dd, J 7.5, 1.6, H_6), 6.66 (1H, dd, J 8.4, 1.0, H_3), 6.64 (1H, td, J 7.5, 1.0, H_5), 5.87–5.67 (2H, m, H_{13}, H_{16}), 5.26–5.13 (2H, m, H_{17}), 5.03–4.92 (2H, m, H_{14}), 4.90 (1H, br d, J 5.2, NH), 3.98 (2H, br s, H_{15}), 3.37 (2H, br s, H_9), 2.80 (3H, d, J 5.2, H_1), 2.02 (2H, br s, H_{12}), 1.60 (2H, quint, J 7.4, H_{10}), 1.35 (2H, br s, H_{11}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.6 (C_8), 147.6 (C_2), 138.5 (C_{13}), 133.8 (C_{16}), 130.8 (C_4), 127.1 (C_6), 120.5 (C_7), 117.5 (C_{17}), 115.7 (C_5), 114.8 (C_{14}), 111.0 (C_3), 46.7 (C_9, C_{15}), 33.4 (C_{12}), 30.4 (C_1), 27.2 (C_{10}), 26.1 (C_{11}). **IR** (film, $CDCl_3$) ν_{max} = 3392 (N–H, br), 3076 (C–H), 2978 (C–H), 2930 (C–H), 2860 (C–H), 2813 (C–H), 1622 (C=O), 1597, 1580, 1514, 1459, 1412, 1315, 1244, 913, 748 cm^{-1}. **HRMS** (ESI$^+$) m/z calcd for $C_{17}H_{24}N_2NaO$ $[M+Na]^+$ 295.1781, found 295.1775.

(2,5-Dihydro-1*H*-pyrrol-1-yl)(2-(methylamino)phenyl)methanone (3.86a)

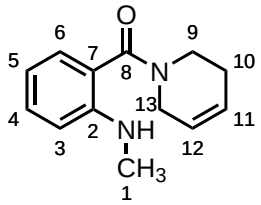


By **GP18**, *N*,*N*-diallyl-2-(methylamino)benzamide (**3.84a**) (1.97 g, 8.55 mmol) was used as the amide that was stirred for 23 h, and purified by flash column chromatography (SiO_2; gradient elution: 7–60% EtOAc in pet. ether) to yield the title compound as a grey solid (1.65 g, 96%).

m.p. = 89–91 °C (DCM). $\boldsymbol{R_f}$ = 0.14 (30% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.27 (1H, ddd, J 8.3, 7.4, 1.5, H_4), 7.23 (1H, dd, J 7.4, 1.5, H_6), 6.68 (1H, d, J 8.3, H_3), 6.66 (1H, td, J 7.4, 1.1, H_5), 5.87 (1H, br s, H_{10a}), 5.74 (1H, br s, H_{10b}), 5.58 (1H, br s, NH), 4.43 (2H, br s, H_{9a}), 4.23 (2H, br s, H_{9b}), 2.81 (3H, s, H_1). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.2 (C_8), 147.7 (C_2), 131.3 (C_4), 127.7 (C_6), 125.8 (C_{10a}), 125.6 (C_{10b}), 120.1 (C_7), 115.6 (C_5), 111.1 (C_3),

55.9 (C_{9a}), 53.3 (C_{9b}), 30.3 (C_1). **IR** (film, $CDCl_3$) ν_{max} = 3379 (N–H, br), 2903 (C–H), 2862 (C–H), 2812 (C–H), 1634 (C=O), 1616, 1579, 1515, 1445, 1427, 1401, 750 cm^{-1}. **HRMS** (ESI^+) m/z calcd for $C_{12}H_{15}N_2O$ $[M+H]^+$ 203.1179, found 203.1185.

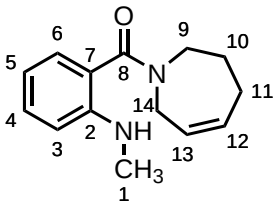
(3,6-Dihydropyridin-1(2*H*-yl)(2-(methylamino)phenyl)methanone (3.86b)



By **GP17**, 1,2,3,6-tetrahydropyridine (700 µL, 7.67 mmol) was used as the amine that was stirred for 45 min to yield the title compound as a yellow oil without further purification (1.39 g, 92%).

***R*$_f$** = 0.33 (30% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.26 (1H, ddd, *J* 8.6, 7.4, 1.7, H_4), 7.07 (1H, dd, *J* 7.4, 1.7, H_6), 6.66 (1H, dd, *J* 8.6, 1.0, H_3), 6.64 (1H, td, *J* 7.4, 1.0, H_5), 5.85 (1H, dtt, *J* 10.0, 4.0, 2.2, H_{11}), 5.66 (1H, d, *J* 10.0, H_{12}), 5.15 (1H, br s, N*H*), 4.07 (2H, br s, H_{13}), 3.63 (2H, br s, H_9), 2.79 (3H, s, H_1), 2.20 (2H, dt, *J* 6.1, 3.0, H_{10}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.7 (C_8), 148.1 (C_2), 131.1 (C_4), 127.6 (C_6), 125.6 (C_{11}), 124.4 (C_{12}), 119.4 (C_7), 115.6 (C_5), 111.0 (C_3), 44.1 (C_9, C_{13}), 30.2 (C_{10}), 25.7 (C_1). **IR** (film, $CDCl_3$) ν_{max} = 3391 (N–H, br), 2919 (C–H), 1659 (C=C), 1617 (C=O), 1579, 1513, 1417, 1244, 749, 726, 654, 630 cm^{-1}. **HRMS** (ESI^+) m/z calcd for $C_{13}H_{16}N_2NaO$ $[M+Na]^+$ 239.1155, found 239.1158.

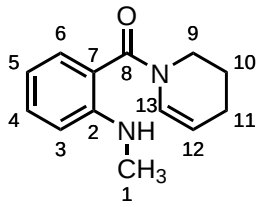
(2-(Methylamino)phenyl)(2,3,4,7-tetrahydro-1*H*-azepin-1-yl)methanone (3.86c)



By **GP18**, *N*-allyl-2-(methylamino)-*N*-(pent-4-en-1-yl)benzamide (**3.84c**) (1.86 g, 7.20 mmol) was used as the amide that was stirred for 48 h, a second portion of Grubbs' first generation catalyst (296 mg, 0.36 mmol, 0.05 eq.) added, the reaction mixture stirred for a further 18 h, and purified by flash column chromatography (SiO_2; gradient elution: 7–60% EtOAc in pet. ether) to yield the title compound as a green-grey solid (1.23 g, 74%).

m.p. = 84–85 °C (DCM). $\boldsymbol{R_f}$ = 0.24 (30% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.24 (1H, ddd, *J* 8.3, 7.4, 1.7, H_4), 7.08 (1H, d, *J* 7.4, H_6), 6.64 (1H, dd, *J* 8.3, 1.0, H_3), 6.62 (1H, td, *J* 7.4, 1.0, H_5), 5.82 (1H, br s, H_{12}), 5.63 (1H, br s, N*H*), 5.07 (1H, br s, H_{13}), 4.00 (2H, br s, H_{14}), 3.69 (2H, br s, H_9), 2.78 (3H, s, H_1), 2.24 (2H, br s, H_{11}), 1.89 (2H, br s, H_{10}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.2 (C_8), 147.8 (C_2), 132.3 (C_{12}), 130.8 (C_4), 127.8 (C_{13}), 127.6 (C_6), 120.0 (C_7), 115.5 (C_5), 110.8 (C_3), 48.5 (C_{14}), 46.7 (C_9), 30.2 (C_1), 26.8 (C_{11}), 26.4 (C_{10}). **IR** (film, $CDCl_3$) ν_{max} = 3395 (N–H, br), 2925 (C–H), 2853 (C–H), 1623 (C=O), 1595, 1582, 1515, 1460, 1416, 750 cm^{-1}. **HRMS** (ESI$^+$) *m*/*z* calcd for $C_{14}H_{19}N_2O$ $[M+H]^+$ 231.1492, found 231.1487.

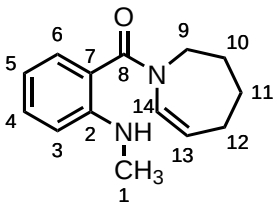
(3,4-Dihydropyridin-1(2*H*-yl)(2-(methylamino)phenyl)methanone (3.74b)



By **GP19**, (3,6-dihydropyridin-1(2*H*-yl)(2-(methylamino)phenyl)methanone (**3.86b**) (1.34 g, 6.20 mmol) was used as the amide that was stirred for 15 h, and purified by flash column chromatography (SiO_2; gradient elution: 2–20% EtOAc in pet. ether) to yield the title compound as an off-white solid (971 mg, 72%).

m.p. = 90–92 °C (DCM). $\boldsymbol{R_f}$ = 0.25 (10% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.27 (1H, ddd, *J* 8.6, 7.3, 1.6, H_4), 7.13 (1H, dd, *J* 7.3, 1.6, H_6), 6.78–6.65 (2H, m, H_3, H_{13}), 6.63 (1H, td, *J* 7.3, 1.0, H_5), 5.43 (1H, d, *J* 5.1, N*H*), 4.93 (1H, br s, H_{12}), 3.88–3.61 (2H, m, H_9), 2.80 (3H, d, *J* 5.1, H_1), 2.11 (2H, tdd, *J* 6.1, 3.8, 2.0, H_{11}), 1.90 (2H, quint, *J* 6.1, H_{10}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.4 (C_8), 148.9 (C_2), 131.7 (C_4), 129.5 (C_6), 127.3 (C_{13}), 117.7 (C_7), 115.2 (C_5), 111.0 (C_3), 107.9 (C_{12}), 41.5 (C_9), 30.1 (C_1), 22.1 (C_{11}), 22.1 (C_{10}). **IR** (film, $CDCl_3$) ν_{max} = 3398 (N–H, br), 2926 (C–H), 1625 (C=O), 1595, 1579, 1515, 1404, 1374, 1252, 993, 751 cm^{-1}. **HRMS** (ESI$^+$) *m*/*z* calcd for $C_{13}H_{16}N_2NaO$ $[M+Na]^+$ 239.1155, found 239.1161.

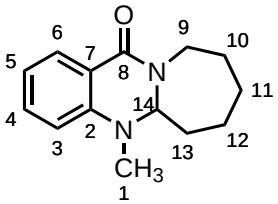
(2-(Methylamino)phenyl)(2,3,4,5-tetrahydro-1*H*-azepin-1-yl)methanone (3.74c)



By **GP19**, (2-(methylamino)phenyl)(2,3,4,7-tetrahydro-1*H*-azepin-1-yl) methanone (**3.86c**) (1.15 g, 4.99 mmol) was used as the amide that was stirred for 23 h, and purified by flash column chromatography (SiO_2; gradient elution: 0–20% EtOAc in pet. ether) to yield the title compound as a beige solid (1.00 g, 87%).

m.p. = 53–55 °C (DCM). $\boldsymbol{R_f}$ = 0.26 (10% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.26 (1H, td, *J* 8.3, 7.6, 1.6, H_4), 7.20 (1H, dd, *J* 7.6, 1.6, H_6), 6.65 (1H, dd, *J* 8.3, 1.0, H_3), 6.60 (1H, td, *J* 7.6, 1.0, H_5), 6.34 (1H, br s, H_{14}), 5.60 (1H, br s, N*H*), 5.12–4.99 (1H, m, H_{13}), 3.90 (2H, t, *J* 6.0, H_9), 2.81 (3H, d, *J* 2.8, H_1), 2.34–2.19 (2H, m, H_{12}), 1.91–1.84 (2H, m, H_{10}), 1.84–1.75 (2H, m, H_{11}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.4 (C_8), 148.7 (C_2), 132.9 (C_{14}), 131.7 (C_4), 129.9 (C_6), 118.7 (C_7), 116.4 (C_{13}), 114.9 (C_5), 110.8 (C_3), 46.5 (C_9), 30.1 (C_1), 28.3 (C_{10}), 26.7 (C_{12}), 24.9 (C_{11}). **IR** (film, $CDCl_3$) ν_{max} = 3390 (N–H, br), 2925 (C–H), 1624 (C=O), 1596, 1578, 1515, 1385, 1313, 747 cm^{-1}. **HRMS** (ESI$^+$) *m*/*z* calcd for $C_{14}H_{18}N_2NaO$ $[M+Na]^+$ 253.1311, found 253.1321.

5-Methyl-5a,6,7,8,9,10-hexahydroazepino[2,1-*b*]quinazolin-12(5*H*)-one (3.76c)

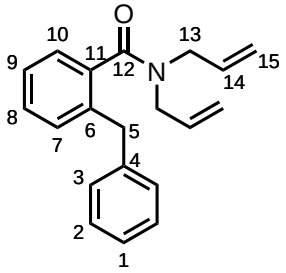


In a microwave vial, (2-(methylamino)phenyl)(2,3,4,5-tetrahydro-1*H*-azepin-1-yl)methanone (**3.74c**) (46 mg, 0.20 mmol, 1.0 eq.) was dissolved in anhydrous THF (1.0 mL). The reaction mixture was cooled to 0 °C, and NaHMDS (220 µL, 1.0 M in THF, 0.22 mmol, 1.1 eq.) added dropwise. The vial was sealed, the reaction mixture stirred at 100 °C under microwave irradiation for 2 h, quenched by the addition of MeOH (10 mL), and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2; gradient elution: 10–60% EtOAc in pet. ether) to yield the title compound as a yellow dry film (31 mg, 68%).

$\boldsymbol{R_f}$ = 0.21 (30% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.94 (1H, dd, *J* 7.5, 1.7, H_6), 7.35 (1H, td, *J* 8.2, 7.5, 1.7, H_4), 6.82 (1H, td, *J* 7.5, 1.0, H_5),

6.57 (1H, dd, J 8.2, 1.0, H_3), 4.56 (1H, ddd, J 14.4, 7.4, 5.4, H_{9a}), 4.51 (1H, dd, J 10.2, 4.1, H_{14}), 2.90 (3H, s, H_1), 2.89–2.82 (1H, m, H_{9b}), 2.20–2.07 (1H, m, H_{10a}), 1.90–1.55 (4H, m, H_{10b}, H_{12a}, H_{13}), 1.52–1.33 (3H, m, H_{11}, H_{12b}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.5 (C_8), 146.8 (C_2), 133.5 (C_4), 128.8 (C_6), 118.1 (C_5), 117.1 (C_7), 112.1 (C_3), 78.1 (C_{14}), 44.8 (C_9), 35.8 (C_1), 30.1 (C_{13}), 27.5 (C_{10}), 25.2 (C_{12}), 25.2 (C_{11}). **IR** (film, $CDCl_3$) ν_{max} = 2926 (C–H), 2858 (C–H), 1644 (C=O), 1606, 1494, 1453, 755 cm^{-1}. **HRMS** (ESI$^+$) m/z calcd for $C_{14}H_{19}N_2O$ $[M+H]^+$ 231.1492, found 231.1495.

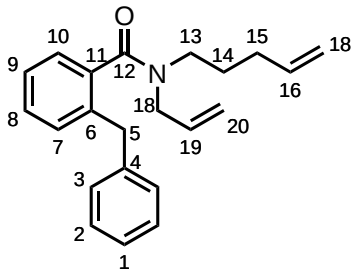
N,*N*-Diallyl-2-benzylbenzamide (3.89a)



By **GP2**, the acid chloride of 2-benzylbenzoic acid (1.06 g, 4.99 mmol) was made by stirring with oxalyl chloride for 13 h. Diallylamine (740 µL, 5.99 mmol) was used as the general amine that was stirred with the acid chloride intermediate for 2.5 h, and purified by flash column chromatography (SiO_2; gradient elution: 7–60% Et_2O in pet. ether) to yield the title compound as a pale yellow oil (1.37 g, 97%).

$\boldsymbol{R_f}$ = 0.20 (30% Et_2O in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32–7.15 (9H, m, H_{Ar}), 5.77 (1H, ddt, J 16.7, 10.4, 6.3, H_{14a}), 5.49 (1H, ddt, J 17.1, 10.2, 5.7, H_{14b}), 5.21–5.11 (3H, m, 2 × $H_{15trans}$, H_{15cis}), 5.05 (1H, dq, J 17.1, 1.6, H_{15cis}), 4.33 (1H, br s, H_{13a}), 4.07 (1H, br s, H_{5a}), 4.01 (1H, br s, H_{5b}), 3.83 (1H, br s, H_{13b}), 3.51 (1H, br s, H_{13c}), 3.34 (1H, br s, H_{13d}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.2 (C_{12}), 140.2 (C_4), 138.0 (C_6), 136.4 (C_{11}), 133.1 (C_{14a}), 132.9 (C_{14b}), 130.7 (C_8), 129.4 (C_2), 129.2 (C_9), 128.5 (C_3), 126.3 (C_{Ar}), 126.2 (C_{Ar}), 126.0 (C_{Ar}), 118.2 (C_{15a}), 118.0 (C_{15b}), 50.5 (C_{13a}), 46.5 (C_{13b}), 38.9 (C_5). **IR** (film, $CDCl_3$) ν_{max} = 3062 (C–H), 3025 (C–H), 2977 (C–H), 2918 (C–H), 1633 (C=O), 1600, 1494, 1453, 1410, 1257, 925, 776, 740, 699 cm^{-1}. **HRMS** (ESI$^+$) m/z calcd for $C_{20}H_{22}NO$ $[M+H]^+$ 292.1696, found 292.1707.

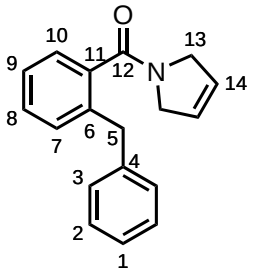
N-Allyl-2-benzyl-*N*-(pent-4-en-1-yl)benzamide (3.89c)



By **GP2**, the acid chloride of 2-benzylbenzoic acid (2.12 g, 9.98 mmol) was made by stirring with oxalyl chloride for 20 h. *N*-Allylpent-4-en-1-amine (**3.82c**) (1.50 g, 12.0 mmol) was used as the general amine that was stirred with the acid chloride intermediate for 4 h, and purified by flash column chromatography (SiO_2; gradient elution: 7–60% Et_2O in pet. ether) to yield the title compound as a pale yellow oil (2.83 g, 89%).

$\boldsymbol{R_f}$ = 0.19 (30% Et_2O in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers in an approximate 60:40 ratio) δ 7.36–7.10 (9H^{maj} + 9H^{min}, m, 9 × H_{Ar}), 5.90–5.76 (1H^{maj} + 1H^{min}, m, $H_{16}{}^{maj}$, $H_{19}{}^{min}$), 5.62–5.42 (1H^{maj} + 1H^{min}, m, $H_{19}{}^{maj}$, $H_{16}{}^{min}$), 5.25–5.16 (2H^{min}, m, H_{20}), 5.11 (1H^{maj}, dq, J 10.2, 1.4, $H_{20\,trans}$), 5.09–5.01 (2H^{maj}, m, H_{17a}, $H_{20\,cis}$), 5.01–4.97 (1H^{maj}, m, H_{17b}), 4.89–4.81 (2H^{min}, m, H_{17}), 4.33–4.13 (1H^{min}, m, H_{18a}), 4.12–3.90 (2H^{maj} + 3H^{min}, m, $H_5{}^{maj}$, $H_5{}^{min}$, $H_{18b}{}^{min}$), 3.56 (1H^{maj}, br s, H_{13a}), 3.53 (1H^{maj}, br s, H_{18a}), 3.29 (1H^{maj}, br s, H_{13b}), 3.26 (1H^{maj}, br s, H_{18b}), 2.87 (1H^{min}, br s, H_{13a}), 2.73 (1H^{min}, br s, H_{13b}), 2.13–2.04 (2H^{maj}, m, H_{15}), 1.83–1.74 (2H^{min}, m, H_{15}), 1.73–1.56 (2H^{maj}, m, H_{14}), 1.52–1.39 (2H^{min}, m, H_{14}). **^{13}C NMR** (101 MHz, $CDCl_3$, mixture of rotamers in an approximate 60:40 ratio) δ 171.2 ($C_{12}{}^{min}$), 171.1 ($C_{12}{}^{maj}$), 140.2 ($C_4{}^{maj}$), 140.1 ($C_4{}^{min}$), 138.0 ($C_{16}{}^{maj}$), 137.8 ($C_6{}^{maj}$), 137.7 ($C_6{}^{min}$), 137.2 ($C_{16}{}^{min}$), 136.8 ($C_{11}{}^{maj}$), 136.7 ($C_{11}{}^{min}$), 133.5 ($C_{19}{}^{min}$), 133.5 ($C_{19}{}^{maj}$), 130.7 ($C_8{}^{maj}$), 130.6 ($C_8{}^{min}$), 129.4 ($C_2{}^{min}$), 129.3 ($C_2{}^{maj}$), 129.0 ($C_9{}^{maj}$), 129.0 ($C_9{}^{min}$), 128.5 ($C_3{}^{maj}$), 128.5 ($C_3{}^{min}$), 126.3 ($C_{Ar}{}^{min}$), 126.3 ($C_{Ar}{}^{maj}$), 126.3 ($C_{Ar}{}^{min}$), 126.2 ($C_{Ar}{}^{maj}$), 126.1 ($C_{Ar}{}^{min}$), 126.0 ($C_{Ar}{}^{maj}$), 117.8 ($C_{20}{}^{maj}$, $C_{20}{}^{min}$), 115.3 ($C_{17}{}^{min}$), 115.1 ($C_{17}{}^{maj}$), 51.6 ($C_{18}{}^{maj}$), 47.7 ($C_{13}{}^{min}$), 47.1 ($C_{18}{}^{min}$), 44.1 ($C_{13}{}^{maj}$), 38.9 ($C_5{}^{maj}$, $C_5{}^{min}$), 31.4 ($C_{15}{}^{maj}$), 30.8 ($C_{15}{}^{min}$), 27.3 ($C_{14}{}^{min}$), 26.4 ($C_{14}{}^{maj}$). **IR** (film, $CDCl_3$) ν_{max} = 3062 (C–H), 3026 (C–H), 2975 (C–H), 2927 (C–H), 1632 (C=O), 1600, 1494, 1454, 1415, 1257, 915, 742, 699 cm^{-1}. **HRMS** (ESI$^+$) m/z calcd for $C_{22}H_{26}NO$ [M+H]$^+$ 320.2009, found 320.2022.

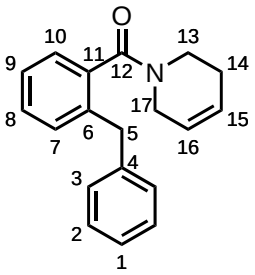
(2-Benzylphenyl)(2,5-dihydro-1*H*-pyrrol-1-yl)methanone (3.91a)



By **GP18**, *N*,*N*-diallyl-2-benzylbenzamide (**3.89a**) (1.35 g, 4.63 mmol) was used as the amide that was stirred for 21 h, and purified by flash column chromatography (SiO_2; gradient elution: 7–60% EtOAc in pet. ether) to yield the title compound as a brown oil (988 mg, 81%).

$\boldsymbol{R_f}$ = 0.21 (30% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37–7.06 (9H, m, H_{Ar}), 5.78–5.72 (1H, m, H_{14a}), 5.49–5.44 (1H, m, H_{14b}), 4.34–4.26 (2H, m, H_{13a}), 4.05 (2H, s, H_5), 3.46 (2H, br s, H_{13b}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.8 (C_{12}), 140.2 (C_4), 138.2 (C_6), 137.3 (C_{11}), 130.6 (C_8), 129.2 (C_2, C_9), 128.4 (C_3), 126.5 (C_7), 126.2 (C_{Ar}), 126.2 (C_{Ar}), 125.4 (C_{14a}), 125.3 (C_{14b}), 54.9 (C_{13a}), 52.5 (C_{13b}), 39.3 (C_5). **IR** (film, $CDCl_3$) ν_{max} = 2861 (C–H), 1639 (C=O), 1620, 1598, 1417, 742, 700 cm^{-1}. **HRMS** (ESI^+) m/z calcd for $C_{18}H_{18}NO$ $[M+H]^+$ 264.1383, found 264.1372.

(2-Benzylphenyl)(3,6-dihydropyridin-1(2*H*)-yl)methanone (3.91b)

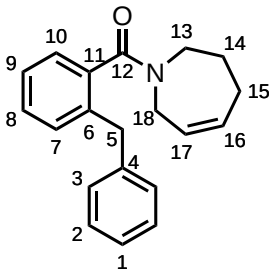


By **GP2**, the acid chloride of 2-benzylbenzoic acid (1.06 g, 4.99 mmol) was made by stirring with oxalyl chloride for 20 h. 1,2,3,6-Tetrahydropyridine hydrochloride (718 mg, 6.00 mmol) was used as the general amine that was stirred with the acid chloride intermediate for 22 h (with the modification of 3.0 eq. of Et_3N instead of 2.0 eq.), and purified by flash column chromatography (SiO_2; gradient elution: 7–60% EtOAc in pet. ether) to yield the title compound as a colourless oil (1.22 g, 88%).

$\boldsymbol{R_f}$ = 0.34 (30% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers in an approximate 65:35 ratio) δ 7.35–7.12 ($9H^{maj}$ + $9H^{min}$, m, 9 × H_{Ar}), 5.81–5.65 ($2H^{maj}$ + $1H^{min}$, m, $H_{15}{}^{maj}$, $H_{16}{}^{maj}$, $H_{16}{}^{min}$), 5.38–5.30 ($1H^{min}$, m, H_{15}), 4.45–4.33 ($1H^{maj}$, m, H_{17a}), 4.15 ($1H^{maj}$, d, J 15.0, H_{5a}), 4.13–4.06 ($1H^{min}$, m,

H_{13a}), 3.93 (1H^{maj}, d, J 15.0, H_{5b}), 3.90–3.83 (2H^{min}, m, H_5), 3.82–3.73 (1H^{maj}, m, H_{17b}), 3.72–3.63 (1H^{min}, m, H_{13b}), 3.59 (1H^{min}, d, J 17.9, H_{17a}), 3.13 (1H^{min}, d, J 17.9, H_{17b}), 3.06 (1H^{maj}, dt, J 13.2, 4.6, H_{13a}), 2.49 (1H^{maj}, ddd, J 13.2, 9.0, 4.6, H_{13b}), 2.23–2.14 (2H^{min}, m, H_{14}), 2.07–1.94 (1H^{maj}, m, H_{14a}), 1.67 (1H^{maj}, d, J 17.1, H_{14b}). **^{13}C NMR** (101 MHz, $CDCl_3$, mixture of rotamers in an approximate 65:35 ratio) δ 170.3 ($C_{12}{}^{maj}$), 169.9 ($C_{12}{}^{min}$), 140.3 ($C_4{}^{maj}$), 140.2 ($C_4{}^{min}$), 138.5 ($C_6{}^{maj}$), 138.1 ($C_6{}^{min}$), 136.7 ($C_{11}{}^{maj}$), 136.6 ($C_{11}{}^{min}$), 130.8 ($C_{Ar}{}^{maj}$), 130.7 ($C_{Ar}{}^{min}$), 129.3 ($C_2{}^{maj}$), 129.2 ($C_2{}^{min}$), 129.1 ($C_{Ar}{}^{maj}$, $C_{Ar}{}^{maj}$), 128.5 ($C_3{}^{min}$), 128.4 ($C_3{}^{maj}$), 126.4 ($C_{Ar}{}^{maj}$), 126.4 ($C_{Ar}{}^{min}$), 126.3 ($C_{Ar}{}^{maj}$), 126.2 ($C_{Ar}{}^{min}$), 126.2 ($C_{16}{}^{min}$), 126.1 ($C_{Ar}{}^{min}$), 125.9 ($C_1{}^{maj}$), 125.0 ($C_{16}{}^{maj}$), 124.2 ($C_{15}{}^{maj}$), 123.5 ($C_{15}{}^{min}$), 46.6 ($C_{17}{}^{min}$), 43.5 ($C_{13}{}^{maj}$), 41.6 ($C_{17}{}^{maj}$), 39.2 ($C_5{}^{maj}$), 38.9 ($C_5{}^{min}$), 38.5 ($C_{13}{}^{min}$), 25.4 ($C_{14}{}^{maj}$), 25.0 ($C_{14}{}^{min}$). **IR** (film, $CDCl_3$) ν_{max} = 3028 (C–H), 2921 (C–H), 2839 (C–H), 1660 (C=C), 1626 (C=O), 1598, 1429, 1258, 770, 742, 700, 655 cm^{-1}. **HRMS** (ESI$^+$) m/z calcd for $C_{19}H_{19}NNaO$ $[M+Na]^+$ 300.1359, found 300.1366.

(2-Benzylphenyl)(2,3,4,7-tetrahydro-1*H*-azepin-1-yl)methanone (3.91c)

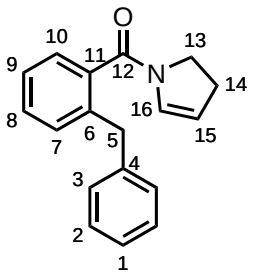


By **GP18**, *N*-allyl-2-benzyl-*N*-(pent-4-en-1-yl)benzamide (**3.89c**) (1.53 g, 4.79 mmol) was used as the amide that was stirred for 48 h, and purified by flash column chromatography (SiO_2; gradient elution: 7–60% EtOAc in pet. ether) to yield the title compound as a green-brown oil (1.19 g, 85%).

***R*$_f$** = 0.35 (30% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers in an approximate 60:40 ratio) δ 7.32–7.11 (9H^{maj} + 9H^{min}, m, 9 × H_{Ar}), 5.88 (1H^{min}, dtt, J 9.8, 4.9, 1.4, H_{17}), 5.82–5.74 (1H^{maj} + 1H^{min}, m, H_{16}), 5.33 (1H^{maj}, dtt, J 11.1, 4.7, 1.7, H_{17}), 4.44 (1H^{min}, d, J 16.2, H_{18a}), 4.25–4.15 (2H^{maj}, m, H_{13}), 4.11 (1H^{maj}, d, J 15.0, H_{5a}), 4.03 (1H^{min}, br s, H_{5a}), 3.98 (1H^{min}, br s, H_{5b}), 3.94 (1H^{maj}, d, J 15.0, H_{5b}), 3.83 (1H^{min}, d, J 16.2, H_{18b}), 3.38–3.11 (2H^{maj} + 1H^{min}, m, $H_{18}{}^{maj}$, $H_{13a}{}^{min}$), 2.89–2.76 (1H^{min}, m, $H_{13b}{}^{min}$), 2.35–1.99 (2H, m, H_{15}), 1.96–1.85 (2H^{maj}, m, H_{14}), 1.72–1.45 (2H^{min}, m, H_{14}). **^{13}C NMR** (101 MHz, $CDCl_3$, mixture of rotamers in an approximate 60:40 ratio) δ 170.9 ($C_{12}{}^{maj}$), 170.3 ($C_{12}{}^{min}$), 140.2 ($C_4{}^{maj}$), 140.2 ($C_4{}^{min}$), 138.0 ($C_6{}^{maj}$), 137.9 ($C_6{}^{min}$), 137.0 ($C_{11}{}^{maj}$), 136.9 ($C_{11}{}^{min}$), 132.9 ($C_{16}{}^{maj}$), 132.2 ($C_{16}{}^{min}$), 130.6 ($C_8{}^{min}$), 130.4 ($C_8{}^{maj}$), 129.4 ($C_2{}^{maj}$), 129.4 ($C_2{}^{min}$), 128.9 ($C_9{}^{maj}$), 128.9 ($C_9{}^{min}$), 128.4 ($C_3{}^{min}$), 128.3 ($C_3{}^{maj}$), 128.1 ($C_{17}{}^{min}$), 127.2 ($C_{17}{}^{maj}$), 126.3 ($C_{Ar}{}^{min}$), 126.3 ($C_{Ar}{}^{min}$), 126.2 (C_1), 126.1 ($C_{Ar}{}^{maj}$), 126.1 ($C_{Ar}{}^{maj}$), 50.7 ($C_{13}{}^{min}$), 47.6 ($C_{18}{}^{maj}$), 46.1 ($C_{13}{}^{maj}$), 43.1 ($C_{18}{}^{min}$), 39.2 ($C_5{}^{maj}$), 39.0 ($C_5{}^{min}$), 27.3 ($C_{15}{}^{maj}$), 27.0 ($C_{14}{}^{min}$),

26.9 ($C_{15}{}^{\text{min}}$), 26.1 ($C_{14}{}^{\text{maj}}$). **IR** (film, $CDCl_3$) ν_{max} = 3060 (C–H), 3023 (C–H), 2931 (C–H), 2866 (C–H), 1628 (C=O), 1599, 1494, 1454, 1424, 1295, 1263, 1146, 774, 741, 700 cm^{-1}. **HRMS** (ESI^+) m/z calcd for $C_{20}H_{22}NO$ $[M+H]^+$ 292.1696, found 292.1710.

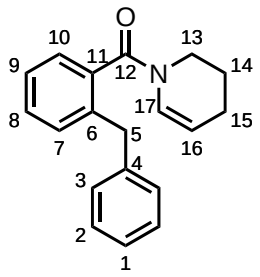
(2-Benzylphenyl)(2,3-dihydro-1*H*-pyrrol-1-yl)methanone (3.92a)



By **GP19**, (2-benzylphenyl)(2,5-dihydro-1*H*-pyrrol-1-yl)methanone (**3.91a**) (957 mg, 3.63 mmol) was used as the amide that was stirred for 20 h, and purified by flash column chromatography (SiO_2; gradient elution: 7–60% EtOAc in pet. ether) to yield the title compound as a yellow oil (725 mg, 76%).

$\boldsymbol{R_f}$ = 0.33 (30% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers in an approximate 80:20 ratio) δ 7.35–7.10 ($9H^{\text{maj}}$ + $9H^{\text{min}}$, m, 9 × H_{Ar}), 7.02 ($1H^{\text{min}}$, dt, J 4.4, 2.2, H_{16}), 5.85 ($1H^{\text{maj}}$, dt, J 4.4, 2.2, H_{16}), 5.25 ($1H^{\text{min}}$, dt, J 4.4, 2.5, H_{15}), 4.97 ($1H^{\text{maj}}$, dt, J 4.4, 2.5, H_{15}), 4.07 ($2H^{\text{min}}$, s, H_5), 4.03 ($2H^{\text{maj}}$, s, H_5), 3.89 ($2H^{\text{maj}}$, t, J 8.8, H_{13}), 2.96 ($2H^{\text{min}}$, t, J 8.6, H_{13}), 2.60 ($2H^{\text{maj}}$, tt, J 8.8, 2.5, H_{14}), 2.33 ($2H^{\text{min}}$, tt, J 8.6, 2.5, H_{14}). **^{13}C NMR** (101 MHz, $CDCl_3$, mixture of rotamers in an approximate 80:20 ratio) δ 166.9 ($C_{12}{}^{\text{maj}}$), 166.8 ($C_{12}{}^{\text{min}}$), 140.3 ($C_4{}^{\text{maj}}$), 140.2 ($C_4{}^{\text{min}}$), 138.8 ($C_6{}^{\text{maj}}$), 138.5 ($C_6{}^{\text{min}}$), 136.9 ($C_{11}{}^{\text{min}}$), 136.3 ($C_{11}{}^{\text{maj}}$), 130.7 ($C_8{}^{\text{maj}}$), 130.6 ($C_8{}^{\text{min}}$), 130.1 ($C_{16}{}^{\text{min}}$), 129.6 ($C_9{}^{\text{maj}}$), 129.4 ($C_2{}^{\text{min}}$, $C_9{}^{\text{min}}$), 129.3 ($C_2{}^{\text{maj}}$), 128.9 ($C_{16}{}^{\text{min}}$), 128.4 ($C_3{}^{\text{maj}}$), 128.4 ($C_3{}^{\text{min}}$), 127.0 ($C_{10}{}^{\text{maj}}$), 126.5 ($C_7{}^{\text{min}}$), 126.4 ($C_7{}^{\text{maj}}$), 126.2 ($C_{\text{Ar}}{}^{\text{min}}$), 126.2 ($C_1{}^{\text{maj}}$), 126.2 ($C_{\text{Ar}}{}^{\text{min}}$), 112.5 ($C_{15}{}^{\text{min}}$), 111.5 ($C_{15}{}^{\text{maj}}$), 47.2 ($C_{13}{}^{\text{min}}$), 44.7 ($C_{13}{}^{\text{maj}}$), 39.3 ($C_5{}^{\text{min}}$), 39.2 ($C_5{}^{\text{maj}}$), 29.8 ($C_{14}{}^{\text{min}}$), 28.6 ($C_{14}{}^{\text{maj}}$). **IR** (film, $CDCl_3$) ν_{max} = 3060 (C–H), 3027 (C–H), 2921 (C–H), 2858 (C–H), 1637 (C=O), 1615, 1494, 1416 cm^{-1}. **HRMS** (ESI^+) m/z calcd for $C_{18}H_{18}NO$ $[M+H]^+$ 264.1383, found 264.1387.

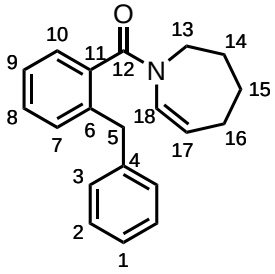
(2-Benzylphenyl)(3,4-dihydropyridin-1(2*H*)-yl)methanone (3.92b)



By **GP19**, (2-benzylphenyl)(3,6-dihydropyridin-1(2*H*)-yl)methanone (**3.91b**) (1.00 g, 3.60 mmol) was used as the amide that was stirred for 20 h, and purified by flash column chromatography (SiO_2; gradient elution: 10–30% Et_2O in pet. ether) to yield the title compound as a yellow oil (697 mg, 70%).

$\boldsymbol{R_f}$ = 0.32 (30% Et_2O in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers in an approximate 70:30 ratio) δ 7.34–7.12 ($9H^{maj}$ + $10H^{min}$, m, 9 × H_{Ar}, $H_{17}{}^{min}$), 6.01 ($1H^{maj}$, dt, *J* 8.4, 2.0, H_{17}), 5.17 ($1H^{min}$, dt, *J* 8.1, 3.9, H_{16}), 4.69 ($1H^{maj}$, dt, *J* 8.1, 3.9, H_{16}), 4.23–4.04 ($2H^{min}$, m, H_5), 4.06–3.92 ($2H^{maj}$, m, H_5), 3.92–3.79 ($1H^{maj}$, m, H_{13a}), 3.78–3.60 ($1H^{maj}$, m, H_{13b}), 3.22–3.09 ($1H^{min}$, m, H_{13a}), 2.85–2.69 ($1H^{min}$, m, H_{13b}), 2.07–1.99 ($2H^{maj}$, m, H_{15}), 1.99–1.91 ($2H^{min}$, m, H_{15}), 1.89–1.79 ($2H^{maj}$, m, H_{14}), 1.62–1.50 ($1H^{min}$, m, H_{14a}), 1.32–1.17 ($1H^{min}$, m, H_{14b}). **^{13}C NMR** (101 MHz, $CDCl_3$, mixture of rotamers in an approximate 70:30 ratio) δ 169.1 ($C_{12}{}^{maj}$), 168.3 ($C_{12}{}^{min}$), 140.1 ($C_4{}^{min}$), 139.9 ($C_4{}^{maj}$), 138.6 ($C_6{}^{maj}$, $C_6{}^{min}$), 136.0 ($C_{11}{}^{min}$), 135.6 ($C_{11}{}^{maj}$), 130.7 ($C_{Ar}{}^{min}$), 130.5 ($C_{Ar}{}^{maj}$), 129.4 ($C_{Ar}{}^{maj}$), 129.3 ($C_2{}^{maj}$), 129.3 ($C_{Ar}{}^{min}$), 129.3 ($C_{Ar}{}^{maj}$), 128.5 (2 × $C_{Ar}{}^{min}$), 128.5 ($C_3{}^{maj}$), 127.1 ($C_{Ar}{}^{maj}$), 126.6 ($C_{17}{}^{maj}$), 126.4 ($C_{Ar}{}^{maj}$), 126.3 (2 × $C_{Ar}{}^{min}$), 126.2 (2 × $C_{Ar}{}^{min}$), 126.2 ($C_{Ar}{}^{min}$), 123.9 ($C_{17}{}^{min}$), 110.6 ($C_{16}{}^{min}$), 107.8 ($C_{16}{}^{maj}$), 45.7 ($C_{13}{}^{min}$), 40.4 ($C_{13}{}^{maj}$), 39.0 ($C_5{}^{maj}$, $C_5{}^{min}$), 22.1 ($C_{15}{}^{min}$), 21.9 ($C_{15}{}^{maj}$), 21.8 ($C_{14}{}^{min}$), 21.4 ($C_{14}{}^{maj}$). **IR** (film, $CDCl_3$) ν_{max} = 2927 (C–H), 1632 (C=O), 1600, 1407, 1377, 1357, 1258, 993, 742, 699 cm^{-1}. **HRMS** (ESI^+) *m*/*z* calcd for $C_{19}H_{19}NNaO$ $[M+Na]^+$ 300.1359, found 300.1357.

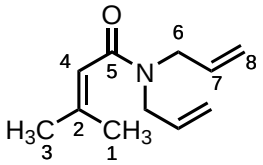
(2-Benzylphenyl)(2,3,4,5-tetrahydro-1*H*-azepin-1-yl)methanone (3.92c)



By **GP19**, (2-benzylphenyl)(2,3,4,7-tetrahydro-1*H*-azepin-1-yl)methanone (**3.91c**) (1.15 g, 3.95 mmol) was used as the amide that was stirred at reflux for 22 h, and purified by flash column chromatography (SiO_2; gradient elution: 7–60% Et_2O in pet. ether) to yield the title compound as a yellow oil (877 mg, 76%).

$\boldsymbol{R_f}$ = 0.28 (30% Et_2O in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers in an approximate 70:30 ratio) δ 7.37–7.11 ($9H^{maj}$ + $9H^{min}$, m, 9 × H_{Ar}), 6.90 ($1H^{min}$, dt, *J* 9.1, 1.7, H_{18}), 5.70 ($1H^{maj}$, dt, *J* 8.7, 1.6, H_{18}), 5.29 ($1H^{min}$, dt, *J* 9.1, 5.4, H_{17}), 4.86 ($1H^{maj}$, dt, *J* 8.7, 5.5, H_{17}), 4.23–3.93 ($2H^{maj}$ + $2H^{min}$, m, H_5), 3.86 ($2H^{maj}$, br s, H_{13}), 3.06 ($1H^{min}$, br s, H_{13a}), 2.80 ($1H^{min}$, br s, H_{13b}), 2.22–2.13 ($2H^{maj}$ + $2H^{min}$, m, H_{16}), 1.89 ($2H^{maj}$, quint, *J* 6.2, H_{14}), 1.80–1.66 ($2H^{maj}$ + $1H^{min}$, m, $H_{15}{}^{maj}$, $H_{15a}{}^{min}$), 1.58 ($2H^{min}$, br s, $H_{15b}{}^{min}$, $H_{14a}{}^{min}$), 1.38 ($1H^{min}$, br s, $H_{14b}{}^{min}$). **^{13}C NMR** (101 MHz, $CDCl_3$, mixture of rotamers in an approximate 70:30 ratio) δ 170.5 ($C_{12}{}^{min}$), 170.1 ($C_{12}{}^{maj}$), 140.2 ($C_4{}^{maj}$), 139.9 ($C_4{}^{min}$), 138.4 ($C_6{}^{maj}$), 138.1 ($C_6{}^{min}$), 136.7 ($C_{11}{}^{maj}$), 136.3 ($C_{11}{}^{min}$), 131.7 ($C_{18}{}^{maj}$), 130.6 ($C_8{}^{min}$), 130.3 ($C_8{}^{maj}$), 129.6 ($C_{18}{}^{min}$), 129.4 ($C_2{}^{maj}$), 129.4 ($C_2{}^{min}$), 129.3 ($C_9{}^{maj}$), 129.2 ($C_9{}^{min}$), 128.5 ($C_3{}^{min}$), 128.4 ($C_3{}^{maj}$), 127.2 ($C_{10}{}^{maj}$), 126.3 ($C_{Ar}{}^{min}$), 126.3 ($C_7{}^{maj}$), 126.2 ($C_{Ar}{}^{min}$), 126.2 ($C_1{}^{maj}$), 126.1 ($C_{Ar}{}^{min}$), 118.3 ($C_{17}{}^{min}$), 117.1 ($C_{17}{}^{maj}$), 49.8 ($C_{13}{}^{min}$), 45.5 ($C_{13}{}^{maj}$), 39.3 ($C_5{}^{min}$), 39.0 ($C_5{}^{maj}$), 28.8 ($C_{14}{}^{min}$), 27.8 ($C_{14}{}^{maj}$), 26.5 ($C_{16}{}^{maj}$), 26.5 ($C_{16}{}^{min}$), 25.1 ($C_{15}{}^{maj}$), 25.0 ($C_{15}{}^{min}$). **IR** (film, $CDCl_3$) ν_{max} = 2929 (C–H), 1633 (C=O), 1602, 1495, 1452, 1407, 1387, 1365, 1315, 1256, 1141, 1079 cm^{-1}. **HRMS** (ESI^+) *m*/*z* calcd for $C_{20}H_{22}NO$ $[M+H]^+$ 292.1696, found 292.1701.

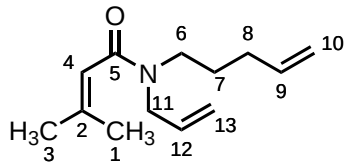
N,*N*-Diallyl-3-methylbut-2-enamide (3.96a)



By **GP2**, the acid chloride of 3,3-dimethylacrylic acid (500 mg, 4.99 mmol) was made by stirring with oxalyl chloride for 2 h. Diallylamine (620 µL, 5.02 mmol) was used as the general amine that was stirred with the acid chloride intermediate for 1 h, and purified by flash column chromatography (SiO_2; gradient elution: 7–60% EtOAc in pet. ether) to yield the title compound as a pale yellow oil (707 mg, 79%).

$\boldsymbol{R_f}$ = 0.37 (30% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.78 (1H, sept, *J* 1.3, H_4), 5.85–5.62 (2H, m, H_7), 5.21–5.06 (4H, m, H_8), 4.04–3.81 (4H, m, H_6), 1.95 (3H, d, *J* 1.3, H_1), 1.81 (3H, d, *J* 1.3, H_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.3 (C_5), 147.8 (C_2), 133.6 (C_{7a}), 133.3 (C_{7b}), 117.7 (C_4), 117.1 (C_{8a}), 116.8 (C_{8b}), 49.7 (C_{6a}), 47.2 (C_{6b}), 26.6 (C_3), 20.3 (C_1). **IR** (film, $CDCl_3$) ν_{max} = 2980 (C–H), 2914 (C–H), 1624 (C=O), 1456, 1409, 1376, 1234, 1179, 993, 921 cm^{-1}. **HRMS** (ESI^+) *m*/*z* calcd for $C_{11}H_{18}NO$ $[M+H]^+$ 180.1383, found 180.1379.

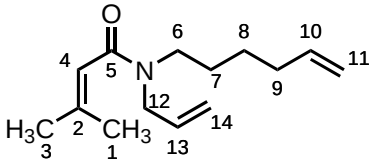
N-Allyl-3-methyl-*N*-(pent-4-en-1-yl)but-2-enamide (3.96c)



By **GP2**, the acid chloride of 3,3-dimethylacrylic acid (500 mg, 4.99 mmol) was made by stirring with oxalyl chloride for 2 h. *N*-Allylpent-4-en-1-amine (**3.82c**) (751 mg, 6.00 mmol) was used as the general amine that was stirred with the acid chloride intermediate for 21 h, and purified by flash column chromatography (SiO_2; gradient elution: 7–60% EtOAc in pet. ether) to yield the title compound as a colourless oil (883 mg, 85%).

$\boldsymbol{R_f}$ = 0.38 (30% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers in an approximate 55:45 ratio) δ 5.86–5.67 ($3H^{maj}$ + $3H^{min}$, m, H_4, H_9, H_{12}), 5.19–5.08 ($2H^{maj}$ + $2H^{min}$, m, H_{13}), 5.06–4.90 ($2H^{maj}$ + $2H^{min}$, m, H_{10}), 3.99 ($2H^{min}$, dt, J 5.9, 1.5, H_{11}), 3.89 ($2H^{maj}$, dt, J 5.1, 1.8, H_{11}), 3.37–3.29 ($2H^{maj}$, m, H_6), 3.28–3.20 ($2H^{min}$, m, H_6), 2.09–1.97 ($2H^{maj}$ + $2H^{min}$, m, H_8), 1.94–1.90 ($3H^{maj}$ + $3H^{min}$, m, H_1), 1.83 ($3H^{min}$ d, J 1.4, H_3), 1.80 ($3H^{maj}$, d, J 1.4, H_3), 1.69–1.56 ($2H^{maj}$ + $2H^{min}$, m, H_7). **^{13}C NMR** (101 MHz, $CDCl_3$, mixture of rotamers in an approximate 55:45 ratio) δ 168.4 ($C_5{}^{maj}$), 168.1 ($C_5{}^{min}$), 147.0 ($C_2{}^{min}$), 146.9 ($C_2{}^{maj}$), 138.1 ($C_9{}^{maj}$), 137.5 ($C_9{}^{min}$), 133.9 ($C_{12}{}^{min}$), 133.6 ($C_{12}{}^{maj}$), 118.2 ($C_4{}^{maj}$), 118.0 ($C_4{}^{min}$), 116.8 ($C_{13}{}^{min}$), 116.7 ($C_{13}{}^{maj}$), 115.5 ($C_{10}{}^{min}$), 114.9 ($C_{10}{}^{maj}$), 50.8 ($C_{11}{}^{maj}$), 47.5 ($C_{11}{}^{min}$), 47.1 ($C_6{}^{min}$), 45.0 ($C_6{}^{maj}$), 31.3 ($C_8{}^{maj}$), 30.8 ($C_8{}^{min}$), 27.8 ($C_7{}^{min}$), 27.0 ($C_7{}^{maj}$), 26.5 ($C_3{}^{min}$), 26.5 ($C_3{}^{maj}$), 20.3 ($C_1{}^{maj}$, $C_1{}^{min}$). **IR** (film, $CDCl_3$) ν_{max} = 2976 (C–H), 2932 (C–H), 2920 (C–H), 1623 (C=O), 1455, 1414, 1375, 1233, 1180, 992, 911, 845 cm^{-1}. **HRMS** (ESI^+) m/z calcd for $C_{13}H_{21}NNaO$ $[M+Na]^+$ 230.1515, found 230.1512.

N-Allyl-*N*-(hex-5-en-1-yl)-3-methylbut-2-enamide (3.96d)

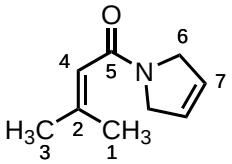


By **GP2**, the acid chloride of 3,3-dimethylacrylic acid (500 mg, 4.99 mmol) was made by stirring with oxalyl chloride for 2 h. *N*-Allylhex-5-en-1-amine (**3.82d**) (835 mg, 6.00 mmol) was used as the general amine that was stirred with the acid chloride intermediate for 21 h, and purified by flash column chromatography (SiO_2; gradient elution: 7–40% EtOAc in pentane) to yield the title compound as a colourless oil (885 mg, 80%).

$\boldsymbol{R_f}$ = 0.39 (30% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers in an approximate 55:45 ratio) δ 5.84–5.67 ($3H^{maj}$ + $3H^{min}$, m, H_4, H_{10},

H_{13}), 5.19–5.07 (2H^{maj} + 2H^{min}, m, H_{14}), 5.03–4.88 (2H^{maj} + 2H^{min}, m, H_{11}), 3.98 (2H^{min}, dt, J 5.9, 1.5, H_{12}), 3.88 (2H^{maj}, dt, J 5.1, 1.8, H_{12}), 3.36–3.28 (2H^{maj}, m, H_6), 3.26–3.20 (2H^{min}, m, H_6), 2.10–2.00 (2H^{maj} + 2H^{min}, m, H_9), 1.92 (3H^{min}, d, J 1.3, H_1), 1.91 (3H^{maj}, d, J 1.3, H_1), 1.82 (3H^{min}, d, J 1.3, H_3), 1.79 (3H^{maj}, d, J 1.3, H_3), 1.58–1.48 (2H^{maj} + 2H^{min}, m, H_7), 1.42–1.30 (2H^{maj} + 2H^{min}, m, H_8). **^{13}C NMR** (101 MHz, $CDCl_3$, mixture of rotamers in an approximate 55:45 ratio) δ 168.4 (C_5^{maj}), 168.0 (C_5^{min}), 146.8 (C_2^{min}), 146.8 (C_2^{maj}), 138.7 (C_{10}^{maj}), 138.3 (C_{10}^{min}), 133.9 (C_{13}^{min}), 133.6 (C_{13}^{maj}), 118.2 (C_4^{maj}), 118.0 (C_4^{min}), 116.8 (C_{14}^{min}), 116.6 (C_{14}^{maj}), 115.0 (C_{11}^{min}), 114.6 (C_{11}^{maj}), 50.6 (C_{12}^{maj}), 47.5 (C_6^{min}, C_{12}^{min}), 45.1 (C_6^{min}), 33.6 (C_9^{maj}), 33.3 (C_9^{min}), 28.1 (C_7^{min}), 27.3 (C_7^{maj}), 26.5 (C_3^{min}), 26.4 (C_3^{maj}), 26.4 (C_8^{maj}), 26.0 (C_8^{min}), 20.3 (C_1^{min}), 20.3 (C_1^{maj}). **IR** (film, $CDCl_3$) ν_{max} = 2975 (C–H), 2930 (C–H), 2858 (C–H), 1623 (C=O), 1456, 1414, 1374, 1231, 1181, 1137, 1067 cm^{-1}. **HRMS** (ESI$^+$) m/z calcd for $C_{14}H_{23}NNaO$ $[M+Na]^+$ 224.1672, found 224.1681.

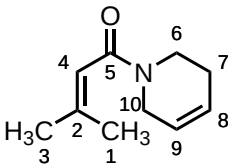
1-(2,5-Dihydro-1*H*-pyrrol-1-yl)-3-methylbut-2-en-1-one (3.97a)



By **GP18**, *N*,*N*-diallyl-3-methylbut-2-enamide (**3.96a**) (409 mg, 2.28 mmol) was used as the amide that was stirred for 23 h, and purified by flash column chromatography (SiO_2; gradient elution: 7–60% EtOAc in pet. ether) to yield the title compound as a beige solid (313 mg, 91%).

m.p. = 59–60 °C (DCM). $\boldsymbol{R_f}$ = 0.11 (30% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.86–5.82 (1H, m, H_4), 5.78–5.73 (2H, m, H_7), 4.27–4.19 (4H, m, H_6), 2.08 (3H, d, J 1.3, H_1), 1.85 (3H, d, J 1.4, H_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.1 (C_5), 150.2 (C_2), 126.4 (C_4), 125.1 (C_{7a}), 117.3 (C_{7b}), 53.6 (C_{6a}), 52.7 (C_{6b}), 27.2 (C_3), 20.1 (C_1). **IR** (film, $CDCl_3$) ν_{max} = 2908 (C–H), 2856 (C–H), 1652, 1634, 1612, 1448, 1417, 1371, 1357, 1344, 1320, 1280, 1203, 1000, 840, 761, 674 cm^{-1}. **HRMS** (ESI$^+$) m/z calcd for $C_9H_{13}NNaO$ $[M+Na]^+$ 174.0889, found 174.0891.

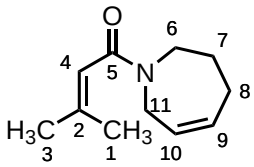
1-(3,6-Dihydropyridin-1(2*H*)-yl)-3-methylbut-2-en-1-one (3.97b)



By **GP2**, the acid chloride of 3,3-dimethylacrylic acid (500 mg, 4.99 mmol) was made by stirring with oxalyl chloride for 2 h. 1,2,3,6-Tetrahydropyridine hydrochloride (598 mg, 5.00 mmol) was used as the general amine that was stirred with the acid chloride intermediate for 1 h (with the modification of 3.0 eq. of Et_3N instead of 2.0 eq.), and purified by flash column chromatography (SiO_2; gradient elution: 7–60% EtOAc in pet. ether) to yield the title compound as a pale yellow oil (613 mg, 74%).

$\boldsymbol{R_f}$ = 0.15 (30% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers in an approximate 55:45 ratio) δ 5.85 (1H^{min}, br d, *J* 10.2, H_8), 5.80 (1H^{maj}, br d, *J* 10.7, H_8), 5.76 (1H^{maj} + 1H^{min}, s, H_4), 5.70 (1H^{maj}, br d, *J* 10.7, H_9), 5.61 (1H^{min}, br d, *J* 10.2, H_9), 4.12–4.00 (2H^{maj}, m, H_{10}), 3.99–3.89 (2H^{min}, m, H_{10}), 3.69 (2H^{min}, t, *J* 5.7, H_6), 3.53 (2H^{min}, t, *J* 5.4, H_6), 2.15 (2H^{maj} + 2H^{min}, br s, H_7), 1.88–1.85 (3H^{maj} + 3H^{min}, m, H_1), 1.82 (3H^{maj} + 3H^{min}, br s, H_3). **^{13}C NMR** (101 MHz, $CDCl_3$, mixture of rotamers in an approximate 55:45 ratio) δ 167.9 ($C_5{}^{maj}$), 167.5 ($C_5{}^{min}$), 145.6 ($C_2{}^{maj}$), 145.4 ($C_2{}^{min}$), 126.5 ($C_8{}^{min}$), 125.0 ($C_9{}^{maj}$), 124.8 ($C_8{}^{maj}$), 123.8 ($C_9{}^{min}$), 118.6 ($C_4{}^{min}$), 118.4 ($C_4{}^{maj}$), 45.7 ($C_{10}{}^{min}$), 43.2 ($C_6{}^{maj}$), 41.7 ($C_{10}{}^{maj}$), 38.1 ($C_6{}^{min}$), 26.2 ($C_3{}^{min}$), 26.1 ($C_3{}^{maj}$), 25.9 ($C_7{}^{maj}$), 25.1 ($C_7{}^{min}$), 20.3 ($C_1{}^{maj}$), 20.2 ($C_1{}^{min}$). **IR** (film, $CDCl_3$) ν_{max} = 2913 (C–H), 2841 (C–H), 1616 (C=O), 1445, 1427, 1376, 1275, 1241, 1176, 1049, 970, 656 cm^{-1}. **HRMS** (ESI$^+$) *m*/*z* calcd for $C_{10}H_{16}NO$ $[M+H]^+$ 166.1226, found 166.1226.

3-Methyl-1-(2,3,4,7-tetrahydro-1*H*-azepin-1-yl)but-2-en-1-one (3.97c)

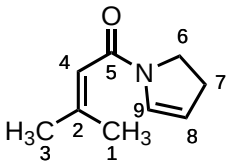


By **GP18**, *N*-allyl-3-methyl-*N*-(pent-4-en-1-yl)but-2-enamide (**3.96c**) (643 mg, 3.10 mmol) was used as the amide that was stirred for 47 h, and purified by flash column chromatography (SiO_2; gradient elution: 7–60% EtOAc in pet. ether) to yield the title compound as a brown oil (352 mg, 63%).

$\boldsymbol{R_f}$ = 0.15 (30% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers in an approximate 55:45 ratio) δ 5.81–5.60 (3H^{maj} + 3H^{min}, m, H_4, H_9, H_{10}), 4.06–4.03 (2H^{min}, m, H_{11}), 3.94–5.91 (2H^{maj}, m, H_{11}), 3.70–3.65 (2H^{maj}, m, H_6), 3.60–3.55 (2H^{min}, m, H_6), 2.21–2.14 (2H^{maj} + 2H^{min}, m, H_8), 1.87 (3H^{min}, d, *J* 1.4, H_1), 1.86 (3H^{maj}, d, *J* 1.4, H_1), 1.89–1.76 (2H^{maj} + 2H^{min}, m, H_7), 1.80 (3H^{min}, d, *J* 1.4, H_3), 1.79 (3H^{maj}, d, *J* 1.4, H_3). **^{13}C NMR** (101 MHz, $CDCl_3$, mixture of rotamers in an approximate 55:45 ratio) δ 168.4 ($C_5{}^{maj}$), 167.8 ($C_5{}^{min}$), 145.8 ($C_2{}^{maj}$), 145.8 ($C_2{}^{min}$), 133.1 ($C_9{}^{maj}$), 131.2 ($C_9{}^{min}$), 128.6 ($C_{10}{}^{min}$), 127.2 ($C_{10}{}^{maj}$), 118.7 ($C_4{}^{maj}$), 118.5 ($C_4{}^{min}$), 49.7 ($C_6{}^{min}$), 47.1 ($C_{11}{}^{maj}$), 45.9 ($C_6{}^{maj}$), 43.6 ($C_{11}{}^{min}$), 27.2 ($C_7{}^{min}$), 26.9 ($C_8{}^{maj}$), 26.6 ($C_8{}^{min}$), 26.2 ($C_3{}^{min}$), 26.2 ($C_7{}^{maj}$), 26.2 ($C_3{}^{maj}$), 20.3 ($C_1{}^{maj}$), 20.2 ($C_1{}^{min}$). **IR** (film, $CDCl_3$) ν_{max} = 2971 (C–H),

2931 (C–H), 2911 (C–H), 2865 (C–H), 1618 (C=O), 1452, 1419, 1376, 1237, 1167, 1064 cm^{-1}. **HRMS** (ESI^+) m/z calcd for $C_{11}H_{17}NNaO$ $[M+Na]^+$ 202.1202, found 202.1210.

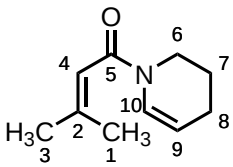
1-(2,3-Dihydro-1*H*-pyrrol-1-yl)-3-methylbut-2-en-1-one (3.98a)



By **GP19**, 1-(2,5-dihydro-1*H*-pyrrol-1-yl)-3-methylbut-2-en-1-one (**3.97a**) (232 mg, 1.53 mmol) was used as the amide that was stirred for 20 h, and purified by flash column chromatography (SiO_2; gradient elution: 7–60% Et_2O in pet. ether) to yield the title compound as a yellow oil (143 mg, 84%).

R_f = 0.23 (30% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers in an approximate 65:35 ratio) δ 6.96 ($1H^{min}$, dt, J 4.4, 2.3, H_9), 6.49 ($1H^{maj}$, dt, J 4.4, 2.2, H_9), 5.79 ($1H^{maj}$, sept, J 1.3, H_4), 5.73 ($1H^{min}$, sept, J 1.3, H_4), 5.19–5.11 ($1H^{maj}$ + $1H^{min}$, m, H_8), 3.88–3.76 ($2H^{maj}$ + $2H^{min}$, m, H_6), 2.76–2.68 ($1H^{min}$, m, H_7), 2.64–2.56 ($1H^{maj}$, m, H_7), 2.10 ($3H^{min}$, d, J 1.3, H_1), 1.97 ($3H^{maj}$, d, J 1.3, H_1), 1.85 ($3H^{min}$, d, J 1.3, H_3), 1.83 ($3H^{maj}$, d, J 1.3, H_3). **^{13}C NMR** (101 MHz, $CDCl_3$, mixture of rotamers in an approximate 65:35 ratio) δ 164.0 ($C_5{}^{maj}$), 163.2 ($C_5{}^{min}$), 152.4 ($C_2{}^{min}$), 148.9 ($C_2{}^{maj}$), 129.6 ($C_9{}^{maj}$), 129.6 ($C_9{}^{min}$), 117.3 ($C_4{}^{maj}$), 116.8 ($C_4{}^{min}$), 111.1 ($C_8{}^{maj}$), 110.4 ($C_8{}^{min}$), 45.9 ($C_6{}^{min}$), 44.8 ($C_6{}^{maj}$), 30.4 ($C_7{}^{min}$), 28.3 ($C_7{}^{maj}$), 27.4 ($C_3{}^{min}$), 26.7 ($C_3{}^{maj}$), 20.3 ($C_1{}^{maj}$), 20.3 ($C_1{}^{min}$). **IR** (film, $CDCl_3$) ν_{max} = 2972 (C–H), 2941 (C–H), 2911 (C–H), 1651, 1625, 1610, 1448, 1410, 1368, 1330, 1282, 1177, 1043, 1021 cm^{-1}. **HRMS** (ESI^+) m/z calcd for $C_9H_{13}NNaO$ $[M+Na]^+$ 174.0889, found 174.0896.

1-(3,4-Dihydropyridin-1(2*H*)-yl)-3-methylbut-2-en-1-one (3.98b)

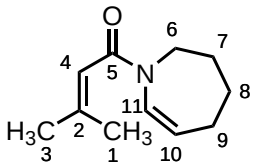


By **GP19**, 1-(3,6-dihydropyridin-1(2*H*)-yl)-3-methylbut-2-en-1-one (**3.97b**) (170 mg, 1.03 mmol) was used as the amide that was stirred for 21 h, and purified by flash column chromatography (SiO_2; gradient elution: 7–60% EtOAc in pet. ether) to yield the title compound as a yellow oil (143 mg, 84%).

R_f = 0.40 (30% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers in an approximate 70:30 ratio) δ 7.18 ($1H^{min}$, dt, J 8.2, 2.1, H_{10}), 6.63

(1H^{maj}, dt, J 8.3, 2.0, H_{10}), 5.83–5.78 (1H^{maj} + 1H^{min}, m, H_4), 5.05 (1H^{min}, dt, J 8.2, 3.9, H_9), 4.87 (1H^{maj}, dt, J 8.1, 3.9, H_9), 3.72–3.64 (1H^{maj}, m, H_6), 3.61–3.54 (1H^{min}, m, H_6), 2.09–2.02 (2H^{maj} + 2H^{min}, m, H_7), 1.95 (3H^{min}, d, J 1.3, H_1), 1.87 (3H^{maj}, d, J 1.3, H_1), 1.84 (3H^{min}, br s, H_3), 1.83 (3H^{maj}, d, J 1.4, H_3), 1.93–1.77 (2H^{maj} + 2H^{min}, m, H_8). **^{13}C NMR** (101 MHz, $CDCl_3$, mixture of rotamers in an approximate 70:30 ratio) δ 166.3 (C_5^{maj}), 165.3 (C_5^{min}), 149.3 (C_2^{min}), 147.7 (C_2^{maj}), 126.4 (C_{10}^{maj}), 124.3 (C_{10}^{min}), 117.6 (C_4^{maj}), 117.5 (C_4^{min}), 108.8 (C_9^{min}), 107.4 (C_9^{maj}), 44.4 (C_6^{min}), 40.1 (C_6^{maj}), 26.7 (C_3^{min}), 26.4 (C_3^{maj}), 22.3 (C_8^{min}), 22.0 (C_7^{maj}), 21.9 (C_7^{min}), 21.7 (C_8^{maj}), 20.5 (C_1^{min}), 20.4 (C_1^{maj}). **IR** (film, $CDCl_3$) ν_{max} = 2932 (C–H), 2868 (C–H), 1625 (C=O), 1446, 1407, 1380, 1366, 1354, 1329, 1314, 1292, 1250, 1174, 1071, 986, 745, 720, 542, 448 cm^{-1}. **HRMS** (ESI$^+$) m/z calcd for $C_{10}H_{15}NNaO$ [M+Na]$^+$ 188.1046, found 188.1052.

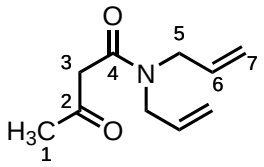
3-Methyl-1-(2,3,4,5-tetrahydro-1*H*-azepin-1-yl)but-2-en-1-one (3.98c)



By **GP19**, 3-methyl-1-(2,3,4,7-tetrahydro-1*H*-azepin-1-yl)but-2-en-1-one (**3.97c**) (319 mg, 1.78 mmol) was used as the amide that was stirred for 24 h, and purified by flash column chromatography (SiO_2; gradient elution: 7–40% Et_2O in pet. ether) to yield the title compound as a pale yellow oil (218 mg, 68%).

***R*$_f$** = 0.20 (30% Et_2O in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers in an approximate 80:20 ratio) δ 6.81 (1H^{min}, d, J 9.0, H_{11}), 6.39 (1H^{maj}, dt, J 8.5, 1.6, H_{11}), 5.85–5.78 (1H^{maj} + 1H^{min}, m, H_4), 5.13 (1H^{maj} + 1H^{min}, dt, J 8.5, 5.5, H_{10}), 3.79–3.71 (2H^{maj}, m, H_6), 3.71–3.63 (2H^{min}, m, H_6), 2.23–2.12 (2H^{maj} + 2H^{min}, qd, J 5.5, 1.6, H_9), 1.97 (3H^{maj}, d, J 1.3, H_1), 1.95 (3H^{min}, br s, H_1), 1.84 (3H^{min}, br s, H_3), 1.83 (3H^{maj}, d, J 1.4, H_3), 1.81–1.72 (2H^{maj} + 2H^{min}, m, H_7^{maj}, H_8^{min}), 1.71–1.58 (2H^{maj} + 2H^{min}, m, H_8^{maj}, H_7^{min}). **^{13}C NMR** (101 MHz, $CDCl_3$, mixture of rotamers in an approximate 80:20 ratio) δ 166.8 (C_5^{maj}, C_5^{min}), 149.1 (C_2^{maj}), 144.7 (C_2^{min}), 131.3 (C_{11}^{maj}), 130.3 (C_{11}^{min}), 118.4 (C_{10}^{maj}), 118.0 (C_4^{maj}), 117.3 (C_4^{min}), 116.9 (C_{10}^{min}), 49.3 (C_6^{min}), 45.3 (C_6^{maj}), 28.0 (C_7^{maj}, C_7^{min}), 26.8 (C_3^{maj}, C_3^{min}), 26.8 (C_9^{maj}, C_9^{min}), 25.0 (C_8^{maj}, C_8^{min}), 20.4 (C_1^{maj}, C_1^{min}). **IR** (film, $CDCl_3$) ν_{max} = 2930 (C–H), 2859 (C–H), 1661, 1629 (C=O), 1449, 1407, 1364, 1150 cm^{-1}. **HRMS** (ESI$^+$) m/z calcd for $C_{11}H_{17}NNaO$ [M+Na]$^+$ 202.1202, found 202.1197.

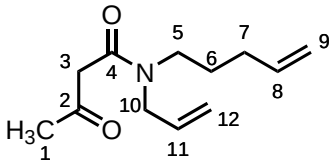
N,*N*-Diallyl-3-oxobutanamide (3.102a)



By **GP20**, diallylamine (2.0 mL, 16.2 mmol) as the amine that was stirred for 19 h, and purified by flash column chromatography (SiO_2; gradient elution: 7–40% EtOAc in pet. ether) to yield the title compound (as a 75:25 keto–enol isomeric mixture) as a yellow-orange oil (2.82 g, 96%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 14.60 (1H^{enol}, s, O*H*), 5.79–5.66 (2H^{keto} + 2H^{enol}, m, H_6), 5.23–5.07 (4H^{keto} + 4H^{enol}, m, H_7), 5.03 (1H^{enol}, q, *J* 0.7, H_3), 3.97 (2H^{keto}, dt, *J* 5.8, 1.5, H_{5a}), 4.00–3.93 (2H^{enol}, m, H_{5a}), 3.82 (2H^{keto}, dt, *J* 4.9, 1.8, H_{5b}), 3.83–3.77 (2H^{enol}, m, H_{5b}), 3.49 (2H^{keto}, s, H_3), 2.24 (3H^{keto}, s, H_1), 1.91 (3H^{enol}, s, H_1). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 202.5 ($C_2{}^{keto}$), 175.2 ($C_2{}^{enol}$), 172.1 ($C_4{}^{enol}$), 166.8 ($C_4{}^{keto}$), 133.2 ($C_{6a}{}^{enol}$), 132.6 ($C_{6a}{}^{keto}$), 132.6 ($C_{6b}{}^{keto}$), 132.5 ($C_{6b}{}^{enol}$), 117.6 ($C_{7a}{}^{keto}$), 117.2 ($C_{7a}{}^{enol}$), 117.1 ($C_{7b}{}^{keto}$), 116.9 ($C_{7b}{}^{enol}$), 87.2 ($C_3{}^{enol}$), 49.9 ($C_{5a}{}^{keto}$), 49.9 ($C_3{}^{keto}$), 49.1 ($C_{5a}{}^{enol}$), 48.0 ($C_{5b}{}^{keto}$), 47.6 ($C_{5b}{}^{enol}$), 30.4 ($C_1{}^{keto}$), 22.0 ($C_1{}^{enol}$). Data consistent with literature.[349]

N-Allyl-3-oxo-*N*-(pent-4-en-1-yl)butanamide (3.102c)

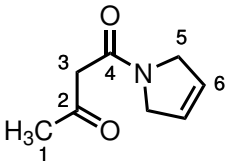


By **GP20**, *N*-allylpent-4-en-1-amine (**3.82c**) (1.32 g, 10.5 mmol) as the amine that was stirred for 23 h, and purified by flash column chromatography (SiO_2; gradient elution: 7–40% EtOAc in pet. ether) to yield the title compound (as a 75:25 keto–enol isomeric mixture) as a yellow oil (1.81 g, 82%).

***R*$_f$** = 0.24 (30% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of keto rotamers in an approximate 60:40 ratio and enol rotamers in an approximate 50:50 ratio) δ 14.73 (1H$^{enol\ both\ rot.}$, s, O*H*), 5.82–5.67 (4H$^{keto\ both\ rot.}$ + 4H$^{enol\ both\ rot.}$, m, H_8, H_{11}), 5.22–5.07 (2H$^{keto\ maj}$ + 2H$^{keto\ min}$ + 2H$^{enol\ both\ rot.}$, m, H_{12}), 5.05 (1H$^{enol\ one\ rot.}$, s, H_3), 5.04–4.95 (1H$^{keto\ maj}$ + 2H$^{enol\ both\ rot.}$ + 1H$^{enol\ one\ rot.}$, m, $H_{9a}{}^{keto\ maj}$, $H_9{}^{enol\ both\ rot.}$, $H_3{}^{enol\ one\ rot.}$), 4.93 (1H$^{keto\ maj}$, ddd, *J* 10.2, 2.1, 1.1, H_{9b}), 3.98–3.93 (2H$^{keto\ maj}$, m, H_{10}), 3.85–3.81 (2H$^{keto\ maj}$ + 2H$^{enol\ both\ rot.}$, m, H_{10}), 3.50 (3H$^{keto\ min}$, s, H_3), 3.45 (3H$^{keto\ maj}$, s, H_3), 3.35–3.28 (2H$^{keto\ maj}$ + 2H$^{enol\ one\ rot.}$, m, H_5), 3.20–3.13 (2H$^{keto\ min}$ + 2H$^{enol\ one\ rot.}$, m, H_5), 2.24 (3H$^{keto\ min}$, s, H_1), 2.22 (3H$^{keto\ maj}$, s, H_1), 2.07–1.98 (2H$^{keto\ both\ rot.}$ + 2H$^{enol\ both\ rot.}$, m, H_7), 1.92 (3H$^{enol\ one\ rot.}$, s, H_1), 1.89 (3H$^{enol\ one\ rot.}$, s, H_1), 1.67–1.57 (2H$^{keto\ both\ rot.}$ + 2H$^{enol\ both\ rot.}$, m, H_6). **^{13}C NMR** (101 MHz, $CDCl_3$,

mixture of keto rotamers in an approximate 60:40 ratio and enol rotamers in an approximate 50:50 ratio) δ 202.7 ($C_2$$^{\text{keto maj}}$), 202.5 ($C_2$$^{\text{keto min}}$), 175.1 ($C_2$$^{\text{enol one rot.}}$), 174.9 ($C_2$$^{\text{enol one rot.}}$), 172.2 ($C_4$$^{\text{enol one rot.}}$), 171.6 ($C_4$$^{\text{enol one rot.}}$), 166.8 ($C_4$$^{\text{keto maj}}$), 166.3 ($C_4$$^{\text{keto min}}$), 137.9 ($C_8$$^{\text{enol one rot.}}$), 137.8 ($C_8$$^{\text{keto maj}}$), 137.3 ($C_8$$^{\text{enol one rot.}}$), 137.1 ($C_8$$^{\text{keto min}}$), 133.5 ($C_{11}$$^{\text{enol one rot.}}$), 132.9 ($C_{11}$$^{\text{keto min}}$), 132.9 ($C_{11}$$^{\text{enol one rot.}}$), 132.9 ($C_{11}$$^{\text{keto maj}}$), 117.3 ($C_{12}$$^{\text{keto min}}$), 116.9 ($C_{12}$$^{\text{keto maj}}$), 116.9 ($C_{12}$$^{\text{enol one rot.}}$), 116.8 ($C_{12}$$^{\text{enol one rot.}}$), 115.9 ($C_9$$^{\text{keto min}}$), 115.7 ($C_9$$^{\text{enol one rot.}}$), 115.1 ($C_9$$^{\text{keto maj}}$), 115.0 ($C_9$$^{\text{enol one rot.}}$), 87.3 ($C_3$$^{\text{enol one rot.}}$), 87.0 ($C_3$$^{\text{enol one rot.}}$), 50.8 ($C_{10}$$^{\text{keto min}}$, $C_{10}$$^{\text{enol one rot.}}$), 50.1 ($C_{10}$$^{\text{enol one rot.}}$), 50.0 ($C_3$$^{\text{keto maj}}$), 49.8 ($C_3$$^{\text{keto min}}$), 48.0 ($C_{10}$$^{\text{keto maj}}$), 47.3 ($C_5$$^{\text{keto min}}$), 46.7 ($C_5$$^{\text{enol one rot.}}$), 45.9 ($C_5$$^{\text{keto maj}}$), 45.5 ($C_5$$^{\text{enol one rot.}}$), 31.1 ($C_7$$^{\text{enol one rot.}}$), 31.1 ($C_7$$^{\text{keto maj}}$), 30.8 ($C_7$$^{\text{enol one rot.}}$), 30.7 ($C_7$$^{\text{keto min}}$), 30.3 ($C_1$$^{\text{keto min}}$), 30.3 ($C_1$$^{\text{keto maj}}$), 27.7 ($C_6$$^{\text{keto min}}$, $C_6$$^{\text{enol one rot.}}$), 27.1 ($C_6$$^{\text{enol one rot.}}$), 26.8 ($C_6$$^{\text{keto maj}}$), 22.1 ($C_1$$^{\text{enol both rot.}}$). **IR** (film, $CDCl_3$) ν_{max} = 2978 (C–H), 2928 (C–H), 1721 (C=O), 1634 (C=O), 1590, 1489, 1432, 1417, 1389, 1357, 1311, 1241, 1207, 1159 cm^{-1}. **HRMS** (ESI^+) m/z calcd for $C_{12}H_{19}NNaO_2$ $[M+Na]^+$ 232.1308, found 232.1317.

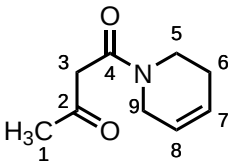
1-(2,5-Dihydro-1*H*-pyrrol-1-yl)butane-1,3-dione (3.103a)



By **GP18**, *N*,*N*-diallyl-3-oxobutanamide (**3.102a**) (970 mg, 5.35 mmol) was used as the amide that was stirred for 23 h, and purified by flash column chromatography (SiO_2; gradient elution: 17–100% EtOAc in pet. ether) to yield the title compound (as a 70:30 keto–enol isomeric mixture) as a dark red-purple oil that solidified upon standing (770 mg, 94%).

m.p. = 47–48 °C (DCM). $\boldsymbol{R_f}$ = 0.18 (70% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 14.50 (1H$^{\text{enol}}$, s, OH), 5.84–5.78 (1H$^{\text{keto}}$ + 1H$^{\text{enol}}$, m, H_{6a}), 5.77–5.69 (1H$^{\text{keto}}$ + 1H$^{\text{enol}}$, m, H_{6b}), 4.90 (1H$^{\text{enol}}$, q, J 0.7, H_3), 4.22–4.09 (4H$^{\text{keto}}$ + 4H$^{\text{enol}}$, m, H_5), 3.43 (2H$^{\text{keto}}$, s, H_3), 2.23 (3H$^{\text{keto}}$, s, H_1), 1.88 (3H$^{\text{enol}}$, d, J 0.7, H_1). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 202.2 ($C_2$$^{\text{keto}}$), 174.6 ($C_2$$^{\text{enol}}$), 170.1 ($C_4$$^{\text{enol}}$), 164.9 ($C_4$$^{\text{keto}}$), 126.1 ($C_{6a}$$^{\text{keto}}$), 126.1 ($C_{6a}$$^{\text{enol}}$), 124.8 ($C_{6b}$$^{\text{enol}}$), 124.8 ($C_{6b}$$^{\text{keto}}$), 88.4 ($C_3$$^{\text{enol}}$), 53.8 ($C_{5a}$$^{\text{keto}}$), 53.0 ($C_{5b}$$^{\text{keto}}$), 52.9 ($C_{5a}$$^{\text{enol}}$), 52.0 ($C_{5b}$$^{\text{enol}}$), 50.8 ($C_3$$^{\text{keto}}$), 30.4 ($C_1$$^{\text{keto}}$), 21.7 ($C_1$$^{\text{enol}}$). **IR** (film, $CDCl_3$) ν_{max} = 3483 (O–H, br), 2904 (C–H), 2862 (C–H), 1717 (C=O), 1640 (C=O), 1618 (C=O), 1587, 1436, 1381, 1357, 1334, 1196, 1161 cm^{-1}. **HRMS** (ESI^+) m/z calcd for $C_8H_{11}NNaO_2$ $[M+Na]^+$ 176.0682, found 176.0684.

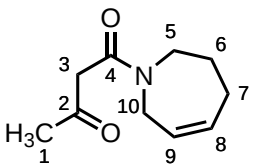
1-(3,6-Dihydropyridin-1(2*H*)-yl)butane-1,3-dione (3.103b)



By **GP20**, 1,2,3,6-tetrahydropyridine hydrochloride (1.26 g, 10.5 mmol) was used as the amine that was stirred for 24 h (with the modification of the addition of Et_3N (1.6 mL, 11.5 mmol, 1.1 eq.)), and purified by flash column chromatography (SiO_2; gradient elution: 17–100% EtOAc in pet. ether) to yield the title compound (as a 80:20 keto–enol isomeric mixture) as an orange oil (775 mg, 44%).

$\boldsymbol{R_f}$ = 0.27 (70% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of keto rotamers in an approximate 55:45 ratio) δ 14.76 (1H^{enol}, s, O*H*), 5.90–5.81 (2H$^{keto\ min}$, m, H_7), 5.81–5.75 (2H$^{keto\ maj}$ + 2H^{enol}, m, H_7), 5.68–5.62 (2H$^{keto\ maj}$ + 2H^{enol}, m, H_8), 5.63–5.53 (2H$^{keto\ min}$, m, H_8), 5.10 (1H^{enol}, br s, H_3), 4.05–4.00 (2H$^{keto\ maj}$ + 2H^{enol}, m, H_9), 3.87–3.82 (2H$^{keto\ min}$, m, H_9), 3.65 (2H$^{keto\ min}$, t, *J* 5.8, H_5), 3.53 (2H$^{keto\ maj}$, s, H_3), 3.50 (2H$^{keto\ min}$, s, H_3), 3.43 (2H$^{keto\ maj}$ + 2H^{enol}, t, *J* 5.7, H_5), 2.23 (3H$^{keto\ maj}$, s, H_1), 2.22 (3H$^{keto\ min}$, s, H_1), 2.17–2.09 (2H$^{keto\ maj}$ + 2H$^{keto\ min}$ + 2H^{enol}, m, H_6), 1.91 (3H^{enol}, d, *J* 0.7, H_1). **^{13}C NMR** (101 MHz, $CDCl_3$, mixture of keto rotamers in an approximate 55:45 ratio) 202.4 ($C_2{}^{keto\ maj}$, $C_2{}^{keto\ min}$), 175.1 ($C_2{}^{enol}$), 171.0 ($C_4{}^{enol}$), 165.5 ($C_4{}^{keto\ maj}$), 165.3 ($C_4{}^{keto\ min}$), 126.6 ($C_7{}^{enol\ min}$), 124.7 ($C_7{}^{keto\ maj}$, $C_7{}^{enol}$), 124.3 ($C_8{}^{keto\ maj}$, $C_7{}^{enol}$), 123.0 ($C_8{}^{keto\ min}$), 86.8 ($C_3{}^{enol}$), 50.5 ($C_3{}^{keto\ min}$), 50.3 ($C_3{}^{keto\ maj}$), 45.6 ($C_9{}^{keto\ min}$), 43.4 ($C_5{}^{keto\ maj}$, $C_5{}^{enol}$), 42.2 ($C_9{}^{keto\ maj}$, $C_9{}^{enol}$), 38.6 ($C_5{}^{keto\ min}$), 30.2 ($C_1{}^{keto\ maj}$, $C_1{}^{keto\ min}$), 25.6 ($C_6{}^{keto\ maj}$, $C_6{}^{enol}$), 24.8 ($C_6{}^{keto\ min}$), 22.0 ($C_1{}^{enol}$). **IR** (film, $CDCl_3$) ν_{max} = 3488 (O–H), br, 2921 (C–H), 2843 (C–H), 1717 (C=O), 1628 (C=O), 1589, 1445, 1385, 1359, 1341, 1246, 1206, 1158 cm^{-1}. **HRMS** (ESI$^+$) *m/z* calcd for $C_9H_{13}NNaO_2$ $[M+Na]^+$ 190.0838, found 190.0838.

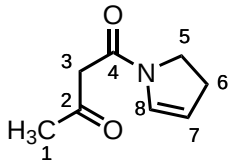
1-(2,3,4,7-Tetrahydro-1*H*-azepin-1-yl)butane-1,3-dione (3.103c)



By **GP18**, *N*-allyl-3-oxo-*N*-(pent-4-en-1-yl)butanamide (**3.102c**) (1.77 g, 8.46 mmol) was used as the amide that was stirred for 5 d, and purified by flash column chromatography (SiO_2; gradient elution: 17–100% EtOAc in pet. ether) to yield the title compound (as a 80:20 keto–enol isomeric mixture) as a dark red-purple oil (1.31 g, 86%).

R_f = 0.26 (70% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of keto rotamers in an approximate 55:45 ratio) δ 14.79 ($1H^{enol}$, s, O*H*), 5.80 ($1H^{keto\ maj}$, dtt, *J* 11.0, 5.5, 1.5, H_8), 5.77–5.68 ($2H^{keto\ min}$ + $2H^{enol}$, m, H_8, H_9), 5.64 ($1H^{keto\ maj}$, dtt, *J* 11.0, 4.6, 1.6, H_9), 5.06 ($1H^{enol}$, s, H_3), 4.06–3.98 ($2H^{keto\ min}$ + $1H^{enol}$, m, H_{10}), 3.90–3.82 ($2H^{keto\ maj}$, m, H_{10}), 3.70–3.62 ($2H^{keto\ maj}$ + $2H^{enol}$, m, H_5), 3.51 ($2H^{keto\ min}$, t, *J* 6.1, H_5), 3.49 ($3H^{keto\ min}$, s, H_3), 3.46 ($3H^{keto\ maj}$, s, H_3), 2.23 ($3H^{keto\ min}$, s, H_1), 2.21 ($3H^{keto\ maj}$, s, H_1), 2.23–2.13 ($2H^{keto\ maj}$ + $2H^{keto\ min}$ + $2H^{enol}$, m, H_7), 1.90 ($3H^{enol}$, s, H_1), 1.87–1.77 ($2H^{keto\ maj}$ + $2H^{keto\ min}$ + $2H^{enol}$, m, H_6). **^{13}C NMR** (101 MHz, $CDCl_3$, mixture of keto rotamers in an approximate 55:45 ratio) δ 202.7 ($C_2{}^{keto\ maj}$), 202.6 ($C_2{}^{keto\ min}$), 174.9 ($C_2{}^{enol}$), 166.3 ($C_4{}^{keto\ maj}$, $C_4{}^{enol}$), 165.6 ($C_4{}^{keto\ min}$), 133.9 ($C_8{}^{keto\ maj}$), 133.6 ($C_8{}^{enol}$), 131.7 ($C_8{}^{keto\ min}$), 131.1 ($C_9{}^{enol}$), 127.9 ($C_9{}^{keto\ min}$), 126.4 ($C_9{}^{keto\ maj}$), 86.9 ($C_3{}^{enol}$), 50.5 ($C_3{}^{keto\ maj}$), 50.2 ($C_3{}^{keto\ min}$), 49.9 ($C_5{}^{keto\ min}$), 47.0 ($C_{10}{}^{keto\ maj}$), 46.7 ($C_5{}^{keto\ maj}$), 45.8 ($C_5{}^{enol}$), 43.8 ($C_{10}{}^{keto\ min}$), 43.5 ($C_{10}{}^{enol}$), 30.2 ($C_1{}^{keto\ min}$), 30.0 ($C_1{}^{keto\ maj}$), 26.9 ($C_6{}^{keto\ min}$), 26.8 ($C_7{}^{keto\ maj}$, $C_6{}^{enol}$, $C_7{}^{enol}$), 26.7 ($C_7{}^{keto\ min}$), 25.8 ($C_6{}^{keto\ maj}$), 22.0 ($C_1{}^{enol}$). **IR** (film, $CDCl_3$) ν_{max} = 3492 (O–H, br), 2932 (C–H), 2879 (C–H), 1717 (C=O), 1628 (C=O), 1586, 1431, 1388, 1356, 1198, 1157 cm^{-1}. **HRMS** (ESI^+) *m*/*z* calcd for $C_{10}H_{16}NO_2$ $[M+H]^+$ 182.1176, found 182.1176.

1-(2,3-Dihydro-1*H*-pyrrol-1-yl)butane-1,3-dione (3.104a)

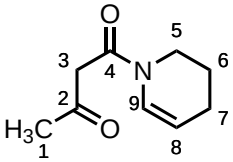


By **GP19**, 1-(2,5-dihydro-1*H*-pyrrol-1-yl)butane-1,3-dione (**3.103a**) (120 mg, 0.78 mmol) was used as the amide that was stirred for 22 h, and purified by flash column chromatography (SiO_2; gradient elution: 17–100% EtOAc in pet. ether) to yield the title compound (as a 70:30 keto–enol isomeric mixture) as a brown oil (108 mg, 90%).

R_f = 0.31 (70% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of keto rotamers in an approximate 70:30 ratio and enol rotamers in an approximate 60:40 ratio) δ 14.46 ($1H^{enol\ maj}$, s, O*H*), 14.14 ($1H^{enol\ min}$, s, O*H*), 6.90–6.84 ($1H^{keto\ min}$ + $1H^{enol\ min}$, m, H_8), 6.48–6.43 ($1H^{enol\ maj}$, m, H_8), 6.39 ($1H^{keto\ maj}$, dt, *J* 4.5, 2.3, H_8), 5.27–5.20 ($1H^{keto\ maj}$ + $1H^{keto\ min}$ + $1H^{enol\ maj}$ + $1H^{enol\ min}$, m, H_7), 5.05 ($1H^{enol\ min}$, s, H_3), 4.90 ($1H^{enol\ maj}$, s, H_3), 3.86–3.80 ($2H^{keto\ maj}$ + $2H^{enol\ min}$, m, H_5), 3.77 ($2H^{keto\ min}$, dd, *J* 9.3, 8.2, H_5), 3.73 ($2H^{enol\ maj}$, dd, *J* 9.4, 8.3, H_5), 3.50 ($2H^{keto\ maj}$, s, H_3), 3.43 ($2H^{keto\ min}$, s, H_3), 2.76–2.68 ($2H^{keto\ min}$ + $2H^{enol\ maj}$, m, H_6), 2.65–2.57 ($2H^{keto\ maj}$ + $2H^{enol\ min}$, m, H_6), 2.26 ($3H^{keto\ min}$, s, H_1), 2.24 ($3H^{keto\ maj}$, s, H_1), 1.92 ($3H^{enol\ maj}$, s, H_1), 1.91 ($3H^{enol\ min}$, s, H_1). **^{13}C NMR** (101 MHz, $CDCl_3$, mixture of keto rotamers in an approximate 70:30 ratio and enol rotamers in an approximate 60:40 ratio) δ 202.0 ($C_2{}^{keto\ min}$), 201.8 ($C_2{}^{keto\ maj}$), 187.1 ($C_2{}^{enol\ min}$), 176.0 ($C_2{}^{enol\ maj}$), 174.1 ($C_4{}^{enol\ maj}$), 167.4 ($C_4{}^{enol\ min}$), 162.2 ($C_4{}^{keto\ min}$), 161.9 ($C_4{}^{keto\ maj}$), 128.9 ($C_8{}^{keto\ min}$), 128.8

($C_8$$^{\text{keto maj}}$), 128.3 ($C_8$$^{\text{enol maj}}$), 128.1 ($C_8$$^{\text{enol min}}$), 113.2 ($C_7$$^{\text{keto maj}}$), 112.3 ($C_7$$^{\text{enol min}}$), 112.0 ($C_7$$^{\text{keto min}}$), 111.2 ($C_7$$^{\text{enol maj}}$), 88.5 ($C_3$$^{\text{enol maj}}$), 88.1 ($C_3$$^{\text{enol min}}$), 51.1 ($C_3$$^{\text{keto min}}$), 51.0 ($C_3$$^{\text{keto maj}}$), 46.1 ($C_5$$^{\text{keto min}}$), 45.2 ($C_5$$^{\text{keto maj}}$), 45.2 ($C_5$$^{\text{enol maj}}$), 44.4 ($C_5$$^{\text{enol min}}$), 30.4 ($C_1$$^{\text{keto min}}$), 30.2 ($C_1$$^{\text{keto maj}}$), 30.1 ($C_6$$^{\text{keto min}}$), 29.8 ($C_6$$^{\text{enol min}}$), 28.4 ($C_6$$^{\text{keto maj}}$), 28.2 ($C_6$$^{\text{enol min}}$), 21.9 ($C_1$$^{\text{enol maj}}$), 21.7 ($C_1$$^{\text{enol min}}$). **IR** (film, $CDCl_3$) ν_{max} = 3417 (O–H, br), 2959 (C–H), 2921 (C–H), 1718 (C=O), 1634 (C=O), 1614 (C=O), 1434, 1355, 1161 cm^{-1}. **HRMS** (ESI^+) m/z calcd for $C_8H_{11}NNaO_2$ $[M+Na]^+$ 176.0682, found 176.0686.

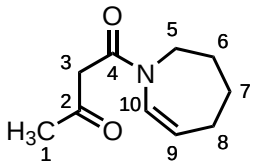
1-(3,4-Dihydropyridin-1(2*H*)-yl)butane-1,3-dione (3.104b)



By **GP19**, 1-(3,6-dihydropyridin-1(2*H*)-yl)butane-1,3-dione (**3.103b**) (669 mg, 4.00 mmol) was used as the amide that was stirred for 22 h, and purified by flash column chromatography (SiO_2; gradient elution: 5–50% EtOAc in pet. ether) to yield the title compound (as a 90:10 keto–enol isomeric mixture) as an orange oil (482 mg, 72%).

$\boldsymbol{R_f}$ = 0.16 (30% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of keto rotamers in an approximate 70:30 ratio and enol rotamers in an approximate 54:45 ratio) δ 14.62 (1H$^{\text{enol min}}$, s, O*H*), 14.32 (1H$^{\text{enol maj}}$, s, O*H*), 7.12 (1H$^{\text{enol min}}$, br s, H_9), 7.09 (1H$^{\text{keto min}}$, dt, *J* 8.3, 2.1, H_9), 6.56–6.51 (1H$^{\text{enol maj}}$, m, H_9), 6.40 (1H$^{\text{keto maj}}$, dt, *J* 8.3, 2.0, H_9), 5.16 (1H$^{\text{enol min}}$, s, H_3), 5.14 (1H$^{\text{enol maj}}$, s, H_3), 5.09 (1H$^{\text{keto min}}$, dt, *J* 8.3, 3.9, H_8), 5.06–5.02 (1H$^{\text{enol min}}$, m, H_8), 4.99–4.93 (1H$^{\text{keto maj}}$ + 1H$^{\text{enol maj}}$, m, H_8), 3.68–3.62 (2H$^{\text{keto maj}}$ + 2H$^{\text{enol min}}$, m, H_5), 3.54 (2H$^{\text{keto min}}$, s, H_3), 3.54 (2H$^{\text{keto maj}}$, s, H_3), 3.49–3.43 (2H$^{\text{keto min}}$ + 2H$^{\text{enol maj}}$, m, H_5), 2.22 (3H$^{\text{keto min}}$, s, H_1), 2.21 (3H$^{\text{keto maj}}$, s, H_1), 2.06–1.99 (2H$^{\text{keto maj}}$ + 2H$^{\text{keto min}}$ + 2H$^{\text{enol maj}}$ + 2H$^{\text{enol min}}$, m, H_7), 1.92 (3H$^{\text{enol min}}$, s, H_1), 1.91 (3H$^{\text{enol maj}}$, s, H_1), 1.85–1.73 (2H$^{\text{keto maj}}$ + 2H$^{\text{keto min}}$ + 2H$^{\text{enol maj}}$ + 2H$^{\text{enol min}}$, m, H_6). **^{13}C NMR** (101 MHz, $CDCl_3$, mixture of keto rotamers in an approximate 70:30 ratio and enol rotamers in an approximate 55:45 ratio) δ 202.1 ($C_2$$^{\text{keto min}}$), 201.9 ($C_2$$^{\text{keto maj}}$), 176.6 ($C_2$$^{\text{enol min}}$), 175.4 ($C_2$$^{\text{enol maj}}$), 169.4 ($C_4$$^{\text{enol maj}}$), 169.1 ($C_4$$^{\text{enol min}}$), 164.3 ($C_4$$^{\text{keto maj}}$), 164.0 ($C_4$$^{\text{keto min}}$), 125.0 ($C_9$$^{\text{keto maj}}$), 124.6 ($C_9$$^{\text{enol maj}}$), 123.8 ($C_9$$^{\text{keto min}}$), 123.2 ($C_9$$^{\text{enol min}}$), 110.1 ($C_8$$^{\text{keto min}}$), 109.9 ($C_8$$^{\text{keto maj}}$), 109.2 ($C_8$$^{\text{enol min}}$), 108.9 ($C_8$$^{\text{enol maj}}$), 86.8 ($C_3$$^{\text{enol min}}$), 86.8 ($C_3$$^{\text{enol maj}}$), 50.2 ($C_3$$^{\text{keto min}}$), 49.9 ($C_3$$^{\text{keto maj}}$), 44.5 ($C_5$$^{\text{keto min}}$), 43.1 ($C_5$$^{\text{enol maj}}$), 40.6 ($C_5$$^{\text{keto maj}}$), 39.7 ($C_5$$^{\text{enol min}}$), 30.2 ($C_1$$^{\text{keto min}}$), 30.1 ($C_1$$^{\text{keto maj}}$), 22.1 ($C_1$$^{\text{enol maj}}$), 22.0 ($C_6$$^{\text{keto min}}$), 22.0 ($CH_2$$^{\text{enol min}}$), 21.9 ($C_1$$^{\text{enol min}}$), 21.9 ($CH_2$$^{\text{enol maj}}$), 21.8 ($C_7$$^{\text{keto maj}}$), 21.7 ($CH_2$$^{\text{enol maj}}$), 21.6 ($C_7$$^{\text{keto min}}$), 21.5 ($CH_2$$^{\text{enol min}}$), 21.4 ($C_6$$^{\text{keto maj}}$). **IR** (film, $CDCl_3$) ν_{max} = 3424 (O–H, br), 2931 (C–H), 2845 (C–H), 1719 (C=O), 1627 (C=O), 1589, 1426, 1392, 1356, 1157 cm^{-1}. **HRMS** (ESI^+) m/z calcd for $C_9H_{14}NO_2$ $[M+H]^+$ 168.1019, found 169.1016.

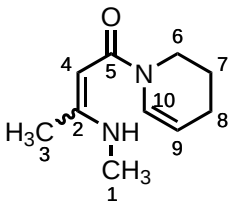
1-(2,3,4,5-Tetrahydro-1*H*-azepin-1-yl)butane-1,3-dione (3.104c)



By **GP19**, 1-(2,3,4,7-tetrahydro-1*H*-azepin-1-yl)butane-1,3-dione (**3.103c**) (1.25 g, 6.90 mmol) was used as the amide that was stirred for 43 h, and purified by flash column chromatography (SiO_2; gradient elution: 7–60% EtOAc in pet. ether) to yield the title compound (as a 70:30 keto–enol isomeric mixture) as an orange oil (856 mg, 68%).

$\boldsymbol{R_f}$ = 0.22 (30% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of keto rotamers in an approximate 85:15 ratio and enol rotamers in an approximate 75:25 ratio) δ 14.59 (1H$^{\text{enol min}}$, s, O*H*), 14.36 (1H$^{\text{enol maj}}$, s, O*H*), 6.73 (1H$^{\text{enol min}}$, d, *J* 8.9, H_{10}), 6.68 (1H$^{\text{keto min}}$, dt, *J* 8.9, 1.7, H_{10}), 6.30 (1H$^{\text{enol maj}}$, d, *J* 8.3, H_{10}), 6.26 (1H$^{\text{keto maj}}$, dt, *J* 8.3, 1.5, H_{10}), 5.28 (1H$^{\text{keto maj}}$, dt, *J* 8.3, 5.6, H_9), 5.29–5.21 (1H$^{\text{enol maj}}$, m, H_9), 5.22–5.16 (1H$^{\text{keto min}}$ + 1H$^{\text{enol min}}$, m, H_9), 5.12 (1H$^{\text{enol min}}$, s, H_3), 5.07 (1H$^{\text{enol maj}}$, s, H_3), 3.71–3.64 (2H$^{\text{keto maj}}$ + 2H$^{\text{enol maj}}$, m, H_5), 3.64–3.60 (2H$^{\text{enol min}}$, m, H_5), 3.60–3.55 (2H$^{\text{keto min}}$, m, H_5), 3.53 (2H$^{\text{keto min}}$, s, H_3), 3.48 (2H$^{\text{keto maj}}$, s, H_3), 2.24 (3H$^{\text{keto min}}$, s, H_1), 2.20 (3H$^{\text{keto maj}}$, s, H_1), 2.19–2.11 (2H$^{\text{keto maj}}$ + 2H$^{\text{keto min}}$ + 2H$^{\text{keto maj}}$ + 2H$^{\text{keto min}}$, m, H_8), 1.91 (3H$^{\text{enol min}}$, s, H_1), 1.89 (3H$^{\text{enol maj}}$, s, H_1), 1.79–1.68 (2H$^{\text{keto maj}}$ + 4H$^{\text{keto min}}$ + 2H$^{\text{keto maj}}$ + 2H$^{\text{keto min}}$, m, H_7, $H_6$$^{\text{keto min}}$), 1.64–1.56 (2H$^{\text{keto maj}}$ + 2H$^{\text{keto maj}}$ + 2H$^{\text{keto min}}$, m, H_6). **^{13}C NMR** (101 MHz, $CDCl_3$, mixture of keto rotamers in an approximate 85:15 ratio and enol rotamers in an approximate 75:25 ratio) δ 202.2 ($C_2$$^{\text{keto min}}$), 202.0 ($C_2$$^{\text{keto maj}}$), 175.0 ($C_2$$^{\text{enol maj}}$, $C_2$$^{\text{enol min}}$), 170.6 ($C_4$$^{\text{enol maj}}$, $C_4$$^{\text{enol min}}$), 165.6 ($C_4$$^{\text{keto maj}}$), 165.5 ($C_4$$^{\text{keto min}}$), 130.4 ($C_{10}$$^{\text{keto maj}}$), 130.2 ($C_{10}$$^{\text{enol maj}}$), 130.1 ($C_{10}$$^{\text{keto min}}$), 129.6 ($C_{10}$$^{\text{enol min}}$), 122.5 ($C_9$$^{\text{keto maj}}$), 121.3 ($C_9$$^{\text{enol maj}}$), 118.3 ($C_9$$^{\text{keto min}}$), 117.8 ($C_9$$^{\text{enol min}}$), 88.2 ($C_3$$^{\text{enol maj}}$), 86.4 ($C_3$$^{\text{enol min}}$), 50.5 ($C_3$$^{\text{keto maj}}$), 49.9 ($C_3$$^{\text{keto min}}$), 49.4 ($C_5$$^{\text{keto min}}$), 48.2 ($C_5$$^{\text{enol min}}$), 46.2 ($C_5$$^{\text{keto maj}}$), 45.0 ($C_5$$^{\text{enol maj}}$), 30.2 ($C_1$$^{\text{keto maj}}$), 30.2 ($C_1$$^{\text{keto min}}$), 28.3 ($C_7$$^{\text{keto min}}$), 28.1 ($C_7$$^{\text{enol maj}}$), 27.9 ($C_7$$^{\text{enol min}}$), 27.8 ($C_7$$^{\text{keto maj}}$), 26.7 ($C_8$$^{\text{enol maj}}$), 26.7 ($C_8$$^{\text{keto maj}}$), 26.1 ($C_8$$^{\text{keto min}}$), 26.0 ($C_8$$^{\text{enol min}}$), 24.5 ($C_6$$^{\text{enol maj}}$), 24.5 ($C_6$$^{\text{keto min}}$), 24.4 ($C_6$$^{\text{keto maj}}$), 24.2 ($C_6$$^{\text{enol min}}$), 22.1 ($C_1$$^{\text{enol min}}$), 21.8 ($C_1$$^{\text{enol maj}}$). **IR** (film, $CDCl_3$) ν_{max} = 3432 (O–H, br), 2931 (C–H), 2860 (C–H), 1720 (C=O), 1660 (C=O), 1632 (C=O), 1590, 1420, 1393, 1359, 1341, 1313, 1212, 1153 cm^{-1}. **HRMS** (ESI$^+$) *m*/*z* calcd for $C_{10}H_{15}NNaO_2$ $[M+Na]^+$ 204.0995, found 204.1005.

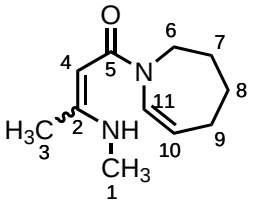
1-(3,4-Dihydropyridin-1(2*H*)-yl)-3-(methylamino)but-2-en-1-one (3.105b)



By **GP21**, 1-(3,4-dihydropyridin-1(2*H*)-yl)butane-1,3-dione (**3.104b**) (412 mg, 2.46 mmol) was used as the 3-oxobutanamide that was stirred for 23 h to yield the title compound as a pale brown oil (310 mg, 70%).

R_f = 0.30 (30% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.44 (1H, br s, N*H*), 6.90 (1H, br s, H_{10}), 4.80 (1H, dt, *J* 8.1, 3.8, H_9), 4.62 (1H, br s, H_4), 3.59–3.50 (2H, m, H_6), 2.86 (3H, d, *J* 5.2, H_1), 2.02 (2H, tdd, *J* 6.1, 3.8, 2.0, H_8), 1.91 (3H, d, *J* 0.6, H_3), 1.79 (2H, quint, *J* 6.1, H_7). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.1 (C_5), 161.7 (C_2), 125.4 (C_{10}), 105.0 (C_9), 80.8 (C_4), 29.5 (C_1), 22.3 (C_7), 21.9 (C_8), 19.8 (C_3). **IR** (film, $CDCl_3$) ν_{max} = 3238 (N−H, br), 2924 (C−H), 2841 (C−H), 1599 (C=O), 1579 (C=C), 1513, 1435, 1395, 1337, 1315, 1291, 1260, 1218, 1073 cm^{-1}. **HRMS** (ESI^+) *m/z* calcd for $C_{10}H_{17}N_2O$ $[M+H]^+$ 181.1335, found 181.1341.

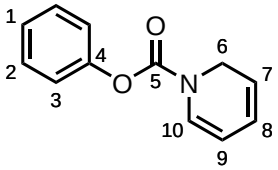
3-(Methylamino)-1-(2,3,4,5-tetrahydro-1*H*-azepin-1-yl) but-2-en-1-one (3.105c)



By **GP21**, 1-(2,3,4,5-tetrahydro-1*H*-azepin-1-yl)butane-1,3-dione (**3.104c**) (796 mg, 4.39 mmol) was used as the 3-oxobutanamide that was stirred for 18 h to yield the title compound as a brown oil (844 mg, 99%).

R_f = 0.36 (30% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.40 (1H, br s, N*H*), 6.46 (1H, br s, H_{11}), 5.04 (1H, dt, *J* 8.4, 5.4, H_{10}), 4.56 (1H, br s, H_4), 3.73–3.64 (2H, m, H_6), 2.86 (3H, d, *J* 5.2, H_1), 2.12–2.11 (2H, m, H_9), 1.89 (3H, d, *J* 0.6, H_3), 1.73 (2H, tt, *J* 6.1, 5.0, H_7), 1.62 (2H, quint, *J* 6.1, H_8). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.3 (C_5), 161.2 (C_2), 131.6 (C_{11}), 116.7 (C_{10}), 81.8 (C_4), 45.2 (C_6), 29.5 (C_1), 28.5 (C_7), 26.7 (C_9), 25.0 (C_8), 19.7 (C_3). **IR** (film, $CDCl_3$) ν_{max} = 3228 (N−H, br), 2925 (C−H), 2856 (C−H), 2835 (C−H), 1601 (C=O), 1582 (C=C), 1511, 1436, 1357, 1335, 1321, 1269, 1199, 1182, 1150, 1076 cm^{-1}. **HRMS** (ESI^+) *m/z* calcd for $C_{11}H_{19}N_2O$ $[M+H]^+$ 195.1492, found 195.1497.

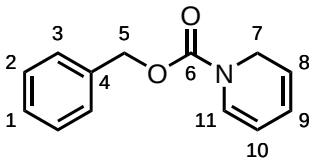
Phenyl pyridine-1(2*H*)-carboxylate (3.110a)



By **GP22**, phenyl chloroformate (1.0 mL, 7.97 mmol) was used as the chloroformate, and purified by flash column chromatography (SiO_2; gradient elution: 1–10% Et_2O in pet. ether) to yield the title compound as a white solid (839 mg, 52%).

^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers in an approximate 65:35 ratio) δ 7.42–7.35 ($2H^{maj}$ + $2H^{min}$, m, H_2), 7.26–7.20 ($1H^{maj}$ + $1H^{min}$, m, H_1), 7.18–7.12 ($2H^{maj}$ + $2H^{min}$, m, H_3), 6.89 ($1H^{maj}$, d, J 7.8, H_{10}), 6.82 ($1H^{min}$, d, J 7.9, H_{10}), 5.95–5.88 ($1H^{maj}$ + $1H^{min}$, m, H_8), 5.64–5.53 ($1H^{maj}$ + $1H^{min}$, m, H_7), 5.32–5.22 ($1H^{maj}$ + $1H^{min}$, m, H_9), 4.60 ($2H^{min}$, dd, J 4.2, 2.1, H_6), 4.46 ($2H^{maj}$, dd, J 4.0, 2.1, H_6). **^{13}C NMR** (101 MHz, $CDCl_3$, mixture of rotamers in an approximate 65:35 ratio) δ 152.7 ($C_5{}^{min}$), 151.6 ($C_5{}^{maj}$), 151.1 ($C_4{}^{maj}$), 151.0 ($C_4{}^{min}$), 129.5 ($C_2{}^{maj}$, $C_2{}^{min}$), 126.2 ($C_{10}{}^{min}$), 125.8 ($C_1{}^{min}$), 125.8 ($C_1{}^{maj}$), 125.5 ($C_{10}{}^{maj}$), 122.4 ($C_8{}^{min}$), 122.0 ($C_8{}^{maj}$), 121.7 ($C_3{}^{maj}$, $C_3{}^{min}$), 119.6 ($C_7{}^{maj}$), 119.0 ($C_7{}^{min}$), 106.2 ($C_9{}^{min}$), 106.0 ($C_9{}^{maj}$), 44.4 ($C_6{}^{min}$), 43.9 ($C_6{}^{maj}$). Data consistent with literature.[350]

Benzyl pyridine-1(2*H*)-carboxylate (3.110b)

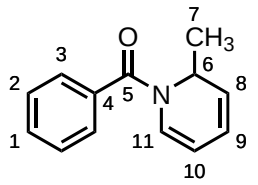


By **GP22**, benzyl chloroformate (1.0 mL, 7.01 mmol) was used as the chloroformate (with the modification of the combined organic extracts being washed sequentially with aqueous HCl (1 M) and aqueous NaOH (1 M), prior to drying with $MgSO_4$), and purified by flash column chromatography (SiO_2; gradient elution: 1–10% Et_2O in pet. ether) to yield the title compound as a colourless liquid (210 mg, 15%). (Note: decomposition to an orange residue was observed when left open to air at room temperature, hence the product was stored at −20 °C under N_2.)

^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers in an approximate 60:40 ratio) δ 7.43–7.29 ($5H^{maj}$ + $5H^{min}$, m, 5 × H_{Ar}), 6.80 ($1H^{min}$, d, J 7.9, H_{11}), 6.71 ($1H^{maj}$, d, J 7.9, H_{11}), 5.90–5.79 ($1H^{maj}$ + $1H^{min}$, m, H_9), 5.59–5.40 ($1H^{maj}$ + $1H^{min}$, m, H_{10}), 5.25–5.05 ($3H^{maj}$ + $3H^{min}$, m, H_5, H_8), 4.44–4.37 ($2H^{maj}$ + $2H^{min}$, m, H_7). **^{13}C NMR** (101 MHz, $CDCl_3$, mixture of rotamers in an approximate 60:40 ratio) δ 154.1 ($C_6{}^{min}$), 153.2 ($C_6{}^{maj}$), 136.2 ($C_4{}^{maj}$, $C_4{}^{min}$), 128.7 ($C_2{}^{maj}$, $C_2{}^{min}$), 128.4

(C_1^{maj}, C_1^{min}), 128.2 (C_3^{maj}, C_3^{min}), 126.4 (C_{11}^{min}), 125.7 (C_{11}^{maj}), 122.4 (C_9^{min}), 122.0 (C_9^{maj}), 119.3 (C_{10}^{maj}), 118.7 (C_{10}^{min}), 105.1 (C_8^{min}), 105.0 (C_8^{maj}), 67.9 (C_5^{maj}, C_5^{min}), 44.0 (C_7^{min}), 43.7 (C_7^{maj}). Data consistent with literature.[351]

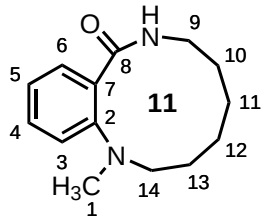
(2-Methylpyridin-1(2*H*)-yl)(phenyl)methanone (3.118a)



By **GP23**, BzCl (600 µL, 5.17 mmol) was used as the acid chloride, and purified by flash column chromatography (SiO_2; gradient elution: 5–10% Et_2O in pet. ether) to yield the title compound as a yellow oil (344 mg, 35%). (Note: a mixture of the title compound and (4-methylpyridin-1(4*H*)-yl)(phenyl)methanone was also obtained, in an approximate 2:1 ratio, as an orange oil (577 mg, 59%).)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55–7.36 (5H, m, H_{Ar}), 6.26 (1H, br s, H_{11}), 5.93 (1H, dd, *J* 9.5, 5.3, H_9), 5.70 (1H, dd, *J* 9.5, 5.7, H_8), 5.23 (2H, br s, H_6, H_{10}), 1.24 (3H, d, *J* 6.2, H_7). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.7 (C_5), 135.0 (C_4), 130.6 (C_1), 128.7 (C_2), 128.5 (C_3), 126.4 (C_{11}), 125.7 (C_8), 120.7 (C_9), 106.4 (C_{10}), 47.7 (C_6), 18.2 (C_7). Data consistent with literature.[284]

1-Methyl-1,2,3,4,5,6,7,8-octahydro-9*H*-benzo[*b*][1,5]diazacycloundecin-9-one (3.122b)

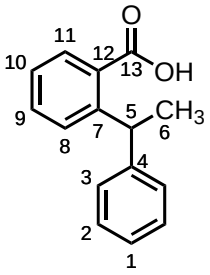


In a microwave vial, (2-(methylamino)phenyl)(2,3,4,5-tetrahydro-1*H*-azepin-1-yl)methanone (**3.74c**) (46 mg, 0.20 mmol, 1.0 eq.) was dissolved in anhydrous THF (1.0 mL). The reaction mixture was cooled to 0 °C, and NaHMDS (220 µL, 1.0 M in THF, 0.22 mmol, 1.1 eq.) added dropwise. The vial was sealed, the reaction mixture stirred at 100 °C under microwave irradiation for 2 h, quenched by the addition of MeOH (0.5 mL), and, in air, transferred into a round-bottom flask with MeOH (0.5 mL). Pd/C (11 mg, 10 wt%, 0.010 mmol, 0.05 eq.) was added, and the reaction mixture stirred at room temperature under H_2 (1 atm, balloon) for 20 h, filtered through Celite, eluting with EtOAc, and concentrated *in vacuo*. The crude residue was purified by flash column

chromatography (SiO_2; gradient elution: 7–60% EtOAc in pet. ether) to yield the title compound as a white solid (26 mg, 57%).

m.p. = 105–106 °C (DCM). $\boldsymbol{R_f}$ = 0.24 (30% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.23 (1H, br s, NH), 8.01 (1H, dd, J 7.7, 1.8, H_6), 7.38 (1H, ddd, J 8.1, 7.2, 1.8, H_4), 7.17 (1H, d, J 8.1, H_3), 7.14 (1H, ddd, J 7.7, 7.2, 1.2, H_5), 3.54 (2H, br s, H_9), 2.86 (2H, t, J 5.6, H_{14}), 2.71 (3H, s, H_1), 1.73 (2H, quint, J 5.8, H_{10}), 1.70–1.62 (2H, m, H_{13}), 1.61–1.51 (4H, m, H_{11}, H_{12}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.6 (C_8), 152.6 (C_2), 131.7 (C_4), 131.3 (C_6), 128.5 (C_7), 124.0 (C_5), 120.3 (C_3), 58.3 (C_{14}), 38.8 (C_9), 38.5 (C_1), 26.1 (C_{10}), 25.9 (C_{13}), 24.5 (C_{11}), 23.3 (C_{12}). **IR** (film, $CDCl_3$) ν_{max} = 3503 (N–H, br), 2927 (C–H), 2856 (C–H), 1640 (C=O), 1605, 1484, 1451, 1311, 754 cm^{-1}. **HRMS** (ESI^+) m/z calcd for $C_{14}H_{20}N_2NaO$ $[M+Na]^+$ 255.1468, found 255.1477.

2-(1-Phenylethyl)benzoic acid (3.133)

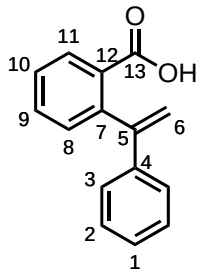


Method 1: By the method of Xu and co-workers[352] with modifications, 2-benzylbenzoic acid (3.18 g, 15.0 mmol, 1.0 eq.) was dissolved in anhydrous THF (75 mL), and cooled to −78 °C. n-BuLi (15.0 mL, 2.5 M in hexanes, 37.5 mmol, 2.5 eq.) was added dropwise, and the reaction mixture stirred at −78 °C for 30 min, warmed to 0 °C, and stirred at 0 °C for 1 h. The reaction mixture was cooled to −78 °C, a solution of MeI (1.9 mL, 30.5 mmol, 2.0 eq.) in anhydrous THF (15 mL) added dropwise, and the reaction mixture stirred at −78 °C for 1.5 h. The reaction mixture was warmed to room temperature, stirred at room temperature for 10 min, quenched by the addition of aqueous HCl (50 mL, 3 M), and extracted with Et_2O (3 × 100 mL). The combined organic extracts were washed sequentially with H_2O (2 × 20 mL) and brine (20 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The crude residue was dissolved in Et_2O (50 mL), and extracted with aqueous KOH (3 × 20 mL, 3.5 M). The combined aqueous extracts were washed with Et_2O (50 mL), adjusted to pH 1 with aqueous HCl (37 wt%), and extracted with Et_2O (3 × 50 mL). The combined organic extracts were washed sequentially with H_2O (20 mL) and brine (20 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2; gradient elution: 0–15% EtOAc + 1% HCO_2H in pet. ether + 1% HCO_2H) to yield the title compound as a white solid (3.16 g, 93%).

Method 2: In air, 3-methyl-3-phenylisobenzofuran-1(3*H*)-one (**3.136**) (4.25 g, 19.0 mmol, 1.0 eq.) was dissolved in MeOH (63 mL), Pd/C (1.00 g, 10 wt%, 0.95 mmol, 0.05 eq.) added, the reaction mixture stirred at room temperature under H_2 (1 atm, balloon) for 17 h, filtered through Celite, eluting with MeOH, and concentrated *in vacuo* to yield the title compound as a white solid (4.37 g, quant.).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.93 (1H, br s, O*H*), 8.01–7.96 (1H, m, H_{11}), 7.46 (1H, ddd, *J* 8.4, 7.2, 1.5, H_9), 7.31–7.23 (6H, m, H_2, H_3, H_8, H_{10}), 7.20–7.14 (1H, m, H_1), 5.33 (1H, q, *J* 7.1, H_5), 1.66 (3H, d, *J* 7.1, H_6). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.8 (C_{13}), 149.1 (C_4), 146.0 (C_7), 132.9 (C_9), 131.2 (C_{11}), 129.1 (C_8), 128.6 (C_{12}), 128.4 (C_2), 128.1 (C_3), 126.1 (C_1), 126.0 (C_{10}), 39.7 (C_5), 22.2 (C_6). Data consistent with literature.[353]

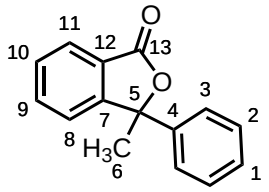
2-(1-Phenylvinyl)benzoic acid (3.135)



By the method of Zhou and co-workers[286] with modifications, methyltriphenylphosphonium bromide (3.57 g, 9.99 mmol, 2.0 eq.) was suspended in anhydrous THF (41 mL), and cooled to 0 °C. KO*t*-Bu (9.0 mL, 20 wt% in THF, 14.9 mmol, 3.0 eq.) was added dropwise, and the reaction mixture stirred at 0 °C for 30 min. 2-Benzoylbenzoic acid (1.13 g, 4.99 mmol, 1.0 eq) was added, the reaction mixture stirred at reflux for 21 h, and concentrated *in vacuo*. Aqueous NaOH (50 mL, 2.5 M) was added, the reaction mixture washed with DCM (25 mL), adjusted to pH 1 with aqueous HCl (3 M), and extracted with EtOAc (3 × 25 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2; gradient elution: 10–30% EtOAc + 1% HCO_2H in pet. ether + 1% HCO_2H) to yield the title compound as a white solid (914 mg, 82%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 (1H, br s, O*H*), 7.93 (1H, dd, *J* 7.6, 1.3, H_{11}), 7.56 (1H, td, *J* 7.6, 1.3, H_9), 7.43 (1H, td, *J* 7.6, 1.3, H_{10}), 7.38 (1H, dd, *J* 7.6, 1.3, H_8), 7.28–7.18 (5H, m, H_1, H_2, H_3), 5.67 (1H, d, *J* 1.0, H_{6a}), 5.22 (1H, d, *J* 1.0, H_{6b}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.4 (C_{13}), 149.7 (C_5), 143.8 (C_4), 141.0 (C_7), 132.5 (C_9), 131.7 (C_8), 130.8 (C_{11}), 129.7 (C_{12}), 128.2 (C_2), 127.8 (C_{10}), 127.6 (C_1), 126.9 (C_3), 114.5 (C_6). Data consistent with literature.[286]

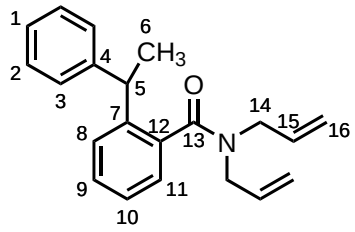
3-Methyl-3-phenylisobenzofuran-1(3*H*)-one (3.136)



2-Benzoylbenzoic acid (4.63 g, 20.5 mmol, 1.0 eq.) was dissolved in anhydrous THF (41 mL), cooled to 0 °C, and MeMgBr (15.0 mL, 3.0 M in Et_2O, 45.0 mmol, 2.2 eq.) added dropwise. The reaction mixture was stirred at 0 °C for 30 min, warmed to room temperature, and stirred at room temperature for 30 min. The reaction mixture was quenched by the addition of aqueous HCl (25 mL, 3 M), and extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$), and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2; gradient elution: 7–20% EtOAc in pet. ether) to yield the title compound as a pale yellow solid (4.26 g, 93%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (1H, dt, *J* 7.5, 1.0, H_{11}), 7.65 (1H, td, *J* 7.5, 1.0, H_9), 7.51 (1H, td, *J* 7.5, 1.0, H_{10}), 7.48–7.43 (3H, m, H_3, H_8), 7.37–7.27 (3H, m, H_1, H_2), 2.04 (3H, s, H_6). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.0 (C_{13}), 154.3 (C_7), 140.8 (C_4), 134.4 (C_9), 129.2 (C_{10}), 128.8 (C_2), 128.4 (C_1), 125.9 (C_{11}), 125.2 (C_3), 125.1 (C_{12}), 122.2 (C_8), 87.6 (C_5), 27.3 (C_6). Data consistent with literature.[352]

N,*N*-Diallyl-2-(1-phenylethyl)benzamide (3.137a)

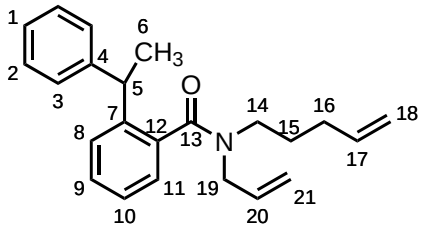


By **GP2**, the acid chloride of 2-(1-phenylethyl)benzoic acid (**3.133**) (1.72 g, 7.61 mmol) was made by stirring with oxalyl chloride for 2.5 h. Diallylamine (1.1 mL, 8.91 mmol) was used as the general amine that was stirred with the acid chloride intermediate for 17 h, and purified by flash column chromatography (SiO_2; gradient elution: 7–30% Et_2O in pet. ether) to yield the title compound as a pale yellow oil (1.77 g, 76%).

R_f = 0.28 (30% Et_2O in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers in an approximate 70:30 ratio) δ 7.45 ($1H^{maj}$, d, *J* 7.9, H_{11}), 7.41–7.33 ($1H^{maj}$ + $2H^{min}$, m, $H_{10}{}^{maj}$, $H_3{}^{min}$), 7.33–7.20 ($3H^{maj}$ + $2H^{min}$, m, $H_2{}^{maj}$, $H_{Ar}{}^{maj}$, $H_{10}{}^{min}$, 2 × $H_{Ar}{}^{min}$), 7.21–7.10 ($4H^{maj}$ + $4H^{min}$, m, $H_3{}^{maj}$, 2 × $H_{Ar}{}^{maj}$, $H_2{}^{min}$, 2 × $H_{Ar}{}^{min}$), 5.99–5.84 ($1H^{min}$, m, H_{15a}), 5.84–5.72 ($1H^{maj}$, m, H_{15a}), 5.72–5.62 ($1H^{min}$, m, H_{15b}), 5.44–5.31 ($1H^{maj}$, m, H_{15b}), 5.29–5.11 ($2H^{maj}$ + $4H^{min}$, m, H_{16}) 5.08

(1H^{maj}, d, J 10.3, $H_{16\,trans}$) 4.99 (1H^{maj}, d, J 16.6, $H_{16\,cis}$), 4.49 (1H^{maj}, q, J 7.2, H_5), 4.56–4.28 (1H^{maj} + 3H^{min}, m, $H_{14a}{}^{maj}$, $H_5{}^{min}$, $H_{14a}{}^{min}$, $H_{14b}{}^{min}$), 3.90 (1H^{min}, dd, J 14.8, 6.6, H_{14c}), 3.82 (1H^{min}, d, J 16.9, H_{14d}), 3.71 (1H^{maj}, dd, J 14.8, 7.3, H_{14b}), 3.31 (1H^{maj}, dd, J 16.4, 4.2, H_{14c}), 2.95 (1H^{maj}, dd, J 16.3, 6.4, H_{14d}), 1.63 (3H^{maj}, d, J 7.2, H_6), 1.62 (3H^{min}, d, J 7.2, H_6). **^{13}C NMR** (126 MHz, $CDCl_3$, mixture of rotamers in an approximate 70:30 ratio) δ 171.2 ($C_{13}{}^{maj}$, $C_{13}{}^{min}$), 145.9 ($C_4{}^{maj}$), 144.9 ($C_4{}^{min}$), 143.8 ($C_7{}^{min}$), 142.4 ($C_7{}^{maj}$), 136.5 ($C_{12}{}^{maj}$), 135.5 ($C_{12}{}^{min}$), 133.0 ($C_{15a}{}^{maj}$, $C_{15a}{}^{min}$), 132.9 ($C_{15b}{}^{maj}$), 132.8 ($C_{15b}{}^{min}$), 129.3 ($C_{10}{}^{min}$), 129.2 ($C_{10}{}^{maj}$), 128.5 ($C_2{}^{maj}$), 128.4 ($C_{Ar}{}^{min}$), 128.3 ($C_2{}^{min}$), 127.9 ($C_3{}^{maj}$), 127.7 ($C_3{}^{min}$), 127.4 ($C_{11}{}^{maj}$), 126.2 ($C_{Ar}{}^{maj}$, $C_{Ar}{}^{min}$), 126.0 ($C_{Ar}{}^{maj}$, $C_{Ar}{}^{min}$), 125.8 ($C_{Ar}{}^{maj}$), 125.7 ($C_{Ar}{}^{min}$), 118.3 ($C_{16a}{}^{maj}$), 118.2 ($C_{16a}{}^{min}$), 118.0 ($C_{16b}{}^{min}$), 117.9 ($C_{16b}{}^{maj}$), 50.7 ($C_{14a}{}^{min}$), 50.4 ($C_{14a}{}^{maj}$), 46.4 ($C_{14b}{}^{maj}$), 46.2 ($C_{14b}{}^{min}$), 41.0 ($C_5{}^{maj}$), 40.5 ($C_5{}^{min}$), 22.7 ($C_6{}^{maj}$), 21.3 ($C_6{}^{min}$). **IR** (film, $CDCl_3$) ν_{max} = 3025 (C–H), 2968 (C–H), 2931 (C–H), 1631 (C=O), 1598, 1492, 1451, 1409, 1285, 1251, 986, 924, 774, 756, 700, 548 cm^{-1}. **HRMS** (ESI$^+$) m/z calcd for $C_{21}H_{24}NO$ $[M+H]^+$ 306.1852, found 306.1850.

N-Allyl-*N*-(pent-4-en-1-yl)-2-(1-phenylethyl)benzamide (3.137c)

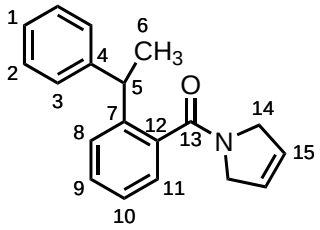


By **GP2**, the acid chloride of 2-(1-phenylethyl)benzoic acid (**3.133**) (1.41 g, 6.23 mmol) was made by stirring with oxalyl chloride for 3 h. *N*-Allylpent-4-en-1-amine (**3.82c**) (936 mg, 7.47 mmol) was used as the general amine that was stirred with the acid chloride intermediate for 19 h, and purified by flash column chromatography (SiO_2; gradient elution: 0–40% Et_2O in pet. ether) to yield the title compound as a pale yellow oil (1.79 g, 86%).

***R*$_f$** = 0.33 (30% Et_2O in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers A/B/C/D in an approximate 45:25:20:10 ratio) δ 7.48–7.09 (9H$^{rot.\,A}$ + 9H$^{rot.\,B}$ + 9H$^{rot.\,C}$ + 9H$^{rot.\,D}$, m, 9 × H_{Ar}), 6.00–5.89 (1H$^{rot.\,C}$, m, H_{20}), 5.89–5.77 (1H$^{rot.\,A}$ + 1H$^{rot.\,C}$ + 1H$^{rot.\,D}$, m, $H_{17}{}^{rot.\,A}$, $H_{17}{}^{rot.\,C}$, $H_{20}{}^{rot.\,D}$), 5.76–5.56 (1H$^{rot.\,B}$ + 1H$^{rot.\,D}$, m, $H_{17}{}^{rot.\,D}$, $H_{20}{}^{rot.\,B}$, $H_{17}{}^{rot.\,D}$), 5.49 (1H$^{rot.\,B}$, ddt, J 16.9, 10.4, 6.6, H_{17}), 5.42–5.30 (1H$^{rot.\,A}$, m, H_{20}), 5.28–5.11 (2H$^{rot.\,B}$ + 2H$^{rot.\,C}$, m, H_{21}), 5.10–4.95 (4H$^{rot.\,A}$ + 2H$^{rot.\,C}$ + 2H$^{rot.\,D}$, m, $H_{18}{}^{rot.\,A}$, $H_{21}{}^{rot.\,A}$, $H_{18}{}^{rot.\,C}$, $H_{21}{}^{rot.\,D}$), 4.95–4.76 (2H$^{rot.\,B}$ + 2H$^{rot.\,D}$, m, H_{18}), 4.49 (1H$^{rot.\,A}$, q, J 7.2, H_5), 4.51–4.41 (1H$^{rot.\,D}$, m, H_{19a}), 4.42 (1H$^{rot.\,B}$, q, J 7.2, H_5), 4.32 (1H$^{rot.\,C}$, q, J 7.2, H_5), 4.28 (1H$^{rot.\,D}$, q, J 7.2, H_5), 4.20 (1H$^{rot.\,B}$, dd, J 14.9, 5.7, H_{19a}), 4.01–3.84 (1H$^{rot.\,B}$ + 1H$^{rot.\,D}$, m, H_{19b}), 3.85–3.78 (1H$^{rot.\,C}$, m, H_{19a}), 3.79–3.65 (2H$^{rot.\,D}$, m, H_{14a}, H_{19b}), 3.55 (1H$^{rot.\,A}$, ddd, J 13.2, 10.4, 5.4, H_{14a}), 3.41–3.36 (1H$^{rot.\,C}$, m, H_{14b}), 3.32 (1H$^{rot.\,A}$, dd, J 16.3, 5.1, H_{19a}), 3.21–3.10 (1H$^{rot.\,A}$ + 1H$^{rot.\,D}$, m, $H_{14b}{}^{rot.\,A}$, $H_{14a}{}^{rot.\,D}$), 3.11–3.07 (1H$^{rot.\,D}$, m, H_{14b}), 2.90 (1H$^{rot.\,A}$, dd, J 16.3, 6.4, H_{19b}),

2.69–2.58 (1H$^{\text{rot. B}}$, m, H_{14a}), 2.33–2.21 (1H$^{\text{rot. B}}$, m, H_{14b}), 2.19–2.13 (2H$^{\text{rot. C}}$, m, H_{16}), 2.12–2.01 (2H$^{\text{rot. A}}$, m, H_{16}), 1.94–1.85 (2H$^{\text{rot. D}}$, m, H_{16}), 1.84–1.72 (1H$^{\text{rot. A}}$ + 2H$^{\text{rot. C}}$, m, $H_{15a}{}^{\text{rot. A}}$, $H_{15}{}^{\text{rot. C}}$), 1.71–1.65 (2H$^{\text{rot. B}}$, m, H_{16}), 1.63 (3H$^{\text{rot. A}}$ + 3H$^{\text{rot. C}}$, d, J 7.2, H_6), 1.63 (3H$^{\text{rot. B}}$ + 3H$^{\text{rot. D}}$, d, J 7.2, H_6), 1.58–1.50 (1H$^{\text{rot. A}}$ + 2H$^{\text{rot. D}}$, m, $H_{15b}{}^{\text{rot. A}}$, $H_{15}{}^{\text{rot. D}}$), 1.34 (2H$^{\text{rot. B}}$, quint, J 7.5, H_{15}). **^{13}C NMR** (126 MHz, $CDCl_3$, mixture of rotamers A/B/C/D in an approximate 45:25:20:10 ratio) δ 171.3 ($C_{13}{}^{\text{rot. C}}$), 171.2 ($C_{13}{}^{\text{rot. A}}$), 171.1 ($C_{13}{}^{\text{rot. B}}$, $C_{13}{}^{\text{rot. D}}$), 145.9 ($C_4{}^{\text{rot. A}}$), 145.8 ($C_4{}^{\text{rot. B}}$), 145.0 ($C_4{}^{\text{rot. D}}$), 144.9 ($C_4{}^{\text{rot. C}}$), 143.7 ($C_7{}^{\text{rot. C}}$), 143.4 ($C_7{}^{\text{rot. D}}$), 142.1 ($C_7{}^{\text{rot. A}}$), 142.1 ($C_7{}^{\text{rot. B}}$), 137.9 ($C_{17}{}^{\text{rot. A}}$, $C_{17}{}^{\text{rot. C}}$), 137.1 ($C_{17}{}^{\text{rot. B}}$, $C_{17}{}^{\text{rot. D}}$), 136.9 ($C_{12}{}^{\text{rot. B}}$), 136.8 ($C_{12}{}^{\text{rot. A}}$), 135.8 ($C_{12}{}^{\text{rot. C}}$), 135.8 ($C_{12}{}^{\text{rot. D}}$), 133.5 ($C_{20}{}^{\text{rot. B}}$), 133.4 ($C_{20}{}^{\text{rot. A}}$), 133.3 ($C_{20}{}^{\text{rot. C}}$), 133.3 ($C_{20}{}^{\text{rot. D}}$), 129.2 ($C_{\text{Ar}}{}^{\text{rot. C}}$, $C_{\text{Ar}}{}^{\text{rot. D}}$), 129.0 ($C_{\text{Ar}}{}^{\text{rot. A}}$), 128.9 ($C_{\text{Ar}}{}^{\text{rot. B}}$), 128.4 ($C_2{}^{\text{rot. A}}$), 128.4 ($C_2{}^{\text{rot. B}}$), 128.3 ($C_2{}^{\text{rot. D}}$), 128.3 ($C_2{}^{\text{rot. C}}$), 128.1 ($C_3{}^{\text{rot. D}}$), 127.9 ($C_3{}^{\text{rot. A}}$), 127.9 ($C_3{}^{\text{rot. B}}$), 127.7 ($C_{\text{Ar}}{}^{\text{rot. B}}$, $C_{\text{Ar}}{}^{\text{rot. D}}$), 127.6 ($C_3{}^{\text{rot. C}}$), 127.3 ($C_{\text{Ar}}{}^{\text{rot. A}}$, $C_{\text{Ar}}{}^{\text{rot. C}}$), 126.1 ($C_{\text{Ar}}{}^{\text{rot. C}}$, $C_{\text{Ar}}{}^{\text{rot. D}}$), 126.1 ($C_{\text{Ar}}{}^{\text{rot. A}}$), 126.1 ($C_{\text{Ar}}{}^{\text{rot. B}}$), 126.0 ($C_{\text{Ar}}{}^{\text{rot. B}}$, $C_{\text{Ar}}{}^{\text{rot. D}}$), 125.9 ($C_{\text{Ar}}{}^{\text{rot. A}}$, $C_{\text{Ar}}{}^{\text{rot. C}}$, $C_{\text{Ar}}{}^{\text{rot. C}}$), 125.9 ($C_{\text{Ar}}{}^{\text{rot. B}}$), 125.8 ($C_{\text{Ar}}{}^{\text{rot. A}}$), 125.6 ($C_{\text{Ar}}{}^{\text{rot. D}}$), 117.9 ($C_{21}{}^{\text{rot. C}}$), 117.8 ($C_{21}{}^{\text{rot. B}}$), 117.7 ($C_{21}{}^{\text{rot. D}}$), 117.7 ($C_{21}{}^{\text{rot. A}}$), 115.4 ($C_{18}{}^{\text{rot. D}}$), 115.2 ($C_{18}{}^{\text{rot. B}}$), 115.2 ($C_{18}{}^{\text{rot. C}}$), 115.0 ($C_{18}{}^{\text{rot. A}}$), 51.7 ($C_{19}{}^{\text{rot. C}}$), 51.3 ($C_{19}{}^{\text{rot. A}}$), 47.8 ($C_{14}{}^{\text{rot. D}}$), 47.7 ($C_{14}{}^{\text{rot. B}}$), 47.0 ($C_{19}{}^{\text{rot. B}}$), 46.8 ($C_{19}{}^{\text{rot. D}}$), 44.0 ($C_{14}{}^{\text{rot. A}}$), 43.9 ($C_{14}{}^{\text{rot. C}}$), 41.1 ($C_5{}^{\text{rot. B}}$), 40.9 ($C_5{}^{\text{rot. A}}$), 40.5 ($C_5{}^{\text{rot. D}}$), 40.5 ($C_5{}^{\text{rot. C}}$), 31.3 ($C_{16}{}^{\text{rot. A}}$), 31.3 ($C_{16}{}^{\text{rot. C}}$), 30.8 ($C_{16}{}^{\text{rot. B}}$, $C_{16}{}^{\text{rot. D}}$), 27.5 ($C_{15}{}^{\text{rot. D}}$), 27.0 ($C_{15}{}^{\text{rot. B}}$), 26.5 ($C_{15}{}^{\text{rot. C}}$), 26.2 ($C_{15}{}^{\text{rot. A}}$), 22.8 ($C_6{}^{\text{rot. B}}$), 22.7 ($C_6{}^{\text{rot. A}}$), 21.2 ($C_6{}^{\text{rot. C}}$), 21.1 ($C_6{}^{\text{rot. D}}$). **IR** (film, DCM) ν_{max} = 3065 (C–H), 3025 (C–H), 2969 (C–H), 2931 (C–H), 2873 (C–H), 1630 (C=O), 1598, 1492, 1453, 1414, 1252 cm^{-1}. **HRMS** (ESI$^+$) m/z calcd for $C_{23}H_{28}NO$ $[M+H]^+$ 334.2165, found 334.2163.

(2,5-Dihydro-1*H*-pyrrol-1-yl)(2-(1-phenylethyl)phenyl)methanone (3.138a)

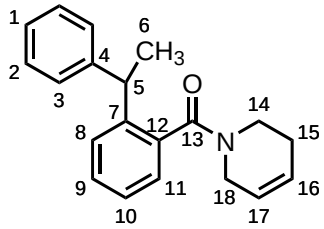


By **GP18**, *N*,*N*-diallyl-2-(1-phenylethyl)benzamide (**3.137a**) (1.72 g, 5.63 mmol) was used as the amide that was stirred for 16 h, and purified by flash column chromatography (SiO_2; gradient elution: 7–60% Et_2O in pet. ether) to yield the title compound as a dark green oil (1.51 g, 97%).

$\boldsymbol{R_f}$ = 0.24 (30% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48 (1H, d, J 7.9, H_{11}), 7.36 (1H, td, J 7.5, 1.6, H_9), 7.21 (1H, td, J 7.9, 1.6, H_{10}), 7.18–7.16 (4H, m, H_2, H_3), 7.15 (1H, dd, J 7.5, 1.6, H_8), 7.11–7.05 (1H, m, H_1), 5.71 (1H, dt, J 6.5, 2.1, H_{15a}), 5.40 (1H, dt, J 6.5, 2.1, H_{15b}), 4.51 (1H, q, J 7.2, H_5), 4.35–4.22 (2H, m, H_{14a}, H_{14b}), 3.74–3.65 (1H, m, H_{14c}), 2.93 (1H, br s, H_{14d}), 1.63

(3H, d, J 7.2, H_6). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.8 (C_{13}), 145.7 (C_4), 142.6 (C_7), 137.3 (C_{12}), 129.2 (C_9), 128.3 (C_2), 127.8 (C_3), 127.0 (C_{11}), 126.2 (C_{10}), 126.1 (C_1), 126.0 (C_8), 125.3 (C_{15a}), 125.2 (C_{15b}), 54.8 (C_{14a}), 52.5 (C_{14b}), 40.9 (C_5), 21.8 (C_6). **IR** (film, $CDCl_3$) ν_{max} = 3025 (C–H), 2966 (C–H), 2860 (C–H), 1637 (C=O), 1618, 1597, 1493, 1449, 1415, 771, 756, 701, 666 cm^{-1}. **HRMS** (ESI$^+$) m/z calcd for $C_{19}H_{20}NO$ $[M+H]^+$ 278.1539, found 278.1537.

(3,6-Dihydropyridin-1(2*H*)-yl)(2-(1-phenylethyl)phenyl)methanone (3.138b)

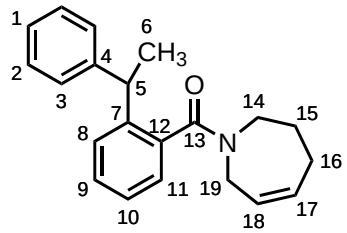


By **GP2**, the acid chloride of 2-(1-phenylethyl)benzoic acid (**3.133** (1.38 g, 6.09 mmol) was made by stirring with oxalyl chloride for 2.5 h. 1,2,3,6-Tetrahydropyridine hydrochloride (718 mg, 6.00 mmol) was used as the general amine that was stirred with the acid chloride intermediate for 22 h (with the modification of 3.0 eq. of Et_3N instead of 2.0 eq.), and purified by flash column chromatography (SiO_2; gradient elution: 7–50% Et_2O in pet. ether) to yield the title compound as a pale yellow oil (1.62 g, 91%).

***R*$_f$** = 0.13 (30% Et_2O in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers A/B/C/D in an approximate 50:25:15:10 ratio) δ 7.53 (1H$^{rot.\ A}$, dd, J 8.1, 1.2, H_{Ar}), 7.45 (1H$^{rot.\ B}$, dd, J 7.9, 1.2, H_{Ar}), 7.40 (1H$^{rot.\ A}$, td, J 7.5, 1.3, H_{Ar}), 7.38–7.04 (7H$^{rot.\ A}$ + 8H$^{rot.\ B}$ + 9H$^{rot.\ C}$ + 9H$^{rot.\ D}$, m, H_{Ar}), 5.93–5.81 (1H$^{rot.\ C}$ + 1H$^{rot.\ D}$, m, $H_{17}{}^{rot.\ C}$, $H_{16}{}^{rot.\ D}$), 5.80–5.74 (1H$^{rot.\ C}$, m, H_{16}), 5.72–5.61 (2H$^{rot.\ A}$ + 1H$^{rot.\ B}$, m, $H_{16}{}^{rot.\ A}$, $H_{17}{}^{rot.\ A}$, $H_{16}{}^{rot.\ B}$), 5.54 (1H$^{rot.\ D}$, d, J 9.9, H_{17}), 5.25–5.16 (1H$^{rot.\ B}$, m, H_{17}), 4.51 (1H$^{rot.\ B}$, q, J 7.2, H_5), 4.48–4.38 (1H$^{rot.\ A}$ + 2H$^{rot.\ C}$, m, $H_{14a}{}^{rot.\ A}$, $H_{14a}{}^{rot.\ C}$, $H_5{}^{rot.\ C}$), 4.30 (1H$^{rot.\ B}$, q, J 7.2, H_5), 4.29 (1H$^{rot.\ B}$, q, J 7.2, H_5), 4.21 (1H$^{rot.\ D}$, dt, J 12.9, 5.2, H_{14a}), 4.05–3.96 (1H$^{rot.\ C}$, m, H_{14b}), 3.83–3.66 (2H$^{rot.\ B}$ + 2H$^{rot.\ D}$, m, $H_{14}{}^{rot.\ B}$, $H_{18}{}^{rot.\ D}$), 3.66–3.58 (1H$^{rot.\ A}$, m, H_{14b}), 3.58–3.54 (1H$^{rot.\ D}$, m, H_{14b}), 3.50–3.38 (1H$^{rot.\ B}$, m, H_{18a}), 3.43–3.32 (1H$^{rot.\ C}$, m, H_{18a}), 3.19–3.09 (1H$^{rot.\ C}$, m, H_{18b}), 2.90–2.82 (1H$^{rot.\ A}$, m, H_{18a}), 2.81–2.72 (1H$^{rot.\ B}$, m, H_{18b}), 2.38–2.22 (2H$^{rot.\ D}$, m, H_{15}), 2.20–2.11 (2H$^{rot.\ B}$ + 1H$^{rot.\ C}$, m, $H_{15}{}^{rot.\ B}$, $H_{15a}{}^{rot.\ C}$), 2.11–2.03 (1H$^{rot.\ A}$, m, H_{18b}), 2.01–1.87 (1H$^{rot.\ A}$ + 1H$^{rot.\ C}$, m, $H_{15a}{}^{rot.\ A}$, $H_{15b}{}^{rot.\ C}$), 1.63 (3H$^{rot.\ C}$, d, J 7.2, H_6), 1.62 (3H$^{rot.\ B}$, d, J 7.2, H_6), 1.62 (3H$^{rot.\ A}$, d, J 7.2, H_6), 1.56 (3H$^{rot.\ D}$, d, J 7.2, H_6), 1.54–1.43 (1H$^{rot.\ A}$, m, H_{15a}). **^{13}C NMR** (126 MHz, $CDCl_3$, mixture of rotamers A/B/C/D in an approximate 50:25:15:10 ratio) δ 170.4 ($C_{13}{}^{rot.\ C}$), 170.3 ($C_{13}{}^{rot.\ A}$), 170.0 ($C_{13}{}^{rot.\ D}$), 169.9 ($C_{13}{}^{rot.\ B}$), 146.2 ($C_4{}^{rot.\ A}$), 145.9 ($C_4{}^{rot.\ B}$), 144.8 ($C_4{}^{rot.\ D}$), 144.6 ($C_4{}^{rot.\ C}$), 143.9 ($C_7{}^{rot.\ C}$), 143.7 ($C_7{}^{rot.\ D}$), 142.5 ($C_7{}^{rot.\ A}$), 142.5 ($C_7{}^{rot.\ B}$), 136.9 ($C_{12}{}^{rot.\ A}$), 136.7 ($C_{12}{}^{rot.\ B}$), 135.9 ($C_{12}{}^{rot.\ D}$), 135.8 ($C_{12}{}^{rot.\ C}$), 129.2 ($C_{Ar}{}^{rot.\ C}$), 129.0 ($C_{Ar}{}^{rot.\ A}$, $C_{Ar}{}^{rot.\ B}$, $C_{Ar}{}^{rot.\ D}$), 128.5 ($C_2{}^{rot.\ D}$), 128.4 ($C_2{}^{rot.\ B}$), 128.4

($C_2$$^{\text{rot. A}}$), 128.3 ($C_2$$^{\text{rot. C}}$), 128.2 ($C_{\text{Ar}}$$^{\text{rot. C}}$), 127.9 ($C_3$$^{\text{rot. A}}$), 127.8 ($C_3$$^{\text{rot. C}}$), 127.8 ($C_3$$^{\text{rot. B}}$), 127.7 ($C_3$$^{\text{rot. D}}$), 127.3 ($C_{\text{Ar}}$$^{\text{rot. B}}$), 126.9 ($C_{\text{Ar}}$$^{\text{rot. A}}$), 126.5 ($C_{16}$$^{\text{rot. D}}$), 126.2 ($C_{\text{Ar}}$$^{\text{rot. C}}$, $C_{\text{Ar}}$$^{\text{rot. D}}$), 126.1 ($C_{\text{Ar}}$$^{\text{rot. A}}$, $C_{\text{Ar}}$$^{\text{rot. B}}$), 126.1 ($C_{\text{Ar}}$$^{\text{rot. A}}$, $C_{\text{Ar}}$$^{\text{rot. C}}$, 2 × $C_{\text{Ar}}$$^{\text{rot. D}}$), 126.1 ($C_{\text{Ar}}$$^{\text{rot. B}}$, $C_{\text{Ar}}$$^{\text{rot. D}}$), 125.9 ($C_{\text{Ar}}$$^{\text{rot. B}}$), 125.8 ($C_{\text{Ar}}$$^{\text{rot. C}}$), 125.7 ($C_{16}$$^{\text{rot. B}}$), 125.7 ($C_{\text{Ar}}$$^{\text{rot. D}}$), 125.6 ($C_{\text{Ar}}$$^{\text{rot. A}}$), 125.0 ($C_{17}$$^{\text{rot. A}}$), 124.8 ($C_{17}$$^{\text{rot. C}}$), 124.5 ($C_{16}$$^{\text{rot. C}}$), 124.0 ($C_{16}$$^{\text{rot. A}}$), 123.7 ($C_{17}$$^{\text{rot. D}}$), 123.4 ($C_{17}$$^{\text{rot. B}}$), 47.0 ($C_{18}$$^{\text{rot. D}}$), 46.5 ($C_{18}$$^{\text{rot. B}}$), 43.9 ($C_{18}$$^{\text{rot. C}}$), 43.2 ($C_{18}$$^{\text{rot. A}}$), 41.7 ($C_{14}$$^{\text{rot. C}}$), 41.4 ($C_{14}$$^{\text{rot. A}}$), 41.0 ($C_5$$^{\text{rot. C}}$), 41.0 ($C_5$$^{\text{rot. B}}$), 40.9 ($C_5$$^{\text{rot. A}}$), 40.6 ($C_5$$^{\text{rot. D}}$), 38.7 ($C_{14}$$^{\text{rot. D}}$), 38.3 ($C_{14}$$^{\text{rot. A}}$), 25.7 ($C_{15}$$^{\text{rot. C}}$), 25.2 ($C_{15}$$^{\text{rot. A}}$), 25.1 ($C_{15}$$^{\text{rot. D}}$), 24.9 ($C_{15}$$^{\text{rot. B}}$), 22.4 ($C_6$$^{\text{rot. B}}$), 22.3 ($C_6$$^{\text{rot. A}}$), 21.3 ($C_6$$^{\text{rot. C}}$), 21.2 ($C_6$$^{\text{rot. D}}$). **IR** (film, $CDCl_3$) ν_{max} = 3029 (C–H), 2967 (C–H), 2928 (C–H), 2838 (C–H), 1625 (C=O), 1597, 1492, 1445, 1428, 1257, 770, 756, 733, 700, 654, 630 cm^{-1}. **HRMS** (ESI^+) m/z calcd for $C_{20}H_{22}NO$ $[M+H]^+$ 292.1696, found 292.1694.

(2-(1-Phenylethyl)phenyl)(2,3,4,7-tetrahydro-1*H*-azepin-1-yl)methanone (3.138c)

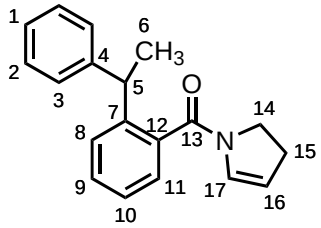


By **GP18**, *N*-allyl-*N*-(pent-4-en-1-yl)-2-(1-phenylethyl)benzamide (**3.137c**) (1.72 g, 5.16 mmol) was used as the amide that was stirred for 43 h, and purified by flash column chromatography (SiO_2; gradient elution: 7–60% Et_2O in pet. ether) to yield the title compound as a green-brown oil (1.57 g, quant.).

$\boldsymbol{R_f}$ = 0.15 (30% Et_2O in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers A/B/C/D in an approximate 45:30:15:10 ratio) δ 7.53–7.05 (9H$^{\text{rot. A}}$ + 9H$^{\text{rot. B}}$ + 9H$^{\text{rot. C}}$ + 9H$^{\text{rot. D}}$, m, 9 × H_{Ar}), 5.99–5.90 (1H$^{\text{rot. D}}$, m, H_{18}), 5.90–5.80 (1H$^{\text{rot. B}}$ + 1H$^{\text{rot. C}}$, m, $H_{18}$$^{\text{rot. B}}$, $H_{17}$$^{\text{rot. C}}$), 5.80–5.68 (1H$^{\text{rot. A}}$ + 1H$^{\text{rot. B}}$ + 1H$^{\text{rot. D}}$, m, H_{17}), 5.49–5.40 (1H$^{\text{rot. C}}$, m, H_{18}), 5.22 (1H$^{\text{rot. A}}$, dddt, J 11.1, 6.3, 3.4, 1.7, H_{18}), 4.60 (1H$^{\text{rot. B}}$, dd, J 16.0, 5.5, H_{19}), 4.47 (1H$^{\text{rot. A}}$, q, J 7.2, H_5), 4.43 (1H$^{\text{rot. B}}$, q, J 7.2, H_5), 4.39–4.30 (1H$^{\text{rot. A}}$ + 1H$^{\text{rot. D}}$, m, $H_{19a}$$^{\text{rot. A}}$, $H_5$$^{\text{rot. D}}$), 4.30–4.21 (1H$^{\text{rot. C}}$, m, $H_5$$^{\text{rot. C}}$), 4.14–4.03 (1H$^{\text{rot. B}}$ + 1H$^{\text{rot. C}}$, m, $H_{19a}$$^{\text{rot. B}}$, $H_{14a}$$^{\text{rot. C}}$), 3.76–3.71 (2H$^{\text{rot. C}}$, m, H_{19}), 3.62–3.45 (1H$^{\text{rot. C}}$ + 2H$^{\text{rot. D}}$, m, $H_{14b}$$^{\text{rot. C}}$, $H_{19}$$^{\text{rot. D}}$), 3.06–2.91 (2H$^{\text{rot. A}}$ + 2H$^{\text{rot. B}}$, m, $H_{14a}$$^{\text{rot. A}}$, $H_{19b}$$^{\text{rot. A}}$, $H_{14}$$^{\text{rot. B}}$), 2.80–2.71 (1H$^{\text{rot. A}}$ + 2H$^{\text{rot. D}}$, m, $H_{14b}$$^{\text{rot. A}}$, $H_{14}$$^{\text{rot. D}}$), 2.37–2.28 (1H$^{\text{rot. A}}$ + 1H$^{\text{rot. C}}$ + 1H$^{\text{rot. D}}$, m, H_{16a}), 2.28–2.12 (1H$^{\text{rot. A}}$ + 2H$^{\text{rot. B}}$ + 1H$^{\text{rot. D}}$, m, $H_{16b}$$^{\text{rot. A}}$, $H_{16}$$^{\text{rot. B}}$, $H_{16b}$$^{\text{rot. D}}$), 2.04–1.93 (3H$^{\text{rot. C}}$, m, $H_{15}$$^{\text{rot. C}}$, $H_{16b}$$^{\text{rot. C}}$), 1.92–1.78 (2H$^{\text{rot. A}}$, m, H_{15}), 1.78–1.69 (2H$^{\text{rot. D}}$, m, H_{15}), 1.63 (3H$^{\text{rot. A}}$, d, J 7.2, H_6), 1.62 (3H$^{\text{rot. C}}$, d, J 7.2, H_6), 1.62 (3H$^{\text{rot. B}}$, d, J 7.2, H_6), 1.61 (3H$^{\text{rot. D}}$, d, J 7.2, H_6), 1.56–1.31 (2H$^{\text{rot. B}}$, m, H_{15}). **^{13}C NMR** (126 MHz, $CDCl_3$, mixture of rotamers A/B/C/D in an approximate 45:30:15:10 ratio) δ 170.9 ($C_{13}$$^{\text{rot. C}}$), 170.9 ($C_{13}$$^{\text{rot. A}}$), 170.4 ($C_{13}$$^{\text{rot. D}}$), 170.3 ($C_{13}$$^{\text{rot. B}}$), 146.0 ($C_4$$^{\text{rot. A}}$), 146.0 ($C_4$$^{\text{rot. B}}$),

145.0 ($C_4$$^{\text{rot. D}}$), 144.9 ($C_4$$^{\text{rot. C}}$), 143.8 ($C_7$$^{\text{rot. C}}$), 143.6 ($C_7$$^{\text{rot. D}}$), 142.2 ($C_7$$^{\text{rot. B}}$), 142.1 ($C_7$$^{\text{rot. A}}$), 137.2 ($C_{12}$$^{\text{rot. A}}$), 137.1 ($C_{12}$$^{\text{rot. B}}$), 136.0 ($C_{12}$$^{\text{rot. C}}$), 135.9 ($C_{12}$$^{\text{rot. D}}$), 132.7 ($C_{17}$$^{\text{rot. C}}$), 132.7 ($C_{17}$$^{\text{rot. A}}$), 132.2 ($C_{17}$$^{\text{rot. B}}$), 132.2 ($C_{17}$$^{\text{rot. D}}$), 129.1 ($C_{\text{Ar}}$$^{\text{rot. C}}$), 128.9 ($C_{\text{Ar}}$$^{\text{rot. A}}$), 128.8 ($C_{\text{Ar}}$$^{\text{rot. B}}$), 128.4 ($C_{\text{Ar}}$$^{\text{rot. D}}$), 128.4 ($C_{\text{Ar}}$$^{\text{rot. C}}$), 128.3 ($C_{\text{Ar}}$$^{\text{rot. C}}$), 128.3 ($C_2$$^{\text{rot. B}}$), 128.3 ($C_2$$^{\text{rot. A}}$), 128.2 ($C_2$$^{\text{rot. D}}$), 128.2 ($C_2$$^{\text{rot. C}}$), 127.9 ($C_3$$^{\text{rot. A}}$), 127.9 ($C_3$$^{\text{rot. B}}$), 127.9 ($C_3$$^{\text{rot. D}}$), 127.8 ($C_{\text{Ar}}$$^{\text{rot. B}}$), 127.8 ($C_3$$^{\text{rot. C}}$), 127.7 ($C_{\text{Ar}}$$^{\text{rot. D}}$), 127.7 ($C_{\text{Ar}}$$^{\text{rot. C}}$), 127.2 ($C_{\text{Ar}}$$^{\text{rot. B}}$), 127.2 ($C_{18}$$^{\text{rot. C}}$), 127.1 ($C_{18}$$^{\text{rot. A}}$), 127.0 ($C_{\text{Ar}}$$^{\text{rot. D}}$), 126.6 ($C_{\text{Ar}}$$^{\text{rot. A}}$), 126.1 ($C_{\text{Ar}}$$^{\text{rot. D}}$), 126.1 ($C_{\text{Ar}}$$^{\text{rot. C}}$), 126.1 ($C_{\text{Ar}}$$^{\text{rot. A}}$), 126.0 ($C_{\text{Ar}}$$^{\text{rot. D}}$), 126.0 ($C_{\text{Ar}}$$^{\text{rot. B}}$), 125.9 ($C_{\text{Ar}}$$^{\text{rot. B}}$), 125.8 ($C_{\text{Ar}}$$^{\text{rot. A}}$), 125.8 ($C_{\text{Ar}}$$^{\text{rot. A}}$), 50.3 ($C_{14}$$^{\text{rot. B}}$), 48.5 ($C_{19}$$^{\text{rot. C}}$), 48.1 ($C_{14}$$^{\text{rot. D}}$), 47.1 ($C_{14}$$^{\text{rot. A}}$), 46.3 ($C_{14}$$^{\text{rot. C}}$), 45.7 ($C_{19}$$^{\text{rot. A}}$), 43.0 ($C_{19}$$^{\text{rot. B}}$, $C_{19}$$^{\text{rot. D}}$), 41.1 ($C_5$$^{\text{rot. D}}$), 41.0 ($C_5$$^{\text{rot. B}}$), 41.0 ($C_5$$^{\text{rot. A}}$), 40.9 ($C_5$$^{\text{rot. C}}$), 27.2 ($C_{16}$$^{\text{rot. A}}$), 27.2 ($C_{16}$$^{\text{rot. C}}$), 27.1 ($C_{16}$$^{\text{rot. D}}$), 27.0 ($C_{15}$$^{\text{rot. D}}$), 26.8 ($C_{15}$$^{\text{rot. B}}$), 26.6 ($C_{16}$$^{\text{rot. B}}$), 26.2 ($C_{15}$$^{\text{rot. C}}$), 25.9 ($C_{15}$$^{\text{rot. A}}$), 22.7 ($C_6$$^{\text{rot. B}}$), 22.6 ($C_6$$^{\text{rot. D}}$), 22.1 ($C_6$$^{\text{rot. A}}$), 21.4 ($C_6$$^{\text{rot. C}}$). **IR** (film, DCM) ν_{max} = 3024 (C–H), 2966 (C–H), 2932 (C–H), 1629 (C=O), 1598, 1492, 1454, 1425, 1269, 1246, 1190, 1147 cm^{-1}. **HRMS** (ESI$^+$) m/z calcd for $C_{21}H_{24}NO$ $[M+H]^+$ 306.1852, found 306.1858.

(2,3-Dihydro-1*H*-pyrrol-1-yl)(2-(1-phenylethyl)phenyl)methanone (3.139a)

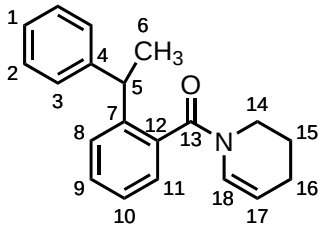


By **GP19**, (2,3-dihydro-1*H*-pyrrol-1-yl)(2-(1-phenylethyl)phenyl)methanone (**3.138a**) (1.44 g, 5.19 mmol) was used as the amide that was stirred for 18 h, and purified by flash column chromatography (SiO_2; gradient elution: 0–30% EtOAc in pet. ether) to yield the title compound as a green gum (1.35 g, 94%).

$\boldsymbol{R_f}$ = 0.41 (30% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers in an approximate 80:20 ratio) δ 7.89–6.95 (9H$^{\text{maj}}$ + 9H$^{\text{min}}$, m, 9 × H_{Ar}), 5.64 (1H$^{\text{maj}}$ + 1H$^{\text{min}}$, br s, H_{17}), 5.23 (1H$^{\text{min}}$, dt, J 4.3, 2.6, H_{16}), 4.85 (1H$^{\text{maj}}$, br s, H_{16}), 4.54 (1H$^{\text{min}}$, q, J 7.2, H_5), 4.43 (1H$^{\text{maj}}$, q, J 7.2, H_5), 4.00–3.88 (1H$^{\text{maj}}$, m, H_{14a}), 3.85 (1H$^{\text{maj}}$, s, H_{14b}), 3.28–3.16 (2H$^{\text{min}}$, m, H_{14}), 2.59 (2H$^{\text{maj}}$, s, H_{15}), 2.43–2.30 (1H$^{\text{min}}$, m, H_{15a}), 2.22–2.05 (1H$^{\text{min}}$, m, H_{15b}), 1.64 (3H$^{\text{min}}$, d, J 7.2, H_6), 1.62 (3H$^{\text{maj}}$, d, J 7.2, H_6). **^{13}C NMR** (126 MHz, $CDCl_3$, mixture of rotamers in an approximate 80:20 ratio) δ 167.0 ($C_{13}$$^{\text{maj}}$), 166.8 ($C_{13}$$^{\text{min}}$), 145.9 ($C_4$$^{\text{maj}}$), 145.7 ($C_4$$^{\text{min}}$), 143.4 ($C_7$$^{\text{maj}}$), 142.8 ($C_7$$^{\text{min}}$), 137.0 ($C_{12}$$^{\text{min}}$), 136.3 ($C_{12}$$^{\text{maj}}$), 130.0 ($C_{17}$$^{\text{maj}}$), 129.5 ($C_{\text{Ar}}$$^{\text{maj}}$), 129.4 ($C_{17}$$^{\text{min}}$), 128.8 ($C_{\text{Ar}}$$^{\text{min}}$), 128.3 ($C_2$$^{\text{maj}}$, $C_2$$^{\text{min}}$), 128.0 ($C_3$$^{\text{min}}$), 127.8 ($C_3$$^{\text{maj}}$), 126.9 ($C_{\text{Ar}}$$^{\text{min}}$), 126.7 ($C_{\text{Ar}}$$^{\text{maj}}$, $C_{\text{Ar}}$$^{\text{maj}}$), 126.2 ($C_{\text{Ar}}$$^{\text{min}}$), 126.1 ($C_{\text{Ar}}$$^{\text{maj}}$), 126.1 ($C_{\text{Ar}}$$^{\text{maj}}$), 126.0 ($C_{\text{Ar}}$$^{\text{min}}$), 126.0 ($C_{\text{Ar}}$$^{\text{min}}$), 112.4 ($C_{16}$$^{\text{maj}}$), 111.2 ($C_{16}$$^{\text{min}}$), 47.1 ($C_{14}$$^{\text{min}}$), 44.6 ($C_{14}$$^{\text{maj}}$), 41.1 ($C_5$$^{\text{maj}}$), 40.8 ($C_5$$^{\text{min}}$), 29.7 ($C_{15}$$^{\text{min}}$), 28.5 ($C_{15}$$^{\text{maj}}$), 21.9 ($C_6$$^{\text{maj}}$), 21.8 ($C_6$$^{\text{min}}$). **IR** (film, $CDCl_3$) ν_{max} =

2965 (C–H), 2930 (C–H), 2875 (C–H), 1629 (C=O), 1597, 1406, 1373, 1356, 1291, 1257, 992, 772, 755, 730, 699 cm^{-1}. **HRMS** (ESI^+) m/z calcd for $C_{19}H_{20}NO$ $[M+H]^+$ 278.1539, found 278.1536.

(3,4-Dihydropyridin-1(2*H*)-yl)(2-(1-phenylethyl)phenyl)methanone (3.139b)

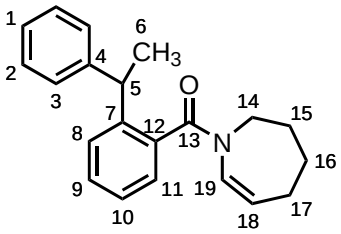


By **GP19**, (3,6-dihydropyridin-1(2H)-yl)(2-(1-phenylethyl)phenyl)methanone (**3.138b**) (1.54 g, 5.29 mmol) was used as the amide that was stirred for 18 h, and purified by flash column chromatography (SiO_2; gradient elution: 0–30% Et_2O in pet. ether) to yield the title compound as a pale yellow oil that solidified upon standing (1.31 g, 85%).

m.p. = 67–69 °C ($CHCl_3$). $\boldsymbol{R_f}$ = 0.34 (30% Et_2O in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers A/B/C/D in an approximate 50:25:25:5 ratio) δ 7.51 ($1H^{\text{rot. B or C}}$, d, J 8.0, H_{Ar}), 7.45–7.05 ($9H^{\text{rot. A}}$ + $18H^{\text{rot. B or C}}$ + $10H^{\text{rot. D}}$, m, ${H_{18}}^{\text{rot. B or C}}$, ${H_{18}}^{\text{D}}$, H_{Ar}), 6.23 ($1H^{\text{rot. B or C}}$, d, J 8.4, H_{18}), 5.80 ($1H^{\text{rot. A}}$, dt, J 8.4, 2.0, H_{18}), 5.25 ($1H^{\text{rot. D}}$, dt, J 8.4, 3.9, H_{17}), 5.14 ($1H^{\text{rot. B or C}}$, dt, J 8.2, 3.9, H_{17}), 4.83 ($1H^{\text{rot. B or C}}$, dt, J 8.3, 3.9, H_{17}), 4.59–4.47 ($1H^{\text{rot. B or C}}$ + $1H^{\text{rot. D}}$, m, ${H_5}^{\text{rot. B or C}}$, ${H_{17}}^{\text{rot. D}}$), 4.38 ($1H^{\text{rot. A}}$, q, J 7.2, H_5), 4.31 ($1H^{\text{rot. D}}$, q, J 7.2, H_5), 4.26 ($1H^{\text{rot. B or C}}$, q, J 7.2, H_5), 3.98–3.81 ($2H^{\text{rot. A}}$, m, H_{14}), 3.59 ($2H^{\text{rot. B or C}}$, ddd, J 12.7, 7.3, 5.1, H_{14}), 3.44–3.27 ($2H^{\text{rot. D}}$, m, H_{14}), 3.03 ($1H^{\text{rot. B or C}}$, ddd, J 12.4, 9.3, 3.1, H_{14a}), 2.43 ($1H^{\text{rot. B or C}}$, ddd, J 12.4, 6.7, 3.4, H_{14b}), 2.16–2.06 ($2H^{\text{rot. B or C}}$ + $2H^{\text{rot. D}}$, m, H_{16}), 2.00–1.86 ($2H^{\text{rot. A}}$ + $3H^{\text{rot. B or C}}$, m, ${H_{16}}^{\text{rot. A}}$, ${H_{15a}}^{\text{rot. B or C}}$, ${H_{16}}^{\text{rot. B or C}}$), 1.83–1.76 ($2H^{\text{rot. A}}$ + $1H^{\text{rot. D}}$, m, ${H_{15}}^{\text{rot. A}}$, ${H_{15a}}^{\text{rot. D}}$), 1.63 ($3H^{\text{rot. A}}$ + $3H^{\text{rot. B or C}}$ + $3H^{\text{rot. D}}$, d, J 7.2, H_6), 1.61 ($3H^{\text{rot. B or C}}$, d, J 7.2, H_6), 1.50–1.36 ($1H^{\text{rot. B or C}}$ + $1H^{\text{rot. D}}$, m, ${H_{15a}}^{\text{rot. B or C}}$, ${H_{15b}}^{\text{rot. D}}$), 1.05–0.93 ($1H^{\text{rot. B or C}}$, m, H_{15b}). **^{13}C NMR** (126 MHz, $CDCl_3$, mixture of rotamers A/B/C/D in an approximate 50:25:25:5 ratio) δ 169.3 (${C_{13}}^{\text{rot. B or C}}$), 169.2 (${C_{13}}^{\text{rot. A}}$), 168.4 (${C_{13}}^{\text{rot. D}}$), 168.4 (${C_{13}}^{\text{rot. B or C}}$), 145.9 (${C_4}^{\text{rot. B or C}}$), 145.5 (${C_4}^{\text{rot. A}}$), 144.8 (${C_4}^{\text{rot. B or C}}$), 144.7 (${C_4}^{\text{rot. D}}$), 144.0 (${C_7}^{\text{rot. B or C}}$, ${C_7}^{\text{rot. D}}$), 143.3 (${C_7}^{\text{rot. A}}$), 142.8 (${C_7}^{\text{rot. B or C}}$), 136.1 (${C_{12}}^{\text{rot. B or C}}$), 135.6 (${C_{12}}^{\text{rot. A}}$), 135.2 (${C_{12}}^{\text{rot. D}}$), 135.0 (${C_{12}}^{\text{rot. B or C}}$), 129.6 (${C_{\text{Ar}}}^{\text{rot. B or C}}$), 129.5 (${C_{\text{Ar}}}^{\text{rot. D}}$), 129.3 (${C_{\text{Ar}}}^{\text{rot. A}}$), 129.2 (${C_{\text{Ar}}}^{\text{rot. B or C}}$), 128.5 (${C_{\text{Ar}}}^{\text{rot. D}}$), 128.5 (${C_{\text{Ar}}}^{\text{rot. A}}$), 128.4 (${C_2}^{\text{rot. A}}$), 128.3 (${C_2}^{\text{rot. B or C}}$), 128.2 (${C_2}^{\text{rot. B or C}}$, ${C_2}^{\text{rot. D}}$), 127.9 (${C_3}^{\text{rot. A}}$, ${C_3}^{\text{rot. B or C}}$), 127.7 (${C_3}^{\text{rot. D}}$), 127.7 (${C_3}^{\text{rot. B or C}}$), 127.3 (${C_{\text{Ar}}}^{\text{rot. A}}$), 127.1 (${C_{18}}^{\text{rot. B or C}}$), 126.9 (${C_{\text{Ar}}}^{\text{rot. B or C}}$), 126.8 (${C_{18}}^{\text{rot. A}}$, ${C_{\text{Ar}}}^{\text{rot. B or C}}$), 126.6 (${C_{\text{Ar}}}^{\text{rot. A}}$), 126.2 (${C_{\text{Ar}}}^{\text{rot. B or C}}$, ${C_{\text{Ar}}}^{\text{rot. D}}$), 126.1 (${C_{\text{Ar}}}^{\text{rot. A}}$, 3 × ${C_{\text{Ar}}}^{\text{rot. B or C}}$), 126.0 (2 × ${C_{\text{Ar}}}^{\text{rot. B or C}}$, ${C_{\text{Ar}}}^{\text{rot. D}}$), 126.0 (${C_{\text{Ar}}}^{\text{rot. D}}$), 124.2 (${C_{18}}^{\text{rot. D}}$), 123.8 (${C_{18}}^{\text{rot. B or C}}$), 110.6 (${C_{17}}^{\text{rot. D}}$), 110.5 (${C_{17}}^{\text{rot. B or C}}$), 107.9 (${C_{17}}^{\text{rot. B or C}}$), 107.4

($C_{17}$$^{\text{rot. A}}$), 45.9 ($C_{14}$$^{\text{rot. D}}$), 45.7 ($C_{14}$$^{\text{rot. B or C}}$), 41.2 ($C_{5}$$^{\text{rot. A}}$), 40.9 ($C_{5}$$^{\text{rot. B or C}}$), 40.8 ($C_{5}$$^{\text{rot. B or C}}$), 40.7 ($C_{5}$$^{\text{rot. D}}$), 40.5 ($C_{14}$$^{\text{rot. B or C}}$), 40.2 ($C_{14}$$^{\text{rot. A}}$), 22.4 ($C_{6}$$^{\text{rot. B or C}}$), 22.3 ($C_{15}$$^{\text{rot. D}}$), 22.2 ($C_{16}$$^{\text{rot. D}}$), 22.2 ($C_{6}$$^{\text{rot. A}}$), 21.9 ($C_{16}$$^{\text{rot. A}}$), 21.7 ($C_{15}$$^{\text{rot. B or C}}$, $C_{16}$$^{\text{rot. B or C}}$), 21.6 ($C_{16}$$^{\text{rot. B or C}}$), 21.5 ($C_{15}$$^{\text{rot. B or C}}$), 21.3 ($C_{15}$$^{\text{rot. A}}$), 21.3 ($C_{5}$$^{\text{rot. D}}$), 21.2 ($C_{6}$$^{\text{rot. B or C}}$). **IR** (film, DCM) ν_{max} = 3058 (C–H), 3025 (C–H), 2965 (C–H), 1634 (C=O), 1613, 1597, 1413, 771, 755, 699 cm^{-1}. **HRMS** (ESI$^+$) m/z calcd for $C_{20}H_{22}NO$ $[M+H]^+$ 292.1696, found 292.1695.

(2-(1-Phenylethyl)phenyl)(2,3,4,5-tetrahydro-1*H*-azepin-1-yl)methanone (3.139c)

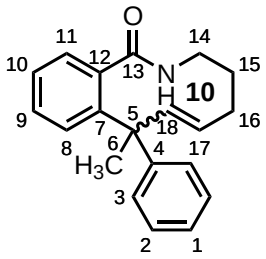


By **GP19**, (2-(1-phenylethyl)phenyl)(2,3,4,7-tetrahydro-1*H*-azepin-1-yl) methanone (**3.138c**) (1.49 g, 4.88 mmol) was used as the amide that was stirred for 18 h, and purified by flash column chromatography (SiO_2; gradient elution: 0–30% Et_2O in pet. ether) to yield the title compound as a pale yellow oil (1.18 g, 79%).

$\boldsymbol{R_f}$ = 0.37 (30% Et_2O in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers A/B/C in an approximate 70:25:5 ratio) δ 7.53 (1H$^{\text{rot. B}}$, d, J 7.8, H_{Ar}), 7.41 (1H$^{\text{rot. B}}$, td, J 7.7, 1.5, H_{Ar}), 7.38–7.07 (9H$^{\text{rot. A}}$ + 7H$^{\text{rot. B}}$ + 9H$^{\text{rot. C}}$, m, H_{Ar}), 6.98 (1H$^{\text{rot. C}}$, d, J 8.8, H_{19}), 6.88 (1H$^{\text{rot. B}}$, d, J 9.0, H_{19}), 6.26–5.38 (1H$^{\text{rot. A}}$, m, H_{19}), 5.36–5.30 (1H$^{\text{rot. C}}$, m, H_{18}), 5.26 (1H$^{\text{rot. B}}$, dt, J 9.0, 5.4, H_{18}), 4.81 (1H$^{\text{rot. A}}$, br s, H_{18}), 4.49 (1H$^{\text{rot. B}}$, q, J 7.2, H_5), 4.43 (1H$^{\text{rot. A}}$, br s, H_5), 4.29 (1H$^{\text{rot. C}}$, q, J 7.2, H_5), 4.20 (1H$^{\text{rot. A}}$, br s, H_{14a}), 3.93–3.18 (1H$^{\text{rot. A}}$ + 2H$^{\text{rot. C}}$, m, $H_{14b}$$^{\text{rot. A}}$, $H_{14}$$^{\text{rot. C}}$), 2.80 (1H$^{\text{rot. B}}$, dt, J 14.6, 4.4, $H_{14a}$$^{\text{rot. B}}$), 2.38 (1H$^{\text{rot. B}}$, ddd, J 14.6, 10.7, 4.0, $H_{14b}$$^{\text{rot. B}}$), 2.30–2.07 (2H$^{\text{rot. A}}$ + 2H$^{\text{rot. B}}$ + 2H$^{\text{rot. C}}$, m, H_{17}), 2.00–1.79 (2H$^{\text{rot. A}}$ + 2H$^{\text{rot. C}}$, m, H_{15}), 1.84–1.66 (2H$^{\text{rot. A}}$ + 1H$^{\text{rot. B}}$ + 2H$^{\text{rot. C}}$, m, $H_{16}$$^{\text{rot. A}}$, $H_{16a}$$^{\text{rot. b}}$, $H_{16}$$^{\text{rot. C}}$), 1.63 (3H$^{\text{rot. A}}$ + 3H$^{\text{rot. B}}$ + 3H$^{\text{rot. C}}$, d, J 7.2, H_6), 1.56–1.43 (2H$^{\text{rot. B}}$, m, H_{15a}, H_{16b}), 1.29–1.15 (1H$^{\text{rot. B}}$, m, H_{15b}). **^{13}C NMR** (126 MHz, $CDCl_3$, mixture of rotamers A/B/C in an approximate 70:25:5 ratio) δ 170.6 ($C_{13}$$^{\text{rot. B}}$), 170.5 ($C_{13}$$^{\text{rot. C}}$), 170.2 ($C_{13}$$^{\text{rot. A}}$), 145.7 ($C_{4}$$^{\text{rot. B}}$), 145.4 ($C_{4}$$^{\text{rot. A}}$), 144.6 ($C_{4}$$^{\text{rot. C}}$), 143.6 ($C_{7}$$^{\text{rot. C}}$), 143.3 ($C_{7}$$^{\text{rot. B}}$), 142.2 ($C_{7}$$^{\text{rot. A}}$), 136.5 ($C_{12}$$^{\text{rot. A}}$, $C_{12}$$^{\text{rot. B}}$), 135.4 ($C_{12}$$^{\text{rot. C}}$), 131.8 ($C_{19}$$^{\text{rot. A}}$), 129.7 ($C_{19}$$^{\text{rot. C}}$), 129.4 ($C_{19}$$^{\text{rot. B}}$), 129.4 ($C_{Ar}$$^{\text{rot. C}}$), 129.3 ($C_{Ar}$$^{\text{rot. A}}$), 129.2 ($C_{Ar}$$^{\text{rot. B}}$), 128.4 ($C_{2}$$^{\text{rot. B}}$), 128.4 ($C_{2}$$^{\text{rot. C}}$), 128.3 ($C_{2}$$^{\text{rot. A}}$), 127.9 ($C_{3}$$^{\text{rot. B}}$), 127.9 ($C_{3}$$^{\text{rot. A}}$), 127.8 ($C_{3}$$^{\text{rot. C}}$), 127.1 ($C_{Ar}$$^{\text{rot. C}}$), 127.0 (2 × $C_{Ar}$$^{\text{rot. A}}$), 126.8 ($C_{Ar}$$^{\text{rot. B}}$), 126.3 ($C_{Ar}$$^{\text{rot. C}}$), 126.2 ($C_{Ar}$$^{\text{rot. B}}$), 126.2 ($C_{Ar}$$^{\text{rot. A}}$), 126.1 (2 × $C_{Ar}$$^{\text{rot. C}}$), 126.0 ($C_{Ar}$$^{\text{rot. C}}$), 125.9 ($C_{Ar}$$^{\text{rot. A}}$), 125.9 (2 × $C_{Ar}$$^{\text{rot. B}}$), 118.3 ($C_{18}$$^{\text{rot. B}}$), 118.0 ($C_{18}$$^{\text{rot. C}}$), 116.8 ($C_{18}$$^{\text{rot. A}}$), 50.2 ($C_{14}$$^{\text{rot. C}}$), 49.5 ($C_{14}$$^{\text{rot. B}}$), 45.5 ($C_{14}$$^{\text{rot. A}}$), 41.1 ($C_{5}$$^{\text{rot. C}}$), 41.0 ($C_{5}$$^{\text{rot. B}}$), 40.8 ($C_{5}$$^{\text{rot. A}}$), 29.0 ($C_{15}$$^{\text{rot. C}}$), 28.5 ($C_{15}$$^{\text{rot. B}}$), 27.7 ($C_{15}$$^{\text{rot. A}}$), 26.6

($C_{17}^{\text{rot. C}}$), 26.5 ($C_{17}^{\text{rot. A}}$), 26.4 ($C_{17}^{\text{rot. B}}$), 25.1 ($C_{16}^{\text{rot. C}}$), 25.0 ($C_{16}^{\text{rot. A}}$), 24.8 ($C_{16}^{\text{rot. B}}$), 22.2 ($C_{6}^{\text{rot. B}}$), 21.7 ($C_{6}^{\text{rot. A}}$), 21.3 ($C_{6}^{\text{rot. C}}$). **IR** (film, DCM) ν_{max} = 3025 (C−H), 2930 (C−H), 1632 (C=O), 1598, 1492, 1450, 1406, 1386, 1365, 1352, 1341, 1315, 1276, 1254, 1224, 1188, 1143, 1077, 1027 cm^{-1}. **HRMS** (ESI^+) m/z calcd for $C_{21}H_{24}NO$ $[M+H]^+$ 306.1852, found 306.1858.

8-Methyl-8-phenyl-3,4,5,8-tetrahydrobenzo[*c*]azecin-1(2*H*)-one (3.140b)

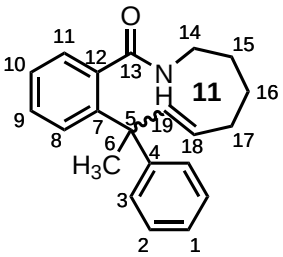


In a microwave vial, (3,4-dihydropyridin-1(2*H*)-yl)(2-(1-phenylethyl)phenyl) methanone (**3.139b**) (58 mg, 0.20 mmol, 1.0 eq.) was dissolved in anhydrous THF (2.0 mL), and KHMDS (400 µL, 1 M in THF, 0.40 mmol, 2.0 eq.) added dropwise. The vial was sealed, the reaction mixture stirred at 100 °C under microwave irradiation for 3.5 h, and quenched by the addition of H_2O (5 mL). The reaction mixture was extracted with EtOAc (3 × 5 mL), the combined organic extracts washed with brine (5 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2; gradient elution: 0–60% EtOAc in pet. ether) to yield **(*E*)-3.140b** as a yellow gum (12 mg, 21%) and **(*Z*)-3.140b** as a yellow gum (23 mg, 39%).

(*E*)-3.140b:
***R*$_f$** = 0.30 (30% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers in an approximate 60:40 ratio) δ 7.43–7.07 ($8H^{maj}$ + $8H^{min}$, m, H_{Ar}), 7.00 ($1H^{maj}$, dd, *J* 8.0, 1.3, H_{Ar}), 6.96 ($1H^{min}$, dd, *J* 7.6, 1.6, H_{Ar}), 6.27 ($1H^{maj}$, dd, *J* 16.0, 1.8, H_{18}), 6.12 ($1H^{min}$, dd, *J* 16.0, 1.7, H_{18}), 5.67 ($1H^{maj}$, ddd, *J* 16.0, 10.7, 3.7, H_{17}), 5.45 ($1H^{maj}$, br t, *J* 11.1, N*H*), 5.42 ($1H^{min}$, br t, *J* 11.1, N*H*), 5.12–5.02 ($1H^{min}$, m, H_{17}), 4.3–4.19 ($1H^{maj}$ + $1H^{min}$, m, H_{14a}), 3.10–3.00 ($1H^{maj}$ + $1H^{min}$, m, H_{14b}), 2.45–2.33 ($1H^{maj}$, m, H_{16a}), 2.31–2.15 ($1H^{maj}$ + $2H^{min}$, m, $H_{16b}{}^{maj}$, $H_{16}{}^{min}$), 1.89 ($3H^{maj}$, s, H_6), 1.88 ($3H^{min}$, s, H_6), 1.75–1.58 ($2H^{maj}$ + $1H^{min}$, m, $H_{15}{}^{maj}$, $H_{15a}{}^{min}$), 1.57–1.33 ($1H^{min}$, m, H_{15b}). **^{13}C NMR** (101 MHz, $CDCl_3$, mixture of rotamers in an approximate 60:40 ratio) δ 173.8 ($C_{13}{}^{min}$), 173.6 ($C_{13}{}^{maj}$), 150.1 ($C_7{}^{maj}$), 148.8 ($C_7{}^{min}$), 147.0 ($C_4{}^{maj}$), 146.2 ($C_4{}^{min}$), 137.8 ($C_{12}{}^{min}$), 137.8 ($C_{18}{}^{maj}$), 137.2 ($C_{12}{}^{maj}$), 137.0 ($C_{18}{}^{min}$), 133.4 ($C_{17}{}^{min}$), 131.4 ($C_{Ar}{}^{min}$), 130.9 ($C_{Ar}{}^{maj}$), 129.4 ($C_{17}{}^{maj}$), 129.1 ($C_{Ar}{}^{maj}$), 128.9 ($C_{Ar}{}^{min}$), 128.4 ($C_2{}^{maj}$, $C_2{}^{min}$), 127.2 ($C_3{}^{maj}$, $C_3{}^{min}$)„ 126.8 ($C_{Ar}{}^{maj}$), 126.7 ($C_{Ar}{}^{maj}$), 126.1 ($C_{Ar}{}^{min}$), 126.0 ($C_{Ar}{}^{maj}$), 126.0 ($C_{Ar}{}^{min}$), 125.9 ($C_{Ar}{}^{min}$), 50.0 ($C_5{}^{min}$), 49.1 ($C_5{}^{maj}$), 40.2 ($C_{14}{}^{min}$), 40.2 ($C_{14}{}^{maj}$), 32.6 ($C_{16}{}^{maj}$), 32.5 ($C_{16}{}^{min}$), 31.1 ($C_6{}^{min}$), 27.9 ($C_{15}{}^{maj}$), 27.9 ($C_{15}{}^{min}$), 27.8 ($C_6{}^{maj}$). **IR** (film, DCM) ν_{max} = 3286 (N−H, br), 3058 (C−H), 2925 (C−H), 1638 (C=O), 1598, 1536, 1439, 1310, 759, 731, 700 cm^{-1}. **HRMS** (ESI^+) m/z calcd for $C_{20}H_{22}NO$ $[M+H]^+$ 292.1696, found 292.1690.

(*Z*)-3.140b:
***R*$_f$** = 0.11 (30% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers in an approximate 65:35 ratio) δ 7.52–7.07 ($9H^{maj}$ + $8H^{min}$, m, H_{Ar}), 6.88–6.82 ($1H^{min}$, m, H_{Ar}), 5.99 ($1H^{min}$, dt, *J* 11.5, 1.8, H_{18}), 5.99 ($1H^{min}$, br s, N*H*), 5.87 ($1H^{maj}$, app br d, *J* 10.5, N*H*), 5.70 ($1H^{maj}$, dd, *J* 11.7, 2.4, H_{18}), 5.53–5.37 ($1H^{maj}$ + $1H^{min}$, m, H_{17}), 3.47–3.20 ($2H^{maj}$ + $2H^{min}$, m, H_{14}), 2.25–2.04 ($2H^{maj}$ + $2H^{min}$, m, H_{16}), 2.04 ($3H^{maj}$, s, H_6), 2.01 ($3H^{maj}$, s, H_6), 1.64–1.53 ($2H^{maj}$ + $2H^{min}$, m, H_{15}). **^{13}C NMR** (101 MHz, $CDCl_3$, mixture of rotamers in an approximate 65:35 ratio) δ 175.9 ($C_{13}{}^{min}$), 175.8 ($C_{13}{}^{maj}$), 152.0 ($C_7{}^{min}$), 147.8 ($C_4{}^{maj}$), 147.0 ($C_7{}^{maj}$), 145.2 ($C_4{}^{min}$), 137.4 ($C_{18}{}^{min}$), 136.1 ($C_{18}{}^{maj}$), 134.3 ($C_{12}{}^{min}$), 133.5 ($C_{12}{}^{maj}$), 132.8 ($C_{17}{}^{min}$), 132.0 ($C_{17}{}^{maj}$), 129.9 ($C_{Ar}{}^{min}$), 129.9 ($C_{Ar}{}^{maj}$), 129.6 ($C_{Ar}{}^{min}$), 129.1 ($C_{Ar}{}^{maj}$), 128.4 ($C_2{}^{min}$), 128.4 ($C_2{}^{maj}$), 128.2 ($C_3{}^{maj}$), 128.1 ($C_3{}^{min}$), 128.0 ($C_{Ar}{}^{min}$), 127.2 ($C_{Ar}{}^{maj}$), 126.3 ($C_{Ar}{}^{maj}$), 126.2 ($C_{Ar}{}^{min}$), 125.9 ($C_{Ar}{}^{maj}$), 125.7 ($C_{Ar}{}^{min}$), 50.1 ($C_5{}^{maj}$), 48.1 ($C_5{}^{min}$), 45.4 ($C_{14}{}^{min}$), 45.2 ($C_{14}{}^{maj}$), 33.3 ($C_6{}^{maj}$), 31.6 ($C_{15}{}^{min}$), 31.1 ($C_{15}{}^{maj}$), 30.2 ($C_6{}^{min}$), 28.7 ($C_{16}{}^{maj}$), 28.4 ($C_{16}{}^{min}$). **IR** (film, DCM) ν_{max} = 3208 (N–H, br), 3058 (C–H), 2938 (C–H), 1648 (C=O), 1435, 1399, 1343, 1029, 908, 764, 728, 698, 592 cm^{-1}. **HRMS** (ESI^+) *m*/*z* calcd for $C_{20}H_{22}NO$ $[M+H]^+$ 292.1696, found 292.1690.

9-Methyl-9-phenyl-2,3,4,5,6,9-hexahydro-1*H*-benzo[*c*][1]azacyclo undecin-1-one (3.140c)



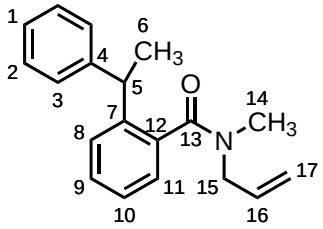
In a microwave vial, (2-(1-phenylethyl)phenyl)(2,3,4,5-tetrahydro-1*H*-azepin-1-yl)methanone (**3.139c**) (153 mg, 0.50 mmol, 1.0 eq.) was dissolved in anhydrous THF (5.0 mL), and KHMDS (1.0 mL, 1 M in THF, 1.00 mmol, 2.0 eq.) added dropwise. The vial was sealed, the reaction mixture stirred at 100 °C under microwave irradiation for 5 h, and quenched by the dropwise addition of saturated aqueous NH_4Cl (5 mL). The reaction mixture was diluted with H_2O (15 mL), and extracted with 3:1 $CHCl_3$/IPA (3 × 5 mL). The combined organic extracts were dried ($MgSO_4$), and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2; gradient elution: 0–60% EtOAc in pet. ether) to yield **(*E*)-3.140c** as a yellow dry film (58 mg, 38%) and **(*Z*)-3.140c** as a yellow dry film (60 mg, 39%).

(*E*)-3.140c:
***R*$_f$** = 0.34 (30% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36–7.27 (1H, m, H_2, H_3), 7.25–7.20 (2H, m, H_1, H_{Ar}), 7.20–7.14 (2H, m, 2 × H_{Ar}), 6.87–6.82 (1H, m, H_{Ar}), 5.93 (1H, dt, *J* 15.8, 1.3, H_{19}), 5.84 (1H, br t, *J* 6.5, N*H*),

5.48 (1H, dt, J 15.8, 7.2, H_{18}), 3.67–3.55 (1H, m, H_{14a}), 3.15–3.03 (1H, m, H_{14b}), 2.11–2.01 (2H, m, H_{17}), 1.97 (3H, s, H_6), 1.93–1.78 (1H, m, H_{15a}), 1.79–1.52 (3H, m, H_{15a}, H_{16}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.4 (C_{13}), 148.4 (C_7), 146.4 (C_4), 138.3 (C_{19}), 138.2 (C_{12}), 130.3 (C_{Ar}), 129.8 (C_{18}), 129.0 (C_{Ar}), 128.1 (C_2, C_3), 127.9 (C_{Ar}), 126.2 (C_{Ar}), 126.1 (C_1), 50.5 (C_5), 41.1 (C_{14}), 33.9 (C_{17}), 28.6 (C_6), 27.9 (C_{15}), 26.6 (C_{16}). **IR** (film, DCM) ν_{max} = 3288 (N–H, br), 3057 (C–H), 2924 (C–H), 2854 (C–H), 1634 (C=O), 1597, 1536, 1440, 1309 cm^{-1}. **HRMS** (ESI$^+$) m/z calcd for $C_{21}H_{24}NO$ $[M+H]^+$ 306.1852, found 306.1853.

(*Z*)-3.140c:
***R*$_f$** = 0.19 (30% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.55 (1H, br s, H_{Ar}), 7.45 (1H, d, J 7.5, H_{Ar}), 7.43–7.39 (2H, m, H_2), 7.39–7.27 (3H, m, H_3, H_{Ar}), 7.24–7.18 (1H, m, H_{Ar}), 7.18 –7.11 (1H, m, H_{Ar}), 5.63 (1H, dd, J 12.0, 2.5, H_{19}), 5.48 (1H, br s, NH), 5.37 (1H, td, J 12.0, 2.3, H_{18}), 3.70–3.59 (1H, m, H_{14a}), 2.76–2.64 (1H, m, H_{14b}), 2.23–2.10 (1H, m, H_{15a}), 1.89 (3H, s, H_6), 1.56 (1H, br d, J 16.3, H_{17a}), 1.47–1.36 (2H, m, H_{16}), 1.16–1.04 (1H, m, H_{15b}), 1.03–0.91 (1H, m, H_{17b}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.3 (C_{13}), 148.8 (C_7), 141.2 (C_4), 139.0 (C_{12}), 135.2 (C_{19}), 131.7 (C_{18}), 130.0 (C_{Ar}), 129.7 (C_2), 129.1 (C_{Ar}), 128.3 (C_3), 127.2 (C_{Ar}), 126.5 (2 × C_{Ar}), 50.6 (C_5), 41.6 (C_{14}), 35.1 (C_6), 29.0 (C_{16}), 27.8 (C_{17}), 24.8 (C_{15}). **IR** (film, DCM) ν_{max} = 3293 (N–H, br), 3057 (C–H), 2920 (C–H), 2853 (C–H), 1637 (C=O), 1598, 1524, 1442, 1308 cm^{-1}. **HRMS** (ESI$^+$) m/z calcd for $C_{21}H_{24}NO$ $[M+H]^+$ 306.1852, found 306.1855.

N-Allyl-*N*-methyl-2-(1-phenylethyl)benzamide (3.137d)

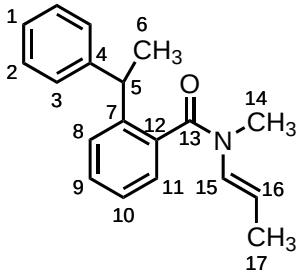


By **GP2**, the acid chloride of 2-(1-phenylethyl)benzoic acid (**3.133**) (1.79 g, 7.91 mmol) was made by stirring with oxalyl chloride for 2.5 h. *N*-Allylmethylamine (910 µL, 9.48 mmol) was used as the general amine that was stirred with the acid chloride intermediate for 24 h, and purified by flash column chromatography (SiO_2; gradient elution: 7–30% EtOAc in pet. ether) to yield the title compound as a pale yellow oil (2.02 g, 91%).

***R*$_f$** = 0.23 (20% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers A/B/C/D in an approximate 45:35:10:10 ratio) δ 7.55–7.45 (1H$^{rot.\ A}$ + 1H$^{rot.\ B}$, m, H_{Ar}), 7.42–7.29 (1H$^{rot.\ A}$ + 1H$^{rot.\ B}$ + 8H$^{rot.\ C\ or\ D}$, m, H_{Ar}), 7.29–7.06 (7H$^{rot.\ A}$ + 7H$^{rot.\ B}$ + 14H$^{rot.\ C\ or\ D}$, m, H_{Ar}), 5.96–5.60 (1H$^{rot.\ B}$ + 2H$^{rot.\ C\ or\ D}$, m, H_{16}), 5.34 (1H$^{rot.\ A}$, dddd, J 16.8, 10.6, 6.2, 4.3, H_{16}), 5.24–5.12 (2H$^{rot.\ A}$ + 2H$^{rot.\ C\ or\ D}$, m, H_{17}), 5.06 (1H$^{rot.\ B}$ + 1H$^{rot.\ C\ or\ D}$, dq, J 10.3, 1.3, $H_{17\,trans}$), 4.97 (1H$^{rot.\ B}$ + 1H$^{rot.\ C\ or\ D}$, dq, J 17.1, 1.7, $H_{17\,cis}$), 4.49 (1H$^{rot.\ A}$ + 1H$^{rot.\ B}$, q, J 7.2, H_5), 4.29 (2H$^{rot.\ C\ or\ D}$, q, J 7.2, H_5), 4.19 (1H$^{rot.\ A}$ + 1H$^{rot.\ C\ or\ D}$, dd, J 14.7, 5.9,

H_{15a}), 3.88–3.73 (2H$^{\text{rot. B}}$ + 2H$^{\text{rot. C or D}}$, m, $H_{15}{}^{\text{rot. B}}$, $H_{15a}{}^{\text{rot. C or D}}$, $H_{15b}{}^{\text{rot. C or D}}$), 3.51 (1H$^{\text{rot. C or D}}$, dd, J 16.4, 5.7, H_{15b}), 3.16 (1H$^{\text{rot. A}}$, ddt, J 16.5, 4.3, 1.9, H_{15a}), 3.04 (3H$^{\text{rot. C or D}}$, s, H_{14}), 2.83 (3H$^{\text{rot. A}}$, s, H_{14}), 2.77 (3H$^{\text{rot. C or D}}$, s, H_{14}), 2.41 (1H$^{\text{rot. A}}$, ddt, J 16.5, 6.2, 1.4, H_{15b}), 2.13 (3H$^{\text{rot. B}}$, s, H_{14}), 1.62 (3H$^{\text{rot. A}}$ + 3H$^{\text{rot. C or D}}$, d, J 7.2, H_6), 1.62 (3H$^{\text{rot. B}}$ + 3H$^{\text{rot. C or D}}$, d, J 7.2, H_6). **^{13}C NMR** (126 MHz, $CDCl_3$, mixture of rotamers A/B/C/D in an approximate 45:35:10:10 ratio) δ 171.5 ($C_{13}{}^{\text{rot. A}}$, $C_{13}{}^{\text{rot. C or D}}$), 171.0 ($C_{13}{}^{\text{rot. B}}$, $C_{13}{}^{\text{rot. C or D}}$), 146.1 ($C_4{}^{\text{rot. A}}$, $C_4{}^{\text{rot. C or D}}$), 146.0 ($C_4{}^{\text{rot. B}}$, $C_4{}^{\text{rot. C or D}}$), 142.1 ($C_7{}^{\text{rot. B}}$, $C_7{}^{\text{rot. C or D}}$), 141.9 ($C_7{}^{\text{rot. A}}$, $C_7{}^{\text{rot. C or D}}$), 136.9 ($C_{12}{}^{\text{rot. B}}$, $C_{12}{}^{\text{rot. C or D}}$), 136.8 ($C_{12}{}^{\text{rot. A}}$, $C_{12}{}^{\text{rot. C or D}}$), 132.9 ($C_{16}{}^{\text{rot. C or D}}$), 132.8 ($C_{16}{}^{\text{rot. A}}$), 132.7 ($C_{16}{}^{\text{rot. B}}$, $C_{16}{}^{\text{rot. C or D}}$), 129.2 ($C_{\text{Ar}}{}^{\text{rot. C or D}}$), 129.0 ($C_{\text{Ar}}{}^{\text{rot. A}}$, $C_{\text{Ar}}{}^{\text{rot. C or D}}$), 128.9 ($C_{\text{Ar}}{}^{\text{rot. B}}$), 128.4 ($C_{\text{Ar}}{}^{\text{rot. C or D}}$), 128.3 ($C_2{}^{\text{rot. A}}$), 128.3 ($C_{\text{Ar}}{}^{\text{rot. B}}$, $C_2{}^{\text{rot. C or D}}$), 128.2 ($C_{\text{Ar}}{}^{\text{rot. C or D}}$), 128.2 ($C_2{}^{\text{rot. C or D}}$), 127.9 ($C_3{}^{\text{rot. B}}$), 127.9 ($C_3{}^{\text{rot. A}}$, $C_3{}^{\text{rot. C or D}}$), 127.8 ($C_3{}^{\text{rot. C or D}}$), 127.0 ($C_{\text{Ar}}{}^{\text{rot. B}}$), 126.7 ($C_{\text{Ar}}{}^{\text{rot. A}}$), 126.1 ($C_{\text{Ar}}{}^{\text{rot. B}}$, $C_{\text{Ar}}{}^{\text{rot. C or D}}$, $C_{\text{Ar}}{}^{\text{rot. C or D}}$), 126.1 ($C_{\text{Ar}}{}^{\text{rot. B}}$, $C_{\text{Ar}}{}^{\text{rot. B}}$), 126.1 ($C_{\text{Ar}}{}^{\text{rot. A}}$, $C_{\text{Ar}}{}^{\text{rot. C or D}}$), 125.9 ($C_{\text{Ar}}{}^{\text{rot. C or D}}$, $C_{\text{Ar}}{}^{\text{rot. C or D}}$), 125.9 ($C_{\text{Ar}}{}^{\text{rot. A}}$, $C_{\text{Ar}}{}^{\text{rot. C or D}}$), 125.8 ($C_{\text{Ar}}{}^{\text{rot. C or D}}$), 125.5 ($C_{\text{Ar}}{}^{\text{rot. A}}$), 117.9 ($C_{17}{}^{\text{rot. A}}$), $C_{17}{}^{\text{rot. C or D}}$), 117.3 ($C_{17}{}^{\text{rot. B}}$, $C_{17}{}^{\text{rot. C or D}}$), 53.6 ($C_{15}{}^{\text{rot. C or D}}$), 52.7 ($C_{15}{}^{\text{rot. A}}$), 49.3 ($C_{15}{}^{\text{rot. C or D}}$), 49.1 ($C_{15}{}^{\text{rot. B}}$), 41.1 ($C_5{}^{\text{rot. C or D}}$), 40.9 ($C_5{}^{\text{rot. A}}$), ($C_5{}^{\text{rot. B}}$), $C_5{}^{\text{rot. C or D}}$), 36.4 ($C_{14}{}^{\text{rot. C or D}}$), 35.7 ($C_{14}{}^{\text{rot. B}}$), 32.1 ($C_{14}{}^{\text{rot. C or D}}$), 31.6 ($C_{14}{}^{\text{rot. A}}$), 22.4 ($C_6{}^{\text{rot. B}}$, $C_6{}^{\text{rot. C or D}}$), 22.2 ($C_6{}^{\text{rot. A}}$), 21.2 ($C_6{}^{\text{rot. C or D}}$). **IR** (film, $CDCl_3$) ν_{max} = 3025 (C–H), 2968 (C–H), 2932 (C–H), 1627 (C=O), 1598, 1493, 1452, 1418, 1398, 1258, 1057, 907, 773, 755, 727, 699, 645, 547 cm^{-1}. **HRMS** (ESI$^+$) m/z calcd for $C_{19}H_{22}NO$ $[M+H]^+$ 280.1696, found 280.1690.

(*E*)-*N*-Methyl-2-(1-phenylethyl)-*N*-(prop-1-en-1-yl)benzamide (3.139d)

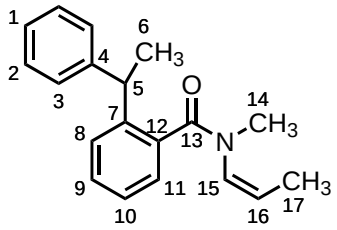


By **GP19**, *N*-allyl-*N*-methyl-2-(1-phenylethyl)benzamide (**3.137d**) (1.39 g, 4.98 mmol) was used as the amide that was stirred for 19 h, and purified by flash column chromatography (SiO_2; gradient elution: 7–30% Et_2O in pet. ether) to yield the title compound as a pale yellow oil (1.29 g, 93%).

***R*$_f$** = 0.30 (30% Et_2O in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers A/B/C/D in an approximate 45:25:20:10 ratio) δ 7.59–7.53 (1H$^{\text{rot. D}}$, m, H_{15}), 7.51 (1H$^{\text{rot. B}}$, d, J 7.7, H_{Ar}), 7.47–7.44 (1H$^{\text{rot. C}}$, m, H_{Ar}), 7.44–7.04 (9H$^{\text{rot. A}}$ + 8H$^{\text{rot. B}}$ + 9H$^{\text{rot. C}}$ + 9H$^{\text{rot. D}}$, m, H_{Ar}, $H_{15}{}^{\text{rot. C}}$), 6.30 (1H$^{\text{rot. C}}$, d, J 13.6, H_{15}), 5.77 (1H$^{\text{rot. A}}$, d, J 13.9, H_{15}), 5.20–5.07 (1H$^{\text{rot. D}}$, m, H_{16}), 5.06–4.96 (1H$^{\text{rot. C}}$, m, H_{16}), 4.91 (1H$^{\text{rot. B}}$, dq, J 13.5, 6.6, H_{16}), 4.69 (1H$^{\text{rot. A}}$, dq, J 13.9, 6.6, H_{16}), 4.41

(1H$^{\text{rot. B}}$, q, J 7.2, H_5), 4.35–4.22 (1H$^{\text{rot. A}}$ + 1H$^{\text{rot. D}}$, m, H_5), 4.19 (1H$^{\text{rot. C}}$, br s, H_5), 3.25 (3H$^{\text{rot. C}}$, s, H_{14}), 3.11 (3H$^{\text{rot. A}}$, s, H_{14}), 2.90 (3H$^{\text{rot. D}}$, s, H_{14}), 2.19 (3H$^{\text{rot. B}}$, s, H_{14}), 1.82 (3H$^{\text{rot. D}}$, d, J 6.7, H_{17}), 1.78 (3H$^{\text{rot. D}}$, dd, J 6.6, 1.6, H_{17}), 1.63 (3H$^{\text{rot. B}}$ + 3H$^{\text{rot. D}}$, d, J 7.2, H_6), 1.61 (3H$^{\text{rot. A}}$ + 3H$^{\text{rot. C}}$, d, J 7.2, H_6), 1.57 (3H$^{\text{rot. C}}$, d, J 6.7, H_{17}), 1.32 (3H$^{\text{rot. A}}$, d, J 6.6, H_{17}). **^{13}C NMR** (126 MHz, $CDCl_3$, mixture of rotamers A/B/C/D in an approximate 45:25:20:10 ratio) δ 170.1 ($C_{13}^{\text{rot. A}}$, $C_{13}^{\text{rot. C}}$), 169.4 ($C_{13}^{\text{rot. B}}$, $C_{13}^{\text{rot. D}}$), 145.6 ($C_4^{\text{rot. B}}$), 145.4 ($C_4^{\text{rot. A}}$), 144.8 ($C_4^{\text{rot. C}}$), 144.6 ($C_4^{\text{rot. D}}$), 143.8 ($C_7^{\text{rot. C}}$), 143.7 ($C_7^{\text{rot. D}}$), 142.9 ($C_7^{\text{rot. A}}$), 142.5 ($C_7^{\text{rot. B}}$), 136.7 ($C_{12}^{\text{rot. B}}$), 136.2 ($C_{12}^{\text{rot. A}}$), 135.6 ($C_{12}^{\text{rot. D}}$), 135.3 ($C_{12}^{\text{rot. C}}$), 130.2 ($C_{15}^{\text{rot. C}}$), 129.8 ($C_{15}^{\text{rot. A}}$), 129.6 ($C_{\text{Ar}}^{\text{rot. D}}$), 129.5 ($C_{\text{Ar}}^{\text{rot. C}}$), 129.3 ($C_{\text{Ar}}^{\text{rot. A}}$), 129.2 ($C_{\text{Ar}}^{\text{rot. B}}$), 128.4 ($C_2^{\text{rot. B}}$), 128.3 ($C_2^{\text{rot. D}}$), 128.2 ($C_2^{\text{rot. A}}$, $C_2^{\text{rot. C}}$), 127.9 ($C_3^{\text{rot. B}}$), 127.8 ($C_3^{\text{rot. A}}$), 127.7 ($C_3^{\text{rot. C}}$, $C_3^{\text{rot. D}}$), 127.4 ($C_{15}^{\text{rot. D}}$), 127.2 ($C_{15}^{\text{rot. B}}$, $C_{\text{Ar}}^{\text{rot. C}}$), 127.1 ($C_{\text{Ar}}^{\text{rot. B}}$), 126.9 ($C_{\text{Ar}}^{\text{rot. B}}$), 126.6 ($C_{\text{Ar}}^{\text{rot. C}}$), 126.6 ($C_{\text{Ar}}^{\text{rot. A}}$, $C_{\text{Ar}}^{\text{rot. D}}$), 126.2 ($C_{\text{Ar}}^{\text{rot. A}}$, $C_{\text{Ar}}^{\text{rot. B}}$, $C_{\text{Ar}}^{\text{rot. D}}$), 126.1 ($C_{\text{Ar}}^{\text{rot. C}}$, $C_{\text{Ar}}^{\text{rot. D}}$), 126.1 ($C_{\text{Ar}}^{\text{rot. A}}$, $C_{\text{Ar}}^{\text{rot. D}}$), 126.1 ($C_{\text{Ar}}^{\text{rot. A}}$, $C_{\text{Ar}}^{\text{rot. C}}$), 125.9 ($C_{\text{Ar}}^{\text{rot. B}}$), 107.7 ($C_{16}^{\text{rot. B}}$), 107.5 ($C_{16}^{\text{rot. D}}$), 105.6 ($C_{16}^{\text{rot. C}}$), 105.0 ($C_{16}^{\text{rot. A}}$), 41.3 ($C_5^{\text{rot. A}}$), 41.1 ($C_5^{\text{rot. B}}$), 41.0 ($C_5^{\text{rot. C}}$, $C_5^{\text{rot. D}}$), 34.4 ($C_{14}^{\text{rot. D}}$), 33.8 ($C_{14}^{\text{rot. B}}$), 29.4 ($C_{14}^{\text{rot. C}}$), 29.1 ($C_{14}^{\text{rot. A}}$), 22.2 ($C_6^{\text{rot. A}}$), 22.1 ($C_6^{\text{rot. B}}$), 21.2 ($C_6^{\text{rot. D}}$), 21.0 ($C_6^{\text{rot. C}}$), 15.6 ($C_{17}^{\text{rot. B}}$, $C_{17}^{\text{rot. D}}$), 15.3 ($C_{17}^{\text{rot. C}}$), 15.1 ($C_{17}^{\text{rot. A}}$). **IR** (film, $CDCl_3$) ν_{max} = 3026 (C–H), 2966 (C–H), 2932 (C–H), 1637 (C=O), 1598, 1488, 1452, 1413, 1390, 1369, 1317, 1280, 1062, 937, 774, 755, 699, 658 cm^{-1}. **HRMS** (ESI$^+$) m/z calcd for $C_{19}H_{22}NO$ $[M+H]^+$ 280.1696, found 280.1695.

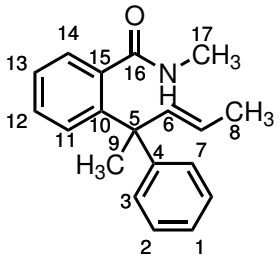
(*Z*)-*N*-Methyl-2-(1-phenylethyl)-*N*-(prop-1-en-1-yl)benzamide (3.139e)



By the method of Clayden and co-workers[276] with modifications, *N*-allyl-*N*-methyl-2-(1-phenylethyl)benzamide (**3.137d**) (495 mg, 1.77 mmol, 1.0 eq.) was dissolved in anhydrous THF (17.7 mL), and cooled to −78 °C. *sec*-BuLi (2.7 mL, 1.4 M in cyclohexane, 3.78 mmol, 2.1 eq.) was added dropwise, and the reaction mixture stirred at −78 °C for 30 min. A solution of 2,4,6-tri-*tert*-butylphenol (976 mg, 3.72 mmol, 2.1 eq.) in anhydrous THF (3.7 mL) was added dropwise, the reaction mixture stirred at −78 °C for 1.5 h, quenched by the dropwise addition of saturated aqueous NH_4Cl (20 mL), diluted with H_2O (20 mL), and extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2; gradient elution: 7–40% Et_2O in pet. ether) to yield the title compound as a yellow oil (197 mg, 40%).

$\boldsymbol{R_f}$ = 0.22 (30% Et_2O in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers in an approximate 50:50 ratio) δ 7.36–7.29 ($2H^{\text{both rot.}}$, m, H_{10}, H_{11}), 7.28–7.12 ($8H^{\text{both rot.}}$, m, H_1, H_2, H_3, H_9), 7.10–7.06 ($1H^{\text{both rot.}}$, m, H_8), 5.32 ($1H^{\text{both rot.}}$, br s, H_{15}), 4.81 ($1H^{\text{both rot.}}$, quint, J 7.2, H_{16}), 4.44 ($1H^{\text{both rot.}}$, q, J 7.1, H_5), 3.16 ($3H^{\text{both rot.}}$, s, H_{14}), 1.64 ($3H^{\text{one rot.}}$, d, J 7.1, H_6), 1.63 ($3H^{\text{one rot.}}$, d, J 7.1, H_6), 1.62 ($3H^{\text{both rot.}}$, d, J 7.2, H_{17}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.7 (C_{13}), 145.7 (C_4), 143.2 (C_7), 136.7 (C_{12}), 131.2 (C_{15}), 129.3 (C_{10}), 128.3 (C_2), 128.0 (C_3), 127.2 (C_{11}), 127.1 (C_8), 126.2 (C_9), 125.8 (C_1), 117.9 (C_{16}), 40.8 (C_5), 35.0 (C_{14}), 21.7 (C_6), 12.9 (C_{17}). **IR** (film, $CDCl_3$) ν_{max} = 3026 (C–H), 2967 (C–H), 2932 (C–H), 1635 (C=O), 1598, 1493, 1450, 1421, 1399, 1357, 1317, 1052, 1039, 1027, 772, 755, 729, 699, 668 cm^{-1}. **HRMS** (ESI^+) m/z calcd for $C_{19}H_{22}NO$ $[M+H]^+$ 280.1696, found 280.1692.

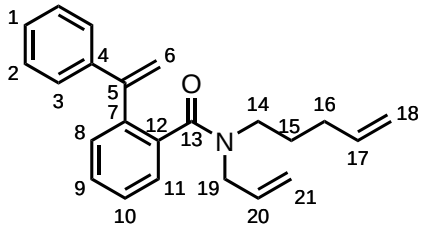
(*E*)-*N*-Methyl-2-(2-phenylpent-3-en-2-yl)benzamide (3.140d)



In a microwave vial, (*E*)-*N*-methyl-2-(1-phenylethyl)-*N*-(prop-1-en-1-yl) benzamide (**3.139d**) (56 mg, 0.20 mmol, 1.0 eq.) was dissolved in anhydrous THF (2.0 mL), and KHMDS (400 µL, 1 M in THF, 0.40 mmol, 2.0 eq.) added dropwise. The vial was sealed, the reaction mixture stirred at 100 °C under microwave irradiation for 3 h, and quenched by the addition of H_2O (5 mL). The reaction mixture was extracted with EtOAc (3 × 5 mL), the combined organic extracts washed with brine (5 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2; gradient elution: 7–60% EtOAc in pet. ether) to yield the title compound as a yellow gum (43 mg, 76%).

$\boldsymbol{R_f}$ = 0.21 (30% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.53 (1H, dd, J 8.0, 1.1, H_{14}), 7.35 (1H, ddd, J 8.0, 6.9, 2.2, H_{13}), 7.29–7.14 (7H, m, H_1, H_2, H_3, H_{11}, H_{12}), 6.17 (1H, dq, J 15.5, 1.6, H_6), 5.33 (1H, dq, J 15.5, 6.4, H_7), 4.75 (1H, q, J 4.9, NH), 2.37 (3H, d, J 4.9, H_{17}), 1.88 (3H, s, H_9), 1.75 (3H, dd, J 6.4, 1.6, H_8). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.0 (C_{16}), 148.7 (C_4), 145.7 (C_{10}), 139.8 (C_6), 137.9 (C_{15}), 129.1 (C_{12}), 129.0 (C_{13}), 128.6 (C_{14}), 128.2 (C_2), 127.7 (C_3), 126.4 (C_{11}), 126.0 (C_1), 123.7 (C_7), 49.9 (C_5), 27.4 (C_9), 26.6 (C_{17}), 18.3 (C_8). **IR** (film, $CDCl_3$) ν_{max} = 3305 (N–H, br), 3024 (C–H), 2935 (C–H), 1642 (C=O), 1529, 1445, 975, 909, 757, 729, 699, 553 cm^{-1}. **HRMS** (ESI^+) m/z calcd for $C_{19}H_{22}NO$ $[M+H]^+$ 280.1696, found 280.1692.

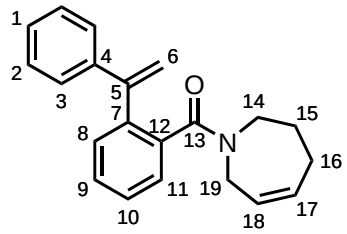
_N_-Allyl-_N_-(pent-4-en-1-yl)-2-(1-phenylvinyl)benzamide (3.143a)



By **GP2**, the acid chloride of 2-(1-phenylvinyl)benzoic acid (**3.135**) (896 mg, 4.00 mmol) was made by stirring with oxalyl chloride for 5 h. _N_-Allylpent-4-en-1-amine (**3.82c**) (600 mg, 4.79 mmol) was used as the general amine that was stirred with the acid chloride intermediate for 18 h, and purified by flash column chromatography (SiO_2; gradient elution: 7–20% EtOAc in pet. ether) to yield the title compound as a pale yellow oil (1.28 g, 96%).

$\boldsymbol{R_f}$ = 0.39 (30% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers in an approximate 60:40 ratio) δ 7.39–7.25 (9H^{maj} + 9H^{min}, m, 9 × H_{Ar}), 5.75 (1H^{maj}, ddt, J 16.9, 10.3, 6.6, H_{17}), 5.66 (1H^{maj}, d, J 1.1, H_{6a}), 5.65 (1H^{min}, d, J 1.1, H_{6a}), 5.64–5.44 (1H^{maj} + 2H^{min}, m, $H_{17}{}^{min}$, H_{20}), 5.38 (1H^{min}, d, J 1.1, H_{6b}), 5.37 (1H^{maj}, d, J 1.1, H_{6b}), 5.15–5.10 (2H^{maj}, m, H_{21}), 5.08–5.03 (2H^{min}, m, H_{21}), 5.01–4.92 (2H^{maj}, m, H_{18}), 4.91–4.85 (2H^{min}, m, H_{18}), 4.24 (1H^{min}, br s, H_{19a}), 3.79 (1H^{maj}, br s, H_{19a}), 3.55 (1H^{maj} + 1H^{min}, br s, $H_{14a}{}^{maj}$, $H_{19b}{}^{min}$), 3.38 (1H^{maj}, br s, H_{19b}), 3.13 (1H^{min}, br s, H_{14a}), 2.90 (1H^{maj}, br s, H_{14b}), 2.76 (1H^{min}, br s, H_{14b}), 2.00–1.89 (2H^{maj}, m, H_{16}), 1.89–1.79 (2H^{min}, m, H_{16}), 1.51 (2H^{min}, br s, H_{15}), 1.33 (2H^{maj}, br s, H_{15}). **^{13}C NMR** (101 MHz, $CDCl_3$, mixture of rotamers in an approximate 60:40 ratio) δ 170.6 ($C_{13}{}^{min}$), 170.5 ($C_{13}{}^{maj}$), 148.0 ($C_5{}^{maj}$), 147.9 ($C_5{}^{min}$), 140.7 ($C_4{}^{maj}$), 140.6 ($C_4{}^{min}$), 139.3 ($C_7{}^{maj}$), 138.9 ($C_7{}^{min}$), 138.0 ($C_{17}{}^{maj}$), 137.2 ($C_{17}{}^{min}$), 136.4 ($C_{12}{}^{min}$), 136.4 ($C_{12}{}^{maj}$), 133.5 ($C_{20}{}^{maj}$), 133.3 ($C_{20}{}^{min}$), 130.6 ($C_{Ar}{}^{maj}$), 130.5 ($C_{Ar}{}^{min}$), 128.8 ($C_{Ar}{}^{maj}$), 128.7 ($C_{Ar}{}^{min}$), 128.2 ($C_2{}^{maj}$), 128.1 ($C_2{}^{min}$), 127.9 ($C_{Ar}{}^{min}$), 127.9 ($C_{Ar}{}^{maj}$), 127.7 ($C_{Ar}{}^{min}$), 127.6 ($C_3{}^{min}$), 127.5 ($C_3{}^{maj}$), 127.5 ($C_{Ar}{}^{maj}$), 127.0 ($C_{Ar}{}^{min}$), 126.6 ($C_{Ar}{}^{maj}$), 117.8 ($C_{21}{}^{maj}$), 117.5 ($C_{21}{}^{min}$), 116.7 ($C_6{}^{min}$), 116.5 ($C_6{}^{maj}$), 115.3 ($C_{18}{}^{min}$), 114.8 ($C_{18}{}^{maj}$), 51.7 ($C_{19}{}^{maj}$), 47.7 ($C_{14}{}^{min}$), 46.8 ($C_{19}{}^{min}$), 43.8 ($C_{14}{}^{maj}$), 31.2 ($C_{16}{}^{maj}$), 30.7 ($C_{16}{}^{min}$), 27.2 ($C_{15}{}^{min}$), 25.6 ($C_{15}{}^{maj}$). **IR** (film, $CDCl_3$) ν_{max} = 3078 (C–H), 2977 (C–H), 2929 (C–H), 1632 (C=O), 1414, 1248, 910, 770, 706 cm^{-1}. **HRMS** (ESI$^+$) m/z calcd for $C_{23}H_{26}NO$ [M+H]$^+$ 332.2009, found 332.2007.

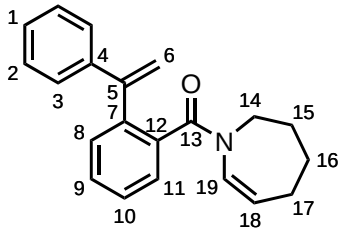
(2-(1-Phenylvinyl)phenyl)(2,3,4,7-tetrahydro-1_H_-azepin-1-yl)methanone (3.144a)



By **GP18**, *N*-allyl-*N*-(pent-4-en-1-yl)-2-(1-phenylvinyl)benzamide (**3.143a**) (1.13 g, 3.41 mmol) was used as the amide that was stirred for 19 h, and purified by flash column chromatography (SiO_2; gradient elution: 7–40% EtOAc in pet. ether) to yield the title compound as a green-brown oil (1.01 g, 89%).

$\boldsymbol{R_f}$ = 0.23 (30% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers in an approximate 55:45 ratio) δ 7.40–7.22 ($9H^{maj}$ + $9H^{min}$, m, 9 × H_{Ar}), 5.82–5.70 ($1H^{maj}$ + $2H^{min}$, m, ${H_{17}}^{maj}$, ${H_{17}}^{min}$, ${H_{18}}^{min}$), 5.61 ($1H^{min}$, d, *J* 1.1, H_{6a}), 5.58 ($1H^{maj}$, d, *J* 1.2, H_{6a}), 5.42 ($1H^{min}$, d, *J* 1.1, H_{6b}), 5.44–5.36 ($1H^{maj}$, m, H_{18}), 5.38 ($1H^{maj}$, d, *J* 1.2, H_{6b}), 4.18 ($1H^{min}$, br s, H_{19a}), 3.96 ($1H^{maj}$, br s, H_{14a}), 3.78–3.61 ($1H^{maj}$, m, H_{19a}), 3.47 ($1H^{maj}$, br s, H_{19b}), 3.42 ($2H^{min}$, br s, H_{14a}, H_{19b}), 3.10 ($1H^{min}$, br s, H_{14b}), 2.86 ($1H^{maj}$, br s, H_{14b}), 2.20 ($2H^{maj}$, br s, H_{16}), 2.13 ($2H^{min}$, br s, H_{16}), 1.89–1.75 ($2H^{maj}$, m, H_{15}), 1.72–1.59 ($2H^{min}$, m, H_{15}). **^{13}C NMR** (101 MHz, $CDCl_3$, mixture of rotamers in an approximate 55:45 ratio) δ 170.1 (${C_{13}}^{maj}$), 169.9 (${C_{13}}^{min}$), 148.6 (${C_5}^{maj}$), 148.3 (${C_5}^{min}$), 141.1 (${C_4}^{maj}$), 140.9 (${C_4}^{min}$), 139.6 (${C_7}^{maj}$), 139.0 (${C_7}^{min}$), 136.5 (${C_{12}}^{maj}$), 136.5 (${C_{12}}^{min}$), 132.5 (${C_{17}}^{maj}$), 131.9 (${C_{17}}^{min}$), 130.4 (${C_{Ar}}^{maj}$), 130.3 (${C_{Ar}}^{min}$), 128.8 (${C_{Ar}}^{maj}$), 128.7 (${C_{Ar}}^{min}$), 128.1 (${C_2}^{min}$), 128.0 (${C_2}^{maj}$), 127.9 (${C_{18}}^{min}$), 127.9 (${C_{Ar}}^{min}$), 127.8 (${C_{Ar}}^{min}$), 127.8 (${C_3}^{maj}$), 127.7 (${C_{Ar}}^{maj}$), 127.6 (${C_3}^{min}$), 127.5 (${C_{Ar}}^{maj}$), 127.3 (${C_{Ar}}^{min}$), 126.8 (${C_{18}}^{maj}$), 126.6 (${C_{Ar}}^{maj}$), 116.8 (${C_6}^{min}$), 116.5 (${C_6}^{maj}$), 50.7 (${C_{14}}^{min}$), 48.4 (${C_{19}}^{maj}$), 45.8 (${C_{14}}^{maj}$), 42.9 (${C_{19}}^{min}$), 27.0 (${C_{15}}^{min}$, ${C_{16}}^{maj}$), 26.7 (${C_{16}}^{min}$), 25.8 (${C_{15}}^{maj}$). **IR** (film, $CDCl_3$) ν_{max} = 3023 (C−H), 2932 (C−H), 1626 (C=O), 1422, 908, 769, 727, 706, 643, 595 cm^{-1}. **HRMS** (ESI^+) *m*/*z* calcd for $C_{21}H_{22}NO$ $[M+H]^+$ 304.1696, found 304.1690.

(2-(1-Phenylvinyl)phenyl)(2,3,4,5-tetrahydro-1*H*-azepin-1-yl)methanone (3.145a)

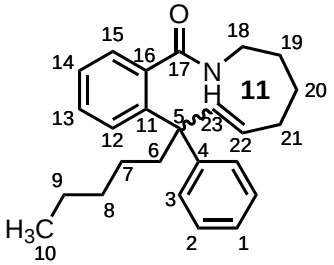


By **GP19**, (2-(1-phenylvinyl)phenyl)(2,3,4,7-tetrahydro-1*H*-azepin-1-yl) methanone (**3.144a**) (863 mg, 2.84 mmol) was used as the amide that was sitrred for 15 h, and purified by flash column chromatography (SiO_2; gradient elution: 5–25% EtOAc in pet. ether) to yield the title compound as a pale brown oil (836 mg, 97%).

$\boldsymbol{R_f}$ = 0.36 (30% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers in an approximate 80:20 ratio) δ 7.43–7.20 ($9H^{maj}$ + $8H^{min}$, m, H_{Ar}), 7.13–7.07 ($1H^{min}$, m, H_{Ar}), 6.39 ($1H^{min}$, dt, *J* 9.1, 1.6, H_{19}), 6.00 ($1H^{maj}$, dt, *J* 8.7, 1.6, H_{19}), 5.62 ($1H^{maj}$, d, *J* 1.1, H_{6a}), 5.59 ($1H^{min}$, d, *J* 1.1, H_{6a}), 5.39 ($1H^{min}$, d, *J* 1.1, H_{6b}), 5.38 (1 H, d, *J* 1.1, H_{6b}), 5.15 ($1H^{min}$, dt, *J* 9.1, 5.5, H_{18}), 4.85 ($1H^{maj}$, dt, *J* 8.7, 5.5, H_{18}), 3.66 ($2H^{maj}$ + $2H^{min}$, t, *J* 6.2, H_{14}), 3.45 ($1H^{min}$, br s, H_{14a}),

3.04 (1H^{min}, br s, H_{14b}), 2.13 (2H^{min}, br s, H_{17}), 2.04 (2H^{maj}, qd, J 5.5, 1.6, H_{17}), 1.73 (2H^{maj} + 2H^{min}, quint, J 6.2, H_{15}), 1.65–1.53 (2H^{maj} + 2H^{min}, m, H_{16}). **^{13}C NMR** (101 MHz, $CDCl_3$, mixture of rotamers in an approximate 80:20 ratio) δ 170.0 (C_{13}^{min}), 169.7 (C_{13}^{maj}), 148.5 (C_5^{min}), 148.0 (C_5^{maj}), 140.9 (C_4^{min}), 140.8 (C_4^{maj}), 139.8 (C_7^{maj}), 139.3 (C_7^{min}), 136.6 (C_{12}^{maj}), 135.9 (C_{12}^{min}), 131.6 (C_{19}^{maj}), 130.4 (C_{Ar}^{maj}, C_{Ar}^{min}), 129.8 (C_{19}^{min}), 129.1 (C_{Ar}^{min}), 129.0 (C_{Ar}^{maj}), 128.1 (C_2^{min}), 128.0 (C_2^{maj}), 128.0 (C_3^{min}), 127.9 (C_3^{maj}), 127.8 (C_{Ar}^{maj}), 127.8 (C_{Ar}^{min}), 127.6 (C_{Ar}^{maj}), 127.5 (C_{Ar}^{maj}), 127.5 (C_{Ar}^{min}), 126.9 (C_{Ar}^{min}), 117.8 (C_{18}^{min}), 117.1 (C_{18}^{maj}), 116.9 (C_6^{min}), 116.5 (C_6^{maj}), 50.3 (C_{14}^{min}), 45.4 (C_{14}^{maj}), 29.2 (C_{16}^{min}), 27.4 (C_{15}^{maj}), 26.5 (C_{17}^{min}), 26.4 (C_{17}^{maj}), 25.1 (C_{15}^{min}), 24.9 (C_{16}^{maj}). **IR** (film, $CDCl_3$) ν_{max} = 3054 (C–H), 2929 (C–H), 1631 (C=O), 1406, 1385, 1365, 1142, 771, 728, 706 cm^{-1}. **HRMS** (ESI$^+$) m/z calcd for $C_{21}H_{22}NO$ $[M+H]^+$ 304.1696, found 306.1700.

9-Pentyl-9-phenyl-2,3,4,5,6,9-hexahydro-1*H*-benzo[*c*][1]azacyclo undecin-1-one (3.148a)



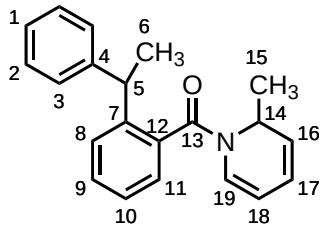
(2-(1-Phenylvinyl)phenyl)(2,3,4,5-tetrahydro-1*H*-azepin-1-yl)methanone (**3.145a**) (61 mg, 0.20 mmol, 1.0 eq.) was dissolved in anhydrous THF (2.0 mL), and cooled to −78 °C. *n*-BuLi (160 µL, 2.5 M in hexanes, 0.40 mmol, 2.0 eq.) was added dropwise, and the reaction mixture stirred at −78 °C for 1 h. DMPU (240 µL, 2.00 mmol. 10.0 eq.) was added dropwise, the reaction mixture stirred at −78 °C for 2 h, warmed to room temperature, and stirred at room temperature for 23 h. The reaction mixture was quenched by the dropwise addition of saturated aqueous NH_4Cl (2 mL), diluted with H_2O (2 mL), and extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2; gradient elution: 0–100% EtOAc in pet. ether) to yield **(*E*)-3.148a** as a pale yellow gum (19 mg, 31%) and **(*Z*)-3.148a** as a pale yellow gum (11 mg, 17%).

(*E*)-3.148a:
***R*$_f$** = 0.36 (30% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32–7.13 (8H, m, 8 × H_{Ar}), 7.04–6.98 (1H, m, H_{Ar}), 5.94 (1H, dd, J 15.8, 1.4, H_{23}), 5.78 (1H, t, J 6.2, NH), 5.30 (1H, dt, J 15.8, 7.3, H_{22}), 3.63–3.50 (1H, m, H_{18a}), 3.10–3.00 (1H, m, H_{18b}), 2.50 (1H, ddd, J 13.5, 11.3, 5.0, H_{6a}), 2.31 (1H, ddd, J 13.9, 11.9, 3.0, H_{6b}), 2.11–1.96 (2H, m, H_{21}), 1.85 (1H, dtd, J 11.9, 8.3, 3.2, H_{19a}), 1.73–1.58 (2H, m, H_{19b}, H_{20a}), 1.57–1.45 (1H, m, H_{20b}), 1.33–1.21 (5H, m, H_{7a}, H_8, H_9), 1.05 (1H, dq, J 13.1, 5.8, 4.5, H_{7b}), 0.87–0.79 (3H, m, H_{10}). **^{13}C NMR**

(101 MHz, $CDCl_3$) δ 172.4 (C_{17}), 147.7 (C_{quat}), 143.9 (C_{quat}), 138.8 (C_{16}), 137.9 (C_{23}), 131.4 (C_{Ar}), 129.8 (C_{22}), 128.6 (C_2), 128.4 (C_{Ar}), 128.1 (C_{Ar}), 128.0 (C_3), 126.2 (C_{Ar}), 125.8 (C_{Ar}), 54.4 (C_5), 41.1 (C_{18}), 39.7 (C_6), 34.2 (C_{21}), 32.6 (C_8), 27.3 (C_{19}), 26.3 (C_{20}), 24.9 (C_7), 22.7 (C_9), 14.3 (C_{10}). **IR** (film, $CDCl_3$) ν_{max} = 3289 (N−H, br), 3057 (C−H), 2927 (C−H), 2869 (C−H), 1635 (C=O), 1541, 1444, 1436, 1309, 908, 731, 701 cm^{-1}. **HRMS** (ESI^+) m/z calcd for $C_{25}H_{32}NO$ $[M+H]^+$ 362.2478, found 362.2477.

(*Z*)-3.148a:
***R*f** = 0.20 (30% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45–7.35 (3H, m, 3 × H_{Ar}), 7.35–7.27 (3H, m, 3 × H_{Ar}), 7.26–7.16 (3H, m, 3 × H_{Ar}), 5.88 (1H, d, J 12.0, H_{23}), 5.43 (1H, td, J 12.0, 2.3, H_{22}), 5.29 (1H, br s, NH), 3.62 (1H, dt, J 13.5, 6.9, H_{18a}), 2.82–2.70 (1H, m, H_{18b}), 2.36–2.14 (2H, m, H_6), 2.14–2.00 (1H, m, H_{19a}), 1.56–1.46 (1H, m, H_{21a}), 1.46–1.32 (3H, m, H_{7a}, H_{20}), 1.31–1.14 (4H, m, H_8, H_9), 1.07 (2H, br s, H_{7b}, H_{19b}), 0.91–0.74 (4H, m, H_{10}, H_{21b}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.5 (C_{17}), 149.6 (C_{11}), 140.2 (C_4), 138.6 (C_{16}), 133.4 (C_{22}), 132.4 (C_{23}), 130.3 (C_{Ar}), 129.9 (C_{Ar}), 129.1 (C_{Ar}), 128.4 (C_2, C_3), 126.9 (C_{Ar}), 126.5 (C_{Ar}), 54.3 (C_5), 46.2 (C_6), 41.4 (C_{18}), 32.7 (C_8), 29.2 (C_{20}), 28.4 (C_{21}), 25.6 (C_{19}), 24.8 (C_7), 22.6 (C_9), 14.2 (C_{10}). **IR** (film, $CDCl_3$) ν_{max} = 3290 (N−H, br), 2925 (C−H), 2869 (C−H), 1640 (C=O), 1519, 1444, 908, 756, 728, 701 cm^{-1}. **HRMS** (ESI^+) m/z calcd for $C_{25}H_{32}NO$ $[M+H]^+$ 362.2478, found 362.2473.

(2-Methylpyridin-1(2*H*)-yl)(2-(1-phenylethyl)phenyl)methanone (3.150)

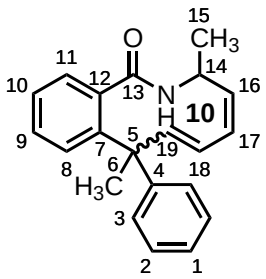


By **GP2**, the acid chloride of 2-(1-phenylethyl)benzoic acid (**3.133**) (1.13 g, 4.99 mmol) was made by stirring with oxalyl chloride for 3 h. By **GP23**, the acid chloride intermediate was used, and purified by flash column chromatography (SiO_2; gradient elution: 7–20% Et_2O in pet. ether) to yield the title compound as a yellow oil (859 mg, 57%).

***R*f** = 0.36 (30% Et_2O in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$, unassigned mixture of diastereomers and rotamers) δ 7.48 (0.35H, d, J 7.9, H_{Ar}), 7.44–7.38 (0.70H, m, H_{Ar}), 7.35–7.06 (7.95 H, m, H_{Ar}), 6.16–6.00 (0.33H, m, H_{19}), 5.92 (0.48H, br s, H_{16}, H_{17}), 5.87–5.75 (0.63H, m, H_{16}, H_{17}), 5.71 (0.30H, br s, H_{16}), 5.68–5.66 (0.69H, m, H_{16}, H_{17}), 5.53 (0.35H, d, J 7.7, H_{19}), 5.39 (0.42H, quint, J 6.3, H_{14}), 5.33 (0.11H, br s, H_{14}), 5.22 (0.49H, quint, J 6.4, H_{14}), 5.17 (0.24H, br s, H_{18}), 5.10–5.02 (0.08H, m, H_{18}), 4.98 (0.38H, t, J 6.6, H_{18}), 4.92 (0.18H, br s, H_{18}), 4.59 (0.38H, q, J 7.2, H_5), 4.41 (0.18H, br s, H_5), 4.30 (0.07H, q, J 7.0, H_5), 4.27–4.17 (0.24H, m, H_5), 4.20–4.10 (0.17H, m, H_5), 1.67 (1.20H, d, J 7.2, H_6),

1.60 (1.75H, d, J 7.2, H_6), 1.29 (1.56H, d, J 6.5, H_{15}), 1.12 (0.30H, d, J 7.3, H_{15}), 1.10 (1.08H, d, J 6.7, H_{15}), 1.02 (0.11H, d, J 6.5, H_{15}). **^{13}C NMR** (126 MHz, $CDCl_3$, unassigned mixture of diastereomers and rotamers) δ 170.7 (C_{13}), 170.6 (C_{13}), 170.4 (C_{13}), 170.3 (C_{13}), 169.9 (C_{13}), 146.0 (C_4), 145.2 (C_{quat}), 145.1 (C_{quat}), 145.0 (C_{quat}), 144.9 (C_{quat}), 144.7 (C_{quat}), 144.0 (C_7), 143.7 (C_7), 135.3 (C_{12}), 135.2 (C_{12}), 135.0 (C_{12}), 134.7 (C_{12}), 134.3 (C_{12}), 129.9 (C_{Ar}), 129.8 (C_{Ar}), 129.8 (C_{Ar}), 129.6 (C_{Ar}), 129.6 (C_{Ar}), 129.6 (C_{Ar}), 129.5 (C_{Ar}), 128.7 (C_{Ar}), 128.5 (C_{Ar}), 128.4 (C_{Ar}), 128.1 (C_{Ar}), 127.9 (C_{Ar}), 127.9 (C_{Ar}), 127.8 (C_{Ar}), 127.7 (C_{Ar}), 127.6 (C_{Ar}), 127.6 (C_{Ar}), 127.5 (C_{Ar}), 127.3 (C_{Ar}), 126.8 (C_{Ar}), 126.5 (C_{Ar}), 126.5 (C_{Ar}), 126.5 (C_{Ar}), 126.4 (C_{sp^2}), 126.3 (C_{sp^2}), 126.2 (C_{sp^2}), 126.0 (C_{sp^2}), 126.0 (C_{sp^2}), 126.0 (C_{19}), 125.8 (C_{sp^2}), 125.7 (C_{sp^2}), 125.5 ($C_{C=C}$), 125.5 ($C_{C=C}$), 125.3 (C_{16}), 125.3 ($C_{C=C}$), 125.2 ($C_{C=C}$), 120.5 (C_{17}), 120.4 (C_{17}), 106.7 (C_{18}), 106.3 (C_{18}), 106.1 (C_{18}), 105.9 (C_{18}), 47.3 (C_{14}), 47.3 (C_{14}), 47.1 (C_{14}), 46.9 (C_{14}), 41.5 (C_5), 41.5 (C_5), 41.0 (C_5), 40.9 (C_5), 40.5 (C_5), 40.4 (C_5), 23.2 (C_6), 22.4 (C_6), 22.3 (C_6), 21.3 (C_6), 21.3 (C_6), 21.1 (C_6), 19.1 (C_{15}), 19.0 (C_{15}), 18.9 (C_{15}), 18.6 (C_{15}), 18.1 (C_{15}). **IR** (film, $CDCl_3$) ν_{max} = 3025 (C−H), 2968 (C−H), 2928 (C−H), 1656, 1640 (C=O), 1574, 1448, 1388, 1347, 1264, 1095, 1014, 923, 771, 756, 733, 700, 641 cm^{-1}. **HRMS** (ESI$^+$) m/z calcd for $C_{21}H_{22}NO$ $[M+H]^+$ 304.1696, found 304.1693.

(4*Z*)-3,8-Dimethyl-8-phenyl-3,8-dihydrobenzo[*c*]azecin-1(2*H*)-one (3.151)



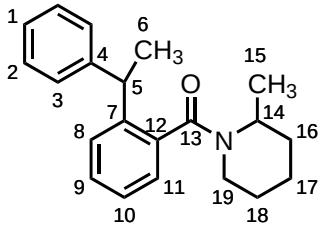
In a microwave vial, (2-methylpyridin-1(2*H*)-yl)(2-(1-phenylethyl)phenyl) methanone (**3.150**) (61 mg, 0.20 mmol, 1.0 eq.) was dissolved in anhydrous THF (2.0 mL), and KHMDS (400 µL, 1 M in THF, 0.40 mmol, 2.0 eq.) added dropwise. The vial was sealed, the reaction mixture stirred at 100 °C under microwave irradiation for 1 h, and quenched by the addition of H_2O (5 mL). The reaction mixture was extracted with EtOAc (3 × 5 mL), the combined organic extracts washed with brine (5 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2; gradient elution: 7–60% EtOAc in pet. ether) to yield **(4*Z*,6*E*)-3.151** as a yellow dry film (6 mg, 9%) and **(4*Z*,6*Z*)-3.151** as a colourless dry film (10 mg, 16%).

(4*Z*,6*E*)-3.151:
***R*$_f$** = 0.20 (30% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of diastereomers and rotamers in an approximate 80:20 ratio) δ 8.18–8.14 ($1H^{maj}$ + $1H^{min}$, m, H_{11}), 7.47–7.35 ($2H^{maj}$ + $2H^{min}$, m, H_9, H_{10}), 7.32–7.17 ($5H^{maj}$ + $5H^{min}$,

m, H_1, H_2, H_3), 6.98–6.92 ($1H^{maj}$ + $1H^{min}$, m, H_8), 6.35 ($1H^{min}$, tt, J 11.6, 1.0, H_{17}), 5.98 ($1H^{maj}$, t, J 11.0, H_{17}), 5.94–5.89 ($1H^{min}$, m, H_{18}), 5.89–5.80 ($1H^{maj}$, m, H_{18}), 5.69 ($1H^{maj}$ + $1H^{min}$, br s, NH), 5.66–5.56 ($1H^{maj}$, m, H_{19}), 5.56–5.46 ($1H^{min}$, m, H_{19}), 5.37–5.28 ($1H^{min}$, m, H_{16}), 5.19–5.11 ($1H^{maj}$, m, H_{16}), 4.96–4.90 ($1H^{maj}$ + $1H^{min}$, m, H_{14}), 1.67–1.59 ($6H^{maj}$ + $6H^{min}$, m, H_6, H_{15}). **^{13}C NMR** (101 MHz, $CDCl_3$, mixture of diastereomers and rotamers in an approximate 80:20 ratio) δ 165.5 ($C_{13}{}^{maj}$, $C_{13}{}^{min}$), 147.6 ($C_7{}^{maj}$, $C_7{}^{min}$), 144.7 ($C_4{}^{maj}$, $C_4{}^{min}$), 133.8 ($C_{17}{}^{maj}$, $C_{17}{}^{min}$), 133.2 ($C_{19}{}^{maj}$, $C_{19}{}^{min}$), 132.8 ($C_9{}^{maj}$), 132.8 ($C_9{}^{min}$), 130.1 ($C_{12}{}^{maj}$, $C_{12}{}^{min}$), 128.4 ($C_{11}{}^{min}$), 128.4 ($C_{11}{}^{maj}$), 128.3 ($C_2{}^{maj}$, $C_3{}^{maj}$), 128.0 ($C_2{}^{min}$, $C_3{}^{min}$), 127.5 ($C_8{}^{maj}$), 127.4 ($C_8{}^{min}$), 127.2 ($C_{10}{}^{min}$), 127.2 ($C_{10}{}^{maj}$), 127.0 ($C_1{}^{maj}$, $C_1{}^{min}$), 125.7 ($C_{18}{}^{maj}$), 125.1 ($C_{16}{}^{min}$), 123.1 ($C_{18}{}^{min}$), 122.8 ($C_{16}{}^{maj}$), 58.4 ($C_{14}{}^{maj}$, $C_{14}{}^{min}$), 47.5 ($C_5{}^{maj}$, $C_6{}^{min}$), 21.7 ($C_6{}^{maj}$, $C_6{}^{min}$), 18.4 ($C_{15}{}^{maj}$), 13.3 ($C_{15}{}^{min}$). **IR** (film, $CDCl_3$) ν_{max} = 3204 (N–H, br), 3027 (C–H), 2974 (C–H), 2923 (C–H), 1670 (C=O), 1602, 1461, 1445, 1376, 752, 731, 700 cm^{-1}. **HRMS** (ESI^+) m/z calcd for $C_{21}H_{22}NO$ $[M+H]^+$ 304.1696, found 304.1693.

(4*Z*,6*Z*)-3.151:
***R*$_f$** = 0.16 (30% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of diastereomers and rotamers in an approximate 80:20 ratio) δ 8.24 ($1H^{maj}$, dd, J 7.7, 1.5, H_{11}), 8.24 ($1H^{min}$, dd, J 7.7, 1.2, H_{11}), 7.53 ($1H^{maj}$, td, J 7.6, 1.5, H_9), 7.56–7.48 ($1H^{min}$, m, H_9), 7.43 ($1H^{maj}$, td, J 7.6, 1.3, H_{10}), 7.47 – 7.39 ($1H^{min}$, m, H_{10}), 7.29 ($1H^{maj}$, dd, J 7.9, 1.3, H_8), 7.28 ($1H^{min}$, dd, J 7.7, 1.3, H_8), 7.24–7.17 ($3H^{maj}$ + $3H^{min}$, m, H_1, H_3), 7.05–6.99 ($2H^{maj}$ + $2H^{min}$, m, H_2), 6.63–6.54 ($1H^{min}$, m, H_{18}), 6.35–6.27 ($1H^{maj}$, m, H_{17}), 6.27–6.19 ($1H^{maj}$ + $1H^{min}$, m, $H_{18}{}^{maj}$, $H_{17}{}^{min}$), 5.91–5.82 ($1H^{maj}$, m, H_{16}), 5.76–5.68 ($1H^{min}$, m, H_{16}), 5.36 ($1H^{maj}$ + $1H^{min}$, br s, NH), 4.93 ($1H^{min}$, t, J 10.6, H_{19}), 4.82–4.73 ($2H^{maj}$ + $1H^{min}$, m, $H_{14}{}^{maj}$, $H_{14}{}^{min}$, $H_{19}{}^{min}$), 1.83 ($3H^{maj}$, s, H_6), 1.82 ($3H^{min}$, s, H_6), 1.80 ($3H^{maj}$, dd, J 7.1, 1.6, H_{15}), 1.79 ($3H^{min}$, dd, J 6.8, 1.5, H_{15}). **^{13}C NMR** (101 MHz, $CDCl_3$, mixture of diastereomers and rotamers in an approximate 80:20 ratio) δ 166.3 ($C_{13}{}^{maj}$), 166.2 ($C_{13}{}^{min}$), 146.5 ($C_7{}^{maj}$, $C_7{}^{min}$), 140.9 ($C_4{}^{maj}$, $C_4{}^{min}$), 134.7 ($C_{18}{}^{maj}$), 134.3 ($C_{16}{}^{maj}$), 133.4 ($C_9{}^{maj}$, $C_9{}^{min}$), 130.9 ($C_{16}{}^{min}$), 129.1 ($C_{12}{}^{maj}$, $C_{12}{}^{min}$), 129.0 ($C_{18}{}^{min}$), 128.8 ($C_2{}^{maj}$, $C_2{}^{min}$), 128.1 ($C_{11}{}^{maj}$, $C_{11}{}^{min}$), 127.9 ($C_3{}^{min}$), 127.9 ($C_3{}^{maj}$), 127.4 ($C_{10}{}^{maj}$, $C_{10}{}^{min}$), 126.8 ($C_1{}^{min}$), 126.8 ($C_1{}^{maj}$), 126.3 ($C_8{}^{maj}$, $C_8{}^{min}$), 126.1 ($C_{17}{}^{maj}$), 125.3 ($C_{19}{}^{min}$), 123.5 ($C_{17}{}^{min}$), 123.1 ($C_{19}{}^{maj}$), 57.5 ($C_{14}{}^{maj}$), 57.2 ($C_{14}{}^{min}$), 45.8 ($C_5{}^{min}$), 45.8 ($C_5{}^{maj}$), 24.1 ($C_6{}^{maj}$), 24.1 ($C_6{}^{min}$), 18.6 ($C_{15}{}^{maj}$), 13.5 ($C_{15}{}^{min}$). **IR** (film, $CDCl_3$) ν_{max} = 3199 (N–H, br), 3062 (C–H), 3027 (C–H), 2980 (C–H), 2913 (C–H), 1669 (C=O), 1602, 1461, 1444, 1379, 909, 756, 729, 698 cm^{-1}. **HRMS** (ESI^+) m/z calcd for $C_{21}H_{22}NO$ $[M+H]^+$ 304.1696, found 304.1692.

(2-Methylpiperidin-1-yl)(2-(1-phenylethyl)phenyl)methanone (3.152)

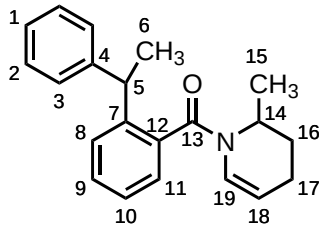


In air, (2-methylpyridin-1(2*H*)-yl)(2-(1-phenylethyl)phenyl)methanone (**3.150**) (61 mg, 0.20 mmol, 1.0 eq.) was dissolved in MeCN (670 µL), Pd/C (11 mg, 10 wt%, 0.010 mmol, 0.05 eq.) added, the reaction mixture stirred at room temperature under H_2 (1 atm, balloon) for 20 h, filtered through Celite, eluting with DCM, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2; gradient elution: 7–60% Et_2O in pet. ether) to yield the title compound as a colourless oil (30 mg, 49%). (Note: (2-methyl-3,4-dihydropyridin-1(2*H*)-yl)(2-(1-phenylethyl)phenyl)methanone (**3.153**) was also isolated as a colourless oil (17 mg, 28%).)

$\boldsymbol{R_f}$ = 0.10 (30% Et_2O in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$, unassigned mixture of diastereomers and rotamers) δ 7.45 (0.32H, dd, *J* 7.9, 1.2, H_{Ar}), 7.44–7.32 (1.65H, m, H_{Ar}), 7.30–7.07 (6.64H, m, H_{Ar}), 7.03 (0.07H, d, *J* 7.6, H_{Ar}), 6.99 (0.17H, dd, *J* 7.5, 1.5, H_{Ar}), 5.21–5.10 (0.17H, m, H_{14}), 5.09–5.02 (0.16H, m, H_{14}), 5.02–4.93 (0.30H, m, H_{14}), 4.75 (0.10H, d, *J* 14.3, H_{19}), 4.69–4.62 (0.23H, m, H_{19}), 4.56 (0.24H, q, *J* 7.2, H_5), 4.53 (0.24H, q, *J* 7.2, H_5), 4.44 (0.35H, q, *J* 7.1, H_5), 4.40–4.28 (0.18H, m, H_5), 4.23 (0.12H, q, *J* 7.2, H_5), 4.02–3.92 (0.05H, m, H_{14}), 3.89–3.74 (0.16H, m, H_{14}), 3.51–3.41 (0.18H, m, H_{14}), 3.35 (0.16H, dt, *J* 13.5, 3.2, H_{19}), 3.13 (0.05H, d, *J* 11.7, H_{19}), 3.06 (0.13H, td, *J* 13.2, 3.1, H_{19}), 2.97–2.69 (1.00H, m, H_{19}), 2.11 (0.30H, ddd, *J* 13.9, 12.4, 3.6, H_{19}), 1.84–1.63 (2.32H, m, H_{CH_2}), 1.62 (1.33H, d, *J* 6.8, H_6), 1.61 (1.36H, d, *J* 7.2, H_6), 1.58 (0.42H, d, *J* 7.3, H_6), 1.55–1.45 (1.66H, m, H_{CH_2}), 1.29 (0.88H, d, *J* 7.0, H_{15}), 1.38–1.25 (0.51H, m, H_{CH_2}), 1.24 (0.25H, d, *J* 6.8, H_{15}), 1.21 (0.75H, d, *J* 7.2, H_{15}), 1.12 (0.51H, d, *J* 6.9, H_{15}), 1.08 (0.89H, d, *J* 7.1, H_{15}), 0.98–0.91 (0.19H, m, H_{CH_2}), 0.58 (0.18H, d, *J* 6.9, H_{15}), 0.32 (0.18H, tt, *J* 13.4, 4.8, H_{CH_2}), 0.22–0.07 (0.16H, m, H_{CH_2}). **^{13}C NMR** (101 MHz, $CDCl_3$, unassigned mixture of diastereomers and rotamers) δ 170.1 (C_{13}), 170.1 (C_{13}), 169.8 (C_{13}), 169.6 (C_{13}), 146.5 (C_{quat}), 146.4 (C_{quat}), 146.2 (C_{quat}), 145.2 (C_{quat}), 145.1 (C_{quat}), 144.9 (C_{quat}), 143.7 (C_{quat}), 143.4 (C_{quat}), 143.2 (C_{quat}), 142.4 (C_{quat}), 142.3 (C_{quat}), 142.3 (C_{quat}), 137.5 (C_{12}), 137.2 (C_{12}), 137.2 (C_{12}), 136.8 (C_{12}), 136.4 (C_{12}), 129.1 (C_{Ar}), 129.0 (C_{Ar}), 129.0 (C_{Ar}), 128.9 (C_{Ar}), 128.8 (C_{Ar}), 128.7 (C_{Ar}), 128.6 (C_{Ar}), 128.5 (C_{Ar}), 128.5 (C_{Ar}), 128.5 (C_{Ar}), 128.4 (C_{Ar}), 128.4 (C_{Ar}), 128.3 (C_{Ar}), 128.3 (C_{Ar}), 128.3 (C_{Ar}), 128.2 (C_{Ar}), 128.1 (C_{Ar}), 128.0 (C_{Ar}), 128.0 (C_{Ar}), 127.9 (C_{Ar}), 127.8 (C_{Ar}), 127.7 (C_{Ar}), 127.7 (C_{Ar}), 127.4 (C_{Ar}), 126.2 (C_{Ar}), 126.2 (C_{Ar}), 126.1 (C_{Ar}), 126.1 (C_{Ar}), 126.1 (C_{Ar}), 126.1 (C_{Ar}), 126.1 (C_{Ar}), 126.0 (C_{Ar}), 126.0 (C_{Ar}), 125.9 (C_{Ar}), 125.8 (C_{Ar}), 125.7 (C_{Ar}), 125.7 (C_{Ar}), 125.6 (C_{Ar}), 125.5 (C_{Ar}), 125.5 (C_{Ar}), 125.4 (C_{Ar}), 125.2 (C_{Ar}), 50.0 (C_{14}), 50.0 (C_{14}), 50.0 (C_{14}), 49.9 (C_{14}), 44.0 (C_{14}), 43.9 (C_{14}), 43.6 (C_{14}), 43.3 (C_{14}), 43.1 (C_{19}), 42.7 (C_{19}), 42.1 (C_{19}), 41.0 (C_5), 40.8 (C_5), 40.8 (C_5), 40.8 (C_5), 40.5 (C_5), 40.3 (C_5), 36.5 (C_{19}), 36.5 (C_{19}), 36.2 (C_{19}), 31.3 (C_{CH_2}), 30.6 (C_{CH_2}), 30.6

(C_{CH_2}), 30.3 (C_{CH_2}), 30.0 (C_{CH_2}), 29.6 (C_{CH_2}), 29.4 (C_{CH_2}), 26.3 (C_{CH_2}), 26.1 (C_{CH_2}), 26.1 (C_{CH_2}), 26.0 (C_{CH_2}), 25.4 (C_{CH_2}), 25.0 (C_{CH_2}), 23.5 (C_6), 23.2 (C_6), 23.0 (C_6), 22.8 (C_6), 21.4 (C_6), 21.1 (C_6), 19.2 (C_{CH_2}), 19.1 (C_{CH_2}), 19.0 (C_{CH_2}), 18.9 (C_{CH_2}), 18.9 (C_{CH_2}), 18.3 (C_{CH_2}), 17.2 (C_{15}), 16.7 (C_{15}), 16.7 (C_{15}), 16.0 (C_{15}), 15.8 (C_{15}), 15.8 (C_{15}), 15.5 (C_{15}). **IR** (film, $CDCl_3$) ν_{max} = 2967 (C–H), 2934 (C–H), 2867 (C–H), 1624 (C=O), 1598, 1424, 1276, 1031, 771, 757, 700 cm^{-1}. **HRMS** (ESI^+) m/z calcd for $C_{21}H_{26}NO$ $[M+H]^+$ 308.2009, found 308.2201.

(2-Methyl-3,4-dihydropyridin-1(2*H*)-yl)(2-(1-phenylethyl)phenyl) methanone (3.153)

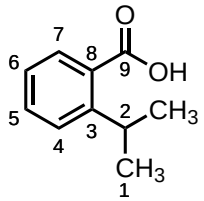


By the method of Doyle and co-workers[291] with modifications, in air, (2-methylpyridin-1(2*H*)-yl)(2-(1-phenylethyl)phenyl)methanone (**3.150**) (152 mg, 0.50 mmol, 1.0 eq.) was dissolved in MeOH (2.6 mL), Lindlar catalyst (32 mg, 0.015 mmol, 0.03 eq.) added, the reaction mixture was stirred at room temperature under H_2 (1 atm, balloon) for 22 h, filtered through Celite, eluting with Et_2O, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2; gradient elution: 7–60% Et_2O in pet. ether) to yield the title compound as a colourless oil (131 mg, 85%).

R_f = 0.28 (30% Et_2O in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$, unassigned mixture of diastereomers and rotamers) δ 7.45–7.06 (9.48H, m, H_{Ar}, H_{19}), 6.17 (0.29H, d, J 8.1, H_{19}), 5.91 (0.20H, d, J 8.2, H_{19}), 5.76 (0.34H, dt, J 8.4, 1.2, H_{19}), 5.29–5.20 (0.05H, m, H_{18}), 5.18–5.11 (0.08H, m, H_{18}), 5.04–4.85 (0.87H, m, H_{14}), 4.85–4.79 (0.33H, m, H_{18}), 4.65–4.58 (0.36H, m, H_{18}), 4.58–4.53 (0.22H, m, H_{18}), 4.45 (0.36H, q, J 7.1, H_5), 4.38 (0.09H, q, J 7.3, H_5), 4.35–4.26 (0.39H, m, H_5), 4.25–4.15 (0.18H, m, H_5), 3.83 (0.04H, br s, H_{14}), 3.39–3.28 (0.08H, m, H_{14}), 2.29–1.68 (4.03H, m, H_{16}, H_{17}), 1.65 (1.15H, d, J 7.2, H_6), 1.62 (0.65H, d, J 7.1, H_6), 1.61 (0.93H, d, J 7.1, H_6), 1.57 (0.56H, d, J 7.2, H_6), 1.28 (0.60H, d, J 6.6, H_{15}), 1.27 (0.50H, d, J 6.6, H_{15}), 1.22 (0.62H, d, J 6.7, H_{15}), 1.12 (1.24H, d, J 6.7, H_{15}), 1.02 (0.22H, d, J 6.6, H_{15}). **^{13}C NMR** (101 MHz, $CDCl_3$, unassigned mixture of diastereomers and rotamers) δ 168.9 (C_{13}), 168.7 (C_{13}), 145.7 (C_{quat}), 145.4 (C_{quat}), 145.1 (C_{quat}), 144.9 (C_{quat}), 144.4 (C_{quat}), 143.8 (C_{quat}), 143.2 (C_{quat}), 135.9 (C_{12}), 135.4 (C_{12}), 134.9 (C_{12}), 129.5 (C_{Ar}), 129.5 (C_{Ar}), 129.2 (C_{Ar}), 128.6 (C_{Ar}), 128.4 (C_{Ar}), 128.4 (C_{Ar}), 128.3 (C_{Ar}), 128.0 (C_{Ar}), 127.9 (C_{Ar}), 127.8 (C_{Ar}), 127.7 (C_{Ar}), 127.7 (C_{Ar}), 127.6 (C_{Ar}), 127.6 (C_{Ar}), 127.5 (C_{Ar}), 126.8 (C_{Ar}), 126.5 (C_{Ar}), 126.4 (C_{Ar}), 126.3 (C_{Ar}), 126.2 (C_{Ar}), 126.2 (C_{Ar}), 126.1 (C_{Ar}), 126.0 (C_{Ar}), 126.0 (C_{Ar}), 125.9 (C_{Ar}), 125.7 (C_{Ar}), 125.5 (C_{19}), 125.5 (C_{19}), 125.4 (C_{19}), 125.1 (C_{19}), 122.3 (C_{19}), 122.1 (C_{19}), 110.1 (C_{18}), 107.0 (C_{18}), 106.8 (C_{18}), 106.5 (C_{18}), 106.4 (C_{18}), 49.0 (C_{14}), 44.6 (C_{14}), 44.4

(C_{14}), 44.1 (C_{14}), 41.4 (C_5), 41.1 (C_5), 41.0 (C_5), 40.4 (C_5), 26.5 (C_{16}), 26.4 (C_{16}), 26.1 (C_{16}), 26.0 (C_{16}), 23.4 (C_6), 22.5 (C_6), 22.3 (C_6), 21.1 (C_6), 21.1 (C_6), 18.3 (C_{17}), 18.0 (C_{17}), 18.0 (C_{17}), 17.9 (C_{17}), 17.7 (C_{17}), 17.2 (C_{15}), 16.8 (C_{15}), 16.7 (C_{15}), 16.4 (C_{15}), 16.1 (C_{15}). **IR** (film, $CDCl_3$) ν_{max} = 2970 (C–H), 2930 (C–H), 1662, 1631 (C=O), 1599, 1413, 1365, 1281, 1038, 924, 773, 757, 700 cm^{-1}. **HRMS** (ESI^+) m/z calcd for $C_{21}H_{24}NO$ $[M+H]^+$ 306.1852, found 306.1845.

2-Isopropylbenzoic acid (3.156)

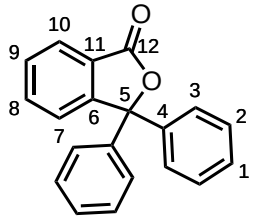


Mg turnings (292 mg, 12.0 mmol, 1.2 eq.) were stirred in anhydrous THF (15 mL), 1,2-dibromoethane (100 µL, 1.16 mmol, 0.11 eq.) added dropwise, and the reaction mixture stirred at room temperature for 10 min. A solution of 1-bromo-2-isopropylbenzene (1.6 mL, 10.4 mmol, 1.0 eq.) in THF (10 mL) was added dropwise, the reaction mixture stirred at reflux for 30 min, and cooled to room temperature to yield the crude Grignard solution that was used without further purification.

Dry ice (ca. 1 g) was cooled to −78 °C, the crude Grignard solution added, and the reaction mixture warmed to room temperature. A further portion of dry ice (ca. 1 g) was carefully added, the reaction mixture stirred at room temperature for 1.5 h, and concentrated *in vacuo*. The residue was diluted with aqueous HCl (25 mL, 2 M), and the reaction mixture extracted with EtOAc (3 × 25 mL). The combined organic extracts were washed with brine (25 mL), dried ($MgSO_4$), and concentrated *in vacuo* to yield the title compound as a beige solid without further purification (1.74 g, quant.)

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.03 (1H, br s, O*H*), 7.95 (1H, dd, *J* 7.8, 1.5, H_7), 7.53 (1H, ddd, *J* 7.6, 7.1, 1.5, H_5), 7.47 (1H, dd, *J* 7.6, 1.4, H_4), 7.27 (1H, ddd, *J* 7.8, 7.1, 1.4, H_6), 3.96 (1H, sept, *J* 6.8, H_2), 1.30 (6H, d, *J* 6.8, H_1). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.3 (C_9), 151.2 (C_3), 132.9 (C_5), 131.1 (C_7), 128.5 (C_8), 126.6 (C_4), 125.7 (C_6), 29.5 (C_2), 24.2 (C_1). Data consistent with literature.[354]

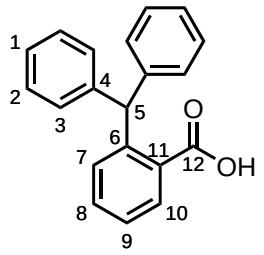
3,3-Diphenylisobenzofuran-1(3*H*)-one (3.158)



Phthalic anhydride (1.48 g, 9.99 mmol, 1.0 eq.) was dissolved in anhydrous THF (25 mL), cooled to 0 °C, and PhMgBr (22 mL, 1.0 M in THF, 22.0 mmol, 2.2 eq.) added dropwise. The reaction mixture was stirred at reflux for 66 h, quenched by the dropwise addition of aqueous HCl (25 mL, 2 M), and extracted with EtOAc (3 × 25 mL). The combined organic extracts were washed with brine (25 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2; gradient elution: 7–30% EtOAc in pet. ether) to yield the title compound as a yellow gum that solidified upon standing (1.97 g, 69%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (1H, dt, *J* 7.6, 1.1, H_{10}), 7.70 (1H, td, *J* 7.6, 1.1, H_8), 7.59 (1H, dd, *J* 7.6, 1.1, H_7), 7.55 (1H, td, *J* 7.6, 1.1, H_9), 7.38–7.31 (10H, m, H_1, H_2, H_3). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.8 (C_{12}), 152.1 (C_6), 141.0 (C_4), 134.3 (C_8), 129.5 (C_9), 128.7 (C_1), 128.6 (C_2), 127.2 (C_3), 126.2 (C_{10}), 125.7 (C_{11}), 124.3 (C_7), 91.8 (C_5). Data consistent with literature.[355]

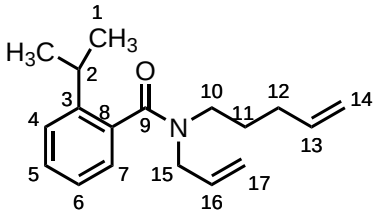
2-Benzhydrylbenzoic acid (3.159)



In air, 3,3-diphenylisobenzofuran-1(3*H*)-one (**3.158**) (1.88 g, 6.57 mmol, 1.0 eq.) was dissolved in MeOH (22 mL), Pd/C (349 mg, 10 wt%, 0.33 mmol, 0.05 eq.) added, the reaction mixture stirred at room temperature under H_2 (1 atm, balloon) for 15 h, filtered through Celite, eluting with MeOH, and concentrated *in vacuo* to yield the title compound as a white solid (1.72 g, 91%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.01 (1H, br s, O*H*), 8.06 (1H, dd, *J* 7.6, 1.5, H_{10}), 7.46 (1H, td, *J* 7.6, 1.5, H_8), 7.33 (1H, td, *J* 7.6, 1.5, H_9), 7.31–7.26 (4H, m, H_3), 7.24–7.19 (2H, m, H_1), 7.13–7.06 (5H, m, H_2, H_7), 6.74 (1H, s, H_5). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.0 (C_{12}), 146.2 (C_6), 143.8 (C_4), 132.7 (C_8), 131.7 (C_{10}), 131.5 (C_7), 129.9 (C_2), 129.0 (C_{11}), 128.4 (C_3), 126.5 (C_9), 126.4 (C_1), 52.3 (C_5). Data consistent with literature.[317]

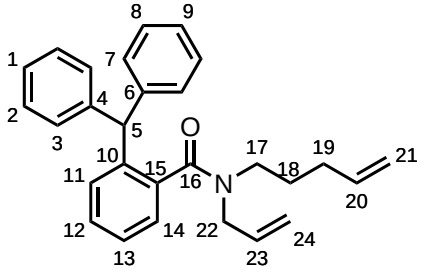
N-Allyl-2-isopropyl-*N*-(pent-4-en-1-yl)benzamide (3.160a)



By **GP2**, the acid chloride of 2-isopropylbenzoic acid (**3.156**) (985 mg, 6.00 mmol) was made by stirring with oxalyl chloride for 3 h. *N*-Allylpent-4-en-1-amine (**3.82c**) (901 mg, 7.20 mmol) was used as the general amine that was stirred with the acid chloride intermediate for 21 h, and purified by flash column chromatography (SiO_2; gradient elution: 0–20% Et_2O in pet. ether) to yield the title compound as a pale yellow oil (1.40 g, 86%).

$\boldsymbol{R_f}$ = 0.27 (30% Et_2O in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers in an approximate 60:40 ratio) δ 7.35–7.30 ($2H^{maj}$ + $2H^{min}$, m, 2 × H_{Ar}), 7.21–7.13 ($1H^{maj}$ + $1H^{min}$, m, H_{Ar}), 7.13–7.08 ($1H^{maj}$ + $1H^{min}$, m, H_{Ar}), 5.95–5.79 ($1H^{maj}$ + $1H^{min}$, m, $H_{13}{}^{maj}$, $H_{16}{}^{min}$), 5.68–5.50 ($1H^{maj}$ + $1H^{min}$, m, $H_{16}{}^{maj}$, $H_{13}{}^{min}$), 5.29–5.20 ($2H^{min}$, m, H_{17}), 5.17–4.97 ($4H^{maj}$, m, H_{14}, H_{17}), 4.89–4.83 ($2H^{min}$, m, H_{14}), 4.39 ($1H^{min}$, dd, *J* 15.0, 5.5, H_{15a}), 3.97 ($1H^{min}$, dd, *J* 15.0, 6.7, H_{15b}), 3.78–3.62 ($3H^{maj}$, m, H_{10a}, H_{15}), 3.32 ($1H^{maj}$, ddd, *J* 13.3, 9.3, 5.9, H_{10b}), 3.09–3.02 ($2H^{min}$, m, H_{10}), 2.96 ($1H^{maj}$, sept, *J* 6.8, H_2), 2.93 ($1H^{min}$, sept, *J* 6.8, H_2), 2.18–2.09 ($2H^{maj}$, m, H_{12}), 1.87–1.79 ($2H^{min}$, m, H_{12}), 1.79–1.71 ($2H^{maj}$, m, H_{11}), 1.60–1.48 ($2H^{min}$, m, H_{11}), 1.25 ($3H^{maj}$, d, *J* 6.8, H_{1a}), 1.24 ($6H^{min}$, d, *J* 6.8, H_1), 1.22 ($3H^{maj}$, d, *J* 6.8, H_{1b}). **^{13}C NMR** (101 MHz, $CDCl_3$, mixture of rotamers in an approximate 60:40 ratio) δ 171.5 ($C_9{}^{maj}$), 171.4 ($C_9{}^{min}$), 145.0 ($C_3{}^{maj}$), 145.0 ($C_3{}^{min}$), 138.0 ($C_{13}{}^{maj}$), 137.1 ($C_{13}{}^{min}$), 135.8 ($C_8{}^{maj}$), 135.7 ($C_8{}^{min}$), 133.4 ($C_{16}{}^{min}$), 133.3 ($C_{16}{}^{maj}$), 129.1 ($C_{Ar}{}^{maj}$, $C_{Ar}{}^{min}$), 125.9 ($C_{Ar}{}^{maj}$), 125.9 ($C_{Ar}{}^{min}$), 125.8 ($C_{Ar}{}^{min}$), 125.8 ($C_{Ar}{}^{maj}$), 125.7 ($C_{Ar}{}^{min}$), 125.5 ($C_{Ar}{}^{maj}$), 117.9 ($C_{17}{}^{maj}$), 117.7 ($C_{17}{}^{min}$), 115.3 ($C_{14}{}^{min}$), 115.2 ($C_{14}{}^{maj}$), 51.6 ($C_{15}{}^{maj}$), 47.7 ($C_{10}{}^{min}$), 46.8 ($C_{15}{}^{min}$), 43.8 ($C_{10}{}^{maj}$), 31.4 ($C_{12}{}^{maj}$), 30.8 ($C_2{}^{min}$), 30.7 ($C_{12}{}^{min}$), 30.7 ($C_2{}^{maj}$), 27.4 ($C_{11}{}^{min}$), 26.5 ($C_{11}{}^{maj}$), 25.0 ($C_{1a}{}^{min}$), 24.7 ($C_{1a}{}^{maj}$), 23.5 ($C_{1b}{}^{maj}$), 23.2 ($C_{1b}{}^{min}$). **IR** (film, $CDCl_3$) ν_{max} = 3075 (C–H), 2961 (C–H), 2929 (C–H), 2869 (C–H), 1632 (C=O), 1463, 1414, 1255, 993, 912, 758 cm^{-1}. **HRMS** (ESI^+) *m*/*z* calcd for $C_{18}H_{26}NO$ $[M+H]^+$ 272.2009, found 272.2011.

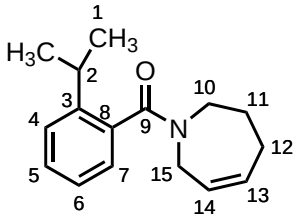
N-Allyl-2-benzhydryl-*N*-(pent-4-en-1-yl)benzamide (3.161a)



By **GP2**, the acid chloride of 2-benzhydrylbenzoic acid (**3.159**) (1.69 g, 5.86 mmol) was made by stirring with oxalyl chloride for 3 h. *N*-Allylpent-4-en-1-amine (**3.82c**) (881 mg, 7.04 mmol) was used as the general amine that was stirred with the acid chloride intermediate for 22 h, and purified by flash column chromatography (SiO_2; gradient elution: 7–30% Et_2O in pet. ether) to yield the title compound as a pale yellow oil (2.33 g, quant.).

$\boldsymbol{R_f}$ = 0.21 (30% Et_2O in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers in an approximate 65:35 ratio) δ 7.32–7.09 ($13H^{maj}$ + $13H^{min}$, m, 13 × H_{Ar}), 7.07 ($1H^{min}$, dd, *J* 7.6, 1.3, H_{Ar}), 7.04 ($1H^{maj}$, dd, *J* 7.6, 1.1, H_{Ar}), 5.98 ($1H^{maj}$, s, H_5), 5.90 ($1H^{min}$, s, H_5), 5.88–5.69 ($1H^{maj}$ + $1H^{min}$, m, $H_{20}{}^{maj}$, $H_{23}{}^{min}$), 5.49 ($1H^{min}$, ddt, *J* 16.9, 10.3, 6.6, H_{20}), 5.31 ($1H^{maj}$, dddd, *J* 17.1, 10.2, 6.3, 5.0, H_{23}), 5.19–5.11 ($2H^{min}$, m, H_{24}), 5.09–4.96 ($4H^{maj}$, m, H_{21}, H_{24}), 4.88–4.79 ($2H^{min}$, m, H_{21}), 4.25 ($1H^{min}$, dd, *J* 15.0, 5.6, H_{22a}), 3.80 ($1H^{min}$, dd, *J* 15.0, 6.9, H_{22b}), 3.61 ($1H^{maj}$, ddd, *J* 13.3, 10.5, 5.4, H_{17a}), 3.34 ($1H^{maj}$, dd, *J* 16.5, 5.0, H_{22a}), 3.04 ($1H^{maj}$, ddd, *J* 13.3, 10.4, 5.3, H_{17b}), 2.84 ($1H^{maj}$, dd, *J* 16.5, 6.3, H_{22b}), 2.65 ($1H^{min}$, ddd, *J* 16.1, 10.5, 5.8, H_{17a}), 2.21 ($1H^{min}$, ddd, *J* 14.6, 10.4, 4.9, H_{17a}), 2.11–1.98 ($2H^{maj}$, m, H_{19}), 1.74–1.60 ($1H^{maj}$ + $2H^{min}$, m, $H_{18a}{}^{maj}$, $H_{19}{}^{min}$), 1.50–1.38 ($1H^{maj}$, m, H_{18b}), 1.38–1.21 ($2H^{min}$, m, H_{18}). **^{13}C NMR** (101 MHz, $CDCl_3$, mixture of rotamers in an approximate 65:35 ratio) δ 171.0 ($C_{16}{}^{maj}$), 170.9 ($C_{16}{}^{min}$), 143.7 ($C_{quat}{}^{min}$), 143.6 ($C_{quat}{}^{maj}$), 142.2 ($C_{quat}{}^{maj}$), 142.0 ($C_{quat}{}^{min}$), 141.0 ($C_{10}{}^{maj}$), 140.8 ($C_{10}{}^{min}$), 137.9 ($C_{20}{}^{maj}$), 137.3 ($C_{15}{}^{min}$), 137.2 ($C_{15}{}^{maj}$), 137.2 ($C_{20}{}^{min}$), 133.4 ($C_{23}{}^{maj}$, $C_{23}{}^{min}$), 130.5 ($C_{Ar}{}^{min}$), 130.5 ($C_{Ar}{}^{maj}$), 129.9 ($C_{Ar}{}^{maj}$, $C_{Ar}{}^{maj}$), 129.8 ($C_{Ar}{}^{min}$, $C_{Ar}{}^{min}$), 129.6 ($C_{Ar}{}^{maj}$, $C_{Ar}{}^{maj}$), 129.6 ($C_{Ar}{}^{min}$, $C_{Ar}{}^{min}$), 128.8 ($C_{Ar}{}^{maj}$), 128.7 ($C_{Ar}{}^{min}$), 128.5 ($C_{Ar}{}^{maj}$, $C_{Ar}{}^{maj}$), 128.4 ($C_{Ar}{}^{min}$, $C_{Ar}{}^{min}$), 128.3 ($C_{Ar}{}^{maj}$, $C_{Ar}{}^{maj}$, $C_{Ar}{}^{min}$, $C_{Ar}{}^{min}$), 126.6 ($C_{Ar}{}^{maj}$, $C_{Ar}{}^{min}$), 126.4 ($C_{Ar}{}^{maj}$, $C_{Ar}{}^{min}$), 126.2 ($C_{Ar}{}^{min}$), 126.1 ($C_{Ar}{}^{maj}$), 126.0 ($C_{Ar}{}^{min}$), 125.8 ($C_{Ar}{}^{maj}$), 117.8 ($C_{24}{}^{min}$), 117.7 ($C_{24}{}^{maj}$), 115.3 ($C_{21}{}^{min}$), 115.0 ($C_{21}{}^{maj}$), 52.5 ($C_5{}^{min}$), 52.4 ($C_5{}^{maj}$), 51.3 ($C_{22}{}^{maj}$), 47.7 ($C_{17}{}^{min}$), 46.9 ($C_{22}{}^{min}$), 43.9 ($C_{17}{}^{maj}$), 31.3 ($C_{19}{}^{maj}$), 30.8 ($C_{19}{}^{min}$), 27.0 ($C_{18}{}^{min}$), 26.1 ($C_{18}{}^{maj}$). **IR** (film, $CDCl_3$) ν_{max} = 3062 (C–H), 3026 (C–H), 2977 (C–H), 2929 (C–H), 1628 (C=O), 1597, 1494, 1451, 1415, 911, 755, 729, 699, 608 cm^{-1}. **HRMS** (ESI^+) *m/z* calcd for $C_{28}H_{30}NO$ $[M+H]^+$ 396.2327, found 396.2326.

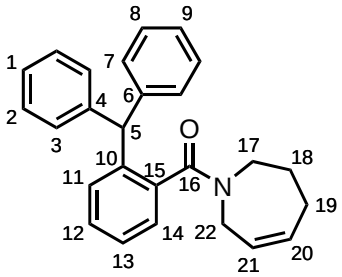
(2-Isopropylphenyl)(2,3,4,7-tetrahydro-1*H*-azepin-1-yl)methanone (3.162a)



By **GP18**, *N*-allyl-*N*-(pent-4-en-1-yl)-2-(1-phenylethyl)benzamide (**3.160a**) (1.36 g, 5.01 mmol) was used as the amide that was stirred for 62 h, and purified by flash column chromatography (SiO_2; gradient elution: 7–50% Et_2O in pet. ether) to yield the title compound as a green-brown oil (1.21 g, quant.).

$\boldsymbol{R_f}$ = 0.12 (30% Et_2O in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers in an approximate 60:40 ratio) δ 7.35–7.29 ($2H^{maj}$ + $2H^{min}$, m, 2 × H_{Ar}), 7.21–7.13 ($1H^{maj}$ + $1H^{min}$, m, H_{Ar}), 7.12–7.08 ($1H^{maj}$ + $1H^{min}$, m, H_{Ar}), 5.92 ($1H^{min}$, dtt, *J* 11.0, 4.8, 1.4, H_{14}), 5.82 ($1H^{maj}$ + $1H^{min}$, dtt, *J* 11.0, 5.6, 1.5, H_{13}), 5.40 ($1H^{maj}$, dtt, *J* 11.0, 4.5, 1.6, H_{14}), 4.40–4.29 ($1H^{min}$, m, H_{15a}), 4.19–4.10 ($1H^{min}$, m, H_{15b}), 4.05 ($1H^{maj}$, dt, *J* 13.2, 6.5, H_{10a}), 3.83–3.73 ($2H^{maj}$, m, H_{15}), 3.68 ($1H^{maj}$, dt, *J* 13.5, 5.7, H_{10b}), 3.47–3.28 ($2H^{min}$, m, H_{10}), 2.97 ($1H^{maj}$, sept, *J* 6.8, H_2), 2.94 ($1H^{min}$, sept, *J* 6.8, H_2), 2.39–2.28 ($2H^{maj}$, m, H_{12}), 2.28–2.12 ($2H^{min}$, m, H_{12}), 2.03–1.94 ($2H^{maj}$, m, H_{11}), 1.80–1.65 ($2H^{min}$, m, H_{11}), 1.24 ($3H^{maj}$, d, *J* 6.8, H_{1a}), 1.24 ($3H^{min}$, d, *J* 6.8, H_{1a}), 1.23 ($3H^{min}$, d, *J* 6.8, H_{1b}), 1.20 ($3H^{maj}$, d, *J* 6.8, H_{1b}). **^{13}C NMR** (101 MHz, $CDCl_3$, mixture of rotamers in an approximate 60:40 ratio) δ 171.3 ($C_9{}^{maj}$), 170.7 ($C_9{}^{min}$), 145.3 ($C_3{}^{min}$), 145.2 ($C_3{}^{maj}$), 136.0 ($C_8{}^{maj}$), 135.8 ($C_8{}^{min}$), 132.8 ($C_{13}{}^{maj}$), 132.1 ($C_{13}{}^{min}$), 129.0 ($C_{Ar}{}^{maj}$, $C_{Ar}{}^{min}$), 128.4 ($C_{14}{}^{min}$), 127.2 ($C_{14}{}^{maj}$), 126.0 ($C_{Ar}{}^{min}$), 125.9 ($C_{Ar}{}^{maj}$, $C_{Ar}{}^{min}$), 125.9 ($C_{Ar}{}^{maj}$), 125.8 ($C_{Ar}{}^{min}$), 125.7 ($C_{Ar}{}^{maj}$), 51.1 ($C_{10}{}^{min}$), 48.4 ($C_{15}{}^{maj}$), 46.3 ($C_{10}{}^{maj}$), 43.0 ($C_{15}{}^{min}$), 30.8 ($C_2{}^{min}$), 30.7 ($C_2{}^{maj}$), 27.2 ($C_{12}{}^{maj}$), 27.1 ($C_{11}{}^{min}$), 26.9 ($C_{12}{}^{min}$), 26.3 ($C_{11}{}^{maj}$), 25.1 ($C_{1a}{}^{min}$), 24.7 ($C_{1a}{}^{maj}$), 23.6 ($C_{1b}{}^{maj}$), 23.4 ($C_{1b}{}^{min}$). **IR** (film, $CDCl_3$) ν_{max} = 3023 (C–H), 2960 (C–H), 2931 (C–H), 2868 (C–H), 1629 (C=O), 1599, 1459, 1421, 1296, 1254, 1144, 760 cm^{-1}. **HRMS** (ESI$^+$) *m*/*z* calcd for $C_{16}H_{22}NO$ $[M+H]^+$ 244.1696, found 244.1692.

(2-Benzhydrylphenyl)(2,3,4,7-tetrahydro-1*H*-azepin-1-yl)methanone (3.163a)

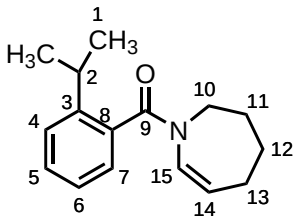


By **GP18**, *N*-allyl-*N*-(pent-4-en-1-yl)-2-(1-benzhydrylethyl)benzamide (**3.161a**) (2.31 g, 5.84 mmol) was used as the amide that was stirred for 81 h, and purified by flash column chromatography (SiO_2; gradient elution: 7–60% Et_2O in pet. ether) to yield the title compound as a green-brown gum (1.91 g, 89%).

$\boldsymbol{R_f}$ = 0.09 (30% Et_2O in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers in an approximate 60:40 ratio) δ 7.32–7.11 ($13H^{maj}$ + $13H^{min}$, m, 13 × H_{Ar}), 7.08 ($1H^{min}$, dd, *J* 7.7, 1.3, H_{Ar}), 7.03 ($1H^{maj}$, dd, *J* 7.7, 1.2, H_{Ar}), 5.94 ($1H^{maj}$, s, H_5), 5.92 ($1H^{min}$, s, H_5), 5.88–5.80 ($1H^{min}$, m, H_{21}), 5.76–5.67 ($1H^{maj}$ +

1H^{min}, m, H_{20}), 5.23 (1H^{maj}, dddt, J 11.0, 5.2, 3.4, 1.7, H_{21}), 4.45 (1H^{min}, dd, J 16.0, 5.3, H_{22a}), 4.29 (1H^{maj}, dddd, J 13.5, 8.6, 5.3, 1.2, H_{17a}), 3.72–3.62 (1H^{min}, m, H_{22b}), 3.11 (1H^{maj}, dd, J 17.5, 5.2, H_{22a}), 3.07–3.00 (1H^{min}, m, H_{17a}), 2.92 (1H^{maj}, dt, J 13.5, 5.3, H_{17b}), 2.83–2.74 (1H^{maj}, m, H_{22b}), 2.41 (1H^{min}, ddd, J 13.6, 8.7, 4.7, H_{17b}), 2.33–2.15 (2H^{maj}, m, H_{19}), 2.15–2.04 (1H^{min}, m, H_{19a}), 1.94–1.78 (2H^{maj}, m, H_{18}), 1.78–1.67 (1H^{min}, m, H_{19b}), 1.57–1.44 (1H^{min}, m, H_{18a}), 1.37–1.25 (1H^{min}, m, H_{18b}). **^{13}C NMR** (101 MHz, $CDCl_3$, mixture of rotamers in an approximate 60:40 ratio) δ 170.6 ($C_{16}{}^{maj}$), 170.1 ($C_{16}{}^{min}$), 143.6 ($C_{quat}{}^{min}$), 143.0 ($C_{quat}{}^{maj}$), 142.3 ($C_{quat}{}^{maj}$), 142.2 ($C_{quat}{}^{min}$), 141.3 ($C_{10}{}^{maj}$), 141.1 ($C_{10}{}^{min}$), 137.6 ($C_{15}{}^{maj}$), 137.4 ($C_{15}{}^{min}$), 132.7 ($C_{20}{}^{maj}$), 132.4 ($C_{20}{}^{min}$), 130.5 ($C_{Ar}{}^{min}$), 129.9 ($C_{Ar}{}^{maj}$, $C_{Ar}{}^{maj}$), 129.9 ($C_{Ar}{}^{maj}$), 129.8 ($C_{Ar}{}^{min}$, $C_{Ar}{}^{min}$), 129.6 ($C_{Ar}{}^{maj}$, $C_{Ar}{}^{maj}$), 129.6 ($C_{Ar}{}^{min}$, $C_{Ar}{}^{min}$), 128.7 ($C_{Ar}{}^{maj}$), 128.6 ($C_{Ar}{}^{min}$), 128.4 ($C_{Ar}{}^{min}$, $C_{Ar}{}^{min}$), 128.4 ($C_{Ar}{}^{maj}$, $C_{Ar}{}^{maj}$), 128.3 ($C_{Ar}{}^{maj}$, $C_{Ar}{}^{maj}$), 128.3 ($C_{Ar}{}^{min}$, $C_{Ar}{}^{min}$), 127.8 ($C_{21}{}^{min}$), 127.1 ($C_{21}{}^{maj}$), 126.6 ($C_{Ar}{}^{min}$), 126.5 ($C_{Ar}{}^{maj}$), 126.4 ($C_{Ar}{}^{maj}$), 126.3 ($C_{Ar}{}^{min}$), 126.2 ($C_{Ar}{}^{min}$), 126.1 ($C_{Ar}{}^{min}$), 126.0 ($C_{Ar}{}^{maj}$), 126.0 ($C_{Ar}{}^{maj}$), 52.7 ($C_5{}^{maj}$), 52.4 ($C_5{}^{min}$), 50.7 ($C_{17}{}^{min}$), 47.4 ($C_{22}{}^{maj}$), 45.8 ($C_{17}{}^{maj}$), 42.9 ($C_{22}{}^{min}$), 27.2 ($C_{19}{}^{maj}$), 26.8 ($C_{18}{}^{min}$), 26.6 ($C_{19}{}^{min}$), 26.0 ($C_{18}{}^{maj}$). **IR** (film, $CDCl_3$) ν_{max} = 3060 (C–H), 3024 (C–H), 2932 (C–H), 1626 (C=O), 1597, 1494, 1451, 1426, 756, 731, 700, 608 cm^{-1}. **HRMS** (ESI$^+$) m/z calcd for $C_{26}H_{26}NO$ $[M+H]^+$ 368.2014, found 368.2018.

(2-Isopropylphenyl)(2,3,4,5-tetrahydro-1*H*-azepin-1-yl)methanone (3.164a)

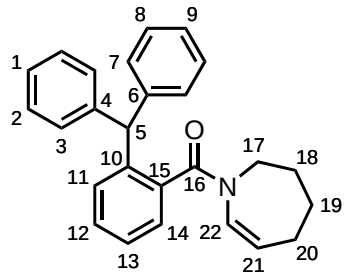


By **GP19**, (2-isopropylphenyl)(2,3,4,7-tetrahydro-1*H*-azepin-1-yl)methanone (**3.162a**) (1.19 g, 4.89 mmol) was used as the amide that was stirred for 40 h, and purified by flash column chromatography (SiO_2; gradient elution: 0–40% Et_2O in pet. ether) to yield the title compound as a pale yellow oil (1.03 g, 87%).

***R*$_f$** = 0.36 (30% Et_2O in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers in an approximate 75:25 ratio) δ 7.36–7.29 (2H^{maj} + 2H^{min}, m, 2 × H_{Ar}), 7.22–7.13 (1H^{maj} + 2H^{min}, m, H_{Ar}), 7.13–7.09 (1H^{min}, m, H_{Ar}), 6.97 (1H^{min}, dt, J 9.1, 1.7, H_{15}), 5.97 (1H^{maj}, dt, J 8.8, 1.6, H_{15}), 5.31 (1H^{min}, dt, J 9.1, 5.4, H_{14}), 4.90 (1H^{maj}, dt, J 8.8, 5.5, H_{14}), 3.96 (2H^{maj}, br s, H_{10}), 3.43 (2H^{min}, t, J 5.9, H_{10}), 2.97 (2H^{maj}, sept, J 6.9, H_2), 2.94 (2H^{min}, sept, J 6.9, H_2), 2.28–2.15 (2H^{maj} + 2H^{min}, m, H_{13}), 1.97–1.87 (2H^{maj}, m, H_{11}), 1.81–1.72 (2H^{maj}, m, H_{12}), 1.73–1.48 (4H^{maj}, m, H_{11}, H_{12}), 1.24 (3H^{min}, d, J 6.9, H_{1a}), 1.24 (3H^{min}, d, J 6.9, H_{1b}), 1.22 (6H^{maj}, d, J 6.9, H_1). **^{13}C NMR** (101 MHz, $CDCl_3$, mixture of rotamers in an approximate 75:25 ratio) δ 170.7 ($C_9{}^{min}$), 170.4 ($C_9{}^{maj}$), 145.3 ($C_3{}^{maj}$), 145.1 ($C_2{}^{min}$), 135.8 ($C_8{}^{maj}$), 135.3 ($C_8{}^{min}$), 131.8 ($C_{15}{}^{maj}$), 129.6 ($C_{15}{}^{min}$), 129.3

($C_{\mathrm{Ar}}{}^{\mathrm{maj}}$), 129.3 ($C_{\mathrm{Ar}}{}^{\mathrm{min}}$), 126.2 ($C_{\mathrm{Ar}}{}^{\mathrm{maj}}$), 125.9 ($C_{\mathrm{Ar}}{}^{\mathrm{min}}$), 125.9 ($C_{\mathrm{Ar}}{}^{\mathrm{maj}}$, $C_{\mathrm{Ar}}{}^{\mathrm{min}}$), 125.8 ($C_{\mathrm{Ar}}{}^{\mathrm{maj}}$), 125.6 ($C_{\mathrm{Ar}}{}^{\mathrm{min}}$), 118.1 ($C_{14}{}^{\mathrm{min}}$), 116.9 ($C_{14}{}^{\mathrm{maj}}$), 50.2 ($C_{10}{}^{\mathrm{min}}$), 45.5 ($C_{10}{}^{\mathrm{maj}}$), 30.9 ($C_{2}{}^{\mathrm{min}}$), 30.7 ($C_{2}{}^{\mathrm{maj}}$), 28.9 ($C_{12}{}^{\mathrm{min}}$), 27.7 ($C_{11}{}^{\mathrm{maj}}$), 26.5 ($C_{13}{}^{\mathrm{min}}$), 26.5 ($C_{13}{}^{\mathrm{maj}}$), 25.1 ($C_{12}{}^{\mathrm{maj}}$), 25.0 ($C_{11}{}^{\mathrm{min}}$), 24.7 ($C_{1\mathrm{a}}{}^{\mathrm{min}}$), 24.0 ($C_{1}{}^{\mathrm{maj}}$), 23.3 ($C_{1\mathrm{b}}{}^{\mathrm{min}}$). **IR** (film, $CDCl_3$) ν_{max} = 2959 (C–H), 2929 (C–H), 2866 (C–H), 1631 (C=O), 1405, 1385, 1364, 1352, 1341, 1255, 1140, 1074, 852, 758, 726 cm^{-1}. **HRMS** (ESI^+) m/z calcd for $C_{16}H_{22}NO$ $[M+H]^+$ 244.1696, found 244.1692.

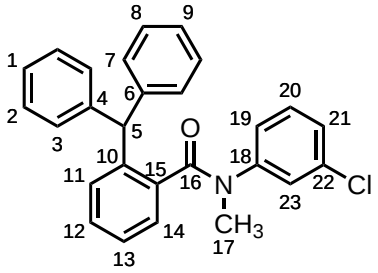
(2-Benzhydrylphenyl)(2,3,4,5-tetrahydro-1*H*-azepin-1-yl)methanone (3.165a)



By **GP19**, (2-benzhydrylphenyl)(2,3,4,7-tetrahydro-1*H*-azepin-1-yl)methanone (**3.163a**) (1.82 g, 4.95 mmol) was used as the amide that was stirred for 47 h, and purified by flash column chromatography (SiO_2; gradient elution: 0–40% Et_2O in pet. ether) to yield the title compound as a yellow oil (1.54 g, 85%).

$\boldsymbol{R_f}$ = 0.24 (30% Et_2O in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers in an approximate 70:30 ratio) δ 7.35–7.10 ($13H^{\mathrm{maj}}$ + $13H^{\mathrm{min}}$, m, 13 × H_{Ar}), 7.08 ($1H^{\mathrm{min}}$, dd, J 7.7, 1.2, H_{Ar}), 7.03 ($1H^{\mathrm{maj}}$, dd, J 7.8, 1.3, H_{Ar}), 6.82 ($1H^{\mathrm{min}}$, dt, J 9.1, 1.6, H_{22}), 5.95 ($1H^{\mathrm{maj}}$, s, H_5), 5.93 ($1H^{\mathrm{min}}$, s, H_5), 5.54 ($1H^{\mathrm{maj}}$, dt, J 8.7, 1.6, H_{22}), 5.24 ($1H^{\mathrm{min}}$, dt, J 9.1, 5.5, H_{21}), 4.75 ($1H^{\mathrm{maj}}$, dt, J 8.7, 5.5, H_{21}), 4.00 ($1H^{\mathrm{maj}}$, br s, $H_{17\mathrm{a}}$), 3.46 ($1H^{\mathrm{maj}}$, br s, $H_{17\mathrm{b}}$), 2.89 ($1H^{\mathrm{min}}$, dt, J 14.5, 4.2, $H_{17\mathrm{a}}$), 2.45 ($1H^{\mathrm{min}}$, ddd, J 14.5, 10.1, 3.8, $H_{17\mathrm{b}}$), 2.17–2.02 ($2H^{\mathrm{maj}}$ + $2H^{\mathrm{min}}$, m, H_{18}), 1.83 ($2H^{\mathrm{maj}}$, br s, H_{18}), 1.75–1.57 ($2H^{\mathrm{maj}}$ + $1H^{\mathrm{min}}$, m, $H_{19}{}^{\mathrm{maj}}$, $H_{19\mathrm{a}}{}^{\mathrm{min}}$), 1.56–1.41 ($2H^{\mathrm{min}}$, m, $H_{18\mathrm{a}}$, $H_{19\mathrm{b}}$), 1.22–1.08 ($1H^{\mathrm{min}}$, m, $H_{18\mathrm{b}}$). **^{13}C NMR** (101 MHz, $CDCl_3$, mixture of rotamers in an approximate 70:30 ratio) δ 170.4 ($C_{16}{}^{\mathrm{min}}$), 169.8 ($C_{16}{}^{\mathrm{maj}}$), 143.0 ($C_{\mathrm{quat}}{}^{\mathrm{min}}$), 142.8 ($C_{\mathrm{quat}}{}^{\mathrm{maj}}$, $C_{\mathrm{quat}}{}^{\mathrm{maj}}$), 141.9 ($C_{\mathrm{quat}}{}^{\mathrm{min}}$), 141.5 ($C_{10}{}^{\mathrm{maj}}$), 141.4 ($C_{10}{}^{\mathrm{min}}$), 137.1 ($C_{15}{}^{\mathrm{maj}}$), 136.8 ($C_{15}{}^{\mathrm{min}}$), 131.7 ($C_{22}{}^{\mathrm{maj}}$), 130.1 ($C_{\mathrm{Ar}}{}^{\mathrm{min}}$), 130.1 ($C_{\mathrm{Ar}}{}^{\mathrm{maj}}$), 129.9 ($C_{\mathrm{Ar}}{}^{\mathrm{min}}$, $C_{\mathrm{Ar}}{}^{\mathrm{min}}$), 129.7 ($C_{\mathrm{Ar}}{}^{\mathrm{maj}}$, $C_{\mathrm{Ar}}{}^{\mathrm{maj}}$, $C_{\mathrm{Ar}}{}^{\mathrm{maj}}$, $C_{\mathrm{Ar}}{}^{\mathrm{maj}}$), 129.6 ($C_{\mathrm{Ar}}{}^{\mathrm{min}}$, $C_{\mathrm{Ar}}{}^{\mathrm{min}}$), 129.5 ($C_{22}{}^{\mathrm{min}}$), 129.0 ($C_{\mathrm{Ar}}{}^{\mathrm{maj}}$), 129.0 ($C_{\mathrm{Ar}}{}^{\mathrm{min}}$), 128.5 ($C_{\mathrm{Ar}}{}^{\mathrm{min}}$, $C_{\mathrm{Ar}}{}^{\mathrm{min}}$), 128.3 ($C_{\mathrm{Ar}}{}^{\mathrm{maj}}$, $C_{\mathrm{Ar}}{}^{\mathrm{maj}}$, $C_{\mathrm{Ar}}{}^{\mathrm{maj}}$, $C_{\mathrm{Ar}}{}^{\mathrm{maj}}$, $C_{\mathrm{Ar}}{}^{\mathrm{min}}$, $C_{\mathrm{Ar}}{}^{\mathrm{min}}$), 127.5 ($C_{\mathrm{Ar}}{}^{\mathrm{maj}}$), 126.7 ($C_{\mathrm{Ar}}{}^{\mathrm{min}}$), 126.5 ($C_{\mathrm{Ar}}{}^{\mathrm{maj}}$, $C_{\mathrm{Ar}}{}^{\mathrm{maj}}$), 126.1 ($C_{\mathrm{Ar}}{}^{\mathrm{maj}}$, $C_{\mathrm{Ar}}{}^{\mathrm{min}}$), 126.0 ($_{\mathrm{Ar}}{}^{\mathrm{min}}$), 118.3 ($C_{21}{}^{\mathrm{min}}$), 116.8 ($C_{21}{}^{\mathrm{maj}}$), 52.7 ($C_{5}{}^{\mathrm{min}}$), 52.6 ($C_{5}{}^{\mathrm{maj}}$), 49.7 ($C_{17}{}^{\mathrm{min}}$), 45.4 ($C_{17}{}^{\mathrm{maj}}$), 28.7 ($C_{18}{}^{\mathrm{min}}$), 27.7 ($C_{18}{}^{\mathrm{maj}}$), 26.5 ($C_{20}{}^{\mathrm{min}}$), 26.5 ($C_{20}{}^{\mathrm{maj}}$), 24.9 ($C_{19}{}^{\mathrm{maj}}$), 24.9 ($C_{19}{}^{\mathrm{min}}$). **IR** (film, $CDCl_3$) ν_{max} = 3059 (C–H), 3025 (C–H), 2930 (C–H), 1631 (C=O), 1597, 1495, 1449, 1407, 1387, 1366, 1142, 1078, 754, 731, 700, 607 cm^{-1}. **HRMS** (ESI^+) m/z calcd for $C_{26}H_{26}NO$ $[M+H]^+$ 368.2009, found 368.2003.

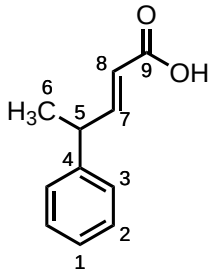
2-Benzhydryl-*N*-(3-chlorophenyl)-*N*-methylbenzamide (3.168a)



By **GP2**, the acid chloride of 2-benzhydrylbenzoic acid (**3.159**) (1.61 g, 5.58 mmol) was made by stirring with oxalyl chloride for 2.5 h. 3-Chloro-*N*-methylaniline (820 µL, 6.69 mmol) was used as the general amine that was stirred with the acid chloride intermediate for 22 h, and purified by flash column chromatography (SiO_2; gradient elution: 7–30% Et_2O in pet. ether), with further purification by trituration with Et_2O to yield the title compound as a white solid (1.48 g, 64%).

m.p. = 148–149 °C (Et_2O). $\boldsymbol{R_f}$ = 0.24 (30% Et_2O in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers in an approximate 70:30 ratio) δ 7.46–6.88 ($17H^{maj}$ + $18H^{min}$, m, 9 × H_{Ar}), 6.56 ($1H^{maj}$, br s, H_{Ar}), 6.32 ($1H^{min}$, br s, H_5), 6.22 ($1H^{maj}$, br s, H_5), 3.41 ($3H^{maj}$, br s, H_{17}), 2.58 ($3H^{min}$, br s, H_{17}). **^{13}C NMR** (126 MHz, $CDCl_3$, mixture of rotamers in an approximate 70:30 ratio) δ 170.9 ($C_{16}{}^{min}$), 170.3 ($C_{16}{}^{maj}$), 145.1 ($C_{18}{}^{maj}$), 143.8 ($C_{18}{}^{min}$), 142.8 ($C_4{}^{maj}$, $C_6{}^{maj}$), 142.3 ($C_4{}^{min}$, $C_6{}^{min}$, $C_{10}{}^{maj}$), 141.8 ($C_{10}{}^{min}$), 136.7 ($C_{15}{}^{min}$), 135.9 ($C_{22}{}^{min}$), 134.4 ($C_{15}{}^{maj}$, $C_{22}{}^{maj}$), 130.4 ($C_{Ar}{}^{maj}$, $C_{Ar}{}^{min}$), 129.9 (2 × $C_{Ar}{}^{maj}$, $C_{Ar}{}^{min}$), 129.7 (4 × $C_{Ar}{}^{maj}$, 4 × $C_{Ar}{}^{min}$), 129.0 ($C_{Ar}{}^{maj}$, $C_{Ar}{}^{min}$), 128.5 (4 × $C_{Ar}{}^{maj}$, 5 × $C_{Ar}{}^{min}$), 126.9 ($C_{Ar}{}^{maj}$, 2 × $C_{Ar}{}^{min}$), 126.7 ($C_{Ar}{}^{maj}$), 126.6 (3 × $C_{Ar}{}^{maj}$), 126.3 ($C_{Ar}{}^{maj}$), 125.5 (2 × $C_{Ar}{}^{min}$), 125.1 (2 × $C_{Ar}{}^{min}$), 52.4 ($C_5{}^{min}$), 51.8 ($C_5{}^{maj}$), 39.7 ($C_{17}{}^{min}$), 37.6 ($C_{17}{}^{maj}$). **IR** (film, $CDCl_3$) ν_{max} = 3061 (C–H), 3026 (C–H), 2929 (C–H), 1642 (C=O), 1590, 1494, 1477, 1361, 782, 754, 731, 699, 682, 608 cm^{-1}. **HRMS** (ESI^+) m/z calcd for $C_{27}H_{22}ClNO$ $[M+H]^+$ 412.1463, found 412.1461.

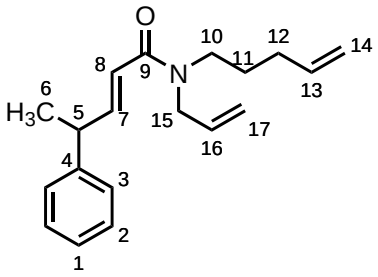
(*E*)-4-Phenylpent-2-enoic acid (3.172)



By the method of Helquist and co-workers[294] with modifications, $Zn(OTf)_2$ (4.97 g, 13.7 mmol, 2.2 eq.) was suspended in anhydrous THF (18 mL), and cooled to 0 °C. Diethylphosphonoacetic acid (1.0 mL, 6.22 mmol, 1.0 eq.), TMEDA (1.1 mL, 7.33 mmol, 1.2 eq.), DBU (3.7 mL, 24.7 mmol, 4.0 eq.), and 2-phenylpropionaldehyde (920 µL, 6.87 mmol, 1.1 eq.) were added, the reaction mixture stirred at room temperature for 23 h, quenched by the addition of aqueous HCl (25 mL, 3 M), and extracted with DCM (3 × 25 mL). The combined organic extracts were dried (Na_2SO_4), and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2; gradient elution: 5–25% EtOAc + 1% HCO_2H in pet. ether + 1% HCO_2H) to yield the title compound as a colourless oil that solidified upon standing (804 mg, 73%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.82 (1H, br s, O*H*), 7.36–7.29 (2H, m, H_2), 7.26–7.17 (4H, m, H_1, H_3, H_7), 5.82 (1H, dd, *J* 15.7, 1.6, H_8), 3.65 (1H, quintd, *J* 7.1, 1.6, H_5), 1.45 (3H, d, *J* 7.1, H_6). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.4 (C_9), 155.6 (C_7), 143.1 (C_4), 128.9 (C_2), 127.5 (C_3), 127.0 (C_1), 119.6 (C_8), 42.3 (C_5), 20.2 (C_6). Data consistent with literature.[294]

(*E*)-*N*-Allyl-*N*-(pent-4-en-1-yl)-4-phenylpent-2-enamide (3.173a)

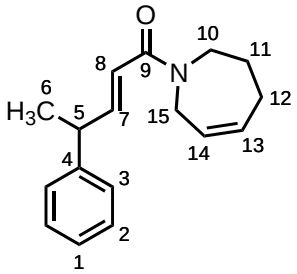


By **GP2**, the acid chloride of (*E*)-4-phenylpent-2-enoic acid (**3.172**) (1.31 g, 7.43 mmol) was made by stirring with oxalyl chloride for 3 h. *N*-Allylpent-4-en-1-amine (**3.82c**) (1.12 g, 8.94 mmol) was used as the general amine that was stirred with the acid chloride intermediate for 15 h, and purified by flash column chromatography (SiO_2; gradient elution: 7–45% Et_2O in pet. ether) to yield the title compound as a pale yellow oil (1.92 g, 91%).

R_f = 0.19 (30% Et_2O in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers in an approximate 50:50 ratio) δ 7.34–7.27 (2H$^{\text{both rot.}}$, m, H_2), 7.25–7.16 (3H$^{\text{both rot.}}$, m, H_1, H_3), 7.10 (1H$^{\text{one rot.}}$, dd, *J* 15.0, 6.7, H_7), 7.06 (1H$^{\text{one rot.}}$, dd, *J* 15.0, 6.7, H_7), 6.08 (1H$^{\text{one rot.}}$, d, *J* 15.0, H_8), 6.07 (1H$^{\text{one rot.}}$, d, *J* 15.0, H_8), 5.86–5.64 (2H$^{\text{both rot.}}$, m, H_{13}, H_{16}), 5.19–5.06 (2H$^{\text{both rot.}}$, m, H_{17}), 5.02 (1H$^{\text{both rot.}}$, dq, *J* 17.1, 1.7, H_{14a}), 4.99–4.93 (1H$^{\text{both rot.}}$, m, H_{14b}), 4.01 (2H$^{\text{one rot.}}$, d, *J* 5.9, H_{15}), 3.89 (2H$^{\text{one rot.}}$, d, *J* 4.8, H_{15}), 3.63 (1H$^{\text{one rot.}}$, quint, *J* 6.7, H_5), 3.60 (1H$^{\text{one rot.}}$, quint, *J* 6.7, H_5), 3.37 (2H$^{\text{one rot.}}$, app td, *J* 7.2, 2.5, H_{10}), 3.22 (2H$^{\text{one rot.}}$, t, *J* 7.2, H_{10}), 2.11–1.95 (2H$^{\text{both rot.}}$, m, H_{12}), 1.65 (2H$^{\text{one rot.}}$, quint, *J* 7.2, H_{11}), 1.61 (2H$^{\text{one rot.}}$, quint, *J* 7.2, H_{11}), 1.44 (3H$^{\text{one rot.}}$, d, *J* 6.7, H_6), 1.41 (3H$^{\text{one rot.}}$, d, *J* 6.7, H_6). **^{13}C NMR** (101 MHz, $CDCl_3$, mixture of rotamers in an

approximate 50:50 ratio) δ 166.9 (C_9[one rot.]), 166.3 (C_9[one rot.]), 150.4 (C_7[one rot.]), 150.0 (C_7[one rot.]), 144.0 (C_4[both rot.]), 138.0 (C_{13}[one rot.]), 137.3 (C_{13}[one rot.]), 133.7 (C_{16}[one rot.]), 133.5 (C_{16}[one rot.]), 128.6 (C_2[both rot.]), 127.5 (C_3[both rot.]), 126.6 (C_1[both rot.]), 119.7 (C_8[one rot.]), 119.4 (C_8[one rot.]), 117.1 (C_{17}[one rot.]), 116.8 (C_{17}[one rot.]), 115.7 (C_{14}[one rot.]), 115.0 (C_{14}[one rot.]), 50.5 (C_{15}[one rot.]), 48.8 (C_{15}[one rot.]), 46.8 (C_{10}[one rot.]), 46.5 (C_{10}[one rot.]), 42.3 (C_5[both rot.]), 31.2 (C_{12}[one rot.]), 30.8 (C_{12}[one rot.]), 28.4 (C_{11}[one rot.]), 27.1 (C_{11}[one rot.]), 20.8 (C_6[both rot.]). **IR** (film, $CDCl_3$) ν_{max} = 3078 (C–H), 2967 (C–H), 2929 (C–H), 1657 (C=O), 1641, 1616, 1413, 991, 911, 761, 699 cm^{-1}. **HRMS** (ESI^+) m/z calcd for $C_{19}H_{26}NO$ $[M+H]^+$ 284.2009, found 284.2007.

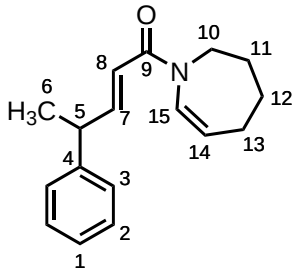
(*E*)-4-Phenyl-1-(2,3,4,7-tetrahydro-1*H*-azepin-1-yl)pent-2-en-1-one (3.174a)



By **GP18**, (*E*)-*N*-allyl-*N*-(pent-4-en-1-yl)-4-phenylpent-2-enamide (**3.173a**) (1.89 g, 6.67 mmol) was used as the amide that was stirred for 67 h, and purified by flash column chromatography (SiO_2; gradient elution: 7–35% EtOAc in pet. ether) to yield the title compound as a brown oil (1.12 g, 66%).

R_f = 0.17 (30% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers in an approximate 50:50 ratio) δ 7.32–7.26 ($2H^{both\ rot.}$, m, H_2), 7.24–7.15 ($3H^{both\ rot.}$, m, H_1, H_3), 7.11–6.94 ($1H^{both\ rot.}$, m, H_7), 6.23–6.07 ($1H^{both\ rot.}$, m, H_8), 5.86–5.62 ($2H^{both\ rot.}$, m, H_{13}, H_{14}), 4.15–4.05 ($2H^{one\ rot.}$, m, H_{15}), 3.97–3.89 ($2H^{one\ rot.}$, m, H_{15}), 3.78–3.68 ($2H^{one\ rot.}$, m, H_{10}), 3.66–3.48 ($2H^{one\ rot.}$ + $2H^{both\ rot.}$, m, H_{10}[one rot.], H_5), 2.38–2.13 ($2H^{both\ rot.}$, m, H_{12}), 1.86 ($2H^{one\ rot.}$, quint, J 6.2, H_{11}), 1.82 ($2H^{one\ rot.}$, quint, J 6.2, H_{11}), 1.46–1.39 ($3H^{both\ rot.}$, m, H_6). **^{13}C NMR** (101 MHz, $CDCl_3$, mixture of rotamers in an approximate 50:50 ratio) δ 166.7 (C_9[one rot.]), 166.1 (C_9[one rot.]), 149.9 (C_7[one rot.]), 149.4 (C_7[one rot.]), 144.1 (C_4[both rot.]), 133.8 (C_{13}[one rot.]), 130.8 (C_{13}[one rot.]), 128.6 (C_2[both rot.]), 128.3 (C_{14}[one rot.]), 127.4 (C_3[both rot.]), 127.0 (C_{14}[one rot.]), 126.5 (C_1[both rot.]), 119.9 (C_8[one rot.]), 119.4 (C_8[one rot.]), 49.0 (C_{15}[one rot.]), 46.8 (C_{15}[one rot.]), 46.4 (C_{10}[one rot.]), 44.7 (C_{10}[one rot.]), 42.3 (C_5[both rot.]), 27.3 (C_{11}[one rot.]), 26.9 (C_{12}[one rot.]), 26.4 (C_{12}[one rot.]), 26.0 (C_{11}[one rot.]), 20.9 (C_6[one rot.]), 20.9 (C_6[one rot.]). **IR** (film, $CDCl_3$) ν_{max} = 3024 (C–H), 2965 (C–H), 2929 (C–H), 2871 (C–H), 1655 (C=O), 1611, 1423, 1283, 1200, 1180, 974, 762, 699 cm^{-1}. **HRMS** (ESI^+) m/z calcd for $C_{17}H_{22}NO$ $[M+H]^+$ 256.1696, found 256.1686.

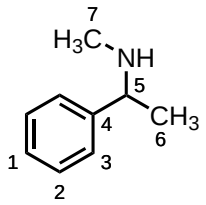
(*E*)-4-Phenyl-1-(2,3,4,5-tetrahydro-1*H*-azepin-1-yl)pent-2-en-1-one (3.175a)



By **GP19**, (*E*)-4-phenyl-1-(2,3,4,7-tetrahydro-1*H*-azepin-1-yl)pent-2-en-1-one (**3.174a**) (1.06 g, 4.15 mmol) was used as the amide that was stirred for 17 h, and purified by flash column chromatography (SiO_2; gradient elution: 15–40% Et_2O in pet. ether) to yield the title compound as a yellow oil (906 mg, 85%).

$\boldsymbol{R_f}$ = 0.24 (30% Et_2O in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers in an approximate 80:20 ratio) δ 7.33–7.27 ($2H^{maj}$ + $2H^{min}$, m, H_2), 7.23–7.18 ($3H^{maj}$ + $3H^{min}$, m, H_1, H_3), 7.07 ($1H^{maj}$ + $1H^{min}$, dd, *J* 15.2, 7.0, H_7), 6.86 ($1H^{min}$, d, *J* 8.3, H_{15}), 6.45 ($1H^{maj}$, d, *J* 8.3, H_{15}), 6.19 ($1H^{maj}$ + $1H^{min}$, dd, *J* 15.2, 1.5, H_8), 5.25 ($1H^{maj}$, dt, *J* 8.3, 5.5, H_{14}), 5.18 ($1H^{min}$, br s, H_{14}), 3.81–3.74 ($2H^{maj}$, m, H_{10}), 3.74–3.67 ($2H^{maj}$, m, H_{10}), 3.62 ($1H^{maj}$ + $1H^{min}$, quintd, *J* 7.0, 1.5, H_5), 2.19 ($2H^{maj}$ + $2H^{min}$, tdd, *J* 6.4, 5.5, 1.5, H_{13}), 1.84–1.74 ($2H^{maj}$ + $4H^{min}$, m, H_{11}, $H_{12}{}^{min}$), 1.64 ($2H^{maj}$, quint, *J* 6.4, H_{12}), 1.42 ($3H^{maj}$ + $3H^{min}$, d, *J* 7.0, H_6) **^{13}C NMR** (101 MHz, $CDCl_3$, mixture of rotamers in an approximate 80:20 ratio) δ 165.2 ($C_9{}^{maj}$, $C_9{}^{min}$), 150.9 ($C_7{}^{min}$), 150.4 ($C_7{}^{maj}$), 143.9 ($C_4{}^{maj}$, $C_4{}^{min}$), 130.7 ($C_{15}{}^{maj}$, $C_{15}{}^{min}$), 128.6 ($C_2{}^{maj}$, $C_2{}^{min}$), 127.3 ($C_3{}^{maj}$, $C_3{}^{min}$), 126.6 ($C_1{}^{maj}$, $C_1{}^{min}$), 120.6 ($C_{14}{}^{maj}$), 119.8 ($C_8{}^{maj}$), 118.8 ($C_8{}^{min}$), 117.3 ($C_{14}{}^{min}$), 48.8 ($C_{10}{}^{min}$), 46.0 ($C_{10}{}^{maj}$), 42.4 ($C_5{}^{maj}$, $C_5{}^{min}$), 28.5 ($C_{11}{}^{min}$), 28.0 ($C_{11}{}^{maj}$), 26.8 ($C_{13}{}^{maj}$), 26.1 ($C_{13}{}^{min}$), 24.6 ($C_{12}{}^{maj}$, $C_{12}{}^{min}$), 20.8 ($C_6{}^{maj}$, $C_6{}^{min}$). **IR** (film, $CDCl_3$) ν_{max} = 3027 (C–H), 2928 (C–H), 2857 (C–H), 1661 (C=O), 1649, 1619, 1450, 1407, 1387, 1365, 1342, 1294, 1203, 1185, 1154, 976, 858, 698, 540 cm^{-1}. **HRMS** (ESI$^+$) *m*/*z* calcd for $C_{17}H_{22}NO$ $[M+H]^+$ 256.1696, found 256.1697.

N-Methyl-1-phenylethan-1-amine (3.179)

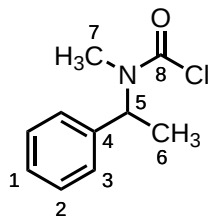


By the method of Blacker and co-workers[356] with modifications, acetophenone (9.7 mL, 83.2 mmol, 1.0 eq.) and EtOH (40 mL) were added to molecular sieves (16.0 g, 3 Å), and the reaction mixture degassed by bubbling N_2 through the solution for 5 min. $MeNH_2$ (22.0 mL, 33 wt% in EtOH, 177 mmol, 2.1 eq.) was added, the reaction mixture stirred at room temperature for 43 h, filtered through Celite, eluting with DCM, and concentrated *in vacuo* to yield the crude imine (10.7 g, 80.3 mmol), which was used without further purification.

The crude imine (10.7 g, 80.3 mmol, 1.0 eq.) was dissolved in MeOH (171 mL), cooled to 0 °C, and $NaBH_4$ (15.8 g, 418 mmol, 5.2 eq.) added portionwise over 2 h. The reaction mixture was stirred at room temperature for 22 h, cooled to 0 °C, aqueous HCl (250 mL, 2 M) added slowly (note: effervescence), and concentrated *in vacuo* to remove MeOH. The residue was diluted with aqueous NaOH (250 mL, 3 M), extracted with DCM (3 × 100 mL), the combined organic extracts dried ($MgSO_4$), and concentrated *in vacuo* to yield the title compound as a pale yellow oil without further purification (9.12 g, 81%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.28 (4H, m, H_2, H_3), 7.26–7.21 (1H, m, H_1), 3.64 (1H, q, J 6.6, H_5), 2.31 (3H, s, H_7), 1.46 (1H, br s, NH), 1.36 (3H, d, J 6.6, H_6). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.5 (C_4), 128.5 (C_2), 127.0 (C_1), 126.7 (C_3), 60.3 (C_5), 34.6 (C_7), 24.0 (C_6). Data consistent with literature.[356]

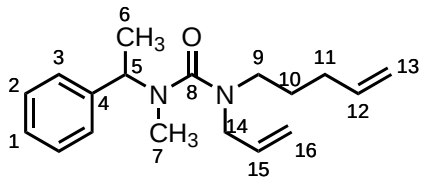
Methyl(1-phenylethyl)carbamic chloride (3.180)



By **GP8**, *N*-methyl-1-phenylethan-1-amine (**3.179**) (947 mg, 7.00 mmol) was used as the amine that was stirred for 22 h to yield the title compound as a brown oil (1.22 g, 88%).

$\boldsymbol{R_f}$ = 0.71 (30% Et_2O in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers in an approximate 70:30 ratio) δ 7.42–7.34 ($2H^{maj}$ + $2H^{min}$, m, H_2), 7.34–7.29 ($3H^{maj}$ + $3H^{min}$, m, H_1, H_3), 5.69 ($1H^{maj}$ + $1H^{min}$, q, J 7.1, H_5), 2.80 ($3H^{maj}$, s, H_7), 2.72 ($3H^{min}$, s, H_7), 1.65–1.55 ($3H^{maj}$ + $3H^{min}$, m, H_6). **^{13}C NMR** (101 MHz, $CDCl_3$, mixture of rotamers in an approximate 70:30 ratio) δ 150.5 ($C_8{}^{maj}$), 149.2 ($C_8{}^{min}$), 138.8 ($C_4{}^{maj}$), 138.7 ($C_4{}^{min}$), 128.8 ($C_2{}^{maj}$, $C_2{}^{min}$), 128.1 ($C_1{}^{maj}$, $C_1{}^{min}$), 127.3 ($C_3{}^{maj}$), 126.9 ($C_3{}^{min}$), 58.2 ($C_5{}^{min}$), 56.0 ($C_5{}^{maj}$), 32.8 ($C_7{}^{maj}$), 31.3 ($C_7{}^{min}$), 16.5 ($C_6{}^{min}$), 15.9 ($C_6{}^{maj}$). **IR** (film, DCM) ν_{max} = 3031 (C–H), 2981 (C–H), 1726 (C=O), 1451, 1382, 1285, 1215, 1077, 1056, 700, 667, 539 cm^{-1}. **HRMS** (APCI$^+$) m/z calcd for $C_{10}H_{13}ClNO$ $[M+H]^+$ 198.0680, found 198.0685.

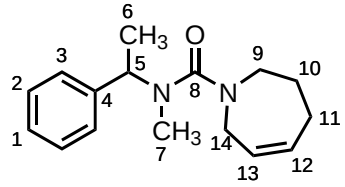
1-Allyl-3-methyl-1-(pent-4-en-1-yl)-3-(1-phenylethyl)urea (3.181a)



By **GP9**, methyl(1-phenylethyl)carbamic chloride (**3.180**) (1.16 g, 5.87 mmol) was used as the carbamoyl chloride and *N*-allylpent-4-en-1-amine (**3.82c**) (881 mg, 7.04 mmol) was used as the amine that were stirred for 22 h, and purified by flash column chromatography (SiO_2; gradient elution: 0–30% Et_2O in pet. ether) to yield the title compound as a pale yellow oil (1.68 g, quant.).

$\boldsymbol{R_f}$ = 0.35 (30% Et_2O in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38–7.28 (4H, m, H_2, H_3), 7.28–7.21 (1H, m, H_1), 5.84 (1H, ddt, J 17.2, 10.3, 5.8, H_{15}), 5.78 (1H, ddt, J 17.1, 10.2, 6.6, H_{12}), 5.22 (1H, q, J 7.0, H_5), 5.25–5.12 (2H, m, H_{16}), 5.01 (1H, dq, J 17.1, 1.5, H_{13a}), 4.95 (1H, dq, J 10.2, 1.5, H_{13b}), 3.76 (2H, dt, J 5.8, 1.6, H_{14}), 3.20–3.05 (2H, m, H_9), 2.54 (3H, s, H_7), 2.02 (2H, tdt, J 7.6, 6.6, 1.5, H_{11}), 1.66 (2H, quint, J 7.6, H_{10}), 1.53 (3H, d, J 7.0, H_6). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.3 (C_8), 141.6 (C_4), 138.1 (C_{12}), 134.8 (C_{15}), 128.5 (C_2), 127.3 (C_3), 127.1 (C_1), 117.0 (C_{16}), 115.0 (C_{13}), 54.8 (C_5), 51.6 (C_{14}), 47.6 (C_9), 31.3 (C_{11}), 31.2 (C_7), 27.0 (C_{10}), 16.4 (C_6). **IR** (film, $CDCl_3$) ν_{max} = 2975 (C–H), 2931 (C–H), 1635 (C=O), 1451, 1392, 1306, 1126 cm^{-1}. **HRMS** (ESI^+) m/z calcd for $C_{18}H_{27}N_2O$ $[M+H]^+$ 287.2118, found 287.2121.

N-Methyl-N-(1-phenylethyl)-2,3,4,7-tetrahydro-1H-azepine-1-carboxamide (3.182a)

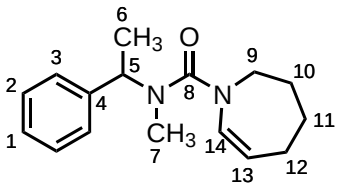


By **GP18**, 1-allyl-3-methyl-1-(pent-4-en-1-yl)-3-(1-phenylethyl)urea (**3.181a**) (1.63 g, 5.59 mmol) was used as the urea that was stirred for 42 h, and purified by flash column chromatography (SiO_2; gradient elution: 0–40% EtOAc in pet. ether) to yield the title compound as a dark green oil (1.23 g, 84%).

$\boldsymbol{R_f}$ = 0.39 (30% Et_2O in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34–7.28 (4H, m, H_2, H_3), 7.25–7.19 (1H, m, H_1), 5.83–5.73 (1H, m, H_{12}), 5.71 (1H, dtt, J 10.6, 4.5, 1.3, H_{13}), 5.18 (1H, q, J 7.0, H_5), 3.79–3.74 (2H, m, H_{14}), 3.46 (2H, t, J 6.2, H_9), 2.51 (3H, s, H_7), 2.27–2.20 (2H, m, H_{11}), 1.93–1.82 (2H, m, H_{10}), 1.52 (3H, d, J 7.0, H_6). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.3 (C_8), 141.6 (C_4), 132.2 (C_{12}), 128.6 (C_{13}), 128.4 (C_2), 127.3 (C_3), 127.0 (C_1), 54.8 (C_5), 50.1 (C_9), 47.6 (C_{14}), 31.2 (C_7), 27.1 (C_{11}), 27.0 (C_{10}), 16.3 (C_6). **IR** (film, $CDCl_3$) ν_{max} = 3023

(C–H), 2970 (C–H), 2930 (C–H), 1628 (C=O), 1448, 1432, 1392, 1281, 1165, 1083, 1051, 786, 770, 636, 699, 636 cm^{-1}. **HRMS** (ESI^+) m/z calcd for $C_{16}H_{23}N_2O$ $[M+H]^+$ 259.1805, found 259.1808.

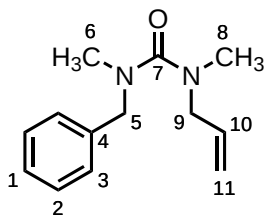
N-Methyl-*N*-(1-phenylethyl)-2,3,4,5-tetrahydro-1*H*-azepine-1-carboxamide (3.183a)



By **GP19**, *N*-methyl-*N*-(1-phenylethyl)-2,3,4,7-tetrahydro-1*H*-azepine-1-carboxamide (**3.182a**) (1.10 g, 4.26 mmol) was used as the urea that was stirred for 18 h, and purified by flash column chromatography (SiO_2; gradient elution: 0–60% Et_2O in pet. ether) to yield the title compound as a green-brown oil (1.08 g, 98%).

$\boldsymbol{R_f}$ = 0.27 (30% Et_2O in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36–7.30 (4H, m, H_2, H_3), 7.29–7.21 (1H, m, H_1), 6.18 (1H, dt, J 8.6, 1.4, H_{14}), 5.35 (1H, q, J 7.0, H_5), 4.97 (1H, dt, J 8.6, 5.7, H_{13}), 3.85 (1H, ddd, J 13.9, 6.6, 4.2, H_{9a}), 3.54 (1H, ddd, J 13.9, 7.9, 4.2, H_{9b}), 2.52 (3H, s, H_7), 2.24–2.08 (2H, m, H_{12}), 1.84–1.70 (2H, m, H_{10}), 1.70–1.56 (2H, m, H_{11}), 1.55 (3H, d, J 7.0, H_6). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.6 (C_8), 141.2 (C_4), 134.5 (C_{14}), 128.5 (C_2), 127.4 (C_3), 127.2 (C_1), 113.3 (C_{13}), 54.9 (C_5), 48.1 (C_9), 31.2 (C_7), 30.0 (C_{10}), 27.3 (C_{12}), 25.3 (C_{11}), 16.1 (C_6). **IR** (film, $CDCl_3$) ν_{max} = 3031 (C–H), 2976 (C–H), 2926 (C–H), 2863 (C–H), 1631 (C=O), 1384, 1339, 1151, 699 cm^{-1}. **HRMS** (ESI^+) m/z calcd for $C_{16}H_{23}N_2O$ $[M+H]^+$ 259.1805, found 259.1805.

1-Allyl-3-benzyl-1,3-dimethylurea (3.208)

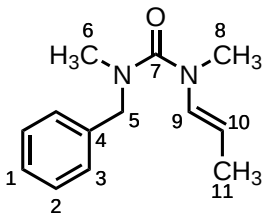


Triphosgene (2.07 g, 6.98 mmol, 0.6 eq.) was dissolved in anhydrous DCM (116 mL), and cooled to 0 °C. Pyridine (940 µL, 11.6 mmol, 1.0 eq.) was added dropwise, and the reaction mixture stirred at 0 °C for 5 min. A solution of *N*-benzylmethylamine (1.5 mL, 11.6 mmol, 1.0 eq.) was added dropwise, the reaction mixture stirred at room temperature for 1 h, and concentrated *in vacuo* to yield the crude carbamoyl chloride, which was used without further purification.

The crude carbamoyl chloride was dissolved in anhydrous MeCN (166 mL), and Et_3N (4.1 mL, 29.4 mmol, 2.5 eq.) and *N*-allylmethylamine (1.5 mL, 15.6 mmol, 1.3 eq.) added. The reaction mixture was stirred at room temperature for 17 h, diluted with saturated aqueous $NaHCO_3$ (100 mL), and extracted with DCM (3 × 100 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2; gradient elution: 7–30% EtOAc in pet. ether) to yield the title compound as a pale yellow oil (2.52 g, 99%).

$\boldsymbol{R_f}$ = 0.33 (30% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35–7.29 (2H, m, H_2), 7.27–7.21 (3H, m, H_1, H_3), 5.82 (1H, ddt, *J* 17.1, 10.2, 5.6, H_{10}), 5.19 (1H, dq, *J* 17.1, 1.6, $H_{10\,cis}$), 5.17 (1H, dq, *J* 10.2, 1.6, $H_{10\,trans}$), 4.37 (2H, s, H_5), 3.76 (2H, dt, *J* 5.6, 1.6, H_9), 2.78 (3H, s, H_8), 2.73 (3H, s, H_6). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.4 (C_7), 138.0 (C_4), 134.1 (C_{10}), 128.6 (C_2), 127.7 (C_3), 127.2 (C_1), 117.1 (C_{11}), 54.3 (C_5), 53.6 (C_9), 36.6 (C_6), 36.1 (C_8). **IR** (film, $CDCl_3$) ν_{max} = 2909 (C–H), 1637 (C=O), 1490, 1452, 1384, 1357, 1099, 923, 732, 699 cm^{-1}. **HRMS** (ESI^+) *m/z* calcd for $C_{13}H_{19}N_2O$ $[M+H]^+$ 219.1487, found 219.1492.

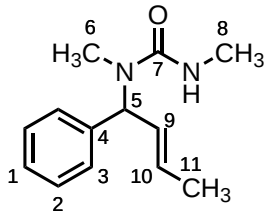
(*E*)-1-Benzyl-1,3-dimethyl-3-(prop-1-en-1-yl)urea (3.185a)



By **GP19**, 1-allyl-3-benzyl-1,3-dimethylurea (**3.208**) (1.38 g, 6.32 mmol) was used as the urea (with the modification of 0.05 eq. of carbonylchlorohydridotris(triphenylphosphine)ruthenium(II) instead of 0.1 eq.) that was stirred for 15 h, and purified by flash column chromatography (SiO_2; gradient elution: 0–15% EtOAc in pet. ether) to yield the title compound as a pale yellow oil (1.15 g, 83%).

$\boldsymbol{R_f}$ = 0.53 (30% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36–7.30 (2H, m, H_2), 7.29–7.22 (3H, m, H_1, H_3), 6.52 (1H, dq, *J* 14.0, 1.5, H_9), 4.77 (1H, dq, *J* 14.0, 6.6, H_{10}), 4.40 (2H, s, H_5), 3.00 (3H, s, H_8), 2.74 (3H, s, H_6), 1.65 (3H, dd, *J* 6.6, 1.5, H_{11}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.4 (C_7), 137.6 (C_4), 132.0 (C_9), 128.6 (C_2), 127.8 (C_3), 127.3 (C_1), 102.2 (C_{10}), 54.4 (C_5), 36.7 (C_6), 33.7 (C_8), 15.3 (C_{11}). **IR** (film, $CDCl_3$) ν_{max} = 2920 (C–H), 1641 (C=O), 1484, 1451, 1389, 1372, 1288, 1261, 1110, 1089, 948, 734, 698 cm^{-1}. **HRMS** (ESI^+) *m/z* calcd for $C_{13}H_{19}N_2O$ $[M+H]^+$ 219.1486, found 219.1492.

(*E*)-1,3-Dimethyl-1-(1-phenylbut-2-en-1-yl)urea (3.186a)

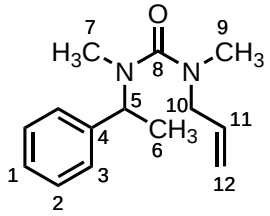


Diisopropylamine (140 µL, 1.00 mmol) was dissolved in anhydrous THF (3.0 mL), cooled to 0 °C, *n*-BuLi (400 µL, 2.5 M in hexanes, 1.00 mmol) added dropwise, and the reaction mixture stirred at 0 °C to yield a solution of LDA (0.28 M in THF).

(*E*)-1-Benzyl-1,3-dimethyl-3-(prop-1-en-1-yl)urea (**3.185a**) (103 mg, 0.47 mmol, 1.0 eq.) was dissolved in anhydrous THF (1.7 mL), and cooled to −78 °C. LDA (2.5 mL, 0.28 M in THF, 0.71 mmol, 1.5 eq.) was added dropwise, the reaction mixture stirred at −78 °C for 1.25 h, quenched by the dropwise addition of saturated aqueous NH_4Cl (2 mL), diluted with H_2O (2 mL), and extracted with DCM (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$), and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2; gradient elution: 0–100% EtOAc in pet. ether) to yield the title compound as a pale yellow oil (98 mg, 95%).

$\boldsymbol{R_f}$ = 0.15 (50% EtOAc in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32–7.26 (2H, m, H_2), 7.25–7.19 (3H, m, H_1, H_3), 5.97–5.92 (1H, m, H_5), 5.70–5.63 (2H, m, H_9, H_{10}), 4.61 (1H, br q, *J* 4.6, N*H*), 2.80 (3H, d, *J* 4.6, H_8), 2.62 (3H, s, H_6), 1.76 (3H, dd, *J* 4.7, 1.1, H_{11}). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.2 (C_7), 140.5 (C_4), 129.4 (C_9), 128.4 (C_2), 127.9 (C_{10}), 127.7 (C_3), 127.1 (C_1), 59.5 (C_5), 30.1 (C_6), 27.7 (C_8), 18.0 (C_{11}). **IR** (film, $CDCl_3$) ν_{max} = 3343 (N–H, br), 2939 (C–H), 2915 (C–H), 1622 (C=O), 1530, 1302, 970, 701 cm^{-1}. **HRMS** (ESI$^+$) *m*/*z* calcd for $C_{13}H_{19}N_2O$ $[M+H]^+$ 219.1489, found 219.1492.

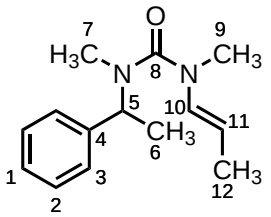
1-Allyl-1,3-dimethyl-3-(1-phenylethyl)urea (3.209)



By **GP9**, methyl(1-phenylethyl)carbamic chloride (**3.180**) (2.16 g, 10.9 mmol) was used as the carbamoyl chloride and *N*-allylmethylamine (1.3 mL, 18.3 mmol) was used as the amine that were stirred for 21 h, and purified by flash column chromatography (SiO_2; gradient elution: 7–40% Et_2O in pet. ether) to yield the title compound as a yellow oil (2.24 g, 88%).

$\boldsymbol{R_f}$ = 0.23 (30% Et_2O in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35–7.29 (4H, m, H_2, H_3), 7.28–7.20 (1H, m, H_1), 5.84 (1H, ddt, J 17.2, 10.2, 5.7, H_{11}), 5.23 (1H, q, J 6.8, H_5), 5.20 (2H, dq, J 17.2, 1.7, $H_{12\,cis}$), 5.17 (1H, dq, J 10.2, 1.5, $H_{12\,trans}$), 3.82–3.66 (2H, m, H_{10}), 2.76 (3H, s, H_9), 2.53 (3H, s, H_7), 1.53 (3H, d, J 7.0, H_6). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.5 (C_8), 141.5 (C_4), 134.3 (C_{11}), 128.4 (C_2), 127.3 (C_3), 127.0 (C_1), 117.0 (C_{12}), 54.6 (C_5), 53.7 (C_{10}), 36.3 (C_9), 31.1 (C_7), 16.2 (C_6). **IR** (film, $CDCl_3$) ν_{max} = 2974 (C–H), 1629 (C=O), 1487, 1449, 1383, 1358, 1284, 1090, 918, 774, 729, 699 cm^{-1}. **HRMS** (ESI$^+$) m/z calcd for $C_{14}H_{21}N_2O$ $[M+H]^+$ 233.1648, found 233.1646.

(*E*)-1,3-Dimethyl-1-(1-phenylethyl)-3-(prop-1-en-1-yl)urea (3.185b)



By **GP19**, 1-allyl-1,3-dimethyl-3-(1-phenylethyl)urea (**3.209**) (1.04 g, 4.48 mmol) was used as the urea (with the modification of 0.05 eq. of carbonylchlorohydridotris(triphenylphosphine)ruthenium(II) instead of 0.1 eq.) that was stirred for 17 h, and purified by flash column chromatography (SiO_2; gradient elution: 5–50% Et_2O in pet. ether) to yield the title compound as a pale yellow oil (931 mg, 90%).

$\boldsymbol{R_f}$ = 0.34 (30% Et_2O in pet. ether). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37–7.28 (4H, m, H_2, H_3), 7.28–7.21 (1H, m, H_1), 6.49 (1H, dq, J 14.0, 1.5, H_{10}), 5.23 (1H, q, J 7.0, H_5), 4.75 (1H, dq, J 14.0, 6.6, H_{11}), 2.99 (3H, s, H_9), 2.54 (3H, s, H_7), 1.66 (3H, dd, J 6.6, 1.5, H_{12}), 1.56 (3H, d, J 7.0, H_6). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.4 (C_8), 141.1 (C_4), 132.2 (C_{10}), 128.5 (C_2), 127.3 (C_3), 127.2 (C_1), 101.9 (C_{11}), 55.0 (C_5), 33.9 (C_9), 31.3 (C_7), 16.2 (C_6), 15.4 (C_{12}). **IR** (film, $CDCl_3$) ν_{max} = 3029 (C–H), 2935 (C–H), 1635 (C=O), 1532, 1484, 1448, 1389, 1377, 1354, 1318, 1281, 1109, 1088, 1023, 946, 781, 767, 736, 699 cm^{-1}. **HRMS** (ESI$^+$) m/z calcd for $C_{19}H_{21}N_2O$ $[M+H]^+$ 233.1648, found 233.1643.

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