DEVELOPMENT OF REDOX-NEUTRAL REACTION CASCADES FOR AMINE FUNCTIONALIZATION AND SYNTHESIS OF BIMETALLIC BISOXAZOLINE COMPLEXES

by

DEEPANKAR DAS

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And approved by

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ABSTRACT OF THE DISSERTATION

Development of Redox-Neutral Reaction Cascades for Amine Functionalization and Synthesis of Bimetallic Bisoxazoline Complexes

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Activation of moderately reactive C–H bonds by metal-catalyzed processes has attracted lot of attention because it can give access to complex structures from simple starting materials. Outlined within this dissertation are our efforts to develop alternative redox-neutral approaches for functionalization of relatively unreactive C–H bonds without requiring the use of expensive metal catalysts, oxidants or other additives. Unique reactivity patterns of in situ formed azomethine ylides for non-pericyclic annulation reactions with pendant nucleophiles were studied. We were able to establish that the redox isomerization from an external iminium ion to an internal iminium ion proceeds through the intermediacy of azomethine ylides. The challenges are summarized and the work was further expanded to the direct, redox-neutral, three-component amine α-alkynylation and α-phosphonation. This approach offers an expeditious route to synthetically and pharmacologically useful building blocks.

Design and synthesis of bimetallic complexes of chiral bisoxazoline ligands also was undertaken for use in asymmetric transformations. These complexes can potentially chelate a single functional group by binding to two metal centers and could result in a higher degree of activation of the substrate.

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Finally, my concluding gratitude is reserved for my family. Thank you for your unending love, constant support and encouragement. You have contributed immensely for making this happen.

Dedicated to my family

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List of Schemes

δ	Chemical shift
π	Pi
Å	Angstrom
μL	Microliter
μW	Microwave
°	Degree
°C	Degree celcius
%	Percent
acac	Acetylacetonate
AcCl	Acyl chloride
AcOH	Acetic acid
app	Apparent
atm	Atmospheric pressure
BARF	Tetrakis(3,5-bis(trifluoromethyl)phenyl)borate
BIPHEP	Biphenylphosphine
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
CSA	Camphorsulfonic acid
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
dtbpy	2,6-Di-*tert*-butylbipyridine
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
nbe	Norbornene
NMM	*N*-Methylmorpholine
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

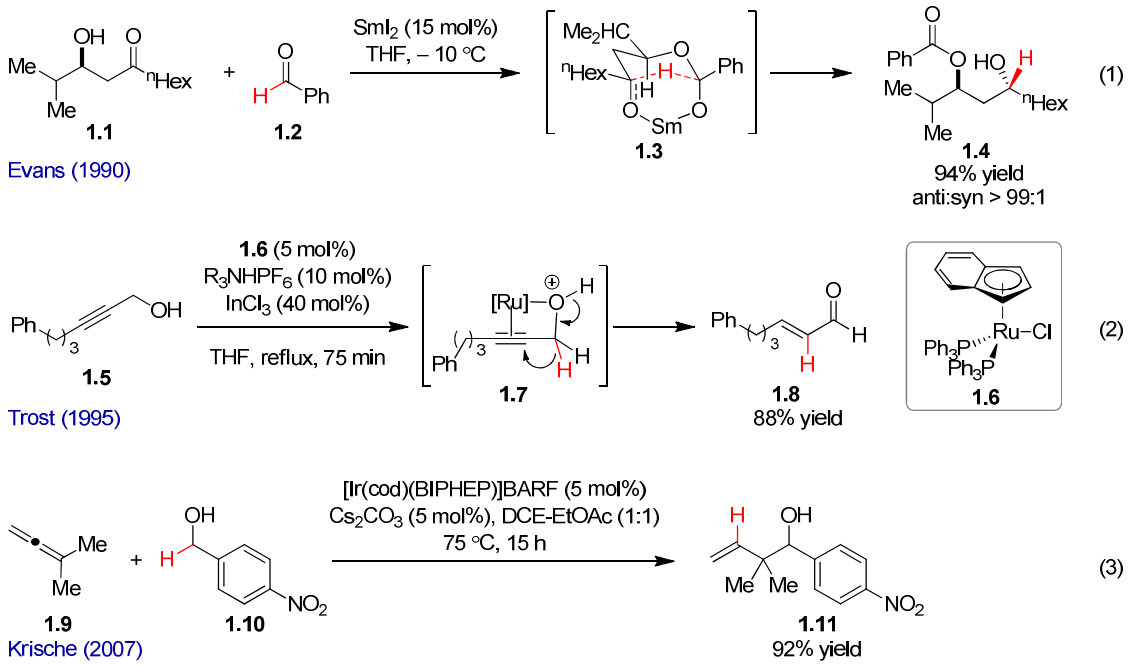
Introduction

1.1 Background

Due the ubiquity of carbon–hydrogen bonds in organic molecules, the development of methods for their direct conversion to carbon–carbon or carbon–heteroatom bonds remains a long sought after goal in synthetic organic chemistry. To obtain the desired selectivity and reactivity, traditional approaches rely on the use of prefunctionalized starting materials. However, preparation of the precursor with an appropriate functional group prior to installation of the desired carbon–carbon, carbon–nitrogen, carbon–oxygen or carbon–sulfur bond adds extra steps to the overall synthetic sequence and lowers the efficiency of the process. As such, overcoming this issue will not only increase atom economy but also improve the overall efficiency in a multi-step sequence. In recent times, there has been a heightened interest in the mild and selective functionalization of relatively unreactive carbon–hydrogen bonds.[1] Exciting developments have been accomplished in this area of research and they encompass a variety of strategies, including the more prevalent transition metal catalyzed approach.

Redox-neutral processes are powerful tools that offer convenient alternatives to address both atom and step economy. Such processes have the advantage of avoiding the distinct reduction and oxidation steps, thereby enhancing its synthetic utility and making it amenable to introduce molecular complexity quickly. The Evans-Tishchenko reaction is an example of a redox-neutral reaction where an aldehyde is coupled with a β-hydroxy ketone by an internal hydride transfer (Figure 1.1, eq 1).[2] Trost and coworkers reported effective methods for ruthenium-catalyzed redox isomerization of both allyl and propargyl alcohols (Figure 1.1, eq 2).[3] Likewise, Krische and coworkers demonstrated unique iridium- and ruthenium-catalyzed intermolecular transfer hydrogenative coupling reactions (Figure 1.1, eq 3).[4]

Figure 1.1 **Examples of Redox-Neutral Processes**



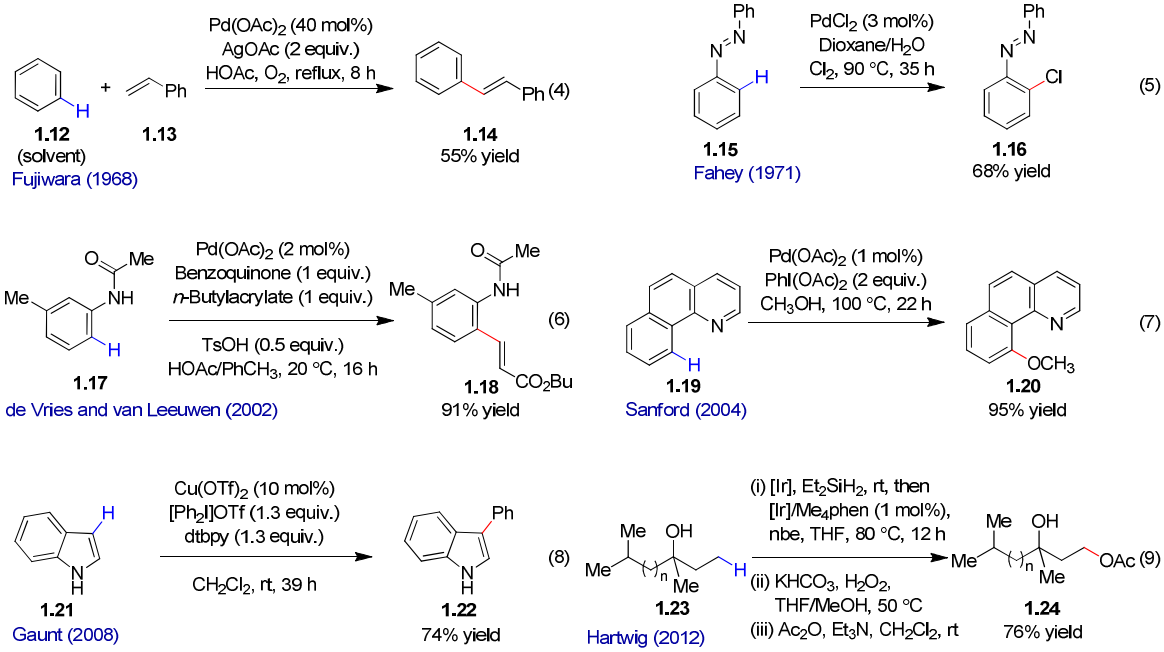
In light of the fascinating advances achieved in this regard, it is imperative to note that redox-neutral C–H functionalization exhibits great advantages and portrays immense potential for the efficient synthesis of complex molecules.

1.2 Transition Metal Catalyzed C–H Bond Functionalization

Transition metal catalyzed C–H functionalization reactions have been extensively studied for the past several decades and continue to be viable alternatives for the construction of carbon–carbon or carbon–heteroatom bonds.[5] Since Fujiwara's pioneering work in the late 1960s on palladium(II)-catalyzed C(sp^2)–H olefination of simple arenes (Figure 1.2, eq 4),[6] there have been impressive developments in the context of oxidative addition of C–H bonds to a transition metal center and thereby setting the stage for further functionalization. In order to address the limitation of regioselectivity in transition metal-catalyzed activation of sp^2 C–H bonds, different

directing groups have been incorporated to bring the metal in close proximity to the desired C–H bond. Seminal work by Fahey showed that coordination-directed cyclometalation can be employed to control positional selectivity and enhance the rate of C–H cleavage (Figure 1.2, eq 5).[7] In 2002, de Vries and van Leeuwen *et al.* revealed mild C–H activation facilitated by a directing group for the oxidative coupling of anilides with olefins (Figure 1.2, eq 6).[8] Sanford and coworkers reported using a series of nitrogen-containing directing groups for oxidative C–H acetoxylation (Figure 1.2, eq 7).[9] A notable example of copper-catalyzed mild C–H functionalization of indoles was reported in 2008 by Gaunt and coworkers (Figure 1.2, eq 8).[10,11] More recently, Hartwig *et al.* demonstrated a remarkable site-selective γ-functionalization of primary C–H bonds regulated by a hydroxyl group (Figure 1.2, eq 9).[12]

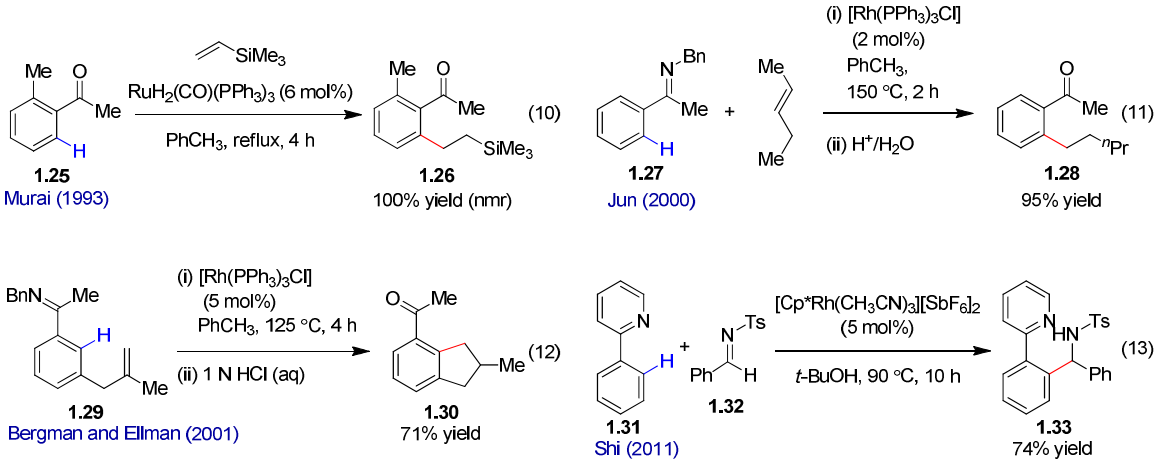
Figure 1.2 **Examples of Transition Metal Catalyzed C–H Functionalization**



The majority of the transformations based on C–H bond activation require an external acidic or basic additive. However, the use of such additives may often be incompatible with sensitive substrates. Since the early 1990s, low-valent rhodium (Rh^{I}) and ruthenium ($Ru^{0–II}$)

catalysts have been extensively studied for C–H activation reactions due to their propensity to form metal–hydride species.[13] Seminal contributions by Murai and coworkers showed that ruthenium catalysts can selectively activate C–H bonds in a variety of aromatic compounds, thereby leading to addition to olefins (Figure 1.3, eq 10).[14] Subsequently, in 2000, Jun reported that the scope of this reaction could be extended to isomerizable alkenes by using a rhodium catalyst and an imine as the directing group (Figure 1.3, eq 11).[15] Bergman and Ellman further broadened the reach of this chemistry to encompass intramolecular reactions (Figure 1.3, eq 12).[16] Recently, the groups of Shi, and Bergman and Ellman independently reported the addition of phenylpyridines to aldimines via rhodium-catalyzed C–H activation (Figure 1.3, eq 13).[17]

Figure 1.3 **Transition Metal Catalyzed C–H Functionalization Under Neutral Conditions**



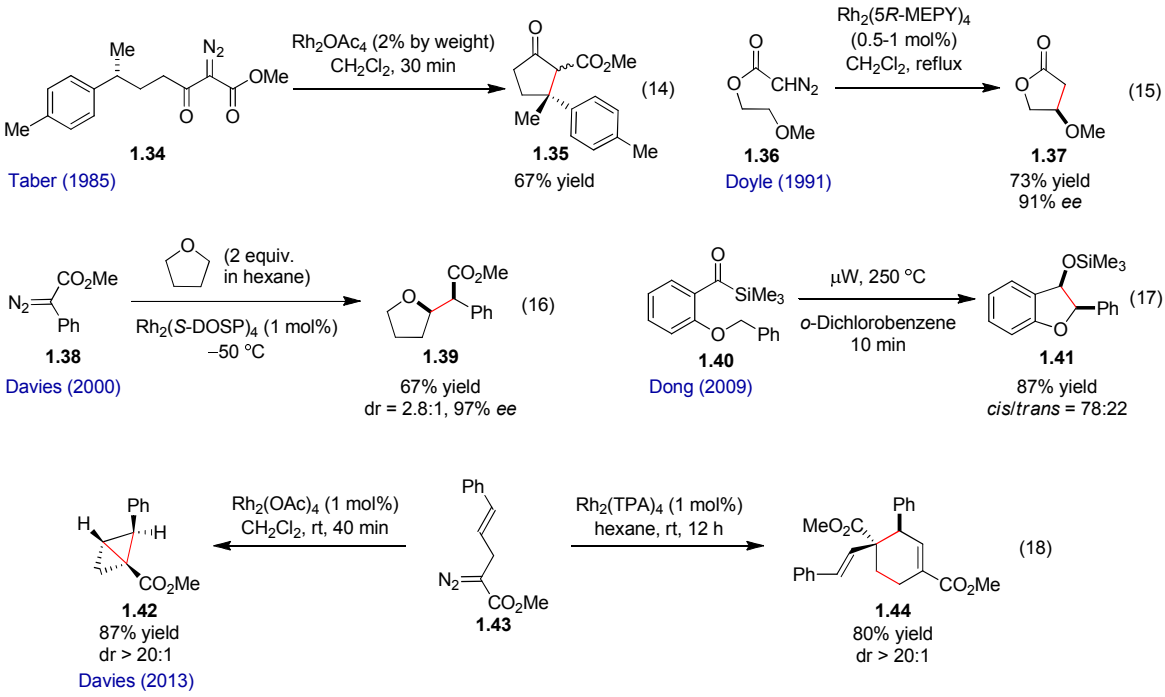
The development of neutral processes for C–H activation is crucial for a wide substrate tolerance and, hence, is highly desirable. In a vast majority of these cases, directing groups on the substrates are indispensable as a means to achieve site-specific selectivity.

1.3 C–H Bond Functionalization by Carbene Insertion

Transition metal catalyzed C–H functionalization processes essentially bank on a C–H "activation" step in which a metal inserts into a C–H bond. As an alternative, C–H functionalization via carbene insertion into a C–H bond provides an efficient strategy for constructing C–C bonds.[18] Carbenes can be generated from diazoalkanes under photochemical or thermal conditions or by the use of transition metals.[19] Transition metal catalysts that can stabilize a carbene by forming metal carbenes are optimal for transferring the carbene moiety into a C–H bond and copper, rhodium and ruthenium stand out as having great potential.[20]

The earliest examples of C–H insertion showed limited selectivity[21] and their synthetic utility was mostly limited to intramolecular reactions in geometrically rigid systems.[22] Wenkert[23] and Taber[24] studied the intramolecular processes with diazocarbonyl compounds which showed that the dirhodium tetraacetate catalyst exhibited great potential. Subsequently, Taber reported that rhodium-catalyzed intramolecular insertion into a C–H bond proceeded with retention of configuration (Figure 1.4, eq 14).[25] Enantioselective intra- and inter-molecular C–H insertion has been successfully developed by Doyle[26] and Davies[27] (for example: Figure 1.4, eqs 15 and 16). While the majority of the carbene insertions have focused on diazocarbonyl compounds as the carbene precursors, Dong and coworkers reported using siloxycarbenes generated from acylsilanes by microwave-assisted Brook rearrangement to functionalize benzylic C(sp^3)–H bonds (Figure 1.4, eq 17).[28] More recently, Davies' group developed a rhodium-catalyzed divergent reaction of α–allyldiazoesters to form either bicyclobutane or cyclohexene derivatives depending upon the catalyst employed (Figure 1.4, eq 18).

Figure 1.4 **Examples of Carbene Insertion into C–H Bonds**

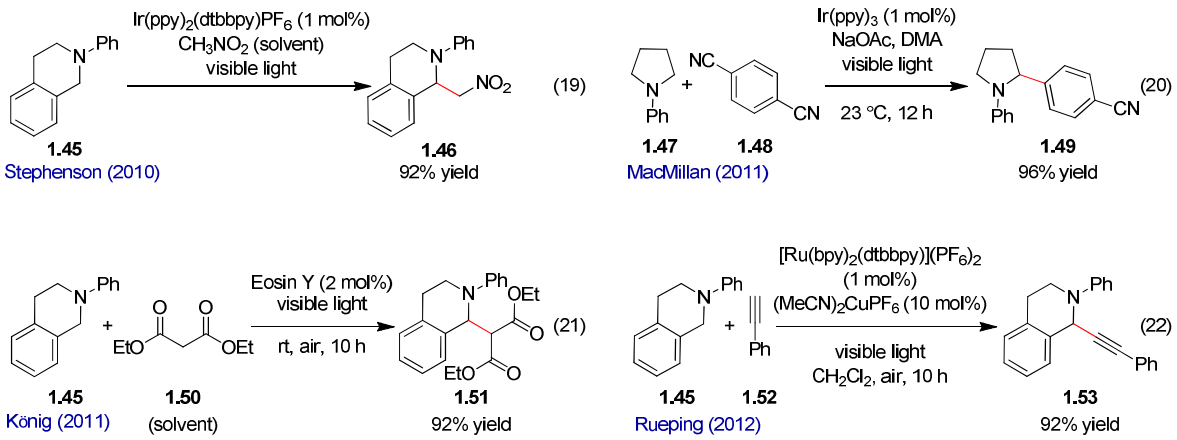


1.4 Photoredox C–H Bond Functionalization

Organic photochemical reactions have been popularly used as synthetic tools in organic chemistry.[29] In recent years, the combination of visible-light catalysis and functionalization of C–H bonds adjacent to heteroatoms has attracted considerable interest.[30] In 2010 the pioneering work from the Stephenson group demonstrated the ability of visible light to achieve C–H bond functionalization adjacent to tertiary *N*-arylamines in the presence of a photosensitizer (Figure 1.5, eq 19).[31] MacMillan and coworkers reported an interesting photoredox amine C–H arylation reaction, which was discovered using an accelerated serendipity strategy (Figure 1.5, eq 20).[32] In another study, König and coworkers demonstrated that activation of C–H bonds adjacent to nitrogen atoms in *N*-aryltetrahydroisoquinolines can be achieved by subjecting them to the redox-active organic dye Eosin Y (Figure 1.5, eq 21).[33] More recently, Rueping and coworkers

described a dual catalytic system, which consists of a photoredox catalyst and a metal catalyst, to afford propargylic amines by functionalization of C(sp^3)–H bonds of *N*-aryl or *N*-alkyl tetrahydroisoquinolines (Figure 1.5, eq 22).[34]

Figure 1.5 **Examples of Photoredox C–H Bond Functionalization**

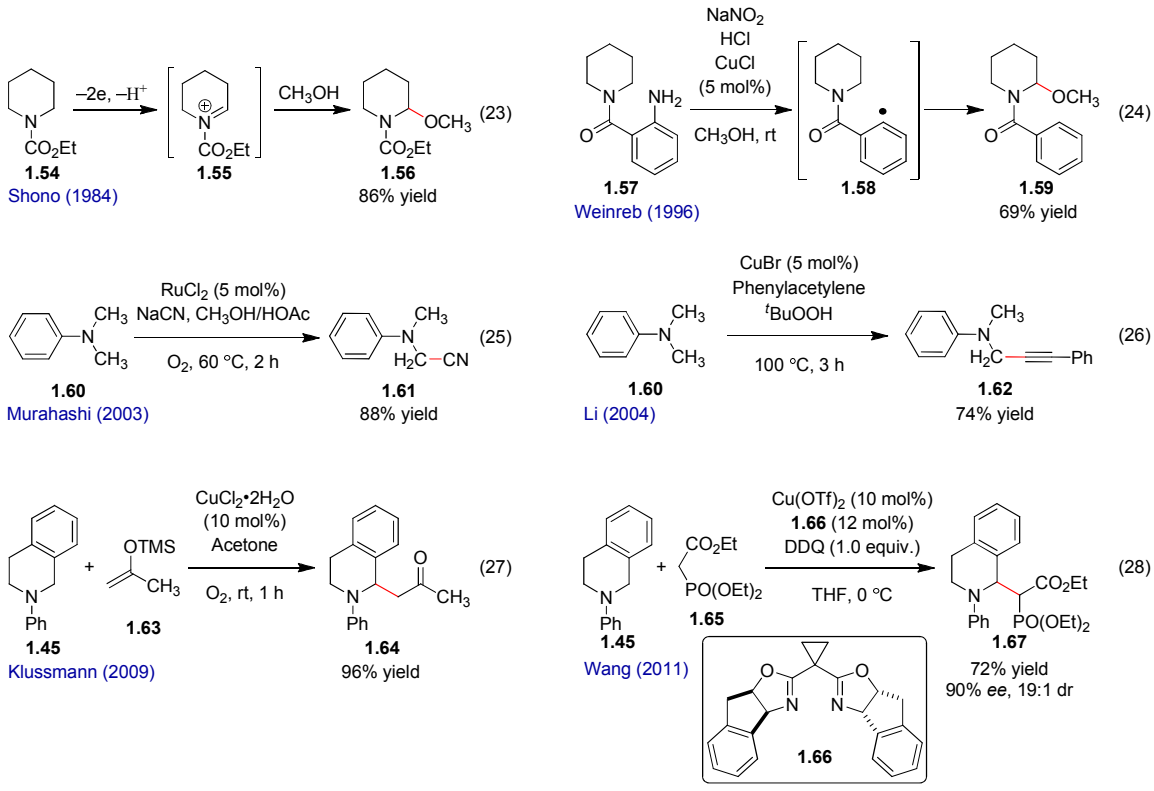


1.5 C–H Bond Functionalization by Oxidation/Oxidative Coupling

One of the earliest known examples of oxidative coupling of *N*-heterocycles was disclosed by Shono where electrochemical anodic oxidation was applied to access an intermediate *N*-acyliminium ion which was subsequently trapped with solvent, leading to the corresponding *N*,*O*-acetal (Figure 1.6, eq 23).[35] Weinreb and coworkers developed a convenient alternative to this electrochemical oxidation which takes advantage of 1,5-hydrogen transfer followed by oxidation and trapping of the *N*-acyliminium ion by methanol to furnish α-methoxybenzamide (Figure 1.6, eq 24).[36] In 2003, Murahashi and coworkers reported a ruthenium-catalyzed oxidative cyanation of tertiary amines that proceeded under fairly mild conditions using oxygen as the stoichiometric oxidant (Figure 1.6, eq 25).[37] Ensuingly, Li and coworkers developed an effective copper-catalyzed oxidative cross coupling between amines and terminal alkynes (Figure

1.6, eq 26)[38] and further broadened the scope of the reaction to introduce the enantioselective version[39] as well as a variety of functionalities at the α-position of cyclic tertiary amines.[40] The Klussmann group described performing the oxidative copper-catalyzed coupling of *N*-aryl tetrahydroisoquinolines with a variety of silyl enolate and silyl ketene acetal nucleophiles to produce the corresponding β-aminoketone derivatives (Figure 1.6, eq 27).[41] Wang and coworkers developed a chiral copper(II)/bisoxazoline complex catalyzed oxidative enantioselective cross-coupling method for the synthesis of α-alkyl amino esters and β-amino phosphonate derivatives (Figure 1.6, eq 28).[42] Besides copper, other transitions metals like iron,[43] vanadium[44] and several others[45] have been successfully applied for oxidative coupling of C–H bonds.

Figure 1.6 **Examples of C–H Oxidation/Oxidative Coupling**

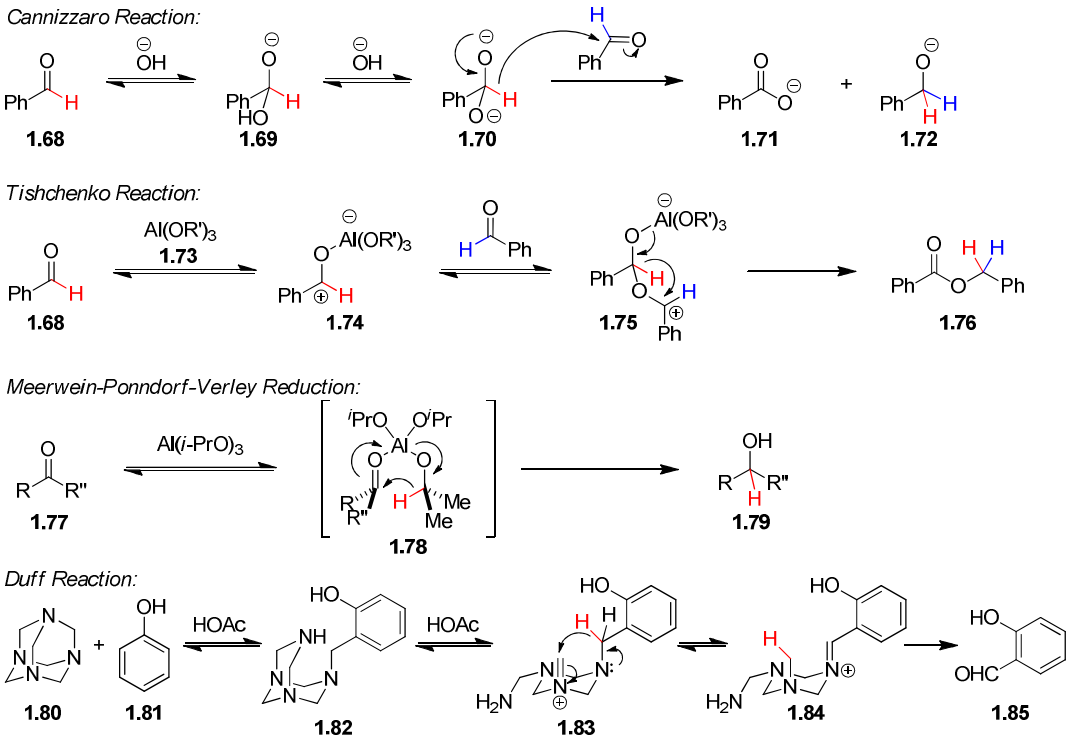


1.6 C–H Bond Functionalization via Hydride Transfer

While most of the prevalent methods for α-functionalization of tertiary amines involve transition metals and/or the use of an external oxidant, hydride transfer approaches present a complementary and convenient alternative for functionalizing C–H bonds.[46] There are many different classical organic reactions, for instance, Cannizzaro,[47] Tishchenko,[48] Meerwein-Ponndorf-Verley,[49] and Duff[50] reactions, that involve inter- or intra-molecular hydride transfer as a key step (Figure 1.7).

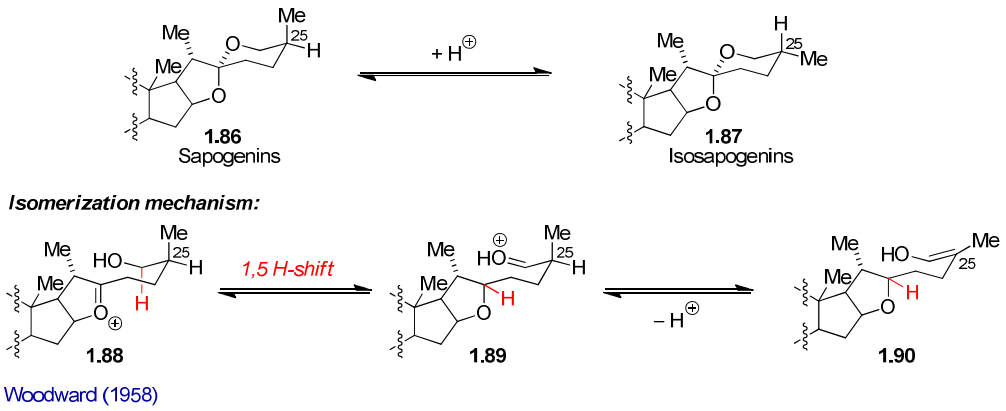
Several reports have emerged that utilize intramolecular α-functionalizations of tertiary amines for the construction of highly functionalized molecular structures. This approach is frequently associated with a 1,5- or 1,6-hydride shift, followed by ring closure.

Figure 1.7 **Organic Reactions in which a H–shift is the Pivotal Step**



An early report of hydride transfer was disclosed by Woodward and coworkers in 1958.[51] In this seminal work, they proposed that the acid-catalyzed isomerization of sapogenins **1.86** to the iso-analogs **1.87** proceeds by a redox mechanism, where the key step involves a reversible 1,5-hydride transfer involving the oxonium ion intermediate **1.88** (Scheme 1.1). Notable contributions from Carlson, Cohen and many others set the initial stage for studies of reaction cascades initiated by hydride shifts.[52]

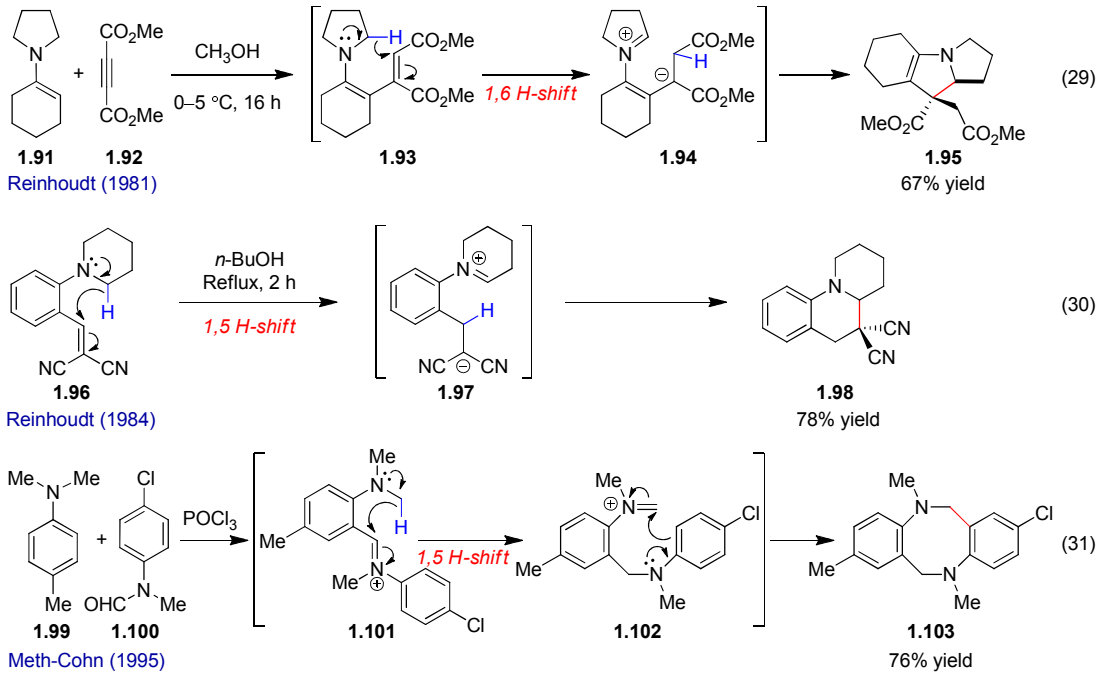
Scheme 1.1 **Acid-Catalyzed Isomerization of Steroidal Sapogenins at C-25**



Reinhoudt and coworkers reported that the reaction of enamines such as **1.91** with the electron-deficient acetylene dimethyl acetylenedicarboxylate (**1.92**) in a polar protic solvent leads to the formation of the pyrrolizine compound **1.95**.[53] It was proposed that after the formation of the initial Michael adduct **1.93**, 1,6-hydride shift takes place to form a dipolar intermediate **1.94**, which subsequently undergoes ring closure to form a new five-membered ring (Figure 1.8, eq 29). Later on, they further revealed that 2-vinyl-*N*,*N*-dialkylanilines such as **1.96**, which possess two geminal electron-withdrawing groups in the vinyl moiety, undergo 1,5-hydride shift under thermal conditions in a polar solvent to form the 1,5-dipolar intermediate **1.97**.[54] Ensuing C–C formation leads to the heterotricyclic compound **1.98**, concomitant with the construction of a six-membered ring (Figure 1.8, eq 30). In 1995, Meth-Cohn reported the cyclization reaction involving *para*-substituted *tert*-aniline (**1.99**) with *N*-formylated *sec*-aniline (**1.100**) in phosphoryl

chloride to form the corresponding diazocine **1.103**.[55] The reaction has been proposed to involve Vilsmeier formylation at the *ortho* position of the *tert*-aniline to form intermediate **1.101**, followed by a 1,5-hydride shift to form intermediate **1.102**. The resulting iminium ion intermediate eventually undergoes ring closure by virtue of attack from the *ortho*-position of the aromatic ring, thereby leading to the formation of an eight-membered ring (Figure 1.8, eq 31).

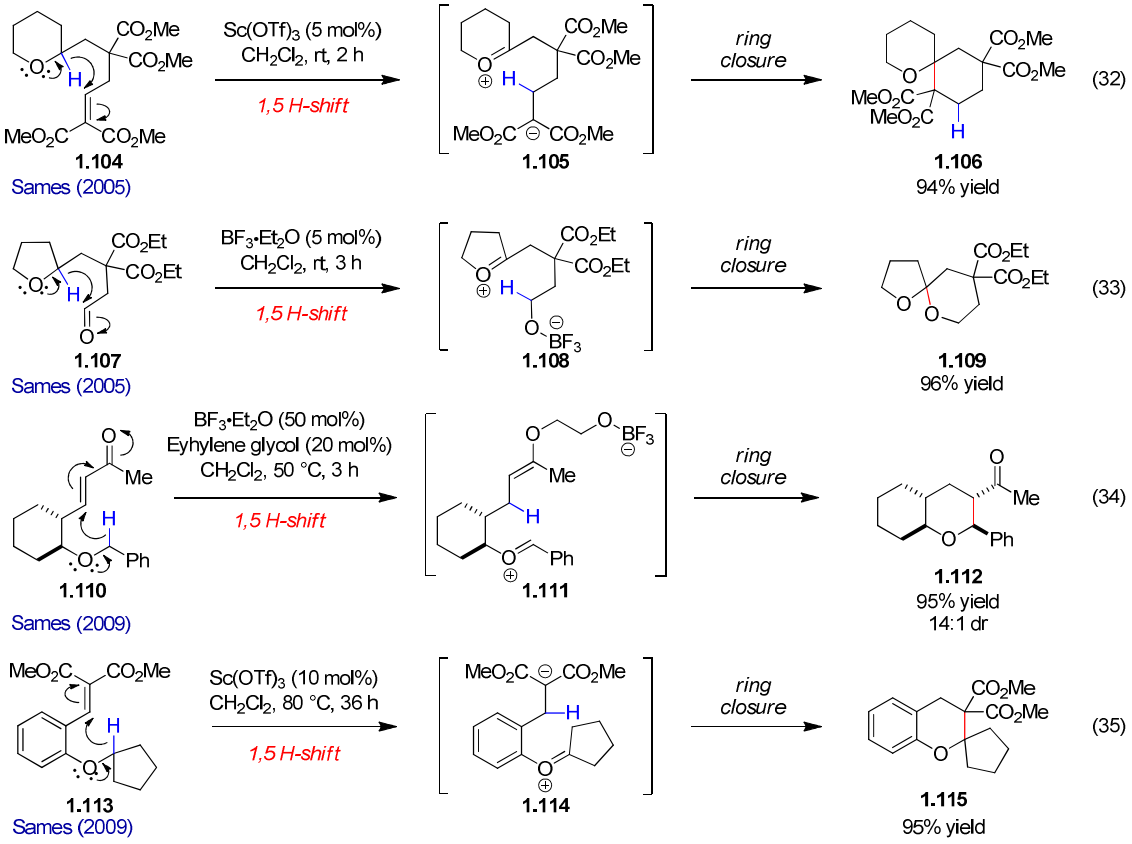
Figure 1.8 **Early examples of Hydride Shift Reactions**



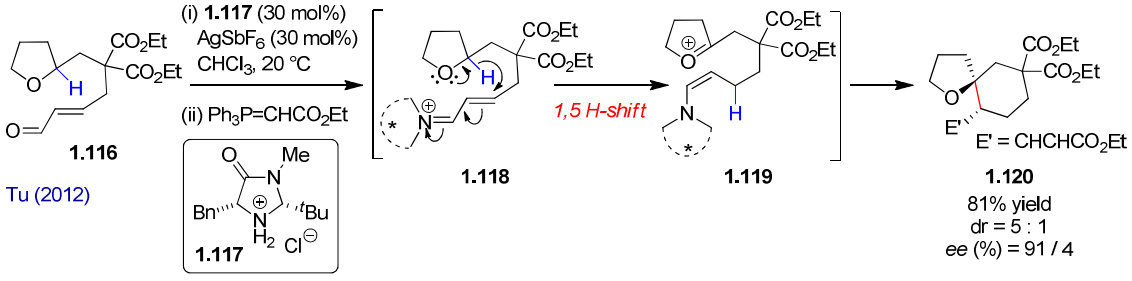
Functionalization of C–H bonds adjacent to oxygen have been explored by the Sames group.[56] Typically, the ether substrates are tethered with a pendant electron-deficient moiety at the 2-position which results in the targeted C–H bond being aligned in a 1,5-relationship with the electrophilic site. Upon treatment with catalytic amounts of Lewis acids, 1,5-hydride transfer from the position adjacent to oxygen occurs to form an oxonium ion intermediate. Subsequent ring closure leads to the formation of a new C–C or C–O bond, accompanied by the generation of spiro or bicyclic ring systems (Figure 1.8, eqs 32–35). Recently, Tu and coworkers developed an organocatalytic enantioselective approach for the functionalization of the α-C–H bond of ethers.[57]

The reaction between a cyclic ether containing a pendant α,β-unsaturated side chain **1.116** and a chiral organocatalyst **1.117** leads to formation of chiral iminium ion intermediate **1.118**, which initiates a 1,5-hydride shift. The resulting oxonium ion and enamine moieties combine to give chiral spiroether **1.120** (Scheme 1.2).

Figure 1.9 **C–H Bond Functionalization of Ethers Initiated by Hydride Shift**

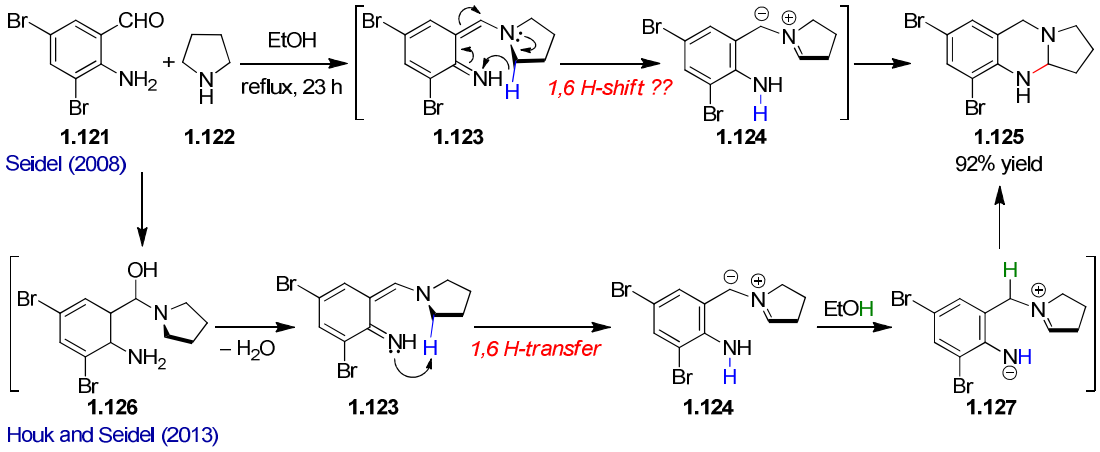


Scheme 1.2 **Catalytic Enantioselective C–H Bond Functionalization of Ether**



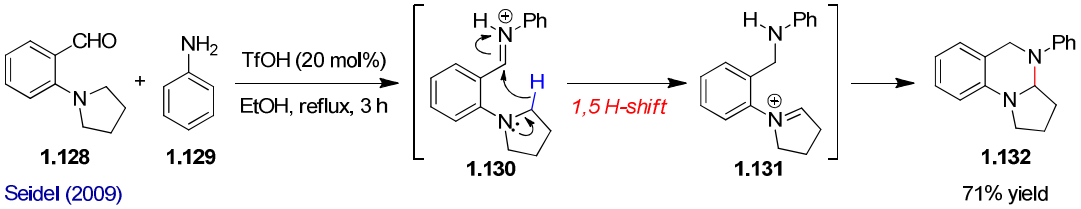
In 2008, our group introduced an efficient protocol for the synthesis of ring-fused aminals by metal-free, mild C–H functionalization of nitrogen heterocycles.[58] It was initially thought that one of the plausible pathways involved condensation of *o*-aminobenzaldehyde with an amine leads to the quinoidal intermediate **1.123** via deprotonation of an intermediate iminium ion (not shown), which could then undergo a 1,6-hydride shift to form azomethine ylide intermediate **1.124**. Sequential ring closure thereafter delivers the cyclic aminal **1.125** (Scheme 1.3). Later on, computational and experimental studies by Houk and Seidel *et. al.* confirmed that the mechanism involves a direct progression of hemiacetal **1.126** to the quinoidal intermediate **1.123**, and not via iminium ion species as was previously anticipated.[59] Intramolecular 1,6-proton transfer then leads to the azomethine ylide **1.124**, which goes on to give the final product **1.125**.

Scheme 1.3 **Formation of Cyclic Aminals**



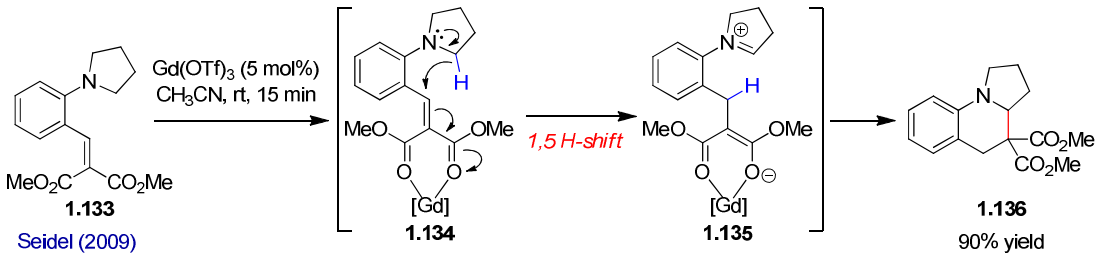
Subsequently, the strategy of cyclic aminal formation was expanded to include Brønsted acid-promoted processes in the reaction between *o-tert*-aminobenzaldehydes and amines.[60] This redox process involves an *in situ* generation of iminium ion **1.130**, followed by 1,5-hydride shift and ring closure (Scheme 1.4).

Scheme 1.4 **Brønsted Acid Promoted Formation of Cyclic Aminals**

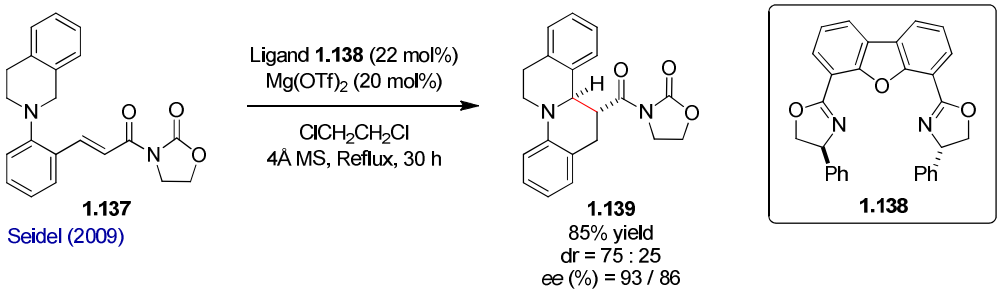


In a related account, Lewis acid was successfully employed in catalyzing 1,5-hydride shifts and ring closures leading to the formation of tetrahydroquinoline derivatives (Scheme 1.5).[61] Following this, the first examples of catalytic enantioselective hydride shift/ring closure reaction cascades were disclosed.[62] It has been shown that the use of catalytic amounts of magnesium triflate in conjunction with chiral DBFox ligand **1.138** led to the formation of ring-fused tetrahydroquinolines in excellent yield and enantioselectivity, but modest diastereoselectivity (Scheme 1.6).

Scheme 1.5 **Lewis Acid Catalyzed Hydride Shift/Ring Closure Sequence**

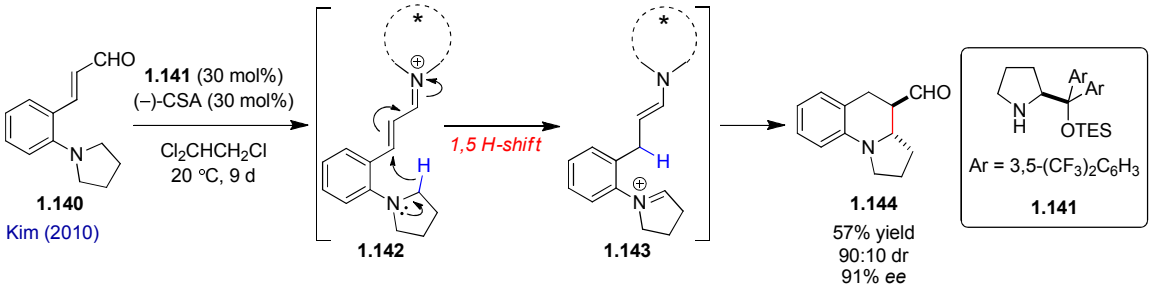


Scheme 1.6 **Catalytic Enantioselective Formation of Ring-Fused Tetrahydroquinolines**



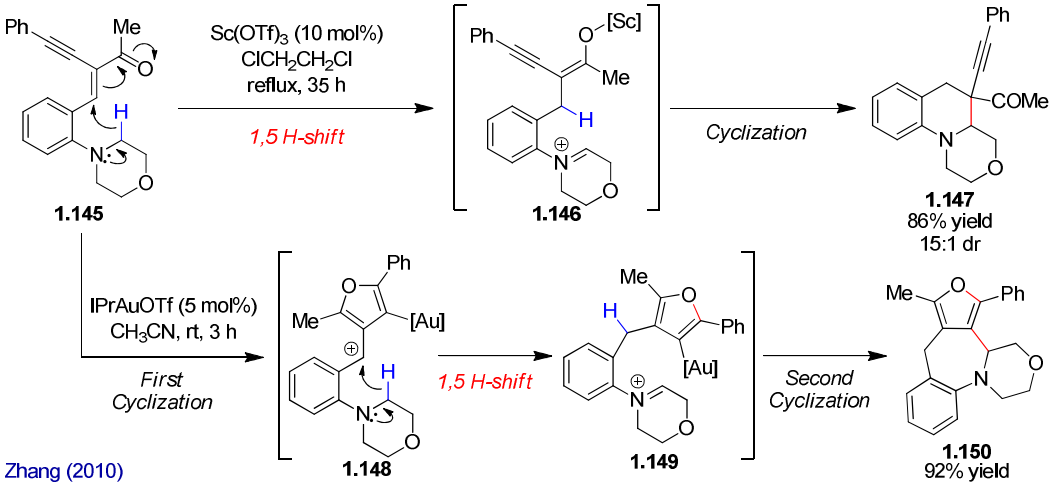
Kim and coworkers employed the 1,5-hydride transfer approach followed by ring closure to develop an organocatalytic enantioselective synthesis of tetrahydroquinoline derivatives, which was promoted by a Brønsted acid.[63] When *ortho*-dialkylamino-substituted cinnamaldehydes **1.140** were allowed to react in the presence of a chiral amine catalyst **1.141** and (–)-camphorsulfonic acid as an additive, ring-fused tetrahydroquinolines were obtained in moderate yields but good diastereoselectivity and enantioselectivity (Scheme 1.7).

Scheme 1.7 **Organocatalytic Enantioselective Hydride Shift/Ring Closure**



Zhang and coworkers developed an intramolecular redox process for the synthesis of ring-fused tetrahydroquinoline and tetrahydrobenzazepine derivatives in which the product selectivity could be conveniently regulated by the type of catalyst employed.[64] While the use of oxophilic scandium triflate led to 1,5-hydride shift/cyclization to furnish the ring-fused tetrahydroquinoline **1.147**, catalytic amounts of carbophilic gold(I) catalyst afforded the ring-fused tetrahydrobenazepine **1.150** (Scheme 1.8).

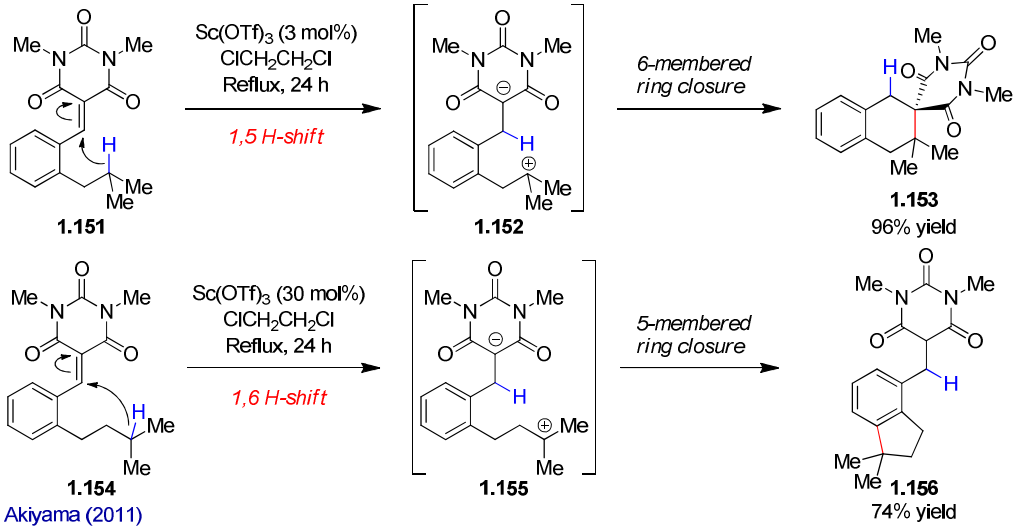
Scheme 1.8 **Lewis Acid Initiated Hydride Shift for Selective Formation of Ring-Fused Tetrahydro-isoquinolines and Tetrahydroazepines**



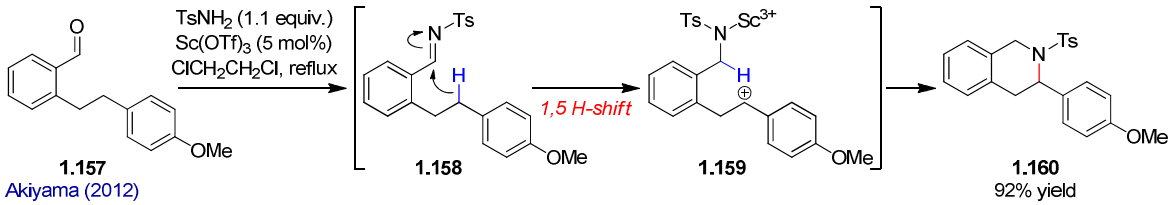
Recently, Akiyama and coworkers reported that an aliphatic tertiary carbon center can readily participate in a hydride shift process.[65] In this Lewis acid-catalyzed method, 2-alkyl-substituted benzylidene barbituric acids were employed as substrates, and the reaction sequence is believed to be driven forward by the generation of a stable tertiary carbocation intermediate. Substrate **1.151**, which contains a β-dialkyl side chain, readily underwent the desired 1,5-hydride shift from the tertiary aliphatic position, and ensuing cyclization led to the tetraline derivative **1.153**. Interestingly, the substrate **1.154**, which possesses a γ-dialkyl side chain, underwent a 1,6-hydride shift and ring closure to provide the indane derivative **1.156** (Scheme 1.9).

They further utilized this type of transformation, wherein hydride shift occurred without the assistance of an adjacent heteroatom, to realize an efficient route to access tetrahydroisoquinoline skeletons.[66] In this process, *in situ* formation of an imine **1.158** and 1,5-hydride shift/cyclization occurred successively to lead to the formation of tetrahydroisoquinoline derivatives **1.160** (Scheme 1.10).

Scheme 1.9 **Hydride Shift From an Aliphatic Tertiary Carbon Center**

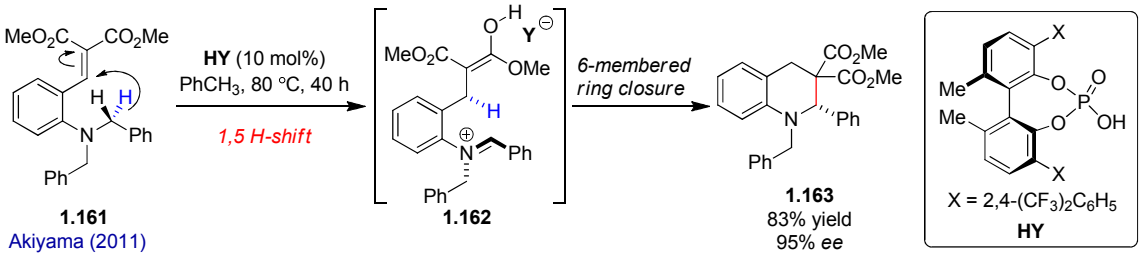


Scheme 1.10 **Lewis Acid Catalyzed C–H Bond Functionalization via Hydride Shift**



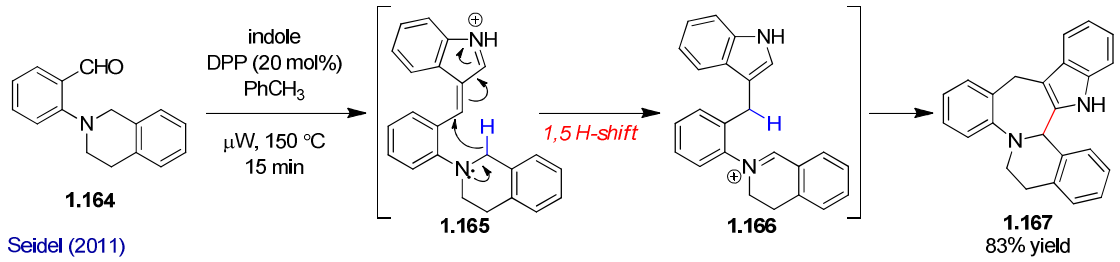
The Akiyama group disclosed an asymmetric C–H bond functionalization catalyzed by a chiral phosphoric acid.[67] This process involves the selective activation of enantiotopic hydrogen by means of chiral phosphoric acid via 1,5-hydride shift. Subsequent ring closure occurred predominantly from the same face as the transferred hydrogen to give the corresponding optically active tetrahydroquinoline (like **1.163**) in good to excellent enantioselectivity (Scheme 1.11).

Scheme 1.11 **Chiral Phosphoric Acid Catalyzed Asymmetric C–H Bond Functionalization via Hydride Shift**



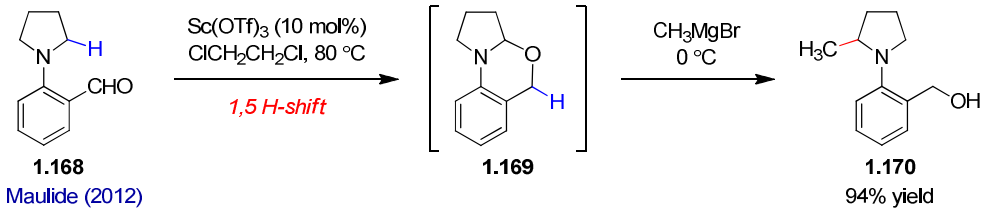
In the recent past, our group presented a novel one-step indole annulation cascade for getting access to indole-fused benzazepines such as **1.167**.[68] In this diphenyl phosphate (DPP) catalyzed reaction, the tertiary aminobenzaldehyde **1.164** initially undergoes condensation with the doubly nucleophilic indole to form the azafulvenium ion intermediate **1.165**. Sequential intramolecular 1,5-hydride transfer and ring-closure through the pendant nucleophilic site (2-position of indole) leads to generation of a new seven-membered ring and, consequently, formation of polycyclic indolobenzazepine **1.167** (Scheme 1.12).

Scheme 1.12 **Indole Annulation Reaction Facilitated by Hydride Shift**



Maulide and coworkers applied this intramolecular redox protocol where the adjacent position of certain tertiary amines contains great propensity to undergo 1,5-hydride transfer for the C–H functionalization by means of sacrificial reduction of a neighboring carboxaldehyde group (Scheme 1.13).[69]

Scheme 1.13 **C–H Bond Functionalization Directed by Sacrificial Reduction of Neighboring Carboxaldehyde via Hydride Shift**



1.7 Objectives

Redox-neutral functionalization of C–H bonds has emerged as an efficient and powerful method towards introducing molecular complexity easily and in few synthetic steps. These processes generally exhibit perfect redox economy and, as such, have been widely employed for assembling polycyclic frameworks of varied biologically and pharmaceutically relevant building blocks. While numerous examples of C–H bond functionalization have been elucidated in the literature, many challenges still remain. For example, although there has been increasing number of reports on regioselective and efficient functionalization of C–H bonds adjacent to heteroatom, most involve an oxidative approach, including photoredox reactions. Secondly, for accessing ring-substituted cyclic secondary amine derivatives, α-amino acids have mostly been utilized for site-specific functionalization via oxidative decarboxylative coupling. Replacing the α-amino acid with a simple amine and performing the transformation in a redox-neutral manner would be a significant advance.

In the research highlighted in this dissertation, the primary focus concerns the development of new redox-neutral strategies for the mild functionalization of C–H bonds. It is important to address the current limitations and provide more accessible solutions to the above mentioned challenges. We hope that our findings can address some prevalent shortcomings and

provide some convenient answers for future studies. Taking this into consideration, Chapter II presented in this dissertation deals with non-pericyclic functionalization of azomethine ylides. Chapter III concerns redox-neutral α-functionalization of amines. In unrelated work, Chapter IV covers a second project which involved the synthesis of various novel chiral bisoxazoline ligands and their corresponding bimetallic complexes.

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Chapter II

Non-Pericyclic Functionalization of Azomethine Ylides

2.1 Background

Azomethine ylide can be characterized as a zwitterionic species that has four electrons spread across the three-atom C–N–C unit.[1] As such, it can be represented by four resonance forms as shown in Figure 2.1. There are several methods by which azomethine ylide can be generated.[2] Figure 2.2 summarizes different ways by which it can be achieved.

Figure 2.1 **Resonance Forms of Azomethine Ylide**

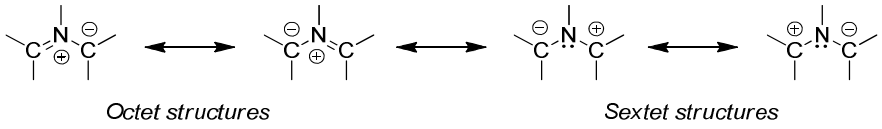
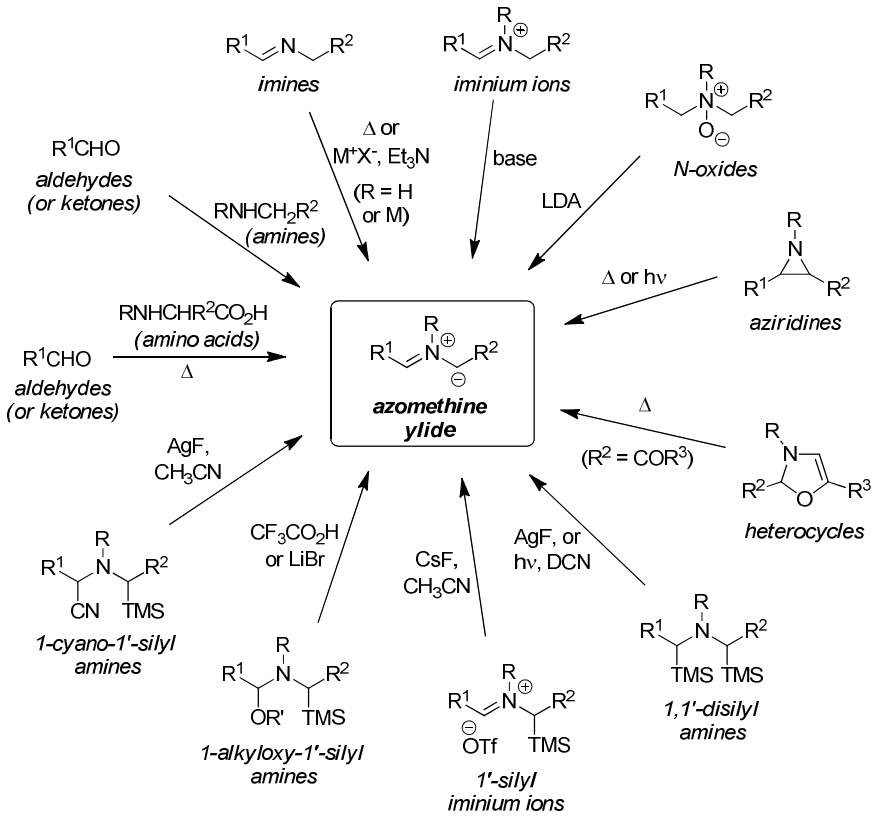


Figure 2.2 **Methods for Generation of Azomethine Ylides**



In 1970, Rizzi first disclosed the intermediacy of azomethine ylides in the condensation of an amino acid with benzophenone (Figure 2.2, eq 1).[2a] Since then it has been well recognized that the condensation of amino acids and aldehydes leads to the formation of azomethine ylides.[3] These reactive intermediates have been widely used in synthesis. The 1,3-dipolar cycloaddition of azomethine ylides is a versatile and effective way for accessing five-membered nitrogen heterocycles (Figure 2.3, eq 2).[4] When the azomethine ylide is in conjugation with a double bond or a 1,3-diene moiety, it has been shown to undergo 1,5- and 1,7-electrocyclizations (Figure 2.3, eqs 3 and 4).[5]

Figure 2.3 **Azomethine Ylide as Intermediates**

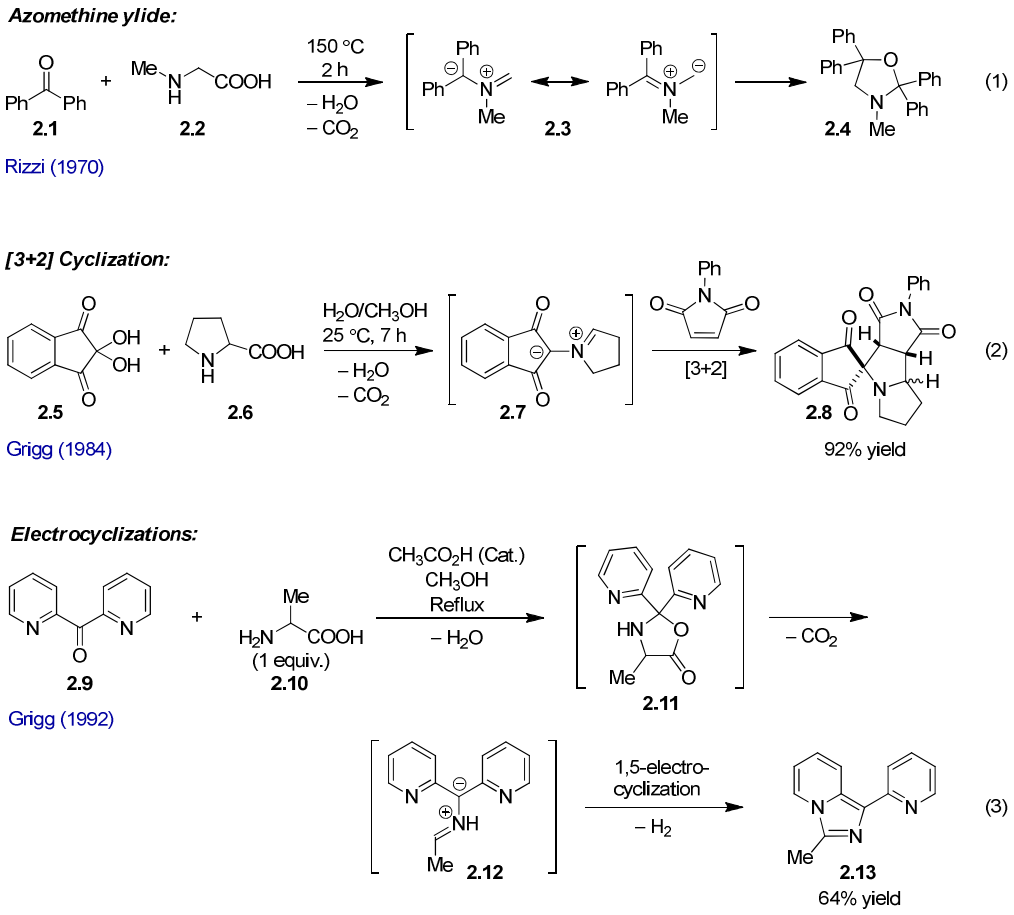
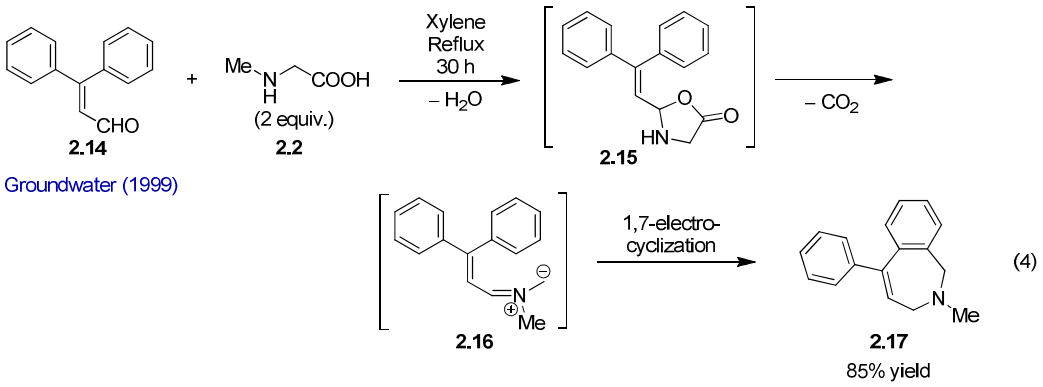


Figure 2.3 **Azomethine Ylide as Intermediates (contd.)**



However, despite its synthetic utility in cycloadditions, there has been relatively little effort to explore the chemistry of azomethine ylides in non-pericyclic reactions. An unique example of a non-pericyclic annulation was disclosed by Cohen *et al*., where the reaction between proline and sterically congested 2-hydroxyacetophenone **2.18** gave *N,O*-acetal **2.20**.[6] Although the scope of this reaction is quite limited, it is worth noting the intriguing feature of this sterically sensitive reaction. Substrates which lack the *ortho*-methyl substituent failed to provide the corresponding product (Figure 2.4, eq. 5).

Figure 2.4 **Non-Conventional Reactions of Azomethine Ylides**

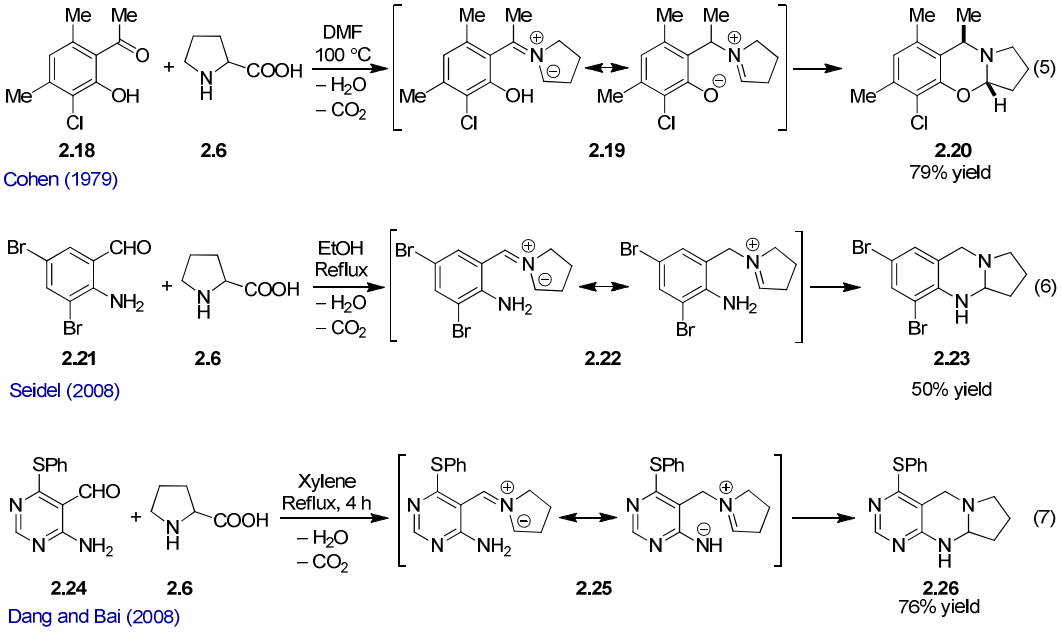
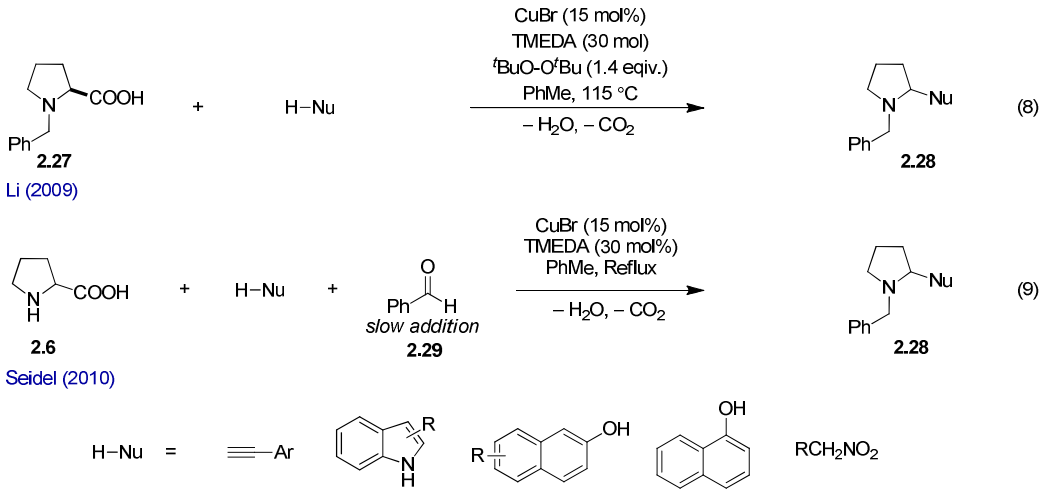


Figure 2.4 **Non-Conventional Reactions of Azomethine Ylides (contd.)**



Seidel and co-workers discovered a novel method for the formation of ring-fused aminals by condensing *ortho*-aminobenzaldehydes **2.21** with amino acids **2.6**.[7] Azomethine ylides can be generated by decarboxylative condensation between proline and aminobenzaldehyde. This reactive intermediate can be protonated in the presence of the protic solvent to form the corresponding iminium ion, followed by nucleophilic attack by the neighboring amine group to form a C–N bond. This efficient method leads to the formation of ring-fused aminals **2.23** (Figure 2.4, eq. 6). Subsequently, Dang and Bai described a related transformation between aminoformylpyrimidines **2.24** and different *N*-alkyl amino acids **2.6** (Figure 2.4, eq. 7).[8]

Li and co-workers reported copper- and iron-catalyzed oxidative decarboxylative couplings of the sp^3-hybridized carbon of α-amino acids leading to C–C bond formation.[9] This intermolecular reaction required superstoichiometric amounts of an oxidant to functionalize the *N*-benzyl α-amino acids **2.27**. This methodology was applied to various $C(sp^3)$–C(sp), $C(sp^3)$–$C(sp^2)$ and $C(sp^3)$–$C(sp^3)$ bond forming reactions (Figure 2.4, eq. 8). Concurrently, our group reported a related decarboxylative three-component coupling reactions of α-amino acids and aldehydes with various nucleophiles (Figure 2.4, eq. 9).[10]

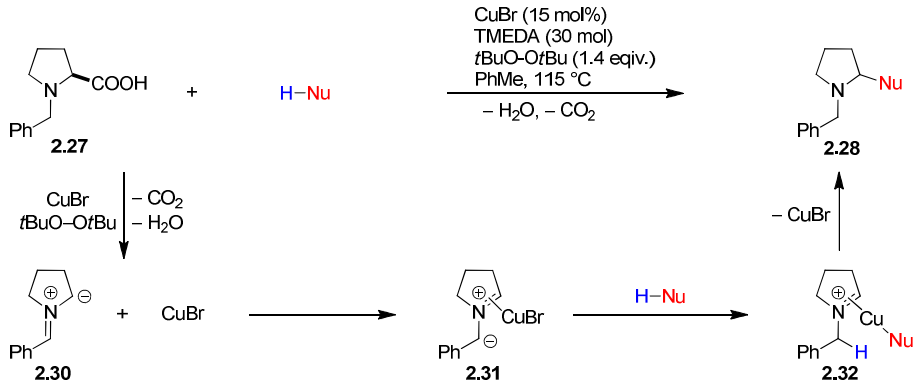
In light of the aforementioned seminal work, we became increasingly interested to delve more into this type of non-traditional functionalization of azomethine ylides. Of the limited examples known for this type of reaction, most are concerned with the formation of C–O and C–N bonds in the ring closure step. Of late, Li and our group have independently reported examples of intermolecular C–C bond-forming reactions by utilizing this strategy. This transformation is thought to proceed by protonation of the initially formed azomethine ylide by the pronucleophile (e.g., indole, 2-naphthol, etc.), leading to the formation of iminium ion intermediate. Subsequent attack by the nucleophilic center leads to α-functionalized heterocycles, concomitant with the formation of a new C–C bond.

2.2 Azomethine Ylide Annulation

2.2.1 General Consideration

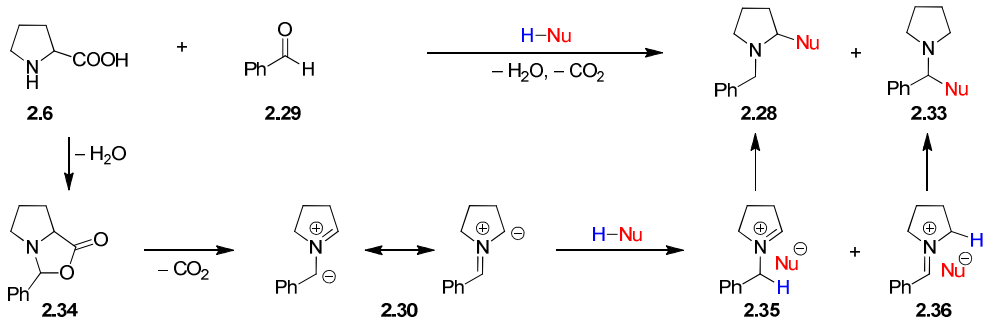
Recently Li and co-workers developed interesting C–C bond-forming reactions of α-amino acids. These decarboxylative reactions require a pre-formed *N*-benzyl amino acid **2.27** and the use of superstoichiometric amounts of an oxidant along with a metal catalyst.[9a,9b] Azomethine ylides **2.30**, formed after oxidative decarboxylation, were proposed as intermediates which possibly bind to the metal catalyst. Subsequent coupling with the nucleophile leads to the desired α-functionalized product **2.28** (Scheme 2.1).

Scheme 2.1 **Li's Proposed Mechanism for the Oxidative Decarboxylative Functionalization of *N*-Alkyl Amino Acids**



Concurrently, our group developed the concept of utilizing *in situ* generated azomethine ylides in closely related reactions.[10] Upon exposing benzaldehyde to proline under thermal conditions, azomethine ylide **2.30** is formed via decarboxylation of the initially formed oxazolidinone **2.34**.[11] Protonation of **2.30** by the relatively acidic proton of the pronucleophile (H–Nu) leads to the iminium ion pairs **2.35** and **2.36**. Ensuing nucleophilic addition leads to the coupling products **2.28** and **2.33**. The charge distribution in the azomethine ylide is an important factor in determining the regioselective outcome of the reaction. For instance, an electron deficient substituent can better accommodate a partial negative charge in the benzylic position. Subsequent protonation leads to the internal iminium ion pair **2.35**, which ultimately leads to product **2.28**. In contrast, electron rich character reduces the tendency of protonation at the benzylic position, thereby paving the way for the formation of more of the product **2.33** (Scheme 2.2).

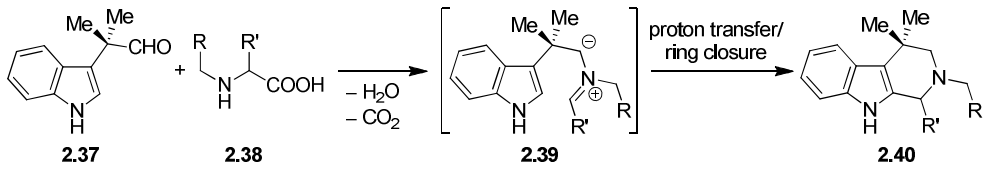
Scheme 2.2 **Three-Component Coupling of α-Amino Acids**



The intermolecular decarboxylative three-component coupling reactions of α-amino acids with various nucleophiles were shown to proceed in a protic environment. Protonation of the intermediate azomethine ylide by the pronucleophile (*e.g.*, 2-naphthol) to form an iminium ion pair, that ultimately leads to the formation of α-functionalized products, is thought to be a key feature of this type of reaction. To be able to perform this transformation in an intramolecular fashion will be a significant advance as it can potentially lead to generation of polycyclic ring systems in a single synthetic step.

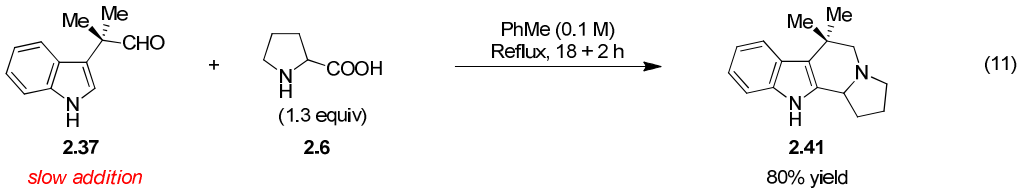
2.2.2 Decarboxylative Annulation of Azomethine Ylides

We envisaged that by linking the aldehyde moiety with a pronucleophile (**2.37**) and allowing the species to react with an amino acid **2.38**, we can gain access to products **2.40** that would otherwise require several steps to synthesize by conventional Pictet-Spengler approach.[12] This unique azomethine ylide annulation does not require a fully conjugated pathway and would provide rapid access to polycyclic ring systems in a single redox-neutral step (eq. 10).



(10)

To our delight, slow addition of the indole-aldehyde **2.37** to a refluxing solution of proline in toluene led to the desired product **2.41** in 80% yield (eq. 11). In an otherwise analogous reaction, when the aldehyde and proline were added together and heated under reflux in toluene, it gave **2.41** in only slightly reduced yield (75%).

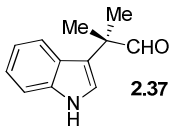
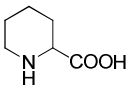
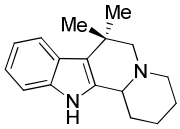
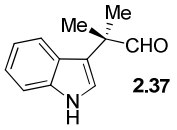
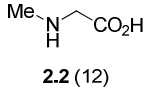
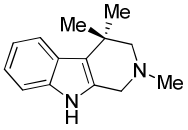
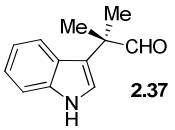
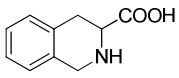
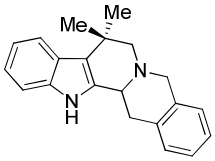
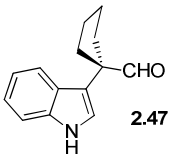
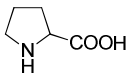
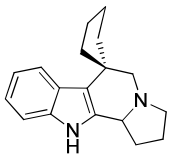
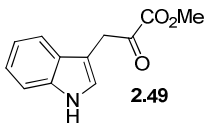
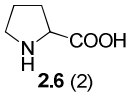
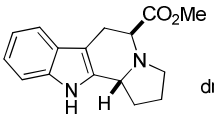
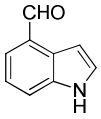
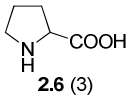
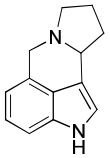
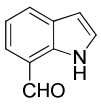
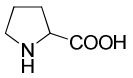
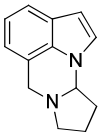
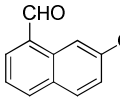
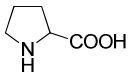
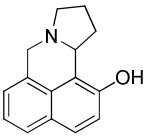


(11)

Apart from proline, other amino acids also readily reacted with indole-aldehyde **2.37**. Pipecolic acid provided the corresponding annulated product **2.43** in excellent yield (90%), although it required an additional 24h for complete consumption of the aldehyde (Table 2.1, entry 1). Sarcosine did not undergo the desired transformation when allowed to react with indole-aldehyde **2.37** under the refluxing toluene conditions. When the reaction was performed at higher temperature by refluxing in xylenes, the desired annulated product **2.44** was obtained in 61% yield. In this case, an excess (12 equiv.) of the amino acid was required to ensure that the reaction went to completion (Table 2.1, entry 2). This can be rationalized by the fact that sarcosine forms nonstabilized azomethine ylide with an aldehyde and subsequently it can undergo decomposition to dimethyl amine (**2.60**), giving back the aldehyde **2.37** (Scheme 2.3). When amino acid **2.45** was employed, no annulation product was observed when heated under reflux in toluene or xylenes. Upon microwave irradiation of the reaction mixture in xylenes, in addition to the expected product **2.46** (52% yield), the corresponding regioisomeric product **2.72** was obtained in 25% yield (Table 2.1, entry 3). This interesting transformation where regioisomeric products were obtained suggests the possibility that there might be additional isomerization of either the initially formed azomethine ylide or iminium ion prior to ring closure. Indole-aldehyde **2.47**, bearing a spirocyclic ring, when allowed to react with proline in refluxing toluene, gave the desired product in good yield (Table 2.1, entry 4). The α-keto ester **2.49**, an enolizable substrate,

reacted readily with proline in refluxing toluene to give the expected annulation product as a mixture of diastereomers (Table 2.1, entry 5).

Table 2.1 **Scope of the Decarboxylative Annulation**[a]

entry	aldehyde	amino acid (equiv)	product		time[b] [h]	yield [%]
1	 **2.37**	 **2.42** (1.5)		**2.43**	18+24	90
2	 **2.37**	 **2.2** (12)		**2.44**	20	61
3[c]	 **2.37**	 **2.45** (2)		**2.46**	20 min	52
4	 **2.47**	 **2.6** (1.3)		**2.48**	18+2	79
5	 **2.49**	 **2.6** (2)		**2.50** dr = 75:25	1.75	52
6	 **2.51**	 **2.6** (3)		**2.52**	18+2	63
7[d]	 **2.53**	 **2.6** (2)		**2.54**	30 min	61
8	 **2.55**	 **2.6** (1.5)		**2.56**	30 min	91

[a] Reactions were performed under reflux in PhMe (entries 1,4,8), in xylenes (entries 2,3,5,7) or in *n*BuOH (entry 6). [b] Slow addition time + additional reaction time (entries 1,4,6) or reaction time (other entries). [c] under μW irradiation at 250 °C. [d] under μW irradiation at 200 °C.

The indole-aldehydes shown above (Table 2.1, entries 1–5) are examples which demonstrate that this unprecedented process does not require a conjugated reaction pathway. Subsequently, we evaluated aldehydes directly linked to π–systems. Slow addition of 4-formyl indole **2.51** to a refluxing solution of proline in *n*-butanol led to the formation of the desired product **2.52** in 63% yield (Table 2.1, entry 6). The analogous aldehyde, 7-formyl indole **2.53**, readily underwent the transformation upon microwave irradiation with proline in xylenes (Table 2.1, entry 7). 8-Formyl-2-naphthol **2.55** showed great reactivity with proline under thermal conditions, giving rise to the desired annulation product **2.56** in 91% yield after 30 minutes. Although these three instances indicate that conjugated π–systems can undergo azomethine-mediated decarboxylative annulation, they are distinctly different from the conventional electrocyclization processes. The azomethine ylide intermediates derived from **2.51**, **2.53** and **2.55** cannot attain a fully conjugated reaction pathway (Figure 2.5).

Scheme 2.3 **Side Process Involving Decomposition of the Azomethine Ylide Derived from Aldehyde and Sarcosine**

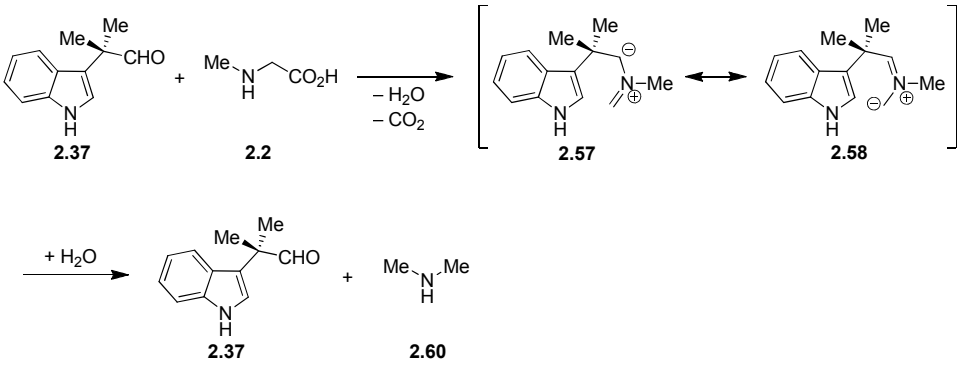
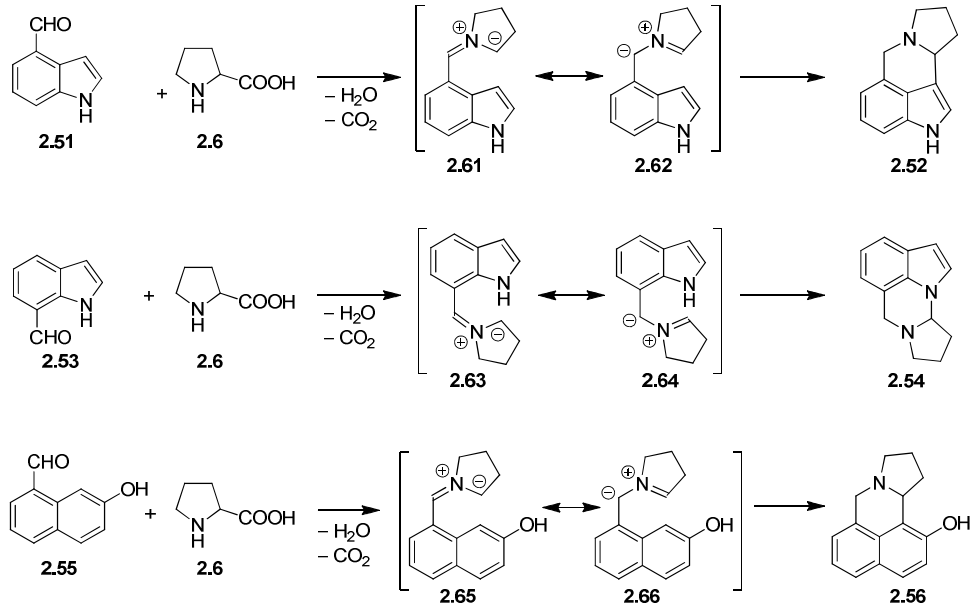


Figure 2.5 **Major Contributing Resonance Structures of Azomethine Ylide Intermediates Derived From 2.51, 2.53 and 2.55 Are Not Fully Conjugated**



2.2.3 Annulation of Azomethine Ylides Derived from Simple Amines

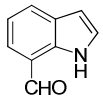
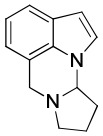
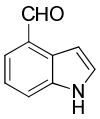
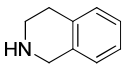
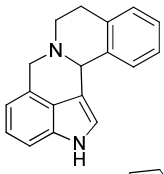
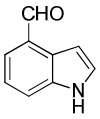
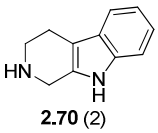
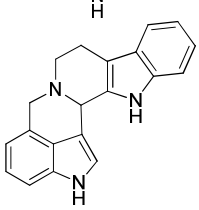
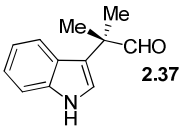
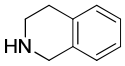
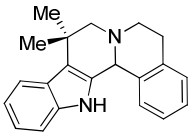
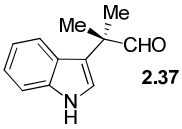
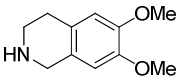
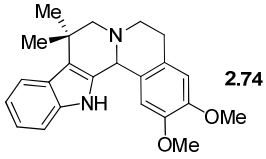
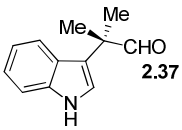
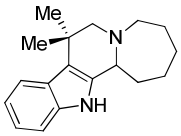
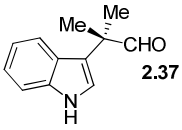
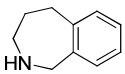
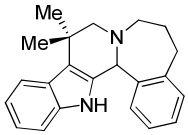
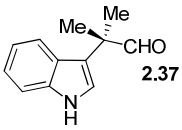
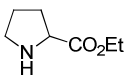
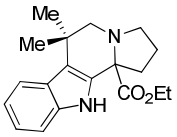
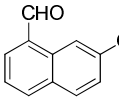
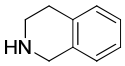
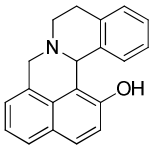
Azomethine ylides are known to be generated by the deprotonation of iminium ions.[3c] This suggests that simple secondary amines and amino acid esters can be used as reaction partners for the indole and 2-naphthol derived aldehydes.

We initiated the investigation by allowing 7-formylindole **2.53** to react with pyrrolidine in *n*-butanol. Gratifyingly, the annulation product was obtained in 81% yield (Table 2.2, entry 1). 4-Formylindole **2.51** readily underwent the reaction with 1,2,3,4-tetrahydroisoquinoline **2.68** and β-carboline **2.70** to give the corresponding desired products in moderate yields (Table 2.2, entries 2 and 3). Apart from aldehydes having conjugated π–systems, the non-conjugated indole-aldehyde **2.37** was also explored. Under thermal conditions, **2.37** showed poor reactivity with tetrahydroisoquinolines **2.68** and **2.73**. However, microwave irradiation and using xylenes as a solvent, improved the reaction outcome (Table 2.2, entries 4 and 5). The reaction of indole-aldehyde **2.37** with azepane **2.75**

in *n*-butanol required microwave irradiation to furnish **2.76** in 43% yield after 5 h (Table 2.2, entry 6). The tetrahydroisoquinoline analog **2.77** readily gave the corresponding polycyclic product **2.78** in 54% yield (Table 2.2, entry 7). Under optimal reaction conditions, the azomethine ylide intermediate derived from indole-aldehyde **2.37** and proline ester **2.79** readily participated in annulation to give **2.80**, bearing one quaternary carbon center, in 73% yield (Table 2.2, entry 8). Finally, 8-formyl-2-naphthol **2.55** exhibited excellent reactivity with tetrahydroisoquinoline **2.68**, furnishing the desired product **2.81** in 81% yield under toluene reflux (Table 2.2, entry 9). This may be related to the higher acidities of naphthols, which would facilitate the azomethine ylide protonation step.

Although cyclic secondary amines and proline ester proved to be optimal reaction partners for the non-decarboxylative annulation, the substrate scope is somewhat limited than the corresponding decarboxylative annulation using amino acids. For example, aliphatic amines showed poor reactivity. This may be attributed to the difficulty of forming the azomethine ylide intermediate by deprotonation of the iminium ion.

Table 2.2 **Scope of the Non-Decarboxylative Annulation**[a]

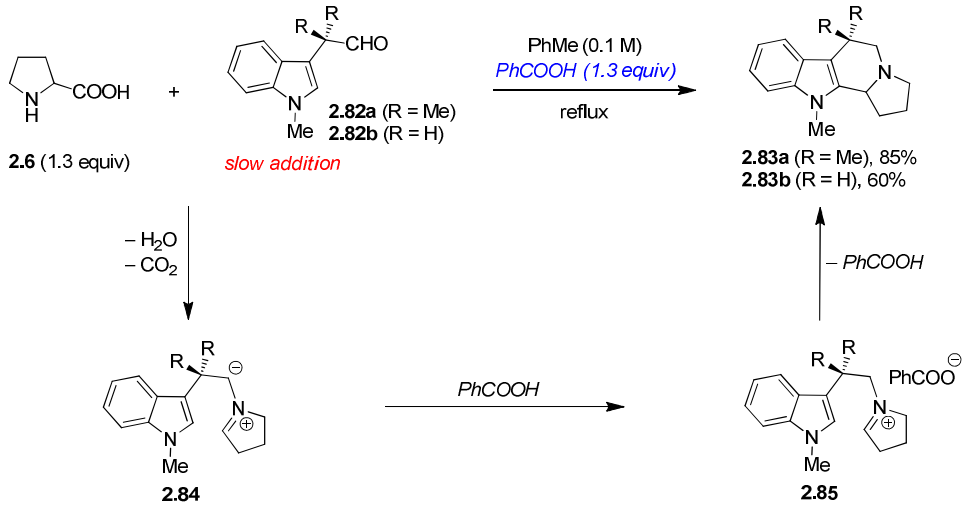
entry	aldehyde		amine (equiv)	product		time[b] [h]	yield [%]
1		**2.53**	 **2.67** (3)		**2.54**	18+1	81
2		**2.51**	 **2.68** (3)		**2.69**	18+2	78
3		**2.51**	 **2.70** (2)		**2.71**	18+2	54
4[c]		**2.37**	 **2.68** (3)		**2.72**	20 min	64
5[d]		**2.37**	 **2.73** (3)		**2.74**	20 min	61
6[c]		**2.37**	 **2.75** (10)		**2.76**	5	43
7[c]		**2.37**	 **2.77** (5)		**2.78**	1	54
8[d]		**2.37**	 **2.79** (3)		**2.80**	20 min	73
9		**2.55**	 **2.68** (3)		**2.81**	30 min	81

[a] Reactions were performed under reflux in *n*BuOH (entries 1,2,3,6), in xylenes (entries 4,5,7,8) or PhMe (entry 9). [b] Slow addition time + additional reaction time (entries 1–3) or reaction time (remaining entries). [c] under μW irradiation at 250 °C. [d] under μW irradiation at 200 °C.

2.2.4 Mechanistic Insights

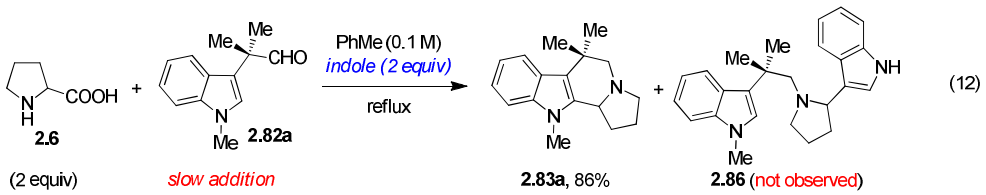
For the annulation reaction to proceed under the optimal reaction conditions, the appended nucleophile must bear an acidic proton. In order to confirm this hypothesis, we exposed the *N*-methylated indole-aldehydes **2.82a** and **2.82b** to standard reaction conditions. As expected, no reaction was observed between proline and either **2.82a** or **2.82b**. However, in the presence of benzoic acid, these reactions proceeded smoothly to give compounds **2.83a** and **2.83b** (Scheme 2.4). The external acid source serves to protonate the azomethine ylide intermediate **2.84** to form iminium ion **2.85** that finally cyclizes to form product. This clearly indicates that the azomethine ylide cannot undergo direct nucleophilic addition by itself and that protonation to form an iminium ion is crucial for the cyclization to happen.

Scheme 2.4 **Plausible Mechanism**



Next we sought to probe the preferred pathway for competing inter- and intra-molecular reactions. When the indole-aldehyde **2.82a** was allowed to react with proline in presence of an excess of indole, the azomethine ylide formed can be protonated by indole. The resulting iminium ion can potentially undergo two pathways – intra-molecular pathway leading to formation of **2.83a** or inter-molecular pathway giving rise to **2.86**. Interestingly,

2.83a was obtained as the sole product suggesting that indole assumes the role of an external acid (eq. 12).

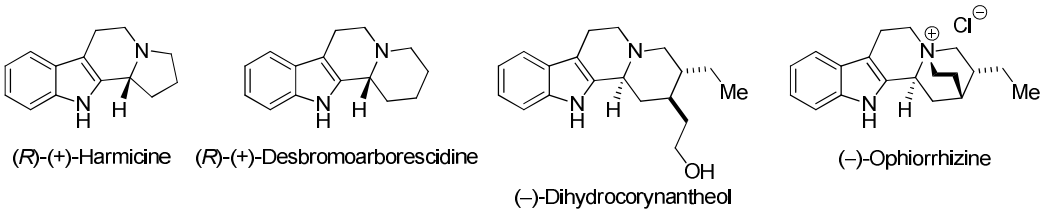


(12)

2.2.5 Summary

We have developed a new 1,6-annulation reaction of azomethine ylides. In general, reaction times can be shortened by the use of microwave irradiation. In cases where thermal conditions were sluggish, microwave irradiation enabled efficient preparation of products. The synthetic utility of the process was demonstrated by the rapid generation of polycyclic ring systems, including analogues of the alkaloid harmicine (**2.41**, **2.48**, **2.50**, **2.80** and **2.83**) (Figure 2.6).[13] It is anticipated that azomethine ylide annulations will find widespread use in the synthesis of natural products and related bioactive compounds.

Figure 2.6 **Alkaloid Harmicine and Some of its Analogues**



2.3 Redox Isomerization via Azomethine Ylide Intermediates

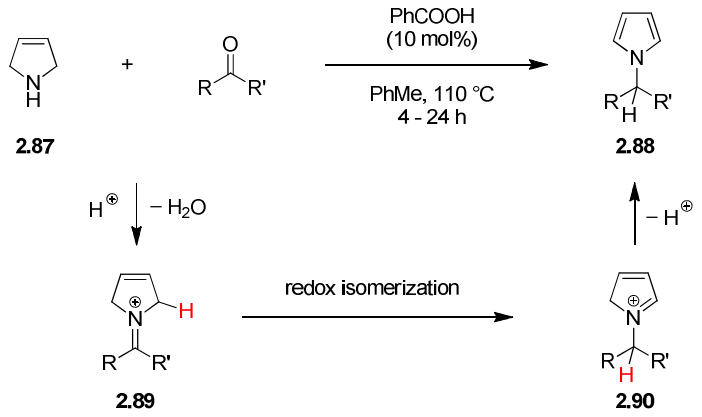
2.3.1 General Consideration

In recent times, there has been heightened interest in redox isomerization processes.[14] These processes have perfect redox economy and can afford a shortened synthetic sequence.

Redox-neutral reactions, such as thermal and acid catalyzed redox aminations have been explored to construct polycyclic frameworks as well as pharmaceutically important building blocks.

Tunge and co-workers illustrated an intriguing redox-neutral approach for the formation of *N*-alkyl pyrroles **2.88**.[15] In presence of a mild Brønsted acid catalyst, a wide array of aldehydes, ketones, and lactols were shown to undergo redox amination when allowed to react with 3-pyrroline (**2.87**). This reaction, apparently, utilizes the inherent reducing capacity of 3-pyrroline to furnish *N*-alkyl pyrroles. As proposed by the authors, the transformation proceeds through a redox isomerization process in which **2.89** and **2.90** are presumed to be key intermediates leading to the formation of pyrroles (Scheme 2.5).

Scheme 2.5 **Tunge's Redox-Neutral Pyrrole Formation**

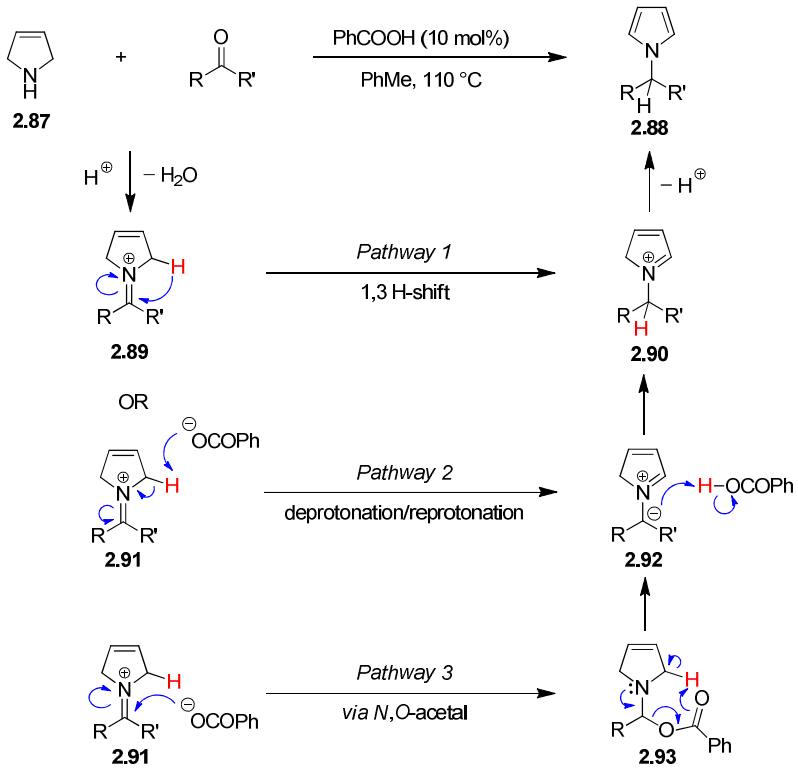


2.3.2 Evidence for Azomethine Ylide Intermediates

During the course of our earlier work on developing redox-neutral amine functionalizations,[16,17] the proposed mechanism of the reaction (Figure 2.7) caught our attention. The most straightforward pathway leading to **2.90** from **2.89** would involve a 1,3-hydride shift.[18] Nonetheless, orbital symmetry considerations state that for a migrating hydrogen, a 1,3-shift would have to occur antarafacially and thus represent an essentially geometry-forbidden pathway.[19] Moreover, taking into account the relatively mild reaction conditions, a 1,3-hydride shift seems to be unlikely (Figure 2.7, Pathway 1).

Upon considering alternative mechanisms, we proposed that deprotonation of the iminium ion **2.91** might lead to the azomethine ylide **2.92**.[20,21] Reprotonation of this dipolar intermediate leads to the iminium ion **2.90**. Ensuing loss of proton leads to aromatization and formation of the pyrrole (Figure 2.7, Pathway 2). Later, as part of a computational investigation by Yu and co-workers, it was suggested that the acid catalyst assisted azomethine ylide formation is the most probable process (Figure 2.7, Pathway 3).[22] *N*,*O*-Acetal **2.93**, which is expected to be in equilibrium with **2.91**, could lead to carboxylic acid extrusion in a concerted fashion leading to formation of azomethine ylide **2.92**.

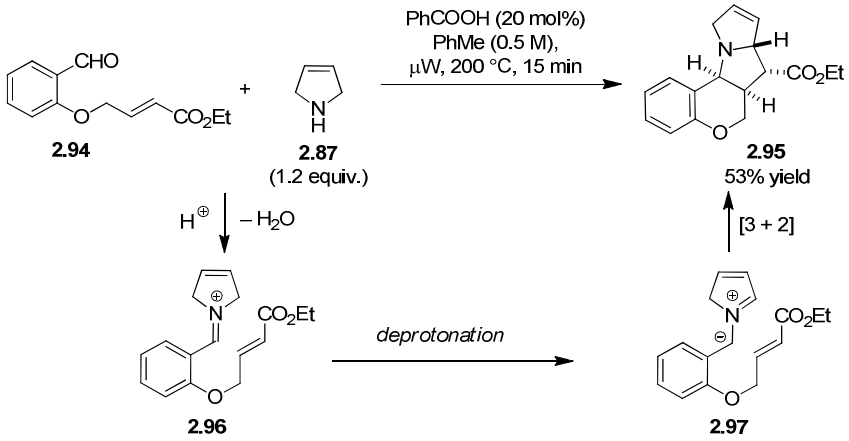
Figure 2.7 **Plausible Mechanisms for Pyrrole Formation**



In order to establish the intermediacy of azomethine ylides such as **2.92**, we decided to probe the reaction of 3-pyrroline (**2.87**) with an aldehyde that has a pendant dipolarophile and can be utilized to trap the dipolar intermediate. Aldehyde **2.94** has previously been used in intramolecular [3+2] cycloadditions with 1,2,3,4-tetrahydroisoquinoline and β-carboline.[20d] Indeed, the reaction between **2.94** and **2.87**, in presence of catalytic amounts of benzoic acid

under microwave irradiation, gave **2.95** in 53% yield. This interesting outcome where the expected [3+2] cycloaddition product **2.95** was obtained as a single diastereomer strongly suggests that azomethine ylides are likely intermediates in this redox-neutral transformation (Scheme 2.6).

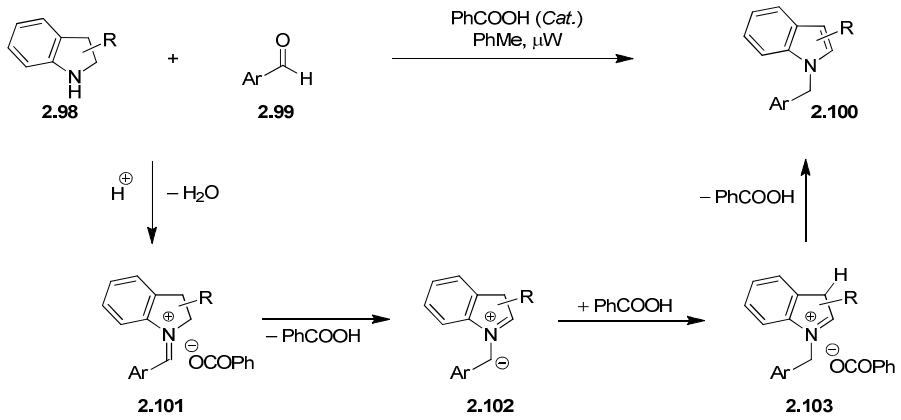
Scheme 2.6 **Evidence for Azomethine Ylide Intermediates**



2.3.3 Formation of *N*-Alkyl Indoles from Indolines and Aldehydes

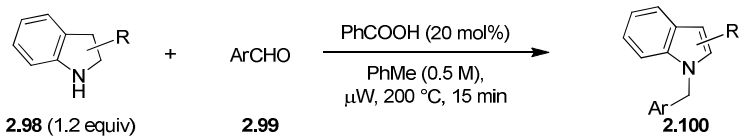
We envisioned applying this method to a closely related reaction – the formation of *N*-alkyl indoles **2.100** from indolines **2.98** and aldehydes **2.99**. Previous syntheses of **2.100** were limited to *N*-alkylation of preformed indoles.[23] This often suffers from the issue of regioselectivity. Despite the fact that iminium ions **2.101** derived from indolines and aldehydes might be rather less acidic than species such as **2.91**, these reactions were expected to proceed efficiently under microwave irradiation conditions (Scheme 2.7).

Scheme 2.7 **Proposed Pathway for Formation of *N*-Alkyl Indoles**

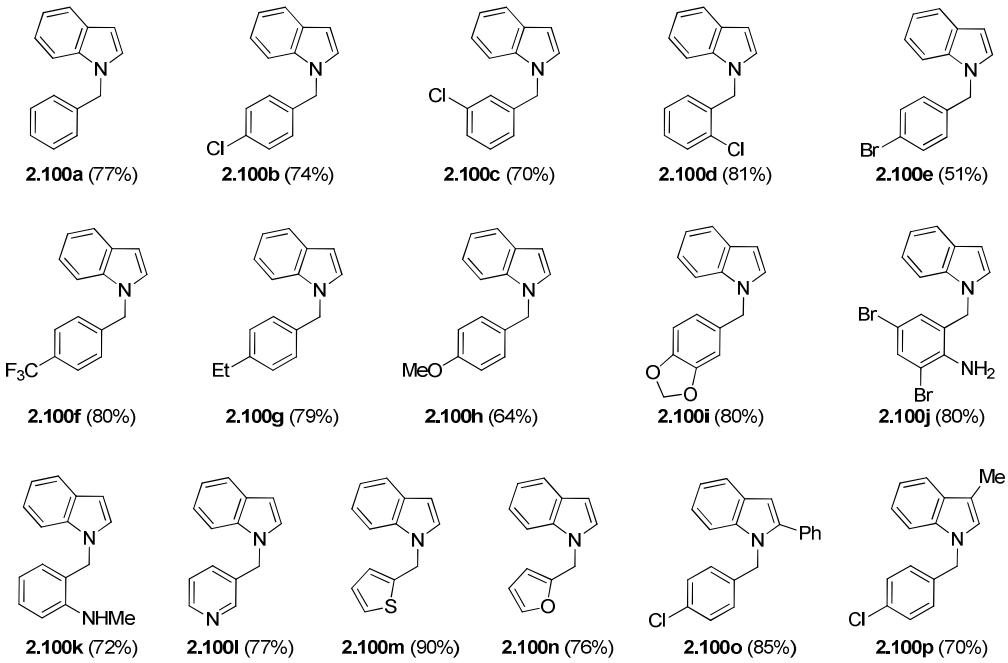


Under the catalysis of benzoic acid, the use of 1.2 equivalents of indoline was found to be optimal for the full consumption of the aldehyde. Several different aldehydes, possessing electron withdrawing as well as electron donating groups, proved to be viable substrates (Table 2.3, **2.100a** – **2.100i**). The reaction between indoline and aminobenzaldehydes led to the formation of only alkylated indoles in good yields. Interestingly, the other possible pathway, namely the formation of aminals, was not observed (Table 2.3, **2.100j** and **2.100k**). Heterocyclic aldehydes like pyridine, thiophene and furan aldehydes gave the alkylated indoles in good to excellent yields (Table 2.3, **2.100l** – **2.100n**). Substituted indolines like 2-phenylindoline and 3-methylindoline also readily underwent the desired transformation (Table 2.3, **2.100o** and **2.100p**). Enolizable aldehydes did not lead to formation of the corresponding *N*-alkyl indole, most likely due to the competitive formation of enamines.

Table 2.3 **Scope of the Synthesis of *N*-Alkylated Indoles**



2.98 (1.2 equiv) **2.99** **2.100**



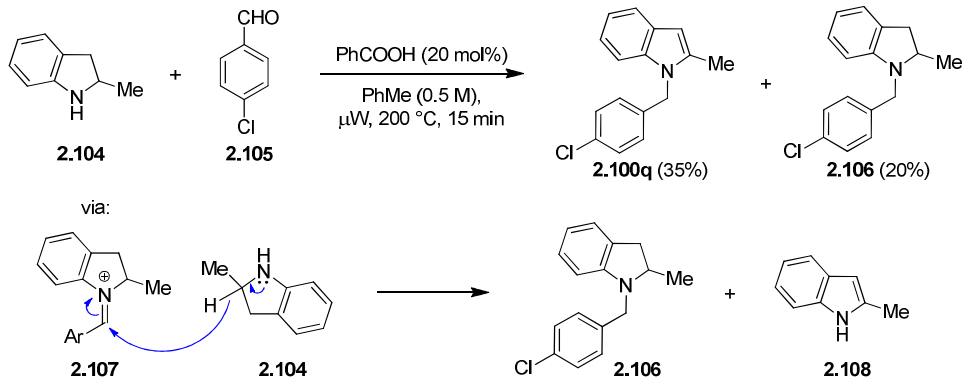
2.100a (77%) **2.100b** (74%) **2.100c** (70%) **2.100d** (81%) **2.100e** (51%)

2.100f (80%) **2.100g** (79%) **2.100h** (64%) **2.100i** (80%) **2.100j** (80%)

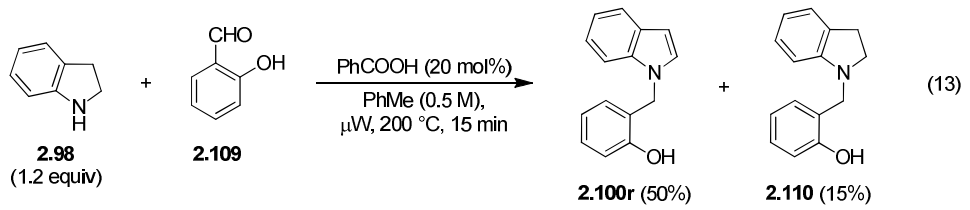
2.100k (72%) **2.100l** (77%) **2.100m** (90%) **2.100n** (76%) **2.100o** (85%) **2.100p** (70%)

Interestingly, for the reaction between 2-methylindoline (**2.104**) and *p*-chlorobenzaldehyde (**2.105**), apart from the expected *N*-alkylated indole product **2.100q**, we observed the formation of *N*-alkylated indoline **2.106** in 20% yield. An additional product formed in this reaction is 2-methylindole (**2.108**), which suggests that **2.106** is formed by intermolecular hydride transfer from 2-methylindoline to the initially formed iminium ion intermediate **2.107** (Figure 2.8).

Figure 2.8 **Redox Isomerization vs Intermolecular Hydride Transfer**



When indoline (**2.98**) was allowed to react with salicylaldehyde **2.109**, considerable amount of the reduced product was also observed. Although *N*-alkyl indole **2.100r** was still the major product (50% yield), the corresponding *N*-alkyl indoline **2.110** was isolated in 15% yield. This observation may be attributed to the presence of an acidic phenol proton. The phenolic proton likely makes regioselective deprotonation of the initial iminium ion to form the azomethine ylide intermediate more difficult. Therefore, the intermolecular hydride transfer pathway becomes more predominant as compared to analogous reactions with aldehydes lacking such an acidic functionality (eq 13).

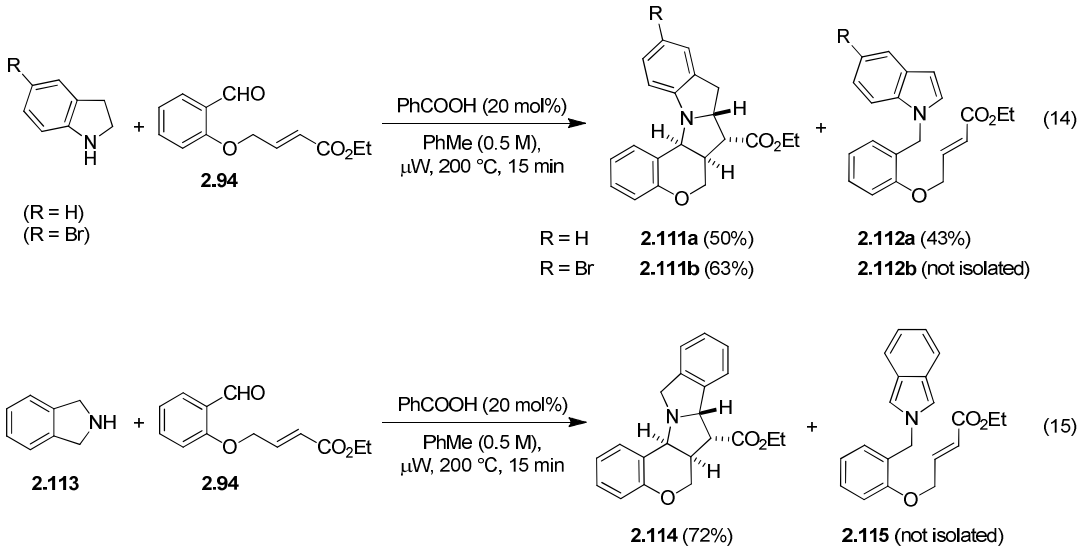


2.3.4 Intramolecular [3 + 2] Reaction

In order to establish the intermediacy of azomethine ylides in the formation of *N*-alkyl indoles, we performed [3 + 2] trapping experiments similar to the one with 3-pyrroline (**2.87**). Indeed, as anticipated, when indoline was allowed to react with aldehyde **2.94** under the optimized reaction conditions, the cycloaddition product **2.111a** was obtained as a single diastereomer in 50% yield. The reaction was also accompanied by the formation of the

corresponding *N*-alkylated indole **2.112a** in 43% yield (Figure 2.9, eq 14). The reaction between 5-bromoindoline and aldehyde **2.94** led to the formation of **2.111b** as a crystalline product, isolated as a single diastereomer in 63% yield. In this instance, although none of the *N*-alkylated indole **2.112b** was observed, the corresponding *N*-alkylated indoline was isolated in 5% yield. In an otherwise analogous reaction, when isoindoline (**2.113**) was exposed to **2.94**, the product **2.114** was obtained in 72% yield (Figure 2.9, eq 15).

Figure 2.9 **Intramolecular [3 + 2] vs Indole Formation**



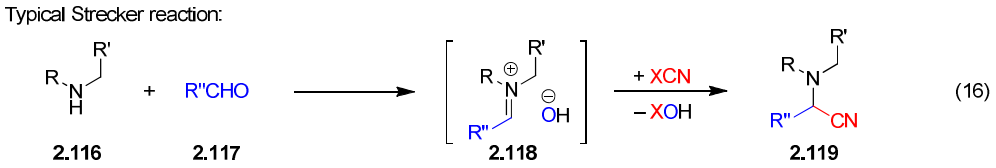
2.3.5 Summary

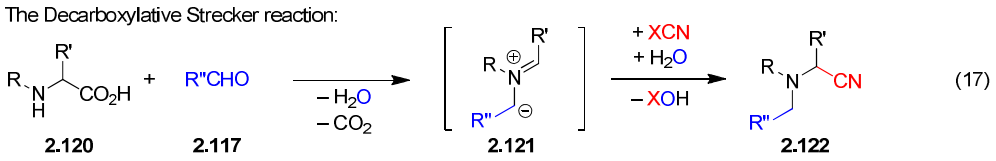
We have developed a facile redox-neutral method for the formation of *N*-alkylated indoles from simple indolines and aldehydes. Because it is orbital symmetry forbidden, the more apparent and direct 1,3-hydride shift mechanism is unlikely. Instead, this reaction involves the intermediacy of azomethine ylides, as established by intramolecular trapping experiments. We speculate that such *in situ* generated azomethine ylides will be used for numerous reactions in the future.

2.4 The Decarboxylative Strecker Reaction

2.4.1 General Consideration

α-Amino nitriles are versatile precursors for the synthesis of amino acids and various other building blocks.[24] First devised by Adolph Strecker in 1850,[25] a typical Strecker reaction consists of the condensation of an aldehyde **2.117** with an amine **2.116** in the presence of a cyanide source to form α-amino nitriles **2.119** (eq 16).[26] Although this classic transformation is an indispensable means for accessing many valuable building blocks, α-amino nitriles included in the ring system cannot be synthesized by this methodology. We reasoned that azomethine ylides **2.121**, derived from condensation of an amino acid **2.120** with an aldehyde **2.117**, could be converted to valuable Strecker products if an appropriate cyanide source was employed (eq 17). Compounds **2.122** have been previously synthesized via oxidative cyanation[27] or other tandem strategies.[28]



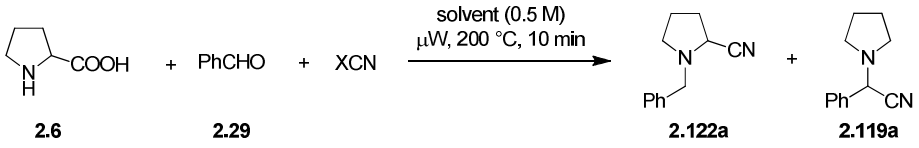


2.4.2 Screening of Reaction Conditions

We initiated our investigation by evaluating the reaction between proline and benzaldehyde in presence of various cyanide sources. Initially conventional thermal conditions were applied. However, microwave conditions were finally chosen as they led to improved reaction outcome and vastly accelerated reaction rates. The reaction proceeded as anticipated and the desired cyclic α-amino nitrile **2.122a** was consistently formed as the major product. To our delight, when benzaldehyde was allowed to react with 2.0 equiv of proline

and 1.2 equiv of TMSCN in toluene under microwave irradiation at 200 ºC for 10 mins, only **2.122a** was formed in 81% isolated yield (Table 2.4, entry 1). Although lowering the amounts of either proline or TMSCN led to improved yields, it had a deleterious effect on the product ratios (Table 2.4, entries 2 and 3). Further lowering proline loading had a detrimental effect on both the yields and product ratios (Table 2.4, entries 4 and 5). When the solvent was changed to *n*-butanol, the reaction between benzaldehyde, 1.5 equiv of proline and 1.2 equiv of TMSCN gave rise to the cyclic α-aminonitrile **2.122a** as the only detectable regioisomer in near-quantitative yield (Table 2.4, entry 6). The use of *n*-butanol also gave the liberty to lower the proline loading to 1.3 equiv without compromising on the yield or product ratio (Table 2.4, entry 7). When proline loading was further lowered, we observed the formation of a small amount of the undesired regioisomeric product **2.119a** (Table 2.4, entry 8). Upon using xylenes as solvent, even though it led to excellent yield, the products **2.122a** and **2.119a** were formed in 17:1 ratio (Table 2.4, entry 9). The use of copper(I) cyanide led to trace amount of products (Table 2.4, entry 10). Other sources of cyanide like potassium cyanide and potassium ferricyanide(III) also enabled product formation, but in lower yield (Table 2.4, entries 11 and 12). When ethyl cyanoformate was employed as the cyanide source, the products were isolated in 5:1 ratio in moderate yield (Table 2.4, entry 13).

Table 2.4 **Evaluation of Reaction Parameters**



2.6 **2.29** **2.122a** **2.119a**

entry	Proline (**2.6**) (equiv)	solvent	XCN (equiv)	ratio **2.122a**:**2.119a**	yield (%)
1	2.0	PhMe	TMSCN (1.2)	**2.122a** only	81
2	1.5	PhMe	TMSCN (1.2)	28:1	90
3	1.5	PhMe	TMSCN (1.1)	17:1	89
4	1.3	PhMe	TMSCN (1.2)	5:1	81
5	1.2	PhMe	TMSCN (1.2)	4:1	77
6	1.5	*n*-BuOH	TMSCN (1.2)	**2.122a** only	>97
7	1.3	*n*-BuOH	TMSCN (1.2)	**2.122a** only	>97
8	1.2	*n*-BuOH	TMSCN (1.2)	31:1	>97
9	1.5	Xylenes	TMSCN (1.2)	17:1	>97
10	1.5	*n*-BuOH	CuCN (1.2)	N/A	Trace
11	1.5	*n*-BuOH	KCN (1.2)	**2.122a** only	53
12	1.5	*n*-BuOH	$K_3[Fe(CN)_6]$ (1.2)	**2.122a** only	8
13	1.5	*n*-BuOH	EtOCOCN (1.2)	5:1	55

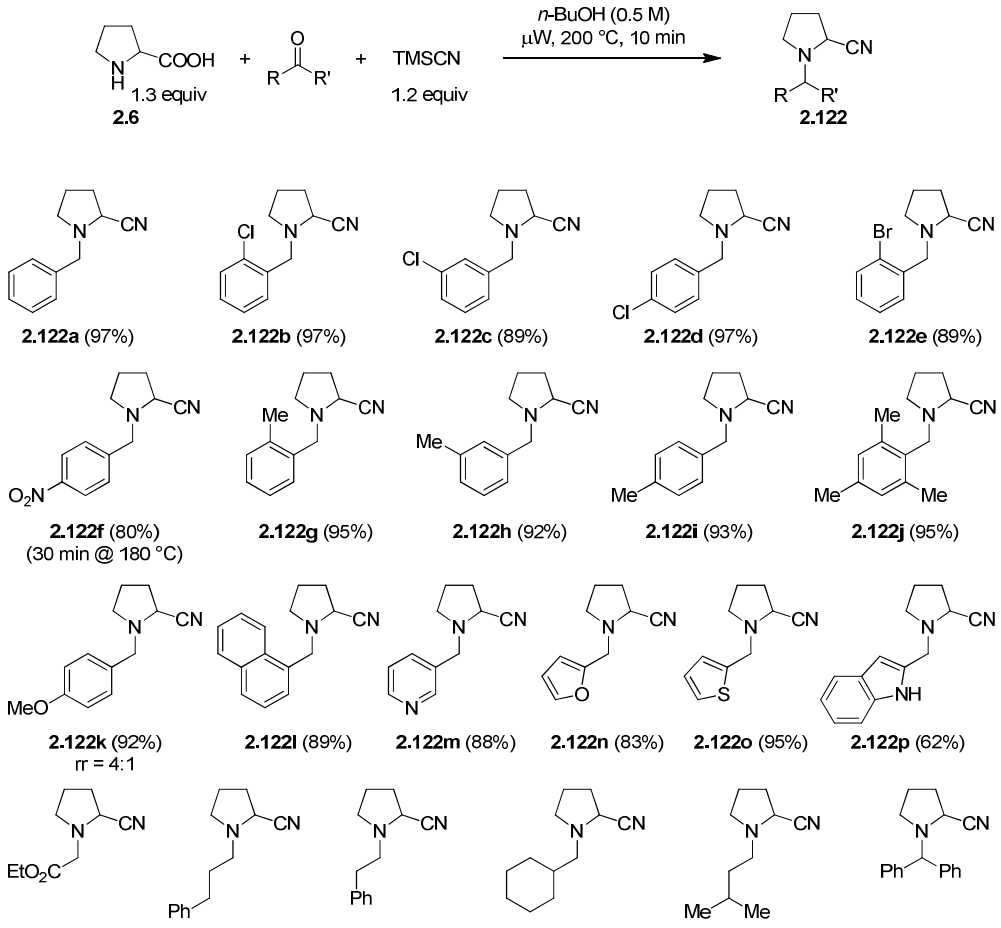
With the aforementioned screening parameters, the reaction of benzaldehyde with 1.3 equiv of proline and 1.2 equiv of TMSCN in *n*-butanol under microwave conditions was found to be optimal for the exclusive formation of cyclic aminonitrile **2.122a** (Table 2.3, entry 7). An especially appealing facet of this reaction is the brief reaction time, requiring only 10 minutes for completion. Conversely, the identical reaction conducted under thermal conditions required 5h and provided **2.122a** in only 64% yield.

2.4.3 Scope of the Reaction with Proline

With the optimized conditions in hand, a series of electronically diverse aldehydes was evaluated. Benzaldehydes having electron-withdrawing group in the ortho, meta or para positions were equally tolerated and the desired products were obtained in excellent yields (Table 2.5, **2.122b** – **2.122e**). Under the standard reaction temperature, lower yields were

obtained with *p*-nitrobenzaldehyde. This was due to the decomposition of the aldehyde at higher temperatures. On performing the reaction at slightly lower temperature for a prolonged time gave the product **2.122f** in 80% yield.

Table 2.5 **Scope of the Decarboxylative Strecker Reaction with Proline**

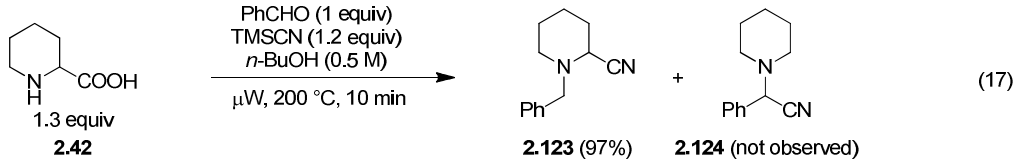


Electron-rich aromatic aldehydes readily underwent the transformation to furnish only the cyclic α-amino nitrile as the detectable regioisomer in excellent yields (Table 2.5, **2.122g** – **2.122j**). Interestingly, *p*-anisaldehyde led to the formation of **2.122k** as a 4:1 regioisomeric mixture. The formation of a small amount of the opposite regioisomer (**2.119k**) is most likely because of enhanced reactivity of the corresponding electron-rich azomethine ylide. 1-Naphthaldehyde or heteroaromatic aldehydes derived from pyridine, furan,

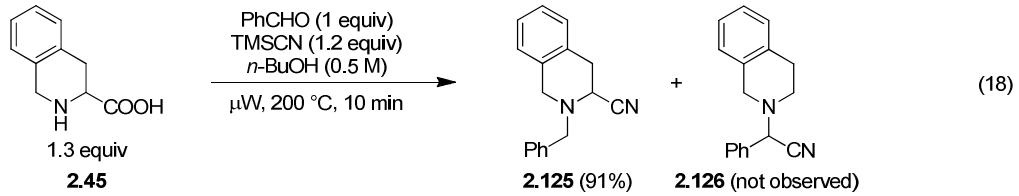
thiophene and indole were also promising substrates (Table 2.5, **2.122l** – **2.122p**). Ethyl glyoxylate and other enolizable aliphatic aldehydes readily engaged in the reaction to give the desired product (Table 2.5, **2.122q** – **2.122u**). Benzophenone, although slightly less reactive under the reaction conditions, led to the formation of the desired cyclic α-amino nitrile **2.122v** in moderate yield.

2.4.4 Scope of the Reaction with Other α-Amino Acids

Subsequently, we sought to expand the scope with α-amino acids other than proline. Under the previously optimized microwave conditions, the analogous reaction with pipecolic acid (**2.42**) afforded the desired product **2.123** as the only detectable regioisomer in near-quantitative yield (eq 17). The corresponding reaction with tetrahydroisoquinoline-3-carboxylic acid (**2.45**) led to formation of the expected product **2.125** in 91% yield (eq 18).

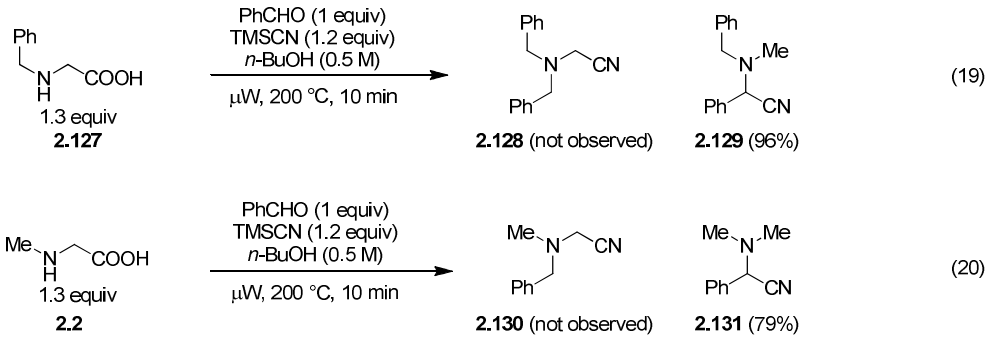


(17)



(18)

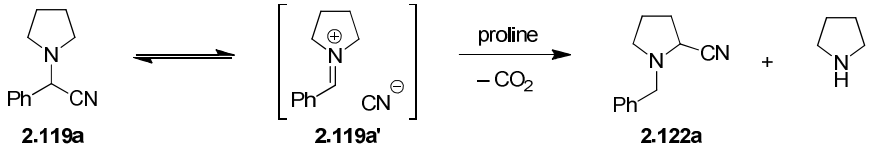
The reactions with *N*-benzyl glycine (**2.127**) and sarcosine (**2.2**) provided single regioisomeric products **2.129** and **2.131**, respectively (eqs 19 and 20). It is worth noting that these products represent the opposite regioisomers than those obtained with cyclic α-amino acids. This observation possibly exemplifies the distinct reactivity of the corresponding azomethine ylides and its preferred protonation sites.



2.4.5 Insights into Regioisomeric Enrichment

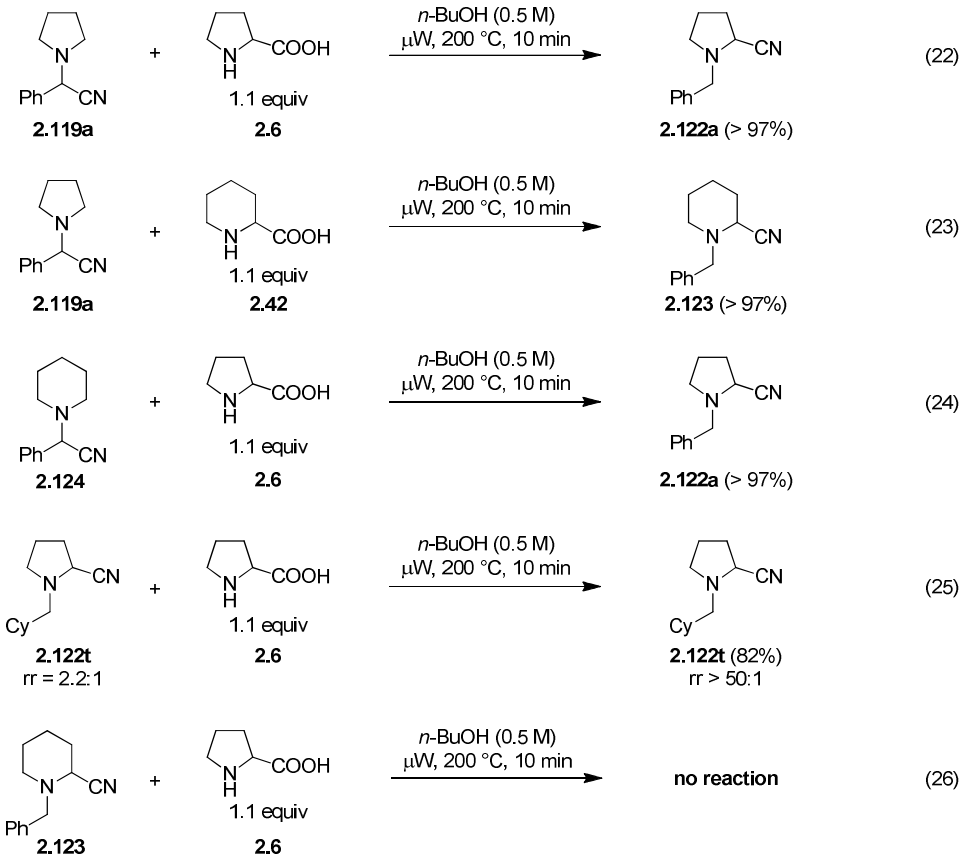
A closer look at the results highlighted in Table 2.4, particularly entries 1, 2, 4 and 5, suggests that the regioisomeric ratios of **2.122a** and **2.119a** are apparently a direct manifest of the amount of proline used. An increase in the equivalents of proline led to a gradual increase in the regioisomeric ratio favoring the desired product **2.122a**, to the extent where **2.119a** could no longer be detected. An attempt to rationalize this interesting finding is elucidated in Scheme 2.8. Under the reaction conditions, the aminonitrile **2.119a** is thought to be in equilibrium with small amounts of the ion pair **2.119a′**. Addition of proline to **2.119a′** and the concomitant formation of pyrrolidine could lead to the desired product **2.122a**, and thus could be a pathway for regioisomeric enrichment.

Scheme 2.8 **Proposed Pathway for Regioisomeric Enrichment**

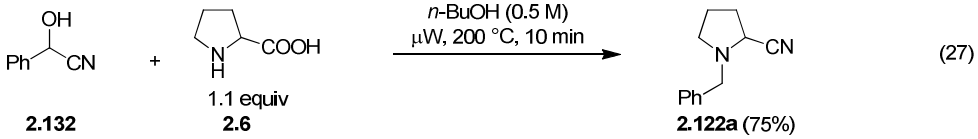


To establish whether the mechanism proposed in Scheme 2.8 is indeed operative, we performed a number of control experiments (eqs 22–26). Under the optimized reaction conditions, a slight excess (1.1 equiv.) of proline was allowed to react with the amino nitrile **2.119a**. In line with our hypothesis, compound **2.122a** was obtained as the only product in near-quantitative yield (eq 22). In an otherwise identical experiment, on substituting pipecolic acid for proline, **2.123** formed as the exclusive product (eq 23). Similarly, on

exposing **2.124** to proline, **2.122a** was isolated as the only product (eq 24). From the above observations, this strategy can be utilized for enhancing product distribution in reactions that are typically less regioselective. For instance, when a 2.2:1 mixture of **2.122t** and its corresponding regioisomer is treated with proline, it led to the formation of regioisomerically pure **2.122t** (eq 25). Not surprisingly, treatment of **2.123** with proline led to no reaction (eq 26).

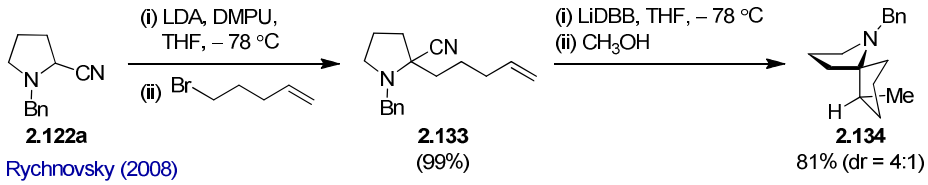


As an interesting side note, the reaction of phenyl cyanohydrin (**2.132**) with proline gave rise to **2.122a** in 75% yield (eq 27).



2.4.6 Product Modification

α-Amino nitriles have been shown to be versatile intermediates in a number of synthetic applications. Though, historically, hydrolysis of the nitrile group to generate α-amino acids is perhaps the most important application of α-amino nitriles, its utility extends much beyond that.[24] For instance, reducing the nitrile group with lithium aluminium hydride is a convenient and simple method to get access to 1,2-diamines.[29] Rychnovsky and co-workers recently demonstrated an intriguing reductive lithiation/intramolecular carbolithiation process using **2.122a** to generate spirocyclic structures (eq 28).[30]



2.122a — Rychnovsky (2008)

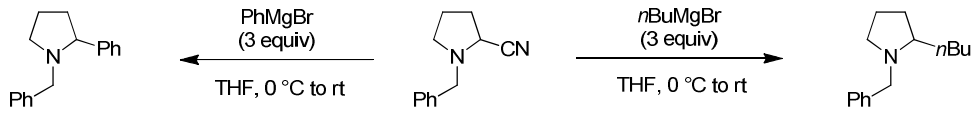
2.133 (99%)

2.134 81% (dr = 4:1)

(28)

Another extremely valuable use of α-amino nitriles is as stable precursors to iminium ions, which can then be trapped by nucleophilic reagents. The Bruylants reaction is such a transformation, specific to α-amino nitriles, which allows an opportunity to replace the nitrile group with a carbon substituent.[31,32] α-Amino nitrile **2.122a**, which according to our knowledge has not been previously used in Bruylants reactions, smoothly engaged in reactions with phenyl magnesium bromide and *n*-butyl magnesium bromide to furnish the corresponding 2-phenyl- and 2-butyl-pyrrolidine products **2.135** and **2.136**, respectively, in good yields (Figure 2.10).

Figure 2.10 **Product Modification via Bruylants Reaction**



2.135 (88%) **2.122a** **2.136** (76%)

2.4.7 Summary

We have introduced a novel decarboxylative variant of the classical Strecker reaction. By employing this strategy we can gain facile access to α-amino nitriles that are inaccessible by traditional Strecker chemistry. Due to the versatility of the resulting α-amino nitriles, this process is expected to find broad application in synthesis.

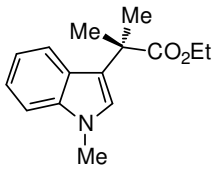
2.5 Conclusion

We have successfully demonstrated both intramolecular as well as intermolecular azomethine ylide functionalization. Rather than the redox isomerization proceeding through seemingly direct 1,3-hydride shift mechanism, this process involves the intermediacy of azomethine ylides. We anticipate that the great synthetic utility of such 1,3-dipoles has many prospects for future development.

Experimental Section

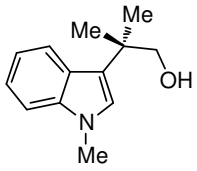
General Information: The amino acids were purchased from commercial sources and used as received. The aldehydes and amines were purified either by distillation or by recrystallization prior to use. Ethyl glyoxalate solution (~50% in toluene) was freshly distilled under nitrogen prior to use. Trimethylsilyl cyanide (TMSCN) and reagent grade *n*-butanol were purchased from Sigma-Aldrich and used as received. Toluene was freshly distilled from sodium under nitrogen prior to use. Microwave reactions were carried out in a CEM Discover reactor. If so mentioned, a silicon carbide passive heating element, purchased from Anton Paar, was used for efficient microwave absorption. Purification of reaction products was carried out by flash chromatography using EM Reagent silica gel 60 (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 and 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 VNMRS-400 instrument and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 7.26 ppm, $(CD_3)_2SO$ at 2.50 ppm). Data are reported as app = apparent, s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, ddd = doublet of doublet of doublets, td = triplet of doublets, m = multiplet, comp = complex; br = broad; and coupling constant(s) in Hz. Proton-decoupled carbon nuclear magnetic resonance spectra (^{13}C-NMR) spectra were recorded on a Varian VNMRS-500 MHz instrument and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.0 ppm, $(CD_3)_2SO$ at 39.5 ppm). Mass spectra were recorded on a Finnigan LCQ-DUO mass spectrometer.

Ethyl 2-methyl-2-(1-methyl-1*H*-indol-3-yl)propanoate (2.137):



THF (28.8 mL) was added to a flame-dried 200-mL round-bottom flask equipped with a septum and a nitrogen inlet. The flask was cooled to –78 ºC, followed by addition of KHMDS (6.5 mL, 0.5 M in toluene, 2.4 mmol). A solution of ethyl 2-(1H-indol-3-yl)-2-methylpropanoate (0.5g, 2.16 mmol) in 5 mL THF was added via syringe. The resulting mixture was then warmed to 0 °C and stirred for 2 hours before re-cooling to –78 ºC. Methyl iodide (0.41 mL, 6.5 mmol) was then added. The mixture was allowed to warm to 0 °C and stirred for 3 hours. The reaction mixture was then placed in a freezer (–20 ºC) for 24 hours. Subsequently, the reaction was quenched by addition of water (10 mL) and then extracted with diethyl ether (3 x 20 mL). The combined organic layers were washed with brine (20 mL) and dried with sodium sulfate. The solvent was removed under reduced pressure and the residue purified by flash column chromatography. The title compound was obtained as a white solid in 75% yield. (R_f = 0.33 in EtOAc/hexanes 10:90 v/v); mp: 74–75 °C; IR (KBr) 3415, 3121, 3059, 2989, 2975, 2933, 2873, 1718, 1485, 1476, 1458, 1444, 1426, 1394, 1382, 1373, 1361, 1339, 1330, 1300, 1261, 1231, 1178, 1154, 1131, 1108, 1097, 1058, 1023, 995, 826, 769, 744, 671 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.68 (app d, *J* = 8.1 Hz, 1H), 7.29 (app d, *J* = 8.2 Hz, 1H), 7.24–7.19 (m, 1H), 7.11–7.06 (m, 1H), 6.94 (s, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.76 (s, 3H), 1.69 (s, 6H), 1.17 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.0, 137.5, 126.1, 125.3, 121.4, 120.5, 119.3, 118.8, 109.3, 60.7, 42.0, 32.7, 26.3, 14.2; *m/z* (ESI-MS) 246.1 $[M + H]^+$.

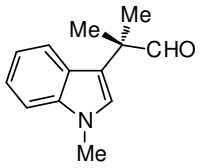
2-Methyl-2-(1-methyl-1*H*-indol-3-yl)propan-1-ol (2.138):



Compound **2.137** (0.43 g, 1.75 mmol), dissolved in ether (10 mL), was added dropwise over 30 minutes to a stirred suspension of lithium aluminum hydride (0.76 g, 20 mmol) in ether (10 mL). The resulting mixture was then heated under reflux for 1 hour. The reaction mixture was allowed to cool to room temperature and excess of lithium aluminum hydride was carefully quenched with ice-

water (100 mL). The organic layer was separated and the aqueous layer was extracted further with ether (5 x 50 mL). The combined organic layers were dried with sodium sulfate and the solvent removed under reduced pressure. The residue was purified by flash column chromatography. The title compound was obtained as colorless oil in 99% yield. (R_f = 0.30 in EtOAc/hexanes 30:70 v/v); IR (film) 3386, 3047, 2961, 2871, 1613, 1543, 1484, 1464, 1423, 1374, 1360, 1327, 1241, 1151, 1107, 1040, 765, 738 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.80 (app dd, *J* = 8.1, 0.8 Hz, 1H), 7.33 (app d, *J* = 8.2 Hz, 1H), 7.25 (ddd, *J* = 8.2, 5.4, 1.0 Hz, 1H), 7.15–7.09 (m, 1H), 6.91 (app d, *J* = 3.4 Hz, 1H), 3.80 (d, *J* = 2.4 Hz, 2H), 3.77 (s, 3H), 1.47 (s, 6H), 1.31 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.8, 127.0, 126.0, 121.4, 120.9, 119.4, 118.6, 109.5, 71.5, 37.6, 32.6, 25.4; *m/z* (ESI-MS) 204.1 $[M + H]^+$.

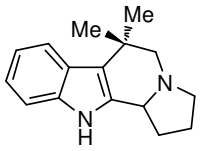
2-Methyl-2-(1-methyl-1*H*-indol-3-yl)propanal (2.82a):



Dichloromethane (4.3 mL) was added to a flame-dried 25-mL round-bottom flask equipped with a septum and a nitrogen inlet. The flask was cooled to –78 ºC and oxalyl chloride (0.20 mL, 2.4 mmol) was added. DMSO (0.32 mL, 4.5 mmol) was then added dropwise and the mixture was allowed to stir at –78 ºC for 10 minutes. Subsequently, **2.138** (0.35 g, 1.7 mmol), dissolved in 4 mL of dichloromethane, was added dropwise at –78 ºC. After stirring for 15 minutes, triethylamine (1.25 mL, 9.0 mmol) was added dropwise and the mixture was allowed to stir for another 15 minutes at –78 ºC. The flask was then transferred into an ice bath and stirred for 10 minutes. The reaction mixture was poured into ice-cold 1 M HCl solution (15 mL), extracted with dichloromethane (3 x 10 mL), washed with pH 7.4 buffer (10 mL) and dried with sodium sulfate. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography. The title compound was obtained as a pink solid in 68% yield. (R_f = 0.30 in EtOAc/hexanes 10:90 v/v); mp: 59–60 °C; IR (KBr) 3409, 3120, 3051, 2986, 2966, 2925, 2807, 2708, 1713, 1676, 1537, 1485, 1463, 1419, 1389, 1379, 1359, 1329, 1253, 1232, 1135, 1108, 1015, 980, 908, 842, 828 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.50 (s, 1H), 7.56 (app d, *J* = 8.1 Hz, 1H), 7.32 (app d, *J* = 8.3 Hz, 1H), 7.26–7.21 (m, 1H), 7.13–7.06 (m,

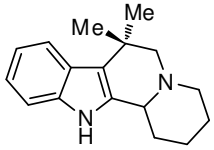
1H), 6.96 (s, 1H), 3.79 (s, 3H), 1.55 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.2, 137.6, 126.6, 126.2, 121.9, 120.2, 119.3, 115.1, 109.5, 46.5, 32.8, 21.9; *m/z* (ESI-MS) 202.2 $[M + H]^+$.

6,6-Dimethyl-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indole (2.41):



Toluene (5 mL) was added to a round-bottom flask containing *L*-proline (0.75 mmol). The flask was then equipped with a reflux condenser containing a septum with a nitrogen inlet and placed into a pre-heated oil bath (130 °C). Using a cannula that was inserted through the septum on top of the reflux condenser, a solution of **2.37** (0.5 mmol) in toluene (0.72 mL) was added slowly by syringe pump over 18 hours. Subsequent to the addition, the reaction mixture was heated under reflux for an additional 2 hours. The reaction mixture was then allowed to cool to room temperature. The residue was purified by flash column chromatography. The title compound was obtained as a yellow solid in 80% yield. (R_f = 0.28 in MeOH/EtOAc 25:75 v/v); mp: 44–47 °C; IR (film) 3398, 3187, 3053, 2956, 2874, 1656, 1620, 1459, 1386, 1361, 1331, 1287, 1264, 1218, 1149, 1093, 1060, 738, 765, 702 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (br s, 1H), 7.68 (app dd, *J* = 13.0, 5.3 Hz, 1H), 7.34–7.28 (m, 1H), 7.16–7.03 (comp, 2H), 3.62 (dd, *J* = 9.5, 6.9 Hz, 1H), 3.08 (ddd, *J* = 10.1, 8.3, 3.2 Hz, 1H), 2.87 (d, *J* = 11.3 Hz, 1H), 2.81 (app dd, *J* = 18.2, 8.3 Hz, 1H), 2.51 (d, *J* = 11.3 Hz, 1H), 2.20–2.08 (m, 1H), 2.01 (app qdd, *J* = 14.6, 9.1, 6.4 Hz, 1H), 1.86–1.67 (comp, 2H), 1.49 (s, 3H), 1.47 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.3, 133.9, 125.9, 120.9, 119.7, 119.1, 116.3, 111.1, 63.2, 59.3, 53.4, 33.7, 28.7, 28.3, 27.8, 22.8; *m/z* (ESIMS) 241.2 $[M + H]^+$.

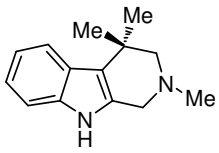
7,7-Dimethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (2.43):



Toluene (5 mL) was added to a round-bottom flask containing DL-pipecolic acid (0.75 mmol). The flask was then equipped with a reflux condenser containing a septum with a nitrogen inlet and placed in a pre-heated oil bath (130 °C). Using a cannula that was inserted through the septum on top of the

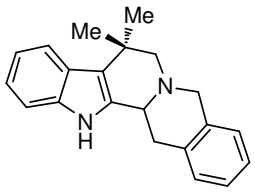
reflux condenser, a solution of **2.37** (0.5 mmol) in toluene (0.72 mL) was added slowly by syringe pump over 18 hours. Subsequent to the addition, the reaction mixture was heated under reflux for an additional 24 hours. The reaction mixture was then allowed to cool to room temperature and concentrated under reduced pressure. The residue was purified by flash column chromatography. The title compound was obtained as a yellow solid in 90% yield. (R_f = 0.35 in EtOAc/hexanes 30:70 v/v); mp: 46–48 °C; IR (film) 3414, 3261, 3053, 2935, 2857, 2796, 2750, 1618, 1459, 1442, 1391, 1373, 1357, 1321, 1307, 1283, 1265, 1205, 1127, 1110, 1082, 1050, 764, 738 703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.73–7.62 (comp, 2H), 7.31 (app d, *J* = 7.9 Hz, 1H), 7.19–7.08 (comp, 2H), 3.13 (dd, *J* = 10.8, 2.5 Hz, 1H), 2.96 (app d, *J* = 11.1 Hz, 1H), 2.59 (d, *J* = 11.2 Hz, 1H), 2.46 (d, *J* = 11.2 Hz, 1H), 2.40–2.30 (m, 1H), 2.03 (app dd, *J* = 16.4, 13.5 Hz, 1H), 1.93 (app d, *J* = 12.3 Hz, 1H), 1.82–1.67 (comp, 2H), 1.62–1.40 (comp, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.1, 134.5, 126.1, 120.7, 119.7, 119.0, 116.7, 110.9, 68.8, 60.4, 55.8, 32.8, 30.1, 28.4, 27.0, 25.8, 24.5; *m/z* (ESI-MS) 255.2 $[M + H]^+$.

2,4,4-Trimethyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole (2.44):



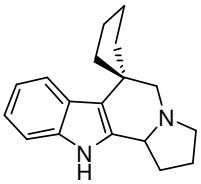
Sarcosine (6.0 mmol) and **2.37** (0.5 mmol) along with 10 mL of xylenes were placed in a round-bottom flask equipped with a reflux condenser containing a nitrogen inlet. The flask was placed in a pre-heated oil bath (170 °C). After 20 hours, the reaction mixture was allowed to cool to room temperature. Following removal of the solvent, the residue was purified by flash column chromatography. The title compound was obtained as a white solid in 61% yield. (R_f = 0.31 in EtOAc/hexanes 70:30 v/v); mp: 174–176 °C; IR (KBr) 3140, 3103, 3060, 2925, 2851, 2796, 2752, 1453, 1397, 1384, 1360, 1330, 1299, 1263, 1238, 1179, 1103, 1031, 881, 742 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.94 (br s, 1H), 7.64 (app t, *J* = 8.4 Hz, 1H), 7.22 (app dd, *J* = 11.7, 4.5 Hz, 1H), 7.13–7.04 (comp, 2H), 3.38 (s, 2H), 2.45 (s, 2H), 2.44 (s, 3H), 1.44 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.3, 130.8, 125.8, 120.9, 119.6, 119.0, 116.6, 111.1, 68.9, 52.8, 46.1, 33.1, 27.8; *m/z* (ESI-MS) 215.1 $[M + H]^+$.

8,8-Dimethyl-5,7,8,13,13b,14-hexahydroindolo[2',3':3,4]pyrido[1,2-*b*]isoquinoline (2.46):



(*S*)-(-)-1,2,3,4-Tetrahydro-3-isoquinolinecarboxylic acid (1.0 mmol) and **2.37** (0.5 mmol) along with 10 mL of xylenes were placed in a microwave reaction vessel containing a silicon carbide passive heating element. The vessel was sealed and irradiated for 20 minutes (250 °C, 160 psi). The reaction mixture was then allowed to cool to room temperature, concentrated under reduced pressure and the residue purified by flash column chromatography. The title compound was obtained as a light orange-colored solid in 52% yield and **2.69** was obtained as a light yellow solid in 25% yield. (R_f = 0.36 in EtOAc/hexanes 15:85 v/v); mp: 58–61 °C; IR (KBr) 3405, 3049, 2952, 2923, 2862, 2797, 2738, 1491, 1458, 1374, 1356, 1340, 1320, 1309, 1263, 1146, 1107, 1085, 742, 686 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.76 (br s, 1H), 7.71 (app d, *J* = 7.8 Hz, 1H), 7.36 (app dd, *J* = 8.0, 0.6 Hz, 1H), 7.24–7.07 (comp, 6H), 4.06 (d, *J* = 14.9 Hz, 1H), 3.74 (d, *J* = 14.9 Hz, 1H), 3.64 (dd, *J* = 11.4, 3.6 Hz, 1H), 3.19 (dd, *J* = 15.5, 3.6 Hz, 1H), 3.06–2.97 (m, 1H), 2.82 (d, *J* = 11.2 Hz, 1H), 2.58 (d, *J* = 11.2 Hz, 1H), 1.52 (s, 3H), 1.51 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.5, 134.9, 133.5, 133.3, 128.7, 126.5, 126.3, 126.1, 125.9, 121.2, 119.9, 119.3, 117.4, 111.0, 67.4, 57.7, 56.5, 34.9, 32.7, 28.4, 26.9; *m/z* (ESI-MS) 303.2 $[M + H]^+$.

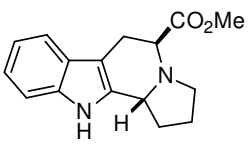
1',2',3',5',11',11b'-Hexahydrospiro[cyclopentane-1,6'-indolizino[8,7-*b*]indole] (2.48):



Toluene (5 mL) was added to a round-bottom flask containing *L*-proline (0.75 mmol). The flask was then equipped with a reflux condenser containing a septum with a nitrogen inlet and placed in a pre-heated oil bath (130 °C). Using a cannula that was inserted through the septum on top of the reflux condenser, a solution of **2.47** (0.5 mmol) in toluene (0.72 mL) was added slowly by syringe pump over 18 hours. Subsequent to the addition, the reaction mixture was heated under reflux for an additional 2 hours. The reaction mixture was then allowed to cool to room temperature and concentrated under reduced pressure. The residue was purified by

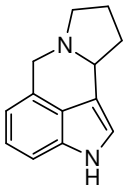
flash column chromatography. The title compound was obtained as a light brown solid in 79% yield. (R_f = 0.20 in MeOH/EtOAc 20:80 v/v); mp: 60–62 °C; IR (film) 3396, 3142, 3053, 2952, 2869, 1453, 1332, 1263, 1181, 1061, 1013, 738, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.22 (br s, 1H), 7.61 (app t, *J* = 10.1 Hz, 1H), 7.28 (app t, *J* = 7.6 Hz, 1H), 7.15–7.03 (comp, 2H), 3.68 (dd, *J* = 8.9, 7.5 Hz, 1H), 3.12–3.01 (m, 1H), 2.94 (d, *J* = 11.5 Hz, 1H), 2.87–2.76 (m, 1H), 2.57 (d, *J* = 11.5 Hz, 1H), 2.30–2.06 (comp, 3H), 2.04–1.89 (comp, 3H), 1.87–1.71 (comp, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.5, 134.6, 125.4, 120.9, 119.2, 119.1, 115.4, 111.2, 61.1, 59.0, 53.2, 44.0, 38.0, 38.0, 28.6, 25.9, 25.8, 23.0; *m/z* (ESI-MS) 267.2 $[M + H]^+$.

Methyl 2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indole-5-carboxylate (2.50):



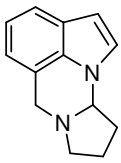
L-Proline (1.0 mmol) and **2.49** (0.5 mmol) along with 10 mL of xylenes were placed in a round-bottom flask equipped with a reflux condenser containing a nitrogen inlet. The flask was placed in a pre-heated oil bath (170 °C). After 1.75 hours, the reaction mixture was allowed to cool to room temperature and concentrated under reduced pressure. The residue was purified by flash column chromatography. The title compound was obtained as a mixture of diastereomers in 52% yield, dr = 75:25 as determined by integration of one set of ^1H-NMR signals (δ_{major} 3.66 ppm, δ_{minor} 3.84 ppm). The relative configuration of the major diastereomer was determined by NOSY. (R_f = 0.15 in EtOAc); IR (film) 3395, 3055, 2951, 2874, 1735, 1621, 1451, 1360, 1328, 1305, 1267, 1206, 1177, 1141, 1107, 1010, 908, 736, 702, 644 cm^{-1}; ^1H NMR of the major diastereomer (500 MHz, $CDCl_3$) δ 7.74 (br s, 1H), 7.53–7.46 (m, 1H), 7.34–7.28 (m, 1H), 7.19–7.07 (comp, 2H), 4.75–4.66 (m, 1H), 4.13 (app t, *J* = 4.2 Hz, 1H), 3.66 (s, 3H), 3.22–3.17 (comp, 2H), 3.01–2.93 (m, 1H), 2.85 (app dd, *J* = 16.1, 8.1 Hz, 1H), 2.44–2.30 (m, 1H), 2.04–1.70 (comp, 3H); ^{13}C NMR of diastereomers (125 MHz, $CDCl_3$) δ 173.2, 172.8, 136.2, 136.0, 135.1, 134.7, 127.2, 127.1, 121.8, 121.6, 119.7, 119.4, 118.1, 110.8, 110.7, 107.3, 105.2, 58.7, 58.1, 57.5, 52.8, 52.3, 52.1, 50.3, 44.3, 30.2, 28.8, 23.1(4), 23.1(3), 19.7, 19.0; *m/z* (ESI-MS) 271.2 $[M + H]^+$.

2,6,8,9,10,10a-Hexahydrodipyrrolo[1,2-*b*:4',3',2'-*de*]isoquinoline (2.52):



n-Butanol (5 mL) was added to a round-bottom flask containing L-proline (1.5 mmol). The flask was then equipped with a reflux condenser containing a septum with a nitrogen inlet and placed in a pre-heated oil bath (140 °C). Using a cannula that was inserted through the septum on top of the reflux condenser, a solution of **2.51** (0.5 mmol) in *n*-butanol (4.5 mL) was added slowly by syringe pump over 18 hours. Subsequent to the addition, the reaction mixture was heated under reflux for an additional 2 hours. The reaction mixture was then allowed to cool to room temperature. The solvent was removed under reduced pressure and the residue purified by flash column chromatography. The title compound was obtained as a pale pink solid in 63% yield. (R_f = 0.19 in MeOH/EtOAc 50:50 v/v); mp: 185–188 °C; IR (KBr) 3407, 3143, 3088, 3054, 3000, 2967, 2933, 2868, 2811, 2738, 1602, 1457, 1444, 1367, 1340, 1311, 1248, 1228, 1150, 1105, 1026, 977, 925, 871, 817, 757, 741 cm^{-1}; ^1H NMR (500 MHz, $(CD_3)_2SO$) δ 10.78 (br s, 1H), 7.17 (app d, *J* = 8.1 Hz, 1H), 7.09–6.97 (comp, 2H), 6.78 (app d, *J* = 7.0 Hz, 1H), 4.17 (d, *J* = 15.2 Hz, 1H), 4.11–3.93 (comp, 2H), 2.85 (app d, *J* = 3.4 Hz, 1H), 2.74 (app d, *J* = 6.8 Hz, 1H), 2.34–2.20 (m, 1H), 1.96–1.70 (comp, 3H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 134.2, 127.6, 125.5, 122.7, 118.56, 114.6, 113.0, 110.0, 59.8, 51.1, 51.0, 29.6, 22.4; *m/z* (ESI-MS) 199.2 $[M + H]^+$.

8,9,10,10a-Tetrahydro-6*H*-dipyrrolo[2,1-*b*:3',2',1'-*ij*]quinazoline (2.54):

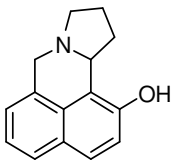


L-Proline (1.0 mmol) and **2.53** (0.5 mmol) along with 5 mL of xylenes were placed in a microwave reaction vessel containing a silicon carbide passive heating element. The vessel was then sealed and irradiated for 30 minutes (200 °C, 110 psi). The reaction mixture was allowed to cool to room temperature, concentrated under reduced pressure and the residue purified by flash column chromatography. The title compound was obtained as a white solid in 61% yield. (R_f = 0.33 in EtOAc/hexanes 30:70 v/v); mp: 84–86 °C; IR (KBr) 3072, 2930, 2840, 1480, 1450, 1361, 1341, 1275, 1195, 1112,

1075, 775, 726 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.49 (app t, *J* = 10.3 Hz, 1H), 7.12 (d, *J* = 3.1 Hz, 1H), 7.10–7.04 (m, 1H), 6.92 (app dd, *J* = 17.8, 7.1 Hz, 1H), 6.51 (d, *J* = 3.1 Hz, 1H), 5.39 (app dt, *J* = 19.9, 10.0 Hz, 1H), 4.53 (d, *J* = 16.5 Hz, 1H), 4.14 (d, *J* = 16.5, 1H), 3.10 (app td, *J* = 9.0, 3.9 Hz, 1H), 2.67 (app td, *J* = 9.2, 7.3 Hz, 1H), 2.52–2.31 (comp, 2H), 2.14–1.96 (m, 1H), 1.90–1.67 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 132.8, 126.0, 122.9, 119.8, 118.6, 118.4, 117.3, 101.1, 73.2, 49.4, 46.8, 30.4, 21.6; *m/z* (ESI-MS) 199.1 $[M + H]^+$.

Alternate preparation of 2.54 (Table 2.2): *n*-Butanol (5 mL) was added to a round-bottom flask containing pyrrolidine (1.5 mmol). The flask was then equipped with a reflux condenser containing a septum with a nitrogen inlet and placed into a pre-heated oil bath (140 °C). Using a cannula that was inserted through the septum on top of the reflux condenser, a solution of **2.53** (0.5 mmol) in *n*-butanol (0.72 mL) was added slowly by syringe pump over 18 hours. Subsequent to the addition, the reaction mixture was heated under reflux for an additional 2 hours. The reaction mixture was then allowed to cool to room temperature and the solvent removed under reduced pressure. The residue was purified by flash column chromatography. The title compound was obtained as a white solid in 81% yield.

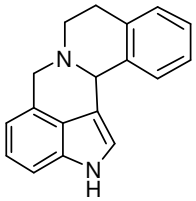
9,10,11,11a-tetrahydro-7*H*-benzo[*de*]pyrrolo[2,1-*a*]isoquinolin-1-ol (2.56):



L-Proline (0.75 mmol) and **2.55** (0.5 mmol) along with 10 mL of toluene were added to a round-bottom flask equipped with a reflux condenser. The flask was placed in a pre-heated oil bath (130 °C). After 30 minutes, the reaction mixture was allowed to cool to room temperature. Following removal of the solvent under vacuo, the residue was purified by flash column chromatography. The title compound was obtained as a white solid in 91% yield. (R_f = 0.30 in MeOH/EtOAc) 25:75 v/v; mp: 176–177 °C; IR (KBr) 3048, 2955, 2877, 2807, 1625, 1587, 1508, 1434, 1381, 1358, 1320, 1308, 1267, 1128, 1112, 1103, 971, 963, 941, 911, 878, 823, 758, 629, 562 cm^{-1}; ^1H NMR (500 MHz, $(CD_3)_2SO$) δ 9.49 (br s, 1H), 7.71–7.48 (comp, 2H), 7.24–7.03 (comp, 3H), 4.06 (d, *J* = 14.3 Hz, 1H), 3.75–3.58 (comp, 2H), 3.13–2.97 (m, 1H), 2.63–2.51 (comp, 2H), 1.95–

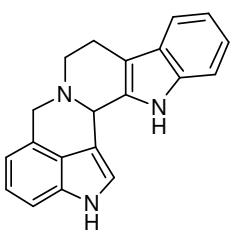
1.63 (comp, 3H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 150.3, 132.4, 129.4, 127.3, 126.8, 125.7, 122.0, 122.0, 118.3, 117.8, 60.8, 52.9, 52.7, 29.5, 21.6; *m/z* (ESI-MS) 226.3 $[M + H]^+$.

6,8,9,13b-Tetrahydro-2*H*-isoquinolino[2,1-*b*]pyrrolo[4,3,2-*de*]isoquinoline (2.69):



n-Butanol (5 mL) was added to a round-bottom flask containing tetrahydroisoquinoline (1.5 mmol). The flask was then equipped with a reflux condenser containing a septum with a nitrogen inlet and placed in a pre-heated oil bath (140 °C). Using a cannula that was inserted through the septum on top of the reflux condenser, a solution of **2.51** (0.5 mmol) in *n*-butanol (4.5 mL) was added slowly by syringe pump over 18 hours. Subsequent to the addition, the reaction mixture was heated under reflux for an additional 2 hours. The reaction mixture was then allowed to cool to room temperature and the solvent removed under reduced pressure. The residue was purified by flash column chromatography. The title compound was obtained as a white solid in 78% yield. (R_f = 0.34 in EtOAc/hexanes 40:60 v/v); mp: 194–197 °C; IR (KBr) 3416, 3136, 3082, 3032, 3000, 2924, 2852, 2791, 2735, 1737, 1614, 1494, 1442, 1381, 1371, 1354, 1298, 1383, 1237, 1153, 1124, 1098, 1064, 1047, 1028, 941, 925, 797, 766, 748, 739, 713, 703, 635, 597, 581, 521 cm^{-1}; ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 10.64 (br s, 1H), 7.43 (app d, *J* = 7.5 Hz, 1H), 7.24 (app t, *J* = 7.3 Hz, 1H), 7.15 (app dt, *J* = 14.8, 7.1 Hz, 3H), 7.01 (app t, *J* = 7.5 Hz, 1H), 6.78–6.68 (comp, 2H), 5.32 (s, 1H), 4.33 (d, *J* = 15.8 Hz, 1H), 3.95 (d, *J* = 15.8 Hz, 1H), 2.99–2.86 (m, 1H), 2.76–2.59 (comp, 3H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 137.4, 133.6, 133.5, 128.9, 127.8, 126.8, 126.0, 125.5, 124.4, 122.0, 119.7, 113.4, 113.2, 109.0, 57.3, 54.9, 46.0, 29.1; *m/z* (ESI-MS) 261.2 $[M + H]^+$.

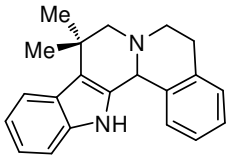
4,6,7,12,12b,14-Hexahydroindolo[2',3':3,4]pyrido[1,2-*b*]pyrrolo[4,3,2-*de*]isoquinoline (2.71):



n-Butanol (5 mL) was added to a round-bottom flask containing **2.70** (1.0 mmol). The flask was then equipped with a reflux condenser containing a septum with a nitrogen inlet and placed in a pre-heated oil

bath (140 °C). Using a cannula that was inserted through the septum on top of the reflux condenser, a solution of **2.51** (0.5 mmol) in *n*-butanol (4.5 mL) was added slowly by syringe pump over 18 hours. Subsequent to the addition, the reaction mixture was heated under reflux for an additional 2 hours. The reaction mixture was.then allowed to cool to room temperature and the solvent removed under reduced pressure. The residue was purified by flash column chromatography. The title compound was obtained as a yellow solid in 54% yield. (R_f = 0.30 in EtOAc/hexanes 60:40 v/v); mp: 226–231 °C; IR (KBr) 3448, 3085, 3050, 2956, 2931, 2882, 2845, 2818, 1617, 1457, 1328, 1307, 1254, 1232, 1113 cm^{-1}; ^1H NMR (500 MHz, $(CD_3)_2SO$) δ 10.94 (br s, 1H), 10.75 (br s, 1H), 7.41–7.35 (comp, 2H), 7.25 (s, 1H), 7.15 (app d, *J* = 8.1 Hz, 1H), 7.07–7.00 (comp, 2H), 6.96 (app t, *J* = 7.4 Hz, 1H), 6.76 (app d, *J* = 7.0 Hz, 1H), 5.27 (s, 1H), 4.18 (d, *J* = 15.3 Hz, 1H), 4.06 (d, *J* = 15.3 Hz, 1H), 3.02 (app dd, *J* = 11.3, 5.6 Hz, 1H), 2.92 (app dt, *J* = 11.7, 5.9 Hz, 1H), 2.80–2.70 (comp, 2H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 136.2, 134.8, 133.1, 128.6, 126.6, 124.8, 122.0, 120.4, 118.9, 118.3, 117.5, 113.2, 111.4, 111.2, 108.9, 105.9, 54.5, 54.1, 49.2, 21.3; *m/z* (ESI-MS) 300.2 $[M + H]^+$.

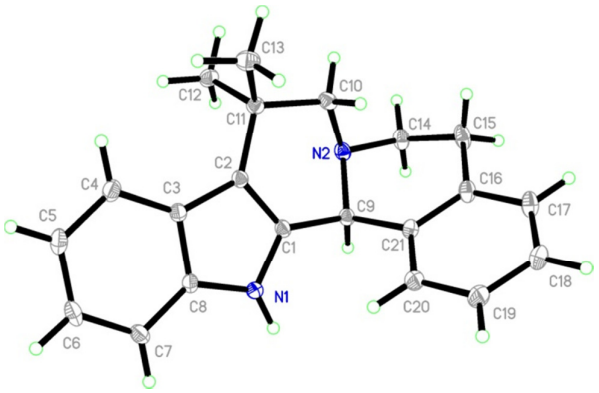
9,9-Dimethyl-5,6,8,9,14,14b-hexahydroindolo[2',3':3,4]pyrido[2,1-*a*]isoquinoline (2.72):



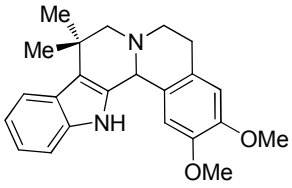
Tetrahydroisoquinoline (1.5 mmol) and **2.37** (0.5 mmol) along with 5 mL of xylenes were placed in a microwave reaction vessel containing a silicon carbide passive heating element. The vessel was then sealed and irradiated for 20 minutes (250 °C, 140 psi). The reaction mixture was allowed to cool to room temperature, concentrated under reduced pressure and the residue purified by flash column chromatography. The title compound was obtained as a light yellow solid in 64% yield. (R_f = 0.21 in EtOAc/hexanes 30:70 v/v); mp: 148–151 °C; IR (KBr) 3140, 3101, 3059, 2925, 2864, 2847, 1457, 1332, 1302, 1262, 1190, 1101, 1075, 970, 908, 880, 742, 662 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.79 (br s, 1H), 7.68 (app d, *J* = 7.8 Hz, 1H), 7.39 (app d, *J* = 7.4 Hz, 1H), 7.32–7.22 (comp, 3H), 7.19 (app d, *J* = 7.3 Hz, 1H), 7.15–7.06 (comp, 2H), 5.22 (s, 1H), 3.27–3.14 (comp, 2H), 3.10–3.03 (comp, 2H), 2.97–2.83 (comp, 2H), 1.53

(s, 3H), 1.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.9, 134.9, 134.8, 132.2, 129.8, 127.0, 126.6, 126.4, 126.2, 121.1, 120.0, 119.2, 115.7, 111.1, 64.7, 57.2, 48.0, 32.2, 29.3, 28.7, 28.2; *m/z* (ESI-MS) 303.2 $[M + H]^+$.

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



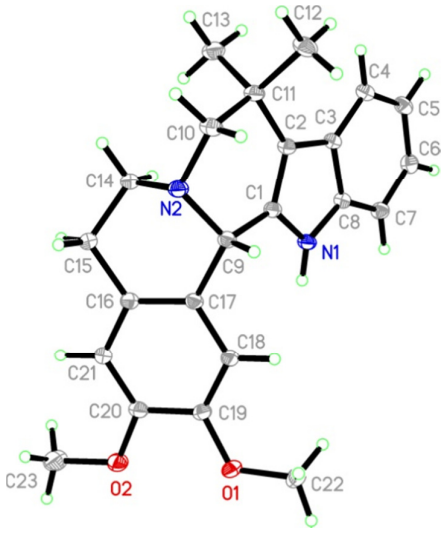
2,3-Dimethoxy-9,9-dimethyl-5,6,8,9,14,14b-hexahydroindolo[2',3':3,4]pyrido[2,1-*a*]isoquinoline (2.74):



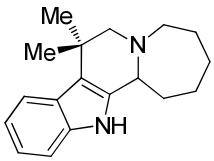
2.73 (1.5 mmol) and **2.37** (0.5 mmol) along with 5 mL of xylenes were placed in a microwave reaction vessel containing a silicon carbide passive heating element. The vessel was then sealed and irradiated for 20 minutes (200 °C, 45 psi). The reaction mixture was allowed to cool to room temperature, concentrated under reduced pressure and the residue purified by flash column chromatography. The title compound was obtained as a white solid in 61% yield. (R_f = 0.31 in EtOAc/hexanes 50:50 v/v); mp: 188–190 °C; IR (KBr) 3379, 2998, 2969, 2954, 2920, 2903, 2861, 2831, 1612, 1519, 1455, 1444, 1374, 1355, 1339, 1327, 1296, 1279, 1259, 1238, 1226, 1212, 1197, 1141, 1102, 1064, 1036, 1012, 871, 845, 180, 744 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (br s, 1H), 7.69 (app d, J = 7.6 Hz, 1H), 7.32 (app d, J = 7.7 Hz, 1H), 7.18–7.05 (comp, 2H), 6.88 (s, 1H), 6.67 (s, 1H), 5.11 (s, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.23 (ddd, J = 12.6, 7.8, 5.1 Hz, 1H), 3.19–3.12 (m, 1H), 3.11–3.01 (comp, 2H), 2.89–2.73 (comp,

2H), 1.53 (s, 3H), 1.46 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.2, 147.5, 136.0, 132.5, 126.9, 126.5, 126.4, 121.0, 120.0, 119.12, 115.6, 112.3, 111.2, 110.1, 64.3, 56.7, 56.3, 55.8, 47.9, 32.1, 29.4, 28.6, 27.5; *m/z* (ESI-MS) 363.2 $[M + H]^+$.

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



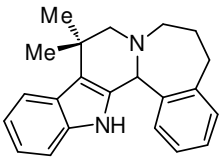
8,8-Dimethyl-2,3,4,5,7,8,13,13b-octahydro-1*H*-azepino[1',2':1,2]pyrido[3,4-*b*]indole (2.76):



Azepane (5.0 mmol) and **2.37** (0.5 mmol) along with 2 mL of *n*-butanol were placed in a microwave reaction vessel containing a silicon carbide passive heating element. The vessel was then sealed and irradiated for 5 hours (200 °C, 45 psi). The reaction mixture was allowed to cool to room temperature, concentrated under reduced pressure and the residue purified by flash column chromatography. The title compound was obtained as yellow oil in 43% yield. (R_f = 0.33 in EtOAc); IR (film) 3404, 3247, 3053, 2926, 2857, 1459, 1376, 1356, 1325, 1274, 1129, 1114, 1082, 1015, 762, 740 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70–7.59 (comp, 2H), 7.32–7.24 (m, 1H), 7.15–7.03 (comp, 2H), 3.74 (dd, *J* = 8.6, 3.4 Hz, 1H), 2.94–2.83 (comp, 2H), 2.70 (d, *J* = 11.5 Hz, 1H), 2.60 (d, *J* = 11.5 Hz, 1H), 2.05–1.95 (m, 1H), 1.92–1.54 (comp, 7H),

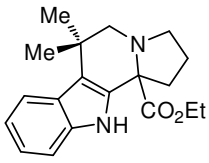
1.46 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.2, 135.9, 126.0, 120.8, 119.8, 118.9, 117.0, 110.8, 66.8, 60.3, 56.8, 33.8, 33.0, 27.7, 27.41, 27.37, 27.0, 25.6; *m/z* (ESI-MS) 269.2 $[M + H]^+$.

10,10-Dimethyl-6,7,9,10,15,15b-hexahydro-5*H*-benzo[3',4']azepino [1',2':1,2]pyrido[3,4-*b*]indole (2.78):



2.77 (2.5 mmol) and **2.37** (0.5 mmol) along with 2 mL of xylenes were placed in a microwave reaction vessel containing a silicon carbide passive heating element. The vessel was then sealed and irradiated for 1 hour (250 °C, 140 psi). The reaction mixture was allowed to cool to room temperature, concentrated under reduced pressure and the residue purified by flash column chromatography. The title compound was obtained as thick yellow oil in 54% yield. (R_f = 0.20 in EtOAc/hexanes 10:90 v/v); IR (film) 3400, 3174, 3056, 2927, 2859, 1458, 1376, 1355, 1327, 1266, 1113, 1079, 740, 635 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (app d, *J* = 7.7 Hz, 1H), 7.61 (br s, 1H), 7.28 (app d, *J* = 7.8 Hz, 1H), 7.20–7.09 (comp, 4H), 7.08–7.03 (m, 1H), 6.52 (app d, *J* = 7.5 Hz, 1H), 5.30 (s, 1H), 3.33–3.22 (m, 1H), 3.04–2.94 (m, 1H), 2.92–2.82 (m, 1H), 2.66–2.57 (m, 1H), 2.50 (d, *J* = 11.6 Hz, 1H), 2.36 (d, *J* = 11.6 Hz, 1H), 2.09–2.01 (m, 1H), 1.96–1.81 (m, 1H), 1.50 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.5, 136.4, 132.3, 128.9, 128.4, 127.5, 126.1, 125.7, 121.2, 120.0, 119.5, 119.1, 111.0, 63.8, 58.7, 33.1, 32.7, 29.7, 27.5(1), 27.4(8), 25.7; *m/z* (ESI-MS) 317.3 $[M + H]^+$.

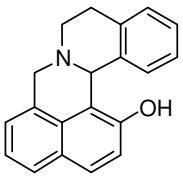
Ethyl 6,6-dimethyl-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indole-11b-carboxylate (2.80):



2.79 (1.5 mmol) and **2.37** (0.5 mmol) along with 5 mL of xylenes were placed in a microwave reaction vessel containing a silicon carbide passive heating element. The vessel was then sealed and irradiated for 20 minutes (250 °C, 114 psi). The reaction mixture was allowed to cool to room temperature, concentrated under reduced pressure and the residue purified by flash column

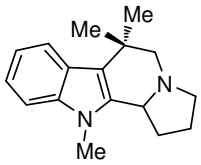
chromatography. The title compound was obtained as thick yellow oil in 74% yield. (R_f = 0.40 in MeOH/EtOAc 10:90 v/v); IR (film) 3388, 3055, 2956, 1715, 1617, 1457, 1385, 1364, 1320, 1297, 1262, 1101, 1023, 857, 765, 738, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.19 (br s, 1H), 7.71 (app t, *J* = 10.3 Hz, 1H), 7.36 (app d, *J* = 8.1 Hz, 1H), 7.21–7.14 (m, 1H), 7.10 (app t, *J* = 7.3 Hz, 1H), 4.31–4.12 (comp, 2H), 3.33 (ddd, *J* = 9.5, 7.3, 5.3 Hz, 1H), 3.21 (app dt, *J* = 9.5, 7.1 Hz, 1H), 3.13 (d, *J* = 13.2 Hz, 1H), 3.00 (d, *J* = 13.2 Hz, 1H), 2.64 (ddd, *J* = 12.5, 7.9, 4.5 Hz, 1H), 2.30–2.15 (m, 1H), 1.94–1.79 (comp, 2H), 1.54 (s, 3H), 1.43 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.1, 136.5, 131.7, 125.5, 121.6, 120.3, 119.1, 118.0, 111.1, 67.3, 61.6, 59.9, 53.1, 37.4, 32.6, 28.5, 28.4, 23.8, 14.2; *m/z* (ESI-MS) 313.2 $[M + H]^+$.

5,6,8,14b-Tetrahydrobenzo[*de*]isoquinolino[1,2-*a*]isoquinolin-14-ol (2.81):



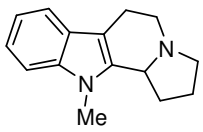
Tetrahydroisoquinoline (1.5 mmol), **2.55** (0.5 mmol) and 10 mL of toluene were added to a round-bottom flask equipped with a condenser containing a nitrogen inlet. The flask was placed in a pre-heated oil bath (130 °C). After 30 minutes, the reaction mixture was allowed to cool to room temperature. The solvent was removed under reduced pressure and the residue purified by flash column chromatography. The title compound was obtained as a white solid in 81% yield. (R_f = 0.27 in EtOAc/hexanes 60:40 v/v); mp: 224–227 °C; IR (KBr) 3056, 2939, 2821, 1629, 1589, 1514, 1484, 1452, 1436, 1374, 1316, 1277, 1121, 1040, 954,881, 820, 763, 744 cm^{-1}; ^1H NMR (500 MHz, $(CD_3)_2SO$) δ 9.81 (br s, 1H), 7.71 (app d, *J* = 8.9 Hz, 1H), 7.60 (app d, *J* = 8.1 Hz, 1H), 7.26 (app d, *J* = 8.9 Hz, 1H), 7.18–7.13 (m, 1H), 7.12–7.05 (comp, 3H), 6.96 (app t, *J* = 7.0 Hz, 1H), 6.74 (app d, *J* = 7.7 Hz, 1H), 5.51 (s, 1H), 4.00 (d, *J* = 14.7 Hz, 1H), 3.79 (d, *J* = 14.7 Hz, 1H), 3.65–3.53 (m, 1H), 3.40–3.34 (m, 1H), 3.24–3.13 (m, 1H), 2.69 (app dd, *J* = 17.7, 6.2 Hz, 1H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 150.3, 135.1, 133.9, 132.3, 128.8, 128.4, 128.4, 127.6, 127.5, 126.2, 125.8, 125.5, 122.2, 121.9, 117.9, 117.6, 55.5, 49.6, 47.8, 22.2; *m/z* (ESI-MS) 288.3 $[M + H]^+$.

6,6,11-Trimethyl-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indole (2.83a):



Toluene (5 mL) was added to a round-bottom flask containing *L*-proline (0.75 mmol) and benzoic acid (0.75 mmol). The flask was then equipped with a reflux condenser containing a septum with a nitrogen inlet and placed in a pre-heated oil bath (130 °C). Using a cannula that was inserted through the septum on top of the reflux condenser, a solution of **2.82a** (0.5 mmol) in toluene (0.72 mL) was added slowly by syringe pump over 18 hours. Subsequent to the addition, the reaction mixture was heated under reflux for an additional 2 hours. The reaction mixture was then allowed to cool to room temperature, neutralized with 10 mL of 1 M NaOH aqueous solution and extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried with sodium sulfate and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography. The title compound was obtained as yellow oil in 85% yield. (R_f = 0.28 in MeOH/EtOAc 5:95 v/v); IR (film) 3416, 3045, 2953, 2870, 2789, 1667, 1468, 1417, 1383, 1359, 1328, 1316, 1291, 1265, 1224, 1196, 1161, 1101, 1083, 1061, 1018, 762, 738 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.73 (app d, *J* = 7.9 Hz, 1H), 7.30 (app d, *J* = 8.2 Hz, 1H), 7.19 (app dd, *J* = 11.2, 4.0 Hz, 1H), 7.11 (app td, *J* = 7.5, 0.9 Hz, 1H), 3.87–3.77 (m, 1H), 3.66 (s, 3H), 3.11 (ddd, *J* = 11.0, 8.3, 2.7 Hz, 1H), 3.02–2.94 (m, 1H), 2.79 (d, *J* = 11.0 Hz, 1H), 2.48 (d, *J* = 11.0 Hz, 1H), 2.34–2.24 (m, 1H), 2.18–2.06 (m, 1H), 1.99–1.77 (comp, 2H), 1.51 (s, 3H), 1.49 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.3, 136.1, 125.3, 120.4, 119.8, 118.6, 115.5, 108.9, 62.7, 58.5, 54.1, 33.6, 30.0, 29.2, 27.9, 27.7, 23.2; *m/z* (ESI-MS) 255.2 $[M + H]^+$.

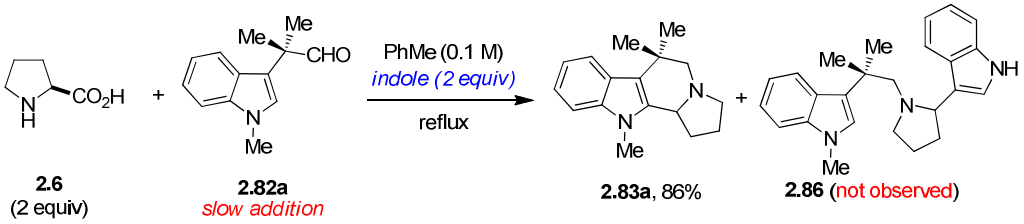
11-Methyl-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indole (2.83b):



Toluene (5 mL) was added to a round-bottom flask containing *L*-proline (0.75 mmol) and benzoic acid (0.75 mmol). The flask was then equipped with a reflux condenser containing a septum with a nitrogen inlet and placed in a pre-heated oil bath (130 °C). Using a cannula that was inserted through the

septum on top of the reflux condenser, a solution of **2.82b** (0.5 mmol) in toluene (0.72 mL) was added slowly by syringe pump over 18 hours. Subsequent to the addition, the reaction mixture was heated under reflux for an additional 2 hours. Then the reaction mixture was cooled to room temperature, neutralized with 10 mL of 1 M NaOH aqueous solution and extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried with sodium sulfate and the solvent removed under reduced pressure. The residue was purified by flash column chromatography. The title compound was obtained as yellow oil in 60% yield. (R_f = 0.25 in MeOH/EtOAc 30:70 v/v); IR (film) 3397, 3049, 2934, 2842, 1660, 1614, 1470, 1376, 1352, 1321, 1283, 1244, 1188, 1157, 1129, 1086, 1011 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.52 (app dd, *J* = 7.8, 0.7 Hz, 1H), 7.29 (app dd, *J* = 8.2, 0.7 Hz, 1H), 7.23–7.18 (m, 1H), 7.14–7.09 (m, 1H), 4.30–4.22 (m, 1H), 3.66 (s, 3H), 3.29–3.20 (m, 1H), 3.06–2.89 (comp, 4H), 2.78–2.68 (m, 1H), 2.50–2.39 (m, 1H), 2.01–1.90 (comp, 2H), 1.90–1.81 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.3, 137.0, 126.6, 120.8, 118.8, 118.0, 108.6, 106.6, 56.2, 50.9, 46.4, 30.3, 30.1, 23.7, 18.7; *m/z* (ESI-MS) 227.2 $[M + H]^+$.

Reaction between indole, 2.82a and *L*-proline:



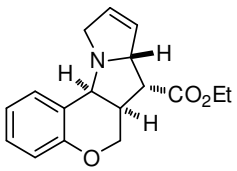
Toluene (5 mL) was added to a round-bottom flask containing *L*-proline (1.0 mmol) and indole (1.0 mmol). The flask was then equipped with a reflux condenser containing a septum with a nitrogen inlet and placed into a pre-heated oil bath (130 °C). Using a cannula that was inserted through the septum on top of the reflux condenser, a solution of **2.82a** (0.5 mmol) in toluene (0.72 mL) was added slowly by syringe pump over 18 hours. Subsequent to the addition, the reaction mixture was heated under reflux for an additional 2 hours. Then the

reaction mixture was allowed to cool to room temperature and the residue was purified by flash column chromatography. Compound **2.83a** was obtained as yellow oil in 86% yield.

General Procedure (A) for the Reaction between Indolines and Aldehydes:

A 10 mL microwave reaction tube was charged with aldehyde (1 mmol, 1 equiv.), indoline (1.2 mmol, 1.2 equiv.), toluene (2.0 mL), benzoic acid (0.2 mmol, 0.2 equiv.) and a 10 x 8 mm SiC passive heating element was carefully added to the reaction tube. The reaction tube was sealed with a Teflon-lined snap cap, and heated in the microwave reactor at 200 ºC, (200 W, 50–170 psi) for the appropriate time (***Note: SiC passive heating elements must not be used in conjunction with stir bars; they may score glass and cause vessel failure***). After cooling with compressed air flow, the crude reaction mixture was diluted with EtOAc (5 mL) and washed with saturated aqueous $NaHCO_3$ (3 x 5 mL). The aqueous layers were extracted with EtOAc (3 x 5 mL) and the combined organic layers dried over anhydrous Na_2SO_4. The solvent was removed in vacuo and the product was purified by silica gel column chromatography.

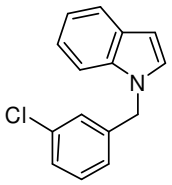
(6a*R*,7*R*,7a*R*,11a*S*)-Ethyl 6,6a,7,7a,10,11a-hexahydrochromeno[3,4-*b*]pyrrolizine-7-carboxylate (2.95):



Following general procedure (A), compound **7** was obtained from 3-pyrroline and (*E*)-ethyl 4-(2-formylphenoxy)but-2-enoate as colorless liquid in 53% yield (R_f = 0.26 in EtOAc/Hexanes 10:90 v/v); IR (KBr) 2978, 2870, 1729, 1583, 1487, 1452, 1626, 1249, 1222, 1180, 1115, 1045, 756, 706 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.40 (app d, *J* = 7.5 Hz, 1H), 7.13 (app t, *J* = 7.6 Hz, 1H), 6.94 (app t, *J* = 7.6 Hz, 1H), 6.80 (app d, *J* = 8.1 Hz, 1H), 5.90 (dd, *J* = 6.2, 1.9 Hz, 1H), 5.60

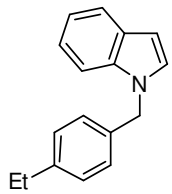
(dd, *J* = 6.2, 2.0 Hz, 1H), 4. 56 (ddd, *J* = 11.2, 5.1, 2.4 Hz, 1H), 4.29–4.09 (comp, 6H), 3.82 (dt, *J* = 5.1, 2.0 Hz, 1H), 3.79 (dt, *J* = 5.1, 2.0 Hz, 1H), 3.15 (dd, *J* = 8.6, 7.0 Hz, 1H), 2.88 (ddd, *J* = 13.3, 6.7, 3.5 Hz, 1H), 1.26 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.3, 153.6, 129.9, 129.8, 128.2, 126.8, 124.6, 121.2, 116.7, 64.8, 63.8, 63.4, 60.5, 48.4, 38.7, 14.2; *m/z* (ESI-MS) 286.2 $[M + H]^+$.

1-(3-Chlorobenzyl)-1*H*-indole (2.100c):



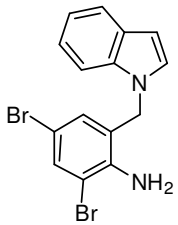
Following general procedure (A), compound **2.100c** was obtained from indoline and 3-chlorobenzaldehyde as white solid in 70% yield (R_f = 0.25 in EtOAc/Hexanes 5:95 v/v); mp: 36–38 ºC; IR (KBr) 3054, 2925, 1598, 1576, 1512, 1463, 1483, 1432, 1396, 1317, 1334, 1252, 1183, 1078, 1012, 884, 880, 741, 779, 763, 680 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (td, *J* = 7.6, 1.0 Hz, 1H), 7.38–7.28 (comp, 3H), 7.27–7.24 (comp, 2H), 7.21 (app t, *J* = 1.7 Hz, 1H), 7.18 (app d, *J* = 3.1 Hz, 1H), 7.00 (app d, *J* = 7.6 Hz, 1H), 6.69 (dd, *J* = 3.2, 0.8 Hz, 1H), 5.29 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.6, 136.1, 134.6, 129.9, 128.7, 128.0, 127.7, 126.7, 124.7, 121.8, 121.0, 119.6, 109.5, 102.0, 49.3; *m/z* (ESI-MS) 242.3 $[M + H]^+$.

1-(4-Ethylbenzyl)-1*H*-indole (2.100g):



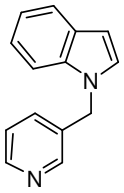
Following general procedure (A), compound **2.100g** was obtained from indoline and 4-ethylbenzaldehyde as white solid in 79% yield (R_f = 0.28 in EtOAc/Hexanes 5:95 v/v); mp: 40–42 ºC; IR (KBr) 3053, 2964, 2929, 2871, 1612, 1513, 1463, 1483, 1439, 1398, 1352, 1317, 1256, 1184, 1122, 1048, 1012, 883, 818, 762, 740, 716, 615 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (app d, *J* = 7.9 Hz, 1H), 7.4 (app d, *J* = 8.0 Hz, 1H), 7.28 (app td, *J* = 7.9, 1.1 Hz, 1H), 7.25–7.19 (comp, 4H), 7.1 (app d, *J* = 8.1 Hz, 2H), 6.7 (app d, *J* = 3.1 Hz, 1H), 5.3 (s, 2H), 2.75-2.67 (q, *J* = 7.6 Hz, 2H), 1.31 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.6, 136.3, 134.7, 128.7, 128.2, 128.1, 126.8, 121.6, 120.9, 119.4, 109.7, 101.5, 49.8, 28.4, 15.5; *m/z* (ESI-MS) 236.1 $[M + H]^+$.

2-((1*H*-Indol-1-yl)methyl)-4,6-dibromoaniline (2.100j):



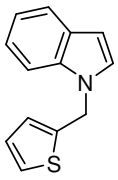
Following general procedure (A), compound **2.100j** was obtained from indoline and 2-amino-3,5-dibromobenzaldehyde as light brown solid in 80% yield (R_f = 0.26 in EtOAc/Hexanes 15:85 v/v); mp: 133–136 ºC; IR (KBr) 3471, 3380, 3054, 1617, 1512, 1461, 1406, 1319, 1251, 1196, 1065, 1011, 864, 763, 741, 690 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.69 (td, *J* = 7.9, 0.8 Hz, 1H), 7.59 (app d, *J* = 2.2 Hz, 1H), 7.35 (app dd, *J* = 8.0, 0.8 Hz, 1H), 7.26 (ddd, *J* = 8.3, 7.0, 1.1 Hz, 1H), 7.19 (ddd, *J* = 7.8, 7.1, 1Hz, 1H), 7.05 (app d, *J* = 2.2 Hz, 1H), 7.00 (app d, *J* = 3.2 Hz, 1H), 6.59 (dd, *J* = 3.1, 0.7 Hz, 1H), 5.08 (s, 2H), 3.89 (br s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.6, 136.1, 134.3, 131.1, 128.8, 127.0, 123.6, 122.2, 121.3, 120.1, 110.9, 109.6, 109.1, 102.9, 47.4 ; *m/z* (ESI-MS) 381.0 $[M + H]^+$.

1-(Pyridin-3-ylmethyl)-1*H*-indole (2.100l):



Following general procedure (A), compound **2.100l** was obtained from indoline and 3-pyridinecarboxaldehyde as colorless liquid in 77% yield (R_f = 0.23 in EtOAc/Hexanes 60:40 v/v); IR (KBr) 3053, 2924, 1610, 1577, 1512, 1483, 1463, 1426, 1397, 1356, 1316, 1360, 1175, 1124, 1026, 1012, 883, 792, 765, 742, 710, 620 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.52 (app s, 2H), 7.78 (app d, *J* = 8.2 Hz, 1H), 7.27 (app d, *J* = 8.3 Hz, 2H), 7.22 (td, *J* = 6.9, 1.3 Hz, 1H), 7.18–7.12 (comp, 2H), 7.10 (app dd, *J* = 3.1, 1.3 Hz, 1H), 6.61 (app d, *J* = 2.9 Hz, 1H), 5.25 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.8, 148.1, 135.8, 134.2, 132.9, 128.6, 127.7, 123.5, 121.8, 120.9, 119.6, 109.3, 102.1, 47.3; *m/z* (ESI-MS) 209.2 $[M + H]^+$.

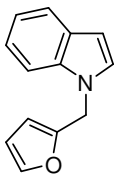
1-(Thiophen-2-ylmethyl)-1*H*-indole (2.100m):



Following general procedure (A), compound **2.100m** was obtained from indoline and thiophene-2-carboxaldehyde as light brown liquid in 90% yield (R_f = 0.20 in EtOAc/Hexanes 5:95 v/v); IR (KBr) 3052, 1610, 1511, 1482, 1462, 1437, 1399, 1313, 1261, 1233, 1184, 851, 763, 740, 703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.78 (app d,

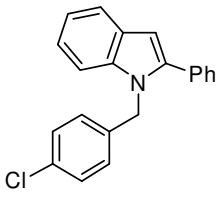
J = 8.2 Hz, 1H), 7.49 (app d, *J* = 8.2 Hz, 1H), 7.34 (dt, *J* = 8.2, 1.0 Hz, 1H), 7.28–7.25 (m, 1H), 7.23 (d, *J* = 3.1 Hz, 1H), 7.02–6.99 (comp, 2H), 6.42 (td, *J* = 3.2, 1.0 Hz, 1H), 6.19–6.17 (m, 1H), 6.10–6.09 (m, 1H), 6.67 (app d, *J* = 3.2 Hz, 1H), 5.49 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.4, 142.5, 136.0, 128.7, 127.7, 121.7, 120.9, 119.5, 110.4, 109.4, 108.0, 101.7, 43.1; *m/z* (ESI-MS) 214.0 $[M + H]^+$.

1-(Furan-2-ylmethyl)-1*H*-indole (2.100n):



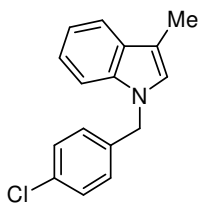
Following general procedure (A), compound **2.100n** was obtained from indoline and 2-furaldehyde as colorless liquid in 76% yield (R_f = 0.23 in EtOAc/Hexanes 5:95 v/v); IR (KBr) 3054, 2923, 1612, 1512, 1484, 1462, 1399, 1334, 1313, 1266, 1233, 1168, 1146, 1074, 1011, 909, 884, 739, 597 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (app dd, *J* = 8.0, 0.8 Hz, 1H), 7.30 (app d, *J* = 8.0 Hz, 1H), 7.23–7.22 (m, 1H), 7.13–7.09 (m, 1H), 7.04–7.00 (comp, 2H), 6.42 (td, *J* = 3.2, 1.0 Hz, 1H), 6.19–6.17 (m, 1H), 6.10–6.09 (m, 1H), 5.11 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.4, 142.5, 136.0, 128.7, 127.7, 121.7, 120.9, 119.5, 110.4, 109.4, 108.0, 101.7, 43.1; *m/z* (ESI-MS) 198.2 $[M + H]^+$.

1-(4-Chlorobenzyl)-2-phenyl-1*H*-indole (2.100o):



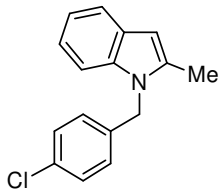
Following general procedure (A), compound **2.100o** was obtained from 2-phenylindoline and 4-chlorobenzaldehyde as pale white solid in 85% yield (R_f = 0.26 in EtOAc/Hexanes 5:95 v/v); mp: 121–124 ºC; IR (KBr) 3057, 1892, 1603, 1490, 1361, 1475, 1443, 1409, 1391, 1367, 1344, 1315, 1238, 1176, 1160, 1088, 1014, 973, 919, 817, 748, 770, 699, 664 cm^{-1}; NMR (500 MHz, $CDCl_3$) δ 7.79–7.77 (m, 1H), 7.52–7.45 (comp, 5H), 7.31–7.30 (comp, 2H), 7.27–7.24 (comp, 3H), 7.01 (app d, *J* = 8.2 Hz, 2H), 6.76 (s, 1H), 5.38 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.6, 137.8, 136.6, 132.9, 132.5, 129.1, 128.8, 128.5, 128.3, 128.1, 127.2, 122.0, 120.6, 120.3, 110.2, 102.6, 47.0; *m/z* (ESI-MS) 308.2 $[M + H]^+$.

1-(4-Chlorobenzyl)-3-methyl-1*H*-indole (2.100p):



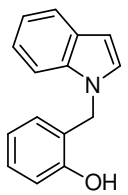
Following general procedure (A), compound **2.100p** was obtained from 3-methylindoline and 4-chlorobenzaldehyde as white solid in 70% yield (R_f = 0.30 in EtOAc/Hexanes 5:95 v/v); mp = 42–44 ºC; IR (KBr) 3052, 2916, 2860, 1614, 1491, 1466, 1438, 1409, 1387, 1351, 1330, 1297, 1177, 1126, 1037, 805, 781, 739 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.67–7.64 (app d, *J* = 7.7 Hz, 1H), 7.31–7.26 (comp, 2H), 7.25–7.21 (comp, 2H), 7.21–7.16 (m, 1H), 7.06 (app d, *J* = 8.1 Hz, 2H), 6.91 (s, 1H), 5.23 (s, 2H), 2.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.5, 136.4, 133.2, 129.0, 128.8, 128.0, 125.6, 121.7, 119.1, 118.9, 111.1, 109.3, 49.1, 9.6; *m/z* (ESI-MS) 256.2 $[M + H]^+$.

1-(4-Chlorobenzyl)-2-methyl-1*H*-indole (2.100q):



Following general procedure (A), compound **2.100q** was obtained from 2-methylindoline and 4-chlorobenzaldehyde as white solid in 35% yield (R_f = 0.21 in EtOAc/Hexanes 5:95 v/v); mp = 104–108 ºC; IR (KBr) 3052, 2980, 2937, 1899, 1578, 1554, 1490, 1478, 1463, 1438, 1398, 1352, 1337, 1252, 1216, 1165, 1139, 1014, 921, 896, 840, 801, 747, 775, 665, 617 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.52–7.51 (m, 1H), 7.19–7.16 (comp, 2H), 7.12–7.09 (m, 1H), 7.07–7.02 (comp, 2H), 6.83 (app d, *J* = 8.6 Hz, 1H), 6.29 (s, 1H), 5.20 (s, 2H), 2.30 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.0, 136.4, 136.3, 133.0, 128.9, 128.2, 127.3, 120.9, 119.8, 119.6, 108.9, 100.7, 45.8, 12.7; *m/z* (ESI-MS) 256.2 $[M + H]^+$.

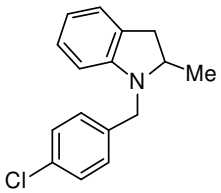
2-((1*H*-Indol-1-yl)methyl)phenol (2.100r):



Following general procedure (A), compound **2.100r** was obtained from indoline and salicylaldehyde as colorless liquid in 50% yield (R_f = 0.26 in EtOAc/Hexanes 15:85 v/v); IR (KBr) 3508, 3053, 2924, 1701, 1610, 1596, 1510, 1482, 1456, 1399, 1318, 1257, 1170, 1097, 1042, 1011, 961, 923, 883, 843, 743, 706, 623 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.66 (app d, *J* = 8.0 Hz, 1H), 7.39

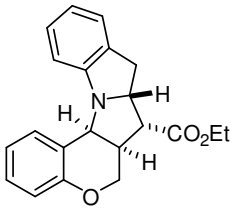
(app dd, *J* = 8.2, 0.8 Hz, 1H), 7.22–7.10 (comp, 4H), 6.88–6.81 (comp, 2H), 7.75(app dd, *J* = 7.9, 0.8 Hz, 1H), 7.56 (app dd, *J* = 3.3, 0.8 Hz, 1H), 6.88–6.81 (m, 2H), 6.75 (app dd, *J* = 8.0, 0.8 Hz, 1H), 6.56 (app dd, *J* = 3.2, 0.8 Hz, 1H), 5.35 (s, 2H), 4.82 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.3, 136.6, 129.2, 129.1, 128.9, 128.6, 124.2, 121.9, 121.5, 121.2, 119.7, 115.7, 110.0, 101.8, 45.4; *m/z* (ESI-MS) 224.2 $[M + H]^+$.

1-(4-Chlorobenzyl)-2-methylindoline (2.106):



Following general procedure (A), compound **2.106** was obtained from 2-methylindoline and 4-chlorobenzaldehyde as colorless liquid in 20% yield (R_f = 0.28 in EtOAc/Hexanes 5:95 v/v); IR (KBr) 3049, 2963, 2838, 1606, 1488, 1461, 1377, 1350, 1306, 1267, 1237, 1145, 1092, 1014, 800, 745, 716 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33–7.27 (comp, 4H), 7.06 (app d, *J* = 7.2 Hz, 1H), 6.99 (app t, *J* = 7.6 Hz, 1H), 6.65 (app t, *J* = 7.5 Hz, 1H), 6.27 (app d, *J* = 7.8 Hz, 1H), 4.3 (d, *J* = 16 Hz, 1H), 4.2 (d, *J* = 16 Hz, 1H), 3.77–3.63 (m, 1H), 3.18 (dd, *J* = 8.3, 15.4 Hz, 1H), 2.69 (dd, *J* = 9.4, 15.6 Hz, 1H), 1.29 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.4, 137.9, 132.5, 128.8, 128.5(8), 128.5(7), 127.3, 124.2, 117.6, 106.8, 60.8, 50.7, 37.3, 19.6; *m/z* (ESI-MS) 258.2 $[M + H]^+$.

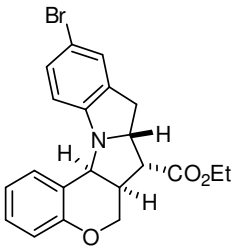
(6a*R*,7*R*,7a*R*,13a*S*)-Ethyl 6,6a,7,7a,8,13a-hexahydrochromeno[3',4':4,5]pyrrolo[1,2-*a*]indole-7-carboxylate (2.111a):



Following general procedure (A), compound **2.111a** was obtained from indoline and (*E*)-ethyl 4-(2-formylphenoxy)but-2-enoate as pale white solid in 50 % yield (R_f = 0.36 in EtOAc/Hexanes 15:85 v/v); mp = 114–116 ºC; IR (KBr) 2977, 1727, 1604, 1583, 1479, 1459, 1356, 1311, 1265, 1221, 1179, 1126, 1036, 750 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (app d, *J* = 8.0 Hz, 1H), 7.22–7.15 (comp, 2H), 7.08 (app d, *J* = 7.3 Hz, 1H), 7.03 (dt, *J* = 7.3, 1.3 Hz, 2H), 6.92 (app d, *J* = 7.8 Hz, 1H), 6.87 (app dd, *J* = 8.1, 1.1 Hz, 1H), 6.84 (dt, *J* = 7.5, 1.0 Hz, 1H), 4.73 (d, *J* = 7.6 Hz, 1H), 4.41 (dt, *J* = 9.0, 4.5 Hz, 1H), 4.25 (dd, *J* = 11.5, 3.5

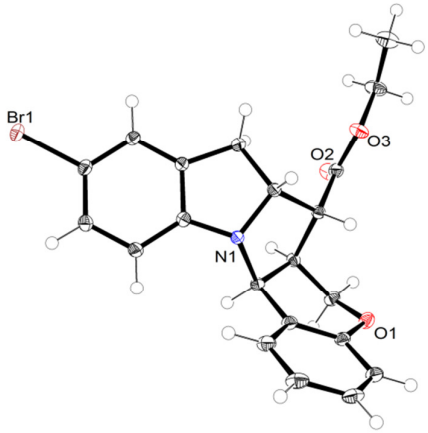
Hz, 1H), 4.13–4.06 (comp, 2H), 4.02–3.95 (m, 1H), 3.24 (t, *J* = 8.3 Hz, 1H), 3.15 (dd, *J* = 16.9, 9.9 Hz, 1H), 3.07 (dd, *J* = 16.9, 4.5 Hz, 1H), 3.03–2.98 (m, 1H), 1.16 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0, 154.5, 153.4, 130.2, 129.8, 128.4, 127.7, 124.4, 124.2, 121.6, 120.5, 116.8, 110.6, 65.3, 64.7, 61.8, 60.8, 48.6, 39.6, 32.2, 13.9; *m/z* (ESI-MS) 336.3 $[M + H]^+$.

(6a*R*,7*R*,7a*R*,13a*S*)-Ethyl 10-bromo-6,6a,7,7a,8,13a-hexahydrochromeno[3',4':4,5]-pyrrolo[1,2-*a*]indole-7-carboxylate (2.111b):

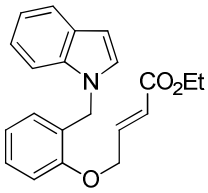


Following general procedure (A), compound **2.111b** was obtained from 5-bromoindoline and (*E*)-ethyl 4-(2-formylphenoxy)but-2-enoate as light brown solid in 63% yield (R_f = 0.22 in EtOAc/Hexanes 10:90 v/v); mp = 110–113 ºC; IR (KBr) 2978, 1727, 1638, 1583, 1486, 1473, 1452, 1356, 1311, 1258, 1221, 1179, 1128, 1091, 1036, 870, 810, 757 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (app d, *J* = 8.5 Hz, 1H), 7.25 (app d, *J* = 8.5 Hz, 1H), 7.19 (app d, *J* = 9.0 Hz, 1H), 7.10 (app s, 1H), 7.01 (app t, *J* = 7.6 Hz, 1H), 6.85 (app d, *J* = 7.9 Hz, 1H), 6.76 (app d, *J* = 8.3 Hz, 1H), 4.67 (d, *J* = 7.5 Hz, 1H), 4.38 (dt, *J* = 9.2, 4.3 Hz, 1H), 4.23 (dd, *J* = 11.5, 3.3 Hz, 1H), 4.13–3.98 (comp, 3H), 3.21 (t, *J* = 8.2 Hz, 1H), 3.12 (dd, *J* = 17.0, 9.7 Hz, 1H), 3.12 (dd, *J* = 16.9, 9.5 Hz, 1H), 3.03 (dd, *J* = 17.0, 4.4 Hz, 1H), 3.00–2.96 (m, 1H), 1.17 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 154.5, 152.5, 132.2, 130.5, 130.0, 128.6, 127.4, 123.6, 121.7, 116.9, 112.3, 111.7, 65.2, 64.9, 61.7, 60.9, 48.5, 39.8, 31.9, 13.9; *m/z* (ESI-MS) 414.2 $[M]^+$, 416.1 $[M + 2]^+$.

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

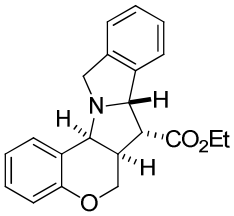


(*E*)-Ethyl 4-(2-((1*H*-indol-1-yl)methyl)phenoxy)but-2-enoate (2.112a):



Following general procedure (A), compound **16a** was obtained from indoline and (*E*)-ethyl 4-(2-formylphenoxy)but-2-enoate as colorless liquid in 43% yield (R_f = 0.27 in EtOAc/Hexanes 15:85 v/v); IR (KBr) 3054, 2980, 2934, 1719, 1664, 1602, 1511, 1492, 1462, 1366, 1335, 1305, 1277, 1241, 1178, 1114, 1078, 1045, 968, 946, 837, 742, 682 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33 (app d, *J* = 8.1 Hz, 1H), 7.24–7.08 (comp, 5H), 6.87–6.81 (comp, 2H), 6.71 (app d, *J* = 7.4 Hz, 1H), 6.56 (app dd, *J* = 3.2, 0.8 Hz, 1H), 6.19 (app dt, *J* = 15.6, 2.2 Hz, 1H), 5.40 (s, 2H), 4.77 (app dd, *J* = 2.0 Hz, 2H), 4.27–4.21 (q, *J* = 7.1 Hz, 2H), 1.32 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 155.3, 142.3, 136.6, 128.9, 128.8, 128.7, 128.4, 126.5, 122.4, 121.8, 121.6, 121.1, 119.6, 111.4, 110.0, 101.8, 66.8, 60.9, 45.3, 14.5; *m/z* (ESI-MS) 336.1 $[M + H]^+$.

(6a*R*,7*R*,7a*S*,13a*S*)-Ethyl 6,6a,7,7a,12,13a-hexahydrochromeno[3',4':4,5]pyrrolo[2,1-*a*]isoindole-7-carboxylate (2.114):

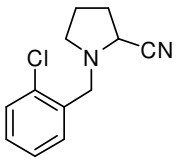


Following general procedure (A), compound **2.114** was obtained from isoindoline and (*E*)-ethyl 4-(2-formylphenoxy)but-2-enoate as white solid in 72 % yield (R_f = 0.29 in EtOAc/Hexanes 20:80 v/v); IR (KBr) 2923, 2360, 1562, 1456, 1337, 1192, 1092, 1089, 755 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.50 (app dd, *J* = 7.8, 1.4 Hz, 1H), 7.25–7.21 (comp, 2H), 7.21–7.15 (comp, 2H), 7.15–7.11 (m, 1H), 6.98 (dt, *J* = 7.4, 1.2 Hz, 1H), 6.86 (app dd, *J* = 8.2, 1.1 Hz, 1H), 5.02 (app dd, *J* = 8.6, 2.2 Hz, 1H), 4.64 (d, *J* = 13.7 Hz, 1H), 4.40 (d, *J* = 6.9 Hz, 1H), 4.36 (dd, *J* = 13.6, 2.4 Hz, 1H), 4.25 (dd, *J* = 13.3, 3.6 Hz, 1H), 4.12 (dd, *J* = 11.2, 6.9 Hz, 1H), 3.91–3.81 (dq, *J* = 10.8, 7.8 Hz, 1H), 3.81–3.71 (dq, *J* = 10.8, 7.8 Hz, 1H), 3.07 (dd, *J* = 8.6, 5.7 Hz, 1H), 3.16–3.09 (m, 1H), 1.05 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 154.1, 140.8, 138.6, 130.0, 128.4, 127.9, 126.7, 124.3, 123.3, 122.4, 121.4, 116.9, 71.3, 65.3, 63.0, 61.1, 60.5, 50.6, 40.9, 13.9; *m/z* (ESI-MS) 336.4 $[M + H]^+$.

General Procedure (B) for the Decarboxylative Strecker Reaction:

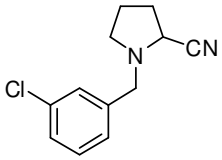
A 10 mL microwave reaction tube was charged with a 10 x 8 mm SiC passive heating element, amino acid (1.3 mmol), *n*-BuOH (2 mL), aldehyde (1 mmol) and TMSCN (1.2 mmol). The reaction tube was sealed with a Teflon-lined snap cap, and heated in a microwave reactor at 200 °C (200 W, 70–150 psi) for 10 minutes (***Note: SiC passive heating elements must not be used in conjunction with stir bars for they may score glass and cause vessel failure***). After cooling with compressed air flow, the reaction mixture was transferred to a round bottom flask and the vessel was rinsed with EtOAc (4 x 2 mL). Solvent was then removed in vacuo and the reaction mixture was loaded onto a short column and purified by silica gel chromatography. ***Note: Due to the use of TMSCN and the potential for HCN formation, all operations should be conducted inside a well-ventilated fume hood.***

1-(2-Chlorobenzyl)pyrrolidine-2-carbonitrile (2.122b):



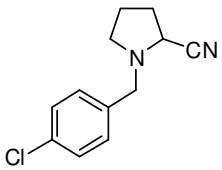
Following the general procedure (B), compound **2.122b** was obtained from *L*-proline and *o*-chlorobenzaldehyde as a colorless liquid in 97% yield (R_f = 0.17 in hexanes/EtOAc 95:5 v/v); IR (KBr) 2960, 2815, 2221, 1572, 1474, 1444, 1376, 1335, 1248, 1138, 1052, 1039, 882, 755 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.43 (app dd, *J* = 7.2, 2.0 Hz, 1H), 7.38–7.34 (m, 1H), 7.27–7.19 (comp, 2H), 3.98 (d, *J* = 13.8 Hz, 1H), 3.86 (d, *J* = 13.8 Hz, 1H), 3.77 (dd, *J* = 7.4, 2.6 Hz, 1H), 2.95–2.88 (m, 1H), 2.70–2.62 (m, 1H), 2.24–2.09 (comp, 2H), 2.02–1.84 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.3, 134.3, 130.5, 129.7, 128.7, 126.7, 118.3, 53.6, 53.5, 51.1, 29.7, 22.0; *m/z* (ESI–MS) 194.2 $[M–CN]^+$.

1-(3-Chlorobenzyl)pyrrolidine-2-carbonitrile (2.122c):



Following the general procedure (B), compound **2.122c** was obtained from *L*-proline and *m*-chlorobenzaldehyde as a colorless liquid in 89% yield (R_f = 0.14 in hexanes/EtOAc 95:5 v/v); IR (KBr) 3062, 2961, 2881, 2820, 2222, 1600, 1576, 1475, 1431, 1373, 1334, 1210, 1144, 1076, 995, 883, 786, 685; ^1H NMR (500 MHz, $CDCl_3$) 7.36 (s, 1H), 7.27–7.20 (comp, 3H), 3.87 (d, *J* = 13.3 Hz, 1H), 3.71 (dd, *J* = 7.5, 2.4 Hz, 1H), 3.65 (d, *J* = 13.2 Hz, 1H), 2.92 (ddd, *J* = 12.7, 8.5, 4.2 Hz, 1H), 2.61–2.52 (m, 1H), 2.23–2.07 (comp, 2H), 2.01–1.87 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.7, 134.3, 129.7, 128.6, 127.6, 126.8, 117.7, 55.8, 53.2, 51.1, 29.4, 21.8; *m/z* (ESI–MS) 194.1 $[M–CN]^+$.

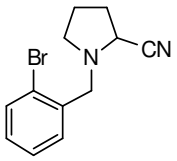
1-(4-Chlorobenzyl)pyrrolidine-2-carbonitrile (2.122d):



Following the general procedure (B), compound **2.122d** was obtained from *L*-proline and *p*-chlorobenzaldehyde as a white sticky solid in 97% yield (R_f = 0.13 in hexanes/EtOAc 95:5 v/v); IR (KBr) 2960, 2819, 2222, 1644, 1491, 1447, 1409, 1376, 1334, 1124, 1084, 1016, 881, 840 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.29 (comp, 4H), 3.87 (d, *J* = 13.2 Hz, 1H), 3.67 (dd, *J* = 7.4, 2.2 Hz, 1H),

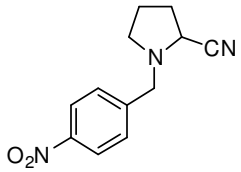
3.63 (d, *J* = 13.2 Hz, 1H), 2.94–2.86 (m, 1H), 2.59–2.51 (m, 1H), 2.20–2.07 (comp, 2H), 2.00–1.84 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.1, 133.1, 130.0, 128.6, 117.7, 55.7, 53.1, 51.1, 29.4, 21.8; *m/z* (ESI–MS) 194.1 $[M–CN]^+$.

1-(2-Bromobenzyl)pyrrolidine-2-carbonitrile (2.122e):



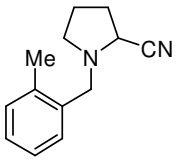
Following the general procedure (B), compound **2.122e** was obtained from *L*-proline and *o*-bromobenzaldehyde as a colorless liquid in 89% yield (R_f = 0.19 in hexanes/EtOAc 93:7 v/v); IR (KBr) 3059, 2959, 2814, 2221, 1567, 1468, 1439, 1375, 1335, 1246, 1134, 1028, 994, 882, 754, 660 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.55 (app dd, *J* = 7.9, 1.2 Hz, 1H), 7.42 (app dd, *J* = 7.6, 1.6 Hz, 1H), 7.28 (app td, *J* = 7.5, 1.2 Hz, 1H), 7.13 (app td, *J* = 7.7, 1.7 Hz, 1H), 3.95 (d, *J* = 13.8 Hz, 1H), 3.85 (d, *J* = 13.8 Hz, 1H), 3.77 (dd, *J* = 7.5, 2.7 Hz, 1H), 2.92 (ddd, *J* = 12.8, 8.4, 4.5 Hz, 1H), 2.66 (m, 1H), 2.40 (s, 3H), 2.23–2.09 (comp, 2H), 2.01–1.84 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.8, 132.9, 130.5, 128.8, 127.3, 124.4, 118.2, 55.9, 53.4, 51.0, 29.6, 22.0; *m/z* (ESI–MS) 239.2 $[M–CN]^+$.

1-(4-Nitrobenzyl)pyrrolidine-2-carbonitrile (2.122f):



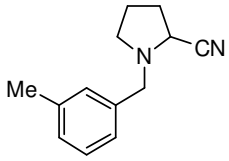
Following the general procedure (B), but performing the reaction at 180 ºC for 30 min, compound **2.122f** was obtained from *L*-proline and *p*-nitrobenzaldehyde as an off-white solid in 80% yield (R_f = 0.24 in hexanes/EtOAc 80:20 v/v); mp: 80–83 ºC; IR (KBr) 2961, 2820, 2220, 1606, 1518, 1346, 1108, 1015, 853, 806, 739 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 8.17 (d, *J* = 8.4 Hz, 2H), 7.53 (d, *J* = 8.4 Hz, 2H), 3.98 (d, *J* = 13.8 Hz, 1H), 3.80 (d, *J* = 13.9 Hz, 1H), 3.72 (dd, *J* = 7.6, 2.5 Hz, 1H), 2.91 (ddd, *J* = 12.7, 8.4, 4.3 Hz, 1H), 2.63–2.56 (m, 1H), 2.26–2.10 (comp, 2H), 2.03–1.87 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.3, 145.2, 129.3, 123.7, 117.6, 55.8, 53.4, 51.3, 29.5, 21.9; *m/z* (ESI–MS) 205.2 $[M–CN]^+$.

1-(2-Methylbenzyl)pyrrolidine-2-carbonitrile (2.122g):



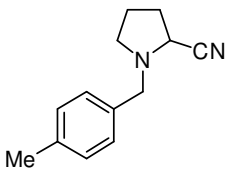
Following the general procedure (B), compound **2.122g** was obtained from *L*-proline and *o*-tolualdehyde as a colorless liquid in 95% yield (R_f = 0.21 in hexanes/EtOAc 95:5 v/v); IR (KBr) 3018, 2957, 2882, 2813, 2221, 1693, 1494, 1460, 1375, 1334, 1286, 1184, 1125, 1051, 882, 745 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.33 (app d, *J* = 7.4 Hz, 1H), 7.23–7.15 (comp, 3H), 3.93 (d, *J* = 13.0 Hz, 1H), 3.67 (d, *J* = 12.9 Hz, 1H), 3.68 (dd, *J* = 7.3, 2.9 Hz, 1H), 2.91 (ddd, *J* = 12.7, 8.4, 4.3 Hz, 1H), 2.65–2.58 (m, 1H), 2.40 (s, 3H), 2.21–2.08 (comp, 2H), 2.01–1.85 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.3, 135.6, 130.3, 129.3, 127.4, 125.7, 118.1, 54.4, 53.2, 51.0, 29.5, 21.8, 18.9; *m/z* (ESI–MS) 174.1 $[M–CN]^+$.

1-(3-Methylbenzyl)pyrrolidine-2-carbonitrile (2.122h):



Following the general procedure (B), compound **2.122h** was obtained from *L*-proline and *m*-tolualdehyde as a colorless liquid in 92% yield (R_f = 0.14 in hexanes/EtOAc 95:5 v/v); IR (KBr) 2959, 2922, 2881, 2814, 2221, 1610, 1487, 1460, 1378, 1334, 1160, 1124, 1089, 886, 789, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.23 (m, 1H), 7.20–7.15 (comp, 2H), 7.10 (app d, *J* = 7.4 Hz, 1H), 3.90 (d, *J* = 12.9 Hz, 1H), 3.71 (dd, *J* = 7.4, 2.4 Hz, 1H), 3.64 (d, *J* = 12.9 Hz, 1H), 2.95 (ddd, *J* = 12.7, 8.5, 4.2 Hz, 1H), 2.63–2.56 (m, 1H), 2.36 (s, 3H), 2.25–2.07 (comp, 2H), 2.02–1.86 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.0, 137.4, 129.4, 128.2, 128.1, 125.8, 117.8, 56.4, 53.1, 51.1, 29.4, 21.7, 21.2; *m/z* (ESI–MS) 174.1 $[M–CN]^+$.

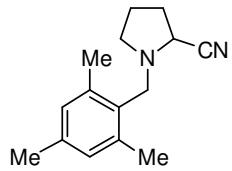
1-(4-Methylbenzyl)pyrrolidine-2-carbonitrile (2.122i):



Following the general procedure (B), compound **2.122i** was obtained from *L*-proline and *p*-tolualdehyde as a colorless liquid in 93% yield (R_f = 0.14 in hexanes/EtOAc 95:5 v/v); IR (KBr) 2960, 2815, 2220, 1633, 1573, 1473, 1445, 1376, 1132, 1052, 1039, 755, 683 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.26 (d, *J* = 7.9 Hz, 2H), 7.15 (d, *J* = 7.8 Hz, 2H), 3.89 (d, *J* = 12.9 Hz, 1H), 3.69 (dd, *J* = 7.4,

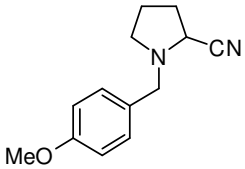
2.6 Hz, 1H), 3.64 (d, *J* = 12.9 Hz, 1H), 2.94 (ddd, *J* = 12.5, 8.4, 4.2 Hz, 1H), 2.62–2.55 (m, 1H), 2.35 (s, 3H), 2.21–2.07 (comp, 2H), 2.01–1.85 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.0, 134.4, 129.1, 128.7, 117.9, 56.1, 53.0, 51.1, 29.4, 21.8, 21.0; *m/z* (ESI–MS) 174.1 $[M–CN]^+$.

1-(2,4,6-Trimethylbenzyl)pyrrolidine-2-carbonitrile (2.122j):



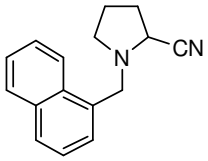
Following the general procedure (B), compound **2.122j** was obtained from *L*-proline and mesitaldehyde as a colorless liquid in 95% yield (R_f = 0.16 in hexanes/EtOAc 97:3 v/v); IR (KBr) 2954, 2858, 2221, 1613, 1461, 1374, 1332, 1120, 1046, 851, 665 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 6.84 (s, 2H), 3.85 (d, *J* = 12.9 Hz, 1H), 3.74 (d, *J* = 12.9 Hz, 1H), 3.70 (dd, *J* = 7.1, 3.4 Hz, 1H), 2.78 (ddd, *J* = 13.0, 8.5, 4.6 Hz, 1H), 2.66–2.55 (m, 1H), 2.37 (s, 6H), 2.27 (s, 3H), 2.15–2.06 (comp, 2H), 1.95–1.85 (m, 1H), 1.85–1.76 (m, 1H); ^{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-(4-Methoxybenzyl)pyrrolidine-2-carbonitrile (2.122k):



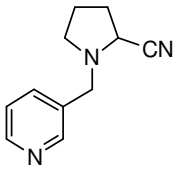
Following the general procedure (B), compound **2.122k** was obtained from *L*-proline and *p*-anisaldehyde as a colorless liquid in 92% yield as a mixture of regioisomers; rr = 4:1 (R_f = 0.19 in hexanes/EtOAc 90:10 v/v); Characterization data of the major regioisomer: IR (KBr) 2958, 2816, 2222, 1612, 1513, 1462, 1377, 1301, 1245, 1174, 10393, 821 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.27 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 3.85 (d, *J* = 12.9 Hz, 1H), 3.79 (s, 3H), 3.65 (dd, *J* = 12.4, 2.7 Hz, 1H), 3.59 (d, *J* = 12.8 Hz, 1H), 2.91 (ddd, *J* = 12.5, 8.5, 4.2 Hz, 1H), 2.59–2.52 (m, 1H), 2.20–2.06 (comp, 2H), 2.00–1.82 (comp, 2H); ^{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, 29.3, 21.7; *m/z* (ESI–MS) 190.0 $[M–CN]^+$.

1-(Naphthalen-1-ylmethyl)pyrrolidine-2-carbonitrile (2.122l):



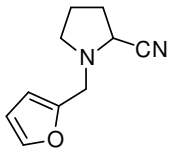
Following the general procedure (B), compound **2.122l** was obtained from *L*-proline and 1-naphthaldehyde as an off-white solid in 89% yield (R_f = 0.27 in hexanes/EtOAc 95:5 v/v);); mp: 42–44 ºC; IR (KBr) 2957, 2817, 2221, 1597, 1509, 1460, 1379, 1331, 1234, 1142, 1019, 880, 779 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 8.26 (app d, *J* = 8.5 Hz, 1H), 7.88 (m, 1H), 7.83 (app d, *J* = 8.2 Hz, 1H), 7.58–7.49 (comp, 3H), 7.44 (m, 1H), 4.45 (d, *J* = 12.8 Hz, 1H), 4.02 (d, *J* = 12.9 Hz, 1H), 3.64 (m, 1H), 3.02 (ddd, *J* = 12.7, 8.5, 4.2, 1H), 2.72–2.63 (m, 1H), 2.15–2.06 (comp, 2H), 2.02–1.85 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) 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 (2.122m):



Following the general procedure B, compound **2.122m** was obtained from *L*-proline and 3-pyridinecarboxaldehyde as a colorless liquid in 88% yield (R_f = 0.19 in hexanes/EtOAc 50:50 v/v); IR (KBr) 2962, 2822, 2222, 1656, 1579, 1479, 1427, 1378, 1330, 1187, 1124, 1029, 799, 714 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 8.54 (s, 1H), 8.47 (app d, *J* = 4.1 Hz, 1H), 7.63 (app d, *J* = 7.9 Hz, 1H), 7.22 (app dd, *J* = 7.8, 4.8 Hz, 1H), 3.85 (d, *J* = 13.4 Hz, 1H), 3.65 (d, *J* = 13.2 Hz, 1H), 3.67–3.64 (m, 1H), 2.84 (ddd, *J* = 12.4, 8.4, 4.4 Hz, 1H), 2.56–2.49 (comp, 1H), 2.18–2.03 (comp, 2H), 1.96–1.79 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.9, 148.7, 136.3, 133.0, 123.3, 117.6, 53.7, 53.1, 51.0, 29.4, 21.8; *m/z* (ESI–MS) 188.1 $[M+H]^+$, 161.2 $[M–CN]^+$.

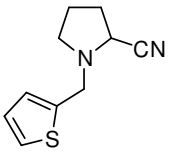
1-(Furan-2-ylmethyl)pyrrolidine-2-carbonitrile (2.122n):



Following the general procedure (B), compound **2.122n** was obtained from *L*-proline and furfural as a colorless liquid in 83% yield (R_f = 0.16 in hexanes/EtOAc 90:10 v/v); IR (KBr) 2962, 2882, 2818, 2222, 1601, 1505, 1445, 1372, 1335, 1224, 1149, 1014, 916, 739, cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.40 (m,

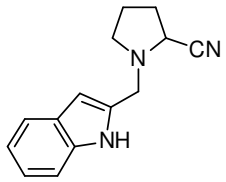
1H), 6.33 (m, 1H), 6.29 (d, *J* = 3.1 Hz, 1H), 3.88 (d, *J* = 13.8 Hz, 1H), 3.76 (d, *J* = 13.9 Hz, 1H), 3.73 (dd, *J* = 7.8, 2.8 Hz, 1H), 2.96 (ddd, *J* = 12.8, 8.4, 4.4 Hz, 1H), 2.66–2.59 (m, 1H), 2.24–2.08 (comp, 2H), 2.02–1.86 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.2, 142.8, 118.0, 110.5, 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 (2.122o):



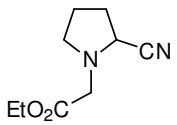
Following the general procedure (B), compound **2.122o** was obtained from *L*-proline and 2-thiophenecarboxaldehyde as a colorless liquid in 95% yield (R_f = 0.24 in hexanes/EtOAc 90:10 v/v); IR (KBr) 2959, 2808, 2222, 1645, 1444, 1377, 1329, 1223, 1117, 951, 851, 696 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.25 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.00 (m, 1H), 6.94 (dd, *J* = 5.1, 3.5 Hz, 1H), 4.07 (d, *J* = 13.8 Hz, 1H), 3.93 (d, *J* = 13.8 Hz, 1H), 3.77 (dd, *J* = 7.6, 2.5 Hz, 1H), 3.01 (ddd, *J* = 12.5, 8.3, 4.2 Hz, 1H), 2.64–2.56 (m, 1H), 2.22–2.08 (comp, 2H), 2.02–1.86 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.6, 126.5, 126.3, 125.4, 117.7, 52.8, 51.0, 50.7, 29.4, 21.8; *m/z* (ESI–MS) 166.0 $[M–CN]^+$.

1-((1*H*-Indol-2-yl)methyl)pyrrolidine-2-carbonitrile (2.122p):



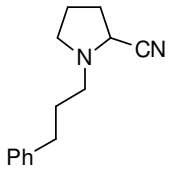
Following the general procedure (B), compound **2.122p** was obtained from *L*-proline and indole-2-carboxaldehyde as a colorless liquid in 62% yield (R_f = 0.25 in hexanes/CH_2Cl_2 20:80 v/v); IR (KBr) 3056, 2961, 2881, 2821, 2224, 1619, 1456, 1421, 1378, 1329, 1289, 1231, 1141, 1087, 995, 927, 879, 791, 750 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 8.32 (br s, 1H), 7.59 (app d, *J* = 7.8 Hz, 1H), 7.34 (app dd, *J* = 8.1, 0.7 Hz, 1H), 7.19 (m, 1H), 7.11 (m, 1H), 6.47 (s, 1H), 4.08 (d, *J* = 13.6 Hz, 1H), 3.86 (d, *J* = 13.7 Hz, 1H), 3.72 (dd, *J* = 7.2, 3.0 Hz, 1H), 2.95 (ddd, *J* = 12.7, 8.4, 4.3 Hz, 1H), 2.69–2.61 (m, 1H), 2.23–2.11 (comp, 2H), 2.05–1.88 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.1, 134.7, 128.1, 121.8, 120.4, 119.7, 117.8, 110.7, 101.8, 53.2, 51.3, 49.5, 29.4, 21.9; *m/z* (ESI–MS) 199.0 $[M–CN]^+$.

Ethyl 2-(2-cyanopyrrolidin-1-yl)acetate (2.122q):



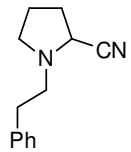
Following the general procedure (B), compound **2.122q** was obtained from *L*-proline and ethyl glyoxalate solution (~50% in toluene) as a colorless liquid in 97% yield (R_f = 0.26 in hexanes/EtOAc 80:20 v/v); IR (KBr) 2982, 2822, 2220, 1743, 1464, 1428, 1384, 1200, 1160, 1028, 863 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 4.13 (t, *J* = 4.1 Hz, 2H), 4.08 (dd, *J* = 7.8, 4.1 Hz, 1H), 3.51–3.40 (comp, 2H), 3.00 (ddd, *J* = 13.0, 8.8, 5.1 Hz, 1H), 2.66–2.58 (m, 1H), 2.26–2.16 (m, 1H), 2.12–2.14 (m, 1H), 1.95–1.84 (comp, 2H), 1.22 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.7, 118.0, 60.7, 52.8, 52.4, 51.3, 29.8, 22.1, 13.9; *m/z* (ESI–MS) 156.1 $[M–CN]^+$.

1-(3-Phenylpropyl)pyrrolidine-2-carbonitrile (2.122r):



Following the general procedure (B), compound **2.122r** was obtained from *L*-proline and hydrocinnamaldehyde as colorless liquid in 72% yield (R_f = 0.16 in hexanes/EtOAc 90:10 v/v); IR (KBr) 3026, 2942, 2813, 2220, 1602, 1496, 1454, 1386, 1318, 1182, 1145, 1123, 1079, 1030, 966, 882, 747, 700 cm^{-1}; ^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* = 12.9, 8.4, 4.6 Hz, 1H), 2.73 (m, 1H), 2.69 (t, *J* = 7.6 Hz, 2H), 2.64–2.52 (comp, 2H), 2.23–2.08 (comp, 2H), 2.01–1.82 (comp, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $[M–CN]^+$.

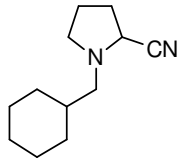
1-Phenethylpyrrolidine-2-carbonitrile (2.122s):



Following the general procedure (B), compound **2.122s** was obtained from *L*-proline and phenylacetaldehyde as a colorless liquid in 91% yield (R_f = 0.24 in hexanes/EtOAc 85:15 v/v); IR (KBr) 3027, 2949, 2815, 2220, 1603, 1497, 1454, 1383, 1342, 1181, 1146, 1122, 1079, 1030, 884, 751, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.33–7.27 (comp, 2H), 7.25–7.18 (comp, 3H), 3.84 (dd, *J* = 7.4, 2.6 Hz, 1H), 3.01–2.91 (comp, 2H), 2.88–2.78 (comp, 3H), 2.63–2.57 (m, 1H), 2.23–2.09 (comp, 2H), 2.01–1.85

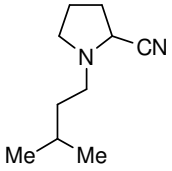
(comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.5, 128.6, 128.4, 126.2, 118.0, 54.2, 53.7, 51.3, 35.1, 29.6, 21.9; *m/z* (ESI–MS) 174.2 $[M–CN]^+$.

1-(Cyclohexylmethyl)pyrrolidine-2-carbonitrile (2.122t):



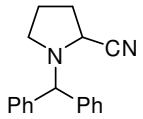
Following the general procedure (B), compound **2.122t** was obtained from *L*-proline and cyclohexanecarboxaldehyde as a colorless liquid in 97% yield as a mixture of regioisomers; rr = 2.2:1 (R_f = 0.23 in hexanes/EtOAc 95:5 v/v); Characterization data of the major regioisomer: IR (KBr) 2923, 2851, 2810, 2221, 1449, 1341, 1244, 1189, 1147, 1114, 1082, 879 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 3.72 (dd, *J* = 7.5, 2.4 Hz, 1H), 2.83 (m, 1H), 2.54–2.42 (comp, 2H), 2.40–2.33 (m, 1H), 2.19–2.04 (comp, 2H), 1.96–1.81 (comp, 2H), 1.80–1.73 (comp, 2H), 1.73–1.60 (comp, 2H), 1.48–1.37 (m, 1H), 1.31–1.09 (comp, 4H), 0.94–0.74 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 118.3, 59.4, 54.1, 51.4, 36.5, 31.6, 31.5, 29.6, 26.7, 25.9(2), 25.9(1), 21.9; *m/z* (ESI–MS) 166.2 $[M–CN]^+$.

1-Isopentylpyrrolidine-2-carbonitrile (2.122u):



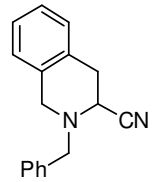
Following the general procedure (B), compound **2.122u** was obtained from *L*-proline and isovaleraldehyde as a colorless liquid in 82% yield as a mixture of regioisomers; rr = 4.6:1 (R_f = 0.25 in hexanes/EtOAc 90:10 v/v); Characterization data of the major regioisomer: IR (KBr) 2956, 2870, 2813, 2220, 1468, 1385, 1367, 1152, 1125, 1097, 885 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 3.75 (dd, *J* = 7.3, 2.7 Hz, 1H), 2.87 (ddd, *J* = 12.8, 8.3, 4.5 Hz, 1H), 2.72–2.62 (m. 1H), 2.57–2.46 (comp, 2H), 2.20–2.05 (comp, 2H), 1.97–1.80 (comp, 2H), 1.62 (app sept, *J* = 6.7 Hz, 1H), 1.41–1.33 (comp, 2H), 0.90 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 118.1, 53.7, 51.2, 50.8, 37.3, 29.5, 26.2, 22.7, 22.5, 21.8; *m/z* (ESI–MS) 140.1 $[M–CN]^+$.

1-Benzhydrylpyrrolidine-2-carbonitrile (2.122v):



Following the general procedure (B), compound **2.122v** was obtained from *L*-proline and benzophenone as a white solid in 57% yield (R_f = 0.22 in hexanes/EtOAc 97:3 v/v); 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, $CDCl_3$) 7.50 (comp, 4H), 7.30 (comp, 4H), 7.24–7.19 (comp, 2H), 4.61 (s, 1H), 3.78 (app d, *J* = 7.3 Hz, 1H), 3.02–2.94 (m, 1H), 2.44–2.36 (m, 1H), 2.25–2.14 (m, 1H), 2.13–2.03 (m, 1H), 2.01–1.87 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.5, 142.0, 128.8, 128.6, 127.6, 127.5, 127.3(1), 127.3(0), 117.7, 71.8, 53.1, 49.9, 29.4, 21.8; *m/z* (ESI–MS) 136.0 $[M–CN]^+$.

2-Benzyl-1,2,3,4-tetrahydroisoquinoline-3-carbonitrile (2.125):



Following the general procedure (B), compound **2.125** was obtained from (*S*)-(-)-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid and benzaldehyde as an off-white solid in 91% yield (R_f = 0.21 in hexanes/EtOAc 93:7 v/v); 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, $CDCl_3$) 7.42–7.30 (comp, 5H), 7.21–7.15 (comp, 2H), 7.13–7.10 (m, 1H), 7.06 (m, 1H), 4.03 (d, *J* = 6.3 Hz, 1H), 3.98 (d, *J* = 15.6 Hz, 1H), 3.92 (d, *J* = 13.2 Hz, 1H), 3.78 (d, *J* = 15.5 Hz, 1H), 3.70 (d, *J* = 13.2 Hz, 1H), 3.31 (dd, *J* = 16.3, 6.1 Hz, 1H), 2.98 (d, *J* = 16.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $[M–CN]^+$.

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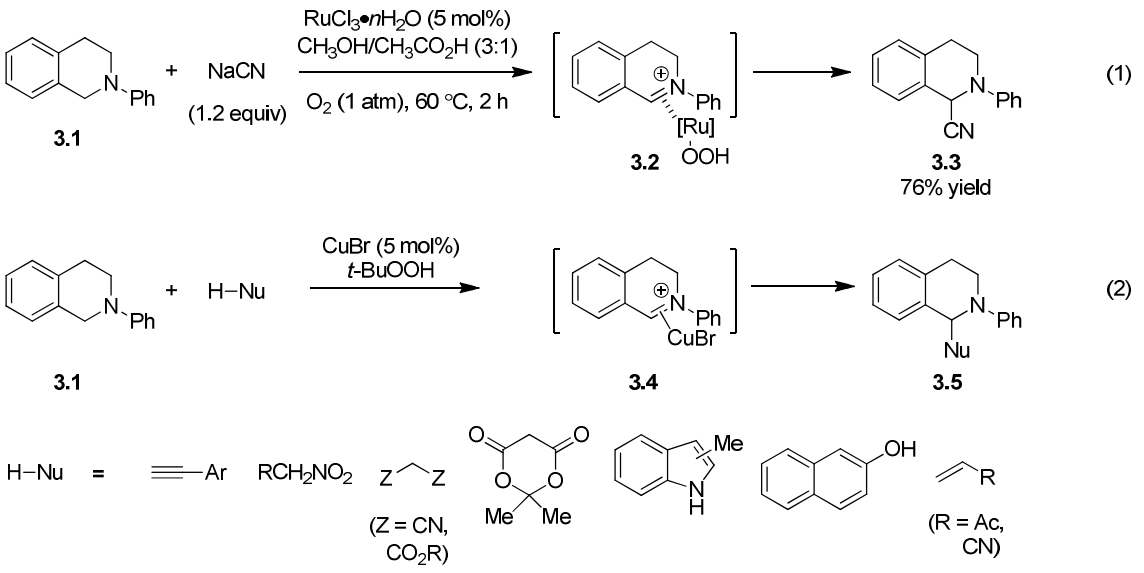
Chapter III

Redox-Neutral C–H Functionalization of Amines

3.1 Background

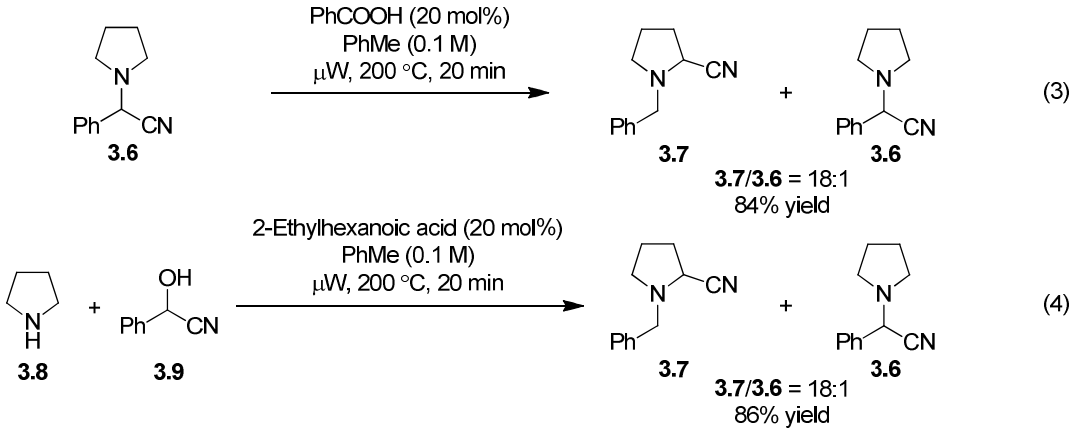
Functionalization of relatively unreactive C–H bonds, such as the ones adjacent to heteroatoms, is an attractive transformation that can give access to complex structures conveniently from simple starting materials.[1] By far, the majority of the contributions in this rapidly developing area of research concerns metal-mediated and metal-catalyzed processes. Murahashi and coworkers reported an aerobic ruthenium-catalyzed oxidative cyanation of tertiary amines (Figure 3.1, eq 1).[2] Subsequently, Li and coworkers broadened the scope of such oxidative processes by employing copper catalysts and superstoichiometric amounts of a strong oxidant (Figure 3.1, eq 2).[3] This copper-catalyzed oxidative process, referred by Li as cross-dehydrogenative coupling (CDC), enabled the association of cyclic tertiary amines with an array of nucleophiles such as alkynes, nitroalkanes, active methylene compounds, indoles, naphthols and Morita–Baylis–Hillman adducts.[4]

Figure 3.1 **Oxidative Functionalization of Tertiary Amines**

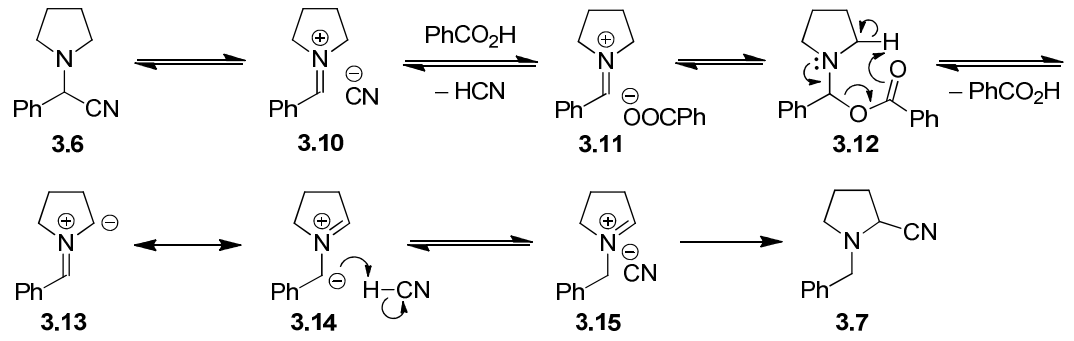


More recently, our group revealed a conceptually new redox-neutral approach for the α-cyanation of amines.[5] α-Aminonitriles that are a part of a ring system, and not accessible by traditional Strecker chemistry, were obtained by α-aminonitrile isomerization (Figure 3.2, eq 3) or alternatively by direct amine α-cyanation and *N*-alkylation (Figure 3.2, eq 4). Iminium ion **3.10**, which is expected to be present in low equilibrium concentration under the reaction conditions[6], could be converted to the azomethine ylide **3.13** under a carboxylic acid catalyzed transformation (Figure 3.1). The azomethine ylide **3.14**, which is a resonance form of **3.13**, is expected to be predominant because of better stabilization by charge distribution by the phenyl group. Subsequent protonation and nucleophilic attack leads to the isomerized product **3.7**. An attractive feature of this strategy is that it does not require any metal-based catalysts.

Figure 3.2 **Redox-Neutral α-Cyanation of Amines**



Scheme 3.1 **Proposed Pathway for α-Aminonitrile Isomerization**

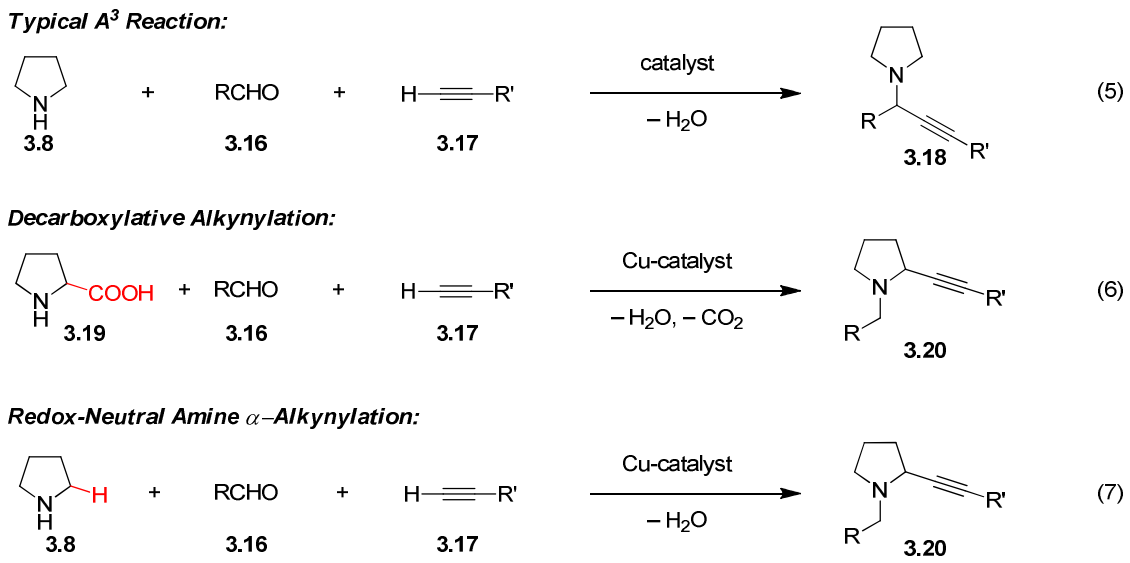


3.2 Redox-Neutral α–Alkynylation of Amines

3.2.1 General Consideration

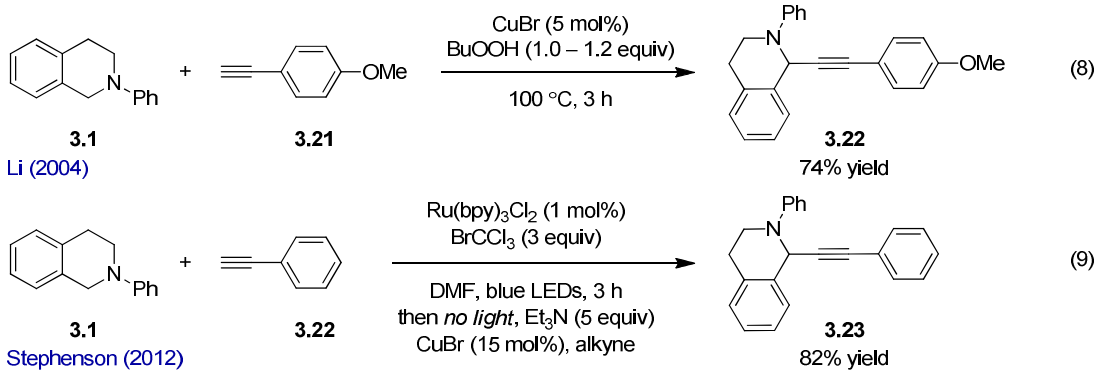
Propargylic amines are important building blocks for the synthesis of various nitrogen-containing compounds and are of great pharmaceutical interest.[7] They can be readily prepared by three-component reaction between amines, aldehydes and alkynes, frequently referred to as A^3 reactions (Figure 3.3, eq 5). Methods by which the ring substituted isomers **3.20** could be directly accessed, are much more limited. As part of our efforts to develop redox-neutral reactions having broad implications, our group recently disclosed an α-amino acid based decarboxylative three-component coupling approach for getting access to propargylic amines such as **3.20** (Figure 3.3, eq 6).[8] At almost the same time, Li and coworkers independently reported a nearly identical method.[9,10] We aimed replacing the α-amino acid with a simple amine to get access to the isomer **3.20** (Figure 3.3, eq 7). This would illustrate a significant advance where a relatively unreactive C–H bond could be replaced by a C–C bond.

Figure 3.3 **General Outline for the A^3 Reaction**



Direct α-alkynylation of tertiary amines has previously been accomplished through oxidative C–H functionalization by the Li group and many others (Figure 3.4, eq 8).[11] Recently, this transformation has also been reported to be performed by a photoredox catalysis approach (Figure 3.4, eq 9).[12] The use of stoichiometric amounts of oxidant is indispensable for these methods which are often limited to *N*-aryl tetrahydroisoquinolines and *N*,*N*-dialkylanilines.

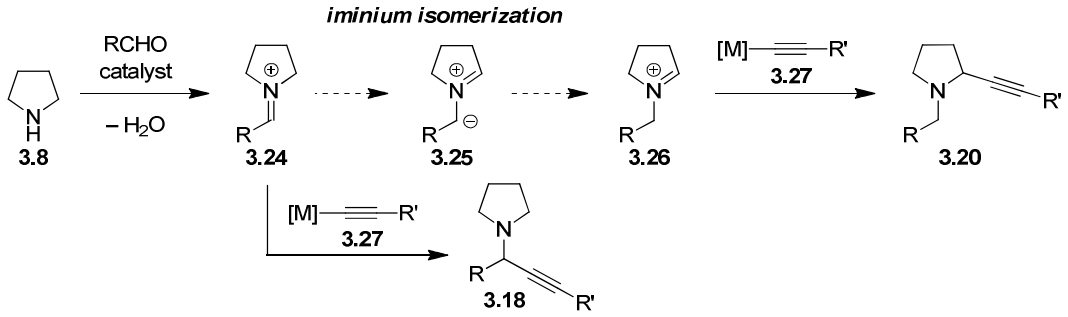
Figure 3.4 **Examples of Oxidative and Photoredox Catalyzed Direct α-Alkynylation of Tertiary Amines**



We envisioned a direct, redox-neutral three-component coupling reaction with concurrent α-alkynylation (Scheme 3.2). To realize such a process, it is inevitable to find conditions that prevent the regular fate in an A^3 reaction, specifically addition of the metal acetylide **3.27** to the initially formed iminium ion **3.24** that leads to the formation of the undesired isomer **3.18**. In order to gain access to the isomer **3.20**, the external iminium ion **3.24** needs to isomerize to the internal iminium ion **3.26**, and that must proceed in presence of the metal acetylide **3.27**. In principle, this could be achieved by iminium ion deprotonation/reprotonation via the azomethine ylide **3.25**. In fact, generation of azomethine ylides by α-deprotonation of iminium ion is a well-established concept.[13] An added challenge of this direct α-alkynylation was to perform it in an intermolecular setting. Upon examining potential solutions, we rationalized that having an electron withdrawing R group in **3.24** would assist in acidifying the amine α-proton, thereby

accelerating the iminium ion isomerization. Moreover, increasing the steric bulk of R would likely impede the rate of formation of **3.18**.

Scheme 3.2 **Competing Reaction Pathways in the Formation of Isomeric Propargylic Amines**

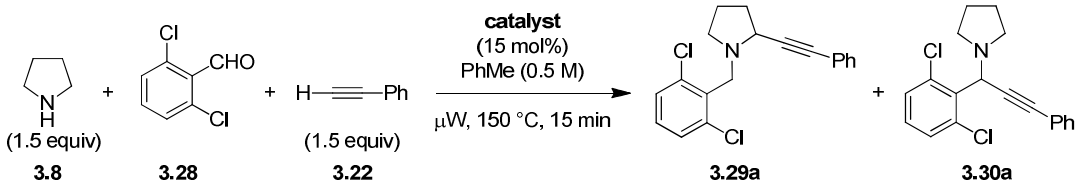


3.2.2 Evaluation of Catalysts

Taking the above factors into consideration, we started our investigation by selecting 2,6-dichlorobenzaldehyde (**3.28**) as the reaction partner in the three-component reaction with pyrrolidine (**3.8**) and phenylacetylene (**3.22**). Different catalysts were evaluated in the three-component coupling reaction conducted under microwave conditions (Table 3.1). Applying the catalyst combination of CuBr and TMEDA that proved optimal for the decarboxylative alkynylation (eq 6),[8] **3.29a** and **3.30a** were obtained as 1:3 mixture in 65% yield (entry 1). Using CuBr or $CuBr_2$ led to improved yields, but less favorable product ratios (entries 2 and 3). Interestingly, employing copper(II) triflate as the catalyst led to a favorable product ratio of 5:1 but had a detrimental effect on the yield (entry 4). Copper(II) acetate gave a slightly improved product ratio of 7:1, without affecting the yield significantly (entry 5). While using copper(II) formate led to the formation of the two regioisomers in 1:1 ratio, copper(II) benzoate furnished the products in 7:1 ratio (entries 6 and 7). Pleasingly, the more soluble copper carboxylates, namely copper(II) 2-ethylhexanoate, copper(II) cyclohexylbutanoate and copper(II) pivalate, led to more favorable product ratios and yields (entries 8 – 10). Notably, copper(II) acetylacetonate

gave quite disparate product ratios than the corresponding perfluorinated catalyst (entries 11 and 12). Copper(II) nitrate gave equal amounts of the two regioisomers (entry 13). As expected, no formation of the desired products were observed when 2-ethylhexanoic acid was used or in absence of any catalyst (entries 14 and 15). In all these copper(II) catalyzed reactions, 1,4-diphenylbuta-1,3-triene, the Glaser coupling product[14] of phenylacetylene was obtained as a side product.

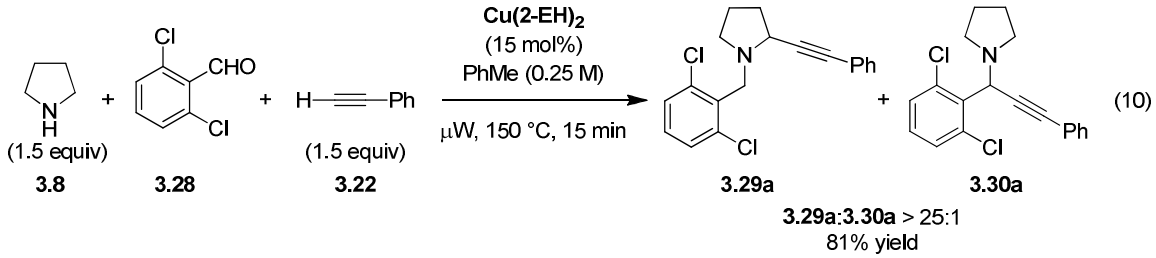
Table 3.1 **Evaluation of Catalysts for the Direct Three-Component α-Alkynylation**



entry	catalyst	ratio (**3.29a**:**3.30a**)	yield **3.29a**+**3.30a** (%)
1	CuBr + TMEDA (30 mol%)	1:3	65
2	CuBr	1:5	94
3	$CuBr_2$	1:4	82
4	$Cu(OTf)_2$	5:1	45
5	$Cu(OAc)_2•H_2O$	7:1	47
6	$Cu(HCOO)_2•H_2O$	1:1	82
7	$Cu(OBz)_2•H_2O$	7:1	74
8	Cu(II) 2-ethylhexanoate	20:1	82
9	Cu(II) cyclohexylbutanoate	14:1	76
10	Cu(II) pivalate	15:1	82
11	$Cu(acac)_2$	1:4	67
12	$Cu(hfacac)_2•H_2O$	3:1	76
13	$Cu(NO_2)_2•H_2O$	1:1	67
14	2-ethylhexanoic acid	N/A	0
15	none	N/A	0

From the above table, it became evident that the use of copper(II) carboxylates with enhanced solubilities led to greatly favorable ratios of **3.29a** and **3.30a** and good combined yields (*viz* entries 8 – 10). Readily available copper(II) 2-ethylhexanoate (**Cu(2-EH)$_2$**), which furnished the regioisomeric products in 20:1 ratio and 82% yield, was identified as the catalyst of choice.

Further analysis of the reaction parameters brought to our attention that replacing the solvent from anhydrous toluene to HPLC grade toluene had no deleterious effect on the reaction outcome. Changing the reaction concentration from 0.5M to 0.25M was found to be beneficial. Under these optimized conditions, the three-component coupling reaction between pyrrolidine, 2,6-dichlorobenzaldehyde and phenylacetylene gave the products **3.29a** and **3.30a** in >25:1 ratio and 81% yield (eq 10).



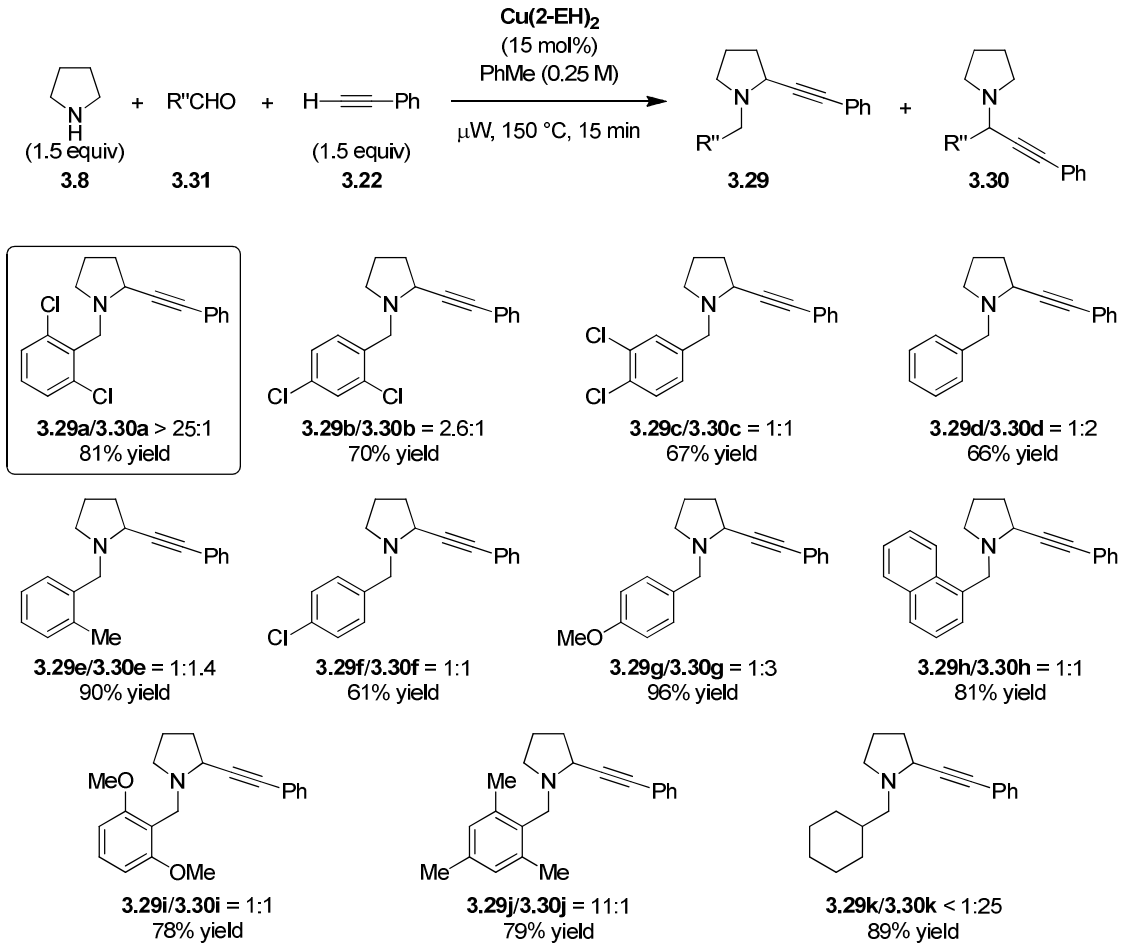
3.2.3 Screening of Aldehydes

To study the effect of the aldehyde on the selectivity of the reaction, we evaluated a series of electronically diverse aldehydes having varied steric demands (Figure 3.5). Interestingly, substituting 2,6-dichlorobenzaldehyde with electronically similar 2,4-dichlorobenzaldehyde led to a significant drop in the product ratio from >25:1 to 2.6:1. When 3,4-dichlorobenzaldehyde was used, the product ratio further dropped to 1:1. Unsubstituted benzaldehyde led to the formation of **3.29d/3.30d** in 1:2 ratio, favoring more of the regular A^3 reaction product. 2-Methylbenzaldehyde provided the products **3.29e/3.30e** in 1:1.4 ratio. A closer look at the results obtained from benzaldehyde, 4-chlorobenzaldehyde and 4-methoxybenzaldehyde (products **3.29d/3.30d**, **3.29f/3.30f** and **3.29g/3.30g**) evidently established the influence of electronic factors on the regiochemical outcome of the reaction, with electron

poor aldehydes leading to more favorable product ratios. 1-Naphthaldehyde and 2,6-dimethoxybenzaldehyde gave the respective products in 1:1 ratios. Mesitaldehyde led to an excellent **3.29j/3.30j** product ratio of 11:1. This shows that steric factor outweigh electronics. On the contrary, cyclohexane-carbaldehyde led to formation of only the regular product of A^3 reaction.

The reaction between 2,6-dichlorobenzaldehyde, pyrrolidine and phenylacetylene can be performed under reflux, but otherwise identical conditions. In this instance, the products **3.29a/3.30a** were obtained in 19:1 ratio and 86% yield after a reaction time of 30 minutes.

Figure 3.5 **Dependence of Product Ratios on Aldehyde**



3.2.4 Scope of the Reaction

Under the optimized microwave conditions, the scope of the three-component α-alkynylation was explored (Table 3.2). The reaction of 2,6-dichlorobenzaldehyde, pyrrolidine with different terminal alkynes gave the desired ring-alkynylated products in good to excellent yields. Various aromatic, alkenyl and aliphatic substituents on the alkyne were conveniently accommodated. The desired products were obtained with excellent regioselectivities, mostly exceeding 25:1 (**3.31a/3.32a** – **3.31l/3.32l**). Piperidine also underwent the **Cu(2-EA)$_2$**-catalyzed α-alkynylation with various alkynes to provide the desired products in excellent yields and regioselectivities ranging from 4:1 to 8:1 (**3.31m/3.32m** – **3.31p/3.32p**). On subjecting azepane and azocane to the reaction conditions, the propargylic amines were obtained in appreciable yields and modest regioisomeric ratios (**3.31q/3.32q** – **3.31s/3.32s**). Although the observed regioselectivities for these relatively challenging amine substrates are lower than for pyrrolidine, they still encompass a synthetically useful range.

Table 3.2 **Scope of the Direct α–Alkynylation**

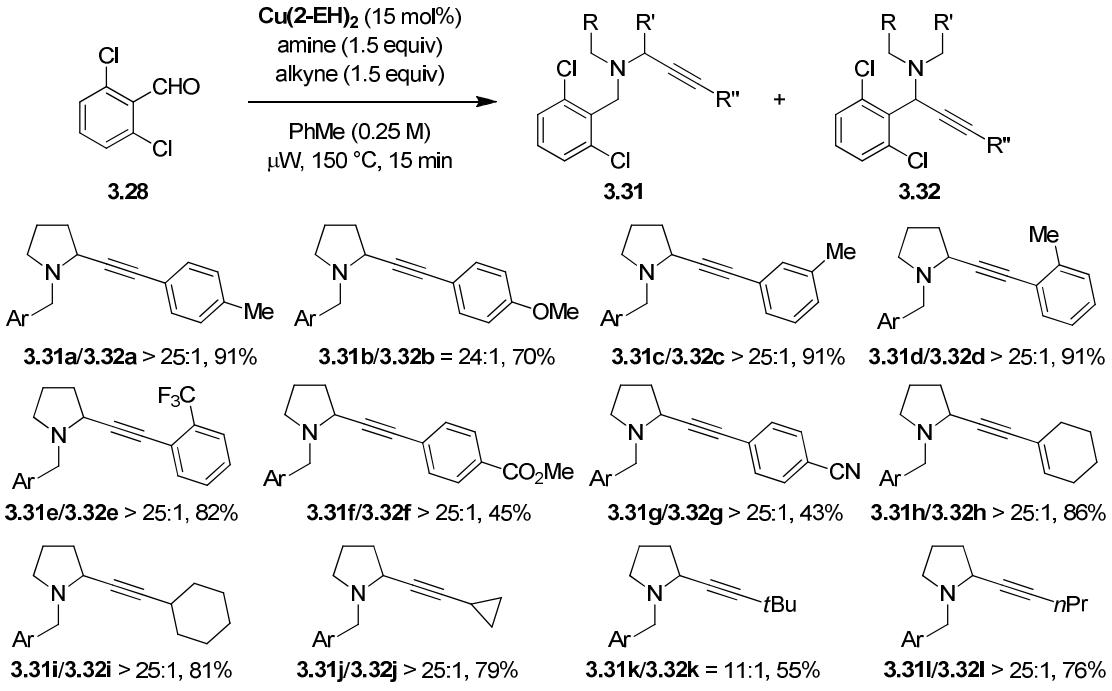
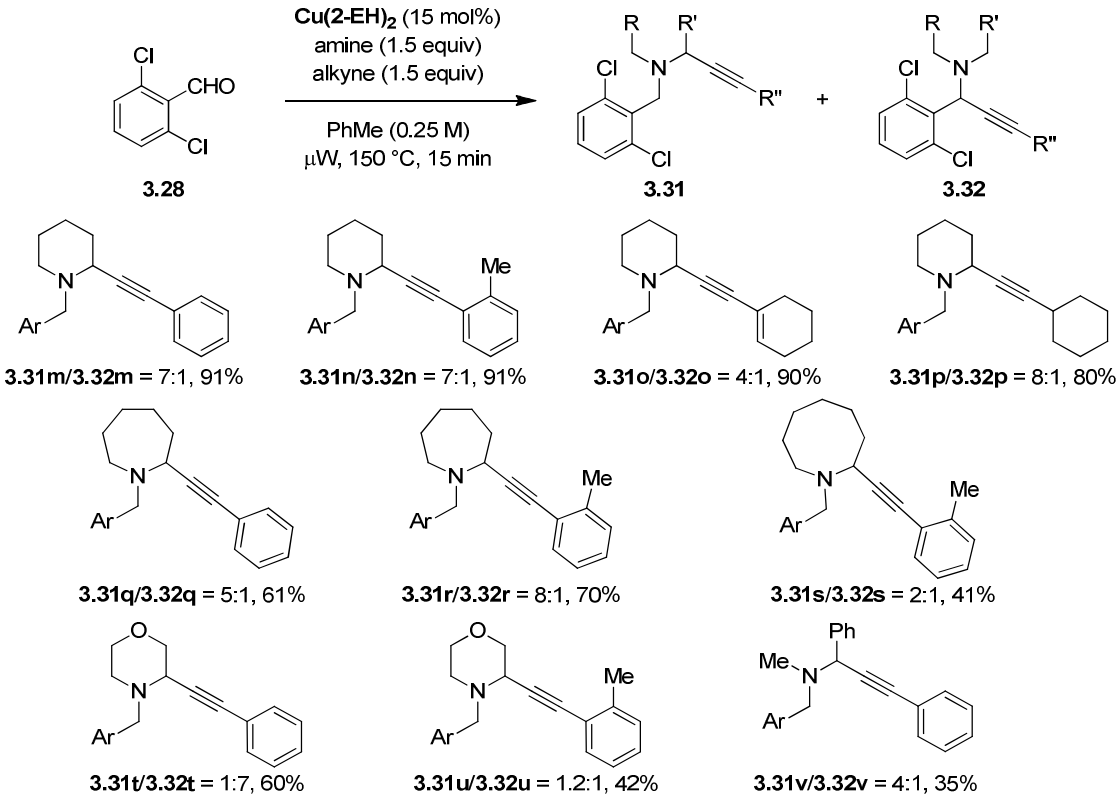


Table 3.2 **Scope of the Direct α–Alkynylation (contd.)**

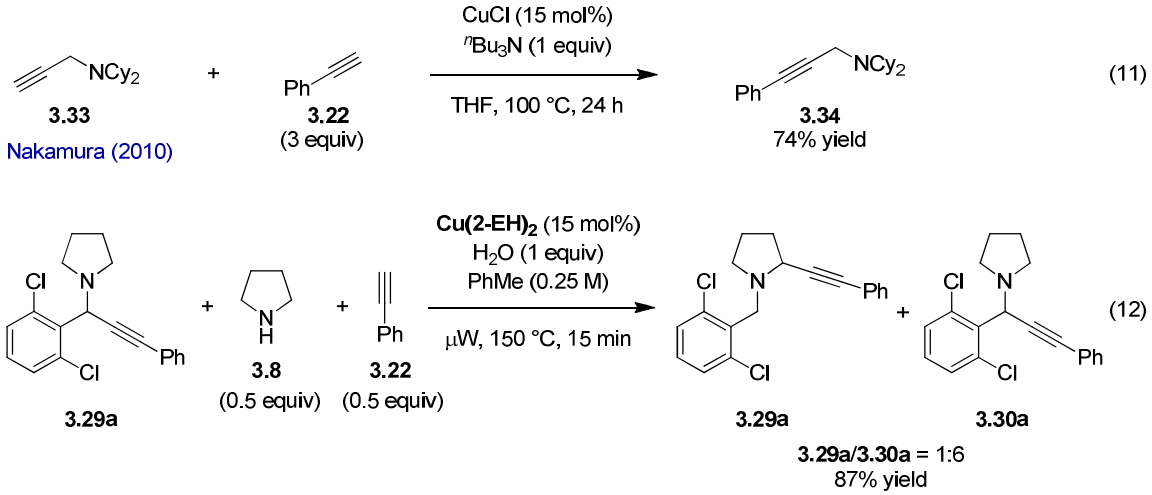


Morpholine gave only a trace amount of the desired regioisomer with phenylacetylene (**3.31t/3.32t** = 1:7). Interestingly, when an *ortho*-methyl group was introduced in the phenyl ring of phenylacetylene, it led to formation of **3.31u/3.32u** in 1.2:1 ratio. Under the optimized reaction conditions, the acyclic amine, *N*-methylbenzylamine, gave products **3.31v/3.32v** in a 4:1 ratio, albeit in 35% yield.

3.2.5 Mechanistic Consideration and Hypothesis

The reversibility in an iminium alkynylation has previously been known for the substitution reactions of propargylic amines carried out in presence of copper(I) catalysts (eq 11).[15] In order to ascertain whether the regioselectivity of the alkynylation could be influenced by product isomerization, we exposed **3.29a** to the reaction conditions (eq 12). To best mimic the original scenario, 0.5 equivalents each of pyrrolidine and phenylacetylene, and 1.0 equivalent of

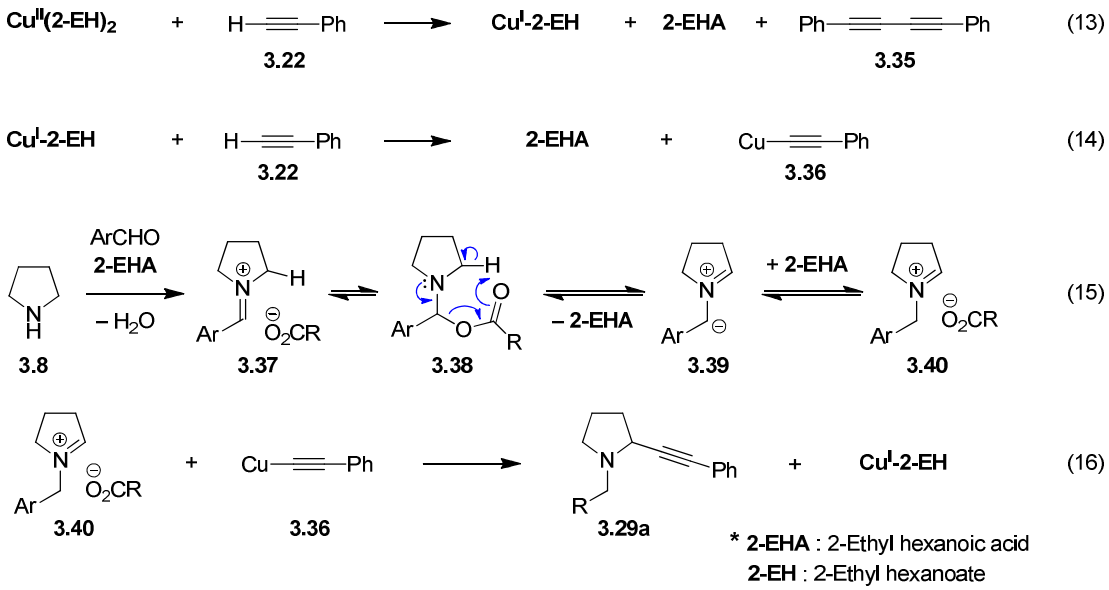
water was added. In addition to the formation of the Glaser coupling product, very little isomerization was observed and the products **3.29a/3.30a** were isolated in 1:6 ratio with 87% combined yield. Although this study shows the potential reversibility of the process, the extent of isomerization is inconsequential to account for the observed regioselectivity of the reaction. Therefore, the regioisomeric product ratios most likely emulate the intrinsic reactivities of the reactive intermediates.



The proposed mechanism for the redox-neutral α-alkynylation of amines is outlined in Figure 3.9. Reaction of **Cu(II)(2-EH)$_2$** with phenylacetylene leads to the generation of one equivalent each of **Cu(I)-2-EH** and **2-EHA**, along with the Glaser product (Figure 3.6, eq 13). **Cu(I)-2-EH** then adds to phenylacetylene to form the active Cu-acetylide **Cu(II)(2-EH)$_2$** with the concomitant formation of another equivalent of **2-EHA** (Figure 3.6, eq 14). **2-EHA** is believed to play a crucial role in the overall outcome of the reaction (Figure 3.6, eq 15). Firstly, it is expected to promote the condensation of the aldehyde with the amine to form the iminium ion **3.37**. Subsequently, the carboxylate anion of **3.37** could propagate the iminium ion isomerization via deprotonation/reprotonation. Alternatively, *N*,*O*-acetal **3.38**, which is expected to be in equilibrium with **3.37**, could lead to formation of the azomethine ylide **3.39** via a concerted pathway and thereby eliminating **2-EHA**. Regioselective protonation of the azomethine ylide

3.39 by **2-EHA** then leads to the internal iminium ion **3.40** which may too exist in equilibrium with the corresponding *N*,*O*-acetal. Eventually, the active acetylide **3.36** adds to the iminium ion **3.40** to from propargyl amine **3.29a** and regenerating **Cu(I)-2-EH** (Figure 3.6, eq 16). Even though **Cu(II)(2-EH)$_2$** is the only additive, the active catalysts **Cu(I)-2-EH** and **2-EHA** are formed in situ and these distinctly activate the two reaction partners. As such, this process can be considered as an example of synergistic catalysis.[16]

Figure 3.6 **Proposed Mechanism of the Direct α–Alkynylation of Amines***

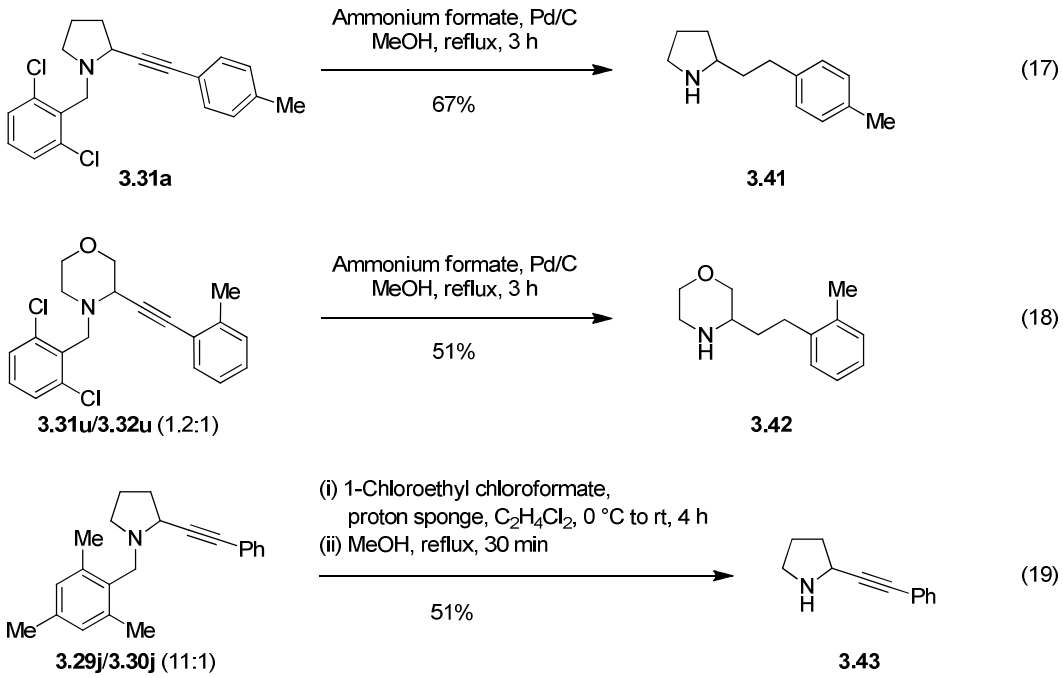


3.2.6 Product Transformation

To demonstrate the synthetic utility of the propargylic amines derived from the redox-neutral α-alkynylation, a number of products were selectively transformed. Simultaneous one-step debenzylation and reduction of the triple bond of the propargyl amine **3.31a** was accomplished by transfer hydrogenation to furnish **3.41** (Figure 3.7, eq 17). This strategy can also be utilized to sequester the undesired isomer in cases where the process is less regioselective. For instance, upon exposing a 1.2:1 regioisomeric mixture of **3.31u/3.32u** to the transfer hydrogenation conditions led to formation of the 2-alkylated morpholine **3.42** (Figure 3.7, eq 18).

Alternatively, a two-step strategy where **3.29j/3.30j** was first converted to the corresponding carbamate and then its removal under methanol reflux, provided the product **3.43** where the alkyne functionality was preserved (Figure 3.7, eq 19).

Figure 3.7 **Selected Transformation of Propargylic Amines**



3.2.7 Summary

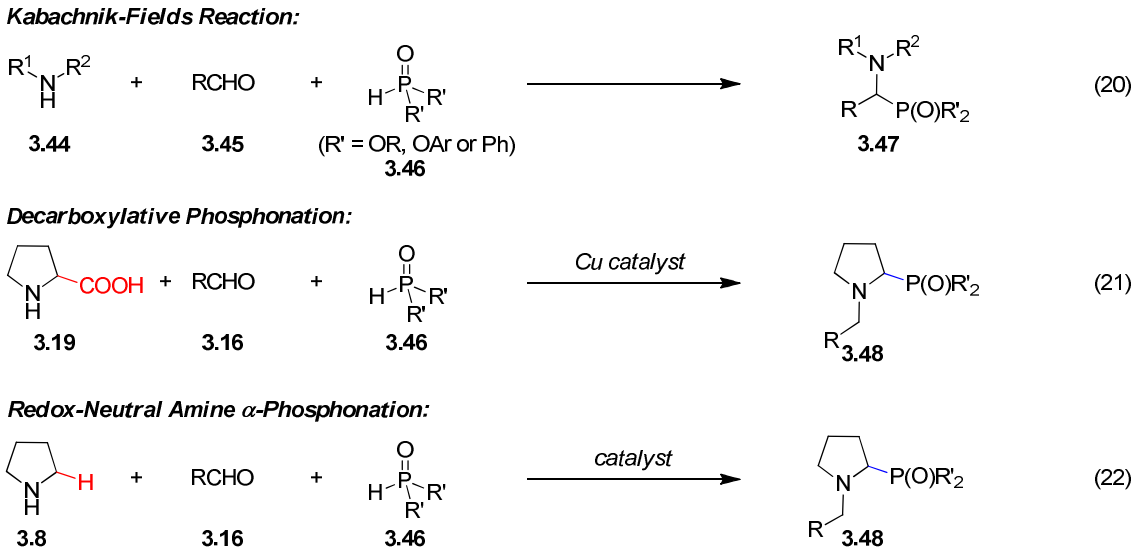
In summary, we have developed an unprecedented approach for achieving access to ring-substituted propargylic amines in one step starting from readily available starting materials. This redox-neutral α-alkynylation does not require the use of α-amino acid and oxidant, or *N*-aryl tetrahydroisoquinolines and *N*,*N*-dialkylanilines as the starting materials. We anticipate that this fairly simple but effective approach will find widespread use for getting access to α-functionalized amines from simple precursors.

3.3 Redox-Neutral α–Phosphonation of Amines

3.3.1 General Consideration

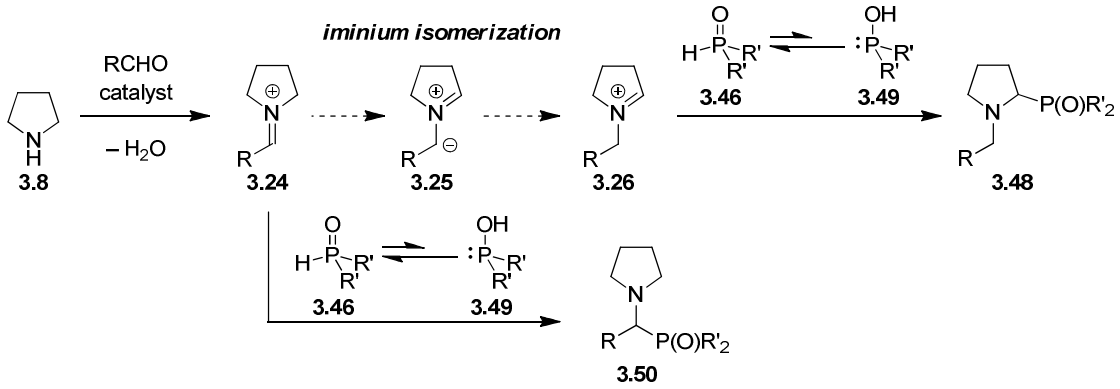
α-Aminophosphonic acids and their phosphonate derivatives have received considerable attention as surrogates of both natural and unnatural α-amino acids.[17] Replacement of the planar carboxylic acid group in amino acids with the tetrahedral phosphonic acid brings about changes not only in the molecular structure, but also in a variety of other properties. α-Aminophosphonates have been found to exhibit outstanding antitumor, antibiotic, pharmacogenetic and pharmacological properties, and are widely applied in agrochemistry.[18] Consequently, much effort has been devoted to the efficient synthesis of α-aminophosphonates.[19] The three-component reaction between amines, carbonyl compounds and phosphonates, frequently referred to as the Kabachnik-Fields reaction,[20] is one of the most useful methods for the synthesis of such compounds (Figure 3.8, eq 20).[21] Direct α-phosphonation of tertiary amines has previously been achieved by oxidative C–H functionalization[22] and photoredox catalysis.[23] One of the major drawbacks of these methods is the requirement of using stoichiometric amounts of an oxidant. Such processes are also often limited to *N*-aryl tetrahydroisoquinolines and *N*,*N*-dialkylanilines. In 2011, Liang, Yang and coworkers reported the first example of copper-catalyzed decarboxylative phosphonation of *N*-benzylproline that leads to α-aminophosphonates such as **3.48**.[24] More recently, Wang's group reported the three-component, copper-catalyzed intermolecular decarboxylative coupling reaction of secondary amino acids to generate **3.48** (Figure 3.8, eq 21).[25] Replacement of the amino acid with an amine would mean a more practical and efficient strategy for C–P bond formation via functionalization of relatively unreactive C–H bond (Figure 3.8, eq 22).

Figure 3.8 **General Scheme for the Kabachnik-Fields Reaction**



In sync with our recent success in developing the three-component coupling with concomitant α-alkynylation, we envisaged to extend the reach of such redox-neutral processes to the three-component aldehyde-induced α-phosphonation of amines (Scheme 3.3). It is well known that the phosphonate **3.46** undergoes phosphonate–phosphite tautomerism, with the phosphite tautomer **3.49** as the nucleophilically active form and the phosphonate tautomer **3.46** as the almost exclusive but non-nucleophilic form..[26] As such, unlike the three-component α-alkynylation, such P-nucleophiles generally do not require co-activation by a metal catalyst.

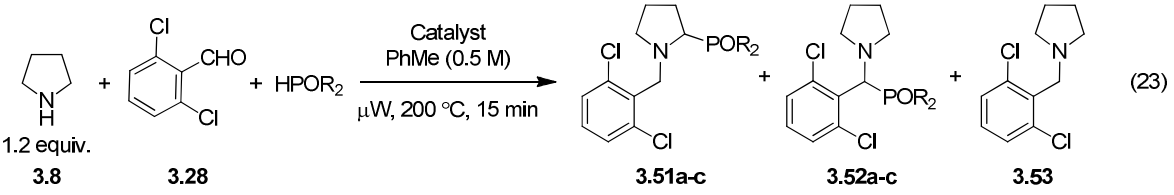
Scheme 3.3 **Competing Reaction Pathways in the Formation of Isomeric α-Aminophosphonates**



3.3.2 Optimization of Reaction Conditions

Taking into consideration our recent accomplishment in the three-component amine α-alkynylation, we chose 2,6-dichlorobenzaldehyde as the reaction partner in the proposed redox-neutral reaction with pyrrolidine and different phosphites or phosphine oxides (eq 23). Different P-nucleophiles were evaluated for the three-component reaction conducted using benzoic acid as the catalyst (Table 3.2). Initial screening of reaction temperatures led us to realize that the reaction progressed smoothly at 200 ºC under microwave irradiation and the desired regioisomer **3.51** was consistently isolated as the major product.

Table 3.3 **Evaluation of Reaction Parameters for the Direct Three-Component α-Phosphonation**

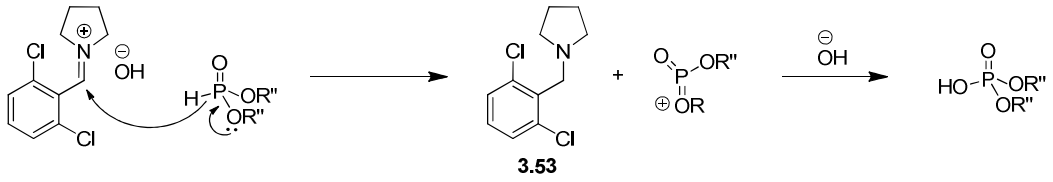


Entry	$HPOR_2$ (equiv)	Catalyst (mol%)	Yield of **3.51** (%)	Yield of **3.52** (%)	Yield of **3.53** (%)
1	$HPO(OEt)_2$ (1.5 equiv.)	PhCOOH (20 mol%)	54	N/A	13
2	$HPO(OBn)_2$ (1.5 equiv.)	PhCOOH (20 mol%)	44	N/A	30
3	$HPOPh_2$ (1.5 equiv.)	PhCOOH (20 mol%)	86	Trace	N/A
4	$HPOPh_2$ (1.2 equiv.)	PhCOOH (20 mol%)	86	Trace	N/A
5	$HPOPh_2$ (1.2 equiv.)	PhCOOH (10 mol%)	56	Trace	N/A
6	$HPOPh_2$ (1.2 equiv.)	2-EHA (20 mol%)	84	Trace	N/A
7	$HPOPh_2$ (1.2 equiv.)	--	86	< 2	N/A
8	$HPOPh_2$ (1.2 equiv.)	$Cu(2\text{-}EH)_2$ (20 mol%)	N/A	N/A	N/A

When 1.5 equiv of diethyl phosphite was allowed to react with 1.2 equiv of pyrrolidine and 2,6-dichlorobenzaldehyde in toluene under microwave irradiation at 200 ºC for 15 min, **3.51** was formed in 54% yield (Table 3.3, entry 1). Not surprisingly, the corresponding reduced product, *N*-(2,6-dichlorobenzyl)pyrrolidine (**3.53**), was also isolated in 13% yield, possibly via intermolecular hydride transfer (Scheme 3.4). Using dibenzyl phosphite led to formation of **3.51** in 44% yield, accompanied by simultaneous formation of 30% of the reduced product (Table 3.3, entry 2). To our delight, when diphenylphosphine oxide was employed as the phosphonating agent, product **3.51** was formed exclusively in 86% yield (Table 3.3, entry 3). Lowering the amount of diphenylphosphine oxide to 1.2 equiv did not have any adverse effect on the outcome of the reaction (Table 3.3, entry 4). However, lowering the catalyst loading to 10 mol% led to a decrease in product yield (Table 3.3, entry 5). It is worth noting that employing 2-ethylhexanoic acid as the catalyst also led to the exclusive formation of **3.51** in excellent yield (Table 3.3, entry 6). Interestingly, under the optimized microwave conditions, the reaction between 2,6-dichlorobenzaldehyde, pyrrolidine and diphenylphosphine oxide proceed without the presence of any external acid catalyst to furnish the desired product **3.51** in 86% yield along with a trace amount of the undesired regioisomer **3.50** (Table 3.3, entry 7). Using Cu(II) $(2\text{-}EH)_2$ as the

catalyst, which proved to be optimal for the three-component amine α–alkynylation, did not lead to any product formation (Table 3.3, entry 8).

Scheme 3.4 **Plausible Pathway for Formation of Reduced Product**

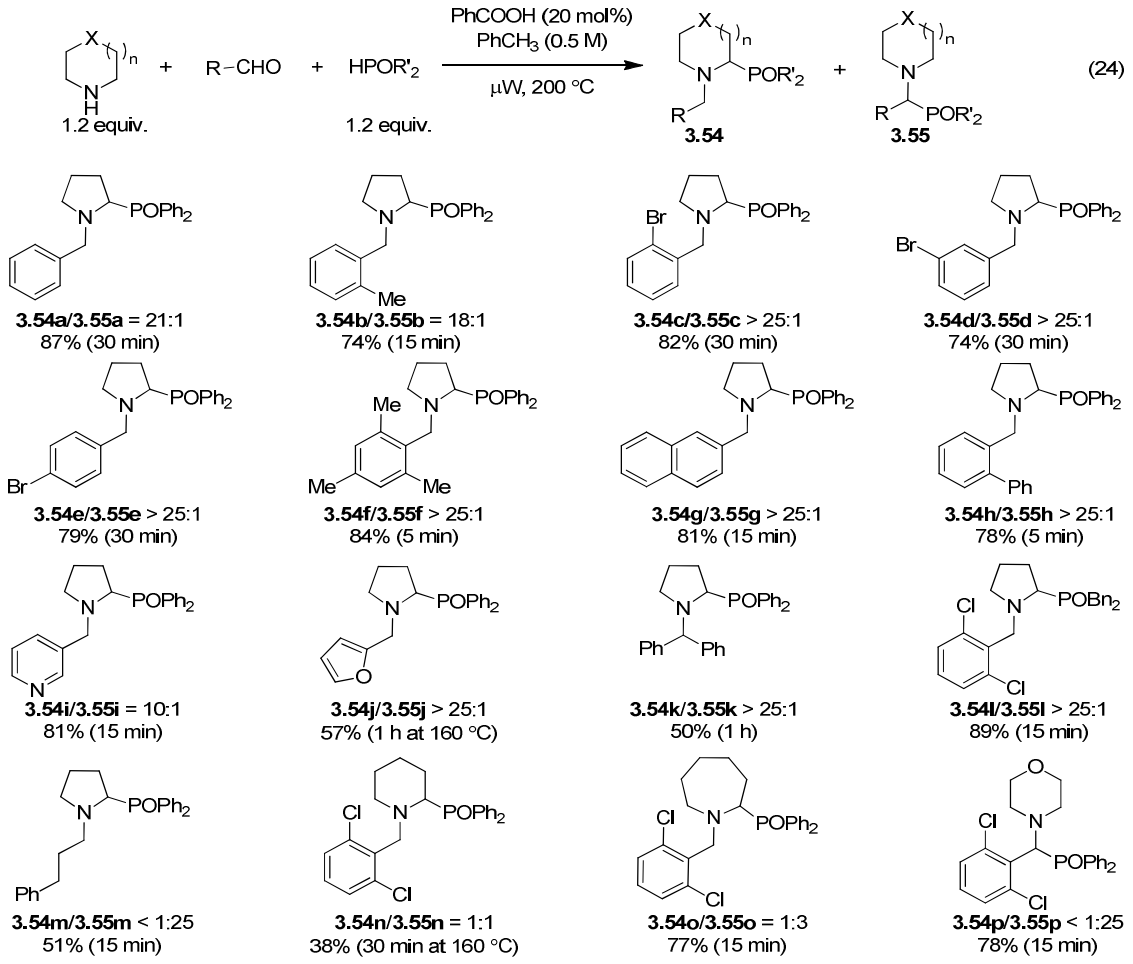


3.3.3 Scope of the Direct α–Phosphonation

With the optimized reaction conditions in hand, we explored the scope of the three component α-phosphonation of amines (Table 3.3). The reaction between pyrrolidine, diphenylphosphine oxide and various aldehydes consistently led to the formation of the desired α-aminophosphonate **3.53** as the major or near exclusive product. When benzaldehyde was used, product **3.54a** was isolated in 83% yield after 30 min, along with a small amount of **3.55a**. Having electron-donating or electron-withdrawing groups in the aromatic ring of the aldehyde was also well tolerated and the desired regioisomer isolated as the sole product (**3.54b** – **3.54f**). 2-Naphthaldehyde and biphenyl-2-carboxaldehyde gave the corresponding α-aminophosphonate in good yields (**3.54g** and **3.54h**). Pyridine-3-carboxyaldehyde gave **3.54i** in 10:1 mixture of regioisomers after 15 min. Furan-2-aldehyde furnished **3.54j** after 1 h at a reduced reaction temperature of 160 ˚C, albeit in slightly lower yield of 57%. Even benzophenone was a viable substrate, leading to exclusive formation of **3.54k** in 50% yield after 1 h. When dibenzylphosphine oxide was employed as the nucleophilic partner in the reaction with pyrrolidine and 2,6-dichlorobenzaldehyde, it led to the formation of **3.54l** as the only isolable product in 89% yield. Conversely, hydrocinnamaldehyde gave only the undesired regioisomer **3.55m** in 51% yield. Upon exposing piperidine and azepane to the reaction conditions with diphenylphosphine oxide and 2,6-dichlorobenzaldehyde, the corresponding products were

obtained in modest regioisomeric ratios, albeit in lower yields (**3.54n** and **3.54o**). Morpholine provided only the regular Kabachnik-Fields reaction product **3.55p**.

Table 3.4 **Scope of the Three-Component Amine α–Phosphonation**

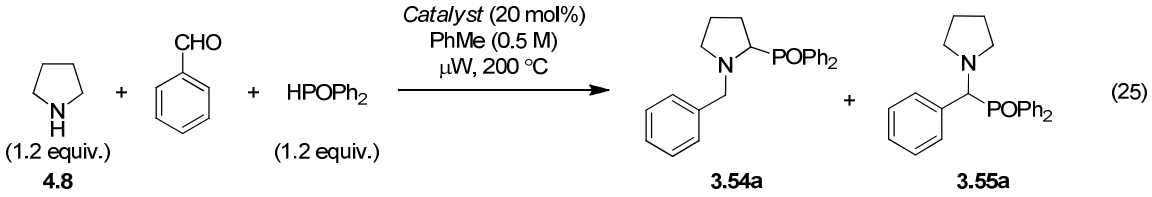


3.3.4 Dependence of Product Yields on Catalyst and Reaction Time

A closer analysis of the results displayed in Table 3.3, in particular entries 4, 6 and 7, revealed that using catalytic amounts of benzoic acid and 2-ethylhexanoic acid, or no catalyst essentially led to similar outcome in which the desired regioisomer **3.51** was obtained in high yields. To evaluate the dependence of the reaction outcome on catalyst or reaction time, we decided to perform the three-component coupling reaction of unsubstituted benzaldehyde with

pyrrolidine and diphenylphosphine oxide (eq 25). Using benzoic acid as the catalyst, it becomes evident that an increase in reaction time resulted in a gradual increase of the regioisomeric ratio favoring the desired regioisomer **3.54a** (Table 3.4, entries 1–3). In absence of any catalyst, the reaction gives predominantly the undesired regioisomer **3.55a** after 30 mins (Table 3.4, entry 4). When 2-ethylhexanoic acid, which turned out to be efficient for the direct amine α-cyanation,[5] was employed as the catalyst, **3.54a** and **3.55a** were obtained in 50% and 42% yields, respectively, after 5 mins (Table 3.4, entry 5). On extending the reaction time to 30 mins, the yield of **3.54a** improved to 77% while that of **3.55a** decreased to 6% (Table 3.2, entry 6). Using trifluoroacetic acid as the catalyst, products **3.54a** and **3.55a** were obtained in equal amounts after 30 mins (Table 3.4, entry 7).

Table 3.5 **Screening of Catalyst and Reaction Time to Determine the Dependence on Reaction Outcome**



Entry	*Catalyst*	Time (min)	Yield of **3.54a** (%)	Yield of **3.55a** (%)
1	PhCOOH	5	70	16
2	PhCOOH	15	79	8
3	PhCOOH	30	83	4
4	--	30	20	66
5	2-Ethylhexanoic acid	5	50	42
6	2-Ethylhexanoic acid	30	77	6
7	TFA	30	33	33

3.3.5 Product Isomerization

In order to determine whether regioselectivity of the α-phosphonation could be influenced by product isomerization, we ran a number of control experiments (Figure 3.9). Indeed, when the undesired regioisomers **3.52** and **3.55a** were exposed to 20 mol% of benzoic acid under microwave irradiation at 200 ºC for 15 mins, the ring-substituted α-aminophosphonates **3.51** and **3.54a** were obtained as the only detectable or major regioisomer (Figure 3.9, eqs 26 and 27). This implies that for α-phosphonation reactions that are intrinsically less regioselective, the product distribution can potentially be improved by modifying the reaction conditions, for instance, extending the reaction time. As may have been anticipated, when **3.51** and **3.54a** were exposed to the same conditions, no isomerization was observed (Figure 3.9, eqs 28 and 29).

Figure 3.9 **Attempts to Improve Regioisomeric Distribution**

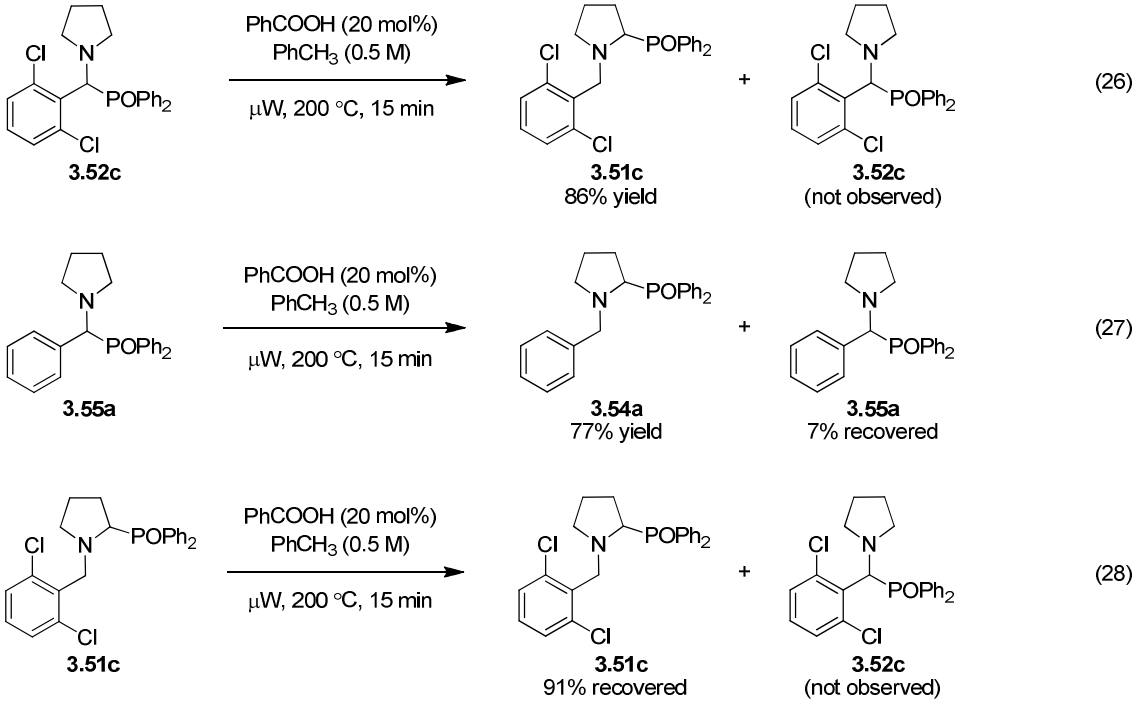
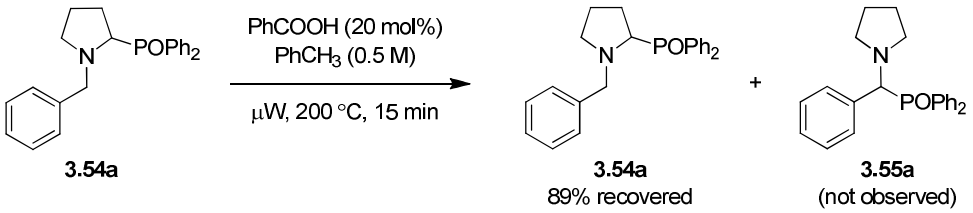


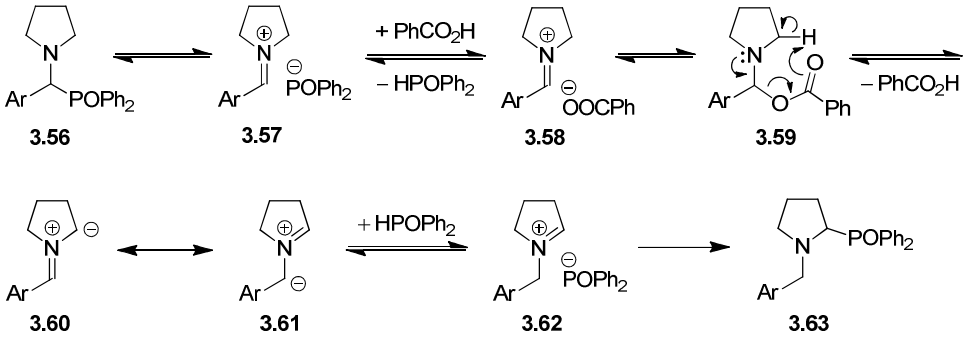
Figure 3.9 **Attempts to Improve Regioisomeric Distribution (contd.)**



(29)

Outlined in scheme 3.5 is a potential pathway for the regioisomeric enrichment process. α-Aminophosphonate **3.56** could be in equilibrium with the iminium ion **3.57** under the reaction conditions. Protonation of the phosphine oxide anion by benzoic acid catalyst leads to iminium ion **3.58**. The benzoate anion could then deprotonate the iminium α-proton, presumably via *N*,*O*-acetal **3.59** in a concerted fashion, to form the azomethine ylide **3.60**. The resonance form **3.61** is expected to be more predominant because of better charge distribution by the electro-withdrawing aromatic group. Protonation of the azomethine ylide **3.61** at the benzylic position forms the new iminium ion **3.62**, which ultimately leads to the formation of α-aminophosphonate **3.63**.

Scheme 3.5 **Plausible Mechanism for Benzoic Acid Catalyzed α–Phosphonate Isomerization**



3.3.6 Summary

We have developed a redox-neutral strategy for the α-phosphonation of amines. Due to the importance of the resulting α-aminophosphonates in pharmacology and agrochemistry, this new method is expected to find widespread use in synthesis.

3.4 Conclusion

We have successfully developed a novel redox-neutral approach for α-functionalization of amines. This process does not use require terminal oxidant. A combination of a reductive amine *N*-alkylation with an oxidative α-functionalization renders such transformation redox-neutral. It is anticipated that this concept will be widely applied as a means to obtain access to α-functionalized amines from simple precursors.

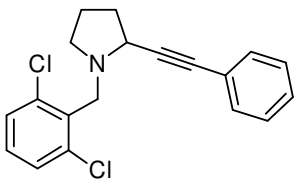
Experimental Section

General Information: Copper(II) 2-ethylhexanoate and 2,6-dichlorobenzaldehyde were purchased from Strem Chemicals and Sigma Aldrich, respectively, and were used as received. Benzoic acid was recrystallized from aqueous ethanol. Other aldehydes, the amines and alkynes were purchased from commercial sources and were purified by distillation or chromatographically (2,6-dimethoxybenzaldehyde and methyl 4-ethynylbenzoate) prior to use. 4-Ethynylbenzonitrile was prepared according to a known procedure.[27] Microwave reactions were carried out in a CEM Discover reactor. Silicon carbide (SiC) passive heating elements were purchased from Anton Paar. 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, and Dragendorff-Munier stains followed by heating. Purification of reaction products was carried out by flash column chromatography using Sorbent Technologies Standard Grade silica gel (60 Å, 230–400 mesh). Infrared spectra were recorded on an ATI Mattson Genesis Series FT-Infrared spectrophotometer. Proton nuclear magnetic resonance spectra (^{1}H-NMR) were recorded on Varian VNMRS-500 MHz and Varian VNMRS-400 MHz instruments 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, sex = sextet, dd = doublet of doublets, ddd = doublet of doublet of doublets, td = triplet of doublets, m = multiplet, comp = complex, br = broad; and coupling constant(s) in Hz. Proton-decoupled carbon nuclear magnetic resonance spectra (^{13}C-NMR) were recorded on Varian VNMRS-500 MHz and Varian VNMRS-400 MHz instruments and are reported in ppm using the solvent as an internal standard ($CDCl_3$ at 77.0 ppm). Proton-decoupled phosphorus nuclear magnetic resonance spectra (^{31}P-NMR) were recorded on a Varian VNMRS-400 MHz instrument and are reported in ppm relative to 85% H_3PO_4 as an external standard. Mass spectra were recorded on a Finnigan LCQ-DUO mass spectrometer.

General Procedure (A) for the Three-Component Alkynylation of Amines:

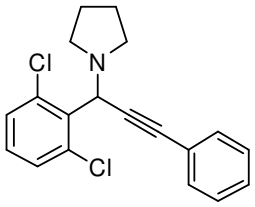
A 10 mL microwave reaction tube was charged with a 10 x 8 mm SiC passive heating element, Cu(II) 2-ethylhexanoate (0.038 mmol, 0.15 equiv.), toluene (1 mL), alkyne (0.375 mmol, 1.5 equiv.), amine (0.375 mmol, 1.5 equiv.) and aldehyde (0.25 mmol). The reaction tube was sealed with a Teflon-lined snap cap, and heated in a microwave reactor at 150 °C (200 W, 30–80 psi) for 15 minutes. After cooling with compressed air flow, the reaction mixture was directly loaded onto a column and purified by silica gel chromatography, eluting first with hexanes (to remove the Glaser coupling product) and then with the appropriate eluent system.

1-(2,6-Dichlorobenzyl)-2-(phenylethynyl)pyrrolidine (3.29a):



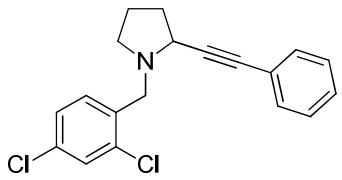
Following the general procedure (A), compound **3.29a** was obtained from pyrrolidine, phenylacetylene and 2,6-dichlorobenzaldehyde as a colorless liquid in 81% yield (> 25:1 mixture of regioisomers) (R_f = 0.31 in hexanes/EtOAc 95:5 v/v); Characterization data of the major regioisomer: IR (KBr) 3079, 2956, 2910, 2808, 1598, 1562, 1489, 1435, 1370, 1356, 1247, 1196, 1105, 1088, 1069, 984, 911, 889, 756, 691 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.48–7.43 (comp, 2H), 7.34–7.28 (comp, 5H), 7.11 (m, 1H), 4.26 (d, *J* = 12.7 Hz, 1H), 4.02 (d, *J* = 12.7 Hz, 1H), 3.83 (dd, *J* = 7.6, 5.0 Hz, 1H), 2.92 (ddd, *J* = 14.0, 8.8, 5.1 Hz, 1H), 2.70 (ddd, *J* = 15.1, 8.7, 6.3 Hz, 1H), 2.24–2.14 (m, 1H), 2.08–2.00 (m, 1H), 1.98–1.88 (m, 1H), 1.84–1.74 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.7, 135.2, 131.6, 128.6, 128.3, 128.1, 127.8, 123.5, 89.3, 84.3, 55.7, 51.6(4), 51.6(0), 31.7, 22.3; *m/z* (ESI–MS) 330.3 ($^{35}Cl/^{35}Cl$) $[M]^+$, 332.2 ($^{35}Cl/^{37}Cl$) $[M]^+$.

1-(1-(2,6-Dichlorophenyl)-3-phenylprop-2-yn-1-yl)pyrrolidine (3.30a):



A mixture of 2,6-dichlorobenzaldehyde (1 mmol), pyrrolidine (1.2 mmol), phenylacetylene (1.5 mmol) and CuI (0.015 mmol) in toluene (3 mL) was stirred under reflux for 2 h. After cooling to room temperature, the crude reaction mixture was directly loaded onto a column and purified by flash chromatography. The title compound **3.30a** was obtained as a colorless liquid in 77% yield (R_f = 0.29 in hexanes/EtOAc 95:5 v/v); IR (KBr) 2964, 2874, 2795, 1598, 1578, 1562, 1490, 1435, 1361, 1341, 1262, 1201, 1182, 1136, 1089, 908, 839, 780, 756, 691 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.49–7.43 (comp, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.31–7.27 (comp, 3H), 7.18–7.12 (m, 1H), 5.42 (s, 1H), 2.90–2.82 (comp, 2H), 2.67–2.59 (comp, 2H), 1.85–1.77 (comp, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.0, 134.7, 131.7, 129.3, 128.9, 128.2, 128.0, 123.3, 86.5, 85.0, 55.9, 52.1, 23.5; *m/z* (ESI–MS) 330.1 ($^{35}Cl/^{35}Cl$) $[M]^+$, 332.1 ($^{35}Cl/^{37}Cl$) $[M]^+$.

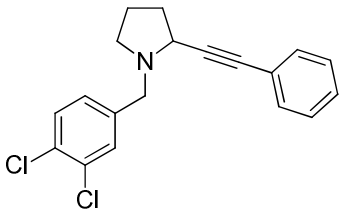
1-(2,4-Dichlorobenzyl)-2-(phenylethynyl)pyrrolidine (3.29b):



Following the general procedure (A), compound **3.29b** was obtained from pyrrolidine, phenylacetylene and 2,4-dichlorobenzaldehyde as a colorless liquid in 70% yield (2.6:1 mixture of regioisomers) (R_f = 0.19 in hexanes/EtOAc 97:3 v/v); Characterization data of the major regioisomer: IR (KBr) 3058, 2956, 2876, 2812, 2226, 1698, 1588, 1489, 1471, 1369, 1320, 1097, 1049, 837, 756, 691 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.3 Hz, 1H), 7.46–7.10 (comp, 2H), 7.37 (d, *J* = 2.1 Hz, 1H), 7.33–7.28 (comp, 3H), 7.22 (dd, *J* = 8.3, 2.1 Hz, 1H), 4.07 (d, *J* = 14.0 Hz, 1H), 3.80 (d, *J* = 14.1 Hz, 1H), 3.68 (dd, *J* = 7.2, 5.1 Hz, 1H), 2.85 (ddd, *J* = 14.1, 8.8, 5.2 Hz, 1H), 2.58 (ddd, *J* = 14.9, 8.8, 6.1 Hz, 1H), 2.25–2.15 (m, 1H), 2.09–2.01 (m, 1H), 2.00–1.90 (m, 1H), 1.88–1.78 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.4, 134.7, 133.0, 131.7, 131.6, 129.1, 128.2, 128.0, 126.9, 123.2, 88.6, 84.9, 54.8, 53.4, 51.8, 31.7, 22.2; *m/z* (ESI–

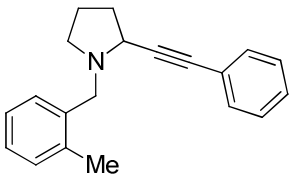
MS) 330.1 ($^{35}Cl/^{35}Cl$) $[M]^+$, 332.1 ($^{35}Cl/^{37}Cl$) $[M]^+$.

1-(3,4-Dichlorobenzyl)-2-(phenylethynyl)pyrrolidine (3.29c):



Following the general procedure (A), compound **3.29c** was obtained from pyrrolidine, phenylacetylene and 3,4-dichlorobenzaldehyde as a colorless liquid in 67% yield (1:1 mixture of regioisomers) (R_f = 0.20 in hexanes/EtOAc 95:5 v/v); Characterization data of **3.29c**: IR (KBr) 2956, 2876, 2814, 1598, 1489, 1470, 1442, 1355, 1129, 1030, 819, 756, 691 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, *J* = 1.8 Hz, 1H), 7.46–7.41 (comp, 2H), 7.38 (d, *J* = 8.2 Hz, 1H), 7.34–7.29 (comp, 3H), 7.23 (dd, *J* = 8.2, 1.8 Hz, 1H), 3.97 (d, *J* = 13.2 Hz, 1H), 3.61 (dd, *J* = 7.4, 5.0 Hz, 1H), 3.57 (d, *J* = 13.2 Hz, 1H), 2.76 (ddd, *J* = 14.3, 8.8, 5.4 Hz, 1H), 2.55 (ddd, *J* = 14.6, 8.7, 5.9 Hz, 1H), 2.23–2.14 (m, 1H), 2.08–2.00 (m, 1H), 2.00–1.89 (m, 1H), 1.88–1.78 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.5, 132.2, 131.7, 130.8(5), 130.8(0), 130.1, 128.3(2), 128.3(0), 128.0, 123.1, 88.2, 85.2, 56.1, 54.5, 51.6, 31.7, 22.1; *m/z* (ESI–MS) 330.2 ($^{35}Cl/^{35}Cl$) $[M]^+$, 332.1 ($^{35}Cl/^{37}Cl$) $[M]^+$.

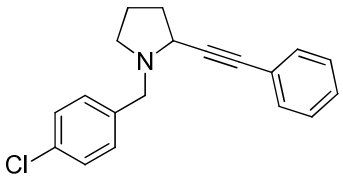
1-(2-Methylbenzyl)-2-(phenylethynyl)pyrrolidine (3.29e):



Following the general procedure (A), compound **3.29e** was obtained from pyrrolidine, phenylacetylene and *o*-tolualdehyde as a colorless liquid in 90% yield (1:1.4 mixture of regioisomers) (R_f = 0.19 in hexanes/EtOAc 97:3 v/v); Characterization data of **3.29e**: IR (KBr) 3061, 3019, 2953, 2803, 1598, 1489, 1458, 1355, 1122, 1101, 1069, 756, 744, 691 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.48–7.43 (comp, 2H), 7.37–7.33 (m, 1H), 7.33–7.19 (comp, 3H), 7.18–7.12 (comp, 3H), 4.09 (d, *J* = 13.0 Hz, 1H), 3.61 (dd, *J* = 7.4, 5.3 Hz, 1H), 3.53 (d, *J* = 13.0 Hz, 1H), 2.80 (ddd, *J* = 14.0, 8.9, 5.1 Hz, 1H), 2.52 (ddd, *J* = 14.8, 8.7, 6.2 Hz, 1H), 2.44 (s, 3H), 2.22–2.12 (m, 1H), 2.07–1.98 (m, 1H), 1.97–1.86 (m, 1H), 1.86–1.75 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.4, 137.3,

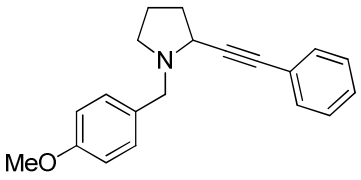
131.6, 130.2, 129.5, 128.2, 127.8, 126.9, 125.5, 123.5, 89.2, 84.6, 55.1, 54.9, 51.8, 31.7, 22.2, 19.2; *m/z* (ESI–MS) 276.1 $[M + H]^+$.

1-(4-Chlorobenzyl)-2-(phenylethynyl)pyrrolidine (3.29f):



Following the general procedure (A), compound **3.29f** was obtained from pyrrolidine, phenylacetylene and 4-chlorobenzaldehyde as a light yellow liquid in 61% yield (1:1 mixture of regioisomers) (R_f = 0.32 in hexanes/EtOAc 93:7 v/v); Characterization data of **3.29f**: IR (KBr) 3054, 2956, 2876, 2808, 1598, 1489, 1443, 1355, 1320, 1098, 1084, 1016, 805, 756, 691 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.49–7.40 (comp, 2H), 7.37–7.26 (comp, 7H), 4.00 (d, *J* = 13.1 Hz, 1H), 3.60–3.57 (m, 1H), 3.58 (d, *J* = 12.9 Hz, 1H), 2.76 (ddd, *J* = 14.2, 8.9, 5.4 Hz, 1H), 2.54 (ddd, *J* = 14.7, 8.7, 6.2 Hz, 1H), 2.22–2.11 (m, 1H), 2.08–1.99 (m, 1H), 1.98–1.88 (m, 1H), 1.87–1.75 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.4, 132.6, 131.7, 130.4, 128.3, 128.2, 128.0, 123.3, 88.5, 85.1, 56.5, 54.4, 51.5, 31.6, 22.0; *m/z* (ESI–MS) 296.2 (^{35}Cl) $[M]^+$, 298.2 (^{37}Cl) $[M]^+$.

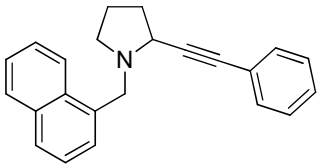
1-(4-Methoxybenzyl)-2-(phenylethynyl)pyrrolidine (3.29g):



Following the general procedure (A), compound **3.29g** was obtained from pyrrolidine, phenylacetylene and *p*-anisaldehyde as a light brown liquid in 96% yield (1:3 mixture of regioisomers) (R_f = 0.30 in hexanes/EtOAc 85:15 v/v); Characterization data of **3.29g**: IR (KBr) 3031, 2954, 2832, 2809, 2061, 1611, 1510, 1463, 1442, 1320, 1246, 1178, 1036, 822, 756, 692 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.50–7.44 (comp, 2H), 7.35–7.28 (comp, 5H), 6.89–6.85 (comp, 2H), 4.00 (d, *J* = 12.8 Hz, 1H), 3.80 (s, 3H), 3.59–3.55 (m, 1H), 3.58 (d, *J* = 12.7 Hz, 1H), 2.78 (ddd, *J* = 14.1, 9.0, 5.2 Hz, 1H), 2.54 (ddd, *J* = 15.0, 8.7, 6.2 Hz, 1H), 2.22–2.12 (m, 1H), 2.09–1.99 (m, 1H), 1.98–1.88 (m, 1H), 1.86–1.75 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.6,

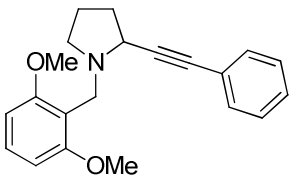
131.7, 130.8, 130.3, 128.2, 127.9, 123.4, 113.5, 88.8, 84.9, 56.4, 55.2, 54.2, 51.4, 31.6, 22.0; *m/z* (ESI–MS) 292.1 $[M + H]^+$.

1-(Naphthalen-1-ylmethyl)-2-(phenylethynyl)pyrrolidine (3.29h):



Following the general procedure (A), compound **3.29h** was obtained from pyrrolidine, phenylacetylene and 1-naphthaldehyde as a colorless liquid in 81% yield (1:1 mixture of regioisomers) (R_f = 0.20 in hexanes/EtOAc 95:5 v/v); Characterization data of **3.29h**: IR (KBr) 3046, 2956, 2876, 2802, 2247, 1737, 1597, 1509, 1489, 1460, 1372, 1353, 1244, 1169, 1070, 909, 778, 732, 756, 691 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.53 (app d, *J* = 8.2 Hz, 1H), 7.90 (app d, *J* = 7.3 Hz, 1H), 7.83 (app d, *J* = 8.2 Hz, 1H), 7.61–7.50 (comp, 5H), 7.49–7.43 (m, 1H), 7.43–7.33 (comp, 3H), 4.70 (d, *J* = 12.7 Hz, 1H), 3.93 (d, *J* = 12.9 Hz, 1H), 3.69 (dd, *J* = 7.3, 5.8 Hz, 1H), 2.87 (ddd, *J* = 13.8, 8.9, 5.0 Hz, 1H), 2.61 (ddd, *J* = 15.3, 8.7, 6.5 Hz, 1H), 2.28–2.18 (m, 1H), 2.15–2.05 (m, 1H), 2.01–1.90 (m, 1H), 1.90–1.78 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.1, 133.8, 132.5, 131.7, 128.3, 128.2, 127.9, 127.8, 127.0, 125.8, 125.5, 125.1, 124.8, 123.5, 89.3, 84.8, 55.5, 55.0, 51.9, 31.7, 22.1; *m/z* (ESI–MS) 312.3 $[M + H]^+$.

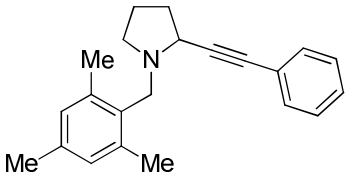
1-(2,6-Dimethoxybenzyl)-2-(phenylethynyl)pyrrolidine (3.29i):



Following the general procedure (A), compound **3.29i** was obtained from pyrrolidine, phenylacetylene and 2,6-dimethoxybenzaldehyde as a light brown liquid in 38% yield (R_f = 0.18 in hexanes/EtOAc 60:40 v/v); **3.30i** was isolated in 40% yield (R_f = 0.17 in MeOH/EtOAc 5:95 v/v); Characterization data of **3.29i**: IR (KBr) 3051, 2958, 2837, 2142, 1686, 1596, 1474, 1435, 1357, 1325, 1252, 1173, 1126, 1039, 909, 738, 693 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.49–7.43 (comp, 2H), 7.33–7.27 (comp, 3H), 7.22–7.16 (m, 1H), 6.55 (d, *J* = 8.4 Hz, 2H), 4.11 (d, *J* = 12.3 Hz, 1H), 3.89 (d, *J* = 12.3 Hz, 1H), 3.81 (s, 6H), 3.58–3.51 (m, 1H), 2.96 (app td, *J* = 8.8, 3.5 Hz, 1H), 2.52–2.44 (m,

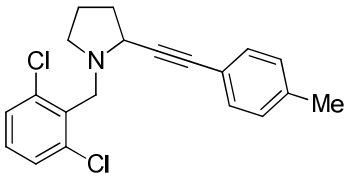
1H), 2.19–2.09 (m, 1H), 2.07–1.97 (m, 1H), 1.95–1.83 (m, 1H), 1.75–1.65 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.4, 131.7, 128.4, 128.1, 127.5, 124.0, 114.8, 103.7, 90.9, 83.0, 55.7, 55.0, 52.0, 43.8, 31.9, 22.3; *m/z* (ESI–MS) 322.1 $[M + H]^+$.

2-(Phenylethynyl)-1-(2,4,6-trimethylbenzyl)pyrrolidine (3.29j):



Following the general procedure (A), compound **3.29j** was obtained from pyrrolidine, phenylacetylene and mesitaldehyde as a pale yellow liquid in 79% yield (11:1 mixture of regioisomers) (R_f = 0.22 in hexanes/EtOAc 97:3 v/v); Characterization data of the major regioisomer: IR (KBr) 2953, 2917, 2855, 2788, 1949, 1613, 1489, 1459, 1366, 1265, 1111, 1070, 910, 882, 851, 756, 738, 691 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48–7.43 (comp, 2H), 7.36–7.30 (comp, 3H), 6.85 (s, 2H), 4.03 (d, *J* = 12.7 Hz, 1H), 3.62–3.57 (m, 1H), 3.61 (d, *J* = 12.6 Hz, 1H), 2.78 (ddd, *J* = 13.2, 8.6, 4.6 Hz, 1H), 2.49 (ddd, *J* = 15.1, 8.4, 6.9 Hz, 1H), 2.45 (s, 6H), 2.28 (s, 3H), 2.21–2.11 (m, 1H), 2.05–1.96 (m, 1H), 1.91–1.80 (m, 1H), 1.80–1.70 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.7, 136.0, 132.9, 131.6, 128.9, 128.2, 127.8, 123.6, 89.8, 84.2, 55.2, 51.3, 50.4, 31.8, 22.2, 20.9, 20.1; *m/z* (ESI–MS) 304.0 $[M + H]^+$.

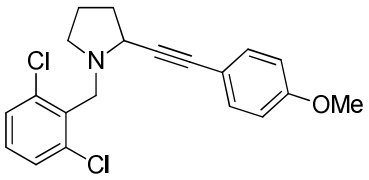
1-(2,6-Dichlorobenzyl)-2-(*p*-tolylethynyl)pyrrolidine (3.31a):



Following the general procedure (A), compound **3.31a** was obtained from pyrrolidine, 4-ethynyltoluene and 2,6-dichlorobenzaldehyde as a colorless liquid in 91% yield (> 25:1 mixture of regioisomers) (R_f = 0.24 in hexanes/EtOAc 95:5 v/v); Characterization data of the major regioisomer: IR (KBr) 3027, 2953, 2858, 2809, 1903, 1698, 1562, 1508, 1435, 1355, 1318, 1247, 1196, 1179, 1105, 1088, 984, 890, 816, 765, 739 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.15–7.08 (comp, 3H), 4.25 (d, *J* = 12.6 Hz, 1H), 4.00 (d, *J* = 12.7 Hz, 1H), 3.81 (dd, *J* = 7.5, 5.1 Hz, 1H), 2.91 (ddd, *J* = 13.9, 8.8, 5.2 Hz, 1H),

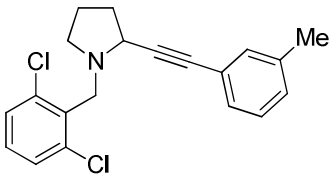
2.69 (ddd, *J* = 15.1, 8.6, 6.4 Hz, 1H), 2.35 (s, 3H), 2.24–2.12 (m, 1H), 2.08–1.98 (m, 1H), 1.98–1.86 (m, 1H), 1.84–1.71 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.8, 136.7, 135.3, 131.5, 128.9, 128.6, 128.3, 120.4, 88.5, 84.4, 55.8, 51.6(5), 51.6(0), 31.7, 22.3, 21.4; *m/z* (ESI–MS) 344.1 (^{35}Cl/^{35}Cl) $[M]^+$, 346.1 (^{35}Cl/^{37}Cl) $[M]^+$.

1-(2,6-Dichlorobenzyl)-2-((4-methoxyphenyl)ethynyl)pyrrolidine (3.31b):



Following the general procedure (A), compound **3.31b** was obtained from pyrrolidine, 4-ethynylanisole and 2,6-dichlorobenzaldehyde as a colorless liquid in 70% yield (24:1 mixture of regioisomers) (R_f = 0.21 in hexanes/EtOAc 95:5 v/v); Characterization data of the major regioisomer: IR (KBr) 3038, 2956, 2910, 2836, 2226, 1606, 1562, 1510, 1435, 1355, 1290, 1210, 1172, 1106, 1033, 909, 832, 734 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, *J* = 9.0 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 7.10 (m, 1H), 6.87–6.81 (comp, 2H), 4.24 (d, *J* = 12.7 Hz, 1H), 3.99 (d, *J* = 12.7 Hz, 1H), 3.80 (s, 3H), 3.80–3.77 (m, 1H), 2.91 (ddd, *J* = 13.7, 8.7, 5.0 Hz, 1H), 2.67 (ddd, *J* = 14.8, 8.5, 6.4 Hz, 1H), 2.22–2.12 (m, 1H), 2.07–1.97 (m, 1H), 1.97–1.85 (m, 1H), 1.83–1.72 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2, 136.7, 135.3, 133.0, 128.6, 128.3, 115.7, 113.8, 87.7, 84.1, 55.8, 55.2, 51.7, 51.6, 31.8, 22.3; *m/z* (ESI–MS) 360.4 (^{35}Cl/^{35}Cl) $[M]^+$, 362.4 (^{35}Cl/^{37}Cl) $[M]^+$.

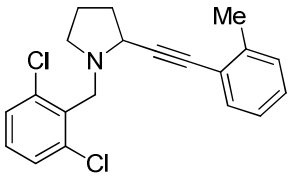
1-(2,6-Dichlorobenzyl)-2-(*m*-tolylethynyl)pyrrolidine (3.31c):



Following the general procedure (A), compound **3.31c** was obtained from pyrrolidine, 3-ethynyltoluene and 2,6-dichlorobenzaldehyde as a colorless liquid in 91% yield (> 25:1 mixture of regioisomers) (R_f = 0.26 in hexanes/EtOAc 95:5 v/v); Characterization data of the major regioisomer: IR (KBr) 3038, 2954, 2857, 2809, 1698, 1581, 1562, 1485, 1435, 1355, 1317, 1196, 1105, 1089, 985, 905, 880, 780, 691 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33–7.24 (comp,

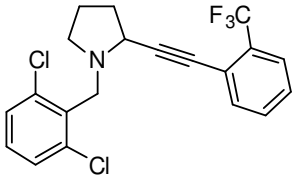
4H), 7.23–7.18 (m, 1H), 7.15–7.09 (comp, 2H), 4.25 (d, *J* = 12.5 Hz, 1H), 4.02 (d, *J* = 12.6 Hz, 1H), 3.87–3.81 (m, 1H), 2.92 (ddd, *J* = 13.9, 8.7, 5.4 Hz, 1H), 2.75–2.67 (m, 1H), 2.34 (s, 3H), 2.23–2.14 (m, 1H), 2.08–1.99 (m, 1H), 1.98–1.87 (m, 1H), 1.84–1.73 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.8, 136.7, 135.2, 132.2, 128.6(8), 128.6(7), 128.6(0), 128.3, 128.1, 123.3, 88.8, 84.5, 55.7, 51.6, 51.5, 31.7, 22.3, 21.2; *m/z* (ESI–MS) 344.2 (^{35}Cl/^{35}Cl) $[M]^+$, 346.1 (^{35}Cl/^{37}Cl) $[M]^+$.

1-(2,6-dichlorobenzyl)-2-(*o*-tolylethynyl)pyrrolidine (3.31d):



Following the general procedure (A), compound **3.31d** was obtained from pyrrolidine, 2-ethynyltoluene and 2,6-dichlorobenzaldehyde as a colorless liquid in 91% yield (> 25:1 mixture of regioisomers) (R_f = 0.30 in hexanes/EtOAc 95:5 v/v); Characterization data of the major regioisomer: IR (KBr) 3060, 3020, 2953, 2911, 2812, 1738, 1581, 1562, 1485, 1435, 1371, 1317, 1243, 1196, 1107, 1088, 1044, 987, 922, 889, 757, 716 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (app d, *J* = 7.4 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.23–19 (comp, 2H), 7.17–7.13 (m, 1H), 7.13–7.09 (m, 1H), 4.23 (d, *J* = 12.7 Hz, 1H), 4.05 (d, *J* = 12.7 Hz, 1H), 3.94 (dd, *J* = 7.5, 4.4 Hz, 1H), 2.90 (ddd, *J* = 14.6, 8.9, 5.7 Hz, 1H), 2.74 (ddd, *J* = 14.4, 8.7, 5.7 Hz, 1H), 2.48 (s, 3H), 2.25–2.15 (m, 1H), 2.09–2.00 (m, 1H), 1.99–1.88 (m, 1H), 1.85–1.74 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.0, 136.7, 135.3, 132.0, 129.3, 128.6, 128.3, 127.8, 125.4, 123.3, 93.1, 83.4, 55.9, 51.5, 51.2, 32.0, 22.3, 20.9; *m/z* (ESI–MS) 344.2 (^{35}Cl/^{35}Cl) $[M]^+$, 346.2 (^{35}Cl/^{37}Cl) $[M]^+$.

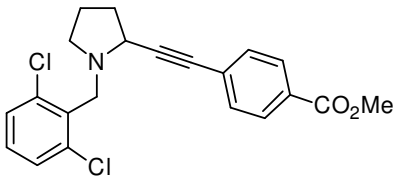
1-(2,6-Dichlorobenzyl)-2-((2-(trifluoromethyl)phenyl)ethynyl)pyrrolidine (3.31e):



Following the general procedure (A), compound **3.31e** was obtained from pyrrolidine, 2-ethynyl-α,α,α-trifluorotoluene and 2,6-dichlorobenzaldehyde as a colorless liquid in 82% yield (> 25:1 mixture of regioisomers) (R_f = 0.24 in hexanes/EtOAc 95:5 v/v); Characterization data of the

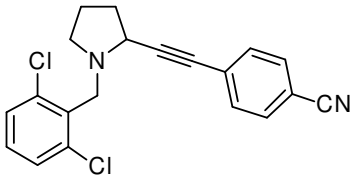
major regioisomer: IR (KBr) 3058, 2957, 2855, 2250, 1603, 1562, 1489, 1450, 1435, 1318, 1264, 1169, 1134, 1059, 1033, 988, 956, 908, 765, 651 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.65 (app d, *J* = 8.0 Hz, 1H), 7.59 (app d, *J* = 7.7 Hz, 1H), 7.48 (app t, *J* = 7.7 Hz, 1H), 7.41–7.35 (m, 1H), 7.30 (d, *J* = 8.1 Hz, 2H), 7.14–7.09 (m, 1H), 4.20 (d, *J* = 12.8 Hz, 1H), 4.08 (d, *J* = 7.8 Hz, 1H), 4.00–3.95 (m, 1H), 2.90 (ddd, *J* = 15.0, 8.9, 6.3 Hz, 1H), 2.79 (ddd, *J* = 14.0, 8.7, 5.4 Hz, 1H), 2.23–2.13 (m, 1H), 2.09–2.01 (m, 1H), 2.00–1.90 (m, 1H), 1.85–1.75 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.6, 135.4, 134.1, 131.5 (q, $J_{C–F}$ = 30.1), 131.3 (q, $J_{C–F}$ = 1.1 Hz), 128.6, 128.3, 127.5, 125.7 (q, $J_{C–F}$ = 5.1), 123.6 (q, $J_{C–F}$ = 273.6 Hz), 121.8 (q, $J_{C–F}$ = 2.3), 95.5, 80.7, 55.6, 51.0(9), 51.0(7), 31.6, 22.3; *m/z* (ESI–MS) 398.2 ($^{35}Cl/^{35}Cl$) $[M]^+$, 400.2 ($^{35}Cl/^{37}Cl$) $[M]^+$.

Methyl 4-((1-(2,6-dichlorobenzyl)pyrrolidin-2-yl)ethynyl)benzoate (3.31f):



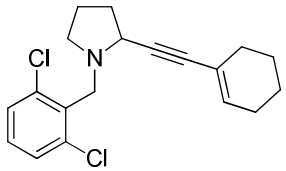
Following the general procedure (A), compound **3.31f** was obtained from pyrrolidine, methyl 4-ethynylbenzoate and 2,6-dichlorobenzaldehyde as a light brown liquid in 45% yield (> 25:1 mixture of regioisomers) (R_f = 0.13 in DCM); Characterization data of the major regioisomer: IR (KBr) 2951, 2844, 2810, 2227, 1932, 1724, 1605, 1436, 1405, 1307, 1275, 1175, 1108, 1018, 858, 738 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.6 Hz, 2H), 7.47 (d, *J* = 8.5 Hz, 2H), 7.29 (app d, *J* = 8.0 Hz, 2H), 7.14–7.08 (m, 1H), 4.21 (d, *J* = 12.7 Hz, 1H), 4.01 (d, *J* = 12.6 Hz, 1H), 3.91 (s, 3H), 3.82 (dd, *J* = 7.1, 5.1 Hz, 1H), 2.91 (ddd, *J* = 13.6, 8.6, 5.0 Hz, 1H), 2.69 (ddd, *J* = 14.8, 8.4, 6.4 Hz, 1H), 2.24–2.14 (m, 1H), 2.08–1.98 (m, 1H), 1.97–1.86 (m, 1H), 1.85–1.74 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6, 136.7, 135.1, 131.5, 129.4, 129.1, 128.7, 128.3(5), 128.3(0), 92.8, 83.7, 55.6, 52.1, 51.8, 51.6, 31.7, 22.4; *m/z* (ESI–MS) 388.3 ($^{35}Cl/^{35}Cl$) $[M]^+$, 390.2 ($^{35}Cl/^{37}Cl$) $[M]^+$.

4-((1-(2,6-Dichlorobenzyl)pyrrolidin-2-yl)ethynyl)benzonitrile (3.31g):



Following the general procedure (A), compound **3.31g** was obtained from pyrrolidine, 4-ethynylbenzonitrile and 2,6-dichlorobenzaldehyde as a light brown liquid in 43% yield (> 25:1 mixture of regioisomers) (R_f = 0.13 in DCM); Characterization data of the major regioisomer: IR (KBr) 2955, 2227, 1604, 1581, 1435, 1105, 839, 765 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.58 (app d, *J* = 7.9 Hz, 2H), 7.47 (app d, *J* = 8.1 Hz, 2H), 7.29 (app d, *J* = 8.0 Hz, 2H), 7.14–7.08 (m, 1H), 4.19 (d, *J* = 12.5 Hz, 1H), 3.99 (d, *J* = 12.6 Hz, 1H), 3.80 (dd, *J* = 7.6, 5.1 Hz, 1H), 2.90 (ddd, *J* = 13.6, 8.6, 5.0 Hz, 1H), 2.69 (ddd, *J* = 15.2, 8.6, 6.4 Hz, 1H), 2.25–2.13 (m, 1H), 2.07–1.96 (m, 1H), 1.96–1.86 (m, 1H), 1.85–1.73 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.6, 134.9, 132.1, 131.9, 128.8, 128.4, 128.3, 118.6, 111.1, 94.5, 82.8, 55.5, 51.9, 51.7, 31.6, 22.4; *m/z* (ESI–MS) 355.3 ($^{35}Cl/^{35}Cl$) $[M]^+$, 357.3 ($^{35}Cl/^{37}Cl$) $[M]^+$.

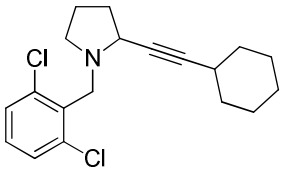
2-(Cyclohex-1-en-1-ylethynyl)-1-(2,6-dichlorobenzyl)pyrrolidine (3.31h):



Following the general procedure (A), compound **3.31h** was obtained from pyrrolidine, 2-ethynylcyclohexene and 2,6-dichlorobenzaldehyde as a colorless liquid in 86% yield (> 25:1 mixture of regioisomers) (R_f = 0.17 in hexanes/EtOAc 97:3 v/v); Characterization data of the major regioisomer: IR (KBr) 3025, 2929, 2857, 2217, 1581, 1562, 1435, 1360, 1317, 1197, 1135, 1104, 1104, 1088, 986, 918, 841, 765 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31–7.26 (comp, 2H), 7.11 (m, 1H), 6.10–6.04 (m, 1H), 4.16 (d, *J* = 12.6 Hz, 1H), 3.91 (d, *J* = 12.6 Hz, 1H), 3.70 (dd, *J* = 7.5, 4.7 Hz, 1H), 2.82 (ddd, *J* = 13.5, 8.4, 4.9 Hz, 1H), 2.67–2.58 (m, 1H), 2.19–2.11 (comp, 2H), 2.11–2.06 (comp, 2H), 1.96–1.80 (comp, 2H), 1.77–1.68 (m, 1H),1.68–1.61 (comp, 3H), 1.61–1.54 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.7, 135.4, 133.9, 128.5, 128.3, 120.7, 86.3, 86.1, 55.8, 51.6, 51.5, 31.8, 29.5, 25.6, 22.4, 22.3, 21.6; m/z (ESI–MS) 334.3 ($^{35}Cl/^{35}Cl$) $[M]^+$, 336.2 ($^{35}Cl/^{37}Cl$)

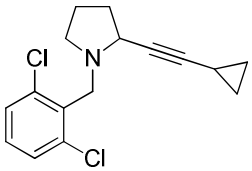
$[M]^+$.

2-(Cyclohexylethynyl)-1-(2,6-dichlorobenzyl)pyrrolidine (3.31i):



Following the general procedure (A), compound **3.31i** was obtained from pyrrolidine, cyclohexylacetylene and 2,6-dichlorobenzaldehyde as a colorless liquid in 81% yield (> 25:1 mixture of regioisomers) (R_f = 0.14 in hexanes/EtOAc 97:3 v/v); Characterization data of the major regioisomer: IR (KBr) 2932, 2854, 1582, 1562, 1449, 1436, 1265, 1197, 1089, 778, 765, 740, 705 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.0 Hz, 2H), 7.11 (m, 1H), 4.16 (d, *J* = 12.5 Hz, 1H), 3.87 (d, *J* = 12.5 Hz, 1H), 3.59–3.53 (m, 1H), 2.86–2.77 (m, 1H), 2.64–2.55 (m, 1H), 2.47–2.38 (m, 1H), 2.12–2.00 (m, 1H), 1.92–1.82 (comp, 2H), 1.82–1.76 (comp, 2H), 1.76–1.65 (comp, 3H), 1.56–1.41 (comp, 3H), 1.40–1.25 (comp, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.7, 135.5, 128.5, 128.3, 88.7, 79.3, 55.6, 51.6, 51.4, 33.0, 32.9, 32.0, 29.1, 26.0, 24.8, 22.2; *m/z* (ESI–MS) 336.2 ($^{35}Cl/^{35}Cl$) $[M]^+$, 338.2 ($^{35}Cl/^{37}Cl$) $[M]^+$.

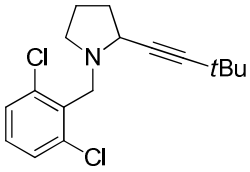
2-(Cyclopropylethynyl)-1-(2,6-dichlorobenzyl)pyrrolidine (3.31j):



Following the general procedure (A), compound **3.31j** was obtained from pyrrolidine, cyclopropylacetylene and 2,6-dichlorobenzaldehyde as a colorless liquid in 79% yield (> 25:1 mixture of regioisomers) (R_f = 0.14 in hexanes/EtOAc 97:3 v/v); Characterization data of the major regioisomer: IR (KBr) 3091, 3009, 2956, 2910, 2807, 2240, 1581, 1562, 1435, 1365, 1319, 1196, 1151, 1104, 1088, 1027, 981, 912, 811, 765 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.0 Hz, 2H), 7.13–7.08 (m, 1H), 4.12 (d, *J* = 12.6 Hz, 1H), 3.84 (d, *J* = 12.6 Hz, 1H), 3.51–3.46 (m, 1H), 2.84–2.77 (m, 1H), 2.56 (ddd, *J* = 15.1, 9.1, 6.3 Hz, 1H), 2.09–1.98 (m, 1H), 1.89–1.76 (comp, 2H), 1.72–1.64 (m, 1H), 1.28–1.21 (m, 1H), 0.77–0.70 (comp, 2H), 0.68–0.61 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.7, 135.4, 128.5, 128.3, 87.4, 74.8, 55.5, 51.6(6), 51.6(5), 31.8, 22.2, 8.2(2), 8.2(0), –0.5;

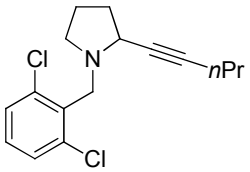
m/z (ESI–MS) 294.2 (^{35}Cl/^{35}Cl) $[M]^+$, 296.2 (^{35}Cl/^{37}Cl) $[M]^+$.

1-(2,6-Dichlorobenzyl)-2-(3,3-dimethylbut-1-yn-1-yl)pyrrolidine (3.31k)



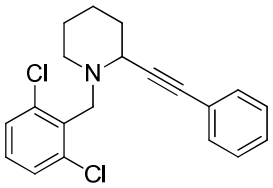
Following the general procedure (A), compound **3.31k** was obtained from pyrrolidine, 3,3-dimethyl-1-butyne and 2,6-dichlorobenzaldehyde as a colorless liquid in 55% yield (11:1 mixture of regioisomers) (R_f = 0.14 in hexanes/EtOAc 97:3 v/v); Characterization data of the major regioisomer: IR (KBr) 2967, 2865, 2811, 2240, 1582, 1562, 1474, 1456, 1435, 1361, 1264, 1204, 1108, 1089, 908, 766, 734 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.0 Hz, 2H), 7.14–7.08 (m, 1H), 4.17 (d, *J* = 12.5 Hz, 1H), 3.84 (d, *J* = 12.6 Hz, 1H), 2.52–2.46 (m, 1H), 2.85–2.77 (m, 1H), 2.60–2.52 (m, 1H), 2.11–1.99 (m, 1H), 1.90–1.77 (comp, 2H), 1.74–1.64 (m, 1H), 1.23 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.7, 135.4, 128.5, 128.3, 92.9, 77.7, 55.5, 51.7, 51.5, 31.9, 31.3, 27.4, 22.1; *m/z* (ESI–MS) 310.2 (^{35}Cl/^{35}Cl) $[M]^+$, 312.2 (^{35}Cl/^{37}Cl) $[M]^+$.

1-(2,6-Dichlorobenzyl)-2-(pent-1-yn-1-yl)pyrrolidine (3.31l):



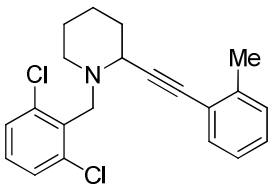
Following the general procedure (A), compound **3.31l** was obtained from pyrrolidine, 1-pentyne and 2,6-dichlorobenzaldehyde as a colorless liquid in 76% yield (> 25:1 mixture of regioisomers) (R_f = 0.20 in hexanes/EtOAc 97:3 v/v); Characterization data of the major regioisomer: IR (KBr) 3058, 2960, 2871, 2839, 1711, 1581, 1562, 1456, 1435, 1355, 1319, 1276, 1196, 1136, 1089, 981, 913, 765 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.0 Hz, 2H), 7.13–7.08 (m, 1H), 4.15 (d, *J* = 12.6 Hz, 1H), 3.88 (d, *J* = 12.6 Hz, 1H), 3.59–3.52 (m, 1H), 2.80 (ddd, *J* = 13.8, 8.5, 5.0 Hz, 1H), 2.59 (ddd, *J* = 14.6, 8.6, 6.0 Hz, 1H), 2.19 (app td, *J* = 7.0, 1.9 Hz, 2H), 2.10–2.01 (m, 1H), 1.92–1.78 (comp, 2H), 1.74–1.65 (m, 1H), 1.54 (app sex, *J* = 7.2 Hz, 2H), 1.01 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.7, 135.4, 128.5, 128.3, 84.3, 79.6, 55.5, 51.6, 51.4, 31.9, 22.4, 22.2, 20.8, 13.5; *m/z* (ESI–MS) 296.2 (^{35}Cl/^{35}Cl) $[M]^+$, 298.2 (^{35}Cl/^{37}Cl) $[M]^+$.

1-(2,6-Dichlorobenzyl)-2-(phenylethynyl)piperidine (3.31m):



Following the general procedure (A), compound **3.31m** was obtained from piperidine, phenylacetylene and 2,6-dichlorobenzaldehyde as a colorless liquid in 91% yield (7:1 mixture of regioisomers) (R_f = 0.19 in hexanes/EtOAc 97:3 v/v); Characterization data of the major regioisomer: IR (KBr) 3079, 3056, 2938, 2857, 2808, 2759, 2246, 1667, 1580, 1489, 1435, 1379, 1350, 1324, 1309, 1277, 1264, 1182, 1151, 1117, 1088, 985, 910, 873, 750, 735, 649 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.53–7.48 (comp, 2H), 7.36–7.31 (comp, 3H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.15–7.10 (m, 1H), 3.99–3.92 (m, 1H), 3.94 (d, *J* = 12.8 Hz, 1H), 3.86 (d, *J* = 12.9 Hz, 1H), 2.75 (app td, *J* = 11.4, 2.7 Hz, 1H), 2.60–2.53 (m, 1H), 1.88–1.77 (comp, 2H), 1.76–1.66 (m, 1H), 1.60–1.50 (comp, 2H), 1.50–1.40 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.1, 135.3, 131.7, 128.5, 128.3, 128.2, 127.8, 123.7, 87.8, 86.4, 55.1, 53.0, 48.1, 31.4, 25.8, 20.4; *m/z* (ESI–MS) 344.2 ($^{35}Cl/^{35}Cl$) $[M]^+$, 346.1 ($^{35}Cl/^{37}Cl$) $[M]^+$.

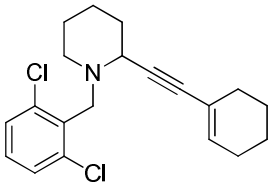
1-(2,6-Dichlorobenzyl)-2-(*o*-tolylethynyl)piperidine (3.31n):



Following the general procedure (A), compound **3.31n** was obtained from piperidine, 2-ethynyltoluene and 2,6-dichlorobenzaldehyde as a colorless liquid in 91% yield (7:1 mixture of regioisomers) (R_f = 0.19 in hexanes/EtOAc 97:3 v/v); Characterization data of the major regioisomer: IR (KBr) 3060, 3020, 2938, 2859, 2805, 1581, 1562, 1484, 1435, 1351, 1323, 1211, 1116, 1088, 971, 756, 715 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.49 (app d, *J* = 7.4 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.26–7.20 (comp, 2H), 7.17 (m, 1H), 7.13 (m, 1H), 4.07–4.02 (m, 1H), 3.96 (d, *J* = 12.8 Hz, 1H), 3.89 (d, *J* = 12.9 Hz, 1H), 2.78 (app td, *J* = 11.5, 2.6 Hz, 1H), 2.64–2.57 (m, 1H), 2.55 (s, 3H), 1.91–1.81 (comp, 2H), 1.80–1.69 (m, 1H), 1.62–1.53 (comp, 2H), 1.52–1.42 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.0, 137.1, 135.3, 132.1, 129.3, 128.5, 128.2, 127.8, 125.5, 123.5, 91.8, 85.2, 55.1,

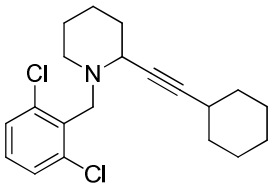
53.2, 48.0, 31.5, 25.9, 21.2, 20.3; *m/z* (ESI–MS) 358.2 ($^{35}Cl/^{35}Cl$) $[M]^+$, 360.2 ($^{35}Cl/^{37}Cl$) $[M]^+$.

2-(Cyclohex-1-en-1-ylethynyl)-1-(2,6-dichlorobenzyl)piperidine (3.31o):



Following the general procedure (A), compound **3.31o** was obtained from piperidine, 2-ethynylcyclohexene and 2,6-dichlorobenzaldehyde as a colorless liquid in 90% yield (4:1 mixture of regioisomers) (R_f = 0.19 in hexanes/EtOAc 97:3 v/v); Characterization data of the major regioisomer: IR (KBr) 3052, 2938, 2860, 2304, 1581, 1561, 1436, 1350, 1323, 1265, 1195, 1116, 1089, 973, 896, 741 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.0 Hz, 2H), 7.10 (m, 1H), 6.16–6.09 (m, 1H), 3.85 (d, *J* = 13.2 Hz, 1H), 3.84–3.80 (m, 1H), 3.75 (d, *J* = 12.9 Hz, 1H), 2.65 (app td, *J* = 11.2, 2.8 Hz, 1H), 2.52–2.45 (m, 1H), 2.24–2.17 (comp, 2H), 2.15–2.08 (comp, 2H), 1.77–1.70 (comp, 2H), 1.69–1.64 (comp, 2H), 1.64–1.56 (comp, 3H), 1.54–1.42 (comp, 2H), 1.42–1.34 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.1, 135.4, 133.7, 128.4, 128.2, 120.9, 88.2, 84.7, 55.0, 53.1, 48.0, 31.5, 29.8, 25.8, 25.6, 22.4, 21.6, 20.3; *m/z* (ESI–MS) 348.3 ($^{35}Cl/^{35}Cl$) $[M]^+$, 350.4 ($^{35}Cl/^{37}Cl$) $[M]^+$.

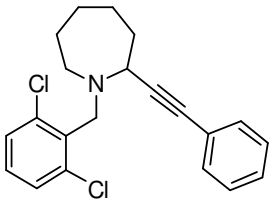
2-(Cyclohexylethynyl)-1-(2,6-dichlorobenzyl)piperidine (3.31p):



Following the general procedure (A), compound **3.31p** was obtained from piperidine, cyclohexylacetylene and 2,6-dichlorobenzaldehyde as a colorless liquid in 80% yield (8:1 mixture of regioisomers) (R_f = 0.22 in hexanes/EtOAc 97:3 v/v); Characterization data of the major regioisomer: IR (KBr) 2930, 2852, 2806, 2255, 1581, 1562, 1434, 1350, 1324, 1297, 1259, 1212, 1183, 1115, 1089, 974, 888, 860, 765, 721 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.0 Hz, 2H), 7.13–7.07 (m, 1H), 3.86 (d, *J* = 12.8 Hz, 1H), 3.75–3.71 (m, 1H), 3.73 (d, *J* = 12.8 Hz, 1H), 2.65 (app td, *J* = 11.2, 2.8 Hz, 1H), 2.57–2.48 (m, 1H), 2.48–2.42 (m, 1H), 1.87–1.74 (comp, 4H), 1.74–1.68 (comp, 2H), 1.68–1.58 (comp, 2H), 1.56–1.42 (comp, 5H), 1.40–1.31 (comp, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ

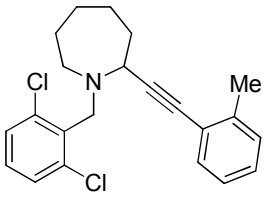
137.1, 135.5, 128.4, 128.2, 90.7, 77.5, 55.0, 52.7, 47.7, 33.2, 33.1, 31.7, 29.0, 26.1, 25.9, 24.7, 20.2; *m/z* (ESI–MS) 350.2 (^{35}Cl/^{35}Cl) $[M]^+$, 352.2 (^{35}Cl/^{37}Cl) $[M]^+$.

1-(2,6-Dichlorobenzyl)-2-(phenylethynyl)azepane (3.31q):



Following the general procedure (A), compound **3.31q** was obtained from azepane, phenylacetylene and 2,6-dichlorobenzaldehyde as a colorless liquid in 61% yield (5:1 mixture of regioisomers) (R_f = 0.34 in hexanes/EtOAc 97:3 v/v); Characterization data of the major regioisomer: IR (KBr) 2927, 2853, 1581, 1561, 1489, 1435, 1339, 1196, 1141, 1089, 952, 775, 755, 690 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50–7.46 (comp, 2H), 7.34–7.28 (comp, 4H), 7.15–7.10 (m, 1H), 4.07 (d, *J* = 13.0 Hz, 1H), 3.97–3.93 (m, 1H), 3.92 (d, *J* = 12.9 Hz, 1H), 2.97–2.87 (m, 1H), 2.68–2.60 (m, 1H), 2.11–2.02 (m, 1H), 1.82–1.74 (m, 1H), 1.74–1.64 (comp, 3H), 1.59–1.51 (m, 1H), 1.50–1.33 (comp, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.0, 135.7, 131.7, 128.5, 128.3, 128.2, 127.7, 123.8, 89.5, 84.9, 54.9, 54.8, 49.1, 35.2, 29.1, 27.9, 23.8; *m/z* (ESI–MS) 358.2 (^{35}Cl/^{35}Cl) $[M]^+$, 360.2 (^{35}Cl/^{37}Cl) $[M]^+$.

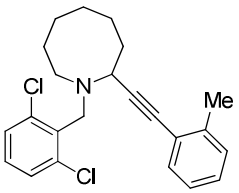
1-(2,6-Dichlorobenzyl)-2-(*o*-tolylethynyl)azepane (3.31r):



Following the general procedure (A), compound **3.31r** was obtained from azepane, 2-ethynyltoluene and 2,6-dichlorobenzaldehyde as a colorless liquid in 70% yield (8:1 mixture of regioisomers) (R_f = 0.34 in hexanes/EtOAc 97:3 v/v); Characterization data of the major regioisomer: IR (KBr) 3068, 3021, 2928, 2853, 1562, 1485, 1455, 1435, 1338, 1196, 1112, 1089, 953, 756, 715 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (app d, *J* = 7.5 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.24–7.18 (comp, 2H), 7.18–7.10 (comp, 2H), 4.09 (d, *J* = 12.9 Hz, 1H), 4.03–3.97 (m, 1H), 3.92 (d, *J* = 12.9 Hz, 1H), 2.97–2.88 (m, 1H), 2.69–2.61 (m, 1H), 2.51 (s, 3H), 2.13–2.04 (m, 1H), 1.84–1.65 (comp, 4H), 1.60–1.51 (m, 1H), 1.49–1.32 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.9, 137.1, 135.7,

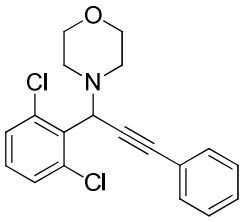
132.0, 129.3, 128.5, 128.3, 127.7, 125.5, 123.6, 93.5, 83.7, 55.0(4), 55.0(0), 49.1, 35.3, 29.1, 27.9, 23.8, 21.1; *m/z* (ESI–MS) 372.1 ($^{35}Cl/^{35}Cl$) $[M]^+$, 374.1 ($^{35}Cl/^{37}Cl$) $[M]^+$.

1-(2,6-Dichlorobenzyl)-2-(*o*-tolylethynyl)azocane (3.31s):



Following the general procedure (A), compound **3.31s** was obtained from azocane, 2-ethynyltoluene and 2,6-dichlorobenzaldehyde as a colorless liquid in 41% yield (2:1 mixture of regioisomers) (R_f = 0.40 in hexanes/EtOAc 97:3 v/v); Characterization data of the major regioisomer: IR (KBr) 3030, 2979, 2870, 2360, 2342, 1728, 1487, 1221, 1181, 1054, 749 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.44 (app d, *J* = 7.2 Hz, 1H), 7.31 (app d, *J* = 8.0 Hz, 2H), 7.24–7.17 (comp, 2H), 7.17–7.10 (comp, 2H), 4.15 (d, *J* = 12.6 Hz, 1H), 3.90 (d, *J* = 12.7 Hz, 1H), 3.80 (dd, *J* = 11.4, 5.7 Hz, 1H), 3.03 (ddd, *J* = 13.6, 8.5, 4.7 Hz, 1H), 2.65–2.56 (m, 1H), 2.50 (s, 3H), 2.07–1.98 (m, 1H), 1.93–1.80 (comp, 2H), 1.70–1.55 (comp, 2H), 1.55–1.48 (m, 1H), 1.47–1.39 (m, 1H), 1.39–1.30 (m, 1H), 1.30–1.22 (m, 1H), 1.22–1.11 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.0, 137.0, 135.8, 132.0, 129.3, 128.6, 128.3, 127.7, 125.4, 123.6, 93.5, 82.8, 56.4, 56.0, 48.2, 34.1, 29.2, 28.8, 25.2, 25.0, 21.1; *m/z* (ESI–MS) 386.4 ($^{35}Cl/^{35}Cl$) $[M]^+$, 388.4 ($^{35}Cl/^{37}Cl$) $[M]^+$.

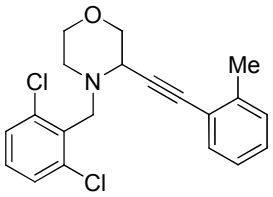
4-(1-(2,6-Dichlorophenyl)-3-phenylprop-2-yn-1-yl)morpholine (3.32t):



Following the general procedure (A), compound **3.32t** was obtained from morpholine, phenylacetylene and 2,6-dichlorobenzaldehyde as a colorless liquid in 60% yield (7:1 mixture of regioisomers) (R_f = 0.20 in hexanes/EtOAc 95:5 v/v); Characterization data of the major regioisomer: IR (KBr) 3054, 2957, 2854, 2810, 2760, 2694, 2226, 1598, 1578, 1562, 1490, 1435, 1310, 1265, 1117, 984, 872, 773, 755, 691 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.48–7.42 (comp, 2H), 7.34 (comp, 2H), 7.32.–7.27 (comp, 3H), 7.20–7.14 (m, 1H), 5.28 (s, 1H), 3.78–3.67 (comp, 4H), 2.99–2.85 (comp, 2H), 2.54–2.45 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.4, 133.5,

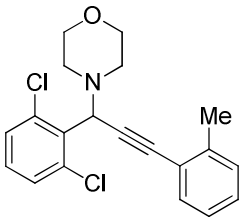
131.7, 129.4, 129.2, 128.2(3), 128.2(0), 123.0, 86.7, 85.0, 67.1, 58.0, 51.2; *m/z* (ESI–MS) 346.2 (^{35}Cl/^{35}Cl) $[M]^+$, 348.2 (^{35}Cl/^{37}Cl) $[M]^+$.

4-(2,6-Dichlorobenzyl)-3-(*o*-tolylethynyl)morpholine (3.31u):



Following the general procedure (A), compound **3.31u** was obtained from morpholine, 2-ethynyltoluene and 2,6-dichlorobenzaldehyde as a colorless liquid in 42% yield (1.2:1 mixture of regioisomers) (R_f = 0.22 in hexanes/EtOAc 95:5 v/v); Characterization data of **3.31u**: IR (KBr) 3054, 2963, 2916, 2857, 2220, 1580, 1562, 1485, 1436, 1320, 1265, 1198, 1117, 981, 864, 759, 738 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (app d, *J* = 7.5 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.24–7.21 (comp, 2H), 7.18–7.14 (comp, 2H), 4.15 (d, *J* = 12.5 Hz, 1H), 3.92 (dd, *J* = 10.9, 3.6 Hz, 1H), 3.89 (d. *J* = 12.9 Hz, 1H), 3.86–3.82 (m, 1H), 3.81–3.78 (m, 1H), 3.78–3.74 (m, 1H), 3.59 (ddd, *J* = 11.5, 9.3, 2.7 Hz, 1H), 3.00–2.94 (m, 1H), 2.53 (s, 3H), 2.52–2.49 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.2, 137.1, 134.2, 132.2, 128.9, 129.3, 128.3, 128.1, 125.4, 123.0, 89.5, 85.2, 70.7, 67.4, 54.5, 53.6, 48.3, 21.1; *m/z* (ESI–MS) 360.2 (^{35}Cl/^{35}Cl) $[M]^+$, 362.3 (^{35}Cl/^{37}Cl) $[M]^+$.

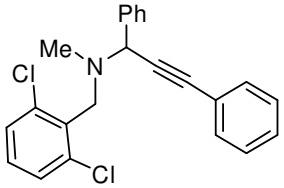
4-(1-(2,6-Dichlorophenyl)-3-(*o*-tolyl)prop-2-yn-1-yl)morpholine (3.32u):



Compound **3.32u** was prepared by a slightly modified literature procedure.[28] A mixture of 2,6-dichlorobenzaldehyde (1 mmol), morpholine (1.2 mmol), 2-ethynyltoluene (1.5 mmol) and CuI (0.015 mmol) in toluene (3 mL) was stirred under reflux for 3 h. After cooling to room temperature, the crude mixture was directly loaded onto a column and purified by flash chromatography. The title compound was obtained as a colorless liquid in 61% yield (R_f = 0.22 in hexanes/EtOAc 95:5 v/v); IR (KBr) 2957, 2854, 2810, 1562, 1450, 1435, 1265, 1117, 986, 872, 767, 757 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (app d, *J* = 7.6 Hz, 1H), 7.34 (d, *J* = 8.0

Hz, 2H), 7.23–7.15 (comp, 3H), 7.14–7.08 (m, 1H), 5.33 (s, 1H), 3.76–3.68 (comp, 4H), 2.99–2.86 (comp, 2H), 2.53–2.46 (comp, 2H), 2.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.3, 136.3, 133.7, 132.2, 129.3(8), 129.3(6), 129.2, 128.2, 125.4, 122.8, 88.6, 85.8, 67.1, 58.2, 51.3, 20.8; *m/z* (ESI–MS) 360.1 (^{35}Cl/^{35}Cl) $[M]^+$, 362.1 (^{35}Cl/^{37}Cl) $[M]^+$.

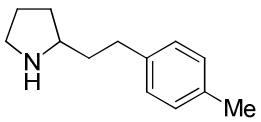
_N_-(2,6-dichlorobenzyl)-_N_-methyl-1,3-diphenylprop-2-yn-1-amine (3.31v):



Following the general procedure (A), compound **3.31v** was obtained from pyrrolidine, 4-ethynylbenzonitrile and 2,6-dichlorobenzaldehyde as a light brown liquid in 35% yield (4:1 mixture of regioisomers) (R_f = 0.40 in DCM/Hexanes 40:60 v/v); Characterization data of the major regioisomer: IR (KBr) 3060, 2953, 2863, 2360, 1562, 1490, 1435, 1323, 960, 777 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (app d, *J* = 7.6 Hz, 2H), 7.62–7.56 (comp, 2H), 7.41–7.35 (comp, 3H), 7.35–7.30 (comp, 4H), 7.30–7.26 (m, 1H), 7.17–7.11 (m, 1H), 5.07 (s, 1H), 4.13 (d, *J* = 12.6 Hz, 1H), 4.00 (d, *J* = 12.6 Hz, 1H), 2.17 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.8, 137.1, 134.9, 131.9, 128.8, 128.4(1), 128.4(0), 128.3, 128.2, 128.0, 127.5, 123.3, 88.7, 84.8, 60.6, 54.2, 36.0; *m/z* (ESI–MS) 379.9 (^{35}Cl/^{35}Cl) $[M]^+$, 381.8 (^{35}Cl/^{37}Cl) $[M]^+$.

Transformation of α–functionalized amines:

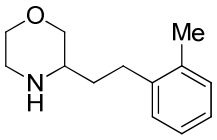
2-(4-Methylphenethyl)pyrrolidine (3.39):



To a suspension of **3.31a** (250 mg, 0.726 mmol) and Pd/C (50 mg, 10% Pd on carbon) in methanol (5 mL), ammonium formate (321 mg, 7 equiv.) was added in one portion. The resulting mixture was stirred under reflux for 3 h. After cooling to room temperature, the mixture was filtered through a celite pad and washed with

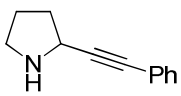
methanol (6 x 5 mL). The filtrate was concentrated *in vacuo* and purified by flash chromatography to give the title compound as a colorless liquid in 67% yield (R_f = 0.16 in EtOAc/MeOH/*i*PrNH$_2$ 88:10:2 v/v); IR (KBr) 3325, 2913, 1602, 1548, 1491, 1190, 1170, 871, 780, 740 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14–7.03 (comp, 4H), 2.70–2.65 (m, 1H), 2.61–2.52 (comp, 2H), 2.32 (s, 3H), 1.67–1.57 (comp, 2H), 1.55 (br s, 1H), 1.49–1.40 (comp, 2H), 1.39–1.29 (comp, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.6, 134.9, 128.9, 128.2, 42.1, 35.4, 33.7, 31.5, 29.1, 26.7, 20.9; *m/z* (ESI–MS) 190.3 $[M + H]^+$.

3-(2-Methylphenethyl)morpholine (3.40):



To a suspension of **3.31u/3.32u** (1.2:1) (180 mg, 0.5 mmol) and Pd/C (50 mg, 10% Pd on carbon) in methanol (3 mL), ammonium formate (221 mg, 3.5 mmol) was added in one portion. The resulting mixture was stirred under reflux for 3 h. After cooling to room temperature, the mixture was filtered through a celite pad and washed with methanol (6 x 5 mL). The filtrate was concentrated *in vacuo* and purified by flash chromatography to give the title compound as a colorless liquid in 51% yield (R_f = 0.32 in EtOAc/MeOH 95:5 v/v); IR (KBr) 3424, 3054, 2959, 2856, 1640, 1451, 1265, 1105, 720, 704 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17–7.08 (comp, 4H), 3.88–3.77 (comp, 2H), 3.52 (app td, *J* = 11.1, 2.6 Hz, 1H), 3.25–3.17 (m, 1H), 3.02–2.94 (m, 1H), 2.94–2.83 (comp, 2H), 2.73–2.65 (m, 1H), 2.64–2.55 (m, 1H), 2.30 (s, 3H), 1.83 (br s, 1H), 1.63–1.49 (comp, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.8, 135.7, 130.3, 128.6, 126.1(4), 126.1(0), 72.5, 67.5, 54.9, 46.1, 33.0, 29.3, 19.2; *m/z* (ESI–MS) 206.2 $[M + H]^+$.

2-(Phenylethynyl)pyrrolidine (3.41):



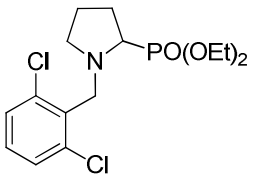
A solution of **3.29j/3.30j** (11:1) (250 mg, 0.824 mmol) and proton sponge (35 mg, 0.165 mmol) in 1,2-dichloroethane (4 mL) was cooled in an ice bath. 1-Chloroethyl chloroformate (178 μL, 1.648 mmol) was then added dropwise and the reaction

mixture was allowed to warm to room temperature. After stirring at room temperature for 3 h, the solvent was evaporated *in vacuo* and the reaction mixture was passed through a short silica pad, eluting with hexanes/EtOAc (90:10 v/v). After concentrating the solution of the crude carbamate *in vacuo*, methanol (3 mL) was added and the mixture stirred under reflux for 30 min. Solvent was then evaporated off and the product mixture purified by flash chromatography. The title compound was obtained as a colorless oil in 51% yield (R_f = 0.27 in EtOAc/MeOH 95:5 v/v); IR (KBr) 3339, 3054, 2969, 2873, 2228, 1640, 1598, 1571, 1489, 1443, 1418, 1334, 1265, 1179, 1071, 1027, 916, 757, 692 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.43–7.35 (comp, 2H), 7.30–7.22 (comp, 3H), 4.02 (dd, *J* = 7.1, 5.4 Hz, 1H), 2.20–2.09 (m, 1H), 2.98–2.87 (m, 1H), 2.17–2.05 (m, 1H), 1.97 (br s, 1H), 1.96–1.83 (comp, 2H), 1.83–1.70 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 131.5, 128.1, 127.8, 123.2, 91.6, 82.3, 49.3, 46.1, 33.2, 24.9; *m/z* (ESI–MS) 172.1 $[M + H]^+$.

General Procedure (B) for the Three-Component Phosphonation of Amines:

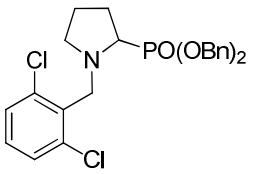
A 10 mL microwave reaction tube was charged with a stir bar, phosphine oxide (0.6, 1.2 equiv.), toluene (1 mL), aldehyde (0.5 mmol, 1 equiv.), amine (0.6 mmol, 1.2 equiv.) and benzoic acid (0.1 mmol, 0.2 equiv.). The reaction tube was sealed with a Teflon-lined snap cap, and heated in a microwave reactor at 200 °C (200 W, 30–80 psi) for the appropriate time under high stirring. After cooling with compressed air flow, the reaction mixture was directly loaded onto a column and purified by silica gel chromatography.

Diethyl (1-(2,6-dichlorobenzyl)pyrrolidin-2-yl)phosphonate (3.51a):



Following the general procedure with a reaction time of 15 min, compound **3.51a** was obtained from diethyl phosphite (0.75 mmol, 1.5 equiv), 2,6-dichlorobenzaldehyde (0.5 mmol, 1 equiv) and pyrrolidine (0.75 mmol, 1.5 equiv) as a colorless liquid in 54% yield (> 25:1 mixture of regioisomers) (R_f = 0.35 in ether); Characterization data of the major regioisomer: IR (KBr) 2978, 1629, 1580, 1562, 1436, 1237, 1055, 1028, 960, 766 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30–7.26 (m, 2H), 7.14–7.08 (m, 1H), 4.46 (d, *J* = 12.2 Hz, 1H), 4.23–4.08 (comp, 4H), 3.92 (d, *J* = 12.2 Hz, 1H), 3.13–3.06 (m, 1H), 2.85–2.77 (m, 1H), 2.61–2.58 (m, 1H), 2.17–2.04 (comp, 2H), 1.80–1.69 (comp, 2H), 1.30(4) (t, *J* = 7.0 Hz, 3H), 1.29(7) (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.8, 134.7, 128.7, 128.3, 62.3 (d, $J_{C,P}$ = 7.0 Hz), 61.7 (d, $J_{C,P}$ = 7.3 Hz), 59.9 (d, $J_{C,P}$ = 171.2 Hz), 53.8 (d, $J_{C,P}$ = 4.1 Hz), 53.4 (d, $J_{C,P}$ = 12.9 Hz), 26.9 (d, $J_{C,P}$ = 1.2 Hz), 23.9 (d, $J_{C,P}$ = 5.3 Hz), 16.5(7) (d, $J_{C,P}$ = 5.2 Hz), 16.5(1) (d, $J_{C,P}$ = 5.2 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.90; *m/z* (ESI–MS) 366.0 ($^{35}Cl/^{35}Cl$) $[M]^+$, 368.0 ($^{35}Cl/^{37}Cl$) $[M]^+$.

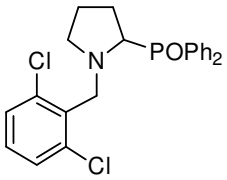
Dibenzyl (1-(2,6-dichlorobenzyl)pyrrolidin-2-yl)phosphonate (3.51b):



Following the general procedure with a reaction time of 15 min, compound **3.51b** was obtained from dibenzyl phosphite (0.75 mmol, 1.5 equiv), 2,6-dichlorobenzaldehyde (0. 5 mmol, 1 equiv) and pyrrolidine (0.75 mmol, 1.5 equiv) as an off-white sticky solid in 44% yield (> 25:1 mixture of regioisomers) (R_f = 0.25 in ether/hexanes 50:50 v/v); Characterization data of the major regioisomer: IR (KBr) 3065, 3033, 2956, 1581, 1562, 1455, 1436, 1237, 1213, 998, 735, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.28 (comp, 12H), 7.13–7.07 (m, 1H), 5.10–5.00 (comp, 4H), 4.49 (d, *J* = 12.2 Hz, 1H), 3.96 (d, *J* = 12.2 Hz, 1H), 3.25–3.15 (m, 1H), 2.88–2.78 (m, 1H), 2.64–2.53 (m, 1H), 2.23–2.02 (comp, 2H), 1.77–1.66 (comp, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.9, 136.8(4),

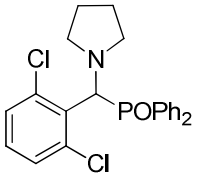
136.8(0), 134.6, 128.8, 128.5, 128.4, 128.3(6), 128.1, 127.9, 127.8(6), 127.8, 68.0 (d, $J_{C,P}$ = 6.9 Hz), 67.1 (d, $J_{C,P}$ = 7.3 Hz), 60.3 (d, $J_{C,P}$ = 170.9 Hz), 54.0 (d, $J_{C,P}$ = 4.5 Hz), 53.4 (d, $J_{C,P}$ = 12.6 Hz), 27.0, 24.1 (d, $J_{C,P}$ = 4.8 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.59; *m/z* (ESI–MS) 489.8 (^{35}Cl/^{35}Cl) $[M]^+$, 491.7 (^{35}Cl/^{37}Cl) $[M]^+$

(1-(2,6-Dichlorobenzyl)pyrrolidin-2-yl)diphenylphosphine oxide (3.51c):



Following the general procedure, compound **3.51c** was obtained from diphenyl phosphine oxide, 2,6-dichlorobenzaldehyde and pyrrolidine as a white solid in 86% yield after 15 min (> 25:1 mixture of regioisomers) (R_f = 0.23 in ether); Characterization data of the major regioisomer: mp: 139–143 ºC; IR (KBr) 3056, 2964, 2861, 1581, 1561, 1436, 1182, 1118, 1097, 781, 707, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 8.04–7.94 (comp, 2H), 7.84–7.74 (comp, 2H), 7.52–7.43 (comp, 2H), 7.43–7.36 (comp, 4H), 7.17 (d, *J* = 8.0 Hz, 2H), 7.04 (app dd, *J* = 7.5, 8.6 Hz, 1H), 3.99 (d, *J* = 12.0 Hz, 1H), 3.89–3.82 (m, 1H), 3.81 (d, *J* = 12.0 Hz, 1H), 2.81–2.71 (m, 1H), 2.69–2.60 (m, 1H), 2.33–2.16 (m, 1H), 2.16–2.01 (m, 1H), 1.76–1.64 (m, 1H), 1.55–1.44 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.7, 134.3, 133.2 (d, $J_{C,P}$ = 93.1 Hz), 132.5, 132.4, 132.8–131.3 (m), 130.8 (d, $J_{C,P}$ = 94.8 Hz), 130.3, 129.0–128.6 (m), 128.6–128.1 (m), 128.1–127.8 (m), 64.1 (d, $J_{C,P}$ = 94.0 Hz), 55.1 (d, $J_{C,P}$ = 6.3 Hz), 53.8 (d, $J_{C,P}$ = 6.8 Hz), 26.9, 24.0 (d, $J_{C,P}$ = 2.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.76; *m/z* (ESI–MS) 430.1 (^{35}Cl/^{35}Cl) $[M]^+$, 432.1 (^{35}Cl/^{37}Cl) $[M]^+$.

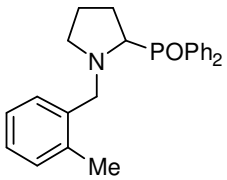
((2,6-Dichlorophenyl)(pyrrolidin-1-yl)methyl)diphenylphosphine oxide (3.52c):



A mixture of diphenyl phosphine oxide (0.55 mmol, 1.1 equiv), 2,6-dichlorobenzaldehyde (0.5 mmol) and pyrrolidine (0.55 mmol, 1.1 equiv) in toluene (2 mL) was allowed to stir under reflux for 30 minutes. The reaction mixture was then cooled to room temperature and purified by flash column chromatography to give the title compound as a white solid in 78% yield (R_f = 0.34 in ether); mp: 159–162 ºC; IR

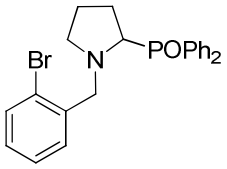
(KBr) 3046, 2972, 2776, 1559, 1435, 1199, 1175, 1114, 1100, 774, 748 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18–8.06 (comp, 2H), 7.71–7.60 (comp, 2H), 7.57–7.46 (comp, 3H), 7.26–7.20 (m, 1H), 7.19–7.06 (comp, 4H), 6.93 (app dt, J = 8.1, 1.3 Hz, 1H), 5.49 (d, $J_{H,P}$ = 7.0 Hz, 1H), 2.76–2.65 (comp, 2H), 2.52–2.41 (comp, 2H), 1.77–1.59 (comp, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.0 (d, $J_{C,P}$ = 4.7 Hz), 136.5 (d, $J_{C,P}$ = 8.1 Hz), 134.6 (d, $J_{C,P}$ = 96.3 Hz), 132.8–132.7 (m), 131.3(5) (d, $J_{C,P}$ = 80.8 Hz), 131.3 (d, $J_{C,P}$ = 8.0 Hz), 130.6 (d, $J_{C,P}$ = 9.2 Hz), 130.1–129.8 (m), 129.1–128.8 (m), 128.4 (d, $J_{C,P}$ = 11.2 Hz), 127.8, 127.5 (d, $J_{C,P}$ = 11.7 Hz), 66.9 (d, $J_{C,P}$ = 81.4 Hz), 53.4 (d, $J_{C,P}$ = 6.0 Hz), 23.2; ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.65; *m/z* (ESI–MS) 430.1 ($^{35}Cl/^{35}Cl$) $[M]^+$, 432.1 ($^{35}Cl/^{37}Cl$) $[M]^+$.

(1-(2-Methylbenzyl)pyrrolidin-2-yl)diphenylphosphine oxide (3.54b):



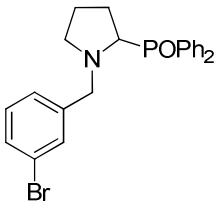
Following the general procedure with a reaction time of 15 min, compound **3.54b** was obtained from diphenyl phosphine oxide, *o*-tolualdehyde and pyrrolidine as a white solid in 76% yield (18:1 mixture of regioisomers) (R_f = 0.17 in ether); Characterization data of the major regioisomer: mp: 135–137 ºC; IR (KBr) 3051, 2967, 2908, 2809, 1512, 1474, 1437, 1376, 1181, 1120, 1095, 716, 692 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11–8.03 (comp, 2H), 7.94–7.85 (comp, 2H), 7.57–7.41 (comp, 6H), 7.05 (app d, J = 7.8 Hz, 2H), 6.99 (app d, J = 7.9 Hz, 2H), 3.69 (d, J = 12.6 Hz, 1H), 3.61 (ddd, $J_{H,P}$ = 10.3 Hz, $J_{H,H}$ = 4.9, 2.9 Hz, 1H), 3.20 (d, J = 12.6 Hz, 1H), 2.85 (ddd, J = 9.7, 6.7, 3.3 Hz, 1H), 2.31 (s, 3H), 2.29–2.23 (m, 1H), 2.23–2.14 (m, 1H), 2.14–2.01 (m, 1H), 1.69–1.58 (m, 1H), 1.53–1.43 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.4, 136.1, 132.8 (d, $J_{C,P}$ = 92.9 Hz), 132.5, 132.4, 131.7(5), 130.6(9), 131.6(6), 131.6(4), 131.6(1), 130.9 (d, $J_{C,P}$ = 94.0 Hz), 128.7 (d, $J_{C,P}$ = 13.8 Hz), 128.4 (d, $J_{C,P}$ = 11.0 Hz), 128.2 (d, $J_{C,P}$ = 11.0 Hz), 63.7 (d, $J_{C,P}$ = 95.3 Hz), 61.2 (d, $J_{C,P}$ = 3.3 Hz), 54.6 (d, $J_{C,P}$ = 9.1 Hz), 27.3, 24.5 (d, $J_{C,P}$ = 3.3 Hz), 21.0 (d, $J_{C,P}$ = 1.1 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 30.94; *m/z* (ESI–MS) 376.1 $[M + H]^+$.

(1-(2-Bromobenzyl)pyrrolidin-2-yl)diphenylphosphine oxide (3.54c):



Following the general procedure with a reaction time of 30 min, compound **3.54c** was obtained from diphenyl phosphine oxide, *o*-bromobenzaldehyde and pyrrolidine as a light brown liquid in 82% yield (> 25:1 mixture of regioisomers) (R_f = 0.20 in ether); Characterization data of the major regioisomer: IR (KBr) 3056, 2967, 1689, 1591, 1465, 1437, 1181, 1118, 1025, 724, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.01–7.91 (comp, 2H), 7.88–7.79 (comp, 2H), 7.50–7.42 (comp, 2H), 7.42–7.32 (comp, 6H), 7.25–7.17 (m, 1H), 7.05–6.97 (m, 1H), 3.77–3.69 (m, 1H), 3.68 (d, *J* = 14.4 Hz, 1H), 3.62 (d, *J* = 14.5 Hz, 1H), 3.03–2.93 (m, 1H), 2.46–2.32 (m, 1H), 2.30–2.16 (m, 1H), 2.16–2.01 (m, 1H), 1.78–1.65 (m, 1H), 1.65–1.54 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 132.8, 132.3–131.8 (m), 131.8–131.3 (m), 130.6, 130.6–131.1 (m), 128.6–127.7 (m), 127.1, 123.2, 64.0 (d, $J_{C,P}$ = 94.3 Hz), 60.6 (d, $J_{C,P}$ = 3.4 Hz), 54.9 (d, $J_{C,P}$ = 7.0 Hz), 27.2, 24.7 (d, $J_{C,P}$ = 3.3 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.05; *m/z* (ESI–MS) 439.9 (^{79}Br) $[M]^+$, 441.8 (^{81}Br) $[M]^+$.

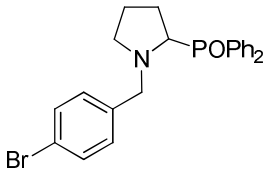
(1-(3-Bromobenzyl)pyrrolidin-2-yl)diphenylphosphine oxide (3.54d):



Following the general procedure with a reaction time of 30 min, compound **3.54d** was obtained from diphenyl phosphine oxide, *m*-bromobenzaldehyde and pyrrolidine as pale white solid in 74% yield (> 25:1 mixture of regioisomers) (R_f = 0.21 in ether/MeOH 99:1 v/v); Characterization data of the major regioisomer: mp: 128–131 ºC; IR (KBr) 3051, 2967, 2940, 2800, 1592, 1435, 1376, 1208, 1142, 1121, 723, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (app t, *J* = 8.8 Hz, 2H), 7.87 (app t, *J* = 9.0 Hz, 2H), 7.58–7.40 (comp, 6H), 7.30 (d, *J* = 7.7 Hz, 1H), 7.20 (s, 1H), 7.13–7.06 (m, 1H), 7.06–7.01 (m, 1H), 3.77 (d, *J* = 13.1 Hz, 1H), 3.66–3.57 (m, 1H), 3.24 (d, *J* = 13.0 Hz, 1H), 2.93–2.83 (m, 1H), 2.33–2.24 (m, 1H), 2.23–2.14 (m, 1H), 2.14–2.01 (m, 1H), 1.72–1.61 (m, 1H), 1.59–1.46 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.7, 132.3 (d, $J_{C,P}$ = 93.2

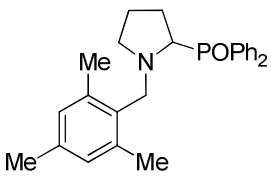
Hz), 132.2 (d, $J_{C,P}$ = 8.2 Hz), 131.8(2), 131.8(0), 131.7(8) (d, $J_{C,P}$ = 3.3 Hz), 131.7, 131.6 (d, $J_{C,P}$ = 19.0 Hz), 131.0 (d, $J_{C,P}$ = 94.2 Hz), 129.8 (d, $J_{C,P}$ = 34.0 Hz), 128.5 (d, $J_{C,P}$ = 11.0 Hz), 128.3 (d, $J_{C,P}$ = 11.0 Hz), 127.0, 122.2, 63.6 (d, $J_{C,P}$ = 94.5 Hz), 61.0 (d, $J_{C,P}$ = 3.0 Hz), 54.8 (d, $J_{C,P}$ = 8.9 Hz), 27.3, 24.6 (d, $J_{C,P}$ = 3.3 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.38; *m/z* (ESI–MS) 440.0 (^{79}Br) $[M]^+$, 441.9 (^{81}Br) $[M]^+$.

(1-(4-Bromobenzyl)pyrrolidin-2-yl)diphenylphosphine oxide (3.54e):



Following the general procedure with a reaction time of 15 min, compound **3.54e** was obtained from diphenyl phosphine oxide, *p*-bromobenzaldehyde and pyrrolidine as a pale white solid in 79% yield (> 25:1 mixture of regioisomers) (R_f = 0.21 in ether/MeOH 99:1 v/v); Characterization data of the major regioisomer: mp: 130–133 ºC; IR (KBr) 3050, 2965, 2908, 2808, 1685, 1487, 1437, 1180, 1120, 1011, 838, 798, 722 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03–7.93 (comp, 2H), 7.90–7.79 (comp, 2H), 7.56–7.38 (comp, 6H), 7.33 (d, *J* = 8.2 Hz, 2H), 6.97 (d, *J* = 8.3 Hz, 2H), 3.73 (d, *J* = 12.9 Hz, 1H), 3.59 (ddd, $J_{H,P}$ = 10.1 Hz, $J_{H,H}$ = 4.7, 3.5 Hz, 1H), 3.22 (d, *J* = 13.0 Hz, 1H), 2.84 (ddd, *J* = 9.6, 6.7, 3.2 Hz, 1H), 2.29–2.20 (m, 1H), 2.20–2.10 (m, 1H), 2.10–1.97 (m, 1H), 1.69–1.57 (m, 1H), 1.55–1.40 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 132.8 (d, $J_{C,P}$ = 93.2 Hz), 132.1. (d, $J_{C,P}$ = 7.8 Hz), 131.8–131.5 (m), 131.3–130.9 (m), 131.0 (d, $J_{C,P}$ = 94.3 Hz), 130.4–130.0 (m), 128.7–128.0 (m), 120.5, 63.5 (d, $J_{C,P}$ = 94.5 Hz), 60.8 (d, $J_{C,P}$ = 2.3 Hz), 54.6 (d, $J_{C,P}$ = 9.1 Hz), 27.3, 24.4 (d, $J_{C,P}$ = 3.3 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.27; *m/z* (ESI–MS) 439.9 (^{79}Br) $[M]^+$, 441.9 (^{81}Br) $[M]^+$.

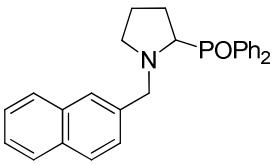
Diphenyl(1-(2,4,6-trimethylbenzyl)pyrrolidin-2-yl)phosphine oxide (3.54f):



Following the general procedure with a reaction time of 5 min, compound **3.54f** was obtained from diphenyl phosphine oxide, mesitaldehyde and pyrrolidine as a pale white solid in 84% yield (> 25:1

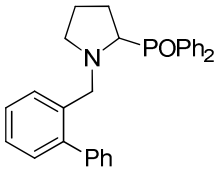
mixture of regioisomers) (R_f = 0.30 in ether); Characterization data of the major regioisomer: mp: 132–135 ºC; IR (KBr) 3055, 2959, 2918, 2866, 1684, 1612, 1484, 1437, 1186, 1118, 1028, 852, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.95–7.85 (comp, 2H), 7.84–7.75 (comp, 2H), 7.54–7.46 (comp, 2H), 7.46–7.38 (comp, 4H), 6.74 (s, 2H), 3.81 (d, *J* = 11.8 Hz, 1H), 3.68 (m, 1H), 3.52 (d, *J* = 12.0 Hz, 1H), 2.75–2.66 (m, 1H), 2.48–2.37 (m, 1H), 2.22 (s, 3H), 2.16 (s, 6H), 2.13–1.99 (comp, 2H), 1.74–1.63 (m, 1H), 1.63–1.50 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.7, 136.2, 133.1 (d, $J_{C,P}$ = 92.9 Hz), 132.2, 132.0–131.6 (m), 131.6–131.3 (m), 131.2(5), 128.9–128.6 (m), 128.5–128.0 (m), 64.0 (d, $J_{C,P}$ = 94.4 Hz), 54.7 (d, $J_{C,P}$ = 5.3 Hz), 53.4 (d, $J_{C,P}$ = 7.8 Hz), 27.0, 23.9 (d, $J_{C,P}$ = 3.4 Hz), 20.7 (d, $J_{C,P}$ = 2.0 Hz), 20.3 (d, $J_{C,P}$ = 1.7 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.74; *m/z* (ESI–MS) 404.3 $[M + H]^+$.

(1-(Naphthalen-2-ylmethyl)pyrrolidin-2-yl)diphenylphosphine oxide (3.54g):



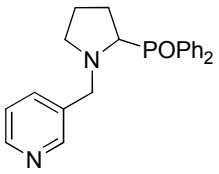
Following the general procedure with a reaction time of 15 min, compound **3.54g** was obtained from diphenyl phosphine oxide, 2-naphthaldehyde and pyrrolidine as a white solid in 81% yield (> 25:1 mixture of regioisomers) (R_f = 0.14 in ether); Characterization data of the major regioisomer: mp: 144–146 ºC; IR (KBr) 3051, 2940, 2905, 2800, 1592, 1568, 1435, 1208, 1142, 998, 723, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.13–8.03 (comp, 2H), 7.98–7.88 (comp, 2H), 7.83–7.74 (comp, 2H), 7.72 (d, *J* = 8.5 Hz, 1H), 7.58–7.52 (comp, 2H), 7.52–7.40 (comp, 7H), 7.28–7.22 (m, 1H), 3.93 (d, *J* = 12.7 Hz, 1H), 3.70 (ddd, $J_{H,P}$ = 10.1 Hz, $J_{H,H}$ = 4.7, 3.6 Hz, 1H), 3.43 (d, *J* = 12.8 Hz, 1H), 2.94–2.83 (m, 1H), 2.42–2.32 (m, 1H), 2.31–2.18 (m, 1H), 2.17–2.04 (m, 1H), 1.72–1.60 (m, 1H), 1.57–1.45 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.9, 133.2, 132.7 (d, $J_{C,P}$ = 93.1 Hz), 132.6, 132.4, 132.3, 131.8, 131.7(4), 131.7, 131.0 (d, $J_{C,P}$ = 93.9 Hz), 128.4 (d, $J_{C,P}$ = 11.0 Hz), 128. 2 (d, $J_{C,P}$ = 10.9 Hz), 127.7, 127.6, 127.5, 127.2–126.8 (m), 125.8, 125.5, 63.8 (d, $J_{C,P}$ = 95.1 Hz), 61.8 (d, $J_{C,P}$ = 3.2 Hz), 54.8 (d, $J_{C,P}$ = 8.8 Hz), 27.3, 24.5 (d, $J_{C,P}$ = 3.2 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.27; *m/z* (ESI–MS) 412.3 $[M + H]^+$.

(1-([1,1'-Biphenyl]-2-ylmethyl)pyrrolidin-2-yl)diphenylphosphine oxide (3.54h):



Following the general procedure with a reaction time of 5 min, compound **3.54h** was obtained from diphenyl phosphine oxide, 2-phenylbenzaldehyde and pyrrolidine as a sticky white solid in 78% yield (> 25:1 mixture of regioisomers) (R_f = 0.19 in ether); Characterization data of the major regioisomer: IR (KBr) 3056, 2969, 2872, 1690, 1478, 1437, 1266, 1179, 1118, 1072, 725, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.03–7.93 (comp, 2H), 7.89–7.79 (comp, 2H), 7.56–7.39 (comp, 7H), 7.38–7.28 (comp, 4H), 7.23 (app td, *J* = 7.5, 1.1 Hz, 1H), 7.13 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.10–7.05 (comp, 2H), 3.67 (d, *J* = 13.9 Hz, 1H), 3.52 (ddd, $J_{H,P}$ = 9.5 Hz, $J_{H,H}$ = 5.3, 4.0 Hz, 1H), 3.37 (d, *J* = 13.9 Hz, 1H), 2.95–2.86 (m, 1H), 2.14–1.94 (comp, 3H), 1.58–1.46 (comp, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.2 (d, $J_{C,P}$ = 2.2 Hz), 136.6, 133.0, 132.2–132.0 (m), 131.7–131.5 (m), 130.7, 129.7–129.4 (m), 129.4–129.0 (m), 129.0–128.8 (m), 128.6–128.0 (m), 128.0–127.7 (m), 127.4–127.0 (m), 127.0–126.6 (m), 126.4–126.0 (m), 63.9 (d, $J_{C,P}$ = 94.7 Hz), 58.3 (d, $J_{C,P}$ = 3.3 Hz), 54.5, 27.1, 24.4 (d, $J_{C,P}$ = 3.6 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.21; *m/z* (ESI–MS) 438.0 $[M + H]^+$.

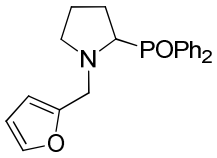
Diphenyl(1-(pyridin-3-ylmethyl)pyrrolidin-2-yl)phosphine oxide (3.54i):



Following the general procedure with a reaction time of 15 min, compound **3.54i** was obtained from diphenyl phosphine oxide, pyridine-3-aldehyde and pyrrolidine as a white solid in 81% yield (10:1 mixture of regioisomers) (R_f = 0.37 in ether/MeOH 93:7 v/v); Characterization data of the major regioisomer: mp: 112–116 ºC; IR (KBr) 3054, 2944, 2819, 1590, 1574, 1436, 1372, 1194, 1118, 1026, 832, 723, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, *J* = 3.9 Hz, 1H), 8.31 (s, 1H), 8.03–7.94 (comp, 2H), 7.90–7.80 (comp, 2H), 7.56–7.38 (comp, 7H), 7.15 (app dd, *J* = 7.8, 4.8 Hz, 1H), 3.80 (d, *J* = 13.0 Hz, 1H), 3.60 (ddd, $J_{H,P}$ = 10.3 Hz, $J_{H,H}$ = 4.8, 3.2 Hz, 1H), 3.28 (d, *J* = 13.1 Hz, 1H), 2.84

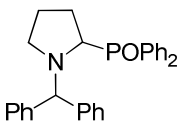
(ddd, J = 9.5, 6.7, 3.1 Hz, 1H), 2.31–2.23 (m, 1H), 2.23–2.12 (m, 1H), 2.12–1.98 (m, 1H), 1.71–1.59 (m, 1H), 1.54–1.42 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.8, 148.3, 136.2, 134.6, 132.6, 132.1 (d, $J_{C,P}$ = 8.2 Hz), 131.8(5) (d, $J_{C,P}$ = 2.6 Hz), 131.7(8) (d, $J_{C,P}$ = 2.3 Hz), 131.7 (d, $J_{C,P}$ = 8.3 Hz), 130.9 (d, $J_{C,P}$ = 94.2 Hz), 128.4 (d, $J_{C,P}$ = 11.1 Hz), 128.3 (d, $J_{C,P}$ = 11.0 Hz), 123.2, 63.6 (d, $J_{C,P}$ = 94.3 Hz), 58.8 (d, $J_{C,P}$ = 3.0 Hz), 54.7 (d, $J_{C,P}$ = 8.9 Hz), 27.3, 24.5 (d, $J_{C,P}$ = 3.3 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.39; *m/z* (ESI–MS) 363.0 $[M + H]^+$.

(1-(Furan-2-ylmethyl)pyrrolidin-2-yl)diphenylphosphine oxide (3.54j):



Following the general procedure with a reaction time of 1 h at 160 ˚C, compound **3.54j** was obtained from diphenyl phosphine oxide, 2-furfuraldehyde and pyrrolidine as a light brown liquid in 57% (> 25:1 mixture of regioisomers) (R_f = 0.2 in ether/MeOH 99:1 v/v); Characterization data of the major regioisomer: IR (KBr) 3055, 2965, 2872, 1590, 1437, 1181, 1118, 1099, 1072, 723, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10–8.02 (comp, 2H), 7.94–7.86 (comp, 2H), 7.54–7.41 (comp, 6H), 7.31 (s, 1H), 6.29–6.23 (m, 1H), 6.00 (d, J = 3.0 Hz, 1H), 3.74–3.65 (m, 1H), 3.53 (d, J = 14.7 Hz, 1H), 3.27 (d, J = 14.6 Hz, 1H), 3.00–2.92 (m, 1H), 2.64–2.54 (m, 1H), 2.12–1.96 (comp, 2H), 1.58–1.49 (m, 1H), 1.49–1.40 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.5, 141.8, 132.6 (d, $J_{C,P}$ = 92.7 Hz), 132.4 (d, $J_{C,P}$ = 8.6 Hz), 131.8–131.4 (m), 130.8 (d, $J_{C,P}$ = 93.7 Hz), 128.4 (d, $J_{C,P}$ = 11.0 Hz), 128.1 (d, $J_{C,P}$ = 10.9 Hz), 109.9, 108.3, 62.0 (d, $J_{C,P}$ = 95.2 Hz), 54.3 (d, $J_{C,P}$ = 8.4 Hz), 51.4 (d, $J_{C,P}$ = 3.3 Hz), 27.3, 24.7 (d, $J_{C,P}$ = 2.8 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.54; *m/z* (ESI–MS) 352.1 $[M + H]^+$.

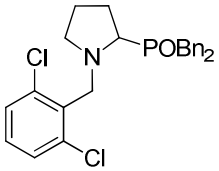
(1-Benzhydrylpyrrolidin-2-yl)diphenylphosphine oxide (3.54k):



Following the general procedure with a reaction time of 1 h, compound **3.54k** was obtained from diphenyl phosphine oxide, benzophenone and pyrrolidine as a pale white solid in 50% yield (> 25:1 mixture of regioisomers) (R_f = 0.20 in ether);

Characterization data of the major regioisomer: mp: 134–136 ºC; IR (KBr) 3057, 3026, 2970, 2871, 1598, 1491, 1437, 1185, 1118, 1028, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89–7.80 (comp, 2H), 7.76–7.67 (comp, 2H), 7.57–7.47 (comp, 2H), 7.47–7.38 (comp, 4H), 7.32–7.26 (comp, 2H), 7.25–7.18 (comp, 3H), 7.18–7.08 (comp, 3H), 7.01–6.99 (comp, 2H), 4.78 (s, 1H), 3.87 (ddd, $J_{H,P}$ = 8.5 Hz, $J_{H,H}$ = 5.0, 3.5 Hz, 1H), 3.22–3.12 (m, 1H), 2.85–2.75 (m, 1H), 2.12–1.98 (comp, 2H), 1.78–1.66 (m, 1H), 1.66–1.53 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.3, 140.9, 132.2 (d, $J_{C,P}$ = 90.8 Hz), 132.1 (d, $J_{C,P}$ = 95.1 Hz), 132.0 (d, $J_{C,P}$ = 8.5 Hz), 131.5(14) (d, $J_{C,P}$ = 8.2 Hz), 131.5(12) (d, $J_{C,P}$ = 2.7 Hz), 131.4(5) (d, $J_{C,P}$ = 2.7 Hz), 128.9, 128.4 (d, $J_{C,P}$ = 10.8 Hz), 128.3(6), 128.2, 128.1 (d, $J_{C,P}$ = 11.1 Hz), 127.9, 127.0, 126.5, 70.5 (d, $J_{C,P}$ = 7.2 Hz), 60.9 (d, $J_{C,P}$ = 92.8 Hz), 50.6 (d, $J_{C,P}$ = 4.2 Hz), 26.2 (d, $J_{C,P}$ = 1.9 Hz), 23.9 (d, $J_{C,P}$ = 2.2 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 32.79; *m/z* (ESI–MS) 438.3 $[M + H]^+$.

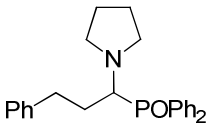
Dibenzyl(1-(2,6-dichlorobenzyl)pyrrolidin-2-yl)phosphine oxide (3.54l):



Following the general procedure with a reaction time of 15 min, compound **3.54l** was obtained from dibenzyl phosphine oxide, 2,6-dichlorobenzaldehyde and pyrrolidine as a sticky white solid in 89% yield (> 25:1 mixture of regioisomers) (R_f = 0.25 in ether); Characterization data of the major regioisomer: IR (KBr) 3061, 3029, 2966, 1581, 1561, 1454, 1435, 1196, 1122, 766, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (app s, 1H), 7.29–7.24 (comp, 8H), 7.24–7.16 (comp, 3H), 7.16–7.09 (m, 1H), 4.37 (d, *J* = 12.0 Hz, 1H), 3.85 (d, *J* = 12.1 Hz, 1H), 3.42–3.28 (m, 1H), 3.20–3.08 (m, 1H), 3.07–2.95 (comp, 2H), 2.92–2.77 (comp, 2H), 2.70–2.56 (m, 1H), 2.17–2.01 (m, 1H), 2.01–1.88 (m, 1H), 1.85–1.72 (m, 1H), 1.72–1.60 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.7, 134.4, 132.3 (d, $J_{C,P}$ = 6.7 Hz), 132.2 (d, $J_{C,P}$ = 7.1 Hz), 129.8–129.6 (m), 128.9, 128.4(7) (d, $J_{C,P}$ = 2.0 Hz), 128.4(2), 128.4 (d, $J_{C,P}$ = 1.8 Hz), 126.5–126.4 (m), 61.2 (d, $J_{C,P}$ = 86.3 Hz), 55.0 (d, $J_{C,P}$ = 5.1 Hz), 54.2 (d, $J_{C,P}$ = 8.4 Hz), 33.1 (d, $J_{C,P}$ = 57.6 Hz), 33.0 (d, $J_{C,P}$ = 59.7 Hz), 26.1, 24.0 (d, $J_{C,P}$ = 3.8 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 47.79; *m/z* (ESI–MS) 458.2 ($^{35}Cl/^{35}Cl$) $[M]^+$,

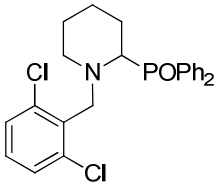
460.1 ($^{35}Cl/^{37}Cl$) $[M]^+$.

Diphenyl(3-phenyl-1-(pyrrolidin-1-yl)propyl)phosphine oxide (3.55m):



Following the general procedure with a reaction time of 15 min, compound **3.55m** was obtained from diphenyl phosphine oxide, cinnamaldehyde and pyrrolidine as a white solid in 51% yield (R_f = 0.31 in ether/hexanes 85:15 v/v); Characterization data of 3.55m: mp: 122–125 ºC; IR (KBr) 2950, 1628, 1496, 1437, 1180, 1116, 747, 720, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.83–7.73 (comp, 4H), 7.52–7.46 (m, 1H), 7.46–7.41 (comp, 3H), 7.41–7.35 (comp, 2H), 7.29–7.22 (comp, 2H), 7.22–7.15 (m, 1H), 7.06 (d, J = 7.4 Hz, 2H), 3.68 (ddd, $J_{H,P}$ = 10.1 Hz, $J_{H,H}$ = 6.2, 3.3 Hz, 1H), 2.90–2.80 (comp, 2H), 2.77–2.70 (comp, 2H), 2.70–2.65 (m, 1H), 2.62–2.52 (m, 1H), 2.30–2.18 (m, 1H), 2.11–1.99 (m, 1H), 1.69–1.56 (comp, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.2, 133.6 (d, $J_{C,P}$ = 93.0 Hz), 133.2 (d, $J_{C,P}$ = 85.7 Hz), 131.6–130.8 (m), 128.8–127.7 (m), 126.1–125.7 (m), 58.6 (d, $J_{C,P}$ = 81.4 Hz), 49.6 (d, $J_{C,P}$ = 4.1 Hz), 33.9 (d, $J_{C,P}$ = 12.3 Hz), 27.3 (d, $J_{C,P}$ = 6.7 Hz), 24.3; ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.53; *m/z* (ESI–MS) 390.1 $[M + H]^+$.

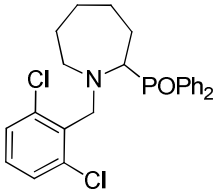
(1-(2,6-Dichlorobenzyl)piperidin-2-yl)diphenylphosphine oxide (3.54n):



Following the general procedure with a reaction time of 30 min at 180 ˚C, compound **3.54n** was obtained from diphenyl phosphine oxide, 2,6-dichlorobenzaldehyde and piperidine as a white solid in 38% yield (1:1 mixture of regioisomers) (R_f = 0.26 in ether/hexanes 70:30 v/v); Characterization data of **3.54n**: mp: 146–148 ºC; IR (KBr) 2933, 1581, 1561, 1436, 1363, 1260, 1195, 1115, 1091, 719, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.75–7.66 (comp, 2H), 7.49–7.36 (comp, 5H), 7.33–7.27 (m, 1H), 7.20–7.11 (comp, 4H), 7.10–7.04 (m, 1H), 4.41 (d, J = 13.1 Hz, 1H), 3. 79 (app td, $J_{H,P}$ = 12.9 Hz, $J_{H,H}$ = 2.6 Hz, 1H), 3.60 (app dd, J = 13.1, 2.4 Hz, 1H), 3.58–3.54 (m, 1H), 2.89–2.82 (m, 1H), 2.25–2.19 (m, 1H), 2.19–2.09 (m, 1H), 1.80–1.70 (m, 1H), 1.70–1.60 (comp, 2H), 1.49–

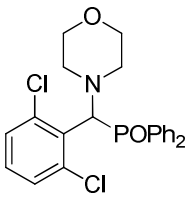
1.41 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.8, 135.0, 133.3 (d, $J_{C,P}$ = 87.9 Hz), 133.1 (d, $J_{C,P}$ = 97.0 Hz), 131.4–131.1 (m), 131.0–130.2 (m), 128. 9–128.0 (m), 128.0–127.6 (m), 55.6 (d, $J_{C,P}$ = 83.7 Hz), 53.2 (d, $J_{C,P}$ = 12.5 Hz), 51.1 (d, $J_{C,P}$ = 6.3 Hz), 21.8, 21.1, 20.0; ^{31}P NMR (162 MHz, $CDCl_3$) δ 34.27; *m/z* (ESI–MS) 443.8 (^{35}Cl/^{35}Cl) $[M]^+$, 445.9 (^{35}Cl/^{37}Cl) $[M]^+$.

(1-(2,6-Dichlorobenzyl)azepan-2-yl)diphenylphosphine oxide (3.54o):



Following the general procedure, compound **3.54o** was obtained from diphenyl phosphine oxide, 2,6-dichlorobenzaldehyde and azepane as a colorless liquid in 77% yield after 15 min (1:3 mixture of regioisomers) (R_f = 0.34 in ether); Characterization data of **3.54o**: IR (KBr) 3053, 2930, 2856, 1647, 1561, 1436, 1172, 1116, 779, 719, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77–7.68 (comp, 2H), 7.56–7.46 (comp, 2H), 7.46–7.37 (comp, 3H), 7.33–7.26 (m, 1H), 7.21–7.12 (comp, 2H), 7.08–7.02 (comp, 2H), 6.99–6.92 (m, 1H), 4.30 (d, *J* = 13.3 Hz, 1H), 3.94 (ddd, $J_{H,P}$ = 10.8 Hz, $J_{H,H}$ = 7.0, 4.3 Hz, 1H), 3.65 (app dd, *J* = 13.4, 1.8 Hz, 1H), 3.56–3.45 (m, 1H), 3.26–3.16 (m, 1H), 2.18–2.09 (m, 1H), 2.08–1.96 (m, 1H), 1.96–1.86 (m, 1H), 1.86–1.76 (m, 1H), 1.76–1.64 (m, 1H), 1.56–1.45 (comp, 2H), 1.43–1.30 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.4, 135.0, 133.5 (d, $J_{C,P}$ = 83.2 Hz), 132.4 (d, $J_{C,P}$ = 95.3 Hz), 131.4–130.9 (m), 130.9–130.7 (m), 130.7–130.4 (m), 128.8–128.2 (m), 128.1–127.7 (m), 58.9 (d, $J_{C,P}$ = 84.6 Hz), 53.8 (d, $J_{C,P}$ = 8.7 Hz), 51.1, 29.8, 27.2 (d, $J_{C,P}$ = 3.3 Hz), 25.5, 25.4; ^{31}P NMR (162 MHz, $CDCl_3$) δ 33.18; *m/z* (ESI–MS) 457.9 (^{35}Cl/^{35}Cl) $[M]^+$, 459.9 (^{35}Cl/^{37}Cl) $[M]^+$.

((2,6-Dichlorophenyl)(morpholino)methyl)diphenylphosphine oxide (3.55p):



Following the general procedure with a reaction time of 15 min, compound **3.55p** was obtained from diphenyl phosphine oxide, 2,6-dichlorobenzaldehyde and morpholine as a light brown liquid in 78% yield (R_f = 0.36 in ether/MeOH 99:1 v/v); Characterization data of **3.55p**: IR (KBr) 3058, 2959, 2855, 1578,

1560, 1436, 1200, 1116, 782, 730, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11–8.01 (comp, 2H), 7.62–7.54 (comp, 2H), 7.54–7.47 (comp, 3H), 7.25–7.20 (m, 1H), 7.19–7.13 (comp, 2H), 7.13–7.07 (comp, 2H), 6.99–6.91 (m, 1H), 5.43 (d, $J_{H,P}$ = 9.9 Hz, 1H), 3.67–3.56 (comp, 4H), 2.82–2.71 (comp, 2H), 2.67–2.56 (comp, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.0 (d, $J_{C,P}$ = 11.4 Hz), 136.9(7), 134.7 (d, $J_{C,P}$ = 98.1 Hz), 132.1, 131.4, 131.2–130.9 (m), 130.7 (d, $J_{C,P}$ = 9.7 Hz), 130.6 (d, $J_{C,P}$ = 9.1 Hz), 130.4–130.0 (m), 129.5–129.1 (m), 128.8–128.2 (m), 128.1–127.3 (m), 67.2 (d, $J_{C,P}$ = 80.4 Hz), 67.0, 52.8 (d, $J_{C,P}$ = 6.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.04; *m/z* (ESI–MS) 446.2 ($^{35}Cl/^{35}Cl$) $[M]^+$, 448.1 ($^{35}Cl/^{37}Cl$) $[M]^+$.

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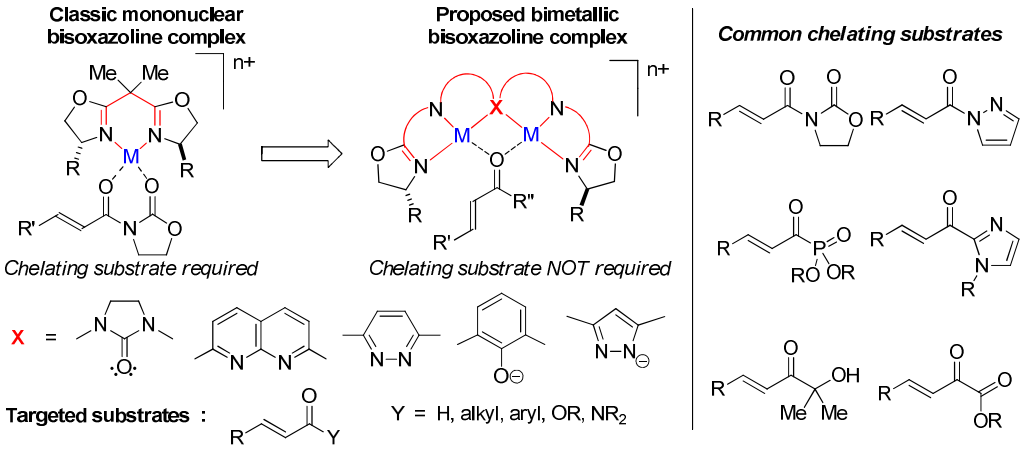
Chapter IV

Bimetallic Complexes of Chiral Bisoxazoline Ligands

4.1 Background

Chiral bisoxazoline ligands play an important role in many different Lewis acid-catalyzed asymmetric transformations.[1] Most of these currently used form mononuclear metal complexes. These ligands bind to Lewis acids via bidentate or tridentate chelation, leading to formation of chiral Lewis acid complexes. Substrates are subsequently activated by coordination to the metal center, thereby inducing enantioselectivity in the reaction. Although these chiral mononuclear Lewis acid complexes are widely used in asymmetric reactions, they require tailored substrates that can chelate to the metal center. This often leads to extra steps in the synthetic sequence, thereby lowering the synthetic efficiency. Our aim was to develop bimetallic complexes of chiral bisoxazoline ligands that can overcome the limitations of these monometallic bisoxazoline complexes (Figure 4.1). It is well known that the activation of a single functional group by simultaneous chelation to two metal centers in close proximity offer marked advantages over interaction with a single metal center.[2] This mode of bimetallic binding is expected to not only render a greater degree of activation but also result in a more well-defined transition state.

Figure 4.1 **Proposed Bimetallic Complexes**



Nature utilizes a variety of bimetallic and multimetallic protein complexes to perform a host of outstanding functions.[3] Urease,[4] hemerythrin,[5] methane monooxygenase,[6] ribonucleotide reductase,[7] catechol oxidase[8] and arginase[9] are some prototypical bimetallic enzymes found in nature (Figure 4.2). Although few of these are known to retain their functionality in nonprotein systems, they continue to inspire synthetic chemists. The use of binuclear metallohydrolases for the hydrolysis of biomolecules has been an area of interest in recent years. Lippard and coworkers synthesized a series of binuclear nickel complexes coordinated with water, hydroxide and ligand **4.1** (Figure 4.3) as models for urease.[10] Brooker and coworkers reported bimetallic complexes of the bis(pyridine)-armed acyclic Schiff base ligand **4.2** with copper, cobalt and nickel.[11] There have been reports of binuclear complexes with phenoxy bridged Schiff base ligands such as **4.3**.[12]

Figure 4.2 **Examples of Bimetallic Sites in Proteins**

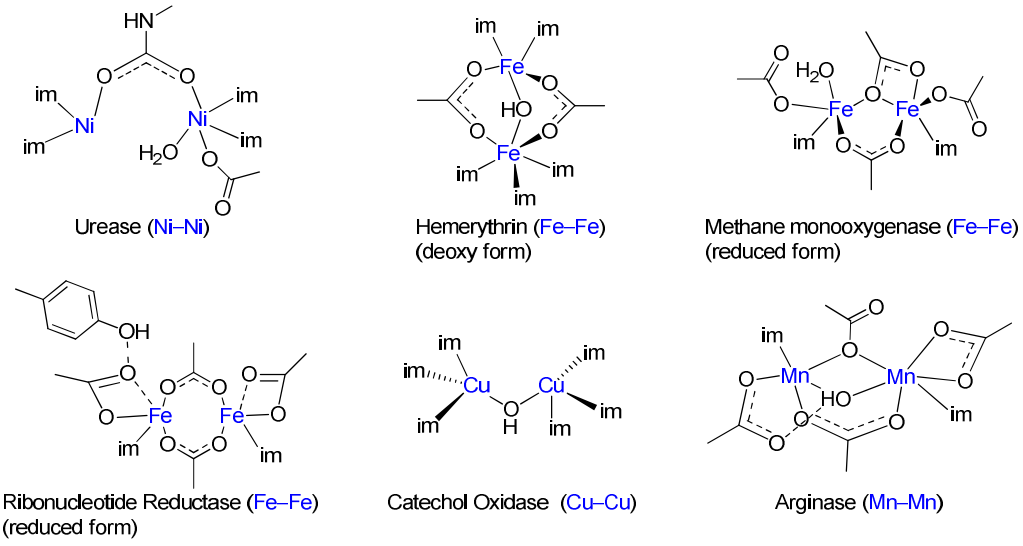
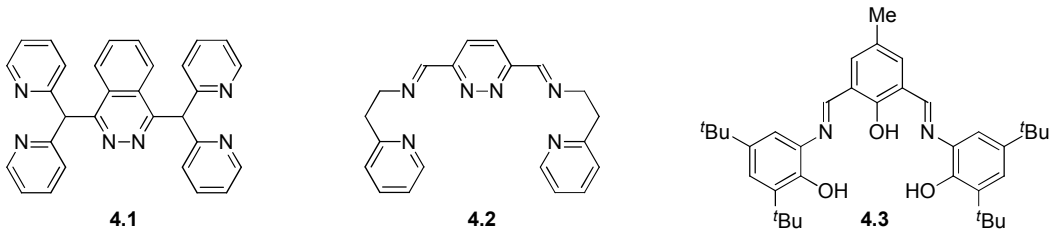


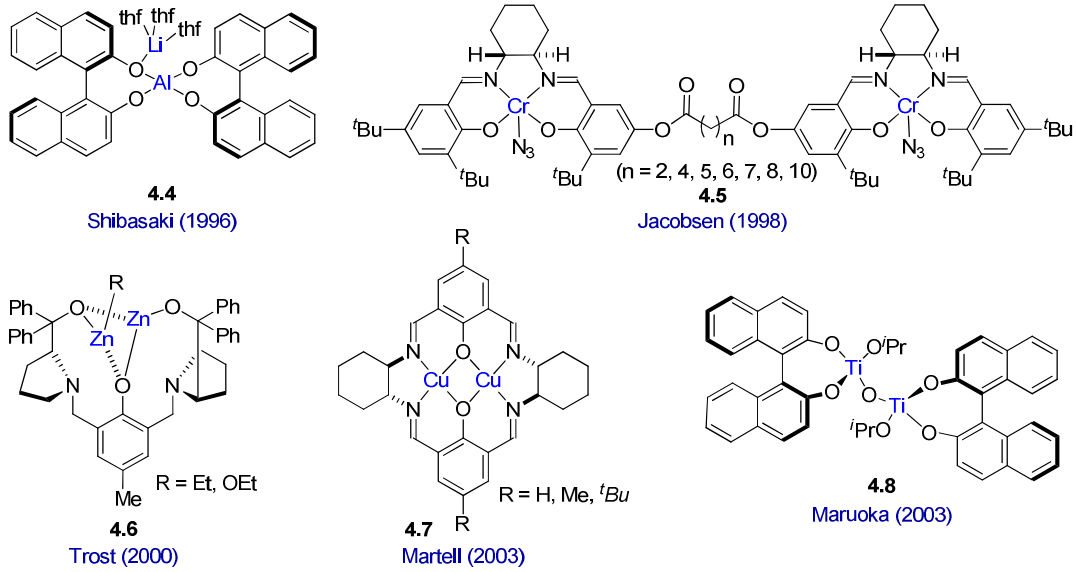
Figure 4.3 **Examples of Achiral Binuclear Ligands**



4.1 Lippard **4.2** Brooker **4.3** Chaudhuri

There are many reports where bi- or multi-metallic complexes have been successfully used in asymmetric catalysis.[2c] Shibasaki introduced a new type of multifunctional heterobimetallic asymmetric catalyst (for example, **4.4**) in which the two different metals play distinct functions (Figure 4.4).[13,14] Jacobsen and coworkers have shown the cooperative reactivity between the two metal centers in the dimeric complexes **4.5** for the asymmetric ring opening of meso epoxides.[15] Trost *et al.* disclosed the synthesis of the dinuclear zinc complex **4.6** and its utility in the enantioselective Aldol reaction[16] and since then it has been shown to promote a number of asymmetric transformations.[17] Other notable contributions in this area have been provided by the groups of Martell,[18] Maruoka,[19] Wuest,[20] and several others.[21] In the majority of the cases where bimetallic complexes are used as the catalytically active species, the two metal centers perform distinct functions.[22] Instead of doubly activating a single reaction partner, one metal center serves to activate the electrophilic reaction partner and the second metal center activates the nucleophilic partner.

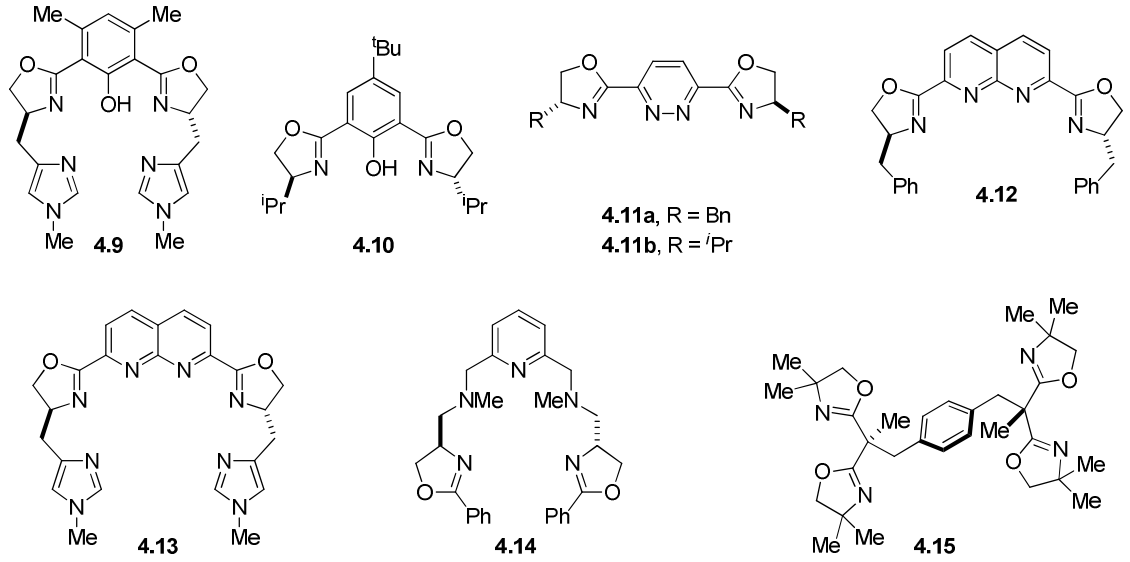
Figure 4.4 **Representative Examples of Bimetallic Complexes**



4.1.1 Chiral Bisoxazoline Containing Ligands

Chiral bisoxazoline containing compounds are widely used as ligands in asymmetric catalysis. Typically, a 1:1 complex with Lewis acid is employed as the catalytically active species. Although there are numerous accounts of using bisoxazoline compounds as mononuclear ligands, advances towards synthesizing analogous bisoxazolines capable of concurrently binding to two metal centers have been limited. Previous work by Pfaltz, Fahrni, Tsukada, Bellemin-Laponnaz and coworkers demonstrated the synthesis of bisoxazoline-based ligands **4.9**–**4.15** that can bind to two metals (Figure 4.5).

Figure 4.5 **Bisoxazoline Ligands Known for Stabilizing Bimetallic Complexes**



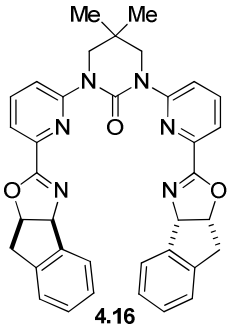
Treatment of **4.9** with two equivalents of copper perchlorate hexahydrate led to the formation of a bis-copper complex.[23] The two Cu(II) ions are coordinated to the pentadentate bisoxazoline-imidazole moiety and bridged by a phenoxy and a hydroxyl group with a Cu···Cu distance of 2.947 Å. Ligand **4.10** formed a complicated binuclear complex with $ZnCl_2$ and $NiCl_2$ involving two metal centers and three ligand units.[23] The 2:3 $ZnCl_2$/ligand complex crystal structure showed the Zn···Zn distance to be 3.056 Å. Compound **4.11a**[23] formed 2:2 complexes with $ZnCl_2$ and $NiCl_2$, whereas **4.11b**[24] was reported to form a bis-palladium complex with one equivalent of $[(\eta^3\text{-}C_3H_3)PdCl]_2$. No details are known about the complexing ability of compounds **4.12** and **4.14**[25]. The naphthyridine-based ligand **4.13** formed a dinuclear complex with nickel(II) acetate (Ni···Ni distance = 3.132 Å).[23] Treatment of the polyoxazoline ligand **4.15** with two equivalents of $ZnCl_2$, $Ni(PPh_3)_2Br_2$ or $Cu(OAc)_2$ resulted in the respective dinuclear complexes (bond distance: Zn···Zn = 8.963 Å; Ni···Ni = 11.341 Å; Cu···Cu = 9.432 Å).[26]

4.2 Novel Chiral Bisoxazoline Ligands with Different Bridging Units

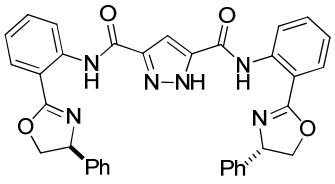
Our design of the ligands was based on the idea that having sp^2 hybridized atoms in the ligand backbone will give rise to a more rigid framework. Having three binding sites per metal center was considered ideal as it likely prevents the potential formation of 2:2 complexes. By changing the spacers, the distance between the metal centers can be altered. Furthermore, the ligand design provides different combinations of five- and six-membered chelate rings, an important aspect influencing metal–metal distances. We have designed and performed convenient synthetic sequences to access a variety of bisoxazoline ligands with different bridging moieties.

Recently our group successfully synthesized chiral bisoxazoline ligands having urea and pyrazole backbone (Figure 4.6). The compound **4.16** with a urea backbone readily forms a bis-copper complex with two equivalents of copper chloride (Cu···Cu distance = 4.291 Å).[27] The pyrazole bridged ligand **4.17** was shown to form a bis-nickel complex with two equivalents of nickel(II) acetate, with a Ni···Ni distance of 4.176 Å.[28]

Figure 4.6 **Previously Synthesized Chiral Bisoxazoline Ligands in the Group**



4.16



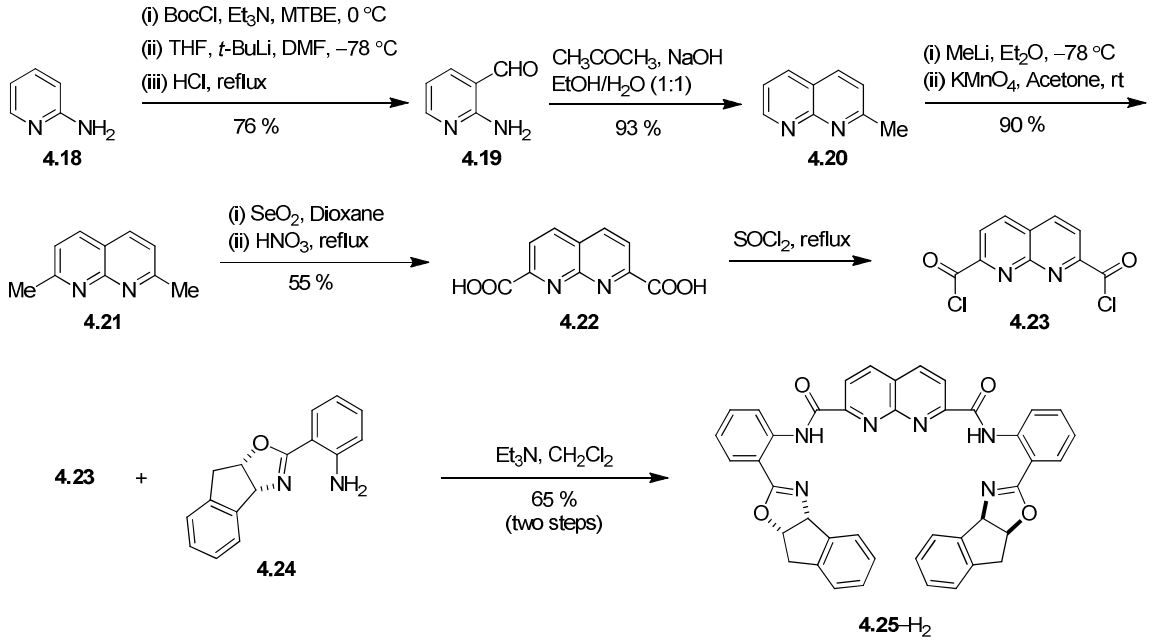
4.17

4.2.1 Naphthyridine Bridged Bisoxazoline Ligands

The synthesis of naphthyridine bridged bisoxazoline ligand **4.25**-H_2 is outlined in Scheme 4.1. Commercially available 2-aminopyridine (**4.18**) was converted to the corresponding 3-

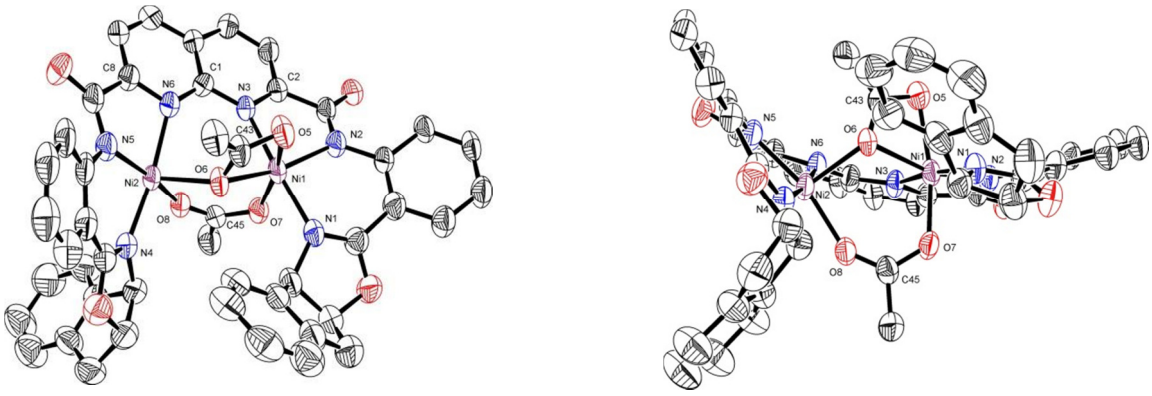
formylated compound **4.19** by following a three-step synthetic sequence.[29] Friedländer condensation of **4.19** with acetone gave compound **4.20**. Nucleophilic addition of methyllithium, followed by potassium permanganate oxidation led to the formation of 2,7-dimethyl-1,8-naphthyridine (**4.21**).[30] Benzylic oxidation of **4.21** using selenium dioxide gave the dialdehyde, which was further oxidized to the dicarboxylic acid **4.22** by refluxing in concentrated nitric acid. The diacyl chloride **4.23** was obtained upon treatment of **4.22** with thionyl chloride. The crude **4.23** was then readily converted to the bisoxazoline ligand **4.25**-H_2 by allowing it to react with two equivalents of the aminoindanol-derived amine **4.24**.

Scheme 4.1 **Synthesis of Naphthyridine–Bisoxazoline Ligand 4.25-H_2**



Upon deprotonation, **4.25**-H_2 provides a dianionic ligand with three donor nitrogen atoms per metal center, including a 1,8-naphthyridine bridge between the two metal centers. The compound **4.25**-H_2 readily forms complexes with various copper, zinc, palladium and nickel salts. Figure 4.7 shows the X-ray crystal structure of **4.25**·2Ni(OAc), obtained from ligand **4.25**-H_2 and two equivalents of nickel(II) acetate.

Figure 4.7 **ORTEP views (50% probability thermal ellipsoids) of the Molecular Structure of 4.25·2Ni(OAc)**



Hydrogen atoms have been omitted for clarity. The complex **4.25**·2Ni(OAc) crystallizes in the orthorhombic space group $P2_12_12_1$ with a = 14.1863(8) Å, b = 14.8670(8) Å, c = 25.2393(14) Å, α = 90º, β = 90º, γ = 90º, V = 5323.2(5) Å^3, Z = 4, D_c = 1.444 mg m^{-3} and μ(Mo-Kα) = 0.967 mm^{-1}.

The asymmetric unit of the crystal **4.25**·2Ni(OAc) contains two nickel(II) centers held in close proximity by three donor nitrogen atoms per metal center and two differently bridged acetate ions inside the coordination sphere. The nitrogens on the naphthyridine and amide moieties bind to the nickel(II) center to form a five-membered metallacycle, subtending N(2)–Ni(1)–N(3) and N(5)–Ni(2)–N(6) angles of 81.2 and 80.5º, respectively. Additionally, the nitrogens on the oxazoline and amide moieties form six-membered rings with the nickel(II) center with N(1)–Ni(1)–N(2) and N(4)–Ni(2)–N(5) angles of 93.3 and 90.2º, respectively. All of the Ni–N distances are between 2.005 and 2.141 Å, typical for complexes of this type. Interestingly, while one of the two acetate ions bridge the two nickel(II) centers by binding through the two oxygens, the second acetate unit has a somewhat different binding pattern: one oxygen binds to Ni(1) and the other oxygen acts as the bridge between Ni(1) and Ni(2). The Ni(1)···Ni(2) distance is 3.448 Å, which is slightly longer than the corresponding Ni···Ni distance in the structurally related ligand **4.13**. The sixth coordination of Ni(2) is fulfilled by the amide oxygen of a second molecule of the complex **4.25**·2Ni(OAc) (not shown in the figure for clarity). When this

interaction is taken into account, both the nickel(II) centers are in distorted octahedral environment. Overall, the ligand backbone of complex **4.25**·2Ni(OAc) shows a helical arrangement. This helicity is facilitated by the innate stereogenic centers of the oxazoline moieties and the flexibility afforded by the amide connections.

Table 4.1 **Selected Bond Lengths (Å) and Bond Angles (º) of the Complex 4.25·2Ni(OAc)**

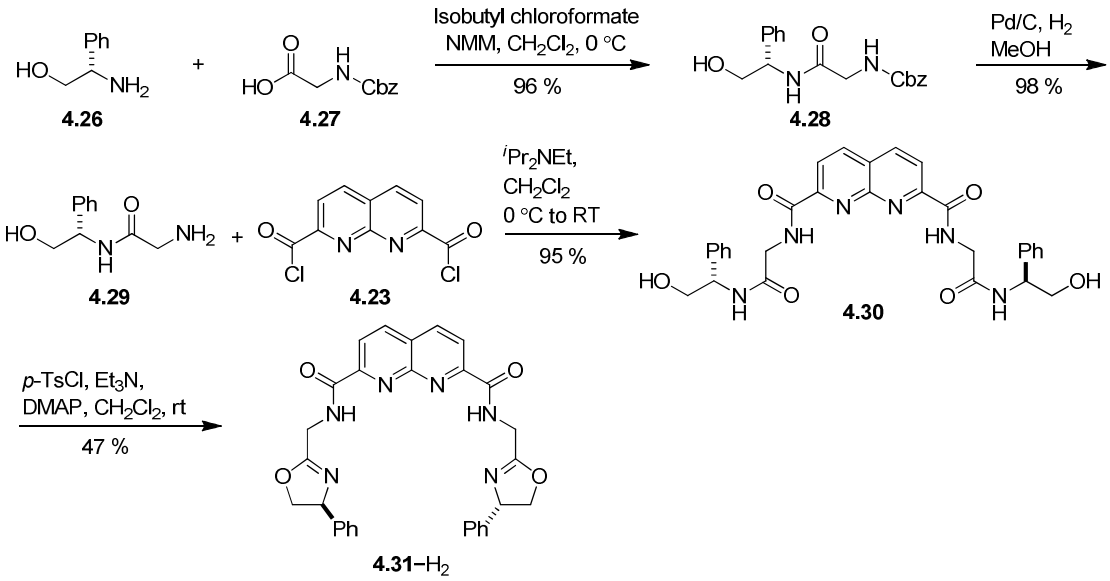
Ni(1)–N(1)	2.072(6)	Ni(2)–O(8)	2.057(5)
Ni(1)–N(2)	2.023(5)	N(3)–C(1)	1.349(8)
Ni(1)–N(3)	2.141(6)	N(3)–C(2)	1.333(8)
Ni(1)–O(5)	2.128(5)	N(6)–C(1)	1.363(9)
Ni(1)–O(6)	2.125(4)	N(6)–C(8)	1.337(8)
Ni(1)–O(7)	2.036(5)	O(5)–C(43)	1.296(9)
Ni(2)–N(4)	2.034(6)	O(6)–C(43)	1.259(1)
Ni(2)–N(5)	2.005(6)	O(7)–C(45)	1.265(8)
Ni(2)–N(6)	2.075(6)	O(8)–C(45)	1.174(9)
Ni(2)–O(6)	2.098(5)	Ni(1)···Ni(2)	3.448
N(1)–Ni(1)–N(2)	93.3(2)	N(4)–Ni(2)–N(5)	90.2(2)
N(2)–Ni(1)–N(3)	81.2(2)	N(5)–Ni(2)–N(6)	80.5(2)
N(3)–Ni(1)–O(6)	95.88(19)	N(6)–Ni(2)–O(6)	86.0(2)
O(6)–Ni(1)–O(7)	104.17(19)	O(6)–Ni(2)–O(8)	94.13(19)
N(1)–Ni(1)–O(5)	95.5(2)	N(4)–Ni(2)–O(6)	95.3(2)
N(1)–Ni(1)–O(6)	91.0(2)	N(4)–Ni(2)–O(8)	90.2(2)
N(1)–Ni(1)–O(7)	83.8(2)	N(5)–Ni(2)–O(6)	100.0(2)
N(2)–Ni(1)–O(5)	99.6(2)	Ni(1)–O(5)–C(43)	89.3(5)
N(2)–Ni(1)–O(7)	94.1(2)	Ni(1)–O(6)–C(43)	90.4(4)

N(3)–Ni(1)–O(5)	90.6(2)	Ni(2)–O(6)–C(43)	129.6(5)
N(3)–Ni(1)–O(7)	91.3(2)	O(5)–C(43)–O(6)	118.1(7)
O(5)–Ni(1)–O(6)	62.05(19)	N(3)–C(1)–N(6)	117.0(6)
Ni(1)–O(6)–Ni(2)	109.5(2)	O(7)–C(45)–O(8)	129.8(8)

From the crystal structure of **4.25**·2Ni(OAc) it is evident that the five- and six-membered chelate rings formed by coordination of the nitrogen donor atoms in the ligand backbone with the nickel centers makes the open-ended side of the ligand somewhat congested. Therefore coordination of the carbonyl functional group of the substrate is presumably hindered, thereby likely lowering any potential catalytic activity. To mitigate this hindrance, we designed the naphthyridine-bridged ligand **4.31**-H_2, which on complexation with two metal centers will form all five-membered chelate rings and potentially open up space for substrate binding.

The sequence of synthetic steps leading to the naphthyridine bridged bisoxazoline ligand **4.31**-H_2 is outlined in Scheme 4.2. By using isobutyl chloroformate as the activating agent, *N*-carboxybenzyl glycine (**4.27**) was coupled with glycinol **4.26** to obtain the amide **4.28**. Under standard carboxybenzyl deprotection conditions, compound **4.28** provided the amido-amine **4.29**. Subsequently, two equivalents of **4.29** were allowed to react with one equivalent of the naphthyridine diacyl chloride **4.23**, leading to the formation of intermediate **4.30**. On treatment of **4.30** with *p*-toluenesulfonyl chloride and triethylamine, in presence of catalytic amount of DMAP, the ligand **4.31**-H_2 was obtained.

Scheme 4.2 **Synthesis of Naphthyridine–Bisoxazoline Ligand 4.30-H_2**

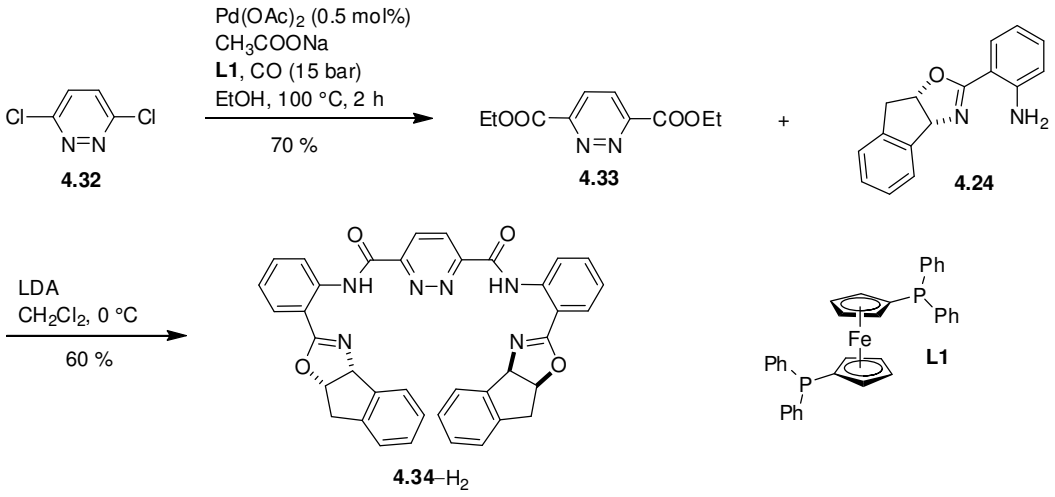


Preliminary experiments have shown that the ligand **4.31**-H_2 readily forms complexes with various nickel and palladium salts. Efforts are ongoing to obtain sufficient quality crystals for molecular structure determinations.

4.2.2 Pyridazine Bridged Bisoxazoline Ligands

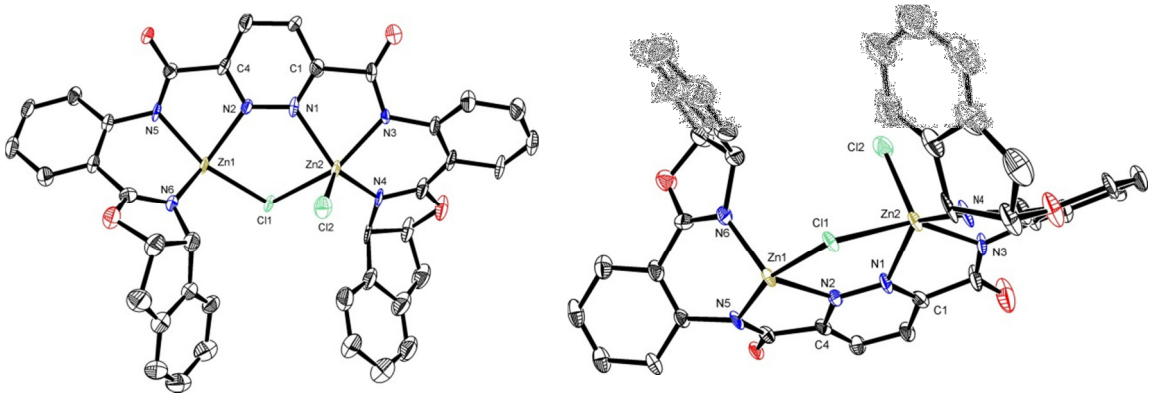
The synthesis of **4.34**-H_2 involved the key intermediate **4.33**,[31] prepared from 3,6-dichloropyridazine (**4.32**) (Scheme 4.3). The amine **4.24** was then treated with LDA, followed by addition of **4.33** to form the pyridazine bridged bisoxazoline ligand **4.34**-H_2.

Scheme 4.3 **Synthesis of Pyridazine–Bisoxazoline Ligand 4.33-H_2**



Upon deprotonation, **4.34**-H_2 provides a dianionic ligand with three donor nitrogen atoms per metal center. The compound **4.34**-H_2 readily forms complexes with different nickel, copper, zinc and palladium salts. Shown in figure 4.8 is the molecular structure of **4.34**·2ZnCl, obtained by treating one equivalent of the ligand **4.34**-H_2 with two equivalents of zinc(II) chloride.

Figure 4.8 **ORTEP views (50% probability thermal ellipsoids) of the Molecular Structure of 4.34·2ZnCl**



Hydrogen atoms have been omitted for clarity. The complex **4.34**·2ZnCl crystallizes in the monoclinic space group C_2 with a = 40.793(8) Å, b = 7.3931(14) Å, c = 14.636(3) Å, α = 90º, β = 108.593(3)º, γ = 90º, V = 4183.5(14) Å^3, Z = 4, D_c = 1.549 mg m^{-3} and μ(Mo-Kα) = 1.397 mm^{-1}.

Each unit of the complex **4.34**·2ZnCl consists of two zinc(II) centers, with each bound by three donor nitrogens from the ligand skeleton and bridged by a chloride ion. The nitrogens on the pyridazine and amide moieties form five-membered chelate rings upon coordination to the zinc centers, subtending N(5)–Zn(1)–N(2) and N(3)–Zn(2)–N(1) angles of 74.83 and 76.71º, respectively. The coordination of the nitrogens on oxazoline and amide moieties with the two zinc centers forms six-membered rings with N(6)–Zn(1)–N(5) and N(4)–Zn(2)–N(3) angles of 86.97 and 88.38º, respectively. All of the Zn–N distances are within 2.025–2.174 Å, as expected for such complexes. Interestingly, the two chloride ions bind in discrete manners. While one of them acts as a bridge between the two zinc centers with a Zn(1)–Cl(1)–Zn(2) angle of 106.11º, the other chloride ion binds to Zn(2) only with a Zn(2)–Cl(2) distance of 2.233 Å. As a consequence, the Zn(1)···Zn(2) distance is 3.857 Å. Different coordination environments are found for Zn(1) and Zn(2). Zn(1) is found to exist in a square planar environment that experiences a significant tetrahedral distortion. In contrast, a distorted square pyramidal binding mode is observed for Zn(2).

Table 4.2 **Selected Bond Lengths (Å) and Bond Angles (º) of the Complex 4.34·2ZnCl**

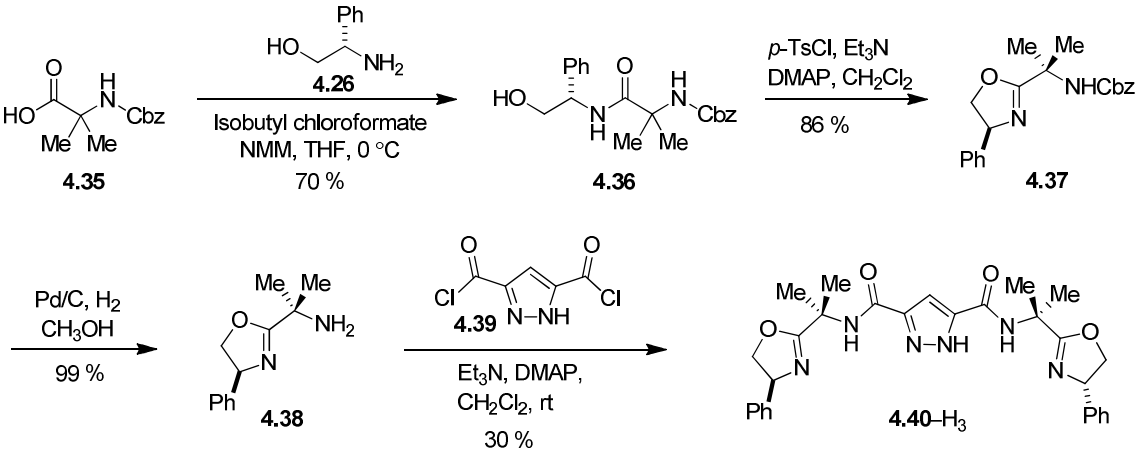
Zn(1)–N(2)	2.174(2)	Zn(2)–N(4)	2.025(2)
Zn(1)–N(5)	2.100(2)	Zn(2)–Cl(1)	2.528(8)
Zn(1)–N(6)	2.029(3)	Zn(2)–Cl(2)	2.233(2)
Zn(1)–Cl(1)	2.293(5)	N(1)–N(2)	1.352(3)
Zn(2)–N(1)	2.148(2)	N(1)–C(1)	1.311(4)
Zn(2)–N(3)	2.077(2)	Zn(1)···Zn(2)	3.857
N(4)–Zn(2)–N(3)	88.38(10)	Zn(1)–Cl(1)–Zn(2)	106.11(3)
N(3)–Zn(2)–N(1)	76.71(9)	N(6)–Zn(1)–N(5)	86.97(10)
N(1)–Zn(2)–Cl(1)	85.55(6)	N(5)–Zn(1)–N(2)	74.83(8)
N(4)–Zn(2)–Cl(1)	90.18(7)	N(6)–Zn(1)–N(2)	115.80(10)

N(4)–Zn(2)–Cl(2)	117.98(8)	N(2)–Zn(1)–Cl(1)	89.41(6)
N(3)–Zn(2)–Cl(2)	108.60(8)	N(6)–Zn(1)–Cl(1)	106.01(7)
N(1)–Zn(2)–Cl(2)	105.29(7)	Zn(1)–N(2)–N(1)	125.92(18)
Cl(1)–Zn(2)–Cl(2)	96.53(3)	Zn(2)–N(1)–N(2)	124.11(19)

4.2.3 Pyrazole Bridged Bisoxazoline Ligands

The synthesis of ligand **4.40**-H_3 started from the *N*-carboxybenzyl amino acid **4.35** (Scheme 4.4). Isobutyl chloroformate mediated coupling of **4.35** with (*S*)-phenyl glycinol **4.26** resulted in the formation of the amide **4.36**. Subsequent treatment with *p*-toluenesulfonyl chloride and triethylamine in presence of catalytic amount of DMAP gave the bisoxazoline **4.37**. After removal of the carboxybenzyl group, the amine **4.38** was allowed to react with half an equivalent of the pyrazole diacyl chloride **4.39** to yield the pyrazole bridged bisoxazoline ligand **4.40**-H_3.

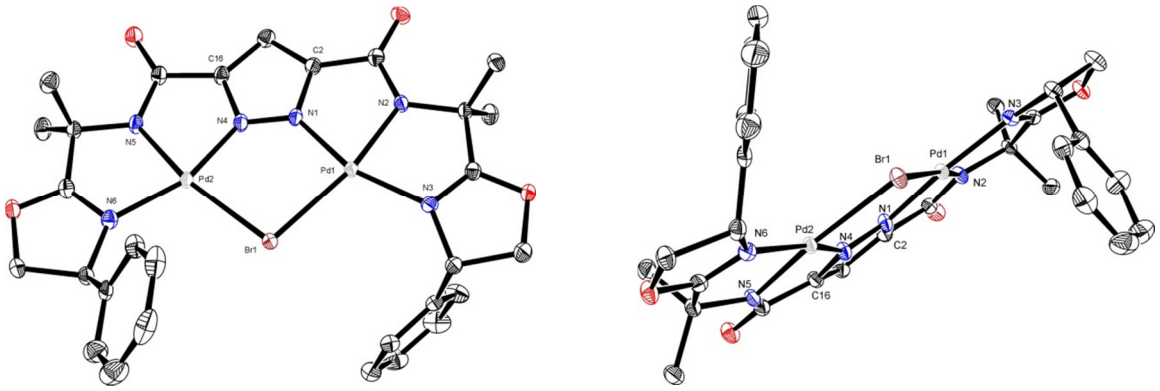
Scheme 4.4 **Synthesis of Pyrazole–Bisoxazoline Ligand 4.40-H_3**



Initial experiments have shown that the trianionic ligand **4.40**-H_3 readily forms complexes with various nickel, copper and palladium salts. Figure 4.9 shows the X-ray crystal

structure of **4.40**·Pd_2Br, obtained from ligand **4.40**-H_2 and two equivalents of palladium(II) bromide.

Figure 4.9 **ORTEP views (50% probability thermal ellipsoids) of the Molecular Structure of 4.40·Pd_2Br**



Hydrogen atoms have been omitted for clarity. The complex **4.34**·2ZnCl crystallizes in the monoclinic space group $P2_1$ with a = 9.8982(7) Å, b = 10.0139(7) Å, c = 16.9675(12) Å, α = 90º, β = 101.277(1)º, γ = 90º, V = 1649.3(2) $Å^3$, Z = 2, D_c = 1.847 mg m^{-3} and μ(Mo-Kα) = 2.510 mm^{-1}.

Table 4.3 **Selected Bond Lengths (Å) and Bond Angles (º) of the Complex 4.40·Pd_2Br**

Pd(1)–N(1)	1.925(3)	Pd(2)–N(6)	2.025(4)
Pd(1)–N(2)	1.970(0)	Pd(2)–Br(1)	2.529(5)
Pd(1)–N(3)	2.018(1)	N(1)–C(2)	1.345(3)
Pd(1)–Br(1)	2.519(2)	N(4)–C(16)	1.348(3)
Pd(2)–N(4)	1.928(1)	N(1)–N(4)	1.312(2)
Pd(2)–N(5)	1.971(8)	Pd(1)···Pd(2)	3.824
N(3)–Pd(1)–N(2)	82.16(7)	N(4)–Pd(2)–Br(1)	89.73(5)
N(2)–Pd(1)–N(1)	79.43(7)	N(6)–Pd(2)–Br(1)	108.74(5)
N(1)–Pd(1)–Br(1)	89.89(5)	Pd(1)–Br(1)–Pd(2)	98.48(09)

N(3)–Pd(1)–Br(1)	108.55(5)	Pd(1)–N(1)–N(4)	130.95(15)
N(6)–Pd(2)–N(5)	82.09(7)	Pd(2)–N(4)–N(1)	130.03(15)
N(5)–Pd(2)–N(4)	79.51(7)		

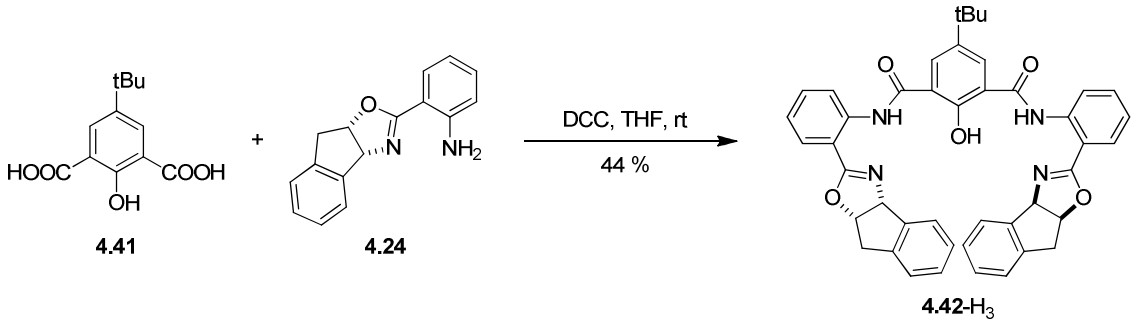
Each of the two palladium(II) centers of the complex **4.40**·Pd_2Br is confined in a slightly distorted square planar geometry by three donor nitrogen atoms from the ligand and a bridging bromide ion. The donor nitrogen atoms from pyrazole, amide and oxazoline moieties coordinate to the palladium centers, forming five-membered chelate rings, with the subtended N–Pd–N angles ranging from 79.43 to 82.26º. The two palladium centers are bridged by the bromide ion and the pyrazole segment. All of the Pd–N bond lengths fall within a relatively narrow range of 1.925 to 2.025 Å. As expected, the Pd–Br bond lengths are slightly longer (2.519 and 2.529 Å) than the Pd–N bonds. The bromide ion bridges the two palladium centers with an angle of 98.48º. The two nitrogen donor atoms from the pyrazole moiety forms the second bridging link between the two metal centers, thereby constraining the N(1)–Pd(1)–Br(1) and N(4)–Pd(2)–Br(1) angles to be 89.89 and 89.73º respectively. The resulting Pd(1)···Pd(2) distance amounts to 3.824 Å.

4.2.4 Phenol Bridged Bisoxazoline Ligands

The ligands involving naphthyridine, pyridazine and pyrazole, that have been discussed till now, involve bridging to two metal centers via attachment through two different donor nitrogen atoms. To explore the effect on the metal–metal distance by changing the linker to phenol, which can act as a single atom phenoxy bridge, we designed ligand **4.42**-H_3. The *tert*-butyl group in the *para*-position was incorporated in the design with the assumption that it would likely increase the overall solubility of the ligand as well as that of any derived complexes. The

required dicarboxylic acid **4.41** was conveniently prepared from cheap 4-*tert*-butyl-phenol.[23] DCC mediated coupling of one equivalent of **4.41** with two equivalents of the chiral amine **4.24** led to the formation of phenol-bridged bisoxazoline ligand **4.42**-H_3 in a single step (Scheme 4.5).

Scheme 4.5 **Synthesis of Phenol–Bisoxazoline Ligand 4.42-H_3**

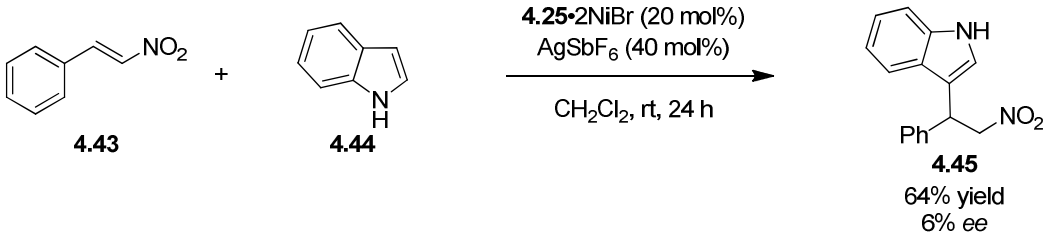


Preliminary experiments have shown that the trianionic ligand **4.41** readily forms complexes with different nickel, copper and palladium salts. Efforts are ongoing to obtain sufficient quality crystal for molecular structure determination.

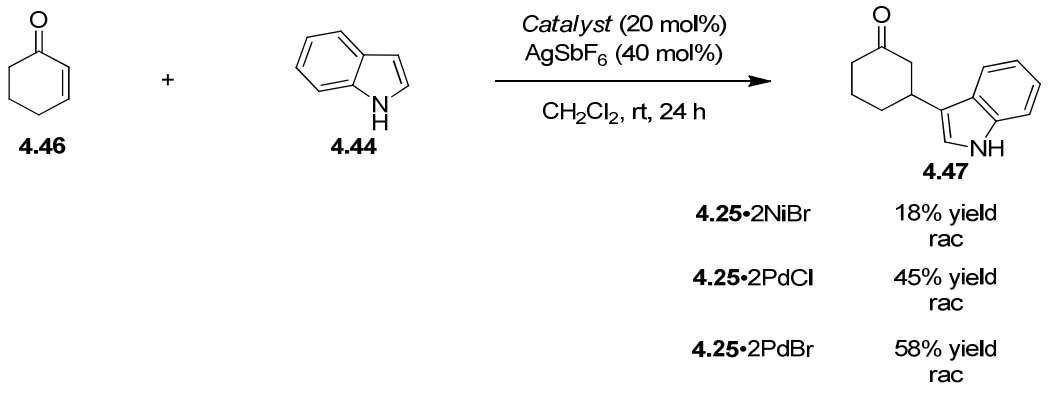
4.3 Preliminary Results

To analyze the catalytic activity of the chiral bisoxazoline-containing bimetallic complexes, we attempted a variety of 1,4-addition reactions of indole as a model reaction. Addition of indole to *trans*-β-nitrostyrene in presence of catalytic amounts of **4.25**·2NiBr and replacing bromide with the weakly coordinating hexafluoroantimonate (SbF_6^-) anion led to modest yield and low enantioselectivity (Scheme 4.6). Unfortunately, the addition of indole to 2-cyclohexenone in presence of various metal salts bound to ligand **4.25** gave the corresponding addition product in low yields and no enantioselectivity (Scheme 4.7).

Scheme 4.6 **Indole Addition to *trans*-β-nitrostyrene**

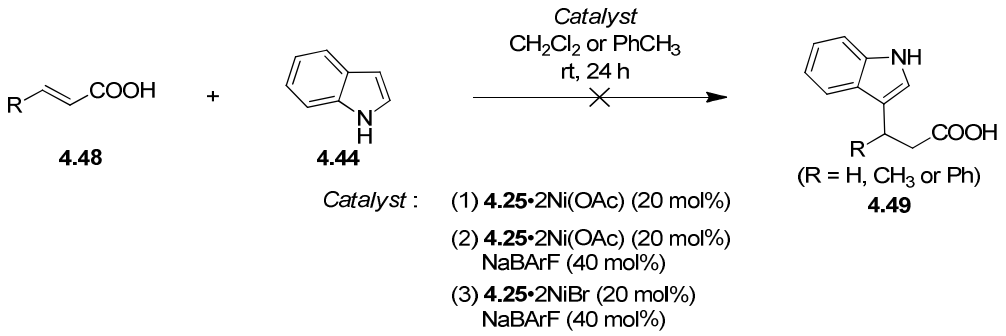


Scheme 4.7 **Indole Addition to 2-Cyclohexenone**

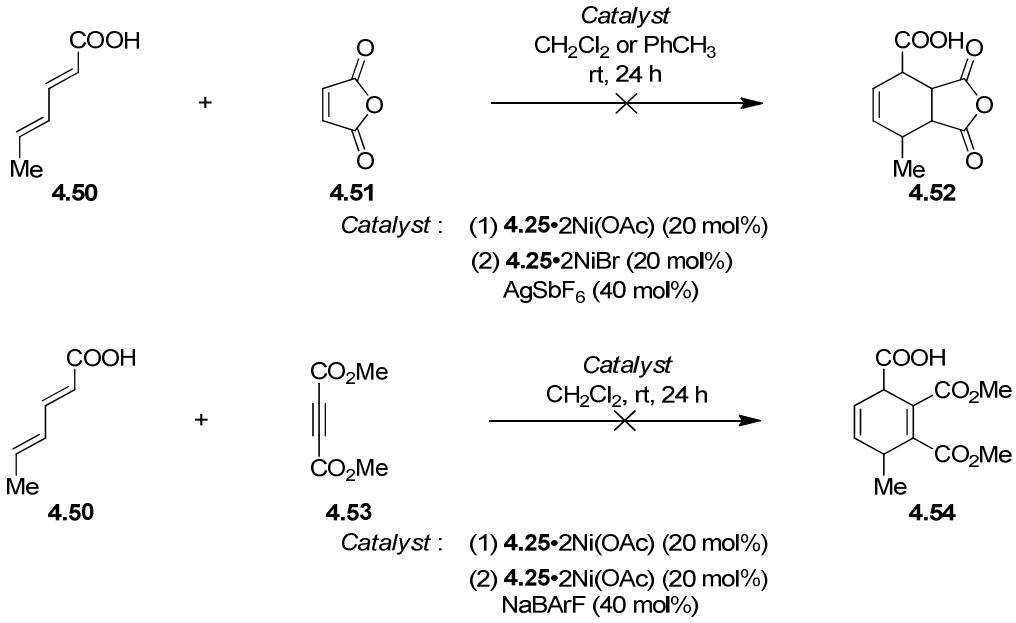


Next we attempted the more challenging conjugate addition of indole to α,β-conjugated acids **4.48**. Upon performing the reaction using **4.25**·2Ni(OAc) or **4.25**·2NiBr, and with or without the weakly coordinating anion $BArF^-$, did not lead to any product formation even after prolonged reaction time (Scheme 4.8). Attempted [4 + 2] cycloaddition of the conjugated diene acid **4.50** with different dienophiles also did not lead to any desired results (Scheme 4.9).

Scheme 4.8 **Attempted Indole Addition to α,β-Conjugated Acids**



Scheme 4.9 **Attempted [4 + 2] Cycloaddition Reaction**



4.4 Conclusion

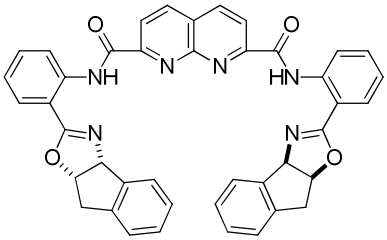
We have synthesized several chiral bisoxazoline ligands that incorporate naphthyridine (**4.25**-H_2 and **4.31**-H_2), pyridazine (**4.34**-H_2), pyrazole (**4.40**-H_3) and phenol (**4.42**-H_3) bridges and can efficiently coordinate to two metal centers. These compounds readily form complexes with various transition metal salts, including nickel(II) acetate, nickel(II) bromide, copper(II) chloride,

palladium(II) chloride, palladium(II) bromide, palladium(II) acetate and zinc(II) chloride. Preliminary investigation conducted by the group on the catalytic enantioselective indole addition to α,β-unsaturated compounds showed modest results. Further applications of metal complexes derived from the chiral bisoxazoline compounds elucidated above and related ligands in various catalytic asymmetric transformations need to be pursued.

Experimental Section

General Information: Reagents were purchased from commercial sources and were used as received. Dichloromethane was freshly distilled from calcium hydride under nitrogen prior to use. Tetrahydrofuran and diethyl ether were freshly distilled from sodium, in the presence of benzophenone as indicator, under nitrogen prior to use. 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, and Dragendorff-Munier stains followed by heating. Purification of reaction products was carried out by flash column chromatography using Sorbent Technologies Standard Grade silica gel (60 Å, 230–400 mesh). Infrared spectra were recorded on an ATI Mattson Genesis Series FT-Infrared spectrophotometer. Melting points were recorded on a Electrothermal Mel-Temp 3.0 melting point apparatus and are uncorrected. Proton nuclear magnetic resonance spectra (^{1}H-NMR) were recorded on a Varian VNMRS-500 MHz and Varian VNMRS-400 MHz instrument and are reported in ppm using the solvent as an internal standard ($CDCl_3$ at 7.26 ppm, $(CD_3)_2SO$ at 2.50 ppm). Data are reported as app = apparent, s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, ddd = doublet of doublet of doublets, td = triplet of doublets, m = multiplet, comp = complex, br = broad; and coupling constant(s) in Hz. Proton-decoupled carbon nuclear magnetic resonance spectra (^{13}C-NMR) were recorded on a Varian VNMRS-500 MHz and Varian VNMRS-400 MHz instrument and are reported in ppm using the solvent as an internal standard ($CDCl_3$ at 77.0 ppm, $(CD_3)_2SO$ at 39.5 ppm). Mass spectra were recorded on a Finnigan LCQ-DUO mass spectrometer.

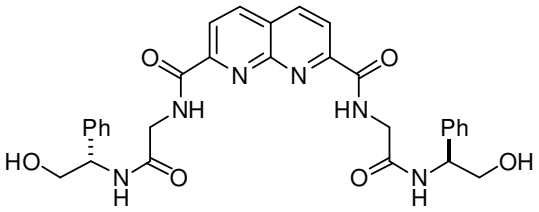
N^2,N^7-Bis(2-((3a*R*,8a*S*)-8,8a-dihydro-3a*H*-indeno[1,2-*d*]oxazol-2-yl)phenyl)-1,8-naphthyridine-2,7-dicarboxamide (4.25–H_2):



A solution of the naphthyridine 2,7-diacid **4.22** in thionyl chloride was heated under reflux for 4 h. Excess solvent was then distilled off and the crude **4.23** mixture dried under vacuum. To a solution of the crude **4.23** (1 equiv.) in dichloromethane, amine **4.24** (2.1 equiv.) was added followed by drop-wise addition of triethylamine (3 equiv.) and the reaction mixture allowed to stir at room temperature for 24 h. The mixture was then washed with 10% hydrochloric acid and water (three times). The organic layer was then separated, dried with anhydrous sodium sulfate and the solvent evaporated *in vacuo*. The residue was purified by flash column chromatography to give the title compound as a pale white solid in 65% yield (R_f = 0.18 in hexanes/EtOAc 75:25 v/v); mp: >230 °C; IR (KBr) 2959, 1734, 1682, 1635, 1582, 1539, 1448, 1353, 1282 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 14.37 (s, 2H), 8.95 (app dd, *J* = 8.4, 0.8 Hz, 2H), 8.61 (d, *J* = 8.5 Hz, 2H), 8.51 (d, *J* = 8.3 Hz, 2H), 7.98 (d, *J* = 7.5 Hz, 2H), 7.93 (dd, *J* = 8.0, 1.6 Hz, 2H), 7.51 (dt, *J* = 7.4, 1.6 Hz, 2H), 7.17–7.13 (m, 2H), 7.13–7.08 (comp, 2H), 6.99 (app t, *J* = 7.3 Hz, 2H), 6.66 (app t, *J* = 7.4 Hz, 2H), 6.26 (d, *J* = 7.9 Hz, 2H), 5.53–5.45 (m, 2H), 3.50 (dd, *J* = 18.0, 6.8 Hz, 2H), 3.37 (d, *J* = 18.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6, 162.9, 154.9, 153.3, 142.1, 139.2, 139.0, 138.6, 132.1, 129.3, 128.1, 127.0, 126.6, 125.3, 124.7, 123.0, 121.4, 120.9, 115.4, 81.9, 77.1, 39.8; *m/z* (ESI-MS) 705.4 $[M + Na]^+$.

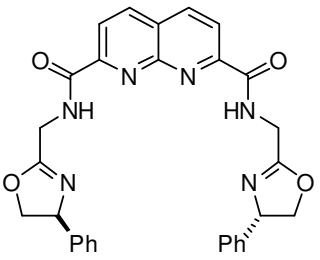
N^2,N^7-Bis(2-((*S*)-2-hydroxy-1-phenylethylamino)-2-oxoethyl)-1,8-naphthyridine-2,7-dicarboxamide (4.30):

In an oven-dried flask equipped with a stir bar, **4.22** and thionyl chloride were added and heated under reflux for 2 h. Excess solvent was then distilled off and the crude **4.23** mixture dried under



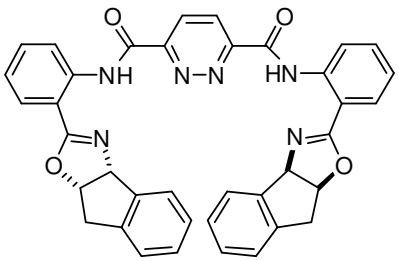
vacuum. A solution of the crude **4.23** (1 equiv.) and Hünig's base (3 equiv.) in dichloromethane was then cooled to 0 ˚C and a solution of **4.29** (2.1 equiv.) was added drop-wise. The reaction mixture was then gradually warmed to room temperature and allowed to stir for 24 h. Upon addition of water, the desired product precipitated out as an off-white solid which was then filtered out, washed with dichloromethane and dried. mp: 195–199 °C; IR (KBr) 3316, 3064, 2935, 1659, 1600, 1532, 1495, 1425, 1270 cm^{-1}; ^1H NMR (500 MHz, dmso-d_6) δ 9.33 (app t, *J* = 5.7 Hz, 2H), 8.80 (d, *J* = 8.4 Hz, 2H), 8.48 (d, *J* = 8.2 Hz, 2H), 8.35 (d, *J* = 8.5 Hz, 2H), 7.41–7.28 (comp, 8H), 7.27–7.20 (comp, 2H), 4.96–4.85 (comp, 4H), 4.18–4.06 (comp, 4H), 3.64–3.53 (comp, 4H); *m/z* (ESI-MS) 593.3 $[M + Na]^+$.

N^2,N^7-Bis(((*S*)-4-phenyl-4,5-dihydrooxazol-2-yl)methyl)-1,8-naphthyridine-2,7-dicarboxamide (4.31–H_2):



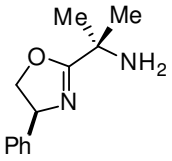
Triethylamine (3 equiv.) was dropwise added to a suspension of **4.30**, *p*-toluenesulfonic acid (2.2 equiv.) and DMAP (0.2 equiv.) in dichloromethane at room temperature. After stirring the reaction mixture for 24 h, it was poured into ice cold saturated aqueous solution of NH_4Cl and extracted with dichloromethane three times. The combined organic extracts were then dried with anhydrous sodium sulfate and solvent evaporated *in vacuo*. The crude mixture was then purified by flash column chromatography to give the title compound in 47% yield (R_f = 0.18 in EtOAc/MeOH 98:2 v/v); ^1H NMR (500 MHz, $CDCl_3$) δ 8.99 (app t, *J* = 5.9 Hz, 2H), 8.42 (d, *J* = 8.5 Hz, 2H), 8.32 (d, *J* = 8.4 Hz, 2H), 7.33–7.26 (comp, 4H), 7.26–7.19 (comp, 6H), 5.25–5.16 (m, 2H), 4.65 (dd, *J* = 10.1, 8.5 Hz, 2H), 4.51 (app d, *J* = 5.8 Hz, 4H), 4.12 (t, *J* = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 163.9, 153.3, 152.6, 141.7, 138.6, 128.6, 127.5, 126.5, 125.3, 121.2, 75.3, 69.4, 37.0. *m/z* (ESI-MS) 557.1 $[M + Na]^+$.

N^3,N^6-Bis(2-((3a*R*,8a*S*)-8,8a-dihydro-3a*H*-indeno[1,2-*d*]oxazol-2-yl)phenyl)pyridazine-3,6-dicarboxamide (4.34–H_2):



A solution of **4.33** and amine **4.24** (2.1 equiv.) in dichloromethane was cooled to 0 ˚C. Freshly prepared LDA (1 M in THF, 2.1 equiv.) was then added slowly through cannula and the mixture was gradually warmed to room temperature. After stirring for 24 h, the reaction mixture was quenched by the addition of ice cold saturated aqueous solution of NH_4Cl. The organic layer was isolated and aqueous part was extracted two more times with dichloromethane. Combined organic extracts were dried with anhydrous sodium sulfate, concentrated *in vacuo* and purified by flash column chromatography to give the title compound as a white solid; mp: 162–165 °C; IR (KBr) 3023, 2958, 1686, 1636, 1603, 1585, 1526, 1449, 1231 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 14.73 (s, 2H), 9.05 (d, *J* = 8.3 Hz, 2H), 8.58 (s, 2H), 8.47 (d, *J* = 7.5 Hz, 2H), 7.95 (dd, *J* = 7.8, 1.2 Hz, 2H), 7.59–7.52 (m, 2H), 7.30–7.15 (comp, 8H), 5.95 (d, *J* = 7.7 Hz, 2H), 5.41–5.33 (m, 2H), 3.50 (dd, *J* = 18.2, 6.6 Hz, 2H), 3.40 (d, *J* = 18.1 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.1, 161.6, 154.6, 142.1, 139.3, 139.1, 132.4, 129.4, 128.6, 127.7, 127.0, 126.7, 125.1, 123.2, 120.6, 115.0, 81.9, 77.0(3), 39.6; *m/z* (ESI-MS) 633.5 $[M+H]^+$.

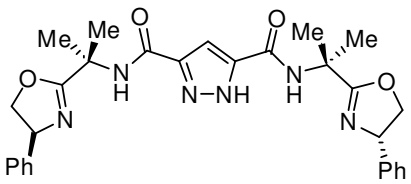
(*S*)-2-(4-Phenyl-4,5-dihydrooxazol-2-yl)propan-2-amine (4.38):



To a solution of **4.36**, *p*-toluenesulfonic acid (1.1 equiv.) and DMAP (0.2 equiv.) in dichloromethane, triethylamine (3 equiv.) was added dropwise and allowed to stir at room temperature for 12 h. The reaction mixture was poured into an ice cold saturated aqueous solution of NH_4Cl and extracted with dichloromethane three times. The combined organic extracts were then dried with anhydrous sodium sulfate and solvent evaporated *in vacuo*. The crude mixture was then purified by flash column chromatography to give the *N*-carboxybenzyl compound **4.37** in 86% yield. **4.37** was then dissolved in anhydrous

methanol and after addition of 10% palladium on charcoal, the heterogenous mixture was stirred under hydrogen for 4 h. The reaction mixture was then filtered through a pad of celtite and rinsed with methanol. After evaporating the solvent under vacuum, the crude mixture was purified by flash column chromatography to give the title compound as a colorless liquid in near-quantitative yield (R_f = 0.15 in EtOAc/MeOH 90:10 v/v); IR (KBr) 3362, 2975, 1655, 1495, 1455, 1131 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31–7.16 (m, 5H), 5.10 (dd, *J* = 10.0, 7.9 Hz, 1H), 4.57 (dd, *J* = 10.1, 8.5 Hz, 1H), 4.07 (t, *J* = 8.1 Hz, 1H), 2.31–1.92 (br, 2H), 1.37 (dd, *J* = 12.5, 3.6 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.7, 142.3, 128.7, 127.5, 126.4, 75.5, 69.4, 50.2, 28.5, 28.3; *m/z* (ESI-MS) 205.3 $[M + H]^+$.

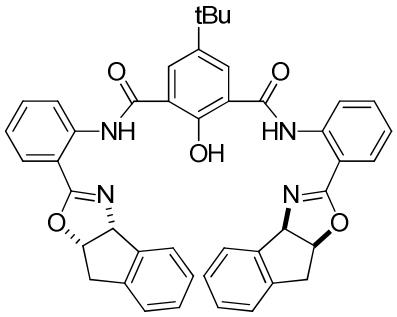
N^3,N^5-bis(2-((*S*)-4-phenyl-4,5-dihydrooxazol-2-yl)propan-2-yl)-1*H*-pyrazole-3,5-dicarboxamide (4.40–H_3):



Pyrrole diacyl chloride **4.39** was taken in dichloromethane alongwith DMAP (0.2 equiv.) and triethylamine (3 equiv.). The mixture was then cooled to 0 ˚C and a solution of **4.38** in dichloromethane was added dropwise. The reaction mixture was then gradually warmed to room temperature and stirred for 24 h. After evaporating the solvent under reduced pressure, the crude mixture was purified by flash column chromatography to give the title compound in 30% yield; ^1H NMR (500 MHz, $CDCl_3$) δ 12.95 (s, 1H), 7.67 (s, 1H), 7.28–7.21 (comp, 4H), 7.21–7.13 (comp, 6H), 6.98 (s, 1H), 5.17 (dd, *J* = 9.7, 1.5 Hz, 2H), 4.69–4.59 (m, 2H), 4.14–4.07 (m, 2H), 1.70 (s, 12H) ; *m/z* (ESI-MS) 529.1 $[M + H]^+$.

5-(*tert*-Butyl)-N^1,N^3-bis(2-((3a*R*,8a*S*)-8,8a-dihydro-3a*H*-indeno[1,2-*d*]oxazol-2-yl)phenyl)-2-hydroxyisophthalamide (4.42–H_3):

To a stirring solution of the phenol-diacid **4.41** and DCC (2.1 equiv.) in THF, a solution of the amine **4.24** (2.1 equiv. in THF) was added over 15 min. The resulting milky white reaction



mixture was allowed to stir for another 5 h, after which the white precipitate was filtered out and rinsed with THF. Solvent was evaporated under reduced pressure and product was purified by flash column chromatography to give the title compound as a white solid in 44% yield. mp: 134–137 °C; IR (KBr) 3026, 2958, 2868, 1668, 1629, 1610, 1535, 1448, 1354, 1277, 1175, 1063, 1001, 955, 750 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.94 (s, 1H), 13.48 (s, 1H), 13.05 (s, 2H), 8.89 (app dd, *J* = 8.6, 0.8 Hz, 2H), 8.35 (s, 2H), 7.92 (app dd, *J* = 8.0, 1.5 Hz, 2H), 7.56–7.50 (m, 2H), 7.45 (app dd, *J* = 7.0, 1.1 Hz, 2H), 7.30–7.20 (comp, 6H), 7.16–7.10 (m, 2H), 5.87 (d, *J* = 7.8 Hz, 2H), 5.48–5.42 (m, 2H), 3.52 (dd, *J* = 18.0, 6.5 Hz, 2H), 3.43 (d, *J* = 17.9 Hz, 2H), 1.58 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.4, 163.9, 158.2, 141.4, 141.1, 139.4, 139.3, 132.4, 130.4, 129.5, 128.6, 127.7, 125.4, 125.3, 122.8, 121.0, 120.0, 114.6, 82.2, 76.7, 39.3, 34.5, 31.6; *m/z* (ESI-MS) 703.3 $[M + H]^+$, 725.4 $[M + Na]^+$.

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Curriculum Vitae

Deepankar Das

Education

09/2007 – 10/2013	Ph.D (Organic Chemistry) *Rutgers, the State University of New Jersey, New Brunswick, NJ.* Advisor: Professor Daniel Seidel
07/2004 – 05/2006	M.Sc (Chemistry) *Indian Institute of Technology Guwahati, Assam, India.* Advisor: Professor Parameswar Krishnan Iyer
06/2001 – 05/2004	B.Sc (Chemistry Honors) *Gauhati University, Guwahati, Assam, India.*

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