DEVELOPMENT OF AMINE FUNCTIONALIZATIONS INVOLVING AZOMETHINE YLIDES

By

LONGLE MA

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ABSTRACT OF THE DISSERTATION

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By LONGLE MA

Dissertation Director: Professor Daniel Seidel

Functionalization of amines is a very important research area in organic chemistry because functionalized amines are important building blocks in many biologically active compounds and pharmaceuticals. Outlined within this dissertation are our efforts toward the development of redox-neutral amine functionalizations involving azomethine ylides. The redox-neutral approach avoids unnecessary manipulations on the oxidation state of a targeted molecular structure. Therefore it has many advantages over conventional methods in which metal catalysts, oxidants or other additives are required. We discovered the isomerization of the iminium ion via the intermediacy of azomethine ylides. We took advantage of this unique reactivity and successfully developed the redox-neutral cyanation of amines and intramolecular Mannich reactions. This redox-neutral Mannich reaction was further applied to the syntheses of natural product thalicatricavine and its unnatural epimer. Furthermore, we have conducted mechanistic studies of the redox-neutral aromatization of amines and provided experimental evidence for several important intermediates proposed for this transformation. The synthetic utilities of some of the intermediates were explored. Lastly, a novel intermolecular hydride transfer triggered functionalization of amines was also investigated.

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Dedication

Dedicated to my family.

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Abbreviations, Symbols and Units

δ	Chemical shift
π	Pi
Å	Angstrom
μL	Microliter
μW	Microwave
°	Degree
°C	Degree celcius
%	Percent
AcCl	Acyl chloride
AcOH	Acetic acid
app	Apparent
atm	Atmospheric pressure
Boc	*tert*-Butoxycarbonyl
Br	Bromide
br	Broad
Bu	Butyl
Bn	Benzyl
$(CH_3)_2CO$	Acetone
$CDCl_3$	Deuterated chloroform
$CHCl_3$	Chloroform
CH_2Cl_2	Dichloromethane
cm	Centimeter
cm^{-1}	Inverse centimeter
cod	1,5-Cyclooctadiene
comp	Complex
DCC	*N*,*N*′-Dicyclohexylcarbodiimide
DCE	1,2-Dichloroethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DMF	*N*,*N*-dimethylformamide
DMSO	Dimethylsulfoxide
dr	Diastereoselectivity
EH	Ethyl hexanoate
EHA	Ethyl hexanoic acid

ee	Enantiomeric excess
equiv	Equivalents
ESI-MS	Electron spray ionization mass spectrometry
Et	Ethyl
EtOAc	Ethyl acetate
Et_2O	Diethyl ether
EtOH	Ethanol
FT-IR	Fourier transform infrared spectroscopy
g	Gram
h	Hour
H	Hydrogen, Proton
^{1}H NMR	Proton Nuclear Magnetic Resonance
H_2O	Water
Hz	Hertz
*i*Pr	Isopropyl
iPr_2NEt	*N*,*N*-diisopropylethylamine
*i*PrOH	Isopropanol
J	Coupling constant
KBr	Potassium bromide
m	Multiplet
M	Molar
Me	Methyl
MeOH	Methanol
mg	Milligram
MHz	Megahertz
min	Minute
mL	Milliliter
mM	Millimolar
mmol	Millimole
mol	Mole
mp	Melting point
MS	Molecular sieves
MTBE	Methyl *tert*-butyl ether
m/*z*	Mass to charge ratio
NMR	Nuclear magnetic resonance
OAc	Acetate

OBz	Benzoate
Ph	Phenyl
phen	1,10-Phenanthroline
PPh_3	Triphenylphosphine
ppm	Parts per million
ppy	4-Pyrrolydinopyridine
*p*TSA	*p*-Toluenesulfonic acid
q	Quartet
R_f	Retention factor
rt	Room temperature
s	Singlet
t	Triplet
*t*Bu	Tertiary butyl
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMEDA	Tetramethylethylenediamine
TMSCl	Trimethylsilyl chloride
v/v	Volumetric ratio

Chapter I Introduction

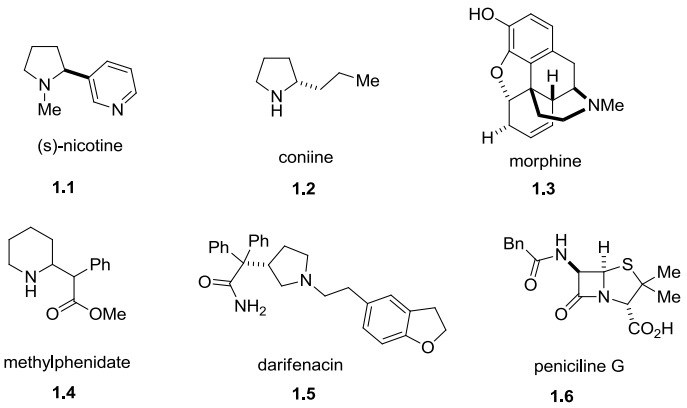
1.1 Background

C–H functionalization has emerged as a hot topic in synthetic organic chemistry.[1,2] In contrast to conventional functional group transformations which often require substrate prefunctionalization and defunctionalization, strategies that involve direct functionalization of C–H bonds have great advantages over conventional functional group transformations by avoiding the superfluous functional group manipulation steps. By utilizing the most commonly present chemical linkage in an organic molecule, direct C–H functionalization can significantly expand the substrate scope and improve the generality of targeted transformations. Recent progress in this area has witnessed the development of various methodologies to introduce different functional groups to organic compounds by replacing C–H bond with C–C, C–O, and C–N bonds.[3] This strategy has provided a powerful tool to rapidly build up molecular complexity and to streamline multistep synthesis. Although great progress has been made in this research area, the major challenge for direct C–H functionalization to activate relatively inert C–H bonds (typically 90–100 kcal/mol) and the regio,[4] diastereo and enantio[5] selective functionalization of C–H bonds still remains.

Given the fact that functionalized cyclic amines are privileged structural motifs present in many pharmaceuticals and biologically active agents (Scheme 1.1),[6] the synthesis of functionalized amines using the C–H functionalization strategy is an important research area in synthetic organic chemistry. The research presented in this dissertation will emphasize the development of amine functionalization reactions. The majority of methods developed so far are in the realm of α-functionalization, and in a few cases β-functionalization due to the moderate activation effect on the C–H bond α to nitrogen atom and slight activation of the β-C–H bonds. Most methodologies fall into four categories, one of them is the α-lithiation followed by electrophile trapping approach, the second one is the oxidative approach using an external oxidant to effect the formation of an imine/iminium intermediate which is subsequently attacked by a nucleophile. The third approach involves the insertion of transition metal

or transition metal carbene/nitrene species into the amine α-C–H bonds. The fourth one is the redox-neutral approach, where the oxidative part and the reductive part remained in the same molecule. The overall oxidation state of the molecule doesn't change and no external oxidant or reductant is needed.

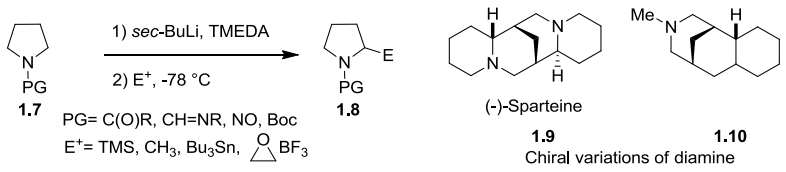
Scheme 1.1 **Examples of Biologically Active Compounds Containing Functionalized Amines**



1.2 α-Functionalization of Amines by Lithiation and Electrophilic Trapping

One traditional method of constructing α-substituted amines involves α-lithiation with alkyllithium/diamine complex followed by electrophilic C–C bond formation.[7] As shown in Scheme 1.2, after deprotonation by a lithium reagent, the lithiated α-carbon was trapped with an electrophile. Directing and protection groups such as amide, formamidine, nitroso and carbamate functionalities were required to facilitate the metalation. Various electrophiles such as trimethylsilyl chloride, alkyl halide and epoxide could be used. Enantioselective lithiation could also be achieved when chiral diamine ligands **1.9** and **1.10** (Scheme 2) were used instead of TMEDA.[8]

Scheme 1.2 **α-Functionalization of Amines by Lithiation and Electrophilic Trapping**

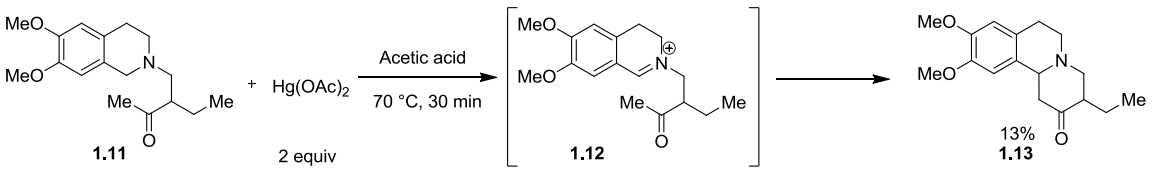


1.3 Oxidative C–H Functionalization of Amines

1.3.1 α-C–H Functionalization Using Transition Metal Salt as Oxidant

Although recent advances in direct functionalization through α-lithiation have provided a valuable method to access functionalized amines, this method requires low temperature, use of strong base and protection of amines. These disadvantages have limited the synthetic utility of this approach. As a complementary strategy to address these drawbacks, oxidative α-C–H functionalization involving transition metals has drawn tremendous attention. One of the earliest examples was reported in 1963 by Whittake and co-workers in an attempt to synthesize 2-oxohexahydrobenzo[a]quinolizine, which is a core structure of the alkaloid rubremetine.[9] Tetrahydroisoquinoline (THIQ) derivative **1.11** was reacted with a super stoichiometric amount of mercury acetate to generate the iminium intermediate **1.12** which was then attacked by the enolate generated in situ to form the ring closure product **1.13**, albeit in low yield.

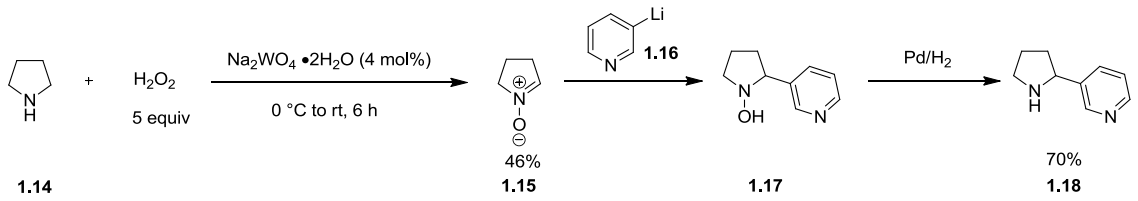
Scheme 1.3 **Oxidation of Amines Using Mercury Acetate**



1.3.2 Biomimetic α-C–H Functionalization of Amines Catalyzed by Transition Metals

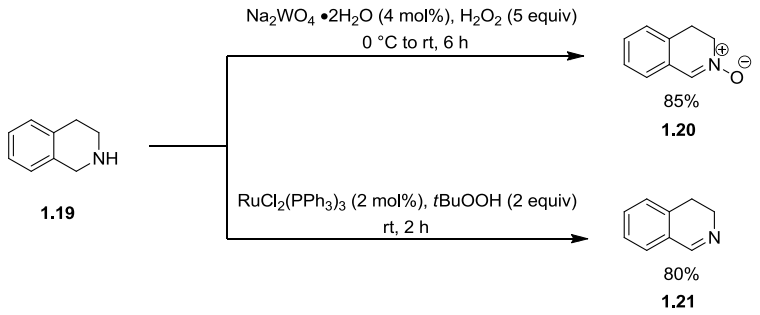
The oxidative metabolism of amine in biological systems is promoted by various enzymes such as the amine oxidases: hepatic flavoenzyme and cytochrome P-450. The simulation of the function of an enzyme with a metal complex catalyst has provided a biomimetic method for the catalytic oxidation of amines. In attempts to simulate the function of hydroperoxyflavin (FlOOH), the use of metal hydroperoxide (MOOH) in the oxidation of secondary amines was reported.[10] Murahashi and co-workers found that the hydroperoxytungstate (generated in situ from sodium tungstate with H_2O_2) was an excellent reagent in synthesis of nitrones from secondary amines and it is a highly valuable synthetic intermediate for the synthesis of nicotine derivatives (Scheme 1.4).[11]

Scheme 1.4 **Biomimetic Hydroperoxytungstate Catalyzed Functionalization of Amines**



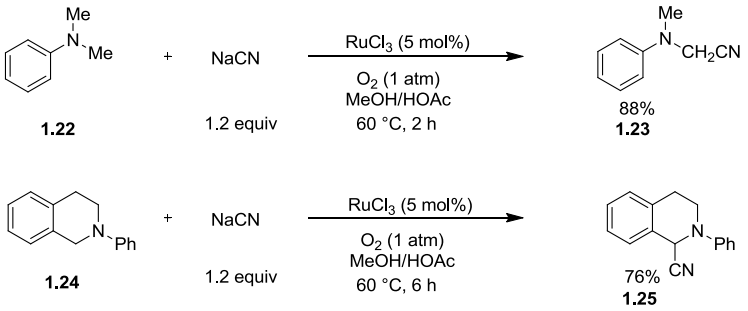
Besides transition metal like Fe which is known to form metal-oxo species in biological systems, there are other transition metals (for example Ru) that are also able to effect oxidative functionalization of amines. There is a lot of recent progress involving the direct α-functionalization of saturated cyclic amines via metal-oxo species. In contrast to the previous example where secondary amines were oxidized to form nitrones, Murahashi and co-workers reported that secondary amine can also be oxidized to the imine with high efficiency by catalytic amount of $RuCl_2(PPh_3)_3$ in combination with *t*BuOOH.[12] In this case tetrahydroisoquinoline was oxidized to dihydroisoquinoline, which could be intercepted with different nucleophiles to give rise to substituted tetrahydroisoquinolines. The oxidation state of the final product was dependent on the catalytic system (Scheme 1.5).

Scheme 1.5 **Reagent Controlled Functionalization of Amines**



In addition to secondary amines, tertiary amines can also be oxidized by similar Ru based catalytic system to generate iminium ion intermediates. In 2003, Murahashi and co-workers reported the aerobic ruthenium-catalyzed oxidative cyanation of tertiary amines with sodium cyanide.[13] In this work, oxidation was achieved with molecular oxygen in place of peroxides under relatively mild conditions. The reaction proceeded selectively to form the iminium ion intermediate which was directly trapped by carbon nucleophiles under oxidative conditions (Scheme 1.6).

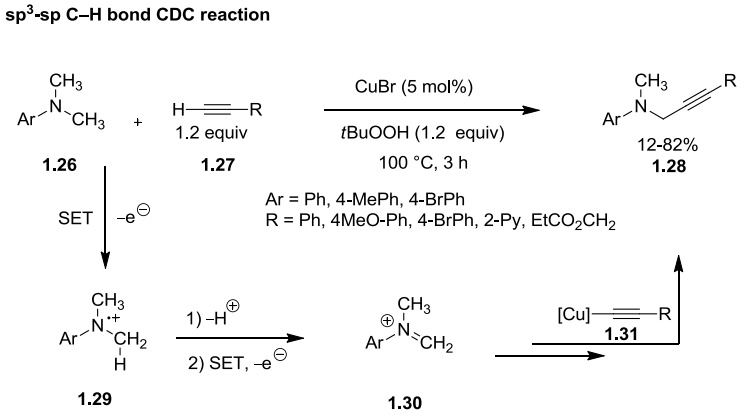
Scheme 1.6 **Ruthenium Catalyzed Aerobic Functionalization of Tertiary Amines**



1.3.3 Cross Dehydrogenative Coupling Reactions

Besides biomimetic metal catalyzed functionalization of amines, more efforts have been devoted to the development of transition metal catalyzed functionalizations of amines recently. Cross dehydrogenative coupling (CDC) is one of the most well developed methods which allows for a broad range of substrates and various functional groups to participate in the C–H functionalization of amines. In these reactions, the newly formed C–C or C–X bond was achieved using only C–H bonds under oxidative conditions.[14] This type of reaction was first developed by Li and co-workers in 2004.[15] In sp^3-sp type alkynylation of tertiary amines, the amine could be converted to radical cation **1.29** during a single electron transfer (SET) process, and this radical cation could be further oxidized to iminium species **1.30** through a proton transfer and a second single electron transfer (SET) which then reacts with copper acetylide **1.31** to afford the alkynylation product (Scheme 1.7).

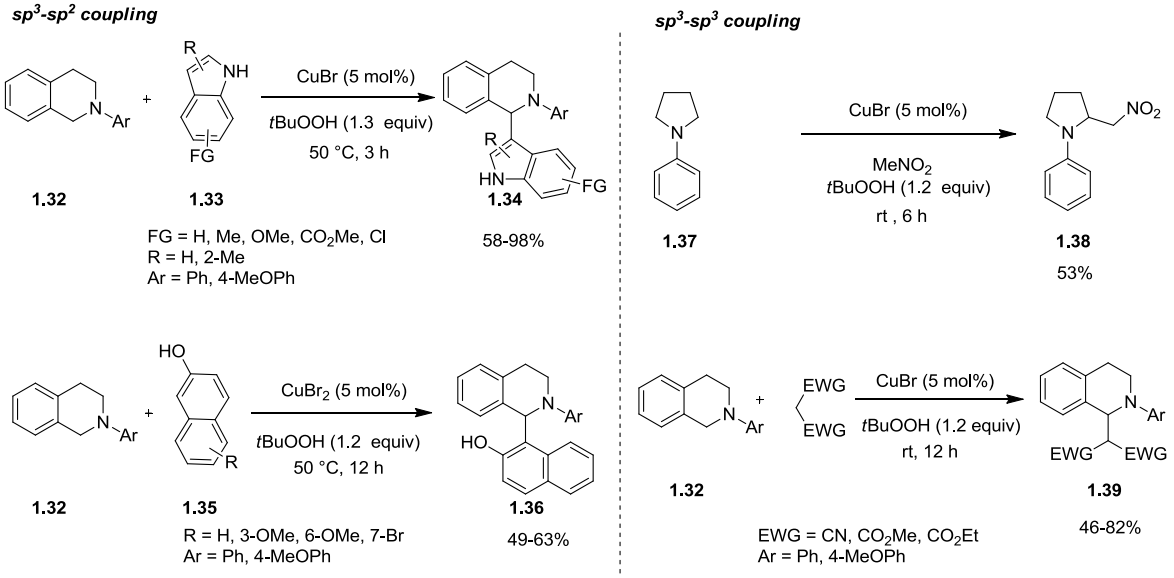
Scheme 1.7 **The Sp^3-sp C–H Bond CDC reaction**



Besides the sp^3-sp C–H bond coupling (α-alkynylation), the scope of the CDC type reaction has been expanded to sp^3-sp^2 C–H bond coupling (α-arylation) and sp^3-sp^3 C–H bond coupling (α-alkylation). In 2006, Li and co-workers reported the Friedel-Crafts type reaction between *N*-aryl tetrahydroisoquinoline and indole (Scheme 1.8). The reaction utilized *t*BuOOH (TBHP) as the

oxidant and CuBr as the catalyst. A wide range of substituted indoles were tolerated and the reaction proceeded smoothly at mild conditions.[16] Similarly, 2-naphthol is another electron-rich aromatic compound that undergoes a CDC reaction with *N*-aryl tetrahydroisoquinoline in the CuBr/TBHP system to generate the corresponding CDC product in good yields (Scheme 1.8). This CDC type reaction can also be applied to sp^3-sp^3 C–H bond couplings including aza-Henry type reaction and Mannich type reaction (Scheme 1.8). Nitroalkanes and malonates bearing acidic protons can undergo nucleophilic addition to the in situ generated iminium species giving rise to the final coupling product.[17] In these reactions, the iminium intermediate was generated in a similar fashion as the previously shown α-alkynylation, and the only difference lies in the nucleophilic coupling partner.

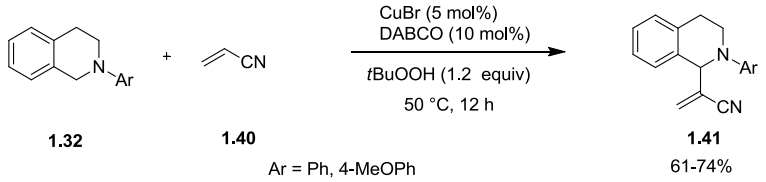
Scheme 1.8 **The Sp^3-sp^2 and sp^3-sp^3 C–H Bond CDC Reaction**



In addition to the electron rich arenes such as indole and napthol which engage in cross dehydrogenative coupling in a Friedel-Crafts reaction manner, electron deficient alkenes can also undergo CDC reactions to generate Morita-Baylis-Hillman (MBH) reaction product. The Li group found they were able to combine CuBr as the transition metal catalyst and 1,4-

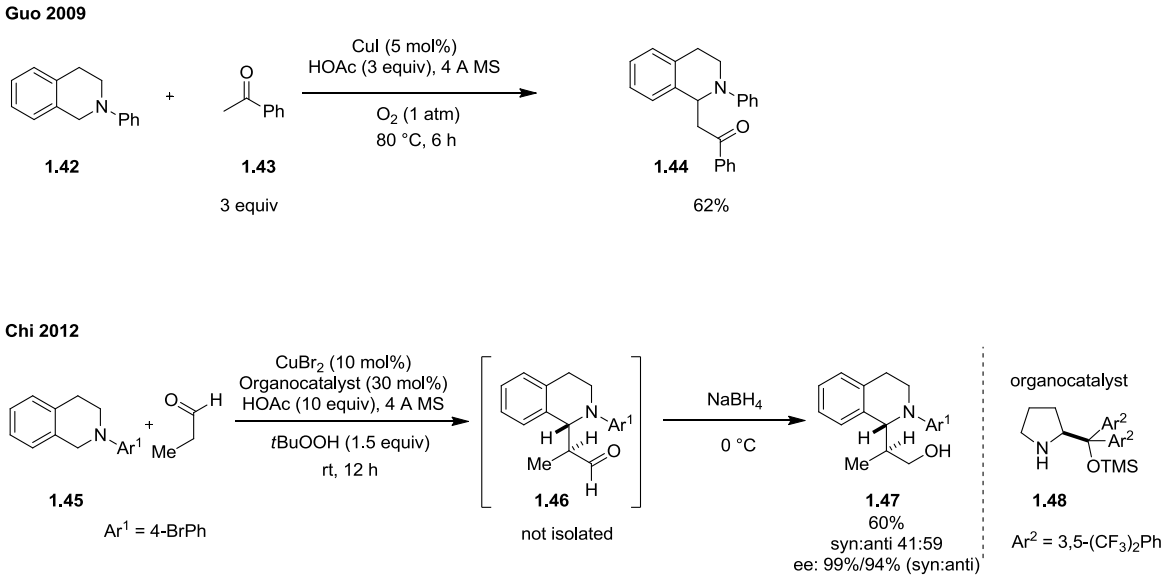
diazabicyclo[2.2.2]octane (DABCO) as the organocatalyst to effect the MBH-CDC reaction between N-aryl tetrahydroisoquinoline and acronylnitriles (Scheme 1.9).[16]

Scheme 1.9 **Morita-Baylis-Hillman (MBH)-CDC Reaction**



In the category of sp^3-sp^3 C–H CDC reactions, in addition to readily enolizable malonates or fairly acidic nitroalkanes, less acidic C–H coupling partners including ketones and aldehydes have also been successfully employed. In order to increase the nucleophilicity of the α-carbon, two strategies are generally utilized. The first strategy relies on the presence of a Brønsted acid or Lewis acid to facilitate the enolization of the carbonyl group; the second strategy introduces a secondary amine which could covert the carbonyl group to an enamine making it a stronger nucleophile. In 2009, Guo and co-workers reported their innovative work of the Mannich type CDC reaction between tertiary amines and ketones (Scheme 1.10).[18] This CuI catalyzed aerobic coupling features the use of acetic acid and molecular sieves. Interestingly, when prolinol derived organocatalyst was introduced into the reaction system, an asymmetric CDC reaction could be achieved (not shown). The Chi group in 2012 successfully showed an example of an efficient enantioselective coupling of *N*-aryl tetrahydroisoquinolines with aliphatic aldehydes.[19] In a catalytic system with a chiral Jørgensen-type catalyst used in combination with $CuBr_2$, acetic acid and TBHP, high enantioselectivities were obtained (Scheme 1.10).

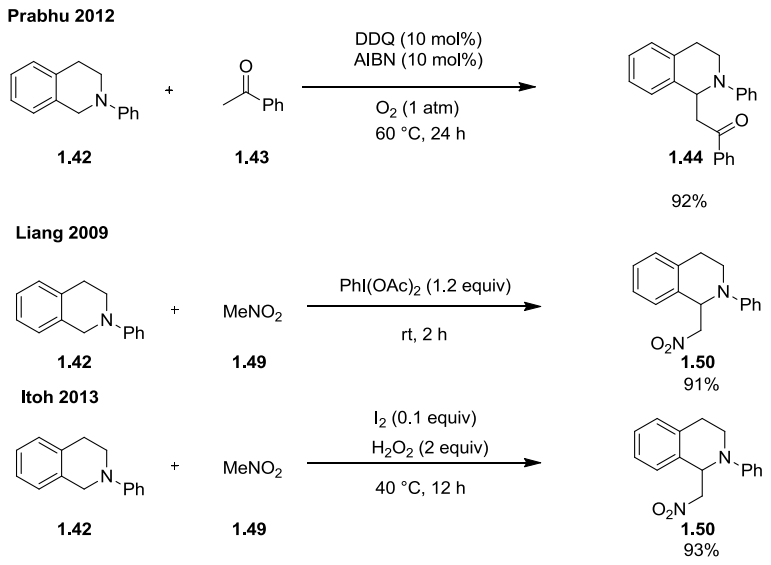
*Scheme 1.*10 **CDC Reaction with Ketone and Asymmetric CDC Reaction**



1.3.4 Cross Dehydrogenative α-C–H Functionalization of Amines Using Organic Oxidant

The majority of the oxidative dehydrogenative coupling reactions are catalyzed by transition metals. Oxidative CDC reaction can also be carried out under metal-free conditions. The Prabhu group reported that 10 mol% DDQ and 10 mol% AIBN under an oxygen atmosphere could enable the reaction between *N*-phenyl tetrahydroisoquinoline and acetophenone (Scheme 1.11).[20] The hypervalent iodine(III) oxidizing reagent (diacetoxy)iodobenzene (DIB) was used for the aza-Henry type reaction between *N*-phenyl tetrahydroisoquinoline and nitromethane by Liang and co-workers (Scheme 1.11).[21] The Itoh group demonstrated that catalytic amounts of molecular iodine in combination with hydrogen peroxide effectively catalyzed the nitroalkylation of various tetrahydroisoquinoline derivatives by generating the catalytic hypoiodous acid (HIO) in situ (Scheme 1.11).[22]

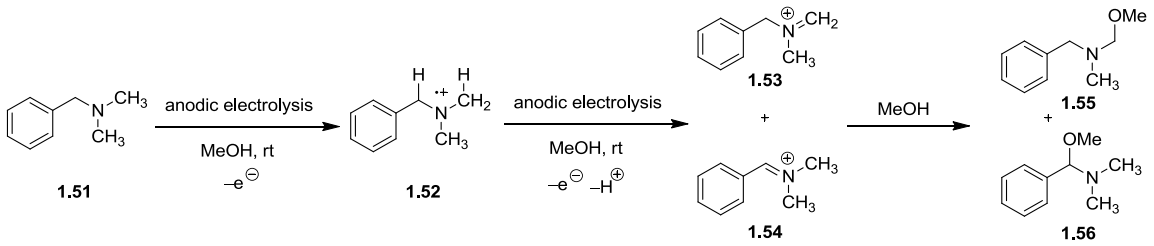
Scheme 1.11 **CDC Reaction with Organic Oxidant**



1.3.5 Electrochemical Functionalization of Amines

In addition to using transition metals to effect the oxidation and functionalization of amines, anodic electrolysis has also been utilized to generate iminium ion from tertiary amines. In 1966, Brown and co-workers discovered that by exposing *N*,*N*-dimethylbenzylamine to anodic electrolysis conditions, *α*-methoxy-*N*,*N*-dimethylbenzylamine and *N*-methoxymethyl-*N*-methylbenzylamine were obtained as a mixture of products with the ratio of 1:4 (**1.55**:**1.56)** (Scheme 1.12).[23] The reaction was proposed to proceed via a radical cation through anodic oxidation. A second anodic oxidation occurred to generate an iminium ion which was trapped by methanol which was used as the solvent.

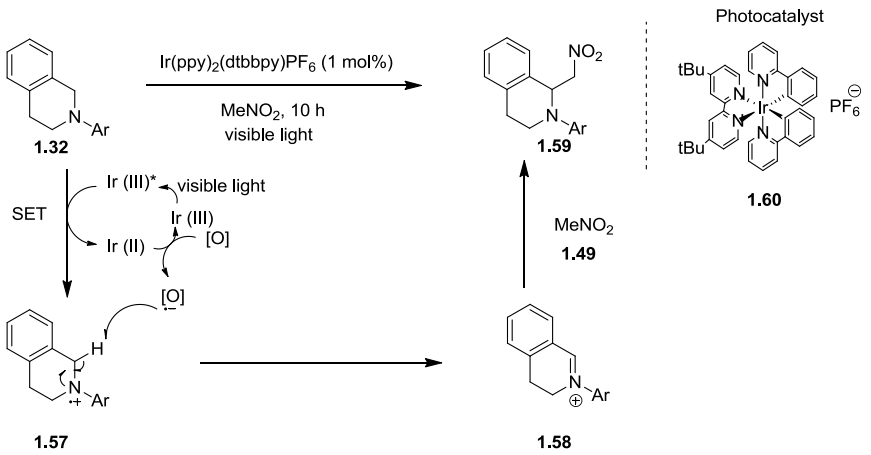
Scheme 1.12 **Electrochemical Functionalization of Amines**



1.3.6 Photocatalyzed Oxidative Functionalization of Amines

In addition to the previous examples where the transformations are carried out under conventional conditions, the α-functionalization of amines could also be enabled by visible-light photoredox catalysis.[24] In 2010, the Stephenson group disclosed their landmark work on photoredox C–H bonds functionalization adjacent to a tertiary nitrogen atom.[25] In this work, photoredox-active Ir catalyst could be excited by visible light to induce electron transfer between the Ir catalyst and a tertiary amine. The radical cation generated could ultimately be transformed into the iminium species which could subsequently be trapped by nucleophiles to give the final product (Scheme 1.13). Stephenson and co-workers also reported an improved protocol later for the generation of the iminium intermediate by changing the stoichiometric oxidant to $BrCCl_3$ which allowed for the successful utility of a broad range of appropriate nucleophiles. The reactions investigated in this paper include the Strecker, Cu-alkynylations, Mannich, Friedel-Crafts, Sakurai and aza-Henry reactions (not shown).[26]

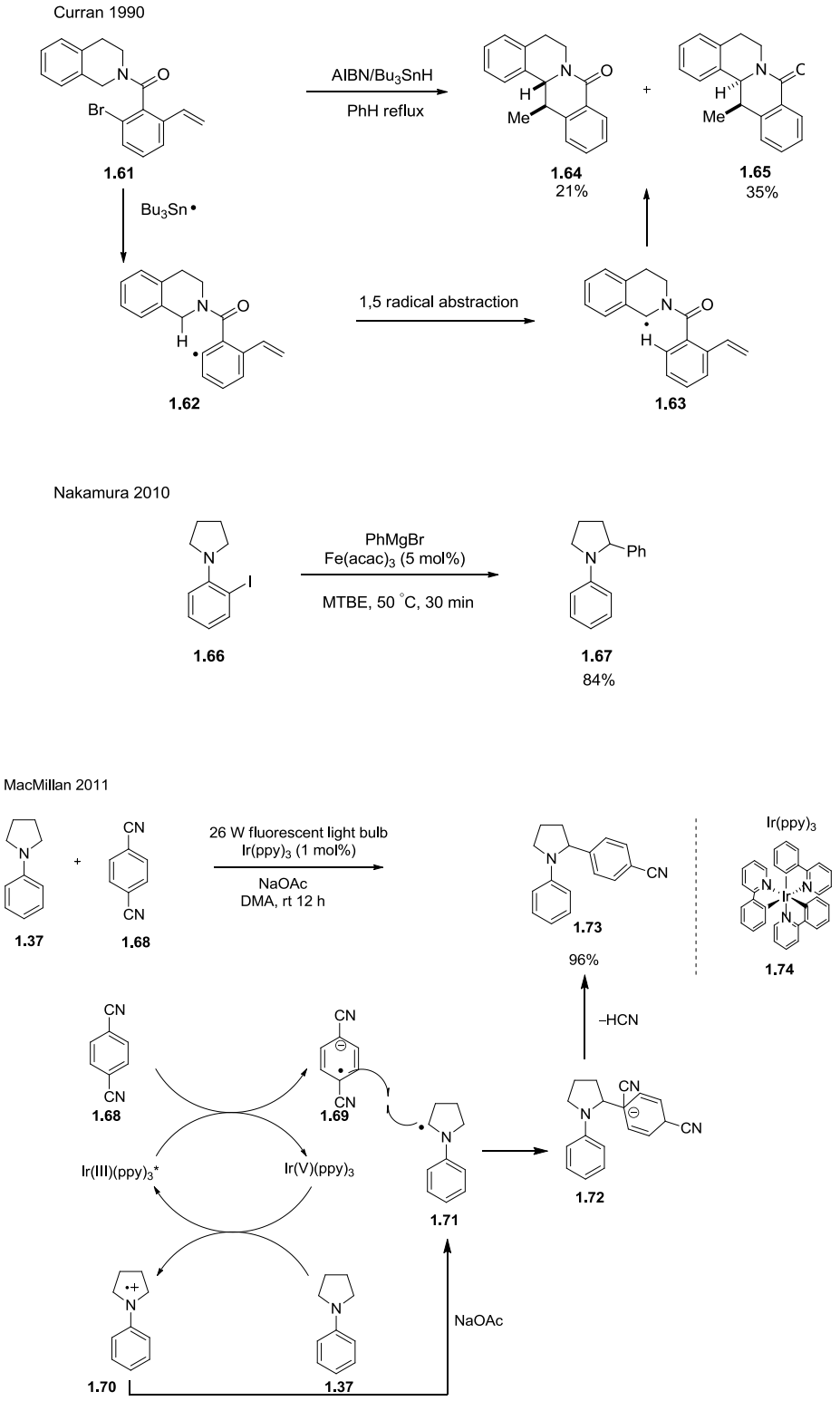
Scheme 1.13 **Photocatalyzed Oxidative Functionalization of Amines**



1.4 C–H Functionalization of Amines via α-Amino Radicals

Besides exploiting polar intermediates such as iminium ion or α-amino carbon anion as precursors for the functionalization of amines, radical-based C−H functionalization of amines has also drawn increasing attention recently. Following the innovative work of Curran and Snieckus in 1990 on the formation of α-amino carbon-centered radicals via 1,5-hydrogen transfer, many more groups developed radical-based α-functionalization of cyclic amines (Scheme 1.14).[27] Nakamura and co-workers developed an iron catalyzed α-functionalization of acyclic and cyclic amines with Grignard or zinc reagents to afford α-aryl pyrrolidines, piperidines, and azepanes. The MacMillan group discovered the photoredox α-amino C−H arylation as a new reactivity by taking advantage of accelerated serendipity.[28] The α-amino radical was generated under photoredox conditions and trapped with electron-deficient arenes or heteroarenes as radical coupling partners (Scheme 1.14).

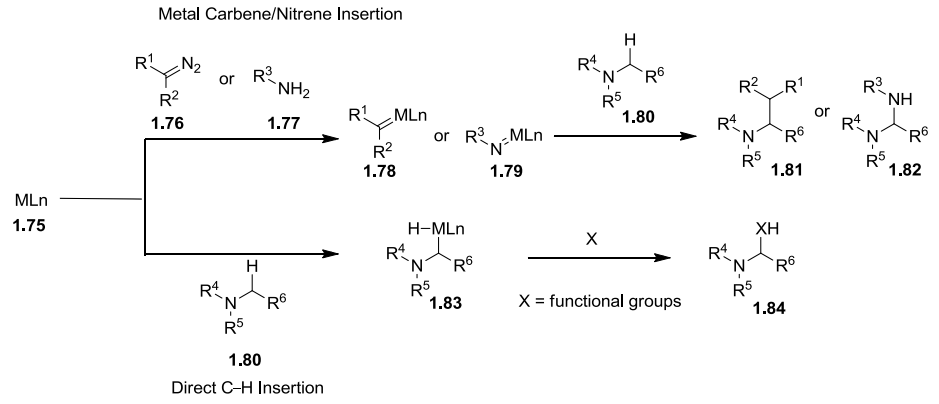
Scheme 1.14 **Redox-Neutral C–H Functionalization of Amines via α-Amino Radicals**



1.5 Functionalization of Amines through Insertions of Transition Metal and Metal Carbene/Nitrene

Although methodologies for the α-functionalization of amines involving intermediates such as α-anions, α-cations, and α-radicals are numerous, there are also some complementary approaches that utilize transition-metal catalysis to directly and selectively introduce new functionalities into the α-position of amines. These approaches either involve the direct insertion into the C−H bonds by a transition metal catalyst or involve the insertion of metal carbene/nitrene species into the C−H bonds (Scheme 1.15). [5]

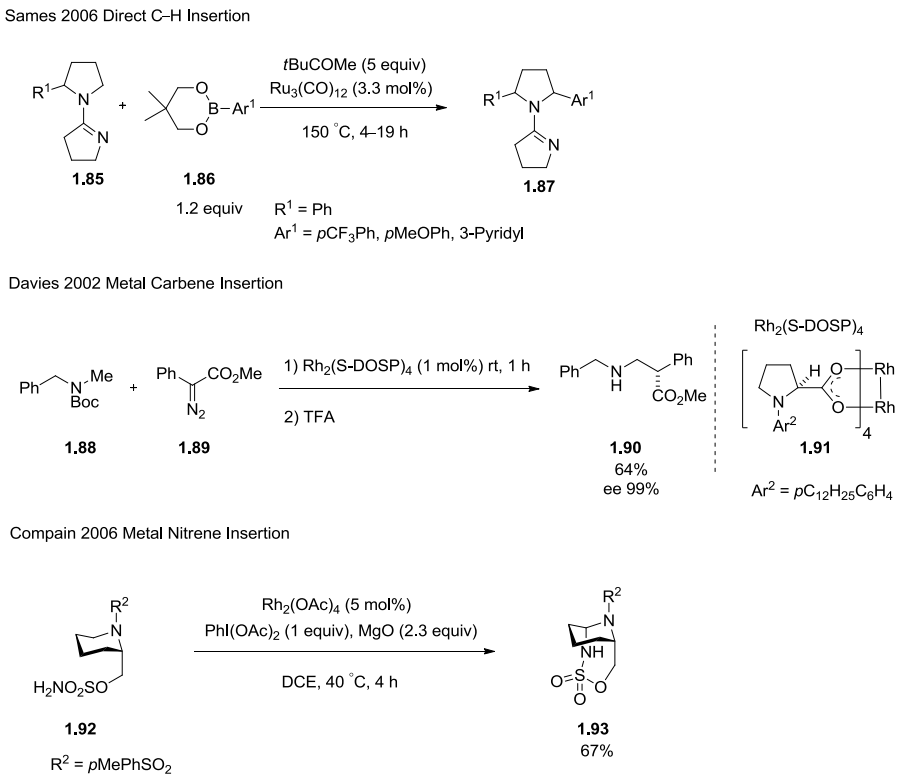
Scheme 1.15 **Functionalization of Amines through Insertions of Transition Metal and Metal Carbene/Nitrene**



For example, in 2006 the Sames group demonstrated the $Ru_3(CO)_{12}$ catalyzed α-arylation of pyrrolidines with arylboronates facilitated by an amidine directing group. In this reaction, the C–H activation was realized by oxidative addition of the C–H bond to the metal catalyst followed by transmetallation and reductive elimination (Scheme 1.16).[29] Alternatively, reactive intermediates such as metal nitrene and metal carbene intermediates could also participate in the C–H insertion process. In 2002, the Davies group disclosed their work on catalytic enantioselective carbene insertion into the

amine α-C–H bonds. A chiral dirhodium catalyst was employed to induce enantioselectivity. Compain and co-workers reported the nitrene insertion into the α-C–H bond of the piperidine skeleton to furnish the bicyclic aminal product (Scheme 1.16).[30]

Scheme 1.16 **Examples of Functionalization of Amines Mediated by Insertions of Transition Metal and Carbene/Nitrene**

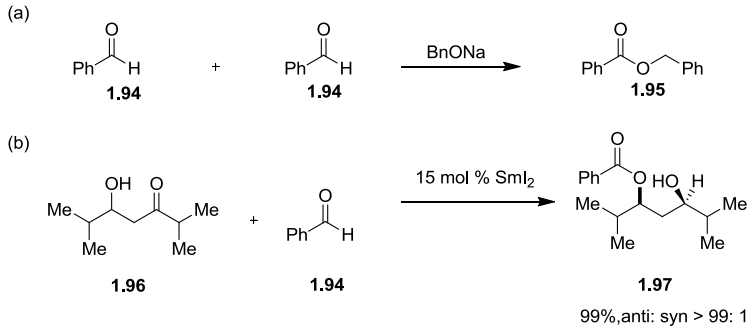


1.6 Redox-Neutral Functionalization of Amines

Although the functionalization of amines has been extensively studied over the last two decades, the majority of these strategies are oxidative in nature. This makes the use of external oxidant a necessity in most of the reactions. An external oxidant can sometimes limit the functional group tolerance in a reaction. In some cases, precious transition metals are not cost-effective to use and poses potential

toxicity issues in pharmaceutical agent syntheses. In order to remediate these disadvantages, the concept of redox economy and redox-neutral transformations have emerged as important concepts in complex molecule synthesis.[31,32] In the context of redox economy, an ideal synthesis has to be dominated by indispensable skeleton construction steps and all unnecessary oxidation/reduction and protection/deprotection manipulations are avoided.[33] In a redox-neutral reaction, instead of introducing the desired oxidation levels of functionalities in separate steps using external oxidizing and reducing reagents, the oxidized and reduced moieties are within the same molecule in the product and the redox process can be completed in a single step. The Tishchenko reaction (Scheme 1.17a)[34] and Evans–Tishchenko reaction[35] (Scheme 1.17b) are typical redox-neutral reactions where two aldehydes or an aldehyde are coupled with a,β-hydroxy ketone via an internal hydride transfer.

Scheme 1.17 **Examples of Redox-Neutral Transformation**

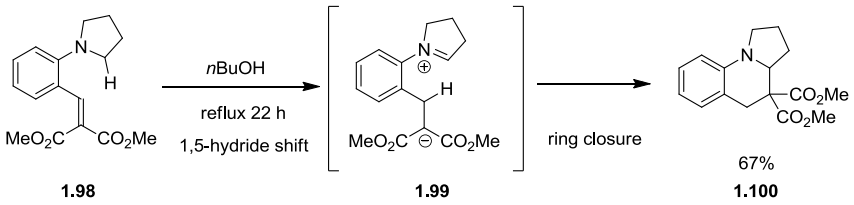


1.6.1 The "*Tert*-amino Effect" Hydride Shift Triggered Functionalization of Amines

Amine functionalization involving hydride shifts are a typical example of the redox-neutral functionalization of amines. The hydride shift triggered functionalization of amines is often induced by "*tert*-amino effect" which was put forward by Meth-Cohn and Suschitzky in 1972.[36] It refers to a tertiary aniline with an *ortho*-substituent which under thermal or Lewis acid catalyzed conditions undergoes an intramolecular hydride shift to form the ring closed product. One common type of *tert*-

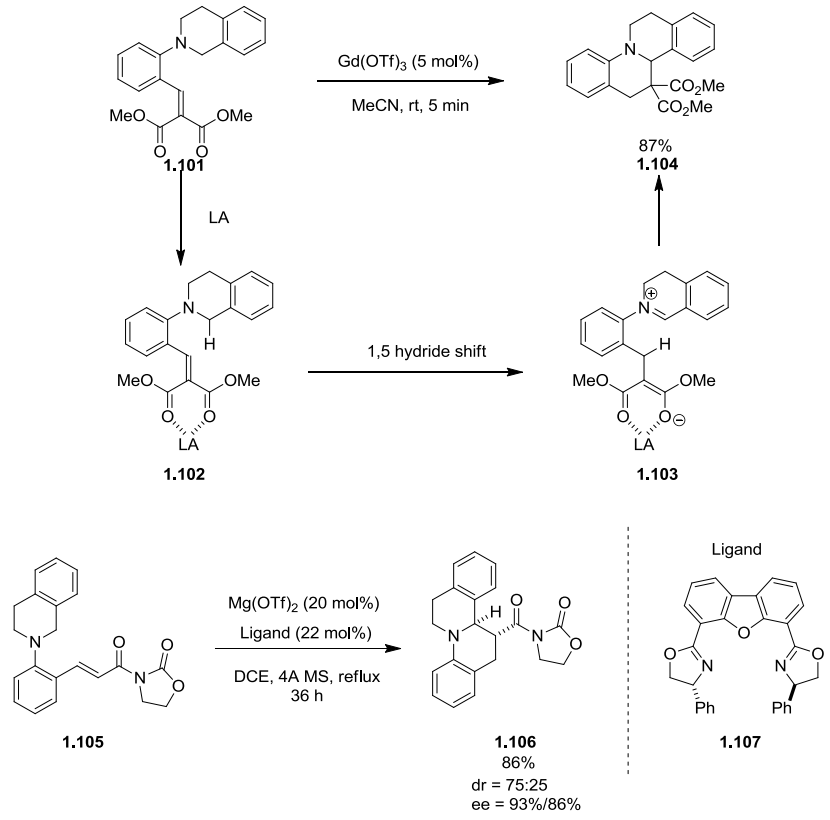
amino effect involves suprafacial 1,5-hydride transfer from the α position of the tertiary amine to the *ortho*-substituent. This process leads to the 1,6-dioplar species which then undergoes ring closure to form a six-membered ring heterocyclic system. In 1984 Reinhoudt and co-workers disclosed their first example of *tert*-amino effect transformation using alkylidene malonate as the hydride acceptor. The reaction proceeded under thermal conditions (Scheme 1.18).[37]

Scheme 1.18 **1,5-Hydride Shift Under Thermal Conditions**



Based on this seminal work, many variants of these reactions have been reported. The Seidel group in 2009 reported an example of Lewis acid catalyzed intramolecular hydride transfer reaction.[38] The reaction proceeded under at temperature and completed in a short period of time to give excellent yields (Scheme 1.19). In the same year, Seidel and co-workers reported the first catalytic enantioselective version of their intramolecular hydride transfer reaction. In this instance, an acyl oxazolidinone moiety on the substrate could act as a hydride acceptor and chelate to a chiral metal complex to induce enantioselectivity. Using $Mg(OTf)_2$ in combination with Ph-DBFox ligand gave excellent diastereoselectivity and enantioselectivity (Scheme 1.19). Interestingly, high enantioselectivity was achieved under relatively high temperature (reflux in 1,2-dichloroethane, 84 °C) which is rather uncommon for asymmetric catalysis.[39]

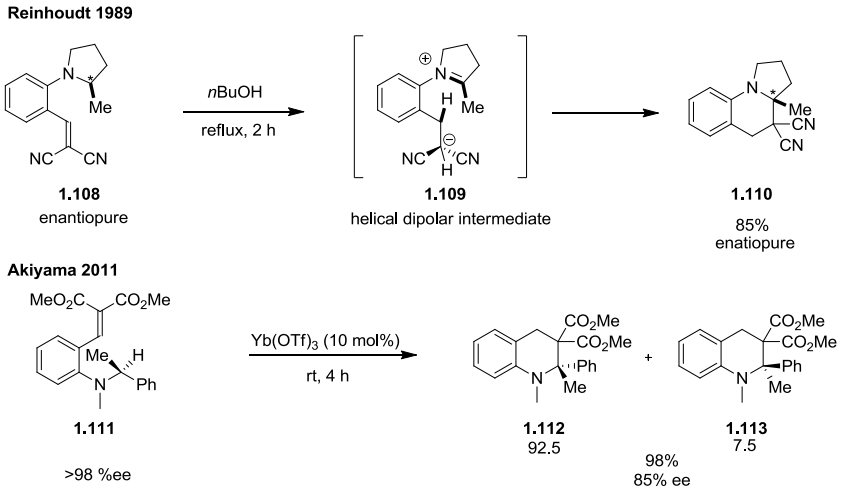
Scheme 1.19 **1,5-Hydride Shift under Lewis Acid Catalyzed Conditions**



Another interesting aspect of the *tert*-amino effect in hydride transfer reaction is the "memory of chirality" effect. It refers to a reaction in which the chiral center is temporarily lost during the course of the reaction, but the chiral information was completely preserved in the product. In 1989 Verboom and Reinhoudt demonstrated that starting from enantiopure starting material **1.108**, after undergoing 1,5-hydride shift process under thermal conditions, enantiopure ring closure product was obtained (Scheme 1.20).[40] Even though the planar intermediate **1.109** was formed during the reaction and the chiral center was temporarily destroyed. In this reaction the 1,5-hydride shift proceeds through an enantio-selective process that gives rise to a chiral helical dipolar intermediate, and the resulting carbon anion of the dipolar intermediate attacks the iminium ion exclusively on the same side from which the migrating hydride was transferred thus leading to enantiopure product. A more recent example of this reaction was reported by the Akiyama group in 2011. In this reaction the chiral

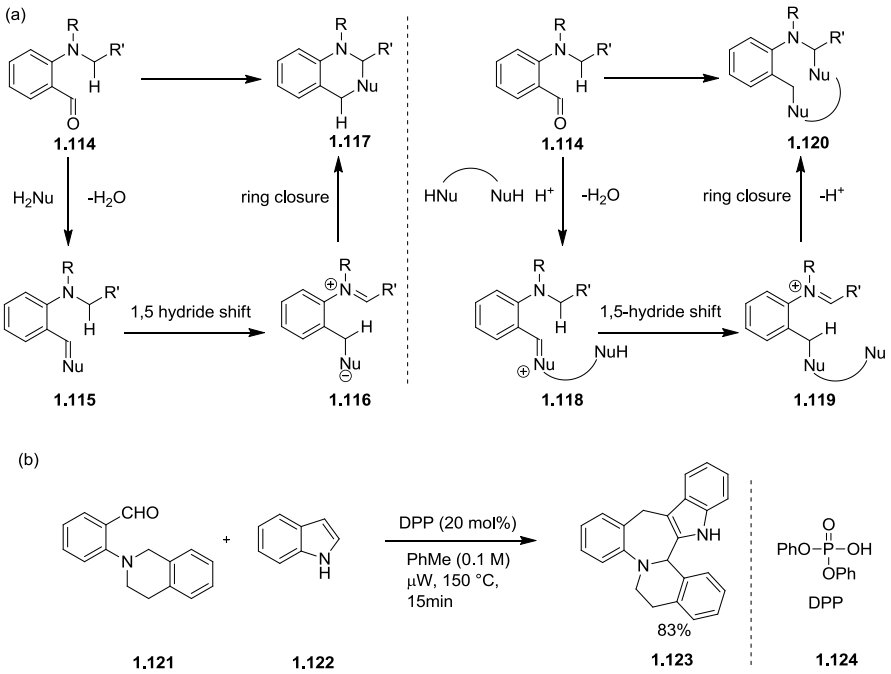
information from the starting material was similarly memorized as a helical chirality in the cationic intermediate generating enantio-enriched product (Scheme 1.20).[41]

Scheme 1.20 **"Memory of Chirality" Effect Hydride Shift Reactions**



The Seidel group further advanced the field by developing a redox-neutral reaction cascade involving an intramolecular hydride shift triggered by the *tert*-amino effect. As shown in Scheme 1.21, this hydride shift/ ring closure process has provided opportunities for the synthesis of many synthetically useful targets (Scheme 1.21b).[42]

Scheme 1.21 **The *Tert*-amino Effect Triggered α-Functionalization of Cyclic Amine and Its Application in Indole Annulation Reaction**

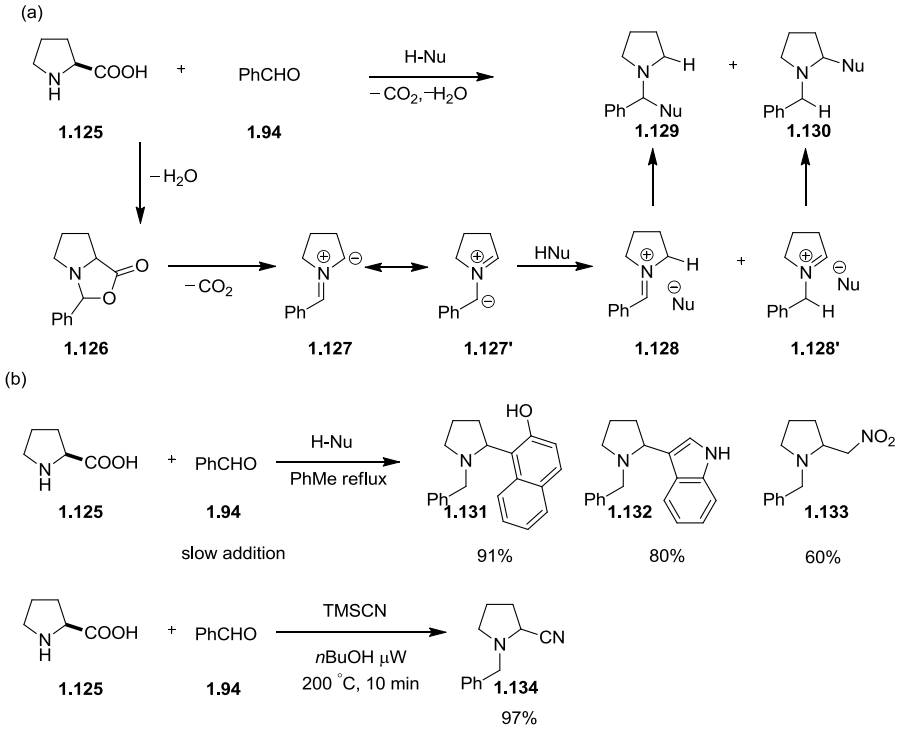


1.6.2 Decarboxylative Three Component Coupling Reaction of Amino Acids via Azomethine Ylides

Although intramolecular hydride shift chemistry has provided a powerful redox-neutral strategy to functionalize amines and construct complex heterocycles, this method is usually limited to functionalizing tertiary amines. As an alternative method to activate the C–H bond adjacent to nitrogen, azomethine ylides have now attracted much attention as a precursor to functionalized cyclic amines. Based on the Rizzi[43] and Grigg's[44] work, amino acids such as proline undergo decarboxylative condensations with aldehydes to furnish nonstabilized azomethine ylides via the intermediacy of **1.126**. The two resonance structures of the azomethine ylides enable them to form two regioisomeric iminium ions and this gives rise to two possible regioisomers after nucleophilic attack (Scheme 1.22a). In 2008 the Seidel group disclosed the decarboxylative three component

coupling reaction between proline and various nucleophiles to generate useful α-functionalized amines (Scheme 1.22b).[45,46]

Scheme 1.22 **Decarboxylative Three Component Coupling Reaction via Azomethine Ylides**

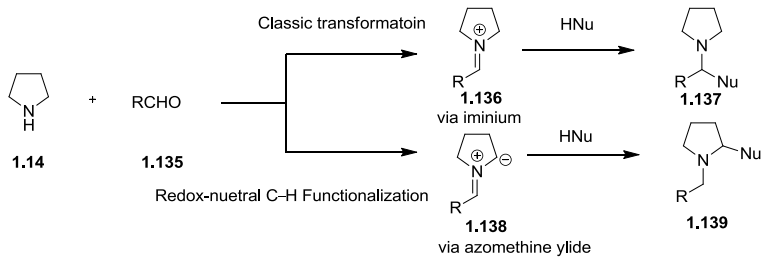


1.6.3 Redox-Neutral C–H Functionalization of Amines via Azomethine Ylides

In contrast to the aforementioned examples using amino acid and aldehyde to generate azomethine ylides, Seidel and co-workers have greatly advanced the field by introducing a mechanistic distinct way to functionalize secondary amines via azomethine ylide intermediates. By using the same substrates that participated in classic transformations like the Strecker, Mannich, and Friedel-Crafts reactions, the regioisomers of these classic reactions products can be obtained enabling the formation of ring-substituted products (Scheme 1.23). This approach involves the condensation between the carbonyl group of an aldehyde or ketone and a secondary amine. The resulting azomethine ylide **1.138** generates the isomerized iminium species which can be intercepted by various nucleophiles to

give the functionalized products **1.139**. The generation of an azomethine ylide was the key step in these transformations and its mechanism has been studied intensively by our group, the details of which will be discussed in Chapter III of this dissertation.

Scheme 1.23 **Redox-Neutral Functionalization vs. Classic Transformation**

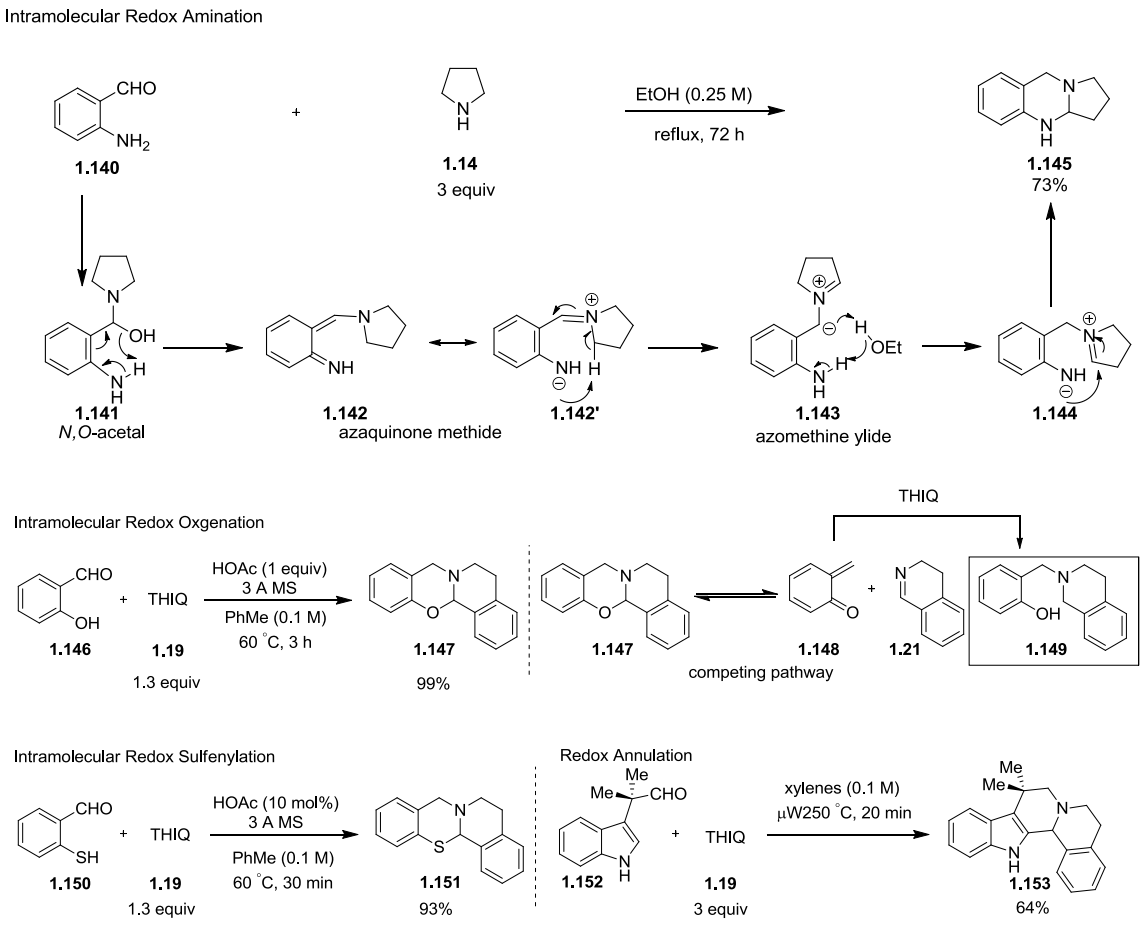


1.6.3.1 Intramolecular Functionalization of Secondary Amines via Azomethine Ylides

The first type of redox-neutral functionalization of amines via azomethine ylides was discovered by the Seidel group in 2008 serendipitously in an attempt to synthesis the Friedlander condensation product.[47] When mixing *ortho*-aminobenzaldehyde with secondary amine in EtOH under reflux, the cyclic aminal product between the pyrrolidine and *ortho*-aminobenzaldehyde was observed (Scheme 1.24). In collaboration with Houk and co-workers, the detailed mechanism of this transformation was investigated experimentally and computationally.[48] The amine condenses with an aldehyde to result in the *N*,*O*-acetal species, which then undergoes elimination of water to generate azaquinone methide **1.142**. Azaquinone methide then undergoes a 1,6-proton transfer to form the azomethine ylide species. The theoretical calculations suggest the rate determine step is the 1,6-proton transfer step which is also consistent with the deuterium labeling studies. With the aid of EtOH, after proton transfer the generation of species **1.144** sets up the stage for the final nucleophilic ring closure step. The whole process of this reaction is redox-neutral as the amine is oxidatively functionalized with concurrent reductive *N*-alkylation. The discovery of this novel reactivity has opened up a new entry to important

molecular targets that might otherwise require lengthy synthetic procedures. The Seidel group extended this chemistry to the intramolecular redox oxygenation[49] and sulfenylation[50] of amines (Scheme 1.24). In the work of α-oxygenation, it was found that conditions using protic solvent and excess amine that were effective for the α-amination was not effective in this case. Instead, the use of acetic acid as the reaction promoter and PhMe as the solvent are crucial for the reaction. The formal reduced product was isolated as the major product when using protic solvent or in the absence of any acid promoters. It likely results from the decomposition of *N*,*O*-acetal **1.147** via a (formal) retro-Diels−Alder reaction to form *ortho*-quinone methide **1.148** and 1,2-dihydroisoquinoline (DHIQ). The *ortho*-quinone methide intermediate is intercepted by THIQ to afford the formal reduced product (Scheme 1.24). Similar conditions were also applied to the α-sulfenylation of amines. In this case, a catalytic amount of acetic acid was sufficient to catalyze the reaction, and the scope with regard to the amine is unusually broad; even relatively unreactive substrates such as morpholine, thiomorpholine, piperazines, and dibenzylamine undergo this transformation. In addition to C–X (X = N, O, S) bond formation, this redox-neutral strategy has been applied to C–C bond formation as well. When aldehydes linked to electron-rich aromatic rings are subject to elevated temperatures under microwave conditions, they readily undergo redox annulation with amines with concurrent C–C bond formation (Scheme 1.24).[51]

Scheme 1.24 **Intramolecular Functionalization of Secondary Amines via Azomethine Ylides**

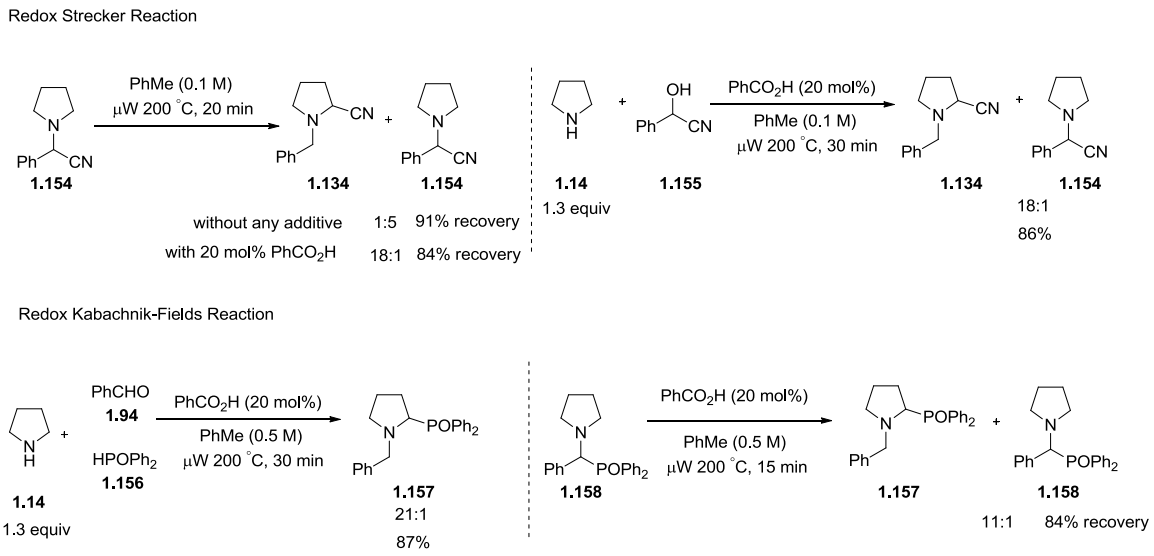


1.6.3.2 Intermolecular Functionalization of Secondary Amines via Azomethine Ylides

Having established the intramolecular redox transformation, the Seidel group sought to investigate the intermolecular redox-neutral transformation. This is intrinsically more challenging because for the intramolecular variants described above, the classic reaction pathway is less favorable than the redox pathway (four-membered vs six-membered ring formation), any intermolecular redox transformation would necessarily have to compete with the conventional direct nucleophilic addition pathway. The first example of the intermolecular redox-neutral functionalization was the α-cyanation reaction of amines by Seidel group in 2012 (Scheme 1.25).[52] In this work, the authors discovered that the classic

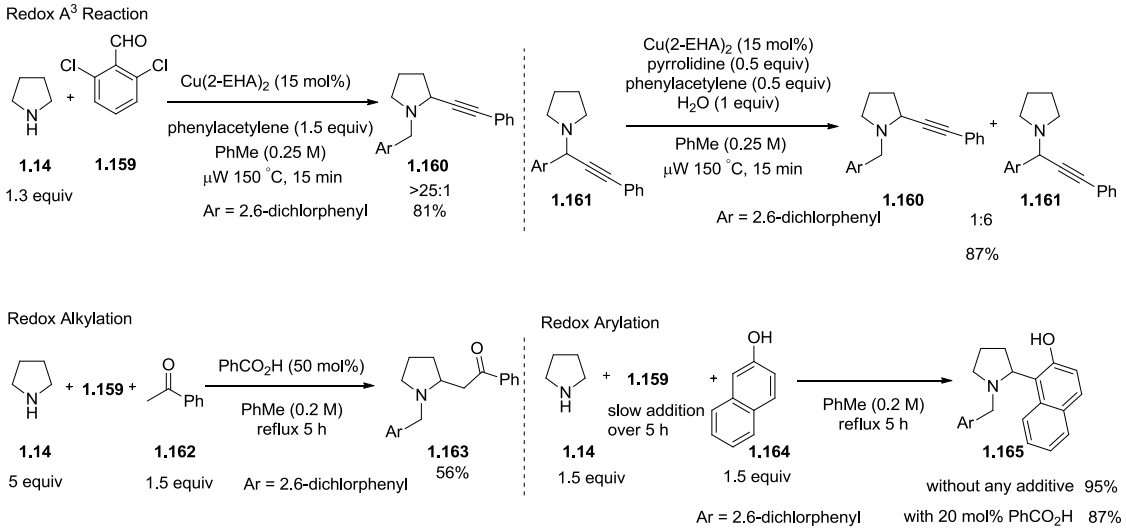
three-component condensation product **1.154** can readily isomerize to its corresponding redox product **1.134**. After careful condition screening, it was found that in the presence of catalytic amount of benzoic acid, α-aminonitrile **1.154** can efficiently isomerize to **1.134** with an 18:1 ratio. Another striking observation that is worth mentioning is that partial isomerization to **1.134** can be achieved in the absence of any additives. Simple heating of a toluene solution of **1.154** to 200 °C (microwave) for 20 min results in a 1:5 mixture of **1.134**/**1.154**, with good overall α-aminonitrile recovery. These discoveries have led to the development of a two component approach to the redox Strecker product from pyrrolidine and cyanohydrins. In this two-component approach, 2-Ethyl hexanoic acid (2-EHA) slightly outperforms benzoic acid. The Seidel group subsequently developed redox-neutral phosphonation variants of this reaction.[53] This transformation is conducted in a three component fashion, starting from the secondary amine, aldehyde and phosphine oxides (Scheme 1.25).[53] Under the optimized conditions, 2-EHA acid is replaced with benzoic acid as developed for the redox-Strecker reaction. One aspect of this reaction which is worth noting is that similarly to the α-aminonitrile isomerization, it was found that the classic Kabachnik−Fields condensation product **1.158** could also isomerize to the apparently thermodynamically more stable redox product **1.157**.

Scheme 1.25 **Redox Strecker and Redox Kabachnik-Fields Reactions**



The aforementioned intermolecular redox-neutral reactions all share the same feature that the nucleophile used is relatively good leaving group (cyanide, phosphine oxide). The ability to use poor leaving groups as nucleophiles was shown by the Seidel group when they carried out the redox-A^3 reaction (Scheme 1.26).[54] In considering the factors that might allow for the development of a redox-A^3 reaction, Seidel and co-workers chose 2,6-dichlorobenzaldehyde as the aldehyde component in the redox reaction. The rationale behind this is that the transformation of iminium ions such as **1.136** to the azomethine ylide **1.138** might be accelerated when **1.136** is derived from a relatively electron-poor aldehyde, and that the classic pathway (copper acetylide addition to **1.136**) should be slowed when iminium ions are generated from a bulky aldehyde. In this case, product isomerization is observed but only to a very minor extent. Exposure of **1.161** to the reaction conditions only leads to minor amounts of **1.160**, with most **1.161** being recovered. In addition to the α-alkynylation, the α-arylation[55] using electron rich phenols and the α-alkylation[56] with ketones, nitromethanes were also successfully developed in the Seidel group (Scheme 1.26). It's interesting that in the redox arylation reaction the condition using 20 mol% $PhCO_2H$ gave inferior result to the one using no additives. This is likely because the phenolic substrate is acidic enough to catalyze the redox reaction.

Scheme 1.26 **Redox A^3 Reaction, Redox Alkylation and Redox Arylation Reaction**

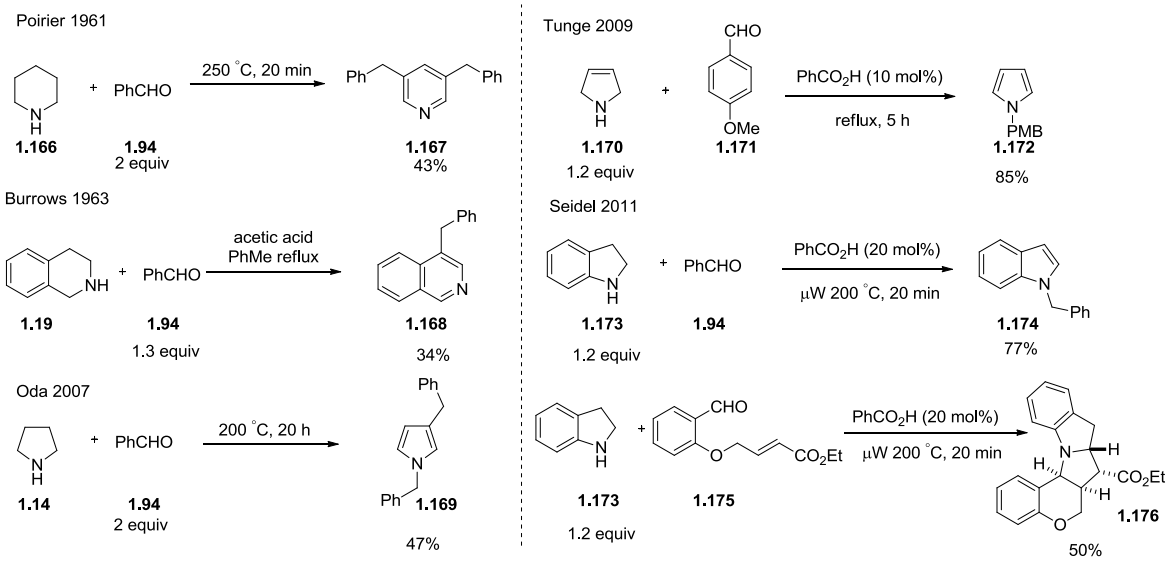


1.6.3.3 Redox-Neutral Aromatization of Amines via Azomethine Ylides

In the study of the redox-neutral functionalization of amines, it was found that if a (partially) saturated secondary amine (e.g. 3-pyrroline) is used as the substrate in some cases the aromatized product could be obtained. One of the earliest example of this type of reaction was reported by Rügheimer in 1891,[57] in this work benzoylpiperidine was heated with benzaldehyde at 250 °C to afford the 3,5-disubstituted pyridine. More related work came from the Poirier group in 1961 (Scheme 1.27),[58] where piperidine reacted with benzaldehyde to form 3,5-dibenzylpyridine with acetic acid as a promoter. Similarly, the Oda group reported the synthesis of 1,3-dibenzylpyrrole from pyrrolidine and benzaldehyde (Scheme 1.27).[59] Starting from 3-pyrroline and aldehydes or ketones, Cook[60] and Tunge[61] later independently reported *N*-alkyl pyrrole formation under thermal conditions. Another report by Burrows describes the synthesis of 4-benzylisoquinoline from THIQ and benzaldehyde under very similar conditions.[62] In 2011, the Seidel group also discovered that the aromatization of indoline could be effected by reacting indole with aldehydes.[63] Azomethine ylide was suggested as a reactive intermediate during the course of the reaction. Inspired by Grigg's work using an aldehyde

carrying a pendent dipolarophile moiety (**1.175)** to trap azomethine ylides,[64] an intramolecular [3+2] trapping experiment was conducted by Seidel and co-workers with indoline to provide supporting evidence for the azomethine ylide formation (Scheme 1.27). In this trapping experiment, the [3+2] cycloaddition product was isolated together with the aromatization product (not shown) suggesting the competing reaction pathways between the cycloaddition and aromatization of the azomethine ylides.

Scheme 1.27 **Redox-Neutral Aromatization of Amines via Azomethine Ylides**

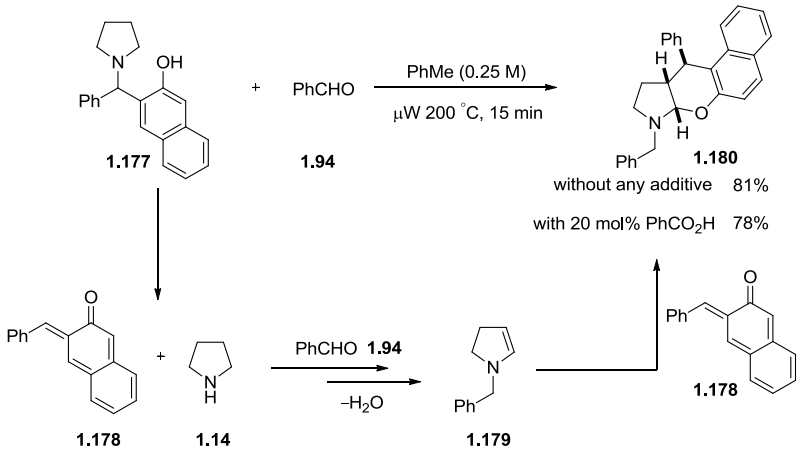


1.6.3.4 Redox-Neutral α,β-Difunctionalization of Amines via Azomethine Ylides

In the studies of the redox aromatization reaction, endocyclic enamine was found to be an apparent reactive intermediate in the reaction process and its presence in the aromatization reaction was also supported by Dannhardt's study in 1990.[65] The Seidel group further developed this reaction and diverted the enamine generated in situ to effect the α,β-difunctionalization of amines in 2014.[66] When **1.177** was exposed to the isomerization condition in the attempt to get its corresponding redox-arylation product (not shown), it was noticed that the unexpected product **1.180** was isolated as a

single diastereomer. The optimal condition for the formation of the α,β-difunctionalized product was by using a slight excess amount of benzaldehyde to react with **1.177** under microwave conditions. Similar to what was observed in the α-arylation reaction, no additive was needed for the transformation. The formation of **1.180** is proposed to initiate from the fragmentation of **1.177** to *ortho*-quinone methide **1.178** with concurrent release of pyrrolidine. Pyrrolidine then reacts with benzaldehyde through a series of steps to generate enamine **1.178**, which undergoes an endo-selective hetero-Diels−Alder reaction with **1.178** to afford product **1.180** (Scheme 1.28).

Scheme 1.28 **Redox-Neutral α,β-Difunctionalization of Amines via Azomethine Ylides**



1.7 Objectives

The redox-neutral functionalization reactions have shown great potential in organic synthesis as they enable quick access to the molecular complexity that would otherwise requires lengthy synthetic procedures. The recent advancement in the research of redox-neutral functionalization of amines has greatly expanded the scope and generality of the transformations and improved the efficiency and simplicity of the operations. However, challenges regarding the explicit control over the reactivity of

azomethine ylides still remain. Furthermore, the mechanism of the azomethine ylide formation and the role of different additives on the outcome of these redox-neutral reactions is still not clear.

In the research presented in this dissertation, the objectives are to develop novel redox-neutral C–H functionalization of amines strategies that involve the formation of azomethine ylides. We are also interested in investigating mechanistic details regarding the formation of azomethine ylide and its transformations to many synthetic useful products. We want to apply newly developed methodologies to natural product synthesis. We also seek to explore new intermolecular hydride shift reaction using secondary amines. We hope that our contributions to this field can address some unsolved problems and provide useful information for further studies. Chapter II will discuss in detail the redox-neutral α-cyanation of amines. Chapter III will discuss mechanistic studies on the redox aromatization of amines and its synthetic utilities. Chapter IV will introduce new intramolecular redox-Mannich reactions. Lastly, chapter V will discuss the intermolecular hydride transfer triggered α-functionalization of amines.

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Chapter II Redox-Neutral α-Cyanation of Amines

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Redox-Neutral α-Cyanation of Amines

Longle Ma, Weijie Chen, Daniel Seidel

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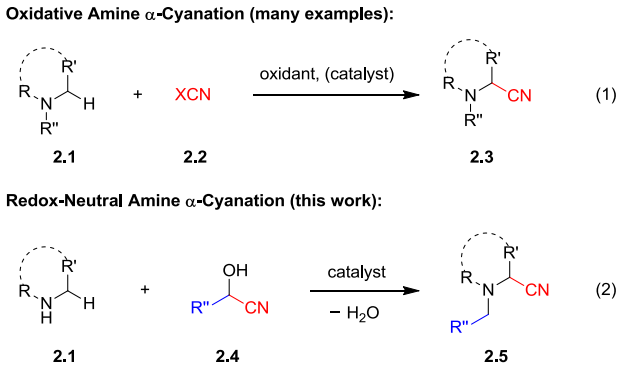
2.1 Background

The exceptional versatility of α-aminonitriles continues to inspire the development of methods that provide access to these valuable building blocks.[1] While the classic Strecker reaction[2,3] remains an important tool in this regard, α-aminonitriles that are part of a ring system cannot easily be prepared by this methodology. A particularly attractive alternative approach to α-aminonitriles such as **2.3** is the replacement of an amine α-C–H bond with a C–CN bond (**2.1** → **2.3**, Scheme 2.1, eq 1). Previous efforts to develop such methods have relied on oxidative approaches,[4,5] including electrochemical methods.[6] Very recently, photo-redox catalysis has emerged as another tool for oxidative amine α-cyanation, although this strategy has largely been limited to *N*-aryl tetrahydroisoquinolines and *N*,*N*-dialkylanilines.[7] Here we report a conceptually new strategy for the α-cyanation of amines (Scheme 2.1, eq 2). In contrast to previous approaches, this method is redox-neutral,[8] and no metal-based catalysts are required.

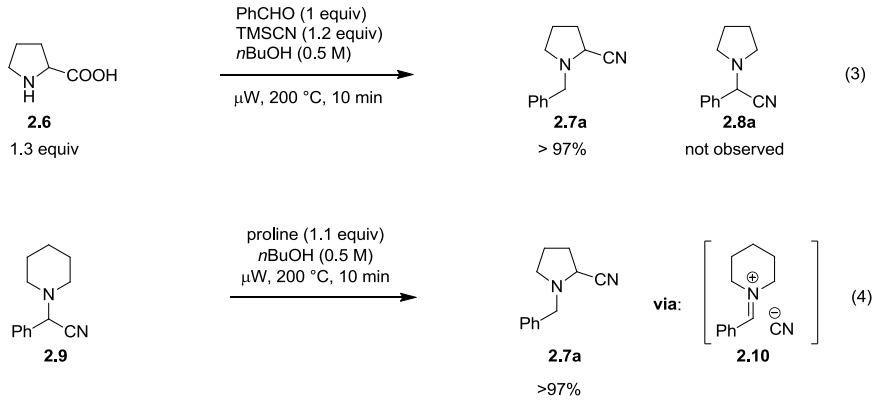
Scheme 2.1 **Oxidative vs. Redox-Neutral Approaches of Amine α-Cyanation**



As part of a program to develop redox-neutral reactions of amines and amino acids for the rapid buildup of molecular complexity,[9,10] we recently reported a decarboxylative version of the classic Strecker reaction (Scheme 2.2, eq 3).[9l] Specifically, we found that α-amino acids such as proline react

with aldehydes and TMSCN to form cyclic α-aminonitriles (e.g., **2.7a**) rapidly under microwave irradiation. In the course of our studies, we also discovered that α-aminonitrile **2.9** reacts with proline to form **2.7a** (Scheme 2.2, eq 4). This reaction most likely proceeds via iminium ion pair **2.10**, which is thought to be present in equilibrium with α-aminonitrile **2.9**.

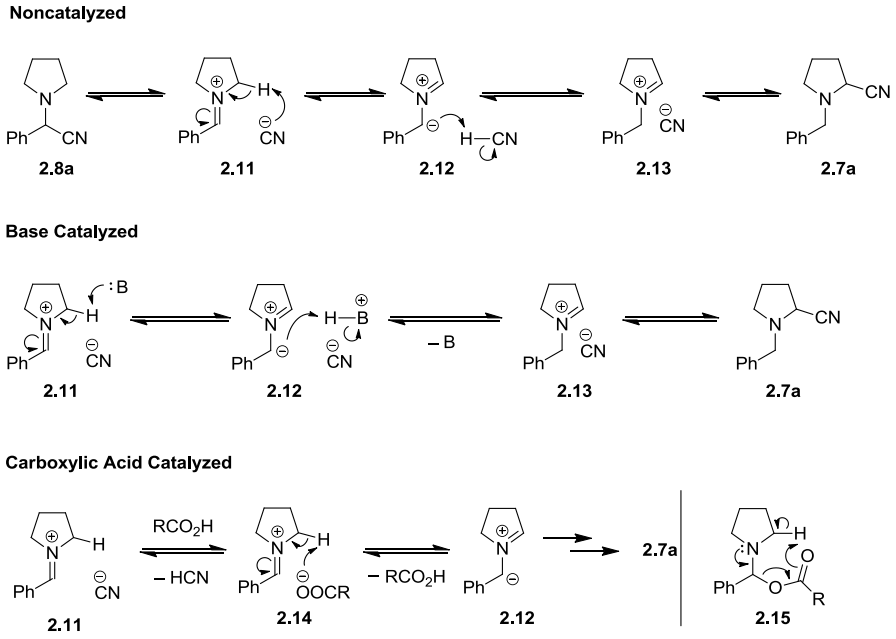
Scheme 2.2 **Decarboxylative Strecker Reaction and α-Aminonitriles Isomerization**



2.2 Concept of Redox-Neutral Isomerization of α-Aminonitriles

The notion that iminium ions such as **2.11** are accessible from their corresponding α-aminonitriles led us to consider the possibility of a novel α-aminonitrile isomerization (Figure 2.1). The ability to generate cyclic α-aminonitriles such as **2.7a** from **2.8a**, which is readily available by standard Strecker chemistry,[11,12] would represent a significant advance as this would enable the use of simple amines as starting materials in place of amino acids. In fact, as outlined in Figure 2.1, a number of potential pathways can be considered that would result in the desired isomerization process.

Figure 2.1 **Potential Pathways for α-Aminonitrile Isomerization**



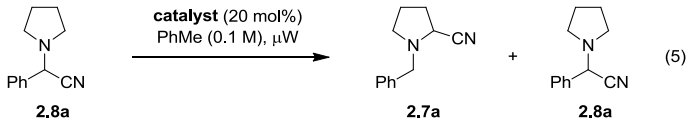
α-Aminonitrile **2.8a** may isomerize to **2.7a** simply by heating in the absence of any additives (noncatalyzed pathway). Iminium ion **2.11**, which is expected to be present in low equilibrium concentrations, could be transformed into azomethine ylide **2.12** via iminium α-deprotonation by the relatively basic cyanide counteranion. The thus formed HCN would subsequently protonate azomethine ylide **2.12** at the benzylic position, resulting in the formation of the new iminium ion **2.13**, the direct precursor of α-aminonitrile **2.7a**.[13,14] A base catalyzed pathway can be envisioned as a variation of this isomerization process. In this case, similar intermediates are accessed with the difference being that the initial deprotonation of iminium ion **2.11** is achieved by an external base more basic than cyanide.

The perhaps most promising approach for α-aminonitrile isomerization is a carboxylic acid catalyzed pathway (Figure 2.1). Here, the cyanide anion of **2.11** is protonated by a carboxylic acid catalyst to form iminium ion **2.14**. The carboxylate anion could subsequently deprotonate the iminium α-proton

to give azomethine ylide **2.12** which goes on to form α-aminonitrile **2.7a**. Alternatively, *N*,*O*-acetal **2.15**, which is expected to exist in equilibrium with **2.14**, could eliminate carboxylic acid to form azomethine ylide **2.12** via a concerted pathway. A closely related mechanism was proposed by Yu et al.[15] as part of a computational investigation of Tunge's benzoic acid catalyzed formation of *N*-alkyl pyrroles from 3-pyrroline.[10l] Independently, we have recently shown by means of intramolecular [3+2] trapping experiments that azomethine ylides are likely intermediates in this and other carboxylic acid catalyzed redox-isomerization processes.[9h]

2.3 Evaluation of Isomerization Conditions

Table 2.1 **Evaluation of Isomerization Conditions.**[a]



Entry	Catalyst	Temperature [°C]	Time [min]	Ratio **2.7a** : **2.8a**	Yield (%)
1	–	200	20	1:5	91
2	NEt_3	200	20	1:4	ND
3	$PhCO_2H$	200	20	18:1	84
4	$MeCO_2H$	200	20	10:1	84
5	2-Ethylhexanoic acid	200	20	16:1	84
6	Pivalic acid	200	20	15:1	70
7	4-MeO-benzoic acid	200	20	12:1	86
8	4-NO_2-benzoic acid	200	20	16:1	43
9	Chloroacetic acid	200	20	7:1	13
10	CF_3CO_2H	200	20	1:2	ND

11	Diphenylphosphate	200	20	<1:20	ND
12[b]	Pyridinium tosylate	200	20	ND	ND
13	Cu (II) benzoate	200	20	15:1	41
14	Cu (II) 2-EHA	200	20	10:1	21
15	$PhCO_2H$	200	5	11:1	90
16	$PhCO_2H$	200	10	13:1	86
17	$PhCO_2H$	200	30	17:1	77
18[c]	$PhCO_2H$	200	20	18:1	79
19[d]	$PhCO_2H$	200	20	4:1	ND
20[e]	$PhCO_2H$	200	20	1:1	ND
21	$PhCO_2H$	150	20	1:2	ND
22	$PhCO_2H$	180	20	13:1	79
23	$PhCO_2H$	250	20	9:1	41

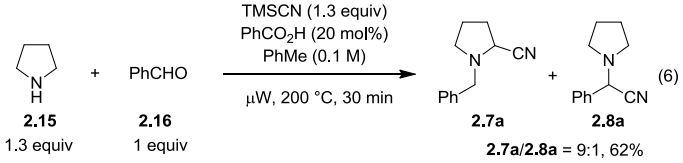
[a] Reactions were performed on a 0.25 mmol scale. Yield corresponds to combined, isolated yields of both regioisomers. ND: not determined. [b] s.m. decomposed[c] in xylenes. [d] in acetonitrile. [e] in *n*-butanol.

Different catalysts were tested in the proposed α-aminonitrile isomerization, using **2.8a** as a model substrate (Table 2.1).[16] Interestingly, brief exposure of **2.8a** to microwave irradiation at 200 °C led to some isomerization in the absence of any additives (entry 1). The addition of triethylamine had no discernible effect on the outcome of the isomerization (entry 2).[17] Gratifyingly, a catalytic amount of benzoic acid (20 mol%) led to almost complete isomerization to the desired α-aminonitrile **2.7a**. Specifically, **2.7a** and **2.8a** were isolated in an 18:1 ratio in 84% combined yield (entry 3).[18] A number of other aliphatic and aromatic carboxylic acid catalysts exhibited a very similar but slightly inferior performance (entries 4–7). Carboxylic acids with increased acidities resulted in less favorable product ratios or led to poor yields. Diphenylphosphate was completely ineffective as a catalyst (entry 11). Pyridinium tosylate led to the decomposition of the starting material. (entry 12). Copper salts are moderately effective in the isomerization process, but giving inferior yields (entry 13–14). Shorter

reaction times led to lower levels of isomerization (entries 15–16) whereas prolonged exposure to microwave irradiation did not serve to improve product ratios but rather led to slightly reduced yields (entry 17). Exchange of toluene for xylenes as the solvent made virtually no difference (entry 18) whereas the degree of isomerization was substantially lower in acetonitrile (entry 19). Interestingly, very little isomerization was observed in *n*-butanol (entry 20), the solvent that was previously found to be optimal in the decarboxylative Strecker reaction. Lastly, reaction temperatures below 200 °C led to incomplete isomerization and higher temperatures resulted in partial decomposition (entries 21–23). In some cases, 1,3-dibenzylpyrrole was observed as a minor byproduct of the isomerization process.[10e]

Having identified convenient conditions for α-aminonitrile isomerization, we next sought to develop a one-pot approach to the synthesis of **2.7a**. Upon exposing a mixture of pyrrolidine, benzaldehyde, TMSCN and benzoic acid (20 mol%) in toluene to microwave irradiation at 200 °C for 30 min, α-aminonitriles **2.8a** and **2.7a** were obtained in a 9:1 ratio and 62% combined yield (Scheme 2.3). Upon further experimentation, we found that it is advantageous to perform the direct α-cyanation of pyrrolidine as a two- rather than three-component reaction, using readily available cyanohydrins as starting materials (Table 2.2, eq 7). In this instance, 2-ethylhexanoic acid (2-EHA) slightly outperformed benzoic acid as the catalyst.

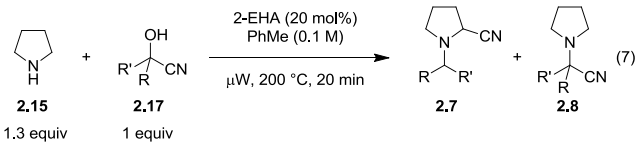
Scheme 2.3 **One-Pot Approach to the Synthesis of 2.7a**



2.4 Substrate Scope of the α-Cyanation

The scope of this reaction with regard to the cyanohydrin is summarized in Table 2.2.Cyanohydrins derived from aromatic aldehydes with various substitution patterns provided α-aminonitriles **2.7** with favorable regioselectivities and in good yields. A number of heteroaromatic substituents were also well tolerated. Cyanohydrins derived from aliphatic aldehydes provided less favorable product ratios. This is perhaps due to a lower ionization propensity of the regular Strecker products. Interestingly, benzophenone-derived cyanohydrin provided α-aminonitrile **2.7p** in essentially regioisomerically pure form.

Table 2.2 **Scope of the Direct α-Cyanation with Pyrrolidine.**[a]



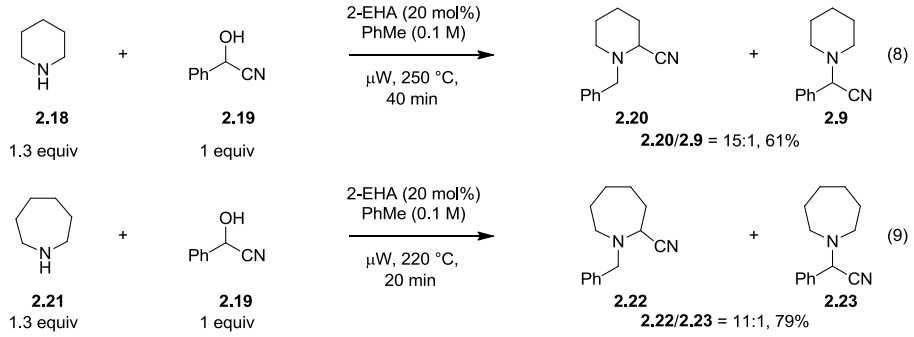
Entry	R	R′	Product **2.7**/**2.8**	Ratio **2.7**:**2.8**	Yield (%)
1[b]	Ph	H	**a**	18:1	86
2	4-Me-C_6H_4	H	**b**	16:1	80
3	4-MeO-C_6H_4	H	**c**	11:1	67
4	4-Cl-C_6H_4	H	**d**	>20:1	94
5[c]	4-NO_2-C_6H_4	H	**e**	1.4:1	41
6	3-Cl-C_6H_4	H	**f**	>20:1	87
7	3-Me-C_6H_4	H	**g**	19:1	79
8	2-Br-C_6H_4	H	**h**	>20:1	85
9	mesityl	H	**i**	>20:1	89
10	1-naphthyl	H	**j**	18:1	85

11	3-pyridyl	H	**k**	>20:1	60
12	2-furyl	H	**l**	20:1	64
13	2-thienyl	H	**m**	>20:1	82
14	CO_2Et	H	**n**	1:1.4	62
15	CH_2CH_2Ph	H	**o**	1:3	74
16	cyclohexyl	H	**p**	1:5	78
17[d]	Ph	Ph	**q**	>20:1	40

[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] Due to partial decomposition, no heating element was used. [d] Benzoic acid was used as the catalyst.

Importantly, the redox-neutral α-cyanation is applicable to amines other than pyrrolidine. For instance, piperidine readily underwent *N*-alkylation/α-cyanation when exposed to benzaldehyde cyanohydrin in the presence of 2-ethylhexanoic acid (Scheme 2.4, eq 8). Products **2.20** and **2.9** were obtained in a favorable 15:1 ratio in 61% overall yield. An increased temperature was required in this instance as a reaction performed at 200 °C provided compound **2.9** as the major product. Azepane underwent the corresponding reaction at 220 °C to give products **2.22** and **2.23** in an 11:1 ratio and 79% combined yield (eq 9).[19]

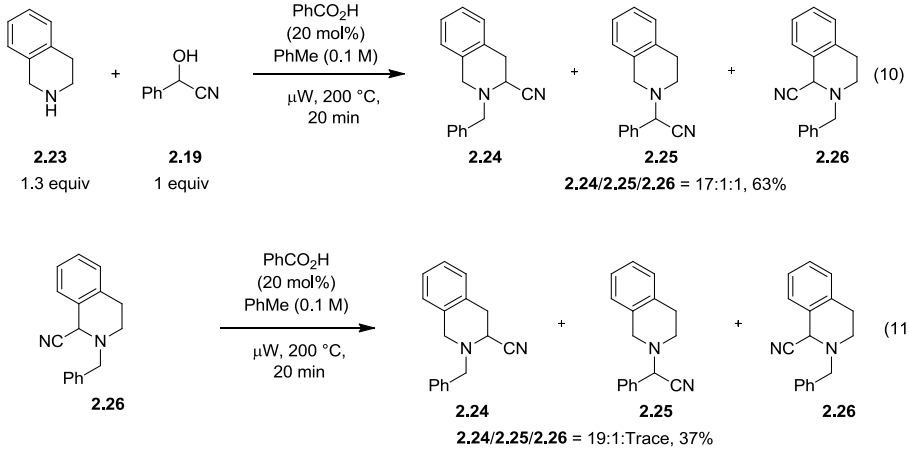
Scheme 2.4 α-**Cyanation with Piperidine and Azepane**



2.5 Regioselectivity of the α-Cyanation

A reaction of tetrahydroisoquinoline with benzaldehyde cyanohydrin gave rise to predominantly one of the three possible regioisomeric products (Scheme 2.5, eq 10). Interestingly, product **2.24** was isolated as the major regioisomer, resulting from the functionalization of the non-benzylic position of the tetrahydroisoquinoline ring. This regioselectivity is complementary to what is observed in any of the oxidative functionalizations of *N*-aryl tetrahydroisoquinolines.[4-7] In addition to the expected α-aminonitrile products, 4-benzylisoquinoline[20] was isolated as a byproduct in 14% yield. To establish whether α-aminonitrile **2.26** could isomerize to **2.24** or **2.25**, an independently prepared sample of **2.26** was exposed to the previously optimized isomerization conditions (Scheme 2.5, eq 11). In this case α-aminonitrile **2.24** was again obtained as the major product.[21] However, the efficiency of this process was rather poor, and 4-benzylisoquinoline was obtained as a byproduct in 17% yield.

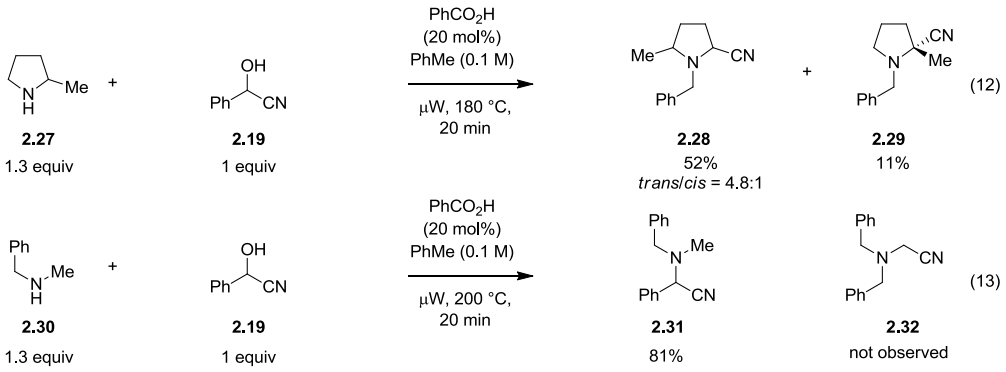
Scheme 2.5 **Regioselectivity of α-Cyanation with Tetrahydroisoquinoline**



As shown in Scheme 2.6, eq 12, a reaction with 2-methyl-pyrrolidine provided a mixture of products **2.28** (52%) and **2.29** (11%). Product **2.28** was obtained as a 4.8:1 mixture of diastereomers.[22] None of the regular Strecker product was isolated. Although acyclic α-aminonitriles are readily obtained by

standard Strecker chemistry, we also conducted a reaction with methylbenzylamine to learn more about the intrinsic reactivity of this substrate class (Scheme 2.6, eq. 13). In this instance, product **2.31** was obtained as the sole product in 81% yield.

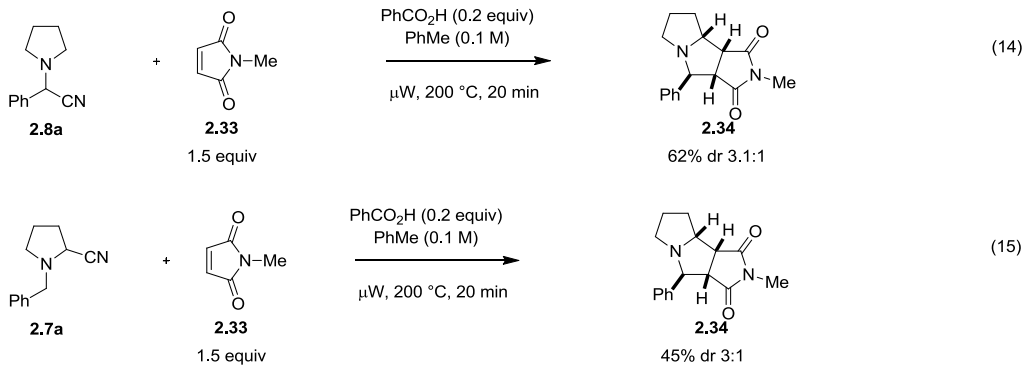
Scheme 2.6 **Regioselectivity of α-Cyanation with Unsymmetric Amines**



2.6 Evidence for the Presence of Azomethine Ylide in the Isomerization of α-Aminonitriles

In order to provide more mechanistic insights into the isomerization of α-aminonitriles, we exposed **2.8a** and **2.7a** to the [3+2] cycloaddition reaction conditions expecting to trap the proposed azomethine ylide species. Interestingly, both **2.8a** and **2.7a** reacted with *N*-methylmaleimide under the conditions for the isomerization reaction to afford the cycloaddition product **2.34** (Scheme 2.7). These results provided evidence for the presence of the proposed azomethine ylide during the process of isomerization reaction.

Scheme 2.7 **Evidence for the Presence of Azomethine Ylide**



2.7 Conclusion

In summary, we have introduced a conceptually new strategy for the direct α-cyanation of amines, a reaction that provides rapid access to synthetically valuable α-aminonitriles not accessible by traditional Strecker chemistry. The overall transformation was rendered redox-neutral by combination of a formally reductive *N*-alkylation with an oxidative α-functionalization.

2.8 Experimental Section

General Information: Starting materials, reagents, and solvents were purchased from commercial sources and used as received unless stated otherwise. Pyrrolidine, piperidine, azepane, 1,2,3,4-tetrahydroisoquinoline, 2-methylpyrrolidine, *N*-benzylmethylamine, and 2-ethylhexanoic acid were distilled prior to use. Benzoic acid was recrystallized from toluene/ethanol. Aldehydes were purified either by distillation or by recrystallization prior to use. 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_{254} 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 (^{1}H-NMR) were recorded on a Varian VNMRS-500 MHz and 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 (^{13}C-NMR) spectra were recorded on a Varian VNMRS-500 MHz and 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. The starting materials **2.8a**,[23] **2.26**[23] and cyanohydrins[24] were prepared according to modified literature procedures. 2-hydroxy-2-(pyridin-3-yl)acetonitrile[25] and 2-hydroxy-2,2-diphenylacetonitrile[26] were prepared according to published procedures. Products **2.7a**–**2.7q**,[27] **2.8p**,[28] **2.20**,[29] **2.24**,[27] **2.29**[30] and **2.31**[31] were previously reported and their published characterization data matched my own in all respects. Ratios of regioisomeric products were determined by ^{1}H-NMR analysis of the crude reaction mixture.

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 (2.8a):

A 10 mL microwave reaction tube was charged with a 10 x 8 mm SiC passive heating element, **6a** (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 $NaHCO_3$ (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 Na_2SO_4. 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% Et_3N).

General Procedure for the Synthesis of Cyanohydrins (adopted from reference 24):

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 Na_2SO_4. 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 (2.7a) via Three-Component Approach:

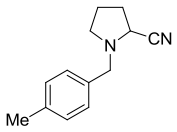
A 10 mL microwave reaction tube was charged with a 10 x 8 mm SiC passive heating element, benzaldehyde (0.25 mmol, 1 equiv), toluene (2.5 mL), pyrrolidine (0.325 mmol, 1.3 equiv), TMSCN (0.325 mmol, 1.3 equiv) and benzoic acid (0.05 mmol, 0.2 equiv). The reaction tube was sealed with a Teflon-lined snap 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 $NaHCO_3$ (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 Na_2SO_4. Solvent was then removed in vacuo and the reaction mixture was loaded onto a column for purification (silica gel, hexanes/EtOAc/Et_3N 95/5/1 v/v/v). Product **5a** 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:

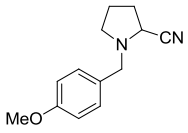
A 10 mL microwave reaction tube was charged with a 10 x 8 mm SiC passive heating element, cyanohydrin (0.25 mmol, 1 equiv), toluene (2.5 mL), pyrrolidine (0.325 mmol, 1.3 equiv) and 2-ethylhexanoic acid (0.05 mmol, 0.2 equiv). The reaction tube was sealed with a Teflon-lined snap cap, and heated in a 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 $NaHCO_3$ (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 Na_2SO_4. 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% Et_3N).

1-(4-Methylbenzyl)pyrrolidine-2-carbonitrile (2.7b): Following the general procedure compound



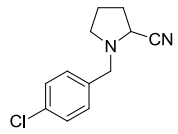
2.7b was obtained from pyrrolidine and *p*-tolualdehyde cyanohydrin as a colorless liquid in 80% yield (16:1 mixture of regioisomers) (R_f = 0.14 in 5% EtOAc in hexanes); Characterization data of the major regioisomer: IR (KBr) 2960, 2815, 2220, 1633, 1573, 1473, 1445, 1376, 1132, 1052, 1039, 755, 683 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.25 (d, *J* = 7.9 Hz, 2H), 7.14 (d, *J* = 7.9 Hz, 2H), 3.89 (d, *J* = 12.9 Hz, 1H), 3.69 (dd, *J* = 7.4, 2.7 Hz, 1H), 3.63 (d, *J* = 12.9 Hz, 1H), 2.93 (ddd, *J* = 9.4, 8.3, 4.2 Hz, 1H), 2.62–2.54 (m, 1H), 2.35 (s, 3H), 2.20–2.07 (comp, 2H), 2.00–1.84 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.1, 134.5, 129.1, 128.8, 118.0, 56.2, 53.1, 51.1, 29.5, 21.8, 21.1; *m/z* (ESI–MS) 174.1 $[M–CN]^+$.

1-(4-Methoxybenzyl)pyrrolidine-2-carbonitrile (2.7c): Following the general procedure compound



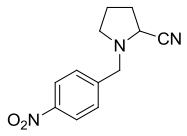
2.7c was obtained from pyrrolidine and *p*-anisaldehyde cyanohydrin as a colorless liquid in 67% yield (11:1 mixture of regioisomers) (R_f = 0.19 in 10% EtOAc in hexanes); Characterization data of the major regioisomer: IR (KBr) 2958, 2816, 2222, 1612, 1513, 1462, 1377, 1301, 1245, 1174, 10393, 821 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.27 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 3.86 (d, *J* = 12.8 Hz, 1H), 3.80 (s, 3H), 3.67 (dd, *J* = 7.3, 2.8 Hz, 1H), 3.60 (d, *J* = 12.8 Hz, 1H), 2.92 (ddd, *J* = 9.4, 8.3, 4.2 Hz, 1H), 2.60–2.52 (m, 1H), 2.20–2.06 (comp, 2H), 2.00–1.84 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.9, 129.9, 129.6, 117.9, 113.7, 55.7, 55.1, 52.9, 51.0, 29.4, 21.8; *m/z* (ESI–MS) 190.0 $[M–CN]^+$.

1-(4-Chlorobenzyl)pyrrolidine-2-carbonitrile (2.7d): Following the general procedure compound



2.7d was obtained from pyrrolidine and *p*-chlorobenzaldehyde cyanohydrin as a white sticky solid in 94% yield (>20:1 mixture of regioisomers) (R_f = 0.13 in 5% EtOAc in hexanes); 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, $CDCl_3$) 7.38–7.27 (comp, 4H), 3.87 (d, *J* = 13.1 Hz, 1H), 3.68 (dd, *J* = 7.4, 2.6 Hz, 1H), 3.64 (d, *J* = 13.1 Hz, 1H), 2.91 (ddd, *J* = 9.4, 8.4, 4.2 Hz, 1H), 2.63–2.53 (m, 1H), 2.25–2.07 (comp, 2H), 2.04–1.84 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $[M–CN]^+$.

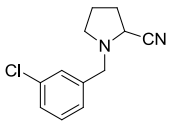
1-(4-Nitrobenzyl)pyrrolidine-2-carbonitrile (2.7e): Following the general procedure for the



synthesis of α-aminonitrile via three-component approach, compound **2.7e** 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 20% EtOAc in hexanes); Characterization data of the major regioisomer: mp: 80–83 ºC; IR (KBr) 2961, 2820, 2220, 1606, 1518, 1346, 1108, 1015, 853, 806, 739 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 8.20 (d, *J* = 8.7 Hz, 2H), 7.54 (d, *J* = 8.8 Hz, 2H), 4.00 (d, *J* = 13.8 Hz, 1H), 3.81 (d, *J* = 13.8 Hz, 1H), 3.72 (dd, *J* = 7.5,

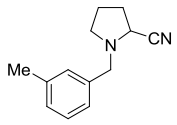
2.7 Hz, 1H), 2.92 (ddd, *J* = 9.4, 8.3, 4.3 Hz, 1H), 2.63–2.56 (m, 1H), 2.26–2.11 (comp, 2H), 2.05–1.87 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.5, 145.2, 129.3, 123.8, 117.6, 55.9, 53.4, 51.3, 29.6, 22.0; *m/z* (ESI–MS) 205.2 $[M–CN]^+$.

1-(3-Chlorobenzyl)pyrrolidine-2-carbonitrile (2.7f): Following the general procedure compound



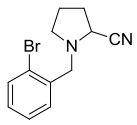
2.7f was obtained from pyrrolidine and *m*-chlorobenzaldehyde cyanohydrin as a colorless liquid in 87% yield (>20:1 mixture of regioisomers) (R_f = 0.14 in 5% EtOAc in hexanes); Characterization data of the major regioisomer: IR (KBr) 3062, 2961, 2881, 2820, 2222, 1600, 1576, 1475, 1431, 1373, 1334, 1210, 1144, 1076, 995, 883, 786, 685; ^{1}H NMR (500 MHz, $CDCl_3$) 7.37 (s, 1H), 7.29–7.21 (comp, 3H), 3.89 (d, *J* = 13.2 Hz, 1H), 3.71 (dd, *J* = 7.5, 2.5 Hz, 1H), 3.65 (d, *J* = 13.2 Hz, 1H), 2.93 (ddd, *J* = 9.4, 8.2, 4.2 Hz, 1H), 2.62–2.54 (m, 1H), 2.24–2.09 (comp, 2H), 2.02–1.86 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.7, 134.3, 129.7, 128.7, 127.7, 126.8, 117.8, 55.9, 53.2, 51.2, 29.5, 21.9; *m/z* (ESI–MS) 194.1 $[M–CN]^+$.

1-(3-Methylbenzyl)pyrrolidine-2-carbonitrile (2.7g): Following the general procedure compound



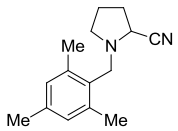
2.7g was obtained from pyrrolidine and *m*-tolualdehyde cyanohydrin as a colorless liquid in 79% yield (19:1 mixture of regioisomers) (R_f = 0.14 in 5% EtOAc in hexanes); Characterization data of the major regioisomer: IR (KBr) 2959, 2922, 2881, 2814, 2221, 1610, 1487, 1460, 1378, 1334, 1160, 1124, 1089, 886, 789, 700 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.25–7.20 (m, 1H), 7.19–7.14 (comp, 2H), 7.09 (app d, *J* = 7.5 Hz, 1H), 3.89 (d, *J* = 12.9 Hz, 1H), 3.70 (dd, *J* = 7.5, 2.6 Hz, 1H), 3.63 (d, *J* = 12.9 Hz, 1H), 2.94 (ddd, *J* = 12.6, 8.2, 4.3 Hz, 1H), 2.63–2.54 (m, 1H), 2.35 (s, 3H), 2.23–2.08 (comp, 2H), 2.02–1.86 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.1, 137.5, 129.5, 128.3, 128.2, 125.9, 118.0, 56.5, 53.2, 51.2, 29.5, 21.8, 21.3; *m/z* (ESI–MS) 174.1 $[M–CN]^+$.

1-(2-Bromobenzyl)pyrrolidine-2-carbonitrile (2.7h): Following the general procedure compound



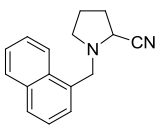
2.7h was obtained from pyrrolidine and *o*-bromobenzaldehyde cyanohydrin as a colorless liquid in 85% yield (>20:1 mixture of regioisomers) (R_f = 0.19 in 3% EtOAc in hexanes); Characterization data of the major regioisomer: IR (KBr) 3059, 2959, 2814, 2221, 1567, 1468, 1439, 1375, 1335, 1246, 1134, 1028, 994, 882, 754, 660 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.56 (app dd, *J* = 7.9, 1.2 Hz, 1H), 7.42 (app dd, *J* = 7.6, 1.6 Hz, 1H), 7.29 (app td, *J* = 7.5, 1.3 Hz, 1H), 7.14 (app td, *J* = 7.9, 1.7 Hz, 1H), 3.96 (d, *J* = 13.7 Hz, 1H), 3.86 (d, *J* = 13.8 Hz, 1H), 3.78 (dd, *J* = 7.6, 2.7 Hz, 1H), 2.93 (ddd, *J* = 9.3, 8.5, 4.5 Hz, 1H), 2.72–2.62 (m, 1H), 2.26–2.09 (comp, 2H), 2.04–1.84 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.9, 133.0, 130.6, 128.9, 127.4, 124.6, 118.3, 56.0, 53.5, 51.1, 29.7, 22.0; *m/z* (ESI–MS) 239.2 $[M–CN]^+$.

1-(2,4,6-Trimethylbenzyl)pyrrolidine-2-carbonitrile (2.7i): Following the general procedure



compound **2.7i** was obtained from pyrrolidine and mesitaldehyde cyanohydrin as a colorless liquid in 89% yield (>20:1 mixture of regioisomers) (R_f = 0.16 in 3% EtOAc in hexanes); 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, $CDCl_3$) 6.84 (s, 2H), 3.85 (d, *J* = 12.8 Hz, 1H), 3.74 (d, *J* = 12.8 Hz, 1H), 3.70 (dd, *J* = 7.1, 3.3 Hz, 1H), 2.77 (ddd, *J* = 9.0, 8.4, 4.5 Hz, 1H), 2.66–2.57 (m, 1H), 2.37 (s, 6H), 2.26 (s, 3H), 2.16–2.06 (comp, 2H), 1.95–1.85 (m, 1H), 1.85–1.76 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $[M–CN]^+$.

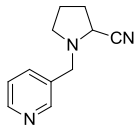
1-(Naphthalen-1-ylmethyl)pyrrolidine-2-carbonitrile (2.7j): Following the general procedure



compound **2.7j** was obtained from pyrrolidine and 1-naphthaldehyde cyanohydrin as an off-white solid in 85% yield (18:1 mixture of regioisomers) (R_f = 0.27 in 5% EtOAc in hexanes); 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}; ^1H NMR (500 MHz, $CDCl_3$) 8.24 (app d, *J* = 8.5 Hz, 1H), 7.90–7.84 (m, 1H), 7.81 (app d, *J* = 8.2 Hz,

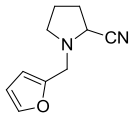
1H), 7.57–7.47 (comp, 3H), 7.47–7.40 (m, 1H), 4.44 (d, *J* = 12.9 Hz, 1H), 4.02 (d, *J* = 12.9 Hz, 1H), 3.69–3.59 (m, 1H), 3.02 (app td, *J* = 8.9, 4.2 Hz, 1H), 2.72–2.63 (m, 1H), 2.18–2.06 (comp, 2H), 2.03–1.85 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.8, 133.3, 132.1, 128.4(2), 128.4(0), 127.2, 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 (2.7k): Following the general procedure



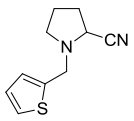
compound **2.7k** was obtained from pyrrolidine and 3-pyridinecarboxaldehyde cyanohydrin as a colorless liquid in 60% yield (>20:1 mixture of regioisomers) (R_f = 0.19 in 50% EtOAc in hexanes); Characterization data of the major regioisomer: IR (KBr) 2962, 2822, 2222, 1656, 1579, 1479, 1427, 1378, 1330, 1187, 1124, 1029, 799, 714 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 8.60 (s, 1H), 8.53 (app d, *J* = 4.2 Hz, 1H), 7.68 (app dt, *J* = 7.8, 1.8 Hz, 1H), 7.26 (app dd, *J* = 7.8, 4.8 Hz, 1H), 3.90 (d, *J* = 13.3 Hz, 1H), 3.70 (d, *J* = 13.3 Hz, 1H), 3.71–3.69 (m, 1H), 2.90 (ddd, *J* = 9.2, 8.4, 4.3 Hz, 1H), 2.63–2.53 (m, 1H), 2.23–2.08 (comp, 2H), 2.02–1.84 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.2, 149.0, 136.4, 133.1, 123.4, 117.7, 53.9, 53.3, 51.2, 29.5, 21.9; *m/z* (ESI–MS) 188.1 $[M+H]^+$, 161.2 $[M–CN]^+$.

1-(Furan-2-ylmethyl)pyrrolidine-2-carbonitrile (2.7l): Following the general procedure compound



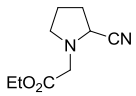
2.7l was obtained from pyrrolidine and furfural cyanohydrin as a colorless liquid in 64% yield (20:1 mixture of regioisomers) (R_f = 0.16 in 10% EtOAc in hexanes); Characterization data of the major regioisomer: IR (KBr) 2962, 2882, 2818, 2222, 1601, 1505, 1445, 1372, 1335, 1224, 1149, 1014, 916, 739, cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.40–7.37 (m, 1H), 6.35–6.31 (m, 1H), 6.31–6.26 (m, 1H), 3.88 (d, *J* = 14.0 Hz, 1H), 3.76 (d, *J* = 14.0 Hz, 1H), 3.73 (dd, *J* = 7.6, 2.7 Hz, 1H), 2.96 (ddd, *J* = 9.3, 8.3, 4.4 Hz, 1H), 2.68–2.58 (m, 1H), 2.25–2.09 (comp, 2H), 2.02–1.86 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 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 (2.7m): Following the general procedure



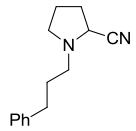
compound **2.7m** was obtained from pyrrolidine and 2-thiophenecarboxaldehyde cyanohydrin as a colorless liquid in 82% yield (>20:1 mixture of regioisomers) (R_f = 0.24 in 10% EtOAc in hexanes); Characterization data of the major regioisomer: IR (KBr) 2959, 2808, 2222, 1645, 1444, 1377, 1329, 1223, 1117, 951, 851, 696 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.25 (app dd, *J* = 5.0, 1.1 Hz, 1H), 7.01 (d, *J* = 3.3 Hz, 1H), 6.94 (dd, *J* = 5.1, 3.5 Hz, 1H), 4.08 (d, *J* = 13.8 Hz, 1H), 3.94 (d, *J* = 13.8 Hz, 1H), 3.78 (dd, *J* = 7.3, 2.5 Hz, 1H), 3.01 (ddd, *J* = 9.1, 7.9, 4.2 Hz, 1H), 2.67–2.57 (m, 1H), 2.25–2.08 (comp, 2H), 2.04–1.86 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.7, 126.6, 126.34, 125.5, 117.7, 52.8, 51.0, 50.8, 29.5, 21.9; *m/z* (ESI–MS) 166.0 $[M–CN]^+$.

Ethyl 2-(2-cyanopyrrolidin-1-yl)acetate (2.7n): Following the general procedure compound **2.7n**



was obtained from pyrrolidine and ethyl glyoxalate cyanohydrin as a colorless liquid in 62% yield (1:1.4 mixture of regioisomers) (R_f = 0.26 in 20% EtOAc in hexanes); Characterization data of **2.7n**: IR (KBr) 2982, 2822, 2220, 1743, 1464, 1428, 1384, 1200, 1160, 1028, 863 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 4.14 (qd, *J* = 7.2, 1.0 Hz, 2H), 4.10 (dd, *J* = 7.9, 2.8 Hz, 1H), 3.53–3.40 (comp, 2H), 3.02 (ddd, *J* = 9.1, 7.7, 5.4 Hz, 1H), 2.66–2.58 (m, 1H), 2.27–2.17 (m, 1H), 2.14–2.05 (m, 1H), 1.97–1.84 (comp, 2H), 1.23 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.7, 118.0, 60.7, 52.8, 52.4, 51.3, 29.8, 22.1, 14.0; *m/z* (ESI–MS) 156.1 $[M–CN]^+$.

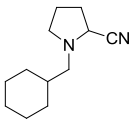
1-(3-Phenylpropyl)pyrrolidine-2-carbonitrile (2.7o): Following the general procedure compound



2.7o was obtained from pyrrolidine and hydrocinnamaldehyde cyanohydrin as colorless liquid in 74% yield (1:3 mixture of regioisomers) (R_f = 0.16 in 10% EtOAc in hexanes); Characterization data of **2.7o**: IR (KBr) 3026, 2942, 2813, 2220, 1602, 1496, 1454, 1386, 1318, 1182, 1145, 1123, 1079, 1030, 966, 882, 747, 700 cm^{-1}; ^1H 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* = 9.4, 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, $CDCl_3$) δ 141.7, 128.3, 128.2, 125.8, 118.1, 53.6,

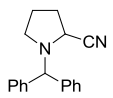
51.8, 51.0, 33.3, 30.0, 29.5, 21.8; *m/z* (ESI–MS) 188.3 $[M–CN]^+$.

1-(Cyclohexylmethyl)pyrrolidine-2-carbonitrile (2.7p): Following the general procedure



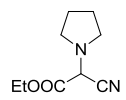
compound **2.7p** was obtained from pyrrolidine and cyclohexanecarboxaldehyde cyanohydrin as a colorless liquid in 78% yield (1:5 mixture of regioisomers) (R_f = 0.23 in 5% EtOAc in hexanes); Characterization data of **2.7p**: IR (KBr) 2923, 2851, 2810, 2221, 1449, 1341, 1244, 1189, 1147, 1114, 1082, 879 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 3.71 (dd, *J* = 7.5, 2.7 Hz, 1H), 2.86–2.79 (m, 1H), 2.54–2.43 (comp, 2H), 2.40–2.33 (m, 1H), 2.19–2.04 (comp, 2H), 1.96–1.81 (comp, 2H), 1.81–1.73 (comp, 2H), 1.73–1.59 (comp, 3H), 1.48–1.37 (m, 1H), 1.29–1.08 (comp, 3H), 0.94–0.81 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 118.3, 59.4, 54.0, 51.4, 36.5, 31.6, 31.5, 29.6, 26.6, 25.8(9), 25.8(8), 21.9; *m/z* (ESI–MS) 166.2 $[M–CN]^+$.

1-Benzhydrylpyrrolidine-2-carbonitrile (2.7q): Following the general procedure but using benzoic



acid as a catalyst compound **2.7q** was obtained from pyrrolidine and benzophenone cyanohydrin as a white solid in 40% yield (>20:1 mixture of regioisomers) (R_f = 0.22 in 3% EtOAc in hexanes); Characterization data of the major regioisomer: mp: 108–111 ºC; IR (KBr) 3061, 3028, 2958, 2821, 2222, 1598, 1491, 1453, 1306, 1186, 1130, 1076, 1028, 927, 887, 748, 706, 628 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.55–7,46 (comp, 4H), 7.34–7.27 (comp, 4H), 7.24–7.17 (comp, 2H), 4.60 (s, 1H), 3.78 (app d, *J* = 7.3 Hz, 1H), 3.03–2.93 (m, 1H), 2.46–2.34 (m, 1H), 2.25–2.13 (m, 1H), 2.13–2.04 (m, 1H), 2.02–1.86 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.5, 142.0, 128.8, 128.6, 127.5(9), 127.5(6), 127.3(3), 127.3(2), 117.7, 71.9, 53.1, 49.9, 29.4, 21.8; *m/z* (ESI–MS) 236.0 $[M–CN]^+$.

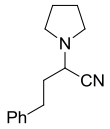
Ethyl 2-cyano-2-(pyrrolidin-1-yl)acetate (2.8n): Following the general procedure compound **2.8n**



was obtained from pyrrolidine and ethyl glyoxalate cyanohydrin as a colorless liquid in 62% yield (1:1.4 mixture of regioisomers) (R_f = 0.20 in 20% EtOAc in hexanes); Characterization data of **2.8n**: IR (KBr) 2976, 2879, 2821, 2359, 1746, 1463, 1445, 1370, 1201, 1154,

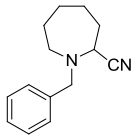
1117, 1024, 904, 851 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 4.59 (s, 1H), 4.25 (q, *J* = 7.3 Hz, 2H), 2.81–2.63 (comp, 4H), 1.91–1.75 (comp, 4H), 1.28 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.0, 112.6, 62.8, 57.8, 50.3, 23.4, 13.8; m/z (ESI-MS) 183.2 $[M + H]^+$.

4-Phenyl-2-(pyrrolidin-1-yl)butanenitrile (2.8o): Following the general procedure compound **2.8o**



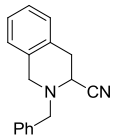
was obtained from pyrrolidine and hydrocinnamaldehyde cyanohydrin as colorless liquid in 74% yield (1:3 mixture of regioisomers) (R_f = 0.32 in 10% EtOAc in hexanes); Characterization data of **2.8o**: IR (KBr) 3062, 3027, 2961, 2811, 2222, 1603, 1496, 1455, 1354, 1318, 1143, 1123, 1030, 903, 869, 752, 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, $CDCl_3$) δ 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-Benzylazepane-2-carbonitrile (2.22): Following the general procedure but conducting the reaction



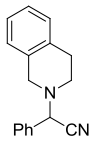
at 220 °C, compound **2.22** was obtained from azepane and benzaldehyde cyanohydrin as colorless liquid in 79% yield (11:1 mixture of regioisomers) (R_f = 0.40 in 10% EtOAc in hexanes); Characterization data of the major regioisomer: IR (KBr) 2931, 2852, 2821, 2220, 1602, 1452, 1357, 1150, 1072, 957, 906, 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 (2.24): Following the general procedure



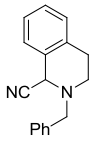
compound **2.24** was obtained from 1,2,3,4-tetrahydroisoquinoline and benzaldehyde cyanohydrin as an off-white solid in 63% yield (17:1:1 mixture of **2.24**, **2.25** and **2.26**) (R_f = 0.21 in 3% EtOAc in hexanes); Characterization data of **2.24**: mp: 110–112 ºC; IR (KBr) 2818, 2222, 1644, 1496, 1455, 1357, 1315, 1145, 1091, 1074, 1028, 989, 741, 701 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.45–7.29 (comp, 5H), 7.21–7.15 (comp, 2H), 7.14–7.09 (m, 1H), 7.08–7.03 (m, 1H), 4.03 (d, *J* = 6.3 Hz, 1H), 3.98 (d, *J* = 15.5 Hz, 1H), 3.92 (d, *J* = 13.2 Hz, 1H), 3.78 (d, *J* = 15.6 Hz, 1H), 3.70 (d, *J* = 13.1 Hz, 1H), 3.31 (dd, *J* = 16.4, 6.2 Hz, 1H), 2.98 (d, *J* = 16.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 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)-2-phenylacetonitrile (2.25): Following a literature



procedure,[23] compound **2.25** was obtained from 1,2,3,4-tetrahydroisoquinoline, benzaldehyde and TMSCN as an off-white solid in 38% yield (R_f = 0.29 in 10% EtOAc in hexanes); mp: 77–80 ºC; IR (KBr) 3044, 2960, 2925, 2834, 2786, 2751, 2360, 2343, 2223, 1494, 1449, 1390, 1317, 1267, 1131, 1094, 1044, 934, 914, 872, 759, 741, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 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, CDCl3) δ 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 (2.26): Following literature procedures,[32]



compound **2.26** was obtained as an off-white solid in 47% yield (three steps) (R_f = 0.32 in 10% EtOAc in hexanes); mp: 72–75 ºC; IR (KBr) 3084, 3065, 3024, 2969, 2928, 2827, 2218, 1493, 1451, 1369, 1336, 1134, 1095, 1050, 936, 738, 698 cm^{-1}; ^1H 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, $CDCl_3$) δ 136.6, 134.4, 129.6, 129.4, 129.1, 128.6, 128.4, 127.8, 127.3, 126.4, 116.6, 59.9, 54.4, 46.6, 28.5; *m/z* (ESI–MS) 222.2 $[M - CN]^+$.

***trans*-1-Benzyl-5-methylpyrrolidine-2-carbonitrile (*trans*-2.28):** 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 (**2.29**, 11%),[30] and *trans*-**2.28**/*cis*-**2.28** (4.8:1, 52%). The relative configuration of the major diastereomer (*trans*-**2.28**) was determined by GCOSY and NOESY. (R_f = 0.27 in 5% EtOAc in hexanes). Characterization data of the major diastereomer *trans*-**2.28**: 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}; ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $[M - CN]^+$.

Figure 2.2 **2D-NMR Analysis for Compound *trans*-2.28, Selected Interactions:**

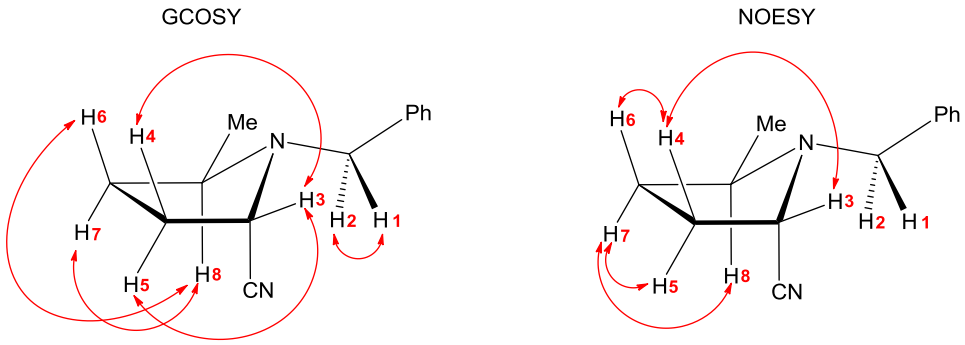


Table 2.3 **^{1}H NMR Shifts**

Protons	Chemical shifts (ppm)
H1, H2	4.08, 3.44
H3	3.68
H4	2.11–2.02
H5	2.01–1.93
H6	1.59–1.50
H7	2.25–2.14
H8	2.89–2.79
Me	1.23

Computational Study:

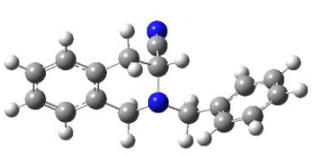
A preliminary computational investigation indicates that compound **2.24** is the thermodynamically most stable of the three regioisomers that are formed in a reaction of 1,2,3,4-tetrahydroisoquinoline with benzaldehyde cyanohydrin. The computed free energies for compounds **2.24**, **2.25** and **2.26** are in good qualitative agreement with our experimental findings and indicate that the reaction is under thermodynamic control.

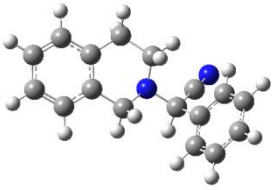
Computational Method: All calculations were carried out with the *Gaussian 09* collection of computer programs.[33] Density functional theory was used as the computational method[34] and the M06 model[35] was employed with the 6-311G(d) basis set.[36]

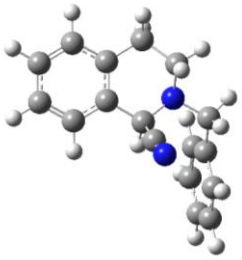
Table 2.4 **Computed Energy Data for 2.24, 2.25 and 2.26**

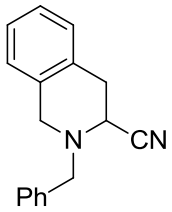
Compound	E (kcal/mol)	H (kcal/mol)	S (kcal/(K·mol))	G (kcal/mol)	ΔG (kcal/mol)
2.24	-480988	-480796	127.853	-480834.5927	0
2.25	-480983	-480792	124.705	-480829.4408	5.15184889
2.26	-480987	-480795	125.663	-480832.8714	1.72125719

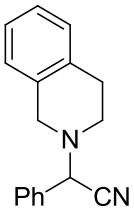
Figure 2.3 **3D Models of Optimized Geometries and Cartesian Coordinates (Å)**

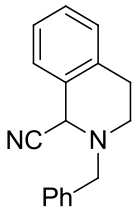












2.24

0 kcal/mol

2.25

5.15 kcal/mol

2.26

1.72 kcal/mol

Compound **2.24**

Row	Symbol	X(Å)	Y(Å)	Z(Å)
1	N	-0.1008220	-0.2646650	0.5774080
2	C	3.5758840	-0.5269650	1.2573340
3	H	3.5721020	-0.6157170	2.3439380
4	C	-0.0154330	0.5480620	-0.6260010

5	H	-0.9794410	0.4737780	-1.1469830
6	C	4.7679640	-0.6149030	0.5612230
7	C	-2.5615220	-0.1987950	0.6415890
8	C	-2.8740470	-1.4666720	0.1547700
9	H	-2.1746060	-2.2843600	0.3237110
10	C	0.1878290	1.9750790	-0.3093600
11	N	0.3249170	3.0737470	0.0117100
12	C	-1.2787250	0.0245310	1.3863900
13	H	-1.2482580	1.0580020	1.7855310
14	C	1.1053380	-0.1896180	1.3862180
15	H	1.0517920	-0.9895870	2.1378520
16	H	1.1409590	0.7637410	1.9563690
17	C	1.0775830	0.0008740	-1.5323690
18	H	0.7159070	-0.9583300	-1.9273440
19	H	1.2211650	0.6672700	-2.3925670
20	C	-4.0522360	-1.6818780	-0.5410330
21	H	-4.2888340	-2.6765690	-0.9127050
22	C	2.3709600	-0.3221410	0.5902760
23	C	2.3692370	-0.2002820	-0.7967390
24	C	-4.9335970	-0.6298600	-0.7618320
25	H	-5.8594300	-0.7997400	-1.3068960
26	C	4.7673400	-0.4930880	-0.8231380
27	C	3.5737850	-0.2858880	-1.4908400
28	H	3.5669290	-0.1833360	-2.5758700
29	C	-4.6274220	0.6361850	-0.2876430
30	H	-5.3101080	1.4647040	-0.4621160
31	C	-3.4441390	0.8493570	0.4084530

32	H	-3.1970830	1.8463170	0.7732480
33	H	-1.2335570	-0.6428440	2.2591260
34	H	5.7010310	-0.7761240	1.0962140
35	H	5.6999810	-0.5547580	-1.3791140

Compound **2.25**

Row	Symbol	X(Å)	Y(Å)	Z(Å)
1	C	-0.7351170	-0.4728570	-0.8362890
2	N	-0.0755220	0.7863220	-0.5509790
3	C	-0.2456920	1.1611630	0.8454550
4	C	-1.7003150	1.5151970	1.0762150
5	C	-2.6249620	0.4547930	0.5518750
6	C	-3.9529950	0.3981040	0.9682140
7	C	-4.8174570	-0.5641730	0.4765760
8	C	-4.3561120	-1.4945370	-0.4465950
9	C	-3.0384150	-1.4460760	-0.8660040
10	C	-2.1669090	-0.4762710	-0.3781270
11	C	1.2981290	0.8252880	-1.0452130
12	C	2.2802150	-0.1010570	-0.3472920
13	C	2.4733940	-1.3874250	-0.8431550
14	C	3.3096460	-2.2801710	-0.1893690
15	C	3.9658270	-1.8918370	0.9692770
16	C	3.7873280	-0.6081490	1.4655470
17	C	2.9505750	0.2826900	0.8105820
18	H	-0.2083210	-1.3266730	-0.3589470
19	H	-0.6931040	-0.6521370	-1.9212210
20	H	0.3870850	2.0293750	1.0647780
21	H	0.0715420	0.3450990	1.5251880
22	H	-4.3087370	1.1293140	1.6943840
23	H	-5.8513670	-0.5920170	0.8129820
24	H	-5.0264250	-2.2549430	-0.8408330
25	H	-2.6722400	-2.1731510	-1.5916590

26	H	1.2502390	0.5298720	-2.1055170
27	H	1.9690460	-1.6894500	-1.7610780
28	H	3.4547510	-3.2801160	-0.5915640
29	H	4.6257680	-2.5878610	1.4816800
30	H	4.3108690	-0.2943450	2.3655390
31	H	2.8348980	1.2951850	1.1941020
32	H	-1.9124900	2.4677720	0.5696050
33	H	-1.8822310	1.6819980	2.1464200
34	C	1.7681880	2.2127390	-1.0271000
35	N	2.1439160	3.3004720	-0.9906540

Compound **2.26**

Row	Symbol	X(Å)	Y(Å)	Z(Å)
1	C	-4.3389760	-1.2623700	-0.5612650
2	C	-3.4531820	-2.1761870	-0.0031090
3	C	-3.9261550	0.0345740	-0.8098790
4	H	-4.6210070	0.7531750	-1.2442290
5	C	-2.1638160	-1.7779990	0.2994430
6	H	-1.4631760	-2.4840460	0.7455150
7	C	-2.6297310	0.4479640	-0.5088060
8	C	-1.7479130	-0.4743600	0.0458960
9	C	-2.1831140	1.8517120	-0.7971390
10	H	-2.9878420	2.5598490	-0.5596470
11	H	-1.9857350	1.9518550	-1.8744630
12	C	-0.9255510	2.2116710	-0.0354970
13	H	-0.5084000	3.1524600	-0.4130990
14	H	-1.1470480	2.3711910	1.0392390
15	C	-0.3373420	-0.0703880	0.4192670
16	H	0.3555550	-0.8623050	0.0962250
17	C	-0.2222980	0.0088360	1.8939560
18	N	-0.0939720	0.1248350	3.0338520
19	N	0.0715170	1.1679110	-0.2216890
20	C	1.4101730	1.5988650	0.1648350
21	H	1.4567080	1.8790760	1.2351970
22	C	2.4537420	0.5628200	-0.1376950
23	C	2.6442960	0.1340330	-1.4501680
24	H	2.0241210	0.5571170	-2.2393290
25	C	3.5976940	-0.8262270	-1.7450570

26	H	3.7397010	-1.1522910	-2.7732180
27	C	4.3744290	-1.3718220	-0.7293080
28	H	5.1239440	-2.1253560	-0.9605650
29	C	4.1880720	-0.9549400	0.5793480
30	H	4.7879400	-1.3822710	1.3796920
31	C	3.2290790	0.0063300	0.8730350
32	H	3.0710100	0.3238560	1.9033650
33	H	1.6214340	2.5141830	-0.4055380
34	H	-5.3564980	-1.5640860	-0.7991730
35	H	-3.7699650	-3.1966890	0.1977540

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(17) Yields were not determined in most instances where poor selectivities were observed.
(18) This reaction appears to be under thermodynamic control. The same ratio of product isomers was obtained when **2.7a** was exposed to identical reaction conditions.
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Chapter III Mechanistic Studies of the Redox-Neutral Aromatization of Cyclic Amines

3.1 Background

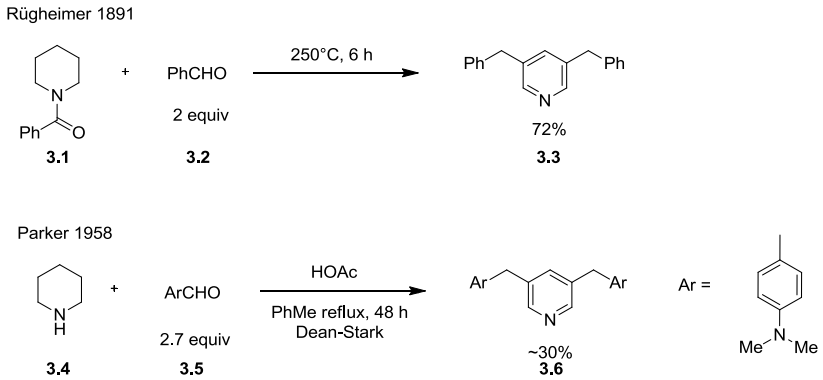
Aromatic heterocycles including pyrroles, pyridines and quinolines are ubiquitous building blocks found in natural products,[1] active pharmaceuticals, and functional materials.[2] The syntheses of pyrroles, pyridines, quinolines and their derivatives have been studied extensively in the past century.[3-5] The classical methods of constructing the pyrrole ring system include the Knorr,[6] Paal-Knorr[7] and Hantzsch[8] pyrrole syntheses and recent advancement in transition-metal catalyzed pyrrole synthesis have provided many versatile methodologies.[9] However, most methodologies prepare unsaturated pyrroles and pyridines by assembling the carbon and nitrogen units in a multi-component fashion.[10] There are only a few precedents in literature which utilize the commercially available and readily accessible saturated cyclic amines to prepare the corresponding unsaturated heterocycles. Furthermore, the mechanisms of these transformations need to be further studied and more experimental evidence needs to be provided. As part of our continued program of developing redox-neutral methodologies toward the syntheses of functionalized amines, we are particularly interested in the mechanism of this transformation due to its redox-neutral characteristic and close relevance to our recent findings in redox-neutral functionalization of cyclic amines. Here, we report the results of our experimental studies for understanding the mechanism of this transformation.

3.2 Precedents in Literature of the Redox-Neutral Aromatization of Amines

In 1891, Rügheimer reported the formation of 3,5-dibenzylpyridine by condensing *N*-benzoylpiperidine and benzaldehyde at 250 °C. This is perhaps the first example of generating pyridine derivatives from the saturated piperidine skeleton, although the mechanism of this reaction was not fully understood at that time (Scheme 3.1).[11] This reactivity was re-discovered by Parker and co-workers accidentally when they investigated the reaction between 4-dimethylaminobenzaldehyde

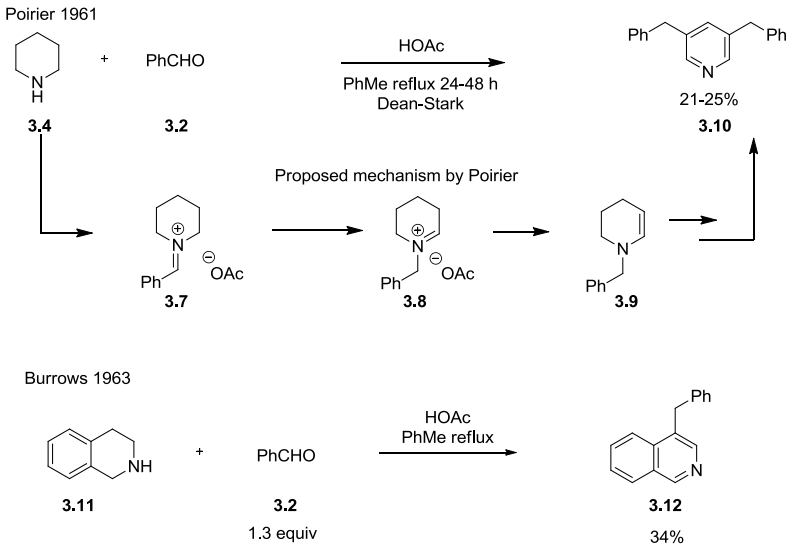
3.5 and piperidinium acetate, and found 3,5-disibutituted pyridine **3.6** formed as a byproduct. At that time the structure of **3.6** was not identified by these researchers (Scheme 3.1).[12]

Scheme 3.1 **Early Examples of 3,5-Disubstituted Pyridine Formation**



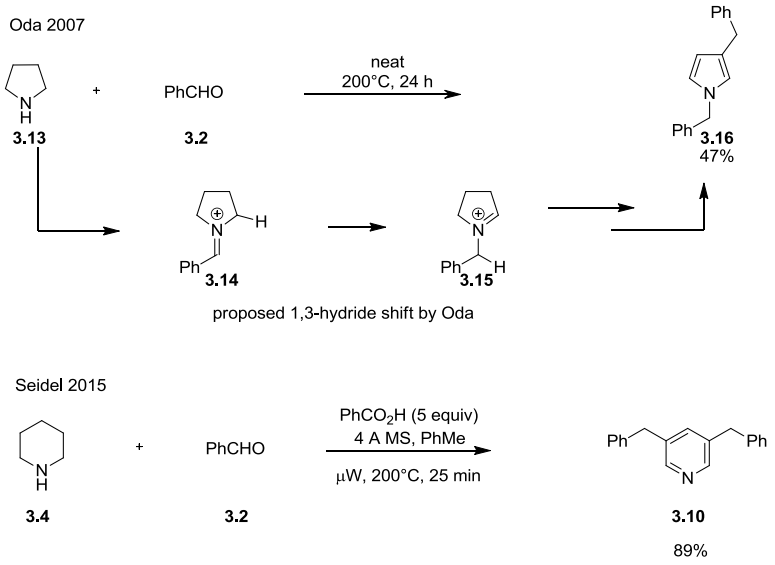
In 1961, Poirier and co-workers confirmed via an independent synthetic route that the structure of byproduct observed by Parker was the 3,5-disubsituted pyridine (Scheme 3.2).[13] They also predicted that Rügheimer's reaction proceeded through a similar pathway: *N*-benzoylpiperidine hydrolyzes to produce piperidine under the reaction conditions and then undergoes condensation with aromatic aldehydes to form pyridine derivatives. In 1963, Burrows and co-workers further developed this reaction by condensing tetrahydroisoquinoline (THIQ) and benzaldehyde using acetic acid as an additive under reflux conditions, observing the formation of 4-substituted aromatized isoquinoline product **3.12** (Scheme 3.2).[14] They proposed that the mechanism of this transformation involved the formation of an enamine which ultimately leads to the aromatized product.

Scheme 3.2 **Further Investigations of the Formationof 3,5-Disubstituted Pyridine in the Literature**



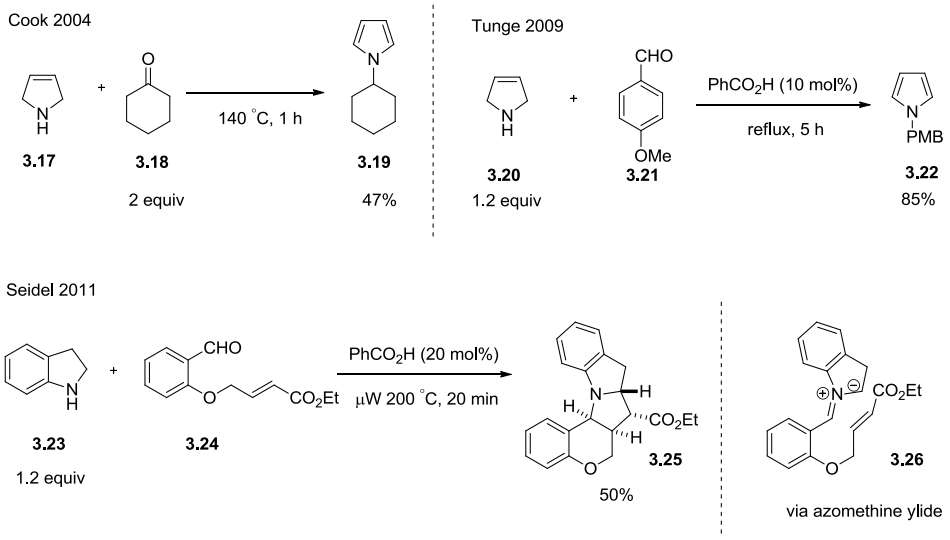
In addition to piperidine and THIQ, the redox-neutral aromatization was also observed with pyrrolidine. In 2007 Oda and co-workers reported 1,3-disbustituted pyrrole **3.16** formation from benzaldehyde and pyrrolidine under thermal conditions (Scheme 3.3).[15] However, they proposed a 1,3-hydride shift process which is very unlikely because a 1,3-hydride shift would require an antarafacial hydride transfer and this is geometrically very unfavorable. In 2015 Seidel and co-workers found that the efficiency of the redox-aromatization reaction can be significantly improved by using super stoichiometric amount of benzoic acid as an additive in the reaction between benzaldehyde and piperidine.[16] High yields for the 3,5-disubstituted pyridine products were obtained under the optimal conditions (Scheme 3.3).

Scheme 3.3 **Recent Development of Redox-Neutral Aromatization of Amines**



In contrast to the case of saturated cyclic amines as shown above, much lower temperature or shorter reaction time was required when using partially saturated amines such as indoline and 3-pyrroline as starting materials in the redox-aromatization reaction. For example, Cook[17] and Tunge[18] independently developed the pyrrole synthesis from 3-pyrroline and a ketone or aldehyde. In both cases, the reaction time is significantly shortened and in Tunge's pyrrole synthesis, reflux temperature in toluene is sufficient to effect the reaction (Scheme 3.4). A closely related indole formation from indoline was disclosed by the Seidel group in 2011 and it was proposed that the azomethine ylide intermediate was involved in the final aromatization of the indoline core.[19] The formation of intramolecular [3+2] product supported the proposed presence of the azomethine ylide (Scheme 3.4). In these examples it was found that a carboxylic acid such as benzoic acid can facilitate the formation of the product.[20]

Scheme 3.4 **Redox-Neutral Aromatization of Partially-Saturated Amines**

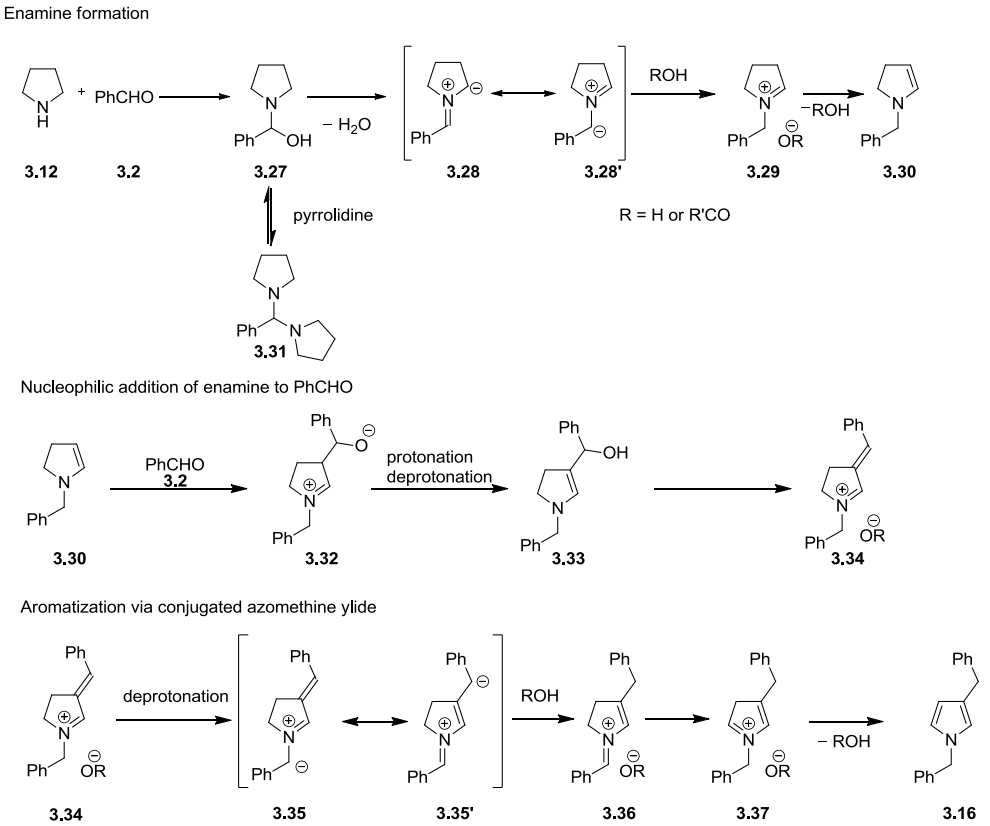


3.3 Hypothesis for the Mechanism of the Redox-Neutral Aromatization of Amines

Based on our recent studies regarding the redox-neutral functionalization of amine via azomethine ylide, we hypothesized the mechanism of the redox aromatization of cyclic amines, choosing the reaction between benzaldehyde and pyrrolidine to form 1,3-dibenzylpyrrole as a prototypical example (Scheme 3.5). The nucleophilic addition of pyrrolidine to benzaldehyde first leads to the formation of *N*,*O*-acetal **3.27**. Subsequently, the initial formed *N*,*O*-acetal can eliminate water to form azomethine ylide species **3.28**. After reprotonation, the azomethine ylide can be transformed into the isomerized iminium ion **3.29**. The isomerized iminium ion **3.29** could rapidly be deprotonated to form the enamine **3.30**. As a nucleophilic intermediate, the enamine **3.30** could then attack another equivalent of benzaldehyde to form intermediate **3.32**.[21] Proton transfer of **3.32** gives rise to the formation of enamine **3.33**, and subsequent elimination of water will result in the formation of iminium ion **3.34** with an exocyclic double bond. Subsequently, conjugated iminium ion **3.34** can be deprotonated to afford azomethine ylide **3.35** with an exocyclic double bond. After reprotonation at the benzylic position, the newly formed iminium ion **3.36** can isomerize via proton transfer to form iminium ion

3.37. Deprotonation of **3.37** will give rise to the final aromatized product **3.16**. As a side note, *N,O*-acetal **3.27** could also react reversibly with pyrrolidine to from aminal **3.31** which can also participate in the reaction pathway.

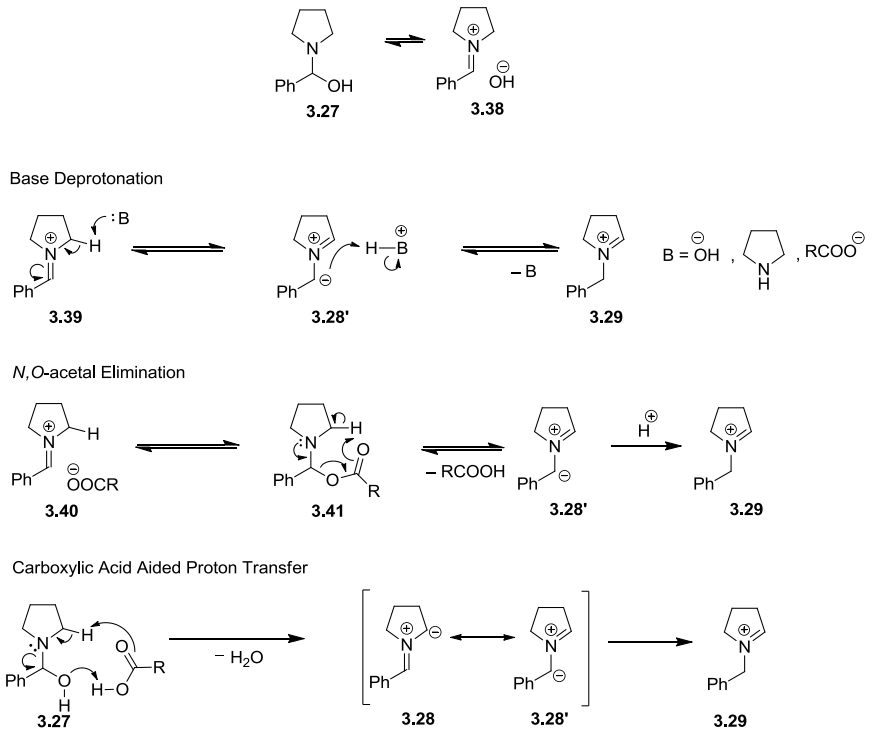
Scheme 3.5 **Hypothesis for the Mechanism of 1,3-Dibenzylpyrrole Formation**



As a key step in the aromatization process, the formation of isomerized iminium ion **3.29** is worth discussing. Based on our previous studies on the α-functionalization of cyclic amines, several potential pathways were considered for the formation of the isomerized iminium ion (Scheme 3.6). In a simple base catalyzed pathway, base (e.g., OH^-, pyrrolidine) deprotonates the iminium α-proton, and subsequently reprotonates the resulting azomethine ylide **3.28'** at the benzylic position. This leads to the formation of isomerized iminium ion **3.29**. Alternatively, when carboxylic acid RCOOH is used

as a catalyst, after proton exchange with OH^- the carboxylate $RCOO^-$ could act as a base to deprotonate the iminium α-proton. Or as shown in Scheme 3.6, *N*,*O*-acetal **3.41** could exist in equilibrium with iminium ion **3.40**, which could eliminate carboxylic acid to generate azomethine ylide **3.28'** via a concerted pathway. In another concerted pathway starting from *N*,*O*-acetal **3.27**, the carboxylic acid can act as a proton shuttle in the process of eliminating water and generating azomethine ylide **3.28'**. The resulting azomethine ylide can reprotonate to form the isomerized iminium ion **3.29**.

Scheme 3.6 **Potential Pathways for the Formation of the Isomerized Iminium Ion**



Several key intermediates are proposed to be involved in the formation of **3.16**. In order to further understand the mechanism of this transformation, we decided to investigate this reaction and we expected to obtain experimental evidence for these intermediates. Due to the transient characteristic of some species, we set out to target some of the most accessible intermediates including the

azomethine ylide **3.28**, enamine **3.30** and azomethine ylide **3.35** by conducting trapping and NMR experiments. Preliminary results demonstrating the substrate scope and synthetic utilities of the enamine **3.30** will also be discussed.

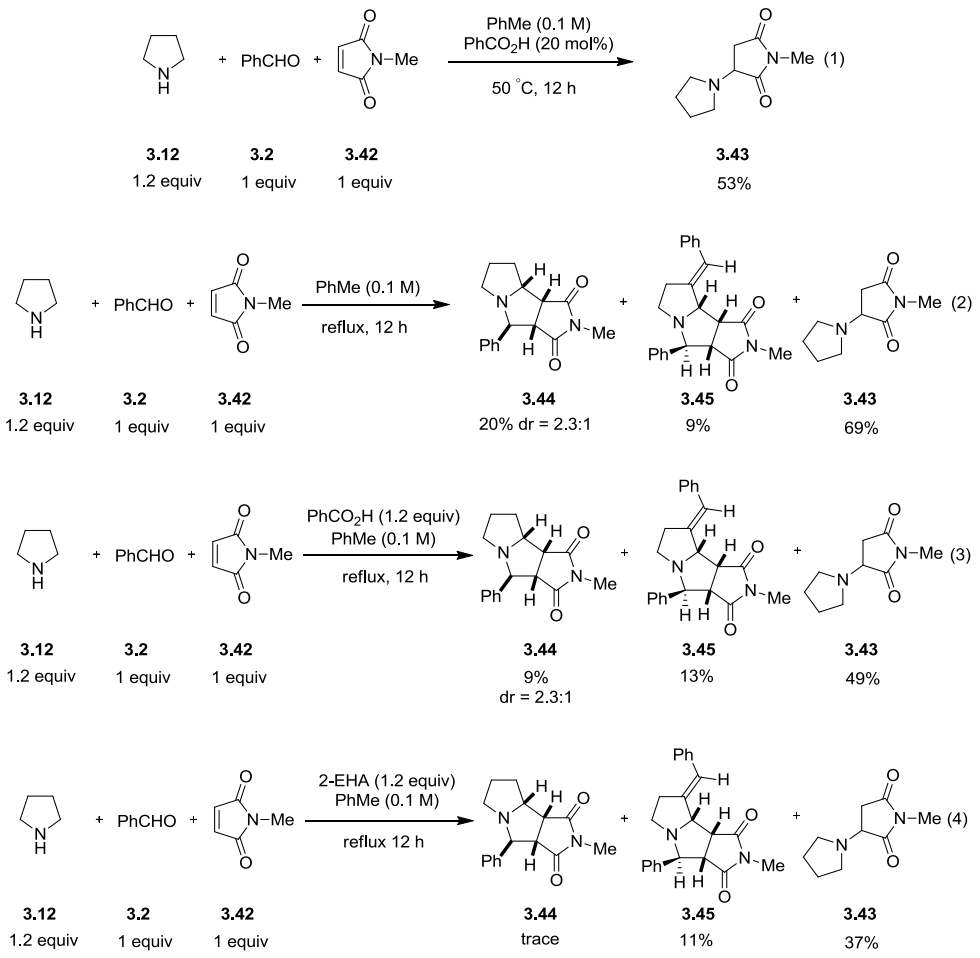
3.4 Results and Discussion

3.4.1 Evidence for the Intermediacy of Azomethine Ylide 3.28

In order to establish the intermediacy of the azomethine ylide **3.28**, we decided to employ a conventional [3+2] cycloaddition reaction to trap **3.28**.[22,23] We started out by reacting pyrrolidine and benzaldehyde with *N*-methylmaleimide as the dipolarphile, expecting to observe the [3+2] product. When the reaction was conducted at 50 °C the conjugate addition product **3.43** was isolated as the only product (Scheme 3.7, eq 1). Interestingly, when the reaction was carried out at reflux temperature in toluene, the formation of conjugate addition product seems to be reversible and the expected [3+2] product was isolated in 20% yield as a mixture of two diastereomers. In addition to the expected **3.44** formation, another [3+2] cycloaddition product **3.45** was also obtained in 18% yield (Scheme 3.7, eq 2). The formation of regular [3+2] product **3.44** suggests the intermediacy of the azomethine ylide **3.28** during the course of the reaction. Also, the formation of product **3.45** suggests the formation of conjugated azomethine ylide **3.35** as proposed in the reaction pathway.

In order to suppress the conjugate addition process and also to facilitate the azomethine ylide formation, benzoic acid and 2-ethyl hexanoic acid (2-EHA) which were known to facilitate the formation of azomethine ylide were used (Scheme 3.7, eq 3 and eq 4).[24] In both cases, the formation of **3.43** was significantly reduced and the yield of **3.45** increased when adding a carboxylic acid as an additive. However, in the case where 2-EHA was used only trace amount of the **3.44** was obtained.

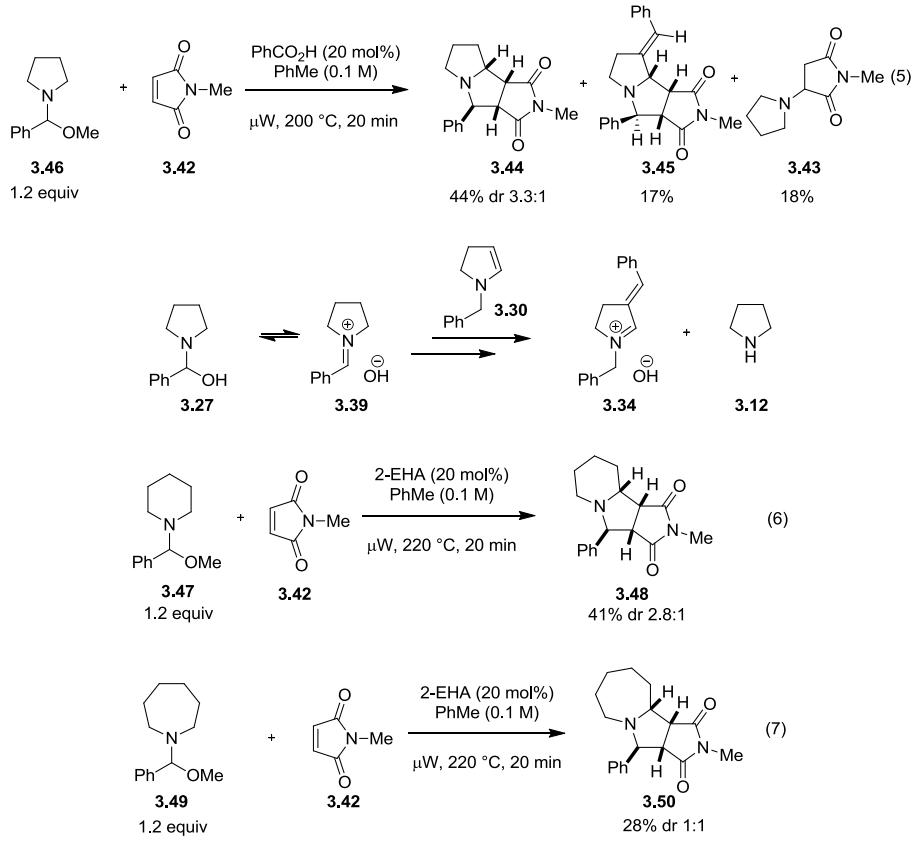
Scheme 3.7 **Three-Component [3+2] Trapping Experiment**



Since the reaction between pyrrolidine and *N*-methylmaleimide limits our ability to experimentally trap the proposed azomethine ylide intermediate without the conjugate addition process competing, we sought to employ *N*,*O*-acetal **3.46** which is analogous to the proposed *N*,*O*-acetal **3.27** as the starting material for the [3+2] trapping experiments. When the prepared **3.46** was exposed to the dipolarophile *N*-methylmaleimide and 20 mol% benzoic acid in toluene at 200 °C under microwave conditions, the [3+2] cycloaddition product **3.44** was obtained in 44% yield with a dr of 3.3:1, with **3.45** also obtained in 34% yield (Scheme 3.8, eq 4). This experiment suggests that analogous *N*,*O*-acetal **3.46** can act as the precursor for the azomethine ylide formation. In addition to the [3+2] cycloaddition products **3.44** and **3.45**, conjugate addition product **3.43** was also obtained in 18% yield. The formation of **3.43**

results from the conjugate addition of pyrrolidine to *N*-methylmaleimide. The presence of pyrrolidine could be attributed to the step where iminium ion **3.39** is attacked by enamine species **3.30** to eliminate pyrrolidine and generate **3.34** (Scheme 3.8). Analogous *N,O*-acetals derived from piperidine and azepane also underwent [3+2] cycloaddition reaction with *N*-methylmaleimide under very similar conditions to afford products **3.48** and **3.50** (Scheme 3.8 , eq 6 and eq 7).

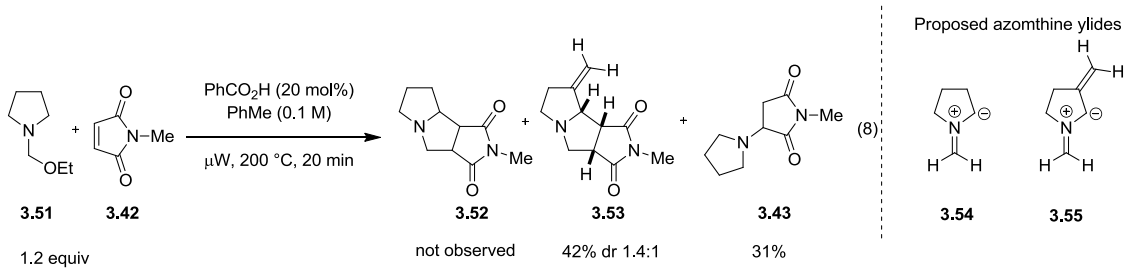
Scheme 3.8 **[3+2] Trapping Experiment with *N,O*-Acetals**



In order to study the effect of the substituent on the formation of the azomethine ylide, we also prepared *N,O*-acetal **3.51** which is lacking the phenyl ring of **3.46**. When exposing **3.51** to the [3+2] cycloaddition trapping conditions (Scheme 3.9, eq 8), we didn't observe any formation of the expected

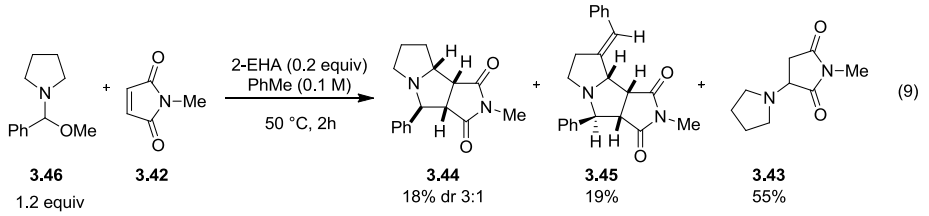
[3+2] product **3.52**. However, the [3+2] cycloaddition product **3.53** (analogous to **3.45)** was isolated in 42% yield with a dr of 1.4:1 along with 36% of the conjugate addition product. This observation suggests that the phenyl ring can significantly stabilize azomethine ylide **3.28** due to conjugation of the aromatic ring and the 4-π electron system of the azomethine ylide. However, when the phenyl ring is absent, we speculate that the initially formed **3.54** would rapidly be converted to **3.55** which bears an exocyclic double bond and the resulting extended conjugated π system. The extended conjugation of the exocyclic double bond likely serves as a driving force for the formation of **3.55**.

Scheme 3.9 **[3+2] Trapping Experiment with *N,O*-Acetal Lacking a Phenyl Ring**



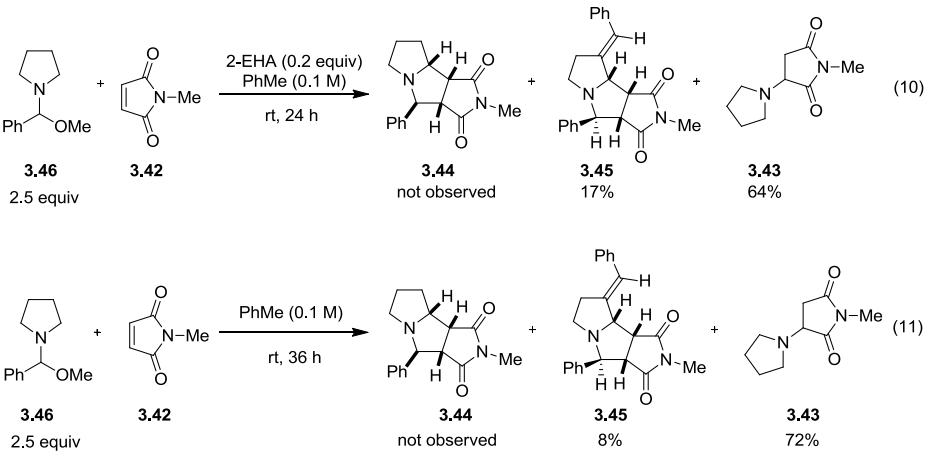
In order to study the effect of temperature on the formation of the azomethine ylides **3.28** and **3.35**, we conducted the trapping reactions under milder conditions. When exposing **3.46** to *N*-methylmaleimide and catalytic amount of 2-EHA at 50 °C for 2 hours, even though the yields of both **3.44** and **3.45** diminished significantly (compared to the reaction run at 200 °C) the formation of the [3+2] products illustrated that the azomethine ylides formation is viable even at 50 °C. The major product in the condition was the conjugate addition product with a yield of 55% (Scheme 3.10).

Scheme 3.10 **[3+2] Trapping Experiment with *N,O*-Acetal Under Milder Conditions**



We next decided to study the role of carboxylic acids in the formation of azomethine ylides **3.28** and **3.35** at room temperature. When 20 mol% of 2-EHA was used as the catalyst in the [3+2] reaction, the majority of the product isolated after reacting for 24 hours at room temperature is the conjugate addition product **3.43**. There was 17% yield of **3.45** obtained and no **3.44** observed (Scheme 3.11, eq 10). However, without acid catalyst added, after 36 hours the reaction was not completed, no [3+2] cycloaddition product **3.44** was observed and only 8% yield of **3.45** was isolated (Scheme 3.11, eq 11). This observation is consistent with our hypothesis that carboxylic acids can facilitate azomethine ylide formation.

Scheme 3.11 **[3+2] Trapping Experiment with *N,O*-Acetal at Room Temperature**



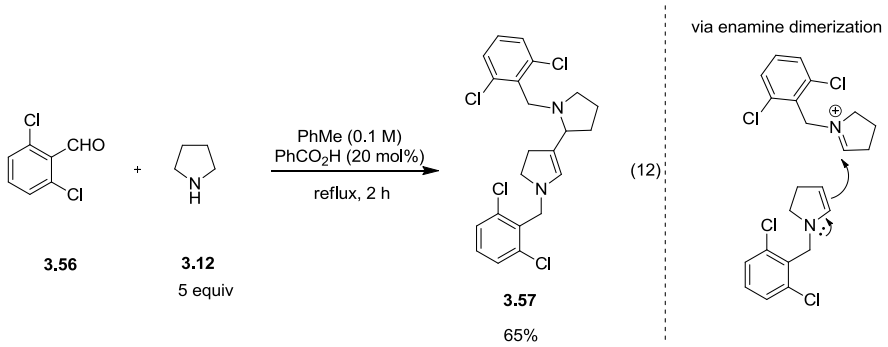
3.4.2 Evidence for the Intermediacy of Enamine 3.30 and Iminium Ion 3.34

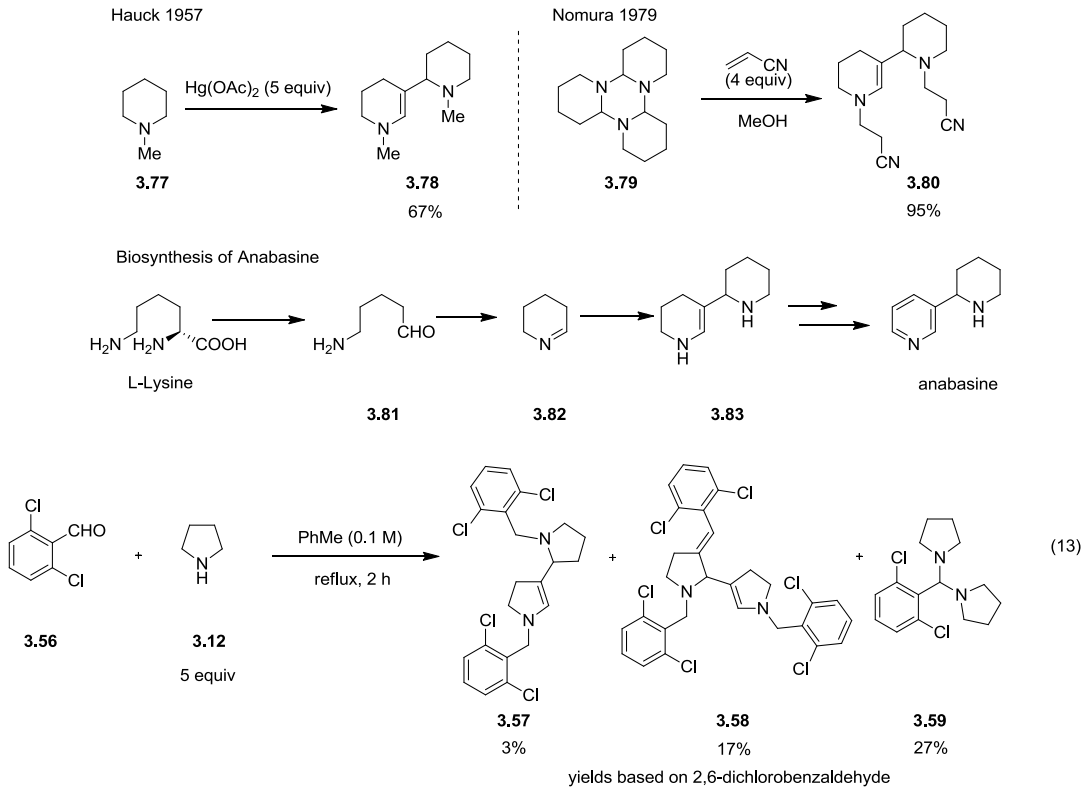
Having found experimental evidence for the presence of azomethine ylides **3.28** and **3.35**, we set out to explore the intermediacy of the enamine **3.30**. Due to the instability of the enamine type compounds[25,26] and their potential reactivity toward many active electrophilic species that are involved in the reaction pathway, we decided to prepare an enamine which is derived from an electron deficient aldehyde to decrease its nucleophilicity. We envisioned that 2,6-dichlorobenzaldehyde would be a good choice given its success participating in many redox-neutral reactions.[27]

We then investigated the proposed enamine formation by mixing 2,6-dichlorobenzaldehyde and pyrrolidine under the catalysis of benzoic acid. After screening several conditions, we found that the reaction went to completion when reacting 2,6-dichlorobenzaldehyde with five equivalents of pyrrolidine and 0.2 equivalent of benzoic acid in toluene at reflux temperature for 2 hours (Scheme 3.12, eq 12), and we were able to isolate the dimer of the enamine **3.30** with 65% yield. This result is consistent with the proposed mechanism but due to the dimerization ability of the enamine **3.30**, enamine dimer **3.57** was the isolated product.[28] There are several precedents in literature about the enamine dimer species. For example, an enamine dimer analogue was reported by Hauck when they used mercury acetate as an oxidant to oxidize *N*-methylpiperidine.[29] Similar enamine dimer product was observed when reacting with compound **3.79** with acrylonitrile.[25] In addition to chemical synthesis, enamine dimer species **3.83** was also present in the biosynthesis of anabasine from L-lysine.[30] It is interesting to note that besides enamine dimer **3.57,** a mixture of higher order enamine oligomers was also observed. However, in a control experiment where no benzoic acid was added (Scheme 3.12, eq 13), the reaction proceeded much slower and 18% of the starting material was recovered after refluxing in toluene for 2 hours. The crude NMR showed a 27% yield of aminal product **3.59** and only a trace amount of the enamine dimer **3.57** was isolated. Interestingly, in this condition there was a new compound isolated in 17% yield and it was characterized as **3.58**. The formation of **3.58** could be explained by the initial formation of the conjugated iminium ion **3.34** and

its subsequent nucleophilic attack of **3.34** by another molecule of enamine **3.30**. These observations have provided strong evidence that the enamine **3.30** and conjugated iminium ion **3.34** are active species in the formation of **3.16**.

Scheme 3.12 **Enamine Formation**

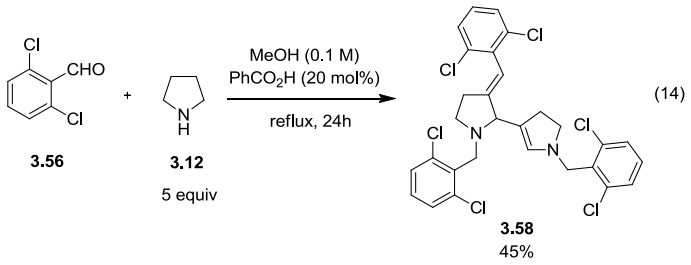




The experiments described above demonstrated that carboxylic acids such as benzoic acid could alter the reaction outcome significantly. Adding 20 mol% of benzoic acid enabled the formation of **3.57** in good yield**,** while in the control experiment where no benzoic acid was added only low yields of **3.57** and **3.58** were observed. This observation is in line with our hypothesis that carboxylic acid facilitates the formation of some key intermediates such as azomethine ylides **3.28** and **3.35**.

Besides the carboxylic acid catalyst, the solvent also has an effect on the outcome of the reaction. When using methanol as the solvent instead of toluene, the reaction between 2,6-dichlorobenzaldehyde and pyrrolidine only gave rise to the conjugated enamine dimer in 45% yield (Scheme 3.13, eq 14). This is likely due to the fact that the protic solvent favors the exsistence of monomeric form of the enamine and this leads to further transformation of the enamine monomer to the conjugated iminium ion **3.34** and ultimately leads to the formation of the thermodynamically more stable product **3.58**.

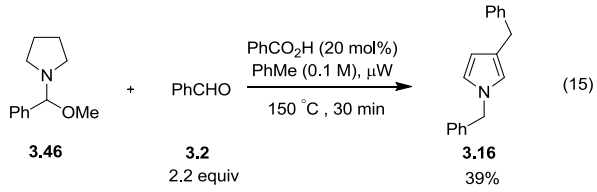
Scheme 3.13 **Redox-Neutral Enamine Formation in Methanol**



3.4.3 Interconversion between Proposed Intermediates and Final Aromatized Product

Having provided experimental evidence for the proposed intermediates, we conducted experiments with the purpose of establishing the connection between these intermediates and the final 1,3-disubstituted pyrrole product. By reacting *N*,*O*-acetal with benzaldehyde and a catalytic amount of benzoic acid under microwave conditions, **3.16** was formed in 39% yield (Scheme 3.14). This is in line with our hypothesis that the *N*,*O*-acetal follows a similar pathway en route to **3.16**.

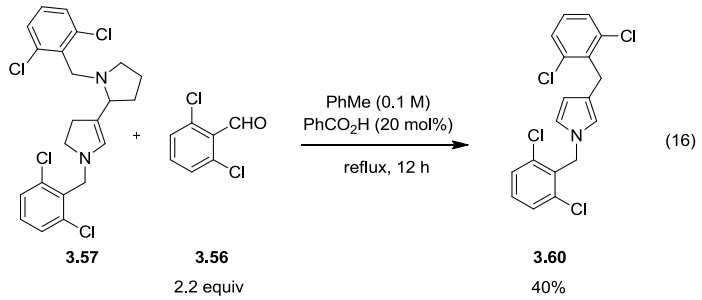
Scheme 3.14 **Formation of 1,3-Dibenzylpyrrole from *N*,*O*-acetal 3.42**



When exposing the enamine dimer **3.57** to 2.2 equivalents of 2,6-dichlorobenzaldehyde and catalytic amount of benzoic acid in toluene and reflux for 12 hours (Scheme 3.15), we observed the formation of **3.58** as an intermediate during the course of the reaction, judging by TLC. However, **3.58** was completely depleted by the end of the reaction, and the 1,3-dibenzylpyrrole product **3.60** was isolated in 40% yield. This suggests that the equilibrium between the enamine dimer **3.57** and enamine

monomer **3.30** exists under the reaction conditions, and that both enamine dimer **3.57** and enamine dimer **3.58** are intermediates that lead to the formation of final aromatized product **3.60**.

Scheme 3.15 **Formation of 1,3-Dibenzylpyrrole from Enamine**



In summary, we have discussed the experimental results found in the mechanistic studies of the reaction between benzaldehyde and pyrrolidine. The results we obtained are consistent with our hypothesis of for the mechanism of 1,3-dibenzylpyrrole formation. The finding and isolation of some important intermediates have also encouraged us to explore the scope of these transformations and the potential synthetic utilities of these intermediates.

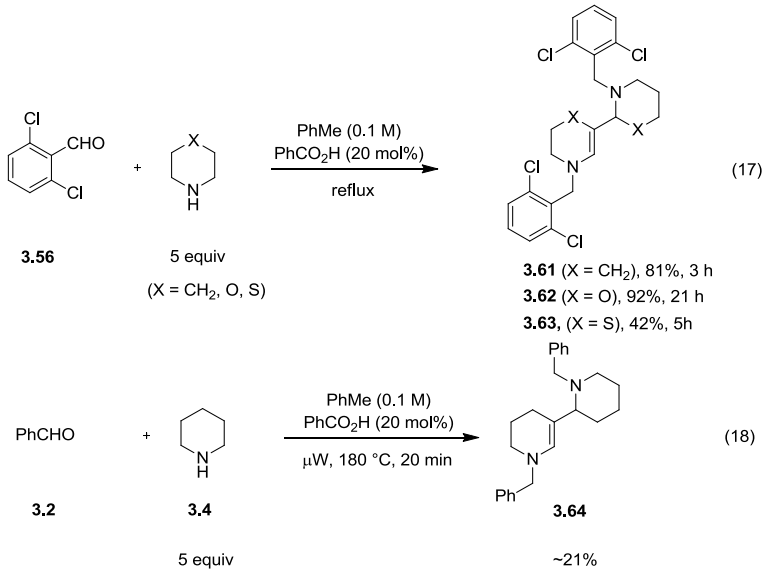
3.5 Substrate Scope and Synthetic Utility of Some Important Intermediates

3.5.1 Substrate Scope for the Formation of Enamine

The redox-neutral enamine formation from of aromatic aldehyde and cyclic secondary amines seems to be general. Pyrrolidine, piperidine, morpholine and thiomorpholine all reacted with 2,6 dichlorobenzaldehyde to afford the corresponding enamine dimers in moderate to good yields (Scheme 3.16, eq 17). In terms of the scope of other aromatic aldehydes, we have found that benzaldehyde also reacted with piperidine under harsher conditions to form the corresponding enamine dimer with a much lower yield (Scheme 3.16, eq 18). The difference in reactivity could be

attributed to the fact that benzaldehyde is more electron rich as compared to 2,6-dichlorobenzaldehyde, therefore the required transformation from iminium species to azomethine ylide would be slower in the case where benzaldehyde is used. The unstable nature of compound **3.64** could also explain the low yield for the enamine formation.

Scheme 3.16 **Substrate Scope of the Enamine Formation**

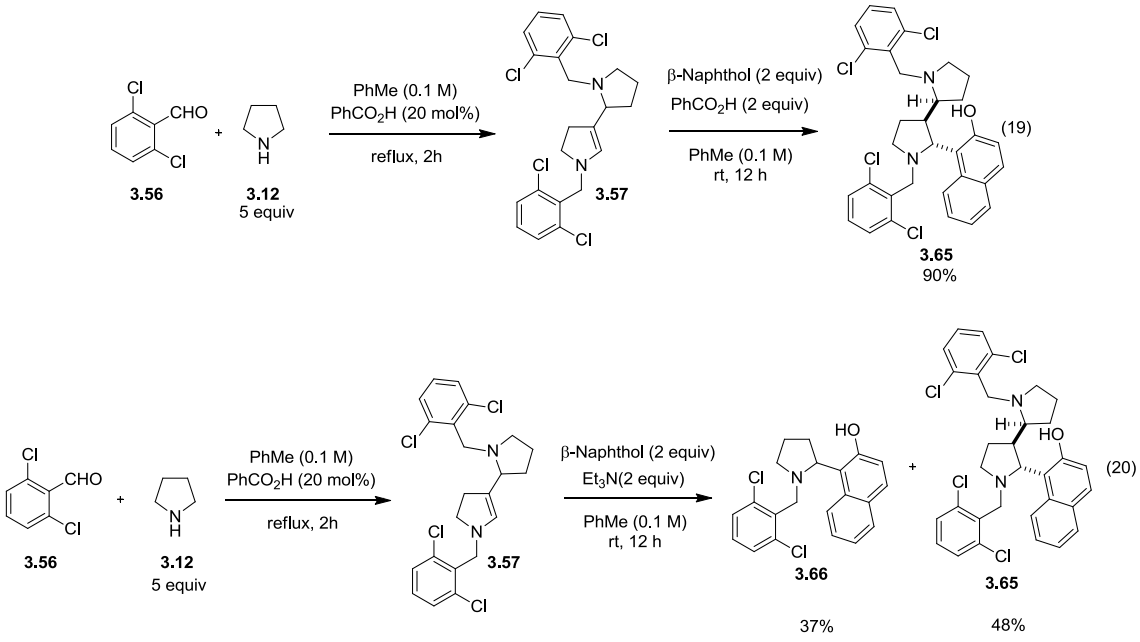


3.5.2 Synthetic Utility of Enamines in the α and β-Functionalization of Cyclic Amine

Enamines have shown tremendous synthetic utility and are employed extensively for the selective formation of C–C bonds.[31] The classic method for the preparation of enamines uses an amine and a carbonyl compound in which acidic, basic, and/or azeotropic conditions are usually required.[32] Alternatively, transition metals are also employed to prepare enamines by dehydrogenation of tertiary amines.[33] The studies of redox-neutral aromatization have provided us with an efficient access to endocyclic enamines which has enabled us to develop methods for both α and β-functionalization of cyclic amines.[34]

We tested the reaction between enamine dimer **3.56** and β-naphthol with the purpose of getting the α-arylated pyrrolidine **3.66**. Interestingly, after a brief screening of different conditions we found that the direct addition product of β-naphthol to the enamine dimer was the major product obtained. It seems that the reaction outcome can be changed significantly by using different additives. With two equivalents benzoic acid added, **3.66** was obtained in high yield and no **3.66** was observed (Scheme 3.17, eq 19). But when triethylamine was used as an additive, **3.66** was obtained in 37% yield along with 48% of **3.65** (Scheme 3.17, eq 20).

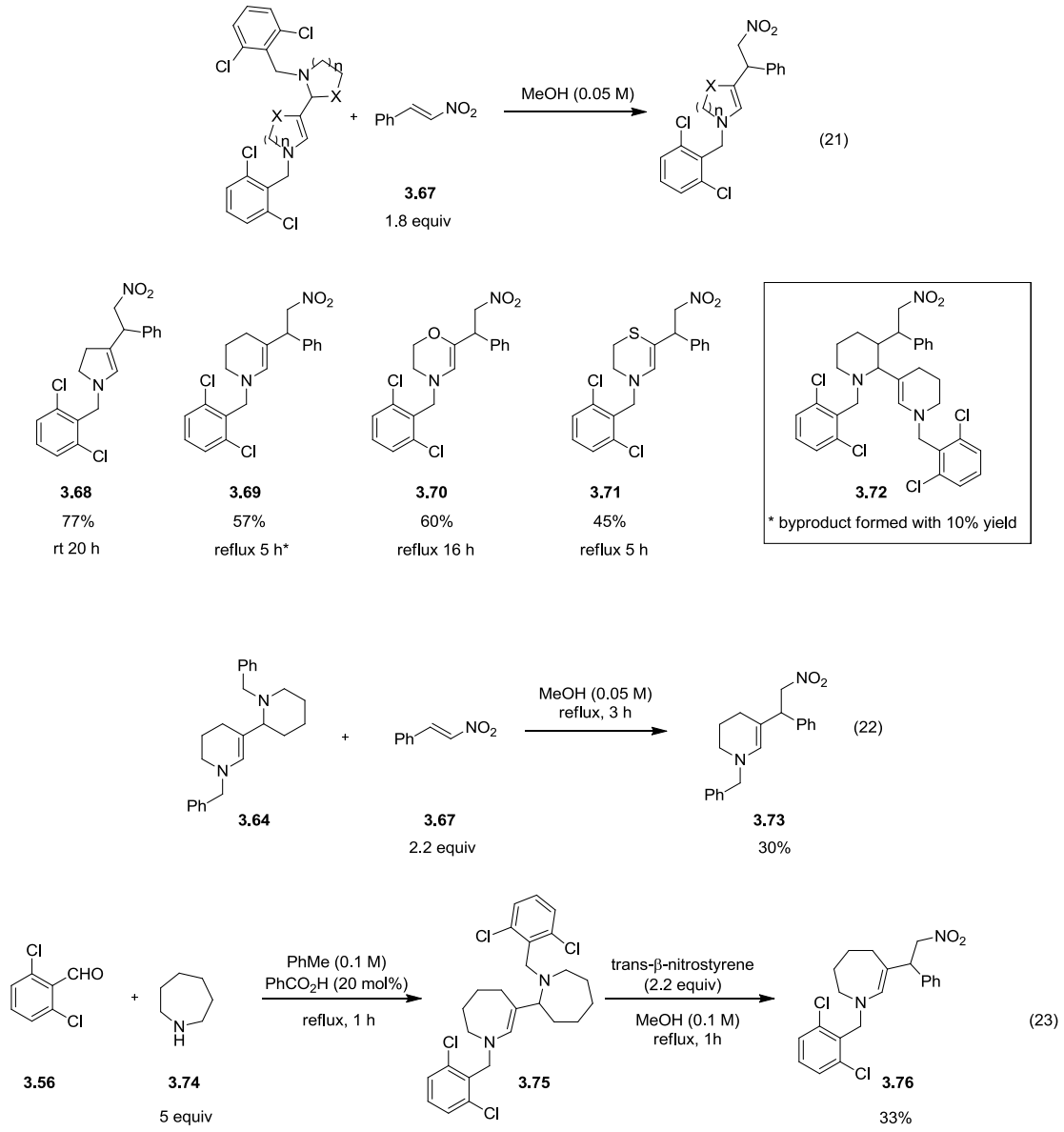
Scheme 3.17 **α-Functionalization of Cyclic Amine**



The β-functionalized cyclic amines exhibit various biological properties and they are common structural motifs in natural products and pharmaceuticals.[35-38] The inert nature of the β-H of cyclic amines has limited the direct functionalization of this challenging position. Most recent methods regarding β-functionalization of amines involve transition metal catalyzed dehydrogenation of saturated cyclic amines.[39-41] Given the equilibrium shown between the enamine monomer and the enamine dimer, we envisioned that the reaction between the enamine dimer and electrophiles would give rise the β-functionalized cyclic amines.

Gratifyingly, we found that the β-functionalized product was obtained when exposing the enamine dimer to β-nitrostyrene in methanol. Enamines derived from pyrrolidine, piperidine, morpholine and thiomorpholine also show good reactivities towards β-nitrostyrene (Scheme 3.18, eq 21). It is interesting to note that when enamine dimer derived from piperidine was employed in the reaction, byproduct **3.72** was also isolated in 10% yield. More challenging substrates like enamine **3.64** could also react with β-nitrostyrene to afford **3.73** in 30% yield (Scheme 3.18, eq 22). In the case where the enamine dimer could not be isolated in the pure form, the crude reaction mixture of azepane and 2,6-dichlorobenzaldehyde could also be exposed to the β-nitrostyrene to afford the corresponding β-functionalized azepane in 33% yield (Scheme 3.18, eq 23).

Scheme 3.18 **β-Functionalization of Cyclic Amine**



3.6 Conclusion

In conclusion, we have demonstrated experimental evidence for the intermediates proposed in the formation of 1,3-dibenzylpyrrole from benzaldehyde and pyrrolidine. This has helped us to gain insights into the mechanism of the redox-neutral aromatization of cyclic amines. The reactive

intermediates are shown to have further synthetic applications in α and β-functionalization of cyclic amines. Computational studies regarding the reaction pathway are currently being investigated in collaboration with Dr. Martin Breugst.

3.7 Experimental Section

General Information: Starting materials, reagents, and solvents were purchased from commercial sources and used as received unless stated otherwise. Pyrrolidine, piperidine, azepane, 1,2,3,4-tetrahydroisoquinoline, and 2-ethylhexanoic acid were distilled prior to use. Benzoic acid and N-methylmaleimide were recrystallized from toluene/ethanol. Aldehydes were purified either by distillation or by recrystallization prior to use. 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) and Basic Alumina silica gel. Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60 F_{254} 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 (^{1}H-NMR) were recorded on a Varian VNMRS-500 MHz and 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 (^{13}C-NMR) spectra were recorded on a Varian VNMRS-500 MHz and 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. The starting materials were prepared according to published procedures. Compounds **3.48,**[42] **3.51,**[43] and **3.66**[44]

were previously reported and their published characterization data matched our own in all respects. Ratios of regioisomeric products were determined by ^{1}H-NMR analysis of the crude reaction mixture.

General Procedure A: Procedure for the Preparation of *N,O*-acetals:

According to reported procedure,[45] in a 25 mL round bottom flask, amine (52 mmol, 1.25 equiv), methanol (105 mmol, 2.5 equiv) and potassium carbonate (K_2CO_3) (63 mmol, 1.5 equiv) were stirred at 0 °C for 10 min. The benzaldehyde (42 mmol, 1 equiv) was then added in one portion and the mixture was stirred at room temperature for 24 hours. The reaction mixture was diluted with anhydrous diethyl ether (20 mL) and K_2CO_3 was filtrated and washed with anhydrous diethyl ether (3 x 20 mL). The resulting filtrate was concentrated under reduced pressure and the product was distilled under reduced pressure (2.7 torr).

General Procedure B: Procedure for the [3+2] Trapping Experiment via Three-Component Approach:

In a 25 mL round bottom flask, pyrrolidine (1.2 mmol, 1.2 equiv) and carboxylic acid catalyst (0.2 mmol, 0.2 equiv) were dissolved in toluene (10 mL). After stirring for 10 min, N-methylmaleimide (1 mmol, 1 equiv) and benzaldehyde (1 mmol, 1 equiv) were added to the reaction mixture. A reflux condenser with a nitrogen inlet was placed on top of the flask which was then heated in an oil bath to the appropriate temperature for designated time. After allowing the flask to cool to room temperature, the mixture was diluted with EtOAc (40 mL) and washed with saturated $NaHCO_3$ solution (3 x 20 mL), water (20 mL), brine (20 mL) and dried over Na_2SO_4. The resulting solution was concentrated under reduced pressure and the residue purified via silica gel chromatography.

General Procedure C: Procedure for the [3+2] Trapping Experiment with *N,O*-acetals Under Microwave Conditions:

A 10 mL microwave reaction tube was charged with a 10 x 8 mm SiC passive heating element, *N,O*-acetal (0.3 mmol, 1.2 equiv), toluene (2.5 mL), *N*-methylmaleimide (0.25 mmol, 1 equiv) 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 $NaHCO_3$ (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 Na_2SO_4. Solvent was then removed in vacuo and the reaction mixture was loaded onto a column for purification (silica gel).

General Procedure D: Procedure for the [3+2] Trapping Experiment with N,O-acetals Under Conventional Thermal Conditions:

In a 10 mL round bottom flask, *N*,*O*-acetal (stated amount), *N*-methylmaleimide (0.25 mmol, 1 equiv), and carboxylic acid catalyst (0.05 mmol, 0.2 equiv) were dissolved in toluene (2.5 mL). A reflux condenser with a nitrogen inlet was placed on top of the flask which was then heated in an oil bath to the appropriate temperature for designated time. After allowing the flask to cool to room temperature, the mixture was diluted with EtOAc (20 mL) and washed with saturated $NaHCO_3$ solution (3 x 20 mL), water (20 mL), brine (20 mL) and dried over Na_2SO_4. The resulting solution was concentrated under reduced pressure and the residue purified via silica gel chromatography.

General Procedure E: Procedure for the Preparation of Enamine Dimer and Extended Enamine:

In a 25 mL round bottom flask, 2,6-dichlorobenzaldehyde (1 mmol, 1 equiv), amine (5 mmol, 5 equiv), and benzoic acid (0.2 mmol, 0.2 equiv) were dissolved in toluene (10 mL). A reflux condenser with a nitrogen inlet was placed on top of the flask which was then heated in an oil bath to reflux temperature for designated time. After allowing the flask to cool to room temperature, the mixture was diluted with EtOAc (20 mL) and washed with saturated $NaHCO_3$ solution (3 x 20 mL), water (20 mL), brine (20 mL) and dried over Na_2SO_4. The resulting solution was concentrated under reduced pressure and the residue purified via basic alumina chromatography.

General Procedure F: Procedure for β-Functionalization of Cyclic Amine:

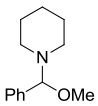
In a 10 mL round bottom flask, enamine dimer (0.125 mmol, 1 equiv) and β-nitrostyrene (0.225 mmol, 1.8 equiv) were dissolved in MeOH (2.5 mL). A reflux condenser with a nitrogen inlet was placed on top of the flask which was then heated in an oil bath to stated temperature for designated time. After allowing the flask to cool to room temperature, the mixture was diluted with EtOAc (20 mL) and

washed with saturated $NaHCO_3$ solution (3 x 20 mL), water (20 mL), brine (20 mL) and dried over Na_2SO_4. The resulting solution was concentrated under reduced pressure and the residue purified via silica gel chromatography.

1-(Methoxy(phenyl)methyl)pyrrolidine (3.46): Following the general procedure A, compound **3.46**

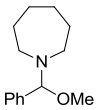
was obtained from pyrrolidine and benzaldehyde as a clear liquid in 56% yield (distilled at 81 °C/2.7 torr); IR (KBr) 3058, 3031, 2966, 2820, 1706, 1452, 1340, 1202, 1150, 1070, 940, 752, 704 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.43–7.38 (comp, 2H), 7.37–7.31 (comp, 2H), 7.31–7.25 (m, 1H), 4.78 (s, 1H), 3.27 (s, 3H), 2.76–2.62 (m, 4H), 1.79–1.68 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.4, 127.9, 127.7, 127.2, 96.9, 55.3, 48.1, 23.7; *m/z* (ESI–MS) 160.2 $[M–MeO]^+$.

1-(Methoxy(phenyl)methyl)piperidine (3.47): Following the general procedure A, compound **3.47**



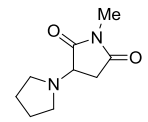
was obtained from piperidine and benzaldehyde as a colorless oil in 60% yield (distilled at 88 °C/2.7 torr); IR (KBr) 3086, 3024, 2933, 2852, 2619, 2751, 1490, 1465, 1451, 1334, 1225, 1158, 1073, 940, 741, 701 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.41–7.33 (comp, 4H), 7.32–7.25 (m, 1H), 4.75 (s, 1H), 3.40 (s, 3H), 2.57 (t, J = 5.4 Hz, 4H), 1.58–1.49 (m, 4H), 1.46–1.39 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.4, 127.7, 127.4, 127.3, 98.4, 56.3, 48.5, 26.1, 24.7; *m/z* (ESI–MS) 174.3 $[M–MeO]^+$.

1-(Methoxy(phenyl)methyl)azepane (3.49): Following the general procedure A, compound **3.49**



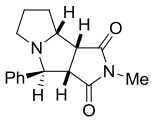
was obtained from azepane and benzaldehyde as a colorless oil in 65% yield; IR (KBr) 3088, 3061, 3031, 2937, 2813, 1948, 1812, 1708, 1601, 1450, 1331, 1239, 1128, 941, 829, 728, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.47–7.41 (comp, 2H), 7.39–7.31 (comp, 2H), 7.31–7.24 (m, 1H), 4.98 (s, 1H), 3.44 (s, 3H), 2.88–2.79 (m, 4H), 1.67–1.51 (comp, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.4, 127.7, 127.4, 127.3, 98.4, 56.3, 48.5, 26.1, 24.7; *m/z* (ESI–MS) 174.3 $[M–MeO]^+$.

1'-Methyl-[1,3'-bipyrrolidine]-2',5'-dione (3.43): Following the general procedure C, compound



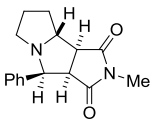
3.43 was obtained from pyrrolidine and **3.42** as an off-white solid in 18% yield (R_f = 0.24 in EtOAc); mp: 47–49 ºC; IR (KBr) 2968, 2878, 2814, 2713, 2658, 1775, 1717, 1436, 1385, 1281, 1208, 971, 908, 866, 793, 677 cm^{-1};^{1}H NMR (500 MHz, $CDCl_3$) 3.73 (dd, *J* = 8.5, 4.8 Hz, 1H), 2.98 (s, 3H), 2.90–2.81 (comp, 3H), 2.71–2.58 (comp, 3H), 1.86–1.74 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.6, 175.1, 60.1, 50.8, 33.3, 24.6, 23.3; *m/z* (ESI–MS) 183.1 $[M+H]^+$.

(3aR,4R,8aR,8bS)-2-Methyl-4-phenylhexahydropyrrolo[3,4-a]pyrrolizine-1,3(2H,8bH)-dione



(3.44, major diastereomer): Following the general procedure C, compound **3.44 (major diastereomer)** was obtained from **3.46** and **3.42** as an off-white solid in 34% yield (R_f = 0.36 in 50% EtOAc in hexanes); mp: 126–127 ºC; IR (KBr) 2965, 2883, 1776, 1698, 1645, 1436, 1385, 1286, 1139, 1064, 758, 700 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.52–7.46 (comp, 2H), 7.40–7.34 (comp, 2H), 7.31–7.26 (m, 1H), 4.11 (d, *J* = 6.0 Hz, 1H), 3.96–3.88 (m, 1H), 3.59 (app t, *J* = 9.0 Hz, 1H), 3.41–3.34 (m, 1H), 3.05–2.96 (m, 1H), 3.00 (s, 3H), 2.69–2.60 (m, 1H), 2.09–1.98 (m, 1H), 1.96–1.87 (m, 1H), 1.87–1.76 (m, 1H), 1.73–1.60 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.5, 175.6, 137.9, 128.2, 128.0, 127.9, 68.8, 67.9, 50.7(8), 50.7(5) ,49.0, 29.6, 24.9, 23.4; *m/z* (ESI–MS) 271.3 $[M+H]^+$.

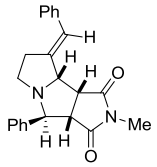
(3aR,4S,8aR,8bS)-2-Methyl-4-phenylhexahydropyrrolo[3,4-a]pyrrolizine-1,3(2H,8bH)-dione



(3.44, minor diastereomer): Following the general procedure C, compound **3.39 (minor diastereomer)** was obtained from **3.46** and **3.42** as a white solid in 10% yield (R_f = 0.37 in 50% EtOAc in hexanes); mp: 126–127 ºC; IR (KBr) 3086, 3056, 2970, 2940, 2880, 2824, 1767, 1698, 1495, 1436, 1367, 1284, 1141, 1083, 1032, 962, 755, 704, 649 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.35–7.27 (comp, 5H), 4.09 (d, *J* = 8.6 Hz, 1H), 3.82–3.76 (m, 1H), 3.51 (app t, *J* = 8.3 Hz, 1H), 3.28 (app d, *J* = 7.8 Hz, 1H), 2.93–2.84 (m, 1H), 2.88 (s, 3H), 2.77–2.70 (m, 1H), 2.20–2.10 (m, 1H), 2.10–1.99 (m, 1H), 1.84–1.75 (m, 1H), 1.75–1.64 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.2, 177.2, 142.0, 128.6, 127.5, 126.9, 69.5, 66.2, 55.5, 51.9, 48.0, 26.7, 24.9, 24.4;

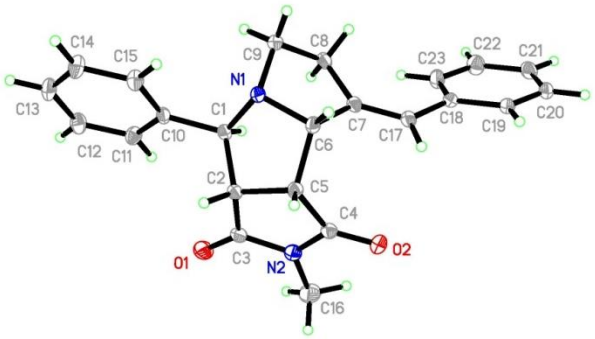
m/z (ESI–MS) 271.3 $[M+H]^+$.

(3aS,4R,8aR,8bR,E)-8-Benzylidene-2-methyl-4-phenylhexahydropyrrolo[3,4-a]pyrrolizine-

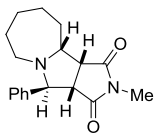


1,3(2H,8bH)-dione (3.45): Following the general procedure C, compound **3.45** was obtained from **3.46** and **3.42** as a reddish solid in 34% yield (R_f = 0.24 in 20% EtOAc in hexanes); mp: 111–114 ºC; IR (KBr) 3096, 3053, 2957, 2804, 2646, 1964, 1890, 1774, 1700, 1482, 1375, 1274, 1106, 1065, 971, 902, 855 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.51 (d, *J* = 7.6 Hz, 2H), 7.41–7.36 (comp, 2H), 7.36–7.31 (comp, 4H), 7.31–7.27 (m, 1H), 7.25–7.20 (m, 1H), 6.64 (s, 1H), 4.63–4.57 (comp, 2H), 3.66 (app t, *J* = 8.9 Hz, 1H), 3.48 (dd, *J* = 8.5, 3.4 Hz, 1H), 3.27–3.19 (m, 1H), 2.91 (s, 3H), 2.83–2.74 (comp, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.6, 175.9, 142.3, 139.0, 137.5, 128.7, 128.3(5), 128.3(0), 127.3, 126.8, 126.4, 126.1, 71.5, 69.1, 55.9, 52.9, 50.7, 30.0, 25.1; *m/z* (ESI–MS) 359.3 $[M+H]^+$.

Figure 3.1 **X–ray Crtystal Structure of Product 3.45**

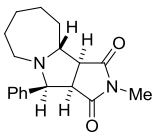


(3aR,4R,10aR,10bS)-2-Methyl-4-phenyloctahydropyrrolo[3',4':3,4]pyrrolo[1,2-a]azepine-



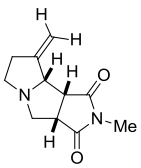
1,3(2H,10bH)-dione (3.50a): Following the general procedure C, compound **3.50a** was obtained from **3.49** and **3.42** as a clear oil in 14% yield (R_f = 0.29 in 25% EtOAc in hexanes; IR (KBr) 3064, 3026, 2932, 2858, 2814, 2730, 1771, 1698, 1495, 1436, 1385, 1287, 1131, 1077, 1003, 966, 823, 703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.39–7.33 (comp, 2H), 7.32–7.27 (m, 1H), 7.23–7.17 (comp, 2H), 4.49 (d, *J* = 1.7 Hz, 1H), 3.42–3.28 (comp, 3H), 3.02 (s, 3H), 2.82–2.74 (m, 1H), 2.11–2.04 (m, 1H), 2.04–1.97 (m, 1H), 1.67–1.59 (m, 1H), 1.58–1.34 (comp, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.9, 177.3, 138.7, 128.3, 128.1, 127.6, 70.0, 63.1, 51.5, 49.1, 48.9, 28.7, 27.5, 27.1, 25.0, 24.5; *m/z* (ESI–MS) 299.3 $[M+H]^+$.

(3aR,4S,10aR,10bS)-2-Methyl-4-phenyloctahydropyrrolo[3',4':3,4]pyrrolo[1,2-a]azepine-



1,3(2H,10bH)-dione (3.50b): Following the general procedure C, compound **3.50a** was obtained from **3.49** and **3.42** as a white solid in 14% yield (R_f = 0.17 in 25% EtOAc in hexanes); mp: 150–153 ºC; IR (KBr) 2095, 2854, 2797, 2364, 1777, 1699, 1490, 1435, 1384, 1284, 1119, 1072, 837, 763, 701 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.35–7.26 (comp, 3H), 7.21–7.14 (comp, 2H), 4.21 (d, *J* = 9.3 Hz, 1H), 3.96 (app d, *J* = 10.4 Hz, 1H), 3.46 (dd, *J* = 9.3, 7.8 Hz, 1H), 3.00–2.89 (comp, 2H), 3.86 (s, 3H), 2.24 (app dd, *J* = 13.1, 8.9 Hz, 1H), 1.95–1.83 (comp, 2H), 1.83–1.74 (m, 1H), 1.73–1.65 (m, 1H), 1.64–1.57 (m, 1H), 1.54–1.41 (comp, 2H), 1.38–1.29 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.1, 176.3, 137.4, 128.3, 128.0, 127.9, 68.1, 65.6, 52.6, 50.3, 50.1, 30.7, 29.5, 27.5, 24.8, 24.5; *m/z* (ESI–MS) 299.3 $[M+H]^+$.

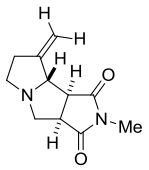
(3aR,8aR,8bS)-2-Methyl-8-methylenehexahydropyrrolo[3,4-a]pyrrolizine-1,3(2H,8bH)-dione



(3.53 major diastereomer): Following the general procedure C, compound **3.53 (major diastereomer)** was obtained from **3.51** and **3.42** as a yellow oil in 25% yield (R_f = 0.24 in EtOAc); IR (KBr) 2987, 1769, 1687, 1647, 1448, 1391, 1300, 1139, 1097, 577 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 5.23–5.20 (m, 1H), 5.15–5.12 (m, 1H), 3.97–3.93 (m, 1H), 3.31–3.22 (comp, 3H), 3.00 (s, 3H), 2.99–2.95 (m, 1H), 2.92–2.85 (m, 1H), 2.81–2.73 (m, 1H), 2.72–

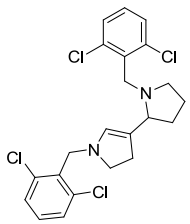
2.62 (m, 1H), 2.57–2.47 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.8, 178.2, 159.2, 108.0, 71.4, 53.7, 50.2, 49.4, 45.8, 29.4, 25.2; *m/z* (ESI–MS) 207.3 $[M+H]^+$.

(3aR,8aS,8bS)-2-Methyl-8-methylenehexahydropyrrolo[3,4-a]pyrrolizine-1,3(2H,8bH)-dione



(3.53 minor diastereomer) : Following the general procedure C, compound **3.53 (minor diastereomer)** was obtained from **3.51** and **3.42** as a yellow solid in 18% yield (R_f = 0.17 in EtOAc); mp: 38–40 ºC; IR (KBr) 2952, 2888, 1771, 1690, 1647, 1441, 1388, 1266, 1101, 1064, 990, 899 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 5.25–5.19 (comp, 2H), 4.19 (d, *J* = 9.1 Hz, 1H), 3.52 (app d, *J* = 12.5 Hz, 1H), 3.42–4.25 (comp, 3H), 3.12–3.03 (m, 1H), 2.88 (s, 3H), 3.83–3.77 (m, 1H), 2.60–2.49 (m, 1H), 2.44–2.30 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.7, 176.3, 144.9, 110.9, 71.6, 54.3, 52.9, 50.0, 48.1, 32.1, 25.1; *m/z* (ESI–MS) 207.3 $[M+H]^+$.

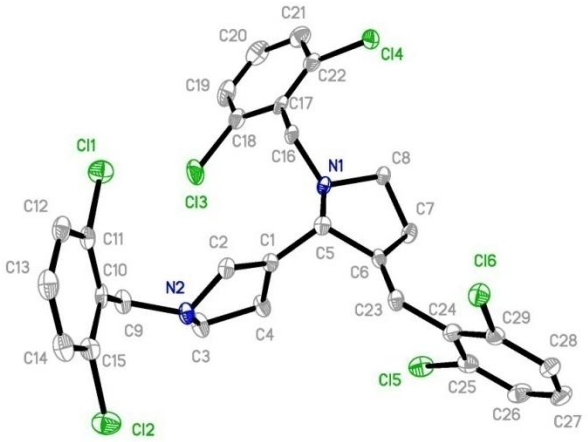
1-(2,6-Dichlorobenzyl)-4-(1-(2,6-dichlorobenzyl)pyrrolidin-2-yl)-2,3-dihydro-1H-pyrrole (3.57):



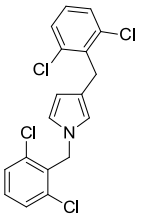
Following the general procedure E, compound **3.57** was obtained from pyrrolidine and *2,6*-dichlorobenzaldehyde as a yellow solid in 68% yield (R_f = 0.50 in 5% EtOAc in hexanes, alumina TLC plate); mp: 69–70 ºC; IR (KBr) 3061, 2951, 2831, 2802, 1702, 1652, 1581, 1560, 1435, 1361, 1254, 1197, 1133, 1090, 949, 852, 762, 733 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.30 (d, *J* = 8.0 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.13 (t, *J* = 8.0 Hz, 1H), 7.09 (t, *J* = 8.0 Hz, 1H), 6.00–5.96 (s, 1H), 4.13 (d, *J* = 12.2 Hz, 1H), 4.12 (d, *J* = 13.0 Hz, 1H), 4.02 (d, *J* = 13.0 Hz, 1H), 3.54 (d, *J* = 12.2 Hz, 1H), 3.31–3.23 (m, 1H), 3.06 (app t, *J* = 7.6 Hz, 1H), 2.94–2.88 (m, 1H), 2.88–2.81 (m, 1H), 2.55–2.46 (m, 1H), 2.46–2.33 (comp, 2H), 1.81–1.71 (m, 1H), 1.71–1.62 (comp, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.9, 136.7, 136.4, 135.7, 134.5, 128.9, 128.4, 128.3, 128.2, 117.0, 64.0, 54.2, 53.9, 52.7, 52.4, 29.2, 28.5, 22.2; *m/z* (ESI–MS) 455.0 (^{35}Cl/^{35}Cl/^{35}Cl/^{35}Cl) $[M+H]^+$, 457.0 (^{35}Cl/^{35}Cl/^{35}Cl/^{37}Cl) $[M+H]^+$, 459.0 (^{35}Cl/^{35}Cl/^{37}Cl/^{37}Cl) $[M+H]^+$.

(E)-1-(2,6-dichlorobenzyl)-4-(1-(2,6-dichlorobenzyl)-3-(2,6-dichlorobenzylidene)pyrrolidin-2-yl)-2,3-dihydro-1H-pyrrole (3.58): Following the general procedure E, but using MeOH as the solvent, compound **3.58** was obtained from pyrrolidine and *2,6*-dichlorobenzaldehyde as a white solid in 45% yield (R_f = 0.56 in 2% EtOAc in hexanes, alumina TLC plate); mp: 161–163 ºC; IR (KBr) 3041, 2957, 2913, 2827, 2792, 1732, 1685, 1645, 1561, 1470, 1435, 1374, 1314, 1205, 1134, 1100, 991, 959, 926, 775, 749 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.32 (d, *J* = 8.0 Hz, 2H), 7.29–7.23 (comp, 4H), 7.19–7.05 (comp, 3H), 6.21–6.14 (m, 1H), 6.06–5.98 (m, 1H), 4.22–4.15 (comp, 2H), 4.10 (d, *J* = 13.1 Hz, 1H), 3.87–3.81 (m, 1H), 3.67 (d, *J* = 12.3 Hz, 1H), 3.31–3.21 (m, 1H), 2.96 (app t, *J* = 8.3 Hz, 1H), 2.94–2.86 (m, 1H), 2.63–2.42 (comp, 3H), 2.34–2.23 (m, 1H), 2.21–2.12 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.8, 140.1, 136.9, 136.6, 136.3, 135.3, 134.8, 134.4, 129.0, 128.5, 128.3, 128.1, 127.7, 116.4, 115.2, 68.7, 54.3, 52.8, 52.5, 52.3, 29.3, 28.3; *m/z* (ESI–MS) 610.9 ($^{35}Cl/^{35}Cl/^{35}Cl/^{35}Cl/^{35}Cl/^{35}Cl$) $[M+H]^+$.

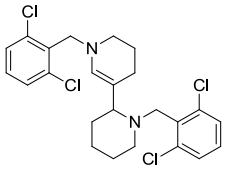
Figure 3.2 **X–ray Crystal Structure of Product 3.58**



1,3-Bis(2,6-dichlorobenzyl)-1H-pyrrole (3.60): In a 10 mL round bottom flask, 2,6-dichlorobenzaldehyde (2.2 mmol, 2.2 equiv), **3.57** (0.25 mmol, 1 equiv), and benzoic acid (0.05 mmol, 0.2 equiv) were dissolved in toluene (2.5 mL). A reflux condenser with a nitrogen inlet was placed on top of the flask which was then heated in an oil bath to reflux temperature for 12 h. After allowing the flask to cool to room temperature, the mixture was diluted with EtOAc (20 mL) and washed with saturated $NaHCO_3$ solution (3 x 20 mL), water (20 mL), brine (20 mL) and dried over Na_2SO_4. The resulting solution was concentrated under reduced pressure and the residue purified via silica gel chromatography. Compound **3.60** was obtained as a light yellow solid in 40% yield (R_f = 0.6 in 10% EtOAc in hexanes); IR (KBr) 2961, 2867, 2361, 1696, 1579, 1560, 1498, 1435, 1338, 1298, 1158, 980, 938, 758, 694 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.33 (d, *J* = 8.1 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.17 (t, *J* = 8.0 Hz, 1H), 7.04 (t, *J* = 8.1 Hz, 1H), 6.79 (s, 1H), 6.69 (s, 1H), 6.12 (s, 1H), 5.28 (s, 2H), 4.11 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.3, 136.4, 135.4, 133.1, 129.9, 128.7, 128.2, 127.4, 120.7, 120.2, 119.5, 108.6, 47.8, 28.8; *m/z* (ESI–MS) 384.4 $[M+H]^+$.

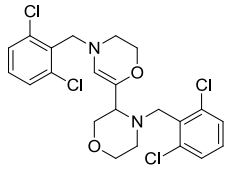


1-(2,6-Dichlorobenzyl)-5-(1-(2,6-dichlorobenzyl)piperidin-2-yl)-1,2,3,4-tetrahydropyridine (3.61): Following the general procedure E, compound **3.61** was obtained from piperidine and *2,6*-dichlorobenzaldehyde as a yellow solid in 81% yield (R_f = 0.37 in 10% EtOAc in hexanes); mp: 89–92 ºC; IR (KBr) 2928, 2844, 2782, 1724, 1654, 1579, 1561, 1435, 1376, 1304, 1194, 1126, 1085, 975, 864, 776, 764 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.30 (d, *J* = 8.0 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.14 (t, *J* = 8.1 Hz, 1H), 7.08 (t, *J* = 8.1 Hz, 1H), 6.05 (s, 1H), 4.18 (s, 2H), 4.13 (d, *J* = 12.5 Hz, 1H), 3.26 (d, *J* = 12.5 Hz, 1H), 3.00–2.92 (m, 1H), 2.90–2.83 (m, 1H), 2.63–2.55 (m, 1H), 2.38–2.26 (comp, 2H), 2.13–1.96 (comp, 2H), 1.82–1.74 (comp, 2H), 1.72–1.67 (comp, 2H), 1.57–1.51 (m, 1H), 1.51–1.44 (m, 1H), 1.39–1.27 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.2, 136.8, 135.6, 134.1, 133.6, 128.9, 128.4, 128.3, 128.1, 111.2, 70.1, 54.7, 53.6, 52.7, 47.6, 31.9, 26.1, 25.2, 22.4, 21,3; *m/z* (ESI–MS) 483.1



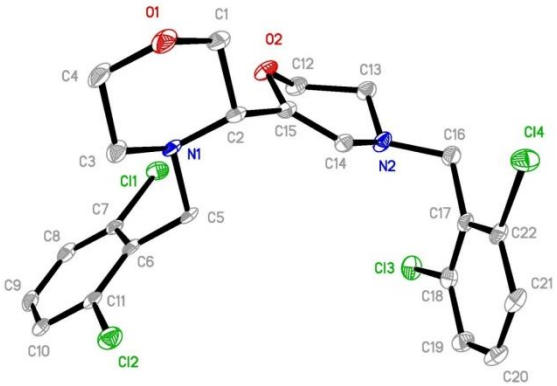
($^{35}Cl/^{35}Cl/^{35}Cl/^{35}Cl$) $[M+H]^+$, 485.1 ($^{35}Cl/^{35}Cl/^{35}Cl/^{37}Cl$) $[M+H]^+$.

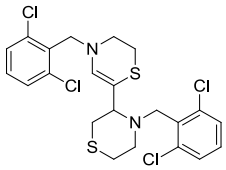
4-(2,6-Dichlorobenzyl)-6-(4-(2,6-dichlorobenzyl)morpholin-3-yl)-3,4-dihydro-2H-1,4-oxazine

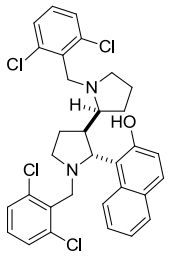


(3.62): Following the general procedure E, compound **3.62** was obtained from morpholine and 2.6-dichlorobenzaldehyde as a reddish solid in 92% yield (R_f = 0.24 in 10% EtOAc in hexanes); mp: 113–115 ºC; IR (KBr) 2957, 2858, 2812, 1734, 1675, 1581, 1562, 1436, 1388, 1361, 1292, 1245, 1115, 1088, 1045, 973, 766, 736 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.32 (d, *J* = 8.0 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.17 (t, *J* = 8.0 Hz, 1H),, 7.11 (t, *J* = 8.0 Hz, 1H), 5.62 (s, 1H), 4.30 (d, *J* = 12.3 Hz, 1H), 4.16–4.08 (comp, 2H), 4.08–4.02 (m, 1H), 3.99–3.92 (m, 1H), 3.83–3.77 (m, 1H), 3.74 (app d, *J* = 10.0 Hz, 1H), 3.72–3.65 (m, 1H), 3.53 (app t, *J* = 11.2 Hz, 1H), 3.46 (app d, *J* = 12.3 Hz, 1H), 3.01 (app t, *J* = 4.1 Hz, 1H), 2.72 (dd, *J* = 9.6, 3.6 Hz, 2H), 2.54 (app d, *J* = 11.7 Hz, 1H), 2.43 (app t, *J* = 11.2, Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.3, 136.7, 133.6, 133.3(6), 133.3(5), 129.2, 128.6, 127.5, 127.1, 105.2, 78.2, 53.5, 53.4(5), 53.4(0), 49.1, 46.6, 22.5, 22.3; *m/z* (ESI–MS) 487.3 ($^{35}Cl/^{35}Cl/^{35}Cl/^{35}Cl$) $[M+H]^+$, 489.1 ($^{35}Cl/^{35}Cl/^{35}Cl/^{37}Cl$) $[M+H]^+$, 491.0 ($^{35}Cl/^{35}Cl/^{37}Cl/^{37}Cl$) $[M+H]^+$.

Figure 3.3 **X–ray Crystal Structure of Product 3.62**

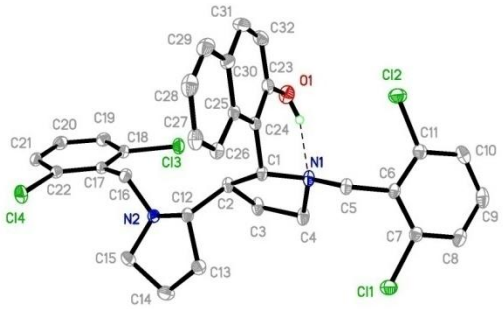


4-(2,6-Dichlorobenzyl)-6-(4-(2,6-dichlorobenzyl)thiomorpholin-3-yl)-3,4-dihydro-2H-1,4-thiazine (3.63):  Following the general procedure compound **3.63** was obtained from thiomorpholine and 2,6-dichlorobenzaldehyde as a brownish oil in 42% yield (R_f = 0.39 in 10% EtOAc in hexanes, alumina TLC plate); IR (KBr) 2923, 2851, 2602, 1633, 1580, 1561, 1435, 1376, 1299, 1199, 1094, 936, 765, 736 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.32 (d, *J* = 8.0 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.18 (t, *J* = 8.0 Hz, 1H), 7.10 (t, *J* = 8.0 Hz, 1H), 6.45 (s, 1H), 4.45–4.25 (comp, 3H), 3.56 (d, *J* = 12.4 Hz, 1H), 3.46–3.28 (comp, 2H), 3.13–3.05 (m, 1H), 3.01–2.94 (m, 1H), 2.92 (dd, *J* = 9.7, 2.5 Hz, 1H), 2.87–2.81 (comp, 2H), 2.69–2.49 (comp, 3H), 2.39–2.31 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.5, 136.7, 134.6, 133.1, 130.1, 129.4, 128.5(7), 128.5(5), 128.3, 101.4, 69.7, 54.0, 53.8, 52.8, 47.7, 33.0, 27.4, 25.0; *m/z* (ESI–MS) 520.8 $[M+H]^+$.

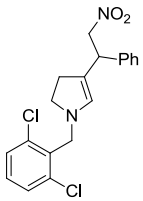
1-(1,1'-Bis(2,6-dichlorobenzyl)-[2,3'-bipyrrolidin]-2'-yl)naphthalen-2-ol (3.65):  In a 25 mL round bottom flask, enamine dimer **3.57** (1 mmol, 1 equiv), β-naphthol (2 mmol, 2 equiv) and benzoic acid (2 mmol, 2 equiv) were dissolved in PhMe (10 mL). The reaction mixture was stirred at room temperature for 12 h. After completion of the reaction, the reaction mixture was diluted with EtOAc (20 mL) and washed with saturated $NaHCO_3$ solution (3 x 20 mL), water (20 mL), brine (20 mL) and dried over Na_2SO_4. The resulting solution was concentrated under reduced pressure and the residue purified via silica gel chromatography. Compound **3.65** was obtained as a white solid in 90% yield (R_f = 0.43 in 15% EtOAc in hexanes); mp: 143–145 ºC; IR (KBr)2964, 2807, 1621, 1598, 1582, 1562, 1466, 1436, 1270, 1237, 1200, 1090, 817, 739 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 11.59–11.36 (br s, 1H), 7.98 (app d, *J* = 8.6 Hz, 1H), 7.76 (app d, *J* = 8.1 Hz, 1H), 7.64 (d, *J* = 8.8 Hz, 1H), 7.45 (t, *J* = 7.0 Hz, 1H), 7.30 (t, *J* = 7.9 Hz, 1H), 7.20–7.11 (comp, 4H), 7.07–6.98 (comp, 3H), 4.32 (d, *J* = 9.2 Hz, 1H), 4.05 (d, *J* = 12.6 Hz, 1H), 3.88 (d, *J* = 12.6 Hz, 1H), 3.74 (d, *J* = 12.3 Hz, 1H), 3.37 (d, *J* = 12.3 Hz, 1H), 3.19 (app t, *J* = 8.6 Hz, 1H), 2.94–2.84 (m, 1H), 2.84–2.71 (comp, 2H), 2.64–2.53 (m, 1H), 2.41–2.29 (m, 1H), 2.23–2.10 (m, 1H), 2.08–2.18 (m, 1H), 1.98–1.87 (comp, 2H), 1.80–1.65 (comp, 2H); ^{13}C

NMR (125 MHz, $CDCl_3$) δ 156.1, 136.7, 136.5, 134.9, 133.4, 133.0, 129.0, 128.8, 128.5, 128.4, 128.3, 128.2(7), 128.2(0), 125.9, 122.1, 121.3, 119.6, 115.7, 68.5, 64.0, 54.3, 53.2, 52.1, 46.8, 29.7, 26.7, 24.9, 23.4; *m/z* (ESI–MS) 602.1 ($^{35}Cl/^{35}Cl/^{35}Cl/^{35}Cl$) $[M+H]^+$, 604.2 ($^{35}Cl/^{35}Cl/^{35}Cl/^{37}Cl$) $[M+H]^+$.

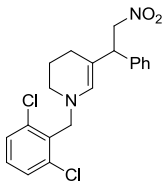
Figure 3.4 **X–ray Crystal Structure of Product 3.65**



1-(2,6-Dichlorobenzyl)-4-(2-nitro-1-phenylethyl)-2,3-dihydro-1H-pyrrole (3.68): Following the general procedure F, compound **3.68** was obtained from **3.57** and β-nitrostyrene as a yellow oil in 77% yield (R_f = 0.49 in 20% EtOAc in hexanes); IR (KBr) 3088, 3061, 3031, 2937, 2813, 1948, 1812, 1708, 1601, 1450, 1331, 1239, 1128, 941, 829, 728, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.34–7.29 (comp, 4H), 7.22–7.14 (comp, 4H), 5.91 (s, 1H), 4.78–4.71 (m, 1H), 4.66–4.60 (m, 1H), 4.23 (t, *J* = 7.9 Hz, 1H), 4.15–4.11 (comp, 2H), 3.15 (app td, *J* = 9.2, 2.2 Hz, 2H), 2.30 (app t, *J* = 9.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.5, 137.1, 136.4, 133.8, 129.2, 128.8, 128.5, 127.6, 127.5, 113.3, 78.9, 53.5, 52.0, 44.1, 31.3; *m/z* (ESI–MS) 377.1 $[M+H]^+$.

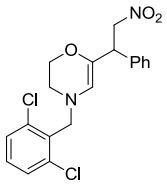


1-(2,6-Dichlorobenzyl)-5-(2-nitro-1-phenylethyl)-1,2,3,4-tetrahydropyridine (3.69): Following the general procedure F, compound **3.69** was obtained from **3.61** and β-nitrostyrene as a yellow oil in 57%yield (R_f = 0.78 in 20% EtOAc in hexanes); IR (KBr) 3026, 2945, 2920, 2636, 1656, 1552, 1435, 1378, 1275, 1203, 1173, 1121, 1062, 963, 764, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.34–7.27 (comp, 4H), 7.25–7.21 (m, 1H), 7.21–7.14 (comp,



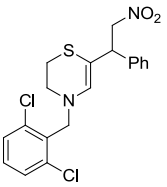
3H), 5.99 (s, 1H), 4.81–4.73 (m, 1H), 4.72–4.65 (m, 1H), 4.25–4.16 (comp, 2H), 4.04 (t, *J* = 8.1 Hz, 1H), 2.91–2.84 (comp, 2H), 1.92–1.80 (m, 1H), 1.81–1.68 (comp, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.3, 136.8, 133.6, 133.4, 129.2, 128.6, 128.5, 127.5, 127.1, 105.2, 78.2, 53.5, 49.1, 46.7, 22.5, 22.3; *m/z* (ESI–MS) 391.0 $[M+H]^+$.

4-(2,6-Dichlorobenzyl)-6-(2-nitro-1-phenylethyl)-3,4-dihydro-2H-1,4-oxazine (3.70): Following



the general procedure F, compound **3.70** was obtained from **3.62** and β-nitrostyrene as a reddish oil in 60% yield (R_f = 0.45 in 10% EtOAc in hexanes); IR (KBr)3066, 2027, 2928, 2871, 1949, 1678, 1552, 1436, 1378, 1215, 1126, 1088, 1062, 779, 701 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.32–7.29 (comp, 6H), 7.28–7.25 (m, 1H), 7.18–7.14 (m, 1H), 5.39 (s, 1H), 4.94–4.85 (m, 1H), 4.68–4.60 (m, 1H), 4.10–4.04 (comp, 3H), 4.04–3.97 (comp, 2H), 3.02–2.97 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.8, 136.8, 133.5, 133.1, 129.4, 128.7, 128.5, 127.7, 127.5, 115.2, 77.6, 64.4, 53.3, 47.1, 46.9; *m/z* (ESI–MS) 393.3 $[M+H]^+$.

4-(2,6-Dichlorobenzyl)-6-(2-nitro-1-phenylethyl)-3,4-dihydro-2H-1,4-thiazine (3.71): Following



the general procedure F, compound **3.71** was obtained from **3.63** and β-nitrostyrene as a red oil in 45% yield (R_f = 0.46 in 10% EtOAc in hexanes); IR (KBr) 2923, 2851, 2802, 1633, 1580, 1561, 1435, 1376, 1199, 1167, 1094, 948, 766 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.36–7.29 (comp, 4H), 7.29–7.23 (m, 3H), 7.21–7.15 (m, 1H), 6.26 (s, 1H), 5.01–4.93 (m, 1H), 4.78–4.70 (m, 1H), 4.35 (d, *J* = 13.9 Hz, 1H), 4.30 (d, *J* = 13.9 Hz, 1H), 4.22 (t, *J* = 8.2 Hz, 1H), 3.40–3.33 (m, 1H), 3.32–3.24 (m, 1H), 2.83–2.78 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.1, 136.7, 132.8, 130.5, 129.5, 128.6(8), 128.6(1), 127.5, 127.4, 97.0, 78.0, 53.8, 49.5, 47.2, 25.2; *m/z* (ESI–MS) 409.1 $[M+H]^+$.

1-(2,6-Dichlorobenzyl)-5-(1-(2,6-dichlorobenzyl)-3-(2-nitro-1-phenylethyl)piperidin-2-yl)-1,2,3,4-tetrahydropyridine (3.72): Following the general procedure E, compound **3.72** was obtained from **3.61** and β-nitrostyreneas a yellow oil in 10% yield (R_f = 0.27 in 20% EtOAc in hexanes); IR (KBr) 3093, 3031, 2936, 2858, 1671, 1553, 1436, 1374, 1260, 1193, 1117, 1087, 1028, 963, 778, 701 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.30–7.25 (comp, 4H), 7.25–7.15 (comp, 3H), 7.15–7.05 (comp, 4H), 5.55 (s, 1H), 4.94 (dd, *J* = 11.8, 9.0 Hz, 1H), 4.24 (d, *J* = 12.7 Hz, 1H), 4.07–4.02 (m, 1H), 4.00 (s, 2H), 3.83 (d, *J* = 12.7 Hz, 1H), 2.99–2.84 (comp, 2H), 2.80–2.69 (m, 1H), 2.57–2.48 (m, 1H), 2.48–2.41 (comp, 2H), 2.40–2.31(m, 1H), 2.90–1.95 (m, 1H), 1.73–1.63 (comp, 2H), 1.60–1.51 (m, 1H), 1.39–1.24 (comp, 3H), 1.14–1.04 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.9, 136.9, 135.9, 136.1, 135.6, 134.4, 129.0, 128.8, 128.6, 128.4, 128.3, 128.0, 127.6, 125.7, 92.7, 64.0, 52.2, 50.8, 48.7, 48.1, 47.8, 41.1, 30.1, 29.6, 26.3, 23.3; *m/z* (ESI–MS) 633.9 $[M+H]^+$.

1-Benzyl-5-(2-nitro-1-phenylethyl)-1,2,3,4-tetrahydropyridine (3.73): Following the general procedure F, compound **3.73** was obtained from the crude product of **3.64** and β-nitrostyrene as a yellow oil in 30% yield (R_f = 0.50 in 10% EtOAc in hexanes); IR (KBr) 3034, 2920, 2841, 1655, 1552, 1497, 1450, 1183, 1136, 1070, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.36–7.28 (comp, 4H), 7.28–7.21 (comp, 4H), 7.21–7.18 (comp, 2H), 6.01 (s, 1H), 4.85–4.75 (m, 1H), 4.75–4.64 (m, 1H), 4.07 (t, *J* = 8.1 Hz, 1H), 4.01–3.94 (comp, 2H), 2.81–2.72 (comp, 2H), 1.94–1.83 (m, 1H), 1.83–1.70 (comp, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.3, 138.3, 133.9, 128.6, 128.4, 128.0, 127.4, 127.1(7), 127.1(2), 106.3, 78.1, 59.5, 49.2, 46.4, 22.2(2), 22.1(7); *m/z* (ESI–MS) 323.8 $[M+H]^+$.

1-(2,6-Dichlorobenzyl)-6-(2-nitro-1-phenylethyl)-2,3,4,5-tetrahydro-1H-azepine (3.76): Following the general procedure F, compound **3.76** was obtained from the crude product of **3.75** and β-nitrostyrene as a yellow oil in 33% yield (R_f = 0.28 in 5%

EtOAc in hexanes); IR (KBr) 3086, 3057, 3029, 2924, 2855, 1652, 1557, 1436, 1378, 1272, 1217, 1086, 963, 874, 764, 699 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.34–7.25 (comp, 4H), 7.25–7.20 (m, 1H), 7.19–7.12 (comp, 3H), 6.06 (s, 1H), 4.76–4.66 (comp, 2H), 4.32 (d, *J* = 13.5 Hz, 1H), 4.28 (d, *J* = 13.5 Hz, 1H), 4.06 (t, *J* = 8.1 Hz, 1H), 3.06–2.94 (comp, 2H), 2.01–1.92 (m, 1H), 1.92–1.82 (m, 1H), 1.57–1.47 (comp, 2H), 1.47–1.35 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.5, 139.1, 136.6, 134.7, 128.9, 128.5(1), 128.4(9), 127.3, 127.0, 113.4, 78.4, 55.4, 52.9, 50.8, 30.0, 28.9, 26.0; *m/z* (ESI–MS) 405.1 $[M+H]^{+}$.

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Chapter IV Intramolecular Redox-Mannich Reactions: Facile Access to the Tetrahydroprotoberberine Core

4.1 Background

The Reinhoudt reaction is a classic example of a redox-neutral amine α-C–H bond functionalization process and is thought to occur via a 1,5-hydride shift/Mannich-type ring-closure sequence (e.g., **4.1** → **4.2**, Scheme 1).[1] First reported in 1984, this and related transformations have recently experienced a renewed and continuously growing interest.[2,3] This is in line with the general trend towards developing new transformations that minimize the generation of unwanted byproducts by virtue of being redox-neutral.[4] While the majority of methods for amine α-C–H bond functionalization typically utilize tertiary amines as starting materials,[5] our group has recently advanced a general concept for the redox-neutral C–H functionalization of secondary amines.[6] This complementary approach effectively combines a reductive *N*-alkylation with an oxidative α-functionalization and involves azomethine ylides[7] as reactive intermediates.[8] The concept has been further extended to redox-neutral β-C–H bond functionalization via the intermediacy of enamines.[9] Here we report a method that provides access to constitutional isomers of Reinhoudt reaction products, differing only in the position of a methylene bridge. Products **4.4**, obtained via intramolecular redox-Mannich reaction of **4.3** with 1,2,3,4-tetrahydroisoquinoline (THIQ) (Scheme 4.1), possess the core structure of the tetrahydroprotoberberine family of natural products (Figure 4.1).[10]

Scheme 4.1 **Reinhoudt vs. Redox-Mannich Reactions**

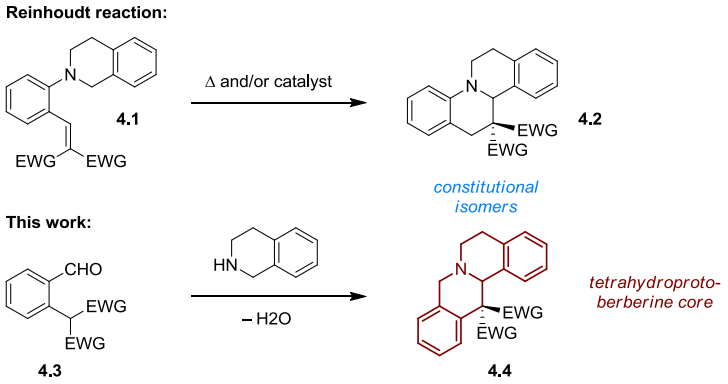
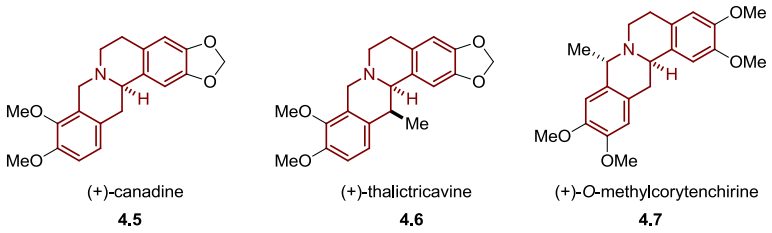


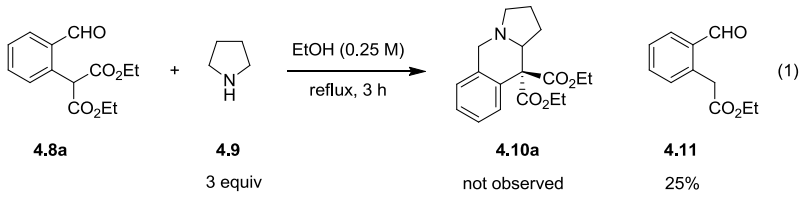
Figure 4.1 **Selected Examples of Tetrahydroprotoberberine Family Natural Products**



4.2 Evaluation of Reaction Conditions

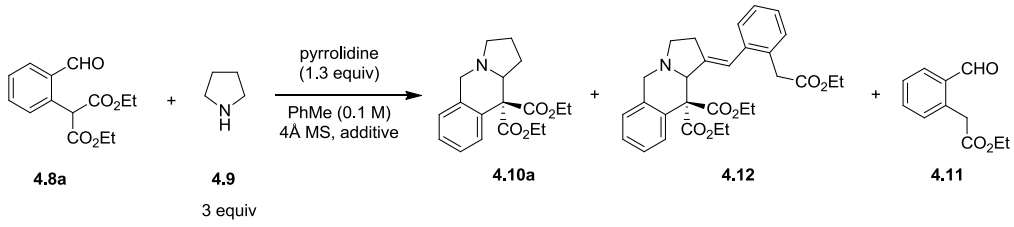
We initiated our investigation of the proposed intramolecular redox-Mannich reaction by employing malonate-aldehyde **4.8a**[11] and pyrrolidine as the model substrates (Scheme 4.2). Accordingly, **4.8a** was exposed to three equivalents of pyrrolidine in ethanol under reflux, conditions that were previously developed for the formation of aminals from *ortho*-aminobenzaldehydes and pyrrolidine.[6b] Following a reaction time of three hours during which **4.8a** was consumed fully, a complex mixture of unidentified polar materials was formed and none of the desired product **4.10a** was observed. Instead, the unexpected dealkoxycarbonylated product **4.11** was formed in 25% yield (*vide infra*).

Scheme 4.2 **Redox-Mannich Reaction Employing the Aminal Formation Conditions**



Conditions that were shown previously to be applicable to a wider range of amine redox-transformations were examined next, namely the use of toluene as the solvent and carboxylic acids as additives (Table 4.1).[6a] Exposure of **4.8a** and pyrrolidine (1.3 equiv) to reflux in toluene in the absence of any additives led to the consumption of **4.8a** within 12 hours (entry 1). As observed before, a complex mixture of unidentified polar materials was observed. Nevertheless, the desired product **4.10a** was obtained, albeit in only 5% yield. In addition, dealkoxycarbonylated product **4.11** was isolated in 8% yield. A dramatically different reaction outcome was observed in the presence of 20 mol% of acetic acid (entry 2). Complete consumption of malonate starting material occurred within four hours and redox-Mannich product **4.10a** was formed in 39% yield. Further reduction of the reaction time and increase in yield of **4.10a** to 53% was achieved with one equivalent of acetic acid (entry 3). In this instance, byproduct **4.12** was isolated in 18% yield, a compound formally resulting from the reaction of **4.10a** with **4.11** (*vide infra*). A further increase of the amount of acetic acid to 10 equivalents led to the isolation of **4.10a** in 68% yield, accompanied by the formation of **4.12** in 15% yield (entry 5). Replacement of acetic acid for 2-ethylhexanoic acid (2-EHA) resulted in the clean formation of **4.10a** in 76% yield and only trace amounts of **4.12** (entry 6). Similar results were obtained with five instead of ten equivalents of 2-EHA (entry 7). The use of other carboxylic acid promoters or the application of microwave conditions did not result in any further improvements (entries 8–11).

Table 4.1 **Evaluation of Reaction Conditions.**[a]



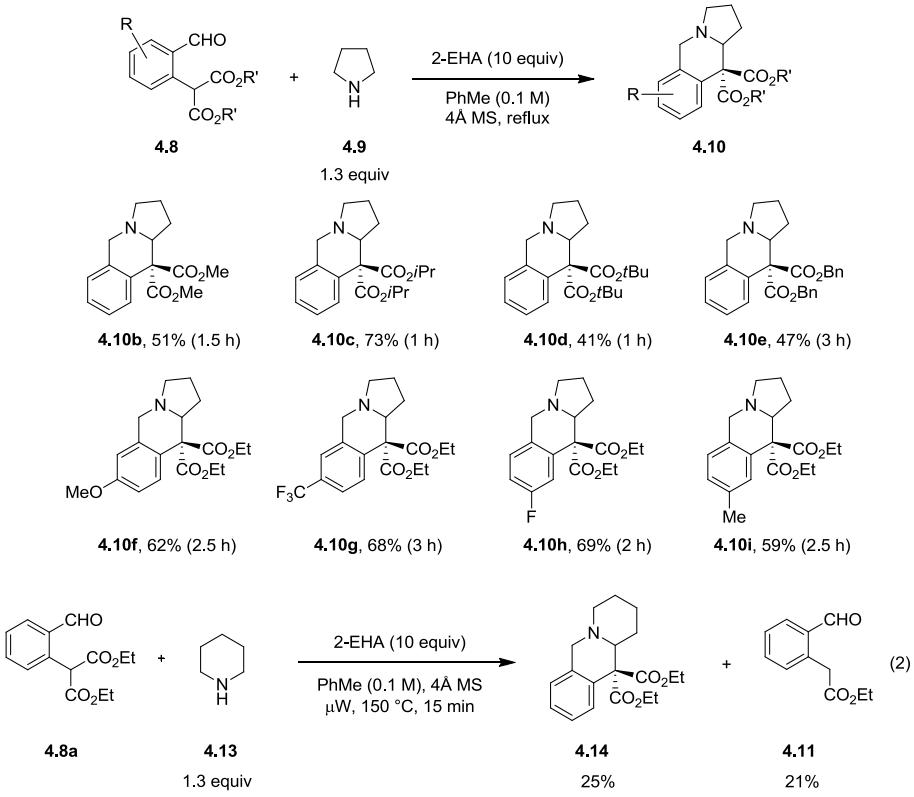
entry	additive (equiv)	Temp [°C]	time	yield **4.10a** (%)	yield **4.12** (%)	yield **4.11** (%)
1	-	reflux	12 h	5	-	8
2	AcOH (0.2)	reflux	4 h	39	-	-
3	AcOH (1)	reflux	1 h	53	18	-
4	AcOH (5)	reflux	1.5 h	54	8	-
5	AcOH (10)	reflux	3 h	68	15	-
6	2-EHA (10)	reflux	1.5 h	76	trace	-
7	2-EHA (5)	reflux	2 h	74	trace	-
8	$PhCO_2H$ (10)	reflux	3 h	52	10	12
9	pivalic acid (10)	reflux	1 h	71	15	-
10	2-EHA (10)	130 (μW)	45 min	57	trace	10
11	2-EHA (10)	150 (μW)	10 min	72	trace	trace

[a] All reactions were performed on a 0.25 mmol scale and were terminated upon the disappearance of **4.8a** as judged by TLC analysis.

4.3 Scope of the Intramolecular Redox-Mannich Reaction

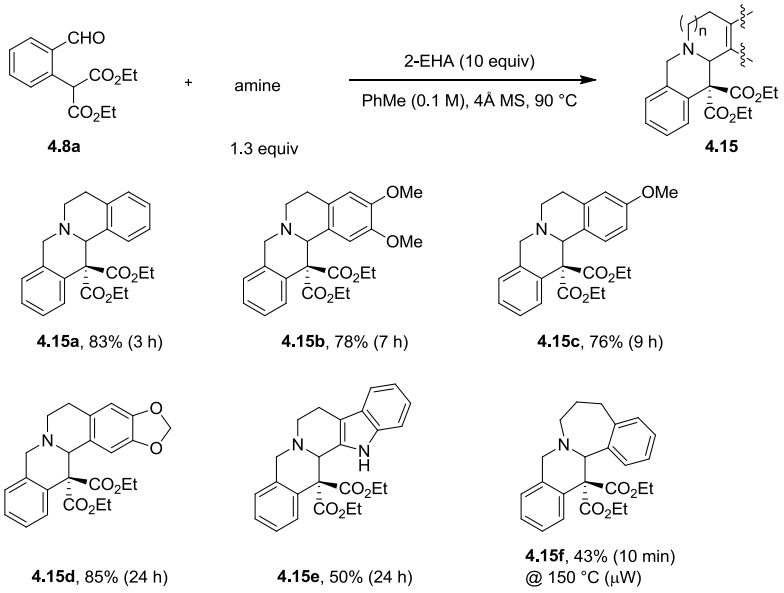
The optimized conditions were subsequently applied in reactions of various malonate-aldehydes with pyrrolidine (Scheme 4.3). Starting materials with different ester groups participated in this transformation. Ring-substitution with electron-donating or -withdrawing substituents was readily tolerated. Products **4.10** were isolated in typically moderate to good yields following relatively brief reaction times.Attempts to extend the substrate scope to piperidine met with limited success (Scheme 4.3, eq 2). In order for **4.8** to engage in a redox-Mannich reaction with piperidine, higher reaction temperatures were required and the best yield for product **4.14** was 25%. Under these conditions, a significant amount of competing dealkoxycarbonylation was noted. The low yield for **4.11** could be attributed to the instability of **4.11** under the relative harsh reaction conditions.[12]

Scheme 4.3 **Scope of the Intramolecular Redox-Mannich Reaction with Pyrrolidine**



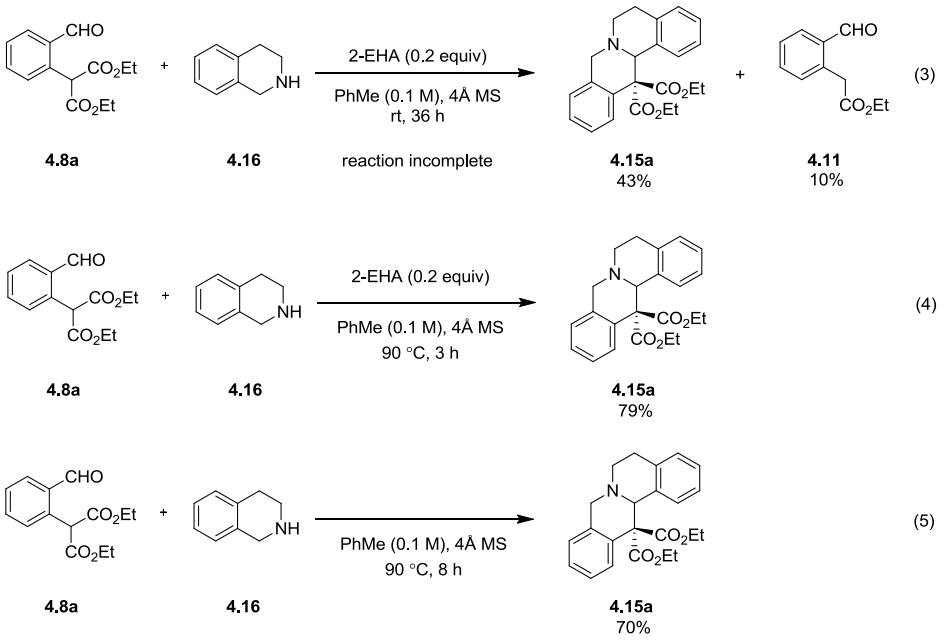
Redox-Mannich reactions were also conducted with THIQ and related amines, providing products that contain the tetrahydroprotoberberine core (Scheme 4.4). As expected, THIQ was found to undergo the reaction with **4.8a** more readily than pyrrolidine. The highest yield of 83% for product **4.15a** was obtained at 90 °C, using conditions otherwise identical to those utilized in pyrrolidine-based reactions. Substituted THIQ's and tryptoline also underwent the title reaction. Interestingly, the closely related benzazepane required higher temperatures in order to undergo the reaction with **4.8a**, yielding **4.15f** in 43% yield.

Scheme 4.4 **Intramolecular Redox-Mannich Reaction with THIQ and Related Amines**



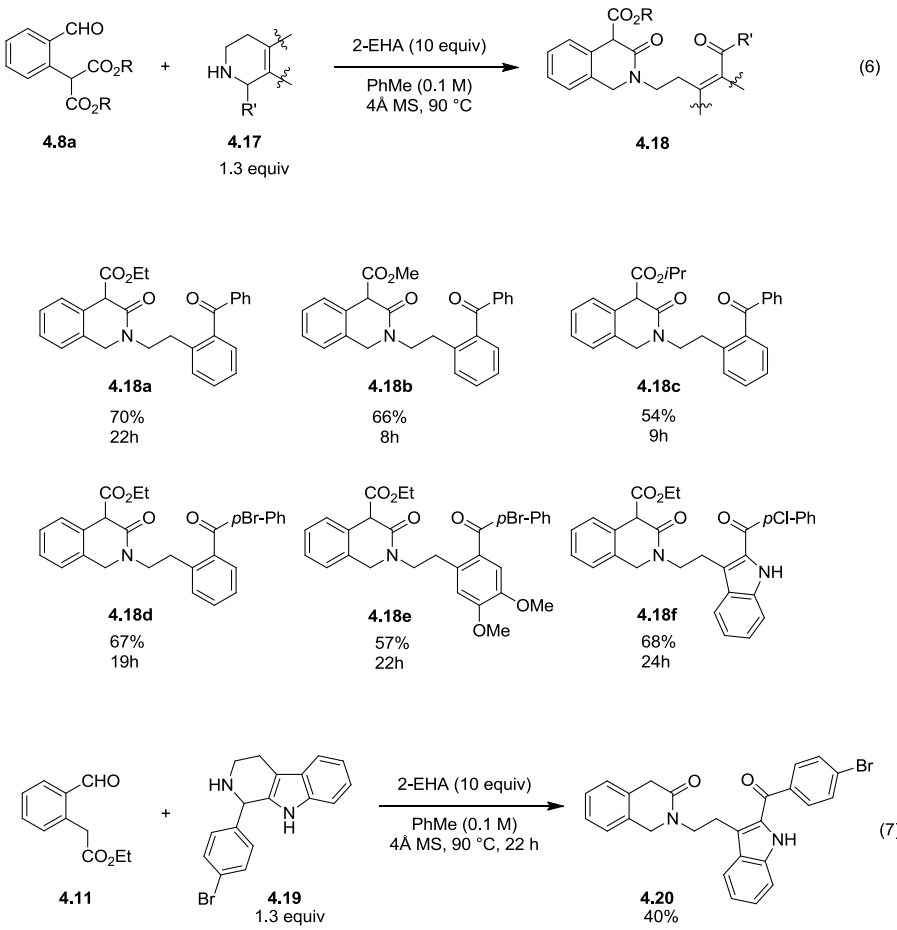
It should be noted that the reaction of **4.8a** with THIQ was very tolerant to deviation from the optimized conditions. In fact, the reaction proceeded even at room temperature, albeit slowly, using only 20 mol% of 2-EHA (Scheme 4.5, eq 3). At the same catalyst loading at 90 °C, product **4.15a** was isolated in 79% yield following a reaction time of three hours. Interestingly, an acid promoter was not strictly required for the reaction of THIQ with **4.8a**. Without acid at 90 °C under otherwise optimal conditions, product **4.15a** was isolated in 70% yield after eight hours (Scheme 4.5, eq 5).

Scheme 4.5 **Intramolecular Redox-Mannich Reaction with THIQ at Various Conditions**



An attempted redox-Mannich reaction with **4.8a** and 1-phenyl THIQ took an unexpected course (Scheme 4.6, eq 6). Exposure of these substrates to the standard conditions did not lead to the isolation of any redox-Mannich product. Instead, product **4.18a** was formed in 70% yield. The formation of this lactam presumably arises from the hydrolysis of an intermediate azomethine ylide or iminium ion by adventitious water, followed by aminolysis of one of the ester groups. It is likely that the steric bulk of the phenyl substituent on the THIQ core hinders the ring closure process and this will lead to the hydrolysis of the azomethine ylide or iminium ion. This reactivity appears to be general for amines of this type and extends to the use of monoester **4.11**. By employing the same reaction conditions, a tryptamine-derived starting material gave rise to the formation of the product **4.20** (Scheme 4.6, eq 7).

Scheme 4.6 **Unexpected Reaction for 1-Phenyl THIQ and Related Amines**

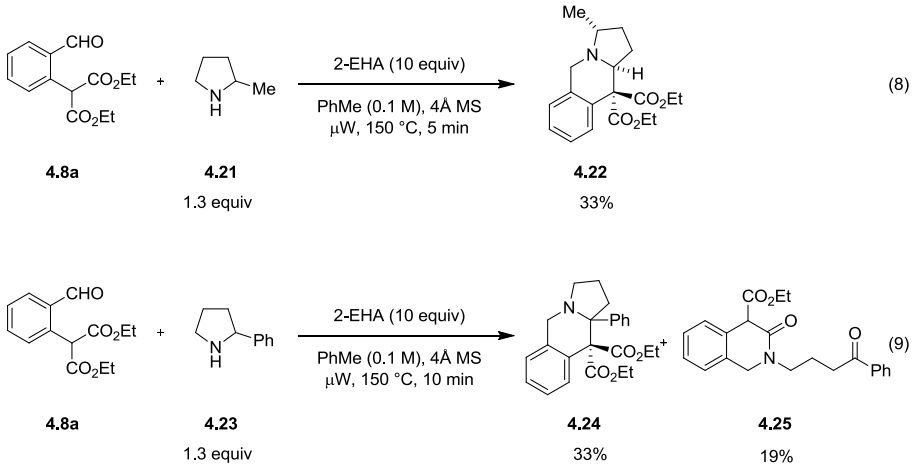


4.4 Regioselectivity of the Intramolecular Redox-Mannich Reaction

A reaction of **4.8a** with 2-methyl-pyrrolidine gave rise to predominantly one regioisomer **4.22** as a single diastereomer. On the contary, the reaction of **4.8a** with 2-phenyl-pyrrolidine showed the opposite regioselectivity. The product with a quartenary carbon center **4.2**4 was the regioisomer isolated. In addition to the regular redox-Mannich product, lactam product **4.25** analogous to **4.18** was also observed (Scheme 4.7). This result is in line with our analysis that the steric hinderance is a critical factor that affects the process of ring closure. Give the fact that the **4.23** is less bulky than 1-

phenyl THIQ but more bulky than THIQ, it is easy to understand that a comibination of both ring closure redox-neutral Mannich product **4.24** and the ring-opening product **4.25** is observed.

Scheme 4.7 **Regioselectivity of the Intramolecular Redox-Mannich Reaction**

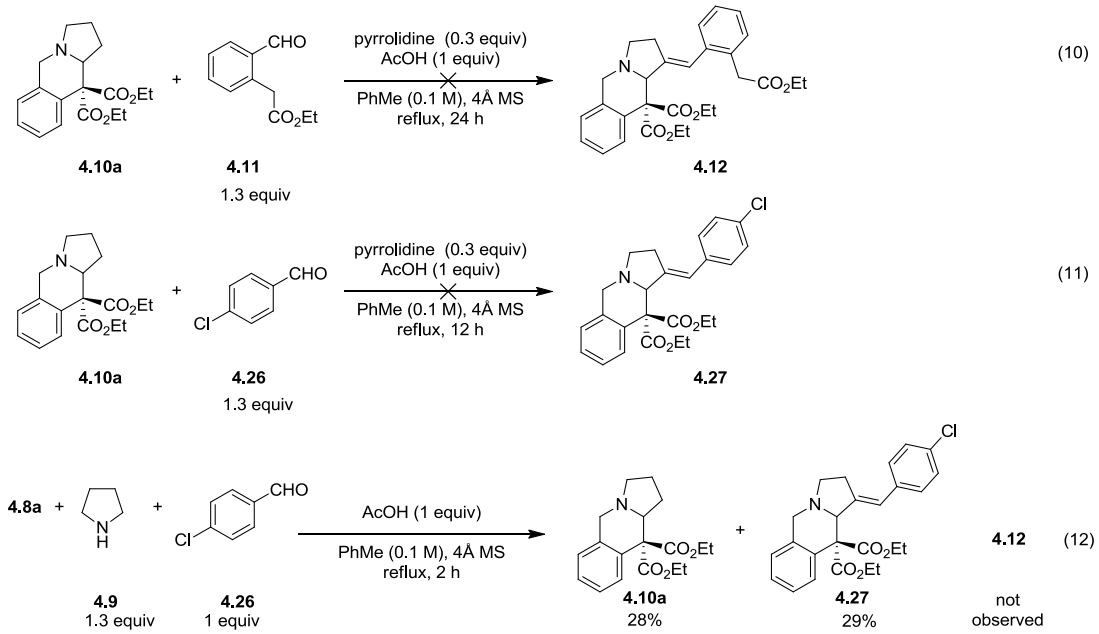


4.5 Study of the Byproduct Formation and Dealkoxycarbonylation

A number of experiments were performed to shed light on the underlying mechanisms for byproduct formation (Scheme 4.8). Regarding the formation of β-functionalized product **4.12**, two scenarios appeared plausible. This product could form either via the reaction of regular redox-Mannich product **4.10a** with dealkoxycarbonylated starting material **4.11**, or β-functionalization could take place in a prior step. To determine which of the two pathways is operative, a mixture of **4.10a** and **4.11** was exposed to reaction conditions known to facilitate the formation of **7** (c.f. Table 4.1, entry 3). However, no **4.12** was isolated in this instance. Similarly, a related experiment in which **4.11** was exchanged for the more electrophilic *p*-chlorobenzaldehyde failed to provide any detectable amounts of product **4.27**. In contrast, an experiment in which a 1:1 mixture of malonate-aldehyde **4.8a** and *p*-chlorobenzaldehyde were allowed to react with pyrrolidine resulted in the isolation of **4.27** in 29% yield, in addition to **4.10a** (28% yield). Compound **4.12** was not observed in this instance. Given

these findings, it appears that the competing β-functionalization step occurs prior to the Mannich ring-closure.

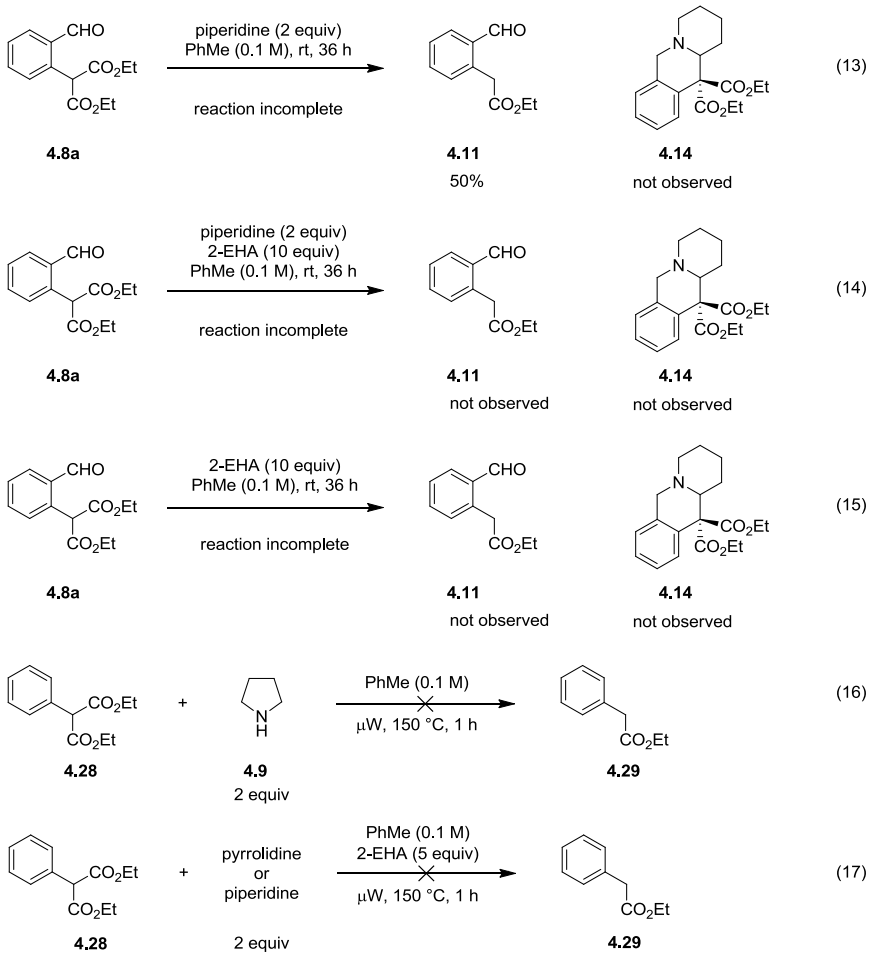
Scheme 4.8 **Pyrrolidine β-Functionalization**



The unusual dealkoxycarbonylation process was also investigated further (Scheme 4.9).[13] Remarkably, dealkoxycarbonylation of **4.8a** could be achieved under exceedingly mild conditions. For instance, exposure of **4.8a** to two equiv of piperidine led to the isolation of dealkoxycarbonylated product **4.11** in 50% yield following a reaction time of 36 hours at room temperature. The reaction remained incomplete and no trace of **4.14** was observed. Under otherwise identical conditions, addition of 2-EHA (10 equiv) or use of 2-EHA (10 equiv) by itself did not lead to any observable dealkoxycarbonylation (Scheme 4.9, eq 14 and 15). Tertiary amines appear to be ineffective promoters. For instance, *N*-methyl pyrrolidine failed to promote the dealkoxycarbonylation of **4.8a** under a variety of conditions. It should be noted that diethyl 2-phenylmalonate (**4.28**) failed to undergo dealkoxycarbonylation to give ethyl 2-phenylacetate (**4.29**) under a variety of conditions. In each case, even under more forcing conditions, **4.28** was recovered unchanged (Scheme 4.9, eq 16).

These findings indicate, perhaps not surprisingly, that the pendent aldehyde plays a crucial role in the dealkoxycarbonylation process.

*Scheme 4.*9 **Study of the Dealkoxycarbonylation**

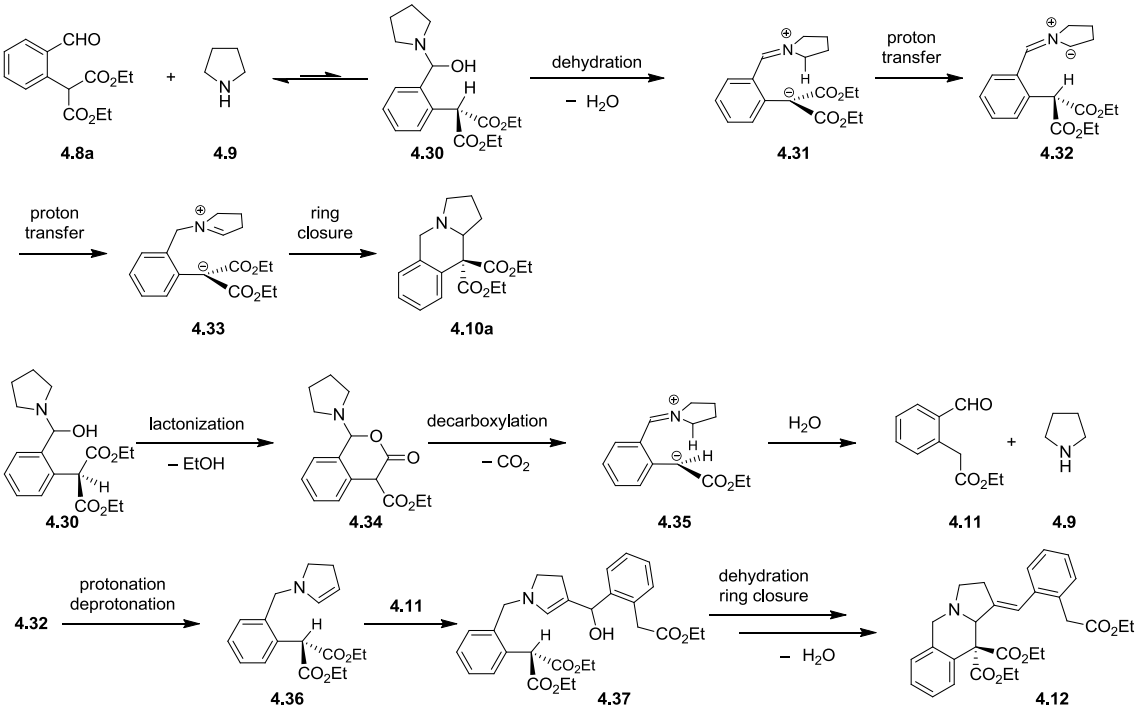


4.6 Mechanistic Considerations of the Intramolecular Redox-Mannich Reaction

A mechanistic rationale accounting for the formation of the main products is presented in Scheme 4.10. Malonatealdehyde **4.8a** and pyrrolidine most likely exist in equilibrium with hemiaminal **4.30**. The latter intermediate can suffer loss of water to form zwitterion **4.31** which can also be considered as an *ortho*-quinoidal species (resonance structure not shown). Subsequent 1,6-proton transfer results

in the formation of azomethine ylide **4.32**. This species can participate in a second proton transfer step to give zwitterion **4.33** followed by ring-closure to provide redox-Mannich product **4.10a**. In analogy to our previous study on the synthesis of benzoxazines,[6j] 2-EHA is likely involved in one if not both proton transfer steps and possibly in the elimination of water during the formation of **4.31**. Hemiaminal **4.30** is also likely involved in the competing dealkoxycarbonylation, a process that could be initiated by the formation of lactone **4.34** with concurrent elimination of ethanol. Lactone **4.34** could then fragment into CO_2 and zwitterion **19**. Subsequent hydrolysis of this species would lead to the dealkoxycarbonylation product **4.11** and pyrrolidine. Azomethine ylide **4.32**, instead of undergoing intramolecular proton transfer to form **4.33**, may also be protonated by external acid to form an endocyclic iminium ion or *N*,*O*-acetal (not shown) that could ultimately be transformed to enamine **4.36**. This intermediate could engage in an aldol-type reaction with **4.11** to give **4.37**. Loss of water and subsequent ring-closure provides a pathway to **4.12**.

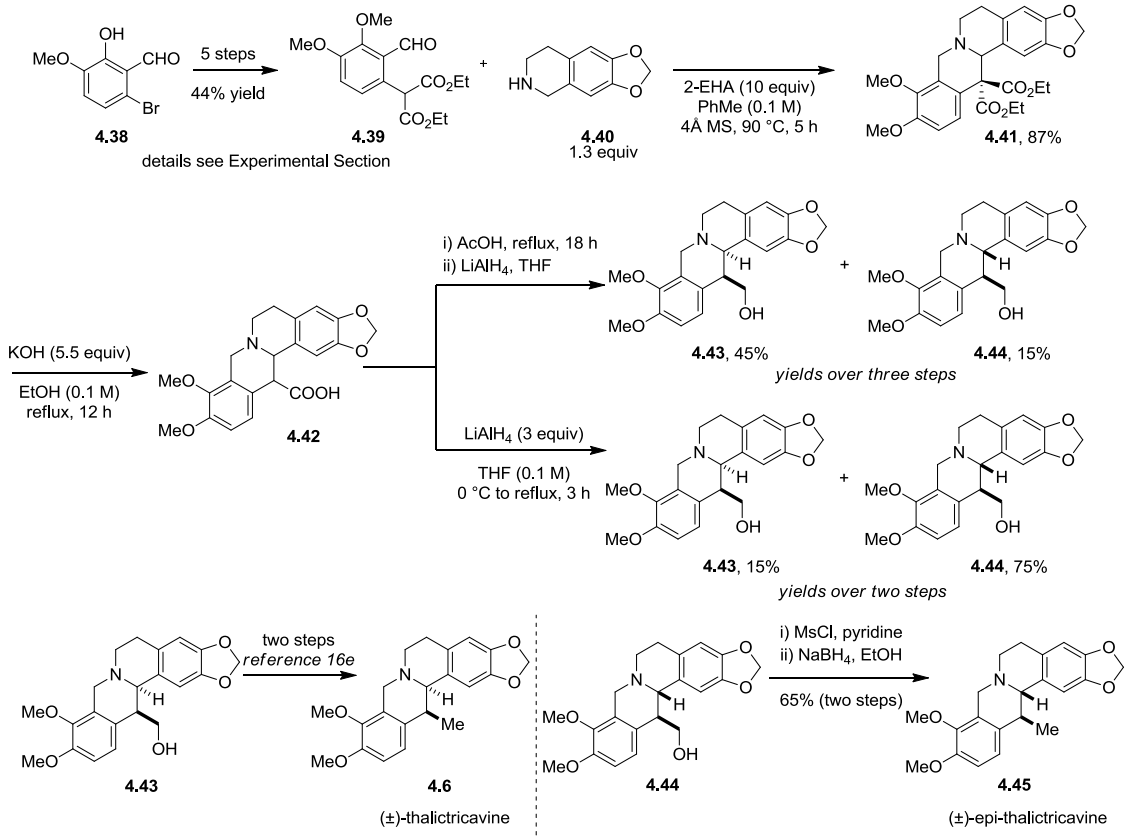
Scheme 4.10 **Mechanistic Considerations**



4.7 Synthetic Applications of the Intramolecular Redox-Mannich Reaction

The redox-Mannich reaction was applied to a formal total synthesis of (±)-thalictricavine[14] and the synthesis of (±)-epi-thalictricavine (Scheme 4.11).[15] Commercially available aldehyde **4.38** was converted into malonate-aldehyde **4.39** in five steps and 44% overall yield.[16] The redox-Mannich reaction of **4.39** with THIQ **4.40** proceeded smoothly to give annulation product **4.41** in 87% yield. Hydrolysis of **4.41** with subsequent decarboxylation provided amino acid **4.42** as a mixture of diastereomers that was processed further without purification. Reduction of **4.42** with lithium aluminum hydride in THF gave rise to the two diastereomeric alcohols **4.43** and **4.44** in 15% and 75% yield, respectively. Treatment of amino acid **4.42** with acetic acid under reflux (conditions known to effect epimerization to the thermodynamically more stable diastereomer)[15c] prior to reduction gave diastereomeric alcohols **4.43** and **4.44** in 45% and 15%, respectively. Alcohol **4.43** is a known precursor of (±)-thalictricavine to which it can be converted in two steps. Application of the known sequence[15e] to **4.44** enabled the synthesis of (±)-epi-thalictricavine in 65% yield over two steps.

Scheme 4.11 **Synthetic Applications**



4.8 Conclusion

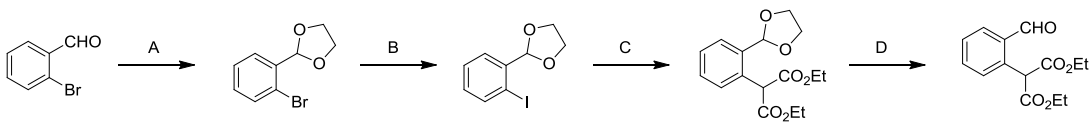
In summary, we have introduced a new type of intramolecular redox-Mannich reaction that is complementary to the classic Reinhoudt reaction in that it provides regioisomeric products differing only in the position of one methylene bridge. This transformation enables rapid access to products containing the tetrahydroprotoberberine core.

4.9 Experimental Section

General Information: Starting materials, reagents, and solvents were purchased from commercial sources and used as received unless stated otherwise. Pyrrolidine, piperidine, 1,2,3,4-

tetrahydroisoquinoline and 2-ethylhexanoic acid were distilled prior to use. Benzoic acid was recrystallized from toluene/ethanol. Aldehydes were purified either by distillation or by recrystallization prior to use. 4 Å powdered molecular sieves were purchased from Alfa Aesar and were activated before use by heating in a furnace to 300 ºC for 2 h and were stored in a desiccator. 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_{254} 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 (^{1}H-NMR) were recorded on a Varian VNMRS-500 MHz and 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 (^{13}C-NMR) spectra were recorded on a Varian VNMRS-500 MHz and 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. Compound **4.11** was previously reported and its published characterization data matched our own in all respects.[17]

Figure 4.2 **General Procedure for the Preparation of Malonate-aldehyde**



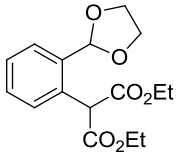
General procedure A: According to a reported procedure,[18] a mixture of 2-bromobenzaldehyde (3.7 g, 20 mmol), ethylene glycol (4.34 g, 70 mmol) and *p*-toluenesulfonic acid monohydrate (0.038 g, 0.2 mmol) in PhMe (20 mL) in a 100 mL round bottom flask was refluxed for 8 hours in presence of a Dean-Stark trap. After completion of the reaction as judged by TLC, the reaction mixture was allowed to cool to room temperature. The reaction mixture was washed with 40 mL of saturated $NaHCO_3$ solution. Subsequently, the aqueous layer was back-extracted with EtOAc (3 x 75 mL). The combined organic layers were washed with water (3 x 100 mL) and subsequently dried with Na_2SO_4. The solution was concentrated under reduced pressure and the resulting crude product was used directly in the next step.

General procedure B: According to a reported procedure,[19] to a solution of the crude 2-bromophenyl compound from the previous step (3.89 g, 17 mmol) in THF (94 mL) under nitrogen at –78 °C was added dropwise *n*-BuLi (6.8 mL, 2.5 M, 17 mmol) and the reaction mixture was stirred at –78 °C for 30 min. A solution of I_2 (4.74 g, 18.7 mmol) in THF (13 mL) was added slowly and the reaction mixture was allowed to warm gradually to room temperature. The mixture was diluted with ether (50 mL), washed with diluted aqueous $Na_2S_2O_3$ solution (50 mL), water (50 mL) and brine (50 mL), and dried over Na_2SO_4. The solution was concentrated under reduced pressure and the resulting residue purified via silica gel chromatography.

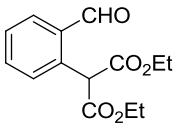
General procedure C: According to a reported procedure,[20] to an oven-dried round bottom flask was added CuI (0.305 g, 1.6 mmol), 2-picolinic acid (0.394 g, 3.2 mmol) and Cs_2CO_3 (7.82 g, 24 mmol). The flask was evacuated and backfilled with nitrogen (3 cycles). Anhydrous 1,4-dioxane (8 mL) was added, followed by distilled diethyl malonate (2.56 g, 16 mmol) and the aryl iodide from the previous step (2.209 g, 8 mmol). The resulting mixture was heated under reflux for 24 hours. After cooling to room temperature, the reaction mixture was diluted with EtOAc (20 mL) and washed with saturated NH_4Cl solution (3 x 20 mL), water (20 mL), brine (20 mL) and dried over Na_2SO_4. The solution was concentrated under reduced pressure and the resulting residue purified via silica gel chromatography.

General procedure D: According to a reported procedure,[21] to a round bottom flask was added protected malonate-aldehyde from the previous step (1.02 g, 3.3 mmol), *p*-toluenesulfonic acid monohydrate (0.063 g, 0.33 mmol), water (3.3 mL) and acetonitrile (33 mL). The reaction mixture was kept at 60 °C for 1.5 hours. After cooling to room temperature, the reaction mixture was washed with saturated $NaHCO_3$ solution (20 mL). Subsequently, the aqueous layer was back-extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with water (3 x 100 mL) and subsequently dried with Na_2SO_4. The solution was concentrated under reduced pressure and the resulting residue purified via silica gel chromatography.

Diethyl 2-(2-(1,3-dioxolan-2-yl)phenyl)malonate: Following general procedure C, the title compound was obtained as a clear oil in 66% yield (R_f = 0.27 in 20% EtOAc in hexanes); IR (KBr) 3073, 2985, 2893, 2770, 1754, 1732, 1630, 1455, 1371, 1302, 1262, 1146, 1033, 939, 862, 763, 645 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.52 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.46 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.39 (app td, *J* = 7.4, 1.5 Hz, 1H), 7.33 (app td, *J* = 7.6, 1.4 Hz, 1H), 5.90 (s, 1H), 5.25 (s, 1H), 4.22 (q, *J* = 7.1 Hz,4H), 4.15–4.07 (m, 2H), 4.06–3.99 (m, 2H), 1.26 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.5, 135.2, 132.0, 129.8, 129.3, 127.9, 127.4, 103.0, 65.0, 61.6, 53.7, 14.0; *m/z* (ESI–MS) 309.1 $[M+H]^+$.



Diethyl 2-(2-formylphenyl)malonate (4.8a): Following general procedure D, compound **4.8a** was obtained as a light green oil in 99% yield (R_f = 0.32 in 20% EtOAc in hexanes); IR (KBr) 3061, 2984, 2903, 2747, 2629, 1752, 1705, 1596, 1579, 1443, 1369, 1301, 1097, 1031, 855, 738, 694 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 10.00 (s, 1H), 7.78 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.55 (app td, *J* = 7.5, 1.6 Hz, 1H), 7.49 (app td, *J* = 7.5, 1.3 Hz, 1H), 7.46–7.42 (m, 1H), 5.78 (s, 1H), 4.25–4.13 (m, 4H), 1.22 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.0, 167.9, 135.0, 133.7, 133.6(0), 133.5(9), 130.1, 128.4, 61.6, 53.7(3), 53.7(2), 13.7(5), 13.7(4); *m/z* (ESI–MS) 287.2 $[M+Na]^+$, 265.1 $[M+H]^+$.



Dimethyl 2-(2-(1,3-dioxolan-2-yl)phenyl)malonate: Following general procedure C, the title compound was obtained as a white solid in 72% yield (R_f = 0.20 in 20% EtOAc in hexanes); mp: 73–74 ºC; IR (KBr) 3073, 2955, 2893, 2841, 2765, 2364, 2330, 1757, 1736, 1497, 1436, 1317, 1271, 1150, 1080, 971, 944, 761 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.52 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.46–7.43 (m, 1H), 7.40 (app td, *J* = 7.4, 1.5 Hz, 1H), 7.34 (app td, *J* = 7.6, 1.2 Hz, 1H), 5.88 (s, 1H), 5.32 (s, 1H), 4.14–4.07 (m, 2H), 4.06–3.99 (m, 2H), 3.74 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.9, 135.1, 131.7, 129.8, 129.5, 128.0, 127.6, 103.1, 65.0, 53.3, 52.8; *m/z* (ESI–MS) 303.2 $[M+Na]^+$.

Dimethyl 2-(2-formylphenyl)malonate (4.8b): Following general procedure D, compound **4.8b** was obtained as a white solid in 99% yield (R_f = 0.27 in 20% EtOAc in hexanes); mp: 41–42 ºC; IR (KBr) 3076, 3004, 2956, 2844, 2755, 1752, 1697, 1600, 1578, 1436, 1225, 1154, 1027, 838, 751, 664 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 9.98 (s, 1H), 7.77 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.55 (app td, *J* = 7.5, 1.5 Hz, 1H), 7.49 (app td, *J* = 7.5, 1.3 Hz, 1H), 7.41 (app d, *J* = 8.6 Hz, 1H), 5.84 (s, 1H), 3.69 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.1, 168.3, 135.1, 133.6, 133.5, 133.2, 130.1, 128.5, 53.2, 52.5; *m/z* (ESI–MS) 259.1 $[M+Na]^+$.

Diisopropyl 2-(2-(1,3-dioxolan-2-yl)phenyl)malonate: Following a literature procedure,[22] the title compound was obtained as a clear oil in 72% yield (R_f = 0.39 in 20% EtOAc in hexanes); IR (KBr) 2982, 2938, 2891, 2357, 1744, 1729, 1472, 1381, 1297, 1267, 1223, 1146, 968, 941, 758 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.51 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.46 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.37 (app td, *J* = 7.5, 1.5 Hz, 1H), 7.31 (app td, *J* = 7.5, 1.4 Hz, 1H), 5.90 (s, 1H), 5.16 (s, 1H), 5.13–5.03 (comp, 2H), 4.13–4.04 (m, 2H), 4.03–3.95 (m, 2H), 1.25 (d, *J* = 6.3 Hz, 6H), 1.22 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.9, 135.3, 132.2, 129.7, 129.1, 127.6, 127.1, 102.8, 69.0, 64.8, 53.9, 21.4(5), 21.3(9); *m/z* (ESI–MS) 359.2 $[M+Na]^+$.

Diisopropyl 2-(2-formylphenyl)malonate (4.8c): Following general procedure D, the title compound **4.8c** was obtained as a white solid in 90% yield (R_f = 0.46 in 20% EtOAc in hexanes); mp: 50–51 ºC; IR (KBr) 2983, 2937, 2878, 2740, 2359, 1729, 1703, 1601, 1578, 1495, 1470, 1376, 1299, 1224, 1166, 1101, 1000, 845, 751 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 10.00 (s, 1H), 7.76 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.53 (app td, *J* = 7.5, 1.6 Hz, 1H), 7.47 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.44–7.41 (m, 1H), 5.67 (s, 1H), 5.09–5.00 (comp, 2H), 1.21 (d, *J* = 6.3 Hz, 6H), 1.19 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.8, 167.4, 134.7, 133.9, 133.8, 133.4, 129.9, 128.2, 69.2, 54.2, 21.3; *m/z* (ESI–MS) 315.2 $[M+Na]^+$.

Di-tert-butyl 2-(2-(1,3-dioxolan-2-yl)phenyl)malonate: Following a literature procedure,[23] the title compound was obtained as a white solid in 46% yield (R_f = 0.46 in 20% EtOAc in hexanes); mp: 62–63 ºC; IR (KBr) 2972, 2891, 2357, 2337, 1752, 1732, 1648, 1369, 1136, 1070, 761 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.52 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.49 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.38 (app td, *J* = 7.5, 1.4 Hz, 1H), 7.31 (app td, *J* = 7.6, 1.4 Hz, 1H), 5.92 (s, 1H), 5.03 (s, 1H), 4.14–4.06 (m, 2H), 4.05–3.99 (m, 2H), 1.47 (s, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.7, 135.4, 132.8, 129.6, 129.1, 127.5, 127.0, 102.8, 81.7, 64.9, 55.6, 27.9; *m/z* (ESI–MS) 387.1 $[M+Na]^+$.

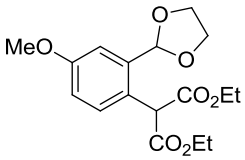
Di-tert-butyl 2-(2-formylphenyl)malonate (4.8d): Following general procedure D, compound **4.8d** was obtained as a clear oil in 87% yield (R_f = 0.53 in 20% EtOAc in hexanes); IR (KBr) 2979, 2934, 2740, 2364, 1728, 1698, 1601, 1578, 1456, 1369, 1301, 1251, 1139, 956, 859, 757 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 10.09 (s, 1H), 7.85–7.82 (m, 1H), 7.60 (app td, *J* = 7.6, 1.5 Hz, 1H), 7.55–7.49 (comp, 2H), 5.57 (s, 1H), 1.48 (s, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.0, 167.4, 134.9, 134.5, 134.1, 133.7, 130.1, 128.2, 82.3, 56.1, 27.9; *m/z* (ESI–MS) 343.1 $[M+Na]^+$.

Dibenzyl 2-(2-(1,3-dioxolan-2-yl)phenyl)malonate: Following general procedure C, the title compound was obtained as a clear oil in 28% yield (R_f = 0.21 in 20% EtOAc in hexanes); IR (KBr) 3066, 3034, 2960, 2888, 1734, 1647, 1498, 1456, 1376, 1078, 971, 761, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.58–7.55 (m, 1H), 7.50–7.47 (m, 1H), 7.42–7.36 (comp, 3H), 7.36–7.30 (comp, 9H), 5.91 (s, 1H), 5.46 (s, 1H), 5.26 (d, *J* = 12.4 Hz, 2H), 5.21 (d, *J* = 12.4 Hz, 2H), 4.05–3.98 (m, 2H), 3.98–3.90 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.1, 135.3, 135.2, 131.5, 129.8, 129.2, 128.3, 128.1, 128.0, 127.9, 127.4, 102.9, 67.1, 64.8, 53.5.; *m/z* (ESI–MS) 455.1 $[M+Na]^+$.

Dibenzyl 2-(2-formylphenyl)malonate (4.8e): Following general procedure D, compound **4.8e** was obtained as a white solid in 93% yield (R_f = 0.31 in 20% EtOAc in hexanes); mp: 85–86 ºC; IR (KBr) 3066, 2977, 2757, 1974, 1752, 1688, 1577, 1499, 1455, 1378, 1325, 1213, 1142, 1079, 973, 836, 758, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 10.05 (s, 1H), 7.82 (dd, *J* = 5.7, 3.4 Hz, 1H), 7.60–7.52 (comp, 2H), 7.41 (dd, *J* = 5.7, 3.4 Hz, 1H), 7.39–7.27 (comp, 10H), 5.98 (s, 1H),5.22 (d, *J* = 12.6 Hz, 2H), 5.19 (d, *J* = 12.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.2, 167.9, 135.4, 135.2, 133.8, 133.4, 130.4, 128.7, 128.5, 128.3, 128.2, 127.0, 67.5, 53.8.; *m/z*(ESI–MS) 411.0 $[M+Na]^+$.

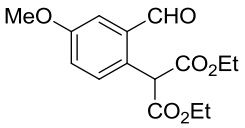
2-(2-iodo-5-methoxyphenyl)-1,3-dioxolane: Following general procedure A, the title compound was obtained as a yellow oil in 99% yield (R_f = 0.49 in 20% EtOAc in hexanes); IR(KBr) 3071, 2958, 2888, 2750, 2055, 1996, 1878, 1590, 1570, 1474, 1393, 1301, 1085, 880, 811, 588 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.68 (d, *J* = 8.7 Hz, 1H), 7.14 (d, *J* = 3.1 Hz, 1H), 6.64 (dd, *J* = 8.6, 3.3 Hz, 1H), 5.85 (s, 1H), 4.15–4.05 (m, 2H), 4.06–3.99 (m, 2H), 3.76 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.6, 139.9, 139.8, 116.8, 113.1, 105.7, 85.1, 65.1, 55.1; *m/z* (ESI–MS) 307.0 $[M+H]^+$.

Diethyl 2-(2-(1,3-dioxolan-2-yl)-4-methoxyphenyl)malonate: Following general procedure C, the



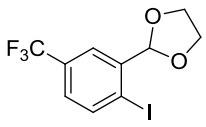
title compound was obtained as a white solid in 62% yield (R_f = 0.23 in 20% EtOAc in hexanes); mp: 107–108 ºC; IR (KBr) 2987, 2900, 2836, 1752, 1732, 1611, 1502, 1460, 1371, 1293, 1173, 1146, 1076, 1036, 963 860 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.40 (d, *J* = 8.6 Hz, 1H), 7.09 (d, *J* = 2.8 Hz, 1H), 6.92 (dd, *J* = 8.7, 2.9 Hz, 1H), 5.90 (s, 1H), 5.14 (s, 1H), 4.22 (q, *J* = 7.2 Hz, 4H), 4.13–4.06 (m, 2H), 4.06–3.99 (m, 2H), 3.81 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.8, 159.1, 136.9, 131.1, 123.8, 114.6, 112.6, 102.5, 65.0, 61.6, 55.3, 53.0, 14.0; *m/z* (ESI–MS) $[M+H]^+$.

Diethyl 2-(2-formyl-4-methoxyphenyl)malonate (4.8f): Following general procedure D, compound



4.8f was obtained as a light yellow solid in 88% yield (R_f = 0.30 in 20% EtOAc in hexanes); mp: 35–36 ºC; IR (KBr) 2982, 2903, 2841, 2747, 2354, 2335, 1749, 1732, 1698, 1606, 1569, 1502, 1304, 1269, 1221, 1152, 1033, 776 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 10.00 (s, 1H), 7.37 (d, *J* = 8.6 Hz, 1H), 7.31 (d, *J* = 2.9 Hz, 1H), 7.08 (dd, *J* = 8.5, 2.9 Hz, 1H), 5.65 (s, 1H), 4.25–4.14 (m, 4H), 3.82 (s, 3H), 1.23 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.4, 168.2, 159.5, 134.8, 131.6, 125.7, 119.2, 119.1, 61.7, 55.4, 53.0, 13.8; *m/z* (ESI–MS) 317.1 $[M+Na]^+$.

2-(2-iodo-5-(trifluoromethyl)phenyl)-1,3-dioxolane: Following general procedure B, the title



compound was obtained as a white solid in 73% yield (R_f = 0.63 in 20% EtOAc in hexanes); mp: 38–39 ºC; IR (KBr) 2987, 2883, 2359, 1606, 1569, 1388, 1329, 1258, 1170, 1128, 1081, 1016, 894, 827 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.96 (d, *J* = 8.2 Hz, 1H), 7.80 (d, *J* = 2.2 Hz, 1H), 7.30 (dd, *J* = 8.2, 2.2 Hz, 1H), 5.91 (s, 1H), 4.20–4.12 (m, 2H), 4.12–4.03 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.6, 140.2, 130.7 (q, $J_{C,F}$ = 33.1 Hz), 127.1 (q, $J_{C,F}$ = 3.1 Hz), 124.3 (q, $J_{C,F}$ = 3.9 Hz), 123.7 (q, $J_{C,F}$ = 272.5 Hz), 105.4, 101.2 (q, $J_{C,F}$ = 1.6 Hz), 65.5; *m/z* (ESI–MS) 344.9 $[M+H]^+$.

Diethyl 2-(2-(1,3-dioxolan-2-yl)-4-(trifluoromethyl)phenyl)malonate: Following general procedure C, the title compound was obtained as a white solid in 73% yield (R_f = 0.35 in 20% EtOAc in hexanes); mp: 43–44 ºC; IR (KBr) 2985, 2900, 2760, 2357, 1757, 1736, 1623, 1470, 1443, 1391, 1166, 1031, 945, 901, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.83 (s, 1H), 7.67–7.61 (comp, 2H), 5.97 (s, 1H), 5.27 (s, 1H), 4.27–4.18 (comp, 4H), 4.13–4.02 (m, 4H), 1.26 (t, J = 7.1 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8, 136.8, 135.7 (q, $J_{C,F}$ = 1.3 Hz), 130.5, 130.1 (q, $J_{C,F}$ = 32.7 Hz), 125.9 (q, $J_{C,F}$ = 3.8 Hz), 123.9 (q, $J_{C,F}$ = 3.8 Hz), 123.8 (q, $J_{C,F}$ = 272.3 Hz), 101.7, 65.2, 62.0, 53.5, 13.9; *m/z* (ESI–MS) 399.2 $[M+Na]^+$.

Diethyl 2-(2-formyl-4-(trifluoromethyl)phenyl)malonate (4.8g): Following general procedure D, compound **3g** was obtained as a white solid in 85% yield (R_f = 0.45 in 20% EtOAc in hexanes); mp: 109–111 ºC; IR (KBr) 2988, 2905, 2651, 1735, 1712, 1628, 1406, 1377, 1274, 1255, 1150, 1125, 1097, 1037, 677 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 10.12 (s, 1H), 8.10 (d, J = 2.0 Hz, 1H), 7.85 (dd, J = 8.0, 1.8 Hz, 2H), 7.67 (d, J = 8.1 Hz, 1H), 5.81 (s, 1H), 4.31–4.19 (m, 4H), 1.27 (t, J = 7.2 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.5, 167.4, 137.5 (q, $J_{C,F}$ = 1.1 Hz), 134.3, 131.4, 131.1 (q, $J_{C,F}$ = 33.7 Hz), 131.0 (q, $J_{C,F}$ = 74.8 Hz), 130.1 (q, $J_{C,F}$ = 3.6 Hz), 123.2 (q, $J_{C,F}$ = 272.5 Hz), 62.2, 53.7, 13.9; *m/z* (ESI–MS) 349.2 $[M+Na]^+$.

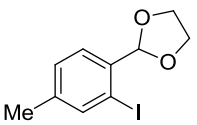
2-(4-Fluoro-2-iodophenyl)-1,3-dioxolane: Following general procedure B, the title compound was obtained as a yellow oil in 36% yield (R_f = 0.45 in 20% EtOAc in hexanes); IR (KBr) 3071, 2972, 2888, 1586, 1481, 1401, 1378, 1232, 1123, 1093, 1028, 943, 864, 655 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.57 (dd, J = 9.0, 2.3 Hz, 1H), 7.52 (dd, J = 8.6, 6.1 Hz, 1H), 7.02 (app td, J = 8.4, 2.4 Hz, 1H), 5.86 (s, 1H), 4.18–4.09 (m, 2H), 4.09–4.01 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.3(d, $J_{C,F}$ = 253.2 Hz), 135.3 (d, $J_{C,F}$ = 3.3 Hz), 128.7 (d, $J_{C,F}$ = 8.5 Hz), 126.4 (d, $J_{C,F}$ = 24.0 Hz), 115.2 (d, $J_{C,F}$ = 20.0 Hz), 105.6, 96.4 (d, $J_{C,F}$ = 8.3 Hz), 65.4; *m/z* (ESI–MS) 317.2 $[M+Na]^+$.

Diethyl 2-(2-(1,3-dioxolan-2-yl)-5-fluorophenyl)malonate: Following general procedure C, the title compound was obtained as a clear oil in 64% yield (R_f = 0.30 in 20% EtOAc in hexanes); IR (KBr) 2980, 2938, 2898, 1754, 1727, 1616, 1591, 1507, 1369, 1238, 1139, 1030 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.50 (dd, J = 8.6, 5.9 Hz, 1H), 7.22 (dd, J = 9.9, 2.6 Hz, 1H), 7.02 (app td, J = 8.5, 2.8 Hz, 1H), 5.86 (s, 1H), 5.24 (s, 1H), 4.23 (q, J = 7.1 Hz, 4H), 4.13–4.07 (m, 2H), 4.06–3.98 (m, 2H), 1.27 (t, J = 7.1 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.2, 163.1 (d, $J_{C,F}$ = 247.9 Hz), 134.6 (d, $J_{C,F}$ = 8.4 Hz), 131.6 (d, $J_{C,F}$ = 3.3 Hz), 129.5 (d, $J_{C,F}$ = 8.7 Hz), 117.4 (d, $J_{C,F}$ = 23.4 Hz), 115.0 (d, $J_{C,F}$ = 21.3 Hz), 102.7, 65.3, 62.2, 53.7 (d, $J_{C,F}$ = 1.5 Hz), 14.2; *m/z* (ESI–MS) 327.3 $[M+H]^+$.

Diethyl 2-(5-fluoro-2-formylphenyl)malonate (4.8h): Following general procedure D, compound **4.8h** was obtained as a white solid in 97% yield (R_f = 0.38 in 20% EtOAc in hexanes); mp: 34–35 ºC; IR (KBr) 3088, 2985, 2940, 2910, 2357, 1735, 1700, 1609, 1587, 1369, 1302, 1239, 1158, 1096, 1032, 887, 825 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 9.96 (s, 1H), 7.81 (dd, J = 8.5, 5.8 Hz, 1H), 7.23–7.15 (comp, 2H), 5.83 (s, 1H), 4.26–4.13 (m, 4H), 1.23 (t, J = 7.1 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.4, 167.4, 166.3, 164.2, 137.6 (d, $J_{C,F}$ = 10.1 Hz), 130.4 (d, $J_{C,F}$ = 3.0 Hz), 117.9 (d, $J_{C,F}$ = 24.0 Hz), 115.4 (d, $J_{C,F}$ = 21.8 Hz), 61.9, 53.3 (d, $J_{C,F}$ = 1.4 Hz), 13.8; *m/z* (ESI–MS) 305.2 $[M+Na]^+$.

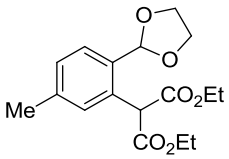
2-(2-Bromo-4-methylphenyl)-1,3-dioxolane: Following general procedure A, the title compound was obtained as a yellow oil in 99% yield (R_f = 0.57 in 20% EtOAc in hexanes); IR (KBr) 2953, 2886, 2750, 2681, 1609, 1566, 1495, 1450, 1382, 1270, 1219, 1142, 1093, 1039, 973, 944, 828, 674 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.47 (d, J = 7.9 Hz, 1H), 7.39 (s, 1H), 7.14 (d, J = 7.9 Hz, 1H), 6.07 (s, 1H), 4.18–4.10 (m, 2H), 4.10–4.02 (m, 2H), 2.33 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.9, 133.6, 133.4, 128.2, 127.6, 122.7, 102.7, 65.4, 20.8; *m/z* (ESI–MS) $[M+H]^+$.

2-(2-Iodo-4-methylphenyl)-1,3-dioxolane: Following general procedure B, the title compound was



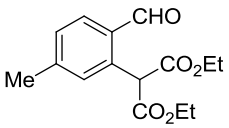
obtained as a yellow oil in 93% yield (R_f = 0.57 in 20% EtOAc in hexanes); IR(KBr) 3064, 2952, 2885, 1603, 1554, 1480, 1448, 1209, 1141, 1089, 1033, 944, 824, 659 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.69 (s, 1H), 7.42 (d, *J* = 7.9 Hz, 1H), 7.20–7.14 (m, 1H), 5.89 (s, 1H), 4.20–4.10 (m, 2H), 4.10–4.00 (m, 2H), 2.30 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.1, 140.0, 136.3, 129.0, 127.3, 106.4, 97.0, 65.4, 20.6; *m/z* (ESI–MS) 291.0 $[M+H]^+$.

Diethyl 2-(2-(1,3-dioxolan-2-yl)-5-methylphenyl)malonate: Following general procedure C, the



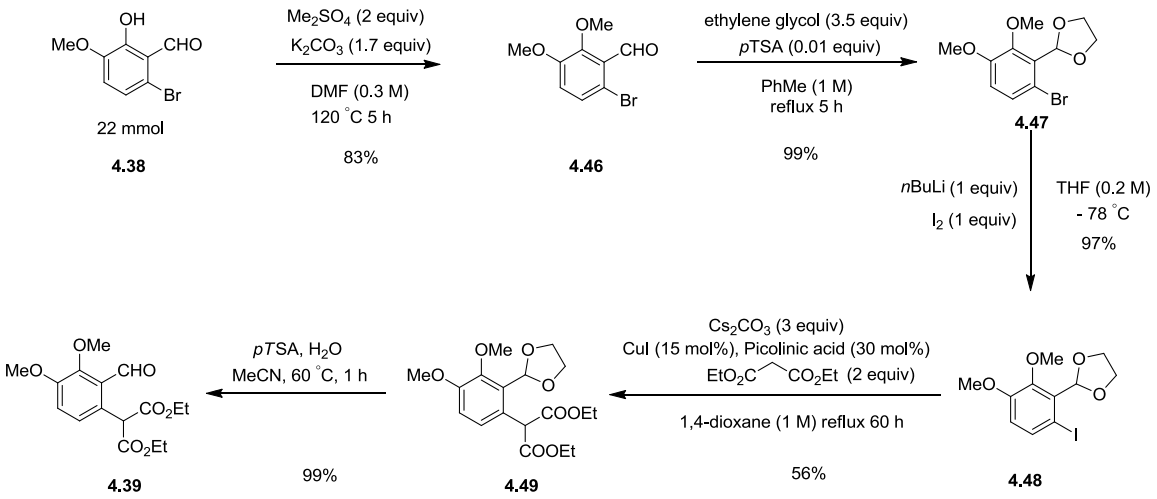
title compound was obtained as a clear oil in 51% yield (R_f = 0.40 in 20% EtOAc in hexanes); IR (KBr) 2983, 2898, 1752, 1732, 1621, 1465, 1448, 1305, 1240, 1147, 1071, 1035, 976, 944, 813 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.39 (d, *J* = 7.9 Hz, 1H), 7.25 (s, 1 H), 7.13 (d, *J* = 7.8 Hz, 1H), 5.86 (s, 1H), 5.23 (s, 1H), 4.23 (q, *J* = 7.1 Hz, 4H), 4.14–4.06 (m, 2H), 4.04–3.96 (m, 2H), 2.35 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6, 139.2, 132.3, 131.7, 130.4, 128.5, 127.5, 103.2, 64.9, 61.6, 53.5, 21.2, 14.0; *m/z* (ESI–MS) 345.2 $[M+Na]^+$.

Diethyl 2-(2-formyl-5-methylphenyl)malonate (4.8i): Following general procedure D, compound



4.8i was obtained as a white solid in 67% yield (R_f = 0.35 in 20% EtOAc in hexanes); mp: 32–33 ºC; IR (KBr) 2980, 2942, 2745, 2362, 2332, 1752, 1733, 1694, 1571, 1301, 1240, 1202, 1150, 1035, 823 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 10.00 (s, 1H), 7.71 (d, *J* = 7.7 Hz, 1H), 7.34 (d, *J* = 7.7 Hz, 1H), 7.27 (s, 1H), 5.82 (s, 1H), 4.30–4.17 (m, 4H), 2.43 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.7, 168.3, 145.0, 135.5, 133.7, 131.6, 131.1, 129.2, 61.8, 53.7, 21.9, 14.0; *m/z* (ESI–MS) 301.1 $[M+Na]^+$.

Scheme 4.12 **Five-Step Synthesis of 4.39 from 4.38**

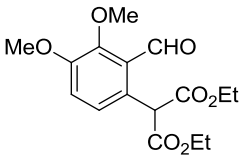


2-(6-Iodo-2,3-dimethoxyphenyl)-1,3-dioxolane (4.48): Starting from known 2-(6-bromo-2,3-dimethoxyphenyl)-1,3-dioxolane[23] and following general procedure B, the title compound was obtained as a white solid in 97% yield (R_f = 0.53 in 25% EtOAc in hexanes); mp: 59–60 ºC; IR(KBr) 3086, 2970, 2940, 2893, 2836, 1640, 1571, 1474, 1381, 1263, 1235, 1004, 800cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.59 (d, *J* = 8.7 Hz, 1H), 6.64 (d, *J* = 8.7 Hz, 1H), 6.21 (s, 1H), 4.34–4.26 (m, 2H), 4.09–4.01 (m, 2H), 3.84 (s, 3H), 3.83 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.7, 149.8, 136.2, 131.0, 115.1, 103.6, 84.0, 65.8, 61.7, 55.9; *m/z* (ESI–MS) 359.3 $[M+Na]^+$.

Diethyl 2-(2-(1,3-dioxolan-2-yl)-3,4-dimethoxyphenyl)malonate (4.49): Following general procedure C, the title compound was obtained as a white solid in 56% yield (R_f = 0.21 in 20% EtOAc in hexanes); mp: 111–112 ºC; IR (KBr) 2984, 2942, 2900, 2834, 1749, 1732, 1645, 1584, 1496, 1458, 1388, 1309, 1266, 1145, 1060, 1046, 961, 790 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.09 (d, *J* = 8.6 Hz, 1H), 6.94 (d, *J* = 8.6 Hz, 1H), 6.17 (s, 1H), 5.33 (s, 1H), 4.25–4.21 (m, 2H), 4.21–4.18 (m, 4H), 4.03–3.95 (m, 2H), 3.86 (s, 3H), 3.81 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.2, 152.0,

148.9, 127.4, 125.9, 125.8, 113.1, 99.0, 64.7, 61.9, 61.4, 55.7, 53.2, 14.1; *m/z* (ESI–MS) 391.1 $[M+Na]^+$.

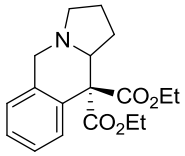
Diethyl 2-(2-formyl-3,4-dimethoxyphenyl)malonate (4.39): Following general procedure D, compound **4.39** was obtained as a light yellow solid in 99% yield (R_f = 0.32 in 25% EtOAc in hexanes); mp: 56–58 ºC; IR (KBr) 2984, 2938, 2903, 2844, 2760, 1752, 1733, 1686, 1580, 1483, 1392, 1151, 1031, 978, 931, 857, 776, 674 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 10.50 (s, 1H), 7.15–7.07 (comp, 2H), 5.66 (s, 1H), 4.29–4.19 (m, 4H), 3.96 (s, 3H), 3.90 (s, 3H), 1.27 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.4, 168.7, 153.9, 152.6, 127.6, 125.5, 125.3, 117.2, 62.3, 61.6, 55.9, 53.5, 14.0; *m/z* (ESI–MS) 347.0 $[M+Na]^+$.



General procedure for the intramolecular redox-Mannich reaction:

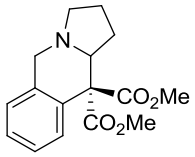
In a 10 mL round bottom flask containing a stir bar, malonate-aldehyde (0.25 mmol) was dissolved in toluene (2.5 mL). Subsequently, 4 Å molecular sieves (50 mg), 2-EHA (0.4 mL, 2.5 mmol) and cyclic amine (1.3 mmol) were added. A reflux condenser with a nitrogen inlet was placed on top of the flask which was then heated in an oil bath to the appropriate temperature until the malonate-aldehyde was consumed as judged by TLC analysis. After allowing the flask to cool to room temperature, the mixture was diluted with EtOAc (20 mL) and washed with saturated $NaHCO_3$ solution (3 x 20 mL), water (20 mL), brine (20 mL) and dried over Na_2SO_4. The resulting solution was concentrated under reduced pressure and the residue purified via silica gel chromatography.

Diethyl 1,2,3,10a-tetrahydropyrrolo[1,2-b]isoquinoline-10,10(5H)-dicarboxylate (4.10a): Following the general procedure, compound **4.10a** was obtained from pyrrolidine and diethyl 2-(2-formylphenyl)malonate as a light yellow solid in 76% yield (R_f = 0.37 in 25% EtOAc in hexanes); mp: 57–59 ºC; IR (KBr) 3071, 2962, 2937, 2874, 2783, 2719, 1732, 1662, 1490, 1463, 1368, 1251, 1094, 1045, 862, 753 cm^{-1}; ^1H NMR (500 MHz,



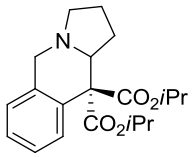
$CDCl_3$) 7.40 (app d, *J* = 7.6 Hz, 1H), 7.25–7.21 (m, 1H), 7.21–7.16 (m, 1H), 7.09 (app d, *J* = 7.6 Hz, 1H), 4.35–4.23 (comp, 2H), 4.21 (d, *J* = 14.8 Hz, 1H), 4.23–4.11 (comp, 2H), 3.52 (d, *J* = 14.8 Hz, 1H), 3.26 (app t, *J* = 7.7 Hz, 1H), 3.04 (dd, *J* = 9.2, 6.9 Hz, 1H), 2.50–2.40 (m, 1H), 2.30–2.21 (m, 1H), 2.05–1.94 (m, 1H), 1.94–1.86 (m, 1H), 1.86–1.76 (m, 1H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.22 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2, 169.2, 135.8, 133.3, 129.1, 127.5, 126.7, 126.0, 66.1, 62.6, 61.5, 61.2, 56.6, 55.2, 26.3, 23.0, 14.1, 14.0; *m/z* (ESI–MS) 318.2 $[M+H]^+$.

Dimethyl 1,2,3,10a-tetrahydropyrrolo[1,2-b]isoquinoline-10,10(5H)-dicarboxylate (4.10b):



Following the general procedure, compound **4.10b** was obtained from pyrrolidine and dimethyl 2-(2-(1,3-dioxolan-2-yl)phenyl)malonate as a white solid in 51% yield (R_f = 0.31 in 25% EtOAc in hexanes); mp: 151–152 ºC; IR (KBr) 2975, 2829, 2788, 2732, 2360, 1741, 1725, 1454, 1434, 1254, 1041, 958, 765 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.39–7.32 (m, 1H), 7.29–7.22 (m, 1H), 7.22–7.16 (m, 1H), 7.13–7.07 (m, 1H), 4.21 (d, *J* = 15.0 Hz, 1H), 3.80 (s, 3H), 3.69 (s, 3H), 3.52 (d, *J* = 15.0 Hz, 1H), 3.26 (app t, *J* = 7.8 Hz, 1H), 3.12–3.02 (m, 1H), 2.45–2.33 (m, 1H), 2.32–2.22 (m, 1H), 2.04–1.94 (m, 1H), 1.94–1.85 (m, 1H), 1.85–1.75 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 169.8, 135.7, 133.0, 129.0, 127.6, 126.8, 126.1, 66.1, 62.7, 56.5, 55.2, 52.6, 52.5, 26.3, 22.9; *m/z* (ESI–MS) 290.1 $[M+H]^+$.

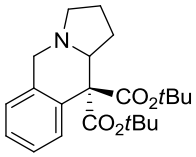
Diisopropyl 1,2,3,10a-tetrahydropyrrolo[1,2-b]isoquinoline-10,10(5H)-dicarboxylate (4.10c):



Following the general procedure, compound **5c** was obtained from pyrrolidine and diisopropyl 2-(2-formylphenyl)malonate as a brownish solid in 73% yield (R_f = 0.40 in 25% EtOAc in hexanes); mp: 53–54 ºC; IR (KBr) 3024, 2978, 2796, 1957, 1917, 1740, 1717, 1452, 1374, 1258, 1104, 1039, 984, 911, 750 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.46–7.40 (m, 1H), 7.25–7.15 (comp, 2H), 7.11–7.04 (m, 1H), 5.21–5.12 (m, 1H), 5.10–5.01 (m, 1H), 4.20 (d, *J* = 14.8 Hz, 1H), 3.50 (d, *J* = 14.8 Hz, 1H), 3.26 (app t, *J* = 7.5 Hz, 1H), 3.00 (dd, *J* = 9.0, 6.9 Hz, 1H), 2.53–2.40 (m, 1H), 2.30–2.19 (m, 1H), 2.04–1.95 (m, 1H), 1.95–1.86 (m, 1H), 1.86–1.76 (m, 1H), 1.31 (d, *J* = 6.3 Hz, 3H), 1.28–1.24 (comp, 6H), 1.17 (d, *J* = 6.3 Hz, 3H);

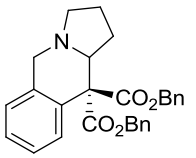
^{13}C NMR (125 MHz, $CDCl_3$) δ 169.7, 168.5, 135.8, 133.4, 129.3, 127.3, 126.6, 125.8, 69.2, 68.6, 66.1, 62.3, 56.6, 55.3, 26.4, 23.0, 21.6(8), 21.6(5), 21.5(5), 21.4(5); *m/z* (ESI–MS) 346.1 $[M+H]^+$.

Di-tert-butyl 1,2,3,10a-tetrahydropyrrolo[1,2-b]isoquinoline-10,10(5H)-dicarboxylate (4.10d):



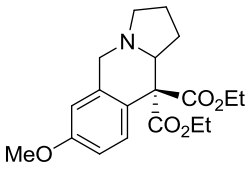
Following the general procedure, compound **4.10d** was obtained from pyrrolidine and di-*tert*-butyl 2-(2-formylphenyl)malonate as a light yellow solid in 41% yield (R_f = 0.48 in 25% EtOAc in hexanes); mp: 84–87 ºC; IR (KBr) 3067, 2971, 2934, 2784, 2729, 2291, 1793, 1736, 1716, 1475, 1367, 1266, 1159, 1089, 844, 750 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.55–7.48 (m, 1H), 7.24–7.15 (comp, 2H), 7.10–7.03 (m, 1H), 4.19 (d, *J* = 14.7 Hz, 1H), 3.46 (d, *J* = 14.8 Hz, 1H), 3.30–3.23 (m, 1H), 2.94–2.87 (m, 1H), 2.52–2.39 (m, 1H), 2.27–2.18 (m, 1H), 2.04–1.96 (m, 1H), 1.96–1.85 (m, 1H), 1.85–1.76 (m, 1H), 1.52 (s, 9H), 1.44 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.4, 168.0, 136.0, 133.6, 129.2, 127.2, 126.7, 125.8, 82.0, 81.3, 66.2, 63.3, 56.7, 55.3, 27.9(8), 27.9(7), 26.8, 23.1; *m/z* (ESI–MS) 374.0 $[M+H]^+$.

Dibenzyl 1,2,3,10a-tetrahydropyrrolo[1,2-b]isoquinoline-10,10(5H)-dicarboxylate (4.10e):



Following the general procedure, compound **4.10e** was obtained from pyrrolidine and dibenzyl 2-(2-formylphenyl)malonate as a yellow solid in 47% yield (R_f = 0.24 in 20% EtOAc in hexanes); mp: 48–50 ºC; IR (KBr) 3035, 2960, 2739, 1745, 1705, 1498, 1454, 1337, 1261, 1140, 1039, 909, 731, 694 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.39–7.21 (comp, 10H), 7.21–7.16 (comp, 2H), 7.16–7.08 (comp, 2H), 5.27 (d, *J* = 12.3 Hz, 1H), 5.19 (d, *J* = 12.3 Hz, 1H), 5.14 (s, 2H), 4.22 (d, *J* = 14.8 Hz, 1H), 3.54 (d, *J* = 14.8 Hz, 1H), 3.22 (app t, *J* = 7.7 Hz, 1H), 3.10 (dd, *J* = 9.4, 6.9 Hz, 1H), 2.45–2.34 (m, 1H), 2.31–2.19 (m, 1H), 1.97–1.81 (m, 1H), 1.84–1.67 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.9, 168.9, 135.8, 135.7, 135.2, 133.0, 129.1, 128.5, 128.3, 128.2(4), 128.2(2), 127.8, 127.7, 127.6, 126.8, 126.0, 67.3, 66.9, 66.1, 62.9, 56.4, 55.1, 26.2, 22.9.; *m/z* (ESI–MS) 442.2 $[M+H]^+$.

Diethyl 7-methoxy-1,2,3,10a-tetrahydropyrrolo[1,2-b]isoquinoline-10,10(5H)-dicarboxylate



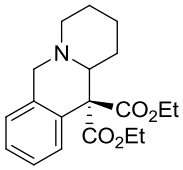
(4.10f): Following the general procedure, compound **4.10f** was obtained from pyrrolidine and diethyl 2-(2-formyl-4-methoxyphenyl)malonate as a brownish solid in 62% yield (R_f = 0.19 in 25% EtOAc in hexanes); mp: 79–80 ºC; IR (KBr) 3093, 2974, 2834, 2729, 1873, 1736, 1719, 1618, 1573, 1428, 1251, 1161, 1026, 901, 855, 791, 684, 603 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.33 (d, *J* = 8.8 Hz, 1H), 6.76 (dd, *J* = 8.8, 2.7 Hz, 1H), 6.62–6.57 (m, 1H), 4.33–4.22 (m, 2H), 4.16 (d, *J* = 14.8 Hz, 1H), 4.22–4.09 (m, 2H), 3.78 (s, 3H), 3.48 (d, *J* = 14.8 Hz, 1H), 3.25 (app t, *J* = 7.7 Hz, 1H), 3.00 (dd, *J* = 9.1, 7.2 Hz, 1H), 2.46–2.36 (m, 1H), 2.29–2.20 (m, 1H), 2.03–1.93 (m, 1H), 1.93–1.85 (m, 1H), 1.85–1.76 (m, 1H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.22 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 169.3, 158.7, 137.1, 130.3, 125.4, 112.3, 111.2, 66.2, 61.8, 61.5, 61.1, 56.6, 55.2, 55.1, 26.3, 22.9, 14.1, 14.0; *m/z* (ESI–MS) 348.1 $[M+H]^+$.

Diethyl 7-(trifluoromethyl)-1,2,3,10a-tetrahydropyrrolo[1,2-b]isoquinoline-10,10(5H)-dicarboxylate (4.10g): Following the general procedure, compound **4.10g** was obtained from pyrrolidine and diethyl 2-(2-formyl-4-(trifluoromethyl)phenyl)malonate as a light yellow solid in 68% yield (R_f = 0.52 in 25% EtOAc in hexanes); mp: 80–81 ºC; IR (KBr) 3444, 2980, 2790, 1927, 1724, 1467, 1428, 1116, 1043, 934, 886, 850, 727, 684, 630, 563 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.55–7.49 (m, 1H), 7.47–7.41 (m, 1H), 7.38–7.32 (m, 1H), 4.36–4.25 (comp, 2H), 4.24 (d, *J* = 15.3 Hz, 1H), 4.25–4.11 (comp, 2H), 3.56 (d, *J* = 15.3 Hz, 1H), 3.27 (app t, *J* = 7.7 Hz, 1H), 3.04 (dd, *J* = 9.3, 6.8 Hz, 1H), 2.51–2.41 (m, 1H), 2.34–2.24 (m, 1H), 2.06–1.95 (m, 1H), 1.95–1.87 (m, 1H), 1.87–1.79 (m, 1H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.22 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.6, 168.5, 137.3 (q, $J_{C,F}$ = 1.5 Hz), 137.0, 129.8, 129.7 (q, $J_{C,F}$ = 32.5 Hz), 124.0 (q, $J_{C,F}$ = 272.2 Hz), 123.7 (q, $J_{C,F}$ = 3.8 Hz), 122.7 (q, $J_{C,F}$ = 3.8 Hz), 65.8, 62.6, 61.9, 61.5, 56.3, 55.1, 26.3, 23.1, 14.1, 13.9; *m/z* (ESI–MS) 386.1 $[M+H]^+$.

Diethyl 8-fluoro-1,2,3,10a-tetrahydropyrrolo[1,2-b]isoquinoline-10,10(5H)-dicarboxylate (4.10h): Following the general procedure, compound **4.10h** was obtained from pyrrolidine and diethyl 2-(5-fluoro-2-formylphenyl)malonate as a light yellow solid in 69% yield (R_f = 0.36 in 25% EtOAc in hexanes); mp: 85–86 ºC; IR (KBr) 3440, 3051, 2871, 2866, 2782, 1878, 1743, 1615, 1498, 1448, 1374, 1265, 1186, 1168, 1140, 1045, 860, 810, 768, 724, 665, 551, 521 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.14 (dd, *J* = 10.3, 2.6 Hz, 1H), 7.08–7.00 (m, 1H), 6.94 (app td, *J* = 8.2, 2.7 Hz, 1H), 4.36–4.24 (comp, 2H), 4.24–4.12 (comp, 3H), 3.46 (d, *J* = 14.5 Hz, 1H), 3.25 (app t, *J* = 7.8 Hz, 1H), 3.01 (dd, *J* = 9.4, 7.1 Hz, 1H), 2.47–2.37 (m, 1H), 2.30–2.21 (m, 1H), 2.05–1.94 (m, 1H), 1.94–1.85 (m, 1H), 1.85–1.76 (m, 1H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.22 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.7, 168.7, 160.9 (d, $J_{C,F}$ = 243.8 Hz), 135.0 (d, $J_{C,F}$ = 7.7 Hz), 131.6 (d, $J_{C,F}$ = 3.1 Hz), 128.0 (d, $J_{C,F}$ = 8.2 Hz), 115.8 (d, $J_{C,F}$ = 22.9 Hz), 114.8 (d, $J_{C,F}$ = 21.7 Hz), 65.8, 62.5 (d, $J_{C,F}$ = 1.4 Hz), 61.8, 61.4, 56.0, 55.1, 26.3, 23.0, 14.1, 14.0; *m/z* (ESI–MS) 336.1 $[M+H]^+$.

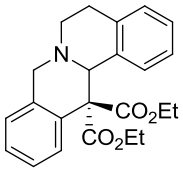
Diethyl 7-(trifluoromethyl)-1,2,3,10a-tetrahydropyrrolo[1,2-b]isoquinoline-10,10(5H)-dicarboxylate (4.10i): Following the general procedure, compound **4.10i** was obtained from pyrrolidine and diethyl 2-(2-formyl-5-methylphenyl)malonate as a brownish solid in 59% yield (R_f = 0.31 in 25% EtOAc in hexanes); mp: 77–78 ºC; IR (KBr) 3414, 2986, 2778, 2732, 1741, 1714, 1618, 1505, 1448, 1378, 1366, 1255, 1199, 894, 857, 810, 689 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.21–7.16 (m, 1H), 7.07–7.02 (m, 1H), 7.00–6.06 (m, 1H), 4.37–4.23 (comp, 2H), 4.18 (d, *J* = 14.8 Hz, 1H), 4.23–4.13 (comp, 2H), 3.47 (d, *J* = 14.6 Hz, 1H), 3.24 (app t, *J* = 7.9 Hz, 1H), 3.04 (dd, *J* = 9.3, 7.0 Hz, 1H), 2.49–2.38 (m, 1H), 2.30 (s, 3H), 2.29–2.20 (m, 1H), 2.05–1.93 (m, 1H), 1.93–1.84 (m, 1H), 1.84–1.76 (m, 1H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.23 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3, 169.3, 135.4, 133.1, 132.7, 129.3, 128.4, 126.5, 66.1, 62.6, 61.5, 61.1, 56.3, 55.2, 26.3, 23.0, 21.2, 14.1, 14.0; *m/z* (ESI–MS) 332.1 $[M+H]^+$.

Diethyl 3,4,6,11a-tetrahydro-1H-pyrido[1,2-b]isoquinoline-11,11(2H)-dicarboxylate (4.14):



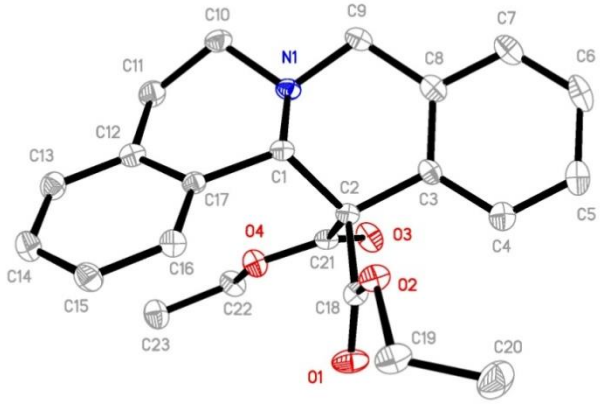
Following the general procedure but performing the reaction in a microwave reactor at 150 °C for 15 min, compound **4.14** was obtained from piperidine and diethyl 2-(2-formylphenyl)malonate as a brownish oil in 25% yield (R_f = 0.24 in 25% EtOAc in hexanes); IR (KBr) 3074, 2980, 2937, 2858, 1732, 1634, 1446, 1367, 1278, 1240, 1113, 1037, 747 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.33 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.21 (app td, *J* = 7.4, 1.5 Hz, 1H), 7.16 (app td, *J* = 7.6, 1.6 Hz, 1H), 7.05 (dd, *J* = 7.6, 1.6 Hz, 1H), 4.30–4.15 (comp, 4H), 3.99 (d, *J* = 15.5 Hz, 1H), 3.44 (d, *J* = 15.5 Hz, 1H), 3.22–3.11 (comp, 2H), 2.30 (app td, *J* = 12.1, 3.2 Hz, 1H), 1.88–1.74 (comp, 3H), 1.70–1.58 (comp, 2H), 1.42–1.34 (m, 1H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.21 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 169.6, 134.7, 131.7, 129.4, 127.4, 126.1, 125.9, 63.3, 63.0, 61.7, 61.3, 57.1, 56.7, 26.5, 24.6, 24.0, 13.9(9), 13.9(5); *m/z* (ESI–MS) 332.2 $[M+H]^+$.

Diethyl 8,13a-dihydro-5H-isoquinolino[3,2-a]isoquinoline-13,13(6H)-dicarboxylate (4.15a):

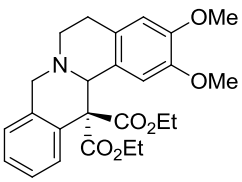


Following the general procedure, compound **9a** was obtained from THIQ and diethyl 2-(2-formylphenyl)malonate as a light yellow solid in 83% yield (R_f = 0.45 in 25% EtOAc in hexanes); mp: 146–147 ºC; IR (KBr) 3432, 3033, 2975, 2902, 2802, 2090, 1912, 1733, 1471, 1367, 1277, 1220, 1116, 989, 942, 862, 768, 693, 617 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.29–7.19 (comp, 4H), 7.19–7.07 (comp, 4H), 4.85 (s, 1H), 4.42–4.26 (comp, 2H), 4.05 (d, *J* = 15.3 Hz, 1H), 4.01 (d, *J* = 15.3 Hz, 1H), 3.91–3.76 (comp, 2H), 3.14–3.07 (m, 1H), 3.06–2.97 (m, 1H), 2.75–2.65 (comp, 2H), 1.29 (t, *J* = 7.2 Hz, 3H), 0.86 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 169.2, 137.0, 135.3, 134.5, 133.8, 129.9, 128.3, 127.4, 126.3, 126.2, 126.1(8), 126.1(7), 125.5, 65.9, 65.2, 61.7, 61.0, 58.5, 49.6, 30.0, 13.9, 13.3; *m/z* (ESI–MS) 380.1 $[M+H]^+$.

Figure 4.3 **X–ray Crystal Structure of Product 4.15a**

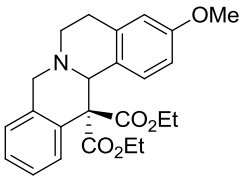


The requisite CIF has been deposited with the CCDC (deposition # 1060415).



Diethyl 2,3-dimethoxy-8,13a-dihydro-5H-isoquinolino[3,2-a]isoquinoline-13,13(6H)-dicarboxylate (4.15b): Following the general procedure, compound **4.15b** was obtained from 6,7-dimethoxy-1,2,3,4- tetrahydroisoquinoline and diethyl 2-(2-formylphenyl)malonate as a yellow oil in 78% yield (R_f = 0.44 in 40% EtOAc in hexanes); IR (KBr) 3066, 2981, 2937, 2903, 2834, 2745, 1732, 1655, 1604, 1518, 1464, 1366, 1236, 1146, 1022, 865, 767, 735 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.28–7.22 (m, 1H), 7.22–7.18 (comp, 2H), 7.14–7.08 (m, 1H), 6.84 (s, 1H), 6.59 (s, 1H), 4.82 (s, 1H), 4.40–4.25 (comp, 2H), 4.02 (s, 2H), 3.94–3.83 (comp, 2H), 3.86 (s, 3H), 3.80 (s, 3H), 3.13–3.04 (m, 1H), 2.98–2.87 (m, 1H), 2.71–2.60 (comp, 2H), 1.28 (t, *J* = 7.1 Hz, 3H), 0.90 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4, 169.3, 147.4, 146.7, 134.3, 133.8, 129.7, 129.3, 127.4, 127.0, 126.3, 126.2, 111.0, 110.2, 65.6, 64.8, 61.7, 61.0, 58.4, 55.8(0), 55.7(6), 49.5, 29.5, 13.9, 13.4; *m/z* (ESI–MS) 440.2 $[M+H]^+$.

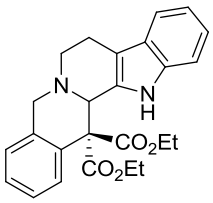
Diethyl 2-methoxy-8,13a-dihydro-5H-isoquinolino[3,2-a]isoquinoline-13,13(6H)-dicarboxylate



(4.15c): Following the general procedure, compound **4.15c** was obtained from 6-methoxy-1,2,3,4-tetrahydroisoquinoline[24] and diethyl 2-(2-formylphenyl)malonate as a yellow solid in 76% yield (R_f = 0.31 in 25% EtOAc in hexanes); mp: 97–99 ºC; IR (KBr) 3409, 2987, 2903, 2813, 2766, 1929, 1732, 1714, 1608, 1469, 1370, 1297, 1170, 1143, 1036, 914, 847, 650 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.28–7.24 (m, 1H), 7.24–7.19 (comp, 2H), 7.15 (d, *J* = 8.7 Hz, 1H), 7.11 (d, *J* = 7.7 Hz, 1H), 6.71–6.67 (m, 1H), 6.66–6.63 (m, 1H), 4.80 (s, 1H), 4.41–4.25 (comp, 2H), 4.04 (d, *J* = 15.2 Hz, 1H), 4.00 (d, *J* = 15.2 Hz, 1H), 3.94–3.80 (comp, 2H), 3.79 (s, 3H), 3.13–3.05 (m, 1H), 3.04–2.96 (m, 1H), 2.72–2.63 (comp, 2H), 1.29 (t, *J* = 7.2 Hz, 3H), 0.91 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 169.3, 157.9, 138.4, 134.5, 133.9, 130.0, 127.5, 127.4(5), 127.4(1), 126.2(1), 126.1(6), 113.2, 111.4, 65.9, 64.9, 61.7, 61.0, 58.5, 55.1, 49.5, 30.1, 13.9, 13.4; *m/z* (ESI–MS) 410.1 $[M+H]^+$.

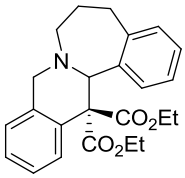
Diethyl 8,13a-dihydro-5H-[1,3]dioxolo[4,5-g]isoquinolino[3,2-a]isoquinoline-13,13(6H)-dicarboxylate (4.15d): Following the general procedure, compound **4.15d** was obtained from compound **4.40** and diethyl 2-(2-formylphenyl)malonate as a yellow oil in 85% yield (R_f = 0.23 in 20% EtOAc in hexanes); IR (KBr) 2980, 2904, 2804, 2755, 1732, 1505, 1487, 1367, 1224, 1144, 1043, 931, 863, 735 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.29–7.23 (m, 1H), 7.23–7.19 (comp, 2H), 7.10 (app d, *J* = 7.5 Hz, 1H), 6.76 (s, 1H), 6.57 (s, 1H), 5.90 (d, *J* = 1.2 Hz, 1H), 5.89 (d, *J* = 1.2 Hz, 1H), 4.80 (s, 1H), 4.41–4.25 (comp, 2H), 4.02 (s, 2H), 3.95–3.82 (comp, 2H), 3.10–3.02 (m, 1H), 3.93–3.83 (m, 1H), 2.69–2.59 (comp, 2H), 1.29 (t, *J* = 7.1 Hz, 3H), 0.95 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 169.2, 146.0, 145.6, 134.2, 133.6, 130.5, 130.0, 127.9, 127.5, 126.2(3), 126.2(1), 108.2, 106.9, 100.7, 66.7, 66.0, 61.9, 61.0, 58.3, 49.2, 29.9, 13.9, 13.5; *m/z* (ESI–MS) 424.5 $[M+H]^+$.

Diethyl 7,8,13,13b-tetrahydroindolo[2',3':3,4]pyrido[1,2-b]isoquinoline-14,14(5H)-dicarboxylate



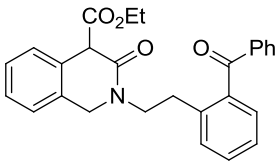
(4.15e): Following the general procedure, compound **4.15e** was obtained from tryptoline and diethyl 2-(2-formylphenyl)malonate as a yellow solid in 50% yield (R_f = 0.56 in 25% EtOAc in hexanes); mp: 161–164 ºC; IR (KBr) 3410, 3051, 2980, 2942, 2896, 2838, 2796, 1743, 1703, 1367, 1259, 1143, 1120, 1083, 1030, 1006, 858, 737, 719, 681 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 8.35 (s, 1H), 7.49 (app d, *J* = 7.7 Hz, 1H), 7.42–7.38 (m, 1H), 7.34–7.28 (comp, 2H), 7.27–7.22 (m, 1H), 7.20–7.13 (comp, 2H), 7.12–7.06 (m, 1H), 4.68 (s, 1H), 4.58–4.50 (m, 1H), 4.48–4.39 (m, 1H), 4.18 (d, *J* = 15.2 Hz, 1H), 3.95 (d, *J* = 15.2 Hz, 1H), 3.89–3.75 (comp, 2H), 3.28–3.21 (m, 1H), 2.94–2.85 (m, 1H), 2.83–2.74 (comp, 2H), 1.41 (t, *J* = 7.2 Hz, 3H), 0.60 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1, 168.7, 135.9, 134.6, 132.5, 131.5, 127.9(3), 127.8(8), 126.8, 126.6, 126.5, 121.5, 119.0, 117.9, 111.4, 110.8, 64.5, 62.5, 61.3, 58.6, 52.2, 21.4, 14.1, 13.1; *m/z* (ESI–MS) 419.1 $[M+H]^+$.

Diethyl 6,7,9,14a-tetrahydrobenzo[3,4]azepino[1,2-b]isoquinoline-14,14(5H)-dicarboxylate



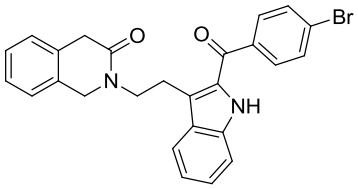
(4.15f): Following the general procedure but performing the reaction in a microwave reactor at 150 °C for 10 min, compound **4.15f** was obtained from benzazepane and diethyl 2-(2-formylphenyl)malonate as a brownish oil in 43% yield (R_f = 0.40 in 15% EtOAc in hexanes); IR(KBr) 3068, 2981, 2931, 2848, 2781, 1736, 1655, 1452, 1365, 1218, 1183, 1026, 748 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 8.15 (s, 1H), 7.30 (app t, *J* = 7.8 Hz, 1H), 7.23–7.17 (m, 1H), 7.15–7.08 (m, 1H), 7.06–6.97 (m, 1H), 6.93–6.86 (m, 1H), 6.80–6.70 (m, 1H), 6.68–6.57 (m, 1H), 5.57 (s, 1H), 4.34–4.21 (m, 1H), 4.19–4.03 (comp, 3H), 3.68–3.39 (comp, 3H), 3.37–3.18 (comp, 2H), 2.89–2.77 (m, 1H), 1.85–1.70 (m, 1H), 1.69–1.58 (m, 1H), 1.25 (t, *J* = 7.1 Hz, 3H), 0.98 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5, 168.7, 143.1, 136.5, 136.4, 131.5, 131.0, 129.0, 127.7, 126.8(0), 126.7(9), 125.8, 125.6, 124.6, 62.4, 61.8(8), 61.8(3), 61.5, 57.7, 49.1, 35.6, 23.5, 14.0, 13.6; *m/z* (ESI–MS) 394.2 $[M+H]^+$.

Ethyl 2-(2-benzoylphenethyl)-3-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (4.18a):



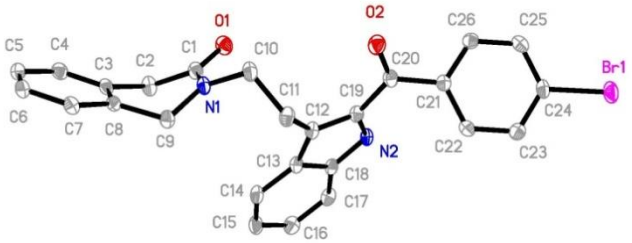
Following the general procedure, compound **4.18a** was obtained from 1-phenyl-THIQ and diethyl 2-(2-formylphenyl)malonate as a yellow oil in 70% yield (R_f = 0.49 in 40% EtOAc in hexanes); IR (KBr) 3071, 2982, 2935, 2359, 1735, 1660, 1597, 1482, 1268, 1155, 1092, 1026, 929, 763, 710 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.84–7.78 (comp, 2H), 7.63–7.57 (m, 1H), 7.51–7.44 (comp, 2H), 7.43–7.37 (comp, 2H), 7.37–7.32 (m, 1H), 7.30–7.22 (comp, 4H), 7.13–7.06 (m, 1H), 4.72 (d, *J* = 15.7 Hz, 1H), 4.54 (s, 1H), 4.15 (d, *J* = 15.7 Hz, 1H), 4.15–4.06 (comp, 2H), 3.90–3.81 (m, 1H), 3.80–3.71 (m, 1H), 3.08–3.92 (comp, 2H), 1.19 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.5, 168.6, 165.4, 138.2(3), 138.1(6), 137.9, 133.2, 131.8, 131.5, 130.8, 130.7, 130.3, 129.3, 128.5, 127.7(0), 127.6(5), 127.5(6), 125.8, 125.6, 61.8, 54.8, 51.3, 49.5, 31.3, 14.0; *m/z* (ESI–MS) 450.1 $[M+Na]^+$.

2-(2-(2-(4-Bromobenzoyl)-1H-indol-3-yl)ethyl)-1,2-dihydroisoquinolin-3(4H)-one (4.20):



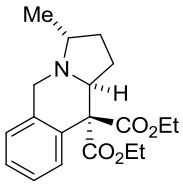
Following the general procedure, compound **4.20** was obtained from 1-(4-bromophenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole and compound **6** as a light yellow solid in 40% yield (R_f = 0.28 in 40% EtOAc in hexanes); mp: 216–217 ºC; IR (KBr) 3229, 3071, 2908, 1729, 1636, 1584, 1531, 1442, 1317, 1254, 1149, 1067, 1011, 837, 759, 744, 637 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 8.69 (s, 1H), 7.89 (app d, *J* = 8.2 Hz, 1H), 7.71 (d, *J* = 8.5 Hz, 2H), 7.65 (d, *J* = 8.5 Hz, 2H), 7.41–7.34 (comp, 2H), 7.25–7.13 (comp, 3H), 7.12 (app d, *J* = 7.3 Hz, 1H), 7.04 (app d, *J* = 7.3 Hz, 1H), 4.16 (s, 2H), 3.69 (t, *J* = 7.5 Hz, 2H), 3.54 (s, 2H), 3.18 (t, *J* = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.5, 168.8, 138.0, 136.6, 132.3, 132.1, 131.5, 130.9, 130.2, 128.3, 127.5, 127.1, 126.9(9), 126.9(8), 126.5, 125.1, 122.7, 121.6, 121.0, 111.9, 51.4, 48.1, 37.6, 23.3; m/z (ESI–MS) 495.2 $[M+Na]^+$.

Figure 4.4 **X–ray Crystal Structure of Product 4.20**



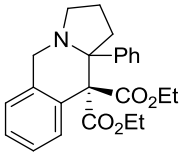
The requisite CIF has been deposited with the CCDC (deposition # 1060416).

Diethyl 3-methyl-1,2,3,10a-tetrahydropyrrolo[1,2-b]isoquinoline-10,10(5H)-dicarboxylate (4.22):



Following the general procedure but performing the reaction in a microwave reactor at 150 °C for 5 min, compound **4.22** was obtained from 2-methyl-pyrrolidine and diethyl 2-(2-formylphenyl)malonate as a light yellow solid in 33% yield (R_f = 0.43 in 15% EtOAc in hexanes); IR (KBr) 3066, 2978, 2928, 1731, 1665, 1459, 1367, 1247, 1046, 864, 750 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.36 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.23 (app td, *J* = 7.5, 1.4 Hz, 1H), 7.20–7.15 (m, 1H), 7.11 (app d, *J* = 7.5, 1H), 4.35–4.22 (comp, 2H), 4.22–4.13 (comp, 2H), 4.16 (d, *J* = 14.7 Hz, 1H), 3.40 (d, *J* = 14.7 Hz, 1H), 3.43–3.37 (m, 1H), 3.22–3.15 (m, 1H), 2.46–2.37 (m, 1H), 1.98–1.86 (comp, 2H), 1.54–1.43 (m, 1H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.21 (t, *J* = 7.1 Hz, 3H), 1.15 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2, 169.4, 135.7, 133.7, 128.6, 127.4, 127.0, 125.9, 67.0, 63.1, 61.5, 61.1(5), 61.1(2), 54.8, 32.4, 24.8, 18.3, 14.1, 14.0; *m/z* (ESI–MS) 332.2 $[M+H]^+$.

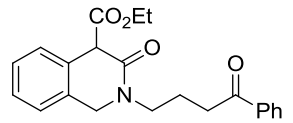
Diethyl 10a-phenyl-1,2,3,10a-tetrahydropyrrolo[1,2-b]isoquinoline-10,10(5H)-dicarboxylate (4.24):



Following the general procedure but performing the reaction in a microwave reactor at 150 °C for 10 min,in addition to compound **4.25** (19% yield), compound **4.24** was obtained from 2-phenyl-pyrrolidine and diethyl 2-(2-formylphenyl)malonate as a brown oil in 33% yield (R_f = 0.57 in 15% EtOAc in hexanes); IR (KBr)

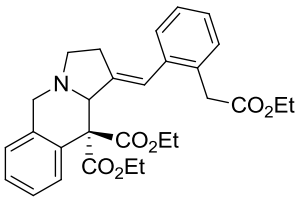
3056, 3026, 2980, 2937, 1732, 1686, 1596, 1491, 1448, 1366, 1244, 1077, 1045, 862, 757, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.41–7.36 (m, 1H), 7.36–7.33 (comp, 2H), 7.33–7.27 (comp, 2H), 7.27–7.21 (m, 1H), 7.21–7.16 (comp, 2H), 7.01–6.95 (m, 1H), 4.40–4.27 (comp, 2H), 4.27–4.20 (comp, 2H), 3.89 (d, *J* = 14.9 Hz, 1H), 3.47–3.41 (m, 2H), 3.46 (d, *J* = 14.9 Hz, 1H), 2.65–2.55 (m, 1H), 2.22–2.04 (comp, 2H), 1.86–1.73 (m, 1H), 1.33 (t, *J* = 7.1 Hz, 3H), 1.26 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 169.5, 142.3, 135.7, 133.8, 128.6, 128.4, 127.5, 127.2(2), 127.2(1), 126.9, 126.0, 70.3, 66.1, 63.3, 61.6, 61.3, 54.6, 35.0, 25.5, 14.1(4), 14.1(2); *m/z* (ESI–MS) 394.1 $[M+H]^+$.

Ethyl 3-oxo-2-(4-oxo-4-phenylbutyl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (4.25):



Following the general procedure but performing the reaction in a microwave reactor at 150 °C for 10 min,in addition to compound **4.24** (33% yield), compound **4.25** was obtained from 2-phenyl-pyrrolidine and diethyl 2-(2-formylphenyl)malonate as a brown oil in 19% yield (R_f = 0.39 in 40% EtOAc in hexanes); IR (KBr) 3062, 2980, 2936, 1733, 1683, 1655, 1482, 1366, 1282, 1207, 1155, 1028, 749, 692 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.97–7.91 (comp, 2H), 7.57–7.50 (m, 1H), 7.48–7.39 (comp, 2H), 7.34–7.27 (comp, 3H), 7.24–7.19 (m, 1H), 4.89 (d, *J* = 15.7 Hz, 1H), 4.55 (s, 1H), 4.31 (d, *J* = 15.7 Hz, 1H), 4.19–4.04 (m, 2H), 3.92–3.83 (m, 1H), 3.56–3.48 (m, 1H), 3.17–3.01 (comp, 2H), 2.19–2.02 (comp, 2H), 1.20 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.6, 168.7, 165.7, 136.8, 133.0, 131.6, 130.7, 128.5, 128.0, 127.9, 127.8, 127.7, 125.6, 61.8, 54.8, 50.7, 46.5, 35.2, 21.5, 14.0; *m/z* (ESI–MS) $[M+H]^+$.

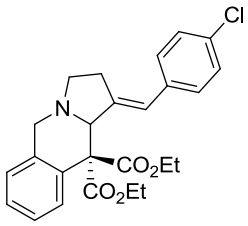
(E)-diethyl 1-(2-(2-ethoxy-2-oxoethyl)benzylidene)-1,2,3,10a-tetrahydropyrrolo[1,2-b]isoquinoline-10,10(5H)-dicarboxylate (4.12):



In a 10 mL round bottom flask containing a stir bar, compound **4.8a** (0.066 g, 0.25 mmol) was dissolved in toluene (2.5 mL). Subsequently, 4 Å molecular sieves (50 mg), AcOH (0.014 mL, 0.25 mmol) and pyrrolidine (0.027 mL, 0.325 mmol) were added. A reflux condenser with a nitrogen inlet was placed on top of the flask

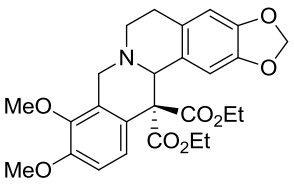
which was then heated under reflux for one hour. After allowing the flask to cool to room temperature, the mixture was diluted with EtOAc (20 mL) and washed with saturated $NaHCO_3$ solution (3 x 20 mL), water (20 mL), brine (20 mL) and dried over Na_2SO_4. The resulting solution was concentrated under reduced pressure and the residue purified via silica gel chromatography. In addition to compound **4.10a** (53% yield), compound **4.12** was obtained as a light yellow oil in 18% yield: (R_f = 0.37 in 20% EtOAc in hexanes); IR (KBr) 3071, 2962, 2937, 2874, 2783, 2719, 1732, 1662, 1490, 1463, 1368, 1251, 1094, 1045, 862, 753 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.50–7.46 (m, 1H), 7.25–7.17 (comp, 4H), 7.17–7.01 (comp, 2H), 7.08 (app d, *J* = 12.3 Hz, 1H), 6.28 (s, 1H), 4.37–4.27 (comp, 2H), 4.26–4.11 (comp, 5H), 4.10–4.05 (m, 1H), 3.96 (d, *J* = 16.2 Hz, 1H), 3.79 (d, *J* = 16.2 Hz, 1H), 3.40 (d, *J* = 13.1 Hz, 1H), 3.01 (ddd, *J* = 10.3, 7.9, 3.3 Hz, 1H), 2.59–2.51 (m, 1H), 2.49–2.41 (m, 1H), 2.30–2.22 (m, 1H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.25 (t, *J* = 7.2 Hz, 3H), 1.14 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.9, 171.5, 167.8, 143.8, 138.2, 134.9, 133.3, 132.4, 130.2, 130.0, 128.4, 127.1, 127.0(6), 127.0(2), 126.7, 126.2, 118.3, 69.9, 63.4, 62.0, 61.1, 60.6, 57.5, 52.4, 38.1, 28.4, 14.2, 14.0(1), 14.0(0).; *m/z* (ESI–MS) 492.2 $[M+H]^+$.

(E)-diethyl 1-(4-chlorobenzylidene)-1,2,3,10a-tetrahydropyrrolo[1,2-b]isoquinoline-10,10(5H)-dicarboxylate (**4.27**): In a 10 mL round bottom flask containing a stir bar, compound **4.8a** (0.066 g, 0.25 mmol) and *p*-Cl-benzaldehyde (0.035 g, 0.25 mmol) were dissolved in toluene (2.5 mL). Subsequently, 4 Å molecular sieves (50 mg), HOAc (0.014 mL, 0.25 mmol) and pyrrolidine (0.027 mL, 0.325 mmol) were added. A reflux condenser with a nitrogen inlet was placed on top of the flask which was then heated to reflux temperature for two hours. After allowing the flask to cool to room temperature, the mixture was diluted with EtOAc (20 mL) and washed with saturated $NaHCO_3$ solution (3 x 20 mL), water (20 mL), brine (20 mL) and dried over Na_2SO_4. The resulting solution was concentrated under reduced pressure and the residue purified via silica gel chromatography. In addition to compound **4.10a** (28% yield), compound **4.27** was obtained as a light yellow oil in 29% yield: (R_f = 0.29 in 20% EtOAc in hexanes); IR (KBr) 3069, 2959, 2871, 2797,

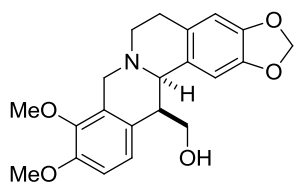


2713, 1728, 1655, 1491, 1460, 1367, 1242, 1092, 866, 734, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$)7.30 (d, *J* = 8.5 Hz, 2H), 7.25 (d, *J* = 8.5 Hz, 2H), 7.24–7.18 (comp, 3H), 7.12 (app d, *J* = 7.8 Hz, 1H), 6.32 (s, 1H), 4.44–4.29 (m, 2H), 4.25–4.10 (comp, 3H), 3.96 (s, 1H), 3.70 (d, *J* = 14.7 Hz, 1H), 3.33 (app t, *J* = 7.9 Hz, 1H), 2.93–2.81 (m, 1H), 2.75–2.64 (m, 1H), 2.43–2.33 (m, 1H), 1.33 (t, *J* = 7.1 Hz, 3H), 1.18 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3, 168.9, 143.6, 136.6, 134.8, 134.1, 131.9, 129.6, 129.3, 128.3, 127.6, 126.7, 126.3, 120.7, 69.2, 65.0, 61.8, 61.3, 55.7, 53.3, 31.6, 14.2, 14.0; *m/z* (ESI–MS) 440.1 $[M+H]^+$.

Diethyl 9,10-dimethoxy-8,13a-dihydro-5H-[1,3]dioxolo[4,5-g]isoquinolino[3,2-a]isoquinoline-13,13(6H)-dicarboxylate (4.41): Following the general procedure, compound **4.41** was obtained from compound **4.39** and compound **4.40** as a light yellow solid in 87% yield (R_f = 0.26 in 25% EtOAc in hexanes); mp: 143–144 ºC; IR (KBr) 2984, 2938, 2903, 2844, 2760, 1752, 1733, 1686, 1580, 1493, 1392, 1255, 1151, 1031, 978, 857, 776, 674 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 6.90 (d, *J* = 8.8 Hz, 1H), 6.82 (d, *J* = 8.8 Hz, 1H), 6.75 (s, 1H), 6.56 (s, 1H), 5.89 (d, *J* = 1.2 Hz, 1H), 5.88 (d, *J* = 1.2 Hz, 1H), 4.66 (s, 1H), 4.41–4.24 (comp, 2H), 4.20 (d, *J* = 16.0 Hz, 1H), 3.98–3.87 (comp, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 3.79 (d, *J* = 16.0 Hz, 1H), 3.12–3.05 (m, 1H), 2.94–2.84 (m, 1H), 2.69–2.56 (comp, 2H), 1.30 (t, *J* = 7.2 Hz, 3H), 0.95 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4, 169.5, 151.2, 145.9, 145.6, 144.5, 130.7, 128.4, 128.1, 127.6, 125.3, 110.6, 108.2, 106.8, 100.6, 65.5, 65.1, 61.8, 61.0, 60.2, 55.6, 53.9, 49.8, 30.1, 13.9, 13.5; *m/z* (ESI–MS) 484.1 $[M+H]^+$.

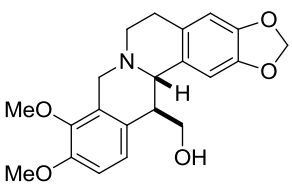


(±)-(4.43): This procedure was adapted from the literature.[25] Compound **4.41** (0.1 g, 0.207 mmol) and KOH (0.064g, 1.138 mmol) were mixed in EtOH (2.07 mL) and the reaction mixture was heated under reflux for 12 hours. After cooling to room temperature, the reaction mixture was diluted with 1 M HCl (20 mL). Subsequently, the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic layers were washed with water (3 x 10 mL) and



subsequently dried with Na_2SO_4. The solution was concentrated under reduced pressure and the resulting crude product **4.42** was used directly in the next step. The diastereomeric mixture of **4.42** (0.085 g, 0.22 mmol) was dissolved in HOAc (2 mL) and heated under reflux for 18 hours. Acetic acid was then removed under reduced pressure and the crude mixture dissolved in anhydrous THF (2.2 mL). This solution was added to a suspension of $LiAlH_4$ (0.025g, 0.66 mmol) in anhydrous THF (3 mL) at 0 °C. The reaction mixture was then heated under reflux for two hours. After cooling to room temperature, the reaction mixture was carefully quenched with 10% NaOH solution (20 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organic layers were washed with water (10 mL) and brine (10 mL), and dried over Na_2SO_4. The solution was concentrated under reduced pressure and the resulting residue purified via silica gel chromatography. In addition to compound **4.44** (15% yield), compound **4.43** was obtained as a light yellow solid in 45% yield over three steps: (R_f = 0.32 in 40% EtOAc in hexanes); mp: 228–230 ºC; IR (KBr) 3440, 2945, 2836, 2750, 2085, 1644, 1485, 1366, 1281, 1247, 1223, 1085, 1034, 734 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 6.99 (d, *J* = 8.5 Hz, 1H), 6.89 (d, *J* = 8.5 Hz, 1H), 6.62 (s, 2H), 5.94 (d, *J* = 1.3 Hz, 1H), 5.93 (d, *J* = 1.3 Hz, 1H), 5.72 (br s, 1 H), 4.24 (d, *J* = 15.9 Hz, 1H), 3.95–3.91 (m, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.79 (dd, *J* = 10.5, 2.1 Hz, 1H), 3.61–3.56 (m, 1H), 3.52 (d, *J* = 15.9 Hz, 1H), 3.22–3.11 (comp, 3H), 2.68–2.52 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.6, 146.5, 146.2, 144.7, 130.0, 129.0, 128.9, 127.6, 123.6, 111.6, 108.7, 105.5, 100.9, 65.6, 63.5, 60.1, 55.9, 54.1, 51.2, 43.8, 29.4; *m/z* (ESI–MS) 370.3 $[M+H]^+$.

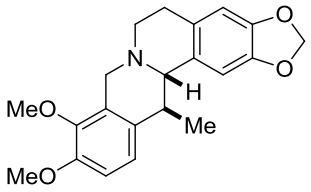
(±)-(4.44): This procedure was adapted from the literature.[25] Compound **4.41** (0.1 g, 0.207 mmol) and



KOH (0.064g, 1.138 mmol) were mixed in EtOH (2.07 mL) and the reaction mixture was heated under reflux for 12 hours. After cooling to room temperature, the reaction mixture was diluted with 1 M HCl (20 mL). Subsequently, the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic layers were washed with water (3 x 10 mL) and subsequently dried with Na_2SO_4. The solution was concentrated under reduced pressure and the resulting crude product **4.42** was used

directly in the next step. The diastereomeric mixture of **4.42** (0.085 g, 0.22 mmol) was dissolved in anhydrous THF (2.2 mL) and then added to a suspension of $LiAlH_4$ (0.025g, 0.66 mmol) in anhydrous THF (3 mL) at 0 °C. The reaction mixture was then heated under reflux for three hours. After cooling to room temperature, the reaction mixture was carefully quenched with 10% NaOH solution (20 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organic layers were washed with water (10 mL) and brine (10 mL), and dried over Na_2SO_4. The solution was concentrated under reduced pressure and the resulting residue purified via silica gel chromatography. In addition to compound **4.43** (15% yield), compound **4.44** was obtained as a light yellow solid in 75% yield over two steps: (R_f = 0.57 in 5% MeOH in EtOAc); mp: 171–173 ºC; IR (KBr) 3416, 2940, 2359, 2075, 1643, 1486, 1279, 1225, 1036 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 6.98 (d, *J* = 8.4 Hz, 1H), 6.80 (d, *J* = 8.4 Hz, 1H), 6.57 (s, 1H), 6.53 (s, 1H), 5.83 (d, *J* = 1.2 Hz, 1H), 5.79 (d, *J* = 1.2 Hz, 1H), 4.27–4.21 (m, 1H), 4.13 (dd, *J* = 10.3, 2.9 Hz, 1H), 3.93 (dd, *J* = 10.3, 3.5 Hz, 1H), 3.83 (d, *J* = 16.2 Hz, 1H), 3.79 (s, 3H), 3.76 (s, 3H), 3.62 (d, *J* = 16.2 Hz, 1H), 3.36–3.27 (comp, 2H), 3.20–3.12 (m, 1H), 3.09–3.00 (m, 1H), 2.73–2.64 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.5, 146.2, 145.8, 144.7, 128.7, 127.9, 127.3, 126.4, 123.8, 111.2, 108.9, 105.8, 100.6, 69.9, 60.0, 59.6, 55.7, 48.5, 44.8, 40.2, 24.2; *m/z* (ESI–MS) 370.3 $[M+H]^+$.

(±)-Epi-thalictricavine (4.45): This procedure was adapted from the literature.[25] Methanesulfonyl chloride (0.034 g, 0.29 mmol) was added to a solution of compound **4.44** (0.058g, 0.16 mmol) in pyridine (0.5 mL). The resulting solution was stirred at room temperature for one hour and then diluted with water (10 mL). The resulting mixture was extracted with dichloromethane (3 x 20 mL) and the combined organic layers were washed with water (10 mL), brine (10 mL) and dried over Na_2SO_4. The solution was concentrated under reduced pressure. The resulting residue was suspended in EtOH (5 mL), and $NaBH_4$ (0.042g, 1.1 mmol) was added. The reaction mixture was heated under reflux for 12 hours. After cooling to room temperature, the reaction was quenched with water (10 mL). The mixture was extracted with dichloromethane (3 x 10



mL), and the combined organic layers were washed with water (10 mL) and brine (10 mL), and dried over Na_2SO_4. The solution was concentrated under reduced pressure and the resulting residue purified via silica gel chromatography. The title compound was obtained as a yellow oil in 55% yield over two steps (R_f = 0.44 in 40% EtOAc in hexanes); IR (KBr) 3059, 2935, 2357, 1738, 1659, 1598, 1485, 1456, 1277, 1221, 1155, 1039, 929, 737, 640 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 6.94 (d, *J* = 8.5 Hz, 1H), 6.80 (d, *J* = 8.5 Hz, 1H), 6.72 (s, 1H), 6.59 (s, 1H), 5.90 (d, *J* = 1.3 Hz, 1H), 5.89 (d, *J* = 1.3 Hz, 1H), 4.09 (d, *J* = 16.4 Hz, 1H), 3.98 (d, *J* = 16.4 Hz, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 3.60 (d, *J* = 8.2 Hz, 1H), 3.12–2.99 (comp, 2H), 2.98–2.86 (comp, 2H), 2.86–2.78 (m, 1H), 1.44 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.1, 146.2, 145.2(2), 145.2(0), 132.5, 131.1, 127.1, 124.0, 123.1, 111.0, 108.9, 107.4, 100.7, 64.1, 60.4, 55.8, 50.6, 46.6, 34.4, 28.2, 22.3; *m/z* (ESI–MS) 354.2 $[M+H]^+$.

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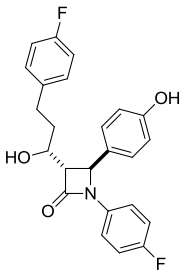
Chapter V Intermolecular Hydride Transfer Triggered α-Functionalization of Cyclic Amines

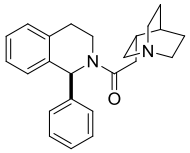
5.1 Background

Functionalized cyclic amines are ubiquitous building blocks in many biologically active compounds and pharmaceuticals (Scheme 5.1).[1,2] Their synthesis has been extensively studied over the last two decades.[3] The development of new methods for the direct C–H functionalization of amines is of particular importance. Nucleophilic addition to imines is a very important tool employed in synthetic organic chemistry to construct α-functionalized amines with a broad range of functionalities. Imines have shown diverse range of reactivity towards various nucleophiles including organolithium,[4] organoboronate,[5] alkylzinc reagent,[6] copper acetylide,[7] enolate,[8,9] cyanide,[10] and nitroalkane.[11] A lot of the synthetic methods to generate α-functionalized amines are based upon the nucleophilic addition to imines with many catalytic enantioselective versions of these transformations having been achieved.[4,12] Although these methods have greatly advanced the scope of the functionalization of amines, there are still some drawbacks. For example, some of the oxidative methods for the functionalization of amines require the use of precious metals and their scope is limited to tertiary amines.[13] Due to the weak electrophilicity of simple imines, the electrophilic species that are able to efficiently participate in a nucleophilic addition reaction are usually activated imines such as *p*-methoxyphenyl-imine (PMP-imine),[14] sulfonamide-imine,[6] *N*-phosphinoyl-imine[15] or even more electrophilic iminium ion or acyl iminium ion. Moreover, in order to access α-functionalized amines, the imines have to be pre-formed, which adds extra steps to a multistep synthesis.[16] Very few examples are reported for the nucleophilic addition to simple endocyclic imines derived from saturated cyclic amines such as pyrrolidine and piperidine. As part of our program of developing new strategies for the redox-neutral functionalization of amines, we hereby report an intermolecular hydride transfer triggered α-functionalization of cyclic secondary amines via in situ generated endocyclic imines.

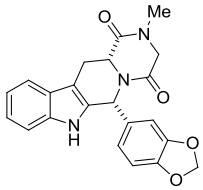
Scheme 5.1 **Examples of α-Functionalized Amines in Pharmaceuticals and Biologically Active Agents**



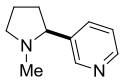
5.1
Zetia



5.2
Vesicare



5.3
Cialis



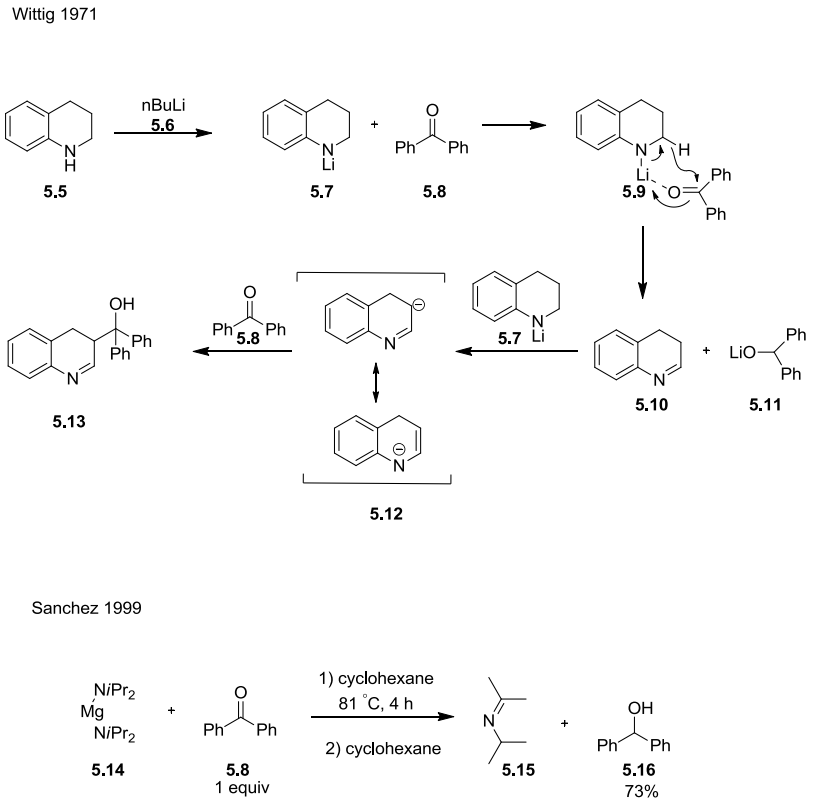
5.4
(S)-Nicotine

5.2 Concept of Intermolecular Hydride Transfer Triggered α-Functionalization of Cyclic Amines

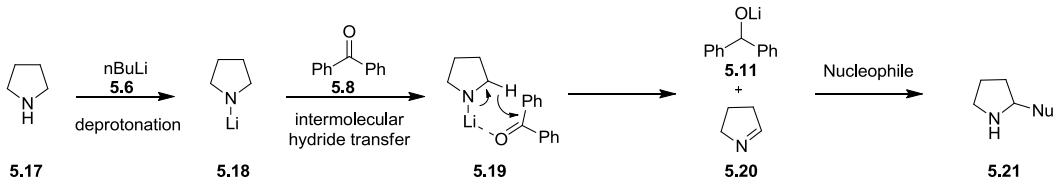
Simple endocyclic imines derived from their corresponding pyrrolidine and piperidine are known to be very unstable due to their high propensity to from the imine trimers (for example, 1-pyrroline exists majorly as the 1-pyrroline trimer[17]). Their syntheses have long-relied on the oxidation of pyrrolidine in aqueous alkaline peroxydisulfate and catalytic amount of silver nitrate to furnish the trimer[17,18] or by using a strong base to deprotonate the chloramine.[19] These methods suffer from either long synthetic sequence, sensitive reagents, low yields, lack of generality or modest functional group tolerance. We were inspired by the work reported by the Wittig group in 1971 where they found that lithiated secondary amines such as tetrahyroquinoline **5.5** can undergo intermolecular hydride transfer to benzophenone **5.8** and generate dihydroquinoline **5.10**.[20-22] The resulting imine can be deprotonated again by the lithiated amine to generate aza-allyl anion species **5.12**. Subsequent nucleophilic attack of the aza-allyl anion on the benzophenone gives rise to the aldo-type product **5.13** (Scheme 5.2). In addition to using lithium amide species as a hydride donor, Sanchez discovered that the solution of magnesium diisopropylamide can undergo hydride transfer to carbonyl compounds and reduce aldehydes or ketones to corresponding carbinols (Scheme 5.2).[23] The reaction of metal-bound

amine acting as a hydride donor to reduce ketone is analogous to the well known Meerwein-Ponndorf-Verley (MPV) reaction in which aluminum-bound alcohol acts as a hydride donor to reduce ketones.[24,25] There are very few reports in the literature taking advantage of the in situ generated imine and use it for further transformations. The major challenge in utilizing the in situ generated imine from this method is to prevent the imine from being deprotonated by strong base to form aza-allyl anion. We envisioned that if we can address this problem, the imine can be intercepted by different nucleophiles to give rise to a wide variety of α-functionalized amines (Scheme 5.3).

Scheme 5.2 **Intermolecular Hydride Transfer between Tetrahydroquinoline and Benzophenone**



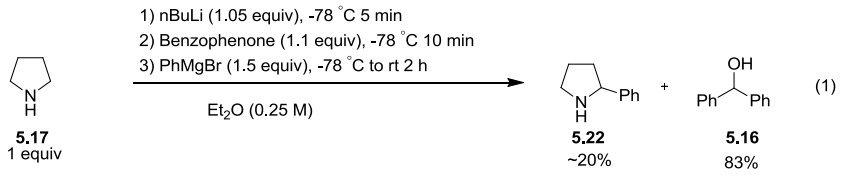
Scheme 5.3 **Proposed Intermolecular Hydride Transfer Triggered α-Functionalization of Cyclic Amines**



5.3 Evaluation of the Reaction Conditions

Based on the results of Wittig's work, we started to test our hypothesis by employing lithiated pyrrolidine as the hydride donor and benzophenone as the hydride acceptor. We first used Grignard reagent PhMgBr as the nucleophile to target the synthesis of 2-phenylpyrrolidine **5.22** (Scheme 5.4). The initial result was exciting because although the desired product was isolated in low yield we managed to observe the reduced product of benzophenone **5.16** in high yield. This is an indication that the hydride transfer from lithiated pyrrolidine to benzophenone is efficient under the reaction conditions.

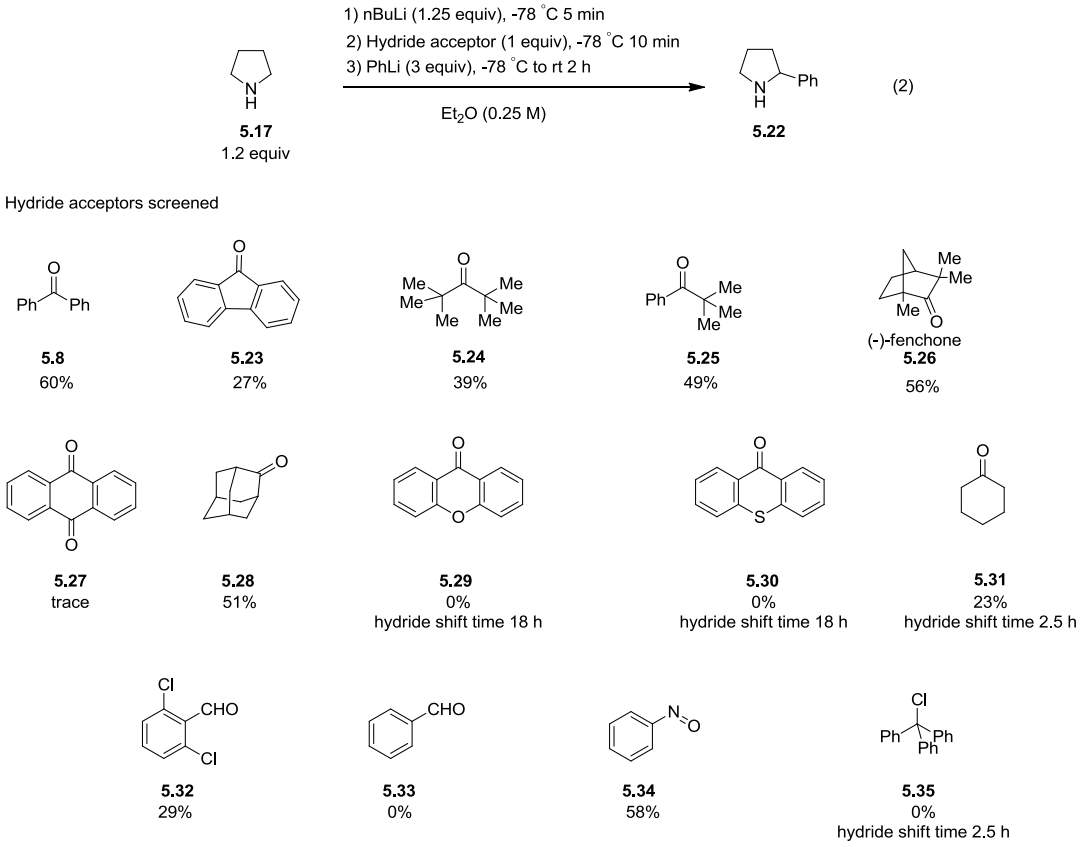
Scheme 5.4 **Initial Result on the Reaction between Pyrrolidine and Benzophenone**



This result led us to use a more nucleophilic reagent. Subsequently, PhLi was used and the yield of the desired product was improved significantly. A wide range of hydride acceptors were then screened and the results are summarized in Scheme 5.5. Most non-enolizable ketones are effective in

the hydride transfer reaction, while benzophenone outperforms other ketones. Surprisingly, xanthone and thioxanthone don't afford any desired product likely because the coordination effect of the heteroatoms on the hydride acceptor with the lithium species. Enolizable ketones and aromatic aldehydes can also participate in the hydride transfer process, but gave lower yields. Nitrosobenzene is also effective as a hydride acceptor but trityl chloride is completely ineffective.

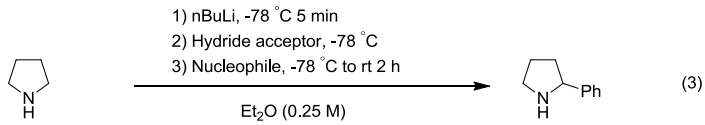
Scheme 5.5 **Screening of Different Hydride Acceptors**



Having chosen benzophenone as the optimal hydride acceptor, various reaction parameters are further evaluated (Table 5.1). Reducing the amount of nucleophile from three equivalents to two equivalents doesn't change the outcome of the reaction, however when further decreasing the amount of PhLi to 1.5 equivalents a lower yield was obtained (Entry 2 and 3). We next screened different solvents using two equivalents of PhLi as the nucleophile. Diethyl ether was identified as the optimal solvent (Entry

4 to 7). Diluting the reaction mixture to 0.1 M seemed detrimental to the reaction (Entry 8). Next we tested the reaction with different stoichiometric ratios of the starting materials. The combination of 1.2 equivalents of pyrrolidine, 1.2 equivalents of *n*BuLi and 1.1 equivalents of benzophenone and one equivalent of PhLi gave the highest yield (Entry 9 to 13). Finally, we screened the reaction time for the hydride transfer process. It turns out that 10 min is sufficient for the hydride transfer process since it gives almost quantitative yield for **5.16**. Extending the hydride transfer time to 30 min and 60 min at –78 °C gave inferior results (Entry 14 and 15).

Table 5.1 **Evaluation of the Reaction Conditions**



5.17 **5.22**

Entry	Pyrrolidine (equiv)	BuLi (equiv)	Hydride acceptor (equiv)	Nucleophile (equiv)	Hydride transfer time	Yield[a]
1	1.2	1.25	Ph_2CO (1)	PhLi (3)	10 min	60%
2	1.2	1.25	Ph_2CO (1)	PhLi (2)	10 min	61%
3	1.2	1.25	Ph_2CO (1)	PhLi (1.5)	10 min	49%
4[b]	1.2	1.25	Ph_2CO (1)	PhLi (2)	10 min	61%
5[c]	1.2	1.25	Ph_2CO (1)	PhLi (2)	10 min	48%
6[d]	1.2	1.25	Ph_2CO (1)	PhLi (2)	10 min	33%
7[e]	1.2	1.25	Ph_2CO (1)	PhLi (2)	10 min	trace
8[f]	1.2	1.25	Ph_2CO (1)	PhLi (2)	10 min	56%
9	1	1.05	Ph_2CO (1)	PhLi (2)	10 min	40%
10	2	2	Ph_2CO (2)	PhLi (1)	10 min	~69%[g]

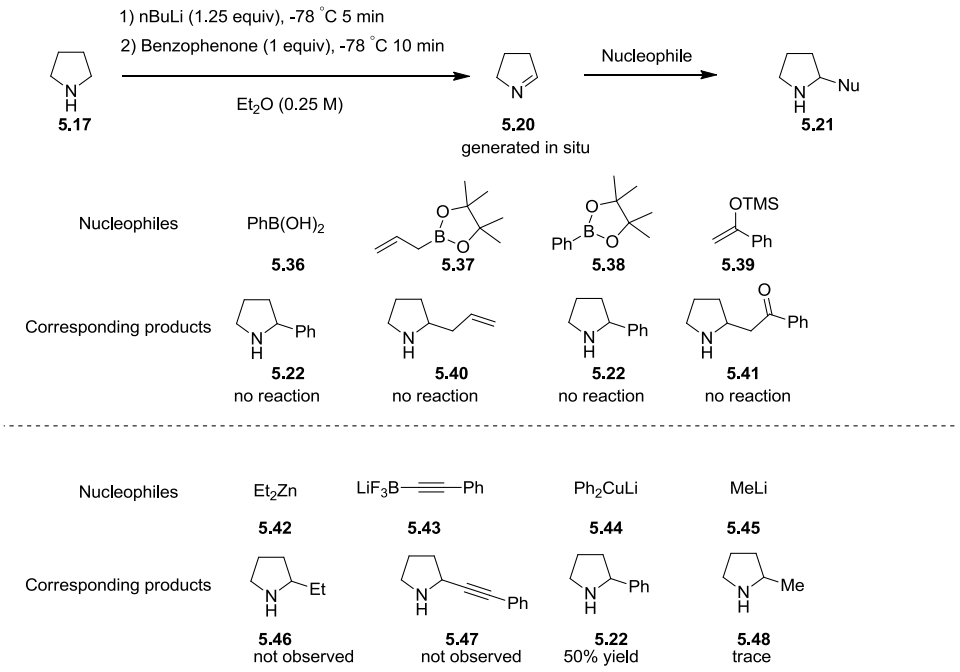
11	1	1	Ph_2CO (1)	PhLi (1)	10 min	54%[g]
12	1.2	1.2	Ph_2CO (1.2)	PhLi (1)	10 min	67%[g]
13	1.2	1.2	Ph_2CO (1.1)	PhLi (1)	10 min	69%[g]
14	1.2	1.25	Ph_2CO (1)	PhLi (2)	30 min	57%
15	1.2	1.25	Ph_2CO (1)	PhLi (2)	60 min	49%

[a]Yields are calculated based on pyrrolidine; [b]The hydride transfer step was carried out at –78°C for 10 min and warmed to 25 °C for 18 h; [c]The hydride transfer step was carried out at –78 °C for 10 min and warmed to 25 °C for 1h; [b]PhMe as solvent; [c]TBME as solvent; [d]THF as solvent; [e]1,2-Dimethoxyethane as solvent; [f]0.1 M concentration; [g]yields are calculated based on PhLi.

5.4 Scope of the Nucleophilic Addition with Other Nucleophiles

Having identified the optimal conditions, we then set out to expand the scope of the nucleophiles for the addition to the in situ generated 1-pyrroline. The results are shown in Scheme 5.6. Among all the nucleophiles tested, only organocuprate **5.44** gives rise to the desired product. These observations may be due to the relatively weak electrophilicity of the 1-pyrroline **5.20** towards relatively weak nucleophiles such as organoboronates, alkyl zinc reagents and silyl enol ethers.

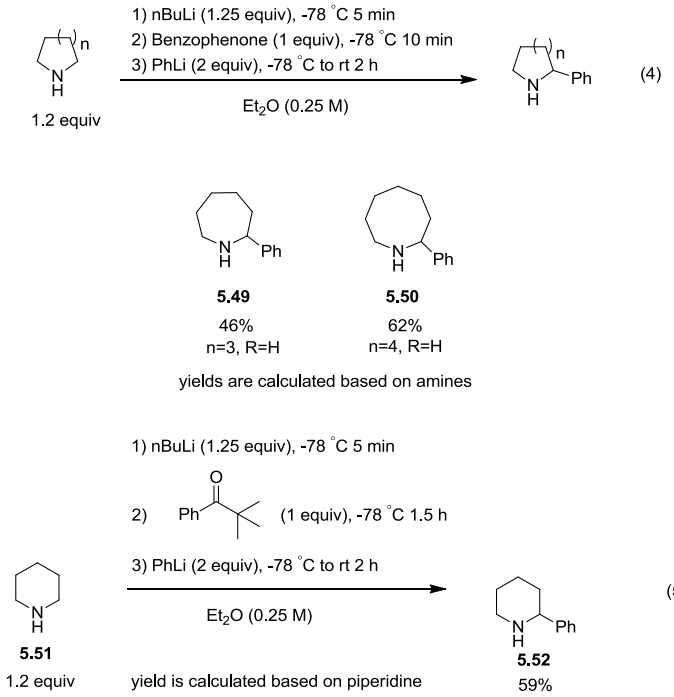
Scheme 5.6 **Scope of the Nucleophilic Addition with Other Nucleophiles**



5.5 Scope of the Hydride Transfer Reaction with Other Amines

Next we explored the substrate scope with other cyclic amines. Gratifyingly, both seven-membered and eight-membered ring skeletons are readily functionalized under the optimized conditions (Scheme 5.7) with moderate to good yields. Interestingly, piperidine only gave very low yield for the 2-phenylpiperidine when exposed to the optimized conditions (not shown). After extensive screening of reaction parameters, it was found that 3,3-Dimethyl-2-butanone was the best hydride acceptor for the piperidine substrate. Good yield was obtained when benzophenone was replaced with 3,3-Dimethyl-2-butanone and the hydride transfer time was allowed to be extended to 1.5 h (Scheme 5.7, eq 5).

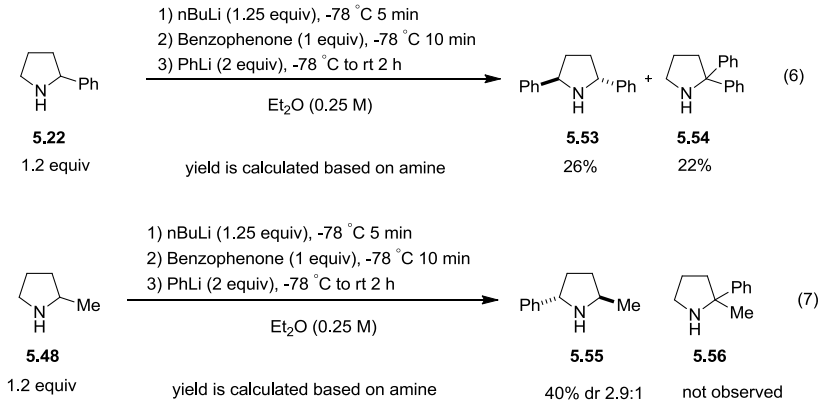
Scheme 5.7 **Scope of the Hydride Transfer Reaction with Other Amines**



5.6 Regioselectivity of the Intermolecular Hydride Transfer Process

We next studied the regioselectivity of the intermolecular hydride transfer process. When 2-subsituted pyrrolidine such as 2-phenylpyrrolidine is subjected to the reaction conditions, both the 2,5-disubstituted and 2,2-disubstituted regioisomers are obtained (Scheme 5.8, eq 6). For the 2,5-diphenylpyrrolidine product **5.53**, only the trans-isomer is observed. While 2-methylpyrrolidine gave a different result, only the *trans*-2,5-disubstituted product is observed under the otherwise identical conditions (Scheme 5.8, eq 7).

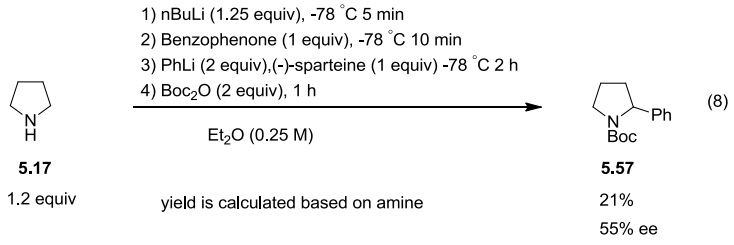
Scheme 5.8 **Regioselectivity of the Intermolecular Hydride Transfer Process**

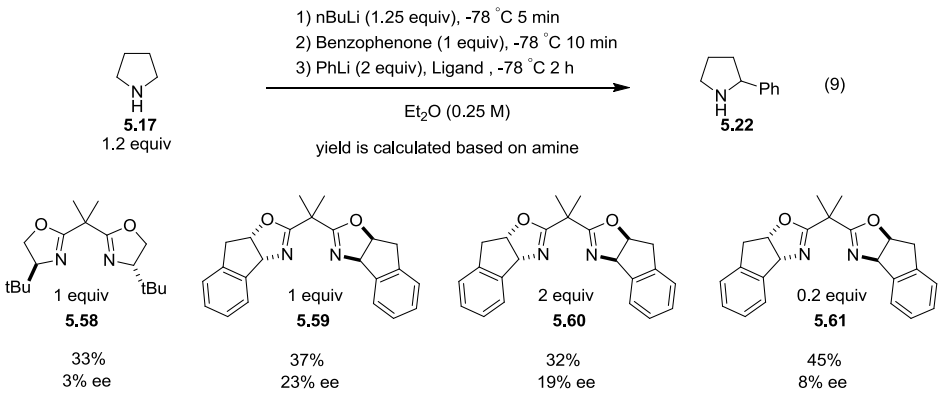


5.7 Asymmetric Synthesis of the α-Functionalized Amines via Intermolecular Hydride Transfer

The versatility of this reaction has prompted us to develop methods that give rise to enantio-enriched α-functionalized products. Since it is extensively studied that organolithium reagent can form chiral complexes with various ligands[26,27] we attempted to conduct an asymmetric addition of PhLi to 1-pyrroline in the presence of chiral ligands. To our delight, when using (-)-sparteine as the ligand in combination with PhLi moderate enantioselectivity was obtained. And 2-phenylpyrrolidine was isolated in 55% *ee* (Scheme 5.9, eq 8). Unfortunately, *t*Bu-bis(oxazoline) (*t*BuBox) ligand **5.58** and the IndaBox ligand **5.59** in varying quantities didn't show good enantioselectivity and lower *ee* values were obtained (Scheme 5.9, eq 9).

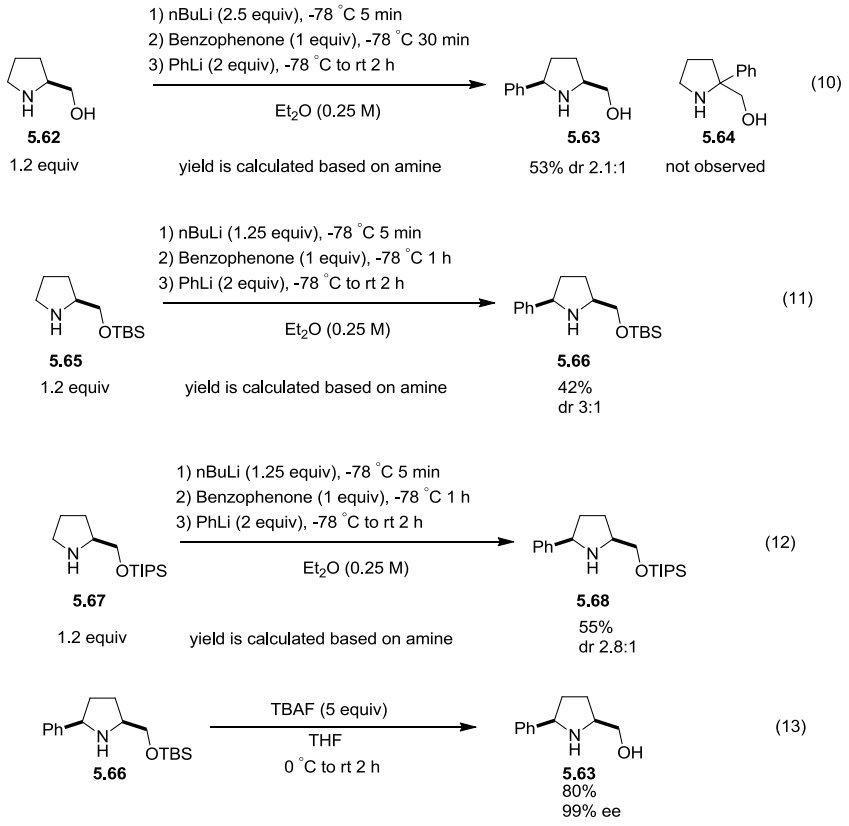
Scheme 5.9 **Asymmetric Addition of PhLi with Chiral Ligands**





Next we selected enantiopure starting materials as the substrates for the hydride transfer reaction. The commercial available (S)-prolinol was tested under the optimized conditions. The reaction proceeded smoothly to afford an inseparable mixture of two diastereomers of the 2,5-disubstituted prolinol **5.63** (Scheme 5.10, eq 10). The *cis*-diastereomer was the major diastereomer observed which is probably due to the directing effect of the oxygen atom on the prolinol side chain. Both TBS and TIPS-protected prolinols also gave rise to the *cis*-diastereomer as the major diastereomer (Scheme 5.10, eq 11 and 12). After deprotection of the silyl protecting group the enantiopure prolinol derivative is obtained (Scheme 5.10, eq 13).

Scheme 5.10 **α-Functionalization of the Prolinol Derivatives**

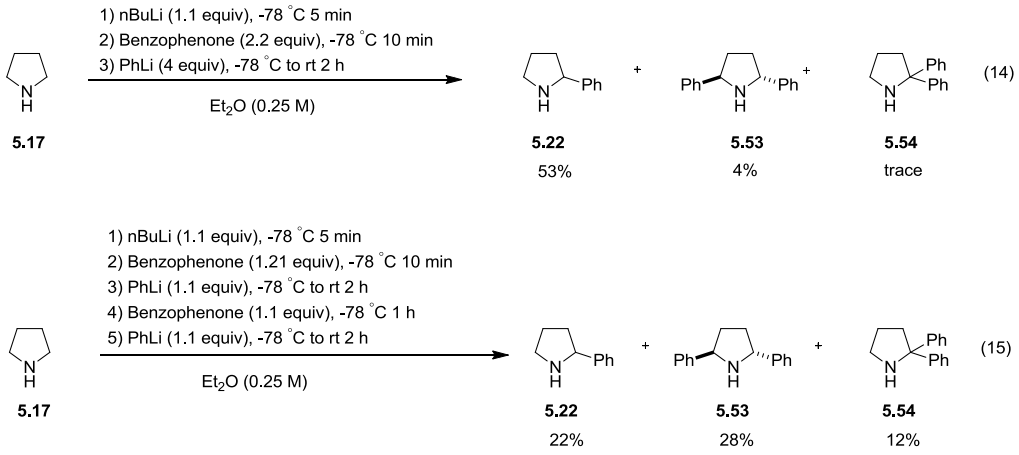


5.8 Attempted One-Pot Synthesis of 2,5-Disubstituted Pyrrolidine

A striking aspect of the intermolecular hydride transfer triggered α-functionalization of amines is that the lithiation of the amine and subsequent hydride transfer between the lithiated amine and benzophenone is much faster than the nucleophilic addition of PhLi to benzophenone. This was illustrated in the experiment where pyrrolidine and benzophenone were mixed in one pot before PhLi was added, and PhLi was acting both as base for the deprotonation step and nucleophile for the addition step. The reaction outcome was quite similar to what was obtained under the optimized stepwise conditions. The difference in the rates of deprotonation/hydride transfer and nucleophilic addition under the reaction conditions gives us a great opportunity to develop an one-pot synthesis of

2,5-disubstituted pyrrolidine. We tested the idea using 2.2 equivalents of benzophenone as the hydride acceptor and then using four equivalents of PhLi as the nucleophile (Scheme 5.11, eq 14). Unfortunately, only a trace amount of **5.53** was obtained. However, when we conduct the hydride transfer-PhLi addition sequence reiteratively, the yield for the **5.53** was greatly improved (Scheme 5.10, eq 14).

Scheme 5.11 **Attempted One-Pot Synthesis of 2,5-Disubstituted Pyrrolidine**



5.9 Conclusion

In summary, we have developed an intermolecular hydride transfer triggered α-functionalization of cyclic amines. The starting materials are all readily accessible and commercially available. The scope of the reaction is broad in terms of cyclic amines and this method can be utilized to prepare enantio-enriched substituted amines. Study of the substrate scope of this transformation and its application in natural product synthesis will continue in our group.

5.10 Experimental Section

General Information: Starting materials, reagents, and solvents were purchased from commercial sources and used as received unless stated otherwise. Pyrrolidine, piperidine, 2-methylpyrrolidine, azepane and azocane were distilled prior to use. Ketones were purified either by distillation or by recrystallization 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, 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 (^{1}H-NMR) were recorded on a Varian VNMRS-500 MHz and 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 (^{13}C-NMR) spectra were recorded on a Varian VNMRS-500 MHz and 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 mixtures. Compounds **5.22**,[28] **5.49**,[29] **5.52**,[29] **5.53**,[30] **5.54**,[31] **5.55**,[32] **5.66**,[33] **5.68**[32] were previously reported and their published characterization data matched our own in all respects.

General procedure A: Procedure for the Intermolecular Hydride Transfer Triggered Functionalization of Amines

A 25 mL flame-dried round bottom flask was charged with a magnetic stir bar, amine (1.2 mmol, 1.2 equiv) and anhydrous diethyl ether (2 mL). The flask was cooled down to –78 °C. Subsequently,

*n*BuLi (1.25 mmol, 1.25 equiv) was added dropwise to the reaction mixture and the reaction mixture was allowed to stir at –78 °C for 10 min. A solution of benzophenone (1 mmol, 1 equiv) in anhydrous diethyl ether (2 mL) was transferred via cannula to the reaction mixture. After complete addition of the benzophenone solution, the reaction mixture was allowed to stir at –78 °C for the designated time. Subsequently, PhLi (2 mmol, 2 equiv) was added to the reaction mixture and the reaction mixture was gradually warmed up to room temperature. After stirring for 2 h, the reaction mixture was quenched with 20 mL 10% aqueous NaOH solution. The aqueous layer was back-extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with water (3 x 100 mL) and subsequently dried with Na_2SO_4. The solution was concentrated under reduced pressure and the resulting residue purified via silica gel chromatography.

Procedure B: Procedure for the Asymmetric Addition of PhLi with Chiral Ligands

The PhLi-ligand complex was pre-formed by mixing PhLi (2 mmol, 2 equiv) and (-)-sparteine (1 mmol, 1 equiv) in anhydrous ether (2 mL) at –78 °C for 30 min.

A 10 mL flame-dried round bottom flask was charged with a magnetic stir bar, amine (1.2 mmol, 1.2 equiv) and anhydrous diethyl ether (2 mL). The flask was cooled down to –78 °C. Subsequently, *n*BuLi (1.25 mmol, 1.25 equiv) was added dropwise to the reaction mixture and the reaction mixture was allowed to stir at –78 °C for 10 min. A solution of benzophenone (1 mmol, 1 equiv) in anhydrous diethyl ether (2 mL) was transferred via cannula to the reaction mixture. After complete addition of the benzophenone solution, the reaction mixture was allowed to stir at –78 °C for 10 min. Subsequently, the pre-formed PhLi-ligand complex was added to the reaction mixture via cannula and the reaction mixture was allowed to react at –78 °C for 2 h. The reaction mixture was quenched with MeOH (10 mL) at –78 °C and was allowed to warm up to room temperature. After adding 20 mL 10% aqueous NaOH solution to the reaction mixture, the aqueous layer was back-extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with water (3 x 100 mL) and subsequently dried

with Na_2SO_4. The solution was concentrated under reduced pressure and the resulting residue purified via silica gel chromatography. For determination of the *ee* value: the free amine (0.25 mmol, 1 equiv) was dissolved in DCM (2.5 mL) and di-tert-butyl dicarbonate (0.5 mmol, 2 equiv) was added to the reaction mixture. The reaction mixture was allowed to stir at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure and the resulting residue purified via silica gel chromatography. The *ee* of the Boc protected amine was determined by HPLC.

General procedure C: Procedure for the One-pot Synthesis of 2,5-Disubstituted Pyrrolidine

A 25 mL flame-dried round bottom flask was charged with a magnetic stir bar, amine (1.2 mmol, 1.2 equiv) and anhydrous diethyl ether (2 mL). The flask was cooled down to –78 °C. Subsequently, *n*BuLi (1.25 mmol, 1.25 equiv) was added dropwise to the reaction mixture and the reaction mixture was allowed to stir at –78 °C for 10 min. A solution of benzophenone (1.25 mmol, 1.25 equiv) in anhydrous diethyl ether (2 mL) was transferred via cannula to the reaction mixture. After complete addition of the benzophenone solution, the reaction mixture was allowed to stir at –78 °C for 10 min. Subsequently, PhLi (2 mmol, 2 equiv) was added to the reaction mixture and the reaction mixture was gradually warmed up to room temperature. After stirring for 2 h, the reaction mixture cooled to –78 °C and a solution of benzophenone (1.25 mmol, 1.25 equiv) in anhydrous diethyl ether (2 mL) was transferred via cannula to the reaction mixture. After complete addition of the benzophenone solution, the reaction mixture was stirred at –78 °C for 1 h. Subsequently, PhLi (2 mmol, 2 equiv) was added to the reaction mixture. The reaction mixture was gradually warmed up to room temperature. After stirring for 2 h, the reaction mixture was quenched with 20 mL 10% aqueous NaOH solution. Subsequently, the aqueous layer was back-extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with water (3 x 100 mL) and dried with Na_2SO_4. The solution was concentrated under reduced pressure and the resulting residue purified via silica gel chromatography.

2-Phenylazocane (5.50): Following the general procedure A, compound **5.50** was obtained as a colorless oil in 74% yield (R_f = 0.63 in 10% MeOH and 2% *i*$PrNH_2$ in EtOAc); IR (KBr) 3060, 3025, 2922, 2849, 2697, 1944, 1881, 1801, 1688, 1601, 1491, 1378, 1278, 1128, 1027, 754, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.41–7.36 (m, 2H), 7.36–7.30 (m, 2H), 7.24 (t, *J* = 7.2 Hz, 1H), 3.84 (dd, *J* = 9.1, 4.0 Hz, 1H), 3.19–3.04 (m, 1H), 2.91–2.74 (m, 1H), 1.98–1.90 (m, 1H), 1.89–1.72 (comp, 5H), 1.71–1.54 (comp, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.2, 128.2, 126.4(2), 126.4(0), 62.5, 47.5, 35.5, 29.7, 27.7, 25.1, 24.3; *m/z* (ESI–MS) 190.1 $[M+H]^+$.

((2S,5R)-5-Phenylpyrrolidin-2-yl)methanol (5.63): In a 10 mL round bottom flask, **5.66** (0.4 mmol, 1 equiv) was dissolved in anhydrous THF (2 mL) and the reaction mixture was cooled to 0 °C. Tetrabutylammonium fluoride (1.0 M in THF; 2 mmol, 2 mL, 5 equiv) was added to the reaction mixture at 0 °C. The mixture was stirred at 0 °C for 10 min and was allowed to gradually warm up to room temperature. After reacting at room temperature for 2 h, the reaction was treated with water (10 mL). Subsequently, the aqueous layer was back-extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with water (3 x 100 mL) and subsequently dried with Na_2SO_4. The solution was concentrated under reduced pressure and the resulting residue purified via silica gel chromatography. **5.66** was obtained as a colorless oil in 80% yield (R_f = 0.13 in 10% MeOH in EtOAc); IR (KBr) 2924, 2869, 2844, 1731, 1603, 1563, 1451, 1407, 1261, 1049, 757, 700 cm^{-1}; $[\alpha]_D^{20}$ +57.3 (c 0.5, $CHCl_3$, >99% *ee*); ^1H NMR (500 MHz, $CDCl_3$) 7.42–7.36 (m, 2H), 7.32 (app t, *J* = 8.0 Hz, 2H), 7.24 (app t, *J* = 7.2 Hz, 1H), 4.28 (dd, *J* = 9.3, 6.6 Hz, 1H), 3.64 (dd, *J* = 10.4, 3.8 Hz, 1H),3.54–3.47 (m, 1H), 3.44 (dd, *J* = 10.4, 5.6 Hz, 1H),2.73–2.53 (comp, 2H),, 2.22–2.11 (m, 1H), 2.01–1.91 (m, 1H), 1.82–1.73 (m, 1H), 1.73–1.63 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.3, 128.3, 127.0, 126.5, 65.2, 62.7, 58.4, 34.6, 27.8; *m/z* (ESI–MS) 178.1 $[M+H]^+$; HPLC: Daicel Chiralpak AD-H, *n*-hexane/*i*-PrOH = 90/10, Flow rate = 1 mL/min, UV = 254 nm, t_R =8.5 min (major) and t_R = 10.5 min (minor).

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Bibliography

Longle Ma was born in the City of Shashi, Hubei Province, China on September 15, 1988. His family was originally from the County of Jiangdu, Jiangsu Province. After finishing his high school in Shashi Middle School in 2006, he went to Nankai University in Tianjin, China to study chemistry. At Nankai, he joined Professor Jian-Yu Zheng and Professor Yi-Zhou Zhu's lab as an undergraduate researcher to study the syntheses of porphyrin derivatives and their optical properties. In June 2010, he obtained the degree of Bachelor of Science from Nankai and in August 2010, he went to New Jersey, US to continue his graduate studies at Rutgers University under the supervision of Professor Daniel Seidel. In Professor Seidel's lab, he was devoted to the development of amine functionalizations involving azomethine ylides. In December 2012, he received Krishnamurthy Award for Outstanding Paper in Synthetic Organic Chemistry, and in December 2013 he received Van Dyke Award for Excellence in Research.