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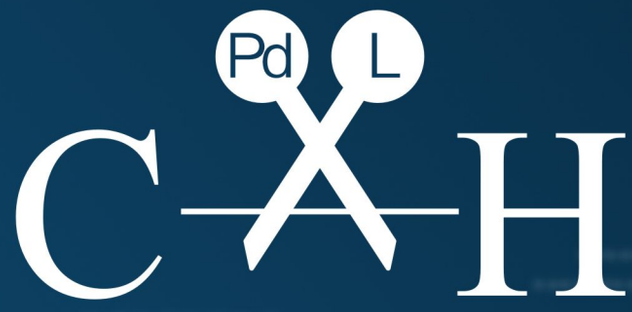

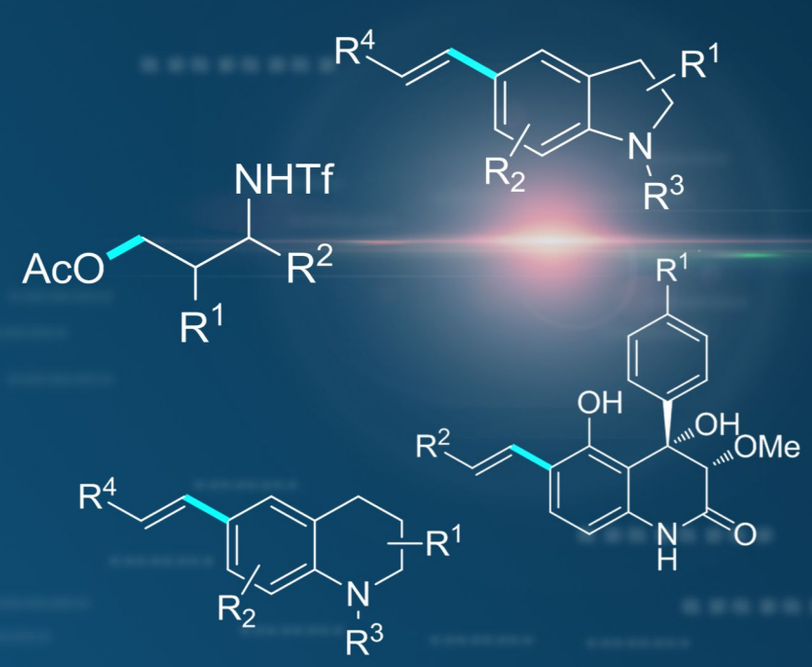

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PALLADIUM CATALYZED C–H FUNCTIONALIZATION OF AMINE DERIVATIVES AND ITS APPLICATION IN TOTAL SYNTHESIS

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Wen-Liang Jia

Geboren Hebei

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TABLE OF CONTENTS

List of abbreviations

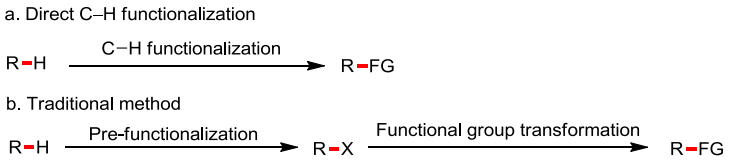
Ac	acetyl
Ad	adamantyl
AIBN	azobisisobutyronitrile
AMLA	ambiphilic metal-ligand activation
APAO	acetyl-protected aminomethyl oxazoline ligands
Ar	aryl
BIES	base-assisted internal electrophilic substitution
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Bu	butyl
BQ	benzoquinone
Bz	benzoyl
CMD	concerted metallation-deprotonation
Cy	cyclohexyl
DCE	1,2-dichloroethane
DCM	dichloromethane
DG	directing group
DIBALH	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DMBQ	dimethylbenzoquinone
DMF	dimethylformamide
DMSO	dimethylsulfoxide
EDC	ethylcarbodiimide
EDDA	ethylenediaminediacetic acid
EI	electron ionization
equiv	equivalent
Et	ethyl
FD	field desorption
FG	functional group
h	hour
het	hetero
HFB	hexafluorobenzene
HFIP	hexafluoroisopropanol
HMDS	hexamethyldisilazane
HOBt	hydroxybenzotriazole
HPMoV	molybdovanadophosphoric acid
HRMS	high resolution mass spectrometry
LAH	lithium aluminium hydride
LiHMDS	lithium bis(trimethylsilyl)amide
LDA	lithium diisopropylamide
m	min
Me	methyl
MOM	methoxymethyl
MPAA	mono-protected amino acid
MS	molecular sieves
MW	microwave
NCL	native chemical ligation
NHPI	*N*-hydroxyphthalimide
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
Ns	*para*-nitrobenzenesulfonyl
on	overnight
PA	picolinamide
PCC	pyridinium chlorochromate
PE	petroleum ether
Ph	phenyl
PIDA	(diacetoxyiodo)benzene
Pin	pinacolato
Piv	pivaloyl
Pr	propyl
Py	pyridine
rt	room temperature
SEM	2-(trimethylsilyl)ethoxymethyl
TBAF	tetrabutylammonium fluoride
TBME	*tert*-butylmethyl ether
TBS	*tert*-butyldimethylsilyl
TDG	traceless directing group
Tf	trifluoromethylsulfonyl
TFA	trifluoroacetic acid
TFE	trifluoroethanol
THF	tetrahydrofuran
THQ	1,2,3,4-tetrahydroquinoline
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	*para*-toluenesulfonyl

CHAPTER 1

PALLADIUM-CATALYZED C–H FUNCTIONALIZATION: A FOCUS ON AMINE DERIVATIVES

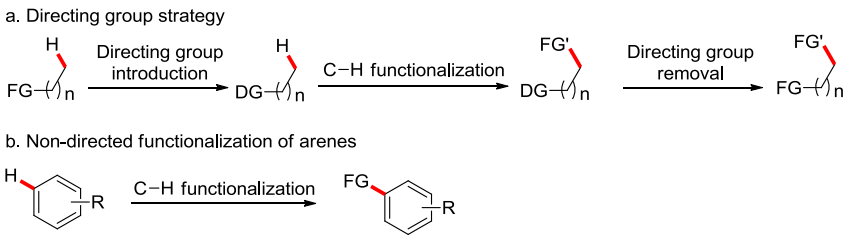
1.1 Introduction

Despite the enormous advancement of organic synthetic methods based on functional group transformations, direct C–H functionalization is still highly desirable since it not only reduces the number of synthetic steps to build a target molecule without the need to pre-functionalize the substrate, but also offers new disconnections and thus potentially alters the way we think about constructing complex molecules (Scheme 1.1).[1] However, the development of direct C–H functionalization has been challenging for mainly two reasons: 1) the general inertness of C–H bonds makes them unreactive towards most of the reagents and, 2) even though a sufficiently reactive reagent can be developed to perform C–H functionalization, it is often difficult to guarantee that the C–H functionalization only occurs at the desired position when many other C–H bonds of similar bond strength are present in the molecule.



Scheme 1.1 Traditional methods *vs* C–H functionalization methods

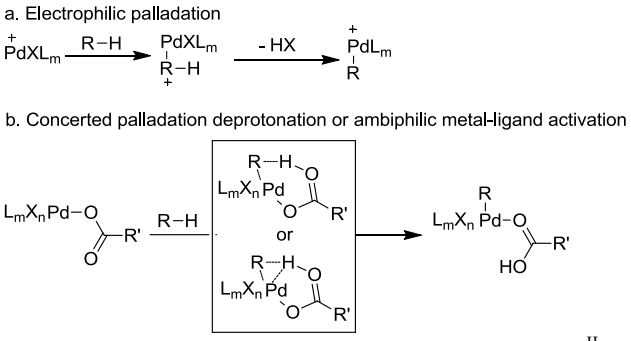
Transition-metals have been demonstrated to react directly with C–H bonds to form C–M bonds in a process known as C–H metallation or C–H activation. Further reaction of the formed C–M complex with other reagents results in functionalization of the substrate. Although some works have shown that certain catalysts can differentiate C–H bonds with different electronic, steric and stereoelectronic properties thus enabling site-selective C–H bond functionalization,[2,3] the most commonly-encountered method to control the site-selectivity while increasing the reactivity is using directing groups (Scheme 1.2a).[4] Directing groups are typically Lewis basic functionalities that are covalently attached to substrates, can bind to transition metal catalyst and deliver the catalyst to a proximal C–H bond. Site-selective C–H metallation then occurs by favorably forming a 5- or 6-membered metallacycle (a process termed as cyclometallation) even when otherwise more reactive C–H bonds are present. The main disadvantage of the directing group strategy is that in most cases, the directing group is not part of the target molecule. Therefore, additional synthetic steps to install the directing group, before performing the C–H functionalization, and to remove it afterwards are necessary, reducing the overall efficiency of this process. In this regard, non-directed C–H activation shows greater advantages since no extra synthetic steps are needed (Scheme 1.2b).[1k,1r] Indeed, in the past years more efforts have been devoted to the development of non-directed C–H functionalization reactions. In general, it has been observed that key to the success of these transformations is the development of novel ligands.[5] These ligands make the catalyst more active and selective, although, in general, the selectivity is mainly controlled by the electronic and steric properties of the substrates.



Scheme 1.2 Strategies for performing C–H bond functionalization

Although, so far, many transition metals have been used to catalyze C–H activation reactions, including Ru[6], Rh[7], Pt[8], Pd[1], Ir[9], Ni[10], Cu[10], Fe[10] and recently arising Co[10] and Mn[10], Pd is the most extensively studied. It is not only because palladium catalysts are easy to handle owing to their general stability towards air and moisture, but also for their tolerance towards many reagents, allowing a wide range of functionalities to be introduced into the substrates. In this introduction, we will focus on palladium-catalyzed C–H activation reactions since this is the transition metal we used for the work presented in this thesis.

Regarding the mechanism of Pd-catalyzed C–H activation, two different reaction modes have often been proposed: a) electrophilic palladation (Scheme 1.3a)[11] and b) concerted metallation-deprotonation (CMD) or ambiphilic metal-ligand activation (AMLA) (Scheme 1.3b)[12].



Scheme 1.3 Reaction mechanisms of C–H activation at Pd^{II} center

Three main C–H activation strategies can be applied depending on the substrate that needs to be functionalized: *i*) a directing group can be introduced *via* the modification of a pre-existing functional group, *ii*) a (native) functional group present in the molecule can act as the directing group and *iii*) a non-directed C–H activation can selectively take place. For the first two strategies, depending on the nature of the existing functional group, the substrates can be classified into different categories: nitrogen containing heteroarenes,[13] (thio)alcohols and their derivatives,[14] ketones, aldehydes and their derivatives,[15] carboxylic acids and their derivatives,[16] and amines and their derivatives[17]. Among them, amines are one of the most intensively studied families of substrates for C–H activation due to their ubiquity in natural products, pharmaceuticals and organic functional materials.[18] In this introduction we will cover the key examples of direct C–H functionalization of amine-containing compounds catalyzed by palladium.

1.2 Palladium-catalyzed C–H functionalization of amine-containing compounds

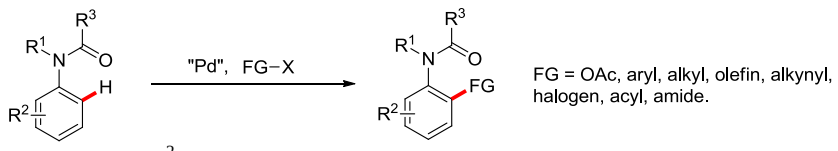
For the direct C–H functionalization of amine-containing compounds, different strategies have been developed including the use of monodentate directing groups, bidentate directing groups, the use of the amino group as native directing group as well as non-directed C–H functionalization reactions.

1.2.1 Monodentate directing groups

When amines, especially primary amines, are treated with palladium(II) salts, they quickly form square-planar, coordinately saturated bisamine palladium(II) complexes, which are difficult to dissociate and normally unreactive towards C–H activation. Therefore, to perform successful catalytic C–H activation reactions on primary and secondary amines in a general fashion, the modification of the amino group to make it suitable for C–H functionalization reactions has been widely used. Two main approaches to modulate the reactivity of the amino moiety as monodentate directing group have been reported: *i*) introducing an exogenous electron-withdrawing directing auxiliary and *ii*) using an electron-withdrawing protecting group to tune the electronic property of the nitrogen, thus enabling the use of nitrogen as the directing moiety.

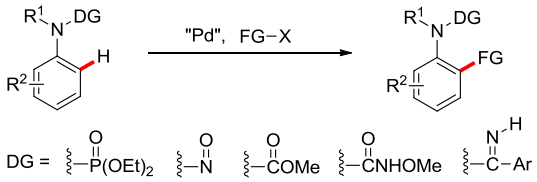
1.2.1.1 Exogenous monodentate directing group attached to the nitrogen atom

The common approach is to convert the amino group into an amide and the oxygen of the newly formed amide works as the anchoring heteroatom to palladium. A seminal work by the group of Van Leeuwen achieved the *ortho*-C(sp^2)–H olefination of acylated anilines at room temperature (Scheme 1.4).[19] The carbonyl group serves as the directing moiety and induces the formation of six-membered palladacycle *via* C–H activation. Since this seminal work, many other functionalities have been introduced in acylated anilines at the *ortho*-C(sp^2)–H position. For example, the group of Sanford used similar method to install aryl and acetoxyl groups by using hypervalent iodine(III) reagents $[Ph_2I]BF_4$ and $PhI(OAc)_2$, respectively.[20,21] More practical arylating reagents such as arylboronic acids were then demonstrated to be effective to perform *ortho*-C(sp^2)–H arylation reactions of fully substituted Ac-protected anilines via Pd^{II}/Pd^0 catalysis.[22,23]



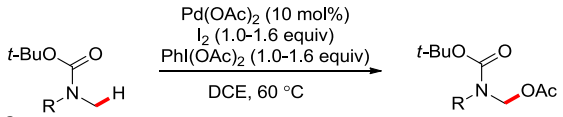
Scheme 1.4 *Ortho*-C(sp^2)–H functionalization of acylated anilines directed by a carbonyl group

Halogenation was also achieved by using CuX_2 (X = Cl, Br) as the halogen source[24] and acyl groups can be introduced using benzaldehydes as acylating reagents.[25] The challenging intermolecular amination reaction was also developed for acyl-protected anilines with *N*-nosyloxycarbamate as the nitrogen source. The authors proposed that the reaction probably proceeded *via* nitrene (generated from *N*-nosyloxycarbamate) insertion to the cyclopalladated Pd(II) intermediate followed by reductive elimination.[26] Further developments involve methylation and alkynylation of acetanilides,[27,28] arylation of substituted enamides with aryl iodides and design of new exogenous directing groups, for example, phosphoramidate[29], *N*-nitroso[30], aniline carbamates[31], ureas[32] and *N*-phenylbenzimidamides[33] (Scheme 1.5).



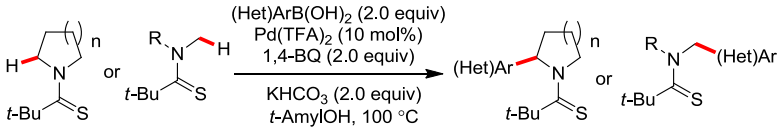
Scheme 1.5 *Ortho*-C(sp^2)–H functionalization of anilines with other directing groups

As the amide carbonyl group is a relatively weak directing group, this strategy has been rarely effective for the functionalization of C(sp^3)–H bonds. A rare example reported by the group of Yu used Boc as the directing group for the acetoxylation of secondary amines (Scheme 1.6).[34] The combination of $PhI(OAc)_2$ and I_2 as acetoxylating reagents was key to the success of this transformation. The reaction occurred via a carbonyl directed C(sp^3)–H activation at the α-methyl group to the nitrogen atom, forming a five-membered palladacycle. Interestingly, when Boc-protected anilines were used as substrates, the reaction was still selective towards α-C(sp^3)–H functionalization over *ortho*-C(sp^2)–H functionalization.[19a]



Scheme 1.6 α-C(sp^3)–H acetoxylation with $PhI(OAc)_2$ and I_2 directed by a carbonyl group

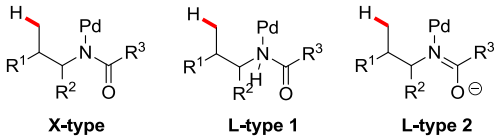
Later, the α-C(sp^3)–H arylation of saturated azacycles and *N*-methylamines with a wide range of (hetero)aromatic boronic acids directed by a thioamide, which possesses a stronger directing ability, was reported (Scheme 1.7).[35] In the case of azacycles, the asymmetric version of this reaction by using a chiral phosphoric acid ligand has also been developed.[36]



Scheme 1.7 α-C(sp^3)–H arylation directed by thioamide

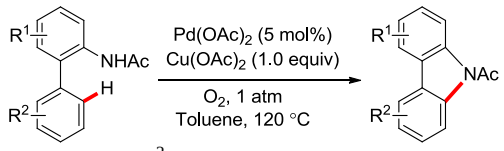
1.2.1.2 Protected amino group as monodentate directing group

The strategy to transform an amino group into an amide or sulfonamide to weaken the affinity of the nitrogen atom to palladium and thus enable the use of the amino group as directing moiety in C–H functionalization reactions has been successfully developed. Different from the first tactic, where the carbonyl group serves as the coordination motif and normally reaction sites are no more than two bonds away from the amino group *via* the formation of six- or five-membered palladacycle, this strategy often leads to the activation of C–H bonds at the γ-position of the nitrogen *via* the formation of a five-membered palladacycle. In this case, the amide is generally considered as an X-type directing group, meaning deprotonation of the amide either directly by palladium catalyst or aided by an external base forms an anionic nitrogen-centered ligand, subsequently binding to the palladium catalyst (Scheme 1.8, X-type). However, some other coordination modes have also been proposed, for example, with the amine serving as a neutral ligand (L-type 1 and L-type 2).[37]



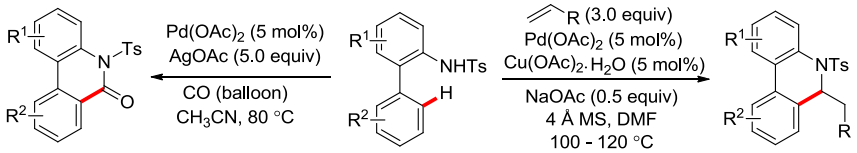
Scheme 1.8 Proposed coordination modes of the amide group through the nitrogen atom

An early example by Buchwald and co-workers utilized Ac-protected 2-phenylanilines as substrates to construct carbazoles, a class of compounds with important photophysical and biological properties (Scheme 1.9).[38,39] Similar substrates have also been used to perform palladium(II)-catalyzed C(sp^2)–H olefination[40] and phosphination[41] as described in later reports from other groups.



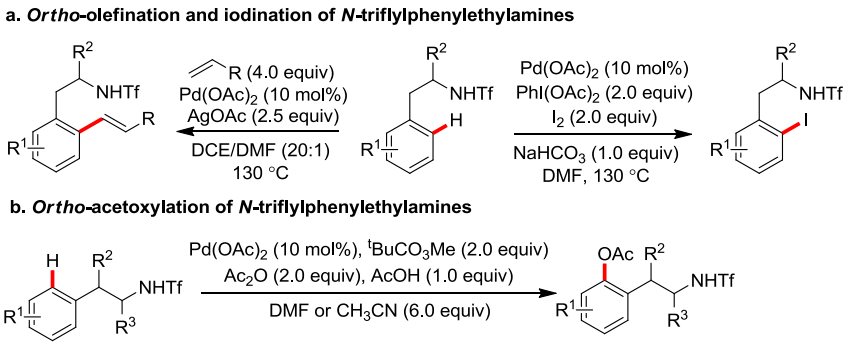
Scheme 1.9 Intramolecular *ortho*-C(sp^2)–H amination directed by an Ac-protected amino group

Additionally, tosyl has also been used as the protecting group in place of acetyl and various C(sp^2)–H functionalization reactions have been achieved.[42-44] For example, carbonylation and acylation using CO and aldehydes, respectively, have been reported (Scheme 1.10).[42,43] For the olefination reaction, unlike Ac-protected substrates, the olefinated product always underwent cyclization *via* intramolecular aza-Michael addition of the tosyl-protected amine to the alkene to give phenanthridine derivatives (Scheme 1.10).[44]



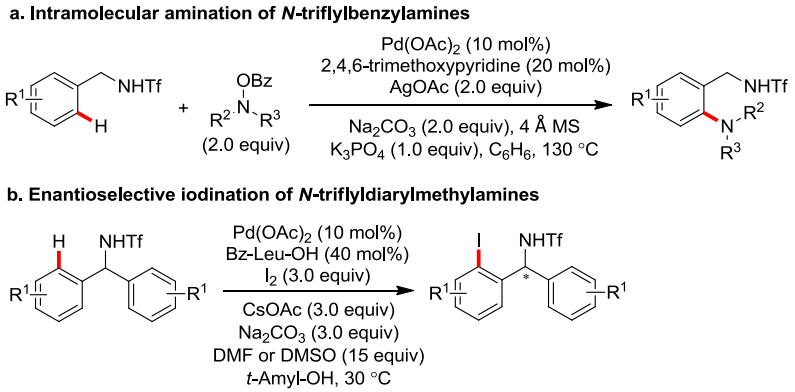
Scheme 1.10 *Ortho*-C(sp^2)–H carbonylation directed by a Ts-protected amino group

In an effort to further expand the scope of protected-amino-directed C–H activation reactions, the group of Yu found out that triflyl-protected amine is a very versatile directing group for this purpose, probably because the stronger acidity of the NH group makes it easier to deprotonate and coordinate to palladium while at the same time, Pd–N complex retains its electrophilicity. The first report involves the iodination and olefination of *N*-triflyl-arylethylamines *via* the formation of a six-membered palladacycle (Scheme 1.11a).[45] Using other strong oxidants [$Ce(SO_4)_2$ or *N*-fluoro-2,4,6-trimethylpyridinium triflate], they could construct indolines from same substrates.[46] Later, the acetoxylation reaction was achieved by using *tert*-butyl peroxyacetate as stoichiometric oxidant (Scheme 1.11b).[47]



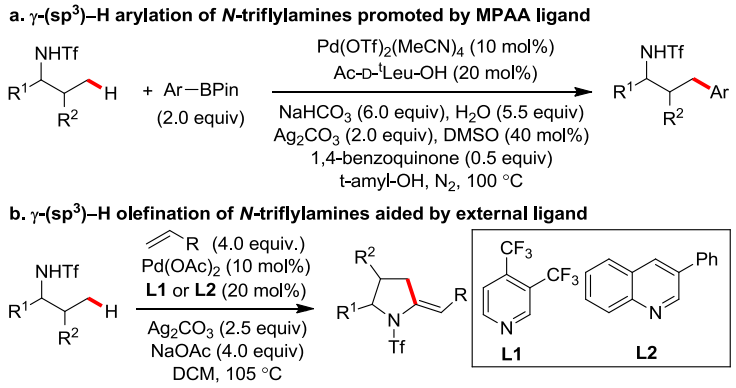
Scheme 1.11 *Ortho*-C(sp^2)–H functionalization of *N*-triflylphenylethylamines

This strategy has also been applied to functionalize benzyl amine substrates. For example, with *N*-fluoro-2,4,6-trimethylpyridinium triflate as the oxidant and fluoride source, the *ortho*-fluorination of *N*-triflylbenzylamines was successfully performed by the group of Yu.[48] Using the same substrates, they also achieved an intermolecular amination reaction by using *O*-benzoyl hydroxylamines as the nitrogen source (Scheme 1.12a) in the presence of an external ligand, 2,4,6-trimethoxypyridine, which was crucial to get high yields of desired products.[49] The enantioselective iodination of *N*-triflyldiarylmethylamines using I_2 as the sole oxidant at room temperature was achieved using a chiral *N*-mono-protected amino acid (MPAA) ligand Bz-L-Leu-OH (Scheme 1.12b).[50,51] Later, substrates containing different aryl groups were iodinated *via* kinetic resolution under near-identical reaction conditions.[52]



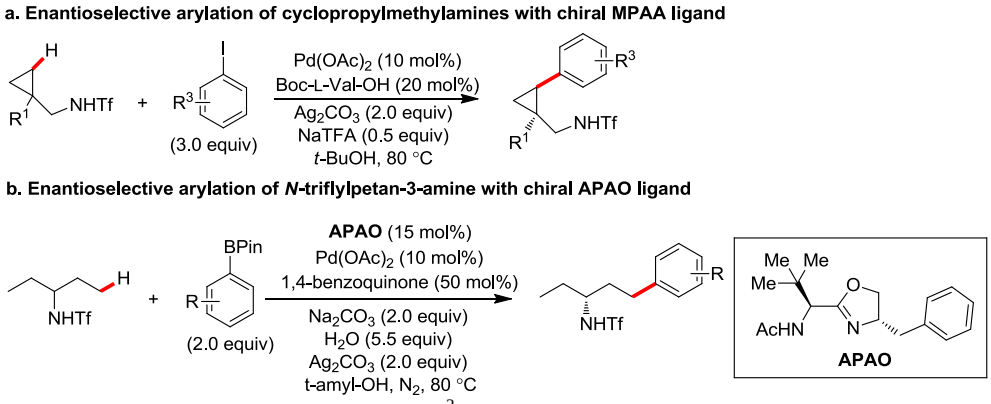
Scheme 1.12 *Ortho*-C(sp^2)–H functionalization of *N*-triflylbenzylamines

The robustness of triflyl-protected amine as directing group was further demonstrated by C(sp^3)–H activation of aliphatic amines in the presence of external ligands. In combination with a MPAA ligand, the γ-C(sp^3)–H arylation reaction of triflyl-protected amines with aryl boronate esters as coupling partners was achieved (Scheme 1.13a).[53] The important role of MPAA ligand was highlighted by the fact that in the absence of this ligand, no background reaction was observed. Using a pyridine or quinoline based ligand, the same substrates could be successfully olefinated and the olefinated product experienced subsequent Aza-Wacker oxidative cyclization reaction forming C-2 alkylated pyrrolidines (Scheme 1.13b).[54] This reaction features great substrate scope regarding both amines and olefins.



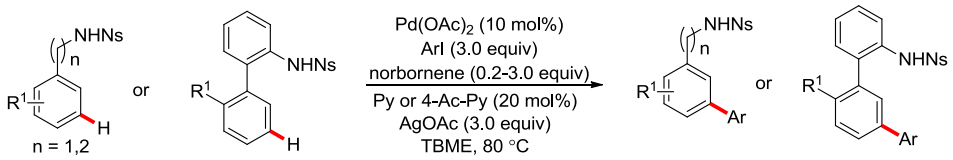
Scheme 1.13 γ-C(sp^3)–H functionalization of *N*-triflyl aliphatic amines

Additionally, the asymmetric γ-C(sp^3)–H arylation reaction of prochiral cyclopropylmethyl-Tf-amines with aryl iodides was realized in high efficiency (up to 99% yield) and enantioselectivity (up to 99.5% ee) in the presence of a chiral MPAA ligand Boc-L-Val-OH (Scheme 1.14a).[55] Chiral *cis*-aryl-cyclopropylmethylamines are exclusively formed. For more challenging simple aliphatic amines, the enantioselective γ-C(sp^3)–H arylation was accomplished by designing a new type of chiral ligands: acetyl-protected aminomethyl oxazoline ligands (APAO).[56] *N*-Triflylpentan-3-amine was desymmetrized with a rich variety of aryl and vinyl boronate esters as coupling partners (Scheme 1.14b). For racemic amines, kinetic resolution was performed using a slightly different chiral APAO ligand.[56]



Scheme 1.14 Asymmetric γ-C(sp^3)–H arylation of *N*-triflyl aliphatic amines

The power of triflyl-protected amino as directing group has been well demonstrated. However, the deprotection of the triflyl could be quite tedious.[54-56] To overcome this problem, the group of Yu adopted another sulfonyl protecting group, 4-nitrobenzenesulfonyl (Ns), which can be easily deprotected using thiophenol and a relatively weak base while, at the same time, the nitro group retains the strong electron-withdrawing properties. The use of Ns-protected amine as directing group has been successfully applied for the functionalization of both, C(sp^2)–H and C(sp^3)–H bonds. The very first example was the asymmetric arylation of *N*-nosyldiarylmethyl amines with aryl boronate esters in the presence of a chiral amino acid derivative, Fmoc-L-Leu-NHOMe.[57] Later, the *meta*-selective arylation of phenylethylamines, benzylamines and 2-phenylanilines was reported using a Ns-protected amine as directing group in combination with Pd/norbornene catalysis (Scheme 1.15).[58-60] The versatility of this type of directing group was further elucidated by introducing other functionalities into aliphatic amines, such as olefins[54], (hetero)aryl groups[61] and alkyl groups[61].



Scheme 1.15 *Meta*-selective C(sp^2)–H aylation of *N*-nosylamines

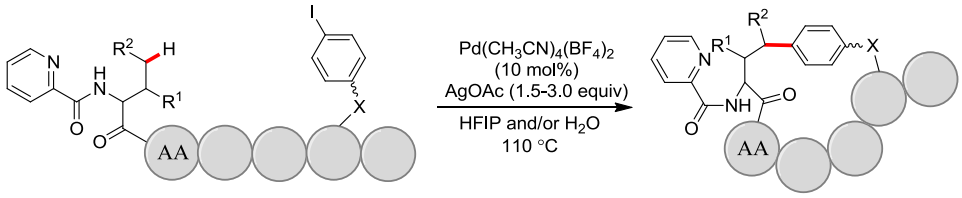
1.2.2 Amine-based bidentate directing groups

Despite the success that has been seen using monodentate directing groups to selectively functionalize aromatic C(sp^2)–H and methyl C(sp^3)–H bonds of amines, more challenging transformations, for example, methylene C(sp^3)–H activation, intramolecular C–N bond formation to construct azetidines, highly effective oxygenation reactions and so on have been relying on the use of bidentate directing groups.

1.2.2.1 Picolinamide and related bidentate directing groups

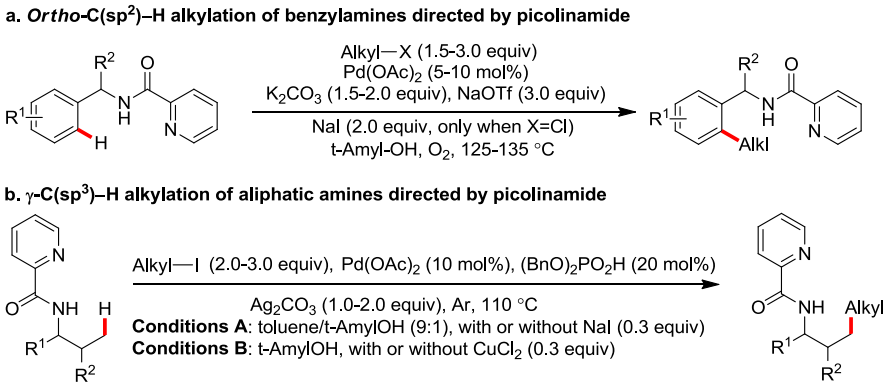
The first example of using bidentate directing group to C–H functionalize amines was reported by Daugulis and co-workers.[16a] The amine group was transformed to picolinamide, where the pyridine moiety serves as a neutral directing moiety (L-type) while the nitrogen atom from the amide binds to palladium after deprotonation (X-type). This X-L combination has since been a model for the design of new bidentate directing groups. Using the picolinamide directing group, the arylation of aromatic C(sp^2)–H bonds, methyl C(sp^3)–H bonds and methylene C(sp^3)–H bonds with aryl iodides was achieved (Scheme 1.15a). After the seminal work by Daugulis and co-workers, the scope of this transformation regarding both the substrates and arylating reagents have been extended including the asymmetric version.[62-66]

Remarkably, this picolinamide strategy was also applied for the highly efficient preparation of cyclophane-braced peptide macrocycles *via* intramolecular γ-selective C(sp^3)–H arylation of different amino acids at *N*-terminus of the peptides (Scheme 1.16).[67] The reaction could be performed in both organic solvents and aqueous media and the reaction tolerated polar amino acids such as Asp (CO_2H), Gln (CO_2NH_2), Lys (NH_2), Thr and Ser (OH), and Arg (guanidine). The reaction concentration for cyclization could be up to 100 mM with only negligible amount of oligomerized side products.



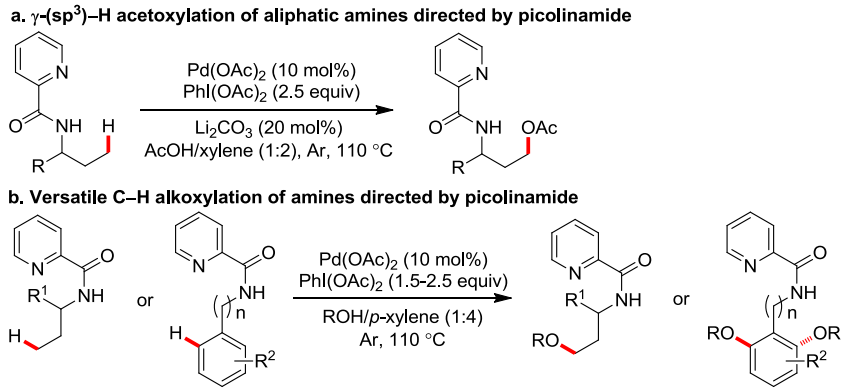
Scheme 1.16 Preparation of cyclic peptides by using picolinamide-directed arylation

Other C–C bond forming reactions involving alkenylation, alkynylation, olefination, alkylation, carbonylation and acylation were also reported. Alkenyl iodides have been used to perform alkenylation of both C(sp^2)–H and C(sp^3)–H bonds.[62a,68] TIPS alkyne bromide was used to introduce alkynyl groups to benzylamines.[68] The olefination of phenylethylamines was effective not only with activated olefins but also unactivated ones, such as styrene, 1-pentene, 1-hexene and 1-octene.[69] Chen and co-workers also reported the *ortho*-C(sp^2)–H alkylation of benzylamines and γ-C(sp^3)–H alkylation of aliphatic amines (Scheme 1.17).[70,71] Acylation of benzylamines and phenylethylamines was conducted with acyl chlorides and benzaldehydes as acyl sources, respectively.[72,73]



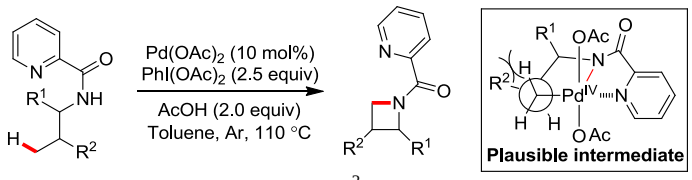
Scheme 1.17 γ-C–H alkylation of amines directed by picolinamide

Both C(sp^2)–H and C(sp^3)–H bond acetoxylation of picolinamides have been reported using $PhI(OAc)_2$ as the oxidant (Scheme 1.18a), such as *ortho*-C(sp^2)–H acetoxylation of benzyl amines,[74,75] C(sp^3)–H acetoxylation of *ortho*-methylanilines at benzylic positions[76] and γ-C(sp^3)–H acetoxylation of aliphatic amines.[75] By simply introducing an alcohol as co-solvent under otherwise identical reaction conditions for acetoxylation reactions, C–H etherification was achieved (Scheme 1.18b).[77]



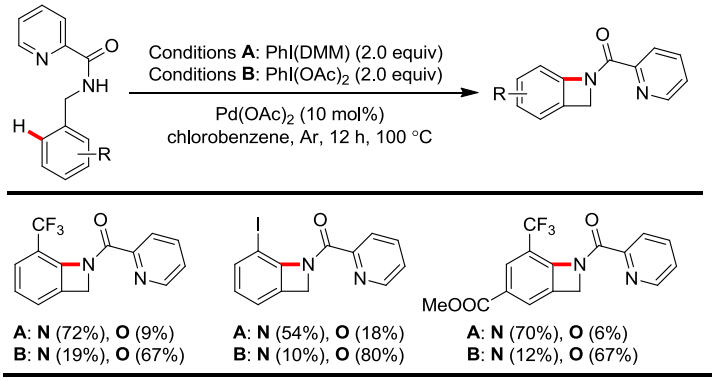
Scheme 1.18 C–H oxygenation of amines directed by picolinamide

Intramolecular C–H amination has been described by using a picolinamide as the directing auxiliary.[78] Aliphatic amines bearing a substituent at the β-position favorably produced γ-aminated over acetoxylated products by using $PhI(OAc)_2$ as the oxidant (Scheme 1.19). When amines lacking this β-substituent were used, acetoxylated products were predominant.[75] The authors interpreted that the observed selectivities probably resulted from the torsional strain imposed by the β-substituent and the γ-C–H bond (and possibly R^1 at α-position) in the palladacycle intermediate (Scheme 1.19).



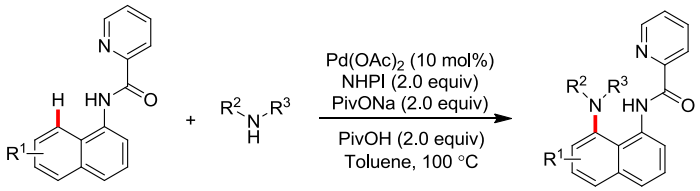
Scheme 1.19 Intramolecular γ-C(sp^3)–H amination of aliphatic amines

Other oxidants were tested in place of $PhI(OAc)_2$ for the cyclization reaction and it was found that the oxidant PhI(DMM) derived from dimethylmalonic acid promotes the intramolecular C–H amination reaction of *ortho*-substituted benzyl amines providing mainly cyclized products with only a small amount of acetoxylated products (Scheme 1.20).[79] It was observed that the use of PhI(DMM) completely switched the selectivity from C–O formation to C–N formation when compared with $PhI(OAc)_2$.



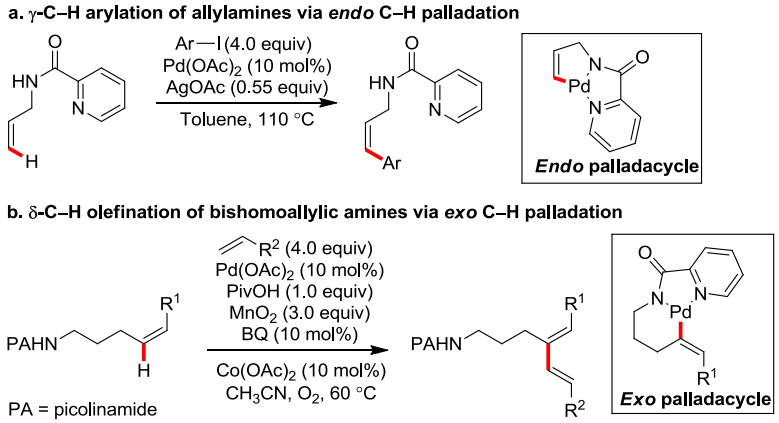
Scheme 1.20 Intramolecular C–H amination of phenylethylamines

Only a single example was reported for palladium-catalyzed intermolecular C–N bond formation reactions of picolinamides, where 1-naphthylamine was aminated at the 8-position with secondary amines (Scheme 1.21).[80] In this system, $PhI(OAc)_2$ was found not effective and *N*-hydroxyphthalimide (NHPI) was the optimal oxidant. Other C–heteroatom bonds, such as C–halogen,[81] C–B,[82] C–Si,[83] C–Se[84] and C–S[85] could also be introduced using the picolinamide auxiliary.



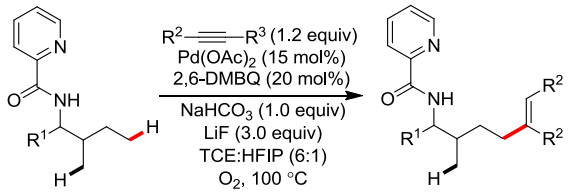
Scheme 1.21 Intermolecular C–H amination of amines

Picolinamide was also used to direct C(sp^2)–H functionalization of unactivated alkenes, to which many competitive traditional reactivity pathways could occur, such as olefin E/Z isomerization, allylic functionalization, and intramolecular nucleopalladation. Depending on the distance of the alkene from the directing picolinamide moiety, *endo* or *exo* cyclopalladated intermediates would be formed. For instance, when applying allylamines in the palladium-catalyzed arylation reaction conditions, the reaction is highly *Z*-selective (E/Z ratios up to 2:98) over *E*-selective (Heck-type arylation).[86] This unique selectivity was presumably coming from the formation of the *endo*-cyclopalladated intermediate *via* C–H palladation (Scheme 1.22a). The Engle group adopted this strategy to achieve the olefination reaction *via* the formation of the *exo* cyclopalladated intermediate (Scheme 1.22b).[87] The Carreira group subsequently reported the iodination[88] and alkynylation[89]of similar substrates.



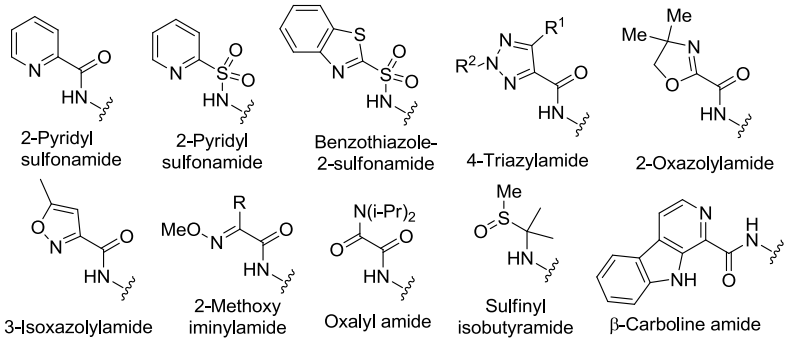
Scheme 1.22 C(sp^2)–H functionalization of alkenes directed by picolinamide

The δ-C–H arylation of amines lacking γ-methyl groups has been also described.[90] In this context, the group of Shi reported a strategy for the δ-C(sp^3)–H alkenylation of amines with internal alkynes as coupling partners directed by picolinamide (Scheme 1.23).[92] The reaction is highly δ-selective even in the presence of γ-methyl groups. When unsymmetrical alkynes were used, regioisomers were generally formed. Preliminary mechanistic studies showed that reversible γ-C(sp^3)–H palladation did occur but this palladacycle was unreactive towards functionalization with alkynes. When arylation was performed under slightly different reaction conditions for the same substrate, only γ-arylated products were detected, highlighting the important role of coupling partners in determining the site-selectivity.[93]



Scheme 1.23 δ-C(sp^3)–H alkenylation of amines with internal alkynes directed by picolinamide

Apart from picolinamide bidentate directing groups, some other amine-derivatized bidentate directing groups were also developed (Scheme 1.24). Most of them were X,L-type *N*,*N*-bidentate directing groups, for example, 2-pyridiylsulfonamide,[94] benzothiazole-2-sulfonamide,[95] 4-triazylamide,[96] 2-oxazolylamide,[97] 5-methyl-(3-isoxazolylamide),[98] 2-methoxyiminylamide,[99] oxalylamide,[100] sulfinyl isobutyramide[101] and even the native functionality β-carboline amide.[102]



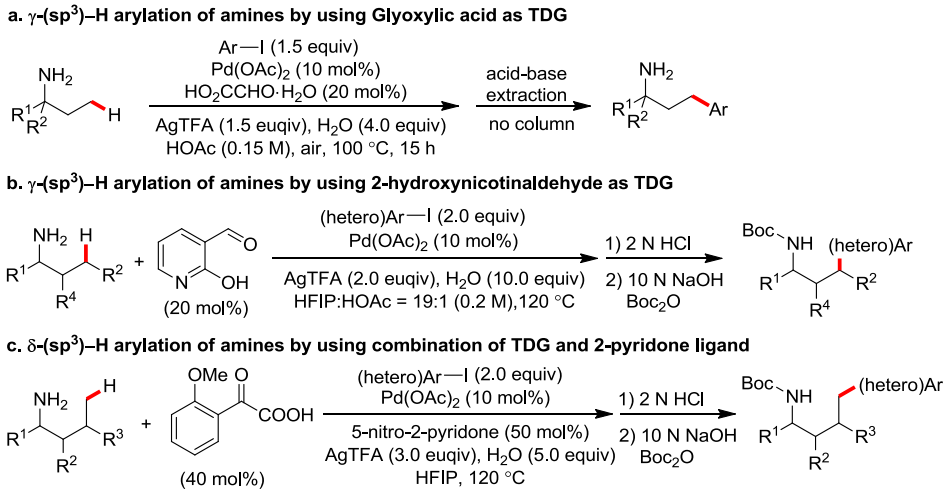
Scheme 1.24 Amine-based bidentate directing groups

The development of new bidentate directing groups not just largely diversified the tools of performing C–H functionalization reactions of amines, but also offered complementary reactivities. Moreover, this broad spectrum of bidentate directing groups offers the possibility of introducing and removing the directing groups using different reaction conditions. Nevertheless, as stated above, using this approach, at least two additional synthetic steps are required, which decreases the overall efficiency of the transformation.

1.2.2.2 Transient bidentate directing groups

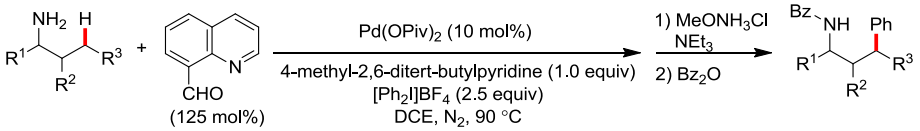
Recently, a new type of directing groups, namely transient directing groups (TDGs), have been developed.

These TDGs are introduced into the molecules *via* a reversible reaction and therefore, the introduction, C–H functionalization and removal of the TDGs take place in one pot. Additionally, this approach allows to use catalytic amounts of TDG. Most of the transient directing groups reported exploited the reversible formation of imines from the condensation of amine substrates with aldehyde-containing TDGs. The first example of palladium-catalyzed C–H functionalization of amine compounds using a catalytic amount of TDG was reported by Ge and co-workers (Scheme 1.25a).[103] Glyoxylic acid was used as the TDG to achieve γ-C(sp^3)–H arylation of amines. The column-free acid-base extraction purification procedure made this method very practical. However, the substrate was mostly limited to amines bearing α-quaternary carbons and only methyl groups could be activated. Not long after, the group of Yu developed a more robust TDG, 2-hydroxynicotinaldehyde (Scheme 1.25b).[104] Its efficiency was demonstrated by the successful γ-C(sp^3)–H arylation of amines with secondary, tertiary and quaternary α-carbons at both methyl and methylene groups. Moreover, the δ-C(sp^3)–H functionalization was reported using the phenyl variant of glyoxylic acid in combination with 5-nitro-2-pyridone as external ligand in the absence of γ-methyl groups (Scheme 1.25c).[105]



Scheme 1.25 C(sp^3)–H arylation of amines by using TDGs

A rare example of using a L,L-type TDG was reported by the group of Dong, where an excess of quinoline-8-carbaldehyde was used (Scheme 1.26).[106] The highly reactive arylating reagent $[Ph_2I]BF_4$ was used to achieve successful γ-C(sp^3)–H arylation reactions of amines. The scope of amines was broad, ranging from the ones comprising α-quaternary carbons to those having a secondary α-carbon.

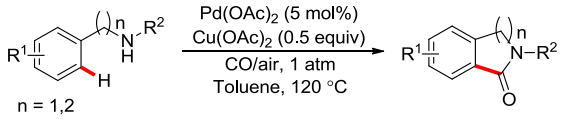


Scheme 1.26 γ-C(sp^3)–H arylation of amines by using an L,L-type TDG

Despite the success using TDGs to functionalize amines, so far, only the arylation reaction has been described.[107] Compared with the fruitful functionalization reactions of aldehydes using amine-containing TDGs, a reversed version of the presented strategy, the functionalization of amines using this approach is still very limited.[108]

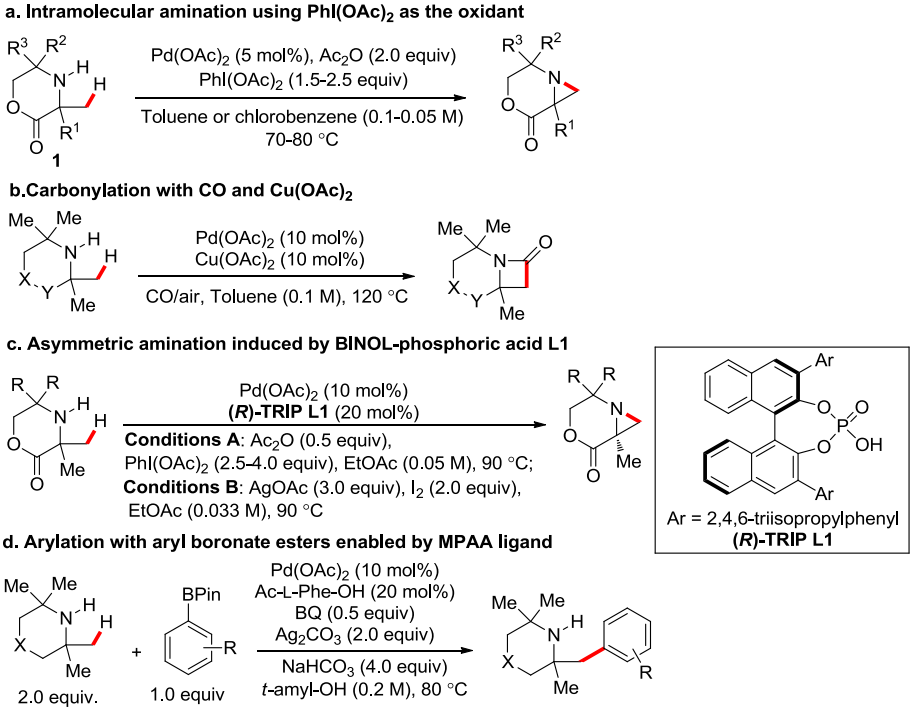
1.2.3 Amino group acts as native directing group

In spite of the fact that amines easily form stable bisamine palladium(II) complexes with palladium(II) salts, the use of the amino group as native directing group for Pd-catalyzed C–H activation reactions has been realized. The work from Orito and co-workers represents a rare example where unhindered secondary amines were directly carbonylated *via* C(sp^2)–H activation using the amino motif as the native directing group forming five- or six-membered benzolactam products (Scheme 1.27).[109]



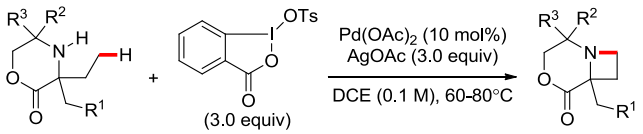
Scheme 1.27 C(sp^2)–H carbonylation of secondary amines

The group of Gaunt then demonstrated that when a highly hindered secondary amine was used, the amino group itself alone could direct β-C(sp^3)–H activation reaction of methyl groups to form aziridines using PIDA as the oxidant (Scheme 1.28a).[110] The bulky environment around the coordinating nitrogen is believed to destabilize the bisamine palladium(II) complex, shifting the equilibrium towards the monoamine palladium(II) complex, from which C–H activation occurs. Interestingly, a four-membered palladacycle was preferably formed even when γ-methyl groups whose C–H activation will result in the formation of a five-membered palladacycle are present. Substrates that do not possess the carbonyl group, produced acetoxylated products instead. In the same paper, they also showed that when CO was used instead of PIDA and in the presence of $Cu(OAc)_2$, carbonylation could also happen delivering four-membered lactams (Scheme 1.28b). Later it was found that when a chiral anionic BINOL-phosphoric acid was incorporated into the reaction, asymmetric aziridination could be achieved (Scheme 1.28c).[111] Additionally, aryl groups were introduced using aryl boronate esters as arylating reagents in the presence of a mono-protected amino acid ligand Ac-L-Phe-OH (Scheme 1.28d). [112]



Scheme 1.28 Transformations of β-C(sp^3)–H bonds of bulky secondary amines

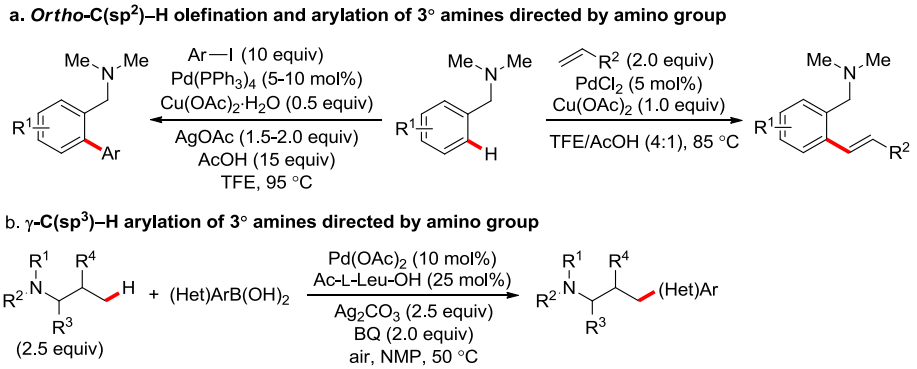
The same authors also reported the γ-C(sp^3)–H olefination of bulky secondary amines[113] and the intramolecular amination, providing the corresponding azetidines by using benziodoxole tosylate as oxidant in combination with AgOAc (Scheme 1.29).[114]



Scheme 1.29 γ-C(sp^3)–H amination of bulky secondary amines

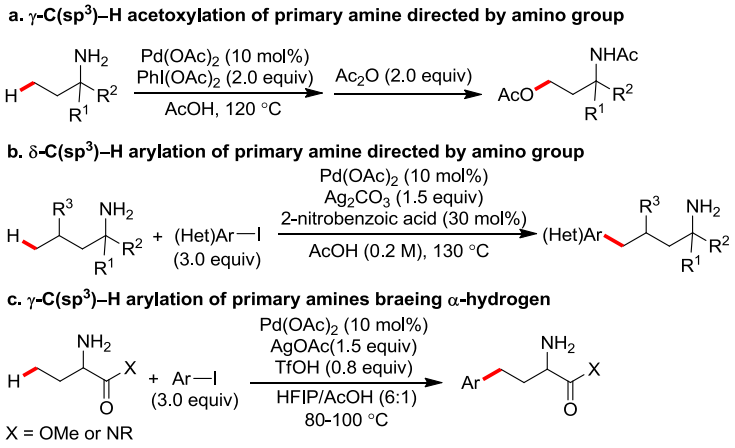
The Shi and Zhang groups independently reported the use of tertiary benzylamines as native directing groups for the *ortho* C–H olefination and arylation reactions, respectively (Scheme 1.30a).[115,116] Acetic acid was found crucial to guarantee high yields of products and was believed to tune the concentration of free amine through base-acid adducts balance. The asymmetric arylation and olefination of dimethylaminomethylferrocenes were

then realized by using chiral MPAA ligands Boc-L-Val-OH and Boc-L-Phe-OH, respectively.[117-119] Moreover, the Gaunt group reported the γ-C(sp^3)–H (hetero)arylation of tertiary amines in the presence of MPAA ligands (Scheme 1.30b).[120]



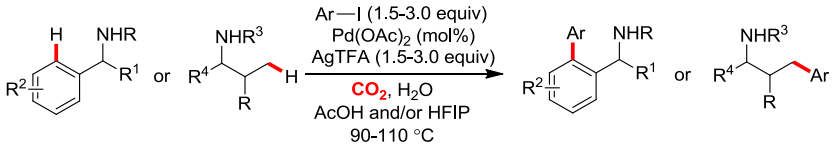
Scheme 1.30 C–H functionalization of tertiary amines

Primary amines, because of their stronger affinity to palladium than secondary and tertiary amines, are generally unreactive towards C–H activation reactions. Despite this fact, some advancements of using primary amino group as the native directing group to achieve C–H functionalization reactions have been made.[121] Seminal work by Daugulis and co-workers achieved the *ortho*-arylation reaction of benzylamines with aryl iodides in the presence of TFA.[121a] Since this initial report, many other transformations using benzylamines, arylethylamines or *ortho*-phenylanilines as substrates *via* C(sp^2)–H activation, including arylation,[121f,h,q,r,u] carbonylation,[121b,c,g,i,n,k], olefination (often followed by subsequent cyclization).[121d,j,m,s] alkynylation,[121o] and trifluoromethylation[121e] have been described. It was not until 2017 that the group of Shi reported the first example of primary amino group directed C(sp^3)–H activation of amines (Scheme 1.31a).[121l] Amines bearing α-quaternary carbons were γ-acetoxylated in modest yields. The first γ-C(sp^3)–H arylation was reported by Yao and co-workers, where α-aminoesters bearing an α-quaternary carbon were coupled with diaryliodonium triflates.[121p] Selective δ-C(sp^3)–H arylation of amines bearing an α-quaternary carbon with aryl iodides was also possible when γ-methyl groups were absent (Scheme 1.31b).[121q] A method was also reported for the γ-C(sp^3)–H arylation reaction of α-aminoesters and oligopeptides bearing an α-hydrogen (Scheme 1.31c).[121r]



Scheme 1.31 C(sp^3)–H Functionalization of primary amines

Recently, the group of Young discovered that CO_2 could be used as a transient mediator to improve the yield and expand the substrate scope of amino-directed arylation reaction of primary and secondary amines with aryl iodides (Scheme 1.32).[122] This transformation was operationally simple and CO_2 was used in the form of dry ice. This methodology was also applied for the *ortho*-C(sp^2)–H arylation of both primary and secondary benzylamines with aryl iodides.[122b]



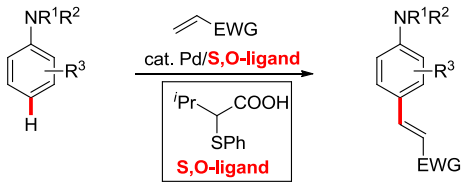
Scheme 1.32 γ-C–H arylation of amines mediated by CO_2

Overall, it was demonstrated that tertiary, secondary and primary amino groups were all capable of acting as directing groups to perform both C(sp^2)–H and C(sp^3)–H functionalization reactions, which has greatly boosted the efficiency of modifying amine compounds. However, sterically congested amines are generally required to achieve highly efficient transformations. Moreover, due to the incompatibility issue of amine compounds with some reagents, only a limited amount of functionalities could be introduced.

1.2.4 Non-directed C–H functionalization of anilines

Direct C(sp^2)–H functionalization of nondirected arenes using palladium catalysis was first reported by Fujiwara.[123] It has since emerged as a research topic of extensive interest.[1r] The efficiency of this transformation has been greatly improved by designing new catalysts as evidenced by the facts that both electron-rich and electron-poor arenes can be used as effective substrates using the arene as the limiting reagent instead of (co-)solvent.[1r] However, the regioselectivity control still remains challenging.

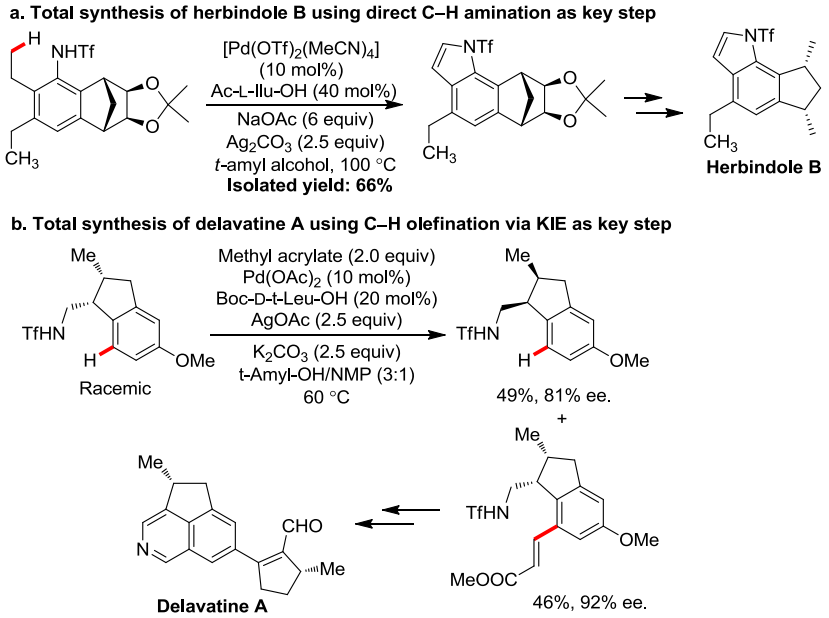
In the specific case of anilines, Pd-catalyzed highly *para*-selective C–H functionalization reactions have been achieved. For example, the group of Ishii reported a strategy for the highly *para*-selective olefination reaction of tertiary anilines catalyzed by Pd/HPMoV with 2,4,6-trimethylbenzoic acid as an additive.[124] A large excess of the anilines (7.5 equiv relative to olefin) was required to obtain the olefinated products in high yields and *para*-selectivities. Pd-catalyzed *para*-selective olefination reaction of anilines using $Cu(OAc)_2$ as the co-oxidant has also been realized.[125] However, for both protocols, only unsubstituted anilines could be used as suitable substrates. The group of Yu reported a strategy for the Pd-catalyzed C(sp^2)–H olefination of simple arenes including indolines and tetrahydroquinolines aided by 2-pyridone as the external ligand.[126] Tosyl was used as the protecting group for the nitrogen, and poor regioselectivities were observed. Recently, our group developed a methodology for the highly *para*-selective olefination of anilines under mild reaction conditions (Scheme 1.33).[127] The key to the success lies in the discovery of a new type of S,O-bidentate ligand, which drastically enhanced the reactivity and selectivity of this transformation. This transformation was highly general and compatible with mono-, di- and trisubstituted tertiary, secondary and primary anilines.



Scheme 1.33 S,O-ligand promoted *para*-selective olefination of anilines

1.3 Synthesis of natural products using the direct C–H functionalization of amine-containing compounds

Although palladium-catalyzed C–H functionalization has not found many applications in industry for large scale production of fine chemicals, its power has long been realized by synthetic organic chemists and it has been widely used in the total synthesis of natural products and drug discovery research.[128] Triflyl-amino-directed intramolecular C–H amination has been utilized as a strategic step to prepare *cis*-trikentrin A and herbindole B natural products (Scheme 1.34a).[129] The C–H amination products indolines underwent attendant oxidation to give the corresponding indoles, present in the natural products. Kinetic resolution of β-alkyl phenylethylamines was developed *via* palladium-catalyzed olefination directed by triflyl-amino motif in the presence of MPAA ligand in the total synthesis of the natural product delavatine A (Scheme 1.34b).[130]



Scheme 1.34 C–H functionalization of amines in the total synthesis of natural products

1.4 Summary and Outlook

Palladium-catalyzed C–H functionalization has emerged as a powerful tool to modify amine containing compounds by directly incorporating a rich variety of functionalities in a regioselective and even stereocontrolled manner. Many different types of directing groups with different properties have been developed, which made up an integrated toolbox for organic chemists to prepare complex amines from simpler ones. The development of more practical directing groups, such as transient directing groups and the use of amino moiety as native directing group further increased the efficiency of this strategy. The discoveries of external ligands dramatically expanded the substrate scope and also greatly rendered the development of asymmetric C–H functionalization reactions. This strategy is finding more and more applications in natural product synthesis and drug discoveries. However, to realize the full potential of this strategy in organic synthesis, new methods are yet to be developed to incorporate new functionalities and to functionalize positions that are currently not available.

1.5 Thesis outline

The aim of this thesis was to develop novel and efficient methodologies to functionalize amine containing compounds. We have adopted different tactics to functionalize different amine substrates. In **Chapter 2**, the combination of a monodentate directing group, triflyl protected amine, with pyridine- or quinoline-based external ligand to promote Pd-catalyzed γ-C(sp^3)–H acetoxylation of aliphatic amines is described. **Chapter 3** describes the non-directed highly *para*-selective olefination reaction of indolines and tetrahydroquinolines by using Pd/S,O-ligand catalysis under mild reaction conditions. This transformation shows broad substrate scope regarding indolines, tetrahydroquinolines and olefins. This chapter also contains examples for late-stage selective functionalization of complex molecules. In **Chapter 4**, the methodology described in Chapter 3 is applied for the divergent total synthesis of yaequinolone related natural products. To achieve this goal, a reliable synthetic sequence for the preparation of 3,4-dioxygenated 5-hydroxy-4-aryl-quinolin-2(1*H*)-ones, which are the core structures of this family of natural products, is described. Then, by performing *para*-selective late-stage olefination on these core structures, we successfully realized the total synthesis of 11 yaequinolone related natural products.

1.6 References

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CHAPTER 2

LIGAND-ENABLED γ-C(sp^3)–H ACETOXYLATION OF TRIFLYL-PROTECTED AMINES

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2.1 Introduction

Amines serve as key functional groups in pharmaceuticals, agrochemicals as well as materials.[1] Traditionally, amines can be synthesized by *i*) *N*-alkylation;[2] *ii*) reductive amination of aldehydes and ketones;[3] *iii*) reduction of amides[4] and nitriles;[5] *iv*) Gabriel amine synthesis;[6] *v*) azidation/reduction sequence;[7] or by *vi*) Del épine amine synthesis.[8] In the last decades, Buchwald-Hartwig amination catalyzed by transition-metal has seen extremely wide application both in industry and academia for the preparation of substituted anilines.[9] Some other methods that involve the use of transition metals have also emerged, for example, allylic amination[10] and hydroamination of unsaturated carbon-carbon bonds.[11]

Alternatively, an ideal route to construct complex amines is the direct functionalization of C–H bonds present in simpler amines, which not only makes use of those existing methods for preparing simple amines but also will streamline the synthesis of *N*-containing natural products and pharmaceuticals by late-stage C–H functionalization. Transition metal catalyzed C–H activation/functionalization reactions of amine compounds have emerged for this purpose. Without prefunctionalization, new functionalities can be directly introduced into the amine containing molecules to give more complex structures that are either not accessible or lengthy to synthesize by other methods. A comprehensive introduction regarding C–H bond functionalization of amine containing compounds was given in Chapter 1.

The γ-hydroxy amine motif widely exists in natural products and pharmaceuticals (Figure 2.1).[12] In the particular case of γ-hydroxy amino acids, they also find broad applications in peptide-based drugs and native chemical ligation (NCL).[13,14] The synthesis of γ-hydroxy amines is often tedious and/or involve multiple steps, for example, sequential reduction and amination of β-halogenated ketones[12g] or Aza-Michael addition of an amine/amino acid to α,β-unsaturated ketones followed by ketone reduction.[15,16]

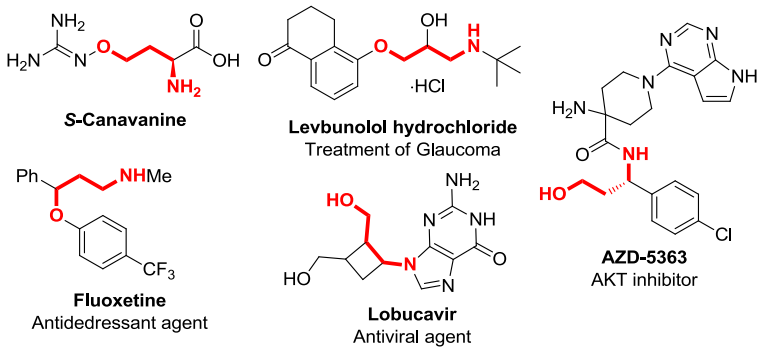
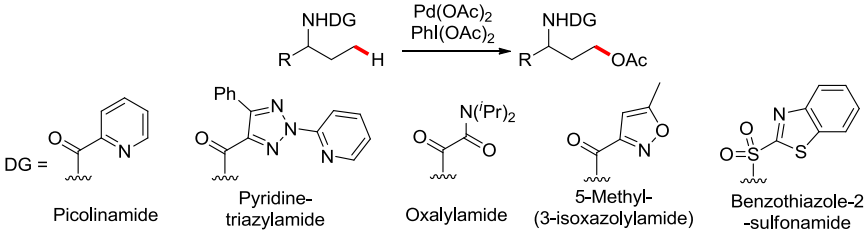


Figure 2.1 Representative natural products and pharmaceuticals containing γ-hydroxy amine

γ-Hydroxy amines have been synthesized via γ-C–H acetoxylation of amines/amino acids promoted by directing groups attached to the nitrogen atom (Scheme 2.1). Several research groups independently developed different bidentate directing groups for this purpose, for example, picolinamide,[17] pyridine-triazylamide,[18] oxalylamide,[19] 5-methyl-(3-isoxazolylamide)[20] and benzothiazole-2-sulfonamide.[21] Although general applicability was often seen in these reports, the deliberately chosen directing group needs to be installed before performing the C–H acetoxylation reaction and removed after, which significantly reduces the overall efficiency of the transformation. Additionally, the γ-C(sp^3)–H acetoxylation of primary amines using the amino functionality as the native directing group has also been reported. However, the scope was only limited to primary amines bearing α-quaternary carbons.[22]



Scheme 2.1 γ-Acetoxylation of amines using bidentate directing group

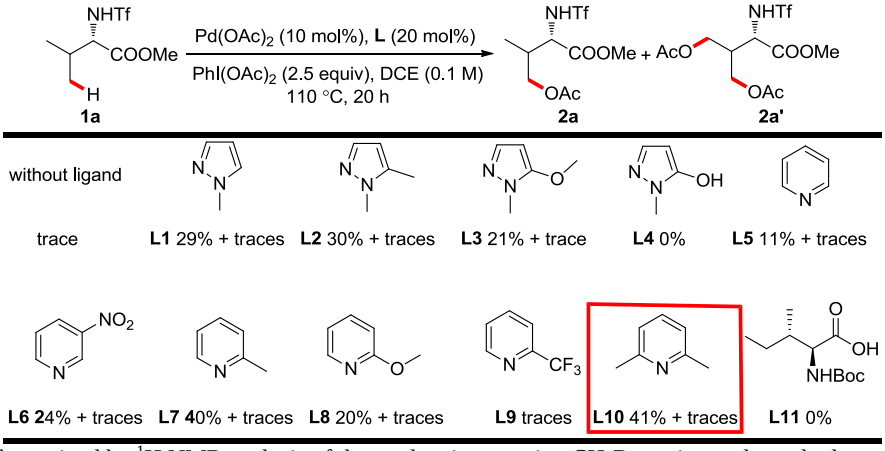
In 2010, the group of Yu reported a strategy for the C(sp^2)–H acetoxylation of arenes directed by triflyl-protected amines as mentioned in Chapter 1.[23] Later on, it was observed that for the functionalization of C(sp^3)–H bonds using triflyl-protected amines, an external ligand was necessary to achieve efficient transformations (See Chapter 1). So far, the direct C(sp^3)–H bond acetoxylation of amine containing compounds using triflyl-protected amines has not been disclosed. Our research group is interested in using external ligands to promote C–H activation reactions. We hypothesize that γ-C(sp^3)–H acetoxylation of triflyl-protected amines can be realized by using an external ligand.

In this chapter, we report the successful establishment of ligand-enabled γ-C(sp^3)–H acetoxylation of triflyl-protected aliphatic amines. The key to the success is the use of two types of external ligands, 2,6-lutidine for amino acid substrates and 2-alkoxyquinoline for amino alcohol substrates. This reaction features high diastereoselectivity and easy scalability.

2.2 Results and discussion

We started our investigations by using methyl *N*-triflyl-L-valinate (**1a**) as model substrate, 10 mol% $Pd(OAc)_2$ as palladium source and (diacetoxyiodo)benzene (PIDA, 2.5 equiv) as oxidant, in DCE (0.1 M) at 110 ℃. After 20 h, unsurprisingly, only a trace amount of acetoxylated product was observed due to the weak directing ability of triflyl-protected amino moiety (Table 2.1). We then tried to improve the efficiency of this reaction by introducing an external ligand. Previously, we found that pyrazole can drastically improve the yields of several different types of C–H activation reactions.[24] Therefore, 20 mol% of *N*-methyl pyrazole (**L1**) was added to the reaction and 29% of monoacetoxylated product was observed together with a trace amount of diacetoxylated product (Table 2.1). We then tested a few substituted electron-rich and electron-poor pyrazoles (**L2**-**L4**). However, none of them was superior to *N*-methyl pyrazole although 1,5-dimethyl pyrazole (**L2**) produced 30% of monoacetoxylated product. Since pyridine-type ligands were well-established to be able to accelerate a series of C–H functionalization reactions,[25] we then moved our attention to this type of ligands (**L5**-**L10**). While bare pyridine (**L5**) was not vey efficient for this reaction, 3-nitro pyridine (**L6**) delivers the monoacetoxylated product in 24% yield. The yield was further improved to 40% when 2-methyl pyridine (**L7**) was used. When the 2-Me group was replaced with OMe group (**L8**), the yield drops to 20%. Only a trace amount of product was detected when 2-trifluoromethyl pyridine ligand (**L9**) was used. We found that the introduction of 2,6-lutidine (**L10**) delivered the monoacetoxylated product in 41% yield. Since mono-protected amino acids (MPAAs) have proven to be successful ligands in a variety of C–H activation reactions of *N*-triflyl amines (see discussion in Chapter 1), we tested Boc-L-isoleucine (**L10**) as ligand in our model reaction but no conversion to the desired product was observed. With all the ligands being tested, the reaction proceeded cleanly and mainly starting material and final product were detected from the analysis of the crude mixture by ^{1}H NMR.

Table 2.1 Ligand optimization[a]

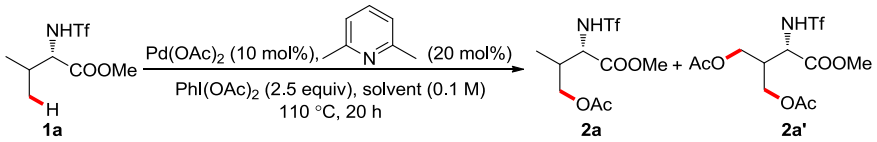


[a] The yield was determined by ^{1}H NMR analysis of the crude mixture using CH_2Br_2 as internal standard.

After having determined 2,6-lutidine as the optimal ligand, we evaluated the effect of different solvents in the reaction (Table 2.2). When DCM was used in place of DCE, a similar yield was obtained (entry 2). Toluene, CH_3CN, and mixtures of $AcOH/Ac_2O$ all failed to improve the yield of product compared with DCM (entries 3-

5). The reaction proceeded similarly when the concentration in DCM was increased to 0.5 M (entry 6).

Table 2.2 Screening of solvents[a]

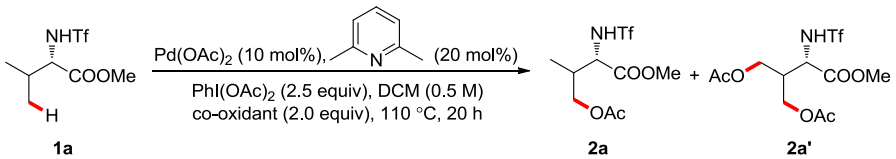


Entry	Solvent	Yield
1	DCE	41% + traces
2	**DCM**	**42% + traces**
3	Toluene	26% + traces
4	CH_3CN	21% + traces
5	$AcOH/Ac_2O$ (9:1, v/v)	< 10%
6	DCM[b]	42% + 3%

[a] The yield was determined by ^1H NMR analysis of the crude mixture using CH_2Br_2 as internal standard. [b] Reaction concentration was 0.5 M.

To further improve the yield of the reaction, we studied the effect of different co-oxidants in the reaction (Table 2.3). Although the presence of 2.0 equiv of $PhCO_3{}^tBu$ inhibits the reaction completely (entry 2), the use of $K_2S_2O_8$ improved the yield to 59% (**2a**+**2a'**) (entry 3). AgOAc worked slightly better than $K_2S_2O_8$, giving 63% combined yield of mono- (58%, **2a**) and di-acetoxylated (5%. **2a'**) products (entry 4). The addition of *p*-benzoquinone did not improve the yield substantially compared with the reaction without co-oxidant (comparing entries 1 and 5).

Table 2.3 Optimization of co-oxidants[a]

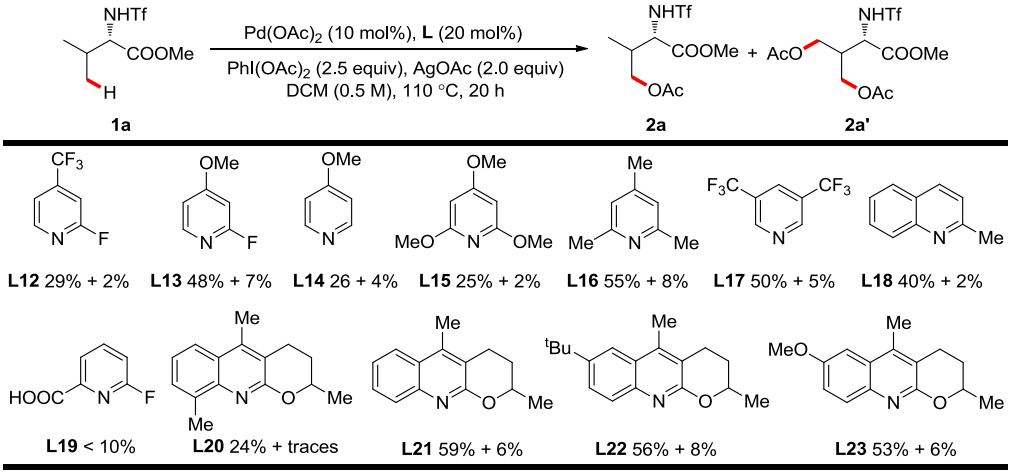


Entry	Co-oxidant	Yield
1	-	42% + 3%
2	$PhCO_3{}^tBu$	Traces
3	$K_2S_2O_8$	53% + 6%
4	**AgOAc**	**58% + 5%**
5	BQ[b]	46% + 2%

[a] The yield was determined by ^1H NMR analysis of the crude mixture using CH_2Br_2 as internal standard. [b] 0.5 equiv of BQ was used.

In an effort to boost the reaction yield more, we did some further ligand screening (Table 2.4). Pyridines bearing one or more substituents were evaluated, but none gave better results than when the reaction was performed in the presence of 2,6-lutidine (**L12**-**L17**). 2-Methyl quinoline (**L18**) could also promote this reaction, despite giving lower yield than 2,6-lutidine. The reaction using the bidentate 6-fluoropicolinic acid (**L19**) provided the acetoxylated product in less than 10% ^1H NMR yield. We additionally tested 2-alkoxyquinoline ligands that have proven to be efficient in several C–H functionalization reactions (**L21**-**L23**).[26] In our case, similar results to 2,6-lutidine were obtained and therefore, we continued the optimization using 2,6-lutidine as the ligand.

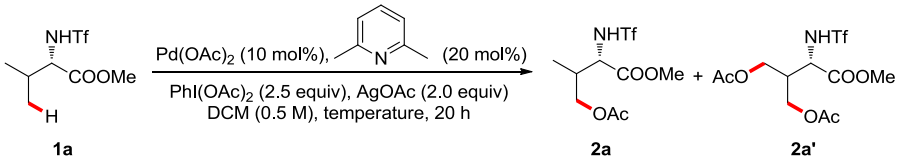
Table 2.4 Additional optimization of ligands[a]



[a] The yield was determined by ^{1}H NMR analysis of the crude mixture using CH_2Br_2 as internal standard.

We continued the optimization of the reaction conditions by varying the reaction temperature (Table 2.5). A lower yield was found when the reaction was performed at 90 ℃ and a similar yield at 130 ℃. However, at 150 ℃ the yield drops slightly compared with the reaction carried out at 110 ℃.

Table 2.5 Optimization of reaction temperature[a]

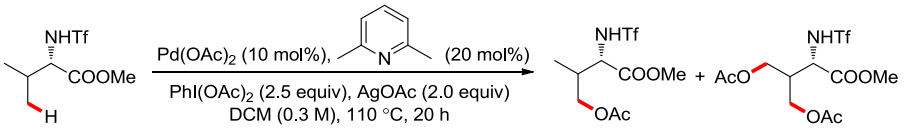


Entry	Temperature	Yield[b]
1	90 ℃	50% + 4%
2	**110 ℃**	**59% + 6%**
3	130 ℃	58% + 7%
4	150 ℃	52% + 6%

[a] The yield was determined by ^{1}H NMR analysis of the crude mixture using CH_2Br_2 as internal standard.

As mentioned previously, the reaction proceeded cleanly and mainly starting material and the final product were detected by ^{1}H NMR. We hypothesized that the moderate conversion observed is due to deactivation of the catalyst. Therefore, we decided to study the effect of batchwise addition of several reagents to the reaction (Table 2.6). We first did batchwise addition of the substrate, and the yield decreased from 63% to 36% (entry 1 *vs* entry 2), which implies that the reaction is mainly taking place at the beginning and the catalyst is deactivated over time. Then, to our surprise, the batchwise addition of $Pd(OAc)_2$/2,6-lutidine did not improve the yield (entry 3). Since PIDA is relatively unstable at higher temperatures, we performed the batchwise addition of PIDA, but again no increase of the yield was observed (entry 4). When the amount of PIDA was increased to 3.5 equiv, a slightly higher combined yield was detected (70%) (entry 4). We also tried to use 20 mol% of catalyst and similar results were observed again (50% *vs* 53%) (entry 7 *vs* entry 8). When 1.0 more equiv of $PhI(OAc)_2$ was added after 2 h together with the second batch of catalyst, little improvement was detected (59%) (entry 9). Since the yield was not substantially increased in any of these experiments, we considered the addition of all chemicals at once as the optimal reaction conditions.

Table 2.6 Batchwise addition of reagents[a]



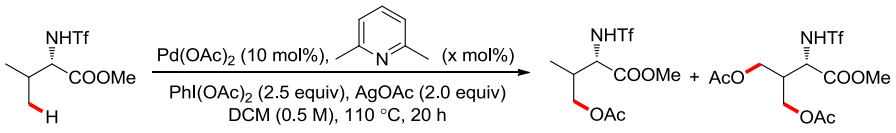
1a **2a** **2a'**

Entry	reaction	Result
1	All chemicals were added at once	58%+5%
2	**1a** was added batchwise (every half an hour, 5 times)	32%+4%
3	$Pd(OAc)_2$/ligand were added batchwise (every half an hour, 5 times)	50%+4%
4[b]	PIDA was added batchwise (every half an hour, 5 times)	50%+4%
5[c]	All chemicals were added at once	59%+6%
6[b,d]	PIDA was added batchwise (every one hour, 3 times)	60%+10%
7	20 mol% of $Pd(OAc)_2$/ligand was added batchwise (every two hours, 2 times)	50%+3%
8	All chemicals were added at once with 20 mol% of $Pd(OAc)_2$/ligand	47%+3%
9	20 mol% of $Pd(OAc)_2$/ligand and 3.5 equiv of PIDA were added batchwise (every two hours, 2 times)	55%+4%

[a] The yield was determined by ^1H NMR analysis of the crude mixture using CH_2Br_2 as internal standard. [b] Because of bad solubility of PIDA in DCM, more DCM was used (600 μL in total). [c] 600 μL of DCM was used. [d] A total of 3.5 equiv of PIDA was used.

Different ratios of ligand and Pd were then tested (Table 2.7). First, as expected, the reaction without ligand provided the acetoxylated product in low yield (entry 1). Then, the reaction provided similar yield when the ratio of Pd/ligand went from 1:1 to 1:2 (entries 2-4). We continued using the ratio of 1:2 to ensure reproducibility in our reactions.

Table 2.7 Optimization of the amount of ligand



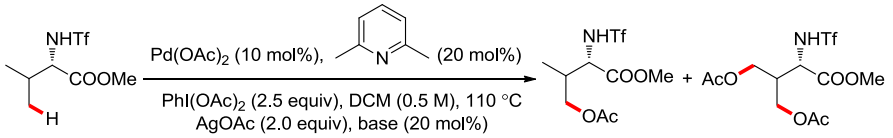
1a **2a** **2a'**

Entry	**x**	**Yield**
1	0	17% + traces
2	10	55%+ 4%
3	15	56% + 5%
4	**20**	**58% + 5%**

[a] The yield was determined by ^1H NMR analysis of the crude mixture using CH_2Br_2 as internal standard.

As described in Chapter 1, when the C–H functionalization reaction is performed using triflyl-protected amino as directing group，the presence of a base is required probably to quench the acetic acid formed during the reaction or to deprotonate the substrate at the nitrogen center. We therefore added 20 mol% of different bases into the reaction as shown in Table 2.7. However, they all failed to improve the yields of the reactions.

Table 2.7 Optimization of bases[a]



1a **2a** **2a'**

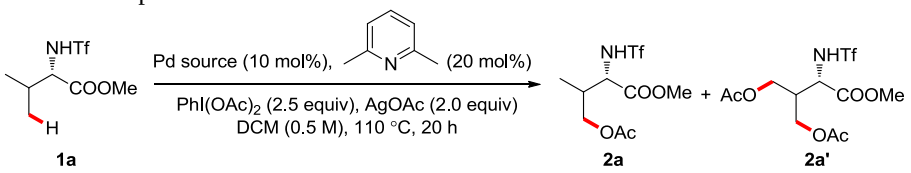
Entry	base	Result
1	NaOAc	50%+3%
2	Na_2CO_3	50%+nd

3	K_2CO_3	50%+nd
4	-	58%+5%

The yield was determined by ^{1}H NMR analysis of the crude mixture using CH_2Br_2 as internal standard. nd = no determined

We also evaluated the effect on the reactivity using different palladium salts (Table 2.8). Lower yields were obtained using $PdCl_2$, Na_2PdCl_4, $Pd(CH_3CN)Cl_2$ and $Pd(TFA)_2$ (entries 2-5). However, the yield was slightly increased to a combined yield of 69% when $Pd(OPiv)_2$ was used (entry 6).

Table 2.8 Optimization of palladium salts[a]

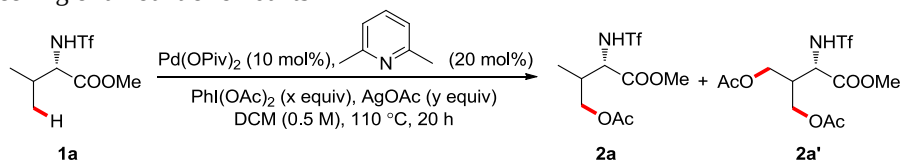


Entry	Palladium source	Yield
1	$Pd(OAc)_2$	58% + 5%
2	$PdCl_2$	32% + 2%
3	Na_2PdCl_4	25% + traces
4	$Pd(CH_3CN)Cl_2$	32% + traces
5	$Pd(TFA)_2$	41% + 2%
6	**$Pd(OPiv)_2$**	**62% + 7%**

[a] The yield was determined by ^{1}H NMR analysis of the crude mixture using CH_2Br_2 as internal standard.

Finally, we optimized the amount of oxidant and co-oxidant that is required in the reaction (Table 2.9). When the reaction was performed with 1.5 equiv of PIDA, a decrease of the yield was observed (entry 1) and when we increased the amount of PIDA to 4.0 equiv, the yield only increased slightly (entry 3). Fortunately, we observed that the amount of AgOAc can be reduced to 1 equiv without influencing the yield substantially (entry 5).

Table 2.9 Screening of amount of oxidants[a]



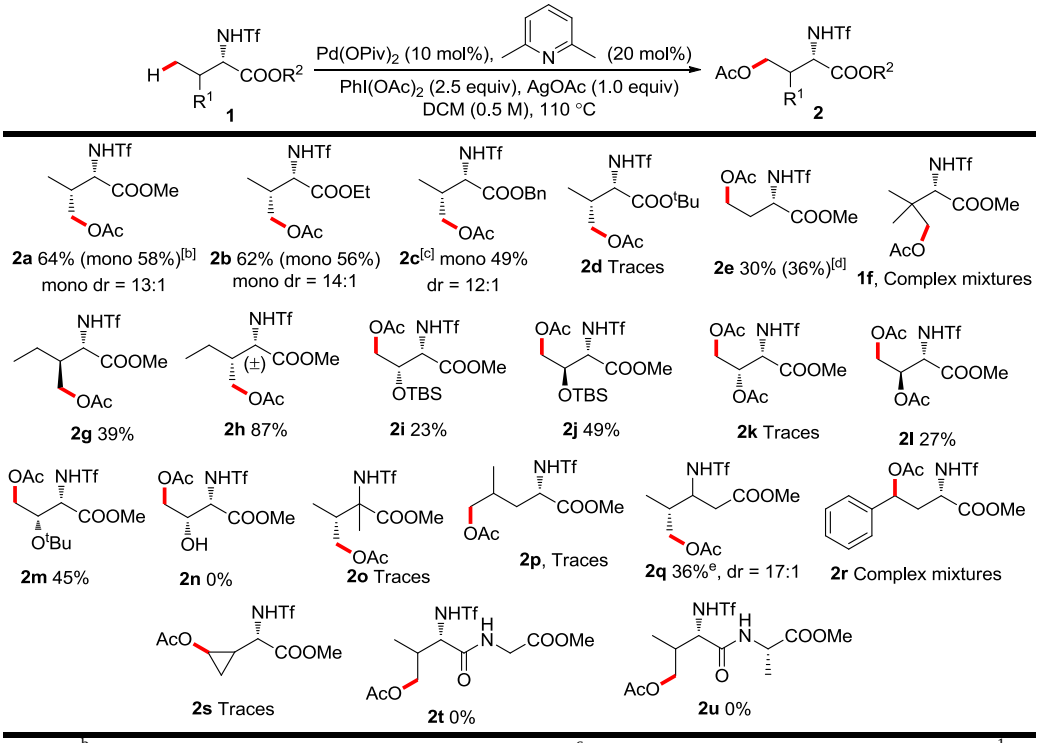
Entry	x	y	Yield
1	1.5	2.0	43% + 6%
2	**2.5**	**2.0**	**62% + 7%**
3	4.0	2.0	69% + 9%
4	2.5	0.5	57% + 6%
5	**2.5**	**1.0**	**60% + 7%**

[a]The yield was determined by ^{1}H NMR analysis of the crude mixture using CH_2Br_2 as internal standard.

Having determined the optimal reaction conditions, we started to explore the substrate scope of this transformation (Table 2.10). First, we performed the acetoxylation reaction of methyl *N*-triflyl-L-valinate (**1a**) in 1.0 mmol scale and, to our delight, a similar yield as found for the small scale reaction was observed, obtaining the mono-acetoxylated product in 58% yield with a diastereoselectivity of 13:1. We then evaluated the effect of different *N*-triflyl-L-valinates on the reactivity. We observed that ethyl and benzyl esters provided the mono-acetoxylated product **2b** and **2c** in 56% and 49% isolated yields, respectively, with very good diastereoselectivities (14:1 for **2b** and 12:1 for **2c**). However, *tert*-butyl *N*-triflyl-L-valinate (**1d**) gave only a trace amount of product. Although the exact reason for this behavior is unclear, we suggested that some

coordination between palladium and one of the oxygens of the ester is needed for the reaction to proceed. Since the *tert*-butyl group might hamper this coordination, this can explain the lack of reactivity observed with **1d**.

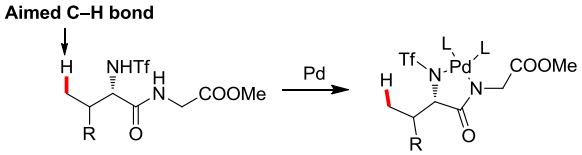
Table 2.10 Substrate scope of amino acids[a]



[a] Isolated yields. [b] The reaction was performed on a 1.0 mmol scale. [c] From the analysis of the crude mixture by ^{1}H NMR, the conversion to the diacetoxylated product was 5%. [d] 20 mol% of $Pd(OPiv)_2$ and 40 mol% of ligand were used. [e] Diacetoxylated product was isolated together with some unidentified byproducts. The ^{1}H NMR yield of the diacetoxylated product could not be determined.

As expected, a decreased yield (30%) was observed when methyl *N*-triflyl-L-homoalaninate (**1e**) was used as the substrate, even when the amount of catalyst was doubled (36% yield). The reaction of methyl *N*-triflyl-L-*tert*-leucinate (**1f**) provided the desired product in small amounts together with a few byproducts that could not be separated by flash column chromatography. Interestingly, a notable difference in reactivity between *N*-triflyl isoleucine (**1g**) and alloisoleucine (**1h**) derivatives was observed. The acetoxylated product **2g** of isoleucine derivative was obtained in 39% isolated yield, while the diastereoisomeric alloisoleucine derivative furnished the acetoxylated product **2h** in 87% isolated yield. The reactivity difference between these two diastereoisomers can be explained by the greater accessibility of the methyl group of the alloisoleucine derivative in C–H activation/palladation step induced by the conformation of the chiral carbon located at β-position of the nitrogen. A similar behavior has been observed previously in other C–H functionalization reactions of similar substrates.[27] Taking into consideration the outcome of the reactions of *N*-triflyl isoleucine and alloisoleucine, we proposed that the γ-acetoxylation of valine derivatives occurs mainly at the pro-*R* methyl group. The reaction of the two diastereoisomers of TBS-protected threonine showed the same trend in reactivity as isoleucine and alloisoleucine derivatives, with threonine derivative **1i** giving 23% isolated yield and allothreonine derivative **1j** giving a higher yield of 49%. We also replaced the TBS protecting group with an acetyl protecting group and it proved to be less efficient than TBS. Acetyl-protected isoleucine **1k** gave only a trace amount of product and acetyl-protected alloisoleucine **1l** gave 27% of acetoxylated product. Replacing the TBS by a *tert*-butyl group provided the acetoxylated product **2m** in 45% yield. We observed that the unprotected allothreonine **1n** gave a complex mixture of products by ^{1}H NMR analysis of the crude mixture. We further evaluated the acetoxylation reaction of methyl *N*-triflyl-2-methyl-valinate (**1o**), that possess an α-quaternary carbon, but only a trace amount of product was detected. We also tested *N*-triflyl-L-leucinate (**1p**), which has two methyl groups at δ-position, but no product was detected, indicating that it is unfavorable to form a six-membered palladacycle. The acetoxylation reaction of the β-amino acid, methyl *N*-triflyl-DL-β-leucinate (**1q**), provided the mono-acetoxylated product (**2q**) in 36% yield with an excellent diastereoselectivity of 17:1. The diacetoxylated

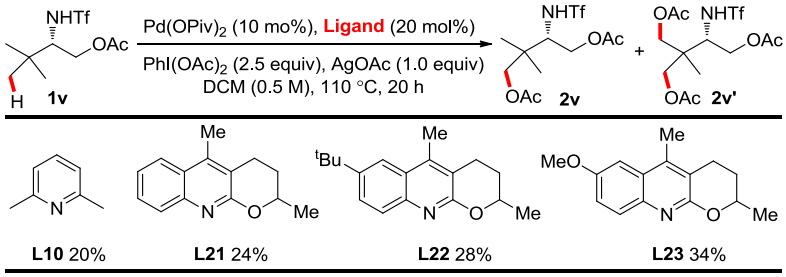
product was also isolated together with some unidentified byproducts. Although we did not observe the acetoxylation of methylene C–H bonds in any of the previous examples, we decided to evaluate the reaction of methyl *N*-triflyl-L-homophenylalaninate (**1r**) and (*R*)-methyl 2-cyclopropyl-2-(trifluoromethylsulfonamido) acetate (**1s**). These classes of methylene C–H bonds present in cyclopropane rings and at benzylic positions are more acidic and generally more reactive in palladium-catalyzed C–H functionalization reactions. Unfortunately, the reaction of **1r** gave a complex mixture of products and almost no conversion was observed using **1s** as the substrate. Finally, we studied the acetoxylation reaction in two dipeptides, Tf-Val-Gly-OMe **1t** and Tf-Ile-Gly-OMe **1u**, but no desired product was detected in either case. In both cases, we observed byproducts that came from the oxidation of the methylene group of the glycine moiety. We attributed the lack of reactivity to the possible coordination of the amide bond of the dipeptide to palladium, which together with *N*-triflyl amine moiety would direct the palladium away from the C–H bonds that were aimed to be activated (Scheme 2.2).[28]



Scheme 2.2 Bidentate potential of dipeptides

After having determined the scope of this transformation for amino acids, we decided to investigate the reactivity of β-amino alcohols, moieties that are widely present in natural products and are used as catalysts in asymmetric catalysis.[29] Unfortunately, the reaction of *O*-acetyl-*N*-triflyl-L-*tert*-leucinol (**1v**) under the optimal reaction conditions used for amino acids provided the acetoxylated product **2v** in only 20% ^{1}H NMR yield (Table 2.11). Therefore, we decided to evaluate three 2-alkoxyquinoline ligands **L21**-**L23** that were found to be almost equally effective to 2,6-lutidine ligand for amino acid substrates. Among them, **L23** bearing a methoxy substituent at the aromatic ring provided higher ^{1}H NMR yield of **2v**.

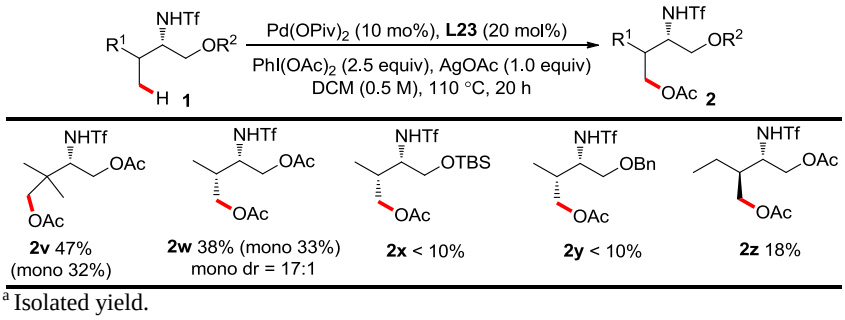
Table 2.11 Ligand optimization for amino alcohol substrate



[a] Yield of mono-acetoxylated product. Only traces amount of diacetoxylated product were detected. The yield was determined by ^{1}H NMR analysis of the crude product using CH_2Br_2 as internal standard.

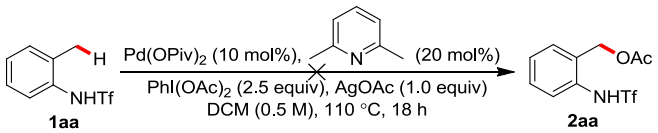
The reaction of *O*-acetyl-*N*-triflyl-L-*tert*-leucinol (**1v**) using **L23** as ligand provided the monoacetoxylated product **2v** in 32% isolated yield together with 15% of diacetoxylated product **2v'** (Table 2.12). *O*-Acetyl-*N*-triflyl-L-valinol (**1w**) gave a mixture of acetoxylated products with a combined yield of 38%. We observed that changing the acetyl protecting group to TBS or Bn resulted in the formation of acetoxylated products in less than 10% ^{1}H NMR yield (**2x** and **2y**). Finally, the reaction of *O*-acetyl-*N*-triflyl-L-isoleucinol (**1z**) provided the acetoxylated product in 18% yield. In this case, the low yield obtained is in accordance with the low reactivity observed with isoleucine substrate.

Table 2.12 Substrate scope of β-amino alcohols[a]



[a] Isolated yield.

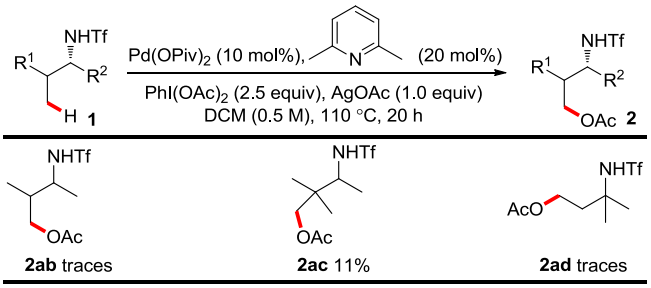
In an effort to further expand the substrate scope, we tried to acetoxylate the benzylic position of 2-methyl-*N*-triflylaniline (**1aa**) (Scheme 2.3). However, almost full decomposition of starting material was detected. We speculated that the substrate is unstable in the presence of PIDA as when we mixed a solution of the substrate in DCM with PIDA, the color immediately changed from pale yellow to dark red.



Scheme 2.3 Acetoxylation of 2-methyl-*N*-triflylaniline (**1aa**)

We also tried to acetoxylate some simple amines using this strategy (Table 2.13). However, only small amounts of acetoxylated products were detected. Taking into account the results presented in this Chapter, we speculated that some coordination between the palladium center and the ester group of the amino acids is necessary to promote the reaction. Thus, in the absence of this coordinating moiety, the reaction does not proceed efficiently.

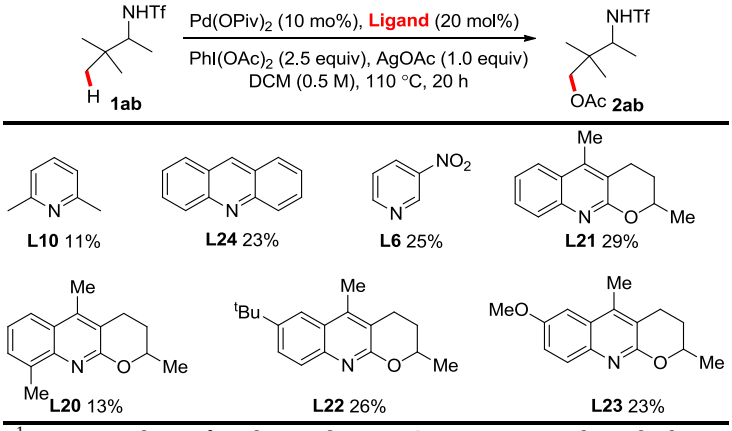
Table 2.13 Scope of simple amines[a]



[a] Yield was determined by ^{1}H NMR analysis of crude sample using CH_2Br_2 as internal standard.

To improve the reaction yield, we tested some other ligands (Table 2.14). We observed that some of the ligands successfully increased the reaction yield, for example, with 3-nitropyridine (**L6**) as the ligand, the acetoxylated product was observed in 25% ^{1}H NMR yield. 2-Alkoxyquinoline ligands (**L21** – **L23**) gave comparable yields to **L6**. However, to achieve synthetically useful yield, new ligands are yet to be found to make this transformation more efficient.

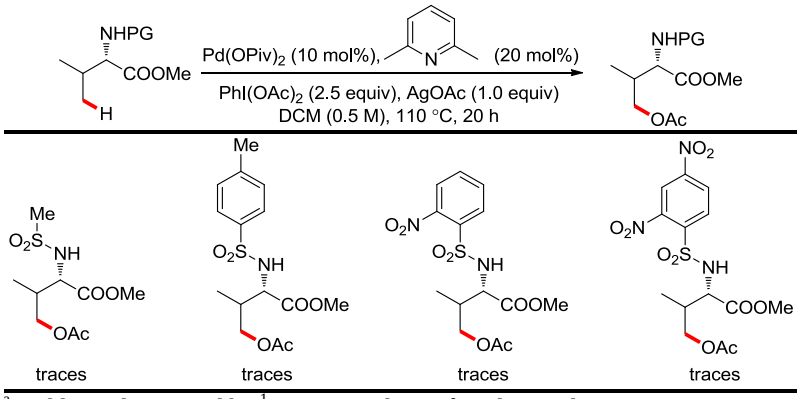
Table 2.14 Optimization of ligands for triflyl-protected amine[a]



[a]Yield was determined by ^{1}H NMR analysis of crude sample using CH_2Br_2 as internal standard.

Additionally, the influence on the reactivity of similar protecting groups to triflyl, such as nosyl and tosyl, was studied with the aim at having a more general strategy for the C–H acetoxylation of amines (Table 2.15). Unfortunately, only a trace amount of product was detected in all cases, highlighting the key role of the pK_a/pH in all these transformations.

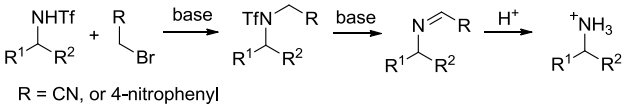
Table 2.15 Evaluation of other protecting groups[a]



[a] Yield was determined by ^{1}H NMR analysis of crude sample.

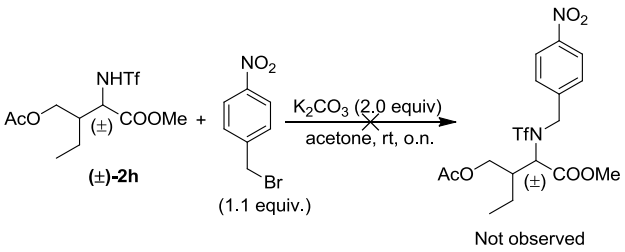
Deprotection of Tf protecting group

Finally, the deprotection of the Tf protecting group was studied. For the deprotection of secondary Tf-protected amines, the most common method is the stepwise procedure shown in Scheme 2.4.[30] In the first step, a substituent with a methylene group is installed into the nitrogen under basic conditions. After, the most acidic proton is removed in the presence of a base to form an imine that can be afterwards hydrolyzed, providing the desired unprotected amine.



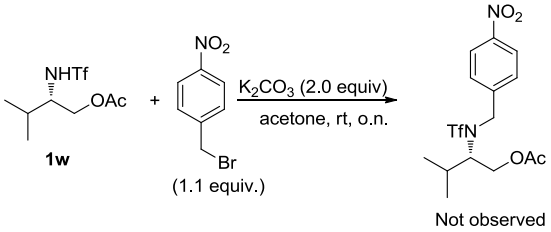
Scheme 2.4 Stepwise deprotection of Tf protecting group

Then, we applied this deprotection strategy with our acetoxylated product **2h** (Scheme 2.5). When treating **2h** with 2.0 equiv of K_2CO_3 and 1.1 equiv of 4-nitrobenzyl bromide in acetone overnight, we observed a mixture of starting material and a new unidentified product in 2:1 ratio by ^{1}H NMR analysis of the crude reaction mixture. We tried to improve the conversion by increasing the temperature (35 ℃) and prolonging the reaction time (2 days) and slightly better conversion was observed (50%). After checking carefully the ^{1}H NMR of the mixture, we confirmed that the new product was not the expected product since the methyl group from the ester was not present anymore. All our attempts to purify and identify this new product were unsuccessful.



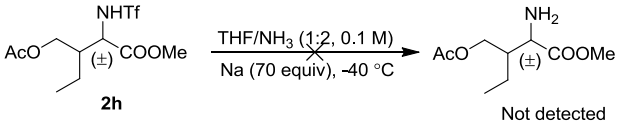
Scheme 2.5 Introduction of the 4-nitrobenzyl group to **(±)-2h**

Then, we decided to study the deprotection of the Tf-protecting group of an amino alcohol. To save some synthetic efforts, we decided to use methyl *N*-triflyl-L-valinate **1w** for our investigation instead of the corresponding acetoxylated product. We tried to install 4-nitrobenzyl under similar reaction conditions that we used before (Scheme 2.6). However, no desired product was observed although more than 60% conversion was detected.



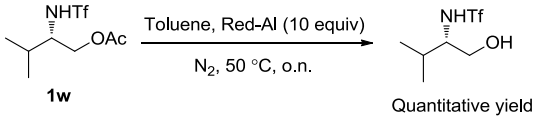
Scheme 2.6 Introduction of the 4-nitrobenzyl group to **1w**

Since this stepwise strategy did not work with our substrates, we decided to test other deprotection methods. The deprotection of Tf-protecting group from a β-amino acid was previously reported using a reducing NH_3/Na mixture.[31] Unfortunately, the reaction of **2h** under these conditions did not provide the desired product (Scheme 2.7).



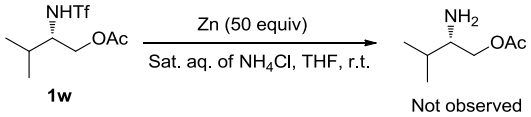
Scheme 2.7 Tf-deprotection using NH_3/Na

We also tried the deprotection of **1w** using Red-Al, that is used for the deprotection of Tf-protecting group from tertiary sulfonamides.[32] However, in our case, only the product coming from the reduction of the acetoxy group was obtained in quantitative yield (Scheme 2.8).



Scheme 2.8 Tf-deprotection using Red-Al

Finally, Zn/NH_4Cl is used to deprotect other sulfonyl protecting group form nitrogen[27] and we tried this method with **1w** as well. However, no conversion was observed. We also tried Mg/MeOH with **1w** and no product was detected.



Scheme 2.8 Tf-deprotection using Zn/NH_4Cl

2.3 Conclusions

In conclusion, we have developed a Pd-catalyzed γ-selective C(sp^3)–H acetoxylation of *N*-triflylamines assisted by external pyridine based-ligands. The reaction was highly diastereoselective giving the acetoxylated products in modest to good yields. Only amines bearing an electron-withdrawing group at adjacent position of the amino group were efficiently acetoxylated. The deprotection of the Tf protecting group in our substrates was unsuccessful. We have also evaluated similar protecting groups but the C–H activation was not taking place efficiently, highlighting the key role of the pKa of the protecting group in these transformations.

2.4 Acknowledgement

Durmus Özbay is kindly acknowledged for his contribution to this chapter. I would also like to thank Ed Zuidinga and Dorette Tromp for the HRMS measurements.

2.5 Experimental Section

General Information

Chromatography: Silicycle Silica Flash P60 size 40-63 μm (230-400 mesh), TLC: Merck silica gel 60 (0.25mm). Visualization of the chromatogram was performed by UV, phosphomolybdic acid, $KMnO_4$ and ninhydrin staining. Mass spectra were recorded on AccuTOF GC v 4g, JMS-T100GCV mass spectrometers. ^1H and ^{13}C were recorded on Bruker 500 AMX, 400 and Bruker DRX 300 using $CDCl_3$ as solvent. Chemical shift values are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: δ 7.26 for ^1H, δ 77.16 for ^{13}C). Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), and integration. IR spectra were recorded on a Bruker Alpha FTIR machine and wavelengths are reported in cm^{-1}. Dichloromethane was dried over CaH_2 and was used freshly after distillation. All reagents and solvents were used as received. $Pd(OAc)_2$ was purchased from Strem. $Pd(OPiv)_2$ was purchased from Sigma-Aldrich. **L20** - **L23** were prepared following the procedure previously reported.[26] The rest of ligands used were purchased and used as received. The melting points were measured using a Büchi Melting Point M-565 apparatus.

2.5.1 Synthesis of triflyl-protected amines

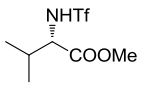
General procedure A for the synthesis of amine ester hydrochloride salt

To a suspension of amino acid (1.0 equiv) in MeOH or EtOH (0.3 M) at 0 ℃ was added thionyl chloride (5.0 equiv) dropwise. The reaction mixture was then heated to reflux and stirred for 3~5 hours. The volatiles were removed *in vacuo* to give the product which was used for the next step without any purification. Ethyl L-valinate hydrochloride, methyl DL-allo-isoleucinate hydrochloride, methyl DL-β-leucinate hydrochloride, methyl L-homophenylalaninate hydrochloride and (*R*)-methyl 2-cyclopropyl-2-amino acetate hydrochloride were prepared using this method.

General procedure B for the synthesis of N-triflyl protected substrates

A reported procedure was followed.[33] In a flame-dried schlenk flask, amine hydrochloride salt (1.0 equiv) (either purchased or prepared from amino acid as indicated for each case) or amine (1.0 equiv), was dissolved in CH_2Cl_2 (0.5 M) and then cooled to -78 ℃. Triethyl amine (2.0 equiv for amine hydrochloride salt; 1.0 equiv for amine) was added and the resulting mixture was stirred for 5 minutes. Trifluoromethanesulfonic anhydride (1.05 equiv) was added dropwise and the reaction was left to stir for 1~2 hours at -78 ℃. The reaction was then warmed up to room temperature slowly and then, ice was added into the reaction. The organic layer was separated and the aqueous layer was extracted with DCM twice. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The products were purified by flash column chromatography on silica gel.

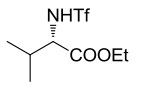
Methyl *N*-triflyl-L-valinate (1a)



1a

Substrate **1a** was prepared from commercially available methyl L-valinate hydrochloride following **general procedure B** in 86% isolated yield after purification by flash column chromatography on silica gel (PE:EtOAc, 8:1), and its ^{1}H NMR data matched with those reported in the literature.[33] **^{1}H NMR** (400 MHz), δ 5.47 (d, *J* = 9.8 Hz, 1H), 4.07 (dd, *J* = 9.9, 4.6 Hz, 1H), 3.81 (s, 3H), 2.63 – 2.10 (m, 1H), 1.04 (d, *J* = 6.9 Hz, 3H), 0.93 (d, *J* = 6.9 Hz, 3H).

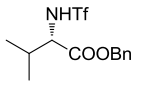
Ethyl *N*-triflyl-L-valinate (1b)



1b

Substrate **1b** was prepared from L-valine following **general procedures A** and **B** as a white solid in 78% isolated yield over two steps after purification by flash column chromatography on silica gel (PE:EtOAc, 8:1). **^{1}H NMR** (300 MHz) δ 5.48 (d, *J* = 9.7 Hz, 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 4.05 (dd, *J* = 9.8, 4.6 Hz, 1H), 2.29 – 2.14 (m, 1H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.05 (d, *J* = 6.8 Hz, 3H), 0.93 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR** (75 MHz) δ 170.44, 119.67 (q, *J* = 318.8 Hz), 62.52, 62.43, 31.75, 18.96, 17.12, 14.25. **IR**: ν 3267, 2973, 2942, 1726, 1450, 1380, 1187, 1137, 1048, 1022, 609, 583, 514 cm^{-1}. **HRMS** (FD) calculated for $C_8H_{14}F_3NO_4S^+$ $[M]^+$: 277.0596; found: 277.0288. mp: 55.2 – 57.4 ℃.

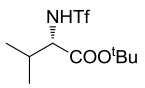
Benzyl *N*-triflyl-L-valinate (1c)



1c

Substrate **1c** was prepared from commercially available benzyl L-valinate hydrochloride following **general procedure B** as a colorless oil in 93% isolated yield after purification by flash column chromatography on silica gel (PE:EtOAc, 10:1). **^{1}H NMR** (400 MHz) δ 7.39 – 7.33 (m, 5H), 5.63 (d, *J* = 9.2 Hz, 1H), 5.33 – 4.76 (m, 2H), 4.10 (dd, *J* = 9.5, 4.6 Hz, 1H), 2.27 – 2.15 (m, *J* = 6.9, 4.5 Hz, 1H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR** (100 MHz) δ 170.45, 134.70, 129.00, 128.86, 128.77, 119.65 (q, *J* = 319.1), 68.17, 62.51, 31.75, 18.96, 17.00. **IR**: ν 3264, 2971, 1728, 1454, 1374, 1232, 1187, 1134, 1049, 751, 697, 610, 580 cm^{-1}. **HRMS** (FD) calculated for $C_{13}H_{16}F_3NO_4S^+$ $[M]^+$: 335.0752; found: 335.0760.

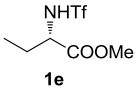
***Tert*-butyl *N*-triflyl-L-valinate (1d)**



1d

Substrate **1d** was prepared from commercially available *tert*-butyl L-valinate hydrochloride following **general procedure B** as a yellow solid in 81% isolated yield after purification by flash column chromatography on silica gel (PE:EtOAc, 10:1). **^{1}H NMR** (400 MHz) δ 5.43 (d, J = 9.7 Hz, 1H), 3.93 (dd, J = 9.8, 4.5 Hz, 1H), 2.22 – 2.14 (m, 1H), 1.48 (d, J = 2.6 Hz, 9H), 1.04 (d, J = 6.8 Hz, 3H), 0.92 (d, J = 6.9 Hz, 3H). **^{13}C NMR** (100 MHz) δ 169.52, 119.75 (q, *J* = 321.5 Hz), 83.75, 62.95, 31.78, 28.01, 18.97, 17.07. **IR**: ν 3222.74, 2976.17, 1709.66, 1371.84, 1184.43, 1148.35, 604.43, 512.79 cm^{-1}. **HRMS** (FD) calculated for $C_5H_9F_3NO_2S^+$ $[M\text{-}COO^tBu]^+$: 204.0306; found: 204.0355. mp: 78 – 80 ℃.

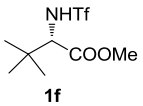
Methyl *N*-triflyl-L-homoalaninate (1e)



1e

Substrate **1e** was prepared from commercially available methyl L-homoalaninate hydrochloride following **general procedure B** in 71% isolated yield after purification by flash column chromatography on silica gel (PE:EtOAc, 8:1), and its ^{1}H NMR data matched with those reported in the literature.[33] **^{1}H NMR** (300 MHz) δ 5.50 (d, *J* = 8.9 Hz, 1H), 4.25 – 4.18 (m, 1H), 3.82 (s, 3H), 2.04 – 1.71 (m, 2H), 0.99 (t, *J* = 7.4 Hz, 3H).

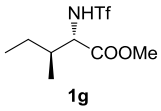
Methyl *N*-triflyl-L-*tert*-leucinate (1f)



1f

Substrate **1f** was prepared from commercially available methyl L-*tert*-leucine ester hydrochloride following **general procedure B** in 89% isolated yield after purification by flash column chromatography on silica gel (PE:EtOAc, 12:1). and its ^{1}H NMR matched with those reported in the literature.[33] **^{1}H NMR** (400 MHz) δ 5.50 (d, *J* = 8.7 Hz, 1H), 3.90 (d, *J* = 1.02 Hz, 1H), 3.80 (s, 3H), 1.04 (s, 3H), 1.03 (s, 3H).

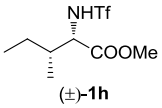
Methyl *N*-triflyl-L-isoleucinate (1g)



1g

Substrate **1g** was prepared from commercially available methyl L-isoleucinate hydrochloride following **general procedure B** after purification by flash column chromatography on silica gel (PE:EtOAc, 8:1), and its ^{1}H NMR matched with those reported in the literature.[34] **^{1}H NMR** (300 MHz) δ 5.48 (d, *J* = 9.5 Hz, 1 H), 4.13 (dd, *J* = 9.7, 4.8 Hz, 1 H), 3.81 (s, 3H), 2.00 – 1.72 (m, 1H), 1.50 – 1.29 (m, 1H), 1.28 – 1.07 (m, 1H), 0.99 (d, *J* = 6.8 Hz, 3 H), 0.94 (t, *J* = 7.3 Hz, 3 H).

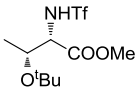
Methyl *N*-triflyl-DL-alloisoleucinate [(±)-1h]



(±)-**1h**

Substrate **(±)-1h** was prepared from DL-alloisoleucine following **general procedures A** and **B** in 87% isolated yield over two steps after purification by flash column chromatography on silica gel (PE:EtOAc, 8:1), and its ^{1}H NMR data matched with those reported in the literature.[34] **^{1}H NMR** (300 MHz) δ 5.39 (d, *J* = 10.0 Hz, 1H), 4.21 (dd, *J* = 9.9, 3.8 Hz, 1H), 3.81 (s, 3H), 1.95 (qd, *J* = 6.8, 3.7 Hz, 1H), 1.61 – 1.44 (m, 2H), 1.40 – 1.19 (m, 1H), 0.97 (t, *J* = 7.4 Hz, 3H), 0.88 (d, *J* = 6.9 Hz, 3H).

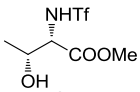
Methyl *O*-(*tert*-butyl)-*N*-triflyl-L-threoninate (1m)



1m

Substrate **1m** was prepared from commercially available methyl *O*-(*tert*-butyl)-L-threoninate hydrochloride following **general procedure B** in 49% isolated yield after purification by flash column chromatography on silica gel (PE:EtOAc, 15:1), and its ^{1}H NMR data matched with those reported in the literature.[34] **^{1}H NMR** (300 MHz) δ 5.68 (d, *J* = 10.0 Hz, 1H), 4.48 – 4.09 (m, 1H), 3.99 (d, *J* = 10.0 Hz, 1H), 3.78 (s, 1H), 1.29 (dd, *J* = 6.2, 1.7 Hz, 3H), 1.11 (s, 9H).

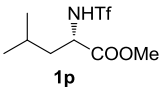
Methyl *N*-triflyl-L-threoninate (1n)



1n

Substrate **1n** was prepared from commercially available methyl L-threoninate hydrochloride following **general procedure B** in 69% isolated yield after purification by flash column chromatography on silica gel (PE:EtOAc, 4:1). **^{1}H NMR** (400 MHz) δ 6.11 (d, *J* = 8.4 Hz, 1H), 4.43 (d, *J* = 5.8 Hz, 1H), 4.08 (dd, *J* = 9.8, 1.4 Hz, 1H), 3.84 (s, 3H), 2.10 (bs, 1H), 1.36 (d, *J* = 6.4 Hz, 3H).

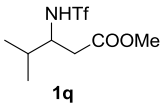
***N*-Triflyl-L-leucinate (1p)**



1p

Substrate **1p** was prepared from commercially available methyl L-Leucinate hydrochloride following **general procedure B** (3.0 equiv of Et_3N and 1.5 equiv of Tf_2O) in 79% isolated yield after purification by flash column chromatography on silica gel (PE:EtOAc, 6:1). Its ^{1}H NMR data matched with those reported in the literature.[35] **^{1}H NMR** (400 MHz) δ 5.35 (d, *J* = 9.6 Hz, 1H), 4.26 – 4.20 (m, 1H), 3.80 (s, 3H), 1.85 – 1.74 (m, 1H), 1.71 – 1.58 (m, 2H), 0.98 (d, *J* = 6.4 Hz, 3H), 0.97 (d, *J* = 6.4 Hz, 3H).

Methyl *N*-triflyl-DL-β-leucinate (1q)

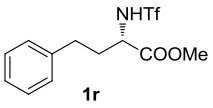


1q

Substrate **1q** was prepared from DL-β-Leucine following **general procedures A and B** in 70% isolated yield after purification by flash column chromatography on silica gel (PE:EtOAc, 6:1). **^{1}H NMR** (400 MHz) δ 5.86 (d, *J* = 9.1 Hz, 1H), 3.76 (s, 3H), 3.73 – 3.49 (m, 1H), 2.73 – 2.63

(m, 2H), 2.00 – 1.88 (m, 1H), 1.03 (d, *J* = 6.8 Hz, 3H), 0.96 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR** (100 MHz) δ 171.9, 119.5 (q, *J* = 255.2 Hz), 58.4, 52.1, 36.2, 31.9, 19.0, 18.95. **HRMS** (FD) calculated for $C_8H_{18}F_3NO_4S^+$ $[M]^+$: 277.0596; found: 277.0590.

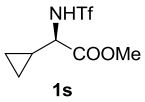
Methyl *N*-triflyl-L-homophenylalaninate (1r)



1r

Substrate **1r** was prepared from L-homophenylalanine following **general procedures A and B** in 33% isolated yield over two steps after purification by flash column chromatography on silica gel (PE:EtOAc, 12:1) and its ^{1}H NMR data matched with those reported in the literature.[33] **^{1}H NMR** (400 MHz) δ 7.33 – 7.29 (m, 2H), 7.24 – 7.17 (m, 3H), 5.62 (d, *J* = 8.3 Hz, 1H), 4.32 – 4.27 (m, 1H), 3.78 (s, 3H), 2.73 (t, *J* = 7.9 Hz, 2H), 2.28 – 2.19 (m, 1H), 2.12 – 2.03 (m, 1H).

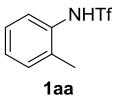
(*R*)-Methyl 2-cyclopropyl-2-(trifluoromethylsulfonamido)acetate (1s)



1s

Substrate **1s** was prepared from methyl (*R*)-α-Amino cyclopropaneacetic acid following **general procedure A and B** in 71% isolated yield over two steps after purification by flash column chromatography (PE:EtOAc, 10:1). Its ^{1}H NMR data matched with those reported in the literature.[30] **^{1}H NMR** (400 MHz) δ 5.56 (bs, 1H), 3.83 (s, 3H), 3.68 – 3.64 (m, 1H), 1.19 – 1.10 (m, 1H), 0.70 – 0.49 (m, 4H).

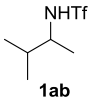
2-Methyl-*N*-triflyl aniline (1aa)



1aa

Substrate **1aa** was prepared from 2-methylaniline following **general procedure B** in 92% isolated yield after purification by flash column chromatography on silica gel (PE:EtOAc, 7:1). Its ^{1}H NMR data matched with those reported in the literature.[33] **^{1}H NMR** (400 MHz) δ 7.41 – 7.39 (m, 1H), 7.27 – 7.23 (m, 2H), 6.48 (bs, 1H), 2.38 (s, 3H).

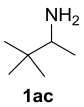
***N*-Triflyl-3-methylbutan-2-amine (1ab)**



1ab

Substrate **1ab** was prepared from 3-methylbutan-2-amine following **general procedure B** in 91% isolated yield after purification by flash column chromatography on silica gel (PE:EtOAc, 8:1). Its ^{1}H NMR data matched with those reported in the literature.[36] **^{1}H NMR** (400 MHz) δ 4.56 (bs, 1H), 3.56 – 3.47 (m, 1H), 1.82 – 1.73 (m, 1H), 1.24 (d, *J* = 6.6 Hz, 3H), 0.96 (d, *J* = 6.4 Hz, 3H), 0.95 (d, *J* = 6.4 Hz, 3H).

***N*-Triflyl-3,3-dimethylbutan-2-amine (1ac)**



1ac

Substrate **1ac** was prepared from 3,3-dimethylbutan-2-amine following **general procedure B** in 78% isolated yield after purification by flash column chromatography on silica gel (PE:EtOAc, 8:1). Its ^{1}H NMR data matched with those reported in the literature.[34] **^{1}H NMR** (400 MHz) δ 4.61 (d, *J* = 6.8 Hz, 1H), 3.47 – 3.35 (m, 1H), 1.24 (d, *J* = 8.8 Hz, 3H), 0.96 (s, 6H).

***N*-Triflyl-2-methylbutan-2-amine (1ad)**

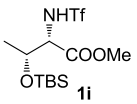
1ad

Substrate **1ad** was prepared from 2-methyl-2-butanamine following **general procedure B** in 86% isolated yield after purification by flash column chromatography on silica gel (PE:EtOAc, 8:1). Its ^{1}H NMR data matched with those reported in the literature.[37] **^{1}H NMR** (400 MHz) δ 4.51 (bs, 1H), 1.67 (q, *J* = 7.4 Hz, 2H), 1.39 (s, 6H), 0.97 (t, *J* = 7.4 Hz, 3H).

General procedure C for the preparation of TBS-protected substrates

In a flame-dried schlenk flask, substrate (1.0 equiv) was dispersed in DCM (0.3 M) and then imidazole (3.0 equiv) was added. The reaction was stirred for another 30 minutes, and TBSCl (1.1 equiv) was added. The reaction mixture was then stirred overnight. The solvent was evaporated *in vacuo*, and the residue was dissolved in water and EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc five times. The combined organic layer was dried with Na_2SO_4, filtered and concentrated. The products were purified by flash column chromatography on silica gel. For the following Tf protection of these products, **General procedure B** was followed.

Methyl *O*-(*tert*-butyldimethylsilyl)-*N*-triflyl-L-threoninate (1i)

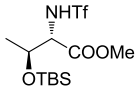


1i

Substrate **1i** was prepared from L-threonine methyl ester hydrochloride following **general procedure C** as a colorless oil in 50% overall isolated yield over two steps (69% and 72% separately) after purification by flash column chromatography on silica gel (PE:EtOAc, 12:1). **^{1}H**

NMR (400 MHz) δ 5.49 (d, *J* = 10.2 Hz, 1H), 4.45 (qd, *J* = 6.3, 1.7 Hz, 1H), 4.02 (d, *J* = 10.1 Hz, 1H), 3.79 (s, 3H), 1.29 (d, *J* = 6.3 Hz, 3H), 0.85 (s, 9H), 0.06 (s, 3H), 0.00 (s, 3H). **^{13}C NMR** (75 MHz) δ 169.55, 119.57 (q, *J* = 318.8 Hz), 68.89, 63.08, 53.06, 25.70, 20.84, 17.96, -4.25, -5.22. **IR**: ν 3299, 2957, 2933, 2990, 2860, 1754, 1430, 1378, 1189, 1144, 1090, 978, 837, 826, 809, 775, 614, 592, 499, 462 cm^{-1}. **HRMS** (FD) calculated for $C_8H_{15}F_3NO_5SSi^+$ [M-^{t}Bu]$^+$: 322.0392; found: 322.0390.

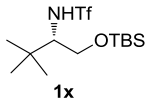
Methyl *O*-(*tert*-butyldimethylsilyl)-*N*-triflyl-L-allothreoninate (1j)



1j

Substrate **1j** was prepared from L-allothreonine methyl ester hydrochloride following **general procedure C** as a colorless oil in 75% overall isolated yield over two steps (93% and 81% separately) after purification by flash column chromatography on silica gel (PE:EtOAc, 12:1). **^{1}H NMR** (300 MHz) δ 5.62 (d, *J* = 9.0 Hz, 1H), 4.78 – 4.00 (m, 2H), 3.81 (s, 3H), 1.27 (d, *J* = 6.2 Hz, 3H), 0.88 (s, 9H), 0.09 – 0.08 (m, 6H). **^{13}C NMR** (75 MHz) δ 168.84, 119.71 (q, *J* = 303.2), 70.73, 62.77, 52.97, 25.72, 20.38, 18.02, -4.32, -4.95. **IR**: ν 3263, 2958, 2933, 2890, 2860, 1736, 1437, 1388, 1260, 1235, 1196, 1148, 997, 833, 779, 609 cm^{-1}. **HRMS** (FD) calculated for $C_8H_{15}F_3NO_5SSi^+$ [M-^{t}Bu]$^+$: 322.0392; found: 322.0389.

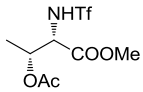
***N*-Triflyl-*O*-TBS-L-tert-leucinol (1x)**



1x

Substrate **1x** was prepared from L-tert-leucinaol following **general procedure C** as a colorless oil in 52% overall isolated yield over two steps (61% and 86% separately) after purification by flash column chromatography on silica gel (PE:EtOAc, 25:1). Its ^{1}H NMR data matched with those reported in the literature.[34] **^{1}H NMR** (400 MHz) δ 5.26 (d, *J* = 1.0 Hz, 1H), 3.90 (d, *J* = 9.2 Hz, 1H), 3.71 (dd, *J* = 10.7, 4.3 Hz, 1H), 3.24 (d, *J* = 7.3 Hz, 1 H), 1.00 (s, 9H), 0.90 (s, 9H), 0.08 (s, 6H).

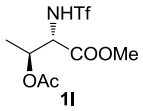
Methyl *O*-acetyl-*N*-triflyl-L-threoninate (1k)



1k

Methyl *N*-triflyl-L-threoninate (**1n**) (780 mg, 2.94 mmol, 1.0 equiv) was dissolved in 10 mL of anhydrous DCM and cooled to 0 ℃. Triethyl amine (620 μL, 4.41 mmol, 1.5 equiv) was then added, followed by dropwise addition of Ac_2O (280 μL, 2.94 mmol, 1.0 equiv). The reaction was then warmed up to room temperature and stirred overnight. The reaction was diluted with DCM and washed with brine twice. Organic layer was dried with Na_2SO_4, filtrated and concentrated *in vacuo*. The product was obtained as a colorless oil after purification by flash column chromatography on silica gel (PE:EtOAc, 8:1). **^{1}H NMR** (400 MHz) δ 5.65 (d, *J* = 10.1 Hz, 1H), 5.45 – 5.40 (m, 1H), 4.19 (d, *J* = 10.1 Hz, 1H), 3.80 (s, 3H), 2.04 (s, 3H), 1.39 (d, *J* = 6.4 Hz, 1H).

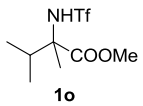
Methyl *O*-acetyl-*N*-triflyl-L-allothreoninate (1l)



1l

Methyl *O*-acetyl-*N*-triflyl-L-allothreoninate **1l** was synthesized as a colorless oil from methyl L-allothreoninate hydrochloride using the same strategy for the preparation of methyl *O*-acetyl-*N*-triflyl-L-allothreoninate (**1k**) in 45% overall yield over two steps (73% for the first step, 62% for the second step) after purification by flash column chromatography on silica gel (PE:EtOAc, 4:1). **^{1}H NMR** (400 MHz) δ 5.82 (d, *J* = 9.3 Hz, 1H), 5.21 – 5.15 (m, 1H), 4.51 (dd, *J* = 9.1, 3.1 Hz, 1H), 3.86 (s, 3H), 2.09 (s, 3H), 1.27 (d, *J* = 6.6 Hz, 3H). **^{13}C NMR** (100 MHz) δ 170.7, 168.3, 119.4 (q, *J* = 255.2 Hz), 69.6, 59.5, 53.4, 20.8, 15.0. **HRMS** (FD) calculated for $C_8H_{12}F_3NO_6S^+$ [M]$^+$: 307.0337; found: 307.0328.

Methyl *N*-triflyl-2-methyl-DL-valinate (1o)



1o

To the solution of α-methyl-DL-valine (450 mg, 3.44 mmol) in MeOH was added concentrated H_2SO_4 (5 mL). The reaction was then stirred under reflux overnight. After cooling to room temperature, the volatiles were removed *in vacuo*. EtOAc (30 mL) and saturated $NaHCO_3$ aqueous solution (30 mL) were added and transferred to a separation funnel. Organic layer was collected, dried with Na_2SO_4, filtered, concentrated *in vacuo*, giving methyl α-methyl-DL-valinate as a colorless oil (240 mg, 48%), which was pure enough to be used directly for the next step. (*Note: **general procedure A** did not work well for this substrate for the preparation of amino ester hydrochloride salt.*) General procedure B was then followed for the Tf protection of this product. The product was obtained as a pale yellow oil (309 mg, 70% over two steps) after purification by flash column chromatography on silica gel (PE:EtOAc, 7:1). **^{1}H NMR** (400 MHz) δ 5.36 (bs, 1H), 3.81 (s, 3H), 2.20 – 2.06 (m, 3H), 1.62 (s, 3H), 0.98 (s, 3H), 0.96 (s, 3H).

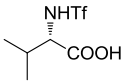
General procedure for the preparation of dipeptides

Step A: Methyl *N*-triflyl amino ester (**1a** or **1h**) (1.0 equiv) was mixed with THF/H_2O/MeOH (2.6:1:1, v/v/v, 2.0

M). LiOH (2.0 M in water, 6.0 equiv) was then added and the reaction was stirred overnight at room temperature. The reaction was acidified with 1 M HCl to pH < 3 and the mixture was extracted with EtOAc three times. The combined organic extracts were dried with Na_2SO_4, filtrated and concentrated *in vacuo* to give the amino acid (together with a small amount of starting material).

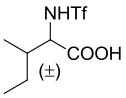
Step B: In a round bottom flask was successively added the crude *N*-triflyl amino acid (1.0 equiv), methyl glycinate hydrochloride (1.0 equiv), HOBt·H_2O (1.1 equiv), EDC·HCl (1.1 equiv), Et_3N (2.0 equiv) and DCM (10 mL). The reaction was then stirred overnight at room temperature. The reaction was then diluted with EtOAc and transferred to a separation funnel. The mixture was sequentially washed with citric acid solution (in water, 0.5 M) four times, saturated aqueous solution of $NaHCO_3$ and brine. The organic layer was dried with Na_2SO_4, filtrated and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel.

_N_-Triflyl-DL-alloisoleucine



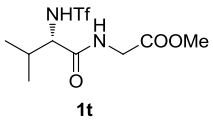
N-Triflyl-DL-alloisoleucine was prepared following the general procedure from methyl *N*-triflyl-L-valinate (**1a**) (3.4 mmol). A mixture of hydrolyzed product and starting material (3:1) was obtained. The crude mixture was used in the next step without purification. Its ^{1}H NMR data matched with those reported in the literature.[38] **^{1}H NMR** (400 MHz) δ 5.57 (d, *J* = 9.6 Hz, 1H), 4.15 (dd, *J* = 12.1, 4.4 Hz, 1H), 2.34 – 2.28 (m, 1H), 1.09 (d, *J* = 6.8 Hz, 3H), 0.97 (d, *J* = 6.8 Hz, 3H).

_N_-Triflyl-DL-alloisoleucine



N-Triflyl-DL-alloisoleucine was prepared following the general procedure from methyl *N*-triflyl-DL-alloisoleucinate (**1h**) (2.2 mmol). A mixture of hydrolyzed product and starting material (4.2:1) was obtained. The crude mixture was used in the next step without purification. Its ^{1}H NMR data matched with those reported in the literature.[38] **^{1}H NMR** (400 MHz) δ 5.60 (d, *J* = 9.9 HZ, 1H), 4.29 (dd, *J* = 9.8, 2.5 Hz, 1H), 2.10 – 2.00 (m, 1H), 1.60 – 1.47 (m, 1H), 1.41 – 1.28 (m, 1H), 0.99 (t, *J* = 7.4Hz, 3H), 0.93 (d, *J* = 6.8 Hz, 3H).

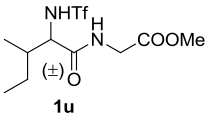
Methyl _N_-triflyl-L-Valylglycinate (1t)



1t

N-Triflyl-L-Valylglycinate (**1t**) was prepared following the general procedure by coupling *N*-triflyl-L-valine with methyl glycinate hydrochloride after purification by flash column chromatography on silica gel (PE:EtOAc, 4:1) as a white solid (24% over two steps). **^{1}H NMR** (400 MHz) δ 6.23 (bs, 1H), 6.02 (d, *J* = 9.2 Hz, 1H), 4.16 (dd, *J* = 18.4, 5.3 Hz, 1H), 4.06 (dd, *J* = 18.4, 4.9 Hz, 1H), 3.88 (dd, *J* = 9.1, 5.6 Hz, 1H), 3.79 (s, 3H), 2.17 – 2.08 (m, 1H), 1.06 (d, *J* = 6.8 Hz, 3H), 1.00 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR** (125 MHz) δ 170.1, 169.9, 119.7 (q, J = 320.0 Hz), 63.5, 52.9, 41.5, 32.3, 19.0, 17.6.

Methyl _N_-triflyl-DL-alloisoleucylglycinate (±)-1u



1u

N-Triflyl-DL-alloisoleucylglycinate (**1u**) was prepared following the procedure above by coupling *N*-triflyl-DL-alloisoleucine with methyl glycinate hydrochloride after purification by flash column chromatography on silica gel (PE:EtOAc, 4:1) as a white solid (37% over two steps). **^{1}H NMR** (400 MHz) δ 6.26 (bs, 1H), 6.13 (d, J = 9.1 Hz, 1H), 4.18 – 4.01 (m, 3H), 3.79 (s, 3H), 1.90 – 1.81 (m, 1H), 1.60 – 1.50 (m, 1H), 1.33 – 1.22 (m, 1H), 0.99 – 0.94 (m, 6H).

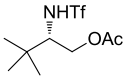
General procedure D for the preparation of O-acetyl-N-triflyl amino alcohols[34]

Step A: In a flame-dried schlenk flask, an amino alcohol (1.0 equiv) was dissolved in CH_2Cl_2 (0.3 M) and cooled to 0 ℃. Triethylamine (1.0 equiv) was added followed by dropwise addition of trifluoromethanesulfonic anhydride (1.1 equiv). The reaction was stirred for 10 minutes and was poured into a separation funnel. After being washed with brine twice, the organic layer was dried with Na_2SO_4, filtered, concentrated *in vacuo*. The obtained crude product could be used for the next step without any purification.

Step B: In a flame-dried schlenk flask, triflyl-protected amino alcohol (1.0 equiv) was mixed with trimethylamine (1.5 equiv) in CH_2Cl_2 (0.5 M) and cooled to 0 ℃. Ac_2O (1.0 equiv) was added dropwise and the reaction was warmed to room temperature. The reaction was stirred overnight, and then poured into a separation funnel. The reaction was then extracted with EtOAc three times. The combined organic extracts were washed with brine twice, dried with Na_2SO_4, filtered and concentrated *in vacuo*. The products were purified by flash

column chromatography on silica gel.

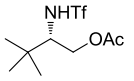
***O*-Acetyl-*N*-triflyl-L-*tert*-leucinol (1v)**



1v

Substrate **1v** was prepared from L-*tert*-leucinol following **general procedure D** after purification by flash column chromatography on silica gel (8:1, PE:EtOAc), and its ^{1}H NMR data matched with those reported in the literature.[34] **^{1}H NMR** (400 MHz) δ 4.82 (d, *J* = 10.1 Hz, 1H), 4.29 (dd, *J* = 12.1, 3.7 Hz, 1H), 4.14 (dd, *J* = 12.0, 8.2 Hz, 1H), 3.53 (ddd, *J* = 10.3, 8.1, 3.7 Hz, 1H), 2.10 (s, 3H), 1.03 (s, 9H).

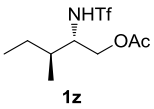
***O*-Acetyl-*N*-triflyl-L-valinol (1w)**



1w

Substrate **1w** was prepared from L-valinol following **general procedure D** after purification by flash column chromatography on silica gel (PE:EtOAc, 8:1), and its ^{1}H NMR data matched with those reported in the literature.[34] **^{1}H NMR** (400 MHz) δ 5.07 (d, *J* = 9.6 Hz, 1H), 4.23 (dd, *J* = 11.9, 6.9 Hz, 1H), 4.15 (dd, *J* = 11.9, 3.9 Hz, 1H), 3.57 (dtd, *J* = 10.3, 6.6, 3.9 Hz, 1H), 2.10 (s, 3H), 2.00 – 1.75 (m, *J* = 6.8 Hz, 1H), 1.03 – 1.01 (m, *J* = 6.9, 3.4 Hz, 6H).

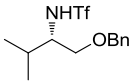
***O*-Acetyl-*N*-triflyl-L-isoleucinol (1z)**



1z

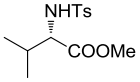
Substrate **1z** was prepared from L-isoleucinol following **general procedure D** after purification by flash column chromatography on silica gel (PE:EtOAc, 8:1), and its ^{1}H NMR data matched with those reported in the literature. **^{1}H NMR** (400 MHz) δ 5.06 (d, *J* = 9.6 Hz, 1H), 4.22 (dd, *J* = 12.0, 7.4 Hz, 1H), 4.14 (d, *J* = 12.0, 3.7 Hz, 1H), 3.71 – 3.64 (m, 1H), 2.10 (s, 1H), 1.76 – 1.66 (m, 1H), 1.60 – 1.50 (m, 1H), 1.27 – 1.16 (m, 1H), 0.98 – 0.94 (m, 6H).

***O*-Benzyl-*N*-Triflyl-L-tert-leucinol (1y)**



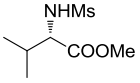
A reported procedure was followed for the benzyl protection.[38] To a solution of L-valinol (516 mg, 5.0mmol, 1.0 equiv) in anhydrous THF (3 mL) was added NaH (300 mg, 60% in paraffin oil, 7.5 mmol, 1.5 equiv) and the resulting suspension was first stirred at room temperature for 15 min and then stirred under reflux for 30 min. Benzyl chloride (575 μL, 5.0 mmol, 1.0 equiv) was then added and the mixture was stirred for another 48 h under reflux. After the reaction was cooled to room temperature, NaOMe (56 mg, 1.0 mmol) was added in one portion and the reaction was stirred for another 30 min. Water was added carefully and the volatiles were removed *in vacuo*. To the residue was added KOH aqueous solution (6 M, 3 mL), brine and DCM. Organic layer was collected, dried over Na_2SO_4, filtrated and concentrated *in vacuo*. The product was isolated as a colorless oil (860 mg, 83%) after purification by flash column chromatography on silica gel (95:5:1, EtOAc:MeOH:Et_3N). The Tf protection was performed (2.0 mmol) by following **general procedure B**, giving *O*-benzyl-*N*-Triflyl-L-*tert*-leucinol as a colorless oil (651 mg, 97%) after purification by flash column chromatography on silica gel (PE:EtOAc, 8:1). **^{1}H NMR** (400 MHz) δ 7.38 – 7.26 (m, 5H), 5.11 (d, *J* = 9.0 Hz, 1H), 4.55 (d, *J* = 11.9 Hz, 1H), 4.50 (d, *J* = 11.8 Hz, 1H), 3.64 (dd, *J* = 9.6, 2.1Hz, 1H), 3.52 (dd, *J* = 9.6, 3.2Hz, 1H), 3.39 – 3.33 (m, 1H), 2.04 – 1.94 (m, 1H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.96 (d, *J* = 6.8 Hz, 3H).

Methyl *N*-tosyl-L-valinate



A reported procedure was followed.[27] In a round bottom flask, L-valine methyl ester hydrochloride (551 mg, 3.3 mmol, 1.0 equiv) was suspended in anhydrous CH_3CN (40 mL) under N_2. Pyridine (2.84 mL, 19.8 mmol, 6.0 equiv) and 4-toluenesulfonyl chloride (935 mg, 4.9 mmol, 1.5 equiv) were added successively. The reaction was then stirred overnight before the volatiles were removed *in vacuo*. The residue was dissolved in EtOAc and washed with 1 M HCl two times. The combined aqueous layers were extracted with EtOAc three times. The combined organic extracts were dried with Na_2SO_4, filtered and concentrated *in vacuo*. The product was obtained as a white solid (871 mg, 93%) after purification by flash column chromatography on silica gel (PE:EtOAc, 5:1). Its ^{1}H NMR data matched with those reported in the literature.[27] **^{1}H NMR** (400 MHz) δ 7.72 – 7.69 (m, 2H), 7.29 – 7.26 (m, 2H), 5.03 (d, *J* = 10.1 Hz, 1H), 3.73 (dd, *J* = 10.1, 5.1 Hz, 1H), 3.44 (s, 3H), 2.41 (s, 3H), 2.04 – 1.98 (m, 1H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.87 (d, *J* = 6.8 Hz, 3H).

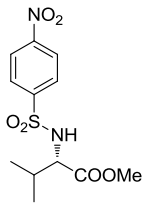
Methyl *N*-mesyl-L-valinate



A reported procedure was followed.[39] In a round bottom flask was added L-valine methyl ester hydrochloride (503 mg, 3.0 mmol, 1.0 equiv) and anhydrous DCM (30 mL) at 0 ℃. Diisopropylethyl amine (992 μL, 6.0 mmol, 2.0 equiv) was then added followed by dropwise

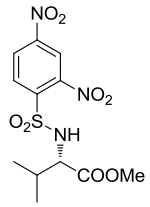
addition of methanesulfonyl chloride (278μL, 3.6 mmol, 1.2 equiv). The reaction was warmed up to room temperature before it was stirred overnight. Water was added and the reaction was extracted with EtOAc three times. The combined organic extracts were dried with Na_2SO_4, filtered and concentrated *in vacuo*. The product was obtained as a colorless oil (517 mg, 82%) after purification by flash column chromatography on silica gel (PE:EtOAc, 3:1). Its ^{1}H NMR data matched with those reported in the literature.[39] **^{1}H NMR** (400 MHz) δ 4.86 (d, *J* = 9.6 Hz, 1H), 3.96 (dd, *J* = 9.9, 4.5 Hz, 1H), 3.80 (s, 3H), 2.93 (s, 3H), 2.23 – 2.15 (m, 1H), 1.03 (d, *J* = 6.8 Hz, 3H), 0.88 (d, *J* = 6.8 Hz, 3H).

Methyl *N*-(4-nitrobenzenesulfonyl)-L-valinate



A reported procedure was followed.[34] In a round bottom flask, L-valine methyl ester hydrochloride (1.97 g, 15.0 mmol, 1.0 equiv) was mixed with anhydrous DCM (40 mL) under N_2. Triethylamine (4.6 mL, 33.0 mmol, 2.2 equiv) and 4-nitrobenzenesulfonyl chloride (3.66 g, 16.5 mmol, 1.1 equiv) were added successively. The reaction was then stirred overnight before water was added. The mixture was extracted with EtOAc three times. The combined organic extracts were dried with Na_2SO_4, filtered and concentrated *in vacuo*. The product was obtained as a yellow solid (2.92 g, 62%) after purification by flash column chromatography on silica gel (PE:EtOAc, 5:1). Its ^{1}H NMR data matched with those reported in the literature.[34] **^{1}H NMR** (400 MHz) δ 8.34 (d, *J* = 8.8 Hz, 2H), 8.02 (d, *J* = 8.8 Hz, 2H), 5.21 (d, *J* = 10.44 Hz, 1H), 3.84 (dd, *J* = 10.0, 4.8 Hz, 1H), 3.51 (s, 3H), 2.14 – 2.06 (m, 1H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.87 (d, *J* = 6.8 Hz, 3H).

Methyl *N*-(2,4-dinitrobenzenesulfonyl)-L-valinate



In a round bottom flask, L-valine methyl ester hydrochloride (1.76 g, 8.4 mmol, 1.0 equiv) was mixed with pyridine (2.72 mL, 33.6 mmol, 4.0 equiv) in anhydrous DCM (18 mL) under N_2. To this solution was added slowly 2,4-dinitrobenzenesulfonyl chloride (2.68 g, 10.1 mmol, 1.2 equiv) at 0 ℃. The reaction was stirred at 0 ℃ for another 1 hour before it was stirred at room temperature overnight. Water was added and the reaction was extracted with EtOAc three times. The combined organic extracts were dried with Na_2SO_4, filtered and concentrated *in vacuo*. The product was obtained as a yellow solid (2.25 g, 74%) after purification by flash column chromatography on silica gel (PE:EtOAc, 5:1). **^{1}H NMR** (400 MHz) δ 8.75 (s, 1H), 8.52 (d, *J* = 6.8 Hz, 1H) 8. 27 (d, *J* = 6.8 Hz, 1H), 6.07 (d, *J* = 7.6 Hz, 1H), 4.10 (dd, *J* = 3.6, 2.6 Hz, 1H), 3.53 (s, 3H), 2.28 – 2.22 (m, 1H), 1.05 (d, *J* = 4.3 Hz, 3H), 0.93 (d, *J* = 4.4 Hz, 3H). **^{13}C NMR** (100 MHz) δ 171.1, 149.8, 147.9, 139.7, 132.0, 127.1, 121.1, 62.3, 52.5, 31.3, 19.1, 17.2. **HRMS** (FD) calculated for $C_{13}H_{16}F_3N_3O_{10}S^+$ $[M+H]^+$: 466.0556; found: 466.0560.

2.5.2 Reaction condition optimization for Pd-catalyzed C–H acetoxylation of Tf-protected amines

Optimization of Ligand

In a pressure tube with a Teflon stirring bar was successively added methyl *N*-triflyl-L-valinate **1a** (26.3 mg, 0.1 mmol, 1.0 equiv), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 10 mol%), $PhI(OAc)_2$ (80.5 mg, 0.25 mmol, 2.5 equiv), corresponding ligand (0.02 mmol, 20 mol%) and DCE (1.0 mL) *[Note: for **L1** – **L4**, a stock solution (0.02 M in DCE, 1.0 mL) was added]*. The pressure tube was then sealed with a screw cap, placed in a preheated oil bath at 110 ℃ and stirred for 20 h. The tube was removed from the oil bath, allowed to cool to room temperature, diluted with DCM, filtrated through Celite, eluting with CH_2Cl_2 and concentrated *in vacuo*. To this crude was added CH_2Br_2 (10 μL) and $CDCl_3$. ^{1}H NMR was recorded to determine the ^{1}H NMR yield.

Optimization of solvent

In a pressure tube with a Teflon stirring bar was successively added methyl *N*-triflyl-L-valinate (26.3 mg, 0.1 mmol, 1.0 equiv), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 10 mol%), $PhI(OAc)_2$ (80.5 mg, 0.25 mmol, 2.5 equiv), 2,6-lutidine (2.3 μL, 0.02 mmol, 20 mol%) and corresponding solvent (1.0 mL or 0.2 mL). The pressure tube was then sealed with a screw cap, placed in a preheated oil bath at 110 ℃ and stirred for 20 h. The tube was removed from the oil bath, allowed to cool to room temperature, diluted with DCM, filtrated through Celite, eluting with CH_2Cl_2 and concentrated *in vacuo*. To this crude was added CH_2Br_2 (10 μL) and $CDCl_3$. ^{1}H NMR was recorded to determine the ^{1}H NMR yield.

Optimization of co-oxidant

In a pressure tube with a Teflon stirring bar was successively added methyl *N*-triflyl-L-valinate (26.3 mg, 0.1

mmol, 1.0 equiv), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 10 mol%), $PhI(OAc)_2$ (80.5 mg, 0.25 mmol, 2.5 equiv), corresponding co-oxidant (0.2 mmol or 0.05 mmol, 2.0 equiv or 0.5 equiv), 2,6-lutidine (2.3 μL, 0.02 mmol, 20 mol%) and DCM (0.2 mL). The pressure tube was then sealed with a screw cap, placed in a preheated oil bath at 110 ℃ and stirred for 20 h. The tube was removed from the oil bath, allowed to cool to room temperature, diluted with DCM, filtrated through Celite, eluting with CH_2Cl_2 and concentrated *in vacuo*. To this crude was added CH_2Br_2 (10 μL) and $CDCl_3$. ^1H NMR was recorded to determine the ^1H NMR yield.

Further optimization of ligand

In a pressure tube with a Teflon stirring bar was successively added methyl *N*-triflyl-L-valinate (26.3 mg, 0.1 mmol, 1.0 equiv), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 10 mol%), $PhI(OAc)_2$ (80.5 mg, 0.25 mmol, 2.5 equiv), AgOAc (33.4 mg, 0.2 mmol, 2.0 equiv), ligand (0.02 mmol, 20 mol%) and DCM (0.2 mL). The pressure tube was then sealed with a screw cap, placed in a preheated oil bath at 110 ℃ and stirred for 20 h. The tube was removed from the oil bath, allowed to cool to room temperature, diluted with DCM, filtrated through Celite, eluting with CH_2Cl_2 and concentrated *in vacuo*. To this crude was added CH_2Br_2 (10 μL) and $CDCl_3$. ^1H NMR was recorded to determine the ^1H NMR yield.

Optimization of reaction temperature

In a pressure tube with a Teflon stirring bar was successively added methyl *N*-triflyl-L-valinate (26.3 mg, 0.1 mmol, 1.0 equiv), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 10 mol%), $PhI(OAc)_2$ (80.5 mg, 0.25 mmol, 2.5 equiv), AgOAc (33.4 mg, 0.2 mmol, 2.0 equiv), 2,6-lutidine (2.3 μL, 0.02 mmol, 20 mol%) and DCM (0.2 mL). The pressure tube was then sealed with a screw cap, placed in a preheated oil bath at the corresponding temperature and stirred for 20 h. The tube was removed from the oil bath, allowed to cool to room temperature, diluted with DCM, filtrated through Celite, eluting with CH_2Cl_2 and concentrated *in vacuo*. To this crude was added CH_2Br_2 (10 μL) and $CDCl_3$. ^1H NMR was recorded to determine the ^1H NMR yield.

Batch-wise addition of reagents

Batch-wise addition of methyl N-triflyl-L-valinate

In a pressure tube with a Teflon stirring bar was successively added $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 10 mol%), $PhI(OAc)_2$ (80.5 mg, 0.25 mmol, 2.5 equiv), AgOAc (33.4 mg, 0.2 mmol, 2.0 equiv), 2,6-lutidine (2.3 μL, 0.02 mmol, 20 mol%), DCM (150 μL) and 30 μL of *N*-triflyl-L-valinate solution in DCM [The solution was made by dissolving methyl *N*-triflyl-L-valinate (52.6 mg, 0.2 mmol) in DCM (300 μL)]. The pressure tube was then sealed with a crimp cap with septa, placed in a preheated oil bath at 110 ℃ and stirred for 0.5 h. Without removing the pressure tube out of the oil bath, another 30 μL of *N*-triflyl-L-valinate solution in DCM was added directly through the septa of the cap using a microsyringe. The reaction was continued to stir for another 0.5 h. The whole process was repeated three more times until the added methyl *N*-triflyl-L-valinate reached 0.1 mmol and at the same time the total amount of DCM reached 300 μL. The reaction was stirred for additional 18 h. The tube was removed from the oil bath, allowed to cool to room temperature, diluted with DCM, filtrated through Celite, eluting with CH_2Cl_2 and concentrated *in vacuo*. To this crude was added CH_2Br_2 (10 μL) and $CDCl_3$. ^1H NMR was recorded to determine the ^1H NMR yield. A reference reaction was also performed: methyl *N*-triflyl-L-valinate (26.3 mg, 0.1 mmol, 1.0 equiv), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 10 mol%), $PhI(OAc)_2$ (80.5 mg, 0.25 mmol, 2.5 equiv), AgOAc (33.4 mg, 0.2 mmol, 2.0 equiv), 2,6-lutidine (2.3 μL, 0.02 mmol, 20 mol%) and DCM (300 μL) at 110 °C for 20 h.

Batch-wise addition of $Pd(OAc)_2$ and 2.6-lutidine (10 mol% in total)

In a pressure tube with a Teflon stirring bar was successively added methyl *N*-triflyl-L-valinate (26.3 mg, 0.1 mmol, 1.0 equiv), $PhI(OAc)_2$ (80.5 mg, 0.25 mmol, 2.5 equiv), AgOAc (33.4 mg, 0.2 mmol, 2.0 equiv), DCM (150 μL) and 30 μL of $Pd(OAc)_2$/2,6-lutidine solution in DCM [The solution was made by dissolving $Pd(OAc)_2$ (4.4 mg, 0.02 mmol) and 2,6-lutidine (4.6 μL, 0.04 mmol) in DCM (300 μL)]. The pressure tube was then sealed with a crimp cap with septa, placed in a preheated oil bath at 110 ℃ and stirred for 0.5 h. Without removing the pressure tube out of the oil bath, another 30 μL of $Pd(OAc)_2$/2,6-lutidine solution in DCM was added directly through the septa of the cap using a microsyringe. The reaction was continued to stir for another 0.5 h. The whole process was repeated three more times until the added $Pd(OAc)_2$ reached 0.01 mmol, 2,6-lutidine reached 0.02 mmol and the total amount of DCM reached 300μL. The reaction was stirred for additional 18 h. The tube was removed from the oil bath, allowed to cool to room temperature, diluted with DCM, filtrated through Celite, eluting with CH_2Cl_2 and concentrated *in vacuo*. To this crude was added CH_2Br_2 (10 μL) and $CDCl_3$. ^1H NMR

was recorded to determine the ^{1}H NMR yield. A reference reaction was also performed: methyl *N*-triflyl-L-valinate (26.3 mg, 0.1 mmol, 1.0 equiv), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 10 mol%), $PhI(OAc)_2$ (80.5 mg, 0.25 mmol, 2.5 equiv), AgOAc (33.4 mg, 0.2 mmol, 2.0 equiv), 2,6-lutidine (2.3 μL, 0.02 mmol, 20 mol%) and DCM (300 μL) at 110 °C for 20 h.

Batch-wise addition of $Pd(OAc)_2$ and 2.6-lutidine (20 mol% in total)

In a pressure tube with a Teflon stirring bar was successively added methyl *N*-triflyl-L-valinate (26.3 mg, 0.1 mmol, 1.0 equiv), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 10 mol%), $PhI(OAc)_2$ (80.5 mg, 0.25 mmol, 2.5 equiv), AgOAc (33.4 mg, 0.2 mmol, 2.0 equiv), 2,6-lutidine (2.3 μL, 0.02 mmol, 20 mol%) and DCM (200 μL). The pressure tube was then sealed with a crimp cap with septa, placed in a preheated oil bath at 110 ℃ and stirred for 2.0 h. Without removing the pressure tube out of the oil bath, 100 μL of $Pd(OAc)_2$/2,6-lutidine solution in DCM [The solution was made by dissolving $Pd(OAc)_2$ (4.4 mg, 0.02 mmol) and 2,6-lutidine (4.6 μL, 0.04 mmol) in DCM (200 μL)] was added directly through the septa of the cap using a microsyringe. The reaction was stirred for additional 18 h. The tube was removed from the oil bath, allowed to cool to room temperature, diluted with DCM, filtrated through Celite, eluting with CH_2Cl_2 and concentrated *in vacuo*. To this crude was added CH_2Br_2 (10 μL) and $CDCl_3$. ^{1}H NMR was recorded to determine the ^{1}H NMR yield. A reference reaction was also performed: methyl *N*-triflyl-L-Valinate (26.3 mg, 0.1 mmol, 1.0 equiv), $Pd(OAc)_2$ (4.4 mg, 0.02 mmol, 40 mol%), $PhI(OAc)_2$ (80.5 mg, 0.25 mmol, 2.5 equiv), AgOAc (33.4 mg, 0.2 mmol, 2.0 equiv), 2,6-lutidine (4.6 μL, 0.04 mmol, 40 mol%) and DCM (300 μL) at 110 °C for 20 h.

Batch-wise addition of $Pd(OAc)_2$ and 2.6-lutidine (20 mol% in total) and $PhI(OAc)_2$ (3.5 equiv)

In a pressure tube with a Teflon stirring bar was successively added methyl *N*-triflyl-L-valinate (26.3 mg, 0.1 mmol, 1.0 equiv), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 10 mol%), $PhI(OAc)_2$ (80.5 mg, 0.25 mmol, 2.5 equiv), AgOAc (33.4 mg, 0.2 mmol, 2.0 equiv), 2,6-lutidine (2.3 μL, 0.02 mmol, 20 mol%) and DCM (100 μL). The pressure tube was then sealed with a crimp cap with septa, placed in a preheated oil bath at 110 ℃ and stirred for 2.0 h. Without removing the pressure tube out of the oil bath, 100 μL of $Pd(OAc)_2$/2,6-lutidine solution in DCM [The solution was made by dissolving $Pd(OAc)_2$ (4.4 mg, 0.02 mmol) and 2,6-lutidine (4.6 μL, 0.04 mmol) in DCM (200 μL)] and 100 μL of $PhI(OAc)_2$ solution in DCM [The solution was made by dissolving $PhI(OAc)_2$ (64.4 mg, 0.2 mmol) in DCM (200 μL)] were added directly through the septa of the cap using a microsyringe. The reaction was stirred for additional 18 h. The tube was removed from the oil bath, allowed to cool to room temperature, diluted with DCM, filtrated through Celite, eluting with CH_2Cl_2 and concentrated *in vacuo*. To this crude was added CH_2Br_2 (10 μL) and $CDCl_3$. ^{1}H NMR was recorded to determine the ^{1}H NMR yield. A reference reaction was also performed: methyl *N*-triflyl-L-valinate (26.3 mg, 0.1 mmol, 1.0 equiv), $Pd(OAc)_2$ (4.4 mg, 0.02 mmol, 40 mol%), $PhI(OAc)_2$ (112.7 mg, 0.35 mmol, 3.5 equiv), AgOAc (33.4 mg, 0.2 mmol, 2.0 equiv), 2,6-lutidine (4.6 μL, 0.04 mmol, 40 mol%) and DCM (300 μL) at 110 °C for 20 h.

Batch-wise addition of $PhI(OAc)_2$ (2.5 equiv in total)

In a pressure tube with a Teflon stirring bar was successively added methyl *N*-triflyl-L-valinate (26.3 mg, 0.1 mmol, 1.0 equiv), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 10 mol%), $PhI(OAc)_2$ (16.1 mg, 0.05 mmol, 0.5 equiv), AgOAc (33.4 mg, 0.2 mmol, 2.0 equiv), 2,6-lutidine (2.3 μL, 0.02 mmol, 20 mol%) and DCM (180 μL). The pressure tube was then sealed with a crimp cap with septa, placed in a preheated oil bath at 110 ℃ and stirred for 0.5 h. Without removing the pressure tube out of the oil bath, 105 μL of $PhI(OAc)_2$ solution in DCM [The solution was made by dissolving $PhI(OAc)_2$ (161.0 mg, 0.5 mmol) in DCM (1050 μL)] was added directly through the septa of the cap using a microsyringe. The reaction was continued to stir for another 0.5 h. The whole process was repeated three more times until the added $PhI(OAc)_2$ reached 0.25 mmol and the total amount of DCM reached 600 μL. The reaction was stirred for additional 18 h. The tube was removed from the oil bath, allowed to cool to room temperature, diluted with DCM, filtrated through Celite, eluting with CH_2Cl_2 and concentrated *in vacuo*. To this crude was added CH_2Br_2 (10 μL) and $CDCl_3$. ^{1}H NMR was recorded to determine the ^{1}H NMR yield. A reference reaction was also performed: methyl *N*-triflyl-L-valinate (26.3 mg, 0.1 mmol, 1.0 equiv), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 10 mol%), $PhI(OAc)_2$ (80.5 mg, 0.25 mmol, 2.5 equiv), AgOAc (33.4 mg, 0.2 mmol, 2.0 equiv), 2,6-lutidine (2.3 μL, 0.02 mmol, 20 mol%) and DCM (600 μL) at 110 ℃ for 20 h.

Batch-wise addition of $PhI(OAc)_2$ (3.5 equiv in total)

In a pressure tube with a Teflon stirring bar was successively added methyl *N*-triflyl-L-valinate (26.3 mg, 0.1

mmol, 1.0 equiv), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 10 mol%), $PhI(OAc)_2$ (48.3 mg, 0.15 mmol, 1.5 equiv), AgOAc (33.4 mg, 0.2 mmol, 2.0 equiv), 2,6-lutidine (2.3 μL, 0.02 mmol, 20 mol%) and DCM (180 μL). The pressure tube was then sealed with a crimp cap with septa, placed in a preheated oil bath at 110 ℃ and stirred for 1.0 h. Without removing the pressure tube out of the oil bath, 210 μL of $PhI(OAc)_2$ solution in DCM [The solution was made by dissolving $PhI(OAc)_2$ (161.0 mg, 0.5 mmol) in DCM (1050 μL)] was added directly through the septa of the cap using a microsyringe. The reaction was continued to stir for another 1.0 h. The whole process was repeated one more time and the added $PhI(OAc)_2$ reached 0.35 mmol and the total amount of DCM reached 600 μL. The reaction was stirred for additional 18 h. The tube was removed from the oil bath, allowed to cool to room temperature, diluted with DCM, filtrated through Celite, eluting with CH_2Cl_2 and concentrated *in vacuo*. To this crude was added CH_2Br_2 (10 μL) and $CDCl_3$. ^1H NMR was recorded to determine the ^1H NMR yield.

Optimization of amount of ligand

In a pressure tube with a Teflon stirring bar was successively added methyl *N*-triflyl-L-valinate (26.3 mg, 0.1 mmol, 1.0 equiv), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 10 mol%), $PhI(OAc)_2$ (80.5 mg, 0.25 mmol, 2.5 equiv), AgOAc (33.4 mg, 0.2 mmol, 2.0 equiv), 2,6-lutidine (x mmol) and DCM (0.2 mL). The pressure tube was then sealed with a screw cap, placed in a preheated oil bath at 110 ℃ and stirred for 20 h. The tube was removed from the oil bath, allowed to cool to room temperature, diluted with DCM, filtrated through Celite, eluting with CH_2Cl_2 and concentrated *in vacuo*. To this crude was added CH_2Br_2 (10 μL) and $CDCl_3$. ^1H NMR was recorded to determine the ^1H NMR yield.

Optimization of base

In a pressure tube with a Teflon stirring bar was successively added methyl *N*-triflyl-L-valinate (26.3 mg, 0.1 mmol, 1.0 equiv), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 10 mol%), $PhI(OAc)_2$ (80.5 mg, 0.25 mmol, 2.5 equiv), AgOAc (33.4 mg, 0.2 mmol, 2.0 equiv), base (0.02 mmol, 20 mol%), 2,6-lutidine (2.3 μL, 0.02 mmol, 20 mol%) and DCM (0.2 mL). The pressure tube was then sealed with a screw cap, placed in a preheated oil bath at 110 ℃ and stirred for 20 h. The tube was removed from the oil bath, allowed to cool to room temperature, diluted with DCM, filtrated through Celite, eluting with CH_2Cl_2 and concentrated *in vacuo*. To this crude was added CH_2Br_2 (10 μL) and $CDCl_3$. ^1H NMR was recorded to determine the ^1H NMR yield.

Optimization of palladium source

In a pressure tube with a Teflon stirring bar was successively added methyl *N*-triflyl-L-valinate (26.3 mg, 0.1 mmol, 1.0 equiv), Palladium source (2.2 mg, 0.01 mmol, 10 mol%), $PhI(OAc)_2$ (80.5 mg, 0.25 mmol, 2.5 equiv), AgOAc (33.4 mg, 0.2 mmol, 2.0 equiv), 2,6-lutidine (2.3 μL, 0.02 mmol, 20 mol%) and DCM (0.2 mL). The pressure tube was then sealed with a screw cap, placed in a preheated oil bath at 110 ℃ and stirred for 20 h. The tube was removed from the oil bath, allowed to cool to room temperature, diluted with DCM, filtrated through Celite, eluting with CH_2Cl_2 and concentrated *in vacuo*. To this crude was added CH_2Br_2 (10 μL) and $CDCl_3$. ^1H NMR was recorded to determine the ^1H NMR yield.

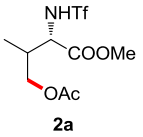
Optimization of amount of (co)oxidant

In a pressure tube with a Teflon stirring bar was successively added methyl *N*-triflyl-L-valinate (26.3 mg, 0.1 mmol, 1.0 equiv), $Pd(OPiv)_2$ (3.1 mg, 0.01 mmol, 10 mol%), $PhI(OAc)_2$ (x mmol), AgOAc (y mmol), 2,6-lutidine (2.3 μL, 0.02 mmol, 20 mol%) and DCM (0.2 mL). The pressure tube was then sealed with a screw cap, placed in a preheated oil bath at 110 ℃ and stirred for 20 h. The tube was removed from the oil bath, allowed to cool to room temperature, diluted with DCM, filtrated through Celite, eluting with CH_2Cl_2 and concentrated *in vacuo*. To this crude was added CH_2Br_2 (10 μL) and $CDCl_3$. ^1H NMR was recorded to determine the ^1H NMR yield.

2.5.3. General procedure for the acetoxylation reaction of triflyl-protected amines

In a pressure tube with a Teflon stirring bar was successively added amine (1.0 equiv), $Pd(OPiv)_2$ (10 mol%), $PhI(OAc)_2$ (2.5 equiv), AgOAc (1.0 equiv), 2,6-lutidine **L10** (20 mol%) or **L23** (20 mol%) and DCM (0.2 M). The pressure tube was sealed with a screw cap, placed in a preheated oil bath at 110 ℃ and stirred over the time period indicated for each example. The tube was removed from the oil bath, allowed to cool to room temperature, diluted with DCM, filtered through Celite, eluting with CH_2Cl_2 and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel.

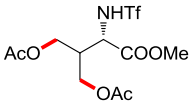
Methyl 4-acetoxy-*N*-triflyl-L-valinate (2a)



2a

Substrate **1a** (0.25 mmol) was acetoxylated using **L10** following the **general procedure** for 20 hours to give the entitled monosubstituted product **2a** as a yellowish solid (36.0 mg, 56%, dr = 13:1) after purification by flash column chromatography on silica gel (PE:EtOAc, 7:1). **^{1}H NMR** (400 MHz) major diastereomer: δ 6.12 (d, *J* = 9.7 Hz, 1H), 4.22 (dd, *J* = 9.8, 3.6 Hz, 1H), 4.10 (dd, *J* = 11.8, 8.7 Hz, 1H), 4.01 – 3.91 (m, 1H), 3.81 (d, *J* = 2.4 Hz, 3H), 2.72 – 2.45 (m, 1H), 2.04 (s, 3H), 1.07 (d, *J* = 7.0 Hz, 3H). **^{13}C NMR** (100 MHz) δ 171.24, 170.44, 119.711 (q, *J* = 332.8Hz), 64.54, 59.35, 53.18, 35.97, 20.80, 13.97. **IR**: ν 3210, 2960, 2923, 2854, 1748, 1722, 1458, 1439, 1381, 1230, 1192, 1147, 1044, 612, 583, 511 cm^{-1}. **HRMS** (FD) calculated for $C_9H_{15}F_3NO_6S^+$ [M+H]$^+$: 322.0572; found: 322.0423.

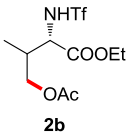
Methyl 4,4'-diacetoxy-*N*-triflyl-L-valinate (2a')



2a'

Substrate **1a** (0.25 mmol) was diacetoxylated using **L10** following the **general procedure** for 20 hours to give the entitled disubstituted product **2a'** as a yellowish solid (5.3 mg, 7%) after purification by flash column chromatography on silica gel [first 7:1 (PE:EtOAc) to get **2a**, then 4:1 (PE:EtOAc) to get **2a'**]. **^{1}H NMR** (300 MHz) δ 6.24 (s, 1H), 4.48 – 4.44 (m, 1H), 4.31 – 4.01 (m, 4H), 3.83 (s, 3H), 2.78 (dddd, *J* = 13.3, 7.8, 5.4, 3.6 Hz, 1H), 2.09 (s, 3H), 2.06 (s, 3H). **^{13}C NMR** (75 MHz) δ 171.04, 170.71, 170.04, 119.59 (q, *J* = 318.8), 61.16, 60.92, 55.88, 53.45, 40.57, 20.78, 20.75. **IR**: ν 3184, 2961, 1745, 1460, 1438, 1383, 1227, 1195, 1147, 1043, 610, 513 cm^{-1}. **HRMS** (FD) calculated for $C_{10}H_{16}NO_6^+$ [M-SO_2CF_3]$^+$: 246.0978; found: 246.4570.

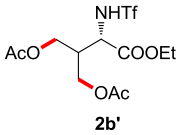
Ethyl 4-acetoxy-*N*-triflyl-L-valinate (2b)



2b

Substrate **1b** (0.25 mmol) was acetoxylated using **L10** following the **general procedure** for 18 hours to give the entitled product **2b** as a white solid (46.6 mg, 56%, dr = 14:1) after purification by flash column chromatography on silica gel (PE:EtOAc, 7:1). **^{1}H NMR** (300 MHz) δ 6.40 (d, *J* = 9.8 Hz, 1H), 4.37 – 4.14 (m, 3H), 4.09 (dd, *J* = 11.7, 8.4 Hz, 1H), 3.96 (dd, *J* = 11.7, 5.3 Hz, 1H), 2.63 – 2.50 (m, 1H), 2.04 (s, 3H), 1.30 (t, *J* = 7.2 Hz, 3H), 1.07 (d, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz) δ 171.42, 169.94, 119.63 (q, *J* = 319.5 Hz), 64.68, 62.55, 59.41, 35.86, 20.77, 14.16, 13.94. **IR**: ν 3211, 2983, 1743, 1721, 1457, 1380, 1262, 1229, 1186, 1146, 1040, 936, 857, 609, 582, 511 cm^{-1}. **HRMS** (FD) calculated for $C_{10}H_{16}F_3NO_6S^+$ [M]$^+$: 335.0650; found: 335.0664.

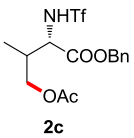
Ethyl 4,4'-diacetoxy-*N*-triflyl-L-valinate (2b')



2b'

Substrate **1b** (0.25 mmol) was diacetoxylated using **L10** following the **general procedure** for 18 hours to give the entitled product **2b'** as a white solid (6.1 mg, 6%) after purification by flash column chromatography on silica gel [first 7:1 (PE:EtOAc) to get **2b**, then 4:1 (PE:EtOAc) to get **2b'**]. **^{1}H NMR** (300 MHz) δ 6.15 (s, 1H), 4.44 (s, 1H), 4.38 – 3.81 (m, 6H), 2.82 – 2.72 (m, 1H), 2.09 (s, 3H), 2.06 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz) δ 170.93, 170.69, 169.48, 119.58 (q, *J* = 319.5 Hz), 63.02, 61.20, 60.91, 56.01, 40.47, 29.52, 20.81, 14.18. **IR**: ν 3202, 2925, 1744, 1536, 1465, 1383, 1371, 1229, 1198, 1148, 1042, 611 cm^{-1}. **HRMS** (FD) calculated for $C_{12}H_{18}F_3NO_8S^+$ [M+Na]$^+$: 416.0603; found: 416.0701.

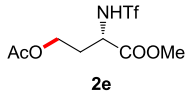
Benzyl 4-acetoxy-*N*-triflyl-L-valinate (2c)



2c

Substrate **1c** (0.25 mmol) was acetoxylated using **L10** following the **general procedure** for 5 hours to give the entitled product **2c** as a white solid (49.0 mg, 49%, dr = 12:1) after purification by flash column chromatography on silica gel (PE:EtOAc, 8:1) (***Note: form crude ^{1}H NMR analysis, disubstituted product was also detected, and the ratio of mono- to di-substituted products was 10:1. However, no pure fraction was obtained for the disubstituted product after the column. It was not separable from byproducts***). **^{1}H NMR** (400 MHz) δ 7.88 – 7.30 (m, 5H), 6.31 (d, *J* = 9.8 Hz, 1H), 5.21 (s, 2H), 4.24 (dd, *J* = 9.8, 3.7 Hz, 1H), 4.08 (dd, *J* = 11.9, 8.7 Hz, 1H), 3.92 (dd, *J* = 11.8, 4.9 Hz, 1H), 2.67 – 2.53 (m, 1H), 1.94 (s, 3H), 1.04 (d, J = 7.0 Hz, 3H). **^{13}C NMR** (100 MHz) δ 171.43, 169.90, 134.61, 129.04, 128.90, 128.70, 119.62 (q, *J* = 321.1 Hz), 68.27, 64.56, 59.47, 35.85, 20.66, 14.03. **IR**: ν 3204, 2974, 1744, 1720, 1457, 1379, 1229, 1189, 1147, 1044, 753, 698, 612, 511 cm^{-1}. **HRMS** (FD) calculated for $C_{15}H_{18}F_3NO_6S^+$ [M]$^+$: 397.0807; found: 397.0779.

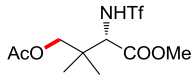
Methyl 4-acetoxy-*N*-triflyl-L-homoalaninate (2e)



2e

Substrate **1e** (0.25 mmol) was acetoxylated using **L10** following the **general procedure** for 20 hours to give the entitled product **2e** as a colorless oil (18.6 mg, 30%) after purification by flash column chromatography on silica gel (PE:EtOAc, 7:1). [**Note:** ***the reaction was also performed in another reaction condition: substrate (1.0 equiv), Pd(OPiv)$_2$ (20 mol%), 2,6-lutidine (40 mol%), PhI(OAc)$_2$ (4.0 equiv) and AgOAc (2.0 equiv) in DCM (0.5 M) were stirred for 20 hours at 110 ℃ (two parallel runs) to give the product in 36% isolated yield (22.5 mg)]***. **^{1}H NMR** (400 MHz) δ 5.96 (d, *J* = 9.0 Hz, 1H), 4.41 – 4.36 (m, 1H), 4.29 (ddd, *J* = 12.0, 7.0, 4.9 Hz, 1H), 4.21 – 4.09 (m, 1H), 3.83 (s, 3H), 2.45 – 2.10 (m, 2H), 2.05 (s, 3H). **^{13}C NMR** (100 MHz) δ 170.97, 170.82, 119.59 (q, *J* = 319.0 Hz), 59.58, 54.49, 53.44, 32.30, 20.84. **IR**: ν 3220, 2961, 2923, 2853, 1743, 1437, 1380, 1229, 1188, 1147, 1127, 1048, 889, 607, 576, 515 cm^{-1}. **HRMS** (ESI) calculated for $C_6H_9F_3NO_4S^+$ [M-COOMe]$^+$: 248.0204; found: 397.0108.

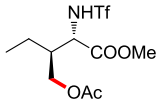
Methyl 4-acetoxy-*N*-triflyl-L-*tert*-leucinate (2f)



2f

Substrate **1f** (0.25 mmol) was acetoxylated using **L10** following the **general procedure** for 20 hours. Crude ^{1}H NMR showed that the reaction was a mess. Purification by flash column chromatography on silica gel was tried. It turned out to be very difficult to fully purify the product. We managed to get some pure fractions to do the characterization. **^{1}H NMR** (300 MHz) δ 5.83 (d, *J* = 10.2 Hz, 1H), 4.14 (d, *J* = 10.3 Hz, 1H), 3.95 (d, *J* = 11.5 Hz, 1H), 3.89 (d, *J* = 11.3 Hz, 1H), 3.80 (s, 3H), 2.10 (s, 3H), 1.07 (s, 3H), 1.06 (s, 3H). **^{13}C NMR** (100 MHz) δ 170.7, 170.1, 119.5 (q, *J* = 319.3 Hz), 69.0, 62.1, 52.8, 37.9, 21.9, 21.4, 20.7. Di-acetoxylated was also observed, but it could not be separated from byproducts.

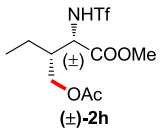
Methyl 4-acetoxy-*N*-triflyl-L-isoleucinate (2g)



2g

Substrate **1g** (0.20 mmol) was acetoxylated using **L10** following the **general procedure** for 15 hours to give the entitled product **2g** as a white solid (26.2 mg, 39%) after purification by flash column chromatography on silica gel (PE:EtOAc, 7:1). **^{1}H NMR** (400 MHz) δ 5.78 (d, *J* = 9.8 Hz, 1H), 4.42 (dd, *J* = 9.9, 3.5 Hz, 1H), 4.22 (dd, *J* = 11.7, 4.0 Hz, 1H), 3.93 (dd, *J* = 11.6, 9.3 Hz, 1H), 3.82 (s, 3H), 2.25 – 2.08 (m, 1H), 2.08 (s, 3H), 1.45 – 1.28 (m, 2H), 0.98 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR** (100 MHz) δ 170.86, 170.69, 119.61 (q, *J* = 321.2 Hz), 62.89, 57.82, 53.30, 43.06, 20.88, 19.91, 11.74. **IR**: ν 3208, 2965, 2923, 2852, 1748, 1720, 1464, 1378, 1265, 1230, 1191, 1179, 1147, 1128, 1021, 998, 971, 887, 779, 613, 584, 525, 503, 441 cm^{-1}. **HRMS** (FD) calculated for $C_{10}H_{16}F_3NO_6S^+$ [M]$^+$: 335.0650; found: 335.0637. **Melting point**: 98.5 – 100.0 ℃.

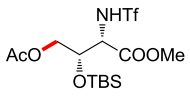
Methyl 4-acetoxy-*N*-triflyl-DL-alloisoleucinate [(±)-2h]



(±)-2h

Substrate **(±)-1h** (0.20 mmol) was acetoxylated using **L10** following the **general procedure** for 15 hours to give the entitled product **(±)-2h** as a white solid (58.3 mg, 87%) after purification by flash column chromatography on silica gel (PE:EtOAc, 8:1). **^{1}H NMR** (400 MHz) δ 6.28 (d, *J* = 9.9 Hz, 1H), 4.30 (dd, *J* = 9.9, 3.0 Hz, 1H), 4.12 (dd, *J* = 11.9, 9.0 Hz, 1H), 4.01 (dd, *J* = 11.9, 4.7 Hz, 1H), 3.80 (s, 2H), 2.38 – 2.30 (m, 1H), 2.03 (s, 3H), 1.45 (ddq, *J* = 26.5, 14.3, 7.2 Hz, 2H), 1.02 (d, *J* = 7.5 Hz, 3H). **^{13}C NMR** (100 MHz) δ 171.42, 170.90, 119.63 (q, *J* = 321.1), 63.23, 57.64, 53.14, 42.49, 21.31, 20.78, 11.47. **IR**: ν 3125, 2959, 2917, 1752, 1710, 1375, 1264, 1229, 1216, 1149, 1131, 1103, 1035, 995, 614, 584, 504, 444 cm^{-1}. **HRMS** (FD) calculated for $C_{10}H_{16}F_3NO_6S^+$ [M]$^+$: 335.0650; found: 335.0662. **Meilting point**: 53.2 – 55.1 ℃.

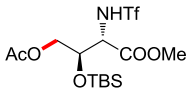
Methyl 4-acetoxy-*O*-(tert-butyldimethylsilyl)-*N*-triflyl-L-threoninate 2i



2i

Substrate **1i** (0.25 mmol) was acetoxylated using **L10** following the **general procedure** for 17 hours to give the entitled product **2i** as a colorless oil (24.6 mg, 23%) after purification by flash column chromatography on silica gel (PE:EtOAc, 12:1). **^{1}H NMR** (400 MHz) δ 5.51 (d, *J* = 10.2 Hz, 1H), 4.43 (ddd, *J* = 8.7, 5.2, 1.6 Hz, 1H), 4.34 (dd, *J* = 10.2, 1.5 Hz, 1H), 4.12 (dd, *J* = 11.2, 5.3 Hz, 1H), 3.99 (dd, *J* = 11.3, 8.6 Hz, 1H), 3.82 (s, 3H), 2.09 (s, 3H), 0.85 (s, 9H), 0.10 – 0.01 (m, 6H). **^{13}C NMR** (100 MHz) δ 170.24, 169.16, 119.34 (q, *J* = 320.4 Hz), 70.15, 62.99, 58.88, 53.18, 25.53, 20.67, 17.86, -4.57, -5.37. **IR**: ν 3227, 2957, 2932, 2860, 1749, 1436, 1382, 1190, 1144, 1099, 1048, 990, 812, 779, 616, 500 cm^{-1}. **HRMS** (FD) calculated for $C_{10}H_{17}F_3NO_7SSi^+$ [M-^{t}Bu]$^+$: 380.0447; found: 380.0447.

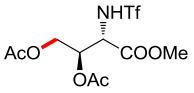
Methyl 4-acetoxy-*O*-(*tert*-butyldimethylsilyl)-*N*-triflyl-L-allothreoninate (2j)



2j

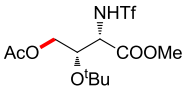
Substrate **1j** (0.25 mmol) was acetoxylated using **L10** following the **general procedure** for 8 hours to give the entitled product **2j** as a colorless oil (53.6 mg, 49%) after purification by flash column chromatography on silica gel (PE:EtOAc, 12:1). **^{1}H NMR** (400 MHz) δ 5.87 (d, *J* = 8.8 Hz, 1H), 4.36 (dd, *J* = 8.9, 2.5 Hz, 1H), 4.22 (td, *J* = 6.3, 2.5 Hz, 1H), 4.17 – 4.06 (m, 2H), 3.83 (s, 3H), 2.08 (s, 3H), 0.87 (d, *J* = 1.2 Hz, 9H), 0.13 – 0.12 (m, 6H). **^{13}C NMR** (100 MHz) δ 170.60, 168.24, 119.60 (q, *J* = 320.9 Hz), 72.64, 64.32, 59.84, 53.34, 25.67, 20.84, 18.07, -4.54, -4.90. **IR**: ν 3235, 2957, 2934, 2859, 1748, 1463, 1438, 1386, 1255, 1231, 1193, 1148, 1047, 990, 839, 780, 608, 505 cm^{-1}. **HRMS** (FD) calculated for $C_{10}H_{17}F_3NO_7SSi^+$ [M-^{t}Bu]$^+$: 380.0447; found: 380.0402.

Methyl 4,*O*-diacetoxy-*N*-triflyl-L-allothreoninate (2l)



Substrate **1l** was acetoxylated using **L10** following the **general procedure** for 17 hours to give the entitled product **2l** as a colorless oil (25.0 mg, 27%) after purification by flash column chromatography on silica gel (PE:EtOAc, 5:1). **^{1}H NMR** (400 MHz) δ 6.36 (d, *J* = 8.5 Hz, 1H), 5.38 – 5.33 (m, 1H), 4.61 (d, *J* = 5.2 Hz, 1H), 4.32 (dd, *J* = 11.9, 6.6 Hz, 1H), 4.19 (dd, *J* = 11.9, 6.0 Hz, 1H), 3.85 (s, 3H), 2.12 (s, 3H), 2.07 (s, 3H). **^{13}C NMR** (100 MHz) δ 170.7, 170.3, 167.8, 119.6 (q, *J* = 319.0 Hz), 70.4, 61.2, 57.4, 53.7, 20.8, 20.7.

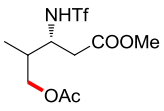
Methyl 4-acetoxy-*O*-(*tert*-butyl)-*N*-triflyl-L-threoninate (2m)



2m

Substrate **1m** (0.20 mmol) was acetoxylated using **L10** following the **general procedure** for 15 hours to give the entitled product **2m** as a white solid (34.0 mg, 45%) after purification by flash column chromatography on silica gel (PE:EtOAc, 12:1). **^{1}H NMR** (400 MHz) δ 5.65 (d, *J* = 10.3 Hz, 1H), 4.35 (d, *J* = 10.2 Hz, 1H), 4.26 – 4.12 (m, 2H), 3.86 (dd, *J* = 12.2, 10.9 Hz, 1H), 3.80 (s, 3H), 2.09 (s, 3H), 1.14 (s, 9H). **^{13}C NMR** (100 MHz) δ 170.50, 169.79, 119.50 (q, *J* = 320.5 Hz), 76.09, 68.91, 62.45, 58.40, 53.15, 28.17, 20.81. **IR**: ν 3227, 2978, 1754, 1730, 1373, 1194, 1145, 1122, 1070, 649, 617, 603, 586, 556, 499, 487, 467 cm^{-1}. **HRMS** (FD) calculated for $C_{11}H_{17}F_3NO_7S^+$ [M-Me]$^+$: 364.0678; found: 364.0684. mp: 111.6 – 115.6 ℃.

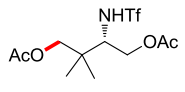
Methyl 5-acetoxy-*N*-triflyl-L-β-valinate (2q)



2q

Substrate **1q** (0.25 mmol) was acetoxylated using **L10** following the **general procedure** for 20 hours to give the entitled product **2q** as a white solid (30.2 mg, 36%, dr = 17:1) with a diastereoselectivity of 17:1 after purification by flash column chromatography on silica gel (PE:EtOAc, 8:1). **^{1}H NMR** (400 MHz) δ 6.17 (d, *J* = 9.5 Hz, 1H), 4.11 (d, *J* = 4.9 Hz, 2H), 3.85 – 3.78 (m, 1H), 3.74 (s, 3H), 2.72 (d, *J* = 4.8 Hz, 2H), 2.24 – 2.14 (m, 1H), 2.08 (s, 3H), 1.02 (d, *J* = 7.0 Hz, 6H). **^{13}C NMR** (100 MHz) δ 171.8, 171.0, 119.7 (q, J = 318.0 Hz), 65.7, 54.6, 52.4, 36.34, 36.31, 20.9, 14.4. Di-acetoxylated was also observed, but it could not be separated from byproducts.

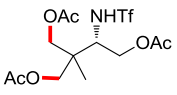
4-Acetoxy-*O*-Acetyl-*N*-triflyl-L-*tert*-leucinol (2v)



2v

Substrate **1v** was acetoxylated using **L23** following the **general procedure** for 17 hours to give the entitled product **2v** as a colorless oil (27.5 mg, 32%) after purification by flash column chromatography on silica gel (PE:EtOAc, 8:1). **^{1}H NMR** (400 MHz) δ 5.47 (d, *J* = 10.1 Hz, 1H), 4.31 (dd, *J* = 10.7, 3.9, 1H), 4.17 (dd, *J* = 12.0, 8.0, 1H), 3.92 (s, 2H), 3.76 – 3.71 (m, 1H), 2.10 – 2.09 (m, 6H), 1.09 – 1.06 (m, 6H). **^{13}C NMR** (100 MHz) δ 171.14, 170.85, 119.57 (q, *J* = 320.6 Hz), 69.91, 63.03, 60.38, 37.45, 22.86, 22.36, 20.96, 20.87. **IR**: ν 3207, 2963, 2924, 2853, 2362, 2336, 1744, 1719, 1457, 1375, 1228, 1190, 1146, 1043, 616 cm^{-1}. **HRMS** (FD) calculated for $C_{11}H_{19}F_3NO_6S^+$ [M+H]$^+$: 350.0885; found: 380.0844.

4,4'-Diacetoxy-*O*-Acetyl-*N*-triflyl-L-*tert*-leucinol (2v')

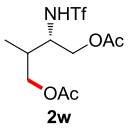


2v'

Substrate **1v** was diacetoxylated using **L23** following the **general procedure** for 17 hours to give the entitled product **2v'** as a white solid (15.8 mg, 15%) after purification by flash column chromatography on silica gel [first 8:1 (PE:EtOAc) to get **2v**, then 4:1 (PE:EtOAc) to get **2v'**]. **^{1}H NMR** (300 MHz) δ 5.45 (d, *J* = 10.1 Hz, 1H), 4.34 (dd, *J* = 12.1, 3.9 Hz, 1H), 4.28 – 4.05 (m, 4H), 4.01 (d, *J* = 11.8 Hz, 1H), 3.95 – 3.89 (m, 1H), 2.12 – 2.11 (m, 9H), 1.11 (s, 3H). **^{13}C NMR** (100 MHz) δ 170.89, 170.73, 170.47, 119.49 (q, *J* = 317.9 Hz), 66.40, 66.16, 62.85, 57.83, 40.81, 29.86, 20.93, 20.85, 18.13. **IR**: ν 3209, 2925, 2363, 1746, 1458, 1377, 1229, 1194, 1045, 616 cm^{-1}.

HRMS (FD) calculated for $C_{11}H_{17}F_3NO_6S^+$ [M-OAc]$^+$: 348.0729; found: 348.1551.

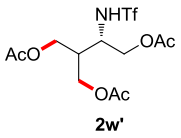
4-Acetoxy-*O*-Acetyl-*N*-triflyl-L-valinol (2w)



2w

Substrate **1w** was acetoxylated using **L23** following the **general procedure** for 16 hours to give the entitled product **2w** as a colorless oil (28.0 mg, 33%) after purification by flash column chromatography on silica gel (PE:EtOAc, 8:1) with a diastereoselectivity of 17:1 (determined by ^{1}H NMR analysis of the diasteromers). **^{1}H NMR** (400 MHz) δ 5.76 (d, *J* = 9.5 Hz, 1H), 4.69 – 3.97 (m, 4H), 3.79 (dtd, *J* = 10.2, 6.5, 3.9 Hz, 1H), 2.60 – 1.92 (m, 7H), 1.08 (d, *J* = 7.0 Hz, 3H). **^{13}C NMR** (100 MHz) δ 171.27, 171.14, 119.61 (q, *J* = 320.6 Hz), 65.62, 64.00, 57.17, 34.93, 20.97, 20.81, 14.05. **IR**: ν 3205, 2975, 1742, 1718, 1454, 1372, 1224, 1187, 1148, 1039, 613, 576, 505 cm^{-1}. **HRMS** (FD) calculated for $C_{10}H_{17}F_3NO_6S^+$ [M+H]$^+$: 336.0729; found: 336.0738.

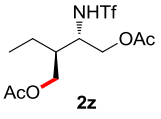
4,4'-Dicetoxy-*O*-Acetyl-*N*-triflyl-L-valinol (2w')



2w'

Substrate **1w** was diacetoxylated using **L23** following the **general procedure** for 16 hours to give the entitled product **2w'** as a white solid (5.0 mg, 5%) after purification by flash column chromatography on silica gel [first 8:1 (PE:EtOAc) to get **2w**, then 4:1 (PE:EtOAc) to get **2w'**]. **^{1}H NMR** (300 MHz) δ 5.92 (d, *J* = 9.5 Hz, 1H), 4.46 – 4.09 (m, 6H), 4.06 – 3.97 (m, 1H), 2.41 – 2.31 (m, 1H), 2.15 – 1.81 (m, 9H). **^{13}C NMR** (125 MHz) δ 170.97, 170.89, 170.84, 120.86 (q, *J* = 320.8 Hz), 63.88, 61.65, 61.52, 54.13, 39.74, 20.94, 20.91, 20.79. **IR**: ν 3207, 2924, 2854, 1743, 1456, 1370, 1225, 1191, 1148, 1041, 608, 575, 516 427 cm^{-1}.

4-Acetoxy-*O*-Acetyl-*N*-triflyl-L-Isoleucinol (2z)



2z

Substrate **1z** was acetoxylated using **L23** following the **general procedure** for 18 hours to give the entitled product **2z** as a colorless oil (21.0 mg, 25%) after purification by flash column chromatography on silica gel (PE:EtOAc, 8:1). **^{1}H NMR** (400 MHz) δ 5.44 (d, *J* = 9.0 Hz, 1H), 4.23 – 4.19 (m, 3H), 4.08 – 4.04 (m, 1H), 3.94 – 3.91 (m, 1H), 2.11 (s, 3H), 2.09 (s, 3H), 1.98 – 1.90 (m, 1H), 1.54 – 1.36 (m, 2H), 1.02 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (100 MHz) δ 171.0, 170.7, 119.5 (q, *J* = 318.0 Hz), 63.1, 63.0, 56.1, 42.6, 21.0, 20.9, 20.7, 11.8. **HRMS** (FD) calculated for $C_{10}H_{18}NO_4^+$ [M-Tf]$^+$: 216.1236; found: 216.0368.

2.5.4. Scale up of the acetoxylation reaction

In a pressure tube containing a suitable stirring bar the substrate **1a** (1.0 mmol, 1.0 equiv) was combined with $Pd(OPiv)_2$ (0.1 mmol, 10 mol%), $PhI(OAc)_2$ (2.5 mmol, 2.5 equiv), AgOAc (1.0 mmol, 1.0 equiv), 2,6-lutidine (0.2 mmol, 20 mol%) and DCM (1.0 mL). The tube was then sealed under air with a screw cap, placed into a pre-heated oil bath at 110 ℃ and stirred for 20 h. The reaction mixture was cooled to room temperature, filtered through Celite, eluting with CH_2Cl_2 and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (form 8:1 to 4:1, PE:EtOAc) providing 186.7 mg **2a** (58%, d.r. = 13:1, determined by ^{1}H NMR analysis of the diastereomers) and 25.0 mg **2a'** (6%).

2.5.5 Deprotection of triflyl group

*Stepwise strategy using 4-nitrobenzyl bromide and **(±)-2h***

Protection of ***(±)-2h*** with 4-nitrobenzyl bromide

In a flame-dried Schlenk flask containing a suitable stirring bar was added *rac*-methyl 4-acetoxy-*N*-triflyl-DL-alloisoleucinate ***(±)-2h*** (34 mg, 0.1 mmol, 1.0 equiv), K_2CO_3 (28 mg, 0.2 mmol, 2.0 equiv), 4-nitrobenzyl bromide (24 mg, 0.11 mmol, 1.0 equiv) and acetone (2 mL). The reaction was then stirred overnight. Water was added and the reaction was extracted with EtOAc three times. The combined organic extracts were washed with brine, dried with Na_2SO_4, filtrated and concentrated *in vacuo*. Crude ^{1}H NMR was measured and analyzed. A new product was detected with a ratio of 1:2 between it and the starting material. *Another reaction at slightly higher temperature (35 ℃) and longer reaction time (2 days) was also performed and a ratio of 1:1 between the newly formed product and the starting material was detected from crude ^{1}H NMR analysis.* Some efforts were put to purify the newly formed product. However, it was not separable from the starting material.

Protection of ***1w*** with 4-nitrobenzyl bromide

Similar reaction was done for the 4-nitrobenzyl protection of **1w**. Although around 60% of conversion was observed, it turned out to be not the desired product.

Procedure for the Tf deprotection using NH_3-Na

In a flame-dried three-necked flask containing a suitable stirring bar was added *rac*-methyl 4-acetoxy-*N*-triflyl-DL-alloisoleucinate **(±)-2h** (61 mg, 0.18 mmol) and cooled to -40 ℃. Around 2 mL of ammonia was added via cold finger technique. Anhydrous THF (1mL) was then added followed by addition of around 50 mg of Na. This deep blue solution was stirred for 50 min and TLC showed no starting material left. Methanol was added before the mixture was warmed up to room temperature. Saturated NH_4Cl aqueous solution was added, and the mixture was extracted with EtOAc three times. The combined organic extracts were washed with brine, dried with Na_2SO_4, filtrated and concentrated *in vacuo*. Crude ^{1}H NMR was messy. Purification was performed, but no desired product was obtained.

Procedure for the Tf deprotection using Red-Al

In a flame-dried Schlenk flask containing a suitable stirring bar was added *O*-acetyl-*N*-triflyl-L-valinol **1w** (55 mg, 0.2 mmol, 1.0 equiv) and anhydrous Toluene (2 mL) under N_2. Red-Al (0.56 mL, 3.6 mol/L, 2.0 mmol, 10 equiv) was then added dropwise at 0 ℃ before it was slowly heated to 50 ℃ and stirred overnight. Saturated aqueous solution of NH_4Cl was added, and the mixture was extracted with DCM three times. The combined organic extracts were washed with brine, dried with Na_2SO_4, filtrated and concentrated *in vacuo*. From analysis of crude ^{1}H NMR, only *N*-triflyl-L-valinol (OAc reduced product) was detected.

Procedure for the Tf deprotection using Zn/NH_4Cl

In a round bottom flask containing a stirring bar, *O*-acetyl-*N*-triflyl-L-valinol **1w** (55 mg, 0.2 mmol, 1.0 equiv) and Zn (654 mg, 10.0 mmol, 50.0 equiv) were added followed by the addition of saturated aqueous solution of NH_4Cl (5 mL) and THF (5 mL). The reaction was stirred overnight at room temperature. The reaction was extracted with EtOAc three times. The combined organic extracts were washed with brine, dried with Na_2SO_4, filtrated and concentrated in vacuo. Only starting material was detected from ^{1}H NMR analysis of the crude reaction mixture.

Procedure for the Tf deprotection using Mg/MeOH

In a round bottom flask containing a stirring bar, *O*-acetyl-*N*-triflyl-L-valinol **1w** (55 mg, 0.2 mmol, 1.0 equiv), Mg (97 mg, 4.0 mmol, 20 equiv) and methanol (3 mL) were added. The reaction was stirred under reflux overnight. Saturated aqueous solution of NH_4Cl was added, and the mixture was extracted with EtOAc three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtrated and concentrated *in vacuo*. Only starting material was detected from ^{1}H NMR analysis of the crude reaction mixture.

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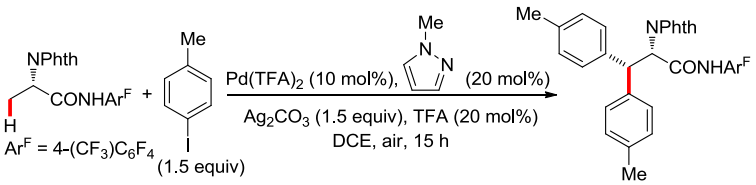
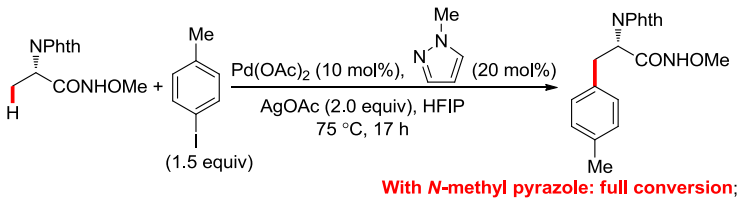
24. We have tested pyrazole as external ligand in several C–H activation reactions, yield improvement was observed for all of them:

a. C(sp^3)–H arylation of amino acid directed by an Ar^F amide auxilliary



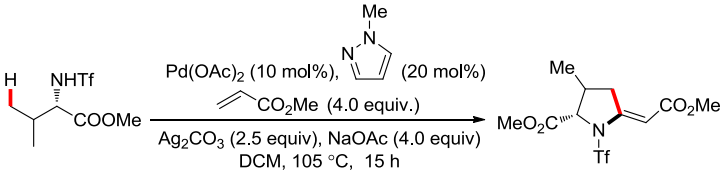
With *N*-methyl pyrazole: full conversion, mono: di = 87 : 13;
Without *N*-methyl pyrazole: 68% conversion, mono : di = 65 : 3.

b. C(sp^3)–H arylation of amino acid directed by an N-methoxyamide auxilliary



With *N*-methyl pyrazole: full conversion;
Without *N*-methyl pyrazole: 44% conversion.

c. C(sp^3)–H olefination of amino acid directed by triflyl-protected amine



With *N*-methyl pyrazole: 53% conversion;
Without *N*-methyl pyrazole: 0% conversion.

25. For selected examples, see: a) Y.-H. Zhang, B.-F. Shi, J.-Q. Yu, *J. Am. Chem. Soc.* **2009**, *131*, 5072–5074; b)

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26. For selected examples, see: a) S. Li, G. Chen, C.-G. Feng, W. Gong, J.-Q. Yu, *J. Am. Chem. Soc.* **2014**, *136*, 5267−5270; b) J. He, R. Takise, H. Fu, J.-Q. Yu, *J. Am. Chem. Soc.* **2015**, *137*, 4618−4621. See also 25c.
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CHAPTER 3

SELECTIVE C–H OLEFINATION OF INDOLINES (C5) AND TETRAHYDROQUINOLINES (C6) BY Pd/S,O-LIGAND CATALYSIS

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3.1 Introduction

Indolines and tetrahydroquinolines (THQs) are ubiquitous structures in natural products and pharmaceuticals that display a wide range of relevant biological activities (Figure 3.1).[1]

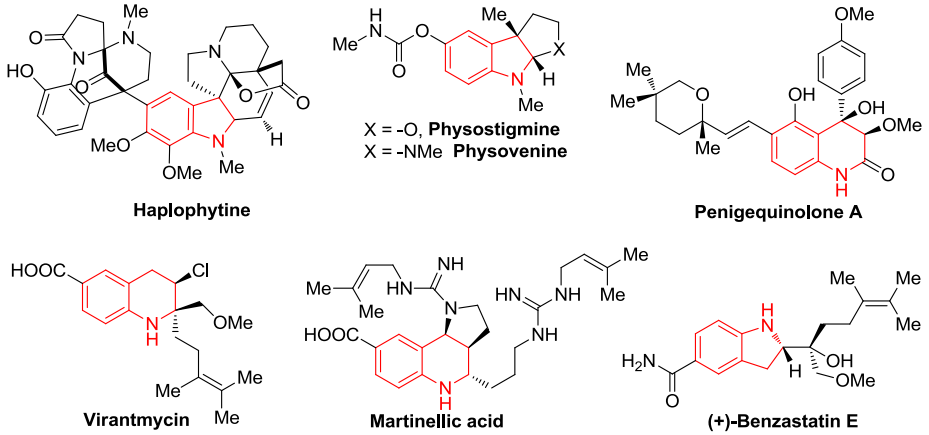
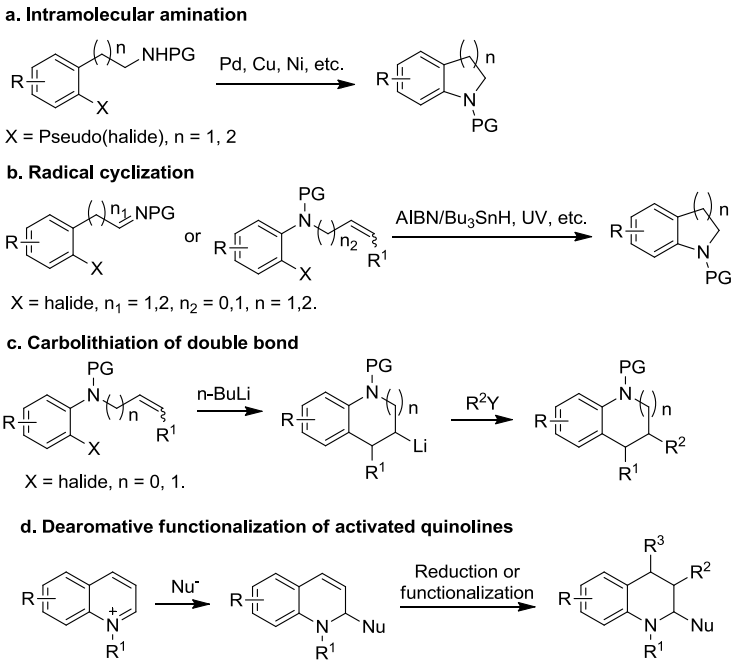


Figure 3.1 Representative natural products and pharmaceuticals containing indolines and THQs

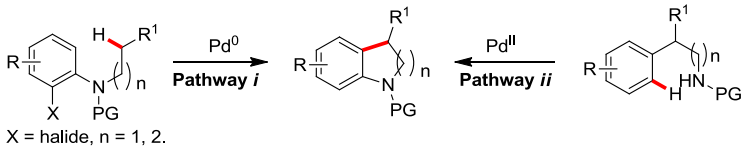
Traditionally, these structures can be prepared from hydrogenation of corresponding indoles and quinolines. To meet the requirement of accessing complex indolines and THQs, a great diversity of methods have been developed.[2] One of the most encountered methods is the intramolecular aryl amination of *N*-substituted aryl halides catalyzed or mediated by transition metals, as exemplified by intramolecular Ullman and Buchwald-Hartwig cross-coupling reactions (Scheme 3.1a).[3] Radical cyclization is also a very powerful way to construct these heterocycles, for example, intramolecular aryl radical addition to an imine or alkene initiated by AIBN/Bu_3SnH, Et_3B/Bu_3SnH or light (Scheme 3.1b).[4] An alternative way involves lithiation of aryl halides, followed by intramolecular carbolithiation of a double bond and anion trap by an electrophile (Scheme 3.1c).[5] Methods dealing with dearomative functionalization of indoles are also well-documented.[6] While for quinoline, dearomative functionalization (either starting from quinoline or activated quinoline) is done followed by reduction or further functionalization of the second double bond (Scheme 3.1d).[7,8] Some other methods that have been illustrated in the introduction of Chapter 2 for the preparation of amines, have also been used for the synthesis of indolines and tetrahydroquinolines.[9-11]



Scheme 3.1 Methodologies for the synthesis of indolines and THQs

Additionally, the synthesis of indolines and THQs *via* C–H activation has also been reported. These

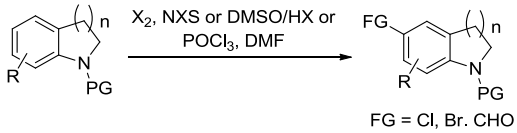
methodologies can be categorized in two: *i*) C–C bond formation directed by C–X bonds[12] and *ii*) C–N bond formation directed by nitrogen-containing functional groups (Scheme 3.2).[13]



Scheme 3.2 Preparation of indolines and THQs *via* C–H activation

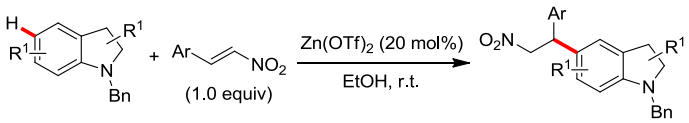
Alternative to the construction of these cores, the direct modification of already-existing indoline and THQ units offers an attractive approach to quickly build more complex and advanced molecules. Compared with traditional approaches that involve the use of prefunctionalized starting materials, the direct functionalization of C–H bonds is a more straightforward synthetic route. In addition, the starting materials are more accessible and therefore a broad range of substrates can be used. More importantly, the C–H functionalization strategy offers an innovative tactic to streamline the synthesis of new medicines by late-stage functionalization.

In this context, the *para*-selective halogenation[14] and formylation[15] of indolines and THQs via an electrophilic aromatic substitution mechanism has been reported (Scheme 3.3).



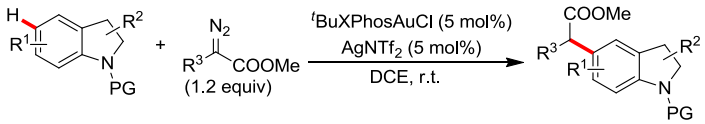
Scheme 3.3 *Para*-selective halogenation of indolines and THQs

A *para*-selective Michael-type Friedel-Crafts alkylation of indolines catalyzed by zinc was realized by the group of Saracoglu. They explained the high *para*-selectivity observed by means of steric hindrance (Scheme 3.4).[16] Similar reactivity for unprotected THQs was reported using $InCl_3$ as the catalyst in water.[17] Additionally, several enantioselective Friedel-Craft reactions have also been developed.[18,19]



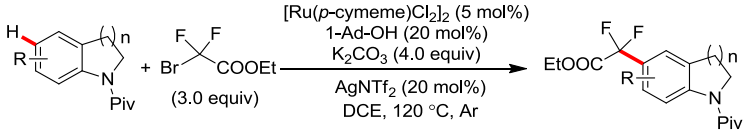
Scheme 3.4 *Para*-selective alkylation of indolines via Friedel-Craft type reaction

In terms of transition-metal catalyzed C–H functionalization, a gold-catalyzed C5-alkylation reaction of indolines with diazo compounds has been described. This methodology is compatible with both electron-rich and electron-poor indolines. The authors proposed that the reaction occurs via addition of the cationic gold intermediate at the *para* position of indoline (Scheme 3.5).[20]



Scheme 3.5 *Para*-selective alkylation of indolines catalyzed by gold

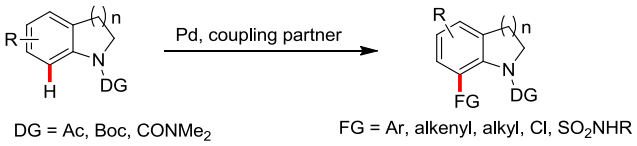
Recently, the group of Zhao reported a strategy for the *para*-selective difluoromethylation of indolines and THQs using a ruthenium catalyst (Scheme 3.6).[21] Preliminary mechanistic studies revealed that this reaction might go via a radical process.



Scheme 3.6 *Para*-selective alkylation of indolines catalyzed by ruthenium

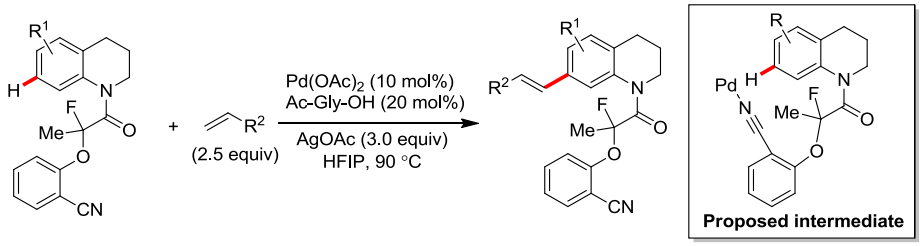
Generally, palladium-catalyzed C–H functionalization of indolines and THQs relies on the use of directing groups attached to the nitrogen atom.[22] Using this approach, the aryl,[22c] alkenyl[22g] as well as other functionalities such as alkyl[22h,22j], chlorine[22b], amide[22k] were introduced at the *ortho*-position to the nitrogen atom in indolines

(C7) and THQs (C8) (Scheme 3.7).



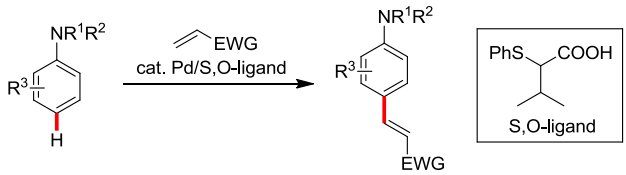
Scheme 3.7 *Ortho* functionalization of indolines and THQs

To achieve novel site selectivity, the group of Yu successfully designed templates that are attached to the nitrogen atom and facilitate *meta* C–H functionalization of indolines (C6) and THQs (C7).[22l,m] In the case of THQs, the template was attached to the nitrogen *via* an amide bond, and the reaction occurred via a highly strained tricyclic-cyclophane-like palladated intermediate (Scheme 3.8).[22l] For the *meta* C–H functionalization of indolines, a similar strategy using nitrile-based template has been reported.[23m] This approach showed very good generality, as many indolines with different electron properties were compatible and various functionalities (olefin, aryl, acetoxyl) were successfully introduced.



Scheme 3.8 *Meta* C–H functionalization of THQs using template

Although the selective C–H alkylation of indolines (C5) and THQs (C6) have been reported, general strategies to selectively obtain C5-olefinated indolines and C6-olefinated THQs are still elusive. Recently, our research group has discovered a new type of bidentate S,O-ligands that are capable of promoting C–H olefination of a series of non-directed arenes.[23] Using $Pd(OAc)_2$ and the S,O-ligand, highly *para*-selective C–H olefination of anilines was achieved. The methodology showed broad substrate scope, including mono-, di-, and trisubstituted tertiary, secondary, and primary anilines. (Scheme 3.9).[23d]



Scheme 3.9 Highly *para*-selective C–H olefination of anilines by Pd/S,O-ligand catalysis

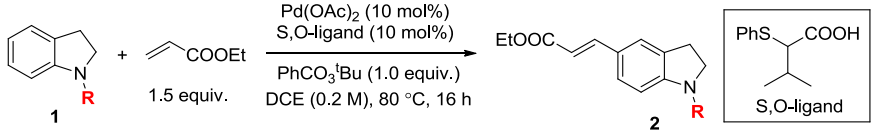
In this chapter, we describe a highly *para*-selective C–H olefination of indolines and THQs by using Pd/S,O-ligand catalyst. The synthetic potential of this methodology is demonstrated by the efficient olefination of several indoline-based natural products.

3.2 Results and discussion

We started our investigation using indoline as model substrate. We first evaluated the effect of different protecting groups in the reaction using similar reaction conditions to the ones reported for the *para*-selective C–H olefination of anilines: indoline (1.0 equiv), ethyl acrylate (1.5 equiv), $Pd(OAc)_2$ (10 mol%), S,O-ligand (10 mol%) and $PhCO_3{}^tBu$ (1.0 equiv) in DCE (0.2 M) at 80 ℃ for 16 h (Table 3.1). The reaction using the unprotected indoline did not show the formation of the desired olefinated product (entry 1). Instead, the olefinated product at the nitrogen center was detected in 39% yield. We observed that under the oxidizing reaction conditions used, the indoline is not stable as it was not detected after the reaction. We then evaluated three different *N*-protecting groups: methyl, Boc and benzyl (entries 2-4). Among them, *N*-methyl group gave the best result, providing the desired product in 38% ^{1}H NMR yield and with excellent regioselectivity (*para*:others > 20:1) (entry 2). Again, decomposition of the starting indoline was significant since no starting material was observed after the reaction. We observed that the use of the Boc-protecting group slightly increases the stability of the substrate as more than 50% combined yield of olefinated product and starting material was detected by ^{1}H NMR analysis (entry 3). However, a mixture of regioisomers (*para*:others = 6:1) was detected.

The low regioselectvity observed for the Boc-protected indoline can be rationalized by the possible coordination of Pd with the carbonyl group of the Boc group, promoting the formation of the *ortho*-olefinated product. Benzyl-protected indoline provided the olefinated product with slightly lower yield than the methyl-protected one (entry 4). In addition, a few minor byproducts, probably olefinated products at the aromatic ring of the benzyl group, were detected by ^{1}H NMR. We also performed the reaction of the methyl-protected indoline without S,O-ligand and no product was observed, highlighting the important role of S,O-ligand for the success of this reaction (entry 5). Instead, we detected the formation of *N*-methyl indole in 39% yield, which can be the reason for the low stability observed for these substrates in this transformation. Indeed, the oxidation of indolines to indoles has been reported with high efficiency using a variety of oxidants.[24]

Table 3.1 Protecting group optimization

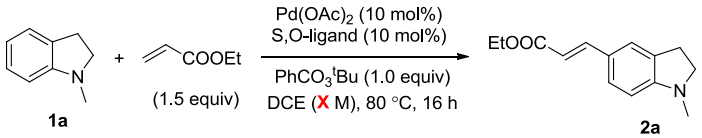


Entry	R	^{1}H NMR yield[a]	Starting material[a]
1	H	0%[b]	0%
2	**Me**	**38%**	**0%**
3	Boc	24%[c]	31%
4	Benzyl	27%[d]	10%
5[e]	Me	0%[f]	0%

[a] Yield was determined by ^{1}H NMR analysis of crude reaction mixture using CH_2Br_2 as internal standard. [b] 39% *N*-olefinated product was observed. [c] A mixture of regioisomers (6:1, *para*:others) was detected. [d] Other regioisomers were observed. [e] Reaction performed without S,O-ligand. [f] 39% oxidized product (*N*-methylindole) was detected.

After having determined the methyl group as the optimal protecting group, we then studied the effect of the concentration of the reaction (Table 3.2). It was found that increasing or decreasing the concentration of the reaction did not affect the yield dramatically and a concentration of 0.2M was optimal (entry 1).

Table 3.2 Optimization of the reaction concentration

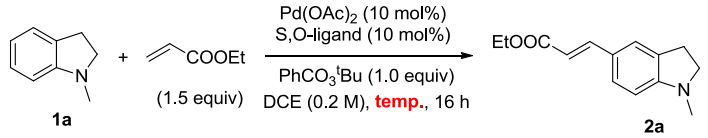


Entry	X	The amount of DCE (mL)	^{1}H NMR yield[a]
1	**0.20**	**1.25**	**38%**
2	0.10	2.50	36%
3	0.17	1.50	37%
4	0.83	0.30	31%

[a] The yield was determined by ^{1}H NMR analysis of crude reaction mixture using CH_2Br_2 as internal standard.

We also performed the reaction at different temperatures (Table 3.3) and we observed that the reaction at 60 ℃ provided the desired olefinated product in 51% yield (entry 2). We attributed this increase in yield to the greater stability of the starting material and product. However, when we carried out the reaction at 40 ℃, only 34% yield of the olefinated product was observed (entry 3). The lowest yield was obtained when the reaction was performed at 100 ℃ due to the instability of the substrates at this temperature (entry 4). Overall, the reaction temperature has a remarkable influence on the yield of the reaction, which highlights the importance to have the optimal temperature in order to keep a balance between reactivity and stability of substrates.

Table 3.3 Optimization of reaction temperature

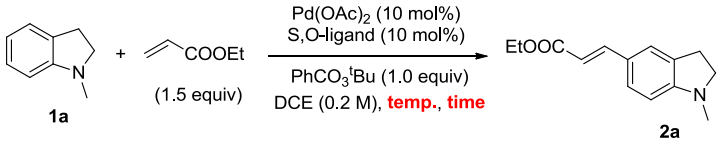


Entry	Temperature (℃)	^{1}H NMR yield[a]
1	80	38%
2	**60**	**51%**
3	40	34%
4	100	24%

[a] The yield was determined by ^{1}H NMR analysis of crude reaction mixture using CH_2Br_2 as internal standard.

Since both substrate and product were not stable at high temperature, but certain temperature was needed to achieve good reaction reactivity, we decided to evaluate the effect of the reaction time at different temperatures to find a balance between reactivity and stability (Table 3.4). It was found that performing the reaction at 80 ℃ for 2 hours gave comparable yield to performing the reaction at 60 ℃ for 16 hours (entry 1 *vs* entry 4). We decided to use 60 ℃ as optimal temperature for further optimization of reaction conditions.

Table 3.4 Optimization of time and temperature

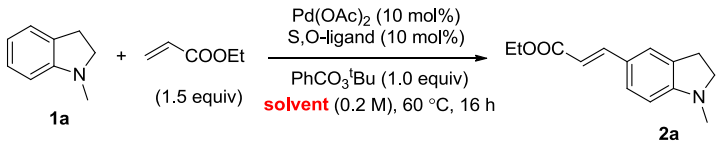


Entry	Reaction time (h)	^{1}H NMR yield (60 ℃)	^{1}H NMR yield (80 ℃)
1	**2**	31%	**50%**
2	4	41%	46%
3	6	46%	39%
4	**16**	**51%**	38%
5	24	41%	-

[a] The yield was determined by ^{1}H NMR analysis of crude reaction mixture using CH_2Br_2 as internal standard.

Different solvents were tested in the olefination reaction of *N*-methyl indoline (Table 3.5). The reaction using protic and/or polar solvents such as *t*-Amyl-OH, HFIP, DMF, MeCN, EtOAc and 1,4-dioxane gave the olefinated product in low yields. To our surprise, DCM gave the olefinated product in 23% yield only (entry 8). We also tested hexafluorobenzene but only a trace amount of product was detected. Therefore, we continue our studies using DCE as solvent.

Table 3.5 Optimization of solvents



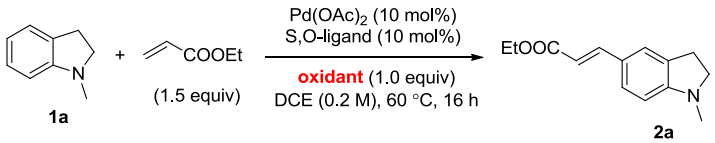
Entry	Solvent	^{1}H NMR yield[a]
1	**DCE**	**51%**
2	*t*-Amyl-OH	< 10%
3	hexafluoroisopropanol	0%
4	*N*,*N*-dimethylformamide	0%
5	acetonitrile	14%
6	ethyl acetate	12%
7	1,4-dioxane	< 10%
8	dichloromethane	23%

9	hexafluorobenzene	traces

[a] The yield was determined by ^{1}H NMR analysis of crude reaction mixture using CH_2Br_2 as internal standard.

The effect on the reaction of several oxidants was evaluated (Table 3.6). The reaction using other peroxides such as ^{t}BuOOH and H_2O_2 gave the olefinated product in less than 10% yield (entries 1-2). Highly oxidizing reagents such as oxone, $K_2S_2O_8$ and $PhI(OAc)_2$ failed to produce the product probably due to their incompatibility with the substrate as no starting material was recovered (entries 3-5). Metal oxidants such as $CuSO_4$ and AgOAc gave only traces of product (entries 6-7). The reaction using BQ as oxidant gave only 13% of the product (entry 8). Oxygen was also tested, and to our delight, the olefinated product was obtained in 44% yield although high pressure of oxygen was needed (entries 9-11). Although for practical issues we decided to continue our optimization with $PhCO_3{}^t$Bu as the oxidant, we proved that the use of oxygen as a sole oxidant is possible. Therefore, this methodology has the potential to be applied in chemical industry as a green method for the preparation of olefinated indolines. We also studied the effect on the reaction when we increase the amount of $PhCO_3{}^t$Bu (entries 13-14). We found out that when using 2 or 3 equiv of oxidant, lower yield was obtained, probably due to the oxidation of the starting material and/or product.

Table 3.6 Optimization of oxidants

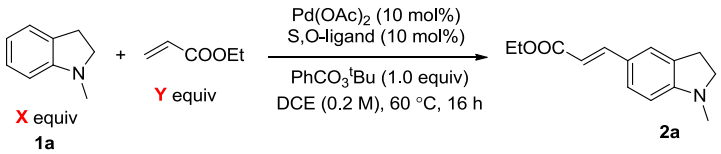


Entry	Oxidant	^{1}H NMR yield[a]
1	^{t}BuOOH (80%, w/w% in water)	< 10%
2	H_2O_2 (35%, w/w% in water)	< 10%
3	oxone	0%
4	$K_2S_2O_8$	0%
5	$PhI(Oac)_2$	0%
6	$CuSO_4$	< 10%
7	AgOAc	< 10%
8	BQ	13%
9	O_2 (1 atm)	< 10%
10	O_2 (6 atm)	39%
11	O_2 (10 atm)	44%
12	**$PhCO_3{}^t$Bu**	**51%**
13[c]	$PhCO_3{}^t$Bu	35%
14[d]	$PhCO_3{}^t$Bu	21%

[a] The yield was determined by ^{1}H NMR analysis of crude reaction sample using CH_2Br_2 as internal standard. [b] 2.0 equivalents of $PhCO_3{}^t$Bu was used. [c] 3.0 equivalents of $PhCO_3{}^t$Bu was used.

Finally, we evaluated the influence of the ratio between the substrate and ethyl acrylate (Table 3.7). When 2.0 equiv of substrate and 1.0 equiv of ethyl acrylate were used, the ^{1}H NMR yield could be increased to 58% and the product could be isolated in identical yield (entry 4). To our surprise, lower yields were obtained when increasing the equivalents of ethyl acrylate (entry 6).

Table 3.7 Screening of the ratio between *N*-methylindoline and ethyl acrylate



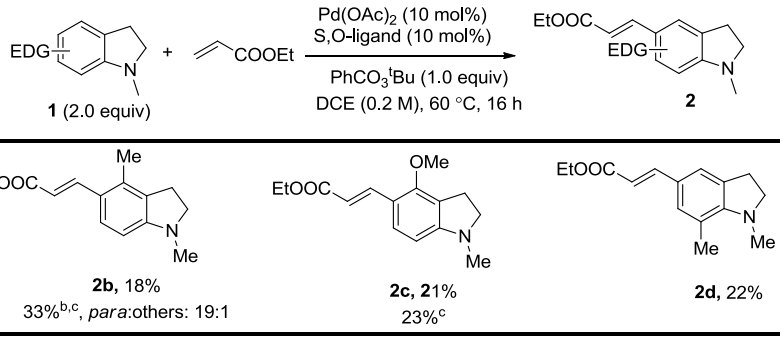
Entry	Ratio (**1a**/ethyl acrylate)	^{1}H NMR yield[a]
1	1.0 : 1.0	45%

2	1.2 : 1.0	47%
3	1.5 : 1.0	50%
4	**2.0 : 1.0**	**58% (58%[b])**
5	1.0 : 1.5	51%
6	1.0 : 3.0	43%

[a] The yield was determined by ^{1}H NMR analysis of crude reaction mixture using CH_2Br_2 as internal standard. [b] Isolated yield.

With the optimal reaction conditions in hand, we investigated the substrate scope of this reaction using *N*-Me-protected indolines. We first evaluated indolines bearing electron donating substituents at the aromatic ring (Table 3.8). The reaction of 4-methyl or 4-methoxy indoline derivatives **1b** and **1c**, provided the olefinated product in low yield. Slightly higher yields were obtained in the olefination reaction of **1b** and **1c** when using hexafluorobenzene (HFB) as solvent. Similarly, when the reaction was performed with 1,7-dimethyl indoline (**1d**), only 22% ^{1}H NMR yield of the olefinated product was detected. We rationalized this by the fact that electron-donating substituents at the aromatic ring make the substrates more prone to be oxidized. Indeed, a significant amount of indole derivatives, including the olefinated one, were detected in the reaction mixture.

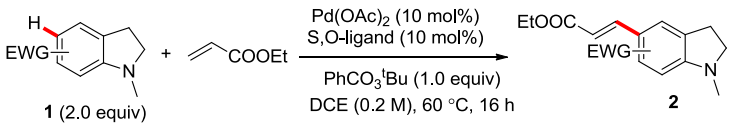
Table 3.8 Substrate scope of electron-rich indolines[a]

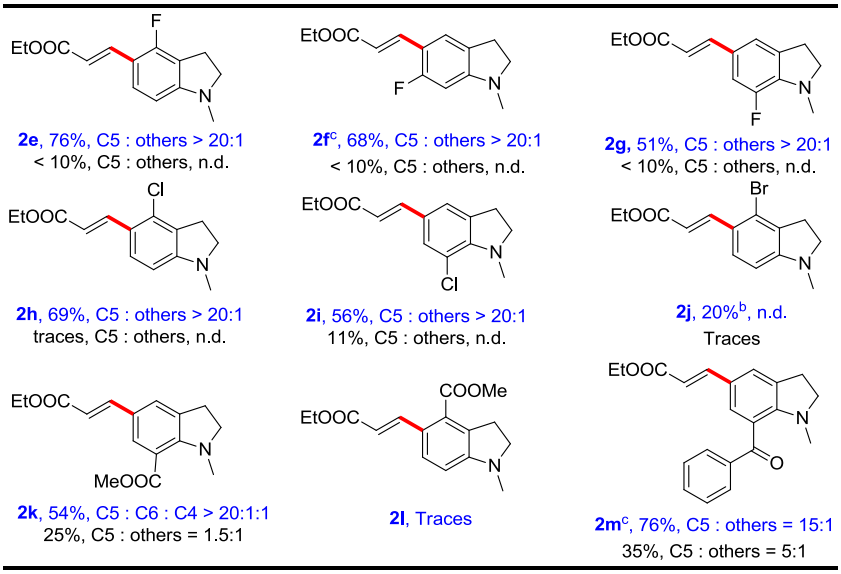


[a] The yield was determined by ^{1}H NMR analysis of crude reaction mixture using CH_2Br_2 as internal standard. [b] Isolated yield. [c] HFB was used instead of DCE as solvent.

We then prepared some indolines bearing an electron-withdrawing substituent at the aromatic ring and treated them under the C–H olefination reaction conditions (Table 3.9). It was found that they are both more stable and reactive than the unsubstituted indolines as no oxidized products were observed. First, we tested several *N*-methyl indolines bearing a fluorine atom at the 4, 6 or 7 position (**1e-g**). These three substrates furnished the olefinated products in good yields (51%–76%) and with excellent regioselectivity (> 20:1) (**2e-2g**, Table 3.9). The lower yield of 7-fluoroindoline substrate can be attributed to the deactivating effect of fluorine atom at its *meta* position. Indeed, a similar trend was observed when the reaction was performed with chlorinated indolines. 4-Chloro indoline **1h** gave 69% of olefinated product **2h**, while 7-chloro indoline **1i** gave the olefinated product **2i** with a slightly lower yield of 56%. We also tested the reaction using a 4-bromo indoline derivative **1j**, but the desired olefinated product was only detected in 20% ^{1}H NMR yield. The substrate bearing an ester group at 7-position provided the olefinated product **2k** with 54% isolated yield. However, when the ester group was at the 4-position, only traces of olefinated product were detected. The reaction with 7-benzoyl indoline **1m** provided the desired olefinated product **2m** in 76% yield with a slight decrease in selectivity (*para*:others = 15:1). We also performed the reaction for all substrates in the absence of the S,O-ligand. Interestingly, low yields and poor regioselectivities were obtained, highlighting the key role of the S,O-ligand in promoting this transformation.

Table 3.9 Substrate scope of electron-poor indolines[a]

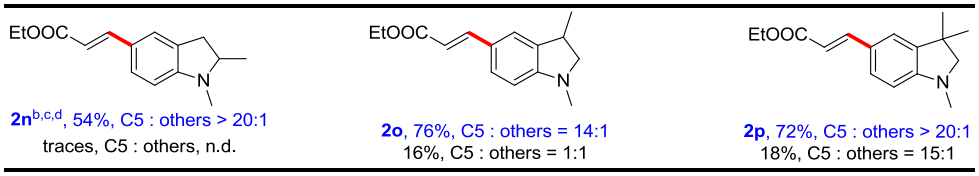


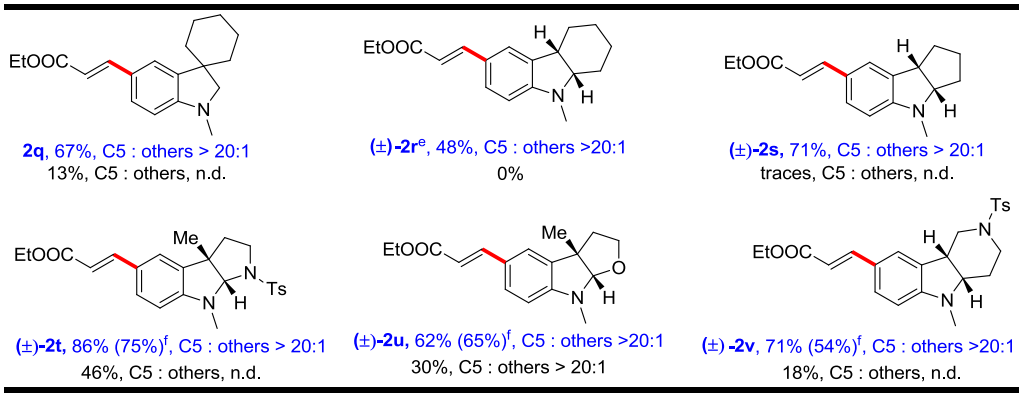


[a] Isolated yield was reported for reactions with S,O-ligand. Yields of reactions without S,O-ligand were determined by ^{1}H NMR analysis of crude reaction mixtures using CH_2Br_2 as internal standard. Selectivities were determined by ^{1}H NMR analysis of the crude sample (n.d., not determined). [b] Yield was determined by ^{1}H NMR analysis of crude reaction samples using CH_2Br_2 as internal standard. [c] A mixture of DCE and HFB (1:4, v/v) was used as solvent.

We also explored some indolines bearing substituents at the C2- and/or C3- positions (Table 3.10). 2-Methyl indoline **1n** delivered the product in 54% isolated yield with excellent regioselectivity (> 20:1) while, 3-methyl indoline gave a higher yield of 76% but with decreased selectivity (*para*:others, 14:1). The exact reason for this difference in the reactivity and selectivity between these two substrates is unclear to us. Good yields (72−67%) and perfect selectivities were obtained using 3,3-dialkyl indolines (**1p** and **1q**). The reaction of 2,3-indoline-fused cyclohexane **1r** and cyclopentane **1s** furnished the olefinated products in 48% and 71% yields, respectively, with perfect C5-selectivity. Pyrroloindoline skeleton is widely found in natural products and pharmaceuticals and was demonstrated to be compatible in this reaction, producing product **2t** in 86% yield with perfect selectivity (> 20:1). Furoindoline also serves as a very important motif in pharmaceuticals and the reaction of its derivative **1u** furnished the product **2u** in 62% isolated yield. Finally, the olefinated product **2v**, obtained from the reaction of tetrahydro-9-pyridoindoline, was isolated in 71% yield with perfect selectivity. The successful C–H olefination of these multiple functional groups containing substrates demonstrated the power of our strategy for selective late stage modifications in complex molecules. To further prove the synthetic utility of this methodology, we performed the reaction of three complex substrates **1t-v** using them as limiting reagents in the reaction. To our delight, similar yields were obtained in all cases. Again, for comparison, we performed the reaction without the S,O-ligand, demonstrating that the S,O-ligand is responsible for the dramatic increase in both reactivity and selectivity of the reaction.

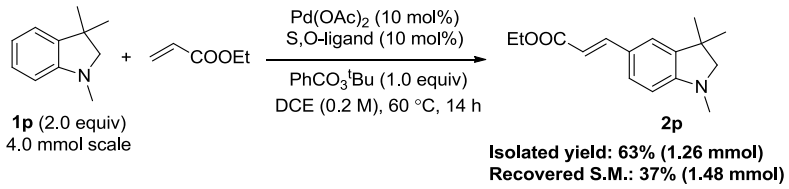
Table 3.10 Scope of C2 and/or C3 substituted indolines[a]





[a] Isolated yields were reported for reactions with S,O-ligand. Yields of reactions without S,O-ligand were determined by ^{1}H NMR analysis of crude mixture by using CH_2Br_2 as internal standard. Selectivities were determined by ^{1}H NMR analysis of the crude mixture (n.d., not determined). [b] A mixture of DCE and HFB (1:4, v/v) was used as solvent. [c] The reaction was performed at 80 °C. [d] The reaction time was 8 h. [e] A mixture of DCE and HFB (1:1, v/v) was used as the solvent. [f] 1.0 equiv of indoline (0.25 mmol) and 2.0 equiv of ethyl acrylate were used.

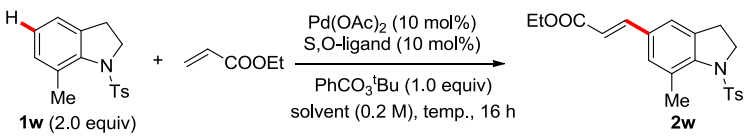
To prove the scalability of this transformation, we performed the C–H olefination reaction of 3,3-dimethyl indoline **1p** on a 4.0 mmol scale (Scheme 3.17). The olefinated product was obtained in 63% yield and 37% of starting material was recovered.



Scheme 3.17 Scale up of *para*-selective C–H olefination reaction

After proving the generality of the reaction with indolines bearing an electron-withdrawing substituent at the aromatic ring and with C2 and/or C3 substituted indolines, we decided to investigate further the reactivity of indolines bearing an electron donating substituent. We attributed the low yields of the olefination reaction to the fact that these substrates are more prone to oxidation due to their more electron-rich nature. Then, we speculated that by changing the methyl protecting group to a more electron-withdrawing protecting group, the stability of these indolines could increase. We first tested the olefination reaction of the *N*-tosyl 7-methyl indoline (**1w**) (Table 3.11). We observed that the substrate was less reactive providing the olefinated product in only 21% yield as a mixture of multiple regioisomers (entry 1). The reactivity was still low even when we elevated the temperature to 100 °C. When we used HFB as solvent, slightly lower yields and a mixture of multiple regioisomers were detected by ^{1}H NMR. The low reactivity observed for this substrate can be attributed to the lower delocalization of the lone pair of electrons of the nitrogen atom into the aromatic ring. Despite the lower yields obtained using the tosyl-protected indoline, it was still encouraging to find out that indeed, the substrate was more stable than the methyl-protected one.

Table 3.11 Olefination reaction of **1w**[a]

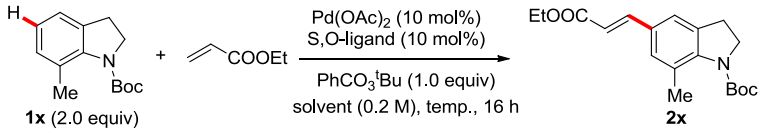


Entry	solvent	Temp.	^{1}H NMR yield	Recorvered S.M.
1	DCE	60	21%, multiple isomers	0.9 equiv
2	HFB	60	< 10%	> 0.95 equiv
3	DCE	80	34%, multiple isomers	0.82 equiv
4	HFB	80	23%, multiple isomers	0.51 equiv
5	DCE	100	32%, multiple isomers	0.84 equiv

[a] Yield was determined by ^{1}H NMR analysis of crude reaction mixture using CH_2Br_2 as internal standard.

We then switched to Boc protecting group using *N*-Boc-7-methylindoline (**1x**) as the substrate (Table 3.12). We observed that the reaction at 60 ℃ provided the olefinated product **2x** in low yield both in DCE and HFB. In both cases, a mixture of regioisomers was detected by ^{1}H NMR analysis. When we increased the reaction temperature to 80 ℃, the olefinated product **2x** was isolated in 62% combined yield of three regioisomers with the *para*-olefinated product being the major one (*para*:others = 5:4). The reaction was also performed at 100 ℃ but slightly lower yield was detected. Overall, the reactivity of the Boc-protected indoline is higher than the Ts-protected one but also is less stable as some decomposition was observed.

Table 3.12 Olefination reaction of **1x**[a]

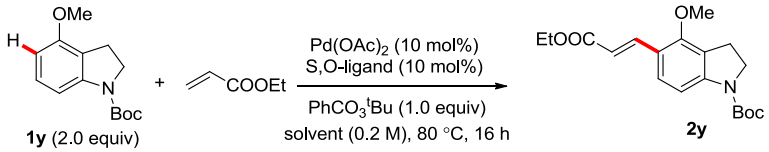


Entry	solvent	Temp.	^{1}H NMR yield	Recorvered S.M.
1	DCE	60	20%, multiple isomers	0.81 equiv
2	HFB	60	15%, multiple isomers	0.77 equiv
3	**DCE**	**80**	**63%, multiple isomers (62%, *para*:others = 5:4)[b]**	**0.43 equiv**
4	DCE	100	59%, multiple isomers	0.46 equiv

[a] The yield was determined by ^{1}H NMR analysis of crude reaction mixture using CH_2Br_2 as internal standard. [b] Isolated yield.

We then decided to test *N*-Boc-4-methoxyindoline (**1y**) to see if the methoxy group could help in improving the selectivity of the reaction, as the methoxy group activates C5 and C7 positions (Table 3.13). When the reaction was performed in DCE, we obtained the olefinated product **2y** with excellent yield (78% ^{1}H NMR yield) although with poor regioselectivity (C5:C7 = 1:1) (Entry 1, Table 3.13). When HFB was used as the solvent, better selectivity was detected but the yield dropped to 58% (Entry 2, Table 3.13).

Table 3.13 Olefination reaction of **1y**[a]



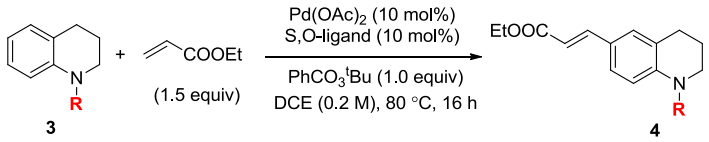
Entry	Solvent	^{1}H NMR yield	Recovered S.M.
1	DCE	78% (*para*:*ortho* = 1:1) (68%, *para*:*ortho* = 1:1)[b]	0.61 equiv
2	HFB	58% (*para*:*ortho* = 4:1)	0.71 equiv

[a] The yield was determined by ^{1}H NMR analysis of crude reaction mixture using CH_2Br_2 as internal standard. [b] Isolated yield.

To conclude, the use of electron withdrawing protecting groups stabilizes the substrates bearing an electron-donating substituent at the aromatic ring. However, both the reactivity and regioselectivity of the reaction are lower than methyl-protective indolines bearing an electron-withdrawing substituent at the aromatic ring. Thus, indolines bearing electron donating substituents at the aromatic ring can be olefinated using our Pd/S,O-ligand catalyst in good yields as a mixture of regioisomers using Boc-protected indolines.

After having determined the substrate scope of indolines using our methodology, we moved our attention to THQ substrates. Considering that THQ substrates are more stable as they are much less prone to be oxidized to quinolines, we decided to optimize the reaction conditions again using THQ as the limiting reagent. First, some protecting groups were evaluated under similar reaction conditions reported for the olefination of anilines (Table 3.14). Like indoline, THQ without a protecting group failed to give any product (entry 1). *N*-Methyl tetrahydroquinoline (**3a**) delivered the olefinated product **4a** in 55% ^{1}H NMR yield with perfect regioselectivity (*para*:others > 20:1) (entry 2). The introduction of a Boc group at the nitrogen center completely inhibits the reactivity of the substrate and no formation of the olefinated product was detected (entry 4). The reaction using the benzyl-protected THQ provided the desired product in 28% ^{1}H NMR yield (entry 4). In the absence of S,O-ligand, the olefinated product of *N*-methyl tetrahydroquinoline was only detected in 11% yield, showcasing again the crucial role of the S,O-ligand in promoting this transformation (entry 5).

Table 3.14 Optimization of protecting groups in the olefination of THQ

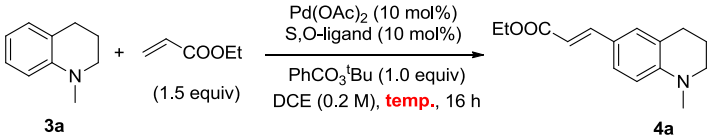


Entry	R	^{1}H NMR yield[a]
1	H	0%
2	**Me**	**55%**
3	Boc	0%
4	Benzyl	28%
5[b]	Me	11%

[a] Yield was determined by ^{1}H NMR analysis of crude reaction sample using CH_2Br_2 as internal standard. [b] Without S,O-ligand.

We then evaluated the reaction parameters using *N*-methyl tetrahydroquinoline (**3a**) as the model substrate. First, we studied the effect of the temperature on the reaction (Table 3.15). When the reaction was performed at higher temperature, a lower yield was obtained (entry 2). In contrast, we found out that lowering the reaction temperature to 40 ℃ has a beneficial effect, giving the desired product in 72% yield (entry 4). The reaction at room temperature provided the product in slightly lower yield (61%, entry 5) .

Table 3.15 Optimization of reaction temperature[a]

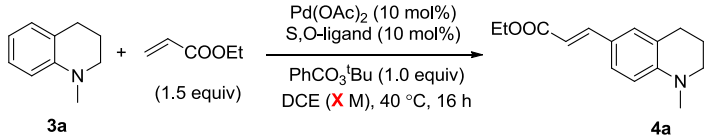


Entry	Temperature (℃)	^{1}H NMR yield
1	80	55%
2	100	26%
3	60	64%
4	**40**	**72%**
5	23	61%

[a] Yield was determined by ^{1}H NMR analysis of crude reaction mixture using CH_2Br_2 as internal standard.

We then evaluated the reaction concentration and both, lower and higher concentration of DCE gave the olefinated product in lower yields (Table 3.16).

Table 3.16 Optimization of reaction concentration[a]



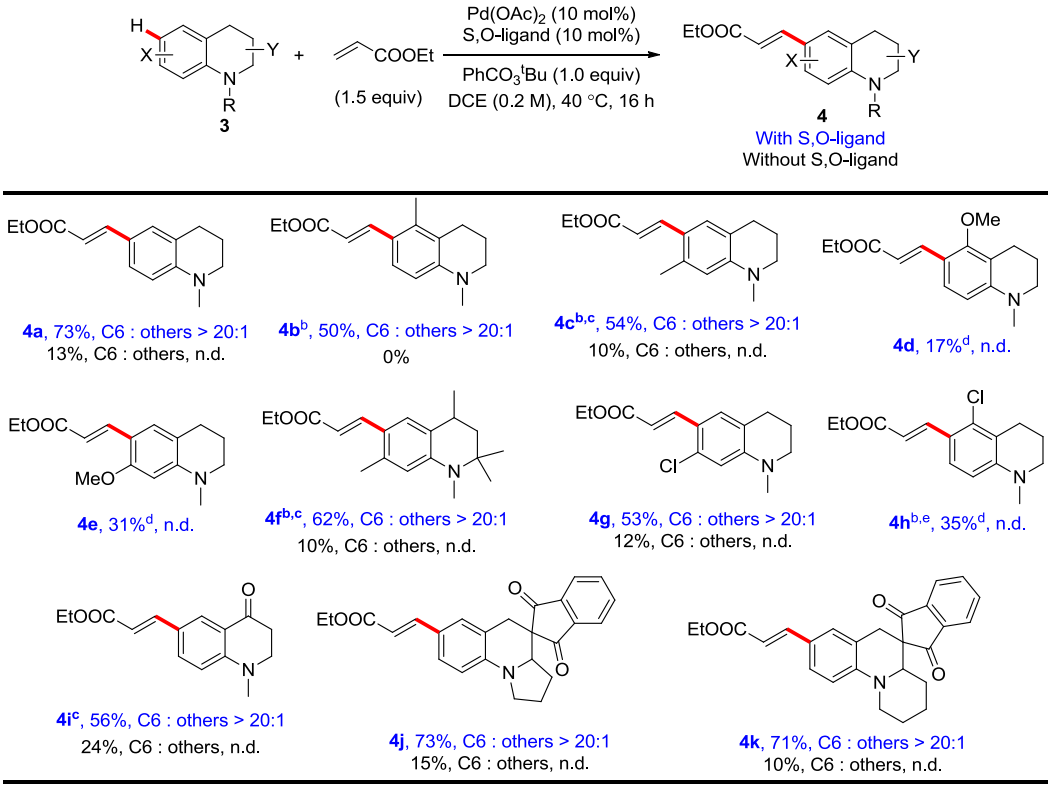
Entry	X	The amount of DCE (mL)	^{1}H NMR yield
1	**0.20**	**1.25**	**72%**
2	0.10	2.50	69%
3	0.30	0.83	57%

[a] Yield was determined by ^{1}H NMR analysis of crude reaction mixture using CH_2Br_2 as internal standard.

With these optimal reaction conditions in hand, we explored the substrate scope (Table 3.17). We first explored the reactivity of THQs bearing a methyl group at different positions of the aromatic ring. Different from indolines, methyl-substituted THQs are stable under the reaction conditions. Both 5- and 7-methyl tetrahydroquinolines **3b** and **3c**, gave olefinated products in 50% and 54% yields respectively with excellent

selectivity (*para*:others > 20:1). However, lower yields were detected when the reaction was performed with 5- and 7-methoxy tetrahydroquinolines **3d** and **3e**. The reaction of *N*-methyl 2,2,4,7-tetramethyl THQ (**3f**) furnished the olefinated product in 62% isolated yield. Then, we performed the reactions of more electron poor THQs. Under optimal conditions, *N*-methyl 7-chloro THQ (**3g**) was olefinated in 53% yield and with excellent selectivity. The reaction using *N*-methyl 5-chloro THQ (**3h**) gave the product with only 35% ^{1}H NMR yield at 60 ℃. The reaction was also compatible with the presence of a carbonyl group as *N*-methyl 2,3-dihydro-1H-quinolin-4-one (**3i**) was olefinated in 56% yield. Spirotetrahydroquinolines **3j** and **3k** were proved to be suitable substrates in this transformation, producing the olefinated products **4j** and **4k** in 73% and 71% isolated yields, respectively.

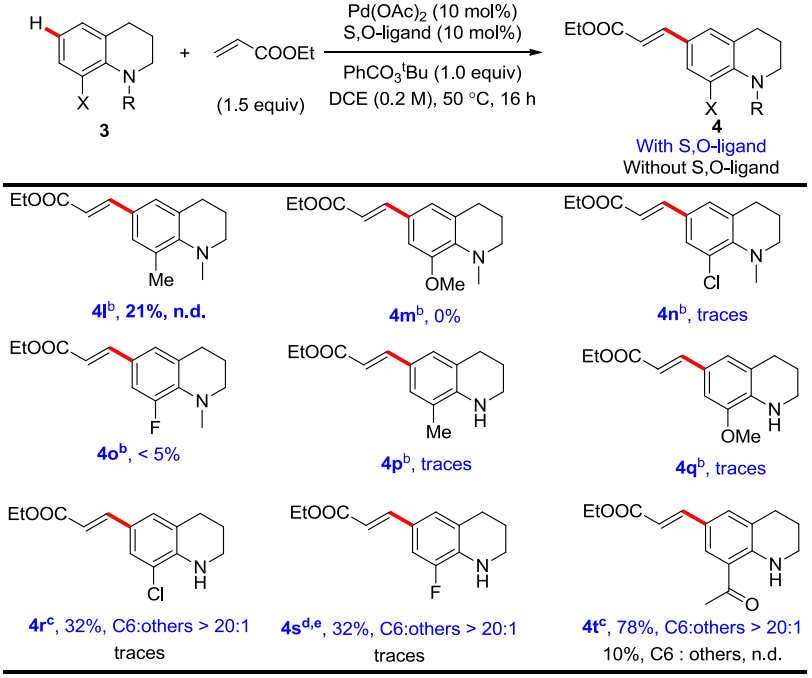
Table 3.17 Substrate scope of tetrahydroquinolines[a]



[a] Isolated yields were reported for reactions with S,O-ligand. Yields for reactions without S,O-ligand were determined by ^{1}H NMR analysis of crude mixtures by using CH_2Br_2 as internal standard. Selectivities were determined by ^{1}H NMR analysis of the crude mixture (n.d., not determined). [b] 1,4-Dioxane was used as solvent. [c] Reaction was performed at 50 ℃. [d] Yields were determined by ^{1}H NMR analysis of crude sample by using CH_2Br_2 as internal standard (n.d., not determined). [e] Reaction was performed at 60 ℃.

We then continued evaluating *N*-methyltetrahydroquinolines bearing a substituent at the 8-position (Scheme 3.18). Unfortunately, the reaction using 8-methyl, 8-methoxy, 8-chloro and 8-fluoro *N*-methyltetrahydroquinolines **4l**–**4o** provided the olefinated products in low yields. We assume that this is probably due to the clash between the substituent and the methyl group on the nitrogen, which forces the nitrogen out of the plane of the aromatic ring, thus deactivating the substrate. To prove this hypothesis, we tested a few unprotected tetrahydroquinolines. Indeed, although substrates substituted with a methyl and methoxy group at 8-position, **3p** and **3q**, failed to give olefinated products, better yields were obtained when THQs were substituted with a chlorine or fluorine atom compared with the *N*-protected ones (**4r**–**4s**). The reaction of the unprotected 8-etanone THQ (**3t**) furnished the olefinated product in 78% yield with excellent selectivity (> 20:1).

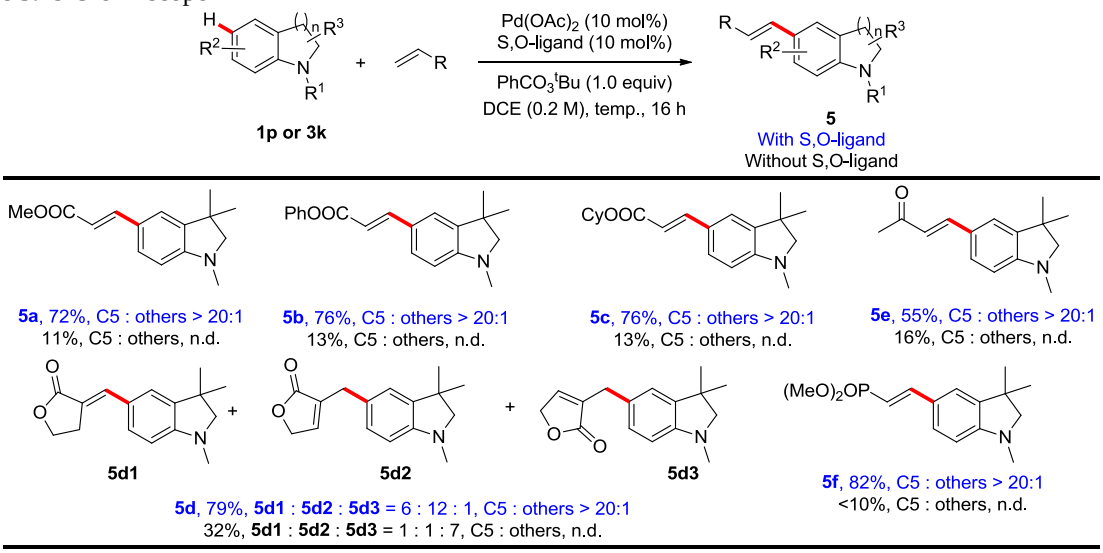
Table 3.18 Substrate scope of 8-substituted tetrahydroquinolines[a]

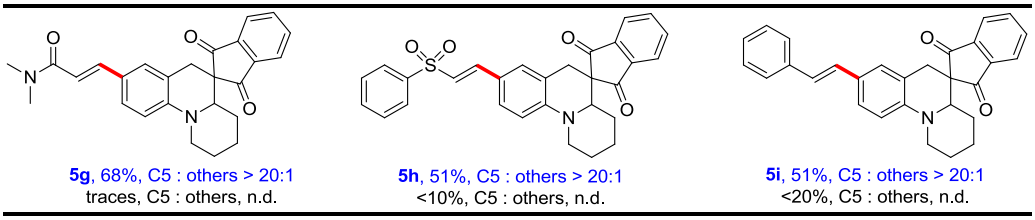


[a] Isolated yields were reported for reactions with S,O-ligand. Yields for reactions without S,O-ligand were determined by ^{1}H NMR analysis of crude mixture by using CH_2Br_2 as internal standard. Selectivities were determined by ^{1}H NMR analysis of the crude mixture (n.d., not determined). [b] Yields were determined by ^{1}H NMR analysis of crude sample by using CH_2Br_2 as internal standard (n.d., not determined). [c] Reaction was performed at 80 ℃. [d] 1,4-Dioxane was used as solvent. [e] Reaction was performed at 60 ℃.

Finally, we evaluated the scope of olefins as shown in Table 3.19. The reaction of *N*-methyl 3,3-dimethyl indoline (**3p**) with several olefins, including methyl, phenyl, and cyclohexylacrylates, furnished the olefinated products **5a**−**c** in high yields (72−76%) and selectivities. α-Methylene-γ-butyrolactone afforded compound **5d** in 79% yield as a mixture of **5d1**, **5d2**, and **5d3** in a ratio of 6:12:1. Other activated olefins such as methyl vinyl ketone and vinylphosphonate were also used, providing the olefinated products **5e** and **5f** in 55 and 82% yields, respectively. We also tested the C−H olefination using the spirotetrahydroquinoline **3k**. The reaction using vinylamide and vinyl sulfonate provided the corresponding olefinated products **5g** and **5h**, respectively, in synthetically useful yields (51−68%). To our delight, the challenging substrate styrene was also a suitable olefin for this reaction, providing the olefinated product **5i** in 51% yield.

Table 3.19 Olefin scope[a]





[a]Isolated yields were reported for reactions with S,O-ligand. Yields for reactions without S,O-ligand were determined by ^{1}H NMR analysis of crude sample by using CH_2Br_2 as internal standard. Selectivities were determined by ^{1}H NMR analysis of the crude mixture (n.d., not determined).

3.3 Conclusions

In conclusion, we have developed a general strategy for the highly *para*-selective C–H olefination of indolines (C5) and tetrahydroquinolines (C6) by using a Pd/S,O-ligand catalyst. The S,O-ligand was key to the success of this transformation and was responsible for the dramatic increase in both the reactivity and regioselectivity. The reaction is operationally simple and easily scalable and shows great substrate scope. A wide range of indolines, tetrahydroquinolines, and olefins can be used. However, electron-rich indolines turned out to be very unstable in this reaction, giving low yields of products. Although the instability issue was solved by introducing an electron-withdrawing protecting group, providing the olefinated products in higher yields, the good regioselectivity was then sacrificed. The synthetic potential of this strategy for late-stage modification of complex structures was also demonstrated by the successful C–H olefination of several highly advanced molecules.

3.4 Acknowledgement

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3.5 Experimental Section

General Information

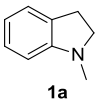
Chromatography: Silicycle Silica Flash P60 size 40-63 μm (230-400 mesh), TLC: Merck silica gel 60 (0.25mm). Visualization of the chromatogram was performed by UV and $KMnO_4$ solution. Mass spectra were recorded on AccuTOF GC v 4g, JMS-T100GCV mass spectrometers. ^{1}H, ^{13}C and ^{31}P were recorded on Bruker 500 AMX, 400 and Bruker DRX 300 using $CDCl_3$ as solvent. Chemical shift values are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: δ 7.26 for ^{1}H, δ 77.16 for ^{13}C). Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublets of doublets, t = triplet, bs = broad singlet, m = multiplet, td = triplet of doublets, dt = doublet of triplets), coupling constants (Hz), and integration. Infrared spectra were recorded on a Bruker IFS 28 FT-spectrophotometer. ATR technique was used in IR spectroscopy. All reagents and solvents were used as received unless it was specified. $Pd(OAc)_2$ was purchased from Strem. S,O-ligand [3-methyl-2-(phenylthio)butanoic acid] was prepared following the procedure reported in the literature.[23]

3.5.1. Synthesis of indoline and tetrahydroquinoline substrates

General procedure for the synthesis of *N*-methyl indolines and tetrahydroquinolines

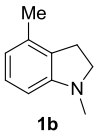
N-methyl protected substates were prepared following the procedure described in the literature.[26] In a flame-dried Schlenk flask under N_2, the corresponding indole or quinoline derivative (1.0 equiv) was added, followed by paraformaldehyde (5.0–10.0 equiv) and acetic acid (0.2 M). At 0 ℃, $NaCNBH_3$ (2.0–10.0 equiv) was then added portionwise. The reaction was stirred at room temperature overnight and was quenched at 0 ℃ by slowly adding cold NaOH aqueous solution (10 M) until the reaction was basic. The mixture was extracted with DCM three times and the combined organic extracts were washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. The product was purified by flash column chromatography on silica gel.

***N*-Methylindoline (1a)**



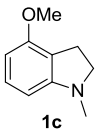
1a was prepared following the general procedure starting from indole (1.11 g, 9.33 mmol) using 5.0 equivalents of paraformaldehyde and 2.0 equivalents of $NaCNBH_3$ as a colorless liquid (0.80 g, 64%) after purification by flash column chromatography (PE:Et_2O, 20:1) and its ^1H NMR data matched with those reported in the literature.[27] **^{1}H NMR** (400 MHz) δ 7.11 – 7.07 (m, 2H), 6.68 (t, *J* = 7.4 Hz, 1H), 6.50 (d, *J* = 8.0 Hz, 1H), 3.29 (t, *J* = 8.2 Hz, 2H), 2.95 (t, *J* = 8.1 Hz, 2H), 2.76 (s, 3H).

1,4-Dimethylindoline (1b)



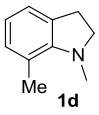
1b was prepared following the general procedure starting from 4-methylindole (0.90 g, 6.88 mmol) using 5.0 equivalents of paraformaldehyde and 5.3 equivalents of $NaCNBH_3$ as a colorless liquid (0.81 g, 81%) after purification by flash column chromatography (PE:Et_2O, 9:1) and its ^1H NMR data matched with those reported in the literature.[27] **^{1}H NMR** (300 MHz) δ 7.02 (t, *J* = 7.7 Hz, 1H), 6.53 (d, *J* = 7.6 Hz, 1H), 6.36 (d, *J* = 7.8 Hz, 1H), 3.31 (t, *J* = 8.2 Hz, 2H), 2.88 (t, *J* = 8.1 Hz, 2H), 2.76 (s, 3H), 2.22 (s, 3H).

***N*-Methyl-4-methoxyindoline (1c)**



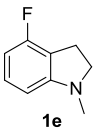
1c was prepared following the general procedure starting from 4-methoxyindole (1.03 g, 7.02 mmol) using 5.0 equivalents of paraformaldehyde and 4.7 equivalents of $NaCNBH_3$ as a colorless liquid (0.69 g, 61%) after purification by flash column chromatography (PE:Et_2O, 4:1). **^{1}H NMR** (300 MHz) 7.07 (t, *J* = 8.0 Hz, 1H), 6.30 (d, *J* = 8.2 Hz, 1H), 6.20 (d, *J* = 7.8 Hz, 1H), 3.82 (s, 3H), 3.31 (t, *J* = 8.3 Hz, 2H), 2.91 (t, *J* = 8.2 Hz, 2H), 2.75 (s, 3H). **^{13}C NMR** (75 MHz,) δ 156.1, 155.2, 128.8, 116.3, 101.4, 101.3, 56.4, 55.3, 36.5, 25.8. **IR**: ν 2948, 2804, 1612, 1482, 1258, 1229, 1062, 754, 705 cm^{-1}. **HRMS** (ESI) calculated for $C_{10}H_{14}NO^+$ $[M+H]^+$: 164.1075; found: 164.1078.

1,7-Dimethylindoline (1d)



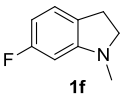
1d was prepared following the general procedure starting from 7-metylindole (1.31 g, 10.0 mmol) using 5.0 equivalents of paraformaldehyde and 5.0 equivalents of $NaCNBH_3$ as a colorless liquid (1.20 g, 83%) after purification by flash column chromatography (PE:Et_2O, 9:1) and its ^1H NMR data matched with those reported in the literature.[27] **^{1}H NMR** (300 MHz) δ 6.96 (d, *J* = 7.1 Hz, 1H), 6.85 (d, *J* = 7.5 Hz, 1H), 6.67 (t, *J* = 7.4 Hz, 1H), 3.29 (t, *J* = 8.4 Hz, 2H), 2.95-2.90 (m, 5H), 2.37 (s, 3H).

4-Fluoro-*N*-methylindoline (1e)



1e was prepared following the general procedure starting from 4-fluoroindole (1.01 g, 7.48 mmol) using 5.0 equivalents of paraformaldehyde and 5.0 equivalents of $NaCNBH_3$ as a pale yellow liquid (0.58 g, 51%) after purification by flash column chromatography (PE:Et_2O, 20:1). **^{1}H NMR** (400 MHz) δ 7.06 – 7.00 (m, 1H), 6.37 (t, *J* = 8.5 Hz, 1H), 6.25 (d, *J* = 7.8 Hz, 1H), 3.37 (t, *J* = 8.3 Hz, 2H), 2.99 (t, *J* = 8.3 Hz, 2H), 2.76 (d, *J* = 1.5 Hz, 3H). **^{13}C NMR** (75 MHz) δ159.6 (d, J_{CF} = 243.4 Hz), 156.2 (d, J_{CF} = 9.2 Hz), 129.2 (d, J_{CF} = 8.7 Hz), 115.3 (d, J_{CF} = 21.5 Hz), 105.1 (d, J_{CF} = 21.3 Hz), 103.0 (d, J_{CF} = 2.4 Hz), 56.2, 36.1, 25.1. **IR**: ν 2952, 2853, 2811, 1629, 1479, 1467, 1291,1273, 1211, 1132, 999, 958, 945, 755, 702 cm^{-1}. **HRMS** (ESI) calculated for $C_9H_{11}FN^+$ $[M+H]^+$: 152.0876; found: 152.0871.

6-Fluoro-*N*-methylindoline (1f)



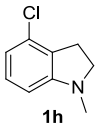
1f was prepared following the general procedure starting from 6-fluoroindole (2.03 g, 15.0 mmol) using 5.0 equivalents of paraformaldehyde and 5.0 equivalents of $NaCNBH_3$ as a pale yellow liquid (1.18 g, 52%) after purification by flash column chromatography (PE:Et_2O, 20:1) and its ^1H NMR data matched with those reported in the literature.[27] **^{1}H NMR** (400 MHz) δ 6.96 – 6.92 (m, 1H), 6.31 (d_{HF}dd, *J* = 9.9, 8.0, 2.2 Hz, 1H), 6.15 (dd, *J* = 10.3, 2.1 Hz, 1H), 3.35 (t, *J* = 8.2 Hz, 2H), 2.90 (t, *J* = 8.2 Hz, 2H), 2.74 (s, 3H).

6-Fluoro-*N*-methylindoline (1g)

1g was prepared following the general procedure starting from 7-fluoroindole (2.03 g, 15.0 mmol) using 5.0 equivalents of paraformaldehyde and 5.0 equivalents of $NaCNBH_3$ as a pale yellow liquid (1.05 g, 46%) after purification by flash column chromatography (PE:Et_2O, 20:1). **^{1}H NMR** (300 MHz) δ 6.94 – 6.79 (m, 2H), 6.66 (d_{HF}dd, *J* = 8.2, 7.2, 4.3 Hz, 1H), 3.35 (t, *J* = 8.3 Hz, 2H), 3.10 – 2.97 (m, 5H). **^{13}C NMR** (100 MHz) δ 149.9 (d, J_{CF} = 240.6 Hz), 139.8 (d, J_{CF} = 8.5 Hz), 134.4 (d, J_{CF} = 5.4 Hz), 120.3 (d, J_{CF} = 2.9 Hz), 119.2 (d, J_{CF} = 6.2 Hz), 115.2 (d, J_{CF} = 19.7 Hz), 57.4, 38.8 (d, J_{CF} = 7.3 Hz), 29.7 (d,

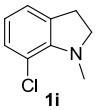
J_{CF} = 1.9 Hz). **IR** ν 2955, 2848, 2807, 1621, 1487, 1463, 1275, 1232, 1188, 1103, 1005, 752, 715 cm^{-1}. **HRMS** (ESI) calculated for $C_9H_{11}FN^+$ $[M+H]^+$: 152.0876; found: 152.0868.

4-Chloro-*N*-methylindoline (**1h**)



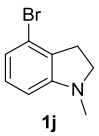
1h was prepared following the general procedure starting from 4-chloroindole (0.71 g, 4.70 mmol) using 7.0 equivalents of paraformaldehyde and 7.0 equivalents of $NaCNBH_3$ as a pale yellow liquid (0.63 g, 80%) after purification by flash column chromatography (PE:Et_2O, 20:1). **^{1}H NMR** (400 MHz) δ 7.00 (t, *J* = 7.9 Hz, 1H), 6.63 (d, *J* = 8.0 Hz, 1H), 6.33 (d, *J* = 7.8 Hz, 1H), 3.36 (t, *J* = 8.3 Hz, 2H), 2.99 (t, *J* = 8.3 Hz, 2H), 2.76 (s, 3H). **^{13}C NMR** (75 MHz) δ 154.7, 130.4, 128.9, 128.2, 117.6, 105.1, 55.4, 36.0, 28.0. **IR**: *ν* 2949, 2846, 2808, 1601, 1449, 1270, 1105, 752 cm^{-1}. **HRMS** (ESI) calculated for $C_9H_{11}ClN^+$ $[M+H]^+$:168.0580; found: 168.0575.

7-Chloro-*N*-methylindoline (**1i**)



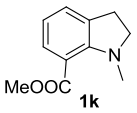
1i was prepared following the general procedure starting from 7-chloroindole (1.30 g, 8.47 mmol) using 7.0 equivalents of paraformaldehyde and 7.0 equivalents of $NaCNBH_3$ as a pale yellow liquid (0.95 g, 67%) after purification by flash column chromatography (PE:Et_2O, 20:1). **^{1}H NMR** (400 MHz) δ 7.01 (d, *J* = 8.1 Hz, 1H), 6.95 (d, *J* = 7.3 Hz, 1H), 6.61 (t, *J* = 7.6 Hz, 1H), 3.36 (t, *J* = 8.5 Hz, 2H), 3.11 (s, 3H), 2.95 (t, *J* = 8.5 Hz, 2H). **^{13}C NMR** (100 MHz) δ 148.5, 133.8, 129.6, 122.9, 119.7, 115.6, 57.3, 39.1, 28.8. **IR**: *ν* 2951, 2842, 2807, 1602, 1451, 1415, 1264, 1091, 1053, 893, 750, 716 cm^{-1}. **HRMS** (ESI) calculated for $C_9H_{11}ClN^+$ $[M+H]^+$: 168.0580; found: 168.0575.

4-Bromo-*N*-methylindoline (**1j**)



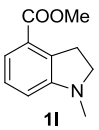
1j was prepared following the general procedure starting from 4-bromoindole (1.96 g, 10.0 mmol) using 10.0 equivalents of paraformaldehyde and 5.0 equivalents of $NaCNBH_3$ as a colorless liquid (1.22 g, 58%) after purification by flash column chromatography (PE:Et_2O, 20:1). **^{1}H NMR** (400 MHz) δ 6.96 (t, *J* = 7.9 Hz, 1H), 6.77 (d, *J* = 8.0 Hz, 1H), 6.36 (d, *J* = 7.8 Hz, 1H), 3.36 (t, *J* = 8.3 Hz, 2H), 2.96 (t, *J* = 8.3 Hz, 2H), 2.75 (s, 3H). **^{13}C NMR** (100 MHz) δ 154.4, 130.4, 129.0, 120.3, 119.4, 105.4, 54.9, 36.0, 29.9. **HRMS** (ESI) calculated for $C_9H_{11}BrN^+$ $[M+H]^+$: 212.0075; found: 168.0079.

Methyl *N*-methylindoline-7-carboxylate (**1k**)



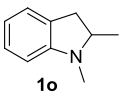
1k was prepared following the general procedure starting from methyl indole-7-carboxylate (1.16 g, 6.62 mmol) using 5.0 equivalents of paraformaldehyde and 5.0 equivalents of $NaCNBH_3$ (*Caution: the reaction was quenched by adding water followed by slow addition of K_2CO_3 until the mixture was basic*) as a pale yellow liquid (1.13 g, 89%) after purification by flash column chromatography (PE:EtOAc, 8:1). **^{1}H NMR** (400 MHz) δ 7.47 (d, *J* = 8.0 Hz, 1H), 7.13 (d, *J* = 7.1 Hz, 1H), 6.65 (dd, *J* = 8.0, 7.0 Hz, 1H), 3.88 (s, 3H), 3.50 (t, *J* = 8.6 Hz, 2H), 2.99 (t, *J* = 8.7 Hz, 2H), 2.86 (s, 3H). **^{13}C NMR** (75 MHz) δ = 168.0, 153.2, 132.9, 129.4, 127.3, 117.3, 112.5, 57.3, 51.8, 39.9, 28.2. **IR** ν 2949, 2841, 1705, 1411, 1287, 1229, 1189, 1130, 1099, 1057, 744 cm^{-1}. **HRMS** (ESI) calculated for $C_{11}H_{14}NO_2^+$ $[M+H]^+$: 192.1025; found: 192.1024.

Methyl *N*-methylindoline-4-carboxylate (**1l**)



1l was prepared following the general procedure starting from methyl indole-7-carboxylate (Prepared from indole-7-carboxylic acid: 2.00 g of indole-7-carboxylic acid was mixed with 30 mL of MeOH and H_2SO_4 was added slowly. After refluxing it for 5 h, the reaction was diluted with water, basified with K_2CO_3 and extracted with DCM three times. The organic extracts were washed with brine, dried with Na_2SO_4, filtrated and concentrated in vacuo. The obtained product was directly used without any further purification) using 10.0 equivalents of paraformaldehyde and 5.0 equivalents of $NaCNBH_3$ (Caution: the reaction was quenched by adding water followed by slow addition of K_2CO_3 till the mixture was basic) as a pale yellow liquid (1.50 g, 63% over two steps from indole-7-carboxylic acid) after purification by flash column chromatography (PE:EtOAc, 8:1). **^{1}H NMR** (400 MHz) δ 7.29 (d, *J* = 7.8 Hz, 1H), 7.13 (t, *J* = 7.8 Hz, 1H), 6.59 (d, *J* = 7.7 Hz, 1H), 3.88 (s, 3H), 3.39 – 3.29 (m, 4H), 2.78 (s, 3H).

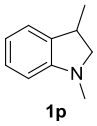
1,2-Dimethylindoline (**1o**)



1o was prepared following the general procedure starting from 2-methylindole (2.01 g, 15.3 mmol) using 5.0 equivalents of paraformaldehyde and 5.0 equivalents of $NaCNBH_3$ as a colorless liquid (1.93 g, 85%) after purification by flash column chromatography (PE:Et_2O, 20:1) and its ^{1}H NMR

data matched with those reported in the literature.[28] **^{1}H NMR** (400 MHz) δ 7.10 – 7.04 (m, 2H), 6.67 (t, *J* = 7.3 Hz, 1H), 6.46 (d, *J* = 7.8 Hz, 1H), 3.45 – 3.36 (m, 1H), 3.12 – 3.06 (m, 1H), 2.72 (s, 3H), 2.64 –2.57 (m, 1H), 1.33 (d, *J* = 6.1 Hz, 3H).

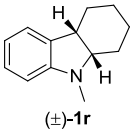
1,3-Dimethylindoline (**1p**)



1p

1p was prepared following the general procedure starting from 3-methylindole (2.62 g, 20.0 mmol) using 10.0 equivalents of paraformaldehyde and 5.0 equivalents of $NaCNBH_3$ as a colorless liquid (2.30 g, 78%) after purification by flash column chromatography (PE:Et_2O, 20:1) and its ^{1}H NMR data matched with those reported in the literature.[29] **^{1}H NMR** (300 MHz) δ 7.17 – 7.03 (m, 2H), 6.71 (t, *J* = 7.3 Hz, 1H), 6.50 (d, *J* = 7.7 Hz, 1H), 3.53 (t, *J* = 8.4 Hz, 1H), 3.28 (h, *J* = 7.5 Hz, 1H), 2.80 (t, *J* = 8.5 Hz, 1H), 2.75 (s, 3H), 1.32 (d, *J* = 6.8 Hz, 3H).

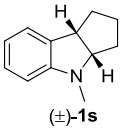
(±)-**9-Methyl-2,3,4,4a,9,9a-hexahydro-1*H*-carbazole** [(±)-**1r**]



(±)-**1r**

(±)-**1r** was prepared following the general procedure starting from 2,3,4,9-tetrahydro-1*H*-carbazole (1.50 g, 8.8 mmol) using 5.0 equivalents of paraformaldehyde and 7.0 equivalents of $NaCNBH_3$ as a white solid (1.35 g, 82%) after purification by flash column chromatography (PE:Et_2O, 20:1) and its ^{1}H NMR data matched with those reported in the literature.[30] **^{1}HNMR** (400 MHz): δ 7.16 – 7.01 (m, 2H), 6.71 (t, *J* = 7.4 Hz, 1H), 6.55 (d, *J* = 7.8 Hz, 1H), 3.23 (dt, *J* = 7.0, 4.5 Hz, 1H), 2.99 (dt, *J* = 9.3, 6.6 Hz, 1H), 2.71 (s, 3H), 1.93 – 1.70 (m, 2H), 1.68 – 1.25 (m, 6H).

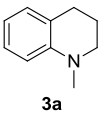
(±)-**4-Methyl-1,2,3,3a,4,8b-hexahydrocyclopenta[b]indole** [(±)-**1s**]



(±)-**1s**

(±)-**1s** was prepared following the general procedure starting from 1,2,3,4-tetrahydrocyclopenta[b]indole (1.51 g, 9.6 mmol) using 4.0 equivalents of paraformaldehyde and 6.5 equivalents of $NaCNBH_3$ as a white solid (1.36 g, 82%) after purification by flash column chromatography (PE:Et_2O, 20:1). **^{1}H NMR** (300 MHz) δ 7.08 – 6.96 (m, 2H), 6.58 (t, *J* = 7.3 Hz, 1H), 6.30 (d, *J* = 7.8 Hz, 1H), 4.00 (ddd, *J* = 8.3, 5.2, 2.1 Hz, 1H), 3.68 (td, *J* = 9.0, 3.2 Hz, 1H), 2.76 (s, 3H), 2.05 – 1.80 (m, 2H), 1.79 – 1.48 (m, 4H). **^{13}C NMR** (100 MHz) δ 153.0, 133.8, 127.6, 124.1, 116.6, 105.3, 71.7, 45.9, 34.9, 33.5, 32.5, 24.8. **IR**: ν 2950, 2864, 1695, 1594, 1505, 1254, 1211 cm^{-1}. **HRMS** (ESI) calculated for $C_{12}H_{16}N^+$ $[M+H]^+$: 174.1283, found: 174.1289.

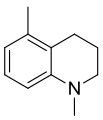
N-**Methyl-1,2,3,4-tetrahydroquinoline** (**3a**)



3a

3a was prepared following the general procedure starting from quinoline (3.73 g, 28.0 mmol) using 10.0 equivalents of paraformaldehyde and 5.0 equivalents of $NaCNBH_3$ as a colorless liquid (2.95 g, 72%) after purification by flash column chromatography (DCM:cyclohexane, 1:1) and its ^{1}H NMR data matched with those reported in the literature.[31] **^{1}H NMR** (400MHz) δ 7.08 (t, *J* = 7.8 Hz, 1H), 6.96 (d, *J* = 7.4 Hz, 1H), 6.62 (t, *J* = 7.4 Hz, 2H), 3.23 (t, *J* = 5.7 Hz, 2H), 2.89 (s, 3H), 2.78 (t, *J* = 6.6 Hz, 2H), 1.99 (p, *J* = 6.2 Hz, 2H).

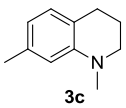
1,5-Dimethyl-1,2,3,4-tetrahydroquinoline (**3b**)



3b

3b was prepared following the general procedure starting from 5-methylquinoline (0.43 g, 3.0 mmol) using 10.0 equivalents of paraformaldehyde and 10.0 equivalents of $NaCNBH_3$ as a colorless liquid (0.24 g, 50%) after purification by flash column chromatography (DCM:cyclohexane, 1:1). **^{1}H NMR** (400MHz) δ 7.17 (t, *J* = 7.9 Hz, 1H), 6.70 (t, *J* = 8.0 Hz, 2H), 3.33 (t, *J* = 5.6 Hz, 2H), 3.04 (s, 3H), 2.82 (t, *J* = 6.8 Hz, 2H), 2.36 (s, 3H), 2.26 – 2.09 (m, 2H). **^{13}C NMR** (75MHz) δ 147.2, 136.3, 126.3, 121.4, 118.6, 109.4, 51.0, 39.9, 24.7, 22.6, 19.9. **IR**: ν 2931, 2862, 1585, 1487, 1320, 1205, 899, 761, 710 cm^{-1}. **HRMS** (ESI) calculated for $C_{11}H_{15}N^+$ $[M]^+$: 161.1204, found: 161.1207.

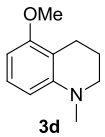
1,7-Dimethyl-1,2,3,4-tetrahydroquinoline (**3c**)



3c

3c was prepared following the general procedure starting from 7-methylquinoline (0.43 g, 3.0 mmol) using 10.0 equivalents of paraformaldehyde and 10.0 equivalents of $NaCNBH_3$ as a colorless liquid (0.34 g, 71%) after purification by flash column chromatography (DCM:cyclohexane, 1:4) and its ^{1}H NMR data matched with those reported in the literature.[32] **^{1}H NMR** (400MHz) δ 6.85 (d, *J* = 7.3 Hz, 1H), 6.44 (d, *J* = 8.3 Hz, 2H), 3.20 (t, *J* = 8 Hz, 2H), 2.88 (s, 3H), 2.73 (t, *J* = 6.5 Hz, 2H), 2.28 (s, 3H), 2.02 – 1.91 (m, 2H).

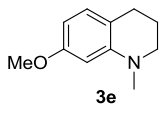
***N*-Methyl-5-methoxytetrahydroquinoline (3d)**



3d

3d was prepared following the general procedure starting from 5-methoxyquinoline using 10.0 equivalents of paraformaldehyde and 10.0 equivalents of $NaCNBH_3$ as a colorless liquid (40%) after purification by flash column chromatography (DCM:cyclohexane, 1:1). **^{1}H NMR** (400 MHz) δ 7.09 (t, *J* = 8.3 Hz, 1H), 6.38 (d, *J* = 8.3 Hz, 1H), 6.32 (d, *J* = 8.2 Hz, 1H), 3.84 (s, 3H), 3.21 (t, *J* = 5.6 Hz, 2H), 2.93 (s, 3H), 2.73 (t, *J* = 6.7 Hz, 2H), 2.04 – 1.98 (m, 2H). **^{13}C NMR** (75 MHz) δ 157.4, 148.0, 126.8, 110.8, 104.9, 99.2, 55.4, 51.1, 39.9, 22.1, 21.2. **HRMS** (ESI) calculated for $C_{11}H_{16}NO^+$ $[M+H]^+$: 178.1232; found 178.1227.

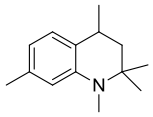
***N*-Methyl-7-methoxytetrahydroquinoline (3e)**



3e

3e was prepared following the general procedure starting from 7-methoxyquinoline using 10.0 equivalents of paraformaldehyde and 10.0 equivalents of $NaCNBH_3$ as a colorless liquid (43%) after purification by flash column chromatography (DCM). **^{1}H NMR** (400 MHz) δ 6.85 (d, *J* = 8.1 Hz, 1H), 6.17 (m, 2H), 3.77 (s, 3H), 3.24 – 3.16 (m, 2H), 2.87 (s, 3H), 2.70 (t, *J* = 6.4 Hz, 2H), 2.00 – 1.90 (m, 2H). **^{13}C NMR** (75 MHz) δ 159.4, 147.7, 129.3, 115.8, 100.5, 97.9, 55.3, 51.3, 39.3, 27.2, 22.8. **HRMS** (ESI) calculated for $C_{11}H_{16}NO^+$ $[M+H]^+$: 178.1232; found 178.1227.

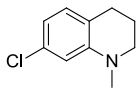
1,2,2,4,7-Pentamethyl-1,2,3,4-tetrahydroquinoline (3f)



3f

3f was prepared following the general procedure starting from 2,2,4,7-tetramethyl-1,2,3,4-tetrahydroquinoline (3.50 g, 18.5 mmol) using 10.0 equivalents of paraformaldehyde and 5.0 equivalents of $NaCNBH_3$ as a colorless liquid (3.05 g, 81%) after purification by flash column chromatography (DCM:cyclohexane, 1:1). **^{1}H NMR** (400 MHz) δ 7.17 (d, *J* = 7.6 Hz, 1H), 6.64 (dd, *J* = 7.6, 1.5 Hz, 1H), 6.56 (d, *J* = 1.7 Hz, 1H), 3.01 – 2.91 (m, 4H), 2.45 (s, 3H), 1.90 (dd, *J* = 12.9, 4.6 Hz, 1H), 1.66 (t, *J* = 12.7 Hz, 1H), 1.47 (d, *J* = 6.7 Hz, 3H), 1.42 (s, 3H), 1.33 (s, 3H). **^{13}C NMR** (75 MHz) δ 146.0, 136.4, 125.8, 125.1, 116.4, 112.0, 54.0, 47.2, 31.5, 29.1, 27.2, 24.4, 21.7, 19.8. **IR**: ν 2964, 2924, 1609, 1505, 1479, 1458, 1331, 1131, 793, 596 cm^{-1}. **HRMS** (ESI) calculated for $C_{14}H_{21}N^+$ $[M]^+$: 203.1674; found: 203.1682.

7-Chloro-*N*-methyl-1,2,3,4-tetrahydroquinoline (3g)

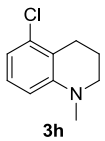


3g

3g was prepared following the general procedure starting from 7-chloroquinoline (0.50 g, 3.0 mmol) using 10.0 equivalents of paraformaldehyde and 10.0 equivalents of $NaCNBH_3$ as a colorless liquid (0.31 g, 56%) after purification by flash column chromatography (DCM:cyclohexane, 1:4). **^{1}H NMR** (400 MHz) δ 6.83 (d, *J* = 7.8 Hz, 1H), 6.59 – 6.47 (m, 2H), 3.26 – 3.17 (m, 2H), 2.87 (s, 3H), 2.70 (t, *J* = 6.4 Hz, 2H), 1.95 (dd, *J* = 6.6, 5.3 Hz, 2H). **^{13}C NMR** (75 MHz) δ 147.6, 132.5, 129.6, 121.1, 115.6, 110.5, 50.9, 39.0, 27.4, 22.2. **IR**: ν 2931, 2839, 1600, 1503, 1310, 828 cm^{-1}. **HRMS** (ESI) calculated for $C_{10}H_{13}ClN^+$ $[M+H]^+$: 182.0737; found: 182.0738.

5-Chloro-*N*-methyl-1,2,3,4-tetrahydroquinoline (3h)

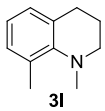
3h was prepared following the general procedure starting from 5-chloroquinoline using 10.0



3h

equivalents of paraformaldehyde and 10.0 equivalents of $NaCNBH_3$ as a colorless liquid (40%) after purification by flash column chromatography (DCM:cyclohexane, 1:1). **^{1}H NMR** (400MHz) δ 7.03 (t, *J* = 8.1 Hz, 1H), 6.74 (d, *J* = 7.9 Hz, 1H), 6.53 (d, *J* = 8.3 Hz, 1H), 3.24 (t, *J* = 5.7 Hz, 2H), 2.93 (s, 3H), 2.86 (t, *J* = 6.7 Hz, 2H), 2.04 (m, 3H). **^{13}C NMR** (75 MHz) δ 148.3, 134.3, 127.3, 120.5, 116.9, 109.4, 50.9, 39.6, 25.4, 22.0. **HRMS** (ESI) calculated for $C_{10}H_{13}ClN^+$ $[M+H]^+$: 182.0737; found: 182.0743.

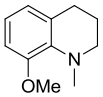
1,8-Dimethyl-1,2,3,4-tetrahydroquinoline (3l)



3l

3l was prepared following the general procedure starting from 8-methylquinoline using 10.0 equivalents of paraformaldehyde and 10.0 equivalents of $NaCNBH_3$ as a colorless liquid (72%) after purification by flash column chromatography (DCM:cyclohexane, 1:1). **^{1}H NMR** (400 MHz) δ 7.01 (d, *J* = 7.2 Hz, 1H), 6.92 (d, *J* = 7.1 Hz, 1H), 6.86 (t, *J* = 7.4 Hz, 1H), 3.14 – 3.12 (m, 2H), 2.82 (t, *J* = 6.7 Hz, 2H), 2.73 (s, 3H), 2.32 (s, 3H), 1.90 – 1.84 (dt, *J* = 12.0, 6.7 Hz, 2H). **^{13}C NMR** (75 MHz) δ 148.0, 131.2, 128.8, 128.8, 127.3, 121.5, 52.1, 42.9, 27.9, 18.7, 17.0. **HRMS** (ESI) calculated for $C_{11}H_{15}N^+$ $[M]^+$: 161.1204; found 161.1197.

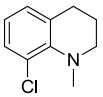
***N*-Methyl-8-methoxytetrahydroquinoline (3m)**



3m

3m was prepared following the general procedure starting from 8-methoxyquinoline using 10.0 equivalents of paraformaldehyde and 10.0 equivalents of $NaCNBH_3$ as a colorless liquid (56%) after purification by flash column chromatography (DCM). **^{1}H NMR** (400 MHz) δ 6.86 (t, *J* = 7.8 Hz, 1H), 6.69 (d, *J* = 3.2 Hz, 1H), 6.67 (d, *J* = 2.7 Hz, 1H), 3.87 (s, 3H), 3.18 – 3.10 (m, 2H), 2.85 (s, 3H), 2.78 (t, *J* = 6.6 Hz, 2H), 1.87 – 1.79 (m, 2H). **^{13}C NMR** (75 MHz) δ 152.2, 137.8, 129.5, 121.8, 121.2, 108.3, 55.2, 52.4, 42.2, 27.8, 17.4. **HRMS** (ESI) calculated for $C_{11}H_{16}NO^+$ $[M+H]^+$: 178.1232; found 178.1234.

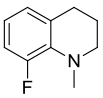
8-Chloro-*N*-methyl-1,2,3,4-tetrahydroquinoline (3n)



3n

3n was prepared following the general procedure starting from 8-chloroquinoline using 10.0 equivalents of paraformaldehyde and 10.0 equivalents of $NaCNBH_3$ as a colorless liquid (40%) after purification by flash column chromatography (DCM:cyclohexane, 1:1). **^{1}H NMR** (400MHz) δ 7.17 (d, *J* = 7.9 Hz, 1H), 6.94 (d, *J* = 7.7 Hz, 1H), 6.82 (t, *J* = 7.7 Hz, 1H), 3.19 – 3.08 (m, 2H), 2.90 (s, 3H), 2.79 (t, *J* = 6.7 Hz, 2H), 1.84 (dt, *J* = 10.0, 6.5 Hz, 2H). **^{13}C NMR** (75MHz) δ 145.8, 131.1, 128.1, 128.1, 127.3, 121.9, 51.9, 42.7, 27.8, 17.1. **IR**: ν 2935, 2861, 1466, 1321, 1171, 1097, 904, 759 cm^{-1}. **HRMS** (ESI) calculated for $C_{10}H_{12}ClN^+$ $[M]^+$: 181.0658; found: 181.0653.

8-Fluoro-*N*-methyltetrahydroquinoline (3o)



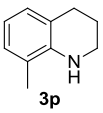
3o

3o was prepared following the general procedure starting from 8-fluoroquinoline using 10.0 equivalents of paraformaldehyde and 10.0 equivalents of $NaCNBH_3$ as a colorless liquid (50%) after purification by flash column chromatography (DCM:cyclohexane, 1:1). **^{1}H NMR** (400MHz) δ 6.88 – 6.73 (m, 2H), 6.67 (td, *J* = 7.8, 4.8 Hz, 1H), 3.17 – 3.10 (m, 2H), 2.96 (d, *J* = 2.3 Hz, 3H), 2.75 (t, *J* = 6.3 Hz, 2H), 1.94 – 1.83 (m, 2H). **^{13}C NMR** (75 MHz) δ 154.2 (d, J_{FC} = 241.5 Hz), 136.2 (d, J_{FC} = 8.3 Hz), 129.4 (d, J_{FC} = 3.8 Hz), 124.8 (d, J_{FC} = 3.0 Hz), 119.0 (d, J_{FC} = 8.25 Hz), 114.2 (d, J_{FC} = 21 Hz), 52.9, 42.8 (d, J_{FC} = 11.3 Hz), 28.2 (d, J_{FC} = 3.0 Hz), 20.3. **HRMS** (ESI) calculated for $C_{10}H_{13}FN^+$ $[M+H]^+$: 166.1032; found: 166.1024.

<u>General procedure for the preparation of unprotected THQs</u>

In a flame-dried Schlenk flask under N_2, the corresponding quinoline derivative (1.0 equiv) was added, followed by acetic acid (0.2 M). At 0 ℃, $NaCNBH_3$ (2.4 – 6.0 equiv) was then added portionwise. The reaction was stirred at room temperature overnight and was quenched at 0 ℃ by slowly adding cold NaOH aqueous solution (10 M) until the reaction was basic. The mixture was extracted with DCM three times and the combined organic extracts were washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. If needed, the product was purified by flash column chromatography.

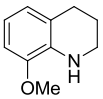
8-Methyltetrahydroquinoline (3p)



3p

3p was prepared following the general procedure starting from 8-methylquinoline (2.48 g, 17.3 mmol) using 4.0 equiv of $NaCNBH_3$ as a brown liquid (1.63 g, 64%) after purification by flash column chromatography (DCM:cyclohexane, 1:3) and its ^{1}H NMR data matched with those reported in the literature.[33] **^{1}H NMR** (400MHz) δ 6.88 – 6.84 (m, 2H), 6.56 (t, *J* = 7.4 Hz, 1H), 3.64 (bs, 1H), 3.37 (t, *J* = 5.3 Hz, 2H), 2.79 (t, *J* = 6.4 Hz, 2H), 2.08 (s, 3H), 1.98 – 1.92 (m, 2H).

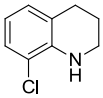
8-Methoxytetrahydroquinoline (3q)



3q

3q was prepared following the general procedure starting from 8-methoxyquinoline (2.75 g, 17.3 mmol) using 4.0 equiv of $NaCNBH_3$ as a dark oil (1.07 g, 38%) after purification by flash column chromatography (2:1, DCM:Toluene with 1% Et_3N) and its ^{1}H NMR data matched with those reported in the literature.[33] **^{1}H NMR** (400MHz) δ 6.74 – 6.66 (m, 3H), 4.30 (bs, 1H), 3.91 (s, 3H), 3.43 (t, *J* = 5.4 Hz, 2H), 2.89 (t, *J* = 6.4 Hz, 2H), 2.07 – 2.01 (m, 2H).

8-Chloro-1,2,3,4-tetrahydroquinoline (3r)

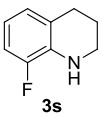


3r

3r was prepared using the following synthetic sequence. In a flame-dried Schlenk flask under N_2, 8-chloroquinoline (2.45 g, 15.0 mmol, 1.0 equiv) was dissolved in AcOH (75 mL). $NaCNBH_3$ (4.71 g, 75.0 mmol, 5.0 equiv) was then added slowly at 0 ℃. The reaction was then stirred overnight at room temperature. Cold 10 M NaOH aqueous solution was then added slowly while cooling the flask with ice-water bath until the mixture was basic. The reaction was then extracted with DCM three times. The combined organic extracts were washed with brine, dried with $MgSO_4$, filtrated and

concentrated in vacuo. A flash column chromatography was performed (20:1, *n*-hexane:Et_2O) yielding a mixture of 8-chloro-1,2,3,4-tetrahydroquinoline and 8-chloro-1,4-dihydroquinoline (4:1 ratio) which were not separable by flash column chromatography. The mixture was further reduced following the procedure reported in the literature.[33] The crude sample was dissolved in DCM followed by addition of I_2 (0.2 g) and HBpin (2.0 mL) under N_2. After stirring it overnight at room temperature, the reaction was quenched with water and extracted with DCM three times. The combined organic extracts were washed with brine, dried with $MgSO_4$, filtrated and concentrated *in vacuo*. The product was purified by flash column chromatography (PE:Et_2O, 20:1) giving **3i** as a colorless oil (2.35 g, 94%). Its ^{1}H NMR data matched with those reported in the literature.[33] **^{1}H NMR** (300 MHz) δ 7.09 (dt, *J* = 7.9, 0.9 Hz, 1H), 6.88 (dq, *J* = 7.4, 1.1 Hz, 1H), 6.53 (t, *J* = 7.7 Hz, 1H), 4.45 (bs, 1H), 3.47 – 3.37 (m, 2H), 2.80 (t, *J* = 6.4 Hz, 2H), 2.04 – 1.89 (m, 2H).

8-Fluorotetrahydroquinoline (**3s**)



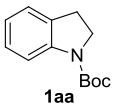
3s

3s was prepared using the following synthetic sequence. In a round bottom flask was successively added $Fe(OTf)_2$ (50 mg, 0.14 mmol, 1 mol%), 8-fluoroquinoline (2.05 g, 13.9 mmol, 1.0 equiv), ethidine (8.79 g, 34.7 mmol, 2.5 equiv) and chloroform (28 mL) under N_2. The reaction mixture was then stirred overnight at 40 ℃. The volatiles were evaporated *in vacuo* and flash column chromatography on silica gel (DCM:cyclohexane, 1:3) was done giving a mixture of desired product and half-reduced product. This impure sample was then mixed with acetic acid (50 mL) and $NaCNBH_3$ (2.53 g, 40.3 mmol) and stirred overnight. Cold NaOH aqueous solution (50%, 80 mL) was added slowly and the mixture was extracted with DCM three times. The combined organic extracts were dried with $MaSO_4$, filtrated and concentrated *in vacuo*. The product was isolated after purification by flash column chromatography on silica gel (DCM:cyclohexane, 1:4) as a colorless oil (0.44 g, 21%). Its ^{1}H NMR data matched with those reported in the literature.[33] **^{1}H NMR** (400MHz) δ 6.85 – 6.76 (m, 2H), 6.56 – 6.51 (m, 1H), 4.03 (bs, 1H), 3.36 (t, *J* = 4.8 Hz, 2H), 2.81 (t, *J* = 6.3 Hz, 2H), 2.01 – 1.96 (m, 2H).

General procedure for the preparation of Boc-protected indolines

Boc-protected indoles were prepared following the procedure described in the literature.[36] The corresponding indoline derivative (1.0 equiv) was added to a solution of $NaHCO_3$ (2.0 equiv) in water (1.25 M) and stirred vigorously for 10 min. The reaction mixture was cooled to 0 ℃. A solution of di-*tert*-butyl dicarbonate (1.0 equiv) in dioxane (0.625 M) was added dropwise. After stirring the reaction mixture for 1 hour at 0 ℃, the ice bath was removed and the reaction was stirred overnight at room temperature. Water was added and the mixture was extracted with EtOAc three times. The combined organic extracts were washed with saturated $NaHCO_3$, dried over Na_2SO_4, filtered and concentrated *in vacuo*. If needed, the product was purified by flash column chromatography on silica gel.

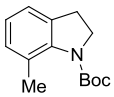
***N*-Boc-indoline (1aa)**



1aa

1aa was prepared following the general procedure starting from indoline (1.19 g, 10.0 mmol) as a colorless oil (1.95 g, 89%) without purification. Its ^{1}H NMR data matched with those reported in the literature.[37] **^{1}H NMR** (300 MHz) δ 8.01 – 7.33 (m, 1H), 7.18 – 7.13 (m, 2H), 6.92 (t, *J* = 7.4 Hz, 1H), 3.97 (t, *J* = 8.7 Hz, 2H), 3.09 (t, *J* = 8.7 Hz, 2H), 1.57 (s, 9H).

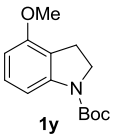
***N*-Boc-4-methylindoline (1x)**



1x

1x was prepared following the general procedure starting from 7-methylindoline (1.19 g, 10.0 mmol) as a colorless oil (1.95 g, 89%) after purification by flash column chromatography on silica gel (PE:Et_2O, 10:1). Its ^{1}H NMR data matched with those reported in the literature.[38] **^{1}H NMR** (300 MHz) δ 7.04 – 6.93 (m, 3H), 4.06 (t, *J* = 7.7 Hz, 2H), 2.97 (t, *J* = 7.7 Hz, 2H), 2.30 (s, 3H), 1.53 (s, 9H).

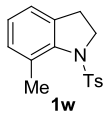
***N*-Boc-4-methoxyindoline (1y)**



1y

1y was prepared following the general procedure starting from 4-methoxyindoline (1.18 g, 7.9 mmol) as a colorless oil (1.90 g, 96%) after purification by flash column chromatography (PE:Et_2O, 6:1). Its ^{1}H NMR data matched with those reported in the literature.[39] **^{1}H NMR** (300 MHz) δ 7.50 – 7.11 (m, 1H), 7.13 (t, *J* = 8.1 Hz, 1H), 6.50 (d, *J* = 8.7 Hz, 2H), 3.98 (t, *J* = 7.9 Hz, 2H), 3.83 (s, 3H), 3.00 (t, *J* = 8.9 Hz, 2H), 1.56 (s, 9H).

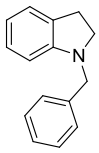
7-Methyl-*N*-tosyl-indoline (1w)



1w

To a solution of 7-methylindoline (1.07 g, 8.0 mmol, 1.0 equiv), DMAP (40 mg) and pyridine (2.0 mL) in DCM (20 mL) was added TsCl (1.83 g, 9.6 mmol, 1.2 equiv) at 0 ℃. The reaction was then warmed up to room temperature and stirred overnight. The reaction was diluted with DCM and successively washed with water, citric acid (0.5 M) and brine. The organic layer was dried with Na_2SO_4, filtrated and concentrated *in vacuo*. **1w** was isolated after flash column chromatography on silica gel (PE:Et_2O, 7:1) as a yellow solid (2.27 g, 99%). Its ^{1}H NMR data matched with those reported in the literature.[40] **^{1}H NMR** (300MHz) δ 7.38 (d, *J* = 8.2 Hz, 2H), 7.16 – 7.10 (m, 3H), 7.05 (t, *J* = 7.3 Hz, 1H), 6.87 (d, *J* = 7.2 Hz, 1H), 3.95 (t, *J* = 7.4 Hz, 2H), 2.58 (s, 3H), 2.39 (s, 3H), 2.12 (t, *J* = 7.3 Hz, 2H).

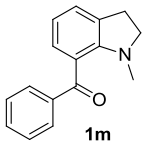
***N*-Benzyl-indoline (1ab)**



1ab

1ab was prepared following the procedure as described in literature.[41] In a two-necked round-bottom flask, indoline (0.56 mL, 5.0 mmol, 1.0 equiv) was added to a solution of $NaHCO_3$ (0.52 g, 6.2 mmol, 1.24 equiv) in water (2 mL). The reaction was heated to 90 ℃. At this temperature, benzyl chloride (0.60 mL, 5.2 mmol, 1.04 equiv) was added dropwise over a period of 5 minutes (Caution, the addition results in formation of bubbles). The reaction mixture was then stirred overnight at 90 ℃. After the reaction was completed, toluene was added to the reaction mixture at 80 ℃ and stirred vigorously. Then, the reaction was left standing until good liquid separation was seen and the organic layer was removed using a Pasteur pipette. The aqueous layer was extracted using toluene. The organic extracts were combined, dried over Na_2SO_4 and concentrated *in vacuo* to yield the product **1ab** as a colorless oil (1.04 g, 99%). Its ^{1}H NMR data matched with those reported in the literature.[42] **^{1}H NMR** (400 MHz) δ 7.48 – 7.37 (m, 4H), 7.35 – 7.32 (m, 1H), 7.17 (d, *J* = 7.2 Hz, 1H), 7.13 (t, *J* = 7.7 Hz, 1H), 6.74 (t, *J* = 7.4 Hz, 1H), 6.58 (d, *J* = 7.8 Hz, 1H), 4.32 (s, 2H), 3.37 (t, *J* = 8.3 Hz, 2H), 3.04 (t, *J* = 8.3 Hz, 2H).

7-Benzoyl-*N*-methylindoline (**1m**)



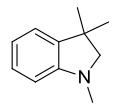
1m

1m was prepared using the following synthetic sequence: **Step A**:[43] In a flame-dried Schlenk flask, indoline (3.0 g, 25.2 mmol, 1.0 equiv) in anhydrous toluene (20 mL) was added slowly to a solution of boron trichloride (1 M in heptane, 28 mL, 1.1 equiv) in anhydrous toluene (28 ml) at 0 ℃. The mixture was then heated to reflux for one hour before it was cooled to room temperature. Dry benzonitrile (13.8 mL, 133.8 mmol, 5.3 equiv) was added to the reaction mixture followed by aluminium trichloride (4.5 g, 33.7 mmol, 1.3 equiv). The mixture was refluxed overnight and hydrochloric acid (1 M, 60 ml) was added. After refluxing the mixture for 1 h, it was allowed to cool down to room temperature. The mixture was thereafter basified to pH = 8 with sodium hydroxide solution. The mixture was then extracted with DCM three times. The combined organic extracts were washed with brine, dried with $MgSO_4$, filtrated and evaporated *in vacuo*. A qucik flash column chromatography (PE:Et_2O, 8:1) was done to remove most of the impurities yielding a solid (2.5 g). **^{1}H NMR** (400 MHz) δ 7.66 – 7.64 (m, 2H), 7.54 – 7.43 (m, 3H), 7.27 (d, *J* = 8.2 Hz, 1H), 7.19 (d, *J* = 6.9 Hz, 1H), 7.10 (bs, 1H), 6.49 (dd, *J* = 8.1, 7.0 Hz, 1H), 3.81 (t, *J* = 8.1 Hz, 2H), 3.11 (t, *J* = 8.5 Hz, 2H). The ^{1}H NMR data matched with those reported in the literature.[43]

Step B: The solid obtained was added to a flame-dried schlenk flask containing dry DMF (25 mL) at 0 ℃. NaH (0.896 g, 60% in mineral oil) was added slowly and the reaction was stirred for 30 min at room temperature followed by the dropwise addition of MeI (1.12 mL) at 0 ℃. After stirring it overnight at room temperature, the reaction was quenched with water and extracted with DCM three times. The combined organic extracts were washed with water three times, brine three times, dried with $MgSO_4$, filtrated, concentrated *in vacuo* and purified by flash column chromatography on silica gel (PE:Et_2O, 10:1) to afford **1h** as a yellow oil (1.9 g, 32% over 2 steps). **^{1}H NMR** (400 MHz) δ 7.95 – 7.87 (m, 2H), 7.59 – 7.53 (m, 1H), 7.46 (dd, *J* = 8.3, 6.9 Hz, 2H), 7.16 (dd, *J* = 7.1, 1.4 Hz, 1H), 7.09 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.61 (t, *J* = 7.5 Hz, 1H), 3.52 (t, *J* = 8.5 Hz, 2H), 3.04 (t, *J* = 8.5 Hz, 2H), 2.63 (s, 3H). **^{13}C NMR** (100 MHz) δ 196.4, 152.8, 138.6, 132.7, 132.7, 130.3, 129.6, 128.4, 126.6, 119.7, 116.2, 57.0, 39.2, 28.3. **IR**: ν 2922, 1650, 1447, 1265, 713 cm^{-1}. **HRMS** (ESI) calculated for $C_{16}H_{16}NO^+$ $[M+H]^+$: 238.1232; found: 238.1277.

1,3,3-Trimethylindoline (**1p**)

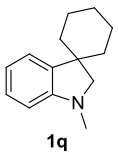
1p was prepared using the following synthetic sequence: **Step A**:[44] 2-Oxindole (3.00 g, 22.5 mmol, 1.0 equiv) was dissolved in anhydrous THF (75 mL) and cooled to 0 ℃. NaH (3.60 g, 60% in mineral oil, 90 mmol, 4.0


1p

equiv) was then added slowly followed by dropwise addition of MeI (4.9 mL, 78.75 mmol, 3.5 equiv). The reaction was warmed up to room temperature and was left stirring overnight. Upon completion, the reaction was quenched with saturated solution of NH_4Cl and extracted with EtOAc three times. The extracts were washed with brine, dried over $MgSO_4$, filtrated and concentrated to dryness to yield 1,3,3'-trimethyloxindole as a yellow liquid which was used for the next step without further purification. **^{1}H NMR** (400 MHz) δ 7.29 (d, *J* = 8.1 Hz, 1H), 7.23 (d, *J* = 7.3 Hz, 1H), 7.09 (t, *J* = 7.5 Hz, 1H), 6.87 (d, *J* = 7.8 Hz, 1H), 3.24 (s, 3H), 1.39 (s, 6H). The ^{1}H NMR data matched with those reported in the literature.[44]

Step B: In a flame-dried Schlenk flask, the obtained crude 1,3,3'-trimethyloxindole was dissolved in anhydrous THF (20 mL), $LiAlH_4$ (2.56 g, 67.5 mmol, 3 equiv) was then added slowly at 0 ℃ under N_2. The reaction was then heated to reflux overnight. After cooling to room temperature, the reaction was quenched with a saturated solution of Na-K tartrate. The reaction was then extracted with EtOAc three times. The combined organic extracts were washed with brine, dried with $MgSO_4$, filtrated and concentrated *in vacuo*. The product was purified by flash column chromatography (PE:Et_2O, 20:1) to yield **1p** as a colorless oil (3.50 g, 96% over 2 steps). **^{1}H NMR** (400 MHz) δ 7.12 (t, *J* = 7.7 Hz, 1H), 7.04 (d, *J* = 7.2 Hz, 1H), 6.73 (t, *J* = 7.3 Hz, 1H), 6.51 (d, *J* = 7.8 Hz, 1H), 3.09 (s, 2H), 2.78 (s, 3H), 1.33 (s, 6H). The ^{1}H NMR data matched those reported in the literarture.[45]

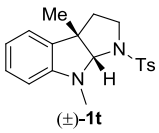
1'-Methylspiro[cyclohexane-1,3'-indoline] (**1q**)


1q

1q was prepared using the following synthetic sequence: **Step A:**[46] To a solution of cyclohexanecarboxaldehyde (0.729 g, 6.5 mmol, 1.0 equiv) in acetic acid (24 mL) was added phenyl hydrazine (0.703 g, 6.5 mmol, 1.0 equiv). The reaction was then heated at 80 ℃ for 3 h. After cooling the reaction to room temperature, $NaBH(OAc)_3$ (1.844 g, 8.7 mmol, 1.3 equiv) was then added portionwise and the reaction was stirred for additional 30 min. The reaction mixture was concentrated *in vacuo* to dryness, diluted with EtOAc and washed with saturated aqueous solution of Na_2CO_3. The organic layer was dried over $MgSO_4$, concentrated and purified by flash column chromatography (PE:EtOAc, 4:1) to afford spiro[cyclohexane-1,3'-indoline] as a yellow liquid (0.573 g, 47%). **^{1}HNMR** (400 MHz) δ 7.11 – 6.99 (m, 2H), 6.75 (t, *J* = 7.4 Hz, 1H), 6.65 (d, *J* = 7.7 Hz, 1H), 3.43 (s, 2H), 1.81 – 1.65 (m, 4H), 1.65 – 1.53 (m, 2H), 1.38 (m, 3H). The ^{1}H NMR data matched with those reported in the literature.[46]

Step B: In a flame-dried Schlenk flask, spiro[cyclohexane-1,3'-indoline] (0.573 g, 3.1 mmol, 1.0 equiv) was dissolved in 20 mL anhydrous THF under N_2 and was cooled to 0 ℃. NaH (0.184 g, 60% in mineral oil, 4.6 mmol) was added slowly and the reaction was stirred for 30 min at room temperature followed by the dropwise addition of MeI (0.658 g, 4.6 mmol, 1.5 equiv) at 0 ℃. The reaction was then warmed up to room temperature and stirred for 4 h. Upon completion determined by TLC, water was slowly added, and the reaction was extracted with EtOAc three times. The combined organic extracts were dried over $MgSO_4$, filtrated, concentrated *in vacuo* and purified by flash column chromatography (PE:EtOAc, 15:1 to 4:1) to afford **1l** as pink liquid (0.311 g, 50%). **^{1}H NMR** (400 MHz) δ 7.23 (t, *J* = 7.6 Hz, 1H), 7.16 (d, *J* = 7.2 Hz, 1H), 6.83 (t, *J* = 7.4 Hz, 1H), 6.61 (d, *J* = 7.8 Hz, 1H), 3.32 (s, 2H), 2.89 (s, 3H), 1.92 – 1.80 (m, 5H), 1.80 – 1.66 (m, 2H), 1.62 – 1.39 (m, 3H). **^{13}C NMR** (100 MHz) δ 152.2, 139.2, 127.6, 122.1, 117.7, 107.2, 65.6, 44.7, 36.3, 35.9, 25.9, 23.3. **IR**: ν 2923, 2854, 1698, 1597, 1507, 1449, 1255, 1147, 1092, 801 cm^{-1}. **HRMS** (ESI) calculated for $C_{14}H_{19}N^+$ $[M+H]^+$: 202.1596; found: 202.1593.

(±)-**3a,8-Dimethyl-1-tosyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole** [(±)-**1t**]


(±)-1t

(±)-**1t** was prepared using the following synthetic sequence.[47] **Step A**: In a flame-dried Schlenk flask was added 2-pyrrolidone (3.0 mL, 38.9 mmol, 1.0 equiv) and anhydrous THF (50 mL) at -78 ℃ under N_2 followed by dropwise addition of *n*-BuLi (1.6 M in hexanes, 25.6 mL, 41.0 mmol, 1.05 equiv) over a period of 6 mins. The mixture was then stirred at -78 ℃ for 1.5 h before a solution of TsCl (7.95 g, 40.88 mmol, 1.05 equiv) in anhydrous THF (15 mL) was added over a period of 20 mins. The reaction was left stirring at -78 ℃ for another 20 mins and then warmed up to room temperature. After stirring it for 1 h, the reaction was quenched by slowly adding saturated aqueous solution of NH_4Cl (30 mL) and extracted with EtOAc three times. The combined organic extracts were washed with brine, dried with $MgSO_4$, filtrated and concentrated *in vacuo*. The product was purified by recrystallization from *n*-hexane to yield 1-Tosyl-2-pyrrolidone as a yellow solid (8.1 g, 87%). **^{1}H NMR** (400 MHz) δ 7.93 (d, *J* =

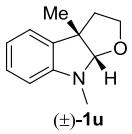
8.3 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 2H), 3.90 (t, *J* = 7.0 Hz, 2H), 2.44 (s, 3H), 2.43 (t, *J* = 8.1 Hz, 2H), 2.11 – 2.03 (m, 2H). The ^{1}H NMR data matched with those reported in the literature.[47]

Step B: In a flame-dried Schlenk flask, to a solution of *N*-Ts-2-pyrrolidone (4.0 g, 16.7 mmol, 1.0 equiv) in anhydrous THF (80 mL) at -78 ℃, NaHMDS (2.0 M in THF, 8.8 mL, 17.6 mmol, 1.05 equiv) was added dropwise over a period of 10 mins. The reaction was stirred for another 1 h at -78 ℃ before MeI (1.56 mL, 25.0 mmol, 1.5 equiv) was added dropwise over a period of 2 mins. After stirring it for 1.5 h, the reaction was quenched by slowly adding saturated aqueous solution of NH_4Cl (60 mL) and extracted with EtOAc three times. The combined organic extracts were washed with brine, dried with $MgSO_4$, filtrated and concentrated *in vacuo*. The product was purified by flash column chromatography (PE:EtOAc, 4:1 to 2:1) to afford the product 3-methyl-1-tosyl-2-pyrrolidone as a yellow solid (3.6 g, 85%). **^{1}H NMR** (300 MHz) δ 7.92 (d, *J* = 8.6 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 3.98 – 3.91 (m, 1H), 3.73 – 3.64 (m, 1H), 2.51 – 2.41 (m, 1H), 2.43 (s, 3H), 2.30 – 2.20 (m, 1H), 1.77 – 1.63 (m, 1H), 1.14 (d, *J* = 7.0 Hz, 3H). The ^{1}H NMR data matched with those reported in the literature.[47]

Step C: In a flame-dried Schlenk flask, 3-methyl-*N*-tosyl-2-pyrrolidone (3.3 g, 13 mmol, 1.0 equiv) was dissolved in anhydrous DCM (50 mL) at -78 ℃ under N_2. DIBALH (1.0 M in THF, 39 mL, 3.0 equiv) was then added to the solution slowly. After stirring it at at -78 ℃ for 2 h, the reaction was quenched by slowly adding a saturated aqueous solution of NH_4Cl (100 mL) at -78 ℃. After warming up to room temperature, the resulting mixture was transferred to a 1 L Erlenmeyer flask containing a saturated aqueous solution of Na-K tartrate (200 mL) and EtOAc (100 mL) and was stirred for 2 h at room temperature. The reaction was then extracted with EtOAc and combined organic extracts were washed with brine, dried with $MgSO_4$, filtrated and concentrated *in vacuo*. The product was purified by flash column chromatography (PE:DCM:Et_2O, 2:1:1) to afford the product 3-methyl-1-tosylpyrrolidin-2-ol as a clear viscous oil (2.8 g, 85%, 43:57 mixture of diastereoisomers). **^{1}H NMR** (400 MHz) δ 7.75 (7.74) (d, *J* = 8.2 Hz, 2H), 7.32 (7.31) (d, *J* = 8.2 Hz, 2H), 4.97 (5.21) (t, *J* = 2.3 Hz, 1H), 3.58 – 3.50 (3.58 – 3.50) (m, 1H), 3.20 (3.03) (dt, *J* = 9.6, 7.3 Hz, 1H), 3.05 (2.74) (d, *J* = 2.6 Hz, 1H), 2.43 (2.43) (s, 3H), 2.22 – 2.13 (2.22 – 2.13) (m, 1H), 1.88 – 1.78 (1.88 – 1.78) (m, 1H), 1.42 – 1.37 (1.42 – 1.37) (m, 1H), 0.71 (1.09) (d, *J* = 6.9 Hz, 3H). The ^{1}H NMR data matched with those reported in the literature.[47]

Step D: In a round bottom flask was added *N*-methyl hydrazine (1.05 g, 8.6 mmol, 1.0 equiv), 3-methyl-1-tosylpyrrolidin-2-ol (2.2 g, 8.6 mmol, 1.0 equiv) and AcOH (40 mL). The reaction was then stirred at room temperature for 40 h. Water (100 mL) was then added and the reaction was basified with K_2CO_3. The reaction was then extracted with EtOAc three times and the combined organic extracts were washed with brine, dried with $MgSO_4$, filtrated, and concentrated *in vacuo*. The product was purified by flash column chromatography (PE:Et_2O, 6:1 to 4:1) to afford (±)-**1o** as a yellow solid (2.05 g, 70%). **^{1}H NMR** (400 MHz) δ 7.78 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 7.9 Hz, 2H), 7.15 – 7.02 (m, 1H), 6.91 (d, *J* = 7.3 Hz, 1H), 6.65 (t, *J* = 7.4 Hz, 1H), 6.40 (d, *J* = 7.9 Hz, 1H), 5.12 (s, 1H), 3.63 – 3.50 (m, 1H), 3.06 (td, *J* = 11.2, 5.7 Hz, 1H), 3.02 (s, 3H), 2.45 (s, 3H), 1.97 – 1.93 (m, 1H), 1.39 (td, *J* = 11.4, 7.4 Hz, 1H), 1.14 (s, 3H). The ^{1}H NMR data matched with those reported in the literature.[47]

(±)-**3a,8-Dimethyl-3,3a,8,8a-tetrahydro-2*H*-furo[2,3-b]indole** [(±)-**1u**]



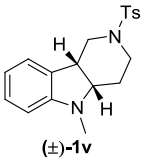
(±)-**1u**

(±)-**1u** was prepared using the following synthetic sequence.[47] **Step A**: In a flame-dried Schlenk flask, α-Methyl-γ-butyrolactone (1.42 mL, 14.98 mmol, 1.0 equiv) was dissolved in DCM (20 mL) at -78 ℃ under N_2. DIBALH (16.5 mL, 1.0 M in hexanes, 1.1 equiv) was then added dropwise over a period of 30 mins via a syringe pump. The reaction was stirred for another 0.5 h and was then quenched with EtOAc. The resulting mixture was then poured into a saturated aqueous solution of Na-K tartrate and was left stirring for 2 h. The mixture was then extracted with DCM three times. The combined organic extracts were washed with brine, dried with $MgSO_4$, filtrated and concentrated *in vacuo* yielding the crude 3-methyltetrahydrofuran-2-ol which was used for the next step without purification.

Step B: In a round bottom flask was added crude 3-methyltetrahydrofuran-2-ol and *N*-methyl hydrazine (1.83 g, 15.0 mmol, 1.0 equiv) and AcOH (60 mL). The reaction was then stirred at 60 ℃ for 2.5 h. After cooling the reaction to room temperature, water (100 mL) was then added and the reaction was basified with K_2CO_3. The reaction was then extracted with EtOAc three times and the combined organic extracts were washed with brine, dried with $MgSO_4$, filtrated, and concentrated *in vacuo*. The product was purified by flash column chromatography (PE:Et_2O, 4:1) to afford (±)-**1u** as an orange oil (0.83 g, 29% over 2 steps). **^{1}H NMR** (300 MHz) δ 7.10 (t, *J* = 7.7 Hz, 1H), 7.05 (d, *J* = 7.3 Hz, 1H), 6.68 (t, *J* = 7.4 Hz, 1H), 6.37 (d, *J* = 7.7 Hz, 1H), 5.07 (s,

1H), 3.95 (ddd, *J* = 8.7, 7.0, 1.8 Hz, 1H), 3.65 – 3.30 (m, 1H), 2.92 (s, 3H), 2.14 (ddd, *J* = 11.9, 5.4, 1.8 Hz, 1H), 2.10 – 1.98 (m, 1H), 1.46 (s, 3H). The ^{1}H NMR data matched with those reported in the literature.[47]

(±)-5-Methyl-2-tosyl-2,3,4,4a,5,9b-hexahydro-1*H*-pyrido[4,3-b]indole [**(±)-1v**]



(±)-1v

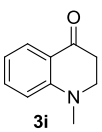
(±)-1v was prepared using the following synthetic sequence. **Step A:**[48] In a round bottom flask, piperidine-4,4-diol hydrochloride (3.07g, 20 mmol, 1.0 equiv) was mixed with H_2O (20 mL). K_2CO_3 (6.64g, 48 mmol, 2.4 equiv) was then added portionwise followed by DCM (20 mL). A solution of *para*-toluenesulfonyl chloride (4.01 g, 21 mmol, 1.05 equiv) in DCM (10 mL) was then added over a period of 10 minutes. The reaction mixture was allowed to stir at room temperature for 16 hours. The organic and aqueous phases were separated and the aqueous phase was then extracted with CH_2Cl_2 two times. The combined organic extracts were washed with saturated aqueous solution of $NaHCO_3$, brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to provide 1-tosylpiperidin-4-one as a white solid (5.01 g, 99%) that was used without further purification. **^{1}H NMR** (400 MHz) δ 7.67 (d, *J* = 8.1 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 3.38 (t, *J* = 6.2 Hz, 4H), 2.53 (t, *J* = 6.2 Hz, 4H), 2.43 (s, 3H). The ^{1}H NMR data matched with those reported in the literature.[48]

Step B:[49] In a round bottom flask, 1-tosylpiperidin-4-one (4.80 g, 19.0 mmol, 1.0 equiv) was mixed with AcOH (20 mL). Phenylhydrazine hydrochloride (2.74g, 19.0 mmol, 1.0 equiv) was added and the reaction was stirred at 70 ℃ for 1 h. The reaction mixture was then diluted with H_2O (200 mL). The yellow precipitate was suspended in water, filtrated, dissolved in DCM and washed with brine. The organic layer was dried over $MgSO_4$, filtrated, concentrated *in vacuo*, and purified by flash column chromatography (DCM:MeOH, 30:1) to afford 2-tosyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-b]indole as a pale yellow solid (3.31 g, 53%). **^{1}H NMR** (300 MHz) δ 7.79 (bs, 1H), 7.75 (d, *J* = 8.3 Hz, 2H), 7.39 (d, *J* = 7.7 Hz, 1H), 7.32 – 7.27 (m, 3H), 7.18 – 7.06 (m, 2H), 4.39 (s, 2H), 3.55 – 3.50 (m, 2H), 2.89 (dt, *J* = 8.0, 3.1 Hz, 1H), 2.41 (s, 1H). The ^{1}H NMR data matched with those reported in the literature.[49]

Step C: In a flame-dried Schlenk flask, DMF (20 mL) was mixed with pre-washed NaH (0. 25 g, 60% in mineral oil, 6.05 mmol, 1.1 equiv) at 0 ℃, followed by the addition of 2-tosyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-b]indole (1.80 g, 5.5 mmol, 1.0 equiv). After stirring at room temperature for 0.5 h, methyl iodide (0.86 g, 6.05 mmol, 1.1 equiv) was added dropwise at 0℃. The reaction was then warmed up to room temperature and stirred for 1 h. Upon completion, the reaction was quenched with water, and extracted with EtOAc three times. The combined organic extracts were washed with water three times and brine twice, dried over Na_2SO_4, filtrated and concentrated *in vacuo* to afford 5-methyl-2-tosyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-b]indole as a yellow solid (1.74 g, 96%) which could be used for the next step without further purification. **^{1}H NMR** (400 MHz) δ 7.78 (d, *J* = 8.0 Hz, 2H), 7.42 (d, *J* = 7.8 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 6.4 Hz, 1H), 7.21 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.15 – 7.06 (m, 1H), 4.41 (d, *J* = 1.6 Hz, 2H), 3.61 (s, 3H), 3.57 (t, *J* = 5.7 Hz, 2H), 2.89 (t, *J* = 5.8 Hz, 2H), 2.44 (s, 3H).

Step D: 5-methyl-2-tosyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-b]indole (1.02g, 3.0 mmol, 1.0 equiv) was dissolved in TFA (20 mL) and cooled to 0 ℃. $NaBH_4$ (0.26g, 6.9 mmol, 2.3 equiv) was added portionwise over a period of 15 min. The reaction was then warmed up to room temperature and stirred for 2 h. Upon completion, the reaction was diluted with water and neutralized with $NaHCO_3$. The reaction was extracted with EtOAc three times. The combined organic extracts were washed with brine, dried over $MgSO_4$, concentrated *in vacuo* and purified by flash column chromatography (PE:EtOAc, 4:1) to afford **(±)-1v** (0.88g, 86%) as pale yellow solid. **^{1}H NMR** (300 MHz) δ 7.59 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 8.3 Hz, 2H), 7.15 – 7.09 (m, 2H), 6.76 – 6.71 (m, 1H), 6.53 (d, *J* = 6.6 Hz, 1H), 3.72 (ddd, *J* = 11.8, 6.4, 2.1 Hz, 1H), 3.65 – 3.58 (m, 1H), 3.34 – 3.27 (m, 1H), 3.26 – 3.21 (m, 1H), 2.61 (s, 3H), 2.55 (td, *J* = 11.0, 4.9 Hz, 1H), 2.38 (s, 3H), 2.13 – 1.99 (m, 3H). **^{13}C NMR** (75 MHz) δ 153.1, 143.6, 133.5, 130.7, 129.9, 128.5, 127.7, 124.0, 119.1, 109.1, 64.2, 48.1, 42.0, 40.2, 33.8, 24.8, 21.6. **IR**: ν 2927, 2853, 1608, 1481, 1254, 1164, 951, 744, 728 cm^{-1}. **HRMS** (ESI) calculated for $C_{19}H_{22}N_2O_2S^+$ $[M+H]^+$: 343.1480; found: 343.1490.

***N*-Methyl-2,3-dihydroquinolin-4(1*H*)-one** (**3i**)

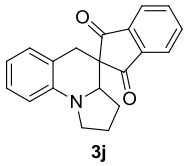


3i

3i was prepared following the reported procedure.[50] 2,3-dihydroquinolin-4(1*H*)-one (1.0 g, 6.7 mmol) was added to a mixture of acetone with potassium carbonate (2.7 g, 20 mmol, 3.0 equiv) and methyl iodide (1.7 mL, 27 mmol, 4.0 equiv). The reaction mixture was heated at 80 ℃ for 16 hours. After cooling down, DCM and brine were added and the water layer was extracted with DCM three times.

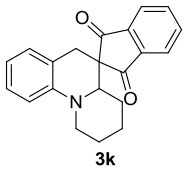
The organic extracts were dried over $MgSO_4$, filtrated and evaporated in vacuo. The product was purified by flash column chromatography (cyclohexane:DCM, 1:1) to afford the pure product as a yellow liquid (0.54 g, 50%). **^{1}H NMR** (400 MHz) δ 7.91 (d, *J* = 8.0 Hz, 1H), 7.41 (t , *J* = 8.0 Hz, 1H), 6.77-6.70 (m, 2H), 3.47 (t, *J* = 8.0 Hz, 2H), 2.99 (s, 3H), 2.74 (t, *J* = 8.0 Hz, 2H). The ^{1}H NMR data matched with those reported in the literature.[50]

2',3',3a',5'-Tetrahydro-1'H-spiro[indene-2,4'-pyrrolo[1,2-a]quinoline]-1,3-dione (**3j**)


3j

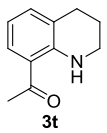
3j was prepared following the reported procedure and its ^{1}H NMR matched with those reported in the literature.[51] **^{1}H NMR** (400 MHz) δ 8.04 – 7.97 (m, 1H), 7.89 – 7.79 (m, 3H), 7.22 – 7.15 (m, 1H), 7.01 (d, *J* = 7.3 Hz, 1H), 6.66 – 6.58 (m, 2H), 3.89 (dd, *J* = 10.2, 5.5 Hz, 1H), 3.59 (td, *J* = 8.3, 7.4, 2.9 Hz, 1H), 3.35 – 3.25 (m, 2H), 2.81 (d, *J* = 16.1 Hz, 1H), 2.02 – 1.89 (m, 2H), 1.88 – 1.82 (m, 1H), 1.35 – 1.22 (m, 1H).

1',2',3',4',4a',6'-Hexahydrospiro[indene-2,5'-pyrido[1,2-a]quinoline]-1,3-dione (**3k**)


3k

3k was prepared following the reported procedure and its ^{1}H NMR matched with those reported in the literature.[51] **^{1}H NMR** (400 MHz) δ 8.03 – 7.97 (m, 1H), 7.97 – 7.91 (m, 1H), 7.84 (dd, *J* = 5.7, 3.1 Hz, 2H), 7.21 – 7.14 (m, 1H), 6.98 (d, *J* = 8.4 Hz, 1H), 6.93 (d, *J* = 7.4 Hz, 1H), 6.70 (t, *J* = 7.3 Hz, 1H), 4.20 – 4.10 (m, 1H), 3.37 (d, *J* = 11.7 Hz, 1H), 3.25 (d, *J* = 16.1 Hz, 1H), 2.86 – 2.71 (m, 2H), 1.77 – 1.67 (m, 2H), 1.67 – 1.59 (m, 1H), 1.51 – 1.42 (m, 1H), 1.34 (tdt, *J* = 12.1, 7.1, 4.2 Hz, 1H), 1.16 (qd, *J* = 12.3, 3.5 Hz, 1H).

8-Acetyl-1,2,3,4-tetrahydroquinoline (**3t**)[43]


3t

In a flame-dried Schlenk flask, 1,2,3,4-tetrahydroquinoline (250 mg, 1.88 mmol, 1.0 equiv) was added to a solution of boron trichloride (1 M in heptane, 2.1 mL, 1.1 equiv) in dry toluene (2 ml) at 0 ℃. Dry acetonitrile (196 μL, 3.76 mmol, 2.0 equiv) was added to the reaction mixture followed by aluminium trichloride (280 mg, 2.1 mmol, 1.1 equiv). The mixture was refluxed overnight and then allowed to cool down to room temperature. The reaction was quenched with hydrochloric acid (1M, 6 ml) and the mixture was thereafter basified to PH = 8 with sodium hydroxide solution. The mixture was then extracted with DCM three times. The combined organic extracts were washed with brine, dried with $MgSO_4$, filtrated and evaporated *in vacuo*. The sample was purified by flash column chromatography on silica gel (cyclohexane:EtOAc, 5:1) to give **3t** as a yellow solid (106 mg, 32%). **^{1}H NMR** (400 MHz) δ 9.00 (s, 1H), 7.53 (d, *J* = 8.2 Hz, 1H), 7.02 (d, *J* = 7.1 Hz, 1H), 6.43 (t, *J* = 7.6 Hz, 1H), 3.48 – 3.34 (m, 2H), 2.76 (t, *J* = 6.4 Hz, 2H), 2.54 (s, 3H), 1.92 – 1.86 (m, 2H). **^{13}C NMR** (100 MHz) δ 200.5, 148.5, 133.9, 130.5, 122.7, 116.2, 113.0, 41.0, 28.0, 27.9, 20.6. **IR**: ν 3320, 2934, 1631, 1572, 1511, 1360, 1237, 940, 732, 660 cm^{-1}. **HRMS** (ESI) calculated for $C_{11}H_{13}NO^+$ $[M]^+$: 175.0997; found: 175.1000.

3.5.2. Reaction condition optimization for selective C(5)–H olefination of indolines

Optimization of protecting group

In a pressure tube containing a suitable stirring bar was added the corresponding indoline derivative (0.25 mmol, 1.0 equiv), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 10 mol%), $PhCO_3{}^tBu$ (46.6 μL, 0.25 mmol, 1.0 equiv), ethyl acrylate (40.8 μL, 0.375 mmol, 1.5 equiv), a stock solution of the S,O-ligand (250 μL, 0.1 M in DCE, 0.025 mmol, 10 mol%) and 1.0 mL of DCE. The tube was sealed with a screw-cap, put in a pre-heated oil bath at 80 ℃ and was stirred for 16 h. After cooling to room temperature, the reaction was diluted with DCM, filtrated through celite, rinsed with DCM and concentrated *in vacuo*. To this crude sample was then added CH_2Br_2 (10 μL) and $CDCl_3$. ^{1}H NMR was recorded to determine the ^{1}H NMR yield.

Optimization of reaction concentration

In a pressure tube containing a suitable stirring bar was added *N*-methylindoline (33.3 mg, 0.25 mmol, 1.0 equiv), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 10 mol%), $PhCO_3{}^tBu$ (46.6 μL, 0.25 mmol, 1.0 equiv), ethyl acrylate (40.8 μL, 0.375 mmol, 1.5 equiv), a stock solution of the S,O-ligand (250 μL, 0.1 M in DCE, 0.025 mmol, 10 mol%) and DCE (0.05 – 1.0 mL). The tube was sealed with a screw-cap, put in a pre-heated oil bath at 80 ℃ and was stirred for 16 h. After cooling to room temperature, the reaction was diluted with DCM, filtrated through celite, rinsed with DCM and concentrated *in vacuo*. To this crude sample was then added CH_2Br_2 (10 μL) and $CDCl_3$. ^{1}H NMR was recorded to determine the ^{1}H NMR yield.

Optimization of reaction temperature

In a pressure tube containing a suitable stirring bar was added *N*-methylindoline (33.3 mg, 0.25 mmol, 1.0 equiv), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 10 mol%), $PhCO_3{}^tBu$ (46.6 μL, 0.25 mmol, 1.0 equiv), ethyl acrylate (40.8 μL, 0.375 mmol, 1.5 equiv), a stock solution of the S,O-ligand (250 μL, 0.1 M in DCE, 0.025 mmol, 10 mol%) and DCE (1.0 mL). The tube was sealed with a screw-cap, put in a pre-heated oil bath at corresponding temperature and was stirred for 16 h. After cooling to room temperature, the reaction was diluted with DCM, filtrated through celite, rinsed with DCM and concentrated *in vacuo*. To this crude sample was then added CH_2Br_2 (10 μL) and $CDCl_3$. ^1H NMR was recorded to determine the ^1H NMR yield.

Optimization of reaction solvent

In a pressure tube containing a suitable stirring bar was added *N*-methylindoline (33.3 mg, 0.25 mmol, 1.0 equiv), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 10 mol%), $PhCO_3{}^tBu$ (46.6 μL, 0.25 mmol, 1.0 equiv), ethyl acrylate (40.8 μL, 0.375 mmol, 1.5 equiv), a stock solution of the S,O-ligand in corresponding solvent (250 μL, 0.1 M, 0.025 mmol, 10 mol%) and corresponding solvent (1.0 mL). The tube was sealed with a screw-cap, put in a pre-heated oil bath at 60 ℃ and was stirred for 16 h. After cooling to room temperature, the reaction was diluted with DCM, filtrated through celite, rinsed with DCM and concentrated *in vacuo*. To this crude sample was then added CH_2Br_2 (10 μL) and $CDCl_3$. ^1H NMR was recorded to determine the ^1H NMR yield.

Optimization of oxidant

In a pressure tube containing a suitable stirring bar was added *N*-methylindoline (33.3 mg, 0.25 mmol, 1.0 equiv), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 10 mol%), oxidant (0.25 mmol, 1.0 equiv) (in cases of O_2, see below), ethyl acrylate (40.8 μL, 0.375 mmol, 1.5 equiv), a stock solution of the S,O-ligand (250 μL, 0.1 M in DCE, 0.025 mmol, 10 mol%) and DCE (1.0 mL). The tube was sealed with a screw-cap, put in a pre-heated oil bath at 60 ℃ and was stirred for 16 h. After cooling to room temperature, the reaction was diluted with DCM, filtrated through celite, rinsed with DCM and concentrated *in vacuo*. To this crude sample was then added CH_2Br_2 (10 μL) and $CDCl_3$. ^1H NMR was recorded to determine the ^1H NMR yield.

Reaction using 1 atmospheric pressure of O_2

In a pressure tube containing a suitable stirring bar was added *N*-methylindoline (33.3 mg, 0.25 mmol, 1.0 equiv), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 10 mol%), ethyl acrylate (40.8 μL, 0.375 mmol, 1.5 equiv), a stock solution of the S,O-ligand (250 μL, 0.1 M in DCE, 0.025 mmol, 10 mol%) and DCE (1.0 mL). The tube was sealed with a crimp cap with septa and a balloon filled with O_2 was connected into the tube via a needle. The tube was then put in a pre-heated oil bath at 60 ℃ and was stirred for 16 h. After cooling to room temperature, the reaction was diluted with DCM, filtrated through celite, rinsed with DCM and concentrated *in vacuo*. To this crude sample was then added CH_2Br_2 (10 μL) and $CDCl_3$. ^1H NMR was recorded to determine the ^1H NMR yield.

Reaction using 6 and 10 atmospheric pressure of O_2

In a vial containing a suitable stirring bar was added *N*-methylindoline (33.3 mg, 0.25 mmol, 1.0 equiv), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 10 mol%), ethyl acrylate (40.8 μL, 0.375 mmol, 1.5 equiv), a stock solution of the S,O-ligand (250 μL, 0.1 M in DCE, 0.025 mmol, 10 mol%) and DCE (1.0 mL). The vial was then placed in a 7-well aluminum block which was introduced in an autoclave. The autoclave was purged with oxygen gas for 2 min and then the pressure was increased to 6 or 10 atmospheric pressure of oxygen. The autoclave was placed inside a preheated aluminum block at 60 ℃ and the reaction was stirred for 16 h. After cooling to room temperature, the reaction was diluted with DCM, filtrated through celite, rinsed with DCM and concentrated *in vacuo*. To this crude sample was then added CH_2Br_2 (10 μL) and $CDCl_3$. ^1H NMR was recorded to determine the ^1H NMR yield.

Optimization of amount of oxidant

In a pressure tube containing a suitable stirring bar was added *N*-methylindoline (33.3 mg, 0.25 mmol, 1.0 equiv), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 10 mol%), $PhCO_3{}^tBu$ (1.0 – 3.0 equiv), ethyl acrylate (40.8 μL, 0.375 mmol, 1.5 equiv), a stock solution of the S,O-ligand (250 μL, 0.1 M in DCE, 0.025 mmol, 10 mol%) and DCE (1.0 mL). The tube was sealed with a screw cap, put in a pre-heated oil bath at 60 ℃ and was stirred for 16 h. After cooling to room temperature, the reaction was diluted with DCM, filtrated through celite, rinsed with DCM and concentrated *in vacuo*. To this crude sample was then added CH_2Br_2 (10 μL) and $CDCl_3$. ^1H NMR was recorded to determine the ^1H NMR yield.

Optimization of reaction time and temperature

In a pressure tube containing a suitable stirring bar was added *N*-methylindoline (33.3 mg, 0.25 mmol, 1.0 equiv), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 10 mol%), $PhCO_3{}^tBu$ (46.6 μL, 0.25 mmol, 1.0 equiv), ethyl acrylate (40.8 μL, 0.375 mmol, 1.5 equiv), a stock solution of the S,O-ligand (250 μL, 0.1 M in DCE, 0.025 mmol, 10 mol%) and DCE (1.0 mL). The tube was sealed with a screw cap, put in a pre-heated oil bath at 60 ℃ or 80 ℃ and was stirred for 2 – 24 h. After cooling to room temperature, the reaction was diluted with DCM, filtrated through celite, rinsed with DCM and concentrated *in vacuo*. To this crude sample was then added CH_2Br_2 (10 μL) and $CDCl_3$. ^{1}H NMR was recorded to determine the ^{1}H NMR yield.

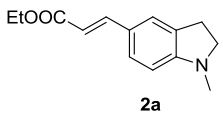
Optimization of the ratio between N-methylindoline and ethyl acrylate

In a pressure tube containing a suitable stirring bar was added *N*-methylindoline (x mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 10 mol%), $PhCO_3{}^tBu$ (46.6 μL, 0.25 mmol, 1.0 equiv), ethyl acrylate (y mmol), a stock solution of the S,O-ligand (250 μL, 0.1 M in DCE, 0.025 mmol, 10 mol%) and DCE (1.0 mL). (*Note: the amount of the limiting reagent is 0.25 mmol.*) The tube was sealed with a screw cap, put in a pre-heated oil bath at 60 ℃ and was stirred for 16 h. After cooling to room temperature, the reaction was diluted with DCM, filtrated through celite, rinsed with DCM and concentrated *in vacuo*. To this crude sample was then added CH_2Br_2 (10 μL) and $CDCl_3$. ^{1}H NMR was recorded to determine the ^{1}H NMR yield.

3.5.3. General procedure for Pd-catalyzed C(5)-H olefination of indolines

In a pressure tube containing a suitable stirring bar was added indoline (0.50 mmol, 2.0 equiv), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 10 mol%), $PhCO_3{}^tBu$ (46.6 μL, 0.25 mmol, 1.0 equiv), ethyl acrylate (27.2 μL, 0.25 mmol, 1.0 equiv), a stock solution of the S,O-ligand (250 μL, 0.1 M in DCE, 0.025 mmol, 10 mol%) and 1.0 mL of DCE. The tube was put in a pre-heated oil bath at 60 ℃ and was stirred for 16 h. After cooling to room temperature, the reaction was filtrated through celite and rinsed with DCM. The filtrate was then washed with a saturated solution of Na_2CO_3, dried with $MgSO_4$, filtrated and concentrated *in vacuo*. The product was then purified by flash column chromatography.

(*E*)-Ethyl 3-(*N*-methyl-5-indolinyl)acrylate (2a)

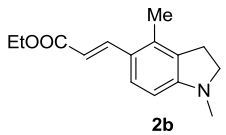


2a

Substrate **1a** (66.6 mg, 0.5 mmol, 2.0 equiv) was olefinated following the general procedure and the product was purified by flash column chromatography (5:1, *n*-hexane/Et_2O) to give **2a** as a yellow oil (33.5 mg, 58%, *para*:others > 20:1). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.60 (d, *J* = 15.8 Hz, 1H), 7.30 – 7.21 (m, 2H), 6.38 (d, *J* = 8.0 Hz, 1H), 6.19 (d, *J* = 15.8 Hz, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.42 (t, *J* = 8.3 Hz, 2H), 2.97 (t, *J* = 8.3 Hz, 2H), 2.81 (s, 3H), 1.32 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (75 MHz, Chloroform-*d*) δ 168.1, 155.3, 145.6, 130.9, 130.2, 123.9, 123.5, 112.3, 106.0, 60.2, 55.5, 35.1, 28.2, 14.6. **IR**: ν 2978, 2926, 2854, 1700, 1602, 1505,1475, 1389, 1366, 1259, 1162, 1084, 1040, 984, 807 cm^{-1}. **HRMS** (FD) calculated for $C_{14}H_{17}NO_2{}^+$ $[M]^+$:231.1259; found: 231.1252.

A parallel reaction without ligand was also performed, and traces of product and 70% oxidized product (N-methyl indole) were observed by ^{1}H NMR analysis with CH_2Br_2 as internal standard.

(*E*)-Ethyl 3-(1,4-dimethyl-5-indolinyl)acrylate (2b)

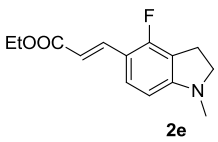


2b

Substrate **1b** (73.6 mg, 0.5 mmol, 2.0 equiv) was olefinated following the general procedure using HFB as solvent and the product was purified by flash column chromatography (8:1, *n*-hexane/Et_2O) to give **2b** as a yellow oil (19.0 mg, 33%, *para*:others = 19:1). **^{1}H NMR** (400 MHz) δ 7.93 (d, *J* = 15.7 Hz, 1H), 7.43 (d, *J* = 8.2 Hz, 1H), 6.30 (d, *J* = 8.2 Hz, 1H), 6.18 (d, *J* = 15.7 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.42 (t, *J* = 8.4 Hz, 2H), 2.93 (t, *J* = 8.4 Hz, 2H), 2.79 (s, 3H), 2.28 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H). In the meantime, 6.0 mg (10% yield) of (*E*)-Ethyl 3-(1,4-dimethyl-2-indolyl)acrylate was also isolated. **^{1}H NMR** (400 MHz) δ 7.80 (d, *J* = 15.8 Hz, 1H), 7.20 – 7.14 (m, 2H), 6.99 (s, 1H), 6.91 (d, *J* = 5.6 Hz, 1H), 6.50 (d, *J* = 15.8 Hz, 1H), 4.29 (q, *J* = 7.1 Hz, 2H), 3.83 (s, 2H), 2.54 (s, 2H), 1.35 (t, *J* = 7.1 Hz, 3H). Its ^{1}H NMR data matched with those reported in the litetature.[56]

(*E*)-Ethyl 3-(4-fluoro-*N*-methyl-5-indolinyl)acrylate (2e)

Substrate **1e** (75.6 mg, 0.5 mmol, 2.0 equiv) was olefinated following the general procedure and the product was purified by flash column chromatography (5:1, *n*-pentane/Et_2O) to give **2e** as a yellow solid (47.2 mg, 76%, *para*:others > 20:1). **^{1}H NMR** (400 MHz) δ 7.68 (d, *J* = 16.0 Hz, 1H), 7.27 – 7.23 (m, 1H), 6.30 (d, *J* = 16.0 Hz,

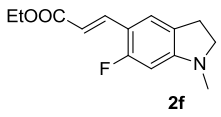


2e

1H), 6.17 (d, *J* = 8.2 Hz, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.48 (t, *J* = 8.5 Hz, 2H), 3.01 (t, *J* = 8.5 Hz, 2H), 2.80 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz) δ 168.1, 158.5 (d, J_{CF} = 250.7 Hz), 157.4 (d, J_{CF} = 10.5 Hz), 138.9, 130.9 (d, J_{CF} = 4.1 Hz), 115.2 (d, J_{CF} = 21.7 Hz), 114.8 (d, J_{CF} = 7.6 Hz), 112.4 (d, J_{CF} = 12.0 Hz), 102.4 (d, J_{CF} = 2.2 Hz), 60.2, 55.7, 34.8, 24.5, 14.5. **IR**: ν 2977, 2852, 1698, 1606, 1519, 1469, 1253, 1166, 988, 816 cm^{-1}. **HRMS** (ESI) calculated for $C_{14}H_{17}FNO_2^+$ $[M+H]^+$: 250.1243; found: 250.1289.

A parallel reaction without ligand was also performed, and less than 10% of product was observed by ^{1}H NMR analysis (para:others, not determined) with CH_2Br_2 as internal standard.

(*E*)-Ethyl 3-(6-fluoro-*N*-methyl-5-indolinyl)acrylate (2f)

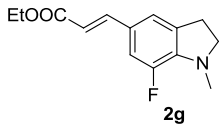


2f

Substrate **1f** (75.6 mg, 0.5 mmol, 2.0 equiv) was olefinated following the general procedure with a mixture of DCE and HFB (1:4, v/v) as solvent and the product was purified by flash column chromatography (5:1 to 4:1, *n*-pentane/Et_2O) to give **2f** as a yellow solid (42.5 mg, 68%, *para*:others > 20:1). **^{1}H NMR** (400 MHz) δ 7.75 (d, *J* = 16.1 Hz, 1H), 7.15 (d, *J* = 7.3 Hz, 1H), 6.21 (d, *J* = 15.9 Hz, 1H), 6.04 (d, *J* = 11.7 Hz, 1H), 4.23 (q, *J* = 7.2 Hz, 2H), 3.46 (t, *J* = 8.4 Hz, 2H), 2.93 (t, *J* = 8.4 Hz, 2H), 2.79 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz) δ 168.0, 163.2 (d, J_{CF} = 251.0 Hz), 156.4 (d, J_{CF} = 13.0 Hz), 138.1 (d, J_{CF} = 4.1 Hz), 126.1 (d, J_{CF} = 1.9 Hz), 123.1 (d, J_{CF} = 5.1 Hz), 113.8 (d, J_{CF} = 5.7 Hz), 110.3 (d, J_{CF} = 12.7 Hz), 93.7 (d, J_{CF} = 27.8 Hz), 60.2, 55.6, 34.6, 27.5, 14.5. **IR**: ν 2851, 1692, 1587, 1518, 1410, 1163, 849 cm^{-1}. **HRMS** (ESI) calculated for $C_{14}H_{16}FNO_2^+$ $[M]^+$: 249.1165; found: 249.1172.

A parallel reaction without ligand was also performed, and less than 10% of product was observed (para:others, not observed) by ^{1}H NMR analysis with CH_2Br_2 as internal standard.

(*E*)-Ethyl 3-(7-fluoro-*N*-methyl-5-indolinyl)acrylate (2g)

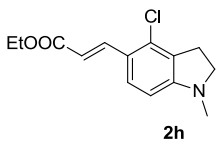


2g

Substrate **1g** (75.6 mg, 0.5 mmol, 2.0 equiv) was olefinated following the general procedure and the product was purified by flash column chromatography (5:1, *n*-pentane/Et_2O) to give **2g** as a yellow solid (32.0 mg, 51%, *para*:others > 20:1). **^{1}H NMR** (300 MHz) δ 7.52 (d, *J* = 15.8 Hz, 1H), 7.03 (s, 1H), 6.98 (d, *J* = 13.1 Hz, 1H), 6.18 (d, *J* = 15.8 Hz, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.40 (t, *J* = 8.5 Hz, 2H), 3.00 (t, *J* = 2.0 Hz, 5H), 1.32 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz,) δ 167.7, 148.7 (d, J_{CF} = 240.6 Hz), 144.3 (d, J_{CF} = 2.3 Hz), 141.8 (d, J_{CF} = 8.9 Hz), 134.4 (d, J_{CF} = 5.9 Hz), 125.4 (d, J_{CF} = 5.9 Hz), 120.1 (d, J_{CF} = 2.0 Hz), 115.9 (d, J_{CF} = 20.0 Hz), 114.3, 60.3, 56.8, 37.5 (d, J_{CF} = 7.3 Hz), 29.1 (d, J_{CF} = 1.9 Hz), 14.5. **IR**: ν 2923, 2851, 1700, 1605, 1159, 847, 592 cm^{-1}. **HRMS** (ESI) calculated for $C_{14}H_{17}FNO_2^+$ $[M+H]^+$: 250.1243; found: 250.1318.

A parallel reaction without ligand was also performed, and less than 10% of product was observed (para:others, not observed) by ^{1}H NMR analysis with CH_2Br_2 as internal standard.

(*E*)-Ethyl 3-(4-chloro-*N*-methyl-5-indolinyl)acrylate (2h)

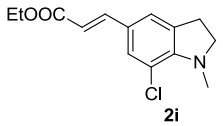


2h

Substrate **1h** (83.8 mg, 0.5 mmol, 2.0 equiv) was olefinated following the general procedure and the product was purified by flash column chromatography (5:1, *n*-pentane/Et_2O) to give **2h** as a yellow solid (46.0 mg, 69%, *para*:others > 20:1). **^{1}H NMR** (300 MHz) δ 8.02 (d, *J* = 15.9 Hz, 1H), 7.43 (d, *J* = 8.3 Hz, 1H), 6.28 (d, *J* = 8.4 Hz, 1H), 6.23 (d, *J* = 15.8 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.48 (t, *J* = 8.5 Hz, 2H), 3.03 (t, *J* = 8.5 Hz, 2H), 2.80 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz) δ 167.7, 155.6, 141.0, 131.7, 128.6, 128.3, 121.1, 114.7, 104.6, 60.3, 54.9, 34.9, 28.1, 14.5. **IR**: ν 2921, 2851, 1688, 1587, 1223, 1156, 981, 804 cm^{-1}. **HRMS** (ESI) calculated for $C_{14}H_{17}ClNO_2^+$ $[M+H]^+$: 266.0948; found: 266.0990.

A parallel reaction without ligand was also performed, and traces of product was observed by ^{1}H NMR analysis with CH_2Br_2 as internal standard.

(*E*)-Ethyl 3-(7-chloro-*N*-methyl-5-indolinyl)acrylate (2i)



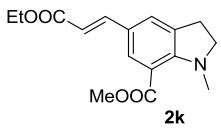
2i

Substrate **1i** (83.8 mg, 0.5 mmol, 2.0 equiv) was olefinated following the general procedure and the product was purified by flash column chromatography (5:1, *n*-pentane/Et_2O) to give **2i** as a yellow solid (37.0 mg, 56%, *para*:others > 20:1). **^{1}H NMR** (300 MHz) δ 7.49 (d, *J* = 15.9 Hz, 1H), 7.15 (s, 1H), 7.11 (s, 1H), 6.18 (d, *J* = 15.8 Hz, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.45 (t, *J* = 8.7 Hz, 2H), 3.17 (s, 3H), 2.96 (t, *J* = 8.6 Hz, 2H), 1.31 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz) δ 167.6, 149.8, 143.8, 133.9, 131.3, 125.7, 121.9, 114.2,

114.1, 60.3, 56.9, 37.9, 28.2, 14.5. **IR**: ν 2921, 2853, 1704, 1597, 1558, 1506, 1414, 1293, 1158, 844, 544 cm^{-1}. **HRMS** (ESI) calculated for $C_{14}H_{17}ClNO_2^+$ $[M+H]^+$: 266.0948; found: 266.0997.

A parallel reaction without ligand was also performed, and 11% of product was observed (para:others, not determined) by ^1H NMR analysis with CH_2Br_2 as internal standard.

(*E*)-Methyl 5-(3-ethoxy-3-oxoprop-1-en-1-yl)-*N*-methylindoline-7-carboxylate (2k)

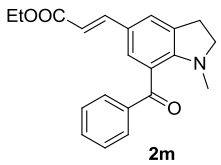


2k

Substrate **1k** (95.6 mg, 0.5 mmol, 2.0 equiv) was olefinated following the general procedure and the product was purified by flash column chromatography (3:1, *n*-pentane/Et_2O) to give **2k** as a yellow solid (39.0 mg, 54%, *para*:others > 20:1). **^{1}H NMR** (400 MHz) δ 7.64 (s, 1H), 7.58 (d, *J* = 15.8 Hz, 1H), 7.32 (s, 1H), 6.22 (d, *J* = 15.8 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 3.90 (s, 3H), 3.63 (t, *J* = 8.6 Hz, 2H), 3.03 (t, *J* = 8.6 Hz, 2H), 2.94 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz) δ 167.7, 167.3, 154.5, 144.4, 133.9, 132.4, 125.1, 123.3, 113.6, 110.9, 60.3, 57.0, 52.0, 39.1, 27.6, 14.51. **IR**: ν 2854, 1697, 1608, 1411, 1258, 1155, 1084, 856 cm^{-1}. **HRMS** (ESI) calculated for $C_{15}H_{16}NO_3^+$ $[M-MeO]^+$: 258.1130; found: 258.1139.

A parallel reaction without ligand was also performed, and 15% of C5-olefinated product was observed together with around 10% other isomers by ^1H NMR analysis with CH_2Br_2 as internal standard.

(*E*)-Ethyl 3-(7-benzoyl-*N*-methyl-5-indolinyl)acrylate (2m)

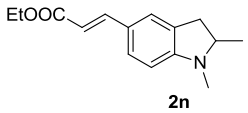


2m

Substrate **1m** (118.6 mg, 0.5 mmol, 2.0 equiv) was olefinated following the general procedure using a solvent mixture of DCE and HFB (1:4, v/v) and the product was purified by flash column chromatography (3:1, *n*-hexane/Et_2O) to give **2m** as a yellow solid (64.0 mg, 76%, *para*:others = 15:1). **^{1}H NMR** (300 MHz) δ 7.91 (d, *J* = 8.1 Hz, 2H), 7.64 – 7.59 (m, 1H), 7.55 – 7.48 (m, 3H), 7.37 (s, 1H), 7.24 (s, 1H), 6.16 (d, *J* = 15.8 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.68 (t, *J* = 8.6 Hz, 2H), 3.10 (t, *J* = 8.6 Hz, 2H), 2.71 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz) δ 195.5, 167.7, 154.2, 144.5, 138.2, 133.7, 133.0, 132.6, 130.3, 128.6, 124.4, 122.4, 118.3, 113.2, 60.2, 56.6, 38.5, 27.6, 14.5. **IR**: ν 2979, 1707, 1448, 1264, 1174, 719 cm^{-1}. **HRMS** (ESI) calculated for $C_{21}H_{22}NO_3^+$ $[M+H]^+$: 336.1600; found: 336.1801.

A parallel reaction without ligand was also performed, and 35% of product was observed with regioselectivity of 5:1 (para:others) by ^1H NMR analysis with CH_2Br_2 as internal standard.

(*E*)-Ethyl 3-(1,2-dimethyl-5-indolinyl)acrylate (2n)

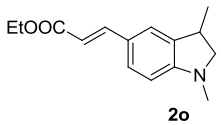


2n

Substrate **1n** (73.6 mg, 0.5 mmol, 2.0 equiv) was olefinated following the general procedure with a mixture of DCE and HFB (1:4, v/v) as solvent at 80 ℃ for 8 h and the product was purified by flash column chromatography (5:1, *n*-pentane/Et_2O) to give **2n** as a yellow liquid (36.2 mg, 59%, *para*:others > 20:1). **^{1}H NMR** (400 MHz) δ 7.60 (d, *J* = 15.8 Hz, 1H), 7.24 – 7.22 (m, 2H), 6.34 (d, *J* = 6.4 Hz, 1H), 6.18 (d, *J* = 15.8 Hz, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.65 – 3.54 (m, 1H), 3.13 (dd, *J* = 15.6, 8.5 Hz, 1H), 2.76 (s, 3H), 2.60 (dd, *J* = 15.7, 9.1 Hz, 1H), 1.34 – 1.30 (dd, *J* = 7.5, 6.7 Hz, 6H). **^{13}C NMR** (100 MHz) δ 168.1, 155.2, 145.7, 130.3, 129.8, 124.0, 123.3, 112.2, 105.9, 62.2, 60.1, 36.8, 32.6, 19.1, 14.6. **IR**: ν 2964, 2926, 1699, 1601, 1500, 1163, 807 cm^{-1}. **HRMS** (ESI) calculated for $C_{15}H_{20}NO_2^+$ $[M+H]^+$: 246.1494; found: 246.1526.

A parallel reaction without ligand was also performed, and traces of product was observed by ^1H NMR analysis with CH_2Br_2 as internal standard.

(*E*)-Ethyl 3-(1,3-dimethyl-5-indolinyl)acrylate (2o)

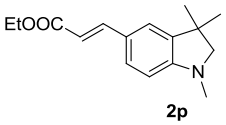


2o

Substrate **1o** (73.6 mg, 0.5 mmol, 2.0 equiv) was olefinated following the general procedure and the product was purified by flash column chromatography (4:1, *n*-hexane/Et_2O) to give **2o** as a yellow liquid (46.3 mg, 76%, *para*:others = 14:1). **^{1}H NMR** (300 MHz) δ 7.62 (d, *J* = 15.9 Hz, 1H), 7.29 – 7.24 (m, 2H), 6.38 (d, *J* = 8.6 Hz, 1H), 6.21 (d, *J* = 15.8 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.61 (t, *J* = 8.7 Hz, 1H), 3.30 (h, *J* = 7.4 Hz, 1H), 2.95 (t, *J* = 8.4 Hz, 1H), 2.79 (s, 3H), 1.35 – 1.30 (t, *J* = 7.0 Hz, 6H). **^{13}C NMR** (75 MHz) δ 168.1, 154.9, 145.6, 135.9, 130.4, 124.0, 122.2, 112.3, 106.1, 63.5, 60.1, 35.0, 34.9, 18.8, 14.5. **IR**: ν 2958, 1698, 1599, 1504, 1254, 1162, 808 cm^{-1}. **HRMS** (ESI) calculated for $C_{15}H_{20}NO_2^+$ $[M+H]^+$: 246.1494; found: 246.1498.

A parallel reaction without ligand was also performed, and 16% of product was observed by ^1H NMR analysis with 1:1 regioselectivity (para:others) with CH_2Br_2 as internal standard.

(*E*)-Ethyl 3-(1,3,3-trimethyl-5-indolinyl)acrylate (2p)

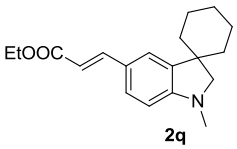


2p

Substrate **1p** (80.6 mg, 0.5 mmol, 2.0 equiv) was olefinated following the general procedure and the product was purified by flash column chromatography (8:1, *n*-hexane/Et_2O) to give **2p** as a yellow liquid (46.8 mg, 72%, *para*:others > 20:1). **^{1}HNMR** (400 MHz): δ 7.64 (d, *J* = 15.8 Hz, 1H), 7.25 (d, *J* = 8.4 Hz, 1H), 7.22 (s, 1H), 6.41 (d, *J* = 8.1 Hz, 1H), 6.24 (d, *J* = 15.8 Hz, 1H), 4.25 (q, *J* = 7.2 Hz, 2H), 3.20 (s, 2H), 2.83 (s, 3H), 1.34 (t, *J* = 7.2 Hz, 3H), 1.32 (s, 6H). **^{13}C NMR** (100 MHz): δ 168.1, 153.9, 145.7, 139.9, 130.4, 124.0, 120.8, 112.2, 106.2, 69.9, 60.2, 40.1, 34.9, 27.8, 14.6. **IR**: ν 2956., 2862, 2814, 1698, 1598, 1464, 1255, 1111, 805 cm^{-1}. **HRMS** (ESI) calculated for $C_{16}H_{22}NO_2^+$ $[M+H]^+$: 260.1606, measured: 260.1651.

A parallel reaction without ligand was also performed, and 18% of product was observed with regioselectivity of 15:1 (para:others) by ^{1}H NMR analysis with CH_2Br_2 as internal standard.

(*E*)-Ethyl 3-(1'-methylspiro[cyclohexane-1,3'-indolin]-5'-yl)acrylate (2q)

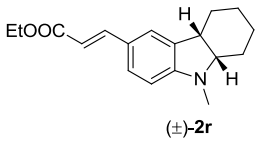


2q

Substrate **1q** (100.7 mg, 0.5 mmol, 2.0 equiv) was olefinated following the general procedure and the product was purified by flash column chromatography (7:1, *n*-hexane/Et_2O) to give **2q** as a yellow solid (51.0 mg, 67%, *para*:others > 20:1). **^{1}H NMR** (300 MHz) δ 7.62 (d, *J* = 15.8 Hz, 1H), 7.4 (d, *J* = 8.0 Hz, 1H), 7.21 (s, 1H), 6.36 (d, *J* = 8.0 Hz, 1H), 6.21 (d, *J* = 15.8 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.30 (s, 2H), 2.82 (s, 3H), 1.76 – 1.30 (m, 13 H). **^{13}C NMR** (75 MHz) δ 168.1, 154.1, 145.8, 139.8, 130.6, 123.8, 121.4, 112.0, 105.9, 65.3, 60.1, 44.5, 36.7, 34.7, 25.8, 23.2, 14.6. **IR**: ν 2953, 2952, 2855, 1708, 1618, 1463, 1415, 1257, 1172 cm^{-1}. **HRMS** (ESI) calculated for $C_{19}H_{26}NO_2^+$ $[M+H]^+$: 300.1964, measured: 300.1947.

A parallel reaction without ligand was also performed, and 13% of product was observed (para:others, not determined) by ^{1}H NMR analysis with CH_2Br_2 as internal standard.

(*E*)-Ethyl 3-[(±)-9-methyl-2,3,4,4a,9,9a-hexahydro-1*H*-carbazol-6-yl]acrylate [(±)-2r]

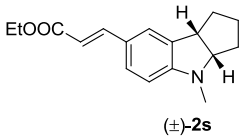


(±)-**2r**

Substrate (±)-**1r** (93.6 mg, 0.5 mmol, 2.0 equiv) was olefinated following the general procedure using a mixture of DCE ad HFB (1:1, v/v) as solvent and the product was purified by flash column chromatography (6:1, *n*-hexane/Et_2O) to give (±)-**2r** as a yellow solid (34.0 mg, 48%, *para*:others > 20:1). **^{1}H NMR** (400 MHz) δ 7.65 (d, *J* = 15.8 Hz, 1H), 7.29 – 7.27 (m, 2H), 6.46 (d, *J* = 8.5 Hz, 1H), 6.24 (d, *J* = 15.8 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 3.40 (q, *J* = 5.3 Hz, 1H), 3.06 (q, *J* = 7.1 Hz, 1H), 2.77 (s, 3H), 1.83 – 1.65 (m, 3H), 1.59 – 1.31 (m, 8H). **^{13}C NMR** (100 MHz) δ 168.1, 154.9, 145.8, 135.3, 130.1, 124.4, 121.9, 112.4, 107.2, 66.0, 60.1, 40.1, 32.3, 28.2, 25.1, 23.1, 21.1, 14.6. **IR**: ν 2975, 2933, 2852, 1705, 1605, 1486, 1300, 1155, 1030, 816 cm^{-1}. **HRMS** (ESI) calculated for $C_{18}H_{24}NO_2^+$ $[M+H]^+$: 286.1807, measured: 286.1783.

A parallel reaction without ligand was also performed, and no product was observed.

(*E*)-Ethyl 3-[(±)-4-methyl-1,2,3,3a,4,8b-hexahydrocyclopenta[b]indol-7-yl]acrylate [(±)-2s]

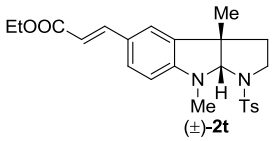


(±)-**2s**

Substrate (±)-**1s** (86.6 mg, 0.5 mmol, 2.0 equiv) was olefinated following the general procedure and the product was purified by flash column chromatography (7:1, *n*-hexane/Et_2O) to give (±)-**2s** as a yellow solid (48.0 mg, 68%, *para*:others > 20:1). **^{1}H NMR** (300 MHz) δ 7.59 (d, *J* = 15.8 Hz, 1H), 7.20 (d, *J* = 7.7 Hz, 2H), 6.23 – 6.10 (m, 2H), 4.23 (q, *J* = 7.1 Hz, 2H), 4.13 (ddd, *J* = 8.0, 6.0, 1.7 Hz, 1H), 3.69 (td, *J* = 8.8, 2.7 Hz, 1H), 2.81 (s, 3H), 2.06 – 1.82 (m, 2H), 1.80 – 1.56 (m, 3H), 1.56 – 1.41 (m, 1H), 1.32 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz) δ 168.3, 154.8, 145.8, 134.5, 130.8, 123.3, 122.9, 111.1, 104.0, 71.3, 60.0, 45.2, 35.2, 32.3, 32.1, 24.5, 14.6. **IR**: ν 2949, 2864, 1695, 1594, 1504, 1145 cm^{-1}. **HRMS** (ESI) calculated for $C_{17}H_{22}NO_2^+$ $[M+H]^+$: 272.1651; found: 272.1815.

A parallel reaction without ligand was also performed, and traces of product was observed.

(*E*)-Ethyl 3-[(±)-3a,8-dimethyl-1-tosyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indol-5-yl] acrylate [(±)-2t]



(±)-**2t**

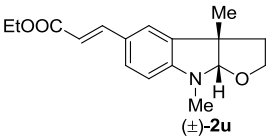
Substrate (±)-**1t** (171.2 mg, 0.5 mmol, 2.0 equiv) was olefinated following the general procedure and the product was purified by flash column chromatography (2:1, *n*-hexane/Et_2O) to give (±)-**2t** as a yellow solid (94.5 mg, 86%, *para*:others = 15:1). **^{1}H NMR** (400 MHz) δ 7.77 (d, *J* = 8.0 Hz, 2H), 7.57 (d, *J* = 15.8 Hz, 1H),

7.35 (d, *J* = 8.0 Hz, 2H), 7.27 (d, *J* = 6.0 Hz, 1H), 7.12 (s, 1H), 6.34 (d, *J* = 8.2 Hz, 1H), 6.17 (d, *J* = 15.8 Hz, 1H), 5.16 (s, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.56 (ddd, *J* = 12.3, 7.3, 2.3 Hz, 1H), 3.09 – 3.02 (m, 1H), 3.03 (s, 3H), 2.45 (s, 3H), 1.90 (ddd, *J* = 12.5, 5.7, 2.3 Hz, 1H), 1.40 – 1.34 (m, 1H), 1.30 (t, *J* = 7.2 Hz, 3H), 1.13 (s, 3H). **^{13}C NMR** (100 MHz) δ 167.8, 152.1, 145.2, 144.0, 136.6, 134.1, 131.1, 130.0, 127.3, 124.2, 121.4, 112.7, 105.4, 90.9, 60.2, 52.9, 48.4, 39.7, 30.9, 24.7, 21.7, 14.5. **IR**: ν 2851, 1692, 1591, 1410, 1214, 1163, 991, 849 cm^{-1}. **HRMS** (ESI) calculated for $C_{24}H_{29}N_2O_4S^+$ $[M+H]^+$: 441.1848; found: 441.1875.

A parallel reaction without ligand was also performed, and 46% of product was observed (para:others, not determined) by ^{1}H NMR analysis with CH_2Br_2 as internal standard.

*The reaction using (±)-**1t** as the limiting reagent was also performed [reaction conditions: (±)-**1t** (85.6 mg, 0.25 mmol, 1.0 equiv), ethyl acrylate (54.4 μL, 0.50 mmol, 2.0 equiv), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 10 mol%), S,O-ligand (5.2 mg, 0.025 mmol, 10 mol%), $PhCO_3{}^tBu$ (46.6 μL, 0.25 mmol, 1.0 equiv), DCE (0.2 M), 60 ℃, 16 h] and the product was obtained in 75% isolated yield after purification by flash column chromatography.*

(*E*)-Ethyl 3-[(±)-3a,8-dimethyl-3,3a,8,8a-tetrahydro-2*H*-furo[2,3-b]indol-5-yl]acrylate [(±)-2u]



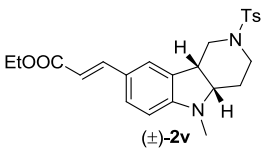
(±)-**2u**

Substrate (±)-**1u** (94.6 mg, 0.5 mmol, 2.0 equiv) was olefinated following the general procedure and the product was purified by flash column chromatography (4:1, *n*-hexane/Et_2O) to give (±)-**2u** as a yellow solid (44.5 mg, 62%, *para*:others > 20:1). **^{1}H NMR** (300 MHz) δ 7.64 (d, *J* = 15.8 Hz, 1H), 7.32 – 7.25 (m, 2H), 6.34 (d, *J* = 8.7 Hz, 1H), 6.23 (d, *J* = 15.8 Hz, 1H), 5.14 (s, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 3.99 (ddd, *J* = 8.7, 6.7, 1.8 Hz, 1H), 3.46 (ddd, *J* = 10.8, 8.8, 5.5 Hz, 1H), 2.97 (s, 3H), 2.20 – 2.00 (m, 2H), 1.49 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz) δ 168.0, 152.5, 145.5, 135.5, 130.9, 124.0, 121.9, 112.4, 105.0, 104.4, 67.4, 60.2, 52.1, 41.9, 30.6, 24.9, 14.5. **IR**: ν 2926, 1697, 1598, 1505, 1446, 1260, 1152, 976, 805 cm^{-1}. **HRMS** (ESI) calculated for $C_{15}H_{16}NO_2^+$ $[M-EtO]^+$: 242.1181; found: 242.1224.

A parallel reaction without ligand was also performed, and 30% of product was observed with regioselectivity of greater than 20:1 (para:others) by ^{1}H NMR analysis with CH_2Br_2 as internal standard.

*The reaction using (±)-**1u** as the limiting reagent was also performed [reaction conditions: (±)-**1u** (47.3 mg, 0.25 mmol, 1.0 equiv), ethyl acrylate (54.4 μL, 0.50 mmol, 2.0 equiv), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 10 mol%), S,O-ligand (5.2 mg, 0.025 mmol, 10 mol%), $PhCO_3{}^tBu$ (46.6 μL, 0.25 mmol, 1.0 equiv), DCE (0.2 M), 60 ℃, 16 h] and the product was obtained in 65% isolated yield after purification by flash column chromatography.*

(*E*)-(±)-5-Methyl-2-tosyl-2,3,4,4a,5,9b-hexahydro-1*H*-pyrido[4,3-b]indol-8-yl)acrylate [(±)-2v]



(±)-**2v**

Substrate (±)-**1v** (171.2 mg, 0.5 mmol, 2.0 equiv) was olefinated following the general procedure and the product was purified by flash column chromatography (5:1:1, *n*-hexane/DCM/EtOAc) to give (±)-**2v** as a yellow solid (78.1 mg, 71%, *para*:others > 20:1). **^{1}H NMR** (400 MHz) δ 7.61 – 7.57 (m, 3H), 7.29 – 7.24 (m, 4H), 6.46 (d, *J* = 8.5 Hz, 1H), 6.22 (d, *J* = 15.8 Hz, 1H), 4.24 (q, *J* = 7.2 Hz, 2H), 3.68 (ddd, *J* = 11.9, 6.4, 1.9 Hz, 1H), 3.61 – 3.56 (m, 1H), 3.39 – 3.29 (m, 2H), 2.66 (s, 3H), 2.56 (dt, *J* = 11.7, 7.7 Hz, 1H), 2.38 (s, 3H), 2.15 – 2.04 (m, 3H), 1.32 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz) δ 167.8, 154.9, 144.9, 143.7, 133.4, 131.2, 130.5, 129.9, 127.7, 125.5, 123.1, 113.9, 108.4, 63.8, 60.3, 47.7, 41.8, 39.8, 32.9, 24.7, 21.6, 14.5. **IR**: ν 2927, 2863, 1697, 1630, 1493, 1162, 725, 547 cm^{-1}. **HRMS** (ESI) calculated for $C_{24}H_{28}N_2O_4S^+$ $[M+H]^+$: 441.1848; found: 441.1892.

A parallel reaction without ligand was also performed, and 18% of product was observed (para:others, not determined) by ^{1}H NMR analysis with CH_2Br_2 as internal standard.

*The reaction using (±)-**1v** as the limiting reagent was also performed [reaction conditions: (±)-**1v** (85.6 mg, 0.25 mmol, 1.0 equiv), ethyl acrylate (54.4 μL, 0.50 mmol, 2.0 equiv), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 10 mol%), S,O-ligand (5.2 mg, 0.025 mmol, 10 mol%), $PhCO_3{}^tBu$ (46.6 μL, 0.25 mmol, 1.0 equiv), DCE (0.2 M), 60 ℃, 16 h] and the product was obtained in 54% isolated yield after purification by flash column chromatography.*

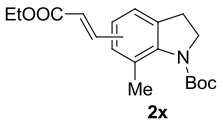
C–H olefination of 7-methyl-*N*-tosylindoline (1w)

In a pressure tube containing a suitable stirring bar was added **1w** (143.7 mg, 0.5 mmol, 2.0 equiv), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 10 mol%), $PhCO_3{}^tBu$ (46.6 μL, 0.25 mmol, 1.0 equiv), ethyl acrylate (27.2 μL, 0.25 mmol, 1.0 equiv), a stock solution of the S,O-ligand in corresponding solvent (250 μL, 0.1 M, 0.025 mmol, 10 mol%) and 1.0 mL of corresponding solvent. The tube was sealed with a screw-cap, put in a pre-heated oil bath at indicated temperature and was stirred for 16 h. After cooling to room temperature, the reaction was diluted with

DCM, filtrated through celite, rinsed with DCM and concentrated *in vacuo*. To this crude sample was then added CH_2Br_2 (10 μL) and $CDCl_3$. ^{1}H NMR was recorded to determine the ^{1}H NMR yield. For all the reactions, low yields and multiple isomers were detected and therefore, no purification was performed.

C–H olefination of *N*-Boc-7-methylindoline (1x)

In a pressure tube containing a suitable stirring bar was added **1x** (116.7 mg, 0.5 mmol, 2.0 equiv), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 10 mol%), $PhCO_3{}^tBu$ (46.6 μL, 0.25 mmol, 1.0 equiv), ethyl acrylate (27.2 μL, 0.25 mmol, 1.0 equiv), a stock solution of the S,O-ligand in corresponding solvent (250 μL, 0.1 M, 0.025 mmol, 10 mol%) and 1.0 mL of corresponding solvent. The tube was sealed with a screw-cap, put in a pre-heated oil bath at indicated temperature and was stirred for 16 h. After cooling to room temperature, the reaction was diluted with DCM, filtrated through celite, rinsed with DCM and concentrated *in vacuo*. To this crude sample was then added CH_2Br_2 (10 μL) and $CDCl_3$. ^{1}H NMR was recorded to determine the ^{1}H NMR yield. Among the reactions we tried, the one using DCE as solvent at 80 ℃ proved optimal and purification was performed by flash column chromatography on silica gel (n-petane:Et_2O, 5:1 to 4:1) yielding **2x** as a mixture of regioisomers (*para*:isomer 1:isomer 2: = 5:3:1), which were not separable from each other.

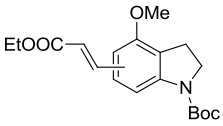


2x

^{1}H NMR (400 MHz) δ 7.97 (d, *J* = 15.8 Hz, $1H_{isomer\ 2}$), 7.68 (d, *J* = 16.0 Hz, $1H_{isomer\ 1}$), 7.61 (d, *J* = 16.0 Hz, $1H_{para}$), 7.29 (d, *J* = 7.8 Hz, $1H_{isomer\ 2}$), 7.21 – 7.20 (m, $1H_{isomer\ 1}$, $1H_{para}$), 7.17 (s, $1H_{para}$), 7.06 – 7.02 (m, $1H_{isomer\ 1}$ and $1H_{isomer\ 2}$), 6.34 (d, *J* = 16.0 Hz, $1H_{isomer\ 1}$), 6.32 (d, *J* = 16.0 Hz, $1H_{para}$), 6.31 (d, *J* = 15.8 Hz, $1H_{isomer\ 2}$), 4.28 – 4.22 (m, $2H_{isomer\ 1}$ and $2H_{isomer\ 2}$, $2H_{para}$), 4.11 – 4.05 (m, $2H_{isomer\ 1}$, $2H_{isomer\ 2}$, $2H_{para}$), 3.09 (t, *J* = 7.6 Hz, $2H_{isomer\ 1}$), 3.00 – 2.96 (m, $2H_{isomer\ 2}$ and $2H_{para}$), 2.30 (m, $3H_{isomer\ 1}$, $3H_{isomer\ 2}$ and $3H_{para}$), 1.53 (s, $9H_{isomer\ 1}$, $9H_{isomer\ 2}$ and $9H_{para}$), 1.34 – 1.31 (m, $3H_{isomer\ 1}$, $3H_{isomer\ 2}$ and $3H_{para}$).

C–H olefination of *N*-Boc-7-methoxyindoline (1y)

In a pressure tube containing a suitable stirring bar was added **1y** (124.7 mg, 0.5 mmol, 2.0 equiv), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 10 mol%), $PhCO_3{}^tBu$ (46.6 μL, 0.25 mmol, 1.0 equiv), ethyl acrylate (27.2 μL, 0.25 mmol, 1.0 equiv), a stock solution of the S,O-ligand in corresponding solvent (250 μL, 0.1 M, 0.025 mmol, 10 mol%) and 1.0 mL of corresponding solvent. The tube was sealed with a screw-cap, put in a pre-heated oil bath at 80 ℃ and was stirred for 16 h. After cooling to room temperature, the reaction was diluted with DCM, filtrated through celite, rinsed with DCM and concentrated *in vacuo*. To this crude sample was then added CH_2Br_2 (10 μL) and $CDCl_3$. ^{1}H NMR was recorded to determine the ^{1}H NMR yield. In the case of DCE as the solvent, a combined yield of 78% (*para*:*ortho* = 1:1) was determine. In the case of HFB as solvent, a combine yield of 58% (*para*:*ortho* = 4:1) was determined. Purification was performed for the reaction using DCE as the solvent by flash column chromatography on silica gel (n-petane:Et_2O, 4:1) yielding **2y** as a mixture of olefinated products (*para*:*ortho* = 1:1), which were not separable from each other.



2y

^{1}H NMR (400 MHz) δ 7.88 (d, *J* = 16.1 Hz, 1H), 7.75 (d, *J* = 16.0 Hz, 1H), 7.68 – 7.36 (m, 1H), 7.44 (d, *J* = 8.8 Hz, 1H), 7.40 (d, J = 8.4 Hz, 1H), 6.63 (d, *J* = 8.8 Hz, 1H), 6.41 (d, *J* = 16.1 Hz, 1H), 6.23 (d, *J* = 16.0 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 4.23 (q, *J* = 7.1 Hz, 2H), 4.12 (t, *J* = 7.8 Hz, 2H), 4.01 (t, *J* = 8.6 Hz, 2H), 3.85 (s, 3H), 3.81 (s, 3H), 3.13 (t, *J* = 8.9 Hz, 2H), 2.90 (t, *J* = 7.8 Hz, 2H), 1.55 (s, 9H), 1.48 (s, 9H), 1.35 – 1.28 (m, $3H_{para}$ and $3H_{ortho}$).

3.5.4. Reaction condition optimization for selective C(6)–H olefination of tetrahydroquinolines

Optimization of protecting group

In a pressure tube containing a suitable stirring bar was added corresponding THQ derivative (0.25 mmol, 1.0 equiv), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 10 mol%), $PhCO_3{}^tBu$ (46.6 μL, 0.25 mmol, 1.0 equiv), ethyl acrylate (40.8 μL, 0.375 mmol, 1.5 equiv), a stock solution of the S,O-ligand (250 μL, 0.1 M in DCE, 0.025 mmol, 10 mol%) and 1.0 mL of DCE. The tube was sealed with a screw-cap, put in a pre-heated oil bath at 80 ℃ and was stirred for 16 h. After cooling to room temperature, the reaction was diluted with DCM, filtrated through celite, rinsed with DCM and concentrated *in vacuo*. To this crude sample was then added CH_2Br_2 (10 μL) and $CDCl_3$. ^{1}H NMR was recorded to determine the ^{1}H NMR yield.

Optimization of reaction temperature

In a pressure tube containing a suitable stirring bar was added *N*-methyltetrahydroquinoline (36.8 mg, 0.25 mmol, 1.0 equiv), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 10 mol%), $PhCO_3{}^tBu$ (46.6 μL, 0.25 mmol, 1.0 equiv), ethyl

acrylate (40.8 μL, 0.375 mmol, 1.5 equiv), a stock solution of the S,O-ligand (250 μL, 0.1 M in DCE, 0.025 mmol, 10 mol%) and DCE (1.0 mL). The tube was sealed with a screw-cap, put in a pre-heated oil bath at corresponding temperature and was stirred for 16 h. After cooling to room temperature, the reaction was diluted with DCM, filtrated through celite, rinsed with DCM and concentrated *in vacuo*. To this crude sample was then added CH_2Br_2 (10 μL) and $CDCl_3$. ^{1}H NMR was recorded to determine the ^{1}H NMR yield.

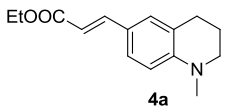
Optimization of reaction concentration

In a pressure tube containing a suitable stirring bar was added *N*-methyltetrahydroquinoline (36.8 mg, 0.25 mmol, 1.0 equiv), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 10 mol%), $PhCO_3{}^tBu$ (46.6 μL, 0.25 mmol, 1.0 equiv), ethyl acrylate (40.8 μL, 0.375 mmol, 1.5 equiv), a stock solution of the S,O-ligand (250 μL, 0.1 M in DCE, 0.025 mmol, 10 mol%) and DCE (0.58–2.25 mL). The tube was sealed with a screw-cap, put in a pre-heated oil bath at 80 ℃ and was stirred for 16 h. After cooling to room temperature, the reaction was diluted with DCM, filtrated through celite, rinsed with DCM and concentrated *in vacuo*. To this crude sample was then added CH_2Br_2 (10 μL) and $CDCl_3$. ^{1}H NMR was recorded to determine the ^{1}H NMR yield.

3.5.5. General procedure for the performance of C(6)-H olefination of tetrahydroquinolines

In a pressure tube containing a suitable stirring bar was added THQ derivative (0.25 mmol, 1.0 equiv), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 10 mol%), $PhCO_3{}^tBu$ (46.6 μL, 0.25 mmol, 1.0 equiv), ethyl acrylate (40.8 μL, 0.375 mmol, 1.5 equiv), a stock solution of the S,O-ligand (250 μL, 0.1 M in DCE, 0.025 mmol, 10 mol%) and 1.0 mL of DCE. The tube was put in a pre-heated oil bath at 40 ℃ and was stirred for 16 h. After cooling to room temperature, the reaction was filtrated through celite and rinsed with DCM. The filtrate was then washed with a saturated solution of Na_2CO_3, dried with $MgSO_4$, filtrated and concentrated *in vacuo*. The product was then purified by flash column chromatography.

(*E*)-Ethyl 3-(*N*-methyl-1,2,3,4-tetrahydroquinolin-6-yl)acrylate (4a)

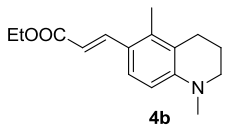


4a

Substrate **3a** (36.8 mg, 0.25 mmol, 1.0 equiv) was olefinated following the general procedure and the product was purified by flash column chromatography (DCM) to give **4a** as a yellow liquid (45.0 mg, 73%, *para*:others > 20:1). **^{1}H NMR** (400 MHz) δ 7.58 (d, *J* = 15.8 Hz, 1H), 7.25 (dd, *J* = 6.3, 2.2 Hz, 1H), 7.14 (d, *J* = 2.1 Hz, 1H), 6.51 (d, *J* = 8.5 Hz, 1H), 6.18 (d, *J* = 15.9 Hz, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.34 – 3.25 (m, 2H), 2.94 (s, 3H), 2.75 (t, *J* = 6.4 Hz, 2H), 2.01 – 1.91 (m, 2H), 1.32 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz) δ 168.2, 148.4, 145.5, 128.7, 128.5, 122.5, 122.1, 112.0, 110.3, 60.1, 51.2, 38.9, 27.9, 22.1, 14.6. **IR**: ν 2933, 1693, 1626, 1516, 1317, 1144, 1037, 727, 490 cm^{-1}. **HRMS** (ESI) calculated for $C_{15}H_{19}NO_2^+$ $[M]^+$: 245.1416; found: 245.1426.

A parallel reaction without ligand was also performed, and 13% of product was observed (para:others, not determined) by ^{1}H NMR analysis with CH_2Br_2 as internal standard.

(*E*)-Ethyl 3-(1,5-dimethyl-1,2,3,4-tetrahydro-6-quinolinyl)acrylate (4b)



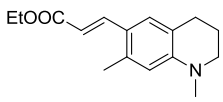
4b

Substrate **3b** (40.3 mg, 0.25 mmol, 1.0 equiv) was olefinated following the general procedure using 1,4-dioxane as solvent and the product was purified by flash column chromatography (DCM:cyclohexane, 1:1) to give **4b** as a yellow liquid (33.0 mg, 50%, *para*:others > 20:1). **^{1}H NMR** (400 MHz) δ 8.03 (d, *J* = 15.6 Hz, 1H), 7.41 (d, *J* = 8.8 Hz, 1H), 6.49 (d, *J* = 8.8 Hz, 1H), 6.17 (d, *J* = 15.6 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.27 – 3.19 (m, 2H), 2.94 (s, 3H), 2.68 (t, *J* = 6.6 Hz, 2H), 2.27 (s, 3H), 2.00 (p, *J* = 6.3 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz) δ 168.2, 148.5, 143.5, 136.7, 125.8, 121.7, 120.9, 113.8, 109.2, 60.2, 50.7, 39.6, 25.3, 22.4, 15.2, 14.6. **IR**: ν 2936, 1698, 1582, 1500, 1323, 1250, 1156, 1058, 801, 486 cm^{-1}. **HRMS** (ESI) calculated for $C_{16}H_{22}NO_2^+$ $[M+H]^+$: 260.1651; found: 260.1644.

A parallel reaction without ligand was also performed, and no product was observed.

(*E*)-Ethyl 3-(1,7-dimethyl-1,2,3,4-tetrahydro-6-quinolinyl)acrylate (4c)

Substrate **3c** (40.3 mg, 0.25 mmol, 1.0 equiv) was olefinated following the general procedure using 1,4-dioxane as solvent at 50 ℃ and the product was purified by flash column chromatography (DCM:cyclohexane, 1:1) to give **4c** as a yellow liquid (35.0 mg, 54%, *para*:others > 20:1). **^{1}H NMR** (400 MHz) δ 7.90 (d, *J* = 15.7 Hz, 1H), 7.23 (s, 1H), 6.33 (s, 1H), 6.16 (d, *J* = 15.7 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.32 – 3.25 (m, 2H), 2.93 (s, 3H), 2.72 (t, *J* = 6.4 Hz, 2H), 2.39 (s, 3H), 2.00 – 1.90 (m, 2H), 1.32 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz) δ 168.3, 148.2,

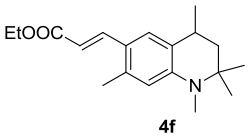


4c

142.5, 138.0, 127.0, 120.6, 120.6, 112.6, 112.0, 60.1, 51.3, 38.9, 27.5, 22.3, 20.1, 14.6. **IR**: ν 2896, 2838, 1695, 1588, 1516, 1307, 1157, 978, 842 cm^{-1}. **HRMS** (ESI) calculated for $C_{16}H_{22}NO_2^+$ $[M+H]^+$: 260.1651; found: 260.1655.

A parallel reaction without ligand was also performed, and less than 10% of product was observed (para:others, not determined) by ^1H NMR analysis with CH_2Br_2 as internal standard.

(*E*)-Ethyl 3-(1,2,2,4,7-pentamethyl-1,2,3,4-tetrahydro-6-quinolinyl)acrylate (**4f**)

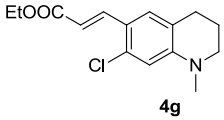


4f

Substrate **3f** (50.8 mg, 0.25 mmol, 1.0 equiv) was olefinated following the general procedure using 1,4-dioxane as solvent at 50 ℃ and the product was purified by flash column chromatography (DCM:cyclohexane, 1:1) to give **4f** as a yellow liquid (47.0 mg, 62%, *para*:others > 20:1). **^{1}H NMR** (400 MHz) δ 7.95 (d, *J* = 15.7 Hz, 1H), 7.40 (s, 1H), 6.34 (s, 1H), 6.20 (d, *J* = 15.7 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 2.88 – 2.77 (m, 4H), 2.41 (s, 3H), 1.78 (dd, *J* = 13.1, 4.3 Hz, 1H), 1.52 (t, *J* = 12.9 Hz, 1H), 1.37 – 1.28 (m, 9H), 1.22 (s, 3H). **^{13}C NMR** (100 MHz) δ 168.3, 147.9, 142.8, 137.9, 126.5, 123.6, 120.1, 112.5, 112.3, 60.1, 54.8, 46.6, 31.6, 29.2, 27.0, 25.1 20.1, 19.5, 14.6. **IR**: ν 2966, 2929, 1697, 1591, 1504, 1237, 1154, 1113, 977, 808 cm^{-1}. **HRMS** (ESI) calculated for $C_{19}H_{28}NO_2^+$ $[M+H]^+$: 302.2120; found: 302.2134.

A parallel reaction without ligand was also performed, and less than 10% of product was observed (para:others, not determined) by ^1H NMR analysis with CH_2Br_2 as internal standard.

(*E*)-Ethyl 3-(7-chloro-*N*-methyl-1,2,3,4-tetrahydro-6-quinolinyl)acrylate (**4g**)

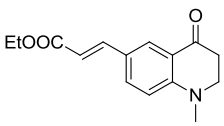


4g

Substrate **3g** (45.3 mg, 0.25 mmol, 1.0 equiv) was olefinated following the general procedure and the product was purified by flash column chromatography (DCM:cyclohexane, 1:1) to give **4g** as a yellow solid (30.0 mg, 43%, *para*:others > 20:1). **^{1}H NMR** (400 MHz) δ 8.01 (d, *J* = 15.9 Hz, 1H), 7.22 (s, 1H), 6.49 (s, 1H), 6.20 (d, *J* = 15.9 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.33 – 3.25 (m, 2H), 2.92 (s, 3H), 2.70 (t, *J* = 6.3 Hz, 2H), 1.99 – 1.89 (m, 2H), 1.32 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz) δ 167.7, 148.7, 140.9, 134.8, 127.2, 121.6, 119.1, 114.2, 110.5, 60.3, 50.9, 38.9, 27.5, 21.9, 14.5. **IR**: ν 2974, 2899, 1699, 1592, 1516, 1430, 1308, 1161, 1024, 981, 845 cm^{-1}. **HRMS** (ESI) calculated for $C_{15}H_{19}ClNO_2^+$ $[M+H]^+$: 280.1104; found: 280.1106.

A parallel reaction without ligand was also performed, and 12% of product was observed (para:others, not determined) by ^1H NMR analysis with CH_2Br_2 as internal standard.

(*E*)-Ethyl-3-(*N*-methyl-4-oxo-1,2,3,4-tetrahydro-6-quinolinyl)acrylate (**4i**)

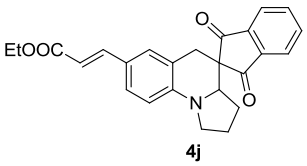


4i

Substrate **3i** (40.3 mg, 0.25 mmol, 1.0 equiv) was olefinated following the general procedure at 50 ℃ and the product was purified by flash column chromatography (*n*-hexane:Et_2O, 2.5:1) to give **4i** as a yellow liquid (36.0 mg, 56%, *para*:others > 20:1). **^{1}H NMR** (300 MHz) δ 8.04 (s, 1H), 7.64 – 7.51 (m, 2H), 6.71 (dd, *J* = 9.0, 2.3 Hz, 1H), 6.29 (d, *J* = 15.8 Hz, 1H), 4.23 (q, *J* = 7.2 Hz, 2H), 3.53 (t, *J* = 7.0 Hz, 2H), 3.04 (s, 3H), 2.80 – 2.66 (t, *J* = 6.6 Hz, 2H), 1.31 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (75 MHz) δ 193.0, 167.5, 153.4, 144.0, 134.5, 128.7, 123.4, 119.5, 115.2, 113.8, 60.4, 51.1, 39.4, 37.9, 14.5. **IR**: ν 3052, 2922, 1677, 1592, 1515, 1324, 1156, 805 cm^{-1}. **HRMS** (ESI) calculated for $C_{15}H_{18}NO_3^+$ $[M+H]^+$: 260.1287, measured: 260.1251.

A parallel reaction without ligand was also performed, and 24% of product was observed (para:others, not determined) by ^1H NMR analysis with CH_2Br_2 as internal standard.

(*E*)-Ethyl 3-(1,3-dioxo-1,2',3,3',3a',5'-hexahydro-1'H-spiro[indene-2,4'-pyrrolo[1,2-a]quinolin]-7'-yl)acrylate (**4j**)

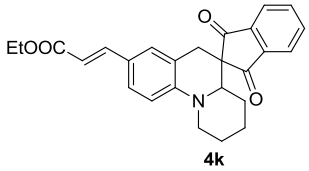


4j

Substrate **3j** (75.8 mg, 0.25 mmol, 1.0 equiv) was olefinated following the general procedure and the product was purified by flash column chromatography (*n*-hexane:EtOAc, 3:1) to give **4**j as a yellow solid (73.1 mg, 73%, *para*:others > 20:1). **^{1}H NMR** (300 MHz) δ 8.06 – 7.96 (m, 1H), 7.90 – 7.80 (m, 3H), 7.58 (d, *J* = 15.8 Hz, 1H), 7.37 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.19 (d, *J* = 1.7 Hz, 1H), 6.56 (d, *J* = 8.5 Hz, 1H), 6.16 (d, *J* = 15.8 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.90 (dd, *J* = 10.5, 5.3 Hz, 1H), 3.61 (td, *J* = 8.5, 2.6 Hz, 1H), 3.40 – 3.18 (m, 2H), 2.80 (d, *J* = 16.2 Hz, 1H), 2.06 – 1.91 (m, 2H), 1.89 – 1.80 (m, 1H), 1.36 – 1.27 (m, 4H). **^{13}C NMR** (75 MHz) δ 202.1, 199.5, 168.0, 145.8, 145.5, 142.4, 141.3, 136.2, 135.8, 129.0, 128.9, 123.4, 123.2, 122.0, 118.3, 112.2, 110.7, 61.2, 60.1, 51.1, 47.5, 34.2, 28.1, 23.8, 14.5. **IR**: ν 2934, 1700, 1598, 1507, 1252, 1143, 730 cm^{-1}. **HRMS** (ESI) calculated for $C_{25}H_{23}NO_4^+$ $[M]^+$:

401.1627; found: 401.1666.
A parallel reaction without ligand was also performed, and 15% of product was observed (para:others, not determined) by ^1H NMR analysis with CH_2Br_2 as internal standard.

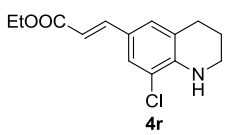
(*E*)-Ethyl 3-(1,3-dioxo-1,1',2',3,3',4',4a',6'-octahydrospiro[indene-2,5'-pyrido[1,2-a]quinolin]-8'-yl)acrylate (4k)



4k

Substrate **3k** (79.3 mg, 0.25 mmol, 1.0 equiv) was olefinated following the general procedure and the product was purified by flash column chromatography (*n*-hexane:EtOAc, 3:1) to give **4k** as a yellow solid (73.7 mg, 72%, *para*:others > 20:1). **^{1}H NMR** (400 MHz) δ 8.01 – 7.97 (m, 1H), 7.94 – 7.91 (m, 1H), 7.85 (dd, *J* = 5.6, 3.1 Hz, 2H), 7.55 (d, *J* = 15.8 Hz, 1H), 7.35 (dd, *J* = 8.7, 2.1 Hz, 1H), 7.09 (d, *J* = 2.1 Hz, 1H), 6.92 (d, *J* = 8.8 Hz, 1H), 6.18 (d, *J* = 15.8 Hz, 1H), 4.23 – 4.14 (m, 3H), 3.45 (dd, *J* = 11.7, 2.4 Hz, 1H), 3.18 (d, *J* = 16.1 Hz, 1H), 2.87 (td, *J* = 12.7, 2.6 Hz, 1H), 2.76 (d, *J* = 16.1 Hz, 1H), 1.73 (d, *J* = 12.3 Hz, 2H), 1.58 (qt, *J* = 12.4, 3.4 Hz, 1H), 1.50 – 1.43 (m, 1H), 1.38 (ddd, *J* = 16.3, 9.7, 3.5 Hz, 1H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.23 – 1.11 (m, 1H). **^{13}C NMR** (100 MHz) δ 201.8, 199.5, 167.8, 147.7, 144.8, 142.1, 141.2, 136.3, 135.8, 129.3, 128.4, 123.6, 123.5, 123.5, 120.3, 113.5, 113.0, 60.1, 59.3, 54.9, 48.6, 32.9, 28.4, 24.9, 24.1, 14.5. **IR**: ν 2976, 1701, 1596, 1518, 1255. 1218, 1156, 730 cm^{-1}. **HRMS** (ESI) calculated for $C_{26}H_{26}NO_4^+$ $[M+H]^+$: 416.1862; found: 416.1899.
A parallel reaction without ligand was also performed, and less than 10% of product was observed (para:others, not determined) by ^1H NMR analysis with CH_2Br_2 as internal standard.

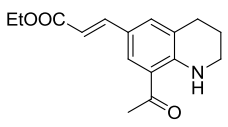
(*E*)-Ethyl-3-(8-chloro-1,2,3,4-tetrahydro-6-quinolinyl)acrylate (4r)



4r

Substrate **3r** (41.9 mg, 0.25 mmol, 1.0 equiv) was olefinated following the general procedure at 80 ℃ and the product was purified by flash column chromatography (*n*-hexane:Et_2O, 8:1) to give **4r** as a yellow solid (21.0 mg, 32%, *para*:others > 20:1). **^{1}H NMR** (400 MHz) δ 7.49 (d, *J* = 15.8 Hz, 1H), 7.28 (d, *J* = 1.9 Hz, 1H), 7.04 (d, *J* = 1.9 Hz, 1H), 6.18 (d, *J* = 15.9 Hz, 1H), 4.76 (bs, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.48 – 3.37 (m, 2H), 2.77 (t, *J* = 6.3 Hz, 2H), 1.99 – 1.88 (m, 2H), 1.31 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz) δ 167.7, 144.3, 142.6, 128.0, 127.2, 122.8, 122.2, 118.0, 113.7, 60.3, 41.9, 27.3, 21.3, 14.5. **IR**: ν 3418, 2929, 2850, 1699, 1599. 1518, 1230, 1162, 979, 720 cm^{-1}. **HRMS** (ESI) calculated for $C_{14}H_{16}ClNO_2^+$ $[M]^+$: 265.0870; found: 265.0870.
A parallel reaction without ligand was also performed, and traces of product was observed.

(*E*)-Ethyl-3-(8-acetyl-1,2,3,4-tetrahydro-6-quinolinyl)acrylate (4t)



4t

Substrate **3t** (43.8 mg, 0.25 mmol, 1.0 equiv) was olefinated following the general procedure at 80 ℃ and the product was purified by flash column chromatography (*n*-hexane:Et_2O, 4:1) to give **4t** as a yellow solid (53.6 mg, 78%, *para*:others > 20:1). **^{1}H NMR** (300 MHz) δ 9.39 (bs, 1H), 7.69 (s, 1H), 7.58 (d, *J* = 15.8 Hz, 1H), 7.29 (s, 1H), 6.20 (d, *J* = 15.8 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 3.56 – 3.40 (m, 2H), 2.81 (t, *J* = 6.2 Hz, 2H), 2.59 (s, 3H), 1.93 (p, *J* = 6.1 Hz, 2H), 1.40 – 1.31 (m, 3H). **^{13}C NMR** (75 MHz) δ 200.6, 167.8, 150.2, 144.7, 133.0, 131.8, 123.6, 119.7, 116.0, 112.8, 60.3, 41.3, 28.0, 27.9, 20.4, 14.5. **HRMS** (ESI) calculated for $C_{16}H_{19}NO_3^+$ $[M]^+$: 273.1365; found: 273.1365.
A parallel reaction without ligand was also performed, and 10% of product was observed (para:others, not determined) by ^1H NMR analysis with CH_2Br_2 as internal standard.

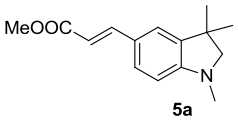
3.5.6. General procedure for the evaluation of olefins

General procedure A: In a pressure tube containing a suitable stirring bar was added **1p** (80.6 mg, 0.50 mmol, 2.0 equiv), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 10 mol%), $PhCO_3{}^tBu$ (46.6 μL, 0.25 mmol, 1.0 equiv), olefin (0.25 mmol, 1.0 equiv), a stock solution of the S,O-ligand (250 μL, 0.1 M in DCE, 0.025 mmol, 10 mol%) and 1.0 mL of DCE. The tube was put in a pre-heated oil bath at 60 ℃ and was stirred for 16 h. After cooling to room temperature, the reaction was filtrated through celite and rinsed with DCM. The filtrate was then washed with a saturated solution of Na_2CO_3, dried with $MgSO_4$, filtrated and concentrated *in vacuo*. The product was then purified by flash column chromatography.

General procedure B: In a pressure tube containing a suitable stirring bar was added **3k** (79.3 mg, 0.25 mmol, 1.0 equiv), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 10 mol%), $PhCO_3{}^tBu$ (46.6 μL, 0.25 mmol, 1.0 equiv), olefin (0.50

mmol, 2.0 equiv), a stock solution of the S,O-ligand (250 μL, 0.1 M in DCE, 0.025 mmol, 10 mol%) and 1.0 mL of DCE. The tube was put in a pre-heated oil bath at 40 ℃ and was stirred for 16 h. After cooling to room temperature, the reaction was filtrated through celite and rinsed with DCM. The filtrate was then washed with a saturated solution of Na_2CO_3, dried with $MgSO_4$, filtrated and concentrated *in vacuo*. The product was then purified by flash column chromatography.

(*E*)-Methyl 3-(1,3,3-trimethyl-5-indolinyl)acrylate (**5a**)

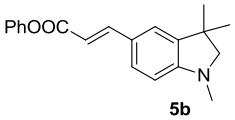


5a

Substrate **1k** (80.6 mg, 0.5 mmol, 2.0 equiv) was olefinated following the **general procedure A** using methyl acrylate as olefin (22.5 μL, 0.25 mmol, 1.0 equiv) and the product was purified by flash column chromatography (*n*-hexane:Et_2O, 8:1) to give **5a** as a yellow liquid (44.3 mg, 72%, *para*:others > 20:1). **^{1}H NMR** (300 MHz) δ 7.63 (d, *J* = 15.8 Hz, 1H), 7.25 (d, *J* = 8.0 Hz, 1H), 7.19 (s, 1H), 6.39 (d, *J* = 8.0 Hz, 1H), 6.22 (d, *J* = 15.8 Hz, 1H), 3.77 (s, 3H), 3.18 (s, 2H), 2.81 (s, 3H), 1.31 (s, 6H). **^{13}C NMR** (75 MHz) δ 168.5, 154.0, 146.0, 139.9, 130.4, 123.9, 120.9, 111.7, 106.2, 69.8, 51.5, 40.1, 34.8, 27.8. **IR**: ν 2953, 1711, 1601, 1466, 1159, 809 cm^{-1}. **HRMS** (ESI) calculated for $C_{15}H_{20}NO_2^+$ $[M+H]^+$: 246.1494; found: 246.1639.

A parallel reaction without ligand was also performed, and 11% of product was observed (para:others, not determined) by ^{1}H NMR analysis with CH_2Br_2 as internal standard.

(*E*)-Phenyl 3-(1,3,3-trimethyl-5-indolinyl)acrylate (**5b**)

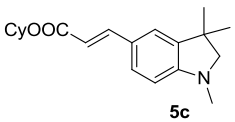


5b

Substrate **1k** (80.6 mg, 0.5 mmol, 2.0 equiv) was olefinated following the **general procedure A** using phenyl acrylate (34.3 μL, 0.25 mmol, 1.0 equiv) as olefin and the product was purified by flash column chromatography (*n*-hexane:Et_2O, 8:1) to give **5b** as a yellow solid (58.3 mg, 76%, *para*:others > 20:1). **^{1}H NMR** (400 MHz) δ 7.82 (d, *J* = 15.8 Hz, 1H), 7.42 – 7.38 (m, 2H), 7.32 (d, *J* = 8.1 Hz, 1H), 7.27 (s, 1H), 7.25 – 7.21 (m, 1H), 7.20 – 7.14 (m, 2H), 6.43 (s, 1H), 6.40 (d, *J* = 7.2 Hz, 1H), 3.23 (s, 2H), 2.84 (s, 3H), 1.34 (s, 6H). **^{13}C NMR** (100 MHz) δ 166.5, 154.3, 151.3, 147.7, 140.0, 131.0, 129.4, 125.5, 123.7, 121.9, 121.1, 110.9, 106.1, 69.8, 40.1, 34.7, 27.9. **IR**: ν 2955, 1715, 1593, 1062, 788 cm^{-1}. **HRMS** (ESI) calculated for $C_{20}H_{22}NO_2^+$ $[M+H]^+$: 308.1651; found: 308.1849.

A parallel reaction without ligand was also performed, and 13% of product was observed (para:others, not determined) by ^{1}H NMR analysis with CH_2Br_2 as internal standard.

(*E*)-Cyclohexyl 3-(1,3,3-trimethyl-5-indolinyl)acrylate (**5c**)

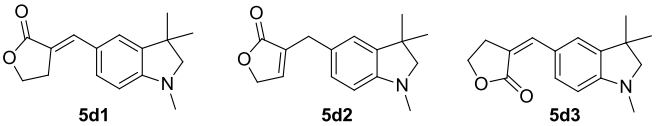


5c

Substrate **1k** (80.6 mg, 0.5 mmol, 2.0 equiv) was olefinated following the **general procedure A** using cyclohexyl acrylate (39.5 μL, 0.25 mmol, 1.0 equiv) as olefin and the product was purified by flash column chromatography (*n*-hexane:Et_2O, 10:1) to give **5c** as a yellow liquid (59.5 mg, 76%, *para*:others > 20:1). **^{1}H NMR** (400 MHz) δ 7.61 (d, *J* = 15.8 Hz, 1H), 7.24 (d, *J* = 8.1 Hz, 1H), 7.20 (s, 1H), 6.38 (d, *J* = 8.1 Hz, 1H), 6.21 (d, *J* = 15.8 Hz, 1H), 4.87 (ddt, *J* = 13.0, 9.0, 3.9 Hz, 1H), 3.18 (s, 2H), 2.81 (s, 3H), 1.92 (dt, *J* = 13.5, 4.0 Hz, 2H), 1.76 (td, *J* = 7.7, 7.1, 4.0 Hz, 2H), 1.59 – 1.35 (m, 6H), 1.30 (s, 6H). **^{13}C NMR** (100 MHz) δ 167.5, 153.9, 145.4, 139.9, 130.4, 124.2, 120.8, 112.9, 106.2, 72.3, 69.9, 40.1, 34.9, 32.0, 27.8, 25.7, 24.0. **IR**: ν 2935, 2858, 1698, 1601, 1505, 1162, 808 cm^{-1}. **HRMS** (ESI) calculated for $C_{20}H_{28}NO_2^+$ $[M+H]^+$: 314.2120; found: 314.2431.

A parallel reaction without ligand was also performed, and 13% of product was observed (para:others, not determined) by ^{1}H NMR analysis with CH_2Br_2 as internal standard.

(*E*)-3-[(1,3,3-Trimethyl-5-indolinyl)methylene]dihydrofuran-2(3*H*)-one (**5d1**), **3-[(1,3,3-trimethyl-5-indolinyl)methyl]furan-2(5*H*)-one** (**5d2**), **(*Z*)-3-[(1,3,3-trimethyl-5-indolinyl)methylene]dihydrofuran-2(3*H*)-one** (**5d3**)

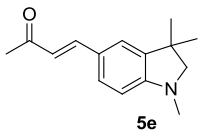


5d1 **5d2** **5d3**

Substrate **1k** (80.6 mg, 0.5 mmol, 2.0 equiv) was olefinated following the **general procedure A** using 3-methylenedihydrofuran-2(3*H*)-one (21.8 μL, 0.25 mmol, 1.0 equiv) as olefin and the product was purified by flash column chromatography (*n*-hexane:Et_2O, 5:1) to give **5d** as a yellow solid (31.4 mg, 55%, **5d1** : **5d2** : **5d3** = 6 : 12 : 1, *para*:others > 20:1). **^{1}H NMR** (400 MHz) δ 7.50 (t, *J* = 2.8 Hz, $1H_A$), 7.29 (dd, *J* = 8.2, 1.8 Hz, $1H_A$), 7.13 (d, *J*

= 1.8 Hz, $1H_A$), 6.98 – 6.93 (m, $2H_B$), 6.87 (d, *J* = 1.8 Hz, $1H_B$), 6.46 – 6.42 (m, $1H_A$+$1H_B$), 4.75 – 4.73 (m, $2H_B$), 4.43 (t, *J* = 7.4 Hz, $2H_A$), 3.51 – 3.49 (m, $2H_B$), 3.24 – 3.19 (m, $4H_A$), 3.06 (s, $2H_B$), 2.83 (s, $3H_A$), 2.74 (s, $3H_B$), 1.32 (s, $6H_A$), 1.28 (s, $6H_B$). **HRMS** (ESI) calculated for $C_{16}H_{20}NO_2^+$ $[M+H]^+$: 258.1494; found: 258.1508.
*A parallel reaction without ligand was also performed, and 32% of product was observed (**5d1**:**5d2**:**5d3** = 1:1:7) (para:others, not determined) by ^1H NMR analysis with CH_2Br_2 as internal standard.*

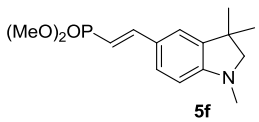
(*E*)-4-(1,3,3-Trimethyl-5-indolinyl)but-3-en-2-one (**5e**)



5e

Substrate **1k** (80.6 mg, 0.5 mmol, 2.0 equiv) was olefinated following the **general procedure A** using but-3-en-2-one (20.2 μL, 0.25 mmol, 1.0 equiv) as olefin and the product was purified by flash column chromatography (*n*-hexane:Et_2O, 5:1) to give **5e** as a yellow liquid (31.4 mg, 55%, *para*:others > 20:1). **^{1}H NMR** (300 MHz) δ 7.46 (d, *J* = 16.1 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 1H), 7.22 (s, 1H), 6.54 (d, *J* = 16.1 Hz, 1H), 6.39 (d, *J* = 8.1 Hz, 1H), 3.20 (s, 2H), 2.82 (s, 3H), 2.33 (s, 3H), 1.31 (d, *J* = 0.9 Hz, 6H). **^{13}C NMR** (75 MHz) δ 198.6, 154.2, 145.0, 140.0, 130.9, 123.7, 122.1, 121.1, 106.2, 69.8, 40.1, 34.7, 27.9, 27.3. **IR**: ν 2957, 1658, 1598, 1254, 1187957, 804 cm^{-1}. **HRMS** (ESI) calculated for $C_{15}H_{20}NO^+$ $[M+H]^+$: 230.1545; found: 230.1721.
A parallel reaction without ligand was also performed, and 16% of product was observed (para:others, not determined) by ^1H NMR analysis with CH_2Br_2 as internal standard.

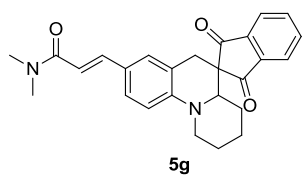
(*E*)-Dimethyl [2-(1,3,3-trimethyl-5-indolinyl)vinyl]phosphonate (**5f**)



5f

Substrate **1k** (80.6 mg, 0.5 mmol, 2.0 equiv) was olefinated following the **general procedure A** using dimethyl vinylphosphonate (28.8 μL, 0.25 mmol, 1.0 equiv) as olefin and the product was purified by flash column chromatography (DCM:MeOH, 100:3) to give **5f** as a yellow solid (60.2 mg, 82%, *para*:others > 20:1). **^{1}H NMR** (400 MHz) δ 7.43 (dd, *J* = 22.7, 17.3 Hz, 1H), 7.22 (d, *J* = 8.2 Hz, 1H), 7.17 (s, 1H), 6.38 (d, *J* = 7.8 Hz, 1H), 5.89 (dd, *J* = 17.7, 17.3 Hz, 1H), 3.76 (s, 3H), 3.73 (s, 3H), 3.18 (s, 2H), 2.80 (s, 3H), 1.30 (s, 6H). **^{13}C NMR** (100 MHz) δ 154.0, 150.7, 139.9, 130.1, 120.4, 106.1, 105.9, 103.9, 69.9, 52.4, 52.4, 40.1, 34.9, 27.8. **^{31}P NMR** (162 MHz) δ 25.01. **IR**: ν 2954, 1599, 1506, 1246, 1186, 1029, 862 cm^{-1}. **HRMS** (ESI) calculated for $C_{15}H_{23}NO_3P^+$ $[M+H]^+$: 296.1416; found: 296.1689.
A parallel reaction without ligand was also performed, and less than 10% of product was observed (para:others, not determined) by ^1H NMR analysis with CH_2Br_2 as internal standard.

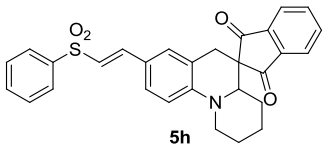
(*E*)-3-(1,3-Dioxo-1,1',2',3,3',4',4a',6'-octahydrospiro[indene-2,5'-pyrido[1,2-a]quinolin]-8'-yl)-*N*,*N*-dimethylacrylamide (**5g**)



5g

Substrate **3h** (79.3 mg, 0.25 mmol, 1.0 equiv) was olefinated following the **general procedure B** using *N*,*N*-dimethylacrylamide (38.6 μL, 0.375 mmol, 1.5 equiv) as the olefin and the product was purified by flash column chromatography (DCM:MeOH, 100:3) to give **5g** as a yellow liquid (70.1 mg, 68%, *para*:others > 20:1). **^{1}H NMR** (400 MHz) δ 8.03 – 7.99 (m, 1H), 7.97 – 7.93 (m, 1H), 7.89 – 7.85 (m, 2H), 7.57 (d, *J* = 15.2 Hz, 1H), 7.37 (dd, *J* = 8.7, 2.1 Hz, 1H), 7.13 (s, 1H), 6.94 (d, *J* = 8.7 Hz, 1H), 6.67 (d, *J* = 15.2 Hz, 1H), 4.18 (d, *J* = 12.7 Hz, 1H), 3.46 (dd, *J* = 11.7, 2.4 Hz, 1H), 3.22 (d, *J* = 16.1 Hz, 1H), 3.14 (s, 3H), 3.05 (s, 3H), 2.88 (td, *J* = 12.6, 2.6 Hz, 1H), 2.79 (d, *J* = 16.1 Hz, 1H), 1.81 – 1.68 (m, 2H), 1.61 (tdt, *J* = 13.0, 9.1, 4.1 Hz, 1H), 1.52 – 1.45 (m, 1H), 1.44 – 1.30 (m, 1H), 1.18 (qd, *J* = 12.4, 3.4 Hz, 1H). **^{13}C NMR** (100 MHz) δ 201.9, 199.6, 167.5, 147.1, 142.6, 142.2, 141.3, 136.2, 135.8, 128.9, 128.1, 124.7, 123.5, 123.4, 120.3, 113.0, 112.9, 59.4, 55.0, 48.7, 37.5, 36.0, 33.0, 28.5, 25.0, 24.2. **IR**: ν 3429, 2931, 1702, 1641, 1589, 1390, 1254, 1132, 978, 729 cm^{-1}. **HRMS** (ESI) calculated for $C_{26}H_{27}N_2O_3^+$ $[M+H]^+$: 415.2022, measured: 415.2068.
A parallel reaction without ligand was also performed, and traces of product was observed.

(*E*)-8'-[2-(Phenylsulfonyl)vinyl]-1',2',3',4',4a',6'-hexahydrospiro[indene-2,5'-pyrido[1,2-a]quinoline]-1,3-dione (**5h**)



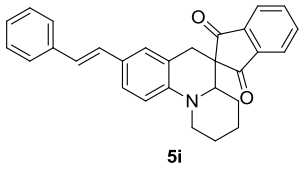
5h

Substrate **3h** (79.3 mg, 0.25 mmol, 1.0 equiv) was olefinated following the **general procedure B** using (vinylsulfonyl)benzene (63.1 mg, 0.375 mmol, 1.5 equiv) as the olefin and the product was purified by flash column chromatography (*n*-hexane:EtOAc, 2:1 to 1:1) to give **5h** as a yellow solid (62.0

mg, 51%, *para*:others > 20:1). **^{1}H NMR** (400 MHz) δ 8.06 – 7.98 (m, 1H), 7.98 – 7.85 (m, 5H), 7.62 – 7.46 (m, 4H), 7.33 (dd, *J* = 8.7, 2.2 Hz, 1H), 7.07 (s, 1H), 6.92 (d, *J* = 8.7 Hz, 1H), 6.58 (d, *J* = 15.1 Hz, 1H), 4.18 (d, *J* = 13.1 Hz, 1H), 3.51 (dd, *J* = 11.7, 2.4 Hz, 1H), 3.17 (d, *J* = 15.9 Hz, 1H), 2.94 (td, *J* = 12.7, 2.5 Hz, 1H), 2.77 (d, *J* = 15.9 Hz, 1H), 1.76 (d, *J* = 13.3 Hz, 2H), 1.62 – 1.54 (m, 1H), 1.54 – 1.44 (m, 1H), 1.43 – 1.32 (m, 1H), 1.19 (qd, *J* = 12.3, 3.4 Hz, 1H). **^{13}C NMR** (100 MHz) δ 201.6, 199.5, 148.5, 143.1, 142.1, 141.9, 141.2, 136.4, 136.0, 133.0, 129.9, 129.3, 129.2, 127.4, 123.6, 123.6, 121.7, 121.2, 120.5, 112.9, 59.3, 54.8, 48.5, 32.9, 28.4, 24.9, 24.1. **IR**: ν 2936, 2836, 1704, 1592, 1510, 1257, 1141, 1083, 791, 530 cm^{-1}. **HRMS** (ESI) calculated for $C_{29}H_{26}NO_4S^+$ $[M+H]^+$: 484.1583, measured: 484.1608.

A parallel reaction without ligand was also performed, and less than 10% of product was observed (para:others, not determined) by ^{1}H NMR analysis with CH_2Br_2 as internal standard.

(*E*)-8'-Styryl-1',2',3',4',4a',6'-hexahydrospiro[indene-2,5'-pyrido[1,2-a]quinoline]-1,3-dione (**5i**)



5i

Substrate **3h** (79.3 mg, 0.25 mmol, 1.0 equiv) was olefinated following the **general procedure B** using styrene (43.0 μL, 0.375 mmol, 1.5 equiv) as the olefin and the product was purified by flash column chromatography (*n*-hexane:EtOAc, 10:1) to give **5i** as a yellow liquid (47.8 mg, 51%, *para*:others > 20:1). **^{1}H NMR** (400 MHz) δ 8.03 – 7.99 (m, 1H), 7.98 – 7.93 (m, 1H), 7.88 – 7.83 (m, 2H), 7.45 (d, *J* = 7.2 Hz, 2H), 7.37 – 7.30 (m, 3H), 7.19 (t, *J* = 7.4 Hz, 1H), 7.11 (d, *J* = 2.1 Hz, 1H), 7.02 – 6.87 (m, 3H), 4.17 (dd, *J* = 13.0, 3.6 Hz, 1H), 3.41 (dd, *J* = 11.7, 2.4 Hz, 1H), 3.26 (d, *J* = 16.1 Hz, 1H), 2.89 – 2.75 (m, 2H), 1.78 – 1.69 (m, 2H), 1.62 – 1.57 (m, 1H), 1.51 – 1.44 (m, 1H), 1.42 – 1.31 (m, 1H), 1.17 (qd, *J* = 12.4, 3.6 Hz, 1H). **^{13}C NMR** (100 MHz) δ 202.3, 199.8, 145.6, 142.3, 141.4, 138.2, 136.2, 135.7, 128.7, 128.7, 127.5, 127.1, 126.9, 126.3, 126.2, 125.1, 123.5, 123.4, 120.5, 113.5, 59.7, 55.2, 49.0, 33.1, 28.7, 25.1, 24.3. **IR**: ν 2930, 1739, 1702, 1592, 1503, 1255, 958, 796, 726 cm^{-1}. **HRMS** (ESI) calculated for $C_{29}H_{26}NO_2^+$ $[M+H]^+$: 420.1964, measured: 420.1981.

A parallel reaction without ligand was also performed, and less than 20% of product was observed (para:others, not determined) by ^{1}H NMR analysis with CH_2Br_2 as internal standard.

3.5.7. Large scale reaction of Pd-catalyzed C5 C–H olefination of 1,3,3-trimethylindoline (1p)

In a 50 mL round bottom flask was added **1p** (1289.9 mg, 8.0 mmol, 2.0 equiv), $Pd(OAc)_2$ (89.8 mg, 0.4 mmol, 10 mol%), $PhCO_3{}^tBu$ (746 μL, 4.0 mmol, 1.0 equiv), a stock solution of the S,O-ligand (4.0 mL, 0.1 M in DCE, 0.4 mmol, 10 mol%), ethyl acrylate (426 μL, 4.0 mmol, 1.0 equiv) and DCE (16.0 mL). The flask was then sealed with a septum and was placed into a pre-heated oil bath at 60 ℃. The reaction was then stirred for 14 h. After cooling to room temperature, a saturated aqueous solution of Na_2CO_3 was added to quench the benzoic acid byproduct. The mixture was extracted with DCM three times and the combined organic extracts were dried with $MgSO_4$, filtrated and concentrated *in vacuo*. The product was purified by flash column chromatography (*n*-hexane:Et_2O, 25:1 to 8:1 to 6:1,) to obtain **2p** as a viscous yellow liquid (654.5 mg, 63%) and the unreacted **1p** was also recovered (480 mg, 37%).

3.6 References

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CHAPTER 4

DIVERGENT TOTAL SYNTHESIS OF YAEQUINOLONE RELATED NATURAL PRODUCTS BY LATE STATE C–H OLEFINATION

4.1 Introduction

Yaequinolones and closely related compounds, which possess 3,4-dioxygenated 5-hydroxy-4-aryl-quinolin-2(1*H*)-one cores, represent a growing family of naturally occurring biologically active alkaloids isolated from plant and marine fungi (Figure 4.1).[1] Its first two members, NTC-47A and B, were isolated in 1995 by Nakaya from the second metabolites of *Penicillium sp.* and they were proved to show insecticidal activities.[2] However, no spectroscopic information of the products was given by the author. In 1996, a mixture of penigequinolone A and B, which show inhibitory activity towards pollen-growth, were isolated from *Penicillium sp*. No. 410 and the relative stereochemistry of the two oxygenated functional groups was determined by NMR to be *syn* (3*R**, 4*R**).[3] Since then, many more related compounds have been isolated and tremendous efforts have been made to evaluate their bioactivities and elucidate their structures (Figure 4.1).[4-9] Interestingly, the relative stereochemistry of yaequinolone A1 was proved to be *anti* (3*S**, 4*R**) and this is so far the only member that has such a stereochemistry. Most of this family of natural products differ from each other in the structure of the olefin at the 6-position.

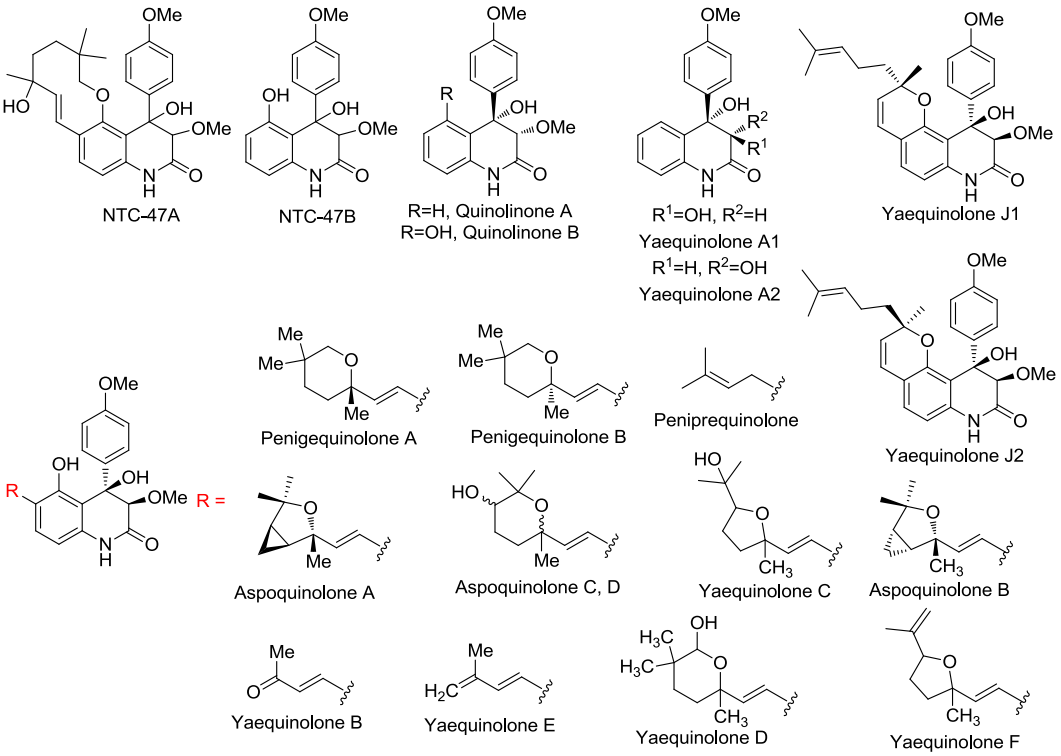


Figure 4.1 Natural products that possess quinolin-2(1*H*)-one core

In 2012, Gloer and co-workers reported the isolation of seven new members, aflaquinolone A−G (Figure 4.2), that comprise a slightly different backbone.[10] Instead of a 4-methoxyphenyl group at the 4-position, they possess a phenyl group. All new members have the *syn* relative stereochemistry between the two oxygenated functionalities except aflaquinolone G, that has the *anti*-stereochemistry. After this report, many more related natural products have been isolated and characterized.[11] Again, most of this family of natural products differ from each other in the structure of the olefin at the 6-position.

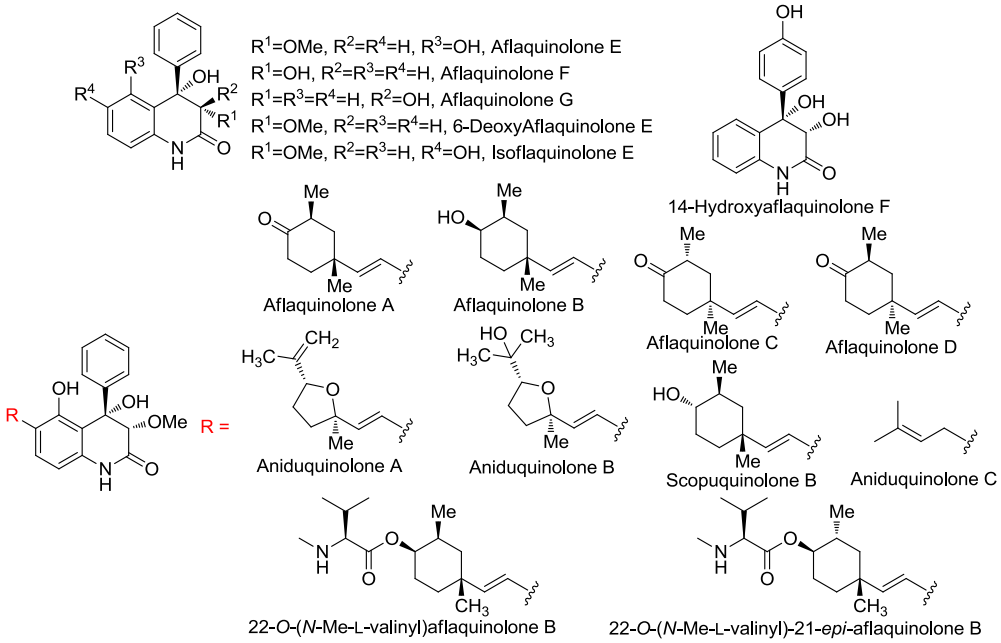
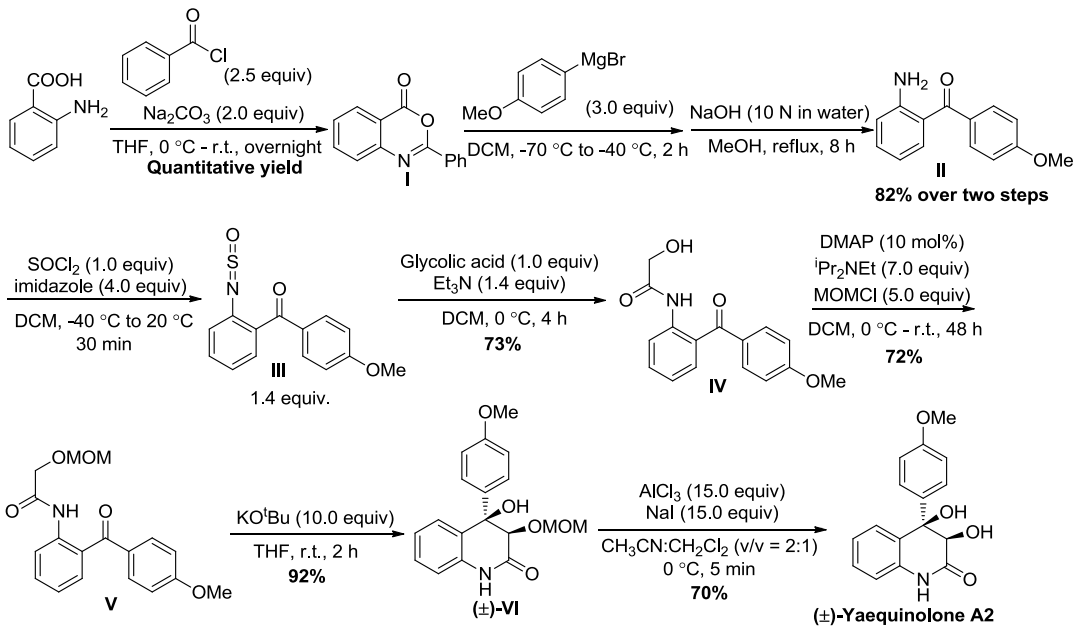


Figure 4.2 Natural products with a phenyl ring at the C4 position

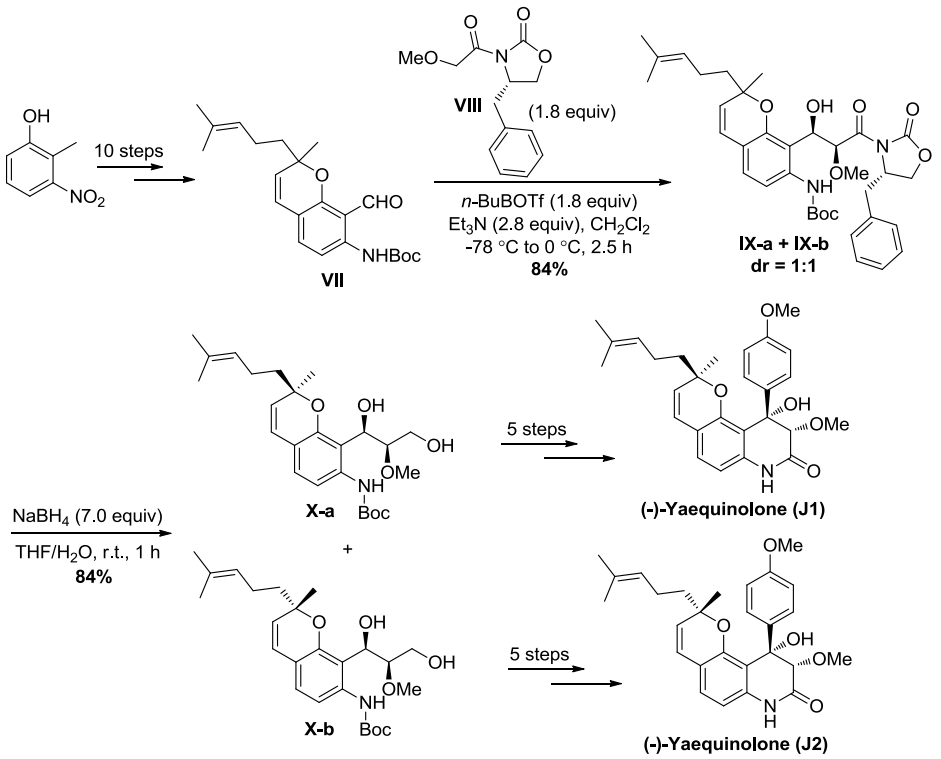
This family of natural products have attracted a great attention from synthetic organic chemists due to their unique structures and biological activities and several total syntheses have been reported in the last years. The reported total synthesis of (±)-yaequinolone A2,[12] which represents the structurally simplest member of this family, is illustrated in Scheme 4.1. The key step of the synthesis is the intramolecular aldol addition of the MOM-protected α-hydroxyanilide **V** mediated by KO^{t}Bu, that provides the MOM-protected yaequinolone A2 **VI**, in high yield and with complete diastereoselectivity.[13] To build the MOM-protected α-hydroxyanilide, the authors started with the reaction of commercially available anthranilic acid with benzoyl chloride followed by basic workup giving 2-phenylbenzoxazinone (**I**) in quantitative yield. Nucleophilic addition of 4-methoxyphenylmagnesium bromide to 2-phenylbenzoxazinone and subsequent hydrolysis furnished the key intermediate aminobenzophenone **II**.[14] Its coupling with glycolic acid to obtain α-hydroxyanilide **IV** was achieved by pre-activating the amine moiety by transforming it to *N*-sulfinylaniline **III**.[15]



Scheme 4.1 Total synthesis of yaequinolone A2

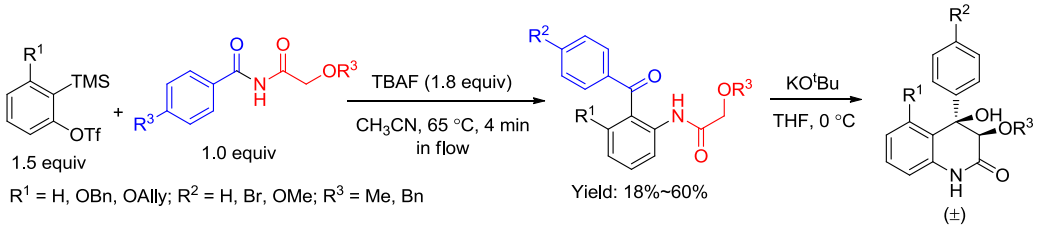
In 2018, the group of Hanessian reported the first total synthesis and absolute stereochemical assignment of yaequinolone J1 and J2.[16] Based on what Tomoda and co-workers assumed about the relative stereochemistry of

yaequinolone J1 and J2, they first completed the total synthesis of *3R, 4R, 3''R*-(+)-yaequinolone J1.[7] By comparing the optical rotation, they concluded that this was the enantiomer of yaequinolone J1 that was isolated and reported by Tomoda and co-workers, as this synthetic molecule has a positive optical rotation value, whereas the isolated molecule has a negative one. Therefore, they synthesized the other enantiomer using the synthetic route outlined in Scheme 4.2. It started with commercially available 2-methyl-3-nitrophenol. After 10 steps, they obtained benzopyran intermediate **VII**.[17] A key step in the synthesis was the asymmetric aldol reaction using Evans-type auxiliary oxazolidinone **VIII**,[18] that provides product **IX** as an inseparable mixture of diastereoisomers (dr = 1:1) with a full stereochemical control of the two new chiral centers formed in a *syn* fashion. After removal of the auxiliary using $NaBH_4$, the corresponding diastereoisomers **X-a** and **X-b** could be separated by flash column chromatography. Then, from **X-a,** (-)-yaequinolone J1 was obtained in 5 steps and its optical rotation value perfectly matches with the reported one.[7] (+)-Yaequinolone J2 was prepared form **X-b** using the same procedure.



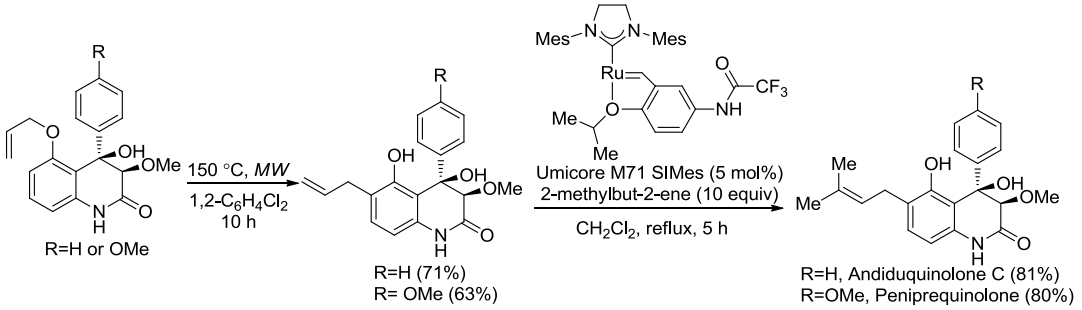
Scheme 4.2 Enantioselective total synthesis of (-)-yaequinolone J1 and J2

The group of Christmann finished the total synthesis of (±)-peniprequinolone, (±)-aflaquinolone E and F, (±)-6-deoxyaflaquinolone E, (±)-quinolinone A and B, and (±)-aniduquinolone C in 2018.[19] Their success relied on the development of a strategy for the synthesis of benzophenone amide *via* aryne insertions into unsymmetrical imides in flow (Scheme 4.3).[20] By performing the reaction in flow, the reaction time was reduced to 4 min, which seems to be crucial since the starting imides are relatively unstable under the reaction conditions. Using this methodology, several *N*-acylated 2-aminobenzophenones were prepared in low to moderate yields, which after cyclization using KO^{t}Bu in THF, generated 3,4-dioxygenated quinoline-2-one cores.[12,13] (±)-aflaquinolone E and F, (±)-6-deoxyaflaquinolone E and (±)-quinolinones A and B were obtained using this approach.



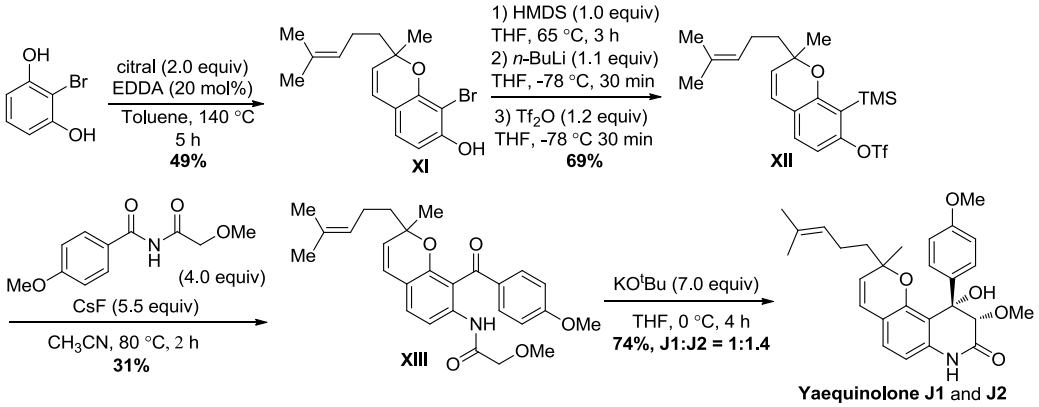
Scheme 4.3 Aryne insertion to unsymmetrical imides in flow and subsequent cyclization reactions.

For the synthesis of (±)-peniprequinolone and (±)-aniduquinolone C, further transformations including a Claisen rearrangement at 150 °C and a Grubbs' olefin cross metathesis were performed (Scheme 4.4).[21]



Scheme 4.4 Total synthesis of (±)-peniprequinolone and (±)-aniduquinolone C

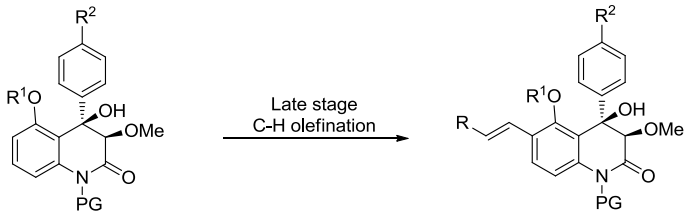
Recently, the same group also finished the total synthesis of yaequinolone J1 and J2 using similar strategy in only four steps (Scheme 4.5).[22] The reaction of 2-bromoresorcinol with citral in the presence of catalytic amounts of ethylenediamine diacetate (EDDA) provided the benzopyran intermediate **XI** *via* tandem Knoevenagel electrocyclization reaction.[23] Then, **XI** was transformed to the aryne precursor **XII** and reacted with the corresponding imide to produce the desired product **XIII** in 31% yield. Cyclisation of racemic **XIII** under the same reaction conditions reported previously gave a mixture of (±)-yaequinolone J1 and J2 with a ratio of 1:1.4. Separation of the two enantiomers of **XIII** by chiral HPLC and further cyclisation furnished (-)-Yaequinolone J1 and J2 in 30% and 40% yield, respectively.



Scheme 4.5 Four-step total synthesis of yaequinolone J1 and J2

Despite the progress that has been made in the synthesis of some of these yaequinolone related natural products, a general strategy that permits the direct access to this family of natural products is still elusive. As previously mentioned, the majority of this family of natural products possess a 3,4-dioxygenated 5-hydroxy-4-aryl-quinolin-2(1*H*)-one core structure and they differ from each other in the structure of the olefin at the 6-position. Therefore, the development of synthetic methods that permit the introduction of the olefin moiety in a late stage is highly desired and will streamline the synthesis of this family of natural products.

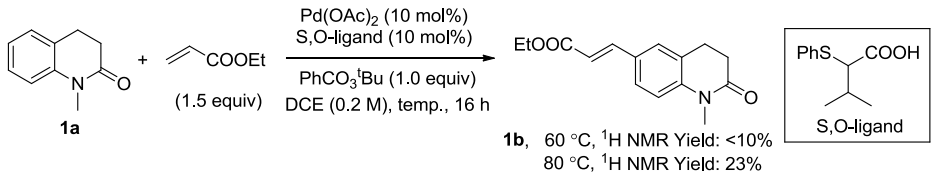
In this chapter, we describe for the first time the divergent total synthesis of a variety of yaequinolone natural products that contain an olefin at the 6-position. The optimization towards the synthesis of 3,4-dioxygenated 5-hydroxy-4-aryl-quinolin-2(1*H*)-one cores is described followed by the selective late-stage Pd-catalyzed C–H olefination using a similar methodology to the one described in Chapter 3 (Scheme 4.6). This synthetic approach allows us to streamline the synthesis of this family of natural products that are at the moment not accessible by other synthetic routes.



Scheme 4.6 Late stage C–H olefination

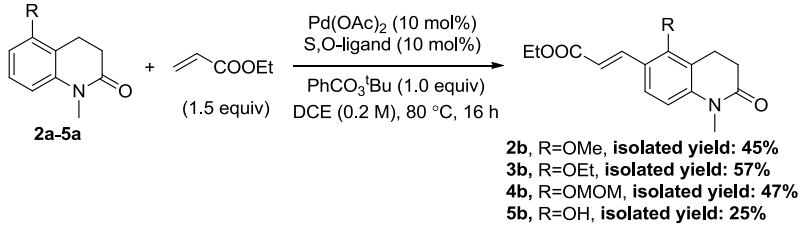
4.2 Results and discussion

In Chapter 3, we reported a highly selective C(6)–H olefination reaction of tetrahydroquinolines by using Pd/S,O-ligand catalysis. With the aim to apply this methodology to the total synthesis of yaequinolone natural products bearing an olefin moiety at the C6 position, we decided to evaluate the C–H olefination of a protected 3,4-dihydro-2(1*H*)-quinolinone, which is the core structure present in this family of natural products. The reaction of *N*-methyl 3,4-dihydro-2(1*H*)-quinolinone (**1a**) under the conditions reported in Chapter 3, only provided the olefinated product **1b** in less than 10% ^{1}H NMR yield (Scheme 4.7). This result was expected since 3,4-dihydro-2(1*H*)-quinolinone core must be less reactive toward an electrophilic palladation or base-assisted internal electrophilic-type substitution (BIES) mechanism than the tetrahydroquinoline core.[24] When we performed the reaction at slightly higher temperature, 23% of olefinated product was detected by ^{1}H NMR.



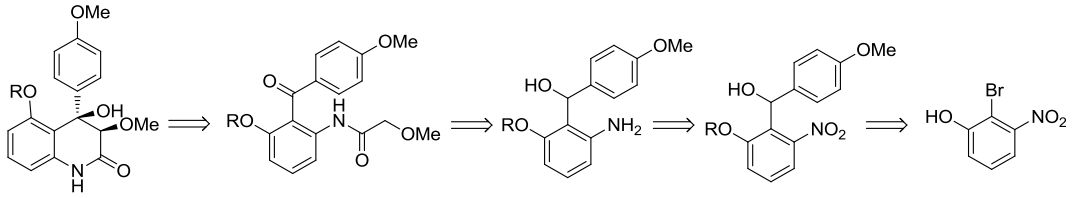
Scheme 4.7 C6-Selective C–H olefination reaction of **1a**

Since all the yaequinolone natural products that possess an olefin at the C6 position, also contain a hydroxyl group at the C5 position, we studied the influence of this functional group in the C–H olefination reaction. We expected that the presence of the hydroxyl group will increase the reactivity as it makes the aromatic ring more electron-rich. We synthesized some 3,4-dihydro-2(1*H*)-quinolinones bearing an oxygenated functional group at 5-position. The reaction of OMe, OEt and OMOM derivatives **2a**-**4a**, provided the olefinated products (**2b**-**4b**) in synthetically useful yields (45-57%) at 80 ℃ (Scheme 4.8). An exception to this trend was the reaction of 5-hydroxy-*N*-methyl-3,4-dihydro-2(1*H*)-quinolinone (**5a**) that gave the olefinated product (**5b**) in only 25% isolated yield due to the instability of the olefinated product under the reaction conditions.



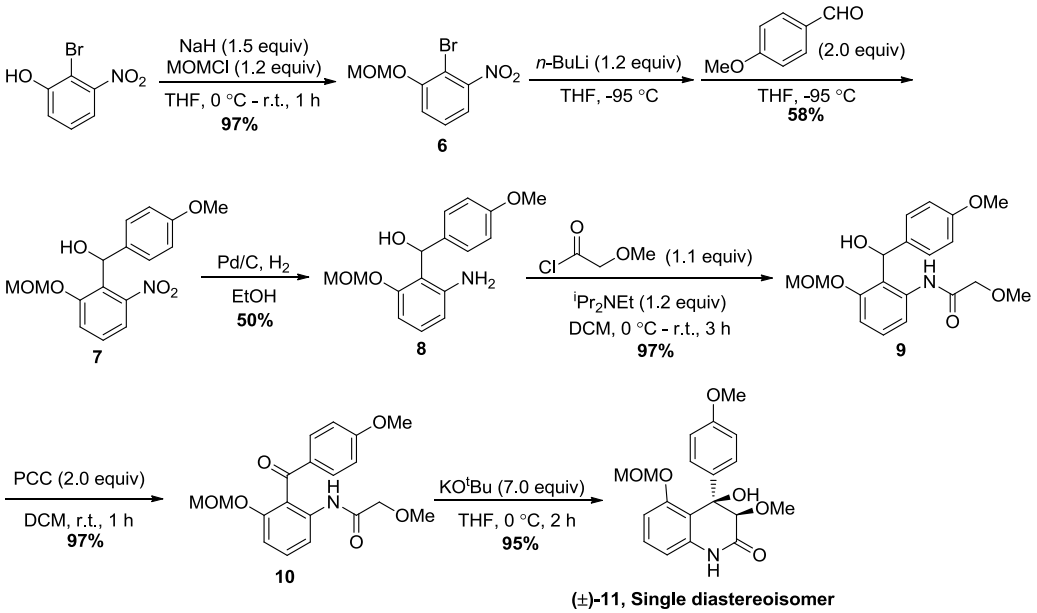
Scheme 4.8 C6-Selective C–H olefination reaction of 5-oxygenated *N*-methyl-3,4-dihydro-2(1*H*)-quinolinone

After proving the feasibility to perform the site-selective C–H olefination of the simplified core structure of yaequinolones, we decided to establish a robust method for the synthesis of 3,4-dioxygenated 5-hydroxy-4-aryl-quinolin-2(1*H*)-one, which is the common structure in this family of natural products (Scheme 4.11). 3,4-Dioxygenated 5-hydroxy-4-aryl-quinolin-2(1*H*)-one can be obtained by cyclization as reported by the group of Christmann. The starting diarylketone can be synthesized from the nucleophilic addition of the corresponding aryllithium reagent to *p*-anisaldehyde followed by oxidation.



Scheme 4.11 Retrosynthetic analysis of 3,4-dioxygenated 5-hydroxy-4-aryl-quinolin-2(1*H*)-one

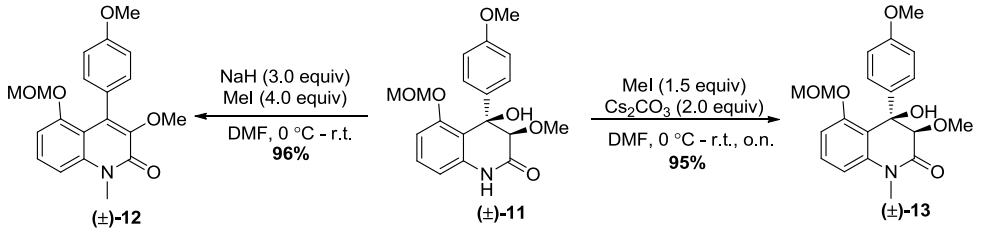
We then started our synthesis from 2-bromo-3-nitrophenol (Scheme 4.12), which was protected with MOM group in nearly quantitative yield. The coupling between the MOM-protected phenol **6** and *p*-anisaldehyde at -95 ℃ delivered the hydroxyl product **7** in 58% isolated yield. Importantly, this reaction is really sensitive to the temperature probably due to the instability of the lithiated intermediate, as we observed a loss of mass balance from ^{1}H NMR analysis of the crude sample. Then, we successfully performed the oxidation of the hydroxyl group to a ketone using PCC. However, selective reduction of the nitro group to an amine in the presence of the ketone proved to be very challenging. We tried two different methods: Na_2S; and Pd/C and H_2. However, in both cases, a mixture of starting material, desired product and the product coming from the reduction of the ketone were detected. We then decided to first reduce the nitro group to the amine using Pd/C and H_2. We found out that this reaction was very sensitive to the reaction time as no desired product was detected after stirring the reaction overnight. In contrast, when the reaction was stopped after 2 h, full conversion was already achieved and product **8** was isolated in 50% yield (the formation of an unidentified byproduct was also observed). The reaction between aniline **8** and methoxyacetyl chloride produced the amide product **9** in nearly quantitative yield, which could be easily oxidized to ketone **10** with PCC in 97% yield. The cyclization reaction of the diarylketone **10** under reported reaction conditions went perfectly, giving **(±)-11** in 95% isolated yield as a single diastereoisomer.



Scheme 4.12 Synthesis of **(±)-11**

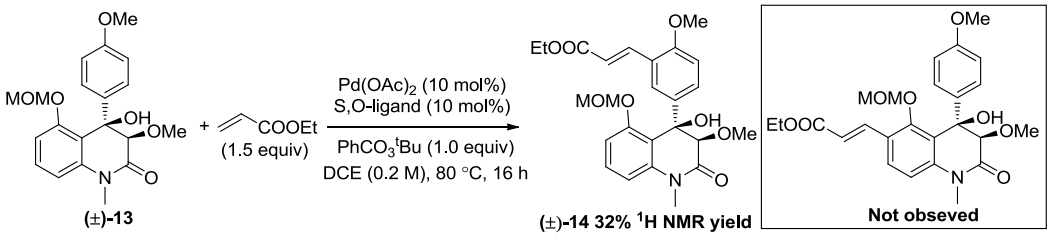
After having a robust method for the synthesis of the core structure **(±)-11** of yaequinolones, we decided to explore different *N*-protecting groups since the nitrogen atom must be protected before performing the C–H olefination as we described in Chapter 3. Although the methyl group was a suitable protecting group in the C–H olefination of tetrahydroquinolines (see Chapter 3) as well as in the model substrate 3,4-dihydro-2(1*H*)-quinolinone, we anticipated that the deprotection of the methyl can be challenging since 3,4-dioxygenated 5-hydroxy-4-aryl-quinolin-2(1*H*)-ones are reported to be unstable, by dehydration, under acidic or basic conditions.[12,13] Indeed, as far as we know, only two methods have been reported for the deprotection of a methyl group from similar molecules.[25,26] The first one occurs *via* a radical mechanism and a basic work-up is required and the second method uses benzyl chloroformate, which is incompatible with the hydroxyl group present in our

target molecules. Nevertheless, we decided to evaluate first the methyl protecting group. The reaction of **(±)-11** with MeI and NaH provided only the dehydrated product **(±)-12** (Scheme 4.13a). Then, we switched to a weaker base, Cs_2CO_3 and the desired product **(±)-13** was isolated in 95% yield with only a trace amount of dehydrated product being detected from ^{1}H NMR analysis of the crude reaction mixture.



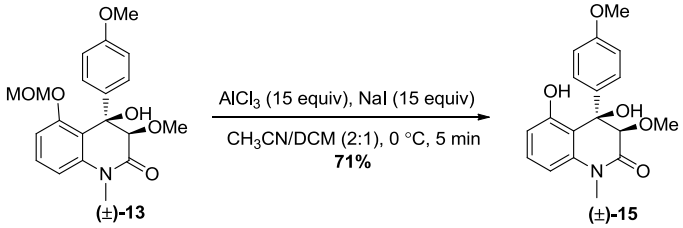
Scheme 4.13 Methyl protection of **(±)-11**

Having **(±)-13** in hand, we tested the olefination reaction under our reported reaction conditions (Scheme 4.14). Unfortunately, no desired product was detected and instead, we observed 32% of olefinated product at the 4-anisole ring **(±)-14** together with the unreacted starting material.



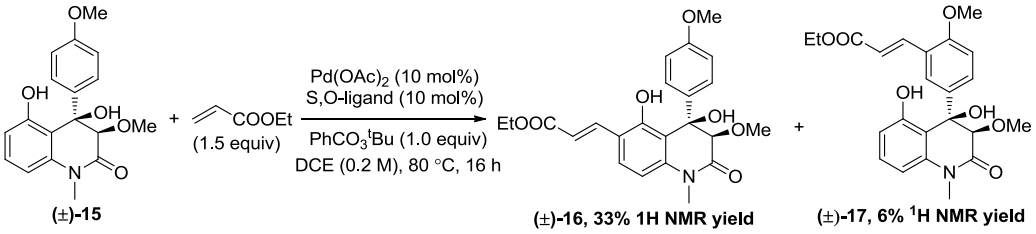
Scheme 4.14 C–H olefination of **(±)-13**

We attributed the lack of reactivity at the 6-position of 3,4-dihydro-2(1*H*)-quinolinone to the presence of the tertiary carbon that might force the MOM group to adopt a conformation that greatly shields the C(6)-position. Therefore, we performed the deprotection of the MOM before performing the C–H olefination reaction. The deprotected product **(±)-15** was isolated in 71% yield (Scheme 4.15).



Scheme 4.15 MOM deprotection of **(±)-13**

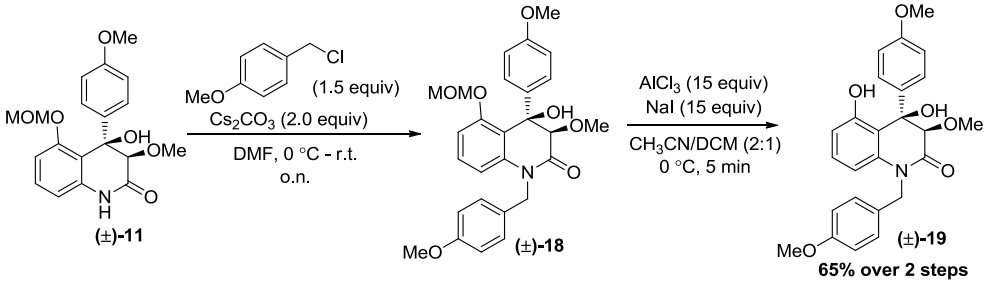
We then performed the olefination reaction of **(±)-15** and the desired product was detected in 33% ^{1}H NMR yield along with 6% of olefinated product at the 4-anisole ring (Scheme 4.16). Unfortunately, we were not able to separate these two regioisomers by flash column chromatography.



Scheme 4.16 C–H olefination of **(±)-15**

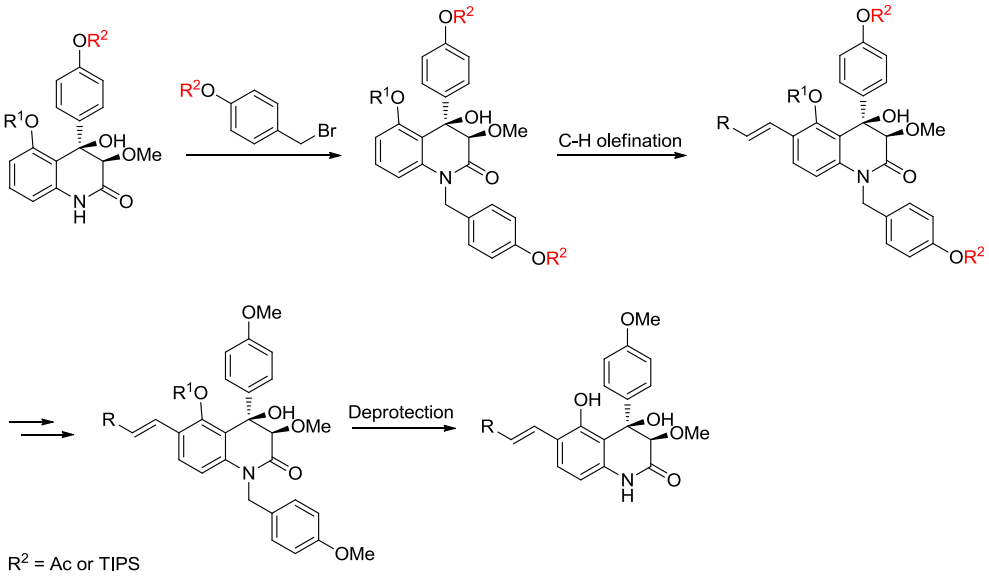
Taking into consideration that we already observed the dehydrated product during the protection reaction using a base, we decided to switch to other nitrogen protecting groups. We then evaluated the *p*-methoxybenzyl protecting group since it can be deprotected under neutral conditions. We prepared the *p*-methoxybenzyl

protected molecule **(±)-19** by first protecting the nitrogen atom with *p*-methoxybenzyl followed by the MOM deprotection under the conditions reported previously (Scheme 4.17). Unfortunately, it turned out that **(±)-19** is not stable under the C–H olefination conditions.



Scheme 4.17 Synthesis of **(±)-82**

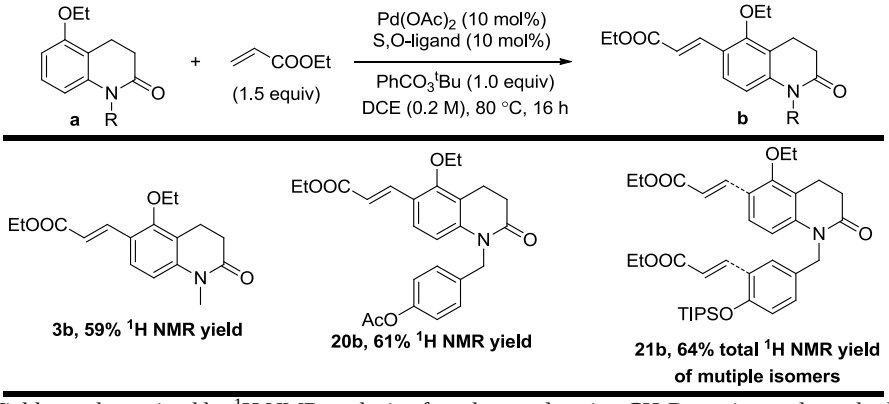
As we were facing some problems regarding the regioselectivity of the C–H olefination of **(±)-15** as well as some stability issues of the *p*-methoxybenzyl protecting group, we envisioned the alternative synthetic strategy that is outlined in Scheme 4.18. We supposed that by reducing the electron density of the aromatic ring located at the 4-position or by increasing the steric hindrance of the OR^2 group, a complete control on the regioselectivity could be achieved. Thus, we proposed to use OAc or OTIPS in the aromatic ring at the 4-position as well as in the benzyl protecting group. Then, after performing the C–H olefination, both groups (OAc or OTIPS) can be deprotected and protected with the methyl group in one pot followed by the deprotection of the *p*-methoxybenzyl group.



Scheme 4.18 Different protecting groups for the synthesis of yaequinolones

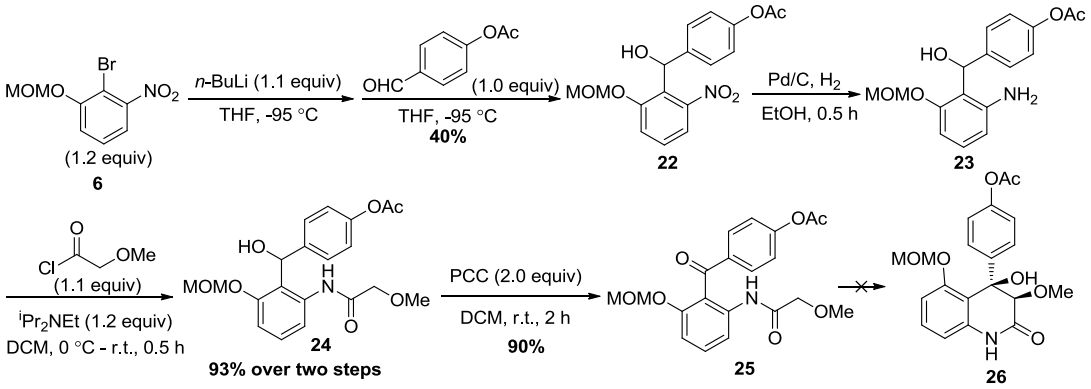
Before we started the total synthesis using the new protecting groups, we tested the C–H olefination in simpler molecules. We prepared 3,4-dihydro-2(1*H*)-quinolinone derivatives with both protecting groups and performed the C–H olefination under standard reaction conditions (Table 4.1). Both 4-dihydro-2(1*H*)-quinolinone derivatives **20a** and **21a** showed great reactivity, equally efficient to methyl protected substrate **3a**, giving the olefinated product **20b** and **21b** in 61% and 64% ^{1}H NMR yield, respectively. However, in the case of the TIPS-protected 3,4-dihydro-2(1*H*)-quinolinone **21b**, a few isomers were observed together with a small amount of diolefinated product. For Ac-protected 3,4-dihydro-2(1*H*)-quinolinone **20b**, full selectivity was observed. With these results in hand, we decided to continue our approach toward the synthesis of yaequinolones using the OAc group.

Table 4.1. Evaluation of protecting groups in the C–H olefination reaction



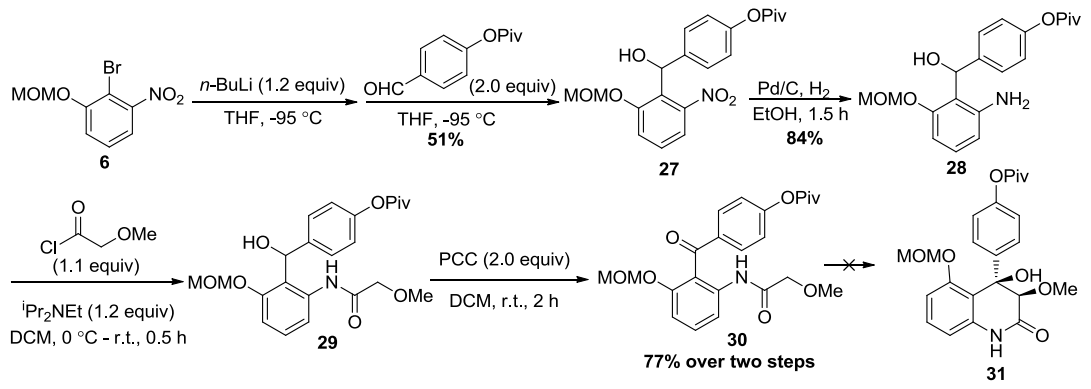
Yield was determined by ^{1}H NMR analysis of crude sample using CH_2Br_2 as internal standard.

We used the same synthetic procedure for the synthesis of Ac-protected 3,4-dihydro-2(1*H*)-quinolinone as the one previously described. All the steps before the cyclization went as expected (Scheme 4.19). However, when the diarylketone **25** was subjected to the cyclization conditions using KO^{t}Bu, no formation of the desired product was detected. Instead, we observed a small amount of the uncyclized product without the Ac-protecting group and the decomposition of the starting material. A weaker base, Cs_2CO_3, was also tried but again no desired product was detected. We then tried a less nucleophilic base, LiHMDS, but only the formation of Ac-deprotected uncyclized product together with some starting material was observed.



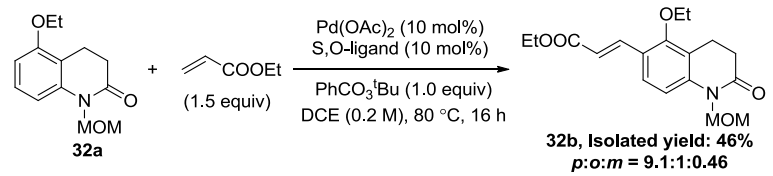
Scheme 4.19 Synthesis of Ac-protected 3,4-dihydro-2(1*H*)-quinolinone derivative **26**

Then, we decided to modify our approach and to change the OAc with OPiv group since we expected that the latter one will be more stable while keeping the same electronic properties as the OAc group. We followed the synthetic procedure that we previously established but again, the cyclization of the Piv-protected 3,4-dihydro-2(1*H*)-quinolinone derivative **30** using KO^{t}Bu did not provide the desired product and the Piv-deprotected uncyclized product was obtained in nearly quantitative yield (Scheme 4.20). We tried other bases such as NaH or BuLi, but no desired product was obtained.



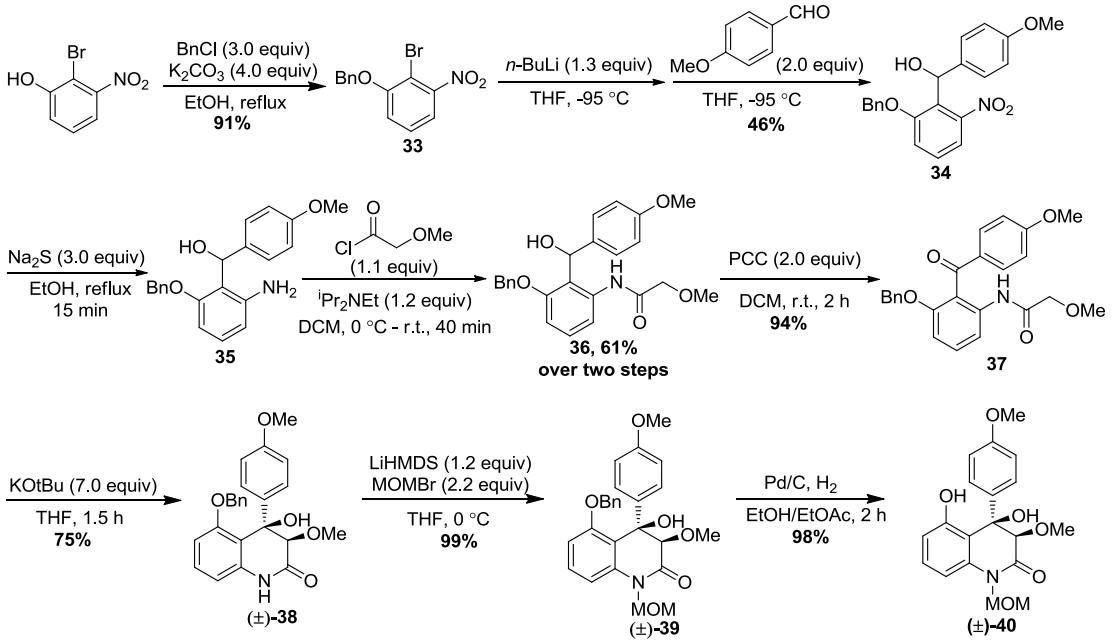
Scheme 4.20 Synthesis of Piv-protected 3,4-dihydro-2(1*H*)-quinolinone derivative **31**

As we failed to prepare Piv- and Ac-protected 3,4-dihydro-2(1*H*)-quinolinone derivatives, we decided to use MOM as the protecting group. Again, we first tried the C–H olefination in a simpler substrate (Scheme 4.21). The reaction of the MOM-protected 3,4-dihydro-2(1*H*)-quinolinone derivative **32a** under standard reaction conditions provided the olefinated product **32b** in 46% isolated yield with slightly lower regioselectivity than the methyl-protected substrate.



Scheme 4.21 C–H Olefination of MOM-protected 3,4-dihydro-2(1*H*)-quinolinone derivative **32a**

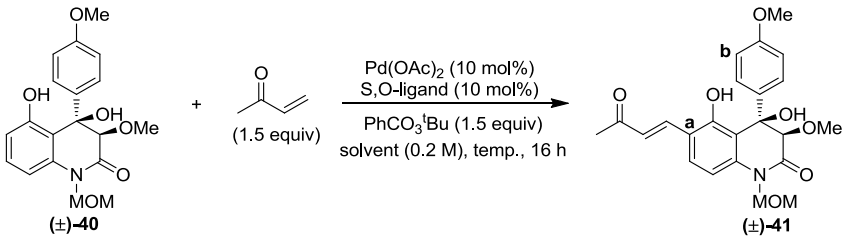
Then, we decided to start our total synthesis using benzyl as the protecting group for the phenol moiety in order to have an orthogonal protecting group with respect to MOM since we need to perform a selective deprotection before C–H olefination. We followed the same procedure that we have developed for the synthesis of **(±)-11** and all the steps went as expected including the cyclization reaction (Scheme 4.22). For the MOM protection of (±)-**38**, when NaH was used as the base, the reaction gave the protected product (±)-**39** in low yield even when the reaction was performed at low temperature (-78 ℃ to 0 ℃). Nevertheless, when LiHMDS was used as the base, the MOM-protected derivative (±)-**39** was obtained in quantitative yield. The deprotection of the benzyl group using Pd/C and H_2 gave the desired product (±)-**40** in 98% yield.



Scheme 4.22 Synthesis of MOM-protected 3,4-dihydro-2(1*H*)-quinolinone derivative (±)-**40**

With (±)-**40** in hand, we tested the C–H olefination reaction using 3-buten-2-one as the olefin (Table 4.2). When the reaction was performed in DCE for 16 h at 80 ℃, the olefinated product (±)-**41** was isolated in 52% yield as a mixture of regioisomers (a:b = 5:1). Unfortunately, we were not able to separate the regioisomers by flash column chromatography. In order to improve the reactivity and regioselectivity of the process, we performed the reaction at lower temperature (entries 2-3) as well as using other solvents (entries 4-6), but in all cases, we observed the formation of the olefinated products in lower yields.

Table 4.2 C–H Olefination of MOM-protected 3,4-dihydro-2(1*H*)-quinolinone derivative (±)-**40**

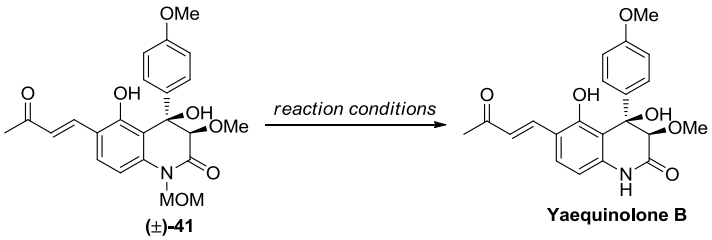


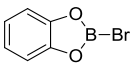
Entry	Solvent	Temp.	^{1}H NMR yield[a]
1	**DCE**	**80 ℃**	**51% (52%)[b,c]**
2	DCE	70 ℃	31%
3	DCE	60 ℃	38%
4	1,4-Dioxane	80 ℃	29%
5[d]	Hexafluorobenzene	80 ℃	21%
6	*t*-Amyl alcohol	80 ℃	traces

[a] ^{1}H NMR yield was determined by using CH_2Br_2 as internal standard and only yield of desired regioisomer was determined. [b] Isolated yield. [c] Regioselectivity: a:b = 5:1. [d] Reaction concentration was 0.1 M due to bad solubility of (±)-**40** in hexafluorobenzene.

Since both the reactivity and selectivity of the C–H olefination reaction of MOM-protected 3,4-dihydro-2(1*H*)-quinolinone derivative (±)-**40** were acceptable, we decided to perform the deprotection of the MOM group to synthesize for the first time (±)-yaequinolone B. However, the deprotection was proved to be more problematic than expected. We tried many different Lewis acids and Bronsted acids as listed in Table 4.3. In most of the cases, the decomposition of the starting material was detected and no formation of the desired product was observed.

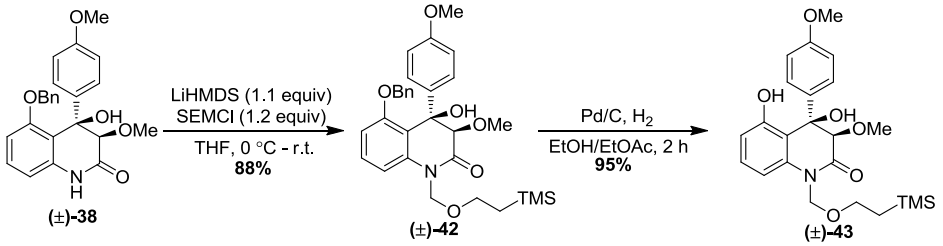
Table 4.3 Deprotection of MOM-protected 3,4-dihydro-2(1*H*)-quinolinone derivative (±)-**41**



Entry	*Reaction conditions*	Results
1	$AlCl_3$(15 equiv), NaI (15 equiv), CH_3CN/DCM (1:1), 0 ℃, 5 min	Recovered s.m.
2	TFA/DCM (1:1), r.t., 3 h	Decomposition, messy crude ^{1}H NMR
3	TMSCl (5.0 equiv), NaI (5.0 equiv), CH_3CN, 0 ℃, 2h, then r.t., 2h	Decomposition, messy crude ^{1}H NMR
4	$TsOH.H_2O$ (4.0 equiv), CH_3CN, 0 ℃, 3 h, then reflux, 1 h	Decomposition, messy crude ^{1}H NMR
5	sodium *p*-toluenesulfinate (2.0 equiv), HCl (2.5 equiv), CH_3CN	Decomposition, messy crude ^{1}H NMR
6	 (3.0 equiv), DCM, -78 ℃ to r.t.	Decomposition, messy crude ^{1}H NMR
7	HCl (2 M, 6M or concentrated)/THF (1:1), r.t.	No desired product

Since we were not able to deprotect the MOM group which was needed to accomplish the total synthesis of (±)-yaequinolone B, we decided to look for an alternative protecting group. We decided to perform the synthesis using SEM [2-(trimethylsilyl)ethoxymethyl] as the protecting group since this protecting group can be deprotected using milder reagents, such as TBAF. In addition, we expected the C–H olefination to take place in a similar way as the MOM protected substrate. We then synthesized the SEM-protected 3,4-dihydro-2(1*H*)-

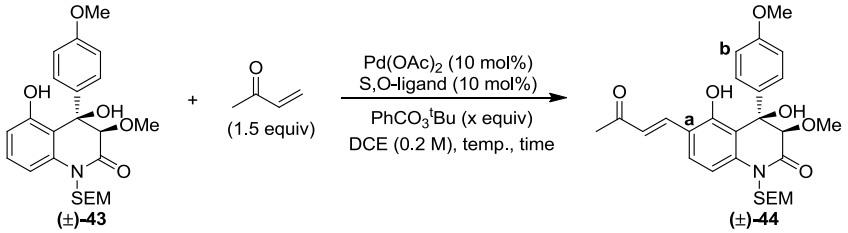
quinolinone derivative (±)-**42** in 88% yield and the benzyl group was selectively deprotected suing Pd/C and H_2 to provide SEM-protected 3,4-dihydro-2(1*H*)-quinolinone derivative (±)-**43** in 95% yield (Scheme 4.23),



Scheme 4.23 Synthesis of SEM-protected 3,4-dihydro-2(1*H*)-quinolinone derivative (±)-**43**

For the C–H olefination of the SEM-protected 3,4-dihydro-2(1*H*)-quinolinone derivative (±)-**43**, we slightly optimized the reaction conditions and found that the best reaction conditions were to use 2.0 equiv of $PhCO_3{}^tBu$ at 80 ℃ in DCE for 16 h, providing the olefinated product (±)-**44** in 59% isolated yield with a regioselectivity of 6:1 (Table 4.4).

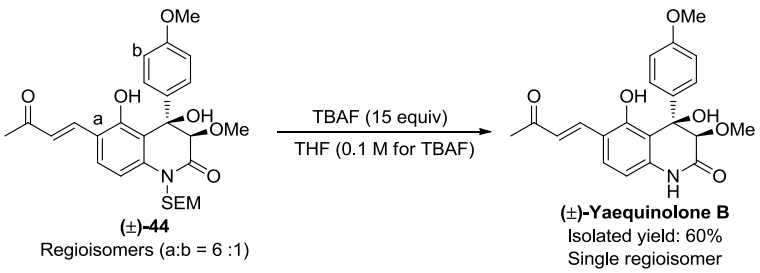
Table 4.4 C–H olefination of SEM-protected 3,4-dihydro-2(1*H*)-quinolinone derivative (±)-**43**



Entry	Temp.	x	Time	^{1}H NMR yield[a]
1	80 ℃	1.5	16 h	49%
2	60 ℃	1.5	16 h	31%
3	80 ℃	1.5	6 h	45%
4	80 ℃	1.0	16 h	42%
5	**80 ℃**	**2.0**	**16 h**	**54% (59%+5%[b])[c,d]**
6[e]	80 ℃	1.5	16 h	55%

[a] ^{1}H NMR yield was determined by using CH_2Br_2 as internal standard and only yield of desired regioisomer was determined. [b] Diolefinated product. [c] Isolated yield. [d] Regioselevtivity: a:b = 6:1. [e] 15 mol% of $Pd(OAc)_2$ and S,O-ligand were used.

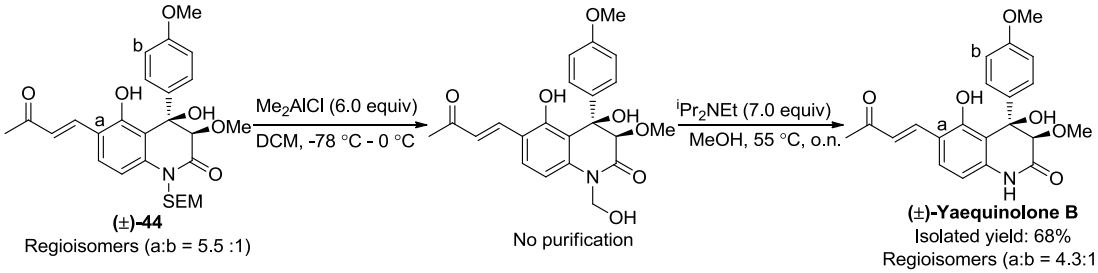
Unfortunately, we were not able to separate the regioisomers by flash column chromatography. Then, we decided to continue with the mixture of regioisomers. We performed the deprotection of the SEM group with TBAF and, we found out that a high concentration of TBAF is required to obtain the desired product in good yield. For instance, when the concentration of TBAF was 0.1 M, no product was observed even after refluxing the reaction for 20 h. When we increased the concentration to 1.0 M, to our delight, the reaction reached full conversion after refluxing for 15 h and the desired (±)-yaequinolone B was obtained as a single regioisomer in 60% isolated yield (Scheme 4.24). Its ^{1}H and ^{13}C NMR data matched with those reported in the literature.[9]



Scheme 4.24 Final deprotection step towards the synthesis of Yaequinolone B using TBAF

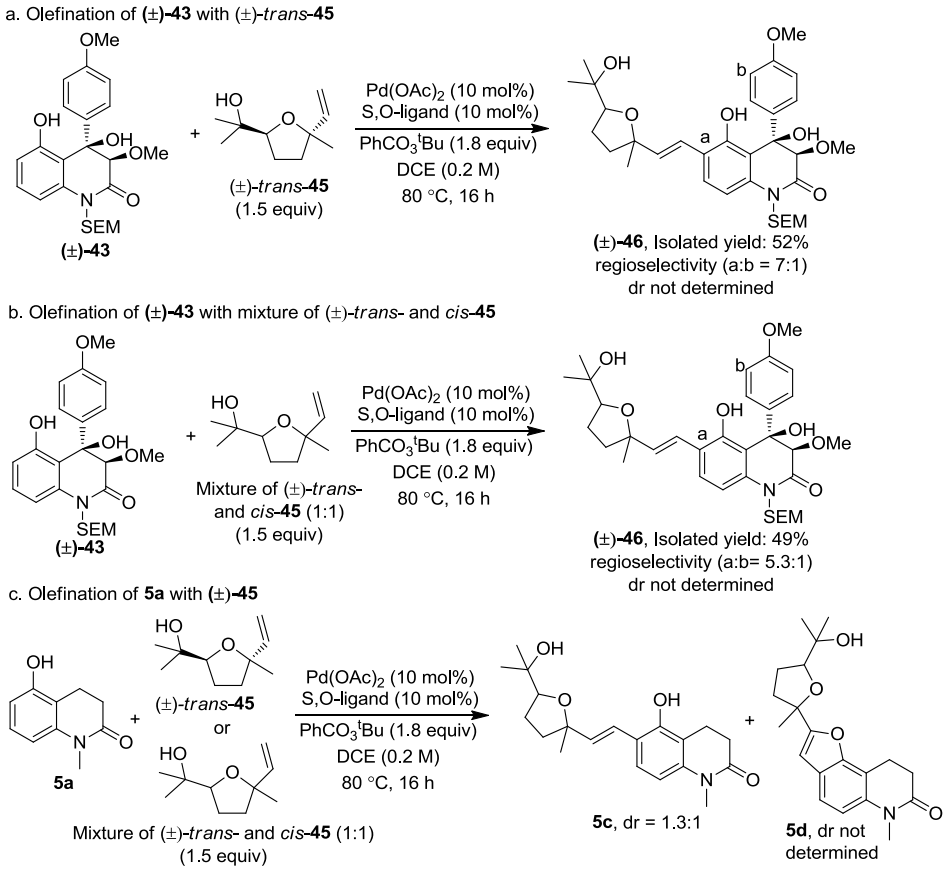
Additionally, we tried another method for the SEM deprotection of (±)-**44** (regioisomers, a:b = 5.5:1) using Me_2AlCl, which first affords the hydroxymethyl-protected intermediate that, after treatment with $^iPr_2NEt$ in MeOH at 55 ℃ overnight, provided (±)-yaequinolone B in 68% isolated yield as a mixture of regioisomers

4.3:1 (Scheme 4.25). Therefore, we decided to establish the deprotection of the SEM group using TBAF as the suitable reaction for the total synthesis of (±)-yaequinolone B. Hence, the total synthesis of (±)-yaequinolone B was obtained in 5.3% overall yield in 10 synthetic steps starting from commercially available 2-bromo-3-nitrophenol.



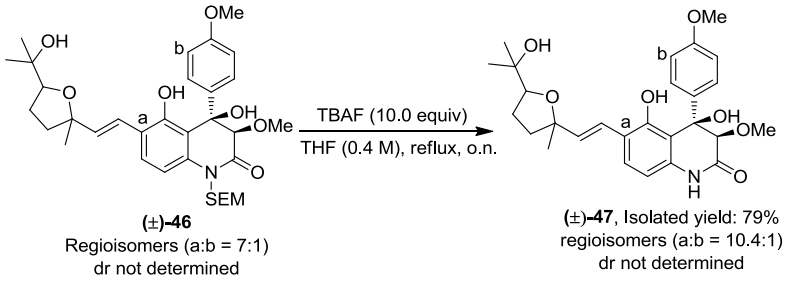
Scheme 4.25 Final deprotection step towards the synthesis of (±)-yaequinolone B using Me_2AlCl

After successfully performing the total synthesis of (±)-yaequinolone B, we decided to further prove the synthetic utility of the C–H olefination developed in our group by synthesizing other yaequinolone natural products. To our delight, the reaction of the SEM-protected 3,4-dihydro-2(1*H*)-quinolinone derivative **(±)-43** with the unactivated olefin *trans*-**45** provided the olefinated product **(±)-46** in 52% isolated yield with a regioselectivity of 7:1 (Scheme 4.26a) as a mixture of four diastereoisomers. We then tried the reaction using a 1:1 mixture of *trans*- and *cis*-**45** and the same four diastereoisomers with slightly different ratio were obtained (see experimental section for further information) (Scheme 4.26b). We also tried the olefination reactions of the simplest 3,4-dihydro-2(1*H*)-quinolinone derivative **5a** with *trans*-**45** and with a 1:1 mixture of *trans*- and *cis*-**45** and in both cases we obtained the olefinated product as a mixture of diastereoisomers in almost 1:1 ratio, indicating that some racemization of one of the chiral centers of the olefin is taking place during the reaction (Scheme 4.26c). We speculated that the carbon at allylic position might have racemized via the normal aNd anti-Tsuji-Trost processes.



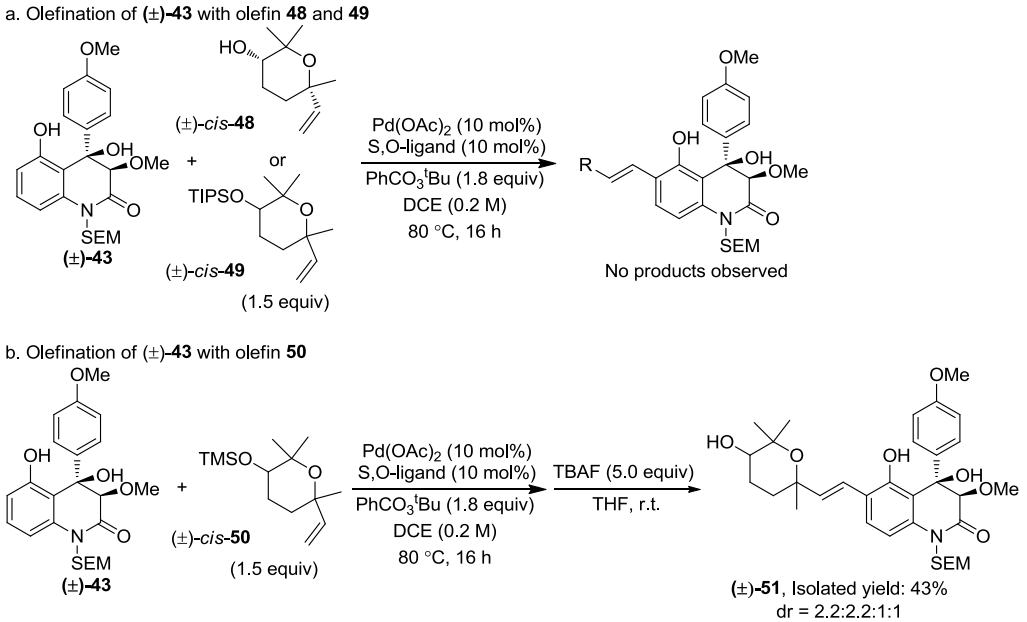
Scheme 4.26 C–H Olefination of 3,4-dihydro-2(1*H*)-quinolinone derivatives **(±)-43** and **5a** with **(±)-45**

The deprotection of olefinated product **(±)-46** using TBAF (1.0 M) gave very low conversion after refluxing overnight. We then increased the reaction concentration to 4.0 M (respect to TBAF) and the reaction reached full conversion after refluxing overnight, providing (±)-yaequinolone C together with three other diastereoisomers in 79% isolated yield with an improved regioselectivity of 10.4:1 (Scheme 4.27). The ^{1}H and ^{13}C NMR data of (±)-yaequinolone C matched with those reported in the literature.[9] As the relative stereochemistry of the olefin moiety of yaequinolone C was not determined in the initial report by the group of Ōmura, we, based on our results, propose that the olefin moiety has a *trans*-configuration (see experimental section for the discussion).[9] Hence, the total synthesis of (±)-yaequinolone C was obtained as a mixture of diastereoisomers (dr not determined) in 6.2% overall yield in 10 synthetic steps starting from commercially available 2-bromo-3-nitrophenol.



Scheme 4.27 Final deprotection step towards the synthesis of yaequinolone (±)-C

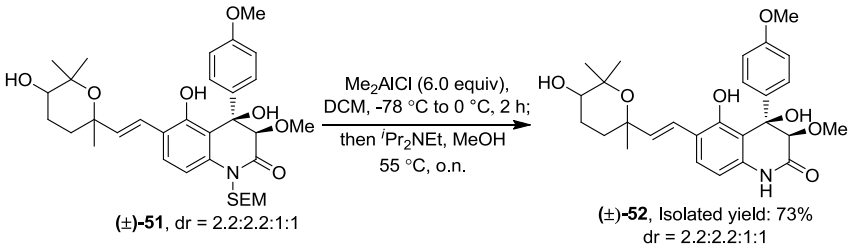
We also performed the coupling using *cis*-**48** as the olefin with the aim to synthesize (±)-aspoquinolone C and D. However, the olefinated product was not detected in crude reaction mixture (Scheme 4.28a). Considering that the free hydroxyl group from the olefin might be the problem, we decided to protect the OH with a silyl group. We first tried TIPS as protecting group but still no olefinated product was detected (Scheme 4.28a). When TMS was used instead, the reaction reached around 50% conversion and a mixture of TMS-protected and unprotected products were detected from ^{1}H NMR and TLC analysis of the crude reaction mixture (Scheme 4.28b). To bring some clarification regarding the selectivity and yield of the olefination reaction, we directly treated the reaction with TBAF at room temperature to deprotect the TMS from the hydroxyl group. After purification, the olefinated product **(±)-51** was isolated in 43% yield as a single regioisomer (the other regioisomer was detected by ^{1}H NMR and separated by preparative TLC). Unfortunately, like in the previous case, the olefin also racemized and four diastereoisomers in the olefinated product **(±)-51** with a ratio of 2.2:2.2:1:1 were detected.



Scheme 4.28 C–H Olefination of 3,4-dihydro-2(1*H*)-quinolinone derivative **(±)-43** with olefin **48**-**50**

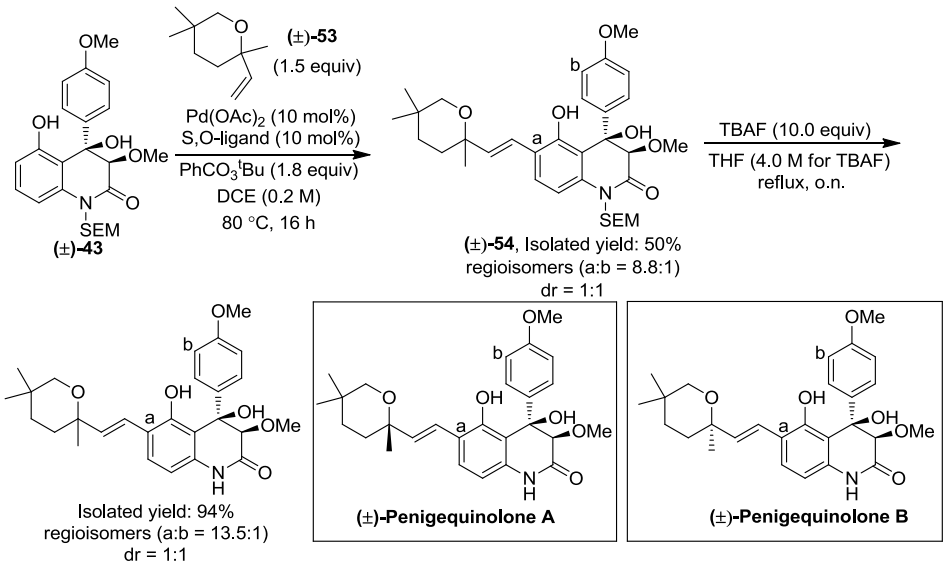
The deprotection of olefinated product **(±)-51** with TBAF (4.0 M) provided only a trace amount of desired

product after refluxing overnight and the decomposition of **(±)-51** was also detected as we had very poor mass balance. We then tried Me_2AlCl and (±)-aspoquinolone C and D, together with two other diastereoisomers, were obtained in 73% isolated yield with remained diastereoselectivity (2.2:2.2:1:1). The ^{1}H and ^{13}C NMR data of (±)-aspoquinolones C and D matched with those reported in the literature.[8] As the relative stereochemistry of the olefin moieties of aspoquinolones C and D was not determined in the initial report by the group of Hertweck, we, based on our results, propose that one has the *cis*-configuration for the olefin moiety and the other one has the *trans*-configuration for the olefin moiety (see experimental section for the discussion). Hence, the total synthesis of (±)-aspoquinolone C and D were obtained as a mixture of diastereoisomers (dr = 2.2:2.2:1:1) in 4.7% overall yield in 10 synthetic steps starting from commercially available 2-bromo-3-nitrophenol.



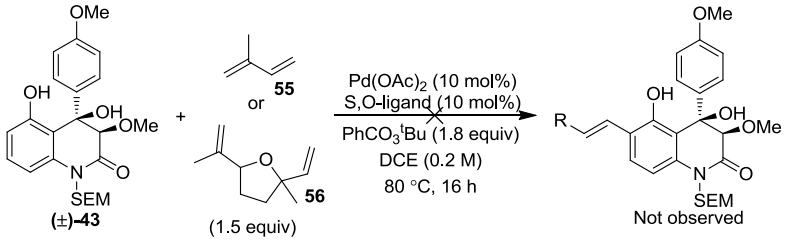
Scheme 4.29 Final deprotection step towards the synthesis of (±)-aspoquinolones C and D

We further applied our methodology towards the synthesis of (±)-penigequinolone A and B. The racemic olefin **53** was prepared after six synthetic steps starting from ethyl isobutyrate (see experimental section for the synthetic sequence). We then performed the C–H olefination of (±)-**43** with **53** as the olefin under standard reaction conditions. To our delight, the olefinated product (±)-**54** was isolated in 50% yield with a regioselectivity of 8.8:1 (a:b) and a diastereoselectivity of 1:1. The deprotection of (±)-**54** using Me_2AlCl did not afford the desired product although full conversion was reached. We then tried TBAF for the deprotection and the reaction almost quantitatively yielded a mixture of (±)-penigequinolone A and B (dr = 1:1) with improved regioselectivity (13.5:1) (Scheme 4.30). Hence, the total synthesis of (±)-penigequinolone A and B were obtained as a mixture of diastereoisomers (dr = 1:1) in 7.0% overall yield in 10 synthetic steps starting from commercially available 2-bromo-3-nitrophenol.



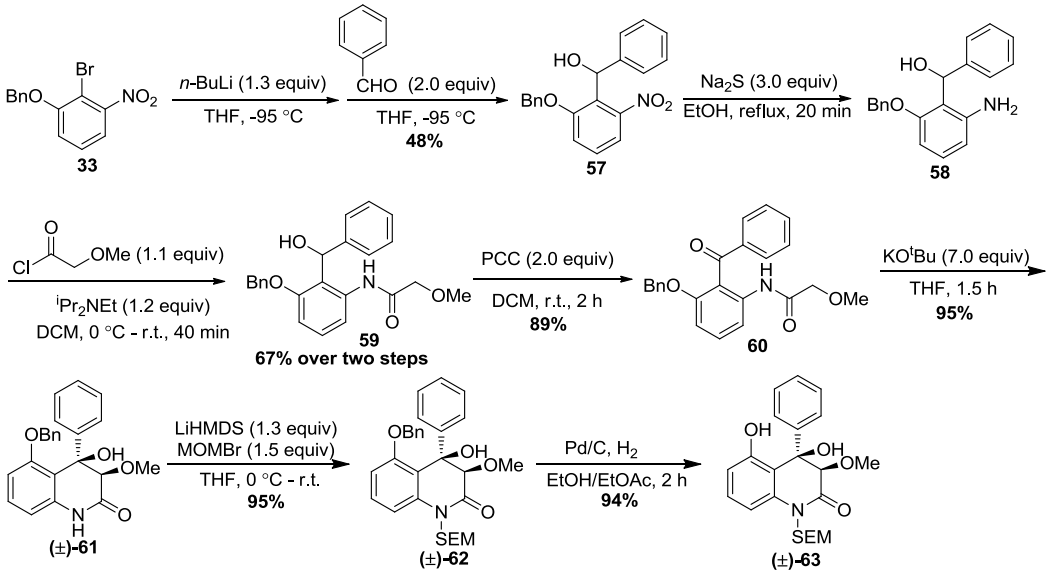
Scheme 4.30 Synthesis of (±)-penigequinolone A and B

We also evaluated the reaction of SEM-protected 3,4-dihydro-2(1*H*)-quinolinone derivative (±)-**43** with the olefins **55** and **56** with the aim to accomplish the total synthesis of yaequinolone E and F (Scheme 4.31). Unfortunately, in both cases, no olefinated products were detected and (±)-**43** was fully recovered, indicating that these olefins are unreactive. We speculated that the lack of reactivity might come from the strong coordination of the dialkenes to palladium, preventing the alkenes from doing migratory insertion and/or poisoning the catalyst.



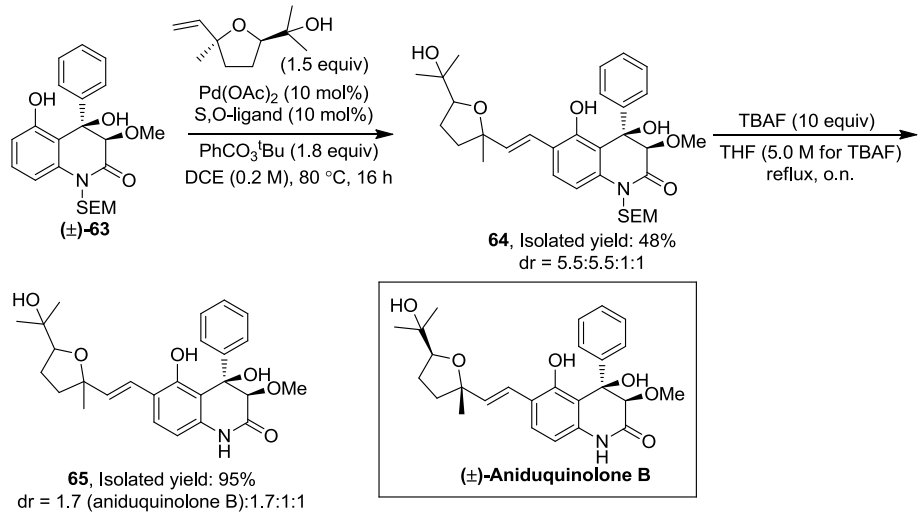
Scheme 4.31 C–H Olefination reactions towards the synthesis of (±)-yaequinolone E and F

After finishing the total synthesis of (±)-yaequinolone B and C, (±)-aspoquinolone C and D and (±)-penigequinolone A and B, we decided to move our attention to the total synthesis of another class of closely related natural products, which all share a slightly different backbone (a phenyl group located at 4-position instead of a 4-methoxyphenyl group) (Figure 4.2). We first prepared the corresponding 3,4-dihydro-2(1*H*)-quinolinone derivative (±)-**63** in seven synthetic steps starting from the nitroarene derivative **33** using the same procedure described previously (Scheme 4.32).



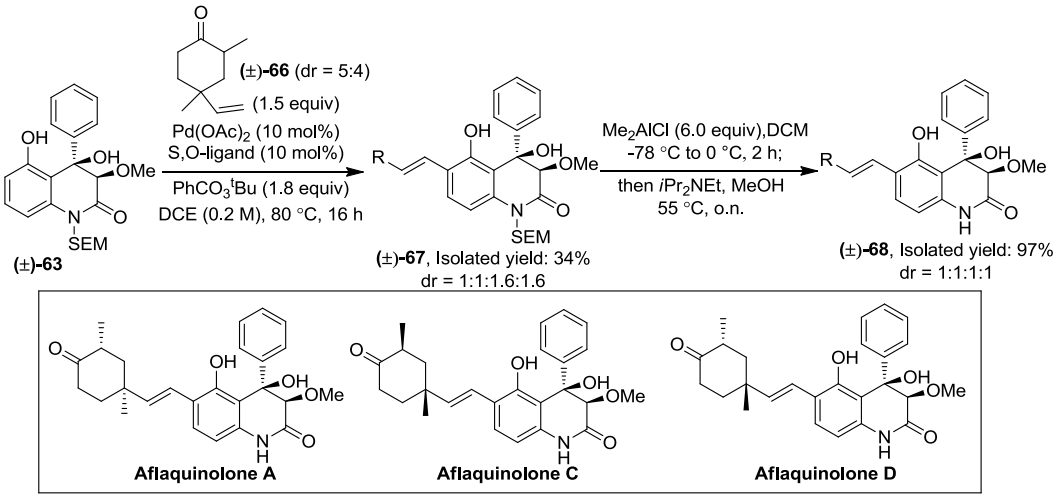
Scheme 4.32 Synthesis of 3,4-dihydro-2(1*H*)-quinolinone derivative (±)-**63**

The reaction of 3,4-dihydro-2(1*H*)-quinolinone derivative (±)-**63** with the *trans*-**45** furnished the desired olefinated product (±)-**64** in 48% isolated yield (Scheme 4.33). As expected, the regioselectivity was excellent (> 20:1) since the phenyl ring at 4-position is less activated towards C–H olefination than the 4-methoxyphenyl moiety. Again, we observed four diastereoisomers in the product with a selectivity of 5.5:5.5:1:1. The deprotection using TBAF furnished (±)-aniduquinolone B together with another three diastereoisomers (1.7:1.7:1:1) in 95% isolated yield. As indicated by the diastereoselectivity change, racemization also occurred during the SEM deprotection. Hence, the total synthesis of (±)-aniduquinolone B was obtained as a mixture of diastereoisomers (dr = 1.7:1.7:1:1) in 10% overall yield in 10 synthetic steps starting from commercially available 2-bromo-3-nitrophenol.



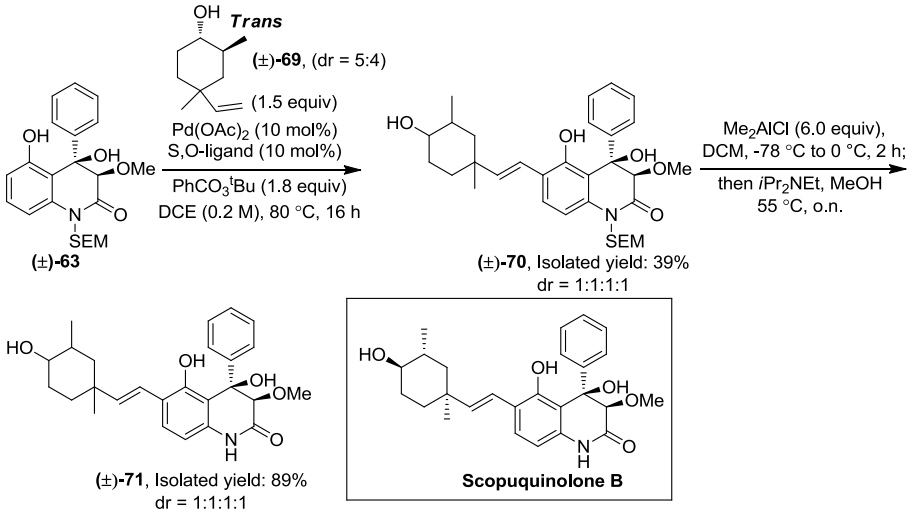
Scheme 4.33 Synthesis of (±)-aniduquinolone B

In order to accomplish the total synthesis of (±)-aflaquinolone A, C and D, the unactivated olefin **66** was prepared in seven synthetic steps starting from ethyl 4-oxocyclohexanecarboxylate (see experimental section for the synthetic sequence). To our delight, the C–H olefination of 3,4-dihydro-2(1*H*)-quinolinone derivative (±)-**63** with the olefin **66**, provided the olefinated product (±)-**67** in 34% yield with a diastereoselectivity of 1:1:1.6:1.6 (Scheme 4.34). The SEM deprotection of (±)-**67** with TBAF failed to give any desired product, while the reaction with Me_2AlCl went smoothly, producing the final product in near-quantitative yield with a diastereoselectivity of 1:1:1:1 (Scheme 4.34). Again, some racemization occurred during the deprotection probably at the α-position of the ketone during the overnight reaction under basic conditions at 55 ℃. The ^1H and ^{13}C data of (±)-aflaquinolone A, C, D matched with those reported in the literature.[10] Hence, the total synthesis of (±)-aflaquinolone A, C and D were obtained as a mixture of diastereoisomers (dr = 1:1:1:1) in 7.3% overall yield in 10 synthetic steps starting from commercially available 2-bromo-3-nitrophenol.



Scheme 4.34 Synthesis of (±)-aflaquinolone A, C, D

Our last target was the synthesis of (±)-scopuquinolone B that can be obtained from the coupling of (±)-**63** with olefin **69**. Racemic **69** with a *trans* configuration between adjacent hydroxyl and methyl groups was obtained by the selective reduction of olefin **66** with $LiAlH_4$ (See experimental section). The C–H olefination of 3,4-dihydro-2(1*H*)-quinolinone derivative (±)-**63** with olefin **69**, furnished the olefinated product (±)-**70** in 39% yield with a diastereoselectivity of 1:1:1:1. The SEM deprotection of (±)-**70** with Me_2AlCl provided the final product in 89% yield with a diastereoselectivity of 1:1:1:1. Hence, the total synthesis of (±)-scopuquinolone B was obtained as a mixture of diastereoisomers (dr = 1:1:1:1) in 7.6% overall yield in 10 synthetic steps starting from commercially available 2-bromo-3-nitrophenol.



Scheme 4.34 Synthesis of scopuquinolone B

4.3 Conclusions

In summary, we have developed an efficient strategy for streamlining the total synthesis of two classes of 3,4-dihydro-2(1*H*)-quinolinone natural products. The fulfillment of this goal was achieved by overcoming three challenges: 1) the establishment of a reliable synthetic route for the construction of 3,4-dihydro-2(1*H*)-quinolinone backbones; 2) the deliberate choosing of SEM as protecting group, which can be easily introduced and removed at very late-stage under mild reaction conditions and 3) the successful implementation of Pd/S,O-ligand catalyzed site-selective late-stage C–H olefination of 3,4-dihydro-2(1*H*)-quinolinones . The power of the olefination reaction was showcased by successfully using unactivated olefins as coupling partners. However, this strategy has also met some limitations such as racemization of some olefins and the lack of reactivity in the C–H olefination reaction using dialkenes. Our future efforts will be devoted to the enantioselective synthesis of this family of natural products.

4.4 Acknowledgement

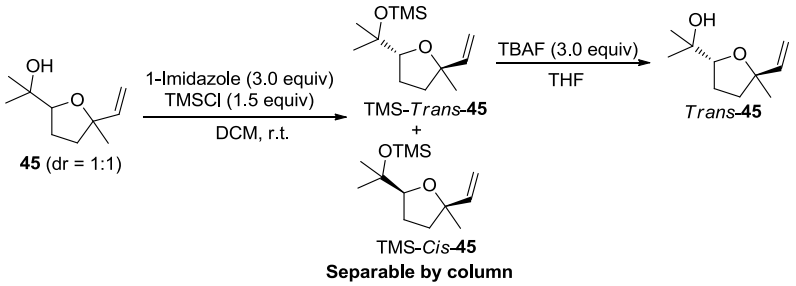
Sabela Vega Ces and Youri van Valen are kindly acknowledged for their contributions to this Chapter. I would also like to thank Ed Zuidinga and Dorette Tromp for the HRMS measurements.

4.5 Experimental section

Chromatography: Silicycle Silica Flash P60 size 40-63 μm (230-400 mesh), TLC: Merck silica gel 60 (0.25mm), preparative TLC: Analtech silica gel G 1500 um 20x20 cm. Visualization of the chromatogram was performed by UV, phosphomolybdic acid and $KMnO_4$. Mass spectra were recorded on AccuTOF GC v 4g, JMS-T100GCV mass spectrometers. ^1H and ^{13}C were recorded on Bruker 500 AMX, 400 and Bruker DRX 300 using $CDCl_3$ as the solvent otherwise it will be noted. Chemical shift values are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: δ 7.26 for ^1H, δ 77.16 for ^{13}C; DMSO: δ 2.50 for ^1H, δ 39.52 for ^{13}C; acetone: δ 2.05 for ^1H, δ 206.26 for ^{13}C). Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), and integration. IR spectra were recorded on a Bruker Alpha FTIR machine and wavelengths are reported in cm^{-1}. THF and diethyl ether were dried over Na using benzophenone as indicator. Dichloromethane was dired over CaH_2 and was used freshly after distillation. Anhydrous DMF was purchased from across and used as received. Absolute ethanol was purchased from VWR Amsterdam and used as received. TBAF solution (1.0 M in THF) was purchased from Fluorochem. $Pd(OAc)_2$ was purchased from Strem.

4.5.1 Synthesis of olefins

***Trans*-linalool oxide (*trans*-45)** was prepared using the following synthetic sequence:



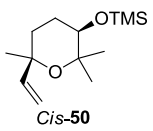
Linalool oxide was purchased from TCI as a mixture of diastereoisomers (1:1) not separable by flash column chromatography. To separate the diastereoisomers, the hydroxyl group was first protected with TMS using the following procedure:

In a round bottom flask was successively added linalool oxide (**45**, dr = 1:1) (1.01 g, 5.92 mmol, 1.0 equiv), DCM (12 mL), 1-imidazole (1.21 g, 17.8 mmol, 3.0 equiv) and TMSCl (1.13 mL, 8.88 mmol, 1.5 equiv). The reaction was then stirred at room temperature for 0.5 h before water was added. The mixture was extracted with Et_2O three times. The combined organic extracts were washed with brine, dried over Na_2SO_4 and evaporated *in vacuo*. The product TMS-*trans*-linalool oxide (TMS-*trans*-**45**) was obtained as a colorless oil after purification by flash column chromatography using PE as the eluent. Its data matched with those reported in the literature.[27] **^{1}H NMR** (400 MHz) δ 5.86 (dd, *J* = 17.2, 10.5 Hz, 1H), 5.16 (d, *J* = 17.3 Hz, 1H), 4.97 (d, *J* = 10.6 Hz, 1H), 3.74 (t, *J* = 6.1 Hz, 1H), 1.94 – 1.76 (m, 3H), 1.71 – 1.63 (m, 1H), 1.30 (s, 3H), 1.21 (s, 3H), 1.20 (s, 3H), 0.11 (s, 9H).

TMS protecting group was then removed by using the following step:

In a round bottom flask was added TMS-*trans*-**45** (2.70 g, 11.13 mmol, 1.0 equiv) and THF (50 mL). TBAF solution (33 mL, 1.0 M in THF, 3.0 equiv) was then added slowly. The reaction was stirred for 1 h before water was added. The mixture was extracted with Et_2O three times. The combined organic extracts were washed with brine, dried over Na_2SO_4 and evaporated *in vacuo*. The sample was purified by flash column chromatography (*n*-hexane:EtOAc, 5:1) giving *trans*-linalool oxide (*trans*-**45**) as a colorless oil (1.70 g, 89%). Its ^{1}H NMR data matched with those reported in the literature.[27] **^{1}H NMR** (400 MHz) δ 5.88 (dd, *J* = 17.3, 10.6 Hz, 1H), 5.19 (d, *J* = 17.3 Hz, 1H), 5.00 (d, *J* = 10.7 Hz, 1H), 3.80 (t, *J* = 7.1 Hz, 1H), 2.10 – 1.79 (m, 5H), 1.78 – 1.67 (m, 1H), 1.32 (s, 3H), 1.23 (s, 3H), 1.14 (s, 3H).

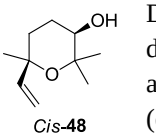
TMS-*cis*-2,2,6-trimethyl-6-vinyltetrahydropyran-3-ol (*Cis*-50)



Cis-**50**

2,2,6-Trimethyl-6-vinyltetrahydropyran-3-ol (**48**) was purchased from TCI as a mixture of diastereoisomers (1:1) not separable by flash column chromatography. TMS protection and deprotection strategy was used to separate them as presented for the separation of linalool oxide. TMS protection was performed using the same procedure as the TMS protection of linalool oxide and *cis*-**50** was isolated as a colorless oil after purification by flash column chromatography with PE as the eluent. **^{1}H NMR** (400 MHz) δ 5.96 (ddd, *J* = 18.2, 10.9, 1.2 Hz, 1H), 4.99 – 4.91 (m, 2H), 3.40 (dd, *J* = 11.3, 4.1 Hz, 1H), 2.10 (dt, *J* = 12.7, 3.3 Hz, 1H), 1.80 – 1.65 (m, 1H), 1.62 – 1.48 (m, 2H), 1.15 (s, 3H), 1.14 (s, 3H), 1.13 (s, 3H), 0.10 (d, *J* = 1.1 Hz, 9H). **^{13}C NMR** (101 MHz) δ 146.6, 110.6, 76.6, 75.7, 73.5, 32.9, 32.2, 30.1, 26.4, 20.9, 0.05. **HRMS** (FD) calculated for $C_{12}H_{24}O_2Si^+$ [M-Me]$^+$: 227.1467; found: 227.1485.

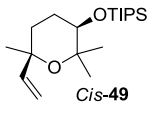
***Cis*-2,2,6-trimethyl-6-vinyltetrahydropyran-3-ol (*Cis*-48)**



Cis-**48**

Deprotection of *cis*-**50** (0.60 g, 2.475 mmol) was performed using the same procedure as the deprotection of TMS-*trans*-linalool oxide. *cis*-**48** was isolated as a wax (0.42 g, quantitative yield) and its ^{1}H NMR data matched with those reported in the literature.[28] **^{1}H NMR** (400 MHz) δ 5.99 (dd, *J* = 18.1, 11.0 Hz, 1H), 5.03 (d, *J* = 5.5 Hz, 1H), 4.99 (d, *J* = 1.1 Hz, 1H), 3.51 – 3.43 (m, 1H), 2.15 (dt, *J* = 13.6, 3.7 Hz, 1H), 1.77 – 1.71 (m, 2H), 1.64– 1.58 (m, 1H), 1.28 (s, 3H), 1.20 (s, 3H), 1.19 (s, 3H).

TIPS-*cis*-2,2,6-trimethyl-6-vinyltetrahydropyran-3-ol (*Cis*-49)

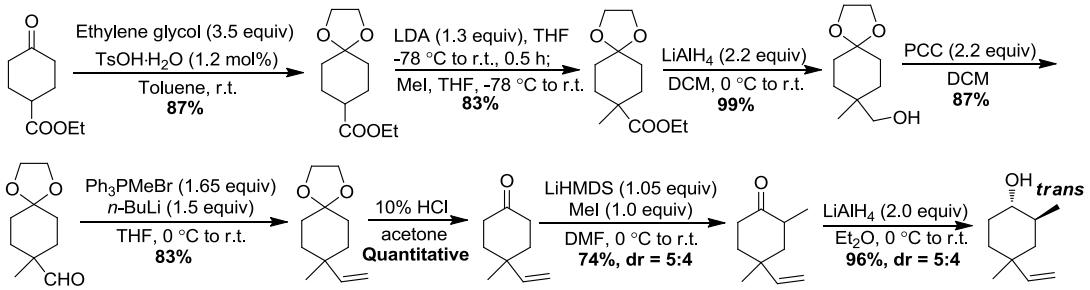


Cis-**49**

In a round bottom flask was successively added *cis*-**48** (0.35 g, 2.06 mmol, 1.0 equiv), DCM (5 mL), 1-imidazole (0.28 g, 4.11 mmol, 2.0 equiv). TIPSOTf (0.66 mL, 3.09 mmol, 1.5 equiv) was then added dropwise. The reaction was stirred at room temperature for 3 h before water

was added. The mixture was extracted with Et_2O three times. The combined organic extracts were washed with brine, dried over Na_2SO_4 and evaporated *in vacuo*. The sample was purified by flash column chromatography (PE:Et_2O, 100:1) giving *cis*-**49** as a colorless oil (0.63 g, 94%). **^{1}H NMR** (500 MHz) δ 5.98 (dd, *J* = 18.9, 10.8 Hz, 1H), 5.00 – 4.92 (m, 2H), 3.59 (dd, *J* = 11.2, 4.6 Hz, 1H), 2.11 (dt, *J* = 13.8, 3.4 Hz, 1H), 1.78 – 1.64 (m, 2H), 1.56 – 1.49 (m, 2H), 1.24 (s, 3H), 1.16 (s, 6H), 1.14 (s, 3H), 1.09 – 1.08 (m, 21 H). **^{13}C NMR** (126 MHz) δ 146.5, 110.4, 77.0, 76.2, 32.8, 32.1, 30.1, 26.4, 20.7, 18.3, 18.2, 12.8.

2,4-Dimethyl-4-vinylcyclohexanone (66) and **2,4-dimethyl-4-vinylcyclohexanol (69)** were prepared using the following synthetic sequence:



In a round-bottom flask was successively added ethyl 4-oxocyclohexane-1-carboxylate (9.29 mL, 10.00 g, 58.8 mmol, 1.0 equiv), ethylene glycol (11.5 mL, 12.77 g, 205.8 mmol, 3.5 equiv), *p*-toluenesulfonic acid monohydrate (137 mg, 0.012 equiv) and anhydrous toluene (30 mL). The reaction was then stirred overnight at room temperature. Saturated aqueous Na_2CO_3 solution was added and the reaction was extracted with EtOAc three times. The combined organic extracts were washed with brine, dried over Na_2SO_4 and evaporated *in vacuo*. The product was purified by flash column chromatography (PE:EtOAc, 15:1) giving ethyl 1,4-dioxaspiro[4.5]decane-8-carboxylate as a colorless oil (10.94 g, 87%). Its ^{1}H NMR data matched with those reported in the literature.[29] **^{1}H NMR** (400 MHz) δ 4.05 (q, *J* = 7.1 Hz, 2H), 3.86 (s, 4H), 2.29 – 2.22 (m, 1H), 1.91 – 1.80 (m, 2H), 1.79 – 1.64 (m, 4H), 1.54 – 1.42 (m, 2H), 1.17 (t, *J* = 7.1 Hz, 3H).

In a flame-dried Schlenk flask was successively added 1,4-dioxaspiro[4.5]decane-8-carboxylate (10.94 g, 51.1 mmol, 1.0 equiv) and anhydrous THF (70 mL). The solution was slowly transferred to another Schlenk flask containing freshly prepared LDA (66.4 mmol, 1.3 equiv) at –78 ℃ over a period of 0.5 h. THF (10 mL) was used to rinse the flask and was also transferred. The reaction was then slowly warmed up to room temperature and stirred for 0.5 h before it was cooled –78 ℃ again. MeI (6.36 mL, 14.50 g, 102.2 mmol, 2.0 equiv) was added dropwise and the reaction was slowly warmed up to room temperature. After stirring it overnight, the reaction was quenched by adding saturated aqueous NH_4Cl solution and was extracted with EtOAc three times. The combined organic extracts were washed with brine, dried over Na_2SO_4 and evaporated *in vacuo*. The product was purified by flash column chromatography (PE:EtOAc, 20:1) giving ethyl 8-methyl-1,4-dioxaspiro[4.5]decane-8-carboxylate as a colorless oil (9.68 g, 83%). Its ^{1}H NMR data matched with those reported in the literature.[29] **^{1}H NMR** (400 MHz) δ 4.02 (q, *J* = 7.1 Hz, 2H), 3.81 (s, 4H), 2.00 (dt, *J* = 13.0, 3.6 Hz, 2H), 1.58 – 1.32 (m, 6H), δ 1.13 (t, *J* = 7.1 Hz, 3H), 1.06 (s, 3H).

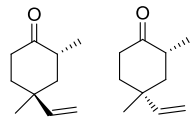
In a flame-dried Schlenk flask was added ethyl 8-methyl-1,4-dioxaspiro[4.5]decane-8-carboxylate (7.20 g, 31.5 mmol, 1.0 equiv) and anhydrous DCM (70 mL). LAH (2.63 g, 69.4 mmol, 2.2 equiv) was added in small portions at 0 ℃. The reaction was stirred at 0 ℃ for 0.5 h before it was warmed up to room temperature slowly. After the reaction was stirred for 1.5 h, the reaction was diluted with DCM and saturated aqueous potassium sodium tartrate solution was carefully added. The reaction was then stirred vigorously for 1 h. The mixture was extracted with DCM three times. The combined organic extracts were washed with brine, dried over Na_2SO_4 and evaporated *in vacuo* to give (8-methyl-1,4-dioxaspiro[4.5]decan-8-yl)methanol as a white solid (5.81 g, 99%), which was pure enough to continue without further purification. Its ^{1}H NMR data matched with those reported in the literature.[29] **^{1}H NMR** (400 MHz) δ 3.94 (d, *J* = 1.7 Hz, 4H), 3.39 (s, 2H), 1.73 – 1.49 (m, 6H), 1.45 – 1.34 (m, 3H), 0.96 (s, 3H).

In a round-bottom flask was successively added (8-methyl-1,4-dioxaspiro[4.5]decan-8-yl)methanol (4.90 g, 26.3 mmol, 1.0 equiv), DCM (60 mL) and PCC (12.48 g, 57.9 mmol, 2.2 equiv). After the reaction was stirred at room temperature for 1 h, it was filtrated through a plug of silica gel and rinsed with EtOAc. The filtrate was evaporated and purified by flash column chromatography (PE:EtOAc, 5:1) giving 8-methyl-1,4-

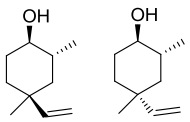
dioxaspiro[4.5]decane-8-carbaldehyde a colorless oil (4.20 g, 87%). Its ^{1}H NMR data matched with those reported in the literature.[30] **^{1}H NMR** (400 MHz) δ 9.46 (s, 1H), 3.93 (s, 4H), 2.07 – 1.92 (m, 2H), 1.70 – 1.49 (m, 6H), 1.04 (s, 3H).

In a flame-dried Schlenk flask was added methyl triphenylphosphonium bromide (13.44 g, 37.6 mmol, 1.65 equiv) and anhydrous THF (75 mL) at 0 ℃. *n*-BuLi (13.7 mL, 2.5 M in hexanes, 34.25 mmol, 1.5 equiv) was then added dropwise. The reaction was warmed up to room temperature and stirred for 0.5 h before it was cooled to 0 ℃ again. In another flask, a solution of 8-methyl-1,4-dioxaspiro[4.5]decane-8-carbaldehyde (4.20 g, 22.8 mmol, 1.0 equiv) in anhydrous THF (20 mL) was prepared and the solution was slowly transferred to the Wittig reagent flask via cannula over a period of 0.5 h. 10 mL of anhydrous THF was used to rinse the flask and was also transferred. The reaction was then stirred at room temperature for 3 h. Acetone (5 mL) was added to quench the Wittig reagent. The mixture was filtrated and washed with Et_2O. The filtrate was evaporated and purified by flash column chromatography (*n*-pentane:Et_2O, 15:1) giving 8-methyl-8-vinyl-1,4-dioxaspiro[4.5]decane as a pale yellow oil (3.46 g, 83%). Its ^{1}H NMR data matched with those reported in the literature.[30] **^{1}H NMR** (400 MHz) δ 5.79 (dd, *J* = 17.8, 10.7 Hz, 1H), 5.01 (d, *J* = 4.6 Hz, 1H), 4.98 (s, 1H), 3.93 (s, 4H), 1.69 – 1.61 (m, 6H), 1.53 – 1.44 (m, 2H), 1.01 (s, 3H).

8-Methyl-8-vinyl-1,4-dioxaspiro[4.5]decane (3.40 g, 18.7 mmol) was dissolved in acetone (60 mL). 10% HCl (24 mL) was then added dropwise. The reaction was stirred for 2.5 h before brine was added. The mixture was extracted with DCM/Et_2O (1:2) three times. The volatiles were carefully evaporated *in vacuo* giving 4-methyl-4-vinylcyclohexan-1-one as a colorless oil (2.57 g, quantitative yield). Its ^{1}H NMR data matched with those reported in the literature.[30] **^{1}H NMR** (400 MHz) δ 5.89 (dd, *J* = 17.5, 11.0 Hz, 1H), 5.18 – 5.08 (m, 2H), 2.45 – 2.25 (m, 4H), 1.97 – 1.90 (m, 2H), 1.74 – 1.67 (m, 2H), 1.12 (d, *J* = 0.9 Hz, 3H).

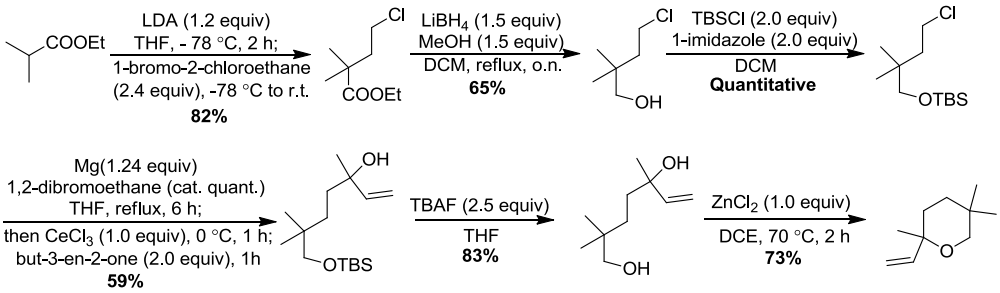


In a flame-dried Schlenk flask was added LiHMDS (7.6 mL, 1.0 M in THF, 7.6 mmol, 1.05 equiv) and 4-methyl-4-vinylcyclohexan-1-one (1.00 g, 7.2 mmol, 1.0 equiv) in DMF (4 mL) was added dropwise at -78 ℃. The reaction was then left to stir for 1.5 h before MeI (446 μL, 7.2 mmol, 1.0 equiv) was added dropwise. The reaction was slowly warmed up to room temperature and stirred overnight. The reaction was quenched by adding saturated aqueous NH_4Cl solution and was extracted with Et_2O three times. The combined extracts were washed with water three times and brine, dried over Na_2SO_4 and evaporated *in vacuo*. The product was purified by flash column chromatography (*n*-pentane:Et_2O, 20:1) giving 2,4-dimethyl-4-vinylcyclohexan-1-one (**66**) as a pale yellow oil (0.82 g, 74%, dr: *trans*/*cis* = 5:4). **^{1}H NMR** (400 MHz) δ 5.98 (dd, *J* = 17.6, 10.9 Hz, 1H$_{trans}$), 5.84 (dd, *J* = 17.5, 10.7 Hz, 1H$_{cis}$), 5.26 – 5.19 (m, 1H$_{trans}$ and 1H$_{cis}$), 5.04 – 4.95 (m, 1H$_{trans}$ and 1H$_{cis}$), 2.66 – 2.41 (m, 2H$_{trans}$ and 2H$_{cis}$), 2.34 (dt, *J* = 14.4, 3.8 Hz, 1H$_{cis}$), 2.25 (ddd, *J* = 14.0, 4.5, 2.5 Hz, 1H$_{trans}$), 2.10 – 2.01 (m, 1H$_{trans}$ and 1H$_{cis}$), 1.81 – 1.77 (m, 1H$_{trans}$), 1.73 – 1.65 (m, 1H$_{cis}$), 1.51 (t, *J* = 13.4 Hz, 1H*cis*), 1.44 (m, t, *J* = 13.4 Hz, 1H$_{trans}$), 1.33 (s, 3H$_{cis}$), 1.06 (s, 3H$_{trans}$), 1.04 (d, *J* = 6.5 Hz, 2H$_{cis}$), 1.01 (d, *J* = 6.5 Hz, 3H$_{trans}$). **^{13}C NMR** (75 MHz) δ 213.9, 213.5, 148.3, 144.8, 113.5, 110.6, 47.0, 46.4, 41.3, 40.7, 38.5 (*trans* and *cis*), 37.9 (*trans* and *cis*), 37.7, 37.5, 30.3, 22.1, 14.7, 14.5. **HRMS** (FD) calculated for $C_9H_{14}O^+$ [M-CH_2]$^+$: 138.1045; found: 138.1072.



In a flame-dried Schlenk flask was added 2,4-dimethyl-4-vinylcyclohexan-1-one (0.36 g, 2.36 mmol, 1.0 equiv) and anhydrous Et_2O (70 mL). LAH (0.18 g, 4.74 mmol, 2.0 equiv) was added in small portions at 0 ℃. The reaction was stirred for 0.5 h before it was warmed up to room temperature slowly. After the reaction was stirred for 1.5 h, the reaction was diluted with Et_2O and saturated aqueous potassium sodium tartrate solution was carefully added. The reaction was then stirred vigorously for 1 h. The mixture was extracted with Et_2O three times. The combined organic extracts were washed with brine, dried over Na_2SO_4 and evaporated *in vacuo*. The product was purified by flash column chromatography (*n*-pentane:Et_2O, 5:1) giving 2,4-dimethyl-4-vinylcyclohexanol (**69**) as a pale yellow oil (0.35 g, 96%, dr: A:B = 5:4). ^{1}H NMR (300 MHz) δ 5.78 (dd, *J* = 17.6, 10.8 Hz, 1H$_A$ and 1H$_B$), 5.07 – 4.84 (m, 2H$_A$ and 2H$_B$), 3.14 – 3.05 (m, 1H$_A$ and 1H$_B$), 1.87 – 1.22 (m, 7H$_A$ and 7H$_B$), 1.05 (s, 3H$_B$), 0.99 (d, *J* = 6.5 Hz, 3H$_B$), 0.97 (d, *J* = 6.7 Hz, 3H$_A$), 0.95 (s, 3H$_A$). **^{13}C NMR** (75 MHz) δ 150.4, 146.2, 112.5, 109.4, 45.4, 44.4, 37.2, 36.5, 36.4, 36.1, 35.5, 35.5, 31.9 (A and B), 31.2, 31.1, 22.4 (A and B), 18.8, 18.7. **HRMS** (FD) calculated for $C_{10}H_{18}NO$ [M]$^+$: 154.1358; found: 154.1360.

2,5,5-Trimethyl-2-vinyltetrahydro-2H-pyran (**53**) was prepared using the following synthetic sequence:



In a flame-dried Schlenk flask was added ethyl isobutyrate (5.563 mL, 4.84 g, 41.7 mmol, 1.0 equiv) and anhydrous THF (40 mL). In another flask, LDA (50 mmol, 1.2 equiv) was prepared and transferred to the substrate flask at -78 ℃ via cannula over a period of 0.5 h. The reaction was stirred for 2 h before 1-bromo-2-chloroethane (8.613 mL, 14.34 g, 100 mmol, 2.4 equiv) was added. The reaction was then warmed up to room temperature and stirred overnight. The reaction was quenched by adding saturated aqueous NH_4Cl solution and was extracted with EtOAc three times. The combined extracts were washed with brine, dried over Na_2SO_4 and evaporated *in vacuo*. The product was purified by flash column chromatography (PE:Et_2O, 100:1 to 50:1) giving ethyl 4-chloro-2,2-dimethylbutanoate as a colorless oil (6.10 g, 82%). Its ^{1}H NMR data matched with those reported in the literature.[31] **^{1}H NMR** (400 MHz) δ 4.16 (q, *J* = 7.1 Hz, 2H), 3.57 – 3.48 (m, 2H), 2.12 – 2.03 (m, 2H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.24 (s, 6H).

In a flame-dried Schlenk flask was added $LiBH_4$ (0.92g, 42 mmol, 1.5 equiv) and anhydrous DCM (20 mL). To this suspension was then slowly added MeOH (1.7 mL). After the evolution of H_2 has ceased, ethyl 4-chloro-2,2-dimethylbutanoate (5.00 g, 28 mmol, 1.0 equiv) was added. The reaction was then heated under reflux at 45 ℃ overnight. The reaction was quenched by carefully adding water and the mixture was extracted with EtOAc three times. The combined extracts were washed with brine, dried over Na_2SO_4 and evaporated *in vacuo*. The product was purified by flash column chromatography (PE:Et_2O, 100:1 to 1:1) giving 4-chloro-2,2-dimethylbutan-1-ol as a colorless oil (2.50 g, 65%). Its ^{1}H NMR data matched with those reported in the literature.[32] **^{1}H NMR** (300 MHz) δ 3.64 – 3.51 (m, 2H), 3.35 (d, *J* = 0.7 Hz, 2H), 1.88 – 1.75 (m, 2H), 0.93 (s, 6H).

In a round-bottom flask was successively added 4-chloro-2,2-dimethylbutan-1-ol (1.37 g, 10 mmol, 1.0 equiv), DCM (15 mL) and TBSCl (3.01 g, 20 mmol, 2.0 equiv). After stirring the mixture for 5 min, 1-imidazole (1.36 g, 20 mmol, 2.0 equiv) was then added and the stirring was continued for another 2 h. Saturated aqueous NH_4Cl solution was added to quench the reaction and the mixture was extracted with EtOAc three times. The combined extracts were washed with brine, dried over Na_2SO_4 and evaporated *in vacuo*. The product was purified by flash column chromatography (PE:Et_2O, 20:1) giving *tert*-butyl(4-chloro-2,2-dimethylbutoxy)dimethylsilane as a colorless oil (2.50 g, quantitative yield). **^{1}H NMR** (300 MHz) δ 3.62 – 3.50 (m, 2H), 3.25 (s, 2H), 1.84 – 1.72 (m, 2H), 0.89 (s, 9H), 0.81 (s, 6H), 0.03 (s, 6H). **^{13}C NMR** (75 MHz) δ 71.7, 42.7, 41.8, 36.0, 26.0, 24.3, 18.4, -5.4. **HRMS** (FD) calculated for $C_8H_{18}ClOSi^+$ [M-^{t}Bu]$^+$: 193.0815; found: 193.0855.

In a flame-dried Schlenk flask was added *tert*-butyl(4-chloro-2,2-dimethylbutoxy)dimethylsilane (1.50 g, 5.98 mmol, 1.0 equiv), Mg (0.18 g, 7.41 mmol, 1.24 equiv) and anhydrous THF (2 mL). The mixture was then heated to reflux and a few drops of 1,2-dibromoethane were slowly added to the reaction. The reaction was continued to stir for another 6 h while refluxing at 80 ℃. In another flame-dried Schlenk flask was added anhydrous $CeCl_3$ (1.47 g, 5.98 mmol, 1.0 equiv) and anhydrous THF (12 mL) and the suspension was stirred at room temperature for 1 h. The freshly prepared Grignard reagent was transferred to the suspension via cannula at 0 ℃. The reaction was further stirred at 0 ℃ for 1 h before but-3-en-2-one (1.0 mL, 11.96 mmol, 2.0 equiv) was added. After stirring it at 0 ℃ for 1 h, the reaction was quenched by adding saturated aqueous NH_4Cl solution and the mixture was extracted with EtOAc three times. The combined extracts were washed with brine, dried over Na_2SO_4 and evaporated *in vacuo*. The product was purified by flash column chromatography (PE:EtOAc, 15:1) giving 7-[(tert-butyldimethylsilyl)oxy]-3,6,6-trimethylhept-1-en-3-ol as a colorless oil (1.01 g, 59%). **^{1}H NMR** (400 MHz) δ 5.89 (dd, *J* = 17.4, 10.7 Hz, 1H), 5.20 (dd, *J* = 17.3, 1.4 Hz, 1H), 5.04 (dd, *J* = 10.8, 1.4 Hz, 1H), 3.22 (s, 2H), 1.51 – 1.46 (m, 2H), 1.27 (s, 3H), 1.25 – 1.20 (m, 2H), 0.89 (s, 9H), 0.02 (s, 6H). **^{13}C NMR** (75 MHz) δ 145.4, 111.8, 77.4, 73.5, 71.4, 36.5, 35.0, 32.5, 27.8, 26.1, 24.3, 24.3, 18.4, -5.4. **IR**: ν 3402, 2954, 2929,

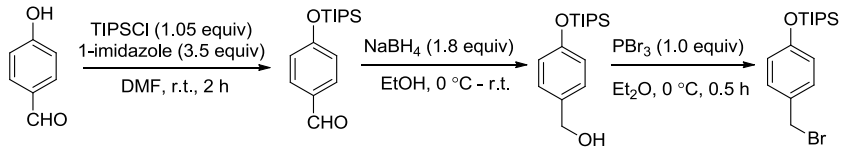
1472, 1362, 1251, 1095, 836 cm^{-1}. **HRMS** (EI) calculated for $C_{12}H_{25}NO_2Si^+$ $[M-^tBu]^+$: 229.1624; found: 226.1597.

In a round-bottom flask was added 7-[(tert-butyldimethylsilyl)oxy]-3,6,6-trimethylhept-1-en-3-ol (1.00 g, 3.49 mmol, 1.0 equiv) and THF (15 mL). TBAF solution (1.0 M in THF, 8.7 mL, 8.7 mmol, 2.5 equiv) was added dropwise. The reaction was left to stir at room temperature for 4 h before it was quenched by adding saturated aqueous NH_4Cl solution. The mixture was extracted with EtOAc three times. The combined extracts were washed with brine, dried over Na_2SO_4 and evaporated *in vacuo*. The product was purified by flash column chromatography (*n*-hexane:EtOAc, 11:1) giving 2,2,5-trimethylhept-6-ene-1,5-diol as a white solid (0.50 g, 83%). **^{1}H NMR** (300 MHz) δ 5.85 (dd, *J* = 17.3, 10.7 Hz, 1H), 5.16 (dd, *J* = 17.4, 1.3 Hz, 1H), 5.01 (dd, *J* = 10.8, 1.3 Hz, 1H), 3.33 – 3.18 (m, 2H), 2.76 (bs, 2H), 1.48 – 1.42 (m, 2H), 1.28 – 1.20 (m, 2H), 1.25 (s, 3H), 0.82 (s, 3H), 0.81 (s, 3H). **^{13}C NMR** (75 MHz) δ 145.2, 111.8, 73.4, 70.7, 35.9, 34.75, 31.6, 27.9, 24.5, 24.2. **HRMS** (FD) calculated for $C_{10}H_{20}O_2^+$ $[M]^+$: 172.1463; found: 172.1470.

In a flame-dried Schlenk flask was successively added 2,2,5-trimethylhept-6-ene-1,5-diol (200 mg, 1.16 mmol, 1.0 equiv), DCE (25 mL) and anhydrous $ZnCl_2$ (158 mg, 1.16 mmol, 1.0 equiv). The reaction was then stirred at 70 ℃ for 2 h before it was quenched by adding saturated aqueous NH_4Cl solution. The mixture was extracted with Et_2O three times. The combined extracts were passed through a short plug of silica gel and rinsed with Et_2O. The filtrate was evaporated *in vacuo* giving 2,5,5-trimethyl-2-vinyltetrahydro-2*H*-pyran (**53**) as a colorless oil (130 mg, 73%). **^{1}H NMR** (400 MHz) δ 5.78 (dd, *J* = 17.4, 11.4 Hz, 1H), 5.17 (s, 1H), 5.13 (dd, *J* = 7.9, 1.3 Hz, 1H), 3.33 (d, *J* = 11.3 Hz, 1H), 3.21 (dd, *J* = 11.3, 2.0 Hz, 1H), 1.73 – 1.61 (m, 2H), 1.45 – 1.37 (m, 1H), 1.35 – 1.28 (m, 1H), 1.23 (s, 3H), 0.99 (s, 2H), 0.81 (s, 2H). **^{13}C NMR** (101 MHz) δ 143.3, 114.3, 74.2, 72.7, 33.5, 30.7, 29.8, 28.7, 26.7, 24.2. **HRMS** (FD) calculated for $C_{10}H_{18}NaO$ $[M+Na]^+$: 177.1255; found: 177.1268.

4.5.2 Synthesis of substituted benzyl bromide

4-(Bromomethyl)phenoxy]triisopropylsilane was prepared using the following synthetic sequence reported in the literature.[33]



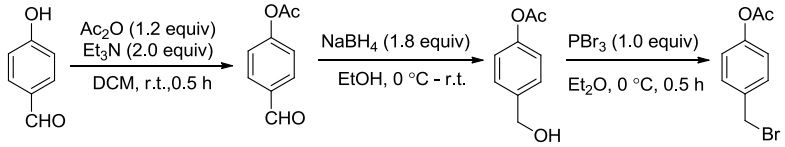
In a flame-dried Schlenk flask was added 4-hydroxybenzaldehyde (12.212 g, 100 mmol, 1.0 equiv), 1-imidazole (23.827 g, 350 mmol, 3.5 equiv) and anhydrous DMF (30 mL) under N_2. TIPSCl (20.244 g, 105 mmol, 1.05 equiv) was then added dropwise at room temperature. The reaction was then stirred for another 2 h. Water was then added to the reaction and the mixture was extracted with Et_2O three times. The combined organic extracts were washed with water two times and brine two times, dried with $MgSO_4$, filtrated and concentrated *in vacuo* to yield the product as a pale yellow oil (27.560 g, 99%) which was pure enough to be directly used for the next step. Its ^{1}H NMR data matched with those reported in the literature.[33] **^{1}H NMR** (400 MHz) δ 9.88 (s, 1H), 7.83 – 7.75 (m, 2H), 7.01 – 6.93 (m, 2H), 1.34 – 1.23 (m, 3H), 1.12 – 1.10 (m, 18H).

In a flame-dried Schlenk flask was added 4-[(triisopropylsilyl)oxy]benzaldehyde (13.923 g, 50 mmol, 1.0 equiv) and absolute EtOH (40 mL). $NaBH_4$ (3.405 g, 90 mmol, 1.8 equiv) was then added portionwise at 0 ℃. After the reaction was stirred for another 2 h at 0 ℃, water was added very carefully to quench the reaction. The mixture was then extracted with DCM three times. The combined organic extracts were washed with brine, dried with $MgSO_4$, filtrated and concentrated *in vacuo* to yield the product as a pale yellow oil (13.800 g, 98%) which was pure enough to be directly used for the next step. Its ^{1}H NMR data matched with those reported in the literature.[33] **^{1}H NMR** (400 MHz) δ 7.25 – 7.19 (m, 2H), 6.89 – 6.84 (m, 2H), 4.61 (s, 2H), 1.30 – 1.20 (m, 3H), 1.11 – 1.09 (d, *J* = 7.4 Hz, 18H).

In a flame-dried Schlenk flask was added {4-[(triisopropylsilyl)oxy]phenyl}methanol (4.207 g, 15 mmol, 1.0 equiv) and dry Et_2O (50 mL). PBr_3 (4.059 g, 1.0 equiv) in dry Et_2O (30 mL) was then added dropwise at 0 ℃. After the reaction was stirred for another 0.5 h at 0 ℃, the reaction was quenched by slowly adding water. The mixture was then extracted with Et_2O three times. The combined organic extracts were washed with brine two times, dried with $MgSO_4$, filtrated and concentrated *in vacuo* to yield the product as a colorless oil (4.800 g, 93%) which was pure enough to be directly used for the next step. Its ^{1}H NMR data matched with those reported

in the literature.[33] **^{1}H NMR** (300 MHz) δ 7.27 – 7.22 (m, 2H), 6.86 – 6.80 (m, 2H), 4.49 (s, 2H), 1.31 – 1.19 (m, 3H), 1.11 – 1.08 (m, 18H).

4-(Bromomethyl)phenyl acetate was prepared using the following synthetic sequence:



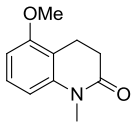
In a flame-dried Schlenk flask was added 4-hydroxybenzaldehyde (6.106 g, 50 mmol, 1.0 equiv), Et_3N (10.119 g, 100 mmol, 2.0 equiv) and anhydrous DCM (100 mL). Ac_2O (6.125 g, 60 mmol, 1.2 equiv) was then added dropwise at 0 ℃. The reaction was then stirred for 0.5 h at room temperature before it was quenched by adding water. The reaction was then extracted with Et_2O three times. The combined organic extracts were washed with brine, dried with $MgSO_4$, filtrated and concentrated *in vacuo* to yield the product as a colorless oil (8.043 g, 98%) which was pure enough to be directly used for the next step. Its ^{1}H NMR data matched with those reported in the literature.[33] **^{1}H NMR** (400 MHz) δ 9.99 (s, 1H), 7.93 – 7.91 (m, 2H), 7.29 – 7.26 (m, 2H), 2.34 (s, 3H).

In a flame-dried Schlenk flask was added 4-formylphenyl acetate (8.000 g, 48.7 mmol, 1.0 equiv) and anhydrous THF (100 mL). $NaBH_4$ (3.316 g, 87.7 mmol, 1.8 equiv) was then added portionwise at 0 ℃. After the reaction was stirred for another 2 h at 0 ℃, water was added very carefully to quench the reaction. The mixture was then extracted with DCM three times. The combined organic extracts were washed with brine, dried with $MgSO_4$, filtrated and concentrated *in vacuo*. The product was purified by flash column chromatography (*n*-hexane:EtOAc, 5:2) giving 4-(hydroxymethyl)phenyl acetate as a colorless oil (5.400 g, 67%). Its ^{1}H NMR data matched with those reported in the literature.[34] **^{1}H NMR** (300 MHz) δ 7.40 – 7.35 (m, 2H), 7.10 – 7.05 (m, 2H), 4.68 (s, 2H), 2.30 (s, 3H).

In a flame-dried Schlenk flask was added 4-(hydroxymethyl)phenyl acetate (2.500 g, 15 mmol, 1.0 equiv) and dry Et_2O (50 mL). PBr_3 (4.059 g, 1.0 equiv) in dry Et_2O (30 mL) was then added dropwise at 0 ℃. After the reaction was stirred for another 0.5 h at 0 ℃, the reaction was then quenched by slowly adding water. The reaction was then extracted with Et_2O three times. The combined organic extracts were washed with brine two times, dried with $MgSO_4$, filtrated and concentrated *in vacuo* to yield the product as a white solid (2.500 g, 73%) which was pure enough to be directly used for the next step (*Caution: the product is extremely unstable when exposed to light*). Its ^{1}H NMR data matched with those reported in the literature.[35] **^{1}H NMR** (400 MHz) δ 7.42 – 7.39 (m, 2H), 7.08 – 7.05 (m, 2H), 4.49 (s, 2H), 2.30 (s, 3H).

4.5.3 Synthesis of simple substrates

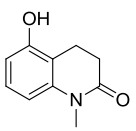
5-Methoxy-*N*-methyl-3,4-dihydroquinolin-2(1*H*)-one (2a)



2a

In a flame-dried Schlenk flask was added 5-hydroxy-3,4-dihydroquinolin-2(1*H*)-one (326 mg, 2.0 mmol, 1.0 equiv) and anhydrous DMF (10 mL) under N_2. NaH (240 mg, 60% in mineral oil, 6.0 mmol, 3.0 equiv) was then added at 0 ℃ and the reaction was stirred at 0 ℃ for 0.5 h. MeI (500 μL, 8.0 mmol, 4.0 equiv) was then added dropwise at 0 °C. The reaction was then warmed up to room temperature and stirred overnight. The reaction was quenched by adding water and extracted with EtOAc three times. The combined organic extracts were washed with water three times and brine two times, dried with Na_2SO_4, filtrated and concentrated *in vacuo* to give **2a** as a pale yellow solid (380 mg, 99%). Its ^{1}H NMR data matched with those reported in the literature.[36] **^{1}H NMR** (400 MHz) δ 7.21 (t, *J* = 8.2 Hz, 1H), 6.64 (d, *J* = 8.3 Hz, 2H), 3.85 (s, 3H), 3.35 (s, 3H), 2.89 (dd, *J* = 8.6, 6.4 Hz, 2H), 2.60 (dd, *J* = 8.6, 6.4 Hz, 2H).

5-Hydroxy-*N*-methyl-3,4-dihydroquinolin-2(1*H*)-one (5a)

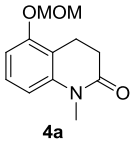


5a

In a flame-dried Schlenk flask was added **2a** (1.15 g, 6.0 mmol, 1.0 equiv) and anhydrous DCM (10 mL) under N_2. A solution of BBr_3 in DCM (18 mL, 1.0 M, 18.0 mmol, 3.0 equiv) was added dropwise at -78 ℃. After stirring the reaction for another 1 h at -78 ℃, the reaction was slowly warmed up to room temperature and stirred for additional 3 h. Water was slowly added to quench the reaction and the reaction was extracted with DCM three times. The combined organic extracts were washed with water and brine, dried with $MgSO_4$, filtrated and concentrated *in vacuo* to give **5a** as a pale yellow solid (1.02 g, 96%). Its ^{1}H NMR data matched with those reported in the literature.[37] **^{1}H NMR** (400

MHz) δ 7.11 (t, *J* = 8.2 Hz, 1H), 6.61 (d, *J* = 8.2 Hz, 1H), 6.54 (d, *J* = 7.9 Hz, 1H), 3.35 (s, 3H), 2.90 (dd, *J* = 8.7, 6.3 Hz, 2H), 2.64 (dd, *J* = 8.5, 6.4 Hz, 2H).

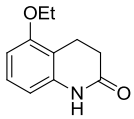
5-(Methoxymethoxy)-*N*-methyl-3,4-dihydroquinolin-2(1*H*)-one (4a)



4a

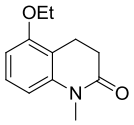
In a flame-dried Schlenk flask was added **5a** (532 mg, 3.0 mmol, 1.0 equiv) and freshly distilled THF (10 mL) under N_2. NaH (156 mg, 60 % in mineral oil, 3.9 mmol, 1.3 equiv) was then added portionwise at 0 ℃. After stirring it at room temperature for 0.5 h, MOMCl (1.127 g, 15.1 mmol, 1.2 equiv) was added to the reaction dropwise at 0 ℃. After stirring it for 3 h at room temperature, the reaction was quenched by slowly adding water and extracted with EtOAc three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtrated and evaporated *in vacuo*. The product was purified by flash column chromatography (*n*-hexane:EtOAc, 3:1) giving **4a** as a pale yellow solid (500 mg, 75%). **^{1}H NMR** (400 MHz) δ 7.18 (t, *J* = 8.3 Hz, 1H), 6.85 (dd, *J* = 8.4, 0.9 Hz, 1H), 6.68 (d, *J* = 8.2 Hz, 1H), 5.21 (s, 2H), 3.49 (s, 3H), 3.35 (s, 3H), 2.93 (dd, *J* = 8.6, 6.4 Hz, 2H), 2.61 (dd, *J* = 8.6, 6.4 Hz, 2H). **^{13}C NMR** (75 MHz) δ 170.6, 154.1, 141.9, 127.8, 115.5, 109.3, 108.8, 94.8, 56.3, 31.2, 29.9, 18.3. **HRMS** (FD) calculated for $C_{12}H_{15}NO_3$ $[M]^+$: 221.1052; found: 221.1061.

5-Ethoxy-3,4-dihydroquinolin-2(1*H*)-one



In a flame-dried Schlenk flask was added 5-hydroxy-3,4-dihydroquinolin-2(1*H*)-one (0. 70 g, 4.29 mmol, 1.0 equiv), K_2CO_3 (1.23 mg, 8.93 mmol, 2.1 equiv), EtBr (0.7 mg, 6.42 mmol, 1.5 equiv) and anhydrous DMF (5 mL) under N_2. The reaction was then stirred for 5 h at 70 ℃. Water was added and the mixture was extracted with EtOAc three times. The combined organic extracts were washed with water three times and brine two times, dried with $MgSO_4$, filtrated and concentrated *in vacuo* to yield the product as a white solid (800 mg, 98%) which was pure enough to be directly used for the next step. Its ^{1}H NMR data matched with those reported in the literature.[38] **^{1}H NMR** (400 MHz) δ 7.58 (bs, 1H), 7.10 (t, *J* = 8.1 Hz, 1H), 6.56 (d, *J* = 8.2 Hz, 1H), 6.35 (d, *J* = 7.9 Hz, 1H), 4.05 (q, *J* = 7.0 Hz, 2H), 2.97 (t, *J* = 7.7 Hz, 2H), 2.60 (dd, *J* = 8.4, 6.9 Hz, 2H), 1.42 (t, *J* = 7.0 Hz, 3H).

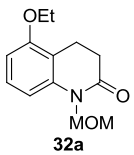
5-Ethoxy-*N*-methyl-3,4-dihydroquinolin-2(1*H*)-one (3a)



3a

In a flame-dried Schlenk flask was added 5-ethoxy-3,4-dihydroquinolin-2(1*H*)-one (191 mg, 1.0 mmol, 1.0 equiv) and anhydrous DMF (2 mL) under N_2. NaH (60 mg, 60% in mineral oil, 1.5 mmol, 1.5 equiv) was then added at 0 ℃ and stirred for 0.5 h. MeI (170 mg, 1.2 mmol, 1.2 equiv) was then added dropwise at 0 ℃. The reaction was then warmed up to room temperature and stirred overnight. The reaction was quenched by adding water and extracted with EtOAc three times. The combined organic extracts were washed with water three times and brine two times, dried with $MgSO_4$, filtrated and concentrated *in vacuo* to give **3a** as a white solid (200 mg, 98%). Its ^{1}H NMR data matched with those reported in the literature.[38] **^{1}H NMR** (400 MHz) δ 7.20 – 7.15 (m, 1H), 6.63 – 6.61 (m, 2H), 4.05 (q, *J* = 7.0 Hz, 2H), 3.34 (s, 3H), 2.93 – 2.88 (m, 2H), 2.60 (t, *J* = 7.3 Hz, 2H), 1.42 (t, *J* = 7.0 Hz, 3H).

5-Ethoxy-*N*-(methoxymethyl)-3,4-dihydroquinolin-2(1*H*)-one (32a)

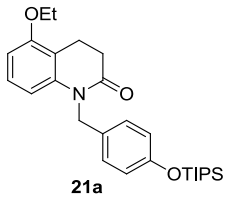


32a

In a flame-dried Schlenk flask was added 5-ethoxy-3,4-dihydroquinolin-2(1*H*)-one (150 mg, 0.78 mmol, 1.0 equiv) and freshly distilled THF (3 mL) under N_2. NaH (47 mg, 60 % in mineral oil, 1.17 mmol, 1.5 equiv) was then added at 0 °C. After stirring it for 0.5 h at 0 °C, MOMCl (70 μL, 0.94 mmol, 1.2 equiv) was added to the reaction at 0 ℃ dropwise. After stirring it for 2 h at room temperature, the reaction was quenched by slowly adding water and extracted with EtOAc three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtrated and evaporated *in vacuo*. The product was purified by flash column chromatography (PE:EtOAc, 4:1) giving **32a** as a pale yellow solid (99 mg, 54%). **^{1}H NMR** (300 MHz) δ 7.21 – 7.12 (m, 1H), 6.93 (d, *J* = 7.9 Hz, 1H), 6.63 (d, *J* = 8.2 Hz, 1H), 5.30 (s, 2H), 4.05 (q, *J* = 6.5 Hz, 2H), 3.40 (s, 3H), 2.93 (t, *J* = 7.5 Hz, 2H), 2.68 – 2.62 (m, 2H), 1.42 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR** (101 MHz) δ 171.7, 155.7, 140.9, 127.9, 114.7, 108.8, 107.1, 74.2, 64.1, 56.4, 31.5, 18.3, 15.0. **HRMS** (FD) calculated for $C_{13}H_{17}NO_3$ $[M]^+$: 235.1208; found: 235.1219.

5-Ethoxy-*N*-{4-[(triisopropylsilyl)oxy]benzyl}-3,4-dihydroquinolin-2(1*H*)-one (21a)

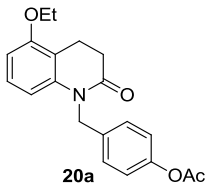
In a flame-dried Schlenk flask was added 5-ethoxy-3,4-dihydroquinolin-2(1*H*)-one (287 mg, 1.5 mmol, 1.0 equiv) and anhydrous DMF (2 mL) under N_2. NaH (72 mg, 60% in mineral oil, 1.8 mmol, 1.2 equiv) was then added at 0 ℃ and stirred for 0.5 h at 0 ℃. [4-



21a

(Bromomethyl)phenoxy]triisopropylsilane (670 mg, 1.95 mmol, 1.3 equiv) in anhydrous DMF (3 mL) was then added dropwise at 0 ℃. The reaction was then warmed up to room temperature and stirred overnight. The reaction was quenched by adding water and extracted with EtOAc three times. The combined organic extracts were washed with water two times and brine two times, dried with $MgSO_4$, filtrated and concentrated *in vacuo*. The product was purified by flash column chromatography (*n*-hexane:EtOAc, 10:1) giving **21a** as a white solid (580 mg, 85%). **^{1}H NMR** (400 MHz) δ 7.06 – 7.00 (m, 3H), 6.81 – 6.78 (m, 2H), 6.56 (d, *J* = 8.3 Hz, 1H), 6.53 (d, *J* = 8.2 Hz, 1H), 5.09 (s, 2H), 4.03 (q, *J* = 7.0 Hz, 2H), 2.97 (dd, *J* = 8.7, 6.3 Hz, 2H), 2.72 (dd, *J* = 8.6, 6.3 Hz, 2H), 1.42 (t, *J* = 7.0 Hz, 1H), 1.26 – 1.18 (m, 3H), 1.08 – 1.06 (m, 18H). **^{13}C NMR** (126 MHz) δ 170.8, 155.8, 155.1, 141.2, 129.7, 127.6, 127.6, 120.2, 114.9, 108.8, 106.7, 64.0, 46.0, 31.5, 18.3, 18.0, 15.1, 12.8. **IR**: ν 2944, 2866, 1677, 1595, 1509, 1468, 1259, 913, 686 cm^{-1}. **HRMS** (FD) calculated for $C_{27}H_{39}NO_3Si^+$ [M]$^+$: 453.2699; found: 453.2686.

4-{[5-Ethoxy-2-oxo-3,4-dihydroquinolin-1(2*H*)-yl]methyl}phenyl acetate (**20a**)

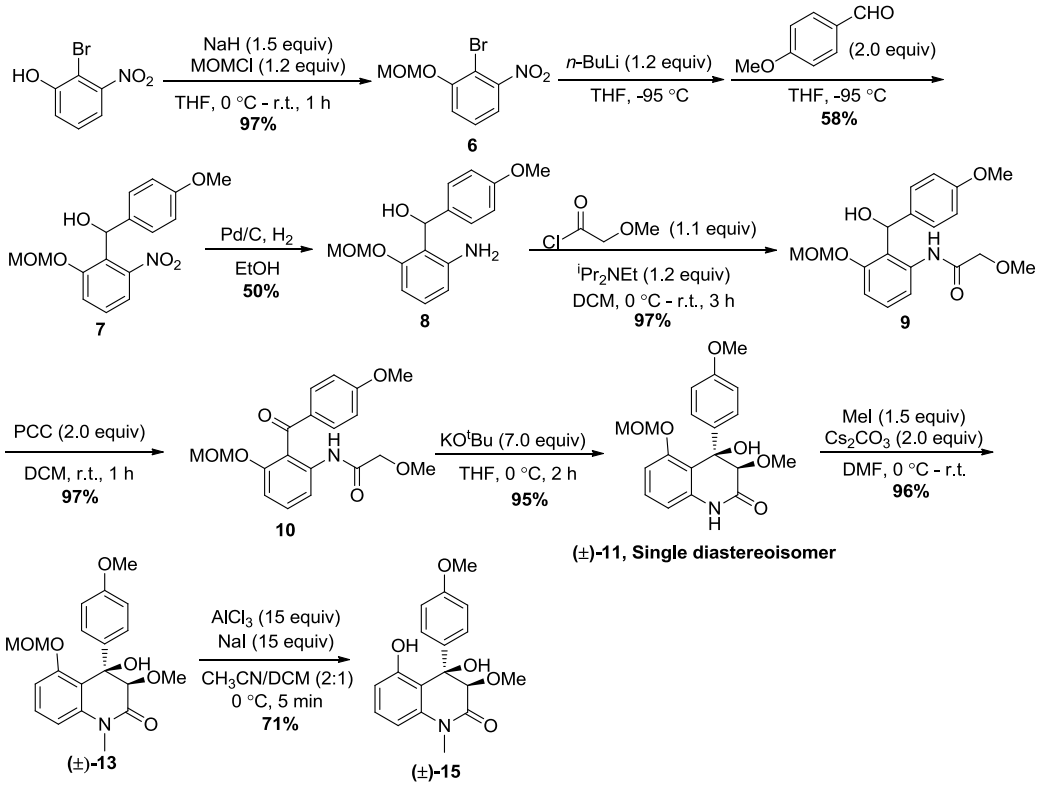


20a

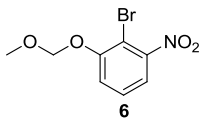
In a flame-dried Schlenk flask was added 5-ethoxy-3,4-dihydroquinolin-2(1*H*)-one (215 mg, 1.12 mmol, 1.0 equiv) and anhydrous DMF (3 mL). NaH (54 mg, 60% in mineral oil, 1.35 mmol, 1.2 equiv) was then added at 0 ℃ and stirred for 0.5 h at 0 ℃. 4-(Bromomethyl)phenyl acetate (332 mg, 1.46 mmol, 1.3 equiv) was then added at 0 ℃. The reaction was then warmed up to room temperature and stirred overnight. The reaction was quenched by adding water and extracted with EtOAc three times. The combined organic extracts were washed with water two times and brine two times, dried with $MgSO_4$, filtrated and concentrated *in vacuo*. The product was purified by flash column chromatography (*n*-hexane:EtOAc, 3:1) giving **20a** as a pale yellow solid (250 mg, 66%). **^{1}H NMR** (400 MHz) δ 7.22 (d, *J* = 8.2 Hz, 2H), 7.07 – 7.01 (m, 3H), 6.58 (d, *J* = 8.3 Hz, 1H), 6.51 (d, *J* = 8.2 Hz, 1H), 5.15 (s, 2H), 4.04 (q, *J* = 6.9 Hz, 2H), 2.98 (dd, *J* = 8.6, 6.3 Hz, 2H), 2.73 (dd, *J* = 8.7, 6.3 Hz, 2H), 2.27 (s, 3H), 1.42 (t, *J* = 6.9, 3H). **^{13}C NMR** (101 MHz) δ 170.8, 169.6, 155.9, 149.7, 141.0, 135.0, 127.8, 127.6, 121.9, 114.8, 108.5, 106.8, 64.1, 46.0, 31.5, 21.3, 18.3, 15.0. **IR**: ν 2977, 1758, 1671, 1594, 1467, 1188, 728 cm^{-1}. **HRMS** (FD) calculated for $C_{20}H_{21}NO_4^+$ [M]$^+$: 339.1471; found: 339.1471.

4.5.4 Synthesis of yaequinolone backbones

Representative synthetic sequence of yaequinolone backbones:



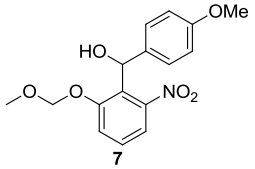
2-Bromo-1-(methoxymethoxy)-3-nitrobenzene (6)



6

In a flame-dried Schlenk flask was added 2-bromo-3-nitrophenol (2.75 g, 12.6 mmol, 1.0 equiv) and freshly distilled THF (40 mL) under N_2. NaH (0.45 g, 60 % in mineral oil, 18.9 mmol, 1.5 equiv) was then added portionwise at 0 °C. After stirring it at room temperature for 0.5 h, MOMCl (1.13 g, 15.1 mmol, 1.2 equiv) was added to the reaction dropwise at 0 °C. After stirring for 1.0 h at room temperature, TLC showed full conversion. The reaction was then quenched by slowly adding water and extracted with EtOAc three times. The combined organic extracts were washed with brine, dried over Na_2SO_4 and evaporated *in vacuo*. The product was purified by flash column chromatography (*n*-hexane:EtOAc, 10:1) giving **6** as a pale yellow oil (3.20 g, 97%). Its NMR data matched with those reported in the literature.[39] **^{1}H NMR** (400 MHz) δ 7.39 – 7.33 (m, 3H), 5.31 (d, *J* = 1.8 Hz, 2H), 3.53 (d, *J* = 1.8 Hz, 3H). **^{13}C NMR** (100 MHz) δ 155.4, 152.0, 128.7, 118.6, 117.9, 105.8, 95.5, 56.8.

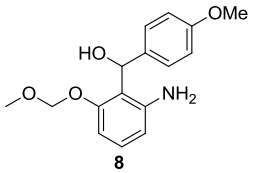
[2-(Methoxymethoxy)-6-nitrophenyl](4-methoxyphenyl)methanol (7)



7

In a flame-dried Schlenk flask was added **6** (3.000 g, 11.45 mmol, 1.0 equiv) and freshly distilled THF (30 mL) under N_2. At -95 °C, *n*-BuLi (5.5 mL, 2.5 M in hexanes, 13.74 mmol, 1.2 equiv) was then added dropwise. The reaction was continued to stir for 1.5 h at -95 °C before a solution of 4-methoxybenzaldehyde (3.117 g, 22.90 mmol, 2.0 equiv) in THF (10 mL) was added dropwise. After stirring the reaction for another 2 h, the reaction was quenched by slowly adding saturated NH_4Cl aqueous solution and extracted with EtOAc three times. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The product was purified by flash column chromatography (*n*-hexane:EtOAc, 5:1 to 3:1 to 2:1) giving **7** as a pale yellow oil (2.120 g, 58%). **^{1}H NMR** (400 MHz) δ 7.46 (dd, *J* = 7.3, 1.9 Hz, 1H), 7.44 – 7.34 (m, 2H), 7.24 (d, *J* = 8.1 Hz, 2H), 6.84 (d, *J* = 8.1 Hz, 2H), 6.25 (d, *J* = 11.2 Hz, 1H), 5.15 (d, *J* = 7.0 Hz, 1H), 5.07 (d, *J* = 6.9 Hz, 1H), 3.78 (s 3H), 3.73 (d, *J* = 11.2 Hz, 1H), 3.24 (s, 3H). **^{13}C NMR** (101 MHz) δ 158.9, 155.9, 150.9, 134.7, 129.3, 127.1, 119.0, 117.8, 113.7, 94.9, 69.3, 56.6, 55.4. **IR**: ν 3545, 2958, 1608, 1531, 1249, 1153, 1006 cm^{-1}. **HRMS** (FD) calculated for $C_{16}H_{17}NO_6^+$ $[M]^+$: 319.1056; found: 319.1061.

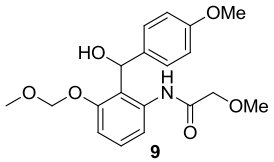
[2-Amino-6-(methoxymethoxy)phenyl](4-methoxyphenyl)methanol (8)



8

In a Schlenk flask was added **7** (2.000 g), EtOH (20 mL) and Pd/C (300 mg, 10 wt%) under N_2. The flask atmosphere was then changed to H_2 by using a balloon filled with H_2. The reaction was then stirred for 2 h under H_2 (1 atm. pressure). The reaction was filtrated and evaporated *in vacuo*. The product was purified by flash column chromatography (*n*-hexane:EtOAc, 5:1 to 3:1) giving **8** as a white solid (0.900 g, 50%). **^{1}H NMR** (400 MHz) δ 7.34 (d, *J* = 7.7 Hz, 2H), 7.03 (t, *J* = 8.1 Hz, 1H), 6.85 (d, *J* = 7.7 Hz, 2H), 6.55 (d, *J* = 8.2 Hz, 1H), 6.44 (s, 1H), 6.33 (d, *J* = 8.2 Hz, 1H), 5.16 (d, *J* = 6.7 Hz, 1H), 5.14 (d, *J* = 6.7 Hz, 1H), 4.06 (br, 2H), 3.78 (s, 3H), 3.41 (s, 3H). **^{13}C NMR** (100 MHz) δ 158.7, 155.4, 146.4, 134.9, 129.1, 127.1, 117.0, 113.7, 111.7, 104.6, 94.8, 68.3, 56.3, 55.3. **IR**: ν 3455, 3372, 2997, 1609, 1509, 1470, 1245, 1025 cm^{-1}. **HRMS** (FD) calculated for $C_{16}H_{19}NO_4^+$ $[M]^+$: 289.1314; found: 289.13120.

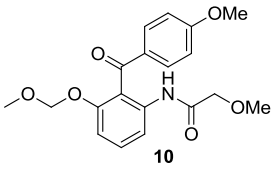
***N*-{2-[Hydroxy(4-methoxyphenyl)methyl]-3-(methoxymethoxy)phenyl}-2-methoxyacetamide (9)**



9

In a flame-dried Schlenk flask was added **8** (289 mg, 1.0 mmol, 1.0 equiv), ^{i}Pr$_2$NEt (155 mg, 1.2 mmol, 1.2 equiv) and freshly distilled DCM (5 mL). 2-Methoxyacetyl chloride (119 mg, 1.1 mmol, 1.1 equiv) was then added dropwise at 0 °C. The reaction was stirred for another 3 h at room temperature before it was quenched by adding water. The reaction was extracted with DCM three times and the combined extracts were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The product was purified by flash column chromatography (*n*-hexane:EtOAc, 1.5:1) giving **9** as a pale yellow oil (350 mg, 97%). **^{1}H NMR** (400 MHz) δ 9.95 (br, 1H), 7.94 (d, *J* = 8.2 Hz, 1H), 7.26 – 7.21 (m, 3H), 6.90 (d, *J* = 8.3 Hz, 1H), 6.84 – 6.76 (m, 2H), 6.57 (d, *J* = 3.7 Hz, 1H), 5.16 (d, *J* = 6.6 Hz, 1H), 5.16 (d, *J* = 6.6 Hz, 1H), 3.87 (d, *J* = 15.5 Hz, 1H), 3.75 (s, 3H), 3.66 (d, *J* = 15.5 Hz, 1H), 3.46 (d, *J* = 3.8 Hz, 1H), 3.39 (s, 3H), 3.25 (s, 3H). **^{13}C NMR** (100 MHz) δ 168.4, 158.8, 154.5, 137.6, 134.1, 129.2, 127.2, 121.5, 116.6, 113.6, 110.4, 95.0, 72.3, 68.1, 59.5, 56.3, 55.3. **IR**: ν 3279, 2936, 1665, 1592, 1471, 1248, 1036, 977 cm^{-1}. **HRMS** (FD) calculated for $C_{19}H_{23}NO_6^+$ $[M]^+$: 361.1525; found: 361.1520.

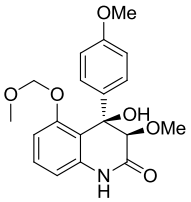
2-Methoxy-*N*-[2-(4-methoxybenzoyl)-3-(methoxymethoxy)phenyl]acetamide (10)



10

In a round bottom flask was added **9** (700 mg, 1.94 mmo, 1.0 equiv) and DCM (13 mL). PCC (836 mg, 3.89 mmol, 2.0 equiv) was then added portionwise. After stirring it at room temperature for 1 h, TLC showed full conversion of starting material. The reaction was quenched by adding saturated Na_2SO_3 aqueous solution and extracted with DCM three times. The combined organic extracts were washed with brine, dried over Na_2SO_4 and evaporated *in vacuo*. The product was purified by flash column chromatography (*n*-hexane:EtOAc, 2:1) giving **10** as a pale yellow oil (678 mg, 97%). **^{1}H NMR** (300 MHz) δ 9.02 (bs, 1H), 7.95 (d, *J* = 7.9 Hz, 1H), 7.88 – 7.75 (m, 2H), 7.38 (t, *J* = 8.3 Hz, 1H), 6.96 (dd, *J* = 8.4, 0.8 Hz, 1H), 6.93 – 6.83 (m, 2H), 4.96 (s, 2H), 3.86 (s, 2H), 3.83 (s, 3H), 3.32 (s, 3H), 3.22 (s, 3H); **^{13}C NMR** (75 MHz) δ 194.7, 168.3, 164.0, 155.2, 135.9, 132.03, 131.6, 131.1, 120.3, 116.0, 113.7, 110.7, 94.8, 72.2, 59.5, 56.3, 55.6. **IR**: ν 3363, 2933, 1693, 1591, 1463, 1250, 1044, 926 cm^{-1}. **HRMS** (FD) calculated for $C_{19}H_{21}NO_6^+$ $[M]^+$: 359.1369; found: 359.1365.

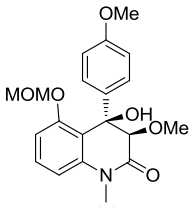
(3*R,4*R**)-4-Hydroxy-3-methoxy-5-(methoxymethoxy)-4-(4-methoxyphenyl)-3,4-dihydroquinolin-2(1*H*)-one [(±)-11]**



(±)-11

In a flame-dried Schlenk flask containing KO^{t}Bu (236 mg, 2.1 mmol, 7.0 equiv) which was weighed in the glove box, was added 2.1 mL of freshly distilled THF. This KO^{t}Bu solution was transferred slowly at 0 ℃ via a cannula to another flame-dried Schlenk flask containing **10** (108 mg, 0.3 mmol, 1.0 equiv) and freshly distilled THF (15 mL). Additional 2 mL of freshly distilled THF was added to the KO^{t}Bu Schlenk flask and was also transferred to make sure the transfer of KO^{t}Bu was complete. After stirring for 2 h at 0 ℃, TLC showed full conversion of starting material. The reaction was quenched by adding water and extracted with EtOAc three times. The combined organic extracts were washed with brine, dried over Na_2SO_4 and evaporated *in vacuo*. The product was purified by flash column chromatography (*n*-hexane:EtOAc, 1:1.5) giving **(±)-11** as a single diastereoisomer: white solid (103 mg, 95%). **^{1}H NMR** (400 MHz) δ 9.01 (bs, 1H), 7.24 – 7.12 (m, 3H), 6.85 (d, *J* = 8.4 Hz, 1H), 6.78 (d, *J* = 8.5 Hz, 2H), 6.55 (d, *J* = 7.9 Hz, 1H), 5.15 (s, 1H), 5.13 (d, *J* = 6.8 Hz, 1H), 5.00 (d, *J* = 6.9 Hz, 1H), 3.83 (s, 1H), 3.73 (s, 3H), 3.58 (s, 3H), 3.22 (s, 3H). **^{13}C NMR** (101 MHz) δ 168.3, 159.7, 156.6, 137.1, 133.5, 129.9, 127.5, 115.6, 114.0, 110.6, 110.3, 94.8, 85.1, 59.6, 56.4, 55.3. **IR**: ν 3513, 3247, 2933, 1693, 1596, 1509, 1253, 1050, 730 cm^{-1}. **HRMS** (FD) calculated for $C_{19}H_{21}NO_6^+$ $[M]^+$: 359.1369; found: 359.1365.

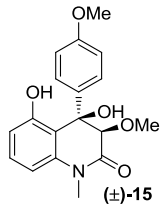
(3*R,4*R**)-4-Hydroxy-3-methoxy-5-(methoxymethoxy)-4-(4-methoxyphenyl)-1-methyl-3,4-dihydroquinolin-2(1*H*)-one [(±)-13]**



(±)-13

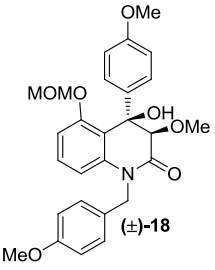
In a flame-dried Schlenk flask under N_2 was added **(±)-11** (36.0 mg, 0.1 mmol, 1.0 equiv), Cs_2CO_3 (65.2 mg, 0.2 mmol, 2.0 equiv) and anhydrous DMF (1.0 mL). MeI (21.3 mg, 1.5 mmol, 1.5 equiv) was then added at 0 ℃. The reaction was stirred at room temperature overnight. The reaction was quenched by adding water. The resultant mixture was extracted with EtOAc three times. The combined organic extracts were washed with water three times, brine two times, dried over Na_2SO_4 and evaporated *in vacuo*. The product was purified by flash column chromatography (*n*-hexane:EtOAc, 1:1) giving **(±)-13** as a pale yellow oil (35.9 mg, 96%). **^{1}H NMR** (300 MHz) δ 7.35 (t, *J* = 8.3 Hz, 1H), 7.14 (d, *J* = 8.9 Hz, 1H), 6.97 (d, *J* = 8.5 Hz, 1H), 6.86 – 6.76 (m, 3H), 5.32 (s, 1H), 5.20 (d, *J* = 6.9 Hz, 1H), 5.06 (d, *J* = 6.9 Hz, 1H), 3.93 (s, 1H), 3.77 (s, 3H), 3.57 (s, 3H), 3.34 (s, 3H), 3.27 (s, 3H). **^{13}C NMR** (75 MHz) δ 166.7, 159.8, 156.2, 140.7, 133.5, 129.7, 127.6, 117.5, 114.1, 110.8, 109.5, 95.0, 85.2, 77.5, 59.5, 56.5, 55.3, 30.2. **IR**: ν 3510, 2931, 1683, 1596, 1488, 1248, 1103, 1007 cm^{-1}. **HRMS** (FD) calculated for $C_{20}H_{23}NO_6^+$ $[M]^+$: 373.1525; found: 137.1539.

(3*R,4*R**)-4,5-Dihydroxy-3-methoxy-4-(4-methoxyphenyl)-1-methyl-3,4-dihydroquinolin-2(1*H*)-one [(±)-15]**



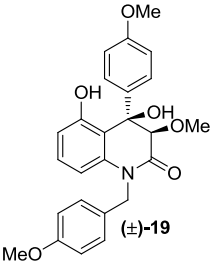
In a round bottom flask was added **(±)-13** (99 mg, 0.3 mmol, 1.0 equiv), CH_3CN (2 mL) and DCM (1 mL) and cooled to 0 ℃. $AlCl_3$ (600 mg, 4.5 mmol, 15 equiv) and NaI (675 mg, 4.5 mmol, 15 equiv) were quickly added. The reaction was then left to stir for 5 min before ice was added to quench the reaction. The mixture was then extracted with DCM three times. The combined organic extracts were washed with brine, dried over Na_2SO_4 and evaporated *in vacuo*. The product was purified by flash column chromatography (PE:EtOAc, 2:1) giving **(±)-15** as a white solid (70 mg, 71%). **^{1}H NMR** (400 MHz) δ 8.95 (s, 1H), 7.29 (t, *J* = 8.2 Hz, 1H), 7.20 – 7.12 (m, 2H), 6.89 – 6.81 (m, 2H), 6.73 (d, *J* = 8.4 Hz, 1H), 6.66 (d, *J* = 8.1 Hz, 1H), 4.55 (s, 1H), 3.84 (s, 1H), 3.78 (s, 3H), 3.59 (s, 3H), 3.35 (s, 3H). **^{13}C NMR** (101 MHz) δ 165.1, 160.3, 157.8, 139.2, 130.3, 129.2, 128.0, 114.3, 113.6, 112.4, 106.6, 84.4, 78.1, 59.0, 55.4, 30.1. **IR**: ν 3306, 2935, 1669, 1612, 1477, 1365, 1244 cm^{-1}. **HRMS** (FD) calculated for $C_{18}H_{19}NO_5^+$ $[M]^+$: 329.1263; found: 329.1270.

(3*R,4*R**)-4-Hydroxy-3-methoxy-1-(4-methoxybenzyl)-5-(methoxymethoxy)-4-(4-methoxyphenyl)-3,4-dihydroquinolin-2(1*H*)-one [(±)-18]**



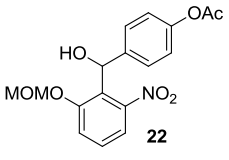
In a flame-dried Schlenk flask under N_2 was added **(±)-11** (72 mg, 0.2 mmol, 1.0 equiv), Cs_2CO_3 (130 mg, 0.4 mmol, 2.0 equiv) and anhydrous DMF (2.0 mL). 4-Methoxybenzyl chloride (47 mg, 3.0 mmol, 1.5 equiv) was then added dropwise. The reaction was then stirred at room temperature overnight. The reaction was quenched by adding water and was extracted with EtOAc three times. The combined organic extracts were washed with water two times and brine two times, dried over $MgSO_4$ and evaporated *in vacuo*. The product was purified by flash column chromatography (*n*-hexane:EtOAc, 1:1.2) giving **(±)-18** as a pale yellow solid (106 mg, 92%). **^{1}H NMR** (300 MHz) δ 7.20 (t, *J* = 8.4 Hz, 1H), 7.12 – 7.08 (m, 4H), 6.89 (d, *J* = 8.5 Hz, 1H), 6.83 – 6.75 (m, 5H), 5.19 – 5.09 (m, 2H), 5.02 (d, *J* = 6.8 Hz, 1H), 4.92 (d, *J* = 15.9 Hz, 1H), 4.00 (s, 1H), 3.77 – 3.77 (m, 6H), 3.61 (s, 3H), 3.23 (s, 3H). **^{13}C NMR** (75 MHz) δ 167.0, 159.8, 158.9, 156.3, 139.7, 133.3, 129.5, 128.6, 128.3, 127.9, 117.6, 114.1, 114.0, 110.7, 110.3, 94.9, 85.2, 77.5, 59.4, 56.5, 55.4, 55.4, 45.5.

(3*R,4*R**)-4,5-Dihydroxy-3-methoxy-1-(4-methoxybenzyl)-4-(4-methoxyphenyl)-3,4-dihydroquinolin-2(1*H*)-one [(±)-19]**



The procedure for the preparation of **[(±)-15]** was followed. 106 mg of **[(±)-18]** (0.22 mmol) was used and purification was performed using *n*-hexane/EtOAc (3:1) as eluent. **[(±)-19]** was isolated as a white solid in 72% yield (69 mg). **^{1}H NMR** (400 MHz) δ 8.90 (s, 1H), 7.17 – 7.07 (m, 5H), 6.83 – 6.78 (m, 4H), 6.65 (d, *J* = 8.2 Hz, 1H), 6.59 (d, *J* = 8.2 Hz, 1H), 5.15 (d, *J* = 15.8 Hz, 1H), 4.95 (d, *J* = 15.8 Hz, 1H), 4.50 (s, 1H), 3.91 (s, 1H), 3.78 (m, 6H), 3.62 (s, 3H). **^{13}C NMR** (101 MHz) δ 165.5, 160.4, 159.0, 157.9, 138.3, 130.2, 128.9, 128.4, 128.4, 128.2, 114.3, 114.2, 113.6, 112.6, 107.5, 84.6, 78.259.0, 55.4, 55.4, 45.5. **IR**: ν 3306, 2932, 1673, 1612, 1512, 1249, 1030, 727 cm^{-1}. **HRMS** (FD) calculated for $C_{25}H_{25}NO_6^+$ $[M]^+$: 435.1682; found: 435.1693.

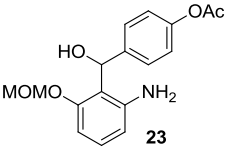
4-{Hydroxy[2-(methoxymethoxy)-6-nitrophenyl]methyl}phenyl acetate (22)



In a flame-dried Schlenk flask was added **6** (943 mg, 3.6 mmol, 1.2 equiv) and freshly distilled THF (20 mL) under N_2. At -95 ℃, *n*-BuLi (1.32 mL, 2.5 M in hexanes, 3.3 mmol, 1.1 equiv) was then added dropwise. The reaction was continued to stir for 1 h before a solution of 4-acetatebenzaldehyde (492 mg, 3.0 mmol, 1.0 equiv) in THF (10 mL) was added dropwise. After stirring the reaction for another 2 h, the reaction was quenched by slowly adding saturated NH_4Cl aqueous solution and extracted with EtOAc three times. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The sample was purified by flash column chromatography (*n*-hexane:EtOAc, 5:1 to 3:1 to 2:1) giving **22** as pale yellow oil (420 mg, 40%). **^{1}H NMR** (400 MHz) δ 7.49 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.42 (t, *J* = 8.1 Hz, 1H), 7.37 – 7.34 (m, 3H), 7.04 – 7.01 (m, 2H), 6.27 (s, 1H), 5.17 (d, *J* = 7.0 Hz, 1H), 5.04 (d, *J* = 6.9 Hz, 1H), 3.15 (s, 3H), 2.28 (s, 3H). **^{13}C NMR** (75 MHz) δ 169.6, 155.7, 150.8, 149.9, 140.3, 129.6, 126.8, 126.6, 121.4, 118.9, 117.6, 94.6, 69.2, 56.6, 21.3. **IR**: ν 3523, 1753, 1531, 1199, 1009, 907 cm^{-1}. **HRMS** (FD) calculated for $C_{17}H_{17}NO_7^+$ $[M]^+$:

347.1005; found: 347.1012.

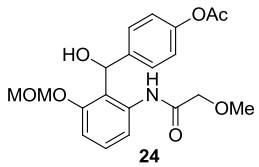
4-{[2-Amino-6-(methoxymethoxy)phenyl](hydroxy)methyl}phenyl acetate (23)



23

In a Schlenk flask was added **22** (480 mg, 1.38 mmol), EtOH (15 mL) and Pd/C (80 mg, 10 wt%) under N_2. The flask atmosphere was then changed to H_2 by using a balloon filled with H_2. The reaction was then stirred for 2 h under H_2 (1 atm. pressure). The reaction was filtrated and the solvent was removed *in vacuo* yielding **23** as pale yellow oil which was pure enough to be directly used for the next step. **^{1}H NMR** (400 MHz) δ 7.43 (d, *J* = 8.6 2H), 7.06 – 7.01 (m, 3H), 6.57 (d, *J* = 8.3 Hz, 1H), 6.46 (s, 1H), 6.35 (d, *J* = 8.0 Hz, 1H), 5.15 (s, 2H), 3.40 (s, 3H), 2.28 (s, 3H). **^{13}C NMR** (101 MHz) δ 169.7, 155.4, 149.7, 146.2, 140.5, 129.4, 127.1, 121.4, 116.9, 111.8, 104.7, 94.8, 68.3, 56.4, 21.3. **HRMS** (FD) calculated for $C_{23}H_{21}NO_4^+$ $[M]^+$: 375.1471; found: 345.1464.

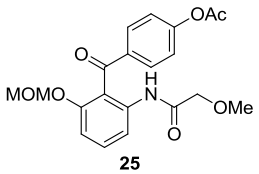
4-{Hydroxy[2-(2-methoxyacetamido)-6-(methoxymethoxy)phenyl]methyl}phenyl acetate (24)



24

The procedure for the preparation of **9** was followed. Crude **23** from previous step was used and the reaction was stirred at 0 ℃ for 0.5 h. Purification was performed using *n*-hexane/EtOAc (1.5:1) as eluent and **24** was isolated as a yellow oil in 93% yield (500 mg) over two steps. **^{1}H NMR** (400 MHz) δ 9.61 (bs, 1H), 7.90 (d, *J* = 8.3 Hz, 1H), 7.37 – 7.35 (m, 2H), 7.28 (t, *J* = 8.3 Hz, 1H), 7.01 – 6.99 (m, 2H), 6.95 (d, *J* = 8.4 Hz, 1H), 6.62 (s, 1H), 5.19 (s, 2H), 3.92 (d, *J* = 15.4 Hz, 1H), 3.69 (d, *J* = 15.4 Hz, 1H), 3.41 (s, 3H), 3.28 (s, 3H), 2.27 (s, 3H). **^{13}C NMR** (75 MHz) δ 169.6, 168.4, 154.7, 149.8, 139.6, 137.5, 129.6, 127.0, 121.4, 121.4, 116.9, 110.6, 95.1, 72.3, 67.8, 59.4, 56.4, 21.2. **IR**: ν 3304, 1754, 1666, 1591, 1471, 1196, 1043, 729 cm^{-1}. **HRMS** (EI) calculated for $C_{20}H_{21}NO_6^+$ $[M\text{-}H_2O]^+$: 371.1369; found: 371.1398.

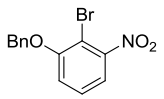
4-[2-(2-Methoxyacetamido)-6-(methoxymethoxy)benzoyl]phenyl acetate (25)



25

The procedure for the preparation of **10** was followed. 389 mg of **24** (0.1 mmol) was used and purification was performed using *n*-hexane/EtOAc (2:1 to 1.5:1) as eluent. **25** was isolated as a white solid (350 mg, 90%). **^{1}H NMR** (400 MHz) δ 9.23 (s, 1H), 8.00 (d, *J* = 8.3 Hz, 1H), 7.85 – 7.82 (m, 2H), 7.43 (t, *J* = 8.4 Hz, 1H), 7.18 – 7.14 (m, 2H), 6.96 (d, *J* = 8.4 Hz, 1H), 4.95 (s, 2H), 3.91 (s, 2H), 3.39 (s, 3H), 3.21 (s, 3H), 2.32 (s, 3H). **^{13}C NMR** (101 MHz) δ 195.49, 168.95, 168.44, 155.70, 154.62, 136.50, 136.30, 132.42, 131.07, 121.79, 119.34, 116.00, 110.52, 94.79, 72.26, 59.60, 56.53, 21.30. **HRMS** (EI) calculated for $C_{20}H_{21}NO_7^+$ $[M]^+$: 387.1318; found: 387.1344.

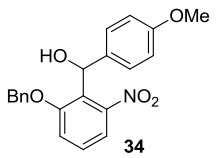
1-(Benzyloxy)-2-bromo-3-nitrobenzene (33)



33

In a round-bottom flask was added 2-bromo-3-nitrophenol (2.18 g, 10.0 mmol, 1.0 equiv), K_2CO_3 (4.15 g, 30.0 mmol, 3.0 equiv), benzyl chloride (2.3 mL, 20 mmol, 2.0 equiv) and EtOH (15 mL) successively. The mixture was then refluxed at 85 ℃ overnight. The volatiles were removed *in vacuo*. The product was purified by flash column chromatography (PE:EtOAc, 3:1) giving **33** as a yellow solid (2.80 g, 91%). **^{1}H NMR** (400 MHz) δ 7.49 (d, *J* = 7.6 Hz, 2H), 7.48 – 7.26 (m, 5H), 7.17 – 7.09 (m, 1H), 5.25 (s, 2H). **^{13}C NMR** (101 MHz) δ 156.6, 135.6, 128.9, 128.7, 128.5, 127.2, 117.0, 116.4, 105.5, 71.8. **HRMS** (FD) calculated for $C_{13}H_{10}BrNO_3$ $[M]^+$: 306.9844; found: 306.9816.

[2-(Benzyloxy)-6-nitrophenyl](4-methoxyphenyl)methanol (34)

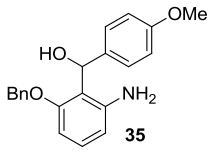


34

The procedure for the preparation of **7** was followed. 4.00 g of **33** (13.0 mmol) was used and purification was performed using PE/EtOAc (5:1 to 3:1) as eluent. **34** was isolated as a yellow oil in 46% yield (2.20 g). **^{1}H NMR** (400 MHz) δ 7.44 – 7.36 (m, 2H), 7.31 – 7.27 (m, 3H), 7.24 – 7.18 (m, 3H), 7.02 (dd, *J* = 7.5, 2.1 Hz, 2H), 6.86 – 6.82 (m, 2H), 6.23 (d, *J* = 10.5 Hz, 1H), 5.07 (d, *J* = 11.5 Hz, 1H), 4.99 (d, *J* = 11.5 Hz, 1H), 3.81 (s, 3H). **^{13}C NMR** (101 MHz) δ 158.8, 157.1, 150.7, 135.1, 134.6, 129.2, 128.6, 128.4, 127.5, 127.1, 126.4, 116.6, 116.5, 113.5, 71.2, 69.4, 55.3. **IR**: ν 3545, 2934, 1604, 1509, 1356, 1246, 1025, 737 cm^{-1}. **HRMS** (FD) calculated for $C_{21}H_{19}NO_5^+$ $[M]^+$: 365.1263; found: 365.1248.

[2-Amino-6-(benzyloxy)phenyl](4-methoxyphenyl)methanol (35)

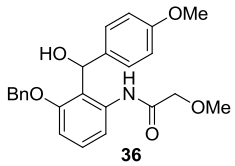
In a round bottom flask was added **34** (2.00 g, 5.5 mmol, 1.0 equiv), EtOH (30 mL) and Na_2S (1.28 g, 16.4 mmol, 3.0 equiv) successively. The reaction was then refluxed at 85 ℃ for 15 min before water was added to



35

quench the reaction. The mixture was then extracted with EtOAc three times. The combined organic extracts were washed with brine, dried over Na_2SO_4 and evaporated *in vacuo*. The obtained sample was directly used for the next step. **^{1}H NMR** (400 MHz) δ 7.38 – 7.30 (m, 8H), 7.04 (t, *J* = 8.1 Hz, 1H), 6.87 – 6.82 (m, 2H), 6.49 (s, 1H), 6.45 (dd, *J* = 8.3, 1.0 Hz, 1H), 6.32 (dd, *J* = 8.0, 0.9 Hz, 1H), 5.08 (d, *J* = 11.7 Hz, 1H), 5.02 (d, *J* = 11.7 Hz, 1H), 3.78 (s, 3H).

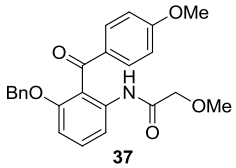
***N*-{3-(Benzyloxy)-2-[hydroxy(4-methoxyphenyl)methyl]phenyl}-2-methoxyacetamide (36)**



36

The procedure for the preparation of **9** was followed. Crude **35** from previous step was used and the reaction was stirred at 0 ℃ for 40 min. Purification was performed using *n*-hexane/EtOAc (2:1) as eluent. **36** was isolated as a yellow oil in 61% yield (1.40 g) over two steps. **^{1}H NMR** (400 MHz) δ 10.09 (bs, 1H), 7.95 (d, *J* = 8.3 Hz, 1H), 7.38 – 7.22 (m, 8H), 6.82 – 6.78 (m, 3H), 6.65 (s, 1H), 5.11 (d, *J* = 11.7 Hz, 1H), 5.04 (d, *J* = 11.7 Hz, 1H), 3.87 (d, *J* = 15.4 Hz, 1H), 3.77 (s, 3H), 3.69 (d, *J* = 15.5 Hz, 1H), 3.28 (s, 3H). **^{13}C NMR** (101 MHz) δ 168.2, 158.3, 155.4, 137.6, 136.6, 134.4, 128.5, 128.3, 127.7, 127.1, 127.0, 121.1, 115.2, 113.2, 108.0, 72.0, 70.3, 67.4, 59.1, 54.9. **IR**: ν 3282, 2934, 2834, 1665, 1593, 1472, 1249, 1116 cm^{-1}. **HRMS** (FD) calculated for $C_{24}H_{25}NO_5^+$ $[M]^+$: 407.1733; found: 407.1746.

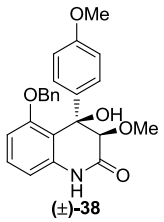
***N*-[3-(Benzyloxy)-2-(4-methoxybenzoyl)phenyl]-2-methoxyacetamide (37)**



37

The procedure for the preparation of **10** was followed. 1.40 g of **36** (3.44 mmol) was used and purification was performed using PE/EtOAc (1.5:1) as eluent. **37** was isolated as a white solid in 94% yield (1.30 g). **^{1}H NMR** (400 MHz) δ 9.32 (bs, 1H), 7.99 (d, *J* = 8.3 Hz, 1H), 7.82 – 7.75 (m, 2H), 7.37 (t, *J* = 8.4 Hz, 1H), 7.19 – 7.06 (m, 3H), 6.91 – 6.82 (m, 4H), 6.78 (d, *J* = 8.3 Hz, 1H), 4.89 (s, 2H), 3.87 (s, 2H), 3.78 (s, 3H), 3.32 (s, 3H). **^{13}C NMR** (101 MHz) δ 194.9, 168.1, 163.7, 156.6, 136.3, 136.0, 131.7, 131.5, 128.0, 127.4, 126.5, 119.1, 114.8, 113.5, 108.3, 71.9, 70.0, 59.2, 55.3. **IR**: ν 3359, 2935, 2837, 1692, 1592, 1461, 1253, 927 cm^{-1}. **HRMS** (FD) calculated for $C_{24}H_{23}NO_5^+$ $[M]^+$: 405.1576; found: 405.1591.

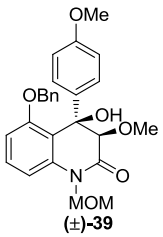
(3*R,4*R**)-5-(Benzyloxy)-4-hydroxy-3-methoxy-4-(4-methoxyphenyl)-3,4-dihydroquinolin-2(1*H*)-one [(±)-38]**



(±)-38

The procedure for the preparation of **(±)-11** was followed. 0.94 g of **37** (2.32 mmol) was used and purification was performed using PE/EtOAc (1:1.5) as eluent. Product **(±)-38** was isolated as a white solid in 80% yield (0.75 g). **^{1}H NMR** (400 MHz) δ 8.80 (bs, 1H), 7.32 – 7.25 (m, 3H), 7.25 – 7.16 (m, 3H), 7.12 (dd, *J* = 6.3, 2.7 Hz, 2H), 6.86 – 6.77 (m, 2H), 6.73 (d, *J* = 8.4 Hz, 1H), 6.55 (dd, *J* = 8.1, 0.9 Hz, 1H), 5.33 (s, 1H), 5.07 (d, *J* = 11.5 Hz, 1H), 4.99 (d, *J* = 11.5 Hz, 1H), 3.83 (s, 1H), 3.77 (d, *J* = 1.0 Hz, 3H), 3.61 (s, 3H). **^{13}C NMR** (101 MHz) δ 168.3, 159.7, 158.0, 137.1, 135.7, 133.6, 129.9, 128.7, 128.4, 127.6, 127.5, 115.3, 114.0, 109.6, 108.7, 85.1, 78.1, 71.1, 59.7, 55.3. **IR**: ν 3509, 2932, 1692, 1607, 1509, 1259, 1103 cm^{-1}. **HRMS** (FD) calculated for $C_{24}H_{23}NO_5^+$ $[M]^+$: 405.1576; found: 405.1591.

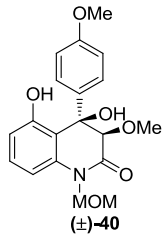
(3*R,4*R**)-5-(Benzyloxy)-4-hydroxy-3-methoxy-1-(methoxymethyl)-4-(4-methoxyphenyl)-3,4-dihydroquinolin-2(1*H*)-one [(±)-39]**



(±)-39

In a flame-dried Schlenk flask was added **(±)-38** (400 mg, 0.99 mmol, 1.0 equiv) and anhydrous THF (10 mL). LiHMDS solution in THF (1.2 mL, 1.0 M, 1.20 mmol, 1.2 equiv) was then added dropwise at 0 ℃. After stirring it for 0.5 h, MOMBr (272 mg, 2.18 mmol, 2.2 equiv) was added dropwise. The reaction was continued to stir at 0 ℃ for 2 h before water was added to quench the reaction. The mixture was extracted with EtOAc three times. The combined organic extracts were washed with brine, dried over Na_2SO_4 and evaporated *in vacuo*. The sample was purified by flash column chromatography (PE:EtOAc, 2:1) giving **(±)-39** as a white solid (440 mg, 99%). **^{1}H NMR** (400 MHz) δ 7.31 (t, *J* = 8.3 Hz, 1H), 7.26 – 7.25 (m, 3H), 7.14 – 7.07 (m, 5H), 6.82 – 6.77 (m, 3H), 5.57 (d, *J* = 10.8 Hz, 1H), 5.46 (s, 1H), 5.07 (d, *J* = 11.5 Hz, 1H), 5.00 – 4.94 (m, 2H), 3.92 (s, 1H), 3.76 (s, 3H), 3.57 (s, 3H), 3.33 (s, 3H). **^{13}C NMR** (101 MHz) δ 167.8, 159.8, 157.5, 139.6, 135.7, 133.4, 129.8, 128.8, 128.4, 127.7, 127.5, 117.0, 114.0, 109.7, 109.4, 85.3, 77.4, 74.0, 71.2, 59.4, 56.4, 55.3. **IR**: ν 3506, 2932, 2831, 1695, 1594, 1467, 1251, 1063, 730 cm^{-1}. **HRMS** (FD) calculated for $C_{26}H_{27}NO_6^+$ $[M]^+$: 449.1838; found: 449.1820.

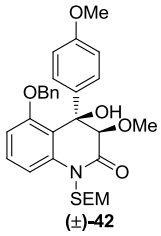
(3*R,4*R**)-4,5-Dihydroxy-3-methoxy-1-(methoxymethyl)-4-(4-methoxyphenyl)-3,4-dihydroquinolin-2(1*H*)-one [(±)-40]**



(±)-40

In a Schlenk flask was added **(±)-39** (440 mg), EtOH (8 mL), EtOAc (8 mL) and Pd/C (300 mg, 10 wt%) under N_2. The flask atmosphere was then changed to H_2 by using a balloon filled with H_2. The reaction was then stirred for 2 h under H_2 (1 atm. pressure). The reaction was filtrated and evaporated *in vacuo*. The product was purified by flash column chromatography (*n*-hexane:EtOAc, 2:1) giving **(±)-40** as white solid (345 mg, 98%). **^{1}H NMR** (400 MHz) δ 8.87 (s, 1H), 7.28 (t, *J* = 8.2 Hz, 1H), 7.17 (d, *J* = 8.5 Hz, 2H), 6.92 (d, *J* = 8.2 Hz, 1H), 6.84 (d, *J* = 8.5 Hz, 2H), 6.75 (d, *J* = 8.2 Hz, 1H), 5.60 (d, *J* = 10.8 Hz, 1H), 5.00 (d, *J* = 10.7 Hz, 1H), 4.53 (s, 1H), 3.87 (s, 1H), 3.78 (s, 3H), 3.60 (s, 3H), 3.35 (s, 3H). **^{13}C NMR** (101 MHz) δ 166.3, 160.4, 157.7, 138.0, 130.5, 128.9, 128.2, 114.4, 114.0, 112.3, 107.5, 84.6, 78.1, 74.0, 58.9, 56.4, 55.4. **IR**: ν 3403, 3243, 2922, 1672, 1459, 1242, 1083, 1020, 885 cm^{-1}. **HRMS** (FD) calculated for $C_{19}H_{21}NO_6^+$ $[M]^+$: 359.1369; found: 359.1354.

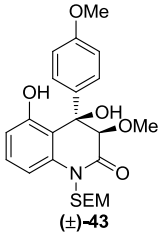
(3*R,4*R**)-5-(Benzyloxy)-4-hydroxy-3-methoxy-4-(4-methoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-3,4-dihydroquinolin-2(1*H*)-one [(±)-42]**



(±)-42

In a flame-dried Schlenk flask was added **(±)-38** (1.20 g, 2.96 mmol, 1.0 equiv) and anhydrous THF (50 mL). LiHMDS solution in THF (3.26 mL, 1.0 M, 3.26 mmol, 1.1 equiv) was then added dropwise at 0 ℃. After stirring it for 0.5 h, SEMCl (0.59 g, 3.55 mmol, 1.2 equiv) was added dropwise. The reaction was continued to stir at 0 ℃ for 2 h before water was added to quench the reaction. The mixture was extracted with EtOAc three times. The combined organic extracts were washed with brine, dried over Na_2SO_4 and evaporated *in vacuo*. The product was purified by flash column chromatography (PE:EtOAc, 3:1) giving **(±)-42** as a white solid (1.40 g, 88%). **^{1}H NMR** (400 MHz) δ 7.33 (t, *J* = 8.3 Hz, 1H), 7.30 – 7.26 (m, 3H), 7.19 – 7.11 (m, 5H), 6.84 – 6.80 (m, 3H), 5.67 (d, *J* = 11.0 Hz, 1H), 5.49 (s, 1H), 5.10 (d, *J* = 11.5 Hz, 1H), 5.01 (d, *J* = 11.5 Hz, 1H), 4.96 (d, *J* = 11.0 Hz, 1H), 3.92 (s, 1H), 3.78 (s, 3H), 3.67 – 3.54 (m, 2H), 3.58 (s, 3H), 0.98 – 0.94 (m, 2H), 0.00 (s, 9H). **^{13}C NMR** (101 MHz) δ 167.6, 159.8, 157.4, 139.8, 135.7, 133.5, 129.7, 128.8, 128.4, 127.7, 127.5, 116.9, 114.0, 110.0, 109.3, 85.3, 77.4, 72.2, 71.2, 66.0, 59.4, 55.3, 18.1, -1.3. **IR**: ν 3508, 2952, 1693, 1594, 1465, 1385, 1247, 1064, 832 cm^{-1}. **HRMS** (FD) calculated for $C_{30}H_{37}NO_6Si^+$ $[M]^+$: 535.2390; found: 535.2383.

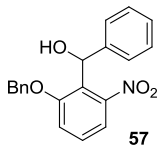
(3*R,4*R**)-4,5-Dihydroxy-3-methoxy-4-(4-methoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-3,4-dihydroquinolin-2(1*H*)-one [(±)-43]**



(±)-43

The procedure for the preparation of **(±)-40** was followed. 430 mg of **(±)-42** (0.80 mmol) and 100 mg Pd/C (10% wt) were used. Purification was performed using PE/EtOAc (3:1) as eluent. Product **(±)-43** was isolated as a white solid in 95% yield (446 mg). **^{1}H NMR** (400 MHz) δ 8.86 (s, 1H), 7.28 (t, *J* = 8.2 Hz, 1H), 7.17 – 7.15 (m, 2H), 6.98 (d, *J* = 8.3 Hz, 1H), 6.85 – 6.82 (m, 2H), 6.74 (d, *J* = 8.3 Hz, 1H), 5.65 (d, *J* = 11.0 Hz, 1H), 5.00 (d, *J* = 10.9 Hz, 1H), 4.53 (s, 1H), 3.85 (s, 1H), 3.77 (s, 3H), 3.63 – 3.53 (m, 2H), 3.59 (s, 3H), 0.96 (t, *J* = 8.3 Hz, 2H), 0.00 (s, 9H). **^{13}C NMR** (101 MHz) δ 166.1, 160.4, 157.6, 138.1, 130.4, 129.0, 128.2, 114.3, 113.8, 112.3, 107.7, 84.6, 78.1, 72.2, 66.1, 58.8, 55.3, 18.1, -1.3. **IR**: ν 3353, 2953, 1677, 1613, 1470, 1243, 1073, 834 cm^{-1}. **HRMS** (FD) calculated for $C_{23}H_{31}NO_6Si^+$ $[M]^+$: 445.1921; found: 445.1939.

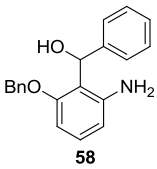
[2-(Benzyloxy)-6-nitrophenyl](phenyl)methanol (57)



57

The procedure for the preparation of **7** was followed. 4.00 g of **33** (13.0 mmol) was used and purification was performed using PE/EtOAc (7:1 to 3:1) as eluent. Product **57** was isolated as a yellow oil in 48% yield (2.10 g). **^{1}H NMR** (400 MHz) δ 7.41 – 7.36 (m, 2H), 7.34 – 7.20 (m, 8H), 7.15 (d, *J* = 7.9 Hz, 1H), 6.94 – 6.87 (m, 2H), 6.26 (s, 1H), 5.02 (dd, *J* = 11.6, 2.8 Hz, 1H), 4.92 (d, *J* = 11.5 Hz, 1H). **^{13}C NMR** (101 MHz) δ 157.3, 151.0, 142.6, 135.0, 129.4, 128.8, 128.6, 128.3, 127.6, 127.3, 126.6, 125.8, 116.8, 77.4, 71.5, 69.6. **IR**: ν 3031, 1528, 1452, 1356, 1023, 737, 697 cm^{-1}. **HRMS** (EI) calculated for $C_{20}H_{16}NO_3^+$ $[M\text{-}OH]^+$: 318.1130; found: 318.1110.

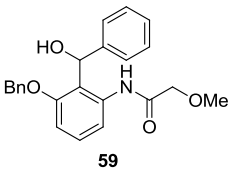
[2-Amino-6-(benzyloxy)phenyl](phenyl)methanol (58)



58

The procedure for the preparation of **35** was followed. 1.80 g of **57** (5.37 mmol) was used and the reaction was refluxed for 0.5 h. Product **58** was used for the next step without purification. **^{1}H NMR** (400 MHz) δ 7.46 (d, *J* = 7.5 Hz, 2H), 7.42 – 7.16 (m, 8H), 7.08 (t, *J* = 8.2 Hz, 1H), 6.57 (s, 1H), 6.49 (d, *J* = 8.3 Hz, 1H), 6.35 (d, *J* = 7.9 Hz, 1H), 5.17 – 5.02 (m, 2H). **^{13}C NMR** (101 MHz) δ 156.9, 146.1, 143.0, 137.1, 129.2, 128.6, 128.3, 128.0, 127.5, 127.0, 125.9, 116.7, 111.2, 102.9, 70.6, 68.5.

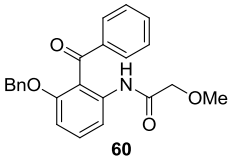
***N*-{3-(Benzyloxy)-2-[hydroxy(phenyl)methyl]phenyl}-2-methoxyacetamide (59)**



59

The procedure for the preparation of **9** was followed. The crude sample **58** from the previous step was used and the reaction was stirred for 40 min. Purification was performed using PE/EtOAc (2.5:1) as eluent and product **59** was isolated as a yellow oil in 67% yield (2.10 g) over two steps. **^{1}H NMR** (400 MHz) δ 9.76 (s, 1H), 7.89 (d, *J* = 8.3 Hz, 1H), 7.41 – 7.16 (m, 11H), 6.82 (d, *J* = 8.4 Hz, 1H), 6.67 (s, 1H), 5.13 (d, *J* = 11.6 Hz, 1H), 5.05 (d, *J* = 11.6 Hz, 1H), 3.89 (d, *J* = 15.4 Hz, 1H), 3.67 (d, *J* = 15.3 Hz, 1H), 3.29 (s, 3H). **^{13}C NMR** (101 MHz) δ 168.3, 156.0, 142.0, 137.7, 136.7, 129.3, 128.7, 128.2, 128.2, 127.6, 127.2, 125.8, 121.4, 116.1, 108.7, 72.4, 71.0, 68.2, 59.5. **IR**: ν 3293, 2934, 1665, 1592, 1443, 1261, 1117, 736 cm^{-1}. **HRMS** (EI) calculated for $C_{23}H_{21}NO_3^+$ $[M-H_2O]^+$: 359.1521; found: 359.1513.

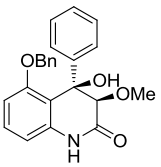
***N*-[2-Benzoyl-3-(benzyloxy)phenyl]-2-methoxyacetamide (60)**



60

The procedure for the preparation of **10** was followed. 1.46 g of **59** (3.87 mmol) was used and purification was performed using PE/EtOAc (2:1) as eluent. Product **60** was isolated as a pale yellow solid in 89% yield (1.29 g). **^{1}H NMR** (400 MHz) δ 9.53 (s, 1H), 8.04 (d, *J* = 8.4 Hz, 1H), 7.79 (d, *J* = 8.5 Hz, 1H), 7.59 – 7.50 (m, 3H), 7.46 – 7.40 (m, 3H), 7.20 – 7.11 (m, 3H), 6.81 (d, *J* = 8.4 Hz, 1H), 6.76 (d, *J* = 7.6 Hz, 2H), 4.88 (d, *J* = 2.0 Hz, 2H), 3.92 (d, *J* = 1.9 Hz, 2H), 3.39 (d, *J* = 2.3 Hz, 3H). **^{13}C NMR** (101 MHz) δ 197.0, 168.4, 157.3, 139.3, 137.0, 135.9, 133.0, 132.4, 129.2, 128.4, 128.2, 127.7, 126.7, 118.6, 115.0, 108.4, 72.2, 70.3, 59.5. **IR**: ν 3354, 2936, 1692, 1581, 1466, 1274, 1070, 923, 697 cm^{-1}. **HRMS** (EI) calculated for $C_{23}H_{21}NO_4^+$ $[M]^+$: 375.1471; found: 345.1464.

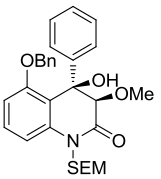
(3*R,4*R**)-5-(Benzyloxy)-4-hydroxy-3-methoxy-4-phenyl-3,4-dihydroquinolin-2(1*H*)-one [(±)-61]**



(±)-61

The procedure for the preparation of **(±)-11** was followed. 1.15 g of **60** (3.06 mmol) was used and purification was performed using PE/EtOAc (1:1) as eluent. Product **(±)-61** was isolated as a white solid in 95% yield (1.10 g). **^{1}H NMR** (400 MHz) δ 8.76 (bs, 1H), 7.27 – 7.18 (m, 9H), 7.06 – 7.03 (m, 2H), 6.70 (d, *J* = 8.3 Hz, 1H), 6.55 (d, *J* = 8.3 Hz, 1H), 5.28 (bs, 1H), 5.03 (d, *J* = 11.6 Hz, 1H), 4.93 (d, *J* = 11.6 Hz, 1H), 3.83 (s, 1H), 3.59 (s, 3H). **^{13}C NMR** (101 MHz) δ 168.1, 158.0, 141.9, 137.2, 135.7, 130.0, 128.7, 128.7, 128.4, 128.3, 127.4, 126.2, 115.2, 109.6, 108.7, 85.0, 78.3, 71.0, 59.8. Its NMR data matched with those reported in the literature.[19]

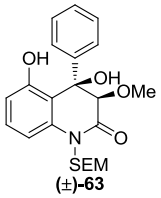
(3*R,4*R**)-5-(Benzyloxy)-4-hydroxy-3-methoxy-4-phenyl-1-{[2-(trimethylsilyl)ethoxy]methyl}-3,4-dihydroquinolin-2(1*H*)-one [(±)-62]**



(±)-62

In a flame-dried Schlenk flask was added **(±)-61** (0.90 g, 2.40 mmol, 1.0 equiv) and anhydrous THF (35 mL). LiHMDS solution in THF (3.12 mL, 1.0 M, 3.12 mmol, 1.3 equiv) was then added dropwise at 0 ℃. After stirring it for 0.5 h, SEMCl (0.60 g, 3.60 mmol, 1.5 equiv) was added dropwise. The reaction was first stirred at 0 ℃ for 0.5 h and then 2 h at room temperature. Water was added to quench the reaction. The mixture was extracted with EtOAc three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtrated and evaporated *in vacuo*. The sample was purified by flash column chromatography (PE:EtOAc, 4:1) giving **(±)-62** as a white solid (1.15 g, 94%). **^{1}H NMR** (400 MHz) δ 7.31 (t, *J* = 8.3 Hz, 1H), 7.29 – 7.20 (m, 8H), 7.16 (d, *J* = 8.4 Hz, 1H), 7.08 – 6.99 (m, 2H), 6.80 (d, *J* = 8.4 Hz, 1H), 5.64 (d, *J* = 11.0 Hz, 1H), 5.47 (bs, 1H), 5.05 (d, *J* = 11.5 Hz, 1H), 4.97 – 4.94 (m, 2H), 3.91 (s, 1H), 3.66 – 3.53 (m, 2H), 3.56 (s, 3H), 0.98 – 0.93 (m, 2H), -0.02 (s, 9H). **^{13}C NMR** (101 MHz) δ 167.5, 157.4, 141.7, 139.9, 135.7, 129.8, 128.7, 128.6, 128.5, 128.3, 127.4, 126.3, 116.7, 109.9, 109.2, 85.2, 77.6, 72.2, 71.2, 66.0, 59.5, 18.1, -1.3. **IR**: ν 3507, 2951, 1693, 1593, 1469, 1376, 1247, 1062, 833, 730, 696 cm^{-1}. **HRMS** (FD) calculated for $C_{29}H_{35}NO_5Si^+$ $[M]^+$: 505.2284; found: 505.2302.

(3*R,4*R**)-4,5-Dihydroxy-3-methoxy-4-phenyl-1-{[2-(trimethylsilyl)ethoxy]methyl}-3,4-dihydroquinolin-2(1*H*)-one [(±)-63]**



(±)-63

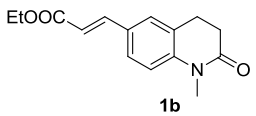
The procedure for the preparation of **(±)-40** was followed. 0.90 g of **(±)-62** (2.17 mmol) was used and purification was performed using PE/EtOAc (4:1) as eluent. Product **(±)-63** was isolated as a white solid in 94% yield (0.70 g). **^{1}H NMR** (400 MHz) δ 8.80 (bs, 1H), 7.32 – 7.29 (m, 3H), 7.28 – 7.20 (m, 3H), 6.98 (d, *J* = 8.2 Hz, 1H), 6.72 (d, *J* = 8.3 Hz, 1H), 5.65 (d, *J* = 10.9 Hz, 1H), 5.00 (d, *J* = 10.9 Hz, 1H), 4.54 (s, 1H), 3.82 (s, 1H), 3.60 – 3.54 (m, 2H), 3.58 (s, 3H), 0.97 – 0.92 (m, 2H), -0.02 (s, 9H). **^{13}C NMR** (101 MHz) δ 165.9, 157.6, 138.3, 137.3, 130.6, 129.5, 129.0, 126.7, 113.9, 112.2, 107.8, 84.6, 78.3, 72.3, 66.2, 58.9, 18.1, -1.3. **IR**: ν 3325, 2952, 1680, 1470, 1241, 1070, 834 cm^{-1}. **HRMS** (FD) calculated for $C_{22}H_{29}NO_5Si^+$ [M]$^+$: 415.1815; found: 415.1836.

4.5.5 Pd-catalyzed C(6)−H olefination of 3,4-dihydro-2(1*H*)-quinolinone derivatives

General procedure for Pd-catalyzed C(6)–H olefination of 3,4-dihydro-2(1*H*)-quinolinone derivatives

In a pressure tube containing a suitable stirring bar was added the corresponding 3,4-dihydro-2(1*H*)-quinolinone derivative (1.0 equiv), $Pd(OAc)_2$ (10 mol%), $PhCO_3{}^tBu$ (1.0 – 2.0 equiv), olefin (1.0 – 2.0 equiv), S,O-ligand stock solution in DCE (0.1 M, 10 mol%) and DCE. The tube was introduced into a pre-heated oil bath at stated temperature and was stirred for stated period of time. After cooling to room temperature, the reaction was filtrated through Celite and rinsed with DCM. The filtrate was then washed with a saturated solution of Na_2CO_3, dried with $MgSO_4$, filtrated and concentrated *in vacuo*. The product was purified by flash column chromatography or preprative TLC.

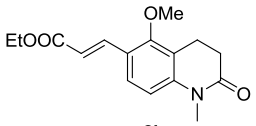
(*E*)-Ethyl 3-(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)acrylate (1b)



1b

Substrate **1a** (16.1 mg, 0.1 mmol) was olefinated using ethyl acrylate (16.3 µL, 0.15 mmol, 1.5 equiv), $PhCO_3{}^tBu$ (18.6 µL, 0.1 mmol, 1.0 equiv) at 80 °C for 16 h following the general procedure and the sample was purified by preparative TLC (PE/EtOAc, 5:1) to give **1b** as a yellow oil (9.0 mg, 35%) as a mixture of regioisomers (*para*:others 4.3:1). **^{1}H NMR** (400 MHz) δ 7.63 (d, *J* = 16.1 Hz, 1H), 7.42 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.35 (d, *J* = 1.9 Hz, 1H), 6.98 (d, *J* = 8.4 Hz, 1H), 6.37 (d, *J* = 16.0 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 3.37 (s, 3H), 2.93 (dd, *J* = 8.6, 6.1 Hz, 2H), 2.68 (dd, *J* = 8.7, 6.0 Hz, 3H), 1.34 (t, *J* = 7.1 Hz, 4H).

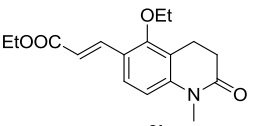
(*E*)-Ethyl 3-(5-methoxy-1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)acrylate (2b)



2b

Substrate **2a** (19.1 mg, 0.1 mmol) was olefinated using ethyl acrylate (16.3 µL, 0.15 mmol, 1.5 equiv), $PhCO_3{}^tBu$ (18.6 µL, 0.1 mmol, 1.0 equiv) at 80 °C for 16 h following the general procedure and the sample was purified by flash column chromatography (PE/EtOAc, 3:1) to give **2b** as a yellow oil (13.0 mg, 45%, *para*:others > 20:1). **^{1}H NMR** (400 MHz) δ 7.88 (d, *J* = 16.1 Hz, 1H), 7.47 (d, *J* = 8.6 Hz, 1H), 6.80 (d, *J* = 8.6 Hz, 1H), 6.45 (d, *J* = 16.1 Hz, 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 3.74 (s, 3H), 3.36 (s, 3H), 2.97 (dd, *J* = 8.6, 6.3 Hz, 2H), 2.63 (dd, *J* = 8.6, 6.2 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz) δ 170.3, 167.4, 156.7, 143.7, 139.0, 127.2, 123.1, 120.1, 118.3, 111.4, 62.0, 60.6, 31.1, 29.9, 18.8, 14.5. **IR**: ν 2923, 2852, 1675, 1628, 1596, 1265, 1167 cm^{-1}. **HRMS** (FD) calculated for $C_{16}H_{19}NO_4^+$ [M]$^+$: 289.1314; found: 289.1319.

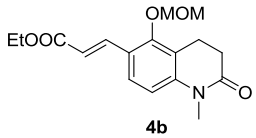
(*E*)-Ethyl 3-(5-ethoxy-1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)acrylate (3b)



3b

Substrate **3a** (20.5 mg, 0.1 mmol) was olefinated using ethyl acrylate (16.3 µL, 0.15 mmol, 1.5 equiv), $PhCO_3{}^tBu$ (18.6 µL, 0.1 mmol, 1.0 equiv) at 80 °C for 16 h following the general procedure and the sample was purified by flash column chromatography (PE/EtOAc, 3:1) to give **3b** as a yellow oil (17.3 mg, 57%, *para*:others > 20:1). **^{1}H NMR** (400 MHz) δ 7.90 (d, *J* = 16.1 Hz, 1H), 7.47 (d, *J* = 8.6 Hz, 1H), 6.79 (d, *J* = 8.6 Hz, 1H), 6.42 (d, *J* = 16.1 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 3.86 (q, *J* = 7.0 Hz, 2H), 3.35 (s, 3H), 2.95 (dd, *J* = 8.6, 6.2 Hz, 2H), 2.61 (dd, *J* = 8.5, 6.2 Hz, 2H), 1.42 (t, *J* = 7.0 Hz, 3H), 1.33 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz) δ 170.3, 167.3, 155.7, 143.7, 139.3, 126.8, 123.3, 120.3, 118.0, 111.3, 70.7, 60.5, 31.2, 29.9, 19.0, 15.6, 14.5. **IR**: ν 2977, 1679, 1598, 1441, 1352, 1177, 1125, 1044 cm^{-1}. **HRMS** (FD) calculated for $C_{17}H_{21}NO_4^+$ [M]$^+$: 303.1471; found: 330.1527.

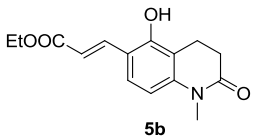
(*E*)-Ethyl 3-[5-(methoxymethoxy)-1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl]acrylate (4b)



4b

Substrate **4a** (22.1 mg, 0.1 mmol) was olefinated using ethyl acrylate (16.3 μL, 0.15 mmol, 1.5 equiv), $PhCO_3^tBu$ (18.6 μL, 0.1 mmol, 1.0 equiv) at 80 °C for 16 h following the general procedure and the sample was purified by flash column chromatography (PE/EtOAc, 3:1) to give **4b** as a yellow oil (15.0 mg, 47%, *para*:others > 20:1). **^{1}H NMR** (400 MHz) δ 7.93 (d, *J* = 16.1 Hz, 1H), 7.50 (d, *J* = 8.5 Hz, 1H), 6.82 (d, *J* = 8.6 Hz, 1H), 6.38 (d, *J* = 16.2 Hz, 1H), 4.97 (s, 2H), 4.25 (q, *J* = 7.2 Hz, 2H), 3.62 (s, 3H), 3.35 (s, 3H), 2.97 (dd, *J* = 8.6, 6.2 Hz, 2H), 2.61 (dd, *J* = 8.6, 6.3 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz) δ 170.3, 167.2, 154.2, 143.7, 139.4, 126.5, 123.5, 120.5, 118.0, 111.8, 100.7, 60.6, 58.1, 31.2, 30.0, 19.6, 14.5. **IR**: ν 2852, 1677, 1598, 1354, 1251, 1124, 812 cm^{-1}. **HRMS** (FD) calculated for $C_{17}H_{21}NO_5^+$ $[M]^+$: 319.1420; found: 319.1415.

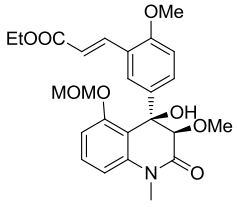
(*E*)-Ethyl 3-(5-hydroxy-1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)acrylate (5b)



5b

Substrate **5a** (17.7 mg, 0.1 mmol) was olefinated using ethyl acrylate (16.3 μL, 0.15 mmol, 1.5 equiv), $PhCO_3^tBu$ (18.6 μL, 0.1 mmol, 1.0 equiv) at 80 °C for 16 h following the general procedure and the sample was purified by preparative TLC (PE/EtOAc, 2:1) to give **5b** as a yellow oil (7.4 mg, 27%). (*The product is not stable, as after the sample solution in $CDCl_3$ was stored overnight at room temperature and was measured again, many new peaks arose.*) **^{1}H NMR** (300 MHz) δ 7.97 (d, *J* = 16.0 Hz, 1H), 7.40 (d, *J* = 8.6 Hz, 1H), 6.64 (d, *J* = 8.6 Hz, 1H), 6.45 (d, *J* = 15.9 Hz, 1H), 5.88 (s, 1H), 4.27 (q, *J* = 7.2 Hz, 2H), 3.36 (s, 3H), 2.96 – 2.83 (m, 2H), 2.67 (dd, *J* = 8.8, 6.2 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H).

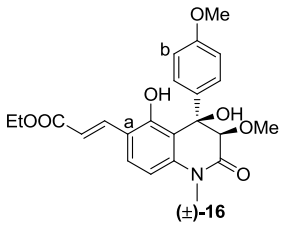
(*E*)-Ethyl 3-{5-[(3*R,4*R**)-4-hydroxy-3-methoxy-5-(methoxymethoxy)-1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-4-yl]-2-methoxyphenyl}acrylate [(±)-14]**



(±)-14

Substrate **(±)-13** (37.3 mg, 0.1 mmol) was olefinated using ethyl acrylate (16.3 μL, 0.15 mmol, 1.5 equiv), $PhCO_3^tBu$ (18.6 μL, 0.1 mmol, 1.0 equiv) at 80 °C for 16 h following the general procedure and the sample was purified by preparative TLC (PE/EtOAc, 2:1) to give **(±)-14** as a yellow oil (14.1 mg, 30%, single regioisomer). **^{1}H NMR** (400 MHz) δ 7.83 (d, *J* = 16.2 Hz, 1H), 7.39 – 7.32 (m, 2H), 7.14 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.96 (d, *J* = 8.5 Hz, 1H), 6.84 (d, *J* = 8.2 Hz, 1H), 6.80 (d, *J* = 8.7 Hz, 1H), 6.43 (d, *J* = 16.1 Hz, 1H), 5.31 (s, 1H), 5.17 (d, *J* = 6.9 Hz, 1H), 5.05 (d, *J* = 6.9 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.89 (s, 1H), 3.84 (s, 3H), 3.55 (s, 3H), 3.33 (s, 3H), 3.25 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz) δ 167.6, 166.6, 158.6, 156.2, 140.7, 140.1, 133.8, 130.0, 129.3, 127.4, 123.6, 119.4, 116.9, 111.3, 110.9, 109.7, 95.0, 85.1, 77.3, 60.5, 59.6, 56.6, 55.7, 30.2, 14.5.

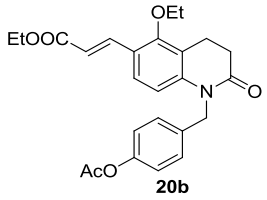
(*E*)-Ethyl 3-[(3*R,4*R**)-4,5-dihydroxy-3-methoxy-4-(4-methoxyphenyl)-1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl]acrylate [(±)-16]**



(±)-16

Substrate **(±)-15** (32.9 mg, 0.1 mmol) was olefinated using ethyl acrylate (16.3 μL, 0.15 mmol, 1.5 equiv), $PhCO_3^tBu$ (18.6 μL, 0.1 mmol, 1.0 equiv) at 80 °C for 16 h following the general procedure and the sample was purified by preparative TLC (PE/EtOAc, 2:1) to give a mixture of regioisomers: **(±)-16** (a) **and (±)-17** (b) (16.0 mg, 37%, yellow oil, a:b = 2:1) (For b, E/Z = 1.6:1). [*The ^{1}H NMR yield was also determined by using CH_2Br_2 as internal standard and only E-**(±)-16** and E-**(±)-17** were detected in 33% and 6% ^{1}H NMR yield respectively.*] **^{1}H NMR** [**(±)-16**] (400 MHz) δ 9.60 (s, 1H), 7.93 (d, *J* = 16.2 Hz, H), 7.54 (d, *J* = 8.6 Hz, H), 7.14 (d, *J* = 9.0 Hz, 2H), 6.84 (d, *J* = 9.0 Hz, 2H), 6.69 (d, *J* = 8.6 Hz, 1H), 6.55 (d, *J* = 16.1 Hz, 1H), 4.58 (s, 1H), 4.29 – 4.23 (m, 2H), 3.85 (s, 1H), 3.79 (s, 3H), 3.60 (s, 3H), 3.37 (s, 3H), 1.34 (t, *J* = 7.2 Hz, 3H).

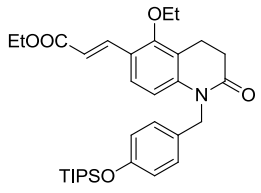
(*E*)-Ethyl 3-[1-(4-acetoxybenzyl)-5-ethoxy-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl]acrylate (20b)



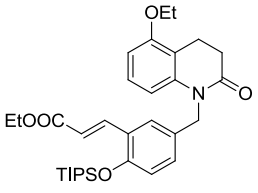
20b

Substrate **20a** (33.9 mg, 0.1 mmol) was olefinated using ethyl acrylate (16.3 µL, 0.15 mmol, 1.5 equiv), $PhCO_3{}^tBu$ (18.6 µL, 0.1 mmol, 1.0 equiv) at 80 °C for 16 h following the general procedure and the sample was purified by flash column chromatography (PE/EtOAc, 3:1 to 2:1) to give **20b** as a yellow oil (21.0 mg, 48%, *para*:others > 20:1). **^{1}H NMR** (400 MHz) δ 7.87 (d, *J* = 16.1 Hz, 1H), 7.34 (d, *J* = 8.7 Hz, 1H), 7.23 – 7.21 (m, 2H), 7.05 – 7.03 (m, 2H), 6.69 (d, *J* = 8.7 Hz, 1H), 6.37 (d, *J* = 16.1 Hz, 1H), 5.15 (s, 2H), 4.25 (q, *J* = 7.1 Hz, 2H), 3.87 (q, *J* = 7.0 Hz, 2H), 3.02 (dd, *J* = 8.6, 6.1 Hz, 2H), 2.78 – 2.72 (m, 2H), 2.28 (s, 3H), 1.44 (t, *J* = 7.0 Hz, 3H), 1.33 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz) δ 170.4, 169.6, 167.3, 155.8, 149.9, 142.8, 139.1, 134.4, 127.7, 126.8, 123.6, 122.0, 120.5, 118.1, 112.0, 70.8, 60.6, 45.9, 31.4, 21.3, 19.2, 15.7, 14.5. **IR**: ν 2927, 1761, 1681, 1371, 1166 cm^{-1}. **HRMS** (FD) calculated for $C_{25}H_{27}NO_6^+$ $[M]^+$: 437.1838; found: 437.1837.

(*E*)-Ethyl 3-(5-ethoxy-2-oxo-1-{4-[(triisopropylsilyl)oxy]benzyl}-1,2,3,4-tetrahydroquinolin-6-yl) acrylate (21b)



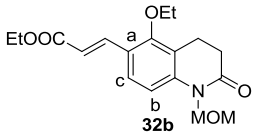
21b-I



21b-II

Substrate **21a** (113.4 mg, 0.25 mmol) was olefinated using ethyl acrylate (40.8 µL, 0.375 mmol, 1.5 equiv), $PhCO_3{}^tBu$ (46.5 µL, 0.25 mmol, 1.0 equiv) at 80 °C for 16 h following the general procedure and the sample was purified by preparative TLC (PE/EtOAc, 8:1) to give **21b-I** as a yellow oil (46 mg, 33%) and **21b-II** as a yellow oil (16 mg, 12%). A tiny quantity of diolefinated product was also observed. **^{1}H NMR** (**21b-I**) (400 MHz) δ 7.87 (d, *J* = 16.1 Hz, 1H), 7.31 (d, *J* = 8.6 Hz, 1H), 7.05 (d, *J* = 8.1 Hz, 2H), 6.81 (d, *J* = 8.3 Hz, 2H), 6.70 (d, *J* = 8.7 Hz, 1H), 5.09 (s, 2H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.85 (q, *J* = 7.0 Hz, 2H), 3.01 (dd, *J* = 8.6, 6.2 Hz, 2H), 2.74 (dd, *J* = 8.7, 6.0 Hz, 2H), 1.43 (t, *J* = 7.0 Hz, 3H), 1.32 (t, *J* = 7.1 Hz, 3H), 1.29 – 1.17 (m, 3H), 1.07 – 1.06 (m, 18H). **^{13}C NMR** (**21b-I**) (101 MHz) δ 170.4, 167.3, 155.7, 155.3, 143.0, 139.2, 129.1, 127.6, 126.7, 123.3, 120.5, 120.3, 117.9, 112.3, 70.8, 60.5, 46.0, 31.4, 19.2, 18.0, 15.6, 14.5, 12.7. **IR** (**21b-I**): ν 2943, 2866, 1681, 1509, 1254, 1162, 911, 684 cm^{-1}. **HRMS** (**21b-I**) (FD) calculated for $C_{32}H_{45}NO_5Si^+$ $[M]^+$: 551.3067; found: 551.3088.

(*E*)-Ethyl 3-[5-ethoxy-1-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl]acrylate (32b)

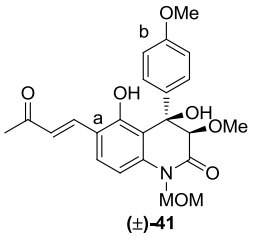


32b

Substrate **32a** (81.6 mg, 0.35 mmol) was olefinated using ethyl acrylate (57.0 µL, 0.525 mmol, 1.5 equiv), $PhCO_3{}^tBu$ (67.0 µL, 0.35 mmol, 1.0 equiv) at 80 °C for 16 h following the general procedure and the sample was purified by flash column chromatography (PE/EtOAc, 3:1) to give a mixture of **32b-a** and **32b-b** as a yellow oil (50.8 mg, 44%, **32b-a**:**32b-b** = 9.1:1) and **32b-c** as a yellow oil (1.7 mg, 1.5%). **^{1}H NMR** (400 MHz) (**32b-a**) δ 7.91 (d, *J* = 16.2 Hz, 1H), 7.46 (d, *J* = 8.5 Hz, 1H), 7.11 (d, *J* = 8.5 Hz, 1H), 6.43 (d, *J* = 16.1 Hz, 1H), 5.31 (s, 2H), 4.26 (q, *J* = 7.1 Hz, 2H), 3.86 (q, *J* = 6.4 Hz, 2H), 3.41 (s, 3H), 2.97 (t, *J* = 7.2 Hz, 2H), 2.76 – 2.63 (m, 2H), 1.43 (t, *J* = 6.3 Hz, 3H), 1.34 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (101 MHz) (**32b-a**) δ 171.1, 167.3, 155.6, 142.6, 139.2, 126.9, 123.9, 120.3, 118.2, 112.5, 74.0, 70.8, 60.5, 56.5, 31.3, 19.1, 15.6, 14.4. **IR** (**32b-a**): ν 2976, 1711, 1680, 1626, 1598, 1393, 1166, 1041 cm^{-1}. **HRMS** (FD) (**32b-a**) calculated for $C_{18}H_{23}NO_5$ $[M]^+$: 333.1576; found: 333.1575. **^{1}H NMR** (400 MHz) (**32b-c**) δ 7.64 (d, *J* = 16.0 Hz, 1H), 7.12 (d, *J* = 1.3 Hz, 1H), 6.79 (d, *J* = 1.4 Hz, 1H), 6.41 (d, *J* = 15.9 Hz, 1H), 5.31 (s, 2H), 4.27 (q, *J* = 7.1 Hz, 2H), 4.08 (q, *J* = 7.0 Hz, 2H), 3.41 (s, 3H), 2.95 – 2.92 (m, 2H), 2.66 (dd, *J* = 8.4, 6.3 Hz, 2H), 1.44 (t, *J* = 7.0 Hz, 3H), 1.34 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz) (**32b-c**) δ 171.4, 167.0, 156.0, 144.7, 141.3, 134.5, 118.5, 117.2, 109.0, 106.1, 74.2, 64.2, 60.7, 56.5, 31.2, 18.5, 15.0, 14.5. **IR** (**32b-c**): ν 2979, 2931, 1690, 1601, 1270, 1177 cm^{-1}. **HRMS** (FD) (**32b-c**) calculated for $C_{18}H_{23}NO_5^+$ $[M]^+$: 333.1576; found: 333.1575.

(3*R,4*R**)-4,5-Dihydroxy-3-methoxy-1-(methoxymethyl)-4-(4-methoxyphenyl)-6-[(E)-3-oxobut-1-en-1-yl]-3,4-dihydroquinolin-2(1*H*)-one [(±)-41]**

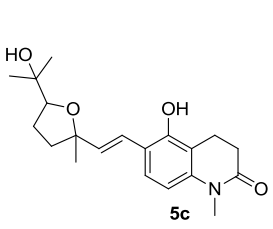
Substrate **(±)-40** (35.9 mg, 0.1 mmol) was olefinated using but-3-en-2-one (12.5 µL, 0.15 mmol, 1.5 equiv), $PhCO_3{}^tBu$ (28.5 µL, 0.15 mmol, 1.5 equiv) at 80 °C for 16 h following the general procedure and the sample was purified by flash column chromatography (PE/EtOAc, 2:1 to 1.5:1) to give **(±)-41** as a mixture of regioisomers (yellow oil, 22.3 mg, 52%, a:b = 5:1). **^{1}H NMR** (400 MHz) δ 9.55 (s, 1H), 7.84 (d, *J* = 16.5 Hz,



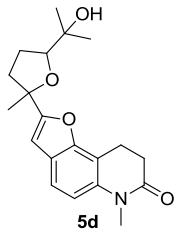
(±)-41

1H), 7.58 (d, *J* = 8.7 Hz, 1H), 7.17 – 7.15 (m, 2H), 6.96 (d, *J* = 8.7 Hz, 1H), 6.86 – 6.84 (m, 2H), 6.75 (d, *J* = 16.4 Hz, 1H), 5.59 (d, *J* = 10.8 Hz, 1H), 5.04 (d, *J* = 10.8 Hz, 1H), 4.61 (s, 1H), 3.88 (s, 1H), 3.78 (s, 4H), 3.62 (s, 3H), 3.35 (s, 3H), 2.37 (s, 3H). **^{13}C NMR** (101 MHz) δ 199.3, 166.1, 160.6, 156.9, 139.7, 138.1, 129.6, 128.3, 128.1, 127.1, 119.7, 114.5, 112.6, 108.0, 84.4, 78.2, 73.8, 59.0, 56.5, 55.4, 27.1. **IR**: ν 3254, 2853, 1691, 1606, 1441, 1366, 1255, 1076, 731 cm^{-1}. **HRMS** (FD) calculated for $C_{23}H_{25}NO_7^+$ [M]$^+$: 427.1631; found: 427.1618.

(*E*)-5-Hydroxy-6-{2-[5-(2-hydroxypropan-2-yl)-2-methyltetrahydrofuran-2-yl]vinyl}-1-methyl-3,4-dihydroquinolin-2(1*H*)-one (5c) and **2-[5-(2-hydroxypropan-2-yl)-2-methyltetrahydrofuran-2-yl]-6-methyl-8,9-dihydrofuro[2,3-f]quinolin-7(6*H*)-one (5d)**



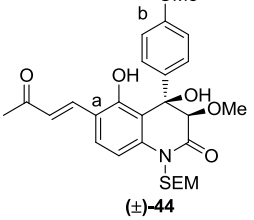
5c



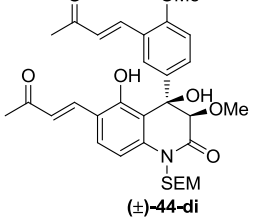
5d

Substrate **5a** (44.3 mg, 0.25 mmol) was olefinated using *trans*-**45** (63.8 mg, 0.375 mmol, 1.5 equiv), $PhCO_3{}^tBu$ (86.0 μL, 0.45 mmol, 1.8 equiv) at 80 °C for 16 h following the general procedure and the sample was purified by preparative TLC (PE/EtOAc, 3:1) to give **5c** as a yellow oil (41.4 mg, 48%, dr = 1.3:1) and **5d** as a yellow oil (15.4 mg, 18%). Another reaction was also performed using a mixture of *trans*-**45** and *cis*-**45** (1:1) as the olefin, same results were obtained regarding both the yield and diastereoselectivity. **^{1}H NMR** (**5c**) (300 MHz) (two diastereoisomers: A/B = 1:1.3) δ 7.17 (d, *J* = 8.5 Hz, $1H_B$), 7.15 (d, *J* = 8.5 Hz, $1H_A$), 6.83 (d, *J* = 16.0 Hz, $1H_A$), 6.71 (d, *J* = 15.9 Hz, $1H_B$), 6.55 (d, *J* = 8.5 Hz, $1H_B$), 6.54 (d, *J* = 8.5 Hz, $1H_A$), 6.12 (d, *J* = 15.9 Hz, $1H_A$), 6.10 (d, *J* = 15.9 Hz, $1H_B$), 3.96 – 3.90 (m, $1H_A$ and $1H_B$), 3.33 (s, $3H_B$), 3.33 (s, $3H_A$), 2.93 – 2.86 (m, $2H_A$ and $2H_B$), 2.63 – 2.57 (m, $2H_A$ and $2H_B$), 2.04 – 1.81 (m, $4H_A$ and $4H_B$), 1.42 (s, $3H_B$), 1.32 (s, $3H_A$), 1.18 (s, $3H_A$), 1.16 (s, $3H_B$). **^{13}C NMR** (**5c**) (75 MHz) δ 170.6 (A and B), 150.3 (A and B), 141.0 (A and B), 137.7 (A or B), 137.1 (A or B), 125.7 (A or B), 125.6 (A or B), 122.0 (A or B), 121.1 (A or B), 120.3 (A or B), 120.0 (A or B), 113.2 (A and B), 107.5 (A and B), 86.1 (A or B), 86.0 (A or B), 83.6 (A or B), 83.1 (A or B), 72.1 (A or B), 72.0 (A or B), 38.7 (A or B), 38.3 (A or B), 31.2 (A and B), 29.9 (A and B), 27.5 (A and B), 27.0 (A or B), 26.9 (A or B), 26.7 (A or B), 26.5 (A or B), 25.3 (A or B), 23.9 (A or B), 18.4 (A and B). **IR** (**5c**): ν 3306, 2972, 2929, 1652, 1624, 1472, 1372, 1126, 1041, 729 cm^{-1}. **HRMS** (FD) (**5c**) calculated for $C_{20}H_{25}NO_4$ [M]$^+$: 343.1784; found: 343.1771. **^{1}H NMR** (**5d**) (400 MHz) (two diastereoisomers: A and B. Ratio was not determined) δ 7.38 (d, *J* = 8.5 Hz, $1H_A$ and $1H_B$), 6.94 (d, *J* = 8.5 Hz, $1H_A$ and $1H_B$), 6.57 (s, $1H_A$ and $1H_B$), 4.05 – 4.01 (m, 1HA and 1HB), 3.44 (s, $3H_A$ and $3H_B$), 3.19 – 3.14 (m, $2H_A$ and $2H_B$), 2.77 – 2.72 (m, $2H_A$ and $2H_B$), 2.52 – 2.43 (m, $1H_A$ and $1H_B$), 2.10 – 1.97 (m, $3H_A$ and $3H_B$), 1.70 (s, $3H_A$), 1.69 (s, $3H_B$), 1.31 (s, $3H_A$), 1.30 (s, $3H_B$), 1.21 (s, $3H_B$), 1.20 (s, $3H_A$). **^{13}C NMR** (**5d**) (75 MHz) δ 170.2 (A and B), 162.4 (A and B), 152.4 (A or B), 152.2 (A or B), 137.8 (A or B), 137.6 (A or B), 124.0 (A or B), 123.8 (A or B), 119.0 (A or B), 118.9 (A or B), 110.9 (A or B), 110.8 (A or B), 109.7 (A and B), 101.5 (A or B), 101.3 (A or B), 86.7 (A and B), 81.0 (A or B), 80.7 (A or B), 71.5 (A or B), 71.3 (A or B), 38.6 (A or B), 37.5 (A or B), 31.3 (A and B), 30.3 (A and B), 27.9 (A and B), 27.4 (A or B), 27.1 (A or B), 26.7 (A or B), 26.6 (A or B), 24.7 (A or B), 24.4 (A or B), 18.7 (A or B), 18.6 (A or B). **IR** (**5d**): ν 3444, 2975, 2928, 1671, 1632, 1470, 1375, 1127, 1026, 819 cm^{-1}. **HRMS** (FD) (**5d**) calculated for $C_{20}H_{27}NO_4^+$ [M]$^+$: 345.1940; found: 345.1944.

(3*R,4*R**)-4,5-Dihydroxy-3-methoxy-4-(4-methoxyphenyl)-6-[(*E*)-3-oxobut-1-en-1-yl]-1-{[2-(trimethylsilyl)ethoxy]methyl}-3,4-dihydroquinolin-2(1*H*)-one [(±)-44]**



(±)-44

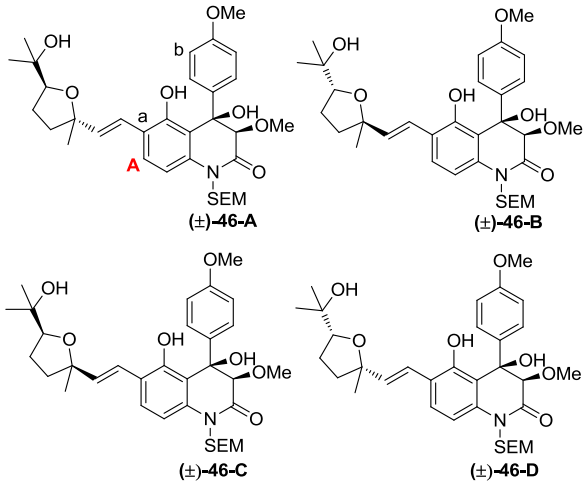


(±)-44-di

Substrate (±)-**43** (44.5 mg, 0.1 mmol) was olefinated using but-3-en-2-one (12.5 μL, 0.15 mmol, 1.5 equiv), $PhCO_3{}^tBu$ (38.0 μL, 0.2 mmol, 2.0 equiv) at 80 °C for 16 h following the general procedure and the sample was purified by flash column chromatography (*n*-hexane/EtOAc, 3:1) to give **(±)-44** as a mixture of regioisomers [30.3 mg, 59%, yellow oil, **(±)-44a**:**(±)-44b** = 6:1] and **(±)-44-di** (2.9 mg, 5%, yellow oil). **^{1}H NMR** (300 MHz) [**(±)-44a**] δ 9.52 (s, 1H), 7.82 (d, *J* = 16.5 Hz, 1H), 7.55 (d, *J* = 8.7 Hz, 1H), 7.15 – 7.10 (m, 2H), 6.99 (d, *J* = 8.6 Hz, 1H), 6.84 – 6.78 (m, 2H), 6.72 (d, *J* = 16.5 Hz, 1H), 5.61 (d, *J* = 10.9 Hz, 1H), 5.01 (d, *J* = 11.1 Hz, 1H), 4.62 (s, 1H), 3.84 (s, 1H), 3.75 (s, 3H),

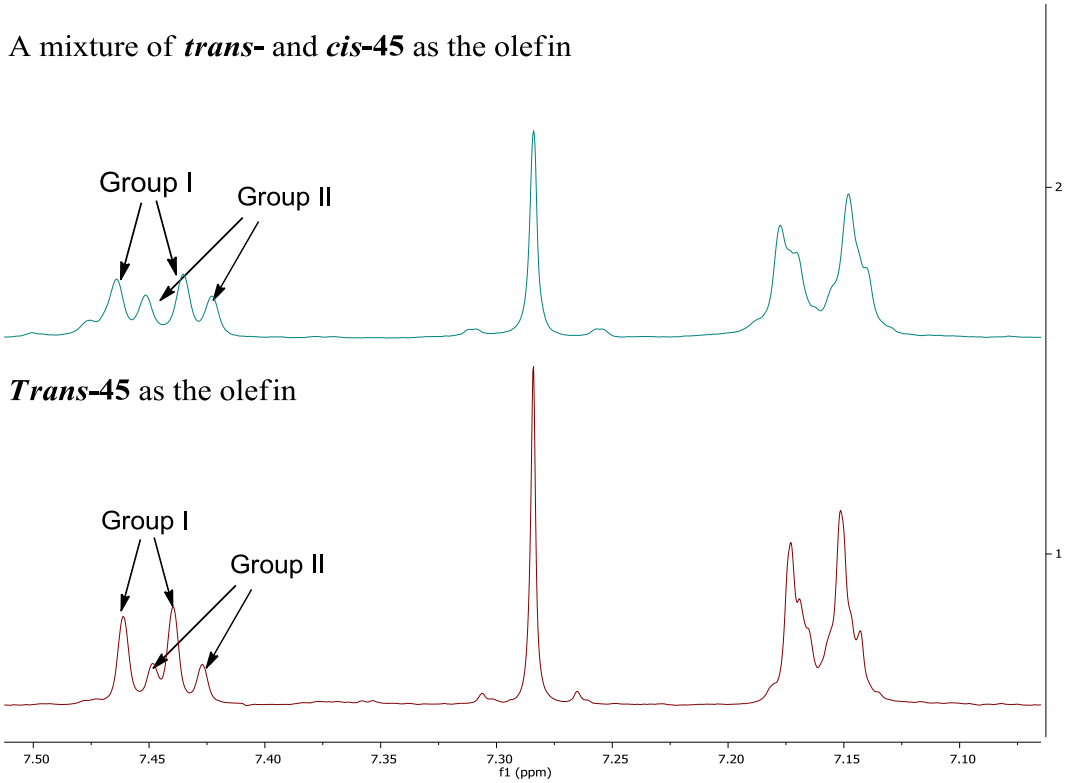
3.58 – 3.52 (m, 5H), 2.34 (s, 3H), 0.96 – 0.93 (m, 2H), -0.03 (s, 9H). **^{13}C NMR** (75 MHz) [**(±)-44a**] δ 199.3, 165.9, 160.6, 156.9, 139.9, 138.1, 129.5, 128.4, 128.1, 127.0, 119.5, 114.5, 112.6, 108.2, 84.4, 78.2, 72.0, 66.4, 58.9, 55.4, 27.0, 18.1, -1.3. **IR** [**(±)-44a**]: ν 3259, 2953, 2926, 1692, 1605, 1369, 1252, 1081, 834 cm^{-1}. **HRMS** (FD) [**(±)-44-a**] calculated for $C_{27}H_{35}NO_7Si^+$ [M]$^+$: 513.2183; found: 513.2208. **^{1}H NMR** (400 MHz) [**(±)-44-di**] δ 9.41 (s, 1H), 7.82 (d, *J* = 16.5 Hz, 1H), 7.75 (d, *J* = 16.5 Hz, 1H), 7.58 (d, *J* = 8.7 Hz, 1H), 7.53 (d, *J* = 2.4 Hz, 1H), 7.05 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.02 (d, *J* = 8.8 Hz, 1H), 6.81 (d, *J* = 8.8 Hz, 1H), 6.74 (d, *J* = 16.5 Hz, 1H), 6.67 (d, *J* = 16.5 Hz, 1H), 5.64 (d, *J* = 10.9 Hz, 1H), 5.01 (d, *J* = 10.8 Hz, 1H), 4.59 (s, 1H), 3.86 (s, 3H), 3.81 (s, 1H), 3.60 (s, 3H), 3.60 – 3.53 (m, 2H), 2.37 (s, 2H), 2.36 (s, 3H), 0.96 – 0.92 (m, 2H), -0.03 (s, 9H). **^{13}C NMR** (101 MHz) [**(±)-44-di**] δ 199.2, 199.1, 165.7, 159.1, 156.8, 139.8, 138.2, 137.9, 129.9, 129.8, 128.9, 128.7, 127.2, 127.2, 124.2, 119.8, 112.1, 111.6, 108.4, 84.3, 78.0, 72.1, 66.4, 59.0, 55.8, 27.4, 27.2, 18.1, -1.3. **IR** [**(±)-44-di**]: ν 3251, 2954, 1692, 1604, 1368, 1253, 1082, 836 cm^{-1}. **HRMS** (FD) [**(±)-44-di**] calculated for $C_{31}H_{39}NO_8Si^+$ [M]$^+$: 581.2445; found: 581.2443.

(*E*)-4,5-Dihydroxy-6-{2-[5-(2-hydroxypropan-2-yl)-2-methyltetrahydrofuran-2-yl]vinyl}-3-methoxy-4-(4-methoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-3,4-dihydroquinolin-2(1*H*)-one (46)

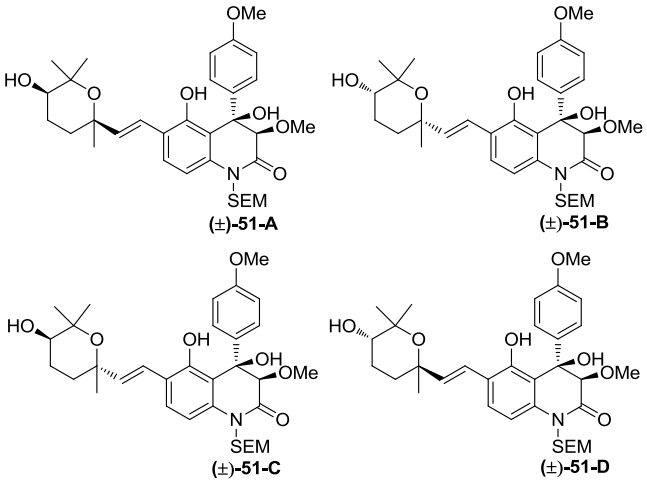


Substrate **(±)-43** (44.5 mg, 0.1 mmol) was olefinated using *trans*-**45** (25.5 mg, 0.15 mmol, 1.5 equiv), $PhCO_3{}^tBu$ (34.2 μL, 0.18 mmol, 1.8 equiv) at 80 °C for 16 h following the general procedure and the sample was purified by flash column chromatography (*n*-hexane/EtOAc, 3:1) to give **46** as a mixture of regioisomers (32.0 mg, 52%, yellow oil, a:b = 7:1, dr: not determined) [From ^{1}H NMR spectra of **46**, we mainly found two groups of peaks. That's because ^{1}H NMR of **(±)-46-A** and **(±)-46-B** were highly identical, while ^{1}H NMR of **(±)-46-C** and **(±)-46-D** were also highly identical. Therefore, we were not able to determine the ratios of **(±)-46-A**/**(±)-46**-B and **(±)-46-C**/**(±)-46-D**, but we assumed that they were both 1:1. Also, because of overlapping of these two groups of peaks, we were not able to determine the ratio of them. A reaction using a mixture of *trans*- and *cis*-**45** (1:1) as the olefin was also performed [0.1 mmol scale for **(±)-43**] and the product **46** was isolated as a mixture of regioisomers (a:b = 5.3:1) (30.0 mg, 50%, mixture of four diastereoisomers). Two sets of doublet peaks at around 7.45 ppm were from the proton located at A position of the products (see below the spectra). As shown in the spectra, group I should have a bigger integration than group II in both cases, although we couldn't calculate the exact ratio. Moreover, the ratio of the integration of group I and the integration of group II when using *trans*-**45** as the olefin is bigger than that when using a mixture of *trans*- and *cis*-**45** as the olefin. From these results we propose that group I belongs to **(±)-46-A** and **(±)-46-B**, that have the *trans*-conformation for the olefin moiety. Group II belongs to **(±)-46-C** **(±)-46-D**, that have the *cis*-conformation for the olefin moiety. **^{1}H NMR** (400 MHz) δ 9.19 (bs, 1H$_A$, 1H$_B$, 1H$_C$ and 1H$_D$), 7.43 (d, *J* = 8.6 Hz, 1H$_A$ and 1H$_B$), 7.41 (d, *J* = 8.6 Hz, 1H$_C$ and 1H$_D$), 7.16 – 7.11 (m, 2H$_A$, 2H$_B$, 2H$_C$ and 2H$_D$), 6.93 (d, *J* = 8.6 Hz, 1H$_A$, 1H$_B$, 1H$_C$ and 1H$_D$), 6.82 – 6.77 (m, 3H$_A$, 3H$_B$, 3H$_C$ and 3H$_D$), 6.33 (d, *J* = 16.4 Hz, 1H$_C$ or 1H$_D$), 6.32 (d, *J* = 16.4 Hz, 1H$_C$ or 1H$_D$), 6.28 (d, *J* = 16.3 Hz, 1H$_A$ or 1H$_B$), 6.27 (d, *J* = 16.3 Hz, 1H$_A$ or 1H$_B$), 5.62 (d, *J* = 10.9 Hz, 1H$_A$ and 1H$_B$), 5.61 (d, *J* = 10.9 Hz, 1H$_C$ and 1H$_D$), 4.98 (d, *J* = 11.0 Hz, 1H$_A$ and 1H$_B$), 4.97 (d, *J* = 11.0 Hz, 1H$_C$ and 1H$_D$), 4.47 (s, 1H$_A$, 1H$_B$, 1H$_C$ and 1H$_D$), 3.91 – 3.82 (m, 1H$_A$, 1H$_B$, 1H$_C$ and 1H$_D$), 3.80 (s, 1H$_A$, 1H$_B$, 1H$_C$ and 1H$_D$), 3.75 (s, 3H$_A$, 3H$_B$, 3H$_C$ and 3H$_D$), 3.59 – 3.52 (m, 2H$_A$, 2H$_B$, 2H$_C$ and 2H$_D$), 3.57 (s, 3H$_A$ and 3H$_B$), 3.56 (3H$_C$ and 3H$_D$), 2.05 – 1.73 (m, 4H$_A$, 4H$_B$, 4H$_C$ and 4H$_D$), 1.41 (s, 3H$_C$ and 3H$_D$), 1.40 (s, 3H$_A$ and 3H$_B$), 1.24 (s, 3H$_A$ and 3H$_B$), 1.23 (s, 3H$_C$ and 3H$_D$), 1.14 (s, 3H$_C$ and 3H$_D$), 1.13 (s, 3H$_A$ and 3H$_B$), 0.95 – 0.91 (m, 2H$_A$, 2H$_B$, 2H$_C$ and 2H$_D$), -0.03 (s, 9H$_A$, 9H$_B$, 9H$_C$ and 9H$_D$). **^{13}C NMR** (101 MHz) δ 165.9 (A, B, C and D), 160.4 (A, B, C and D), 154.9 (A, B, C and D), 137.2 (C or D), 137.1 (C or D), 137.0 (A and B), 136.0 (C or D), 135.9 (C or D), 135.6 (A or B), 135.5 (A or B), 128.9 (A and B), 128.8 (C and D), 128.2 (A, B, C and D), 127.8 (A or B), 127.7 (A or B), 127.6 (C and D), 122.3 (A, B, C and D), 121.3 (C and D), 120.9 (A and B), 114.4 (A, B, C and D), 112.2 (A, B, C and D), 107.7 (A, B, C and D), 85.8 (C and D), 85.7 (A and B), 84.7 (A, B, C and D), 83.4 (A and B), 83.2 (C and D), 78.3 (A, B, C and D), 72.1 (A, B, C and D), 71.3

(A and B), 71.2 (C and D), 66.2 (A, B, C and D), 58.9 (A, B, C and D), 55.4 (A, B, C and D), 38.7 (C or D), 38.6 (C or D), 38.1 (A and B), 27.5 (A, B, C and D), 26.6 (A, B, C and D), 24.3 (A, B, C and D), 18.1 (A, B, C and D), -1.3 (A, B, C and D). **IR**: ν 3295, 2967, 2929, 1688, 1611, 1511, 1441, 1374, 1082, 835 cm^{-1}. **HRMS** (FD) calculated for $C_{33}H_{47}NO_8Si^+$ $[M]^+$: 613.3071; found: 613.3064.



(*E*)-4,5-Dihydroxy-6-[2-(5-hydroxy-2,6,6-trimethyltetrahydro-2H-pyran-2-yl)vinyl]-3-methoxy-4-(4-methoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-3,4-dihydroquinolin-2(1*H*)-one (51)

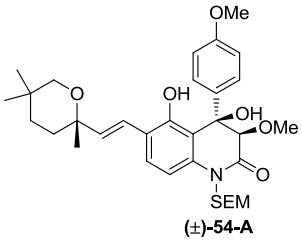


Substrate **(±)-43** (44.5 mg, 0.1 mmol) was olefinated using olefin *cis*-**50** (36.4 mg, 0.15 mmol, 1.5 equiv), $PhCO_3{}^tBu$ (34.2 µL, 0.18 mmol, 1.8 equiv) at 80 ℃ for 16 h following the general procedure. Before performing purification, the crude sample was deprotected by using the following procedure:

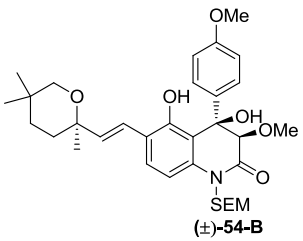
The sample was dissolved in THF (2 mL) and TBAF solution (1.0 mL, 1.0 M in THF) was added dropwise. After stirring it for 4 h, the reaction was quenched by adding water. The mixture was extracted with EtOAc three times. The combined extracts were washed with brine, dried with $MgSO_4$ and evaporated in *vacuo*. the sample was purified by preparative TLC (*n*-hexane/EtOAc, 4:1) to give **51** as a single regioisomer (26.3 mg, 43%, yellow oil, dr = 2.2:2.2:1:1). **^{1}H NMR** (300 MHz) [two groups of diastereoisomers: (A+B)/(C+D) = 2.2:1] 9.21 – 9.19 (m, $1H_A$, $1H_B$, $1H_C$ and $1H_D$), 7.45 (d, J = 8.6 Hz, $1H_A$), 7.45 (d, J = 8.6 Hz, $1H_A$ and $1H_B$), 7.44 (d, J = 8.6 Hz, $1H_C$ and $1H_D$), 7.19 – 7.14 (m, $2H_A$, $2H_B$, $2H_C$ and $2H_D$), 6.96 (d, J = 8.7 Hz, $1H_A$, $1H_B$, $1H_C$ and $1H_D$), 6.89 – 6.79 (m, $3H_A$, $3H_B$, $3H_C$ and $3H_D$), 6.38 – 6.26 (m, $1H_A$, $1H_B$, $1H_C$ and $1H_D$), 5.64 (d, J = 10.9 Hz, $1H_A$, $1H_B$, $1H_C$ and $1H_D$), 5.01 (d, J = 10.9 Hz, $1H_A$, $1H_B$, $1H_C$ and $1H_D$), 4.48 (s, $1H_A$ and $1H_B$), 4.47 (s, $1H_C$ and $1H_D$), 3.95 – 3.88 (m, $1H_A$, $1H_B$, $1H_C$ and $1H_D$), 3.78 (s, $3H_A$, $3H_B$, $3H_C$ and $3H_D$), 3.62 – 3.54 (m, $2H_A$, $2H_B$, $2H_C$ and $2H_D$), 3.59 (s, $3H_A$, $3H_B$, $3H_C$ and $3H_D$), 2.08 – 1.70 (m, $4H_A$, $4H_B$, $4H_C$ and $4H_D$), 1.44 (s, $3H_C$ and $3H_D$), 1.42 ($3H_A$ and $3H_C$), 1.26 (s, $3H_A$, $3H_B$, $3H_C$ and $3H_D$), 1.16 (s, $3H_A$, $3H_B$, $3H_C$ and $3H_D$), 0.98 – 0.92 (m, $2H_A$, $2H_B$, $2H_C$ and $2H_D$), -0.01 (s, $9H_A$, $9H_B$, $9H_C$ and $9H_D$). **^{13}C NMR** (75 MHz) δ 167.2 (A, B, C and D),

161.7 (A, B, C and D), 156.1 (A, B, C and D), 138.4 (C and D), 136.8 (A and B), 137.3 (C or D), 137.1 (C or D), 136.8 (A and B), 130.1 (A, B, C and D), 129.4 (A, B, C and D), 129.1 (A or B), 129.0 (A or B), 128.9 (C or D), 128.8 (C or D), 123.6 (A or B), 123.5 (A or B), 123.51 (C and D), 122.6 (C or D), 122.5 (C or D), 122.2 (A or B), 122.1 (A or B), 115.6 (A, B, C and D), 113.5 (A, B, C and D), 109.0 (A, B, C and D), 87.1 (C and D), 86.9 (A and B), 85.9 (A, B, C and D), 84.7 (A and B), 84.4 (C and D), 79.5 (A, B, C and D), 73.4 (A, B, C and D), 72.6 (A, B, C and D), 67.5 (A and B), 67.4 (C and D), 60.1 (A, B, C and D), 56.6 (A, B, C and D), 40.0 (C or D), 39.9 (C or D), 39.4 (A and B), 29.0 (C or D), 28.9 (C or D), 28.8 (A and B), 28.7 (A, B, C and D), 28.0 (C and D), 27.8 (A and B), 25.8 (C and D), 25.6 (A and B), 19.4 (A, B, C and D), 0.0 (A, B, C and D). **IR**: ν 3296, 2956, 2927, 1688, 1611, 1511, 1441, 1250, 1082, 834 cm^{-1}. **HRMS** (FD) calculated for $C_{33}H_{47}NO_8Si^+$ $[M]^+$: 613.3071; found: 613.3084.

(*E*)-4,5-Dihydroxy-3-methoxy-4-(4-methoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-6-[2-(2,5,5-trimethyltetrahydro-2H-pyran-2-yl)vinyl]-3,4-dihydroquinolin-2(1*H*)-one (54)



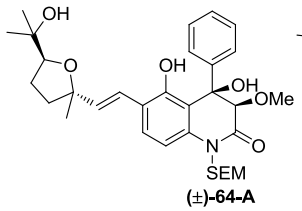
(±)-54-A



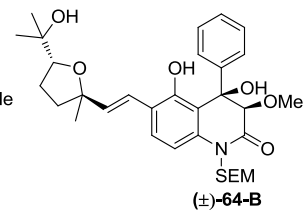
(±)-54-B

Substrate **(±)-43** (111.2 mg, 0.25 mmol) was olefinated using olefin **53** (57.8 mg, 0.375 mmol, 1.5 equiv), $PhCO_3{}^tBu$ (86.0 µL, 0.45 mmol, 1.8 equiv) at 80 °C for 16 h following the general procedure and the sample was purified by preparative TLC (*n*-hexane/acetone, 6:1) to give **54** as a mixture of regioisomers (75.0 mg, 50%, yellow oil, regioselectivity: 8.7:1, dr = 1:1). **^{1}H NMR** (400 MHz) (two diastereoisomers: A and B) δ 9.18 (bs, $1H_A$ or $1H_B$), 9.17 (bs, $1H_A$ or $1H_B$), 7.48 (d, *J* = 8.6 Hz, $1H_A$ and $1H_B$), 7.18 – 7.13 (m, $2H_A$ + $2H_B$), 6.96 (d, *J* = 8.6 Hz, $1H_A$ and $1H_B$), 6.83 – 6.80 (m, $2H_A$ + $2H_B$), 6.77 (d, *J* = 16.7 Hz, $1H_A$ and $1H_B$), 6.18 (d, *J* = 16.7 Hz, $1H_A$ or $1H_B$), 6.17 (d, *J* = 16.7 Hz, $1H_A$ or $1H_B$), 5.63 (d, *J* = 10.9 Hz, $1H_A$ and $1H_B$), 4.99 (d, *J* = 10.9 Hz, $1H_A$ and $1H_B$), 4.45 (s, $1H_A$ and $1H_B$), 3.81 (s, $1H_A$ or $1H_B$), 3.80 (s, $1H_A$ or $1H_B$), 3.76 (s, $3H_A$ or $3H_B$), 3.75 (s, $3H_A$ or $3H_B$), 3.59 – 3.53 (m, $2H_A$ + $2H_B$), 3.58 (s, $3H_A$ or $3H_B$), 3.57 (s, $3H_A$ or $3H_B$), 3.41 – 3.36 (m, $1H_A$ + $1H_B$), 3.25 – 3.21 (m, $1H_A$ + $1H_B$), 1.86 – 1.79 ($1H_A$ + $1H_B$), 1.75 – 1.67 ($1H_A$ + $1H_B$), 1.52 – 1.44 ($1H_A$ + $1H_B$), 1.36 – 1.32 ($1H_A$ + $1H_B$), 1.31 (s, $3H_A$ and $3H_B$), 1.01 (s, $3H_A$ or $3H_B$), 1.00 (s, $3H_A$ or $3H_B$), 0.95 – 0.91 ($2H_A$ + $2H_B$), 0.79 (s, $3H_A$ and $3H_B$), -0.03 (s, $9H_A$ and $9H_B$). **^{13}C NMR** (101 MHz) δ 165.9 (A and B), 160.5 (A and B), 154.7 (A and B), 137.1 (A and B), 134.8, 134.7, 128.8 (A and B), 128.2 (A and B), 127.4, 127.3, 123.3 (A and B), 122.4 (A and B), 114.4 (A and B), 112.3 (A and B), 107.7 (A and B), 84.7 (A and B), 78.3 (A and B), 74.5 (A and B), 73.0, 72.9, 72.1 (A and B), 66.2 (A and B), 58.9 (A and B), 55.4 (A and B), 33.7 (A and B), 31.3, 31.1, 29.9 (A and B), 29.4, 29.2, 26.8 (A and B), 24.2, 24.1, 18.2 (A and B), -1.3 (A and B). **IR**: ν 3314, 2950, 1690, 1611, 1511, 1441, 1390, 1250, 1083, 834 cm^{-1}. **HRMS** (FD) calculated for $C_{33}H_{47}NO_7Si^+$ $[M]^+$: 597.3122; found: 597.3134.

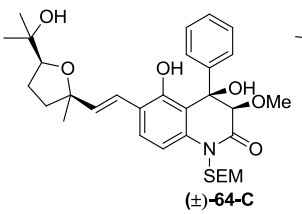
(*E*)-4,5-Dihydroxy-6-{2-[5-(2-hydroxypropan-2-yl)-2-methyltetrahydrofuran-2-yl]vinyl}-3-methoxy-4-phenyl-1-{[2-(trimethylsilyl)ethoxy]methyl}-3,4-dihydroquinolin-2(1*H*)-one (64)



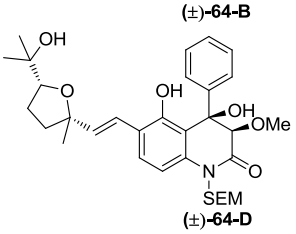
(±)-64-A



(±)-64-B



(±)-64-C

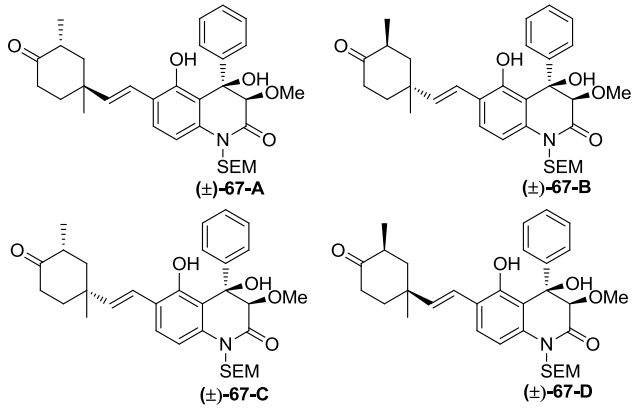


(±)-64-D

Substrate **(±)-63** (41.6 mg, 0.1 mmol) was olefinated using olefin *trans*-**45** (25.5 mg, 0.15 mmol, 1.5 equiv), $PhCO_3{}^tBu$ (34.2 µL, 0.18 mmol, 1.8 equiv) at 80 °C for 16 h following the general procedure and the sample was purified by flash column chromatography (*n*-hexane/EtOAc, 4:1) to give **64** as a yellow oil (28.0 mg, 48%, regioselectivity: > 20:1, dr = 5.5:5.5:1:1). **^{1}H NMR** (400 MHz) [two groups of diastereoisomers: (A+B)/(C+D) = 5.5:1] δ 9.16 (A and B), 9.14 (C and D), 7.44 (d, *J* = 8.6 Hz, $1H_A$ and $1H_B$), 7.42 (d, *J* = 8.6 Hz, $1H_A$ and $1H_B$), 7.32 – 7.27 (m, $3H_A$, $3H_B$, $3H_C$ and $3H_D$), 7.25 – 7.21 (m, $2H_A$, $2H_B$, $2H_C$ and $2H_D$), 6.95 (d, *J* = 8.6 Hz, $1H_A$, $1H_B$, $1H_C$ and $1H_D$), 6.83 (d, *J* = 16.3 Hz, $1H_C$ and $1H_D$), 6.79 (d, *J* = 16.3 Hz, $1H_A$ and $1H_B$), 6.33 (d, *J* = 16.2 Hz, $1H_C$ or $1H_D$), 6.32 (d, *J* = 16.2 Hz, $1H_C$ or $1H_D$), 6.28 (d, *J* = 16.2 Hz, $1H_A$ or $1H_B$), 6.27 (d, *J* = 16.2 Hz, $1H_A$ or $1H_B$), 5.64 (d, *J* = 10.9 Hz,

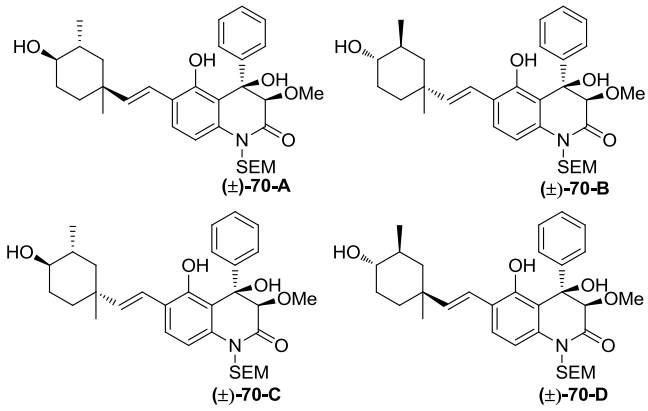
$1H_A$ and $1H_B$), 5.63 (d, *J* = 10.9 Hz, $1H_C$ and $1H_D$), 5.00 (d, *J* = 10.9 Hz, $1H_A$ and $1H_B$), 4.99 (d, *J* = 10.9 Hz, $1H_C$ and $1H_D$), 4.55 (s, $1H_A$ or $1H_B$), 4.54 (s, $1H_A$ or $1H_B$), 4.53 (C and D), 3.91 – 3.82 (m, $1H_A$, $1H_B$, $1H_C$ and $1H_D$), 3.80 (C and D, A or B), 3.79 (A or B), 3.58 (s, $3H_A$ and $3H_B$), 3.57 (s, $3H_C$ and $3H_D$), 3.59 – 3.53 (m, $2H_A$, $2H_B$, $2H_C$ and $2H_D$), 2.04 – 1.98 (m, $1H_A$, $1H_B$, $1H_C$ and $1H_D$), 1.94 – 1.71 (m, $3H_A$, $3H_B$, $3H_C$ and $3H_D$), 1.40 (s, $3H_A$, $3H_B$, $3H_C$ and $3H_D$), 1.24 (s, $3H_A$ and $3H_B$), 1.23 (s, $3H_C$ and $3H_D$), 1.43 (s, $3H_A$, $3H_B$, $3H_C$ and $3H_D$), 0.96 – 0.92 (m, $2H_A$, $2H_B$, $2H_C$ and $2H_D$), -0.03 (s, $9H_A$, $9H_B$, $9H_C$ and $9H_D$). **^{13}C NMR** (126 MHz) δ 165.8 (A, B, C and D), 154.9 (A, B, C and D), 139.0 (A, B, C and D), 137.2 (A, B, C and D), 136.1 (C or D), 136.0 (C or D), 135.7 (A or B), 135.6 (A or B), 129.5 (A, B, C and D), 129.0 (A, B, C and D), 127.9 (A or B), 127.8 (A or B), 127.7 (C and D), 126.7 (A, B, C and D), 122.4 (A, B, C and D), 121.3 (C or D), 121.2 (C or D), 120.9 (A or B), 120.8 (A or B), 121.2 (A, B, C and D), 107.8 (A, B, C and D), 85.9 (C or D), 85.8 (C or D), 85.7 (A and B), 84.6 (A, B, C and D), 83.8 (A and B), 83.2 (C or D), 82.8 (C or D), 78.5 (A, B, C and D), 72.2 (A, B, C and D), 71.4 (C and D), 71.3 (A and B), 66.3 (A, B, C and D), 58.9 (A, B, C and D), 38.7 (C or D), 38.6 (C or D), 38.1 (A and B), 27.7 (A, B, C and D), 27.5 (A, B, C and D), 26.7 (C and D), 26.36 (A and B), 24.6 (C and D), 24.3 (A and B), 18.2 (A, B, C and D), -1.2 (A, B, C and D). **IR**: ν 3291, 2967, 1687, 1612, 1440, 1374, 1244, 1079, 836 cm^{-1}. **HRMS** (FD) calculated for $C_{32}H_{45}NO_7Si^+$ $[M]^+$: 583.2965; found: 583.2972.

(*E*)-6-[2-(1,3-Dimethyl-4-oxocyclohexyl)vinyl]-4,5-dihydroxy-3-methoxy-4-(4-methoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-3,4-dihydroquinolin-2(1*H*)-one (67)



Substrate **(±)-63** (103.9 mg, 0.25 mmol) was olefinated using olefin **66** (dr = 5:4, 57.1 mg, 0.375 mmol, 1.5 equiv), $PhCO_3{}^tBu$ (86.0 µL, 0.45 mmol, 1.8 equiv) at 80 °C for 16 h following the general procedure and the sample was purified by flash column chromatography (*n*-hexane/EtOAc, 2.5:1) to give **67** as a yellow oil (48.0 mg, 34%, regioselectivity > 20:1, dr = 1:1:1.6:1.6). **^{1}H NMR** (400 MHz) [two groups of diastereoisomers: (A+B)/(C+D) = 1:1.6] δ 9.18 (s, $1H_A$ and $1H_B$), 9.17 (C and D), 7.49 (d, *J* = 8.7 Hz, $1H_A$ and $1H_B$), 7.42 (d, *J* = 8.6 Hz, $1H_C$ and $1H_D$), 7.31 – 7.21 (m, $5H_A$, $5H_B$, $5H_C$ and $5H_D$), 6.98 (d, *J* = 8.7 Hz, $1H_A$ and $1H_B$), 6.95 (d, *J* = 8.6 Hz, $1H_C$ and $1H_D$), 6.82 (d, *J* = 16.6 Hz, $1H_A$ and $1H_B$), 6.65 (d, *J* = 16.5 Hz, $1H_C$ and $1H_D$), 6.31 (d, *J* = 16.6 Hz, $1H_A$ and $1H_B$), 6.18 (d, *J* = 16.4 Hz, $1H_C$ and $1H_D$), 5.65 (d, *J* = 10.9 Hz, $1H_A$ and $1H_B$), 5.63 (d, *J* = 10.9 Hz, $1H_C$ and $1H_D$), 5.02 (d, *J* = 10.8 Hz, $1H_A$ and $1H_B$), 5.00 (d, *J* = 10.8 Hz, $1H_C$ and $1H_D$), 4.59 (s, $1H_A$ and $1H_B$), 4.58 (s, $1H_C$ and $1H_D$), 3.80 (s, $1H_A$, $1H_B$, $1H_C$ and $1H_D$), 3.59 – 3.53 (m, $2H_A$, $2H_B$, $2H_C$ and $2H_D$), 3.58 (s, $3H_A$ and $3H_B$), 3.57 (s, $3H_C$ and $3H_D$), 2.66 – 2.46 (m, $2H_A$, $2H_B$, $2H_C$ and $2H_D$), 2.37 – 2.09 (m, $2H_A$, $2H_B$, $2H_C$ and $2H_D$), 1.91 – 1.84 (m, $1H_A$, $1H_B$, $1H_C$ and $1H_D$), 1.76 – 1.68 (m, $1H_C$ and $1H_D$), 1.63 – 1.55 (m, $1H_A$ and $1H_B$), 1.51 – 1.43 (m, $1H_A$, $1H_B$, $1H_C$ and $1H_D$), 1.40 (s, $3H_C$ and $3H_D$), 1.11 (s, $3H_A$ and $3H_B$), 1.02 (d, *J* = 6.4 Hz, $3H_C$ and $3H_D$), 0.99 (d, *J* = 6.5 Hz, $3H_A$ and $3H_B$), 0.95 – 0.91 (m, $2H_A$, $2H_B$, $2H_C$ and $2H_D$), -0.03 (s, $9H_A$, $9H_B$, $9H_C$ and $9H_D$). **^{13}C NMR** (75 MHz) δ 213.9 (A and B), 213.5 (C and D), 165.8 (A, B, C and D), 154.5 (A, B, C and D), 139.9 (A, B, C and D), 137.2 (A or B), 137.1 (C or D), 137.1 (A or B), 137.0 (C or D), 136.2 (A, B, C and D), 129.5 (A and B), 129.0 (C and D), 129.0 (A, B, C and D), 127.2 (A, B, C and D), 126.6 (A, B, C and D), 122.8 (C and D), 122.6 (A and B), 119.8 (A, B, C and D), 112.3 (A and B), 112.2 (C and D), 107.8 (A, B, C and D), 84.6 (A, B, C and D), 78.5 (A, B, C and D), 72.1 [(A and B) or (C and D)], 71.5 [(A and B) or (C and D)], 66.3 [(A and B) or (C and D)], 66.0 [(A and B) or (C and D)], 58.9 (A, B, C and D), 47.7 (A and B), 46.9 (C or D), 46.8 (C or D), 41.4 (A and B), 40.8 (C and D), 38.7 (A, B, C and D), 38.5 (A and B), 38.2 (C or D), 38.1 (C or D), 38.0 (C and D), 37.5 (A and B), 30.6 (A, B, C and D), 18.2 (A, B, C and D), 14.7 (C and D), 14.6 (A and B), -1.3 (A, B, C and D). **IR**: ν 3294, 2955, 2926, 1689, 1612, 1439, 1376, 1246,1079, 836 cm^{-1}. **HRMS** (FD) calculated for $C_{32}H_{43}NO_6Si^+$ $[M]^+$: 565.2860; found: 565.2885.

(*E*)-4,5-Dihydroxy-6-[2-(4-hydroxy-1,3-dimethylcyclohexyl)vinyl]-3-methoxy-4-(4-methoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-3,4-dihydroquinolin-2(1*H*)-one (70)



Substrate **(±)-63** (41.6 mg, 0.1 mmol) was olefinated using olefin **69** (dr = 5:4, 23.1 mg, 0.15 mmol, 1.5 equiv), $PhCO_3{}^tBu$ (34.2 μL, 0.18 mmol, 1.8 equiv) at 80 ℃ for 16 h following the general procedure and the sample was purified by flash column chromatography (*n*-hexane/EtOAc, 3:1 to 1:1) to give **70** as a yellow oil (22.0 mg, 39%, regioselectivity: > 20:1, dr = 1:1:1:1). **^{1}H NMR** (400 MHz) [two groups of diastereoisomers: (A+B)/(C+D) = 1:1] δ 9.13 [s, ($1H_A$ and $1H_B$) or ($1H_C$ and $1H_D$)], 9.11 [s, ($1H_A$ and $1H_B$) or ($1H_C$ and $1H_D$)], 7.45 [d, *J* = 8.6 Hz, ($1H_A$ and $1H_B$) or ($1H_C$ and $1H_D$)], 7.43 [d, *J* = 8.6 Hz, ($1H_A$ and $1H_B$) or ($1H_C$ and $1H_D$)], 7.31 – 7.21 (m, $5H_A$, $5H_B$, $5H_C$ and $5H_D$), 6.95 [d, *J* = 8.6 Hz, ($1H_A$ and $1H_B$) or ($1H_C$ and $1H_D$)], 6.93 [d, *J* = 8.6 Hz, ($1H_A$ and $1H_B$) or ($1H_C$ and $1H_D$)], 6.63 [d, *J* = 16.7 Hz, ($1H_A$ and $1H_B$) or ($1H_C$ and $1H_D$)], 6.59 [d, *J* = 16.7 Hz, ($1H_A$ and $1H_B$) or ($1H_C$ and $1H_D$)], 6.17 [d, *J* = 16.4 Hz, ($1H_A$ and $1H_B$) or ($1H_C$ and $1H_D$)], 6.16 [d, *J* = 8.6 Hz, ($1H_A$ and $1H_B$) or ($1H_C$ and $1H_D$)], 5.63 (d, *J* = 10.9 Hz, $1H_A$, $1H_B$,$1H_C$ and $1H_D$), 5.00 (d, *J* = 10.9 Hz, $1H_A$, $1H_B$,$1H_C$ and $1H_D$), 4.55 (s, $1H_A$, $1H_B$, $1H_C$ and $1H_D$), 3.79 (s, $1H_A$, $1H_B$, $1H_C$ and $1H_D$), 3.57 (s, $3H_A$, $3H_B$, $3H_C$ and $3H_D$), 3.59 – 3.53 (m, $2H_A$, $2H_B$, $2H_C$ and $2H_D$), 3.15 – 3.06 (m, $1H_A$, $1H_B$, $1H_C$ and $1H_D$), 1.88 – 1.73 (m, $3H_A$, $3H_B$, $3H_C$ and $3H_D$), 1.66 – 1.20 (m, $4H_A$, $4H_B$, $3H_C$ and $3H_D$), 1.14 (s, $3H_C$ and $3H_D$), 1.07 (t, *J* = 12.9 Hz, $1H_A$ and $1H_B$), 1.06 (s, $3H_A$ and $3H_B$), 1.01 – 0.98 (m, $3H_A$, $3H_B$, $3H_C$ and $3H_D$). **^{13}C NMR** (101 MHz) δ 165.8 (A, B, C and D), 154.4 [(A and B) or (C and D)], 154.3 [(A and B) or (C and D)], 142.3 (A, B, C and D), 138.0 (A, B, C and D), 137.2 (A, B, C and D), 129.5 (A, B, C and D), 129.0 (A, B, C and D), 127.1 [(A and B) or (C and D)], 127.0 [(A and B) or (C and D)], 126.7 (A, B, C and D), 123.3 (A, B, C and D),121.6 (A, B, C and D), 112.1 (A, B, C and D), 107.8 [(A and B) or (C and D)], 107.7 [(A and B) or (C and D)], 84.6 (A, B, C and D), 78.5 (A, B, C and D), 76.3 (A, B, C and D), 72.1 (A, B, C and D), 66.2 (A, B, C and D), 58.9 (A, B, C and D), 46.0 [(A and B) or (C and D)], 44.8 [(A and B) or (C and D)], 37.4 (A, B, C and D), 37.4 (A, B, C and D), 37.2 (A, B, C and D), 34.0 (C and D), 32.9 (A and B), 32.1 [(A and B) or (C and D)], 32.0 [(A and B) or (C and D)], 18.8 [(A and B) or (C and D)], 18.7 [(A and B) or (C and D)], 18.2 (A, B, C and D), -1.3 (A, B, C and D). **IR**: ν 3338, 2952, 2926, 2855, 1689, 1612, 1440, 1375, 1247, 1080, 1043, 804 cm^{-1}. **HRMS** (FD) calculated for $C_{32}H_{45}NO_6Si^+$ $[M]^+$: 567.3016; found: 567.3011.

4.5.6 Deprotection of SEM to complete the total synthesis of yaequinolone natural products

General procedure for the deprotection of SEM with TBAF

In a 10 mL round bottom flask containing the substrate (1.0 equiv) was added a solution of TBAF (1.0 M in THF, 10 – 15 equiv) (In the cases where more concentrated TBAF was required, after mixing TBAF solution with substrate in the flask, the THF was quickly evaporated using rotary evaporator and the right amount of THF was then added). The reaction was then left to stir under reflux at 80 ℃ overnight. The reaction was then quenched by adding water. The mixture was extracted with EtOAc three times. The combined extracts were washed with brine, dried with Na_2SO_4, filtrated and concentrated *in vacuo*. The sample was purified by flash column chromatography.

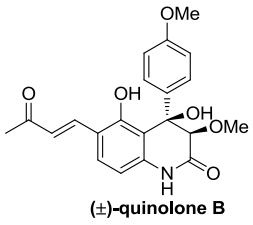
General procedure for the deprotection of SEM with Me_2AlCl

In a flame-dried Schlenk flask was added substrate (1.0 equiv) and anhydrous DCM (0.4 – 0.5 M) under N_2. A solution of Me_2AlCl (1.0 in hexanes, 6.0 equiv) was then added dropwise at -78 ℃ and the reaction was stirred for 1 h before it was warmed up to 0 ℃. After stirring it for another 1 h, the reaction was quenched by adding water. The mixture was extracted with EtOAc three times. The combined extracts were washed with brine, dried with Na_2SO_4, filtrated and concentrated *in vacuo* to give hydroxymethyl protected intermediate, which was then mixed with MeOH (0.4 – 0.5 M) and $^iPr_2NEt$ (7.0 equiv) and heated at 55 ℃ overnight. The reaction was quenched by adding saturated aqueous solution of NH_4Cl and extracted with EtOAc three times. The combined extracts were washed with brine, dried with Na_2SO_4 and concentrated *in vacuo*. The sample was purified by

flash column chromatography.

(±)-Yaequinolone B

SEM deprotection of **(±)-44** with TBAF:



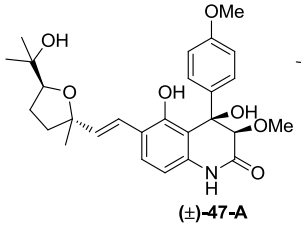
(±)-quinolone B

20 mg of **(±)-44** [regioisomers (6:1), 0.039 mmol, 1.0 equiv] and 600 μL TBAF (1.0 M in THF, 15 equiv) solution were used. Purification was performed using *n*-hexane/EtOAc (1:1) as eluent to give **(±)-yaequinolone B** as a single regioisomer (pale yellow solid, 9.0 mg, 60%). **^{1}H NMR** (400 MHz) δ 9.44 (s, 1H), 7.80 (d, *J* = 16.5 Hz, 1H), 7.70 (bs, 1H), 7.49 (d, *J* = 8.4 Hz, 1H), 7.20 – 7.13 (m, 2H), 6.86 – 6.78 (m, 2H), 6.70 (d, *J* = 16.5 Hz, 1H), 6.40 (d, *J* = 8.3 Hz, 1H), 4.62 (s, 1H), 3.77 (s, 3H), 3.73 (d, *J* = 1.5 Hz, 1H), 3.62 (s, 3H), 2.35 (s, 3H). **^{13}C NMR** (100 MHz) δ 199.3, 165.5, 160.6, 157.5, 138.1, 137.2, 129.8, 128.6, 127.9, 126.8, 119.3, 114.5, 111.2, 107.5, 84.0, 78.8, 59.1, 55.5, 27.1. **IR**: ν 3251, 2926, 1691, 1599, 1257, 1079, 805 cm^{-1}. Its data matched with those reported in the literature.[9]

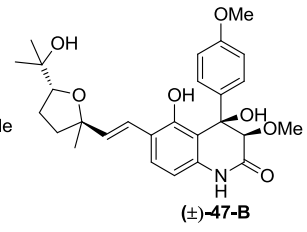
Deprotection of **(±)-44** with Me_2AlCl:

20 mg of **(±)-44** [regioisomers (5.5:1), 0.039 mmol, 1.0 equiv] was used and the product was isolated as a mixture of regioisomers (4.3:1) (pale yellow solid, 9.9 mg, 68%) after purification with *n*-hexane/EtOAc (1:1) as eluent.

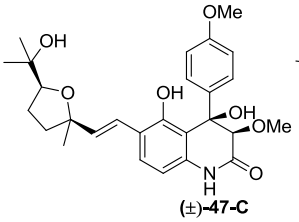
(±)-Yaequinolone C



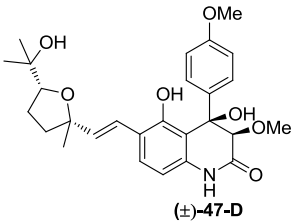
(±)-47-A



(±)-47-B



(±)-47-C



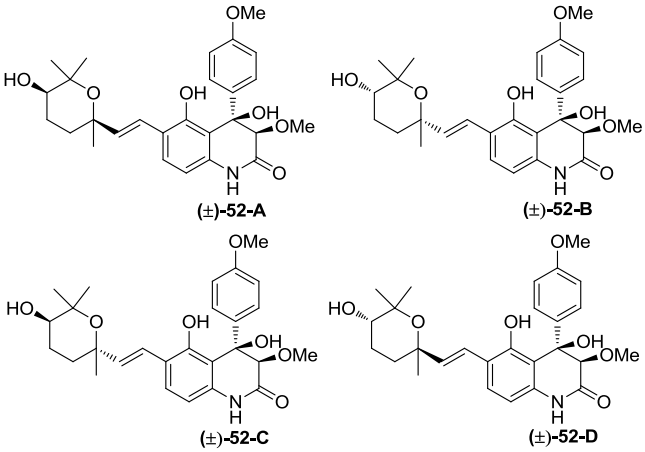
(±)-47-D

Deprotection of **46** with TBAF:

24 mg of **46** [regioisomers (6.8:1), dr not determined, 0.039 mmol, 1.0 equiv] and 400 μL TBAF (1.0 M in THF, 10 equiv) solution were first mixed in the reaction flask. After quickly removing the THF using rotary evaporator, 100 μL THF was added. Purification was performed using *n*-hexane/EtOAc (1.5:1) as eluent to give the product **47** as a mixture of regioisomers (10:1, dr not determined) (pale yellow solid, 15.0 mg, 79%). **^{1}H NMR** (400 MHz) [Two groups of diastereoisomers: (A+B)/(C+D) > 1. The NMR data of group A and B matched with those of **yaequinolone C** reported in the literature.[9] Therefore, either **(±)-47-A** or **(±)-47-B** is **(±)-yaequinolone C**. The olefin moiety of **(±)-yaequinolone C** has the *trans*-configuration.] δ 9.16 (A and/or B and/or C and/or D), 9.15 (A and/or B and/or C and/or D), 7.84 (A, B, C and D), 7.37 [d, *J* = 8.2 Hz, ($1H_A$ and $1H_B$) or ($1H_C$ and $1H_D$)], 7.36 [d, *J* = 8.2 Hz, ($1H_A$ and $1H_B$) or ($1H_C$ and $1H_D$)], 7.22 – 7.17 (m, $2H_A$, $2H_B$, $2H_C$ and $2H_D$), 6.85 – 6.83 (m, $2H_A$, $2H_B$, $2H_C$ and $2H_D$), 6.79 [d, *J* = 16.4 Hz, ($1H_A$ and $1H_B$) or ($1H_C$ and $1H_D$)], 6.78 [d, *J* = 8.2 Hz, ($1H_A$ and $1H_B$) or ($1H_C$ and $1H_D$)], 6.34 – 6.21 (m, $2H_A$, $2H_B$, $2H_C$ and $2H_D$), 4.56 [s, ($1H_A$ and $1H_B$) or ($1H_C$ and $1H_D$)], 4.57 [s, ($1H_A$ and $1H_B$) or ($1H_C$ and $1H_D$)], 3.91 – 3.83 (m, $1H_A$, $1H_B$, $1H_C$ and $1H_D$), 3.76 [s, ($3H_A$ and $3H_B$) or ($3H_C$ and $3H_D$)], 3.75 [s, ($3H_A$ and $3H_B$) or ($3H_C$ and $3H_D$)], 3.69 – 3.68 (m, $1H_A$, $1H_B$, $1H_C$ and $1H_D$), 3.60 (s, $3H_A$, $3H_B$, $3H_C$ and $3H_D$), 2.04 – 1.75 (m, $4H_A$, $4H_B$, $4H_C$ and $4H_D$), 1.40 [s, ($3H_A$ and $3H_B$) or ($3H_C$ and $3H_D$)], 1.39 [s, ($3H_A$ and $3H_B$) or ($3H_C$ and $3H_D$)], 1.24 (s, $3H_A$, $3H_B$, $3H_C$ and $3H_D$), 1.14 (s, $3H_A$, $3H_B$, $3H_C$ and $3H_D$). **^{13}C NMR** (101 MHz) δ 165.7 (A, B, C and D), 160.4 (A, B, C and D), 155.4 (A, B, C and D), 135.7 (A or B or C or D), 135.6 (A or B or C or D), 135.3 (A and/or B and/or C and/or D), 134.5 (A or B or C or D), 134.4 (A or B or C or D), 134.3 (A and/or B and/or C and/or D), 129.2 [(A and B) or (C and D)], 129.1 [(A and B) or (C and D)], 128.0 (A, B, C and D), 127.9 [(A and B) or (C and D)], 127.8 [(A and B) or (C and D)], 122.0 [(A and B) or (C and D)], 121.9 [(A and B) or (C and D)], 121.3 [(A and B) or (C and D)], 121.0 (A or B or C or D), 120.9 (A or B or C or D), 114.4 (A, B, C and D), 110.9 (A, B, C and D), 107.0 (A, B, C and D), 85.8 [(A and B) or (C and D)], 85.7 [(A and B) or (C and D)], 84.3 (A, B, C and D), 83.4 [(A and B) or (C and D)], 83.2 [(A and B) or (C and D)], 78.9 (A, B, C and D), 71.4 [(A and B) or (C and D)], 71.3 [(A and B) or (C and D)], 59.0 (A, B, C and D), 55.4 (A, B, C and D), 38.7 (A or B or C or D), 38.6 (A or B or C or D), 38.1 [(A and B) or (C and D)], 27.5 (A, B, C and D), 26.7 (A, B, C and D), 26.6 (A, B, C and D), 24.6 (A or B or C or D), 24.5 (A or B or C or D), 24.3 [(A and B) or (C and D)]. **IR**: ν 3249, 2966, 2927, 1686, 1602, 1419, 1373, 1254, 1030, 804 cm^{-1}. **HRMS**

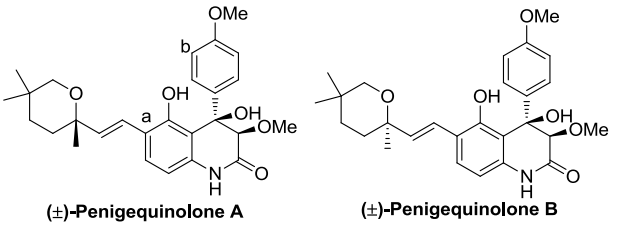
(FD) calculated for $C_{27}H_{33}NO_7^+$ $[M]^+$: 483.2257; found: 483.2262.

(±)-Aspoquinolone C and **D**



Deprotection of **51** with Me_2AlCl:
38 mg of **51** (dr = 2.2:2.2:1:1, 0.062 mmol) was used and the product **52** was isolated as a mixture of diastereoisomers (dr = 2.2:2.2:1:1) (pale yellow solid, 22.0 mg, 73%) after purification with *n*-hexane/EtOAc (1:1) as eluent. **^{1}H NMR** (400 MHz) [Two groups of diastereoisomers: (A+B)/(C+D) = 2.2:1. Aspoquinolone C and D were reported as a mixture and we found out that one of the mixture matched with the NMR data of group A and the other one matched with those of Group B. Therefore, we concluded that one of the natural product has *cis*-configuration for the olefin moiety and the other has the *trans*-configuration for the olefin moiety. δ 9.13 (bs, $1H_A$ or $1H_B$), 9.13 (bs, $1H_C$ or $1H_D$), 9.12 (bs, $1H_A$ or $1H_B$), 9.11 (bs, $1H_C$ or $1H_D$), 8.12 (bs, $1H_C$ and $1H_D$), 8.08 (bs, $1H_A$ and $1H_B$), 7.35 – 7.31 (m, $1H_A$, $1H_B$, $1H_C$ and $1H_D$), 7.18 – 7.14 (m, $2H_A$, $2H_B$, $2H_C$ and $2H_D$), 6.82 – 6.73 (m, $3H_A$, $3H_B$, $3H_C$ and $3H_D$), 6.34 – 6.21 (m, $2H_A$, $2H_B$, $2H_C$ and $2H_D$), 4.59 – 4.57 (m, $1H_A$, $1H_B$, $1H_C$ and $1H_D$), 3.90 – 3.83 (m, $1H_A$, $1H_B$, $1H_C$ and $1H_D$), 3.75 – 3.74 (m, $3H_A$, $3H_B$, $3H_C$ and $3H_D$), 3.69 – 3.68 (m, $1H_A$, $1H_B$, $1H_C$ and $1H_D$), 3.60 – 3.59 (m, $3H_A$, $3H_B$, $3H_C$ and $3H_D$), 2.03 – 1.74 (m, $4H_A$, $4H_B$, $4H_C$ and $4H_D$), 1.40 – 1.38 (m, $3H_A$, $3H_B$, $3H_C$ and $3H_D$), 1.25 – 1.23 (m, $3H_A$, $3H_B$, $3H_C$ and $3H_D$), 1.13 (s, $3H_A$, $3H_B$, $3H_C$ and $3H_D$). **^{13}C NMR** (75 MHz) δ 165.9 (A, B, C and D), 160.4 (A, B, C and D), 155.4 (A, B, C and D), 135.7 (C or D), 135.6 (C or D), 135.3 (A or B), 135.2 (A or B), 134.4 (C and D), 134.4 (C and D), 129.2 (A and B), 129.1 (C and D), 128.0 (A and B), 127.9 (C or D), 127.8 (C or D), 122.0 (C and D), 121.9 (A and B), 121.4 (C or D), 121.3 (C or D), 121.0 (A or B), 120.9 (A or B), 114.4 (A, B, C and D), 110.9 (A, B, C and D), 107.0 (A, B, C and D), 85.8 (C and D), 85.7 (A and B), 84.3 (A, B, C and D), 83.4 (A and B), 83.2 (C and D), 78.9 (A and B), 78.8 (C and D), 71.4 (C and D), 71.3 (A and B), 59.0 (A, B, C and D), 55.4 (A, B, C and D), 38.7 (C and D), 38.6 (A and B), 27.7 (C and D), 27.5 (A, B, C and D), 27.4 (A and B), 26.8 (C or D), 26.7 (C or D), 26.7 (A or B), 26.6 (A or B), 24.6 (C or D), 24.5 (C or D), 24.3 (A and B). **IR**: ν 3261, 2924, 1686, 1600, 1377, 1262, 1077, 1026, 734 cm^{-1}. **HRMS** (FD) calculated for $C_{27}H_{33}NO_7^+$ $[M]^+$: 483.2257; found: 483.2272.

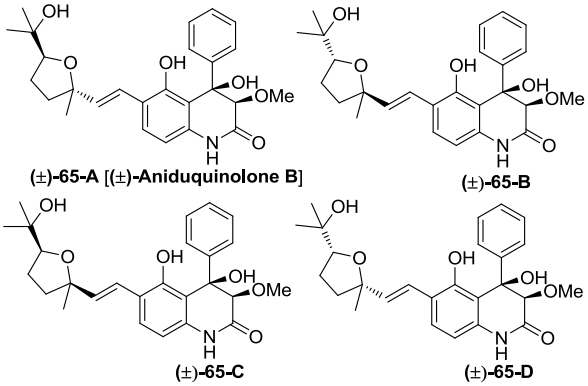
(±)-Penigequinolone A and B



Deprotection of **54** with TBAF:
23 mg of **54** [regioisomers (8.7:1), dr = 1:1, 0.0385 mmol, 1.0 equiv] and 385 μL TBAF (1.0 M in THF, 10 equiv) solution were first mixed in the reaction flask. After quickly removing the THF using rotary evaporator, 90 μL THF was added. Purification was performed using *n*-hexane/EtOAc (2:1) as eluent to give the product as a mixture of regioisomers (a:b = 13.5:1, dr = 1:1) (pale yellow solid, 16.9 mg, 94%). **^{1}H NMR** (400 MHz) (Two diastereoisomers) δ 9.12 (bs, $1H_A$ and $1H_B$), 7.84 (bs, $1H_A$ and $1H_B$), 7.40 (d, J = 8.3 Hz, $1H_A$ or $1H_B$), 7.39 (d, J = 8.3 Hz, $1H_A$ or $1H_B$), 7.21 – 7.16 (m, $2H_A$ and $2H_B$), 6.84 – 6.80 (m, $2H_A$ and $2H_B$), 6.73 (d, J = 16.3 Hz, $1H_A$ and $1H_B$), 6.35 (d, J = 8.3 Hz, $1H_A$ or $1H_B$), 6.34 (d, J = 8.3 Hz, $1H_A$ or $1H_B$), 6.14 (d, J = 16.7 Hz, $1H_A$ or $1H_B$), 6.13 (d, J = 16.7 Hz, $1H_A$ or $1H_B$), 4.56 (bs, $1H_A$ and $1H_B$), 3.76 (s, $3H_A$ and $3H_B$), 3.70 (d, J = 1.5 Hz, $1H_A$ or $1H_B$), 3.69 (d, J = 1.5 Hz, $1H_A$ or $1H_B$), 3.60 (s, $3H_A$ and $3H_B$), 3.38 (d, J = 11.3 Hz, $1H_A$ or $1H_B$), 3.37 (d, J = 11.3 Hz, $1H_A$ or $1H_B$), 3.24 – 3.20 (m, $1H_A$ and $1H_B$), 1.84 – 1.76 (m, $1H_A$ and $1H_B$), 1.73 – 1.66 (m, $1H_A$ and $1H_B$), 1.51 – 1.46 (m, $1H_A$ and $1H_B$), 1.30 (s, $3H_A$ and $3H_B$), 1.00 (s, $3H_A$ and $3H_B$), 0.79 (s, $3H_A$ and $3H_B$). **^{13}C NMR** (101 MHz) δ 165.8 (A and B), 160.4 (A and B), 155.3 (A and B), 134.5, 134.43, 134.37 (A and B), 129.1 (A and B), 128.0 (A and B), 127.6, 127.5, 123.3 (A and B), 122.1 (A and B), 114.4 (A and B), 110.9 (A and B), 107.0 (A and B), 84.3 (A and B), 74.5 (A and B), 72.9 (A and B), 59.0 (A and

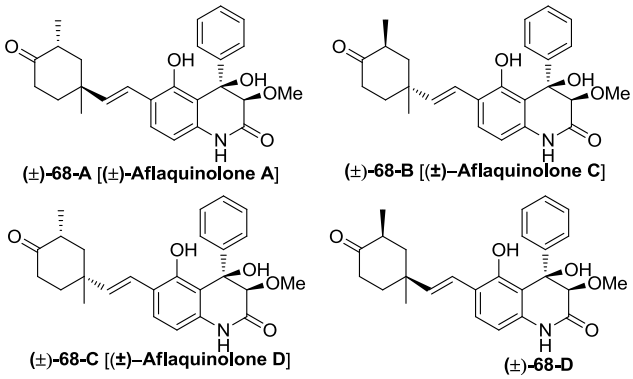
B), 55.4 (A and B), 33.7 (A and B), 31.2, 31.1, 29.9 (A and B), 29.3 (A and B), 26.8, 26.7, 24.2 (A and B). **IR**: ν 3269, 2927, 1686, 1616, 1508, 1256, 1079, 806 cm^{-1}. **HRMS** (FD) calculated for $C_{27}H_{33}NO_6^+$ $[M]^+$: 467.2308; found: 467.2287.

(±)-Aniduquinolone B



Deprotection of **64** with TBAF:
25 mg of **64** [dr = 5.5:5.5:1:1, 0.043 mmol, 1.0 equiv] and 430 μL TBAF (1.0 M in THF, 10 equiv) solution were first mixed in the reaction flask. After quickly removing the THF using rotary evaporator, 90 μL THF was added. Purification was performed using *n*-hexane/EtOAc (1.5:1) as eluent to give the product **65** as a mixture of diastereoisomers (dr = 1.7:1.7:1:1) (pale yellow solid, 20.0 mg, 95%). **^{1}H NMR** (400 MHz, DMSO-d_6) [Two groups of diastereoisomers: (A+B)/(C+D) = 1.7:1. The NMR data of group A and B matched with those of anidoquinolone B reported in the literature.[11a]] δ 10.29 (s, $1H_A$, $1H_B$, $1H_C$ and $1H_D$), 9.81 (s, $1H_A$, $1H_B$, $1H_C$ and $1H_D$), 7.53 (s, $1H_A$, $1H_B$, $1H_C$ and $1H_D$), 7.37 – 7.30 (m, $4H_A$, $4H_B$, $4H_C$ and $4H_D$), 7.21 – 7.19 (m, $2H_A$, $2H_B$, $2H_C$ and $2H_D$), 6.69 (d, *J* = 16.4 Hz, $1H_C$ or $1H_D$), 6.68 (d, *J* = 16.4 Hz, $1H_C$ or $1H_D$), 6.64 (d, *J* = 16.4 Hz, $1H_A$ and $1H_B$), 6.44 (d, *J* = 8.3 Hz, $1H_A$, $1H_B$, $1H_C$ and $1H_D$), 6.31 (d, *J* = 16.3 Hz, $1H_C$ or $1H_D$), 6.30 (d, *J* = 16.3 Hz, $1H_C$ or $1H_D$), 6.20 (d, *J* = 16.3 Hz, $1H_A$ or $1H_B$), 6.19 (d, *J* = 16.4 Hz, $1H_A$ or $1H_B$), 4.09 – 4.06 (m, $1H_A$, $1H_B$, $1H_C$ and $1H_D$), 3.74 – 3.67 (m, $1H_A$, $1H_B$, $1H_C$ and $1H_D$), 3.62 – 3.60 (m, $1H_A$, $1H_B$, $1H_C$ and $1H_D$), 3.44 (s, $3H_A$, $3H_B$, $3H_C$ and $3H_D$), 1.90 – 1.62 (m, $4H_A$, $4H_B$, $4H_C$ and $4H_D$), 1.30 (s, $3H_A$ and $3H_B$), 1.27 (s, $3H_C$ and $3H_D$), 1.08 – 1.03 (m, $3H_A$, $3H_B$, $3H_C$ and $3H_D$). **^{13}C NMR** (75 MHz, DMSO-d_6) δ 166.1 (A, B, C and D), 154.7 (C and D), 154.6 (A and B), 139.8 (A or B, and/or C, and/or D), 139.7 (A or B, and/or C, and/or D), 136.0 (A, B, C and D), 135.0 (A, B, C and D), 134.4 (A or B, and/or C, and/or D), 134.3 (A or B, and/or C, and/or D), 128.7 (C and D), 128.6 (A and B), 126.7 (A and B), 126.6 (C and D), 126.2 (A, B, C and D), 120.0 (C and D), 119.9 (A and B), 119.7 (C or D), 119.6 (C or D), 119.5 (A and B), 111.0 (A, B, C and D), 106.9 (A, B, C and D), 85.3 (A or B), 85.2 (A or B), 85.1 (C or D), 85.0 (C or D), 84.2 (A, B, C and D), 82.7 (A, B, C and D), 82.4 (A, B, C and D), 78.6 (A, B, C and D), 70.3 (C and D), 70.2 (A and B), 58.3 (A, B, C and D), 38.1 (C or D), 38.0 (C or D), 37.5 (A and B), 27.3 (C and D), 27.2 (A and B), 26.9 (C and D), 26.8 (A and B), 26.2 (C and D), 26.0 (A and B), 25.0 (C and D), 25.0 (A and B). **IR**: ν 3268, 2967, 2928, 1685, 1600, 1375, 1080, 977 cm^{-1}. **HRMS** (FD) calculated for $C_{26}H_{31}NO_6^+$ $[M]^+$: 453.2151; found: 453.2129.

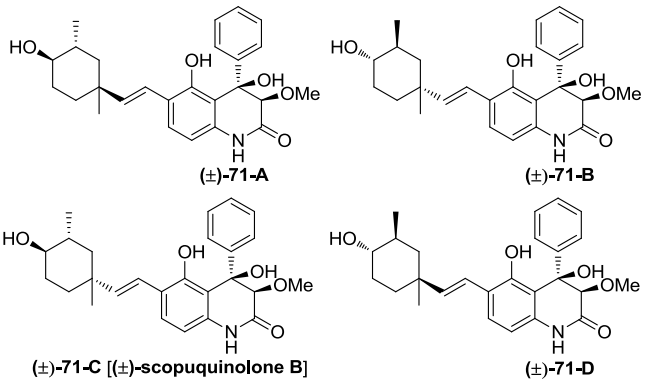
(±)-Aflaquinolone A, C and **D**



Deprotection of **67** with Me_2AlCl:
40 mg of **67** (dr = 1:1:1.6:1.6, 0.071 mmol) was used and the product **68** was isolated as a mixture of regioisomers (14:1, dr = 1:1:1:1) (pale yellow solid, 30.0 mg, 97%) after purification with *n*-hexane/EtOAc (1.5:1) as eluent. **^{1}H NMR** (400 MHz) [two groups of diastereoisomers: (A+B)/(C+D) = 1:1, The ^{1}H NMR data of (±)-aflaquinolone A, C, D matched with those reported in the literature.[10]] δ 9.11 [bs, ($1H_A$ and $1H_B$) or ($1H_C$ and $1H_D$)], 9.09 [bs, ($1H_A$ and $1H_B$) or ($1H_C$ and $1H_D$)], 8.35 [bs, ($1H_A$ and $1H_B$) or ($1H_C$ and $1H_D$)], 8.33 [bs, ($1H_A$ and $1H_B$) or ($1H_C$ and $1H_D$)], 7.39 (d, *J* = 8.3 Hz, $1H_A$ and $1H_B$), 7.34 – 7.25 (m, $5H_A$, $5H_B$, $6H_C$ and $6H_D$), 6.78 (d, *J* = 16.6 Hz, $1H_C$ and $1H_D$), 6.61 (d, *J* = 16.5 Hz, $1H_A$ and $1H_B$), 6.39 (d, *J* = 8.1 Hz, $1H_C$ and $1H_D$), 6.36 (d, *J* = 8.2 Hz, $1H_A$ and $1H_B$), 6.27 (d, *J* = 16.6 Hz, $1H_A$ and $1H_B$), 6.13 (d, *J* = 16.4 Hz, $1H_C$ and $1H_D$), 4.69 [s, ($1H_A$ and $1H_B$) or ($1H_C$ and $1H_D$)], 4.67 [s, ($1H_A$ and $1H_B$) or ($1H_C$ and $1H_D$)], 3.69 (d, *J* = 1.6 Hz, $1H_A$, $1H_B$, $1H_C$ and $1H_D$), 3.61 (s, $3H_A$, $3H_B$, $3H_C$ and $3H_D$), 2.65 – 2.44 (m, $2H_A$, $2H_B$, $2H_C$ and $2H_D$), 2.36 –

2.31 (m, $1H_C$ and $1H_D$), 2.28 – 2.21 (m, $1H_A$ and $1H_B$), 2.21 – 2.08 (m, $1H_A$, $1H_B$, $1H_C$ and $1H_D$), 1.76 – 1.68 (m, $1H_A$ and $1H_B$), 1.62 – 1.54 (m, $1H_C$ and $1H_D$), 1.43 – 1.39 (m, $1H_A$, $1H_B$, $1H_C$ and $1H_D$) 1.39 (s, $3H_C$ and $3H_D$), 1.10 (s, $3H_A$ and $3H_B$), 1.02 (d, J = 6.5 Hz, $3H_C$ and $3H_D$), 0.93 (d, J = 6.5 Hz, $3H_A$ or $3H_B$), 0.92 (d, J = 6.5 Hz, $3H_A$ or $3H_B$). **^{1}H NMR** (400 MHz, Acetone-d_6) δ 9.62 (bs, $1H_A$ or $1H_B$ or $1H_C$ or $1H_D$), 9.61 (bs, $1H_A$ or $1H_B$ or $1H_C$ or $1H_D$), 9.59 [bs, ($1H_A$ and $1H_B$) or ($1H_C$ and $1H_D$)], 9.37 [bs, ($1H_A$ and $1H_B$) or ($1H_C$ and $1H_D$)], 9.36 [bs, ($1H_A$ and $1H_B$) or ($1H_C$ and $1H_D$)], 7.53 (d, J = 8.3 Hz, $1H_A$ or $1H_B$), 7.52 (d, J = 8.3 Hz, $1H_A$ or $1H_B$), 7.43 (d, J = 8.4 Hz, $1H_C$ and $1H_D$), 7.37 – 7.32 (m, $5H_A$, $5H_B$, $5H_C$ and $5H_D$), 6.84 (d, J = 16.7 Hz, $1H_A$ and $1H_B$), 6.65 (d, J = 16.5 Hz, $1H_C$ and $1H_D$), 6.60 (d, J = 8.6 Hz, 1H), 6.57 (d, J = 8.5 Hz, 1H), 6.44 (d, J = 16.6 Hz, $1H_A$ and $1H_B$), 6.37 (s, $1H_A$ or $1H_B$ or $1H_C$ or $1H_D$), 6.36 (s, $1H_A$ or $1H_B$ or $1H_C$ or $1H_D$), 6.36 [s, ($1H_A$ and $1H_B$) or ($1H_C$ and $1H_D$)], 6.23 (d, J = 16.4 Hz, $1H_C$ and $1H_D$), 3.68 (d, J = 1.4 Hz, $1H_A$, $1H_B$, $1H_C$ and $1H_D$), 3.52 [s, ($3H_A$ and $3H_B$) or ($3H_C$ and $3H_D$)], 3.51 [s, ($3H_A$ and $3H_B$) or ($3H_C$ and $3H_D$)], 2.73 – 2.47 (m, $2H_A$, $2H_B$, $2H_C$ and $2H_D$), 2.22 – 2.09 (m, $2H_A$, $2H_B$, $2H_C$ and $2H_D$), 1.91 – 1.81 (m, $1H_A$, $1H_B$, $1H_C$ and $1H_D$), 1.75 – 1.67 (m, $1H_A$ and $1H_B$), 1.58 – 1.49 (m, $1H_C$ and $1H_D$), 1.43 – 1.39 (m, $1H_A$, $1H_B$, $1H_C$ and $1H_D$), 1.42 (s, $3H_C$ and $3H_D$), 1.11 (s, $3H_A$ and $3H_B$), 0.95 (d, J = 6.5 Hz, $3H_C$ and $3H_D$), 0.93 (d, J = 6.5 Hz, $3H_A$ and $3H_B$), 0.92 (d, J = 6.5 Hz, $3H_A$ and $3H_B$). **^{13}C NMR** (101 MHz) δ 214.0 [(A and B) or (C and D)], 213.6 [(A and B) or (C and D)], 165.9 (A, B, C and D), 155.0 (A, B, C and D), 137.4 (A, B, C and D), 136.0 (A, B, C and D), 134.5 [(A and B) or (C and D)], 134.4 [(A and B) or (C and D)], 129.4 (A, B, C and D), 129.1 [(A and B) or (C and D)], 129.0 [(A and B) or (C and D)], 127.4 [(A and B) or (C and D)], 127.3 [(A and B) or (C and D)], 126.4 (A, B, C and D), 122.6 (A, B, C and D), 122.5 [(A and B) or (C and D)], 122.4 [(A and B) or (C and D)], 110.9 [(A and B) or (C and D)], 110.8 [(A and B) or (C and D)], 107.2 (A, B, C and D), 84.2 (A, B, C and D), 79.0 (A, B, C and D), 59.1 (A, B, C and D), 47.7 (A or B), 47.6 (A or B), 46.9 (C or D), 46.8 (C or D), 41.5 (A and B), 40.8 (C and D), 38.7 (A, B, C and D), 38.5 [(A and B) or (C and D)], 38.2 [(A and B) or (C and D)], 38.0 (C and D), 37.4 (A and B), 30.6 (A, B, C and D), 14.7 (A or B or C or D), 14.6 (A or B or C or D), 14.3 [(A and B) or (C and D)]. **IR**: ν 3221, 2923, 1689, 1377, 1260, 1080, 1026, 800 cm^{-1}. **HRMS** (FD) calculated for $C_{26}H_{29}NO_5^+$ [M]$^+$: 435.2046; found: 435.2047.

(±)-Scopuquinolone B



Deprotection of **70** with Me_2AlCl:
19 mg of **70** (dr = 1:1:1:1, 0.0335 mmol) was used and the product **71** was isolated as a mixture of daistereosiomers (dr = 1:1:1:1) (pale yellow solid, 13.0 mg, 89%) after purification with *n*-hexane/EtOAc (1:1) as eluent. **^{1}H NMR** (400 MHz, Acetone-d_6) [two groups of diastereoisomers: (A+B)/ (C+D) = 1:1. The NMR data of group C and D matched with those of scopuquinolone B reported in the literature.[11e]] δ 9.55 (bs, $1H_A$, $1H_B$, $1H_C$ and $1H_D$), 9.33 (bs, $1H_A$, $1H_B$, $1H_C$ and $1H_D$), 7.44 [d, J = 8.3 Hz, ($1H_A$ and $1H_B$) or ($1H_C$ and $1H_D$)], 7.42 [d, J = 8.3 Hz, ($1H_A$ and $1H_B$) or ($1H_C$ and $1H_D$)], 7.37 – 7.32 (m, $5H_A$, $5H_B$, $5H_C$ and $5H_D$), 6.65 – 6.55 (m, $2H_A$, $2H_B$, $2H_C$ and $2H_D$), 6.34 – 6.33 (m, $1H_A$, $1H_B$, $1H_C$ and $1H_D$), 6.20 [d, J = 16.5 Hz, ($1H_A$ and $1H_B$) or ($1H_C$ and $1H_D$)], 6.17 [d, J = 16.5 Hz, ($1H_A$ and $1H_B$) or ($1H_C$ and $1H_D$)], 3.66 (d, J = 1.5 Hz, $1H_A$, $1H_B$, $1H_C$ and $1H_D$), 3.52 [s, ($3H_A$ and $3H_B$) or ($3H_C$ and $3H_D$)], 3.51 [s, ($3H_A$ and $3H_B$) or ($3H_C$ and $3H_D$)], 3.06 – 2.97 (m, $1H_A$, $1H_B$, $1H_C$ and $1H_D$), 1.81 – 1.68 (m, bs, $3H_A$, $3H_B$, $3H_C$ and $3H_D$), 1.64 – 1.27 (m, $4H_A$, $4H_B$, $3H_C$ and $3H_D$), 1.13 (s, $3H_C$ and $3H_D$), 1.07 (t, J = 12.9 Hz, $1H_A$ and $1H_B$), 1.01 (s, $3H_A$ and $3H_B$), 0.98 (d, J = 6.4 Hz, 1H), 0.96 – 0.94 (m, $3H_C$ and $3H_D$). **^{13}C NMR** (101 MHz, Acetone-d_6) δ 166.3 (A, B, C and D), 156.1 (C and D), 155.9 (A and B), 141.8 (C and D), 140.3 (A and B), 137.6 (A, B, C and D), 136.9 (A, B, C and D), 129.7 (A, B, C and D), 129.6 (A, B, C and D), 127.5 [(A and B) or (C and D)], 127.5 [(A and B) or (C and D)], 127.4 [(A and B) or (C and D)], 127.3 [(A and B) or (C and D)], 122.6 (A, B, C and D), 122.3 (A, B, C and D), 112.1 (A, B, C and D), 107.7 (A, B, C and D), 85.8 (A, B, C and D), 80.0 (A, B, C and D), 76.8 (A, B, C and D), 59.0 (A, B, C and D), 46.9 (A and B), 45.9 (C and D), 37.7 (A, B, C and D), 37.7 (A, B, C and D), 37.0 [(A and B) or (C and D)], 36.9 [(A and B) or (C and D)], 34.0 (C and D), 33.1 (A and B), 31.9 [(A and B) or (C and D)], 31.8 [(A and B) or (C and D)], 19.5 [(A and B) or (C and D)], 19.4 [(A and B) or (C and D)]. **IR**: ν 3274, 2926, 1687, 1620, 1452, 1378, 1261, 1082, 1039, 803 cm^{-1}. **HRMS** (FD) calculated for $C_{26}H_{31}NO_5^+$

$[M]^+$: 437.2202; found: 437.2198.

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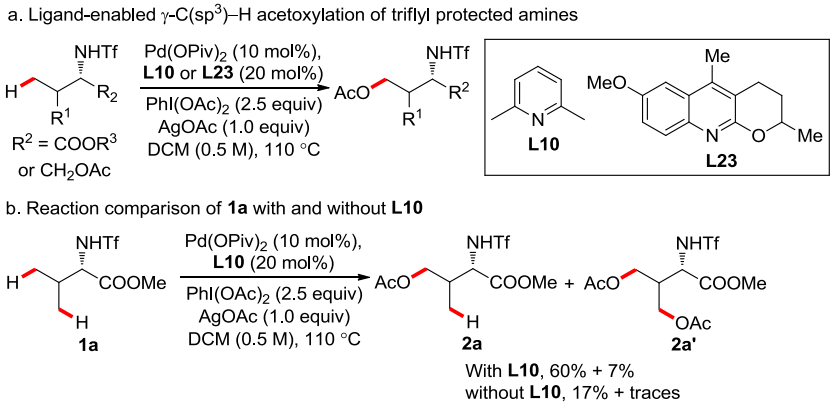
Summary

Transition-metal-catalyzed C–H functionalization has emerged as a research area of great interest in the last decades. The ability of introducing new functional groups without the need to pre-functionalize the starting material has the potential of revolutionizing the way that complex molecules are built and accelerating drug discovery research by enabling late-stage C–H functionalization. In particular, because of the important role of amine derivatives in natural products, pharmaceuticals and organic functional materials, a wide range of methodologies have been reported for the direct C–H functionalization of these compounds and some of the methodologies have been successfully applied for the total synthesis of natural products. However, to realize the full potential of this strategy in organic synthesis, new methods have to be developed.

In this thesis, we adopted different strategies based on Pd-catalysis to functionalize a variety of amine derivatives. In all of the developed methodologies, the use of external ligands was key to improving the reactivity and/or selectivities of these processes. The robustness of one of these strategies was demonstrated in the divergent and streamlined total synthesis of 11 yaequinolone related natural products.

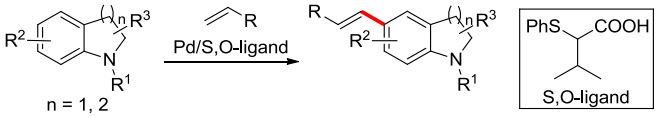
In **Chapter 2**, we combined a triflyl-protected amine as a monodentate directing group with an external ligand for the γ-C(sp^3)–H acetoxylation of amines (Scheme 1a). For amino esters, 2,6-lutidine (**L10**) was found to be the optimal external ligand, while for amino alcohols, quinoline-based **L23** gave the best results. The reactions furnished acetoxylated products in modest to good yields with high diastereoselectivities. The important role of the external ligands was showcased by the fact that the reaction of **1a** without ligand, under otherwise the same reaction conditions provided the desired product in low yield (Scheme 1b). Unfortunately, trials to remove the triflyl group from the products were not successful.



Scheme 1 γ-C(sp^3)–H acetoxylation of amine derivatives

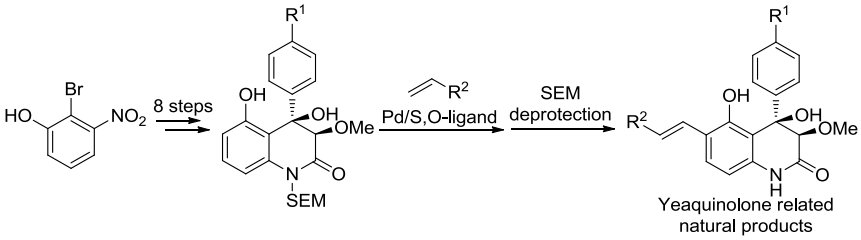
In **Chapter 3**, we achieved the non-directed site-selective C–H olefination of indolines (C5) and tetrahydroquinolines (THQs) (C6) by using our Pd/S,O-ligand catalyst (Scheme 2). Indolines bearing an electron-withdrawing substituent on the aromatic ring or substituted at the 2- and/or 3-positions were good substrates giving the olefinated products in both high yields and regioselectivities. However, due to the instability of indolines having an electron-donating group on the aromatic ring, the olefinated products were obtained in low yields. To tackle this problem, Boc was used as the protecting group for the nitrogen instead of the methyl group and higher yields were obtained. However, using this protecting group, low regioselectivities were observed. We also showed the power of this strategy for the late-stage modification of several highly advanced molecules. For THQs, due to their better stability under the reaction conditions, the C–H olefination of THQs bearing both electron-withdrawing and donating groups on the aromatic ring provided the desired products in good yields. However, low yields were observed when the substituent was located at 8-postion, probably due to the clash between the substituent and the methyl protecting group, forcing the nitrogen to go out of the plane of the aromatic ring, thus reducing the electron-donating ability to the aromatic ring. We proved our hypothesis by successfully olefinating some unprotected 8-substituted THQs. Moreover, we also showed that many olefins are suitable coupling partners including unactivated styrene. By comparing the results with and

without S,O-ligand, we proved that this ligand was responsible for the dramatic improvements in substrate scope and regioselectivities.



Scheme 2 Selective C–H olefination of indolines (C5) and THQs (C6) by Pd/S,O-ligand catalysis

In **Chapter 4**, we successfully applied the methodology described in Chapter 3 for the divergent and streamlined total synthesis of 11 yeaquinolone related natural products. We first established a robust method for the construction of 3,4-dioxygenated 4-aryl-5-hydroxyquinolin-2(1H)-ones, core structures of this family of natural products, starting from commercially available 2-bromo-3-nitrophenol in 8 synthetic steps. The C–H olefination reaction of these core structures with both activated and unactivated olefins is efficient and site-selective under mild reaction conditions in the presence of the Pd/S,O-ligand catalyst.



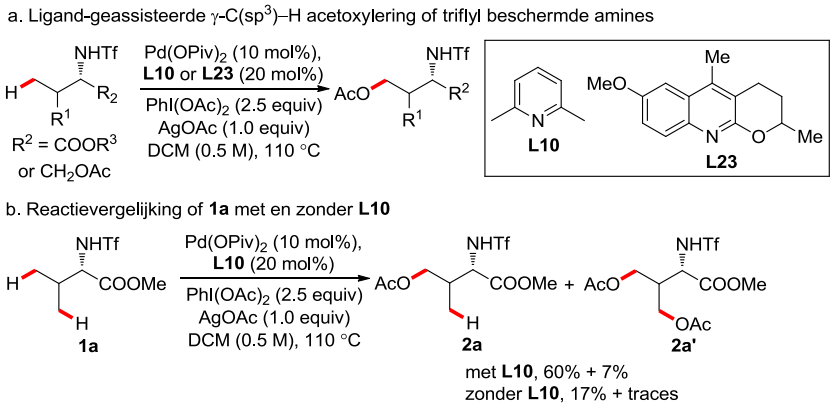
Scheme 3 Total synthesis of yaequinolone related natural products by late-stage C–H olefination

Samenvatting

Overgangsmetaal gekatalyseerde C–H functionalisering is in de laatste decennia een belangrijk onderzoeksgebied geworden. Het vermogen om nieuwe functionele groepen te introduceren zonder de noodzaak om het uitgangsmateriaal vooraf te functionaliseren heeft het potentieel om een revolutie teweeg te brengen in de manier waarop complexe moleculen worden gesynthetiseerd. Tevens zal het onderzoek naar nieuwe geneesmiddelen versneld worden doordat C–H activering functionalisatie in een laat stadium mogelijk maakt. Vanwege de belangrijke rol van aminederivaten in natuurstoffen, geneesmiddelen en functionele organische materialen, is een breed scala aan methodologieën gerapporteerd voor de directe C–H functionalisering van deze verbindingen. Sommige van deze methodologieën zijn met succes toegepast in de totaalsynthese van natuurstoffen. Om het volledige potentieel van deze strategie in organische synthese te realiseren, moeten er echter nog nieuwe methoden worden ontwikkeld.

In dit proefschrift staat de ontwikkeling van verschillende strategieën beschreven op basis van Pd-katalyse om een verscheidenheid aan aminederivaten te synthetiseren. In alle ontwikkelde methodologieën was het gebruik van externe liganden de sleutel tot het verbeteren van de reactiviteit en/of selectiviteiten van deze processen. De robuustheid van een van deze strategieën werd aangetoond door de efficiënte totaalsynthese van 11 yaequinolon-type natuurstoffen.

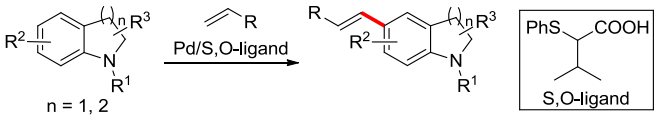
In **Hoofdstuk 2** hebben we een triflyl-beschermd amine gebruikt als een monodentaat-sturende groep in combinatie met een externe ligand voor de γ-C(sp^3)–H acetoxylering van amines (Schema 1a). Voor aminoesters bleek 2,6-lutidine (**L10**) het optimale externe ligand te zijn, terwijl voor aminoalcoholen het op quinoline gebaseerde ligand **L23** de beste resultaten gaf. De reacties leverden geacetoxyleerde producten op in bescheiden tot goede opbrengsten met hoge diastereoselectiviteiten. De belangrijke rol van de externe liganden werd aangetoond door het feit dat de reactie van **1a** zonder ligand, onder verder dezelfde reactieomstandigheden, het gewenste product opleverde echter slechts in een lage opbrengst (Schema 1b). Helaas waren experimenten om de triflylgroep af te splitsen niet succesvol.



Schema 1 γ-C (sp^3)–H acetoxylering van aminederivaten

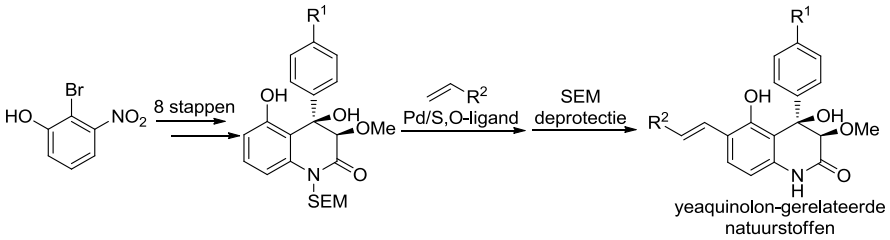
In **Hoofdstuk 3** werd de niet-gerichte regioselectieve C–H olefinering van indolines (**C5**) en tetrahydroquinolines (THQ's) (**C6**) bewerkstelligd door gebruik te maken van onze Pd/S,O-ligand katalysator (Schema 2). Indolinen die een elektronenzuigende substituent op de aromatische ring of op de 2- en/of 3-posities droegen waren goede substraten en gaven de geolefineerde producten in zowel hoge opbrengsten als regioselectiviteiten. Vanwege de instabiliteit van indolinen met een elektronendonerende groep op de aromatische ring, werden de geolefineerde producten verkregen in lage opbrengsten. Om dit probleem aan te pakken werd de Boc gebruikt als beschermende groep voor de stikstof in plaats van de methylgroep en werden hogere opbrengsten verkregen. Bij gebruikmaking van deze beschermende groep werden echter lage regioselectiviteiten waargenomen. We toonden ook potentie van deze strategie aan voor de late-fase modificatie van verschillende zeer geavanceerde moleculen. Voor THQ's, vanwege hun betere stabiliteit onder de reactieomstandigheden, leverde de CH-olefinering van zowel THQ's met elektronenzuigende als donerende groepen op de aromatische ring de gewenste producten met goede opbrengsten op. Er werden echter lage opbrengsten verkregen wanneer de substituent zich op een 8-positie bevond, waarschijnlijk als gevolg van

sterische hinder tussen de substituent en de methylbeschermende groep, waardoor de stikstof uit het vlak van de aromatische ring werd gedwongen, waardoor de elektronendonatie werd verminderd. We hebben onze hypothese bewezen door met succes enkele onbeschermde 8-gesubstitueerde THQ's te olefineren. Bovendien hebben we ook aangetoond dat veel olefinen geschikte koppelingspartners zijn, waaronder niet-geactiveerd styreen. Door de resultaten met en zonder S,O-ligand te vergelijken, hebben we aangetoond dat dit ligand verantwoordelijk was voor de dramatische verbeteringen in geschiktheid voor een breed palet aan substraten en regioselectiviteiten.



Schema 2 Selectieve C–H olefinering van indolines (**C5**) en THQ's (**C6**) door Pd/S,O-ligand-katalyse

In **Hoofdstuk 4** hebben we de methodologie beschreven in Hoofdstuk 3 met succes toegepast voor een efficiënte totaalsynthese van 11 yeaquinolon-gerelateerde natuurstoffen. We hebben eerst een robuuste methode ontwikkeld voor de constructie van 3,4-gedioxygeneerde 4-aryl-5-hydroxychinoline-2(1H)-onen als het skelet van deze familie van natuurlijke producten, uitgaande van het commercieel verkrijgbaar 2-broom-3-nitrofenol in 8 synthetische stappen. De C–H olefineringsreactie van dit chinoline met zowel geactiveerde als niet-geactiveerde olefinen verliep efficiënt en regioselectief onder milde reactieomstandigheden in aanwezigheid van de Pd/S, O-ligand-katalysator.



Schema 3 Totaalsynthese van yaequinolon-gerelateerde natuurstoffen met behulp van late-fase C–H olefinering

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Time flies! It's been over four years since I came to the Netherlands to pursue my Ph.D. degree. This journey has come to an end with lots of success. I would like to express my gratefulness to my supervisors, colleagues, friends and families who made this possible.

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List of publications

Part of the thesis

1. **W.-L. Jia,** M. A. Fernández-Ibáñez**,** Ligand-enabled γ-C(sp^3)–H acetoxylation of triflyl-protected amines. *Eur. J. Org. Chem.* **2018**, 6088–6091.

2. **W.-L. Jia**, N. Westerveld, K. M. Wong, T. Morsch, M. Hakkennes, K. Naksomboon, M. A. Fernández-Ibáñez, Selective C–H olefination of indolines (C5) and tetrahydroquinolines (C6) by Pd/S,O-ligand catalysis. *Org. Lett.* **2019**, *21*, 9339−9342.

3. **W.-L. Jia**, S. Vega Ces, M. A. Fernández-Ibáñez, Divergent total synthesis of yaequinolone related natural products by late-stage C–H olefination, manuscript submitted.

Outside of the thesis

1. L. Wang, X.-J. Wei, **W.-L. Jia**, J.-J. Zhong, L.-Z. Wu, Q. Liu, Visible-light-driven difluoroacetamidation of unactive arenes and heteroarenes by direct C–H functionalization at room temperature. *Org. Lett.* **2014**, *16*, 5842–5845.

2. X.-J. Wei, L. Wang, **W.-L. Jia**, S.-F. Du, L.-Z. Wu, Q. Liu, Metal-free-mediated oxidation aromatization of 1,4-dihydropyridines to pyridines using visible light and air. *Chin. J. Chem.* **2014**, *32*, 1245–1250.

3. S. Wang, **W.-L. Jia**, L. Wang, Q. Liu, Preparation of 6-difluoromethylphosphonated phenanthridines by visible-lighit-driven radical cyclization of 2-isocyanobiphenyls. *Eur. J. Org. Chem.* **2015**, 6817–6821.

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5. S. Wang, **W.-L. Jia**, L. Wang, Q. Liu, L.-Z. Wu, Domino radical addition/oxidation sequence with photocatalysis: one-pot synthesis of polysubstituted furans from α-chloro-alkyl ketones and styrenes. *Chem. Eur. J.* **2016**, *22*, 13794–13798.

6. **W.-L. Jia**, J. He, J.-J. Yang, X.-W. Gao, Q. Liu, L.-Z. Wu, Homocoupling of 3-halooxindole via visible light photocatalysis: a mild access to 3,3′-bioxindoles. *J. Org. Chem.* **2016**, *81*, 7172−7181.