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On DABAL-Me_3 promoted formation of amides

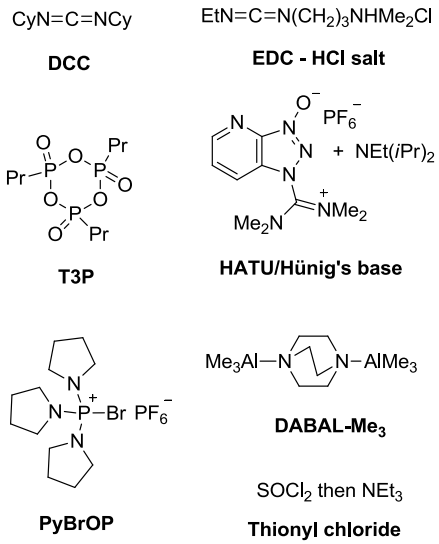
Nathalie Dubois,[a] Daniel Glynn,[a] Thomas Mcinally,[a] Barrie Rhodes,[b] Simon Woodward,[a] * Derek J. Irvine[c] and Chris Dodds[c]

[a] School of Chemistry, University of Nottingham, Nottingham NG7 2RD UK. FAX +44-(0)115-9513541; e-mail: simon.woodward@nottingham.ac.uk
[b] Aesica Pharmaceuticals Ltd, Quorum Business Park, Benton lane, Newcastle upon Tyne, NE12 8BS UK
[c] Department of Chemical and Environmental Engineering, University of Nottingham, Nottingham NG7 2RD UK.

Abstract. The range and utility of DABAL-Me_3 couplings of methyl esters and free carboxylic acids with primary and secondary amines under a variety of conditions (reflux, sealed tube, microwave) has been compared for a significant range of coupling partners of relevance to the preparation of amides of interest in pharmaceutical chemistry. Commercial microwave reactors promote the fastest couplings and allow the use of significantly sterically hindered amines (primary and secondary) and carboxylic acids derivatives. The influence of microwave energy on the reaction system was shown to be typically related to thermal effects (over-pressuring and superheating).

1. Introduction

The formation of amide linkages from carboxylic acid derivatives and amines constitutes a fundamental process in organic chemistry that is of high utility in the preparation of pharmaceutical and medicinal chemistry intermediates and is extensively used in ubiquitous poly-peptide preparations.[1] Typically, the combination of R^1CO_2H and HNR^2R^3 (1^o or 2^o amines) requires the presence of an activating 'coupling agent' to facilitate removal of the elements of water from the two components. Over 300 such 'coupling agents' are described in key reviews covering this area[2] and some of the more commonly used species are shown in Scheme 1. In 2006[3] and 2008[4] we provided preliminary details of the use of $DABCO\cdot(AlMe_3)_2$ (which we call DABAL-Me_3) in such roles - based on the seminal direct coupling of RCO_2Me and amines using $AlMe_3$ by Weinreb.[5] Recently, related $AlMe_3$ alone couplings of free carboxylic acids and amines have also appeared.[6] The study herein arose out of a number of underlying questions that were frequently put to us regarding our own chemistry: (i) How wide is the scope of the DABAL-Me_3 amide coupling? (ii) Are functional groups present in typical active pharmaceutical ingredients (APIs) tolerated? (iii) How adaptable and scalable are these reactions? (iv) Can free carboxylic acids be used? (v) Finally, how does DABAL-Me_3 compare against the literature standard 'coupling agents' in Scheme 1 – does it offer any competitive advantage for particular combinations? In this regard it is insightful to initially compare the reagents of Scheme 1 in a hypothetical $R^1CO_2H(Me)/HNR^1R^2$ coupling on a 5 mmol scale against several criteria (Table 1). It might be suggested, based on Table 1, that $AlMe_3$-based 'coupling agents'[3-4,6] are: mid-cost, rather too active for peptide coupling, uniquely able to use both free carboxylic acids and their esters (see later), but of significant utility for formation of *tert*-amides.



Scheme 1. Commonly used RCO_2H/amine 'coupling agents' and the structure of DABAL-Me_3.

Table 1. Comparison of 'coupling agents' in Scheme 1 for simple amide formation at a 5 mmol scale.

Coupling agent (minimum viable amount)	Rel. cost/£[a]	Can use RCO_2H directly ?	Can use RCO_2Me directly ?	Efficient for tertiary amides ?	Rac ?[b]	By products formed and any complications	Mass waste (in g) per 5 mmol acid[c]	Waste stream
Thionyl chloride/NEt_3 (1.0 eq. each)	0.1	✓	×	✓	✓	SO_2, 2 x $HNEt_3Cl$; $SOCl_2$ often used in large excess; racemization very common	0.34	Aq.
DCC (1.0 eq.)	0.2	✓	×	×	×/✓	CyNHC(O)NHCy (often poor separation); HOBt can be needed to avoid racemisation	1.12	Org.
EDC-HCl (1.0 eq.)	7	✓	×	×	×/✓	EtNHC(O)NH$(CH_2)_3$NHMe_2Cl; HOBt can be needed to avoid racemisation	1.05	Aq.
T3P (1.0 eq.)	8	✓	×	×/✓[d]	×/✓	HOP(O)PrOPPr(O)OP(O)PrOH; 2 eq. T3P needed for minimised recemisation.[e]	1.68	Aq.
HATU/Hünig's base	28	✓	×	✓[f]	×	Triazole, $Me_2NC(O)NMe_2$, [NHEt*i*Pr_2]PF_6; excess amine can be required to avoid formation of tetramethyl guanadinium derivatives	2.64	Aq.
PyBrOP (1.0 eq.)	29	✓	×	✓[g]	×	P(O)$(NC_4H_4)_3$, HBr, HPF_6; *N*-Boc a-aminoacids not viable partners.[h]	2.42	Aq.
DABAL-Me_3 (0.8 eq.), present paper	14	✓	✓	✓	×/✓	2 x Al^{3+}, 6 x MeH, DABCO (0.8 eq. of each)	2.09	Aq.

[a] Approximation based on costs (£) for 5-100 g quantities from Sigma-Aldrich (2013). Self-prepared DABAL-Me_3 (ref. 7) is ~£2.5 per 5 mmol coupling.

[b] Tendency of the reagent to racemise stereochemically labile centres; ×/✓ indicates mixed success in the primary literature.

[c] Only that generated explicitly by the 'coupling agent' (excludes solvent and any external aqueous quench acids and other quench agents).

[d] Only limited examples have been reported to date (ref. 8).

[e] See ref. 9.

[f] Higher quantities of HATU are often required and yields suffer as the steric profile of the amine increases. For instructive comparisons see ref. 10.

[g] For comparisons of PyBroP against HATU, EDC and T3P see ref. 11.

[h] See ref. 12.

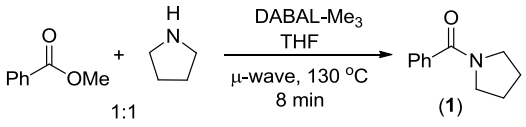
This present paper attempts to provide comprehensive answers to the questions (i)-(v) posed above and thus more fully define the scope and limitations of these DABAL-Me_3 promoted couplings.

2. Results and discussion

2.1. Comparison of heating methods, solvents and scales

DABAL-Me_3 amide formation has been reported to proceed slowly in refluxing THF under conventional heating (CH), such as isomantles or oil baths,[3] but much more rapidly when microwave heating (MWH) is used.[4] In previous reports, we had recommended the use of 0.8 equivalents of DABAL-Me_3 per equivalent of a 1:1 methyl ester:amine mixture at 0.25 M in THF.[4] However, when model couplings of methyl benzoate and pyrrolidine were compared applying the varying reaction conditions detailed in Table 2 (1 mmol scales in $PhCO_2Me$) it was observed that with DABAL-Me_3 loadings at or below 0.8 equivalents (with 0.25 M [substrate]) conversion efficiency could become poor or erratic. This was attributed the presence of minor variations in THF solvent quality (which result if it has not been rigorously dried). Increasing the ester/amine concentrations to ca. 1 M was found to produce a much more robust MWH process, i.e. complete conversion to the target compound was attained in >20 repeat reactions. However, it was noted that anhydrous THF is still a requirement to achieve success.

Table 2. Optimization of the microwave-based reaction.[a]



Run	DABAL-Me_3 (eq.)	[$PhCO_2Me$]/M	Yield (**1**)/%
1	0.8	0.25	78-92b
2	1.0	0.25	90
3	0.8	1.0	≥90
4	0.8	Neat	0c
5	1.0	1.0	84

[a] Reactions carried out on 1.00 mmol $PhCO_2Me$ and pyrrolidine in THF (1-4 mL) in a CEM Discover microwave reactor.

[b] A range of yields were found.

[c] Intractable tar formed.

A comparison between MWH and CH processing was conducted using the same model system (i.e. **1**) in various solvents. In this case sealed tubes were used for MWH (130 °C) and CH (85 or 120 °C) vs. overnight CH refluxes in standard glassware at atmospheric pressure. The results of these reactions

are contained in Table 3. Furthermore, to ensure a fair comparison between the MWH and CH sealed tube experiments the oil baths used were pre-equilibrated at 120 ^{o}C (for toluene) and 85 ^{o}C (for ethers) and run for 35 min (to simulate the advantageous heating in the 20 min 'cool down' period that follows 8 min of heating at 130 ^{o}C in our CEM reactor). Reflux reactions were conducted overnight as these were initially expected to be a lot slower. The solvents selected for comparison against THF were toluene, MTBE, 2-MeTHF as these provide a range of polarities and boiling points.

Table 3. Comparison of heating modes and solvents for reaction of $PhCO_2Me$ with pyrolidine to produce (**1**).[a]

Solvent (b.p./^{o}C)	Yield microwave (8 min at 130 ^{o}C)/%	Yield sealed tube[b] (35 min)/%	Yield reflux (15 h at solvent b.p.)/%
THF (66)	90%	86%	88% (5% ester)
Toluene (110)	80%	79%	84%
2-MeTHF (80)	83%	86%	69% (20% ester)
MTBE (55)	72%	56%	90% (9% ester)

[a] Conducted on a 1mmol scale (1:1 $PhCO_2Me$: pyrrolidine, 1 M in solvent) with 0.8 eq. DABAL-Me_3. Crude yields (^{1}H NMR spectra indicate clean reactions containing only *tert*-amide or unreacted $PhCO_2Me$ in all cases. Complete conversions were attained in all non-reflux reactions.

[b] THF, 2-MeTHF, MTBE heated at 85 ^{o}C, toluene at 120 ^{o}C.

These results showed, with the exception of MTBE, that the sealed tube reaction results (MWH vs. CH) are very similar; both in terms of yield attained and conversion. Again, with the exception of MTBE, they were close to the yield observed from the 16 hour reflux reaction, but in the latter full conversion was not always attained. Shorter reaction times and higher temperatures favoured the model transformation. The increased reaction rate in the sealed systems was attributed to over pressures resulting from heating the system above its solvent b.p. leading to superheating in the system. The reduced reaction time of the sealed tube experiments were ascribed to higher than target internal reaction temperatures. This may be exacerbated in the CEM reactor as its reaction temperature monitoring is achieved by indirect IR measurement of the vessel wall. This method has been extensively shown to underestimate the true bulk temperature of the bulk reaction medium contributing to further overheating. Typically, a direct measurement of the bulk temperature would be used to offset this issue. However, the use of sealed tubes prevented us from screening this. The anomalous high temperature behavior of MTBE may be due to solvent degradation at high temperatures.

The technical simplicity of the toluene reflux conditions (combine all components and heat under argon) was appealing, so these conditions were investigated further. It was found that on a 1 mmol scale such reactions such were typically complete within 1 h. Therefore a key conclusion was that all the effects observed here are either thermal (i.e. superheating) or concentration (DABAL and substrate) based.

In a related study, using methyl-4-iodobenzoate and pyrrolidine, at increased scales (5 mmol of ester and amine, 1 M) the rate of the reflux reaction was found to slow significantly and extended reflux was required to attain even moderate yields of amide **2** (Fig. 1). Further extension of the reflux time

did not significantly improve the yield. However, conducting the formation of **2** at a *1 mmol scale*, using a toluene reflux was found to result in an 80% yield of **2** within 60 min (approximately 6 x faster than the 5 mmol scale reaction of Fig. 1) even though the concentration of all the reagents was identical.

In comparison, comparative MWH reactions (130 °C, toluene, 1 M in substrates) for the preparation of *N*-benzylnicotinamide (**3** in Fig 1) at both 1 and 5 mmol scales intriguingly produced essentially identical high yields of **3** (80 and 78%) and achieved complete conversions within only 8 min. Comparative 5 mmol scale sealed-tube CH reaction, was also found to produce **3** in 85-64% yields in 60-120 min (toluene, 1 M, 130 °C on 1-5 mmol scales). This again stressed the importance of the higher reaction temperatures to the system and that microwave heating is likely to produce a greater level of superheating due to a combination of the IR temperature measure and potentially the dielectric properties of the differing precursors and products.

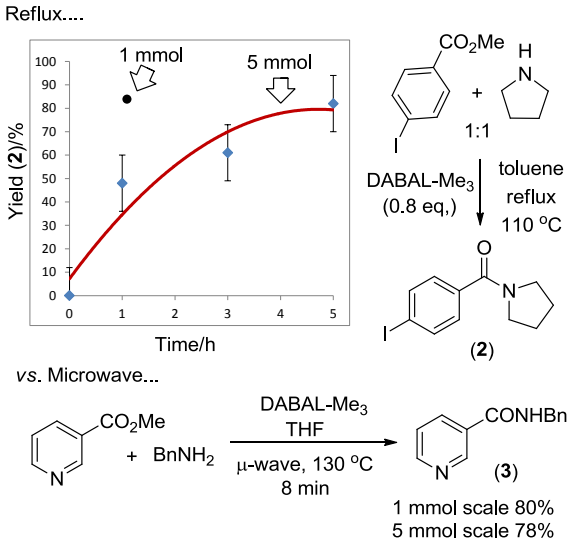


Fig 1. Course of 5 mmol coupling under reflux conditions[a] compared to microwave conditions.

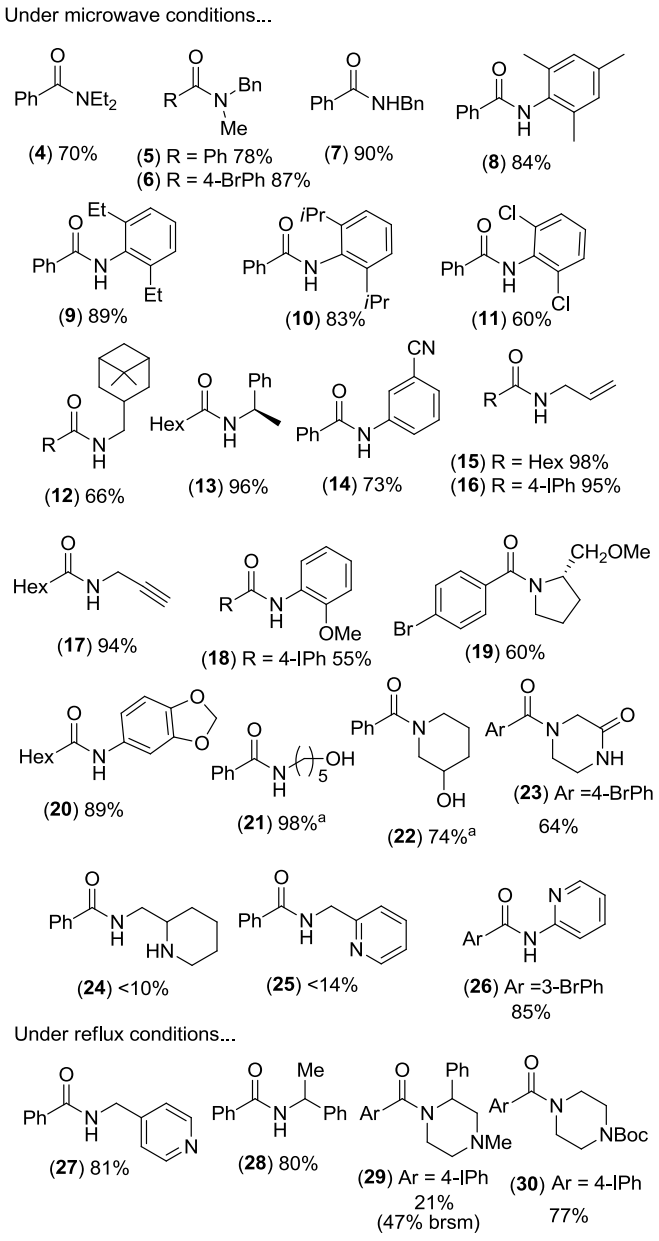
[a] In toluene 1 M ester and amine; yields of **2** determined by ^{1}H NMR spectroscopy. A first order fit to the 5 mmol data produces an approximate rate constant of ca. 0.3 h^{-1}. A 1 mmol preparation of **2** produced an 80% yield within 60 min under reflux conditions.

We believe two factors are important in explaining these findings. Firstly, it is known that DABAL-Me_3 binds $AlMe_3$ relatively loosely (Al-N *ca*. 30 kcal mol^{-1}) and the latter is quite volatile (b.p. 125 °C).[13] A simple Raoult's law analysis indicates that $AlMe_3$ will account of 36 mol% of the vapour above a reaction mixture in refluxing toluene at 110 °C. We believe that partial loss of $AlMe_3$ to the vapour head-space phase is facilitated in large apparatus and this can stave the reaction of 'coupling agent' slowing the coupling. The influence of this effect will be significantly reduced in the overpressure experiments (regardless of the heating method) which will retain a far more dissolved $AlMe_3$. Further credence is given to this idea by observation that larger scale couplings using methyl-*p*-iodobenzoate (1.31 g, 10 mmol) in an lower 'dead volume' steel bomb at 130 °C gave *ca*. 70% yields after 2 h. Finally, the DABAL-Me_3 coupling reaction also seems to be simply favoured by rapid heating/superheating in a manner akin to the positive affects observed in other rapid heating procedures, e.g. flash vacuum pyrolysis.[14] By comparison, the slower temperature increase/time

profiles associated with large reflux reactions result in less efficient heat transfer with time and thus impaired reaction efficiency.

2.2. Amine coupling partner scope

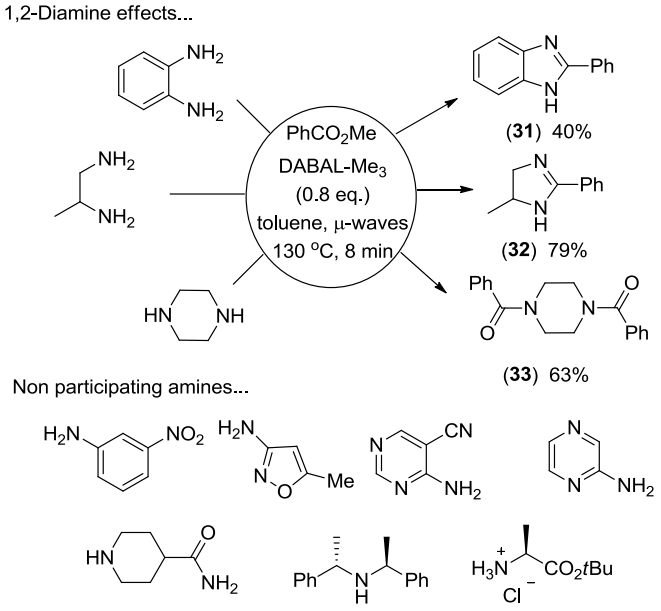
For convenience of analysis we initially focused on variation of the amine partner. The tolerance of the DABAL-Me_3 induced reactions to changes in the steric and electronic properties of the amine using the simple esters RCO_2Me (R = Ph, halophenyl and Hex = nC_6H_{13}). The two most useful conditions identified earlier: microwave promotion in THF at 130 ^oC and simple reflux in toluene were used at 1 mmol scales. The outcomes of these studies are reported in Scheme 2. Reactions containing products with protonatable functional groups were quenched with Rochelle salt, all others with aqueous 2M HCl.



Scheme 2. Amine structure effects in DABAL-Me_3 couplings. Duplicate yields in reflux reactions (1 h, 1 mmol) were typically within 5% of the microwave reactions (8 min) so only representative examples are shown (but see also scale effects of Section 2.1).

[a] Additional DABAL-Me_3 (1.6 equiv. *vs*. 0.8 normally used).

Comparison of compounds **4-6** (*tert*-amides) *vs*. **9-11** (*sec*-amides) shows that while the reaction is more tolerant of steric hindrance in primary amines, acceptable yields are attained in all but the most challenging cases **29** (21%) for both *sec* and *tert*-amide formation regardless of the heating methods used at a 1 mmol scale. In the formation of *sec*-amides even highly demanding 2,6-diisopropyl aniline was tolerated (**10**, 83%). Electronically and sterically deactivated 2,6-dichloroaniline gave **11** (60%, 8 min) which is comparable to Li's $AlMe_3/RCO_2H$ couplings to perfluoroaniline (80-85% yield after 18 h).[6a] The convenience of DABAL-Me_3 mediated couplings to provide sterically hindered amides should be compared to other recent organometallic approaches where the use of an isocyanate is required.[15] Phenylethylamine (*R* >98% *ee*) was coupled to ethylheptanoate in THF (giving **11**, 96%) without any detectable racemisation as measured by chiral HPLC. The following functional groups were also tolerated in the amine coupling partner: C(sp^2)-halides, OMe, alkenes, alkynes, C(sp)-H, tertiary amines, *sec*-amides, nitriles and in some cases Boc groups and *tert*-butyl esters. Free hydroxyl functions were additionally tolerated, but more DABAL-Me_3 was required to ensure higher yield (**21-22**), presumably through *in situ* OH deprotonation. Unfortunately, this could not be extended to allow use of hydroxylamine (H_2NOH). Strongly chelating functions dramatically downgrade the coupling efficiency and product purity (**24-25**). Low yields were also attained for some 1,2-diamines (**31** and **32**) and in this case the reactions resulted in the formation of benzimidazoles (Scheme 3) instead of the desired *bis*-amides. This is probably a proximity effect as 1,4-diamines were tolerated and gave the expected products. Other problematic and intractable amine coupling functional groups are also shown in Scheme 3.



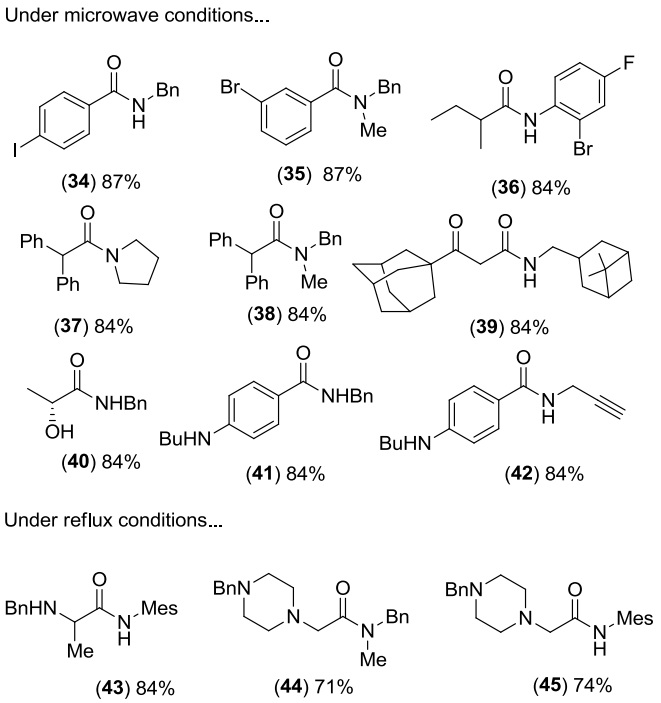
Scheme 3. Diamine effects and amines incompatible with DABAL-Me_3 couplings.

Use of substrates containing: nitro, isoxazole, and pyrazine functions resulted in extensive byproduct formation. Coupling partners containing highly hindered *sec*-amines, primary amide, pyrimidine and

aminoacid-HCl salts led also to recovery of starting materials. Free carboxylic acids were also not tolerated as these proved substrates for amide coupling themselves (see Section 2.4).

2.3. Ester coupling partner scope

Further coupling reactions on various methyl esters of differing steric profile and containing representative functional groups were carried out and these are summarized in Scheme 4.



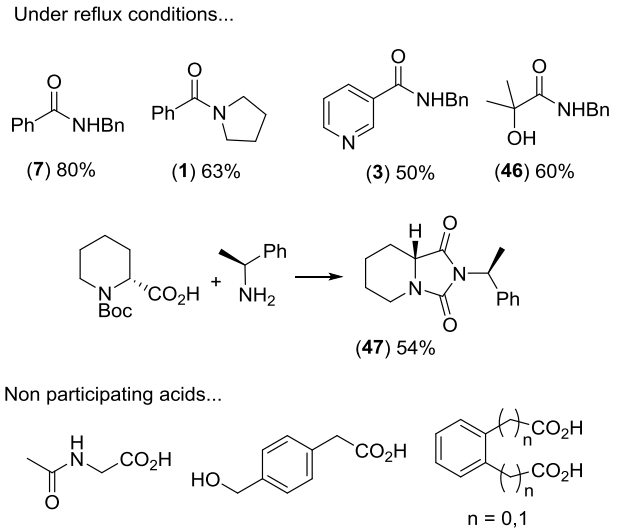
Scheme 4. Ester structure effects in DABAL-Me_3 couplings. Under either microwave conditions (8 min, 130 ^{o}C, THF) or toluene reflux (60 min); 1 mmol scale; Mes = mesityl.

Again the coupling was tolerant of a range of moderate steric factors in the ester and could accommodate functional groups of low reactivity, especially halogens, but was incompatible with functions more electrophilic that *tert*-butyl esters (especially aldehydes). (-)-(L)-Lactate coupled in THF (providing **40**, 94%) with retention of enantio purity (>95% *ee*). *sec*-Amines and alcohols could be used provided extra DABAL-Me_3 was employed; but for reasons that were not initially clear, primary alcohols and phenols caused issues leading to low yields, even in the presence of additional DABAL-Me_3. To estimate the pKa of DABAL-Me_3 in toluene at 110 ^{o}C a series of known enolate forming carbonyl species $R^1COCH_2R^2$ were briefly refluxed with equimolar DABAL-Me_3 in toluene, the reactions cooled and quenched with D_2O. These studies revealed that only species more acidic than deoxybenzoin R^1,R^2 = Ph; pKa 17.7) were deprotonated. This result might indicate that while *sec*-alcohols and amines survive deprotonation in the reaction primary alcohols and phenols do not leading to potentially less active aluminium alkoxides that fail to couple. Credence to this idea is given by the fact that although (±)-BnNHCHMeCO_2Me couples in toluene to provide **43** in good yield use of the (*R*) enantiomically pure starting material led to essentially racemic **43** based on its negligible $[a]_D$ value, presumably through deprotonation.

2.4. Carboxylic acid coupling partner scope

During our scoping reactions we discovered that direct coupling of free carboxylic acids under toluene reflux is possible using only the standard 0.8 equivalents of DABAL-Me_3 despite the presence of the additional acidic OH unit. Reactions under microwave promotion proved too vigorous to be

controlled. While the yields of these direct coupling reflux reactions were somewhat suppressed compared to the ester couplings of Sections 2.2-2.3 the technical simplicity of the reactions led us to briefly investigate short scope study, which is reported in Scheme 5.



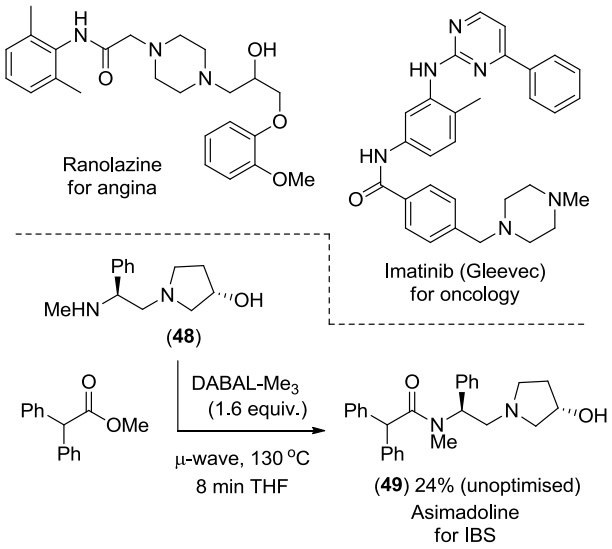
Scheme 5. Carboxylic acid structure effects in DABAL-Me_3 couplings; toluene reflux (60 min); 1 mmol scale.

The range of yields in Scheme 5 (50-80%) is of use in medicinal discovery chemistry but not as high as our processes based on methyl esters. We have typically found both *tert*-butyl ester and Boc groups reliable in our couplings and the formation of the unusual bicycle (**47**) is probably a proximity effect. As far as we can determine it is formed as a single diastereomer, but in moderate yield (no other stereoisomer was present in the crude mixture as far as determined by ^{1}H NMR spectroscopy). In view of the extensive racemization of **43** this behavior is notable. Presumably its cyclic structure accounts for its stereo-integrity. As in the amine component, potentially deprotonatable functional groups were not tolerated. Surprisingly, attempts to use 1,2 structurally related diacids led only to their recovery regardless of the reagent stoichiometry used.

2.5. Applications and other systems

A number of sub-structures accessible by DABAL-Me_3 chemistry are directly applicable to amide structures currently in commercial production. In particular for Ranolazine and Imatinib (Gleevec) (Scheme 6). However, we selected Asmadoline (**49**) as a target for the precursor amine (**48**) as it is commercially available (if rather expensive). Amine (**48**) is a stern test for any 'coupling agent' as the acyclic hindered NMeH unit combined with potentially epimerisable centres and unprotected hydroxyl group are all challenging motifs. In fact the commercial route couples **48** with the Ph_2COCl yielding **49** in just 70% yield only after vigorous heating.[16] In a single, unoptimised run microwave coupling of **48** and Ph_2CO_2Me provided analytically pure **10** in 25% yield (45% crude with ca. 60% conversion of **48**).

Finally, as direct coupling of R^1CO_2Me and H_2NR^2 represent only one of a potentially greater set of combinations we attempted some related DABAL-Me_3 promoted couplings of $TolSO_2OMe$, dimethylcarbonate and the urethane $PhCHMeNHCO_2Et$ under microwave conditions. The sulfonate and the carbonate reactions provided only highly polar mixtures. The urethane provided traces of product but this was not isolable in a pure form with the present reaction conditions.



Scheme 6. Relation of this work to commercial targets.

3. Conclusions

While DABAL-Me_3 is a rather too aggressive reagent for peptide synthesis it is quite useful in general amide preparation and is able to accommodate a significant range of functional groups and steric demands in both coupling partners. It seems of particular use for:

- Formation of *tert*-amides where routes via acid chlorides are non-viable or non-desirable.
- When either the amine or carboxylic acid coupling partner is 'precious' (no excess of either is required).
- Direct coupling of esters containing free *sec*-amines or alcohols without protection of the latter.

Reactions may be conducted quickly (8-60 min) at small scales (≤ 1mmol). Larger scale reactions are best conducted by microwave promotion or through use of sealed reactors but scales of at least 5 mmol could be realized easily. Stereogenic centres in the amine partner were coupled without racemisation while a-stereocentres in aminoacids are extensively racemised unless special factors operate (cyclic substrate or deprotonatable a-OH groups). A summary of the utility of DABAL-Me_3 based couplings is given in Table 1.

δH

4. Experimental

General. All reactions involving air sensitive materials were carried out under argon atmosphere using standard Schlenk techniques. Microwave reactions were conducted in a CEM Discover benchtop reactor (1 mmol) or a Biotage Initiator with an 8 position robot (5 mmol). Reagents and catalysts were purchased reagent grade and used without further purification. Tetrahydrofuran was distilled from sodium-benzophenone. Toluene and other solvents were anhydrous reagent grade. Flash column chromatography: silica gel 35-70 m, 60A. ^{1}H and ^{13}C NMR spectra were recorded on Bruker (DPX400 or AV400) or Jeol (EX270) spectrometers; *J* values are given in Hertz. Many of the amide products show restricted CO-NR^1R^2 rotation; in some cases improved spectra were attained at 90 ^{o}C. Infrared spectra were recorded using Bruker Tensor 27 spectrometer. Mass spectra were obtained on Bruker Daltonics micro TOF (ESI), Bruker Daltonics APEX 4 ECR FTMS (EI) and VG Autospec (EI). Optical rotations were determined on an ADP 440 polarimeter at ambient temperatures (20-22 ^{o}C). The general procedures and spectroscopic data for new chemical entities is

reported below. The equivalent information for literature compounds is restricted to the Supporting Data.

4.1. General Procedures

A. Microwave. Neat samples of amine (1.00 mmol) and carboxylic derivative (methyl ester or acid, 1.00 mmol) and DABAL-Me_3 (202 mg, 0.8 equiv.) were placed in a 5 mL microwave vial and dry THF added (1 mL) under a blanket of argon. For coupling partners containing acidic hydrogens additional DABAL-Me_3 (total of 410 mg, 1.6 equiv.) was used. The vial was promptly capped and placed in a CEM Discover microwave reactor. After irradiation (290 W, 130 ^oC, 8 min) and programmed cool-down (ca. 20 min). The reactions were quenched by cautious addition of HCl (2 M, 4 mL) or aqueous solutions of Rochelle salt (saturated potassium sodium tartrate, 4 mL) (*CARE*: methane liberated). Extraction with dichloromethane, drying ($MgSO_4$) and evaporation frequently provided the pure products directly. If purification was required column chromatography 3:2 to 2:3 hexane:EtOAc was used for amides lacking highly polar functional groups (CH_2Cl_2 with 2% v/v MeOH was used for amides bearing pendant amines, alcohols and other polar functional groups).

B. Sealed tube reactions. Thick walled (3 mm) Pyrex tubes (ca. 190 mm long, diameter 25 mm sealable with Young's taps) were charged as in A above and placed in pre-equilibrated heated baths (*CARE*: ensure blast screen protection). Reactions were worked up exactly as described in A above.

C. Reflux. Carried out under an inert atmosphere in the normal way.

*4.2. N-Myrtenylheptanamide (**12**)*

Colourless oil isolated by chromatography (140 mg, 66%). n_{max} ($CHCl_3$) /cm^{-1} 3449, 3000, 2928, 2870, 1660, 1518. ^1H NMR (400 MHz, $CDCl_3$) d_H = 5.50 (br, s, 1H, NH), 3.29-3.24 (m, 2H, CH_2), 2.38-2.35 (m, 1H, CH), 2.18-2.14 (m, 3H, CH, CH_2), 1.97-1.85 (m, 5H, CH, $2CH_2$), 1.65-1.61 (m, 2H, CH_2), 1.52-1.47 (m, 1H, CH), 1.34-1.27 (m, 6H, $3CH_2$), 1.20 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 0.91-0.87 (m, 4H, CH, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) d_C = 173.1, 45.1, 43.8, 41.4, 41.3, 38.7, 36.9, 33.2, 31.6, 29.0, 28.0, 26.0, 25.8, 23.2, 22.5, 19.8, 14.0. HRMS (EI^+) *m/z*: $[M+Na]^+$ Expected $C_{17}H_{31}NNaO^+$: 288.2298. Found: 288.2281.

*4.3. N-(3-Cyanophenyl)benzamide (**14**)*

Yellow powder isolated by chromatography (161 mg, 73%). M.p. 138 – 139 °C. n_{max} ($CHCl_3$) /cm^{-1} 3433, 3007, 2360, 2234, 1685, 1605, 1587, 1528. ^1H NMR (400 MHz, $CDCl_3$) d_H = 8.08 (1H, m), 7.90 – 7.85 (3H, m), 7.61 (1H, m), 7.55 – 7.44 (4H, m), 1.56 (1H, bs). ^{13}C NMR (101 MHz, $CDCl_3$) d_C = 165.8 (CO), 138.8 (C), 134.1 (C), 132.4 (CH), 129.9 (CH), 129.0 (CH), 127.9 (CH), 127.0 (CH), 124.2 (CH), 123.2 (CH), 118.4 (C), 113.2 (C). HRMS (ESI^+) *m/z*: $[M+Na]^+$ Expected $C_{14}H_{10}N_2NaO^+$: 245.0685. Found: 245.0685.

*4.4. N-2-Methoxyphenyl-4-iodobenzamide (**18**)*

Solid isolated by chromatography (144 mg, 51%). M.p. 129 – 131 °C. n_{max} ($CHCl_3$) /cm^{-1} 3426, 3011, 2941, 2840, 1675, 1603, 1587, 1525. ^1H NMR (400 MHz, $CDCl_3$) d_H = 8.54-8.51 (m, 2H,Aryl CH), 7.89-7.86 (m, 2H, Aryl CH), 7.66-7.39 (m, 2H, 2ArCH), 7.13 (m, 1H, Aryl CH), 7.05 (m, 1H, Aryl CH), 6.95 (dd, 1H, *J* = 8.0, 1.3 Hz, Aryl CH), 3.96 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) d_C = 164.5, 148.1, 138.0,

134.8, 128.7, 124.1, 121.3, 119.9, 110.0, 98.7, 55.9. HRMS (EI^+) *m/z*: $[M+Na]^+$ Expected $C_{14}H_{12}INNaO^+$: 375.9805. Found: 375.9803.

*4.5. (S)-(4-Bromophenyl)(2-(methoxymethyl)pyrrolidin-1-yl)methanone (**19**)*

Colourless oil isolated by chromatography (178 mg, 60%). $[a]_D$ –115 (*c* = 5.2, $CHCl_3$); n_{max} ($CHCl_3$) /cm^{-1} 2985, 2925, 2882, 2827, 1619, 1424, 1079, 1012. ^1H NMR (270 MHz, DMSO-d_6, 90 °C) d_H = 7.61 (2H, d, *J* = 8.4 Hz, CH_{Ar}), 7.41 (2H, d, *J* = 8.4 Hz, CH_{Ar}), 7.20 (1H, m, NCH), 3.42 – 3.35 (7H, m, NCH_2, CH_2OCH_3), 2.01 – 1.80 (4H, m, $(CH_2)_2$). ^{13}C NMR (68 MHz, DMSO-d_6, 90 °C) d_C = 167.3 (CO), 136.2 (C), 130.7 (CH), 128.5 (CH), 122.3 (C), 72.1 (CH), 57.9 (CH_2), 56.2 (CH_2), 48.0 (CH_3), 27.2 (CH_2), 23.1 (CH_2). HRMS (ESI^+) *m/z*: $[M+Na]^+$ Expected $^{79}BrC_{13}H_{16}NNaO_2^+$: 320.0262. Found: 320.0264. Expected $^{81}BrC_{13}H_{16}NNaO_2^+$: 322.0242. Found: 322.0246.

*4.6. N-(3,4-Methelenedioxyphenyl)heptanamide (**20**)*

Solid isolated by chromatography (177mg, 89 %). M.p. 76 – 78 °C. n_{max} ($CHCl_3$) /cm^{-1} 3437, 3008, 2958, 2930, 2860, 1682, 1504, 1489. ^1H NMR (400 MHz, $CDCl_3$) d_H = 7.25 (d, 1H, J = 2.0 Hz, Aryl CH), 7.20 (br, s, 1H, NH), 6.79 (dd, 1H, *J* = 8.3, 2.0 Hz, Aryl CH), 6.74 (d, 1H, *J* = 8.3 Hz, Aryl CH), 5.95 (s, 2H, CH_2), 2.33 (t, 2H, *J* = 7.5 Hz, CH_2), 1.76-1.68 (m, 2H, CH_2), 1.42-1.28 (m, 6H, $3CH_2$), 0.90 (t, 3H, *J* = 6.7 Hz, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) d_C = 171.3, 147.8, 144.2, 132.2, 113.0, 108.0, 102.9, 101.2, 37.7, 31.6, 29.0, 25.6, 22.5, 14.0. HRMS (EI^+) *m/z*: $[M+Na]^+$ Expected $C_{14}H_{19}NNaO_3^+$: 272.1257. Found: 272.1256.

*4.7. 4-(4-Bromobenzoyl)piperazin-2-one (**23**)*

Pale yellow powder isolated by chromatography (180 mg, 64%). M.p. 155 – 157 °C. n_{max} ($CHCl_3$) /cm^{-1} 3409, 3009, 1680, 1642, 1428, 1333. ^1H NMR (400 MHz, $CDCl_3$) d_H = 7.59 (2H, d, *J* = 8.4 Hz, CH_{Ar}), 7.33 (2H, d, *J* = 8.4 Hz, CH_{Ar}), 6.55 (1H, s, NH), 4.22 (2H, bs), 3.86 (2H, bs), 3.46 (2H, bs). ^{13}C NMR (101 MHz, $CDCl_3$) d_C = 169.4 (CO), 133.3 (C), 132.0 (CH), 128.9 (CH), 125.0 (C). Peaks from the piperazonone could not be distinguished due to exchange leading to broad envelopes at 41.0 and 166.8 ppm. HRMS (ESI^+) *m/z*: $[M+Na]^+$ Expected $^{79}BrC_{11}H_{11}N_2NaO_2^+$: 304.9902. Found: 304.9896. Expected $^{81}BrC_{11}H_{11}N_2NaO_2^+$: 306.9881. Found: 306.9871.

*4.8. N-(Pyridin-4-ylmethyl)benzamide (**27**)*

Yellow powder isolated by chromatography (172 mg, ca. 81%) traces of the starting amine (<5%) co-elute with (**27**). M.p. 102 – 104 °C. n_{max} ($CHCl_3$) /cm^{-1} 3455, 3008, 1664, 1603, 1517, 1486, 1417, 1284. ^1H NMR (400 MHz, $CDCl_3$) d_H = 8.52 (2H, d, *J* = 5.6 Hz, CH_{Pyr}), 7.83 (2H, d, *J* = 7.1 Hz, CH_{Pyr}), 7.52 (1H, d, *J* = 7.6 Hz, CH_{Ar}), 7.44 (2H, dd, *J* = 7.6, 7.1 Hz, CH_{Ar}), 7.23 (2H, d, *J* = 5.6 Hz, CH_{Ar}), 6.98 (1H, bs, NH), 4.63 (2H, d, *J* = 6.1 Hz, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$) d_C = 167.7 (CO), 149.9 (CH), 147.5 (C), 133.8 (C), 131.8 (CH), 128.7 (CH), 127.0 (CH), 122.3 (CH), 42.7 (CH_2). HRMS (ESI^+) *m/z*: $[M+H]^+$ Expected $C_{13}H_{13}N_2O^+$: 213.1022. Found: 213.1024.

*4.9. (4-Iodophenyl)(4-methyl-2-phenylpiperazin-1-yl)methanone (**29**)*

Yellow oil isolated by chromatography (89 mg, 21%), 45% of the starting amine also recovered. ^1H NMR (400 MHz, $CDCl_3$) d_H = 7.77 (2H, d, *J* = 8.1 Hz), 7.50 (2H, br), 7.42 – 7.37 (2H, m), 7.33 – 7.27 (1H, m), 7.22 – 7.15 (2H, m), 5.91 (1H, vbr), 3.42 (1H, d), 5.33 (1H, s), 3.45 (1H, br d, *J* = 12.2 Hz), 3.45

(1H, br t, *J* = 12.2 Hz), 2.79 (1H, br d, *J* = 7.9 Hz), 2.47 (1H, dd, *J* = 12.2, 4.1 Hz), 2.34 (3H, s), 2.12 3.45 (1H, br d, *J* = 12.2 Hz), 1.64 (1H, br). Partial ^{13}C NMR (101 MHz, $CDCl_3$) d_C = 137.7 (CH), 135.4 (CH), 128.7 (CH), 127.3 (CH), 95.8 (CH), 55.4 (CH_2), 46.3 (CH_3). Due to fluxional exchange quaternary and a-NCH/NCH_2 signals were not observed. HRMS (ESI^+) *m/z*: $[M+H]^+$ Expected $C_{18}H_{20}IN_2O^+$: 407.0615. Found: 407.0617.

*4.10. tert-Butyl 4-(4-iodobenzoyl)piperazine-1-carboxylate (**30**)*

Colourless powder isolated by chromatography (319 mg, 77%). M.p. 125 – 127 °C. n_{max} ($CHCl_3$) /cm^{-1} 3008, 1690, 1629, 1458, 1422, 1367, 1249, 1157, 1004. ^{1}H NMR (270 MHz, DMSO-d_6, 90 °C) d_H = 7.81 (2H, d, *J* = 8.4 Hz), 7.21 (2H, d, *J* = 8.4 Hz), 3.46 – 3.36 (8H, m), 1.43 (9H, s). ^{13}C NMR (101 MHz, $CDCl_3$) d_C = 169.7 (CO), 154.5 (CO), 137.8 (CH), 134.8 (C), 128.8 (CH), 96.1 (C), 80.4 (C), 47.4 (CH_2), 43.6 (CH_2), 28.3 (CH_3). HRMS (ESI^+) *m/z*: $[M+Na]^+$ Expected $C_{16}H_{21}IN_2NaO_3^+$: 439.0489. Found: 439.0491.

*4.11. N-Benzyl-3-bromo-N-methylbenzamide (**35**)*

Colourless oil isolated by chromatography (228 mg, 75%). n_{max} ($CHCl_3$) /cm^{-1} 3008, 1628, 1402, 1255, 1077. ^{1}H NMR (270 MHz, DMSO-d_6, 90 °C) d_H = 7.65 – 7.59 (2H, m, CH_{Ar}), 7.54 – 7.35 (4H, m, CH_{Ar}), 7.32 – 7.26 (3H, m, CH_{Ar}), 4.59 (2H, s, CH_2), 2.88 (3H, s, CH_3). ^{13}C NMR (68 MHz, DMSO-d_6, 90 °C) d_C = 168.5 (CO), 138.4 (C), 136.6 (C), 131.7 (CH), 130.0 (CH), 128.9 (CH), 128.0 (CH), 126.8 (CH), 126.7 (CH), 125.1 (CH), 121.1 (C), 51.4 (CH_2), 34.7 (CH_3). HRMS (ESI^+) *m/z*: $[M+Na]^+$ Expected $^{79}BrC_{15}H_{14}NNaO^+$: 326.0156. Found: 326.0143. Expected $^{81}BrC_{15}H_{14}NNaO^+$: 328.0136. Found: 328.0125.

*4.12. N-2-Bromo-4-fluorophenyl -2-methylbutanamide (**36**)*

Solid isolated by chromatography (205 mg, 94%,). M.p. 96 – 98 °C. n_{max} ($CHCl_3$) /cm^{-1} 3414, 3011, 2970, 2935, 1694, 1596, 1518. ^{1}H NMR (400 MHz, DMSO-d_6) d_H = 9.46 (br s, 1H, NH), 7.63 (dd, 1H, *J* = 8.5, 2.9 Hz, Aryl CH), 7.50 (dd, 1H, *J* = 8.9, 5.7 Hz, Aryl CH), 7,26 (td, 1H, *J* = 8.5, 2.9 Hz, Aryl CH), 2.49-2.46 (m, 1H, CH), 1.67-1.58 (m, 1H, CH), 1.46-1.37 (m, 1H, CH), 1.11 (d, 3H, *J* = 6.9 Hz, CH_3), 0.92 (t, 3H, *J* = 7.4 Hz, CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) d_C = 175.3, 159.7 (d, *J*(C-F) = 246 Hz, C-F), 133.6 (d, *J*(C-F) = 3.0 Hz, C), 129.8 (d, *J*(C-F) = 8.3 Hz, CH), 120.1(d, *J*(C-F) = 9.2 Hz, C-Br), 119.8 (d, *J*(C-F) = 25.2 Hz, CH), 115.4 (d, *J*(C-F) = 22.1 Hz, CH), 41.8, 27.2, 17.9, 12.3. HRMS (EI^+) *m/z*: $[M+Na]^+$ Expected $C_{11}H_{13}BrFNNaO^+$: 296.0057. Found: 296.0052.

*4.13. N-Benzyl-N-methyl-2,2-diphenylacetamide (**38**)*

Yellow oil isolated by chromatography (282 mg, 89%). n_{max} ($CHCl_3$) /cm^{-1} 3008, 1645, 1495, 1453, 1401. ^{1}H NMR (270 MHz, DMSO-d_6, 90 °C) d_H = 7.30 – 7.17 (15H, m), 5.47 (1H, s), 4.60 (2H, s), 2.93 (3H, s). ^{13}C NMR (68 MHz, DMSO-d_6, 90 °C) d_C = 170.9 (CO), 139.6 (C), 137.0 (C), 128.4 (CH), 127.9 (CH), 127.6 (CH), 127.0 (CH), 126.5 (CH), 126.0 (CH), 52.8 (CH_2), 50.2 (CH_3), 34.6 (CH). HRMS (ESI^+) *m/z*: $[M+Na]^+$ Expected $C_{22}H_{21}NNaO^+$: 338.1515. Found: 338.1519.

*4.14. N-Myrtenyl-(1-adamantyl)-3-oxoproprionamide (**39**)*

Oil isolated by chromatography (240 mg, 84 %). n_{max} ($CHCl_3$) /cm^{-1} 3690, 3300, 3005,2910, 2854, 1731, 1692. ^{1}H NMR (400 MHz, $CDCl_3$) d_H = 7.17 (br, s, 1H, NH), 3.46 (s, 2H, CH_2), 3.30-3.26 (m, 2H, CH_2), 2.39-2.35 (m, 1H, CH), 2.25-2.19 (m, 1H, CH), 2.09 (s, 3H, CH_3), 1.94-1.68 (m, 17H), 1.52-1.47 (m, 1H, CH), 1.21 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 0.92-0.90 (m, 2H, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$) d_C

= 212.5, 165.8, 47.4, 45.2, 43.8, 42.8, 41.3, 41.1, 38.7, 37.6, 36.3, 33.2, 28.0, 27.8, 26.0, 23.2, 19.8. HRMS (EI^+) *m/z*: $[M+Na]^+$ Expected $C_{12}H_{17}NNaO_2^+$: 364.1519. Found: 364.1527.

*4.15. N-Benzyl-N-butylbenzamide (**41**)*

Solid isolated by chromatography (171 mg, 91 %). M.p. 117 – 119 °C. n_{max} ($CHCl_3$) /cm^{-1} 3453, 3010, 2962, 2932, 1645, 1609, 1502. ^1H NMR (400 MHz, $CDCl_3$) d_H = 7.68-7.65 (m, 2H, Aryl CH), 7.37-7.35 (m, 3H, Aryl CH), 7.31-7.28 (m, 2H, Aryl CH), 6.58-6.54 (m, 2H, Aryl CH). 6.36 (br, s, 1H, NH), 4.63 (d, 2H, *J* = 5.7 Hz, CH_2), 4.05 (br, s, 1H, NH), 3.16 (t, 2H, *J* = 7.0 Hz, CH_2), 1.66-1.59 (m, 2H, CH_2), 1.48-1.42 (m, 2H, CH_2), 0.98 (t, 3H, *J* = 7.3 Hz, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) d_C = 167.3, 151.2, 138.8, 128.7, 127.9, 127.4, 122.1, 111.6, 43.9, 43.2, 31.4, 20.2, 13.9. HRMS (ESI^+) *m/z*: $[M+Na]^+$ Expected $C_{18}H_{22}N_2NaO^+$: 305.1624. Found: 305.1621.

*4.16. N-Propargyl-N-butylbenzamide (**42**)*

Solid isolated by chromatography (164 mg, 89%). M.p. 93 – 95 °C. n_{max} ($CHCl_3$) /cm^{-1} 3462, 3308, 3010, 2962, 2932, 2874, 1651, 1609, 1574, 1531, 1498. ^1H NMR (400 MHz, $CDCl_3$) d_H = 7.67-7.63 (m, 2H, Aryl CH), 6.59-6.55 (m, 2H, Aryl CH), 6.17 (br, s, 1H, NH), 4.25 (q, 2H, *J* = 2.6 Hz, CH_2), 4.05 (br, s, 1H, NH), 3.16 (t, 2H, *J* = 7.0 Hz, CH_2), 2.27 (t, 1H, *J* = 5.1 Hz, ≡CH), 1.66-1.59 (m, 2H, CH_2), 1.49-1.41 (m, 2H, CH_2), 0.98 (t, 3H, *J* = 7.3 Hz, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) d_C = 167.0, 151.3, 128.8, 121.4, 111.6, 80.1, 71.5, 43.2, 31.4, 29.6, 20.2, 13.9. HRMS (ESI^+) *m/z*: $[M+Na]^+$ Expected $C_{14}H_{18}N_2NaO^+$: 253.1311. Found: 253.1313.

*4.17. 2-(Benzylamino)-N-mesitylpropanamide (**43**)*

Pale yellow paste isolated by chromatography (135 mg, 46%). n_{max} ($CHCl_3$) /cm^{-1} 3320, 2973, 2923, 2861, 1667, 1495, 1445. ^1H NMR (400 MHz, $CDCl_3$) d_H = 8.70 (1H, s, NH), 7.37 -7.30 (5H, m, CH_{Ar}), 6.91 (2H, s, CH_{Ar}), 3.98 (1H, d, *J* = 13.1 Hz, C*H*$_a$H$_b$), 3.87 (1H, d, *J* = 13.1 Hz, CH$_a$*H*$_b$), 3.46 (1H, q, *J* = 6.9 Hz, C*H*CH_3), 2.28 (3H, s, CH_3), 2.21 (6H, s, CH_3), 1.67 (1H, bs, NH), 1.48 (3H, d, *J* = 6.9 Hz, CHC*H*$_3$). ^{13}C NMR (101 MHz, $CDCl_3$) d_C = 173.3 (CO), 139.4 (C), 136.7 (C), 134.9 (C), 131.0 (C), 128.9 (CH), 128.7 (CH), 127.9 (CH), 127.5 (CH), 58.5 (CH), 53.1 (CH_2), 20.9 (CH_3), 20.3 (CH_3), 18.4 (CH_3). HRMS (ESI^+) *m/z*: $[M+H]^+$ Expected $C_{19}H_{25}N_2O^+$: 297.1961. Found: 297.1965.

*4.18. N-Benzyl-2-(4-benzylpiperazin-1-yl)-N-methylacetamide (**44**)*

Yellow-orange oil isolated by chromatography (241 mg, 71%). n_{max} ($CHCl_3$) /cm^{-1} 3009, 2940, 2817, 1637, 1454, 1011. ^1H NMR (270 MHz, DMSO-d_6, 90 °C) d_H = 7.34 – 7.21 (10H, m), 4.56 (2H, s), 3.47 (2H, s), 3.20 (2H, s), 2.92 (3H, s), 2.41 – 2.39 (8H, m). ^{13}C NMR (68 MHz, DMSO-d_6, 90 °C) d_C = 168.7 (CO), 137.8 (C), 137.3 (C), 128.2 (CH), 127.8 (CH), 127.5 (CH), 126.7 (CH), 126.4 (CH), 126.2 (CH), 61.6 (CH_2), 59.9 (CH_2), 52.2 (CH_2), 52.0 (CH_2), 50.3 (CH_2), 33.6 (CH_3). HRMS (ESI^+) *m/z*: $[M+H]^+$ Expected $C_{21}H_{28}N_3O^+$: 338.2227. Found: 338.2231.

*4.19. 2-(4-Benzylpiperazin-1-yl)-N-mesitylacetamide (**45**)*

Colourless powder isolated by chromatography (258 mg, 74%). M.p. 139 – 140 °C. n_{max} ($CHCl_3$) /cm^{-1} 3008, 2943, 2821, 1676, 1503. ^{1}H NMR (400 MHz, $CDCl_3$) d_H = 8.59 (1H, bs), 7.34 – 7.32 (4H, m), 7.28 (1H, m), 6.91 (2H, s), 3.55 (2H, s), 3.20 (2H, s), 2.73 (4H, bs), 2.55 (4H, bs), 2.28 (3H, s), 2.19 (6H, s). ^{13}C NMR (101 MHz, $CDCl_3$) d_C = 168.7 (CO), 137.9 (C), 136.8 (C), 134.7 (C), 130.9 (C), 129.1 (CH), 128.9 (CH), 128.3 (CH), 127.1 (CH), 62.9 (CH_2), 61.7 (CH_2), 53.8 (CH_2), 53.2 (CH_2), 20.8 (CH_3), 18.5 (CH_3). HRMS (ESI^+) *m/z*: $[M+H]^+$ Expected $C_{22}H_{30}N_3O^+$: 352.2383. Found: 352.2386.

*4.20. (R)-2-((S)-1-Phenylethyl)tetrahydroimidazo[1,5-a]pyridine-1,3(2H,5H)-dione (**47**)*

Colourless oil isolated by chromatography (140 mg, 54%). $[a]_D$ –36.0 (*c* = 2.8, $CHCl_3$). n_{max} ($CHCl_3$) /cm^{-1} 3069, 2983, 2945, 2861, 1763, 1702, 1445, 1431.. ^{1}H NMR (400 MHz, $CDCl_3$) d_H = 7.48 – 7.46 (2H, m, CHAr), 7.36 – 7.31 (2H, m, CHAr), 7.28 (1H, m, CHAr), 5.34 (1H, q, *J* = 7.3 Hz, C*H*CH_3), 4.14 (1H, dt, *J* = 13.4, 4.1 Hz, NCH_aH_b), 3.68 (1H, td, *J* = 11.9, 4.1 Hz, NC*H*CO), 2.79 (1H, m, NCH_aH_b), 2.18 (1H, m, $NCHCH_aH_b$), 1.97 (1H, m, $N(CH_2)_2CH_aH_b$), 1.85 (3H, d, *J* = 7.3 Hz, $CHCH_3$), 1.71 (1H, m, $NCH_2CH_aH_b$), 1.49 – 1.20 (3H, m, $NCH_2CH_aH_bCH_aH_bCH_aH_b$). ^{13}C NMR (101 MHz, $CDCl_3$) d_C = 172.9 (CO), 154.3 (C), 140.4 (C), 128.9 (C), 128.4 (CH), 127.6 (CH), 127.5 (CH), 127.4 (CH), 127.3 (CH), 57.0 (CH), 50.2 (CH), 39.2 (CH_2), 27.7 (CH_2), 24.9 (CH_2), 22.7 (CH_2), 17.2 (CH_3). HRMS (ESI^+) *m/z*: $[M+Na]^+$ Expected $C_{15}H_{18}N_2NaO_2^+$: 281.1260. Found: 281.1261.

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Supplementary data

Experimental data for literature compounds and copies of ^{1}H and ^{13}C NMR spectra (all compounds). Supplementary data related to this article can be found at XXXXXX.

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