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DEVELOPMENT OF NEW CONCEPTS FOR THE C–H FUNCTIONALIZATION OF CYCLIC AMINES

by

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ABSTRACT OF THE DISSERTATION

Development of New Concepts for the C–H Functionalization of Cyclic Amines

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The functionalization of non-activated C–H bond of cyclic amines is of great importance due to the ubiquity of complex molecular structures containing functionalized cyclic amine moieties. Most previously developed methods for this purpose involve the use of deprotonating bases, external oxidants and/or metal catalysts. An alternative pathway for the C–H functionalization of cyclic amines via the intermediacy of azomethine ylides will be discussed in this dissertation. Transformations developed combine a reductive N-alkylation with an oxidative C–H functionalization, thus enabling the functionalization of cyclic amines in a redox-neutral fashion. Specific research projects outlined include α-cyanation, α-arylation, the redox-Mannich reaction, α,β-difunctionalization and the redox-annulation involving β-ketoaldehydes. Functionalized amine products are obtained from readily available starting materials in the presence of simple carboxylic acid, and in some cases, no additive is required.

The majority of established methods for the C–H functionalization of cyclic amines require pre-functionalization on the amine nitrogen, thus extra steps for the removal of directing/protecting group are often needed in order to obtain N-H amines. To avoid this limitation, an α-functionalization of cyclic N-H amines via intermolecular hydride transfer is developed and will also be discussed in this dissertation. Aryllithium reagents are used as nucleophiles for most reactions of this type demonstrated in this dissertation, and a few examples involving trans-styryllithium and alkyllithium reagents are also shown.
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DEDICATION

Dedicated to past days
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Chapter I

Introduction

1.1 Background

Functionalized amines are widespread structural motifs in natural products and biologically active compounds. Extensive efforts thus have been made on the facile functionalization of amines, especially the activation of the sp<sup>3</sup> C–H bonds adjacent to the nitrogen atoms of cyclic amines, considering the ubiquity of the α-functionalized cyclic amines.<sup>1</sup> The mainstream methods for the α-functionalization of cyclic amines can be divided into several categories, according to the reactive α-amino species generated in the chemical reaction (Figure 1.1). Although most methods still heavily rely on the function of strong base, metals and/or external oxidants, there are a few reported redox-neutral approaches which attract much attention and interest due to their atom-economy.

Figure 1.1 Major Reactive α-Amino Species involved in the α-Functionalization of Amines

Redox economy is an important concept in modern organic synthesis.<sup>2</sup> The goal is to avoid the unnecessary fluctuation of the overall oxidation state of a compound in a synthetic sequence, in other words, the non-strategic or corrective oxidation or reduction steps. To achieve this, it is crucial to choose proper reactions and orders to break each bond in a compound in terms of the retro-synthetic analysis. Another way to realize the goal of the redox economy in a
synthesis is using redox-neutral reactions which either undergo a redox isomerization process or couple an oxidation step with a reduction step, so no external oxidant or reductant is needed.\textsuperscript{3} Figure 1.2 shows some of the representative examples of redox-neutral reactions.

**Figure 1.2 Redox-Neutral Reactions**

\[ \text{MeCH}_2 \text{CHO} + \text{SmI}_2 (15 \text{ mol\%}) \rightarrow \text{MeCH}_2 \text{SmI}_2 \rightarrow \text{MeCH}_2 \text{SmI}_2 \rightarrow \text{MeCH}_2 \text{CHO} \]

1.2 α-Amino Anions as Reactive Intermediates

Perhaps the oldest and most practical method for the α-functionalization of cyclic amines is the deprotonative α-lithiation by alkyl lithium, in most cases in the presence of a diamine ligand, followed by treating the generated α-amino anion intermediate with an electrophile. A dipole-stabilizing group is usually pre-installed on the nitrogen atom of the amine, directing the deprotonation of the α-proton and stabilizing the formed C–Li dipole. Among those dipole-stabilizing groups used, the tert-butyl carbamate (Boc) group is the most common one. The diamine ligand is involved in 1) changing the aggregation state of the organolithium reagent and accelerating the α-deprotonation of the amine; 2) stabilizing the dipole of the α-amino anion intermediate; 3) rendering enantioselectivity to the reaction when enantioenriched chiral diamine...
ligand is used. The first deprotonative $\alpha$-functionalization of amines was reported in 1989 by Beak and co-workers, where $N$-Boc cyclic amines were deprotonated by $s$-BuLi in the presence of $N,N,N'N'$-tetramethylethylenediamine (TMEDA) at $-78^\circ$C followed by reaction with TMSCl (Figure 1.3, eq 6).\textsuperscript{4} Nearly twenty years later O’Brien and co-workers found that the strong coordination ability of THF could facilitate the $\alpha$-lithiation of $N$-Boc amines, and therefore developed a diamine-free lithiation strategy for the $\alpha$-functionalization of $N$-Boc amines using THF as the solvent.\textsuperscript{5} Beak and co-workers later reported the enantioselective $\alpha$-functionalization of $N$-Boc pyrrolidine with $(-)$-sparteine as the chiral ligand.\textsuperscript{6} Good to excellent yields and enantiomeric ratios were obtained when trapping the $\alpha$-amino anion with different electrophiles. The opposite enantiomer of $(-)$-sparteine is not naturally occurring, however, $(+)$-sparteine surrogate was developed by O’Brien and co-workers in 2002 (Figure 1.3, eq 7).\textsuperscript{7} and the same group also developed a modified asymmetric reaction involving only catalytic amounts of $(+)$-sparteine surrogate and stoichiometric amounts of a “dummy” ligand bispidine \textsuperscript{1.26} (Figure 1.3, eq 8).\textsuperscript{8} In 2006, Campos at Merck reported a method which involved the transmetallation of the deprotonated $\alpha$-aminoorganolithium intermediate with zinc chloride. The stable organozinc species could then undergo a Negishi-type coupling with an arylhalide to provide enantioenriched 2-aryl $N$-Boc pyrrolidine (Figure 1.3, eq 9).\textsuperscript{9} Prior to this example, Dieter and co-workers had developed a deprotonative enantioselective coupling reaction involving $\alpha$-aminoorganocuprates, in order to avoid the configurational lability of the $\alpha$-aminoorganolithium intermediates and thus expand the scope of the coupling partner.\textsuperscript{10} The Fu group demonstrated that such enantioselective coupling reactions involving organozinc species could also be catalyzed by nickel, using alkylhalides as coupling partners. Excellent yields and enantioselectivities were obtained (Figure 1.3, eq 10).\textsuperscript{11}
1.3 Iminium Ions as Reactive Intermediates

1.3.1 Transition-Metal-Catalyzed Amine α-Functionalization

One of the earliest examples of reactions involving α-amino cation intermediates was reported by Murahashi and co-workers in 2003. An oxidative cyanation of tertiary amines was reported using ruthenium chloride as the metal catalyst and molecular oxygen as the stoichiometric oxidant (Figure 1.4, eq 11). Li and co-workers later developed a methodology which was termed the Cross Dehydrogenative Coupling (CDC) reaction, employing a copper salt as the catalyst and an external oxidant such as tert-butyl hydroperoxide. The scope of nucleophiles in CDC reactions was very broad, including alkynes, malonates, nitromethanes and aromatic compounds. The first enantioselective dehydrogenative alkylation was also reported by the same group with a copper triflate/pyridinyl bisoxazoline (Pybox) complex as the
catalyst. Moderate yields and enantiomeric ratios were obtained (Figure 1.4, eq 12).\textsuperscript{15} Besides ruthenium and copper, many other transition metals were also reported as catalysts for the oxidation of cyclic amines to iminium ions, including iron,\textsuperscript{16} vanadium,\textsuperscript{17} gold,\textsuperscript{18} rhodium\textsuperscript{19} and palladium.\textsuperscript{20} Although most metal-based oxidative methods required the use of stoichiometric external oxidant, Liang and co-workers have discovered that PtCl\textsubscript{2} could catalyze the CDC reaction of cyclic amines without other oxidant (Figure 1.4, eq 13).\textsuperscript{21} The formation of hydrogen was detected in this reaction.

\textbf{Figure 1.4 Transition-Metal-Catalyzed Amine $\alpha$-Functionalization}

\textbf{1.3.2 Metal-Free Oxidative Amine $\alpha$-Functionalization}

Several reported methods have achieved the metal-free functionalization of amines. Qing and co-workers have reported the $\alpha$-trifluoromethylation of $N$-protected tetrahydroisoquinolines (THIQs) via oxidation with benzoyl peroxide (Figure 1.5, eq 14). Besides TMSCF\textsubscript{3}, other nucleophiles such as indole, nitromethane, cyanide and alkyne were also compatible with the reaction conditions and gave good to excellent yields of the corresponding products.\textsuperscript{22} In 2009, the Liang group reported the oxidation and functionalization of cyclic $N$-aryl amines employing the hypervalent iodine reagent PhI(OAc)\textsubscript{2} (Figure 1.5, eqs 15–16).\textsuperscript{23} When amines containing $\beta$-hydrogens such as $N$-aryl piperidines were used, an cis-$\alpha$,$\beta$-diacetoxylation reaction occurred which was proposed to go through the corresponding enamine intermediates. Substrates without
a β-hydrogen such as N-aryl THIQs provided benzylic α-functionalized products upon addition of nucleophiles to the reaction mixture. A unique method for the α-cyanation of tertiary amines was reported by Lambert and co-workers where tropylium ion was used as the chemical oxidant for the oxidation of amines (Figure 1.5, eq 17).24

**Figure 1.5 Chemical Oxidant-Mediated Amine Functionalization**

![Diagram of chemical reactions](image)

1.3.3 The “Cation Pool” Method

The electrochemical oxidation, sometimes called the “Cation Pool” method, was developed by Yoshida and co-workers and provides N-acyliminium ions by anodic oxidation of N-acylamines in an electrolysis process. The iminium ion generated by the irreversible electrochemical oxidation at low temperature can be stabilized and accumulated in high concentration, rapidly reacting with a wide scope of nucleophiles (Figure 1.6). Tetrabutylammonium tetrafluoroborate (n-Bu₄NBF₄) is often used as the electrolyte and dichloromethane as the solvent due to its low viscosity at low temperature. The cathodic chamber is filled with trifluoromethanesulfonic acid (TfOH) solution which is reduced to hydrogen gas.25
1.3.4 The Catalytic Photo-Oxidation of Amines

Another methodology recently discovered and rapidly developed for the α-functionalization of tertiary amines involves a photo-oxidation process. Intermediate iminium ions are generated in the presence of a photocatalyst activated by visible light. The photocatalyst can be metal-based (e.g., iridium or ruthenium complexes). In 2010, Stephenson and co-workers reported a photoredox nitro-Mannich reaction of N-aryl THIQ and nitromethane (Figure 1.7, eq 19). In contrast to N-aryl THIQ, N-aryl pyrrolidine was a poor substrate for this reaction, and only low yield of the desired product was obtained. Besides metal-based photocatalysts, organic dyes are alternatives for this type of reaction. The group of König reported an Eosin Y-catalyzed photooxidative C–H functionalization of N-aryl THIQ (Figure 1.7, eq 20). A wide scope of nucleophiles are compatible with the reaction conditions, such as dialkyl phosphonates, malonitriles, nitroalkanes and malonates, giving moderate to excellent yields.
1.4 α-Amino Radicals as Reactive Intermediates

The α-amino radical is another important type of reactive intermediates involved in the α-functionalization of amines. As early as in 1990, Snieckus and Curran reported that treating ortho-halobenzamide with tributyltin hydride and AIBN generated the radical on the phenyl ring, which underwent a 1,5-hydrogen atom transfer to translocate the radical at the α-amino position. The α-amino radical could be trapped by an olefin both intermolecularly and intramolecularly (Figure 1.8, eq 21). Undheim and co-workers then extended this method to ortho-iodobenzyl-protected tertiary amines. Besides phenyl radicals, vinyl radicals were also demonstrated by Robertson and co-workers to undergo a similar process. The resulting α-amino radical however reacted rapidly with the pendent vinyl group intramolecularly to form the cyclization product (Figure 1.8, eq 22). As a complement to using tin hydride and AIBN as the radical generator, Murakami and Ito reported that samarium iodide could be used as well to generate the phenyl radical through the deiodination of the ortho-iodobenzyl-protected amine (Figure 1.8, eq 23). In addition to the methods generating α-amino radicals via the 1,5-hydrogen atom transfer, there were other ways reported to form the desired radical intermediates. In 2005, Yoshimitsu and Nagaoka found that ethyl radical formed from the aerobic oxidation of triethylborane could abstract an α-hydrogen atom from lactams or tertiary amines. The α-amino radicals generated then underwent radical hydroxyalkylation with aldehydes (Figure 1.8, eq 24). tert-Butyl hydroperoxide was used as a radical initiator for a thiolation reaction involving N-methyl pyrrolidinone and disulfides. Yoshida’s “Cation Pool” chemistry was also applied to the radical-based α-functionalization of amines. The N-acyl iminium ion produced from the electrochemical oxidation underwent the one-electron reduction to form the N-acyl α-amino radical, which reacted with acrylates to give final products (Figure 1.8, eq 25). Photosensitizers can be used in the presence of light to oxidize amines to the corresponding α-amino radicals. The group of Yoshimitsu reported a benzophenone catalyzed photochemical C–H carbamoylation reaction in their total synthesis of (±)-Kainic acid (Figure 1.8, eq 26). In 2011, MacMillan and co-workers reported an iridium photocatalyzed α-arylation of N-aryl amines (Figure 1.8, eq 27). 4-Substituted cyanoarenes were reduced by photo-excited
[Ir^{III}(ppy)_3] complex to form arene radical anions. The oxidized [Ir^{IV}(ppy)_3] complex then underwent a single-electron transfer from N-aryl amines to produce amine radical cations, which were deprotonated by a base to form α-amino radicals. The arene radical cation could react with the α-amino radical to provide the final product with loss of a cyanide ion.

**Figure 1.8 Functionalizations Involving α-Amino Radical Intermediates**

1.5 Transition-Metal-Catalyzed Amine α-Functionalization (without the Formation of Iminium Intermediates)

1.5.1 Inner Sphere Mechanism – the Oxidative Insertion into a C–H Bond

Although few, there are reports emerging in recent years using transition metals to catalyze the C–H bond activation of amines without the formation of iminium ion intermediates. Methods going through the inner sphere mechanism involve the oxidative addition of a C–H bond to the metal center. In 2006, the Sames group first reported a ruthenium catalyzed α-arylation of
amidines, directed by a $N$-pyrroline group (Figure 1.9, eq 28). The reaction mechanism was proposed to involve an oxidative addition of the pyrrolidine $\alpha$-C–H bond to the ruthenium, followed by a hydride transfer from the metal center to the oxidizing reagent tert-butyl methylketone.

**Figure 1.9 Ru-Catalyzed $\alpha$-Arylation of Tertiary Amines**

![Image](image.png)

**1.5.2 Outer Sphere Mechanism – the Carbenoid/Nitrenoid Insertion**

The functionalization of amines via the outer sphere mechanism involves the insertion of a carbenoid or nitrenoid into the $\alpha$-C–H bond of the amine. An important example of this methodology was reported by Davies and co-workers where aryl diazoacetates enantioselectively inserted into the $\alpha$-C–H bond of $N$-Boc cyclic amines catalyzed by a chiral dirhodium complex 1.68 (Figure 1.10, eq 29). Although the reaction had a broad substrate scope regarding the amine moiety, the six-membered $N$-Boc piperidine gave very slow reaction rate. It was proposed that the chair conformation of piperidine was sterically unfavorable for the catalyst. The screening of the prolinate ligands showed that complex 1.69 was an improved catalyst for the reaction involving piperidine. Preceding Davies’ studies, the group of Winkler in 1999 reported the same transformation using catalyst 1.71, which improved diastereoselectivity while exhibiting lower enantioselectivity. When the mono-carbenoid insertion product was exposed to the same reaction conditions, excellent yield and diastereoselectivity of the C$_2$-symmetric 2,5-disubstituted $N$-Boc pyrrolidine was obtained (Figure 1.10, eq 30). A one-pot process was also developed giving the disubstituted product directly from $N$-Boc pyrrolidine, giving even higher enantioselectivities. Further studies demonstrated that the chirality of only one enantiomer of the catalyst matched the chirality of the enantioenriched 2-substituted $N$-Boc pyrrolidine, and the mismatched enantiomer of the catalyst produced complex mixtures. This finding led the authors to successfully develop a kinetic resolution of racemic 2- and 3-substituted pyrrolidines.
Du Bois and co-workers have reported a rhodium-catalyzed nitrenoid insertion converting carbamates to oxazolidinones (Figure 1.10, eq 31).\textsuperscript{41} The carbamate amino group was oxidized to the nitrenoid by PhI(OAc)\textsubscript{2} in the presence of 5 mol\% of dirhodium catalyst, which intramolecularly inserted into a β-C–H bond forming the oxazolidinone. Magnesium oxide was used to neutralize the acetic acid byproduct. Oxazolidinones could then be hydrolyzed to provide 1,2-amino alcohols. Sulfamate esters underwent similar reactions furnishing γ-C–H insertion products, which were transformed into γ-amino alcohols and β-amino acids (Figure 1.10, eq 32).\textsuperscript{42}

**Figure 1.10 Syntheses of α-Functionalized Amines by Carbenoid/Nitrenoid Insertion**

1.6 α-Functionalization of Amines via the Intramolecular Hydride Transfer

Many reactions involving the intramolecular hydride transfer as the key step for the α-functionalization of amines have been developed. An early example was reported in 1984 by
Reinhoudt and co-workers where 2-vinyl-N,N-dialkylanilines underwent a 1,5-hydride transfer followed by the annulation providing the cyclized products (Figure 1.11, eq 33). The electron-withdrawing groups at the vinyl β-position were important to induce a facile intramolecular hydride transfer and thus improve the yield of the reaction. In 2009, Seidel and co-workers reported the cyclic aminal formation of 2-aminobenzaldehydes and primary amines via a Brønsted acid-promoted redox process (Figure 1.11, eq 34). This reaction was proposed to go through a 1,5-hydride transfer mechanism. The same group also reported a gadolinium triflate catalyzed intramolecular redox-annulation via the 1,5-hydride transfer, providing tetrahydroisoquinoline derivatives (Figure 1.11, eq 35). An enantioselective version of this reaction was realized by using magnesium triflate and a bisoxazoline-based ligand as the catalyst (Figure 1.11, eq 36). Notably, the reaction was performed in refluxing 1,2-dichloroethane with good yields and enantiomeric ratios obtained, although diastereomeric ratios were only low to moderate. In addition, cobalt(II)/N,N'-dioxide and Mg(II)/phosphoric acid complexes were reported to catalyze such reactions enantioselectively in similar manners, and Akiyama et al. used the chiral phosphoric acid to catalyze the asymmetric reaction via an ion-pair pathway. In 2010, Kim and co-workers reported an enantioselective tandem 1,5-hydride transfer-annulation reaction involving iminium catalysis (Figure 1.11, eq 37). Zhang and co-workers later developed a divergent intramolecular redox reaction controlled by the Lewis acid catalyst forming ring-fused tetrahydroisoquinoline or tetrahydroazepine products (Figure 1.11, eq 38). The hard oxophilic Lewis acid scandium triflate activated the carbonyl group, triggering a 1,5-hydride transfer followed by the annulation. In contrast, the soft carbophilic Lewis acid IPrAuOTf activated the alkyne moiety leading the reaction to the furan formation through a 1,5-hydride transfer-annulation pathway. The enantioselective version of the latter reaction was later developed using Au/(R)-MeO-dtbm-biphep complex as the catalyst and AgOTf as the additive. In 2011, Gong and co-workers successfully developed an enantioselective variant of the previously mentioned aminal formation reaction reported by the Seidel group, using (2-aminophenyl)ketosterers as starting materials with the ion-pair intermediates formation catalyzed by a chiral bisphosphoric acid. Although most annulations following the redox hydride transfer formed a new six-membered ring, the Seidel group in 2011 reported an exception.
where 2-tertiary aminobenzaldehyde reacted with the doubly nucleophilic compound such as indole giving benzazepine with a new seven-membered ring (Figure 1.11, eq 39). The reaction was catalyzed by diphenyl phosphate under microwave conditions. Maulide and co-workers subsequently reported an intramolecular \textit{N,O}-acetal formation with 2-pyrrolidinobenzaldehyde triggered by the hydride transfer in the presence of scandium triflate. The \textit{N,O}-acetals formed were treated with nucleophiles to give \textit{\alpha}-functionalized pyrrolidines (Figure 1.11, eq 40). The 1,5-hydride transfer process described in the mentioned reactions involved the shift of a hydride adjacent to the nitrogen atom of a tertiary amine, to a pendant double bond, which is usually termed the “\textit{tert}-amino effect”. Notably, these examples of the amine \textit{\alpha}-functionalization via the intramolecular hydride transfer represent a class of redox-neutral reactions.

**Figure 1.11 Amine \textit{\alpha}-Functionalization via the Intramolecular 1,5-Hydride Transfer**

In the diagram:
- 1.80: Reaction of benzaldehyde with ligand 1.88 (22 mol%) and Mg(OtBu)$_2$ (20 mol%) in DCE, 4 Å MS, reflux, 30 h.
- 1.81: Reaction of benzaldehyde with n-BuOH, reflux, 2 h.
- 1.82: Reaction of benzaldehyde with Gd(OTf)$_3$ (5 mol%) in MeCN, rt, 15 min.
- 1.83: Reaction of benzaldehyde with Gd(OTf)$_3$ (5 mol%) in MeCN, rt, 15 min.

Seidel, 2009

Seidel, 2009

Kim, 2010
1.7 Objectives

The methodologies introduced above provide various entries to obtain functionalized amines, especially cyclic amines, which are extremely important structures in natural products and bioactive compounds. However, most reported methods require the use of sensitive chemicals, external oxidants or heavy metals. In addition, the pre-functionalization of the free NH proton of the amine is necessary in the vast majority of cases.

The research highlighted in this dissertation aims to find more efficient ways for the functionalization of amines, which can provide alternative methods for the facile construction of complex molecular structures containing functionalized amine moieties. Chapter II will discuss the redox-neutral α-functionalization of cyclic amines via the azomethine ylide intermediate, with detailed description of three projects: α-cyanation, α-arylation and the redox-Mannich reaction. Chapter III will discuss a serendipitously discovered redox-neutral α,β-difunctionalization of cyclic amines, which represents the first example of the metal-free functionalization of amine β-positions without a simultaneous amine aromatization. Chapter IV will discuss the redox-annulation involving cyclic amines and β-ketoaldehydes. The last chapter will discuss the α-functionalization of cyclic N-H amines via a different chemical process which involves intermolecular hydride transfer.
References


For a recent review on CDC reactions, see: Li, C. Acc. Chem. Res. 2009, 42, 335.


Chapter 2

Redox-Neutral α-Functionalization of Cyclic Amines via Azomethine Ylide Intermediates

2.1 The Chemistry of Azomethine Ylides

An azomethine ylide is a chemical species which contains four \( \pi \)-electrons along a C–N–C unit; a zwitterion represented by four resonance structures (Figure 2.1). The two major resonance structures of an azomethine ylide are the ones with a positive charge on the nitrogen atom and a negative charge on one of the two carbon atoms, and the negative charge distribution on each carbon is determined by the substituents on it. The main methods for the generation of azomethine ylides are summarized in Figure 2.2.\(^1,2\)

Figure 2.1 Resonance Structures of the Azomethine Ylide

Azomethine ylides are reactive intermediates widely employed to construct complex molecular structures. The most typical reaction type involving azomethine ylides is the [3+2] dipolar cycloaddition. Because of the electron-rich properties of the azomethine ylide dipole, it usually reacts with an electron-poor dipolarophile where the electrons flow from the HOMO of the
azomethine ylide to the LUMO of the unsaturated reaction partner. The first azomethine ylide preparation and related dipolar cycloaddition were reported by Huisgen and co-workers in 1963 (Figure 2.3, eq 1). The iminium ion formed via the condensation of THIQ and p-nitrobenzaldehyde was deprotonated by triethylamine in hot pyridine. The corresponding azomethine ylide generated was not stable but could rapidly react with dimethylfumarate in situ to give the cycloaddition product in good yield. Besides cycloaddition reactions, azomethine ylides are also known to undergo electrocyclization reactions. The Grigg group demonstrated that the azomethine ylide formed from the reaction between THIQ and a divinyl ketone in the presence of dibutyltin dichloride underwent a 1,5-electrocyclization followed by the aromatization to provide pyrrolo dihydroisoquinolines (Figure 2.3, eq 2). In 1999, Groundwater and co-workers developed a 1,7-electrocyclization reaction yielding dihydrobenzazepines (Figure 2.3, eq 3).

**Figure 2.3 Typical Reactions Involving Azomethine Ylide Intermediates**

![Diagram of typical reactions involving azomethine ylide intermediates](image)

Some non-conventional reactions involve the protonation of the negative charge in the azomethine ylide. Cohen and co-workers discovered an annulation forming polycyclic N,O-acetals from o-hydroxyacetophenones and proline (Figure 2.4, eq 4). The azomethine ylide was generated by the condensation of the carbonyl group and proline followed by the
intramolecular decarboxylation process, which was first reported by Rizzi in 1970\textsuperscript{3b} and further developed by Grigg and co-workers.\textsuperscript{7} Notably, the reaction disclosed in this report was only applicable to ketones bearing a methyl group at the other ortho-position. The Seidel group demonstrated that 2-aminobenzaldehydes react with cyclic amines in ethanol providing ring-fused aminals (Figure 2.4, eq 5).\textsuperscript{8} On the basis of extensive experimental and computational studies, the reaction was proposed to go through azomethine ylide intermediate 2.16 formed via a 1,6-proton transfer, followed by the protonation and annulation. Intermolecular nucleophilic additions are also reported after the protonation step. In 2009, Li and co-workers reported a reaction using FeSO\textsubscript{4} as the catalyst and tert-butyl peroxide as the stoichiometric oxidant (Figure 2.4, eq 6).\textsuperscript{9} The Seidel group in 2010 reported a three-component decarboxylative \( \alpha \)-functionalization of \( \alpha \)-amino acids (Figure 2.4, eq 7),\textsuperscript{10} which was almost simultaneously reported by the Li group as well in a slightly different fashion.\textsuperscript{11} In 2009, Tunge and co-workers developed an intermolecular redox-amination involving 3-pyrroline and aliphatic aldehydes catalyzed by benzoic acid (Figure 2.4, eq 8). The aromatization occurred to give \( N \)-alkylpyrroles after the protonation of the azomethine ylide negative charge.\textsuperscript{12} The Pang group and the Seidel group then independently disclosed the corresponding redox-indole formation (Figure 2.4, eq 9).\textsuperscript{13,14}

Figure 2.4 Non-Conventional Reactions Involving Azomethine Ylide Intermediates

\( \begin{align*}
\text{2.11} & \quad \text{Cohen, 1979} \\
\text{2.12} & \quad \text{DMF, 100 °C} \\
\text{2.13} & \quad \text{Me} \\
\text{2.14} & \quad \text{75%} \\
\text{2.15} & \quad \text{Seidel, 2008} \\
\text{2.16} & \quad \text{OH} \\
\text{2.17} & \quad \text{73%} \\
\text{2.18} & \quad \text{OH} \\
\text{2.19} & \quad \text{Li, 2009} \\
\text{2.20} & \quad \text{78%} \\
\text{2.20} & \quad \text{91%} \\
\end{align*} \)
2.2 Redox-Neutral α-Cyanation of Amines

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2.2.1 Research Background

α-Aminonitriles are important structural motifs in organic synthesis which can be transformed to α-amino acids and other valuable building blocks. However, α-aminonitriles which are part of a ring system cannot easily be obtained from the classic Strecker reaction, thus new methods are essential for the construction of those structures. Previously established methods for the synthesis of such compounds rely on oxidative approaches and photo-redox catalysis.

As part of our work on the decarboxylative α-functionalization of α-amino acids, we developed a decarboxylative Strecker reaction in 2011 (Figure 2.5). The three-component reaction involving proline, benzaldehyde and TMSCN gave rise to α-cyanated N-benzyl pyrrolidines. The reaction was proposed to involve azomethine ylide intermediate formed via the condensation of proline and benzaldehyde followed by an intramolecular decarboxylation. A related computational study on the electron distribution of azomethine ylide shows that there is more negative charge at the benzylic position, where the protonation is more likely to occur. An interesting discovery from this reaction was that the amount of proline used influenced the ratio of the regular Strecker product to the desired α-cyanation product. As shown in Figure 2.6, by increasing the amount of proline from 1.2 equiv to 2.0 equiv, the ratio of product 2.23a to 2.24a improved from 4:1 to > 25:1. To explain this, an equilibrium between the regular
Strecker product and iminium ion-cyanide ion pair 2.25 was proposed. Iminium ion 2.25 further reacts with excess proline to form the desired α-aminonitrile. Due to the postulated equilibrium between 2.24a and 2.25, we hypothesized that if a catalyst, ideally cheap and commercially available, enables the isomerization of iminium ion 2.25 to iminium ion 2.27, presumably via the intermediacy of azomethine ylide 2.26, a redox-neutral α-cyanation of unfunctionalized simple cyclic amines can be realized. This hypothesized reaction process would couple a reductive N-alkylation with an oxidative α-cyanation, rendering the whole reaction redox-neutral.

Figure 2.5 Decarboxylative Strecker Reaction

Figure 2.6 The Influence of Proline on the Product Distribution and the Proposed Pathway for the Regioisomeric Enrichment

2.2.2 Reaction Development

As the starting point of our research, we screened different conditions for the isomerization of the regular Strecker product to the desired α-cyanation product. The best result came from a reaction under microwave irradiation at 200 °C for 20 min in toluene, and 20 mol% of benzoic acid was used as the catalyst (Table 2.1, entry 3). Under the optimal conditions, an 18:1 ratio of product 2.23a and starting material 2.24a were obtained in a combined yield of 84%. Most other carboxylic acids tested also gave good regioisomeric ratios and yields, however, results were
inferior to benzoic acid (Table 2.1, entries 4–7). With organic base such as triethylamine as the catalyst or without any catalyst, the desired isomerization was negligible (Table 2.1, entries 1–2). The acidity of the catalyst seemed to be significant, since more acidic acids provided poorer regioisomeric ratios (Table 2.1, entries 8–11). Surprisingly, n-butanol, which is a good solvent for the decarboxylative Strecker reaction, was not a suitable solvent for this reaction (Table 2.1, entry 17).

### Table 2.1 Evaluation of Parameters for the Isomerization of Undesired α-Aminonitrile

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Temperature [°C]</th>
<th>Time [min]</th>
<th>Ratio 2.23a/2.24a</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>–</td>
<td>200</td>
<td>20</td>
<td>1:5</td>
<td>91</td>
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<td>2</td>
<td>NEt3</td>
<td>200</td>
<td>20</td>
<td>1:4</td>
<td>ND</td>
</tr>
<tr>
<td>3</td>
<td>PhCO₂H</td>
<td>200</td>
<td>20</td>
<td>18:1</td>
<td>84</td>
</tr>
<tr>
<td>4</td>
<td>MeCO₂H</td>
<td>200</td>
<td>20</td>
<td>10:1</td>
<td>84</td>
</tr>
<tr>
<td>5</td>
<td>2-Ethylhexanoic acid</td>
<td>200</td>
<td>20</td>
<td>16:1</td>
<td>84</td>
</tr>
<tr>
<td>6</td>
<td>Pivalic acid</td>
<td>200</td>
<td>20</td>
<td>15:1</td>
<td>70</td>
</tr>
<tr>
<td>7</td>
<td>4-MeO-benzoic acid</td>
<td>200</td>
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<td>12:1</td>
<td>86</td>
</tr>
<tr>
<td>8</td>
<td>4-NO₂-benzoic acid</td>
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<td>7:1</td>
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<td>&lt;1:20</td>
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</tr>
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<td>5</td>
<td>11:1</td>
<td>90</td>
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<td>13</td>
<td>PhCO₂H</td>
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<td>10</td>
<td>13:1</td>
<td>86</td>
</tr>
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<td>14</td>
<td>PhCO₂H</td>
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<td>30</td>
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<td>15b</td>
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<td>20</td>
<td>18:1</td>
<td>79</td>
</tr>
<tr>
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<td>20</td>
<td>4:1</td>
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<tr>
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<td>20</td>
<td>1:2</td>
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<td>PhCO₂H</td>
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<td>20</td>
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<td>79</td>
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<tr>
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<td>PhCO₂H</td>
<td>250</td>
<td>20</td>
<td>9:1</td>
<td>41</td>
</tr>
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</table>

*a* Reactions were performed on a 0.25 mmol scale. Yields correspond to combined, isolated yields of both regioisomers. *b* in xylenes. *c* in acetonitrile. *d* in n-butanol.

#### 2.2.3 Scope of the Direct α-Cyanation of Pyrrolidine

A three-component α-cyanation reaction involving pyrrolidine, benzaldehyde and TMSCN was first studied under the optimal conditions (Figure 2.7). The desired product was obtained
with the undesired regular Strecker product as a 9:1 mixture in a combined yield of 62%. Due to the unsatisfactory result of the three-component reaction, we turned to perform an alternative two-component reaction employing readily prepared cyanohydrins. 2-Ethylhexanoic acid (2-EHA) was a better catalyst in this instance. Reactions involving aromatic cyanohydrins, including heteroaromatic cyanohydrins all provided high regioselectivities and excellent yields (Table 2.2, entries 1–12). On the other hand, aliphatic cyanohydrins mainly yielded undesired regioisomers (Table 2.2, entries 13–15). Sterically hindered benzophenone cyanohydrins gave only the desired product, although the yield was low (Table 2.2, entry 16).

**Figure 2.7 Three-Component α-Cyanation of Pyrrolidine**

![Figure 2.7 Three-Component α-Cyanation of Pyrrolidine](image-url)
Table 2.2 Scope of the Two-Component α-Cyanation of Pyrrolidine

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R′</th>
<th>Product</th>
<th>Ratio</th>
<th>Yield (%)</th>
</tr>
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<td>H</td>
<td>a</td>
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</tr>
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<td>2</td>
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<td>H</td>
<td>b</td>
<td>16:1</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>4-MeO-C₆H₄</td>
<td>H</td>
<td>c</td>
<td>11:1</td>
<td>67</td>
</tr>
<tr>
<td>4</td>
<td>4-Cl-C₆H₄</td>
<td>H</td>
<td>d</td>
<td>&gt;20:1</td>
<td>94</td>
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<tr>
<td>5</td>
<td>3-Cl-C₆H₄</td>
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<td>e</td>
<td>&gt;20:1</td>
<td>87</td>
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<td>3-Me-C₆H₄</td>
<td>H</td>
<td>f</td>
<td>19:1</td>
<td>79</td>
</tr>
<tr>
<td>7</td>
<td>2-Br-C₆H₄</td>
<td>H</td>
<td>g</td>
<td>&gt;20:1</td>
<td>85</td>
</tr>
<tr>
<td>8</td>
<td>mesityl</td>
<td>H</td>
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<td>&gt;20:1</td>
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<tr>
<td>9</td>
<td>1-naphthyl</td>
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<td>i</td>
<td>18:1</td>
<td>85</td>
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<tr>
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<td>j</td>
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<td>Ph</td>
<td>Ph</td>
<td>p</td>
<td>&gt;20:1</td>
<td>40</td>
</tr>
</tbody>
</table>

a Reactions were performed on a 0.25 mmol scale. Yield corresponds to combined, isolated yields of both regioisomers.  
b Reaction time was 30 min.  
c Benzoic acid was used as the catalyst.

2.2.4 α-Cyanation of Other Amines

The conditions for the redox-neutral α-cyanation could also be applied to other amines in addition to pyrrolidine. Cyclic amines containing larger-sized rings such as piperidine and azepane provided corresponding α-cyanation products in moderate to good yields and high regioselectivities (Figure 2.8, eqs 15–16). However, these substrates required higher reaction temperature or longer reaction time compared to pyrrolidine, probably due to their higher α-C–H bond energy. THIQ was another good candidate for this reaction. In stark contrast to most oxidative methods where cyanation occurs at the benzylic position giving the kinetically-favored product, our redox-neutral reaction performed at high temperature mainly provided the thermodynamically-favored product which was functionalized on the other side of the ring (Figure 2.8, eq 17). A control experiment demonstrated that N-benzyl-1-cyano-THIQ
2.35 also isomerized when exposed to the same reaction conditions, and 3-cyano regioisomer 2.33 was still obtained as the major product (Figure 2.8, eq 18). The reaction involving 2-methylpyrrolidine yielded a mixture of regioisomers 2.36 (trans: cis = 4.8:1) in 52% and 2.37 in 11% (Figure 2.8, eq 19). Although acyclic α-aminonitriles are readily obtained by standard Strecker chemistry, we also conducted a reaction with methylbenzylamine to probe the reactivity of this substrate class (Figure 2.8, eq 20). In this instance, 2.38 was obtained as the sole product in 81% yield.

Figure 2.8 Scope of Amines for the α-Cyanation
2.2.5 Summary

In summary, we developed a direct \( \alpha \)-cyanation of simple cyclic amines, providing \( \alpha \)-aminonitriles that are not accessible by the traditional Strecker reaction. This is the first time that such reactions can be achieved from free amines with simple carboxylic acid as the catalyst. The reaction produced the thermodynamically-favored product as the main regioisomer, and the combined reductive \( N \)-alkylation and oxidative \( \alpha \)-cyanation render the whole reaction redox-neutral.

2.3 Redox-Neutral \( \alpha \)-Arylation of Cyclic Amines

Parts of this section were adapted with permission from the article “Redox-Neutral \( \alpha \)-Arylation of Amines” (Org. Lett. 2014, 16, 730). Copyright © 2014, American Chemical Society

2.3.1 Research Background

Following the redox-neutral \( \alpha \)-cyanation reaction, our group successively developed the corresponding redox-neutral \( \alpha \)-alkynylation (Figure 2.9, eq 21)\(^{23}\) and \( \alpha \)-phosphonation (Figure 2.9, eq 22)\(^{24}\) reactions. The redox-alkynylation is catalyzed by 15 mol% of copper 2-ethylhexanoate. Unlike the redox-cyanation where the undesired regular Strecker product isomerized to the desired product in the presence of benzoic acid, the isomerization of the undesired alkynylation product to the desired regioisomer was negligible (Figure 2.9, eq 23). Without a significant isomerization pathway, the choice of aldehyde substrate in the reaction partner was of great importance. Only 2,6-dichlorobenzaldehyde bearing bulky and electro-withdrawing substituents at both \textit{ortho}-positions gave excellent regioselectivities. Mesitylaldehyde was also a favorable reaction partner, providing the desired and undesired products in a ratio of 11:1 and a combined yield of 79%. However, other aldehydes tested gave poor regioselectivities. The redox-phosphonation on the other hand was similar to the redox-cyanation in that the undesired regioisomer readily isomerized to the desired one catalyzed by 20 mol% benzoic acid, thus had a wide scope for aldehyde substrates.
Ma and co-workers reported the redox-neutral alkynylation of THIQ catalyzed by copper (I) bromide in the presence of triphenylphosphine. A catalytic amount of triphenylphosphine was of great importance for the regioselectivity of this reaction, and the regular $\text{A}^3$ product was obtained as the major product without the addition of triphenylphosphine. The same group also reported an enantioselective version of the same reaction using copper (I) iodide as the catalyst and $(R,R)$-N-pinap as the ligand (Figure 2.10). Benzoic acid was added to improve the product yield in this instance. This was the first enantioselective redox-neutral $\alpha$-functionalization of cyclic amines incorporating this particular type of redox-isomerization.
Our study was further extended to reactions involving other nucleophiles. Aromatic compounds are important classes of nucleophiles previously utilized in the amine functionalization by oxidative,\textsuperscript{26} metal-catalysis,\textsuperscript{27} radical,\textsuperscript{28} photoredox\textsuperscript{29} and decarboxylative approaches.\textsuperscript{30} We therefore wanted to develop a corresponding redox-neutral $\alpha$-arylation of cyclic amines.

### 2.3.2 Research Development

We initiated our study on the redox-neutral $\alpha$-arylation of cyclic amines by directly heating pyrrolidine, 2,6-dichlorobenzaldehyde and $\beta$-naphthol in refluxing toluene in the presence of 20 mol\% benzoic acid as the additive (Figure 2.11, eq 25). The reaction was complete in only 15 min indicated by the full consumption of the limiting reagent 2,6-dichlorobenzaldehyde. However, the reaction yielded complex mixtures. Besides the desired $\alpha$-arylation product 2.43\textsuperscript{a} obtained in 22\% yield, compounds 2.44 and 2.45 containing a $\beta$-exocyclic double bond were also isolated in 22\% and 33\% yields respectively, consistent with the intermediacy of the corresponding enamine. Because the formation of byproducts 2.44 and 2.45 required more than one equivalent of the aldehyde, we tried to improve the yield of the desired product by employing slow addition techniques (Figure 2.11, eq 26). When 2,6-dichlorobenzaldehyde was slowly added over 5 hours under the otherwise identical conditions, the yield of the desired product was drastically improved to 81\%. To our surprise, the yield of 2.43\textsuperscript{a} was further improved to 96\% without any acidic additive, which showed that $\beta$-naphthol was apparently capable of catalyzing the redox-isomerization.
We next evaluated reaction parameters for the reaction involving an indole nucleophile. Without any additive, a mixture of regioisomers $2.43b$ and $2.46b$ was obtained in a ratio of 1:1.8 and a combined yield of 76% (Table 2.3, entry 1). Upon adding 20 mol% of benzoic acid, the regioselectivity dramatically changed to yield $2.43b$ as the main product (Table 2.3, entry 2). Further screening of other carboxylic acids and the catalyst loading indicated that the best result came from the reaction using 1 equiv of 2-EHA as the additive (Table 2.3, entry 6). Unlike the reaction involving β-naphthol as the nucleophile where slow addition is essential for achieving high yield of the product, decent yield could also be obtained for the reaction with indole when all reagents were mixed directly and heated under reflux (Table 2.3, entry 7). The much weaker acidity of indole compared to β-naphthol might explain the difference in the amount of carboxylic acid required for the two reactions.
Table 2.3 Evaluation of Reaction Parameters for the α-Arylation of Pyrrolidine with Indole\textsuperscript{a}

![Chemical Reaction Diagram]

<table>
<thead>
<tr>
<th>entry</th>
<th>additive (mol%)</th>
<th>ratio 2.43b/2.46b</th>
<th>yield 2.43b+2.46b (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>–</td>
<td>1:1.8</td>
<td>76</td>
</tr>
<tr>
<td>2</td>
<td>PhCOOH (20)</td>
<td>9.5:1</td>
<td>79</td>
</tr>
<tr>
<td>3</td>
<td>4-Dimethylamino benzoic acid (20)</td>
<td>11.3:1</td>
<td>81</td>
</tr>
<tr>
<td>4</td>
<td>2-Ethylhexanoic acid (20)</td>
<td>11.6:1</td>
<td>80</td>
</tr>
<tr>
<td>5</td>
<td>2-Ethylhexanoic acid (50)</td>
<td>21:1</td>
<td>85</td>
</tr>
<tr>
<td>6</td>
<td>2-Ethylhexanoic acid (100)</td>
<td>&gt; 25:1</td>
<td>86</td>
</tr>
<tr>
<td>7\textsuperscript{b}</td>
<td>2-Ethylhexanoic acid (100)</td>
<td>&gt; 25:1</td>
<td>71</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Reactions were performed on a 0.5 mmol scale. \textsuperscript{b}All reagents were mixed directly and heated in toluene (0.25 M) under reflux for 15 min.

2.3.3 Impact of Aldehyde on the Regioselectivity

In addition to 2,6-dichlorobenzaldehyde, we also tested two other representative aromatic aldehydes as the reaction partner for the redox-arylation. The reaction involving benzaldehyde provided mainly the undesired regioisomer while mesitylaldehyde gave excellent regioselectivity (Figure 2.12). This is consistent with the redox-alkynylation reaction, which indicated the low isomerization potential of the undesired regioisomer. As a result, aldehydes with bulky and/or electron-withdrawing substituents at ortho-positions were required to favor the redox-isomerization and suppress the competing reaction that generated undesirable regioisomers.
Figure 2.12 Control of Regioselectivity by the Aldehyde

![Reaction Scheme](image)

2.3.4 Scope of the Reaction

The redox-neutral α-arylation has a rather wide scope in terms of aromatic nucleophiles (Figure 2.13). Substituted β-naphthols and phenols provided the desired products as single regioisomers in moderate to high yields without any catalyst. Substituted indoles also gave high to excellent regioisomeric ratios and good yields when 1 equiv of 2-EHA was added. N-Methyl indole, on the other hand, required the addition of super-stoichiometric amount of 2-EHA, probably due to the lack of acidic indole NH-proton. Pyrroles readily reacted as well, although yields of the products were only moderate. Piperidine was a more difficult substrate for this reaction. When exposed to the optimal conditions, reactions involving β-naphthol and indole produced the desired products in 16% and 64% yield respectively, with albeit over 25:1 regioisomeric ratio in both cases. Other tested cyclic amines failed to yield any detectable desired products.
**Figure 2.13 Substrate Scope for the α-Arylation**

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Yield</th>
<th>Selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.43g/2.46g</td>
<td>&gt; 25:1, 85%</td>
<td></td>
</tr>
<tr>
<td>2.43l/2.46l</td>
<td>&gt; 25:1, 98%</td>
<td></td>
</tr>
<tr>
<td>2.43m/2.46m</td>
<td>&gt; 25:1, 90%</td>
<td></td>
</tr>
<tr>
<td>2.43n/2.46n</td>
<td>&gt; 25:1, 80%</td>
<td></td>
</tr>
<tr>
<td>2.43o/2.46o</td>
<td>&gt; 25:1, 75%</td>
<td></td>
</tr>
<tr>
<td>2.43p/2.46p</td>
<td>&gt; 25:1, 30%</td>
<td></td>
</tr>
<tr>
<td>2.43q/2.46q</td>
<td>&gt; 25:1, 72%</td>
<td></td>
</tr>
<tr>
<td>2.43r/2.46r</td>
<td>&gt; 25:1, 80%</td>
<td></td>
</tr>
</tbody>
</table>

*a* Reactions were performed on a 1 mmol scale. Yields correspond to the desired regio-isomers. *b* Reactions with β-naphthols and indoles: Ar'H (1.5 equiv); reactions with phenols or pyrroles: Ar'H (5 equiv); reactions with indoles and pyrroles: 2-EHA (1 equiv). *c* 2.5 equiv of 2-EHA were used. *d* Disubstituted pyrrole product was isolated as a byproduct in 19% (dr = 3:1).

### 2.3.5 Summary

In summary, we developed a redox-neutral α-arylation employing a wide scope of aromatic compounds as nucleophiles. 2,6-Dichlorobenzaldehyde was essential to achieve high regioselectivities due to the low isomerization potential of undesired arylation products, and slow addition technique was used in order to avoid the formation of β-functionalized byproducts. The carboxylic acid additive was only required for reactions involving indole and pyrrole substrates, possibly because of their weaker acidity compared to β-naphthols and phenols.
2.4 The Redox-Mannich Reaction

2.4.1 Research Background

The three-component Mannich reaction employing a non-enolizable aldehyde and a carbonyl compound bearing an acidic α-proton remains a useful tool for C–C bond construction. Among the most extensively studied variants are oxidative two-component approaches with tertiary amines that provide access to ring-substituted β-amino ketones, products not available by the classic Mannich approach. In the context of developing novel metal and oxidant-free methods for the amine functionalization, we have successfully realized the activation of cyclic amine α-C–H bonds and the coupling of sp³-sp and sp³-sp² carbons. As an important component of this research area, we developed the redox-Mannich reaction, enabling us to expand our chemistry to the α-alkylation of cyclic amines.

2.4.2 Research Development

We chose 2,6-dichlorobenzaldehyde, pyrrolidine and acetophenone as our model substrates to optimize reaction conditions for the redox-Mannich reaction. The best yield was obtained when a toluene solution of the aldehyde and acetophenone was slowly added over 5 hours to a refluxing mixture of pyrrolidine and 50 mol% benzoic acid in toluene (Table 2.4, entry 1). The desired product was isolated in 56% yield under the optimized conditions. The reaction showed remarkable tolerance towards changes of the reaction parameters, although the yield of the product was inferior under all these other conditions. On the other hand, 2,6-dichlorobenzaldehyde was the only aldehyde used in this reaction yielding the desired redox-Mannich product.
Table 2.4 Evaluation of Reaction Conditions for the Redox-Mannich Reaction Involving Pyrrolidine

<table>
<thead>
<tr>
<th>entry</th>
<th>deviation from optimized conditions</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>56</td>
</tr>
<tr>
<td>2</td>
<td>no PhCOOH</td>
<td>trace</td>
</tr>
<tr>
<td>3</td>
<td>100 mol % of PhCOOH</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>20 mol % of PhCOOH</td>
<td>48</td>
</tr>
<tr>
<td>5</td>
<td>direct mixing of all reagents, reflux, 1 h</td>
<td>45</td>
</tr>
<tr>
<td>6</td>
<td>2 equiv of pyrrolidine</td>
<td>45</td>
</tr>
<tr>
<td>7</td>
<td>with 4 Å MS</td>
<td>43</td>
</tr>
<tr>
<td>8</td>
<td>slow addition of aldehyde only</td>
<td>51</td>
</tr>
<tr>
<td>9</td>
<td>2-EHA instead of PhCOOH</td>
<td>39</td>
</tr>
<tr>
<td>10</td>
<td>4-Me_2N-C_6H_4-COOH instead of PhCOOH</td>
<td>28</td>
</tr>
<tr>
<td>11</td>
<td>4-MeO-C_6H_4-COOH instead of PhCOOH</td>
<td>42</td>
</tr>
</tbody>
</table>

*Reactions were performed on a 0.5 mmol scale. A mixture of aldehyde and ketone in 0.5 mL of toluene was added to a solution of pyrrolidine in 2 mL over 5 h. All yields correspond to isolated yields. 2-EHA: 2-ethylhexanoic acid.

2.4.3 Scope of the Redox-Mannich Reaction

With the optimal conditions in hand, we demonstrated the scope of the redox-Mannich reaction involving pyrrolidine by employing different aromatic ketones (Figure 2.14). Acetophenones bearing electron-donating and electro-withdrawing substituents at meta- and para-positions were well tolerated and generally provided redox-alkylation products in moderate yields. Suprisingly, ortho-substituted acetophenones did not react under the standard conditions. We thought the steric of the ortho-substituent might prevent the acetyl from being co-planar with the phenyl ring, thus decreasing the acidity of the acetyl α-proton and preventing the formation of the enol tautomer. Piperidine and azepane proved not to be viable substrates for this redox-Mannich reaction.

THIQ was found to be another good amine substrate for the redox-Mannich reaction (Figure 2.15). Unlike reactions involving pyrrolidine which were performed in refluxing toluene, reactions of THIQ proceeded at 50 °C and the functionalization occurred at the benzylic position. This was probably due to the much higher reactivity of the benzylic C–H bond. At such reaction
temperature, the addition of molecular sieves was beneficial to accelerate the rate of the reaction possibly by facilitating the condensation of THIQ and the aldehyde. The reaction has a broad aldehyde scope, and acetone was also shown to react with THIQ and benzaldehyde.

**Figure 2.14 Scope of the Redox-Mannich Reaction Involving Pyrrolidine**

\[
\begin{align*}
\text{Pyrrolidine} & \quad \text{Aldehyde} \quad \text{Ketone} \quad \text{PhCOOH (50 mol\%)} \quad \text{PhMe (0.2 M)} \quad \text{reflux, 5 - 6.5 h} \\
5 \text{ equiv} & \quad 1 \text{ equiv} & \quad 1.5 \text{ equiv} & \quad \text{(32)} \\
\end{align*}
\]

Figure 2.14 Scope of the Redox-Mannich Reaction Involving Pyrrolidine

![Reaction scheme](image)

To further explore the scope of this reaction, nitroalkanes were tested as nucleophiles and reacted with both pyrrolidine and THIQ under the optimal conditions (Figure 2.16). Gratifyingly, excellent yields of the desired products were obtained. However, the nitro-Mannich products were thought to easily undergo retro-nitro-Mannich reaction. The products were unstable to column chromatography conditions, so the isolated yields were always lower than the NMR yields. Notably, the only nitro-Mannich reaction that provides \(N\)-benzyl products was previously reported by Klussmann using vanadium catalyst and stoichiometric \(m\)-CPBA as oxidant.\(^\text{26f}\)
Figure 2.15 Scope of the Redox-Mannich Reaction Involving THIQ

Reactions were performed on a 0.5 mmol scale. The substrates were mixed directly. All yields correspond to isolated yields. 3 equivalents of acetone were used.

Figure 2.16 Redox-Nitro-Mannich Reaction

Reactions were performed on a 0.5 mmol scale. Yields were determined by 1H-NMR using an internal standard. Yields in parentheses correspond to isolated yields.

2.4.4 Regioselectivity of the Redox-Mannich Reaction

In contrast to other redox-neutral α-functionalization of amines we previously developed, we never observed the formation of undesired regioisomers for the redox-Mannich reaction. A
simple explanation for this was that once undesired regioisomers formed, they quickly eliminated amines and produced chalcones. In fact, the equilibriums shown (eqs 36–37) were always observed in the conjugate addition of amines to chalcones. Under the conditions for the redox-Mannich reaction, amines reacted with chalcones in other fashions, i.e., the 1,2-addition followed by 1,5-electrocyclization, thus driving the equilibrium towards the direction where undesired regioisomers decomposed. Compound 2.47a on the other hand would not suffer from this instability through forming the elusive species 2.53 via a retro-Mannich process.

**Figure 2.17 Stability of Undesired Regioisomers**

2.47a

\[
\begin{align*}
\text{Ph} & \quad \text{N} \\
\text{Ph} & \quad \text{O} \\
\text{Ph} & \quad \text{N} \\
\text{Ph} & \quad \text{O} \\
\end{align*}
\]

(36)

2.51

2.52

2.5a

Ar = 2,5-di-chlorophenyl

2.53

(38)

2.4.5 Summary

In summary, we developed a redox-Mannich reaction producing ring-substituted β-amino ketones as a complement to the dominant oxidative methods. Although yields for most substrates were only moderate, the simplicity of the reaction conditions partially compensates for this shortcoming.

2.5 Proposed Mechanisms for the Redox-Isomerization

Although the detailed mechanism for the redox-isomerization has not been elucidated, we propose a possible pathway for the generation of azomethine ylide intermediates where the carboxylic acid reacts with hemi-N,O-acetal 2.54 to form N,O-acetal intermediate 2.55, which eliminates the carboxylic acid intramolecularly to form the azomethine ylide (Figure 2.18). Yu and co-workers earlier proposed a similar chemical process according to the computational study
on the formation of pyrrole from 3-pyrroline and aldehydes.\textsuperscript{35} The extensive computational study on a related asymmetric redox-annulation between 4-nitrobutyraldehyde and cyclic amines later developed by our group also corroborates this proposed reaction pathway (Chapter 4).\textsuperscript{36}

**Figure 2.18 Proposed Mechanism for the Redox-Isomerization**

In 2014, Hajra and co-workers reported a redox-neutral [3+2] dipolar cycloaddition between cyclic amines and aromatic aldehydes producing cyclic N,O-acetals which was proposed to involve the same redox-isomerization step and the azomethine ylide intermediate (Figure 2.19).\textsuperscript{37} In order to find experimental evidence for the above-proposed mechanism, we used this reaction as a model reaction to study the influence of the catalyst on the reaction outcome (Table 2.5).

**Figure 2.19 Redox-Neutral [3+2] Dipolar Cycloaddition Involving Pyrrolidine and 4-Cl-Benzaldehyde**

As demonstrated in Table 2.5, the carboxylate is essential to yield the product. Without the additive or adding acetic acid gave poorer results (Table 2.5, entries 1–2). Notably, the negligible formation of the desired cycloaddition product in the presence of acetic acid might be due to the fast protonation of the formed azomethine ylide intermediate rather than the inaccessibility of it. Changing the cation from the more Lewis acidic lithium ion to a less Lewis acidic potassium ion slightly improved the yield (Table 2.5, entries 3–5). A dramatic increase in yield was observed when equal amount of 18-crown-6 was added with KOAc, which indicated that a “naked” carboxylate was beneficial to the redox-isomerization (Table 2.5, entry 7).
Several tetraalkylammonium carboxylates thus were also tested as the catalyst due to the non-Lewis acid nature of such cations (Table 2.5, entries 9–13). Tetramethylammonium acetate was the most effective catalyst, giving the product in 56% yield. Apparently, the carboxylate is more reactive with a less Lewis acidic and interactive countercation, thus facilitating the formation of \(N,O\)-acetal intermediate 2.55. A detailed study of the mechanism of the redox-isomerization is the subject of future work in this field.

Table 2.5 Evaluation of the Catalyst for the Redox-Neutral \(N,O\)-Acetal Formation

<table>
<thead>
<tr>
<th>entry</th>
<th>additive</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>AcOH</td>
<td>trace</td>
</tr>
<tr>
<td>3</td>
<td>LiOAc</td>
<td>34</td>
</tr>
<tr>
<td>4</td>
<td>NaOAc</td>
<td>36</td>
</tr>
<tr>
<td>5</td>
<td>KOAc</td>
<td>39</td>
</tr>
<tr>
<td>6</td>
<td>K(2-EA)</td>
<td>25</td>
</tr>
<tr>
<td>7</td>
<td>KOAc/18-crown-6</td>
<td>52</td>
</tr>
<tr>
<td>8</td>
<td>KSAc/18-crown-6</td>
<td>41</td>
</tr>
<tr>
<td>9</td>
<td>NMe\textsubscript{4}OAc</td>
<td>56</td>
</tr>
<tr>
<td>10</td>
<td>NMe\textsubscript{4}OBz</td>
<td>38</td>
</tr>
<tr>
<td>11</td>
<td>NMe\textsubscript{4}(2-EA)</td>
<td>40</td>
</tr>
<tr>
<td>12</td>
<td>NBn\textsubscript{2}Me\textsubscript{2}(OAc)</td>
<td>35</td>
</tr>
<tr>
<td>13</td>
<td>NMe\textsubscript{4}(pyridine-2-hydroxylate)</td>
<td>50</td>
</tr>
</tbody>
</table>

\(^a\) Reaction were performed on a 0.5 mmol scale. All yields correspond to isolated yields.

2.6 Conclusion

In conclusion, we discovered and developed new redox-neutral approaches to the \(\alpha\)-functionalizations of cyclic amines. Our reactions are proposed to go through a common azomethine ylide intermediate via the redox-isomerization catalyzed by simple carboxylic acids, although in some cases no catalyst is required. These reactions combine a reductive \(N\)-alkylation with an oxidative amine \(\alpha\)-functionalization, rendering the overall reaction redox-neutral. Our methods successfully avoid using stoichiometric external oxidants which are usually employed in
the previous oxidative amine functionalization, and thus are a complement to established synthetic approaches in the field of amine functionalization.
Experimental Section

**General Information:** Starting materials, reagents, and solvents were purchased from commercial sources and used as received unless stated otherwise. All amines, 2-ethylhexanoic acid, 1-methylindole, 2,4-dimethylphenol, pyrroles, acetophenone, nitroalkanes and all liquid aldehydes were distilled prior to use. 4-Chlorophenol and 2-methylindole were purified by Kugelrohr distillation. Benzoic acid, 4-methoxybenzoic acid, 4-(dimethylamino)benzoic acid, 2-naphthol and 4-t-butylphenol were recrystallized from toluene/ethanol. 4-Chlorobenzaldehyde was recrystallized from ethanol/water. Microwave reactions were carried out in a CEM Discover reactor. Silicon carbide (SiC) passive heating elements were purchased from Anton Paar. Purification of reaction products was carried out by flash column chromatography using Sorbent Technologies Standard Grade silica gel (60 Å, 230–400 mesh). Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60 F<sub>254</sub> plates. Visualization was accomplished with UV light, potassium permanganate or Dragendorff-Munier stains, followed by heating. Melting points were recorded on a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on an ATI Mattson Genesis Series FT-Infrared spectrophotometer. Proton nuclear magnetic resonance spectra (¹H-NMR) were recorded on a Varian VNMRS-500 MHz or Varian VNMRS-400 MHz and are reported in ppm using the solvent as an internal standard (CDCl<sub>3</sub> at 7.26 ppm). Data are reported as app = apparent, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, comp = complex, br = broad; coupling constant(s) in Hz. Proton-decoupled carbon nuclear magnetic resonance spectra (¹³C-NMR) spectra were recorded on a Varian VNMRS-500 MHz or Varian VNMRS-400 MHz and are reported in ppm using the solvent as an internal standard (CDCl<sub>3</sub> at 77.0 ppm). Mass spectra were recorded on a Finnigan LCQ-DUO mass spectrometer. Ratios of regioisomeric products were determined by ¹H-NMR analysis of the crude reaction mixture. NMR yields were determined by ¹H-NMR using 1,3,5-trimethoxybenzene as the internal standard. The starting materials 2.24a, 2.35, 2.36 and cyanohydrins were prepared according to modified literature procedures. 2-hydroxy-2-(pyridin-3-yl)acetonitrile and 2-hydroxy-2,2-diphenylacetonitrile were prepared according to published procedures. Products 2.23a, 2.24p, 2.29, 2.37 and
2.38 were previously reported and their published characterization data matched our own in all respects. Arylation products 2.43c, 2.43e, 2.46c and 2.46e were previously reported and their published characterization data matched our own in all respects.9,10,46,47

**Caution:** Due to the potential for HCN formation, all operations should be conducted inside a well ventilated fume hood. SiC passive heating elements must not be used in conjunction with stir bars; they may score glass and cause vessel failure.

**General Procedure for the Isomerization of 2-Phenyl-2-(pyrrolidin-1-yl)acetonitrile (2.24a):**

A 10 mL microwave reaction tube was charged with a 10 x 8 mm SiC passive heating element, 2.24a (0.25 mmol, 1 equiv), solvent (2.5 mL) and catalyst (0.05 mmol, 0.2 equiv). The reaction tube was sealed with a Teflon-lined snap cap, and heated in a microwave reactor at stated temperatures for the designated time. After cooling with compressed air flow, the reaction mixture was diluted with EtOAc (10 mL) and washed with saturated aqueous NaHCO₃ (3 x 5 mL). The combined aqueous layers were extracted with EtOAc (3 x 5 mL), the combined organic layer was washed with water (20 mL) and brine (20 mL), and dried over anhydrous Na₂SO₄. Solvent was then removed in vacuo and the reaction mixture was loaded onto a column for purification (silica gel, pre-basified by 1% Et₃N).

**General Procedure for the Synthesis of Cyanohydrins (adopted from reference 39):**

In a 25 mL round bottom flask, aldehyde (5 mmol, 1 equiv) and Cu(OTf)₂ (0.25 mmol, 0.05 equiv) were added to dichloromethane (7.5 mL) at room temperature. The resulting mixture was stirred for 15 min, followed by slow addition of TMSCN (6.5 mmol, 1.3 equiv). The reaction mixture was stirred at room temperature for 18 hours. The solvent was then removed in vacuo, and acetonitrile (5 mL) and HCl (1M, 5 mL) were added to the residue. It was stirred at 0 °C for 10 min and then extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with water (10 mL), brine (10 mL), and dried over anhydrous Na₂SO₄. Solvent was then removed in vacuo and the reaction mixture was loaded onto a column for purification (silica gel) or recrystallized from EtOAc/Hexanes. Due to the use of excess TMSCN and potential formation of HCN, all steps must be carried out inside a well ventilated fume hood.
Procedure for the Synthesis of 1-Benzylpyrrolidine-2-carbonitrile (2.23a) via Three-Component Approach:

A 10 mL microwave reaction tube was charged with a 10 x 8 mm SiC passive heating element, benzaldehyde (0.25 mmol, 1 equiv), toluene (2.5 mL), pyrrolidine (0.325 mmol, 1.3 equiv), TMSCN (0.325 mmol, 1.3 equiv) and benzoic acid (0.05 mmol, 0.2 equiv). The reaction tube was sealed with a Teflon-lined snap cap, and heated in a microwave reactor at 200 °C (200 W, 70–100 psi) for 30 minutes. After cooling with compressed air flow, the reaction mixture was diluted with EtOAc (10 mL) and washed with saturated aqueous NaHCO₃ (3 x 5 mL). The combined aqueous layers were extracted with EtOAc (3 x 5 mL), the combined organic layer was washed with water (20 mL), brine (20 mL), and dried over anhydrous Na₂SO₄. Solvent was then removed in vacuo and the reaction mixture was loaded onto a column for purification (silica gel, hexanes/EtOAc/Et₃N 95/5/1 v/v/v). Product 2.23a was obtained as a colorless oil in 62% yield as 9:1 mixture of regioisomers.

General Procedure for the Direct α-Cyanation of Pyrrolidine with Cyanohydrins:

A 10 mL microwave reaction tube was charged with a 10 x 8 mm SiC passive heating element, cyanohydrin (0.25 mmol, 1 equiv), toluene (2.5 mL), pyrrolidine (0.325 mmol, 1.3 equiv) and 2-ethylhexanoic acid (0.05 mmol, 0.2 equiv). The reaction tube was sealed with a Teflon-lined snap cap, and heated in a microwave reactor at 200 °C (200 W, 70–100 psi) for the designated time. After cooling with compressed air flow, the reaction mixture was diluted with EtOAc (10 mL) and washed with saturated aqueous NaHCO₃ (3 x 5 mL). The combined aqueous layers were extracted with EtOAc (3 x 5 mL), the combined organic layer was washed with water (20 mL) and brine (20 mL), and dried over anhydrous Na₂SO₄. Solvent was then removed in vacuo and the reaction mixture was loaded onto a column for purification (silica gel, pre-basified with eluent containing 1% Et₃N).

1-(4-Methylbenzyl)pyrrolidine-2-carbonitrile (2.23b): Following the general procedure compound 2.23b was obtained from pyrrolidine and p-tolualdehyde cyanohydrin as a colorless liquid in 80% yield (16:1 mixture of regioisomers)
(Rf = 0.14 in hexanes/EtOAc 95:5 v/v); Characterization data of the major regioisomer: IR (KBr) 2960, 2815, 2220, 1633, 1473, 1445, 1376, 1132, 1052, 1039, 755, 683 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 7.26 (d, J = 7.9 Hz, 2H), 7.15 (d, J = 7.8 Hz, 2H), 3.89 (d, J = 12.9 Hz, 1H), 3.69 (dd, J = 7.4, 2.6 Hz, 1H), 3.64 (d, J = 12.9 Hz, 1H), 2.94 (dd, J = 12.5, 8.4, 4.2 Hz, 1H), 2.62–2.55 (m, 1H), 2.35 (s, 3H), 2.21–2.07 (comp, 2H), 2.01–1.85 (comp, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 137.0, 134.4, 129.1, 128.7, 117.9, 56.1, 53.0, 51.1, 29.4, 21.8; m/z (ESI–MS) 174.1 [M–CN]⁺.

1-(4-Methoxybenzyl)pyrrolidine-2-carbonitrile (2.23c): Following the general procedure compound 2.23c was obtained from pyrrolidine and p-anisaldehyde cyanohydrin as a colorless liquid in 67% yield (11:1 mixture of regioisomers) (Rf = 0.19 in hexanes/EtOAc 90:10 v/v); Characterization data of the major regioisomer: IR (KBr) 2958, 2816, 1612, 1513, 1462, 1377, 1301, 1245, 1174, 1039, 821 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 7.27 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 3.85 (d, J = 12.9 Hz, 1H), 3.79 (s, 3H), 3.65 (dd, J = 12.4, 2.7 Hz, 1H), 3.59 (d, J = 12.8 Hz, 1H), 2.91 (dd, J = 12.5, 8.5, 4.2 Hz, 1H), 2.59–2.52 (m, 1H), 2.20–2.06 (comp, 2H), 2.00–1.82 (comp, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 158.9, 129.9, 129.6, 117.9, 113.7, 55.7, 55.1, 52.9, 51.0, 29.3, 21.7; m/z (ESI–MS) 190.0 [M–CN]⁺.

1-(4-Chlorobenzyl)pyrrolidine-2-carbonitrile (2.23d): Following the general procedure compound 2.23d was obtained from pyrrolidine and p-chlorobenzaldehyde cyanohydrin as a white sticky solid in 94% yield (>20:1 mixture of regioisomers) (Rf = 0.13 in hexanes/EtOAc 95:5 v/v); Characterization data of the major regioisomer: IR (KBr) 2960, 2819, 2222, 1644, 1491, 1447, 1409, 1376, 1334, 1124, 1084, 1016, 881, 840 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 7.29 (comp, 4H), 3.87 (d, J = 13.2 Hz, 1H), 3.67 (dd, J = 7.4, 2.2 Hz, 1H), 3.63 (d, J = 13.2 Hz, 1H), 2.94–2.86 (m, 1H), 2.59–2.51 (m, 1H), 2.20–2.07 (comp, 2H), 2.00–1.84 (comp, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 136.1, 133.1, 130.0, 128.6, 117.7, 55.7, 53.1, 51.1, 29.4, 21.8; m/z (ESI–MS) 194.1 [M–CN]⁺.
1-(4-Nitrobenzyl)pyrrolidine-2-carbonitrile (2.23e): Following the general procedure for the synthesis of α-aminonitrile via three-component approach, compound 2.23e was obtained from pyrrolidine, p-nitrobenzaldehyde and TMSCN as an off-white solid in 41% yield (1.4:1 mixture of regioisomers) (R_f = 0.24 in hexanes/EtOAc 80:20 v/v); Characterization data of the major regioisomer: mp: 80–83 °C; IR (KBr) 2961, 2820, 2220, 1606, 1518, 1346, 1108, 1015, 853, 806, 739 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 8.17 (d, J = 8.4 Hz, 2H), 7.53 (d, J = 8.4 Hz, 2H), 3.98 (d, J = 13.8 Hz, 1H), 3.80 (d, J = 13.9 Hz, 1H), 3.72 (dd, J = 7.6, 2.5 Hz, 1H), 2.91 (ddd, J = 12.7, 8.4, 4.3 Hz, 1H), 2.63–2.56 (m, 1H), 2.26–2.10 (comp, 2H), 2.03–1.87 (comp, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 147.3, 145.2, 129.3, 123.7, 117.6, 55.8, 53.4, 51.3, 29.5, 21.9; m/z (ESI–MS) 205.2 [M–CN]⁺.

1-(3-Chlorobenzyl)pyrrolidine-2-carbonitrile (2.23f): Following the general procedure compound 2.23f was obtained from pyrrolidine and m-chlorobenzaldehyde cyanohydrin as a colorless liquid in 87% yield (>20:1 mixture of regioisomers) (R_f = 0.14 in hexanes/EtOAc 95:5 v/v); Characterization data of the major regioisomer: IR (KBr) 3062, 2961, 2881, 2820, 2222, 1600, 1576, 1475, 1431, 1373, 1334, 1210, 1144, 1076, 995, 883, 786, 685; ¹H NMR (500 MHz, CDCl₃) 7.36 (s, 1H), 7.27–7.20 (comp, 3H), 3.87 (d, J = 13.3 Hz, 1H), 3.71 (dd, J = 7.5, 2.4 Hz, 1H), 3.65 (d, J = 13.2 Hz, 1H), 2.92 (ddd, J = 12.7, 8.5, 4.2 Hz, 1H), 2.61–2.52 (m, 1H), 2.23–2.07 (comp, 2H), 2.01–1.87 (comp, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 139.7, 134.3, 129.7, 128.6, 127.6, 126.8, 117.7, 55.8, 53.2, 51.1, 29.4, 21.8; m/z (ESI–MS) 194.1 [M–CN]⁺.

1-(3-Methylbenzyl)pyrrolidine-2-carbonitrile (2.23g): Following the general procedure compound 2.23g was obtained from pyrrolidine and m-tolualdehyde cyanohydrin as a colorless liquid in 79% yield (19:1 mixture of regioisomers) (R_f = 0.14 in hexanes/EtOAc 95:5 v/v); Characterization data of the major regioisomer: IR (KBr) 2959, 2922, 2881, 2814, 2221, 1610, 1487, 1460, 1378, 1334, 1160, 1124, 1089, 886, 789, 700 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 7.23 (m, 1H), 7.20–7.15 (comp, 2H), 7.10 (app d, J = 7.4 Hz, 1H), 3.90 (d, J = 12.9 Hz, 1H), 3.71 (dd, J = 7.4, 2.4 Hz, 1H), 3.64 (d, J = 12.9 Hz, 1H), 2.95 (ddd, J = 12.7, 8.5, 4.2 Hz, 1H), 2.63–2.56 (m, 1H), 2.36 (s, 3H), 2.25–2.07
(comp, 2H), 2.02–1.86 (comp, 2H); 13C NMR (125 MHz, CDCl3) δ 138.0, 137.4, 129.4, 128.2, 128.1, 125.8, 117.8, 56.4, 53.1, 51.1, 29.4, 21.7, 21.2; m/z (ESI–MS) 174.1 [M–CN]+.

1-(2-Bromobenzyl)pyrrolidine-2-carbonitrile (2.23h): Following the general procedure compound 2.23h was obtained from pyrrolidine and o-bromobenzaldehyde cyanohydrin as a colorless liquid in 85% yield (>20:1 mixture of regioisomers) (Rf = 0.19 in hexanes/EtOAc 93:7 v/v); Characterization data of the major regioisomer: IR (KBr) 3059, 2959, 2814, 2221, 1567, 1468, 1439, 1375, 1335, 1246, 1134, 1028, 994, 882, 754, 660 cm⁻¹; 1H NMR (500 MHz, CDCl3) 7.55 (app dd, J = 7.9, 1.2 Hz, 1H), 7.42 (app dd, J = 7.6, 1.6 Hz, 1H), 7.28 (app td, J = 7.5, 1.2 Hz, 1H), 7.13 (app td, J = 7.7, 1.7 Hz, 1H), 3.95 (d, J = 13.8 Hz, 1H), 3.85 (d, J = 13.8 Hz, 1H), 3.77 (dd, J = 7.5, 2.7 Hz, 1H), 2.92 (ddd, J = 12.8, 8.4, 4.5 Hz, 1H), 2.66 (m, 1H), 2.40 (s, 3H), 2.23–2.09 (comp, 2H), 2.01–1.84 (comp, 2H); 13C NMR (125 MHz, CDCl3) δ 136.8, 132.9, 130.5, 128.8, 127.3, 124.4, 118.2, 55.9, 53.4, 51.0, 29.6, 22.0; m/z (ESI–MS) 239.2 [M–CN]+.

1-(2,4,6-Trimethylbenzyl)pyrrolidine-2-carbonitrile (2.23i): Following the general procedure compound 2.23i was obtained from pyrrolidine and mesitaldehyde cyanohydrin as a colorless liquid in 89% yield (>20:1 mixture of regioisomers) (Rf = 0.16 in hexanes/EtOAc 97:3 v/v); Characterization data of the major regioisomer: IR (KBr) 2954, 2858, 2221, 1613, 1461, 1374, 1332, 1120, 1046, 851, 665 cm⁻¹; 1H NMR (500 MHz, CDCl3) 6.84 (s, 2H), 3.85 (d, J = 12.9 Hz, 1H), 3.74 (d, J = 12.9 Hz, 1H), 3.70 (dd, J = 7.1, 3.4 Hz, 1H), 2.78 (ddd, J = 13.0, 8.5, 4.6 Hz, 1H), 2.66–2.55 (m, 1H), 2.37 (s, 6H), 2.27 (s, 3H), 2.15–2.06 (comp, 2H), 1.95–1.85 (m, 1H), 1.85–1.76 (m, 1H); 13C NMR (125 MHz, CDCl3) δ 137.7, 136.7, 131.2, 129.1, 118.8, 53.5, 50.2, 49.5, 29.7, 22.0, 20.8, 20.0; m/z (ESI–MS) 202.0 [M–CN]+.

1-(Naphthalen-1-ylmethyl)pyrrolidine-2-carbonitrile (2.23j): Following the general procedure compound 2.23j was obtained from pyrrolidine and 1-naphthaldehyde cyanohydrin as an off-white solid in 85% yield (18:1 mixture of regioisomers) (Rf = 0.27 in hexanes/EtOAc 95:5 v/v); Characterization data of the major regioisomer: mp: 42–44 ºC; IR (KBr) 2957, 2817, 2221, 1597,
1509, 1460, 1379, 1331, 1234, 1142, 1019, 880, 779 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) 8.26 (app d, \(J = 8.5\) Hz, 1H), 7.88 (m, 1H), 7.83 (app d, \(J = 8.2\) Hz, 1H), 7.58–7.49 (comp, 3H), 7.44 (m, 1H), 4.45 (d, \(J = 12.8\) Hz, 1H), 4.02 (d, \(J = 12.9\) Hz, 1H), 3.64 (m, 1H), 3.02 (ddd, \(J = 12.7, 8.5, 4.2\) Hz, 1H), 2.72–2.63 (m, 1H), 2.15–2.06 (comp, 2H), 2.02–1.85 (comp, 2H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 133.8, 133.3, 132.1, 128.4(2), 128.4(0), 127.2, 125.9, 125.7, 125.2, 124.3, 118.1, 54.7, 53.2, 51.1, 29.5, 21.8; \(m/z\) (ESI–MS) 210.1 [M–CN]\(^+\).

1-(Pyridin-3-ylmethyl)pyrrolidine-2-carbonitrile (2.23k): Following the general procedure compound 2.23k was obtained from pyrrolidine and 3-pyridinecarboxaldehyde cyanohydrin as a colorless liquid in 60% yield (>20:1 mixture of regioisomers) \((R_f = 0.19\) in hexanes/EtOAc 50:50 v/v); Characterization data of the major regioisomer: IR (KBr) 2962, 2822, 2222, 1656, 1579, 1479, 1427, 1378, 1330, 1187, 1124, 1029, 799, 714 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) 8.54 (s, 1H), 8.47 (app d, \(J = 4.1\) Hz, 1H), 7.63 (app d, \(J = 7.9\) Hz, 1H), 7.22 (app dd, \(J = 7.8, 4.8\) Hz, 1H), 3.85 (d, \(J = 13.4\) Hz, 1H), 3.65 (d, \(J = 13.2\) Hz, 1H), 3.67–3.64 (m, 1H), 2.84 (ddd, \(J = 12.4, 8.4, 4.4\) Hz, 1H), 2.56–2.49 (comp, 1H), 2.18–2.03 (comp, 2H), 1.96–1.79 (comp, 2H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 149.9, 148.7, 136.3, 133.0, 123.3, 117.6, 53.7, 53.1, 51.0, 29.4, 21.8; \(m/z\) (ESI–MS) 188.1 [M+H]\(^+\), 161.2 [M–CN]\(^+\).

1-(Furan-2-ylmethyl)pyrrolidine-2-carbonitrile (2.23l): Following the general procedure compound 2.23l was obtained from pyrrolidine and furfural cyanohydrin as a colorless liquid in 64% yield (20:1 mixture of regioisomers) \((R_f = 0.16\) in hexanes/EtOAc 90:10 v/v); Characterization data of the major regioisomer: IR (KBr) 2962, 2882, 2818, 2222, 1601, 1505, 1445, 1372, 1335, 1224, 1149, 1014, 916, 739, cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) 7.40 (m, 1H), 6.33 (m, 1H), 6.29 (d, \(J = 3.1\) Hz, 1H), 3.88 (d, \(J = 13.8\) Hz, 1H), 3.76 (d, \(J = 13.9\) Hz, 1H), 3.73 (dd, \(J = 7.8, 2.8\) Hz, 1H), 2.96 (ddd, \(J = 12.8, 8.4, 4.4\) Hz, 1H), 2.66–2.59 (m, 1H), 2.24–2.08 (comp, 2H), 2.02–1.86 (comp, 2H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 151.2, 142.8, 118.0, 110.5, 109.1, 53.2, 51.4, 48.7, 29.8, 22.2; \(m/z\) (ESI–MS) 150.1 [M–CN]\(^+\).
1-(Thiophen-2-ylmethyl)pyrrolidine-2-carbonitrile (2.23m): Following the general procedure, compound 2.23m was obtained from pyrrolidine and 2-thiophenecarboxaldehyde cyanohydrin as a colorless liquid in 82% yield (>20:1 mixture of regioisomers) ($R_f = 0.24$ in hexanes/EtOAc 90:10 v/v); Characterization data of the major regioisomer: IR (KBr) 2959, 2808, 2222, 1645, 1444, 1377, 1329, 1223, 1117, 951, 851, 696 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$3$) 7.25 (dd, $J = 5.1, 1.1$ Hz, 1H), 7.00 (m, 1H), 6.94 (dd, $J = 5.1, 3.5$ Hz, 1H), 4.07 (d, $J = 13.8$ Hz, 1H), 3.93 (d, $J = 13.8$ Hz, 1H), 3.77 (dd, $J = 7.6, 2.5$ Hz, 1H), 3.01 (ddd, $J = 12.5, 8.3, 4.2$ Hz, 1H), 2.64–2.56 (m, 1H), 2.22–2.08 (comp, 2H), 2.02–1.86 (comp, 2H); $^{13}$C NMR (125 MHz, CDCl$3$) $\delta$ 140.6, 126.5, 126.3, 125.4, 117.7, 52.8, 51.0, 50.7, 29.4, 21.8; m/z (ESI–MS) 166.0 [M–CN]$^+$. Ethyl 2-(2-cyanopyrrolidin-1-yl)acetate (2.23n) and ethyl 2-cyano-2-(pyrrolidin-1-yl)acetate (2.24n): Following the general procedure compounds 2.23n and 2.24n were obtained from pyrrolidine and ethyl glyoxalate cyanohydrin as a colorless liquid in 62% yield (1:1.4 mixture of regioisomers). Characterization data of 5n: $R_f = 0.26$ in hexanes/EtOAc 80:20 v/v; IR (KBr) 2982, 2822, 2220, 1743, 1464, 1428, 1384, 1200, 1160, 1028, 863 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$3$) 4.13 (t, $J = 4.1$ Hz, 2H), 4.08 (dd, $J = 7.8, 4.1$ Hz, 1H), 3.51–3.40 (comp, 2H), 3.00 (ddd, $J = 13.0, 8.8, 5.1$ Hz, 1H), 2.66–2.58 (m, 1H), 2.26–2.16 (m, 1H), 2.12–2.14 (m, 1H), 1.95–1.84 (comp, 2H), 1.22 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$3$) $\delta$ 169.7, 118.0, 60.7, 52.8, 51.3, 29.8, 22.1, 13.9; m/z (ESI–MS) 156.1 [M–CN]$^+$. Characterization data of 2.24n: $R_f = 0.20$ in 20% EtOAc in hexanes; IR (KBr) 2976, 2879, 2821,2359, 1746, 1463, 1445, 1370, 1201, 1154, 1117, 1024, 904, 851 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$3$) 4.59 (s, 1H), 4.25 (q, $J = 7.3$ Hz, 2H), 2.81–2.63 (comp, 4H), 1.91–1.75 (comp, 4H), 1.28 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$3$) $\delta$ 164.0, 112.6, 62.8, 57.8, 50.3, 23.4, 13.8; m/z (ESI-MS) 183.2 [M + H]$^+$. 
1-(3-Phenylpropyl)pyrrolidine-2-carbonitrile (2.23o) and 4-phenyl-2-(pyrrolidin-1-yl)butanenitrile (2.24o): Following the general procedure compounds 2.23o and 2.24o were obtained from pyrrolidine and hydrocinnamaldehyde cyanohydrin as colorless liquid in 74% yield (1:3 mixture of regioisomers). Characterization data of 2.23o: \( R_f = 0.16 \) in hexanes/EtOAc 90:10 v/v; IR (KBr) 3026, 2942, 2813, 2220, 1602, 1496, 1454, 1386, 1318, 1182, 1145, 1123, 1079, 1030, 966, 882, 747, 700 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( 7.33 - 7.27 \) (comp, 2H), \( 7.23 - 7.18 \) (comp, 3H), \( 3.76 \) (dd, \( J = 7.6, 2.8 \) Hz, 1H), \( 2.89 \) (ddd, \( J = 12.9, 8.4, 4.6 \) Hz, 1H), \( 2.73 \) (m, 1H), \( 2.69 \) (t, \( J = 7.6 \) Hz, 2H), \( 2.64 - 2.52 \) (comp, 2H), \( 2.23 - 2.08 \) (comp, 2H), \( 2.01 - 1.82 \) (comp, 4H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta = 141.7, 128.3, 128.2, 125.8, 118.1, 53.6, 51.8, 51.0, 33.3, 30.0, 29.5, 21.8; \( m/z \) (ESI–MS) 188.3 [M–CN]\(^+\).

Characterization data of 2.24o: \( R_f = 0.32 \) in 10% EtOAc in hexanes; IR (KBr) 3062, 3027, 2961, 2811, 1603, 1496, 1455, 1354, 1318, 1143, 1123, 1030, 903, 869, 752, 700 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( 7.35 - 2.28 \) (comp, 2H), \( 7.26 - 7.18 \) (comp, 3H), \( 3.69 \) (t, \( J = 7.9 \) Hz, 1H), \( 2.91 - 2.77 \) (comp, 2H), \( 2.77 - 2.68 \) (comp, 2H), \( 2.68 - 2.56 \) (comp, 2H), \( 2.14 - 2.04 \) (comp, 2H), \( 1.90 - 1.79 \) (comp, 4H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta = 139.8, 128.3(2), 128.3(0), 126.1, 117.2, 53.9, 49.6, 33.8, 31.6, 23.2; \( m/z \) (ESI–MS) 188.1 [M–CN]\(^+\).

1-(Cyclohexylmethyl)pyrrolidine-2-carbonitrile (2.24p): Following the general procedure compound 2.24p was obtained from pyrrolidine and cyclohexanecarboxaldehyde cyanohydrin as a colorless liquid in 78% yield (1:5 mixture of regioisomers) (\( R_f = 0.23 \) in hexanes/EtOAc 95:5 v/v); Characterization data of the major regioisomer: IR (KBr) 2923, 2851, 2810, 2221, 1449, 1341, 1244, 1189, 1147, 1114, 1082, 879 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( 3.72 \) (dd, \( J = 7.5, 2.4 \) Hz, 1H), \( 2.83 \) (m, 1H), \( 2.54 - 2.42 \) (comp, 2H), \( 2.40 - 2.33 \) (m, 1H), \( 2.19 - 2.04 \) (comp, 2H), \( 1.96 - 1.81 \) (comp, 2H), \( 1.80 - 1.73 \) (comp, 2H), \( 1.73 - 1.60 \) (comp, 2H), \( 1.48 - 1.37 \) (m, 1H), \( 1.31 - 1.09 \) (comp, 4H), \( 0.94 - 0.74 \) (comp, 2H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta = 118.3, 59.4, 54.1, 51.4, 36.5, 31.6, 31.5, 29.6, 26.7, 25.9(2), 25.9(1), 21.9; \( m/z \) (ESI–MS) 166.2 [M–CN]\(^+\).
1-Benzhydrylpyrrolidine-2-carbonitrile (2.23q): Following the general procedure compound 2.23q was obtained from pyrrolidine and benzophenone cyanohydrin as a white solid in 40% yield (>20:1 mixture of regioisomers) (Rf = 0.22 in hexanes/EtOAc 97:3 v/v); Characterization data of the major regioisomer: mp: 108–111 °C; IR (KBr) 3061, 3028, 2958, 2821, 2222, 1598, 1491, 1453, 1306, 1186, 1130, 1076, 1028, 927, 887, 748, 706, 628 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) 7.50 (comp, 4H), 7.30 (comp, 4H), 7.24–7.19 (comp, 2H), 4.61 (s, 1H), 3.78 (app d, J = 7.3 Hz, 1H), 3.02–2.94 (m, 1H), 2.44–2.36 (m, 1H), 2.25–2.14 (m, 1H), 2.13–2.03 (m, 1H), 2.01–1.87 (comp, 2H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) δ 142.5, 142.0, 128.8, 128.6, 127.6, 127.5, 127.3(1), 127.3(0), 117.7, 71.8, 53.1, 49.9, 29.4, 21.8; \(m/z\) (ESI–MS) 136.0 [M–CN]\(^+\).

1-Benzylazepane-2-carbonitrile (2.31): Following the general procedure but conducting the reaction at 220 °C, compound 2.31 was obtained from azepane and benzaldehyde cyanohydrin as colorless liquid in 79% yield (11:1 mixture of regioisomers) (Rf = 0.4 in 10% EtOAc in Hexanes); Characterization data of the major regioisomer: IR (KBr) 2931, 2852, 2821, 2220, 1602, 1452, 1357, 1150, 957, 747, 698 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) 7.38–7.33 (comp, 3H), 7.33–7.30 (m, 1H), 7.30–7.25 (m, 1H), 3.80 (d, J = 13.4 Hz, 1H), 3.76 (dd, J = 7.5, 5.6 Hz, 1H), 3.73 (d, J = 13.4 Hz, 1H), 2.75 (app dd, J = 6.8, 4.6 Hz, 2H), 2.08–2.00 (m, 1H), 1.90–1.82 (m, 1H), 1.81–1.71 (comp, 3H), 1.71–1.59 (comp, 2H), 1.59–1.50 (m, 1H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) δ 138.2, 128.7, 128.4, 127.5, 118.4, 61.1, 54.3, 51.2, 32.4, 28.5, 27.2, 23.4; \(m/z\) (ESI–MS) 188.3 [M–CN]\(^+\).

2-Benzyl-1,2,3,4-tetrahydroisoquinoline-3-carbonitrile (2.33): Following the general procedure compound 2.33 was obtained from (S)-(1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid and benzaldehyde as an off-white solid in 91% yield (Rf = 0.21 in hexanes/EtOAc 93:7 v/v); mp: 110–112 °C; IR (KBr) 2818, 1644, 1496, 1455, 1357, 1315, 1145, 1091, 1074, 1028, 989, 741, 701 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) 7.42–7.30 (comp, 5H), 7.21–7.15 (comp, 2H), 7.13–7.10 (m, 1H), 7.06 (m, 1H), 4.03 (d, J = 6.3 Hz, 1H), 3.98 (d, J = 15.6 Hz, 1H), 3.92 (d, J = 13.2 Hz, 1H), 3.78 (d, J = 15.5 Hz, 1H), 3.70 (d, J = 13.2 Hz, 1H), 3.31 (dd, J = 16.3, 6.1 Hz, 1H), 2.98 (d, J =
16.5 Hz, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 136.4, 132.8, 129.8, 129.0, 128.7(2), 128.7(0), 127.9, 126.7, 126.6, 126.5, 116.3, 60.2, 51.6, 49.3, 32.6; $m/z$ (ESI–MS) 222.2 [M–CN]$^+$. 

2-(3,4-dihydroisoquinolin-2(1H)-yl)-1-phenylacetonitrile (2.34): Following a literature procedure,$^1$ compound 2.34 was obtained from 1,2,3,4-tetrahydroisoquinoline, benzaldehyde and TMSCN as a off-white solid in 38% yield (R$_f$ = 0.29 in 10% EtOAc in Hexanes); mp: 77–80 °C; IR (KBr) 3044, 2960, 2925, 2834, 2786, 2751, 2630, 2343, 2223, 1494, 1449, 1390, 1317, 1267, 1131, 1094, 1044, 934, 914, 872, 759, 741, 702 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.65–7.58 (comp, 2H), 7.47–7.37 (comp, 3H), 7.18–7.10 (comp, 3H), 7.02–6.98 (m, 1H), 5.08 (s, 1H), 3.83–3.74 (comp, 2H), 3.02–2.81 (comp, 4H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 133.7, 133.6, 133.0, 129.0, 128.8, 128.7, 127.8, 126.6, 126.4, 125.8, 115.3, 62.2, 52.4, 47.5, 29.3; $m/z$ (ESI–MS) 222.1 [M–CN]$^+$. 

2-Benzyl-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (2.35): Following literature procedures,$^7$ compound 2.35 was obtained as an off-white solid in 47% yield (three steps) (R$_f$ = 0.32 in 10% EtOAc in Hexanes); mp: 72–75 °C; IR (KBr) 3084, 3065, 3024, 2969, 2928, 2827, 2218, 1493, 1451, 1369, 1336, 1134, 1095, 1050, 936, 738, 698 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) 7.46–7.41 (comp, 2H), 7.40–7.35 (comp, 2H), 7.35–7.30 (m, 1H), 7.28–7.23 (m, 1H), 7.21–7.16 (comp, 2H), 7.16–7.12 (m, 1H), 4.69 (s, 1H), 3.94 (d, $J$ = 13.2 Hz, 1H), 3.84 (d, $J$ = 13.2 Hz, 1H), 3.14–3.02 (comp, 2H), 2.94–2.85 (m, 1H), 2.83–2.76 (m, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 133.7, 133.6, 133.0, 129.0, 128.8, 127.8, 127.6, 126.4, 126.1, 115.3, 62.2, 52.4, 47.5, 29.3; $m/z$ (ESI–MS) 222.2 [M–CN]$^+$. 

trans-1-benzyl-5-methylpyrrolidine-2-carbonitrile (trans-2.36): According to the general procedure, 2-methylpyrrolidine and benzaldehyde cyanohydrin were allowed to react at 180 °C to give rise to a colorless liquid consisting of a mixture of 1-benzyl-2-methylpyrrolidine-2-carbonitrile (2.37, 11%)$^{44}$, and trans-2.36/cis-2.36 (4.8:1, 52%). The relative configuration of the major diastereomer (trans-2.36) was determined by GCOSY and NOESY. (R$_f$ = 0.27 in 5% EtOAc in Hexanes). Characterization data of the major diastereomer trans-2.36: IR (KBr) 3029.5, 2963.9, 2812.7, 2221.0, 1495.4, 1454.3, 1324.7, 1153.6, 1136.9, 1075.7, 1028.7, 970.6, 848.3, 741.8, 699.5 cm$^{-1}$; 

trans-2.36/cis-2.36.
I H NMR (500 MHz, CDCl3) 7.41–7.36 (comp, 2H), 7.36–7.30 (comp, 2H), 7.29–7.26 (m, 1H), 4.08 (d, J = 13.3 Hz, 1H), 3.68 (app d, J = 7.5 Hz, 1H), 3.44 (d, J = 13.3 Hz, 1H) 2.89–2.79 (m, 1H), 2.25–2.14 (m, 1H), 2.11–2.02 (m, 1H), 2.01–1.93 (m, 1H), 1.59–1.50 (m, 1H), 1.23 (d, J = 6.0 Hz, 3H); 13C NMR (125 MHz, CDCl3) δ 138.0, 128.9, 128.5, 127.4, 117.9, 57.0, 53.6, 53.4, 30.9, 27.3, 19.4; m/z (ESI–MS) 174.1 [M – CN]+.

2D-NMR Analysis for Compound trans-2.36, Selected Interactions:

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General Procedure for the Redox-Neutral α-Arylation of Amines with Naphthols or Phenols as Nucleophiles:

To a solution of the naphthol (1.5 mmol, 1.5 equiv) or phenol (5 mmol, 5 equiv) in toluene (4 mL) was added the amine (1.5 mmol, 1.5 equiv). The mixture was heated under reflux and aldehyde (1 mmol, 1 equiv, 1 M solution in toluene) was delivered through the top of the reflux condenser over 5 hours via syringe pump. Subsequently, the reaction mixture was allowed to cool to room temperature and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography.

General Procedure for the Redox-Neutral α-Arylation of Amines with Indoles or Pyrroles as Nucleophiles:

To a solution of the indole (1.5 mmol, 1.5 equiv) or pyrrole (5 mmol, 5 equiv) in toluene (4 mL) was added the amine (1.5 mmol, 1.5 equiv) and 2-ethylhexanoic acid (1 mmol, 1 equiv). The mixture was heated under reflux and aldehyde (1 mmol, 1 equiv, 1 M solution in toluene) was delivered through the top of the reflux condenser over 5 hours via syringe pump. Subsequently, the reaction mixture was allowed to cool to room temperature, diluted with EtOAc (10 mL) and was washed with saturated aqueous NaHCO₃ (3 x 10 mL). The combined aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organic layer was washed with water (40 mL), brine (40 mL), and dried over anhydrous Na₂SO₄. Solvent was then removed under reduced pressure. The residue was purified by silica gel chromatography.

1-(1-(2,6-dichlorobenzyl)pyrrolidin-2-yl)naphthalen-2-ol (2.43a): Following the general procedure compound 2.43a was obtained from 2-naphthol, pyrrolidine and 2,6-dichlorobenzaldehyde as a colorless oil in 96% yield (Rᵣ = 0.37 in hexanes/EtOAc 90:10 v/v); IR (KBr) 3063, 2944, 2905, 2842, 1621, 1595, 1581, 1561, 1464, 1519, 1332, 1272, 1234, 1127, 1086, 959, 814, 776, 764, 750 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 12.13 (br s, 1H), 7.93 (app d, J = 8.6 Hz, 1H), 7.74 (app d, J = 8.1 Hz, 1H), 7.58 (d, J = 8.8 Hz, 1H), 7.46 (ddd, J = 8.6, 6.8, 1.3 Hz, 1H), 7.29 (ddd, J = 8.1, 6.8, 1.0 Hz, 1H), 7.15 (d, J = 8.0 Hz, 2H), 7.01 (t, J = 8.0 Hz, 1H), 6.96 (d, J = 8.8 Hz, 1H), 4.71 (app t, J = 8.6 Hz,
1H), 4.18 (d, J = 12.7 Hz, 1H), 4.08 (d, J = 12.7 Hz, 1H), 3.36–3.29 (m, 1H), 2.83 (app td, J = 9.7, 7.5 Hz, 1H), 2.59–2.43 (m, 1H), 2.15–1.90 (comp, 3H); 13C NMR (125 MHz, CDCl3) δ 155.5, 136.7, 132.7, 132.5, 129.1, 128.6, 128.3, 128.1, 125.9, 122.1, 121.2, 119.4, 116.2, 65.4, 54.1, 53.5, 32.7, 23.5; m/z (ESI–MS) 372.1 (35Cl/35Cl) [M + H]+, 374.1 (35Cl/37Cl) [M + H]+.

3-(1-(2,6-dichlorobenzyl)pyrrolidin-2-yl)-1H-indole (2.43b): Following the general procedure compound 2.43b was obtained from indole, pyrrolidine and 2,6-dichlorobenzaldehyde as a colorless oil in 86% yield (Rf = 0.24 in hexanes/EtOAc 75:25 v/v); IR (KBr) 3446, 3123, 3059, 2971, 2833, 2794, 1616, 1576, 1559, 1456 cm⁻¹; 1H NMR (500 MHz, CDCl3) 8.05 (br s, 1H), 7.89 (d, J = 7.8 Hz, 1H), 7.34–7.29 (m, 1H), 7.27–7.13 (comp, 5H), 7.01 (t, J = 8.0 Hz, 1H), 4.05 (d, J = 12.2 Hz, 1H), 3.87 (app t, J = 8.3 Hz, 1H), 3.74 (d, J = 12.2 Hz, 1H), 3.15–3.06 (m, 1H), 2.67 (app q, J = 8.8 Hz, 1H), 2.36–2.24 (m, 1H), 2.21–2.08 (m, 1H), 2.06–1.94 (m, 1H), 1.93–1.84 (m, 1H); 13C NMR (125 MHz, CDCl3) δ 136.5, 136.4, 135.2, 128.2, 128.1, 126.9, 122.4, 121.6, 120.1, 118.8, 117.5, 110.9, 62.5, 53.7, 52.7, 32.9, 22.4; m/z (ESI–MS) 345.0 (35Cl/35Cl) [M + H]+, 347.0 (35Cl/37Cl) [M + H]+.

1-(1-(2,4,6-trimethylbenzyl)pyrrolidin-2-yl)naphthalen-2-ol (2.43d): Following the general procedure compound 2.43d was obtained from 2-naphthol, pyrrolidine and mesitaldehyde as a colorless oil in 76% yield (Rf = 0.37 in hexanes/EtOAc 90:10 v/v); IR (KBr) 3059, 2967, 2915, 2873, 1622, 1599, 1521, 1467, 1414, 1360, 1270, 1240, 1134, 1090, 951, 854, 816, 745 cm⁻¹; 1H NMR (500 MHz, CDCl3) 12.78 (br s, 1H), 8.02 (app d, J = 8.8 Hz, 1H), 7.84 (app d, J = 8.2 Hz, 1H), 7.74 (d, J = 8.8 Hz, 1H), 7.54 (ddd, J = 8.8, 6.8, 1.4 Hz, 1H), 7.38 (ddd, J = 8.2, 6.8, 1.0 Hz, 1H), 7.18 (d, J = 8.8 Hz, 1H), 6.88 (s, 2H), 4.64–4.58 (m, 1H), 4.03 (d, J = 12.9 Hz, 1H), 3.68 (d, J = 12.9 Hz, 1H), 3.17–3.10 (m, 1H), 2.66–2.58 (m, 1H), 2.58–2.50 (m, 1H), 2.40 (s, 6H), 2.31 (s, 3H), 2.09–1.95 (comp, 3H); 13C NMR (125 MHz, CDCl3) δ 155.5, 137.7, 136.8, 132.6, 130.8, 129.1, 128.8, 128.3, 126.2, 122.2, 120.8, 119.5, 116.1, 66.1, 52.8, 52.2, 32.3, 23.4, 20.7, 20.5; m/z (ESI–MS) 346.1 [M + H]+.
3-(1-(2,4,6-trimethylbenzyl)pyrrolidin-2-yl)-1H-indole (2.43f): Following the general procedure compound 2.43f was obtained from indole, pyrrolidine and mesitaldehyde as a yellow oil in 60% yield (R_f = 0.25 in hexanes/EtOAc 75:25 v/v); IR (KBr) 3412, 3056, 2961, 2915, 1670, 1613, 1456, 1375, 1095, 1013, 887, 851, 805, 741 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 8.14 (br s, 1H), 7.87 (d, J = 7.9 Hz, 1H), 7.45–7.35 (m, 1H), 7.32–7.19 (comp, 2H), 7.14 (ddd, J = 8.0, 7.1, 1.1 Hz, 1H), 6.79 (s, 2H), 3.78 (d, J = 12.4 Hz, 1H), 3.74–3.64 (m, 1H), 3.31 (d, J = 12.4 Hz, 1H), 3.06–2.94 (m, 1H), 2.46–2.31 (m, 1H), 2.25 (s, 3H), 2.21 (s, 6H), 2.03–1.90 (m, 1H), 1.88–1.76 (m, 1H), 1.51–1.26 (m, 1H), 1.02–0.87 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 137.6, 136.7, 135.7, 133.3, 128.7, 126.7, 122.6, 121.7, 120.3, 118.9, 117.8, 111.1, 63.0, 53.5, 51.8, 32.3, 22.6, 20.8, 20.2; m/z (ESI–MS) 319.1 [M + H]+.

1-(1-(2,6-dichlorobenzyl)pyrrolidin-2-yl)-6-bromonaphthalen-2-ol (2.43g): Following the general procedure compound 2.43g was obtained from 6-bromo-2-naphthol, pyrrolidine and 2,6-dichlorobenzaldehyde as a yellow oil in 85% yield (R_f = 0.37 in hexanes/EtOAc 90:10 v/v); IR (KBr) 3059, 2976, 2874, 1615, 1590, 1562, 1507, 1436, 1361, 1270, 1237, 1090, 901, 879, 814, 778, 765, 737 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 12.19 (br s, 1H), 7.84 (d, J = 2.1 Hz, 1H), 7.76 (d, J = 9.1 Hz, 1H), 7.47 (dd, J = 9.1, 2.1 Hz, 1H), 7.42 (d, J = 8.8 Hz, 1H), 7.08 (d, J = 8.0 Hz, 2H), 7.00–6.94 (m, 1H), 6.89 (d, J = 8.8 Hz, 1H), 4.64 (app t, J = 8.6 Hz, 1H), 4.13 (d, J = 12.8 Hz, 1H), 4.08 (d, J = 12.8 Hz, 1H), 3.36 (ddd, J = 9.6, 7.2, 2.4 Hz, 1H), 2.81 (app td, J = 9.6, 7.7 Hz, 1H), 2.52–2.41 (m, 1H), 2.10–1.94 (comp, 2H), 1.94–1.85 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 155.7, 136.6, 132.4, 130.9, 130.3, 129.4, 129.1, 128.9, 128.0, 127.6, 123.1, 120.4, 116.5, 115.5, 65.1, 54.4, 53.5, 32.9, 23.5; m/z (ESI–MS) (³⁵Cl/³⁵Cl/⁷⁹Br) 450.0 [M + H]+, (³⁵Cl/³⁵Cl/³⁷Br) or (³⁵Cl/³⁷Cl/⁷⁹Br) 452.0 [M + H]+, (³⁵Cl/³⁷Cl/³⁷Br) 454.0 [M + H]+.
1-(1-(2,6-dichlorobenzyl)pyrrolidin-2-yl)-7-methoxynaphthalen-2-ol (2.43h): Following the general procedure compound 2.43h was obtained from 7-methoxy-2-naphthol, pyrrolidine and 2,6-dichlorobenzaldehyde as a yellow oil in 98% yield (Rf = 0.26 in hexanes/EtOAc 90:10 v/v); IR (KBr) 3055, 2955, 2874, 2836, 1622, 1583, 1562, 1519, 1467, 1436, 1267, 1225, 1135, 1091, 1035, 778, 765, 737 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 12.14 (br s, 1H), 7.63 (d, J = 8.9 Hz, 1H), 7.49 (d, J = 8.9 Hz, 1H), 7.24–7.21 (m, 1H), 7.14 (d, J = 8.0 Hz, 2H), 7.04–6.96 (comp, 2H), 6.82 (d, J = 8.7 Hz, 1H), 4.62 (app t, J = 8.4 Hz, 1H), 4.19 (d, J = 12.7 Hz, 1H), 4.07 (d, J = 12.7 Hz, 1H), 3.96 (d, J = 12.7 Hz, 1H), 3.32 (ddd, J = 9.7, 6.9, 2.1 Hz, 1H), 2.83 (app td, J = 9.7, 7.4 Hz, 1H), 2.57–2.46 (m, 1H), 2.10–1.90 (comp, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 158.3, 156.5, 137.1, 134.0, 133.0, 130.5, 129.5, 128.7, 128.5, 124.1, 117.4, 115.7, 113.9, 101.5, 65.8, 55.6, 54.5, 53.8, 32.8, 23.9; m/z (ESI–MS) (35Cl/35Cl) 402.1 [M + H]+, (35Cl/37Cl) 404.1 [M + H]+.

2-(1-(2,6-dichlorobenzyl)pyrrolidin-2-yl)phenol (2.43i): Following the general procedure compound 2.43i was obtained from phenol, pyrrolidine and 2,6-dichlorobenzaldehyde as a colorless oil in 49% yield (Rf = 0.43 in hexanes/EtOAc 90:10 v/v); IR (KBr) 3140, 3077, 2951, 2880, 2823, 1615, 1581, 1561, 1489, 1451, 1436, 1364, 1255, 1143, 1091, 896, 783, 751 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 10.46 (br s, 1H), 7.16 (d, J = 8.0 Hz, 2H), 7.06–6.98 (comp, 3H), 6.73–6.68 (m, 1H), 6.68–6.64 (m, 1H), 4.07 (d, J = 12.6 Hz, 1H), 3.97 (d, J = 12.6 Hz, 1H), 3.75–3.70 (m, 1H), 3.24–3.17 (m, 1H), 2.73–2.65 (m, 1H), 2.31–2.21 (m, 1H), 2.02–1.84 (comp, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 156.9, 136.5, 133.0, 129.1, 128.2(9), 128.1(2), 125.8, 118.6, 116.2, 70.4, 54.3, 53.3, 33.2, 23.0; m/z (ESI–MS) 322.0 (35Cl/35Cl) [M + H]+, (35Cl/37Cl) 324.0 (35Cl/37Cl) [M + H]+.

2-(1-(2,6-dichlorobenzyl)pyrrolidin-2-yl)-4-tert-butylphenol (2.43j): Following the general procedure compound 2.43j was obtained from 4-t-butylphenol, pyrrolidine and 2,6-dichlorobenzaldehyde as a colorless oil in 90% yield (Rf = 0.46 in hexanes/EtOAc 90:10 v/v); IR (KBr) 3123, 3061, 2962, 2863, 2822, 1560, 1500, 1438, 1383, 1251, 1203, 1176, 1104, 949, 890, 788, 630 cm⁻¹; ¹H NMR
(500 MHz, CDCl₃) 10.14 (br s, 1H), 7.10 (d, J = 8.0 Hz, 2H), 7.03–6.93 (comp, 3H), 6.52 (d, J = 8.3 Hz, 1H), 4.05 (d, J = 12.7 Hz, 1H), 4.02 (d, J = 12.7 Hz, 1H), 3.71 (app t, J = 8.2 Hz, 1H), 3.32–3.23 (m, 1H), 2.68 (app q, J = 9.0 Hz, 1H), 2.33–2.22 (m, 1H), 2.06–1.84 (comp, 3H), 1.29 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 154.2, 140.8, 136.4, 133.0, 128.9, 127.9, 125.0, 124.8, 124.7, 115.3, 70.7, 54.7, 53.5, 33.8, 33.4, 31.5, 22.9; m/z (ESI–MS) (³⁵Cl/³⁵Cl) 378.1 [M + H]+, (³⁵Cl/³⁵Cl) 380.1 [M + H]+.

2-(1-(2,6-dichlorobenzyl)pyrrolidin-2-yl)-4,6-dimethylphenol (2.43k): Following the general procedure compound 2.43k was obtained from 2,4-dimethylphenol, pyrrolidine and 2,6-dichlorobenzaldehyde as a colorless oil in 75% yield (Rᵣ = 0.61 in hexanes/EtOAc 90:10 v/v); IR (KBr) 3013, 2971, 2853, 2814, 1581, 1560, 1485, 1462, 1381, 1330, 1245, 1200, 1129, 1107, 1086, 951, 856, 779, 745 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 10.25 (br s, 1H), 7.19 (d, J = 8.0 Hz, 2H), 7.02 (t, J = 8.0 Hz, 1H), 6.81–6.75 (m, 1H), 6.74–6.68 (m, 1H), 4.06 (d, J = 12.6 Hz, 1H), 3.93 (d, J = 12.6 Hz, 1H), 3.63 (app t, J = 8.4 Hz, 1H), 3.23–3.14 (m, 1H), 2.73–2.63 (m, 1H), 2.33–2.21 (comp, 4H), 2.13 (s, 3H), 2.07–1.93 (comp, 2H), 1.93–1.84 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 152.3, 136.5, 133.1, 130.0, 128.9, 128.0, 126.9, 126.7, 124.7(4), 124.6(8), 70.6, 54.0, 53.0, 32.7, 22.9, 20.3, 15.5; m/z (ESI–MS) (³⁵Cl/³⁵Cl/³⁵Cl) 350.1 [M + H]+, (³⁵Cl/³⁵Cl/³⁵Cl) 352.1 [M + H]+.

2-(1-(2,6-dichlorobenzyl)pyrrolidin-2-yl)-4-chlorophenol (2.43l): Following the general procedure compound 2.43l was obtained from 4-chlorophenol, pyrrolidine and 2,6-dichlorobenzaldehyde as a yellow oil in 30% yield (Rᵣ = 0.46 in hexanes/EtOAc 90:10 v/v); IR (KBr) 3051, 2946, 2841, 1580, 1483, 1383, 1260, 1178, 1084, 823, 782, 763, 685 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 10.51 (br s, 1H), 7.16 (d, J = 8.0 Hz, 2H), 7.01 (t, J = 8.0 Hz, 1H), 6.97 (d, J = 2.2 Hz, 1H), 6.96–6.91 (m, 1H), 6.55 (d, J = 8.5 Hz, 1H), 4.05 (d, J = 12.7 Hz, 1H), 4.01 (d, J = 12.7 Hz, 1H), 3.74–3.67 (m, 1H), 3.30–3.22 (m, 1H), 2.78–2.66 (m, 1H), 2.34–2.21 (m, 1H), 2.05–1.86 (comp, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 155.5, 136.6, 132.6, 129.3, 128.2, 127.9, 127.8, 127.4, 123.1, 117.5, 69.8, 54.6, 53.4, 33.2, 23.1; m/z (ESI–MS) (³⁵Cl/³⁵Cl/³⁵Cl) 356.1 [M + H]+, (³⁵Cl/³⁵Cl/³⁵Cl) 358.1 [M + H]+.
2-(1-(2,6-dichlorobenzyl)pyrrolidin-2-yl)-4-methoxyphenol (2.43m): Following the general procedure compound 2.43m was obtained from 4-methoxyphenol, pyrrolidine and 2,6-dichlorobenzaldehyde as a colorless oil in 72% yield (Rf = 0.35 in hexanes/EtOAc 90:10 v/v); IR (KBr) 3079, 2972, 2831, 1623, 1581, 1560, 1498, 1470, 1436, 1383, 1331, 1304, 1250, 1206, 1157, 1036, 947, 849, 821, 778, 761, 657 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 9.90 (br s, 1H), 7.17 (d, J = 8.0 Hz, 2H), 7.01 (t, J = 8.0 Hz, 1H), 6.61–6.55 (comp, 3H), 4.05 (d, J = 12.6 Hz, 1H), 3.96 (d, J = 12.6 Hz, 1H), 3.74 (s, 3H), 3.65 (app t, J = 8.3 Hz, 1H), 3.23–3.16 (m, 1H), 2.71–2.63 (m, 1H), 2.31–2.22 (m, 1H), 2.02–1.83 (comp, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 152.0, 150.6, 136.5, 133.0, 129.1, 128.1, 126.5, 116.5, 114.1, 113.2, 70.5, 55.7, 54.3, 53.3, 33.0, 23.0; m/z (ESI–MS) (³⁵Cl/³⁵Cl) 352.1 [M + H]⁺, (³⁵Cl/³⁷Cl) 354.1 [M + H]⁺.

3-(1-(2,6-dichlorobenzyl)pyrrolidin-2-yl)-5-methoxy-1H-indole (2.43n): Following the general procedure compound 2.43n was obtained from 5-methoxyindole, pyrrolidine and 2,6-dichlorobenzaldehyde as a yellow oil in 80% yield (Rf = 0.35 in hexanes/EtOAc 75:25 v/v); IR (KBr) 3413, 3051, 2953, 2831, 1672, 1625, 1582, 1561, 1485, 1436, 1364, 1288, 1212, 1171, 1091, 1029, 925, 797, 765, 737 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 8.04 (br s, 1H), 7.34 (d, J = 2.3 Hz, 1H), 7.20 (d, J = 2.0 Hz, 1H), 7.19–7.13 (comp, 3H), 6.96 (t, J = 8.0 Hz, 1H), 6.86 (dd, J = 8.8, 2.3 Hz, 1H), 4.02 (d, J = 12.2 Hz, 1H), 3.93 (s, 3H), 3.79 (app t, J = 8.3 Hz, 1H), 3.73 (d, J = 12.2 Hz, 1H), 3.13–3.05 (m, 1H), 2.64 (app q, J = 8.8 Hz, 1H), 2.29–2.19 (m, 1H), 2.16–2.06 (m, 1H), 2.00–1.92 (m, 1H), 1.90–1.80 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 153.2, 136.5, 135.2, 131.7, 128.1, 128.0, 127.2, 123.4, 117.0, 111.8, 111.5, 102.3, 62.7, 55.9, 53.7, 52.7, 32.7, 22.4; m/z (ESI–MS) (³⁵Cl/³⁵Cl) 375.0 [M + H]⁺, (³⁵Cl/³⁷Cl) 377.0 [M + H]⁺.

3-(1-(2,6-dichlorobenzyl)pyrrolidin-2-yl)-5-bromo-1H-indole (2.43o): Following the general procedure compound 2.43o was obtained from 5-bromoindole, pyrrolidine and 2,6-dichlorobenzaldehyde as a yellow oil in 76% yield (Rf = 0.35 in hexanes/EtOAc 75:25 v/v); IR (KBr) 3445, 3197, 2966, 2875, 2841, 2799, 1581, 1561, 1459, 1435, 1264, 1196, 1091, 881, 794, 765, 738 cm⁻¹; ¹H NMR (400 MHz, CDCl₃)
8.07 (br s, 1H), 7.97 (d, J = 1.7 Hz, 1H), 7.25–7.16 (comp, 2H), 7.15–7.07 (comp, 3H), 6.92 (t, J = 8.0 Hz, 1H), 3.93 (d, J = 12.3 Hz, 1H), 3.79–3.68 (comp, 2H), 3.17–3.05 (m, 1H), 2.61 (app q, J = 8.9 Hz, 1H), 2.26–2.15 (m, 1H), 2.10–1.90 (comp, 2H), 1.88–1.77 (m, 1H); 13C NMR (100 MHz, CDCl₃) δ 136.4, 135.1, 134.8, 128.3, 128.1, 128.0, 124.4, 123.7, 123.0, 117.3, 117.3, 112.2, 112.1, 62.6, 53.9, 52.7, 33.0, 22.4; m/z (ESI–MS) (35Cl/35Cl/79Br) 423.0 [M + H]+, (35Cl/35Cl/81Br) 425.0 [M + H]+, (35Cl/37Cl/81Br) 427.0 [M + H]+.

3-(1-(2,6-dichlorobenzyl)pyrrolidin-2-yl)-6-chloro-1H-indole (2.43p): Following the general procedure compound 2.43p was obtained from 6-chloroindole, pyrrolidine and 2,6-dichlorobenzaldehyde as a yellow oil in 79% yield (Rf = 0.44 in hexanes/EtOAc 75:25 v/v); IR (KBr) 3451, 2965, 2876, 2842, 2802, 1620, 1561, 1455, 1435, 1371, 1334, 1196, 1090, 905, 804, 777, 765, 739 cm⁻¹; 1H NMR (500 MHz, CDCl₃) 8.01 (br s, 1H), 7.74 (d, J = 8.5 Hz, 1H), 7.25–7.23 (m, 1H), 7.18 (d, J = 2.2 Hz, 1H), 7.12 (d, J = 8.0 Hz, 2H), 7.08–7.03 (m, 1H), 6.99–6.93 (m, 1H), 3.95 (d, J = 12.2 Hz, 1H), 3.75 (app t, J = 8.2 Hz, 1H), 3.69 (d, J = 12.2 Hz, 1H), 3.11–3.04 (m, 1H), 2.61 (app q, J = 8.9 Hz, 1H), 2.26–2.17 (m, 1H), 2.09–2.00 (m, 1H), 1.99–1.88 (m, 1H), 1.87–1.78 (m, 1H); 13C NMR (125 MHz, CDCl₃) δ 136.8, 136.5, 135.0, 128.2, 128.1, 127.4, 125.3, 123.0, 121.3, 119.5, 117.8, 110.7, 62.5, 53.9, 52.7, 32.8, 22.5; m/z (ESI–MS) (35Cl/35Cl/35Cl) 379.0 [M + H]+, (35Cl/35Cl/37Cl) 381.0 [M + H]+.

3-(1-(2,6-dichlorobenzyl)pyrrolidin-2-yl)-1-methyl-1H-indole (2.43q): Following the general procedure compound 2.43q was obtained from 1-methylindole, pyrrolidine and 2,6-dichlorobenzaldehyde as a yellow oil in 46% yield (Rf = 0.58 in hexanes/EtOAc 75:25 v/v); IR (KBr) 3050, 2954, 2875, 2798, 1615, 1581, 1561, 1474, 1435, 1327, 1241, 1196, 1155, 1093, 1012, 887, 765, 739 cm⁻¹; 1H NMR (500 MHz, CDCl₃) 7.87 (d, J = 8.0 Hz, 1H), 7.30 (d, J = 8.1 Hz, 1H), 7.28–7.22 (m, 1H), 7.18 (d, J = 8.0 Hz, 2H), 7.16–7.11 (comp, 2H), 7.00 (t, J = 8.0 Hz, 1H), 4.03 (d, J = 12.2 Hz, 1H), 3.83 (app t, J = 8.3 Hz, 1H), 3.77 (s, 3H), 3.73 (d, J = 12.2 Hz, 1H), 3.12–3.06 (m, 1H), 2.65 (app q, J = 8.9 Hz, 1H), 2.32–2.23 (m, 1H), 2.19–2.08 (m, 1H), 2.05–1.94 (m, 1H), 1.93–1.82 (m, 1H); 13C NMR (125 MHz, CDCl₃) δ 137.2, 136.5, 135.4, 128.0(3), 128.0(1), 127.3, 127.2, 121.2, 120.3,

3-(1-(2,6-dichlorobenzyl)pyrrolidin-2-yl)-2-methyl-1H-indole (2.43r): Following the general procedure compound 2.43r was obtained from 2-methylindole, pyrrolidine and 2,6-dichlorobenzaldehyde as a yellow oil in 97% yield (Rf = 0.53 in hexanes/EtOAc 75:25 v/v); IR (KBr) 3403, 3054, 2961, 2915, 2835, 2795, 1618, 1581, 1561, 1460, 1435, 1374, 1298, 1265, 1195, 1153, 1092, 889, 765, 742 cm⁻¹; 1H NMR (500 MHz, CDCl₃) 7.86 (d, J = 7.6 Hz, 1H), 7.66 (br s, 1H), 7.23 (d, J = 7.9 Hz, 1H), 7.19–7.10 (comp, 3H), 7.10–7.04 (m, 1H), 7.01–6.93 (m, 1H), 3.93 (d, J = 12.1 Hz, 1H), 3.74 (app t, J = 8.6 Hz, 1H), 3.62 (d, J = 12.1 Hz, 1H), 3.08 (app t, J = 8.1 Hz, 1H), 2.63–2.54 (m, 1H), 2.49 (s, 3H), 2.32–2.21 (m, 1H), 2.19–2.09 (m, 1H), 2.07–1.96 (m, 1H), 1.93–1.82 (m, 1H); 13C NMR (125 MHz, CDCl₃) δ 136.5, 135.3, 135.2, 132.5, 128.1, 128.0(0), 127.9(7), 120.6, 120.3, 118.5, 111.7, 109.8, 62.1, 53.9, 52.4, 31.0, 22.7, 12.1; m/z (ESI–MS) (35Cl/35Cl) 359.1 [M + H]+, (35Cl/37Cl) 361.1 [M + H]+.

2-(1-(2,6-dichlorobenzyl)pyrrolidin-2-yl)-1H-pyrrole (2.43s): Following the general procedure compound 2.43s was obtained from pyrrole, pyrrolidine and 2,6-dichlorobenzaldehyde as a brown solid in 48% yield (Rf = 0.39 in hexanes/EtOAc 75:25 v/v); mp: 88–90 ºC; IR (KBr) 3457, 3285, 3056, 2954, 2843, 1578, 1560, 1458, 1436, 1370, 1359, 1195, 1122, 1088, 1028, 885, 814, 779, 763, 730, 602 cm⁻¹; 1H NMR (500 MHz, CDCl₃) 8.62 (br s, 1H), 7.28 (d, J = 8.0 Hz, 2H), 7.10 (t, J = 8.0 Hz, 1H), 6.76–6.68 (m, 1H), 6.17–6.11 (m, 1H), 6.10–6.04 (m, 1H), 3.95 (d, J = 12.2 Hz, 1H), 3.72 (d, J = 12.2, 1H), 3.70–3.62 (m, 1H), 3.00–2.88 (m, 1H), 2.66–2.54 (m, 1H), 2.26–2.13 (m, 1H), 1.91–1.73 (comp, 3H); 13C NMR (125 MHz, CDCl₃) δ 136.5, 134.8, 133.3, 128.5, 128.4, 116.6, 107.8, 105.9, 62.8, 53.1, 52.5, 33.2, 22.5; m/z (ESI–MS) (35Cl/35Cl) 295.0 [M + H]+, (35Cl/37Cl) 297.0 [M + H]+.
3-(1-(2,6-dichlorobenzyl)pyrrolidin-2-yl)-2,5-dimethyl-1H-pyrrole (2.43t): Following the general procedure compound 2.43t was obtained from 2,5-dimethylpyrrole, pyrrolidine and 2,6-dichlorobenzaldehyde as a yellow oil in 57% yield (Rf = 0.31 in hexanes/EtOAc 75:25 v/v); IR (KBr) 3451, 3364, 3054, 2966, 2836, 1561, 1435, 1196, 1150, 1090, 890, 765, 736, 636 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 7.40 (br s, 1H), 7.24 (d, J = 8.1 Hz, 2H), 7.06 (t, J = 8.1 Hz, 1H), 5.91–5.87 (m, 1H), 3.92 (d, J = 12.0 Hz, 1H), 3.50 (d, J = 12.0 Hz, 1H), 3.37–3.30 (m, 1H), 2.98–2.91 (m, 1H), 2.50 (app q, J = 8.7 Hz, 1H), 2.26 (s, 3H), 2.22 (s, 3H), 2.10–2.02 (m, 1H), 1.91–1.79 (comp, 2H), 1.78–1.69 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 136.7, 135.8, 128.2, 128.1, 124.8, 123.6, 119.5, 105.9, 62.4, 53.4, 52.1, 32.6, 22.0, 13.0, 11.2; m/z (ESI–MS) (³⁵Cl/³⁵Cl) 323.0 [M + H]⁺, (³⁵Cl/³⁷Cl) 325.0 [M + H]⁺.

1-(1-(2,6-dichlorobenzyl)piperidin-2-yl)naphthalen-2-ol (2.43u): Following the general procedure compound 2.43u was obtained from 2-naphthol, piperidine and 2,6-dichlorobenzaldehyde as a colorless oil in 16% yield (Rf = 0.47 in hexanes/EtOAc 90:10 v/v); IR (KBr) 3059, 2937, 2856, 1621, 1599, 1582, 1561, 1519, 1467, 1436, 1407, 1271, 1243, 1232, 1090, 931, 815, 779, 765, 743, 711 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 11.20 (br s, 1H), 8.02 (d, J = 8.7 Hz, 1H), 7.77 (d, J = 8.1 Hz, 1H), 7.51–7.44 (m, 1H), 7.34–7.27 (m, 1H), 7.21 (d, J = 8.0 Hz, 2H), 7.11–7.00 (comp, 2H), 4.30 (dd, J = 11.3, 3.1 Hz, 1H), 4.15 (d, J = 12.8 Hz, 1H), 3.71 (d, J = 12.8 Hz, 1H), 3.01–2.93 (m, 1H), 2.52–2.41 (m, 1H), 2.13–1.98 (m, 1H), 1.93–1.81 (comp, 2H), 1.81–1.72 (m, 1H), 1.65 (app qt, J = 13.0, 3.1 Hz, 1H), 1.49 (app qt, J = 13.0, 3.7 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 154.9, 137.2, 132.4, 132.0, 129.2, 129.0, 128.9, 128.7, 128.3, 126.2, 122.3, 120.8, 119.2, 117.9, 64.4, 55.8, 52.4, 30.9, 25.7, 24.3; m/z (ESI–MS) (³⁵Cl/³⁵Cl) 386.2 [M + H]⁺, (³⁵Cl/³⁷Cl) 388.2 [M + H]⁺.

3-(1-(2,6-dichlorobenzyl)piperidin-2-yl)-1H-indole (2.43v): Following the general procedure compound 2.43v was obtained from indole, piperidine and 2,6-dichlorobenzaldehyde as a yellow oil in 64% yield (Rf = 0.22 in hexanes/EtOAc 75:25 v/v); IR (KBr) 3412, 3184, 2931, 2846, 2796, 1579,
8.07 (br s, 1H), 7.89 (app d, J = 7.9 Hz, 1H), 7.39–7.32 (m, 1H), 7.32–7.27 (m, 1H), 7.23–7.15 (comp, 3H), 7.15–7.09 (m, 1H), 7.04–6.97 (m, 1H), 3.90 (d, J = 11.9 Hz, 1H), 3.55 (app d, J = 10.5 Hz, 1H), 3.45 (d, J = 11.9 Hz, 1H), 2.89–2.79 (m, 1H), 2.39–2.28 (m, 1H), 2.14–2.00 (m, 1H), 1.94–1.75 (comp, 2H), 1.70–1.54 (comp, 2H), 1.52–1.39 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 137.2, 136.0, 128.2, 128.1, 127.3, 122.6, 121.8, 120.2, 119.0, 111.0, 61.6, 54.7, 53.0, 34.6, 26.1, 25.2; m/z (ESI–MS) (³⁵Cl/³⁷Cl) 359.1 [M + H]⁺, (³⁵Cl/³⁷Cl) 361.1 [M + H]⁺.

(E)-1-(1-(2,6-dichlorobenzyl)-3-(2,6-dichlorobenzylidene)pyrrolidin-2-yl)naphthalen-2-ol (2.44) and (E)-1-(1-(2,6-dichlorobenzyl)-3-(1-(2,6-dichlorobenzylidene)pyrrolidin-2-yl)pyrrolidin-2-yl)naphthalen-2-ol (2.45): To a solution of 2-naphthol (0.75 mmol, 1.5 equiv) in toluene (2 mL) were added benzoic acid (0.1 mmol, 0.2 equiv), pyrrolidine (0.75 mmol, 1.5 equiv) and 2,6-dichlorobenzaldehyde (0.5 mmol, 1 equiv). The mixture was heated under reflux for 15 min. Subsequently, the reaction mixture was allowed to cool to room temperature, diluted with EtOAc (10 ml) and washed with saturated aqueous NaHCO₃ (3 x 5 mL). The combined aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organic layer was washed with water (20 mL), brine (20 mL) and dried over anhydrous Na₂SO₄. Solvent was then removed under reduced pressure and the residue was purified by silica gel chromatography. Compound 2.43a was obtained in 22% yield.

In addition, compound 2.44 was obtained as a colorless oil in 22% yield (Rₘ = 0.40 in hexanes/EtOAc 90:10 v/v); IR (KBr) 3060, 2966, 2834, 2248, 1932, 1675, 1621, 1598, 1581, 1560, 1517, 1467, 1436, 1406, 1361, 1271, 1235, 1199, 1141, 1091, 944, 816, 775, 744, 674, 645 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 11.30 (br s, 1H), 8.16 (d, J = 8.7 Hz, 1H), 7.78 (d, J = 8.1 Hz, 1H), 7.66 (d, J = 8.8 Hz, 1H), 7.53 (ddd, J = 8.7, 6.8, 1.2 Hz, 1H), 7.35–7.30 (m, 1H), 7.19 (d, J = 8.0 Hz, 2H), 7.14 (d, J = 8.0 Hz, 2H), 7.05–6.99 (comp, 3H), 5.78–5.74 (m, 1H), 5.37–5.33 (m, 1H), 4.22 (d, J = 12.7 Hz, 1H), 4.08 (d, J = 12.7 Hz, 1H), 3.34 (app t, J = 8.6 Hz, 1H), 2.92 (ddd, J = 11.5, 9.3, 7.4 Hz, 1H), 2.75–2.64 (m, 1H), 2.54–2.45 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 156.1, 147.9, 136.8, 135.2, 134.5, 133.6, 132.4, 129.4, 129.2, 128.6, 128.3(2), 128.3(1),
In addition, compound 2.45 was obtained as a yellow oil in 33% yield (mixture of diastereomers) (Rf = 0.33 in hexanes/EtOAc 90:10 v/v); IR (KBr) 3054, 2960, 2918, 2850, 2807, 1621, 1598, 1517, 1466, 1436, 1364, 1304, 1270, 1236, 1199, 1091, 909, 816, 776, 735 cm⁻¹; ¹H NMR (Note: Due to overlapping peaks, integration values of the diastereomers are reported together) (500 MHz, CDCl₃) 11.79 (br s, 1.2H), 8.39 (d, J = 8.6 Hz, 1.0H), 8.32 (d, J = 8.6 Hz, 0.3H), 7.88–7.73 (comp, 1.5H), 7.70–7.60 (comp, 1.4H), 7.52–7.35 (comp, 4.0H), 7.35–7.25 (comp, 4.0H), 7.23 (d, J = 8.0 Hz, 2.2H), 7.21–7.13 (comp, 4.2H), 7.13–6.97 (comp, 4.4H), 6.78 (s, 1.1H), 6.12–6.04 (m, 0.3H), 5.05 (d, J = 8.0 Hz, 0.3H), 4.96 (d, J = 8.1 Hz, 1.0H), 4.20–3.99 (comp, 2.6H), 3.95 (d, J = 12.7 Hz, 1.0H), 3.73 (d, J = 12.4 Hz, 1.1H), 3.69 (s, 0.3H), 3.51 (d, J = 12.4 Hz, 1.3H), 3.49–3.44 (comp, 0.9H), 3.33–3.19 (comp, 1.2H), 3.18–2.95 (comp, 3.2H), 2.89–2.71 (comp, 1.5H), 2.65–2.54 (comp, 0.4H), 2.55–2.44 (comp, 1.1H), 2.42–2.06 (comp, 6.0H); ¹³C NMR of the diastereomers (125 MHz, CDCl₃) δ 156.4, 156.3, 149.2, 137.1, 136.8, 136.7, 136.6, 135.8, 135.7, 135.0, 134.8, 134.6(4), 134.5(8), 133.5, 133.3(0), 133.2(8), 133.0, 129.1, 129.0(5), 129.0(0), 128.9, 128.8, 128.7(3), 128.7(1), 128.6, 128.5(4), 128.4(9), 128.4(2), 128.3, 128.2(5), 128.2(1), 127.9, 127.8, 125.9, 125.6, 122.3, 122.2, 122.1(4), 122.1(0), 119.9, 119.8, 117.8, 117.4, 117.2, 115.8, 70.2, 68.9, 67.5, 67.2, 54.6, 53.3(4), 53.3(2), 52.8, 52.7, 51.5, 51.1, 50.7, 48.3, 34.6, 34.5, 31.6, 30.7, 30.0, 29.7, 29.0, 26.6, 26.3, 25.3, 22.6, 20.7, 14.1, 11.4; m/z (ESI–MS) (35Cl/35Cl/35Cl/35Cl/35Cl) 754.7 [M + H]+, (35Cl/35Cl/35Cl/35Cl/35Cl/37Cl) 756.7 [M + H]+, (35Cl/35Cl/35Cl/35Cl/37Cl) 758.7 [M + H]+.
2D-NMR Analysis for Compound 2.44, Selected Interactions (Ar = 2,6-Dichlorophenyl)

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General Procedure for the Redox-Neutral Mannich Reaction with Pyrrolidine:

To a solution of benzoic acid (0.25 mmol, 0.5 equiv) in toluene (2 mL) was added pyrrolidine (2.5 mmol, 5 equiv). The mixture was heated under reflux and a mixture of 2,6-dichlorobenzaldehyde (0.5 mmol, 1 equiv, 1M solution in toluene) and the ketone (0.75 mmol, 1.5 equiv, 1.5 M solution in toluene) was delivered through the top of the reflux condenser over 5 hours via syringe pump. The reaction was then refluxing for a further 0-30 minutes at which time the aldehyde was consumed as judged by TLC analysis. Subsequently, the reaction mixture was allowed to cool to room temperature, diluted with EtOAc (10 mL) and washed with saturated aqueous NaHCO₃ (3 x 10 mL). The combined aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organic layer was washed with water (40 mL), brine (40 mL), and dried over anhydrous Na₂SO₄. Solvent was then removed under reduced pressure. The residue was purified by silica gel chromatography.

General Procedure for the Redox-Neutral Mannich Reaction with 1,2,3,4-Tetrahydroisoquinoline:

A 10 mL round-bottom flask was charged with 4Å molecular sieves (200 wt%), benzoic acid (0.1 mmol, 0.2 equiv), toluene (2 mL), the aldehyde (0.5 mmol, 1 equiv), acetophenone (0.75 mmol, 1.5 equiv) or acetone (1.5 mmol, 3 equiv) and tetrahydroisoquinoline (0.75 mmol, 1.5 equiv). The mixture was stirred at 50 °C for 12 hours at which time the aldehyde was consumed as judged by TLC analysis. The mixture was allowed to cool to room temperature and filtered through a short pad of celite and washed with EtOAc (6 x 5 mL). The filtrate was then washed with saturated aqueous NaHCO₃ (3 x 10 mL). The combined aqueous layer was extracted with EtOAc (3 x 10 mL), and the combined organic layer was washed with water (40 mL), brine (40 mL), and dried over anhydrous Na₂SO₄. Solvent was then removed under reduced pressure and the residue was purified by silica gel chromatography.
2-(1-(2,6-dichlorobenzyl)pyrrolidin-2-yl)-1-phenylethanone (2.47a): Following the general procedure compound 2.47a was obtained from acetophenone, pyrrolidine and 2,6-dichlorobenzaldehyde as a light yellow solid in 56% yield (Rf = 0.40 in hexanes/EtOAc 80:20 v/v); mp: 116–118 °C; IR (KBr) 3054, 2979, 2935, 2911, 2870, 2850, 2822, 2802, 1679, 1596, 1581, 1561, 1461, 1436, 1375, 1366, 1339, 1297, 1240, 1210, 1194, 1144, 1116, 1085, 998, 975, 898, 789, 762, 751, 689 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.00–7.93 (comp, 2H), 7.59–7.52 (m, 1H), 7.50–7.42 (comp, 2H), 7.29 (d, J = 8.0 Hz, 2H), 7.12 (d, J = 8.0 Hz, 1H), 4.08 (d, J = 12.4 Hz, 1H), 3.51 (d, J = 12.4 Hz, 1H), 3.55 (dd, J = 16.6, 2.9 Hz, 1H), 3.31–3.18 (m, 1H), 3.05 (dd, J = 16.6, 9.1 Hz, 1H), 2.96–2.81 (m, 1H), 2.54 (app q, J = 8.6 Hz, 1H), 2.15 (app dq, J = 12.8, 8.2 Hz, 1H), 1.78–1.63 (comp, 2H), 1.55–1.43 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 199.6, 137.2, 136.5, 135.0, 132.9, 128.7, 128.4(5), 128.0, 60.8, 53.6, 52.5, 44.0, 31.2, 22.5; m/z (ESI–MS) 348.0 (³⁵Cl/³⁵Cl) [M + H]+, 350.0 (³⁵Cl/³⁷Cl) [M + H]+.

2-(1-(2,6-dichlorobenzyl)pyrrolidin-2-yl)-1-(3-chlorophenyl)ethanone (2.47b): Following the general procedure compound 2.47b was obtained from 3’-chloroacetophenone, pyrrolidine and 2,6-dichlorobenzaldehyde as a yellow oil in 59% yield (Rf = 0.45 in hexanes/EtOAc 80:20 v/v); IR (KBr) 3066, 2961, 2874, 2845, 2804, 1687, 1562, 1435, 1366, 1335, 1298, 1264, 1242, 1204, 1154, 1113, 1087, 998, 971, 899, 778, 765, 737, 706, 681 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 7.91 (app t, J = 1.9 Hz, 1H), 7.83–7.78 (m, 1H), 7.52 (ddd, J = 7.9, 2.1, 1.0 Hz, 1H), 7.39 (t, J = 7.9 Hz, 1H), 7.28 (d, J = 8.0 Hz, 2H), 7.15–7.09 (m, 1H), 4.05 (d, J = 12.4 Hz, 1H), 3.80 (d, J = 12.4 Hz, 1H), 3.47 (dd, J = 16.7, 3.8 Hz, 1H), 3.29–3.19 (m, 1H), 3.00 (dd, J = 16.7, 8.9 Hz, 1H), 2.94–2.84 (m, 1H), 2.54 (app q, J = 8.8 Hz, 1H), 2.14 (app dq, J = 12.7, 8.3 Hz, 1H), 1.78–1.64 (comp, 2H), 1.53–1.43 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 198.3, 138.7, 136.5, 134.9, 132.8, 129.8, 128.7, 128.5, 128.1, 126.1, 60.6, 54.3, 52.5, 44.2, 31.3, 22.5; m/z (ESI–MS) 382.0 (³⁵Cl/³⁵Cl/³⁷Cl) [M + H]+, 384.0 (³⁵Cl/³⁵Cl/³⁷Cl) [M + H]+.
2-(1-(2,6-dichlorobenzyl)pyrrolidin-2-yl)-1-(3-bromophenyl)ethanone (2.47c): Following the general procedure compound 2.47c was obtained from 3'-bromoacetophenone, pyrrolidine and 2,6-dichlorobenzaldehyde as a yellow oil in 52% yield (Rf = 0.46 in hexanes/EtOAc 80:20 v/v); IR (KBr) 3063, 2961, 2873, 2845, 2807, 2360, 1687, 1581, 1562, 1366, 1333, 1297, 1264, 1243, 1154, 1112, 1088, 1068, 996, 777, 765, 736, 680 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) 8.09–8.05 (m, 1H), 7.88–7.83 (m, 1H), 7.70–7.64 (m, 1H), 7.33 (t, \(J = 7.9\) Hz, 1H), 7.29 (d, \(J = 8.0\) Hz, 2H), 7.14–7.10 (m, 1H), 4.05 (d, \(J = 12.4\) Hz, 1H), 3.81 (d, \(J = 12.4\) Hz, 1H), 3.47 (dd, \(J = 16.8, 3.9\) Hz, 1H), 3.28–3.20 (m, 1H), 3.00 (dd, \(J = 16.8, 8.9\) Hz, 1H), 2.94–2.85 (m, 1H), 2.54 (app q, \(J = 8.8\) Hz, 1H), 2.13 (app dq, \(J = 12.7, 8.3\) Hz, 1H), 1.78–1.64 (comp, 2H), 1.53–1.43 (m, 1H); \(^1\)C NMR (125 MHz, CDCl\(_3\)) δ 198.2, 138.9, 136.5, 135.8, 134.8, 131.1, 130.1, 128.7, 128.5, 126.6, 122.9, 60.6, 53.7, 52.5, 44.2, 31.3, 22.5; m/z (ESI–MS) 425.9 ([M + H]\(^+\), 427.9 ([M + H]\(^+\)).

2-(1-(2,6-dichlorobenzyl)pyrrolidin-2-yl)-1-m-tolylethanone (2.47d): Following the general procedure compound 2.47d was obtained from 3'-methylacetophenone, pyrrolidine and 2,6-dichlorobenzaldehyde as a yellow oil in 54% yield (Rf = 0.46 in hexanes/EtOAc 80:20 v/v); IR (KBr) 3064, 2958, 2871, 2844, 2804, 1682, 1604, 1583, 1562, 1435, 1365, 1335, 1299, 1240, 1194, 1153, 1112, 1088, 1041, 1000, 898, 778, 765, 690 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) 7.82–7.73 (comp, 2H), 7.41–7.32 (comp, 2H), 7.29 (d, \(J = 8.0\) Hz, 2H), 7.12 (t, \(J = 8.0\) Hz, 1H), 4.08 (d, \(J = 12.4\) Hz, 1H), 3.81 (d, \(J = 12.4\) Hz, 1H), 3.52 (dd, \(J = 16.6, 3.7\) Hz, 1H), 3.29–3.19 (m, 1H), 3.04 (dd, \(J = 16.6, 9.0\) Hz, 1H), 2.96–2.82 (m, 1H), 2.54 (app q, \(J = 8.8\) Hz, 1H), 2.41 (s, 3H), 2.14 (app dq, \(J = 12.7, 8.1\) Hz, 1H), 1.80–1.61 (comp, 2H), 1.55–1.44 (m, 1H); \(^1\)C NMR (125 MHz, CDCl\(_3\)) δ 199.9, 138.3, 137.3, 136.5, 135.0, 133.7, 128.7, 128.5(2), 128.4(6), 128.3(9), 125.3, 60.9, 53.6, 52.5, 44.1, 31.2, 22.5, 21.3; m/z (ESI–MS) 362.0 (\(^{35}\)Cl/\(^{35}\)Cl/\(^{79}\)Br) [M + H]\(^+\), 364.0 (\(^{35}\)Cl/\(^{37}\)Cl/\(^{81}\)Br) [M + H]\(^+\).
2-(1-(2,6-dichlorobenzyl)pyrrolidin-2-yl)-1-(4-chlorophenyl)ethanone (2.47e): Following the general procedure compound 2.47e was obtained from 4'-chloroacetophenone, pyrrolidine and 2,6-dichlorobenzaldehyde as a yellow oil in 47% yield (R_f = 0.45 in hexanes/EtOAc 80:20 v/v); IR (KBr) 3056, 2960, 2871, 2848, 2802, 1683, 1588, 1562, 1435, 1400, 1367, 1334, 1282, 1207, 1175, 1153, 1092, 1013, 995, 815, 777, 765, 735 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 7.92–7.85 (comp, 2H), 7.45–7.40 (comp, 2H), 7.28 (d, J = 8.0 Hz, 2H), 7.12 (t, J = 8.0 Hz, 1H), 4.05 (d, J = 12.4 Hz, 1H), 3.80 (d, J = 12.4 Hz, 1H), 3.48 (dd, J = 16.7, 3.7 Hz, 1H), 3.28–3.19 (m, 1H), 3.00 (dd, J = 16.7, 9.0 Hz, 1H), 2.95–2.84 (m, 1H), 2.54 (app q, J = 8.8 Hz, 1H), 2.13 (app dq, J = 12.8, 8.3 Hz, 1H), 1.87–1.65 (comp, 2H), 1.53–1.43 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 198.4, 139.4, 136.5, 135.5, 134.9, 129.4, 128.7, 128.5, 60.7, 53.7, 52.5, 44.1, 31.2, 22.5; m/z (ESI–MS) 382.0 (³⁵Cl/³⁵Cl/³⁵Cl) [M + H]+, 384.0 (³⁵Cl/³⁵Cl/³⁷Cl) [M + H]+.

2-(1-(2,6-dichlorobenzyl)pyrrolidin-2-yl)-1-(4-fluorophenyl)ethanone (2.47f): Following the general procedure compound 2.47f was obtained from 4'-fluoroacetophenone, pyrrolidine and 2,6-dichlorobenzaldehyde as a yellow oil in 47% yield (R_f = 0.40 in hexanes/EtOAc 80:20 v/v); IR (KBr) 3066, 2962, 2873, 2844, 2804, 1683, 1597, 1562, 1506, 1436, 1410, 1365, 1332, 1298, 1279, 1232, 1208, 1156, 1098, 995, 834, 779, 765, 736, 587 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 8.01–7.94 (comp, 2H), 7.29 (d, J = 8.0 Hz, 2H), 7.16–7.07 (comp, 3H), 4.06 (d, J = 12.4 Hz, 1H), 3.80 (d, J = 12.4 Hz, 1H), 3.49 (dd, J = 16.7, 3.8 Hz, 1H), 3.28–3.19 (m, 1H), 3.01 (dd, J = 16.7, 9.0 Hz, 1H), 2.94–2.84 (m, 1H), 2.54 (app q, J = 8.8 Hz, 1H), 2.14 (app dq, J = 12.7, 8.3 Hz, 1H), 1.77–1.62 (comp, 2H), 1.53–1.43 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 198.0, 165.7 (d, J_C,F = 254.7 Hz), 136.5, 134.9, 133.7 (d, J_C,F = 3.0 Hz), 130.6 (d, J_C,F = 9.3 Hz), 128.7, 128.5, 115.6 (d, J_C,F = 11.1 Hz), 60.8, 53.7, 52.6, 44.0, 31.3, 22.5; m/z (ESI–MS) 366.0 (³⁵Cl/³⁵Cl) [M + H]+, 368.0 (³⁵Cl/³⁷Cl) [M + H]+.
2-(1-(2,6-dichlorobenzyl)pyrrolidin-2-yl)-1-(4-(trifluoromethyl)phenyl)ethanone \( (2.47g) \):

Following the general procedure compound \( 2.47g \) was obtained from 4'-trifluoromethylacetophenone, pyrrolidine and 2,6-dichlorobenzaldehyde as a yellow oil in 35% yield \( (R_f = 0.35 \) in hexanes/EtOAc 80:20 v/v); IR \( (\text{KBr}) 3058, 2979, 2936, 2878, 2848, 2819, 2799, 2361, 2340, 1694, 1582, 1561, 1510, 1461, 1437, 1410, 1379, 1332, 1207, 1170, 1131, 1106, 1069, 998, 899, 829, 787, 764, 725, 605 \ cm\(^{-1}\); \(^{1}\)H NMR \( (500 \text{ MHz, CDCl}_3) 8.04 \text{ (app d, } J = 8.1 \text{ Hz, 2H}), 7.73 \text{ (app d, } J = 8.1 \text{ Hz, 2H}), 7.29 \text{ (d, } J = 8.0 \text{ Hz, 2H}), 7.13 \text{ (t, } J = 8.0 \text{ Hz, 1H}), 4.06 \text{ (d, } J = 12.4 \text{ Hz, 1H}), 3.82 \text{ (d, } J = 12.4 \text{ Hz, 1H}), 3.53 \text{ (dd, } J = 16.9, 3.8 \text{ Hz, 1H}), 3.31–3.22 \text{ (m, 1H)}, 3.06 \text{ (dd, } J = 16.9, 8.8 \text{ Hz, 1H}), 2.95–2.87 \text{ (m, 1H)}, 2.56 \text{ (app q, } J = 8.9 \text{ Hz, 1H}), 2.16 \text{ (app dq, } J = 12.7, 8.2 \text{ Hz, 1H}), 1.79–1.67 \text{ (comp, 2H)}, 1.54–1.44 \text{ (m, 1H)); } ^{13}\text{C NMR (125 MHz, CDCl}_3) \delta 198.6, 139.8, 136.5, 134.3 \text{ (q, } J_{C-F} = 32.5 \text{ Hz), 128.8, 128.5, 128.4, 125.6 \text{ (q, } J_{C-F} = 3.8 \text{ Hz), 123.6 \text{ (q, } J_{C-F} = 272.3 \text{ Hz), 60.6, 53.7, 52.6, 44.5, 31.3, 22.6; } m/z \text{ (ESI–MS) 416.0 (}^{35}\text{Cl/}^{35}\text{Cl) [M + H]}^+, 418.0 (}^{35}\text{Cl/}^{37}\text{Cl) [M + H]}^+. \)

4-(2-(1-(2,6-dichlorobenzyl)pyrrolidin-2-yl)acetyl)benzonitrile \( (2.47h) \): Following the general procedure compound \( 2.47h \) was obtained from 4'-cyanoacetophenone, pyrrolidine and 2,6-dichlorobenzaldehyde as a yellow oil in 50% yield \( (R_f = 0.27 \) in hexanes/EtOAc 80:20 v/v); IR \( (\text{KBr}) 2960, 2872, 2864, 2807, 2362, 2335, 2231, 1690, 1581, 1562, 1436, 1404, 1366, 1293, 1207, 1154, 1109, 997, 825, 779, 765 \ cm\(^{-1}\); \(^{1}\)H NMR \( (500 \text{ MHz, CDCl}_3) 8.06–7.99 \text{ (comp, 2H), 7.80–7.74 \text{ (comp, 2H), 7.30 \text{ (d, } J = 8.0 \text{ Hz, 2H}), 7.14 \text{ (t, } J = 8.0 \text{ Hz, 1H}), 4.18–3.97 \text{ (m, 1H)}, 3.94–3.76 \text{ (m, 1H)}, 3.62–3.44 \text{ (m, 1H)}, 3.39–3.19 \text{ (m, 1H)}, 3.17–2.82 \text{ (comp, 2H), 2.68–2.49 \text{ (m, 1H), 2.25–2.10 \text{ (m, 1H), 1.86–1.64 \text{ (comp, 2H), 1.59–1.41 (m, 1H)); } ^{13}\text{C NMR (125 MHz, CDCl}_3) \delta 198.2, 140.0, 136.6, 132.5, 128.9, 128.6, 128.5, 117.9, 116.3, 60.6, 53.7, 52.6, 44.4, 31.3, 22.6; } m/z \text{ (ESI–MS) 372.9 (}^{35}\text{Cl/}^{35}\text{Cl) [M + H]}^+, 374.9 (}^{35}\text{Cl/}^{37}\text{Cl) [M + H]}^+. \)
2-(1-(2,6-dichlorobenzyl)pyrrolidin-2-yl)-1-p-tolylethanone (2.47i): Following the general procedure compound \(2.47\text{i}\) was obtained from \(4'\)-methylacetophenone, pyrrolidine and 2,6-dichlorobenzaldehyde as a yellow oil in 49% yield \((R_f = 0.40\) in hexanes/EtOAc 80:20 v/v); IR (KBr) 3056, 3030, 2979, 2913, 2851, 2797, 1679, 1606, 1582, 1561, 1461, 1437, 1416, 1378, 1369, 1338, 1298, 1240, 1223, 1208, 1181, 1166, 1146, 1117, 1085, 1000, 973, 898, 806, 788, 760, 720, 570 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(7.91 – 7.83\) (comp, 2H), \(7.34 – 7.22\) (comp, 4H), \(7.12\) (t, \(J = 8.0\) Hz, 1H), \(4.08\) (d, \(J = 12.4\) Hz, 1H), \(3.80\) (d, \(J = 12.4\) Hz, 1H), \(3.52\) (dd, \(J = 16.5, 3.5\) Hz, 1H), \(3.29 – 3.18\) (m, 1H), \(3.03\) (dd, \(J = 16.5, 9.1\) Hz, 1H), \(2.95 – 2.82\) (m, 1H), \(2.53\) (app q, \(J = 8.7\) Hz, 1H), \(2.41\) (s, 3H), \(2.13\) (app dq, \(J = 12.7, 8.2\) Hz, 1H), \(1.80 – 1.61\) (comp, 2H), \(1.55 – 1.44\) (m, 1H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) δ 199.3, 143.7, 136.5, 135.0, 134.8, 129.2, 128.7, 128.5, 128.2, 60.9, 53.6, 52.5, 43.9, 31.2, 22.5, 21.6; \(m/z\) (ESI–MS) 362.0 (\(^{35}\)Cl/\(^{35}\)Cl) [M + H]\(^+\), 364.0 (\(^{35}\)Cl/\(^{37}\)Cl) [M + H]\(^+\).

2-(1-(2,6-dichlorobenzyl)pyrrolidin-2-yl)-1-(4-methoxyphenyl)ethanone (2.47j): Following the general procedure compound \(2.47\text{j}\) was obtained from \(4'\)-methoxyacetophenone, pyrrolidine and 2,6-dichlorobenzaldehyde as a yellow oil in 52% yield \((R_f = 0.24\) in hexanes/EtOAc 80:20 v/v); IR (KBr) 3055, 2976, 2936, 2850, 2803, 1671, 1607, 1576, 1560, 1504, 1455, 1423, 1376, 1368, 1339, 1303, 1263, 1212, 1181, 1108, 1029, 992, 898, 832, 805, 788, 758, 721, 593, 573 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(7.98 – 7.91\) (comp, 2H), \(7.28\) (d, \(J = 8.0\) Hz, 2H), \(7.11\) (t, \(J = 8.0\) Hz, 1H), \(6.97 – 6.89\) (comp, 2H), \(4.08\) (d, \(J = 12.3\) Hz, 1H), \(3.86\) (s, 3H), \(3.79\) (d, \(J = 12.3\) Hz, 1H), \(3.49\) (dd, \(J = 16.4, 3.8\) Hz, 1H), \(3.27 – 3.17\) (m, 1H), \(3.00\) (dd, \(J = 16.4, 9.1\) Hz, 1H), \(2.93 – 2.82\) (m, 1H), \(2.59 – 2.48\) (m, 1H), \(2.12\) (app dq, \(J = 12.7, 8.2\) Hz, 1H), \(1.77 – 1.61\) (comp, 2H), \(1.54 – 1.43\) (m, 1H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) δ 198.2, 163.4, 136.5, 135.0, 130.4, 130.3, 128.7, 128.5, 113.6, 61.0, 55.4, 53.6, 52.5, 43.6, 31.2, 22.5; \(m/z\) (ESI–MS) 377.9 (\(^{35}\)Cl/\(^{35}\)Cl) [M + H]\(^+\), 379.9 (\(^{35}\)Cl/\(^{37}\)Cl) [M + H]\(^+\).
2-(1-(2,6-dichlorobenzyl)pyrrolidin-2-yl)-1-(naphthalen-2-yl)ethanone (2.47k): Following the general procedure compound 2.47k was obtained from 2-acetonaphthone, pyrrolidine and 2,6-dichlorobenzaldehyde as a yellow oil in 56% yield (Rf = 0.36 in hexanes/EtOAc 80:20 v/v); IR (KBr) 3056, 2961, 2874, 2809, 1679, 1628, 1581, 1562, 1469, 1435, 1367, 1297, 1275, 1186, 1154, 1124, 1088, 862, 821, 778, 765, 739 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 8.51–8.46 (m, 1H), 8.04 (dd, J = 8.6, 1.7 Hz, 1H), 7.97 (d, J = 8.0 Hz, 1H), 7.92–7.84 (comp, 2H), 7.63–7.51 (comp, 2H), 7.29 (d, J = 8.0 Hz, 2H), 7.11 (t, J = 8.0 Hz, 1H), 4.13 (d, J = 12.4 Hz, 1H), 3.85 (d, J = 12.4 Hz, 1H), 3.65 (dd, J = 16.3, 3.7 Hz, 1H), 3.37–3.27 (m, 1H), 3.20 (dd, J = 12.4, 9.0 Hz, 1H), 2.99–2.87 (m, 1H), 2.57 (app q, J = 8.7 Hz, 1H), 2.17 (app dq, J = 12.8, 8.1 Hz, 1H), 1.81–1.65 (comp, 2H), 1.61–1.50 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 199.6, 136.5, 135.5, 135.0, 134.6, 132.5, 129.7, 129.6, 128.7, 128.5, 128.4, 128.3, 127.7, 126.7, 123.8, 61.0, 53.7, 52.6, 44.1, 31.3, 22.5; m/z (ESI–MS) 398.0 ([M + H]⁺), 400.0 ([¹⁵Cl/³⁷Cl] [M + H]⁺).

2-(1-(2,6-dichlorobenzyl)pyrrolidin-2-yl)-1-(thiophen-2-yl)ethanone (2.47l): Following the general procedure compound 2.47l was obtained from 2-acetyltiophene, pyrrolidine and 2,6-dichlorobenzaldehyde as a yellow oil in 40% yield (Rf = 0.32 in hexanes/EtOAc 80:20 v/v); IR (KBr) 3054, 2979, 2934, 2916, 2850, 2825, 2796, 1655, 1581, 1560, 1520, 1437, 1422, 1366, 1336, 1301, 1223, 1214, 1117, 1086, 1057, 974, 897, 787, 765, 725 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 7.71 (dd, J = 3.8, 1.1 Hz, 1H), 7.63 (dd, J = 4.9, 1.1 Hz, 1H), 7.29 (d, J = 8.0 Hz, 2H), 7.16–7.10 (comp, 2H), 4.08 (d, J = 12.4 Hz, 1H), 3.82 (d, J = 12.4 Hz, 1H), 3.45 (dd, J = 15.7, 3.2 Hz, 1H), 3.30–3.15 (m, 1H), 2.98 (dd, J = 15.7, 9.0 Hz, 1H), 2.93–2.79 (m, 1H), 2.54 (app q, J = 8.6 Hz, 1H), 2.11 (app dq, J = 12.7, 8.1 Hz, 1H), 1.79–1.64 (comp, 2H), 1.60–1.48 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 192.4, 144.8, 136.5, 135.0, 133.6, 131.9, 128.7, 128.5, 128.1, 61.0, 53.6, 52.5, 44.8, 31.1, 22.5; m/z (ESI–MS) 353.9 ([¹³Cl/³⁵Cl] [M + H]⁺), 355.9 ([³⁵Cl/³⁷Cl] [M + H]⁺).
**2-(2-benzyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-phenylethanone (2.48a):** Following the general procedure compound **2.48a** was obtained from acetophenone, tetrahydroisoquinoline and benzaldehyde as a yellow oil in 46% yield (R\(_f\) = 0.49 in hexanes/EtOAc 80:20 v/v); IR (KBr) 3061, 3026, 2923, 2829, 2807, 2362, 2332, 1679, 1597, 1580, 1493, 1449, 1355, 1283, 1265, 1200, 1103, 1075, 1022, 749, 691 cm\(^{-1}\); \(^1^H\) NMR (500 MHz, CDCl\(_3\)) 7.99–7.94 (comp, 2H), 7.59–7.54 (m, 1H), 7.50–7.43 (comp, 2H), 7.30–7.10 (comp, 9H), 4.69–4.60 (m, 1H), 3.82–3.58 (comp, 3H), 3.27–3.16 (comp, 2H), 3.01 (ddd, \(J = 16.8, 10.8, 6.0\) Hz, 1H), 2.88–2.78 (m, 1H), 2.67–2.56 (m, 1H); \(^1^C\) NMR (125 MHz, CDCl\(_3\)) δ 198.9, 139.0, 138.1, 137.4, 134.2, 132.8, 129.1, 128.8, 128.5, 128.2, 128.1, 127.6, 126.9, 126.3, 126.0, 58.2, 57.8, 45.6, 42.2, 24.2; m/z (ESI–MS) 342.1 [M + H\(^+\)].

**1-(2-benzyl-1,2,3,4-tetrahydroisoquinolin-1-yl)propan-2-one (2.48b):** Following the general procedure compound **2.48b** was obtained from acetone, tetrahydroisoquinoline and benzaldehyde as a yellow oil in 45% yield (R\(_f\) = 0.42 in hexanes/EtOAc 80:20 v/v); IR (KBr) 3061, 2924, 2362, 2332, 1709, 1647, 1493, 1453, 1429, 1358, 1277, 1229, 1162, 1102, 1076, 1035, 756, 739, 699 cm\(^{-1}\); \(^1^H\) NMR (500 MHz, CDCl\(_3\)) 7.37–7.30 (comp, 4H), 7.30–7.24 (m, 1H), 7.20–7.15 (comp, 2H), 7.15–7.10 (m, 1H), 7.10–7.05 (m, 1H), 4.38–4.30 (m, 1H), 3.78–3.69 (comp, 2H), 3.22–3.13 (m, 1H), 3.08–2.93 (comp, 2H), 2.89–2.80 (m, 1H), 2.70 (dd, \(J = 15.3, 5.2\) Hz, 1H), 2.62–2.51 (m, 1H), 2.11 (s, 3H); \(^1^C\) NMR (125 MHz, CDCl\(_3\)) δ 207.4, 138.9, 137.3, 134.1, 129.2, 129.0, 128.2, 127.4, 127.1, 126.4, 126.1, 57.9, 57.6, 50.6, 42.1, 30.3, 23.6; m/z (ESI–MS) 280.1 [M + H\(^+\)].

**2-(2-(2-chlorobenzyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-phenylethanone (2.48c):** Following the general procedure compound **2.48c** was obtained from acetophenone, tetrahydroisoquinoline and 2-chlorobenzaldehyde as a yellow oil in 42% yield (R\(_f\) = 0.53 in hexanes/EtOAc 80:20 v/v); IR (KBr) 3061, 2924, 2839, 2359, 2332, 1682, 1597, 1580, 1447, 1354, 1282, 1121, 1037, 750, 690 cm\(^{-1}\); \(^1^H\) NMR (500 MHz, CDCl\(_3\)) 7.96–7.90 (comp, 2H), 7.57–7.51 (m, 1H), 7.47–7.40 (comp, 2H), 7.39–7.31 (m, 1H), 7.31–7.29 (m, 1H), 7.23–7.05 (comp, 6H), 4.68–4.57 (m, 1H), 3.92 (d, \(J = 14.2\) Hz, 1H).
1H), 3.73 (d, J = 14.2 Hz, 1H), 3.62 (dd, J = 15.5, 7.6 Hz, 1H), 3.30–3.14 (comp, 2H), 3.13–2.99 (m, 1H), 2.90–2.77 (m, 1H), 2.69–2.55 (m, 1H); 13C NMR (125 MHz, CDCl3) δ 198.9, 138.2, 137.4, 136.6, 134.2, 134.0, 132.8, 130.6, 129.2, 128.5, 128.0, 127.6, 126.5, 126.4, 126.0, 58.6, 54.6, 45.7, 42.7, 24.5; m/z (ESI–MS) 375.9 [M + H]+.

2-(2-(3-chlorobenzyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-phenylethanone (2.48d):

Following the general procedure compound 2.48d was obtained from acetophenone, tetrahydroisoquinoline and 3-chlorobenzaldehyde as a yellow oil in 46% yield (Rf = 0.51 in hexanes/EtOAc 80:20 v/v); IR (KBr) 3060, 3019, 2923, 2833, 1683, 1597, 1578, 1448, 1429, 1354, 1280, 1200, 1105, 1075, 1020, 776, 750, 690 cm−1; 1H NMR (500 MHz, CDCl3) 8.00–7.93 (comp, 2H), 7.60–7.54 (m, 1H), 7.50–7.44 (comp, 2H), 7.25–7.04 (comp, 8H), 4.66–4.55 (m, 1H), 3.80–3.57 (comp, 3H), 3.27–3.13 (comp, 2H), 3.00 (ddd, J = 16.8, 11.1, 6.1 Hz, 1H), 2.86–2.75 (m, 1H), 2.67–2.55 (m, 1H); 13C NMR (125 MHz, CDCl3) δ 198.8, 141.3, 137.8, 137.3, 134.1, 134.0, 132.9, 129.3, 129.2, 128.7, 128.5, 128.1, 127.6, 127.1, 126.8, 126.4, 126.1, 58.4, 57.3, 45.6, 42.2, 24.0; m/z (ESI–MS) 375.9 [M + H]+.

2-(2-(3-methoxybenzyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-phenylethanone (2.48e):

Following the general procedure compound 2.48e was obtained from acetophenone, tetrahydroisoquinoline and m-anisaldehyde as a yellow oil in 50% yield (Rf = 0.32 in hexanes/EtOAc 80:20 v/v); IR (KBr) 3059, 3022, 2937, 2834, 2360, 1682, 1598, 1585, 1488, 1449, 1354, 1263, 1199, 1153, 1043, 1022, 778, 749, 692 cm−1; 1H NMR (500 MHz, CDCl3) 8.00–7.94 (comp, 2H), 7.59–7.53 (m, 1H), 7.49–7.42 (comp, 2H), 7.22–7.11 (comp, 5H), 6.90–6.80 (comp, 2H), 6.77 (app dd, J = 8.1, 2.0 Hz, 1H), 4.69–4.60 (m, 1H), 3.80–3.61 (comp, 6H), 3.27–3.14 (comp, 2H), 3.01 (ddd, J = 16.9, 10.8, 5.9 Hz, 1H), 2.90–2.79 (m, 1H), 2.67–2.55 (m, 1H); 13C NMR (125 MHz, CDCl3) δ 198.8, 159.5, 140.7, 138.0, 137.4, 134.2, 132.8, 129.1, 129.0, 128.5, 128.1, 127.6, 126.3, 126.0, 121.0, 113.8, 112.8, 58.4, 57.8, 55.0, 45.6, 42.2, 24.2; m/z (ESI–MS) 372.0 [M + H]+.
2-(2-(4-chlorobenzyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-phenylethanone (2.48f):

Following the general procedure compound 2.48f was obtained from acetophenone, tetrahydroisoquinoline and 4-chlorobenzaldehyde as a yellow oil in 45% yield (Rf = 0.44 in hexanes/EtOAc 80:20 v/v); IR (KBr) 3061, 3022, 2924, 2831, 1682, 1597, 1490, 1448, 1407, 1355, 1284, 1201, 1089, 1015, 749, 690 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 7.96–7.89 (comp, 2H), 7.60–7.54 (m, 1H), 7.49–7.41 (comp, 2H), 7.22–7.04 (comp, 8H), 4.63–4.50 (m, 1H), 3.78–3.51 (comp, 3H), 3.30–3.13 (comp, 2H), 2.99 (ddd, J = 16.9, 11.2, 6.0 Hz, 1H), 2.88–2.74 (m, 1H), 2.69–2.52 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 198.7, 137.8, 137.5, 137.2, 134.1, 132.9, 132.5, 130.1, 129.2, 128.5, 128.1(9), 128.1(6), 127.6, 126.5, 126.1, 58.1, 57.0, 45.7, 42.3, 23.9; m/z (ESI–MS) 375.9 [M + H]⁺.

2-(2-(4-bromobenzyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-phenylethanone (2.48g):

Following the general procedure compound 2.48g was obtained from acetophenone, tetrahydroisoquinoline and 4-bromobenzaldehyde as a yellow oil in 45% yield (Rf = 0.46 in hexanes/EtOAc 80:20 v/v); IR (KBr) 3060, 3019, 2924, 2833, 2360, 1682, 1597, 1580, 1487, 1448, 1404, 1355, 1284, 1264, 1200, 1096, 1069, 1011, 750, 691 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 7.96–7.90 (comp, 2H), 7.60–7.54 (m, 1H), 7.50–7.42 (comp, 2H), 7.36–7.29 (comp, 2H), 7.22–7.10 (comp, 4H), 7.10–7.02 (comp, 2H), 4.60–4.52 (m, 1H), 3.70 (d, J = 13.4 Hz, 1H), 3.66–3.52 (comp, 2H), 3.28–3.15 (comp, 2H), 2.99 (ddd, J = 16.9, 11.2, 6.2 Hz, 1H), 2.87–2.75 (m, 1H), 2.66–2.53 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 198.7, 138.0, 137.7, 137.2, 134.0, 132.9, 131.1, 130.4, 129.2, 128.5, 128.1, 127.6, 126.5, 126.1, 120.7, 58.1, 57.0, 45.7, 42.3, 23.9; m/z (ESI–MS) 419.9 (⁷⁹Br) [M + H]⁺, 421.9 (⁸¹Br) [M + H]⁺.

2-(2-(4-methylbenzyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-phenylethanone (2.48h):

Following the general procedure compound 2.48h was obtained from acetophenone, tetrahydroisoquinoline and p-tolualdehyde as a yellow oil in 46% yield (Rf = 0.35 in hexanes/EtOAc 80:20 v/v); IR (KBr) 3055, 3013, 2936, 2903, 2887, 2802, 2360, 2342, 1683, 1595, 1578, 1512, 1488, 1447, 1431, 1408, 1359, 1315, 1295, 1264, 1239, 1210, 1119, 1102, 976, 963, 805, 753, 686, 650 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 7.98–7.89 (m, 2H), 7.60–7.54 (m, 1H), 7.50–7.42 (comp, 2H), 7.36–7.29 (comp, 2H), 7.22–7.10 (comp, 4H), 7.10–7.02 (comp, 2H), 4.60–4.52 (m, 1H), 3.70 (d, J = 13.4 Hz, 1H), 3.66–3.52 (comp, 2H), 3.28–3.15 (comp, 2H), 2.99 (ddd, J = 16.9, 11.2, 6.2 Hz, 1H), 2.87–2.75 (m, 1H), 2.66–2.53 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 198.7, 138.0, 137.7, 137.2, 134.0, 132.9, 131.1, 130.4, 129.2, 128.5, 128.1, 127.6, 126.5, 126.1, 120.7, 58.1, 57.0, 45.7, 42.3, 23.9; m/z (ESI–MS) 419.9 (⁷⁹Br) [M + H]⁺, 421.9 (⁸¹Br) [M + H]⁺.
MHz, CDCl$_3$) 7.98–7.93 (comp, 2H), 7.60–7.54 (m, 1H), 7.49–7.42 (comp, 2H), 7.22–7.10 (comp, 6H), 7.09–7.03 (comp, 2H), 4.69–4.59 (m, 1H), 3.79–3.57 (comp, 3H), 3.28–3.15 (comp, 2H), 3.01 (ddd, $J = 16.9, 10.8, 5.9$ Hz, 1H), 2.90–2.79 (m, 1H), 2.68–2.55 (m, 1H), 2.34 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 198.9, 138.1, 137.4, 136.4, 135.8, 134.2, 132.7, 129.1, 128.8, 128.7, 128.4, 128.2, 127.6, 126.3, 126.0, 58.1, 57.5, 45.6, 42.2, 24.2, 21.0; $m/z$ (ESI–MS) 356.1 [M + H]$^+$. 

2-(2-(4-methoxybenzyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-phenylethanone (2.48i): Following the general procedure compound 2.48i was obtained from acetophenone, tetrahydroisoquinoline and $p$-anisaldehyde as a yellow oil in 44% yield ($R_f = 0.24$ in hexanes/EtOAc 80:20 v/v); IR (KBr) 3061, 2932, 2834, 1682, 1611, 1449, 1355, 1301, 1284, 1246, 1179, 1101, 1035, 833, 750, 691 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) 7.96–7.91 (comp, 2H), 7.57–7.52 (m, 1H), 7.47–7.41 (comp, 2H), 7.20–7.07 (comp, 6H), 6.80–6.73 (comp, 2H), 4.67–4.56 (m, 1H), 3.78 (s, 3H), 3.73–3.56 (comp, 3H), 3.25–3.14 (comp, 2H), 2.99 (ddd, $J = 16.9, 10.9, 5.9$ Hz, 1H), 2.88–2.77 (m, 1H), 2.66–2.54 (m, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 198.8, 158.6, 138.0, 137.4, 134.2, 132.8, 130.9, 129.9, 129.1, 128.5, 128.2, 127.6, 126.3, 126.0, 113.5, 58.0, 57.1, 55.1, 45.7, 42.1, 24.1; $m/z$ (ESI–MS) 372.0 [M + H]$^+$.

2-(2-(naphthalen-2-ylmethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-phenylethanone (2.48j): Following the general procedure compound 2.48j was obtained from acetophenone, tetrahydroisoquinoline and 2-naphthaldehyde as a yellow oil in 46% yield ($R_f = 0.40$ in hexanes/EtOAc 80:20 v/v); IR (KBr) 3057, 3019, 2923, 2834, 1683, 1598, 1580, 1508, 1492, 1448, 1353, 1266, 1199, 1123, 1103, 1021, 855, 822, 748, 691 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) 7.98–7.93 (comp, 2H), 7.83–7.78 (m, 1H), 7.77–7.69 (comp, 2H), 7.65 (br s, 1H), 7.55–7.49 (m, 1H), 7.48–7.34 (comp, 5H), 7.24–7.11 (comp, 4H), 4.75–4.66 (m, 1H), 3.94 (d, $J = 13.3$ Hz, 1H), 3.87 (d, $J = 13.3$ Hz, 1H), 3.77–3.62 (m, 1H), 3.31–3.17 (comp, 2H), 3.05 (ddd, $J = 16.8, 10.9, 6.0$ Hz, 1H), 2.93–2.82 (m, 1H), 2.69–2.55 (m, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 198.9, 138.0, 137.3, 136.6, 134.2, 133.2, 133.0,
132.8(0), 132.7(6), 129.2, 128.5, 128.2, 127.8, 127.6(4), 127.6(2), 127.6, 127.2, 126.4, 126.1, 125.7, 125.4, 58.4, 58.0, 45.7, 42.2, 24.1; m/z (ESI–MS) 392.0 [M + H]+.

2-(2-(furan-2-ylmethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-phenylethanone (2.48k):

Following the general procedure compound 2.48k was obtained from acetophenone, tetrahydroisoquinoline and 2-furaldehyde as a yellow oil in 33% yield (Rf = 0.28 in hexanes/EtOAc 80:20 v/v); IR (KBr) 3061, 3022, 2923, 2834, 1682, 1645, 1597, 1580, 1491, 1448, 1353, 1282, 1201, 1149, 1103, 1077, 1014, 918, 748, 691 cm^-1; ^1H NMR (400 MHz, CDCl3) 7.97–7.87 (comp, 2H), 7.58–7.49 (m, 1H), 7.48–7.40 (comp, 2H), 7.33–7.30 (m, 1H), 7.19–7.07 (comp, 4H), 6.31–6.25 (m, 1H), 6.22–6.14 (m, 1H), 4.74–4.59 (m, 1H), 3.86–3.71 (comp, 2H), 3.69–3.57 (m, 1H), 3.34–3.19 (comp, 2H), 3.07–2.88 (comp, 2H), 2.78–2.62 (m, 1H); ^13C NMR (100 MHz, CDCl3) δ 198.4, 152.0, 142.1, 137.7, 137.2, 133.8, 132.9, 129.0, 128.5, 128.2, 128.1, 127.6, 126.3, 110.0, 108.6, 56.7, 50.4, 46.0, 43.7, 24.6; m/z (ESI–MS) 332.0 [M + H]+.

1-phenyl-2-(2-(thiophen-2-ylmethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)ethanone (2.48l):

Following the general procedure compound 2.48l was obtained from acetophenone, tetrahydroisoquinoline and 2-thiophenecarboxaldehyde as a yellow oil in 38% yield (Rf = 0.45 in hexanes/EtOAc 80:20 v/v); IR (KBr) 3061, 3019, 2923, 2833, 1682, 1597, 1580, 1490, 1448, 1351, 1280, 1200, 1104, 1020, 750, 691 cm^-1; ^1H NMR (400 MHz, CDCl3) 7.99–7.93 (comp, 2H), 7.60–7.52 (m, 1H), 7.50–7.42 (comp, 2H), 7.21–7.09 (comp, 5H), 6.92–6.81 (comp, 2H), 4.74–4.66 (m, 1H), 3.99 (d, J = 14.0 Hz, 1H), 3.89 (d, J = 14.0 Hz, 1H), 3.71–3.56 (m, 1H), 3.30–3.16 (comp, 2H), 3.05–2.88 (comp, 2H), 2.71–2.57 (m, 1H); ^13C NMR (100 MHz, CDCl3) δ 198.7, 143.2, 137.8, 137.3, 134.0, 132.8, 129.1, 128.5, 128.2, 127.6, 127.0, 126.8, 126.2, 125.4, 124.9, 57.7, 52.5, 45.9, 42.6, 24.4; m/z (ESI–MS) 348.0 [M + H]+.
1-(2,6-dichlorobenzyl)-2-(nitromethyl)pyrrolidine (2.49a): To a solution of benzoic acid (0.25 mmol, 0.5 equiv) in toluene (2 mL) were added nitromethane (1.5 mmol, 3 equiv) and pyrrolidine (0.75 mmol, 1.5 equiv). The mixture was heated under reflux and 2,6-dichlorobenzaldehyde (0.5 mmol, 1 equiv, 1M solution in toluene) was delivered through the top of the reflux condenser over 5 hours via syringe pump. Subsequently, the reaction mixture was allowed to cool to room temperature, diluted with EtOAc (10 mL) and washed with saturated aqueous NaHCO$_3$ (3 x 10 mL). The combined aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organic layer was washed with water (40 mL), brine (40 mL), and dried over anhydrous Na$_2$SO$_4$. Solvent was then removed under reduced pressure and the residue was purified by eluting through a short silica gel plug with hexanes/EtOAc (80:20 v/v). Compound 2.49a was obtained as a yellow oil in 59% yield (R$_f$ = 0.45 in hexanes/EtOAc 90:10 v/v); IR (KBr) 3078, 2966, 2918, 2852, 2815, 1582, 1548, 1436, 1385, 1359, 1245, 1206, 1123, 1089, 968, 916, 869, 779, 766, 745, 710, 642 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) 7.31 (d, $J$ = 8.0 Hz, 2H), 7.15 (t, $J$ = 8.0 Hz, 1H), 4.53 (dd, $J$ = 11.8, 3.6 Hz, 1H), 4.24–4.14 (m, 1H), 4.06 (d, $J$ = 12.5 Hz, 1H), 3.99 (d, $J$ = 12.5 Hz, 1H), 3.53–3.44 (m, 1H), 2.95–2.85 (m, 1H), 2.68–2.59 (m, 1H), 2.13–2.01 (m, 1H), 1.84–1.66 (comp, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 136.4, 134.2, 129.1, 128.5, 79.1, 61.7, 53.7, 52.6, 29.4, 23.1; $m/z$ (ESI–MS) 289.0 ([35Cl/$^{37}$Cl] [M + H]$^+$), 291.0 ([35Cl/$^{37}$Cl] [M + H]$^+$).

1-(2,6-dichlorobenzyl)-2-(1-nitroethyl)pyrrolidine (2.49b): The synthetic procedure followed was the same as for 2.49a. Compound 2.49b was obtained from nitroethane, pyrrolidine and 2,6-dichlorobenzaldehyde in 91% NMR yield (2:1 of two diastereomers) (R$_f$ = 0.55 in hexanes/EtOAc 90:10 v/v) (Note: The product isolated by silica gel chromatography contained impurities that could not be removed); IR (KBr) 3081, 2968, 2871, 2849, 2814, 1579, 1544, 1529, 1436, 1389, 1339, 1326, 1301, 1206, 1097, 984, 886, 871, 781, 766, 744 cm$^{-1}$; $^1$H NMR (Note: due to overlapping peaks, integration values of the diastereomers and the impurities are reported together) (500 MHz, CDCl$_3$) 7.39 (d, $J$ = 8.0 Hz, 2.16H), 7.34–7.28 (comp, 4.68H), 7.18–7.11 (comp, 1.84H), 4.61 (app dq, $J$ = 6.7, 4.6 Hz, 1.00H), 4.48–4.40 (m, 0.77H), 4.10 (d, $J$ = 12.5 Hz, 0.88H), 4.05 (d, $J$ = 12.4 Hz, 1.09H), 4.02–3.95
(comp, 1.83H), 3.46 (ddd, $J = 4.6, 4.6, 4.2$ Hz, 1.00H), 3.26 (ddd, $J = 9.0, 5.7, 3.6$ Hz, 0.79H), 2.93–2.81 (comp, 1.93H), 2.70–2.58 (comp, 1.98H), 2.03–1.49 (comp, 8.64H), 1.46 (d, $J = 6.7$ Hz, 2.98H), 1.43 (d, $J = 6.8$ Hz, 2.39H); $^{13}$C NMR of the diastereomers and the impurities (125 MHz, CDCl$_3$) $\delta$ 136.7, 136.5, 134.4, 134.3, 134.2, 130.5(8), 130.5(7), 129.0(2), 129.0(1), 128.5(0), 128.4(8), 128.3, 128.2, 85.3, 84.0, 67.0, 66.1, 53.8, 53.7, 53.6, 52.9, 27.1, 25.7, 24.4, 23.5, 16.4, 14.3, 12.4; m/z (ESI–MS) 303.0 ($^{35}$Cl/$^{35}$Cl) $[M + H]^+$, 305.0 ($^{35}$Cl/$^{37}$Cl) $[M + H]^+$.

1-(2,6-dichlorobenzyl)-2-(1-nitropropyl)pyrrolidine (2.49c): The synthetic procedure followed was the same as for 2.49a. Compound 2.49c was obtained from 1-nitropropane, pyrrolidine and 2,6-dichlorobenzaldehyde in 98% NMR yield (1.4:1 of two diastereomers) ($R_f = 0.58$ in hexanes/EtOAc 90:10 v/v) (Note: The product isolated by silica gel chromatography contained impurities that could not be removed); IR (KBr) 2972, 2879, 2851, 2809, 1581, 1545, 1459, 1436, 1376, 1356, 1339, 1205, 1088, 780, 766 cm$^{-1}$; $^1$H NMR (Note: due to overlapping peaks, integration values of the diastereomers and the impurities are reported together) (500 MHz, CDCl$_3$) 7.40–7.37 (comp, 0.61H), 7.35–7.27 (comp, 3.64H), 7.18–7.10 (comp, 1.68H), 4.43–4.36 (m, 1.00H), 4.28 (ddd, $J = 9.8, 6.4, 4.5$ Hz, 0.63H), 4.12 (d, $J = 12.5$ Hz, 0.69H), 4.04 (d, $J = 12.3$ Hz, 1.07H), 4.01–3.93 (comp, 1.67H), 3.34 (app dt, $J = 8.3, 4.9$ Hz, 1.01H), 3.21 (ddd, $J = 8.8, 6.4, 3.7$ Hz, 0.64H), 2.93–2.80 (comp, 1.74H), 2.67–2.55 (comp, 1.96H), 2.48 (app q, $J = 7.4$ Hz, 0.62H), 2.01–1.52 (comp, 11.14H), 1.06 (t, $J = 7.4$ Hz, 0.84H), 0.92–0.83 (comp, 5.29H); $^{13}$C NMR of the diastereomers and the impurities (125 MHz, CDCl$_3$) $\delta$ 136.8, 136.5, 134.3, 134.2, 130.4, 129.0(4), 128.9(9), 128.4(8), 128.4(7), 127.5, 92.2, 91.9, 66.2(5), 66.2(1), 64.5, 53.6(2), 53.5(9), 53.4, 53.0, 50.0, 26.7, 26.2, 24.6, 24.3, 23.5, 23.0, 21.4, 20.3, 11.3, 10.8, 10.6, 10.2; m/z (ESI–MS) 317.0 ($^{35}$Cl/$^{35}$Cl) $[M + H]^+$, 319.0 ($^{35}$Cl/$^{37}$Cl) $[M + H]^+$.

2-benzyl-1-(nitromethyl)-1,2,3,4-tetrahydroisoquinoline (2.50): A 10 mL round-bottom flask was charged with 4Å molecular sieves (200 wt%), benzoic acid (0.1 mmol, 0.2 equiv), toluene (2 mL), benzaldehyde (0.5 mmol, 1 equiv), nitromethane (1.5 mmol, 3 equiv) and tetrahydroisoquinoline (0.75 mmol, 1.5 equiv). The mixture was stirred at 50 °C for 12 hours at which time the aldehyde was consumed as judged by
TLC analysis. The mixture was allowed to cool to room temperature and filtered through a short pad of celite and washed with EtOAc (6 x 5 mL). The filtrate was then washed with saturated aqueous NaHCO$_3$ (3 x 10 mL). The combined aqueous layer was extracted with EtOAc (3 x 10 mL), and the combined organic layer was washed with water (40 mL), brine (40 mL), and dried over anhydrous Na$_2$SO$_4$. Solvent was then removed under reduced pressure and the residue was purified by eluting through a short silica gel plug with hexanes/EtOAc (80:20 v/v). Compound 2.50 was obtained as a yellow oil in 83% yield ($R_f = 0.50$ in hexanes/EtOAc 90:10 v/v); IR (KBr) 3062, 3025, 2922, 2834, 2809, 2740, 1553, 1494, 1454, 1428, 1381, 1319, 1264, 1209, 1123, 1027, 742, 700, 660 cm$^{-1}$. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.39–7.16 (comp, 8H), 7.13–7.08 (m, 1H), 4.75 (dd, $J = 11.8$, 10.2 Hz, 1H), 4.58 (dd, $J = 10.2$, 4.5 Hz, 1H), 4.49 (dd, $J = 11.8$, 4.5 Hz, 1H), 3.86 (d, $J = 13.3$ Hz, 1H), 3.77 (d, $J = 13.3$ Hz, 1H), 3.23 (ddd, $J = 13.8$, 11.5, 4.4 Hz, 1H), 3.06 (ddd, $J = 17.0$, 11.5, 5.7 Hz, 1H), 2.99–2.91 (m, 1H), 2.60–2.50 (m, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 138.2, 135.2, 132.1, 129.6, 128.7, 128.3, 127.6, 127.5, 127.3, 126.5, 79.4, 59.6, 57.5, 41.7, 22.8; m/z (ESI–MS) 222.1 [M–CH$_2$NO$_2$]$^+$. 

3-(3,4-dihydroisoquinolin-2(1H)-yl)-1,3-diphenylpropan-1-one (2.51): Compound 2.51 was synthesized according to a literature procedure.$^{49}$ To a suspension of chalcone (10 mmol, 1 equiv) in 95% ethanol (8 mL) was added tetrahydroisoquinoline (10.4 mmol, 1.04 equiv). The mixture was heated to reflux and then allowed to stir at room temperature for 2 days followed by standing in a -20 °C refrigerator for 4 days. The solid formed was filtered off and washed with cold 95% ethanol followed by recrystallization from 95% ethanol. Compound 2.51 was obtained as a white solid in 56% yield ($R_f = 0.27$ in hexanes/EtOAc 80:20 v/v); mp: 78–80 °C; IR (KBr) 3058, 3027, 2968, 2920, 2793, 2755, 1672, 1596, 1580, 1497, 1464, 1449, 1377, 1341, 1304, 1284, 1225, 1185, 1092, 1001, 991, 935, 758, 738, 709, 683, 648, 561 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.00–7.91 (comp, 2H), 7.59–7.52 (m, 1H), 7.51–7.40 (comp, 4H), 7.39–7.32 (comp, 2H), 7.31–7.24 (m, 1H), 7.18–7.05 (comp, 3H), 7.02–6.93 (m, 1H), 4.47 (app t, $J = 6.6$ Hz, 1H), 3.81–3.66 (comp, 3H), 3.55 (dd, $J = 16.5$, 7.4 Hz, 1H), 2.97–2.79 (comp, 3H), 2.72–2.59 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 198.2,
m/z (ESI–MS) 342.3 [M + H]^+.

3-(2,6-dichlorophenyl)-1-phenyl-3-(pyrrolidin-1-yl)propan-1-one (2.52): Compound 2.52 was synthesized according to a literature procedure making similar compounds.\(^5\) A mixture of the corresponding chalcone\(^5\) (0.5 mmol, 1 equiv), pyrrolidine (5 mmol, 10 equiv) and water (5 mmol, 10 equiv) was stirred at room temperature for 2 days. The mixture was then diluted with EtOAc (10 mL), washed with water (40 mL) and brine (40 mL), and dried over anhydrous Na\(_2\)SO\(_4\). Solvent was then removed under reduced pressure and \(^1\)H-NMR was taken for the crude product (Note: the crude product contained unreacted chalcone which was not removed). \(^1\)H NMR of aliphatic protons (400 MHz, CDCl\(_3\)) 5.03 (dd, \(J = 7.1, 5.9\) Hz, 1H), 3.89 (dd, \(J = 17.2, 7.1\) Hz, 1H), 3.77 (dd, \(J = 17.2, 5.9\) Hz, 1H), 2.70–2.57 (comp, 2H), 2.45–2.34 (comp, 2H), 1.83–1.64 (comp, 4H).
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(48) For the reaction with 1-methylindole as the nucleophile, 2.5 equiv of 2-EHA was added.


Chapter 3

Redox-Neutral $\alpha,\beta$-Difunctionalization of Cyclic Amines

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3.1 β-Functionalization of Amines

Although limited compared to the $\alpha$-functionalization of amines, there are a few reports on the direct $\beta$-functionalization of amines. The Bruneau group has developed a ruthenium-catalyzed concurrent $N$- and $C3$-dibenzylation involving a hydrogen transfer processes.$^{1,2}$ Cyclic amines such as pyrrolidine react with benzylalcohol in the presence of ruthenium catalyst 3.2 and camphor sulfonic acid (CSA) giving 3-benzyl-$N$-benzylamines (Figure 3.1, eq 1). The reaction was proposed to start from the oxidation of benzylalcohol to benzaldehyde via hydrogen transfer to the Ru-catalyst. The iminium ion 3.3 forms by the condensation of benzaldehyde and the amine isomerizes, and the newly formed iminium ion 3.4 is in equilibrium with the corresponding enamine 3.5. The final product is formed following nucleophilic addition of the enamine to another molecule of benzaldehyde, followed by loss of water and the reduction of the conjugated iminium ion intermediate by a hydrogen atom transfer back from the Ru-catalyst. Alternatively, the substitution reaction occurs between the enamine and benzyl alcohol followed by the reduction of the formed iminium ion to provide the final product. The reaction is an example of the concept of “Borrowing Hydrogen”.$^3$ The iminium ion isomerization was proposed to proceed via a [1,3]-hydride shift by the authors, although it is an antarafacial shift and essentially geometrically forbidden. From our point of view, this isomerization could alternatively go through a similar mechanism to our redox-isomerization chemistry.$^4$ The Bruneau group later successfully employed an iridium catalyst for a similar reaction preparing $N$-arylpiperidines from anilines, 1,5-diols and aromatic aldehydes.$^5$ Liang and co-workers reported a platinum-catalyzed Michael-type addition of $N$-phenyl amines to nitroalkenes and a related Michael addition-cyclization cascade between the amines and
*-*hydroxynitrostyrenes (Figure 3.1, eq 2). Oisaki and Kanai in 2013 reported a similar reaction using FeCl₃ as the catalyst and di-tert-butyl peroxide as the stoichiometric oxidant. A catalytic amount of DMAP was needed to suppress the product inhibition in order to obtain good yields.

Palladium catalysts can also activate the β-position of cyclic amines, although through a different mechanism. Fujii and Ohno reported a palladium catalyzed indoline-formation from N-alkyl-2-bromoanilines (Figure 3.1, eq 3). The proposed mechanism did not involve the intermediacy of an enamine, in contrast to previous examples. Instead, it is thought to involve a Pd-catalyzed metallation-deprotonation pathway. Similar reactions were achieved enantioselectively by employing chiral phosphine and N-heterocyclic carbene ligands. A unique example of the amine β-functionalization was reported in 2014 by the Baudoin group, where they extended the classic lithiation-transmetallation-coupling method for the amine α-functionalization to the amine β-functionalization, by tuning the ligand used in the reaction (Figure 3.1, eq 4). The authors proposed the mechanism as shown according to extensive computational studies. The direct reductive elimination of intermediate 3.16 afforded the typical α-arylation product. However, in the reaction developed for the β-arylation of N-Boc piperidines, 3.16 underwent a ring-flip forming twist-boat conformation 3.17 with a β-C–H agostic interaction. β-Elimination of intermediate 3.17 produced π-complex 3.18 followed by a rotation of the coordinated olefin affording 3.19. The 1,2-insertion of the olefin into the Pd–H bond and the subsequent reductive elimination of intermediate 3.20 gave rise to the less stable conformer 3.21, which then underwent the ring-flip forming the final product with the β-aryl group at the equatorial position. The reductive elimination of intermediate 3.20 was calculated to be the rate determining step (RDS) with the highest energy barrier along the reaction pathway forming the β-arylation product, however, being 1.3 kcal/mol lower than the highest energy barrier along the pathway leading to the α-arylation product, and this difference was influenced by the ligand used in the reaction.
3.2 Research Background

In the course of developing the redox-neutral α-arylation (Chapter 2, Section 2.3), we studied the isomerization potential of the undesired regioisomer (Figure 3.2). To our surprise,
although the desired regioisomer was observed in a 4:1 ratio with the recovered starting material, neither of them were the major compound isolated from the reaction. The major product obtained from the attempted isomerization was the polycyclic \(N,O\)-acetal 3.25a with concurrent functionalization at both \(\alpha\)- and \(\beta\)-positions of the amine. The structure and relative configuration of 3.25a was established by X-ray crystallography. Considering that the formation of one equivalent of 3.25a required two equivalents of benzaldehyde, compound 3.23a was allowed to react with a slight excess of benzaldehyde under otherwise identical conditions. With 20-mol\% of benzoic acid as the catalyst, the desired \(N,O\)-acetal was isolated in 78% yield. Interestingly, the addition of benzoic acid was not required, and in fact the yield of the product slightly improved without any additive (Figure 3.3).

**Figure 3.2 Discovery of an \(\alpha,\beta\)-Difunctionalization of Amines**

![Diagram](image)

**Figure 3.3 Optimal Conditions for the \(\alpha,\beta\)-Difunctionalization of Amines**

![Diagram](image)

3.3 Mechanism of the \(\alpha,\beta\)-Difunctionalization of Amines

To study the mechanism of the difunctionalization, we performed several control reactions (Figure 3.4). Compound 3.23a reacted with 4-chlorobenzaldehyde under the optimal conditions providing an \(N,O\)-acetal 3.25b bearing the \(N\)-4-Cl-benzyl group in 82% yield, while compound 3.23b and benzaldehyde gave \(N,O\)-acetal 3.25c bearing the \(N\)-benzyl group in 75% yield. Both reactions were regioselective and diastereoselective. Based upon the results obtained, we proposed that the reaction started from the fragmentation of 3.23b to generate ortho-quinone
methide 3.26 and pyrrolidine. The crystallographic structure of a similar compound exhibits hydrogen bonding between the hydroxyl group and the amine nitrogen of the starting material, which is thought to facilitate the fragmentation step. The released pyrrolidine then reacts with benzaldehyde giving enamine intermediate 3.5, probably via the redox-isomerization and the intermediacy of the azomethine ylide. Enamine 3.5 and ortho-quinone methide 3.26 participate in an endo-selective hetero-Diels-Alder reaction producing the final N,O-acetal product.

**Figure 3.4 Mechanism of the α,β-Difunctionalization of Amines**

![Mechanism of the α,β-Difunctionalization of Amines](image)

**3.4 Scope of the Reaction**

The scope of the α,β-difunctionalization was explored (Figure 3.5). A number of 1-(aminomethyl)-β-naphthols and 2-(aminomethyl)-phenols readily underwent the difunctionalization with various aromatic aldehydes. The reaction generally provided the N,O-acetals in good yields and high to excellent diastereoselectivities. In addition to pyrrolidine, a range of other cyclic amines were viable substrates as well. However, six-membered amines such as piperidine and morpholines needed high reaction temperature up to 250 °C. Thiomorpholine and N-Cbz-piperazine were even more challenging substrates that could only react with electron-poor 2,6-dichlorobenzaldehyde furnishing the desired products in decent yields.
Substrates derived from azepane, tetrahydroisoquinoline and 2-methylpyrrolidine unfortunately failed to participate in the reaction yielding desired difunctionalization products.

Figure 3.5 Scope of the α,β-Difunctionalization

[Chemical structures and yields are shown here.]

\[^a\] Reactions were performed on a 0.5 mmol scale. \[^b\] Substrates containing pyrrolidine and piperidine/morpholine moieties were heated at 200 and 250 °C, respectively. \[^c\] Yields are combined yields of both diastereomers (if any), major diastereomer shown.

3.5 One-Pot Reaction and Product Modification

Given that starting materials of the difunctionalization are easily prepared from amines, β-naphthols or phenols and aromatic aldehydes, we wanted to develop a one-pot, stepwise amine α,β-difunctionalization from these commercially available compounds (Figure 3.6). Under the
conditions designed for this transformation, the N,O-acetal was isolated in only slightly decreased yield compared to the two-step procedure. Meanwhile, we tested the one-pot reaction on a gram-scale, which demonstrated the scalability of this reaction. The C–O bond of the N,O-acetal was found to be labile, which provided various opportunities for product transformations. For instance, N,O-acetal 3.25e was reduced by LiAlH₄ giving β-functionalized compound 3.28, and 3.25e also reacted with alkyl and aryl Grignard reagents to furnish α,β-difunctionalized products 3.29 (Figure 3.7).

**Figure 3.6 One-Pot Redox-Neutral α,β-Difunctionalization of Pyrrolidine**

![Figure 3.6](image)

**Figure 3.7 Product Modification**

![Figure 3.7](image)

### 3.6 Conclusion

In conclusion, we discovered and developed the first redox-neutral α,β-difunctionalization of cyclic amines. Structurally complex polycyclic N,O-acetals were obtained by the concurrent activation of the amine α,β-C–H bonds in good to excellent yields, regioselectivities and diastereoselectivities in the absence of any additives. The reaction is proposed to go through an enamine intermediate. This is also, to the best of our knowledge, the first example of a metal-free amine β-C–H bond functionalization without a simultaneous amine aromatization.¹³
Experimental Section

**General Information:**  See Chapter 2 Experimental Section.

**General Procedure A for the Synthesis of Starting Materials:**\(^{14}\)

A solution of the amine (7.5 mmol, 1 equiv), 2-naphthol (7.5 mmol, 1 equiv) and the aldehyde (9.75 mmol, 1.3 equiv) in the specified solvent (4 mL) was stirred at the given temperature. The reaction progress was monitored by TLC. When complete, the reaction mixture was allowed to cool to room temperature and the product was purified as specified.

**General Procedure B for the Synthesis of Starting Materials:**\(^{15}\)

To a solution of the corresponding amine (7.5 mmol, 1 equiv) in ethanol (95%, 4 mL) cooled in an ice bath was added formaldehyde (7.5 mmol, 1 equiv, 37% water solution) dropwise. After a few minutes, a solution of the corresponding 2-naphthol (7.5 mmol, 1 equiv) in ethanol (95%, 3 mL) was added. The mixture was stirred at room temperature for 1 hour and the product was purified as specified.

**General Procedure for the Redox-Neutral α,β-Difunctionalization of Amines:**

A 10 mL microwave reaction tube was charged with a 10 x 8 mm SiC passive heating element, the 1-(aminomethyl)-β-naphthol or 2-(aminomethyl)-phenol (0.5 mmol, 1 equiv), toluene (2 mL) and the aldehyde (0.55 mmol, 1.1 equiv). The reaction tube was sealed with a Teflon-lined snap cap, and heated in a microwave reactor at 200 °C (200 W, 70–100 psi, for substrates containing a pyrrolidine moiety) or 250 °C (200W, 150–200 psi, for substrates containing piperidine/morpholine moieties) for 15 minutes. After cooling with compressed air flow, the solution was transferred to a 50 mL round-bottom flask. The solvent was then removed under reduced pressure and the residue was purified by silica gel chromatography.

**Procedure for the One-pot Redox-Neutral α,β-Difunctionalization of Pyrrolidine:**

A 35 mL microwave reaction tube was charged with 4Å molecular sieves (200 wt%), 2-naphthol (5 mmol, 1 equiv), toluene (20 mL), benzaldehyde (10.5 mmol, 2.1 equiv) and pyrrolidine (5
mmol, 1 equiv). The mixture was stirred at room temperature for 5 hours at which time 2-naphthol was consumed as judged by TLC analysis. The stir bar was removed and a 10 x 18 mm SiC passive heating element was added. The reaction tube was sealed with a Teflon-lined snap cap, and heated in a microwave reactor at 200 °C (200 W, 110–130 psi) for 15 minutes. After cooling with compressed air flow, the solution was transferred to a 250 mL round-bottom flask. The solvent was then removed under reduced pressure and the residue was purified by silica gel chromatography.

**Note:** SiC passive heating elements must not be used in conjunction with stir bars; they may score glass and cause vessel failure.

1-(phenyl(pyrrolidin-1-yl)methyl)naphthalen-2-ol (3.23a): The title compound was synthesized following the general procedure A. Ethanol (95%) was used as the solvent and the reaction conducted under reflux. Upon completion, the reaction mixture was allowed to cool to room temperature. The resulting precipitate was filtered and washed with cold ethanol. After drying under high vacuum, the product was obtained as a white solid in 77% yield. Compound 3.23a was previously reported and its published characterization data matched our own in all respects.¹⁴

1-((4-chlorophenyl)(pyrrolidin-1-yl)methyl)naphthalen-2-ol (3.23b): The title compound was synthesized following the general procedure A. Ethanol (95%) was used as the solvent and the reaction conducted under reflux. Upon completion, the reaction mixture was allowed to cool to room temperature. The solvent was then removed under reduced pressure. The residue was purified by silica gel chromatography, followed by recrystallization from hexanes/ethyl acetate. After drying under high vacuum, the product was obtained as colorless crystals in 56% yield. Compound 3.23b was previously reported and its published characterization data matched our own in all respects.¹⁶
ethyl-2-(2-hydroxynaphthalen-1-yl)-2-(pyrrolidin-1-yl)acetate (3.23c): The title compound was synthesized following the general procedure A. Toluene was used as the solvent and the reaction conducted at room temperature. Upon completion, the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography. After drying under high vacuum, the product was obtained as a white solid in 48% yield ($R_f = 0.26$ in hexanes/ethyl acetate 85:15 v/v); mp: 93–95 °C; IR (KBr) 3054, 2980, 2876, 2819, 1736, 1622, 1596, 1522, 1470, 1418, 1369, 1349, 1326, 1270, 1242, 1210, 1187, 1138, 1022, 949, 911, 850, 828, 756 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) 12.08 (br s, 1H), 8.05 (d, $J = 8.6$ Hz, 1H), 7.77–7.73 (m, 1H), 7.70 (d, $J = 8.9$ Hz, 1H), 7.52–7.45 (m, 1H), 7.34–7.27 (m, 1H), 7.11 (d, $J = 8.9$ Hz, 1H), 4.91 (s, 1H), 4.18–4.05 (comp, 2H), 2.95–2.61 (comp, 4H), 1.96–1.86 (comp, 4H), 1.13 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 169.7, 156.8, 132.2, 130.5, 128.7, 128.5, 126.7, 122.6, 121.7, 119.5, 110.5, 67.9, 61.2, 52.4, 23.5, 14.0; $m/z$ (ESI–MS) 299.9 [M + H]$^+$. 

1-(pyrrolidin-1-ylmethyl)naphthalen-2-ol (3.23d): The title compound was synthesized following the general procedure B. Upon completion, the resulting precipitate was filtered and washed with cold ethanol, followed by recrystallization from ethanol. After drying under high vacuum, the product was obtained as colorless crystals in 56% yield. Compound 3.23d was previously reported and its published characterization data matched our own in all respects.\textsuperscript{15}

7-methoxy-1-(pyrrolidin-1-ylmethyl)naphthalen-2-ol (3.23e): The title compound was synthesized following the general procedure B. Upon completion, the resulting precipitate was filtered and washed with cold ethanol, followed by recrystallization from ethanol. After drying under high vacuum, the product was obtained as colorless crystals in 65% yield ($R_f = 0.15$ in hexanes/ethyl acetate 20:80 v/v); mp: 118–121 °C; IR (KBr) 3061, 3031, 3004, 2964, 2873, 2829, 1624, 1518, 1490, 1471, 1390, 1340, 1314, 1265, 1229, 1133, 1060, 1028, 931, 839, 823, 809 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) 12.2 (br s, 1H), 7.66 (d, $J = 8.9$ Hz, 1H), 7.61 (d, $J = 8.7$ Hz, 1H), 7.10 (d, $J = 2.4$ Hz, 1H), 7.00–6.96 (comp, 2H), 4.23 (s, 2H), 3.93 (s, 3H), 2.82–2.71 (comp, 4H), 1.95–1.87
(comp, 4H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 158.1, 157.2, 133.4, 130.2, 128.7, 123.6, 116.6, 113.9, 110.8, 100.7, 55.1, 54.2, 53.8, 23.6; m/z (ESI–MS) 258.0 [M + H]$^+$. 

6-bromo-1-(pyrrolidin-1-ylmethyl)naphthalen-2-ol (3.23f): The title compound was synthesized following the general procedure B. Upon completion, the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography. After drying under high vacuum, the product was obtained as a yellow oil in 55% yield. Compound 3.23f was previously reported and its published characterization data matched our own in all respects.$^{15}$

4-chloro-2-(phenyl(pyrrolidin-1-yl)methyl)phenol (3.23g): The title compound was synthesized following the general procedure A. Toluene was used as the solvent and the reaction conducted at 80 °C. Upon completion, the reaction mixture was allowed to cool to room temperature. The solvent was then removed under reduced pressure. The residue was purified by silica gel chromatography. After drying under high vacuum, the product was obtained as a yellow oil in 40% yield ($R_f = 0.38$ in hexanes/EtOAc 90:10 v/v); IR (KBr) 3061, 3028, 2972, 2877, 2821, 2681, 1605, 1583, 1478, 1453, 1385, 1255, 1168, 1108, 1033, 890, 817, 727, 698, 645 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) 12.45 (br s, 1H), 7.50–7.43 (m, 2H), 7.34–7.22 (comp, 3H), 7.07 (dd, $J = 8.7$, 2.6 Hz, 1H), 6.97 (d, $J = 2.6$ Hz, 1H), 6.82 (d, $J = 8.7$ Hz, 1H), 4.34 (s, 1H), 2.63 (br s, 2H), 2.54–2.41 (m, 2H), 1.90–1.75 (comp, 4H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 155.3, 141.3, 128.7, 128.1, 127.9(2), 127.8(8), 127.6, 123.4, 118.1, 75.1, 53.0, 23.3; m/z (ESI–MS) 287.9 [M + H]$^+$. 

4-methoxy-2-(phenyl(pyrrolidin-1-yl)methyl)phenol (3.23h): The title compound was synthesized following the general procedure A. Toluene was used as the solvent and the reaction conducted at 80 °C. Upon completion, the reaction mixture was allowed to cool to room temperature. The solvent was then removed under reduced pressure. The residue was purified by silica gel chromatography. After drying under high vacuum, the product was obtained as a yellow oil in 26% yield. Compound 3.23h was previously reported and its published characterization data matched our own in all respects.$^{16}$
2-(pyrrolidin-1-ylmethyl)phenol (3.23i): Compound 3.23i was synthesized according to a literature procedure,\textsuperscript{16} and its published characterization data matched our own in all respects.\textsuperscript{17}

1-(phenyl(piperidin-1-yl)methyl)naphthalen-2-ol (3.23j): The title compound was synthesized following the general procedure A. Ethanol (95\%) was used as the solvent and the reaction conducted under reflux. Upon completion, the reaction mixture was allowed to cool to room temperature. The resulting precipitate was filtered and washed with cold ethanol. After drying under high vacuum, the product was obtained as a white solid in 75\% yield. Compound 3.23j was previously reported and its published characterization data matched our own in all respects.\textsuperscript{16}

4-chloro-2-(phenyl(piperidin-1-yl)methyl)phenol (3.23k): The title compound was synthesized following the general procedure A. Toluene was used as the solvent and the reaction conducted at 80 °C. Upon completion, the reaction mixture was allowed to cool to room temperature. The solvent was then removed under reduced pressure. The residue was purified by silica gel chromatography. After drying under high vacuum, the product was obtained as a colorless oil in 51\% yield (R\textsubscript{f} = 0.49 in hexanes/EtOAc 90:10 v/v); IR (KBr) 3061, 3028, 2937, 2855, 2809, 2678, 1604, 1581, 1480, 1453, 1389, 1256, 1167, 1108, 1032, 875, 812, 727, 699 644 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) 12.69 (br s, 1H), 7.48–7.24 (comp, 5H), 7.06 (dd, J = 8.6, 2.6 Hz, 1H), 6.87 (d, J = 2.6 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 4.43 (s, 1H), 2.40 (br s, 4H), 1.72–1.31 (comp, 6H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) δ 155.8, 138.6, 128.8, 128.1(0), 128.0(7), 127.0, 123.3, 118.2, 76.0, 52.4, 25.9, 23.9; m/z (ESI–MS) 301.9 [M + H]\textsuperscript{+}. 
1-(morpholino(phenyl)methyl)naphthalen-2-ol (3.23i): The title compound was synthesized following the general procedure A. Toluene was used as the solvent and the reaction conducted at 80 °C. Upon completion, the reaction mixture was allowed to cool to room temperature. The solvent was then removed under reduced pressure. The residue was purified by silica gel chromatography, followed by recrystallization from hexanes/ethyl acetate. After drying under high vacuum, the product was obtained as colorless crystals in 42% yield. Compound 3.23i was previously reported and its published characterization data matched our own in all respects.16

1-((cis-2,6-dimethylmorpholino)methyl)naphthalen-2-ol (3.23m): The title compound was synthesized following the general procedure B. Upon completion, the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography. After drying under high vacuum, the product was obtained as a colorless oil in 85% yield ($R_f = 0.28$ in hexanes/EtOAc 90:10 v/v); IR (KBr) 3055, 2973, 2934, 2856, 1622, 1599, 1522, 1469, 1413, 1369, 1320, 1264, 1236, 1193, 1083, 1000, 882, 816, 747, 706 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) 11.47 (br s, 1H), 7.84 (app d, $J = 8.6$ Hz, 1H), 7.79 (app d, $J = 8.1$ Hz, 1H), 7.73 (d, $J = 8.8$ Hz, 1H), 7.48 (app t, $J = 7.5$ Hz, 1H), 7.33 (app t, $J = 7.5$ Hz, 1H), 7.16 (d, $J = 8.8$ Hz, 1H), 4.11 (s, 2H), 3.82–3.73 (m, 2H), 2.91 (app d, $J = 11.2$ Hz, 2H), 1.95 (app t, $J = 10.9$ Hz, 2H), 1.19 (d, $J = 6.3$ Hz, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 156.1, 132.5, 129.2, 128.8, 128.4, 126.3, 122.4, 120.8, 119.0, 110.3, 71.5, 58.4, 56.2, 18.8; m/z (ESI–MS) 271.8 [M + H]$^+$.

1-(thiomorpholinomethyl)naphthalen-2-ol (3.23n): The title compound was synthesized following the general procedure B. Upon completion, the resulting precipitate was filtered and washed with cold ethanol, followed by recrystallization from acetone. After drying under high vacuum, the product was obtained as light yellow crystals in 82% yield ($R_f = 0.38$ in hexanes/ethyl acetate 85:15 v/v); mp: 156–158 °C; IR (KBr) 3056, 2970, 2915, 2838, 1621, 1597, 1518, 1471, 1362, 1298, 1238, 1161, 1127, 1100, 1007, 951, 814, 751, 710 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) 11.75 (br s, 1H), 7.81 (app d, $J = 8.6$ Hz, 1H), 7.77 (app d, $J = 8.1$ Hz, 1H), 7.71 (d, $J = 8.8$ Hz, 1H), 7.49–7.43 (m, 1H), 7.34–7.28 (m, 1H),
benzyl-4-((2-hydroxynaphthalen-1-yl)methyl)piperazine-1-carboxylate (3.23o): The title compound was synthesized following the general procedure B. Upon completion, the resulting precipitate was filtered and washed with cold ethanol. After drying under high vacuum, the product was obtained as a white solid in 73% yield \((R_f = 0.37)\) in hexanes/ethyl acetate 70:30 v/v; mp: 103–104 °C; IR (KBr) 3061, 3029, 2954, 2900, 2853, 156.2, 132.6, 129.3, 128.8, 128.5, 126.4, 122.5, 120.8, 119.0, 110.3, 57.0, 54.5, 27.8; \(m/z\) (ESI–MS) 259.9 [M + H]+.

7a-trans-10a-trans-8-benzyl-11-phenyl-7a,8,9,10a,11-hexahydrobenzo[5,6]chromeno[2,3-b]pyrrole 3.25a): Following the general procedure compound 3.25a was obtained from the corresponding 1-(aminomethyl)-β-naphthol and benzaldehyde as an off-white solid in 81% yield \((R_f = 0.33)\) in hexanes/ethyl ether 93:7 v/v; mp: 162–163 °C; IR (KBr) 3078, 3063, 2952, 2876, 2834, 1621, 1597, 1492, 1464, 1451, 1366, 1228, 1192, 1153, 1066, 1025, 958, 816, 749, 728, 700 cm⁻¹; \(^1\)H NMR (500 MHz, CDCl₃) 7.86–7.79 (comp, 2H), 7.41–7.35 (comp, 3H), 7.35–7.27 (comp, 5H), 7.26–7.19 (comp, 3H), 5.19 (d, \(J = 3.9\) Hz, 1H), 4.64 (s, 1H), 4.37 (d, \(J = 13.5\) Hz, 1H), 4.00 (d, \(J = 13.5\) Hz, 1H), 3.08 (app td, \(J = 8.8, 5.5\) Hz, 1H), 3.01 (app tdd, \(J = 9.9, 3.9, 1.7\) Hz, 1H), 2.86–2.79 (m, 1H), 2.32–2.22 (m, 1H), 1.75 (app dtd, 12.6, 10.3, 5.5 Hz, 1H); \(^{13}\)C NMR (125 MHz, CDCl₃) δ 152.9, 145.3, 139.1, 133.2, 129.2, 129.0, 128.7, 128.6, 128.4, 128.2, 127.6, 126.9, 126.4, 126.3, 122.8, 122.3, 118.8, 112.5, 89.6, 53.6, 49.4, 45.8, 41.3, 27.9; \(m/z\) (ESI–MS) 392.1 [M + H]+.
The title compound was further characterized by X-ray crystallography:

The requisite CIF has been deposited with the CCDC (deposition # 963306).

7a-trans-10a-trans-8-(4-chlorobenzyl)-11-phenyl-7a,8,9,10a,11-hexahydrobenzo[5,6]chromeno[2,3-b]pyrrole (3.25b): Following the general procedure compound 3.25b was obtained from the corresponding 1-(aminomethyl)-β-naphthol and 4-chlorobenzaldehyde as a colorless oil in 82% yield (R<sub>f</sub> = 0.33 in hexanes/ethyl ether 93:7 v/v); IR (KBr) 3059, 3024, 2930, 2873, 2841, 1623, 1599, 1514, 1491, 1402, 1361, 1262, 1226, 1191, 1150, 1081, 1067, 1013, 966, 838, 813, 744, 702 cm<sup>−1</sup>; ¹H NMR (500 MHz, CDCl₃) 7.89–7.83 (comp, 2H), 7.73 (d, J = 8.4 Hz, 1H), 7.44–7.35 (comp, 6H), 7.35–7.30 (comp, 3H), 7.29–7.22 (comp, 3H), 5.18 (d, J = 3.8 Hz, 1H), 4.68 (s, 1H), 4.34 (d, J = 13.7 Hz, 1H), 3.99 (d, J = 13.7 Hz, 1H), 3.12–2.99 (comp, 2H), 2.86–2.77 (m, 1H), 2.34–2.25 (m, 1H), 1.83–1.72 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 152.7, 145.2, 137.5, 133.1, 132.5, 129.8, 129.2, 129.0, 128.7, 128.4(2), 128.3(6), 127.6, 126.4(1), 126.3(8), 122.9, 122.3, 118.7, 112.5, 89.3, 52.9, 49.4, 45.8, 41.2, 27.8; m/z (ESI–MS) 426.1 [M + H]<sup>+</sup>. 
7a-trans-10a-trans-8-benzyl-11-(4-chlorophenyl)-7a,8,9,10a,11-hexahydrobenzo[5,6]chromeno[2,3-b]pyrrole (3.25c): Following the general procedure compound 3.25c was obtained from the corresponding 1-(aminomethyl)-β-naphthol and benzaldehyde as a colorless oil in 75% yield (Rf = 0.29 in hexanes/ethyl ether 93:7 v/v); IR (KBr) 3061, 3029, 2930, 2876, 2838, 1623, 1599, 1514, 1489, 1466, 1453, 1401, 1225, 1150, 1069, 1014, 966, 815, 745 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 7.88–7.82 (comp, 2H), 7.65 (d, J = 8.4 Hz, 1H), 7.51–7.46 (comp, 2H), 7.45–7.39 (comp, 3H), 7.38–7.30 (comp, 3H), 7.30–7.25 (comp, 2H), 7.20–7.14 (comp, 2H), 5.17 (d, J = 3.8 Hz, 1H), 4.62 (s, 1H), 4.39 (d, J = 13.5 Hz, 1H), 4.03 (d, J = 13.5 Hz, 1H), 3.11 (app td, J = 8.9, 5.6 Hz, 1H), 2.99 (app tdd, J = 10.0, 3.8, 1.7 Hz, 1H), 2.89–2.81 (m, 1H), 2.33–2.23 (m, 1H), 1.76 (app dtd, J = 12.6, 10.3, 5.6 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 152.8, 143.7, 138.9, 133.0, 132.1, 129.2(3), 129.2(2), 129.0, 128.8, 128.6, 128.5, 128.2, 126.9, 126.5, 123.0, 122.1, 118.9, 112.0, 89.3, 53.6, 49.3, 45.7, 40.7, 27.8; m/z (ESI–MS) 426.1 [M + H]⁺.

The title compound was further characterized by X-ray crystallography:

The requisite CIF has been deposited with the CCDC (deposition # 963308).

7a-trans-10a-trans-ethyl-8-benzyl-7a,8,9,10a,11-hexahydrobenzo[5,6]chromeno[2,3-b]pyrrole-11-carboxylate (3.25d): Following the general procedure compound 3.25d was obtained from the corresponding 1-(aminomethyl)-β-naphthol and benzaldehyde as a yellow oil in 72% yield (Rf = 0.40 in hexanes/ethyl acetate 85:15 v/v); IR (KBr) 3059, 3024, 2976, 2841, 1729, 1624, 1600, 1515, 1467, 1403, 1365, 1329, 1227, 1152, 1074, 1026, 970, 818, 747, 699 cm⁻¹; ¹H NMR (500 MHz, CDCl₃)
7.93 (d, J = 8.5 Hz, 1H), 7.81–7.77 (m, 1H), 7.73 (d, J = 8.9 Hz, 1H), 7.51 (ddd, J = 8.5, 6.9, 1.3 Hz, 1H), 7.46–7.42 (m, 2H), 7.40–7.33 (comp, 3H), 7.32–7.26 (m, 1H), 7.16 (d, J = 8.9 Hz, 1H), 5.44 (d, J = 4.2 Hz, 1H), 4.33 (d, J = 13.4 Hz, 1H), 4.27 (d, J = 1.4 Hz, 1H), 4.17–4.07 (comp, 2H), 3.97 (d, J = 13.4 Hz, 1H), 3.88 (d, J = 13.4 Hz, 1H), 3.11 (ddd, J = 9.8, 4.2, 1.6 Hz, 1H), 2.99 (td, J = 8.7, 5.6 Hz, 1H), 2.75–2.68 (m, 1H), 2.19–2.10 (m, 1H), 1.54 (app dtd, J = 12.6, 10.0, 5.5 Hz, 1H), 1.18 (t, J = 7.1 Hz, 3H); 

13C NMR (125 MHz, CDCl3) δ 173.3, 152.8, 138.9, 133.2, 129.5, 129.1, 128.7, 128.5, 128.3, 127.0, 126.6, 123.0, 121.8, 119.2, 109.0, 90.2, 61.1, 48.9, 41.5, 39.5, 27.1, 14.1; m/z (ESI–MS) 388.1 [M + H]+.

10a-cis-8-benzyl-7a,8,9,10,10a,11-hexahydrobenzo[5,6]chromeno[2,3-b]pyrrole (3.25e): Following the general procedure compound 3.25e was obtained from the corresponding 1-(aminomethyl)-β-naphthol and benzaldehyde as a colorless oil in 73% yield (Rf = 0.22 in hexanes/ethyl ether 93:7 v/v); IR (KBr) 3056, 3027, 2970, 2905, 2852, 1622, 1597, 1512, 1495, 1469, 1452, 1398, 1362, 1317, 1236, 1177, 1152, 1069, 930, 831, 814, 746, 726, 695 cm−1; 1H NMR (500 MHz, CDCl3) 7.89–7.83 (comp, 2H), 7.73 (d, J = 8.8 Hz, 1H), 7.59–7.49 (comp, 3H), 7.46–7.39 (comp, 3H), 7.38–7.32 (m, 1H), 7.22 (d, J = 8.8 Hz, 1H), 5.09 (d, J = 4.0 Hz, 1H), 4.36 (d, J = 13.4 Hz, 1H), 4.07 (d, J = 13.4 Hz, 1H), 3.26–3.06 (comp, 3H), 3.00–2.93 (m, 1H), 2.92–2.86 (m, 1H), 2.20–2.11 (m, 1H), 1.73 (app dtd, J = 12.5, 10.1, 6.1 Hz, 1H); 13C NMR (125 MHz, CDCl3) δ 151.9, 139.1, 133.1, 129.0, 128.7, 128.4, 128.2, 127.7, 126.9, 126.1, 122.9, 121.6, 119.2, 112.4, 91.3, 53.7, 49.7, 36.8, 27.9, 23.8; m/z (ESI–MS) 316.1 [M + H]+.

10a-cis-8-benzyl-2-methoxy-7a,8,9,10,10a,11-hexahydrobenzo[5,6]chromeno[2,3-b]pyrrole (3.25f): Following the general procedure compound 3.25f was obtained from the corresponding 1-(aminomethyl)-β-naphthol and benzaldehyde as a white solid in 68% yield (Rf = 0.32 in hexanes/ethyl acetate 85:15 v/v); mp: 98–100 °C; IR (KBr) 3086, 3029, 2997, 2942, 2909, 2874, 2839, 1621, 1513, 1494, 1422, 1365, 1316, 1221, 1175, 1152, 1135, 1080, 1037, 1028, 936, 838, 740, 697 cm−1; 1H NMR (500 MHz, CDCl3) 7.73 (d, J = 8.8 Hz, 1H), 7.64 (d, J = 8.8 Hz, 1H), 7.54–7.48 (m, 2H), 7.45–7.38 (m, 2H), 7.36–7.31 (m, 1H), 7.12 (d, J = 2.3 Hz, 1H), 7.10–7.04 (comp, 2H), 5.06 (d, J
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= 3.9 Hz, 1H), 4.35 (d, J = 13.3 Hz, 1H), 4.05 (d, J = 13.3 Hz, 1H), 3.97 (s, 3H), 3.21–3.14 (m, 1H), 3.14–3.02 (comp, 2H), 3.00–2.92 (m, 1H), 2.92–2.85 (m, 1H), 2.21–2.12 (m, 1H), 1.74 (app dtd, J = 12.5, 10.1, 6.1 Hz, 1H); 13C NMR (125 MHz, CDCl3) δ 158.1, 152.4, 139.1, 134.3, 129.9, 128.7, 128.2, 127.4, 126.9, 116.6, 114.8, 111.3, 101.0, 91.1, 55.1, 53.7, 49.7, 36.7, 27.9, 24.0; m/z (ESI–MS) 346.2 [M + H]+.

10a-cis-8-benzyl-3-bromo-7a,8,9,10a,11-hexahydrobenzo[5,6]chromeno[2,3- b]pyrrole (3.25g): Following the general procedure compound 3.25g was obtained from the corresponding 1-(aminomethyl)-β-naphthol and benzaldehyde as a white solid in 61% yield (Rf = 0.43 in hexanes/ethyl acetate 85:15 v/v); mp: 143–145 ºC; IR (KBr) 3058, 3026, 2972, 2903, 2840, 1615, 1587, 1496, 1464, 1394, 1366, 1316, 1233, 1176, 1149, 1075, 1065, 973, 926, 878, 806, 781, 753, 699 cm−1; 1H NMR (500 MHz, CDCl3) 7.92 (s, 1H), 7.65 (d, J = 8.9 Hz, 1H), 7.59–7.51 (comp, 2H), 7.45 (app d, J = 7.5 Hz, 2H), 7.37 (app t, J = 7.5 Hz, 2H), 7.33–7.27 (m, 1H), 7.14 (d, J = 8.9 Hz, 1H), 5.03 (d, J = 3.8 Hz, 1H), 4.28 (d, J = 13.4 Hz, 1H), 4.00 (d, J = 13.4 Hz, 1H), 3.21–3.11 (m, 1H), 3.10–3.00 (comp, 2H), 2.97–2.88 (m, 1H), 2.87–2.79 (m, 1H), 2.17–2.06 (m, 1H), 1.71–1.59 (m, 1H); 13C NMR (125 MHz, CDCl3) δ 152.2, 139.0, 131.7, 130.3, 130.2, 129.3, 128.7, 128.3, 126.9, 126.8, 123.5, 120.3, 116.6, 112.6, 91.4, 53.7, 49.7, 36.6, 27.8, 23.8; m/z (ESI–MS) 394.2 (79Br) [M + H]+, 396.2 (81Br) [M + H]+.

10a-cis-8-(2-chlorobenzyl)-7a,8,9,10a,11-hexahydrobenzo[5,6]chromeno[2,3-b]pyrrole (3.25h): Following the general procedure compound 3.25h was obtained from the corresponding 1-(aminomethyl)-β-naphthol and 2-chlorobenzaldehyde as a yellow oil in 74% yield (Rf = 0.40 in hexanes/ethyl ether 90:10 v/v); IR (KBr) 3061, 2929, 2841, 1624, 1599, 1467, 1435, 1399, 1363, 1227, 1178, 1151, 1076, 926, 811, 746 cm−1; 1H NMR (500 MHz, CDCl3) 7.89–7.80 (comp, 2H), 7.71 (d, J = 8.8 Hz, 1H), 7.61–7.56 (m, 1H), 7.56–7.51 (m, 1H), 7.44 (dd, J = 7.8, 1.2 Hz, 1H), 7.42–7.37 (m, 1H), 7.30 (app td, J = 7.4, 1.2 Hz, 1H), 7.25 (app td, J = 7.6, 1.7 Hz, 1H), 7.19 (d, J = 8.8 Hz, 1H), 5.10 (d, J = 4.0 Hz, 1H), 4.48 (d, J = 14.5 Hz, 1H), 4.17 (d, J = 14.5 Hz, 1H), 3.27–3.18 (m, 1H), 3.17–3.07 (comp, 2H), 3.02–2.89 (comp, 2H), 2.19–
2.09 (m, 1H), 1.74 (app dtd, \( J = 12.5, 10.1, 6.4 \text{ Hz}, 1H \));  
\(^{13}\text{C NMR (125 MHz, CDCl}_3\) \( \delta 151.8, 136.8, 134.0, 133.1, 130.3, 129.4, 129.1, 128.4, 128.1, 127.7, 126.5, 126.1, 123.0, 121.7, 119.3, 112.4, 91.7, 50.9, 49.9, 36.8, 28.0, 23.8; m/z (ESI–MS) 350.2 [M + H]⁺.

10a-cis-8-(3-chlorobenzyl)-7a,8,9,10a,11-hexahydrobenzo[5,6]chromeno[2,3-b]pyrrole

Following the general procedure compound \( \text{3.25i} \) was obtained from the corresponding 1-(aminomethyl)-β-naphthol and 3-chlorobenzaldehyde as a yellow oil in 72% yield (Rf = 0.31 in hexanes/ethyl ether 90:10 v/v); IR (KBr) 3061, 2929, 2844, 1624, 1599, 1575, 1514, 1468, 1434, 1399, 1362, 1228, 1178, 1150, 1075, 811, 746, 684 cm⁻¹; \(^{1}H\) NMR (500 MHz, CDCl₃) 7.87–7.79 (comp, 2H), 7.69 (d, \( J = 8.8 \text{ Hz}, 1H \)), 7.55–7.46 (comp, 2H), 7.41–7.35 (m, 1H), 7.35–7.27 (comp, 3H), 7.15–7.06 (m, 1H), 7.03–6.94 (m, 1H), 6.92–6.83 (m, 1H), 6.80–6.71 (m, 1H), 2.20–2.11 (m, 1H), 1.73 (app dtd, \( J = 12.6, 10.1, 6.2 \text{ Hz}, 1H \)); \(^{13}\text{C NMR (125 MHz, CDCl}_3\) \( \delta 151.7, 141.4, 134.1, 133.1, 129.5, 129.1, 128.7, 128.4, 127.7, 127.0, 126.7, 126.2, 123.0, 121.7, 119.1, 112.3, 91.3, 53.2, 49.7, 36.7, 27.9, 23.8; m/z (ESI–MS) 350.2 [M + H]⁺.

10a-cis-8-(4-methylbenzyl)-7a,8,9,10a,11-hexahydrobenzo[5,6]chromeno[2,3-b]pyrrole

Following the general procedure compound \( \text{3.25j} \) was obtained from the corresponding 1-(aminomethyl)-β-naphthol and p-tolualdehyde as a yellow oil in 74% yield (Rf = 0.26 in hexanes/ethyl ether 90:10 v/v); IR (KBr) 3051, 2920, 2843, 1624, 1599, 1514, 1467, 1399, 1228, 1177, 1151, 1075, 926, 810, 746 cm⁻¹; \(^{1}H\) NMR (500 MHz, CDCl₃) 7.73 (d, \( J = 8.9 \text{ Hz}, 1H \)), 7.60–7.52 (m, 1H), 7.46–7.38 (comp, 3H), 7.29–7.19 (comp, 3H), 5.08 (d, \( J = 3.9 \text{ Hz}, 1H \)), 4.32 (d, \( J = 13.2 \text{ Hz}, 1H \)), 4.03 (d, \( J = 13.2 \text{ Hz}, 1H \)), 3.27–3.19 (m, 1H), 3.18–3.06 (comp, 2H), 3.01–2.92 (m, 1H), 2.92–2.86 (m, 1H), 2.44 (s, 3H), 2.20–2.11 (m, 1H), 1.73 (app dtd, \( J = 12.6, 10.1, 6.2 \text{ Hz}, 1H \)); \(^{13}\text{C NMR (125 MHz, CDCl}_3\) \( \delta 151.9, 136.4, 136.0, 133.1, 129.0, 128.9, 128.7, 128.4, 127.6, 126.1, 122.9, 121.6, 119.2, 112.3, 91.2, 53.4, 49.7, 36.7, 27.8, 23.8, 21.1; m/z (ESI–MS) 330.3 [M + H]⁺.
10a-cis-8-(4-methoxybenzyl)-7a,8,9,10a,11-hexahydrobenzo[5,6]chromeno[2,3-b]pyrrole (3.25k): Following the general procedure compound 3.25k was obtained from the corresponding 1-(aminomethyl)-β-naphthol and p-anisaldehyde as a white solid in 71% yield (Rf = 0.32 in hexanes/ethyl acetate 85:15 v/v); mp: 89–90 °C; IR (KBr) 3054, 3004, 2902, 2835, 1622, 1610, 1597, 1512, 1467, 1435, 1398, 1362, 1248, 1227, 1178, 1144, 1073, 1028, 929, 816, 769, 745 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 7.89–7.79 (comp, 2H), 7.70 (d, J = 8.8 Hz, 1H), 7.56–7.49 (m, 1H), 7.45–7.35 (comp, 3H), 7.18 (d, J = 8.8 Hz, 1H), 6.98–6.90 (m, 2H), 5.04 (d, J = 3.9 Hz, 1H), 4.25 (d, J = 13.1 Hz, 1H), 3.97 (d, J = 13.1 Hz, 1H), 3.85 (s, 3H), 3.24–3.16 (m, 1H), 3.15–3.02 (comp, 2H), 2.98–2.89 (m, 1H), 2.89–2.82 (m, 1H), 2.18–2.09 (m, 1H), 1.70 (app dt, J = 12.5, 10.1, 6.1 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 158.6, 151.9, 133.1, 131.1, 129.9, 129.0, 128.4, 127.6, 126.1, 122.9, 119.2, 113.6, 112.4, 91.0, 55.2, 53.0, 49.6, 36.7, 27.8, 23.8; m/z (ESI–MS) 346.2 [M + H]+.

3a-trans-9a-trans-1-benzyl-6-chloro-4-phenyl-1,2,3,3a,4,9a-hexahydrochromeno[2,3-b]pyrrole (3.25l): Following the general procedure compound 3.25l was obtained from the corresponding 2-(aminomethyl)-phenol and benzaldehyde as a yellow oil in 79% yield (6.5:1 mixture of two diastereomers) (Rf = 0.39 in hexanes/ethyl ether 93:7 v/v); Characterization data of the major diastereomer: IR (KBr) 3083, 3061, 3027, 2932, 2878, 2842, 1598, 1579, 1482, 1453, 1363, 1220, 1194, 1156, 1093, 1029, 846, 816, 738, 700 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) 7.44–7.38 (comp, 3H), 7.38–7.34 (comp, 3H), 7.34–7.31 (m, 1H), 7.31–7.26 (comp, 2H), 7.22 (dd, J = 8.6, 2.5 Hz, 1H), 7.20–7.13 (comp, 2H), 7.03 (d, J = 2.5 Hz, 1H), 6.97 (d, J = 8.6 Hz, 1H), 5.07 (d, J = 4.6 Hz, 1H), 4.24 (d, J = 13.7 Hz, 1H), 4.04–3.96 (comp, 2H), 3.02–2.78 (comp, 3H), 2.26–2.13 (m, 1H), 1.77–1.64 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 153.8, 143.9, 138.8, 129.8, 128.6, 128.5, 128.2(1), 128.1(8), 127.8, 126.9, 126.6, 125.8, 125.0, 118.1, 91.5, 53.7, 49.1, 45.5, 45.4, 28.1; m/z (ESI–MS) 376.1 [M + H]+.
**3a-trans-9a-trans-1-benzyl-6-methoxy-4-phenyl-1,2,3,3a,4,9a-hexahydrochromeno[2,3-b]pyrrole (3.25m):** Following the general procedure, compound 3.25m was obtained from the corresponding 2-(aminomethyl)-phenol and benzaldehyde as a yellow oil in 60% (7.5:1 mixture of two diastereomers) (Rf = 0.26 in hexanes/ethyl ether 93:7 v/v); Characterization data of the major diastereomer:

IR (KBr) 3081, 3060, 3027, 2934, 2832, 1601, 1494, 1453, 1362, 1272, 1208, 1150, 1041, 950, 875, 851, 739, 700 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) 7.44–7.37 (comp, 3H), 7.37–7.31 (comp, 4H), 7.31–7.25 (comp, 2H), 7.24–7.19 (comp, 2H), 6.97 (d, J = 8.8 Hz, 1H), 6.84 (dd, J = 8.8, 3.0 Hz, 1H), 6.58 (d, J = 3.0 Hz, 1H), 5.02 (d, J = 4.9 Hz, 1H), 4.22 (d, J = 13.6 Hz, 1H), 4.03 (d, J = 13.6 Hz, 1H), 3.98 (d, J = 3.2 Hz, 1H), 3.74 (s, 3H), 2.98–2.80 (comp, 3H), 2.24–2.11 (m, 1H), 1.79–1.67 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 153.6, 149.0, 144.2, 139.0, 128.6, 128.5, 128.2, 128.0, 126.8, 126.4, 125.8, 117.5, 114.8, 113.7, 91.4, 55.5, 53.9, 49.3, 46.1, 45.9, 28.5; m/z (ESI–MS) 372.1 [M + H]+.

**9a-cis-1-benzyl-1,2,3,3a,4,9a-hexahydrochromeno[2,3-b]pyrrole (3.25n):** Following the general procedure, compound 3.25n was obtained from the corresponding 2-(aminomethyl)-phenol and benzaldehyde as a colorless oil in 38% yield (Rf = 0.31 in hexanes/ethyl ether 90:10 v/v); IR (KBr) 3062, 3026, 2931, 2840, 1603, 1585, 1487, 1456, 1364, 1226, 1150, 1108, 895, 805, 753, 700 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 7.48–7.43 (m, 2H), 7.42–7.37 (m, 2H), 7.34–7.29 (m, 1H), 7.24–7.18 (m, 1H), 7.15–7.10 (m, 1H), 6.98–6.91 (comp, 2H), 5.10 (d, J = 5.2 Hz, 1H), 4.22 (d, J = 13.4 Hz, 1H), 4.05 (d, J = 13.4 Hz, 1H), 3.04 (dd, J = 15.6, 5.9 Hz, 1H), 2.93–2.83 (comp, 2H), 2.77 (app td, J = 9.0, 5.0 Hz, 1H), 2.63 (dd, J = 15.6, 2.6 Hz, 1H), 2.10–2.00 (m, 1H), 1.65–1.56 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 155.3, 149.0, 144.2, 139.0, 128.7, 128.2, 127.4, 126.8, 123.5, 120.5, 116.9, 93.0, 53.8, 49.8, 37.7, 28.3, 27.7; m/z (ESI–MS) 266.0 [M + H]+.
7a-trans-11a-trans-8-benzyl-12-phenyl-8,9,10,11,11a,12-hexahydro-7aH-benzo[5,6]chrome pyridine (3.25o): Following the general procedure compound 3.25o was obtained from the corresponding 1-(aminomethyl)-β-naphthol and benzaldehyde as an off-white solid in 75% yield (R_f = 0.44 in hexanes/ethyl ether 93:7 v/v); mp = 177–179 °C; IR (KBr) 3081, 3059, 3017, 2966, 2966, 2935, 2862, 1622, 1598, 1492, 1464, 1450, 1403, 1230, 1148, 1083, 987, 843, 813, 749, 728, 700 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 7.86–7.77 (comp, 2H), 7.57 (d, J = 7.8 Hz, 1H), 7.43–7.38 (comp, 2H), 7.37–7.26 (comp, 8H), 7.26–7.21 (m, 1H), 7.21–7.16 (comp, 2H), 5.01 (s, 1H), 4.48 (s, 1H), 4.12 (d, J = 13.9 Hz, 1H), 4.03 (d, J = 13.9 Hz, 1H), 2.83 (app td, J = 10.9, 4.4 Hz, 1H), 2.66–2.58 (m, 1H), 2.42–2.34 (m, 1H), 1.84–1.69 (comp, 3H), 1.65–1.53 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 152.7, 145.8, 139.1, 133.2, 129.3, 128.9, 128.4(8), 128.4(7), 128.4, 128.2, 128.1, 126.8, 126.3(0), 126.2(5), 123.0, 122.7, 118.8, 112.1, 85.5, 59.0, 45.6, 44.0, 42.0, 25.8, 25.0; m/z (ESI–MS) 406.2 [M + H]⁺.

The title compound was further characterized by X-ray crystallography:

The requisite CIF has been deposited with the CCDC (deposition # 963307).

4a-trans-10a-trans-1-benzyl-7-chloro-5-phenyl-2,3,4,4a,5,10a-hexahydro-1H-chromeno[2,3-b]pyridine (3.25p): Following the general procedure compound 3.25p was obtained from the corresponding 2-(aminomethyl)-phenol and benzaldehyde as a yellow oil in 67% yield (7.5:1 mixture of two diastereomers) (R_f = 0.46 in hexanes/ethyl ether 93:7 v/v); Characterization data of the major diastereomer: IR (KBr) 3081, 3061, 3026, 2929, 2853, 1601, 1576, 1481, 1452, 1403, 1355, 1265, 1234, 1169, 1111, 977, 939, 851, 828, 815, 737, 700 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) 7.36–7.29 (comp, 7H), 7.29–
7.24 (comp, 2H), 7.20 (dd, $J = 8.7, 2.6$ Hz, 1H), 7.09–7.03 (comp, 2H), 7.00 (d, $J = 2.6$ Hz, 1H), 6.96 (d, $J = 8.7$ Hz, 1H), 4.84 (d, $J = 2.1$ Hz, 1H), 4.02 (d, $J = 13.9$ Hz, 1H), 3.99–3.92 (comp, 2H), 2.81–2.70 (m, 1H), 2.61–2.50 (m, 1H), 2.28–2.14 (m, 1H), 1.79–1.61 (comp, 3H); 1H NMR (500 MHz, CDCl$_3$) $\delta$ 153.6, 145.5, 138.9, 130.4, 128.4(3), 128.4(1), 128.3, 128.1, 128.0, 126.8, 126.4, 124.6, 122.9, 117.8, 86.2, 58.8, 48.1, 44.0, 41.5, 25.7, 24.8; m/z (ESI–MS) 390.1 [M + H]$^+$.  

7a-trans-11a-trans-8-benzyl-12-phenyl-7a,8,9,10,11a,12-hexahydrobenzo[5,6]chromeno[3,2-b][1,4]oxazine (3.25q): Following the general procedure compound 3.25q was obtained from the corresponding 1-(aminomethyl)-β-naphthol and benzaldehyde as a yellow oil in 40% yield (R$_f$ = 0.20 in hexanes/ethyl ether 93:7 v/v); IR (KBr) 3060, 3025, 2962, 2908, 2851, 1624, 1600, 1515, 1493, 1467, 1450, 1346, 1227, 1127, 1099, 1066, 1014, 975, 835, 744, 699 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) 7.83–7.77 (comp, 2H), 7.58–7.53 (m, 1H), 7.43–7.38 (comp, 2H), 7.38–7.34 (comp, 2H), 7.34–7.28 (comp, 6H), 7.26–7.21 (comp, 3H), 4.87 (s, 1H), 4.83 (d, $J = 1.9$ Hz, 1H), 4.15–4.09 (comp, 2H), 4.03 (d, $J = 13.6$ Hz, 1H), 3.98–3.93 (m, 1H), 3.88 (app td, $J = 11.7, 2.8$ Hz, 1H), 3.08 (app td, $J = 11.7, 3.7$ Hz, 1H), 2.45–2.39 (m, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 152.3, 142.0, 138.0, 132.8, 129.5, 129.2, 128.7(5), 128.7(3), 128.6(6), 128.4, 128.3, 127.1, 126.9, 126.4, 123.0, 122.7, 118.3, 111.1, 82.1, 76.4, 67.2, 58.4, 45.1, 43.5; m/z (ESI–MS) 408.1 [M + H]$^+$.  

7a-cis-11a-cis-8-benzyl-10,11a-dimethyl-7a,8,9,10,11a,12-hexahydrobenzo[5,6]chromeno  

|3,2-b][1,4]oxazine (3.25r): Following the general procedure compound 3.25r was obtained from the corresponding 1-(aminomethyl)-β-naphthol and benzaldehyde as a yellow oil in 65% yield (5:1 mixture of two diastereomers) (R$_f$ = 0.37 in hexanes/ethyl ether 93:7 v/v); Characterization data of the major diastereomer: IR (KBr) 3061, 3026, 2972, 2932, 2896, 2845, 1626, 1602, 1470, 1401, 1263, 1231, 1109, 1070, 991, 912, 809, 745, 699 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) 7.83–7.76 (comp, 2H), 7.70 (d, $J = 8.8$ Hz, 1H), 7.55–7.50 (comp, 3H), 7.46–7.39 (comp, 2H), 7.39–7.34 (comp, 2H), 7.20 (d, $J = 8.8$ Hz, 1H), 4.54 (s, 1H), 4.30–4.19 (m, 1H), 4.16 (d, $J = 13.6$ Hz, 1H), 3.95 (d, $J = 13.6$ Hz, 1H), 3.35 (d, $J = 17.4$ Hz, 1H), 3.00 (d, $J = 17.4$ Hz, 1H), 2.80 (app t, $J = 11.1$ Hz, 1H), 2.54 (app t, $J = 11.1$ Hz, 1H), 2.44 (app t, $J = 11.1$ Hz, 1H).
2.50 (dd, J = 11.1, 3.0 Hz, 1H), 1.67 (s, 3H), 1.09 (d, J = 6.1 Hz, 3H); 13C NMR (100 MHz, CDCl3) δ 151.3, 138.5, 132.6, 128.8(5), 128.7(9), 128.3, 127.5, 127.1, 126.1, 122.8, 121.8, 118.2, 113.5, 110.9, 87.5, 71.0, 69.5, 65.6, 58.1, 50.8, 36.1, 22.4; m/z (ESI–MS) 360.1 [M + H]+.

11-cis-8-(2,6-dichlorobenzyl)-7a,8,9,10,11a,12-hexahydrobenzo[5,6]chromeno[3,2-b][1,4]thiazine (3.25s): Following the general procedure (reaction performed at 180 °C for 45 minutes) compound 3.25s was obtained from the corresponding 1-(aminomethyl)-β-naphthol and 2,6-dichlorobenzaldehyde as a yellow oil in 53% yield (Rf = 0.59 in hexanes/ethyl acetate 85:15 v/v); IR (KBr) 3061, 2928, 2910, 2849, 1624, 1600, 1581, 1435, 1400, 1228, 1209, 1154, 1061, 986, 926, 888, 812, 768, 739 cm−1; 1H NMR (500 MHz, CDCl3) 7.81–7.76 (m, 1H), 7.74–7.66 (comp, 2H), 7.48 (app td, J = 6.8, 1.3 Hz, 1H), 7.37–7.29 (comp, 3H), 7.18–7.13 (comp, 2H), 4.91 (d, J = 1.3 Hz, 1H), 4.31 (d, J = 13.3 Hz, 1H), 4.24 (d, J = 13.3 Hz, 1H), 3.68–3.63 (m, 1H), 3.54 (app d, J = 17.5, 6.8 Hz, 1H), 3.36 (app td, J = 11.8, 2.7 Hz, 1H), 3.10 (app d, J = 17.5 Hz, 1H), 3.06–2.97 (m, 1H), 2.88 (app dt, J = 11.8, 3.2 Hz, 1H), 2.53 (app dt, J = 13.3, 2.7 Hz, 1H); 13C NMR (125 MHz, CDCl3) δ 150.9, 137.1, 134.3, 132.8, 129.1(1), 129.0(7), 128.5, 128.4, 128.2, 126.3, 123.2, 121.7, 119.0, 110.6, 85.6, 53.9, 45.2, 37.2, 28.9, 28.5; m/z (ESI–MS) 415.9 (35Cl/37Cl) [M + H]+, 417.9 (35Cl/35Cl) [M + H]+.

11-cis-benzyl-8-(2,6-dichlorobenzyl)-9,10,11a,12-tetrahydro-7aH-benzo[5,6]chromeno[2,3-b]pyrazine (3.25t): Following the general procedure (reaction performed at 170 °C for 45 minutes) compound 3.25t was obtained from the corresponding 1-(aminomethyl)-β-naphthol and 2,6-dichlorobenzaldehyde as a yellow oil in 58% yield (Rf = 0.21 in hexanes/ethyl acetate 90:10 v/v); IR (KBr) 3061, 3031, 2950, 2854, 2821, 1701, 1627, 1561, 1435, 1354, 1314, 1270, 1225, 1117, 1082, 968, 904, 811, 768, 746, 696 cm−1; 1H NMR (500 MHz, CDCl3) 7.82–7.73 (comp, 2H), 7.62 (d, J = 8.9 Hz, 1H), 7.53–7.46 (m, 1H), 7.44–7.29 (comp, 5H), 7.18–7.11 (m, 2H), 7.10–6.99 (comp, 2H), 5.20 (s, 2H), 4.86–4.78 (m, 1H), 4.60–4.49 (comp, 2H), 4.00–3.90 (m, 1H), 3.63 (app d, J = 12.6 Hz, 1H), 3.40 (dd, J = 15.6, 11.0 Hz, 1H), 3.35–3.25 (m, 1H), 3.12 (dd, J = 15.6, 6.4 Hz, 1H), 2.83–2.73 (m, 1H), 2.56 (app td, J = 11.9, 3.9
110 Hz, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 155.2, 148.8, 137.1, 136.3, 133.4, 132.5, 129.2, 128.8, 128.5, 128.4, 128.2, 128.1, 128.0, 127.8, 126.3, 123.4, 121.7, 118.3, 112.1, 87.0, 67.5, 50.8, 49.9, 49.0, 39.0, 21.0; $m/z$ (ESI–MS) 533.0 ($^{35}$Cl/$^{37}$Cl) [M + H]$^+$, 535.0 ($^{35}$Cl/$^{37}$Cl) [M + H]$^+$.

Transformation of α,β-difunctionalized amines:

1-((1-benzylpyrrolidin-3-yl)methyl)naphthalen-2-ol (3.28): To a solution of 3.25e (0.25 mmol, 1 equiv) in dry THF (2.5 mL) cooled in an ice bath, LiAlH$_4$ (0.75 mmol, 3 equiv) was added in one portion. The resulting mixture was stirred at 0 °C for one hour, then quenched with saturated aqueous NH$_4$Cl. The mixture was filtered through a short pad of celite and washed with EtOAc (6 x 5 mL). The filtrate was then washed with saturated aqueous NaHCO$_3$ (3 x 10 mL). The combined aqueous layer was extracted with EtOAc (3 x 10 mL), and the combined organic layer was washed with water (40 mL), brine (40 mL), and dried over anhydrous Na$_2$SO$_4$. Solvent was then removed under reduced pressure. The residue was purified by silica gel chromatography as a yellow oil in 69% yield ($R_f = 0.31$ in ethyl acetate); IR (KBr) 3060, 3026, 2955, 2873, 2814, 1623, 1595, 1514, 1454, 1437, 1354, 1265, 1242, 814, 748, 700 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) 9.51 (br s, 1H), 7.88 (d, $J = 8.4$ Hz, 1H), 7.79 (d, $J = 8.0$ Hz, 1H), 7.66 (d, $J = 8.8$ Hz, 1H), 7.58–7.04 (comp, 8H), 4.07 (d, $J = 12.5$ Hz, 1H), 3.42 (d, $J = 12.5$ Hz, 1H), 3.27 (dd, $J = 14.5$, 6.7 Hz, 1H), 3.22–3.13 (m, 1H), 3.11–2.97 (m, 1H), 2.87–2.60 (comp, 2H), 2.51–2.22 (comp, 2H), 2.21–2.04 (m, 1H), 1.93–1.77 (m, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 155.1, 137.1, 133.3, 129.3, 128.9, 128.5, 127.8, 127.5, 126.0, 122.5(4), 122.4(8), 119.6, 118.3, 60.1, 57.8, 50.2, 36.8, 30.6, 29.8; $m/z$ (ESI–MS) 318.2 [M + H]$^+$.

1-((1-benzyl-2-methylpyrrolidin-3-yl)methyl)naphthalen-2-ol (3.29a): To a solution of 3.25e (0.25 mmol, 1 equiv) in dry THF (2.5 mL) cooled in an ice bath, MeMgBr (0.5 mmol, 2 equiv, 3 molar solution in THF) was added. The resulting mixture was warmed up to room temperature and stirred for 30 minutes, then quenched with saturated aqueous NH$_4$Cl. The mixture was diluted with EtOAc (10 mL) and washed with saturated aqueous NaHCO$_3$ (3 x 10 mL). The combined aqueous layer was extracted with EtOAc (3 x 10 mL), and the combined organic layer was washed with water (40
mL), brine (40 mL), and dried over anhydrous Na$_2$SO$_4$. Solvent was then removed under reduced pressure. The residue was purified by silica gel chromatography as a yellow oil in 86% yield (3:1 mixture of two diastereomers) ($R_f = 0.44$ in ethyl acetate); IR (KBr) 3061, 3026, 2964, 2873, 2794, 1624, 1601, 1514, 1453, 1436, 1376, 1355, 1267, 1243, 1143, 812, 745, 700 cm$^{-1}$; $^1$H NMR (Note: due to overlapping peaks, integration values of the diastereomers are reported together) (500 MHz, CDCl$_3$) 9.61 (br s, 1.03H), 7.95 (d, $J = 8.6$ Hz, 0.35H), 7.89 (d, $J = 8.6$ Hz, 1.04H), 7.81–7.73 (comp, 1.38H), 7.61 (d, $J = 8.8$ Hz, 1.02H), 7.57 (d, $J = 8.8$ Hz, 0.40H), 7.52–7.28 (comp, 9.89H), 7.12 (d, $J = 8.8$ Hz, 1.00H), 6.97 (d, $J = 8.8$ Hz, 0.32H), 4.15 (d, $J = 12.7$ Hz, 1.0H), 3.85 (d, $J = 12.4$ Hz, 0.34H), 3.66 (d, $J = 12.4$ Hz, 0.33H), 3.43 (d, $J = 12.7$ Hz, 1.03H), 3.29 (dd, $J = 14.5$, 7.4 Hz, 1.07H), 3.24–3.09 (comp, 1.79H), 2.90–2.82 (m, 1.03H), 2.81–2.69 (comp, 3.09H), 2.54–2.46 (m, 0.34H), 2.28–2.19 (m, 1.02H), 1.93 (ddd, $J = 17.5$, 12.5, 8.7 Hz, 0.35H), 1.71–1.51 (comp, 2.57H), 1.45 (d, $J = 6.6$ Hz, 3.07H), 1.15 (d, $J = 6.3$ Hz, 1.01H); $^{13}$C NMR of the diastereomers (125 MHz, CDCl$_3$) δ 153.9, 153.3, 137.7, 136.8, 134.1, 133.5, 129.6, 129.4, 129.0, 128.7, 128.5(0), 128.4(7), 128.4(3), 128.3, 127.6, 127.5, 127.4, 127.3, 125.9(0), 125.8(8), 122.9, 122.7, 122.4, 122.3, 119.7, 119.4, 118.7(4), 118.6(8), 63.3, 62.9, 57.7, 56.9, 51.8, 49.6, 44.2, 40.7, 29.8, 28.1, 26.7, 24.1, 14.2, 13.6; m/z (ESI–MS) 332.2 [M + H]$^+$.

1-((1-benzyl-2-phenylpyrrolidin-3-yl)methyl)naphthalen-2-ol (3.29b): The synthetic procedure followed was the same as for 3.29a. Compound 3.29b was obtained from 3.25e and PhMgBr (1 molar solution in THF) as a yellow oil in 98% yield (3.5:1 of two diastereomers) ($R_f = 0.41$ in hexanes/ethyl acetate 80:20 v/v); IR (KBr) 3060, 3028, 2960, 2871, 2795, 1625, 1601, 1584, 1514, 1494, 1453, 1436, 1358, 1265, 1239, 1143, 1068, 1028, 958, 907, 812, 747, 701 cm$^{-1}$; $^1$H NMR (Note: due to overlapping peaks, integration values of the diastereomers are reported together) (500 MHz, CDCl$_3$) 7.80–7.66 (comp, 2.24H), 7.64–7.19 (comp, 19.25H), 7.04 (d, $J = 8.8$ Hz, 0.29H), 6.87 (d, $J = 8.8$ Hz, 1.00H), 6.11 (br s, 0.89H), 4.13 (d, $J = 13.2$ Hz, 0.24H), 3.93 (d, $J = 6.9$ Hz, 0.26H), 3.87 (d, $J = 13.0$ Hz, 0.95H), 3.35 (d, $J = 7.1$ Hz, 1.16H), 3.29–2.77 (comp, 5.26H), 2.72–2.55 (comp, 1.31H), 2.49 (app td, $J = 8.7$, 8.7 Hz, 1.06H), 2.34 (app td, $J = 8.5$, 8.5 Hz, 0.33H), 1.97–1.51 (comp, 2.76H); $^{13}$C NMR of the diastereomers (125 MHz, CDCl$_3$) δ 151.8, 151.2, 141.7,
138.9, 133.5, 133.3, 129.3, 129.2, 129.1, 129.0, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 127.7,
127.6, 127.5, 127.3, 127.1, 126.9, 126.1, 123.0, 122.9, 122.7, 118.8, 118.4, 117.8, 76.0, 72.5, 58.0,
51.9(2), 51.7(9), 49.5, 47.7, 42.4, 28.5, 28.0, 27.9, 26.2; \[m/z\] (ESI–MS) 394.2 [M + H]^+.
2D-NMR Analysis for Compound 3.25l, Selected Interactions:

![Diagram of Compound 3.25l](image)

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2D-NMR Analysis for Compound 3.25r, Selected Interactions:

![Diagram of Compound 3.25r](image)

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<td>1.09</td>
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References


(13) For examples of metal-free amine $\beta$–C–H bond functionalization with a simultaneous amine aromatization, see a modified Rügheimer-Burrows reaction developed by our group and references cited therein: Platonova, A. Y.; Seidel, D. Tetrahedron Lett. 2015, 56, 3147.


Chapter 4

Redox-Annulation of Cyclic Amines and β-Ketoaldehydes

4.1 Research Background

To further explore the chemical space of our redox-neutral methods for the amine functionalization, we successively developed a number of intramolecular redox-annulation reactions. Pyrrolidine and tetrahydroisoquinoline (THIQ) were demonstrated to undergo an intramolecular redox-Mannich reaction with ortho-malonate benzaldehydes in toluene in the presence of 10 equiv of 2-ethylhexanoic acid (Figure 4.1, eq 1), a strategy that was applied to the formal total syntheses of (±)-thalictricavine and its C14-epimer containing the tetrahydroprotoberberine core.1 THIQ reacts with enantioenriched 4-nitrobutyraldehydes which are readily obtained from the well-established organocatalytic conjugate addition between aldehydes and nitroalkenes, providing tricyclic compounds 4.4 and 4.5 enantiospecifically (Figure 4.1, eq 2).2 The reaction was performed in refluxing toluene with 10 equiv of acetic acid as the additive. Due to the enolizability of 4-nitrobutyraldehydes, this annulation usually provided a mixture of epimers with low diastereoselectivities, unless the aldehyde bears a secondary α-carbon. A notable feature of this reaction was that the regioselectivity could be changed by slightly altering the reaction conditions. Tricyclic compounds 4.6 and 4.7 functionalized at the 3-position of THIQ were isolated as the major regioisomers, by employing the slow addition of the aldehyde at elevated temperatures with 10 equiv of 2-EHA as the additive (Figure 4.1, eq 3). A detailed DFT study corroborated the mechanism in which an azomethine ylide intermediate is generated by the elimination of acetic acid from acetylated hemi-N,O-acetals. Yu and co-workers previously proposed a similar chemical process according to a computational study on the formation of pyrrole from 3-pyrroline and aldehydes.3 The annulation between THIQ and 4-nitrobutyraldehydes was applied to a facile total synthesis of (−)-protoemetinol.

Inspired by the redox-annulation reactions introduced above and the three-component intermolecular redox-Mannich reaction we have developed, we wanted to consider the opportunity to develop an intramolecular redox-Mannich reaction involving cyclic amines and readily
available β-ketoaldehydes. The annihilation products obtained from such a reaction are benzo[a]quinolizine-2-ones, which are core structures and important synthetic intermediates for a range of benzo[a]quinolizine natural products and bioactive compounds (Figure 4.2).

Figure 4.1 Redox-Annulation of Cyclic Amines with ortho-Malonate Benzaldehydes and 4-Nitrobutyraldehydes

\[
\text{4.1} \quad \begin{array}{c}
\text{CHO} \\
\text{CO}_2\text{Me} \\
\text{CO}_2\text{Me}
\end{array} + \begin{array}{c}
\text{NH}
\end{array} \xrightarrow{2\text{-EHA (10 equiv)}} \begin{array}{c}
\text{CHO} \\
\text{CO}_2\text{Me}
\end{array} \quad (1)
\]

\[
\text{4.2} \quad 51\%
\]

\[
\text{4.3} \quad \begin{array}{c}
\text{CHO} \\
\text{Ph}
\end{array} + \begin{array}{c}
\text{NH}
\end{array} \xrightarrow{2\text{-EHA (10 equiv)}} \begin{array}{c}
\text{H} \\
\text{N} \\
\text{Me}
\end{array} \quad (2)
\]

\[
\text{4.4} \quad \begin{array}{c}
\text{N}
\end{array} \quad \begin{array}{c}
\text{Me}
\end{array} \quad \begin{array}{c}
\text{Ph}
\end{array} \quad \begin{array}{c}
\text{N}
\end{array} \quad \begin{array}{c}
\text{Me}
\end{array} \quad \begin{array}{c}
\text{Ph}
\end{array}
\]

\[
\text{4.5} \quad 71\%, 4.4/4.5 = 2.1
\]

\[
\text{4.3} \quad \begin{array}{c}
\text{CHO} \\
\text{Ph}
\end{array} \xrightarrow{2\text{-EHA (10 equiv)}} \begin{array}{c}
\text{CHO} \\
\text{Ph}
\end{array} \quad (3)
\]

\[
\text{4.6} \quad \begin{array}{c}
\text{N}
\end{array} \quad \begin{array}{c}
\text{Me}
\end{array} \quad \begin{array}{c}
\text{Ph}
\end{array} \quad \begin{array}{c}
\text{N}
\end{array} \quad \begin{array}{c}
\text{Me}
\end{array} \quad \begin{array}{c}
\text{Ph}
\end{array}
\]

\[
\text{4.7} \quad 52\%, 4.6/4.7 = 1.2:1 \quad (4.6+4.7)/(4.6+4.7) = 9.6:1
\]

Figure 4.2 Selected Bioactive Compounds Containing the Benzo[a]quinolizine and Related Structural Motifs

4.2 Research Development

The optimization of reaction conditions involved THIQ and non-enolizable 2,2-dimethyl-3-oxobutyraldehyde. The optimal reaction conditions for the three-component intermolecular redox-Mannich reaction performed at low temperature with only catalytic amount of benzoic acid yielded complex reaction mixtures (Table 4.1, entry 1). Changing the additive to stoichiometric acetic acid resulted in successful isolation of the desired annihilation product, albeit
in only 12% yield (Table 4.1, entry 2). Similar to our previously developed redox-annulation reactions, an increase of acetic acid to 10 equiv dramatically improved the product yield to 71%, and higher additive loading gave nearly identical result (Table 4.1, entries 3–4). The other two carboxylic acids commonly used as additives in our redox-chemistry were tested as well. Product 4.9a was obtained in 65% yield with 10 equiv of benzoic acid (Table 4.1, entry 5), while 2-EHA was an inferior additive which only produced the product in 37% yield (Table 4.1, entry 6).

Table 4.1 Evaluation of Reaction Conditions for the Redox-Annulation between THIQ and 2,2-Dimethyl-3-oxobutyraldehyde

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<th>acid additive (equiv)</th>
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<tr>
<td>1b</td>
<td>PhCOOH (0.2)</td>
<td>complex</td>
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<tr>
<td>2</td>
<td>AcOH (1)</td>
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<tr>
<td>3</td>
<td>AcOH (10)</td>
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<td>4</td>
<td>AcOH (20)</td>
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<tr>
<td>5</td>
<td>PhCOOH (10)</td>
<td>65</td>
</tr>
<tr>
<td>6</td>
<td>2-EHA (10)</td>
<td>38</td>
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</table>

*Reactions were performed on a 0.5 mmol scale. All yields correspond to isolated yields of purified products. 2-EHA: 2-ethylhexanoic acid. bReaction was performed at 50 °C for 12 hours.

4.3 Scope of the Reaction

The optimal conditions were then applied to a number of non-enolizable β-ketoaldehydes (Figure 4.3). THIQ and tryptoline provided good yields of redox-annulation products upon reaction with 2,2-dimethyl-3-oxobutyraldehyde or 1-acetylcyclohexanecarbaldehyde. Substitution of THIQ at the 1-position was well tolerated. A reaction with 1-phenyl-THIQ gave rise to the desired product 4.9e in 51% yield. A reaction of THIQ with 2,2-dimethyl-3-oxophenylbutyraldehyde provided product 4.9g as a 2:1 mixture of diastereomers in a combined yield of 53%.
The scope of the β-ketoaldehyde was then extended to more challenging enolizable β-ketoaldehydes bearing only one substituent at the 2-position, considering that most relevant bioactive compounds only possess one substituent at the corresponding positions in the products (Figure 4.4). The standard conditions for the non-enolizable aldehydes employing direct refluxing of all starting materials were not applicable to enolizable aldehydes. Under such conditions, only low yields of the desired products were isolated, probably due to a competing aldol reaction. Gratifyingly, yields of the products could be significantly improved when the aldehydes were slowly added to a refluxing mixture of the amine and acetic acid. THIQ and tryptolines readily underwent the title reaction with 2-alkyl β-ketoaldehydes, providing the tricyclic products in moderate to good yields and synthetically useful diastereoselectivity. Reactions involving 2-benzyl-3-oxobutyraldehyde did not require slow addition, presumably due to the low solubility of this aldehyde in toluene minimizing the competing aldol reaction pathway. Notably, THIQ with electron-donating substituents on the aryl ring generally produced products in higher yields than the parent THIQ. Tryptoline with a free indole NH-proton failed to undergo the desired redox annulation with enolizable β-ketoaldehydes.
Reactions were performed on a 0.5 mmol scale. A solution of the aldehyde in 0.75 mL of toluene was added slowly over 15 h to a mixture of the amine, acetic acid and 4 Å MS in 2 mL of toluene. All yields correspond to isolated yields of purified products. All reagents were mixed directly and heated under reflux in toluene (0.25 M) for 20 hours.

The interconversion between benzo[a]quinolizine-2-one and the corresponding ring-opened isoquinolinium ions under acidic conditions is a well-known process. As a consequence, the diastereomeric ratios of the annulation products likely represent the thermodynamic equilibrium ratios of the two diastereomers. Consistent with this notion, exposure of either diastereomerically pure cis-4.9g or trans-4.9g to the optimal reaction conditions resulted in the identical 2:1 ratio of both diastereomers, the same ratio that was observed in the initial reaction (Figure 4.5). This experiment further served to establish the stability of the products under the reaction conditions, as the starting material was recovered essentially quantitatively.
In order to explore the reactivity of related carbonyl substrates, a $\beta$-diketone was used in place of a $\beta$-ketoaldehyde (Figure 4.6). Interestingly, acetylacetones such as 4.10 provided no expected product under the standard conditions for enolizable $\beta$-ketoaldehydes. Instead, N-acetyl THIQ was isolated in 80%. The formation of this species is consistent with a retro-Claisen pathway.\(^8\)

Products of the intramolecular redox-Mannich reaction, in particularly those shown in Figure 4.2, are closely related to a number of natural products and other bioactive compounds. For instance, compound 4.9n is known as tetrabenazine, a drug used to treat chorea such as Huntington’s disease.\(^9\) Enantiomerically pure (+)-4.9n is readily available via the resolution of the racemic mixture by (+)-camphorsulfonic acid.\(^{9b}\) Compound 4.9i has previously been converted to (±)-protoemetinol and (±)-emetin via short synthetic sequences.\(^{4a,5c}\)

### 4.5 Conclusion

In conclusion, we developed an intramolecular redox-Mannich reaction between cyclic amines and $\beta$-ketoaldehydes as a facile entry to benzo[a]quinolizine-2-one derivatives.
Challenging enolizable β-ketoaldehydes provided the desired products with useful levels of diastereoselectivity.
Experimental Section

General Information: See Chapter 2 Experimental Section.

6,7-Methylenedioxy-1,2,3,4-tetrahydroisoquinoline, 9-methyltryptoline, 2,2-dimethyl-3-oxobutyraldehyde, 1-acetylcyclohexanecarbaldehyde, 2,2-dimethyl-3-oxo-4-phenylbutyraldehyde, 4-benzylx-1-bromobutane, and 3-ethylpentane-2,4-dione were prepared according to literature procedures. Compounds 4.9n, 4.15a-4.15d, 4.17a, and 4.17d were previously reported and their published characterization data matched our own in all respects.

Scheme S1: Synthesis of 2-alkyl-3-oxobutyraldehydes:

methyl 2-acetyl-6-(benzyloxy)hexanoate (4.15e): To a suspension of NaH (60% in mineral oil, 0.96 g, 24 mmol, 1.2 equiv) in a mixture of dry toluene (12 mL) and DMF (10 mL) was slowly added methyl acetoacetate (2.16 mL, 20 mmol, 1 equiv) over 20 minutes at room temperature. The mixture was then allowed to stir for 15 minutes at room temperature before benzyloxy-1-bromobutane (5.83 g, 24 mmol, 1.2 equiv) was added in one portion. The reaction mixture was allowed to stir at 100 °C for 8 hours. After cooling to room temperature, the reaction was quenched by the addition of saturated aqueous NH₄Cl. 6 M HCl (5 mL) was then added to the reaction mixture. The reaction mixture was washed with water (2 x 75 mL), and the combined aqueous layers were extracted with ethyl ether (3 x 50 mL). The combined organic layers were then washed with brine (150 mL) and dried over anhydrous Na₂SO₄. Solvent was then removed under reduced pressure. The residue was purified by silica gel chromatography and compound 4.15e was obtained as a yellow oil in 77%
yield (4.29 g), (Rf = 0.22 in hexanes/EtOAc 90:10 v/v); IR (KBr) 2951, 2861, 1742, 1716, 1643, 1496, 1455, 1433, 1360, 1245, 1208, 1151, 1095, 737, 699 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 7.37-7.29 (comp, 4H), 7.29-7.24 (m, 1H), 4.51-4.45 (comp, 2H), 3.72 (s, 3H), 3.48-3.40 (comp, 3H), 2.21 (s, 3H), 1.92-1.79 (comp, 2H), 1.67-1.57 (comp, 2H), 1.42-1.31 (comp, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 203.0, 170.2, 138.5, 128.3, 127.6, 127.5, 72.9, 69.8, 59.6, 52.3, 29.4, 28.8, 28.0, 24.1; m/z (ESI–MS) 301.2 [M + Na]⁺.

**General Procedure A for converting 4.15 to 4.16:**

A mixture of 2-alkyl methyl acetoacetate (20 mmol, 1 equiv), ethylene glycol (1.34 mL, 24 mmol, 1.2 equiv) and p-TSA monohydrate (76 mg, 0.4 mmol, 0.02 equiv) in toluene (30 mL) was heated under reflux with a Dean-Stark apparatus for 18 hours. The reaction mixture was allowed to cool to room temperature and then diluted with ethyl ether (30 mL). The mixture was washed with saturated aqueous NaHCO₃ (3 x 30 mL), and the combined aqueous layers were washed with ethyl ether (3 x 30 mL). The combined organic layers were washed with brine and dried over anhydrous Na₂SO₄. Solvent was then removed under reduced pressure and the residue was further dried under high vacuum. The crude product was directly used in the next step without further purification.

**General Procedure B for converting 4.16 to 4.17:**

To an ice-cooled suspension of LiAlH₄ (1.43 g, 37.5 mmol, 2.5 equiv) in dry THF (60 mL) was slowly added a solution of compound 4.16 (15 mmol, 1 equiv) in dry THF (15 mL). The mixture was allowed to stir at room temperature for 2 hours, followed by quenching with 30% aqueous ammonia cooled in an ice bath. The lithium and aluminum hydroxide salts were then filtered through a short pad of celite and washed with EtOAc (6 x 50 mL). The solvent was then removed under reduced pressure, and the residue was purified by silica gel chromatography.

New compounds were characterized as below:
2-(2-methyl-1,3-dioxolan-2-yl)hexan-1-ol (4.17b): Following the general procedures A and B compound 4.17b was obtained from compound 4.15b as a colorless oil in 61% yield over two steps (1.72 g), (Rf = 0.34 in hexanes/EtOAc 70:30 v/v); IR (KBr) 3385, 2956, 2895, 2764, 1701, 1658, 1085, 1041, 882 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 3.99–3.94 (comp, 4H), 3.67–3.58 (comp, 2H), 2.96 (br s, 1H), 1.79–1.72 (m, 1H), 1.51–1.21 (comp, 8H), 1.17–1.08 (m, 1H), 0.88 (t, J = 7.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 113.1, 64.5, 64.2, 62.7, 47.8, 30.2, 26.6, 22.9, 20.5, 13.9; m/z (ESI–MS) 167.0 [M + Na–C₂H₄O]⁺.

4-methyl-2-(2-methyl-1,3-dioxolan-2-yl)pentan-1-ol (4.17c): Following the general procedures A and B compound 4.17c was obtained from compound 4.15c as a colorless oil in 64% yield over two steps (1.81 g), (Rf = 0.34 in hexanes/EtOAc 70:30 v/v); IR (KBr) 3385, 2957, 2935, 2873, 1701, 1643, 1465, 1418, 1369, 1247, 1208, 1186, 1085, 1041, 882 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 4.02–3.92 (comp, 4H), 3.63–3.57 (comp, 2H), 3.10 (br s, 1H), 1.89–1.83 (m, 1H), 1.68–1.57 (m, 1H), 1.29 (s, 3H), 1.89 (ddd, J = 13.7, 9.7, 3.2 Hz, 1H), 1.08 (ddd, J = 13.7, 9.9, 4.6 Hz, 1H), 0.92–0.85 (comp, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 113.2, 64.5, 64.2, 63.1, 45.4, 36.2, 25.9, 23.8, 21.7, 20.5; m/z (ESI–MS) 167.0 [M + Na–C₂H₄O]⁺.

6-(benzylxoy)-2-(2-methyl-1,3-dioxolan-2-yl)hexan-1-ol (4.17e): Following the general procedures A and B compound 4.17e was obtained from compound 4.15e as a colorless oil in 70% yield over two steps (3.09 g), (Rf = 0.26 in hexanes/EtOAc 70:30 v/v); IR (KBr) 3422, 2938, 2863, 2360, 2337, 1647, 1453, 1364, 1098, 1040, 946, 860 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 7.37–7.32 (comp, 4H), 7.30–7.25 (m, 1H), 4.50 (s, 2H), 4.00–3.92 (comp, 4H), 3.69–3.59 (comp, 2H), 3.47 (app t, J = 6.6 Hz, 2H), 3.00 (br s, 1H), 1.81–1.75 (m, 1H), 1.73–1.44 (comp, 4H), 1.43–1.33 (m, 1H), 1.30 (s, 3H), 1.21–1.12 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 138.6, 128.3, 127.6, 127.5, 113.0, 72.9, 70.2, 64.5, 64.2, 62.7, 47.9, 30.0, 26.8, 24.7, 20.5; m/z (ESI–MS) 317.2 [M + Na]⁺.
General Procedure C for converting 4.17 to 4.18:

To a stirred solution of oxalyl chloride (1.71 mL, 20 mmol, 2 equiv) in dry CH₂Cl₂ (20 mL) was slowly added dry DMSO (2.84 mL, 40 mmol, 4 equiv) at −78 ºC. The mixture was allowed to stir at the same temperature for 15 minutes, then a solution of the alcohol 4.17 (10 mmol, 1 equiv) in CH₂Cl₂ (25 mL) was slowly added. After stirring at −78 ºC for 30 minutes, NEt₃ (8.36 mL, 60 mmol, 6 equiv) was slowly added and the reaction mixture was allowed to warm to room temperature and stirred for another hour. The reaction mixture was diluted with ethyl ether (50 mL) and washed with water (3 x 50 mL). The combined aqueous layers were extracted with ethyl ether (3 x 50 mL). The combined organic layers were then washed with brine and dried over anhydrous Na₂SO₄. Solvent was then removed under reduced pressure and the crude product was directly used in the next step without further purification.

General Procedure D for converting 4.18 to 4.19:

The crude compound 7 (10 mmol) was dissolved in a mixture of THF (15 mL) and 3 M HCl (10 mL). The mixture was allowed to stir at room temperature for 12 hours. The reaction mixture was then diluted with ethyl ether (20 mL) and washed with water (3 x 30 mL). The combined aqueous layers were extracted with ethyl ether (3 x 30 mL). The combined organic layers were then washed with brine and dried over anhydrous Na₂SO₄. Solvent was then removed under reduced pressure and the residue was purified by Kugelrohr distillation (4.19a-c), recrystallization from EtOAc/hexanes (4.19d) or silica gel chromatography (4.19e).

New compounds were characterized as below:

2-ethyl-3-oxobutanal (4.19a): Following the general procedures C and D compound 4.19a was obtained from compound 4.17a as a white solid in 85% yield over two steps (0.97 g), (R_f = 0.39 in hexanes/EtOAc 90:10 v/v); mp: 39–41 ºC; IR (KBr) 2972, 2925, 2871, 1634, 1435, 1366, 1258, 1212, 1117, 1071, 1024, 912 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 7.86 (br s, 1H), 2.18 (q, J = 7.5 Hz, 2H), 2.14 (s, 3H), 1.05 (t, J = 7.5 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 195.7, 175.5, 114.4, 24.0, 21.0, 15.4; m/z (ESI–MS) 169.1 [M + Na + MeOH]+.
2-acetylhexanal (4.19b): Following the general procedures C and D compound 4.19b was obtained from compound 4.17b as a yellow oil in 87% yield over two steps (1.24 g), (R<sub>f</sub> = 0.56 in hexanes/EtOAc 80:20 v/v); IR (KBr) 2958, 2930, 2862, 2686, 1718, 1617, 1406, 1354, 1277, 1216, 1126, 1026, 961, 919 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.93 (d, <i>J</i> = 6.8 Hz, 1H), 2.17–2.11 (comp, 5H), 1.42–1.27 (comp, 4H), 0.91 (t, <i>J</i> = 7.2 Hz, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 194.7, 177.0, 112.9, 33.1, 27.4, 23.7, 13.8; m/z (ESI–MS) 142.7 [M + H]<sup>+</sup>.

2-acetyl-4-methylpentanal (4.19c): Following the general procedures C and D compound 4.19c was obtained from compound 4.17c as a white solid in 86% yield over two steps (1.23 g), (R<sub>f</sub> = 0.56 in hexanes/EtOAc 80:20 v/v); mp: 49–52 ºC; IR (KBr) 2958, 2866, 2364, 2340, 1705, 1637, 1408, 1235, 1129, 973 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.00 (d, <i>J</i> = 5.5 Hz, 1H), 2.12 (s, 3H), 2.02 (d, <i>J</i> = 7.2 Hz, 2H), 1.69–1.54 (m, 1H), 0.90 (d, <i>J</i> = 6.8 Hz, 6H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 193.6, 179.3, 111.7, 36.8, 29.3, 23.5, 22.0; m/z (ESI–MS) 142.7 [M + H]<sup>+</sup>.

2-benzyl-3-oxobutanal (4.19d): Following the general procedures C and D compound 4.19d was obtained from compound 4.17d as a white solid in 90% yield over two steps (1.58 g), (R<sub>f</sub> = 0.38 in hexanes/EtOAc 80:20 v/v); mp: 98–101 ºC; IR (KBr) 3111, 2672, 1962, 1836, 1652, 1559, 1496, 1390, 1275, 1193, 1076, 1023, 973, 841, 808, 795, 726, 701, 654, 615, 526 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.87 (d, <i>J</i> = 7.4 Hz, 1H), 7.35–7.28 (comp, 2H), 7.23 (app t, <i>J</i> = 7.5 Hz, 1H), 7.20–7.16 (comp, 2H), 3.54 (s, 2H), 2.04 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 197.3, 174.9, 139.3, 128.3, 127.6, 126.1, 111.4, 33.4, 24.7; m/z (ESI–MS) 199.0 [M + Na]<sup>+</sup>, 231.0 [M + Na + MeOH]<sup>+</sup>.

2-acetyl-6-(benzyloxy)hexanal (4.19e): Following the general procedures C and D compound 4.19e was obtained from compound 4.17e as a yellow oil in 93% yield (2.31 g), (R<sub>f</sub> = 0.18 in hexanes/EtOAc 90:10 v/v); IR (KBr) 3064, 3030, 2936, 2861, 2792, 2695, 1707, 1617, 1496, 1454, 1406, 1362, 1265, 1212, 1103, 1028, 959, 907, 737, 699 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.94 (d, <i>J</i> = 6.8 Hz, 1H), 7.38–7.25 (comp, 5H), 4.50 (s, 2H), 3.49 (t, <i>J</i> = 6.1 Hz, 2H), 2.18 (t, <i>J</i> = 7.7 Hz, 2H), 2.13 (s, 3H), 1.68–1.60 (m,
$^1$H NMR (100 MHz, CDCl$_3$) $\delta$ 194.7, 177.1, 138.4, 128.4, 127.6(1), 127.5(6), 112.6, 73.0, 69.9, 29.2, 27.6, 27.5, 23.8; $m/z$ (ESI–MS) 249.0 [M + H]$^+$.  

**General Procedure for the Redox-Annulation Involving Non-enolizable β-Ketoaldehydes:**

To a mixture of the aldehyde (0.5 mmol, 1 equiv) and 4Å MS (150 mg) in toluene (2 mL) were added acetic acid (0.29 mL, 5 mmol, 10 equiv) and the amine (0.75 mmol, 1.5 equiv). The mixture was heated under reflux for 2 hours. The reaction mixture was then allowed to cool to room temperature and filtered through a short pad of celite and washed with EtOAc (6 x 5 mL). The filtrate was then washed with saturated aqueous NaHCO$_3$ (3 x 10 mL). The combined aqueous layers were extracted with EtOAc (3 x 10 mL), and the combined organic layers were washed with water (40 mL), brine (40 mL), and dried over anhydrous Na$_2$SO$_4$. Solvent was then removed under reduced pressure and the residue was purified by silica gel chromatography.

**General Procedure for the Redox-Annulation Involving Enolizable β-Ketoaldehydes:**

To a suspension of 4Å MS (150 mg) in toluene (2 mL) were added acetic acid (0.29 mL, 5 mmol, 10 equiv) and the amine (0.75 mmol, 1.5 equiv). The mixture was heated under reflux and a solution of the aldehyde (0.5 mmol, 1 equiv) in toluene was delivered through the top of the reflux condenser over 15 hours via syringe pump. The reaction was stopped immediately after the slow addition was completed. The reaction mixture was then allowed to cool to room temperature and filtered through a short pad of celite and washed with EtOAc (6 x 5 mL). The filtrate was then washed with saturated aqueous NaHCO$_3$ (3 x 10 mL). The combined aqueous layers were extracted with EtOAc (3 x 10 mL), and the combined organic layers were washed with water (40 mL), brine (40 mL), and dried over anhydrous Na$_2$SO$_4$. Solvent was then removed under reduced pressure and the residue was purified by silica gel chromatography.

**3,3-dimethyl-3,4,6,7-tetrahydro-1H-pyrido[2,1-a]isoquinolin-2(11bH)-one (4.9a):** Following the general procedure compound 4.9a was obtained from THIQ (95 µL) and 2,2-dimethyl-3-oxobutyraldehyde (57 mg) as a yellow oil in 71% yield (82 mg). ($R_f = 0.47$ in hexanes/EtOAc 90:10 v/v); IR (KBr) 3063, 3022, 2961, 2923, 2805, 2758, 1713, 1633, 1495, 1469, 1453, 1427, 1377, 1355, 1300, 1248, 1188, 1145, 1133, 1112,
$^1$H NMR (400 MHz, CDCl$_3$) 7.24–7.12 (comp, 3H), 7.12–7.06 (m, 1H), 3.52–3.44 (m, 1H), 3.24 (dd, $J = 15.7, 11.8, 5.7$ Hz, 1H), 3.03 (dd, $J = 11.3, 5.8, 1.2$ Hz, 1H), 2.88 (dd, $J = 14.6, 3.3$ Hz, 1H), 2.82 (d, $J = 11.5$ Hz, 1H), 2.79–2.72 (m, 1H), 2.68 (dd, $J = 14.6, 12.1$ Hz, 1H), 2.54 (app td, $J = 11.8, 3.5$ Hz, 1H), 2.45(d, $J = 11.5$ Hz, 1H), 1.34 (s, 3H), 1.08 (s, 3H);

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 213.2, 136.9, 134.3, 128.9, 126.4, 126.0, 124.6, 67.9, 62.8, 51.3, 46.0, 44.3, 29.7, 25.7, 21.5; $m/z$ (ESI–MS) 230.2 [M + H$^+$], 262.0 [M + H + MeOH$^+$].

9,10-dimethoxy-3,3-dimethyl-3,4,6,7-tetrahydro-1H-pyrido[2,1-a]isoquinolin-2(11bH)-one (4.9b):

Following the general procedure compound 4.9b was obtained from 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (145 mg) and 2,2-dimethyl-3-oxobutyraldehyde (57 mg) as a yellow solid in 86% yield (124 mg), ($R_f$ = 0.56 in hexanes/EtOAc 60:40 v/v); mp: 127–128 °C; IR (KBr) 3383, 2957, 2928, 2863, 2836, 2816, 2777, 2762, 2246, 1702, 1611, 1522, 1454, 1379, 1361, 1261, 1227, 1150, 1106, 1021, 919, 867, 88, 741, 711, 575 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) 6.59 (s, 1H), 6.53 (s, 1H), 3.82 (s, 3H), 3.79 (s, 3H), 3.41–3.29 (m, 1H), 3.20–3.04 (m, 1H), 2.97 (dd, $J = 11.2, 5.7, 1.1$ Hz, 1H), 2.85–2.72 (comp, 2H), 2.70–2.55 (comp, 2H), 2.53–2.35 (comp, 2H), 1.29 (s, 3H), 1.03 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 213.2, 147.5, 147.3, 128.6, 126.3, 111.3, 107.6, 67.7, 62.4, 55.8, 55.7, 51.4, 45.9, 44.5, 29.2, 25.6, 21.4; $m/z$ (ESI–MS) 290.2 [M + H$^+$], 322.0 [M + H + MeOH$^+$].

3,3-dimethyl-3,4,6,7-tetrahydro-1H-[1,3]dioxolo[4,5-g]pyrido[2,1-a]isoquinolin-2(12bH)-one (4.9c):

Following the general procedure compound 4.9c was obtained from 6,7-methyleneoxy-1,2,3,4-tetrahydroisoquinoline (133 mg) and 2,2-dimethyl-3-oxobutyraldehyde (57 mg) as a yellow solid in 69% yield (94 mg), ($R_f$ = 0.46 in hexanes/EtOAc 80:20 v/v); mp: 121–123 °C; IR (KBr) 3382, 2947, 2879, 2808, 1860, 1705, 1507, 1483, 1380, 1355, 1327, 1292, 1233, 1139, 1039, 934, 867, 820, 773, 743, 546 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) 6.56 (s, 1H), 6.53 (s, 1H), 5.91–5.86 (comp, 2H), 3.41–3.28 (m, 1H), 3.19–3.04 (m, 1H), 3.02–2.92 (m, 1H), 2.84–2.68 (comp, 2H), 2.67–2.54 (comp, 2H), 2.53–2.33 (comp, 2H), 1.30 (s, 3H), 1.04 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ
Following the general procedure compound 4.9d was obtained from tryptoline (129 mg) and 2,2-dimethyl-3-oxobutyraldehyde (57 mg) as a yellow solid in 67% yield (90 mg). (Rf = 0.37 in hexanes/EtOAc 80:20 v/v); mp: 193–194 °C; IR (KBr) 3059, 2965, 2921, 2846, 1705, 1623, 1467, 1455, 1383, 1370, 1352, 1324, 1283, 1223, 1173, 1162, 1105, 961, 798, 739, 709, 667, 625 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta 8.36\) (br s, 1H), 7.54 (d, \(J = 7.7\) Hz, 1H), 7.37 (d, \(J = 7.9\) Hz, 1H), 7.24–7.10 (comp, 2H), 3.61–3.48 (m, 1H), 3.16 (dd, \(J = 10.9, 5.4\) Hz, 1H), 3.12–3.00 (m, 1H), 2.98–2.73 (comp, 4H), 2.65 (app td, \(J = 11.1, 3.4\) Hz, 1H), 2.55 (d, \(J = 11.5\) Hz, 1H), 1.39 (s, 3H), 1.15 (s, 3H); \(^1^3\)C NMR (125 MHz, CDCl\(_3\)) \(\delta 213.3, 136.2, 133.3, 126.9, 121.6, 119.5, 118.1, 111.1, 108.4, 67.2, 59.5, 52.1, 46.5, 42.7, 25.8, 21.7(3), 21.6(9); \(m/z\) (ESI–MS) 269.2 [M + H]\(^+\), 301.1 [M + H + MeOH]\(^+\).

Following the general procedure compound 4.9e was obtained from 1-phenyl-THIQ (157 mg) and 2,2-dimethyl-3-oxobutyraldehyde (57 mg) as a yellow solid in 51% yield (78 mg). (Rf = 0.64 in hexanes/EtOAc 80:20 v/v); mp: 101–104 °C; IR (KBr) 3061, 3022, 2960, 2908, 2846, 1969, 1954, 1929, 1895, 1813, 1698, 1596, 1443, 1393, 1372, 1347, 1300, 1167, 1128, 958, 765, 745, 70 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) 7.28–7.22 (comp, 2H), 7.22–7.07 (comp, 6H), 7.01 (d, \(J = 7.7\) Hz, 1H), 3.27–3.21 (m, 1H), 3.21–3.06 (comp, 3H), 3.00–2.93 (m, 1H), 2.82–2.75 (m, 1H), 2.68–2.60 (comp, 2H), 1.25–1.17 (comp, 6H); \(^1^3\)C NMR (125 MHz, CDCl\(_3\)) \(\delta 214.4, 144.6, 140.0, 134.0, 129.0, 128.1, 127.9, 127.7, 126.8, 126.5, 126.1, 66.3, 61.0, 49.1, 46.2, 46.0, 27.7, 25.3, 23.1; \(m/z\) (ESI–MS) 306.2 [M + H]\(^+\).
Following the general procedure compound **4.9f** was obtained from THIQ (95 µL) and 1-acetylcyclohexanecarbaldehyde (77 mg) as a yellow oil in 71% yield (96 mg), (R<sub>f</sub> = 0.53 in hexanes/EtOAc 90:10 v/v); IR (KBr) 3063, 3022, 2954, 2801, 1708, 1632, 1494, 1452, 1426, 1364, 1300, 1275, 1241, 1153, 1112, 1031, 879, 747, 769, 730 cm<sup>-1</sup>; 1H NMR (500 MHz, CDCl<sub>3</sub>) 7.21–7.11 (comp, 3H), 7.11–7.04 (m, 1H), 3.50–3.41 (m, 1H), 3.23 (ddd, <i>J</i> = 15.8, 11.6, 5.8 Hz, 1H), 3.14 (d, <i>J</i> = 11.7 Hz, 1H), 3.08–2.99 (m, 1H), 2.84 (dd, <i>J</i> = 14.0, 3.2 Hz, 1H), 2.79–2.65 (comp, 2H), 2.54 (app td, <i>J</i> = 11.6, 3.0 Hz, 1H), 2.28 (d, <i>J</i> = 11.7 Hz, 1H), 2.02–1.87 (comp, 2H), 1.85–1.71 (comp, 2H), 1.62–1.52 (m, 1H), 1.52–1.29 (comp, 4H), 1.23–1.11 (m, 1H); 13C NMR (125 MHz, CDCl<sub>3</sub>) δ 213.4, 136.9, 134.2, 128.8, 126.3, 126.0, 124.5, 64.8, 62.9, 51.5, 49.5, 44.4, 33.5, 30.4, 29.7, 26.1, 21.7, 21.6; m/z (ESI–MS) 270.3 [M + H]<sup>+</sup>, 302.1 [M + H + MeOH]<sup>+</sup>.

**II-cis-3,3-dimethyl-1-phenyl-3,4,6,7-tetrahydro-1H-pyrido[2,1-a]isoquinolin-2(11bH)-one**

**(cis-4.9g):** Following the general procedure compound **cis-4.9g** was obtained from THIQ (95 µL) and 2,2-dimethyl-3-oxo-4-phenyl-butyraldehyde (95 mg) as a yellow solid in 35% yield (53 mg), (R<sub>f</sub> = 0.64 in hexanes/EtOAc 80:20 v/v); mp: 114–117 ºC; IR (KBr) 3061, 2950, 2755, 1698, 1597, 1494, 1466, 1401, 1379, 1353, 1291, 1247, 1113, 1047, 1031, 921, 897, 741, 719, 693, 628 cm<sup>-1</sup>; 1H NMR (500 MHz, CDCl<sub>3</sub>) 7.60–7.52 (comp, 2H), 7.12 (d, <i>J</i> = 7.6 Hz, 1H), 7.09–6.98 (comp, 4H), 6.98–6.90 (comp, 2H), 4.34 (d, <i>J</i> = 4.4 Hz, 1H), 3.99 (d, <i>J</i> = 4.4 Hz, 1H), 3.49–3.38 (m, 1H), 3.26–3.17 (m, 1H), 2.93 (d, <i>J</i> = 11.4 Hz, 1H), 2.90–2.83 (m, 1H), 2.63–2.55 (m, 1H), 2.51 (d, <i>J</i> = 11.4 Hz, 1H), 1.10 (s, 3H), 1.01 (s, 3H); 13C NMR (125 MHz, CDCl<sub>3</sub>) δ 213.1, 136.0, 135.3, 134.7, 134.2, 128.8, 126.3, 126.0, 124.5, 64.8, 62.9, 51.5, 49.5, 44.4, 33.5, 30.4, 29.7, 26.1, 21.7, 21.6; m/z (ESI–MS) 306.2 [M + H]<sup>+</sup>.
11-trans-3-ethyl-3,4,6,7-tetrahydro-1H-pyrido[2,1-a]isoquinolin-2(11bH)-one (4.9h):

Following the general procedure compound 4.9h was obtained from THIQ (95 μL) and 2-ethyl-3-oxobutyraldehyde (57 mg) in 40% yield (46 mg, 6:1 mixture of two diastereomers). The major diastereomer was isolated as a yellow solid (Rf = 0.32 in hexanes/EtOAc 80:20 v/v); mp: 96–98 ºC; IR (KBr) 3026, 2956, 2873, 2792, 1705, 1609, 1519, 1467, 1410, 1370, 1331, 1289, 1262, 1232, 1158, 1146, 1105, 1007, 861, 771 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 6.60 (s, 1H), 6.53 (s, 1H), 3.83 (s, 3H), 3.80 (s, 3H), 3.53 (app d, J = 11.8 Hz, 1H), 3.32 (dd, J = 11.6, 6.2 Hz, 1H), 2.39 (app t, J = 11.6 Hz, 1H), 1.95–1.83 (m, 1H), 0.96 (t, J = 7.5 Hz, 3H; ¹³C NMR (125 MHz, CDCl₃) δ 209.5, 136.5, 133.8, 128.9, 126.6, 126.1, 124.8, 126.6, 126.1, 124.8, 62.6, 60.6, 50.9, 50.4, 47.1, 29.6, 19.2, 11.6; m/z (ESI–MS) 262.0 [M + H + MeOH⁺].

11-trans-3-ethyl-9,10-dimethoxy-3,4,6,7-tetrahydro-1H-pyrido[2,1-a]isoquinolin-2(11bH)-one (4.9i):

Following the general procedure compound 4.9i was obtained from 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (145 mg) and 2-ethyl-3-oxobutyraldehyde (57 mg) in 51% yield (74 mg, 6:1 mixture of two diastereomers). The major diastereomer was isolated as a yellow solid (Rf = 0.25 in hexanes/EtOAc 60:40 v/v); mp: 104–106 ºC; IR (KBr) 2937, 2835, 2795, 1705, 1609, 1519, 1467, 1410, 1370, 1331, 1289, 1262, 1232, 1158, 1146, 1105, 1007, 861, 771 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 6.60 (s, 1H), 6.53 (s, 1H), 3.83 (s, 3H), 3.80 (s, 3H), 3.53 (app d, J = 11.8 Hz, 1H), 3.32 (dd, J = 11.6, 6.2 Hz, 1H), 2.87 (dd, J = 13.6, 2.8 Hz, 1H), 2.77–2.68 (m, 1H), 2.67–2.49 (comp, 3H), 2.38 (app t, J = 11.6 Hz, 1H), 1.93–1.81 (m, 1H), 1.29–1.17.
(m, 1H), 0.94 (t, J = 7.5 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 209.5, 147.8, 147.4, 128.2, 125.9, 111.4, 107.7, 62.3, 60.5, 55.9, 55.8, 50.8, 50.4, 47.3, 29.1, 19.2, 11.6; m/z (ESI–MS) 322.1 [M + H + MeOH]*.

12-trans-3-ethyl-3,4,6,7-tetrahydro-1H-[1,3]dioxolo[4,5-g]pyrido[2,1-a]isoquinolin-2(12bH)-one (4.9j): Following the general procedure compound 4.9j was obtained from 6,7-methylenedioxy-1,2,3,4-tetrahydrosoquinoline (133 mg) and 2-ethyl-3-oxobutyaldehyde (57 mg) in 44% yield (60 mg, 7:1 mixture of two diastereomers). The major diastereomer was isolated as a yellow solid (Rᵥ = 0.51 in hexanes/EtOAc 60:40 v/v); mp: 143–145 °C; IR (KBr) 3046, 2965, 2926, 2836, 2755, 1709, 1489, 1382, 1347, 1285, 1235, 1142, 1030, 921, 899, 795, 753 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 6.57 (s, 1H), 6.52 (s, 1H), 5.89 (s, 2H), 3.52–3.45 (m, 1H), 3.30–3.32 (dd, J = 11.5, 6.2 Hz, 1H), 3.16–3.03 (comp, 2H), 2.81 (dd, J = 13.7, 3.0 Hz, 1H), 2.74–2.66 (m, 1H), 2.65–2.53 (comp, 2H), 2.49 (app t, J = 13.0 Hz, 1H), 2.36 (app t, J = 11.5 Hz, 1H), 1.93–1.82 (m, 1H), 1.30–1.18 (m, 1H), 0.94 (t, J = 7.5 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 209.5, 147.8, 147.4, 128.2, 125.9, 111.4, 107.7, 62.3, 60.5, 55.9, 55.8, 50.8, 50.4, 47.3, 29.1, 19.2, 11.6; m/z (ESI–MS) 306.1 [M + H + MeOH]*.

12-trans-3-ethyl-12-methyl-1,3,4,6,7,12b-hexahydroindolo[2,3-a]quinolizin-2(12H)-one (4.9k): Following the general procedure compound 4.9k was obtained from 9-methyltryptoline (140 mg) and 2-ethyl-3-oxobutyaldehyde (57 mg) in 45% yield (64 mg, 8:1 mixture of two diastereomers). The major diastereomer was isolated as a yellow solid (Rᵥ = 0.51 in hexanes/EtOAc 60:40 v/v); mp: 177–178 °C; IR (KBr) 3046, 2958, 2923, 2876, 2835, 2803, 1701, 1471, 1425, 1380, 1363, 1316, 1299, 1283, 1184, 1150, 1087, 1000, 736, 696 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 7.53 (d, J = 7.8 Hz, 1H), 7.28 (d, J = 8.2 Hz, 1H), 7.25–7.20 (m, 1H), 7.15–7.10 (m, 1H), 4.10 (dd, J = 11.4, 2.8 Hz, 1H), 3.64 (s, 3H), 3.48 (dd, J = 12.9, 6.1 Hz, 1H), 3.38–3.30 (m, 1H), 3.07–2.90 (comp, 3H), 2.85 (app t, J = 12.9 Hz, 1H), 2.77 (dd, J = 13.6, 3.2 Hz, 1H), 2.73–2.58 (comp, 2H), 1.97–1.86 (m, 1H), 1.34–1.21 (m, 1H), 1.00 (t, J = 7.5 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 209.0,
133.6, 135.0, 126.3, 121.5, 119.1, 118.2, 108.9, 107.7, 60.4, 57.7, 49.2, 47.3, 45.2, 30.3, 22.3, 19.2, 11.6; m/z (ESI–MS) 315.1 [M + H + MeOH]+.

11-trans-3-buty1-9,10-dimethoxy-3,4,6,7-tetrahydro-1H-pyrido[2,1-a]isoquinolin-2(11bH)-one (4.9l): Following the general procedure compound 4.9l was obtained from 6,7-dimethoxy-1,2,3,4-tetrahydrossoquinoline (145 mg) and 2-n-butyl-3-oxobutyraldehyde (71 mg) in 56% yield (89 mg, 13:1 mixture of two diastereomers). The major diastereomer was isolated as a yellow solid (Rf = 0.4 in hexanes/EtOAc 60:40 v/v); mp: 110–111 °C; IR (KBr) 2960, 2854, 2760, 1701, 1610, 1514, 1466, 1408, 1363, 1290, 1248, 1160, 1108, 1033, 1009, 872, 768 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 6.59 (s, 1H), 6.52 (s, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.48 (dd, J = 12.0, 2.2 Hz, 1H), 3.29 (dd, J = 12.0, 6.3 Hz, 1H), 3.17–3.03 (comp, 2H), 2.86 (dd, J = 13.6, 3.0 Hz, 1H), 2.76–2.45 (comp, 4H), 2.35 (app t, J = 11.7 Hz, 1H), 1.91–1.80 (m, 1H), 1.43–1.24 (comp, 4H), 1.21–1.11 (m, 1H), 0.95–0.86 (m, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 209.8, 147.7, 147.3, 128.4, 126.0, 111.3, 107.7, 62.3, 61.0, 55.8, 55.7, 50.4, 49.4, 47.4, 29.3, 29.2, 25.7, 22.7, 13.9; m/z (ESI–MS) 318.3 [M + H]+.

11-trans-3-isobuty1-3,4,6,7-tetrahydro-1H-pyrido[2,1-a]isoquinolin-2(11bH)-one (4.9m): Following the general procedure compound 4.9m was obtained from THIQ (95 µL) and 2-i-buty1-3-oxobutyraldehyde (71 mg) as a yellow oil in 34% yield (44 mg, 3:1 mixture of two diastereomers) (Rf = 0.41 in hexanes/EtOAc 90:10 v/v); IR (KBr) 3061, 3019, 2954, 2920, 2866, 2806, 2757, 1712, 1630, 1585, 1550, 1490, 1466, 1367, 1297, 1247, 1220, 1144, 1109, 742 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) (Note: due to overlapping peaks, integration values of the diastereomers are reported together) 7.21–7.11 (comp, 3.14H), 7.11–7.05 (comp, 1.14H), 3.64–3.50 (comp, 1.21H), 3.30 (dd, J = 11.5, 6.3 Hz, 1.00H), 3.26–3.11 (comp, 2.09H), 3.07–2.70 (comp, 4.18H), 2.69–2.50 (comp, 2.63H), 2.36 (app t, J = 11.7 Hz, 1.04H), 1.86–1.74 (comp, 1.29H), 1.73–1.60 (comp, 1.11H), 1.59–1.48 (m, 0.59H), 1.09–0.99 (m, 1.08H), 0.99–0.82 (comp, 6.83H); ¹³C NMR of the diastereomers (125 MHz, CDCl₃) δ 209.7, 147.7, 147.3, 128.4, 126.0, 111.3, 107.7, 62.3, 61.0, 55.8, 55.7, 50.4, 49.4, 47.4, 29.3, 29.2, 25.7, 22.7, 13.9; m/z (ESI–MS) 318.3 [M + H]+.
124.8, 124.7, 62.6, 61.4, 47.4, 47.2, 35.0, 29.6, 25.7, 25.3, 23.2, 22.6, 22.3, 22.0;  \textit{m/z} (ESI–MS) 290.1 [M + H + MeOH]⁺.

\textbf{11-trans-3-benzyl-9,10-dimethoxy-3,4,6,7-tetrahydro-1H-pyrido[2,1-a]isoquinolin-2(11bH)-one (4.9o):} Following the general procedure compound 4.9o was obtained from 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (145 mg) and 2-benzyl-3-oxobutyaldehyde (88 mg) in 60% yield (105 mg, 6.5:1 mixture of two diastereomers). The major diastereomer was isolated as a yellow solid (R\textsubscript{f} = 0.39 in hexanes/EtOAc 60:40 v/v); mp: 114–117 °C; \textit{IR} (KBr) 3009, 2930, 2834, 2809, 2761, 1701, 1611, 1514, 1465, 1453, 1366, 1328, 1256, 1228, 1151, 1112, 1098, 1028, 1010, 911, 857, 766, 735, 704 cm\textsuperscript{-1}; \textit{\textsuperscript{1}H NMR} (500 MHz, CDCl\textsubscript{3}) 7.31–7.25 (comp, 2H), 7.23–7.15 (comp, 3H), 6.59 (s, 1H), 6.54 (s, 1H), 3.82(5) (s, 3H), 3.81(6) (s, 3H), 3.56–3.49 (m, 1H), 3.33 (dd, \textit{J} = 14.2, 4.4 Hz, 1H), 3.13 (dd, \textit{J} = 11.6, 6.2 Hz, 1H), 3.08–2.91 (comp, 4H), 2.73–2.61 (m, 1H), 2.61–2.48 (comp, 2H); 1\textsuperscript{3}C NMR (125 MHz, CDCl\textsubscript{3}) δ 208.8, 147.6, 147.3, 139.3, 128.8, 128.3, 128.2, 126.0, 125.9, 111.3, 107.7, 62.2, 60.3, 55.8, 55.7, 50.9, 50.2, 47.3, 32.4, 29.1; \textit{m/z} (ESI–MS) 384.0 [M + H + MeOH]⁺.

\textbf{12-trans-3-benzyl-12-methyl-1,3,4,6,7,12b-hexahydroindolo[2,3-a]quinolinizin-2(12H)-one (4.9p):} Following the general procedure compound 4.9p was obtained from 9-methyltryptoline (140 mg) and 2-benzyl-3-oxobutyaldehyde (88 mg) in 53% yield (91 mg, 8:1 mixture of two diastereomers). The major diastereomer was isolated as a yellow oil (R\textsubscript{f} = 0.47 in hexanes/EtOAc 70:30 v/v); \textit{IR} (KBr) 3057, 3027, 2950, 2918, 2843, 1701, 1496, 1470, 1454, 1421, 1385, 1338, 1309, 1273, 1216, 1188, 1142, 1077, 1031, 1013, 910, 737, 700 cm\textsuperscript{-1}; \textit{\textsuperscript{1}H NMR} (500 MHz, CDCl\textsubscript{3}) 7.54–7.50 (m, 1H), 7.37–7.31 (comp, 2H), 7.31–7.21 (comp, 5H), 7.16–7.11 (m, 1H), 4.12 (dd, \textit{J} = 11.6, 2.6 Hz, 1H), 3.65 (s, 3H), 3.41–3.33 (comp, 2H), 3.24 (dd, \textit{J} = 11.0, 6.2, 4.3 Hz, 1H), 3.06–2.98 (m, 1H), 2.96–2.79 (comp, 5H), 2.74 (app t, \textit{J} = 12.1 Hz, 1H), 2.46 (dd, \textit{J} = 14.3, 8.8 Hz, 1H); 1\textsuperscript{3}C NMR (125 MHz, CDCl\textsubscript{3}) δ 208.2, 139.4, 137.6, 134.8, 128.9, 128.5, 126.3, 126.2, 121.6, 119.2, 118.2, 108.9, 107.8, 60.1, 57.8, 49.4, 47.3, 45.2, 32.4, 30.4, 22.2; \textit{m/z} (ESI–MS) 377.1 [M + H + MeOH]⁺.
11-trans-3-(4-(benzyloxy)butyl)-9,10-dimethoxy-3,4,6,7-tetrahydro-1H-pyrido[2,1-a]isoquinolin-2(11bH)-one (4.9q): Following the general procedure compound 4.9q was obtained from 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (145 mg) and 2-(4-benzyloxy)butyl-3-oxobutyraldehyde (124 mg) in 57% yield (121 mg, 5:1 mixture of two diastereomers). The major diastereomer was isolated as a yellow solid (Rf = 0.23 in hexanes/EtOAc 60:40 v/v); mp: 101–103 °C; IR (KBr) 2992, 2940, 2849, 1702, 1609, 1517, 1463, 1367, 1328, 1291, 1262, 1210, 1156, 1141, 1100, 1011, 867, 734 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 7.37–7.30 (comp, 4H), 7.30–7.24 (m, 1H), 6.61 (s, 1H), 6.54 (s, 1H), 4.50 (s, 2H), 3.85 (s, 3H), 3.82 (s, 3H), 3.51–3.46 (comp, 3H), 3.31 (dd, J = 11.4, 6.2 Hz, 1H), 3.17–3.05 (comp, 2H), 2.88 (dd, J = 13.6, 2.4 Hz, 1H), 2.77–2.63 (comp, 2H), 2.63–2.47 (comp, 2H), 2.38 (app t, J = 11.8 Hz, 1H), 1.95–1.83 (m, 1H), 1.72–1.56 (comp, 2H), 1.50–1.36 (comp, 2H), 1.28–1.14 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 209.7, 147.8, 147.4, 138.6, 128.4, 128.3, 127.6, 127.5, 126.0, 111.4, 107.8, 72.9, 70.1, 62.3, 61.0, 55.9, 55.8, 50.4, 49.4, 47.5, 29.9, 29.3, 25.9, 23.8; m/z (ESI–MS) 456.0 (³⁵Cl/³⁵Cl) [M + H + MeOH]⁺.
References


Chapter 5

α-Functionalization of Cyclic N-H Amines via Intermolecular Hydride Transfer

5.1 Synthesis of Functionalized Cyclic N-H Amines

The majority of methods introduced in previous chapters for the synthesis of functionalized cyclic amines require pre-functionalization, in particular, the pre-installment of directing/protecting groups on the amine nitrogen. Meanwhile, products obtained by those methods are also N-functionalized and extra steps are often needed in order to deprotect amines for further modifications. However, a few well-established reaction types offer direct access to functionalized N-H amines.

5.1.1 Intramolecular Hydroamination of Primary Aminoalkenes

Hydroaminations, reactions with direct addition of an amino group to an unsaturated C–C bond, are of great importance to provide numerous amine compounds in an atom-economic and waste-free way from readily available alkenes and alkynes. The intramolecular hydroamination of primary aminoalkenes produces functionalized cyclic N-H amines as products. Hydroamination reactions usually have high energy barriers, and reactions involving alkenes as substrates are particularly difficult compared to those involving alkynes due to the low reactivity and electron density of a C=C double bond. As a result, various catalytic systems, most of which involve metals, were developed to catalyze hydroamination reactions. The delicate design and tuning of ligands coordinating to the metal center can realize hydroamination reactions enantioselectively. Hydroamination reactions are reported to be catalyzed by complexes containing rare-earth metals, alkaline-earth metals, group IV and V metals as well as late-transition metals. Selective representative examples of metal-catalyzed intramolecular hydroamination reactions of primary aminoalkenes are shown in Figure 5.1.
The intramolecular hydroamination reaction involving primary aminoalkenes can also be catalyzed by strong bases. In 2003, Ates and co-workers first disclosed an n-butyllithium catalyzed intramolecular hydroamination of aminoalkenes (Figure 5.2, eq 9). A mixture of the cyclization product and the isomerized alkene was obtained with substrates lacking the gem-dimethyl substituents. Hultzsch and co-workers in 2006 prepared a dimeric proline-derived diamidobinaphthyl dilithium salt 5.11 which was used as a chiral catalyst for the enantioselective intramolecular hydroamination reaction (Figure 5.2, eq 10).
5.1.2 Hydroaminoalkylation of Secondary Amines

Hydroaminoalkylations which involve the addition of an N-H amine α-C(sp³)–H bond to a C=–C double bond represent another important class of reactions directly providing α-functionalized N-H amines as products.α α-Functionalized secondary amines, targets of most reactions developed by our group, mostly can be obtained by intermolecular hydroaminoalkylations between secondary amines and simple alkenes. Hydroaminoalkylations were reported to be successfully catalyzed by group IV and V metals. The two earliest examples of catalytic hydroaminoalkylations of secondary amines were reported by the Maspero group and the Nugent group in 1980 and 1983 respectively. Maspero and co-workers first reported a catalytic intermolecular hydroaminoalkylation reaction between dimethylamine or diethylamine and simple aliphatic terminal alkenes (Figure 5.3, eq 11).9 The reactions could be catalyzed by homoleptic complexes containing zirconium, niobium or tantalum. Although yields of the desired products were low, the reactions were regioselective and only branched products were obtained. A few years later, Nugent and co-workers disclosed a similar catalytic reaction between dimethylamine and 1-pentene, and at the same time demonstrated deuterium exchange experiments of N-D dimethylamine (Figure 5.3, eq 12).10 The mechanism was proposed by the authors which involved a metallaziridine intermediate. In 2009, Doye and co-workers developed a dimethylamido-titanium (IV) complex catalyzed hydroaminoalkylation between N-methylanilines and terminal alkenes (Figure 5.3, eq 13).11 The reaction preferentially provided branched products, and in contrast to the intramolecular hydroaminoalkylation which is often
associated with the competing hydroamination, this reaction exclusively gave hydroaminoalkylation products over hydroamination side products. The same group also employed other Ti (IV) complexes for intermolecular hydroaminoalkylations involving other substrates. Although branched regioisomers in most cases are the major products of hydroaminoalkylation reactions, in 2013, the Doye group reversed the regioselectivity of certain reactions involving styrenes by using a catalyst in situ generated from Ti(NMe₂)₄ and N-methyl-2-aminopyridine, and in 2014 further improved the linear regioselectivity with a related 2,6-bis(phenylamino)pyridinatotitanium catalyst. Compared to group IV metals, group V metals such as niobium and tantalum catalyze intermolecular hydroaminoalkylations with broader substrate scope (Figure 5.3, eq 14) and under milder conditions (Figure 5.3, eq 15). Moreover, enantioselective reactions catalyzed by group V metals were also reported (Figure 5.3, eq 16).

Figure 5.3 Hydroaminoalkylations of Secondary Amines

![Diagram of hydroaminoalkylation reactions](image-url)
5.1.3 Reduction of Cyclic Imines

The reduction of cyclic imines is another important way to provide functionalized cyclic N-H amines. Racemic amines can be obtained simply by the reaction with reducing metal hydride reagents such as lithium aluminum hydride or sodium borohydride. Focus has been placed on the asymmetric hydrogenation of such imines to give enantioenriched amines.\(^{18}\) Asymmetric hydrogenation reactions involving aromatic ring-fused cyclic imines such as 3,4-dihydroisoquinoline or indoline usually give higher yields and enantioselectivities compared to those involving simple cyclic imines such as 1-pyrroline or 3,4,5,6-tetrahydropyridine. In 1992, Buchwald and co-workers reported a titanocene catalyzed asymmetric hydrogenation of cyclic imines (Figure 5.4, eq 17).\(^{19}\) Activated catalyst 5.28 formed by the activation of pre-catalyst 5.29 with catalytic n-butyllithium and phenylsilane. Good to excellent yields and enantiomeric ratios were obtained for cyclic imines bearing either 2-aryl or alkyl substituents. In addition to the titanocene complex, the zirconocene complex was also known as the catalyst for the asymmetric hydrogenation of 2-phenyl-1-pyrroline.\(^{20}\) In 1995, Tani and co-workers reported an iridium(I)/tolBINAP complex catalyzed asymmetric hydrogenation of 2-phenyl-tetrahydropyridine (Figure 5.4, eq 18).\(^{21}\) Interestingly, the reaction could be performed in both polar protic solvent and non-polar aprotic solvent. In protic solvent such as methanol, benzylamine was used as the additive to enhance the enantioselectivity, and the product with
R-configuration was obtained using a catalyst containing the \((S)\)-tolBINAP ligand. However, benzylamine diminished the reactivity in aprotic solvent such as benzene. In this instance, alcohols were added as additives instead, and the product with S-configuration was obtained using the same catalyst. There are a few more reports where Ir(I)-phosphine complexes are utilized for the efficient catalysis of the asymmetric hydrogenation of non-activated cyclic imines.\(^{22}\) In addition to iridium complexes, rhodium and ruthenium complexes were used to catalyze such reactions as well. The Xiao group in 2008 demonstrated that Rh(III)-TsDPEN complex \(5.34\), which is well-known for the asymmetric transfer hydrogenation could catalyze the asymmetric hydrogenation of 1-alkyl dihydroisoquinolines (Figure 5.4, eq 19).\(^{23}\) Neutral pre-catalyst \(5.34\) was treated with silver hexafluoroantimonate \((\text{AgSbF}_6)\) to form the active cationic Rh(III) species. The ionic nature of the catalyst was found to be important for the catalyst activity, and a corresponding 16-electron neutral complex \(5.35\) failed to catalyze the reaction. The reaction showed a dramatic anion effect where only the catalyst with the bulky, non-coordinating hexafluoroantimonate counteranion drove the reaction to over 90\% conversion. Fan and co-workers later in 2011 employed a similar Ru(II)-MsDPEN catalyst for the asymmetric hydrogenation of 2-substituted simple cyclic imines.\(^{24}\) Notably, although the asymmetric hydrogenation of cyclic imines provides direct access to enantioenriched functionalized cyclic \(N\)-H amines, the preparation of most imine substrates require multiple synthetic steps.
Figure 5.4 Asymmetric Hydrogenation of Non-Activated Cyclic Imines

5.1.4 Reduction of N-Heteroaromatic Compounds

N-Heteroaromatic compounds can be directly reduced to saturated N-heterocycles, and in many cases, enantioselectively.\textsuperscript{25} Although the majority of such reductions require the activation of substrates by N-functionalization to weaken the aromaticity, a few reports successfully avoid this limitation. Pyridines bearing electron-withdrawing chiral auxiliaries were reported to undergo diastereoselective heterogeneous hydrogenation affording substituted piperidines.\textsuperscript{26} In 2013, Mashima and co-workers reported a direct synthesis of enantioenriched 1- and 3-substituted tetrahydroisoquinolines by the iridium catalyzed asymmetric hydrogenation of isoquinolinium hydrochloride salt (Figure 5.5, eq 20).\textsuperscript{27} Isoquinoline substrates were activated by protonation, and free tetrahydroisoquinolines were obtained by a simple basic work-up of the hydrogenation products. The Zhang group later in 2016 used a rodium-thiourea chiral diphosphine complex to catalyze the asymmetric hydrogenation of isoquinolinium salts (Figure 5.5, eq 21).\textsuperscript{28} The anion binding interaction between the chloride and the thiourea moiety in the catalyst was proposed to
play a significant role for the stereoselectivity. In contrast to Mashima’s work where aryl-substituted substrates gave higher enantiomeric ratios, the catalytic system developed by the Zhang group was more effective for reactions involving alkyl-substituted isoquinolinium salts, while aryl-substituted ones only gave moderate ees.

Figure 5.5 Asymmetric Hydrogenation of Isoquinolinium Hydrochloride Salts

5.1.5 SnAP Reagents

Since 2013, the Bode group developed a class of tin-containing reagents termed “SnAP” [Sn (tin) Amine Protocol] reagents for the cross-coupling reactions with aldehydes or ketones to build saturated N-heterocycles. The first SnAP reagent was reported to condense with aldehydes, and the formed imine intermediates cyclized in the presence of stoichiometric copper triflate and 2,6-lutidine, providing α-substituted thiomorpholines (Figure 5.6). The use of hexafluoroisopropanol as a co-solvent for the cyclization step proved to be essential for high product yields, probably due to the activation of the imine intermediate by protonation. The scope of the aldehyde was not limited to aromatic aldehydes. Aliphatic aldehydes were also viable substrates for the cross-coupling with the SnAP reagent giving moderate yields of the products. The mechanism of this reaction was proposed to involve a primary carbon radical generated by the copper-mediated oxidation upon protonation of the imine nitrogen. Besides the sulfur-based SnAP reagent for the synthesis of thiomorpholines, other SnAP reagents have been
prepared for the facile synthesis of functionalized mopholines,\textsuperscript{31} piperazines,\textsuperscript{31} medium-ring saturated $N$-heterocycles\textsuperscript{32} as well as various spirocyclic $N$-heterocycles,\textsuperscript{33} and a catalytic cross-coupling reaction between SnAP reagents and aldehydes was also realized.\textsuperscript{34} However, in addition to the drawback of using toxic tin reagents for the preparation of SnAP reagents, SnAP reagents to date are only used to synthesize cyclic $N$-H amines with more heteroatoms on the ring other than the amine nitrogen. Cyclic amines with all carbons on the ring except the amine nitrogen such as pyrrolidine, piperidine, azepane and azocane are inaccessible by this strategy due to the difficulty in the preparation of corresponding SnAP reagents.\textsuperscript{29}

Figure 5.6 Synthesis of $\alpha$-Substituted Thiomopholines by the Cross-Coupling between SnAP Reagent and Aldehydes

5.2 Research Background

The nucleophilic addition of organometallic reagents to imines is an important tool for the construction of structurally diverse amines.\textsuperscript{35} However, other chemical processes often compete with the desired nucleophilic addition due to the low electrophilicity of inactivated azomethine imines. For example, when alkyl Grignard reagents are used to react with imines derived from enolizable aldehydes or ketones, they often serve as bases to deprotonate and enolize the imines. In consequence, imines involved in nucleophilic addition reactions usually require prior activation to increase their electrophilicity. Lewis acids have been used to bind to the imine nitrogen in order to enhance the reactivity of imines.\textsuperscript{36} Meanwhile, imines bearing electron-withdrawing
groups on the nitrogen are widely used for their increased electrophilicity, which include $N$-phosphinoylimines, $N$-sulfonylimines, $N$-sulfinylimines, $N$-carbamoylimines, $N$-acylimine and $N$-acyliminium ion. Enantioselective versions of the nucleophilic addition of organometallic reagents to imines have been achieved both catalytically and by employing chiral auxiliaries on substrates.

Imines prepared from aromatic aldehydes usually are stable enough to be isolated, whereas imines obtained from aliphatic aldehydes are prone to decompose and normally made in situ and immediately react, except for $N$-sulfinylimines which can be prepared and stored regardless of the aldehyde moiety. As a research group focusing on the functionalization of aliphatic cyclic amines, we are particularly interested in cyclic imines derived from these amines, such as 1-pyrroline and 3,4,5,6-tetrahydropyridine, because the addition of nucleophiles to such imines gives rise to $\alpha$-functionalized cyclic $N$-H amines. However, the targeted cyclic imines in their monomeric forms are not very stable and easily trimerize, and the corresponding imine trimers are usually used as monomer precursors decomposing under acidic conditions or upon heating. Previous diastereoselective preparations of imine trimers rely on the silver nitrate catalyzed oxidation of pyrrolidine with sodium peroxydisulfate (Figure 5.7, eq 23) or the deprotonation of $N$-chloroamines by strong bases such as sodium methoxide (Figure 5.7, eq 24). These cyclic imine trimers have been widely used for the synthesis of $\alpha$- and $\beta$-functionalized cyclic amines. To our knowledge, there are very limited examples where the in situ generated imine monomer reacts with nucleophiles producing $\alpha$-functionalized amines. Scully reported that organolithium reagents reacted with imine monomers prepared by the oxidation of $N$-chloroamines with potassium superoxide and provided 2-aryl cyclic amines in moderate yields (Figure 5.8). It was mentioned that the unsatisfactory yields might be due to the low reactivity of imine trimers possibly formed in the reaction.
In 1971, Wittig and co-workers reported a chemical process producing 3-alkylpyrroles from lithium pyrrolidide and azomethines. The authors proposed a hydride transfer between lithium pyrrolidide and the azomethine giving unstable 1-pyrroline intermediate 5.55. 5.55 was not isolable and was rapidly deprotonated under the reaction conditions by another molecule of lithium pyrrolidide, forming an aza-allyl anion which could react with the azomethine. The loss of lithium amide from intermediate 5.57 produced conjugated imine 5.58 which then underwent the aromatization giving the 3-alkylpyrrole product (Figure 5.9). In addition to azomethines, ketones such as benzophenone were also reported to be viable hydride acceptors for similar transformations.
Although it was mentioned in Wittig’s original work that under their reaction conditions the deprotonation of in situ generated 1-pyrroline intermediate forming an aza-allyl anion presumably is faster than the hydride transfer between lithium pyrrolidide and the azomethine, we were intrigued by this chemical process and the possibility to intercept the 1-pyrroline intermediate and prevent it from being deprotonated to form an aza-allyl anion. Thus, the intermolecular hydride transfer between lithium amides and hydride acceptors could become a convenient way for the in situ preparation of aliphatic cyclic imines which in turn could react with nucleophiles providing α-functionalized N-H amines. This methodology allows the late-stage α-functionalization of cyclic N-H amines, in contrast to many previously developed strategies (Section 5.1) where substituents of cyclic amines were installed in the synthesis of substrates.

5.3 Research Development

The reaction involving pyrrolidine and phenyllithium was chosen as the model reaction to evaluate reaction conditions. Reactions were performed in a one-pot, stepwise fashion. In order to minimize the formation of an aza-allyl anion by deprotonation, reactions were kept at –78 °C for the hydride transfer step. 1.5 Equiv of phenyllithium proved to be optimal (Table 5.1, entries 1–4). More phenyllithium lowered the product yield, probably due to the increased possibility of the competing deprotonation of 1-pyrroline. A number of structurally simple hydride acceptors were tested for the hydride transfer and Table 5.1 shows examples (Table 5.1, entries 5–13). A range of ketones gave promising results, among which benzophenone was the
best. An attempt to increase the electrophilicity of benzophenone by introducing electron-withdrawing substituents such as fluorine atoms on phenyl rings did not improve the yield. Notably, commercially available chiral ketone (−)-fenchone produced the product in 50% yield, which offered opportunities for the development of related enantioselective reactions such as the desymmetrization of meso cyclic amines (*vide infra*). Benzaldehyde was an ineffective hydride acceptor and did not yield any detectable product, however, more electron-deficient 2,6-dichlorobenzaldehyde gave 26% yield of the product. Increasing the amount of benzophenone to 1.5 equiv failed to improve the result (Table 5.1, entry 14). The hydride transfer from lithium pyrrolidide to benzophenone was demonstrated to be a rapid process even at −78 °C, completing within 10 minutes. Neither shortened nor prolonged hydride transfer time provided improved yields (Table 5.1, entries 15–17). In order to further decrease the possibility of the competing deprotonation, the stoichiometry of n-butyllithium was lowered to 1 equiv. Gratifyingly, the yield was slightly improved to 60% (Table 5.1, entry 18). Considering the high reactivity of organolithium reagents with imines, the reaction was also tried being kept at −78 °C for 8 hours after the addition of phenyllithium. However, the yield of the product dropped to 48% (Table 5.1, entry 19). The appearance of alcohols reduced from corresponding hydride acceptors could be conveniently monitored by thin layer chromatography (TLC), indicating the effectiveness of the hydride transfer step. The moderate yield obtained even under the optimal conditions might be due to the formation of small amount of unreactive pyrroline trimer.
Table 5.1 Evaluation of Reaction Conditions for the α-Arylation of Pyrrolidine via the Intermolecular Hydride Transfer

<table>
<thead>
<tr>
<th>Entry</th>
<th>Hydride Acceptor (equiv)</th>
<th>Equiv of PhLi</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>benzophenone (1.2)</td>
<td>1.2</td>
<td>42</td>
</tr>
<tr>
<td>2</td>
<td>benzophenone (1.2)</td>
<td>1.5</td>
<td>55</td>
</tr>
<tr>
<td>3</td>
<td>benzophenone (1.2)</td>
<td>2.0</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>benzophenone (1.2)</td>
<td>3.0</td>
<td>39</td>
</tr>
<tr>
<td>5</td>
<td>4,4′-difluorobenzophenone (1.2)</td>
<td>1.5</td>
<td>50</td>
</tr>
<tr>
<td>6</td>
<td>t-Bu phenyl ketone (1.2)</td>
<td>1.5</td>
<td>44</td>
</tr>
<tr>
<td>7</td>
<td>(–)-fenchone (1.2)</td>
<td>1.5</td>
<td>50</td>
</tr>
<tr>
<td>8</td>
<td>2-admantanone (1.2)</td>
<td>1.5</td>
<td>46</td>
</tr>
<tr>
<td>9</td>
<td>nitrosobenzene (1.2)</td>
<td>1.5</td>
<td>51</td>
</tr>
<tr>
<td>10</td>
<td>tetramethyl-3-pentanone (1.2)</td>
<td>1.5</td>
<td>35</td>
</tr>
<tr>
<td>11</td>
<td>fluorenone (1.2)</td>
<td>1.5</td>
<td>24</td>
</tr>
<tr>
<td>12</td>
<td>benzaldehyde (1.2)</td>
<td>1.5</td>
<td>NR</td>
</tr>
<tr>
<td>13</td>
<td>2,6-dichlorobenzaldehyde (1.2)</td>
<td>1.5</td>
<td>26</td>
</tr>
<tr>
<td>14</td>
<td>benzophenone (1.5)</td>
<td>1.5</td>
<td>47</td>
</tr>
<tr>
<td>15&lt;sup&gt;b&lt;/sup&gt;</td>
<td>benzophenone (1.2)</td>
<td>1.5</td>
<td>48</td>
</tr>
<tr>
<td>16&lt;sup&gt;c&lt;/sup&gt;</td>
<td>benzophenone (1.2)</td>
<td>1.5</td>
<td>53</td>
</tr>
<tr>
<td>17&lt;sup&gt;d&lt;/sup&gt;</td>
<td>benzophenone (1.2)</td>
<td>1.5</td>
<td>48</td>
</tr>
<tr>
<td>18&lt;sup&gt;e&lt;/sup&gt;</td>
<td>benzophenone (1.2)</td>
<td>1.5</td>
<td>60</td>
</tr>
<tr>
<td>19&lt;sup&gt;f&lt;/sup&gt;</td>
<td>benzophenone (1.2)</td>
<td>1.5</td>
<td>48</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reactions were performed on a 1 mmol scale. Yields correspond to isolated yields of the product. <sup>b</sup>Hydride transfer time was 5 min. <sup>c</sup>Hydride transfer time was 15 min. <sup>d</sup>Hydride transfer time was 20 min. <sup>e</sup>n-BuLi was 1 equiv. <sup>f</sup>The reaction was allowed to stir at −78 °C for 8 h after the addition of PhLi.

5.4 Scope of the Reaction

With the optimal conditions in hand, we explored the scope of this reaction involving simple cyclic N-H amines (Figure 5.10). Aryllithium reagents readily prepared from the lithium-halogen exchange reaction between the corresponding arylbromide and n-butyllithium reacted with in situ generated 1-pyrroline giving 2-arylpyrrolidines. Other cyclic amines with different ring sizes required slightly modified conditions for the hydride transfer step. For instance, benzophenone was not an effective hydride acceptor for reactions involving piperidine and azepane. Instead, t-butyl phenylketone proved to be efficient, although longer hydride
transfer time was usually necessary. The reaction was also applicable to \textit{trans}-styryllithium nucleophiles, providing 2-\textit{trans}-styryl amines. The yields were moderate for most substrates, except for azocane which gave the desired product in 80% yield.

**Figure 5.10 Scope of the α-Arylation and α-Alkenylation of Simple Cyclic Amines via Intermolecular Hydride Transfer$^a$**

$^a$ Reactions were performed on a 1 mmol scale. For reactions involving PhLi the concentration was 0.23 M; for reactions involving other nucleophiles the concentration was 0.17 M. Yields correspond to isolated yields of the products. Aryllithium was prepared by the lithium-halogen exchange reaction between the corresponding arylbromide (1.5 equiv) and \textit{n}-BuLi (1.5 equiv) in 2 mL ether at $–78$ °C for 30 min, then rt for 30 min. $^b$ The hydride transfer step was performed using \textit{t}-Bu phenylketone as the hydride acceptor at $–78$ °C for 1.5 h. $^c$ 2-Lithiathiophene was prepared by the lithiation of thiophene (1.5 equiv) with \textit{n}-BuLi (1.5 equiv) in 2 mL ether at $–78$ °C for 30 min, then rt for 30 min. $^d$ The hydride transfer step was performed using \textit{t}-Bu phenylketone as the hydride acceptor at $–78$ °C for 30 min. $^e$ \textit{trans}-Styryllithium was prepared by the reaction between \textit{trans}-triphenylstyrlltin (1.5 equiv) and phenyllithium (1.5 equiv) in 4 mL ether at 0 °C to rt for 1.5 h.

Although 1-aryl tetrahydroisoquinolines often can be synthesized by other methods such as the Pictet-Spengler reaction, we were curious to learn whether such compounds are accessible from the addition of aryllithium reagents to dihydroisoquinolines prepared in situ by our intermolecular hydride transfer protocol (Figure 5.11). Gratifyingly, the hydride transfer involving tetrahydroisoquinoline was facile using \textit{t}-butyl phenylketone as the hydride acceptor, and a 72% yield of 1-phenyl-tetrahydroisoquinoline was obtained upon adding phenyllithium. Under the same conditions, the reaction involving 6,7-dimethoxy-tetrahydroisoquinoline gave the
desired product in 52% yield. However, the attempt to further functionalize the 3-position of 1-phenyl-tetrahydroisoquinoline with this strategy failed to yield the desired 1,3-disubstituted product due to an inefficient hydride transfer. Tryptoline dianion formed by deprotonation with 2 equiv of n-butylithium also proved to be a poor hydride donor.

Figure 5.11 α-Arylation of Tetrahydroisoquinolines via Intermolecular Hydride Transfer

Cyclic amines containing additional heteroatoms in the ring such as morpholine, thiomorpholine and piperazine were not viable substrates for this reaction. Hydride transfer was not observed for reactions involving these amines, possibly due to chelation of the deprotonated amine to lithium ion. Amines with the nitrogen in conjugation with an aromatic ring such as tetrahydroquinoline and indoline were also poor hydride donors at low temperature upon deprotonation, presumably due to the lowered electron density of the nitrogen. Elevated reaction temperature promoted the hydride transfer as described by Wittig and co-workers, however, also increased the potential of further deprotonation of the corresponding imines forming aza-allyl anions.

We next studied if the scope of this α-arylation of cyclic N-H amines could be extended to more complex substrates such as substituted amines. For the purpose of improving the diastereoselectivity, reactions involving substituted amines were performed at −78 °C after the addition of aryllithium. O-TIPS protected prolinol readily underwent the α-arylation reaction under standard conditions employing benzophenone as the hydride acceptor (Figure 5.12, eq 29). The reaction was regioselective and only the 2,5-disubstituted product was isolated in 79% yield. However, the diastereoselectivity was low even at low temperature, and a mixture of two diastereomers was obtained in a ratio of 1.8:1. The major diastereomer was determined to be the cis-isomer, possibly because the oxygen atom coordinates to the lithium and directs the cis-addition of phenyllithium to the imine. Free prolinol as well as prolinol derivatives with
other O-protecting groups such as TBS, TBDPS and MOM gave lower yields of the corresponding arylation products without a significant improvement in the diastereoselectivity. O-TIPS 2-piperidinemethanol was a challenging substrate for the hydride transfer step and only small amount of diphenylmethanol reduced from benzophenone was observed by thin-layer chromatography indicating an incomplete hydride transfer process. Gratifyingly, 1.7 equiv of t-butyl phenylketone served as a good hydride acceptor for O-TIPS-2-piperidinemethanol (Figure 5.12, eq 30). In stark contrast to the reaction involving O-TIPS-prolinol which produced a mixture of two diastereomers in a low ratio, this reaction was highly diastereoselective and only the trans-product was isolated. Notably, the relative configuration of product \( 5.64 \) was opposite to that of the major diastereomer \( 5.62 \) obtained from the reaction involving O-TIPS prolinol. 2-Methylpyrrolidine and 2-methylpiperidine were also tested for this transformation, and 1.2 equiv of t-butyl phenylketone was used as the hydride acceptor (Figure 5.12, eq 31). Reactions involving both substrates were regioselective, however, 2-methylpiperidine gave significantly higher diastereoselectivity than 2-methylpyrrolidine. Excellent diastereoselectivities were also obtained for reactions employing 2-aryl amines with various ring sizes, including 2-arylpyrrolidine (Figure 5.12, eqs 32–33). 2,2,2-Trifluoroacetophenone was found to be a better hydride acceptor for reactions involving 2-arylpyrrolidine, probably due to its increased electrophilicity.\(^{52}\) The “turbo-amide” prepared by the deprotonation of 2-phenylpiperidine with \( i-\text{PrMgCl-LiCl} \) at room temperature\(^{53}\) and the zinc amide prepared by the transmetallation of lithium 2-phenylpiperidide with \( \text{ZnCl}_2 \) proved to be inefficient hydride donors.
4-Phenylpiperidine prepared by known procedures\textsuperscript{54} was exposed to conditions where 1.7 equiv of 2,2,2-trifluoroacetophenone was used as the hydride acceptor (Figure 5.13). Good yield of the trans-2,4-diphenylpiperidine was obtained with excellent diastereoselectivity. The second arylation under the same reaction conditions provided unsymmetrical 2,4,6-triphenylpiperidine as the single diastereomer, albeit in only 31\% yield. In addition, 10\% of the regioisomeric imine 5.71 was also isolated.

In addition to aryllithium nucleophiles, cyclic imines generated via the intermolecular hydride transfer could react with alkyllithium nucleophiles as well. In order to demonstrate the synthetic utility of our methodology at the same time, we aimed to use 1-undecyllithium prepared from 1-bromoundecane and t-butyllithium as the nucleophile and synthesize natural product (–)-solenopsin A.\textsuperscript{55} Enantioenriched 2-methylpiperidine was resolved from the racemate with
(S)-mandelic acid and over 99% ee was obtained after two recrystallization of the salt. The desired product was obtained in a combined yield of 66% and 4:1 diastereomeric ratio (Figure 5.14). The major diastereomer could be isolated in pure form by basic alumina chromatography with a retained ee of over 99%. This is to our knowledge the shortest synthesis of natural product (–)-solenopsin A which previously usually required multiple-step synthesis.

**Figure 5.13 α-Arylation of 4-Phenylpiperidine via the Intermolecular Hydride Transfer**

![Diagram](image)

**Figure 5.14 α-Alkylation of 2-Methylpiperidine and One-Step Synthesis of (–)-Solenopsin A**

![Diagram](image)

### 5.5 Enantiospecificity of the Reaction

The application of our methodology to the synthesis of (–)-solenopsin A demonstrated the enantiospecificity of this transformation. In order to explore whether reactions of this type are generally enantiospecific, enantioenriched 2-phenylpyrrolidine was used as the starting material for this reaction (Figure 5.15). (R)-2-Phenylpyrrolidine with 90% ee was prepared by the classic lithiation-transmetallation-Negishi coupling protocol developed by Campos and co-workers. Under the optimal conditions, trans-2,5-diphenylpyrrolidine was isolated in 53% yield with completely retained ee. Interestingly, the t-butyl phenymethanol reduced from t-butyl phenylketone was racemic, which seemingly indicated that the chirality of the starting material did not interfere with the hydride transfer.
As mentioned above, commercially available chiral ketone (−)-fenchone was also a viable hydride acceptor for reactions involving pyrrolidine, although giving slightly inferior result. This prompted us to consider a desymmetrization reaction of meso cyclic amines. Amine 5.73 thus was prepared in the form of its hydrochloride salt and used as the starting material for the desymmetrization reaction. Benzophenone was first used as the hydride acceptor to study the potential of deprotonated amine 5.73 as the hydride donor. Good yield of the corresponding arylation product was obtained with excellent diastereoselectivity, which showed that amine 5.73 was an ideal hydride donor being deprotonated (Figure 5.16, eq 37). (−)-Fenchone was then employed as the hydride acceptor for the reaction. For the convenience of product isolation and ee measurement, the arylation product was protected by a benzoyl group. The highest ee was obtained from the reaction using THF as the solvent, which produced the desired product in 47% yield over two steps with 50% ee (Figure 5.16, eq 38). When (−)-fenchone was used in conjunction with 2 equiv of TMEDA, the product was obtained with the same ee, albeit in lower yield. Reactions performed in other solvents such as ether, MTBE and toluene gave lower ees. Chiral imine 5.76 prepared from (−)-tert-butanesulfinamide and benzaldehyde proved to be an ineffective hydride acceptor. Considering that the ineffectiveness of 5.76 might be due to its low electrophilicity, the corresponding N-sulfinyl imine 5.77 prepared from 2,2,2-trifluoroacetophenone was also tested. The arylation product was gratifyingly obtained in 78% yield with 5.77 as the hydride acceptor, however, in racemic form. Another meso cyclic amine 4-phenylpiperidine was also exposed to desymmetrization conditions involving (−)-fenchone. However, the intermolecular hydride transfer between deprotonated 4-phenylpiperidine and (−)-fenchone was very slow and incomplete. The evaluation of
desymmetrization reaction conditions involving a chiral hydride acceptor was restricted by the limitation of easily accessible chiral hydride acceptors, and is the subject of future study.

**Figure 5.16 Desymmetrization of meso Cyclic Amines with Chiral Hydride Acceptors**

Inspired by the well-developed asymmetric lithiation of N-Boc cyclic amines using alkyllithium and chiral diamine ligands such as (−)-sparteine, we wanted to utilize this strategy for the desymmetrization of meso cyclic amines instead of using a chiral hydride acceptor. Stoichiometric (−)-sparteine was thus added in the deprotonation step to generate the ligand-coordinated lithium amide. However, under such conditions, the reaction suffered from incomplete hydride transfer with benzophenone as the acceptor, and low yield of the arylation product was obtained. To overcome this problem, ketones with increased electrophilicity such as 2,2,2-trifluoroacetophenone was tried. The product was racemic despite the excellent yield of the product isolated (Figure 5.17, eq 39). The racemic product was also obtained when similar conditions employing (−)-sparteine were applied to 4-phenylpiperidine (Figure 5.17, eq 40).
5.7 Isolation of Imine Intermediates

In view of the presumably high reactivity of the in situ generated imine intermediates, we hoped to isolate the imines which ideally could be employed as starting materials to synthesize various α-functionalized cyclic amines. The reaction involving 2-phenylpyrrolidine was directly quenched after the hydride transfer step, and pyrroline 5.79 was isolated in 60% yield in the monomeric form. Meanwhile, the regioisomeric pyrroline 5.26 was also obtained in 10% yield (Figure 5.18). O-TIPS prolinol produced the corresponding imine 5.80 in 70% yield. Notably, both imines 5.79 and 5.80 were much less stable compared to imine 5.26 and easily decomposed at room temperature.
5.8 Control Experiments

As previously discussed, readily prepared 1-pyrroline and tetrahydropridine trimers react with nucleophiles providing α-substituted pyrrolidines and piperidines. We were curious to know if these trimers can be used as imine precursors in our reactions. The formation of the desired product was negligible from the reaction involving 1-pyrroline trimer (Figure 5.19, eq 43). For the purpose of maximizing the similarity between the control experiment involving 1-pyrroline trimer and our methodology which contains 1 equiv of lithium diphenylmethoxide in the reaction system, 1 equiv of lithium diphenylmethoxide was prepared in situ by the deprotonation of diphenylmethanol with phenyllithium. The same result was obtained with only trace product (Figure 5.19, eq 44). The results of control experiments demonstrated that our methodology involving in situ generated cyclic imine monomers via the intermolecular hydride transfer could not be replaced by reactions using the corresponding trimers as starting materials, probably because the basic environment of our reactions was not beneficial to the decomposition of unreactive trimers providing reactive imine monomers.

Figure 5.19 Control Experiments Involving 1-Pyrroline Trimer

In another rate-competing experiment, instead of using the optimal conditions where a one-pot, stepwise protocol was adopted, 2.5 equiv of phenyllithium was directly added to a mixture of pyrrolidine and benzophenone in ether under otherwise identical conditions. Nearly the same yield of the product was obtained (Figure 5.20). The experiment showed that the rate of the hydride transfer is faster than both the nucleophilic addition of phenyllithium to benzophenone and the depronation of 1-pyrroline forming the aza-allyl anion.
5.9 Conclusion

In conclusion, we developed an unprecedented $\alpha$-arylation of cyclic $N$-H amines via intermolecular hydride transfer which generated the reactive cyclic imine monomer intermediates. The methodology provided direct access to free $\alpha$-substituted cyclic amines without the need for pre-functionalization and the subsequent removal of protecting/directing groups. Related enantioselective reactions and further exploration of other transformations involving the intermolecular hydride transfer process are subjects of our future work.
Experimental Section

General Information: Starting materials, reagents, and solvents were purchased from commercial sources and used as received unless stated otherwise. All liquid amines, all liquid bromoarenes, all liquid hydride acceptors, 1-bromoundecane, thiophene, (−)-sparteine and \(N,N,N^\prime,N^\prime\)-tetramethylethylenediamine were distilled prior to use. All solid bromoarenes, all solid hydride acceptors were recrystallized prior to use. Alkyllithium reagents, PhLi and PhMgBr were freshly titrated prior to use. Purification of reaction products was carried out by flash column chromatography using Sorbent Technologies Standard Grade silica gel (60 Å, 230–400 mesh). Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60 F\(_{254}\) plates. Visualization was accomplished with UV light or Dragendorff-Munier stains, followed by heating. Melting points were recorded on a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on an ATI Mattson Genesis Series FT-Infrared spectrophotometer. Proton nuclear magnetic resonance spectra (\(^1\)H-NMR) were recorded on a Varian VNMRS-500 MHz and chemical shifts are reported in ppm using the solvent as an internal standard (CDCl\(_3\) at 7.26 ppm). Data are reported as app = apparent, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, comp = complex, br = broad; coupling constant(s) in Hz. Proton-decoupled carbon nuclear magnetic resonance spectra (\(^1\)C-NMR) spectra were recorded on a Varian VNMRS-500 MHz and chemical shifts are reported in ppm using the solvent as an internal standard (CDCl\(_3\) at 77.0 ppm). Mass spectra were recorded on a Finnigan LCQ-DUO mass spectrometer. Ratios of diastereomeric products were determined by \(^1\)H-NMR analysis of the crude reaction mixture. \(t\)-Butylphenylketone,\(^{61}\) trans-triphenylstyrylvin,\(^{62}\) O-TIPS-L-prolinol,\(^{63}\) O-TIPS-piperidinemethanol,\(^{63}\) 6,7-dimethoxy-tetrahydroisoquinoline,\(^{64}\) amine 5.73,\(^{65}\) 4-phenylpiperidine,\(^{54}\) (\(R\))-2-methylpiperidine,\(^{56}\) (\(R\))-2-phenylpyrrolidine,\(^{58}\) N-sulfinyl imine 5.76\(^{68}\) and N-sulfinyl imine 5.77\(^{69}\) were prepared according to literature procedures. Compounds 5.60a and 5.60b were previously reported and their published characterization data matched our own in all respects.\(^{70,71}\)
General Procedure for the Preparation of Aryllithium Reagents:

To a solution of the arylbromide (1.5 mmol, 1.5 equiv to the amine) in anhydrous ether (2 mL) cooled at −78 °C was slowly added n-BuLi in hexanes (1.5 mmol, 1.5 equiv to the amine) under the protection of nitrogen. The resulting mixture was allowed to stir at the same temperature for 30 min, then warm up to room temperature and stir for another 30 min to give the corresponding aryllithium ether solution.

General Procedure for the α-Arylation/α-Alkenylation of Cyclic N-H Amines and Tetrahydroisoquinolines via the Intermolecular Hydride Transfer:

To a solution of the amine (1 mmol, 1.0 equiv) in anhydrous ether (2 mL) cooled at −78 °C was slowly added n-BuLi in hexanes (1 mmol, 1.0 equiv) under the protection of nitrogen, and the resulting solution was allowed to stir at the same temperature for 10 min. To this was then slowly added via the cannula a solution of the corresponding hydride acceptor (1.2 mmol, 1.2 equiv) in anhydrous ether (1 mL), and the resulting mixture was allowed to continue stirring at −78 °C for the indicated time followed by slow addition of PhLi in dibutyl ether (1.5 mmol, 1.5 equiv) or the corresponding aryllithium or trans-styryllithium in ether. The mixture was allowed to warm up to room temperature and stir for another 2 hours before quenching with the addition of methanol (1 mL) at 0 °C. The reaction mixture was diluted with ether (20 mL) and washed with water (50 mL). The aqueous layer was extracted with ether (3 x 20 mL) and the combined organic layers were washed with brine (30 mL) and dried over anhydrous Na2SO4. Solvent was removed under reduced pressure. The residue was purified by silica gel chromatography.

General Procedure for the α-Arylation/α-Alkylation of Substituted Cyclic N-H Amines via the Intermolecular Hydride Transfer:

To a solution of the amine (0.5 mmol, 1.0 equiv) in anhydrous ether (1 mL) cooled at −78 °C was slowly added n-BuLi in hexanes (0.5 mmol, 1.0 equiv), and the resulting solution was allowed to stir at the same temperature for 10 min. To this was then slowly added via the cannula a solution of the corresponding hydride acceptor (0.6 mmol, 1.2 equiv) in anhydrous ether (1 mL), and the resulting mixture was allowed to continue stirring at −78 °C for the indicated time followed by
slow addition of PhLi in dibutyl ether (0.75 mmol, 1.5 equiv) or 1-undecyllithium in ether. The mixture was kept at −78 °C for 8 hours before quenching with the addition of methanol (0.5 mL) at the same temperature. The reaction mixture was allowed to warm up to room temperature and diluted with ether (20 mL) and washed with water (30 mL). The aqueous layer was extracted with ether (3 x 20 mL) and the combined organic layers were washed with brine (30 mL) and dried over anhydrous Na₂SO₄. Solvent was removed under reduced pressure. The residue was purified by silica gel chromatography.

**General Procedure for the N-Benzoylation of Functionalized Cyclic Amines:**

To a solution of the corresponding amine (0.1 mmol, 1 equiv) in dichloromethane (1 mL) was added 10% NaOH aqueous solution (1 mL). To this was added benzoyl chloride (0.15 mmol, 1.5 equiv) in one portion. The resulting biphasic mixture was vigorously stirred at room temperature overnight. The mixture was subsequently diluted with EtOAc (10 mL) and washed with water (20 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organic layers were washed with brine (20 mL) and dried over anhydrous Na₂SO₄. Solvent was removed under reduced pressure. The residue was purified by silica gel chromatography.

**2-phenylpyrrolidine (5.27a):** Following the general procedure compound 5.27a was obtained from pyrrolidine and phenyllithium using benzophenone as the hydride acceptor. The hydride transfer time was 10 min. Compound 5.27a was obtained as a yellow oil in 60% yield (88 mg) (R₁ = 0.16 in EtOAc/MeOH/i-PrNH₂ 90:9:1 v/v); IR (KBr) 3332, 3284, 3060, 3026, 2961, 2869, 2829, 2657, 1949, 1876, 1806, 1751, 1602, 1493, 1455, 1422, 1398, 1334, 1283, 1176, 1102, 1068, 1028, 901, 754, 699 cm⁻¹; ^1^H NMR (500 MHz, CDCl₃) δ 7.40–7.35 (comp, 2H), 7.34–7.29 (comp, 2H), 7.25–7.20 (m, 1H), 4.11 (app t, J = 7.7 Hz, 1H), 3.21 (ddt, J = 10.1, 7.8, 5.2 Hz, 1H), 3.01 (ddd, J = 10.1, 8.2, 6.9 Hz, 1H), 2.25–2.14 (m, 1H), 2.05 (br s, 1H), 1.98–1.80 (comp, 2H), 1.72–1.63 (m, 1H); ^13^C NMR (125 MHz, CDCl₃) δ 144.8, 128.2, 126.7, 126.4, 62.5, 46.9, 34.3, 25.5; m/z (ESI-MS) 148.1 [M + H]^+.
2-phenylpiperidine (5.27b): Following the general procedure compound 5.27b was obtained from piperidine and phenyllithium using t-Bu phenylketone as the hydride acceptor. The hydride transfer time was 1.5 hours. Compound 5.27b was obtained as a yellow oil in 61% yield (98 mg) (Rf = 0.19 in EtOAc/MeOH/i-PrNH2 90:9:1 v/v); IR (KBr) 3324, 3290, 3061, 3027, 2931, 2857, 2697, 1944, 1601, 1491, 1453, 1393, 1368, 1326, 1308, 1109, 1021, 847, 754, 699 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 7.39–7.34 (comp, 2H), 7.34–7.28 (comp, 2H), 7.26–7.21 (m, 1H), 3.59 (dd, J = 10.4, 2.3 Hz, 1H), 3.23–3.16 (m, 1H), 2.80 (app td, J = 11.4, 1.4 Hz, 1H), 1.95–1.82 (comp, 2H), 1.82–1.76 (m, 1H), 1.70–1.61 (m, 1H), 1.61–1.46 (comp, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 145.5, 128.3, 127.0, 126.6, 62.3, 47.8, 34.9, 25.9, 25.4; m/z (ESI–MS) 162.1 [M + H]+.

2-(p-tolyl)pyrrolidine (5.27c): Following the general procedure compound 5.27c was obtained from pyrrolidine and 4-Me-phenyllithium using benzophenone as the hydride acceptor. The hydride transfer time was 10 min. Compound 5.27c was obtained as a yellow oil in 62% yield (100 mg) (Rf = 0.13 EtOAc/MeOH/i-PrNH2 90:9:1 v/v); IR (KBr) 3334, 3287, 2962, 2871, 1901, 1739, 1644, 1513, 1447, 1418, 1373, 1242, 1179, 1100, 1046, 904, 813, 754 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 7.26 (d, J = 7.9 Hz, 2H), 7.14 (d, J = 7.9 Hz, 2H), 4.08 (app t, J = 6.9 Hz, 1H), 3.27–3.14 (m, 1H), 3.08–2.93 (m, 1H), 2.34 (s, 3H), 2.23–2.12 (m, 1H), 2.01 (br s, 1H), 1.97–1.79 (comp, 2H), 1.72–1.59 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 141.6, 136.2, 128.9, 126.3, 62.3, 46.8, 34.2, 25.5, 20.9; m/z (ESI–MS) 162.1 [M + H]+.

2-(m-tolyl)pyrrolidine (5.27d): Following the general procedure compound 5.27d was obtained from pyrrolidine and 3-Me-phenyllithium using benzophenone as the hydride acceptor. The hydride transfer time was 10 min. Compound 5.27d was obtained as a yellow oil in 58% yield (Rf = 0.12 in EtOAc/MeOH/i-PrNH2 90:9:1 v/v); IR (KBr) 3341, 3280, 2962, 2870, 2360, 2334, 1739, 1608, 1489, 1457, 1373, 1241, 1092, 1046, 910, 783, 733, 702 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 7.24–7.18 (comp, 2H), 7.18–7.12 (m, 1H), 7.08–7.02 (m, 1H), 4.16–4.02 (m, 1H), 3.28–3.16 (m, 1H), 3.10–2.93 (m, 1H), 2.36 (s, 3H), 2.25–2.13 (m, 1H), 2.05 (br s, 1H), 1.98–1.79 (comp, 2H), 1.73–1.62 (m, 1H); ¹³C NMR (125 MHz,
CDCl$_3$) $\delta$ 144.7, 137.8, 128.1, 127.4, 127.1, 123.5, 62.5, 46.9, 34.2, 25.5, 21.4; (ESI–MS) 162.1 [M + H]$^+$.  

2-(o-tolyl)pyrrolidine (5.27e): Following the general procedure compound 5.27e was obtained from pyrrolidine and 2-Me-phenyllithium using benzophenone as the hydride acceptor. The hydride transfer time was 10 min. Compound 5.27e was obtained as a yellow oil in 53% yield ($R_f = 0.16$ in EtOAc/MeOH/($i$-PrNH$_2$) 90:9:1 v/v); IR (KBr) 3337, 3064, 3020, 2964, 2870, 2361, 1739, 1604, 1483, 1460, 1373, 1242, 1096, 1075, 1047, 908, 868, 754 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) 7.51 (d, $J = 7.6$ Hz, 1H), 7.24–7.17 (m, 1H), 7.17–7.08 (comp, 2H), 4.33 (app t, $J = 7.5$ Hz, 1H), 3.24 (ddd, $J = 10.2$, 7.7, 5.2 Hz, 1H), 3.09–2.97 (m, 1H), 2.37 (s, 3H), 2.26–2.16 (m, 1H), 2.04 (br s, 1H), 1.98–1.81 (comp, 2H), 1.64–1.51 (m, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 143.1, 135.2, 130.1, 126.3, 126.0, 124.8, 58.6, 46.9, 32.9, 25.5, 19.4; $m/z$ (ESI–MS) 162.1 [M + H]$^+$.  

2-(4-methoxyphenyl)pyrrolidine (5.27f): Following the general procedure compound 5.27f was obtained from pyrrolidine and 4-MeO-phenyllithium using benzophenone as the hydride acceptor. The hydride transfer time was 10 min. Compound 5.27f was obtained as a yellow oil in 48% yield ($R_f = 0.09$ EtOAc/MeOH/($i$-PrNH$_2$) 90:9:1 v/v); IR (KBr) 3337, 2959, 2872, 2835, 2061, 1884, 1738, 1612, 1583, 1513, 1464, 1443, 1373, 1300, 1246, 1179, 1101, 1038, 910, 830, 733 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) 7.27 (d, $J = 8.6$ Hz, 2H), 6.84 (d, $J = 8.6$ Hz, 2H), 4.04 (app t, $J = 7.5$ Hz, 1H), 3.77 (s, 3H), 3.17 (ddd, $J = 10.2$, 8.1, 5.4 Hz, 1H), 3.05–2.91 (m, 1H), 2.33 (br s, 1H), 2.21–2.07 (m, 1H), 1.97–1.77 (comp, 2H), 1.68–1.59 (m, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 158.4, 136.5, 127.5, 113.6, 62.0, 55.1, 46.7, 34.1, 25.4; $m/z$ (ESI–MS) 178.0 [M + H]$^+$.  

2-(4-chlorophenyl)pyrrolidine (5.27g): Following the general procedure compound 5.27g was obtained from pyrrolidine and 4-Cl-phenyllithium using benzophenone as the hydride acceptor. The hydride transfer time was 10 min. Compound 5.27g was obtained as a yellow oil in 56% yield ($R_f = 0.16$ in EtOAc/MeOH/($i$-PrNH$_2$) 90:9:1 v/v); IR (KBr) 3337, 3229, 2966, 2871, 2832, 2664, 2361, 2341, 1901, 1737, 1593, 1490, 1410, 1373, 1243, 1176, 1090, 1046, 1014, 905, 823 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) 7.31–7.20 (comp,
2-(4-bromophenyl)pyrrolidine (5.27h): Following the general procedure compound 5.27h was obtained from pyrrolidine and 4-Br-phenyllithium using benzophenone as the hydride acceptor. The hydride transfer time was 10 min. Compound 5.27h was obtained as a yellow oil in 57% yield (Rf = 0.22 in EtOAc/MeOH/i-PrNH2 90:9:1 v/v); IR (KBr) 2964, 2872, 2361, 2336, 1538, 1486, 1398, 1336, 1070, 1008, 818 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.41 (d, J = 8.3 Hz, 2H), 7.22 (d, J = 8.3 Hz, 2H), 4.06 (app t, J = 6.8 Hz, 1H), 3.23–3.10 (m, 1H), 3.06–2.93 (m, 1H), 2.25–1.98 (comp, 2H), 1.95–1.76 (comp, 2H), 1.63–1.54 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 143.4, 132.1, 128.3, 127.8, 61.7, 46.8, 34.4, 25.4; m/z (ESI–MS) 182.0 ([M + H]⁺), 184.0 ([M + Br]⁺).

2-(4-fluorophenyl)pyrrolidine (5.27i): Following the general procedure compound 5.27i was obtained from pyrrolidine and 4-F-phenyllithium using benzophenone as the hydride acceptor. The hydride transfer time was 10 min. Compound 5.27i was obtained as a yellow oil in 48% yield (Rf = 0.13 in EtOAc/MeOH/i-PrNH2 90:9:1 v/v); IR (KBr) 2962, 2872, 2359, 2341, 2254, 1889, 1740, 1604, 1508, 1447, 1373, 1243, 1158, 1095, 1047, 913, 835, 733 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.34–7.29 (comp, 2H), 7.03–6.95 (comp, 2H), 4.08 (app t, J = 7.7 Hz, 1H), 3.18 (ddd, J = 10.1, 7.8, 5.3 Hz, 1H), 3.07–2.96 (m, 1H), 2.25–2.11 (m, 1H), 2.11–1.77 (comp, 3H), 1.68–1.56 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 161.7 (d, JCF = 245.0), 140.5, (d, JCF = 2.9 Hz), 127.9 (d, JCF = 7.9 Hz), 115.0 (d, JCF = 21.2 Hz), 61.8, 46.9, 34.4, 25.5; m/z (ESI–MS) 166.1 [M + H]⁺.

2-(4-(trifluoromethyl)phenyl)pyrrolidine (5.27j): Following the general procedure compound 5.27j was obtained from pyrrolidine and 4-CF₃-phenyllithium using benzophenone as the hydride acceptor. The hydride transfer time was 10 min. Compound 5.27j was obtained as a yellow oil in 61% yield (Rf = 0.19 in EtOAc/MeOH/i-PrNH₂ 90:9:1 v/v); IR (KBr) 3342, 3292, 2968, 2874, 2647, 2356, 2084, 1924,
1738, 1619, 1418, 1374, 1324, 1244, 1162, 1123, 1067, 1017, 905, 837, 734 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 7.55 (d, J = 8.1 Hz, 2H), 7.47 (d, J = 8.1 Hz, 2H), 4.24–4.12 (m, 1H), 3.23–3.13 (m, 1H), 3.10–2.96 (m, 1H), 2.32–2.15 (m, 1H), 2.08 (br s, 1H), 1.96–1.78 (comp, 2H), 1.66–1.57 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 149.3, 128.8 (q, J_C-F = 32.2 Hz), 126.7, 125.1 (q, J_C-F = 3.8 Hz), 124.3 (q, J_C-F = 272.0 Hz), 61.9, 46.9, 34.5, 25.5; m/z (ESI-MS) 216.1 [M + H]⁺.

**2-(naphthalen-2-yl)pyrrolidine (5.27k):** Following the general procedure compound 5.27k was obtained from pyrrolidine and 2-naphthyllithium using benzophenone as the hydride acceptor. The hydride transfer time was 10 min. Compound 5.27k was obtained as a yellow oil in 62% yield (Rf = 0.14 in EtOAc/MeOH/i-PrNH₂ 90:9:1 v/v); IR (KBr) 3340, 3054, 2963, 2870, 2361, 2334, 1919, 1735, 1633, 1598, 1508, 1372, 1324, 1243, 1121, 1095, 1046, 893, 856, 819, 748 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 7.55–7.41 (comp, 3H), 4.28 (app t, J = 7.7 Hz, 1H), 3.26 (ddd, J = 10.2, 7.9, 5.3 Hz, 1H), 3.14–3.01 (m, 1H), 2.34–2.14 (comp, 2H), 2.03–1.84 (comp, 2H), 1.82–1.71 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 142.2, 133.3, 132.5, 127.9, 127.6, 127.5, 125.8, 125.3, 125.1, 124.5, 62.5, 46.9, 34.2, 25.5; m/z (ESI-MS) 198.1 [M + H]⁺.

**2-(naphthalen-1-yl)pyrrolidine (5.27l):** Following the general procedure compound 5.27l was obtained from pyrrolidine and 1-naphthyllithium using benzophenone as the hydride acceptor. The hydride transfer time was 10 min. Compound 5.27l was obtained as a yellow oil in 50% yield (Rf = 0.19 in EtOAc/MeOH/i-PrNH₂ 90:9:1 v/v); IR (KBr) 3342, 3049, 2965, 2870, 1944, 1732, 1641, 1596, 1510, 1445, 1394, 1373, 1324, 1243, 1161, 1104, 1046, 908, 855, 799, 779, 734 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 8.17 (d, J = 8.3 Hz, 1H), 7.88 (d, J = 7.9 Hz, 1H), 7.76 (d, J = 8.1 Hz, 1H), 7.72 (d, J = 7.1 Hz, 1H), 7.58–7.44 (comp, 3H), 4.98–4.83 (m, 1H), 3.37–3.23 (m, 1H), 3.21–3.04 (m, 1H), 2.51–2.18 (comp, 2H), 2.02–1.87 (comp, 2H), 1.85–1.72 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 140.6, 133.7, 131.3, 128.6, 127.0, 125.6, 125.2, 123.6, 122.0, 58.4, 46.7, 33.3, 25.4; m/z (ESI-MS) 198.1 [M + H]⁺.
2-(thiophen-2-yl)pyrrolidine (5.27m): Following the general procedure compound 5.27m was obtained from pyrrolidine and 2-lithiothiophene using benzophenone as the hydride acceptor. The hydride transfer time was 10 min. Compound 5.27m was obtained as a yellow oil in 50% yield (Rf = 0.28 in EtOAc/MeOH/i-PrNH2 90:9:1 v/v). IR (KBr) 3333, 3285, 3099, 3067, 2964, 2870, 2659, 1783, 1613, 1531, 1369, 1316, 1231, 1077, 1043, 897, 850, 825, 754, 696 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 7.19–7.11 (m, 1H), 6.98–6.85 (comp, 2H), 4.39 (app t, J = 7.2 Hz, 1H), 3.21–3.12 (m, 1H), 3.03–2.93 (m, 1H), 2.26–2.14 (m, 1H), 2.10–1.71 (comp, 4H); ¹³C NMR (125 MHz, CDCl₃) δ 149.7, 126.5, 123.4, 122.8, 58.1, 46.6, 34.8, 25.3; m/z (ESI–MS) 154.0 [M + H]+.

3-(pyrrolidin-2-yl)pyridine (5.27n): Following the general procedure compound 5.27n was obtained from pyrrolidine and 3-lithiopyridine using benzophenone as the hydride acceptor. The hydride transfer time was 10 min. Compound 5.27n was obtained as a yellow oil in 56% yield (Rf = 0.09 in EtOAc/MeOH/i-PrNH2 90:9:1 v/v); IR (KBr) 3297, 3029, 2963, 2870, 2361, 2344, 1573, 1476, 1425, 1316, 1183, 1100, 1025, 905, 803, 716 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 8.50 (s, 1H), 8.43–8.34 (m, 1H), 7.67–7.59 (m, 1H), 7.14 (dd, J = 7.6, 4.9 Hz, 1H), 4.06 (app t, J = 7.5 Hz, 1H), 3.10 (ddd, J = 10.3, 7.9, 5.4 Hz, 1H), 3.01–2.90 (m, 1H), 2.20–1.94 (comp, 2H), 1.92–1.72 (comp, 2H), 1.62–1.52 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 148.4, 148.0, 140.1, 133.8, 123.1, 59.8, 46.8, 34.2, 24.3; m/z (ESI–MS) 149.1 [M + H]+.

3-(piperidin-2-yl)pyridine (5.27o): Following the general procedure compound 5.27o was obtained from piperidine and 3-lithiopyridine using t-Bu phenylketone as the hydride acceptor. The hydride transfer time was 1.5 hours. Compound 5.27o was obtained as a yellow oil in 58% yield (Rf = 0.09 in EtOAc/MeOH/i-PrNH2 90:9:1 v/v); IR (KBr) 3277, 3029, 2931, 2853, 2790, 2722, 2700, 1590, 1576, 1441, 1423, 1371, 1317, 1299, 1265, 1207, 1183, 1149, 1110, 1051, 1025, 849, 793, 763, 715 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 8.60–8.54 (m, 1H), 8.49–8.43 (m, 1H), 7.72–7.66 (m, 1H), 7.21 (dd, J = 7.8, 4.9 Hz, 1H), 3.63–3.57 (m, 1H), 3.20–3.14 (m, 1H), 2.83–2.73 (m, 1H), 1.93–1.81 (m, 1H), 1.81–1.58 (comp, 3H),
1.58–1.39 (comp, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 148.6(4), 148.5(5), 140.7, 134.1, 123.4, 59.8, 47.6, 34.8, 25.7, 25.2; m/z (ESI–MS) 163.1 [M + H]$^+$. 

2-phenylazepane (5.27p): Following the general procedure compound 5.27p was obtained from azepane and phenyllithium using t-Bu phenylketone as the hydride acceptor. The hydride transfer time was 30 min. Compound 5.27p was obtained as a yellow oil in 55% yield (R$_f$ = 0.38 in EtOAc/Methanol/i-PrNH$_2$ 90:9:1 v/v); IR (KBr) 3336, 3082, 3060, 3025, 2926, 2852, 1879, 1803, 1658, 1601, 1491, 1449, 1355, 1337, 1276, 1143, 1072, 1027, 999, 952, 914, 754, 700 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) 7.40–7.33 (comp, 2H), 7.33–7.27 (comp, 2H), 7.25–7.18 (m, 1H), 3.75 (dd, $J$ = 10.1, 3.5 Hz, 1H), 3.14 (app dt, $J$ = 13.5, 4.6 Hz, 1H), 2.92–2.79 (m, 1H), 2.04–1.92 (m, 1H), 1.92–1.56 (comp, 8H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 147.0, 128.3, 126.6, 126.3, 64.9, 48.2, 39.0, 30.8, 26.8, 26.1; m/z (ESI–MS) 176.1 [M + H]$^+$. 

2-phenylazocane (5.27q): Following the general procedure compound 5.27q was obtained from azocane and phenyllithium using benzophenone as the hydride acceptor. The hydride transfer time was 10 min. Compound 5.27q was obtained as a yellow oil in 80% yield (R$_f$ = 0.42 in EtOAc/Methanol/i-PrNH$_2$ 90:9:1 v/v); IR (KBr) 3352, 3060, 3025, 2919, 2849, 1941, 1874, 1740, 1601, 1491, 1450, 1372, 1240, 1128, 1071, 1047, 1027, 908, 754, 701 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) 7.40–7.35 (comp, 2H), 7.35–7.30 (comp, 2H), 7.26–7.21 (m, 1H), 3.84 (dd, $J$ = 8.8, 3.9 Hz, 1H), 3.11 (dd, $J = 13.9, 6.4, 4.7$ Hz, 1H), 2.82 (ddd, $J = 13.9, 7.5, 4.3$ Hz, 1H), 2.00–1.89 (m, 1H), 1.89–1.48 (comp, 10H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 147.3, 128.2, 126.4(5), 126.3(9), 62.6, 47.6, 35.6, 29.8, 27.7, 25.1, 24.3; m/z (ESI–MS) 190.1 [M + H]$^+$. 

(E)-2-styrylpyrrolidine (5.27r): trans-Styryllithium was prepared according to reported procedures.$^{52}$ Following the general procedure compound 5.27r was obtained from pyrrolidine and trans-styryllithium using benzophenone as the hydride acceptor. The hydride transfer time was 10 min. Compound 5.27r was obtained as a yellow oil in 59% yield (R$_f$ = 0.12 in EtOAc/Methanol/i-PrNH$_2$ 90:9:1 v/v); IR (KBr) 3335, 3059, 3026, 2963, 2871, 2184, 1944, 1874, 1801, 1638, 1596, 1493, 1449, 1419, 1071, 965, 909, 748, 733, 693 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) 7.40–7.33 comp, (2H), 7.32–7.26 (comp, 2H), 7.23–7.17 (m, 1H),
6.50 (d, J = 15.8 Hz, 1H), 6.21 (dd, J = 15.8, 7.2 Hz, 1H), 3.69 (app q, J = 7.2 Hz, 1H), 3.09 (ddd, J = 10.2, 7.9, 5.6 Hz, 1H), 2.97–2.88 (m, 1H), 2.23 (br s, 1H), 2.04–1.94 (m, 1H), 1.91–1.73 (comp, 2H), 1.61–1.50 (m, 1H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) δ 137.1, 132.6, 129.5, 128.4, 127.2, 126.2, 60.8, 46.4, 32.3, 25.2;  m/z (ESI–MS) 174.0 [M + H]\(^+\).

\((E)-2\)-styrylpiperidine (5.27s): Following the general procedure compound 5.27s was obtained from piperidine and \(trans\)-styryllithium using \(\tau\)-Bu phenylketone as the hydride acceptor. The hydride transfer time was 1.5 hours. Compound 5.27s was obtained as a yellow solid in 63% yield; mp = 73–77 °C; \((R_f = 0.13\) in EtOAc/MeOH/\(\tau\)-PrNH\(_2\) 90:9:1 v/v); IR (KBr) 3219, 2926, 2697, 1488, 1438, 1326, 1128, 1105, 1003, 960, 898, 830, 795, 743, 688 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) 7.39–7.32 (comp, 2H), 7.32–7.26 (comp, 2H), 7.23–7.17 (m, 1H), 6.50 (d, J = 16.0, 1H), 6.21 (dd, J = 16.0, 6.7 Hz, 1H), 3.28–3.18 (m, 1H), 3.16–3.07 (m, 1H), 2.71 (app td, J = 11.6, 2.6 Hz, 1H), 1.96–1.70 (comp, 3H), 1.66–1.58 (m, 1H), 1.52–1.28 (comp, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) δ 137.2, 133.6, 128.9, 128.4, 127.2, 126.9, 126.1, 59.1, 46.8, 32.9, 25.9, 24.6;  m/z (ESI–MS) 188.1 [M + H]\(^+\).

\((2R,5S)-2\)-phenyl-5-(((triisopropylsilyl)oxy)methyl)pyrrolidine (cis-5.62): Following the general procedure compound cis-5.62 was obtained from \((S)-2-(((triisopropylsilyl)oxy)methyl)pyrrolidine and phenyllithium using benzophenone as the hydride acceptor. The hydride transfer time was 10 min. Compound cis-5.62 was obtained as a yellow oil in 50% yield (R\(_f = 0.12\) in hexanes/EtOAc 90:10 v/v); IR (KBr) 3062, 3024, 2942, 2865, 1944, 1879, 1806, 1743, 1641, 1601, 1488, 1463, 1383, 1246, 1104, 1068, 1013, 993, 883, 793, 754, 699, 682 cm\(^{-1}\); 1H NMR (500 MHz, CDCl\(_3\)) 7.43–7.36 (comp, 2H), 7.35–7.28 (comp, 2H), 7.25–7.20 (m, 1H), 4.17 (app t, J = 7.9 Hz, 1H), 3.81 (dd, J = 9.7, 4.8 Hz, 1H), 3.75 (dd, J = 9.7, 5.4 Hz, 1H), 3.42–3.32 (m, 1H), 2.37–2.11 (comp, 2H), 1.94–1.84 (m, 1H), 1.80–1.63 (comp, 2H), 1.22–0.93 (comp, 21H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) δ 144.7, 128.3, 126.8, 126.5, 66.7, 62.8, 60.5, 34.3, 27.8, 18.0, 12.0;  m/z (ESI–MS) 334.2 [M + H]\(^+\).
(2S,5S)-2-phenyl-5-(((triisopropylsilyl)oxy)methyl)pyrrolidine (**trans-5.62**): Following the general procedure compound **trans-5.62** was obtained from (S)-2-(((triisopropylsilyl)oxy)methyl)pyrrolidine and phenyllithium using benzophenone as the hydride acceptor. The hydride transfer time was 10 min. Compound **trans-5.62** was obtained as a yellow oil in 28% yield (R<sub>f</sub> = 0.14 in hexanes/EtOAc 90:10 v/v); IR (KBr) 3342, 3062, 3027, 2942, 2865, 2724, 1941, 1871, 1742, 1602, 1491, 1463, 1372, 1240, 1101, 1069, 918, 883, 796, 755, 700. 682 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.42 – 7.35 (comp, 2H), 7.35 – 7.28 (comp, 2H), 7.25 – 7.19 (m, 1H), 4.28 (dd, J = 8.0, 6.9 Hz, 1H), 3.66 (app d, J = 5.8 Hz, 2H), 3.61 – 3.54 (m, 1H), 2.33 (br s, 1H), 2.26 – 2.17 (m, 1H), 2.09 – 1.98 (m, 1H), 1.75 (app dq, J = 12.3, 8.7 Hz, 1H), 1.67 – 1.55 (m, 1H), 1.23 – 0.97 (comp, 21H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 145.3, 128.3, 126.7, 126.5, 66.3, 60.9, 59.8, 34.9, 27.7, 18.0, 12.0; m/z (ESI–MS) 334.2 [M + H]<sup>+</sup>.

**trans-2-phenyl-6-(((triisopropylsilyl)oxy)methyl)piperidine (5.64):** Following the general procedure compound **5.64** was obtained from 2-(((triisopropylsilyl)oxy)methyl)piperidine and phenyllithium (1 mmol, 2 equiv) using t-Bu phenylketone (0.85 mmol, 1.7 equiv) as the hydride acceptor. The hydride transfer time was 1 hour. Compound **5.64** was obtained as a yellow oil in 64% yield (R<sub>f</sub> = 0.22 in hexanes/EtOAc 90:10 v/v); IR (KBr) 3059, 3027, 2941, 2866, 2719, 2361, 2334, 1743, 1463, 1372, 1328, 1240, 1102, 1067, 1013, 915, 882, 801, 753, 699, 682, 649 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) 7.45 – 7.37 (comp, 2H), 7.36 – 7.28 (comp, 2H), 7.26 – 7.19 (m, 1H), 4.02 (dd, J = 8.0, 3.4 Hz, 1H), 3.95 (app t, J = 9.7 Hz, 1H), 3.60 (dd, J = 9.5, 4.4 Hz, 1H), 3.22 – 3.10 (m, 1H), 2.68 (br s, 1H), 1.91 – 1.68 (comp, 3H), 1.68 – 1.54 (comp, 2H), 1.52 – 1.41 (m, 1H), 1.24 – 0.82 (comp, 21H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 144.9, 128.2, 126.7, 126.5, 63.7, 54.1, 53.5, 32.7, 26.0, 20.7, 18.0, 11.9; m/z (ESI–MS) 348.3 [M + H]<sup>+</sup>.

**trans-2-methyl-5-phenylpyrrolidine (5.65a):** Following the general procedure compound **5.65a** was obtained from 2-methylpyrrolidine and phenyllithium using t-Bu phenylketone as the hydride acceptor. The hydride transfer time was 1 hour. Compound **5.65a** was obtained as a yellow oil in 60% yield (2.3:1 mixture of two diastereomers)
(Rf = 0.19 in EtOAc/MeOH/i-PrNH2 90:9:1 v/v); IR (KBr) 3329, 3061, 3026, 2959, 2869, 2359, 2336, 2196, 1946, 1869, 1803, 1602, 1541, 1491, 1452, 1397, 1341, 1115, 1081, 1028, 910, 754, 733, 700 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) Compound xx was reported as a mixture of diastereomers: 7.41–7.27 (comp, 5.28H), 7.25–7.18 (comp, 1.30H), 4.35 (app t, J = 7.5 Hz, 1.00H), 4.15 (app t, J = 7.8 Hz, 0.38H), 3.58–3.46 (m, 1.02H), 3.35–3.25 (m, 0.39H), 2.34–2.23 (m, 1.09H), 2.22–1.94 (comp, 3.98H), 1.83–1.70 (comp, 1.51H), 1.51–1.39 (comp, 1.52H), 1.25 (d, J = 6.1 Hz, 1.37H), 1.21 (d, J = 6.3 Hz, 3.25H); ¹³C NMR (125 MHz, CDCl₃) δ 145.8, 144.7, 128.3, 128.2, 126.7, 126.5, 62.9, 61.5, 54.7, 54.0, 35.4, 34.8, 34.1, 33.5, 22.2, 21.5; m/z (ESI–MS) 162.1 [M + H]⁺.

trans-2-methyl-6-phenylpiperidine (5.65b): Following the general procedure compound 5.65b was obtained from 2-methylpiperidine and phenyllithium using t-Bu phenylketone as the hydride acceptor. The hydride transfer time was 1 hour. Compound 5.65b was obtained as a yellow oil in 78% yield (Rf = 0.19 in EtOAc/MeOH/i-PrNH2 90:9:1 v/v); IR (KBr) 3363, 3082, 3060, 2960, 2868, 1949, 1874, 1803, 1602, 1492, 1451, 1403, 1360, 1304, 1282, 1205, 1180, 1155, 1096, 1067, 1028, 909, 877, 756, 699 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 145.0, 128.2, 126.6, 126.5, 54.0, 47.1, 33.2, 31.2, 19.8, 19.7; m/z (ESI–MS) 176.1 [M + H]⁺.

trans-2,5-diphenylpyrrolidine (5.66a): Following the general procedure compound 5.66a was obtained from 2-phenylpyrrolidine and phenyllithium using t-Bu phenylketone as the hydride acceptor. The hydride transfer time was 1 hour. Compound 5.66a was obtained as a yellow oil in 51% yield (Rf = 0.20 in hexanes/EtOAc 90:10 v/v); IR (KBr) 3363, 3082, 3060, 2960, 2868, 1949, 1874, 1803, 1602, 1492, 1451, 1403, 1360, 1304, 1282, 1205, 1180, 1155, 1096, 1067, 1028, 909, 877, 756, 699 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 145.7, 128.4, 126.7, 126.3, 62.2, 35.5; m/z (ESI–MS) 224.1 [M + H]⁺.
Enantioenriched (2R,5R)-2,5-diphenylpyrrolidine was obtained as a yellow oil in 53% yield from (R)-2-phenylpyrrolidine (90% ee) and phenyllithium following the same procedure. \([\alpha]D_{20}^{p} 78.8 \text{ (c 0.1, CHCl}_3, 90\% \text{ ee)}\); HPLC: Daicel Chiralpak OJ-H, n-hexane/i-PrOH = 90/10, Flow rate = 1 mL/min, UV = 230 nm, \(t_R = 11.0 \text{ min (minor)}\) and \(t_R = 14.2 \text{ min (major)}\). The reduced t-Bu phenylmethanol was obtained as a colorless oil in 81% yield in racemic form.

**trans-2-phenyl-5-(thiophen-2-yl)pyrrolidine (5.66b):** Following the general procedure compound 5.66b was obtained from 2-(thiophen-2-yl)pyrrolidine and phenyllithium using t-Bu phenylketone as the hydride acceptor. The hydride transfer time was 1 hour. Compound 5.66b was obtained as a yellow oil in 37% yield (\(R_t = 0.27 \text{ in hexanes/EtOAc 90:10 v/v)}\); IR (KBr) 3355, 3062, 3027, 2964, 2870, 1949, 1884, 1738, 1602, 1492, 1451, 1400, 1372, 1313, 1242, 1093, 1070, 1046, 911, 849, 827, 758, 700 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) 7.43–7.38 (comp, 2H), 7.38–7.32 (comp, 2H), 7.29–7.23 (m, 1H), 7.20 (app t, \(J = 3.1 \text{ Hz, 1H})\), 7.00–6.94 (comp, 2H), 4.84 (app t, \(J = 6.6 \text{ Hz, 1H})\), 4.53 (app t, \(J = 7.3 \text{ Hz, 1H})\), 2.50–2.38 (comp, 2H), 2.21 (br s, 1H), 2.08–1.98 (m, 1H), 1.95–1.83 (m, 1H); \(^13\)C NMR (125 MHz, CDCl\(_3\)) \(\delta 150.8, 145.4, 128.4, 126.8, 126.7, 126.3, 123.6, 123.0, 61.5, 57.8, 35.6, 35.0; \(m/z\) (ESI–MS) 230.0 [M + H]\(^{+}\).

**3-(trans-5-phenylpyrrolidin-2-yl)pyridine (5.66c):** Following the general procedure compound 5.66c was obtained from 3-(pyrrolidin-2-yl)pyridine and phenyllithium using t-Bu phenylketone as the hydride acceptor. The hydride transfer time was 1 hour. Compound 5.66c was obtained as a yellow oil in 56% yield (\(R_t = 0.49 \text{ in EtOAc/MeOH/i-PrNH}_2 90:9:1 \text{ v/v)}\); IR (KBr) 3344, 3024, 2963, 1944, 1577, 1423, 1363, 1314, 1296, 1209, 1182, 1101, 1074, 1026, 805, 756, 699 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) 8.48 (d, \(J = 3.8 \text{ Hz, 1H})\), 7.79–7.71 (m, 1H), 7.42–7.37 (comp, 2H), 7.37–7.31 (comp, 2H), 7.28–7.21 (comp, 2H), 4.57 (app t, \(J = 7.0 \text{ Hz, 1H})\), 4.51 (app t, \(J = 6.9 \text{ Hz, 1H})\), 2.48–2.34 (comp, 2H), 2.08 (br s, 1H), 1.98–1.81 (comp, 2H); \(^13\)C NMR (125 MHz, CDCl\(_3\)) \(\delta 148.4, 148.2, 145.3, 141.0, 133.8, 128.5, 126.9, 126.2, 123.3, 62.3, 59.7, 35.4, 35.3; \(m/z\) (ESI–MS) 225.1 [M + H]\(^{+}\).
trans-2,7-diphenylazepane (5.66d): Following the general procedure compound 5.66d was obtained from 2-phenylazepane and phenyllithium using t-Bu phenylketone as the hydride acceptor. The hydride transfer time was 1 hour. Compound 5.66d was obtained as a yellow oil in 73% yield (Rf = 0.24 in hexanes/EtOAc 90:10 v/v); mp = 38–40 °C; IR (KBr) 3079, 3057, 3028, 2926, 2847, 1600, 1490, 1467, 1445, 1340, 1133, 1070, 1025, 910, 754, 699 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 7.43–7.37 (comp, 4H), 7.37–7.31 (comp, 4H), 7.28–7.22 (comp, 2H), 4.24 (dd, J = 10.9, 3.3 Hz, 2H), 2.24–2.13 (comp, 2H), 2.11–2.00 (comp, 2H), 1.99–1.81 (comp, 3H), 1.74–1.60 (comp, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 147.3, 128.4, 126.4, 126.1, 59.1, 38.7, 28.3; m/z (ESI–MS) 252.1 [M + H]^⁺.

The title compound was further characterized by X-ray crystallography:

trans-2,6-diphenylpiperidine (5.67a): Following the general procedure compound 5.67a was obtained from 2-phenylpiperidine and phenyllithium (1 mmol, 2 equiv) using 2,2,2-trifluoroacetophenone (0.85 mmol, 1.7 equiv) as the hydride acceptor. The hydride transfer time was 1 hour. Compound 5.67a was obtained as a yellow oil in 68% yield (Rf = 0.21 in hexanes/EtOAc 90:10 v/v); IR (KBr) 3340, 3084, 3059, 3026, 2934, 2861, 1949, 1884, 1803, 1739, 1600, 1494, 1446, 1372, 1325, 1241, 1155, 1117, 1069, 1048, 1031, 1003, 918, 824, 783, 757, 725, 700 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 7.49–7.42 (comp, 4H), 7.41–7.34 (comp, 4H), 7.31–7.25 (comp, 2H), 4.15 (dd, J = 6.1, 4.3 Hz, 2H), 2.34 (br s, 1H), 2.07–1.90 (comp, 4H), 1.78–1.69 (comp, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 144.2, 128.4, 126.7, 126.5, 54.7, 31.4, 20.7; m/z (ESI–MS) 238.1 [M + H]^⁺.
3-(trans-6-phenylpiperidin-2-yl)pyridine (5.67b): Following the general procedure compound 5.67b was obtained from 3-(piperidin-2-yl)pyridine and phenyllithium (1 mmol, 2 equiv) using 2,2,2-trifluoroacetophenone (0.85 mmol, 1.7 equiv) as the hydride acceptor. The hydride transfer time was 1 hour. Compound 5.67b was obtained as a yellow oil in 70% yield (R_f = 0.58 in EtOAc/MeOH/i-PrNH_2 90:9:1 v/v); IR (KBr) 3277, 3031, 2930, 1586, 1571, 1492, 1480, 1444, 1417, 1313, 1105, 1025, 833, 799, 761, 753, 716, 701 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl_3) δ 8.66 (d, \(J = 1.8\) Hz, 1H), 8.49 (dd, \(J = 4.6, 1.1\) Hz, 1H), 7.79–7.73 (m, 1H), 7.43–7.38 (comp, 2H), 7.38–7.31 (comp, 2H), 7.30–7.21 (comp, 2H), 4.18–4.12 (m, 1H), 4.07 (dd, \(J = 6.2, 4.2\) Hz, 1H), 2.17 (br s, 1H), 2.04–1.88 (comp, 4H), 1.78–1.62 (comp, 2H); \(^{13}\)C NMR (125 MHz, CDCl_3) δ 148.8, 148.0, 143.7, 139.3, 134.4, 128.5, 126.7, 126.6, 123.3, 54.6, 52.8, 31.1(9), 31.1(7), 20.5; m/z (ESI–MS) 239.1 [M + H]^+.

trans-2,4-diphenylpiperidine (5.69): Following the general procedure compound 5.69 was obtained from 4-phenylpiperidine and phenyllithium (1 mmol, 2 equiv) using 2,2,2-trifluoroacetophenone (0.85 mmol, 1.7 equiv) as the hydride acceptor. The hydride transfer time was 1 hour. Compound 5.69 was obtained as a yellow oil in 72% yield (R_f = 0.38 in EtOAc/MeOH/i-PrNH_2 90:9:1 v/v); IR (KBr) 3324, 3084, 3059, 3026, 2931, 2872, 1876, 1801, 1739, 1601, 1494, 1451, 1372, 1312, 1242, 1046, 937, 757, 700 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl_3) δ 7.52–7.45 (comp, 2H), 7.44–7.33 (comp, 6H), 7.32–7.20 (comp, 2H), 4.19 (dd, \(J = 6.0, 4.3\) Hz, 1H), 3.12–2.98 (comp, 3H), 2.76 (br s, 1H), 2.37 (ddd, \(J = 13.6, 11.0, 4.3\) Hz, 1H), 2.27 (ddd, \(J = 13.6, 7.8, 3.9\) Hz, 1H), 2.08–1.93 (comp, 2H); \(^{13}\)C NMR (125 MHz, CDCl_3) δ 145.2, 143.4, 128.4, 128.3, 127.2, 126.7, 126.5, 125.8, 55.1, 41.9, 37.6, 36.5, 32.2; m/z (ESI–MS) 238.1 [M + H]^+.

4-trans-6-trans-2,4,6-triphenylpiperidine (5.70): Following the general procedure compound 5.70 was obtained from trans-2,4-diphenylpiperidine and phenyllithium (1 mmol, 2 equiv) using 2,2,2-trifluoroacetophenone (0.85 mmol, 1.7 equiv) as the hydride acceptor. The hydride transfer time was 1 hour. Compound 5.70 was obtained as a yellow oil in 31% yield (R_f = 0.24 in hexanes/EtOAc 90:10 v/v); IR (KBr) 3084, 3059, 3026, 2931, 2872, 1600, 1494, 1453, 1151, 1121, 1028, 757, 699 cm\(^{-1}\); \(^1\)H NMR (500 MHz,
CDCl₃) 7.61–7.53 (comp, 2H), 7.52–7.43 (comp, 4H), 7.43–7.19 (comp, 9H), 4.64 (app d, J = 2.9 Hz, 1H), 4.07 (dd, J = 11.3, 1.4 Hz, 1H), 3.06–2.92 (m, 1H), 2.73–2.60 (m, 1H), 2.49 (br s, 1H), 2.32 (td, J = 13.2, 5.1 Hz, 1H), 2.07–2.00 (m, 1H), 1.85 (app q, J = 12.0 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 146.2, 144.8, 142.6, 128.7, 128.5, 127.2, 126.8, 126.6, 126.5, 126.2(5), 126.2(1), 55.0, 54.8, 42.3, 38.0, 35.7; m/z (ESI–MS) 314.1 [M + H]+.

(2R,6R)-2-methyl-6-undecylpiperidine [(−)-solenopsin A, 5.72]: 1-Undecyllithium ether solution was prepared by the lithium-halogen exchange reaction between 1-bromoundecane and t-BuLi: to a stirred solution of 1-bromoundecane (1.5 mmol, 1.5 equiv to the amine) in anhydrous ether (2 mL) was slowly added t-BuLi in pentane (3 mmol, 3 equiv to the amine). The resulting mixture was allowed to stir at the same temperature for 30 min, then warm up to room temperature and stir for another 30 min to give 1-undecyllithium ether solution. Following the general procedure (−)-solenopsin A was obtained from (−)-2-methylpiperidine and 1-undecyllithium using t-Bu phenylketone as the hydride acceptor. The hydride transfer time was 1 hour. (−)-Solenopsin A was obtained as a yellow oil in 53% yield. (Rₛ = 0.20 in EtOAc/MeOH/i-PrNH₂ 90:9:1 v/v); [α]D₂⁰ −6.6 (c 0.1, CHCl₃, 99% ee); IR (KBr) 2924, 2853, 1465, 1375, 1276, 1258, 1211, 1183, 1138, 1093, 1063, 750, 721 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 3.07–2.96 (m, 1H), 2.88–2.78 (m, 1H), 1.73 (br s, 1H), 1.65–1.09 (comp, 26H), 1.03 (d, J = 6.4 Hz, 3H), 0.83 (t, J = 7.1 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 50.8, 45.8, 34.0, 32.9, 31.8, 30.7, 29.7, 29.5(9), 29.5(8), 29.5(6), 29.3 26.4, 22.6, 21.1, 19.5, 14.0; m/z (ESI–MS) 254.2 [M + H]+. HPLC (N-Bz-5.72): Daicel Chiralpak AD-H, n-hexane/i-PrOH = 95/5, Flow rate = 1 mL/min, UV = 254 nm, tᵣ = 4.8 min (major) and tᵣ = 5.8 min (minor).

1-phenyl-2,3,3a,4,7,7a-hexahydro-1H-4,7-methanoisindole (5.74): Compound 5.74 was obtained from the corresponding amine hydrochloride salt 5.73 and phenyllithium using 2 equiv of n-BuLi as the deprotonating reagent and benzophenone as the hydride acceptor. The hydride transfer time was 1 hour. Compound 5.74 was obtained as a yellow oil in 73% yield (Rₛ = 0.19 in EtOAc/MeOH/i-PrNH₂ 90:9:1 v/v); IR (KBr) 3058, 3025, 2961, 2867, 2361, 1946, 1879, 1806, 1738, 1601, 1492, 1454, 1346, 1241, 1113, 1046, 1028, 909, 859, 802, 735, 699 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 7.38–7.28 (comp, 4H), 7.25–
7.18 (m, 1H), 6.32 (dd, \( J = 5.6, 2.8 \text{ Hz}, 1H \)), 6.28 (dd, \( J = 5.6, 2.8 \text{ Hz}, 1H \)), 3.75 (d, \( J = 5.3 \text{ Hz}, 1H \)), 3.11 (dd, \( J = 10.3, 8.4 \text{ Hz}, 1H \)), 3.05–2.92 (comp, 2H), 2.90–2.79 (comp, 2H), 2.60 (dd, \( J = 10.8, 5.8 \text{ Hz}, 1H \)), 2.07 (br s, 1H), 1.71–1.64 (m, 1H), 1.59–1.53 (m, 1H); 13C NMR (125 MHz, CDCl3) δ 145.3, 136.7, 136.5, 128.3, 126.4, 126.2, 64.6, 57.1, 53.7, 49.7, 48.9, 45.5, 45.4; m/z (ESI–MS) 212.1 [M + H]+.

Compound 5.74 was also obtained from the reaction performed in THF using (–)-fenchone as the hydride acceptor. The N-benzoyl product was obtained as a colorless oil in 47% yield with 50% ee after two steps. HPLC (N-Bz-5.74): Daicel Chiralpak AD-H, n-hexane/i-PrOH = 95/5, Flow rate = 1 mL/min, UV = 230 nm, \( t_R = 11.3 \text{ min} \) (major) and \( t_R = 12.7 \text{ min} \) (minor).

(S)-2-(((triisopropylsilyl)oxy)methyl)-3,4-dihydro-2H-pyrrole (5.80): To a solution of O-TIPS protected prolinol (0.5 mmol, 1.0 equiv) in anhydrous ether (1.5 mL) cooled at –78 °C was slowly added n-BuLi in hexanes (0.5 mmol, 1.0 equiv) under the protection of nitrogen, and the resulting solution was allowed to stir at the same temperature for 10 min. To this was then slowly added via the cannula a solution of benzophenone (0.6 mmol, 1.2 equiv) in anhydrous ether (1 mL), and the resulting mixture was allowed to continue stirring at –78 °C for 1 h before quenching with the addition of MeOH (0.5 mL) at the same temperature. The reaction mixture was allowed to warm up to room temperature and diluted with ether (20 mL) and washed with water (30 mL). The aqueous layer was extracted with ether (3 x 20 mL) and the combined organic layers were washed with brine (30 mL) and dried over anhydrous Na2SO4. Solvent was removed under reduced pressure. The residue was purified by silica gel chromatography. Compound 5.80 was obtained as a colorless oil in 70% yield (\( R_t = 0.25 \) in hexanes/EtOAc 80:20 v/v); IR (KBr) 2943, 2866, 1626, 1463, 1383, 1246, 1112, 1068, 918, 883, 791, 681 cm\(^{-1}\); 1H NMR (500 MHz, CDCl3) 7.60–7.57 (m, 1H), 4.21–4.13 (m, 1H), 3.94 (dd, \( J = 9.8, 4.0 \text{ Hz}, 1H \)), 3.72 (dd, \( J = 9.8, 5.5 \text{ Hz}, 1H \)), 2.62–2.53 (m, 1H), 2.52–2.43 (m, 1H), 1.93–1.71 (comp, 2H), 1.14–0.93 (comp, 2H); 13C NMR (125 MHz, CDCl3) δ 167.3, 74.7, 66.0, 37.1, 23.0, 17.9, 11.9; m/z (ESI–MS) 256.1 [M + H]+.
2D-NMR Analysis for Compound 5.62, 5.64, 5.69 and 5.74, Selected Interactions:

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<tr>
<td>H4</td>
<td>3.61–3.54</td>
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<tr>
<td>H5</td>
<td>2.26–2.17</td>
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<tr>
<td>H6</td>
<td>2.09–1.98</td>
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<tr>
<td>H7</td>
<td>1.75</td>
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<td>H8</td>
<td>1.65–1.55</td>
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**1H NMR shifts**

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<td>H5, H6</td>
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<tr>
<td>H7</td>
<td>1.78–1.68</td>
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<tr>
<td>H8, H9</td>
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<td>H10</td>
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HPLC profile of (2R,5R)-5.66a

Racemic
HPLC Profile of N-Bz-5.72

Racemic
HPLC Profile of N-Bz-5.72

Racemic
References


(51) In Wittig’s original work, the hydride transfer step was performed at 0 °C.


(59) A low yield and enantiomeric ratio of the product were also obtained for the enantioselective α-arylation of pyrrolidine involving 1 equiv of (−)-sparteine as the chiral ligand.


