Palladium(0)/Palladium(II) catalysed C(sp$^3$)-H activation:

From Direct to Remote Functionalization

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Abstract

Over the past decades, the transition metal-catalysed intramolecular activation of unactivated C-H bonds has emerged as a powerful tool for organic chemists according to the abundance of such bonds. Selective functionalizations of C-H bonds provide a rapid access to molecular complexity in an atom- and step-economical fashion. The research in our group is centered on the activation and functionalization of C(sp\(^3\))-H bonds that lead to the development of new methodologies and applications including asymmetric catalysis, mechanistic studies and total synthesis of natural products.

Within this field, my Ph.D. thesis was focused on the development of new methodologies involving Pd\(^0\)/Pd\(^{II}\) catalysed C(sp\(^3\))-H activation to access valuable heterocyclics building blocks or natural products. My thesis is divided into two distinct parts, namely “direct C(sp\(^3\))-H functionalization” and “remote C(sp\(^3\))-H functionalization”.

In the first part of this thesis, we present the synthesis of lycorine alkaloids, in an elegant and straightforward manner. Then, we propose a new synthesis of β-lactams, using carbagomoylation reaction. The last chapter of this part is focusing on the synthesis of benzoxazine, after benzazetidine rearrangement.

In the second part of this thesis, we developed new synthetic methods for the remote functionalization of distal C-H bonds. First, the synthesis of γ-lactams and indanones after palladium migration. Then, the synthesis of benzofurans, indolines and chromanones using a similar methodology.

Keywords: C-H functionalization, C-H activation, organometallic catalysis, palladium, natural products, lycorine alkaloids, β-lactams, benzazetidines, benzoxazines, 1,4-Pd shift, migration, γ-lactams, indanones, benzofurans, indolines, chromanones.

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1- Redox-neutral Coupling between Two \( \text{C(sp}^3\text{-H)} \) Bonds Enabled by 1,4-Palladium Shift for the Synthesis of Fused Heterocycles, R. Rocaboy, I. Anastasiou, O. Baudoin, *Angew. Chem. Int. Ed.* 2019, ASAP


4- A Four-Step Synthesis of (±)-\( \gamma \)-Lycorane via Pd\(^0\)-Catalysed Double \( \text{C(sp}^3\text{-H/C(sp}^3\text{-H)} \) Arylation; R. Rocaboy, D. Dailler, O. Baudoin, *Org. Lett.* 2018, 20, 772-775

Abbreviations:

Ac: Acetyl
$\text{Ac}_2\text{O}$: Acetic anhydride
AcOH: Acetic acid
Ad: Adamantyl
Ar: Aryl
Atm: atmospheric pressure
B.C.: Before Christ
BCB: Benzocyclobutene
BDE: Bond Dissociation Energy
Cat.: catalytic
CDC: cross dehydrogenative coupling
Choi: 2-Carboxy-6-hydroxyoctahydroindole
CMD: Concerted Metalation Deprotonation
COgen: Carbon monoxide generator; 9-Methylfluorene-9-carbonyl chloride
Cy: Cyclohexyl
Cyp: Cyclopentyl
d.r.: Diastereoisomeric ratio
dba: Dibenzylideneacetone
Db: Dibenzylideneacetone
DCE: 1,2-dichloroethane
DCM: Dichloromethane
DFT: Density functional theory
DHB: Dihydrobenzofuran
DKP: Diketopiperazine
DibAl-H: Diisobutylaluminium hydride
DMAP: N,N-dimethylaminopyridine
DMF: Dimethylformamide
DMSO: Dimethylsulfoxide
e.r.: Enantiomeric ratio
equiv.: Equivalent
Et: Ethyl
FG: Functional Group
F-TOTP: tri(5-fluoro-2-methylphenyl)phosphine
HFIP: Hexafluoroisopropanol
HPLA: Hydroxyphenyllactic acid
HPLC: High pressure liquid chromatography
IAC: Intramolecular acylal cyclisation
KIE: Kinetic isotopic effect
L: Ligand
MHz: Megahertz
MS: Molecular sieve
NBE: norbornene
NBS: N-bromosuccinimide
n-Bu: 1-Butyl
NHCs: N-heterocyclic carbenes
NMR: Nuclear magnetic resonance
PBP: penicillin-binding proteins
PCC: Pyridinium Chloro Chromate

Ph: Phenyl

PhI(DMM): phenyl-iodonium dimethylmalonate

PivOCs: Cesium pivalate

PivOH : Pivalic acid

PivOK: Potassium pivalate

PtBu₃: Tri-tert-butylphosphine

Py: Pyridine

RT: Room temperature

SM: Starting material

T°C: Temperature

TADDOL: \(\alpha,\alpha,\alpha',\alpha'-\text{Tetraaryl-2,2-disubstituted 1,3-dioxolane-4,5-dimethanol}\)

TBS: \textit{tert}-Butyldimethylsilyl

Tf: Triflyl

TFA: Trifluoroacetic acid

TFAA: Trifluoroacetic anhydride

TFE: 2,2,2-trifluoroethanol

THF: Tetrahydrofuran

TMB: Trimethoxybenzyle

TMEDA: Tetramethylethylene diamine

\(\beta\)-H : \(\beta\)-Hydride
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Introduction and bibliographic part

1. Generality

Before the discovery of organic chemistry with the synthesis of urea by Wöhler in 1828 and the rationalization of catalysis, chemistry was in a way, already mastered by human civilizations with the process of bread cooking or beer brewing using enzyme catalysis (estimated 14000 B.C. and 7000 B.C. respectively).

The 20th century has then witnessed the emergence of organic chemistry as a tool for industrial development in the field of pharmaceutical, petroleum, plastics or polymers. Some of the subsequent developed industrial processes are still used nowadays.

The ultimate goal of synthetic chemistry is the assembly of molecules from commercial feedstocks, with minimal waste generation and in an efficient manner. Over the past century, the classical approach to access chemical diversity was based on strategy of functional-group interconversion, requiring tedious and time-consuming manipulations (Scheme 1).

New synthetic processes have then been investigated to answer the need of modern organic synthesis.

More recently, transition-metal-catalysis tremendously expended the synthetic organic chemistry toolbox to develop new efficient transformations. Among those, palladium-catalysis has emerged as a new way to form carbon-carbon or carbon-heteroatom bonds and has been developed to access molecular complexity in a straightforward, convenient and selective fashion. Palladium-catalyzed cross-coupling reactions are nowadays used as routines reactions in academic laboratories and industries. The impact of these transformations drastically changed the vision of organic chemistry, and the main actors of this revolution were gratifyingly rewarded by a Nobel Chemistry Prize in 2010. (R. F. Heck, E. Negishi and A. Suzuki).

These reactions require pre-functionalized starting materials (halide/pseudohalide-functionalized substrate) and involve an oxidative addition and reductive elimination to furnished the coupled product.
In a mechanistic point of view, the Heck reaction differs from a Negishi or Suzuki-Miyaura cross-coupling (Figure 1). This reaction is initiated by oxidative addition of Pd\(^0\) into a carbon-leaving group bond (leaving group = halide or pseudohalide) of a pre-functionalized starting material. Complexation of the olefin to the Pd complex, followed by migratory insertion generates an alkylpalladium moiety, which after \(\beta\)-hydride elimination, undergoes the functionalized olefin. The presence of a base regenerates the active Pd\(^0\) catalyst to insure the turn-over of the reaction.

![Figure 1: Overview of the Heck coupling](image)

In the Negishi or Suzuki-Miyaura cross-coupling, the reaction is also initiated by the oxidative addition of a Pd\(^0\) complex into a carbon-halide/pseudohalide bond generating an electrophilic Pd\(^{III}\) species (Figure 2). After transmetallation with a nucleophilic organometallic compound (Zinc or Boron), and reductive elimination, the cross-coupled product can be afforded.
While those methods proved their robustness and usefulness through multiple applications, the necessity to pre-functionalize the starting material and the generation of stoichiometric wastes motivated chemists to direct their research in the field of C-H functionalization.

Considering the abundance of C-H bonds in organic feedstocks or elaborated molecules (Figure 3), such as simple hydrocarbons, bioactives molecules, biopolymers or organic materials, selective functionalizations of C-H bonds would deliver a method of choice for organic derivatizations.

However, the low reactivity of intrinsic C-H bonds, combined with selectivity issues for the direct functionalization of complex structures, motivated chemists to develop new methods involving transition-metal catalysts to answer the need of transformations based on C-H activation. This introduction will highlight the main advances in the field of C-H activation allowing to overcome the aforementioned limitations.
2. C(sp²)-H functionalization

Initially introduced in the first half of the 20\textsuperscript{th} century,\textsuperscript{[7]} transition-metal-catalyzed C–H bond functionalization has been exponentially developed since the 21\textsuperscript{th} century, with the emergence of methods to generate new carbon–carbon and carbon–heteroatom bonds from diverse C–H bonds.\textsuperscript{[8]} In most cases, the reaction substrates are readily accessible, leading to valuable functionalized products in a step-economical manner. The power of these catalytic methods has been translated into numerous applications including the synthesis of natural products,\textsuperscript{[9]} pharmacologically active substances, and organic functional materials.\textsuperscript{[10]}

The C(sp³)-H functionalization has rapidly emerged in the field of transition-metal-catalyzed reactions.\textsuperscript{[11]} The metal can engage the C-H cleavage with the target C-H bond after an initial π-orbital interaction with the substrate (Scheme 2). The initial report for such transformation using palladium was described by Fujiwara\textsuperscript{[12]} and co-workers in 1968, for the formation of stilbene from styrene. Coordination-directed metatation has also been well exploited for selective C-H functionalization at arene rings in the ortho position to a suitable functional group (Scheme 2). The key discovery in this area was made by Murai and co-workers who demonstrated the first efficient, catalytic and selective coupling of an arene C-H bond and an alkene.\textsuperscript{[13]}

![Scheme 2: Arene C-H functionalization](image)

3. C(sp³)-H functionalizations

Among all types of C-H bonds, C(sp³)-H bonds of alkyl have been recognized as particularly difficult to cleave because they possess additional conformational degrees of freedom and as they don’t benefit from precoordination of the transition-metal to a π or π* orbitals.

One of the biggest synthetic challenge over the past 60 years was the selective conversion of light alkanes to alcohols or olefins using selective C(sp³)-H functionalization (Figure 4). The simple transformation of methane to the high-value-added methanol would allow gaseous methane\textsuperscript{[14]} to be transported as liquid product or methanol to be used in reactions that form C-
C bonds in higher hydrocarbons.\textsuperscript{[15]} Nowadays, none of these goals have been achieved in a practical fashion.

While considering the “parafins” C(sp\textsuperscript{3})-H bonds, the poor reactivity of such bonds is often explained by their high energies (90 to 100 kcal/mol), their low acidity (pKa = 45-60) and their unreactive molecular orbitals.\textsuperscript{[16]}

However, even if the C(sp\textsuperscript{3})-H bonds are more difficult than others to cleave, they have proved to not be completely inert. Alkanes can react with extremely active species such as radicals, carbenes and highly acidic compounds. Additionally, the obstinacy of chemists to make new developments in this field brought a library of transition-metal-catalysed reactions which allows the functionalization of such C-H bonds.\textsuperscript{[8]}

The fields of C-H functionalizations or C-H activations are really broad, and in permanent development. After the initial reports of Corey\textsuperscript{[17]} in 1958 and later Shilov in C(sp\textsuperscript{3})-H halogenation,\textsuperscript{[18]} Woodward in C-H amination,\textsuperscript{[19]} Cory, Scott and DeCicco in C-H insertion,\textsuperscript{[20]} Bergman in iridium-catalysed C(sp\textsuperscript{3})-H activation\textsuperscript{[21]} and the great development of C(sp\textsuperscript{2})-H arylation initiated by Ames,\textsuperscript{[22]} the emergence of palladium-catalysed C(sp\textsuperscript{3})-H activation has proved to be a method of choice for such functionalization.

\textbf{4. Palladium-catalysed C(sp\textsuperscript{3})-H functionalizations:}

\textit{4.1- C(sp\textsuperscript{3})-H activation of alkanes using palladium catalysis:}

Among the library of reactions for C-H bonds functionalizations, only few depicts the selective functionalization of C(sp\textsuperscript{3})-H bonds of alkanes. Indeed, most of them are carried out on symmetric or relatively simple alkanes. Among these few examples, Fujiwara reported in 1989 the functionalization of cyclohexane using Pd(II)-catalysed C(sp\textsuperscript{3})-H carboxylation to afford the corresponding carboxylic acid (Scheme 3).\textsuperscript{[23]} In their conditions, the cyclohexane is used as solvent, under high pressure of CO (20-40 atm), Pd(II)/Cu(II) as catalytic system in trifluoroacetic acid at 80°C and afforded the cyclohexanecarboxylic acid 1 in 4.3% yield based on cyclohexane. In a similar fashion, they reported later the carboxylation of gaseous propane under similar conditions (Scheme 3). While using a high pressure of propane (10 atm), with high pressure of CO (20 atm) and Pd(O\textsubscript{2}CEt)\textsubscript{2}, CuSO\textsubscript{4}, and K\textsubscript{2}S\textsubscript{2}O\textsubscript{8} in TFA at 80°C, a mixture of isobutyric and butyric acids isomers were obtained respectively in 360% and 300% based
on Pd. To explain these reactions, they proposed the in situ generation of a cationic [Pd(TFA)]⁺ species as electrophilic intermediate, which could undergo a nucleophilic addition of a C(sp³)-H bond of the alkane to generate an [alkyl-Pd-TFA] intermediate. Further carboxylation and oxidation would then generate the corresponding carboxylic acids.

Scheme 3: Early examples of alkanes functionalization by Fujiwara

In 2002, Strassner and co-workers reported the use of a Pd/NHC complex as catalyst for the C(sp³)-H activation of methane (Scheme 4).[24] A mixture of catalyst 5, with K₂S₂O₈ as stoichiometric oxidant, TFA and trifluoroacetic anhydride (TFAA) under 30 bars of methane led to the formation of trifluoroacetic acid methyl ester 6 in 3000% based on 5. The authors proposed a C(sp³)-H activation by Pd(II) followed by bromine oxidation to undergo a Pd(IV) intermediate for C-H functionalization.[24]

Scheme 4: Oxidation of methane to trifluoroacetic acid methyl ester

According to the lack of reports and as shown with these few examples, alkanes are non-polar and hydrophobic and thereby, react weakly with Pd species. However, with a large excess of the alkane reagent, with highly reactive Pd species and harsh conditions, the functionalization of such feedstock is possible. Nevertheless, such an approach cannot allow the control of regio- and chemoselectivity, and can undergo overfunctionalization. Therefore, the Pd-catalysed C(sp³)-H activation using substrates bearing pre-existing functional groups as directing group (DG) to coordinate the Pd species has then emerged as a powerful tool for selective functionalizations.
5. Directed palladium-catalysed C(sp³)-H activation

With the issues encountered for the selective functionalization of alkanes, the use of substrates containing one or several functional groups that can chelate the Pd catalyst allows the selective functionalization of C-H bonds. Traditionally, the strong σ-donor or π-acceptor of nitrogen, sulfur, or phosphorus-containing moieties are required and can be used as non-covalent directing groups for the coordination to palladium to direct C-H activation, and form stable, well-defined palladacycles (Figure 5).[25] The central point of this methodology is based on the formation of a stable 5- or 6-membered palladacycle. The formation of such palladacycles intermediates lowers the activation energy barrier during the C(sp³)–H cleavage step, underlining the importance of directing group for achieving high reactivity in Pd-catalysed C(sp³)–H activation.

In addition to non-covalent directing groups for selective C-H activation, oxidative addition of palladium into a carbon-leaving group such as halides (I, Br or Cl) or pseudo-halides (OTf) can be used (Figure 5). In this case, the substrate becomes the ligand of the metal. The C(sp³)-H activation directed by carbon-leaving group bonds will be discussed later and used as a central point for this thesis.

Figure 5: Directed C(sp³)-H activation by non-covalent directing group or from oxidative addition

5.1. Palladium-catalysed C(sp³)-H activation directed by non-covalent directing group

First introduced by Trofimenko in 1973, the term cyclometalation involves the cleavage of C(sp²)-H and C(sp³)-H bonds by transition-metals to form [M-R] species.[26] Different metals, as well as different mechanisms can be involved in this process. The main mechanisms for cyclometalation include oxidative addition, electrophilic activation, concerted metallation/deprotonation (CMD) and σ-bond metathesis.

According to the more reactive C(sp³)-H towards C(sp³)-H bonds, numerous examples of cyclopalladation have been reported on the former in the early literature.[27] However, only few examples described the cyclopalladation of unactivated aliphatic C(sp³)-H bonds.
Early examples are using oximes, pyridines or amines as strongly coordinating directing groups. Further developments using less-coordinating directing groups, such as carboxylic acids, hydroxamic acids, amides were then developed to enhance the reactivity of the in situ formed palladacycle.

In 1978, Shaw and co-workers induced the formation of the 5-membered palladacycle dimer 8 after C(sp\(^3\))-H bond cleavage using a stoichiometric Pd source (Na\(_2\)PdCl\(_4\)) and NaOAc with the tert-butyl-methyl ketone oxime 7 (Scheme 5). This stable palladium moiety has been fully characterized using NMR and IR studies.

A 6-membered palladacycle 10 was isolated by Hiraki and co-workers in 1983, after C(sp\(^3\))-H cleavage directed by a pyridine moiety (Scheme 5). In both cases, the presence of a quaternary carbon in \(\alpha\)- to the cleaved C-H bonds avoid from \(\beta\)-H elimination.

These isolated and stables palladacycles have then been subjected to a range of conditions to afford a C(sp\(^3\))-C or C(sp\(^3\))-heteroatom coupled product. Baldwin and co-workers converted Shaw’s palladacycle 8 to the alkyl-halide product 11 after treatment with chlorine in CCl\(_4\), and subsequent reduction with sodium cyanoborohydride (Scheme 6). The product 11 resulting from Pd-Cl exchange was isolated in 64% yield. Moreover, a ligand exchange with pyridine from 8 could lead to the monomeric palladacycle 12. Further treatment with Pb(OAc)\(_4\) and reduction furnished the acetoxyalted product 13 in quantitative yield.

Sanford and co-workers developed in 2004 the catalytic version of such reaction in the presence of a stoichiometric oxidant (Scheme 7). While using a less-chelating methoxy-oxime
directing group and with a fine tuning of the reaction conditions, the desired acetylated oxime 14 was obtained from 15, after formation of a 5-membered palladacycle.

Later, the applicability of such oxime-directed acetoxylation was demonstrated for the synthesis of the natural product paspaline by Johnson and co-workers (Scheme 7).[35]

In addition to non-covalent directing groups for C-H functionalizations, oxidative addition of palladium into a carbon-leaving also allows such selective functionalization.

In 1992, Dyker reported the first C(sp³)-H activation of a methoxy group directed by oxidative addition (Scheme 8).[36] Starting from 18, and while using Pd(OAc)₂ as catalyst, K₂CO₃ as stoichiometric base in DMF, he could afford the dimer 20 via formation of the palladacycle 19. The method was extended later to the C(sp³)-H activation of a tert-butyl moiety for the synthesis of benzocyclobutene 22 (BCB), using similar conditions with an external aryl-bromide reagent 21.[37] These first two examples are now considered as the starting point for the development of palladium-catalysed C(sp³)-H activation for the synthesis of medium-sized rings.
The mechanism for BCB synthesis is described scheme 9. The reaction starts with the oxidative addition of in situ formed Pd(0) into the C-I bond of 21, to form a Pd(II) intermediate 23. Then, the C(sp\(^3\))-H activation of the tert-butyl moiety after CMD process promoted by K\(_2\)CO\(_3\), undergo the formation of the palladacycle 24. At this point, the presence of an external aryl-bromide can undergo oxidative addition to palladium, and give the highly oxidize Pd(IV) intermediate 25. This intermediate can then undergo reductive elimination, to form the aryl-aryl bond, and generate an alkylpalladium moiety 26. The proximity of the C-H bond on the aromatic ring can then undergo a C(sp\(^2\))-H arylation reaction to form the 5-membered palladacycle 27. Finally, reductive elimination furnished the BCB 22 and regenerate the Pd(0) catalyst to insure the turn-over of the reaction.
With the absence of ligand in Dyker’s reports, the reaction suffers from a lack of control and undergoes aryl-aryl coupling and BCB formation. However, these two pioneer results represent a great proof-of-concept in the field of palladium-catalysed C(sp^3)-H activation to afford valuable products in a straightforward manner. Dozens of reports in this field will then follow, extending the library of possibilities for ring constructions and finding applications in the fields of bioactive compounds or natural products synthesis.[38]

5.3. Early improvement using a phosphine ligand

In 2003, Baudoin reported the first example of Pd(0)/Pd(II) catalysed C(sp^3)-H activation with the presence of a phosphine ligand starting from aryl bromide 28 (Scheme 10).[39] In their improved synthesis of BCB, the use of tri-orthotolylphosphine (TOTP) shuts down the second oxidative addition, preventing the formation of oligomeric products. In addition, Baudoin and co-workers showed that methylene C-H bonds could also be activated, thereby furnishing after β-hydride elimination, a mixture of olefins 31 and 32. Indeed, the reductive elimination after cleavage of the latter is difficult notably for steric hindrance reasons, leading exclusively to the alkenes.
After further investigations, they found out that two phosphines could favor each reaction pathway to obtain either olefins 35 or BCB 36 (Scheme II). A fine design of reaction substrates, combined with adapted conditions were necessary. First, the use of a relatively electron-deficient triarylphosphine ligand (tri(5-fluoro-2-methylphenyl)phosphine : F-TOTP) could decrease the required reaction temperature from 150°C to 100°C and favored olefins formation, increase the selectivity for internal olefins and reactivity for hindered substrates (Scheme II).\cite{40} On the other hand, they discovered that the bulky PrBu₃ ligand allows a higher efficiency and a broader scope for the synthesis of BCB as well as the use of aryl chlorides as starting materials.\cite{41} This work underlines the importance of phosphine ligands in such reaction.

**Scheme II: Selective synthesis of olefins and BCB by Baudoin**

### 5.4. Reaction mechanism

With the development of transition-metal-catalysed C(sp²)-H activation in aryl-aryl couplings, reaction mechanisms have been investigated. Computational studies by Davies\cite{42} and McGregor,\cite{43} combined with the work of Echavarren and Maseras\cite{44} excluded...
carbopalladation, electrophilic aromatic substitution or σ-bond metathesis (SBM) as mechanism pathway to propose the concerted-metalation-deprotonation (CMD) mechanism in the C(sp²)-H cleavage.\textsuperscript{[45]}

Then, Baudoin\textsuperscript{[41]} and Fagnou\textsuperscript{[46]} proved that this CMD mechanism was as well involved in the C(sp³)-H activation.\textsuperscript{[47]} As shown for the synthesis of BCB or olefins (Figure 6), the reaction mechanism starts with oxidative addition of palladium into the carbon-halide bond of 37. Pd(0) is generated \textit{in situ} from Pd(II) and the phosphine ligand (L). Ligand exchange with a carbonate or carboxylate undergo the formation of the electrophilic Pd(II) species 38. Then, the CMD mechanism occurs to form a palladacycle 39. Depending of the design of the substrate, 5-, 6- or even 7-membered palladacycles can be formed. The formation of such palladacycle is generally favoured with strong Thorpe-Ingold effect (R₁ and R₂). Further decoordination of the base and reductive elimination undergo the formation of the cyclic product 36. Another pathway can be the proton transfer of 39 to generate the alkylpalladium intermediate 40. This intermediate, as in the Heck reaction can then undergo β-hydride elimination and form the olefin 35.

\[ \text{RCO}_{2}^{-} \]

For the C-H cleavage step, DFT calculations were made by Baudoin and Clot for the synthesis of the BCB 45 (Figure 7).\textsuperscript{[48]} After simplifying the system (use of carbonate and PrBu₃ as phosphine ligand) on the substrate 41, they proposed two plausible reaction pathways. They suggested two similar transition states (TS), operating in an intramolecular fashion:

\[ \text{HO}(R)\text{C}=O \]

\[ \text{Pd}^{II} \]

\[ \text{R}_{1}\text{R}_{2}\text{L} \]

\[ \text{R}_{1}\text{R}_{2}\text{L} \]

\[ \text{Pd}^{II}\text{L} \]
First, a cis-activation model, previously proposed by Fagnou and Gorelsky was simulated, via the formation of a stable precomplex 42 involving κ²-carbonate coordination (Figure 7). According to calculations, this model possesses a high activation barrier (37.9 kcal/mol) for the C-H activation step.

Then, Baudoin and Clot proposed a trans-activation giving rise to a less stable precomplex 46, but a lower activation barrier (26.2 kcal/mol) (Figure 7). Interestingly, compared to 42, agostic interaction was observed in the precomplex 46 which enhances the protic character of the geminal proton. Thanks to this interaction and κ¹-precomplex coordination, a lower activation barrier is required to reach the transition state. The C-H bond cleaved in this mode is not the agnostic one, but the geminal.

Baudoin and Clot concluded that the trans-coordination appears to be the favored one according to DFT calculations for the formation of BCB, but both mechanisms should be considered in the case of other substrates.

![Proposed TSs for C-H activation step after DFT calculations](image)

Thanks to these computational studies and accumulated experimental data, a selectivity guideline for the Pd(0)-catalysed intramolecular C(sp³)-H activation has been proposed. This selectivity trend is ruled by several factors:

- First, the acidity of the cleaved C-H bonds (benzylic>aromatic>cyclopropyl>methyl>methylene>methine) are of first importance.
- Then, the size of the palladacycle formed after C-H cleavage (5-membered>6-membered>>7-membered) which translate into the following preference for the formation of cyclic products: 4-membered>5-membered>>6-membered.
These are guidelines, and of course other factors should be taken in consideration: the steric environment (Thorpe-Ingold effect, steric hindrance…), the stability and ring-strain of the product as well as reaction conditions can influence the reaction outcome.[49]

Depending of the substrates, the main side reactions involve proto-debromination, homo-coupling, β-hydride elimination or nucleophilic addition of palladium. Keeping all this factors in mind is crucial for the design of new reactions.

5.5. **Intramolecular activation of unactivated C(sp³)-H bonds using Pd⁰/Pd⁺ catalysis: representative examples**

With these parameters, developments have been made for the synthesis of medium-sized rings involving C(sp³)-H activation reaction. According to the accumulated reports, two distincts reaction conditions appeared to be relevant for the synthesis of (fused)-cyclic products:

- First, a combination of inorganic base, in a high-boiling and polar solvent, with the presence of Pd⁰/Ligand as catalytic system
- Then, a combination of organic base (carboxylate, phosphate, pivalamide…) with an inorganic base in a high-boiling apolar solvent can be used and Pd⁰/Ligand as catalytic system.

Generally, reactions require temperatures > 90°C to operate. Both conditions can be used as starting point for a reaction screening.

After the initial reports exposed earlier, several research group started to be interested in this methodology for the construction of medium-sized rings. The scheme 12 depicts a non-exhaustive list of relevant examples.

Hetero- or non-heterocyclic products can be obtained with different sizes, including dihydrobenzofurans 49,[50] indolines 50,[51] indanones 51,[46] lactams,[46] hexahydroindoles 53[52] or quinolinones 54.[53] Most of the reports depicts the formation of 5-membered rings, for their high stability and the well-favoured formation of the 6-membered palladacycles. These methodologies allowed the formation of valuable scaffolds for drug discovery or natural product synthesis, in an atom-economical and straightforward manner.
The usefulness of such methodology has been translated into several applications, notably for the construction of natural product scaffolds or bioactive molecules. Moreover, the C(sp³)-H activation showed its robustness for the synthesis of valuable building blocks over gram scale, with excellent yield and selectivity.

In 2012, Baudoin and co-workers constructed the tricyclic core of the natural product glionitrin B after intramolecular C(sp³)-H activation on the diketopiperazine derivative 56 (DKP) (Scheme 13). The reaction proceeded with good yield while using the predefined Pd(PCy₃)₂ catalyst, in presence of a mixture of carbonates and pivalic acid. Shortly after, Baudoin and co-workers developed specific conditions to generate an array of 1-indanoles and 1-indanamines (Scheme 13). In their case, exclusive formation of the indane was observed with selectivity towards the trans isomer. The method was used to synthesize the synthetic precursor 59 of the herbicide indaziflam. After removal of the phtalimide group with treatment with hydrazine, the indanamine 60 was obtained.
In 2012, starting from cycloalkenyl bromides 61, the Baudoin’s group built the hexahydroindoles core of *Aeruginosins* through Pd(0)-catalysed intramolecular C(sp<sup>3</sup>)-H alkenylation in a really efficient manner (Scheme 14). The efficiency of the method was later exploited for the synthesis of the natural products *Aeruginosin* 298A and 98A-C (Scheme 14).

In this report, 4.8 grams of the common intermediate 63 were obtained using C(sp<sup>3</sup>)-H alkenylation of 62. The synthesis of *Aeruginosin* 298A was completed on 700 mg scale, with an overall yield of 8.2% for 17 steps. This direct application of C(sp<sup>3</sup>)-H activation showed its robustness and applicability for complex molecules synthesis.
In organic synthesis, the selective synthesis of one enantiomer of a product is always challenging. During a C(sp^3)-H activation reaction, the CMD step can be enantiodetermining for the discrimination of two enantiotopics methyl groups or two methylene C-H bonds. According to the plausible transition state, enantioselectivities can be reached with the use of a chiral base or a chiral ligand.

The first example of enantioselective Pd-catalysed C(sp^3)-H activation has been reported by Kündig and co-workers in 2011 (Scheme 15).[57] While using a C2-symmetric NHC, they were able to achieve very high enantioselectivities for the enantiodiscrimination of two methylene C-H bonds despite the need of high reaction temperatures (140-160°C) in their synthesis of trans-fused indolines 65 (Scheme 15). The enantiodiscrimination of two methyl groups was later reported by Kagan for the synthesis of enantioenriched indolines 68 introducing a new type of bidentate-type ligand (Scheme 15).[58] Finally, the group of Cramer introduced the monodentate TADDOL-derived phosphoramidites and phosphonites ligands for the direct C(sp^3)-H
activation of a cyclopropyl moiety (Scheme 15). Good yield, as well as good enantioselectivities can be achieved for the synthesis of tetrahydroquinolines 71.

According to the increasing interest from chemists and biologist for enantioselective synthesis, the field of C(sp\(^3\))-H activation using chiral ligand or chiral base is in intensive development to reach high enantioselectivities in the discrimination of both methyl groups or secondary C-H bonds.[60]

6. Research developments and projects covered in this thesis

All along this thesis, we tried to develop new systems based on intramolecular C(sp\(^3\))-H activation to access medium-sized rings. With the growing concurrence in this field, we tried to reach a high degree or originality, applicability and scalability for these new processes.

This manuscript is divided into two parts: the first part will cover the direct C(sp\(^3\))-H activation reactions. First, the efficient synthesis of lycorine alkaloids using a double palladium-catalysed C(sp\(^2\))/C(sp\(^3\))-H activation reaction. Then, a new approach for the synthesis of β-lactams from carbamoyl chlorides will be covered. Finally, the last chapter will cover the synthesis of benzoxazines through benzazetidines rearrangement.
The second part of this thesis will cover the remote (or distal) C(sp³)-H activation, notably using 1,4-Pd shift. The first chapter will deal with the synthesis of γ-lactams and indanones via C(sp²)-C(sp³) coupling. The second chapter will focus on the formation of C(sp³)-C(sp³) bonds for the synthesis of benzofurans, indolines, chromanones and benzofuranols.
Part 1: Direct $C(sp^3)$-H activation
Chapter 1.1:

Synthesis of lycorine alkaloids using Pd-catalysed C-H arylation
1. Lycorine alkaloids and derivatives:

In this first chapter of this manuscript, we focus our attention on the synthesis of lycorine alkaloids.

More than ten congeners of the lycorine alkaloids have been extracted and characterized from the plants belonging to Amaryllidaceae species by Wildman and co-workers in 1955. Pratosine, hippadine, assoanine, lycorine and its degradation product (γ)-lycorane are representative of this family of molecules (Figure 8).[61] Today, about 30 congeners of this family have been identified.[62] [63]

![Figure 8: some relevant Lycorine alkaloids family members](image)

To understand the relations between Amaryllidaceae alkaloids, their biosynthesis, including lycorines, have been elucidated (Figure 9).[64] These molecules are derived from the amino acids L-phenylalanine and L-tyrosine, which can provide protocatechuic aldehyde and tyramine respectively. Imine formation, followed by reduction and methylation leads to the common precursor o-methylnorbelladine. Alternative ways of oxidative phenol coupling produce three main skeleton which offer diversity in the Amaryllidaceae alkaloids. A complex process of enzymatic steps is occurring on the different alkaloids which gives a spectrum of compounds that differs between species and cultivars, and even between the different tissues of the same plant.[64] Each Amaryllidaceae species produces a mixture of alkaloids, often with a few major compounds and a larger number of compounds at low concentrations.
The pharmacological activities of pyrrolophenanthridine derivatives, or lycorine alkaloids, have been widely studied in the past decades. Their biological activities, including cancer cell growth inhibition, anti-Alzheimer (acetylcholinesterase inhibition), but also anti-tripanosomal and anti-fungal activities have consequently received attention from both chemists and biologists.\cite{65}

According to the diverse biological activites of theses molecules, chemists focused their attention on the development of new libraries of non-natural lycorines derivatives for medical uses. For instance, Evidente and co-workers could identify a lycorine analogue which was 100 times more potent against an U373 human glioblastoma model in vitro.\cite{66} This recent example highlights the interest of developing a general method to access diverse lycorine alkaloids derivatives, in a simple and efficient manner.

2. Previous synthesis:
A variety of total synthesis of natural lycorine alkaloids have been reported, after the initial work of Kotera in 1958.\cite{67} Today, more than 30 synthesis of these compounds have been described in the literature.
2.1. Previous synthesis involving Pd-catalysis

According to the numerous reports relative to lycorine alkaloids synthesis, this part will be dedicated to relevant synthesis of such molecules.

Palladium catalysis, involving cross-coupling reactions has been largely used for the construction of the polycyclic core of lycorine alkaloids. Most of the synthetic strategies are relying on the use of an indole derivative for the construction of the polycyclic core of the pyrrolophenanthridine. The main disconnections for the lycorine core are described figure 10.

![Figure 10: Previous disconnections for lycorine core synthesis](image)

To illustrate this and in complement to metal-catalysed cross-coupling reactions, Kerr reported the formation of isoquinoline structure using an oxidative aryl-aryl coupling from 1.1 using hypervalent iodine (Scheme 16). Further DDQ oxidation to indole underwent facile and rapid access to hippadine.\[68\]

![Scheme 16: Synthesis of Hippadine by Kerr](image)

The shortest synthesis of (±)-γ-lycorane was published in 2017 by the group of Hilton (Scheme 17).\[69\] This synthesis is using a sequential intramolecular acylal cyclisation (IAC) from 1.5 followed by an intramolecular Heck reaction to furnish 1.7. After hydrogenation of the two olefins, followed by amide reduction, the product was obtained in 31% overall yield, over 6-7 steps. This synthesis is to the best of our knowledge, the shortest and most efficient synthesis of (±)-γ-lycorane.
In 2014, the group of Take moto reported the synthesis of pratosine and hippadine using an intramolecular C-H functionalization strategy (Scheme 18).\(^{[70]}\) The polycyclic core was constructed in a stepwise manner including a C(sp\(^3\))-H activation between a carbamoyl chloride and a benzylic C-H bond. The authors are using Pd(OAc)\(_2\) as catalyst, Ad\(_2\)Pn-Bu as ligand and PivNHO\(^-\) as base for the CMD, under CO atmosphere. The desired intermediate 1.9 was obtained in moderate yield, with decarbonylated side product 1.10 as major product. The intermediate 1.9 can then be reduced using DIBAL-H, leading to the indole which after further oxidation, afforded the pratosine.

Scheme 17: Synthetic path for rapid access to \((\pm)\)-\(\gamma\)-lycorane by Hilton et al.

Scheme 18: Synthesis of pratosine by Takemoto et al.
3. Initial work on Pd-catalysed C-H arylation:

3.1. Initial work on palladium catalysed C-H arylation of carbonyls compounds

From 1997, the groups of Buchwald,[71] Hartwig[72] and Miura[73] developed the first intermolecular coupling of aryl halides and ketone enolates, for the synthesis of $\alpha$-aryl ketones 1.12 (Scheme 19).[71] Based on these methodologies, they later explored the arylation of other substrates such as carboxylic acid derivatives. In 1998, Hartwig published the first inter and intramolecular $\alpha$-arylation of amides, for the synthesis of substituted amides and oxindoles 1.18.[74] Based on the in situ formation of an enolate with the presence of a strong base (tBuOK), followed by palladium-catalysed C-H arylation, this methodology allows the formation of a broad range of valuable products.

Scheme 19: General $\alpha$-functionalization of carbonyl compounds and synthesis of oxindoles by Hartwig et al.

Later, improvements by Zhu showed that the use of carbonate as milder base could generate the formation of oxindole 1.20 from 1.19 (Scheme 20).[75]

Scheme 20: Zhu’s $\alpha$-arylation for the synthesis of oxindoles

3.2. Palladium-catalysed intramolecular double C-H activation methodology:

3.2.1. Intramolecular double C(sp$^2$)-H arylation

Intramolecular double C-H activation reactions have been widely studied in the past decades, notably for the efficient access to polycyclic compounds. First introduced by Echavarren and
co-workers in 1996 in a C(sp²)/C(sp²) manner,[76] and later explored by Kamikawa for helicenes
1.24 synthesis,[77] these methods were later extended from carbocycles to heterocycles (Scheme 21). Tanaka proposed a new synthesis of fused indolines 1.26 using this approach, starting from
a bis-halogenated substrate 1.25.[78] Indeed, the fast oxidative addition of palladium into the C-
Br bond of 1.25 allowed the formation of the 5-membered ring. Subsequently, oxidative addition
of palladium into the C-Cl bond, followed by C-H arylation, afforded the fused indoline 1.26 in
63% yield.

Scheme 21: Early examples of double C-H arylation by Echavarren, Kamikawa and Tanaka

3.2.2. Intramolecular double C(sp²)/C(sp³)-H arylation

More recently, Baudoin developed a new type of double C-H activation reaction for the rapid
construction of polycyclic molecules, involving a C(sp³)-H-arylation combined with a C(sp³)-
H-arylation in a one-pot manner (Scheme 22).[79] In this case, the choice of leaving group
(bromide and chloride) is crucial for the formation of the product as a single isomer. Starting
from 1.27, the fast oxidative addition in the C-Br bond, followed by aryl-aryl coupling affords
the formation of the 6-membered ring. Then, C(sp³)-H arylation can occur after oxidative
addition of palladium into the C-Cl bond. Pd(OAc)², combined with PCy₃ generates in situ the
active Pd(0) species. Inorganic base (K₂CO₃) and polar solvent (DMF) at 140°C afford the
heterocyclic product 1.28 in 87% yield. This method is the first report of such double C-H
activation reaction, involving a C(sp³)-H activation.

Based on these precedents, we estimated that double C-H arylation methodology could be a
powerful tool for the rapid construction of lycorine alkaloids.
Scheme 22: Double C(sp²)-H-arylation and C(sp³)-H arylation for rapid access to polycyclic molecules

4. Goal of this project and retrosynthetic analysis:
With these previous reports in hand, we considered the following retrosynthetic plan for lycorine alkaloids synthesis: amide reduction and selective arene hydrogenation of 1.29 would lead to the (±)-γ-lycorane (Scheme 23). Additionally, hippadine and pratosine could be obtained respectively from the tetracyclic intermediate 1.29 and 1.9. To obtain the pyrrolophenanthridinone core, we envisioned disconnecting compounds simultaneously at bonds a and b using a Pd⁰-catalysed double C–X/C–H arylation. Starting from a bis-halogenated precursors 1.30 and 1.31 with the halogens atoms located either on ring A and C or both on ring C, we believed that the polycyclic core of the molecule could be constructed. Finally, precursors for C–H arylation could be obtained by simple alkylation of readily available starting material 1.32 and 1.33.
4.1. **Double C-H activation investigations for lycorine alkaloids synthesis**

4.1.1. **Substrate design and mechanism**

For the synthesis of lycorine alkaloids using double C-H activation strategy, we started by investigating for the most appropriated bis-halogenated substrate to perform this reaction (Scheme 24).

The double C–X/C–H arylation was first conducted with compound 1.30 bearing the two bromine atoms on the same aromatic ring. PCy₃ was chosen as the ligand, as it was previously employed in both individual C(sp²)–Hₘ₈⁴ and C(sp³)–H arylation. The well-defined Pd(PCy₃)₂ complex, which was found to provide superior yields in previous C(sp³)–H activation reactions, was employed as the catalyst, combined with catalytic PivOK/K₂CO₃ as the basic system. Under these conditions, the double C–Br/C–H arylation took place, but isomer 1.34, arising from the electronically favoured activation of the C(sp²)–Hₜ position instead of the more stericly accessible C(sp²)–Hₜ position was isolated as the major product. This observation was consistent with initial observations from Harayama and co-workers.

![Mechanism pathway](image_url)

To solve this regioselectivity issue, we examined the reaction of isomeric dibromide 1.31a, bearing bromine atoms on rings A and C (Scheme 25). Under the same conditions, the desired product 1.29 was isolated, albeit in low yield (22%) and with byproducts from competitive arylation at C–Hₜ position. A simple solution was found by replacing the bromine atom on ring C with a chlorine atom starting from 1.31b. Indeed, in this case the oxidative addition of the C–Br bond to Pd⁰ is faster than that of the C–Cl bond, to give intermediate 1.37. Upon activation of the most reactive C(sp²)–Hₜ bond vs the less reactive C(sp³)–Hₜ bonds, ring B would be formed with the correct regiochemistry via palladacycle 1.38. Then C–Cl oxidative addition, would lead to complex 1.40, followed by activation of a C–H bond to give palladacycle 1.41,
which would allow for the construction of ring D after reductive elimination. Accordingly, compound 1.31b furnished the desired product 1.29 in higher yield (37%), and isomers byproducts were not detected.

![Scheme 25: Synthesis of pyrrolophenanthridinone core](image)

**4.1.2. Reaction optimization**

With this first result in hand, we started the optimization of the reaction for the synthesis of 1.29. Decreasing the temperature from 140 to 120°C considerably affect the yield (28%) (Table 1, Entry 2). Switching the base from K₂CO₃ to Cs₂CO₃, the yield was increased to 50% (Entry 3). By reducing the equivalents of base from 4 to 2 equivalents, the desired product 1.29 could be obtained in 92% isolated yield (Entry 4). Palladium loading could be decreased to 5 mol% and afford the product still in good yield (70%) (Entry 5). Moreover, in situ catalyst generation from Pd(OAc)₂/PCy₃ or Pd₂dba₃/PCy₃ could also be employed but provided a lower yield than the well defined Pd(PCy₃)₂ complex (respectively 53% and 50%) (Entries 6-7). When the reaction was stopped at incomplete conversion (15 min), the monocyclized intermediate 1.39, from C(sp²)–Br/C(sp²)–H arylation, was isolated in 68% yield, thereby validating the initial mechanistic hypothesis.
<table>
<thead>
<tr>
<th>Entries</th>
<th>Pd/L</th>
<th>Additive</th>
<th>Base (equiv)</th>
<th>T°C</th>
<th>^1H NMR yield (isolated)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(PCy$_3$)$_2$ (10 mol%)</td>
<td>PivOK</td>
<td>K$_2$CO$_3$ (4 equiv)</td>
<td>140</td>
<td>37%</td>
</tr>
<tr>
<td>2</td>
<td>Pd(PCy$_3$)$_2$ (10 mol%)</td>
<td>PivOK</td>
<td>K$_2$CO$_3$ (4 equiv)</td>
<td>120</td>
<td>28%</td>
</tr>
<tr>
<td>3</td>
<td>Pd(PCy$_3$)$_2$ (10 mol%)</td>
<td>PivOH</td>
<td>Cs$_2$CO$_3$ (4 equiv)</td>
<td>140</td>
<td>50%</td>
</tr>
<tr>
<td>4</td>
<td>Pd(PCy$_3$)$_2$ (10 mol%)</td>
<td>PivOH</td>
<td>Cs$_2$CO$_3$ (2 equiv)</td>
<td>140</td>
<td>90% (92%)</td>
</tr>
<tr>
<td>5</td>
<td>Pd(PCy$_3$)$_2$ (5 mol%)</td>
<td>PivOH</td>
<td>Cs$_2$CO$_3$ (2 equiv)</td>
<td>140</td>
<td>70%</td>
</tr>
<tr>
<td>6</td>
<td>Pd(OAc)$_2$/PCy$_3$ (10 mol%)</td>
<td>PivOH</td>
<td>Cs$_2$CO$_3$ (2 equiv)</td>
<td>140</td>
<td>53%</td>
</tr>
<tr>
<td>7</td>
<td>Pd(dbu)/PCy$_3$ (10 mol%)</td>
<td>PivOH</td>
<td>Cs$_2$CO$_3$ (2 equiv)</td>
<td>140</td>
<td>50%</td>
</tr>
</tbody>
</table>

*Using trichloroethylene as internal standard

Table 1: Optimization table for the double C-H arylation

4.1.3. Scope and limitations

With this optimized conditions in hand, we next studied the scope of the double C(sp$^3$)/C(sp$^3$)-H arylation (Scheme 26). We found out that different substituents with electron donating or electron withdrawing properties on the aromatic ring were suitable for this reaction. As explained before, as far as the oxidative addition is occurring in the C-Br bond first, product could be obtained in good yield as a single regioisomer. By increasing the electron density on ring A, and decreasing the electron density on ring C the compounds 1.49 and 1.50 were obtained in moderate yields (respectively 54% and 27%), as single product. In all other cases, good to excellent yields of the polycyclic product were obtained. Functional groups, such as methyl ester 1.52, nitriles 1.48, pyridine 1.47 or protected phenols 1.51 were also tolerated in these conditions. Substituents in α-position to the amide were also well tolerated (1.53-1.55), consistent with previous results on the individual C(sp$^3$)–H arylation reaction.[74]
4.2. **Selective arene hydrogenation of the pyrrolophenanthridinone core**

Gratifyingly, the synthesis of 1.29 could be scaled up, without significant decrease in efficacy (Scheme 27).

Then, we considered directly converting 1.29 to (±)-γ-lycorane through selective arene hydrogenation. Selectivity for ring C over ring A might be particularly difficult because, as shown with the calculated HOMO of 1.29 (Figure II), both aromatic rings have almost similar electron density and should react at comparable rates.

However, ring C is more strained than ring A due to the adjacent ring fusions with rings B and D and could potentially be reduced more easily by ring strain release. This is shown with the more distorted bond angles in ring C (Figure II).
Several reports are describing the arene reduction of indoles, indolines and oxindoles, notably by using heterogeneous catalysts such as PtO₂, Pd/C or Rh/C.\[^{[84]}\]\[^{[85]}\]\[^{[86]}\] Fluorinated solvents are often used in hydrogenation conditions for their low nucleophilicity toward nucleophilic addition on olefins. In homogenous fashion, Zeng and co-workers developed a Rh/NHC catalyst for the hydrogenation of aromatic rings.\[^{[87]}\]

However, selective arene reduction is really rare, and has only been reported by Kotera and co-workers on polycyclic system, for the hemisynthesis of (±)-γ-lycorane.\[^{[88]}\]

With those previous reports, we started our investigations for selective arene hydrogenation of pyrrolophenanthridinone 1.29 (Table 2). Starting with PtO₂ in AcOH did not give any traces of product even when the reaction was run under 50 bar of H₂ (Entry 1). Then, while changing to Pd/C in HFIP with 50 bar of H₂, the desired isomer 1.58 was obtained in 41%, with an expected cis,cis relationship (d.r. > 95:5) (Entry 2). Increasing the catalyst loading (20 mol%) gave the desired product in 55% yield, whereas with a significant amount of the undesired isomer 1.59 (17%) (Entry 3). Then, by replacing Pd/C to the more reactive Rh/C with only 6 bar of H₂, we could achieve the synthesis of 1.58 with 62% yield as a single isomer (Entry 4). Moreover, by increasing the pressure to 10 bar showed the apparition of the over reduced product 1.60 in 60% yield (Entry 5).

We also examined different homogenous rhodium catalysts, and notably Rh/NHC complexes used by Zheng and co-workers for the hydrogenation of oxindoles.\[^{[89]}\] The Rh/NHC complexes
were preformed from \([\text{Rh(COD)Cl}]_2\), and used directly for the selective arene hydrogenation of 1.29 under 50 bar H₂. In this case, CAAC carbene or SiMes showed good activities, with yield for the desired product from 64 to 73% (Entries 6-7). However, the reaction scale-up could not be performed with similar yields.

![Reaction Scheme]

Table 2: Selected conditions for hydrogenation of 1.29; a: At 50°C;

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>P(H₂) (bar)</th>
<th>¹H NMR yield* (isolated) for 1.58</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PtO₂ (10 mol%)</td>
<td>AcOH</td>
<td>50</td>
<td>–</td>
</tr>
<tr>
<td>2*</td>
<td>Pd/C (10 mol%)</td>
<td>HFIP</td>
<td>50</td>
<td>41% + 5% 1.59</td>
</tr>
<tr>
<td>3*</td>
<td>Pd/C (20 mol%)</td>
<td>HFIP</td>
<td>50</td>
<td>55% + 17% 1.59</td>
</tr>
<tr>
<td>4</td>
<td>Rh/C (30 mol%)</td>
<td>HFIP</td>
<td>6</td>
<td>66% (62%)</td>
</tr>
<tr>
<td>5</td>
<td>Rh/C (30 mol%)</td>
<td>HFIP</td>
<td>10</td>
<td>30% + 60% 1.60</td>
</tr>
<tr>
<td>6</td>
<td>[Rh(COD)Cl]₂/CAAC·HCl/t-BuOK (20 mol %)</td>
<td>TFE</td>
<td>50</td>
<td>64%</td>
</tr>
<tr>
<td>7</td>
<td>[Rh(COD)Cl]₂/SiMes·HCl/t-BuOK (20 mol %)</td>
<td>TFE</td>
<td>50</td>
<td>73%</td>
</tr>
</tbody>
</table>

*Using trichloroethylene as internal standard

4.3. (±)-γ-lycorane and derivatives synthesis completion

The arene reduction of 1.29 could be scaled up to 0.5 mmol by using Rh/C with 6 bar H₂. After amide reduction with LiAlH₄ in THF under reflux, the desired (±)-γ-lycorane was obtained (58% over two steps) (Scheme 28). Moreover, the intermediate 1.29 can be easily converted to hippadine, following Takemoto procedure.\[90\]
To conclude, (±)-\(\gamma\)-lycorane was obtained in only 4 steps, starting from commercially available starting material, with an overall yield of 47%. To our knowledge, this is the shortest and most efficient synthesis of this product (Previous shortest synthesis: Hilton, 6-7 steps, 30.6 % overall yield).\(^6\)

In addition to 1.29, dimethoxy-substituted compound 1.45 was converted to (±)-\(\gamma\)-lycorane analogue 1.61 through the same reductive sequence (Scheme 29). The pyrrolophenanthridinone 1.45 is valuable platforms for the synthesis of more oxidized lycorine alkaloids such as pratosine which were synthesized as previously reported.

**Scheme 29: Synthesis of lycorane analogue and pratosine**

**5. Conclusion**

To summarize, we developed a new double C(sp\(^2\))/C(sp\(^3\))-H arylation methodology for the access to lycorine alkaloids derivatives, thanks to a judicious choice of precursor. The double C-H arylation methodology was applied to a broad scope of molecules, allowing the easy access to lycorine alkaloids products. Furthermore, this methodology has been applied for the first time for the synthesis of natural product, herein hippadine and pratosine. The synthesis of the racemic metabolite (±)-\(\gamma\)-lycorane was also achieved using this double closing catalysed by
palladium, followed by selective arene hydrogenation. To date, this sequence remains the shortest and most efficient synthetic pathway for this molecule (Scheme 30).[91]

Scheme 30: Overview of the (±)-γ-lycorane synthesis
Chapter 1.2:

Synthesis of $\beta$-Lactams

by Palladium(0)-Catalysed $C(sp^3)$-H Carbamoylation

Work realized with Dr. David Dailler as principal author
1. Naturally occurring β-lactams, biosynthesis and interests

β-lactams heterocycles are one of the most studied heterocycles from the last century, by either chemists but also biologists or medical professionals. The history of β-lactams started with the accidental discovery by Sir Alexander Fleming of the natural penicillin, and its ability to annihilate pathogenic bacteria. β-lactam antibiotics target the penicillin-binding proteins or PBPs, a group of enzymes found anchored in the cell membrane, which are involved in the cross-linking of the bacterial cell wall. The β-lactam ring portion of this group of antibiotics binds to these different PBPs, rendering them unable to perform their role in cell wall synthesis. This then leads to death of the bacterial cell due to osmotic instability or autolysis.

Natural β-lactams are subdivided in 4 families: penicillin/cephalosporins, clavams, carbapenems and the monocyclic β-lactams. (Figure 12)

![Figure 12: Representatives structures of the families of β-lactams](image-url)

To date, two distinct methods for the biosynthesis of β-lactams have been described. The first pathway discovered was that of the penams and cephems (Figure 13). This path begins with the linear tripeptide δ-(L-α-aminoacidyl)-L-cysteine-D-valine (ACV) which cyclizes via enzymatic oxidation and gives the bicyclic intermediate isopenicillin N. This intermediate is then converted to the penam core structure. Various transamidations lead to the different natural penicillins.

While the ring closure in penams and cephems between positions 1 and 4 of the β-lactam is oxidative, the clavams and carbapenems have their rings closed by two-electron processes between positions 1 and 2 (Figure 13). A specific enzyme, the β-lactam synthetase undergo the cyclization of 2.1 to 2.2.

In contrast, the biosynthesis of monobactams is still today not known in detail.
2. Interest for β-lactams and previous synthesis

Today, the increasing microbial resistance against the classical antibacterial agents is truly problematic and have lead the scientists to elaborate more active β-lactams and β-lactamase inhibitors (β-lactamase are a family of enzymes involved in bacterial resistance to antibiotics. They act by opening the β-lactam ring of the penicillins, thereby shutting down their activity). [96]

Since the first report by Staudinger in 1907 for the synthesis of β-lactam scaffold between imines and ketenes, many new approaches have been reported in the literature (Scheme 31). Modified Staudinger reaction,[97][98] carbonylation,[99] or umpolung[100] approaches are some relevant synthesis which have been widely developed in the last years for the efficient access to 2-azetidinone core and provided wide variety of β-lactam containing molecules.

3. Synthesis of β-lactam by C(sp³)-H functionnalization

Since the early report of Corey[101] using C-H insertion of a diazo intermediate in their synthesis of penicillin and with the recent emergence of transition-metal catalysed or transition-metal-
free C-H insertion methodologies, new approaches have been employed for the synthesis of β-lactam.[102]

Based on previous reports developed by the group of Daugulis[103] and Chen[104] for the synthesis of pyrrolidines and azetidines, the groups of Shi[105] and Wu[106] [107] have employed a pyridine- or quinoline-based directing group (DG), respectively, to form the nitrogen-carbon bond of the β-lactam ring 2.12 (Scheme 32). In these methodologies, a stoichiometric amount of oxidant is required to perform the PdII/PdIV catalytic process by regenerating the PdII. Additionally, the installation and removal of a directing group is also required. Finally, these methodologies were at that time restricted to the activation of methylene C-H bonds.

Cramer and co-workers published an enantioselective synthesis of β-lactam 2.14, by intramolecular C(sp³)-H activation of methylene C-H bond, starting from chloroacetamides compounds 2.13 (Scheme 32).[108] In this report, the use of a phosphoramidite ligand allows direct access to enantioenriched products, with the generation of a new C(sp³)-C(sp³) bond. The reaction allows direct C-C coupling but is only applicable for the cleavage of benzyl C-H bonds.

Finally, Gaunt and co-workers published the synthesis of β-lactams 2.16 starting directly from aliphatic amines 2.15 and through a carbonylative process (Scheme 32).[109] Using PdII-Pd0-PdII catalysis, with an oxidative system (CuII as co-catalyst and benzoquinone (BQ) as oxidant) and under an atmosphere of CO, they were able to obtain a wide range of β-lactams starting directly from aliphatic amines.

Scheme 32: Previous synthesis of β-lactams by C-H functionalization
4. Reactivity of carbamoyl chlorides in transition-metal-catalysis

4.1. In intermolecular fashion

The first report about the use of carbamoyl chloride in palladium catalysis was developed in 1991 by the group of Jousseaume reacting aryl, vinyl or allyl stannanes 2.17 in a Stille-like reaction (Scheme 33). Some years later, a Suzuki-Miyaura cross-coupling was developed with carbamoyl chloride by the group of Takemoto and co-workers with in situ formed alkyl boron reagents 2.20 as partners. With these pioneer examples, several other palladium cross-couplings reactions have been developed such as modified Negishi or Corriu-Kumada involving carbamoyl chlorides.

Scheme 33: Early examples of palladium catalysis including carbamoyl chloride as partner

4.2. In intramolecular fashion

With the great interest for oxindoles and γ-lactams synthesis for biological applications, Grigg, Tong and Takemoto developed new accesses to these motifs involving oxidative addition of palladium into the C-Cl bond of the carbamoyl chloride (Scheme 34). Grigg proposed a domino reaction involving carbopalladation of alkyne from 2.22, followed by intermolecular cross-coupling with organoboran or organotin reagents to access oxindoles 2.23. In their case, exclusive formation of the cis isomer of the product is formed.

With a similar approach, Takemoto proposed an intramolecular Heck reaction after oxidative addition of palladium into a C-Cl, C-CN or C-S bond of 2.24, followed by trapping of the π-allyl palladium intermediate by a soft nucleophile to access oxindoles 2.26 (Scheme 34).

Finally, Tong used a similar approach for their synthesis of γ-lactams 2.28, with the trapping or the π-allyl palladium intermediate with sodium iodide after carbopalladation of 2.27.
Based on the report from Grigg and co-workers, Lautens and Schoenebeck also developed two stereoselective synthesis of oxindoles 2.31 and 2.32, starting from alkyne-tethered carbamoyl chloride 2.30,[117] [118] and involving either a trans or cis alkyne chloropalladation (Scheme 35). By a slightly change of the reaction conditions, they were able to obtain selectively the trans or the cis alkene product.

Takemoto and co-workers developed an intramolecular C(sp³)-H activation of orthotolylcarbamoyl chloride 2.33 to afford oxindoles 2.34 (Scheme 36). In their conditions, the use of Ad₂P₉Bu as ligand and an atmosphere of carbon monoxide are required to minimize the decarbonylation to 2.35. With this optimized conditions, they could access a broad scope of oxindoles, possessing different functionalities on the aromatic ring.
Takemoto proposed a mechanism for this reaction (Scheme 36). Oxidative addition of the in situ formed Pd\(^0\) catalyst into the C-Cl bond of 2.33 lead to 2.36. At this point, the decarbonylation of 2.36 can occur but can be avoided using an atmosphere of CO. The possibility of a CO reinsertion to reform 2.36 after decarbonylation is proposed. Then, the ligand exchange and the concerted metalation-deprotonation with PivNHO' lead to 2.39 which after reductive elimination, gives 2.34 and regenerate the Pd\(^0\) catalyst to ensure the turn-over of the reaction.

**Scheme 36: Takemoto’s synthesis of oxindoles and proposed mechanism**

5. **Formation of β-lactam by palladium catalysed C(sp\(^3\))-H carbamoylation**

5.1. **Reaction design and optimization**

Inspired by the work of Takemoto and co-workers, we decided to turn our attention to the synthesis of β-lactams and use the same reactivity of the carbamoyl chlorides to form the C(O)-C\(_\alpha\) bond of the four member ring. At the outset of this work, we looked for the most appropriate substrate for the optimization (Table 3). Trimethoxybenzyl (TMB) protected isopropylamine 2.40 was easily accessible and constituted a good substrate for the reaction optimization to obtain a non-volatile product 2.41 and after deprotection, the free β-lactam. Carbamoyl chlorides are easily feasible from secondary amines, by reacting triphosgene in benzene with the presence of triethylamine as base.
As described earlier, we were aware of the decarboxylation side reaction that could occur with palladium catalysis at high temperature. This side reaction would affect the reaction efficiency and to limit it, we started to run the experiments under an atmosphere of carbon monoxide, while screening different conditions.

We started our investigations under classical conditions using Pd(PPh₃)₄ as catalyst, pivalic acid (30 mol%), Cs₂CO₃ (1.5 equiv) in xylene at 120°C and under an atmosphere of CO (balloon). (Table 3, Entry 1) In these conditions, the product 2.41 was formed in 27% ¹H NMR yield.

We next studied the Pd/Ligand catalyst. The use of the bulky and electron rich ligand Ad₂P(n-Bu).HI, previously used by Takemoto and co-workers, combined with a Pd¹II source such as Pd(OPiv)₂, Pd(MeCN)₂Cl₂, or PdMe₂(TMEDA) provided the product in good yield (62-66%, entries 4-8). The use of PdCl₂ as precataylst provided the products 2.41 in 76% (entry 9) and by increasing the base from 1.5 equivalent to 3 equivalent in mesitylene, the product was isolated in 85% (entry 11).

We also studied the impact of the temperature on the reaction, but the reaction proceed less efficiently at lower (110°C, 57%) and higher temperature (130°C, 58%) (Entries 12-13).

Replacing the Ad₂P(n-Bu) ligand by more classical alkyl or aryl phosphines, the yield dropped significantly to less than 50% (Entries 14-19).

The bench stable PAd₂(n-Bu)-Pd-G3 or the well defined palladium catalyst Pd[PAd₂(n-Bu)]₂ were also tested, giving comparable yield than the catalyst formed in situ (80 % and 85% isolated yield respectively).

While starting directly from the secondary amine 2.40r, no traces of desired product 2.41 were detected (entry 22).

The yield could be increased significantly by using the double-chamber system developed by the group of Skrydstrup, with the in situ generation of CO from decarboxylation of COgen precursor (Figure 14).[119] Equivalents of CO can be controlled, and the COgen provides a safe, versatile and convenient solid source of CO. While using 3 equivalents of CO from COgen, the desired product 2.41 could be isolated in 92% yield.

Control experiments were tested without atmosphere of CO to provide the product in 75% NMR yield or by using technical grade solvent under non-inert conditions (75% isolated) (Entries 24 and 26).
Finally, the reaction was scaled up to 1.26 mmol and provides the desired β-lactam 2.41 over 330 mg scale.
2.40 \[\text{Pd catalyst (10 mol\%)} \]
\[\text{Ph(OAc)}_2 \] (20 mol\%)
\[\text{Cs}_2\text{CO}_x \] (1.5 equiv)
\[\text{CO balloon} \]
\[\text{solvent (0.05 M), 120\degree C, 15 h} \]
\rightarrow \[\text{2.41} \]

<table>
<thead>
<tr>
<th>Entry</th>
<th>[Pd]</th>
<th>Ligand</th>
<th>n</th>
<th>Solvent</th>
<th>CO source</th>
<th>Temp [\degree C]</th>
<th>Yield 2a [%][f]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(PPh$_3$)$_3$</td>
<td>–</td>
<td>1.5</td>
<td>Xylene</td>
<td>balloon</td>
<td>120</td>
<td>27%</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc)$_2$</td>
<td>PPh$_3$</td>
<td>1.5</td>
<td>Xylene</td>
<td>balloon</td>
<td>120</td>
<td>10%</td>
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<td>Ad$_3$P(n-Bu)HIl</td>
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<td>Xylene</td>
<td>balloon</td>
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<td>45%</td>
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<td>Ad$_3$P(n-Bu)HIl</td>
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<td>balloon</td>
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<td>62%</td>
</tr>
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<td>Ad$_3$P(n-Bu)HIl</td>
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<td>Xylene</td>
<td>balloon</td>
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<td>Ad$_3$P(n-Bu)HIl</td>
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<td>Xylene</td>
<td>balloon</td>
<td>120</td>
<td>35%</td>
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<td>balloon</td>
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<td>64%</td>
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<td>Ad$_3$P(n-Bu)HIl</td>
<td>1.5</td>
<td>Xylene</td>
<td>balloon</td>
<td>120</td>
<td>66%</td>
</tr>
<tr>
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<td>Ad$_3$P(n-Bu)HIl</td>
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<td>Xylene</td>
<td>balloon</td>
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</tr>
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<td>Ad$_3$P(n-Bu)HIl</td>
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<td>Xylen</td>
<td>balloon</td>
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</tr>
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<td>Ad$_3$P(n-Bu)HIl</td>
<td>3</td>
<td>Mesitylene</td>
<td>balloon</td>
<td>120</td>
<td>92% (85%)</td>
</tr>
<tr>
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<td>Ad$_3$P(n-Bu)HIl</td>
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<td>Mesitylene</td>
<td>balloon</td>
<td>110</td>
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<tr>
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<td>P((\alpha)-tol)$_3$</td>
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<td>15%</td>
</tr>
<tr>
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<td>PPh$_3$</td>
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<td>PCy$_3$</td>
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<td>Mesitylene</td>
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<td>P(n-Bu)•HBF$_4$</td>
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<td>balloon</td>
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<td>21%</td>
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<td>28%</td>
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<td>20</td>
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<td>Mesitylene</td>
<td>balloon</td>
<td>120</td>
<td>80%</td>
</tr>
<tr>
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<td>Pd[PAd$_3$(n-Bu)$_2$]$_2$</td>
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<td>balloon</td>
<td>120</td>
<td>88% (85%)</td>
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<td>PAd$_3$(n-Bu)HIl</td>
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<td>0%</td>
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<td>balloon</td>
<td>120</td>
<td>95% (75%)</td>
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</table>

Table 3: Optimization table for \(\beta\)-lactam synthesis: [a] Performed using 0.133 mmol of 1a unless otherwise stated. [b] 9-Methylfluorene-9-carboxyl chloride (COgen), Pd(OAc)$_2$/P(\(\alpha\)-tol)$_3$, Cy$_3$NMe, mesitylene, two-chamber system (COware), both reaction chambers were placed at the same temperature. [c] Determined by NMR analysis using trichloroethylene as internal standard. Yield of isolated product 2a is given within parentheses. [d] Using amine 3a instead of 1a. [e] Performed using 1.33 mmol (400 mg) of 1a. [f] Performed using technical-grade mesitylene under non-inert conditions. TMB = 2,4,6-trimethoxybenzyl.
5.2. Mechanistic studies

For the synthesis of the β-lactam 2.41 using carbamoylation reaction, mechanistic studies were performed.

First, we wanted to confirm the formation of the oxidative addition complex, and its reactivity toward C(sp³)-H activation conditions. For this, we simplified the system, and used diisopropylamine carbamoyl chloride 2.42 (Scheme 37). The formation of the palladium complex 2.43 was performed using stoichiometric Pd(PPh₃)₄ in toluene, at 80°C. The desired complex was recrystallized and reacted in the presence of pivalic acid (30 mol%), Cs₂CO₃ (3 equiv), in mesitylene at 120°C to afford the desired β-lactam 2.44 in 26% yield. In parallel, 2.42 was reacted in the standard conditions to afford the β-lactam 2.44 in similar yield (35%).

Furthermore, we studied the reversibility of the decarbonylation/reinsertion of CO (Scheme 38). When the reaction was run under ¹³CO source (3 equivalents) with 2.40, a slight insertion (2.5%) of ¹³C was observed for the β-lactam 2.41. This suggested that the CO is rather important to avoid decarbonylation by saturating the reaction atmosphere, and thereby, validating the mechanism below (Figure 15).
With these observations, we proposed the following mechanism (Figure 15). Oxidative addition of Pd\(^0\) occurs in the C-Cl bond to provide the palladium intermediate 2.46. At this point, irreversible decarbonylation can occur to led to the amine 2.48 as a side product. After ligand exchange and C-H cleavage, the palladacycle 2.49 is formed. Finally, the reductive elimination, gives the desired product 2.50.

5.3. Scope of the reaction

After optimizing the conditions for the β-lactam 2.41 synthesis, we next studied the scope and limitations starting from different carbamoyl chlorides. For this, we started with several commercially available primary amines which were converted to secondary amines 2.52a and 2.52b after 1,4 Michael addition and reductive amination (Scheme 39). Amines were then converted to carbamoyl chlorides 2.51a and 2.51b using triphosgene in benzene in the presence of Et\(_3\)N.
The reactions were carried out using either a CO balloon or CO from COgen precursor. In all cases, the use of COgen furnishes similar or better yield than the use of CO balloon. A possible explanation could be the poisoning of the palladium catalyst by a too high CO concentration in the reaction, thereby reducing the efficiency of the catalytic system. In most cases, decarbonylation product, as well as ureas resulting from nucleophilic addition of amine on the carbamoyl chlorides are observed as side products.

We first tried to activate primary C-H bonds by changing the moiety at R₂ and by using a removable TMB (2,4,6-trimethoxybenzyl) protecting group on the nitrogen (Scheme 40). The reaction proceeds efficiently, providing in most cases the desired β-lactams. The yield decreased significantly while using an ethyl substituent 2.53, which could probably be explained by less effective Thorpe-Ingold effect. Enantiopures β-lactams (2.57-2.60) were obtained from enantiopures commercially available amines. Interestingly, competitive C(sp³) vs. C(sp³)-H activation was tested, furnishing a mixture of 2.61/2.62 with the β-lactam 2.61 as major product (ratio [7:3]). Indeed, this result shows the most favoured formation of 5-membered palladacycle vs. 6-membered palladacycle.

We also modified the substituent at R₁. Alkyl 2.63, long-chain substituted aryl (2.64, 2.66-2.67), ester 2.68 and phtalimide 2.69 provided the desired β-lactams in good to excellent yield, without observation of undesired isomers or degradation of the functional groups (43-81%).
Next, the activation of primary C-H bonds with tetrasubstituted Cβ were tested (Scheme 41). Despite the fact that 2.55 and 2.56 could not be obtain in our conditions, several other tetrasubstituted Cβ were obtained in good to excellent yields (2.70-2.71). Moreover, substituents bearing intracyclic insaturation did not provide any traces of competitive Heck product (2.72-2.74). The applicability of the reaction was also demonstrated while forming the fused bicycle 2.75 in 70% yield.

Activation of activated secondary and tertiary C-H bonds were tested, thereby furnishing the carbamoylation product in good yield (2.76-2.79). Benzyl as well as methine from cyclopropane C-H bonds were tolerated, providing original structures such as spiro 2.77 or fused β-lactams 2.79.

Finally, to complete the scope of this transformation, the reaction was run on unactivated methylene C-H bonds. The reaction was efficient to provide different sized bicyclic systems (2.80-2.83) after activation of an inert methylene C-H bond, albeit with variable yields. The latter was maximal for 2.80 using COgen whereas the CO-balloons conditions were much less efficient (40%). Such reaction on unactivated C-H bonds with a Pd0/PdII catalytic system remained underdeveloped, and these results could open the way to new applications.

Scheme 40: Scope of Palladium catalysed C(sp³)-H carbamoylation: first part
An interesting feature for the synthesis of \( \beta \)-lactams through carbamoylation reaction could be the enantiotopic differentiation of methyl groups toward the synthesis of highly enantioenriched products. Several previous reports show enantiotopic discrimination of two methyl groups by using a chiral base\(^{120} \) or a chiral ligand\(^{121} \)\(^{122} \)\(^{123} \)\(^{124} \) in the synthesis of indanes, indolines etc. With these previous reports in hand, we tried to develop a new enantioselective synthesis of \( \beta \)-lactams.

While starting from the substrate 2.40 bearing two enantiotopic methyl groups, intensive investigations were made using chiral bases and different families of chiral ligands, including NHCs, binepines, binol-derived phosphonites and phosphoramidites, and we found out that TADDOL-phosphonites ligands showed the best reactivity and gave the best enantiomeric ratios for the product. After further optimization of the reaction by synthesizing new TADDOL-phosphonites ligands but also by screening all the reaction parameters (T°C, concentration, base, equivalents...), we finally obtained the desired \( N \)-protected \( \beta \)-lactam 2.85 with 92:8 enantiomeric ratio (Scheme 42).\(^{125} \) In this case, 20 mol% of the TADDOL-phosphonite ligand 2.84 is required, under an atmosphere of CO. The use of COgen gives a better yield for the product than with CO balloon, but with a slight decrease of the enantiomeric ratio. Furthermore, the TMB group was removed under oxidative conditions, to give the free enantioreichened \( \beta \)-
lactam 2.86 in 76% yield. The absolute configuration of 2.86 was determined based on a previous report.\cite{126}

Scheme 42: Enantioselective synthesis of 2.85 and deprotection of the TMB group

With this optimized conditions in hand, we then try to apply it to different substrates bearing two enantiotopic methyls (Scheme 43). Similar $N$-substituted carbamoyl chlorides were tested, showing comparable enantiomeric ratios in the selected conditions (2.88-2.91). However, turning the system to quaternary center 2.92 shows a drop in the enantiomeric ratio (e.r. 37.63). Higher steric hindrance could be an explanation for the drop of selectivity in the enantiodetermining step.

The conditions were also tested on enantiotopic methylenes or methyne C-H bonds (2.93-2.94). In this case, low yield and enantiomeric ratio were obtained, showing the limits of the developed method.
Scheme 43: Scope and limitations of the enantioselective synthesis of β-lactams

5.5. Synthesis of enantiopure β-amino acid

Finally, the applicability of the palladium catalysed C(sp³)-H carbamoylation was used for the synthesis of the compound 2.98 (Scheme 44). This β-amino acid is accessible through enzymatic process in 4 steps with an overall yield of 29%[127] and used as a building block for bioactive molecules synthesis.[128]

Starting from commercially available enantiopure amine 2.95, we first introduce the TMB under reductive amination conditions. The secondary amine intermediate was reacted with triphosgene to give the substrate 2.96. Standard conditions for C-H carbamoylation gave the desired β-lactam in 82%, which was deprotected under oxidative conditions and give the free β-lactam 2.97 in 91%. Finally, hydrolysis of the amide in acidic conditions (6M HCl) provided the enantiopure β-amino acid 2.98, in a 5 steps sequence and with an overall yield of 65%, including only 2 purifications.
6. Conclusion

In this project, we developed a new method to access valuable β-lactams using palladium-catalysed C(sp$^3$)-H carbamoylation. The applicability of the reaction was studied and applied to a broad scope of β-lactams bearing different moieties. This reaction is suitable with primary, secondary and tertiary C-H bond, as well as unactivated C-H bonds. Then, an enantioselective version was demonstrated and successfully applied for methyl discrimination. Finally, the applicability of the reaction was demonstrated through the synthesis of valuable enantiopure β-amino acid for bioactive molecule synthesis (Scheme 45).[129]
Chapter 1.3:

*Domino Pd\(^0\)-Catalysed C(sp\(^3\))–H Arylation/Electrocyclic Reactions via Benzazetidine Intermediates*

In collaboration with Spirochem and Dr. E. Clot
1. Toward the synthesis of benzazetidines

1.1. Interest for nitrogen-containing heterocycles

As presented in the previous chapter entitled “Synthesis of β-Lactams by Palladium(0)-Catalysed C(sp³)-H Carbamoylation”, small sized nitrogen heterocycles are very important scaffolds in organic and medicinal chemistry. In 2014, among 1994 FDA (Food and Drug Administration) approved drugs, including 1086 single small molecule drug, 640 small molecules were including nitrogen heterocycles (Figure 23). With the context of drug discovery, new access to well-known heterocycles as well as access to new motifs are really important for pharmaceuticals companies or academic research labs.

Recent organic synthesis reports show a lack of diversity and accessibility in term of fused 4-membered N-heterocycles. Small and strained nitrogen heterocycles are of particular interest for organic chemists to elucidate new chemical reactivities and investigate new chemical spaces for biomedical research. This is particularly true with the non-natural occurring benzazetidines, with almost no general method to access them.
### 1.2. Benzazetidines synthesis: early reports

Benzazetidines contains a highly rigid benzo-fused 4-membered azetidine core. It has been shown that the strained structure of $N$-H free benzazetidine 3.1 easily undergo electrocyclic opening to generate the reactive aza-ortho-xyylene 3.2 which can further react in pericyclics or electrocyclics reactions (Figure 24).[131] [132]

![Figure 17: Equilibrium between benzazetidine and aza-ortho-xyylene](image)

In the literature, several reports are describing the synthesis of benzazetidines after reaction in harsch conditions, but few providing a general access to them.

In 1966, Burgess described the first example of benzazetidine synthesis by $N_2$ extrusion of substituted triazine 3.3 (Scheme 46).[133]

35 years later, the synthesis of benzazetidine has been more widely studied by Singal and co-workers (Scheme 46).[134] Through a $[2+2]$ cycloaddition between $in$ $situ$ generated benzyne and imine 3.5, they could provide a method for the access of 1,2-diaryl benzazetidines 3.6. Different electron-donating or electron-withdrawing groups could be introduced on the aryl, thereby providing 17 examples of benzazetidines albeit in moderate yields.

Few years later, Kobayashi proposed a different approach for their synthesis (Scheme 46).[135] Using a intramolecular iodoamination of $o$-(acylamino)styrene 3.7, they could afford $N$-acyl benzazetidines products 3.8. Unfortunately, the scope of the reaction was really limited.

The most relevant and general synthesis of benzazetidines was developed in 2016 by the group of Chen, employing a palladium-catalysed C(sp$^2$)-H amination strategy (Scheme 46).[136] The efficiency of this reaction is inherent with the use of picolinamide directing group, previously developed by Daugulis[28] and an oligomeric iodine (III) oxidant PhI(DMM) (dimethyl malonate). Good yields were achieved but the reaction was limited to benzazetidines 3.10 bearing ortho substituents. Furthermore, competitive C-O coupling from dimethyl malonate was observed in most cases.
2. Recent reports and attempts for benzazetidine synthesis

2.1. Previous reports

With our understanding in the field of Pd$^{0}$-catalysed C(sp$^{3}$)-H activation and according to the literature precedents, we considered a new approach to access benzazetidines.

On one hand, the synthesis of 5-membered rings indolines 3.12 is known since the report from Ohno and co-workers through a Pd$^{0}$-catalysed C(sp$^{3}$)-activation (Scheme 47a).[51]

On another hand, the C-H activation of a N-Me as been reported by Fagnou and co-workers for the synthesis of isoxindoles 3.14 (Scheme 47b).[46]

Finally, other strained 4-membered rings benzocyclobutenes 36 [41] or β-lactams[125] have been efficiently constructed through this approach (Scheme 47c).

With these precedents, we hypothesized that benzazetidine 3.16 could be obtained through intramolecular C(sp$^{3}$)-H activation, starting from easily accessible aniline precursors 3.15 (Scheme 47d).
Scheme 47: Previous syntheses of indolines and benzocyclobutenes and our strategy for the synthesis of benzazetidines

However, if the structure similarities of benzazetidine with indolines, β-lactams or benzocyclobutenes are obvious, their synthesis seems to be much more challenging (Figure 25):

- First, the high energy barrier for the C-C reductive elimination leading to the highly strained benzazetidine in comparison with indolines might be difficult to achieve.

- In comparison to the synthesis of benzocyclobutenes that benefited from Thorpe–Ingold effects due to the presence of a quaternary carbon, the C-H activation step might be more difficult.

- Finally, the instability of the benzazetidine ring system under the high temperatures that are usually required in such reactions should also be considered.

Figure 18: Structure similarity between β-lactam, indoline, benzocyclobutene and benzazetidines

3. Attempts for benzazetidine synthesis

We started our investigations toward the synthesis of benzazetidines. The initial idea was to use N-methyl-o-bromoaniline 3.15 as precursor and perform an intramolecular C(sp³)-H arylation using standard conditions (Scheme 48). We first studied the influence of the substituents on the
nitrogen. We hypothesized that the choice of substituent should be crucial to overcome the challenges mentioned above.

We started from \(N,N\)-dimethylaniline 3.15a, and by using \(^{\text{Pd(PCy}_3\text{)}}_2\) (10 mol%), \(^{\text{CsOPiv}}\) (30 mol%) and \(^{\text{Cs}_2\text{CO}_3}\) (3 equiv) in mesitylene at 160°C as standard conditions, this furnished the demethylation product 3.17 (Scheme 48). This indicates that the C-H activation occurs but the reductive elimination is difficult compared to the possible demethylation.

Electron-withdrawing groups were introduced on the nitrogen to increase the bulk of the substrate or decrease the donor effect of the nitrogen. Boc-protected anilines 3.15b only leads to degradation. Other protecting-groups such as methyloxycarbonyl 3.15c, trifluomethanesulfonyl 3.15d, and trifluoroacetyl 3.15e were also tested, but only the former gave traces of product (< 5%).

The use of a cyclobutanamide derivative 3.15f provided the spiro product 3.19 resulting from \(\alpha\)-arylation.\(^{[137]}\) To suppress this \(\alpha\)-arylation reaction, a pivalamide group was introduced. Unfortunately, exclusive \(^{\text{C(sp}^3\text{)}}\)-H arylation on the tert-butyl group was observed, furnishing the 3,4-dihydroquinolone 3.20 in 80% yield.\(^{[53]}\)

To disfavour this competing \(^{\text{C(sp}^3\text{)}}\)-H arylation, we proposed to introduce a bulky and unactivated adamantamide group 3.15h. Surprisingly, this substrates furnished the unexpected benoxazine 3.21 in 54% yield.

\[\text{Scheme 48: Influence of the nitrogen substituent. [a] yield determined by } ^1\text{H NMR. [b] Based on GCMS analysis [c] Yield of the isolated product}\]

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4. Synthesis of 4H-benzoxazines via Domino Pd\textsuperscript{0}-Catalysed C(sp\textsuperscript{3})–H Arylation/Electrocyclic Reaction

4.1. Initial result, mechanism, and DFT calculations

With the unexpected formation of the benzoxazine 3.21 starting from o-bromo-N-methyladamantamide 3.15h, we tried to find a plausible mechanism.

After the classical steps for C(sp\textsuperscript{3})-H activation reaction and reductive elimination, we postulated that the benzazetidine 3.22 was formed (Scheme 49). This benzazetidine intermediate, in the harsh reaction conditions could presumably undergo a 4\pi electrocyclic ring opening, to afford the really unstable aza-ortho-xylylene 3.23 (relative calculated energy: \(\Delta G = 12.0 \text{ kcal mol}^{-1}\)) (Gibbs free energies relative to 3.23 [DFT, \(\omega\text{B97X-D/6–311G\text{*}}\text{*}\)). This second intermediate 3.23 could rearrange in a 6\pi electrocyclic reaction to afford the more thermodynamically stable product 3.21. Relatives calculated energies indicates that the reaction tends to the more stable benzoxazine 3.21 (relative calculated energy: \(\Delta G = -14.4 \text{ kcal mol}^{-1}\)) thereby leading exclusively to this product. This observation is to the best of our knowledge, the first example of domino Pd-catalysed C(sp\textsuperscript{3})-H activation/electrocyclic rearrangement.

![Scheme 49: Initial observation of benzoxazine and plausible mechanism pathway](image)

To try to understand the role of the adamantamide substituent, additional calculations have been performed by Dr. E. Clot on the system (Figure 26). The idea was to compare the activation barriers (\(\Delta G^*\)) for reductive elimination of several nitrogen substituted substrates. DFT calculations were done for the reductive elimination step with different substituents on the nitrogen (3.24 R=Me, 3.25 R= CO\textsubscript{2}Me and 3.26 R= CO(Ad)) The results showed a lower activation barrier for R= C(O)Ad (21.7 kcal.mol\textsuperscript{-1}) compared to R= Me or R= CO\textsubscript{2}Me (27.6 kcal.mol\textsuperscript{-1} and 26.8 kcal.mol\textsuperscript{-1} respectively) which is in agreement with the observed result. Moreover, stabilizing dispersive interactions shown by non-covalent interaction map between the adamantyl and the tricyclohexylphosphine could also be a reason for a lower energy activation barrier. Theses interactions are inexistent for R = Me or R = CO\textsubscript{2}Me.
4.2. Synthesis of 4H-benzoxazines: reaction optimization and deuteriation experiments

With this initial result in hand, further optimizations for the synthesis of 3.21 were investigated. We started the reaction development by changing the solvent (Table 4). With mesitylene as a first result (54%), we realized that this reaction was really solvent dependant. Common polar and apolar high boiling point solvents were tested with the same catalytic system. While changing with the isomer 1,2,4-trimethylbenzene, the yield dropped to 17% (Entry 2). More polar solvents such as anisole gave similar result (48%) whereas switching to benzonitrile did not give any trace of product (Entries 3-5). Mixture of xylenes was then employed and the desired benzoxazine was obtained in 70% yield (Entry 6). After testing all the isomers of xylene separately, the 4H-benzoxazine 3.21 was obtained in 84% isolated yield with o-xylene (Entry 9).
According to the proposed mechanism, further investigations have been done to observe and isolate the benzazetidine intermediate 3.22 (Scheme 50). Reduction of the temperature, as well as reduction of the reaction time did not give satisfying results. In the first case, a slight decrease of the temperature showed only protodebrominated product. In the second case, starting material with small amount of benzoxazine 3.21 was recovered after 1, 2 or 3 hours.

From previous observation, we postulated that the C-H activation step might be the rate limiting. However, the absence of isotopic effect in intermolecular competition experiments between protiated and deuterated substrates 3.15h and 3.15h-d3 showed that the C-H activation step is not rate-determining for the synthesis of benzoazines (Scheme 51).
4.3. Scope of the domino reaction

We next investigated the scope of the C(sp³)-H activation/electrocyclic rearrangement (Scheme 53). The different substrates were synthesized from commercially available o-bromo anilines 3.23, with freshly synthesized acid chlorides (Scheme 52). Further alkylation with corresponding iodoalkyles afforded the desired substrates 3.24.

First, we introduced different functionalities on the para position to the amide on the aromatic ring (Scheme 53). Electron withdrawing groups such as methyl ester 3.28, fluoride 3.29, trifluoromethyl 3.30 or nitrile 3.31 were successfully introduced with formation of 4H-benzoxazine in good yields (55-81%). Electron donating group such as methoxy 3.32 or methyl 3.33 were also introduced, without significant decrease of the yield (63-86%). The trends showed the moderate influence of a substituent on the yield. An X-Ray analysis from 3.30 confirmed the structure of the final product. Moreover, a scale-up of the reaction using the bench stable Pd-G4-PCy₃ catalyst could afford the desired benzoxazine 3.21 over gram scale.

The reaction was next run with subsituent on the meta position to the amide on the aromatic ring. In this case, mixture of isomers from palladacycle reopening are obtained (Scheme 53) (3.34-3.37). This observation correlates with previous observations for benzocyclobutenes synthesis. After C-H activation, a proton transfer can undergo palladacycle opening, which after rotation, C(sp²)-H arylation and reductive elimination, afford an isomer of the directly coupled-product (Scheme 54).[41] The ratio between the two isomers tends to undergo the formation of less hindered products, by replacing PivO⁻ with AdCO₂⁻ as the CMD base. Acidity is also determining to understand the isomers ratio. When R = F (3.36), the isomeric mixture for m/m’ reaches [2.7:1]. The acidic C(sp³)-H bond adjacent to the –F, combined with moderates
hindrance afford the undesired isomer in important quantity. As far as the steric hindrance is increased (3.37), the undesired isomer is obtained as traces (m/m’ [6.7:1]).

Scheme 53: Scope of 4H-benzoxazines. [a] using AdCO₃H instead of PivOCS; [b] parenthesis showed the isolated yield of major isomer; [c] X-ray structure (ellipsoids set at 50% probability)
Next, we investigated the substituents for $R_1$ (Scheme 55). We focused on bulky and unactivated moieties toward C-H activation conditions (3.44-3.47 and 3.50-3.51). These groupment enabled the reaction, in particular compound 3.45 bearing a modified cyclohexyl moiety. Other bridged bicyclic substrates from commercially available from Spirochem were also affording the desired product in moderate to good yield (36-50%, 3.46-3.47 and 3.50-3.51), thereby providing original benzoxazine structures. These biisoesters of a $p$-substituted benzene ring showed more moderate yield than while using adamantayl group, presumably because of thermal stability.

Finally, reactivity investigations were performed while changing subsitutent $R_3$. While replacing the $N$-methyl with an $N$-ethyl substituent 3.48, exclusive formation of indoline 3.49 was observed (80%). This can be explained by the more reactive methyl vs. methylene toward C(sp$^3$)-H activation conditions, furnishing exclusively the latter mentioned product.
4.4. 4H-Benzoxazines derivatizations:

4H-benzoxazines are interesting scaffold for drug discovery\textsuperscript{[138]} but they can also be synthetic intermediates for the synthesis of more elaborated nitrogen heterocycles. For example, \textbf{3.36} can be easily reduced to the fully saturated NH-benzoxazines \textbf{3.52} using sodium borohydride (Scheme 56).

![Scheme 56: Reduction of benzoxazine](image)

More interestingly, the electrophilic benzylic position of the benzoxazine \textbf{3.29} allows an HCl-mediated ring opening of the heterocycle to afford the intermediate \textbf{3.53} in quantitative yield (Scheme 57). This intermediate can further react in an annulation reaction following a procedure described by Garg and co-workers.\textsuperscript{[139]} After reacting with \textit{N}-methylostatole \textbf{3.54} and Cs\textsubscript{2}CO\textsubscript{3}, the tetracyclic product \textbf{3.55} can be afforded in 50\% yield. Finally, hydrolysis of the adamantamide can be performed, providing tetrahydroindoloquinoline \textbf{3.56} which possesses the tetracyclic core of the communesin family derivatives.\textsuperscript{[140]}
According to the proposed reaction mechanism for benzoxazines synthesis, we hypothesized that the aza-ortho-xylylene intermediate 3.23 could potentially react in intermolecular cyclisation reaction (Scheme 58).

Based on the formation of the tetracyclic product 3.55, we believed that N-methylskatole 3.54 could directly undergo formation of 3.55, starting from N-methyl-o-bromoanilide 3.15h, through nucleophilic annelation or electrocyclisation. Unfortunately, exclusive formation of 4H-benzoxazine 3.21, resulting from the most favored intramolecular electrocyclic ring formation was observed (75%). Similar investigations were done to try to react 3.15h in intermolecular pericyclic reactions. However, while running the reaction in the presence of different dienophiles, exclusive formation of the benzoxazine was observed 3.21.

**Conclusion:**

In conclusion, we reported the unexpected synthesis of 4H-benzoxazines after an unprecedented domino C(sp³)-H activation/electrocyclic rearrangement of unstable benzazetidines.
intermediates. 20 different benoxazines could be afforded while using a bulky and unactivated amide substituent. 4H-benoxazines products can then be converted to polycyclic products that can be find in natural products such as communesin alkaloids (Scheme 59).[141]

Scheme 59: Synthesis of 4H-benoxazines by Pd$^{0}$-catalysed C(sp$^{3}$)-H activation/electrocyclic rearrangement of benzotidine intermediates
Part 2: Remote $C(sp^3)$-H activation
Chapter 2.1:

1,4-Palladium Shift/C(sp\(^3\))-H Activation Strategy for the

Construction of 5-Membered Rings
1. Introduction to 1,4-Pd shift

Over the past decades, reports on C-H activation have increased exponentially. Many transition metals have been discovered to catalyze C-H activation. However, palladium is the most powerful and most widely used transition metal in organic chemistry, and has been found to be capable of catalyzing various C-H activation in recent years. This is particularly true for the activation of “parafins” C-H bonds. An interesting feature of palladium-catalyzed C-H activation is that palladium, in most cases, only activates C-H bonds that are in close vicinity to a chelation-directing group. While such directing group affords selective C-H activation, it also significantly limit the synthetic utility of the functionalization (Figure 27).

Therefore, methods have been developed to functionalize remote C-H bonds.

![Figure 20: Direct C-H functionalization limitations](image)

The distal functionalization of C-H bonds can be achieved via a two-steps process, also called through-space palladium migration (Figure 60). In this approach, the palladium is first introduced after oxidative addition or carbopalladation to an initial position. In the second step, the proximity of the palladium species with a C-H bond can lead to the cleavage of this C-H bond and form a palladacycle. Then, a proton mediated palladacycle opening can undergo the relocation of the palladium to a remote carbone. The resulting effect is a palladium migration. This migration introduces a palladium moiety to a remote position, where its direct introduction might be difficult and thereby, can allow the functionalization of distal positions than the one where the palladium was initially installed.\[142\]

![Scheme 60: 1,n-Pd shift](image)

In the literature, several 1,n-palladium migrations have been reported, notably for the formation of carbo- or heterocyclic products (Scheme 61).\[143\] \[144\] \[145\] \[146\] \[147\] \[148\] Such migrations have received special attention from computational chemists, who have conducted studies on the mechanism and transition state.\[149\] \[150\] Additional to palladium, rhodium,\[142\] platinium\[151\] and iridium\[152\] are also known to undergo similar migrations.
Among all palladium migrations, the 1,4-Pd migration is the most commonly observed (Figure 28). The 1,4-Pd shift is facilitated by the formation of a relatively strain-free 5-membered ring palladacycle. In this case, the shift mostly relies on the inability of palladium to undergo reductive elimination, and form strained products.

It has been reported in the literature that palladium can migrate from a wide range of C(sp^2) or C(sp^3)-hybridized positions to C(sp^2)/C(sp^3) remote positions.\textsuperscript{[154]} [144]

2. Early examples of 1,4-Palladium shift/cross-couplings reactions

The initial observation of 1,4-Pd shift has been reported by Heck in 1972 (Scheme 62).\textsuperscript{[155]} After transmetallation of palladium with an alkyl-mercury moiety \textit{4.3}, a mixture of coupled product \textit{4.4} and \textit{4.5} resulting from direct functionalization and product from 1,4-Pd shift/Heck coupling was observed. This early alkyl-to-aryl palladium shift was later extended in the reverse order in a Suzuki-Miyaura cross-coupling by Buchwald (Scheme 62).\textsuperscript{[156]} Starting from \textit{4.6}, after initial oxidative addition of palladium into the C-Br bond, a 1,4-Pd shift from aryl-to-alkyl can occur, followed by the trapping of the palladium intermediate in a Suzuki-Miyaura reaction. The presence of two ortho substituents on the arylbromide is in this case necessary to avoid direct aryl-aryl coupling. Further extensions were proposed later.\textsuperscript{[157]}
In the early 2000’s, Larock proposed a new aryl-to-aryl palladium shift, combined with an olefin coupling, directly inspired from the pioneer work from Heck (Scheme 63).[158] Ethyl acrylate was chosen as partner. In this report, the ratio between the olefin isomers 4.9 and 4.10 could be modulated by changing the reaction parameters: by reacting 4.8 while using PivOCs as base in a diluted reaction, a 1:1 mixture of the two isomers can be obtained; the use of NaHCO₃ in the presence of TBAC and high concentration afforded exclusively the direct coupling product 4.10 (100%).

More recently, Lin developed the first aryl-to-vinyl palladium shift starting from 4.11 (Scheme 63). Here, the shifted palladium species can react in a borylation[159] or Heck reaction[160] to form functionalized olefins 4.12 and 4.13 with good yields and selectivities.

Several other reports are also using 1,4-Pd shift to access olefins 4.15 after β-hydride elimination[161] [162] [39] [40] or C-O coupling products 4.17 (Scheme 64).[161]
3.1,4-Pd migration/ C-H functionalizations

After a 1,4-Pd shift, the shifted organopalladium species can further react in any kind of palladium-catalyzed reaction. Initiated by the pionner work of Larock, the shifted palladium species can react for example in a C-H activation reaction.

In 2000, Larock developed a new annulation process, involving iodobenzene 4.18 and diphenylacetylene, using palladium-catalysed C-H arylation conditions to afford 9-benzylidene-9H-fluorene 4.21 (Scheme 65).[154] In this process, an oxidative addition/carbopalladation sequence occurs to form 4.19, followed by a 1,4-Pd migration from vinyl-to-aryl position to lead to 4.20. Then, the shifted organopalladium species 4.20 reacted in a C(sp²)-H arylation reaction to afford the desired tricyclic product 4.21.

This first example of 1,4-Pd shift/C-H activation reaction was further extended by Larock in another similar C(sp²)-H arylation methodology (Scheme 66). In this report, o-iodobiaryl
substrates 4.22 were used. Oxidative addition of palladium into the C-I bond, followed by 1,4-aryl-to-aryl palladium shift gives a palladium intermediate 4.24 which can easily react in a C-H arylation reaction, and afford complex tricyclics compounds such as dibenzofurans or fluorenes 4.25.

In a different fashion, Larock also developed an alkyl-to-aryl 1,4-Pd shift/ C-H arylation sequence to access another range of fused products 4.29 in an efficient way (Scheme 66). This transformation starts with an oxidative addition of palladium followed by carbopalladation on 4.26 to generate an alkyl palladium species 4.27. This intermediate could undergo 1,4-migration to aryl, followed by C-H arylation step to afford the desired product.

Scheme 66: 1,4-Pd shift/ C-H functionalization from Larock in a C-H arylation manner

**4.1,4-Pd migration/C(sp³)-H activation**

In the middle of the 2000’s, the 1,4-Pd shift has been used in combination with C(sp³)-H bonds activation to functionalize less reactive positions (Scheme 67).

First introduced by Larock to generate fused cyclopropanes, a 1,4-Pd migration/carbopalladation/C(sp³)-H activation sequence starting from 4.30 lead to the formation of 4.36 in 67% yield.[163] Surprisingly, the authors observed exclusively the product resulting from C-H activation of methylene vs. methyle group in this case. The product 4.34 resulting from C-H arylation was observed as traces. This example is to the best of our knowledge, the first example of 1,4-Pd migration/C(sp³)-H activation sequence.
Scheme 67: First example of 1,4-Pd shift/C(sp^3)-H activation sequence

A few years later, Zhu described a method to access fused oxindoles 4.41 through a carbopalladation/1,4-Pd shift/C(sp^3)-H activation of methylene C-H bonds after ingenious substrate design (Scheme 68).\[164\] This method afforded a broad range of products bearing different moieties in moderate to excellent yields.

Scheme 68: Zhu’s synthesis of oxindoles

As shown with these examples, the 1,4-Pd shift is a well-established process. However, there is no example in the literature of 1,4-Pd-shift/C(sp^3)-H activation. Moreover, as discussed earlier,
the aryl-to-vinyl palladium shift is a well-known process, there is no report suggesting an aryl-to-α,β-unsaturated carbonyl palladium migration (Scheme 69).

Scheme 69: Lack of report for simple 1,4-Pd shift/C(sp^3)-H activation and aryl to α,β-insaturated carbonyl Pd shift

5.1,4-Pd shift/C(sp^3)-H activation to access 5-membered rings

5.1. Reaction design

In 2016, Baudoin reported the synthesis of strained γ-lactams 4.45 from akenyl bromides 4.42 (Scheme 70a). After initial oxidative addition of palladium into the C-Br bond, direct C(sp^3)-H activation occurred to form the desired γ-lactams 4.45. With this report in hand, we believe that the organopalladium intermediate arising from direct oxidative addition (4.43), could also be generated after a 1,4-Pd shift from a remote C-Br bond on an aromatic ring (4.43') starting from 4.46 (Scheme 70b). This strategy could allow the access to a variety of 5-membered ring products.

Scheme 70: Synthesis of γ-lactams from “direct” C-H activation and by combining with a 1,4-shift

5.2. Reaction design and optimization

As a starting point, we selected the substrate 4.48 to investigate the 1,4-Pd shift/C(sp^3)-H activation sequence and afford the γ-lactam 4.49 (Table 5). The reaction was conducted at 160°C to avoid proto-debromination and favour the reductive elimination of the relatively
strained γ-lactam. Pd(PPh₃)₄ was selected as initial catalyst (10 mol%), combined with pivalic acid (30 mol%) and rubidium carbonate (1.5 equiv) in mesitylene at 160°C. Traces of product 4.49 were observed in this case (8%), with proto-debrominated product as the major product (Entry 1). Changing the catalyst to Pd(P₂Bu₃)₂ did not give any traces of product, whereas the use of Pd₂dba/PCy₃ afforded the desired product in 31% NMR yield (Entry 3). Turning our attention to the most reactive Pd(PCy₃)₂ could increased the yield to 65% (Entry 4). Finally, the desired γ-lactam 4.49 could be afforded in 94% isolated yield while reducing the concentration to [0.025M] (Entry 5).

![Chemical structure](image)

Table 5: Optimization table for 1,4-Pd shift/C-H activation

<table>
<thead>
<tr>
<th>Entries</th>
<th>Pd source</th>
<th>Additive (30 mol%)</th>
<th>Base</th>
<th>Solvent</th>
<th>NMR yield (Isolated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(PPh₃)₄ (10 mol%)</td>
<td>PivOH</td>
<td>Rb₂CO₃ (1.5 equiv.)</td>
<td>Mesitylene [0.05M]</td>
<td>8%</td>
</tr>
<tr>
<td>2</td>
<td>Pd(P₂Bu₃)₂ (10 mol%)</td>
<td>PivOH</td>
<td>Rb₂CO₃ (1.5 equiv.)</td>
<td>Mesitylene [0.05M]</td>
<td>0%</td>
</tr>
<tr>
<td>3</td>
<td>Pd₂dba/PCy₃ (10 mol%)</td>
<td>PivOH</td>
<td>Rb₂CO₃ (1.5 equiv.)</td>
<td>Mesitylene [0.05M]</td>
<td>31%</td>
</tr>
<tr>
<td>4</td>
<td>Pd(PCy₃)₂ (10 mol%)</td>
<td>PivOH</td>
<td>Rb₂CO₃ (1.5 equiv.)</td>
<td>Mesitylene [0.05M]</td>
<td>65%</td>
</tr>
<tr>
<td>5</td>
<td>Pd(PCy₃)₂ (10 mol%)</td>
<td>PivOH</td>
<td>Rb₂CO₃ (1.5 equiv.)</td>
<td>Mesitylene [0.025M]</td>
<td>100% (94%)</td>
</tr>
</tbody>
</table>

5.3. Mechanism and deuteration experiment

The proposed mechanism for the developed reaction is depicted scheme 71. After oxidative addition of palladium into the C-Br bond of 4.56, ligand exchange with the pivalate can afford the intermediate 4.50. This intermediate can undergo a carboxylate mediated C(sp²)-H activation with H¹ to afford the palladacycle 4.51. This palladium moiety is then too strained to undergo reductive elimination, and can open by proton transfer with the pivalic acid to afford 4.52. The palladium is then in the ideal position to undergo C(sp³)-H activation from H², affording the palladacycle 4.53, which after reductive elimination give the desired 5-membered ring γ-lactam 4.54.
To test the proposed mechanism, deuteration experiments were run in the standard conditions (Scheme 72). Starting from 4.48-d₇, no deuterium incorporation was observed on the aromatic ring. Proton incorporation on the γ-lactam brings evidence for the reversibility of the C(sp³)-H activation step. This H/D exchange can be assigned to an external proton source (presumably from mesitylene or traces of water) exchanging with the deuterium atom on the Pd-bounded pivalate, consistent with previous observations. Similar H/D exchanges were observed from partially deuterated substrates 4.48-d₆ and 4.48-d₁. These experiments are underlining on one hand the non-reversibility of the 1,4-Pd shift. On another hand, the reversibility of the C(sp³)-H activation reaction seems to be confirmed.

Scheme 72: Deuteration experiments for 1,4-Pd shift/C(sp³)-H activation
5.4. Scope of the 1,4-Pd shift/C(sp³)-H activation: access to γ-lactams

With the optimized conditions in hand, we next studied the scope of the reaction for the synthesis of α-arylidene γ-lactams (Scheme 74). Substrates were synthesised from primary amines using aza-Michael additions or reductive amination on ketones or aldehydes (Scheme 73). These secondary amines **4.56a** and **4.56b** could then be reacted with 2-bromocinnamic acids derivatives **4.58**, previously obtained from Knoevenagel reaction with commercial feedstocks.

![Scheme 73: Substrates synthesis](image)

We first tested the reactivity of the arylchloride compared to the arylbromide (Scheme 74). Starting from 2-chlorocinnamic acid derivative gave lower yield than with the model substrate **4.49** (55%). Modifications at R₂ were then performed while keeping the TMB-protected nitrogen. Average to good yield were obtained for t-Bu **4.62**, cyclopropyl **4.63** and ethyl **4.61**. The former was in this case challenging because of the lack of Thorpe-Ingold effect. Comparison between C(sp³) and C(sp²)-H activation clearly appears to be in favour of the latter with exclusive formation of the oxindoles **4.64** and **4.65** in average to good yield, thereby providing an alternative access to these scaffolds.

Modifications on the nitrogen with R₁ = diethyl **4.67** and diisopropyl **4.66** furnished the product in low to excellent yield respectively. As a comparison, **4.67** was obtained in only 31%, whereas **4.61** was obtained in 45%. This can maybe be explain by the presence of the more bulky TMB group compared to ethyl, which could favour the reductive elimination process. Then, substrates **4.68** to **4.70** gave exclusive formation of the desired γ-lactams as a single
isomer. Furthermore, sensitive moieties such as nitrile 4.71, sulfone 4.72 and ester 4.73 remained untouched. In some cases, the use of 10% PCy₃ is necessary to prevent from the catalyst degradation.

Scheme 74: Scope for γ-lactams with modifications at R₂ and at the nitrogen; [a]: Using additional PCy₃ (10 mol%) 

In the second part of the scope, we made some modifications on the aryl moiety R₃ (Scheme 75) (4.74-4.80). Substituents at the meta or para position to the bromine were well tolerated, giving the products in good to excellent yields (4.74-4.78). These scaffolds are of particular interest, according to similar products showing antiparasitic activities toward Colletotrichum orbiculare.[166]

We finally turned our attention to the synthesis of bicyclic γ-lactams. Fused pyrrolidine 4.81 and azepane 4.83, relevant to the synthesis of pyrrolizidine[167] and Stemona alkaloids[168] were obtained in acceptable yield (51% and 40% respectively) with proto-debrominated side product. This method represent an interesting alternative for the obtention of these patterns. As a comparison, the fused 5,6 γ-lactam 4.82 was obtained with almost quantitative yield (98%). The trend was confirmed with the obtention of several 5,6-fused γ-lactams bearing heteroatoms such as oxaninanes 4.84 and 4.85 and the enantiopure N-Boc protected piperazine 4.86.
5.5. Attempts for the synthesis of anantine and derivatives

$\gamma$-lactams are of particular interest for their biological activities\textsuperscript{[166]} and can be found in numerous natural products.\textsuperscript{[169]} Their synthesis has been largely studied for drug discovery,\textsuperscript{[170]} and extended for $\gamma$-lactams-containing natural product.

The $\alpha$-arylidene-$\gamma$-lactam motif can be found in natural products anantine, isoanantine and cynometrine (Figure 30).\textsuperscript{[171]} These three imidazole alkaloids were isolated from the leaves of *Cynometra* species which have been used as a traditional medicine in Africa and which possesses antitussive and analgesic activities.\textsuperscript{[172]}

First synthesized by Naito and co-workers in 1993 through a radical cyclization,\textsuperscript{[171]} we suggested a new approach for the synthesis of (±)-anantine and (±)-cynometrine using a 1,4-Pd shift/C(sp\textsuperscript{3})-H activation sequence (Scheme 76). For this, we proposed the following retrosynthetic plan: anantine and cynometrine could be formed from the intermediates 4.87\textsuperscript{a} and 4.87\textsuperscript{b}. These $\gamma$-lactams could be synthesized respectively from 4.88\textsuperscript{a} and 4.88\textsuperscript{b} using the 1,4-Pd shift/C(sp\textsuperscript{3})-H activation. Precursors 4.88\textsuperscript{a} and 4.88\textsuperscript{b} could be obtained after nitrogen protection of 1-methylhistamine 4.91 and amide coupling with 4.90.
Before starting our investigations for the synthesis of anantine and cynometrine, we were aware that the 1,4-Pd shift/C(sp³)-H activation sequence might be difficult according to the following considerations: 1) The absence of a Thorpe-Ingold effect to favour the reaction on substrates 4.88a and 4.88b; 2) The possibility of 4.88a and 4.88b to undergo β-hydride elimination after the C-H cleavage; 3) Finally, the strongly coordinating propensity of imidazole to chelate palladium which could undergo catalyst deactivation.

The precursors for C-H activation were synthesized starting from commercially available 1-methylhistamine 4.91 (Scheme 77). Reductive amination were used for the introduction of a methyl or TMB on the primary amine. Then, amide couplings with the 2-bromocinnamic acid chloride 4.94 were performed to afford 4.88a and 4.88b.

With these substrates in hand, we tried to react in the optimized conditions for 1,4-Pd shift/C(sp³)-H activation (Scheme 78). Starting from 4.88a, only starting material was recovered. In the case of 4.88b, the reaction undergo complete degradation. Further optimizations for these reactions were made (T°C, base, ligand, concentration…) but the desired products could not be observed, probably for the reasons outlined before.
5.6. Formal synthesis of (−)-pyrrolam-A

After the attempt to apply a 1,4-Pd shift/C(sp^3)-H activation strategy to afford anantine and cynometrine, we focused our attention on the synthesis of the enantiopure 5,5-fused γ-lactam 4.99, relevant to the synthesis of (−)-pyrrolam A, an alkaloid extracted from *Streptomyces olivaceus* (Scheme 79).[173]

Starting from commercially available (S)-2-methylpyrrolidine 4.97 and 2-bromocinnamic acid 4.90, classical amide coupling was performed. Then, the substrate 4.98 was reacted in the standard conditions to afford the desired γ-lactam 4.99 in 50% yield. 4.99 can finally be converted to (−)-pyrrolam A according to previous report, after ozonolysis, triflation, and pro-todetriflation. This 1,4-Pd shift/C(sp^3)-H process provides a new formal synthesis to the latter in only 5 steps (previously described in 7 steps from D-proline).[174]

5.7. Scope of the 1,4-Pd shift/C(sp^3)-H activation: access to indanones

In the next part of the scope, we try to investigate 1,4-Pd shift/C(sp^3)-H activation conditions on other α,β-insaturated carbonyl substrates. We examined the reactivity of chalcone 4.102 bearing activable benzylic C(sp^3)-H bonds. The substrates were easily accessible after aldolisation of the corresponding acetophenone 4.100 and o-bromo-benzaldehyde 4.101 (Scheme 80).
Using the same conditions for C-H activation, the reaction proceeded remarkably well, furnishing several arylidene indanones derivatives (Scheme 81). Electron-rich (4.105-4.108) and electron-deficient substitutions (4.109) could be introduced, as well as free aniline (4.110). Of note, these compounds found interesting biological properties for Alzheimer disease, breast cancer, leukemia or as inhibitor of tubulin assembly.[175]

Scheme 81: Scope of indanones; [a]: Using additional PCy3 (10 mol%)

6. Conclusion

In conclusion, we reported an unprecedented 1,4-Pd shift followed by C(sp³)-H activation on unactivated and benzylic positions to afford a broad range of α-arylidene γ-lactams and indanones through C(sp²)-C(sp³) bond formation.[176] The applicability of the method was demonstrated with the formal synthesis of (-)-pyrrolam. This report represents a new domino reaction and open the way to the development of new C(sp³)-H functionalization reactions that are difficult to achieve through direct methods (Scheme 82).

Scheme 82: 1,4-Pd shift/C(sp³)-H activation for the construction of 5-membered rings
Chapter 2.2:

Redox-neutral Coupling between Two C(sp$^3$)–H Bonds

Enabled by 1,4-Palladium Shift for the Synthesis of Fused Heterocycles
Introduction to $C(\text{sp}^3)-C(\text{sp}^3)$ couplings through palladium-catalyzed single C-H bond cleavage

The formation of carbon-carbon bonds using transition-metal catalysis has been widely developed in the past decades. Cross-coupling reactions as well as C-H activations reactions showed their robustness for the formation of $C(\text{sp}^3)-C(\text{sp}^3)$ or $C(\text{sp}^2)-C(\text{sp}^3)$ bonds to afford valuable products in a straightforward manner.\cite{177} In these methodologies, the new C-C bond are generally selectively formed at positions which bear the leaving group (Scheme 83a).

In the field of C-H activation, direct and remote functionalization using palladium catalysis usually undergo $C(\text{sp}^2)-C(\text{sp}^2)$ or $C(\text{sp}^2)-C(\text{sp}^3)$ bonds formation (Scheme 83b). However, if this method has shown its ability to undergo such bond formation, the formation of $C(\text{sp}^3)-C(\text{sp}^3)$ bonds is still very limited.\cite{178}

Among the few reports describing such $C(\text{sp}^3)-C(\text{sp}^3)$ coupling, reactions are facilitated by the formation of an alkylpalladium species (Scheme 84). This alkylpalladium intermediate then undergo a C(sp$^3$)-H activation reaction to afford the C(sp$^3$)-C(sp$^3$) coupled products. The alkylpalladium species are formed after carbopalladation or oxidative addition. Additionally, the presence of a quaternary carbone in the β-position to the Pd avoid the β-hydride elimination and ensure the viability of the alkylpalladium species.

In 2009, Larock and co-workers reported the formation of fused cyclopropanes through C(sp$^3$)-C(sp$^3$) bond formation (Scheme 85). The alkylpalladium intermediate 5.2 is formed after
carbopalladation of 5.1. This alkylpalladium intermediate 5.2 can further react in a C(sp$^3$)-H activation on a methylene C-H bond to form the fused cyclopropane 5.3.\[163\]

Similarly, Loh described the formation of pyrroloisindolone 5.6 after reaction of alkylpalladium species in a C(sp$^3$)-H activation reaction (Scheme 85).\[179\] In this case, the alkylpalladium species is also generated after carbopalladation.

In a different fashion, Cramer reported in 2015 the enantioselective synthesis of $\gamma$-lactam 5.8 (Scheme 85). In this report, the oxidative addition of palladium into a C(sp$^3$)-Cl bond can yield an alkylpalladium species that further react in a C(sp$^3$)-H activation.\[180\]

Finally, Lee and co-workers described a palladium-catalysed divergent cyclopropanation after C(sp$^3$)-H activation of methyl or methylene C-H bonds (Scheme 85).\[181\] With a fine tuning of the reaction conditions, spiro- 5.10 or fused-cyclopropanes 5.11 can be formed via C(sp$^3$)-C(sp$^3$) coupling. In this case, the alkylpalladium species are also generated from carbopalladation of 5.9.

Scheme 85: Precedents for C(sp$^3$)-C(sp$^3$) coupling using C(sp$^3$)-H activation
2. Early report from Dyker and alkylpalladium species in cross-couplings

In addition to oxidative addition and carbopalladation, alkylpalladium species can also be generated after 1,4-Pd shift from a C(sp²) to a C(sp³).

In the 90’s, Dyker reported an interesting result while generating an alkylpalladium intermediate from C(sp³)-H activation at a methoxy group (Scheme 86). While reacting 1-iodo-2-methoxy-3-methylbenzene 5.12 with catalytic Pd(OAc)₂, the alkylpalladium intermediate could undergo the formation of C(sp²)-C(sp³) bond (5.13) as well as C(sp³)-C(sp³) bond (5.14).

Mechanistically, the oxidative addition of palladium is occurring into the C-I bond of 5.12, followed by base mediated C(sp³)-H activation of the methoxy group to generate the palladacycle 5.15 (Scheme 87). With the absence of ligand, 5.15 can undergo a second oxidative addition of 5.12 to generate the palladium (IV) intermediate 5.16. After reductive elimination and formation of the biaryl moiety, the alkylpalladium intermediate 5.17 is formed. At this point, C(sp²)-H activation followed by reductive elimination can occur to furnish the benzopyran 5.13; C(sp³)-H activation of the ortho methyl group can occur to form the dihydrobenzofuran 5.14.
In a synthetic point of view, this reaction seems to be limited and lead to mixtures of polyarylated products. The absence of a ligand promotes the second undesired oxidative addition. However, with the formation of benzofurans, Dyker described herein a potentially valuable method to generate C(sp^3)-C(sp^3) bonds. Recent developments showed that unproductive oxidative addition can be shut down with ancillary ligands.\[^{39}\] [\[^{183}\]\] Moreover, it was shown that aryl bromide can generate alkylpalladium species after 1,4-Pd shift. Buchwald\[^{156}\] [\[^{157}\]\] and Romo\[^{184}\] generated alkylpalladium species from aryl bromide, and reacted them in Buchwald-Hartwig or Suzuki-Miyaura cross-coupling. As shown in scheme 88, in the case of Buchwald, the alkylpalladium is generated on a ter-butyl
group, whereas in Romo’s synthesis of Hypercalin C, the alkylpalladium species is generated on a methoxy group.

Scheme 88: Precedent trapping of alkylpalladium species in Buchwald-Hartwig or Suzuki-Miyaura couplings

3. Redox-neutral coupling between two C(sp³)-H bonds enabled by 1,4-Pd shift for the synthesis of fused heterocycles

3.1. 1,4-Pd shift as a tool for the construction of C(sp³)-C(sp³) bonds: toward the synthesis of dihydrobenzofurans

Inspired from Dyker and Larock, we investigated a new approach to generate C(sp³)-C(sp³) bonds after 1,4-Pd shift (Scheme 89).

Starting from 5.24, we envisaged to synthesize the dihydrobenzofuran 5.28. After an initial oxidative addition of palladium into the C-Br bond, followed by C(sp³)-H activation, the intermediate 5.25 could be obtained. We hypothesized that if the intermediate 5.25 could undergo a proton mediated palladacycle opening to form 5.26, this alkylpalladium moiety could directly undergo C(sp³)-H activation of a methyl at the ortho position followed by reductive elimination and generate simple dihydrobenzofurans 5.28. The proton mediated palladacycle opening could be favoured toward reductive elimination of 5.25. Indeed, the highly strained benzoxetane 5.27 formation would be disfavoured.
3.1.1. **Interest for dihydrobenzofurans**

The 2,3-dihydrobenzofurans (DHB) are present in a large number of natural products, such as (-)-linderol A, (+)-conocarpan or (+)-lithospermic acid (Figure 31).\textsuperscript{[185]} These natural products display various biological activities, and chemists focused their attention on the development of new libraries of non-natural DHB derivatives for medical uses.\textsuperscript{[186]} As a consequence, a broad catalogues of reactions using traditional or modern synthetic methods for accessing DHB skeleton have been developed.

![Representative DHB examples in natural products](image)

The major strategies for DHB 5.29 synthesis are depicted scheme 90.\textsuperscript{[185]} These methodologies mostly relies on oxygen-carbon or C₂-C₃ bonds formation. However, the formation of C₁-C₂ bond is under-represented, with C-H insertion of carbene 5.37 via transition-metal-catalysis as one of the only example.\textsuperscript{[187]}
3.1.2. Synthesis of dihydrobenzofurans

For the synthesis of DHB through C(sp^3)-C(sp^3) coupling, we started our investigations using 5.39. The substrate was chosen to afford a non-volatile product after C-H activation reaction. We used classical conditions as starting point to afford 5.40 (Table 6). Pd(PCy_3)_2 was selected as the catalyst, combined with a stoichiometric base in toluene. According to Dyker and our previous results, a high dilution was necessary to undergo a 1,4-Pd migration.[176] Combination of catalytic cesium pivalate and Cs_2CO_3 (1 equiv) at 120°C showed traces of product 5.40 (Entry 1). By replacing Cs_2CO_3 to Rb_2CO_3 or stoichiometric cesium pivalate (1-3 equiv), significant amount of DHB 5.40 was observed by ^1H NMR (20-25%) (Entries 2-4). Finally, higher temperature (140°C) was required to form 5.40 in good yield after purification (92%) (Entry 5).

<table>
<thead>
<tr>
<th>Entries</th>
<th>Additive (equiv.)</th>
<th>Base (equiv.)</th>
<th>T°C</th>
<th>NMR yield * (isolated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CsOPiv (30 mol%)</td>
<td>Cs_2CO_3 (1 equiv)</td>
<td>120°C</td>
<td>Traces</td>
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<td>Rb_2CO_3 (1 equiv)</td>
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</tr>
<tr>
<td>3</td>
<td>CsOPiv (1 equiv)</td>
<td>-</td>
<td>120°C</td>
<td>25%</td>
</tr>
<tr>
<td>4</td>
<td>CsOPiv (3 equiv)</td>
<td>-</td>
<td>120°C</td>
<td>25%</td>
</tr>
<tr>
<td>5</td>
<td>CsOPiv (1 equiv)</td>
<td>-</td>
<td>140°C</td>
<td>88% (92%)</td>
</tr>
</tbody>
</table>

*Using trichloroethylene as internal standard

Table 6: optimization table for dihydrobenzofuran synthesis
3.1.3. **Scope and limitations for DHB synthesis**

With the optimized conditions in hand for the synthesis of DHB 5.40, we studied the scope and limitations of the C(sp³)-H/C(sp³)-H coupling reaction (Scheme 92). Substrates were prepared according to known procedure, starting from commercially available phenol 5.41 (Scheme 91). Selective ortho-bromation, followed by alkylation gave the desired substrates 5.42.

![Scheme 91: Synthesis of reaction substrate for dihydrobenzofurans](image)

We first studied the influence of the substituents on the aromatic ring (R₃) toward DHB synthesis (Scheme 92). Aldehyde was tolerated, furnishing the desired product 5.45 in good yield (91%). Lower yield were obtained for 5.46 and 5.47, presumably because of their high volatility. Additionally, ortho-substituent was tolerated (5.48, 79%).

We then turned our attention to substrates bearing carbonyl substituents at R₂. Reactions proceeded with good yield for R₂ = CO₂Me (5.49-5.50) or R₂ = CO₂NR₂ (5.51-5.52, 53-88%). Modification at R₁ = –CO₂Me 5.53 also lead to the product, thereby allowing possible functionalization at C₂ (73%). Of note, these products are obtained through an unprecedented 1,4-Pd shift on activated methylene position, possibly occurring through enolate formation and palladation. Additionally, methyl ester 5.54 at R₁ and R₂ provided the desired product in 41%, as a single trans diastereoisomer. We also investigated the formation of DHB 5.55 starting from modified Bisphenol C as precursor. In this case, the double C(sp³)-H/C(sp³)-H coupling furnished the desired product in 68% with 20 mol% catalyst, and the activation of four C(sp³)-H bonds. Finally, for R₂ = Me (5.56), only traces of product were observed, indicating that the current reaction is limited to primary or acidic secondary C(sp³)-H bonds.
Scheme 92: Scope and limitations for dihydrobenzofurans synthesis. a: performed at 160°C; b: using 20 mol% Pd(PCy\textsubscript{3})\textsubscript{2}.

3.2. Extension to the synthesis of indolines

To extend our method for C(sp\textsuperscript{3})-H/C(sp\textsuperscript{3})-H coupling, we next considered the synthesis of indolines (Scheme 93).

According to previous reports, C(sp\textsuperscript{3})-H activation of N-methyl aniline derivative is occurring, furnishing demethylation product after iminium formation or direct coupling products\textsuperscript{[141]}. In a similar fashion, we hypothesized that if the C(sp\textsuperscript{3})-H activation would occur on N-methyl aniline derivative 5.62, the generated alkylpalladium 5.64 could react with an ortho-methyl substitutents in a C(sp\textsuperscript{3})-H activation reaction to furnish indolines 5.66 (Scheme 93).

3.2.1. Interest for indolines

The indoline scaffold is present in numerous naturally bioactive alkaloids such as (-)-physostigmine or (+)-aspidospermidine and is also a structural component of several pharmaceutically active compounds (Pentopril) (Figure 32).
Nowadays, a large spectra of reactions have been designed for the synthesis of indolines \textsuperscript{5,67}. The main disconnections for indoline synthesis are depicted scheme \textsuperscript{94}.\textsuperscript{[189]} Most of the approaches relies on the formation of the \textit{N}-aryl bond, through copper-catalyzed Ullmann-Goldberg reaction\textsuperscript{[190]} or Buchwald-Hartwig coupling.\textsuperscript{[191]} However, only few reports described the direct formation of \textit{C}_1-\textit{C}_2 bond. Carbene insertion from \textsuperscript{5,76}\textsuperscript{[192]} or copper-catalyzed radical cyclisation from \textsuperscript{5,75} are representative examples for such bond formation.\textsuperscript{[193]}

\textbf{Scheme 94: Main disconnections for indoline synthesis}

3.2.2. \textit{Reaction optimization}

For the synthesis of indolines through \textit{C}(sp\textsuperscript{3})-\textit{C}(sp\textsuperscript{3}) coupling, we started our investigations with \textit{N}-methyl aniline bearing trifluoroacetyl substituent \textsuperscript{5,77} to access \textsuperscript{5,78} (Table 7). The protecting group was selected to reduce de demethylation side reaction.

Using the predefined Pd(PCy\textsubscript{3})\textsubscript{2} catalyst, combinations of additives/bases were tested in toluene [0.025M] at 160°C (Table 7). Starting from cesium pivalate as stoichiometric base gave us as initial result the desired indoline \textsuperscript{5,78} in 10% yield (Entry 1). Surprisingly, combination of PivOH/Cs\textsubscript{2}CO\textsubscript{3} did not give any product (Entry 2). Finally, using Rb\textsubscript{2}CO\textsubscript{3} (1.5 equiv) in combination with adamantoic acid as CMD base, \textsuperscript{5,78} was isolated in 74% (Entry 4).
Table 7: Optimization table for indoline synthesis

<table>
<thead>
<tr>
<th>Entries</th>
<th>Additive (equiv.)</th>
<th>Base (equiv.)</th>
<th>NMR yield* (isolated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CsOPiv (1 equiv)</td>
<td>-</td>
<td>10%</td>
</tr>
<tr>
<td>2</td>
<td>PivOH (30 mol%)</td>
<td>Cs$_2$CO$_3$ (1.5 equiv)</td>
<td>0%</td>
</tr>
<tr>
<td>3</td>
<td>PivOH (30 mol%)</td>
<td>Rb$_2$CO$_3$ (1.5 equiv)</td>
<td>23%</td>
</tr>
<tr>
<td>4</td>
<td>AdCO$_2$H (30 mol%)</td>
<td>Rb$_2$CO$_3$ (1.5 equiv)</td>
<td>72% (74%)</td>
</tr>
</tbody>
</table>

*Using trichloroethylene as internal standard

3.2.3. Scope and limitations for indolines synthesis

With the optimized conditions in hand, we next studied the scope for indolines synthesis (Scheme 96). Reaction substrates 5.80 were obtained after o-bromination of commercially available anilines 5.79, followed by trifluoroacetylation and methylation (Scheme 95).

Different substituents on the aromatic ring (R$_3$) were well tolerated, furnishing the desired indolines in moderate to good yield (Scheme 96, 5.77-5.85, 38-62%). However, attempts to introduce a methyl ester moiety at R$_1$ (5.87) or R$_2$ (5.86) did not give any trace of the desired product. In these cases, only degradation was observed by $^1$H NMR. Changing the trifluoroacetyl protecting group to other protecting groups such as methyl carbamate did not furnish the desired product 5.88. With these observations, it seems that the acidity of the C-H bond of the N-methyl is determining for the reaction to occur. Nevertheless, diverse indolines were successfully isolated and this method provides an alternative synthesis to this scaffold.
Scheme 96: Scope and limitations for indolines synthesis

3.3. Extensions on o-methoxyphenylketones

3.3.1. Synthesis of chroman-4-ones

After the synthesis of 5-membered heterocycles DHB and indolines, we next investigated the formation of 6-membered rings via 1,4-Pd shift. As discussed earlier, it appears that only activated C(sp³)-H bonds are suitable for this transformation. We turned our attention to o-methoxyphenylketones 5.89 bearing enolisable substituent to access chroman-4-ones 5.90 (Scheme 97).[194]

![Scheme 97: Hypothesis for the synthesis of chroman-4-ones](image)

For this, we investigated the reactivity of 5.91 toward C(sp³)-H/C(sp³)-H coupling conditions to access 5.92 (Table 8). First, Pd(PCy₃)₂ was selected as catalyst, in combination with PivOH/Rb₂CO₃ in toluene [0.025M] at 120°C. In this case, the desired product was formed in 35% NMR yield (Entry 1). Further optimizations were made, notably by changing the additive/base system, increasing the yield for the chroman-4-one 5.92 to 72% yield with a mixture of adamantioic acid and Cs₂CO₃ (Entry 4).
<table>
<thead>
<tr>
<th>Entries</th>
<th>Additive (equiv.)</th>
<th>Base (equiv.)</th>
<th>NMR yield* (isolated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PivOH (30 mol%)</td>
<td>Rb₂CO₃ (1.5 equiv)</td>
<td>35%</td>
</tr>
<tr>
<td>2</td>
<td>PivOH (30 mol%)</td>
<td>Rb₂CO₃ (1 equiv)</td>
<td>45%</td>
</tr>
<tr>
<td>3</td>
<td>AdCO₂H (30 mol%)</td>
<td>Rb₂CO₃ (1 equiv)</td>
<td>60%</td>
</tr>
<tr>
<td>4</td>
<td>AdCO₂H (30 mol%)</td>
<td>Cs₂CO₃ (1 equiv)</td>
<td>71% (72%)</td>
</tr>
</tbody>
</table>

*Using trichloroethylene as internal standard

Table 8: Optimization table for chroman-4-one synthesis

3.3.2. Scope of chroman-4-ones

With the optimized conditions in hand, we investigated the scope of the reaction for the chroman-4-ones synthesis (Scheme 98). Starting materials 5.93 were obtained from commercially available phenol, after electrophilic bromination and methylation reactions.

For the synthesis of chroman-4-ones, substitutents on the aromatic ring (R₂) furnished the desired products with good yields (5.92-5.97, 52-68%). Moreover, alkyl substituents can be introduced at R₁, providing C₃-subsituted chroman-4-ones (5.98-5.99, 55-82%).

Scheme 98: Scope of chroman-4-ones

3.3.3. Deuteration experiments

In order to rationalize the plausible reaction mechanism, deuteration experiments were conducted for the synthesis of chroman-4-one (Scheme 99). Initially, we tried to perform the reaction on the deuterated compound 5.96r-d₃ using our standard conditions. Surprisingly, no trace of desired product was observed after different reaction time. This result might suggest a really high kinetic isotope effect (KIE) (similar results were obtained while using deuterated indolines precursor). Then, an equimolar mixture of 5.96r and 5.96r-d₃-2 were reacted under
the same conditions. $^1$H NMR analysis of the crude showed 50% deuterium incorporation in 5.96d-2. These two results tends to show that the first C(sp$^3$)-H activation might be the rate limiting step in this transformation.

Scheme 99: Deuteration experiments for chroman-4-one synthesis

3.3.4. Nucleophilic addition of alkylpalladium intermediate on arylketones

In the previous parts of this chapter, the in situ generated alkylpalladium species were reacted in a C(sp$^3$)-H activation reaction, affording dihydrobenzofurans, indolines and chromanones. Precedents reports from Yamamoto,$^{195}$ Muir,$^{196}$ Shibasaki,$^{197}$ or Ley$^{199}$ showed that arylpalladium or alkylpalladium species can also react as nucleophiles, with electrophilic ketones or imines (Scheme 100). While using 5.100, the absence of enolizable position in alpha to a ketone could undergo nucleophilic addition to generate a tertiary alcohol 5.102 and access another class of functionalized products.

Scheme 100: Hypothesis for alkylpalladium reactivity in nucleophilic addition

To confirm our hypothesis, investigations were made starting with biarylketone derivative 5.103 (Table 9). We started using Pd(PCI)$_3$ as catalyst, in combinations with additive/base under higher temperature (160°C) in toluene [0.025M]. As initial result, pivalic acid (30 mol%), combined with cesium carbonate (1.5 equiv) provided the desired tertiary alcohol 5.104 in 10% yield (Entry 1). Replacing Cs$_2$CO$_3$ by Rb$_2$CO$_3$ did not affect the reaction whereas the use of stoichiometric pivalic acid and cesium carbonate furnished 5.104 in 50% yield (Entries 2-3). In
the presence of cesium pivalate (3 equiv), the desired product was isolated in 69% yield (Entry 5).

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Entries</th>
<th>Additive (equiv.)</th>
<th>Base (equiv.)</th>
<th>NMR yield* (isolated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PivOH (30 mol%)</td>
<td>Cs₂CO₃ (1.5 equiv)</td>
<td>10%</td>
</tr>
<tr>
<td>2</td>
<td>PivOH (30 mol%)</td>
<td>Rb₂CO₃ (1.5 equiv)</td>
<td>18%</td>
</tr>
<tr>
<td>3</td>
<td>PivOH (3 equiv)</td>
<td>Cs₂CO₃ (3 equiv)</td>
<td>50%</td>
</tr>
<tr>
<td>4</td>
<td>CsOPiv (1.5 equiv)</td>
<td>-</td>
<td>40%</td>
</tr>
<tr>
<td>5</td>
<td>CsOPiv (3 equiv)</td>
<td>-</td>
<td>77% (69%)</td>
</tr>
</tbody>
</table>

*Using trichloroethylene as internal standard

Table 9: Optimization table for nucleophilic addition

In a mechanistic point of view, this reaction is supposed to require a stoichiometric reductant to regenerate the Pd⁰ catalyst after nucleophilic addition. In the reaction mixture, the only stoichiometric reagent is the cesium pivalate. We postulated that the generated palladium pivalate would decompose to Pd⁰ particles, thereby allowing the turn over of the reaction. Indeed, while heating Pd(OPiv)₂ in toluene at 160°C, particles of Pd⁰ were observed. According to previous studies, the decomposition of Pd(OAc)₂ showed that Pd⁰ metal particles were observed while heating the catalyst at T°C > 47°C.

3.3.5. Scope of 2,3-dihydrobenzofuran-3-ol

With our optimized conditions, we next studied the scope for the 2,3-dihydrobenzofuran-3-ol synthesis (Scheme 102). Starting from commercially available 2-hydroxybenzaldehyde derivatives 5.105, ortho bromination followed by methylation of the phenol were performed to generate 5.106 (Scheme 101). The substrates were then reacted with aryl Grignard reagents, followed by PCC oxidation, to afford the desired substrates 5.107.

![Chemical structures](image)

Scheme 101: Synthesis of substrates for nucleophilic addition
For the synthesis of 2,3-dihydrobenzofuran-3-ol, electron-withdrawing or electron-donating groups could be introduced on both aromatic rings, furnishing tertiary alcohols in moderate to good yields (Scheme 102) (5.104-5.114, 50-78%). The reaction seems to occur with higher efficiency while using an electron-withdrawing group on the aromatic ring (5.110 and 5.114). Additionally, attempts to react imines derivatives in these conditions afforded the desired amines, albeit in low yields (5.115-5.117).

Finally, the moderate stability of 2,3-dihydrobenzofuran-3-ol 5.113 and 5.114 can undergo water elimination to afford benzofurans 5.118 and 5.119 when reacted in CDCl3 at room temperature (Scheme 103).

4. Perspectives

With these results in hand, we are now pursuing our investigations for 1,4-Pd shift/C-H activation reaction on new substrates (Scheme 104). For example, using 5.120 as substrate, benzofuran-3-one 5.121 arising from C(sp²)-C(sp³) coupling can be observed in 49% 1H NMR yield after C(sp²)-H activation of the aldehyde moiety. This initial result can open new perspectives to access such building blocks.
Furthermore, alternatives to methoxy or N-methyl anilines were tested as suitable groupments for 1,4-Pd shift (Scheme 105). Notably, acetyl moiety seemed to be promising while running reactions with 5.122. Indeed, the desired C(sp³)-C(sp³) coupling indanone 5.123 was observed in 23% ¹H NMR yield. This cascade process involving 1,4-Pd shift afford a new method to synthesize such bicyclic product.

5. Conclusion

After taking advantage of the 1,4-Pd shift to form C(sp³)-C(sp³) coupling products, we developed here a new method to afford different valuable heterocycles through C(sp³)-C(sp³) coupling. Complementary to CDC (cross-dehydrogenative-coupling) methods, our conditions have the advantage to be redox-neutral, with the C-Br bond acting as an internal oxidant. We described the synthesis of functionalized DHB, indolines and chroman-4-ones by double C(sp³)-H activation. Furthermore, the in situ generation of an alkylpalladium species can undergo nucleophilic addition on keto-substrates to afford 2,3-dihydrobenzofuran-3-ol, which can easily be converted to functionalized benzofurans (Scheme 106).[201]
General conclusion

Over the past decade, the transition metal-catalysed intramolecular activation of unactivated C-H bonds has emerged as a powerful tool for organic chemists according to their abundance. Selective functionalizations of C-H bonds provide a rapid access to molecular complexity in an atom- and step-economical fashion. Within this field, my Ph.D. thesis was focused on the development of new methodologies involving Pd\(^{0}\)/Pd\(^{II}\) catalysed C(sp\(^3\))-H activation to access valuable building blocks or natural products. My thesis is divided into two distinct parts, namely “direct C(sp\(^3\))-H functionalization” and “remote C(sp\(^3\))-H functionalization”.

First, we developed a double C(sp\(^2\))/C(sp\(^3\))-H arylation method to access lycorine alkaloids derivatives, according to a fine design of reaction substrate. The scope of the double C-H arylation was studied, allowing the access to lycorine derivatives in an efficient manner. Moreover, this methodology has been applied for the first time for the synthesis of natural products hippadine and pratosine as well as the metabolite (±)-γ-lycorane, involving a selective arene hydrogenation. The sequence remains, the shortest and most efficient synthetic path for this molecule (Scheme 107).

![Scheme 107: Synthesis of (±)-γ-lycorane using double C(sp\(^3\))/C(sp\(^3\))-H arylation](image)

Then, we developed a new method to access β-lactams using palladium catalysed C(sp\(^3\))-H carbamoylation under carbon monoxide atmosphere. The applicability of the reaction was studied and applied to a broad scope of β-lactams bearing different functionalities. This reaction is suitable with primary, secondary and tertiary C-H bond, as well as unactivated C-H bonds. Additionally, an enantioselective version was developed to afford enantioenriched β-lactams. Finally, the applicability of the reaction was demonstrated through the synthesis of enantiopure β-amino acid for bioactive molecule synthesis (Scheme 108).
With our synthesis of $\beta$-lactams, we investigated the synthesis of other nitrogen-containing 4-membered ring benzazetidines. However, the low stability of these compounds gave us the unexpected benzoxazines through an unprecedented domino C(sp$^3$)-H activation/electrocyclic rearrangement of the benzazetidines intermediates. 20 examples of benzoxazine could be afforded while using a bulky and unactivated nitrogen substituent, to favour reductive elimination during the process. Benzoxazines can then be converted to the polycyclic core of natural product alkaloids (Scheme 109).

In addition to direct C(sp$^3$)-H functionalization, remote functionalization of C(sp$^3$)-H bonds using a 1,4-Pd migration was investigated. We reported an unprecedented 1,4-Pd shift followed by C(sp$^3$)-H activation on unactivated positions to afford a broad range of $\alpha$-arylidene $\gamma$-lactams and indanones through C(sp$^2$)-C(sp$^3$) bonds formation. The applicability of the method was demonstrated with the formal synthesis of (-)-pyrrolam (Scheme 110).

After taking advantage of the 1,4-Pd shift to form C(sp$^3$)-C(sp$^3$) coupling products, we extended the method to create C(sp$^3$)-C(sp$^3$) bonds. Here, the ability of palladium to undergo a 1,4-shift
generates an alkylpalladium species, which can react in a second C(sp\(^3\))-H activation reaction or in a nucleophilic addition. We described the synthesis of functionalized dihydrobenzofurans, indolines and chroman-4-ones by double C(sp\(^3\))-H activation and 2,3-dihydrobenzofuran-3-ol through nucleophilic addition. Our method presents the advantage to be redox-neutral (Scheme III).

*Scheme III: 1,4-Shift/C(sp\(^3\))-H activation for the access to various heterocycles*
Bibliographic part

Experimental part:
Part 1: Direct C(sp³)-H activation

Chapter 1.1: Synthesis of lycorine alkaloids using Pd-catalysed CH-arylation:

General information

Techniques: All reactions involving air-sensitive material were carried out in pre-dried glassware under an argon atmosphere by using Schlenk techniques employing double-line argon-vacuum lines and working in an argon-filled glove box. Analytical thin layer chromatography (TLC) was performed using pre-coated Merck silica gel 60 F254 plates (0.25 mm). Visualization of the developed chromatogram was performed by UV absorbance (254 nm) or TLC stains (KMnO₄ and Phosphomolybdic acid). Flash chromatography was performed using Silicycle SiliaFlash P60 (230-400 mesh) with the indicated solvent system, using gradients of increasing polarity in most cases.

Chemicals:

Anhydrous solvents were obtained by distillation over calcium hydride (xylenes) or by distillation over sodium (mesitylene, toluene). Anhydrous THF, DME, DMF, DMSO, were purchased from Acros Organics. The solvents were degassed by three cycles of freeze-pump-thaw and storing in single-necked flasks equipped with a J-Young PTFE valve when necessary. Pd(PCy₃)₂, PdCl₂, Pd(OAc)₂, Pd(PPh₃)₄ were purchased from Strem. All other chemical reagents were purchased from Sigma-Aldrich, Acros Organics, Fisher, Solvias and Fluorochem and used as received without further purification unless otherwise stated. CO gas was purchased from PanGas in 3.8 quality.

Instrumentation:

HPLC analyses were performed using a Shimadzu Prominence system with SIL-20A auto sample, CTO-20AC column oven, LC-20AD pump system, DGU-20A3 degasser and SPD M20A Diode Array or UV/VIS detector. The following chiral columns from Daicel Chemical Industries were used: OD-H (chiralcel), OJ-H (chiralcel) or IA (chiralpak) in 4.6 x 250 mm size. Infrared spectra were taken on a Bruker ALPHA FT-IR spectrometer and are reported in reciprocal centimeters (cm⁻¹). Nuclear magnetic resonance spectra were recorded on a Bruker Advance 250 (250 MHz), Bruker Advance 400 (400 MHz), Bruker Advance 500 (500 MHz) in deuterated chloroform (residual peaks ¹H δ = 7.26 ppm, ¹³C δ = 77.16 ppm) unless otherwise
noted. $^{31}$P NMR spectra were on a Bruker Advance 400 (400 MHz). $^{19}$F spectra were referenced to external CFCl$_3$. $^{31}$P spectra were referenced to external 95% solution of H$_3$PO$_4$. Data are reported in parts per million (ppm) as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintuplet, sept = septuplet, m = multiplet and br s = broad signal), coupling constant in Hz and integration. High resolution mass spectra were recorded by Dr. H. Nadig (Department of Chemistry, University of Basel) and Dr. M. Pfeffer on a Bruker maXis 4G QTOF ESI mass spectrometer. Optical rotations were measured on a Perkin Elmer 341 Polarimeter in a 1 mL micro cuvette (cell length 100mm) with NaD-Line ($\lambda = 589$ nm) at 20 °C.

**Synthesis of anilines:**

**GENERAL PROCEDURE A FOR ACYLATION OF ANILINES:**

Anilines (1 equiv) were dissolved in DCM (0.1 M) in presence of Et$_3$N (2 equiv) and cooled to 0°C. Acid chlorides (1.2 equiv) were carefully added and the mixture was allowed to reach room temperature. After completion, the reaction was quenched with HCl 1M, and extracted with DCM. The crude was washed with NaOH 1M, dried over Na$_2$SO$_4$, filtered and purified by chromatography on silica gel using cyclohexane/AcOEt as solvent.

**GENERAL PROCEDURE B FOR ACYLATION OF ANILINES:**

Anilines (1 equiv) were dissolved in DCM (0.1 M) in presence DMAP (0.05 equiv) and cooled to 0°C. Acetic anhydride (1.1 equiv) was carefully added and the mixture was allowed to reach room temperature. After completion, the reaction was quenched with HCl 1M, and extracted with DCM. The crude was washed with NaOH 1M, dried over Na$_2$SO$_4$, filtered and purified by chromatography on silica gel using cyclohexane/AcOEt as solvent.

**GENERAL PROCEDURE FOR ALKYLATION OF AMIDES:**

Amides (1 equiv) were dissolved in dry THF (0.1 M) and cooled to 0°C with an ice bath. The solution was placed under argon, and NaH (60 % dispersion in oil, 3 equiv) was carefully added. The mixture was stirred for 10 minutes, followed by addition of the bromobenzyle partners (or chlorobenzyle as specified) (1.1 equiv) dissolved in dry THF (0.1 M). The mixture was then stirred overnight under reflux, cooled to room temperature and carefully quenched with water. The crude was extracted with AcOEt, dried over Na$_2$SO$_4$, filtered, evaporated and purified over silica gel using cyclohexane/AcOEt to afford the pure compounds.
GENERAL PROCEDURE FOR THE DOUBLE C(sp²)-H/C(sp³)-H ARYLATION UNDER OPTIMIZED CONDITIONS:

In a 10 mL screw-cap vial, previously charged with substrate (0.15 mmol, 1 equiv) and stirring bar, was weighted in a glovebox Cs₂CO₃ (98 mg, 0.30 mmol, 2 equiv), pivalic acid (4.6 mg, 0.045 mmol, 0.3 equiv) and Pd(PCy₃)₂ (10 mg, 0.015 mmol, 0.1 equiv). The vial was removed from the glovebox and mesitylene (3 mL) was added. The sealed vial was stirred in a pre-heated heating block at 140 °C for 16 h. Then, the mixture was cooled to room temperature and directly charged on silica for chromatography on gel. The mesitylene was flushed using cyclohexane and the mixture was purified using cyclohexane /AcOEt to afford the desired compounds.
**N-(2,6-Dibromophenyl)acetamide 1.33a:**

\[
\begin{array}{c}
\text{Br} \\
\text{HN-} \\
\text{Br} \\
\text{O}
\end{array}
\]

Chemical Formula: C$_8$H$_7$Br$_2$NO  
Exact Mass: 290.8894

Following general procedure A for acylation of anilines, 2,6-dibromoaniline (2 g, 7.97 mmol, 1 equiv), Et$_3$N (2.3 mL, 15.9 mmol, 2 equiv) and acetyl chloride (0.68 mL, 9.56 mmol, 1.2 equiv) were reacted in DCM. N-(2,6-dibromophenyl)acetamide was obtained after chromatography on silica gel as a yellowish solid (1 g, 3.41 mmol, 43 %). $^1$

$^1$H NMR (400 MHz, Methanol-d$_4$) $\delta$ = 7.69 – 7.66 (m, 2H), 7.16 – 7.12 (m, 1H), 2.17 (s, 3H)

$^{13}$C NMR (101 MHz, Methanol-d$_4$) $\delta$ = 172.1, 136.7, 133.5, 131.3, 125.5, 22.4.

**N-(2-Bromophenyl)acetamide 1.31sa:**

\[
\begin{array}{c}
\text{Br} \\
\text{HN-} \\
\text{O}
\end{array}
\]

Chemical Formula: C$_8$H$_8$BrNO  
Exact Mass: 212.9789

Following general procedure A for acylation of anilines, 2-bromoaniline (3 g, 17.1 mmol, 1 equiv), Et$_3$N (4.80 mL, 34.2 mmol, 2 equiv) and acetyl chloride (1.46 mL, 20.5 mmol, 1.2 equiv) were reacted in DCM. N-(2-bromophenyl)acetamide was obtained after chromatography on silica gel as a yellowish solid (2.36 g, 11.0 mmol, 64 %). $^2$

$^1$H NMR (400 MHz, Methanol-d$_4$) $\delta$ = 7.67 – 7.58 (m, 2H), 7.36 – 7.34 (m, 1H), 7.11 (td, $J$ = 7.8, 1.6 Hz, 1H), 2.18 (s, 3H).

$^{13}$C NMR (101 MHz, Methanol-d$_4$) $\delta$ = 172.0, 137.2, 133.9, 129.0, 128.4, 128.1, 119.2, 23.2.
N-(2-Chloro-4-fluorophenyl)acetamide 1.49sa:

![Chemical structure](image)

Following general procedure B for acylation of anilines, 2-chloro-4-fluoroaniline (1 g, 6.87 mmol, 1 equiv), DMAP (42 mg, 0.34 mmol, 0.05 equiv) and acetic anhydride (0.71 mL, 7.56 mmol, 1.1 equiv) were reacted in DCM. N-(2-chloro-4-fluorophenyl)acetamide was obtained after chromatography on silica gel as a white solid (940 mg, 5.0 mmol, 73%).

$^1$H NMR (400 MHz, Chloroform-d) δ = 8.35 - 8.27 (m, 1H), 7.49 (s, 1H), 7.17 - 7.09 (m, 1H), 7.03 - 6.97 (m, 1H), 2.23 (s, 3H).

$^{13}$C NMR (101 MHz, Chloroform-d) δ = 168.3, 158.5 (d, J = 250 Hz), 131.2, 123.5, 123.1 (d, J = 6.6 Hz), 116.3 (d, J = 27 Hz), 114.7(d, J = 22 Hz), 24.9.

N-(3,4,5-Trimethoxyphenyl)acetamide 1.51ssa:

![Chemical structure](image)

Following general procedure B for acylation of anilines, 3,4,5-trimethoxyaniline (1.5 g, 8.19 mmol, 1 equiv), DMAP (50 mg, 0.41 mmol, 0.05 equiv) and acetic anhydride (0.84 mL, 9.0 mmol, 1.1 equiv) were reacted in DCM. N-(3,4,5-trimethoxyphenyl)acetamide was obtained after chromatography on silica gel as a yellowish solid (1.54 g, 6.9 mmol, 83%).

$^1$H NMR (400 MHz, Chloroform-d) δ = 7.97 (s, 1H), 6.81 (s, 2H), 3.78 (s, 3H), 3.74 (m, 6H), 2.12 (s, 3H).

$^{13}$C NMR (101 MHz, Chloroform-d) δ = 168.8, 153.2, 135.0, 134.4, 97.7, 61.0, 56.0, 24.5.
N-(2-Chloro-3,4,5-trimethoxyphenyl)acetamide 1.51sa:

\[
\text{Chemical Formula: } C_{11}H_{14}ClNO_4
\]
\[
\text{Exact Mass: } 259.0611
\]

N-Chlorosuccinimide (593 mg, 4.5 mmol, 1 equiv) was added to a solution of 1.51ssa (1.0 g, 4.5 mmol, 1 equiv) in acetonitrile (20 mL). The reaction mixture was heated at 65 °C overnight, cooled to room temperature and quenched with saturated aqueous NaHCO\textsubscript{3} solution (140 mL). The aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organic were washed wit NaOH 10 % (2 x 20 mL), dried over Na\textsubscript{2}SO\textsubscript{4}, filtered, and concentrated. The product was purified by chromatography on silica gel using cyclohexane/AcOEt as solvent (568 mg, 2.2 mmol, 50 % yield). ⁵

\[^{1}\text{H NMR (400 MHz, Chloroform-d)}\] \(\delta = 7.90\) (s, 1H), \(7.56\) (s, 1H), \(3.91\) (s, 3H), \(3.87\) (s, 3H), \(3.85\) (s, 3H), \(2.23\) (s, 3H).

\[^{13}\text{C NMR (101 MHz, Chloroform-d)}\] \(\delta = 168.5, 152.4, 149.7, 139.4, 131.0, 108.6, 101.0, 61.4, 56.3, 25.1.\)

HRMS (ESI): Calculated for C\textsubscript{11}H\textsubscript{15}ClNO\textsubscript{4} ([M+H]\textsuperscript{+}): 260.0690; found 260.0684

IR (neat) : \(\nu = 1660, 1457\) cm\textsuperscript{-1}

N-(4-(Benzyloxy)-3-methylphenyl)acetamide 1.52ssa:

\[
\text{Chemical Formula: } C_{16}H_{17}NO_2
\]
\[
\text{Exact Mass: } 255.1259
\]

4-Amino-2-methylphenol (79.3 mmol, 9.76 g, 1 equiv) was dissolved in 160 mL of ethyl acetate and placed under argon atmosphere. Ac\textsubscript{2}O (79.3 mmol, 7.43 mL, 1 equiv) was slowly added to the turning solution, which was then stirred for 2 h. The reaction was quenched with water (50
mL), and the organic phase was back extracted with AcOEt (2 x 30 mL). The combined organic mixture were washe
錯

错

错

K₂CO₃ (90.9 mmol, 12.6 g, 3 equiv), and N-(4-hydroxy-3-methylphenyl)acetamide (30.3 mmol, 5 g, 1 equiv) were stirred at room temperature in 300 mL of acetone. Benzyle bromide (32.8 mmol, 3.92 mL, 1.08 equiv) was slowly added to the mixture, which was then heated at reflux for 16 h. The brownish mixture was cooled to room temperature and acetone was evaporated under vacuum. The remaining solid was dissolved in AcOEt (120 mL) and water (120 mL). The crude was extracted with AcOEt (3 x 40 mL) and the combined organic layers were dried over Na₂SO₄, filtered and evaporated under vacuum. N-(4-(benzyloxy)-3-methylphenyl)acetamide was obtained without any further purification (7.74 g, 100 %).

¹H NMR (400 MHz, Chloroform-d) δ = 7.45 – 7.36 (m, 4H), 7.34 – 7.31 (m, 1H), 7.28 – 7.27 (m, 1H), 7.25 – 7.23 (m, 1H), 6.81 (d, J = 8.5 Hz, 1H), 5.05 (s, 2H), 2.26 (s, 3H), 2.13 (s, 3H).

¹³C NMR (101 MHz, Chloroform-d) δ = 168.4, 153.9, 137.5, 130.9, 128.6, 127.9, 127.2, 123.5, 119.1, 112.0, 70.3, 24.5, 16.6.

HRMS (ESI): Calculated for C₁₆H₁₈NO₄ ([M+H]⁺): 256.1338; found 256.1341

IR (neat) : ν =1640, 1455 cm⁻¹

N-(4-(Benzyloxy)-2-chloro-5-methylphenyl)acetamide 1.52sa:

Chemical Formula: C₁₆H₁₈ClNO₂
Exact Mass: 289.0870

N-Chlorosuccinimide (3.65 g, 27.3 mmol, 1 equiv) was added to a solution of 1.52ssa (7.0 g, 27.3 mmol, 1 equiv) in acetonitrile (140 mL). The reaction mixture was heated at 65 °C overnight, cooled to room temperature and quenched with saturated aqueous NaHCO₃ solution (140 mL). The aqueous layer was extracted with ethyl acetate (3 x 60 mL). The combined organic were washed wit NaOH 10 % (2 x 50 mL), dried over Na₂SO₄, filtered, and concentrated. The product was obtained as a brownish solid (7.5 g, 25.9 mmol, 95 % yield).
$^1$H NMR (400 MHz, Chloroform-d) $\delta = 8.03$ (s, 1H), 7.44 – 7.33 (m, 5H), 6.88 (s, 1H), 5.03 (s, 2H), 2.25 (s, 3H), 2.21 (s, 3H).

$^{13}$C NMR (101 MHz, Chloroform-d) $\delta = 168.1, 153.6, 136.7, 128.6, 128.0, 127.6, 127.1, 126.9, 124.6, 120.8, 112.2, 70.4, 24.6, 16.3$.

HRMS (ESI): Calculated for C$_{16}$H$_{17}$ClNO$_2$ ([M+H]$^+$): 290.0948; found 290.0944

IR (neat): $\nu = 1637, 1569$ cm$^{-1}$

mp: 160-162°C

N-(2-Chlorophenyl)propionamide 1.53sa:

Following general procedure A for acylation of anilines, 2-chloroaniline (1 g, 7.84 mmol, 1 equiv), Et$_3$N (2.2 mL, 15.7 mmol, 2 equiv) and propionyl chloride (0.75 mL, 8.62 mmol, 1.1 equiv) were reacted in DCM. N-(2-chlorophenyl)propionamide was obtained after chromatography on silica gel as a white solid (1.44 g, 7.84 mmol, 100%).

$^1$H NMR (400 MHz, Chloroform-d) $\delta = 8.43 – 8.37$ (m, 1H), 7.65 (s, 1H), 7.39 – 7.31 (m, 1H), 7.31 – 7.22 (m, 1H), 7.03 (td, J = 7.8, 1.5 Hz, 1H), 2.47 (q, J = 7.6 Hz, 2H), 1.28 (t, J = 7.6 Hz, 3H).

$^{13}$C NMR (101 MHz, Chloroform-d) $\delta = 171.9, 134.6, 128.9, 127.8, 124.4, 122.5, 121.5, 31.0, 9.6$.

N-(2-Chlorophenyl)-2-phenylacetamide 1.54sa:
Following general procedure A for acylation of anilines, 2-chloroaniline (1 g, 7.84 mmol, 1 equiv), Et$_3$N (2.2 mL, 15.7 mmol, 2 equiv) and phenylacetyl chloride (1.25 mL, 9.41 mmol, 1.2 equiv) were reacted in DCM. N-(2-chlorophenyl)-2-phenylacetamide was obtained after chromatography on silica gel as a yellowish solid (1.8 g, 7.33 mmol, 94 %). 

$^1$H NMR (500 MHz, Chloroform-d) $\delta$ = 8.41 – 8.35 (m, 1H), 7.66 (s, 1H), 7.46 – 7.40 (m, 2H), 7.40 – 7.34 (m, 3H), 7.29 – 7.21 (m, 1H), 7.27 – 7.22 (m, 1H), 7.00 (td, $J = 7.7, 1.5$ Hz, 1H), 3.80 (s, 2H).

$^{13}$C NMR (126 MHz, Chloroform-d) $\delta$ = 169.2, 134.6, 134.1, 129.8, 129.5, 129.0, 128.0, 127.8, 124.8, 122.8, 121.3, 45.3.

N-(2-Chlorophenyl)isobutyramide 1.55sa:

Chemical Formula: C$_{10}$H$_{12}$ClNO
Exact Mass: 197.0607

Following general procedure A for acylation of anilines, 2-chloroaniline (638 mg, 5 mmol, 1 equiv), Et$_3$N (1.41 mL, 10 mmol, 2 equiv) and isobutyryl chloride (0.63 mL, 6.0 mmol, 1.2 equiv) were reacted in DCM. N-(2-chlorophenyl)isobutyramide was obtained after chromatography on silica gel as a white solid (780 mg, 3.95 mmol, 79 %). 

$^1$H NMR (400 MHz, Chloroform-d) $\delta$ = 8.40 (m, 1H), 7.70 (s, 1H), 7.39 – 7.31 (m, 1H), 7.30 – 7.23 (m, 1H), 7.07 -7.01 (m, 1H), 2.66 – 2.54 (sep, $J = 7.1$ Hz, 1H), 1.30 (d, $J = 6.9$ Hz, 6H).

$^{13}$C NMR (101 MHz, Chloroform-d) $\delta$ = 175.3, 134.9, 129.1, 127.9, 124.6, 121.7, 37.2, 19.7.

N-(Benzo[d][1,3]dioxol-5-ylmethyl)-N-(2,6-dibromophenyl)acetamide 1.30:

Chemical Formula: C$_{16}$H$_{13}$Br$_2$NO$_3$
Exact Mass: 424.9262
Following general procedure for alkylation of amides, aniline (1.5 mmol, 439 mg, 1 equiv) was reacted with NaH (4.5 mmol, 180 mg, 3 equiv) and 5-(bromomethyl)benzo[d][1,3]dioxole (1.65 mmol, 355 mg, 1.1 equiv). **1.30** was obtained after purification as a yellowish solid (620 mg, 1.45 mmol, 96 %).

**$^1$H NMR (400 MHz, Chloroform-d)** $\delta = 7.59$ (s, 1H), 7.57 (s, 1H), 7.09 - 7.01 (m, 1H), 6.83 – 6.78 (m, 1H), 6.63 – 6.57 (m, 2H), 5.90 (s, 2H), 4.75 (s, 2H), 1.83 (s, 3H).

**$^{13}$C NMR (101 MHz, Chloroform-d)** $\delta = 170.1, 147.4, 147.3, 140.3, 133.2, 130.8, 129.8, 126.2, 124.1, 111.3, 107.9, 101.0, 51.1, 22.5.$

HRMS (ESI): Calculated for C$_{16}$H$_{14}$Br$_2$NO$_3$ ([M+H]$^+$): 425.9340; found 425.9344

IR (neat) : ν = 1640, 1555 cm$^{-1}$

mp: 240-243°C

**N-((6-Bromobenzo[d][1,3]dioxol-5-vl)methyl)-N-(2-bromophenyl)acetamide 1.31a:**

Following general procedure for alkylation of amides, 2-bromoacetanilide (7.1 mmol, 1.5 g, 1 equiv) was reacted with NaH (21.3 mmol, 850 mg, 3 equiv) and 5-bromo-6-(bromomethyl)benzo[d][1,3]dioxole (7.8 mmol, 2.3 g, 1.1 equiv). **1.31a** was obtained after purification as a yellowish solid (3.03 g, 7.1 mmol, 99 %).

**$^1$H NMR (400 MHz, Chloroform-d)** $\delta = 7.69 – 7.62$ (m, 1H), 7.24 – 7.17 (m, 2H), 7.00 (s, 1H), 6.88 – 6.84 (m, 2H), 5.95 (m, 2H), 5.47 (d, $J = 14.6$ Hz, 1H), 4.39 (d, $J = 14.6$ Hz, 1H), 1.84 (s, 3H).

**$^{13}$C NMR (101 MHz, Chloroform-d)** $\delta = 170.5, 148.0, 147.7, 140.8, 133.9, 131.2, 130.0, 129.5, 128.6, 124.2, 115.4, 112.4, 111.2, 101.9, 50.2, 22.5.$

HRMS (ESI): Calculated for C$_{16}$H$_{14}$Br$_2$NO$_3$ ([M+H]$^+$): 425.9340; found 425.9339

IR (neat) : ν = 1648, 1575 cm$^{-1}$
**N-((6-Bromobenzo[d][1,3]dioxol-5-yl)methyl)-N-(2-chlorophenyl)acetamide 1.31b:**

Following general procedure for alkylation of amides, 2-chloroacetanilide (59.6 mmol, 10.1 g, 1 equiv) was reacted with NaH (177 mmol, 7.1 g, 3 equiv) and 5-bromo-6-(bromomethyl)benzo[d][1,3]dioxole (65.0 mmol, 19.1 g, 1.1 equiv). **1.31b** was obtained after purification as a brownish solid (22.1 g, 59.6 mmol, 100%).

**\(^1\)H NMR (400 MHz, Chloroform-d)** \(\delta = 7.50 - 7.45 (m, 1H), 7.30 - 7.24 (m, 1H), 7.20 - 7.15 (m, 1H), 6.99 (s, 1H), 6.92 - 6.85 (m, 1H), 6.86 (s, 1H), 5.98 - 5.90 (m, 2H), 5.43 (d, \(J = 14.6\) Hz, 1H), 4.44 (d, \(J = 14.6\) Hz, 1H), 1.84 (s, 3H).**

**\(^13\)C NMR (101 MHz, Chloroform-d)** \(\delta = 170.7, 148.0, 147.7, 139.4, 133.6, 131.1, 130.7, 129.8, 129.5, 128.0, 115.2, 112.4, 111.1, 101.9, 50.3, 22.3.**

**HRMS (ESI):** Calculated for C\(_{16}\)H\(_{13}\)BrClNaNO\(_3\) ([M+Na]\(^+\): 403.9665; found 403.9666

**IR (neat):** \(\nu = 1660\), 1555 cm\(^{-1}\)

**mp: 268-270°C**

**N-(2-Bromobenzyl)-N-(2-chlorophenyl)acetamide 1.44r:**

Following general procedure for alkylation of amides 2-chloroacetanilide (2 mmol, 340 mg, 1 equiv) was reacted with NaH (6 mmol, 240 mg, 3 equiv) and 2-bromobenzyle bromide (2.2
mmol, 550 mg, 1.1 equiv). 1.44r was obtained after purification as a yellowish oil (590 mg, 1.74 mmol, 87 %).

$^1$H NMR (400 MHz, Chloroform-d) $\delta =$ 7.48 – 7.40 (m, 3H), 7.28 – 7.20 (m, 2H), 7.16 – 7.05 (m, 2H), 6.91 -6.87 (m, 1H), 5.56 (d, $J = 14.7$ Hz, 1H), 4.50 (d, $J = 14.7$ Hz, 1H), 1.86 (s, 3H).

$^{13}$C NMR (101 MHz, Chloroform-d) $\delta =$ 170.6, 139.5, 136.3, 133.6, 132.8, 131.6, 131.0, 130.7, 129.8, 129.2, 127.9, 127.7, 124.6, 50.6, 22.3.

HRMS (ESI): Calculated for C$_{15}$H$_{14}$BrClNO ([(M+H)$^+$]): 337.9947; found 337.9942

IR (neat) : $\nu =$1640, 1558 cm$^{-1}$

N-(2-Bromo-4,5-dimethoxybenzyl)-N-(2-chlorophenyl)acetamide 1.45r:

Following general procedure for alkylation of amides, 2-chloroacetanilide (0.98 mmol, 166 mg, 1 equiv) was reacted with NaH (2.94 mmol, 118 mg, 3 equiv) and 1-bromo-2-(bromomethyl)-4,5-dimethoxybenzene (1.08 mmol, 334 mg, 1.1 equiv). 1.45r was obtained after purification as a brownish oil (345 mg, 0.87 mmol, 88 %).

$^1$H NMR (400 MHz, Chloroform-d) $\delta =$ 7.49 – 7.43 (m, 1H), 7.29 -7.22 (m, 1H), 7.17 – 7.11 (m, 1H), 6.99 (s, 1H), 6.86 – 6.81 (m, 2H), 5.43 (d, $J = 14.3$ Hz, 1H), 4.51 (d, $J = 14.3$ Hz, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 1.83 (s, 3H).

$^{13}$C NMR (101 MHz, Chloroform-d) $\delta =$ 170.6, 149.1, 148.6, 139.2, 133.7, 131.1, 130.6, 129.7, 128.4, 127.9, 115.0, 114.9, 114.2, 56.2, 56.2, 50.0, 22.4

HRMS (ESI): Calculated for C$_{17}$H$_{17}$BrClNO$_3$ ([M+Na]$^+$): 419.9978; found 419.997

IR (neat) : $\nu =$1630, 1548 cm$^{-1}$

N-(2-Bromo-5-fluorobenzyl)-N-(2-chlorophenyl)acetamide 1.46r:
Following general procedure for alkylation of amides, 2-chloroacetanilide (4.13 mmol, 700 mg, 1 equiv) was reacted with NaH (12.4 mmol, 496 mg, 3 equiv) and 1-bromo-2-(bromomethyl)-4-fluorobenzene (4.54 mmol, 1.2 g, 1.1 equiv). 1.46r was obtained after purification as a brownish solid (1.4 g, 3.9 mmol, 95 %).

$^1$H NMR (400 MHz, Chloroform-d) $\delta$ = 7.52 – 7.47 (m, 1H), 7.42 -7.39 (m, 1H), 7.30 -7.26 (m, 1H), 7.24 – 7.15 (m, 2H), 6.99 – 6.92 (m, 1H), 6.86 – 6.82 (m, 1H), 5.47 (d, $J$ = 15.0 Hz, 1H), 4.47 (d, $J$ = 15.1 Hz, 1H), 1.87 (s, 3H).

$^{13}$C NMR (101 MHz, Chloroform-d) $\delta$ = 170.8, 162.1 (d, $J$ = 247.2 Hz), 139.5, 138.5 (d, $J$ = 7.3 Hz), 133.9 (d, $J$ = 7.9 Hz), 133.5, 130.9, 130.8, 130.0, 128.1, 118.3 (d, $J$ = 3.3 Hz), 118.1 (d, $J$ = 23.2 Hz), 116.4 (d, $J$ = 22.4 Hz), 50.9 (d, $J$ = 1.3 Hz), 22.3.

$^{19}$F NMR (376 MHz, Chloroform-d) $\delta$ = -110.0.

HRMS (ESI): Calculated for C$_{15}$H$_{13}$BrClNO ([M+H]$^+$): 355.9853; found 355.9848

IR (neat) : $\nu$ =1630, 1458 cm$^{-1}$

N-(2-Chlorophenyl)-N-((2-chloropyridin-3-yl)methyl)acetamide 1.47r:

Following general procedure for alkylation of amides, 2-chloroacetanilide (2.95 mmol, 500 mg, 1 equiv) was reacted with NaH (8.85 mmol, 354 mg, 3 equiv) and 2-chloro-3-(chloromethyl)pyridine (3.25 mmol, 526 mg, 1.1 equiv). 1.47r was obtained after purification as a white solid (595 mg, 2.02 mmol, 68 %).
H NMR (400 MHz, Chloroform-d) δ = 8.29 – 8.21 (m, 1H), 7.88 – 7.81 (m, 1H), 7.50 – 7.43 (m, 1H), 7.31 – 7.27 (m, 1H), 7.23 – 7.15 (m, 2H), 7.03 – 6.97 (m, 1H), 5.37 (d, J = 15.0 Hz, 1H), 4.59 (d, J = 15.1 Hz, 1H), 1.86 (s, 3H).

13C NMR (101 MHz, Chloroform-d) δ = 171.0, 151.1, 148.8, 140.2, 139.6, 133.3, 131.4, 130.9, 130.6, 130.1, 128.2, 122.8, 48.6, 22.2.

HRMS (ESI): Calculated for C_{14}H_{13}Cl_{2}N_{2}O ([M+H]^+): 295.0405; found 295.0399

IR (neat): ν = 1640, 1498 cm⁻¹

mp: 226-228°C

N-(2-Bromobenzyl)-N-(2-chloro-4-cyanophenyl)acetamide 1.44r:

Following general procedure A for acylation of anilines, 4-amino-3-chlorobenzonitrile (392 mg, 2.57 mmol, 1 equiv), Et₃N (0.72 mL, 5.14 mmol, 2 equiv) and acetyl chloride (0.22 mL, 3.1 mmol, 1.2 equiv) were reacted in DCM. N-(2-chloro-4-cyanophenyl)acetamide was obtained after extraction and used directly for next step without further purification (500 mg, 2.57 mmol, 100%).

Following general procedure for alkylation of amides, N-(2-chloro-4-cyanophenyl)acetamide (2.57 mmol, 500 mg, 1 equiv) was reacted with NaH (7.71 mmol, 308 mg, 3 equiv) and 2-bromobenzyle bromide (2.83 mmol, 707 mg, 1.1 equiv). 1.44r was obtained after purification as a yellowish oil (280 mg, 0.77 mmol, 30%).

H NMR (250 MHz, Chloroform-d) δ = 7.80 – 7.75 (m, 1H), 7.43 (m, 3H), 7.29 – 7.20 (m, 1H), 7.16 – 7.07 (m, 1H), 7.03 – 6.97 (m, 1H), 5.57 (d, J = 14.6 Hz, 1H), 4.54 (d, J = 14.6 Hz, 1H), 1.85 (s, 3H).

13C NMR (101 MHz, Chloroform-d) δ = 169.5, 143.7, 135.6, 135.2, 134.1, 132.9, 132.1, 131.9, 131.6, 129.8, 128.0, 124.7, 116.7, 114.0, 50.2, 22.4.
HRMS (ESI): Calculated for C\textsubscript{16}H\textsubscript{13}BrClN\textsubscript{2}O ([M+H]\textsuperscript{+}): 362.9900; found 362.9894

IR (neat): \( \nu = 2220, 1640, 1557 \text{ cm}^{-1} \)

N-((6-Bromobenzo[d][1,3]dioxol-5-yl)methyl)-N-(2-chloro-4-fluorophenyl)acetamide

1.49r:

Following general procedure for alkylation of amides, N-(2-chloro-4-fluorophenyl)acetamide (2.13 mmol, 400 mg, 1 equiv) was reacted with NaH (6.39 mmol, 260 mg, 3 equiv) and 5-bromo-6-(bromomethyl)benzo[d][1,3]dioxole (2.34 mmol, 690 mg, 1.1 equiv). 1.49r was obtained after purification as a white solid (710 mg, 1.77 mmol, 83%).

\[^{1}H\text{ NMR (400 MHz, Chloroform-d) } \delta = 7.22\ (dd, J = 8.0, 2.7 \text{ Hz}, 1H), 6.97\ (s, 1H), 6.92\ – 6.82\ (m, 3H), 5.98\ – 5.93\ (m, 2H), 5.42\ (d, J = 14.5 \text{ Hz}, 1H), 4.40\ (d, J = 14.5 \text{ Hz}, 1H), 1.83\ (s, 3H).\]

\[^{13}C\text{ NMR (101 MHz, Chloroform-d) } \delta = 170.6, 162.0\ (d, J = 252.3 \text{ Hz}), 148.1, 147.7, 135.6\ (d, J = 3.9 \text{ Hz}), 134.7\ (d, J = 10.9 \text{ Hz}), 132.1\ (d, J = 9.2 \text{ Hz}), 129.3, 118.0\ (d, J = 25.6 \text{ Hz}), 115.3\ (d, J = 8.7 \text{ Hz}), 115.1, 112.5, 111.2, 102.0, 50.2, 22.3.\]

\[^{19}F\text{ NMR (376 MHz, Chloroform-d) } \delta = -114.3.\]

HRMS (ESI): Calculated for C\textsubscript{16}H\textsubscript{15}BrClNO\textsubscript{3} ([M+H]\textsuperscript{+}): 399.9751; found 399.9746

IR (neat): \( \nu = 1670, 1585 \text{ cm}^{-1} \)

mp: 248-250°C

N-(2-Bromobenzyl)-N-(2-chloropyridin-3-yl)acetamide 1.50r:
Following general procedure A for acylation of anilines, 2-chloropyridin-3-amine (330 mg, 2.57 mmol, 1 equiv), Et$_3$N (0.72 mL, 5.14 mmol, 2 equiv) and acetyl chloride (0.22 mL, 3.1 mmol, 1.2 equiv) were reacted in DCM. N-(2-chloropyridin-3-yl)acetamide was obtained after extraction and used directly for next step without further purification (438 mg, 2.57 mmol, 100%).

Following general procedure for alkylation of amides, N-(2-chloropyridin-3-yl)acetamide (2.57 mmol, 438 mg, 1 equiv) was reacted with NaH (7.71 mmol, 308 mg, 3 equiv) and 2-bromobenzyle bromide (2.83 mmol, 707 mg, 1.1 equiv). 1.50r was obtained after purification as a yellowish solid (270 mg, 0.80 mmol, 31%).

$^1$H NMR (400 MHz, Chloroform-d) $\delta = 8.39 - 8.33$ (m, 1H), 7.48 – 7.41 (m, 2H), 7.26 – 7.22 (m, 1H), 7.20 – 7.07 (m, 3H), 5.62 (d, $J = 14.5$ Hz, 1H), 4.50 (d, $J = 14.5$ Hz, 1H), 1.88 (s, 3H).

$^{13}$C NMR (101 MHz, Chloroform-d) $\delta =$ 170.0, 151.1, 149.4, 139.6, 136.1, 135.8, 133.0, 132.0, 129.7, 128.0, 124.7, 123.2, 50.1, 22.5.

HRMS (ESI): Calculated for C$_{14}$H$_{13}$BrClN$_2$O ([M+H]$^+$): 338.9900; found 338.9904

IR (neat) : ν =1660, 1602 cm$^{-1}$

mp: 222-225°C

N-((6-Bromobenzo[d][1,3]dioxol-5-yl)methyl)-N-(2-chloro-3,4,5-trimethoxyphenyl)acetamide 1.51r:

Chemical Formula: C$_{19}$H$_{19}$BrClNO$_6$

Exact Mass: 471.0084
Following general procedure for alkylation of amides, 1.51sa (1.16 mmol, 301 mg, 1 equiv) was reacted with NaH (3.48 mmol, 140 mg, 3 equiv) and 5-bromo-6-(bromomethyl)benzo[d][1,3]dioxole (1.22 mmol, 360 mg, 1.1 equiv). 1.51r was obtained after purification as a yellowish oil (507 mg, 1.16 mmol, 100%).

\[ \text{1H NMR (400 MHz, Chloroform-d)} \delta = 6.94 (s, 1H), 6.83 (s, 1H), 6.15 (s, 1H), 5.94 – 5.89 (m, 2H), 5.33 (d, \text{J} = 14.4 \text{ Hz, 1H}), 4.36 (d, \text{J} = 14.4 \text{ Hz, 1H}), 3.86 (s, 3H), 3.84 (s, 3H), 3.60 (s, 3H), 1.83 (s, 3H). \]

\[ \text{13C NMR (101 MHz, Chloroform-d)} \delta = 170.5, 152.1, 150.7, 147.9, 147.5, 143.5, 134.6, 129.5, 120.0, 115.4, 112.2, 111.2, 109.5, 101.9, 61.3, 61.3, 56.2, 50.2, 22.1. \]

\[ \text{HRMS (ESI): Calculated for C}_{19}\text{H}_{20}\text{BrClNO}_6 ([M+H]^+): 472.0163; found 472.0157} \]

\[ \text{IR (neat): } \nu = 1648, 1555 \text{ cm}^{-1} \]

Methyl 4-((N-((4-benzyloxy)-2-chloro-5-methylphenyl)acetamido)methyl)-3-bromobenzoate 1.52r:

\[ \text{Chemical Formula: C}_{25}\text{H}_{23}\text{BrClNO}_4 \\
\text{Exact Mass: 515.0499} \]

To methyl 3-bromo-4-methylbenzoate (26.2 mmol, 6 g, 1 equiv) in dry CCl₄ (198 mL) was added NBS (26.2 mmol, 4.68 g, 1 equiv) and the reaction mixture was irradiated with a 250-W lamp for 16 h with a cooling system to keep the temperature at 20 °C. The reaction mixture was quenched with aqueous NaHCO₃ (100 mL) and the crude was extracted with DCM (3 x 30 mL). The combined organic layers were further washed with 10 % NaOH, brine, dried over Na₂SO₄, filtered and evaporated under vacuum. The mixture is then used without further purification. \[ \text{1H NMR: Desired product (73 %) + dibromobenzyle (15 %) + starting material (12 %).} \]

Under argon, 1.52sa (11.2 mmol, 3.25 g, 1 equiv) was dissolved in 150 mL of dry THF. Then, LiHMDS (17.9 mmol, 3 g, 1.6 equiv) was carefully added at room temperature to the turning solution, which was stirred for 10 minutes. A solution of mixture of benzylbromide (4.5 g) in
dry THF (100 mL) was added and the reaction was heated at 65 °C for 3 h. The solution was cooled to room temperature, and quenched with water (100 mL). The aqueous phase was extracted with AcOEt (3 x 40 mL), dried over Na$_2$SO$_4$, filtered and evaporated. The crude was purified by chromatography on silicagel, using cyclohexane/AcOEt [8 :2] as eluent. The desired product was obtained as an orange oil (5.22 g, 10.2 mmol, 91 % yield).

$^1$H NMR (400 MHz, Chloroform-d) $\delta$ = 8.17 – 8.11 (m, 1H), 7.93 – 7.89 (m, 1H), 7.55 – 7.50 (m, 1H), 7.43 – 7.32 (m, 5H), 6.95 (s, 1H), 6.77 – 6.70 (m, 1H), 5.42 (d, $J$ = 15.1 Hz, 1H), 5.05 (s, 2H), 4.57 (d, $J$ = 15.1 Hz, 1H), 3.91 (s, 3H), 2.11 (s, 3H), 1.89 (s, 3H).

$^{13}$C NMR (101 MHz, Chloroform-d) $\delta$ = 171.6, 165.9, 157.3, 141.6, 136.4, 134.0, 132.1, 131.8, 131.1, 131.0, 130.9, 128.9, 128.7, 128.4, 127.6, 127.5, 124.3, 113.2, 70.7, 52.6, 51.4, 22.3, 16.2.

HRMS (ESI): Calculated for C$_{25}$H$_{24}$BrClNO$_4$ ([M+H]$^+$): 516.0577; found 516.0572

IR (neat): $\nu$=1735, 1640, 1485 cm$^{-1}$

N-((6-Bromobenzo[d][1,3]dioxol-5-yl)methyl)-N-(2-chlorophenyl)propionamide 1.53r:

Following general procedure for alkylation of amides N-(2-chlorophenyl)propionamide (1.5 mmol, 275 mg, 1 equiv) was reacted with NaH (4.5 mmol, 180 mg, 3 equiv) and 5-bromo-6 (bromomethyl)benzo[d][1,3]dioxole (1.65 mmol, 485 mg, 1.1 equiv). 1.53r was obtained after purification as a brownish solid (505 mg, 1.26 mmol, 85 %).

$^1$H NMR (400 MHz, Chloroform-d) $\delta$ = 7.51 – 7.44 (m, 1H), 7.29 – 7.24 (m, 1H), 7.20 – 7.15 (m, 1H), 7.00 (s, 1H), 6.91 – 6.84 (m, 1H), 6.86 (s, 1H), 5.98 – 5.89 (m, 2H), 5.46 (d, $J$ = 14.6 Hz, 1H), 4.43 (d, $J$ = 14.6 Hz, 1H), 2.03 – 1.97 (m, 2H), 1.09 (t, $J$ = 7.4 Hz, 3H).

$^{13}$C NMR (101 MHz, Chloroform-d) $\delta$ = 173.9, 147.9, 147.7, 139.1, 133.7, 131.3, 130.7, 129.8, 129.7, 127.9, 115.3, 112.4, 111.1, 101.9, 50.4, 27.5, 9.5.

HRMS (ESI): Calculated for C$_{17}$H$_{15}$BrClNO$_3$ ([M+H]$^+$): 396.0002; found 396.0005

IR (neat): $\nu$=1641, 1587 cm$^{-1}$
mp: 268-270°C

N-((6-Bromobenzo[d][1,3]dioxol-5-yl)methyl)-N-(2-chlorophenyl)-2-phenylacetamide 1.54r:

Under argon, amide 1.54sa (0.407 mmol, 100 mg, 1 equiv) was dissolved in 3 mL of dry THF. Then, LiHMDS (0.650 mmol, 106 mg, 1.6 equiv) was carefully added at room temperature to the turning solution, which was stirred for 10 minutes. A solution of 5-bromo-6-(bromomethyl)benzo[d][1,3]dioxole (0.448 mmol, 132 mg, 1.1 equiv) in dry THF (3 mL) was then added and the reaction was heated at 65 °C for 3 h. The solution was cooled to room temperature, and quenched with water (6 mL). The aqueous phase was extracted with AcOEt (3 x 3 mL), dried over Na$_2$SO$_4$, filtered and evaporated. The crude was purified by chromatography on silicagel, using cyclohexane/AcOEt [8:2] as eluent. The desired product was obtained as a yellowish solid (142 mg, 0.31 mmol, 76 % yield).

$^1$H NMR (250 MHz, Chloroform-d) $\delta =$ 7.53 – 7.45 (m, 1H), 7.33 – 7.26 (m, 1H), 7.25 – 7.19 (m, 3H), 7.17 – 7.11 (m, 1H), 7.07 – 7.02 (m, 2H), 6.97 (s, 1H), 6.85 (s, 1H), 6.80 – 6.72 (m, 1H), 5.97 – 5.91 (m, 2H), 5.45 (d, $J =$ 14.5 Hz, 1H), 4.45 (d, $J =$ 14.5 Hz, 1H), 3.45 (d, $J =$ 15.0 Hz, 1H), 3.33 (d, $J =$ 15.0 Hz, 1H).

$^{13}$C NMR (126 MHz, Chloroform-d) $\delta =$ 171.1, 148.0, 147.6, 138.7, 134.9, 133.8, 131.7, 130.7, 129.9, 129.5, 129.4, 128.5, 127.8, 126.9, 115.3, 112.4, 111.2, 101.9, 50.6, 41.3.

HRMS (ESI): Calculated for C$_{22}$H$_{18}$BrClNO$_3$ ([M+H]$^+$): 458.0159; found 458.0153

IR (neat) : v =1682, 1587 cm$^{-1}$

mp: 277-280°C

N-((6-Bromobenzo[d][1,3]dioxol-5-yl)methyl)-N-(2-chlorophenyl)isobutyramide 1.55r:
Following general procedure for alkylation of amides, 2-chloroacetanilide (2.02 mmol, 400 mg, 1 equiv) was reacted with NaH (6.06 mmol, 242 mg, 3 equiv) and 5-bromo-6-(bromomethyl)benzo[d][1,3]dioxole (2.22 mmol, 650 mg, 1.1 equiv). 1.55r was obtained after purification as a brownish oil (525 mg, 1.40 mmol, 69 %).

^1H NMR (400 MHz, Chloroform-d) δ = 7.53 – 7.46 (m, 1H), 7.30 – 7.22 (m, 1H), 7.20 – 7.11 (m, 1H), 6.95 (s, 1H), 6.91 – 6.86 (m, 2H), 5.99 – 5.92 (m, 2H), 5.49 (d, J = 14.6 Hz, 1H), 4.38 (d, J = 14.6 Hz, 1H), 2.27 (sept, J = 6.7 Hz, 1H), 1.10 (d, J = 6.6 Hz, 3H), 1.04 (d, J = 6.8 Hz, 3H).

^13C NMR (101 MHz, Chloroform-d) δ = 177.6, 147.9, 147.7, 139.1, 133.8, 131.1, 130.7, 129.8, 129.7, 127.8, 115.3, 112.5, 111.0, 101.9, 50.3, 31.9, 20.2, 19.4.

HRMS (ESI): Calculated for C_{18}H_{18}BrClNO_3 ([M+H]^+): 410.0159; found 410.0153

IR (neat): ν = 1647, 1565 cm^{-1}

Double C(sp^2)-H/C(sp^3)-H arylation:

6H-[1,3]Dioxolo[4,5-k]pyrrolo[3,2,1-de]phenanthridin-8(9H)-one 1.34:

In a 10 mL srew-cap vial, previously charged with 1.34r (0.15 mmol, 64 mg, 1 equiv) and stirring bar, was weighted in a glovebox K_2CO_3 (83 mg, 0.60 mmol, 4 equiv), potassium pivalate (6.3 mg, 0.045 mmol, 0.3 equiv) and Pd(PCy_3)_2 (10 mg, 0.015 mmol, 0.1 equiv). The vial was removed from the glovebox and mesitylene (3 mL) was added. The sealed vial was stirred in a pre-heated heating block at 140 °C for 16 h. Then, the mixture was cooled to room temperature
and directly charged on silica for chromatography. The mesitylene was flushed using cyclohexane and the mixture was purified using cyclohexane /AcOEt to afford 1.34 as a yellowish solid. (0.09 mmol, 24 mg, 60 %).

$^1$H NMR (400 MHz, Chloroform-d) $\delta = 7.93 – 7.89$ (m, 1H), $7.15 – 7.11$ (m, 1H), $7.06 – 7.00$ (m, 2H), $6.72$ (d, $J = 8.0$ Hz, 1H), $6.68 – 6.63$ (m, 1H), $6.10$ (s, 2H), $4.94$ (d, $J = 1.1$ Hz, 2H), $3.55 – 3.52$ (m, 2H) + Cyclohexane.

$^{13}$C NMR (101 MHz, Chloroform-d) $\delta = 174.8, 147.5, 144.8, 140.0, 124.9, 124.1, 123.0, 122.7, 122.6, 120.6, 114.9, 113.1, 108.0, 101.6, 42.9, 36.5.$

7H-[1,3]Dioxolo[4,5-j]pyrrolo[3,2,1-de]phenanthridin-5(4H)-one 1.29:

In a 10 mL screw-cap vial, previously charged with 1.31a (0.15 mmol, 64 mg, 1 equiv) and stirring bar, was weighted in a glovebox K$_2$CO$_3$ (83 mg, 0.60 mmol, 4 equiv), potassium pivalate (6.3 mg, 0.045 mmol, 0.3 equiv) and Pd(PCy$_3$)$_2$ (10 mg, 0.015 mmol, 0.1 equiv). The vial was removed from the glovebox and mesitylene (3 mL) was added. The sealed vial was stirred in a pre-heated heating block at 140 °C for 16 h. Then, the mixture was cooled to room temperature, filtered through celite, and evaporated under vacuum. $^1$H NMR of the crude, using C$_2$HCl$_3$ (13.6 uL, 0.15 mmol, 1 equiv) as internal standard shows the presence of the desired product 1.29 (22 %) and numerous side products.

In a 10 mL screw-cap vial, previously charged with 1.31b (0.15 mmol, 57 mg, 1 equiv) and stirring bar, was weighted in a glovebox K$_2$CO$_3$ (83 mg, 0.60 mmol, 4 equiv), potassium pivalate (6.3 mg, 0.045 mmol, 0.3 equiv) and Pd(PCy$_3$)$_2$ (10 mg, 0.015 mmol, 0.1 equiv). The vial was
removed from the glovebox and mesitylene (3 mL) was added. The sealed vial was stirred in a pre-heated heating block at 140 °C for 16 h. Then, the mixture was cooled to room temperature and directly charged on silica for chromatography on gel. The mesitylene was flushed using cyclohexane and the mixture was purified using cyclohexane /AcOEt to afford 1.29 as a yellowish solid. (0.057 mmol, 15 mg, 37 %).

$^1$H NMR (400 MHz, Chloroform-d) $\delta$ = 7.40 (dd, $J = 7.9$, 1.0 Hz, 1H), 7.20 (s, 1H), 7.07 (dd, $J = 7.4$, 1.0 Hz, 1H), 6.98 (t, $J = 7.6$ Hz, 1H), 6.61 (s, 1H), 6.00 (s, 2H), 4.95 (s, 2H), 3.52 (s, 2H).

$^{13}$C NMR (101 MHz, Chloroform-d) $\delta$ = 174.7, 148.1, 148.0, 139.7, 123.5, 123.2, 122.9, 122.9, 122.8, 120.0, 117.2, 107.7, 102.8, 101.7, 43.5, 36.50.

Optimization of the reaction - selected conditions:

<table>
<thead>
<tr>
<th>Pd source</th>
<th>Ligand</th>
<th>Additive (30 mol %)</th>
<th>Base</th>
<th>Solvent (0.05 M)</th>
<th>Temperature (°C)</th>
<th>NMR yield (isolated)</th>
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<tbody>
<tr>
<td>Pd(PCy$_3$)$_2$ (10 mol%)</td>
<td>-</td>
<td>PivOK</td>
<td>K$_2$CO$_3$ (4 equiv)</td>
<td>Mesitylene</td>
<td>140</td>
<td>37 %</td>
</tr>
<tr>
<td>Pd(PCy$_3$)$_2$ (10 mol%)</td>
<td>-</td>
<td>PivOK</td>
<td>K$_2$CO$_3$ (2 equiv)</td>
<td>Mesitylene</td>
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<td>45 %</td>
</tr>
<tr>
<td>Pd(PCy$_3$)$_2$ (10 mol%)</td>
<td>-</td>
<td>PivOK</td>
<td>K$_2$CO$_3$ (2 equiv)</td>
<td>Mesitylene</td>
<td>120</td>
<td>28 %</td>
</tr>
<tr>
<td>Pd(PCy$_3$)$_2$ (10 mol%)</td>
<td>-</td>
<td>-</td>
<td>K$_2$CO$_3$ (2 equiv)</td>
<td>DMF</td>
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<tr>
<td>Pd(PCy$_3$)$_2$ (10 mol%)</td>
<td>-</td>
<td>PivOK</td>
<td>Cs$_2$CO$_3$ (2 equiv)</td>
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<td>75 %</td>
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<tr>
<td>Pd(PCy$_3$)$_2$ (10 mol%)</td>
<td>-</td>
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<td>Cs$_2$CO$_3$ (2 equiv)</td>
<td>Mesitylene</td>
<td>140</td>
<td>90 % (92 %)</td>
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<tr>
<td>Pd(PCy$_3$)$_2$ (5 mol%)</td>
<td>-</td>
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<td>Cs$_2$CO$_3$ (2 equiv)</td>
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<td>70 %</td>
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<td>Pd(OAc)$_2$ (10 mol%)</td>
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<td>Mesitylene</td>
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<td>53 %</td>
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<td>Pd$_2$(dba)$_3$ (5 mol%)</td>
<td>PCy$_3$ (10 mol%)</td>
<td>PivOH</td>
<td>Cs$_2$CO$_3$ (2 equiv)</td>
<td>Mesitylene</td>
<td>140</td>
<td>50 %</td>
</tr>
</tbody>
</table>

[a] Performed with 0.1 mmol of substrate. $^1$HNMR yield performed using trichloroethylene as internal standard.
1-(4-Chloro-[1,3]dioxolo[4,5-j]phenanthridin-5(6H)-yl)ethan-1-one 1.39:

Following general procedure, 1.31b (57 mg, 0.15 mmol, 1 equiv) was reacted with Cs$_2$CO$_3$ (98 mg, 0.30 mmol, 2 equiv), pivalic acid (4.6 mg, 0.045 mmol, 0.3 equiv) and Pd(PCy$_3$)$_2$ (10 mg, 0.015 mmol, 0.1 equiv) in mesitylene (3 mL) at 140°C for 15 min. The mixture was purified by chromatography on silicagel using cyclohexane/AcOEt as solvent to afford 1.39 as a yellowish oil (31 mg, 0.103 mmol, 68 %)

$^1$H NMR (400 MHz, Chloroform-d) $\delta =$ 7.53 (dd, $J$ = 7.8, 1.5 Hz, 1H), 7.35 (dd, $J$ = 8.1, 1.4 Hz, 1H), 7.29 – 7.24 (m, 1H), 7.21 (s, 1H), 6.79 (s, 1H), 5.98 (s, 2H), 5.65 (d, $J$ = 15.0 Hz, 1H), 3.86 (d, $J$ = 15.0 Hz, 1H), 2.00 (s, 3H).

$^{13}$C NMR (101 MHz, Chloroform-d) $\delta =$ 171.4, 148.1, 147.9, 135.5, 133.2, 131.2, 130.5, 128.7, 127.7, 125.4, 122.7, 107.0, 104.4, 101.5, 45.8, 21.8.

HRMS (ESI): Calculated for C$_{16}$H$_{12}$ClNO$_3$ ([M+H]$^+$): 302.0584; found 302.0578

IR (neat) : $\nu =$1698, 1640, 1555 cm$^{-1}$

7H-Pyrrolo[3,2,1-de]phenanthridin-5(4H)-one 1.44:

Following general procedure, 1.44r (0.15 mmol, 51 mg, 1 equiv) was reacted with Cs$_2$CO$_3$ (98 mg, 0.30 mmol, 2 equiv), pivalic acid (4.6 mg, 0.045 mmol, 0.3 equiv) and Pd(PCy$_3$)$_2$ (10 mg, 0.015 mmol, 0.1 equiv) in mesitylene (3 mL) at 140°C for 16 h. The mixture was purified by
chromatography on silicagel using cyclohexane/AcOEt as solvent to afford 1.44 as a yellowish solid (0.15 mmol, 33 mg, 100%).

\[ ^1H \text{ NMR (400 MHz, Chloroform-d)} \delta = 7.77 – 7.71 (m, 1H), 7.59 – 7.54 (m, 1H), 7.34 – 7.29 (m, 1H), 7.28 – 7.23 (m, 1H), 7.18 – 7.10 (m, 1H), 7.12 – 7.08 (m, 1H), 7.05 - 6.97 (m, 1H), 5.01 (s, 2H), 3.50 (d, J = 1.2 Hz, 2H). \]

\[ ^13C \text{ NMR (101 MHz, Chloroform-d)} \delta = 174.7, 140.3, 129.0, 128.8, 128.4, 128.1, 127.8, 124.2, 123.5, 122.8, 122.5, 120.5, 117.0, 43.3, 36.3. \]

HRMS (ESI): Calculated for C\(_{15}\)H\(_{12}\)NO ([M+H]+): 222.0919; found 222.0913

IR (neat): ν =1693, 1630, 1560 cm\(^{-1}\)

mp: 206-208°C

7H-[1,3]Dioxolo[4,5-j]pyrrolo[3,2,1-de]phenanthridin-5(4H)-one 1.29:

Following general procedure, 1.31b (0.15 mmol, 57 mg, 1 equiv) was reacted with Cs\(_2\)CO\(_3\) (98 mg, 0.30 mmol, 2 equiv), pivalic acid (4.6 mg, 0.045 mmol, 0.3 equiv) and Pd(PCy\(_3\))\(_2\) (10 mg, 0.015 mmol, 0.1 equiv) in mesitylene (3 mL) at 140°C for 16 h. The mixture was purified by chromatography on silicagel using cyclohexane/AcOEt as solvent to afford 1.29 as a brownish solid (0.139 mmol, 37 mg, 92 %).

\[ ^1H \text{ NMR (400 MHz, Chloroform-d)} \delta = 7.40 (dd, J = 7.9, 1.0 Hz, 1H), 7.20 (s, 1H), 7.07 (dd, J = 7.4, 1.0 Hz, 1H), 6.98 (t, J = 7.6 Hz, 1H), 6.61 (s, 1H), 6.00 (s, 2H), 4.95 (s, 2H), 3.52 (s, 2H). \]

\[ ^13C \text{ NMR (101 MHz, Chloroform-d)} \delta = 174.7, 148.1, 148.0, 139.7, 123.5, 123.2, 122.9, 122.8, 120.0, 117.2, 107.7, 102.8, 101.7, 43.5, 36.50. \]

9,10-Dimethoxy-7H-pyrrolo[3,2,1-de]phenanthridin-5(4H)-one 5e:
Following general procedure, \textbf{1.31b} (0.15 mmol, 60 mg, 1 equiv) was reacted with Cs$_2$CO$_3$ (98 mg, 0.30 mmol, 2 equiv), pivalic acid (4.6 mg, 0.045 mmol, 0.3 equiv) and Pd(PCy$_3$)$_2$ (10 mg, 0.015 mmol, 0.1 equiv) in mesitylene (3 mL) at 140°C for 16 h. The mixture was purified by chromatography on silicagel using cyclohexane/AcOEt as solvent to afford \textbf{1.29} as a yellowish solid (0.130 mmol, 37 mg, 89 %).

$^1$H NMR (400 MHz, Chloroform-d) $\delta =$ 7.48 (dd, $J = 7.9$, 1.0 Hz, 1H), 7.23 (s, 1H), 7.11 – 7.06 (m, 1H), 7.01 (t, $J = 7.6$ Hz, 1H), 6.63 (s, 1H), 5.00 (s, 2H), 3.97 (s, 3H), 3.91 (s, 3H), 3.57 – 3.51 (m, 2H).

$^{13}$C NMR (126 MHz, Chloroform-d) $\delta =$ 174.7, 149.4, 148.8, 139.6, 123.2, 123.1, 122.6, 121.4, 121.3, 119.6, 117.2, 110.2, 105.3, 56.1, 56.1, 43.0, 36.3.

\textit{9-Fluoro-7H-pyrrolo[3,2,1-de]phenanthridin-5(4H)-one 1.46:}

Following general procedure, \textbf{1.46r} (54 mg, 0.15 mmol, 1 equiv) was reacted with Cs$_2$CO$_3$ (98 mg, 0.30 mmol, 2 equiv), pivalic acid (4.6 mg, 0.045 mmol, 0.3 equiv) and Pd(PCy$_3$)$_2$ (10 mg, 0.015 mmol, 0.1 equiv) in mesitylene (3 mL) at 140°C for 16 h. The mixture was purified by chromatography on silicagel using cyclohexane/AcOEt as solvent to afford \textbf{1.46} as a grey solid (36 mg, 0.15 mmol, 100 %)

$^1$H NMR (400 MHz, Chloroform-d) $\delta =$ 7.73 – 7.69 (m, 1H), 7.52 – 7.48 (m, 1H), 7.14 – 7.08 (m, 1H), 7.02 – 6.98 (m, 2H), 6.88 – 6.82 (m, 1H), 4.98 (s, 2H), 3.50 (s, 2H).
$^{13}$C NMR (101 MHz, Chloroform-d) $\delta = 174.6, 162.7$ (d, $J = 250.3$ Hz), $139.8, 131.3$ (d, $J = 8.3$ Hz), $125.1$ (d, $J = 3$ Hz), $124.4$ (d, $J = 8.5$ Hz), $124.1, 123.5, 122.9, 120.3, 116.2, 115.3$ (d, $J = 22.1$ Hz), $114.7$ (d, $J = 22.6$ Hz), $43.2$ (d, $J = 2.1$ Hz), 36.4.

$^{19}$F NMR (376 MHz, Chloroform-d) $\delta = -113.0$.

HRMS (ESI): Calculated for C$_{15}$H$_{11}$FNO ([M+H]$^+$): 240.0825; found 240.0819

IR (neat) : $\nu = 1685, 1622, 1545, 1105$ cm$^{-1}$

mp: 225-227°C

7H-Indolo[1,7-g][1,6]naphthyridin-5(4H)-one 1.47:

Following general procedure, 1.47 (51 mg, 0.15 mmol, 1 equiv) was reacted with Cs$_2$CO$_3$ (98 mg, 0.30 mmol, 2 equiv), pivalic acid (4.6 mg, 0.045 mmol, 0.3 equiv) and Pd(PCy$_3$)$_2$ (10 mg, 0.015 mmol, 0.1 equiv) in mesitylene (3 mL) at 140°C for 16 h. The mixture was purified by chromatography on silicagel using cyclohexane/AcOEt as solvent to afford 1.47 as a white solid (32 mg, 0.144 mmol, 96 %).

$^1$H NMR (400 MHz, Chloroform-d) $\delta = 8.55 – 8.52$ (m, 1H), $8.03 – 7.98$ (m, 1H), $7.47 – 7.44$ (m, 1H), $7.24 – 7.16$ (m, 1H), $7.20 – 7.13$ (m, 1H), $7.10 – 7.01$ (m, 1H), $5.10$ (s, 2H), $3.55$ (s, 2H).

$^{13}$C NMR (101 MHz, Chloroform-d) $\delta = 174.5, 149.2, 148.0, 142.3, 135.2, 125.9, 124.7, 123.1, 123.0, 122.8, 122.4, 117.7, 43.1, 36.3$.

HRMS (ESI): Calculated for C$_{14}$H$_{10}$N$_2$O ([M+H]$^+$): 223.0871; found 223.0866

IR (neat) : $\nu = 1697, 1638, 1565$ cm$^{-1}$

mp: 214-217°C

5-Oxo-4,5-dihydro-7H-pyrrolo[3,2,1-de]phenanthridine-2-carbonitrile 1.48:
Following general procedure, 1.48r (55 mg, 0.15 mmol, 1 equiv) was reacted with Cs₂CO₃ (98 mg, 0.30 mmol, 2 equiv), pivalic acid (4.6 mg, 0.045 mmol, 0.3 equiv) and Pd(PCy₃)₂ (10 mg, 0.015 mmol, 0.1 equiv) in mesitylene (3 mL) at 140°C for 16 h. The mixture was purified by chromatography on silica gel using cyclohexane/AcOEt as solvent to afford 1.48 as a white solid (32 mg, 0.13 mmol, 86 %).

¹H NMR (400 MHz, Chloroform-d) δ = 7.89 (d, J = 1.2 Hz, 1H), 7.79 – 7.71 (m, 1H), 7.41 – 7.32 (m, 3H), 7.23 – 7.19 (m, 1H), 5.08 (s, 2H), 3.59 (s, 2H).

¹³C NMR (101 MHz, Chloroform-d) δ = 174.3, 144.2, 129.9, 128.9, 128.8, 128.2, 127.6, 126.9, 125.8, 124.3, 123.0, 119.7, 118.0, 106.1, 43.4, 35.9.

HRMS (ESI): Calculated for C₁₆H₁₁N₂O ([M+H]⁺): 247.0871; found 247.0866

IR (neat) : ν = 2247, 1694, 1627, 1589 cm⁻¹

mp: 235-237°C

2-Fluoro-7H-[1,3]dioxolo[4,5-i]pyrrolo[3,2,1-de]phenanthridin-5(4H)-one 1.49:

Following general procedure, 1.49r (60 mg, 0.15 mmol, 1 equiv) was reacted with Cs₂CO₃ (98 mg, 0.30 mmol, 2 equiv), pivalic acid (4.6 mg, 0.045 mmol, 0.3 equiv) and Pd(PCy₃)₂ (10 mg, 0.015 mmol, 0.1 equiv) in mesitylene (3 mL) at 140°C for 16 h. The mixture was purified by
chromatography on silicagel using cyclohexane/AcOEt as solvent to afford \textbf{1.49} as a yellow oil (23 mg, 0.081 mmol, 54 %).

\textbf{1H NMR (500 MHz, DMSO-d6)} $\delta = 7.56 - 7.52$ (m, 2H), 6.99 - 6.96 (m, 1H), 6.89 (s, 1H), 6.06 (s, 2H), 4.84 (s, 2H), 3.54 (s, 2H).

\textbf{13C NMR (126 MHz, DMSO-d6)} $\delta = 173.6, 159.2$ (d, $J = 237.2$ Hz), 147.9, 147.5 135.5, 124.7 (d, $J = 9.5$ Hz), 123.6, 121.5 (d, $J = 2.1$ Hz), 117.3 (d, $J = 9.1$ Hz), 110.9 (d, $J = 26.6$ Hz), 107.8, 106.8 (d, $J = 25.3$), 103.3, 101.6, 42.8, 35.9.

\textbf{19F NMR (376 MHz, Chloroform-d)} $\delta = -111.4$.

\textbf{HRMS (ESI)}: Calculated for C$_{16}$H$_{11}$FNO$_3$ ([M+H]$^+$): 284.0723; found 284.0718

\textbf{IR} (neat) : $\nu = 1697, 1638, 1565, 1221$ cm$^{-1}$

\textbf{7H-Benzof[c]pyrrolo[3,2,1-ij][1,7]naphthyridin-5(4H)-one 1.50}:

\begin{center}
\includegraphics[width=0.2\textwidth]{image.png}
\end{center}

Chemical Formula: C$_{14}$H$_{10}$N$_2$O
Exact Mass: 222.0793

Following general procedure, \textbf{1.50r} (51 mg, 0.15 mmol, 1 equiv) was reacted with Cs$_2$CO$_3$ (98 mg, 0.30 mmol, 2 equiv), pivalic acid (4.6 mg, 0.045 mmol, 0.3 equiv) and Pd(PCy)$_3$$_2$ (10 mg, 0.015 mmol, 0.1 equiv) in mesitylene (3 mL) at 140°C for 16 h. The mixture was purified by chromatography on silicagel using cyclohexane/AcOEt as solvent to afford \textbf{1.50} as a yellowish oil (9 mg, 0.04 mmol, 27 %)

\textbf{1H NMR (400 MHz, Chloroform-d)} $\delta = 8.20$ (d, $J = 5.5$ Hz, 1H), 7.82 – 7.77 (m, 1H), 7.42 – 7.35 (m, 3H), 7.25 – 7.19 (m, 1H), 5.13 (s, 2H), 3.67 (s, 2H).

\textbf{13C NMR (101 MHz, Chloroform-d)} $\delta = 172.5, 146.3, 144.0, 130.4, 130.1, 128.4, 128.1, 126.5, 125.6, 123.6, 122.7, 114.5, 43.0, 38.0.$

\textbf{HRMS (ESI)}: Calculated for C$_{14}$H$_{10}$N$_2$O ([M+H]$^+$): 223.0871; found 223.0866

\textbf{IR} (neat) : $\nu = 1691, 1671, 1545$ cm$^{-1}$

\textbf{1,2,3-Trimethoxy-7H-[1,3]dioxolo[4,5-j]pyrrolo[3,2,1-de]phenanthridin-5(4H)-one 1.51}:
Following general procedure, 1.51r (71 mg, 0.15 mmol, 1 equiv) was reacted with Cs$_2$CO$_3$ (98 mg, 0.30 mmol, 2 equiv), pivalic acid (4.6 mg, 0.045 mmol, 0.3 equiv) and Pd(PCy$_3$)$_2$ (10 mg, 0.015 mmol, 0.1 equiv) in mesitylene (3 mL) at 140°C for 16 h. The mixture was purified by chromatography on silicagel using cyclohexane/AcOEt as solvent to afford 1.51 as a brownish solid (43 mg, 0.121 mmol, 81 %).

$^1$H NMR (400 MHz, Chloroform-d) $\delta =$ 8.05 (s, 1H), 6.60 (s, 1H), 5.98 (s, 2H), 4.85 (s, 2H), 3.99 (s, 3H), 3.92 (s, 3H), 3.85 (s, 3H), 3.58 (s, 2H).

$^{13}$C NMR (101 MHz, Chloroform-d) $\delta =$ 174.3, 151.8, 149.7, 147.8, 147.1, 141.6, 136.6, 122.4, 122.4, 107.4, 107.4, 106.6, 106.5, 101.5, 61.5, 60.8, 59.8, 43.5, 35.2.

HRMS (ESI): Calculated for C$_{19}$H$_{18}$NO$_6$ ([M+H]+): 356.1134; found 356.1129

IR (neat) : $\nu =$1696, 1627, 1521, 1495, 1482, 1359, 1223 cm$^{-1}$

mp: 266-269°C

Methyl 2-(benzyloxy)-1-methyl-5-oxo-4,5-dihydro-7H-pyrrolo[3,2,1-de]phenanthridine-10-carboxylate 1.52:
Following general procedure, **1.52r** (78 mg, 0.15 mmol, 1 equiv) was reacted with Cs$_2$CO$_3$ (98 mg, 0.30 mmol, 2 equiv), pivalic acid (4.6 mg, 0.045 mmol, 0.3 equiv) and Pd(PCy)$_3$$_2$ (10 mg, 0.015 mmol, 0.1 equiv) in mesitylene (3 mL) at 140°C for 16 h. The mixture was purified by chromatography on silicagel using cyclohexane/AcOEt as solvent to afford **1.52** as a yellowish solid (33 mg, 0.083 mmol, 55 %).

**$^1$H NMR (400 MHz, Chloroform-d) $\delta$ =** 8.75 – 8.67 (m, 1H), 7.96 – 7.89 (m, 1H), 7.48 – 7.31 (m, 5H), 7.33 – 7.26 (m, 1H), 6.89 (s, 1H), 5.06 (s, 2H), 4.96 (s, 2H), 3.95 (s, 3H), 3.52 (s, 2H), 2.72 (s, 3H).

**$^{13}$C NMR (101 MHz, Chloroform-d) $\delta$ =** 175.0, 166.8, 154.1, 137.4, 135.9, 135.8, 131.5, 129.8, 128.8, 128.7, 128.2, 128.1, 127.4, 124.2, 121.0, 117.7, 111.5, 72.3, 52.5, 43.9, 36.7, 15.4.

**HRMS (ESI):** Calculated for C$_{25}$H$_{21}$NaNO$_4$ ([M+Na$^+$]+): 422.1368; found 422.1360

**IR (neat) :** $\nu$ = 1740, 1688, 1637 cm$^{-1}$

**mp:** 254-256°C

4-Methyl-7H-[1,3]dioxolo[4,5-j]pyrrolo[3,2,1-de]phenanthridin-5(4H)-one **1.53**:

![Chemical Structure](image)

**Chemical Formula:** C$_{17}$H$_{19}$NO$_3$

**Exact Mass:** 279.0895

Following general procedure, **1.53r** (60 mg, 0.15 mmol, 1 equiv) was reacted with Cs$_2$CO$_3$ (98 mg, 0.30 mmol, 2 equiv), pivalic acid (4.6 mg, 0.045 mmol, 0.3 equiv) and Pd(PCy)$_3$$_2$ (10 mg, 0.015 mmol, 0.1 equiv) in mesitylene (3 mL) at 140°C for 16 h. The mixture was purified by chromatography on silicagel using cyclohexane/AcOEt as solvent to afford **1.53** as a yellowish oil (31 mg, 0.11 mmol, 74 %).

**$^1$H NMR (400 MHz, Chloroform-d) $\delta$ =** 7.45 – 7.38 (m, 1H), 7.21 (s, 1H), 7.09 – 7.05 (m, 1H), 7.05 – 6.97 (m, 1H), 6.65 – 6.58 (m, 1H), 6.00 (s, 2H), 5.04 – 4.90 (m, 2H), 3.47 (q, $J$ = 7.5 Hz, 1H), 1.50 (d, $J$ = 7.7 Hz, 3H).

**$^{13}$C NMR (101 MHz, Chloroform-d) $\delta$ =** 178.3, 148.1, 148.0, 138.4, 129.2, 123.1, 123.0, 122.8, 122.7, 120.0, 117.2, 107.8, 102.8, 101.7, 43.5, 41.7, 15.2.
HRMS (ESI): Calculated for C\textsubscript{17}H\textsubscript{14}NO\textsubscript{3} ([M+H]	extsuperscript{+}): 280.0974; found 280.0971

IR (neat): \(\nu = 1699, 1642, 1513, 1472\) cm\textsuperscript{-1}

**4-Phenyl-7H-[1,3]dioxolo[4,5-j]pyrrolo[3,2,1-de]phenanthridin-5(4H)-one 1.54:**

![Chemical structure of 4-Phenyl-7H-[1,3]dioxolo[4,5-j]pyrrolo[3,2,1-de]phenanthridin-5(4H)-one 1.54](image)

Chemical Formula: C\textsubscript{22}H\textsubscript{16}NO\textsubscript{3}
Exact Mass: 341.1052

Following general procedure, 1.54r (69 mg, 0.15 mmol, 1 equiv) was reacted with Cs\textsubscript{2}CO\textsubscript{3} (98 mg, 0.30 mmol, 2 equiv), pivalic acid (4.6 mg, 0.045 mmol, 0.3 equiv) and Pd(PCy\textsubscript{3})\textsubscript{2} (10 mg, 0.015 mmol, 0.1 equiv) in mesitylene (3 mL) at 140°C for 16 h. The mixture was purified by chromatography on silicagel using cyclohexane/ACOEt as solvent to afford 1.54 as a white solid (17 mg, 0.048 mmol, 32 %).

\textsuperscript{1}H NMR (400 MHz, Chloroform-d) \(\delta = 7.49 – 7.45\) (m, 1H), 7.37 – 7.29 (m, 4H), 7.28 – 7.25 (m, 2H), 7.25 (s, 1H), 7.04 – 7.00 (m, 2H), 6.64 (s, 1H), 6.01 (s, 2H), 5.06 – 4.91 (m, 2H), 4.64 (s, 1H).

\textsuperscript{13}C NMR (101 MHz, Chloroform-d) \(\delta = 175.6, 148.2, 148.1, 138.9, 136.2, 129.1, 128.6, 127.8, 127.4, 124.1, 123.2, 123.0, 120.5, 117.4, 107.8, 102.8, 101.7, 53.0, 43.7.

HRMS (ESI): Calculated for C\textsubscript{22}H\textsubscript{16}NO\textsubscript{3} ([M+H]	extsuperscript{+}): 342.1130; found 342.1128

IR (neat): \(\nu = 1689, 1632, 1517, 1471\) cm\textsuperscript{-1}

mp: 252-254°C

**4,4-Dimethyl-7H-[1,3]dioxolo[4,5-j]pyrrolo[3,2,1-de]phenanthridin-5(4H)-one 1.55:**

![Chemical structure of 4,4-Dimethyl-7H-[1,3]dioxolo[4,5-j]pyrrolo[3,2,1-de]phenanthridin-5(4H)-one 1.55](image)

Chemical Formula: C\textsubscript{18}H\textsubscript{16}NO\textsubscript{3}
Exact Mass: 293.1052

174
Following general procedure, **1.55r** (62 mg, 0.15 mmol, 1 equiv) was reacted with Cs$_2$CO$_3$ (98 mg, 0.30 mmol, 2 equiv), pivalic acid (4.6 mg, 0.045 mmol, 0.3 equiv) and Pd(PCy$_3$)$_2$ (10 mg, 0.015 mmol, 0.1 equiv) in mesitylene (3 mL) at 140°C for 16 h. The mixture was purified by chromatography on silicagel using cyclohexane/AcOEt as solvent to afford **1.55** as a white solid (39 mg, 0.133 mmol, 88 %).

$^1$H NMR (400 MHz, Chloroform-d) $\delta =$ 7.44 – 7.38 (m, 1H), 7.22 (s, 1H), 7.06 – 6.97 (m, 2H), 6.67 – 6.60 (m, 1H), 6.00 (s, 2H), 4.98 (s, 2H), 1.40 (s, 6H).

$^{13}$C NMR (101 MHz, Chloroform-d) $\delta =$ 181.0, 148.0, 148.0, 137.0, 134.3, 123.2, 123.1, 123.0, 121.4, 119.8, 117.2, 107.8, 102.8, 101.6, 45.6, 43.5, 24.2.

HRMS (ESI): Calculated for C$_{18}$H$_{16}$NO$_3$ ([M+H]$^+$): 294.1130; found 294.1121

IR (neat) : $\nu =$ 1695, 1635, 1537, 1475 cm$^{-1}$

mp: 238-240°C

**Synthesis of (±)-(γ)-lycorane and analogues**

**7H-[1,3]Dioxolo[4,5-j]pyrrolo[3,2,1-de]phenanthridin-5(4H)-one 1.29 (gram-scale reaction):**

In a 250 mL Schlenck tube equipped with stirring bar and charged with substrate **1.31b** (6.5 mmol, 2.49 g, 1 equiv) was weighted in a glovebox Cs$_2$CO$_3$ (4.24 g, 13 mmol, 2 equiv), pivalic acid (200 mg, 1.95 mmol, 0.3 equiv) and Pd(PCy$_3$)$_2$ (434 mg, 0.65 mmol, 0.1 equiv). The Schlenk was removed from glovebox and mesitylene (130 mL) was added. The mixture was then stirred in a previously heated oil bath at 140 °C for 16 h. The mixture was cooled to room temperature, and directly charged on chromatography on silica gel. Mesitylene was flushed using cyclohexane and the crude was purified using cyclohexane/AcOEt [5:5] to give **1.29** as a brown solid (1.4 g, 5.28 mmol, 81 %).
\[ \text{H NMR (400 MHz, Chloroform-d)} \delta = 7.40 (dd, J = 7.9, 1.0 Hz, 1H), 7.20 (s, 1H), 7.07 (dd, J = 7.4, 1.0 Hz, 1H), 6.98 (t, J = 7.6 Hz, 1H), 6.61 (s, 1H), 6.00 (s, 2H), 4.95 (s, 2H), 3.52 (s, 2H). \]

\[ \text{C NMR (101 MHz, Chloroform-d)} \delta = 174.7, 148.1, 148.0, 139.7, 123.5, 123.2, 122.9, 122.9, 122.8, 120.0, 117.2, 107.7, 102.8, 101.7, 43.5, 36.50. \]

2,3,3a,4,7,12b-Hexahydro-1H-[1,3]dioxolo[4,5-j]pyrrolo[3,2,1-de]phenanthridin-5(3aH)-one 1.58:

\[
\text{Chemical Formula: C}_{16}\text{H}_{17}\text{NO}_3 \\
\text{Exact Mass: 271.1208}
\]

In an autoclave, equipped with stirring bar and charged with \textbf{1.29} (289 mg, 1.1 mmol, 1 equiv) and HFIP (20 mL) was added under an argon atmosphere \( \text{Rh/C} \) (5 % wt, 673 mg, 0.327 mmol, 30 mol%). The autoclave was sealed and purged three times with \( \text{H}_2 \). The mixture was stirred at room temperature under 6 bar \( \text{H}_2 \) for 30 h (followed by TLC). The mixture was then filtered through celite, evaporated and purified by chromatography on silica gel (Cyclohexane/AcOEt). The product was obtained as a yellowish oil (180 mg, 0.664 mmol, 61 %).

\[ \text{H NMR (400 MHz, Chloroform-d)} \delta = 6.61 (s, 1H), 6.59 (s, 1H), 5.95 – 5.90 (m, 2H), 4.54 (d, J = 17.3 Hz, 1H), 4.32 (d, J = 17.3 Hz, 1H), 3.76 (t, J = 4.6 Hz, 1H), 2.75 (dt, J = 12.7, 4.4 Hz, 1H), 2.57 (ddt, J = 16.1, 6.9, 1.1 Hz, 1H), 2.47 – 2.36 (m, 1H), 2.09 (d, J = 16.1 Hz, 1H), 1.79 – 1.66 (m, 3H), 1.40 – 1.29 (m, 1H), 1.27 – 1.09 (m, 2H). \]

\[ \text{C NMR (101 MHz, Chloroform-d)} \delta = 175.8, 146.9, 146.8, 131.8, 123.5, 108.6, 106.8, 101.2, 55.9, 42.9, 40.5, 40.0, 33.1, 30.4, 28.0, 23.8. \]

7a,8,8a,11a,12a-Hexahydro-7H-[1,3]dioxolo[4,5-j]pyrrolo[3,2,1-de]phenanthridin-5(4H)-one 1.59:
In an autoclave, equipped with stirring bar and charged with 1.29 (28.1 mg, 0.1 mmol, 1 equiv) and HFIP (1.8 mL) was added under an argon atmosphere Pd/C (10 % wt, 21.3 mg, 0.02 mmol). The autoclave was sealed and purged three times with H₂. The mixture was stirred at 50 °C under 50 bar H₂ for 48 h (followed by TLC). The mixture was then filtered through celite, evaporated and purified by chromatography on silica gel (Cyclohexane/AcOEt), to give 1.59 (5 mg, 0.017 mmol, 17 %) and 1.58 (14.5 mg, 0.05 mmol, 51 %) as oils.

**¹H NMR (400 MHz, Chloroform-d)** δ = 7.10 – 7.07 (m, 1H), 7.06 – 7.03 (m, 1H), 6.97 – 6.92 (m, 1H), 5.05 (d, J = 1.0 Hz, 1H), 4.88 (d, J = 0.9 Hz, 1H), 4.23 (ddd, J = 9.3, 6.3, 4.7 Hz, 1H), 4.04 (td, J = 4.5, 3.2 Hz, 1H), 3.87 (dd, J = 13.4, 4.4 Hz, 1H), 3.74 (dd, J = 13.4, 10.9 Hz, 1H), 3.51 (s, 2H), 2.82 (dt, J = 12.4, 3.9 Hz, 1H), 2.24 – 2.07 (m, 2H), 2.02 – 1.95 (m, 1H), 1.76 – 1.66 (m, 2H).

**¹³C NMR (101 MHz, Chloroform-d)** δ = 174.1, 140.4, 126.0, 123.4, 123.3, 122.5, 122.1, 94.1, 73.5, 73.3, 40.5, 36.8, 33.9, 31.3, 29.5, 28.6.

**HRMS (ESI):** Calculated for C₁₇H₁₄NO₃ ([M+H]⁺): 272.1287; found 272.1279

**IR (neat)**: ν = 1688, 1631 cm⁻¹

(±)-γ-Lycorane:

Compound 1.58 (141 mg, 0.52 mmol, 1 equiv) was dissolved in THF (14 mL) and placed under argon atmosphere. LiAlH₄ (79 mg, 2.1 mmol, 4 equiv) was added portionwise to the turning solution at room temperature. The mixture was heated at reflux for 15 h, cooled to room temperature, and the solution was poured over sodium sulfate. The crude was extracted with...
dichloromethane (3 x 10 mL), filtered, and evaporated under vacuum. The crude was filtered on a silica plug, using AcOEt as solvent. (±)-γ-lycorane was obtained as a yellowish solid (126 mg, 0.49 mmol, 95 %).

¹H NMR (400 MHz, Chloroform-d) δ = 6.61 (s, 1H), 6.49 (s, 1H), 5.90 – 5.86 (m, 2H), 4.01 (d, J = 14.4 Hz, 1H), 3.38 (td, J = 9.2, 3.9 Hz, 1H), 3.21 (d, J = 14.3 Hz, 1H), 2.74 (dt, J = 12.0, 4.7 Hz, 1H), 2.38 (t, J = 4.9 Hz, 1H), 2.24 – 2.11 (m, 2H), 2.02 (dddd, J = 12.3, 10.9, 8.2, 3.9 Hz, 1H), 1.81 – 1.67 (m, 2H), 1.67 – 1.60 (m, 1H), 1.53 – 1.42 (m, 2H), 1.37 – 1.25 (m, 2H).

¹³C NMR (101 MHz, Chloroform-d) δ = 146.2, 145.8, 133.3, 127.4, 108.5, 106.4, 100.8, 63.1, 57.3, 53.9, 39.6, 37.5, 31.9, 30.6, 29.4, 25.4.

³¹H NMR (400 MHz, Chloroform-d) δ =
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<td>1.39 – 1.29 (m)</td>
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$^{13}$C NMR (101 MHz, Chloroform-$d$) δ =

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9,10-Dimethoxy-2,3,3a,4,7,11b-hexahydro-1H-pyrrolo[3,2,1-de]phenanthridin-5(3aH)-one
1.45p:

In an autoclave, equipped with stirring bar and charged with 1.45 (33 mg, 0.116 mmol, 1 equiv) and HFIP (2.1 mL) was added under an argon atmosphere Rh/C (5 % wt, 72 mg, 0.035 mmol, 30 mol%). The autoclave was sealed and purged three times with H₂. The mixture was stirred at room temperature under 6 bar H₂ for 30h (followed by TLC). The mixture was then filtered through celite, evaporated and purified by chromatography on silica gel (Cyclohexane/AcOEt). The product was obtained as a yellowish solid (17 mg, 0.059 mmol, 51 %).

\[^1\text{H NMR (400 MHz, Chloroform-d)}\] δ = 6.64 (s, 1H), 6.61 (s, 1H), 4.58 (d, J = 17.2 Hz, 1H), 4.34 (d, J = 17.3 Hz, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.78 (t, J = 4.7 Hz, 1H), 2.78 (dt, J = 12.8, 4.4 Hz, 1H), 2.58 (dd, J = 16.1, 6.9 Hz, 1H), 2.44 (dt, J = 11.9, 5.9 Hz, 1H), 2.10 (d, J = 16.1 Hz, 1H), 1.80 – 1.70 (m, 3H), 1.43 – 1.31 (m, 1H), 1.26 – 1.13 (m, 2H).

\[^{13}\text{C NMR (101 MHz, Chloroform-d)}\] δ = 175.9, 148.3, 148.2, 130.5, 122.3, 111.6, 109.6, 56.1, 56.0, 42.5, 40.1, 39.9, 33.1, 30.5, 28.1, 23.8.

HRMS (ESI): Calculated for C\textsubscript{17}H\textsubscript{22}NO\textsubscript{3} ([M+H]⁺): 288.1600; found 288.1604

IR (neat): ν = 1698, 1622 cm\textsuperscript{-1}

mp: 224-226°C

9,10-Dimethoxy-2,3,3a,3a1,4,5,7,11b-octahydro-1H-pyrrolo[3,2,1-de]phenanthridine 1.61:
Compound 1.45p (14.5 mg, 0.0505 mmol, 1 equiv) was dissolved in THF (1.5 mL) and placed under argon atmosphere. LiAlH₄ (8 mg, 0.202 mmol, 4 equiv) was added portionwise to the turning solution at room temperature. The mixture was heated at reflux for 15 h, cooled to room temperature, and the solution was poured over sodium sulfate. The crude was extracted with dichloromethane (3 x 3 mL), filtered, and evaporated under vacuum. The crude was filtered on a silica plug, using AcOEt as solvent. Compound 1.61 was obtained as a yellowish oil (12.7 mg, 0.046 mmol, 92 %).

\[ ^1H \text{NMR (400 MHz, Chloroform-d)} \delta = 6.65 (s, 1H), 6.53 (s, 1H), 4.06 (d, J = 14.1 Hz, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.43 – 3.35 (m, 1H), 3.25 (d, J = 14.2 Hz, 1H), 2.81 – 2.74 (m, 1H), 2.42 – 2.36 (m, 1H), 2.25 – 2.14 (m, 2H), 2.08 – 1.97 (m, 1H), 1.84 – 1.76 (m, 1H), 1.73 – 1.61 (m, 2H), 1.54 – 1.39 (m, 2H), 1.39 – 1.22 (m, 2H). \]

\[ ^13C \text{NMR (126 MHz, Chloroform-d)} \delta = 147.7, 147.3, 132.2, 126.4, 111.4, 109.4, 63.1, 56.9, 56.1, 56.0, 39.3, 37.5, 31.8, 30.6, 29.4, 25.4. \]

HRMS (ESI): Calculated for C₁₇H₂₄NO₂ ([M+H]⁺): 274.1807; found 274.1809

IR (neat) : ν = 1634 cm⁻¹

**Hippadine:**

![Chemical Structure of Hippadine](image_url)

Chemical Formula: C₁₉H₁₂NO₃  
Exact Mass: 263.0582

Hippadine was synthesized from 1.29 according to a reported literature procedure.

\[ ^1H \text{NMR (500 MHz, Chloroform-d)} \delta = 8.04 (dd, J = 3.6, 0.4 Hz, 1H), 7.98 (s, 1H), 7.92 (dd, J = 7.7, 0.6 Hz, 1H), 7.75 (dd, J = 7.7, 0.7 Hz, 1H), 7.65 (s, 1H), 7.47 (t, J = 7.7 Hz, 1H), 6.90 (d, J = 3.6 Hz, 1H), 6.17 (s, 2H). \]

\[ ^13C \text{NMR (126 MHz, Chloroform-d)} \delta = 158.3, 152.7, 148.7, 131.8, 131.1, 128.6, 124.1, 123.7, 122.8, 122.7, 118.5, 116.8, 110.9, 108.2, 102.4, 101.9. \]
Pratosine was synthesized from 1,45 according to a reported literature procedure.

$^1$H NMR (400 MHz, Chloroform-d) $\delta = 8.03 \text{ (d, } J = 3.6 \text{ Hz, 1H), 7.96 \text{ (s, 1H), 7.93 \text{ (d, } J = 7.7 \text{ Hz, 1H), 7.73 \text{ (dd, } J = 7.7, 0.8 \text{ Hz, 1H), 7.60 \text{ (s, 1H), 7.46 \text{ (t, } J = 7.7 \text{ Hz, 1H), 6.88 \text{ (d, } J = 3.6 \text{ Hz, 1H), 4.10 \text{ (s, 3H), 4.05 \text{ (s, 3H).}}}$

$^{13}$C NMR (101 MHz, Chloroform-d) $\delta = 158.5, 153.7, 149.7, 131.2, 129.5, 128.6, 124.0, 123.6, 122.5, 120.8, 118.1, 116.8, 110.8, 110.1, 103.8, 56.4, 56.4$. 

Chemical Formula: C$_{17}$H$_{13}$NO$_3$

Exact Mass: 279.0895
Computational details

Geometry optimizations were performed with the oB97X-D functional/6-31G** basis set in vacuum, using the Spartan '16 software (Wavefunction, Inc.).

**Compound 1.29**

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Chapter 1.2: Synthesis of β-Lactams by Palladium(0)-Catalysed C(sp³)-H Carbamoylation

General information:

Techniques: All reactions involving air-sensitive material were carried out in pre-dried glassware under an argon atmosphere by using Schlenk techniques employing double-line argon-vacuum lines and working in an argon-filled glove box. Analytical thin layer chromatography (TLC) was performed using pre-coated Merck silica gel 60 F254 plates (0.25 mm). Visualization of the developed chromatogram was performed by UV absorbance (254 nm) or TLC stains (KMnO₄ and Phosphomolybdic acid). Flash chromatography was performed using Silicycle SiliaFlash P60 (230-400 mesh) with the indicated solvent system, using gradients of increasing polarity in most cases.

Chemicals:

Anhydrous solvents were obtained by distillation over calcium hydride (xylenes) or by distillation over sodium (mesitylene, toluene). Anhydrous THF, DME, DMF, DMSO, were purchased from Acros Organics. The solvents were degassed by three cycles of freeze-pump-thaw and storing in single-necked flasks equipped with a J-Young PTFE valve when necessary. PdCl₂, Pd(OAc)₂, Pd(PPh₃)₄ were purchased from Strem. All other chemical reagents were purchased from Sigma-Aldrich, Acros Organics, Fisher, Solvias and Fluorochem and used as received without further purification unless otherwise stated. CO gas was purchased from PanGas in 3.8 quality.

Instrumentation:

HPLC analyses were performed using a Shimadzu Prominence system with SIL-20A auto sample, CTO-20AC column oven, LC-20AD pump system, DGU-20A3 degasser and SPD M20A Diode Array or UV/VIS detector. The following chiral columns from Daicel Chemical Industries were used: OD-H (chiralcel), OJ-H (chiralcel) or IA (chiralpak) in 4.6 x 250 mm size. Infrared spectra were taken on a Bruker ALPHA FT-IR spectrometer and are reported in reciprocal centimeters (cm⁻¹). Nuclear magnetic resonance spectra were recorded on a Bruker Advance 250 (250 MHz), Bruker Advance 400 (400 MHz), Bruker Advance 500 (500 MHz) in deuterated chloroform (residual peaks 1H δ = 7.26 ppm, 13C δ = 77.16 ppm) unless otherwise noted. ³¹P NMR spectra were on a Bruker Advance 400 (400 MHz). ¹⁹F spectra were referenced to external CFCl₃. ³¹P spectra were referenced to external 95% solution of H₃PO₄. Data are
reported in parts per million (ppm) as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintuplet, sept = septuplet, m = multiplet and br s = broad signal), coupling constant in Hz and integration. High resolution mass spectra were recorded by Dr. H. Nadig (Department of Chemistry, University of Basel) on a Bruker maXis 4G QTOF ESI mass spectrometer. Optical rotations were measured on a Perkin Elmer 341 Polarimeter in a 1 mL micro cuvette (cell length 100mm) with NaD-Line (λ = 589 nm) at 20 °C.

Optimization of the racemic conditions: selected conditions:

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[1] Yields are reported as the average of three runs.
[a] Performed using 0.133 mmol of 1a unless otherwise stated. [b] 9-Methylfluorene-9-carbonyl chloride (COgen), Pd(OAc)$_2$/P(±-Bu)$_3$•HBF$_4$ cat., Cy$_2$NMe, mesitylene, two-chamber system (COware), both reaction chambers were placed at the same temperature. [c] Determined by NMR analysis using trichloroethylene as internal standard. Yield of isolated product 2a is given within parentheses. [d] Using amine 3a instead of 1a. [e] Performed using 1.33 mmol (400 mg) of 1a. [f] Performed using technical-grade mesitylene under non-inert conditions. TMB = 2,4,6-trimethoxybenzyl.

With alternative sources of CO:

Ru$_3$CO$_{12}$ (1 equiv) instead of CO balloon: 0%

Paraformaldehyde (3 equiv) instead of CO balloon: 45%

Pivalic-formic (3 equiv) instead of CO balloon: 36%

Mechanistic studies

**Synthesis of complex 2.43**

To a solution of tetrakistriphenylphosphine palladium(0) (500 mg, 0.433 mmol, 1 equiv) in toluene (9 mL) was added N,N-diisopropylcarbamoyl chloride (106 mg, 0.648 mmol, 1.5 equiv) and stirred at 80 °C overnight. The solution was cooled to ambient temperature and concentrated in vacuo. The residue was washed with diethyl ether and dried in vacuo to give the complex 2.43 as a yellow powder (300 mg, 0.378 mmol, 87%).

$^1$H NMR (500 MHz, Chloroform-d) $\delta = 7.81 – 7.76$ (m, 12H), 7.40 – 7.32 (m, 18H), 6.26 (hept, $J = 6.7$ Hz, 1H), 2.72 (hept, $J = 6.7$ Hz, 1H), 0.91 (d, $J = 6.7$ Hz, 6H), 0.29 (d, $J = 6.8$ Hz, 6H).

$^{31}$P NMR (202 MHz, CDCl$_3$) $\delta = 19.5$.

The physical and spectroscopic properties matched those described in the literature.

*Formation of $\beta$-lactam from 2.43*
In a vial was charged complex 2.43 (103 mg, 0.133 mmol, 1 equiv) with pivalic acid (4.7 mg, 0.04 mmol, 0.3 equiv) and cesium carbonate (130 mg, 0.399 mmol, 3.0 equiv) in mesitylene (2.6 mL). The mixture was heated to 120°C overnight. The reaction mixture was cooled to ambient temperature, filtered through celite pad, washed with Et₂O and the filtrated was concentrated in vacuo. Trichloroethylene (12.1 μL, 0.133 mmol, 1.0 equiv) was added to the crude mixture and the NMR yield of the β-lactam was determined (26%).

**Formation of β-lactam from corresponding carbamoyl chloride**

In a vial charged with N,N-diisopropylcarbamoyl chloride (21.8 mg, 0.133 mmol, 1 equiv) was reacted with PdCl₂ (2.4 mg, 0.0133 mmol, 10 mol%), cataXium A.HI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL). The mixture was heated to 120°C overnight. The reaction mixture was cooled to ambient temperature, filtered through celite pad, washed with Et₂O and the filtrated was concentrated in vacuo. Trichloroethylene (12.1 μL, 0.133 mmol, 1.0 equiv) was added to the crude mixture and the NMR yield of the β-lactam was determined (35%).

**Synthesis of Taddol Phosphine**

**TADDOL**

In a two-neck-flask equipped with a magnetic stirring bar and reflux condenser were placed active magnesium turnings (53 mmol, 5.3 equiv) and THF (30 mL) was added. To this suspension, a solution of the aryl halide (50 mmol, 5.0 equiv) in THF (10 mL) was added. If the exothermic reaction did not start after 5 min, iodine was added and the reaction mixture was warmed using an oil bath. After the start of the exothermic reaction, the reaction mixture was refluxed for 30 min and then cooled down to rt. A solution of chiral diester (10 mmol, 1.0 equiv) in THF or ether (40 mL) was added slowly, keeping the internal temperature below the boiling
point of the solvent. After complete addition, the reaction mixture was refluxed for 8-14 h and then cooled down to rt. Saturated ammonium chloride solution (40 mL), hydrochloric acid (1.0 M, 10 mL) and water (50 mL) were added carefully. The resulting biphasic mixture was extracted with ether (4x 50 mL). The combined organic extracts were washed with brine (30 mL) and dried over sodium sulfate. All volatiles were removed under reduced pressure. The crude mixture was purified by column chromatography (SiO₂, Pentane:Et₂O).

**Dichloroarylphosphine**

To a solution of chlorobis(diethylamino)phosphine (1.1 equiv) in dry Et₂O (1 mL/mmol) at –78°C was added a freshly prepared solution of a Grignard or an organolithium reagent (1.0 to 1.5 equiv, 0.5 to 2 M in Et₂O) slowly via cannula. After complete addition, the reaction mixture was allowed to warm up to rt and stirred for an additional hour. In case an organolithium reagent was used, the reaction mixture was used as such for the next step. When a Grignard reagent was used, the reaction mixture was filtered using a Schlenk-frit and the residue was washed with additional Et₂O (~0.5 mL/mmol). The filtrate was concentrated with a rotary evaporator under N₂-atmosphere and the obtained oil was redissolved in Et₂O (~0.5 mL/mmol). The reaction mixture was cooled to 0 °C and a solution of hydrogen chloride (4.4 to 5 equiv equiv, 2M in Et₂O) was added dropwise. After complete addition, the reaction mixture was allowed to warm up to rt and stirred for an additional hour. The formed white precipitate was filtered off (Schlenk-frit). The residue was washed with additional Et₂O (~0.5 mL/mmol) and the filtrate was concentrated with a rotary evaporator under N₂-atmosphere. The crude mixture was purified by distillation under high vacuum.

**Phosphonite**

To a mixture of TADDOL of (0.3 mmol, 1 equiv) and 4Å MS (75 mg) in THF (1.2 mL) at 0°C was added triethylamine (0.70 mmol, 2.34 equiv). Next, the dichloroarylphosphine (0.33 mmol, 1.1 equiv) was added dropwise. The reaction was allowed to warm to rt and stirred for 2 h. The reaction was diluted with Et₂O, filtered through celite, and concentrated under reduced pressure. Purification by column chromatography (SiO₂, Pentane:Et₂O) afforded the phosphonite ligand as a white solid.

**Diethyl (2R,3R)-2,3-dimethoxysuccinate 2.84a**
Diethyl tartrate (3.41 mL, 20.0 mmol) and dimethyl sulfate (3.89 mL, 41.0 mmol) were added sequentially to a cooled (0°C) suspension of NaH (960 mg, 40.0 mmol) in diethyl ether (200 mL) and the resulting mixture was stirred overnight at rt. The reaction was quenched with sat. NaHCO$_3$ (100 mL), the aqueous phase extracted with diethyl ether (3 x 50 mL), the combined organic layers were washed with NH$_4$OH (50 mL, 10% in H$_2$O), dried over MgSO$_4$, filtered and the solvent was removed under reduced pressure to provide oil the title compound in quantitative yield as a colorless liquid.

$^1$H NMR (400 MHz, Chloroform-d) : $\delta = 4.33-4.19$ (m, 4H), 4.21 (s, 2H), 3.45 (s, 6H), 1.30 (t, $J = 7.2$ Hz, 6 H)

$^{13}$C NMR (101 MHz, Chloroform-d) : $\delta = 169.2, 81.2, 61.3, 59.6, 14.2$

IR (neat): $\nu = 2985, 2933, 2833, 1754, 1730, 1465, 1447, 1390, 1369, 1348, 1267, 1218, 1185, 1149, 1108, 1026, 926, 858, 810$ cm$^{-1}$.

The physical and spectroscopic properties matched those described in the literature.$^{10}$

(2R,3R)-1,1,4,4-Tetrakis(3,5-bis(trifluoromethyl)phenyl)-2,3-dimethoxybutane-1,4-diol 2.84b

Following general procedure “TADDOL”, the Grignard reagent generated from 3,5-bis(trifluoromethyl)bromobenzene (12.5 g, 42.7 mmol, 5.0 equiv) and magnesium (1.1 g, 45.3 mmol, 5.3 equiv) in THF was reacted with diethyl (2R,3R)-2,3-dimethoxysuccinate (2 g, 8.54 mmol, 1.0 equiv). The crude mixture was purified by flash chromatography affording 6.3 g (6.31 mmol, 74%) of a yellow oil which solidified under vacuum.
\(^{1}\)H NMR (400 MHz, Chloroform-\(d\)) : \(\delta = 8.11 – 8.06 \) (m, 4H), 7.95 – 7.91 (m, 4H), 7.92 – 7.90 (m, 2H), 7.86 – 7.84 (m, 5H), 4.42 (s, 2H), 4.23 (s, 2H), 2.46 (s, 6H).

\(^{13}\)C NMR (101 MHz, Chloroform-\(d\)) : \(\delta = 146.72, 144.93, 132.71 \) (q, \(J_{C,F} = 33.7 \) Hz), 132.07 (q, \(J_{C,F} = 33.6 \) Hz), 127.39 – 127.16 (m), 126.77 – 126.46 (m), 123.2 (q, \(J_{C,F} = 273 \) Hz), 123.1 (q, \(J_{C,F} = 273 \) Hz), 122.47 (m), 122.42 – 122.21 (m), 84.21, 78.77, 60.66.

\(^{19}\)F NMR (376 MHz, Chloroform-\(d\)) : \(\delta = -63.12, -63.24\).

IR (neat): \(\nu = 3290, 2884, 1625, 1460, 1365, 1005, 762 \) cm\(^{-1}\).

HRMS (ESI): Calculated for C\(_{38}\)H\(_{22}\)F\(_{24}\)O\(_4\) ([M-H]\(^-\)): 997.1077; found: 997.1062

Optical rotation : \([\alpha]_{D}^{20} = -1^\circ \) (c = 1.0, CHCl\(_3\))

(5R,6R)-4,4,7,7-Tetraakis(3,5-bis(trifluoromethyl)phenyl)-2-(3,5-di-tert-butyl-4-methoxyphenyl)-5,6-dimethoxy-1,3,2-dioxaphosphepane 2.84

Following general procedure “Phosphonite”, 2.84 was obtained as a yellow solid (310 mg, 0.249 mmol, 83 %).

\(^{1}\)H NMR (400 MHz, Chloroform-\(d\)) : \(\delta = 8.29 – 8.25 \) (m, 2H), 8.10 – 8.05 (m, 2H), 7.94 – 7.91 (m, 1H), 7.81 – 7.80 (m, 1H), 7.79 – 7.77 (m, 2H), 7.75 – 7.73 (m, 1H), 7.72 – 7.67 (m, 3H), 7.19 (s, 2H), 4.64 (dd, \(J = 7.9, 5.6 \) Hz, 1H), 3.71 (s, 3H), 3.68 (s, 3H), 3.65 – 3.61 (m, 1H), 2.47 (s, 3H), 1.42 (s, 9H), 1.34 (s, 9H).

\(^{13}\)C NMR (101 MHz, Chloroform-\(d\)) : Many signals due to C-P and C-F coupling

\(^{31}\)P NMR (162 MHz, Chloroform-\(d\)) : \(\delta = 161.3\).

\(^{19}\)F NMR (376 MHz, Chloroform-\(d\)) : \(\delta = -63.01, -63.05, -63.12\).

Optical rotation : \([\alpha]_{D}^{20} = -20.3^\circ \) (c = 1.06, CHCl\(_3\))

HRMS (ESI): Calculated for C\(_{53}\)H\(_{44}\)F\(_{24}\)O\(_5\)P ([M+H]\(^+\)): 1247.2538; found: 1247.2523
Synthesis of secondary amines

N-(2,4,6-Trimethoxybenzyl)propan-2-amine 2.40r:

\[
\text{Chemical Formula: } C_{13}H_{22}NO_3 \\
\text{Exact Mass: 239.1521}
\]

N-(2,4,6-trimethoxybenzyl)propan-2-amine was obtained according to a known procedure. The physical and spectroscopic properties matched those described in the literature. \(^{11}\)

N-(2,4,6-trimethoxybenzyl)ethanamine 2.53a:

Following general procedure A, ethylamine (70 % in MeOH, 25.5 mmol, 5 equiv), 2,4,6-trimethoxybenzaldehyde (1 g, 5.1 mmol, 1 equiv), were reacted in THF (10 mL) for 4h with 4Å MS (2.5 g, 6.5 mmol.). NaBH\(_4\) (580 mg, 15.3 mmol, 3 equiv) in EtOH (6 mL) was carefully added and the mixture was stirred overnight. The crude mixture was filtered through celite, acidified using a solution of HCl (0.1M) and stirred for 30 min. The mixture was then basified using NaOH solution (0.1M) and extracted three times using AcOEt. The combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum. The excess of starting material was removed under high vacuum. The crude mixture was purified by chromatography on silica gel using DCM/MeOH as eluent to provide oil N-(2,4,6-trimethoxybenzyl)ethanamine as a yellowish oil (1.1 g, 4.90 mmol, 96 %).

\(^1\)H NMR (400 MHz, Chloroform-d) : \(\delta = 6.11\) (s, 2H), 3.79 (s, 3H), 3.78 (s, 6H), 3.76 (s, 2H), 2.59 (q, \(J = 7.2\) Hz, 2H), 1.65 (br s, 1H), 1.08 (t, \(J = 7.1\) Hz, 3H).

\(^1\)C NMR (Chloroform-d, 101 MHz) : \(\delta = 160.3, 159.4, 109.5, 90.4, 55.7, 55.4, 43.2, 41.2, 15.5.\)

IR (neat): \(\nu = 2953, 1581, 1473\) cm\(^{-1}\).

HRMS (ESI): Calculated for C\(_{12}\)H\(_{20}\)NO\(_3\) ([M+H]+): 226.1438; found: 226.1440
2-Methyl-N-(2,4,6-trimethoxybenzyl)propan-2-amine 2.55a:

Following general procedure B, 2,4,6-trimethoxybenzaldehyde (1 g, 5.1 mmol, 1 equiv), tert-butylamine (0.541 mL, 5.1 mmol, 1 equiv), AcOH (0.583 mL, 10.2 mmol, 2 equiv) and NaBH(OAc)$_3$ (2.16 g, 10.2 mmol, 2 equiv) were reacted in DCE (25 mL) overnight. Then, the mixture was quenched using a solution of NaOH (1M) and the crude mixture was stirred for further 30 min. The crude mixture was extracted twice with DCM, dried over sodium sulfate, filtered, evaporated under vacuum and purified by chromatography on silica gel using DCM/MeOH as eluent, yielding slightly yellow oil $S_c$ (1.25 g, 5.0 mmol, 97%).

$^1$H NMR (400 MHz, Chloroform-$d$): $\delta = 6.10$ (s, 2H), 3.79 (s, 6H), 3.78 (s, 3H), 3.70 (s, 2H), 1.43 (br. ns, 1H), 1.16 (s, 9H).

$^{13}$C NMR (Chloroform-$d$, 101 MHz): $\delta = 160.2$, 159.2, 110.3, 90.7, 55.7, 55.4, 50.6, 35.1, 29.2.

IR (neat): $\nu = 2960$, 1598, 1463, 1205 cm$^{-1}$.

HRMS (ESI): Calculated for C$_{14}$H$_{24}$NO$_3$ ([M+H]$^+$): 254.1751; found: 254.1753

2-Phenyl-N-(2,4,6-trimethoxybenzyl)propan-2-amine 2.56a:

Following general procedure B, 2,4,6-trimethoxybenzaldehyde (700 mg, 3.57 mmol, 1 equiv), cumylamine (483 mg, 3.57 mmol, 1 equiv), AcOH (0.408 mL, 7.14 mmol, 2 equiv) and NaBH(OAc)$_3$ (1.51 g, 7.14 mmol, 2 equiv) were reacted in DCE (15 mL) overnight. Then, the mixture was quenched using a solution of NaOH (1M) and the crude mixture was stirred for further 30 min. The crude mixture was extracted twice with DCM, dried over sodium sulfate, filtered, evaporated under vacuum and purified by chromatography on silica gel using DCM/MeOH as eluent, yielding slightly yellow oil $S_d$ (1.02 g, 3.2 mmol, 90%).

$^1$H NMR (400 MHz, Chloroform-$d$) $\delta = 7.57 – 7.47$ (m, 2H), 7.33 (dd, $J = 8.5$, 7.0 Hz, 2H), 7.24 – 7.17 (m, 1H), 6.07 (s, 2H), 3.75 (s, 3H), 3.75 (s, 6H), 3.45 (s, 2H), 1.52 (s, 6H).
$^{13}$C NMR (101 MHz, Chloroform-$d$) δ = 160.2, 159.1, 148.0, 127.8, 126.1, 125.9, 109.8, 90.6, 55.9, 55.6, 55.3, 35.5, 29.8.

IR (neat): ν = 2961, 1596, 1460, 1127 cm$^{-1}$.

HRMS (ESI): Calculated for C$_{19}$H$_{26}$NO$_3$ ([M+H]$^+$): 316.1913; found: 316.1917

(R)-3,3-Dimethyl-N-(2,4,6-trimethoxybenzyl)butan-2-amine 2.57a:

Following general procedure B, 2,4,6-trimethoxybenzaldehyde (1 g, 5.1 mmol, 1 equiv), (R)-3,3-dimethylbutan-2-amine (0.7 mL, 5.1 mmol, 1 equiv), AcOH (0.583 mL, 10.2 mmol, 2 equiv) and NaBH(OAc)$_3$ (2.16 g, 10.2 mmol, 2 equiv) were reacted in DCE (25 mL) overnight. Then, the mixture was quenched using a solution of NaOH (1M) and the crude mixture was stirred for further 30 min. The crude mixture was extracted twice with DCM, dried over sodium sulfate, filtered, evaporated under vacuum and purified by chromatography on silica gel using DCM/MeOH as eluent, yielding slightly yellow oil (1.4 g, 5.0 mmol, 98%).

$^1$H NMR (400 MHz, Chloroform-$d$): δ = 6.11 (s, 2H), 3.88 – 3.71 (m, 11H), 2.09 (q, $J = 6.4$ Hz, 1H), 1.83 (br s, 1H), 0.97 (d, $J = 6.3$ Hz, 3H), 0.81 (s, 9H).

$^{13}$C NMR (Chloroform-$d$, 101 MHz): δ = 160.1, 159.6, 109.6, 90.5, 60.4, 55.7, 55.4, 40.1, 34.1, 26.6, 14.8.

IR (neat): ν = 2954, 1607, 1140, 1204 cm$^{-1}$.

HRMS (ESI): Calculated for C$_{16}$H$_{28}$NO$_3$ ([M+H]$^+$): 282.2064; found: 282.2062

(S)-N-(2,4,6-Trimethoxybenzyl)octan-2-amine 2.58a:

Following general procedure B, 2,4,6-trimethoxybenzaldehyde (1.38 g, 7.03 mmol, 1 equiv), (S)-octan-2-amine (1 g, 7.03 mmol, 1 equiv), AcOH (0.804 mL, 14.06 mmol, 2 equiv) and
NaBH(OAc)₃ (2.98 g, 14.06 mmol, 2 equiv) were reacted in DCE (14 mL) overnight. Then, the mixture was quenched using a solution of NaOH (1M) and the crude mixture was stirred for further 30 min. The crude mixture was extracted twice with DCM, dried over sodium sulfate, filtered, evaporated under vacuum and purified by chromatography on silica gel using DCM/MeOH as eluent, yielding slightly yellow oil (1.8 g, 5.8 mmol, 83%).

**¹H NMR (400 MHz, Chloroform-d)**: δ = 6.08 (s, 2H), 3.84 – 3.72 (m, 11H), 2.71 – 2.62 (m, 1H), 2.55 – 2.46 (m, 1H), 1.52 – 1.38 (m, 1H), 1.32 – 1.17 (m, 10H), 1.04 (d, J = 6.3 Hz, 3H), 0.84 (t, J = 6.6 Hz, 3H).

**¹³C NMR (Chloroform-d, 101 MHz)**: δ = 160.3, 159.4, 108.8, 90.4, 55.6, 55.3, 51.7, 38.7, 36.8, 32.0, 29.5, 26.0, 22.7, 20.2, 14.2.

**IR (neat):** ν = 2933, 2820, 1623, 1156 cm⁻¹.

**HRMS (ESI):** Calculated for C₁₈H₃₂NO₃ ([M+H]^+) : 310.2382; found: 310.2387

(R)-1-Cyclohexyl-N-(2,4,6-trimethoxybenzyl)ethan-1-amine 2.59a:

Following general procedure B, 2,4,6-trimethoxybenzaldehyde (1.38 g, 7.03 mmol, 1 equiv), R-(-)-Cyclohexylethylamine (0.95 mL, 7.03 mmol, 1 equiv), AcOH (0.804 mL, 14.06 mmol, 2 equiv) and NaBH(OAc)₃ (2.98 g, 14.06 mmol, 2 equiv) were reacted in DCE (14 mL) overnight. Then, the mixture was quenched using a solution of NaOH (1M) and the crude mixture was stirred for further 30 min. The crude mixture was extracted twice with DCM, dried over sodium sulfate, filtered, evaporated under vacuum and purified by chromatography on silica gel using DCM/MeOH as eluent, yielding slightly yellow oil (1.95 g, 6.33 mmol, 90%).

**¹H NMR (400 MHz, Chloroform-d)**: δ = 6.11 (s, 2H), 3.83 – 3.72 (m, 11H), 2.37 – 2.29 (m, 1H), 1.76 – 1.61 (m, 5H), 1.40 – 1.29 (m, 1H), 1.27 – 1.07 (m, 3H), 1.00 (d, J = 6.4 Hz, 3H), 0.97 – 0.84 (m, 2H).

**¹³C NMR (Chloroform-d, 101 MHz)**: δ = 160.3, 159.5, 90.5, 56.5, 55.8, 55.4, 42.7, 39.1, 29.9, 28.3, 26.9, 26.8, 26.7, 16.7.

**IR (neat):** ν = 2923, 2850, 1603, 1149 cm⁻¹.

**HRMS (ESI):** Calculated for C₁₈H₃₀NO₃ ([M+H]^+) : 308.2220; found: 308.2222
(R)-2-((2,4,6-Trimethoxybenzyl)amino)propan-1-ol 2.60aa:

Following general procedure C, 2,4,6-trimethoxybenzaldehyde (1.5 g, 7.63 mmol, 1 equiv), L-alaninol (573 mg, 7.63 mmol, 1 equiv) and Pd/C (812 mg, 10% w/w, 10 mol%) were reacted in MeOH (11 mL) and stirred overnight under H₂ atmosphere. The crude mixture was then filtered through celite, the solvent evaporated and the crude mixture purified by chromatography on silica gel to provide oil N-isopropyl-2,3-dihydro-1H-inden-2-amine (686 mg, 2.67 mmol, 35%).

^1H NMR (400 MHz, Chloroform-d) δ = 6.10 (s, 2H), 3.81 (d, J = 12.5 Hz, 1H + NH), 3.78 – 3.77 (m, 9H), 3.73 (d, J = 12.6 Hz, 1H), 3.59 (dd, J = 10.7, 4.0 Hz, 1H), 3.24 (dd, J = 10.7, 6.3 Hz, 1H), 2.70 (td, J = 6.4, 4.0 Hz, 1H + OH), 1.02 (d, J = 6.5 Hz, 3H).

^13C NMR (101 MHz, Chloroform-d) δ = 160.4, 159.4, 108.9, 90.5, 65.1, 55.7, 55.4, 53.0, 38.5, 17.4.
IR (neat): v = 3132, 2925, 2840, 1608, 1139 cm⁻¹.
HRMS (ESI): Calculated for C_{13}H_{22}NO_4 ([M+H]⁺): 256.1543; found: 256.1544

(R)-2-((2,4,6-Trimethoxybenzyl)amino)propyl pivalate 2.60a:

(R)-2-((2,4,6-Trimethoxybenzyl)amino)propan-1-ol (300 mg, 1.18 mmol, 1 equiv) was dissolved in dichloromethane (6 mL) and cooled to 0 °C. Triethylamine (0.201 mL, 1.43 mmol, 1.2 equiv) and DMAP (7.2 mg, 0.06 mmol, 5 mol%) were added, followed by dropwise addition of pivaloyl chloride (0.163 mL, 1.3 mmol, 1.1 equiv). The reaction mixture was allowed to warm slowly to ambient temperature and stirred for 16 h. The reaction mixture was quenched with water (10 mL) and extracted with dichloromethane (2 x 10 mL). The combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum. The residue was purified by chromatography on silica gel using DCM/MeOH as eluent to afford (R)-2-((2,4,6-trimethoxybenzyl)amino)propyl pivalate as yellowish oil (200 mg, 0.58 mmol, 50%).
**1H NMR (400 MHz, Chloroform-d)** \( \delta = 6.11 \) (s, 2H), 4.05 – 4.00 (m, 1H), 3.92 – 3.86 (m, 1H), 3.82 (d, \( J = 5.5 \) Hz, 2H), 3.80 (s, 3H), 3.78 (s, 6H), 3.33 (br s, 1H), 2.90 – 2.80 (m, 1H), 1.17 (s, 9H), 1.09 (d, \( J = 6.4 \) Hz, 3H).

**13C NMR (101 MHz, Chloroform-d)** \( \delta = 178.2, 160.4, 159.3, 108.6, 90.3, 68.3, 55.6, 55.3, 50.5, 38.8, 38.5, 27.1, 16.9. \)

**IR (neat):** \( \nu = 2957, 1729, 1608, 1150 \, \text{cm}^{-1} \).

**HRMS (ESI):** Calculated for C\(_{18}\)H\(_{30}\)NO\(_5\) ([M+H]+): 340.2118; found: 340.2119

**(S)-1-Phenyl-N-(2,4,6-trimethoxybenzyl)ethan-1-amine 2.61a:**

![Chemical Structure](image)

Following general procedure B, 2,4,6-trimethoxybenzaldehyde (1.38 g, 7.03 mmol, 1 equiv), (S)-1-phenylethan-1-amine (900 mg, 7.03 mmol, 1 equiv), AcOH (0.804 mL, 14.06 mmol, 2 equiv) and NaBH(OAc)\(_3\) (2.98 g, 14.06 mmol, 2 equiv) were reacted in DCE (14 mL) overnight. Then, the mixture was quenched using a solution of NaOH (1M) and the crude mixture was stirred for further 30 min. The crude mixture was extracted twice with DCM, dried over sodium sulfate, filtered, evaporated under vacuum and purified by chromatography on silica gel using DCM/MeOH as eluent, yielding slightly yellow oil (1.75 g, 5.8 mmol, 82%).

**1H NMR (400 MHz, Chloroform-d)** \( \delta = 7.40 – 7.27 \) (m, 4H), 7.27 – 7.17 (m, 1H), 6.10 (s, 2H), 3.79 (s, 3H), 3.75 (s, 6H), 3.66 (s, 2H), 2.15 (s, 1H), 1.33 (d, \( J = 6.6 \) Hz, 3H).

**13C NMR (Chloroform-d, 101 MHz)**: \( \delta = 160.4, 159.5, 146.3, 128.2, 127.0, 126.7, 109.3, 90.5, 57.3, 55.6, 55.4, 39.5, 24.5. \)

**IR (neat):** \( \nu = 2923, 2857, 1613 \, \text{cm}^{-1} \).

**HRMS (ESI):** Calculated for C\(_{18}\)H\(_{24}\)NO\(_3\) ([M+H]+): 302.1756; found: 302.1758

**(N-(Cyclopentylmethyl)propan-2-amine 2.63a:**

![Chemical Structure](image)

Following general procedure C, cyclopentanecarboxaldehyde (1 g, 10.2 mmol, 1 equiv), isopropylamine (0.874 mL, 10.2 mmol, 1 equiv) and Pd/C (1.09 g, 10% w/w, 10 mol%) were
reacted in MeOH (25 mL) and stirred overnight under H₂ atmosphere. The crude mixture was then filtered through celite, and the solvent evaporated to provide oil N-(cyclopentylmethyl)propan-2-amine as a yellowish oil (1.30 g, 9.18 mmol, 90 %).

**¹H NMR (400 MHz, Chloroform-d):** δ = 2.78 (hept, J = 6.2 Hz, 1H), 2.52 (d, J = 7.1 Hz, 2H), 2.08 – 1.89 (m, 1H), 1.85 – 1.68 (m, 3H), 1.65 – 1.48 (m, 4H), 1.22 – 1.09 (m, 2H), 1.06 (d, J = 6.2 Hz, 6H).

**¹³C NMR (Chloroform-d 101 MHz):** δ = 53.3, 48.9, 40.1, 30.9, 25.2, 22.8.

**IR (neat):** ν = 2953, 2867, 1452, 730 cm⁻¹.

**HRMS (ESI):** Calculated for C₉H₂₀N ([M+H]+): 142.1590; found: 142.1592

**N-(2,4,6-Trimethylbenzyl)propan-2-amine 2.64a:**

Following general procedure B, mesitaldehyde (500 mg, 3.37 mmol, 1 equiv), isopropylamine (0.577 mL, 6.74 mmol, 2 equiv), AcOH (0.385 mL, 6.74 mmol, 2 equiv) and NaBH(OAc)₃ (1.58 g, 6.74 mmol, 2 equiv) were reacted in DCE (10 mL) overnight. Then, the mixture was quenched using a solution of NaOH (1M) and the crude mixture was stirred for further 30 min. The crude mixture was extracted twice with DCM, dried over sodium sulfate, filtered, evaporated under vacuum and purified by chromatography on silica gel using DCM/MeOH as eluent, yielding slightly yellow oil (505 mg, 2.64 mmol, 78 %).

**¹H NMR (400 MHz, Chloroform-d):** δ = 6.85 (s, 2H), 4.48 (d, J = 14.7 Hz, 1H), 4.34 (d, J = 14.7 Hz, 1H), 3.47 – 3.40 (m, 1H), 3.0I (dd, J = 14.4, 5.0 Hz, 1H), 2.48 – 2.42 (m, 1H), 2.33 (s, 6H), 2.26 (s, 3H), 1.06 (d, J = 6.1 Hz, 3H).

**¹³C NMR (Chloroform-d 101 MHz):** δ = 166.8, 137.6, 137.4, 129.4, 128.5, 47.6, 44.1, 38.9, 21.0, 20.1, 19.4.

**IR (neat):** ν = 2965, 2361 cm⁻¹.

**HRMS (ESI):** Calculated for C₁₃H₂₂N ([M+H]+): 192.1747; found: 192.1749

**N-Benzylpropan-2-amine 2.65a:**

Following general procedure B, mesitaldehyde (500 mg, 3.37 mmol, 1 equiv), isopropylamine (0.577 mL, 6.74 mmol, 2 equiv), AcOH (0.385 mL, 6.74 mmol, 2 equiv) and NaBH(OAc)₃ (1.58 g, 6.74 mmol, 2 equiv) were reacted in DCE (10 mL) overnight. Then, the mixture was quenched using a solution of NaOH (1M) and the crude mixture was stirred for further 30 min. The crude mixture was extracted twice with DCM, dried over sodium sulfate, filtered, evaporated under vacuum and purified by chromatography on silica gel using DCM/MeOH as eluent, yielding slightly yellow oil (505 mg, 2.64 mmol, 78 %).

**¹H NMR (400 MHz, Chloroform-d):** δ = 6.85 (s, 2H), 4.48 (d, J = 14.7 Hz, 1H), 4.34 (d, J = 14.7 Hz, 1H), 3.47 – 3.40 (m, 1H), 3.0I (dd, J = 14.4, 5.0 Hz, 1H), 2.48 – 2.42 (m, 1H), 2.33 (s, 6H), 2.26 (s, 3H), 1.06 (d, J = 6.1 Hz, 3H).

**¹³C NMR (Chloroform-d 101 MHz):** δ = 166.8, 137.6, 137.4, 129.4, 128.5, 47.6, 44.1, 38.9, 21.0, 20.1, 19.4.

**IR (neat):** ν = 2965, 2361 cm⁻¹.

**HRMS (ESI):** Calculated for C₁₃H₂₂N ([M+H]+): 192.1747; found: 192.1749
Following general procedure A, isopropylamine (3.62 mL, 42.3 mmol, 3 equiv), benzaldehyde (1.5 g, 14.1 mmol, 1 equiv), were reacted in THF (10 mL) for 4h with 4Å MS (5 g, 14 mmol). NaBH₄ (1.6 g, 42.3 mmol, 3 equiv) in EtOH (10 mL) was carefully added and the mixture was stirred overnight. The crude mixture was filtered through celite, acidified using a solution of HCl (0.1M) and stirred for 30 min. The mixture was then basified using NaOH solution (0.1M) and extracted three times using AcOEt. The combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum. The excess of starting material was removed under high vacuum. The crude mixture was purified by chromatography on silica gel using DCM/MeOH as eluent to provide oil N-benzylpropan-2-amine as a yellowish oil (400 mg, 2.68 mmol, 19%).

**1H NMR (400 MHz, Chloroform-d):** δ = 7.36 – 7.20 (m, 5H), 3.78 (s, 2H), 2.86 (hept, 1H), 1.46 (br s, 1H), 1.10 (d, J = 6.3 Hz, 6H).

**13C NMR (Chloroform-d, 101 MHz):** δ = 140.9, 128.5, 128.2, 127.0, 51.8, 48.2, 23.0

**IR (neat):** ν = 2964, 2362, 1453, 1171 cm⁻¹.

**HRMS (ESI):** Calculated for C₁₀H₁₆N ([M+H]⁺): 150.1283; found: 150.1284

**N-Phenethylpropan-2-amine 2.66a:**

Following general procedure C, acetone (1.17 mL, 15.9 mmol, 1 equiv), 2-phenylethan-1-amine (2 mL, 15.9 mmol, 1 equiv) and Pd/C (1.69 g, 10% w/w, 10 mol%) were reacted in MeOH (15 mL) and stirred overnight under H₂ atmosphere. The crude mixture was then filtered through celite, and the solvent evaporated to provide oil N-phenethylpropan-2-amine (2.4 g, 14.6 mmol, 92%).

**1H NMR (400 MHz, Chloroform-d):** δ = 7.36 – 7.11 (m, 5H), 2.93 – 2.68 (m, 5H), 1.10 (br s, 1H), 1.03 (d, J = 6.3 Hz, 6H).

**13C NMR (Chloroform-d, 101 MHz):** δ = 140.0, 128.6, 128.4, 126.0, 48.7, 48.5, 36.5, 22.9.

**IR (neat):** ν = 2962, 2825, 1473, 1173, 697 cm⁻¹.

**HRMS (ESI):** Calculated for C₁₁H₁₈N ([M+H]⁺): 164.1434; found: 164.1437

The physical and spectroscopic properties matched those described in the literature.

**N-Isopropyl-3-phenylpropan-1-amine 2.67a:**
Following general procedure B, 3-phenylpropionaldehyde (2 g, 14.9 mmol, 1 equiv), isopropylamine (3.83 mL, 44.7 mmol, 3 equiv), AcOH (1.7 mL, 29.8 mmol, 2 equiv) and NaBH(OAc)$_3$ (6.32 g, 29.8 mmol, 2 equiv) were reacted in DCE (75 mL) overnight. Then, the mixture was quenched using a solution of NaOH (1M) and the crude mixture was stirred for further 30 min. The crude mixture was extracted twice with DCM, dried over sodium sulfate, filtered, evaporated under vacuum and purified by chromatography on silica gel using DCM/MeOH as eluent, yielding slightly yellow oil (2 g, 11.3 mmol, 76%).

$^1$H NMR (400 MHz, Chloroform-d): $\delta = 7.34 – 7.26$ (m, 2H), 7.21 (d, $J = 7.3$ Hz, 3H), 2.80 (hept, $J = 6.3$ Hz, 1H), 2.72 – 2.62 (m, 4H), 1.90 – 1.79 (m, 2H), 1.20 (br s, 1H), 1.07 (d, $J = 6.3$ Hz, 6H).

$^{13}$C NMR (Chloroform-d, 101 MHz): $\delta = 142.3, 128.5, 128.4, 125.9, 48.8, 47.3, 34.0, 32.2, 23.1$.

IR (neat): $\nu = 2964, 2861, 1473, 699$ cm$^{-1}$.

HRMS (ESI): Calculated for C$_{12}$H$_{20}$N ([M+H]$^+$): 178.1590; found: 178.1592.

The physical and spectroscopic properties matched those described in the literature.$^{13}$

**Ethyl 3-(isopropylamino)propanoate 2.68a:**

To a solution of isopropylamine (20 mmol, 1.18 g, 2.0 equiv) in ethanol (13 mL) at 0°C was added, via addition funnel, a solution of ethyl acrylate (10 mmol, 1 g, 1.0 equiv) in ethanol (7 mL). The reaction mixture was allowed to warm to ambient temperature then stirred at ambient temperature for 24 h and concentrated under vacuum. The excess of amine was removed under high vacuum to provide oil the pure desired compound (1.59 g, 10 mmol, 100%).

$^1$H NMR (400 MHz, Chloroform-d): $\delta = 4.14$ (q, $J = 7.1$ Hz, 2H), 2.92 – 2.72 (m, 3H), 2.49 (t, $J = 6.6$ Hz, 2H), 1.33 – 1.21 (m, 4H), 1.05 (d, $J = 6.2$ Hz, 6H).

$^{13}$C NMR (Chloroform-d, 101 MHz): $\delta = 172.8, 60.3, 48.4, 42.5, 35.0, 22.9, 14.2$.

IR (neat): $\nu = 1732, 1191$ cm$^{-1}$.
HRMS (ESI): Calculated for C₈H₁₈NO₂ ([M+H]⁺): 160.1332; found: 160.1331

The physical and spectroscopic properties matched those described in the literature.¹⁴

2-(3-(Isopropylamino)propyl)isoindole-1,3-dione 2.69a:

3-Phthalimidopropionaldehyde was prepared following an analogous procedure described by Livinghouse and co-worker. Acroleine (561 mg, 10 mmol, 1 equiv) and phthalimide (1.47 g, 10 mmol, 1 equiv) were suspended in AcOEt (6.5 mL) and stirred at 65 °C for 10 min. Then, Triton B (40 % solution of benzyltrimethylammonium hydroxide in MeOH, 90 μL, 0.2 mmol, 2 mol%) was added to the solution, which was further stirred for 20 min. The mixture was then cooled to rt, the solvent removed under vacuum and the resulting yellowish solid triturated with Et₂O. The resulting solid was then filtered to provide oil 3-phthalimidopropionaldehyde (2.02 g, 10 mmol, 100 %). Then, following general procedure C, 3-phthalimidopropionaldehyde (2.02 g, 10 mmol, 1 equiv), isopropylamine (0.852 mL, 10 mmol, 1 equiv) and Pd/C (1.06 g, 10% w/w, 10 mol%) were reacted in MeOH (25 mL) and stirred overnight under H₂ atmosphere. The crude mixture was then filtered through celite, and the solvent evaporated to provide oil 2-(3-(isopropylamino)propyl)isoindole-1,3-dione as a yellowish oil (1.84 g, 7.5 mmol, 75 %).

¹H NMR (400 MHz, Chloroform-d) : δ = 7.88 – 7.81 (m, 2H), 7.76 – 7.66 (m, 2H), 3.76 (t, J = 6.8 Hz, 2H), 2.75 (hept, J = 6.2 Hz, 1H), 2.62 (t, J = 7.0 Hz, 2H), 1.94 – 1.79 (m, 3H), 1.03 (d, J = 6.2 Hz, 6H).

¹³C NMR (Chloroform-d, 101 MHz) : δ = 168.5, 133.9, 132.2, 123.2, 48.7, 44.3, 36.0, 29.2, 22.9.

IR (neat): ν = 1773, 1705, 1468, 1442 cm⁻¹.

HRMS (ESI): Calculated for C₁₄H₁₉N₂O₂ ([M+H]⁺): 247.1441; found: 247.1442

The physical and spectroscopic properties matched those described in the literature.¹⁵

2-Methyl-N-(3-phenylpropyl)butan-2-amine 2.70a:
Following general procedure B, 3-phenylpropionaldehyde (1 g, 7.45 mmol, 1 equiv), tert-amylamine (2.61 mL, 22.4 mmol, 3 equiv), AcOH (0.852 mL, 14.9 mmol, 2 equiv) and NaBH(OAc)₃ (3.16 g, 14.9 mmol, 2 equiv) were reacted in DCE (37 mL) overnight. Then, the mixture was quenched using a solution of NaOH (1M) and the crude mixture was stirred for further 30 min. The crude mixture was extracted twice with DCM, dried over sodium sulfate, filtered, evaporated under vacuum and purified by chromatography on silica gel using DCM/MeOH as eluent, yielding slightly yellow oil (1.35 g, 6.57 mmol, 88 %).

**¹H NMR (400 MHz, Chloroform-d):** \(\delta = 7.34 – 7.13 \text{ (m, 5H)}, 3.73 \text{ (s, 1H)}, 2.72 – 2.62 \text{ (m, 2H)}, 2.60 – 2.47 \text{ (m, 2H)}, 1.86 – 1.69 \text{ (m, 2H)}, 1.47 – 1.32 \text{ (m, 2H)}, 1.01 \text{ (s, 6H)}, 0.82 \text{ (t, } J = 7.5 \text{ Hz, 3H).}

**¹³C NMR (Chloroform-d, 101 MHz):** \(\delta = 142.2, 128.3, 128.2, 125.6, 52.3, 41.5, 33.8, 33.0, 32.6, 26.5, 8.2.

**IR (neat):** \(\nu = 3028, 2935, 1475, 1442 \text{ cm}^{-1}.

**HRMS (ESI):** Calculated for C₁₄H₂₄N ([M+H]⁺): 206.1903; found: 206.1902

**3-Phenyl-N-(2-phenylpropan-2-yl)propan-1-amine 2.71a:**

Following general procedure B, phenylpropionaldehyde (500 mg, 3.73 mmol, 1 equiv), cumylamine (504 mg, 3.73 mmol, 1 equiv), AcOH (0.427 mL, 7.46 mmol, 2 equiv) and NaBH(OAc)₃ (1.58 g, 7.1 mmol, 2 equiv) were reacted in DCE (19 mL) overnight. Then, the mixture was quenched using a solution of NaOH (1M) and the crude mixture was stirred for further 30 min. The crude mixture was extracted twice with DCM, dried over sodium sulfate, filtered, evaporated under vacuum and purified by chromatography on silica gel using DCM/MeOH as eluent, yielding slightly yellow oil (832 mg, 3.28 mmol, 88 %).

**¹H NMR (400 MHz, Chloroform-d) :** \(\delta = 7.46 – 7.41 \text{ (m, 2H)}, 7.36 – 7.30 \text{ (m, 2H)}, 7.27 – 7.19 \text{ (m, 3H)}, 7.18 – 7.10 \text{ (m, 3H)}, 2.62 – 2.55 \text{ (m, 2H)}, 2.38 \text{ (t, } J = 7.1 \text{ Hz, 2H)}, 1.82 – 1.70 \text{ (m, 2H), 1.47 (s, 6H).}
$^{13}$C NMR (Chloroform-$d$, 101 MHz): $\delta = 142.3, 128.5, 128.4, 128.3, 126.4, 125.9, 125.8, 56.2, 42.8, 33.8, 32.5, 29.6.$

IR (neat): $\nu = 3026, 2928, 1495, 1452, 699 \text{ cm}^{-1}.$

HRMS (ESI): Calculated for C$_{18}$H$_{24}$N ([M+H]$^+$): 254.1903; found: 254.1908

$N$-(tert-Butyl)-3,7-dimethyloct-6-en-1-amine 2.72a:

\[
\begin{align*}
\text{Chemical Formula: C}_{18}\text{H}_{24}\text{N} \\
\text{Exact Mass: 211.2300}
\end{align*}
\]

Following general procedure B, (±)-citronellal (1.66 g, 10 mmol, 1 equiv), tert-butylamine (1.06 mL, 10 mmol, 1 equiv), AcOH (1.14 mL, 20 mmol, 2 equiv) and NaBH(OAc)$_3$ (4.23 g, 20 mmol, 2 equiv) were reacted in DCE (25 mL) overnight. Then, the mixture was quenched using a solution of NaOH (1M) and the crude mixture was stirred for further 30 min. The crude mixture was extracted twice with DCM, dried over sodium sulfate, filtered, evaporated under vacuum and purified by chromatography on silica gel using DCM/MeOH as eluent, yielding slightly yellow oil (1.77 g, 8.4 mmol, 84%).

$^1$H NMR (400 MHz, Chloroform-$d$): $\delta = 5.08 - 4.99$ (m, 1H), $2.59 - 2.38$ (m, 2H), $1.99 - 1.85$ (m, 2H), 1.62 (d, $J = 1.3$ Hz, 3H), 1.53 (s, 3H), 1.48 - 1.07 (m, 6H), 1.04 (s, 9H), 0.83 (d, $J = 6.3$ Hz, 3H).

$^{13}$C NMR (Chloroform-$d$, 101 MHz): $\delta = 131.1, 124.9, 50.3, 40.4, 38.3, 37.3, 30.8, 29.1, 25.8, 25.5, 19.7, 17.7.$

IR (neat): $\nu = 2964, 2917, 2362, 1449, 731 \text{ cm}^{-1}.$

HRMS (ESI): Calculated for C$_{14}$H$_{30}$N ([M+H]$^+$): 212.2378; found: 212.2379

$N$-((1S,5R)-6,6-dimethylbicyclo[3.1.1]hept-2-en-3-yl)methyl)-2-methylpropan-2-amine 2.73a:

\[
\begin{align*}
\text{Chemical Formula: C}_{14}\text{H}_{25}\text{N} \\
\text{Exact Mass: 207.1987}
\end{align*}
\]

Following general procedure B, (-)-myrtenal (800 mg, 5.33 mmol, 1 equiv), tert-butylamine (0.565 mL, 5.33 mmol, 1 equiv), AcOH (0.610 mL, 10.7 mmol, 2 equiv) and NaBH(OAc)$_3$ (2.26
g, 10.7 mmol, 2 equiv) were reacted in DCE (25 mL) overnight. Then, the mixture was quenched using a solution of NaOH (1 M) and the crude mixture was stirred for further 30 min. The crude mixture was extracted twice with DCM, dried over sodium sulfate, filtered, evaporated under vacuum and purified by chromatography on silica gel using DCM/MeOH as eluent, yielding slightly yellow oil (970 mg, 4.69 mmol, 88%).

\( ^1H \) NMR (400 MHz, Chloroform-\( d \)) : \( \delta = 5.41 – 5.35 \) (m, 1H), 3.12 – 3.02 (m, 2H), 2.36 (dt, \( J = 8.5, 5.6 \) Hz, 1H), 2.30 – 2.15 (m, 2H), 2.06 (dd, \( J = 5.7, 1.6 \) Hz, 2H), 1.26 (s, 3H), 1.18 (s, 3H), 0.81 (s, 3H).

\( ^{13}C \) NMR (Chloroform-\( d \), 101 MHz) : \( \delta = 146.6, 117.1, 50.9, 47.9, 45.1, 41.0, 38.2, 31.7, 31.3, 28.9, 26.4, 21.2. \)

IR (neat): \( \nu = 2960, 2913, 1483, 733 \) cm\(^{-1} \).

HRMS (ESI): Calculated for C\(_{14}\)H\(_{26}\)N ([M+H]\(^{+}\)) : 208.2060; found: 208.2061

\((S)-2\)-Methyl-N-((4-(prop-1-en-2-yl)cyclohex-1-en-1-yl)methyl)propan-2-amine 2.74a:

Following general procedure B, (\(-\))-perillaldehyde (1.5 g, 10 mmol, 1 equiv), tert-butylamine (1.06 mL, 10 mmol, 1 equiv), AcOH (1.15 mL, 20 mmol, 2 equiv) and NaBH(OAc)\(_3\) (4.23 g, 20 mmol, 2 equiv) were reacted in DCE (25 mL) overnight. Then, the mixture was quenched using a solution of NaOH (1 M) and the crude mixture was stirred for further 30 min. The crude mixture was extracted twice with DCM, dried over sodium sulfate, filtered, evaporated under vacuum and purified by chromatography on silica gel using DCM/MeOH as eluent, yielding slightly yellow oil (1.84 g, 8.9 mmol, 89%).

\( ^1H \) NMR (400 MHz, Chloroform-\( d \)) : \( \delta = 5.64 – 5.57 \) (m, 1H), 4.73 – 4.64 (m, 2H), 3.13 – 3.00 (m, 2H), 2.19 – 2.04 (m, 4H), 2.00 – 1.89 (m, 1H), 1.87 – 1.76 (m, 1H), 1.75 – 1.70 (m, 3H), 1.59 – 1.35 (m, 2H), 1.11 (s, 9H).

\( ^{13}C \) NMR (Chloroform-\( d \), 101 MHz) : \( \delta = 150.2, 136.7, 121.5, 108.6, 50.6, 48.8, 41.4, 30.8, 29.1, 28.1, 20.9. \)

IR (neat): \( \nu = 2960, 2922, 1463, 790 \) cm\(^{-1} \).

HRMS (ESI): Calculated for C\(_{14}\)H\(_{26}\)NO ([M+H]\(^{+}\)) : 208.2060; found: 208.2062
l-Cyclopropyl-N-(2,4,6-trimethoxybenzyl)methanamine 2.76a:

Following general procedure B, 2,4,6-trimethoxybenzaldehyde (1 g, 5.1 mmol, 1 equiv), cyclopropylmethanamine (0.445 mL, 5.1 mmol, 1 equiv), AcOH (0.583 mL, 10.2 mmol, 2 equiv) and NaBH(OAc)₃ (2.16 g, 10.2 mmol, 2 equiv) were reacted in DCE (25 mL) overnight. Then, the mixture was quenched using a solution of NaOH (1M) and the crude mixture was stirred for further 30 min. The crude mixture was extracted twice with DCM, dried over sodium sulfate, filtered, evaporated under vacuum and purified by chromatography on silica gel using DCM/MeOH as eluent, yielding slightly yellow oil (1.25 g, 5.0 mmol, 98 %).

¹H NMR (400 MHz, Chloroform-d): δ = 6.10 (s, 2H), 3.81 – 3.75 (m, 11H), 2.44 (br s, 1H), 2.41 (d, J = 7.0 Hz, 2H), 1.03 – 0.92 (m, 1H), 0.47 – 0.39 (m, 2H), 0.10 – 0.02 (m, 2H).

¹³C NMR (Chloroform-d, 101 MHz): δ = 160.4, 159.4, 109.0, 90.5, 55.7, 55.4, 54.1, 41.3, 11.4, 3.5.

IR (neat): ν = 3000, 2362, 1604, 1459, 1130 cm⁻¹.

HRMS (ESI): Calculated for C₁₆H₂₂NO₃ ([M+H]+): 252.1594; found: 252.1597

II-Dicyclopropyl-N-(2,4,6-trimethoxybenzyl)methanamine 2.77a:

Following general procedure B, 2,4,6-trimethoxybenzaldehyde (697 mg, 3.55 mmol, 1 equiv), dicyclopropylmethanamine (395 mg, 3.55 mmol, 1 equiv), AcOH (0.406 mL, 7.1 mmol, 2 equiv) and NaBH(OAc)₃ (1.5 g, 7.1 mmol, 2 equiv) were reacted in DCE (18 mL) overnight. Then, the mixture was quenched using a solution of NaOH (1M) and the crude mixture was stirred for further 30 min. The crude mixture was extracted twice with DCM, dried over sodium sulfate, filtered, evaporated under vacuum and purified by chromatography on silica gel using DCM/MeOH as eluent, yielding slightly yellow oil (847 mg, 2.91 mmol, 82 %).
\(^1\)H NMR (400 MHz, Chloroform-\(d\)) : \(\delta = 6.08\) (s, 2H), 3.86 (s, 2H), 3.81 – 3.75 (m, 9H), 1.04 (t, \(J = 8.6\) Hz, 1H), 0.96 – 0.85 (m, 2H), 0.48 – 0.37 (m, 4H), 0.20 – 0.07 (m, 4H).

\(^1\)C NMR (Chloroform-\(d\), 101 MHz) : \(\delta = 160.3, 159.3, 109.0, 90.4, 67.0, 55.6, 55.4, 40.2, 16.2, 2.8, 2.2\).

IR (neat): \(\nu = 3001, 2939, 1604, 1459, 1149\) cm\(^{-1}\).

HRMS (ESI): Calculated for C\(_{17}\)H\(_{26}\)NO\(_3\) ([M+H]\(^{+}\)): 292.1907; found: 292.1911

\(N\)-Isopropyl-2,3-dihydro-1\(H\)-inden-2-amine S\(_{2.78a}\):

Following general procedure C, acetone (0.276 mL, 3.75 mmol, 1 equiv), 2,3-dihydro-1\(H\)-inden-2-amine (500 mg, 3.75 mmol, 1 equiv) and Pd/C (400 mg, 10% w/w, 10 mol%) were reacted in MeOH (7 mL) and stirred overnight under H\(_2\) atmosphere. The crude mixture was then filtered through celite, and the solvent evaporated to provide oil \(N\)-isopropyl-2,3-dihydro-1\(H\)-inden-2-amine (526 mg, 3 mmol, 80%).

\(^1\)H NMR (400 MHz, Chloroform-\(d\)) : \(\delta = 7.22 – 7.17\) (m, 2H), 7.17 – 7.11 (m, 3H), 3.74 (p, \(J = 7.1\) Hz, 1H), 3.18 (dd, \(J = 15.4, 7.1\) Hz, 2H), 2.98 (hept, \(J = 6.2\) Hz, 1H), 2.72 (dd, \(J = 15.4, 7.1\) Hz, 2H), 1.27 (br s, 1H), 1.10 (d, \(J = 6.3\) Hz, 6H).

\(^1\)C NMR (Chloroform-\(d\), 101 MHz) : \(\delta = 141.9, 126.5, 124.8, 57.1, 46.6, 40.5, 23.3\).

IR (neat): \(\nu = 2962, 1475, 1175, 741\) cm\(^{-1}\).

HRMS (ESI): Calculated for C\(_{12}\)H\(_{18}\)N ([M+H]\(^{+}\)): 176.1434; found: 176.1437

\(N-(2,4,6\)-Trimethoxybenzyl\)-2,3-dihydro-1\(H\)-inden-2-amine 2.79a:

Following general procedure C, 2,4,6-trimethoxybenzaldehyde (447 mg, 2.28 mmol, 1 equiv), 2,3-dihydro-1\(H\)-inden-2-amine (304 mg, 2.28 mmol, 1 equiv) and Pd/C (243 mg, 10% w/w, 10 mol%) were reacted in MeOH (10 mL) and stirred overnight under H\(_2\) atmosphere. The crude mixture was then filtered through celite, the solvent evaporated and purified by chromatography.
on silica gel to provide oil N-(2,4,6-trimethoxybenzyl)-2,3-dihydro-1H-inden-2-amine (215 mg, 0.684 mmol, 30 %).

\(^1\)H NMR (400 MHz, Chloroform-\(d\)): \(\delta = 7.21 – 7.07\) (m, 4H), 6.12 (s, 2H), 3.84 (s, 2H), 3.81 (s, 9H), 3.60 (p, \(J = 6.9\) Hz, 1H), 3.15 (dd, \(J = 15.6, 7.1\) Hz, 2H), 2.79 (dd, \(J = 15.6, 6.8\) Hz, 2H), 1.73 (br s, 1H).

\(^1^3\)C NMR (Chloroform-\(d\) 101 MHz): \(\delta = 160.4, 159.4, 142.4, 126.3, 124.7, 109.4, 90.5, 58.8, 55.8, 55.5, 40.4, 39.9\).

IR (neat): \(\nu = 2937, 2361, 1597, 1131\) cm\(^{-1}\).

HRMS (ESI): Calculated for C\(_{19}\)H\(_{24}\)NO\(_3\) ([M+H]\(^+\)): 314.1751; found: 314.1754

\(N\)-(2,4,6-Trimethoxybenzyl)-1,2,3,4-tetrahydronaphthalen-1-amine 2.80a:

\[
\begin{align*}
\text{Chemical Formula: } & \text{C}_{20}\text{H}_{26}\text{NO}_3 \\
\text{Exact Mass: } & 327.1834
\end{align*}
\]

Following general procedure B, 2,4,6-trimethoxybenzaldehyde (691 mg, 3.52 mmol, 1 equiv), 1,2,3,4-tetrahydronaphthalen-1-amine (518 mg, 3.52 mmol, 1 equiv), AcOH (0.403 mL, 7.04 mmol, 2 equiv) and NaBH(OAc)\(_3\) (1.49 g, 7.04 mmol, 2 equiv) were reacted in DCE (10 mL) overnight. Then, the mixture was quenched using a solution of NaOH (1M) and the crude mixture was stirred for further 30 min. The crude mixture was extracted twice with DCM, dried over sodium sulfate, filtered, evaporated under vacuum, yielding slightly yellow oil (950 mg, 2.9 mmol, 83 %).

\(^1\)H NMR (250 MHz, Chloroform-\(d\)) \(\delta = 7.11 – 7.02\) (m, 4H), 6.15 (s, 2H), 3.88 (d, \(J = 1.8\) Hz, 2H), 3.82 (s, 9H), 3.72 – 3.66 (m, 1H), 2.90 – 2.61 (m, 2H), 2.12 – 1.95 (m, 3H), 1.87 – 1.61 (m, 2H).

\(^1^3\)C NMR (63 MHz, Chloroform-\(d\)) \(\delta = 160.4, 159.6, 140.0, 137.8, 129.0, 128.8, 126.4, 125.7, 109.7, 90.7, 55.8, 55.5, 54.2, 39.4, 29.7, 28.0, 19.0\).

IR (neat): \(\nu = 2936, 2361, 1607, 1131\) cm\(^{-1}\).

HRMS (ESI): Calculated for C\(_{20}\)H\(_{26}\)NO\(_3\) ([M+H]\(^+\)): 328.1907; found: 328.1912

(R)-\(N\)-(2,4,6-Trimethoxybenzyl)-1,2,3,4-tetrahydronaphthalen-1-amine 2.98a:
Following general procedure B, 2,4,6-trimethoxybenzaldehyde (2.67 g, 13.6 mmol, 1 equiv), (R)-1,2,3,4-tetrahydronaphthalen-1-amine (2 g, 13.6 mmol, 1 equiv), AcOH (1.56 mL, 27.2 mmol, 2 equiv) and NaBH(OAc)₃ (5.76 g, 27.2 mmol, 2 equiv) were reacted in DCE (30 mL) overnight. Then, the mixture was quenched using a solution of NaOH (1M) and the crude mixture was stirred for further 30 min. The crude mixture was extracted twice with DCM, dried over sodium sulfate, filtered, evaporated under vacuum, yielding slightly yellow oil (4.45 g, 13.6 mmol, 100 %).

**1H NMR (250 MHz, Chloroform-d)** $\delta = 7.13 – 7.00$ (m, 4H), $6.15$ (s, 2H), $3.88$ (d, $J = 1.8$ Hz, 2H), $3.82$ (s, 9H), $3.72 – 3.65$ (m, 1H), $2.94 – 2.59$ (m, 2H), $2.22 – 1.93$ (m, 3H), $1.88 – 1.51$ (m, 2H).

**13C NMR (63 MHz, Chloroform-d)** $\delta = 160.4, 159.6, 140.0, 137.8, 129.0, 128.8, 126.4, 125.7, 109.7, 90.7, 55.8, 55.5, 54.2, 39.4, 29.7, 28.0, 19.0$.

**IR (neat):** $\nu = 2938, 2355, 1635, 1115$ cm⁻¹.

**HRMS (ESI):** Calculated for C₂₀H₂₆NO₃ ([M+H]+): 328.1907; found: 328.1912

**N-(2,4,6-trimethoxybenzyl)pentan-3-amine 2.83a:**

Following general procedure B, 2,4,6-trimethoxybenzaldehyde (1 g, 5.1 mmol, 1 equiv), Penta-3-amine (0.88 g, 10.2 mmol, 2 equiv), AcOH (0.58 mL, 10.2 mmol, 2 equiv) and NaBH(OAc)₃ (2.16 g, 10.2 mmol, 2 equiv) were reacted in DCE (25 mL) overnight. Then, the mixture was quenched using a solution of NaOH (1M) and the crude mixture was stirred for further 30 min. The crude mixture was extracted twice with DCM, dried over sodium sulfate, filtered, evaporated under vacuum, yielding slightly yellow oil (1.02 g, 3.8 mmol, 75 %).

**1H NMR (400 MHz, Chloroform-d)** $\delta = 6.07$ (s, 2H), $3.76$ (s, 3H), $3.76$ (s, 6H), $3.71$ (s, 2H), $2.20$ (p, $J = 6.0$ Hz, 1H), $1.91$ (s, 1H), $1.46 – 1.26$ (m, 4H), $0.81$ (t, $J = 7.5$ Hz, 6H).
**$^{13}$C NMR (101 MHz, Chloroform-\textit{d})** $\delta = 160.2, 159.4, 109.7, 90.5, 59.3, 55.7, 55.4, 38.8, 26.1, 10.2.$

**IR (neat):** $\nu = 2928, 2840, 1623, 1139 \text{ cm}^{-1}.$

**HRMS (ESI):** Calculated for C$_{20}$H$_{26}$NO$_3$ ([M+H]$^+$): 269.1913; found: 269.1917

**Synthesis of carbamoyl chlorides**

The carbamoyl chlorides were not submitted to heating. The carbamoyl chlorides were freshly used and stored in a freezer (–30 °C). The yield of the reaction did not show any loss of efficiency after storing in the freezer for several days.

**Isopropyl(2,4,6-trimethoxybenzyl)carbamoyl chloride 2.54c:**

\[ 
\text{Chemical Formula: C}_{14}\text{H}_{20}\text{ClNO}_4 
\]

Following general procedure for the synthesis of carbamoyl chlorides, $N$-(2,4,6-trimethoxybenzyl)propan-2-amine (800 mg, 3.34 mmol 1 equiv) dissolved in dry benzene (8 mL, 0.4M) and Et$_3$N (0.560 mL, 4.01 mmol, 1.2 equiv) were slowly added to a stirred solution of triphosgene (337 mg, 1.14 mmol, 0.34 equiv) in dry benzene (8 mL, 0.4M) at 0 °C. The mixture was then slowly allowed to reach rt and was stirred overnight. The crude mixture was then quenched with HCl solution (1M) and extracted twice with DCM. The combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum. The excess of benzene was removed by coevaporation with CHCl$_3$. The desired carbamoyl chloride was obtained as a grey solid (792 mg, 2.74 mmol, 82 %) and used without further purification.

**$^1$H NMR (400 MHz, Chloroform-\textit{d})** $\delta = 6.11$ (s, 2H), 4.72 (s, 2H), 3.83 – 3.82 (m, 9H), 3.57 (sept, $J = 6.8$ Hz, 1H), 1.11 (d, $J = 6.8$ Hz, 6H).

**Ethyl(2,4,6-trimethoxybenzyl)carbamoyl chloride 2.53c:**

\[ 
\text{Chemical Formula: C}_{13}\text{H}_{14}\text{ClNO}_4 
\]

Following general procedure for the synthesis of carbamoyl chlorides, $N$-(2,4,6-trimethoxybenzyl)ethanamine (401 mg, 1.78 mmol, 1 equiv) dissolved in dry benzene (4.5 mL, 0.4M) and Et$_3$N (0.560 mL, 4.01 mmol, 1.2 equiv) were slowly added to a stirred solution of triphosgene (337 mg, 1.14 mmol, 0.34 equiv) in dry benzene (8 mL, 0.4M) at 0 °C. The mixture was then slowly allowed to reach rt and was stirred overnight. The crude mixture was then quenched with HCl solution (1M) and extracted twice with DCM. The combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum. The excess of benzene was removed by coevaporation with CHCl$_3$. The desired carbamoyl chloride was obtained as a grey solid (792 mg, 2.74 mmol, 82 %) and used without further purification.
0.4M) and Et$_3$N (0.301 mL, 2.14 mmol, 1.2 equiv) were slowly added to a stirred solution of triphosgene (180 mg, 0.60 mmol, 0.34 equiv) in dry benzene (4.5 mL, 0.4M) at 0 °C. The mixture was then slowly allowed to reach rt and was stirred overnight. The crude mixture was then quenched with HCl solution (1M) and extracted twice with DCM. The combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum. The excess of benzene was removed by coevaporation with CHCl$_3$. The desired carbamoyl chloride was obtained as a white solid (472 mg, 1.64 mmol, 92 %) and used without further purification.

$^1$H NMR (400 MHz, Chloroform-d) $\delta =$ 6.11 (s, 2H), 4.69 – 4.66 (m, 2H), 3.82 (s, 3H), 3.81 (s, 6H), 3.31 – 3.17 (m, 2H), 1.06 – 1.01 (m, 3H).

**Tert-butyl(2,4,6-trimethoxybenzyl)carbamoyl chloride 2.55c:**

Following general procedure for the synthesis of carbamoyl chlorides, 2-methyl-$N$-(2,4,6-trimethoxybenzyl)propan-2-amine (400 mg, 1.58 mmol, 1 equiv) dissolved in dry benzene (4 mL, 0.4M) and Et$_3$N (0.267 mL, 1.90 mmol, 1.2 equiv) were slowly added to a stirred solution of triphosgene (159 mg, 0.537 mmol, 0.34 equiv) in dry benzene (4 mL, 0.4M) at 0 °C. The mixture was then slowly allowed to reach rt and was stirred overnight. The crude mixture was then quenched with HCl solution (1M) and extracted twice with DCM. The combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum. The excess of benzene was removed by coevaporation with CHCl$_3$. The desired carbamoyl chloride was obtained as a yellowish oil (229 mg, 0.73 mmol, 46 %) and used without further purification.

$^1$H NMR (250 MHz, Chloroform-d) $\delta =$ 6.07 (s, 2H), 4.12 – 4.04 (m, 2H), 3.87 (s, 6H), 3.78 (s, 3H), 1.33 (s, 9H).

**2-(Phenylpropan-2-yl)(2,4,6-trimethoxybenzyl)carbamoyl chloride 2.56c:**
Following general procedure for the synthesis of carbamoyl chlorides, 2-phenyl-N-(2,4,6-trimethoxybenzyl)propan-2-amine (400 mg, 1.27 mmol, 1 equiv) dissolved in dry benzene (3.8 mL, 0.4M) and Et3N (0.214 mL, 1.52 mmol, 1.2 equiv) were slowly added to a stirred solution of triphosgene (128 mg, 0.432 mmol, 0.34 equiv) in dry benzene (3.8 mL, 0.4M) at 0 °C. The mixture was then slowly allowed to reach rt and was stirred overnight. The crude mixture was then quenched with HCl solution (1M) and extracted twice with DCM. The combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum. The excess of benzene was removed by coevaporation with CHCl3. The desired carbamoyl chloride was obtained as an orange oil (341 mg, 0.9 mmol, 71 %) and used without further purification.

\[ ^1H\text{ NMR (400 MHz, Chloroform-d)} \delta = 7.70 – 7.61 (m, 2H), 7.41 – 7.36 (m, 3H), 5.93 (s, 2H), 3.81 (s, 6H), 3.70 (s, 3H), 1.83 (s, 6H). \]

(S)-(3,3-Dimethylbutan-2-yl)(2,4,6-trimethoxybenzyl)carbamoyl chloride 2.57c:

\[ \text{Chemical Formula: C}_{17}\text{H}_{36}\text{ClNO}_4 \]

Following general procedure for the synthesis of carbamoyl chlorides, (S)-3,3-dimethyl-N-(2,4,6-trimethoxybenzyl)butan-2-amine (300 mg, 1.07 mmol, 1 equiv) dissolved in dry benzene (2.7 mL, 0.4M) and Et3N (0.180 mL, 1.28 mmol, 1.2 equiv) were slowly added to a stirred solution of triphosgene (108 mg, 0.367 mmol, 0.34 equiv) in dry benzene (2.7 mL, 0.4M) at 0 °C. The mixture was then slowly allowed to reach rt and was stirred overnight. The crude mixture was then quenched with HCl solution (1M) and extracted twice with DCM. The combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum. The excess of benzene was removed by coevaporation with CHCl3. The desired carbamoyl chloride was obtained as a greenish solid (304 mg, 0.89 mmol, 84 %) and used without further purification.

\[ ^1H\text{ NMR (400 MHz, Chloroform-d)} \delta = 6.16 – 6.10 (m, 2H), 5.04 – 4.45 (m, 2H), 3.87 – 3.78 (m, 9H), 3.16 – 2.35 (m, 1H), 1.42 – 1.02 (m, 3H), 0.99 – 0.90 (m, 9H). \]

(cyclopropylmethyl)(2,4,6-trimethoxybenzyl)carbamoyl chloride 2.76c:
Following general procedure for the synthesis of carbamoyl chlorides, 1-cyclopropyl-N-(2,4,6-trimethoxybenzyl)methanamine (400 mg, 1.59 mmol 1 equiv) dissolved in dry benzene (4 mL, 0.4M) and Et₃N (0.268 mL, 1.91 mmol, 1.2 equiv) were slowly added to a stirred solution of triphosgene (161 mg, 0.541 mmol, 0.34 equiv) in dry benzene (4 mL, 0.4M) at 0 °C. The mixture was then slowly allowed to reach rt and was stirred overnight. The crude mixture was then quenched with HCl solution (1M) and extracted twice with DCM. The combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum. The excess of benzene was removed by coevaporation with CHCl₃. The desired carbamoyl chloride was obtained as a yellow oil (428 mg, 1.36 mmol, 86 %) and used without further purification.

\[^{1}H\text{ NMR (250 MHz, Chloroform-d)}\delta = 6.10 (s, 2H), 4.77 – 4.71 (m, 2H), 3.80 (s, 3H), 3.79 (s, 9H), 3.09 – 3.01 (m, 2H), 1.21 (m, 1H), 0.51 – 0.35 (m, 2H), 0.27 – 0.10 (m, 2H).

(S)-Octan-2-yl(2,4,6-trimethoxybenzyl)carbamoyl chloride 2.58c:

Following general procedure for the synthesis of carbamoyl chlorides, (S)-N-(2,4,6-trimethoxybenzyl)octan-2-amine (400 mg, 2.45 mmol, 1 equiv) dissolved in dry benzene (7.5 mL, 0.4M) and Et₃N (0.413 mL, 2.94 mmol, 1.2 equiv) were slowly added to a stirred solution of triphosgene (247 mg, 0.833 mmol, 0.34 equiv) in dry benzene (7.5 mL, 0.4M) at 0 °C. The mixture was then slowly allowed to reach rt and was stirred overnight. The crude mixture was then quenched with HCl solution (1M) and extracted twice with DCM. The combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum. The excess of benzene was removed by coevaporation with CHCl₃. The desired carbamoyl chloride was obtained as a yellowish solid (515 mg, 2.28 mmol, 93 %) and used without further purification.
$^1$H NMR (400 MHz, Chloroform-d) $\delta = 6.12 - 6.10$ (m, 2H), 4.78 – 4.64 (m, 2H), 3.82 (s, 3H), 3.82 (s, 6H), 3.32 (dt, $J = 8.1$, 6.4 Hz, 1H), 1.84 – 1.72 (m, 1H), 1.46 – 1.33 (m, 1H), 1.30 – 1.10 (m, 8H), 1.05 (d, $J = 6.7$ Hz, 3H), 0.86 (t, $J = 7.0$ Hz, 3H).

(R)-(1-Cyclohexylethyl)(2,4,6-trimethoxybenzyl)carbamoyl chloride 2.59c:

Following general procedure for the synthesis of carbamoyl chlorides, (R)-1-cyclohexyl-N-(2,4,6-trimethoxybenzyl)ethan-1-amine (600 mg, 1.95 mmol, 1 equiv) dissolved in dry benzene (5.0 mL, 0.4M) and Et3N (0.329 mL, 2.34 mmol, 1.2 equiv) were slowly added to a stirred solution of triphosgene (197 mg, 0.663 mmol, 0.34 equiv) in dry benzene (5.0 mL, 0.4M) at 0 °C . The mixture was then slowly allowed to reach rt and was stirred overnight. The crude mixture was then quenched with HCl solution (1M) and extracted twice with DCM. The combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum. The excess of benzene was removed by coevaporation with CHCl3. The desired carbamoyl chloride was obtained as a red oil (528 mg, 1.42 mmol, 73 %) and used without further purification.

$^1$H NMR (400 MHz, Chloroform-d) $\delta = 6.11$ (s, 2H), 4.82 (d, $J = 14.2$ Hz, 1H), 4.57 (d, $J = 14.1$ Hz, 1H), 3.82 (s, 3H), 3.81 (s, 6H), 2.89 (dq, $J = 10.2$, 6.7 Hz, 1H), 1.96 – 1.85 (m, 1H), 1.78 – 1.60 (m, 4H), 1.26 – 1.04 (m, 4H), 1.00 (d, $J = 6.8$ Hz, 3H), 0.75 – 0.52 (m, 2H).

(R)-2-((Chlorocarbonyl)(2,4,6-trimethoxybenzyl)amino)propyl pivalate 2.60c:
Following general procedure for the synthesis of carbamoyl chlorides, (R)-2-((2,4,6-trimethoxybenzyl)amino)propyl pivalate (188 mg, 0.553 mmol, 1 equiv) dissolved in dry benzene (1.4 mL, 0.4M) and Et3N (0.093 mL, 0.66 mmol, 1.2 equiv) were slowly added to a stirred solution of triphosgene (56 mg, 0.188 mmol, 0.34 equiv) in dry benzene (1.4 mL, 0.4M) at 0 °C. The mixture was then slowly allowed to reach rt and was stirred overnight. The crude mixture was then quenched with HCl solution (1M) and extracted twice with DCM. The combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum. The excess of benzene was removed by coevaporation with CHCl3. The desired carbamoyl chloride was obtained as a brownish solid (190 mg, 0.47 mmol, 85 %) and used without further purification.

**1H NMR (250 MHz, Chloroform-d)** \(\delta = 6.11 \text{ (s, 2H)}, 4.90 \text{ (d, } J = 14.3 \text{ Hz, 1H)}, 4.62 \text{ (d, } J = 14.3 \text{ Hz, 1H)}, 4.33 \text{ (dd, } J = 11.2, 9.1 \text{ Hz, 1H)}, 4.07 \text{ (dd, } J = 11.2, 5.3 \text{ Hz, 1H}), 3.82 \text{ (s, 3H)}, 3.81 \text{ (s, 6H)}, 3.73 – 3.59 \text{ (m, 1H)}, 1.21 \text{ (s, 9H)}, 0.99 \text{ (d, } J = 6.9 \text{ Hz, 3H}).

(S)-(1-Phenylethyl)(2,4,6-trimethoxybenzyl)carbamoyl chloride 2.61c:

![Chemical Structure](https://example.com/structure.png)

Following general procedure for the synthesis of carbamoyl chlorides, (S)-1-phenyl-N-(2,4,6-trimethoxybenzyl)ethan-1-amine (300 mg, 0.995 mmol, 1 equiv) dissolved in dry benzene (3.9 mL, 0.4M) and Et3N (0.167 mL, 1.19 mmol, 1.2 equiv) were slowly added to a stirred solution of triphosgene (100 mg, 0.338 mmol, 0.34 equiv) in dry benzene (3.9 mL, 0.4M) at 0 °C. The mixture was then slowly allowed to reach rt and was stirred overnight. The crude mixture was then quenched with HCl solution (1M) and extracted twice with DCM. The combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum. The excess of benzene was removed by coevaporation with CHCl3. The desired carbamoyl chloride was obtained as a brownish solid (325 mg, 0.9 mmol, 90 %) and used without further purification.

**1H NMR (400 MHz, Chloroform-d)** \(\delta = 7.24 – 7.16 \text{ (m, 5H)}, 6.09 – 5.98 \text{ (m, 2H)}, 4.89 – 4.80 \text{ (m, 2H)}, 4.74 – 4.64 \text{ (m, 1H)}, 3.81 \text{ (s, 3H)}, 3.78 \text{ (s, 6H)}, 1.50 \text{ (d, } J = 7.1 \text{ Hz, 3H}).

(Cyclopentylmethyl)(isopropyl)carbamoyl chloride 2.63c:
Following general procedure for the synthesis of carbamoyl chlorides, \( N \)-(cyclopentylmethyl)propan-2-amine (400 mg, 2.83 mmol, 1 equiv) dissolved in dry benzene (8.5 mL, 0.4M) and Et₃N (0.477 mL, 3.40 mmol, 1.2 equiv) were slowly added to a stirred solution of triphosgene (286 mg, 0.962 mmol, 0.34 equiv) in dry benzene (8.5 mL, 0.4M) at 0 \(^\circ\)C. The mixture was then slowly allowed to reach rt and was stirred overnight. The crude mixture was then quenched with HCl solution (1M) and extracted twice with DCM. The combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum. The excess of benzene was removed by coevaporation with CHCl₃. The desired carbamoyl chloride was obtained as a yellowish oil (507 mg, 2.49 mmol, 88 %) and used without further purification.

\(^1\)H NMR (400 MHz, Chloroform-d) \( \delta = 4.55 – 3.77 \) (m, 1H), \( 3.40 – 3.20 \) (m, 2H), \( 2.28 – 2.15 \) (m, 1H), \( 1.82 – 1.50 \) (m, 8H), \( 1.37 – 1.19 \) (m, 6H).

Isopropyl(2,4, 6-trimethylbenzyl)carbamoyl chloride 2.64c:

Following general procedure for the synthesis of carbamoyl chlorides, \( N \)-isopropyl-3-phenylpropan-1-amine (400 mg, 2.09 mmol, 1 equiv) dissolved in dry benzene (5.2 mL, 0.4M) and Et₃N (0.352 mL, 2.51 mmol, 1.2 equiv) were slowly added to a stirred solution of triphosgene (211 mg, 0.711 mmol, 0.34 equiv) in dry benzene (5.2 mL, 0.4M) at 0 \(^\circ\)C. The mixture was then slowly allowed to reach rt and was stirred overnight. The crude mixture was then quenched with HCl solution (1M) and extracted twice with DCM. The combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum. The excess of benzene was removed by coevaporation with CHCl₃. The desired carbamoyl chloride was obtained as a brownish solid (418 mg, 1.65 mmol, 79 %) and used without further purification.

\(^1\)H NMR (400 MHz, Chloroform-d) \( \delta = 6.87 \) (s, 2H), \( 4.76 \) (s, 2H), \( 3.23 – 3.10 \) (m, 1H), \( 2.33 \) (s, 6H), \( 2.28 \) (s, 3H), \( 1.20 \) (d, \( J = 6.8 \) Hz, 6H).

Isopropyl(phenyl)carbamoyl chloride 2.65c:
Following general procedure A, aniline (130 mg, 1.4 mmol, 1 equiv), acetone (0.103 mL, 1.4 mmol, 1 equiv) and 4Å MS (200 mg) were stirred for 4h in THF (14 mL). Then, a solution of NaBH₄ (106 mg, 2.8 mmol, 2 equiv) in EtOH (5 mL) was carefully added to the mixture. The reaction was stirred at room temperature overnight, and was then filtered through celite. The crude mixture was then acidified using a solution of HCl (0.1M) and stirred for 30 min. The mixture was then basified using NaOH solution (0.1M) and extracted three times using AcOEt. The combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum.

Following general procedure for the synthesis of carbamoyl chlorides, N-isopropylaniline (189 mg, 1.4 mmol, 1 equiv) dissolved in dry benzene (3.5 mL, 0.4M) and Et₃N (0.236 mL, 1.36 mmol, 1.2 equiv) were slowly added to a stirred solution of triphosgene (141 mg, 2.01 mmol, 0.34 equiv) in dry benzene (3.5 mL, 0.4M) at 0 °C . The mixture was then slowly allowed to reach rt and was stirred overnight. The crude mixture was then quenched with HCl solution (1M) and extracted twice with DCM. The combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum. The excess of benzene was removed by coevaporation with CHCl₃. The desired carbamoyl chloride was obtained as a yellowish solid (218 mg, 1.1 mmol, 79 %) and used without further purification.

1H NMR (400 MHz, Chloroform-d) δ = 7.45 – 7.39 (m, 2H), 7.18 – 7.14 (m, 2H), 4.68 (sept, J = 6.8 Hz, 1H), 1.17 (d, J = 6.8 Hz, 6H).

Benzyl(isopropyl)carbamoyl chloride 2.65c:

Following general procedure for the synthesis of carbamoyl chlorides, N-benzylpropan-2-amine (150 mg, 1.1 mmol, 1 equiv) dissolved in dry benzene (2.5 mL, 0.4M) and Et₃N (0.170 mL, 1.21 mmol, 1.2 equiv) were slowly added to a stirred solution of triphosgene (102 mg, 0.343 mmol, 0.34 equiv) in dry benzene (2.5 mL, 0.4M) at 0 °C . The mixture was then slowly allowed to reach rt and was stirred overnight. The crude mixture was then quenched with HCl solution
and extracted twice with DCM. The combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum. The excess of benzene was removed by coevaporation with CHCl₃. The desired carbamoyl chloride was obtained as a yellowish solid (64 mg, 0.33 mmol, 30 %) and used without further purification.

**1H NMR (400 MHz, Chloroform-d) δ = 7.39 – 7.27 (m, 5H), 4.67 (s, 2H), 4.30 – 4.20 (m, 1H), 1.20 (d, J = 6.8 Hz, 6H).**

**Isopropyl(phenethyl)carbamoyl chloride 2.66c:**

Following general procedure for the synthesis of carbamoyl chlorides, N-phenethylpropan-2-amine (400 mg, 2.45 mmol, 1 equiv) dissolved in dry benzene (7.5 mL, 0.4M) and Et₃N (0.413 mL, 2.94 mmol, 1.2 equiv) were slowly added to a stirred solution of triphosgene (247 mg, 0.833 mmol, 0.34 equiv) in dry benzene (7.5 mL, 0.4M) at 0 °C. The mixture was then slowly allowed to reach rt and was stirred overnight. The crude mixture was then quenched with HCl solution (1M) and extracted twice with DCM. The combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum. The excess of benzene was removed by coevaporation with CHCl₃. The desired carbamoyl chloride was obtained as a yellowish solid (515 mg, 2.28 mmol, 93 %) and used without further purification.

**1H NMR (400 MHz, Chloroform-d) δ = 7.37 – 7.18 (m, 5H), 4.61 – 4.27 (m, 1H), 3.55 – 3.37 (m, 2H), 3.02 – 2.89 (m, 2H), 1.29 – 1.18 (m, 6H).**

**Isopropyl(3-phenylpropyl)carbamoyl chloride 2.67c:**

Following general procedure for the synthesis of carbamoyl chlorides, N-isopropyl-3-phenylpropan-1-amine (302 mg, 0.916 mmol, 1 equiv) dissolved in dry benzene (2.4 mL, 0.4M) and Et₃N (0.154 mL, 1.1 mmol, 1.2 equiv) were slowly added to a stirred solution of triphosgene (96 mg, 0.311 mmol, 0.34 equiv) in dry benzene (2.4 mL, 0.4M) at 0 °C. The mixture was then slowly allowed to reach rt and was stirred overnight. The crude mixture was then quenched
with HCl solution (1M) and extracted twice with DCM. The combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum. The excess of benzene was removed by coevaporation with CHCl₃. The desired carbamoyl chloride was obtained as a brownish solid (298 mg, 0.76 mmol, 83 %) and used without further purification.

**¹H NMR (400 MHz, Chloroform-d)** δ = 7.33 – 7.27 (m, 2H), 7.25 – 7.16 (m, 3H), 4.56 – 4.16 (m 1H), 3.35 – 3.09 (m, 2H), 2.71 – 2.49 (m, 2H), 2.08 – 1.87 (m, 2H), 1.22 – 1.14 (m, 6H).

**Ethyl 3-((chlorocarbonyl)(isopropyl)amino)propanoate 2.68c:**

![Chemical Structure](image1)

Chemical Formula: C₉H₁₆ClNO₃

Following general procedure for the synthesis of carbamoyl chlorides, ethyl 3-((isopropylamino)propanoate (400 mg, 2.52 mmol, 1 equiv) dissolved in dry benzene (7.5 mL, 0.4M) and Et₃N (0.425 mL, 3.02 mmol, 1.2 equiv) were slowly added to a stirred solution of triphosgene (254 mg, 0.857 mmol, 0.34 equiv) in dry benzene (7.5 mL, 0.4M) at 0 °C . The mixture was then slowly allowed to reach rt and was stirred overnight. The crude mixture was then quenched with HCl solution (1M) and extracted twice with DCM. The combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum. The excess of benzene was removed by coevaporation with CHCl₃. The desired carbamoyl chloride was obtained as an orange oil (465 mg, 2.09 mmol, 83 %) and used without further purification.

**¹H NMR (400 MHz, Chloroform-d)** δ = 4.60 – 4.26 (m, 1H), 4.21 – 4.11 (m, 2H), 3.67 – 3.49 (m, 2H), 2.74 – 2.62 (m, 2H), 1.32 – 1.21 (m, 9H).

**{(3-((1,3-Dioxoisodolin-2-yl)propyl)(isopropyl)carbamoyl chloride 2.69c:**

![Chemical Structure](image2)

Chemical Formula: C₁₅H₁₇ClN₃O₃

Following general procedure for the synthesis of carbamoyl chlorides, 2-((isopropylamino)propyl)isoindoline-1,3-dione (300 mg, 1.22 mmol 1 equiv) dissolved in dry benzene (3.1 mL, 0.4M) and Et₃N (0.206 mL, 1.46 mmol, 1.2 equiv) were slowly added to a stirred solution of triphosgene (123 mg, 0.415 mmol, 0.34 equiv) in dry benzene (3.1 mL, 0.4M) at 0 °C . The mixture was then slowly allowed to reach rt and was stirred overnight. The crude
mixture was then quenched with HCl solution (1M) and extracted twice with DCM. The combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum. The excess of benzene was removed by coevaporation with CHCl₃. The desired carbamoyl chloride was obtained as a yellowish solid (302 mg, 1.0 mmol, 82%) and used without further purification.

**¹H NMR (400 MHz, Chloroform-d)** δ = 8.08 – 7.67 (m, 4H), 4.57 – 4.17 (m, 1H), 3.77 – 3.69 (m, 2H), 3.54 – 3.26 (m, 2H), 2.08 – 2.00 (m, 2H), 1.28 – 1.22 (m, 6H).

**Tert-pentyl(3-phenylpropyl)carbamoyl chloride 2.70c:**

Following general procedure for the synthesis of carbamoyl chlorides, 2-methyl-N-(3-phenylpropyl)butan-2-amine (400 mg, 1.95 mmol, 1 equiv) dissolved in dry benzene (5 mL, 0.4M) and Et₃N (0.329 mL, 2.34 mmol, 1.2 equiv) were slowly added to a stirred solution of triphosgene (197 mg, 0.663 mmol, 0.34 equiv) in dry benzene (5 mL, 0.4M) at 0 °C. The mixture was then slowly allowed to reach rt and was stirred overnight. The crude mixture was then quenched with HCl solution (1M) and extracted twice with DCM. The combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum. The excess of benzene was removed by coevaporation with CHCl₃. The desired carbamoyl chloride was obtained as a yellowish oil (400 mg, 1.53 mmol, 77%) and used without further purification.

**¹H NMR (400 MHz, Chloroform-d)** δ = 7.33 – 7.17 (m, 5H), 3.45 (t, J = 8.4 Hz, 2H), 2.61 (t, J = 7.6 Hz, 2H), 2.03 – 1.93 (m, 2H), 1.83 (q, J = 7.5 Hz, 2H), 1.34 (s, 6H), 0.80 (t, J = 7.5 Hz, 3H).

**(2-Phenylpropan-2-yl)(3-phenylpropyl)carbamoyl chloride 2.71c:**

Following general procedure for the synthesis of carbamoyl chlorides, 3-phenyl-N-(2-phenylpropan-2-yl)propan-1-amine (250 mg, 0.987 mmol 1 equiv) dissolved in dry benzene
(2.5mL, 0.4M) and Et₃N (0.166 mL, 1.18 mmol, 1.2 equiv) were slowly added to a stirred solution of triphosgene (100 mg, 0.336 mmol, 0.34 equiv) in dry benzene (2.5 mL, 0.4M) at 0 °C. The mixture was then slowly allowed to reach rt and was stirred overnight. The crude mixture was then quenched with HCl solution (1M) and extracted twice with DCM. The combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum. The excess of benzene was removed by coevaporation with CHCl₃. The desired carbamoyl chloride was obtained as a white solid (290 mg, 0.91 mmol, 92 %) and used without further purification.

1H NMR (400 MHz, Chloroform-d) δ 7.34 – 7.26 (m, 5H), 7.25 – 7.18 (m, 5H), 3.65 – 3.58 (m, 1H), 2.65 (t, J = 7.6 Hz, 2H), 2.19 – 2.11 (m, 2H), 1.68 (s, 6H).

Tert-butyl(3,7-dimethyloct-6-en-1-yl)carbamoyl chloride 2.72c:

Following general procedure for the synthesis of carbamoyl chlorides, N-(tert-butyl)-3,7-dimethyloct-6-en-1-amine (400 mg, 1.89 mmol, 1 equiv) dissolved in dry benzene (5.6 mL, 0.4M) and Et₃N (0.319 mL, 2.27 mmol, 1.2 equiv) were slowly added to a stirred solution of triphosgene (191 mg, 0.643 mmol, 0.34 equiv) in dry benzene (5.6 mL, 0.4M) at 0 °C. The mixture was then slowly allowed to reach rt and was stirred overnight. The crude mixture was then quenched with HCl solution (1M) and extracted twice with DCM. The combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum. The excess of benzene was removed by coevaporation with CHCl₃. The desired carbamoyl chloride was obtained as a yellowish solid (404 mg, 1.47 mmol, 78 %) and used without further purification.

1H NMR (400 MHz, Chloroform-d) δ = 5.07 (dtd, J = 7.1, 3.5, 2.7, 1.4 Hz, 1H), 3.59 – 3.40 (m, 2H), 1.99 (dq, J = 14.3, 7.3 Hz, 2H), 1.68 (d, J = 1.4 Hz, 3H), 1.71 – 1.62 (m, 1H), 1.60 (s, 3H), 1.45 (s, 9H), 1.38 – 1.13 (m, 3H) 0.92 (d, J = 6.4 Hz, 3H).

Tert-butyl((1S,5R)-6,6-dimethylbicyclo[3.1.1]hept-2-en-3-yl)methyl)carbamoyl chloride 2.73c:
Following general procedure for the synthesis of carbamoyl chloride, dimethylbicyclo[3.1.1]hept-2-en-2-yl)methyl)-2-methylpropan-2-amine (280 mg, 1.35 mmol, 1 equiv) dissolved in dry benzene (3.5 mL, 0.4M) and Et₃N (0.228 mL, 1.62 mmol, 1.2 equiv) were slowly added to a stirred solution of triphosgene (136 mg, 0.459 mmol, 0.34 equiv) in dry benzene (3.5 mL, 0.4M) at 0 °C. The mixture was then slowly allowed to reach rt and was stirred overnight. The crude mixture was then quenched with HCl solution (1M) and extracted twice with DCM. The combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum. The excess of benzene was removed by coevaporation with CHCl₃. The desired carbamoyl chloride was obtained as a yellowish solid (270 mg, 1.0 mmol, 74 %) and used without further purification.

H NMR (400 MHz, Chloroform-d)  δ = 5.39 – 5.35 (m, 1H), 4.12 – 3.92 (m, 2H), 2.44 – 2.21 (m, 4H), 2.13 (dt, J = 5.8, 2.9, 1.3 Hz, 1H), 1.95 (td, J = 5.6, 1.6 Hz, 1H), 1.46 (s, 9H), 1.29 (s, 3H), 0.86 (s, 3H).

(S)-Tert-butyl((4-(prop-1-en-2-yl)cyclohex-1-en-1-yl)methyl)carbamoyl chloride 2.74c:

Following general procedure for the synthesis of carbamoyl chlorides, (S)-2-methyl-N-((4-(prop-1-en-2-yl)cyclohex-1-en-1-yl)methyl)propan-2-amine (259 mg, 1.25 mmol 1 equiv) dissolved in dry benzene (3.8 mL, 0.4M) and Et₃N (0.211 mL, 1.5 mmol, 1.2 equiv) were slowly added to a stirred solution of triphosgene (126 mg, 0.425 mmol, 0.34 equiv) in dry benzene (3.8 mL, 0.4M) at 0 °C. The mixture was then slowly allowed to reach rt and was stirred overnight. The crude mixture was then quenched with HCl solution (1M) and extracted twice with DCM. The combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum. The excess of benzene was removed by coevaporation with CHCl₃. The desired carbamoyl chloride was obtained as a reddish oil (300 mg, 1.11 mol, 89 %) and used without further purification.
\[\text{H NMR (400 MHz, Chloroform-}d\text{)} \delta = 5.61 - 5.58 \text{ (m, 1H), 4.76 - 4.65} \text{ (m, 2H), 4.15 - 3.94} \text{ (m, 2H), 2.23 - 2.11} \text{ (m, 2H), 2.07 - 1.81} \text{ (m, 2H), 1.74 (s, 3H), 1.44 (s, 9H).}\]

**3,3-Dimethyl-1-oxa-4-azaspiro[4.5]decane-4-carbamoyl chloride 2.75c:**

Following general procedure for the synthesis of carbamoyl chlorides, 3,3-dimethyl-1-oxa-4-azaspiro[4.5]decane (1 g, 5.91 mmol, 1 equiv) dissolved in dry benzene (15 mL, 0.4M) and Et\textsubscript{3}N (0.997 mL, 7.10 mmol, 1.2 equiv) were slowly added to a stirred solution of triphosgene (596 mg, 2.01 mmol, 0.34 equiv) in dry benzene (15 mL, 0.4M) at 0 °C. The mixture was then slowly allowed to reach rt and was stirred overnight. The crude mixture was then quenched with HCl solution (1M) and extracted twice with DCM. The combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum. The excess of benzene was removed by coevaporation with CHCl\textsubscript{3}. The desired carbamoyl chloride was obtained as a yellowish solid (1.29 g, 5.55 mmol, 94 %) and used without further purification.

\[\text{H NMR (400 MHz, Chloroform-}d\text{)} \delta = 3.79 - 3.71 \text{ (m, 2H), 2.57 - 2.29} \text{ (m, 2H), 1.73 - 1.55} \text{ (m, 7H), 1.53 - 1.44} \text{ (m, 6H), 1.27 - 1.15} \text{ (m, 1H).}\]

**Cyclopropylmethyl)(2,4,6-trimethoxybenzyl)carbamoyl chloride 2.76c:**

Following general procedure for the synthesis of carbamoyl chlorides, 1-cyclopropyl-N-(2,4,6-trimethoxybenzyl)methanamine (400 mg, 1.59 mmol, 1 equiv) dissolved in dry benzene (4 mL, 0.4M) and Et\textsubscript{3}N (0.268 mL, 1.91 mmol, 1.2 equiv) were slowly added to a stirred solution of triphosgene (161 mg, 0.541 mmol, 0.34 equiv) in dry benzene (4 mL, 0.4M) at 0 °C. The mixture was then slowly allowed to reach rt and was stirred overnight. The crude mixture was then quenched with HCl solution (1M) and extracted twice with DCM. The combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum. The excess of benzene
was removed by coevaporation with CHCl₃. The desired carbamoyl chloride was obtained as a yellowish solid (428 mg, 1.36 mmol, 83%) and used without further purification.

**¹H NMR (250 MHz, Chloroform-d)**:  δ = 6.10 (s, 2H), 4.78 (s, 1H), 4.69 (s, 1H), 3.81 – 3.78 (m, 9H), 3.05 (dd, J = 18.5, 7.2 Hz, 2H), 1.26 – 1.16 (m, 1H), 0.55 – 0.32 (m, 2H), 0.29 – 0.12 (m, 2H).

(Dicyclopymethyl)(2,4,6-trimethoxybenzyl)carbamoyl chloride 2.77c:

Following general procedure for the synthesis of carbamoyl chlorides, 1,1-dicyclopymethyl-N-(2,4,6-trimethoxybenzyl)methanamine (300 mg, 1.03 mmol, 1 equiv) dissolved in dry benzene (3 mL, 0.4M) and Et₃N (0.174 mL, 1.24 mmol, 1.2 equiv) were slowly added to a stirred solution of triphosgene (104 mg, 0.350 mmol, 0.34 equiv) in dry benzene (3 mL, 0.4M) at 0 °C. The mixture was then slowly allowed to reach rt and was stirred overnight. The crude mixture was then quenched with HCl solution (1M) and extracted twice with DCM. The combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum. The excess of benzene was removed by coevaporation with CHCl₃. The desired carbamoyl chloride was obtained as a yellowish solid (287 mg, 0.81 mmol, 79%) and used without further purification.

**¹H NMR (400 MHz, Chloroform-d)**:  δ = 6.09 (s, 2H), 4.80 (s, 2H), 3.82 (s, 3H), 3.79 (s, 6H), 1.31 – 1.18 (m, 1H), 0.57 – 0.41 (m, 4H), 0.26 – 0.18 (m, 4H), -0.07 – -0.21 (m, 2H).

(2,3-Dihydro-1H-inden-2-yl)(isopropyl)carbamoyl chloride 2.78c:

Following general procedure for the synthesis of carbamoyl chloride, N-isopropyl-2,3-dihydro-1H-inden-2-amine (150 mg, 0.856 mmol 1 equiv) dissolved in dry benzene (2.1 mL, 0.4M) and Et₃N (0.144 mL, 1.03 mmol, 1.2 equiv) were slowly added to a stirred solution of triphosgene (86 mg, 0.291 mmol, 0.34 equiv) in dry benzene (2.1 mL, 0.4M) at 0 °C. The mixture was then slowly allowed to reach rt and was stirred overnight. The crude mixture was then quenched
with HCl solution (1M) and extracted twice with DCM. The combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum. The excess of benzene was removed by coevaporation with CHCl₃. The desired carbamoyl chloride was obtained as a yellowish oil (160 mg, 0.67 mmol, 78 %) and used without further purification.

**¹H NMR (400 MHz, Chloroform-d)** \( \delta = 7.23 - 7.14 \text{ (m, 4H)}, 5.23 - 4.60 \text{ (m, 1H)}, 4.22 - 3.71 \text{ (m, 1H)}, 3.69 - 3.38 \text{ (m, 2H)}, 3.31 - 2.88 \text{ (m, 2H)}, 1.26 - 1.40 \text{ (m, 6H)}.\)

(2,3-Dihydro-1H-inden-2-yl)(2,4,6-trimethoxybenzyl)carbamoyl chloride 2.79c:

Following general procedure for the synthesis of carbamoyl chlorides, \( N-(2,4,6\text{-trimethoxybenzyl})-2,3\text{-dihydro-1H-inden-2-amine} \) (269 mg, 0.858 mmol 1 equiv) dissolved in dry benzene (2.1 mL, 0.4M) and Et₃N (0.144 mL, 1.03 mmol, 1.2 equiv) were slowly added to a stirred solution of triphosgene (86 mg, 0.291 mmol, 0.34 equiv) in dry benzene (2.1 mL, 0.4M) at 0 °C. The mixture was then slowly allowed to reach rt and was stirred overnight. The crude mixture was then quenched with HCl solution (1M) and extracted twice with DCM. The combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum. The excess of benzene was removed by coevaporation with CHCl₃. The desired carbamoyl chloride was obtained as a white solid (290 mg, 0.77 mmol, 90 %) and used without further purification.

**¹H NMR (250 MHz, Chloroform-d)** \( \delta = 7.07 \text{ (s, 4H)}, 6.10 \text{ (s, 2H)}, 4.83 \text{ (s, 2H)}, 4.15 - 3.99 \text{ (m, 1H)}, 3.82 \text{ (s, 3H)}, 3.80 \text{ (s, 6H)}, 3.49 - 3.33 \text{ (m, 2H)}, 2.74 - 2.59 \text{ (m, 2H)}.\)

(1,2,3,4-Tetrahydronaphthalen-1-yl)(2,4,6-trimethoxybenzyl)carbamoyl chloride 2.80c:
Following general procedure for the synthesis of carbamoyl chlorides, \( N-(2,4,6\text{-trimethoxybenzyl})-1,2,3,4\text{-tetrahydronaphthalen}-1\text{-amine} \) (490 mg, 1.50 mmol, 1 equiv) dissolved in dry benzene (3.7 mL, 0.4M) and \( \text{Et}_3\text{N} \) (0.253 mL, 1.80 mmol, 1.2 equiv) were slowly added to a stirred solution of triphosgene (151 mg, 0.510 mmol, 0.34 equiv) in dry benzene (3.7 mL, 0.4M) at 0 °C. The mixture was then slowly allowed to reach rt and was stirred overnight. The crude mixture was then quenched with HCl solution (1M) and extracted twice with DCM. The combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum. The excess of benzene was removed by coevaporation with \( \text{CHCl}_3 \). The desired carbamoyl chloride was obtained as a yellowish solid (480 mg, 1.23 mmol, 82 %) and used without further purification.

\(^1\text{H NMR (250 MHz, Chloroform-}d\text{)} \delta = 7.09 – 6.97 \text{ (m, 4H), 6.10 – 6.03 \text{ (m 2H), 5.03 – 4.83 \text{ (m, 2H), 4.71 – 4.50 \text{ (m, 1H), 3.81 \text{ (s, 3H), 3.80 \text{ (s, 6H), 3.80 – 3.73 \text{ (m, 2H), 2.86 – 2.50 \text{ (m, 2H), 1.97 – 1.66 \text{ (m, 2H).}}}}}}

\((R)-(1,2,3,4\text{-Tetrahydronaphthalen}-1\text{-yl})(2,4,6\text{-trimethoxybenzyl})\text{carbamoyl chloride}\)

\[ \text{2.96:} \]

Following general procedure for the synthesis of carbamoyl chlorides, \((R)-N-(2,4,6\text{-trimethoxybenzyl})-1,2,3,4\text{-tetrahydronaphthalen}-1\text{-amine} \) (600 mg, 1.83 mmol, 1 equiv) dissolved in dry benzene (5 mL, 0.4M) and \( \text{Et}_3\text{N} \) (0.308 mL, 2.20 mmol, 1.2 equiv) were slowly added to a stirred solution of triphosgene (185 mg, 0.622 mmol, 0.34 equiv) in dry benzene (5 mL, 0.4M) at 0 °C. The mixture was then slowly allowed to reach rt and was stirred overnight at 60°C. The crude mixture was then quenched with HCl solution (1M) and extracted twice with DCM. The combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum. The excess of benzene was removed by coevaporation with \( \text{CHCl}_3 \). The desired carbamoyl chloride was obtained as a yellowish solid (613 mg, 1.53 mmol, 86 %) and used without further purification.
**H NMR (250 MHz, Chloroform-d) δ = 7.09 – 6.95 (m, 4H), 6.10 – 6.03 (m, 2H), 5.03 – 4.82 (m, 2H), 4.71 – 4.49 (m, 1H), 3.81 (s, 3H), 3.80 (s, 6H), 3.79 – 3.73 (m, 2H), 2.87 – 2.52 (m, 2H), 1.99 – 1.67 (m, 2H).

(2,3-Dihydro-1H-inden-1-yl)(2,4,6-trimethoxybenzyl)carbamoyl chloride 2.81c:

Following general procedure B for the synthesis of secondary amines, 2,3-dihydro-1H-inden-1-amine (200 mg, 1.5 mmol, 1 equiv), 2,4,6-trimethoxybenzaldehyde (294 mg, 1.5 mmol, 1 equiv), and AcOH (0.172 mL, 3 mmol 2 equiv) were stirred at rt in DCE (15 mL) for 30 min. NaBH(OAc)$_3$ (636 mg, 3 mmol, 2 equiv) was then added to the resulting solution, which was stirred overnight. Then, the mixture was quenched using a solution of NaOH (1M) and the crude mixture was stirred for further 30 min. The crude mixture was extracted twice with DCM, dried over sodium sulfate, filtered and evaporated under vacuum.

Following general procedure for the synthesis of carbamoyl chlorides, N-(2,4,6-trimethoxybenzyl)-2,3-dihydro-1H-inden-1-amine (470 mg, 1.50 mmol, 1 equiv) dissolved in dry benzene (3.8 mL, 0.4M) and Et$_3$N (0.632 mL, 4.50 mmol, 1.2 equiv) were slowly added to a stirred solution of triphosgene (151 mg, 0.51 mmol, 0.34 equiv) in dry benzene (3.8 mL, 0.4M) at 0 °C. The mixture was then slowly allowed to reach rt and was stirred overnight. The crude mixture was then quenched with HCl solution (1M) and extracted twice with DCM. The combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum. The excess of benzene was removed by coevaporation with CHCl$_3$. The desired carbamoyl chloride was obtained as a yellowish solid (430 mg, 1.14 mmol, 76 %) and used without further purification.

**H NMR (250 MHz, Chloroform-d) δ = 7.29 – 6.96 (m 4H), 6.11 – 5.93 (m, 2H), 5.07 – 4.75 (m, 2H), 3.85 – 3.75 (m, 9H), 3.70 – 3.61 (m, 2H), 3.51 – 3.40 (m, 1H), 3.14 – 3.05 (m, 1H), 2.19 – 2.01 (m, 1H).
**Dicyclohexylcarbamoyl chloride 2.82c:**

![Chemical Structure](attachment:image.png)

Following general procedure for the synthesis of carbamoyl chlorides, dicyclohexylamine (363 mg, 2.0 mmol 1 equiv) dissolved in dry benzene (5 mL, 0.4M) and Et₃N (0.337 mL, 2.24 mmol, 1.2 equiv) were slowly added to a stirred solution of triphosgene (202 mg, 0.68 mmol, 0.34 equiv) in dry benzene (5 mL, 0.4M) at 0 °C. The mixture was then slowly allowed to reach rt and was stirred overnight. The crude mixture was then quenched with HCl solution (1M) and extracted twice with DCM. The combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum. The excess of benzene was removed by coevaporation with CHCl₃. The desired carbamoyl chloride was obtained as a yellowish solid (450 mg, 1.84 mmol, 92 %) and used without further purification.

**¹H NMR (400 MHz, Chloroform-d)** \( \delta = 4.12 \) (s, 1H), \( 3.10 \) (s, 1H), \( 2.19 \) (s, 2H), \( 1.85 - 1.80 \) (m, 6H), \( 1.65 - 1.54 \) (m, 2H), \( 1.54 - 1.04 \) (m, 10H).

**Pentan-3-yl(2,4,6-trimethoxybenzyl)carbamoyl chloride 2.83c:**

![Chemical Structure](attachment:image.png)

Following general procedure for the synthesis of carbamoyl chlorides, \( N-(2,4,6-\text{trimethoxybenzyl})\text{-pentan-3-amine} \) (400 mg, 1.5 mmol 1 equiv) dissolved in dry benzene (3.5 mL, 0.4M) and Et₃N (0.250 mL, 1.8 mmol, 1.2 equiv) were slowly added to a stirred solution of triphosgene (151 mg, 0.51 mmol, 0.34 equiv) in dry benzene (3.5 mL, 0.4M) at 0 °C. The mixture was then slowly allowed to reach rt and was stirred overnight. The crude mixture was then quenched with HCl solution (1M) and extracted twice with DCM. The combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum. The excess of
benzene was removed by coevaporation with CHCl₃. The desired carbamoyl chloride was obtained as a yellowish solid (430 mg, 1.30 mmol, 87%) and used without further purification.

**IH NMR (250 MHz, Chloroform-d)** δ = 6.16 – 6.06 (m, 2H), 4.75 – 4.60 (m, 2H), 3.88 – 3.78 (m, 9H), 3.10 – 2.93 (m, 1H), 1.89 – 1.64 (m, 2H), 1.54 – 1.33 (m, 2H), 0.96 – 0.52 (m, 6H).

**Synthesis of β-lactams**

4-Methyl-1-(2,4,6-trimethoxybenzyl)azetidin-2-one **2.54**: 

```
Chemical Formula: C₉H₁₆NO₄
Exact Mass: 265.1314
```

**Standard scale synthesis: Conditions A**: Two-chamber system:

Following general procedure A, Chamber A was filled with Pd(OAc)₂ (8.9 mg, 0.04 mmol, 30 mol%), P(r-Bu)₃.HBF₄ (12 mg, 0.04 mmol, 30 mol%), COgen (97 mg, 0.4 mmol, 3.0 equiv), Cy₂NMe (161 mg, 0.798 mmol, 6.0 equiv) and mesitylene (0.5 mL). Chamber B, previously charged with isopropyl(2,4,6-trimethoxybenzyl)carbamoyl chloride (40 mg, 0.133 mmol, 1 equiv) was reacted with PdCl₂ (2.4 mg, 0.0133 mmol, 10 mol%), cataXium A.HI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL). The two chambers system was reacted for 18h at 120 °C. The crude mixture was purified by flash chromatography using first cyclohexane to elute mesitylene and then cyclohexane/EtOAc (75:25 to 0:1) as eluent., to provide oil **2.54** (32.5 mg, 0.122 mmol, 92%).

**¹³C-labeled standard scale synthesis: Conditions A**: Two-chamber system:

Following general procedure A, Chamber A was filled with Pd(OAc)₂ (8.9 mg, 0.04 mmol, 30 mol%), P(r-Bu)₃.HBF₄ (12 mg, 0.04 mmol, 30 mol%), ¹³C-COgen (98 mg, 0.4 mmol, 3.0 equiv), Cy₂NMe (161 mg, 0.798 mmol, 6.0 equiv) and mesitylene (0.5 mL). Chamber B, previously charged with isopropyl(2,4,6-trimethoxybenzyl)carbamoyl chloride (40 mg, 0.133 mmol, 1 equiv) was reacted with PdCl₂ (2.4 mg, 0.0133 mmol, 10 mol%), cataXium A.HI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol,
3.0 equiv) in mesitylene (2.62 mL). The two chambers system was reacted for 18h at 120 °C. The crude mixture was purified by flash chromatography using first cyclohexane to elute mesitylene and then cyclohexane/EtOAc (75:25 to 0:1) as eluent, to provide 2.54 (32.5 mg, 0.11 mmol, 89 %).

$^{13}$C-NMR spectra shows a low enrichment of the $^{13}$C of the final product (3.1 %). This low increasing of $^{13}$C compared to the standard procedure, shows the really low incorporation of $^{13}$CO from COgen during the reaction.

**Standard scale synthesis: Conditions B: CO atmosphere**

Following general procedure B, isopropyl(2,4,6-trimethoxybenzyl)carbamoyl chloride (40 mg, 0.133 mmol, 1 equiv) was reacted with PdCl$_2$ (2.4 mg, 0.0133 mmol, 10 mol%), cataXium A.HI (12 mg , 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL), under CO atmosphere. The mixture was stirred for 18h at 120 °C. The crude mixture was purified by flash chromatography using first cyclohexane to elute mesitylene and then cyclohexane/EtOAc (75:25 to 0:1) as eluent, to provide oil 2.54 (30.0 mg, 0.064 mmol, 85 %).

**Enantioselective reaction: CO atmosphere**

Following general procedure B, Isopropyl(2,4,6-trimethoxybenzyl)carbamoyl chloride (400 mg, 1.33 mmol, 1 equiv) was reacted with PdCl$_2$ (24 mg, 0.133 mmol, 10 mol%), L 2.84 (332 mg , 0.266 mmol, 20 mol%), pivalic acid (41 mg, 0.4 mmol, 30 mol%) and cesium carbonate (650 mg, 2 mmol, 1.5 equiv) in mesitylene (26.2 mL), under CO atmosphere. The mixture was stirred for 18h at 120 °C. The crude mixture was purified by flash chromatography using first cyclohexane to elute mesitylene and then cyclohexane/EtOAc (75:25 to 0:1) as eluent, to provide oil 2.85 (266 mg, 1 mmol, 75 %, e.r.: 92:8).

**Optical rotation :** $[\alpha]_{D}^{20} = +71.8^\circ$ (c = 1.0, CHCl$_3$)

**Enantioselective reaction: Two-chamber system:**

Following general procedure A, Chamber A was filled with Pd(OAc)$_2$ (8.9 mg, 0.04 mmol, 30 mol%), P(t-Bu)$_3$HBF$_4$ (12 mg , 0.04 mmol, 30 mol%), COgen (97 mg, 0.4 mmol, 3.0 equiv), Cy$_2$NMe (161 mg, 0.798 mmol, 6.0 equiv) and mesitylene (0.5 mL). Chamber B, previously charged with isopropyl(2,4,6-trimethoxybenzyl)carbamoyl chloride (40 mg, 0.133 mmol, 1 equiv) was reacted with PdCl$_2$ (2.4 mg, 0.0133 mmol, 10 mol%), L 2.84 (33.2 mg , 0.0266 mmol, 20
mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (65 mg, 0.2 mmol, 1.5 equiv) in mesitylene (2.62 mL). The two chambers system was reacted for 18h at 120 °C. The crude mixture was purified by flash chromatography using first cyclohexane to elute mesitylene and then cyclohexane/EtOAc (75:25 to 0:1) as eluent., to provide oil 2.85 (30.5 mg, 0.114 mmol, 86 %, e.r.: 86:14).

**Tenfold scale synthesis:**

**Conditions A:** Two-chamber system:

Following general procedure A, Chamber A was filled with Pd(OAc)$_2$ (89 mg, 0.4 mmol, 30 mol%), P(t-Bu)$_3$HBF$_4$ (120 mg, 0.4 mmol, 30 mol%), COgen (970 mg, 4 mmol, 3.0 equiv), Cy$_2$NMe (1.610 g, 7.98 mmol, 6.0 equiv) and mesitylene (5 mL). Chamber B, previously charged with isopropyl(2,4,6-trimethoxybenzyl)carbamoyl chloride (400 mg, 1.33 mmol, 1 equiv) was reacted with PdCl$_2$ (24 mg, 0.133 mmol, 10 mol%), catacXium A.HI (120 mg, 0.266 mmol, 20 mol%), pivalic acid (41 mg, 0.4 mmol, 30 mol%) and cesium carbonate (1.30 g, 4 mmol, 3.0 equiv) in mesitylene (26.2 mL). The two chambers system was reacted for 18h at 120 °C. The crude mixture was purified by flash chromatography using first cyclohexane to elute mesitylene and then cyclohexane/EtOAc (75:25 to 0:1) as eluent., to provide oil 2.54 (337 mg, 1.26 mmol, 95 %).

**Conditions A:** Two-chamber system: Under air atmosphere:

Following general procedure A, Chamber A was filled with Pd(OAc)$_2$ (89 mg, 0.4 mmol, 30 mol%), P(t-Bu)$_3$HBF$_4$ (120 mg, 0.4 mmol, 30 mol%), COgen (970 mg, 4 mmol, 3.0 equiv), Cy$_2$NMe (1.610 g, 7.98 mmol, 6.0 equiv) and mesitylene (commercial batch under argon atmosphere) (5 mL). Chamber B, previously charged with isopropyl(2,4,6-trimethoxybenzyl)carbamoyl chloride (400 mg, 1.33 mmol, 1 equiv) was reacted with PdCl$_2$ (24 mg, 0.133 mmol, 10 mol%), catacXium A.HI (120 mg, 0.266 mmol, 20 mol%), pivalic acid (41 mg, 0.4 mmol, 30 mol%) and cesium carbonate (1.30 g, 4 mmol, 3.0 equiv) in mesitylene (commercial batch under argon atmosphere) (26.2 mL). The two chambers system was reacted for 18h at 120 °C under air atmosphere. The crude mixture was purified by flash chromatography using first cyclohexane to elute mesitylene and then cyclohexane/EtOAc (75:25 to 0:1) as eluent., to provide oil 2.54 (266 mg, 1.0 mmol, 75 %).

$^1$H NMR (400 MHz, Chloroform-$d$) : δ = 6.11 (s, 2H), 4.57 (d, $J = 13.9$ Hz, 1H), 4.13 (d, $J = 13.8$, 1H), 3.81 (s, 9H), 3.41 – 3.33 (m, 1H), 2.90 (dd, $J = 14.2$, 4.9 Hz, 1H), 2.38 (dd, $J = 14.2$, 2.2, 1H), 1.17 (d, $J = 6.0$ Hz, 3H).
$^{13}$C NMR (Chloroform-\textit{d}, 101 MHz): $\delta = 166.5$, 161.2, 159.7, 104.6, 90.3, 55.8, 55.5, 47.0, 43.8, 32.4, 18.7.

IR (neat): $\nu = 2946$, 1739, 1600, 1140 cm$^{-1}$.

HRMS (ESI): Calculated for C$_{14}$H$_{19}$NNaO$_4$ ([M+Na]$^+$): 288.1206; found: 288.1208
Analysis Report

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2/23/2017 8:00:43 PM
Large-scale synthesis using a home-made two-chamber system
1-(2,4,6-Trimethoxybenzyl)azetidin-2-one 2.53:

**Conditions A:** Two-chamber system:

Following general procedure A, Chamber A was filled with Pd(OAc)$_2$ (8.9 mg, 0.04 mmol, 30 mol%), P(t-Bu)$_3$HBF$_4$ (12 mg, 0.04 mmol, 30 mol%), COgen (97 mg, 0.4 mmol, 3.0 equiv), Cy$_2$NMe (161 mg, 0.798 mmol, 6.0 equiv) and mesitylene (0.5 mL). Chamber B, previously charged with ethyl(2,4,6-trimethoxybenzyl)carbamoyl chloride (38.3 mg, 0.133 mmol, 1 equiv) was reacted with PdCl$_2$ (2.4 mg, 0.0133 mmol, 10 mol%), cataXium A.HI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL). The two chambers system was reacted for 18h at 120 °C. The crude mixture was purified by flash chromatography using first cyclohexane to elute mesitylene and then cyclohexane/EtOAc (75:25 to 0:1) as eluent, to provide oil 2.53 (16.0 mg, 0.064 mmol, 48 %).

**Conditions B:** CO atmosphere

Following general procedure B, ethyl(2,4,6-trimethoxybenzyl)carbamoyl chloride (38.3 mg, 0.133 mmol, 1 equiv) was reacted with PdCl$_2$ (2.4 mg, 0.0133 mmol, 10 mol%), cataXium A.HI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL), under CO atmosphere. The mixture was stirred for 18h at 120 °C. The crude mixture was purified by flash chromatography using first cyclohexane to elute mesitylene and then cyclohexane/EtOAc (75:25 to 0:1) as eluent, to provide oil 2.53 (11.4 mg, 0.045 mmol, 34 %).

$^1$H NMR (400 MHz, Chloroform-d): $\delta = 6.12$ (s, 2H), 4.38 (s, 2H), 3.82 (s, 3H), 3.81 (s, 6H), 3.01 (t, $J = 4.0$ Hz, 2H), 2.79 (t, $J = 4.0$ Hz, 2H).

$^{13}$C NMR (Chloroform-d, 101 MHz): $\delta =$ 167.2, 161.2, 159.7, 104.2, 90.4, 55.9, 55.5, 38.7, 36.2, 34.1.

IR (neat): $\nu = 2939, 1737, 1596, 1145, 814$ cm$^{-1}$.

HRMS (ESI): Calculated for C$_{13}$H$_{17}$NNaO$_4$ ([M+Na]$^+$): 274.1050; found: 274.1051
(S)-4-(Tert-butyl)-1-(2,4,6-trimethoxybenzyl)azetidin-2-one 2.57:

\[
\text{Chemical Formula: C}_{17}\text{H}_{26}\text{NO}_4 \\
\text{Exact Mass: 307.1764}
\]

**Conditions A**: Two-chamber system:

Following general procedure A, Chamber A was filled with Pd(OAc)\(_2\) (8.9 mg, 0.04 mmol, 30 mol%), \(\text{P(t-Bu)}_3\cdot\text{HBF}_4\) (12 mg, 0.04 mmol, 30 mol%), COgen (97 mg, 0.4 mmol, 3.0 equiv), \(\text{Cy}_2\text{NMe}\) (161 mg, 0.798 mmol, 6.0 equiv) and mesitylene (0.5 mL). Chamber B, previously charged with (S)-(3,3-dimethylbutan-2-yl)(2,4,6-trimethoxybenzyl)carbamoyl chloride (47.6 mg, 0.133 mmol, 1 equiv) was reacted with PdCl\(_2\) (2.4 mg, 0.0133 mmol, 10 mol%), cataXium A.HI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL). The two chambers system was reacted for 18h at 120 °C. The crude mixture was purified by flash chromatography using first cyclohexane to elute mesitylene and then cyclohexane/EtOAc (75:25 to 0:1) as eluent, to provide oil 2.57 (30.7 mg, 0.100 mmol, 75 %).

**Conditions B**: CO atmosphere

Following general procedure B, (S)-(3,3-dimethylbutan-2-yl)(2,4,6-trimethoxybenzyl)carbamoyl chloride (47.6 mg, 0.133 mmol, 1 equiv) was reacted with PdCl\(_2\) (2.4 mg, 0.0133 mmol, 10 mol%), cataXium A.HI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL), under CO atmosphere. The mixture was stirred for 18h at 120 °C, The crude mixture was purified by flash chromatography using first cyclohexane to elute mesitylene and then cyclohexane/EtOAc (75:25 to 0:1) as eluent, to provide oil 2.57 (15.5 mg, 0.051 mmol, 38 %).

\(\text{\textsuperscript{1}H NMR (400 MHz, Chloroform-d)}\): \(\delta = 6.10\) (s, 2H), 4.64 (d, \(J = 14.5\) Hz, 1H), 4.21 (dd, \(J = 14.5, 1.4\) Hz, 1H), 3.82 (s, 3H), 3.78 (s, 6H), 2.97 (dd, \(J = 5.4, 2.6\) Hz, 1H), 2.65 (dd, \(J = 14.6, 5.4\) Hz, 1H), 2.5 (ddd, \(J = 14.5, 2.6, 1.4\) Hz, 1H), 0.82 (s, 9H).

\(\text{\textsuperscript{13}C NMR (Chloroform-d, 101 MHz):} \delta = 169.0, 161.0, 159.6, 103.8, 90.3, 59.9, 55.7, 55.4, 37.8, 35.3, 32.4, 25.7.

\(\text{IR (neat):} \nu = 2975, 1739, 743\ \text{cm}^{-1}\).

\(\text{HRMS (ESI):} \text{Calculated for C}_{17}\text{H}_{26}\text{NO}_4 ([M+H]^+) : 308.1856; found: 308.1859}\)
Optical rotation: \([\alpha]_D^{20} = +50.1^\circ\) (c = 0.7, CHCl₃)

\((R)-4\text{-Hexyl-1-(2,4,6-trimethoxybenzyl)azetidin-2-one 2.58:}\)

![Chemical structure](image)

**Conditions A:** Two-chamber system:

Following general procedure A, Chamber A was filled with Pd(OAc)_2 (8.9 mg, 0.04 mmol, 30 mol%), P(t-Bu)_3HBF_4 (12 mg, 0.04 mmol, 30 mol%), COgen (97 mg, 0.4 mmol, 3.0 equiv), Cy₂NMe (161 mg, 0.798 mmol, 6.0 equiv) and mesitylene (0.5 mL). Chamber B, previously charged with (S)-octan-2-yl(2,4,6-trimethoxybenzyl)carbamoyl chloride (49.5 mg, 0.133 mmol, 1 equiv) was reacted with PdCl₂ (2.4 mg, 0.0133 mmol, 10 mol%), cataXium A.HI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL). The two chambers system was reacted for 18h at 120 °C. The crude mixture was purified by flash chromatography using first cyclohexane to elute mesitylene and then cyclohexane/EtOAc (75:25 to 0:1) as eluent, to provide oil 2.58 (41 mg, 0.122 mmol, 92%).

**Conditions B:** CO atmosphere

Following general procedure B, (S)-octan-2-yl(2,4,6-trimethoxybenzyl)carbamoyl chloride (49.5 mg, 0.133 mmol, 1 equiv) was reacted with PdCl₂ (2.4 mg, 0.0133 mmol, 10 mol%), cataXium A.HI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL), under CO atmosphere. The mixture was stirred for 18h at 120 °C. The crude mixture was purified by flash chromatography using first cyclohexane to elute mesitylene and then cyclohexane/EtOAc (75:25 to 0:1) as eluent, to provide oil 2.58 (39.3 mg, 0.117 mmol, 88%).

**H NMR (400 MHz, Chloroform-d):** \(\delta = 6.10\) (s, 2H), \(4.56\) (d, \(J = 14.0\) Hz, 1H), \(4.13\) (d, \(J = 14.0\) Hz, 1H), \(3.81 – 3.78\) (m, 9H), \(3.26 – 3.20\) (m, 1H), \(2.81\) (dd, \(J = 14.2, 5.0\) Hz, 1H), \(2.45 – 2.39\) (m, 1H), \(1.80 – 1.69\) (m, 1H), \(1.28 – 1.18\) (m, 9H), \(0.86\) (t, \(J = 6.9\) Hz, 3H).

**C NMR (Chloroform-d, 101 MHz):** \(\delta = 166.9, 161.2, 159.6, 104.5, 90.3, 55.8, 55.4, 51.2, 41.8, 32.7, 32.5, 31.8, 29.3, 25.0, 22.7, 14.2.\)
IR (neat): ν = 2962, 1739, 1608, 1140, 732 cm⁻¹.

HRMS (ESI): Calculated for C₁₉H₃₀NO₄ ([M+H]+): 336.2169; found: 336.2167

Optical rotation: [α]D²⁰ = +46.6° (c = 1.3, CHCl₃)

(S)-4-Cyclohexyl-1-(2,4,6-trimethoxybenzyl)azetidin-2-one 2.59:

Conditions A: Two-chamber system:

Following general procedure A, Chamber A was filled with Pd(OAc)₂ (8.9 mg, 0.04 mmol, 30 mol%), P(t-Bu)₃.HBF₄ (12 mg, 0.04 mmol, 30 mol%), COgen (97 mg, 0.4 mmol, 3.0 equiv), Cy₂NMe (161 mg, 0.798 mmol, 6.0 equiv) and mesitylene (0.5 mL). Chamber B, previously charged with (S)-(1-cyclohexylethyl)(2,4,6-trimethoxybenzyl)carbamoyl chloride (49.2 mg, 0.133 mmol, 1 equiv) was reacted with PdCl₂ (2.4 mg, 0.0133 mmol, 10 mol%), catacXium A.HI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL). The two chambers system was reacted for 18h at 120 °C. The crude mixture was purified by flash chromatography using first cyclohexane to elute mesitylene and then cyclohexane/EtOAc (75:25 to 0:1) as eluent, to provide oil 2.59 (44.4 mg, 0.133 mmol, 100 %).

Conditions B: CO atmosphere

Following general procedure B, (S)-(1-cyclohexylethyl)(2,4,6-trimethoxybenzyl)carbamoyl chloride (49.2 mg, 0.133 mmol, 1 equiv) was reacted with PdCl₂ (2.4 mg, 0.0133 mmol, 10 mol%), catacXium A.HI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL), under CO atmosphere. The mixture was stirred for 18h at 120 °C, The crude mixture was purified by flash chromatography using first cyclohexane to elute mesitylene and then cyclohexane/EtOAc (75:25 to 0:1) as eluent, to provide oil 2.59 (39.1 mg, 0.117 mmol, 88 %).
$^1$H NMR (400 MHz, Chloroform-d): $\delta = 6.09$ (s, 2H), 4.57 (d, $J = 14.0$ Hz, 1H), 4.16 (d, $J = 14.0$ Hz, 1H), 3.80 (s, 3H), 3.79 (s, 6H), 3.13–3.08 (m, 1H), 2.65 (dd, $J = 14.3$, 5.1 Hz, 1H), 2.53 (d, $J = 14.3$ Hz, 1H), 1.70–1.46 (m, 5H), 1.19–1.04 (m, 4H), 0.91–0.72 (m, 2H).

$^{13}$C NMR (Chloroform-d, 101 MHz) $\delta = 167.7$, 161.1, 159.6, 104.1, 90.3, 55.7, 55.4, 55.4, 39.2, 38.0, 33.7, 29.5, 26.5, 26.3, 26.3, 26.0.

IR (neat): $\nu = 2972$, 1729, 1628, 1120, 734 cm$^{-1}$.


Optical rotation: $[\alpha]_D^{20} = -38.2^\circ$ (c = 1.6, CHCl$_3$)

(S)-(4-Oxo-1-(2,4,6-trimethoxybenzyl)azetidin-2-yl)methyl pivalate 2.60:

![Chemical Structure](image)

**Conditions A:** Two-chamber system:

Following general procedure A, Chamber A was filled with Pd(OAc)$_2$ (8.9 mg, 0.04 mmol, 30 mol%), P($r$-Bu)$_3$.HBF$_4$ (12 mg, 0.04 mmol, 30 mol%), COgen (97 mg, 0.4 mmol, 3.0 equiv), Cy$_2$NMe (161 mg, 0.798 mmol, 6.0 equiv) and mesitylene (0.5 mL). Chamber B, previously charged with (S)-2-((chlorocarbonyl)(2,4,6-trimethoxybenzyl)amino)propyl pivalate (53.5 mg, 0.133 mmol, 1 equiv) was reacted with PdCl$_2$ (2.4 mg, 0.0133 mmol, 10 mol%), catacXium A.HI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL). The two chambers system was reacted for 18h at 120 °C. The crude mixture was purified by flash chromatography using first cyclohexane to elute mesitylene and then cyclohexane/EtOAc (75:25 to 0:1) as eluent, to provide oil 2.60 (48.6 mg, 0.133 mmol, 100 %).

**Conditions B:** CO atmosphere

Following general procedure B, (S)-2-((chlorocarbonyl)(2,4,6-trimethoxybenzyl)amino)propyl pivalate (53.5 mg, 0.133 mmol, 1 equiv) was reacted with PdCl$_2$ (2.4 mg, 0.0133 mmol, 10 mol%), catacXium A.HI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL), under CO atmosphere. The mixture was stirred for 18h at 120 °C, The crude mixture was purified by flash...
chromatography using first cyclohexane to elute mesitylene and then cyclohexane/EtOAc (75:25 to 0:1) as eluent, to provide oil 2.60 (42.7 mg, 0.117 mmol, 88 %).

\[^1^H \text{NMR (500 MHz, Chloroform-d)}\] \(\delta = 6.10 \text{ (s, 2H), 4.60 (d, } J = 14.0 \text{ Hz, 1H), 4.25 (dd, } J = 11.8, 4.3 \text{ Hz, 1H), 4.11 - 4.04 \text{ (m, 2H), 3.81 - 3.78 \text{ (m, 9H), 3.54 - 3.49 \text{ (m, 1H), 2.83 (dd, } J = 14.3, 5.1 \text{ Hz, 1H), 2.70 (dd, } J = 14.2, 2.4, 1H), 1.18 \text{ (s, 9H).}\)

\[^1^3^C \text{NMR (126 MHz, Chloroform-d)}\] \(\delta = 178.3, 166.2, 161.3, 159.5, 104.3, 90.4, 62.0, 55.8, 55.4, 49.4, 39.3, 39.1, 32.9, 27.2.\)

IR (neat): \(\nu = 1738, 1598, 904, 723 \text{ cm}^{-1}.\)

HRMS (ESI): Calculated for \(\text{C}_{19}\text{H}_{27}\text{NNaO}_6 ([M+Na]^+) \approx 388.1731; \text{ found: 388.1735}\)

Optical rotation : \([\alpha]_D^{20} = +41.3^\circ \text{ (c = 1.2, CHCl}_3\)\]

(\(S\))-4-phenyl-1-(2,4,6-trimethoxybenzyl)azetidin-2-one 2.61 and (\(S\))-3-methyl-2-(2,4,6-trimethoxybenzyl)isoindolin-1-one 2.62:

Conditions A: Two-chamber system:

Following general procedure A, Chamber A was filled with \(\text{Pd(OAc)}_2 (8.9 \text{ mg, 0.04 mmol, 30 mol\%), P(t-Bu)_3\text{HBF}_4 (12 \text{ mg, 0.04 mmol, 30 mol\%), }\text{COgen (97 mg, 0.4 mmol, 3.0 equiv), }\) \(\text{Cy}_2\text{NMe (161 mg, 0.798 mmol, 6.0 equiv) and mesitylene (0.5 mL).} \) Chamber B, previously charged with (\(S\)-(1-phenylethyl)(2,4,6-trimethoxybenzyl)carbamoyl chloride (48.4 mg, 0.133 mmol, 1 equiv) was reacted with \(\text{PdCl}_2 (2.4 \text{ mg, 0.0133 mmol, 10 mol\%}, \) catacXium A.HI (12 mg , 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL). The two chambers system was reacted for 18h at 120 °C. The crude mixture was purified by flash chromatography using first cyclohexane to elute mesitylene and then cyclohexane/EtOAc (75:25 to 0:1) as eluent, to provide oil 2.61 and 2.62 as an inseparable mixture (29.6 mg, 0.09 mmol, 68 %, 7/3).

Conditions B: CO atmosphere

Following general procedure B, (\(S\)-(1-phenylethyl)(2,4,6-trimethoxybenzyl)carbamoyl chloride (48.4 mg, 0.133 mmol, 1 equiv) was reacted with \(\text{PdCl}_2 (2.4 \text{ mg, 0.0133 mmol, 10 mol\%}, \)
catacXium A.HI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL), under CO atmosphere. The mixture was stirred for 18h at 120 °C. The crude mixture was purified by flash chromatography using first cyclohexane to elute mesitylene and then cyclohexane/EtOAc (75:25 to 0:1) as eluent, to provide oil 2.61 and 2.62 as an inseparable mixture (29.6 mg, 0.09 mmol, 68 %, 7/3).

(\(S\))-4-phenyl-1-(2,4,6-trimethoxybenzyl)azetidin-2-2.61: Beta-lactam product:

\(^1\)H NMR (400 MHz, Chloroform-\(d\)): \(\delta = 7.34 - 7.22\) (m, 3H), 7.22 – 7.16 (m, 2H), 5.99 (s, 2H), 4.67 (d, \(J = 13.8\) Hz, 1H), 4.27 (dd, \(J = 5.3, 2.4\) Hz, 1H), 4.11 (dd, \(J = 13.8, 1.1\) Hz, 1H), 3.79 (s, 3H), 3.61 (s, 6H), 3.23 (dd, \(J = 14.4, 5.3\) Hz, 1H), 2.72 (ddd, \(J = 14.4, 2.4, 1.0\) Hz, 1H).

\(^{13}\)C NMR (Chloroform-\(d\), 101 MHz) : \(\delta = 167.2, 161.2, 159.5, 139.8, 130.9, 127.8, 126.2, 104.0, 90.1, 55.5, 55.4, 54.0, 46.7, 33.1\).

IR (neat): \(\nu = 2950, 1737, 1680, 1595, 1150, 907, 727\) cm\(^{-1}\).

HRMS (ESI): Calculated for C\(_{19}\)H\(_{21}\)NNaO\(_4\) ([M+Na]\(^+\)): 350.1363; found: 350.1365

(\(S\))-3-Methyl-2-(2,4,6-trimethoxybenzyl)isoindolin-1-one 2.62 : Oxindole product:

\(^1\)H NMR (400 MHz, Chloroform-\(d\) ) : \(\delta = 7.86\) (m, 1H), 7.48 (m, 1H), 7.44 – 7.40 (m, 1H), 7.33 – 7.31 (m, 1H), 6.13 (s, 2H), 5.27 (d, \(J = 14.2\) Hz, 1H), 4.44 (d, \(J = 14.1\) Hz, 1H), 4.19 (q, \(J = 6.7\) Hz, 1H), 3.82 (s, 3H), 3.80 (s, 6H), 1.44 (d, \(J = 6.6\) Hz, 3H).

\(^{13}\)C NMR (Chloroform-\(d\), 101 MHz) : \(\delta = 167.3, 161.2, 160.0, 147.6, 132.5, 128.4, 127.7, 123.6, 121.8, 105.5, 90.4, 55.9, 55.5, 55.0, 32.5, 18.4\).

1-(Cyclopentylmethyl)-4-methylazetidin-2-one 2.63:

Chemical Formula: C\(_{13}\)H\(_{17}\)NO
Exact Mass: 167.1310

Conditions A: Two-chamber system:

Following general procedure A, Chamber A was filled with Pd(OAc)\(_2\) (8.9 mg, 0.04 mmol, 30 mol%), P(\(-\)Bu)\(_3\)HBF\(_4\) (12 mg, 0.04 mmol, 30 mol%), COgen (97 mg, 0.4 mmol, 3.0 equiv), Cy\(_2\)NMe (161 mg, 0.798 mmol, 6.0 equiv) and mesitylene (0.5 mL). Chamber B, previously charged with (cyclopentylmethyl)(isopropyl)carbamoyl chloride (27.1 mg, 0.133 mmol, 1 equiv) was reacted with PdCl\(_2\) (2.4 mg, 0.0133 mmol, 10 mol%), catacXium A.HI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol,
3.0 equiv) in mesitylene (2.62 mL). The two chambers system was reacted for 18h at 120 °C. The crude mixture was purified by flash chromatography using first cyclohexane to elute mesitylene and then cyclohexane/EtOAc (75:25 to 0:1) as eluent, to provide oil 2.63 (16.7 mg, 0.100 mmol, 75 %).

**Conditions B: CO atmosphere**

Following general procedure B, (cyclopentylmethyl)(isopropyl)carbamoyl chloride (27.1 mg, 0.133 mmol, 1 equiv) was reacted with PdCl₂ (2.4 mg, 0.0133 mmol, 10 mol%), catacXium A.HI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL), under CO atmosphere. The mixture was stirred for 18h at 120 °C, The crude mixture was purified by flash chromatography using first cyclohexane to elute mesitylene and then cyclohexane/EtOAc (75:25 to 0:1) as eluent, to provide oil 2.63 (13.0 mg, 0.078 mmol, 59 %).

**¹H NMR (400 MHz, Chloroform-d):** δ = 3.74 – 3.59 (m, 1H), 3.25 (dd, J = 13.9, 7.9 Hz, 1H), 3.04 (dd, J = 14.4, 4.8 Hz, 1H), 2.87 (dd, J = 14.0, 7.1 Hz, 1H), 2.47 (d, J = 14.4 Hz, 1H), 2.19 – 2.00 (m, 1H), 1.85 – 1.46 (m, 5H), 1.31 (d, J = 5.9 Hz, 3H), 1.26 – 1.14 (m, 3H).

**¹³C NMR (Chloroform-d, 101 MHz):** δ = 167.1, 47.7, 45.5, 44.0, 38.9, 30.9, 30.8, 25.5, 25.2, 18.8.

**IR (neat):** ν = 2956, 1731, 907, 729 cm⁻¹.

**HRMS (ESI):** Calculated for C₁₀H₁₇NNaO ([M+Na⁺]): 190.1202; found: 190.1202

**4-Methyl-1-(2,4,6-trimethylbenzyl)azetidin-2-one 2.64:**

![Chemical Structure](image)

**Conditions A: Two-chamber system:**

Following general procedure A, Chamber A was filled with Pd(OAc)₂ (8.9 mg, 0.04 mmol, 30 mol%), P(t-Bu)₃·HBF₄ (12 mg, 0.04 mmol, 30 mol%), COgen (97 mg, 0.4 mmol, 3.0 equiv), Cy₂NMe (161 mg, 0.798 mmol, 6.0 equiv) and mesitylene (0.5 mL). Chamber B, previously charged with isopropyl(2,4,6-trimethylbenzyl)carbamoyl chloride (33.8 mg, 0.133 mmol, 1 equiv) was reacted with PdCl₂ (2.4 mg, 0.0133 mmol, 10 mol%), cataXium A.HI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL). The two chambers system was reacted for 18h at 120 °C. The
crude mixture was purified by flash chromatography using first cyclohexane to elute mesitylene and then cyclohexane/EtOAc (75:25 to 0:1) as eluent, to provide oil 2.64 (20.2 mg, 0.093 mmol, 70 %).

**Conditions B:** CO atmosphere

Following *general procedure B*, isopropyl(2,4,6-trimethylbenzyl)carbamoyl chloride (33.8 mg, 0.133 mmol, 1 equiv) was reacted with PdCl₂ (2.4 mg, 0.0133 mmol, 10 mol%), cataXium A.HI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL), under CO atmosphere. The mixture was stirred for 18h at 120 °C, The crude mixture was purified by flash chromatography using first cyclohexane to elute mesitylene and then cyclohexane/EtOAc (75:25 to 0:1) as eluent, to provide oil 2.64 (19.4 mg, 0.078 mmol, 67 %).

**1H NMR (400 MHz, Chloroform-d):** \( \delta = 6.85 \ (s, \ 2H) \), 4.48 (d, \( J = 14.7 \) Hz, 1H), 4.34 (d, \( J = 14.7 \) Hz, 1H), 3.48 – 3.38 (m, 1H), 3.01 (dd, \( J = 14.4, 5.0 \) Hz, 1H), 2.48 – 2.40 (m, 1H), 2.33 (s, 6H), 2.26 (s, 3H), 1.06 (d, \( J = 6.1 \) Hz, 3H).

**13C NMR (Chloroform-d, 101 MHz):** \( \delta = 166.8, 137.6, 137.4, 129.4, 128.5, 47.6, 44.1, 38.9, 21.0, 20.1, 19.4.\)

**IR (neat):** \( \nu = 1733, 907, 731 \) cm\(^{-1}\).

**HRMS (ESI):** Calculated for C\(_{14}\)H\(_{19}\)NNaO ([M+Na]\(^+\)): 240.1359; found: 240.1360

**4-Methyl-1-phenethylazetidin-2-one 2.66:**

![Chemical Structure](image)

**Conditions A:** Two-chamber system:

Following *general procedure A*, Chamber A was filled with Pd(OAc)\(_2\) (8.9 mg, 0.04 mmol, 30 mol%), P(t-Bu)\(_3\).HBF\(_4\) (12 mg, 0.04 mmol, 30 mol%), COgen (97 mg, 0.4 mmol, 3.0 equiv), Cy\(_2\)NMe (161 mg, 0.798 mmol, 6.0 equiv) and mesitylene (0.5 mL). Chamber B, previously charged with isopropyl(phenethyl)carbamoyl chloride (30.0 mg, 0.133 mmol, 1 equiv) was reacted with PdCl₂ (2.4 mg, 0.0133 mmol, 10 mol%), cataXium A.HI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL). The two chambers system was reacted for 18h at 120 °C. The crude mixture was purified by flash chromatography using first cyclohexane to elute mesitylene
and then cyclohexane/EtOAc (75:25 to 0:1) as eluent, to provide oil **2.66** (13.5 mg, 0.071 mmol, 54 %).

**Conditions B:** CO atmosphere

Following general procedure B, isopropyl(phenethyl)carbamoyl chloride (30.0 mg, 0.133 mmol, 1 equiv) was reacted with PdCl₂ (2.4 mg, 0.0133 mmol, 10 mol%), catacXium A.HI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL), under CO atmosphere. The mixture was stirred for 18h at 120 °C, The crude mixture was purified by flash chromatography using first cyclohexane to elute mesitylene and then cyclohexane/EtOAc (75:25 to 0:1) as eluent, to provide oil **2.66** (7 mg, 0.037 mmol, 28 %).

**1H NMR (400 MHz, Chloroform-d)** δ = 7.26 – 7.18 (m, 2H), 7.18 – 7.10 (m, 3H), 3.52 (dt, J = 14.6, 7.4 Hz, 1H), 3.46 – 3.39 (m, 1H), 3.15 (dt, J = 14.4, 7.4 Hz, 1H), 2.91 (dd, J = 14.4, 4.9 Hz, 1H), 2.80 (t, J = 7.4 Hz, 2H), 2.36 (dd, J = 14.4, 2.2 Hz, 1H), 1.11 (d, J = 6.2 Hz, 3H).

**13C NMR (101 MHz, Chloroform-d)** δ = 167.0, 138.8, 128.7, 128.7, 126.7, 47.7, 44.0, 41.8, 34.7, 18.5.

**IR (neat):** ν = 2960, 1740, 1399, 700 cm⁻¹.

**HRMS (ESI):** Calculated for C₁₂H₁₅NNaO ([M+Na⁺]: 212.1246; found: 212.1246

**4-Methyl-1-(3-phenylpropyl)azetidin-2-one 2.67:**

![Chemical Structure](image)

**Exact Mass:** 203.1310

**Conditions A:** Two-chamber system:

Following general procedure A, Chamber A was filled with Pd(OAc)₂ (8.9 mg, 0.04 mmol, 30 mol%), P(t-Bu)₃.HBF₄ (12 mg , 0.04 mmol, 30 mol%), COgen (97 mg, 0.4 mmol, 3.0 equiv), Cy₂NMe (161 mg, 0.798 mmol, 6.0 equiv) and mesitylene (0.5 mL). Chamber B, previously charged with isopropyl(3-phenylpropyl)carbamoyl chloride (31.9 mg, 0.133 mmol, 1 equiv) was reacted with PdCl₂ (2.4 mg, 0.0133 mmol, 10 mol%), catacXium A.HI (12 mg , 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL). The two chambers system was reacted for 18h at 120 °C. The crude mixture was purified by flash chromatography using first cyclohexane to elute mesitylene and then cyclohexane/EtOAc (75:25 to 0:1) as eluent, to provide oil **2.67** (21.9 mg, 0.108 mmol, 81 %).
Conditions B: CO atmosphere

Following general procedure B, isopropyl (3-phenylpropyl)carbamoyl chloride (31.9 mg, 0.133 mmol, 1 equiv) was reacted with PdCl$_2$ (2.4 mg, 0.0133 mmol, 10 mol%), catacXium A.HI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL), under CO atmosphere. The mixture was stirred for 18h at 120 °C, the excess of mesitylene was removed by flushing cyclohexane on silica gel, and the resulting crude mixture was purified by chromatography using cyclohexane/AcOEt as eluent, to provide oil 2.67 (16.0 mg, 0.078 mmol, 59 %).

$^1$H NMR (400 MHz, Chloroform-d): $\delta = 7.26 – 7.17$ (m, 2H), 7.15 – 7.07 (m, 3H), 3.60 – 3.52 (m, 1H), 3.31 – 3.22 (m, 1H), 3.02 – 2.91 (m, 2H), 2.57 (t, $J = 7.7$ Hz, 2H), 2.40 (dd, $J = 14.4$, 2.2 Hz, 1H), 1.84 – 1.74 (m, 2H), 1.23 (d, $J = 6.1$ Hz, 3H).

$^{13}$C NMR (Chloroform-d, 101 MHz): $\delta = 167.1, 141.3, 128.6, 128.4, 126.1, 47.3, 43.9, 40.0, 33.5, 29.9, 18.8.$

IR (neat): $\nu = 2925, 1738, 1400, 701$ cm$^{-1}$.

HRMS (ESI): Calculated for C$_{15}$H$_{17}$NNaO$_4$ ([M+Na$^+$]: 226.1202; found: 226.1203

Methyl 3-(2-methyl-4-oxoazetidin-1-yl)propanoate 2.68:

![Chemical Structure](image)

Chemical Formula: C$_{8}$H$_{15}$NO$_3$

Exact Mass: 185.0952

Conditions A: Two-chamber system:

Following general procedure A, Chamber A was filled with Pd(OAc)$_2$ (8.9 mg, 0.04 mmol, 30 mol%), P(t-Bu)$_3$.HBF$_4$ (12 mg, 0.04 mmol, 30 mol%), COgen (97 mg, 0.4 mmol, 3.0 equiv), Cy$_2$NMe (161 mg, 0.798 mmol, 6.0 equiv) and mesitylene (0.5 mL). Chamber B, previously charged with methyl 3-((chlorocarbonyl)(isopropyl)amino)propanoate (29.5 mg, 0.133 mmol, 1 equiv) was reacted with PdCl$_2$ (2.4 mg, 0.0133 mmol, 10 mol%), catacXium A.HI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL). The two chambers system was reacted for 18h at 120 °C. The crude mixture was purified by flash chromatography using first cyclohexane to elute mesitylene and then cyclohexane/EtOAc (75:25 to 0:1) as eluent, to provide oil 2.68 (12.5 mg, 0.065 mmol, 50 %).

Conditions B: CO atmosphere
Following general procedure B, methyl 3-((chlorocarbonyl)(isopropyl)amino)propanoate (29.5 mg, 0.133 mmol, 1 equiv) was reacted with PdCl$_2$ (2.4 mg, 0.0133 mmol, 10 mol%), cataXium A.HI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL), under CO atmosphere. The mixture was stirred for 18h at 120 °C. The crude mixture was purified by flash chromatography using first cyclohexane to elute mesitylene and then cyclohexane/EtOAc (75:25 to 0:1) as eluent, to provide oil 2.68 (12 mg, 0.060 mmol, 49%).

$^1$H NMR (400 MHz, Chloroform-d) : $\delta = 4.15$ (q, $J = 7.1$ Hz, 2H), 3.72 – 3.64 (m, 1H), 3.60 (dt, $J = 14.5$, 6.5 Hz, 1H), 3.33 – 3.23 (m, 1H), 3.03 (dd, $J = 14.5$, 4.9 Hz, 1H), 2.66 – 2.50 (m, 2H), 2.47 (dd, $J = 14.5$, 2.3 Hz, 1H), 1.32 (d, $J = 6.1$ Hz, 3H), 1.26 (t, $J = 7.1$ Hz, 3H).

$^{13}$C NMR (Chloroform-d, 101 MHz) : $\delta = 171.6, 167.1, 60.1, 48.0, 44.2, 36.0, 33.6, 18.7, 14.3.$

IR (neat): $\nu = 2923, 1737, 1396, 1183$ cm$^{-1}$.

HRMS (ESI): Calculated for C$_9$H$_{15}$NNaO$_3$ ([M+Na$^+$]): 208.0944; found: 208.0946

2-(3-(2-Methyl-4-oxoazetidin-1-yl)propyl)isoindoline-1,3-dione 2.69 :

Chemical Formula: C$_{10}$H$_{16}$N$_2$O$_3$

Exact Mass: 272.1161

Conditions A: Two-chamber system:

Following general procedure A, Chamber A was filled with Pd(OAc)$_2$ (8.9 mg, 0.04 mmol, 30 mol%), P(t-Bu)$_3$.HBF$_4$ (12 mg, 0.04 mmol, 30 mol%), COgen (97 mg, 0.4 mmol, 3.0 equiv), Cy$_2$NMe (161 mg, 0.798 mmol, 6.0 equiv) and mesitylene (0.5 mL). Chamber B, previously charged with (3-(1,3-dioxoisooindolin-2-yl)propyl)(isopropyl)carbamoyl chloride (41.1 mg, 0.133 mmol, 1 equiv) was reacted with PdCl$_2$ (2.4 mg, 0.0133 mmol, 10 mol%), cataXium A.HI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL). The two chambers system was reacted for 18h at 120 °C. The crude mixture was purified by flash chromatography using first cyclohexane to elute mesitylene and then cyclohexane/EtOAc (75:25 to 0:1) as eluent, to provide oil 2.69 (15.6 mg, 0.057 mmol, 43%).

Conditions B: CO atmosphere
Following general procedure B, (3-(1,3-dioxoisindolin-2-yl)propyl)(isopropyl)carbamoyl chloride (41.1 mg, 0.133 mmol, 1 equiv) was reacted with PdCl$_2$ (2.4 mg, 0.0133 mmol, 10 mol%), cataXium A.HI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL), under CO atmosphere. The mixture was stirred for 18h at 120 °C. The crude mixture was purified by flash chromatography using first cyclohexane to elute mesitylene and then cyclohexane/EtOAc (75:25 to 0:1) as eluent, to provide oil 2.69 (8.0 mg, 0.029 mmol, 22%).

$^1$H NMR (400 MHz, Chloroform-d): $\delta =$ 7.87 – 7.80 (m, 2H), 7.76 – 7.69 (m, 2H), 3.82 – 3.66 (m, 3H), 3.46 – 3.31 (m, 1H), 3.15 – 3.01 (m, 2H), 2.50 (dd, $J =$ 14.5, 2.3 Hz, 1H), 2.01 – 1.85 (m, 3H), 1.34 (d, $J =$ 6.1 Hz, 3H).

$^{13}$C NMR (Chloroform-d, 101 MHz) : $\delta =$ 168.4, 167.2, 134.2, 132.2, 123.4, 47.6, 44.1, 38.1, 35.8, 27.3, 18.9.

IR (neat): $\nu =$ 1711, 1742, 1397, 722 cm$^{-1}$.

HRMS (ESI): Calculated for C$_{15}$H$_{16}$N$_2$O$_3$ ([M+Na]$^+$): 295.1059; found: 295.1057

4-Ethyl-4-methyl-1-(3-phenylpropyl)azetidin-2-one 2.70:

Chemical Formula: C$_{16}$H$_{22}$NO
Exact Mass: 231.1623

Conditions A: Two-chamber system:

Following general procedure A, Chamber A was filled with Pd(OAc)$_2$ (8.9 mg, 0.04 mmol, 30 mol%), P(r-Bu)$_3$.HBF$_4$ (12 mg, 0.04 mmol, 30 mol%), COgen (97 mg, 0.4 mmol, 3.0 equiv), Cy$_2$NMe (161 mg, 0.798 mmol, 6.0 equiv) and mesitylene (0.5 mL). Chamber B, previously charged with tert-pentyl(3-phenylpropyl)carbamoyl chloride (35.6 mg, 0.133 mmol, 1 equiv) was reacted with PdCl$_2$ (2.4 mg, 0.0133 mmol, 10 mol%), cataXium A.HI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL). The two chambers system was reacted for 18h at 120 °C. The crude mixture was purified by flash chromatography using first cyclohexane to elute mesitylene and then cyclohexane/EtOAc (75:25 to 0:1) as eluent, to provide oil 2.70 (22.5 mg, 0.097 mmol, 73%).
Conditions B: CO atmosphere

Following general procedure B, tert-pentyl(3-phenylpropyl)carbamic chloride (35.6 mg, 0.133 mmol, 1 equiv) was reacted with PdCl₂ (2.4 mg, 0.0133 mmol, 10 mol%), cataXium A.HI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL), under CO atmosphere. The mixture was stirred for 18h at 120 °C. The crude mixture was purified by flash chromatography using first cyclohexane to elute mesitylene and then cyclohexane/EtOAc (75:25 to 0:1) as eluent, to provide oil 2.70 (22.2 mg, 0.096 mmol, 72 %).

1H NMR (400 MHz, Chloroform-d) : δ = 7.30 – 7.17 (m, 5H), 3.21 – 3.03 (m, 2H), 2.75 (d, J = 14.3 Hz, 1H), 2.70 – 2.61 (m, 2H), 2.57 (d, J = 14.3 Hz, 1H), 1.95 – 1.85 (m, 2H), 1.76 – 1.67 (m, 1H), 1.64 – 1.55 (m, 1H), 1.35 (s, 3H), 0.92 (t, J = 7.5 Hz, 3H).

13C NMR (Chloroform-d, 101 MHz) : δ = 167.1, 141.4, 128.5, 128.5, 126.1, 58.8, 47.1, 39.4, 33.7, 31.0, 30.8, 23.1, 9.1.

IR (neat): ν = 2924, 1739, 1399, 733 cm⁻¹.

HRMS (ESI): Calculated for C₁₁H₁₂NO ([M+H]⁺): 232.1696; found: 232.1699

4-Methyl-4-phenyl-1-(3-phenylpropyl)azetidin-2-one 2.71:

Conditions A: Two-chamber system:

Following general procedure A, Chamber A was filled with Pd(OAc)₂ (8.9 mg, 0.04 mmol, 30 mol%), P(r-Bu)₃.HBF₄ (12 mg, 0.04 mmol, 30 mol%), COgen (97 mg, 0.4 mmol, 3.0 equiv), Cy₂NMe (161 mg, 0.798 mmol, 6.0 equiv) and mesitylene (0.5 mL). Chamber B, previously charged with (2-phenylpropan-2-yl)(3-phenylpropyl)carbamoyl chloride (42 mg, 0.133 mmol, 1 equiv) was reacted with PdCl₂ (2.4 mg, 0.0133 mmol, 10 mol%), cataXium A.HI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL). The two chambers system was reacted for 18h at 120 °C. The crude mixture was purified by flash chromatography using first cyclohexane to elute mesitylene and then cyclohexane/EtOAc (75:25 to 0:1) as eluent, to provide oil 2.71 (20.8 mg, 0.074 mmol, 56 %).

Conditions B: CO atmosphere
Following **general procedure B**, (2-phenylpropan-2-yl)(3-phenylpropyl)carbamoyl chloride (42 mg, 0.133 mmol, 1 equiv) was reacted with PdCl₂ (2.4 mg, 0.0133 mmol, 10 mol%), cataXium A.HI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL), under CO atmosphere. The mixture was stirred for 18h at 120 °C. The crude mixture was purified by flash chromatography using first cyclohexane to elute mesitylene and then cyclohexane/EtOAc (75:25 to 0:1) as eluent, to provide oil **2.71** (21.2 mg, 0.076 mmol, 57 %).

**1H NMR (400 MHz, Chloroform-d):** δ = 7.42 – 7.07 (m, 10H), 3.32 – 3.24 (m, 1H), 3.03 (s, 2H), 3.01 – 2.95 (m, 1H), 2.69 – 2.53 (m, 2H), 1.92 – 1.80 (m, 2H), 1.84 (s, 3H).

**13C NMR (Chloroform-d, 101 MHz):** δ = 167.7, 142.1, 141.3, 128.9, 128.5, 128.4, 127.9, 126.1, 125.6, 59.0, 53.9, 40.5, 33.7, 30.4, 23.4.

**IR (neat):** ν = 2926, 1743, 1395, 732 cm⁻¹.

**HRMS (ESI):** Calculated for C₁₉H₂₁NNaO ([M+Na]⁺): 302.1515; found: 302.1517

**1-(3,7-Dimethyloct-6-en-1-yl)-4,4-dimethylazetidin-2-one 2.72:**

![Chemical structure](image)

**Chemical Formula:** C₁₉H₂₃NO

**Exact Mass:** 237.2093

**Conditions A:** Two-chamber system:

Following **general procedure A**, Chamber A was filled with Pd(OAc)₂ (8.9 mg, 0.04 mmol, 30 mol%), P(t-Bu)₃.HBF₄ (12 mg, 0.04 mmol, 30 mol%), COgen (97 mg, 0.4 mmol, 3.0 equiv), Cy₂NMe (161 mg, 0.798 mmol, 6.0 equiv) and mesitylene (0.5 mL). Chamber B, previously charged with tert-buty1(3,7-dimethyloct-6-en-1-yl)carbamoyl chloride (36.4 mg, 0.133 mmol, 1 equiv) was reacted with PdCl₂ (2.4 mg, 0.0133 mmol, 10 mol%), cataXium A.HI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL). The two chambers system was reacted for 18h at 120 °C. The crude mixture was purified by flash chromatography using first cyclohexane to elute mesitylene and then cyclohexane/EtOAc (75:25 to 0:1) as eluent, to provide oil **2.72** (31.6 mg, 0.133 mmol, 100 %).

**Conditions B:** CO atmosphere

Following **general procedure B**, tert-buty1(3,7-dimethyloct-6-en-1-yl)carbamoyl chloride (36.4 mg, 0.133 mmol, 1 equiv) was reacted with PdCl₂ (2.4 mg, 0.0133 mmol, 10 mol%), cataXium
A.HI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL), under CO atmosphere. The mixture was stirred for 18h at 120 °C. The crude mixture was purified by flash chromatography using first cyclohexane to elute mesitylene and then cyclohexane/EtOAc (75:25 to 0:1) as eluent, to provide oil 2.72 (24 mg, 0.101 mmol, 76%).

\[ ^1H\text{NMR (400 MHz, Chloroform-}d\text{): } \delta = 5.12 - 5.02 (\text{m, } 1\text{H}), 3.09 (\text{t, } J = 7.7 \text{ Hz, } 2\text{H}), 2.68 \text{ (s, } 2\text{H}), 2.03 - 1.88 \text{ (m, } 2\text{H}), 1.69 - 1.65 \text{ (m, } 3\text{H}), 1.58 \text{ (s, } 3\text{H}), 1.36 \text{ (s, } 6\text{H}), 1.54 - 1.09 \text{ (m, } 5\text{H}), 0.90 \text{ (d, } J = 6.3 \text{ Hz, } 3\text{H}). \]

\[ ^13\text{C NMR (Chloroform-}d, 101 \text{ MHz): } \delta = 166.5, 131.5, 124.7, 55.4, 50.4, 37.7, 37.0, 36.1, 30.6, 25.8, 25.5, 25.3, 19.3, 17.8. \]

\[ \text{IR (neat): } \nu = 2925, 1736, 1402, 911, 732 \text{ cm}^{-1}. \]

\[ \text{HRMS (ESI): Calculated for } C_{15}H_{27}NNaO ([M+Na]^+): 260.1985; \text{ found: 260.1985} \]

**1-(((1R,5S)-6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl)methyl)-4,4-dimethylazetidin-2-one**

**2.73:**

![Chemical Structure](Chemical-Formula-C18H23NO.jpg)

**Conditions A:** Two-chamber system:

Following general procedure A, Chamber A was filled with Pd(OAc)$_2$ (8.9 mg, 0.04 mmol, 30 mol%), P(t-Bu)$_3$.HBF$_4$ (12 mg, 0.04 mmol, 30 mol%), COgen (97 mg, 0.4 mmol, 3.0 equiv), Cy$_3$NMe (161 mg, 0.798 mmol, 6.0 equiv) and mesitylene (0.5 mL). Chamber B, previously charged with tert-butyl(((1R,5S)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)methyl)carbamoyl chloride (35.9 mg, 0.133 mmol, 1 equiv) was reacted with PdCl$_2$ (2.4 mg, 0.0133 mmol, 10 mol%), catacXium A.HI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL). The two chambers system was reacted for 18h at 120 °C. The crude mixture was purified by flash chromatography using first cyclohexane to elute mesitylene and then cyclohexane/EtOAc (75:25 to 0:1) as eluent, to provide oil 2.73 (16.5 mg, 0.07 mmol, 53%).

**Conditions B:** CO atmosphere
Following general procedure B, tert-butyl((1R,5S)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)methyl)carbamoyl chloride (35.9 mg, 0.133 mmol, 1 equiv) was reacted with PdCl₂ (2.4 mg, 0.0133 mmol, 10 mol%), cataCXium A.HI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL), under CO atmosphere. The mixture was stirred for 18h at 120 °C. The crude mixture was purified by flash chromatography using first cyclohexane to elute mesitylene and then cyclohexane/EtOAc (75:25 to 0:1) as eluent, to provide oil 2.73 (15.5 mg, 0.067 mmol, 50 %).

\[ \text{H NMR (} 400 \text{ MHz, Chloroform-}d) \text{: } \delta = 5.46 - 5.40 \text{ (m, 1H)}, 3.82 \text{ (dq, } J = 15.5, 2.2 \text{ Hz, 1H}), 3.38 \text{ (d, } J = 15.5 \text{ Hz, 1H}), 2.71 \text{ (s, 2H)}, 2.39 \text{ (dt, } J = 8.6, 5.6 \text{ Hz, 1H}), 2.29 - 2.18 \text{ (m, 2H)}, 2.17 - 2.14 \text{ (m, 1H)}, 2.11 - 2.01 \text{ (m, 1H)}, 1.37 \text{ (s, 3H)}, 1.35 \text{ (s, 3H)}, 1.27 \text{ (s, 3H)}, 1.13 \text{ (d, } J = 8.6 \text{ Hz, 1H)}, 0.81 \text{ (s, 3H).} \]

\[ \text{C NMR (Chloroform-}d, 101 \text{ MHz): } \delta = 166.9, 144.1, 120.1, 55.7, 50.6, 44.3, 43.8, 40.7, 38.2, 31.8, 31.4, 26.2, 26.0, 24.6, 21.0. \]

\[ \text{IR (neat): } \nu = 1731, 907, 728 \text{ cm}^{-1}. \]

\[ \text{HRMS (ESI): Calculated for C}_{15}\text{H}_{23}\text{NNaO (}[\text{M+Na}^+]): 256.1672; found: 256.1672} \]

\[ \text{Optical rotation : } [\alpha]_D^{20} = -59.1^\circ \text{ (c = 0.8, CHCl}_3) \]

\[ (S)-4,4-\text{Dimethyl-1-((4-(prop-1-en-2-yl)cyclohex-1-en-1-yl)methyl)azetidin-2-one 2.74:} \]

According to Conditions A: Two-chamber system:

Following general procedure A, Chamber A was filled with Pd(OAc)₂ (8.9 mg, 0.04 mmol, 30 mol%), P(t-Bu)₃.HBF₄ (12 mg, 0.04 mmol, 30 mol%), COgen (97 mg, 0.4 mmol, 3.0 equiv), Cy₂NMe (161 mg, 0.798 mmol, 6.0 equiv) and mesitylene (0.5 mL). Chamber B, previously charged with (S)-tert-butyl((4-(prop-1-en-2-yl)cyclohex-1-en-1-yl)methyl)carbamoyl chloride (35.9 mg, 0.133 mmol, 1 equiv) was reacted with PdCl₂ (2.4 mg, 0.0133 mmol, 10 mol%), cataCXium A.HI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL). The two chambers system was reacted for 18h at 120 °C. The crude mixture was purified by flash chromatography...
using first cyclohexane to elute mesitylene and then cyclohexane/EtOAc (75:25 to 0:1) as eluent, to provide oil 2.74 (18.9 mg, 0.081 mmol, 68 %).

**Conditions B: CO atmosphere**

Following general procedure B, (S)-tert-butyl((4-(prop-1-en-2-yl)cyclohex-1-en-1-yl)methyl)carbamoyl (35.9 mg, 0.133 mmol, 1 equiv) was reacted with PdCl₂ (2.4 mg, 0.0133 mmol, 10 mol%), cataXium A.HI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL), under CO atmosphere. The mixture was stirred for 18h at 120 °C, The crude mixture was purified by flash chromatography using first cyclohexane to elute mesitylene and then cyclohexane/EtOAc (75:25 to 0:1) as eluent, to provide oil 2.74 (18.3 mg, 0.078 mmol, 59 %).

**1H NMR (400 MHz, Chloroform-d):** δ = 5.66 – 5.60 (m, 1H), 4.74 – 4.67 (m, 2H), 3.70 (d, J = 15.0 Hz, 1H), 3.57 (d, J = 15.0 Hz, 1H), 2.72 (s, 2H), 2.21 – 1.77 (m, 7H), 1.75 – 1.71 (m, 3H), 1.38 (s, 3H), 1.35 (s, 3H).

**13C NMR (Chloroform-d, 101 MHz):** δ = 166.9, 149.7, 133.5, 124.9, 108.8, 55.9, 50.8, 45.6, 41.0, 30.8, 27.6, 26.9, 25.2, 24.8, 20.9.

**IR (neat):** ν = 2921, 1745, 1392, 732 cm⁻¹.

**HRMS (ESI):** Calculated for C₁₅H₂₃NNaO ([M+Na]+): 256.1672 found: 256.1672

**Optical rotation:** [α]D²⁰ = -65.5° (c = 1.1, CHCl₃)

5-Methyl-3-oxa-1-azaspiro[bicyclo[3.2.0]heptane-2,1'-cyclohexan]-7-one 2.75:

![Chemical Structure](image)

Chemical Formula: C₁₄H₁₇NO₂
Exact Mass: 256.1259

**Conditions A: Two-chamber system:**

Following general procedure A, Chamber A was filled with Pd(OAc)₂ (8.9 mg, 0.04 mmol, 30 mol%), P(t-Bu)₃.HBF₄ (12 mg, 0.04 mmol, 30 mol%), COgen (97 mg, 0.4 mmol, 3.0 equiv), Cy₂NMe (161 mg, 0.798 mmol, 6.0 equiv) and mesitylene (0.5 mL). Chamber B, previously charged with 3,3-dimethyl-1-oxa-4-azaspiro[4.5]decanec-4-carbamoyl chloride (30.8 mg, 0.133 mmol, 1 equiv) was reacted with PdCl₂ (2.4 mg, 0.0133 mmol, 10 mol%), cataXium A.HI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL). The two chambers system was reacted for
18h at 120 °C. The crude mixture was purified by flash chromatography using first cyclohexane to elute mesitylene and then cyclohexane/EtOAc (75:25 to 0:1) as eluent, to provide oil 2.75 (18.2 mg, 0.093 mmol, 70 %).

**Conditions B: CO atmosphere**

Following general procedure B, ethyl(2,4,6-trimethoxybenzyl)carbamoyl chloride (30.8 mg, 0.133 mmol, 1 equiv) was reacted with PdCl₂ (2.4 mg, 0.0133 mmol, 10 mol%), cataXium A.HI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL), under CO atmosphere. The mixture was stirred for 18h at 120 °C. The crude mixture was purified by flash chromatography using first cyclohexane to elute mesitylene and then cyclohexane/EtOAc (75:25 to 0:1) as eluent, to provide oil 2.75 (18.2 mg, 0.093 mmol, 70 %).

**1H NMR (400 MHz, Chloroform-d):** \( \delta = 3.89 \text{ (d, } J = 9.0 \text{ Hz, } 1\text{H}), 3.82 \text{ (d, } J = 9.0 \text{ Hz, } 1\text{H}), 2.91 \text{ (d, } J = 15.9 \text{ Hz, } 1\text{H}), 2.86 \text{ (d, } J = 15.9 \text{ Hz, } 1\text{H}), 2.21 \text{ (m, } 1\text{H}), 1.88 – 1.56 \text{ (m, } 6\text{H}), 1.55 \text{ (s, } 3\text{H}), 1.53 – 1.39 \text{ (m, } 3\text{H}).

**13C NMR (Chloroform-d, 101 MHz):** \( \delta = 175.4, 98.5, 73.9, 59.1, 47.7, 35.9, 32.7, 25.2, 24.5, 23.9, 23.5. \)

**IR (neat):** \( \nu = 2935, 2859, 1768, 1450, 1264, 913, 731 \text{ cm}^{-1}. \)

**HRMS (ESI):** Calculated for C₁₁H₁₇Nlando ([M+Na]⁺): 218.1151; found: 218.1150

5-(2,4,6-Trimethoxybenzyl)-5-azaspiro[2.3]hexan-4-one 2.76:

![Chemical structure](https://example.com/structure.png)

Chemical Formula: C₁₄H₁₉Nlando

Exact Mass: 277.1314

**Conditions A: Two-chamber system:**

Following general procedure A, Chamber A was filled with Pd(OAc)₂ (8.9 mg, 0.04 mmol, 30 mol%), P(\text{-}Bu)₃.HBF₄ (12 mg, 0.04 mmol, 30 mol%), COgen (97 mg, 0.4 mmol, 3.0 equiv), Cy₂NMe (161 mg, 0.798 mmol, 6.0 equiv) and mesitylene (0.5 mL). Chamber B, previously charged with (cyclopropylmethyl)(2,4,6-trimethoxybenzyl)carbamoyl chloride (41.7 mg, 0.133 mmol, 1 equiv) was reacted with PdCl₂ (2.4 mg, 0.0133 mmol, 10 mol%), cataXium A.HI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130
mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL). The two chambers system was reacted for 18h at 120 °C. The crude mixture was purified by flash chromatography using first cyclohexane to elute mesitylene and then cyclohexane/EtOAc (75:25 to 0:1) as eluent, to provide oil 2.76 (27.6 mg, 0.100 mmol, 75 %).

**Conditions B:** CO atmosphere

Following general procedure B, ((cyclopropylmethyl)(2,4,6-trimethoxybenzyl)carbamoyl chloride (41.7 mg, 0.133 mmol, 1 equiv) was reacted with PdCl₂ (2.4 mg, 0.0133 mmol, 10 mol%), catacXium A.HI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL), under CO atmosphere. The mixture was stirred for 18h at 120 °C. The crude mixture was purified by flash chromatography using first cyclohexane to elute mesitylene and then cyclohexane/EtOAc (75:25 to 0:1) as eluent, to provide oil 2.76 (27.7 mg, 0.102 mmol, 76 %).

**1H NMR (400 MHz, Chloroform-d):** δ = 6.13 (s, 2H), 4.47 (s, 2H), 3.84 – 3.79 (m, 9H), 3.21 (s, 2H), 1.14 – 1.06 (m, 2H), 0.86 – 0.79 (m, 2H).

**13C NMR (Chloroform-d, 101 MHz):** δ = 172.0, 161.2, 159.7, 104.7, 90.5, 55.9, 55.5, 48.5, 34.4, 31.6, 7.3.

**IR (neat):** ν = 2968, 1745, 1608, 1147, 669 cm⁻¹.

**HRMS (ESI):** Calculated for C₁₅H₁₉NNaO₄ ([M+Na]+): 300.1206; found: 300.1208

**6-Cyclopropyl-5-(2,4,6-trimethoxybenzyl)-5-azaspiro[2.3]hexan-4-one 2.77:**

**Conditions A:** Two-chamber system:

Following general procedure A, Chamber A was filled with Pd(OAc)₂ (8.9 mg, 0.04 mmol, 30 mol%), P(t-Bu)₃.HBF₄ (12 mg, 0.04 mmol, 30 mol%), COgen (97 mg, 0.4 mmol, 3.0 equiv), Cy₂NMe (161 mg, 0.798 mmol, 6.0 equiv) and mesitylene (0.5 mL). Chamber B, previously charged with (dicyclopropylmethyl)(2,4,6-trimethoxybenzyl)carbamoyl chloride (47.1 mg, 0.133 mmol, 1 equiv) was reacted with PdCl₂ (2.4 mg, 0.0133 mmol, 10 mol%), catacXium A.HI (12 mg
Conditions B: CO atmosphere

Following general procedure B, (dicyclopropylmethyl)(2,4,6-trimethoxybenzyl)carbamoyl chloride (47.1 mg, 0.133 mmol, 1 equiv) was reacted with PdCl₂ (2.4 mg, 0.0133 mmol, 10 mol%), catacXium A.HI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL) under CO atmosphere. The mixture was stirred for 18h at 120 °C. The crude mixture was purified by flash chromatography using first cyclohexane to elute mesitylene and then cyclohexane/EtOAc (75:25 to 0:1) as eluent, to provide oil 2.77 (34 mg, 0.107 mmol, 81%).

1H NMR (400 MHz, Chloroform-d): δ = 6.10 (s, 2H), 4.59 (d, J = 14.0 Hz, 1H), 4.41 (d, J = 14.0 Hz, 1H), 3.82 – 3.78 (m, 9H), 2.55 (d, J = 9.3 Hz, 1H), 1.16 – 0.98 (m, 1H), 0.95 – 0.85 (m, 1H), 0.83 – 0.73 (m, 1H), 0.71 – 0.58 (m, 1H), 0.41 – 0.26 (m, 2H), -0.02 – -0.11 (m, 1H), -0.19 – -0.28 (m, 1H).

13C NMR (Chloroform-d, 101 MHz): δ = 172.4, 161.0, 159.7, 104.9, 90.3, 64.1, 55.7, 36.6, 33.5, 11.6, 7.2, 5.9, 2.4, 0.1.

IR (neat): ν = 2937, 1736, 1597, 1138, 728 cm⁻¹.


1-Isopropyl-1,2a,7,7a-tetrahydro-2H-indeno[2,1-b]azet-2-one 2.78:

Chemical Formula: C₁₉H₁₉NO
Exact Mass: 201.1154

Conditions A: Two-chamber system:

Following general procedure A, Chamber A was filled with Pd(OAc)₂ (8.9 mg, 0.04 mmol, 30 mol%), P(t-Bu)₃HBF₄ (12 mg, 0.04 mmol, 30 mol%), COgen (97 mg, 0.4 mmol, 3.0 equiv), Cy₂NMe (161 mg, 0.798 mmol, 6.0 equiv) and mesitylene (0.5 mL). Chamber B, previously charged with (2,3-dihydro-1H-inden-2-yl)(isopropyl)carbamoyl chloride (31.6 mg, 0.133 mmol, 1 equiv) was reacted with PdCl₂ (2.4 mg, 0.0133 mmol, 10 mol%), catacXium A.HI (12 mg, 0.0266
mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL). The two chambers system was reacted for 18h at 120 °C. The crude mixture was purified by flash chromatography using first cyclohexane to elute mesitylene and then cyclohexane/EtOAc (75:25 to 0:1) as eluent, to provide oil *2.78* (20.9 mg, 0.104 mmol, 78 %).

**Conditions B: CO atmosphere**

Following general procedure B, (2,3-dihydro-1H-inden-2-yl)(isopropyl)carbamoyl chloride (31.6 mg, 0.133 mmol, 1 equiv) was reacted with PdCl₂ (2.4 mg, 0.0133 mmol, 10 mol%), cataXium A.HI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL), under CO atmosphere. The mixture was stirred for 18h at 120 °C. The crude mixture was purified by flash chromatography using first cyclohexane to elute mesitylene and then cyclohexane/EtOAc (75:25 to 0:1) as eluent, to provide oil *2.78* (20.9 mg, 0.104 mmol, 78 %).

**1H NMR (400 MHz, Chloroform-d):** δ = 7.46 – 7.39 (m, 1H), 7.25 – 7.19 (m, 3H), 4.48 (d, J = 4.0 Hz, 1H), 4.40 (ddd, J = 6.3, 4.0, 1.3 Hz, 1H), 3.83 (hept, J = 6.8 Hz, 1H), 3.24 – 2.99 (m, 3H), 1.30 (d, J = 6.8 Hz, 3H), 1.23 (d, J = 6.8 Hz, 3H).

**13C NMR (Chloroform-d, 101 MHz):** δ = 168.5, 142.1, 137.7, 127.9, 127.4, 126.3, 125.2, 61.5, 53.6, 44.3, 35.4, 22.1, 20.7.

**IR (neat):** ν = 2973, 1742, 672 cm⁻¹.

**HRMS (ESI):** Calculated for C₁₅H₁₅NNaO ([M+Na]⁺): 224.1046; found: 224.1043

1-(2,4,6-Trimethoxybenzyl)-1,2a,7,7a-tetrahydro-2H-indeno[2,1-b]azet-2-one *2.79*:

![Chemical structure](image)

**Conditions A: Two-chamber system:**

Following general procedure A, Chamber A was filled with Pd(OAc)₂ (8.9 mg, 0.04 mmol, 30 mol%), P(t-Bu)₃HBF₄ (12 mg, 0.04 mmol, 30 mol%), COgen (97 mg, 0.4 mmol, 3.0 equiv), Cy₂NMe (161 mg, 0.798 mmol, 6.0 equiv) and mesitylene (0.5 mL). Chamber B, previously charged with (2,3-dihydro-1H-inden-2-yl)(2,4,6-trimethoxybenzyl)carbamoyl chloride (52 mg, 0.133 mmol, 1 equiv) was reacted with PdCl₂ (2.4 mg, 0.0133 mmol, 10 mol%), cataXium A.HI
(12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL). The two chambers system was reacted for 18h at 120 °C. The crude mixture was purified by flash chromatography using first cyclohexane to elute mesitylene and then cyclohexane/EtOAc (75:25 to 0:1) as eluent, to provide oil 2.79 (42 mg, 0.124 mmol, 93 %).

**Conditions B:** CO atmosphere

Following general procedure B, (2,3-dihydro-1H-inden-2-yl)(2,4,6-trimethoxybenzyl)carbamoyl chloride (52 mg, 0.133 mmol, 1 equiv) was reacted with PdCl$_2$ (2.4 mg, 0.0133 mmol, 10 mol%), catacXium A.HI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL), under CO atmosphere. The mixture was stirred for 18h at 120 °C, The crude mixture was purified by flash chromatography using first cyclohexane to elute mesitylene and then cyclohexane/EtOAc (75:25 to 0:1) as eluent, to provide oil 2.79 (30.6 mg, 0.09 mmol, 68 %).

$^1$H NMR (400 MHz, Chloroform-d): $\delta = 7.44 – 7.39$ (m, 1H), 7.23 – 7.16 (m, 3H), 6.13 (s, 2H), 4.56 (d, $J = 13.9$ Hz, 1H), 4.43 (d, $J = 3.9$ Hz, 1H), 4.20 (d, $J = 13.9$ Hz, 1H), 4.12 – 4.05 (m, 1H), 3.83 (s, 3H), 3.80 (s, 6H), 3.06 (d, $J = 17.6$ Hz, 1H), 2.82 (dd, $J = 17.5$, 6.8 Hz, 1H).

$^{13}$C NMR (Chloroform-d, 101 MHz): $\delta = 168.3, 161.3, 159.6, 142.7, 138.1, 127.7, 127.1, 126.2, 125.2, 104.4, 90.4, 62.0, 55.8, 55.5, 55.1, 33.3, 32.2.$

IR (neat): $\nu = 2939, 1737, 1596, 1459, 1131, 728$ cm$^{-1}$.

HRMS (ESI): Calculated for C$_{20}$H$_{21}$N$_2$NaO$_4$ ([M+Na]$^+$): 362.1363; found: 362.1365

1-(2,4,6-Trimethoxybenzyl)-2a,3,4,8b-tetrahydronaphtho[1,2-b]azet-2(1H)-one 2.80:

![Chemical Structure](image)

**Conditions A:** Two-chamber system:

Following general procedure A, Chamber A was filled with Pd(OAc)$_2$ (8.9 mg, 0.04 mmol, 30 mol%), P(t-Bu)$_3$HBF$_4$ (12 mg, 0.04 mmol, 30 mol%), COgen (97 mg, 0.4 mmol, 3.0 equiv), $\text{Cy}_2\text{NMe}$ (161 mg, 0.798 mmol, 6.0 equiv) and mesitylene (0.5 mL). Chamber B, previously
charged with (1,2,3,4-tetrahydronaphthalen-1-yl)(2,4,6-trimethoxybenzyl)carbamoyl chloride (51.9 mg, 0.133 mmol, 1 equiv) was reacted with PdCl₂ (2.4 mg, 0.0133 mmol, 10 mol%), cataCXium A.HI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL). The two chambers system was reacted for 18h at 120 °C. The crude mixture was purified by flash chromatography using first cyclohexane to elute mesitylene and then cyclohexane/EtOAc (75:25 to 0:1) as eluent, to provide oil 2.80 (47.0 mg, 0.133 mmol, 100%).

Conditions B: CO atmosphere

Following general procedure B, (1,2,3,4-tetrahydronaphthalen-1-yl)(2,4,6-trimethoxybenzyl)carbamoyl chloride (51.9 mg, 0.133 mmol, 1 equiv) was reacted with PdCl₂ (2.4 mg, 0.0133 mmol, 10 mol%), cataCXium A.HI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL), under CO atmosphere. The mixture was stirred for 18h at 120 °C. The crude mixture was purified by flash chromatography using first cyclohexane to elute mesitylene and then cyclohexane/EtOAc (75:25 to 0:1) as eluent, to provide oil 2.80 (22.6 mg, 0.064 mmol, 48%).

\(^1\)H NMR (400 MHz, Chloroform-d): \(\delta = 7.22 – 7.12 \text{ (m, } 1\text{H}), 7.12 – 7.06 \text{ (m, } 1\text{H}), 7.02 \text{ (m, } 1\text{H}), 6.80 \text{ (m, } 1\text{H}), 6.00 \text{ (s, } 2\text{H}), 4.44 \text{ (d, } J = 13.9 \text{ Hz, } 1\text{H}), 4.31 \text{ (d, } J = 4.9 \text{ Hz, } 1\text{H}), 4.04 \text{ (d, } J = 13.8 \text{ Hz, } 1\text{H}), 3.80 \text{ (s, } 3\text{H}), 3.73 \text{ (s, } 6\text{H}), 3.55 – 3.47 \text{ (m, } 1\text{H}), 2.86 – 2.56 \text{ (m, } 2\text{H}), 2.37 – 2.24 \text{ (m, } 1\text{H}), 1.57 \text{ – 1.36 \text(m, } 1\text{H}).

\(^13\)C NMR (Chloroform-d, 101 MHz): \(\delta = 169.4, 161.2, 159.6, 139.9, 133.2, 130.6, 128.4, 127.8, 125.6, 103.8, 90.2, 55.6, 55.5, 53.6, 49.7, 33.0, 27.0, 23.0.\)

IR (neat): \(v = 2935, 1737, 1597, 1133 \text{ cm}^{-1}.\)

HRMS (ESI): Calculated for C\(_{21}\)H\(_{23}\)NNaO\(_4\) ([M+Na]⁺): 376.1519; found: 376.1521

(−)\(2(aR,8bR)-1-(2,4,6\text{-Trimethoxybenzyl})-2a,3,4,8b\text{-tetrahydronaphtho}[1,2-b]azet-2(1H)\text{-one 2.97p:}

[Diagram of the molecule]

Chemical Formula: C\(_{21}\)H\(_{23}\)NO\(_4\)
Exact Mass: 353.1627
**Standard synthesis:**

**Conditions A:** Two-chamber system:

Following general procedure A, Chamber A was filled with Pd(OAc)$_2$ (8.9 mg, 0.04 mmol, 30 mol%), P(t-Bu)$_3$.HBF$_4$ (12 mg, 0.04 mmol, 30 mol%), COgen (97 mg, 0.4 mmol, 3.0 equiv), Cy$_2$NMe (161 mg, 0.798 mmol, 6.0 equiv) and mesitylene (0.5 mL). Chamber B, previously charged with (1,2,3,4-tetrahydronaphthalen-1-yl)(2,4,6-trimethoxybenzyl)carbamoyl chloride (51.9 mg, 0.133 mmol, 1 equiv) was reacted with PdCl$_2$ (2.4 mg, 0.0133 mmol, 10 mol%), catacXium A.HI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL). The two chambers system was reacted for 18h at 120 °C. The crude mixture was purified by flash chromatography using first cyclohexane to elute mesitylene and then cyclohexane/EtOAc (75:25 to 0:1) as eluent, to provide oil **2.97p** (46.0 mg, 0.130 mmol, 98 %).

**Conditions B:** CO atmosphere

Following general procedure B, (1,2,3,4-tetrahydronaphthalen-1-yl)(2,4,6-trimethoxybenzyl)carbamoyl chloride (51.9 mg, 0.133 mmol, 1 equiv) was reacted with PdCl$_2$ (2.4 mg, 0.0133 mmol, 10 mol%), catacXium A.HI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL), under CO atmosphere. The mixture was stirred for 18h at 120 °C. The crude mixture was purified by flash chromatography using first cyclohexane to elute mesitylene and then cyclohexane/EtOAc (75:25 to 0:1) as eluent, to provide oil **2.97p** (32 mg, 0.09 mmol, 63 %).

**Tenfold scale synthesis:**

**Conditions A:** Two-chamber system:

Following general procedure A, Chamber A was filled with Pd(OAc)$_2$ (89 mg, 0.4 mmol, 30 mol%), P(t-Bu)$_3$.HBF$_4$ (120 mg, 0.4 mmol, 30 mol%), COgen (970 mg, 4 mmol, 3.0 equiv), Cy$_2$NMe (1.610 g, 7.98 mmol, 6.0 equiv) and mesitylene (5 mL). Chamber B, previously charged with (1,2,3,4-tetrahydronaphthalen-1-yl)(2,4,6-trimethoxybenzyl)carbamoyl chloride (519 mg, 1.33 mmol, 1 equiv) was reacted with PdCl$_2$ (24 mg, 0.133 mmol, 10 mol%), catacXium A.HI (120 mg, 0.266 mmol, 20 mol%), pivalic acid (41 mg, 0.4 mmol, 30 mol%) and cesium carbonate (130 g, 4 mmol, 3.0 equiv) in mesitylene (26.2 mL). The two chambers system was reacted for 18h at 120 °C. The crude mixture was purified by flash chromatography using first cyclohexane...
to elute mesitylene and then cyclohexane/EtOAc (75:25 to 0:1) as eluent, to provide oil 2.97p (385 mg, 1.09 mmol, 82 %).

Optical rotation : $[\alpha]_{D}^{20} = -38.8^\circ$ (c = 1.3, CHCl$_3$)

1-(2,4,6-Trimethoxybenzyl)-1,2a,3,7b-tetrahydro-2H-indeno[1,2-b]azet-2-one 2.81:

Conditions A: Two-chamber system:

Following general procedure A, Chamber A was filled with Pd(OAc)$_2$ (8.9 mg, 0.04 mmol, 30 mol%), P(t-Bu)$_3$HBF$_4$ (12 mg, 0.04 mmol, 30 mol%), COgen (97 mg, 0.4 mmol, 3.0 equiv), Cy$_2$NMe (161 mg, 0.798 mmol, 6.0 equiv) and mesitylene (0.5 mL). Chamber B, previously charged with (2,3-dihydro-1H-inden-1-yl)(2,4,6-trimethoxybenzyl)carbamoyl chloride (50 mg, 0.133 mmol, 1 equiv) was reacted with PdCl$_2$ (2.4 mg, 0.0133 mmol, 10 mol%), catacXium A.HI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL). The two chambers system was reacted for 18h at 120 °C. The crude mixture was purified by flash chromatography using first cyclohexane to elute mesitylene and then cyclohexane/EtOAc (75:25 to 0:1) as eluent, to provide oil 2.81 (21 mg, 0.062 mmol, 47 %).

Conditions B: CO atmosphere

Following general procedure B, (2,3-dihydro-1H-inden-1-yl)(2,4,6-trimethoxybenzyl)carbamoyl chloride (50 mg, 0.133 mmol, 1 equiv) was reacted with PdCl$_2$ (2.4 mg, 0.0133 mmol, 10 mol%), catacXium A.HI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL), under CO atmosphere. The mixture was stirred for 18h at 120 °C, The crude mixture was purified by flash chromatography using first cyclohexane to elute mesitylene and then cyclohexane/EtOAc (75:25 to 0:1) as eluent, to provide oil 2.81 (11 mg, 0.032 mmol, 25 %).

$^1$H NMR (400 MHz, Chloroform-d) $\delta$ = 7.28 – 7.23 (m, 2H), 7.15 – 7.11 (m, 2H), 6.13 (s, 2H), 4.72 (dd, $J = 4.2$, 1.0 Hz, 1H), 4.56 (d, $J = 14.1$ Hz, 1H), 4.04 (d, $J = 14.1$ Hz, 1H), 3.85 – 3.82 (m, 1H), 3.36 – 3.27 (m, 1H), 2.97 (dd, $J = 17.4$, 10.4 Hz, 1H).
**13C NMR (101 MHz, Chloroform-\textit{d})\ δ = 169.7, 161.3, 159.7, 145.2, 139.6, 128.7, 126.4, 126.0, 104.7, 90.5, 62.0, 55.8, 55.5, 52.3, 33.0, 33.0, 30.2.**

**IR (neat):** ν = 1743, 670 cm\textsuperscript{-1}.

**HRMS (ESI):** Calculated for C\textsubscript{20}H\textsubscript{21}NNaO\textsubscript{4} ([M+Na]\textsuperscript{+}): 312.1368; found: 312.1369

**7-Cyclohexyl-7-azabicyclo[4.2.0]octan-8-one 2.82:**

![Chemical structure of 7-Cyclohexyl-7-azabicyclo[4.2.0]octan-8-one 2.82]

**Chemical Formula:** C\textsubscript{15}H\textsubscript{19}NO

**Exact Mass:** 207.1623

**Conditions A:** Two-chamber system:

Following **general procedure A**, Chamber A was filled with Pd(OAc)\textsubscript{2} (8.9 mg, 0.04 mmol, 30 mol%), P(t-Bu)\textsubscript{3}HBF\textsubscript{4} (12 mg, 0.04 mmol, 30 mol%), COgen (97 mg, 0.4 mmol, 3.0 equiv), Cy\textsubscript{2}NMe (161 mg, 0.798 mmol, 6.0 equiv) and mesitylene (0.5 mL). Chamber B, previously charged with dicyclohexylcarbamoyl chloride (32.4 mg, 0.133 mmol, 1 equiv) was reacted with PdCl\textsubscript{2} (2.4 mg, 0.0133 mmol, 10 mol%), catacXium A.HI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL). The two chambers system was reacted for 18h at 120 °C. The crude mixture was purified by flash chromatography using first cyclohexane to elute mesitylene and then cyclohexane/EtOAc (75:25 to 0:1) as eluent, to provide oil 2.82 (8.5 mg, 0.041 mmol, 29 %).

**Conditions B:** CO atmosphere

Following **general procedure B**, dicyclohexylcarbamoyl chloride (32.4 mg, 0.133 mmol, 1 equiv) was reacted with PdCl\textsubscript{2} (2.4 mg, 0.0133 mmol, 10 mol%), catacXium A.HI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL), under CO atmosphere. The mixture was stirred for 18h at 120 °C. The crude mixture was purified by flash chromatography using first cyclohexane to elute mesitylene and then cyclohexane/EtOAc (75:25 to 0:1) as eluent, to provide oil 2.82 (7 mg, 0.034 mmol, 25 %).

**1H NMR (250 MHz, Chloroform-d)** δ = 3.78 (dt, J = 5.5, 3.6 Hz, 1H), 3.46 (ddt, J = 11.5, 7.8, 3.6 Hz, 1H), 3.08 (td, J = 5.5, 4.1 Hz, 1H), 1.89 – 1.20 (m, 22H + H\textsubscript{2}O).

**13C NMR (63 MHz, Chloroform-d)** δ = 170.3, 51.5, 49.3, 46.1, 32.0, 30.7, 25.4, 25.3, 24.7, 19.6, 18.7, 16.9.
IR (neat): \( \nu = 2932, 1732 \text{ cm}^{-1} \).

HRMS (ESI): Calculated for \( \text{C}_{13}\text{H}_{21}\text{NNaO} \) ([M+Na]+): 230.1515; found: 230.1513

**Trans-4-ethyl-3-methyl-1-(2,4,6-trimethoxybenzyl)azetidin-2-one** and **Cis-4-ethyl-3-methyl-1-(2,4,6-trimethoxybenzyl)azetidin-2-one 2.83:**

![Chemical Structure](image_url)

**Conditions A:** Two-chamber system:

Following general procedure A, Chamber A was filled with Pd(OAc)\(_2\) (8.9 mg, 0.04 mmol, 30 mol%), P(t-Bu)\(_3\)HBF\(_4\) (12 mg, 0.04 mmol, 30 mol%), COgen (97 mg, 0.4 mmol, 3.0 equiv), Cy\(_2\)NMe (161 mg, 0.798 mmol, 6.0 equiv) and mesitylene (0.5 mL). Chamber B, previously charged with Pentan-3-yl(2,4,6-trimethoxybenzyl)carbamoyl (43.9 mg, 0.133 mmol, 1 equiv) was reacted with PdCl\(_2\) (2.4 mg, 0.0133 mmol, 10 mol%), cataXium A.HI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL). The two chambers system was reacted for 18h at 120 °C. The crude mixture was purified by flash chromatography using first cyclohexane to elute mesitylene and then cyclohexane/EtOAc (75:25 to 0:1) as eluent, to provide oil 2.83 (20 mg, 0.068 mmol, 51%).

**Conditions B:** CO atmosphere

Following general procedure B, Pentan-3-yl(2,4,6-trimethoxybenzyl)carbamoyl (43.9 mg, 0.133 mmol, 1 equiv) was reacted with PdCl\(_2\) (2.4 mg, 0.0133 mmol, 10 mol%), cataXium A.HI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL), under CO atmosphere. The mixture was stirred for 18h at 120 °C. The crude mixture was purified by flash chromatography using first cyclohexane to elute mesitylene and then cyclohexane/EtOAc (75:25 to 0:1) as eluent, to provide oil 2.83 (16 mg, 0.055 mmol, 41%).

**Trans-4-ethyl-3-methyl-1-(2,4,6-trimethoxybenzyl)azetidin-2-one :**
\(^1\)H NMR (500 MHz, Chloroform-\(d\)) \(\delta = 6.11\) (s, 2H), 4.55 (d, \(J = 13.9\) Hz, 1H), 4.16 (dd, \(J = 13.9, 1.1\) Hz, 1H), 3.82 (s, 3H), 3.80 (s, 6H), 2.78 – 2.74 (m, 1H), 2.66 – 2.61 (m, 1H), 1.71 – 1.63 (m, 1H), 1.34 – 1.26 (m, 1H), 1.17 (d, \(J = 7.3\) Hz, 3H), 0.81 (t, \(J = 7.5\) Hz, 3H).

\(^{13}\)C NMR (126 MHz, Chloroform-\(d\)) \(\delta = 170.5, 161.1, 159.7, 104.5, 90.3, 55.8, 55.4, 48.9, 32.7, 25.2, 13.4, 9.4\).

IR (neat): \(\nu = 2952, 1749, 1610, 1140, 740\) cm\(^{-1}\).

HRMS (ESI): Calculated for C\(_{16}\)H\(_{23}\)NNaO\(_4\) ([M+Na]\(^+\)): 316.1525; found: 316.1528

Cis-4-ethyl-3-methyl-1-(2,4,6-trimethoxybenzyl)azetidin-2-one:

\(^1\)H NMR (500 MHz, Chloroform-\(d\)) \(\delta = 6.11\) (s, 2H), 4.58 (d, \(J = 13.4\) Hz, 1H), 4.11 (d, \(J = 14.0\) Hz, 1H), 3.81 (s, 3H), 3.80 (s, 6H), 3.18 – 3.14 (m, 1H), 3.10 – 3.04 (m, 1H), 1.72 – 1.66 (m, 1H), 1.43 – 1.35 (m, 1H), 1.16 (d, \(J = 6.6\) Hz, 3H), 0.81 (t, \(J = 7.5\) Hz, 3H).

\(^{13}\)C NMR (126 MHz, Chloroform-\(d\)) \(\delta = 171.0, 56.3, 55.8, 46.3, 32.6, 21.3, 10.7, 9.0\).

\((R)\)-4-Methylazetidin-2-one 2.86:

\[\text{Chemical Formula: C}_{2}\text{H}_{7}\text{NO} \]

Exact Mass: 85.0528

4-methyl-1-(2,4,6-trimethoxybenzyl)azetidin-2-one (135 mg, 0.509 mmol, 1 equiv), K\(_2\)S\(_2\)O\(_8\) (275 mg, 1.02 mmol, 2 equiv) and Na\(_2\)HPO\(_4\).7H\(_2\)O (273 mg, 1.02 mmol, 2equiv) were stirred for 3h at 80 \(^\circ\)C in MeCN/H\(_2\)O [2:1] (18 mL). Then, the crude mixture was dried over MgSO\(_4\), filtered and evaporated. The residue was purified by chromatography on silica gel using AcOEt/EtOH [95:5] as eluent to provide \((R)\)-4-methylazetidin-2-one 2.86 (33 mg, 0.388 mmol, 76 \%) as a yellowish oil.

\(^1\)H NMR (250 MHz, Chloroform-\(d\)) \(\delta = 5.89\) (br s, 1H), 3.83 – 3.73 (m, 1H), 3.11 (ddd, \(J = 14.7, 5.0, 2.1\) Hz, 1H), 2.55 (ddd, \(J = 14.8, 2.4, 1.5\) Hz, 1H), 1.36 (d, \(J = 6.1\) Hz, 3H).

\(^{13}\)C NMR (63 MHz, Chloroform-\(d\)) \(\delta = 168.2, 45.1, 44.0, 21.3\).

IR (neat): \(\nu = 1739, 1381, 908, 728\) cm\(^{-1}\).

\([\alpha]_D^{20} = +2.8^\circ\) (c = 1.14, CHCl\(_3\)) ; lit. +3.6 (c = 2.3, CHCl\(_3\)).

The physical and spectroscopic properties matched those described in the literature.\(^{16}\)

\((-\)2a,3,4,8b-Tetrahydronaphtho[1,2-b]azet-2(1\(H\)))-one 2.97:
Compound **2.97p** (95 mg, 0.269 mmol, 1 equiv), K$_2$S$_2$O$_8$ (145 mg, 0.538 mmol, 2 equiv) and Na$_2$HPO$_4$.7H$_2$O (144 mg, 0.538 mmol, 2 equiv) were stirred for 3h at 80 °C in MeCN/H$_2$O [2:1] (9.4 mL). Then, the crude mixture was filtered through a pad of MgSO$_4$, and rinsed with MeCN. The filtrate was then treated with NBS (52.7 mg, 0.296 mmol, 1.1 equiv) and TMSCl (3.5 mL, 0.0269 mmol, 0.1 equiv) and stirred for 30 min. The crude mixture was then evaporated and purified by chromatography on silica gel using DCM/MeOH 99:1 as eluent to provide oil compound **2.97** (42 mg, 0.245 mmol, 91 %).

$^1$H NMR (250 MHz, Chloroform-$_d$) $\delta = 7.27 – 7.06$ (m, 4H), 6.21 (s, 1H), 4.59 (d, $J = 5.0$ Hz, 1H), 3.65 – 3.59 (m, 1H), 2.83 – 2.57 (m, 2H), 2.28 – 2.17 (m, 1H), 1.69 – 1.42 (m, 1H).

$^{13}$C NMR (63 MHz, Chloroform-$_d$) $\delta = 170.8, 139.4, 134.1, 129.7, 129.1, 128.5, 126.6, 51.5, 50.6, 26.9, 23.0$.

HRMS (ESI): Calculated for C$_{11}$H$_{11}$NNaO ([M+Na]$^+$): 196.0733; found: 196.0731

Optical rotation : $[\alpha]_{D}^{20} = -89.3^\circ$ (c = 1.0, CHCl$_3$)

The physical and spectroscopic properties matched those described in the literature.$^{17}$

**(1R,2R)-1-Amino-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid hydrochloride 2.98:**

Following a methodology from F. Fulöp et al., compound **2.97** was refluxed for 3h in an aqueous HCl solution (2 mL, 6M). The solvent was removed under vacuum to provide oil compound **2.98** as a yellowish solid (32 mg, 0.139 mmol, 100 %).

$^1$H NMR (250 MHz, D$_2$O) $\delta = 7.42 – 7.24$ (m, 4H), 4.82 (d, $J = 3.5$ Hz, 1H), 3.19 (dt, $J = 12.0, 3.5$ Hz, 1H), 3.10 – 2.91 (m, 2H), 2.37 – 2.23 (m, 1H), 2.15 – 1.95 (m, 1H).

$^{13}$C NMR (101 MHz, D$_2$O) $\delta = 176.8, 136.6, 130.0, 129.7, 129.5, 128.8, 126.6, 49.5, 41.3, 27.0, 20.2$.

The physical and spectroscopic properties matched those described in the literature.
Chapter 1.3: Domino Pd\textsuperscript{0}-Catalysed C(sp\textsuperscript{3})-H Arylation/Electrocyclic Reactions via Benzazetidine Intermediates

**Supplementary schemes**

**Scheme S1.** Unified mechanism explaining the formation of the demethylated product and benzoxazine isomers.

After oxidative addition of substrate 1 and substitution of the bromide with pivalate, base-mediated C(sp\textsuperscript{3})–H activation\textsuperscript{18} leads to palladacycle B\textsuperscript{1}. Carbonate-mediated decoordination of pivalic acid leads to palladacycle C, which furnishes BAZ1 upon reductive elimination. Thermal 4\(\pi\)/6\(\pi\) electrocyclic reactions lead ultimately to BOX1. Alternatively, complex B\textsuperscript{1} undergoes proton transfer to the aromatic ring to give the open Pd complex D.\textsuperscript{19} The latter can undergo pivalate-mediated C(sp\textsuperscript{3})–H activation to give palladacycle B\textsuperscript{2}, which leads to isomeric BOX2 via BAZ2 in a similar way to B\textsuperscript{1}. However, when Z is a methyl group, complex D preferentially undergoes elimination to give the iminium E, which hydrolyzes to give the observed demethylated product.\textsuperscript{20}
**Scheme S2.** Top: computed reductive elimination leading to benzazetidines with three different nitrogen substituents; bottom: Non-Covalent Interaction (NCI) maps\textsuperscript{21} of the three transition states.

(a) $Z = \text{Me}$

(b) $Z = \text{CO}_2\text{Me}$

(c) $Z = \text{CO}(1\text{-Ad})$

See also computational details.
General procedures

**General procedure for acid chloride synthesis:**

Carboxylic acids (1 eq) were dissolved in dichloromethane (0.1 M) with DMF (1 drop). Oxalyl chloride (2 eq) was added and the reaction was stirred for 2 h. The volatiles were removed under vacuum and the acid chlorides were used without further purification.

**General procedure for amide synthesis:**

Acid chloride (1.5 eq) were dissolved in dichloromethane (0.1M) or 1,2-dichloroethane (0.1 M) (as specified) and o-bromo substituted anilines (1 eq), Et₃N (2 eq) in dichloromethane (0.1M) or 1,2-dichloroethane (0.1 M) (as specified) were added carefully at room temperature. The mixture was stirred at 60°C and followed by TLC (Cyclohexane/AcOEt). After completion, the solvent was removed under vacuum and the crude mixture was purified by chromatography over silica gel (cyclohexane/AcOEt).

Amides (1 eq) were dissolved in THF (0.1 M) and sodium hydride (60 % dispersion in oil, 2 eq) was carefully added to the turning solution. The mixture was stirred for 10 minutes, followed by addition of alkyl iodide (2 eq). The mixture was stirred at reflux, and the reaction was followed by TLC (cyclohexane/AcOEt). After completion, the reaction was carefully quenched with water, and extracted 3 times with AcOEt. The combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum. The desired N-methylated amides were purified by chromatography on silica gel, using cyclohexane/AcOEt.

**General procedure for benzoxazine synthesis:**

In a 10 mL screw-cap tube charged with amide (0.1 mmol, 1 equiv) was weighted in a glovebox Pd(PCy₃)₂ (0.01 mmol, 6.7 mg, 10 mol %), cesium pivalate (0.03 mmol, 7.1 mg, 30 mol %) (or Adamantane carboxylic acid (0.03 mmol, 5.4 mg, 30 mol %) as specified) and Cs₂CO₃ (0.3 mmol, 98 mg, 3 equiv). The vial was charged with o-xylene (2 mL), sealed and stirred under argon in a previously heated heating block at 160 °C for 15 h. The reaction was cooled to room temperature, filtered over celite, and evaporated under vacuum. The crude mixture was purified by preparative HPLC using gradient of solvent (H₂O: MeCN) [90:10] to [10:90]. The collected fraction were evaporated under vacuum to afford the desired product.
Synthesis of C–H activation substrates

**tert-butyl (2-bromophenyl)(methyl)carbamate 3.15b**

\[
\begin{align*}
\text{Chemical Formula: } & C_{12}H_{16}BrNO_2 \\
\text{Exact Mass: } & 285.0364
\end{align*}
\]

2-bromoaniline (1 g, 5.81 mmol, 1 eq), Boc₂O (1.9 g, 8.72 mmol, 1.5 eq) and sodium carbonate (925 mg, 8.72 mmol, 1.5 eq) were reacted in dioxane/water [1:1] (5 mL) at 80 °C for 6 h. After cooling to room temperature, the crude mixture was quenched with water (20 mL) and extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried over Na₂SO₄, filtered and evaporated under vacuum. The crude mixture was purified by chromatography on silica gel using cyclohexane/AcOEt [9:1]. The desired carbamate was used for next step (1.35 g, 4.96 mmol, 85 %).

The intermediate amide (1.35 g, 4.96 mmol, 1 eq) was dissolved in THF (30 mL) and sodium hydride (60 % dispersion in oil, 400 mg, 9.92 mmol, 2 eq) was carefully added. The mixture was stirred for 10 minutes at room temperature, followed by addition of iodomethane (0.60 mL, 9.92 mmol, 2 eq). The reaction was then stirred for 2 h, and quenched with water (30 mL). The crude mixture was extracted with AcOEt (3 x 20 mL) and the combined organic phases were dried over Na₂SO₄, filtered and evaporated under vacuum. The crude mixture was purified by chromatography over silica gel using cyclohexane/AcOEt as solvent [9:1] to afford the pure compound as a colorless oil (1 g, 3.5 mmol, 71%).

**¹H NMR (400 MHz, Chloroform-d)** \(\delta = 7.63 – 7.56 \text{ (m, } 1H)\), 7.33 – 7.27 (m, 1H), 7.24 – 7.18 (m, 1H), 7.16 – 7.10 (m, 1H), 3.15 (s, 3H), 1.34 (s, 9H).

**¹³C NMR (101 MHz, CDCl₃)** \(\delta = 154.6, 142.7, 133.6, 133.2, 130.1, 129.5, 128.9, 128.6, 128.3, 123.5, 123.4, 80.7, 80.2, 37.4, 36.4, 28.5, 28.3.\)
methyl (2-bromophenyl)(methyl)carbamate 3.15c:

\[
\begin{array}{c}
\text{\ding{115}} \\
\begin{array}{c}
\text{N} \\
\text{O}
\end{array}
\end{array}
\]

Chemical Formula: C_{9}H_{10}BrNO_{2}

Exact Mass: 242.9895

O-bromo-N-methylaniline (150 mg, 0.806 mmol, 1 eq) was stirred in methylchloroformate (3 mL) at reflux for 14 h. The crude mixture was evaporated under vacuum and purified by chromatography on silica gel using cyclohexane/AcOEt as solvent [9:1]. The product was obtained as a colorless oil (171 mg, 0.7 mmol, 87 %).

\[ \text{^1H NMR (400 MHz, Chloroform-d) } \delta = 7.64 - 7.59 (m, 1H), 7.36 - 7.31 (m, 1H), 7.27 - 7.23 (m, 1H), 7.20 - 7.13 (m, 1H), 3.82 - 3.56 (m, 3H), 3.20 (s, 3H). \]

\[ \text{^13C NMR (101 MHz, CDCl}_3) \delta = 156.0, 142.0, 133.5, 129.5, 129.1, 128.6, 123.4, 53.3, 37.3. \]

N-(2-bromophenyl)-1,1,1-trifluoro-N-methylmethanesulfonamide 3.15d:

\[
\begin{array}{c}
\text{\ding{115}} \\
\begin{array}{c}
\text{N} \\
\text{SO}_2\text{CF}_3
\end{array}
\end{array}
\]

Chemical Formula: C_{8}H_{7}BrF_{3}NO_{2}S

Exact Mass: 316.9333

O-bromo-N-methylaniline (150 mg, 0.806 mmol, 1 eq) was dissolved in dichloromethane (5 mL) and sodium hydride (60 % dispersion in oil, 65 mg, 1.61 mmol, 2 eq) was carefully added. The mixture was stirred for 10 minutes at room temperature, followed by addition of Tf\textsubscript{2}O (0.41 mL, 2.42 mmol, 3 eq). The reaction was then stirred for 2 h, and quenched with water (5 mL). The crude mixture was extracted with dichloromethane (3 x 5 mL) and the combined organic phases were dried over Na\textsubscript{2}SO\textsubscript{4}, filtered and evaporated under vacuum. The crude mixture was purified by chromatography over silica gel using cyclohexane/AcOEt as solvent [9:1]. The product was obtained as a yellowish solid (170 mg, 0.53 mmol, 66 %).

\[ \text{^1H NMR (400 MHz, Chloroform-d) } \delta = 7.72 - 7.67 (m, 1H), 7.44 - 7.36 (m, 2H), 7.32 - 7.27 (m, 1H), 3.41 (s, 3H). \]
$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ = 138.4, 134.4, 131.1, 130.8, 129.0, 125.0, 124.6, 121.8, 118.6, 115.4, 40.1.

$^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ = -74.85.

HRMS (ESI): Calculated for C$_8$H$_8$BrF$_3$NO$_2$S ([M+H]$^+$): 317.9411; found: 317.9413

m.p.: 70-72°C

N-(2-bromophenyl)-2,2,2-trifluoro-N-methylacetamide 3.15e:

![Chemical Structure](image)

Chemical Formula: C$_9$H$_7$BrF$_3$NO

Exact Mass: 280.9663

O-bromo-N-methylaniline (150 mg, 0.806 mmol, 1 eq) was dissolved in dichloromethane (5 mL) and sodium hydride (60% dispersion in oil, 65 mg, 1.61 mmol, 2 eq) was carefully added. The mixture was stirred for 10 minutes at room temperature, followed by addition of (CF$_3$CO)$_2$O (0.34 mL, 2.42 mmol, 3 eq). The reaction was then stirred for 2 h, and quenched with water (5 mL). The crude mixture was extracted with dichloromethane (3 x 5 mL) and the combined organic phases were dried over Na$_2$SO$_4$, filtered and evaporated under vacuum. The crude mixture was purified by chromatography over silica gel using cyclohexane/AcOEt as solvent [9:1]. The product was obtained as a yellowish oil (140 mg, 0.49 mmol, 61%).

$^1$H NMR (500 MHz, Chloroform-d) $\delta$ = 7.70 – 7.66 (m, 1H), 7.43 – 7.37 (m, 1H), 7.33 – 7.28 (m, 2H), 3.44 – 3.42 (m, 0.3H), 3.31 (s, 2.7H).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ = 157.4, 157.2, 156.9, 156.6, 141.0, 139.5, 134.1, 133.9, 130.9, 130.3, 130.1, 130.0, 130.0, 129.2, 128.7, 128.7, 123.3, 121.6, 119.6, 117.3, 115.0, 112.7, 38.1.

$^{19}$F NMR (471 MHz, CDCl$_3$) $\delta$ = -68.7, -70.2.

HRMS (ESI): Calculated for C$_9$H$_7$BrF$_3$NO ([M+H]$^+$): 281.9741; found: 281.9743

IR (neat) : $\nu$ = 1662 cm$^{-1}$
N-(2-bromophenyl)-N-methylcyclobutanecarboxamide 3.15f:

![Chemical structure](image)

Chemical Formula: C$_{12}$H$_{14}$BrNO
Exact Mass: 267.0259

Following general procedure for amides synthesis, cyclobutane acid chloride (270 mg, 2.28 mmol, 2 eq), o-bromoaniline (200 mg, 1.15 mmol, 1 eq), Et$_3$N (0.32 mL, 2.28 mmol, 2 eq) were reacted in dichloromethane (12 mL). After purification, the cyclobutane amide (289 mg, 1.15 mmol, 1 eq) was reacted with sodium hydride (60 % dispersion in oil, 130 mg, 3.2 mmol, 3 eq), iodomethane (0.40 mL, 6 mmol, 6 eq) in THF (10 mL). After extraction and purification, the desired amide was obtained as a white solid (240 g, 0.89 mmol, 77 %).

$^1$H NMR (500 MHz, Chloroform-d) $\delta = 7.68 – 7.65$ (m, 1H), 7.38 – 7.34 (m, 1H), 7.26 – 7.23 (m, 1H), 7.23 – 7.19 (m, 1H), 3.18 (s, 3H), 2.90 – 2.82 (m, 1H), 2.44 – 2.37 (m, 1H), 2.29 – 2.22 (m, 1H), 1.79 – 1.69 (m, 4H).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta = 174.8, 142.7, 133.9, 130.3, 129.7, 128.8, 123.8, 38.2, 36.0, 26.4, 25.0, 18.1.$

HRMS (ESI): Calculated for C$_{12}$H$_{15}$BrNO ([M+H]$^+$): 268.0337; found: 268.0327

IR (neat) : $\nu = 2944, 1659$ cm$^{-1}$

m.p.: 90-92°C

N-(2-bromophenyl)-N-methylpivalamide 3.15g 24:

![Chemical structure](image)

Chemical Formula: C$_{12}$H$_{16}$BrNO
Exact Mass: 269.0415

Following general procedure for amides synthesis, pivaloyl acid chloride (1.75 mL, 13.9 mmol, 1.2 eq), o-bromoaniline (2 g, 11.5 mmol, 1 eq), Et$_3$N (3.26 mL, 23.2 mmol, 2 eq) were reacted in dichloromethane (50 mL). After purification, the pivaloyl amide (2.7 g, 10.5 mmol, 1 eq) was reacted with sodium hydride (60 % dispersion in oil, 630 mg, 15.8 mmol, 1.5 eq), iodomethane
(0.98 mL, 15.8 mmol, 1.5 eq) in THF (30 mL). After extraction and purification, the desired amide was obtained as a white solid (2.11 g, 7.81 mmol, 68%).

\[^1\text{H} \text{NMR (400 MHz, Chloroform-}d\text{)} \delta = 7.66 - 7.61 (m, 1H), 7.37 - 7.27 (m, 2H), 7.23 - 7.18 (m, 1H), 3.17 (s, 3H), 1.07 (s, 9H).\]

\[^{13}\text{C} \text{NMR (101 MHz, CDCl}_3\text{)} \delta = 178.0, 144.3, 133.9, 130.7, 129.6, 128.4, 124.4, 39.6, 29.1.\]

(3r,5r,7r)-N-(2-bromophenyl)-N-methyladamantane-1-carboxamide 3.15h:

Following general procedure for amides synthesis, adamantyl acid chloride (2.98 g, 15 mmol, 1.5 eq), o-bromoaniline (1.7 g, 10 mmol, 1 eq), Et\textsubscript{3}N (2.77 mL, 20 mmol, 2 eq) were reacted in dichloromethane (60 mL). After purification, the adamantyl amide (2.9 g, 8.7 mmol, 1 eq) was reacted with sodium hydride (60 % dispersion in oil, 696 mg, 17.4 mmol, 2 eq), iodomethane (1.07 mL, 17.4 mmol, 2 eq) in THF (50 mL). After extraction and purification, the desired amide was obtained as a white solid (2.3 g, 6.6 mmol, 75%).

\[^1\text{H} \text{NMR (400 MHz, Chloroform-}d\text{)} \delta = 7.66 - 7.60 (m, 1H), 7.37 - 7.31 (m, 1H), 7.30 - 7.27 (m, 1H), 7.24 - 7.18 (m, 1H), 3.14 (s, 3H), 1.91 - 1.83 (m, 6H), 1.69 - 1.64 (m, 4H), 1.60 - 1.48 (m, 5H).\]

\[^{13}\text{C} \text{NMR (101 MHz, CDCl}_3\text{)} \delta = 183.5, 177.7, 144.2, 133.7, 130.6, 129.4, 128.2, 124.2, 43.8, 40.4, 39.8, 39.6, 38.6, 36.4, 28.4, 27.8.\]

HRMS (ESI): Calculated for C\textsubscript{18}H\textsubscript{22}BrNO ([M+H]\textsuperscript{+}): 348.0963; found: 348.0958

IR (neat) : ν = 2361, 1622, 911 cm\textsuperscript{-1}

m.p.: 95-97°C

(3s)-N-(2-bromophenyl)-N-(methyl-d3)adamantane-1-carboxamide 3.15h-D3:
Following general procedure for amides synthesis, adamantyl acid chloride (300 mg, 1.5 mmol, 1.5 eq), o-bromoaniline (170 mg, 1 mmol, 1 eq), Et$_3$N (0.28 mL, 2 mmol, 2 eq) were reacted in dichloromethane (6 mL). After purification, the adamantyl amide (290 mg, 0.87 mmol, 1 eq) was reacted with sodium hydride (60 % dispersion in oil, 70 mg, 1.74 mmol, 2 eq), iodomethane-d$_3$ (0.11 mL, 0.17 mmol, 2 eq) in THF (5 mL). After extraction and purification, the desired amide was obtained as a white solid (210 mg, 0.6 mmol, 69 %).

$^1$H NMR (400 MHz, Chloroform-d) $\delta$ = 7.66 – 7.61 (m, 1H), 7.37 – 7.27 (m, 2H), 7.24 – 7.19 (m, 1H), 1.92 – 1.82 (m, 6H), 1.70 – 1.64 (m, 3H), 1.61 – 1.48 (m, 6H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ = 177.7, 144.1, 133.7, 130.6, 129.4, 128.2, 124.3, 43.8, 39.6, 36.4, 28.4.

HRMS (ESI): Calculated for C$_{18}$H$_{19}$D$_3$BrNO ([M+H]$^+$): 351.1151; found: 351.1154

IR (neat): $\nu$ = 2908, 1629, 1473 cm$^{-1}$

m.p.: 97-99°C

methyl 3-bromo-4-((3s)-N-methyladamantane-1-carboxamido)benzoate 3.28r:

Following general procedure for amides synthesis, adamantyl acid chloride (379 mg, 1.91 mmol, 1.5 eq), methyl-amino-3-bromobenzoate (291 mg, 1.27 mmol, 1 eq), Et$_3$N (0.35 mL, 2.54 mmol, 2 eq) were reacted in 1,2-dichloromethane (10 mL) at 60°C. After purification, the adamantyl amide (284 mg, 0.724 mmol, 1 eq) was reacted with sodium hydride (60 % dispersion in oil, 58 mg, 1.48 mmol, 2 eq), iodomethane (0.1 mL, 1.48 mmol, 2 eq) in THF (5 mL) at 65°C. After
extraction and purification, the desired amide was obtained as a yellowish solid (208 mg, 0.512 mmol, 40 %).

$^1$H NMR (400 MHz, Chloroform-d) $\delta = 8.33 – 8.31$ (m, 1H), 8.02 – 7.99 (m, 1H), 7.38 – 7.33 (m, 1H), 3.95 (s, 3H), 3.14 (s, 3H), 1.90 – 1.82 (m, 6H), 1.73 – 1.66 (m, 3H), 1.62 – 1.47 (m, 6H).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta = 177.7, 165.2, 148.5, 135.1, 131.2, 130.6, 129.6, 124.4, 52.8, 44.1, 39.9, 39.8, 36.5, 28.4.$

HRMS (ESI): Calculated for C$_{20}$H$_{25}$BrNO$_3$ ([M+H]$^+$): 406.1018; found: 406.1012

IR (neat) : $\nu = 2361, 1720, 1285$ cm$^{-1}$

m.p.: 122-124°C

(3s)-N-(2-bromo-4-(trifluoromethyl)phenyl)-N-methyladamantane-1-carboxamide 3.30r:

Following general procedure for amides synthesis, adamantyl acid chloride (1.57 g, 7.9 mmol, 1.5 eq), 2-bromo-4-trifluoromethylelaniline (1.26 g, 5.26 mmol, 1 eq), Et$_3$N (1.46 mL, 10.5 mmol, 2 eq) were reacted in 1,2-dichloroethane (40 mL) at 60 °C. After purification, the adamantyl amide (1.39 g, 3.47 mmol, 1 eq) was reacted with sodium hydride (60 % dispersion in oil, 278 mg, 6.94 mmol, 2 eq), iodomethane (0.45 mL, 6.94 mmol, 2 eq) in THF (30 mL) at 65°C. After extraction and purification, the desired amide was obtained as a white solid (940 mg, 2.26 mmol, 43 %).

$^1$H NMR (400 MHz, Chloroform-d) $\delta = 7.93 – 7.90$ (m, 1H), 7.64 – 7.59 (m, 1H), 7.42 – 7.38 (m, 1H), 3.15 (s, 3H), 1.92 – 1.83 (m, 6H), 1.76 – 1.67 (m, 3H), 1.65 – 1.50 (m, 6H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta = 177.6, 147.7, 131.6, 131.3, 131.0, 130.9, 125.3$ (q, J = 4.1 Hz), 124.6, 124.2, 121.5, 43.9, 39.7, 39.7, 36.3, 28.3.

HRMS (ESI): Calculated for C$_{19}$H$_{21}$BrF$_3$NONa ([M+Na]$^+$): 438.0656; found: 438.0654

IR (neat) : $\nu = 2909, 1629$ cm$^{-1}$

m.p.: 115-117°C
(3s)-N-(2-bromo-4-fluorophenyl)-N-methyladamantane-1-carboxamide 3.29r:

![Chemical Structure](image)

Chemical Formula: C_{18}H_{21}BrFNO  
Exact Mass: 365.0791

Following general procedure for amides synthesis, adamantyl acid chloride (257 mg, 1.19 mmol, 1.5 eq), 2-bromo-4-fluoroaniline (151 mg, 0.80 mmol, 1 eq), Et$_3$N (0.2 mL, 1.59 mmol, 2 eq) were reacted in 1,2-dichloroethane (7 mL) at 60°C. After purification, the adamantyl amide (196 mg, 0.56 mmol, 1 eq) was reacted with sodium hydride (60 % dispersion in oil, 45 mg, 1.11 mmol, 2 eq), iodomethane (0.07 mL, 1.11 mmol, 2 eq) in THF (5 mL) at 65°C. After extraction and purification, the desired amide was obtained as a yellowish solid (120 mg, 0.310 mmol, 39 %).

$^1$H NMR (400 MHz, Chloroform-d) $\delta = 7.40 – 7.36$ (m, 1H), $7.29 – 7.24$ (m, 1H), $7.09 – 7.04$ (m, 1H), $3.12$ (s, 3H), $1.90 – 1.82$ (m, 6H), $1.71 – 1.65$ (m, 3H), $1.62 – 1.50$ (m, 6H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta = 177.94$, $161.6$ (d, $J = 252.1$ Hz), $140.8$ (d, $J = 3.9$ Hz), $131.5$ (d, $J = 8.2$ Hz), $125.0$ (d, $J = 9.1$ Hz), $121.1$ (d, $J = 25.5$ Hz), $115.5$ (d, $J = 21.2$ Hz), $44.0$, $40.1$, $39.9$, $36.6$, $28.6$.

$^{19}$F NMR (376 MHz, CDCl$_3$) $\delta = -111.0$.

HRMS (ESI): Calculated for C$_{18}$H$_{22}$BrFNO ([M+H]$^+$): 366.0869; found: 366.0863

IR (neat) : $\nu = 1634$, $1490$ cm$^{-1}$

m.p.: 99-101°C

(3s)-N-(2-bromo-4-cyanophenyl)-N-methyladamantane-1-carboxamide 3.31r:

![Chemical Structure](image)

Chemical Formula: C$_{19}$H$_{21}$BrN$_2$O  
Exact Mass: 372.0837

Following general procedure for amides synthesis, adamantyl acid chloride (414 mg, 2.09 mmol, 1.5 eq), 4-amino-3-bromobenzonitrile (274 mg, 1.39 mmol, 1 eq), Et$_3$N (0.3 mL, 2.78 mmol, 2 eq) were reacted in 1,2-dichloroethane (12 mL) at 60°C. After purification, the
Adamantyl amide (355 mg, 0.987 mmol, 1 eq) was reacted with sodium hydride (60% dispersion in oil, 78 mg, 1.96 mmol, 2 eq), iodomethane (0.13 mL, 1.96 mmol, 2 eq) in THF (7 mL) at 65°C. After extraction and purification, the desired amide was obtained as a white solid (212 mg, 0.568 mmol, 41%).

$^1$H NMR (400 MHz, Chloroform-d) $\delta = 7.95 – 7.93$ (m, 1H), 7.67 – 7.63 (m, 1H), 7.41 – 7.37 (m, 1H), 3.14 (s, 3H), 1.91 – 1.85 (m, 3H), 1.83 – 1.68 (m, 6H), 1.63 – 1.47 (m, 6H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta = 177.5, 148.9, 137.2, 132.1, 131.3, 125.1, 116.8, 113.3, 44.0, 39.8, 39.6, 39.6, 36.4, 28.3$.

HRMS (ESI): Calculated for C$_{19}$H$_{21}$BrN$_2$ONa ([M+Na]$^+$): 395.0735; found: 395.0729

IR (neat): $\nu = 2906, 1640$ cm$^{-1}$

m.p.: 118-120°C

(3s)-N-(2-bromo-4-methoxyphenyl)-N-methyladamantane-1-carboxamide 3.32r:

Following general procedure for amides synthesis, adamantyl acid chloride (1.23 g, 6.18 mmol, 1.5 eq), 2-bromo-4-methoxylaniline (832 mg, 4.12 mmol, 1 eq), Et$_3$N (1.14 mL, 8.24 mmol, 2 eq) were reacted in dichloromethane (30 mL). After purification, the adamantyl amide (1.3 g, 3.58 mmol, 1 eq) was reacted with sodium hydride (60% dispersion in oil, 287 mg, 7.17 mmol, 2 eq), iodomethane (0.44 mL, 7.17 mmol, 2 eq) in THF (20 mL) at 65°C. After extraction and purification, the desired amide was obtained as a yellow solid (1.15 g, 3.04 mmol, 74%).

$^1$H NMR (400 MHz, Chloroform-d) $\delta = 7.17 – 7.12$ (m, 2H), 6.85 – 6.82 (m, 1H), 3.81 (s, 3H), 3.08 (s, 3H), 1.89 – 1.80 (m, 6H), 1.70 – 1.62 (m, 3H), 1.59 – 1.46 (m, 6H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta = 178.0, 159.4, 137.0, 130.9, 124.7, 118.6, 113.9, 55.8, 43.8, 40.1, 39.7, 36.5, 28.5, 27.0$.

HRMS (ESI): Calculated for C$_{19}$H$_{23}$BrNO$_2$ ([M+H]$^+$): 378.1069; found: 378.1063

IR (neat): $\nu = 1617, 1495$ cm$^{-1}$

m.p.: 124-126°C
(3s)-N-(2-bromo-4-methylphenyl)-N-methyladamantane-1-carboxamide 3.33r:

![Chemical Structure]

Chemical Formula: C_{19}H_{24}BrNO
Exact Mass: 361.1041

Following general procedure for amides synthesis, adamantyl acid chloride (447 mg, 2.25 mmol, 1.5 eq), 2-bromo-4-methylaniline (279 mg, 1.50 mmol, 1 eq), Et₃N (0.416 mL, 3 mmol, 2 eq) were reacted in dichloromethane (15 mL). After purification, the adamantyl amide (475 mg, 1.37 mmol, 1 eq) was reacted with sodium hydride (60 % dispersion in oil, 109 mg, 2.73 mmol, 2 eq), iodomethane (0.17 mL, 2.73 mmol, 2 eq) in THF (10 mL) at 65°C. After extraction and purification, the desired amide was obtained as a white solid (482 mg, 1.33 mmol, 89 %).

^1H NMR (500 MHz, Chloroform-d) δ = 7.45 – 7.43 (m, 1H), 7.16 – 7.10 (m, 2H), 3.10 (s, 3H), 2.37 (s, 3H), 1.8 – 1.84 (m, 6H), 1.70 – 1.65 (m, 3H), 1.59 – 1.49 (m, 6H).

^13C NMR (126 MHz, CDCl₃) δ = 177.9, 141.6, 139.9, 134.2, 130.2, 129.0, 123.9, 43.9, 40.0, 39.8, 36.6, 28.5, 21.0.

HRMS (ESI): Calculated for C_{19}H_{25}BrNO ([M+H]^+): 362.1120; found: 362.1119

IR (neat): ν = 1623 cm⁻¹

m.p.: 111-113°C

(3s)-N-(2-bromo-5-methylphenyl)-N-methyladamantane-1-carboxamide 3.34r:

![Chemical Structure]

Chemical Formula: C_{19}H_{24}BrNO
Exact Mass: 361.1041

Following general procedure for amides synthesis, adamantyl acid chloride (1.57 g, 7.9 mmol, 1.5 eq), 2-bromo-5-methylaniline (980 mg, 5.26 mmol, 1 eq), Et₃N (1.46 mL, 10.5 mmol, 2 eq) were reacted in dichloromethane (40 mL). After purification, the adamantyl amide (1.45 g, 4.16 mmol, 1 eq) was reacted with sodium hydride (60 % dispersion in oil, 337 mg, 8.42 mmol, 2 eq), iodomethane (0.52 mL, 8.42 mmol, 2 eq) in THF (30 mL) at 65°C. After extraction and purification, the desired amide was obtained as a yellowish solid (1.35 g, 3.73 mmol, 71 %).
**1H NMR (400 MHz, Chloroform-d)** \( \delta = 7.51 – 7.47 \) (m, 1H), \( 7.10 – 7.08 \) (m, 1H), \( 7.04 – 7.00 \) (m, 1H), 3.12 (s, 3H), 2.33 (s, 3H), 1.92 – 1.82 (m, 6H), 1.71 – 1.65 (m, 3H), 1.61 – 1.49 (m, 6H).

**13C NMR (101 MHz, CDCl₃)** \( \delta = 177.8, 144.0, 138.6, 133.4, 131.2, 130.3, 120.7, 43.9, 39.9, 39.8, 36.6, 28.5, 21.0. \)

**HRMS (ESI):** Calculated for C₁₉H₂₅BrNO ([M+H]⁺): 362.1120; found: 362.1118

**IR (neat):** ν = 1625 cm⁻¹

**m.p.:** 120-122°C

(3s)-N-(2-bromo-5-methoxyphenyl)-N-methyladamantane-1-carboxamide 3.35r:

Following general procedure for amides synthesis, adamantyl acid chloride (441 mg, 2.45 mmol, 1.5 eq), 2-bromo-5-methoxyaniline (329 mg, 1.63 mmol, 1 eq), Et₃N (0.45 mL, 3.26 mmol, 2 eq) were reacted in dichloromethane (10 mL). After purification, the adamantyl amide (481 g, 1.32 mmol, 1 eq) was reacted with sodium hydride (60 % dispersion in oil, 106 mg, 2.64 mmol, 2 eq), iodomethane (0.16 mL, 2.64 mmol, 2 eq) in THF (10 mL). After extraction and purification, the desired amide was obtained as a yellowish solid (354 mg, 0.94 mmol, 57 %).

**1H NMR (400 MHz, Chloroform-d)** \( \delta = 7.51 – 7.49 \) (m, 1H), \( 6.84 – 6.82 \) (m, 1H), \( 6.81 – 6.76 \) (m, 1H), 3.81 (s, 3H), 3.13 (s, 3H), 1.94 – 1.84 (m, 6H), 1.74 – 1.68 (m, 3H), 1.62 – 1.51 (m, 6H).

**13C NMR (101 MHz, CDCl₃)** \( \delta = 177.8, 159.5, 145.0, 134.0, 116.5, 115.2, 114.6, 55.9, 44.1, 39.9, 39.9, 36.6, 28.5. \)

**HRMS (ESI):** Calculated for C₁₉H₂₅BrNO₂ ([M+H]⁺): 378.1069; found: 378.1062

**IR (neat):** ν = 2908, 1617, 1495 cm⁻¹

**m.p.:** 111-113°C

(3s)-N-(2-bromo-5-fluorophenyl)-N-methyladamantane-1-carboxamide 3.36r:
Following general procedure for amides synthesis, adamantyl acid chloride (257 mg, 1.19 mmol, 1.5 eq), 2-bromo-5-fluoroaniline (151 mg, 0.80 mmol, 1 eq), Et₃N (0.2 mL, 1.59 mmol, 2 eq) were reacted in dichloromethane (7 mL). After purification, the adamantyl amide (196 mg, 0.56 mmol, 1 eq) was reacted with sodium hydride (60 % dispersion in oil, 45 mg, 1.11 mmol, 2 eq), iodomethane (0.07 mL, 1.11 mmol, 2 eq) in THF (5 mL) at 65°C. After extraction and purification, the desired amide was obtained as a yellowish solid (108 mg, 0.295 mmol, 37 %).

**1H NMR (400 MHz, Chloroform-d)**: δ = 7.63 – 7.54 (m, 1H), 7.06 – 7.02 (m, 1H), 7.01 – 6.94 (m, 1H), 3.13 (s, 3H), 1.90 – 1.85 (m, 6H), 1.74 – 1.67 (m, 3H), 1.63 – 1.50 (m, 6H).

**13C NMR (101 MHz, CDCl3)**: δ = 177.63, 161.9 (d, J = 247.0 Hz), 145.6 (d, J = 9.5 Hz), 134.5 (d, J = 8.9 Hz), 118.9 (d, J = 3.9 Hz), 118.1 (d, J = 22.9 Hz), 116.8 (d, J = 23.1 Hz), 44.0, 39.8, 39.8, 36.5, 28.5.

**19F NMR (376 MHz, CDCl3)**: δ = -112.5.

**HRMS (ESI):** Calculated for C₁₈H₂₂BrFNO ([M+H]^+): 366.0869; found: 366.0863

**IR (neat):** ν = 1636, 1490 cm⁻¹

**m.p.:** 101-103°C

(3S)-N-(2-bromo-5-(trifluoromethoxy)phenyl)-N-methyladamantane-1-carboxamide

3.37r:

Following general procedure for amides synthesis, adamantyl acid chloride (2.98 g, 15 mmol, 1.5 eq), 2-bromo-5-(trifluoromethoxy)aniline (2.56 g, 10 mmol, 1 eq), Et₃N (2.77 mL, 20 mmol, 2 eq) were reacted in dichloromethane (120 mL). After purification, the adamantyl amide (3.3 g, 7.89 mmol, 1 eq) was reacted with sodium hydride (60 % dispersion in oil, 630 mg, 15.8 mmol, 2 eq), iodomethane (0.97 mL, 15.8 mmol, 2 eq) in THF (100 mL) at reflux. After
extraction and purification, the desired amide was obtained as a white solid (2.2 g, 5.0 mmol, 51%).

$^1$H NMR (400 MHz, Chloroform-d) $\delta = 7.68 - 7.65$ (m, 1H), 7.19 - 7.17 (m, 1H), 7.13 - 7.09 (m, 1H), 3.14 (s, 3H), 1.89 - 1.81 (m, 6H), 1.70 - 1.49 (m, 9H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta = 177.6, 148.5$ (q, J = 1.9 Hz), 145.6, 134.7, 123.6, 122.4, 122.2, 120.3 (q, J = 260.1 Hz), 44.0, 39.8, 39.7, 36.5, 28.5.

$^{19}$F NMR (376 MHz, CDCl$_3$) $\delta = -58.1$.

HRMS (ESI): Calculated for C$_{19}$H$_{22}$BrF$_3$NO$_2$ ([M+H]$^+$): 432.0786; found: 432.0788

IR (neat) : $\nu = 2906, 1614, 1494$ cm$^{-1}$

m.p.: 117-119°C

(3s)-N-(2-bromo-3-fluorophenyl)-N-methyladamantane-1-carboxamide 3.38r:

Following general procedure for amides synthesis, adamantyl acid chloride (257 mg, 1.19 mmol, 1.5 eq), 2-bromo-3-fluoroaniline (151 mg, 0.80 mmol, 1 eq), Et$_3$N (0.2 mL, 1.59 mmol, 2 eq) were reacted in 1,2-dichloroethane (7 mL) at 60°C. After purification, the adamantyl amide (196 mg, 0.56 mmol, 1 eq) was reacted with sodium hydride (60 % dispersion in oil, 45 mg, 1.11 mmol, 2 eq), iodomethane (0.07 mL, 1.11 mmol, 2 eq) in THF (5 mL) at 65°C. After extraction and purification, the desired amide was obtained as a yellowish solid (110 mg, 0.30 mmol, 32 %).

$^1$H NMR (400 MHz, Chloroform-d) $\delta = 7.35 - 7.29$ (m, 1H), 7.17 - 7.09 (m, 2H), 3.14 (s, 3H), 1.90 - 1.83 (m, 6H), 1.71 - 1.65 (m, 3H), 1.62 - 1.50 (m, 6H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta = 177.9, 160.1$ (d, J = 246.1 Hz), 146.30, 128.7 (d, J = 9.2 Hz), 126.0 (d, J = 3.7 Hz), 116.1 (d, J = 22.7 Hz), 112.0 (d, J = 19.9 Hz), 44.0, 39.9, 39.8, 36.5, 28.5.

$^{19}$F NMR (376 MHz, CDCl$_3$) $\delta = -102.6$.

HRMS (ESI): Calculated for C$_{18}$H$_{22}$BrFNO ([M+H]$^+$): 366.0869; found: 366.0865
IR (neat) : ν = 1636, 1495 cm⁻¹

m.p.: 104-106°C

methyl 3-bromo-4-(N,1-dimethylcyclohexane-1-carboxamido)benzoate 3.44r:

![Chemical structure](image)

Chemical Formula: C₁₇H₂₂BrNO₃
Exact Mass: 367.0783

Following general procedure for amides synthesis, 1-methylcyclohexane-1-carboxylic acid (1.05 g, 6.59 mmol, 1.5 eq), methyl 4-amino-3-bromobenzoate (1.01 g, 4.39 mmol, 1 eq), Et₃N (1.22 mL, 8.78 mmol, 2 eq) were reacted in 1,2-dichloroethane (70 mL) at 60°C. After purification, the amide (1.1 g, 3.12 mmol, 1 eq) was reacted with sodium hydride (60 % dispersion in oil, 249 mg, 6.2 mmol, 2 eq), iodoethane (0.4 mL, 6.2 mmol, 2 eq) in THF (30 mL). After extraction and purification, the desired amide was obtained as a colorless oil (800 mg, 2.17 mmol, 50 %).

¹H NMR (400 MHz, Chloroform-d) δ = 8.33 – 8.31 (m, 1H), 8.01 – 7.97 (m, 1H), 7.36 – 7.32 (m, 1H), 3.94 (s, 3H), 3.19 (s, 3H), 1.90 – 1.78 (m, 2H), 1.54 – 1.46 (m, 3H), 1.45 – 1.31 (m, 8H), 1.09 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ = 177.7, 165.1, 148.4, 135.1, 131.0, 130.6, 129.4, 123.9, 52.6, 44.6, 39.6, 37.0, 35.7, 25.8, 24.2, 22.9, 22.7.

HRMS (ESI): Calculated for C₁₇H₂₂BrNO₃([M+H]⁺): 368.0861 found: 368.0862

IR (neat) : ν = 2973, 2361, 1379 cm⁻¹

1-(2-(benzyloxy)ethyl)-N-(2-bromophenyl)-N-methycyclohexane-1-carboxamide 3.45r:
((2-bromoethoxy)methyl)benzene (2.22 mL, 14 mmol, 1 eq) was reflux in acetone (20 mL) overnight with NaI (8.8 g, 58.5 mmol, 5 eq). The mixture was cooled to room temperature and the solvent was removed under vacuum. The crude mixture was then dissolved in water (20 mL) and extracted with Et₂O (3 x 20 mL). The combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum to afford ((2-iodoethoxy)methyl)benzene as a colorless oil (2.72 mL, 14 mmol, 100%).

To diisopropylamine (1.8 mL, 12.7 mmol, 1.2 eq) in dry THF (30 mL) at 0°C was added n-butyllithium (2.5 M in hexanes, 5.2 mL, 12.7 mmol, 1.2 eq). The solution was stirred for 10 minutes and methyl cyclohexanecarboxylate (1.6 g, 11.7 mmol, 1 eq) in dry THF (10 mL) was added. The mixture was warm to room temperature and then heated at reflux for 15 minutes. ((2-iodoethoxy)methyl)benzene (2.72 mL, 14 mmol, 1.2 eq) in dry THF (10 mL) was then quickly added to the mixture which was further reacted for 3 h at reflux. The mixture was cooled to room temperature, quenched with water (50 mL) and extracted with AcOEt (3 x 30 mL). The combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum. The intermediate ester was purified by chromatography on silica gel using cyclohexane/AcOEt [8:2] as solvent (1.82 g, 6.55 mmol, 56%).

The intermediate ester (1.81 g, 6.55 mmol, 1.5 eq) was dissolved in THF (20 mL) and slowly added to a turning solution of o-bromoaniline (0.47 mL, 4.33 mmol, 1 eq) in THF (20 mL) with LiHMDS (1.45 g, 8.66 mmol, 2 eq). The mixture was stirred overnight at reflux, cooled to room temperature and quenched with water (40 mL). The aqueous phase was extracted with AcOEt (3 x 30 mL) and the combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum. The crude mixture was purified by chromatography on silica gel.
using cyclohexane/AcOEt [7:3] to afford the intermediate amide as a yellowish solid (926 mg, 2.22 mol, 51%).

The intermediate amide (926 mg, 2.22 mmol, 1 eq) was dissolved in THF (20 mL) and sodium hydride (60 % dispersion in oil, 178 mg, 4.45 mmol, 2 eq) was added. The mixture was stirred for 10 min, and iodomethane (0.28 mL, 4.45 mmol, 2 eq) was added. The mixture was stirred at reflux for 2 h and cooled to room temperature. The crude mixture was quenched with water (20 mL), extracted with AcOEt (3 x 20 mL) and the combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum. The crude mixture was purified by chromatography on silica gel using cyclohexane/AcOEt [7:3] as solvent. The desired amide was obtained as a yellowish oil (550 mg, 1.28 mmol, 57 %, 16 % overall yield).

**Mixture of rotamers:**

**1H NMR (400 MHz, Chloroform-d)** \(\delta = 7.64 - 7.61\) (m, 1H), 7.58 - 7.40 (m, 2H), 7.39 - 7.31 (m, 3H), 7.29 - 7.26 (m, 2H), 7.20 - 7.12 (m, 1H), 4.84 - 4.37 (m, 2H), 3.93 - 3.47 (m, 2H), 3.44 - 3.03 (m, 3H), 2.05 - 1.76 (m, 3H), 1.73 - 1.63 (m, 1H), 1.57 - 1.25 (m, 7H), 1.13 - 0.99 (m, 1H).

**13C NMR (101 MHz, CDCl3)** \(\delta = 175.7, 138.7, 133.9, 130.8, 129.3, 128.5, 128.3, 128.0, 127.7, 73.4, 67.0, 47.1, 39.9, 37.9, 35.6, 34.7, 26.1, 23.5, 23.0.

**HRMS (ESI):** Calculated for C\(_{23}\)H\(_{28}\)BrNO\(_2\)Na ([M+Na]+): 452.1201; found: 452.1201

**IR (neat):** \(\nu = 2909, 1631, 906\) cm\(^{-1}\)

**N-(2-bromo-4-methoxyphenyl)-N-methylbicyclo[2.2.2]octane-1-carboxamide 3.50r:**

Following general procedure for amides synthesis, bicyclo[2.2.2]octane-1-carbonyl chloride (224 mg, 1.3 mmol mmol, 1.1 eq), 2-bromo-4-methoxyaniline (238 mg, 1.18 mmol, 1.0 eq), Et\(_3\)N (0.33 mL, 2.4 mmol, 2 eq) were reacted in dichloromethane (5 mL). After purification, the intermediate amide (266 mg, 0.78 mmol, 1 eq) was reacted with sodium hydride (60 % dispersion in oil, 63 mg, 1.57 mmol, 2 eq), iodomethane (0.1 mL, 1.57 mmol, 2 eq) in THF (5 mL) at 65°C. After extraction and purification, the desired amide was obtained as a yellowish oil (180 mg, 0.51 mmol, 65 %).
$^1$H NMR (400 MHz, Chloroform-d) $\delta = 7.16 – 7.10$ (m, 2H), 6.87 – 6.82 (m, 1H), 3.83 (s, 3H), 3.09 (s, 3H), 1.77 – 1.65 (m, 3H), 1.58 – 1.49 (m, 3H), 1.49 – 1.45 (m, 1H), 1.45 – 1.38 (m, 6H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta = 178.2$, 159.4, 137.1, 131.1, 124.7, 118.6, 114.1, 55.9, 41.4, 40.1, 28.8, 25.9, 23.7.

HRMS (ESI): Calculated for C$_{17}$H$_{23}$BrNO$_2$ ([M+H]$^+$): 352.0912; found: 352.0914

IR (neat): $\nu = 1660$ cm$^{-1}$

$\text{N-(2-bromo-4-cyanophenyl)-N-methylbicyclo[2.2.2]octane-1-carboxamide 3.51r:}$

Following general procedure for amides synthesis, bicyclo[2.2.2]octane-1-carbonyl chloride (224 mg, 1.3 mmol mmol, 1.1 eq), 4-amino-3-bromobenzonitrile (232 mg, 1.18 mmol, 1.0 eq), Et$_3$N (0.33 mL, 2.4 mmol, 2 eq) were reacted in dichloromethane (5 mL). After purification, the intermediate amide (157 mg, 0.47 mmol, 1 eq) was reacted with sodium hydride (60 % dispersion in oil, 38 mg, 0.94 mmol, 2 eq), iodomethane (0.05 mL, 0.94 mmol, 2 eq) in THF (5 mL) at 65°C. After extraction and purification, the desired amide was obtained as a yellowish oil (111 mg, 0.32 mmol, 68 %).

$^1$H NMR (400 MHz, Chloroform-d) $\delta = 7.95 – 7.94$ (m, 1H), 7.67 – 7.62 (m, 1H), 7.36 – 7.33 (m, 1H), 3.15 (s, 3H), 1.68 – 1.56 (m, 6H), 1.55 – 1.52 (m, 1H), 1.50 – 1.44 (m, 6H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta = 177.7$, 149.0, 137.3, 132.2, 131.5, 125.0, 116.8, 113.3, 41.7, 39.6, 28.9, 25.7, 23.5.

HRMS (ESI): Calculated for C$_{17}$H$_{20}$BrN$_2$O ([M+H]$^+$): 347.0759; found: 347.0761

IR (neat): $\nu = 2304$ cm$^{-1}$

$\text{N-(2-bromo-5-methoxyphenyl)-N-methylbicyclo[2.2.2]octane-1-carboxamide 3.46r:}$
Following general procedure for amides synthesis, bicyclo[2.2.2]octane-1-carbonyl chloride (78 mg, 0.454 mmol, 1.0 eq), 2-bromo-5-methoxylaniline (92 mg, 0.454 mmol, 1.0 eq), Et₃N (0.128 mL, 0.91 mmol, 2 eq) were reacted in dichloromethane (7mL). After purification, the intermediate amide (90 mg, 0.266 mmol, 1 eq) was reacted with sodium hydride (60 % dispersion in oil, 21 mg, 0.532 mmol, 2 eq), iodomethane (0.033 mL, 0.532 mmol, 2 eq) in THF (5 mL) at 65°C. After extraction and purification, the desired amide was obtained as a colorless oil (41 mg, 0.116 mmol, 26 %).

**1H NMR (500 MHz, Chloroform-d)** δ = 7.50 – 7.46 (m, 1H), 6.79 – 6.76 (m, 2H), 3.80 (s, 3H), 3.11 (s, 3H), 1.78 – 1.70 (m, 3H), 1.59 – 1.51 (m, 3H), 1.51 – 1.47 (m, 1H), 1.45 – 1.40 (m, 6H).

**13C NMR (126 MHz, CDCl₃)** δ = 178.0, 159.6, 145.0, 134.0, 116.6, 115.1, 114.5, 55.9, 41.6, 39.8, 28.9, 25.9, 23.7.

**HRMS (ESI):** Calculated for C₁₇H₂₃BrNO₂ ([M+H]⁺): 352.0912; found: 352.0913

**IR (neat):** ν = 1622 cm⁻¹

**methyl 4-((2-bromo-4-cyanophenyl)(methyl)carbamoyl)bicyclo[2.2.2]octane-1-carboxylate 3.47r:**

Following general procedure for amides synthesis, methyl 4-(chlorocarbonyl)bicyclo[2.2.2]octane-1-carboxylate (127 mg, 0.54 mmol, 1.2 eq), 4-amino-3-bromobenzonitrile (90 mg, 0.45 mmol, 1.0 eq), Et₃N (0.125 mL, 0.91 mmol, 2 eq) were reacted in dichloromethane (7 mL). After purification, the intermediate amide (141 mg, 0.36 mmol, 1 eq) was reacted with sodium hydride (60 % dispersion in oil, 29 mg, 0.72 mmol, 2 eq),
iodomethane (0.047 mL, 0.72 mmol, 2 eq) in THF (5 mL) at 65°C. After extraction and purification, the desired amide was obtained as a yellowish oil (43 mg, 0.106 mmol, 25 %).

\( ^1H \text{NMR (400 MHz, Chloroform-d)} \delta = 7.97 - 7.93 \text{ (m, 1H)}, 7.68 - 7.63 \text{ (m, 1H)}, 7.38 - 7.30 \text{ (m, 1H)}, 3.59 \text{ (s, 3H)}, 3.15 \text{ (s, 3H)}, 1.73 - 1.62 \text{ (m, 12H)}. \)

\( ^{13}C \text{NMR (101 MHz, CDCl}_3) \delta = 177.7, 176.7, 148.6, 137.4, 132.3, 131.4, 125.0, 116.7, 113.6, 51.8, 41.8, 39.6, 38.4, 28.5, 28.0. \)

HRMS (ESI): Calculated for C_{19}H_{22}BrN_{2}O_{3} ([M+H]^+): 405.0814; found: 405.0808

IR (neat) : \( \nu = 2973, 2369, 1710 \text{ cm}^{-1} \)

(3r,5r,7r)-N-(2-bromophenyl)-N-ethyladamantane-1-carboxamide 3.48r:

Following general procedure for amides synthesis, adamantyl acid chloride (2.98 g, 15 mmol, 1.5 eq), o-bromoaniline (1.7 g, 10 mmol, 1 eq), Et\(_3\)N (2.77 mL, 20 mmol, 2 eq) were reacted in dichloromethane (60 mL). After purification, the adamantyl amide (2.9 g, 8.7 mmol, 1 eq) was reacted with sodium hydride (60 % dispersion in oil, 696 mg, 17.4 mmol, 2 eq), iodoethane (1.43 mL, 17.4 mmol, 2 eq) in THF (50 mL). After extraction and purification, the desired amide was obtained as a white solid (2.3 g, 6.6 mmol, 75 %).

\( ^1H \text{NMR (400 MHz, Chloroform-d)} \delta = 7.67 - 7.62 \text{ (m, 1H)}, 7.36 - 7.29 \text{ (m, 1H)}, 7.24 - 7.19 \text{ (m, 2H)}, 4.22 \text{ (dq, J = 14.0, 7.1 Hz, 1H)}, 2.94 \text{ (dq, J = 13.8, 7.0 Hz, 1H)}, 1.91 - 1.80 \text{ (m, 6H)}, 1.67 - 1.46 \text{ (m, 9H)}, 1.10 \text{ (t, J = 7.1 Hz, 3H)}. \)

\( ^{13}C \text{NMR (101 MHz, CDCl}_3) \delta = 177.1, 142.4, 133.9, 132.0, 129.4, 127.7, 125.0, 46.5, 44.0, 39.7, 36.6, 28.5, 12.6. \)

HRMS (ESI): Calculated for C_{19}H_{25}BrNO ([M+H]^+): 362.1120; found: 362.1115

IR (neat) : \( \nu = 1622 \text{ cm}^{-1} \)

m.p.: 121-123°C
Benzoxazine products:

1'-methylspiro[cyclobutane-1,3'-indolin]-2'-one 3.19:

\[ \text{Chemical Formula: } C_{12}H_{13}NO \]
\[ \text{Exact Mass: } 187.0997 \]

In a 10 mL screw-cap tube charged with amide 3.15f (0.1 mmol, 27 mg, 1 equiv) was weighted in a glovebox \( \text{Pd(PCy}_{3})_{2} \) (0.01 mmol, 6.7 mg, 10 mol%), cesium pivalate (0.03 mmol, 7.1 mg, 30 mol%) and \( \text{Cs}_{2}\text{CO}_{3} \) (0.3 mmol, 98 mg, 3 equiv). The vial was charged with mesitylene (2 mL), sealed and stirred under argon in a previously heated heating block at 160 °C for 15 h. The reaction was cooled to room temperature, filtered over celite, and evaporated under vacuum. The crude mixture was purified by preparative HPLC using gradient of solvent (H\(_2\)O: MeCN) [90:10] to [10:90]. The collected fraction were evaporated under vacuum to afford the desired product as a yellowish oil (13.1 mg, 0.07 mmol, 70%).

\(^{1}\text{H NMR (400 MHz, Chloroform-}d\text{)}^{\delta} 7.53 - 7.47 (m, 1H), 7.29 - 7.20 (m, 1H), 7.13 - 7.06 (m, 1H), 6.80 - 6.76 (m, 1H), 3.18 (s, 3H), 2.71 - 2.61 (m, 2H), 2.42 - 2.23 (m, 4H).

\(^{13}\text{C NMR (101 MHz, CDCl}_{3}\text{)}^{\delta} 180.3, 143.1, 134.5, 127.9, 122.7, 122.4, 107.7, 48.3, 31.4, 26.3, 16.9.

HRMS (ESI): Calculated for \( C_{12}H_{14}NO ([M+H]^+) \): 188.1075; found: 188.1070

IR (neat): \( \nu = 2973, 2362, 1694, 1379 \text{ cm}^{-1} \)

1,3,3-trimethyl-3,4-dihydroquinolin-2(1H)-one 3.20:

\[ \text{Chemical Formula: } C_{12}H_{14}NO \]
\[ \text{Exact Mass: } 189.1154 \]

In a 10 mL screw-cap tube charged with amide 3.15g (0.1 mmol, 27 mg, 1 equiv) was weighted in a glovebox \( \text{Pd(PCy}_{3})_{2} \) (0.01 mmol, 6.7 mg, 10 mol%), cesium pivalate (0.03 mmol, 7.1 mg, 30 mol%) and \( \text{Cs}_{2}\text{CO}_{3} \) (0.3 mmol, 98 mg, 3 equiv). The vial was charged with mesitylene (2 mL), sealed and stirred under argon in a previously heated heating block at 160 °C for 15 h. The reaction was cooled to room temperature, filtered over celite, and evaporated under vacuum. The crude mixture was purified by preparative HPLC using gradient of solvent (H\(_2\)O: MeCN) [90:10] to [10:90]. The collected fraction were evaporated under vacuum to afford the desired product as a yellowish oil (13.1 mg, 0.07 mmol, 70%).

\(^{1}\text{H NMR (400 MHz, Chloroform-}d\text{)}^{\delta} 7.53 - 7.47 (m, 1H), 7.29 - 7.20 (m, 1H), 7.13 - 7.06 (m, 1H), 6.80 - 6.76 (m, 1H), 3.18 (s, 3H), 2.71 - 2.61 (m, 2H), 2.42 - 2.23 (m, 4H).

\(^{13}\text{C NMR (101 MHz, CDCl}_{3}\text{)}^{\delta} 180.3, 143.1, 134.5, 127.9, 122.7, 122.4, 107.7, 48.3, 31.4, 26.3, 16.9.

HRMS (ESI): Calculated for \( C_{12}H_{14}NO ([M+H]^+) \): 188.1075; found: 188.1070

IR (neat): \( \nu = 2973, 2362, 1694, 1379 \text{ cm}^{-1} \)
mL), sealed and stirred under argon in a previously heated heating block at 160 °C for 15 h. The reaction was cooled to room temperature, filtered over celite, and evaporated under vacuum. The crude mixture was purified by preparative HPLC using gradient of solvent (H2O: MeCN) [90:10] to [10:90]. The collected fraction were evaporated under vacuum to afford the desired product as a colorless oil (15.1 mg, 0.08 mmol, 80%).

\[ \text{H NMR (500 MHz, Chloroform-d)} \delta = 7.21 – 7.16 \text{ (m, 1H)}, 7.09 – 7.06 \text{ (m, 1H)}, 6.96 – 6.92 \text{ (m, 1H)}, 6.90 – 6.87 \text{ (m, 1H)}, 3.29 \text{ (s, 3H)}, 2.69 \text{ (s, 2H)}, 1.09 \text{ (s, 6H)}. \]

\[ \text{C NMR (126 MHz, CDCl3)} \delta = 175.6, 140.3, 128.4, 127.4, 125.2, 122.8, 114.2, 40.3, 37.5, 30.1, 24.8. \]

2-((3r,5r,7r)-adamantan-1-yl)-4H-benzol[d][1,3]oxazine 3.21:

\[
\begin{array}{c}
\text{Chemical Formula: C}_{19}\text{H}_{24}\text{NO} \\
\text{Exact Mass: 267.1623}
\end{array}
\]

Following general procedure for benzoxazine synthesis, 3.15h (35 mg, 0.1 mmol, 1eq) was reacted with Pd(PCy3)2 (6.7 mg, 0.01 mmol, 10 mol%), cesium pivalate (7.1 mg, 0.03 mmol, 30 mol%) and Cs2CO3 (98 mg, 0.3 mmol, 3 eq) in o-xylene (2 mL) at 160°C for 15h. After purification, 3.21 was obtained as a yellowish oil (23 mg, 0.084 mmol, 84%).

**Scale up:**

Following general procedure for benzoxazine synthesis, 3.15h (2.17 g, 6.25 mmol, 1eq) was reacted with Pd-G4-PCy3 (415 mg, 0.625 mmol, 10 mol%), PCy3 (175 mg, 0.625 mmol, 10 mol%) cesium pivalate (440 mg, 1.88 mmol, 30 mol%) and Cs2CO3 (6.1 g, 18.8 mmol, 3 eq) in o-xylene (125 mL) at 160°C for 15h in a 250 mL schlenk tube. The crude mixture was cooled to room temperature, and the solvent was flushed on silica gel using cyclohexane. The crude mixture was purify by chromatography on silica gel using cyclohexane/AcOEt as solvent [9:1]. 3.21 was obtained as a yellowish oil (1.05 g, 3.92 mmol, 62%).

\[ \text{H NMR (400 MHz, Chloroform-d)} \delta = 7.27 – 7.22 \text{ (m, 1H)}, 7.17 – 7.09 \text{ (m, 2H)}, 6.94 – 6.90 \text{ (m, 1H)}, 5.15 \text{ (s, 2H)}, 2.07 – 2.03 \text{ (m, 4H)}, 1.97 – 1.95 \text{ (m, 6H)}, 1.76 – 1.72 \text{ (m, 6H)}. \]

\[ \text{C NMR (101 MHz, CDCl3)} \delta = 168.8, 139.7, 128.9, 126.1, 124.4, 123.7, 122.5, 66.2, 39.6, 39.5, 36.9, 28.3. \]
2-((3r,5r,7r)-adamantan-1-yl)-6-methyl-4H-benzo[d][1,3]oxazine 3.28:

Following general procedure for benzoxazine synthesis, 3.28r (41 mg, 0.1 mmol, 1 eq) was reacted with Pd(PCy$_3$)$_2$ (6.7 mg, 0.01 mmol, 10 mol%), cesium pivalate (7.1 mg, 0.03 mmol, 30 mol%) and Cs$_2$CO$_3$ (98 mg, 0.3 mmol, 3 eq) in o-xylene (2 mL) at 160°C for 15 h. After purification, 3.28 was obtained as a white solid (27 mg, 0.081 mmol, 81%).

$^1$H NMR (400 MHz, Chloroform-d) $\delta$ = 7.95 – 7.91 (m, 1H), 7.65 – 7.62 (m, 1H), 7.19 – 7.14 (m, 1H), 5.19 (s, 2H), 3.89 (s, 3H), 2.07 – 2.02 (m, 3H), 1.97 – 1.92 (m, 6H), 1.79 – 1.69 (m, 6H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ = 171.0, 166.7, 144.0, 130.7, 127.5, 125.4, 124.2, 122.4, 66.1, 52.2, 39.8, 39.4, 36.8, 28.2.

HRMS (ESI): Calculated for C$_{20}$H$_{24}$NO$_3$ ([M+H]$^+$): 326.1756; found: 326.1752

IR (neat) : $\nu$ = 1622, 1490, 911 cm$^{-1}$

m.p.: 70–72°C

2-((3r,5r,7r)-adamantan-1-yl)-6-(trifluoromethyl)-4H-benzo[d][1,3]oxazine 3.30:

Following general procedure for benzoxazine synthesis, 3.30r (42 mg, 0.1 mmol, 1 eq) was reacted with Pd(PCy$_3$)$_2$ (6.7 mg, 0.01 mmol, 10 mol%), cesium pivalate (7.1 mg, 0.03 mmol, 30 mol%) and Cs$_2$CO$_3$ (98 mg, 0.3 mmol, 3 eq) in o-xylene (2 mL) at 160°C for 15 h. After purification, 3.30 was obtained as a white solid (18.5 mg, 0.055 mmol, 55%).

$^1$H NMR (400 MHz, Chloroform-d) $\delta$ = 7.52 – 7.47 (m, 1H), 7.23 – 7.15 (m, 2H), 5.18 (s, 2H), 2.08 – 2.03 (m, 3H), 1.96 – 1.90 (m, 6H), 1.79 – 1.68 (m, 6H).
$^{13}$C NMR (126 MHz, CDCl$_3$) δ = 170.8, 142.9 (d, J = 1.9 Hz), 127.9 (q, J = 31.9 Hz), 126.1 (q, J = 3.3 Hz), 124.6, 124.2 (q, J = 269.2 Hz), 122.9, 121.0 (q, J = 4.0 Hz), 65.9, 39.8, 39.4, 36.8, 28.2.

$^{19}$F NMR (376 MHz, CDCl$_3$) δ = -62.20.

HRMS (ESI): Calculated for C$_{19}$H$_{21}$FNO ([M+H]$^+$): 336.1575; found: 336.1573

IR (neat) : ν = 2909, 2361, 1603, 1331 cm$^{-1}$

m.p.: 77-79°C

2-((3r,5r,7r)-adamantan-1-yl)-6-fluoro-4H-benzo[d][1,3]oxazine 3.29:

Following general procedure for benzoxazine synthesis, 3.29r (37 mg, 0.1 mmol, 1eq) was reacted with Pd(PCy$_3$)$_2$ (6.7 mg, 0.01 mmol, 10 mol%), cesium pivalate (7.1 mg, 0.03 mmol, 30 mol%) and Cs$_2$CO$_3$ (98 mg, 0.3 mmol, 3 eq) in o-xylene (2 mL) at 160°C for 15h. After purification, 3.29 was obtained as a yellowish solid (23 mg, 0.080 mmol, 80%).

$^1$H NMR (400 MHz, Chloroform-d) δ = 7.13 – 7.06 (m, 1H), 6.95 – 6.89 (m, 1H), 6.67 – 6.59 (m, 1H), 5.12 (s, 2H), 2.07 – 2.00 (m, 3H), 1.96 – 1.90 (m, 6H), 1.78 – 1.68 (m, 6H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ = 168.1, 160.9 (d, J = 245 Hz), 135.8 (d, J = 2.4 Hz), 125.9 (d, J = 8.3 Hz), 124.0 (d, J = 8.1 Hz), 115.3 (d, J = 22.3 Hz), 110.7 (d, J = 22.7 Hz), 65.7 (d, J = 2.2 Hz), 39.5, 39.4, 36.8, 28.3.

$^{19}$F NMR (376 MHz, CDCl$_3$) δ = -116.0.

HRMS (ESI): Calculated for C$_{18}$H$_{20}$FNO ([M+H]$^+$): 286.1607; found: 286.1607

IR (neat) : ν = 2361, 906 cm$^{-1}$

m.p.: 65-67°C

2-((3r,5r,7r)-adamantan-1-yl)-4H-benzo[d][1,3]oxazine-6-carbonitrile 3.31:
Following general procedure for benzoxazine synthesis, **3.31r** (46 mg, 0.1 mmol, 1eq) was reacted with Pd(PCy$_3$)$_2$ (6.7 mg, 0.01 mmol, 10 mol%), cesium pivalate (7.1 mg, 0.03 mmol, 30 mol%) and Cs$_2$CO$_3$ (98 mg, 0.3 mmol, 3 eq) in o-xylene (2 mL) at 160°C for 15h. After purification, **3.31** was obtained as a yellowish solid (28.5 mg, 0.079 mmol, 79%).

**$^1$H NMR (400 MHz, Chloroform-d) $\delta$**: 7.56 – 7.51 (m, 1H), 7.24 – 7.22 (m, 1H), 7.20 – 7.17 (m, 1H), 5.17 (s, 2H), 2.08 – 2.02 (m, 3H), 1.96 – 1.90 (m, 6H), 1.78 – 1.68 (m, 6H).

**$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$**: 171.8, 143.9, 133.3, 127.6, 125.0, 123.5, 119.0, 109.1, 65.5, 39.9, 39.4, 36.7, 28.2.

**HRMS (ESI)**: Calculated for C$_{19}$H$_{21}$N$_2$O ([M+H]$^+$): 293.1654; found: 293.1652

**IR** (neat): $\nu = 2907, 2361, 1594$ cm$^{-1}$

**m.p.**: 69-71°C

**2-((3r,5r,7r)-adamantan-1-yl)-6-methoxy-4H-benzo[d][1,3]oxazine 3.32:**

Following general procedure for benzoxazine synthesis, **3.32r** (38 mg, 0.1 mmol, 1eq) was reacted with Pd(PCy$_3$)$_2$ (6.7 mg, 0.01 mmol, 10 mol%), cesium pivalate (7.1 mg, 0.03 mmol, 30 mol%) and Cs$_2$CO$_3$ (98 mg, 0.3 mmol, 3 eq) in o-xylene (2 mL) at 160°C for 15h. After purification, **3.32** was obtained as a yellowish solid (18.5 mg, 0.063 mmol, 63%).

**$^1$H NMR (400 MHz, Chloroform-d) $\delta$**: 7.11 – 7.05 (m, 1H), 6.79 – 6.75 (m, 1H), 6.48 – 6.45 (m, 1H), 5.11 (s, 2H), 3.78 (s, 3H), 2.06 – 2.01 (m, 3H), 1.95 – 1.93 (m, 6H), 1.74 – 1.70 (m, 6H).

**$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$**: 166.9, 157.9, 133.1, 125.5, 123.6, 113.5, 109.4, 66.1, 55.6, 39.5, 39.4, 36.9, 28.3.

**HRMS (ESI)**: Calculated for C$_{19}$H$_{24}$NO$_2$ ([M+H]$^+$): 298.1807; found: 298.1803
IR (neat) : $\nu = 2904, 2360, 1612 \text{ cm}^{-1}$

m.p.: 70-72°C

2-((3r,5r,7r)-adamantan-1-yl)-6-methyl-4H-benzo[d][1,3]oxazine 3.33:

![Chemical Structure]

Chemical Formula: $C_{19}H_{23}NO$
Exact Mass: 281.1780

Following general procedure for benzoxazine synthesis, 3.33r (36 mg, 0.1 mmol, 1eq) was reacted with Pd(PCy$_3$)$_2$ (6.7 mg, 0.01 mmol, 10 mol%), cesium pivalate (7.1 mg, 0.03 mmol, 30 mol%) and Cs$_2$CO$_3$ (98 mg, 0.3 mmol, 3 eq) in o-xylene (2 mL) at 160°C for 15h. After purification, 3.33 was obtained as a white solid (24.3 mg, 0.086 mmol, 86%).

$^1$H NMR (400 MHz, Chloroform-d) $\delta = 7.05 - 7.03$ (m, 2H), 6.75 – 6.72 (m, 1H), 5.10 (s, 2H), 2.30 (s, 3H), 2.07 – 2.02 (m, 3H), 1.96 – 1.92 (m, 6H), 1.76 – 1.70 (m, 6H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta = 168.1, 137.2, 135.8, 129.4, 124.2, 124.2, 122.3, 66.2, 39.5, 39.5, 36.9, 28.3, 21.2.$

HRMS (ESI): Calculated for C$_{19}$H$_{24}$NO ([M+H]$^+$): 282.1858; found: 282.1858

IR (neat) : $\nu = 2925, 2045, 911 \text{ cm}^{-1}$

m.p.: 77-79°C

2-((3s)-adamantan-1-yl)-7-methyl-4H-benzo[d][1,3]oxazine and 2-((3r,5r,7r)-adamantan-1-yl)-5-methyl-4H-benzo[d][1,3]oxazine 3.34/3.34':

![Chemical Structure]

Chemical Formula: $C_{19}H_{23}NO$
Exact Mass: 281.1780

Following general procedure for benzoxazine synthesis, 3.34r (36 mg, 0.1 mmol, 1eq) was reacted with Pd(PCy$_3$)$_2$ (6.7 mg, 0.01 mmol, 10 mol%), cesium pivalate (7.1 mg, 0.03 mmol, 30 mol%) and Cs$_2$CO$_3$ (98 mg, 0.3 mmol, 3 eq) in o-xylene (2 mL) at 160°C for 15h. $^1$H NMR of
the crude mixture shows a ratio [2.9:1] (3.34/3.34'). After purification, 3.34/3.34' was obtained mixture of 2 products (27 mg, [2.6:1] mixture, 0.096 mmol, 96%).

**Major product:**

\[ ^{1}H\text{ NMR (500 MHz, Chloroform-d)} \delta = 6.99 - 6.98 (m, 1H), 6.95 - 6.91 (m, 1H), 6.82 - 6.79 (m, 1H), 5.11 (s, 2H), 2.31 (s, 3H), 2.07 - 2.02 (m, 3H), 1.97 - 1.93 (m, 6H), 1.78 - 1.70 (m, 6H). \]

\[ ^{13}C\text{ NMR (126 MHz, CDCl}_{3}\) \delta \ = \ 168.7, 139.4, 138.6, 126.5, 124.9, 123.3, 119.3, 66.0, 39.4, 36.7, 28.2, 21.2. \]

**Minor product:**

\[ ^{1}H\text{ NMR (500 MHz, Chloroform-d)} \delta = 7.15 - 7.10 (m, 1H), 6.99 - 6.96 (m, 1H), 6.94 - 6.91 (m, 1H), 5.17 (s, 2H), 2.15 (s, 3H), 2.06 - 2.02 (m, 3H), 1.96 - 1.92 (m, 6H), 1.77 - 1.69 (m, 6H). \]

\[ ^{13}C\text{ NMR (126 MHz, Chloroform-d)} \delta = 168.0, 139.4, 132.5, 128.3, 127.8, 122.2, 120.8, 64.3, 39.5, 36.9, 28.3, 17.5. \]

**HRMS (ESI):** Calculated for C_{19}H_{24}NO ([M+H]^+): 282.1858; found: 282.1858

**IR (neat):** \( \nu = 2926, 2046, 907 \text{ cm}^{-1} \)

**m.p.:** 68-70°C

2-((3r,5r,7r)-adamantan-1-yl)-7-methoxy-4H-benzo[d][1,3]oxazine 3.35:

![Chemical structure](image)

Chemical Formula: C_{19}H_{23}NO_{2}

Exact Mass: 297.1729

Following general procedure for benzoxazine synthesis, 3.35r (38 mg, 0.1 mmol, 1eq) was reacted with Pd(PCy$_3$)$_2$ (6.7 mg, 0.01 mmol, 10 mol%), adamantane carboxylic acid (5.4 mg, 0.03 mmol, 30 mol%) and Cs$_2$CO$_3$ (98 mg, 0.3 mmol, 3 eq) in o-xylene (2 mL) at 160°C for 15h. \[ ^{1}H\text{ NMR of the crude mixture shows a ratio [4:1]} (3.35/3.35'). \] After purification, 3.35 was obtained as a yellowish solid (24 mg, 0.081 mmol, 81% and 19 mg, 0.062 mmol, 62% for the major isomer).

\[ ^{1}H\text{ NMR (400 MHz, Chloroform-d)} \delta = 6.84 - 6.81 (m, 1H), 6.74 - 6.72 (m, 1H), 6.70 - 6.66 (m, 1H), 5.10 (s, 2H), 3.79 (s, 3H), 2.07 - 2.02 (m, 3H), 1.97 - 1.93 (m, 6H), 1.79 - 1.68 (m, 6H). \]
$^{13}$C NMR (101 MHz, CDCl$_3$) δ = 169.3, 160.3, 140.9, 124.4, 114.5, 112.6, 109.0, 66.0, 55.6, 39.6, 39.5, 36.8, 28.3.

HRMS (ESI): Calculated for C$_{19}$H$_{24}$NO$_2$ ([M+H]$^+$): 298.1807; found: 298.1802

IR (neat): v = 2905, 2361, 1609 cm$^{-1}$

m.p.: 79-81°C

2-((3r,5r,7r)-adamantan-1-yl)-7-fluoro-4H-benzo[d][1,3]oxazine 3.36:

Following general procedure for benzoxazine synthesis, 3.36r (37 mg, 0.1 mmol, 1eq) was reacted with Pd(PCy$_3$)$_2$ (6.7 mg, 0.01 mmol, 10 mol%), adamantane carboxylic acid (5.4 mg, 0.03 mmol, 30 mol%) and Cs$_2$CO$_3$ (98 mg, 0.3 mmol, 3 eq) in o-xylene (2 mL) at 160°C for 15h. $^1$H NMR of the crude mixture shows a ratio [2.7:1] (3.36/3.36'). After purification, 3.36 was obtained as a yellowish solid (21 mg, 0.073 mmol, 73% for the mixture and 15 mg, 0.051 mmol, 51% for the major isomer).

$^1$H NMR (400 MHz, Chloroform-d) δ = 6.90 – 6.76 (m, 3H), 5.12 (s, 2H), 2.07 – 2.01 (m, 3H), 1.95 – 1.92 (m, 6H), 1.79 – 1.69 (m, 6H).

$^{13}$C NMR (126 MHz, CDCl$_3$) δ = 169.76, 163.2 (d, J = 245.8 Hz), 141.5 (d, J = 11.2 Hz), 124.6 (d, J = 9.2 Hz), 118.1 (d, J = 3.3 Hz), 112.6 (d, J = 22.3 Hz), 111.5 (d, J = 22.2 Hz), 65.9, 39.6, 39.4, 36.8, 28.3.

$^{19}$F NMR (376 MHz, CDCl$_3$) δ = -113.7.

HRMS (ESI): Calculated for C$_{18}$H$_{21}$FNO ([M+H]$^+$): 286.1607; found: 286.1608

IR (neat): v = 2361, 906 cm$^{-1}$

m.p.: 68-70°C

2-((3s)-adamantan-1-yl)-7-(trifluoromethoxy)-4H-benzo[d][1,3]oxazine 3.37:
Following general procedure for benzoxazine synthesis, 3.37r (43 mg, 0.1 mmol, 1eq) was reacted with Pd(PCy\(_3\))\(_2\) (6.7 mg, 0.01 mmol, 10 mol%), adamantane carboxylic acid (5.4 mg, 0.03 mmol, 30 mol%) and Cs\(_2\)CO\(_3\) (98 mg, 0.3 mmol, 3 eq) in o-xylene (2 mL) at 160°C for 15h. \(^1\)H NMR of the crude mixture shows a ratio [6.7:1] (3.37/3.37'). After purification, 3.37 was obtained as a yellowish oil (23 mg, 0.066 mmol, 66% and 19 mg, 0.054 mmol, 54% for the major isomer).

\(^1\)H NMR (400 MHz, Chloroform-d) \(\delta = 7.04 - 7.03\) (m, 1H), 6.98 – 6.90 (m, 2H), 5.15 (s, 2H), 2.08 – 2.01 (m, 3H), 1.95 – 1.93 (m, 6H), 1.78 – 1.69 (m, H).

\(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta = 169.9, 149.6\) (q, J = 2.1 Hz), 141.1, 124.5, 120.8, 120.5 (q, J = 260.1 Hz), 118.2, 116.9, 65.7, 39.6, 39.3, 36.6, 28.1.

\(^{19}\)F NMR (376 MHz, CDCl\(_3\)) \(\delta = -57.9\).

HRMS (ESI): Calculated for C\(_{19}\)H\(_{20}\)F\(_3\)NO\(_2\) ([M+H]\(^+\)): 352.1524; found: 352.1526

IR (neat) : \(\nu = 1628, 1494\) cm\(^{-1}\)

2-((3r,5r,7r)-adamantan-1-yl)-5-fluoro-4H-benzo[d][1,3]oxazine 3.38':

Following general procedure for benzoxazine synthesis, 3.38r (37 mg, 0.1 mmol, 1eq) was reacted with Pd(PCy\(_3\))\(_2\) (6.7 mg, 0.01 mmol, 10 mol%), adamantane carboxylic acid (5.4 mg, 0.03 mmol, 30 mol%) and Cs\(_2\)CO\(_3\) (98 mg, 0.3 mmol, 3 eq) in o-xylene (2 mL) at 160°C for 15h. \(^1\)H NMR of the crude mixture shows a ratio [2.2:1] (3.38/3.38'). After purification, 3.38 was obtained as a yellowish solid (8.5 mg, 0.03 mmol, 30%) and 3.38' was obtained as a yellowish solid (4 mg, 0.014 mmol, 14%).
**1H NMR (400 MHz, Chloroform-d)** δ = 7.22 – 7.15 (m, 1H), 6.95 – 6.92 (m, 1H), 6.86 – 6.79 (m, 1H), 5.24 (s, 2H), 2.08 – 2.02 (m, 3H), 1.96 – 1.92 (m, 6H), 1.78 – 1.68 (m, 6H).

**13C NMR (101 MHz, CDCl3)** δ = 169.1, 157.4 (d, J = 246.2 Hz), 141.1 (d, J = 4.15 Hz), 129.2 (d, J = 8.2 Hz), 120.0 (d, J = 2.9 Hz), 112.7 (d, J = 21.7 Hz), 109.3 (d, J = 18.2 Hz), 60.9 (d, J = 3.1 Hz), 39.6, 39.3, 36.7, 28.1.

**19F NMR (376 MHz, CDCl3)** δ = -123.3.

**HRMS (ESI):** Calculated for C18H21FNO ([M+H]+): 286.1607; found: 286.1607

**IR (neat):** ν = 2361, 911 cm⁻¹

**m.p.:** 65-67°C

**methyl 2-(1-methylcyclohexyl)-4H-benzo[d][1,3]oxazine-6-carboxylate 3.44:**

Following general procedure for benzoxazine synthesis, 3.44r (24 mg, 0.1 mmol, 1eq) was reacted with Pd(PCy3)2 (6.7 mg, 0.01 mmol, 10 mol%), cesium pivalate (7.1 mg, 0.03 mmol, 30 mol%) and Cs2CO3 (98 mg, 0.3 mmol, 3 eq) in o-xylene (2 mL) at 160°C for 15h. After purification, 3.44 was obtained as a colorless oil (6.2 mg, 0.033 mmol, 33%).

**1H NMR (500 MHz, Chloroform-d)** δ = 7.96 – 7.92 (m, 1H), 7.67 – 7.64 (m, 1H), 7.19 – 7.16 (m, 1H), 5.20 (s, 2H), 3.90 (s, 3H), 2.13 – 2.05 (m, 2H), 1.58 – 1.45 (m, 4H), 1.37 – 1.29 (m, 2H), 1.22 (s, 3H).

**13C NMR (126 MHz, CDCl3)** δ = 170.7, 166.8, 144.0, 130.7, 127.6, 125.4, 124.2, 122.3, 66.2, 52.2, 41.9, 35.7, 26.1, 23.1.

**HRMS (ESI):** Calculated for C17H22NO3 ([M+H]+): 288.1600; found: 288.1601

**IR (neat):** ν = 2361, 1622, 1492 cm⁻¹

**2-(1-(2-(benzyloxy)ethyl)cyclohexyl)-4H-benzo[d][1,3]oxazine 3.45:**
Following general procedure for benzoxazine synthesis, 3.45r (43 mg, 0.1 mmol, 1eq) was reacted with Pd(PCy$_3$)$_2$ (6.7 mg, 0.01 mmol, 10 mol%), cesium pivalate (7.1 mg, 0.03 mmol, 30 mol%) and Cs$_2$CO$_3$ (98 mg, 0.3 mmol, 3 eq) in o-xylene (2 mL) at 160°C for 15h. After purification, 3.45 was obtained as a yellowish oil (29 mg, 0.082 mmol, 82%).

$^1$H NMR (250 MHz, Chloroform-d) $\delta =$ 7.30 – 7.23 (m, 1H), 7.23 – 7.20 (m, 5H), 7.18 – 7.09 (m, 2H), 6.91 – 6.84 (m, 1H), 5.05 (s, 2H), 4.41 (s, 2H), 3.57 (t, $J = 6.9$ Hz, 2H), 2.22 – 2.10 (m, 2H), 1.93 (t, $J = 7.0$ Hz, 2H), 1.82 – 1.71 (m, 1H), 1.58 – 1.50 (m, 3H), 1.40 – 1.24 (m, 4H).

$^{13}$C NMR (63 MHz, CDCl$_3$) $\delta =$ 166.4, 139.5, 138.4, 128.7, 128.2, 127.7, 127.4, 125.9, 124.1, 123.6, 122.5, 73.1, 66.8, 65.9, 43.5, 34.4, 26.9, 26.1, 22.8.

HRMS (ESI): Calculated for C$_{23}$H$_{28}$NO$_2$ ([M+H]$^+$): 350.2120; found: 350.2122

IR (neat) : $\nu =$ 2361, 1622 cm$^{-1}$

2-(bicyclo[2.2.2]octan-1-yl)-6-methoxy-4H-benzo[d][1,3]oxazine 3.50:

Following general procedure for benzoxazine synthesis, 3.50r (35 mg, 0.1 mmol, 1eq) was reacted with Pd(PCy$_3$)$_2$ (6.7 mg, 0.01 mmol, 10 mol%), cesium pivalate (7.1 mg, 0.03 mmol, 30 mol%) and Cs$_2$CO$_3$ (98 mg, 0.3 mmol, 3 eq) in o-xylene (2 mL) at 160°C for 15h. After purification, 3.50 was obtained as a white solid (13.5 mg, 0.050 mmol, 50%).

$^1$H NMR (400 MHz, Chloroform-d) $\delta =$ 7.08 – 7.05 (m, 1H), 6.78 – 6.74 (m, 1H), 6.46 – 6.44 (m, 1H), 5.09 (s, 2H), 3.77 (s, 3H), 1.82 – 1.75 (m, 6H), 1.65 – 1.57 (m, 6H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta =$ 166.8, 157.8, 132.9, 125.3, 123.3, 113.4, 109.3, 65.9, 55.5, 37.1, 28.5, 25.6, 24.1.
HRMS (ESI): Calculated for C_{17}H_{22}NO_{2} ([M+H]^+): 272.1651; found: 272.1645

IR (neat) : ν = 906 cm\(^{-1}\)

m.p.: 90-92°C

2-(bicyclo[2.2.2]octan-1-yl)-4H-benzo[d][1,3]oxazine-6-carbonitrile 3.5l:

Following general procedure for benzoxazine synthesis, 3.5lr (35 mg, 0.1 mmol, 1eq) was reacted with Pd(PCy\(_3\))^2 (6.7 mg, 0.01 mmol, 10 mol%), cesium pivalate (7.1 mg, 0.03 mmol, 30 mol%) and Cs\(_2\)CO\(_3\) (98 mg, 0.3 mmol, 3 eq) in o-xylene (2 mL) at 160°C for 15h. After purification, 3.5l was obtained as a white solid (10.5 mg, 0.039 mmol, 39%).

\(^1\)H NMR (400 MHz, Chloroform-d) δ = 7.54 – 7.50 (m, 1H), 7.23 – 7.20 (m, 1H), 7.18 – 7.14 (m, 1H), 5.15 (s, 2H), 1.82 – 1.76 (m, 6H), 1.68 – 1.64 (m, 1H), 1.64 – 1.57 (m, 6H).

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) δ = 172.0, 143.8, 133.3, 127.6, 125.0, 123.4, 119.0, 109.1, 65.5, 37.8, 28.6, 25.6, 24.1.

HRMS (ESI): Calculated for C_{17}H_{19}N_{2}O ([M+H]^+): 267.1497; found: 267.1493

IR (neat) : ν = 2361, 903 cm\(^{-1}\)

m.p.: 82-84°C

2-(bicyclo[2.2.2]octan-1-yl)-7-methoxy-4H-benzo[d][1,3]oxazine 3.46:

Following general procedure for benzoxazine synthesis, 3.46r (35 mg, 0.1 mmol, 1eq) was reacted with Pd(PCy\(_3\))^2 (6.7 mg, 0.01 mmol, 10 mol%), adamantane carboxylic acid pivalate (5.6 mg, 0.03 mmol, 30 mol%) and Cs\(_2\)CO\(_3\) (98 mg, 0.3 mmol, 3 eq) in o-xylene (2 mL) at
160°C for 15h. $^1$H NMR of the crude mixture shows a ratio [4:1] ($3.46/3.46^*$). After purification, 3.46 was obtained as a colorless oil (10 mg, 0.036 mmol, 36% for the mixture and 6 mg, 0.021 mmol, 21% for the major isomer).

$^1$H NMR (500 MHz, Chloroform-d) $\delta =$ 6.83 – 6.79 (m, 1H), 6.72 – 6.70 (m, 1H), 6.69 – 6.65 (m, 1H), 5.09 (s, 2H), 3.79 (s, 3H), 1.82 – 1.77 (m, 6H), 1.66 – 1.58 (m, 7H).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta =$ 169.4, 160.3, 140.8, 124.4, 114.4, 112.6, 109.0, 66.0, 55.6, 37.4, 28.7, 25.8, 24.2.

HRMS (ESI): Calculated for C$_{17}$H$_{22}$NO$_2$ ([M+H]$^+$): 272.1651; found: 272.1653

IR (neat) : $\nu =$ 2361, 906 cm$^{-1}$

methyl 4-(6-cyano-4H-benzo[d][1,3]oxazin-2-yl)bicyclo[2.2.2]octane-1-carboxylate 3.47:

Following general procedure for benzoxazine synthesis, 3.47 (40 mg, 0.1 mmol, 1eq) was reacted with Pd(PCy$_3$)$_2$ (6.7 mg, 0.01 mmol, 10 mol%), cesium pivalate (7.1 mg, 0.03 mmol, 30 mol%) and Cs$_2$CO$_3$ (98 mg, 0.3 mmol, 3 eq) in o-xylene (2 mL) at 160°C for 15h. After purification, 3.47 was obtained as a yellowish oil (14.5 mg, 0.045 mmol, 45%).

$^1$H NMR (400 MHz, Chloroform-d) $\delta =$ 7.56 – 7.51 (m, 1H), 7.24 – 7.21 (m, 1H), 7.18 – 7.14 (m, 1H), 5.17 (s, 2H), 3.66 (s, 3H), 1.86 (s, 12H).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta =$ 178.1, 170.9, 143.5, 133.4, 127.6, 125.1, 123.2, 118.9, 109.4, 65.6, 51.9, 39.0, 38.2, 28.3, 28.0.

HRMS (ESI): Calculated for C$_{19}$H$_{21}$N$_2$O$_3$ ([M+H]$^+$): 325.1552; found: 325.1544

IR (neat) : $\nu =$ 2359, 905 cm$^{-1}$

((3r,5r,7r)-adamantan-1-yl)(indolin-1-yl)methanone 3.49:
Following general procedure for benzoxazine synthesis, \textbf{3.48r} (36 mg, 0.1 mmol, 1 eq) was reacted with Pd(PCy$_3$)$_2$ (6.7 mg, 0.01 mmol, 10 mol%), cesium pivalate (7.1 mg, 0.03 mmol, 30 mol%) and Cs$_2$CO$_3$ (98 mg, 0.3 mmol, 3 eq) in o-xylene (2 mL) at 160°C for 15h. After purification, \textbf{3.49} was obtained as a yellowish oil (22.5 mg, 0.080 mmol, 80%).

\textbf{1H NMR (400 MHz, Chloroform-$d$)} $\delta$ = 8.25 – 8.19 (m, 1H), 7.21 – 7.13 (m, 2H), 7.03 – 6.98 (m, 1H), 4.32 (t, $J$ = 8.1 Hz, 2H), 3.12 (t, $J$ = 8.1 Hz, 2H), 2.12 – 2.06 (m, 9H), 1.78 – 1.72 (m, 6H).

\textbf{13C NMR (101 MHz, CDCl$_3$)} $\delta$ = 176.1, 145.0, 130.7, 127.3, 124.2, 123.5, 118.6, 49.6, 43.1, 38.3, 36.6, 29.6, 28.4.

\textbf{HRMS (ESI)}: Calculated for C$_{19}$H$_{24}$NO ([M+H]$^+$): 282.1858; found: 282.1858

\textbf{IR} (neat) : $\nu$ = 2904, 2848, 1634, 1374 cm$^{-1}$

\textbf{2-((3s)-adamantan-1-yl)-7-fluoro-1,4-dihydro-2H-benzo[d][1,3]oxazine 3.52:}

Benzoxazine \textbf{3.36} (0.05 mmol, 14 mg, 1 equiv) was dissolved in a mixture of THF/MeOH/DMF [1:1:1] (0.5 mL) and cooled to 0°C with an ice bath. Then, sodium borohydride (0.15 mmol, 5.7 mg, 3 equiv) was added and the mixture was slowly warm to room temperature. The reaction was monitored by TLC using Cyclohexane/AcOEt [9:1] as solvent. After completion, the reaction was quenched with NaOH (1M, 1 mL) and the crude mixture was extracted with AcOEt (3 x 2mL). The combined organic layers were dried over sodium sulfate, filtered, evaporated and purified by preparative HPLC using water/MeCN as solvent. The product was obtained as a colorless oil (9 mg, 0.031 mmol, 62%).
$^1$H NMR (500 MHz, Chloroform-d) $\delta = 6.84 - 6.79$ (m, 1H), $6.46 - 6.41$ (m, 1H), $6.37 - 6.33$ (m, 1H), $4.87 - 4.82$ (m, 1H), $4.79 - 4.75$ (m, 1H), $4.06$ (s, 2H), $2.06 - 2.02$ (m, 3H), $1.79 - 1.67$ (m, 9H), $1.66 - 1.61$ (m, 3H).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta = 162.4$ (d, $J = 245.2$ Hz), $143.8$ (d, $J = 11.0$ Hz), $126.0$ (d, $J = 11.0$ Hz), $117.5$ (d, $J = 2.9$ Hz), $105.5$ (d, $J = 22.0$ Hz), $102.8$ (d, $J = 24.2$ Hz), $90.5$, $67.9$, $37.2$, $37.1$, $36.0$, $28.1$.

$^{19}$F NMR (471 MHz, CDCl$_3$) $\delta = -115.58$.

HRMS (ESI): Calculated for C$_{18}$H$_{23}$FNO ([M+H]$^+$): 288.1764; found: 288.1765

IR (neat) : $\nu = 2361, 911$ cm$^{-1}$

**N-methylskatole 3.54:**

![Chemical Structure](image)

Chemical Formula: C$_{10}$H$_{11}$N

Exact Mass: 145.0891

The product was synthesized following a described procedure from the literature. Analysis data matches with previous report.$^{27}$

$^1$H NMR (250 MHz, Chloroform-d) $\delta = 7.62 - 7.56$ (m, 1H), $7.31 - 7.18$ (m, 2H), $7.17 - 7.09$ (m, 1H), $6.79 - 6.77$ (m, 1H), $3.68$ (s, 3H), $2.35$ (d, $J = 1.1$ Hz, 3H).

$^{13}$C NMR (63 MHz, CDCl$_3$) $\delta = 137.1$, $128.7$, $126.6$, $121.5$, $119.0$, $118.6$, $110.1$, $109.1$, $32.5$, $9.7$.

($(3R,5R,7R)$-adamantan-1-yl)($5aR,10bR$)-2-fluoro-6,10b-dimethyl-5a,6,10b,11-tetrahydro-5H-indolo[2,3-b]quinolin-5-yl)methanone 3.55:

![Chemical Structure](image)

Chemical Formula: C$_{29}$H$_{31}$FN$_2$O

Exact Mass: 430.2420
In a 10 mL flask, 3.29 (0.080 mmol, 23 mg, 1 eq) was refluxed in HCl/Dioxane (4 M, 3 mL) for 3 h. The reaction was cooled to room temperature and quenched with water (5 mL). The crude mixture was extracted with AcOEt (3 x 5 mL) and the combined organic phases were dried over sodium sulfate, filtered and evaporated under vacuum. The intermediate was used without further purification (25.7 mg, 0.08 mmol, 100 %).

In a 10 mL flask with N-methylskatole 3.54 (34.8 mg, 0.24 mmol, 3 eq) and Cs2CO3 (52 mg, 0.16 mmol, 2 eq) was added the chlorobenzylintermediate (25.7 mg, 0.08 mmol, 1 eq) in 1,2-dichloroethane (0.5 mL). The mixture was stirred overnight at 80°C, cooled to room temperature, quenched with water (2 mL) and extracted with AcOEt (3 x 2 mL). The combined organic phases were dried over sodium sulfate, filtered and evaporated. The crude mixture was purified by preparative HPLC using MeCN/Water as solvent, to afford 3.55 (17 mg, 0.04 mmol, 50%) as a yellowish oil.

\[
\begin{align*}
^{1}H\text{ NMR (500 MHz, Chloroform-d)} & \ \delta = 7.04 - 6.98 (m, 1H), 6.90 - 6.83 (m, 2H), 6.79 - 6.73 (m, 1H), 6.68 - 6.63 (m, 1H), 6.51 - 6.46 (m, 1H), 6.04 - 6.00 (m, 1H), 5.96 (s, 1H), 2.82 (s, 3H), 2.79 (d, J = 13.6 Hz, 1H), 2.71 (d, J = 13.6 Hz, 1H), 1.96 - 1.89 (m, 6H), 1.80 - 1.75 (m, 3H), 1.66 - 1.53 (m, 6H), 1.52 (s, 3H). \\
^{13}C\text{ NMR (126 MHz, CDCl}_3) & \ \delta = 180.3, 161.1 (d, J = 245.2 Hz), 150.7, 137.3 (d, J = 8.5 Hz), 135.2 (d, J = 2.9 Hz), 133.2, 128.1, 127.5 (d, J = 8.9 Hz), 121.9, 116.6, 115.3 (d, J = 21.7 Hz), 113.1 (d, J = 24.7 Hz), 104.1, 85.3, 51.0, 45.1, 40.8, 40.5, 36.6, 30.6, 28.9, 28.6. \\
^{19}F\text{ NMR (471 MHz, CDCl}_3) & \ \delta = -115.1.
\end{align*}
\]

HRMS (ESI): Calculated for C28H32FN2O ([M+H]+): 431.2499; found: 431.2501

IR (neat) : ν = 2361, 903 cm⁻¹

(5aS,10bR)-2-fluoro-6,10b-dimethyl-5a,6,10b,11-tetrahydro-5H-indolo[2,3-b]quinolone 3.56:

![Chemical Structure](image)

Chemical Formula: C_{19}H_{17}FN_{2}

Exact Mass: 268.1376
3.55 (17 mg, 0.04 mmol, 1 eq) was dissolved in MeOH (1 mL) and NaOH (32 mg, 0.8 mmol, 20 eq) was added. The mixture was stirred at 90°C overnight, and the volatile were removed under vacuum. The crude mixture was quenched with water (2 mL) and extracted with AcOEt (3 x 2 mL). The combined phases were dried over sodium sulfate, filtered and evaporated under vacuum. The crude mixture was purified by preparative HPLC using MeCN/Water as solvent to afford 3.56 as a yellowish oil (7.5 mg, 0.028 mmol, 69%).

$^1$H NMR (500 MHz, Chloroform-d) $\delta =$ 7.14 – 7.10 (m, 1H), 7.10 – 7.08 (m, 1H), 6.78 – 6.73 (m, 2H), 6.73 – 6.69 (m, 1H), 6.56 – 6.53 (m, 1H), 6.52 – 6.49 (m, 1H), 4.51 (br. s, 1H), 4.14 (s, 1H), 2.79 (d, J = 15.1 Hz, 1H), 2.76 (s, 3H), 2.48 (d, J = 15.2 Hz, 1H), 1.23 (s, 3H).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta =$ 156.1 (d, J = 234.9 Hz), 149.3, 137.4 (d, J = 2.1 Hz), 136.7, 128.02, 123.2 (d, J = 7.3 Hz), 121.5, 118.8, 115.5 (d, J = 22.1 Hz), 114.2 (d, J = 8.2 Hz), 113.6 (d, J = 22.3 Hz), 108.0, 84.1, 39.5, 37.8, 32.2, 22.0.

$^{19}$F NMR (471 MHz, CDCl$_3$) $\delta =$ -127.4.

HRMS (ESI): Calculated for C$_{17}$H$_{18}$FN$_2$ ([M+H]+): 269.1454; found: 269.1457

IR (neat) : $\nu = 901$ cm$^{-1}$
checkCIF/PLATON report

Structure factors have been supplied for datablock(s) 1

THIS REPORT IS FOR GUIDANCE ONLY. IF USED AS PART OF A REVIEW PROCEDURE FOR PUBLICATION, IT SHOULD NOT REPLACE THE EXPERTISE OF AN EXPERIENCED CRYSTALLOGRAPHIC REFEREE.

No syntax errors found.

CIF dictionary

Interpreting this report

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S = 1.085
Npar= 217
The following ALERTS were generated. Each ALERT has the format test-name_ALERT_alert-type_alert-level.
Click on the hyperlinks for more details of the test.

**Alert level B**
PLAT910_ALERT_3_B Missing # of FCF Reflection(s) Below Theta(Min). 12 Note

**Alert level C**
PLAT913_ALERT_3_C Missing # of Very Strong Reflections in FCF .... 7 Note
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0 ALERT level A = Most likely a serious problem - resolve or explain
1 ALERT level B = A potentially serious problem, consider carefully
2 ALERT level C = Check. Ensure it is not caused by an omission or oversight
9 ALERT level G = General information/check it is not something unexpected

3 ALERT type 1 CIF construction/syntax error, inconsistent or missing data
2 ALERT type 2 Indicator that the structure model may be wrong or deficient
3 ALERT type 3 Indicator that the structure quality may be low
1 ALERT type 4 Improvement, methodology, query or suggestion
3 ALERT type 5 Informative message, check
It is advisable to attempt to resolve as many as possible of the alerts in all categories. Often the minor alerts point to easily fixed oversights, errors and omissions in your CIF or refinement strategy, so attention to these fine details can be worthwhile. In order to resolve some of the more serious problems it may be necessary to carry out additional measurements or structure refinements. However, the purpose of your study may justify the reported deviations and the more serious of these should normally be commented upon in the discussion or experimental section of a paper or in the "special_details" fields of the CIF. checkCIF was carefully designed to identify outliers and unusual parameters, but every test has its limitations and alerts that are not important in a particular case may appear. Conversely, the absence of alerts does not guarantee there are no aspects of the results needing attention. It is up to the individual to critically assess their own results and, if necessary, seek expert advice.

Publication of your CIF in IUCr journals

A basic structural check has been run on your CIF. These basic checks will be run on all CIFs submitted for publication in IUCr journals (Acta Crystallographica, Journal of Applied Crystallography, Journal of Synchrotron Radiation); however, if you intend to submit to Acta Crystallographica Section C or E or IUCrData, you should make sure that full publication checks are run on the final version of your CIF prior to submission.

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Please refer to the Notes for Authors of the relevant journal for any special instructions relating to CIF submission.

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PLATON version of 23/04/2018; check.def file version of 23/04/2018
**Computational details**

Geometry optimizations were performed with the oB97X-D functional/6-311+G** basis set in vacuum, using the Spartan '16 software (Wavefunction, Inc.). The geometry of the optimized structures is available as a single xyz file alongside the Supporting Information.

Geometry optimizations were performed using Gaussian 16, Revision A03 at the PBE0 level of hybrid density functional theory, with inclusion of D3(bj) corrections in the optimization process. The geometry of all the optimized structures is available as a single xyz file alongside the Supporting Information. The atoms C, H, N, P and O were represented by an svp basis set. The Pd atom was represented by Dolg’s pseudo potential and the associated basis set. The solvent (mesitylene) influence was taken into consideration through single-point calculations on the gas-phase optimized geometries with SCRF calculations within the SMD model. For the SCRF calculations, the atoms were treated with a def2-qzvp basis set. All energies reported are Gibbs free energies obtained by summing the SMD energy (including D3 corrections) and the gas phase Gibbs contribution at 433 K and 1 atm.
Part 2: Remote C(sp³)-H activation

Chapter 2.1: 1,4-Palladium Shift/C(sp³)-H Activation

Strategy for the Construction of 5-Membered Rings

General procedures:

**GENERAL PROCEDURE FOR KNOEVENAGEL CONDENSATIONS:**
In a round bottom flask was stirred the *ortho*-bromobenzaldehyde derivatives (1 equiv), malonic acid (1.1 equiv), piperidine (1.1 equiv) in pyridine (2.5 M) at 90 °C for 15h. Pyridine was removed under vacuum, the crude mixture was acidified with HCl (2 M) and extracted with AcOEt (3 times). The crude mixture was dried over sodium sulfate, filtered and evaporated under vacuum. The acid was purified by precipitated in Et₂O or used without further purifications for next step.

**GENERAL PROCEDURE FOR ALDOLISATION REACTION:**
Aldehyde (1 equiv) and ketone (1 equiv) were dissolved in EtOH (1 M), followed by addition of NaOH (1 equiv) in water (1 M). The reaction was stirred at 45°C until completion and evaporated under vacuum. The crude was dissolved in dichloromethane and the organic phase was washed with water. The crude was dried over sodium sulfate, filtered and evaporated under vacuum. The desired chalcones were purified by chromatography on silica gel using cyclohexane/AcOEt as solvent.

**GENERAL PROCEDURE FOR AMIDE SYNTHESIS:**
The carboxylic acid (1 equiv) was suspended in dichloromethane (0.05 M) with DMF (0.01 equiv). Oxalyl chloride (1.5 equiv) was carefully added to the resulting mixture, which was then stirred for 2h. The solvent and excess of oxalyl chloride were removed under vacuum, and the crude was dissolved in dichloromethane (0.05 M). Then, a solution of amine (1 equiv) and Et₃N (2 equiv) in dichloromethane (0.05 M) was carefully added. The reaction was followed by TLC (cyclohexane/AcOEt). After completion, the solvent was removed and the crude was purified by chromatography on silica gel, using cyclohexane/AcOEt as solvent.

**GENERAL PROCEDURE FOR THE 1,4-Pd SHIFT/C(sp³)-H ACTIVATION:**
In a 10 mL screw cap charged with amide (0.1 mmol, 1 equiv) was weighted in a glovebox Pd(PCy₃)₂ (0.01 mmol, 10 mol %), PCy₃ (when mentioned) (2.8 mg, 0.01 mmol, 10 mol%), pivalic acid (0.03 mmol, 30 mol %) and Rb₂CO₃ (0.15 mmol, 1.5 equiv). The vial was charged...
with mesitylene (4 mL) and stirred under argon in a previously heated heating block at 160 °C for 16 h. The reaction was cooled to room temperature, filtered over celite, and evaporated under vacuum. The crude was purified by preparative HPLC using gradient of solvent (H₂O: MeCN) [90:10] to [10:90]. The collected fractions were evaporated under vacuum to afford the desired product.

**1,4-Pd shift/C(sp³)-H activation reaction optimization:**

<table>
<thead>
<tr>
<th>Pd source</th>
<th>Additive (30 mol%)</th>
<th>Base</th>
<th>Solvent</th>
<th>NMR yield (Isolated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pd(Pt-Bu₃)₂ (10 mol%)</td>
<td>PivOH</td>
<td>Rb₂CO₃ (1.5 equiv.)</td>
<td>Mesitylene [0.05M]</td>
<td>0%</td>
</tr>
<tr>
<td>Pd(PPh₃)₄ (10 mol%)</td>
<td>PivOH</td>
<td>Rb₂CO₃ (1.5 equiv.)</td>
<td>Mesitylene [0.05M]</td>
<td>8%</td>
</tr>
<tr>
<td>[Pd(η³-allyl)Cl₂]/PPh₃ (10 mol%)</td>
<td>PivOH</td>
<td>Cs₂CO₃ (2 equiv.)</td>
<td>Mesitylene [0.05M]</td>
<td>0%</td>
</tr>
<tr>
<td>Pd₂dba₃/PCy₃ (10 mol%)</td>
<td>PivOH</td>
<td>Rb₂CO₃ (1.5 equiv.)</td>
<td>Mesitylene [0.05M]</td>
<td>31%</td>
</tr>
<tr>
<td>Pd(PCy₃)₂ (10 mol%)</td>
<td>PivOH</td>
<td>Rb₂CO₃ (1.5 equiv.)</td>
<td>Mesitylene [0.05M]</td>
<td>65%</td>
</tr>
<tr>
<td>Pd(PCy₃)₂ (10 mol%)</td>
<td>PivOH</td>
<td>Rb₂CO₃ (1.5 equiv.)</td>
<td>Mesitylene [0.025M]</td>
<td>100% (94%)</td>
</tr>
<tr>
<td>Pd(PCy₃)₂ (5 mol%)</td>
<td>PivOH</td>
<td>Rb₂CO₃ (1.5 equiv.)</td>
<td>Mesitylene [0.025M]</td>
<td>51%</td>
</tr>
</tbody>
</table>

*Using trichloroethylene as internal standard*
Amines:

\( N-(2,4,6\text{-trimethoxybenzyl})\text{propan-2-amine 2.40r:} \)

\[
\begin{align*}
\text{Chemical Formula: } & C_{13}H_{21}NO_3 \\
\text{Exact Mass: } & 239.1521
\end{align*}
\]

\( N-(2,4,6\text{-trimethoxybenzyl})\text{propan-2-amine was obtained according to a known procedure.} \)

The physical and spectroscopic properties matched those described in the literature.\(^{37}\)

\( N-(2,4,6\text{-trimethoxybenzyl})\text{ethanamine 2.53a:} \)

\[
\begin{align*}
\text{Chemical Formula: } & C_{12}H_{19}NO_3 \\
\text{Exact Mass: } & 225.1365
\end{align*}
\]

\( N-(2,4,6\text{-trimethoxybenzyl})\text{ethanamine was obtained according to a known procedure.} \)

The physical and spectroscopic properties matched those described in the literature.\(^1\)

\( 2\text{-Methyl-}N-(2,4,6\text{-trimethoxybenzyl})\text{propan-2-amine 2.55a:} \)

\[
\begin{align*}
\text{Chemical Formula: } & C_{14}H_{23}NO_3 \\
\text{Exact Mass: } & 253.1678
\end{align*}
\]

2-Methyl-N-(2,4,6-trimethoxybenzyl)propan-2-amine was obtained according to a known procedure.

The physical and spectroscopic properties matched those described in the literature.\(^1\)
N-(Cyclopentylmethyl)propan-2-amine 2.63a:

Chemical Formula: C₉H₁₉N
Exact Mass: 141.1517

N-(Cyclopentylmethyl)propan-2-amine was obtained according to a known procedure. The physical and spectroscopic properties matched those described in the literature.¹

Synthesis of reaction substrates:

(E)-3-(2-bromophenyl)-N-isopropyl-N-(2,4,6-trimethoxybenzyl)acrylamide 4.48:

Chemical Formula: C₂₂H₂₆BrNO₄
Exact Mass: 447.1045

Following the general procedure for amide synthesis, 2-bromocinnamic acid (411 mg, 1.81 mmol, 1 equiv) was reacted with oxalyl chloride (0.26 mL, 2.72 mmol, 1.5 equiv) with DMF (1 drop) in dichloromethane. The acid chloride was then reacted with 2.40r (433 mg, 1.81 mmol, 1 equiv) and Et₃N (0.51 mL, 3.62 mmol, 2 equiv) in dichloromethane. After evaporation and purification, 4.48 was obtained as a white solid (720 mg, 1.6 mmol, 89 %).

¹H NMR (400 MHz, Chloroform-d) δ = 7.88 (d, J = 15.4 Hz, 1H), 7.61 – 7.55 (m, 2H), 7.31 – 7.28 (m, 1H), 7.24 – 7.18 (m, 1H), 7.18 – 7.10 (m, 1H), 6.10 (s, 2H), 4.60 (s, 2H), 4.14 – 4.05 (sept, J = 7.0 Hz, 1H), 3.81 (s, 3H), 3.78 (s, 6H), 1.17 (d, J = 6.9 Hz, 6H).

¹³C NMR (101 MHz, Chloroform-d) δ = 166.7, 161.2, 159.7, 138.1, 136.6, 133.4, 130.0, 127.6, 127.5, 125.0, 124.9, 106.4, 90.5, 55.6, 55.4, 49.1, 39.7, 19.9.

HRMS (ESI): Calculated for C₂₂H₂₆BrNaNO₄ ([M+Na]+): 470.0943; found: 470.0937

IR (neat) : v = 2362, 1596, 1467 cm⁻¹

m.p.: 86 - 88°C
(E)-3-(2-bromophenyl)-N-(propan-2-yl-1,1,3,3,3-d6)-N-(2,4,6)trimethoxybenzyl)acrylamide-4.48-d7:

(2,4,6-trimethoxyphenyl)methanamine hydrochloride (500 mg, 2.14 mmol, 1 equiv) was exchanged with methanol-D₄ (10 mL) by stirring at room temperature overnight. After evaporation of the volatiles, the free amine was reacted with acetone-D₆ (2.4 mL, 32 mmol, 15 equiv) in dry benzene (20 mL) and refluxed in a Dean-Stark apparatus overnight. The volatiles were removed under vacuum, and the imine was then dissolved in diglyme (15 mL) and cooled to 0°C with an ice batch. NaBD₄ (4.28 mmol, 179 mg, 2 equiv) was carefully added to the solution, which was slowly warmed to room temperature. After completion, the reaction was quenched with 2M NaOH (20 mL) and extracted with DCM (3 x 15 mL). The combined organic phases were dried over sodium sulfate, filtered and evaporated under vacuum. The desired amine was obtained without further purification. (508 mg, 2.12 mmol, 99%).

Malonic acid-D₄ (3 g, 27.8 mmol, 1 equiv), 2-Bromobenzaldehyde (5.14 g, 27.8 mmol, 1 equiv), piperidine (2 drops) were refluxed in pyridine (50 mL) for 3h. Solvent were removed, and the reaction was quenched with 2M HCl (50 mL) and extracted with DCM (3 x 25 mL). The combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum to afford the deuterated cinnamic acid derivative (6.26 g, 27.45 mmol, 99%).

The deuterated cinnamic acid derivative (274 mg, 1.2 mmol, 1 equiv) was reacted with oxalyl chloride (0.17 mL, 1.8 mmol, 1.5 equiv) with DMF (1 drop) in dichloromethane. The acid chloride was then reacted with the deuterated amine (294 mg, 1.2 mmol, 1 equiv) and Et₃N (0.33 mL, 2.4 mmol, 2 equiv) in
dichloromethane. After evaporation and purification, 4.48-d7 was obtained as a white solid (412 mg, 0.9 mmol, 75 %).

**1H NMR (400 MHz, Chloroform-d)** δ = 7.91 – 7.86 (m, 1H), 7.60 – 7.55 (m, 2H), 7.31 – 7.28 (m, 1H), 7.18 – 7.12 (m, 1H), 6.11 (s, 2H), 4.59 (s, 2H), 4.12 – 4.04 (m, 1H), 3.81 (s, 3H), 3.78 (s, 6H).

**13C NMR (101 MHz, Chloroform-d)** δ = 166.7, 161.1, 159.7, 138.0, 136.6, 133.4, 129.9, 127.6, 127.5, 124.9, 106.4, 90.5, 55.5, 55.4, 49.0, 39.7.

(E)-3-(2-bromophenyl)-N-(propan-2-yl-1,1,1,3,3,3-d6)-N-(2,4,6-trimethoxybenzyl)acrylamide 4.48-d6:

Following the general procedure for amide synthesis, 2-bromocinnamic acid (182 mg, 0.8 mmol, 1 equiv) was reacted with oxalyl chloride (0.11 mL, 1.2 mmol, 1.5 equiv) with DMF (1 drop) in dichloromethane. The acid chloride was then reacted with the deuterated amine (195 mg, 0.8 mmol, 1 equiv) and Et3N (0.22 mL, 1.6 mmol, 2 equiv) in dichloromethane. After evaporation and purification, 4.48-d6 was obtained as a white solid (302 mg, 0.66 mmol, 83 %).

**1H NMR (400 MHz, Chloroform-d)** δ = 7.87 (d, J = 15.5 Hz, 1H), 7.59 – 7.54 (m, 2H), 7.30 – 7.27 (m, 1H), 7.21 (d, J = 15.4 Hz, 1H), 7.17 – 7.11 (m, 1H), 6.10 (s, 2H), 4.59 (s, 2H), 4.12 – 4.03 (m, 1H), 3.80 (s, 3H), 3.77 (s, 6H).

**13C NMR (101 MHz, Chloroform-d)** δ = 166.8, 161.1, 159.7, 138.0, 136.6, 133.4, 129.9, 127.6, 127.5, 124.9, 106.4, 90.6, 55.5, 55.4, 39.7.

(E)-3-(2-bromophenyl)-N-isopropyl-N-(2,4,6-trimethoxybenzyl)acrylamide-2-d 4.48-d1:

Following the general procedure for amide synthesis, 2-bromocinnamic acid (182 mg, 0.8 mmol, 1 equiv) was reacted with oxalyl chloride (0.11 mL, 1.2 mmol, 1.5 equiv) with DMF (1 drop) in dichloromethane. The acid chloride was then reacted with the deuterated amine (195 mg, 0.8 mmol, 1 equiv) and Et3N (0.22 mL, 1.6 mmol, 2 equiv) in dichloromethane. After evaporation and purification, 4.48-d6 was obtained as a white solid (302 mg, 0.66 mmol, 83 %).

**1H NMR (400 MHz, Chloroform-d)** δ = 7.87 (d, J = 15.5 Hz, 1H), 7.59 – 7.54 (m, 2H), 7.30 – 7.27 (m, 1H), 7.21 (d, J = 15.4 Hz, 1H), 7.17 – 7.11 (m, 1H), 6.10 (s, 2H), 4.59 (s, 2H), 4.12 – 4.03 (m, 1H), 3.80 (s, 3H), 3.77 (s, 6H).

**13C NMR (101 MHz, Chloroform-d)** δ = 166.8, 161.1, 159.7, 138.0, 136.6, 133.4, 129.9, 127.6, 127.5, 124.9, 106.4, 90.6, 55.5, 55.4, 39.7.
The deuterated cinnamic acid derivative (251 mg, 1.1 mmol, 1 equiv) was reacted with oxalyl chloride (0.15 mL, 1.65 mmol, 1.5 equiv) with DMF (1 drop) in dichloromethane. The acid chloride was then reacted with \textbf{2.40r} (261 mg, 1.1 mmol, 1 equiv) and Et\textsubscript{3}N (0.31 mL, 2.2 mmol, 2 equiv) in dichloromethane. After evaporation and purification, \textbf{4.48-d} was obtained as a white solid (451 mg, 1.0 mmol, 91\%).

**1H NMR (400 MHz, Chloroform-d) \( \delta = 7.91 – 7.83 \) (m, 1H), 7.59 – 7.54 (m, 2H), 7.30 – 7.25 (m, 1H), 7.17 – 7.10 (m, 1H), 6.10 (s, 2H), 4.58 (s, 2H), 4.08 (sept, \( J = 6.9 \) Hz, 1H), 3.80 (s, 3H), 3.77 (s, 6H), 1.16 (d, \( J = 6.9 \) Hz, 6H).

**13C NMR (101 MHz, Chloroform-d) \( \delta = 166.7, 161.1, 159.7, 138.0, 136.5, 133.4, 129.9, 127.6, 127.5, 124.9, 106.4, 90.5, 55.5, 55.4, 49.1, 39.6, 19.9).**

\textbf{(E)-3-\((2\text{-chlorophenyl})-N\text{-isopropyl-N-(2,4,6\text{-trimethoxybenzyl})acrylamide 4.49r'}:}

![Chemical Structure]

\textit{Chemical Formula: C\textsubscript{22}H\textsubscript{26}ClNO\textsubscript{4}  
Exact Mass: 403.1550}

Following the general procedure for amide synthesis, 2-chlorocinnamic acid (139 mg, 0.76 mmol, 1 equiv) was reacted with oxalyl chloride (0.1 mL, 1.14 mmol, 1.5 equiv) with DMF (1 drop) in dichloromethane. The acid chloride was then reacted with \textbf{2.40r} (182 mg, 0.76 mmol, 1 equiv) and Et\textsubscript{3}N (0.21 mL, 1.52 mmol, 2 equiv) in dichloromethane. After evaporation and purification, \textbf{4.49r'} was obtained as a white solid (210 mg, 0.52 mmol, 68\%).

**1H NMR (400 MHz, Chloroform-d) \( \delta = 7.93 \) (d, \( J = 15.6 \) Hz, 1H), 7.61 – 7.56 (m, 1H), 7.41 – 7.37 (m, 1H), 7.30 – 7.20 (m, 3H), 6.10 (s, 2H), 4.59 (s, 2H), 4.08 (sept, \( J = 6.9 \) Hz, 1H), 3.80 (s, 3H), 3.77 (s, 6H), 1.17 (d, \( J = 6.9 \) Hz, 6H).

**13C NMR (101 MHz, CDCl\textsubscript{3}) \( \delta = 166.8, 161.1, 159.7, 135.6, 134.8, 134.5, 130.1, 129.7, 127.5, 126.9, 124.8, 106.4, 90.5, 55.5, 55.4, 49.1, 39.7, 19.9).**

**HRMS (ESI):** Calculated for C\textsubscript{22}H\textsubscript{26}ClNaNO\textsubscript{4} ([M+Na\textsuperscript{+}]): 426.1448; found: 426.1451

**IR (neat):** \( \nu = 2362, 1592, 1463 \text{ cm}^{-1} \)

**m.p.:** 67 - 69°C
(E)-3-(2-bromophenyl)-N-ethyl-N-(2,4,6-trimethoxybenzyl)acrylamide 4.61r:

Chemical Formula: C_{21}H_{26}BrNO_4
Exact Mass: 433.0889

Following the general procedure for amide synthesis, 2-bromocinnamic acid (300 mg, 1.32 mmol, 1 equiv) was reacted with oxalyl chloride (0.17 mL, 1.98 mmol, 1.5 equiv) with DMF (1 drop) in dichloromethane. The acid chloride was then reacted with 2.53a (297 mg, 1.32 mmol, 1 equiv) and Et_3N (0.37 mL, 2.64 mmol, 2 equiv) in dichloromethane. After evaporation and purification, 4.61r was obtained as a yellowish oil (487 mg, 1.12 mmol, 85%).

^1H NMR (400 MHz, Chloroform-d) δ = 8.04 – 7.90 (m, 1H), 7.66 – 7.54 (m, 2H), 7.36 – 7.28 (m, 1.8H), 7.20 – 7.14 (m, 1H), 6.80 (d, J = 15.4 Hz, 0.2H), 6.15 – 6.09 (m, 2H), 4.78 (s, 0.4H), 4.61 (s, 1.6H), 3.83 – 3.76 (m, 9H), 3.38 (q, J = 7.0 Hz, 1.6H), 3.27 (q, J = 7.0 Hz, 0.4H), 1.07 (t, J = 6.9 Hz, 3H).

^13C NMR (101 MHz, Chloroform-d) δ = 165.8, 161.2, 159.8, 138.8, 136.4, 133.3, 129.9, 127.5, 127.4, 124.9, 123.3, 105.5, 90.3, 55.3, 39.6, 12.6.

HRMS (ESI): Calculated for C_{21}H_{25}BrNO_4 ([M+H]^+): 434.0967; found: 434.0961

IR (neat) : ν = 1597, 1468 cm^{-1}

(E)-3-(2-bromophenyl)-N-(tert-butyl)-N-(2,4,6 trimethoxybenzyl)acrylamide 4.62r:

Chemical Formula: C_{23}H_{28}BrNO_4
Exact Mass: 461.1202

Following the general procedure for amide synthesis, 2-bromocinnamic acid (1 g, 4.4 mmol, 1 equiv) was reacted with oxalyl chloride (0.62 mL, 6.6 mmol, 1.5 equiv) with DMF (1 drop) in dichloromethane. The acid chloride was then reacted with 2.55a (1.11 g, 4.4 mmol, 1 equiv) and Et_3N (1.24 mL, 8.8 mmol, 2 equiv) in dichloromethane. After evaporation and purification, 4.62r was obtained as a colorless oil (1.45 g, 3.13 mmol, 72%).
\textbf{H NMR (400 MHz, Chloroform-d)} $\delta = 7.73$ (d, $J = 15.5$ Hz, 1H), 7.57 – 7.53 (m, 1H), 7.52 – 7.48 (m, 1H), 7.26 – 7.22 (m, 1H), 7.14 – 7.09 (m, 1H), 6.08 (s, 2H), 4.70 (s, 2H), 3.79 (s, 3H), 3.76 (s, 6H), 1.37 (s, 9H).

\textbf{C NMR (101 MHz, Chloroform-d)} $\delta = 169.3, 160.7, 159.3, 136.6, 136.6, 133.2, 129.8, 128.0, 127.6, 127.5, 124.7, 107.5, 90.6, 57.5, 55.4, 55.4, 40.5, 28.5.$

\textbf{HRMS (ESI):} Calculated for C$_{23}$H$_{28}$BrN$\text{NaN}_4$ ([M+Na$^+$]): 484.1099; found: 484.1094

\textbf{IR (neat):} $\nu = 1605, 1465, 1402, 1128$ cm$^{-1}$

\textbf{(E)-3-(2-bromophenyl)-N-cyclopropyl-N-(2,4,6-trimethoxybenzyl)acrylamide 4.63r:}

In a 250 mL round bottom flask equipped with stirring bar, cyclopropanamine (0.22 mL, 3.16 mmol, 1.2 equiv), 2,4,6-trimethoxybenzaldehyde (496 mg, 2.53 mmol, 1 equiv) and AcOH (0.29 mL, 5.06 mmol, 2 equiv) were stirred for 2 h in 1,2-dichloroethane (50 mL) at room temperature. Then, NaBH(OAc)$_3$ (1.07 g, 5.06 mmol, 2 equiv) was added to the mixture which was stirred overnight. The crude was quenched with NaOH (2 M, 50 mL) and the crude was extracted with DCM (3 x 50 mL). The combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum. The intermediate amine (592 mg, 2.50 mmol, 99 %) was obtained as a clear oil and directly used for next step.

Following the general procedure for amide synthesis, 2-bromocinnamic acid (143 mg, 0.632 mmol, 1 equiv) was reacted with oxalyl chloride (0.09 mL, 0.948 mmol, 1.5 equiv) with DMF (1 drop) in dichloromethane. The acid chloride was then reacted with N-protected cyclopropanamine intermediate (150 mg, 0.632 mmol, 1 equiv) and Et$_3$N (0.180 mL, 1.26 mmol, 2 equiv) in dichloromethane. After evaporation and purification, 4.63r was obtained as a yellowish oil (236 mg, 0.529 mmol, 84 %).

\textbf{H NMR (400 MHz, Chloroform-d)} $\delta = 7.96$ (d, $J = 15.5$ Hz, 1H), 7.63 – 7.53 (m, 2H), 7.31 – 7.26 (m, 1H), 7.18 – 7.10 (m, 2H), 6.11 (s, 2H), 4.72 (s, 2H), 3.80 (s, 3H), 3.78 (s, 6H), 2.35 – 2.25 (m, 1H), 0.81 – 0.64 (m, 4H).

\textbf{C NMR (101 MHz, Chloroform-d)} $\delta = 167.7, 160.8, 160.0, 139.2, 136.2, 133.4, 130.2, 127.8, 127.5, 125.0, 123.7, 105.9, 90.3, 55.8, 55.4, 38.4, 28.0, 9.2.$
HRMS (ESI): Calculated for C_{22}H_{25}BrNO_4 ([M+H]^+): 446.0967; found: 446.0961

IR (neat) : ν = 2361, 1646, 1132 cm\(^{-1}\)

(E)-3-(2-bromophenyl)-N-isopropyl-N-phenylacrylamide 4.64r:

Following the general procedure for amide synthesis, 2-bromocinnamic acid (143 mg, 0.63 mmol, 1 equiv) was reacted with oxalyl chloride (0.1 mL, 0.95 mmol, 1.5 equiv) with DMF (1 drop) in dichloromethane. The acid chloride was then reacted with N-isopropylaniline (86 mg, 0.63 mmol, 1 equiv) and Et\(_3\)N (0.18 mL, 1.26 mmol, 2 equiv) in dichloromethane. After evaporation and purification, 4.64r was obtained as a white solid (151 mg, 0.44 mmol, 69 %).

\(^1\)H NMR (400 MHz, Chloroform-d) \(\delta = 7.97\) (d, \(J = 15.4\) Hz, 1H), 7.55 – 7.50 (m, 1H), 7.48 – 7.39 (m, 3H), 7.18 – 7.04 (m, 5H), 6.04 (d, \(J = 15.4\) Hz, 1H), 5.12 (sept, \(J = 6.8\) Hz, 1H), 1.13 (d, \(J = 6.8\) Hz, 6H).

\(^{13}\)C NMR (101 MHz, Chloroform-d) \(\delta = 165.0, 140.0, 138.4, 135.6, 133.3, 130.7, 130.3, 129.4, 128.5, 127.8, 127.4, 125.1, 122.9, 46.7, 21.1\).

HRMS (ESI): Calculated for C_{18}H_{18}BrNaNO ([M+Na]^+): 366.0469; found: 366.0464

IR (neat) : ν = 2363, 1650 cm\(^{-1}\)

m.p.: 80 - 82°C

(E)-3-(2-bromophenyl)-1-(2-methyl-3,4-dihydroquinolin-1(2H)-yl)prop-2-en-1-one 4.65r:

Following the general procedure for amide synthesis, 2-bromocinnamic acid (568 mg, 2.5 mmol, 1 equiv) was reacted with oxalyl chloride (0.35 mL, 3.75 mmol, 1.5 equiv) with DMF (1 drop) in dichloromethane.
The acid chloride was then reacted with 2-methyl-1,2,3,4-tetrahydroquinoline (368 mg, 2.5 mmol, 1 equiv) and Et₃N (0.69 mL, 5 mmol, 2 equiv) in dichloromethane. After evaporation and purification, \textit{4.65r} was obtained as a white solid (720 mg, 2.02 mmol, 81\%).

\textbf{\textit{1}H NMR (400 MHz, Chloroform-d)} \(\delta = 8.06\) (d, \(J = 15.5\) Hz, 1H), 7.60 – 7.56 (m, 1H), 7.38 – 7.34 (m, 1H), 7.24 – 7.07 (m, 6H), 6.66 (d, \(J = 15.5\) Hz, 1H), 4.95 – 4.86 (m, 1H), 2.68 (dt, \(J = 14.9, 5.1\) Hz, 1H), 2.63 – 2.54 (m, 1H), 2.45 – 2.36 (m, 1H), 1.48 – 1.38 (m, 1H), 1.22 (d, \(J = 6.4\) Hz, 3H).

\textbf{\textit{13}C NMR (101 MHz, Chloroform-d)} \(\delta = 165.1, 140.2, 137.2, 135.7, 133.5, 130.5, 127.8, 127.8, 127.6, 126.5, 126.4, 125.9, 125.2, 123.3, 49.2, 32.7, 26.2, 20.4\).


\textbf{IR (neat):} \(\nu = 2361, 1650\) cm\(^{-1}\)

\textbf{m.p.:} 97 - 99°C

\textbf{(E)-3-(2-bromophenyl)-N,N-diisopropylacrylamide 4.66r:}

\textit{Chemical Formula: C}_{15}\textit{H}_{20}\textit{BrNO}

\textit{Exact Mass: 309.0728}

Following the general procedure for amide synthesis, 2-bromocinnamic acid (1.5 g, 6.61 mmol, 1 equiv) was reacted with oxalyl chloride (0.94 mL, 9.92 mmol, 1.5 equiv) with DMF (1 drop) in dichloromethane. The acid chloride was then reacted with diisopropylamine (0.94 mL, 6.61 mmol, 1 equiv) and Et₃N (1.9 mL, 13.2 mmol, 2 equiv) in dichloromethane. After evaporation and purification, \textit{4.66r} was obtained as a colorless oil (1.76 g, 5.68 mmol, 86\%).

\textbf{\textit{1}H NMR (400 MHz, Chloroform-d)} \(\delta = 7.83\) (d, \(J = 15.5\) Hz, 1H), 7.61 – 7.53 (m, 2H), 7.33 – 7.27 (m, 1H), 7.20 – 7.15 (m, 1H), 6.76 (d, \(J = 15.5\) Hz, 1H), 4.10 (br s, 1H), 3.83 (br s, 1H), 1.47 – 1.23 (m, 12H).

\textbf{\textit{13}C NMR (101 MHz, Chloroform-d)} \(\delta = 165.9, 139.0, 136.1, 133.5, 130.3, 127.7, 127.6, 125.0, 124.2\).

\textbf{HRMS (ESI):} Calculated for \textit{C}_{15}\textit{H}_{20}\textit{BrNaNO} ([M+Na]⁺): 332.0626; found: 332.0621

\textbf{IR (neat):} \(\nu = 2362, 1598\) cm\(^{-1}\)
(E)-3-(2-bromophenyl)-N,N-diethylacrylamide 4.67r:

Chemical Formula: C_{13}H_{16}BrNO
Exact Mass: 281.0415

Following the general procedure for amide synthesis, 2-bromocinnamic acid (232 mg, 1.02 mmol, 1 equiv) was reacted with oxalyl chloride (0.15 mL, 1.53 mmol, 1.5 equiv) with DMF (1 drop) in dichloromethane. The acid chloride was then reacted with diethylamine (0.1 mL, 1.02 mmol, 1 equiv) and Et₃N (0.29 mL, 2.04 mmol, 2 equiv) in dichloromethane. After evaporation and purification, 4.67r was obtained as a yellowish oil (187 mg, 0.663 mmol, 65%).

$^{1}H$ NMR (400 MHz, Chloroform-d) $\delta =$ 7.99 (d, $J = 15.4$ Hz, 1H), 7.61 – 7.58 (m, 1H), 7.58 – 7.54 (m, 1H), 7.33 – 7.27 (m, 1H), 7.22 – 7.15 (m, 1H), 6.76 (d, $J = 15.4$ Hz, 1H), 3.56 – 3.40 (m, 4H), 1.29 – 1.16 (m, 6H).

$^{13}$C NMR (101 MHz, Chloroform-d) $\delta =$ 165.4, 140.8, 135.9, 133.5, 130.5, 127.9, 127.6, 125.1, 121.3, 42.5, 41.2, 15.2, 13.3.

HRMS (ESI): Calculated for C_{13}H_{16}BrNO ([M+H]^+): 282.0494; found: 282.0488

IR (neat) : $\nu =$ 2363, 1649 cm$^{-1}$

(E)-3-(2-bromophenyl)-N-isopropyl-N-(3-phenylpropyl)acrylamide 4.68r:

Chemical Formula: C_{21}H_{24}BrNO
Exact Mass: 385.1041

In a 250 mL round bottom flask equipped with stirring bar, hydrocinnamaldehyde (0.72 mL, 5.43 mmol, 1 equiv), isopropylamine (0.93 mL, 10.9 mmol, 2 equiv) and AcOH (0.62 mL, 10.9 mmol, 2 equiv) were stirred for 2 h in 1,2-dichloroethane (30 mL) at room temperature. Then, NaBH(OAc)$_3$ (2.3 g, 10.9 mmol, 2 equiv) was added to the mixture which was stirred overnight. The crude was quenched with NaOH (2 M, 30 mL) and the crude was extracted with DCM (3 x 30 mL). The combined organic layers were dried over sodium sulfate, filtered and evaporated
under vacuum. The intermediate amine (956 mg, 10.8 mmol, 99%) was obtained as a clear oil and directly used for next step.

Following the general procedure for amide synthesis, 2-bromocinnamic acid (136 mg, 0.6 mmol, 1 equiv) was reacted with oxalyl chloride (0.08 mL, 0.9 mmol, 1.5 equiv) with DMF (1 drop) in dichloromethane. The acid chloride was then reacted with the intermediate amine (106 mg, 0.6 mmol, 1 equiv) and Et$_3$N (0.17 mL, 1.2 mmol, 2 equiv) in dichloromethane. After evaporation and purification, 4.68r was obtained as a colorless oil (187 mg, 0.484 mmol, 81%).

$^1$H NMR (500 MHz, Chloroform-$d$) $\delta$ = 8.00 – 7.88 (m, 1H), 7.61 – 7.55 (m, 1H), 7.31 – 7.26 (m, 3H), 7.25 – 7.15 (m, 5H), 6.84 – 6.78 (m, 0.4H), 6.50 – 6.44 (m, 0.6H), 4.86 – 4.75 (m, 0.6H), 4.31 – 4.22 (m, 0.4H), 3.36 – 3.22 (m, 2H), 2.68 (t, J = 7.2 Hz, 2H), 2.04 – 1.95 (m, 2H), 1.23 – 1.15 (m, 6H).

$^{13}$C NMR (126 MHz, Chloroform-$d$) $\delta$ = 166.2, 165.6, 141.8, 140.9, 140.8, 140.1, 135.7, 133.5, 130.4, 128.8, 128.6, 127.9, 127.8, 127.6, 126.4, 126.0, 125.2, 122.1, 121.7, 49.0, 45.9, 42.4, 41.4, 33.9, 33.4, 33.3, 31.1, 21.7, 20.7.

HRMS (ESI): Calculated for C$_{21}$H$_{24}$BrNaNO ([M+Na]$^+$): 408.0939; found: 408.0933

IR (neat) : $\nu$ = 2363, 1647, 1420 cm$^{-1}$

(E)-3-(2-bromophenyl)-N-(cyclopentylmethyl)-N-isopropylacrylamide 4.69r:

Following the general procedure for amide synthesis, 2-bromocinnamic acid (82 mg, 0.363 mmol, 1 equiv) was reacted with oxalyl chloride (0.047 mL, 0.543 mmol, 1.5 equiv) with DMF (1 drop) in dichloromethane. The acid chloride was then reacted with $\text{S}_4$ (51 mg, 0.363 mmol, 1 equiv) and Et$_3$N (0.1 mL, 0.72 mmol, 2 equiv) in dichloromethane. After evaporation and purification, 4.69r was obtained as a colorless oil (74 mg, 0.211 mmol, 58%).

$^1$H NMR (500 MHz, Chloroform-$d$) $\delta$ = 7.99 – 7.86 (m, 1H), 7.63 – 7.49 (m, 2H), 7.33 – 7.28 (m, 1H), 7.20 – 7.14 (m, 1H), 6.88 – 6.77 (m, 1H), 4.44 – 4.20 (m, 1H), 3.35 – 3.28 (m, 2H), 2.33 – 2.11 (m, 1H), 1.84 – 1.71 (m, 2H), 1.68 – 1.63 (m, 2H), 1.60 – 1.53 (m, 2H), 1.31 – 1.21 (m, 8H).

$^{13}$C NMR (126 MHz, Chloroform-$d$) $\delta$ = 180.4, 166.1, 145.1, 140.1, 139.8, 135.9, 133.4, 130.2, 127.7, 127.5, 124.9, 122.7, 49.8, 49.1, 48.9, 46.1, 43.5, 41.7, 40.1, 35.6, 31.0, 30.8, 30.0, 27.0, 25.8, 24.9, 23.7, 21.9, 20.5.
HRMS (ESI): Calculated for C₁₈H₂₄BrNaNO ([M+Na]⁺): 372.0939; found: 372.0931

IR (neat) : v = 2361, 1648, 1423 cm⁻¹

(E)-3-(2-bromophenyl)-N-isopropyl-N-(3-methoxypropyl)acrylamide 4.70r:

\[ \text{H₂N} \xrightarrow[\text{Chemical Formula: C₁₈H₂₂BrNO₂}]{} \xrightarrow[\text{Exact Mass: 339.0834}]{} \text{O} \]

In a 250 mL round bottom flask equipped with stirring bar, 3-methylxoypropylamine (0.92 mL, 9.05 mmol, 1 equiv), acetone (2.7 mL, 36.2 mmol, 4 equiv) and AcOH (1.0 mL, 18.1 mmol, 2 equiv) were stirred for 2 h in 1,2-dichloroethane (50 mL) at room temperature. Then, NaBH(OAc)₃ (3.8 g, 18.1 mmol, 2 equiv) was added to the mixture which was stirred overnight. The crude was quenched with NaOH (2 M, 50 mL) and the crude was extracted with DCM (3 x 50 mL). The combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum. The intermediate amine (976 mg, 8.33 mmol, 92%) was obtained as a clear oil and directly used for next step.

Following the general procedure for amide synthesis, 2-bromocinnamic acid (227 mg, 1 mmol, 1 equiv) was reacted with oxalyl chloride (0.13 mL, 1 mmol, 1.5 equiv) with DMF (1 drop) in dichloromethane. The acid chloride was then reacted with the intermediate amine (117 mg, 1 mmol, 1 equiv) and Et₃N (0.28 mL, 2 mmol, 2 equiv) in dichloromethane. After evaporation and purification, 4.70r was obtained as a colorless oil (267 mg, 0.82 mmol, 81%).

¹H NMR (400 MHz, Chloroform-d) \( \delta = 8.03 \) (d, \( J = 15.3 \) Hz, 0.6H), 7.91 (d, \( J = 15.4 \) Hz, 0.4H), 7.66 – 7.55 (m, 2H), 7.32 – 7.30 (m, 1H), 7.20 – 7.17 (m, 1H), 6.94 (d, \( J = 15.3 \) Hz, 0.6H), 6.83 (d, \( J = 15.4 \) Hz, 0.4H), 4.85 – 4.75 (m, 0.6H), 4.34 – 4.25 (m, 0.4H), 3.50 – 3.37 (m, 4H), 3.37 – 3.32 (m, 3H), 1.96 – 1.85 (m, 2H), 1.29 – 1.19 (m, 6H).

¹³C NMR (101 MHz, Chloroform-d) \( \delta = 166.2, 165.9, 140.8, 140.0, 135.9, 133.5, 130.4, 127.9, 127.7, 127.6, 125.2, 125.0, 122.2, 122.1, 71.1, 69.8, 58.9, 58.7, 49.1, 46.0, 40.4, 39.2, 32.3, 29.7, 21.6, 20.6.

HRMS (ESI): Calculated for C₁₆H₂₂BrNaNO₂ ([M+Na]⁺): 362.0732; found: 362.0726

IR (neat) : v = 2361, 1642 cm⁻¹
(E)-3-(2-bromophenyl)-N-(2-cyanoethyl)-N-isopropylacrylamide 4.71r:

\[
\begin{align*}
&\text{HCN} \quad \rightarrow \quad \begin{array}{c}
\text{H} \\
\text{CN}
\end{array} \quad \rightarrow \quad \begin{array}{c}
\text{H} \\
\text{N}
\end{array} \quad \rightarrow \quad \begin{array}{c}
\text{H} \\
\text{N}
\end{array} \\
&\quad \text{Br} \quad \text{CN}
\end{align*}
\]

Chemical Formula: C_{16}H_{17}BrN_{2}O
Exact Mass: 320.0524

In a 25 mL double-neck flask charged with isopropylamine (1.1 mL, 12.6 mmol, 2 equiv) in EtOH (6 mL) and cooled to 0°C was added via dropping funnel, a solution of acrylonitrile (0.41 mL, 6.32 mmol, 1 equiv) in EtOH (6 mL). The reaction was allowed to reach room temperature, and the volatiles were removed under vacuum. The desired amine was pure enough to react in next step (454 mg, 4.04 mmol, 64%).

Following the general procedure for amide synthesis, 2-bromocinnamic acid (143 mg, 0.63 mmol, 1 equiv) was reacted with oxalyl chloride (0.1 mL, 0.95 mmol, 1.5 equiv) with DMF (1 drop) in dichloromethane. The acid chloride was then reacted with the intermediate amine (70 mg, 0.63 mmol, 1 equiv) and Et$_3$N (0.18 mL, 1.26 mmol, 2 equiv) in dichloromethane. After evaporation and purification, 4.71r was obtained as a yellowish oil (134 mg, 0.42 mmol, 66%).

$^1$H NMR (400 MHz, Chloroform-d) $\delta$ = 7.95 (d, J = 15.2 Hz, 1H), 7.63 – 7.55 (m, 2H), 7.35 – 7.30 (m, 1H), 7.24 – 7.18 (m, 1H), 6.80 (d, J = 15.3 Hz, 1H), 4.37 – 4.27 (m, 1H), 3.57 (t, J = 7.0 Hz, 2H), 2.82 (t, J = 7.0 Hz, 2H), 1.30 (d, J = 6.7 Hz, 6H).

$^{13}$C NMR (101 MHz, Chloroform-d) $\delta$ = 167.0, 141.5, 135.4, 133.6, 130.9, 127.8, 127.7, 125.2, 120.8, 118.5, 49.1, 37.8, 21.7, 17.2.

HRMS (ESI): Calculated for C$_{15}$H$_{17}$BrNa$_{2}$O$_{4}$ ([M+Na]$^+$): 343.0422; found: 343.0416

IR (neat) : $\nu$ = 2363, 1646, 1418 cm$^{-1}$

(E)-3-(2-bromophenyl)-N-isopropyl-N-(3 (phenylsulfonyl)propyl)acrylamide 4.72r:

\[
\begin{align*}
&\text{SO}_2\text{Ph} \quad \rightarrow \quad \begin{array}{c}
\text{H} \\
\text{SO}_2\text{Ph}
\end{array} \quad \rightarrow \quad \begin{array}{c}
\text{H} \\
\text{SO}_2\text{Ph}
\end{array} \\
&\quad \text{Br} \quad \text{SO}_2\text{Ph}
\end{align*}
\]

Chemical Formula: C$_{21}$H$_{24}$BrNO$_3$S
Exact Mass: 449.0660
In a 25 mL double-neck flask charged with isopropylamine (1.1 mL, 12.6 mmol, 2 equiv) in EtOH (6 mL) and cooled to 0°C was added via dropping funnel, a solution of phenyl vinyl sulfone (1.06 g, 6.32 mmol, 1 equiv) in EtOH (6 mL). The reaction was allowed to reach room temperature, and the volatiles were removed under vacuum. The desired amine was pure enough to react in next step (1.4 g, 6.31 mmol, 99%).

Following the general procedure for amide synthesis, 2-bromocinnamic acid (143 mg, 0.63 mmol, 1 equiv) was reacted with oxalyl chloride (0.1 mL, 0.95 mmol, 1.5 equiv) with DMF (1 drop) in dichloromethane. The acid chloride was then reacted with the intermediate amine (144 mg, 0.63 mmol, 1 equiv) and Et$_3$N (0.18 mL, 1.26 mmol, 2 equiv) in dichloromethane. After evaporation and purification, 4.72r was obtained as a colorless oil (202 mg, 0.46 mmol, 73%).

**1H NMR (400 MHz, Chloroform-d)**: $\delta = 8.00 - 7.82$ (m, 3H), 7.70 – 7.64 (m, 1H), 7.63 – 7.43 (m, 4H), 7.31 – 7.27 (m, 1H), 7.22 – 7.12 (m, 1H), 6.78 – 6.57 (m, 1H), 4.91 – 4.66 (m, 0.3H), 4.33 – 4.21 (m, 0.7H), 3.81 – 3.71 (m, 0.7H), 3.68 – 3.43 (m, 3H), 3.40 – 3.26 (m, 0.4H), J = 6.5 Hz, 5H), 1.25 (d, 1.17 – 1.06 (m, 1H).

**13C NMR (101 MHz, CDCl3)**: $\delta = 166.5$, 141.3, 139.1, 135.4, 134.0, 133.5, 130.8, 129.5, 128.0, 127.8, 127.7, 125.1, 120.6, 54.5, 49.3, 35.6, 29.8, 21.4, 20.4.

HRMS (ESI): Calculated for C$_{21}$H$_{24}$BrNaNO$_3$ ([M+Na]$^+$): 458.0401; found: 458.0396

IR (neat): $\nu = 2362$, 904 cm$^{-1}$

**ethyl (E)-3-(3-(2-bromophenyl)-N-isopropylacrylamido)propanoate 4.73r:**

$$
\text{CO}_2\text{Et} \quad \text{N} \quad \text{CO}_2\text{Et} \quad \text{Br} \quad \text{N} \quad \text{OEt} \\
\text{Chemical Formula: C}_{17}\text{H}_{22}\text{BrNO}_3 \\
\text{Exact Mass: 367.0783}
$$

In a 25 mL double-neck flask charged with isopropylamine (1.1 mL, 12.6 mmol, 2 equiv) in EtOH (6 mL) and cooled to 0°C was added via dropping funnel, a solution of ethyl acrylate (633 mg, 6.32 mmol, 1 equiv) in EtOH (6 mL). The reaction was allowed to reach room temperature, and the volatiles were removed under vacuum. The desired amine was pure enough to react in next step (876 mg, 5.5 mmol, 87%).
Following the general procedure for amide synthesis, 2-bromocinnamic acid (143 mg, 0.63 mmol, 1 equiv) was reacted with oxalyl chloride (0.1 mL, 0.95 mmol, 1.5 equiv) with DMF (1 drop) in dichloromethane. The acid chloride was then reacted with the intermediate amine (101 mg, 0.63 mmol, 1 equiv) and Et$_3$N (0.18 mL, 1.26 mmol, 2 equiv) in dichloromethane. After evaporation and purification, **4.73r** was obtained as a yellowish oil (152 mg, 0.41 mmol, 65 %).

$^1$H NMR (400 MHz, Chloroform-d) $\delta = 8.07 – 7.85$ (m, 1H), 7.61 – 7.53 (m, 2H), 7.33 – 7.27 (m, 1H), 7.22 – 7.14 (m, 1H), 6.80 (d, $J = 15.4$ Hz, 1H), 4.88 – 4.74 (m, 0.4H), 4.33 – 4.23 (m, 0.6H), 4.15 (q, $J = 7.2$ Hz, 2H), 3.70 – 3.55 (m, 2H), 2.75 – 2.58 (m, 2H), 1.31 – 1.13 (m, 10H).

$^{13}$C NMR (101 MHz, Chloroform-d) $\delta =$ 172.2, 171.2, 166.3, 165.7, 141.7, 140.5, 135.7, 133.5, 130.6, 127.8, 127.7, 125.0, 121.6, 121.3, 61.1, 60.6, 49.1, 46.0, 38.7, 37.3, 36.8, 34.1, 21.5, 20.5, 14.3.

HRMS (ESI): Calculated for C$_{17}$H$_{22}$BrNaNO$_3$ ([M+Na$^+$]): 390.0681; found: 390.0677

IR (neat) : $\nu =$ 2362, 1624, 1423 cm$^{-1}$

(E)-3-(2-bromo-5-fluorophenyl)-N-isopropyl-N-(2,4,6-trimethoxybenzyl)acrylamide

$\textbf{4.74r}$:

Chemical Formula: C$_{22}$H$_{26}$BrFNO$_4$

Exact Mass: 465.0951

Following the general procedure for amide synthesis, 2-Bromo-5-fluorocinnamic acid (186 mg, 0.76 mmol, 1 equiv) was reacted with oxalyl chloride (0.1 mL, 1.14 mmol, 1.5 equiv) with DMF (1 drop) in dichloromethane. The acid chloride was then reacted with S$_a$ (182 mg, 0.76 mmol, 1 equiv) and Et$_3$N (0.22 mL, 1.52 mmol, 2 equiv) in dichloromethane. After evaporation and purification, **4.74r** was obtained as a white solid (302 mg, 0.65 mmol, 85 %).

$^1$H NMR (400 MHz, Chloroform-d) $\delta =$ 7.80 (d, $J = 15.4$ Hz, 1H), 7.56 – 7.50 (m, 1H), 7.27 – 7.23 (m, 1H), 7.18 (d, $J = 15.4$ Hz, 1H), 6.92 – 6.87 (m, 1H), 6.11 (s, 2H), 4.57 (s, 2H), 4.15 – 4.07 (m, 1H), 3.81 (s, 3H), 3.78 (s, 6H), 1.18 (d, $J = 6.9$ Hz, 6H).

$^{13}$C NMR (101 MHz, Chloroform-d) $\delta =$ 166.2, 163.1, 161.1, 160.7, 159.5, 137.0, 134.4 (d, $J = 9.3$ Hz), 125.9, 118.9 (d, $J = 3.9$ Hz), 117.0 (d, $J = 22.1$ Hz), 114.1 (d, $J = 21.4$ Hz), 106.2, 90.5, 55.4, 55.3, 49.3, 39.6, 19.8.

$^{19}$F NMR (376 MHz, Chloroform-d) $\delta =$ -114.9.
HRMS (ESI): Calculated for C$_{22}$H$_{26}$BrFNO$_4$ ([M+H]$^+$): 466.1029; found: 466.1026

IR (neat) : $\nu = 2360, 1597, 1464$ cm$^{-1}$

m.p.: 92 - 94°C

(E)-3-(2-bromo-5-(trifluoromethyl)phenyl)-N-isopropyl-N-(2,4,6-trimethoxybenzyl)acrylamide 4.75r:

Following the general procedure for Knoevenagel condensation, 2-bromo-5-(trifluoromethyl)benzaldehyde (500 mg, 1.98 mmol, 1 equiv) was reacted with malonic acid (227 mg, 2.18 mmol, 1.1 equiv), piperidine (0.22 mL, 2.18 mmol, 1.1 equiv) in pyridine at 90 °C for 15h. After evaporation and purification, the intermediate carboxylic acid (584 mg, 1.98 mmol, 1 equiv) was reacted with oxalyl chloride (0.28 mL, 2.97 mmol, 1.5 equiv) with DMF (1 drop) in dichloromethane. The acid chloride was then reacted with S$_8$ (474 mg, 1.98 mmol, 1 equiv) and Et$_3$N (0.55 mL, 3.96 mmol, 2 equiv) in dichloromethane. After evaporation and purification, 4.75r was obtained as a colorless oil (896 mg, 1.73 mmol, 88%).

$^1$H NMR (400 MHz, Chloroform-d) $\delta = 7.88$ – 7.82 (m, 1H), 7.76 – 7.74 (m, 1H), 7.74 – 7.70 (m, 1H), 7.41 – 7.37 (m, 1H), 7.27 – 7.20 (m, 1H), 6.11 (s, 2H), 4.58 (s, 2H), 4.15 (sept, $J = 6.9$ Hz, 1H), 3.81 (s, 3H), 3.79 (s, 6H), 1.21 (d, $J = 6.9$ Hz, 6H).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta = 166.1, 161.3, 159.7, 137.6, 136.7, 134.0, 130.1$ (q, $J = 32.6$ Hz), 128.5, 126.6, 126.1, 124.3 (q, $J = 2.9$ Hz), 123.9 (q, $J = 271.9$ Hz), 106.4, 90.6, 55.5, 55.4, 49.4, 39.7, 19.9.

$^{19}$F NMR (471 MHz, CDCl$_3$) $\delta = -62.7$.

HRMS (ESI): Calculated for C$_{23}$H$_{25}$BrF$_3$NO$_4$ ([M+Na]$^+$): 538.0817; found: 538.0812

IR (neat) : $\nu = 2362, 1648$ cm$^{-1}$
(E)-3-(2-bromo-5-methoxyphenyl)-N-isopropyl-N-(2,4,6-trimethoxybenzyl)acrylamide

4.76r:

Following the general procedure for Knoevenagel condensation, 2-bromo-5-methoxybenzaldehyde (2 g, 9.02 mmol, 1 equiv) was reacted with malonic acid (1.03 g, 9.92 mmol, 1.1 equiv), piperidine (0.98 mL, 9.92 mmol, 1.1 equiv) in pyridine at 90 °C for 15h. After evaporation and purification, the intermediate carboxylic acid (195 mg, 0.76 mmol, 1 equiv) was reacted with oxalyl chloride (0.1 mL, 1.14 mmol, 1.5 equiv) with DMF (1 drop) in dichloromethane. The acid chloride was then reacted with S₅ (182 mg, 0.76 mmol, 1 equiv) and Et₃N (0.214 mL, 1.52 mmol, 2 equiv) in dichloromethane. After evaporation and purification, 4.76r was obtained as a white solid (284 mg, 0.594 mmol, 78 %).

¹H NMR (400 MHz, Chloroform-d) δ = 7.82 (d, J = 15.4 Hz, 1H), 7.49 – 7.42 (m, 1H), 7.18 (d, J = 15.4 Hz, 1H), 7.12 – 7.07 (m, 1H), 6.76 – 7.70 (m, 1H), 6.10 (s, 2H), 4.58 (s, 2H), 4.09 (sept, J = 6.9 Hz, 1H), 3.80 (s, 3H), 3.80 (s, 6H), 3.77 (s, 6H), 1.16 (d, J = 6.8 Hz, 6H).

¹³C NMR (101 MHz, CDCl₃) δ = 166.7, 161.2, 159.7, 159.0, 138.1, 137.3, 133.9, 125.1, 115.7, 115.6, 113.2, 106.4, 90.5, 55.6, 55.6, 55.4, 49.1, 39.7, 19.9.

HRMS (ESI): Calculated for C₂₃H₂₈BrNaNO₅ ([M+Na]+): 500.1049; found: 500.1043

IR (neat) : ν = 2364 cm⁻¹

m.p.: 104 - 106°C
(E)-3-(5-(benzyloxy)-2-bromophenyl)-N-isopropyl-N-(2,4,6-trimethoxybenzyl)acrylamide 4.77r:

In a 100 mL flask charged with 2-bromo-5-hydroxybenzaldehyde (500 mg, 2.48 mmol, 1 equiv) and K₂CO₃ (1.02 g, 7.44 mmol, 3 equiv) in DMF (10 mL) was added benzyl bromide (0.45 mL, 3.72 mmol, 1.5 equiv). The reaction was stirred to room temperature and monitored by TLC using Cyclohexane/AcOEt as solvent. After completion, the reaction was quenched with water (10 mL) and extracted with AcOEt (3 x 10 mL). The combined organic phases were washed with 10% LiCl solution (3 x 10 mL) and the crude was dried over sodium sulfate, filtered and evaporated under vacuum. The crude was used in next step without further purification (720 mg, 2.48 mmol, 99%).

Following the general procedure for Knoevenagel condensation, 5-(benzyloxy)-2-bromobenzaldehyde (720 mg, 2.48 mmol, 1 equiv) was reacted with malonic acid (284 mg, 2.73 mmol, 1.1 equiv), piperidine (0.25 mL, 2.73 mmol, 1.1 equiv) in pyridine at 90 °C for 15h. After evaporation and purification, the intermediate carboxylic acid (333 mg, 1.0 mmol, 1 equiv) was reacted with oxalyl chloride (0.14 mL, 1.5 mmol, 1.5 equiv) with DMF (1 drop) in dichloromethane. The acid chloride was then reacted with S₈ (239 mg, 1.0 mmol, 1 equiv) and Et₃N (0.28 mL, 2 mmol, 2 equiv) in dichloromethane. After evaporation and purification, 4.77r was obtained as a yellowish solid (387 mg, 0.7 mmol, 70%).

³H NMR (400 MHz, Chloroform-d) δ = 7.85 – 7.79 (m, 1H), 7.48 – 7.45 (m, 1H), 7.42 – 7.29 (m, 5H), 7.18 – 7.11 (m, 2H), 6.82 – 6.78 (m, 1H), 6.11 (s, 2H), 5.05 (s, 2H), 4.58 (s, 2H), 4.16 – 4.07 (m, 1H), 3.79 (s, 3H), 3.76 (s, 6H), 1.17 (d, J = 6.9 Hz, 6H).
\[ ^1\text{H} \text{NMR (400 MHz, Chloroform-}d\text{)} \delta = 7.83 \text{ (d, } J = 15.4 \text{ Hz, } 1\text{H}), 7.11 - 6.99 \text{ (m, } 3\text{H), 6.11 \text{ (s, } 2\text{H), 5.99 \text{ (s, } 2\text{H), 4.57 \text{ (s, } 2\text{H), 4.09 \text{ (sept, } J = 6.8 \text{ Hz, } 1\text{H), 3.81 \text{ (s, } 3\text{H), 3.78 \text{ (s, } 6\text{H), 1.17 \text{ (d, } J = 6.9 \text{ Hz, } 6\text{H).}}\]

\[ ^{13}\text{C NMR (101 MHz, CDCl}_3\text{)} \delta = 166.9, 161.2, 159.7, 149.0, 147.8, 138.0, 129.8, 123.1, 116.8, 113.2, 106.5, 102.1, 90.6, 55.6, 55.4, 49.3, 39.7, 19.9.\]

HRMS (ESI): Calculated for C\(_{23}\)H\(_{26}\)BrNaNO\(_6\) ([M+Na\(^+\)]: 514.0841; found: 514.0836

IR (neat) : \(v = 2362, 1596, 1474 \text{ cm}^{-1}\)

m.p.: 115-117°C

(E)-3-(6-bromo-4-fluorophenyl)-N-isopropyl-N-(2,4,6-trimethoxybenzyl)acrylamide 4.78r:

Following the general procedure for Knoevenagel condensation, 6-Bromopiperonal (2.29 g, 10 mmol, 1 equiv) was reacted with malonic acid (1.15 g, 11 mmol, 1.1 equiv), piperidine (1.1 mL, 11 mmol, 1.1 equiv) in pyridine at 90 °C for 15h. After evaporation and purification, the intermediate carboxylic acid (148 mg, 0.547 mmol, 1 equiv) was reacted with oxalyl chloride (0.07 mL, 0.821 mmol, 1.5 equiv) with DMF (1 drop) in dichloromethane. The acid chloride was then reacted with S\(_a\) (131 mg, 1.547 mmol, 1 equiv) and Et\(_3\)N (0.154 mL, 1.09 mmol, 2 equiv) in dichloromethane. After evaporation and purification, 4.78r was obtained as a yellowish solid (202 mg, 0.41 mmol, 75 %).

\[ ^1\text{H} \text{NMR (400 MHz, Chloroform-}d\text{)} \delta = 7.83 \text{ (d, } J = 15.4 \text{ Hz, } 1\text{H), 7.11 - 6.99 \text{ (m, } 3\text{H), 6.11 \text{ (s, } 2\text{H), 5.99 \text{ (s, } 2\text{H), 4.57 \text{ (s, } 2\text{H), 4.09 \text{ (sept, } J = 6.8 \text{ Hz, } 1\text{H), 3.81 \text{ (s, } 3\text{H), 3.78 \text{ (s, } 6\text{H), 1.17 \text{ (d, } J = 6.9 \text{ Hz, } 6\text{H).}}\]

\[ ^{13}\text{C NMR (101 MHz, CDCl}_3\text{)} \delta = 166.9, 161.2, 159.7, 149.0, 147.8, 138.0, 129.8, 123.1, 116.8, 113.2, 106.5, 102.1, 90.6, 55.6, 55.4, 49.3, 39.7, 19.9.\]

HRMS (ESI): Calculated for C\(_{23}\)H\(_{26}\)BrNaNO\(_6\) ([M+Na\(^+\)]: 514.0841; found: 514.0836

IR (neat) : \(v = 2362, 1596, 1474 \text{ cm}^{-1}\)

m.p.: 115-117°C

(E)-3-(2-bromo-4-fluorophenyl)-N-isopropyl-N-(2,4,6-trimethoxybenzyl)acrylamide 4.79r:
Following the general procedure for Knoevenagel condensation, 2-bromo-4-fluorobenzaldehyde (812 mg, 4 mmol, 1 equiv) was reacted with malonic acid (458 mg, 4.4 mmol, 1.1 equiv), piperidine (0.44 mL, 4.4 mmol, 1.1 equiv) in pyridine at 90 °C for 15h. After evaporation and purification, the intermediate carboxylic acid (155 mg, 0.63 mmol, 1 equiv) was reacted with oxalyl chloride (0.08 mL, 0.95 mmol, 1.5 equiv) with DMF (1 drop) in dichloromethane. The acid chloride was then reacted with S₃ (151 mg, 0.63 mmol, 1 equiv) and Et₃N (0.18 mL, 1.26 mmol, 2 equiv) in dichloromethane. After evaporation and purification, 4.79r was obtained as a yellowish solid (236 mg, 0.506 mmol, 80 %).

^1H NMR (400 MHz, Chloroform-d) δ = 7.82 (d, J = 15.4 Hz, 1H), 7.56 – 7.54 (m, 1H), 7.36 – 7.32 (m, 1H), 7.15 (d, J = 15.4 Hz, 1H), 7.05 – 7.00 (m, 1H), 6.10 (s, 2H), 4.58 (s, 2H), 4.08 (sept, J = 6.9 Hz, 1H), 3.81 (s, 3H), 3.77 (s, 6H), 1.16 (d, J = 6.9 Hz, 6H).

^13C NMR (101 MHz, CDCl₃) δ = 166.6, 162.7 (d, J = 257 Hz), 161.1, 159.7, 137.0, 132.9, 128.6 (d, J = 8.2 Hz), 125.0, 124.9, 124.8, 120.4 (d, J = 24.7 Hz), 114.9 (d, J = 21.2 Hz), 106.4, 55.6, 55.4, 49.2, 39.7, 19.9.

^19F NMR (376 MHz, CDCl₃) δ = -111.1

HRMS (ESI): Calculated for C₂₂H₂₆BrFNO₄ ([M+H]⁺): 466.1029; found: 466.1024

IR (neat) : ν = 2361, 159, 1460 cm⁻¹

m.p.: 95 - 97°C
(E)-3-(2-bromo-4-methylphenyl)-N-isopropyl-N-(2,4,6-trimethoxybenzyl)acrylamide

**4.80r:**

![Chemical structure of 4.80r](image)

Chemical Formula: $\text{C}_{23}\text{H}_{28}\text{BrNO}_4$

Exact Mass: 461.1202

Following the general procedure for Knoevenagel condensation, 2-bromo-4-methylbenzaldehyde (500 mg, 2.51 mmol, 1 equiv) was reacted with malonic acid (287 mg, 2.76 mmol, 1.1 equiv), piperidine (0.27 mL, 2.76 mmol, 1.1 equiv) in pyridine at 90 °C for 15h. After evaporation and purification, the intermediate carboxylic acid (605 mg, 2.51 mmol, 1 equiv) was reacted with oxalyl chloride (0.35 mL, 3.76 mmol, 1.5 equiv) with DMF (1 drop) in dichloromethane. The acid chloride was then reacted with $\text{S}_8$ (601 mg, 2.51 mmol, 1 equiv) and $\text{Et}_3\text{N}$ (0.70 mL, 5.0 mmol, 2 equiv) in dichloromethane. After evaporation and purification, 4.80r was obtained as a white solid (812 mg, 1.75 mmol, 70 %).

$^1\text{H NMR (400 MHz, Chloroform-}$d$)$ $\delta = 7.90 – 7.80$ (m, 1H), $7.49 – 7.45$ (m, 1H), $7.43 – 7.41$ (m, 1H), $7.23 – 7.16$ (m, 1H), $7.11 – 7.07$ (m, 1H), $6.10$ (s, 2H), $4.59$ (s, 2H), $4.08$ (sept, $J = 6.8$ Hz, 1H), $3.81$ (s, 3H), $3.77$ (s, 6H), $2.33$ (s, 3H), $1.16$ (d, $J = 6.9$ Hz, 6H).

$^{13}\text{C NMR (126 MHz, CDCl}_3)$ $\delta = 166.9, 161.1, 159.7, 140.5, 138.0, 133.8, 133.6, 128.5, 127.3, 124.8, 123.9, 106.5, 90.6, 55.6, 55.4, 49.1, 39.7, 21.0, 19.9$.

HRMS (ESI): Calculated for $\text{C}_{23}\text{H}_{29}\text{BrNO}_4$ ([M+H]$^+$): 462.1280; found: 462.1274

IR (neat) : $\nu = 1598, 1458, 1130$ cm$^{-1}$

m.p.: 94 - 96°C

(E)-3-(2-bromophenyl)-1-(2-methylpyrrolidin-1-yl)prop-2-en-1-one 4.81r:

![Chemical structure of 4.81r](image)

Chemical Formula: $\text{C}_{14}\text{H}_{16}\text{BrNO}$

Exact Mass: 293.0415
Following the general procedure for amide synthesis, 2-bromocinnamic acid (330 mg, 1.45 mmol, 1 equiv) was reacted with oxalyl chloride (0.20 mL, 2.18 mmol, 1.5 equiv) with DMF (1 drop) in dichloromethane. The acid chloride was then reacted with 2-methylpyrrolidine (0.14 mL, 1.45 mmol, 1 equiv) and Et$_3$N (0.41 mL, 2.90 mmol, 2 equiv) in dichloromethane. After evaporation and purification, 4.81r was obtained as a yellowish solid (369 mg, 1.25 mmol, 86 %).

$^1$H NMR (400 MHz, Chloroform-d) $\delta =$ 8.06 – 7.95 (m, 1H), 7.62 – 7.52 (m, 2H), 7.32 – 7.26 (m, 1H), 7.19 – 7.12 (m, 1H), 6.72 – 6.61 (m, 1H), 4.39 – 4.14 (m, 1H), 3.74 – 3.51 (m, 2H), 2.13 – 1.87 (m, 3H), 1.76 – 1.59 (m, 1H), 1.28 – 1.23 (m, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta =$ 164.1, 164.0, 140.3, 140.1, 135.9, 135.8, 133.5, 133.5, 130.5, 127.9, 127.9, 127.6, 125.2, 125.1, 122.7, 122.2, 53.4, 53.1, 47.1, 46.1, 33.4, 32.1, 24.1, 22.3, 22.0, 19.7.

HRMS (ESI): Calculated for C$_{14}$H$_{16}$BrNO ([M+Na]$^+$): 316.0313; found: 316.0307

IR (neat) : $\nu =$ 1649, 1603, 1407 cm$^{-1}$

m.p.: 78 - 80°C

**S.E)-3-(2-bromophenyl)-1-(2-methylpyrrolidin-1-yl)prop-2-en-1-one 4.98:**

![Chemical Structure](image)

Chemical Formula: C$_{14}$H$_{16}$BrNO
Exact Mass: 293.0415

Following the general procedure for amide synthesis, 2-bromocinnamic acid (2.65 g, 11.7 mmol, 1 equiv) was reacted with oxalyl chloride (1.66 mL, 17.6 mmol, 1.5 equiv) with DMF (1 drop) in dichloromethane. The acid chloride was then reacted with (S)-2-methylpyrrolidine (1 g, 11.7 mmol, 1 equiv) and Et$_3$N (3.25 mL, 23.4 mmol, 2 equiv) in dichloromethane. After evaporation and purification, 4.98 was obtained as a yellowish oil (3.44 g, 11.7 mmol, 100 %).

$^1$H NMR (400 MHz, Chloroform-d) $\delta =$ 8.04 – 7.95 (m, 1H), 7.61 – 7.50 (m, 2H), 7.33 – 7.27 (m, 1H), 7.21 – 7.13 (m, 1H), 6.73 – 6.62 (m, 1H), 4.38 – 4.15 (m, 1H), 3.73 – 3.54 (m, 2H), 2.15 – 1.90 (m, 3H), 1.77 – 1.58 (m, 1H), 1.29 – 1.23 (m, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta =$ 164.1, 164.0, 140.3, 140.1, 135.9, 135.8, 133.5, 133.5, 130.5, 127.9, 127.9, 127.6, 125.2, 125.1, 122.7, 122.2, 53.4, 53.1, 47.1, 46.1, 33.4, 32.1, 24.1, 22.3, 22.0, 19.7.

HRMS (ESI): Calculated for C$_{14}$H$_{16}$BrNNaO ([M+Na]$^+$): 316.0313; found: 316.0306

332
IR (neat): $\nu = 1649, 1407 \text{ cm}^{-1}$

(E)-3-(2-bromophenyl)-1-(2-methylpiperidin-1-yl)prop-2-en-1-one 4.82r:

![Chemical Structure](image)

Chemical Formula: $C_{15}H_{18}BrNO$

Exact Mass: 307.0572

Following the general procedure for amide synthesis, 2-bromocinnamic acid (232 mg, 1.02 mmol, 1 equiv) was reacted with oxalyl chloride (0.14 mL, 1.53 mmol, 1.5 equiv) with DMF (1 drop) in dichloromethane. The acid chloride was then reacted with 2-methylpiperidine (0.12 mL, 1.02 mmol, 1 equiv) and Et$_3$N (0.28 mL, 2.04 mmol, 2 equiv) in dichloromethane. After evaporation and purification, 4.82r was obtained as a yellowish oil (292 mg, 0.95 mmol, 93%).

$^1$H NMR (400 MHz, Chloroform-d) $\delta = 7.88$ (d, $J = 15.5$ Hz, 1H), 7.58 (ddd, $J = 8.9, 7.9, 1.5$ Hz, 2H), 7.32 – 7.28 (m, 1H), 7.19 – 7.15 (m, 1H), 6.80 (d, $J = 15.5$ Hz, 1H), 4.47 (br s, 1H), 3.25 – 2.74 (m, 1H), 1.76 – 1.54 (m, 6H), 1.54 – 1.42 (m, 1H), 1.30 – 1.18 (m, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta = 165.2, 140.0, 135.9, 133.3, 130.2, 127.6, 127.5, 124.8, 121.8, 18.9$.

HRMS (ESI): Calculated for $C_{15}H_{10}BrNO$ ([M+H]$^+$): 308.0650; found: 308.0645

IR (neat): $\nu = 2362, 2157, 1644 \text{ cm}^{-1}$

(E)-3-(2-bromophenyl)-1-(2-methylazepan-1-yl)prop-2-en-1-one 4.83r:

![Chemical Structure](image)

Chemical Formula: $C_{16}H_{20}BrNO$

Exact Mass: 321.0728

Following the general procedure for amide synthesis, 2-bromocinnamic acid (300 mg, 1.32 mmol, 1 equiv) was reacted with oxalyl chloride (0.17 mL, 1.98 mmol, 1.5 equiv) with DMF (1 drop) in dichloromethane. The acid chloride was then reacted with 2-methylazepane hydrochloride (198 mg, 1.32 mmol, 1 equiv) and Et$_3$N (0.37 mL, 2.64 mmol, 2 equiv) in dichloromethane. After evaporation and purification, 4.83r was obtained as a colorless oil (205 mg, 0.64 mmol, 48%).
$^1$H NMR (400 MHz, Chloroform-d) $\delta =$ 8.06 – 7.94 (m, 1H), 7.62 – 7.58 (m, 1H), 7.57 – 7.53 (m, 1H), 7.33 – 7.28 (m, 1H), 7.20 – 7.14 (m, 1H), 6.86 – 6.79 (m, 1H), 4.68 – 4.56 (m, 0.6H), 4.23 – 4.15 (m, 0.4H), 4.10 – 3.97 (m, 0.4H), 3.78 – 3.67 (m, 0.6H), 3.14 – 3.04 (m, 0.5H), 2.79 – 2.67 (m, 0.5H), 1.71 – 1.62 (m, 0.5H), 1.57 – 1.49 (m, 0.5H), 1.47 – 1.36 (m, 1H), 1.34 – 1.23 (m, 2H), 1.21 (d, $J = 6.4$ Hz, 1.5H), 1.12 (d, $J = 6.4$ Hz, 1.5H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta =$ 165.7, 165.6, 140.8, 140.4, 135.9, 135.9, 133.4, 133.4, 130.3, 130.3, 127.8, 127.7, 127.5, 125.0, 124.9, 121.6, 121.5, 53.0, 50.1, 41.7, 40.4, 36.4, 35.6, 30.7, 29.9, 29.4, 28.3, 25.2, 25.0, 21.2, 19.4.

HRMS (ESI): Calculated for C$_{16}$H$_{21}$BrNO ([M+H]$^+$): 322.0807; found: 322.0801

IR (neat): $\nu = 2362, 1623$ cm$^{-1}$

(E)-3-(2-bromophenyl)-1-(2-methyl-1,3-oxazinan-3-yl)prop-2-en-1-one 4.84r:

![Chemical Structure](image)

Chemical Formula: C$_{14}$H$_{17}$BrNO$_2$
Exact Mass: 309.0364

Following the general procedure for amide synthesis, 2-bromocinnamic acid (350 mg, 1.54 mmol, 1 equiv) was reacted with oxalyl chloride (0.20 mL, 2.31 mmol, 1.5 equiv) with DMF (1 drop) in dichloromethane. The acid chloride was then reacted with 2-methyl-1,3-oxazinane (156 mg, 1.54 mmol, 1 equiv) and Et$_3$N (0.43 mL, 3.08 mmol, 2 equiv) in dichloromethane. After evaporation and purification, 4.84r was obtained as a yellowish oil (36l mg, 1.16 mmol, 76%).

$^1$H NMR (400 MHz, Chloroform-d) $\delta =$ 7.94 – 7.85 (m, 1H), 7.60 – 7.53 (m, 2H), 7.32 – 7.27 (m, 1H), 7.20 – 7.15 (m, 1H), 6.75 – 6.66 (m, 1H), 5.92 – 5.85 (m, 1H), 4.27 (br. s, 1H), 3.99 (ddd, $J = 11.9, 10.3, 4.2$ Hz, 1H), 3.75 – 3.68 (m, 1H), 3.35 – 3.23 (m, 1H), 2.00 – 1.86 (m, 1H), 1.73 – 1.65 (m, 1H), 1.52 (d, $J = 6.2$ Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta =$ 164.6, 141.1, 135.4, 133.4, 130.6, 127.7, 127.6, 124.9, 120.7, 79.5, 59.7, 25.7, 16.5.

HRMS (ESI): Calculated for C$_{14}$H$_{17}$BrNO$_2$ ([M+H]$^+$): 310.0443; found: 310.0437

IR (neat): $\nu = 1625, 1424, 1107$ cm$^{-1}$
(E)-3-(2-bromophenyl)-1-(3-methylmorpholino)prop-2-en-1-one 4.85r:

![Chemical structure](image)

Chemical Formula: C_{14}H_{18}BrNO_{2}
Exact Mass: 309.0364

Following the general procedure for amide synthesis, 2-bromocinnamic acid (568 mg, 2.5 mmol, 1 equiv) was reacted with oxalyl chloride (0.35 mL, 3.75 mmol, 1.5 equiv) with DMF (1 drop) in dichloromethane. The acid chloride was then reacted with 3-methylmorpholine (253 mg, 2.5 mmol, 1 equiv) and Et_{3}N (0.69 mL, 5 mmol, 2 equiv) in dichloromethane. After evaporation and purification, 4.85r was obtained as a colorless oil (580 mg, 1.87 mmol, 75 %).

^1H NMR (400 MHz, Chloroform-d) δ = 7.96 (d, J = 15.4 Hz, 1H), 7.61 – 7.57 (m, 1H), 7.57 – 7.54 (m, 1H), 7.32 – 7.27 (m, 1H), 7.21 – 7.16 (m, 1H), 6.74 (d, J = 15.4 Hz, 1H), 4.80 – 4.00 (m, 2H), 3.97 – 3.91 (m, 1H), 3.76 – 3.70 (m, 1H), 3.67 – 3.61 (m, 1H), 3.52 – 3.46 (m, 1H), 3.30 (br. s, 1H), 1.37 (d, J = 7.0 Hz, 3H).

^13C NMR (101 MHz, CDCl_{3}) δ = 165.3, 141.4, 135.6, 133.5, 130.7, 127.8, 127.7, 125.0, 120.4, 71.0, 67.1.

HRMS (ESI): Calculated for C_{14}H_{17}BrNO_{2} ([M+H]^+) 310.0443; found: 310.0438

IR (neat) : ν = 1625, 1425, 1106 cm^{-1}

tert-butyl (E)-4-(3-(2-bromophenyl)acryloyl)-3-methylpiperazine-1-carboxylate 4.86r:

![Chemical structure](image)

Chemical Formula: C_{19}H_{26}BrN_{2}O_{3}
Exact Mass: 408.1049

(R)-2-methylpiperazine (600 mg, 6 mmol, 1 equiv) was dissolved in dry dichloromethane (80 mL) and cooled to 0°C. A solution of the Boc_{2}O (1.31 g, 6 mmol, 1 equiv) in 20 mL of dry dichloromethane was added dropwise in 30 min and then pyridine (0.73 mL, 9 mmol, 1.5 equiv). The reaction mixture was allowed to reach room temperature and was stirred overnight. The crude was quenched with NaOH (1M, 60 mL) and the aqueous phase was extracted with DCM (3 x 20 mL). The combined organic layers were dried over sodium sulfate, filtered and
evaporated under vacuum. The N-Boc protected piperazine was then used without further purification for next step.

Following the general procedure for amide synthesis, 2-bromocinnamic acid (568 mg, 2.5 mmol, 1 equiv) was reacted with oxalyl chloride (0.35 mL, 3.75 mmol, 1.5 equiv) with DMF (1 drop) in dichloromethane. The acid chloride was then reacted with N-Boc protected piperazine (500 mg, 2.5 mmol, 1 equiv) and Et₃N (0.69 mL, 5 mmol, 2 equiv) in dichloromethane. After evaporation and purification, 4.86g was obtained as a yellowish oil (684 mg, 1.67 mmol, 67%).

^1H NMR (400 MHz, Chloroform-d) δ = 7.94 (d, J = 15.4 Hz, 1H), 7.62 – 7.54 (m, 2H), 7.33 – 7.28 (m, 1H), 7.22 – 7.16 (m, 1H), 6.75 (d, J = 15.5 Hz, 1H), 4.98 – 3.74 (m, 4H), 3.46 – 2.79 (m, 3H), 1.48 (s, 9H), 1.26 (d, J = 7.1 Hz, 3H).

^13C NMR (101 MHz, CDCl₃) δ = 165.4, 155.1, 141.4, 135.6, 133.5, 130.7, 127.8, 127.7, 125.1, 120.7, 80.4, 28.5.

HRMS (ESI): Calculated for C₁₉H₂₅BrNaN₂O₃ ([M+Na]⁺): 431.0946; found: 431.0941

IR (neat) : ν = 2362, 1690, 1423 cm⁻¹
(E)-3-(2-bromophenyl)-1-(o-tolyl)prop-2-en-1-one 4.104r:

Chemical Formula: C_{16}H_{13}BrO
Exact Mass: 300.0150

Following the general procedure for aldolisation reaction, 2-bromobenzaldehyde (1.11 g, 6 mmol, 1 equiv), 1-(o-tolyl)ethan-1-one (805 mg, 6 mmol, 1 equiv), and NaOH (240 mg, 6 mmol, 1 equiv) were reacted in EtOH/water at 45 °C. After completion, the crude was extracted and purified by chromatography on silica gel to afford 4.104r as a yellowish solid (1.8 g, 6 mmol, 100%).

The physical and spectroscopic properties matched those described in the literature. 38

H NMR (400 MHz, Chloroform-d) δ = 7.84 (d, J = 16.0 Hz, 1H), 7.70 – 7.66 (m, 1H), 7.62 – 7.59 (m, 1H), 7.55 – 7.52 (m, 1H), 7.42 – 7.32 (m, 2H), 7.31 – 7.26 (m, 2H), 7.26 – 7.21 (m, 1H), 7.06 (d, J = 16.0 Hz, 1H), 2.48 (s, 3H).

C NMR (101 MHz, CDCl3) δ = 196.2, 144.4, 138.7, 137.3, 134.9, 133.6, 131.5, 130.8, 129.4, 129.3, 128.5, 128.0, 127.9, 125.9, 125.6, 20.5.

(E)-3-(2-bromophenyl)-1-(2,6-dimethylphenyl)prop-2-en-1-one 4.105r:

Chemical Formula: C_{17}H_{15}BrO
Exact Mass: 314.0306

Following the general procedure for aldolisation reaction, 2-bromobenzaldehyde (1.11 g, 6 mmol, 1 equiv), 1-(2,6-dimethylphenyl)ethan-1-one (889 mg, 6 mmol, 1 equiv), and NaOH (240 mg, 6 mmol, 1 equiv) were reacted in EtOH/water at 45 °C. After completion, the crude was extracted and purified by chromatography on silica gel to afford 4.105r as a colorless oil (1.89 g, 6 mmol, 99%).
\( ^1H\) NMR (400 MHz, Chloroform-\( d \)) \( \delta = 7.68 - 7.64 \) (m, 1H), 7.60 - 7.56 (m, 1H), 7.37 - 7.32 (m, 1H), 7.25 - 7.19 (m, 2H), 7.10 - 7.06 (m, 2H), 6.83 (d, \( J = 16.2 \) Hz, 1H), 2.25 (s, 6H).

\( ^13C\) NMR (101 MHz, CDCl\( _3 \)) \( \delta = 201.2, 145.9, 139.6, 134.7, 134.2, 133.5, 131.8, 130.7, 129.0, 128.1, 128.0, 127.8, 125.8, 19.6, 19.6.\)

HRMS (ESI): Calculated for C\(_{17}\)H\(_{16}\)BrO ([M+H\(^+\)]: 315.0385; found: 315.0379

IR (neat): \( \nu = 1650, 1462 \) cm\(^{-1}\)

(E)-3-(2-bromophenyl)-1-(4-methoxy-2-methylphenyl)prop-2-en-1-one 4.106r:

A solution of 1-(4-hydroxy-2-methylphenyl)ethan-1-one (1.0 g, 6.66 mmol, 1 equiv), K\(_2\)CO\(_3\) (1.2 g, 8.66 mmol, 1.3 equiv) and iodomethane (0.62 ml, 10 mmol, 1.5 equiv) in acetone (25 ml) was heated to 70 °C for 6 h. After cooling to room temperature, the crude was evaporated under vacuum, dissolved in DCM (30 mL) and washed with water (3 x 10 mL). The organic phase was dried over sodium sulfate, filtered and evaporated under vacuum. The desired product was used without further purification (6.65 mmol, 1.09 g, 99%).

Following the general procedure for aldolisation reaction, 2-bromobenzaldehyde (555 mg, 3 mmol, 1 equiv), 1-(4-methoxy-2-methylphenyl)ethan-1-one (493 mg, 3 mmol, 1 equiv), and NaOH (120 mg, 3 mmol, 1 equiv) were reacted in EtOH/water at 45 °C. After completion, the crude was extracted and purified by chromatography on silica gel to afford 4.106r as a yellowish oil (992 mg, 3 mmol, 99%).

\( ^1H\) NMR (400 MHz, Chloroform-\( d \)) \( \delta = 7.89 \) (d, \( J = 15.9 \) Hz, 1H), 7.70 - 7.60 (m, 3H), 7.37 - 7.32 (m, 1H), 7.26 - 7.20 (m, 1H), 7.14 (d, \( J = 15.9 \) Hz, 1H), 6.82 - 6.73 (m, 2H), 3.86 (s, 3H), 2.54 (s, 3H).

\( ^13C\) NMR (101 MHz, CDCl\( _3 \)) \( \delta = 193.8, 161.8, 143.0, 141.4, 135.3, 133.6, 131.6, 131.3, 131.1, 129.1, 128.0, 127.8, 125.8, 117.3, 110.7, 55.5, 21.5.

HRMS (ESI): Calculated for C\(_{17}\)H\(_{16}\)BrO\(_2\) ([M+H\(^+\)]: 331.0334; found: 331.0330

338
IR (neat) : ν = 1652, 1465 cm$^{-1}$

(E)-1-(4-(benzyloxy)-2-methylphenyl)-3-(2-bromophenyl)prop-2-en-1-one 4.107r:

1-(4-hydroxy-2-methylphenyl)ethan-1-one (1.0 g, 6.66 mmol, 1 equiv) and K$_2$CO$_3$ (1.2 g, 8.66 mmol, 1.3 equiv) were stirred in DMF (25 mL). Benzyl bromide (0.96 mL, 8 mmol, 1.2 equiv) was added and the mixture was stirred at 70°C for 6 h. After cooling to room temperature, the crude was quenched with water (25 mL) and extracted with Et2O (3 x 30 mL). The combined organic layers were then washed with LiCl (10%, 50 mL), dried over sodium sulfate, filtered and evaporated under vacuum. The crude was used in the next step without further purification (1.6 g, 6.66 mmol, 100%).

Following the general procedure for aldolisation reaction, 2-bromobenzaldehyde (1.23 g, 6.66 mmol, 1 equiv), 1-(4-benzyl-2-methylphenyl)ethan-1-one (1.6 g, 6.66 mmol, 1 equiv), and NaOH (270 mg, 6.66 mmol, 1 equiv) were reacted in EtOH/water at 45 °C. After completion, the crude was extracted and purified by chromatography on silica gel to afford 4.107r as a yellowish oil (2.7 g, 6.65 mmol, 99%).

$^1$H NMR (400 MHz, Chloroform-d) δ = 7.90 (d, J = 15.9 Hz, 1H), 7.70 – 7.61 (m, 3H), 7.46 – 7.38 (m, 4H), 7.37 – 7.31 (m, 2H), 7.25 – 7.21 (m, 1H), 7.14 (d, J = 15.9 Hz, 1H), 6.91 – 6.84 (m, 2H), 5.13 (s, 2H), 5.13 (s, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ = 193.8, 160.9, 143.0, 141.4, 136.6, 135.2, 133.6, 131.6, 131.3, 131.3, 129.1, 128.8, 128.3, 128.0, 127.9, 127.6, 125.9, 118.2, 111.5, 70.1, 21.5.

HRMS (ESI): Calculated for C$_{23}$H$_{20}$BrO$_2$ ([M+H]$^+$): 407.0647; found: 407.0641

IR (neat) : ν = 1620, 1455 cm$^{-1}$

(E)-3-(2-bromophenyl)-1-(2,4-dimethylphenyl)prop-2-en-1-one 4.108r:
Following the general procedure for aldolisation reaction, 2-bromobenzaldehyde (555 mg, 3 mmol, 1 equiv), 1-(2,4-dimethylphenyl)ethan-1-one (445 mg, 3 mmol, 1 equiv), and NaOH (120 mg, 3 mmol, 1 equiv) were reacted in EtOH/water at 45 °C. After completion, the crude was extracted and purified by chromatography on silica gel to afford 4.108r as a yellowish oil (941 mg, 2.99 mmol, 99%).

\[ \text{HRMS (ESI): Calculated for C}_{17}\text{H}_{16}\text{BrO ([M+H]^{+})}: 315.0385; found: 315.0378} \]

\[ \text{IR (neat) : v = 1650, 1464 cm}^{-1} \]

(E)-3-(2-bromophenyl)-1-(4-fluoro-2-methylphenyl)prop-2-en-1-one 4.109r:

Following the general procedure for aldolisation reaction, 2-bromobenzaldehyde (555 mg, 3 mmol, 1 equiv), l-(4-fluoro-2-methylphenyl)ethan-1-one (457 mg, 3 mmol, 1 equiv), and NaOH (120 mg, 3 mmol, 1 equiv) were reacted in EtOH/water at 45 °C. After completion, the crude was extracted and purified by chromatography on silica gel to afford 4.109r as a colorless oil (812 mg, 2.54 mmol, 85%).

\[ \text{HRMS (ESI): Calculated for C}_{16}\text{H}_{12}\text{BrFO ([M+H]^{+})}: 318.0056} \]
H NMR (500 MHz, Chloroform-d) δ = 7.84 (d, J = 16.0 Hz, 1H), 7.70 – 7.66 (m, 1H), 7.64 – 7.60 (m, 1H), 7.59 – 7.55 (m, 1H), 7.37 – 7.33 (m, 1H), 7.27 – 7.23 (m, 1H), 7.05 (d, J = 16.0 Hz, 1H), 7.01 – 6.95 (m, 2H), 2.49 (s, 3H).

13C NMR (126 MHz, CDCl3) δ = 194.8, 163.9 (d, J = 251.8 Hz), 144.4, 141.2 (d, J = 8.5 Hz), 134.8, 133.7, 131.6, 131.0 (d, J = 8.9 Hz), 129.1, 128.0 (d, J = 6.1 Hz), 126.0, 118.4 (d, J = 22.4 Hz), 112.6 (d, J = 21.6 Hz), 20.8 (d, J = 1.3 Hz).

19F NMR (376 MHz, CDCl3) δ = -109.1.


IR (neat) : ν = 1625, 1456 cm⁻¹

(E)-1-(4-amino-2-methylphenyl)-3-(2-bromophenyl)prop-2-en-1-one 4.110r:

Following the general procedure for aldolisation reaction, 2-bromobenzaldehyde (555 mg, 3 mmol, 1 equiv), N-(4-acetyl-3-methylphenyl)acetamide (574 mg, 3 mmol, 1 equiv), and NaOH (120 mg, 3 mmol, 1 equiv) were reacted in EtOH/water at 45 °C. After completion, the crude was extracted and purified by chromatography on silica gel to afford 4.110r as a yellowish oil (178 mg, 0.56 mmol, 19%).

H NMR (400 MHz, Chloroform-d) δ = 7.91 (d, J = 15.7 Hz, 1H), 7.70 – 7.66 (m, 1H), 7.65 – 7.59 (m, 2H), 7.36 – 7.28 (m, 1H), 7.24 – 7.18 (m, 2H), 6.55 – 6.45 (m, 2H), 4.01 (br. s, 2H), 2.52 (s, 3H).

13C NMR (101 MHz, CDCl3) δ = 192.4, 149.7, 142.2, 141.8, 135.6, 133.6, 132.5, 131.0, 129.0, 128.3, 127.9, 127.8, 125.7, 117.8, 111.2, 22.0.

HRMS (ESI): Calculated for C16H15BrNO ([M+H]+): 316.0337; found: 316.0334

IR (neat) : ν = 1652, 1449 cm⁻¹
1,4-Pd shift/C(sp³)-H activation products:

(E)-3-benzylidene-5-methyl-1-(2,4,6-trimethoxybenzyl)pyrrolidin-2-one 4.49:

Following the general procedure for the 1,4-Pd shift/C(sp³)-H activation, 4.49r (45 mg, 0.1 mmol, 1 equiv) was reacted with Pd(PCy₃)₂ (6.7 mg, 0.01 mmol, 10 mol%), pivalic acid (3.1 mg, 0.03 mmol, 30 mol%) and Rb₂CO₃ (35 mg, 0.15 mmol, 1.5 equiv) in mesitylene (4 mL) at 160°C for 16h. After purification, 4.49 was obtained as a yellowish oil (36.5 mg, 0.099 mmol, 100%).

^1H NMR (400 MHz, Chloroform-d) δ = 7.49 – 7.42 (m, 2H), 7.42 – 7.33 (m, 3H), 7.33 – 7.23 (m, 1H), 6.12 (s, 2H), 5.12 (d, J = 14.1 Hz, 1H), 4.28 (d, J = 14.2 Hz, 1H), 3.81 (s, 3H), 3.79 (s, 6H), 3.48 – 3.39 (m, 1H), 3.08 (dd, J = 17.0 Hz, 7.6 Hz, 1H), 2.58 – 2.47 (m, 1H), 1.20 (d, J = 6.3 Hz, 3H).

^13C NMR (101 MHz, CDCl₃) δ = 168.1, 161.1, 160.1, 136.5, 132.1, 129.5, 129.4, 128.7, 128.1, 104.7, 90.5, 55.9, 55.4, 50.2, 33.7, 33.3, 20.9.

HRMS (ESI): Calculated for C₂₂H₂₅NaNO₄ ([M+Na⁺]: 390.1681; found: 390.1676

IR (neat): v = 2362, 1682, 1607, 1417 cm⁻¹

(E)-3-benzylidene-5-methyl-1-(2,4,6-trimethoxybenzyl)pyrrolidin-2-one 4.55-d7:

^1H NMR (400 MHz, Chloroform-d) δ = 7.47 – 7.43 (m, 2H), 7.40 – 7.35 (m, 3H), 7.31 – 7.28 (m, 1H), 6.12 (s, 2H), 5.12 (d, J = 14.2 Hz, 1H), 4.28 (d, J = 14.1 Hz, 1H), 3.82 (s, 3H), 3.79 (s, 6H), 3.46 – 3.41 (m, 1H), 3.12 – 3.02 (m, 0.59H), 2.57 – 2.50 (m, 0.58H), 1.22 – 1.15 (m, 1.63H).

^13C NMR (101 MHz, CDCl₃) δ = 168.2, 161.2, 160.2, 136.5, 129.5, 128.7, 128.1, 104.7, 90.5, 55.9, 55.5, 33.3, 26.5.
(E)-3-benzyldiene-5-methyl-1-(2,4,6-trimethoxybenzyl)pyrrolidin-2-one 4.55-d6:

![Chemical structure diagram]

$^1$H NMR (400 MHz, Chloroform-d) $\delta = 7.47 – 7.43$ (m, 2H), 7.40 – 7.35 (m, 3H), 7.31 – 7.26 (m, 1H), 6.12 (s, 2H), 5.12 (d, $J = 14.1$ Hz, 1H), 4.30 – 4.25 (m, 1H), 3.82 (s, 3H), 3.79 (s, 6H), 3.47 – 3.41 (m, 1H), 3.11 – 3.03 (m, 0.51H), 2.57 – 2.49 (m, 0.50H), 1.22 – 1.18 (m, 1.59H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta =$ 168.2, 161.2, 160.2, 136.5, 129.5, 128.7, 128.1, 104.7, 90.5, 55.9, 55.5, 33.3, 26.5.

(E)-3-benzyldiene-5-methyl-1-(2,4,6-trimethoxybenzyl)pyrrolidin-2-one 4.55-d1:

![Chemical structure diagram]

$^1$H NMR (400 MHz, Chloroform-d) $\delta = 7.47 – 7.44$ (m, 2H), 7.40 – 7.35 (m, 3H), 7.31 – 7.28 (m, 1H), 6.12 (s, 2H), 5.12 (d, $J = 14.1$ Hz, 1H), 4.30 (d, $J = 14.2$ Hz, 1H), 3.82 (s, 3H), 3.79 (s, 6H), 3.50 – 3.40 (m, 1H), 3.08 (ddd, $J = 17.4$, 8.1, 3.0 Hz, 1H), 2.57 – 2.51 (m, 1H), 1.21 (d, $J = 6.2$ Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta =$ 168.2, 161.2, 160.2, 136.5, 132.1, 129.6, 129.4, 128.7, 128.1, 104.7, 90.5, 55.9, 55.5, 50.2, 33.7, 33.3, 21.0.
(E)-3-benzylidene-1-(2,4,6-trimethoxybenzyl)pyrrolidin-2-one 4.61:

\[
\text{Chemical Formula: } 
C_{21}H_{23}NO_4 \\
\text{Exact Mass: } 353.1627
\]

Following the general procedure for the 1,4-Pd shift/C(sp^3)-H activation, 4.61 (43.4 mg, 0.1 mmol, 1 equiv) was reacted with Pd(PCy_3)_2 (6.7 mg, 0.01 mmol, 10 mol%), pivalic acid (3.1 mg, 0.03 mmol, 30 mol%), PCy_3 (2.8 mg, 0.01 mmol, 10 mol%) and Rb_2CO_3 (35 mg, 0.15 mmol, 1.5 equiv) in mesitylene (4 mL) at 160°C for 16h. After purification, 4.61 was obtained as a yellow oil (16 mg, 0.045 mmol, 45%).

^1H NMR (500 MHz, Chloroform-d) \( \delta = 7.47 – 7.44 \) (m, 2H), \( 7.39 – 7.34 \) (m, 3H), \( 7.30 – 7.28 \) (m, 1H), \( 6.13 \) (s, 2H), \( 4.66 \) (s, 2H), \( 3.82 \) (s, 3H), \( 3.81 \) (s, 6H), \( 3.26 \) (dd, \( J = 7.1 \), 5.9 Hz, 2H), \( 2.92 \) (ddd, \( J = 8.9 \), 5.9, 2.9 Hz, 2H).

^13C NMR (126 MHz, CDCl_3) \( \delta = 168.4, 161.2, 160.0, 136.3, 132.2, 129.4, 129.0, 128.6, 128.0, 104.4, 90.3, 55.8, 55.3, 43.5, 35.3, 24.3 \).

HRMS (ESI): Calculated for C_{21}H_{23}NaNO_4 ([M+Na]^+): 376.1525; found: 376.1519

IR (neat) : \( \nu = 2362, 1604 \text{ cm}^{-1} \)

(E)-3-benzylidene-5,5-dimethyl-1-(2,4,6-trimethoxybenzyl)pyrrolidin-2-one 4.62:

\[
\text{Chemical Formula: } 
C_{23}H_{27}NO_4 \\
\text{Exact Mass: } 381.1940
\]

Following the general procedure for the 1,4-Pd shift/C(sp^3)-H activation, 4.62 (46.2 mg, 0.1 mmol, 1 equiv) was reacted with Pd(PCy_3)_2 (6.7 mg, 0.01 mmol, 10 mol%), pivalic acid (3.1 mg, 0.03 mmol, 30 mol%) and Rb_2CO_3 (35 mg, 0.15 mmol, 1.5 equiv) in mesitylene (4 mL) at 160°C for 16h. After purification, 4.62 was obtained as a colorless oil (19.5 mg, 0.051 mmol, 51%).

^1H NMR (500 MHz, Chloroform-d) \( \delta = 7.47 – 7.43 \) (m, 2H), \( 7.42 – 7.36 \) (m, 3H), \( 7.31 – 7.27 \) (m, 1H), \( 6.10 \) (s, 2H), \( 4.71 \) (s, 2H), \( 3.81 \) (s, 9H), \( 2.80 \) (s, 2H), \( 1.13 \) (s, 6H).
$\text{C NMR (126 MHz, CDCl}_3$) $\delta = 168.3, 161.0, 159.8, 136.6, 131.7, 129.6, 129.4, 128.7, 128.1, 107.0, 90.5, 59.3, 55.9, 55.4, 42.5, 32.3, 27.7.$

HRMS (ESI): Calculated for C$_{23}$H$_{28}$NO$_4$ ([M+H]$^+$): 382.2018; found: 382.2013

$\text{IR (neat): } \nu = 2363, 912 \text{ cm}^{-1}$

(E)-4-benzylidene-2-(2,4,6-trimethoxybenzyl)-2-azabicyclo[3.1.0]hexan-3-one 4.63:

\[
\text{Chemical Formula: C$_{22}$H$_{23}$NO$_4$}
\]
\[
\text{Exact Mass: 365.1627}
\]

Following the general procedure for the 1,4-Pd shift/C(sp$^3$)-H activation, 4.63 (44.6 mg, 0.1 mmol, 1 equiv) was reacted with Pd(PCy$_3$)$_2$ (6.7 mg, 0.01 mmol, 10 mol%), pivalic acid (3.1 mg, 0.03 mmol, 30 mol%) and Rb$_2$CO$_3$ (35 mg, 0.15 mmol, 1.5 equiv) in mesitylene (4 mL) at 160°C for 16h. After purification, 4.63 was obtained as a colorless oil (25.5 mg, 0.070 mmol, 70%).

$^1$H NMR (400 MHz, Chloroform-d) $\delta = 7.55 – 7.52$ (m, 2H), 7.32 – 7.25 (m, 3H), 7.23 – 7.18 (m, 1H), 6.04 (s, 2H), 4.54 (d, $J = 1.9$ Hz, 2H), 3.73 (s, 3H), 3.72 (s, 6H), 3.01 – 2.92 (m, 1H), 2.22 – 2.14 (m, 1H), 0.93 (dt, $J = 8.5$, 5.1 Hz, 1H), 0.49 – 0.44 (m, 1H).

$^13$C NMR (101 MHz, CDCl$_3$) $\delta = 168.0, 161.3, 160.1, 136.2, 134.6, 130.0, 129.6, 129.4, 128.7, 128.5, 128.3, 104.9, 90.4, 55.9, 55.5, 35.2, 20.4, 13.1.$

HRMS (ESI): Calculated for C$_{22}$H$_{23}$NaNO$_4$ ([M+Na]$^+$): 388.1525; found: 388.1519

$\text{IR (neat): } \nu = 1681, 1612, 1419 \text{ cm}^{-1}$

(E)-3-benzylidene-1-isopropylindolin-2-one 4.64:

\[
\text{Chemical Formula: C$_{18}$H$_{17}$NO}
\]
\[
\text{Exact Mass: 263.1310}
\]
Following the general procedure for the 1,4-Pd shift/C(sp$^3$)-H activation, $4.64r$ (34.4 mg, 0.1 mmol, 1 equiv) was reacted with Pd(PCy$_3$)$_2$ (6.7 mg, 0.01 mmol, 10 mol%), pivalic acid (3.1 mg, 0.03 mmol, 30 mol%) and Rb$_2$CO$_3$ (35 mg, 0.15 mmol, 1.5 equiv) in mesitylene (4 mL) at 160°C for 16h. After purification, $4.64$ was obtained as a yellow oil (12.5 mg, 0.048 mmol, 48%).

$^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ = 7.83 (s, 1H), 7.65 – 7.60 (m, 3H), 7.49 – 7.41 (m, 3H), 7.25 – 7.19 (m, 1H), 7.02 – 6.97 (m, 1H), 6.87 – 6.81 (m, 1H), 4.72 (sept, $J$ = 7.0 Hz, 1H), 1.53 (d, $J$ = 7.0 Hz, 6H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ = 168.0, 142.9, 136.9, 135.1, 129.5, 129.4, 129.2, 128.6, 127.5, 122.9, 121.7, 121.2, 109.8, 43.8, 19.5.

HRMS (ESI): Calculated for C$_{18}$H$_{17}$NaNO ([M+Na]$^+$): 286.1208; found: 286.1202

IR (neat) : $\nu$ = 2361, 1701, 1463 cm$^{-1}$

(E)-1-benzylidine-4-methyl-5,6-dihydro-4H-pyrrolo[3,2,1-ij]quinolin-2(1H)-one $4.65$:

Following the general procedure for the 1,4-Pd shift/C(sp$^3$)-H activation, $4.65r$ (36 mg, 0.1 mmol, 1 equiv) was reacted with Pd(PCy$_3$)$_2$ (6.7 mg, 0.01 mmol, 10 mol%), pivalic acid (3.1 mg, 0.03 mmol, 30 mol%) and Rb$_2$CO$_3$ (35 mg, 0.15 mmol, 1.5 equiv) in mesitylene (4 mL) at 160°C for 16h. After purification, $4.65$ was obtained as a yellow oil (24 mg, 0.088 mmol, 88%).

$^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ = 7.82 (s, 1H), 7.68 – 7.64 (m, 2H), 7.49 – 7.38 (m, 4H), 7.05 – 6.99 (m, 1H), 6.82 – 6.76 (m, 1H), 4.56 – 4.47 (m, 1H), 2.91 – 2.80 (m, 1H), 2.71 (dt, $J$ = 16.6, 3.8 Hz, 1H), 1.98 – 1.92 (m, 3H), 1.34 (d, $J$ = 6.7 Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ = 167.3, 139.9, 137.0, 135.3, 129.6, 129.5, 128.7, 128.7, 128.5, 121.2, 120.8, 120.0, 119.9, 44.2, 27.0, 20.8, 18.5.

HRMS (ESI): Calculated for C$_{19}$H$_{17}$NaNO ([M+Na]$^+$): 298.1208; found: 298.1202

IR (neat) : $\nu$ = 2363, 1701, 1460 cm$^{-1}$

(E)-3-benzylidene-1-isopropyl-5-methylpyrrolidin-2-one $4.66$:
Following the general procedure for the 1,4-Pd shift/C(sp³)-H activation, 4.66r (31 mg, 0.1 mmol, 1 equiv) was reacted with Pd(PCy₃)₂ (6.7 mg, 0.01 mmol, 10 mol%), pivalic acid (3.1 mg, 0.03 mmol, 30 mol%) and Rb₂CO₃ (35 mg, 0.15 mmol, 1.5 equiv) in mesitylene (4 mL) at 160°C for 16h. After purification, 4.66 was obtained as a colorless oil (21 mg, 0.097 mmol, 97%).

H NMR (400 MHz, Chloroform-d) δ = 7.47 – 7.43 (m, 2H), 7.41 – 7.36 (m, 2H), 7.34 – 7.29 (m, 1H), 4.23 (sept, J = 7.0 Hz, 1H), 3.95 – 3.86 (m, 1H), 3.23 (ddd, J = 17.4, 8.1, 3.1 Hz, 1H), 2.62 – 2.59 (m, 1H), 1.35 (t, J = 8.1 Hz, 6H), 1.31 (d, J = 6.4 Hz, 3H).

C NMR (126 MHz, CDCl₃) δ = 168.8, 136.2, 131.6, 129.6, 129.6, 128.7, 128.3, 50.9, 45.2, 34.4, 23.8, 21.8, 19.6.

HRMS (ESI): Calculated for C₁₅H₁₉NO ([M+Na]⁺): 252.1364; found: 252.1360

IR (neat) : ν = 2363, 1682, 1423 cm⁻¹

(E)-3-benzyldiene-1-ethylpyrrolidin-2-one 4.67:

Following the general procedure for the 1,4-Pd shift/C(sp³)-H activation, 4.67r (28.2 mg, 0.1 mmol, 1 equiv) was reacted with Pd(PCy₃)₂ (6.7 mg, 0.01 mmol, 10 mol%), pivalic acid (3.1 mg, 0.03 mmol, 30 mol%) and Rb₂CO₃ (35 mg, 0.15 mmol, 1.5 equiv) in mesitylene (4 mL) at 160°C for 16h. After purification, 4.67 was obtained as a yellow oil (6.3 mg, 0.031 mmol, 31%).

H NMR (400 MHz, Chloroform-d) δ = 7.50 – 7.46 (m, 2H), 7.43 – 7.38 (m, 2H), 7.36 – 7.28 (m, 2H), 3.55 – 3.47 (m, 4H), 3.10 – 3.02 (m, 2H), 1.20 (t, J = 7.3 Hz, 3H).

C NMR (101 MHz, CDCl₃) δ = 168.9, 136.1, 131.5, 129.8, 129.6, 128.4, 128.3, 50.9, 45.2, 34.4, 23.8, 12.7.

HRMS (ESI): Calculated for C₁₃H₁₅NaNO ([M+Na]⁺): 224.1051; found: 224.1046
IR (neat) : ν = 2364, 1679, 1608, 1419 cm⁻¹

(E)-3-benzyldiene-5-methyl-1-(3-phenylpropyl)pyrrolidin-2-one 4.68:

Chemical Formula: C₂₃H₂₃NO
Exact Mass: 305.1780

Following the general procedure for the 1,4-Pd shift/C(sp³)-H activation, 4.68r (39 mg, 0.1 mmol, 1 equiv) was reacted with Pd(PCy₃)₂ (6.7 mg, 0.01 mmol, 10 mol%), PCy₃ (2.8 mg, 0.01 mmol, 10 %), pivalic acid (3.1 mg, 0.03 mmol, 30 mol%) and Rb₂CO₃ (35 mg, 0.15 mmol, 1.5 equiv) in mesitylene (4 mL) at 160°C for 16h. After purification, 4.68 was obtained as a yellowish oil (25 mg, 0.082 mmol, 82%).

¹H NMR (400 MHz, Chloroform-d) δ = 7.48 – 7.44 (m, 2H), 7.42 – 7.34 (m, 3H), 7.34 – 7.28 (m, 3H), 7.23 – 7.15 (m, 3H), 3.86 – 3.74 (m, 2H), 3.26 – 3.11 (m, 2H), 2.67 (t, J = 7.8 Hz, 2H), 2.61 – 2.57 (m, 1H), 2.02 – 1.81 (m, 2H), 1.24 (d, J = 6.3 Hz, 3H).

¹³C NMR (126 MHz, CDCl₃) δ = 169.1, 141.6, 136.1, 131.0, 130.0, 129.6, 128.8, 128.6, 128.5, 128.4, 126.1, 51.1, 40.6, 33.8, 33.5, 29.2, 20.9.

HRMS (ESI): Calculated for C₂₃H₂₃NO ([M+H]+): 306.1858; found: 306.1852

IR (neat) : ν = 1679, 1423 cm⁻¹

(E)-3-benzyldiene-1-(cyclopentylmethyl)-5-methylpyrrolidin-2-one 4.69:

Chemical Formula: C₁₉H₂₃NO
Exact Mass: 269.1780

Following the general procedure for the 1,4-Pd shift/C(sp³)-H activation, 4.69r (35 mg, 0.1 mmol, 1 equiv) was reacted with Pd(PCy₃)₂ (6.7 mg, 0.01 mmol, 10 mol%), PCy₃ (2.8 mg, 0.01 mmol, 10 %), pivalic acid (3.1 mg, 0.03 mmol, 30 mol%) and Rb₂CO₃ (35 mg, 0.15 mmol, 1.5 equiv) in mesitylene (4 mL) at 160°C for 16h. After purification, 4.69 was obtained as a colorless oil (18 mg, 0.067 mmol, 67%).
\( ^1\text{H NMR (400 MHz, Chloroform-d)} \delta = 7.48 - 7.44 \text{ (m, 2H)}, 7.42 - 7.34 \text{ (m, 3H)}, 7.33 - 7.28 \text{ (m, 1H)}, 3.90 - 3.81 \text{ (m, 1H)}, 3.76 \text{ (dd, } J = 13.7, 9.5 \text{ Hz, 1H)}, 3.26 \text{ (ddd, } J = 17.4, 7.8, 2.8 \text{ Hz, 1H)}, 3.02 \text{ (dd, } J = 13.7, 6.2 \text{ Hz, 1H)}, 2.63 - 2.60 \text{ (m, 2H)}, 2.29 - 2.18 \text{ (m, 1H)}, 1.83 - 1.73 \text{ (m, 1H)}, 1.71 - 1.62 \text{ (m, 3H)}, 1.57 - 1.50 \text{ (m, 2H)}, 1.32 - 1.24 \text{ (m, 5H)}. \)

\( ^{13}\text{C NMR (126 MHz, CDCl}_3\) \delta = 169.2, 136.2, 131.2, 129.9, 129.6, 128.8, 128.4, 51.1, 45.3, 38.1, 33.9, 31.0, 30.4, 25.4, 25.1, 20.8. \)

HRMS (ESI): Calculated for C\(_{18}\)H\(_{24}\)NO ([M+H]\(^+\)) : 270.1858; found: 270.1852

IR (neat) : \(\nu = 1685, 1419 \text{ cm}^{-1}\)

(E)-3-benzylidene-1-(3-methoxypropyl)-5-methylpyrrolidin-2-one 4.70:

Following the general procedure for the 1,4-Pd shift/C\(^{sp^3}\)-H activation, 4.70r (34 mg, 0.1 mmol, 1 equiv) was reacted with Pd(PCy\(_3\))\(_2\) (6.7 mg, 0.01 mmol, 10 mol%), pivalic acid (3.1 mg, 0.03 mmol, 30 mol%) and Rb\(_2\)CO\(_3\) (35 mg, 0.15 mmol, 1.5 equiv) in mesitylene (4 mL) at 160°C for 16h. After purification, 4.70 was obtained as a yellowish oil (15.5 mg, 0.060 mmol, 60%).

\( ^1\text{H NMR (400 MHz, Chloroform-d)} \delta = 7.49 - 7.44 \text{ (m, 2H)}, 7.43 - 7.39 \text{ (m, 2H)}, 7.36 - 7.29 \text{ (m, 2H)}, 3.87 - 3.72 \text{ (m, 2H)}, 3.44 \text{ (t, } J = 6.3 \text{ Hz, 2H)}, 3.34 \text{ (s, 3H)}, 3.31 - 3.20 \text{ (m, 2H)}, 2.64 - 2.59 \text{ (m, 1H)}, 1.99 - 1.77 \text{ (m, 2H)}, 1.29 \text{ (d, } J = 6.3 \text{ Hz, 3H)}. \)

\( ^{13}\text{C NMR (101 MHz, CDCl}_3\) \delta = 169.1, 136.0, 130.9, 129.7, 129.5, 128.6, 128.3, 70.4, 58.7, 51.3, 38.2, 33.7, 27.8, 20.9. \)

HRMS (ESI): Calculated for C\(_{15}\)H\(_{19}\)NaNO\(_2\) ([M+Na]\(^+\)) : 282.1470; found: 282.1465

IR (neat) : \(\nu = 1681, 1421, 1115 \text{ cm}^{-1}\)
(E)-3-(3-benzylidene-5-methyl-2-oxopyrrolidin-1-yl)propanenitrile 4.71:

\[
\begin{align*}
&\text{Chemical Formula: } C_{15}H_{16}N_2O \\
&\text{Exact Mass: } 240.1263
\end{align*}
\]

Following the general procedure for the 1,4-Pd shift/C(sp³)-H activation, 4.71r (32 mg, 0.1 mmol, 1 equiv) was reacted with Pd(PCy₃)₂ (6.7 mg, 0.01 mmol, 10 mol%), pivalic acid (3.1 mg, 0.03 mmol, 30 mol%) and Rb₂CO₃ (35 mg, 0.15 mmol, 1.5 equiv) in mesitylene (4 mL) at 160°C for 16h. After purification, 4.71 was obtained as a colorless oil (12 mg, 0.051 mmol, 51%).

\(^1\)H NMR (400 MHz, Chloroform-d) \(\delta = 7.49 - 7.45 \) (m, 2H), 7.44 – 7.41 (m, 1H), 7.40 – 7.33 (m, 2H), 4.03 – 3.94 (m, 1H), 3.88 (dt, J = 17.3, 6.7 Hz, 1H), 3.54 – 3.45 (m, 1H), 3.34 (dd, J = 15.8, 6.7 Hz, 3H), 2.85 – 2.76 (m, 1H), 2.74 – 2.64 (m, 2H), 2.21 (s, 3H), 1.36 (d, J = 6.7 Hz, 3H).

\(^13\)C NMR (101 MHz, CDCl₃) \(\delta = 168.4, 135.6, 131.2, 129.6, 129.4, 128.7, 128.1, 52.0, 37.7, 31.8, 20.9, 16.6\).

HRMS (ESI): Calculated for C₁₅H₁₆NaN₂O (\([\text{M+Na}]^+\)): 263.1160; found: 263.1155

IR (neat) : ν = 2362, 1682, 1615 cm⁻¹

(E)-3-benzylidene-5-methyl-1-(2-(phenylsulfonyl)ethyl)pyrrolidin-2-one 4.72:

\[
\begin{align*}
&\text{Chemical Formula: } C_{20}H_{21}NO₃S \\
&\text{Exact Mass: } 355.1242
\end{align*}
\]

Following the general procedure for the 1,4-Pd shift/C(sp³)-H activation, 4.72r (43.6 mg, 0.1 mmol, 1 equiv) was reacted with Pd(PCy₃)₂ (6.7 mg, 0.01 mmol, 10 mol%), pivalic acid (3.1 mg, 0.03 mmol, 30 mol%) and Rb₂CO₃ (35 mg, 0.15 mmol, 1.5 equiv) in mesitylene (4 mL) at 160°C for 16h. After purification, 4.72 was obtained as a colorless oil (14.5 mg, 0.040 mmol, 40%).

\(^1\)H NMR (400 MHz, Chloroform-d) \(\delta = 7.96 - 7.92 \) (m, 2H), 7.69 – 7.63 (m, 1H), 7.61 – 7.55 (m, 2H), 7.45 – 7.37 (m, 4H), 7.35 – 7.30 (m, 1H), 7.29 – 7.27 (m, 1H), 4.01 – 3.92 (m, 1H), 3.92 – 3.83 (m, 1H), 3.68 – 3.56 (m, 2H), 3.42 – 3.31 (m, 1H), 3.23 – 3.13 (m, 1H), 2.63 – 2.59 (m, 1H), 1.28 (d, J = 6.3 Hz, 3H).

350
\(^{13}\text{C NMR (101 MHz, CDCl}_3\) δ = 169.5, 139.2, 135.7, 134.1, 130.8, 129.8, 129.7, 129.6, 128.8, 128.0, 53.3, 52.0, 35.5, 33.8, 21.0.

**HRMS (ESI):** Calculated for C\(_{20}\)H\(_{21}\)NaNO\(_3\)S \([\text{M+Na}^+]\): 378.1140; found: 378.1137

**IR (neat):** ν = 1681, 1614, 1419 cm\(^{-1}\)

**ethyl (E)-3-(3-benzylidene-5-methyl-2-oxopyrrolidin-1-yl)propanoate 4.73:**

![Chemical Structure](image)

**Chemical Formula:** C\(_{17}\)H\(_{21}\)NO\(_3\)
**Exact Mass:** 287.1521

Following the general procedure for the 1,4-Pd shift/C(sp\(^3\))-H activation, 4.73r (37 mg, 0.1 mmol, 1 equiv) was reacted with Pd(PCy\(_3\))\(_2\) (6.7 mg, 0.01 mmol, 10 mol%), pivalic acid (3.1 mg, 0.03 mmol, 30 mol%) and Rb\(_2\)CO\(_3\) (35 mg, 0.15 mmol, 1.5 equiv) in mesitylene (4 mL) at 160°C for 16h. After purification, 4.73 was obtained as a yellowish oil (18 mg, 0.062 mmol, 62%).

\(^1\text{H NMR (400 MHz, Chloroform-)}\_d\) δ = 7.48 – 7.44 (m, 2H), 7.42 – 7.37 (m, 2H), 7.37 – 7.29 (m, 2H), 4.15 (q, J = 7.2 Hz, 2H), 4.00 – 3.91 (m, 1H), 3.90 – 3.81 (m, 1H), 3.47 (dt, J = 14.3, 7.2 Hz, 1H), 3.26 (ddd, J = 17.4, 7.9, 2.9 Hz, 1H), 2.73 (dt, J = 16.2, 7.3 Hz, 1H), 2.66 – 2.54 (m, 2H), 1.30 (d, J = 6.3 Hz, 3H), 1.26 (t, J = 7.2 Hz, 3H).

\(^{13}\text{C NMR (101 MHz, CDCl}_3\) δ = 171.8, 169.1, 135.8, 130.4, 130.1, 129.5, 128.7, 128.4, 60.8, 51.6, 36.8, 33.7, 32.8, 20.9, 14.2.

**HRMS (ESI):** Calculated for C\(_{17}\)H\(_{21}\)NaNO\(_3\) \([\text{M+Na}^+]\): 310.1419; found: 310.1414

**IR (neat):** ν = 2361, 1978, 1732, 1419 cm\(^{-1}\)

**(E)-3-(3-fluorobenzylidene)-5-methyl-1-(2,4,6-trimethoxybenzyl)pyrrolidin-2-one 4.74:**

![Chemical Structure](image)

**Chemical Formula:** C\(_{22}\)H\(_{24}\)FNO\(_4\)
**Exact Mass:** 385.1689

Following the general procedure for the 1,4-Pd shift/C(sp\(^3\))-H activation, 4.74r (46.6 mg, 0.1 mmol, 1 equiv) was reacted with Pd(PCy\(_3\))\(_2\) (6.7 mg, 0.01 mmol, 10 mol%), pivalic acid (3.1 mg, 0.03 mmol, 30
mol%) and Rb$_2$CO$_3$ (35 mg, 0.15 mmol, 1.5 equiv) in mesitylene (4 mL) at 160°C for 16 h. After purification, 4.74 was obtained as a colorless oil (19.5 mg, 0.051 mmol, 51%).

$^1$H NMR (400 MHz, Chloroform-d) $\delta$ = 7.37 – 7.29 (m, 2H), 7.24 – 7.20 (m, 1H), 7.16 – 7.11 (m, 1H), 7.01 – 6.95 (m, 1H), 6.12 (s, 2H), 5.11 (d, J = 14.2 Hz, 1H), 4.28 (d, J = 14.2 Hz, 1H), 3.81 (s, 3H), 3.79 (s, 6H), 3.49 – 3.42 (m, 1H), 3.10 – 3.00 (m, 1H), 2.54 – 2.48 (m, 1H), 1.21 (d, J = 6.2 Hz, 3H).

$^{13}$C NMR (101 MHz, Chloroform-d) $\delta$ = 167.7, 162.9 (d, J = 245.5 Hz), 161.2, 160.1, 138.6 (d, J = 7.7 Hz), 133.5, 130.1 (d, J = 8.4 Hz), 128.2 (d, J = 2.9 Hz), 125.5 (d, J = 2.9 Hz), 115.7 (d, J = 21.7 Hz), 115.0 (d, J = 21.4 Hz), 104.5, 90.4, 55.9, 55.4, 50.2, 33.6, 33.3, 20.9.

$^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ = -113.01.

HRMS (ESI): Calculated for C$_{22}$H$_{24}$F$_3$NaNO$_4$ ([M+Na]$^+$): 408.1587; found: 408.1582

IR (neat): $\nu$ = 1679, 1608, 1419 cm$^{-1}$

(E)-5-methyl-3-(4-(trifluoromethyl)benzylidene)-1-(2,4,6-trimethoxybenzyl)pyrrolidin-2-one 4.75:

Chemical Formula: C$_{23}$H$_{24}$F$_3$NO$_4$

Exact Mass: 435.1657

Following the general procedure for the 1,4-Pd shift/C(sp$^3$)-H activation, 4.75r (51.6 mg, 0.1 mmol, 1 equiv) was reacted with Pd(PCI$_3$)$_2$ (6.7 mg, 0.01 mmol, 10 mol%), pivalic acid (3.1 mg, 0.03 mmol, 30 mol%) and Rb$_2$CO$_3$ (35 mg, 0.15 mmol, 1.5 equiv) in mesitylene (4 mL) at 160°C for 16 h. After purification, 4.75 was obtained as a colorless oil (33.5 mg, 0.077 mmol, 77%).

$^1$H NMR (400 MHz, Chloroform-d) $\delta$ = 7.68 (m, 1H), 7.62 – 7.60 (m, 1H), 7.56 – 7.46 (m, 2H), 7.40 – 7.38 (m, 1H), 6.12 (s, 2H), 5.12 (d, J = 14.2 Hz, 1H), 4.29 (d, J = 14.1 Hz, 1H), 3.82 (s, 3H), 3.80 (s, 6H), 3.53 – 3.44 (m, 1H), 3.09 (ddd, J = 17.4, 8.1, 3.1 Hz, 1H), 2.56 – 2.48 (m, 1H), 1.23 (d, J = 6.3 Hz, 3H).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ = 167.6, 161.2, 160.1, 137.2, 134.2, 132.7, 131.3, 131.0, 129.2, 127.8, 125.6 (q, J = 3.9 Hz), 124.6 (q, J = 3.1 Hz), 124.3 (q, J = 271.3 Hz), 104.5, 90.5, 55.9, 55.5, 50.2, 33.6, 33.4, 20.9.

$^{19}$F NMR (471 MHz, CDCl$_3$) $\delta$ = -62.8.

HRMS (ESI) Calculated for C$_{23}$H$_{25}$F$_3$NO$_4$ ([M+H]$^+$): 436.1736; found: 436.1730
(E)-3-(3-methoxybenzylidene)-5-methyl-1-(2,4,6-trimethoxybenzyl)pyrrolidin-2-one 4.76:

Following the general procedure for the 1,4-Pd shift/C(sp^3)-H activation, 4.76r (47.8 mg, 0.1 mmol, 1 equiv) was reacted with Pd(PCy_3)_2 (6.7 mg, 0.01 mmol, 10 mol%), pivalic acid (3.1 mg, 0.03 mmol, 30 mol%) and Rb_2CO_3 (35 mg, 0.15 mmol, 1.5 equiv) in mesitylene (4 mL) at 160°C for 16h. After purification, 4.76 was obtained as a yellowish oil (40 mg, 0.039 mmol, 100%).

^1H NMR (400 MHz, Chloroform-d) δ = 7.35 – 7.33 (m, 1H), 7.29 (t, J = 7.9 Hz, 1H), 7.07 – 7.03 (m, 1H), 7.00 – 6.96 (m, 1H), 6.87 – 6.81 (m, 1H), 6.11 (s, 2H), 5.11 (d, J = 14.1 Hz, 1H), 4.27 (d, J = 14.1 Hz, 1H), 3.81 (s, 6H), 3.78 (s, 6H), 3.49 – 3.38 (m, 1H), 3.07 (ddd, J = 17.4, 8.2, 3.0 Hz, 1H), 2.56 – 2.47 (m, 1H), 1.20 (d, J = 6.2 Hz, 3H).

^13C NMR (101 MHz, CDCl_3) δ = 168.0, 161.1, 160.1, 159.7, 137.8, 132.4, 129.6, 129.3, 122.1, 115.0, 113.6, 104.6, 90.4, 55.9, 55.4, 55.4, 55.4, 50.2, 33.6, 33.3, 20.9.

HRMS (ESI): Calculated for C_{23}H_{27}NO_5 ([M+Na]^+): 420.1787; found: 420.1781.

IR (neat) : v = 1690, 1423 cm^{-1}

(E)-3-(3-(benzyloxy)benzylidene)-5-methyl-1-(2,4,6-trimethoxybenzyl)pyrrolidin-2-one 4.77:

Following the general procedure for the 1,4-Pd shift/C(sp^3)-H activation, 4.77r (55 mg, 0.1 mmol, 1 equiv) was reacted with Pd(PCy_3)_2 (6.7 mg, 0.01 mmol, 10 mol%), pivalic acid (3.1 mg, 0.03 mmol, 30 mol%)
and Rb₂CO₃ (35 mg, 0.15 mmol, 1.5 equiv) in mesitylene (4 mL) at 160°C for 16h. After purification, 4.77 was obtained as a yellowish oil (34.5 mg, 0.073 mmol, 73%).

¹H NMR (400 MHz, Chloroform-d) δ = 7.45 – 7.41 (m, 2H), 7.39 – 7.36 (m, 2H), 7.35 – 7.26 (m, 3H), 7.08 – 7.03 (m, 2H), 6.95 – 6.90 (m, 1H), 6.12 (s, 2H), 5.13 – 5.06 (m, 3H), 4.27 (d, J = 14.1 Hz, 1H), 3.81 (s, 3H), 3.79 (s, 6H), 3.46 – 3.37 (m, 1H), 3.00 (ddd, J = 17.4, 8.1, 3.0 Hz, 1H), 2.51 – 2.40 (m, 1H), 1.18 (d, J = 6.8 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ = 167.9, 161.0, 160.0, 158.8, 137.7, 136.9, 132.4, 129.5, 129.1, 128.6, 128.0, 127.4, 122.4, 115.7, 114.6, 104.6, 90.3, 70.1, 55.8, 55.7, 50.1, 33.5, 33.2, 20.8.

HRMS (ESI): Calculated for C₂₃H₂₉BrNaNO₄ ([M+Na⁺]): 496.2100; found: 496.2094

IR (neat) : ν = 1681, 1596, 1416 cm⁻¹

(E)-3-(benzo[d][1,3]dioxol-5-ylmethylene)-5-methyl-1-(2,4,6-trimethoxybenzyl)pyrrolidin-2-one 4.78:

Following the general procedure for the 1,4-Pd shift/C(sp³)-H activation, 4.78r (49 mg, 0.1 mmol, 1 equiv) was reacted with Pd(PCy₃)₂ (6.7 mg, 0.01 mmol, 10 mol%), pivalic acid (3.1 mg, 0.03 mmol, 30 mol%) and Rb₂CO₃ (35 mg, 0.15 mmol, 1.5 equiv) in mesitylene (4 mL) at 160°C for 16h. After purification, 4.78 was obtained as a yellowish solid (29 mg, 0.071 mmol, 71%).

¹H NMR (400 MHz, Chloroform-d) δ = 7.29 – 7.27 (m, 1H), 6.98 – 6.93 (m, 2H), 6.84 – 6.80 (m, 1H), 6.11 (s, 2H), 5.97 (s, 2H), 5.10 (d, J = 14.2 Hz, 1H), 4.26 (d, J = 14.1 Hz, 1H), 3.81 (s, 3H), 3.79 (s, 6H), 3.48 – 3.38 (m, 1H), 3.02 (ddd, J = 17.2, 8.2, 3.0 Hz, 1H), 2.52 – 2.42 (m, 1H), 1.20 (d, J = 6.2 Hz, 3H).

¹³C NMR (126 MHz, CDCl₃) δ = 168.3, 161.1, 160.1, 148.0, 147.6, 130.8, 130.1, 129.2, 124.6, 109.0, 108.7, 104.8, 101.4, 90.5, 55.9, 55.4, 50.2, 33.6, 33.3, 21.0.

HRMS (ESI): Calculated for C₂₃H₂₅NaNO₆ ([M+Na⁺]): 434.1580; found: 434.1574

IR (neat) : ν = 1679, 1608, 1416 cm⁻¹

m.p. : 58 – 60 °C

(E)-3-(4-fluorobenzylidene)-5-methyl-1-(2,4,6-trimethoxybenzyl)pyrrolidin-2-one 4.79:
Following the general procedure for the 1,4-Pd shift/C(sp³)-H activation, **4.79r** (47 mg, 0.1 mmol, 1 equiv) was reacted with Pd(PCy₃)₂ (6.7 mg, 0.01 mmol, 10 mol%), pivalic acid (3.1 mg, 0.03 mmol, 30 mol%) and Rb₂CO₃ (35 mg, 0.15 mmol, 1.5 equiv) in mesitylene (4 mL) at 160°C for 16h. After purification, **4.79** was obtained as a yellowish oil (25 mg, 0.064 mmol, 64%).

**¹H NMR (400 MHz, Chloroform-d)** δ = 7.45 – 7.39 (m, 2H), 7.34 – 7.32 (m, 1H), 7.09 – 7.02 (m, 2H), 6.12 (s, 2H), 5.11 (d, J = 14.1 Hz, 1H), 4.27 (d, J = 14.1 Hz, 1H), 3.81 (s, 3H), 3.79 (s, 6H), 3.50 – 3.40 (m, 1H), 3.04 (ddd, J = 17.3, 8.1, 3.1 Hz, 1H), 2.55 – 2.45 (m, 1H), 1.21 (d, J = 6.3 Hz, 3H).

**¹³C NMR (101 MHz, CDCl₃)** δ = 168.0, 163.6, 161.1, 160.1, 132.67 (d, J = 3.5 Hz) 131.6 (d, J = 2.4 Hz), 131.2 (d, J = 8.0 Hz), 128.2, 115.7 (d, J = 22.0 Hz), 104.6, 90.4, 55.9, 55.5, 50.2, 33.5, 33.3, 21.0.

**¹⁹F NMR (376 MHz, CDCl₃)** δ = -112.8.

HRMS (ESI): Calculated for C₂₂H₂₄FNaNO₄ ([M+Na⁺]): 408.1587; found: 408.1583

IR (neat): ν = 1677, 1608, 1422 cm⁻¹

**(E)-5-methyl-3-(4-methylbenzylidene)-1-(2,4,6-trimethoxybenzyl)pyrrolidin-2-one 4.80:**

Following the general procedure for the 1,4-Pd shift/C(sp³)-H activation, **4.80r** (46 mg, 0.1 mmol, 1 equiv) was reacted with Pd(PCy₃)₂ (6.7 mg, 0.01 mmol, 10 mol%), PCy₃ (2.8 mg, 0.01 mmol, 10%), pivalic acid (3.1 mg, 0.03 mmol, 30 mol%) and Rb₂CO₃ (35 mg, 0.15 mmol, 1.5 equiv) in mesitylene (4 mL) at 160°C for 16h. After purification, **4.80** was obtained as a colorless oil (25 mg, 0.076 mmol, 76%).
\textbf{H NMR (500 MHz, Chloroform-d)} \( \delta = 7.36 - 7.33 \) (m, 3H), 7.19 – 7.16 (m, 2H), 6.12 (s, 2H), 5.11 (d, \( J = 14.1 \) Hz, 1H), 4.26 (d, \( J = 14.1 \) Hz, 1H), 3.81 (s, 3H), 3.79 (s, 6H), 3.44 (ddt, \( J = 8.3, 6.2, 3.1 \) Hz, 1H), 3.06 (ddd, \( J = 17.2, 8.1, 3.0 \) Hz, 1H), 2.56 – 2.48 (m, 1H), 2.36 (s, 3H), 1.20 (d, \( J = 6.3 \) Hz, 3H).

\textbf{C NMR (126 MHz, CDCl3)} \( \delta = 168.2, 161.0, 160.0, 138.1, 133.6, 130.9, 129.4, 129.3, 129.2, 104.7, 90.3, 55.8, 55.3, 50.1, 33.6, 33.1, 21.3, 20.8.$

HRMS (ESI): Calculated for C\textsubscript{23}H\textsubscript{28}NO\textsubscript{4} ([M+H]\textsuperscript{+}): 382.2018; found: 382.2013

IR (neat): \( \nu = 2361, 1680, 1608, 1416 \text{ cm}^{-1} \)

\textbf{(E)-2-benzylidenehexahydro-3H-pyrrolizin-3-one 4.81:}

\begin{center}
\includegraphics[width=0.2\textwidth]{image}
\end{center}

Chemical Formula: C\textsubscript{14}H\textsubscript{15}NO

Exact Mass: 213.1154

Following the general procedure for the 1,4-Pd shift/C(sp\textsuperscript{3})-H activation, 4.81r (29.4 mg, 0.1 mmol, 1 equiv) was reacted with Pd(PCy\textsubscript{3})\textsubscript{2} (6.7 mg, 0.01 mmol, 10 mol%), PCy\textsubscript{3} (2.8 mg, 0.01 mmol, 10 mol%), pivalic acid (3.1 mg, 0.03 mmol, 30 mol%) and Rb\textsubscript{2}CO\textsubscript{3} (35 mg, 0.15 mmol, 1.5 equiv) in mesitylene (4 mL) at 160°C for 16 h. After purification, 4.81 was obtained as a yellowish oil (11 mg, 0.051 mmol, 51%).

\textbf{H NMR (400 MHz, Chloroform-d)} \( \delta = 7.49 - 7.45 \) (m, 2H), 7.43 – 7.37 (m, 2H), 7.34 – 7.29 (m, 2H), 3.89 – 3.86 (m, 1H), 3.75 (dt, \( J = 12.0, 8.2 \) Hz, 1H), 3.34 – 3.22 (m, 2H), 2.86 – 2.78 (m, 1H), 2.22 – 2.00 (m, 3H), 1.33 – 1.19 (m, 1H).

\textbf{C NMR (101 MHz, CDCl3)} \( \delta = 170.4, 136.0, 133.9, 130.5, 129.7, 128.8, 128.6, 59.3, 42.2, 32.4, 31.4, 26.3.$

HRMS (ESI): Calculated for C\textsubscript{14}H\textsubscript{15}NaNO ([M+Na]\textsuperscript{+}): 236.1051; found: 236.1046

IR (neat): \( \nu = 2361, 1681, 1419 \text{ cm}^{-1} \)

\textbf{(R,E)-2-benzylidenehexahydro-3H-pyrrolizin-3-one 4.99:}

\begin{center}
\includegraphics[width=0.2\textwidth]{image}
\end{center}

Chemical Formula: C\textsubscript{14}H\textsubscript{15}NO

Exact Mass: 213.1154
Following the general procedure for the 1,4-Pd shift/C(sp³)-H activation, 4.99r (29.4 mg, 0.1 mmol, 1 equiv) was reacted with Pd(PCy3)2 (6.7 mg, 0.01 mmol, 10 mol%), PCy3 (2.8 mg, 0.01 mmol, 10 mol%), pivalic acid (3.1 mg, 0.03 mmol, 30 mol%) and Rb2CO3 (35 mg, 0.15 mmol, 1.5 equiv) in mesitylene (4 mL) at 160°C for 16h. After purification, 4.99 was obtained as a yellowish oil (10.5 mg, 0.050 mmol, 50%).

**1H NMR (400 MHz, Chloroform-d)** δ = 7.49 – 7.45 (m, 2H), 7.42 – 7.37 (m, 2H), 7.34 – 7.29 (m, 2H), 3.91 – 3.82 (m, 1H), 3.79 – 3.72 (m, 1H), 3.34 – 3.22 (m, 2H), 2.82 (dt, J = 17.6, 3.3 Hz, 1H), 2.21 – 1.97 (m, 3H), 1.33 – 1.21 (m, 1H).

**13C NMR (126 MHz, CDCl3)** δ = 170.4, 136.0, 133.9, 130.6, 129.7, 128.8, 128.6, 59.3, 42.2, 32.4, 31.5, 26.3.

(E)-2-benzylidenehexahydroindolizin-3(2H)-one 4.82:

![Chemical Structure](image)

Chemical Formula: C15H17NO

Exact Mass: 227.1310

Following the general procedure for the 1,4-Pd shift/C(sp³)-H activation, 4.82r (30.8 mg, 0.1 mmol, 1 equiv) was reacted with Pd(PCy3)2 (6.7 mg, 0.01 mmol, 10 mol%), pivalic acid (3.1 mg, 0.03 mmol, 30 mol%) and Rb2CO3 (35 mg, 0.15 mmol, 1.5 equiv) in mesitylene (4 mL) at 160°C for 16h. After purification, 4.82 was obtained as a colorless oil (22.2 mg, 0.098 mmol, 98%).

**1H NMR (500 MHz, Chloroform-d)** δ = 7.49 – 7.44 (m, 2H), 7.42 – 7.37 (m, 2H), 7.36 – 7.34 (m, 1H), 7.33 – 7.28 (m, 1H), 4.35 – 4.28 (m, 1H), 3.58 – 3.51 (m, 1H), 3.24 (ddd, J = 17.5, 7.8, 2.7 Hz, 1H), 2.81 – 2.77 (m, 1H), 2.66 – 2.58 (m, 1H), 2.01 – 1.86 (m, 2H), 1.77 – 1.70 (m, 1H), 1.57 – 1.36 (m, 2H), 1.27 – 1.13 (m, 1H).

**13C NMR (126 MHz, CDCl3)** δ = 167.7, 136.2, 131.0, 129.9, 129.6, 128.8, 128.4, 55.2, 40.9, 34.1, 32.3, 24.8, 24.1.

**HRMS (ESI):** Calculated for C15H17NaNO ([M+Na]+): 250.1208; found: 250.1202

**IR (neat):** ν = 2937, 1632, 1444 cm⁻¹
(E)-2-benzylideneoctahydro-3H-pyrrolo[1,2-a]azepin-3-one 4.83:

![Chemical structure](image)

Chemical Formula: C_{16}H_{19}NO
Exact Mass: 241.1467

Following the general procedure for the 1,4-Pd shift/C(sp³)-H activation, 4.83r (32.2 mg, 0.1 mmol, 1 equiv) was reacted with Pd(PCy₃)₂ (6.7 mg, 0.01 mmol, 10 mol%), pivalic acid (3.1 mg, 0.03 mmol, 30 mol%) and Rb₂CO₃ (35 mg, 0.15 mmol, 1.5 equiv) in mesitylene (4 mL) at 160°C for 16h. After purification, 4.83 was obtained as a yellowish oil (9.5 mg, 0.039 mmol, 40%).

**¹H NMR (400 MHz, Chloroform-d) δ =** 7.48 – 7.44 (m, 2H), 7.42 – 7.36 (m, 2H), 7.34 – 7.28 (m, 2H), 3.94 – 3.81 (m, 2H), 3.29 – 3.15 (m, 2H), 2.64 – 2.57 (m, 1H), 1.98 – 1.89 (m, 1H), 1.85 – 1.75 (m, 1H), 1.75 – 1.62 (m, 4H), 1.60 – 1.51 (m, 2H).

**¹³C NMR (101 MHz, CDCl₃) δ =** 169.4, 136.2, 131.8, 129.6, 129.1, 128.8, 128.3, 57.0, 43.5, 36.8, 33.6, 29.6, 27.4, 25.3.

**HRMS (ESI):** Calculated for C₁₆H₁₀NaNO ([M+Na]⁺): 264.1364; found: 264.1359

**IR (neat):** ν = 1650, 1421 cm⁻¹

(E)-7-benzylidenetetrahydro-2H-pyrrolo[2,1-b][1,3]oxazin-6(7H)-one 4.84:

![Chemical structure](image)

Chemical Formula: C_{14}H_{18}NO₂
Exact Mass: 229.1103

Following the general procedure for the 1,4-Pd shift/C(sp³)-H activation, 4.84r (31 mg, 0.1 mmol, 1 equiv) was reacted with Pd(PCy₃)₂ (6.7 mg, 0.01 mmol, 10 mol%), pivalic acid (3.1 mg, 0.03 mmol, 30 mol%) and Rb₂CO₃ (35 mg, 0.15 mmol, 1.5 equiv) in mesitylene (4 mL) at 160°C for 16h. After purification, 4.84 was obtained as a colorless oil (20.5 mg, 0.090 mmol, 90%).

**¹H NMR (400 MHz, Chloroform-d) δ =** 7.48 – 7.45 (m, 2H), 7.42 – 7.37 (m, 3H), 7.35 – 7.30 (m, 1H), 5.06 (dd, J = 6.7, 1.8 Hz, 1H), 4.36 (ddt, J = 13.3, 5.4, 1.7 Hz, 1H), 4.12 (ddt, J = 11.6, 4.5, 1.7 Hz, 1H), 3.78 (ddd, J = 12.6, 11.8, 2.3 Hz, 1H), 3.26 (ddd, J = 17.9, 6.6, 2.7 Hz, 1H), 3.17 – 3.08 (m, 1H), 2.88 (dt, J = 17.9, 2.3 Hz, 1H), 1.93 – 1.80 (m, 1H), 1.58 – 1.51 (m, 1H).
\[^{13}\text{C NMR (101 MHz, CDCl}_3\] \(\delta = 167.6, 135.6, 131.4, 129.7, 128.8, 128.4, 127.9, 85.4, 67.2, 39.0, 32.7, 24.8\).

HRMS (ESI): Calculated for C\(_{14}\)H\(_{16}\)NO\(_2\) ([M+H]\(^+\)): 230.1181; found: 230.1178

IR (neat): \(\nu = 2364, 1685, 1449\) cm\(^{-1}\)

**(E)-7-benzylidenehexahydro-6H-pyrrolo[2,1-c][1,4]oxazin-6-one 4.85**:}

![E-7-benzylidenehexahydro-6H-pyrrolo[2,1-c][1,4]oxazin-6-one 4.85](attachment:image)

Chemical Formula: C\(_{14}\)H\(_{16}\)NO\(_2\)

Exact Mass: 229.1103

Following the general procedure for the 1,4-Pd shift/C(sp\(^3\))-H activation, 4.85r (31 mg, 0.1 mmol, 1 equiv) was reacted with Pd(PCy\(_3\))\(_2\) (6.7 mg, 0.01 mmol, 10 mol\%), PCy\(_3\) (2.8 mg, 0.01 mmol, 10 mol\%), pivalic acid (3.1 mg, 0.03 mmol, 30 mol\%) and Rb\(_2\)CO\(_3\) (35 mg, 0.15 mmol, 1.5 equiv) in mesitylene (4 mL) at 160°C for 16h. After purification, 4.85 was obtained as a colorless oil (16 mg, 0.069 mmol, 69%).

\[^1\text{H NMR (500 MHz, Chloroform-d) \(\delta = 7.51 – 7.48\) (m, 2H), 7.45 – 7.41 (m, 3H), 7.38 – 7.34 (m, 1H), 4.18 (dd, \(J = 13.3, 3.0\) Hz, 1H), 4.08 (dd, \(J = 11.1, 3.9\) Hz, 1H), 4.00 – 3.96 (m, 1H), 3.91 – 3.84 (m, 1H), 3.48 – 3.42 (m, 1H), 3.24 – 3.12 (m, 1H), 2.60 – 2.52 (m, 1H).\)]

\[^{13}\text{C NMR (126 MHz, CDCl}_3\] \(\delta = 167.6, 135.7, 131.1, 129.7, 129.4, 128.9, 128.8, 72.6, 66.5, 53.2, 41.1, 27.5\).

HRMS (ESI): Calculated for C\(_{14}\)H\(_{16}\)NO\(_2\) ([M+H]\(^+\)): 230.1181; found: 230.1176

IR (neat): \(\nu = 2361, 1682, 1447\) cm\(^{-1}\)

tert-butyl (E)-7-benzylidene-6-oxohexahydropyrrolo[1,2-a]pyrazine-2(1H)-carboxylate 4.86:

![tert-butyl (E)-7-benzylidene-6-oxohexahydropyrrolo[1,2-a]pyrazine-2(1H)-carboxylate 4.86](attachment:image)

Chemical Formula: C\(_{19}\)H\(_{24}\)N\(_2\)O\(_3\)

Exact Mass: 328.1787

Following the general procedure for the 1,4-Pd shift/C(sp\(^3\))-H activation, 4.86r (41 mg, 0.1 mmol, 1 equiv) was reacted with Pd(PCy\(_3\))\(_2\) (6.7 mg, 0.01 mmol, 10 mol\%), pivalic acid (3.1 mg, 0.03 mmol, 30 mol\%)
and Rb_2CO_3 (35 mg, 0.15 mmol, 1.5 equiv) in mesitylene (4 mL) at 160°C for 16h. After purification, 4.86 was obtained as a colorless oil (17 mg, 0.052 mmol, 52%).

**H NMR (500 MHz, Chloroform-d)** δ = 7.49 – 7.45 (m, 2H), 7.43 – 7.39 (m, 3H), 7.36 – 7.32 (m, 1H), 4.35 (br. s, 1H), 4.25 – 4.19 (m, 1H), 4.15 (br. s, 1H), 3.72 – 3.65 (m, 1H), 3.22 (ddd, J = 17.7, 7.9, 2.7 Hz, 1H), 2.99 – 2.93 (m, 1H), 2.77 (br. s, 1H), 2.64 – 2.57 (m, 1H), 2.47 (br. s, 1H), 1.49 (s, 9H).

**C NMR (126 MHz, CDCl₃)** δ = 167.7, 154.5, 135.7, 131.1, 129.7, 129.5, 129.0, 128.9, 128.8, 127.9, 80.8, 53.4, 40.3, 28.8, 28.5.

HRMS (ESI): Calculated for C₁₉H₂₄NaN₂O₃ ([M+Na]^+): 351.1685; found: 351.1679

IR (neat): ν = 2361, 1688, 1422 cm⁻¹

(E)-2-benzylidene-2,3-dihydro-1H-inden-1-one 4.104:

Chemical Formula: C₁₆H₁₂O
Exact Mass: 220.0888

Following the general procedure for the 1,4-Pd shift/C(sp³)-H activation, 4.104r (30 mg, 0.1 mmol, 1 equiv) was reacted with Pd(PCy₃)₂ (6.7 mg, 0.01 mmol, 10 mol%), PCy₃ (2.8 mg, 0.01 mmol, 10 mol%), pivalic acid (3.1 mg, 0.03 mmol, 30 mol%) and Rb₂CO₃ (35 mg, 0.15 mmol, 1.5 equiv) in mesitylene (4 mL) at 160°C for 16h. After purification, 4.104 was obtained as a white solid (14.5 mg, 0.066 mmol, 66%).

The physical and spectroscopic properties matched those described in the literature. 39

**H NMR (400 MHz, Chloroform-d)** δ = 7.94 – 7.91 (m, 1H), 7.70 – 7.67 (m, 3H), 7.64 – 7.60 (m, 1H), 7.58 – 7.55 (m, 1H), 7.49 – 7.38 (m, 4H), 4.06 (d, J = 2.1 Hz, 2H).

**C NMR (101 MHz, CDCl₃)** δ = 194.5, 149.8, 138.2, 135.6, 134.9, 134.8, 134.1, 130.9, 129.8, 129.1, 127.8, 126.3, 124.6, 32.6.
(E)-2-benzylidene-7-methyl-2,3-dihydro-1H-inden-1-one 4.105:

Chemical Formula: C₁₇H₁₄O
Exact Mass: 234.1045

Following the general procedure for the 1,4-Pd shift/C(sp³)-H activation, 4.105 (31.5 mg, 0.1 mmol, 1 equiv) was reacted with Pd(PCy₃)₂ (6.7 mg, 0.01 mmol, 10 mol%), PCy₃ (2.8 mg, 0.01 mmol, 10 mol%), pivalic acid (3.1 mg, 0.03 mmol, 30 mol%) and Rb₂CO₃ (35 mg, 0.15 mmol, 1.5 equiv) in mesitylene (4 mL) at 160°C for 16h. After purification, 4.105 was obtained as a white solid (16.5 mg, 0.070 mmol, 70%).

¹H NMR (400 MHz, Chloroform-d) δ = 7.69 – 7.65 (m, 2H), 7.62 – 7.60 (m, 1H), 7.48 – 7.43 (m, 3H), 7.42 – 7.38 (m, 1H), 7.38 – 7.34 (m, 1H), 7.18 – 7.14 (m, 1H), 4.01 (d, J = 2.2 Hz, 2H), 2.75 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ = 195.4, 150.4, 139.7, 135.7, 135.6, 135.4, 134.1, 133.1, 130.8, 129.7, 129.8, 129.0, 123.6, 32.3, 18.7.

HRMS (ESI): Calculated for C₁₇H₁₅O ([M+H]⁺): 235.1123; found: 235.1118
IR (neat) : ν = 1693, 1629 cm⁻¹
m.p.: 230 - 232°C (decomp.)

(E)-2-benzylidene-5-methoxy-2,3-dihydro-1H-inden-1-one 4.106:

Chemical Formula: C₁₇H₁₄O₂
Exact Mass: 250.0994

Following the general procedure for the 1,4-Pd shift/C(sp³)-H activation, 4.106 (33 mg, 0.1 mmol, 1 equiv) was reacted with Pd(PCy₃)₂ (6.7 mg, 0.01 mmol, 10 mol%), PCy₃ (2.8 mg, 0.01 mmol, 10 mol%), pivalic acid (3.1 mg, 0.03 mmol, 30 mol%) and Rb₂CO₃ (35 mg, 0.15 mmol, 1.5 equiv) in mesitylene (4 mL) at 160°C for 16h. After purification, 4.106 was obtained as a white solid (20 mg, 0.081 mmol, 81%).

The physical and spectroscopic properties matched those described in the literature.
$^1$H NMR (500 MHz, Chloroform-$d$) $\delta = 7.88 - 7.85$ (m, 1H), 7.68 - 7.66 (m, 2H), 7.63 - 7.61 (m, 1H), 7.48 - 7.44 (m, 2H), 7.41 - 7.37 (m, 1H), 7.01 - 6.99 (m, 1H), 6.98 - 6.95 (m, 1H), 4.02 (d, $J = 1.7$ Hz, 2H), 3.92 (s, 3H).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta =$ 192.9, 165.4, 152.7, 135.8, 135.4, 132.8, 131.6, 130.7, 129.5, 129.0, 126.4, 115.4, 109.9, 55.9, 32.7.

(E)-2-benzylidene-5-(benzyloxy)-2,3-dihydro-1H-inden-1-one 4.107:

![Chemical structure of (E)-2-benzylidene-5-(benzyloxy)-2,3-dihydro-1H-inden-1-one](attachment:image)

Chemical Formula: C$_{23}$H$_{18}$O$_2$

Exact Mass: 326.1307

Following the general procedure for the 1,4-Pd shift/C($sp^3$)-H activation, 4.107r (41 mg, 0.1 mmol, 1 equiv) was reacted with Pd(PCy$_3$)$_2$ (6.7 mg, 0.01 mmol, 10 mol%), PCy$_3$ (2.8 mg, 0.01 mmol, 10 mol%), pivalic acid (3.1 mg, 0.03 mmol, 30 mol%) and Rb$_2$CO$_3$ (35 mg, 0.15 mmol, 1.5 equiv) in mesitylene (4 mL) at 160°C for 16h. After purification, 4.107r was obtained as a white solid (26 mg, 0.080 mmol, 80%).

$^1$H NMR (500 MHz, Chloroform-$d$) $\delta =$ 7.87 - 7.85 (m, 1H), 7.67 - 7.65 (m, 2H), 7.63 - 7.61 (m, 1H), 7.47 - 7.42 (m, 4H), 7.42 - 7.35 (m, 4H), 7.07 - 7.03 (m, 2H), 5.18 (s, 2H), 4.00 (d, $J = 1.6$ Hz, 2H).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta =$ 192.9, 164.5, 152.6, 136.2, 135.7, 135.4, 132.9, 131.8, 130.7, 129.5, 129.0, 128.9, 128.5, 127.6, 126.4, 116.1, 110.9, 70.6, 32.7.

HRMS (ESI): Calculated for C$_{23}$H$_{19}$O$_2$ ([M+H]$^+$): 327.1385; found: 327.1380

IR (neat) : $\nu =$ 1682 cm$^{-1}$

m.p.: 256 - 258°C (decomp.)

(E)-2-benzylidene-5-methyl-2,3-dihydro-1H-inden-1-one 4.108:

![Chemical structure of (E)-2-benzylidene-5-methyl-2,3-dihydro-1H-inden-1-one](attachment:image)

Chemical Formula: C$_{17}$H$_{14}$O

Exact Mass: 234.1045
Following the general procedure for the 1,4-Pd shift/C(sp³)-H activation, 4.108 was reacted with Pd(PCy₃)₂, pivalic acid, and Rb₂CO₃ in mesitylene at 160°C for 16 h. After purification, 4.108 was obtained as a white solid (11.5 mg, 0.050 mmol, 50%).

**1H NMR (400 MHz, Chloroform-d)** δ = 7.81 (d, J = 7.8 Hz, 1H), 7.71 – 7.63 (m, 3H), 7.51 – 7.42 (m, 2H), 7.44 – 7.37 (m, 1H), 7.37 – 7.33 (m, 1H), 7.28 – 7.20 (m, 1H), 4.01 (s, 2H), 2.48 (s, 3H).

**13C NMR (126 MHz, CDCl₃)** δ = 193.9, 150.1, 145.9, 135.8, 135.5, 135.2, 133.4, 130.6, 129.5, 128.9, 126.5, 124.3, 32.3, 22.3.

**HRMS (ESI):** Calculated for C₁₇H₁₅O ([M+H]⁺): 235.1123; found: 235.1117

**IR (neat):** ν = 1692, 1631, 1273 cm⁻¹

**m.p.:** 222 - 224°C (decomp.)

**Chemical Formula:** C₁₆H₁₅FO

**Exact Mass:** 238.0794

Following the general procedure for the 1,4-Pd shift/C(sp³)-H activation, 4.109 was reacted with Pd(PCy₃)₂, PCy₃, pivalic acid, and Rb₂CO₃ in mesitylene at 160°C for 16 h. After purification, 4.109 was obtained as a white solid (21 mg, 0.089 mmol, 89%).

The physical and spectroscopic properties matched those described in the literature.²¹

**1H NMR (400 MHz, Chloroform-d)** δ = 7.94 – 7.90 (m, 1H), 7.69 – 7.64 (m, 3H), 7.50 – 7.38 (m, 3H), 7.24 – 7.20 (m, 1H), 7.16 – 7.10 (m, 1H), 4.05 (s, 2H).

**13C NMR (101 MHz, CDCl₃)** δ = 192.7, 167.2 (d, J = 256.2 Hz), 152.5 (d, J = 10.1 Hz), 135.3, 134.6 (d, J = 1.9 Hz), 134.4, 134.2, 130.8, 129.9, 129.1, 126.9 (d, J = 10.2 Hz), 116.1 (d, J = 23.8 Hz), 113.1 (d, J = 22.9 Hz), 32.6 (d, J = 2.2 Hz).

**19F NMR (376 MHz, CDCl₃)** δ = -102.5.
(E)-5-amino-2-benzylidene-2,3-dihydro-1H-inden-1-one 4.110:

Chemical Formula: C_{16}H_{13}NO
Exact Mass: 235.0997

Following the general procedure for the 1,4-Pd shift/C(sp^3)-H activation, 4.110r (31.5 mg, 0.1 mmol, 1 equiv) was reacted with Pd(PCy)_3_2 (6.7 mg, 0.01 mmol, 10 mol%), PCy_3 (2.8 mg, 0.01 mmol, 10 mol%), pivalic acid (3.1 mg, 0.03 mmol, 30 mol%) and Rb_2CO_3 (35 mg, 0.15 mmol, 1.5 equiv) in mesitylene (4 mL) at 160°C for 16h. After purification, 4.110 was obtained as a white solid (14 mg, 0.060 mmol, 60%).

The physical and spectroscopic properties matched those described in the literature. 42

^1^H NMR (400 MHz, Chloroform-d) δ = 7.76 – 7.72 (m, 1H), 7.66 – 7.62 (m, 2H), 7.58 – 7.55 (m, 1H), 7.47 – 7.41 (m, 2H), 7.39 – 7.34 (m, 1H), 6.70 – 6.68 (m, 1H), 6.67 – 6.63 (m, 1H), 4.30 (br. s, 2H), 3.91 (d, J = 2.1 Hz, 2H).

^13^C NMR (101 MHz, CDCl_3) δ = 192.3, 152.9, 152.8, 135.9, 135.9, 131.7, 130.4, 129.2, 129.1, 128.8, 126.6, 114.9, 109.5, 32.3.
Checkcif for compound 4.84:

checkCIF/PLATON report

Structure factors have been supplied for datablock(s) RR2369_130K_0m

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No syntax errors found. CIF dictionary interpreting this report

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AbsCorr - MULTI-SCAN

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Click on the hyperlinks for more details of the test.

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0 ALERT level A = Most Likely a serious problem - resolve or explain
1 ALERT level B = A potentially serious problem, consider carefully
2 ALERT level C = Check. Ensure it is not caused by an omission or oversight
10 ALERT level G = General information/check it is not something unexpected

5 ALERT type 1 CIF construction/syntax error, inconsistent or missing data
3 ALERT type 2 Indicator that the structure model may be wrong or deficient
4 ALERT type 3 Indicator that the structure quality may be low
2 ALERT type 4 Improvement, methodology, query or suggestion
0 ALERT type 5 Informative message, check

### Validation response form

Please find below a validation response form (VRF) that can be filled in and pasted into your CIF.

```none
# start Validation Reply Form
_vrf_PLAT09_RR2369_130K_0m

PROBLEM: _diffrn_measured_fraction_theta full value Low . 0.968 Why?
RESPONSE: ...

_PROBLEM: Ratio of Maximum / Minimum Residual Density .... 2.14 Report
RESPONSE: ...

_PROBLEM: Large K Value in the Analysis of Variance .... 2.341 Check
RESPONSE: ...

_PROBLEM: Missing POF Refl Between Tmin & STH/Lc 0.000 6 Report
RESPONSE: ...
```

366
It is advisable to attempt to resolve as many as possible of the alerts in all categories. Often the minor alerts point to easily fixed oversights, errors and omissions in your CIF or refinement strategy, so attention to these fine details can be worthwhile. In order to resolve some of the more serious problems it may be necessary to carry out additional measurements or structure refinements. However, the purpose of your study may justify the reported deviations and the more serious of these should normally be commented upon in the discussion or experimental section of a paper or in the "special_details" fields of the CIF. checkCIF was carefully designed to identify outliers and unusual parameters, but every test has its limitations and alerts that are not important in a particular case may appear. Conversely, the absence of alerts does not guarantee there are no aspects of the results needing attention. It is up to the individual to critically assess their own results and, if necessary, seek expert advice.

Publication of your CIF in IUCr journals

A basic structural check has been run on your CIF. These basic checks will be run on all CIFs submitted for publication in IUCr journals (Acta Crystallographica, Journal of Applied Crystallography, Journal of Synchrotron Radiation); however, if you intend to submit to Acta Crystallographica Section C or E or IUCr Data, you should make sure that full publication checks are run on the final version of your CIF prior to submission.

Publication of your CIF in other journals

Please refer to the Notes for Authors of the relevant journal for any special instructions relating to CIF submission.

PLATON version of 19/10/2018; check.def file version of 15/10/2018

[Diagram of a molecule with atomic labels and coordinates]
Chapter 2.2: Redox-neutral Coupling between Two
C(sp³)–H Bonds Enabled by 1,4-Palladium Shift for the
Synthesis of Fused Heterocycles

General information:

Techniques
All reactions involving air-sensitive material were carried out in pre-dried glassware under an argon atmosphere by using Schlenk techniques employing double-line argon-vacuum lines and working in an argon-filled glove box. Analytical thin layer chromatography (TLC) was performed using pre-coated Merck silica gel 60 F254 plates (0.25 mm). Visualization of the developed chromatogram was performed by UV absorbance (254 nm) or TLC stains (KMnO₄ and Phosphomolybdic acid). Flash chromatography was performed using Silicycle SiliaFlash P60 (230-400 mesh) with the indicated eluent system, using gradients of increasing polarity in most cases.

Chemicals
Anhydrous THF, DMF, DCM, toluene were purchased from Acros Organics or Sigma-Aldrich. The solvents were degassed by three cycles of freeze-pump-thaw and storing in single-necked flasks equipped with a J-Young PTFE valve when necessary. Pd(PCy₃)₂ was synthesized from known procedure. All other chemical reagents were purchased from Sigma-Aldrich, Acros Organics, Fisher, and Fluorochem and used as received without further purification unless otherwise stated.

Instrumentation
Preparative HPLC was performed using a preparative Shimadzu HPLC system with a Gemini 10 μm NX-C18, LC Column 150 × 30mm.
Melting points were obtained on a Büchi B-565, and are uncorrected. IR spectra were recorded on an ATR Varian Scimitar 800 and are reported in reciprocal centimeters (cm⁻¹).
Nuclear magnetic resonance spectra were recorded on a Bruker Advance 400 (400 MHz), on a Bruker Advance 500 (500 MHz) or a Bruker Advance 600 (600 MHz) in deuterated chloroform S4 (residual peaks IH δ 7.26 ppm, 13C δ 77.16 ppm) unless otherwise noted. ¹⁹F NMR spectra were referenced to external CFCl₃. Data are reported in parts per million (ppm) as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintuplet, sept = septuplet, m = multiplet and br. s = broad singlet), coupling constant in Hz
and integration. High resolution mass spectra were recorded by Dr. M. Pfeffer (Department of Chemistry, University of Basel) on a Bruker maXis 4G QTOF ESI mass spectrometer.
General procedures:

**GENERAL PROCEDURE A FOR BROMINATION OF PHENOLS:**

To a 1M solution of phenol (1 equiv) in DMF was added dropwise a 1M solution of NBS (1.1 equiv) in DMF. The reaction evolution was followed by TLC using cyclohexane/AcOEt as eluent. After completion, the mixture was quenched with water, and extracted with Et₂O. The combined organic layers were washed with brine, dried over sodium sulfate, filtered and evaporated. The crude mixture was used without further purification or purified by chromatography on silica gel using cyclohexane/AcOEt as eluent to afford the pure brominated phenols.

**GENERAL PROCEDURE B FOR METHYLATION OF PHENOLS:**

Phenols were dissolved in acetone or DMF as precised (0.1M), followed by addition of K₂CO₃ (1.5 equiv) and MeI (3 equiv). The mixture was stirred until completion. Volatiles were removed under vacuum and the crude mixture was extracted with DCM, washed with water and brine, dried over sodium sulfate, filtered and evaporated. The methylated phenols were purified by chromatography on silica gel using cyclohexane/AcOEt as eluent to afford the pure compounds.

**GENERAL PROCEDURE C FOR BROMINATION OF ANILINES:**

Anilines (1 equiv) were dissolved in DCM (0.12 M) and NBS (1.1 equiv) was added portionwise to the stirred solution. After completion, the reaction was quenched with water, and extracted with DCM. The combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum. The crude mixture was purified by chromatography on silica gel using cyclohexane/AcOEt as eluent to afford the pure brominated anilines.

**GENERAL PROCEDURE D FOR TRIFLUOROACETYlation OF ANILINES:**

Anilines (1 equiv) were dissolved in 1,2-dichloroethane (0.2 M) followed by addition of DMAP (0.05 equiv) and trifluoroacetic anhydride (2 equiv). After completion, the reaction was quenched with water, extracted with DCM, and the combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum. Trifluoroacetylanilines were purified by chromatography on silica gel using cyclohexane/AcOEt as eluent.
GENERAL PROCEDURE E FOR METHYLATION OF ANILINES:

Anilines (1 equiv) were dissolved in dry THF (0.12 M) or dry DMF (0.12 M) as specified under argon atmosphere and NaH (60% dispersion in oil, 3 equiv) was added portionwise. The reaction was stirred for 5 minutes, followed by addition of MeI (3 equiv). After completion, the reaction was carefully quenched with water. The aqueous phase was then extracted with AcOEt, and the combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum. The crude mixture was purified by chromatography on silica gel using cyclohexane/AcOEt as eluent.

Note: In case of deprotection of the aniline during methylation step, the obtained methylated aniline was treated with trifluoroacetic anhydride (2 equiv), and DMAP (0.05 equiv) in 1,2-dichloroethane (0.2 M). The crude mixture was quenched with water, extracted with DCM, and the combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum. Anilines could then be used without further purification.

GENERAL PROCEDURE F FOR KETONE SYNTHESIS:

Aldehydes (1 equiv) were dissolved in dry THF (0.2 M) under argon and cooled to -78°C. Then, a solution of Grignard reagent (2 equiv) was added dropwise. After addition, the cooling bath was removed and the reaction was further stirred for one hour at room temperature. The reaction was then quenched with water, and extracted with AcOEt. The combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum. The crude mixture secondary alcohols were then dissolved in DCM (0.1 M), followed by addition of PCC (2.5 equiv) and celite (1 g celite for 1 g PCC). The mixture was stirred overnight, filtered through celite, evaporated over vacuum and purified by chromatography on silica gel using cyclohexane/AcOEt as eluent.

GENERAL PROCEDURE G FOR THE DIHYDROBENZOFURANS SYNTHESIS:

In a 10 mL screw cap charged with substrate (0.15 mmol, 1 equiv) was weighted in a glovebox Pd(PCy₃)₂ (10 mg, 0.015 mmol, 10 mol %), and cesium pivalate (35 mg, 0.15 mmol, 1 equiv) The vial was charged with toluene (6 mL) and stirred under argon in a heating block preheated at 140 °C or (160°C as mentioned) for 16 h. The reaction was cooled to room temperature, filtered through celite, and evaporated under vacuum. The crude mixture was analysed by ¹H NMR and purified by chromatography on silica gel to afford the pure compounds.
**GENERAL PROCEDURE H FOR INDOLINES SYNTHESIS:**

In a 10 mL screw cap charged with substrate (0.15 mmol, 1 equiv) was weighted in a glovebox Pd(PCy$_3$)$_2$ (10 mg, 0.015 mmol, 10 mol %), AdCO$_2$H (8.1 mg, 0.45 mmol, 30 mol %) and Rb$_2$CO$_3$ (52 mg, 0.23 mmol, 1.5 equiv). The vial was charged with toluene (6 mL) and stirred under argon in a heating block preheated at 160 °C for 16 h. The reaction was cooled to room temperature, filtered through celite, and evaporated under vacuum. The crude mixture was analysed by $^1$H NMR and purified by chromatography on silica gel to afford the pure compounds.

**GENERAL PROCEDURE I FOR THE CHROMANONES SYNTHESIS:**

In a 10 mL screw cap charged with substrate (0.15 mmol, 1 equiv) was weighted in a glovebox Pd(PCy$_3$)$_2$ (10 mg, 0.015 mmol, 10 mol %), AdCO$_2$H (8.1 mg, 0.45 mmol, 30 mol %) and Cs$_2$CO$_3$ (49 mg, 1 equiv, 0.15 mmol). The vial was charged with toluene (6 mL) and stirred under argon in a heating block preheated at 120 °C for 16 h. The reaction was cooled to room temperature, filtered through celite, and evaporated under vacuum. The crude mixture was analysed by $^1$H NMR and purified by chromatography on silica gel to afford the pure compounds.

**GENERAL PROCEDURE J FOR NUCLEOPHILIC ADDITION:**

In a 10 mL screw cap charged with substrate (0.15 mmol, 1 equiv) was weighted in a glovebox Pd(PCy$_3$)$_2$ (10 mg, 0.015 mmol, 10 mol %) and CsOPiv (105 mg, 3 equiv, 0.45 mmol). The vial was charged with toluene (6 mL) and stirred under argon in a heating block preheated at 160 °C for 16 h. The reaction was cooled to room temperature, filtered through celite, and evaporated under vacuum. The crude mixture was analysed by $^1$H NMR and purified by preparative HPLC to afford the pure compounds. $^1$H NMR was performed in C$_6$D$_6$ to avoid elimination product. Elimination products were obtained after leaving the tertiary alcohol in “old” CDCl$_3$ for 24h and extracted with CHCl$_3$, dried over sodium sulfate, filtered and evaporated under vacuum.
Optimizations tables:

**Benzofurans:**

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Additive (equiv.)</th>
<th>Base (equiv.)</th>
<th>T°C</th>
<th>NMR yield * (isolated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CsOPiv (30 mol%)</td>
<td>Cs₂CO₃ (1 equiv)</td>
<td>120°C</td>
<td>Traces</td>
</tr>
<tr>
<td>CsOPiv (30 mol%)</td>
<td>Rb₂CO₃ (1 equiv)</td>
<td>120°C</td>
<td>20%</td>
</tr>
<tr>
<td>CsOPiv (1 equiv)</td>
<td>-</td>
<td>120°C</td>
<td>25%</td>
</tr>
<tr>
<td>CsOPiv (3 equiv)</td>
<td>-</td>
<td>120°C</td>
<td>25%</td>
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<tr>
<td>CsOPiv (1 equiv)</td>
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<td>140°C</td>
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</tbody>
</table>

*Using trichloroethylene as internal standard

**Indolines:**

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Additive (equiv.)</th>
<th>Base (equiv.)</th>
<th>T°C</th>
<th>NMR yield* (isolated)</th>
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</thead>
<tbody>
<tr>
<td>CsOPiv (1 equiv)</td>
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<td>160°C</td>
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</tr>
<tr>
<td>PivOH (30 mol%)</td>
<td>Cs₂CO₃ (1.5 equiv)</td>
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<td>0%</td>
</tr>
<tr>
<td>PivOH (30 mol%)</td>
<td>Rb₂CO₃ (1.5 equiv)</td>
<td>160°C</td>
<td>23%</td>
</tr>
<tr>
<td>AdCO₂H (30 mol%)</td>
<td>Rb₂CO₃ (1.5 equiv)</td>
<td>160°C</td>
<td>72% (74%)</td>
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</tbody>
</table>

*Using trichloroethylene as internal standard
Chromanones:

\[
\text{Additive (equiv.)} \quad \text{Base (equiv.)} \quad T^\circ\text{C} \quad \text{NMR yield* (isolated)}
\]

<table>
<thead>
<tr>
<th>Additive (equiv.)</th>
<th>Base (equiv.)</th>
<th>T°C</th>
<th>NMR yield* (isolated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PivOH (30 mol%)</td>
<td>Rb₂CO₃ (1.5 equiv)</td>
<td>120°C</td>
<td>35%</td>
</tr>
<tr>
<td>PivOH (30 mol%)</td>
<td>Rb₂CO₃ (1 equiv)</td>
<td>120°C</td>
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</tr>
<tr>
<td>AdCO₂H (30 mol%)</td>
<td>Rb₂CO₃ (1 equiv)</td>
<td>120°C</td>
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<td>AdCO₂H (30 mol%)</td>
<td>Cs₂CO₃ (1 equiv)</td>
<td>120°C</td>
<td>71% (72%)</td>
</tr>
</tbody>
</table>

*Using trichloroethylene as internal standard

Nucleophilic addition:

\[
\text{Additive (equiv.)} \quad \text{Base (equiv.)} \quad T^\circ\text{C} \quad \text{NMR yield* (isolated)}
\]

<table>
<thead>
<tr>
<th>Additive (equiv.)</th>
<th>Base (equiv.)</th>
<th>T°C</th>
<th>NMR yield* (isolated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PivOH (30 mol%)</td>
<td>Cs₂CO₃ (1.5 equiv)</td>
<td>160°C</td>
<td>10%</td>
</tr>
<tr>
<td>PivOH (30 mol%)</td>
<td>Rb₂CO₃ (1.5 equiv)</td>
<td>160°C</td>
<td>18%</td>
</tr>
<tr>
<td>PivOH (3 equiv)</td>
<td>Cs₂CO₃ (3 equiv)</td>
<td>160°C</td>
<td>50%</td>
</tr>
<tr>
<td>CsOPiv (1.5 equiv)</td>
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<td>160°C</td>
<td>40%</td>
</tr>
<tr>
<td>CsOPiv (3 equiv)</td>
<td>-</td>
<td>160°C</td>
<td>77% (69%)</td>
</tr>
</tbody>
</table>

*Using trichloroethylene as internal standard
Synthesis of substrates:

**methyl 3-bromo-4-methoxy-5-methylbenzoate 5.39:**

![Chemical structure](image)

**Chemical Formula:** C_{10}H_{11}BrO_{3}
**Exact Mass:** 257.9892

Following General procedure A for bromination of phenols methyl 4-hydroxy-3-methylbenzoate (997 mg, 6.0 mmol, 1 equiv) was reacted with NBS (1.17 g, 6.6 mmol, 1.1 equiv) in DMF. After quenching with water, the crude mixture was extracted with Et_{2}O, and the combined organic layers were washed with brine, and purified by chromatography on silica gel using cyclohexane/AcOEt [9:1] to afford the phenol (910 mg, 3.7 mmol, 62%).

Following General procedure B for methylation of phenols, methyl 3-bromo-4-hydroxy-5-methylbenzoate (910 mg, 3.7 mmol, 1 equiv), K_{2}CO_{3} (770 mg, 5.6 mmol, 1.5 equiv) and MeI (0.69 mL, 11.1 mmol, 3 equiv) were reacted in acetone. After evaporation, extraction and purification, the desired product 5.39 was obtained as a colorless oil (770 mg, 2.97 mmol, 80%).

**^{1}H NMR (400 MHz, Chloroform-d) δ =** 8.10 – 8.08 (m, 1H), 7.84 – 7.82 (m, 1H), 3.92 (s, 3H), 3.87 (s, 3H), 2.38 (s, 3H).

**^{13}C NMR (101 MHz, CDCl_{3}) δ =** 165.8, 159.4, 133.4, 132.7, 131.9, 127.1, 117.4, 60.4, 52.4, 16.8.

**HRMS (ESI):** Calculated for C_{10}H_{12}BrO_{3} ([M+H]^{+}): 258.9970; found: 258.9973

**IR (neat):** ν = 1766 cm^{-1}

**1-bromo-2-methoxy-3-methylbenzene 5.46:**

![Chemical structure](image)
Following General procedure B for methylation of phenols, 2-bromo-6-methylphenol (436 mg, 2.33 mmol, 1 equiv), K\(_2\)CO\(_3\) (483 mg, 3.49 mmol, 1.5 equiv) and MeI (0.43 mL, 7.0 mmol, 3 equiv) were reacted in acetone. After evaporation, extraction and purification, the desired product 5.46r was obtained as a yellowish oil (460 mg, 2.30 mmol, 98%).

\(^1\)H NMR (400 MHz, Chloroform-\(d\)) \(\delta = 7.40 – 7.35 \text{(m, 1H)}, 7.14 – 7.09 \text{(m, 1H)}, 6.91 – 6.86 \text{(m, 1H)}, 3.82 \text{(s, 3H)}, 2.33 \text{(s, 3H)}\).

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta = 155.5, 133.4, 131.2, 130.5, 125.3, 117.5, 60.3, 16.7\).

1-bromo-5-fluoro-2-methoxy-3-methylbenzene 5.46r:

Following General procedure A for bromination of phenols, 4-fluoro-2-methylphenol (1.26 g, 10.0 mmol, 1 equiv) was reacted with NBS (1.96 g, 11 mmol, 1.1 equiv) in DMF. After quenching with water, the crude mixture was extracted with Et\(_2\)O, and the combined organic layers were washed with brine, and purified by chromatography on silica gel using cyclohexane/ACOEt [9:1] to afford the phenol (1.45 g, 7.0 mmol, 70%).

Following General procedure B for methylation of phenols, 2-bromo-4-fluoro-6-methylphenol (1.45 g, 7.0 mmol, 1 equiv), K\(_2\)CO\(_3\) (1.45 g, 10.5 mmol, 1.5 equiv) and MeI (1.3 mL, 21.0 mmol, 3 equiv) were reacted in acetone. After evaporation, extraction and purification, the desired product was obtained as a yellowish oil (1.08 g, 4.93 mmol, 70%).

\(^1\)H NMR (400 MHz, Chloroform-\(d\)) \(\delta = 7.16 – 7.11 \text{(m, 1H)}, 6.89 – 6.85 \text{(m, 1H)}, 3.80 \text{(s, 3H)}, 2.34 \text{(s, 3H)}\).
\[^{13}\text{C}\ NMR\ (101\ \text{MHz, Chloroform-}	ext{d})\ \delta = 158.4\ (d,\ J = 246.0\ \text{Hz}),\ 151.9\ (d,\ J = 3.2\ \text{Hz}),\ 134.4\ (d,\ J = 8.5\ \text{Hz}),\ 117.8\ (d,\ J = 25.5\ \text{Hz}),\ 117.3\ (d,\ J = 10.8\ \text{Hz}),\ 117.0\ (d,\ J = 22.2\ \text{Hz}),\ 60.5\ (d,\ J = 1.5\ \text{Hz}),\ 16.9\ (d,\ J = 1.5\ \text{Hz}).\]

\[^{19}\text{F}\ NMR\ (376\ \text{MHz, CDCl}_3)\ \delta = -117.6.\]

\textbf{HRMS\ (ESI):}\ \text{Calculated\ for\ C}_8\text{H}_9\text{BrFO\ ([M+H]}^+)\ :\ 218.9821;\ \text{found:}\ 218.9824

\textbf{IR\ (neat)}:\ \nu = 1245\ \text{cm}^{-1}

\textbf{3-bromo-4-methoxy-5-methylbenzaldehyde 5.45r:} 45

\begin{center}
\includegraphics[width=0.2\textwidth]{image.png}
\end{center}

\text{Chemical\ Formula: C}_9\text{H}_8\text{BrO}_2 \text{Exact\ Mass: 227.9786}

Following General procedure A for bromination of phenols, 4-hydroxy-3-methylbenzaldehyde (820 mg, 6.0 mmol, 1 equiv) was reacted with NBS (1.17 g, 6.6 mmol, 1.1 equiv) in DMF. After quenching with water, the crude mixture was extracted with Et\textsubscript{2}O, and the combined organic layers were washed with brine, and purified by chromatography on silica gel using cyclohexane/ACOEt [9:1] to afford the phenol (645 mg, 3.0 mmol, 50%).

Following General procedure B for methylation of phenols, 3-bromo-4-hydroxy-5-methylbenzaldehyde (645 mg, 3.0 mmol, 1 equiv), K\textsubscript{2}CO\textsubscript{3} (622 mg, 4.5 mmol, 1.5 equiv) and MeI (0.55 mL, 9.0 mmol, 3 equiv) were reacted in DMF. After evaporation, extraction and purification, the desired product was obtained as a colorless oil (285 mg, 1.24 mmol, 42 %).

\[^{1}\text{H}\ NMR\ (400\ \text{MHz, Chloroform-}	ext{d})\ \delta = 9.86\ (s,\ 1\text{H}),\ 7.93 – 7.91\ (m,\ 1\text{H}),\ 7.67 – 7.65\ (m,\ 1\text{H}),\ 3.88\ (s,\ 3\text{H}),\ 2.40\ (s,\ 3\text{H}).\]

\[^{13}\text{C}\ NMR\ (101\ \text{MHz, CDCl}_3)\ \delta = 190.2,\ 160.7,\ 134.4,\ 133.5,\ 133.0,\ 131.8,\ 118.4,\ 60.5,\ 16.8.\]

\textbf{methyl 4-bromo-3-methoxy-2-methylbenzoate 5.48r:} 46

378
In a 250 mL round bottom flask, toluene (50 mL) and tBuNH$_2$ (1.2 mL, 11.4 mmol, 1.9 equiv) were stirred and cooled to -78°C. Bromine (0.29 mL, 5.72 mmol, 0.95 equiv) in toluene (5 mL) was then slowly added to the stirred mixture, which was further reacted for 1h at this temperature. methyl 3-hydroxy-2-methylbenzoate (1 g, 6 mmol, 1 equiv) in dichloromethane (30 mL) was then added slowly to the mixture, which was warm to room temperature over 5h. The reaction was quenched with water (60 mL) and extracted with DCM (3 x 30 mL) and the combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum. The crude mixture was purified by chromatography on silicagel to afford the brominated product (420 mg, 1.71 mmol, 28 %).

Following general procedure B for methylation of phenols, intermediate phenol ester (120 mg, 0.49 mmol, 1 equiv) was reacted with K$_2$CO$_3$ (102 mg, 0.74 mmol, 1.5 equiv) and MeI (0.1 mL, 1.47 mmol, 3 equiv) in DMF. After extraction and purification, methoxy phenol was obtained (112 mg, 0.43 mmol, 88%).

$^1$H NMR (400 MHz, Chloroform-d) $\delta$ = 7.52 – 7.49 (m, 1H), 7.45 – 7.42 (m, 1H), 3.89 (s, 3H), 3.80 (s, 3H), 2.56 (s, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ = 167.5, 156.1, 135.6, 131.1, 130.5, 127.2, 122.2, 60.5, 52.2, 14.2.

**methyl 2-(2-bromo-6-methylphenoxy)acetate**

Following general procedure for alkylation of phenols, 2-bromo-6-methylphenol (500 mg, 2.67 mmol, 1 equiv), K$_2$CO$_3$ (557 mg, 4.0 mmol, 1.5 equiv) and methyl 2-bromoacetate (0.76 mL,
8.0 mmol, 3 equiv) were reacted in DMF. After evaporation, extraction and purification, the desired product was obtained as a colorless oil (600 mg, 2.32 mmol, 86 %).

\(^1\text{H NMR (400 MHz, Chloroform-}d\text{)} \delta = 7.38 – 7.35 (m, 1H), 7.14 – 7.10 (m, 1H), 6.94 – 6.89 (m, 1H), 4.56 (s, 2H), 3.84 (s, 3H), 2.35 (s, 3H).

\(^{13}\text{C NMR (101 MHz, CDCl}_3\text{)} \delta = 169.1, 153.6, 133.5, 131.3, 130.6, 126.0, 116.9, 69.1, 52.3, 16.8.

HRMS (ESI): Calculated for C\(_{10}\)H\(_{12}\)BrO\(_3\) ([M+H]\(^+\)): Exact Mass: 258.9970; found: 258.9964

IR (neat): \(\nu = 1764, 1461, 1207\) cm\(^{-1}\)

**methyl 2-(3-bromo-2-methoxyphenyl)acetate 5.49r:**

\[
\begin{align*}
\text{CO}_2\text{Me} & \quad \rightarrow \quad \text{CO}_2\text{Me} \\
\text{Br} & \quad \rightarrow \quad \text{Br} \\
\text{Chemical Formula: C}_{10}\text{H}_{11}\text{BrO}_3 \\
\text{Exact Mass: 257.9892}
\end{align*}
\]

In a 250 mL round bottom flask, toluene (60 mL) and tBuNH\(_2\) (1.9 mL, 18 mmol, 1.5 equiv) were stirred and cooled to -78°C. Bromine (0.5 mL, 9.6 mmol, 0.8 equiv) in toluene (5 mL) was then slowly added to the stirred mixture, which was further reacted for 1h at this temperature. Methyl 2-(2-hydroxyphenyl)acetate (2 g, 12 mmol, 1 equiv) in dichloromethane (30 mL) was then added slowly to the mixture, which was cooled to room temperature over 5h. The reaction was quenched with water (60 mL) and extracted with DCM (3 x 30 mL) and the combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum. The crude mixture was purified by chromatography on silicagel to afford a mixture of mono/dibrominated product (80/20) (1.25 g, 5.1 mmol, 53 %).

Following general procedure B for methylation of phenols, intermediate phenol ester mixture (80/20) (490 mg, 2 mmol, 1 equiv) was reacted with K\(_2\)CO\(_3\) (415 mg, 3 mmol, 1.5 equiv) and MeI (0.37 mL, 6 mmol, 3 equiv) in DMF. After extraction and purification, methoxy phenol was obtained (370 mg, 1.43 mmol, 71%).

\(^1\text{H NMR (400 MHz, Chloroform-}d\text{)} \delta = 7.50 – 7.45 (m, 1H), 7.21 – 7.18 (m, 1H), 6.99 – 6.94 (m, 1H), 3.84 (s, 3H), 3.71 (s, 3H), 3.70 (s, 2H).
\[ ^{13}C \text{ NMR (101 MHz, CDCl}_3 \] \( \delta = 171.8, 155.6, 133.0, 130.5, 130.0, 125.5, 117.4, 61.1, 52.3, 36.0. \]

**methyl 2-(3-bromo-5-fluoro-2-methoxyphenyl)acetate 5.50r:**

\[
\text{Chemical Formula: } C_{10}H_{10}BrFO_3 \\
\text{Exact Mass: } 275.9797
\]

In a 50 mL flask was charged 2-(5-fluoro-2-hydroxyphenyl)acetic acid (500 mg, 2.94 mmol, 1 equiv) in methanol (10 mL). Then, SOCl\(_2\) (2.13 mL, 29.4 mmol, 10 equiv) was added dropwise to the mixture, which was stirred to reflux for 2 h. The volatiles were removed under vacuum, and the crude mixture was quenched with NaOH 3M (30 mL) and extracted with Et\(_2\)O (3 x 15 mL). The combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum. The desired product methyl-ester product was obtained and used without further purification (540 mg, 2.94 mmol, 99%).

Following General procedure A for bromination of phenols, methyl 2-(5-fluoro-2-methoxyphenyl)acetate (220 mg, 1.11 mmol, 1 equiv) was reacted with NBS (395 mg, 2.2 mmol, 2 equiv) in DMF at 70°C. After quenching with water, the crude mixture was extracted with Et\(_2\)O, and the combined organic layers were washed with brine, and purified by chromatography on silica gel using cyclohexane/AcOEt [9:1] to afford the phenol (235 mg, 0.85 mmol, 76%).

Following general procedure for methylation of phenol, intermediate phenol ester mixture (80/20) (235 mg, 0.85 mmol, 1 equiv) was reacted with K\(_2\)CO\(_3\) (250 mg, 3 mmol, 1.5 equiv) and MeI (0.15 mL, 2.5 mmol, 3 equiv) in DMF. After extraction and purification, methoxy phenol was obtained (208 mg, 0.71 mmol, 83%).

\[ ^1H \text{ NMR (400 MHz, Chloroform-d) } \delta = 7.24 – 7.18 (m, 1H), 6.99 – 6.95 (m, 1H), 3.81 (s, 3H), 3.73 (s, 3H), 3.69 (s, 2H). \]

\[ ^{13}C \text{ NMR (126 MHz, Chloroform-d) } \delta = 171.2, 158.4 (d, J = 247.1 Hz), 152.1 (d, J = 3.3 Hz), 130.7 (d, J = 8.7 Hz), 119.8 (d, J = 25.4 Hz), 117.4 (d, J = 10.6 Hz), 117.2 (d, J = 22.9 Hz), 61.3 (d, J = 1.4 Hz), 52.4, 35.9 (d, J = 1.5 Hz). \]
\[^{19}\text{F} \text{NMR (376 MHz, Chloroform-d) } \delta = -116.7 \text{ (dd, } J = 8.5, 7.6 \text{ Hz).} \]

**HRMS (ESI):** Calculated for C\(_{10}\)H\(_{11}\)BrFO\(_3\) ([M+H]\(^{+}\)): 276.9876; found: 276.9879

**IR (neat):** \(\nu = 1768, 1459 \text{ cm}^{-1}\)

2-(3-bromo-2-methoxyphenyl)-N,N-diisopropylacetamide 5.51r:

In a 250 mL round bottom flask, toluene (60 mL) and \( t\text{BuNH}_2 \) (1.9 mL, 18 mmol, 1.5 equiv) were stirred and cooled to -78°C. Bromine (0.5 mL, 9.6 mmol, 0.8 equiv) in toluene (5 mL) was then slowly added to the stirred mixture, which was further reacted for 1h at this temperature. Methyl 2-(2-hydroxyphenyl)acetate (2 g, 12 mmol, 1 equiv) in dichloromethane (30 mL) was then added slowly to the mixture, which was cooled to room temperature over 5h. The reaction was quenched with water (60 mL) and extracted with DCM (3 x 30 mL) and the combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum. The crude mixture was purified by chromatography on silicagel to afford a mixture of mono/dibrominated product (80/20) (1.25 g, 5.1 mmol, 53 %).

Following general procedure B for methylation of phenols, intermediate phenol ester mixture (80/20) (490 mg, 2 mmol, 1 equiv) was reacted with K\(_2\)CO\(_3\) (415 mg, 3 mmol, 1.5 equiv) and MeI (0.37 mL, 6 mmol, 3 equiv) in DMF. After extraction and purification, methoxy phenol was obtained (370 mg, 1.43 mmol, 71%).
Methyl ester intermediate (181 mg, 0.7 mmol, 1 equiv) was dissolved in THF/water [3:1] (10 mL) followed by addition of LiOH (84 mg, 3.5 mmol, 5 equiv) and heated at 80°C for 2h. After cooling to room temperature, the crude mixture was quenched with 2 M HCl, extracted with AcOEt (3 x 5 mL) and the combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum. The carboxylic acid was used without further purification (170 mg, 0.7 mmol, 100%).

To this carboxylic acid (75 mg, 0.3 mmol, 1 equiv) in dichloromethane (5 mL) was added oxalyl chloride (0.06 mL, 0.6 mmol, 2 equiv). The mixture was stirred for 1h, before volatiles were removed under vacuum. Then, the acid chloride was redissolved in dichloromethane (5 mL) followed by addition of diisopropylamine (0.09 mL, 0.6 mmol, 2 equiv) and Et3N (0.08 mL, 0.6 mmol, 2 equiv) in dichloromethane (2 mL). After completion, the mixture was quenched with water (5 mL), extracted with dichloromethane (3 x 5 mL) and the combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum. The crude mixture was purified under vacuum to afford the desired product as a yellow oil (71 mg, 0.22 mmol, 72%).

^1H NMR (400 MHz, Chloroform-d) δ = 7.46 – 7.41 (m, 1H), 7.24 – 7.19 (m, 1H), 6.99 – 6.90 (m, 1H), 3.93 (sept, J = 6.7 Hz, 1H), 3.81 (s, 3H), 3.72 (s, 2H), 3.42 (br. s, 1H), 1.40 (d, J = 6.8 Hz, 6H), 1.08 (d, J = 6.7 Hz, 6H).

^13C NMR (101 MHz, CDCl3) δ = 169.6, 154.8, 132.3, 131.7, 129.7, 125.6, 117.3, 61.0, 46.0, 37.3, 20.8, 20.7.

HRMS (ESI): Calculated for C_{15}H_{23}BrNO_2 ([M+H]^+): Exact Mass: 328.0912; found: 328.0907

IR (neat): ν = 1641, 1443 cm\(^{-1}\)

2-(3-bromo-2-methoxyphenyl)-1-morpholinoethan-1-one 5.52r:
In a 250 mL round bottom flask, toluene (60 mL) and tBuNH₂ (1.9 mL, 18 mmol, 1.5 equiv) were stirred and cooled to -78°C. Bromine (0.5 mL, 9.6 mmol, 0.8 equiv) in toluene (5 mL) was then slowly added to the stirred mixture, which was further reacted for 1h at this temperature. Methyl 2-(2-hydroxyphenyl)acetate (2 g, 12 mmol, 1 equiv) in dichloromethane (30 mL) was then added slowly to the mixture, which was cooled to room temperature over 5h. The reaction was quenched with water (60 mL) and extracted with DCM (3 x 30 mL) and the combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum. The crude mixture was purified by chromatography on silicagel to afford a mixture of mono/dibrominated product (80/20) (1.25 g, 5.1 mmol, 53 %).

Following general procedure B for methylation of phenols, intermediate phenol ester mixture (80/20) (490 mg, 2 mmol, 1 equiv) was reacted with K₂CO₃ (415 mg, 3 mmol, 1.5 equiv) and MeI (0.37 mL, 6 mmol, 3 equiv) in DMF. After extraction and purification, methoxy phenol was obtained (370 mg, 1.43 mmol, 71%).

Methyl ester intermediate (181 mg, 0.7 mmol, 1 equiv) was dissolved in THF/water [3:1] (10 mL) followed by addition of LiOH (84 mg, 3.5 mmol, 5 equiv) and heated at 80°C for 2h. After cooling to room temperature, the crude mixture was quenched with 2 M HCl, extracted with AcOEt (3 x 5 mL) and the combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum. The carboxylic acid was used without further purification (170 mg, 0.7 mmol, 100%).
To this carboxylic acid (75 mg, 0.3 mmol, 1 equiv) in dichloromethane (5 mL) was added oxalyl chloride (0.06 mL, 0.6 mmol, 2 equiv). The mixture was stirred for 1h, before volatiles were removed under vacuum. Then, the acid chloride was redissolved in dichloromethane (5 mL) followed by addition of morpholine (0.06 mL, 0.6 mmol, 2 equiv) and Et₃N (0.08 mL, 0.6 mmol, 2 equiv) in dichloromethane (2 mL). After completion, the mixture was quenched with water (5 mL), extracted with dichloromethane (3 x 5 mL) and the combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum. The crude mixture was purified under vacuum to afford the desired product as a colorless oil (86 mg, 0.27 mmol, 89%).

$^{1}$H NMR (400 MHz, Chloroform-d) δ = 7.48 – 7.44 (m, 1H), 7.24 – 7.21 (m, 1H), 7.00 – 6.94 (m, 1H), 3.82 (s, 3H), 3.76 (s, 2H), 3.64 (s, 4H), 3.54 – 3.51 (m, 2H), 3.45 – 3.41 (m, 2H).

$^{13}$C NMR (101 MHz, CDCl₃) δ = 169.4, 154.7, 132.7, 130.6, 129.6, 125.8, 117.4, 66.9, 66.7, 61.1, 46.5, 42.4, 34.9.

HRMS (ESI): Calculated for C₁₃H₁₇BrNO₃ ([M+H]⁺): Exact Mass: 314.0386; found: 314.0392

IR (neat): ν = 1644, 1426 cm⁻¹

**methyl 2-(3-bromo-2-(2-methoxy-2-oxoethoxy)phenyl)acetate 5.54r:**

In a 250 mL round bottom flask, toluene (60 mL) and tBuNH₂ (1.9 mL, 18 mmol, 1.5 equiv) were stirred and cooled to -78°C. Bromine (0.5 mL, 9.6 mmol, 0.8 equiv) in toluene (5 mL) was then slowly added to the stirred mixture, which was further reacted for 1h at this temperature. Methyl 2-(2-hydroxyphenyl)acetate (2 g, 12 mmol, 1 equiv) in dichloromethane (30 mL) was then added slowly to the mixture, which was cooled to room temperature over 5h. The reaction was quenched with water (60 mL) and extracted with DCM (3 x 30 mL) and the combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum. The crude mixture was purified by chromatography on silicagel to afford a mixture of mono/dibrominated product (80/20) (1.25 g, 5.1 mmol, 53%).
Following general procedure B for alkylation of phenols, the mixture of mono/dibrominated phenol (80/20) (250 mg, 1 mmol, 1 equiv) was reacted with K₂CO₃ (211 mg, 1.5 mmol, 1.5 equiv) and methylbromoacetate (0.29 mL, 3 mmol, 3 equiv) in DMF. After extraction and purification, the product was obtained as a colorless oil (250 mg, 0.77 mmol, 77%).

**¹H NMR (400 MHz, Chloroform-d)**  δ = 7.50 – 7.46 (m, 1H), 7.21 – 7.18 (m, 1H), 7.02 – 6.97 (m, 1H), 4.69 (s, 2H), 3.84 (s, 2H), 3.82 (s, 3H), 3.69 (s, 3H).

**¹³C NMR (101 MHz, CDCl₃)**  δ = 172.0, 169.3, 154.2, 133.1, 130.6, 130.2, 126.1, 116.9, 70.0, 52.3, 52.2, 35.9.

**5,5’-(propane-2,2-diyl)bis(l-bromo-2-methoxy-3-methylbenzene) 5.55r:**

![Chemical structure](https://example.com/structure.png)

Chemical Formula: C₁₉H₂₂Br₂O₂
Exact Mass: 439.9987

Following General procedure A for bromination of phenols, 4,4’-(propane-2,2-diyl)bis(2-methylphenol) (1 g, 3.9 mmol, 1 equiv) was reacted with NBS (1.52 g, 8.6 mmol, 1.1 equiv) in DMF. After quenching with water, the crude mixture was extracted with Et₂O, and the combined organic layers were washed with brine, and purified by chromatography on silica gel using cyclohexane/AcOEt [9:1] to afford the phenol (880 mg, 2.12 mmol, 55%).

Following General procedure B for methylation of phenols, 4,4’-(propane-2,2-diyl)bis(2-bromo-6-methylphenol) (400 mg, 0.96 mmol, 1 equiv), K₂CO₃ (400 mg, 2.9 mmol, 3 equiv) and MeI (0.36 mL, 5.8 mmol, 6 equiv) were reacted in acetone. After evaporation, extraction and purification, the desired product was obtained as a colorless oil (420 mg, 0.95 mmol, 98%).

**¹H NMR (400 MHz, Chloroform-d)**  δ = 7.23 – 7.21 (m, 2H), 6.90 – 6.88 (m, H), 3.80 (s, 6H), 2.28 (s, 6H), 1.58 (s, 6H).

**¹³C NMR (101 MHz, CDCl₃)**  δ = 153.4, 147.2, 132.6, 129.2, 129.1, 117.0, 60.3, 42.2, 30.9, 17.0.
HRMS (ESI): Calculated for C$_{19}$H$_{23}$Br$_2$O$_2$ ([M+H]$^+$): 441.0065; found: 441.0062

IR (neat): $\nu = 906$ cm$^{-1}$

N-(2-bromo-6-methylphenyl)-2,2,2-trifluoro-N-methylacetamide 5.77:

Following General procedure D for trifluoroacetylation of anilines, 2-bromo-6-methylaniline (1 g, 5.37 mmol, 1 equiv), DMAP (33 mg, 0.27 mmol, 0.05 equiv), and anhydride trifluoroacetic (1.49 mL, 10.7 mmol, 2 equiv) were reacted in 1,2-dichloroethane. After evaporation, extraction and purification, the desired product was obtained as a yellowish oil (1.45 g, 5.1 mmol, 96%).

Following General procedure E for methylation of anilines, intermediate aniline (1.45 g, 5.1 mmol, 1 equiv), NaH (60% dispersion in oil, 620 mg, 15.3 mmol, 3 equiv), and MeI (0.95 mL, 15.3 mmol, 3 equiv) were reacted in DMF. After evaporation, extraction and purification, the desired product was obtained as a yellowish oil (1.1 g, 3.4 mmol, 67%).

$^1$H NMR (400 MHz, Chloroform-d) $\delta =$ 7.52 – 7.49 (m, 1H), 7.26 – 7.23 (m, 1H), 7.20 – 7.15 (m, 1H), 3.27 (s, 3H), 2.30 (s, 3H).

$^{13}$C NMR (101 MHz, Chloroform-d) $\delta =$ 157.5, 157.1, 156.8, 138.7 (q, $J = 0.9$ Hz)), 138.2, 137.4, 131.5, 131.3, 130.6, 130.5, 130.4, 130.0, 124.2 (q, $J = 1.0$ Hz), 121.9, 120.4, 117.5, 114.6, 36.6, 18.3 (q, $J = 1.4$ Hz), 18.0.

$^{19}$F NMR (376 MHz, CDCl$_3$) $\delta = -$70.6.

HRMS (ESI): Calculated for C$_{10}$H$_{10}$BrF$_3$NO ([M+H]$^+$): Exact Mass: 295.9898; found: 295.9892

IR (neat): $\nu = 1704, 1198$ cm$^{-1}$

N-(2-bromo-4,6-dimethylphenyl)-2,2,2-trifluoro-N-methylacetamide 5.82r:
Following General procedure D for trifluoroacetylation of anilines, 2-bromo-4,6-dimethylaniline (2 g, 10 mmol, 1 equiv), DMAP (61 mg, 0.5 mmol, 0.05 equiv), and anhydride trifluoroacetic (2.78 mL, 20 mmol, 2 equiv) were reacted in 1,2-dichloroethane. After evaporation, extraction and purification, the desired product was obtained as a yellowish oil (2.62 g, 8.85 mmol, 88%).

Following General procedure E for methylation of anilines, intermediate aniline (2.62 g, 8.85 mmol, 1 equiv), NaH (60% dispersion in oil, 1.1 g, 26.6 mmol, 3 equiv), and MeI (1.65 mL, 26.6 mmol, 3 equiv) were reacted in DMF. After evaporation, extraction and purification, the desired product was obtained as a yellow oil (2.1 g, 6.77 mmol, 77%).

**1H NMR (400 MHz, Chloroform-d)** $\delta = 7.32 - 7.31$ (m, 1H), $7.05 - 7.03$ (m, 1H), $3.37 - 3.35$ (m, 0.5H), $3.24$ (s, 2.5H), $2.32$ (s, 2.5H), $2.31$ (s, 0.5H), $2.25$ (s, 2.5H), $2.20$ (s, 0.5H).

**13C NMR (101 MHz, CDCl3)** $\delta = 157.6, 157.3, 140.9, 140.4, 138.1, 138.1, 136.7, 135.6, 131.9, 131.7, 131.6, 131.3, 131.1, 130.6, 123.7$ (q, $J = 1.1$ Hz), $121.5, 117.5, 114.7, 36.8, 20.9, 20.9, 18.3$ (q, $J = 1.3$ Hz), 17.9.

**19F NMR (376 MHz, CDCl3)** $\delta = -70.2, -70.5$.

**HRMS (ESI):** Calculated for C$_{11}$H$_{12}$BrF$_3$NO ([M+H]$^+$): Exact Mass: 310.0054; found: 310.0049

**IR (neat):** $\nu = 1702, 1195$ cm$^{-1}$

**methyl 3-bromo-5-methyl-4-(2,2,2-trifluoro-N-methylacetamido)benzoate 5.83r:**

Following General procedure D for trifluoroacetylation of anilines, methyl 4-amino-3-bromo-5-methylbenzoate (1 g, 4.1 mmol, 1 equiv), DMAP (25 mg, 0.25 mmol, 0.05 equiv), and
anhydride trifluoroacetic (1.14 mL, 8.2 mmol, 2 equiv) were reacted in 1,2-dichloroethane. After evaporation, extraction and purification, the desired product was obtained as a yellowish oil (1.32 g, 3.88 mmol, 95 %).

Following General procedure E for methylation of anilines, intermediate aniline (1.32 g, 3.88 mmol, 1 equiv), NaH (60% dispersion in oil, 470 mg, 11.6 mmol, 3 equiv), and MeI (0.72 mL, 11.6 mmol, 3 equiv) were reacted in DMF. After evaporation, extraction and purification, the desired product was obtained as a colorless oil (910 mg, 2.57 mmol, 66 %).

$^1$H NMR (400 MHz, Chloroform-d) $\delta = 8.17 - 8.15$ (m, 1H), 7.93 – 7.91 (m, 1H), 3.93 (s, 2.4H), 3.92 (s, 0.6H), 3.39 – 3.37 (m, 0.6H), 3.26 (s, 2.4H), 2.35 (s, 2.4H), 2.30 (s, 0.6H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta =$ 165.2, 165.0, 157.2, 156.8, 156.4, 142.0, 139.0, 139.0, 137.7, 132.6, 132.3, 132.1, 131.7, 131.7, 131.5, 124.4, 124.4, 122.2, 117.4, 114.5, 52.8, 52.7, 36.4, 36.4, 36.3, 18.4 (q, $J$ = 1.4 Hz), 18.1.

$^{19}$F NMR (376 MHz, CDCl$_3$) $\delta =$ -70.4, -70.6

HRMS (ESI): Calculated for C$_{12}$H$_{11}$BrF$_3$NO$_3$ ([M+H]$^+$): Exact Mass: 353.9953; found: 353.9947

IR (neat) : $\nu =$ 1702, 1682, 1192 cm$^{-1}$

**N-(2-bromo-4-fluoro-6-methylphenyl)-2,2,2-trifluoro-N-methylacetamide 5.84r:**

Following General procedure D for trifluoroacetylation of anilines, 2-bromo-4,6-dimethylaniline (1.5 g, 7.35 mmol, 1 equiv), DMAP (45 mg, 0.36 mmol, 0.05 equiv), and anhydride trifluoroacetic (2.1 mL, 14.7 mmol, 2 equiv) were reacted in 1,2-dichloroethane. After evaporation, extraction and purification, the desired product was obtained as a yellowish oil (2.1 g, 6.96 mmol, 94 %).

Following General procedure E for methylation of anilines, intermediate aniline (1.3 g, 4.33 mmol, 1 equiv), NaH (60% dispersion in oil, 520 mg, 13.3 mmol, 3 equiv), and MeI (0.8 mL, 13.3 mmol, 3 equiv) were reacted in DMF. After evaporation, extraction and purification, the desired product was quickly treated anhydride trifluoroacetic (0.8 mL) and DMAP (20 mg) in
dichloromethane (20 mL). After extraction, the product was obtained as a colorless oil (800 mg, 2.55 mmol, 59%).

$^1$H NMR (400 MHz, Chloroform-d) $\delta =$ 7.27 – 7.23 (m, 1H), 7.00 – 6.96 (m, 1H), 3.38 – 3.36 (m, 0.6H), 3.25 (s, 2.4H), 2.30 (s, 2.4H), 2.25 (s, 0.6H).

$^{13}$C NMR (126 MHz, CDCl₃) $\delta =$ 162.9, 162.7, 160.9, 160.7, 157.8, 157.6, 157.3, 156.4, 140.6, 140.5, 139.2, 139.1, 135.9, 134.6, 134.6, 124.9, 124.8, 122.5, 122.4, 119.4, 118.9, 118.8, 118.7, 118.6, 117.7, 117.6, 117.4, 117.3, 117.2, 117.1, 115.4, 114.9, 112.6, 36.8, 36.7, 36.7, 29.7, 29.6, 18.7, 18.7, 18.7, 18.6, 18.3, 18.3.

$^{19}$F NMR (376 MHz, CDCl₃) $\delta =$ -70.3, -70.6, -109.7, -110.9.

HRMS (ESI): Calculated for C₁₀H₉BrF₄NO ([M+H]+): Exact Mass: 313.9804; found: 313.9798

IR (neat) : $\nu =$ 1705 cm⁻¹

N-(2-bromo-4-cyano-6-methylphenyl)-2,2,2-trifluoro-N-methylacetamide 5.85r:

Following General procedure C for bromination of anilines, 4-amino-3-methylbenzonitrile (2 g, 15.1 mmol, 1 equiv), NBS (2.95 g, 16.6 mmol, 1.1 equiv) were reacted in DCM at room temperature. After completion, quenching, extraction and purification the desired product brominated aniline was obtained (1.61 g, 7.63 mmol, 50%).

Following General procedure D for trifluoroacetylation of anilines 4-amino-3-bromo-5-methylbenzonitrile (610 mg, 2.89 mmol, 1 equiv), DMAP (17 mg, 0.15 mmol, 0.05 equiv), and anhydride trifluoroacetic (0.81 mL, 5.8 mmol, 2 equiv) were reacted in 1,2-dichloroethane. After evaporation, extraction and purification, the desired product was obtained as a yellowish oil (790 mg, 2.6 mmol, 89%).

Following General procedure E for methylation of anilines, , intermediate aniline (450 mg, 1.47 mmol, 1 equiv), NaH (60% dispersion in oil, 180 mg, 4.4 mmol, 3 equiv), and MeI (0.27 mL, 4.4 mmol, 3 equiv) were reacted in DMF. After evaporation, extraction and purification, the desired product was quickly treated anhydride trifluoroacetic (0.8 mL) and DMAP (20 mg) in
dichloromethane (20 mL). After extraction, the product was obtained as a colorless oil (260 mg, 0.81 mmol, 55 %).

$^1$H NMR (400 MHz, Chloroform-d) $\delta = 7.83 – 7.80$ (m, 1H), 7.58 – 7.56 (m, 1H), 3.40 – 3.38 (m, 0.6H), 3.27 (s, 2.4H), 2.36 (s, 2.4H), 2.31 – 2.31 (m, 0.6H).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta = 157.2, 156.9, 156.6, 156.4, 143.8, 142.5, 140.4, 139.2, 134.8, 134.5, 134.0, 133.9, 125.3, 123.2, 119.3, 117.5, 117.0, 116.7, 116.4, 115.2, 114.8, 114.7, 114.3, 112.4, 36.4, 18.4, 18.4, 18.1.

$^{19}$F NMR (376 MHz, CDCl$_3$) $\delta = -70.4, -70.6.$

HRMS (ESI): Calculated for C$_{11}$H$_9$BrF$_3$N$_2$O ([M+H]$^+$): Exact Mass: 320.9850; found: 320.9848

IR (neat) : $\nu = 1712$ cm$^{-1}$

1-(3-bromo-2-methoxyphenyl)ethan-1-one 5.91: 49

![Chemical Structure](image)

Chemical Formula: C$_9$H$_9$BrO$_2$

Exact Mass: 227.9786

Following General procedure B for methylation of phenols, 1-(3-bromo-2-hydroxyphenyl)ethan-1-one (500 mg, 2.33 mmol, 1 equiv), K$_2$CO$_3$ (483 mg, 3.49 mmol, 1.5 equiv) and MeI (0.43 mL, 7 mmol, 3 equiv) were reacted in acetone. After evaporation, extraction and purification, the desired product was obtained as a colorless oil (498 mg, 2.17 mmol, 93 %).

$^1$H NMR (400 MHz, Chloroform-d) $\delta = 7.71 – 7.68$ (m, 1H), 7.57 – 7.54 (m, 1H), 7.08 – 7.03 (m, 1H), 3.87 (s, 3H), 2.64 (s, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta = 199.7, 156.2, 137.2, 135.3, 129.2, 125.6, 118.5, 62.6, 30.7.$

1-(3-bromo-2-methoxy-5-methylphenyl)ethan-1-one 5.95r: 50
Following General procedure A for bromination of phenols, 1-(2-hydroxy-5-methylphenyl)ethan-1-one (2.04 g, 13.3 mmol, 1 equiv) was reacted with NBS (2.6 g, 14.6 mmol, 1.1 equiv) in DMF. After quenching with water, the crude mixture was extracted with Et₂O, and the combined organic layers were washed with brine, and purified by chromatography on silica gel using cyclohexane/AcOEt [9:1] to afford the phenol (1.8 g, 7.9 mmol, 60%).

Following General procedure B for methylation of phenols, 1-(3-bromo-2-hydroxy-5-methylphenyl)ethan-1-one (1.8 g, 7.9 mmol, 1 equiv), K₂CO₃ (1.64 g, 11.9 mmol, 1.5 equiv) and MeI (1.5 mL, 23.7 mmol, 3 equiv) were reacted in acetone. After evaporation, extraction and purification, the desired product was obtained as a yellowish oil (1.5 g, 6.17 mmol, 78%).

**¹H NMR (400 MHz, Chloroform-d)**: 
δ = 7.50 – 7.49 (m, 1H), 7.34 – 7.33 (m, 1H), 3.83 (s, 3H), 2.62 (s, 3H), 2.30 (s, 3H).

**¹³C NMR (101 MHz, CDCl₃)**: 
δ = 199.9, 153.9, 137.6, 135.6, 134.6, 129.5, 118.0, 62.5, 30.7, 20.5.

**1-(3-bromo-5-fluoro-2-methoxyphenyl)ethan-1-one 5.96r:**

Following General procedure A for bromination of phenols, 1-(5-fluoro-2-hydroxyphenyl)ethan-1-one (2 g, 13 mmol, 1 equiv) was reacted with NBS (2.54 g, 14.3 mmol, 1.1 equiv) in DMF. After quenching with water, the crude mixture was extracted with Et₂O, and the combined organic layers were washed with brine, and purified by chromatography on silica gel using cyclohexane/AcOEt [9:1] to afford the phenol (1.4 g, 6.0 mmol, 46%).

Chemical Formula: C₁₀H₁₁BrO₂
Exact Mass: 241.9942

Chemical Formula: C₉H₈BrFO₂
Exact Mass: 245.9692
Following General procedure B for methylation of phenols, 1-(3-bromo-5-fluoro-2-hydroxyphenyl)ethan-1-one (1.4 g, 6.0 mmol, 1 equiv), K$_2$CO$_3$ (1.24 g, 9 mmol, 1.5 equiv) and MeI (1.1 mL, 18 mmol, 3 equiv) were reacted in acetone. After evaporation, extraction and purification, the desired product was obtained as a yellowish oil (940 mg, 3.8 mmol, 64%).

$^1$H NMR (400 MHz, Chloroform-d) $\delta =$ 7.45 – 7.42 (m, 1H), 7.30 – 7.27 (m, 1H), 3.85 (s, 3H), 2.64 (s, 3H).

$^{13}$C NMR (101 MHz, Chloroform-d) $\delta =$ 198.2 (d, $J = 1.5$ Hz), 158.4 (d, $J = 249.2$ Hz), 152.7 (d, $J = 3.3$ Hz), 135.5 (d, $J = 6.5$ Hz), 134.2 (d, $J = 25.7$ Hz), 118.9 (d, $J = 9.4$ Hz), 115.7 (d, $J = 23.7$ Hz), 62.7 (d, $J = 1.4$ Hz), 30.5 (d, $J = 0.7$ Hz).

$^{19}$F NMR (376 MHz, CDCl$_3$) $\delta =$ -115.4.

HRMS (ESI): Calculated for C$_9$H$_9$BrFO$_2$ ([M+H]$^+$): Exact mass: 246.9770; found: 246.9767

IR (neat) : $\nu = 1682$ cm$^{-1}$

1-(3-bromo-5-fluoro-2-(methoxy-d3)phenyl)ethan-1-one 5.96r-d3-1:

![Chemical Structure](image)

Chemical Formula: C$_9$H$_9$D$_3$BrFO$_2$

Exact Mass: 248.9880

Following General procedure A for bromination of phenols, 1-(5-fluoro-2-hydroxyphenyl)ethan-1-one (2 g, 13 mmol, 1 equiv) was reacted with NBS (2.54 g, 14.3 mmol, 1.1 equiv) in DMF. After quenching with water, the crude mixture was extracted with Et$_2$O, and the combined organic layers were washed with brine, and purified by chromatography on silica gel using cyclohexane/AcOEt [9:1] to afford the phenol (1.4 g, 6.0 mmol, 46%).

Following General procedure B for methylation of phenols, 1-(3-bromo-5-fluoro-2-hydroxyphenyl)ethan-1-one (233 mg, 1 mmol, 1 equiv), K$_2$CO$_3$ (207 mg, 1.5 mmol, 1.5 equiv) and CD$_3$I (0.19 mL, 3 mmol, 3 equiv) were reacted in acetone. After evaporation, extraction and purification, the desired product was obtained as a yellowish oil (202 mg, 0.82 mmol, 82%).

$^1$H NMR (400 MHz, Chloroform-d) $\delta =$ 7.32 – 7.27 (m, 1H), 7.17 – 7.13 (m, 1H), 2.52 – 2.50 (m, 3H).
$^{13}$C NMR (101 MHz, Chloroform-d) δ = 197.3 (d, J = 1.5 Hz), 157.9 (d, J = 248.9 Hz), 152.5 (d, J = 3.2 Hz), 135.1 (d, J = 6.5 Hz), 123.7 (d, J = 25.7 Hz), 118.6 (d, J = 9.3 Hz), 115.3 (d, J = 23.7 Hz), 61.5 (m), 30.1 (d, J = 0.8 Hz).

$^{19}$F NMR (376 MHz, CDCl$_3$) δ = -115.5.

1-(3-bromo-5-ethyl-2-methoxyphenyl)ethan-1-one 5.97r:

Following General procedure A for bromination of phenols, 1-(5-ethyl-2-hydroxyphenyl)ethan-1-one (985 mg, 6 mmol, 1 equiv) was reacted with NBS (1.17 g, 6.6 mmol, 1.1 equiv) in DMF. After quenching with water, the crude mixture was extracted with Et$_2$O, and the combined organic layers were washed with brine, and purified by chromatography on silica gel using cyclohexane/AcOEt [9:1] to afford the phenol (1.2 g, 4.94 mmol, 82%).

Following General procedure B for methylation of phenols, 1-(3-bromo-5-ethyl-2-hydroxyphenyl)ethan-1-one (1.11 g, 4.9 mmol, 1 equiv), K$_2$CO$_3$ (1.0 g, 7.35 mmol, 1.5 equiv) and MeI (0.9 mL, 14.7 mmol, 3 equiv) were reacted in acetone. After evaporation, extraction and purification, the desired product was obtained as a colorless oil (1.24 g, 4.82 mmol, 98%).

$^1$H NMR (400 MHz, Chloroform-d) δ = 7.54 – 7.52 (m, 1H), 7.38 – 7.36 (m, 1H), 3.84 (s, 3H), 2.64 – 2.57 (m, 4H), 1.22 (t, J = 7.7 Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ = 200.0, 154.1, 141.9, 136.5, 134.8, 128.4, 118.1, 62.5, 30.7, 28.0, 15.4.

HRMS (ESI): Calculated for C$_{11}$H$_{14}$BrO$_2$ ([M+H]$^+$): Exact mass: 257.0177; found: 257.0179

IR (neat): ν = 1685, 1469 cm$^{-1}$

1-(3-bromo-2-methoxy-5-methylphenyl)propan-1-one 5.98r: 51
Following General procedure A for bromination of phenols, 1-(2-hydroxy-5-methylphenyl)propan-1-one (985 mg, 6 mmol, 1 equiv) was reacted with NBS (1.17 g, 6.6 mmol, 1.1 equiv) in DMF. After quenching with water, the crude mixture was extracted with Et₂O, and the combined organic layers were washed with brine, and purified by chromatography on silica gel using cyclohexane/ AcOEt [9:1] to afford the phenol (735 mg, 3.0 mmol, 50%).

Following General procedure B for methylation of phenols, 1-(2-hydroxy-3-methyl-5-bromo phenyl)propan-1-one (735 mg, 3.0 mmol, 1 equiv), K₂CO₃ (622 mg, 4.5 mmol, 1.5 equiv) and MeI (0.55 mL, 9 mmol, 3 equiv) were reacted in acetone. After evaporation, extraction and purification, the desired product was obtained as a colorless oil (380 mg, 1.5 mmol, 50 %).

\(^1\)H NMR (400 MHz, Chloroform-d) δ = 7.49 – 7.48 (m, 1H), 7.25 – 7.24 (m, 1H), 3.81 (s, 3H), 2.96 (q, J = 7.3 Hz, 2H), 2.31 (s, 3H), 1.17 (t, J = 7.3 Hz, 3H).

\(^13\)C NMR (101 MHz, CDCl₃) δ = 203.8, 153.3, 136.9, 135.6, 135.2, 129.1, 117.9, 62.6, 36.3, 20.6, 8.5.

**1-(3-bromo-2-methoxyphenyl)-3-phenylpropan-1-one 5.99r:**

In a 250 mL round bottom flask, toluene (22 mL) and tBuNH₂ (0.69 mL, 6.63 mmol, 1.5 equiv) were stirred and cooled to -78°C. Bromine (0.18 mL, 3.54 mmol, 0.8 equiv) in toluene (5 mL) was then slowly added to the stirred mixture, which was further reacted for 1h at this temperature. 1-(2-hydroxyphenyl)-3-phenylpropan-1-one (2 g, 12 mmol, 1 equiv) in dichloromethane (12 mL) was then added slowly to the mixture, which was cooled to room temperature over 5h. The reaction was quenched with water (40 mL) and extracted with DCM
(3 x 15 mL) and the combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum. The crude mixture was purified by chromatography on silicagel to afford the desired product brominated phenol (600 mg, 1.96 mmol, 40%).

Following General procedure B for methylation of phenols, 1-(3-bromo-2-hydroxyphenyl)-3-phenylpropan-1-one (600 mg, 1.96 mmol, 1 equiv), K$_2$CO$_3$ (406 mg, 2.94 mmol, 1.5 equiv) and iodomethane (0.36 mL, 5.88 mmol, 3 equiv) were reacted in DMF. After evaporation, extraction and purification, the desired product was obtained as a yellowish oil (620 mg, 1.95 mmol, 99%).

$^1$H NMR (400 MHz, Chloroform-d) $\delta = 7.57 - 7.52$ (m, 1H), 7.34 – 7.29 (m, 1H), 7.19 – 7.14 (m, 2H), 7.13 – 7.04 (m, 3H), 6.94 – 6.87 (m, 1H), 3.66 (s, 3H), 3.18 (t, $J = 7.9$, 2H), 2.93 (t, $J = 7.5$ Hz, 2H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta = 201.6$, 155.5, 141.0, 136.7, 135.6, 135.6, 128.7, 128.5, 126.2, 125.5, 118.3, 62.5, 44.5, 30.2.

HRMS (ESI): Calculated for C$_{16}$H$_{16}$BrO$_2$ ([M+H]$^+$): Exact Mass: 319.0334; found: 319.0337

IR (neat) : $\nu = 1687$ cm$^{-1}$

3-bromo-2-methoxybenzaldehyde 5.106a: 52

[Chemical structure image]

Chemical Formula: C$_8$H$_7$BrO$_2$

Exact Mass: 213.9629

Following General procedure B for methylation of phenols, 3-bromo-2-hydroxybenzaldehyde (4 g, 19.9 mmol, 1 equiv), K$_2$CO$_3$ (4.12 g, 29.8 mmol, 1.5 equiv) and iodomethane (3.68 mL, 59.7 mmol, 3 equiv) were reacted in DMF. After evaporation, extraction and purification, the desired product was obtained as a yellowish oil (3.2 g, 14.9 mmol, 74%).

$^1$H NMR (400 MHz, Chloroform-d) $\delta = 10.35$ (d, $J = 0.8$ Hz, 1H), 7.82 – 7.77 (m, 2H), 7.15 – 7.09 (m, 1H), 3.98 (s, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta = 189.2$, 160.2, 139.6, 131.1, 128.0, 125.9, 118.3, 63.6.

3-bromo-2-methoxy-5-methylbenzaldehyde 5.106b: 53

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Following General procedure B for methylation of phenols, 2-hydroxy-5-methylbenzaldehyde (1.6 g, 7.34 mmol, 1 equiv), K₂CO₃ (1.5 g, 11 mmol, 1.5 equiv) and iodomethane (1.37 mL, 22 mmol, 3 equiv) were reacted in DMF. After evaporation, extraction and purification, the desired product was obtained as a colorless oil (1.59 g, 6.95 mmol, 95 %).

¹H NMR (400 MHz, Chloroform-d) δ = 10.30 (s, 1H), 7.62 – 7.60 (m, 1H), 7.58 – 7.56 (m, 1H), 3.94 (s, 3H), 2.33 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ = 189.4, 158.1, 140.1, 136.0, 130.4, 128.1, 117.8, 63.6, 20.5.

3-bromo-5-fluoro-2-methoxybenzaldehyde 5.106c: ⁵⁴

Following General procedure B for methylation of phenols, 3-bromo-5-fluoro-2-hydroxybenzaldehyde (1.6 g, 7.34 mmol, 1 equiv), K₂CO₃ (1.5 g, 11 mmol, 1.5 equiv) and iodomethane (1.37 mL, 22 mmol, 3 equiv) were reacted in DMF. After evaporation, extraction and purification, the desired product was obtained as a colorless oil (1.52 g, 6.52 mmol, 89 %).

¹H NMR (400 MHz, Chloroform-d) δ = 10.30 (d, J = 3.2 Hz, 1H), 7.62 – 7.60 (m, 1H), 7.58 – 7.56 (m, 1H), 3.94 (s, 3H).

¹³C NMR (101 MHz, Chloroform-d) δ = 188.1 (d, J = 1.8 Hz), 158.8 (d, J = 250.2 Hz), 156.9 (d, J = 3.1 Hz), 131.3 (d, J = 6.7 Hz), 126.7 (d, J = 26.2 Hz), 118.9 (d, J = 8.9 Hz), 113.8 (d, J = 23.3 Hz), 64.0 (d, J = 1.4 Hz).

¹⁹F NMR (376 MHz, CDCl₃) δ = -114.3.

(3-bromo-2-methoxyphenyl)(phenyl)methanone 5.103:
Following General procedure F for ketone synthesis, \textbf{5.106a} (500 mg, 2.33 mmol, 1 equiv) was reacted with phenyl magnesium bromide (3 M in THF, 1.55 mL, 4.7 mmol, 2 equiv) in THF at -78°C. After quenching and extraction, the crude mixture was reacted with PCC (1.26 g, 5.83 mmol, 2.5 equiv) on celite in DCM. After purification, the desired product ketone was obtained as a colorless oil (420 mg, 1.44 mmol, 62%).

$^1$H NMR (400 MHz, Chloroform-d) $\delta = 7.84 – 7.79$ (m, 2H), 7.73 – 7.69 (m, 1H), 7.62 – 7.57 (m, 1H), 7.48 – 7.44 (m, 2H), 7.32 – 7.29 (m, 1H), 7.11 – 7.06 (m, 1H), 3.74 (s, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta = 195.4, 155.0, 136.9, 135.7, 135.2, 133.7, 130.2, 128.7, 125.2, 118.0, 62.6$.

HRMS (ESI): Calculated for C$_{14}$H$_{12}$BrO$_2$ ([M+H$^+$]): Exact Mass: 291.0021; found: 291.0026

IR (neat): $\nu = 1658$ cm$^{-1}$

\textbf{(3-bromo-2-methoxy-5-methylphenyl)(phenyl)methanone 5.109r:}

Following General procedure F for ketone synthesis, \textbf{5.106b} (535 mg, 2.33 mmol, 1 equiv) was reacted with phenyl magnesium bromide (3 M in THF, 1.55 mL, 4.7 mmol, 2 equiv) in THF at -78°C. After quenching and extraction, the crude mixture was reacted with PCC (1.26 g, 5.83 mmol, 2.5 equiv) on celite in DCM. After purification, the desired product ketone was obtained as a colorless oil (523 mg, 1.71 mmol, 74%).

$^1$H NMR (400 MHz, Chloroform-d) $\delta = 7.84 – 7.78$ (m, 2H), 7.61 – 7.56 (m, 1H), 7.53 – 7.51 (m, 1H), 7.48 – 7.43 (m, 2H), 7.10 – 7.07 (m, 1H), 3.69 (s, 3H), 2.33 – 2.33 (m, 3H).

Chemical Formula: C$_{14}$H$_{11}$BrO$_2$

Exact Mass: 289.9942

Chemical Formula: C$_{15}$H$_{13}$BrO$_2$

Exact Mass: 304.0099
C NMR (101 MHz, CDCl\textsubscript{3}) \(\delta = 195.6, 152.7, 137.0, 136.1, 135.3, 134.8, 133.7, 130.1, 129.0, 128.6, 117.5, 62.6, 20.6\).

HRMS (ESI): Calculated for C\textsubscript{15}H\textsubscript{10}BrO\textsubscript{2} \([M+H]^+\): Exact Mass: 305.0177; found: 305.0179

IR (neat) : \(\nu = 1661\) cm\(^{-1}\)

(3-bromo-5-fluoro-2-methoxyphenyl)(phenyl)methanone 5.110r:

![Chemical Structure](image)

Chemical Formula: C\textsubscript{15}H\textsubscript{10}BrFO\textsubscript{2}

Following General procedure F for ketone synthesis, 5.106c (543 mg, 2.33 mmol, 1 equiv) was reacted with phenyl magnesium bromide (3 M in THF, 1.55 mL, 4.7 mmol, 2 equiv) in THF at -78°C. After quenching and extraction, the crude mixture was reacted with PCC (1.26 g, 5.83 mmol, 2.5 equiv) on celite in DCM. After purification, the desired product ketone was obtained as a colorless oil (320 mg, 1.03 mmol, 44%).

\(^1\)H NMR (400 MHz, Chloroform-d) \(\delta = 7.83 – 7.76\) (m, 2H), \(7.62 – 7.58\) (m, 1H), \(7.50 – 7.42\) (m, 3H), \(7.05 – 6.99\) (m, 1H), \(3.70\) (s, 3H).

\(^13\)C NMR (101 MHz, Chloroform-d) \(\delta = 193.8\) (d, \(J = 1.6\) Hz), \(157.9\) (d, \(J = 249.6\) Hz), \(151.3\) (d, \(J = 3.4\) Hz), \(136.2, 135.6\) (d, \(J = 6.8\) Hz), \(133.9, 132.4, 130.0, 128.6, 128.3, 122.4\) (d, \(J = 25.5\) Hz), \(118.3\) (d, \(J = 9.5\) Hz), \(115.1\) (d, \(J = 23.8\) Hz), \(62.7\) (d, \(J = 1.3\) Hz).

\(^19\)F NMR (376 MHz, CDCl\textsubscript{3}) \(\delta = -115.78\).

HRMS (ESI): Calculated for C\textsubscript{14}H\textsubscript{11}BrFO\textsubscript{2} \([M+H]^+\): Exact Mass: 308.9926; found: 308.9929

IR (neat) : \(\nu = 1652\) cm\(^{-1}\)

(3-bromo-2-methoxyphenyl)(3,5-dimethoxyphenyl)methanone 5.111r:
Following General procedure F for ketone synthesis, 5.106a (500 mg, 2.33 mmol, 1 equiv) was reacted with 3,5-dimethoxyphenyl magnesium bromide (1 M in THF, 4.7 mL, 4.7 mmol, 2 equiv) in THF at -78°C. After quenching and extraction, the crude mixture was reacted with PCC (1.26 g, 5.83 mmol, 2.5 equiv) on celite in DCM. After purification, the desired product ketone was obtained as a colorless oil (587 mg, 1.67 mmol, 72%).

\[ ^1H \text{NMR (400 MHz, Chloroform-d)} \delta = 7.71 - 7.66 (m, 1H), 7.29 - 7.25 (m, 1H), 7.09 - 7.03 (m, 1H), 6.96 - 6.93 (m, 2H), 6.69 - 6.66 (m, 1H), 3.80 (s, 6H), 3.77 (s, 3H). \]

\[ ^{13}C \text{NMR (101 MHz, CDCl}_3) \delta = 194.9, 160.9, 155.1, 138.9, 135.7, 135.1, 128.5, 124.9, 118.0, 108.0, 106.1, 62.7, 55.7. \]

HRMS (ESI): Calculated for C_{16}H_{16}BrO_4 ([M+H]^+): Exact Mass: 351.0232; found: 351.0235.

IR (neat): ν = 1662 cm\(^{-1}\)

(3-bromo-2-methoxyphenyl)(3-methoxy-4-(trifluoromethyl)phenyl)methanone 5.112r:

Following General procedure F for ketone synthesis, 5.106a (500 mg, 2.33 mmol, 1 equiv) was reacted with 3-methoxy, 4-trifluoromethylphenyl magnesium bromide (1 M in THF, 4.7 mL, 4.7 mmol, 2 equiv) in THF at -78°C. After quenching and extraction, the crude mixture was reacted with PCC (1.26 g, 5.83 mmol, 2.5 equiv) on celite in DCM. After purification, the desired product ketone was obtained as a colorless oil (350 mg, 0.89 mmol, 38%).
\[^1\]H NMR (400 MHz, Chloroform-\textit{d}) \(\delta = 8.15 – 8.12\) (m, 1H), \(7.94 – 7.90\) (m, 1H), \(7.73 – 7.70\) (m, 1H), \(7.30 – 7.27\) (m, 1H), \(7.13 – 7.08\) (m, 1H), \(7.05 – 7.02\) (m, 1H), \(3.98\) (s, 3H), \(3.73\) (s, 3H).

\[^{13}\]C NMR (101 MHz, Chloroform-\textit{d}) \(\delta = 192.9, 161.6\) (q, \(J = 1.5\) Hz), \(154.9, 136.3\) (d, \(J = 1.0\) Hz), \(135.9, 134.7, 129.4\) (q, \(J = 5.3\) Hz), \(129.2, 128.5, 125.4, 123.2\) (q, \(J = 272.3\) Hz), \(119.1\) (q, \(J = 31.9\) Hz), \(118.1, 111.6, 62.7, 56.5\).

\[^{19}\]F NMR (376 MHz, CDCl\textsubscript{3}) \(\delta = -62.9\).

HRMS (ESI): Calculated for C\textsubscript{16}H\textsubscript{13}BrF\textsubscript{3}O\textsubscript{3} ([M+H]\textsuperscript{+}): Exact Mass: 389.0000; found: 389.0004

IR (neat): \(\nu = 1658\) cm\textsuperscript{-1}

(3-bromo-2-methoxyphenyl)(4-methoxyphenyl)methanone 5.113r:

Following General procedure F for ketone synthesis, 5.106a (500 mg, 2.33 mmol, 1 equiv) was reacted with \(p\)-methoxyphenyl magnesium bromide (1 M in THF, 4.7 mL, 4.7 mmol, 2 equiv) in THF at -78°C. After quenching and extraction, the crude mixture was reacted with PCC (1.26 g, 5.83 mmol, 2.5 equiv) on celite in DCM. After purification, the desired product ketone was obtained as a colorless oil (510 mg, 1.58 mmol, 68%).

\[^1\]H NMR (400 MHz, Chloroform-\textit{d}) \(\delta = 7.82 – 7.78\) (m, 2H), \(7.70 – 7.66\) (m, 1H), \(7.28 – 7.25\) (m, 1H), \(7.09 – 7.04\) (m, 1H), \(6.95 – 6.90\) (m, 2H), \(3.87\) (s, 3H), \(3.74\) (s, 3H).

\[^{13}\]C NMR (101 MHz, CDCl\textsubscript{3}) \(\delta = 193.9, 164.2, 154.7, 135.5, 135.3, 132.6, 129.9, 128.5, 125.1, 117.9, 113.9, 62.6, 55.7\).

HRMS (ESI): Calculated for C\textsubscript{15}H\textsubscript{14}BrO\textsubscript{3} ([M+H]\textsuperscript{+}): Exact Mass: 321.0126; found: 321.0129

IR (neat): \(\nu = 1658, 1596\) cm\textsuperscript{-1}

(3-bromo-2-methoxyphenyl)(4-fluorophenyl)methanone 5.114r:
Following General procedure F for ketone synthesis, 5.106a (500 mg, 2.33 mmol, 1 equiv) was reacted with p-fluorophenyl magnesium bromide (1 M in THF, 4.7 mL, 4.7 mmol, 2 equiv) in THF at -78°C. After quenching and extraction, the crude mixture was reacted with PCC (1.26 g, 5.83 mmol, 2.5 equiv) on celite in DCM. After purification, the desired product ketone was obtained as a colorless oil (410 mg, 1.32 mmol, 56%).

$^1$H NMR (400 MHz, Chloroform-d) δ = 7.87 – 7.80 (m, 2H), 7.73 – 7.69 (m, 1H), 7.31 – 7.28 (m, 1H), 7.16 – 7.07 (m, 3H), 3.73 (s, 3H).

$^{13}$C NMR (101 MHz, Chloroform-d) δ = 193.8, 166.2 (d, J = 256.0 Hz), 154.9, 135.9, 134.9, 133.3 (d, J = 2.9 Hz), 132.8 (d, J = 9.5 Hz), 128.6, 125.3, 118.0, 115.9 (d, J = 22.1 Hz), 62.7.

$^{19}$F NMR (376 MHz, CDCl₃) δ = -104.0.

HRMS (ESI): Calculated for C₁₄H₁₁BrFO₂ ([M+H]+): Exact Mass: 308.9926; found: 308.9928

IR (neat) : ν = 1661 cm⁻¹

Experiments with deuterated substrates:

![Diagram of chemical reactions]
1) Following the General procedure I for the chromanones synthesis, 5.96r-d3 (37 mg, 0.15 mmol, 1 equiv) was reacted with Pd(PCy\textsubscript{3})\textsubscript{2} (10 mg, 0.015 mmol, 10 mol%), AdCO\textsubscript{2}H (8.1 mg, 0.045 mmol, 30 mol%), Cs\textsubscript{2}CO\textsubscript{3} (49 mg, 0.15 mmol, 1 equiv) in toluene (6 mL) at 120°C for 16h. After filtration and evaporation of volatiles, \textsuperscript{1}H NMR shows no traces of desired product.

2) Following the General procedure I for the chromanones synthesis, 5.96r (17 mg, 0.075 mmol, 0.5 equiv) and 5.96r-d3-2 (17 mg, 0.075 mmol, 0.5 equiv) were reacted with Pd(PCy\textsubscript{3})\textsubscript{2} (10 mg, 0.015 mmol, 10 mol%), AdCO\textsubscript{2}H (8.1 mg, 0.045 mmol, 30 mol%), Cs\textsubscript{2}CO\textsubscript{3} (49 mg, 0.15 mmol, 1 equiv) in toluene (6 mL) at 120°C for 5h. After filtration and evaporation of volatiles, the deuterium content was determined by integration of the \textsuperscript{1}H NMR spectrum of the crude reaction mixture.

C-H activation products:

**methyl 2,3-dihydrobenzofuran-5-carboxylate 5.40:**

\[
\text{Chemical Formula: C}_{15}\text{H}_{10}\text{O}_3 \\
\text{Exact Mass: 178.0630}
\]

Following the General procedure G for the dihydrobenzofuran synthesis, 5.39 (39 mg, 0.15 mmol, 1 equiv) was reacted with Pd(PCy\textsubscript{3})\textsubscript{2} (10 mg, 0.015 mmol, 10 mol%), cesium pivalate (35 mg, 0.15 mmol, 1 equiv) in toluene (6 mL) at 140°C for 16h. After purification, 5.40 was obtained as a colorless oil (24.5 mg, 0.137 mmol, 92%).

**\textsuperscript{1}H NMR (400 MHz, Chloroform-d) \textsuperscript{\textsuperscript{\textsuperscript{\textsuperscript{\textsuperscript{\textsuperscript{o}}} }} \delta = 7.88 – 7.81 (m, 2H), 6.79 – 6.74 (m, 1H), 4.67 – 4.56 (m, 2H), 3.86 (s, 3H), 3.24 – 3.16 (m, 2H).**

**\textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) \textsuperscript{\textsuperscript{\textsuperscript{\textsuperscript{\textsuperscript{\textsuperscript{o}}} }} \delta = 167.0, 164.2, 131.1, 127.4, 126.8, 122.6, 109.0, 72.1, 51.9, 29.1.**

**2,3-dihydrobenzofuran 5.46:**

\[
\text{Chemical Formula: C}_{8}\text{H}_{8}\text{O} \\
\text{Exact Mass: 120.0575}
\]
Following the General procedure G for the dihydrobenzofurans synthesis, 5.46r (30 mg, 0.15 mmol, 1 equiv) was reacted with Pd(PCy₃)₂ (10 mg, 0.015 mmol, 10 mol%), cesium pivalate (35 mg, 0.15 mmol, 1 equiv) in toluene (6 mL) at 140°C for 16h. After purification, 5.46 was obtained as a colorless oil (7.2 mg, 0.06 mmol, 40%).

\[ ^1H \text{ NMR (400 MHz, Chloroform-}d \text{)} \delta = 7.24 – 7.21 (m, 1H), 7.16 – 7.11 (m, 1H), 6.90 – 6.85 (m, 1H), 6.84 – 6.81 (m, 1H), 4.58 (t, J = 8.7 Hz, 2H), 3.23 (t, J = 8.7 Hz, 2H). \]

\[ ^{13}C \text{ NMR (101 MHz, CDCl}_3\text{)} \delta = 160.1, 128.0, 126.9, 125.0, 120.4, 109.4, 71.1, 29.8. \]

**5-fluoro-2,3-dihydrobenzofuran 5.47: ⁵⁷**

![Chemical Structure](image)

Chemical Formula: C₈H₇FO
Exact Mass: 138.0481

Following the General procedure G for the dihydrobenzofurans synthesis, 5.47r (33 mg, 0.15 mmol, 1 equiv) was reacted with Pd(PCy₃)₂ (10 mg, 0.015 mmol, 10 mol%), cesium pivalate (35 mg, 0.15 mmol, 1 equiv) in toluene (6 mL) at 140°C for 16h. After purification, 5.47 was obtained as a yellowish oil (12 mg, 0.087 mmol, 57%).

\[ ^1H \text{ NMR (400 MHz, Chloroform-}d \text{)} \delta = 6.91 – 6.87 (m, 1H), 6.78 (td, J = 8.9, 2.8 Hz, 1H), 6.70 – 6.86 (m, 1H), 4.59 – 4.54 (m, 2H), 3.21 – 3.15 (m, 2H). \]

\[ ^{13}C \text{ NMR (101 MHz, Chloroform-}d \text{)} \delta = 157.5 (d, J = 236.4 Hz), 156.1 (d, J = 1.4 Hz), 128.4 (d, J = 8.8 Hz), 114.0 (d, J = 24.1 Hz), 112.1 (d, J = 24.8 Hz), 109.3 (d, J = 8.6 Hz), 71.7, 30.1 (d, J = 1.8 Hz). \]

\[ ^{19}F \text{ NMR (376 MHz, CDCl}_3\text{)} \delta = -125.0 (m) \]

**2,3-dihydrobenzofuran-5-carbaldehyde 5.45: ⁵⁸**

![Chemical Structure](image)

Chemical Formula: C₉H₆O₂
Exact Mass: 148.0524

Following the General procedure G for the dihydrobenzofurans synthesis, 5.45r (35 mg, 0.15 mmol, 1 equiv) was reacted with Pd(PCy₃)₂ (10 mg, 0.015 mmol, 10 mol%), cesium pivalate (35 mg, 0.15 mmol, 1 equiv) in toluene (6 mL) at 140°C for 16h. After purification, 5.45 was obtained as a yellowish oil (12 mg, 0.087 mmol, 57%).

\[ ^1H \text{ NMR (400 MHz, Chloroform-}d \text{)} \delta = 7.36 – 7.32 (m, 1H), 7.24 – 7.19 (m, 1H), 6.77 – 6.72 (m, 1H), 6.70 – 6.67 (m, 1H), 4.57 (t, J = 8.7 Hz, 2H), 3.22 (t, J = 8.7 Hz, 2H). \]

\[ ^{13}C \text{ NMR (101 MHz, CDCl}_3\text{)} \delta = 160.1, 128.0, 126.9, 125.0, 120.4, 109.4, 71.1, 29.8. \]

\[ ^{19}F \text{ NMR (376 MHz, CDCl}_3\text{)} \delta = -125.0 (m) \]
equiv) in toluene (6 mL) at 140°C for 16h. After purification, **5.45** was obtained as a yellowish oil (20.5 mg, 0.136 mmol, 91%).

\[ \text{\textsuperscript{1}H NMR (400 MHz, Chloroform-d) } \delta = 9.77 \text{ (s, 1H), 7.71 -- 7.65 (m, 1H), 7.64 -- 7.59 (m, 1H), 6.84 -- 6.79 (m, 1H), 4.67 -- 4.57 (m, 3H), 3.21 (t, } J = 8.8 \text{ Hz, 3H)} \]

\[ \text{\textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) } \delta = 190.6, 165.6, 132.9, 130.4, 128.5, 125.9, 109.6, 72.4, 28.7. \]

methyl 2,3-dihydrobenzofuran-4-carboxylate **5.48:**

\[
\begin{align*}
\text{Chemical Formula: } C_{19}H_{10}O_3 \\
\text{Exact Mass: } 178.0630
\end{align*}
\]

Following the General procedure G for the dihydrobenzofurans synthesis, **5.48r** (39 mg, 0.15 mmol, 1 equiv) was reacted with Pd(PCy\textsubscript{3})\textsubscript{2} (10 mg, 0.015 mmol, 10 mol%), cesium pivalate (35 mg, 0.15 mmol, 1 equiv) in toluene (6 mL) at 160°C for 16h. After purification, **5.48** was obtained as a colorless oil (21 mg, 0.118 mmol, 79%).

\[ \text{\textsuperscript{1}H NMR (400 MHz, Chloroform-d) } \delta = 7.52 -- 7.49 (m, 1H), 7.20 -- 7.15 (m, 1H), 6.98 -- 6.94 (m, 1H), 4.60 (t, } J = 8.8 \text{ Hz, 2H), 3.90 (s, 3H), 3.54 (t, } J = 8.9, 2H). \]

\[ \text{\textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) } \delta = 167.0, 161.0, 129.9, 128.1, 127.1, 121.9, 113.6, 71.6, 52.0, 31.2. \]

methyl 2,3-dihydrobenzofuran-2-carboxylate **5.53:**

\[
\begin{align*}
\text{Chemical Formula: } C_{19}H_{10}O_3 \\
\text{Exact Mass: } 178.0630
\end{align*}
\]

Following the General procedure G for the dihydrobenzofurans synthesis, **5.53r** (39 mg, 0.15 mmol, 1 equiv) was reacted with Pd(PCy\textsubscript{3})\textsubscript{2} (10 mg, 0.015 mmol, 10 mol%), cesium pivalate (35 mg, 0.15 mmol, 1 equiv) in toluene (6 mL) at 160°C for 16h. After purification, **5.53** was obtained as a colorless oil (19.5 mg, 0.109 mmol, 73%).

405
$^1$H NMR (400 MHz, Chloroform-$d$) $\delta = 7.19 - 7.11$ (m, 2H), 6.92 – 6.87 (m, 2H), 5.21 (dd, $J = 10.5$, 6.8 Hz, 1H), 3.81 (s, 3H), 3.61 – 3.51 (m, 1H), 3.43 – 3.34 (m, 1H).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta = 171.90, 159.1, 128.6, 124.9, 124.8, 121.4, 110.0, 79.1, 52.7, 34.0$.

**methyl 2,3-dihydrobenzofuran-3-carboxylate 5.49:**

![Chemical Structure](image)

Chemical Formula: C$_{10}$H$_{10}$O$_3$

Exact Mass: 178.0630

Following the General procedure G for the dihydrobenzofurans synthesis, 5.49 (39 mg, 0.15 mmol, 1 equiv) was reacted with Pd(PCy$_3$)$_2$ (10 mg, 0.015 mmol, 10 mol%), cesium pivalate (35 mg, 0.15 mmol, 1 equiv) in toluene (6 mL) at 160°C for 16h. After cooling to room temperature, the crude mixture was filtered through celite and evaporated under vacuum. The crude mixture was then dissolved in dry DCM (2 mL) and cooled to -78°C. BBr$_3$ (5.1 L, 0.3 mmol, 2 equiv) was added and the reaction was stirred for 30 minutes at this temperature. After quenching with water (2 mL), the crude mixture was extracted with DCM (3 x 3 mL) and the combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum. After purification by chromatography on silica gel, 5.49 was obtained as a yellowish oil (23.5 mg, 0.109 mmol, 88%).

$^1$H NMR (400 MHz, Chloroform-$d$) $\delta = 7.39 - 7.35$ (m, 1H), 7.22 – 7.16 (m, 1H), 6.91 – 6.86 (m, 1H), 6.84 – 6.81 (m, 1H), 4.93 (dd, $J = 9.2$, 6.6 Hz, 1H), 4.67 (t, $J = 9.5$ Hz, 1H), 4.35 (dd, $J = 9.8$, 6.6 Hz, 1H), 3.78 (s, 3H).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta = 171.8, 159.9, 129.6, 125.5, 124.3, 120.8, 110.1, 72.6, 52.7, 47.3$.

**methyl 5-fluoro-2,3-dihydrobenzofuran-3-carboxylate 5.50:**

![Chemical Structure](image)

Chemical Formula: C$_{10}$H$_{9}$FO$_3$

Exact Mass: 196.0536
Following the General procedure G for the dihydrobenzofurans synthesis, 5.50r (42 mg, 0.15 mmol, 1 equiv) was reacted with Pd(PCy3)2 (10 mg, 0.015 mmol, 10 mol%), cesium pivalate (35 mg, 0.15 mmol, 1 equiv) in toluene (6 mL) at 140°C for 16h. After cooling to room temperature, the crude mixture was filtered through celite and evaporated under vacuum. The crude mixture was then dissolved in dry DCM (2 mL) and cooled to -78°C. BBr3 (5.1 µL, 0.3 mmol, 2 equiv) was added and the reaction was stirred for 30 minutes at this temperature. After quenching with water (2 mL), the crude mixture was extracted with DCM (3 x 3 mL) and the combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum. After purification by chromatography on silica gel, 5.50 was obtained as a colorless oil (20.5 mg, 0.104 mmol, 70%).

\[1H \text{ NMR (400 MHz, Chloroform-}d) \delta = 7.11 - 7.07 (m, 1H), 6.91 - 6.85 (m, 1H), 6.75 - 6.70 (m, 1H), 4.94 (dd, \text{ } J = 9.3, 6.8 \text{ Hz, } 1H), 4.69 (t, \text{ } J = 9.6 \text{ Hz, } 1H), 4.36 - 4.30 (m, 1H), 3.79 (s, 3H).\]

\[13C \text{ NMR (126 MHz, Chloroform-}d) \delta = 171.2, 157.5 (d, J = 237.6 \text{ Hz}), 156.0 (d, J = 1.6 \text{ Hz}), 125.4 (d, J = 9.3 \text{ Hz}), 116.0 (d, J = 24.2 \text{ Hz}), 112.7 (d, J = 25.5 \text{ Hz}), 110.2 (d, J = 8.5 \text{ Hz}), 73.2, 52.9, 47.4 (d, J = 1.8 \text{ Hz}).\]

\[19F \text{ NMR (376 MHz, CDCl}_3) \delta = -124.0.\]

N,N-diisopropyl-2,3-dihydrobenzofuran-3-carboxamide 5.51:

Chemical Formula: C_{16}H_{21}NO₂
Exact Mass: 247.1572

Following the General procedure G for the dihydrobenzofurans synthesis, 5.51r (49 mg, 0.15 mmol, 1 equiv) was reacted with Pd(PCy3)2 (10 mg, 0.015 mmol, 10 mol%), cesium pivalate (35 mg, 0.15 mmol, 1 equiv) in toluene (6 mL) at 160°C for 16h. After purification, 5.51 was obtained as a colorless oil (30 mg, 0.121 mmol, 81%).

\[1H \text{ NMR (400 MHz, Chloroform-}d) \delta = 7.17 - 7.13 (m, 1H), 7.12 - 7.09 (m, 1H), 6.88 - 6.84 (m, 1H), 6.84 - 6.80 (m, 1H), 4.86 - 4.80 (m, 1H), 4.72 - 4.65 (m, 1H), 4.57 - 4.50 (m, 1H), 4.22 - 4.13 (m, 1H), 3.72 - 3.59 (m, 1H), 1.41 - 1.37 (m, 9H), 1.26 (d, J = 6.6 \text{ Hz, } 3H).\]

\[13C \text{ NMR (126 MHz, CDCl}_3) \delta = 160.4, 129.1, 124.4, 120.7, 110.1, 74.4, 46.7, 46.4, 21.7, 20.8, 20.7.\]
HRMS (ESI): Calculated for C₁₅H₂₂NO₂ ([M+H]⁺): Exact Mass: 248.1651; found: 248.1654

IR (neat): ν = 1645 cm⁻¹

**(2,3-dihydrobenzofuran-3-yl)(morpholinomethanone 5.52:**

![Chemical structure](image)

Chemical Formula: C₁₁H₁₆NO₂
Exact Mass: 233.1052

Following the General procedure G for the dihydrobenzofurans synthesis, 5.52 (47 mg, 0.15 mmol, 1 equiv) was reacted with Pd(PCy₃)₂ (10 mg, 0.015 mmol, 10 mol%), cesium pivalate (35 mg, 0.15 mmol, 1 equiv) in toluene (6 mL) at 160°C for 16h. After purification, 5.52 was obtained as a colorless oil (18.5 mg, 0.079 mmol, 53%).

**¹H NMR (400 MHz, Chloroform-d) δ:** 7.14 – 7.08 (m, 1H), 7.06 – 7.03 (m, 1H), 6.82 – 6.75 (m, 2H), 4.89 – 4.84 (m, 1H), 4.64 – 4.58 (m, 1H), 4.55 – 4.49 (m, 1H), 3.73 – 3.55 (m, 8H).

**¹³C NMR (126 MHz, CDCl₃) δ:** 169.9, 160.3, 129.5, 125.6, 124.2, 120.8, 110.4, 73.8, 67.1, 66.9, 46.6, 44.6, 42.9.

HRMS (ESI): Calculated for C₁₁H₁₆NO₂ ([M+H]⁺): Exact Mass: 234.1130; found: 234.1135

IR (neat): ν = 1647 cm⁻¹

**dimethyl 2,3-dihydrobenzofuran-2,3-dicarboxylate 5.54:**

![Chemical structure](image)

Chemical Formula: C₁₂H₁₂O₆
Exact Mass: 236.0686

Following the General procedure G for the dihydrobenzofurans synthesis, 5.54 (48 mg, 0.15 mmol, 1 equiv) was reacted with Pd(PCy₃)₂ (10 mg, 0.015 mmol, 10 mol%), cesium pivalate (35 mg, 0.15 mmol, 1 equiv) in toluene (6 mL) at 160°C for 16h. After purification, 5.54 was obtained as a yellowish oil (14.5 mg, 0.061 mmol, 41%).

**¹H NMR (400 MHz, Chloroform-d) δ:** 7.32 – 7.29 (m, 1H), 7.19 – 7.13 (m, 1H), 6.90 – 6.84 (m, 2H), 5.59 (d, J = 6.0 Hz, 1H), 4.48 – 4.46 (m, 1H), 3.75 (s, 6H).
\[^{13}\text{C} \text{NMR (126 MHz, CDCl}_3\] \(\delta = 170.6, 170.5, 158.7, 130.1, 125.3, 122.6, 121.7, 110.5, 81.0, 53.2, 53.1, 51.1.\)

HRMS (ESI): Calculated for C\(_{12}\)H\(_{13}\)O\(_5\) ([M+H]\(^+\)): Exact Mass: 237.0763; found: 237.0766

IR (neat): \(\nu = 1740 \text{ cm}^{-1}\)

5,5\textsuperscript{\prime}-(propane-2,2-diyl)bis(2,3-dihydrobenzofuran) 5.55:

\[
\text{Chemical Formula: } \text{C}_{19}\text{H}_{21}\text{O}_2 \\
\text{Exact Mass: } 281.1463
\]

Following the General procedure G for the dihydrobenzofurans synthesis, 5.55r (66 mg, 0.15 mmol, 1 equiv) was reacted with Pd(PCy\(_3\))\(_2\) (20 mg, 0.03 mmol, 20 mol%), cesium pivalate (70 mg, 0.30 mmol, 2 equiv) in toluene (6 mL) at 160°C for 16h. After purification, 5.55 was obtained as a colorless oil (28.5 mg, 0.102 mmol, 68%).

\[^1\text{H} \text{NMR (400 MHz, Chloroform-}d\] \(\delta = 7.07 – 7.05 \text{ (m, 2H)}, 7.04 – 7.00 \text{ (m, 2H)}, 6.72 – 6.68 \text{ (m, 2H)}, 4.56 \text{ (t, } J = 8.7 \text{ Hz, 4H)}, 3.17 \text{ (t, } J = 9.2, 8.1 \text{ Hz, 4H)}, 1.65 \text{ (s, 6H}).\)

\[^{13}\text{C} \text{NMR (126 MHz, CDCl}_3\] \(\delta = 158.0, 143.6, 126.7, 126.2, 123.7, 108.5, 71.4, 42.2, 31.6, 30.1.\)

HRMS (ESI): Calculated for C\(_{19}\)H\(_{21}\)O\(_2\) ([M+H]\(^+\)): Exact mass: 281.1542; found: 281.1545

IR (neat): \(\nu = 906 \text{ cm}^{-1}\)

2,2,2-trifluoro-1-(indolin-1-yl)ethan-1-one 5.78: \(^{62}\)

\[
\text{Chemical Formula: } \text{C}_{10}\text{H}_{8}\text{F}_3\text{NO} \\
\text{Exact Mass: } 215.0558
\]

Following the General procedure H for indolines synthesis, 5.77 (45 mg, 0.15 mmol, 1 equiv) was reacted with Pd(PCy\(_3\))\(_2\) (10 mg, 0.015 mmol, 10 mol%), AdCO\(_2\)H (8.1 mg, 0.045 mmol, 30 mol%), Rb\(_2\)CO\(_3\) (52
mg, 0.15 mmol, 1 equiv) in toluene (6 mL) at 160°C for 16h. After purification, 5.78 was obtained as a colorless oil (24 mg, 0.112 mmol, 74%).

\[ ^1H \text{NMR (400 MHz, Chloroform-d)} \delta = 8.22 - 8.19 (m, 1H), 7.30 - 7.27 (m, 2H), 7.18 - 7.14 (m, 1H), 4.31 - 4.24 (m, 2H), 3.27 (t, } J = 8.3 \text{ Hz, 2H).} \]

\[ ^{13}C \text{NMR (101 MHz, Chloroform-d)} \delta = 154.1 \text{ (q, } J = 37.2 \text{ Hz), 141.6, 131.8, 127.6, 125.8, 124.8, 117.7, 116.1 \text{ (q, } J = 287.9 \text{ Hz), 47.7 \text{ (q, } J = 4.2 \text{ Hz), 28.3 \text{ (q, } J = 1.1 \text{ Hz).}} \]

\[ ^{19}F \text{NMR (376 MHz, CDCl}_3 \text{) } \delta = -72.7. \]

2,2,2-trifluoro-1-(5-methylindolin-1-yl)ethan-1-one 5.82: 63

\[
\begin{array}{c}
\text{O} \\
\text{CF}_{3}
\end{array}
\]

Chemical Formula: C_{11}H_{10}F_{3}NO

Exact Mass: 229.0714

Following the General procedure H for indolines synthesis, 5.82 (47 mg, 0.15 mmol, 1 equiv) was reacted with Pd(PCy)_3 (10 mg, 0.015 mmol, 10 mol%), AdCO_2H (8.1 mg, 0.045 mmol, 30 mol%), Rb_2CO_3 (52 mg, 0.15 mmol, 1 equiv) in toluene (6 mL) at 160°C for 16h. After purification, 5.82 was obtained as a colorless oil (21 mg, 0.092 mmol, 62%).

\[ ^1H \text{NMR (400 MHz, Chloroform-d)} \delta = 8.08 - 8.04 (m, 1H), 7.09 - 7.04 (m, 2H), 4.28 - 4.21 (m, 2H), 3.24 - 3.17 (m, 2H), 2.34 (s, 3H). \]

\[ ^{13}C \text{NMR (101 MHz, Chloroform-d)} \delta = 154.0 \text{ (q, } J = 37.2 \text{ Hz), 139.4, 135.9, 131.9, 128.4, 125.6, 117.7, 116.3 \text{ (q, } J = 287.1 \text{ Hz) 48.0 \text{ (q, } J = 4.2 \text{ Hz), 28.5 \text{ (q, } J = 1.1 \text{ Hz), 21.2.}} \]

\[ ^{19}F \text{NMR (376 MHz, CDCl}_3 \text{) } \delta = -72.5, -72.5, -72.5. \]

methyl 1-(2,2,2-trifluoroacetyl)indoline-5-carboxylate 5.83: 64

\[
\begin{array}{c}
\text{MeO}_2\text{C} \\
\text{O} \\
\text{CF}_{3}
\end{array}
\]

Chemical Formula: C_{12}H_{10}F_{3}NO_3

Exact Mass: 273.0613
Following the General procedure H for indolines synthesis, 5.83r (53 mg, 0.15 mmol, 1 equiv) was reacted with Pd(PCy₃)₂ (10 mg, 0.015 mmol, 10 mol%), AdCO₂H (8.1 mg, 0.045 mmol, 30 mol%), Rb₂CO₃ (52 mg, 0.15 mmol, 1 equiv) in toluene (6 mL) at 160°C for 16h. After purification, 5.83 was obtained as a yellowish oil (25 mg, 0.092 mmol, 61%).

\[ ^1H \text{ NMR (400 MHz, Chloroform-}d\text{)} \delta = 8.22 – 8.18 (m, 1H), 7.97 – 7.93 (m, 1H), 7.92 – 7.89 (m, 1H), 4.36 – 4.27 (m, 2H), 3.90 (s, 3H), 3.31 – 3.25 (m, 2H). \]

\[ ^13C \text{ NMR (101 MHz, Chloroform-}d\text{)} \delta = 166.5, 154.7 (q, J = 37.8 Hz), 145.6, 132.0, 130.2, 1277, 126.3, 117.4, 116.0 (q, J = 287.8 Hz), 52.3, 48.3 (q, J = 4.2 Hz), 28.1 (d, J = 1.2 Hz). \]

\[ ^19F \text{ NMR (376 MHz, CDCl}_3\text{) } \delta = -72.8. \]

**2,2,2-trifluoro-1-(5-fluorooindolin-1-yl)ethan-1-one 5.84:**

![Chemical structure](image1)

Chemical Formula: C₁₀H₁₅F₄NO
Exact Mass: 233.0464

Following the General procedure H for indolines synthesis, 5.84r (47 mg, 0.15 mmol, 1 equiv) was reacted with Pd(PCy₃)₂ (10 mg, 0.015 mmol, 10 mol%), AdCO₂H (8.1 mg, 0.045 mmol, 30 mol%), Rb₂CO₃ (52 mg, 0.15 mmol, 1 equiv) in toluene (6 mL) at 160°C for 16h. After purification, 5.84 was obtained as a yellowish oil (13 mg, 0.056 mmol, 38%).

\[ ^1H \text{ NMR (400 MHz, Chloroform-}d\text{)} \delta = 8.20 – 8.14 (m, 1H), 6.99 – 6.92 (m, 2H), 4.34 – 4.27 (m, 2H), 3.30 – 3.21 (m, 2H). \]

\[ ^13C \text{ NMR (101 MHz, Chloroform-}d\text{)} \delta = 160.6 (d, J = 245.2 Hz), 154.1 (q, J = 37.4 Hz), 137.8, 134.0 (d, J = 8.8 Hz), 119.0 (d, J = 8.5 Hz), 116.2 (q, J = 286.2 Hz), 114.4 (d, J = 23.1 Hz), 112.3 (d, J = 24.3 Hz), 48.2 (q, J = 4.2 Hz), 28.5 (q, J = 2.1, 1.1 Hz). \]

\[ ^19F \text{ NMR (376 MHz, CDCl}_3\text{) } \delta = -72.5, -72.6. \]

**indoline-5-carbonitrile 5.85:**

![Chemical structure](image2)

Chemical Formula: C₉H₈N₂
Exact Mass: 144.0687
Following the General procedure H for indolines synthesis, 5.85r (48 mg, 0.15 mmol, 1 equiv) was reacted with Pd(PCy3)2 (10 mg, 0.015 mmol, 10 mol%), AdCO2H (8.1 mg, 0.045 mmol, 30 mol%), Rb2CO3 (52 mg, 0.15 mmol, 1 equiv) in toluene (6 mL) at 160°C for 16h. After purification, 5.85 was obtained as a yellowish oil (10 mg, 0.069 mmol, 45%).

1H NMR (400 MHz, Chloroform-d) δ = 7.31 – 7.27 (m, 2H), 6.55 – 6.51 (m, 1H), 4.23 (br. s, 1H), 3.66 (t, J = 8.6 Hz, 2H), 3.09 – 2.97 (m, 2H).

13C NMR (101 MHz, CDCl3) δ = 155.5, 133.2, 129.6, 128.1, 128.1, 120.9, 108.1, 99.7, 47.1, 28.9.

**chroman-4-one 5.92:**

![Chemical Structure](image)

Chemical Formula: C9H8O2
Exact Mass: 148.0524

Following the General procedure I for the chromanones synthesis, 5.91 (35 mg, 0.15 mmol, 1 equiv) was reacted with Pd(PCy3)2 (10 mg, 0.015 mmol, 10 mol%), AdCO2H (8.1 mg, 0.045 mmol, 30 mol%), Cs2CO3 (49 mg, 0.15 mmol, 1 equiv) in toluene (6 mL) at 120°C for 16h. After purification, 5.92 was obtained as a colorless oil (16 mg, 0.108 mmol, 72%).

1H NMR (400 MHz, Chloroform-d) δ = 7.87 – 7.82 (m, 1H), 7.45 – 7.39 (m, 1H), 6.99 – 6.90 (m, 2H), 4.51 – 4.46 (m, 2H), 2.78 – 2.74 (m, 2H).

13C NMR (101 MHz, CDCl3) δ = 191.8, 161.8, 135.9, 127.1, 121.3, 121.3, 117.9, 67.0, 37.8.

**6-methylchroman-4-one 5.95:**

![Chemical Structure](image)

Chemical Formula: C10H10O2
Exact Mass: 162.0681

Following the General procedure I for the chromanones synthesis, 5.95r (37 mg, 0.15 mmol, 1 equiv) was reacted with Pd(PCy3)2 (10 mg, 0.015 mmol, 10 mol%), AdCO2H (8.1 mg, 0.045 mmol, 30 mol%), Cs2CO3
(49 mg, 0.15 mmol, 1 equiv) in toluene (6 mL) at 120°C for 16h. After purification, 5.95 was obtained as a colorless oil (16.5 mg, 0.102 mmol, 68%).

$^1$H NMR (400 MHz, Chloroform-d) $\delta = 7.68 - 7.66$ (m, 1H), 7.29 - 7.25 (m, 1H), 6.88 - 6.84 (m, 1H), 4.51 - 4.47 (m, 2H), 2.80 - 2.75 (m, 2H), 2.29 (s, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta = 192.2$, 160.0, 137.1, 130.9, 126.8, 121.0, 117.8, 67.1, 37.9, 20.5.

6-fluorochroman-4-one 5.96: 69

![Chemical Structure](image)

Chemical Formula: C$_9$H$_7$FO$_2$

Exact Mass: 166.0430

Following the General procedure I for the chromanones synthesis, 5.96r (37 mg, 0.15 mmol, 1 equiv) was reacted with Pd(PCy$_3$)$_2$ (10 mg, 0.015 mmol, 10 mol%), AdCO$_2$H (8.1 mg, 0.045 mmol, 30 mol%), Cs$_2$CO$_3$ (49 mg, 0.15 mmol, 1 equiv) in toluene (6 mL) at 120°C for 16h. After purification, 5.96 was obtained as a colorless oil (15.5 mg, 0.093 mmol, 62%).

$^1$H NMR (400 MHz, Chloroform-d) $\delta = 7.53 - 7.47$ (m, 1H), 7.20 - 7.14 (m, 1H), 6.96 - 6.90 (m, 1H), 4.52 - 4.48 (m, 2H), 2.80 - 2.76 (m, 2H).

$^{13}$C NMR (101 MHz, Chloroform-d) $\delta = 191.1$ (d, $J = 1.9$ Hz), 158.2 (d, $J = 1.8$ Hz), 157.3 (d, $J = 241$ Hz), 123.6 (d, $J = 24.6$ Hz), 121.8 (d, $J = 6.4$ Hz), 119.7 (d, $J = 7.3$ Hz), 112.1 (d, $J = 23.2$ Hz), 67.3, 37.6 (d, $J = 1.3$ Hz).

$^{19}$F NMR (376 MHz, CDCl$_3$) $\delta = -121.5$.

6-ethylchroman-4-one 5.97: 70

![Chemical Structure](image)

Chemical Formula: C$_{11}$H$_{12}$O$_2$

Exact Mass: 176.0837

Following the General procedure I for the chromanones synthesis, 5.97r (39 mg, 0.15 mmol, 1 equiv) was reacted with Pd(PCy$_3$)$_2$ (10 mg, 0.015 mmol, 10 mol%), AdCO$_2$H (8.1 mg, 0.045 mmol, 30 mol%), Cs$_2$CO$_3$
(49 mg, 0.15 mmol, 1 equiv) in toluene (6 mL) at 120°C for 16 h. After purification, **5.97** was obtained as a colorless oil (14 mg, 0.079 mmol, 52%).

\[^1\text{H} \text{ NMR (400 MHz, Chloroform-}d\text{)} \delta = 7.66 – 7.63 (m, 1H), 7.28 – 7.23 (m, 1H), 6.85 – 6.81 (m, 1H), 4.46 – 4.42 (m, 2H), 2.75 – 2.70 (m, 2H), 2.54 (q, J = 7.5 Hz, 2H), 1.15 (t, J = 7.6 Hz, 3H).\]

\[^{13}\text{C} \text{ NMR (126 MHz, CDCl}_3\text{)} \delta = 192.3, 160.2, 137.4, 136.2, 125.7, 121.2, 117.9, 67.2, 38.0, 28.1, 15.7.\]

HRMS (ESI): Calculated for C_{11}H_{13}O_2 ([M+H]^+): Exact Mass: 177.0916; found: 177.0920

IR (neat): ν = 1685, 1469 cm\(^{-1}\)

**3,6-dimethylchroman-4-one 5.98:**

![](chemical_formula.png)

Chemical Formula: C_{11}H_{12}O_2

Exact Mass: 176.0837

Following the General procedure I for the chromanones synthesis, **5.98r** (39 mg, 0.15 mmol, 1 equiv) was reacted with Pd(PCy_3)_2 (10 mg, 0.015 mmol, 10 mol%), AdCO_2H (8.1 mg, 0.045 mmol, 30 mol%), Cs_2CO_3 (49 mg, 0.15 mmol, 1 equiv) in toluene (6 mL) at 120°C for 16 h. After purification, **5.98** was obtained as a yellowish oil (22 mg, 0.125 mmol, 82%).

\[^1\text{H} \text{ NMR (400 MHz, Chloroform-}d\text{)} \delta = 7.70 – 7.67 (m, 1H), 7.30 – 7.27 (m, 1H), 6.88 – 6.84 (m, 1H), 4.47 (dd, J = 11.3, 5.0 Hz, 1H), 4.12 (t, J = 11.0 Hz, 1H), 2.89 – 2.78 (m, 1H), 2.31 (s, 3H), 1.21 (d, J = 7.0 Hz, 3H).\]

\[^{13}\text{C} \text{ NMR (101 MHz, CDCl}_3\text{)} \delta = 195.3, 159.9, 136.9, 130.9, 127.0, 120.3, 117.6, 72.4, 40.9, 20.6, 11.0.\]

HRMS (ESI): Calculated for C_{11}H_{13}O_2 ([M+H]^+): Exact Mass: 177.0916; found: 177.0919

IR (neat): ν = 1682 cm\(^{-1}\)

**3-benzylchroman-4-one 5.99:**

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Following the General procedure I for the chromanones synthesis, 5.99 (48 mg, 0.15 mmol, 1 equiv) was reacted with Pd(PCy$_3$)$_2$ (10 mg, 0.015 mmol, 10 mol%), AdCO$_2$H (8.1 mg, 0.045 mmol, 30 mol%), Cs$_2$CO$_3$ (49 mg, 0.15 mmol, 1 equiv) in toluene (6 mL) at 120°C for 16h. After purification, 5.99 was obtained as a yellowish oil (26 mg, 0.082 mmol, 55%).

$^1$H NMR (400 MHz, Chloroform-d) $\delta = 7.97 - 7.93$ (m, 1H), 7.52 – 7.46 (m, 1H), 7.37 – 7.31 (m, 2H), 7.29 – 7.23 (m, 3H), 7.08 – 7.02 (m, 1H), 7.01 – 6.96 (m, 1H), 4.39 (dd, $J = 11.5$, 4.4 Hz, 1H), 4.19 (dd, $J = 11.5$, 8.4 Hz, 1H), 3.31 (dd, $J = 13.9$, 4.5 Hz, 1H), 3.00 – 2.91 (m, 1H), 2.73 (dd, $J = 14.0$, 10.3 Hz, 1H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta = 193.9$, 161.7, 138.4, 136.0, 129.2, 128.8, 127.6, 126.8, 121.6, 120.7, 117.9, 69.5, 47.8, 32.5.

3-phenyl-2,3-dihydrobenzofuran-3-ol 5.104:

Following General procedure J for nucleophilic addition, 5.103 (44 mg, 0.15 mmol, 1 equiv) was reacted with Pd(PCy$_3$)$_2$ (10 mg, 0.015 mmol, 10 mol%) and CsOPiv (105 mg, 0.45 mmol, 3 equiv) in toluene (6 mL) at 160°C for 16h. After purification, 5.104 was obtained as a colorless oil (22 mg, 0.104 mmol, 69%).

$^1$H NMR (400 MHz, Chloroform-d) $\delta = 7.53 – 7.49$ (m, 2H), 7.40 – 7.35 (m, 2H), 7.34 – 7.29 (m, 2H), 7.12 – 7.09 (m, 1H), 6.99 – 6.93 (m, 2H), 4.71 (d, $J = 10.3$ Hz, 1H), 4.52 (d, $J = 10.3$ Hz, 1H), 2.29 (s, 1H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta = 160.8$, 142.7, 132.3, 130.8, 128.4, 127.7, 126.2, 124.5, 121.6, 110.9, 86.3, 82.7.

5-methyl-3-phenyl-2,3-dihydrobenzofuran-3-ol 5.109:
Following General procedure J for nucleophilic addition, \textbf{5.109r} (46 mg, 0.15 mmol, 1 equiv) was reacted with \text{Pd(PCy}_3\text{)}_2 (10 mg, 0.015 mmol, 10 mol\%) and \text{CsOPiv} (105 mg, 0.45 mmol, 3 equiv) in toluene (6 mL) at 160°C for 16h. After purification, \textbf{5.109} was obtained as a colorless oil (21 mg, 0.093 mmol, 63\%).

\textbf{1H NMR (400 MHz, Benzene-\text{d}_6)} \delta = 7.46 – 7.38 (m, 2H), 7.13 – 7.08 (m, 2H), 7.06 – 7.00 (m, 1H), 6.86 – 6.84 (m, 2H), 6.68 (br. s, 1H), 4.43 (d, \text{J} = 10.1 \text{ Hz}, 1H), 4.32 (d, \text{J} = 10.1 \text{ Hz}, 1H), 1.98 (s, 3H).

\textbf{13C NMR (126 MHz, C\text{6D6})} \delta = 159.1, 143.5, 132.9, 130.9, 130.2, 128.0, 127.1, 126.1, 124.8, 110.1, 86.4, 82.3, 20.3.

\textit{5-fluoro-3-phenyl-2,3-dihydrobenzofuran-3-ol 5.110:}\n
Following General procedure J for nucleophilic addition, \textbf{5.110r} (46 mg, 0.15 mmol, 1 equiv) was reacted with \text{Pd(PCy}_3\text{)}_2 (10 mg, 0.015 mmol, 10 mol\%) and \text{CsOPiv} (105 mg, 0.45 mmol, 3 equiv) in toluene (6 mL) at 160°C for 16h. After purification, \textbf{5.110} was obtained as a colorless oil (27 mg, 0.117 mmol, 78\%).

\textbf{1H NMR (400 MHz, Benzene-\text{d}_6)} \delta = 7.30 – 7.23 (m, 2H), 7.09 – 7.00 (m, 3H), 6.71 – 6.64 (m, 1H), 6.62 – 6.57 (m, 1H), 6.54 – 6.50 (m, 1H), 4.33 (d, \text{J} = 10.2 \text{ Hz}, 1H), 4.22 (d, \text{J} = 10.2 \text{ Hz}, 1H).

\textbf{13C NMR (126 MHz, Benzene-\text{d}_6)} \delta = 158.7, 156.8 (d, \text{J} = 6.7 \text{ Hz}), 142.6, 133.8 (d, \text{J} = 7.6 \text{ Hz}), 128.1, 125.8, 116.8 (d, \text{J} = 24.5 \text{ Hz}), 111.1 (d, \text{J} = 24.5 \text{ Hz}), 111.0 (d, \text{J} = 8.1 \text{ Hz}), 86.5, 82.1 (d, \text{J} = 1.8 \text{ Hz}).

\textbf{19F NMR (471 MHz, C\text{6D6})} \delta = -122.7
3-(3,5-dimethoxyphenyl)-2,3-dihydrobenzofuran-3-ol 5.III:

![Chemical Structure](image)

Chemical Formula: C_{16}H_{17}O_{4}
Exact Mass: 272.1049

Following General procedure J for nucleophilic addition, 5.IIIr (53 mg, 0.15 mmol, 1 equiv) was reacted with Pd(PCy$_3$)$_2$ (10 mg, 0.015 mmol, 10 mol%) and CsOPiv (105 mg, 0.45 mmol, 3 equiv) in toluene (6 mL) at 160°C for 16h. After purification, 5.III was obtained as a yellowish oil (24 mg, 0.088 mmol, 59%).

$^1$H NMR (400 MHz, Benzene-d$_6$) $\delta = 7.05 - 7.00$ (m, 1H), 6.99 – 6.95 (m, 1H), 6.92 – 6.88 (m, 1H), 6.82 – 6.79 (m, 2H), 6.75 – 6.65 (m, 1H), 6.50 – 6.47 (m, 1H), 4.46 (d, $J = 10.1$ Hz, 1H), 4.41 (d, $J = 10.1$ Hz, 1H), 3.25 (s, 6H).

$^{13}$C NMR (101 MHz, C$_6$D$_6$) $\delta = 161.1, 161.0, 145.9, 132.6, 130.4, 124.5, 121.1, 110.6, 104.5, 99.7, 86.2, 82.3, 54.5$.

HRMS (ESI): Calculated for C$_{16}$H$_{17}$O$_4$ ([M+H]$^+$): Exact Mass: 273.1127; found: 273.1129

IR (neat) : $\nu = 1340$ cm$^{-1}$

3-(3-methoxy-4-(trifluoromethyl)phenyl)-2,3-dihydrobenzofuran-3-ol 5.II2:

![Chemical Structure](image)

Chemical Formula: C$_{16}$H$_{19}$F$_3$O$_3$
Exact Mass: 310.0817

Following General procedure J for nucleophilic addition, 5.II2r (58 mg, 0.15 mmol, 1 equiv) was reacted with Pd(PCy$_3$)$_2$ (10 mg, 0.015 mmol, 10 mol%) and CsOPiv (105 mg, 0.45 mmol, 3 equiv) in toluene (6 mL) at 160°C for 16h. After purification, 5.II2 was obtained as a yellowish oil (23 mg, 0.075 mmol, 50%).
\[ ^1H \text{ NMR (400 MHz, Benzene-}d_6) \delta = 8.01 - 7.97 (m, 1H), 7.19 - 7.16 (m, 1H), 7.05 - 7.00 (m, 1H), 6.91 - 6.87 (m, 1H), 6.82 - 6.78 (m, 1H), 6.72 - 6.66 (m, 1H), 6.31 - 6.25 (m, 1H), 4.33 (d, J = 10.3 Hz, 1H), 4.15 (d, J = 10.3 Hz, 1H), 3.15 (s, 3H). \]

\[ ^{13}C \text{ NMR (101 MHz, Benzene-}d_6) \delta = 160.9, 156.8 (q, J = 1.6 Hz), 135.1, 132.2, 131.0 (q, J = 1.1 Hz), 130.6, 124.7 (q, J = 5.3 Hz), 124.3, 124.2 (q, J = 275.2 Hz), 121.2, 118.2, 111.6, 110.7, 85.8, 81.5, 55.0. \]

\[ ^{19}F \text{ NMR (376 MHz, C}_6\text{D}_6) \delta = -61.9. \]

HRMS (ESI): Calculated for C\textsubscript{16}H\textsubscript{14}F\textsubscript{3}O\textsubscript{3} ([M+H]\textsuperscript{+}): Exact Mass: 311.0895; found: 311.0899

IR (neat) : \nu = 2361, 1330 cm\textsuperscript{-1}

3-(4-methoxyphenyl)-2,3-dihydrobenzofuran-3-ol 5.113:

Following General procedure J for nucleophilic addition, 5.113r (48 mg, 0.15 mmol, 1 equiv) was reacted with Pd(PCy\textsubscript{3})\textsubscript{2} (10 mg, 0.015 mmol, 10 mol%) and CsOPiv (105 mg, 0.45 mmol, 3 equiv) in toluene (6 mL) at 160°C for 16h. After purification, 5.113 was obtained as a colorless oil (21 mg, 0.087 mmol, 57%).

\[ ^1H \text{ NMR (400 MHz, Benzene-}d_6) \delta = 7.34 - 7.28 (m, 2H), 7.07 - 7.01 (m, 1H), 6.94 - 6.90 (m, 2H), 6.76 - 6.67 (m, 3H), 4.44 (d, J = 10.1 Hz, 1H), 4.31 (d, J = 10.1 Hz, 1H), 3.27 (s, 3H). \]

\[ ^{13}C \text{ NMR (126 MHz, C}_6\text{D}_6) \delta = 161.0, 159.1, 135.3, 133.0, 130.2, 127.3, 124.5, 121.0, 113.5, 110.6, 86.2, 81.9, 54.4. \]

3-(4-fluorophenyl)-2,3-dihydrobenzofuran-3-ol 5.114:
Following General procedure J for nucleophilic addition, 5.114r (46 mg, 0.15 mmol, 1 equiv) was reacted with Pd(PCy$_3$)$_2$ (10 mg, 0.015 mmol, 10 mol%) and CsOPiv (105 mg, 0.45 mmol, 3 equiv) in toluene (6 mL) at 160°C for 16h. After purification, 5.114 was obtained as a colorless oil (26 mg, 0.113 mmol, 74%).

$^1$H NMR (400 MHz, Benzene-$d_6$) $\delta =$ 7.14 – 7.10 (m, 2H), 7.05 – 7.00 (m, 1H), 6.90 – 6.87 (m, 1H), 6.78 – 6.75 (m, 1H), 6.75 – 6.66 (m, 3H), 4.32 (d, $J = 10.2$ Hz, 1H), 4.13 (d, $J = 10.2$ Hz, 1H).

$^{13}$C NMR (126 MHz, Benzene-$d_6$) $\delta =$ 163.1, 161.2, 160.9, 139.0 (d, $J = 3.1$ Hz), 132.5, 130.4, 124.3, 121.1, 114.7 (d, $J = 21.3$ Hz), 110.6, 86.0, 81.2.

$^{19}$F NMR (471 MHz, C$_6$D$_6$) $\delta =$ -115.6.

HRMS (ESI): Calculated for C$_{14}$H$_{12}$FO$_2$ ([M+H]$^+$): Exact Mass: 231.0821; found: 231.0825

IR (neat) : $\nu =$ 1351 cm$^{-1}$

3-(4-methoxyphenyl)benzofuran 5.118: 76

After leaving 5.113 in CDCl$_3$ overnight at 25°C, the organic phase was washed with water, dried over sodium sulfate, filtered and evaporated to give the desired product pure product 5.118 as a colorless oil (19 mg, 0.087 mmol, 100%).
After leaving 5.114 in CDCl₃ overnight at 25°C, the organic phase was washed with water, dried over sodium sulfate, filtered and evaporated to give the desired product 5.119 as a colorless oil (24 mg, 0.112 mmol, 100%).

**3-(4-fluorophenyl)benzofuran 5.119:**

![Chemical structure of 3-(4-fluorophenyl)benzofuran](attachment:image)

Chemical Formula: C₁₄H₉FO
Exact Mass: 212.0637
NMR spectra

1.1: A Four-Step Synthesis of (±)-γ-lycorane via Pd⁰-
Catalyzed Double C(sp²)–H/C(sp³)–H Arylation

(Numbering based on Org. Lett. 2018, 203, 772-775)
448
1.2: Synthesis of β-Lactams by Palladium(0)-Catalyzed 
$\text{C}(\text{sp}^3)\text{-H Carbamoylation}$

Chemical Formula: C_{43}H_{64}ClINOP_{2}Pd
Exact Mass: 793.16215
Chemical Formula: C_{12}H_{12}Cl_{2}OP
Exact Mass: 320.08636
Chemical Formula: C₃₅H₂₂F₂₄O₄
Exact Mass: 998.11349
Chemical Formula: C_{18}H_{23}N
Exact Mass: 253.1830

Chemical Formula: C_{18}H_{23}N
Exact Mass: 253.1830
Chemical Formula: C_{18}H_{23}NO_3
Exact Mass: 309.2304
S_7
Chemical Formula: C₇H₁₃N
Exact Mass: 141.1517
Chemical Formula: C₁₃H₁₃N
Exact Mass: 191.1674
Chemical Formula: C_{11}H_{15}N
Exact Mass: 149.1204
Chemical Formula: C$_{11}$H$_{17}$N
Exact Mass: 163.1361
Chemical Formula: C_{12}H_{19}N
Exact Mass: 177.1517
Chemical Formula: C₆H₁₀NO₂
Exact Mass: 145.1103
Chemical Formula: C_{14}H_{18}N_{2}O_{2}
Exact Mass: 246.1368

Chemical Formula: C_{14}H_{18}N_{2}O_{2}
Exact Mass: 246.1368
Chemical Formula: $C_9H_{14}N$
Exact Mass: 208.1830

Chemical Formula: $C_{14}H_{23}N$
Exact Mass: 205.1830
Chemical Formula: \( C_{10}H_{12}N \)
Exact Mass: 253.1830

\( s_1 \)
Chemical Formula: C_{14}H_{29}N
Exact Mass: 211.2300
Chemical Formula: C_{44}H_{52}N
Exact Mass: 207.1987
Chemical Formula: C_{12}H_{12}N

Exact Mass: 175.1361

$S_{ss}$
Chemical Formula: C10H12NO3
Exact Mass: 313.1678
Chemical Formula: C_{13}H_{22}NO_{3}

Chemical Formula: C_{14}H_{20}CINO_{4}

1a
Chemical Formula: $C_{17}H_{26}ClNO_4$

1e

Chemical Formula: $C_{13}H_{24}ClNO_4$

1g
Chemical Formula: C_{10}H_{15}CINO

1k

Chemical Formula: C_{14}H_{29}CINO

11
Chemical Formula: C_{10}H_{12}ClNO

Chemical Formula: C_{11}H_{14}ClNO
Chemical Formula: C₉H₁₈ClNO₃

Chemical Formula: C₁₃H₁₇ClN₂O₃
Chemical Formula: C_{15}H_{25}ClNO
1u

Chemical Formula: C_{15}H_{25}ClNO
1v
Chemical Formula: \( \text{C}_{15}\text{H}_{24}\text{ClNO} \)

\( 1w \)

Chemical Formula: \( \text{C}_{10}\text{H}_{16}\text{ClNO}_2 \)

\( 1x \)
Chemical Formula: C_{13}H_{16}ClNO

1aa

Chemical Formula: C_{20}H_{22}ClNO_4

1ab
Chemical Formula: C_{13}H_{22}ClNO

Chemical Formula: C_{20}H_{22}ClNO_4
Chemical Formula: C_{12}H_{18}NO_4
Exact Mass: 250.1314
$^{13}$C labeled reaction:
Chemical Formula: C_{13}H_{17}NO_4
Exact Mass: 251.1158
Chemical Formula: C_{19}H_{26}NO_{4}
Exact Mass: 335.2097
2f
Chemical Formula: C_{12}H_{22}NO_{4}
Exact Mass: 333.1940
2g
Chemical Formula: C₁₆H₁₂NO₄
Exact Mass: 327.1471
Chemical Formula: C_{14}H_{19}NO
Exact Mass: 217.1467
Chemical Formula: C11H10NO
Exact Mass: 189.1154
Chemical Formula:
C_{13}H_{12}N_{2}O_{4}
Exact Mass:
289.1188
2r
Chemical Formula: $C_{15}H_{21}NO$

Exact Mass: 231.1623

2s
Chemical Formula: C₁₃H₂₁NO
Exact Mass: 279.1623

2t
Chemical Formula: $C_{15}H_{23}NO$
Exact Mass: 233.1790
Chemical Formula:
C_{14}H_{23}NO

Exact Mass:
233.1780
Chemical Formula: C\textsubscript{11}H\textsubscript{17}NO\textsubscript{2}
Exact Mass: 195.1259

2x

[Diagram of molecular structure]

Chemical Formula: C\textsubscript{11}H\textsubscript{17}NO\textsubscript{2}
Exact Mass: 195.1259

2x

[Diagram of molecular structure]
Chemical Formula: C_{15}H_{14}NO_{4}
Exact Mass: 277.1314

2y
Chemical Formula: C₁₀H₁₃NO₄
Exact Mass: 317.1627

2z

Chemical Formula: C₁₀H₁₃NO₄
Exact Mass: 317.1627

2z
Chemical Formula: C₂₀H₁₂NO₄
Exact Mass: 339.1471

2ab
Chemical Formula: C_{22}H_{22}NO_{4}
Exact Mass: 353.1627
2ac
Chemical Formula: C₂₁H₂₃NO₄
Exact Mass: 353.1627
(−)-2ac
Chemical Formula: C_{10}H_{12}NO_{4}
Exact Mass: 293.1627
85:15
2af
cis-product (minor product)
cis-product (minor product)
Chemical Formula: C\textsubscript{10}H\textsubscript{8}NO
Exact Mass: 173.0841
(-)-4ac
Chemical Formula: \( C_{11}H_{14}ClNO_{2} \)

Exact Mass: 227.0713

(+)Sac
1.3: Domino Pd$^0$-Catalyzed C(sp$^3$)–H Arylation/Electrocyclic Reactions via Benzazetidine Intermediates

Products:

2f

2f
2g

1H NMR (CDCl₃, ppm): 6.80-7.00 (m, 2H), 7.20-7.40 (m, 2H).

13C NMR (CDCl₃, ppm): 150.0 (C), 140.0 (C), 130.0 (C), 120.0 (C).

Chemical shifts and coupling constants (Hz) are also provided for specific peaks.
2h
2.1: 1,4-Palladium Shift/C(sp$^3$)–H Activation Strategy for the Remote Construction of Five-Membered Rings

(Numbering base on *Org. Lett.* 2019, 21, 1434–1437)
639
2.3: Redox-Neutral Coupling between Two C(sp³)–H Bonds Enabled by 1,4-Palladium Shift for the Synthesis of Fused Heterocycles

(Numbering based on Angew. Chem. Int. Ed. 10.1002/anie.201908460)
Curriculum Vitae

Ronan ROCABOY
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Actual position: 4th year PhD student (Pr. O. Baudoin), Basel University

Languages: French (native), English (fluent), Spanish (good level), German (Basic Knowledge)

References: olivier.baudoin@unibas.ch; xavier.bugaut@univ-amu.fr; cyril.bressy@univ-amu.fr; buurma@cardiff.ac.uk; jacques.lebreton@univ-nantes.fr

Profile: 4th year PhD student in synthetic organic chemistry, with expertise in organic synthesis, catalysis and analytical methods. Highly motivated, rigorous, good communication, organized and team-work skills.

- PhD R&D in Organic Chemistry
- Analytical Technics expertise: Commons NMR analysis, HPLC, GCMS, HRMS analysis
- Research project manager
- Scientific communication
- Scientific and technical coach of students in chemistry and manager of small teams.
- Strong publication record

Education:

2015 – To present: 4th year PhD Student in synthetic organic chemistry, Basel University, Switzerland.

2014- 2015: Master Science in Chemistry with honor, Chimie fine et thérapeutique, Université de Nantes, France.

2010 – 2013: Bachelor degree in Chemistry with distinction, Licence de Chimie, Université de Nantes, France.

Experiences:

2015 – To present: PhD in synthetic organic chemistry, Basel University, Switzerland. New access to medium-sized heterocycles using palladium catalysed C-H activation. Advisor: Pr. D. O. Baudoin.

4 years R&D experience in organic chemistry: Development of new synthetic processes. Synthesis of heterocycles with palladium catalysis. Applications for the
synthesis of natural products, and building blocks with biological activities. **Multi-step synthesis. Synthesis optimisation. Analytical technics:** $^1$H, $^{13}$C, $^{19}$F, $^{31}$P and 2D NMR spectroscopy, IR/Raman, Preparative HPLC, GCMS, TLC-MS. Chromatography, preparative HPLC, distillation, recrystallization. **Independent project leader. Project collaboration with a company** (Spirochem, Basel). Best oral presentation prize, 2018 Regiosymposium, Falkau, Germany. Results were published in very high impact, peer-reviewed journals.

**2015: 6 months M. Sc. Internship in organic chemistry,** Aix-Marseille Université, France. Advisors: Pr. D. C. Bressy and Dr. X. Bugaut.

Synthesis of pyridines atropisomers: conversion of chirality from central to axial.

**2014: 4 months M. Sc. internship in organic and physical chemistry,** Cardiff University, Wales. Advisor: Dr. Niklaas Buurma.

Development of new DNA-binders.

**2013: 2 months B. Sc. internship in synthetic organic chemistry,** Nantes University. Advisors: Dr. M. Mathe-Allainmat; P. D. J. Lebreton.

Synthesis of bioactive piperidines derivatives for the treatment of breast cancer.

**Teaching:**

**2015 - 2018:** Lab supervisor for bachelor students: Tuition of undergraduates in practical skills in organic chemistry (3rd semester organic chemistry students).

**2015 - 2019:** Supervisor for 1 PhD student, 2 B. Sc. students and 1 Master student.

**List of publications:**

1- Redox-neutral Coupling between Two C(sp$^3$)-H Bonds Enabled by 1,4-Palladium Shift for the Synthesis of Fused Heterocycles, **R. Rocaboy, I. Anastasiou, O. Baudoin,** *Angew. Chem. Int. Ed.* **2019,** ASAP

2- 1,4-Palladium Shift/C(sp$^3$)–H Activation Strategy for the Remote Construction of Five-Membered Rings, **R. Rocaboy, O. Baudoin,** *Org. Lett.,* **2019,** 21, 1434–1437


4- A Four-Step Synthesis of (+)-γ-Lycorane via Pd$^0$-Catalysed Double C(sp$^3$)–H/C(sp$^3$)–H Arylation, **R. Rocaboy, D. Dailler, O. Baudoin,** *Org. Lett.** **2018,** 20, 772-775

5- Synthesis of β-Lactams by Palladium$^0$-Catalysed C(sp$^3$)–H Carbamoylation, **D. Dailler, R. Rocaboy, O. Baudoin,** *Angew. Chem. Int. Ed.,* **2017,** 56, 7218-7222
Participation in scientific forums and communications:

2018: Best oral presentation award: Regiosymposium conference, Falkau, Germany

2018: Travel award for conference and Poster presentation, Belgian Organic Synthesis Symposium (BOSS XVI), Brussels.


2017: Poster presentation, SCS fall meeting, Bern.

Informatic skills:

Analytical tools: Mestrenova, Top-spin, Mercury, Shimadzu software (Lab Solution for Shimadzu preparative and chiral HPLC, GCMS solution software), TLC-MS software.


Personal interests:

Sports (Football (trainer for 6 years old children), Tennis, Badminton), guitar, cooking, travelling, reading.
3. R. Jiang et al., *Jingxi Shiyou Huagong*, 2013, 30, 12-16
7. Z. Xu et al., *Synlett*, 2006 (12), 1953-1955