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Transition Metal-Catalyzed Alkene Hydroacylation as a Platform for Enantioselective Synthesis of Polycyclic Nitrogen Heterocycles

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Transition Metal-Catalyzed Alkene Hydroacylation as a Platform for Enantioselective Synthesis of Polycyclic Nitrogen Heterocycles

by

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Babai & Mummy
Thank you for not losing hope in me!!

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ABSTRACT

The prevalence of nitrogen heterocycles in medicinally important compounds has, for years, inspired synthetic chemists for developing strategies to form new heterocyclic scaffolds and methods that streamline the syntheses of complex heterocycles. Giving into the cause, this dissertation primarily focuses on development of transition-metal catalyzed hydroacylation of alkenes as a platform for enantioselective synthesis of multiple classes of polycyclic nitrogen heterocycles.

Development of catalytic, enantioselective intramolecular hydroacylation of *N*-vinylindole-2-carboxaldehydes that occur in the presence of a readily accessible rhodium catalyst and form chiral, non-racemic 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-ones in high yields and enantioselectivities has been described. The dihydropyrroloindolone products can be readily transformed to dihydropyrroloindoles that are core structures present in a variety of natural products and biologically relevant compounds. This methodology could be extended to hydroacylations of *N*-allylindole- and *N*-allylpyrrole-2-carboxaldehydes in construction of six-membered rings that generated 7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)ones and 6,7-dihydroindolizin-8(5*H*)-ones in moderate to high yields with excellent enantioselectivities. In contrast to many alkene hydroacylations that form six-membered rings, these *endo*-selective annulative processes occur in the absence of ancillary functionality to stabilize the acylrhodium(III) hydride intermediate.

Our protocol for rhodium-catalyzed hydroacylation of *N*-vinylindole-2-carboxaldehyde could be leveraged for installation of stereochemical triad in 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]-indole core of putative structure of yuremamine. The enantioselective model synthesis was achieved in 39% overall yield and 96% ee over 5 steps. An

enantioselective synthesis of a densely functionalized dihydropyrroloindolone that maps onto the putative structure of yuremamine is demonstrated in 26% yield and 97% ee over 8 steps.

Additionally, *exo*-selective nickel- and NHC-catalyzed hydroacylations could be coupled with catalytic enantioselective α-(hetero)arylation reactions in a sequential synthetic strategy to form a wide variety of nitrogen-containing heterocyclic ketones bearing α-chiral quaternary stereogenic centers. *E*xo-selective, intramolecular Ni-catalyzed hydroacylations of *N*-homoallylindole- and *N*-homoallylpyrrole-2-carboxaldehydes form α-substituted six-membered heterocyclic ketones in up to 95% yield, while *N*-heterocyclic carbene (NHC)-catalyzed hydroacylations of *N*-allylindole- and *N*-allylpyrrole-2-carboxaldehydes form α-substituted five-membered heterocyclic ketones in up to 99% yield. The racemic five- and six-membered products of Ni- and NHC-catalyzed hydroacylation reactions are readily transformed into heterocyclic ketones containing an α-chiral quaternary stereogenic center by enantioselective Ni-catalyzed α-arylation and α-heteroarylation reactions. The identity of the precatalyst for Ni-catalyzed α-(hetero)arylation is dictated by the identity of the α–substituted heterocyclic ketone starting material. α-(Hetero)arylations of six-membered heterocyclic ketones occur at 65-85 °C in the presence of a catalyst generated *in situ* from $Ni(COD)_2$ and (*R*)-BINAP or (*R*)-DIFLUORPHOS. α-(Hetero)arylation of five-membered heterocyclic ketones must be conducted at room temperature in the presence of an [((*R*)-BINAP)Ni(η^2-NC-Ph)] precatalyst or a catalyst generated *in situ* from $Ni(COD)_2$, (*R*)-DIFLUORPHOS and benzonitrile.

Finally, studies on Ni_2P nanocrystal catalyzed hydrogenation of phenylacetylene have been reported. The model reaction is studied with both hollow and solid Ni_2Ps in two different solvents (1,4-dioxane and 1-propanol). Recycling studies in both solvents

demonstrated increase in catalytic activity of Ni_2P nanocrystals over reaction cycles. Structural characterization of recycled Ni_2P nanocrystals via powder XRD, TEM and XPS analyses revealed reduction in size of hollow nanoparticles along with the formation of Ni(II) species after hydrogenation reactions. Systematic characterization of Ni_2P nanocrystals isolated after each reaction throughout the lifetime of recycling study (in both 1,4-dioxane and 1-propanol) has been demonstrated.

THESIS ORGANIZATION

This thesis comprises of six chapters. Chapter 1 is a brief literature survey on progress of transition-metal catalyzed hydroacylation of olefins over last four decades. A portion of the review presented in Chapter 1 was published as a *highlight* in *Organic Chemistry Frontiers* with contributions from Kirsten F. Johnson, Kevin L. Vickerman and James A. Walker. Chapter 2 describes our studies on synthesis of indole- and pyrrole-based chiral, non-racemic polycyclic nitrogen heterocycles via rhodium-catalyzed intramolecular hydroacylation reactions. Rhodium-catalyzed hydroacylation of *N*-allylindole-2-carboxaldehydes was developed by Dr. Xiang Wei Du (Postdoctoral fellow in Stanley group) based on the initial results obtained by the author of this thesis. Chapter 3 describes an enantioselective model synthesis of the core and progress toward the total synthesis of the putative structure of yuremamine utilizing enantioselctive hydroacylation methodology as described in Chapter 2 as the key synthetic step. David T. Bainbridge is an undergraduate student at ISU who helped with the synthesis of TBS-protected tryptophol. Chapter 4 describes a sequential protocol involving *exo*-selective nickel or NHC-catalyzed hydroacylation and enantioselective α-arylation reactions that constructs a wide variety of highly enantioenriched nitrogen containing heterocyclic ketones bearing α-chiral quaternary stereogenic centers. James A. Walker Jr. is a graduate student in Stanley group who developed the NHC-catalyzed hydroacylation protocol and helped with the identification of nickel catalyst for α-arylation of five-membered nitrogen heterocycles. Iowa State University's crystallographer, Dr. Arkady Ellern collected all X-ray data and determined the absolute configuration of the structures. Chapter 5 describes our studies toward nickel phosphide (Ni_2P) nanocrystal catalyzed hydrogenation of phenylacetylene. This work has

been performed in close collaboration with Himashi Andaraarachchi, a graduate student in Prof. Javier Vela's group. Chapter 6 is general conclusion and outlook. It summarizes the key findings in each chapter and identifies areas for further research.

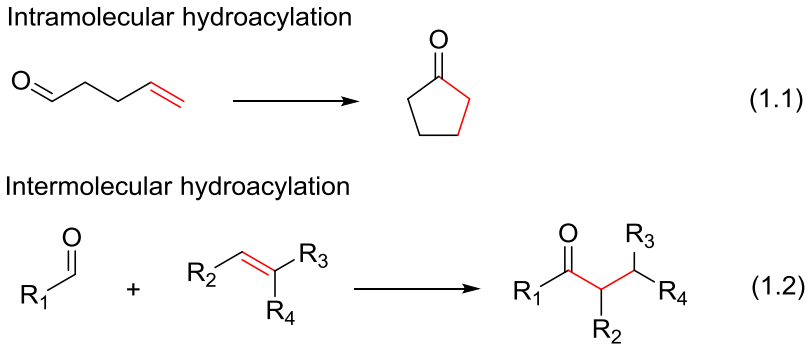
CHAPTER I

A SNAPSHOT INTO FORTY YEARS OF TRANSITION-METAL CATALYZED HYDROACYLATION OF ALKENES

A *portion* of the review is published as a *Highlight* in *Organic Chemistry Frontiers*[1]

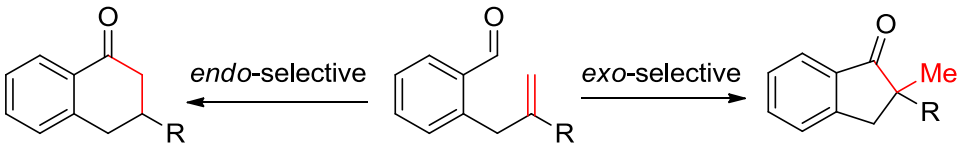
1.1 General Introduction and Scope

Transition metal-catalyzed alkene hydroacylation, the formal addition of an aldehyde C-H bond across an unsaturated C-C bond (Equation 1.1 and 1.2), has emerged as a powerful, catalytic process to synthesize ketones over the past four decades.[1] The identification and development of new catalysts has greatly expanded the scope and synthetic utility of these hydroacylation reactions in recent years. Intramolecular alkene hydroacylation reactions are now



well-established methods to synthesize carbocyclic and heterocyclic ketones, often with high enantioselectivities. These transformations generally occur in the presence of transition-metal or NHC catalysts, and the selection of the specific catalyst type determines the regiochemical outcome of the reaction. NHC-catalyzed intramolecular hydroacylations occur with *exo*-selectivity (formal Markovnikov selectivity), while transition metal-catalyzed hydroacylations can occur with either *endo*-selectivity (formal anti-Markovnikov selectivity) or *exo*-selectivity (Equation 1.3). The potential for complementary regioselectivity can be utilized for synthesis of

[1] Ghosh, A.; Johnson, K. F.; Vickerman, K. L.; Walker Jr., J. A.; Stanley, L. M. *Org. Chem. Front.*, **2016**, *3*, 639-644.



(1.3)

two distinct ketone products from the same substrate. In addition, the development of intermolecular hydroacylations of new combinations of alkenes and alkynes with aldehydes continues to rapidly expand and provide direct routes to new ketones from simple starting materials.

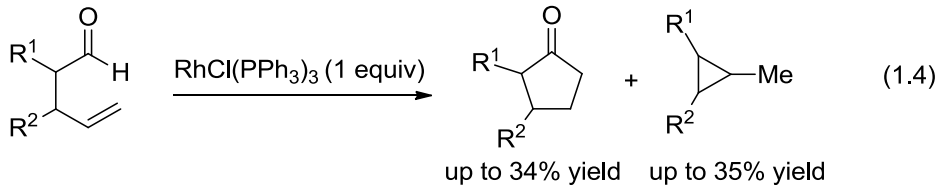
Despite recent advances in catalytic alkene hydroacylation reactions, many challenges remain to fully harness the synthetic potential of these valuable processes. These challenges include: intramolecular hydroacylations to form medium and large rings in the absence of functional groups to stabilize catalytic intermediates; intermolecular hydroacylations that encompass a much broader array of substrates; and new catalyst types that improve activity, complement the selectivity, and reduce the cost of widely studied rhodium complexes of bisphosphine ligands.

Since the initial report by Sakai and co-workers in 1972,[2] hydroacylation of alkenes has evolved to encompass reactions catalyzed by not only transition metal complexes, but also *N*-heterocyclic carbenes (NHCs)[3] and photocatalysts.[4] This review will focus on recent developments in transition metal-catalyzed alkene hydroacylation reactions. The discussion is divided by catalyst type and includes highlights of rhodium-, cobalt-, ruthenium-, iridium-, and nickel-catalyzed processes.

1.2 Rhodium-Catalyzed Alkene Hydroacylation

The first transition metal-catalyzed olefin hydroacylation reaction was reported by Sakai and co-workers in 1972 in which reaction of a variety of 4-enals generated cyclopentanones in

presence of a stoichiometric amount of Wilkinson's complex along with the formation of cyclopropanes as byproducts via a decarbonylative pathway (Equation 1.4).[2]



Since the first report of transition metal-catalyzed olefin hydroacylation, rhodium-catalyzed alkene hydroacylation reactions have remained at the forefront of studies in the area. A generally accepted mechanism for rhodium-catalyzed hydroacylation is illustrated in Figure 1.1. The key steps involve oxidative addition of Rh(I) across the aldehyde C-H bond to form an acyl rhodium(III)hydride intermediate, coordination of alkene to the metal center followed by migratory insertion. Finally reductive elimination yields the ketone product with regeneration of the Rh(I) catalyst.

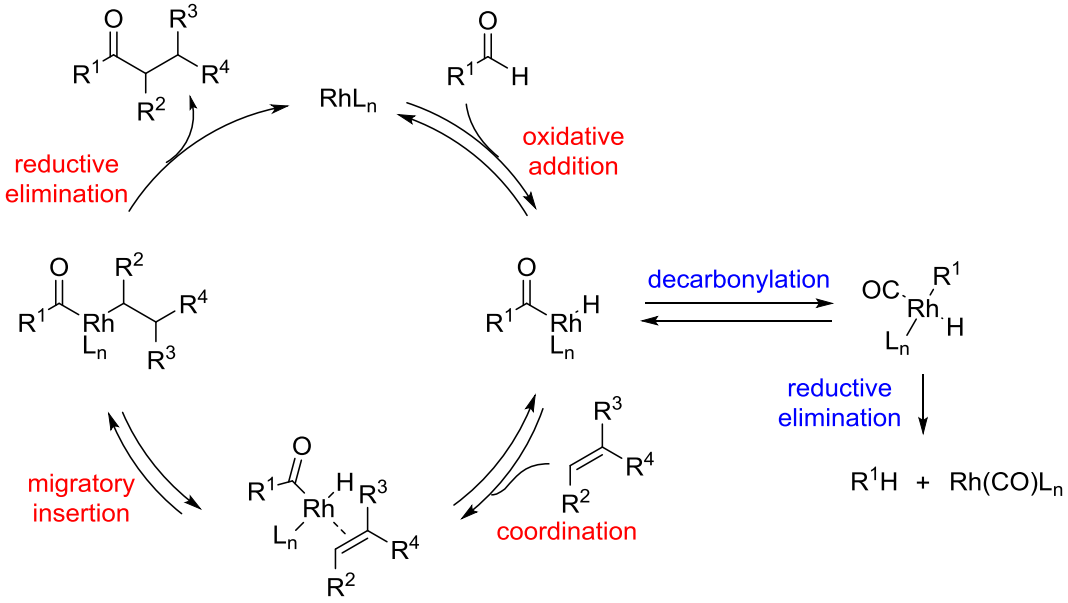


Figure 1.1 Reaction mechanism of rhodium-catalyzed hydroacylation and decarbonylation

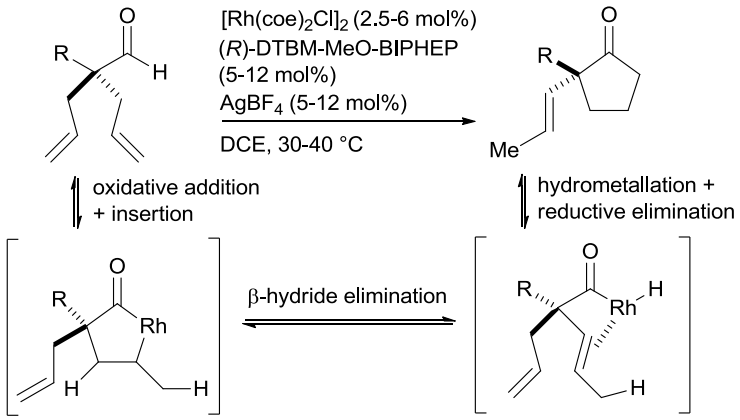
An unproductive catalyst decomposition pathway involving decarbonylation and reductive elimination is often competitive with hydroacylation pathway. Strategies to stabilize the acyl rhodium(III)hydride intermediate by utilizing additional chelating functionality often reduce the extent of decarbonylation (Discussed in detail later).

After the first report on hydroacylation, subsequent examples of hydroacylative cycloisomerizations using sub-stoichiometric amounts of rhodium catalysts (up to 50 mol%) were reported by the Miller and Larock groups that employed ethylene saturated solvents for the synthesis of cyclopentanone derivatives from substituted γ-pentenals.[5] They noted formation of a considerable amount of byproducts from a reductive decarbonylation pathway. The first enantioselective example of hydroacylation, a serendipitous discovery by James and Young in 1983 during their attempt toward kinetic resolution of 4-pentenals by aldehyde decarbonylation, generated α-quaternary cyclopentenones in 40-50% yield and up to 52% ee.[6] However, the most significant advancement in early alkene hydroacylation came from the laboratory of Bosnich in 1988. Bosnich and co-workers developed catalyst systems involving cationic rhodium species in combination with bisphosphine ligands that significantly reduced the formation byproducts arising from competing reductive decarbonylation pathway even in the presence of 1 mol % catalyst.[7] Ever since this discovery, a large number of reports including many recent ones effectively utilized cationic rhodium species as the catalyst for hydroacylation of varied substrate classes. Both Bosnich and Sakai groups independently illustrated catalytic enantioselective intramolecular hydroacylation of 4-substituted-4-pentenals using cationic rhodium perchlorate catalysts derived from BINAP or Me-Duphos.[8] Identifying the appropriate chiral ligand for particular substrates was the key for obtaining high enantioselectivity. A number of reports

including desymmetrizations and kinetic resolutions for synthesis of enantiopure 3,4-disubstituted cyclopentanones followed this report.[9]

Inspired by Tanaka and Suemune's report on desymmetrization of β-bis(alkenyl)aldehydes to generate cyclopentanones bearing β-quaternary stereogenic centers,[10] Dong and coworkers recently developed an enantioselective desymmetrization of α-trisubstituted aldehydes to form cyclopentanones with α-quaternary stereogenic centers (Scheme 1.1).[11] A catalyst generated in situ from $[Rh(coe)_2Cl]_2$, (*R*)-DTBM-MeO-BIPHEP and $AgBF_4$ facilitates the desymmetrization of the α-quaternary center through an isomerization-hydroacylation cascade. Key to this isomerization-hydroacylation cascade is a rare endocyclic β-hydride elimination for which this study provides experimental evidence that supports previous theoretical studies. The chiral Rh catalyst enables selective formation of a variety of α-vinylcyclopentanones (R = alkyl, aryl, heteroaryl) in high yields (73-91%) with excellent enantioselectivities (91-99% ee).

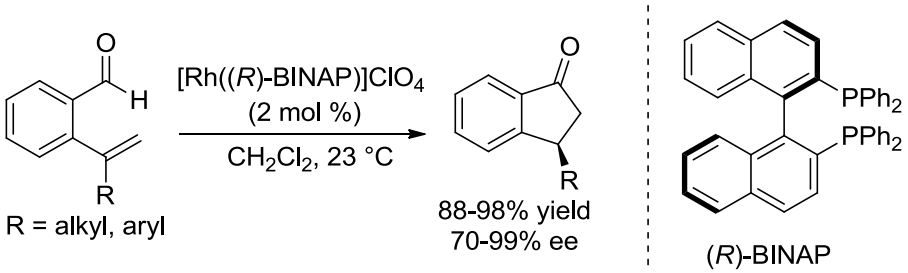
Scheme 1.1 Desymmetrization of α-quaternary centers by isomerization-hydroacylation



R	yield (%)	ee (%)
n-C_5H_{11}	73	99
Ph	91	97
Bn	76	91
Furyl	87	93

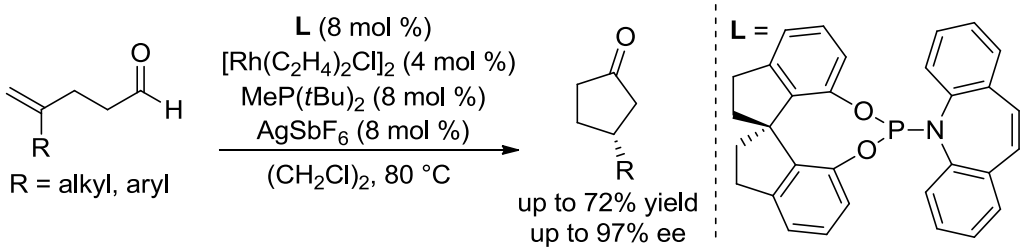
Morehead and coworkers reported enantioselective hydroacylation of α-substituted 2-vinyl benzaldehydes to access a range of chiral 3-substituted indanones with high yield (88-98%) and high enantioselectivity (70-99%).[12] They noted that 2-vinyl benzaldehyde with no substitution at the double bond formed the dimerized product in up to 75% yield (Scheme 1.2). However, the hydroacylation product, 1-indanone was isolated in up to 95% yield when the substrate was added slowly over 18 hours.

Scheme 1.2 Access to chiral 3-substituted indanones via asymmetric intramolecular hydroacylation



In 2011, Carriera and co-workers reported highly enantioselective, intramolecular hydroacylation of 4-pentenals catalyzed by cationic rhodium complexes featuring phosphoramidite-alkene ligands and an achiral phosphine co-ligand (Scheme 1.3).[13]

Scheme 1.3 Asymmetric intramolecular hydroacylation catalyzed by rhodium(I)phosphoramidite-alkene complex

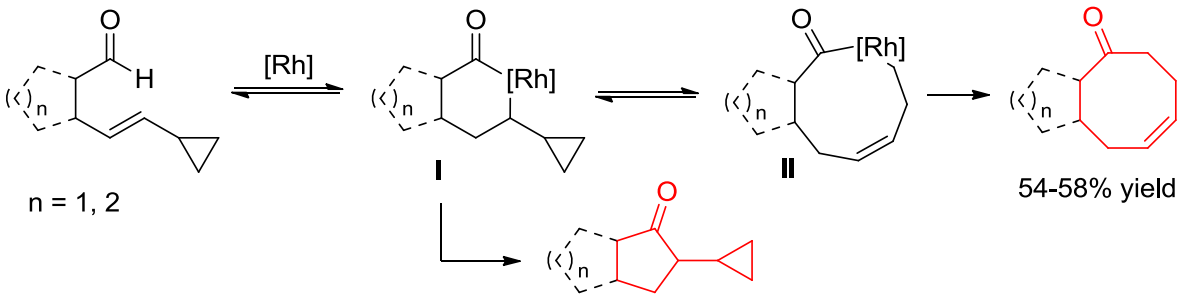


Examples of intramolecular hydroacylation reactions to form larger rings were often limited due to catalyst decomposition by reductive decarbonylation becoming prominent as the

ring size increases and rate of cyclization decreases. Thus, hydroacylation to form rings of greater than five atoms are often driven by strain release or rely on heteroatom functionality contained at specific sites within the substrate molecules to stabilize acylrhodium(III) hydride intermediates and prevent catalyst decomposition. Gable and co-workers in 1991 reported formation of six-membered cyclohexanone derivatives by hydroacylation of hexenals with a rigid carbohydrate backbone.[14] They hypothesized that formation of a cyclopentanone ring was disfavored due to the ring strain that would be present in the resulting 5,5,5-tricyclic product.

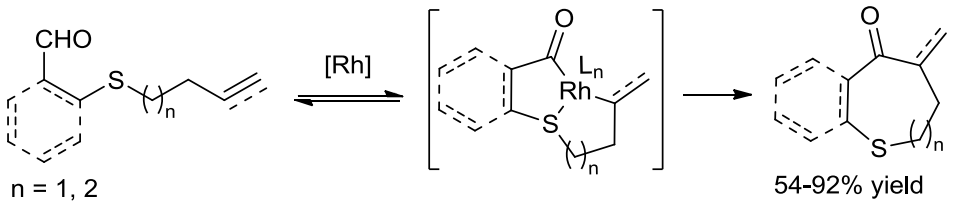
Shair and co-workers in 2000 showed that intramolecular hydroacylation could be extended to the synthesis of eight-membered rings by strategically placing in the substrate a cyclopropane ring capable of fragmentation (Scheme 1.4).[15] The principal step in this transformations involved fragmentation and isomerization of rhodacycle **I** to ring-expanded rhodacycle **II**, followed by reductive elimination to generate eight-membered cyclic product.

Scheme 1.4 Synthesis of eight-membered rings via intramolecular hydroacylation



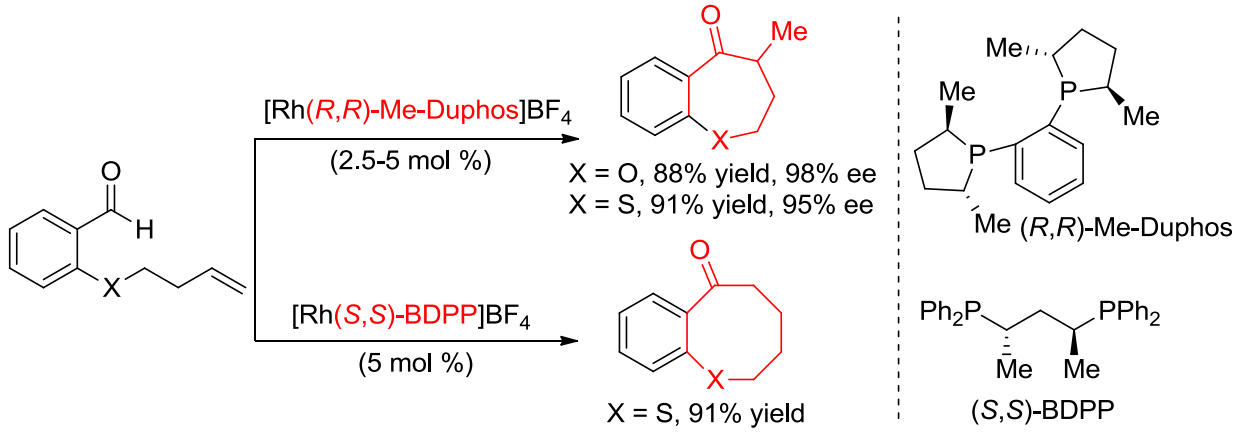
In 2002, Mori and co-workers reported the first example of synthesis of cycloheptanones via intramolecular hydroacylation of 4,6-dienals.[16] In the same year, Bendorf *et. al* reported synthesis of medium ring sulfur heterocycles from ω-alkenals and alkynals containing a sulfur tether atom appropriately positioned in the substrate to stabilize the acyl rhodium(III)hydride intermediate (Scheme 1.5).[17]

Scheme 1.5 Synthesis of seven- and eight-membered sulfur heterocycles via chelation-assisted intramolecular hydroacylation



In 2009, Dong and co-workers developed the first asymmetric hydroacylation strategy that synthesized enantiopure medium-sized rings (seven and eight-membered) utilizing coordinating heteroatoms (ether, sulfide and sulfoxide) in the tether to promote hydroacylation over decarbonylation.[18] Furthermore, they illustrated a switch in the regioselectivity of the transformation by modulating the ligand structure. Thus, they could access both seven- (*endo*-selectivity) and eight-membered (*exo*-selectivity) rings from the same substrate with excellent regio- and enantiocontrol by using two different chiral ligands in combination with the rhodium(I) precursor (Scheme 1.6).

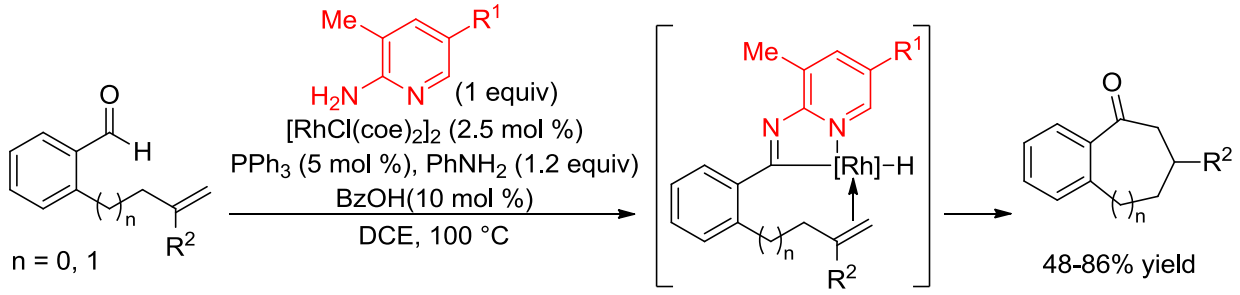
Scheme 1.6 Accessing formal Markovnikov and anti-Markovnikov products by a ligand switch



Douglas and co-workers utilized Jun's strategy of metal-organic cooperative catalysis to access six- and seven-membered cyclic ketones.[19] These hydroacylation reactions involved *in*

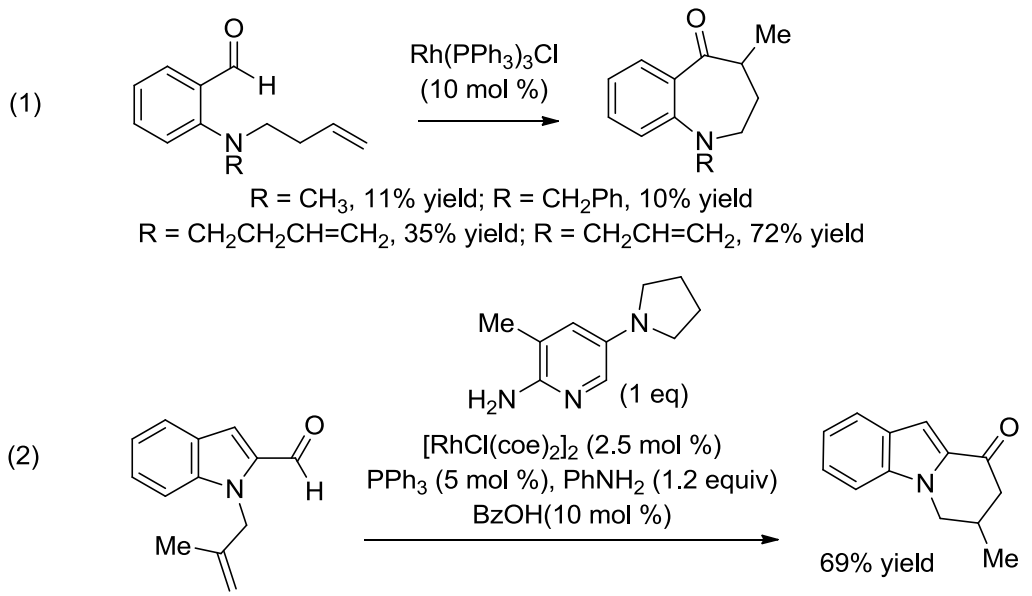
situ formation of imines to install chelating functionality to stabilize the resulting iminorhodium(III) hydride intermediate (Schem1 1.7).

Scheme 1.7 Synthesis of medium-sized rings by intramolecular hydroacylation via cooperative catalysis



Even though six-, seven- and eight-membered carbocycles and oxygen or sulfur containing heterocycles were accessible from alkene hydroacylation reactions, alkene hydroacylations to generate nitrogen-containing heterocycles were rare. Bendorf and co-workers reported amine-directed, intramolecular hydroacylation of 2-(homoallylamino)benzaldehydes (Scheme 1.8, Equation 1).[20] These amine-directed hydroacylation reactions occur in the presence of 10 mol % of Wilkinson's catalyst, and the efficiency of the reactions is greatly influenced by the identity of the substituents on the nitrogen atom. Douglas reported hydroacylation of *N*-allylindole-2-carboxaldehydes and *N*-allylpyrrole-2-carboxaldehydes (Scheme 1.8, Equation 2). These hydroacylation reactions involved *in situ* formation of imines to install chelating functionality to stabilize the resulting iminorhodium(III) hydride intermediate.[19] The heterocyclic ketone products are formed in good yields, but the requirement for chelation assistance leads to poor atom economy and efforts to develop a highly enantioselective catalyst were unsuccessful.

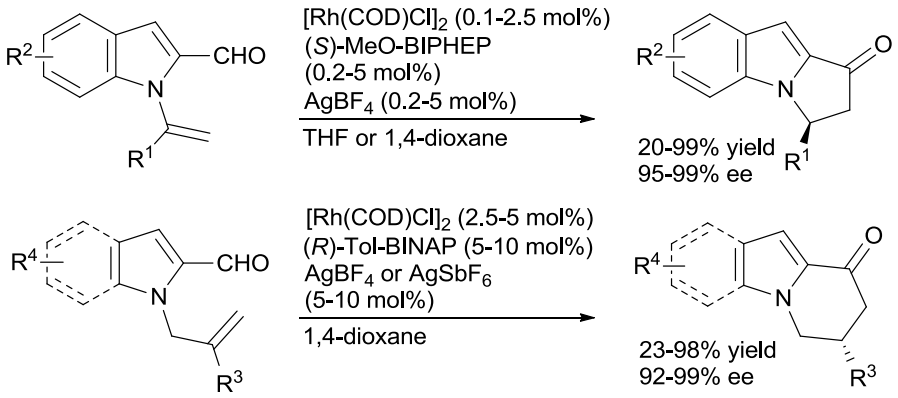
Scheme 1.8 Hydroacylation of olefins to generate nitrogen heterocycles



Our group investigated alkene hydroacylation reactions as a strategy to synthesize polycyclic nitrogen heterocycles with high enantioselectivity and without the need for strategies to stabilize the acylrhodium(III) hydride intermediate. We initially reported highly enantioselective, intramolecular hydroacylation of *N*-vinylindole-2-carboxaldehydes to generate dihydropyrroloindolones in high yield with excellent enantioselectivities (Scheme 1.9).[21] More recently, we reported catalytic, enantioselective hydroacylations of *N*-allylindole-2-carboxaldehydes and *N*-allylpyrrole-2-carboxaldehydes to form dihydropyridoindolones and dihydroindolizinones in moderate-to-high yields with high enantioselectivities.[22] These reactions represent the first examples of highly enantioselective, transition metal-catalyzed hydroacylation to form six-membered rings in the absence of chelation-assistance and encompass an array of *N*-allylindole- and *N*-allylpyrrole-2-carboxaldehydes substrates. These studies will be discussed in detail in Chapter 2 of this dissertation. The ability to form six-membered rings in the absence of

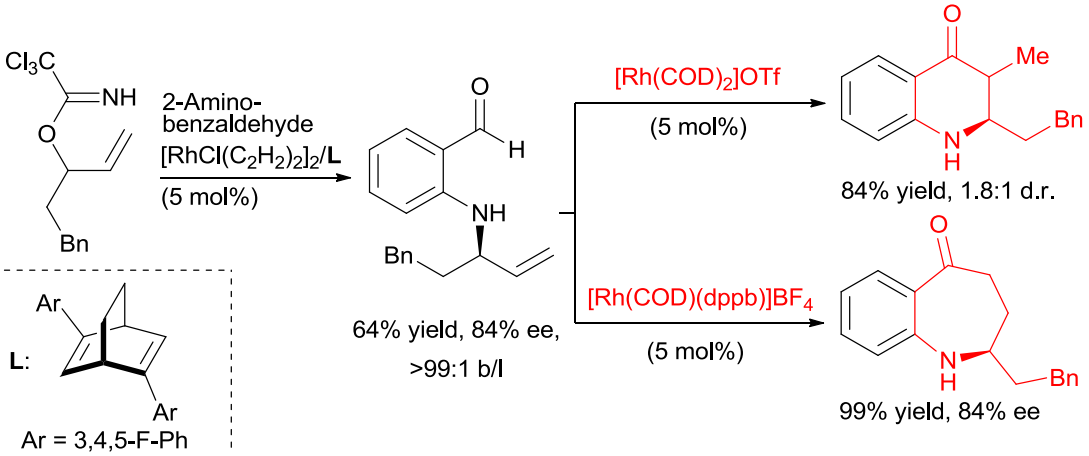
chelation-assistance led to the development of a related catalyst system for *endo*- and enantioselective hydroacylation of *ortho*-allylbenzaldehydes.[23]

Scheme 1.9 Enantioselective hydroacylation to access polycyclic nitrogen heterocycles



The coupling of alkene and alkyne hydroacylation reactions in sequence or in tandem with additional bond-forming processes has expanded the types of heterocyclic ketones that are readily accessible from simple starting materials. Nguyen and coworkers reported a sequential approach to the synthesis of dihydroquinolinones and tetrahydrobenzo[*b*]azepinones involving Rh-catalyzed asymmetric allylic amination followed by intramolecular alkene hydroacylation reactions.[24] The enantioenriched allylic amine, formed by Rh-catalyzed dynamic kinetic asymmetric transformation (DYKAT) of racemic allylic trichloroacetimidates with 2-aminobenzaldehyde, is a suitable substrate for alkene hydroacylation to form six- or seven-membered ring aza-ketones based on the choice of the rhodium catalyst (Scheme 1.10).

Scheme 1.10 Sequential allylic amination and hydroacylation reactions to access six- and seven-membered nitrogen heterocycles

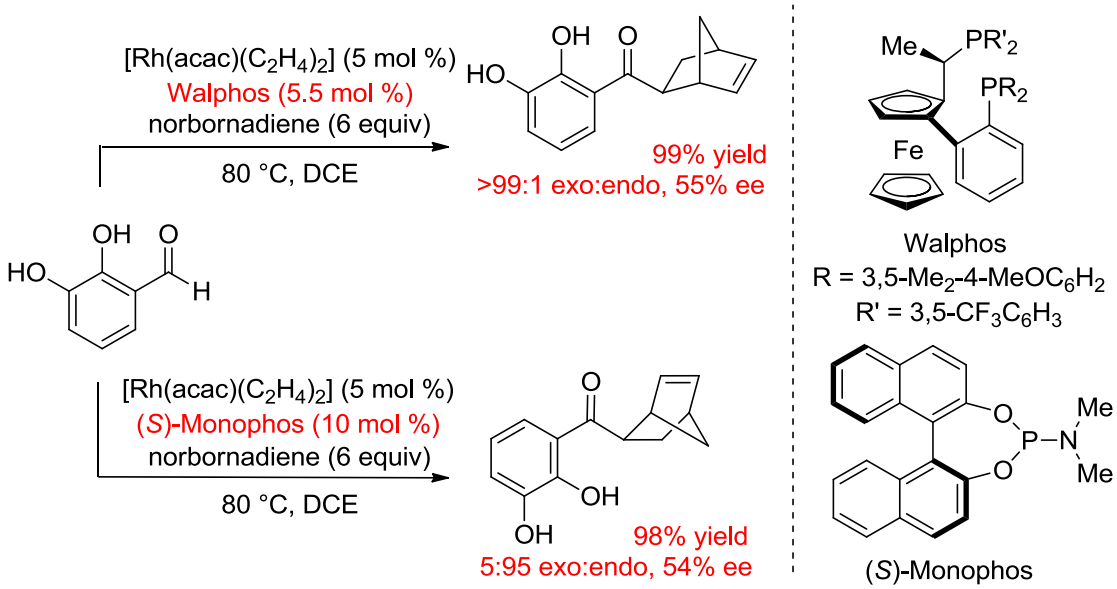


Intermolecular hydroacylation is considered to be more challenging compared to intramolecular hydroacylation owing to faster catalyst decomposition via reductive decarbonylation pathway.[1c] In 1978, Suggs revealed that decarbonylation could be suppressed by employing β-chelating aldehydes as that would lead to the formation of a highly strained four-membered metallacycle.[25]

Following Suggs' report, numerous studies with substrates containing various chelating functionalities including olefinic aldehydes,[26] salicyldehydes,[27] β-sulfido aldehydes[28] and (*N*-2-pyridyl)aldimines[29] were found to be effective in diminishing decarbonylative products. The first enantioselective intermolecular hydroacylation was reported by Bolm and co-workers in 2007 where salicyldehydes were coupled with strained alkenes like norbornadienes. A ligand-controlled switch in diastereoselectivity (*exo* vs *endo*) was observed by the authors in this report. *Exo*-selectivity was observed by use of the bidentate bisphosphine ligand Walphos, while the monodentate phosphoramidite ligand (*S*)-Monophos facilitated *endo*-selective hydroacylation by

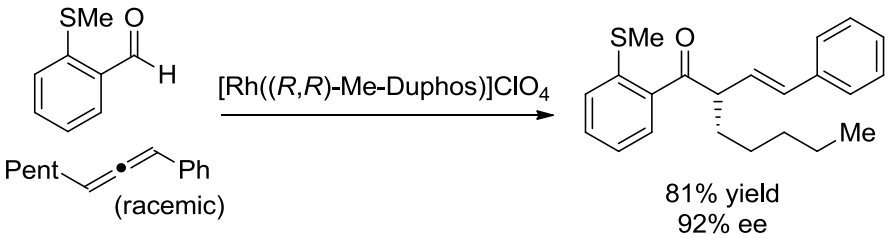
promoting norbornadiene to coordinate to the metal center in a bidentate manner (Scheme 1.11).[30]

Scheme 1.11 Intermolecular enantioselective hydroacylation of salicylaldehydes with norbornadienes



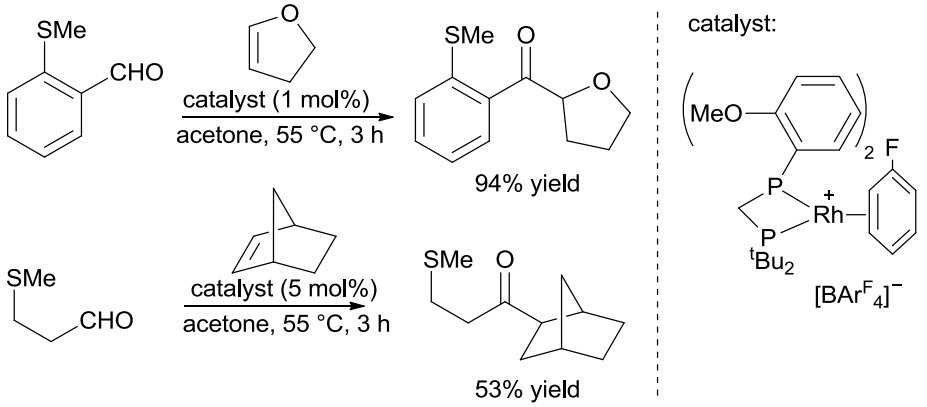
The Willis group in 2008 reported intermolecular hydroacylation of β-sulfur chelating aldehydes with racemic allenes with excellent regio- and stereocontrol in the presence of a cationic rhodium catalyst derived froma Rh(I) precursor and Me-Duphos ligand (Scheme 1.12).[31] The Willis and Weller groups further identified a catalyst for general linear-selective intermolecular hydroacylation of β-sulfur chelating aldehydes.[28, 32]

Scheme 1.12 Enantioselective intermolecular hydroacylation of allenes



Development in the Willis and Weller labs of catalysts containing small-bite-angle bisphosphine ligands with the general structure $[Rh(R_2PCH_2PR_2)(\eta^6\text{-}C_6H_5F)][BArF_4]$ has substantially improved the activity and stability of rhodium catalysts in intermolecular hydroacylation of alkenes with β-substituted aldehydes. Recently, these groups reported a catalyst with this general structure based on the non-symmetrical ligand $t\text{Bu}_2\text{PCH}_2\text{P}(o\text{-MeOC}_6\text{H}_4)_2$ that enables intermolecular hydroacylation of a wide range of functionalized internal alkenes with β-substituted aldehydes (Scheme 1.13).[33] Detailed mechanistic studies suggest that the $o\text{-MeOC}_6\text{H}_4$ group on phosphorous plays a key role in the stability and activity of the catalyst by increasing the rate of olefin insertion in to the rhodium hydride bond, which prevents decarbonylation by maintaining a low concentration of the acyl hydride intermediate. This catalyst system enables hydroacylations of a range of both 1,1- and 1,2-disubstituted alkenes, including cycloalkenes, cyclic and acyclic vinyl ethers, and α,β-unsaturated esters, with aryl and non-aryl aldehydes.

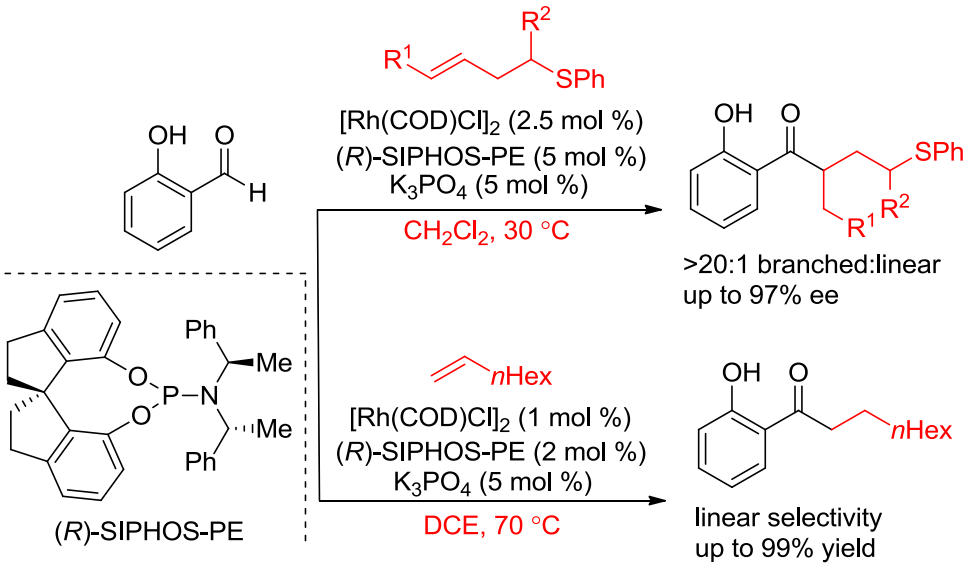
Scheme 1.13 Intermolecular hydroacylation of internal alkenes with β-substituted aldehydes



The Suemune and Dong groups in 2009 and 2010 independently reported enantioselective, intermolecular hydroacylation strategies with salicylaldehydes that generated α-

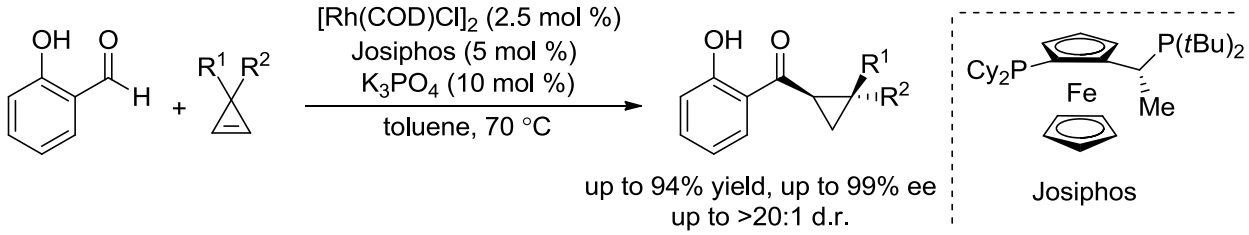
branched ketone products.[27b, 27d, 34] Suemune's work employed 1,5-hexadienes as the chelating alkene partner. While the coordinating heteroatom functionality in salicylaldehyde suppressed decarbonylation, coordinating dienes facilitated formation of branched products over linear ketone products (12:1 branched:linear selectivity with achiral ligand). However, hydroacylation in presence of the chiral ligand (*S*)-BINAP formed ketone products in 84% ee and 1:1 branched:linear selectivity.[27d] Dong's report employed homoallylic sulfides as the chelating alkene partner and generated ketone products in >20:1 branched:linear selectivity. Reactions in the presence of rhodium(I) precursor in combination with a chiral spiro-phosphoramidite ligand generated chiral, non-racemic branched ketone products with excellent enantio- and regioselectivity.[27b] Interestingly, the selectivity of the reaction switched with non-chelating alkene acceptors at higher temperature (70 °C) and formed highly linear ketone products under similar reaction conditions (Scheme 1.14).[35] These reactions encompassed a variety of both terminal and 1,2-disubstituted olefins.

Scheme 1.14 Intermolecular hydroacylation of salicylaldehydes with homoallylic sulfides and unactivated terminal alkenes



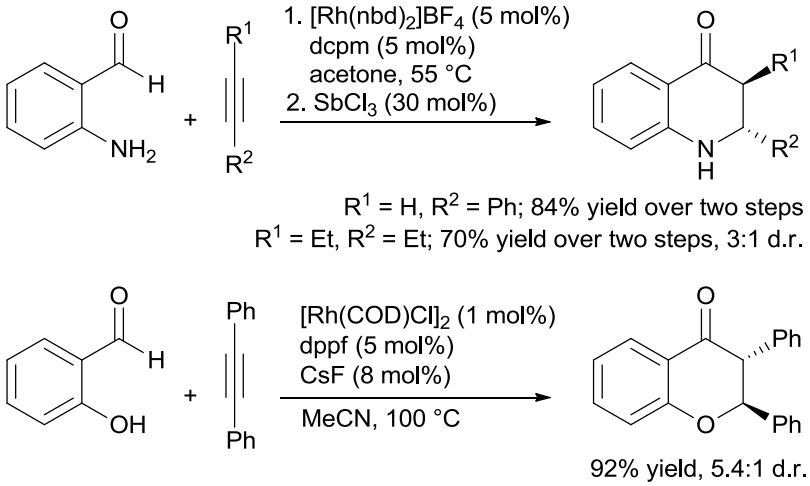
Dong and co-workers also reported highly enantio- and diastereoselective desymmetrization reactions via strain-release driven hydroacylation reactions of salicylaldehydes and strained cyclopropenes in the presence of a catalyst generated in situ from $[Rh(COD)Cl]_2$ and Josiphos ligand (Scheme 1.15).[27a]

Scheme 1.15 Enantio- and diastereoselective desymmetrization reaction of salicylaldehydes



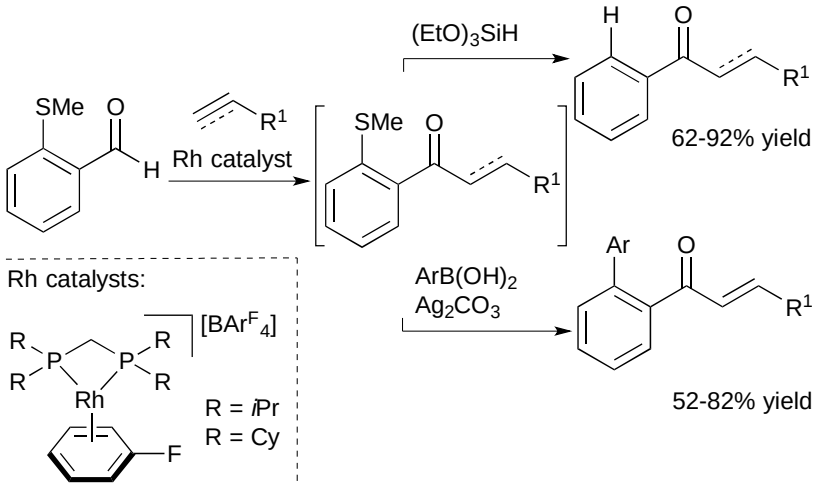
Aldehydes containing β-heteroatoms are privileged substrates in transition metal-catalyzed alkene and alkyne hydroacylation reactions due their ability to coordinate acylmetal hydride intermediates and suppress catalyst deactivation pathways. Often these β-chelating units are viewed as a limitation to the scope of alkene and alkyne hydroacylation processes. Recent reports from Willis and our laboratory demonstrated sequential and tandem reaction strategies that utilize these β-heteroatom functional groups as synthetic handles for the construction of dihydroquinolones and chromanones (Scheme 1.16). Willis and coworkers reported a sequential protocol for the hydroacylation of alkynes with 2-aminobenzaldehydes followed by Lewis acid-catalyzed, intramolecular aza-Michael addition that gave rapid access to dihydroquinolones.[36] Later, our group developed a tandem process for the synthesis of *trans*-2,3-disubstituted chroman-4-ones involving hydroacylation of symmetrical alkynes with salicylaldehydes followed by oxo-Michael addition reactions.[37] The *trans*-2,3-disubstituted chroman-4-ones could be readily fluorinated to form trans-3-fluoro-2,3-disubstituted chroman-4-ones in high yields (67-93%) and excellent diastereoselectivities (up to >20:1).

Scheme 1.16 Sequential and tandem alkyne hydroacylation aza- and oxo-Michael addition reactions to form dihydroquinolones and chromanones



Willis, Weller and co-workers also reported a traceless hydroacylation cascade involving Rh-catalyzed hydroacylation of alkenes, allenes, and alkynes coupled to a Rh-catalyzed, silane-mediated sulfide reduction (Scheme 1.17).[38] These cascades utilize the methyl sulfide functionality in the aldehyde substrate to stabilize the acylhydride intermediate formed during the hydroacylation cycle, and removed the chelating sulfide group in the Rh-catalyzed reduction. The same group also successfully sequenced alkyne hydroacylation to Suzuki coupling with the methyl sulphide group functioning as a pseudohalide for cross-coupling with aryl and alkenyl boronic acids.[39] The utility of this approach was further illustrated through a three-component hydroacylation/Suzuki coupling cascade using a single rhodium catalyst.

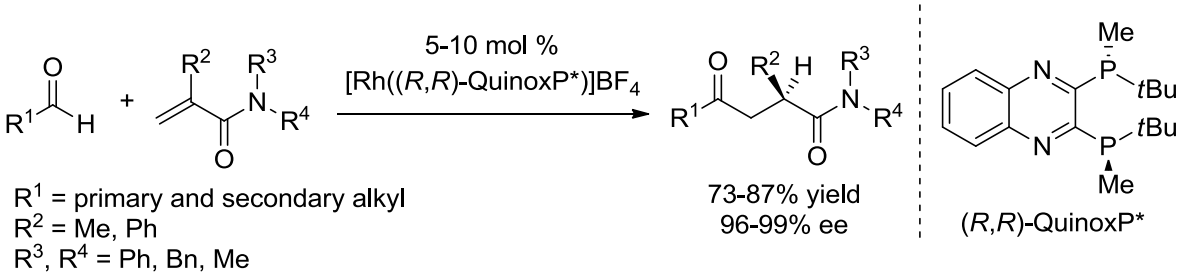
Scheme 1.17 Traceless chelation-assisted hydroacylation and alkyne hydroacylation/Suzuki coupling cascade



While much progress has been made in the development of alkene and alkyne hydroacylation reactions with aldehydes containing functional groups capable of coordinating the rhodium center, intermolecular alkene hydroacylations with simple aromatic and aliphatic aldehydes remain challenging.

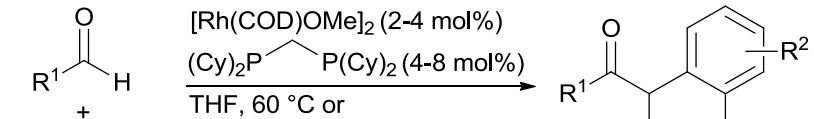
In 2009, Tanaka and co-workers reported a rare example of enantioselective intermolecular hydroacylation of aldehydes without any chelating functionality and acrylamide acceptors catalyzed by cationic a rhodium(I)/QuinoxP complex.[40] The presence of amide functionality in alkene acceptors was instrumental to the success of these reactions as the amide group is involved in stabilizing the acyl rhodium(III) intermediate (Scheme 1.18). The strategy worked great for aliphatic aldehydes without any chelating group and formed linear selective ketone products with excellent enantioselectivity (96-99%). Reaction of benzaldehyde was sluggish and formed the ketone product in modest yield and enantioselectivity.

Scheme 1.18 Enantioselective intermolecular hydroacylation of acrylamides and non-chelating aldehydes



Dong and co-workers recently reported highly branched-selective intermolecular hydroacylation reactions of a variety of non-chelating aliphatic, aromatic, and alkenyl aldehydes with ortho-vinylphenols (Scheme 1.19).[41] $[Rh(COD)(OMe)]_2$ and a small-bite-angle bisphosphine ligand, bis(dicyclohexylphosphino)methane (dcpm), combine with the *ortho*-vinylphenol substrate to generate an electron-rich and neutral rhodium complex that has a lower barrier for the turnover-limiting, non-directed oxidative addition of Rh to the aldehyde C-H bond. This catalyst promotes reactions of an array of non-chelating aldehydes with a wide range of substituted *ortho*-vinylphenols to form branched ketone products (typically >20:1 selectivity) in 50-99% yield. The α-aryl ketone products can readily undergo acid-catalyzed cyclocondensation to form benzofurans in high yields.

Scheme 1.19 Hydroacylation of vinylphenols with non-chelating aldehydes



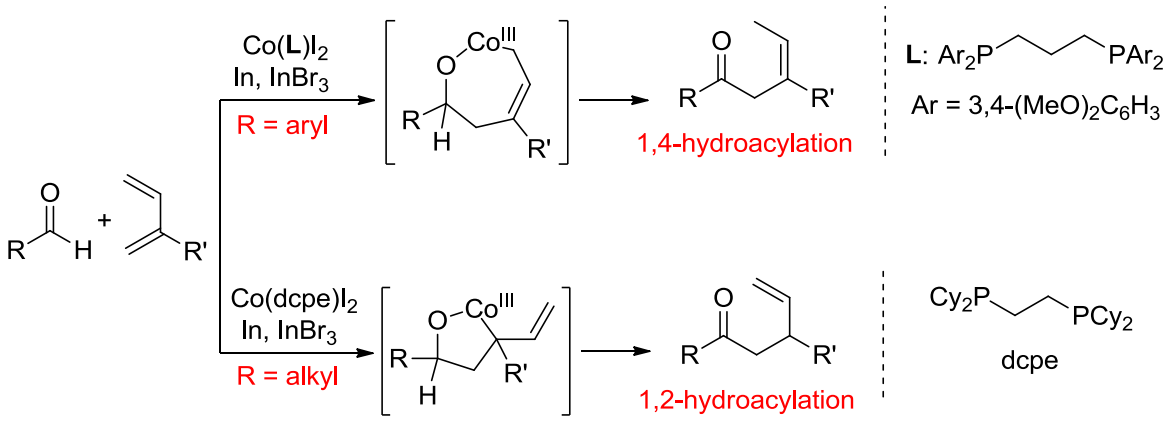
R^1	R^2	yield (%)	b/l
*i*Bu	4-NO_2	91	>20:1
Cy	3-Me	95	>20:1
Ph	6-OMe	88	19:1

1.3 Cobalt-Catalyzed Alkene Hydroacylation

The use of cobalt complexes as catalysts for alkene and alkyne hydroacylation is attractive due to the abundance and cost of cobalt relative to the 2nd- and 3rd-row group metals rhodium and iridium. Brookhart and coworkers demonstrated the first examples of cobalt-catalyzed alkene hydroacylations nearly twenty years ago.[42] However, the utility of cobalt catalysts in alkene hydroacylation reactions remained limited until a recent flurry of reports.

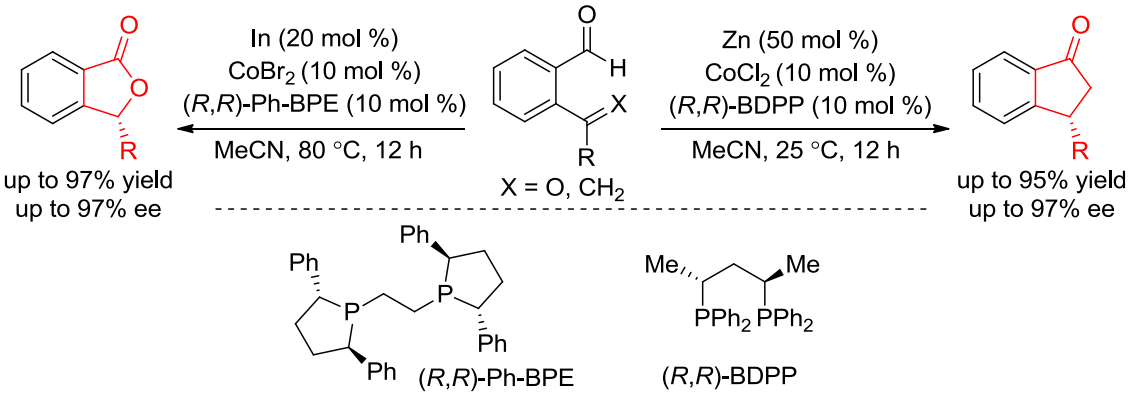
In 2014, Dong and coworkers developed Co-catalyzed hydroacylations of 1,3-dienes that occur with regioselectivity that is distinct from previously reported ruthenium catalysts.[43] Based on the identity of the bisphosphine ligand, cobalt complexes catalyze the C1-selective hydroacylations of 1,3-dienes with aromatic and aliphatic aldehydes to form products of 1,4-addition and 1,2-addition respectively (Scheme 1.20). These cobalt-catalyzed hydroacylations proceed in the absence of chelation assistance without significant decarbonylation of the aldehyde starting materials. Mechanistic studies support a pathway involving an oxidative cyclization step, which contrasts the traditional mechanism of transition metal-catalyzed hydroacylation and prevents decarbonylation of the aldehyde substrate by avoiding the formation of an acylmetal hydride intermediate.

Scheme 1.20 Cobalt-catalyzed intermolecular hydroacylation of 1,3-dienes



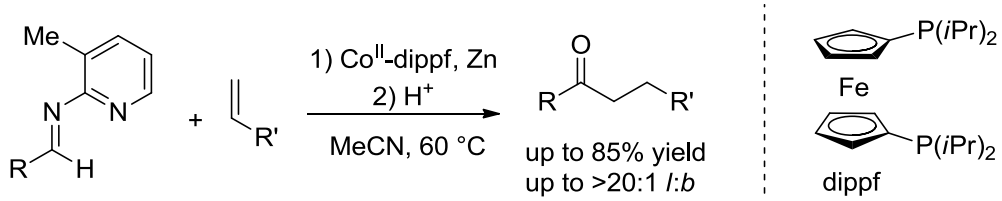
Yoshikai and Yang reported the first enantioselective, Co-catalyzed intramolecular hydroacylations of alkenes and ketones.[44] A catalyst generated by in situ reduction of a Co(II)-BDPP complex with zinc metal promotes highly enantioselective hydroacylations of 2-alkenylbenzaldehydes to form indanone derivatives (Scheme 1.21). Although the scope of enantioselective, Co-catalyzed alkene hydroacylation is limited relative to related enantioselective, rhodium-catalyzed hydroacylations of 2-alkenylbenzaldehydes, this work is likely to serve as a foundation for the development of new Co-catalyzed, enantioselective alkene hydroacylation reactions.

Scheme 1.21 Enantioselective hydroacylation of 2-alkenylbenzaldehydes



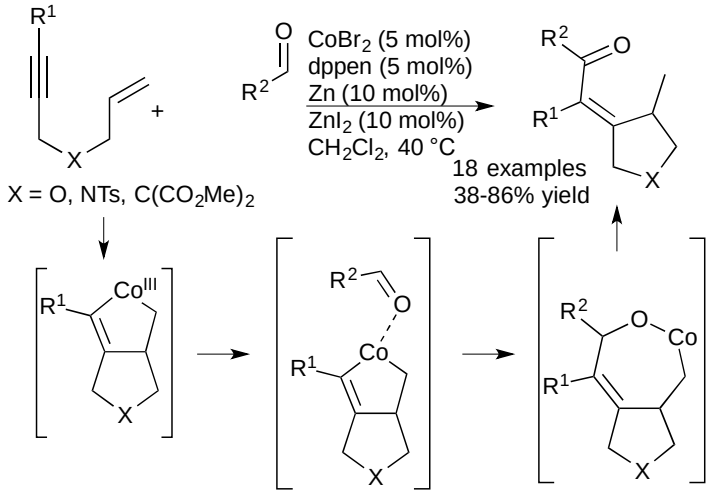
Yoshikai and coworkers subsequently developed chelation-assisted, Co-catalyzed intermolecular hydroacylation of alkenes with aldimines generated from 2-amino-3-methylpyridine.[45] The formal hydroacylation process encompasses a wide range of alkenes, including styrenes, vinylsilanes, allylsilanes, and simple alkenes, and forms, after hydrolysis, the corresponding ketone products in moderate-to-good yields with high linear-to-branched ratios (Scheme 1.22).

Scheme 1.22 Cobalt-catalyzed hydroacylation of alkenes with aldimines



Cheng and coworkers recently reported a cobalt-catalyzed cyclization of 1,6-enynes with aldehydes (Scheme 1.23).[46] The scope of these reactions included a variety of N-, O-, and malonate-tethered enynes and an array of aromatic, heterocyclic, and aliphatic aldehydes. The formal hydroacylation is proposed to proceed via a novel cobaltacycle intermediate that is generated from the reaction of the enyne substrate with the cobalt catalyst. Interestingly, the cobalt catalyst system demonstrated switchable C-H functionalization activity depending on the electronic nature of the ancillary ligand enabling the authors to achieve either hydroacylation or hydroarylation processes.

Scheme 1.23 Cobalt-catalyzed formal hydroacylation of enynes



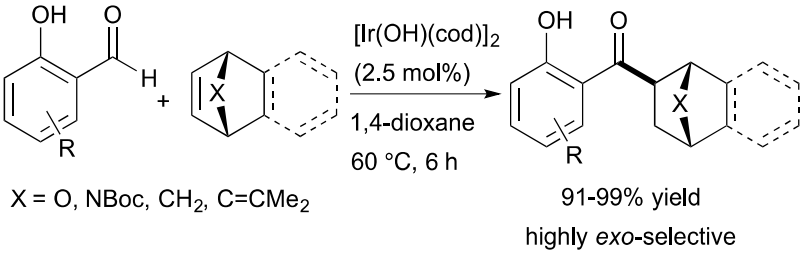
1.4 Ruthenium-, Iridium- and Nickel-Catalyzed Alkene Hydroacylation

Although rhodium complexes are the most common transition metal catalysts employed for alkene hydroacylation reactions, the competition between hydroacylation and decarbonylation pathways observed with rhodium catalysts has led to a growing interest in the use of alternative transition metals for these processes. In particular, recent developments have been made in ruthenium-, iridium- and nickel-catalyzed alkene and alkyne hydroacylations.

Work on Ru-catalyzed hydroacylation of dienes by Krische and coworkers showed that these processes do not proceed through an acylmetal hydride intermediate.[47] The absence of this intermediate precludes the decarbonylation pathway that has historically plagued olefin hydroacylation reactions.

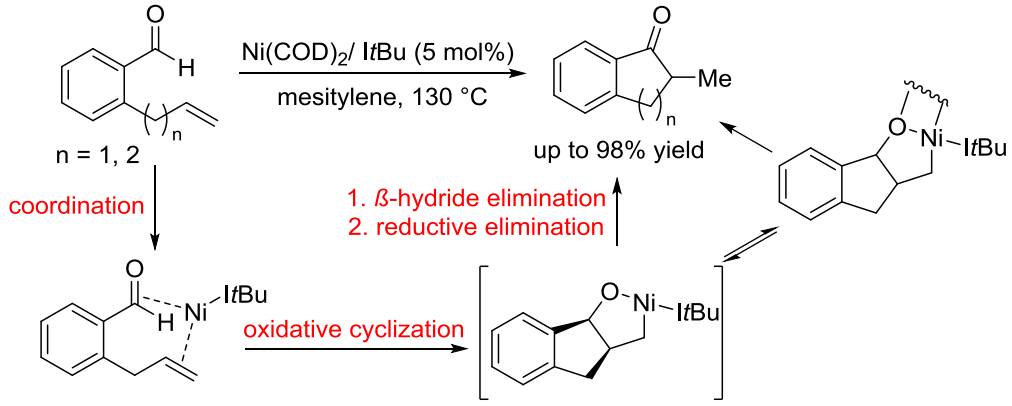
Recently, Nagamoto and Nishimura reported the iridium-catalyzed hydroacylation of bicyclic alkenes with salicylaldehydes (Scheme 1.24).[48] A readily available iridium complex, $[Ir(OH)(cod)]_2$, catalyzes the hydroacylation of a variety of bicyclic alkenes with salicylaldehydes, and the ketone products are formed in high yields (91-99%) with nearly perfect *exo*-selectivity. The authors note that in contrast to the previously reported rhodium-catalyzed hydroacylation of norbornadiene with salicylaldehyde,[49] the iridium-catalyzed reaction is highly *exo*-selective and generates the mono-acylation product in 85% yield. The authors also demonstrate an enantioselective variant of these reactions using an iridium catalyst containing a chiral diene ligand to form the corresponding ketone product in 97% yield with 86% ee.

Scheme 1.24 Iridium-catalyzed hydroacylation of bicyclic alkenes



Reports on nickel-catalyzed alkene hydroacylation are becoming more frequent. In 2012, Ogoshi and coworkers reported *exo*-selective hydroacylations of *ortho*-allyl- and *ortho*-homoallylbenzaldehydes in the presence of a Ni(0)/NHC complex (Scheme 1.25).[50] α-Substituted indanones and tetralones are readily prepared from these reactions, including products containing a quaternary carbon center.

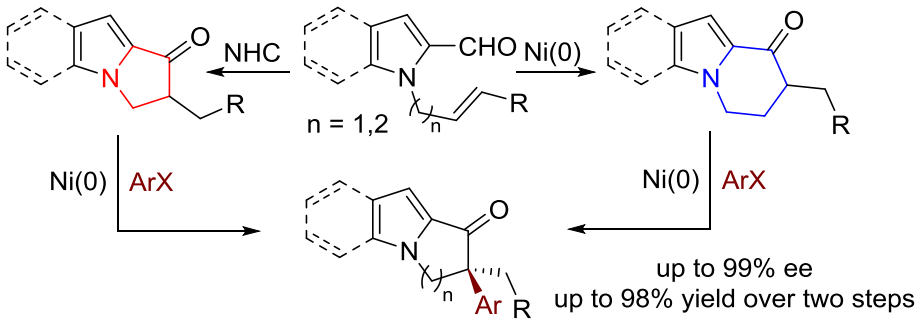
Scheme 1.25 Nickel-catalyzed hydroacylation of o-allyl- and o-homoallylbenzaldehydes



Inspired by Ogoshi's report on intramolecular hydroacylation to generate carbocyclic ketones, our group has recently reported *exo*-selective, intramolecular nickel(0)-catalyzed hydroacylation of *N*-allylindole, *N*-homoallylindole- and *N*-homoallylpyrrole-2-carboxaldehydes that generated a range of α-substituted polycyclic, nitrogen containing heterocyclic ketones. The *exo*-selective nickel(0)-catalyzed hydroacylation was further coupled with enantioselective, intermolecular nickel(0)-catalyzed α-arylation/heteroarylation reactions that provided access to

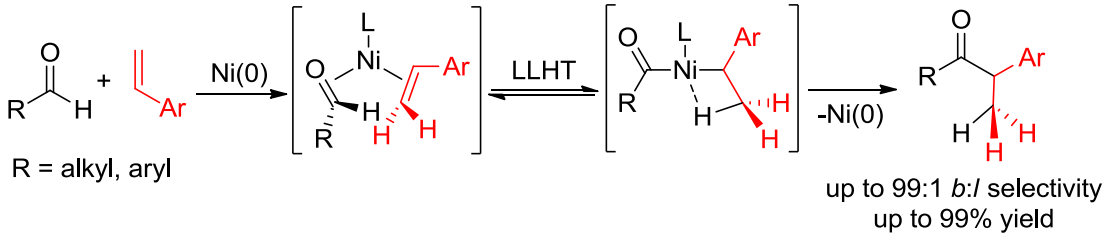
a wide range of highly enantioenriched nitrogen-containing heterocyclic ketones with α-chiral quaternary stereocenters (Scheme 1.26).[51] These sequential hydroacylation and α-arylation studies will be discussed in detail in Chapter 4 of this dissertation.

Scheme 1.26 Sequential *exo*-selective hydroacylation and enantioselective α-arylation reaction



Recently, Xu, Zhou and coworkers reported intermolecular hydroacylation reactions of styrenes and simple aldehydes that do not require any chelating functionality.[52] These reactions occur in the presence of a catalyst generated in situ from a 1:3 mixture of $Ni(COD)_2$ and PCy_3 ligand and form highly branched-selective ketone products (up to >99:1) in high yields (up to 99%). Both computational studies and experimental evidence suggests involvement of a ligand-to-ligand hydrogen transfer (LLHT) pathway that includes the aldehyde hydrogen transfer to a coordinated alkene to form an acyl-nickel-benzyl intermediate without oxidative addition (Scheme 1.27).

Scheme 1.27 Nickel-catalyzed intermolecular hydroacylation of styrenes with simple aldehydes via LLHT pathway



1.5 Conclusions

The development of new transition metal-catalyzed alkene hydroacylation reactions has progressed rapidly in the past few years. Rhodium-catalyzed hydroacylation remains an active area of study with new intermolecular alkene and alkyne hydroacylation reactions and applications to the synthesis of new heterocyclic ketones emerging in recent years. However, the field of alkene and alkyne hydroacylation is rapidly expanding beyond rhodium catalysts. Cobalt catalysts hold great promise for the discovery of new hydroacylation reactions and as a replacement for traditional rhodium catalysts. In addition, ruthenium, iridium, and nickel catalysts of alkene hydroacylation have emerged to improve upon or complement previous catalyst systems.

1.6 References

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CHAPTER 2

RHODIUM-CATALYZED ENANTIOSELECTIVE INTRAMOLECULAR HYDROACYLATION AS A ROUTE TO POLYCYCLIC NITROGEN HETEROCYCLES: CONSTRUCTION OF FIVE- AND SIX-MEMBERED RINGS IN THE ABSENCE OF CHELATION ASSISTANCE

Modified from a paper published in *Chemical Communications*[1] and a paper published in *Organic Letters*[2]

Avipsa Ghosh, Xiang Wei Du, and Levi M. Stanley*

2.1 Abstract

We report catalytic, enantioselective intramolecular hydroacylation of *N*-vinylindole-2-carboxaldehydes. These hydroacylation reactions occur in the presence of a readily accessible rhodium catalyst and form chiral, non-racemic 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-ones in high yields with excellent enantioselectivities. The dihydropyrroloindolone products can be readily transformed to dihydropyrroloindoles that are core structures present in a variety of natural products and biologically relevant compounds. This methodology could be extended to hydroacylations of *N*-allylindole- and *N*-allylpyrrole-2-carboxaldehydes in construction of six-membered rings that generated 7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)ones and 6,7-dihydroindolizin-8(5*H*)-ones in moderate to high yields with excellent enantioselectivities. In contrast to many alkene hydroacylations that form six-membered rings, these *endo*-selective annulative processes occur in the absence of ancillary functionality to stabilize the acylrhodium(III) hydride intermediate.

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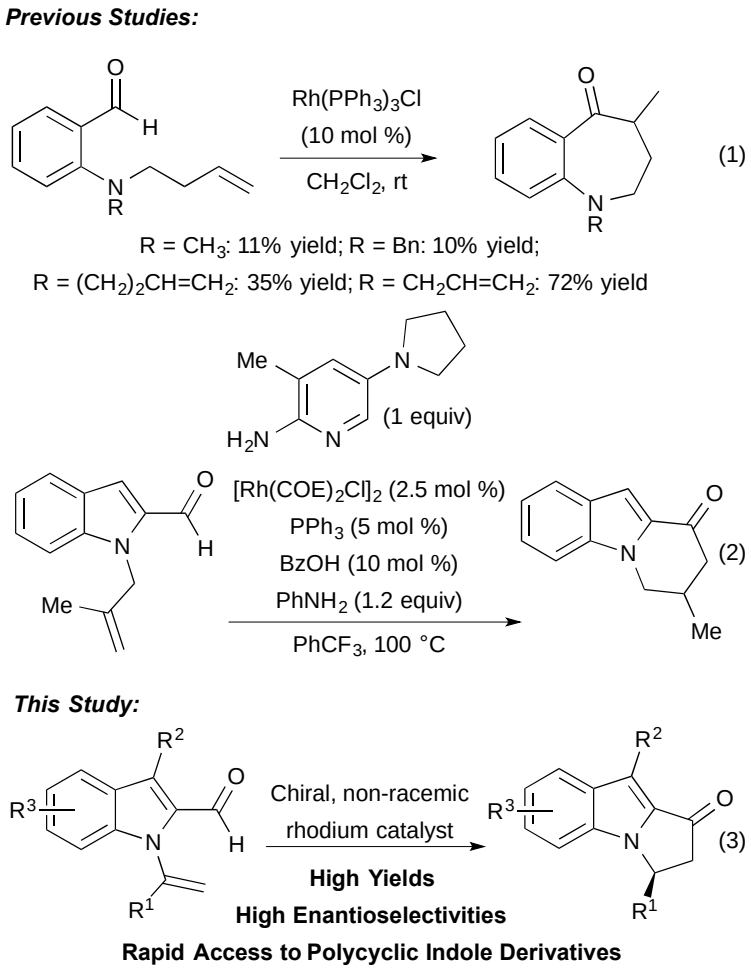
2.2 Introduction

Chemical reactions that couple C-H bond activation with carbon-carbon bond formation and those that generate nitrogen heterocycles from simple starting materials are two of the most important classes of reactions in modern organic, medicinal, and materials chemistry. Intramolecular hydroacylation of alkenes in the presence of transition metal catalysts is a well-known process that couples C-H bond activation with carbon-carbon bond formation to form synthetically valuable ketone products.[1] Hydroacylations of substituted 4-pentenals and 2-vinylbenzaldehydes to form cyclopentanones are common[2] and occur with high enantioselectivities in the presence of chiral, non-racemic catalysts.[3] Recent reports have also shown that six-, seven- and eight-membered carbocycles and heterocycles are accessible from intramolecular alkene hydroacylation reactions.[4] However, alkene hydroacylations to generate nitrogen-containing heterocycles are rare.[4e,5,6]

To date, there are only two reports of alkene hydroacylation to generate nitrogen-containing heterocycles. Bendorf and co-workers reported amine-directed, intramolecular hydroacylation of 2-(homoallylamino)benzaldehydes (Scheme 2.1, eq 1).[5a] These amine-directed hydroacylation reactions occur in the presence of 10 mol % of Wilkinson's catalyst, and the efficiency of the reactions is greatly influenced by the identity of the substituents on the nitrogen atom. Recently, Douglas reported hydroacylation of *N*-allylindole-2-carboxaldehydes and *N*-allylpyrrole-2-carboxaldehydes (Scheme 2.1, eq 2).[5b] These hydroacylation reactions involve *in situ* formation of imines to install chelating functionality to stabilize the resulting iminorhodium(III) hydride intermediate.[2j,7] The heterocyclic ketone

products are formed in good yields, but the requirement for chelation assistance leads to poor atom economy and efforts to develop a highly enantioselective catalyst were unsuccessful. Although reports by Bendorf and Douglas provide an entry into practical alkene hydroacylation reactions to generate nitrogen containing heterocycles, the opportunity exists to form nitrogen heterocycles by alkene hydroacylations that occur 1) with high enantioselectivity and 2) without the need for strategies to stabilize the acylrhodium(III) hydride intermediate.

Scheme 2.1 Synthesis of nitrogen heterocycles by intramolecular alkene hydroacylation



The potential for enantioselective intramolecular hydroacylation to create a rapid entry into dihydropyrroloindoles led us to study Rh-catalyzed hydroacylation of *N*-vinylindole-2-carboxaldehydes (Scheme 2.1, eq 3). Dihydropyrroloindoles are core structures of a variety of indole alkaloids including yuremamine[8,9] and antimalarial bis-indoles from the *Flindersia* species, such as the isoborreverines (Figure 2.1).[10] Thus, we report the synthesis of highly enantioenriched 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indolones by intramolecular hydroacylation of *N*-vinylindole-2-carboxaldehydes in the presence of a rhodium catalyst prepared *in situ* from commercially available precursors.

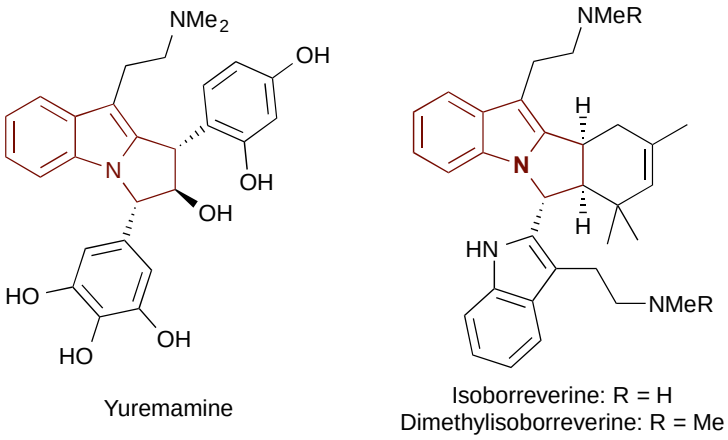


Figure 2.1 Dihydropyrroloindoles as Core Elements of Indole Alkaloids

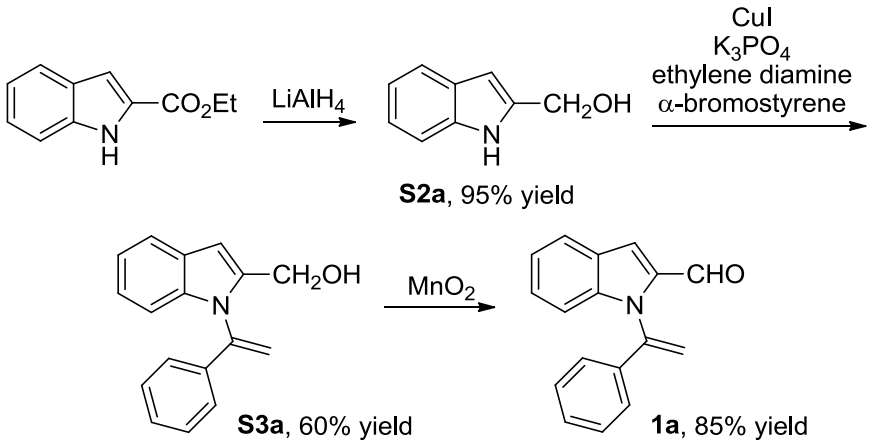
2.3 Results and Discussion

2.3.1 Synthesis of 1-(1-phenylvinyl)-1*H*-indole-2-carboxaldehyde 1a

1-(1-phenylvinyl)-1*H*-indole-2-carboxaldehyde **1a** was synthesized from ethyl indole-2-carboxylate in 48% yield over three steps (Scheme 2.2). The ester functionality in ethyl indole-2-carboxylate was reduced in presence of $LiAlH_4$ to form (1*H*-indol-2-yl)methanol **S2a** in 95% yield. (1*H*-Indol-2-yl)methanol **S2a** was coupled with α-bromostyrene in presence of copper(I) iodide, ethylenediamine and potassium phosphate

in 1,4-dioxane at 110 °C to form (1-(1-phenylvinyl)-1*H*-indol-2-yl)methanol **S3a** in 60% yield. (1-(1-Phenylvinyl)-1*H*-indol-2-yl)methanol **S3a** was further oxidized in presence of activated MnO_2 in acetonitrile to generate 1-(1-phenylvinyl)-1*H*-indole-2-carboxaldehyde **1a** in 85% yield.[11]

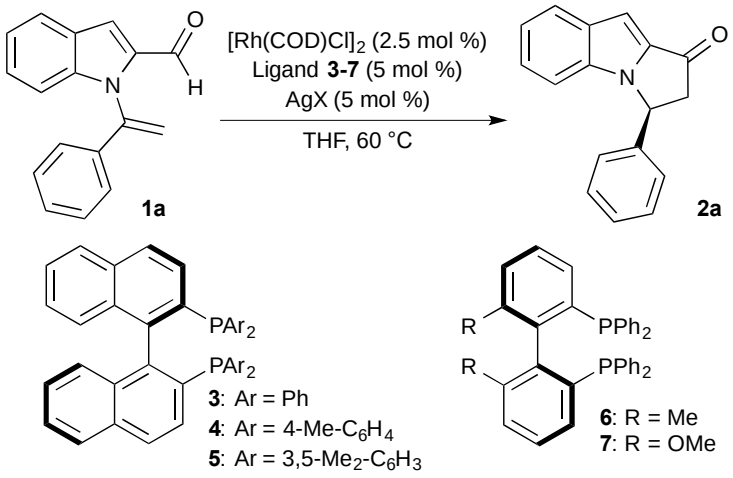
Scheme 2.2 Synthesis of 1-(1-phenylvinyl)-1*H*-indole-2-carboxaldehyde **1a**



2.3.2 Identification of Reaction Conditions for Rh-Catalyzed Intramolecular Hydroacylation of 1a

Initial studies to develop catalytic, enantioselective hydroacylations of *N*-vinylindole-2-carboxaldehydes were guided by hydroacylations of 2-vinylbenzaldehydes catalyzed by a rhodium(I)-BINAP complex. To test whether hydroacylation of *N*-vinylindole-2-carboxaldehydes could occur with similar catalysts, we studied the reaction of 1-(1-phenylvinyl)-1*H*-indole-2-carboxaldehyde **1a** catalyzed by complexes prepared *in situ* from $[Rh(COD)Cl]_2$, (*R*)-BINAP **3**, and a variety of silver salts having counteranions with varying degrees of coordinating strength (Table 2.1, entries 1-7). We found that the hydroacylation of **1a** did not occur in THF at 60 °C when the rhodium(I) catalysts contained

Table 2.1 Identification of catalysts for Rh-catalyzed hydroacylation of 1-(1-phenylvinyl)-1*H*-indole-2-carboxaldehyde **1a**[a]



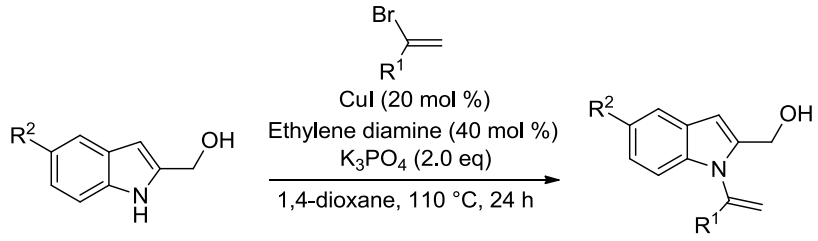
Entry	AgX	Ligand	Conversion (%)[b]	Yield (%)[c]	ee (%)[d]
1	--	**3**	0	--	--
2	$AgNO_3$	**3**	0	--	--
3	AgOMs	**3**	0	--	--
4	$AgClO_4$	**3**	96	10	ND
5	$AgBF_4$	**3**	75	54	94
6	$AgPF_6$	**3**	72	49	91
7	$AgSbF_6$	**3**	99	61	95
8	$AgBF_4$	**4**	95	75	96
9	$AgBF_4$	**5**	42	35	98
10	$AgBF_4$	**6**	80	63	97
11	$AgBF_4$	**7**	95	90	99

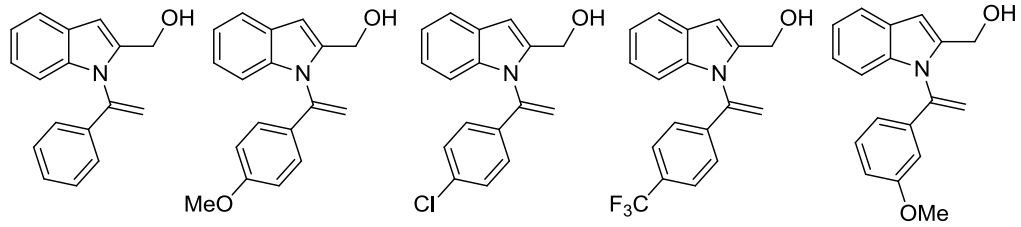
[a] **1a** (0.100 mmol), $[Rh(COD)Cl]_2$ (0.0025 mmol), ligand **3-7** (0.0050 mmol), $AgBF_4$ (0.0050 mmol) and THF (0.7 mL). [b] Determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. [c] Isolated yield of **2a**. [d] Determined by chiral HPLC analysis.

coordinating counteranions, such as chloride, nitrate, and mesylate (entries 1-3). However, the hydroacylation of **1a** formed dihydropyrroloindolone **2a** in low to modest yield when the rhodium catalyst contained a weakly coordinating counteranion. The hydroacylation of **1a** catalyzed by a rhodium catalyst with a perchlorate counteranion occurred to high conversion, but formed **2a** in low yield (entry 4). In contrast, the reaction of **1a** generated dihydropyrroloindolone **2a** in 49-61% yield in the presence of rhodium complexes with tetrafluoroborate, hexafluorophosphate, and hexafluoroantimonate counteranions (entries 5-7). Although the catalyst containing a hexafluoroantimonate counterion led to the highest yield of **2a**, this catalyst also promoted undesired side reactions. We chose to continue our study with rhodium catalysts containing a tetrafluoroborate counterion since we observed less decomposition of **1a** with this catalyst system.

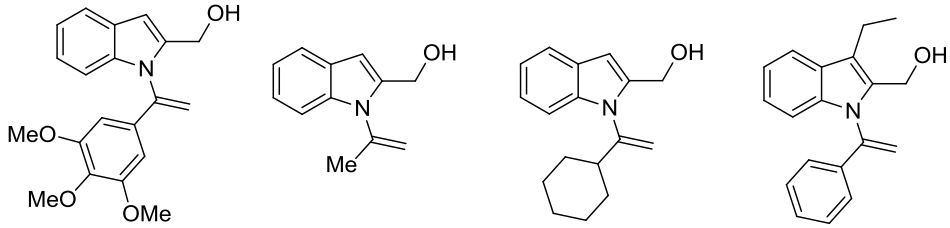
To improve the yield and selectivity of our model reaction, we studied the hydroacylation of **1a** in the presence of catalysts prepared from $[Rh(COD)Cl]_2$, $AgBF_4$, and a selection of aromatic bisphosphine ligands **3**-**7** containing axial chiral backbones (Table 2.1, entries 5, 8-11). The rhodium(I) complex of (*R*)-Tol-BINAP **4** catalyze the hydroacylation of **1a** to form **2a** in higher yield than the rhodium complex of the parent (*R*)-BINAP ligand, while the rhodium(I) complex of (*R*)-Xyl-BINAP catalyzes the formation of **2a** in lower yield (compare entries 8 and 9 with entry 5). Rhodium complexes of both (*R*)-Tol-BINAP and (*R*)-Xyl-BINAP catalyze the formation of **2a** with higher enantioselectivity. The reaction of **1a** occurred with the best combination of yield and enantioselectivity in the presence of rhodium complexes of (*S*)-Me-BIPHEP and (*S*)-

Scheme 2.3 Synthesis of (1-vinyl-1*H*-indol-2-yl)methanols **S3a-S3p**

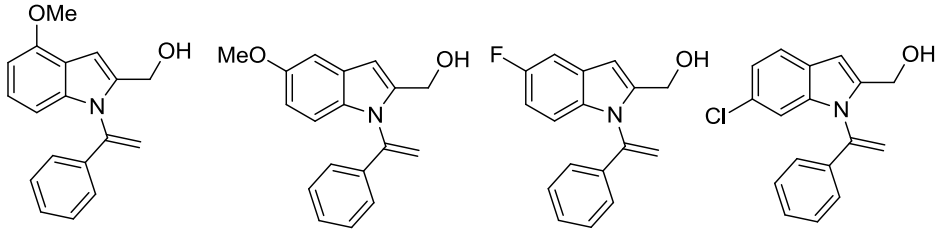




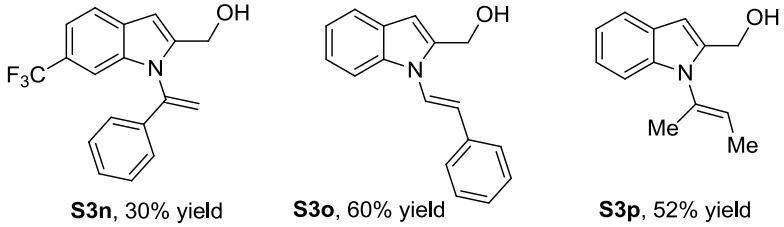
S3a, 60% yield **S3b**, 37% yield **S3c**, 20% yield **S3d**, 17% yield **S3e**, 10% yield



S3f, 12% yield **S3g**, 52% yield **S3h**, 9% yield **S3i**, 37% yield

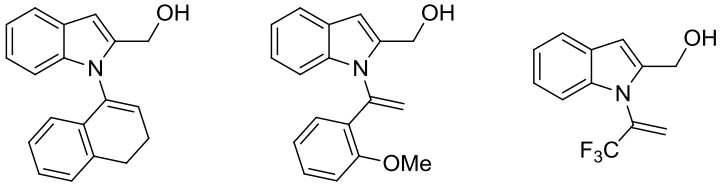


S3j, 48% yield **S3k**, 52% yield **S3l**, 29% yield **S3m**, 53% yield



S3n, 30% yield **S3o**, 60% yield **S3p**, 52% yield

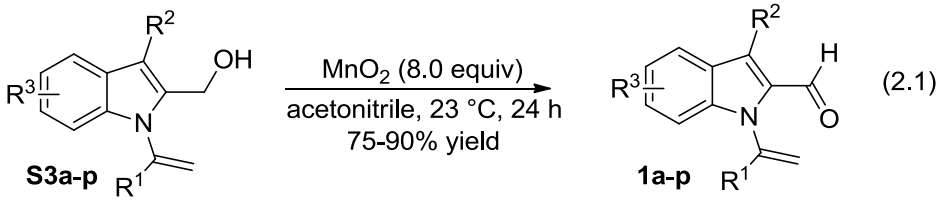
Unsuccesful examples:



MeO-BIPHEP (entries 10-11). The hydroacylation of **1a** catalyzed by rhodium(I) complex of (*S*)-MeO-BIPHEP formed dihydropyrroloindolone **2a** in 90% yield with 99% ee (entry 11).

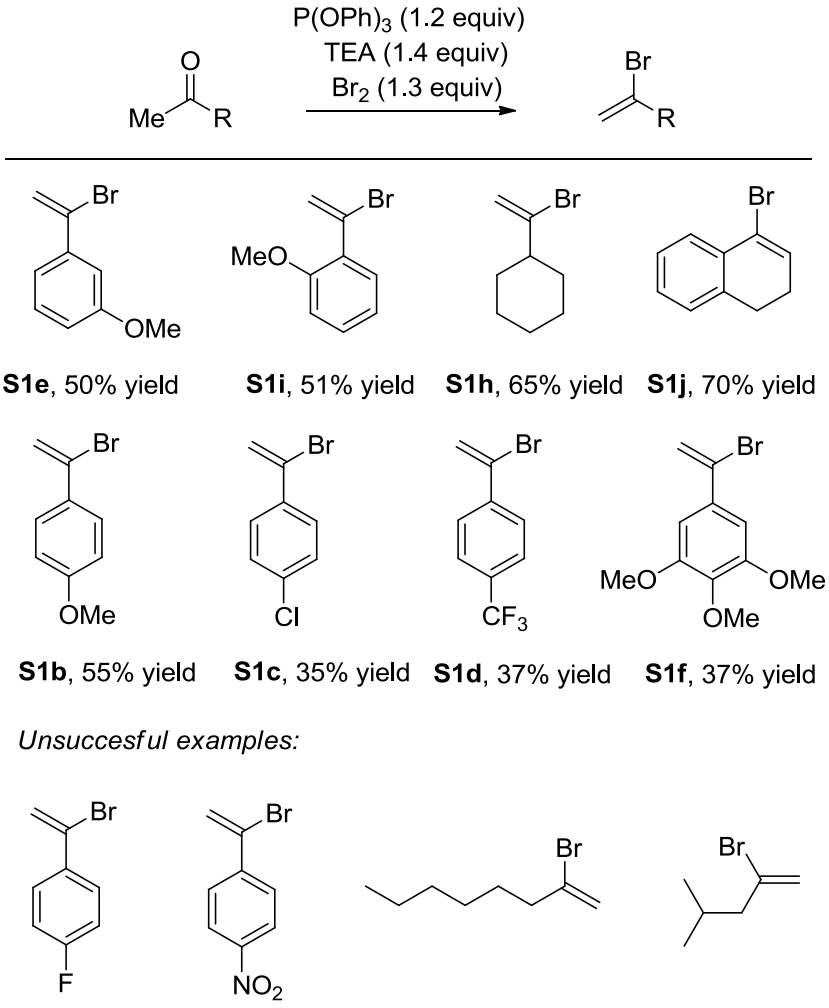
2.3.3 Synthesis of *N*-Vinylindole-2-carboxaldehydes 1a-p

A variety of *N*-vinylindole-2-carboxaldehydes were synthesized by coupling (1*H*-indol-2-yl)methanols with substitutions at 3-,4-,5- and 6- position in the indole ring with various 1,1-disubstituted, 1,2-disubstituted, 1,1,2-trisubstituted α-bromoalkenes in presence of copper iodide, ethylene diamine and potassium phosphate in 1,4-dioxane (Scheme 2.3).[11] These isolated (1-vinyl-1*H*-indol-2-yl)methanols were subjected to MnO_2 oxidation reaction conditions to obtain *N*-vinylindole-2-carboxaldehydes **1a**-**1p** in 75-90% yields (eq 2.1). Various α-bromoalkenes were synthesized from the corresponding methyl ketone starting material in presence of triphenyl phosphite, triethylamine and bromine in 35-70% yield (Scheme 2.4).[12] 5-Methoxy-, 6-chloro-, (6-(trifluoromethyl)-1*H*-indol-2-yl)methanols were synthesized from 3-methoxy-, 4-chloro-, 4-trifluoromethylbenzaldehydes over 5 steps in 18-32% yields (Scheme 2.5).[13]

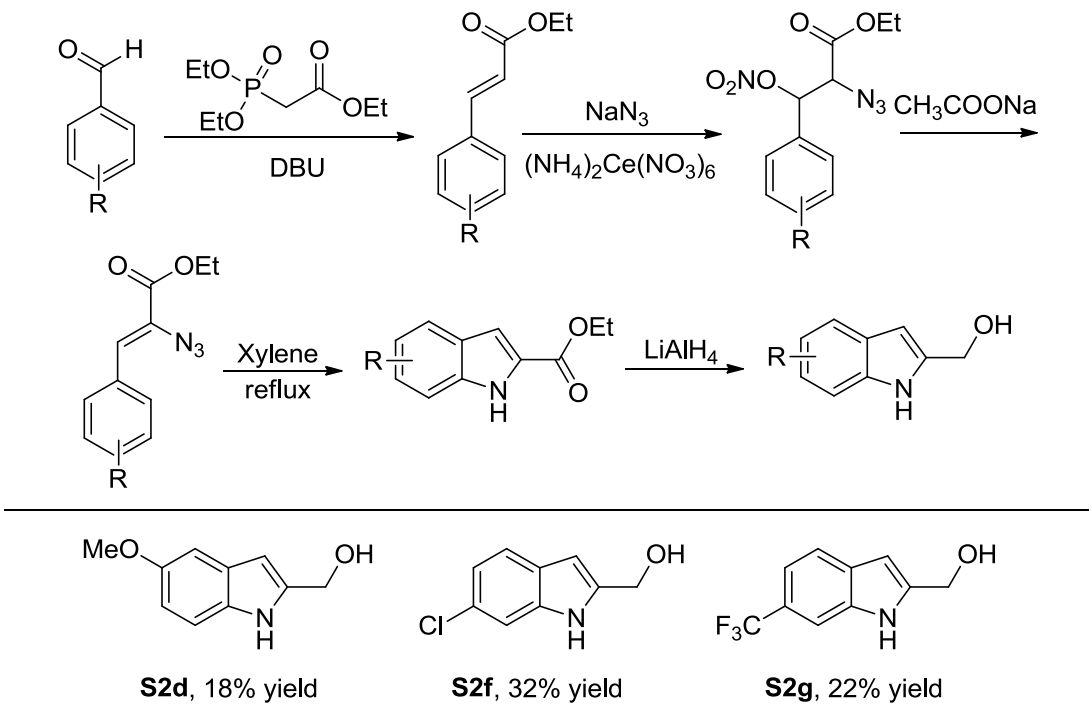


(2.1)

Scheme 2.4 Synthesis of α-bromoalkenes



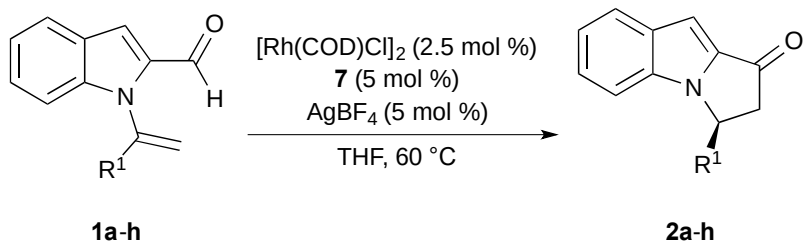
Scheme 2.5 Synthesis of 5- and 6-substituted-(1*H*-indol-2-yl)methanols



2.3.4 Rh-Catalyzed Intramolecular Hydroacylation of *N*-Vinylindole-2-carboxaldehydes: Substrate Scope

The results of intramolecular hydroacylations of *N*-vinylindole-2-carboxaldehydes containing a range of substituted vinyl units are shown in Table 2.2. The hydroacylations of *N*-vinylindole-2-carboxaldehydes containing electron-neutral or electron-rich aryl groups at the 1-position of the *N*-vinyl moiety gave the corresponding dihydropyrroloindolones **2a** (R^1 = Ph) and **2b** (R^1 = 4-MeO-C_6H_4) in high yields (90-99%) with 99% enantiomeric excess (entries 1 and 2). The hydroacylation of *N*-vinylindole-2-carboxaldehydes substituted with electron-deficient aryl groups at the 1-position of the vinyl group formed dihydropyrroloindolones **2c** (R^1 = 4-Cl-C_6H_4) and **2d** (R^1 = 4-F_3C-C_6H_4) in lower yield (68% and 30%, entries 3 and 4). However, these hydroacylations occurred with excellent enantioselectivity (98-99% ee), and the yield of

Table 2.2 Rhodium-catalyzed enantioselective hydroacylation of *N*-vinylindole-2-carboxaldehydes **1a-h**[a]



1a-h **2a-h**

Entry	R_1 (**1**)	**2**	Yield (%)[b]	ee (%)[c]
1	Ph (**1a**)	**2a**	90	99
2	4-MeO-C_6H_4 (**1b**)	**2b**	99	99
3	4-Cl-C_6H_4 (**1c**)	**2c**	68	98
4	4-F_3C-C_6H_4 (**1d**)	**2d**	30	99
5[d]	4-F_3C-C_6H_4 (**1d**)	**2d**	70	99
6	3-MeO-C_6H_4 (**1e**)	**2e**	92	98
7	3,4,5-$(MeO)_3$-C_6H_2 (**1f**)	**2f**	82	99
8	Me (**1g**)	**2g**	99	99
9	Cyclohexyl (**1h**)	**2h**	20	97
10[e]	Cyclohexyl (**1h**)	**2h**	45	95

[a] **1a-h** (0.100 mmol), $[Rh(COD)Cl]_2$ (0.0025 mmol), ligand **7** (0.0050 mmol), $AgBF_4$ (0.0050 mmol) and THF (0.7 mL). [b] Isolated yield of **2**. [c] Determined by chiral HPLC analysis. [d] Reaction run in the presence of 10 mol % catalyst. [e] Reaction run at 100 °C in 1,4-dioxane.

2d improved to 70% when the reaction was run in the presence of 10 mol % rhodium catalyst (entry 5).

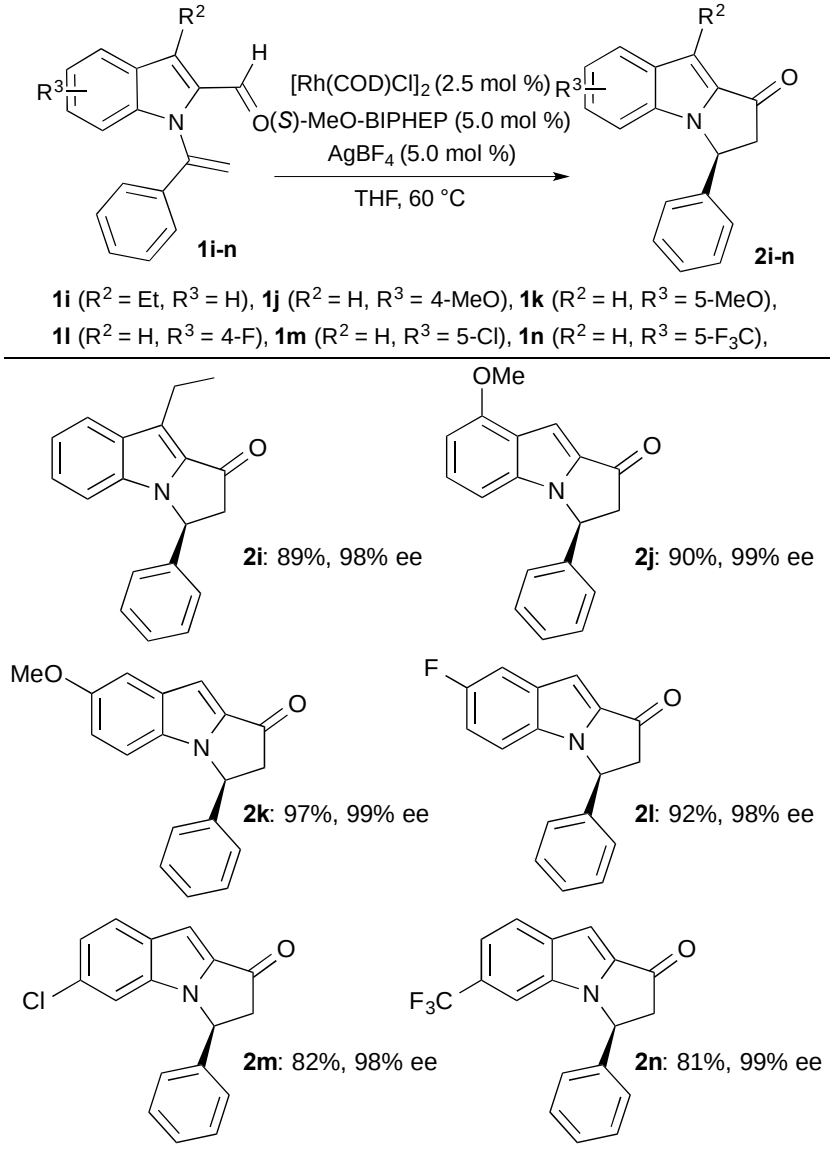
N-Vinylindole-2-carboxaldehydes containing *meta*-substituted aryl groups at the 1-position of the *N*-vinyl moiety are also excellent substrates for these intramolecular

hydroacylations. *N*-vinylindole-2-carboxaldehydes **1e** (R^1 = 3-MeO-C_6H_4) and **1f** (R^1 = 3,4,5-$(MeO)_3$-C_6H_2) reacted to form dihydropyrroloindolones **2e** and **2f** in 82-92% yield with 98-99% ee (entries 6 and 7). We were unable to generate data on hydroacylations of *N*-vinylindole-2-carboxaldehydes containing *ortho*-substituted aryl groups at the 1-position of the *N*-vinyl moiety because Ullmann-type coupling of appropriately substituted indoles and α-halogenated styrenes were unproductive in our hands.

Reactions of *N*-vinylindole-2-carboxaldehydes containing alkyl groups at the 1-position of the *N*-vinyl moiety also occurred with high enantioselectivity. The reaction of **1g** (R^1 = Me) formed **2g** in nearly quantitative yield and nearly perfect enantioselectivity (entry 8). The reaction of *N*-vinylindole-2-carboxaldehyde **1h** bearing a bulky cyclohexyl group formed the corresponding dihydropyrroloindole **2h** with 97% enantiomeric excess (entry 9). However, the yield of **2h** was low when the reaction was run under our standard conditions. The yield of **2h** improved to 45% with a modest decrease in enantioselectivity when the reaction was performed in 1,4-dioxane at 100 °C (entry 10).

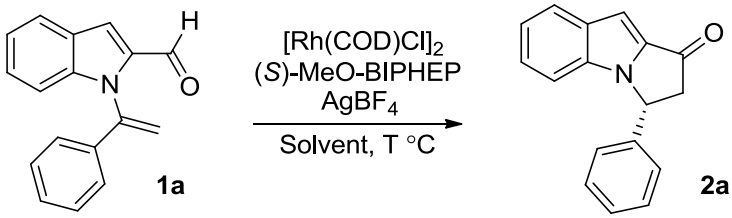
Scheme 2.6 summarizes the results of hydroacylations with *N*-vinylindole-2-carboxaldehydes containing substitution at the 3-, 4-, 5-, and 6-positions on the indole moiety. A variety of *N*-vinylindole-2-carboxaldehydes containing electron-donating and electron-withdrawing substituents, as well as halogens, were excellent substrates for the intramolecular alkene hydroacylation. Alkyl substitution at the 3-position of the indole ring was well tolerated, and the hydroacylation of 3-ethyl-1-(1-phenylvinyl)-*1H*-indole-2-carboxaldehyde **1i** (R^2 = Et, R^3 = H) formed product **2i** in 89% yield with 98% ee. Hydroacylations of 4-MeO, 5-MeO, and 5-F substituted *N*-vinylindole-2-carboxaldehydes

Scheme 2.6 Rhodium-catalyzed enantioselective hydroacylation of *N*-vinylindole-2-carboxaldehydes **1i-n**



1j-l occurred with excellent enantioselectivity (98-99%), and dihydropyrroloindolones **2j-l** were isolated in 90-97% yield. Intramolecular hydroacylations of 6-chloro- and 6-trifluoromethyl-1-(1-phenylvinyl)-*1H*-indole-2-carboxaldehydes (**1m** and **1n**) formed dihydropyrroloindolones **2m** and **2n** in slightly lower yield (81-82%), but the enantioselectivity remained high (98-99% ee).

Table 2.3 Impact of lower catalyst loading on the enantioselective hydroacylation of *N*-vinylindole-2-carboxaldehyde **1a**[a]



Entry	[Rh] (mol %)	Solvent	Conv (%)	NMR yield (%)[b]	ee (%)[c]
1	5.00	THF	99	95 (92)	99
2	2.50	THF	46	44	ND
3	2.50	1,4-dioxane	99	99 (99)	95
4	1.00	1,4-dioxane	99	99 (95)	96
5	0.50	1,4-dioxane	95	85 (83)	98
6	0.20	1,4-dioxane	94	78 (79)	98
7	0.10	1,4-dioxane	56	40	ND

[a] **1a** (0.100-2.00 mmol), $[Rh(COD)Cl]_2$ (0.0020-0.025 mmol), ligand **7** (0.0040-0.050 mmol), $AgBF_4$ (0.0040-0.050 mmol), and THF/1,4-dioxane (0.7-14 mL). [b] Determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard, isolated yield of **2a** is given in parenthesis. [c] Determined by chiral HPLC analysis.

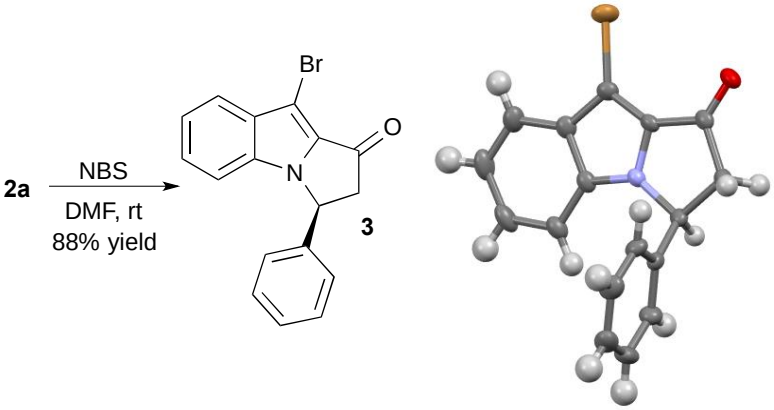
Although reactions of *N*-vinylindole-2-carboxaldehydes to establish the scope of these hydroacylations are conducted in the presence of 5 mol % of the rhodium catalyst, this relatively high catalyst loading is not a requirement to achieve high isolated yields and enantioselectivities (Table 2.3). The hydroacylation of 1-(1-phenylvinyl)-1*H*-indole-2-carboxaldehyde **1a** performed in the presence of 1 mol % of the rhodium catalyst at 100 °C in 1,4-dioxane generates dihydropyrroloindolone **2a** in 95% yield with 98% ee.

Decreasing the catalyst loading to 0.2 mol % led to a lower yield (79%) of dihydropyrroloindolone **2a**, but this heterocyclic ketone was still formed with excellent enantioselectivity (98% ee).

2.3.5 Absolute Stereochemistry of 2a

The absolute configuration of dihydropyrroloindolone **2a** was determined after bromination (Scheme 2.7). Treatment of **2a** with *N*-bromosuccinimide occurred to form **3** in 88% yield. The absolute configuration of 9-bromo-3-phenyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-one **3** was determined to be (3*S*) by X-ray crystallographic analysis. Thus, the catalyst generated from (*S*)-MeO-BIPHEP **7** leads to the formation of (*S*)-**3**. We thank Dr. Arkady Ellern and the Molecular Structure Laboratory (Iowa State University) for X-ray diffraction data collection and structure determination.

Scheme 2.7 Absolute stereochemistry and structure of **3** based on X-ray diffraction data.



2.3.6 Plausible Recation Mechanism

Figure 2.2 illustrates the plausible reaction mechanism for Rh-catalyzed enantioselective hydroacylation of *N*-vinylindole-2-carboxaldehydes. Oxidative addition of Rh(I) to *N*-vinylindole-2-carboxaldehyde **1** generates acylrhodium(III) hydride intermediate **A**. Coordination of alkene in **A** to rhodium center generates **B** which undergoes migratory insertion

to form six-membered rhodacycle **C**. Reductive elimination of rhodium in **C** finally leads to the formation of product **2**, with regeneration of Rh(I) catalyst.

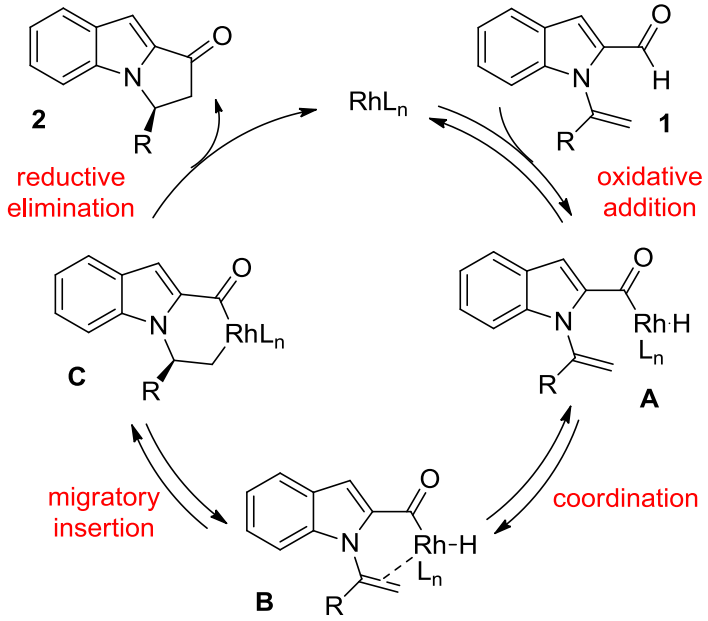
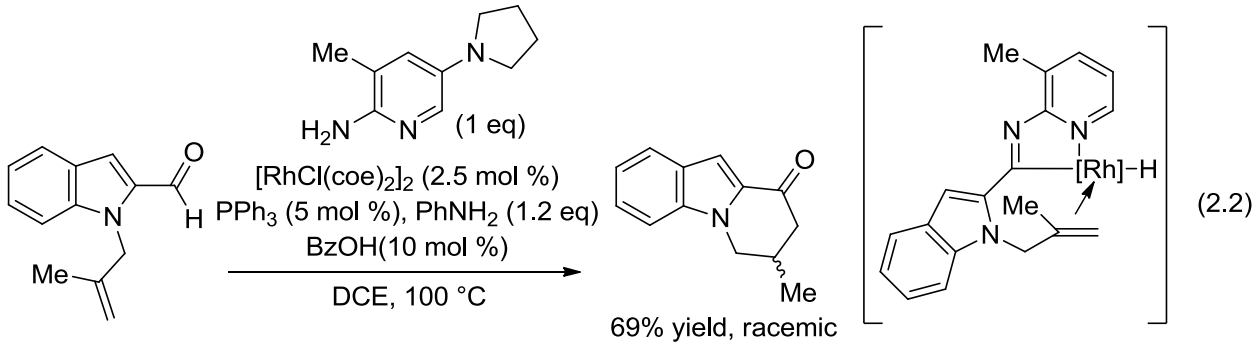


Figure 2.2 Plausible reaction mechanism for Rh-catalyzed hydroacylation of *N*-vinylindole-2-carboxaldehydes

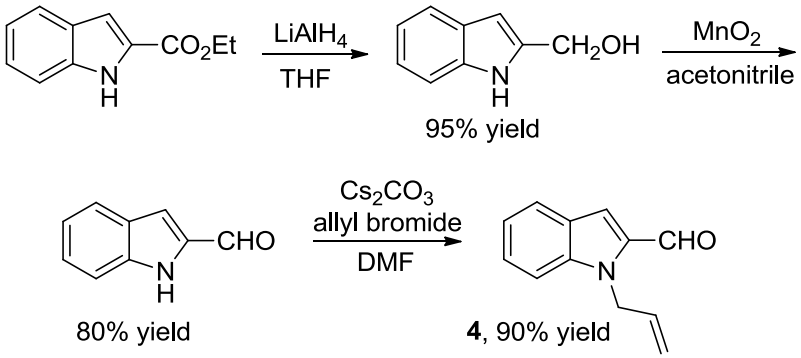
2.3.7 Rh-Catalyzed Intramolecular Hydroacylation of *N*-Allylindole-2-carboxaldehyde

Hydroacylation reactions to form rings of greater than five atoms are often driven by strain release or rely on heteroatom functionality contained at specific sites within the substrate molecules to stabilize acylrhodium(III) hydride intermediates and prevent catalyst decomposition.[5] Thus hydroacylations of *N*-allylindole-2-carboxaldehydes have proven more challenging because these processes involve the formation of a six-membered ring instead of a five-membered ring. During our studies, Douglas reported the first example of alkene hydroacylation involving *N*-allylindole-2-carboxaldehydes (eq 2.2).[5b] These hydroacylation reactions are enabled by transient generation of a 2-aminopicoline-based aldimine that stabilizes the acylrhodium hydride intermediate. However, this approach to chelation assistance requires a

complex mixture of catalyst precursors and additives, and highly enantioselective hydroacylations involving 2-aminopicoline based aldimines have not been reported.

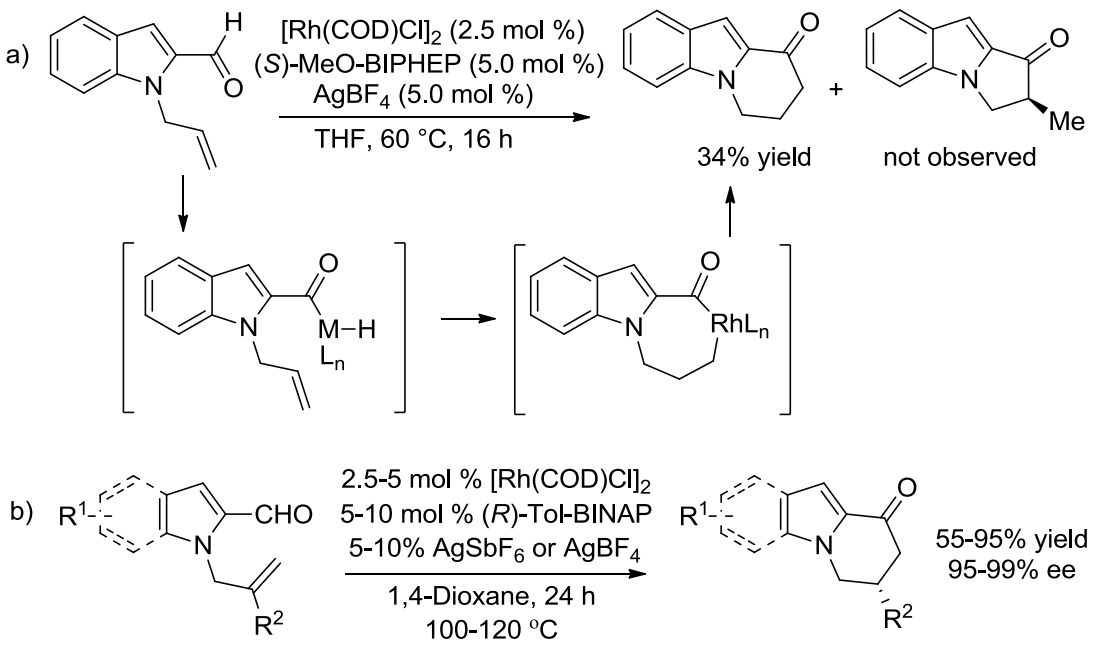


Scheme 2.8 Synthesis of *N*-allylindole-2-carboxaldehyde



We synthesized *N*-allylindole-2-carboxaldehyde from ethyl indole-2-carboxylate over 3 steps in 68% yield (Scheme 2.8). Our attempt for intramolecular hydroacylation of *N*-allylindole-2-carboxaldehyde in presence of catalyst generated in situ from $[Rh(COD)Cl]_2$, MeO-BIPHEP and $AgBF_4$ formed the dihydropyridoindolone **4** in 34% yield as the only product via *endo*-selective pathway presumably through formation of seven-membered rhodacycle (Scheme 2.9a). This represents the first example of construction of six-membered ring via hydroacylation reaction in the absence chelation assistance. The chelation-free intramolecular hydroacylation reactions of *N*-allylindole-2-carboxaldehydes were further explored by Dr. Xiang Wei Du and the results are summarized in Scheme 2.9b.

Scheme 2.9 Construction of six-membered rings via Rh-catalyzed hydroacylation reaction in the absence of chelation assistance



Even though Rh-catalyzed enantioselective, intramolecular hydroacylation reactions of *N*-vinylindole-, *N*-allylindole- and *N*-allylpyrrole-2-carboxaldehydes containing 1,1-disubstituted alkenes worked great for the construction of five- and six-membered rings, hydroacylations of indole and pyrrole based substrates containing 1,2-disubstituted and 1,1,2-trisubstituted alkenes were unproductive under our reaction conditions and did not form the desired hydroacylation products.

2.4 Conclusion

In conclusion, we have established a method for highly enantioselective intramolecular hydroacylation of *N*-vinylindole-2-carboxaldehydes in the presence of a rhodium catalyst prepared *in situ* from commercially available precursors. These reactions encompass a broad range of *N*-vinylindole-2-carboxaldehydes bearing a variety of aryl and alkyl substituents on the olefin moiety and substitution throughout the indole

core. The enantioenriched dihydropyrroloindolone products are generated with consistently high enantioselectivity (95-99% ee) even at low catalyst loadings (0.2-5 mol% Rh). This methodology could be extended to hydroacylations of *N*-allylindole- and *N*-allylpyrrole-2-carboxaldehydes in construction of six-membered rings that generated 7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)ones and 6,7-dihydroindolizin-8(5*H*)-ones in moderate to high yields with excellent enantioselectivities.

2.5 Experimental Details

2.5.1 General experimental details

All air-sensitive procedures were conducted under inert atmosphere in a nitrogen-filled dry box or by standard Schlenk techniques. All reactions were performed under an atmosphere of nitrogen unless otherwise stated. All glassware for moisture sensitive reactions was dried at 140 °C in an oven. THF and CH_2Cl_2 were degassed by purging with argon for 45 minutes and dried with a solvent purification system by passing through a one-meter column of activated alumina. Anhydrous acetonitrile, toluene, 1,2-dichloroethane and 1,4-dioxane were purchased from Aldrich. Flash column chromatography was performed on Fisher brand silica gel 60 (230-400 mesh) using hexanes/EtOAc, hexanes/ether or hexanes/dichloromethane mixtures. Reaction products were visualized on TLC by UV light or by staining with $KMnO_4$ or 2,4-dinitro-phenylhydrazine.

HRMS (EI) analysis was performed at the Iowa State University Chemical Instrumentation Facility on a Waters GCT GC-MS spectrometer. Optical rotations were measured on an Atago AP-300 automatic polarimeter. HPLC analyses were carried out on a Water Alliance HPLC system with an e2695 Separations Module and a 2489 (UV/Vis) dual

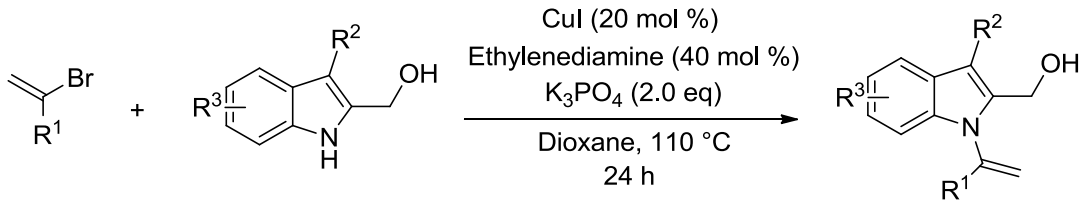
wavelength detector. NMR spectra were acquired on Varian MR-400 and Bruker Avance III 600 spectrometers at the Iowa State University Chemical Instrumentation Facility. Chemical shifts are reported in ppm relative to a residual solvent peak ($CDCl_3$ = 7.26 ppm for ^1H and 77.36 ppm for ^{13}C; C_6D_6 = 7.16 for ^1H and 128.06 for ^{13}C). ^{19}F NMR shifts are reported in ppm relative to trifluoroacetic acid as an external standard (F_3CCO_2H = -76.55 ppm). Coupling constants are reported in hertz.

2.5.2 Materials

(1-Bromovinyl)benzene **S1a** was purchased from Sigma-Aldrich and used without further purification. 1-(1-Bromovinyl)-4-methoxybenzene **S1b**, 1-(1-bromovinyl)-4-chlorobenzene **S1c**, 1-(1-bromovinyl)-4-(trifluoromethyl)benzene **S1d**, 1-(1-bromovinyl)-3-methoxybenzene **S1e**, 5-(1-bromovinyl)-1,2,3-trimethoxybenzene **S1f**, and (1-bromovinyl)cyclohexane were prepared according to a previously reported procedure. 2-Bromopropene was purchased from Alfa-Aesar and used without further purification. Ethyl indole-2-carboxylate, ethyl 5-methoxyindole-2-carboxylate, and ethyl 5-fluoroindole-2-carboxylate were purchased from AK Scientific and used without further purification. Ethyl 3-ethylindole-2-carboxylate, ethyl 4-methoxyindole-2-carboxylate, ethyl 6-chloroindole-2-carboxylate, ethyl 6-trifluoromethylindole-2-carboxylate were synthesized according to a literature procedure.[13] (1*H*-Indol-2-yl)methanols **S2a**-**g** by reduction of the corresponding ethyl indole-2-carboxylate with $LiAlH_4$.[14] Manganese dioxide, copper iodide, ethylenediamine and Martin Sulfurane were purchased from Sigma-Aldrich and used without further purification. $[Rh(COD)Cl]_2$, (*R*)-BINAP, *rac*-BINAP, (*R*)-tolyl-BINAP, (*R*)-xylyl-BINAP, (*S*)-Me-BIPHEP, (*S*)-MeO-BIPHEP, (*R*)-MeO-BIPHEP, silver nitrate, silver mesylate, silver triflate, silver perchlorate, silver tetrafluoroborate, silver hexafluorophosphate,

and silver hexafluoroantomonate were purchased from Strem Chemicals and used without further purification.

2.5.3 General Procedure for Synthesis of (1-(1-Arylvinyl)-1*H*-indol-2-yl)methanols (S3a-f, S3i-n) and (1-(1-Alkylvinyl)-1*H*-indol-2-yl)methanols (S3g-h)



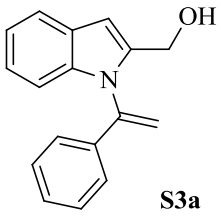
S1a; R^1 = Ph
S1b; R^1 = 4-MeO-C_6H_4
S1c; R^1 = 4-Cl-C_6H_4
S1d; R^1 = 4-F_3C-C_6H_4
S1e; R^1 = 3-MeO-C_6H_4
S1f; R^1 = 3,4,5-MeO_3-C_6H_2
S1g; R^1 = Me
S1h; R^1 = C_6H_{11}

S2a; R^2 = H, R^3 = H
S2b; R^2 = C_2H_5, R^3 = H
S2c; R^2 = H, R^3 = 4-MeO
S2d; R^2 = H, R^3 = 5-MeO
S2e; R^2 = H, R^3 = 5-F
S2f; R^2 = H, R^3 = 6-Cl
S2g; R^2 = H, R^3 = 6-F_3C

S3a; R^1 = Ph, R^2 = H, R^3 = H
S3b; R^1 = 4-MeO-C_6H_4, R^2 = H, R^3 = H
S3c; R^1 = 4-Cl-C_6H_4, R^2 = H, R^3 = H
S3d; R^1 = 4-F_3C-C_6H_4, R^2 = H, R^3 = H
S3e; R^1 = 3-MeO-C_6H_4, R^2 = H, R^3 = H
S3f; R^1 = 3,4,5-MeO_3-C_6H_2, R^2 = H, R^3 = H
S3g; R^1 = Me, R^2 = H, R^3 = H
S3h; R^1 = C_6H_{11}, R^2 = H, R^3 = H
S3i; R^1 = Ph, R^2 = C_2H_5, R^3 = H
S3j; R^1 = Ph, R^2 = H, R^3 = 4-MeO
S3k; R^1 = Ph, R^2 = H, R^3 = 5-MeO
S3l; R^1 = Ph, R^2 = H, R^3 = 5-F
S3m; R^1 = Ph, R^2 = H, R^3 = 6-Cl
S3n; R^1 = Ph, R^2 = H, R^3 = 6-F_3C

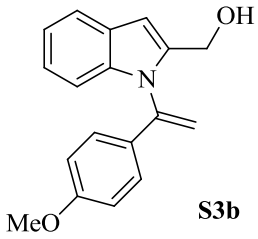
(1-(1-Arylvinyl)-1*H*-indol-2-yl)methanols (**S3a-f**, **S3i-n**) and (1-(1-alkylvinyl)-1*H*-indol-2-yl)methanols (**S3g-h**) were prepared according to a modified literature procedure from the appropriate vinyl bromides **S1a-h** and (1*H*-indol-2-yl)methanols **S2a-g**. In a nitrogen-filled glovebox, to a 20 mL scintillation vial or a 250 mL pressure vessel equipped with a vacuum valve were added CuI (0.200 equiv), the appropriate (1*H*-indol-2-yl)methanol **S2a-g** (1.20 equiv), K_3PO_4 (2.00 equiv), the appropriate vinyl bromide **S1a-h** (1.00 equiv), ethylenediamine (0.400 equiv), and 1,4-dioxane (0.55 M final concentration of vinyl bromides **S1a-h**). The

scintillation vial or pressure vessel was sealed with a teflon-lined septum cap or a PTFE stopper. The reaction vessel was removed from the glovebox, and the reaction mixture was stirred at 110 °C for 24 h. The reaction mixture was cooled to room temperature, diluted with EtOAc, and stirred for an addition 15 min. Solids were removed by filtration and washed with EtOAc (3x). The organic layers were combined and concentrated under reduced pressure. The crude product was purified by flash column silica gel chromatography (hexane:EtOAc) to give the appropriate (1-(1-arylvinyl)-1*H*-indol-2-yl)methanol (**S3a-f**, **S3i-n**) and (1-(1-alkylvinyl)-1*H*-indol-2-yl)methanol (**S3g-h**).



S3a

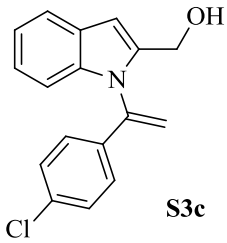
(1-(1-Phenylvinyl)-1*H*-indol-2-yl)methanol (S3a): Prepared according to the general procedure from **S1a** (5.00 g, 27.3 mmol) and **S2a** (4.82 g, 32.8 mmol). The mixture was purified by flash column chromatography (80:20 hexane:EtOAc) to give **S3a** as a yellow oil in 65% yield (4.42 g, 17.7 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.63 – 7.55 (m, 1H), 7.32 – 7.04 (m, 8H), 6.60 (s, 1H), 6.00 (s, 1H), 5.46 (s, 1H), 4.54 (s, 2H), 1.62 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.9, 139.9, 138.6, 137.1, 129.5, 129.1, 127.9, 126.0, 122.7, 121.0, 120.6, 114.1, 111.3, 103.1, 57.8. **HRMS** (EI): Calcd. for $C_{17}H_{15}NO$ ([M]+): 249.1154, Found: 249.1149.



S3b

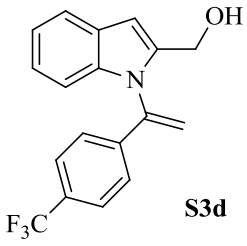
(1-(1-(4-Methoxyphenyl)vinyl)-1*H*-indol-2-yl)methanol (S3b): Prepared according to the general procedure from **S1b** (1.95 g, 9.15 mmol) and **S2a** (1.62 g, 11.0 mmol). The mixture was purified by flash column chromatography (80:20 hexane: EtOAc) to give **S3b** as a light yellow solid in 37% yield (0.950 g, 3.40 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.70 – 7.62 (m, 1H), 7.28 –

7.06 (m, 5H), 6.84 – 6.78 (m, 2H), 6.65 (s, 1H), 5.93 (s, 1H), 5.40 (s, 1H), 4.61 (s, 2H), 3.78 (s, 3H), 1.77 (br s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.6, 142.5, 140.0, 138.6, 129.6, 127.8, 127.4, 122.6, 120.9, 120.5, 114.4, 112.0, 111.4, 102.9, 57.8, 55.6. **HRMS** (EI): Calcd. for $C_{18}H_{17}NO_2$ ([M]+): 279.1259, Found: 279.1259.



S3c

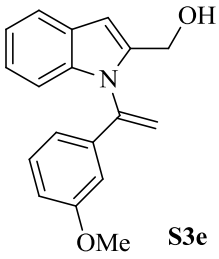
(1-(1-(4-Chlorophenyl)vinyl)-1*H*-indol-2-yl)methanol (S3c): Prepared according to the general procedure from **S1c** (1.50 g, 6.90 mmol) and **S2a** (1.22 g, 8.28 mmol). The mixture was purified by flash column chromatography (80:20 hexanes:EtOAc) to give **S3c** as a light yellow oil in 20% yield (0.400 g, 1.41 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.93 – 7.83 (m, 1H), 7.52 – 7.45 (m, 2H), 7.42 – 7.26 (m, 5H), 6.88 (s, 1H), 6.27 (d, *J* = 1.4 Hz, 1H), 5.76 (d, *J* = 1.4 Hz, 1H), 4.84 (s, 2H), 1.89 (br s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.0, 139.8, 138.5, 135.6, 135.4, 129.3, 127.9, 127.4, 122.9, 121.1, 120.8, 114.6, 111.3, 103.4, 57.8. **HRMS** (EI): Calcd. for $C_{17}H_{14}ClNO$ ([M]+): 283.0764, Found: 283.0760.



S3d

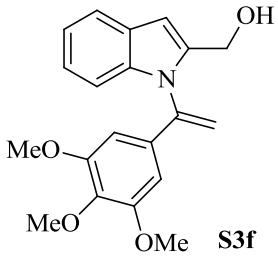
(1-(1-(4-(Trifluoromethyl)phenyl)vinyl)-1*H*-indol-2-yl)methanol (S3d): Prepared according to the general procedure from **S1d (**2.00 g, 7.97 mmol) and **S2a** (1.41 g, 9.56 mmol). The mixture was purified by flash column chromatography (80:20 hexane:EtOAc) to give **S3d** as a dark yellow oil in 17% yield (0.425 g, 1.34 mmol). **^{1}H NMR** (400 MHz, C_6D_6) δ 7.68 (dq, *J* = 8.0, 1.2, 0.80 Hz, 1H), 7.22 – 7.01 (m, 5H), 6.79 – 6.69 (m, 2H), 6.51 (q, *J* = 1.2, 0.40 Hz, 1H), 5.45 (s, 1H), 5.11 (s, 1H), 4.21 (d, *J* = 5.6 Hz, 2H), 0.43 (s, 1H). **^{13}C NMR** (101 MHz, C_6D_6) δ 141.8, 140.5, 140.1, 138.7, 130.9, 130.6, 126.4, 125.9, 125.8, 125.8, 125.8, 123.0, 121.3, 121.1, 115.8, 111.2, 103.3,

57.3. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -63.0. **HRMS** (EI): Calcd. for $C_{18}H_{14}F_3NO$ ([M]+): 317.1027, Found: 317.1030.



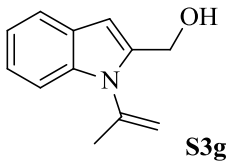
S3e

(1-(1-(3-Methoxyphenyl)vinyl)-1*H*-indol-2-yl)methanol (S3e): Prepared according to the general procedure from **S1e** (1.95 g, 9.15 mmol) and **S2a** (1.62 g, 11.0 mmol). The mixture was purified by flash column chromatography (80:20 hexane:EtOAc) to give **S3e** as a light yellow solid in 15% yield (0.260 g, 0.930 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.78 – 7.70 (m, 1H), 7.38 – 6.20 (m, 4H), 6.98 (dd, *J* = 8.4, 1.6 Hz, 1H), 6.89 – 6.79 (m, 2H), 6.77 – 6.74 (m, 1H), 6.15 (s, 1H), 5.63 (s, 1H), 4.71 (s, 2H), 3.84 (s, 3H), 1.79 (br s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.2, 142.8, 139.9, 138.7, 130.2, 127.9, 122.7, 121.0, 120.6, 118.6, 114.7, 114.4, 111.9, 111.3, 103.1, 57.8, 55.6. **HRMS** (EI): Calcd. for $C_{18}H_{17}NO_2$ ([M]+): 279.1259, Found: 279.1249.



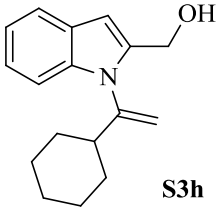
S3f

(1-(1-(3,4,5-Trimethoxyphenyl)vinyl)-1*H*-indol-2-yl)methanol (S3f): Prepared according to the general procedure from **S1f** (1.150 g, 4.210 mmol) and **S2a** (0.744 g, 5.05 mmol). The mixture was purified by flash column chromatography (70:30 hexane:EtOAc) to give **S3f** as a light yellow solid in 12% yield (0.170 g, 0.500 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.67 – 7.58 (m, 1H), 7.25 – 7.06 (m, 3H), 6.64 (s, 1H), 6.38 (s, 2H), 5.96 (s, 1H), 5.47 (s, 1H), 4.62 (s, 2H), 3.84 (s, 3H), 3.70 (s, 6H), 1.63 (br s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.7, 142.9, 140.0, 139.3, 138.8, 132.9, 127.8, 122.7, 121.0, 120.6, 113.4, 111.3, 103.4, 103.2, 61.2, 57.8, 56.4. **HRMS** (EI): Calcd. for $C_{20}H_{21}NO_4$ ([M]+): 339.1471, Found: 339.1484.



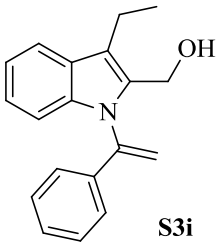
S3g

(1-(Prop-1-en-2-yl)-1*H*-indol-2-yl)methanol (S3g): Prepared according to the general procedure from **S1g (**1.50 g, 12.4 mmol) and **S2a** (2.19 g, 14.9 mmol). The mixture was purified by flash column chromatography (80:20 hexane:ethylacetate) to give **S3g** as a light yellow solid in 52% yield (1.22 g, 6.49 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.06 (dd, *J* = 8.0, 0.4 Hz, 1H), 6.90 (dddd, *J* = 36.4, 15.2, 7.2, 1.2 Hz, 2H), 6.26 (s, 1H), 5.20 (q, *J* = 2.8, 1.2 Hz, 1H), 4.93 (s, 1H), 4.48 (s, 2H), 1.91 (s, 3H), 1.56 (br s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.1, 138.8, 137.4, 127.8, 122.5, 121.0, 120.3, 115.9, 110.8, 102.5, 57.7, 22.2. **HRMS** (EI): Calcd. for $C_{12}H_{13}NO$ ([M]+): 187.0997, Found: 187.1004.



S3h

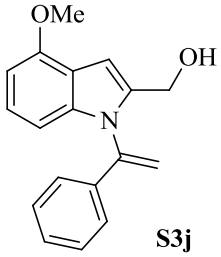
(1-(1-Cyclohexylvinyl)-1*H*-indol-2-yl)methanol (S3h): Prepared according to the general procedure from **S1h** (1.70 g, 8.99 mmol) and **S2a** (1.59 g, 10.8 mmol). The mixture was purified by flash column chromatography (80:20 hexane:EtOAc) to give **S3h** as a light yellow oil in 9% yield (0.210 g, 0.822 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.75 – 7.67 (m, 1H), 7.45 – 7.35 (m, 1H), 7.27 (dddd, *J* = 30.0, 15.2, 8.4, 7.2, 1.2 Hz, 2H), 6.69 (q, *J* = 1.6, 0.40 Hz, 1H), 5.57 (d, *J* = 1.6 Hz, 1H), 5.35 (d, *J* = 0.40 Hz, 1H), 4.85 (s, 2H), 2.57 - 2.50 (m, 1H), 1.97 – 1.76 (m, 6H), 1.49 – 1.21 (m, 5H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.0, 139.7, 138.1, 127.7, 122.3, 120.9, 120.2, 113.4, 111.3, 102.2, 57.9, 43.6, 31.9, 26.6, 26.4. **HRMS** (EI): Calcd. for $C_{17}H_{21}NO$ ([M]+): 255.1623, Found: 255.1627.



S3i

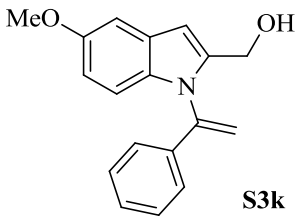
(3-Ethyl-1-(1-phenylvinyl)-1*H*-indol-2-yl)methanol (S3i): Prepared according to the general procedure from **S1a (**0.800 g, 4.37 mmol) and **S2b**

(0.919 g, 5.24 mmol). The mixture was purified by flash column chromatography (80:20 hexane:EtOAc) to give **S3i** as a light yellow solid in 30% yield (0.370 g, 1.33 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.73 – 7.53 (m, 1H), 7.44 – 7.23 (m, 3H), 7.25 – 7.08 (m, 5H), 6.06 (s, 1H), 5.54 (s, 1H), 4.61 (s, 2H), 2.89 (q, *J* = 15.2, 7.6 Hz, 2H), 1.36 – 1.32 (t, *J* = 7.6 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.2, 137.9, 137.6, 134.8, 129.5, 129.2, 127.6, 126.1, 123.0, 120.0, 119.5, 118.7, 114.2, 111.3, 54.9, 18.0, 16.7. **HRMS** (EI): Calcd. for $C_{19}H_{19}NO$ ([M]+): 277.1467, Found: 277.1469.



S3j

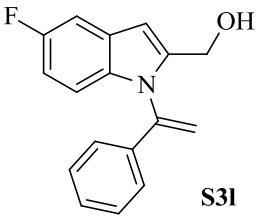
(4-Methoxy-1-(1-phenylvinyl)-1*H*-indol-2-yl)methanol (S3j): Prepared according to the general procedure from **S1a** (0.900 g, 4.92 mmol) and **S2c** (1.05 g, 5.90 mmol). The mixture was purified by flash column chromatography (80:20 hexane:EtOAc) to give **S3j** as a light yellow solid in 51% yield (0.700 g, 2.51 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.24 – 7.04 (m, 3H), 6.90 (dt, *J* = 8.4, 2.0 Hz, 3H), 6.67 – 6.57 (m, 2H), 6.39 (dd, *J* = 7.6, 0.80 Hz, 1H), 5.87 (d, *J* = 1.6 Hz, 1H), 5.35 (d, *J* = 1.6 Hz, 1H), 4.40 (s, 2H), 3.81 (d, *J* = 1.2 Hz, 3H), 1.67 (br s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.2, 142.7, 139.7, 138.3, 137.1, 136.8, 136.0, 129.2, 128.8, 128.5, 127.4, 126.1, 125.7, 124.1, 124.0, 123.2, 121.6, 118.1, 113.9, 104.9, 104.5, 101.9, 101.0, 100.2, 57.4, 55.4. **HRMS** (EI): Calcd. for $C_{18}H_{17}NO_2$ ([M]+): 279.1259, Found: 279.1272.



S3k

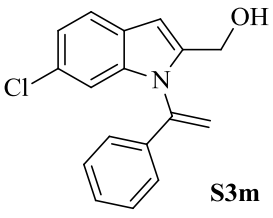
(5-Methoxy-1-(1-phenylvinyl)-1*H*-indol-2-yl)methanol (S3k): Prepared according to the general procedure from **S1a (**1.30 g, 7.10 mmol) and **S2d** (1.51 g, 8.52 mmol). The mixture was purified by flash column chromatography (80:20 hexane:EtOAc) to give **S3k** as a light yellow solid in 29% yield (0.568 g, 2.03 mmol). **^{1}H**

NMR (400 MHz, $CDCl_3$) δ 7.26 – 7.09 (m, 3H), 7.05 – 6.86 (m, 4H), 6.65 (dd, *J* = 8.8, 2.0 Hz, 1H), 6.43 (s, 1H), 5.86 (s, 1H), 5.35 (s, 1H), 4.43 (s, 2H), 3.71 (s, 3H), 1.66 (br s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.8, 143.0, 140.5, 137.2, 133.8, 129.5, 129.1, 128.2, 126.1, 113.8, 112.8, 112.1, 102.8, 102.6, 57.8, 56.1. **HRMS** (EI): Calcd. for $C_{18}H_{17}NO_2$ ([M]+): 279.1259, Found: 279.1267.



S3l

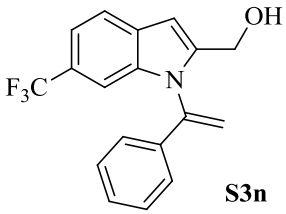
5-Fluoro-1-(1-phenylvinyl)-1*H*-indol-2-yl)methanol (S3l): Prepared according to the general procedure from **S1a (**0.688 g, 3.76 mmol) and **S2e** (0.745 g, 4.51 mmol). The mixture was purified by flash column chromatography (80:20 hexane:EtOAc) to give **S3l** as a light yellow solid in 55% yield (0.551 g, 2.06 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.25 – 7.06 (m, 4H), 6.96 - 6.90 (m, 2H), 6.86 (dd, *J* = 9.2, 4.4 Hz, 1H), 6.67 (tdd, *J* = 9.2, 2.4, 0.80 Hz, 1H), 6.40 (s, 1H), 5.84 (s, 1H), 5.30 (s, 1H), 4.38 (s, 2H), 1.69 (br s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.7, 157.3, 142.8, 141.5, 136.8, 135.1, 129.6, 129.2, 128.2, 128.1, 126.0, 114.2, 112.1, 112.0, 111.2, 110.9, 105.9, 105.6, 102.9, 102.9, 57.8. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -124.5. **HRMS** (EI): Calcd. for $C_{17}H_{14}FNO$ ([M]+): 267.1059, Found: 267.1068.



S3m

(6-Chloro-1-(1-phenylvinyl)-1*H*-indol-2-yl)methanol (S3m): Prepared according to the general procedure from **S1a** (1.95 g, 10.6 mmol) and **S2f** (2.32 g, 12.8 mmol). The mixture was purified by flash column chromatography (80:20 hexane:EtOAc) to give **S3m** as a light yellow oil in 53% yield (1.60 g, 5.64 mmol). **^{1}H NMR** (400 MHz, C_6D_6) δ 7.40 – 7.35 (m, 2H), 7.18 - 7.16 (m, 3H), 6.98 – 6.82

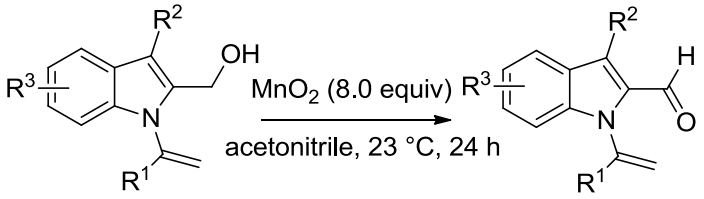
(m, 3H), 6.43 (s, 1H), 5.44 (s, 1H), 4.95 (s, 1H), 4.20 (s, 2H), 1.65 (s, 1H). **^{13}C NMR** (101 MHz, C_6D_6) δ 142.4, 141.3, 139.3, 136.8, 129.3, 129.0, 125.9, 122.0, 121.6, 114.1, 111.3, 102.7, 57.5. **HRMS** (EI): Calcd. for $C_{17}H_{14}ClNO$ ([M]+): 283.0764, Found: 283.0762.



S3n

(1-(1-Phenylvinyl)-6-(trifluoromethyl)-1*H*-indol-2-yl)methanol (S3n): Prepared according to the general procedure from **S1a** (1.20 g, 6.56 mmol) and **S2g** (1.69 g, 7.87 mmol). The mixture was purified by flash column chromatography (80:20 hexane:EtOAc) to give **S3n** as a light yellow oil in 30% yield (0.620 g, 1.95 mmol). **^{1}H NMR** (400 MHz, C_6D_6) δ 7.69 (s, 1H), 7.53 – 7.39 (m, 2H), 6.97 – 6.76 (m, 5H), 6.49 (s, 1H), 5.43 (s, 1H), 4.92 (s, 1H), 4.19 (s, 2H), 1.44 (br s, 1H). **^{13}C NMR** (101 MHz, C_6D_6) δ 143.3, 142.2, 137.8, 136.5, 130.7, 129.4, 129.0, 127.4, 125.8, 125.2, 124.9, 124.7, 124.6, 124.3, 121.5, 117.4, 114.3, 108.6, 102.5, 57.5. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -60.7. **HRMS** (EI): Calcd. for $C_{18}H_{14}F_3NO$ ([M]+): 317.1027, Found: 317.1023.

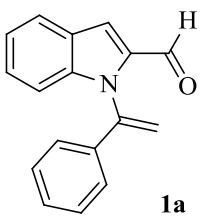
2.5.4 General Procedure for Synthesis of 1-(1-Arylvinyl)-1*H*-indole-2-carbaldehydes (1a-f, 1i-n) and 1-(1-Alkylvinyl)-1*H*-indole-2-carboxaldehydes (1g-h)



S3a-n **1a-n**

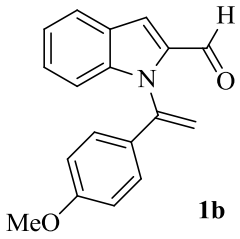
1a; R^1 = Ph, R^2 = H, R^3 = H
1b; R^1 = 4-MeO-C_6H_4, R^2 = H, R^3 = H
1c; R^1 = 4-Cl-C_6H_4, R^2 = H, R^3 = H
1d; R^1 = 4-F_3C-C_6H_4, R^2 = H, R^3 = H
1e; R^1 = 3-MeO-C_6H_4, R^2 = H, R^3 = H
1f; R^1 = 3,4,5-MeO_3-C_6H_2, R^2 = H, R^3 = H
1g; R^1 = Me, R^2 = H, R^3 = H
1h; R^1 = C_6H_{11}, R^2 = H, R^3 = H
1i; R^1 = Ph, R^2 = C_2H_5, R^3 = H
1j; R^1 = Ph, R^2 = H, R^3 = 4-MeO
1k; R^1 = Ph, R^2 = H, R^3 = 5-MeO
1l; R^1 = Ph, R^2 = H, R^3 = 5-F
1m; R^1 = Ph, R^2 = H, R^3 = 6-Cl
1n; R^1 = Ph, R^2 = H, R^3 = 6-F_3C

To an acetonitrile solution (0.40 M) of the appropriate (1-(1-arylvinyl)-1*H*-indol-2-yl)methanol (**S3a-f**, **S3i-n**) or (1-(1-alkylvinyl)-1*H*-indol-2-yl)methanol (**S3g-h**) (1.00 equiv) in a round-bottom flask was manganese dioxide (8.00 equiv) added. The reaction mixture was stirred at room temperature under N_2 atmosphere for 24 hours. The reaction mixture was filtered through celite, washed with mixture of hexane:EtOAc (60:40), and the filtrate was concentrated under reduced pressure. The crude product was purified by flash column silica gel chromatography (hexane:EtOAc) to give the appropriate 1-(1-arylvinyl)-1*H*-indole-2-carboxaldehydes (**1a-f**, **1i-n**) or 1-(1-alkylvinyl)-1*H*-indole-2-carboxaldehydes (**1g-h**).



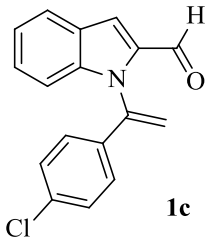
1a

1-(1-Phenylvinyl)-1*H*-indole-2-carboxaldehyde (1a): Prepared according to the general procedure from **S3a** (5.00 g, 20.1 mmol). The mixture was purified by flash column chromatography (90:10 hexane:EtOAc) to give **1a** as a light yellow solid in 85% yield (4.20 g, 17.0 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.72 (d, *J* = 1.2 Hz, 1H), 7.72 (dq, *J* = 8.4, 1.6, 0.80 Hz, 1H), 7.35 (q, *J* = 1.2, 0.8 Hz, 1H), 7.33 – 7.25 (m, 2H), 7.24 – 7.12 (m, 3H), 7.06 – 7.00 (m, 2H), 6.02 (d, *J* = 0.4 Hz, 1H), 5.41 (d, *J* = 0.4 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 181.7, 143.1, 141.0, 137.3, 136.7, 129.4, 129.0, 127.5, 126.8, 125.7, 123.6, 122.1, 115.7, 113.9, 112.1. **HRMS** (EI): Calcd. for $C_{17}H_{13}NO$ ([M]+): 247.0997, Found: 247.1006.



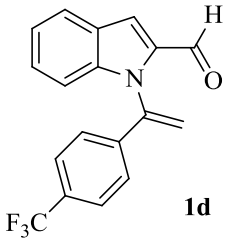
1b

1-(1-(4-Methoxyphenyl)vinyl)-1*H*-indole-2-carboxaldehyde (1b): Prepared according to the general procedure from **S3b** (0.958 g, 3.43 mmol). The mixture was purified by flash column chromatography (90:10 hexane:EtOAc) to give **1b** as a light yellow solid in 80% yield (0.760 g, 2.740 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.87 (s, 1H), 7.84 (dt, *J* = 8.0, 0.80 Hz, 1H), 7.47 (d, *J* = 0.80, 1H), 7.45 – 7.37 (m, 2H), 7.32 – 7.23 (m, 1H), 7.16 – 7.07 (m, 2H), 6.88 – 6.80 (m, 2H), 6.03 (s, 1H), 5.42 (s, 1H), 3.79 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 181.6, 160.4, 142.4, 140.8, 136.6, 129.7, 127.3, 126.9, 126.6, 123.4, 121.9, 115.1, 114.2, 112.0, 111.8, 55.4. **HRMS** (EI): Calcd. for $C_{18}H_{15}NO_2$ ([M]+): 277.1103, Found: 277.1112.



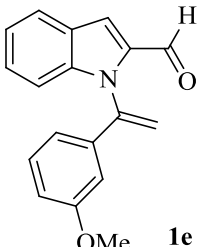
1c

1-(1-(4-Chlorophenyl)vinyl)-1*H*-indole-2-carboxaldehyde (1c): Prepared according to the general procedure from **S3c** (0.373 g, 1.31 mmol). The mixture was purified by flash column chromatography (90:10 hexane:EtOAc) to give **1c** as a light yellow solid in 80% yield (0.295g, 1.05 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.67 (s, 1H), 7.69 (dt, *J* = 8.0, 1.2 Hz, 1H), 7.36 – 7.22 (m, 3H), 7.22 – 7.07 (m, 3H), 6.97 – 6.88 (m, 2H), 5.95 (s, 1H), 5.38 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 181.4, 142.2, 141.0, 136.5, 135.9, 135.2, 129.3, 127.7, 127.0, 126.8, 123.7, 122.2, 116.7, 114.2, 111.9. **HRMS** (EI): Calcd. for $C_{17}H_{12}ClNO$ ([M]+): 281.0607, Found: 281.0600.



1d

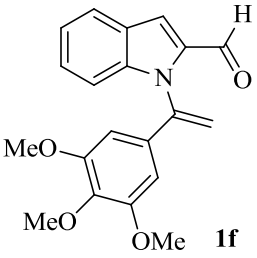
1-(1-(4-(Trifluoromethyl)phenyl)vinyl)-1*H*-indole-2-carboxaldehyde (1d): Prepared according to the general procedure from **S3d** (0.425 g, 1.34 mmol). The mixture was purified by flash column chromatography (90:10 hexane:EtOAc) to give **1d** as a light yellow solid in 80% yield (0.339 g, 1.08 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.70 (s, 1H), 7.74 (dt, *J* = 8.0, 0.80 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.40 – 7.26 (m, 3H), 7.18 – 7.13 (m, 1H), 7.10 (d, *J* = 8.4 Hz, 2H), 6.09 (s, 1H), 5.52 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 181.3, 142.2, 141.1, 140.8, 136.4, 131.5, 131.2, 130.8, 130.5, 127.9, 126.8, 125.9, 125.6, 123.8, 122.8, 122.3, 117.4, 115.8, 111.7. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -63.1. **HRMS** (EI): Calcd. for $C_{18}H_{12}F_3NO$ ([M]+): 315.0871, Found: 315.0881.



1e

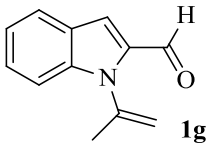
1-(1-(3-Methoxyphenyl)vinyl)-1*H*-indole-2-carboxaldehyde (1e): Prepared according to the general procedure from **S3e** (0.147 g, 0.526 mmol). The

mixture was purified by flash column chromatography (90:10 hexane:EtOAc) to give **1e** as a light yellow solid in 74% yield (0.108 g, 0.389 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.68 (s, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.33 – 7.19 (m, 3H), 7.17 – 7.01 (m, 2H), 6.76 – 6.68 (m, 1H), 6.62 – 6.54 (m, 2H), 5.98 (s, 1H), 5.37 (s, 1H), 3.60 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 181.6, 160.1, 142.8, 141.0, 138.7, 136.6, 130.0, 127.4, 126.6, 123.5, 122.0, 118.1, 115.6, 114.4, 114.1, 111.9, 111.6, 55.4. **HRMS** (EI): Calcd. for $C_{18}H_{15}NO_2$ ([M]+): 277.1103, Found: 277.1111.



1f

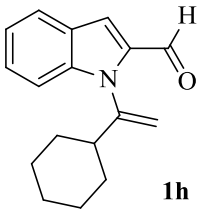
1-(1-(3,4,5-Trimethoxyphenyl)vinyl)-1*H*-indole-2-carboxaldehyde (1f): Prepared according to the general procedure from **S3f** (0.170 g, 0.501 mmol). The mixture was purified by flash column chromatography (80:20 hexane:EtOAc) to give **1f** as a light yellow solid in 83% yield (0.140 g, 0.415 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.53 (d, *J* = 1.6 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.17 – 7.13 (m, 1H), 7.12 – 7.05 (m, 2H), 6.99 – 6.90 (m, 1H), 6.05 (d, *J* = 1.2 Hz, 2H), 5.74 (s, 1H), 5.16 (s, 1H), 3.54 (d, *J* = 1.2 Hz, 3H), 3.41 (d, *J* = 1.2 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 181.7, 153.7, 142.8, 141.1, 139.3, 136.8, 133.0, 127.5, 126.7, 123.6, 122.1, 115.5, 113.3, 112.1, 103.2, 61.2, 56.4. **HRMS** (EI): Calcd. for $C_{20}H_{19}NO_4$ ([M]+): 337.1314, Found: 337.1303.



1g

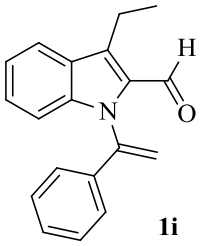
1-(Prop-1-en-2-yl)-1*H*-indole-2-carboxaldehyde (1g): Prepared according to the general procedure from **S3g** (1.10 g, 5.87 mmol). The mixture was purified by flash column chromatography (90:10 hexane:EtOAc) to give **1g** as a light yellow solid in 84% yield (0.914g, 4.94 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.68 (bs, 1H),

7.53 (dq, *J* = 8.0, 2.0, 1.2 Hz, 1H), 7.31 – 7.15 (m, 2H), 7.11 (bs, 1H), 7.00 (ddt, *J* = 7.6, 1.6, 1.2 Hz, 1H), 5.28 (q, *J* = 2.8, 1.2 Hz, 1H), 4.96 (bs, 1H), 1.96 (bs, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 181.5, 141.1, 139.9, 135.7, 127.3, 126.5, 123.3, 121.5, 117.2, 114.6, 111.6, 22.4. **HRMS** (EI): Calcd. for $C_{12}H_{11}NO$ ([M]+): 185.0841, Found: 185.0837.



1h

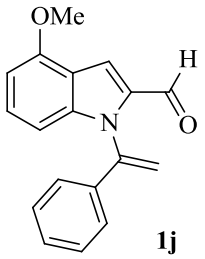
1-(1-Cyclohexylvinyl)-1*H*-indole-2-carboxaldehyde (1h): Prepared according to the general procedure from **S3h** (0.253 g, 0.992 mmol). The mixture was purified by flash column chromatography (90:10 hexane:EtOAc) to give **1h** as a light yellow solid in 77% yield (0.193g, 0.763 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.81 (bs, 1H), 7.64 (dt, *J* = 8.4, 0.80 Hz, 1H), 7.36 – 7.24 (m, 3H), 7.09 (ddd, *J* = 7.6, 6.4, 1.2 Hz, 1H), 5.37 (d, *J* = 1.6 Hz, 1H), 5.11 (bs, 1H), 2.29 – 2.18 (m, 1H), 2.13 – 0.73 (m, 10H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 181.8, 150.0, 141.0, 136.1, 127.1, 126.3, 123.3, 121.5, 116.6, 112.2, 111.9, 44.3, 26.4. **HRMS** (EI): Calcd. for $C_{17}H_{19}NO$ ([M]+): 253.1467, Found: 253.1475.



1i

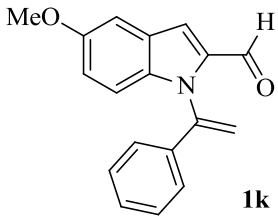
3-Ethyl-1-(1-phenylvinyl)-1*H*-indole-2-carboxaldehyde (1i): Prepared according to the general procedure from **S3i** (0.260 g, 0.937 mmol). The mixture was purified by flash column chromatography (90:10 hexane:EtOAc) to give **1i** as a light yellow solid in 74% yield (0.192 mg, 0.697 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.88 (s, 1H), 7.70 (dt, *J* = 8.4, 0.80 Hz, 1H), 7.29 – 7.09 (m, 6H), 7.05 – 6.99 (m, 2H), 5.98 (s, 1H), 5.38 (s, 1H), 3.10 (q, *J* = 7.6 Hz, 2H), 1.30 (t, *J* = 7.6 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 181.5, 143.2, 140.1, 137.5, 132.4, 131.5, 129.3, 129.0, 127.6,

126.8, 125.7, 121.6, 121.3, 113.8, 111.9, 17.9, 16.6. **HRMS** (EI): Calcd. for $C_{19}H_{17}NO$ ([M]+): 275.1310, Found: 275.1323.



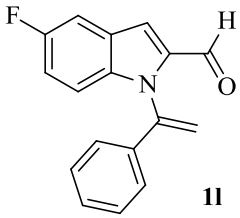
1j

4-Methoxy-1-(1-phenylvinyl)-1*H*-indole-2-carboxaldehyde (1j): Prepared according to the general procedure from **S3j** (0.490 g, 1.75 mmol). The mixture was purified by flash column chromatography (90:10 hexane:EtOAc) to give **1j** as a light yellow solid in 80% yield (0.390 g, 1.41 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.71 (s, 1H), 7.45 – 7.42 (m, 1H), 7.20 – 7.12 (m, 4H), 7.03 – 6.98 (m, 2H), 6.86 (dt, *J* = 8.4, 0.80 Hz, 1H), 6.46 (d, *J* = 7.6, 1H), 5.96 (d, *J* = 0.4 Hz, 1H), 5.37 (d, *J* = 0.4 Hz, 1H), 3.89 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 181.1, 155.3, 143.2, 142.5, 137.2, 135.7, 129.2, 128.9, 128.7, 125.6, 118.4, 114.0, 113.8, 104.6, 100.8, 55.8. **HRMS** (EI): Calcd. for $C_{18}H_{15}NO_2$ ([M]+): 277.1103, Found: 277.1091.



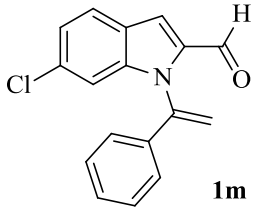
1k

5-Methoxy-1-(1-phenylvinyl)-1*H*-indole-2-carboxaldehyde (1k): Prepared according to the general procedure from **S3k** (0.500 g, 1.79 mmol). The mixture was purified by flash column chromatography (90:10 hexane:EtOAc) to give **1k** as a light yellow solid in 80% yield (0.400 g, 1.44 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.76 (s, 1H), 7.34 (d, *J* = 0.8 Hz, 1H), 7.31 – 7.24 (m, 4H), 7.16 – 7.09 (m, 3H), 7.03 (dd, J = 9.2, 2.4 Hz, 1H), 6.08 (d, *J* = 0.4 Hz, 1H), 5.48 (d, *J* = 0.4 Hz, 1H), 3.88 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 181.6, 155.7, 143.1, 137.3, 136.9, 136.5, 129.4, 129.0, 127.1, 125.7, 119.4, 114.6, 113.9, 113.1, 102.9, 56.0. **HRMS** (EI): Calcd. for $C_{18}H_{15}NO_2$ ([M]+): 277.1103, Found: 277.1111.



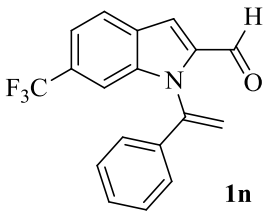
1l

5-Fluoro-1-(1-phenylvinyl)-1*H*-indole-2-carboxaldehyde (1l): Prepared according to the general procedure from **S3l** (0.515 g, 1.93 mmol). The mixture was purified by flash column chromatography (90:10 hexane:EtOAc) to give **1l** as a light yellow solid in 72% yield (0.367 g, 1.38 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.79 (s, 1H), 7.42 (dd, *J* = 8.8, 2.4, 0.4 Hz, 1H), 7.38 (d, *J* = 0.8 Hz, 1H), 7.34 – 7.24 (m, 4H), 7.16 – 7.07 (m, 3H), 6.11 (d, *J* = 0.8 Hz, 1H), 5.49 (d, *J* = 0.8 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 181.7, 160.1, 157.7, 143.0, 137.7, 137.1, 129.6, 129.1, 126.8, 125.6, 116.8, 116.6, 114.8, 114.2, 113.3, 107.7, 107.5. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -121.8. **HRMS** (EI): Calcd. for $C_{17}H_{12}FNO$ ([M]+): 265.0903, Found: 265.0896.



1m

6-Chloro-1-(1-phenylvinyl)-1*H*-indole-2-carboxaldehyde (1m): Prepared according to the general procedure from **S3m** (1.30 g, 4.58 mmol). The mixture was purified by flash column chromatography (90:10 hexane:EtOAc) to give **1m** as a light yellow solid in 77% yield (1.00 g, 3.55 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.64 (bs, 1H), 7.58 (dd, *J* = 8.4, 0.4 Hz, 1H), 7.28 – 7.24 (m, 2H), 7.21 – 7.12 (m, 3H), 7.07 (dd, *J* = 8.8, 1.6 Hz, 1H), 6.99 – 6.94 (m, 2H), 5.98 (d, *J* = 0.8 Hz, 1H), 5.36 (d, *J* = 0.8 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 181.4, 142.8, 141.3, 137.2, 136.9, 133.6, 129.6, 129.1, 125.6, 125.2, 124.6, 123.3, 115.4, 114.2, 111.9. **HRMS** (EI): Calcd. for $C_{17}H_{12}ClNO$ ([M]+): 281.0607, Found: 281.0598.

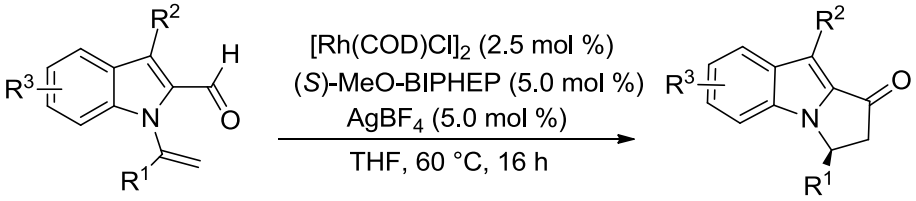


1n

1-(1-Phenylvinyl)-6-(trifluoromethyl)-1*H*-indole-2-carboxaldehyde (1n): Prepared according to the general procedure from **S3n** (0.584 g,

1.84 mmol). The mixture was purified by flash column chromatography (90:10 hexane:EtOAc) to give **1n** as a light yellow solid in 72% yield (0.420 g, 1.33 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.71 (bs, 1H), 7.78 (d, *J* = 8.4, 1H), 7.63 – 7.57 (m, 1H), 7.38 – 7.30 (m, 2H), 7.23 – 7.11 (m, 3H), 7.02 – 6.94 (m, 2H), 6.04 (bs, 1H), 5.41 (bs, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 181.6, 142.6, 139.7, 138.4, 136.8, 129.7, 129.2, 125.5, 124.4, 118.5, 114.5, 109.7. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -61.9. **HRMS** (EI): Calcd. for $C_{18}H_{12}F_3NO$ ([M]+): 315.0871, Found: 315.0862.

2.5.5 General Procedure for Synthesis of 3-Aryl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-ones (2a-f, 2i-n) and 3-Alkyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-ones (2g-h)

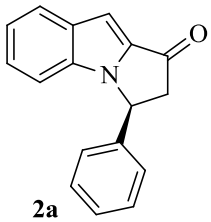


1a-n **2a-n**

2a; R^1 = Ph, R^2 = H, R^3 = H
2b; R^1 = 4-MeO-C_6H_4, R^2 = H, R^3 = H
2c; R^1 = 4-Cl-C_6H_4, R^2 = H, R^3 = H
2d; R^1 = 4-F_3C-C_6H_4, R^2 = H, R^3 = H
2e; R^1 = 3-MeO-C_6H_4, R^2 = H, R^3 = H
2f; R^1 = 3,4,5-MeO_3-C_6H_2, R^2 = H, R^3 = H
2g; R^1 = Me, R^2 = H, R^3 = H
2h; R^1 = C_6H_{11}, R^2 = H, R^3 = H
2i; R^1 = Ph, R^2 = C_2H_5, R^3 = H
2j; R^1 = Ph, R^2 = H, R^3 = 4-MeO
2k; R^1 = Ph, R^2 = H, R^3 = 5-MeO
2l; R^1 = Ph, R^2 = H, R^3 = 5-F
2m; R^1 = Ph, R^2 = H, R^3 = 6-Cl
2n; R^1 = Ph, R^2 = H, R^3 = 6-F_3C

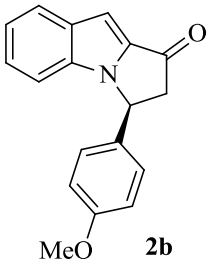
In a nitrogen-filled glovebox, the appropriate 1-(1-arylvinyl)-1*H*-indole-2-carboxaldehyde (**1a-f**, **1i-n**) or 1-(1-alkylvinyl)-1*H*-indole-2-carboxaldehyde (**1g-h**) (0.10 mmol, 1.0 equiv), $[Rh(COD)Cl]_2$ (1.2 mg, 0.0025 mmol, 0.025 equiv), (*S*)-MeO-BIPHEP (2.9 mg,

0.0050 mmol, 0.050 equiv), $AgBF_4$ (1.0 mg, 0.0050 mmol, 0.050 equiv) and THF (0.7 mL) were added to a 1-dram vial. The vial was sealed with a PTFE/silicone-lined septum cap and removed from the glovebox. The reaction mixture was stirred at 60 °C in an oil bath for 16 h. The vial was removed from the oil bath and allowed to cool to room temperature. The reaction mixture was filtered through short plug of silica gel (eluting with 20 ml of 3:2 hexanes:EtOAc). The crude reaction mixture was concentrated under reduced pressure. The crude reaction mixture was purified by flash column silica gel chromatography (hexanes:EtOAc) to give the appropriate 3-aryl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-ones (**2a-f**, **2i-n**) or 3-alkyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-ones (**2g-h**).



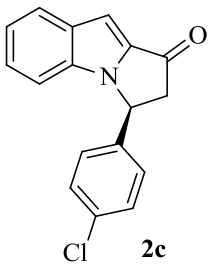
2a

(*S*)-3-Phenyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-one (2a) (Table 2, entry 1): Prepared according to the general procedure from **1a** (25.0 mg, 0.101 mmol). The mixture was purified by flash column chromatography (90:10 hexane:EtOAc) to give **2a** as a light yellow solid in 92% yield (23.0 mg, 0.0930 mmol). The enantiomeric excess was determined by HPLC analysis (220 nm, 25 °C) t_R 15.6 min (major); t_R 12.9 min (minor) [Chiracel AD-H (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 95:5, 1.0 mL/min] to be 99% ee. $[\alpha]_D^{24}$ = -209.0° (c 0.31, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.85 – 7.73 (m, 1H), 7.39 – 7.31 (m, 3H), 7.22 – 7.09 (m, 5H), 6.97 – 6.91 (m, 1H), 5.74 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.68 (dd, *J* = 18.4, 8.0 Hz, 1H), 3.07 (dd, *J* = 18.4, 4.0 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 192.4, 140.2, 136.5, 135.2, 132.8, 129.6, 128.8, 126.3, 125.6, 124.5, 121.9, 112.0, 99.5, 57.5, 50.6. **HRMS** (EI): Calcd. for $C_{17}H_{13}NO$ ([M]+): 247.0997, Found: 247.0989.



2b

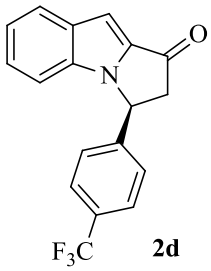
(*S*)-3-(4-Methoxyphenyl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-one (2b) (Table 2, entry 2): Prepared according to the general procedure from **1b** (28.0 mg, 0.101 mmol). The mixture was purified by flash column chromatography (90:10 hexane:EtOAc) to give **2b** as a light yellow solid in 99% yield (27.9 mg, 0.101 mmol). The enantiomeric excess was determined by HPLC analysis (220 nm, 25 °C) t_R 16.9 min (major); t_R 7.37 min (minor) [Chiracel OD-H (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90:10, 1.0 mL/min] to be 99% ee. $[\alpha]_D^{24}$ = -226.0° (c 0.88, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.81 – 7.72 (m, 1H), 7.16 (ddd, *J* = 9.3, 7.8, 1.2 Hz, 2H), 7.11 – 7.04 (m, 3H), 6.97 – 6.92 (m, 1H), 6.91 – 6.84 (m, 2H), 5.69 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.80 (s, 3H), 3.65 (dd, *J* = 18.4, 8.0 Hz, 1H), 3.05 (dd, *J* = 18.4, 4.0 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 192.6, 159.9, 136.5, 135.2, 132.8, 132.2, 127.6, 125.5, 124.4, 121.8, 114.9, 112.1, 99.3, 57.1, 55.6, 50.7. **HRMS** (EI): Calcd. for $C_{18}H_{15}NO_2$ ([M]+): 277.1103, Found: 277.1109.



2c

(*S*)-3-(4-Chlorophenyl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-one (2c) (Table 2, entry 3): Prepared according to the general procedure from **1c** (29.0 mg, 0.103 mmol). The mixture was purified by flash column chromatography (90:10 hexane:EtOAc) to give **2c** as a light yellow solid in 68% yield (19.7 mg, 0.070 mmol). The enantiomeric excess was determined by HPLC analysis (220 nm, 25 °C) t_R 28.9 min (major); t_R 33.5 min (minor) [Chiracel AD-H (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 95:5, 1.0 mL/min] to be 98% ee. $[\alpha]_D^{24}$ = +150.2° (c 0.35, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.81 – 7.76 (m, 1H), 7.37 – 7.30 (m, 2H), 7.24 – 7.13 (m, 2H), 7.11 (d, *J* = 0.4 Hz, 1H), 7.10 – 7.03 (m, 2H), 6.92 (dq, *J* = 8.4, 2.0, 1.2 Hz, 1H), 5.74

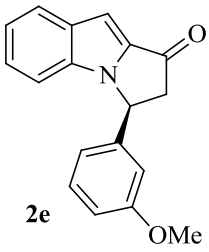
(dd, *J* = 8.0, 3.6 Hz, 1H), 3.69 (dd, *J* = 18.4, 8.0 Hz, 1H), 3.02 (dd, *J* = 18.4, 3.6 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 191.9, 138.8, 136.4, 135.1, 134.8, 132.9, 129.9, 127.7, 125.8, 124.7, 122.1, 111.9, 99.9, 56.8, 50.5. **HRMS** (EI): Calcd. for $C_{17}H_{12}ClNO$ ([M]+): 281.0607, Found: 281.0602.



2d

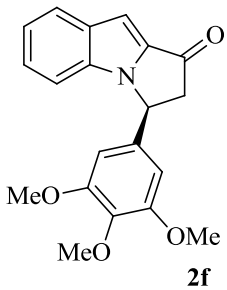
(*S*)-3-(4-(Trifluoromethyl)phenyl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-one (2d) (Table 2, entry 4): Prepared according to a modified version of the general procedure from **1d** (32.0 mg, 0.101 mmol). In a nitrogen-filled glovebox, **1d** (32.0 mg, 0.101 mmol), $[Rh(COD)Cl]_2$ (2.5 mg, 0.00505 mmol, 0.0500 equiv), (*S*)-MeO-BIPHEP (5.9 mg, 0.0101 mmol, 0.100 equiv), $AgBF_4$ (2.0 mg, 0.0101 mmol, 0.100 equiv) and THF (0.7 mL) were added to a 1-dram vial. The vial was sealed with a PTFE/silicone-lined septum cap and removed from the glovebox. The reaction mixture was stirred at 60 °C in an oil bath for 16 h. The vial was removed from the oil bath and allowed to cool to room temperature. The reaction mixture was filtered through short plug of silica gel (eluting with 20 mol of 3:2 hexanes:EtOAc). The crude reaction mixture was concentrated under reduced pressure. The crude reaction mixture was purified by flash column silica gel chromatography (90:10 hexanes:EtOAc) to give **2d** as a light yellow solid in 70% yield (22.5 mg, 0.0713 mmol). The enantiomeric excess was determined by HPLC analysis (220 nm, 25 °C) t_R 34.6 min (major); t_R 47.9 min (minor) [Chiracel AD-H (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 99:1, 1.0 mL/min] to be 99% ee. $[\alpha]_D^{24}$ = -253.0° (c 0.24, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.87 – 7.74 (m, 1H), 7.69 – 7.57 (m, 2H), 7.27 – 7.15 (m, 4H), 7.14 (d, *J* = 0.8 Hz, 1H), 6.91 (dq, *J* = 8.4, 2.4,1.2 Hz, 1H), 5.83 (dd, *J* = 8.0, 3.6 Hz, 1H), 3.73 (dd, *J* = 18.4, 8.0 Hz, 1H), 3.03 (dd, *J* = 18.4, 3.6 Hz, 1H). **^{13}C NMR** (101 MHz,

$CDCl_3$) δ 191.5, 144.3, 136.4, 135.1, 132.9, 131.4, 131.0, 126.8, 126.8, 126.7, 126.7, 126.0, 125.5, 124.7, 122.8, 122.2, 111.8, 100.1, 56.9, 50.3. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -63.1. **HRMS** (EI): Calcd. for $C_{18}H_{12}F_3NO$ ([M]+): 315.0871, Found: 315.0886.



2e

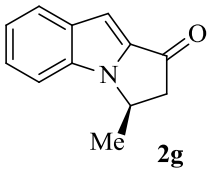
(*S*)-3-(3-Methoxyphenyl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-one (2e) (Table 2, entry 5): Prepared according to the general procedure from **1e** (28.0 mg, 0.101 mmol). The mixture was purified by flash column chromatography (90:10 hexane:EtOAc) to give **2e** as a light yellow solid in 92% yield (25.8 mg, 0.0930 mmol). The enantiomeric excess was determined by HPLC analysis (220 nm, 25 °C) t_R 14.5 min (major); t_R 10.5 min (minor) [Chiracel AD-H (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90:10, 1.0 mL/min] to be 98% ee. $[\alpha]_D^{23}$ = -206.6° (c 0.54, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.79 – 7.75 (m, 1H), 7.21 – 7.11 (m, 2H), 7.11 – 7.05 (m, 3H), 6.95 (dq, *J* = 8.4, 2.4, 1.2 Hz, 1H), 6.91 – 6.84 (m, 2H), 5.69 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.80 (s, 3H), 3.65 (dd, *J* = 18.4, 8.0 Hz, 1H), 3.05 (dd, *J* = 18.4, 4.0 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 192.4, 160.6, 141.9, 136.5, 135.3, 132.8, 130.8, 125.6, 124.5, 121.9, 118.5, 113.9, 112.2, 99.5, 57.4, 55.6, 50.5. **HRMS** (EI): Calcd. for $C_{18}H_{15}NO_2$ ([M]+): 277.1103, Found: 277.1102.



2f

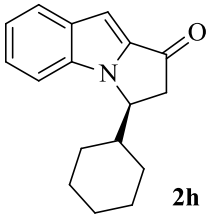
(*S*)-3-(3,4,5-Trimethoxyphenyl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-one (2f) (Table 2, entry 6): Prepared according to the general procedure from **1f** (34.0 mg, 0.100 mmol). The mixture was purified by flash column chromatography (80:20 hexane:EtOAc) to give **2f** as a light yellow solid in

82% yield (27.8 mg, 0.0820 mmol). The enantiomeric excess was determined by HPLC analysis (220 nm, 25 °C) t_R 21.8 min (major); t_R 18.8 min (minor) [Chiracel AD-H (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90:10, 1.0 mL/min] to be 99% ee. $[\alpha]_D^{24}$ = -229.1° (c 0.48, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.80 – 7.76 (m, 1H), 7.20 (dddd, *J* = 24.4, 14.8, 6.8, 0.8 Hz, 2H), 7.10 (d, *J* = 0.4 Hz, 1H), 7.01 (dq, *J* = 8.4, 2.0, 1.2 Hz, 1H), 6.32 (s, 2H), 5.66 (dd, *J* = 8.0, 3.6 Hz, 1H), 3.84 (s, 3H), 3.74 (s, 6H), 3.66 (dd, *J* = 18.4, 8.0 Hz, 1H), 3.08 (dd, *J* = 18.4, 3.6 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 192.4, 154.3, 138.3, 136.6, 135.9, 135.4, 132.8, 125.7, 124.5, 122.0, 112.2, 103.2, 99.7, 61.2, 57.8, 56.5, 50.6. **HRMS** (EI): Calcd. for $C_{20}H_{19}NO_4$ ([M]+): 337.1314, Found: 337.1306.



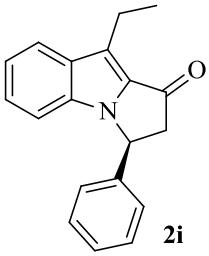
2g

(*R*)-3-Methyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-one (2g) (Table 2, entry 7): Prepared according to the general procedure from **1g** (19.0 mg, 0.102 mmol). The mixture was purified by flash column chromatography (80:20 hexane:EtOAc) to give **2g** as a light yellow solid in 99% yield (18.9 mg, 0.102 mmol). The enantiomeric excess was determined by HPLC analysis (220 nm, 25 °C) t_R 27.2 min (major); t_R 23.9 min (minor) [Chiracel AD-H (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 99:1, 1.0 mL/min] to be 99% ee. $[\alpha]_D^{24}$ = -127.6° (c 0.75, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.4, 1H), 7.53 – 7.43 (m, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.19 (t, *J* = 7.6 Hz, 1H), 6.99 (bs, 1H), 4.99 – 4.83 (m, 1H), 3.43 (dd, *J* = 18.4, 7.6 Hz, 1H), 2.80 (dd, *J* = 18.4, 3.2 Hz, 1H), 1.69 (d, *J* = 6.4 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 193.1, 135.9, 134.9, 132.7, 125.4, 124.7, 121.6, 111.5, 110.3, 99.1, 49.6, 48.7, 22.0. **HRMS** (EI): Calcd. for $C_{12}H_{11}NO$ ([M]+): 185.0841, Found: 185.0842.



2h

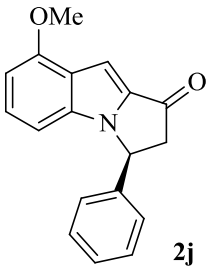
(*S*)-3-Cyclohexyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-one (2h) (Table 2, entry 8): Prepared according to a modified version of the general procedure from **1h** (26.0 mg, 0.102 mmol). In a nitrogen-filled glovebox, **1h** (26.0 mg, 0.102 mmol), $[Rh(COD)Cl]_2$ (1.3 mg, 0.00255 mmol, 0.0250 equiv), (*S*)-MeO-BIPHEP (3.0 mg, 0.00513 mmol, 0.0500 equiv), $AgBF_4$ (1.0 mg, 0.00513 mmol, 0.0500 equiv) and 1,4-dioxane (0.7 mL) were added to a 1-dram vial. The vial was sealed with a PTFE/silicone-lined septum cap and removed from the glovebox. The reaction mixture was stirred at 101 °C in an oil bath for 16 h. The vial was removed from the oil bath and allowed to cool to room temperature. The reaction mixture was filtered through short plug of silica gel (eluting with 20 mol of 3:2 hexanes:EtOAc). The crude reaction mixture was concentrated under reduced pressure. The crude reaction mixture was purified by flash column silica gel chromatography (90:10 hexanes:EtOAc) to give **2h** as a light yellow solid in 45% yield (11.7 mg, 0.0462 mmol). The enantiomeric excess was determined by HPLC analysis (220 nm, 25 °C) t_R 12.3 min (major); t_R 8.66 min (minor) [Chiracel AD-H (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 95:5, 1.0 mL/min] to be 95% ee. $[\alpha]_D^{24}$ = +253.9° (c 0.16, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.0 Hz, 1H), 7.54 – 7.45 (m, 1H), 7.35 (t, *J* = 7.6 Hz, 1H), 7.18 (t, *J* = 7.6 Hz, 1H), 6.97 (bs, 1H), 4.86 – 4.77 (m, 1H), 3.14 (dd, *J* = 18.4, 8.0 Hz, 1H), 2.96 (dd, *J* = 18.4, 2.4 Hz, 1H), 2.37 – 2.25 (m, 1H), 1.89 – 1.76 (m, 2H), 1.74 – 1.55 (m, 2H), 1.41 – 1.19 (m, 2H), 1.19 – 0.78 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 193.5, 136.5, 135.2, 132.7, 125.3, 124.7, 121.6, 111.9, 98.7, 58.4, 42.5, 41.4, 30.0, 26.5, 25.8, 25.0. **HRMS** (EI): Calcd. for $C_{17}H_{19}NO$ ([M]+): 253.1467, Found: 253.1468.



2i

(*S*)-9-Ethyl-3-phenyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-one (2i)

(Table 3, entry 1): Prepared according to the general procedure from **1i** (28.0 mg, 0.101 mmol). The mixture was purified by flash column chromatography (90:10 hexane:EtOAc) to give **2i** as a light yellow solid in 89% yield (25.0 mg, 0.0900 mmol). The enantiomeric excess was determined by HPLC analysis (220 nm, 25 °C) t_R 8.57 min (major); t_R 12.6 min (minor) [Chiracel OD-H (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 95:5, 1.0 mL/min] to be 98% ee. $[\alpha]_D^{24}$ = -160.9° (c 0.65, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.78 (dq, *J* = 8.0, 1.2, 0.4 Hz, 1H), 7.40 – 7.29 (m, 3H), 7.21 – 7.08 (m, 4H), 6.88 (dt, *J* = 8.4, 0.8 Hz, 1H), 5.68 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.65 (dd, *J* = 18.4, 8.0 Hz, 1H), 3.12 (qd, *J* = 15.2, 7.6, 1.6 Hz, 2H), 3.04 (dd, *J* = 18.4, 4.0 Hz, 1H), 1.40 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 192.6, 140.7, 135.0, 132.8, 132.1, 129.6, 128.7, 126.4, 125.6, 122.7, 120.9, 119.9, 112.0, 57.1, 51.1, 17.9, 15.9. **HRMS** (EI): Calcd. for $C_{19}H_{17}NO$ ([M]+): 275.1310, Found: 275.1315.

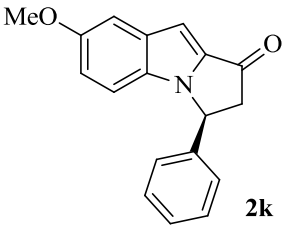


2j

(*S*)-8-Methoxy-3-phenyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-one (2j)

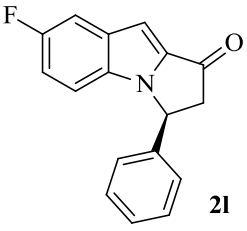
(Table 3, entry 2): Prepared according to the general procedure from **1j** (28.0 mg, 0.100 mmol). The mixture was purified by flash column chromatography (90:10 hexane:EtOAc) to give **2j** as a light yellow solid in 90% yield (25.2 mg, 0.0900 mmol). The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 20.4 min (major); t_R 27.8 min (minor) [Chiracel AD-H (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 95:5, 1.0 mL/min] to be 99% ee. $[\alpha]_D^{24}$ = -185.3° (c 0.71, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 – 7.31 (m, 2H), 7.22 (d, *J* = 0.4 Hz, 1H), 7.14 – 7.09 (m, 3H), 6.50 (dd, *J* = 11.6, 8.4 Hz, 2H), 5.71 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.96 (s, 3H), 3.67

(dd, *J* = 18.4, 8.0 Hz, 1H), 3.05 (dd, *J* = 18.4, 4.0 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 191.9, 155.9, 140.3, 136.5, 135.4, 129.6, 128.8, 126.7, 126.3, 124.5, 104.8, 100.4, 97.4, 57.5, 55.7, 50.7. **HRMS** (EI): Calcd. for $C_{18}H_{15}NO_2$ ([M]+): 277.1103, Found: 277.1107.



2k

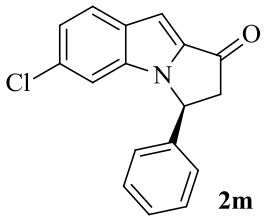
(*S*)-7-Methoxy-3-phenyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-one (2k) (Table 3, entry 3): Prepared according to the general procedure from **1k** (28.0 mg, 0.101 mmol). The mixture was purified by flash column chromatography (90:10 hexane:EtOAc) to give **2k** as a light yellow solid in 97% yield (27.2 mg, 0.0980 mmol). The enantiomeric excess was determined by HPLC analysis (220 nm, 25 °C) t_R 23.7 min (major); t_R 17.8 min (minor) [Chiracel AD-H (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 95:5, 1.0 mL/min] to be 98% ee. $[\alpha]_D^{24}$ = -226.2° (c 0.88, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 – 7.30 (m, 3H), 7.15 – 7.09 (m, 3H), 7.01 (d, *J* = 0.4 Hz, 1H), 6.89 – 6.79 (m, 2H), 5.72 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.83 (s, 3H), 3.67 (dd, *J* = 18.8, 8.0 Hz, 1H), 3.05 (dd, *J* = 18.8, 4.0 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 191.9, 155.5, 140.3, 137.0, 133.3, 130.9, 129.6, 128.8, 126.3, 118.2, 113.0, 103.3, 98.9, 57.5, 55.8, 50.5. **HRMS** (EI): Calcd. for $C_{18}H_{15}NO_2$ ([M]+): 277.1103, Found: 277.1105.



2l

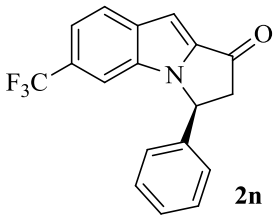
(*S*)-7-Fluoro-3-phenyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-one (2l) (Table 3, entry 4): Prepared according to the general procedure from **1l** (27.0 mg, 0.102 mmol). The mixture was purified by flash column chromatography (90:10 hexane:EtOAc) to give **2l** as a light yellow solid in 92% yield (24.9 mg, 0.0940 mmol). The enantiomeric excess was determined by HPLC analysis (220 nm, 25 °C) t_R 16.9 min (major); t_R 12.4 min (minor) [Chiracel AD-H (0.46 cm x 25

cm)(from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 95:5, 1.0 mL/min] to be 98% ee. $[\alpha]_D^{24}$ = -145.6° (c 0.73, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43 – 7.31 (m, 4H), 7.17 – 7.08 (m, 2H), 7.04 (d, *J* = 0.4 Hz, 1H), 6.95 (td, *J* = 9.2, 2.4 Hz, 1H), 6.86 (dd, *J* = 9.2, 4.4 Hz, 1H), 5.73 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.68 (dd, *J* = 18.8, 8.0 Hz, 1H), 3.06 (dd, *J* = 18.8, 4.0 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 192.0, 159.9, 157.5, 139.9, 137.9, 133.0, 132.9, 131.9, 129.7, 129.0, 126.3, 115.4, 115.1, 113.1, 113.0, 108.4, 108.2, 99.2, 57.7, 50.5. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -121.3. **HRMS** (EI): Calcd. for $C_{17}H_{12}FNO$ ([M]+): 265.0903, Found: 265.0899.



2m

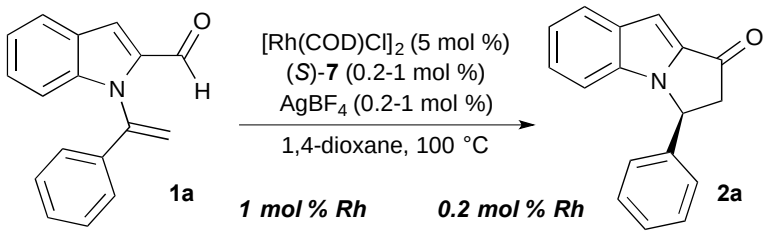
(*S*)-6-Chloro-3-phenyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-one (2m) (Table 3, entry 5): Prepared according to the general procedure from **1m** (28.5 mg, 0.101 mmol). The mixture was purified by flash column chromatography (90:10 hexane:EtOAc) to give **2m** as a light yellow solid in 82% yield (23.4 mg, 0.0830 mmol). The enantiomeric excess was determined by HPLC analysis (220 nm, 25 °C) t_R 34.5 min (major); t_R 58.3 min (minor) [Chiracel AD-H (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 99:1, 1.0 mL/min] to be 98% ee. $[\alpha]_D^{24}$ = -270.6° (c 0.70, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.8, 1H), 7.44 – 7.30 (m, 3H), 7.15 – 7.08 (m, 3H), 7.06 (d, *J* = 0.8 Hz, 1H), 6.93 (bs, 1H), 5.71 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.68 (dd, *J* = 18.8, 8.0 Hz, 1H), 3.06 (dd, *J* = 18.8, 4.0 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 191.6, 139.4, 136.9, 134.9, 131.3, 130.9, 129.5, 128.8, 125.9, 125.1, 122.7, 111.3, 99.4, 57.3, 50.2. **HRMS** (EI): Calcd. for $C_{17}H_{12}ClNO$ ([M+H]+): 281.0607, Found: 281.0594.



2n

(*S*)-3-Phenyl-6-(trifluoromethyl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-one (2n) (Table 3, entry 6): Prepared according to the general procedure from **1n** (32.0 mg, 0.101 mmol). The mixture was purified by flash column chromatography (90:10 hexane:EtOAc) to give **2n** as a light yellow solid in 81% yield (26.0 mg, 0.0820 mmol). The enantiomeric excess was determined by HPLC analysis (220 nm, 25 °C) t_R 29.9 min (major); t_R 45.6 min (minor) [Chiracel AD-H (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 99:1, 1.0 mL/min] to be 99% ee. $[\alpha]_D^{24}$ = -234.1° (c 0.73, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.4 Hz, 1H), 7.43 – 7.33 (m, 4H), 7.24 – 7.20 (m, 1H), 7.17 – 7.10 (m, 3H), 5.81 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.72 (dd, *J* = 18.8, 8.0 Hz, 1H), 3.11 (dd, *J* = 18.8, 4.0 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 192.2, 139.5, 138.8, 134.6, 133.7, 129.9, 129.3, 127.4, 127.1, 126.2, 126.1, 125.2, 123.4, 118.2, 109.6, 99.3, 57.8, 50.5. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -61.9. **HRMS** (EI): Calcd. for $C_{18}H_{12}F_3NO$ ([M]+): 315.0871, Found: 315.0878.

2.5.6 Procedures for Synthesis of 2a at 0.2 and 1 mol % Catalyst Loading



1 mol % Rh	*0.2 mol % Rh*
99% conversion	94% conversion
95% yield	79% yield
98% ee	98% ee

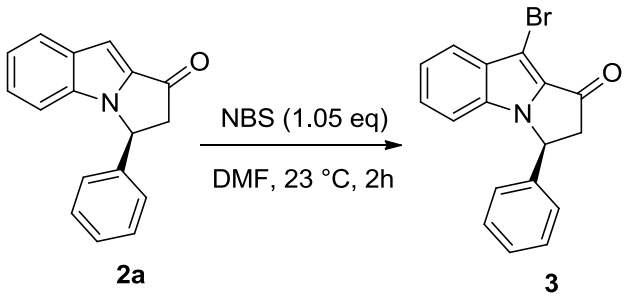
1 mol % Catalyst Loading: In a nitrogen-filled glovebox, 1-(1-phenylvinyl)-1*H*-indole-2-carboxaldehyde (**1a)** (100 mg, 0.400 mmol, 1.00 equiv), $[Rh(COD)Cl]_2$ (1.0 mg, 0.0020 mmol, 0.0050 equiv), (*S*)-MeO-BIPHEP (**7**) (2.3 mg, 0.0040 mmol, 0.010 equiv), $AgBF_4$ (0.8 mg, 0.004 mmol, 0.01 equiv) and 1,4-dioxane (2.8 mL) were added to a 1-dram vial. The vial was sealed

with a PTFE/silicone-lined septum cap and removed from the glovebox. The reaction mixture was stirred at 101 °C in an oil bath for 16 h. The vial was removed from the oil bath and allowed to cool to room temperature. The reaction mixture was filtered through short plug of silica gel (eluting with 50 ml of 3:2 hexanes:EtOAc). The crude reaction mixture was concentrated under reduced pressure. The crude reaction mixture was purified by flash column silica gel chromatography (90:10 hexanes:EtOAc) to give (*S*)-3-phenyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-one (**2a)** as a light yellow solid in 95% yield (95 mg, 0.38 mmol). The enantiomeric excess was determined by HPLC analysis (220 nm, 25 °C) t_R 15.6 min (major); t_R 12.9 min (minor) [Chiracel AD-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 95:5, 1.0 mL/min] to be 98% ee.

0.2 mol % Catalyst Loading: In a nitrogen-filled glovebox, 1-(1-phenylvinyl)-1*H*-indole-2-carboxaldehyde (**1a)** (500 mg, 2.0 mmol, 1.0 equiv), $[Rh(COD)Cl]_2$ (1.0 mg, 0.0020 mmol, 0.0010 equiv), (*S*)-MeO-BIPHEP (**7**) (2.3 mg, 0.0040 mmol, 0.0020 equiv), $AgBF_4$ (0.8 mg, 0.0040 mmol, 0.0020 equiv) and 1,4-dioxane (14 mL) were added to a 20 mL scintillation vial. The vial was sealed with a PTFE/silicone-lined septum cap and removed from the glovebox. The reaction mixture was stirred at 101 °C in an oil bath for 16 h. The vial was removed from the oil bath and allowed to cool to room temperature. The reaction mixture was filtered through short plug of silica gel (eluting with 150 ml of 3:2 hexanes:EtOAc). The crude reaction mixture was concentrated under reduced pressure. The crude reaction mixture was purified by flash column silica gel chromatography (90:10 hexanes:EtOAc) to give (*S*)-3-phenyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-one (**2a)** as a light yellow solid in 79% yield (395 mg, 1.60 mmol). The enantiomeric excess was determined by HPLC analysis (220 nm, 25 °C) t_R 15.6 min (major); t_R

12.9 min (minor) [Chiracel AD-H (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 95:5, 1.0 mL/min] to be 98% ee.

2.5.7 Synthesis of (*S*)-9-Bromo-3-phenyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-one (3)



2a **3**

To a solution of (*S*)-3-phenyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-one (**2a**) (150.0 mg, 0.606 mmol) in DMF (10 ml) was added *N*-bromosuccinimide (113.0 mg, 0.637 mmol). The reaction mixture was stirred for 2 hours at 23 °C under a nitrogen atmosphere. The reaction mixture was diluted with ethyl acetate and washed with brine. The organic layer was dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash column silica gel chromatography (90:10 hexane:EtOAc) to give (*S*)-9-bromo-3-phenyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-one (**3**) as an off-white solid in 88% yield (175 mg, 0.535 mmol). The resulting product was recrystallized from methanol to obtain colorless single crystals for single crystal XRD analysis. m.p. = 134-136 °C (decomposition) $[\alpha]_D^{24}$ = -151.2° (c 0.65, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.77 – 7.68 (m, 1H), 7.46 – 7.30 (m, 3H), 7.25 – 7.19 (m, 2H), 7.18 – 7.12 (m, 2H), 6.96 – 6.86 (m, 1H), 5.71 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.70 (dd, *J* = 18.8, 8.0 Hz, 1H), 3.10 (dd, *J* = 18.4, 4.0 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 190.6, 139.7, 134.9, 132.9, 132.2, 129.7, 129.1, 126.7, 126.4, 122.6, 112.2, 88.8, 57.6, 50.9. **HRMS** (EI): Calcd. for $C_{17}H_{12}BrNO$ ([M]+): 325.0102, Found: 325.0108.

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CHAPTER 3

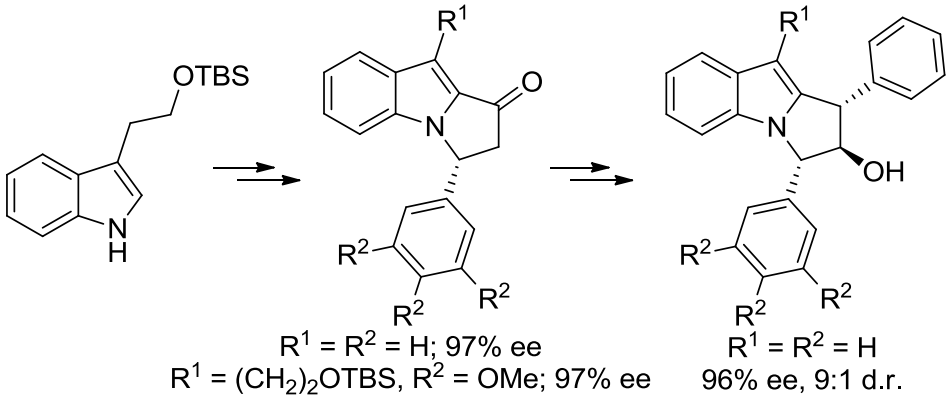
AN ENANTIOSELECTIVE MODEL SYNTHESIS AND PROGRESS TOWARD THE PUTATIVE STRUCTURE OF YUREMAMINE

Modified from a paper published in *The Journal of Organic Chemistry*[1]

Avipsa Ghosh, David T. Bainbridge, and Levi M. Stanley*

3.1 Abstract

An enantioselective model synthesis of 2,3-Dihydro-1*H*-pyrrolo[1,2-*a*]-indole core of putative structure of yuremamine is reported in 39% overall yield and 96% ee over 5 steps. The model synthesis leverages enantioselective, rhodium-catalyzed hydroacylation of an *N*-vinylindole-2-carboxaldehyde as the key step in the installation of the stereochemical triad. An enantioselective synthesis of a densely functionalized dihydropyrroloindolone that maps onto the putative structure of yuremamine is demonstrated in 26% yield and 97% ee over 8 steps.



[1] Ghosh, A.; Bainbridge, D. T.; Stanley, L. M. *J. Org. Chem.* **2016**, 10.1021/acs.joc.6b01730

3.2 Introduction

2,3-Dihydro-1*H*-pyrrolo[1,2-*a*]-indole and oxidized derivatives are recurring motifs in natural products and drug candidates including the antimalarial flinderoles[1] and isoborreverines,[2] the antitumor antibiotic mitomycin C,[3] the PKC inhibitor JTT-010[4] and isatisine A[5] which exhibits antiviral activity. Yuremamine, a phytoindole alkaloid with hallucinogenic and psychoactive properties was isolated from the stem bark of *Mimosa hostilis* in 2005 by Callaway and co-workers.[6] The structure of yuremamine, originally proposed to be the densely functionalized dihydropyrroloindole **1** with three contiguous stereogenic centers, was recently revised to the flavonoidal indole **2** by Sperry and co-workers (Figure 3.1).[7]

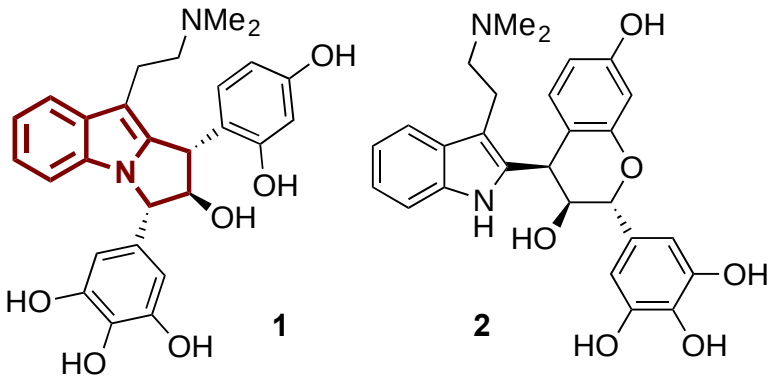
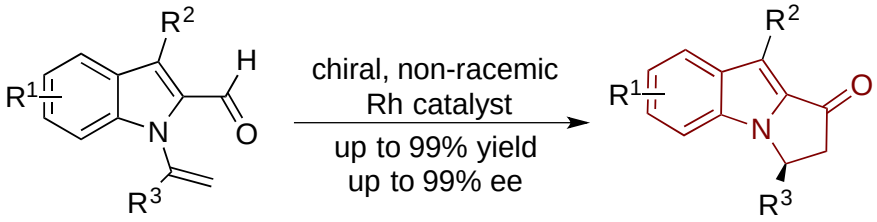


Figure 3.1 Originally proposed structure and revised structure of yuremamine

The intriguing molecular architecture of **1** prompted numerous synthetic studies towards the putative structure since the isolation of yuremamine. While several synthetic strategies towards the dihydropyrroloindole core of **1** have been developed by the Kerr, Shi, Dethe, Chen, France, You, Sperry and Zu groups,[8] the first racemic total synthesis was reported by the Iwasawa group in 2015.[9] Despite these synthetic efforts during the past decade, enantioselective

total synthesis of **1** or synthetic approaches to generate the chiral dihydropyrroloindole core with control of the absolute configuration of the stereochemical triad have not been reported.

Scheme 3.1 Enantioselective Hydroacylation of *N*-Vinylindole-2-carboxadehydes to Access Chiral Dihydropyrroloindolones

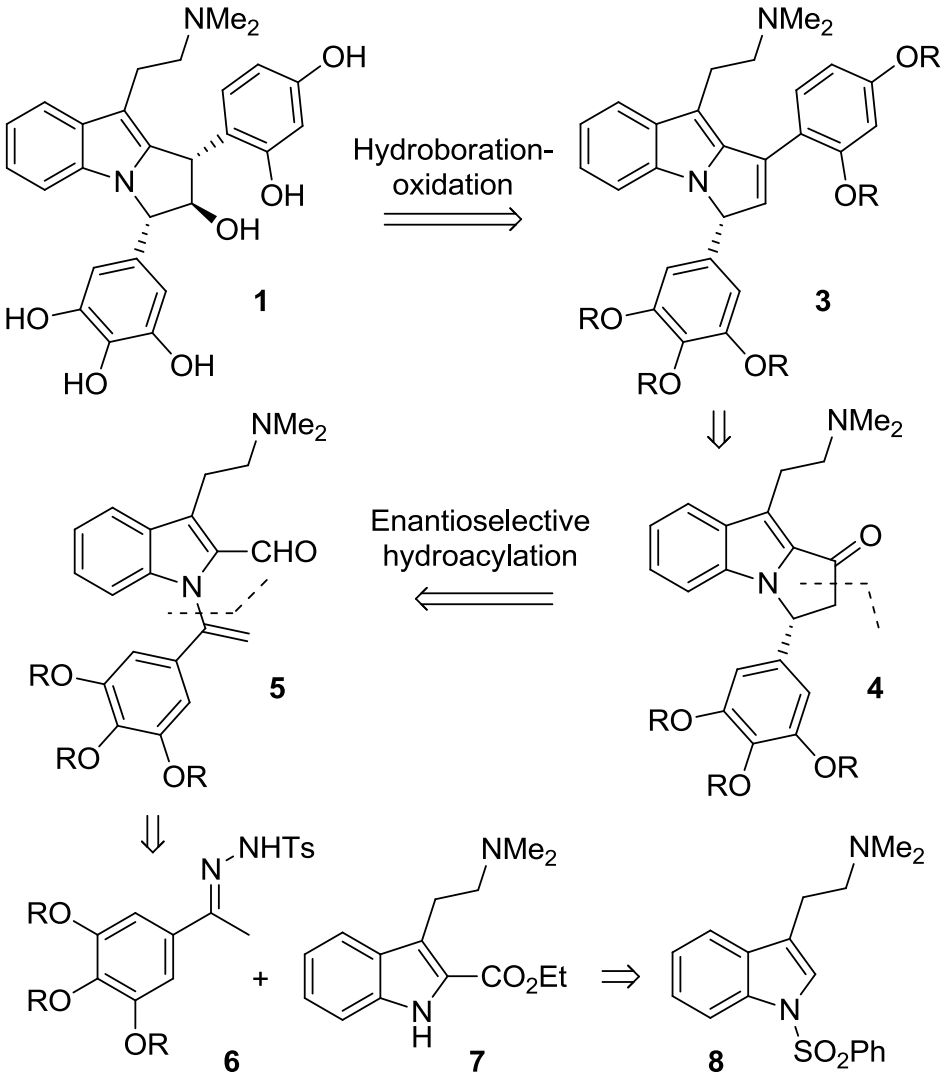


Compound **1** is a fundamentally challenging target due to the lack of well-established enantioselective methods to generate chiral 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]-indoles.[10] The dihydropyrroloindole core of **1** contains three contiguous stereogenic centers that must be formed in a stereocontrolled fashion. Recently, we reported catalytic, intramolecular hydroacylations of *N*-vinylindole-2-carboxaldehydes to form β-substituted dihydropyrroloindolones with high enantioselectivities that offer the potential to address these challenges (Scheme 3.1).[11] The enantioselective hydroacylation would enable control of the absolute configuration of one of the requisite stereogenic centers present in the dihydropyrroloindole core. In addition, the ketone functionality present in the dihydropyrroloindolone product of hydroacylation can serve as a synthetic handle to install the additional stereogenic centers with precise control of the absolute and relative configuration of the stereochemical triad.

Herein, we report an enantioselective model synthesis of the 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole core of **1** utilizing enantioselective rhodium-catalyzed hydroacylation of an *N*-vinylindole-2-carboxaldehyde as the key step for installation of the three contiguous stereogenic centers. We also report an enantioselective synthesis of a functionalized chiral dihydropyrroloindolone that maps onto the structure of **1**.

3.3 Retrosynthetic Analysis and Synthesis Plan

Scheme 3.2 Retrosynthetic Analysis for the Enantioselective Synthesis of Compound **1**



Scheme 3.2 illustrates the strategy we originally envisioned to complete an enantioselective synthesis of **1**. Installation of the stereochemical triad in **1** would be achieved by a sequence of hydroboration and oxidation occurring on the face of the olefin opposite to the aryl group attached to the stereogenic center in **3**.[12] Compound **3** would be synthesized by a sequence of Grignard addition to the chiral dihydropyrroloindolone **4** followed by dehydration of the

resulting tertiary alcohol to form the required alkene. Based on our previous studies, we planned the synthesis of **4** from *N*-vinylindole-2-carboxaldehyde **5** by an enantioselective, intramolecular rhodium-catalyzed hydroacylation reaction.[11] Compound **5** would be generated by a palladium-catalyzed cross-coupling reaction of indole **7** and hydrazone **6**.[13] Indole **7** could be derived from **8** by direct installation of the ester functionality at the 2-position of the indole followed by removal of the protecting group from the indole nitrogen.

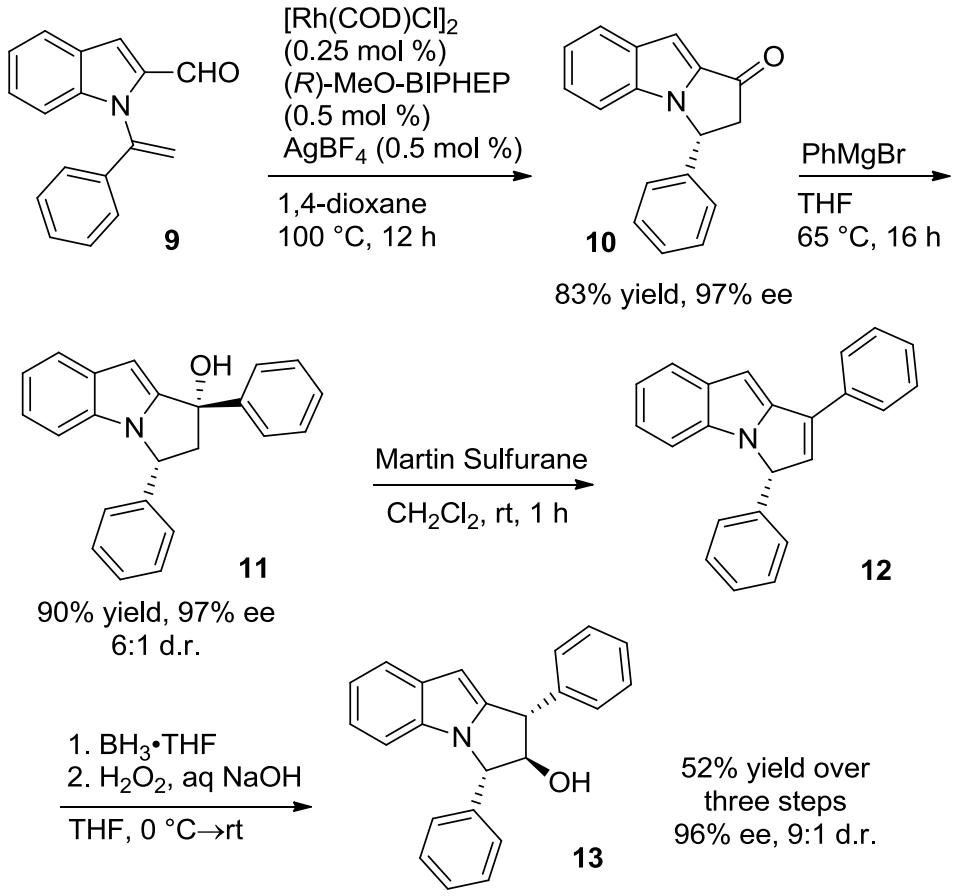
3.4 Results and Discussion

3.4.1 Enantioselective model synthesis of dihydropyrroloindole core of putative yuremamine

We were aware that intermediate **3** may be susceptible to olefin isomerization that could racemize the stereogenic center set by enantioselective hydroacylation. To test our strategy to install the three contiguous stereogenic centers in an enantioselective and diastereoselective fashion, we conducted a model study starting from *N*-vinylindole-2-carboxaldehyde **9** (Scheme 3.3). Enantioselective hydroacylation of **9** in the presence of 0.5 mol% of a Rh catalyst prepared in situ from $[Rh(COD)Cl]_2$, (*R*)-MeO-BIPHEP, and $AgBF_4$ formed dihyropyrroloindolone **10** in 83% yield with 97% ee. Addition of phenylmagnesium bromide to **10** generated the tertiary alcohol **11** in 90% yield as a 6:1 mixture of diastereomers with complete retention of enantiomeric excess (97% ee). Subsequent dehydration of the resulting tertiary alcohol with Martin sulfurane generated (*R*)-1,3-diphenyl-3*H*-pyrrolo[1,2-*a*]indole **12**.[14] The carbon skeleton present in the dihydropyrroloindole core of **1** was established by immediate hydroboration of **12** followed by oxidation of the resulting alkylborane with basic hydrogen peroxide. Dihydropyrroloindole **13** was isolated as a 9:1 mixture of diastereomers in 52% yield over three steps without significant loss of enantioselectivity (96% ee). Consistent with hydroboration and

oxidations of 1,3-diarylcyclopent-1-enes, the hydroboration and oxidation of **12** preferentially occurs on the face of the olefin opposite to the phenyl group attached to the stereogenic center.[12] This sequence occurs to set a stereochemical triad with both aryl groups *trans* to the hydroxyl group. The relative stereochemistry of the dihydropyrroloindole core **13** was established by geminal carbon-proton spin coupling-constant ($^2J_{C,H}$) values (*J*-based configuration analysis) and the dependence of these values on dihedral angles.[15]

Scheme 3.3 Enantioselective Model Synthesis of the 2,3-Dihydro-1*H*-pyrrolo[1,2-*a*]indole Core of **1**



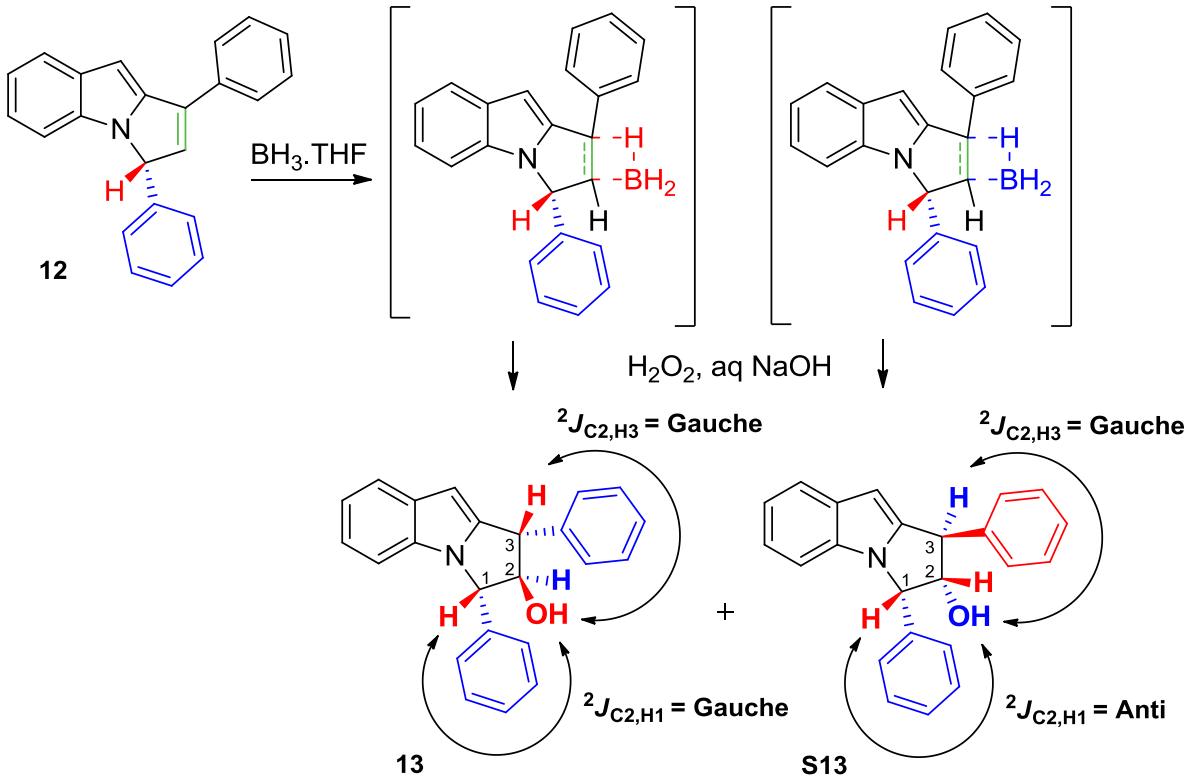


Figure 3.2 Possible products of hydroboration-oxidation reaction of **12**

3.4.2 Stereochemical Analysis of 13

The relative stereochemistry of **13** was established based on the geminal carbon-proton spin coupling-constant ($^2J_{C,H}$) values (*J*-based configuration analysis) and the dependence of these values on dihedral angles (Figure 3.2 and Figure 3.3b). The magnitude of coupling between ^{13}C and ^1H across two bonds, the $^2J_{C,H}$ value including (+/-) sign, depends on the relative spatial arrangement of the proton and the electronegative substituent on the particular carbon. If an oxygen atom on a carbon atom is gauche to its geminal proton, the $^2J_{C,H}$ values are large; and the values become small when the oxygen atom is anti to its germinal proton. $^2J_{C2,H1}$ and $^2J_{C2,H3}$ values in compound **13** were determined to be -5.0 Hz and -6.2 Hz respectively, consistent with the gauche orientation of the hydroxyl group with both H1 and H3 methine protons (Figure 3.2 and Figure 3.3). These carbon-proton spin coupling-constant values were determined by a hetero

half-filtered TOCSY experiment, often called HETLOC (HETeronuclear LOng-range Coupling). The (+/-) sign of $^{2}J_{Cx,Ha}$ was determined from the slope of the linked line between the split peaks against the slope of the diagonal peaks (Figure 3.3c); the $^{2}J_{Cx,Ha}$ value is positive if the coefficients for the slope of both lines take the same (+/-) signs, whereas the value is negative if they have different signs for the coefficients. The magnitude of $^{2}J_{Cx,Ha}$ values were evaluated from a chemical shift difference of the two Hx(*F*1)-Ha(*F*2) peaks split in the *F*2 dimension (Figure 3.3d).

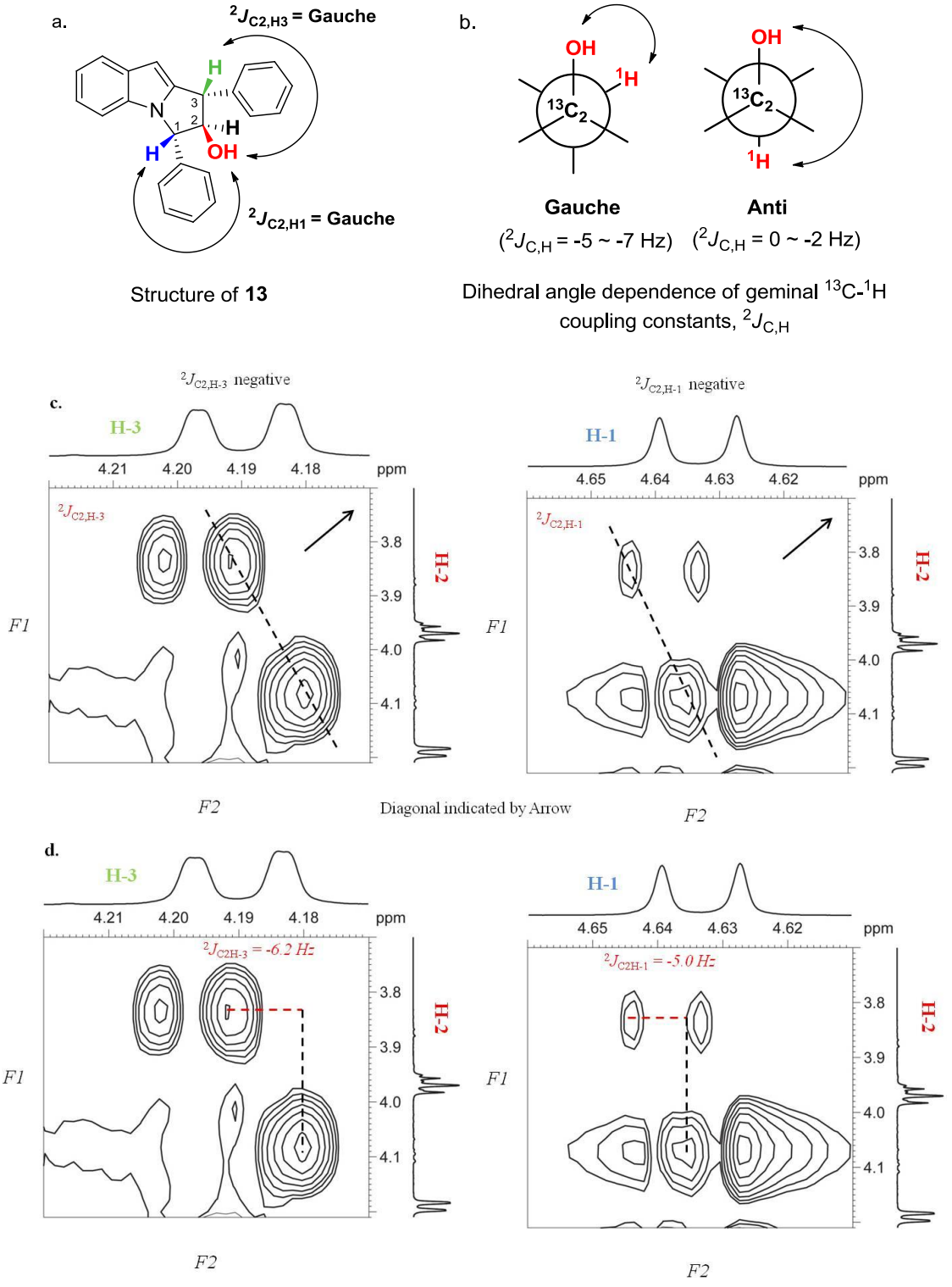


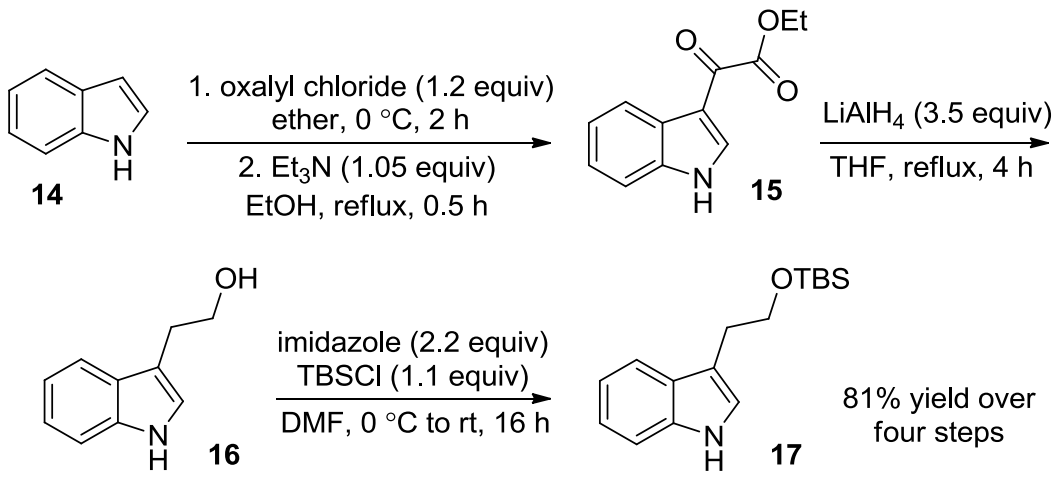
Figure 3.3 (a) Structure of **13**; (b) Dihedral angle dependence of geminal ^{13}C-^{1}H coupling constants, $^2J_{C,H}$; (c) Determination of sign (+/-) for $^2J_{C,H}$ coupling constant values in partial HETLOC spectrum of **13**, and (d) Determination of $^2J_{C,H}$ coupling constant values in partial HETLOC spectrum of **13**.

3.4.3 Progress toward enantioselective synthesis of putative structure of yuremamine

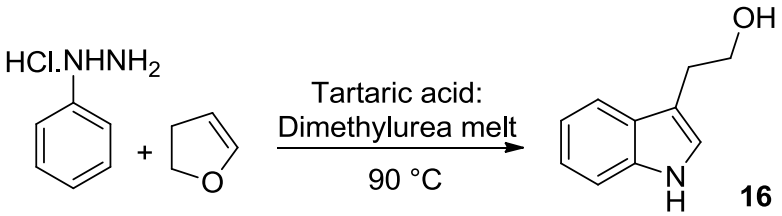
Encouraged by the results of our model synthesis, we initiated studies toward an enantioselective synthesis of **1**. We conducted our studies starting from the TBS ether of tryptophol **17**. Scheme 3.4 illustrates synthesis of tryptophol **17** starting from indole **14** over 4 steps in 81% yield.[16] Reaction of **14** with oxalyl chloride formed 3-indolylglyoxylyl chloride which on refluxing in ethanol in presence of triethylamine generated ethyl 3-indolylglyoxylate **15**. $LiAlH_4$ reduction of **15** generated tryptophol **16**. The alcohol in **16** was protected in presence of imidazole and TBSCl to generate TBS protected tryptophol **17**. Attempts for one-step synthesis of tryptophol **16** proved challenging especially when the reactions were carried out in multigram scale (Scheme 3.5).[17]

Scheme 3.6 illustrates the synthesis of indole **20** from the TBS ether of tryptophol **17**.[16c] The indole nitrogen in **17** was protected using benzenesulfonyl chloride in the presence of tetrabutylammonium hydrogensulfate (TBAHS) to furnish **18** in 99% yield.[18] We envisioned direct installation of an ester at the 2-position of indole via lithiation followed by quenching with an appropriate electrophile. Interestingly, common lithiating agents such as *n*-BuLi, *sec*-BuLi, and *tert*-BuLi led to the formation of complex mixtures of multiple products even with less than one equivalent of base (Equation 3.1).[19] However, lithiation in the presence of freshly prepared lithium diisopropylamide (LDA) at -78 °C followed by reaction with diethyl carbonate or ethyl chloroformate formed the desired ethyl indole-2-carboxylate **19** as the only product in 30-75% yield (Table 3.1, entries 1 and 3). The use of ethyl chloroformate as the electrophile and increasing the reaction temperature improved the yield of the desired product to 90% (Table 3.1, entry 4).

Scheme 3.4 Synthesis of TBS protected Tryptophol **17**

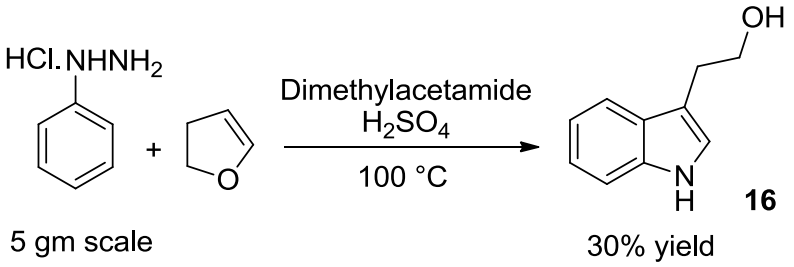


Scheme 3.5 One-Step Synthesis of Tryptophol **16**



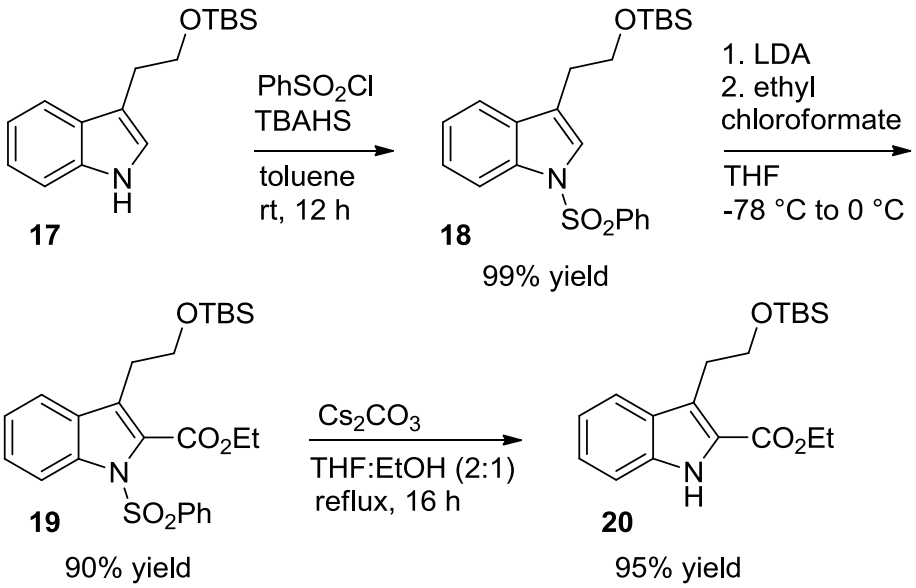
(1)

entry	scale (gm)	yield (%)
1	2	35
2	5	10
3	10	4



(2)

Scheme 3.6 Synthesis of Indole **20**



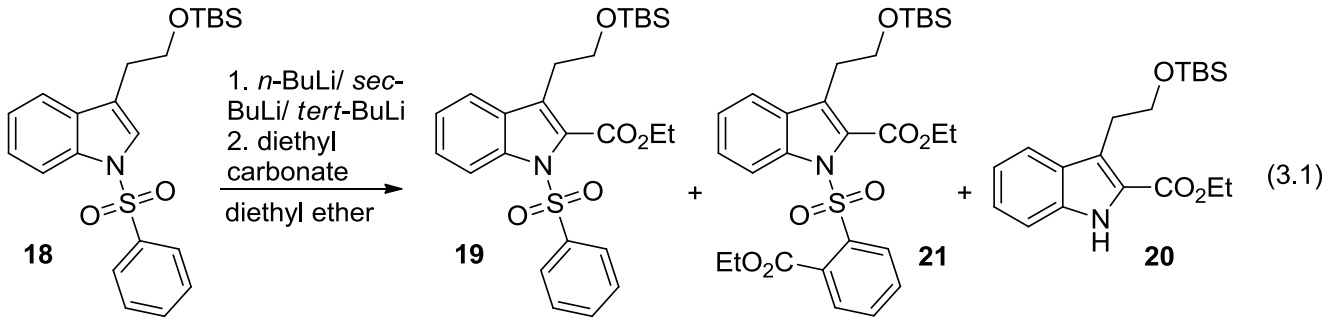
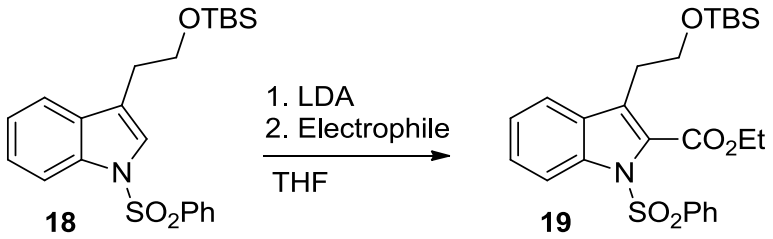


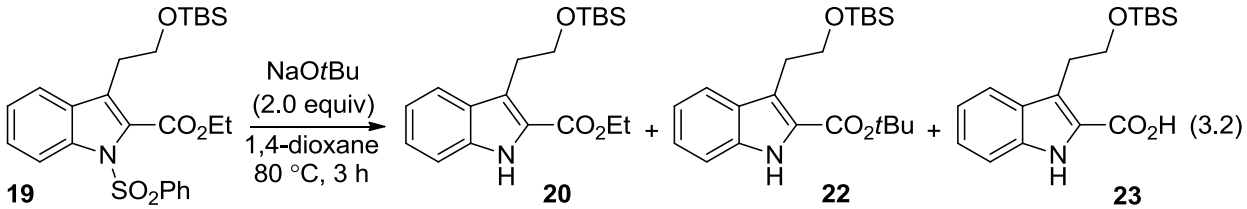
Table 3.1 Identification of Reaction Conditions for Synthesis of Ester **19**[a]



entry	temp (°C)	electrophile	Yield (%)[b]
1	-78	diethyl carbonate	30
2	-78→0	diethyl carbonate	60
3	-78	ethyl chloroformate	75
4	-78→0	ethyl chloroformate	90

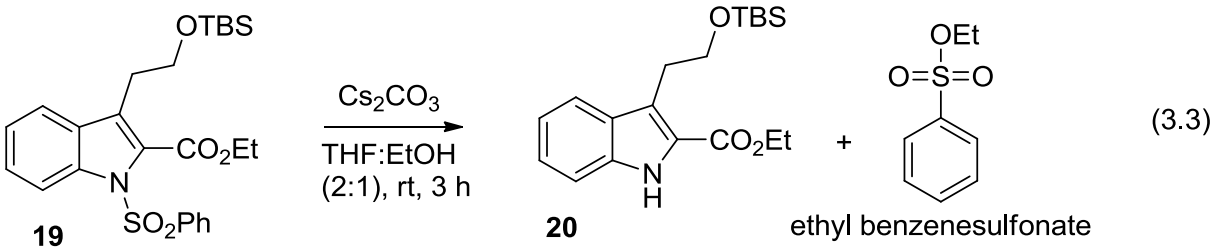
[a]Reaction conditions: **18** (1.20 mmol, 1.00 equiv), LDA (1.20 mmol, 1.00 equiv), Electrophile (1.44 mmol, 1.20 equiv) and THF (7.0 mL). [b]Isolated yield of **19** after column chromatography.

With a suitable method to install the ester functionality, we attempted to remove the benzenesulfonyl protecting group in **19**. Although many methods are established to accomplish similar transformations, the deprotection of **19** proved challenging.[20] Deprotection in the presence of Na-Hg/Na_2HPO_4 led to incomplete conversion (60%) of **19** to indole **20**.[20a] The reaction of **19** in presence of sodium *tert*-butoxide in 1,4-dioxane was plagued by undesired transesterification and hydrolysis of the ester (Equation 3.2).[20b]



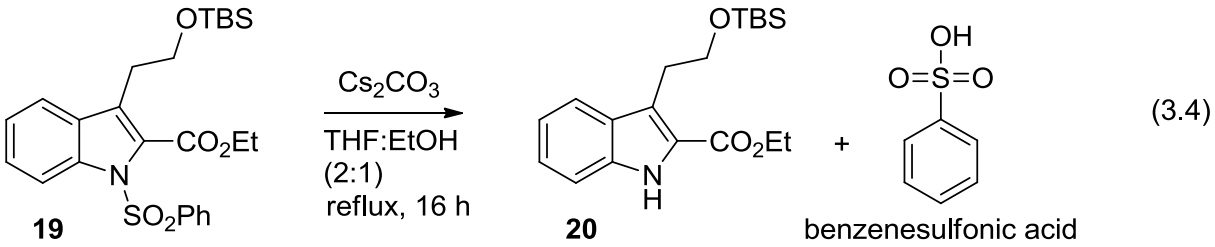
Deprotection of **19** in the presence of Cs_2CO_3 in a 2:1 mixture of THF:ethanol at room temperature led to 99% conversion of **19** to **20** along with the formation of ethyl

benzenesulfonate (Equation 3.3).[21] However, the similar polarities of **20** and ethyl benzenesulfonate rendered isolation of pure **20** challenging by standard chromatographic techniques. Conducting the reaction at reflux for 16 h led to the formation of **20** in 95% yield along with benzenesulfonic acid, which were easily separable by flash column chromatography (Equation 3.4). All the synthetic transformations shown in Scheme 3.4 and Scheme 3.6 are robust and were conducted in multi-millimolar scale (up to 20 mmole).



(3.3)

*Similar polarity of **20** and ethyl benzenesulfonate leads to difficult separation*

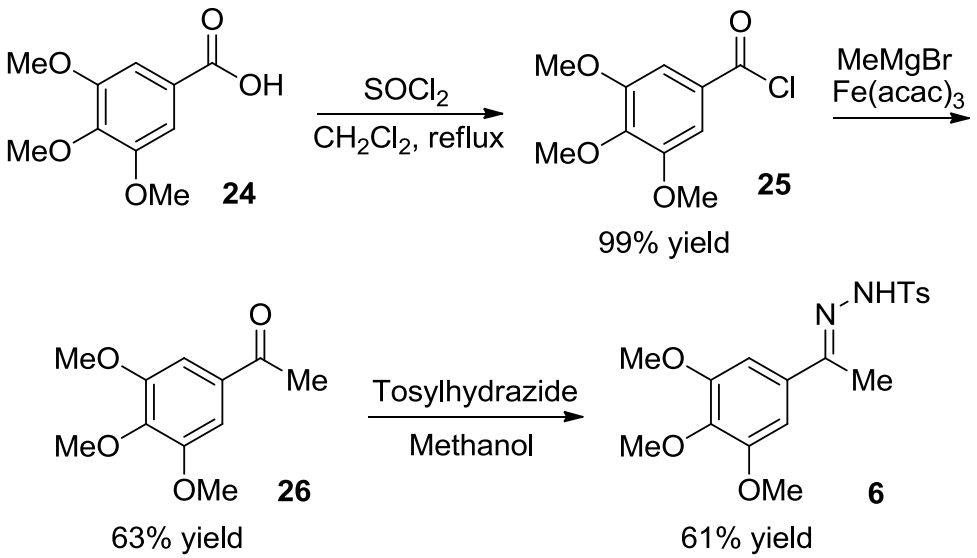


(3.4)

*Easy separation of **20** and benzenesulfonic acid*

Scheme 3.7 describes the synthesis of *N*-tosylhydrazone **6** from 3,4,5-trimethoxybenzoic acid **24** over three steps in 38% yield.[13, 22] Reaction of **24** with thionyl chloride under reflux conditions formed acid chloride **26**. Reaction of **26** with methyl magnesium bromide in presence of $Fe(acac)_3$ generated 1-(3,4,5-trimethoxyphenyl)ethanone **27** in 63% yield which in the presence of tosylhydrazide in methanol at 60 °C formed *N*-tosylhydrazone **6** in 61% yield.

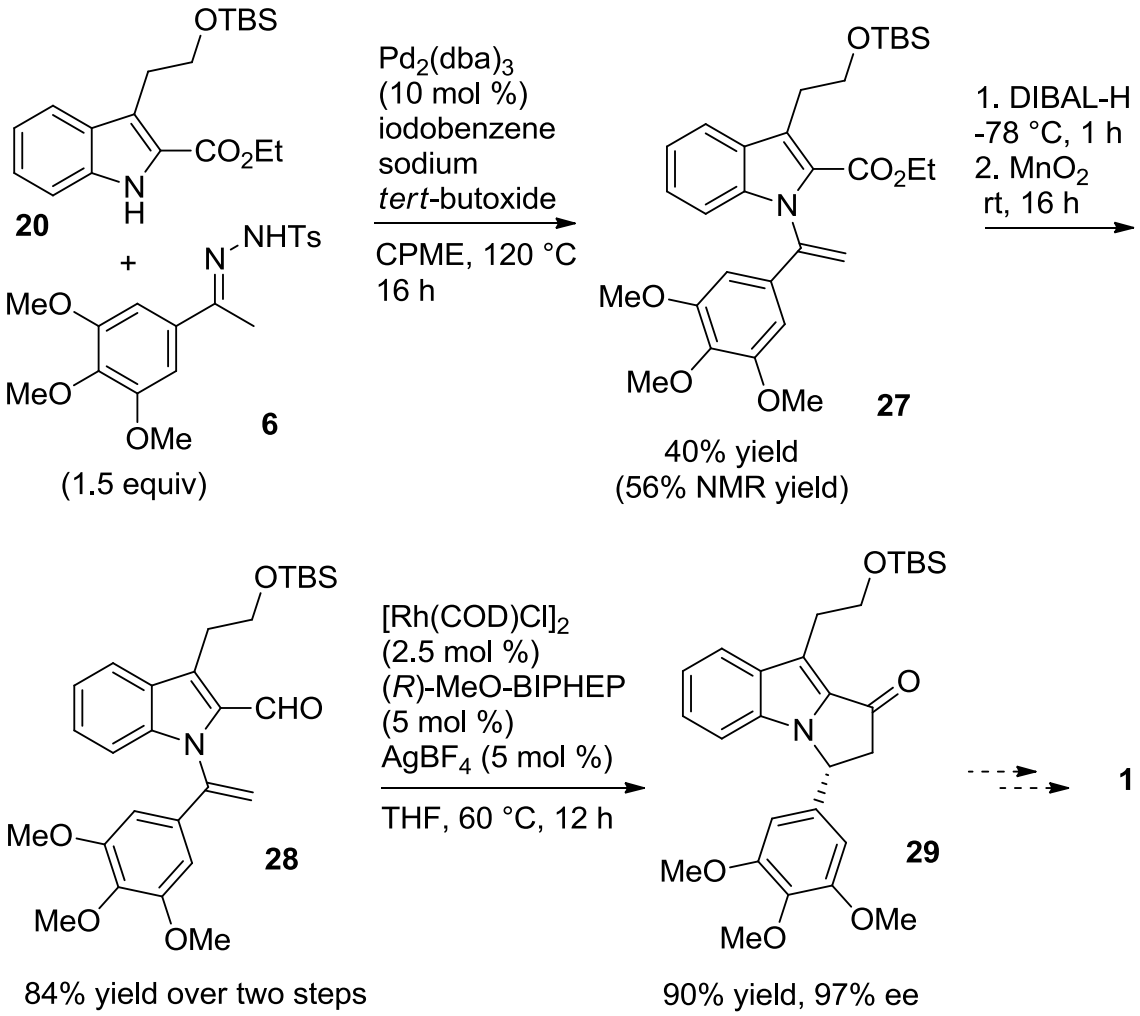
Scheme 3.7 Synthesis of *N*-tosylhydrazone **6**



Scheme 3.8 illustrates the enantioselective synthesis of the functionalized chiral dihydropyrroloindolone **29**. Palladium-catalyzed cross-coupling of **20** with hydrazone **6** generated ethyl *N*-vinylindole-2-carboxylate **27** in 40% isolated yield. A sequence of DIBAL-H mediated reduction of **27** followed by oxidation of the resulting crude alcohol with MnO_2 furnished *N*-vinylindole-2-carboxaldehyde **28** in 84% yield over two steps. Enantioselective, intramolecular hydroacylation of **28** in the presence of a catalyst generated in situ from $[Rh(COD)Cl]_2$, (*R*)-MeO-BIPHEP, and $AgBF_4$ formed dihyropyrroloindolone **29** in 90% yield with 97% ee.

Chiral dihydropyrroloindolone **29** is suitably functionalized to complete an enantioselective synthesis of **1** based on the model synthesis illustrated in Scheme 3.3. However, we elected to terminate our efforts toward **1** following the structural reassignment of yuremamine from a dihydropyrroloindole to a flavonoidal indole.

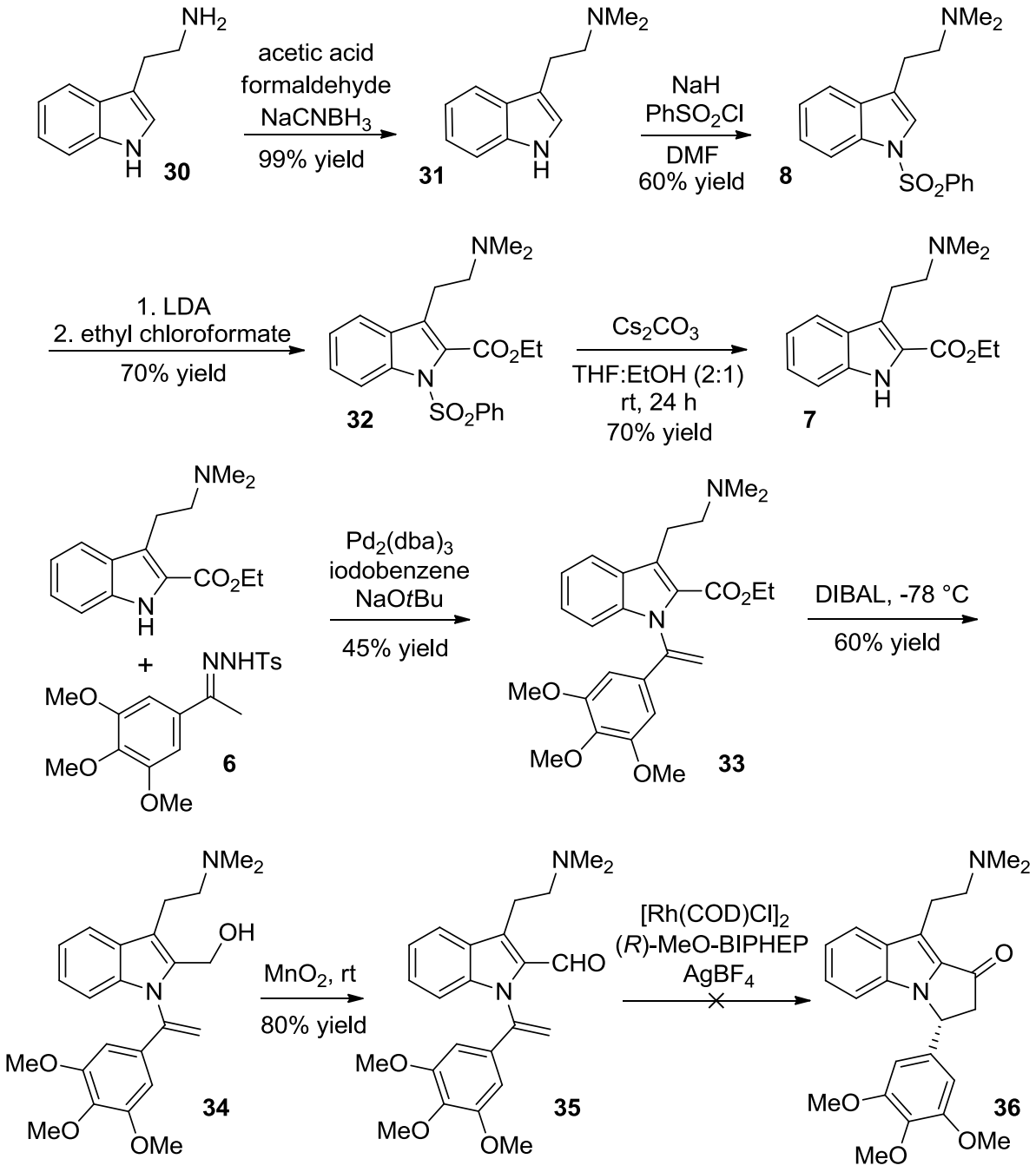
Scheme 3.8 Synthesis of Dihydropyrroloindolone **29**



As an alternate synthetic route, we explored synthesis of chiral dihydropyrroloindolone **36** from tryptamine **30** as the starting material (Scheme 3.9). Reductive methylation of tryptamine followed by phenyl sulfonyl protection of indole nitrogen in **31** formed **8**. Direct installation of ester group at the 2-position of indole in presence of LDA and ethyl chloroformate followed by deprotection of phenyl sulfonyl group in **32** generated **7**. Palladium(0)-catalyzed coupling of **7** with **6** formed **33** in 45% yield. DIBAL-H reduction of **33** followed by oxidation of **34** in presence of activated manganese dioxide generated **35**. The key hydroacylation step with

N,*N*-dimethyltryptamine derivative **35** was not encouraging, presumably due to coordination of the basic nitrogen in **35** to the rhodium center (Scheme 3.9).

Scheme 3.9 Attempt towards synthesis of dihydropyrroloindolone **36**



3.5 Conclusion

In conclusion, we have developed an enantioselective model synthesis of the 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole core present in the putative structure of yuremamine. The 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole core containing three contiguous stereogenic centers was synthesized in 39% overall yield and 96% ee in 5 steps. The catalytic protocol for enantioselective rhodium-catalyzed hydroacylation of *N*-vinylindole-2-carboxaldehyde reported by our group was utilized in multi-milllimolar scale as the key step for installation of the stereochemical triad. The ketone functionality present in the hydroacylation product served as a synthetic handle for the installation of additional stereocenters with precise control of absolute and relative stereochemistry. Progress toward enantioselective synthesis of the putative structure of yuremamine is reported, and the enantioselective synthesis of a densely functionalized dihydropyrroloindolone core that maps onto this structure has been demonstrated in 26% yield and 97% ee over 8 steps. The synthetic strategy is likely to be amenable to synthesis of other natural products containing a 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]-indole core and highlights the utility of our hydroacylation protocol in the construction of complex molecular scaffolds.

3.6 Experimental Details

3.6.1 General experimental details

All air-sensitive procedures were conducted under inert atmosphere in a nitrogen-filled dry box or by standard Schlenk techniques. All reactions were performed under an atmosphere of nitrogen unless otherwise stated. All glassware for moisture sensitive reactions was dried at 140 °C in an oven. THF, DMF, CH_2Cl_2 and diethyl ether were degassed by purging with argon for 45 minutes and dried with a solvent purification system by passing through a one-meter column of activated alumina. Anhydrous cyclopentyl methyl ether (CPME), acetonitrile, toluene and 1,4-

dioxane were purchased from Sigma-Aldrich. Flash column chromatography was performed on SiliFlash® P60 silica gel (40-63μm, 60 Å) using hexanes/EtOAc or hexanes/ether mixtures. Reaction products were visualized on TLC by UV light or by staining with $KMnO_4$ or 2,4-dinitro-phenylhydrazine.

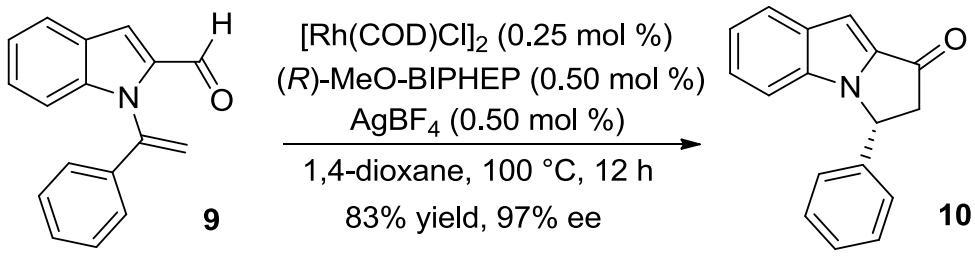
HRMS (ESI) analysis was performed on an Agilent 6540 QTOF spectrometer at the Iowa State University Chemical Instrumentation Facility. Optical rotations were measured on an Atago AP-300 automatic polarimeter. HPLC analyses were carried out on a Water Alliance HPLC system with an e2695 Separations Module and a 2489 (UV/Vis) dual wavelength detector. NMR spectra were acquired on Varian MR-400 and Bruker Avance III 600 spectrometers at the Iowa State University Chemical Instrumentation Facility. Chemical shifts are reported in ppm relative to a residual solvent peak ($CDCl_3$ = 7.26 ppm for ^1H and 77.16 ppm for ^{13}C; C_6D_6 = 7.16 for ^1H and 128.06 for ^{13}C). Coupling constants are reported in hertz.

3.6.2 Materials

N-Vinylindole-2-carboxaldehyde **9** was synthesized according to a literature procedure from ethyl indole-2-carboxylate.[11] 3′,4′,5′-Trimethoxyacetophenone **26** was synthesized from 3′,4′,5′-trimethoxybenzoic acid according to a literature procedure.[22] Activated manganese dioxide, Martin Sulfurane, iodobenzene, sodium *tert*-butoxide (NaO*t*Bu), *tert*-butyldimethylsilyl chloride (TBSCl), benzenesulfonyl chloride, tetrabutylammonium hydrogensulfate (TBAHS), imidazole, ethyl chloroformate, diethyl carbonate, p-toluenesulfonyl hydrazide, oxalyl chloride, lithium aluminum hydride were purchased from Sigma-Aldrich and used without further purification. Phenylmagnesium bromide (3.0 M in diethyl ether), DIBAL-H (1.0 M in toluene), borane-THF complex (1.0 M in THF), *n*-butyllithium (2.5 M in hexane), *sec*-butyllithium (1.4 M

in cyclohexane), *tert*-butyllithium (1.7 M in pentane) were also purchased from Sigma-Aldrich and used without further purification. $[Rh(COD)Cl]_2$, $Pd_2(dba)_3$, *rac*-BINAP, (*R*)-MeO-BIPHEP, silver tetrafluoroborate were purchased from Strem Chemicals and used without further purification. Ethyl indole-2-carboxylate, indole and cesium carbonate were purchased from AK Scientific and used without further purification.

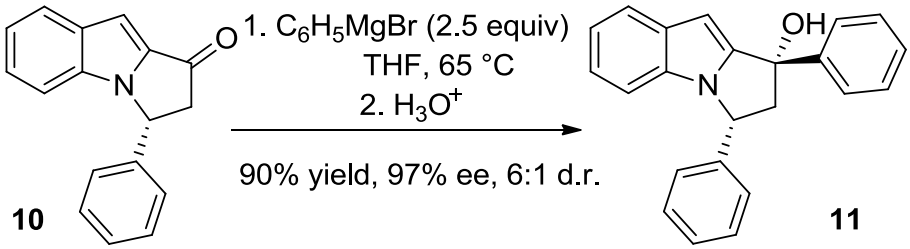
3.6.3 Synthesis of (*R*)-3-Phenyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-one (10)



In a nitrogen-filled glovebox, *N*-vinylindole-2-carboxaldehyde **9** (500 mg, 2.02 mmol, 1.00 equiv), $[Rh(COD)Cl]_2$ (2.50 mg, 0.00500 mmol, 0.00250 equiv), (*R*)-MeO-BIPHEP (5.80 mg, 0.0100 mmol, 0.00500 equiv), $AgBF_4$ (1.90 mg, 0.0100 mmol, 0.00500 equiv) and 1,4-dioxane (14.0 mL) were added to a 20 mL scintillation vial. The vial was sealed with a PTFE/silicone-lined septum cap and removed from the glovebox. The reaction mixture was stirred at 100 °C in an oil bath for 12 h. The vial was removed from the oil bath and allowed to cool to room temperature. The reaction mixture was filtered through a short plug of silica gel (eluting with 100 mL of 3:2 hexanes:EtOAc). The crude reaction mixture was concentrated under reduced pressure. The mixture was purified by flash column chromatography (90:10 hexane:EtOAc) to give (*R*)-3-phenyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-one **10** as a light yellow solid in 83% yield (415 mg, 1.68 mmol). The enantiomeric excess was determined by HPLC analysis (220 nm, 25 °C) t_R 17.7 min (major); t_R 21.1 min (minor) [Chiracel AD-H (0.46

cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 95:5, 1.0 mL/min] to be 97%. $[\alpha]_D^{24}$ = +232.2° (c 0.51, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.07 (dd, *J* = 18.4, 4.0 Hz, 1H), 3.68 (dd, *J* = 18.4, 8.0 Hz, 1H), 5.74 (dd, *J* = 8.0, 4.0 Hz, 1H), 6.93 – 6.95 (m, 1H), 7.11 – 7.21 (m, 5H), 7.32 – 7.39 (m, 3H), 7.77 – 7.79 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 50.4, 57.3, 99.3, 111.8, 121.7, 124.3, 125.4, 126.1, 128.6, 129.4, 132.6, 135.0, 136.3, 140.1, 192.2. **HRMS** (ESI): Calcd. for $C_{17}H_{14}NO$ ($[M+H]^+$): 248.1070, Found: 248.1069.

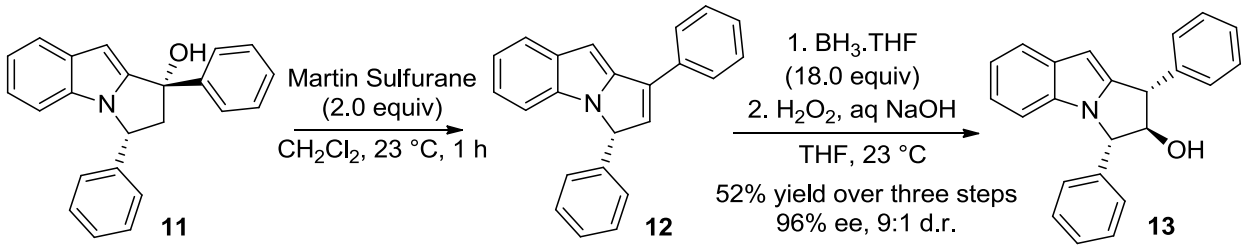
3.6.4 Synthesis of (1*S*,3*R*)-1,3-Diphenyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-ol (11)



A 3.0 M solution of phenylmagnesium bromide (0.670 mL, 2.00 mmol, 2.50 equiv) in diethyl ether was added to a solution of (*R*)-3-phenyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-one **10** (200 mg, 0.808 mmol, 1.00 equiv) in THF (5.0 mL) under a nitrogen atmosphere. The reaction mixture was heated at 65 °C and stirred for 16 h. The mixture was cooled in an ice/water bath and then quenched with saturated aqueous NH_4Cl (20 mL). The organic layer was separated and the aqueous phase was extracted with ether (3 × 30 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (85:15 hexane:EtOAc) to give (1*S*,3*R*)-1,3-diphenyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-ol **11** as a yellow oil in 90% yield (237 mg, 0.728 mmol) as a 6.1:1 diastereomeric ratio. The enantiomeric excess was determined by HPLC

analysis (220 nm, 25 °C) t_R 13.6 min [(1*R*,3*R*)]; t_R 16.2 min [(1*S*,3*S*)], t_R 20.5 min [(1*S*,3*R*)]; t_R 36.3 min [(1*R*,3*S*)] [Chiracel AD-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 93:7, 1.0 mL/min] to be 96% for the (1*R*,3*R*)-diastereomer and 97% for the (1*S*,3*R*)-diastereomer. $[\alpha]_D^{24}$ = +78.7° (c 0.25, $CHCl_3$). **^{1}H NMR** (600 MHz, C_6D_6) δ 1.87 (s, 1H), 2.72 (dd, *J* = 13.3, 4.2 Hz, 1H), 2.95 (dd, *J* = 13.3, 8.1 Hz, 1H), 5.02 (dd, *J* = 8.1, 4.2 Hz, 1H), 6.27 (s, 1H), 6.88 – 6.96 (m, 3H), 7.02 – 7.03 (m, 3H), 7.06 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.12 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.17 – 7.21 (m, 3H), 7.47 (d, *J* = 8.0 Hz, 2H), 7.72 (d, *J* = 8.0 Hz, 1H). **^{13}C NMR** (151 MHz, C_6D_6) δ 57.6, 59.7, 78.7, 93.85, 111.3, 120.45, 122.0, 122.1, 126.1, 126.75, 127.7, 128.35, 128.5, 129.0, 132.85, 133.7, 141.3, 145.7, 148.8. **HRMS** (ESI): Calcd. for $C_{23}H_{20}NO$ ($[M+H]^+$): 326.1539, Found: 326.1546.

3.6.5 Synthesis of (1*S*,2*R*,3*S*)-1,3-Diphenyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-2-ol (13)

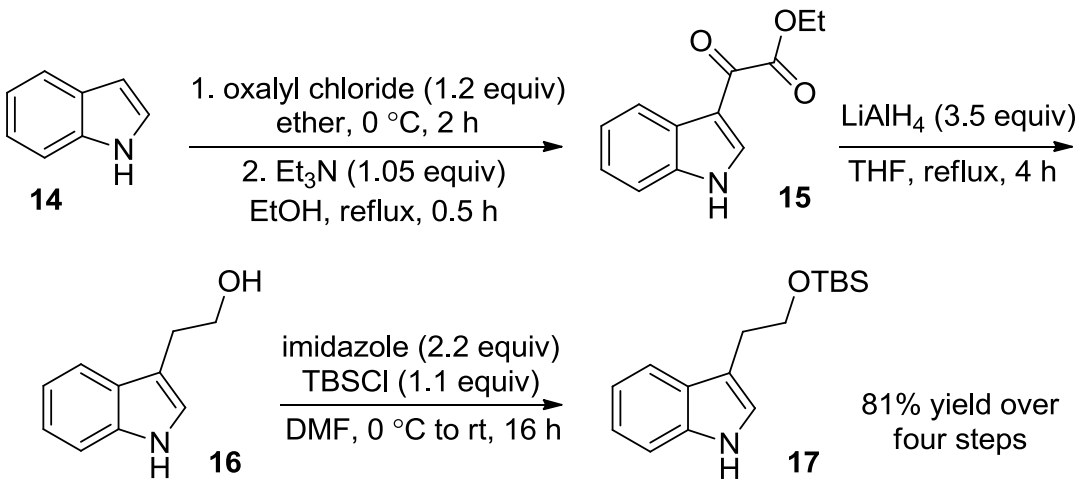


Martin sulfurane[23] (465 mg, 0.691 mmol, 1.50 equiv) was added to the solution of (1*S*,3*R*)-1,3-diphenyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-ol **11** (150 mg, 0.461 mmol, 1.00 equiv) in CH_2Cl_2 (5.0 mL) under a nitrogen atmosphere. The reaction was stirred for 30 min at 23 °C. The reaction was quenched with sat. aq $NaHCO_3$ solution, extracted with EtOAc, and washed with 1 M NaOH (4x). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was immediately purified by flash column chromatography using silica gel, pre-treated with 0.1% triethylamine, (95:5

hexane:EtOAc) to give (*R*)-1,3-diphenyl-3*H*-pyrrolo[1,2-*a*]indole, **12** as a bluish white solid (132 mg, 0.429 mmol).

After isolation, compound **12** (60.0 mg, 0.195 mmol) was immediately dissolved in anhydrous THF (2.0 mL), cooled to 0 °C under a nitrogen atmosphere and a 1.0 M solution of BH_3·THF (3.50 mL, 3.51 mmol, 18.0 equiv) was added. The reaction mixture was stirred at room temperature overnight. The reaction mixture was then cooled to 0 °C and treated with 15% aqueous sodium hydroxide (0.25 mL) and 30% hydrogen peroxide (0.50 mL). This mixture was stirred at room temperature for 2 hours and extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (80:20 hexane:EtOAc) to give (1*S*,2*R*,3*S*)-1,3-diphenyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-2-ol **13** as a yellow solid in 52% yield (35.6 mg, 0.109 mmol) over three steps as a 9:1 mixture of diastereomers. The enantiomeric excess was determined by HPLC analysis (220 nm, 25 °C) t_R 17.8 min [(1*R*,2*S*,3*S*)]; t_R 23.0 min [(1*S*,2*R*,3*R*)]; t_R 28.3 min [(1*S*,2*R*,3*S*)]; t_R 38.0 min [(1*R*,2*S*,3*R*)] [Chiracel AD-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 95:5, 1.0 mL/min] to be 97% for the (1*R*,2*S*,3*S*)-diastereomer and 96% for the (1*S*,2*R*,3*S*)-diastereomer. $[\alpha]_D^{24}$ = +107.6° (c 0.23, $CHCl_3$). **^{1}H NMR** (600 MHz, C_6D_6) δ 1.37 (d, *J* = 6.1 Hz, 1H), 3.96 (m, 1H), 4.18 (d, *J* = 8.1 Hz, 1H), 4.63 (d, *J* = 7.2 Hz, 1H), 6.26 (s, 1H), 6.72 (d, *J* = 8.2 Hz, 1H), 6.98 (t, *J* = 7.6 Hz, 1H), 7.05 – 7.09 (m, 5H), 7.22 (t, *J* = 7.6 Hz, 3H), 7.40 (d, *J* = 7.6 Hz, 3H), 7.68 (d, *J* = 7.9 Hz, 1H). **^{13}C NMR** (151 MHz, C_6D_6) δ 52.7, 68.1, 91.5, 95.7, 111.2, 120.1, 121.2, 121.3, 127.5, 127.7, 128.35, 128.6, 129.96, 129.00, 129.2, 133.2, 138.5, 140.5, 143.2. **HRMS** (ESI): Calcd. for $C_{23}H_{20}NO$ ($[M+H]^+$): 326.1539, Found: 326.1535.

3.6.6 Synthesis of 3-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-1*H*-indole (17)



To a stirred solution of indole **14** (11.0 g, 93.9 mmol, 1.00 equiv) in anhydrous diethyl ether (200 mL) at 0 °C, oxalyl chloride (9.50 mL, 113 mmol, 1.20 equiv) was added dropwise over 30 min. The reaction mixture was stirred at the same temperature for 2 h. The resulting yellow crystals of 3-indolylglyoxylyl chloride were filtered and washed with anhydrous diethyl ether.

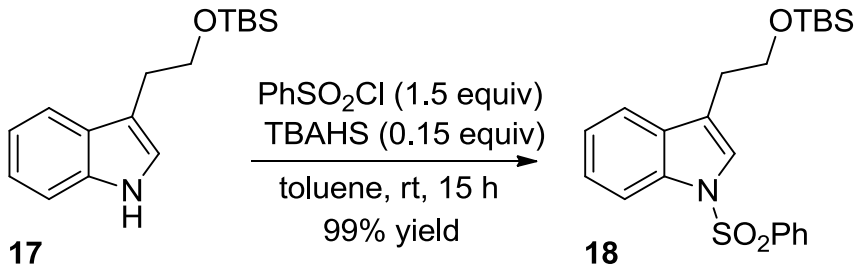
3-Indolylglyoxylyl chloride (19.0 g, 91.5 mmol, 1.00 equiv) was refluxed for 30 min in a mixture of ethanol (60 mL) and triethylamine (13.4 mL, 96.1 mmol, 1.05 equiv). The reaction mixture was cooled to 0 °C and the solid ethyl indolylglyoxylate **15** was isolated by filtration. The solid was washed with cold diethyl ether, dried under reduced pressure and used directly for the next step.

A solution of ethyl indolylglyoxylate **15** (18.0 g, 82.9 mmol, 1.00 equiv) in THF (100 mL) was added dropwise to a suspension of $LiAlH_4$ (11.6 g, 290 mmol, 3.50 equiv) in THF (300 mL) at 0 °C. The reaction mixture was refluxed for 4 h, cooled to 0 °C and quenched with a saturated aqueous solution of potassium sodium tartrate (400 mL). The resulting solution was

then filtered and washed with EtOAc (500 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude product of **16** was dried and used directly for the next step without further purification.

To a cooled solution (0 °C) of tryptophol **16** (12.4 g, 76.7 mmol, 1.00 equiv) and imidazole (11.6 g, 169 mmol, 2.20 equiv) in anhydrous DMF (120 mL), TBS-Cl (13.1 g, 84.3 mmol, 1.10 equiv) was added, and the reaction mixture was stirred for 16 h at room temperature. Ethyl acetate (250 mL) was then added and the organic phase was washed with brine (200 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column silica gel (98:2 hexane:EtOAc) to give 3-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-1*H*-indole **17** as a yellow solid in 81% yield over four steps (21.0 g, 76.2 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.93 (s, 9H), 3.02 (t, *J* = 7.4 Hz, 2H), 3.91 (t, *J* = 7.4 Hz, 2H), 7.04 (s, 1H), 7.13 (ddd, *J* = 7.8, 7.4, 1.2 Hz, 1H), 7.20 (ddd, *J* = 8.1, 7.4, 1.2 Hz, 1H), 7.36 (d, *J* = 8.1 Hz, 1H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.96 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ -5.1, 18.5, 26.1, 29.1, 64.05, 111.2, 113.0, 118.95, 119.3, 121.9, 122.2, 127.7, 136.2.

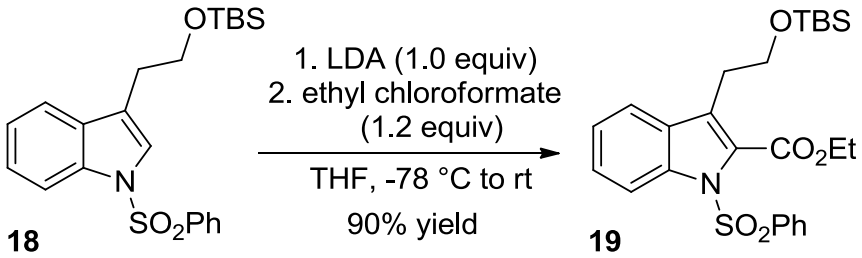
3.6.7 Synthesis of 3-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-1-(phenylsulfonyl)-1*H*-indole (18)[18]



To a stirred mixture of **17** (6.00 g, 21.8 mmol, 1.00 equiv) and tetrabutylammonium hydrogensulfate (1.10 g, 3.30 mmol, 0.150 equiv) in toluene (90 mL) at 0 °C was added aq.

NaOH (50 wt %, 90 mL) followed by benzenesulfonyl chloride (4.20 mL, 32.7 mmol, 1.50 equiv). The resulting suspension was allowed to warm to room temperature and vigorously stirred at this temperature for 15 h. The reaction mixture was diluted with water (250 mL) and extracted with EtOAc (250 mL). The organic layer was washed with water (250 mL) and brine (250 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column silica gel (99:1 hexane:EtOAc) to give 3-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-1-(phenylsulfonyl)-1*H*-indole **18** as a white solid in 99% yield (9.00 g, 21.6 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ -0.02 (s, 6H), 0.87 (s, 9H), 2.88 (t, *J* = 6.7 Hz, 2H), 3.87 (t, *J* = 6.7 Hz, 2H), 7.22 – 7.25 (m, 1H), 7.29 – 7.33 (m, 1H), 7.40 – 7.44 (m, 3H), 7.49 – 7.53 (m, 2H), 7.87 (d, *J* = 7.5 Hz, 2H), 7.99 (d, *J* = 8.3 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ -5.2, 18.4, 26.1, 28.7, 62.7, 113.8, 119.7, 120.45, 123.2, 123.6, 124.75, 126.85, 129.3, 131.4, 133.8, 135.2, 138.5. **HRMS** (ESI): Calcd. for $C_{22}H_{29}NO_3SSiNa$ ($[M+Na]^+$): 438.1530, Found: 438.1538.

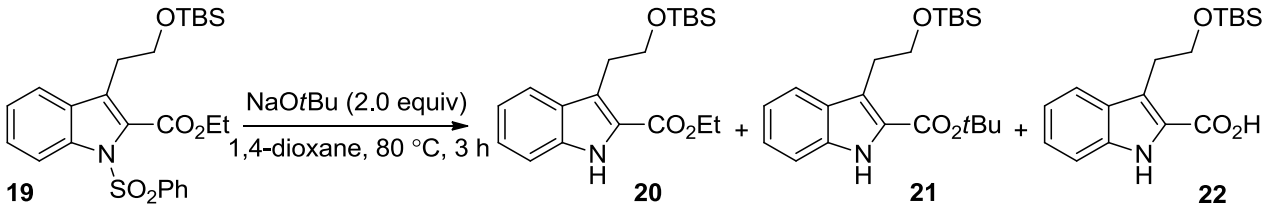
3.6.8 Synthesis of ethyl 3-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate (19)



To a solution of lithium diisopropylamide (19.3 mmol, 1.00 equiv) prepared from diisopropylamine (2.80 mL, 20.2 mmol, 1.05 equiv) and *n*-butyllithium (13.5 mL, 1.43 M in hexane; 19.3 mmol, 1.00 equiv) in dry THF (50 mL) under argon at -78 °C was added dropwise via syringe over 5 min a solution of **18** (8.00 g, 19.3 mmol, 1.00 equiv) in dry THF (50 mL). The

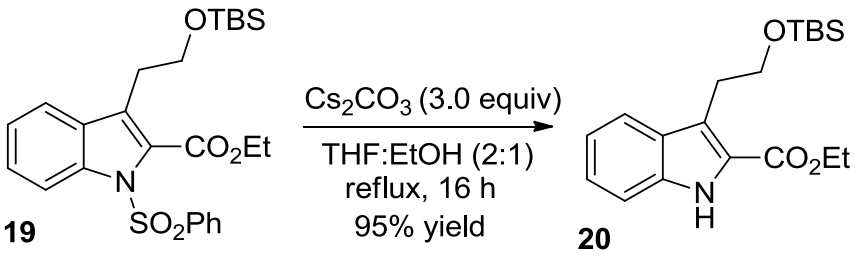
mixture was stirred for 1 h at -78 °C and then allowed to warm slowly to 0 °C over 3 h. The resulting solution was cooled to -78 °C and treated with a solution of ethyl chloroformate (2.20 mL, 23.1 mmol, 1.20 equiv) in THF (10 mL). The reaction mixture was stirred for 3 h at the same temperature and then warmed to room temperature overnight. The reaction mixture was quenched with a saturated aqueous NH_4Cl solution (100 mL) at 0 °C and extracted with diethyl ether (2 x 250 mL). The combined organic extracts were washed with water (200 mL), brine (200 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (95:5 hexane:ether) to give 3-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate **19** as a yellow oil in 90% yield (8.50 g, 17.4 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ -0.10 (s, 6H), 0.79 (s, 9H), 1.41 (t, *J* = 7.2 Hz, 3H), 3.00 (t, *J* = 6.9 Hz, 2H), 3.78 (t, *J* = 6.9 Hz, 2H), 4.45 (q, *J* = 7.2 Hz, 2H), 7.22 – 7.28 (m, 1H), 7.35 – 7.43 (m, 3H), 7.46 – 7.58 (m, 2H), 7.89 (d, *J* = 7.4 Hz, 2H), 8.02 (d, *J* = 8.4 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ -5.4, 14.2, 18.4, 26.0, 28.4, 62.2, 63.1, 115.5, 121.3, 124.1, 126.9, 127.0, 127.3, 128.9, 129.1, 130.5, 133.8, 137.1, 137.7, 162.4. **HRMS** (ESI): Calcd. for $C_{25}H_{34}NO_5SSi$ ($[M+H]^+$): 488.1921, Found: 488.1925.

3.6.9 NaO*t*Bu-Mediated synthesis of ethyl 3-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-1*H*-indole-2-carboxylate (20)



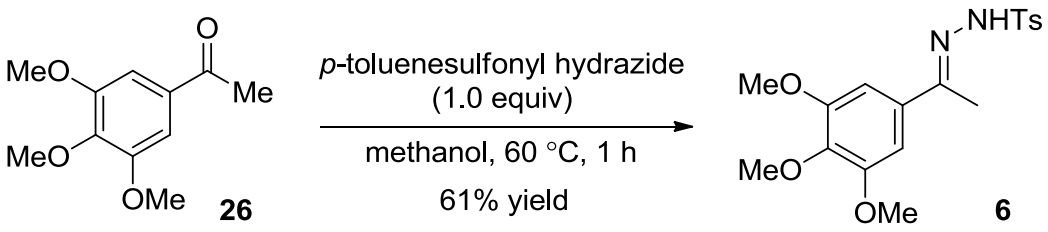
To a solution of **19** (0.500 g, 1.03 mmol, 1.00 equiv) in 1,4-dioxane (7.5 mL), NaO*t*Bu (0.148 g, 1.54 mmol, 1.50 equiv) was added under nitrogen atmosphere. The reaction mixture was stirred at 80 °C for 3 h, cooled to room temperature and filtered through a short plug of celite (eluting with 150 mL EtOAc). The crude reaction mixture was concentrated under reduced pressure. The crude reaction product obtained was a mixture of compounds **20**, **21** and **22**. The crude mixture was purified by flash column chromatography on silica gel (90:10 hexane:ether) to give ethyl 3-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-1*H*-indole-2-carboxylate **20** as a white solid in 20% yield (0.0710 g, 0.204 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ -0.03 (s, 6H), 0.85 (s, 9H), 1.43 (t, *J* = 7.1 Hz, 3H), 3.36 (t, *J* = 7.3 Hz, 2H), 3.86 (t, *J* = 7.3 Hz, 2H), 4.43 (q, *J* = 7.1 Hz, 2H), 7.09 – 7.19 (m, 1H), 7.28 – 7.34 (m, 1H), 7.37 (d, *J* = 8.3 Hz, 1H), 7.74 (d, *J* = 8.1 Hz, 1H), 8.76 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ -5.2, 14.6, 18.5, 26.1, 28.8, 60.9, 63.8, 111.7, 120.2, 121.3, 121.4, 123.8, 125.7, 128.7, 135.9, 162.4. **HRMS** (ESI): Calcd. for $C_{21}H_{34}NO_3Si$ ($[M+C_2H_5]^+$): 376.2302, Found: 376.2308.

3.6.10 Synthesis of ethyl 3-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-1*H*-indole-2-carboxylate (20)



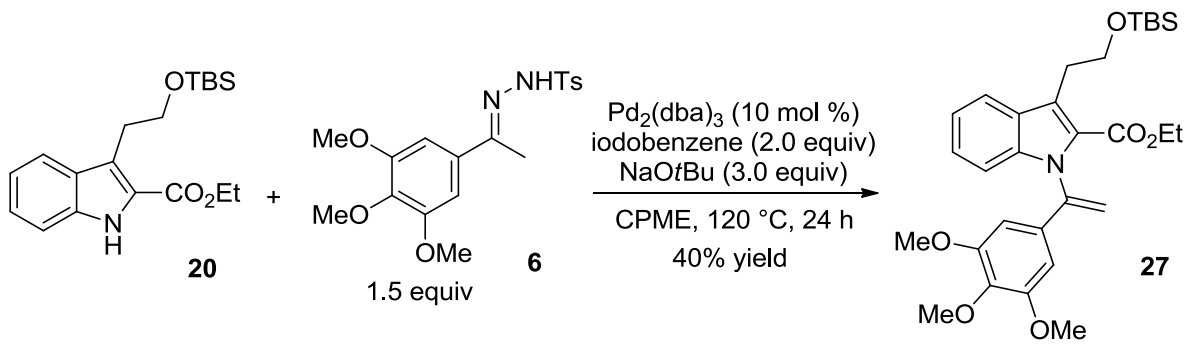
Ethyl 3-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-1*H*-indole-2-carboxylate **19** (10.0 g, 20.5 mmol, 1.00 equiv) was dissolved in a mixture of THF (150 mL) and EtOH (75 mL) at room temperature. Cesium carbonate (20.4 g, 61.5 mmol, 3.00 equiv) was added to the clear solution. The resulting mixture was stirred at reflux for 16 h, cooled and concentrated under reduced pressure. The mixture was treated with water (200 mL) and extracted with diethyl ether (3 × 200 mL). The organic extracts were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (90:10 hexane:ether) to give ethyl 3-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-1*H*-indole-2-carboxylate **20** as a white solid in 95% yield (6.80 g, 19.6 mmol). ^{1}H NMR and ^{13}C NMR spectra of the isolated product comply with the characterization data of **20** as reported above. **HRMS** (ESI): Calcd. for $C_{21}H_{34}NO_3Si$ ($[M+C_2H_5]^+$): 376.2302, Found: 376.2311.

3.6.11 Synthesis of (*E*)-4-methyl-*N*'-(1-(3,4,5-trimethoxyphenyl)ethylidene)benzenesulfonohydrazide (6)



1-(3,4,5-Trimethoxyphenyl)ethanone **26** (10.0 g, 47.6 mmol, 1.00 equiv), *p*-toluenesulfonyl hydrazide (9.10 g, 47.6 mmol, 1.00 equiv) and dry methanol (120 mL) were charged in a round-bottom flask equipped with a reflux condenser. The reaction mixture was heated to 60 °C and stirred for 1 h. The mixture was cooled to 0 °C, and the product was collected by filtration on a Buchner funnel, washed with diethyl ether, and then dried under reduced pressure to afford the pure product (*E*)-4-methyl-*N*-(1-(3,4,5-trimethoxyphenyl)ethylidene)benzenesulfonohydrazide **6** as a light yellow solid in 61% yield (11.0 g, 29.1 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.14 (s, 3H), 2.41 (s, 3H), 3.85 (s, 3H), 3.86 (s, 6H), 6.86 (s, 2H), 7.31 (d, *J* = 8.2 Hz, 2H) 7.92 (d, *J* = 8.2 Hz, 2H), 8.35 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 13.8, 21.6, 56.1, 60.9, 103.8, 128.3, 129.5, 132.9, 135.4, 139.5, 144.3, 152.7, 152.9.

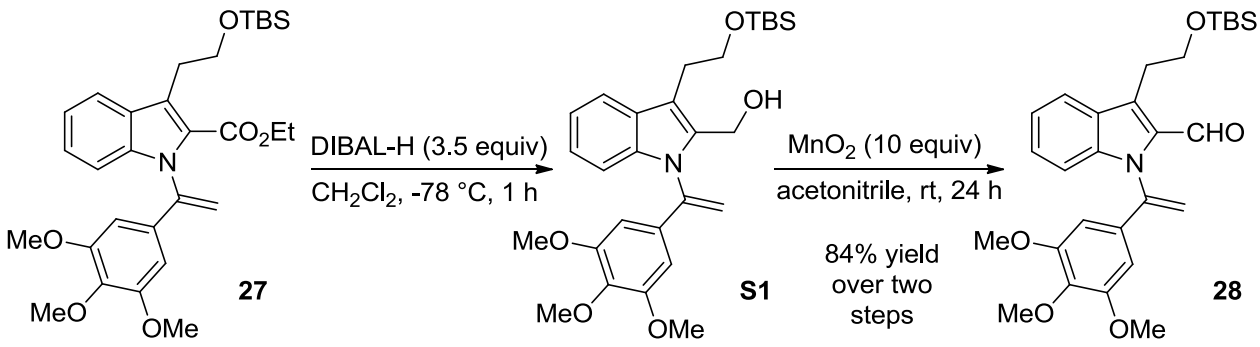
3.6.12 Synthesis of ethyl 3-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-1-(1-(3,4,5-trimethoxyphenyl)vinyl)-1*H*-indole-2-carboxylate (27)



A 50 mL pressure reaction tube was charged with indole **20** (0.200 g, 0.575 mmol, 1.00 equiv), *N*-tosylhydrazone **6** (0.327 g, 0.863 mmol, 1.50 equiv), iodobenzene (0.100 mL, 0.860 mmol, 1.50 equiv), $Pd_2(dba)_3$ (0.0527 g, 0.0575 mmol, 0.100 equiv), NaO*t*Bu (0.155 g, 1.61 mmol, 2.80 equiv) and CPME (25 mL). The flask was immersed in a preheated oil bath and stirred at 120 °C for 24 h. The crude reaction mixture was allowed to cool to room temperature, EtOAc was added and stirred for 10 min. The reaction mixture was filtered through celite (eluting with 50 mL EtOAc) and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (80:20 hexane:ether) to give ethyl 3-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-1-(1-(3,4,5-trimethoxyphenyl)vinyl)-1*H*-indole-2-carboxylate **27** as a colorless oil in 40% yield (0.125 g, 0.232 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ -0.02 (s, 6H), 0.86 (s, 9H), 1.20 (t, *J* = 7.1 Hz, 3H), 3.35 (t, *J* = 7.3 Hz, 2H), 3.82 (s, 3H), 3.70 (s, 6H), 3.88 (t, *J* = 7.3 Hz, 2H), 4.19 (q, *J* = 7.1 Hz, 2H), 5.32 (s, 1H), 5.90 (s, 1H), 6.33 (s, 2H), 7.19 (ddd, *J* = 8.0, 6.6, 1.3 Hz, 1H), 7.32 – 7.27 (m, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ -5.2, 14.3, 18.5, 26.1, 29.1, 56.2, 60.7, 61.0, 64.0, 103.1, 111.1, 111.6, 120.9, 121.2, 122.8, 125.8, 126.8, 127.7, 133.6, 138.8, 139.3,

144.3, 153.3, 161.8. **HRMS** (ESI): Calcd. for $C_{30}H_{42}NO_6Si$ ($[M+H]^+$): 540.2776, Found: 540.2772.

3.6.13 Synthesis of 3-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-1-(1-(3,4,5-trimethoxyphenyl)vinyl)-1*H*-indole-2-carboxaldehyde (28)

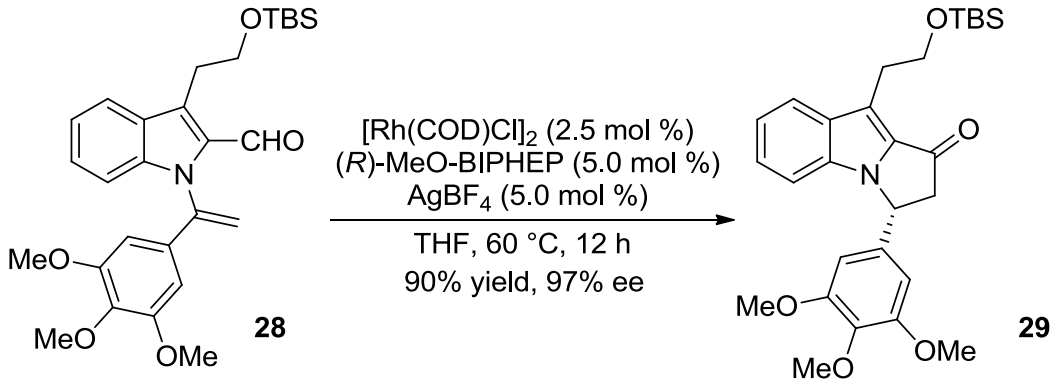


A 1.0 M solution of DIBAL-H in toluene (0.830 mL, 0.840 mmol, 3.50 equiv) was added to a solution of **27** (125 mg, 0.239 mmol, 1.00 equiv) in anhydrous dichloromethane (1.0 mL) at –78 °C under a nitrogen atmosphere. The resulting solution was stirred for 1 h at the same temperature. The mixture was then quenched with saturated aqueous NH_4Cl (10 mL). The organic layer was separated and the aqueous phase was extracted with diethyl ether (3 × 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was directly taken to the next step without further purification.

Activated manganese dioxide (311 mg, 3.60 mmol, 15.0 equiv) was added to an acetonitrile (1.0 mL) solution of **S1** (115 mg, 0.239 mmol, 1.00 equiv) in a round-bottom flask. The reaction mixture was stirred at room temperature under a nitrogen atmosphere for 24 h. The reaction mixture was filtered through celite, washed with a 1:1 mixture of hexane:EtOAc, and the filtrate was concentrated under reduced pressure. The crude product was purified by flash column silica gel chromatography (80:20 hexane:ether) to give 3-(2-((*tert*-

butyldimethylsilyl)oxy)ethyl)-1-(1-(3,4,5-trimethoxyphenyl)vinyl)-1*H*-indole-2-carboxaldehyde **28** as colorless oil in 84% yield (96.0 mg, 0.200 mmol) over two steps. **^{1}H NMR** (400 MHz, C_6D_6) δ -0.03 (s, 6H), 0.91 (s, 9H), 3.20 (s, 6H), 3.34 (t, *J* = 6.5 Hz, 2H), 3.76 (s, 3H), 3.89 (t, *J* = 6.5 Hz, 2H), 5.07 (s, 1H), 5.63 (s, 1H), 6.41 (s, 2H), 7.09 (ddd, *J* = 8.0, 7.0, 0.9 Hz, 1H), 7.20 (ddd, *J* = 8.4, 7.0, 1.1 Hz, 1H), 7.35 (d, *J* = 8.4 Hz, 1H), 7.70 (dt, *J* = 8.1, 0.9 Hz, 1H), 10.12 (s, 1H). **^{13}C NMR** (101 MHz, C_6D_6) δ -5.3, 18.5, 26.1, 28.25, 30.5, 55.75, 60.5, 63.9, 104.0, 111.9, 112.7, 121.5, 122.0, 125.9, 126.0, 127.4, 133.3, 133.4, 140.0, 140.7, 143.4, 154.4, 181.3. **HRMS** (ESI): Calcd. for $C_{28}H_{38}NO_5Si$ ($[M+H]^+$): 496.2514, Found: 496.2516.

3.6.14 Synthesis of (*R*)-9-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-(3,4,5-trimethoxyphenyl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-one (29)



In a nitrogen-filled glovebox, **28** (20.0 mg, 0.0400 mmol, 1.00 equiv), $[Rh(COD)Cl]_2$ (0.500 mg, 0.00100 mmol, 0.0250 equiv), (*R*)-MeO-BIPHEP (1.20 mg, 0.00200 mmol, 0.0500 equiv), $AgBF_4$ (0.400 mg, 0.00200 mmol, 0.0500 equiv) and THF (0.50 mL) were added to a 1-dram vial. The vial was sealed with a PTFE/silicone-lined septum cap and removed from the glovebox. The reaction mixture was stirred at 60 °C in an oil bath for 12 h. The vial was removed from the oil bath and allowed to cool to room temperature. The reaction mixture was filtered through a short plug of silica gel (eluting with 20 mL of 3:2 hexanes:EtOAc). The crude reaction mixture was concentrated under reduced pressure. The crude reaction mixture was

purified by flash column silica gel chromatography (80:20 hexanes:ether) to give (*R*)-9-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-(3,4,5-trimethoxyphenyl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-one **29** as a white solid in 90% yield (18.0 mg, 0.0360 mmol). The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 14.3 min (minor); t_R 17.3 min (major) [Chiracel AD-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 95:5, 1.0 mL/min] to be 97%. $[\alpha]_D^{25}$ = -76.9° (c 0.52, $CHCl_3$). **^{1}H NMR** (400 MHz, C_6D_6) δ 0.070 (s, 3H), 0.077 (s, 3H), 0.97 (s, 9H), 2.79 (dd, *J* = 18.2, 4.4 Hz, 1H), 3.09 (dd, *J* = 18.2, 8.0 Hz, 1H), 3.20 (s, 6H), 3.55 (t, *J* = 7.0 Hz, 2H), 3.78 (s, 3H), 4.18 (t, *J* = 7.0 Hz, 2H), 4.76 (dd, *J* = 8.0, 4.4 Hz, 1H), 6.14 (s, 2H), 6.95 (dd, *J* = 6.4, 2.6 Hz, 1H), 7.08 – 7.03 (m, 2H), 7.78 (dd, *J* = 6.1, 2.6 Hz, 1H). **^{13}C NMR** (101 MHz, C_6D_6) δ -5.1, 18.5, 26.2, 28.5, 30.5, 50.8, 55.8, 57.2, 60.5, 64.15, 103.5, 110.4, 112.0, 113.95, 121.2, 123.2, 125.5, 125.9, 128.1, 133.3, 134.0, 135.2, 136.0, 139.3, 154.8, 191.2. **HRMS** (ESI): Calcd. for $C_{28}H_{38}NO_5Si$ ($[M+H]^+$): 496.2514, Found: 496.2517.

3.7 References

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CHAPTER 4

COUPLING CATALYTIC ALKENE HYDROACYLATION AND α-ARYLATION: ENANTIOSELECTIVE SYNTHESIS OF HETEROCYCLIC KETONES WITH α-CHIRAL QUATERNARY STEREOCENTERS

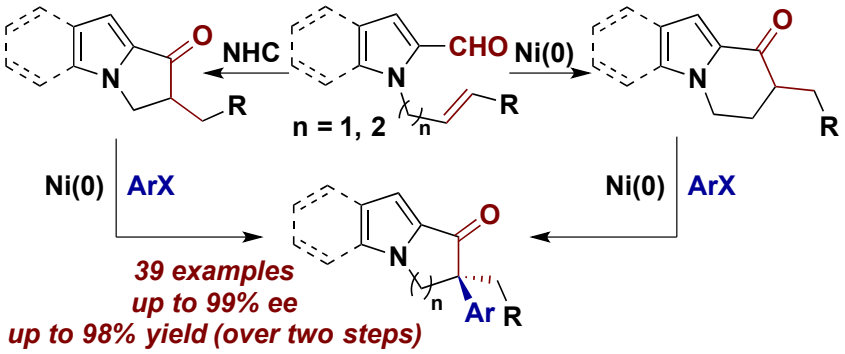
Modified from a paper published in *ACS Catalysis*[1]

Avipsa Ghosh, James A. Walker Jr., Arkady Ellern, and Levi M. Stanley*

4.1 Abstract

We report a catalytic strategy that combines alkene hydroacylation and enantioselective α-(hetero)arylation reactions to form a wide variety of nitrogen-containing heterocyclic ketones bearing α-chiral quaternary stereogenic centers. *E*xo-selective, intramolecular Ni-catalyzed hydroacylations of *N*-homoallylindole- and *N*-homoallylpyrrole-2-carboxaldehydes form α-substituted six-membered heterocyclic ketones in up to 95% yield, while *N*-heterocyclic carbene (NHC)-catalyzed hydroacylations of *N*-allylindole- and *N*-allylpyrrole-2-carboxaldehydes form α-substituted five-membered heterocyclic ketones in up to 99% yield. The racemic five- and six-membered products of Ni- and NHC-catalyzed hydroacylation reactions are readily transformed into heterocyclic ketones containing an α-chiral quaternary stereogenic center by enantioselective Ni-catalyzed α-arylation and α-heteroarylation reactions. The chiral, non-racemic products of sequential alkene hydroacylation and α-(hetero)arylation reactions are formed in moderate-to-high yields (44-99%) with excellent enantioselectivities (typically >95% ee). The identity of the precatalyst for Ni-catalyzed α-(hetero)arylation is dictated by the identity of the α–substituted heterocyclic ketone starting material. α-(Hetero)arylations of six-membered heterocyclic ketones occur at 65-85 °C in the presence of a catalyst generated *in situ* from $Ni(COD)_2$ and (*R*)-BINAP or (*R*)-DIFLUORPHOS. α-(Hetero)arylation of five-membered heterocyclic ketones must be conducted at room temperature in the presence of an [((*R*)-BINAP)Ni(η^2-NC-Ph)] precatalyst or a catalyst generated *in situ* from $Ni(COD)_2$, (*R*)-DIFLUORPHOS and benzonitrile.

[1] Ghosh, A.; Walker Jr., J. A.; Ellern, A.; Stanley, L. M. *ACS Catal.* **2016**, *6*, 2673-2680.



4.2 Introduction

Nitrogen-containing heterocycles possessing quaternary stereogenic centers are common structural motifs present in biologically active natural products and small molecules.[1] Despite many advances over the past decades, enantioselective synthesis of quaternary stereogenic centers remains a significant synthetic challenge.[2] The composition of current pharmaceutical agents provides a snapshot into this challenge. In 2011, 12% of the top 200 prescription drugs sold in United States contained quaternary stereogenic centers.[2a, 3] However, the majority of these compounds are synthesized from naturally occurring compounds (steroids, opioids, taxane and diterpenoids) with the natural product precursor providing the quaternary stereogenic centers.[2a, 4] Thus, approaches to molecular scaffolds, particularly heterocyclic scaffolds, containing quaternary stereogenic centers offer the potential to create and provide access to new classes of biologically active compounds.

Extensive development over the past decade has rendered palladium- and nickel-catalyzed α-arylation of carbonyl enolates a practical strategy to form benzylic quaternary stereogenic centers alpha to a carbonyl group.[5] However, the majority of the metal-catalyzed, enantioselective α-arylation studies focus on reactions of ketones with carbocyclic backbones[6] or lactones.[6c, 7]

Enantioselective α-arylation of nitrogen-containing heterocycles to form benzylic quaternary stereogenic centers has been studied to a much lesser extent and is largely limited to reactions of oxindoles.[8] We focused on our studies developing strategies to synthesize indole and pyrrole derivatives containing benzylic quaternary stereogenic centers due to the presence of this structural feature in the indole alkaloid haplophytine[9] and polycyclic indoles with antiandrogenic,[10] antiarrhythmic,[11] and antihypertensive[12] activities (Figure 4.1).

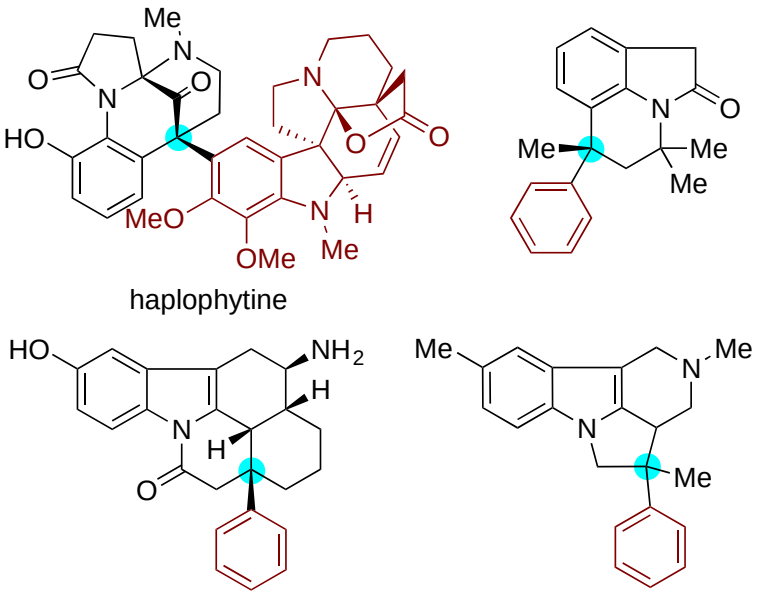


Figure 4.1 Biologically active indoles derivatives containing benzylic quaternary stereogenic centers.

Glorius *et al*. recently reported a direct method to form cyclic ketones containing α-quaternary stereogenic centers by chiral *N*-heterocyclic carbene (NHC)-catalyzed intramolecular hydroacylation.[13] They report the formation of chiral, non-racemic five- and six-membered carbocyclic ketones and two five-membered nitrogen-containing heterocyclic ketones. However, a general strategy that encompasses formation of both five- and six-membered nitrogen-containing heterocyclic ketones with α-chiral quaternary stereogenic centers has not been reported. We sought to develop a versatile strategy combining intramolecular alkene

hydroacylation with enantioselective α-arylation to provide access to a wide variety of indole and pyrrole derivatives containing benzylic quaternary stereogenic centers.

Intramolecular hydroacylation of alkenes has emerged as a promising, atom-economic transformation to generate a wide variety of carbocyclic and heterocyclic ketones.[14] These transformations generally occur in the presence of transition-metal or NHC catalysts, and the selection of the specific catalyst type determines the regiochemical outcome of the reaction. In 2014, we reported enantioselective Rh-catalyzed hydroacylations of *N*-vinylindole-2-carboxaldehydes to form β-substituted dihydropyrroloindolones[15] and *N*-allylindole- and *N*-allylpyrrole-2-carboxaldehydes to form β-substituted dihydropyridoindolones and dihydroindolizinones that occur exclusively with *endo* selectivity.[16] We envisioned forming α-substituted dihydropyrroloindolones and dihydropyridoindolones by *exo*-selective Ni- or NHC-catalyzed intramolecular hydroacylations of *N*-allyl- and *N*-homoallylindole-2-carboxaldehydes due to the complementary regioselectivity often observed with these types of catalysts.[17] We further hypothesized that these five- and six-membered α-substituted ketones could serve as substrates for enantioselective α-arylation reactions to access heterocyclic ketones bearing α-chiral quaternary stereocenters. Due to wide range of carbonyl functionalization reactions, this sequence of alkene hydroacylation and α-arylation reactions is poised to serve as a strategic approach to the synthesis of a range of complex chiral heterocycles possessing benzylic quaternary stereocenters.[18]

Herein, we report a catalytic strategy that combines alkene hydroacylation and α-arylation to generate five- and six-membered nitrogen-containing heterocyclic ketones bearing α-chiral quaternary stereocenters (Figure 4.2). Our studies reveal that *exo*-selective Ni-catalyzed hydroacylations of *N*-homoallylindole-2-carboxaldehydes form six-membered heterocyclic

ketones in higher yields and require lower catalyst loading compared to Ni-catalyzed hydroacylation of *N*-allylindole-2-carboxaldehydes to form five-membered heterocyclic ketones. This reactivity is complementary to NHC-catalyzed hydroacylations which are known to form five-membered nitrogen-containing, α-substituted heterocyclic ketones in excellent yields.[13, 17m] Our studies reveal that nitrogen-containing five- and six-membered heterocyclic ketones exhibit significantly different reactivity towards Ni-catalyzed, enantioselective α-arylations compared to previously studied carbocyclic ketones.[6a] Finally, we have successfully demonstrated a sequential "one-pot" synthesis of a dihydropyridoindolone by *exo*-selective alkene hydroacylation and enantioselective α-arylation reactions using two distinct nickel catalysts.

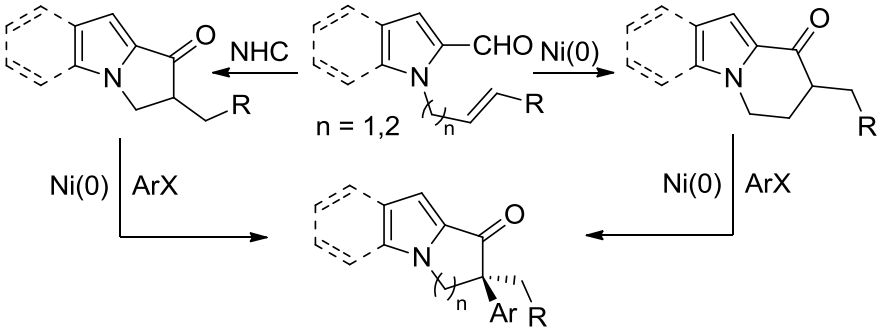


Figure 4.2 Coupling alkene hydroacylation and ketone α-arylation reactions.

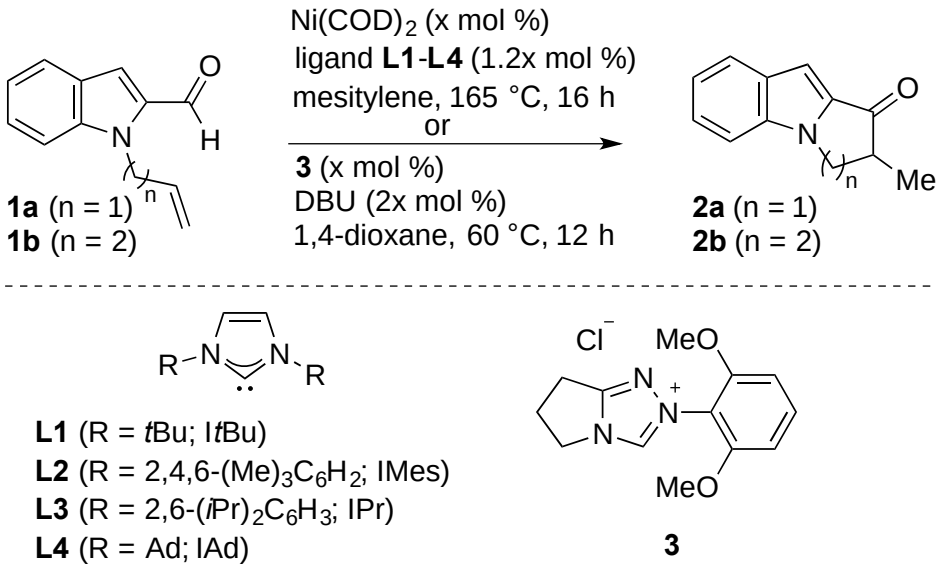
4.3 Results and Discussion

4.3.1 *Exo*-Selective Intramolecular Hydroacylation

Initial studies to develop intramolecular, *exo*-selective Ni-catalyzed hydroacylations of *N*-allylindole-2-carboxaldehydes were guided by hydroacylations of 2-allylbenzaldehyde catalyzed by Ni(0) complexes of NHC ligands.[17a] To test whether hydroacylation of *N*-allylindole-2-carboxaldehyde **1a** could occur under similar reaction conditions to those reported for carbocyclic ketone formation, we studied the reaction of **1a** in the presence of catalysts generated

in situ from $Ni(COD)_2$ and various NHC ligands at 130 °C (Table 4.1, entries 1-4). We found that *exo*-selective hydroacylation of **1a** occurs to form dihydropyrroloindolone **2a** in low yields (8-34%), with the reaction catalyzed by a Ni complex containing the *N*-adamantylcarbene (IAd) ligand **L4** forming the desired product in the highest yield. The yield of the model hydroacylation of **1a** improved to 60% when the reaction was conducted at 165 °C and further to 72% when the reaction occurred in the presence of 15 mol % of the catalyst (Table 4.1, entries 5 and 6). In contrast, an NHC catalyst, generated *in situ* from 10 mol % **3** and 20 mol % 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), led to the formation of **2a** in 97% yield when the reaction was conducted at 60 °C (Table 4.1, entry 7).[19]

Table 4.1 Identification of Catalysts for *exo*-Selective Hydroacylation of *N*-allyl- and *N*-Homoallylindole-2-carboxaldehyde[a,b]



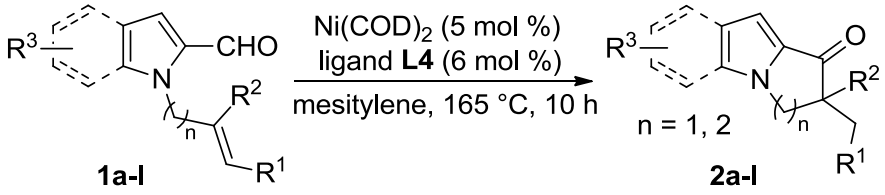
entry	**1**	precatalyst	mol %	ligand	temp (°C)	yield (%)[c]
1	**1a**	$Ni(COD)_2$	10	**L1**	130	16
2	**1a**	$Ni(COD)_2$	10	**L2**	130	8
3	**1a**	$Ni(COD)_2$	10	**L3**	130	9
4	**1a**	$Ni(COD)_2$	10	**L4**	130	34 (30)
5	**1a**	$Ni(COD)_2$	10	**L4**	165	60 (60)
6	**1a**	$Ni(COD)_2$	15	**L4**	165	72 (70)
7	**1a**	**3**	10	--	60	99 (97)
8	**1b**	$Ni(COD)_2$	5	**L4**	165	99 (95)
9	**1b**	**3**	10	--	60	30

[a] Reaction conditions for Ni-catalyzed hydroacylation: **1a-b** (0.200 mmol), $Ni(COD)_2$ (0.010-0.030 mmol), ligand **L1-L4** (0.012-0.036 mmol), and mesitylene (1.0 mL). [b] Reaction conditions for NHC-catalyzed hydroacylation: **1a-b** (0.200 mmol), **3** (0.020 mmol), DBU (0.040 mmol), and 1,4-dioxane (1.0 mL). [c] Yield of **2a** or **2b** determined by ^{1}H NMR spectroscopy using dibromomethane as the internal standard; isolated yield of **2a** or **2b** is shown in parentheses.

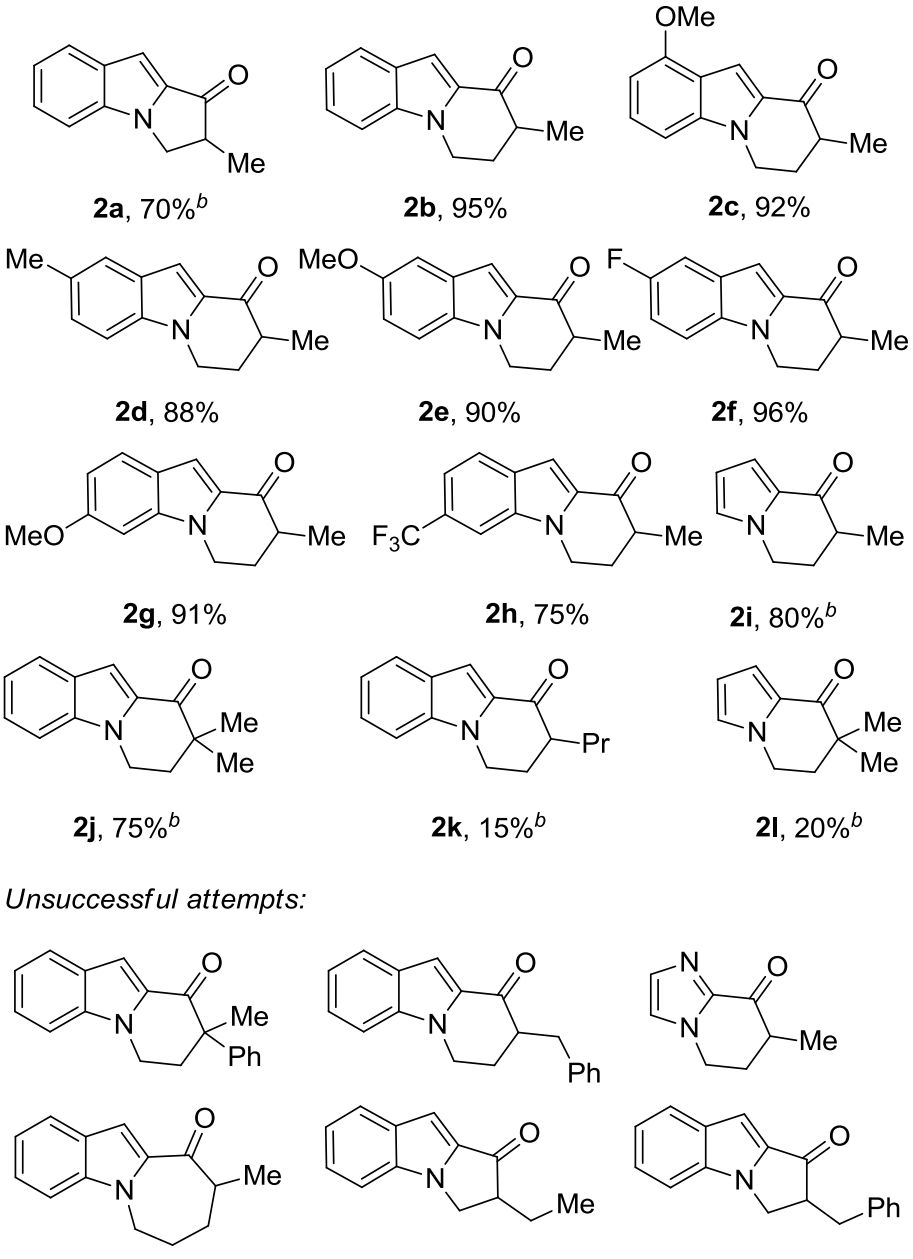
In general, formation of six-membered rings by transition metal-catalyzed intramolecular hydroacylation reactions is challenging compared to the formation of five-membered rings.[20] Surprisingly, the Ni-catalyzed hydroacylation of *N*-homoallylindole-2-carboxaldehyde **1b** forms the six-membered heterocyclic ketone **2b** in 95% yield with only 5 mol % Ni catalyst (Table 1, entry 8). However, a catalyst generated *in situ* from 10 mol % **3** and 20 mol % DBU at 60 °C forms **2b** in only 30% yield (Table 4.1, entry 9).

With a practical Ni catalyst system in hand, we evaluated the hydroacylations of various *N*-homoallylindole-2-carboxaldehydes containing substitution at the 4-, 5-, 6-positions on the indole backbone (Scheme 4.1). A variety of *N*-homoallylindole-2-carboxaldehydes containing electron-donating and electron-withdrawing substituents are excellent substrates for the Ni-catalyzed *exo*-selective intramolecular hydroacylations. Hydroacylations of electron-rich 4-MeO, 5-Me, 5-MeO, 6-MeO-substituted *N*-homoallylindole-2-carboxaldehydes occur with 5 mol % Ni catalyst and form dihydropyridoindolones **2c**-**2e** and **2g** in 88-92% yield. Hydroacylations of electron-deficient 5-F, 6-CF_3-substituted *N*-homoallylindole-2-carboxaldehydes also form dihydropyridoindolones **2f** and **2h** in 96% and 75% yields. Intramolecular hydroacylation of *N*-homoallylpyrrole-2-carboxaldehyde **1i** forms product **2i** in 80% yield with 15 mol % Ni catalyst.

Scheme 4.1 Intramolecular *exo*-Selective Ni-Catalyzed Hydroacylation[a]



1a-l **2a-l**



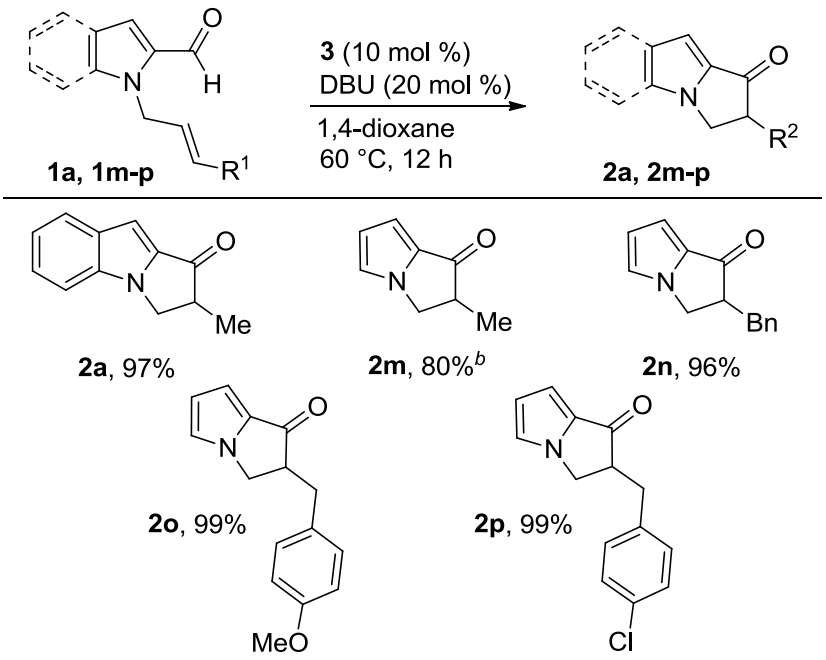
Unsuccessful attempts:

[a] Reaction conditions: **1a-l** (0.100 mmol), $Ni(COD)_2$ (0.005-0.015 mmol), ligand **L4** (0.006-0.018 mmol) and mesitylene (0.5 mL); yields of **2** are isolated yields after column chromatography. [b] Reaction run in the presence of 15 mol % $Ni(COD)_2$ and 18 mol % ligand **L4**.

Although substitution at the 4-, 5-, and 6-positions of the indole core is well-tolerated, substitution on the double bond of the *N*-homoallyl moiety had a detrimental effect on Ni-catalyzed intramolecular hydroacylation. The hydroacylation of 1-(3-methylbut-3-en-1-yl)-1*H*-indole-2-carboxaldehyde **1j** requires 15 mol % Ni catalyst to form **2j** in 75% yield, while the hydroacylation of 1-(hex-3-en-1-yl)-1*H*-indole-2-carboxaldehyde **1k** affords **2k** in only 15% yield. The hydroacylation of 1-(3-methylbut-3-en-1-yl)-1*H*-pyrrole-2-carboxaldehyde **1l** generated **2l** in 20% yield. The formation of six-membered ketones by an *exo*-selective pathway was exclusive; formation of seven-membered ketone products by an *endo*-selective pathway was not observed.

The results of NHC-catalyzed intramolecular hydroacylations of *N*-allylindole-2-carboxaldehyde and *N*-allylpyrrole-2-carboxaldehydes containing a range of 1-substituted allyl units are shown in Scheme 4.2. Hydroacylations of **1m-p** containing phenyl, 4-methoxyphenyl and 4-chlorophenyl substituents at the terminal carbon of the allyl unit forms the hydroacylation products **2m-p** in excellent yields (80-99%).

Scheme 4.2 Intramolecular *exo*-Selective NHC-Catalyzed Hydroacylation[a]



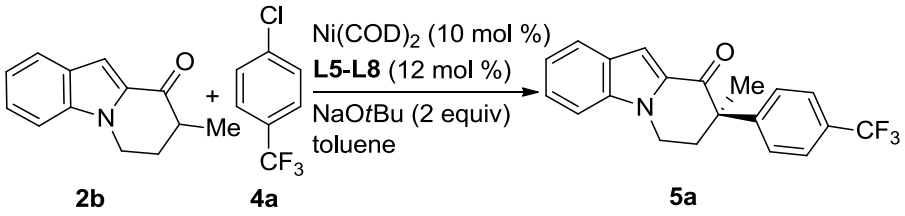
[a] Reaction conditions: **1a, 1m-p** (0.200 mmol), **3** (0.020 mmol), DBU (0.040 mmol), and 1,4-dioxane (1.0 mL); Yields of **2** are isolated yields after column chromatography; [b] 24 h reaction time.

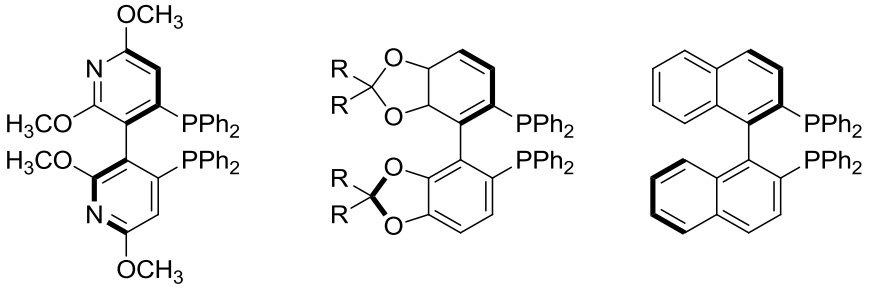
4.3.2 α-Arylation of Nitrogen-containing Six-membered Heterocyclic Ketones

Initial studies to develop catalytic, enantioselective α-arylations of α-methyl dihydropyridoindolones were guided by α-arylations of 2-methyl-1-indanones and 2-methyl-1-tetralones catalyzed by a Ni(0) complex of BINAP.[6a] To test the feasibility of nitrogen-containing heterocyclic ketones as substrates for α-arylations, we evaluated the reaction of 8-methyl-7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-one **2b** with 1-chloro-4-(trifluoromethyl)benzene **4a** catalyzed by complexes prepared *in situ* from $Ni(COD)_2$ and a selection of aromatic bisphosphine ligands **L5-L8** containing axial chiral backbones (Table 4.2, entries 1-3, entry 6). At 80 °C, complexes generated *in situ* from $Ni(COD)_2$ and ligands **L5-L8** catalyzed the formation of α-arylated product **5a** in yields ranging from 45-77% with 95-97% ee. However,

we found that subtle changes in temperature had a marked influence on the yield of **5a**. For example, the yield of **5a** increased from 60% to 72% to 99% as the temperature of the reaction decreased from 80 °C to 70 °C to 65 °C (compare entries 6-8) when the α-arylation of **2b** was run in the presence of $Ni(COD)_2$ and **L8**. Lower reaction temperatures likely minimize catalyst inactivation through thermal decomposition of the Ni(II) complex formed after oxidative addition of aryl chloride **4a** which leads to the pronounced influence of temperature on the yield of **5a** (Figure 4.3).[6a, 21]

Table 4.2 Identification of Catalyst for Ni-catalyzed α-Arylation of 8-Methyl-7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-one[a]





L5 ((*R*)-CTH-P-PHOS) **L6** (R = H; (*R*)-SEGPHOS) **L7** (R = F; (*R*)-DIFLUORPHOS) **L8** ((*R*)-BINAP)

entry	ligand	temp (°C)	time (h)	conv[b] (%)	yield[c] (%)	ee[d] (%)
1	**L5**	80	48	99	77	95
2	**L6**	80	48	99	72	97
3	**L7**	80	48	80	45	97
4	**L7**	70	48	75	42	99
5	**L7**	60	48	75	69	99
6	**L8**	80	48	99	60	97
7	**L8**	70	48	99	72	98
8	**L8**	65	48	99	99	99
9	**L8**	65	24	75	60	98
10	**L8**	60	48	60	55	98
11	**L8**	60	60	85	80	99

[a] Reaction conditions: **2b** (0.200 mmol), **4a** (0.400 mmol), NaO*t*Bu (0.400 mmol), $Ni(COD)_2$ (0.020 mmol), ligand **L5-L8** (0.024 mmol), and toluene (1.0 mL). [b] Conversion of **2b** was determined by ^1H NMR spectroscopy. [c] Isolated yield after column chromatography. [d] Determined by chiral HPLC analysis.

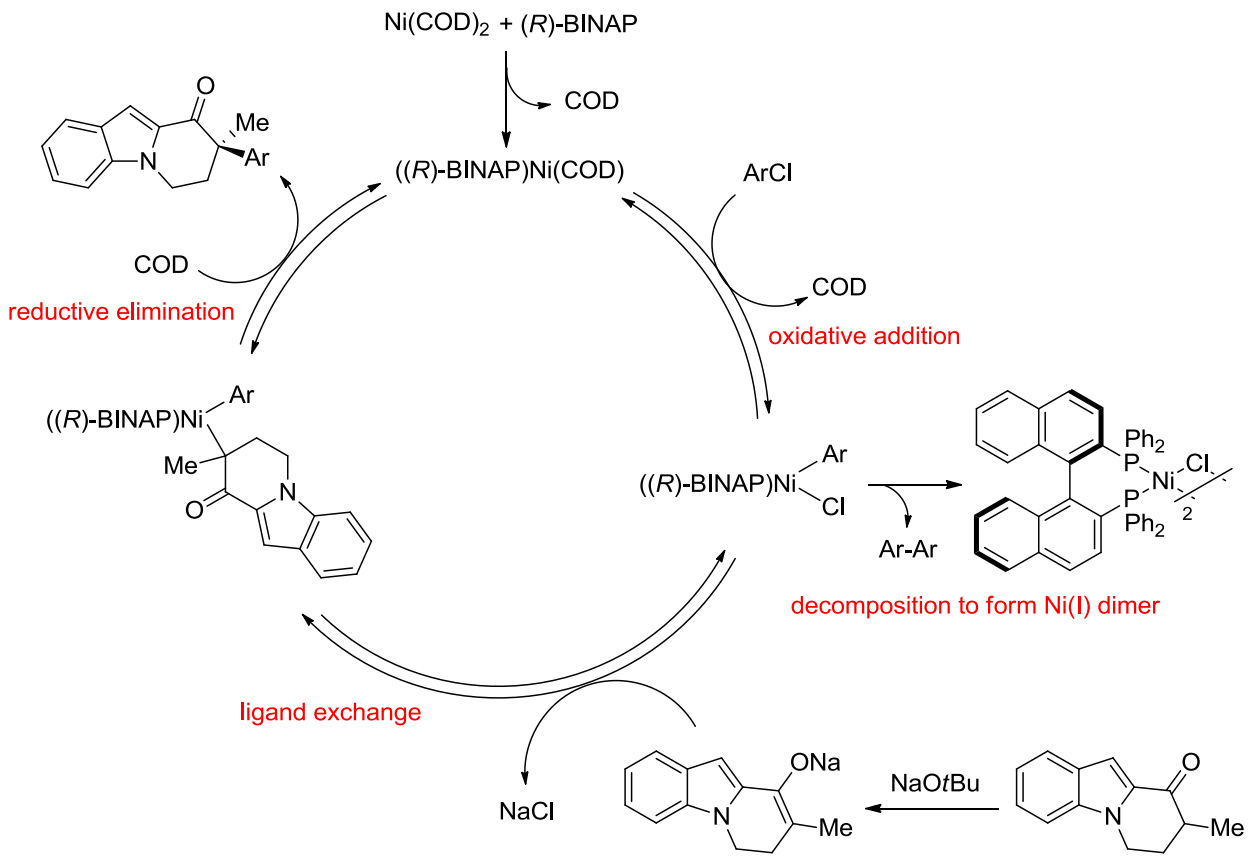
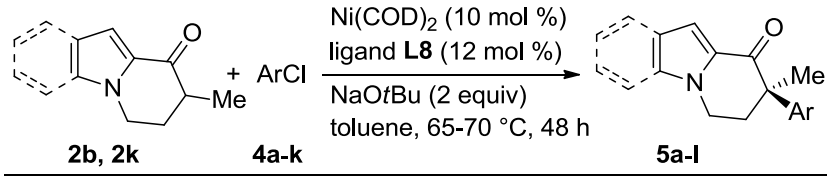


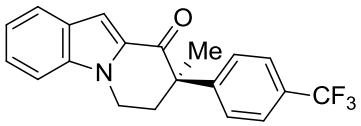
Figure 4.3 Proposed Reaction Mechanism for Ni-catalyzed α-Arylation of 8-Methyl-7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-one (**2b**) with Aryl Chloride

Scheme 4.3 summarizes the results of α-arylations of **2b** with a range of aryl chlorides catalyzed by the complex generated *in situ* from $Ni(COD)_2$ and (*R*)-BINAP. A variety of electron-rich, electron-neutral and electron-deficient aryl chlorides react to generate α-arylated products with high yields (75-99%) and excellent enantioselectivities (97-99% ee). Reactions of aryl chlorides containing electron-withdrawing groups at the *para*-position and electron-donating groups at the *meta*-position form **5a-d** in high yields when the reactions are performed at 65 °C. The reaction of **2b** with methyl 4-chlorobenzoate **4c** is notable as it generated *tert*-butyl ester **5c** as the only α-arylated product, presumably due to complete transesterification in the presence of NaO*t*Bu. Reactions of electron-neutral aryl chlorides and aryl chlorides with electron-donating groups at the *para*-position and electron-withdrawing groups at the *meta*-position require a

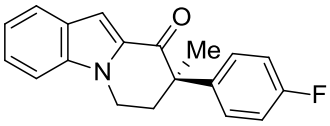
reaction temperature of 70 °C to form products **5e-i** and **5k** in high yields. 2-Chloronaphthalene **4j** also reacted with **2b** at 70 °C to generate **5j** in 95% yield and 99% ee. Although the α-arylation of **2b** tolerates a range of functional groups on the aryl chloride partners, *ortho*-substituted aryl chlorides do not react under our standard reaction conditions. The α-arylation of dihydroindolizinone **2k** with 1-chloro-3-methoxybenzene formed **5l** in 70% yield and 91% ee.

Scheme 4.3 Ni-Catalyzed Enantioselective α-Arylation of Dihydropyridoindolone and Dihydroindolizinone with Aryl Chlorides[a,b]

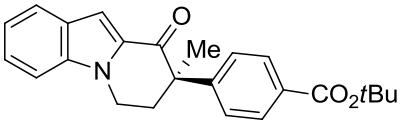




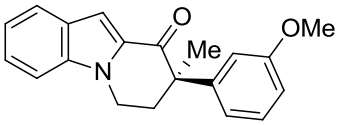
5a, 99%, 99% ee, 65 °C



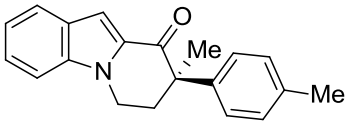
5b, 95%, 99% ee, 65 °C



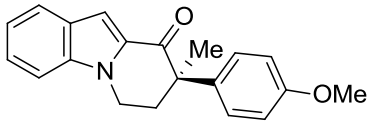
5c, 85%, 99% ee, 65 °C



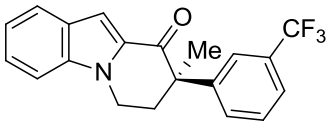
5d, 93%, 99% ee, 65 °C



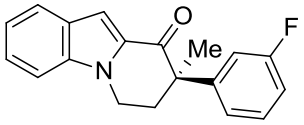
5e, 83%, 99% ee, 70 °C



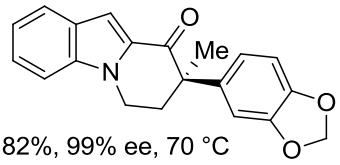
5f, 92%, 97% ee, 70 °C



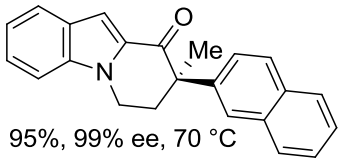
5g, 90%, 99% ee, 70 °C



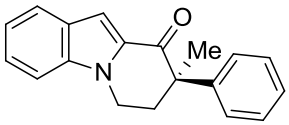
5h, 75%, 99% ee, 70 °C



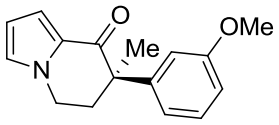
5i, 82%, 99% ee, 70 °C



5j, 95%, 99% ee, 70 °C



5k, 99%, 98% ee, 70 °C



5l, 70%, 91% ee, 65 °C

[a] Reactions conditions: **2b** or **2k** (0.100 mmol), **4a-k** (0.200 mmol), NaO*t*Bu (0.200 mmol), $Ni(COD)_2$ (0.010 mmol), **L8** (0.012 mmol), and toluene (0.5 mL); [b] Yields of **5** are isolated yields after column chromatography; enantiomeric excesses of **5** were determined by chiral HPLC analysis.

The absolute configuration of the quaternary stereocenter in **5d** was unambiguously determined by X-ray crystallographic analysis to be (*R*). Thus, the catalyst generated from (*R*)-BINAP leads to the formation of (*R*)-**5d** (Figure 4.4).

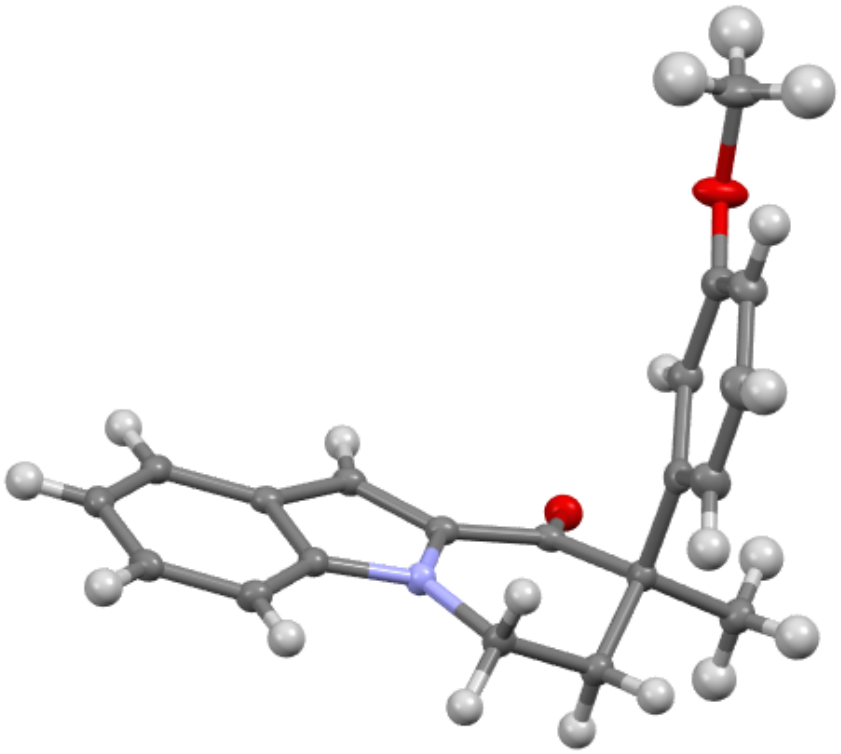


Figure 4.4 Determination of absolute stereochemistry of **5d** by X-ray crystallographic analysis

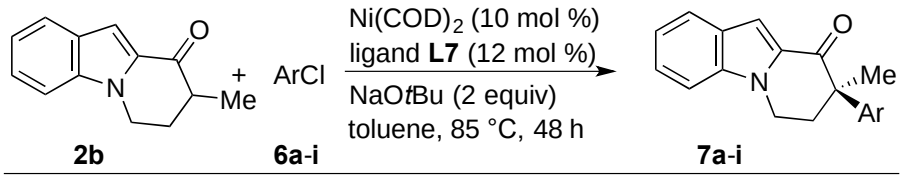
Single crystal X-ray structure determination of **5d** was performed by Dr. Arkady Ellern using Cu radiation to determine the absolute configuration of the molecule. The systematic absences in the diffraction data were consistent for the stated space group. The position of almost all non-hydrogen atoms were found by direct methods. The remaining atoms were located in an alternating series of least-squares cycles on difference Fourier maps. All non-hydrogen atoms were refined in full matrix anisotropic approximation. All hydrogen atoms were placed in the structure factor calculation at idealized positions and were allowed to ride on the neighboring atoms with relative isotropic displacement coefficients. Flack, Hooft, and Parsons parameters

were calculated with PLATON software. Flack, Hooft, and Parsons parameters of 0.12(11), 0.08(9), and 0.03(10) in combination with the enantiomeric purity of **5d** (99% ee by chiral HPLC analysis) are consistent with our assignment of the absolute configuration as (*R*). CCDC 1447403 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

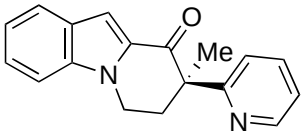
4.3.3 α-Heteroarylation of Nitrogen-containing Six-membered Heterocyclic Ketones

Encouraged by the ability to form α-arylated heterocyclic ketones with indole and pyrrole backbones in high yields and enantioselectivities, we evaluated the enantioselective Ni-catalyzed α-heteroarylation of **2b** with 2-chloropyridine **6a**. The catalyst generated *in situ* from $Ni(COD)_2$ and (*R*)-BINAP **L8** did not yield any α-heteroarylated product with >95% recovery of **2b** after 48 h. However, the complex generated *in situ* from $Ni(COD)_2$ and (*R*)-DIFLUORPHOS **L7** at 80 °C catalyzed the formation of α-heteroarylated product **7a** in 72% isolated yield and 99% ee (Scheme 4.4).

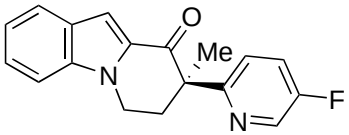
Scheme 4.4 Ni-Catalyzed Enantioselective α-Heteroarylation of Dihydropyridoindolone with Heteroaryl Chlorides[a,b]



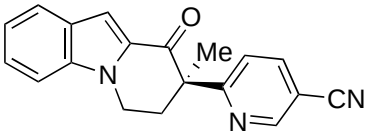
2b **6a-i** **7a-i**



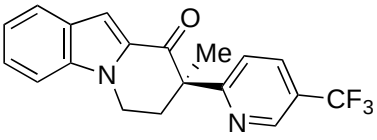
7a, 72%, 99% ee[c]



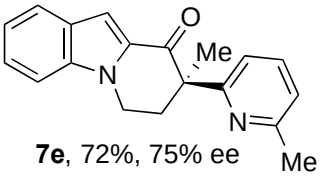
7b, 82%, 98% ee



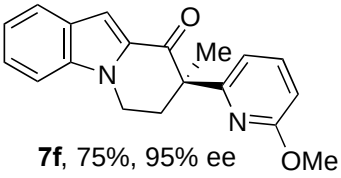
7c, 93%, 29% ee



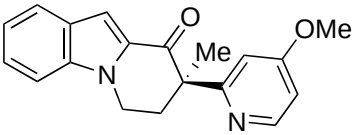
7d, 55%, 65% ee



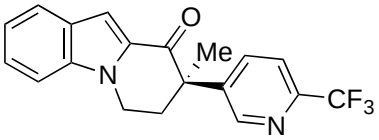
7e, 72%, 75% ee



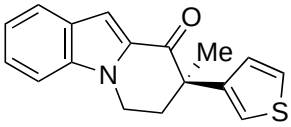
7f, 75%, 95% ee



7g, 50%, 86% ee



7h, 80%, 99% ee



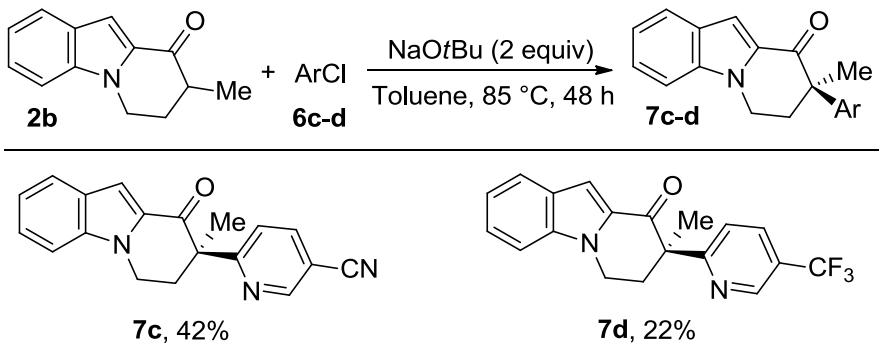
7i, 92%, 94% ee

[a] Reaction conditions: **2b** (0.100 mmol), **6a-i** (0.200 mmol), NaO*t*Bu (0.200 mmol), $Ni(COD)_2$ (0.010 mmol), **L7** (0.012 mmol), and toluene (0.5 mL); [b] Yields of **7** are isolated yields after column chromatography; enantiomeric excesses of **7** were determined by chiral HPLC analysis; [c] Reaction run at 80 °C.

Scheme 4.4 summarizes the results of α-heteroarylation reactions of **2b** with a range of 2-chloropyridines containing electron-donating and electron-withdrawing substituents at the 4-, 5- and 6-positions of the pyridine ring, as well as 5-chloro-2-(trifluoromethyl)pyridine and 3-

chlorothiophene. Ni-catalyzed α-heteroarylation of **2b** with 2-chloro-5-fluoropyridine forms the heteroarylated ketone **7b** in 82% yield with 98% ee. α-Heteroarylation of **2b** with electron-deficient heteroaryl chlorides, 6-chloronicotinonitrile **6c** and 2-chloro-5-trifluoromethylpyridine **6d**, generated the heteroarylated products **7c** and **7d** in 93% and 55% yield, but the enantioselectivities were poor (29-65% ee). The decrease in enantioselectivity results from uncatalyzed nucleophilic aromatic substitution of these electron-deficient heteroaryl chlorides by the sodium enolate of **2b**. Additions of **2b** to **6c** and **6d** at 85 °C in the absence of catalyst formed the α-arylated products **7c** and **7d** in 42% and 22% yields by ^{1}H NMR analysis (Scheme 4.5).

Scheme 4.5 Background reaction of **2b** with electron-deficient heteroaryl chlorides **6c-d** in presence of NaO*t*Bu

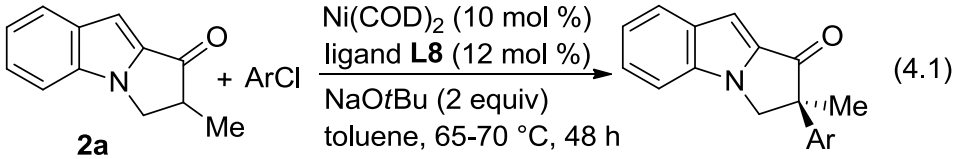


[a] Reaction conditions: **2b** (0.100 mmol), **6c-d** (0.200 mmol), NaO*t*Bu (0.200 mmol) and toluene (0.5 mL); [b] Yields of **7** are determined by ^{1}H NMR spectroscopy of crude reaction mixture using dibromomethane as internal standard.

α-Heteroarylation of **2b** with electron-rich heteroaryl chlorides, 2-chloro-4-methoxypyridine, 2-chloro-6-methylpyridine and 2-chloro-6-methoxypyridine, formed the α-heteroarylated ketones **7e-g** in moderate-to-good yields (50-75%) with moderate to high enantioselectivities (75-95%). 5-Chloro-2-(trifluoromethyl)pyridine and 3-chlorothiophene proved to be excellent substrates for α–heteroarylation of **2b**. Reactions of these heteroaryl chlorides formed **7h** and **7i** in high yields (80-92%) with excellent enantioselectivities (94-99%).

4.3.4 α-Arylation of Nitrogen-containing Five-membered Heterocyclic Ketones

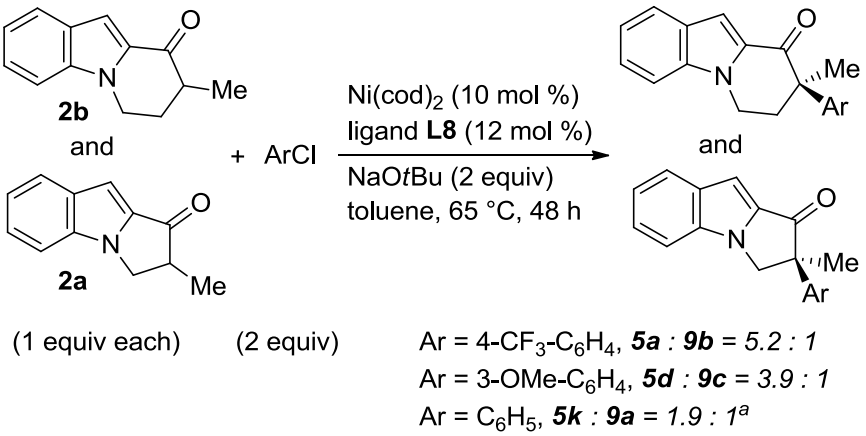
The ability to form a range of dihydropyridoindolones with α-chiral quaternary stereocenters in high yield with excellent stereocontrol led us to investigate Ni-catalyzed α-arylation reactions of five-membered heterocyclic ketones. Surprisingly, α-arylation of **2a** with chlorobenzene at 70 ℃ in the presence of a catalyst generated *in situ* from $Ni(COD)_2$ and (*R*)-BINAP **L8** formed the α-arylated product **9a** in only 19% yield, while the analogous reaction with 1-chloro-3-methoxybenzene at 65 ℃ generated a 5% yield of the coupled product **9b** (Equation 4.1).



9a; Ar = C_6H_5, 70 °C, 19% yield
9b; Ar = 3-MeO-C_6H_4, 65 °C, 5% yield

To understand the relative reactivity of the five-membered and six-membered heterocyclic ketones towards Ni-catalyzed α–arylation reaction, we ran competition experiments between them with three different aryl chlorides (Scheme 4.6). In each case, formation of the dihydropyridoindolone product (**5a**, **5d**, **5k**) dominated over the formation of dihydropyrroloindolone product (**9b**, **9c**, **9a**). However, the ratio of the dihydropyridoindolone vs dihydropyrroloindolone product formed, varied significantly with the identity of the aryl chloride employed in the reaction. Ni-Catalyzed α-arylation with 1-chloro-4-(trifluoromethyl)benzene resulted in 5.2:1 ratio of the dihydropyridoindolone vs dihydropyrroloindolone product, while 3-methoxychlorobenzene formed the products in 3.9:1 ratio. The competition experiment with simple chlorobenzene resulted in the formation of 1.9:1 ratio of the six-membered vs five-membered heterocycle.

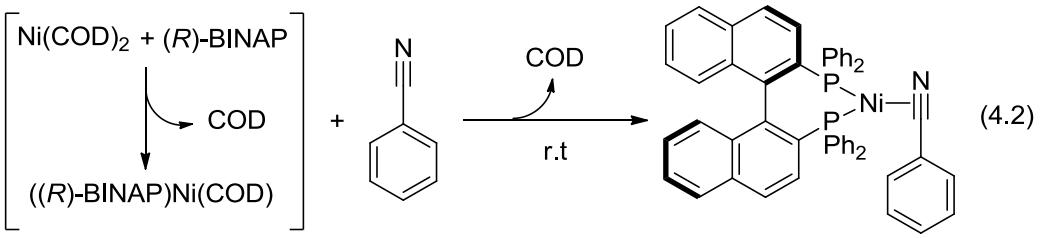
Scheme 4.6 Competition experiments to demonstrate relative reactivities of dihydropyridoindolones vs dihydropyrroloindolones towards α-arylation reactions



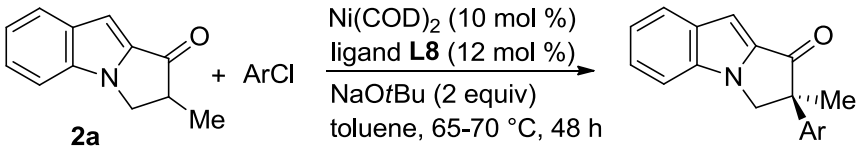
2a & **2b** (0.100 mmol), ArCl (0.200 mmol), NaO*t*Bu (0.200 mmol), $Ni(COD)_2$ (0.010 mmol), and ligand L8 (0.012 mmol) in toluene (0.5 mL); ratio determined by ^{1}H NMR spectroscopy of crude reaction mixture; [a] run at 70 °C

The poor yields observed in α-arylations of dihydropyrroloindolone **2a** may result from decomposition of the [**L8**]Ni(Ar)(Cl) intermediate formed after oxidative addition becoming competitive with the productive reaction pathway at elevated temperatures. To test the plausibility of this hypothesis, we performed the α-arylation of **2a** in the presence of a single component [**L8**]Ni(η^2-NC-Ph) precatalyst (Equation 4.2) that is known to oxidatively add aryl halides at 25 °C and attenuate decomposition of the oxidative addition product [**L8**]Ni(Ar)(Cl).[6a, 21-22]

The reactions of **2a** with chlorobenzene and bromobenzene formed **9a** in 38% and 47% yield, respectively, when the reactions were performed at 25 °C in the presence of 10 mol % [**L8**]Ni(η^2-NC-Ph) (Equation 4.3). α-Arylations of dihydropyrroloindolone **2a** occurred in the highest yields when performed at 25 °C in the presence of 15 mol % [**L8**]Ni(η^2-NC-Ph) (Scheme 5). α-Arylations of **2a** with bromobenzene, 3-methoxybromobenzene and 4-trifluoromethylbromobenzene formed **9a-9c** in 44-78% yield and 99% ee.

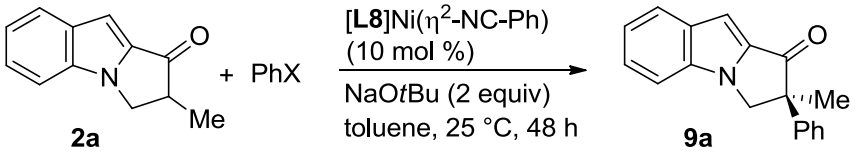


(4.2)



(4.1)

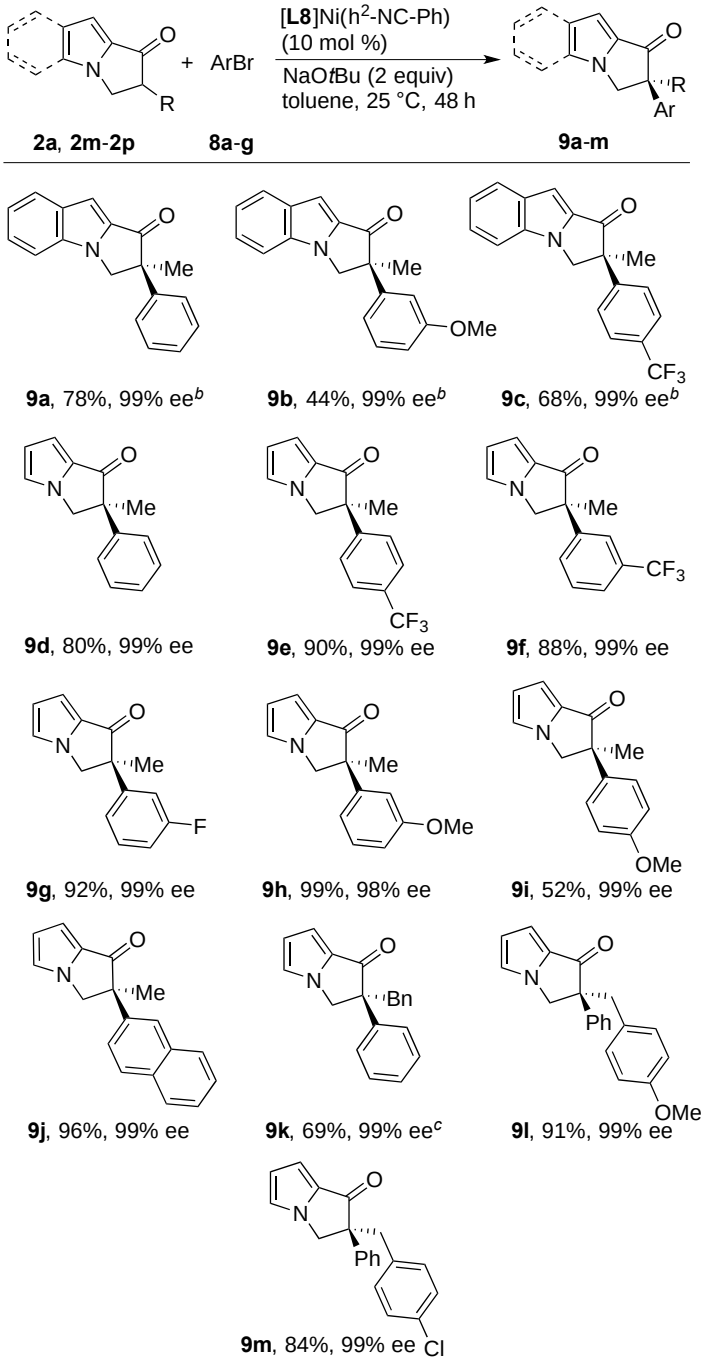
9a; Ar = C_6H_5, 70 °C, 19% yield
9b; Ar = 3-MeO-C_6H_4, 65 °C, 5% yield



(4.3)

from PhCl, 38% yield
from PhBr, 47% yield

Scheme 4.7 Ni-Catalyzed Enantioselective α-Arylation of Dihydropyrroloindolone and Dihydropyrrolizinones with Aryl Bromides[a]



[a] Reaction conditions: **2a, 2m-p** (0.200 mmol), **8a-g** (0.400 mmol), NaO*t*Bu (0.400 mmol), and [**L8**]Ni(η^2-NC-Ph) (0.020-0.030 mmol), and toluene (1.0 mL); yields of **9** are isolated yields after column chromatography; enantiomeric excesses of **9** were determined by chiral HPLC analysis. [b] Reaction run in the presence of 15 mol % catalyst. [c] Reaction run at 10 °C.

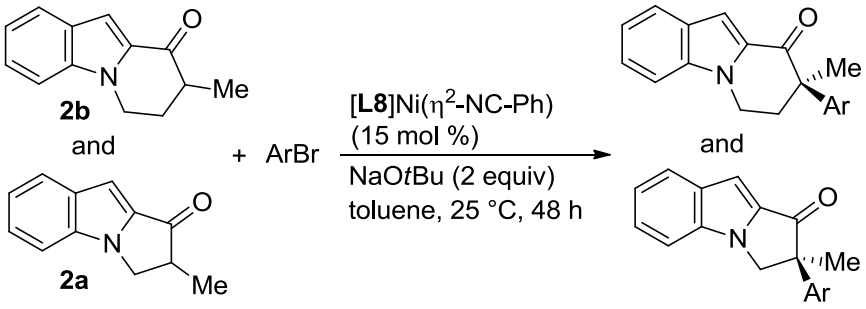
The identification of a catalyst system enabling the synthesis of dihydropyrroloindolones with α-chiral quaternary stereocenters by enantioselective α-arylation led us to investigate the analogous α-arylations of 2-methyl-2,3-dihydro-1*H*-pyrrolizin-1-one **2m** (Scheme 4.7). Aryl bromides with electron-deficient groups at the *meta* and *para* positions (-F, -CF_3) and an electron-donating group (-OMe) at the meta position reacted with **2m** in the presence of 10 mol % [**L8**]Ni(η^2-NC-Ph) to form the α-arylated ketones **9d-h** in high yields (80-99%) with excellent enantioselectivities (98-99%). The α-arylation of **2m** with *p*-bromoanisole occurred with high enantioselectivity, but formed product **9i** in 52% yield. 2-Bromonapthalene also reacted with **2m** to form **9j** in 96% yield and 99% ee.

This methodology can also be applied to heterocyclic ketones containing α-substitution beyond a methyl group. These reactions form α-arylated products in high yield and high enantioselectivity. As shown in Scheme 5, dihydropyrrolizinones **2n-p** with substituted and unsubstituted benzyl groups at the α-position reacted with bromobenzene in the presence of 10 mol % [**L8**]Ni(η^2-NC-Ph) to form α-arylated ketones **9k-9m** in 69-91% yield and 99% ee. The chemoselectivity of the α-arylation is highlighted by the reaction of dihydropyrrolizinone **2p** (R = 4-$ClC_6H_4CH_2$). Dihydropyrrolizinone **2p** reacted exclusively with bromobenzene to form α-arylated ketone **9m** in high yield and ee.

To test the relative reactivity of the five- and six-membered heterocyclic ketones towards α-arylation reactions in the presence of benzonitrile ligated Ni(0)-**L8** complex at ambient temperature, we conducted competition reactions between them with three different aryl bromides (Scheme 4.8). Again, in each case, formation of the dihydropyridoindolone product (**5a**, **5d**, **5k**) slightly dominated over the formation of dihydropyrroloindolone product (**9b**, **9c**, **9a**). However, the identity of the aryl bromide employed in the reaction did not have as

significant impact on the product ratios as that in scheme 4.6. α-Arylation with 1-bromo-4-(trifluoromethyl)benzene resulted in 1.2:1 ratio of the dihydropyridoindolone vs dihydropyrroloindolone product, while 3-methoxybromobenzene formed the products in 1.5:1 ratio. The competition experiment with simple bromobenzene resulted in the formation of 1.4 : 1 ratio of the six-membered vs five-membered heterocycle.

Scheme 4.8 Competition Experiments to Demonstrate Relative Reactivities of Dihydropyridoindolones vs Dihydropyrroloindolones Towards α-Arylation Reactions

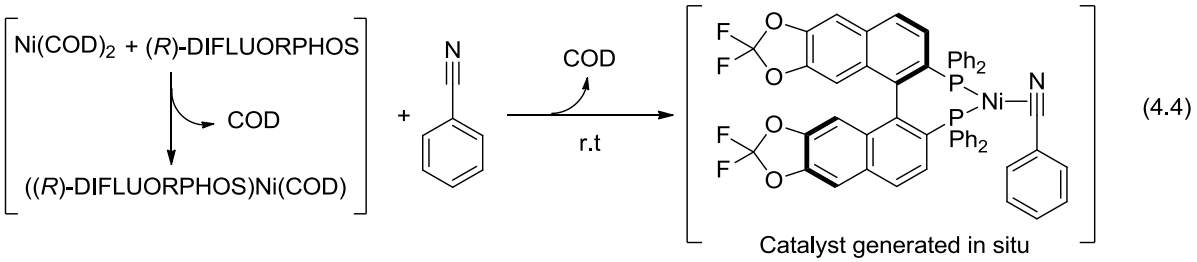


2a & **2b** (0.100 mmol), ArBr (0.200 mmol), NaO*t*Bu (0.200 mmol) and [**L8**]Ni(η^2-NC-Ph) (0.015 mmol) in toluene (0.5 mL); ratio determined by ^{1}H NMR spectroscopy of crude reaction mixture

4.3.5 α-Heteroarylation of Nitrogen-containing Five-membered Heterocyclic Ketones

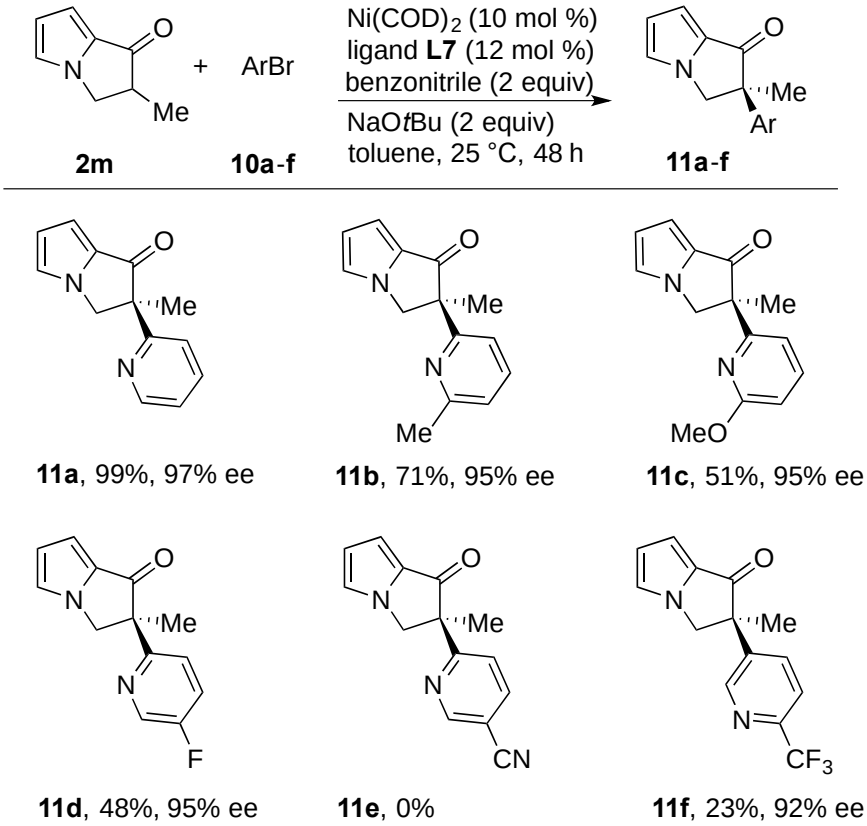
After successfully demonstrating α-arylations of dihydropyrrolizinones with aryl bromides in the presence of benzonitrile ligated Ni(0)-**L8** complex, we sought to identify a benzonitrile-ligated Ni(0)-**L7** complex to enable the formation of α-heteroarylated derivatives. We conducted α-heteroarylations of dihydropyrrolizinone **2m** with various heteroaryl bromides in the presence of a catalyst generated *in situ* from 10 mol % Ni(COD)$_2$, 12 mol % ligand **L7**, and 2 equivalents of benzonitrile (Equation 4.4, Scheme 4.9). Dihydropyrrolizinone **2m** reacts with 2-bromopyridine to form the α-heteroarylated product **11a** in 99% isolated yield and 97%

ee. Reactions of 5- and 6-substituted-2-bromopyridines with **2m** generated α-heteroarylated ketones **11b-d** in 48-71% yield with 95% ee. However, the α-heteroarylation of **2m** with 6-bromonicotinonitrile was unproductive and the corresponding ketone **11e** was not observed under our reaction conditions. The reaction of 5-bromo-2-(trifluoromethyl)pyridine with **2m** forms **11f** in low yield, but the enantioselectivity of the α-heteroarylation remains high (92% ee).



(4.4)

Scheme 4.9 Ni-Catalyzed Enantioselective α-Heteroarylation of Dihydropyrrolizinone with Heteroaryl Bromides[a]

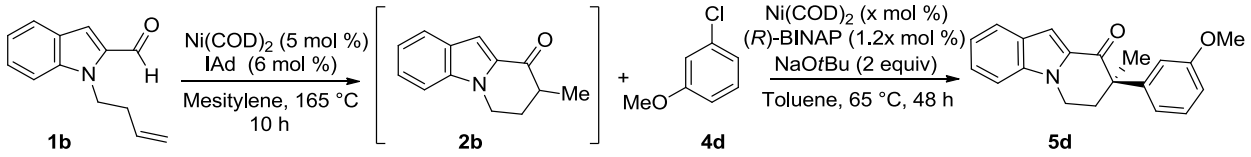


[a] Reaction conditions: **2m** (0.200 mmol), **10a-f** (0.400 mmol), NaO*t*Bu (0.400 mmol), $Ni(COD)_2$ (0.020 mmol), ligand **L7** (0.024 mmol), benzonitrile (0.400 mmol) and toluene (1.0 mL). Yields of **11** are isolated yields after column chromatography. Enantiomeric excesses of 11 were determined by chiral HPLC analysis.

4.3.6 One-pot Sequential Alkene Hydroacylation and α-Arylation Processes

One-pot multicatalytic transformations are attractive processes for sustainable chemical synthesis because these processes improve efficiency and eliminate waste and labor associated with isolation and purification of intermediate products. However, these processes are often challenging to achieve due to the incompatibility of catalysts, reagents, and solvents employed in each step.[23]

Table 4.3 Identification of Reaction Conditions for One-pot Synthesis of (*R*)-8-(3-Methoxyphenyl)-8-methyl-7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-one (**5d**) via Sequential Hydroacylation/α-Arylation



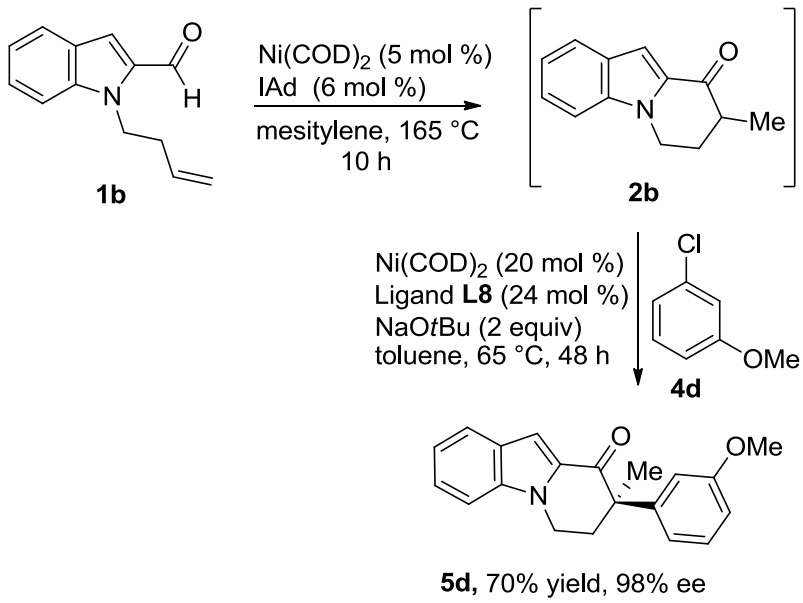
	Hydroacylation[d]		α-Arylation					
Entry	Mesitylene (mL)	Conv[a] of **1b** (%)	Catalyst loading (x mol %)	Toluene (mL)	Final conc (M)	Conv[a] of **2b** (%)	Yield[b] **5d** (%)	ee[c] (%)
1[e]	0.50	99	10	0.50	0.10	20	15	ND
2[f]	0.50	99	10	0.50	0.10	22	19	ND
3	0.50	99	10	0.50	0.10	43	40 (40)	98
4	0.50	99	10	0	0.20	0	0	--
5	0.25	99	10	0.50	0.13	45	40	ND
6	0.13	99	10	0.50	0.16	50	40	ND
7	0.25	99	10	0.25	0.20	30	10	ND
8	0.13	99	10	0.37	0.20	50	30	ND
9	0.50	99	15	0.50	0.10	70	54 (51)	99
10	0.50	99	20	0.50	0.10	99	75 (70)	98

Reaction conditions: **1b** (0.100 mmol), **4d** (0.200 mmol), NaO*t*Bu (0.200 mmol) [a] Conversion of **1b** and **2b** were determined by ^{1}H NMR spectroscopy. [b] NMR yield using dibromomethane as internal standard, isolated yield of **5d** is shown in parentheses. [c] Determined by chiral HPLC analysis. [d] The crude reaction mixture was exposed to air for 5-10 mins before addition of reagents for α–arylation under inert atmosphere. [e] The crude reaction mixture was not exposed to air before addition of reagents for α–arylation. [f] Bubbled N_2 for 15 mins before addition of reagents for α–arylation under inert atmosphere. ND = Not determined

To test the feasibility of Ni(0)/IAd-catalyzed *exo*-selective intramolecular alkene hydroacylation and enantioselective Ni(0)/(*R*)-BINAP-catalyzed α-arylation reactions in a single pot, we conducted a series of sequential reactions involving hydroacylation of *N*-homoallylindole-2-carboxaldehyde **1b** and α-arylation of the resulting ketone **2b** with 1-chloro-3-methoxybenzene (Table 4.3).

In a typical sequence, $Ni(COD)_2$, (*R*)-BINAP, NaO*t*Bu, 1-chloro-3-methoxybenzene and toluene were added to the reaction mixture under nitrogen atmosphere upon completion of the hydroacylation reaction. The enantioselectivity of these sequential reactions was high (>95% ee), but the yield of α–arylated ketone **5d** was low (30-40%). However, the yield of the sequential hydroacylation and α–arylation could be improved significantly by exposing the reaction mixture to air for 5-10 minutes before addition of reagents for α–arylation and increasing the catalyst loading to 20 mol %. Under these conditions, the one-pot, sequential hydroacylation and α–arylation generated ketone **5d** in 70% yield and 98% ee (Scheme 4.10).

Scheme 4.10 One-pot Sequential Hydroacylation and α-Arylation Reactions[a]



[a] Reaction conditions: **1b** (0.100 mmol), $Ni(COD)_2$ (0.005 mmol), IAd (0.006 mmol) and mesitylene (0.5 mL); **4d** (0.200 mmol), NaO*t*Bu (0.200 mmol), $Ni(COD)_2$ (0.020 mmol), and ligand **L8** (0.024 mmol) and toluene (0.5 mL). Yield of **5d** is the isolated yield after column chromatography. Enantiomeric excess of **5d** was determined by chiral HPLC analysis.

4.4 Conclusions

In summary, we have developed a convenient catalytic strategy that combines alkene hydroacylation and enantioselective α-(hetero)arylation reactions to form a wide variety of five- and six-membered nitrogen-containing heterocyclic ketones bearing non-racemic, α-chiral quaternary stereocenters. The potential to further functionalize the remaining carbonyl moiety makes this sequential reaction an attractive strategy to access wide range of complex chiral heterocycles having benzylic quaternary stereocenters. This sequential alkene hydroacylation/α-arylation protocol can also be performed in one-pot procedure with good yield and high enantioselectivity.

The intramolecular Ni-catalyzed hydroacylations proceed with complete *exo*-selectivity to form the six-membered nitrogen-containing heterocyclic ketones in moderate-

to-high yields from various indole and pyrrole substrates, while NHC-catalyzed hydroacylations of *N*-allylindoles and *N*-allylpyrroles occur with *exo*-selectivity to form α-substituted five-membered heterocyclic ketones in high yields. The five- and six-membered nitrogen-containing heterocyclic ketones formed by hydroacylation reactions are convenient substrates for Ni-catalyzed α-(hetero)arylation reactions that occur in moderate-to-high yields with excellent enantioselectivities. The six-membered heterocyclic ketones react with (hetero)aryl chlorides in the presence of catalyst complex generated *in situ* from $Ni(COD)_2$ and (*R*)-BINAP or (*R*)-DIFLUORPHOS at 65-85 °C, while reactions of five-membered heterocyclic ketones demand milder reaction conditions to form the desired coupling products with chiral quaternary stereocenters in moderate-to-high yields. Studies to develop additional tandem and sequential processes that combine olefin hydroacylation reactions with additional catalytic transformations are ongoing in our laboratory.

4.5 Experimental Details

4.5.1 General experimental details

All air-sensitive procedures were conducted under inert atmosphere in a nitrogen-filled dry box or by standard Schlenk techniques. All reactions were performed under an atmosphere of nitrogen unless otherwise stated. All glassware for moisture sensitive reactions was dried at 140 °C in an oven. Toluene and *N*,*N*-dimethylformamide, tetrahydrofuran were degassed by purging with argon for 45 minutes and dried with a solvent purification system by passing through a one-meter column of activated alumina. Anhydrous 1,4-dioxane was purchased from Sigma-Aldrich and used as received. Mesitylene was purchased from Sigma-Aldrich and was freshly distilled from sodium benzophenone ketyl under vacuum. Flash column chromatography was performed on SiliFlash® P60 silica gel (40-63μm, 60Å) or using a Teledyne Isco Combiflash® R*f* system

with Redi*Sep* GoldTM columns using hexanes/ethyl acetate, hexanes/diethyl ether, hexanes/dichloromethane mixtures. Reaction products were visualized on TLC by UV light or by staining with $KMnO_4$ or 2,4-dinitro-phenylhydrazine.

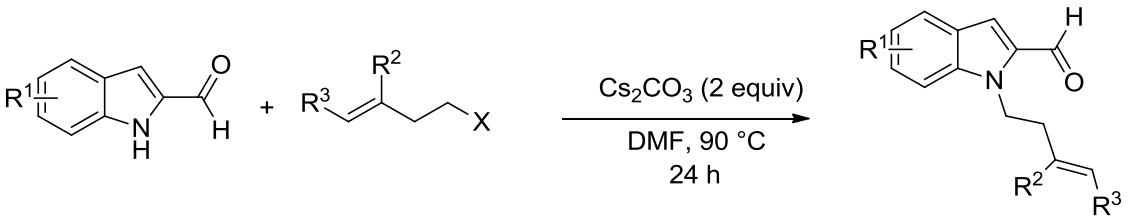
HRMS (ESI) analysis was performed at the Iowa State University Chemical Instrumentation Facility on an Agilent 6540 QTOF spectrometer. Optical rotations were measured on an Atago AP-300 automatic polarimeter. HPLC analyses were carried out on a Water Alliance HPLC system with an e2695 Separations Module and a 2489 (UV/Vis) dual wavelength detector. NMR spectra were acquired on Varian MR-400, Bruker DRX-400 and Bruker Avance III 600 spectrometers at the Iowa State University Chemical Instrumentation Facility. Chemical shifts are reported in ppm relative to a residual solvent peak ($CDCl_3$ = 7.26 ppm for ^1H and 77.36 ppm for ^{13}C; DMSO-d_6 = 2.50 for ^1H and 39.52 for ^{13}C). ^{19}F NMR shifts are reported in ppm relative to trifluoroacetic acid as an external standard (F_3CCO_2H = -76.55 ppm). Coupling constants are reported in hertz.

4.5.2 Materials

5-Methylindole-2-carboxaldehyde, 5-methoxyindole-2-carboxaldehyde, and 6-methoxyindole-2-carboxaldehyde were synthesized according to reported literature procedures.[24] 4-Methoxyindole-2-carboxaldehyde and 6-trifluoromethylindole-2-carboxaldehyde were synthesized according to the known literature procedure.[24e, 25] 5-Fluoroindole-2-carboxaldehyde was synthesized according to a literature procedure.[24e, 26] Indole-2-carboxaldehyde was synthesized from ethyl indole-2-carboxylate according to a known literature procedure.[24e] Ethyl indole-2-carboxylate, 4-bromobut-1-ene **S2a** and pyrrole-2-carboxaldehyde **S1h** were purchased from AK Scientific and used without further purification. 3-Methylbut-3-en-1-ol, (*E*)-hex-3-en-1-ol, allyl bromide, cinnamyl bromide, activated manganese dioxide, sodium *tert*-butoxide,

lithium aluminum hydride, benzonitrile, anhydrous 1,4-dioxane, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were purchased from Sigma-Aldrich and used without further purification. 4-bromo-2-methylbut-1-ene **S2b** was synthesized from 3-methylbut-3-en-1-ol according to a known literature procedure.[27] (*E*)-Hex-3-en-1-yl 4-methylbenzenesulfonate **S2c** was synthesized from (*E*)-hex-3-en-1-ol according to a known literature procedure.[28] Substituted cinnamyl bromides **S2d** and **S2e** were synthesized according to the known literature procedure.[24a, 29] **1a**, **1m**, **1n** were synthesized according to the known literature procedure.[24e] Organocatalyst **3** was synthesized according to the known literature procedure.[30] IAd, I*t*Bu, IMes, IPr were synthesized according to the known literature procedure.[31] Aryl chlorides **4a**, **4c**, **4e-f**, **4j**, heteroaryl chlorides **6b**, **6e-h** were purchased from Combi-blocks and used without further purification. Aryl chloride **4g**, heteroaryl chlorides **6c-d**, aryl bromides **8a-f** and heteroaryl bromides **10a-f** were purchased from AK scientific and used without further purification. Aryl chloride **4d**, heteroaryl chloride **6i** were purchased from TCI America and used without further purification. Aryl chloride **4i** and aryl bromide **8g** were purchased from Alfa Aesar and used without further purification. Aryl chloride **4h** was purchased from Oakwood Chemicals and used without further purification. Aryl chloride **4k** and heteroaryl chloride **6a** were purchased from Sigma-Aldrich and used without further purification. Aryl chloride **4b** was purchased from Acros Organics and used without further purification. $Ni(COD)_2$, (*R*)-BINAP, *rac*-BINAP, (*R*)-SEGPHOS, (*R*)-xylyl-BINAP, (*S*)-DIFLUORPHOS, (*R*)-DIFLUORPHOS, (*R*)-CTH-P-PHOS were purchased from Strem Chemicals and used without further purification. [(*R*)-BINAP]Ni(η^2-NC-Ph) was synthesized according to the known literature procedure.[6a]

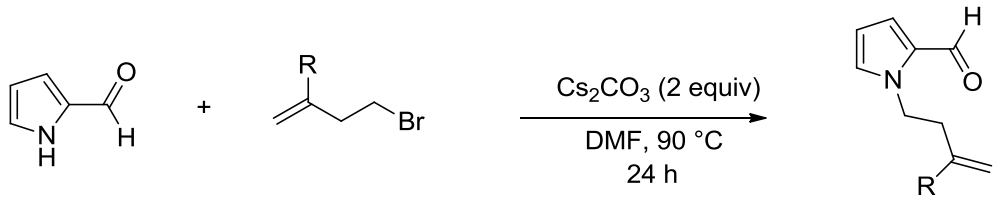
4.5.3 General Procedure A: Synthesis of *N*-Homoallylindole-2-carboxaldehydes (1b-h, 1j-k) and *N*-Homoallylpyrrole-2-carboxaldehydes (1i, 1l)



S1a; R^1 = H
S1b; R^1 = 4-MeO
S1c; R^1 = 5-Me
S1d; R^1 = 5-MeO
S1e; R^1 = 5-F
S1f; R^1 = 6-MeO
S1g; R^1 = 6-F_3C

S2a; R^2 = H, R^3 = H, X = Br
S2b; R^2 = Me, R^3 = H, X = Br
S2c; R^2 = H, R^3 = C_2H_5, X = OTs

1b; R^1 = H, R^2 = H, R^3 = H
1c; R^1 = 4-MeO, R^2 = H, R^3 = H
1d; R^1 = 5-Me, R^2 = H, R^3 = H
1e; R^1 = 5-MeO, R^2 = H, R^3 = H
1f; R^1 = 5-F, R^2 = H, R^3 = H
1g; R^1 = 6-MeO, R^2 = H, R^3 = H
1h; R^1 = 6-F_3C, R^2 = H, R^3 = H
1j; R^1 = H, R^2 = Me, R^3 = H
1k; R^1 = H, R^2 = H, R^3 = C_2H_5



S1h

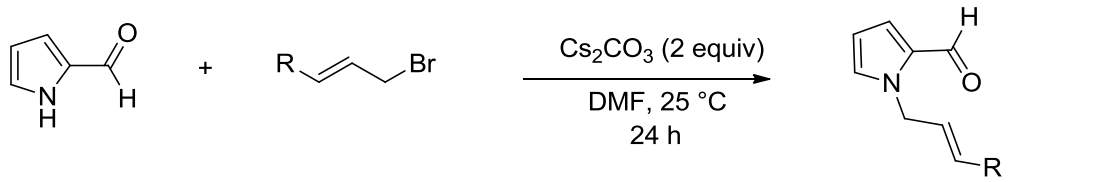
S2a; R = H
S2b; R = Me

1i; R = H
1l; R = Me

N-Homoallylindole-2-carboxaldehydes (**1b-h, 1j-k**) and *N*-homoallylpyrrole-2-carboxaldehydes (**1i, 1l**) were prepared from the appropriate homoallyl bromides or tosylates (**S2a-c)** and indole- and pyrrole-2-carboxaldehydes (**S1a-h)**. To the appropriate indole-2-carboxaldehyde (**S1a-g)** or pyrrole-2-carboxaldehyde **S1h** (1.0 equiv) and Cs_2CO_3 (1.2 equiv) was added DMF (0.27 M **S1**). The resulting mixture was stirred at room temperature for 0.5 h. The appropriate homoallylic bromide or tosylate **S2** (1.2 equiv) was added dropwise. The mixture was heated to 90 °C and stirred at the same temperature for 24 h. The reaction mixture was cooled to room temperature, quenched with water, and the resulting solution was extracted with EtOAc (3x). The combined organic layers were washed with water, washed with brine,

dried over Mg_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (hexane:EtOAc) to give the appropriate *N*-homoallylindole-2-carboxaldehyde (**1b-h, 1j-k**) or *N*-homoallylpyrrole-2-carboxaldehyde (**1i, 1l**).

4.5.4 General Procedure B: Synthesis of 1-Cinnamyl-1*H*-pyrrole-2-carboxaldehydes (1o-p)

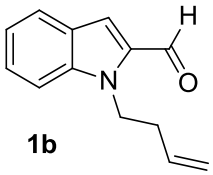


S1h

S2d; R = 4-MeO-C_6H_4
S2e; R = 4-Cl-C_6H_4

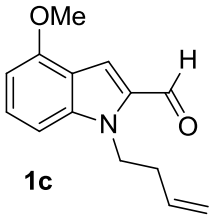
1o; R = 4-MeO-C_6H_4
1p; R = 4-Cl-C_6H_4

1-Cinnamyl-1*H*-pyrrole-2-carboxaldehydes (**1o-p**) were prepared according to a modified literature procedure from the appropriate cinnamyl bromides (**S2d-e)** and pyrrole-2-carboxaldehyde (**S1h).**[24e] To the pyrrole-2-carboxaldehyde (1.0 equiv) and Cs_2CO_3 (1.2 equiv) was added DMF (0.27 M **S1h**). The resulting mixture was stirred at room temperature for 0.5 h. The appropriate cinnamyl bromide (1.2 equiv) was added dropwise. The mixture was stirred at room temperature until the reaction was judged to be complete by thin-layer chromatography. Water was added to the reaction mixture and the resulting solution was extracted with EtOAc (3x). The combined organic layers were washed with water, brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (hexane:EtOAc) to give the appropriate 1-cinnamyl-1*H*-pyrrole-2-carboxaldehydes (**1o-p**).



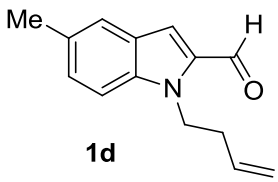
1b

1-(But-3-en-1-yl)-1*H*-indole-2-carboxaldehyde (1b): Prepared according to the general procedure A from **S1b** (3.00 g, 20.7 mmol) and **S2a** (3.35 g, 24.8 mmol). The mixture was purified by flash column chromatography (95:5 hexane:EtOAc) to give **1b** as a light yellow solid in 62% yield (2.55 g, 12.8 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.36 (dt, *J* = 7.2, 7.2 Hz, 2H), 4.43 (t, *J* = 7.2 Hz, 2H), 4.82 – 4.89 (m, 2H), 5.65 (ddt, *J* = 17.0, 10.2, 7.2 Hz, 1H), 6.99 – 7.04 (m, 2H), 7.23 – 7.24 (m, 2H), 7.55 (dd, *J* = 8.1, 0.8 Hz, 1H), 9.69 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 35.0, 44.2, 110.9, 117.4, 118.1, 121.0, 123.6, 126.5, 127.0, 134.7, 135.4, 140.3, 182.6. **HRMS** (ESI): Calcd. for $C_{13}H_{14}NO^+$ ($[M+H]^+$): 200.1070, Found: 200.1068.



1c

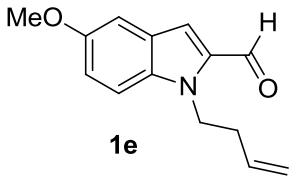
1-(But-3-en-1-yl)-4-methoxy-1*H*-indole-2-carboxaldehyde (1c): Prepared according to the general procedure A from **S1b** (0.258 g, 1.47 mmol) and **S2a** (0.239 g, 1.77 mmol). The mixture was purified by column chromatography (90:10 hexane:EtOAc) to give **1c** as yellow oil in 34% yield (0.115 g, 0.502 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.53 (dt, *J* = 7.3, 7.3 Hz, 2H), 3.96 (s, 3H), 4.58 (t, *J* = 7.3 Hz, 2H), 4.97 – 5.05 (m, 2H), 5.81 (ddt, *J* = 17.1, 10.2, 7.3 Hz, 1H), 6.50 (d, *J* = 8.0 Hz, 1H), 6.98 (d, *J* = 8.0 Hz, 1H), 7.32 (t, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 0.8 Hz, 1H), 9.80 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 35.1, 44.7, 55.6, 99.9, 103.7, 116.1, 117.5, 118.4, 128.4, 134.6, 134.9, 141.9, 155.4, 182.3. **HRMS** (ESI) Calcd. for $C_{14}H_{16}NO_2^+$ ($[M+H]^+$): 230.1176, Found: 230.1179.



1d

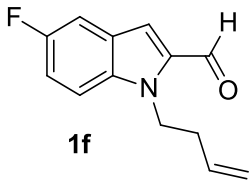
1-(But-3-en-1-yl)-5-methyl-1*H*-indole-2-carboxaldehyde (1d): Prepared according to the general procedure A from **S1c** (0.242 g, 1.52 mmol) and **S2a** (0.246 g, 1.82 mmol). The mixture was purified by flash column chromatography (95:5 hexane: EtOAc) to give **1d** as a light yellow oil in 59% yield

(0.191 g, 0.895 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.48 (s, 3H), 2.55 (dt, *J* = 7.2, 7.2 Hz, 2H), 4.62 (t, *J* = 7.2 Hz, 2H), 4.99 – 5.08 (m, 2H), 5.83 (ddt, *J* = 17.1, 10.2, 7.2 Hz, 1H), 7.19 (d, *J* = 0.64 Hz, 1H), 7.26 – 7.28 (m, 1H), 7.34 (d, *J* = 8.6 Hz, 1H), 7.52 – 7.53 (m, 1H), 9.87 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 21.6, 35.2, 44.5, 110.7, 117.5, 117.7, 122.9, 126.9, 129.3, 130.6, 135.0, 135.6, 139.1, 182.8. **HRMS** (ESI): Calcd. for $C_{14}H_{16}NO^+$ ($[M+H]^+$): 214.1226, Found: 214.1225.



1e

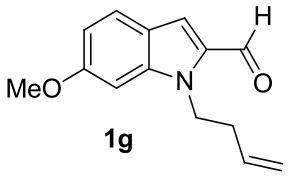
1-(But-3-en-1-yl)-5-methoxy-1*H*-indole-2-carboxaldehyde (1e): Prepared according to the general procedure A from **S1d** (0.343 g, 1.96 mmol) and **S2a** (0.317 g, 2.35 mmol). The mixture was purified by flash column chromatography (90:10 hexanes:EtOAc) to give **1e** as yellow solid in 60% yield (0.270 g, 1.18 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.49 (dt, *J* = 7.0, 7.0 Hz, 2H), 3.82 (s, 3H), 4.54 (t, *J* = 7.0 Hz, 2H), 4.95 – 5.01 (m, 2H), 5.71 – 5.82 (m, 1H), 7.05 – 7.11 (m, 3H), 7.27 (d, *J* = 9.0 Hz, 1H), 9.80 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 35.1, 44.4, 55.8, 102.8, 111.9, 117.2, 117.5, 119.2, 126.8, 134.8, 135.6, 136.1, 154.9, 182.5. **HRMS** (ESI) Calcd. for $C_{14}H_{16}NO_2^+$ ($[M+H]^+$): 230.1176, Found: 230.1176.



1f

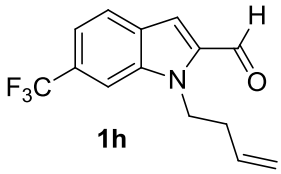
1-(But-3-en-1-yl)-5-fluoro-1*H*-indole-2-carboxaldehyde (1f): Prepared according to the general procedure A from **S1e** (0.136 g, 0.834 mmol) and **S2a** (0.135 g, 1.00 mmol). The mixture was purified by column chromatography (95:5 hexanes:EtOAc) to give **1f** as yellow oil in 55% yield (0.100 g, 0.460 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.52 (dt, *J* = 7.2, 7.2 Hz, 2H), 4.60 (t, *J* = 7.2 Hz, 2H), 4.97 - 5.03 (m, 2H), 5.78 (ddt, *J* = 17.1, 10.2, 7.2 Hz, 1H), 7.17 (ddd, *J* = 9.1, 9.1, 2.5 Hz, 1H), 7.22 (s, 1H), 7.34 - 7.37 (m, 2H), 9.87 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 35.2, 44.7, 107.6

(d, *J* = 23.2 Hz, 1C), 112.1 (d, *J* = 9.1 Hz, 1C), 116.4 (d, *J* = 27.3 Hz, 1C), 117.5 (d, *J* = 6.1 Hz, 1C), 117.8, 126.6 (d, *J* = 10.3 Hz, 1C), 134.7, 136.6, 137.2, 158.4 (d, *J* = 239.4 Hz, 1C), 182.9. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -122.8 (m, 1F). **HRMS** (ESI) Calcd. for $C_{13}H_{13}FNO^+$ ($[M+H]^+$): 218.0976, Found: 218.0970.



1g

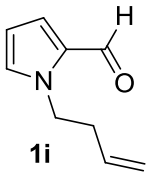
1-(But-3-en-1-yl)-6-methoxy-1*H*-indole-2-carboxaldehyde (1g): Prepared according to the general procedure A from **S1f (**0.283 g, 1.62 mmol) and **S2a** (0.262 g, 1.94 mmol). The mixture was purified by flash column chromatography (90:10 hexane:EtOAc) to give **1g** as a dark yellow oil in 57% yield (0.211 g, 0.920 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.53 (dt, *J* = 7.2, 7.2 Hz, 2H), 3.89 (s, 3H), 4.56 (t, *J* = 7.2 Hz, 2H), 4.99 – 5.07 (m, 2H), 5.82 (ddt, *J* = 17.1, 10.2, 7.2 Hz, 1H), 6.73 (m, 1H), 6.83 (dd, *J* = 8.8, 2.2 Hz, 1H), 7.16 (s, 1H), 7.58 (d, *J* = 8.8 Hz, 1H), 9.73 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 34.9, 44.4, 55.8, 92.3, 113.0, 117.5, 119.0, 121.2, 124.6, 135.0, 135.2, 141.9, 160.3, 181.6. **HRMS** (ESI) Calcd. for $C_{14}H_{16}NO_2^+$ ($[M+H]^+$): 230.1176, Found: 230.1174.



1h

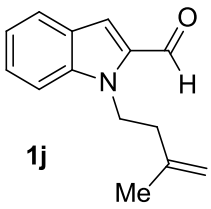
1-(But-3-en-1-yl)-6-(trifluoromethyl)-1*H*-indole-2-carboxaldehyde (1h): Prepared according to the general procedure A from **S1g** (0.512 g, 2.40 mmol) and **S2a** (0.389 g, 2.88 mmol). The mixture was purified by column chromatography (90:10 hexanes:EtOAc) to give **1h** as yellow oil in 17% yield (0.110 g, 0.412 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.55 (dt, *J* = 7.2, 7.2 Hz, 2H), 4.66 (t, *J* = 7.2 Hz, 2H), 4.99 - 5.04 (m, 2H), 5.79 (ddt, *J* = 17.1, 10.2, 7.2 Hz, 1H), 7.31 (m, 1H), 7.39 (dd, *J* = 8.4, 1.0 Hz, 1H), 7.70 (s, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 9.94 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 35.2, 44.8, 108.8 (q, *J* = 4.0 Hz, 1C), 117.4, 117.6 (q, *J* = 3.0 Hz, 1C), 118.1, 124.5, 124.9 (q, *J* =

272.7 Hz, 1C), 128.6, 128.9, 134.4, 137.4, 139.2, 183.1. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -61.2. **HRMS** (ESI) Calcd $C_{14}H_{13}F_3NO^+$ ($[M+H]^+$): 268.0944, Found: 268.0948.



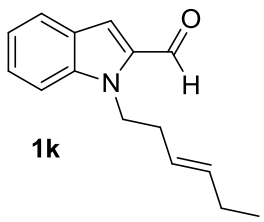
1i

1-(But-3-en-1-yl)-1*H*-pyrrole-2-carboxaldehyde (1i): Prepared according to the general procedure A from **S1h** (0.539 g, 5.67 mmol) and **S2a** (0.918 g, 6.80 mmol). The mixture was purified by flash column chromatography (95:5 hexane:EtOAc) to give **1k** as a green oil in 57% yield (0.480 g, 3.22 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.47 (dt, *J* = 7.0, 7.0 Hz, 2H), 4.34 (t, *J* = 7.0 Hz, 2H), 4.97 (s, 1H), 5.00 – 5.02 (m, 1H), 5.71 (ddt, *J* = 17.6, 9.6, 7.0 Hz, 1H), 6.17 (dd, *J* = 3.6, 2.6 Hz, 1H), 6.89 – 6.90 (m, 2H), 9.51 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 35.8, 48.8, 109.6, 117.7, 125.1, 131.4, 131.6, 134.4, 179.4. **HRMS** (ESI) Calcd $C_9H_{12}NO^+$ ($[M+H]^+$): 150.0913, Found: 150.0915.

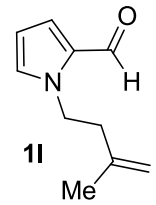


1j

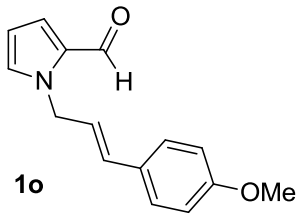
1-(3-Methylbut-3-en-1-yl)-1*H*-indole-2-carboxaldehyde (1j): Prepared according to the general procedure A from **S1a (**0.500 g, 3.44 mmol) and 17% solution of **S2b** (3.620 g, 4.13 mmol) in THF. The mixture was purified by flash column chromatography (90:10 hexane:EtOAc) to give **1i** as a light yellow solid in 30% yield (0.220 g, 1.03 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.85 (s, 3H), 2.47 (t, *J* = 7.8 Hz, 2H), 4.67 (t, *J* = 7.8 Hz, 2H), 4.72 (s, 1H), 4.81 (s, 1H), 7.17 – 7.21 (m, 1H), 7.25 (s, 1H), 7.42 (d, *J* = 4.2 Hz, 2H), 7.75 (dd, *J* = 8.2, 0.8 Hz, 1H), 9.89 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 22.9, 38.6, 43.8, 110.8, 112.6, 118.1, 121.1, 123.7, 126.7, 127.1, 135.5, 140.3, 142.7, 182.7. **HRMS** (ESI): Calcd. for $C_{14}H_{16}NO^+$ ($[M+H]^+$): 214.1226, Found: 214.1226.



(*E*)-1-(Hex-3-en-1-yl)-1*H*-indole-2-carboxaldehyde (1k): Prepared according to the general procedure A from **S1a (**1.000 g, 6.89 mmol) and **S2c** (2.100 g, 8.27 mmol). The mixture was purified by flash column chromatography (90:10 hexane:EtOAc) to give **1j** as a dark yellow oil in 91% yield (1.43 g, 6.290 mmol) as a 6:1 mixture of **1j** and its isomer. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.4 Hz, 3H), 1.89 – 1.96 (m, 2H), 2.44 – 2.49 (m, 2H), 4.56 (t, *J* = 7.2 Hz, 2H), 5.39 - 5.42 (m, 2H), 7.15 – 7.18 (m, 1H), 7.11 (s, 1H), 7.30 - 7.32 (m, 2H), 7.63 (ddd, *J* = 8.2, 1.0, 1.0 Hz, 1H), 9.78 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 13.6, 25.6, 33.8, 44.7, 111.0, 117.9, 120.9, 123.5, 124.9, 126.5, 126.8, 135.0, 135.4, 140.4, 182.5. **HRMS** (ESI) Calcd $C_{15}H_{18}NO^+$ ($[M+H]^+$): 228.1383, Found: 228.1386.

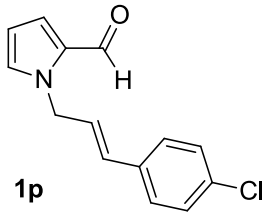


1-(3-Methylbut-3-en-1-yl)-1*H*-pyrrole-2-carboxaldehyde (1l): Prepared according to the general procedure A from **S1h** (1.000 g, 10.52 mmol) and 17% solution of **S2b** (11.06 g, 12.62 mmol) in THF. The mixture was purified by flash column chromatography (90:10 hexane:EtOAc) to give **1l** as a dark yellow oil in 43% yield (0.733 g, 4.49 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.71 (s, 3H), 2.41 (t, *J* = 7.4 Hz, 2H), 4.38 (t, *J* = 7.4 Hz, 2H), 4.61 (m, 1H), 4.73 (m, 1H), 6.16 (dd, *J* = 4.0, 2.6 Hz, 1H), 6.87 – 6.89 (m, 2H), 9.50 (d, *J* = 1.0 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 22.5, 39.6, 47.9, 109.6, 112.7, 125.0, 131.3, 131.5, 142.1, 179.3. **HRMS** (ESI) Calcd $C_{10}H_{14}NO^+$ ($[M+H]^+$): 164.1070, Found: 164.1074.



(*E*)-1-(3-(4-Methoxyphenyl)allyl)-1*H*-pyrrole-2-carboxaldehyde (1o): Prepared according to the general procedure B from **S1h** (0.156 g, 1.65 mmol) and **S2d** (0.451 g, 1.98 mmol). The mixture was purified by flash column chromatography (90:10 hexane:EtOAc gradient) to give the **1o** as a white solid

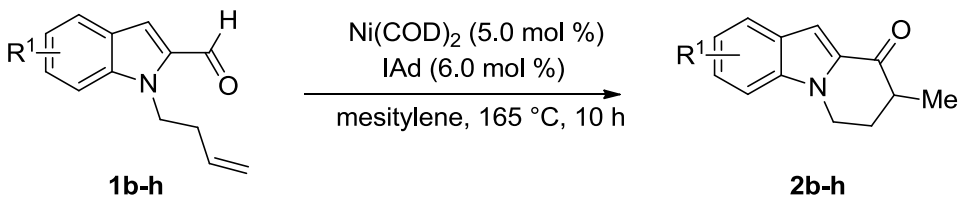
in 39% yield (0.155 g, 0.643 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.80 (s, 3H), 5.10 (dd, *J* = 6.4, 1.0 Hz, 2H), 6.19 (ddd, *J* = 15.8, 6.4, 6.4 Hz, 1H), 6.26 (dd, *J* = 4.0, 2.6 Hz, 1H), 6.43 (d, *J* = 15.8 Hz, 1H), 6.83 (d, *J* = 8.8 Hz, 2H), 6.96 (dd, *J* = 4.0, 1.7 Hz, 1H), 7.03 (m, 1H), 7.28 (d, *J* = 8.8 Hz, 2H), 9.57 (s, 1H). **^{13}C NMR** (101 MHz $CDCl_3$) δ 51.0, 55.6, 110.3, 114.3, 123.1, 125.1, 128.1, 129.3, 131.2, 131.7, 132.8, 158.8, 179.8. **HRMS** (ESI): Calcd. for $C_{15}H_{16}NO_2^+$ ($[M+H]^+$): 242.1176, found 242.1179.



1p

(*E*)-1-(3-(4-Chlorophenyl)allyl)-1*H*-pyrrole-2-carboxaldehyde (1p): Prepared according to the general procedure B from **S1h** (0.200 g, 2.10 mmol) and **S2e** (0.584 g, 2.52 mmol). The mixture was purified by flash column chromatography (90:10 hexane:EtOAc) to give the **1p** as a white solid in 74% yield (0.382 g, 1.55 mmol). **^{1}H NMR** (400 MHz, DMSO-d_6) δ 5.09 (d, *J* = 5.6 Hz, 2H), 6.29 (dd, *J* = 3.8, 2.6 Hz, 1H), 6.34 (d, *J* = 16.0 Hz, 1H), 6.47 (ddd, *J* = 16.0, 5.6, 5.6 Hz, 1H), 7.07 (dd, *J* = 3.8, 1.6 Hz, 1H), 7.34 - 7.37 (m, 3H), 7.41 (d, *J* = 8.8 Hz, 1H), 9.54 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 50.8, 110.3, 110.4, 125.2, 126.2, 128.1, 129.05, 131.3, 131.7, 133.9, 135.05, 179.8. **HRMS** (ESI): Calcd. For $C_{14}H_{13}ClNO^+$ ($[M+H]^+$): 246.0681, found 246.0683.

4.5.5 General Procedure C: Synthesis of 8-Methyl-7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-ones (2b-h)



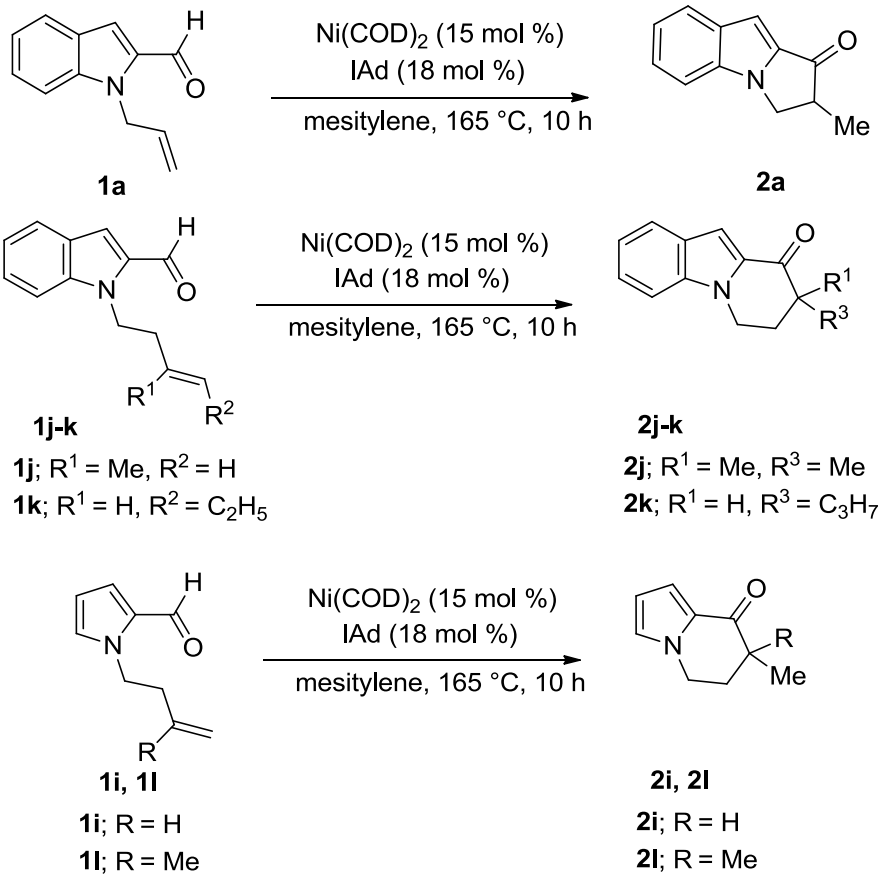
1b-h **2b-h**

1b; R^1 = H
1c; R^1 = 4-MeO-C_6H_4
1d; R^1 = 5-Me-C_6H_4
1e; R^1 = 5-MeO-C_6H_4
1f; R^1 = 5-F-C_6H_4
1g; R^1 = 6-MeO-C_6H_4
1h; R^1 = 6-CF_3-C_6H_4

2b; R^1 = H
2c; R^1 = 4-MeO-C_6H_4
2d; R^1 = 5-Me-C_6H_4
2e; R^1 = 5-MeO-C_6H_4
2f; R^1 = 5-F-C_6H_4
2g; R^1 = 6-MeO-C_6H_4
2h; R^1 = 6-CF_3-C_6H_4

In a nitrogen-filled glovebox, the appropriate *N*-homoallylindole-2-carboxaldehyde (**1b-h**) (0.100 mmol, 1.0 equiv) was added to a 1-dram vial containing $Ni(COD)_2$ (1.4 mg, 0.00500 mmol, 0.050 equiv) and IAd (2.0 mg, 0.00600 mmol, 0.060 equiv) in mesitylene (0.5 mL). The vial was sealed with a PTFE/silicone-lined septum cap and removed from the glovebox. The reaction mixture was stirred at 165 °C in an oil bath for 10 h. The vial was removed from the oil bath and allowed to cool to room temperature. The reaction mixture was filtered through a short plug of silica gel (eluting with 20 ml of 3:2 hexanes:EtOAc). The crude reaction mixture was concentrated under reduced pressure. The crude reaction mixture was purified by flash column silica gel chromatography (hexanes:EtOAc) to give the appropriate 8-methyl-7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-ones (**2b-h**).

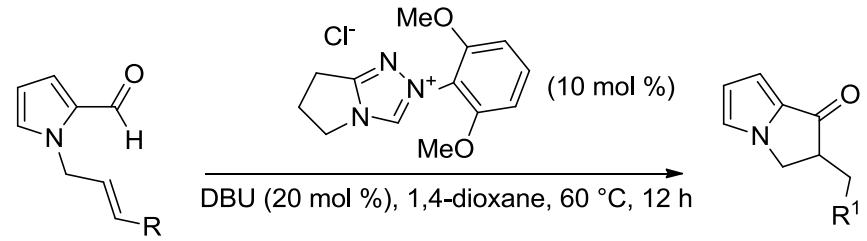
4.5.6 General Procedure D: Synthesis of 2-Methyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-one (2a), 7,8-Dihydropyrido[1,2-*a*]indol-9(6*H*)-ones (2j-k) and 7-Methyl-6,7-dihydroindolizin-8(5*H*)-ones (2i, 2l)



In a nitrogen-filled glovebox, the appropriate *N*-allylindole-2-carboxaldehyde (**1a**) or *N*-homoallylindole-2-carboxaldehyde (**1j-k**) or *N*-homoallylpyrrole-2-carboxaldehyde (**1i, 1l**) (0.100 mmol, 1.0 equiv) was added to a 1-dram vial containing $Ni(COD)_2$ (4.1 mg, 0.0151 mmol, 0.150 equiv) and IAd (6.1 mg, 0.0181 mmol, 0.180 equiv) in mesitylene (0.5 mL). The vial was sealed with a PTFE/silicone-lined septum cap and removed from the glovebox. The reaction mixture was stirred at 165 °C in an oil bath for 10 h. The vial was removed from the oil bath and allowed to cool to room temperature. The reaction mixture was filtered through a short plug of silica gel (eluting with 20 mL of 3:2 hexanes:EtOAc). The crude reaction mixture was

concentrated under reduced pressure. The crude reaction mixture was purified by flash column silica gel chromatography (hexanes:EtOAc) to give the appropriate 2-methyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-one (**2a**), 7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-ones (**2j-k**) or 7-methyl-6,7-dihydroindolizin-8(5*H*)-ones (**2i, 2l**).

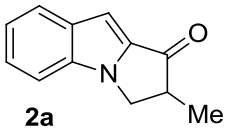
4.5.7 General Procedure E: Synthesis of 2-Methyl-2,3,-dihydro-1*H*-pyrrolizin-1-one (2m) and 2-Benzyl-2,3-dihydro-1*H*-pyrrolizin-1-ones (2n-p)



1m; R = H
1n; R = C_6H_5
1o; R = 4-OMe-C_6H_4
1p; R= 4-Cl-C_6H_4

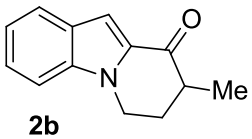
2m; R^1 = H
2n; R^1 = C_6H_5
2o; R^1 = 4-OMe-C_6H_4
2p; R^1 = 4-Cl-C_6H_4

2-methyl-2,3-dihydro-1*H*-pyrrolizin-1-one (**2m**) and 2-benzyl-2,3-dihydro-1*H*-pyrrolizin-1-one (**2n-p**) were prepared according to a modified literature procedure from the appropriate 1-allyl-1*H*-pyrrole-2-carboxaldehyde (**1m-p**).[30] In a nitrogen-filled glovebox, to a 1-dram vial was added NHC **3** (5.7 mg, 0.0200 mmol, 0.1 equiv), the appropriate 1-allyl-1*H*-pyrrole-2-carboxaldehyde **1m-p** (0.200 mmol, 1.0 equiv), DBU (6.1 mg, 0.0400 mmol, 0.2 equiv), and 1,4-dioxane (1.0 mL, 0.2 M **1**). The vial was sealed with a Teflon-lined septum cap. The reaction vessel was removed from the glovebox, and the reaction mixture was stirred at 60 °C for 12 h. The reaction was cooled to room temperature, and filtered through a plug of silica gel with EtOAc as eluent. The filtrate was concentrated under reduced pressure. The crude product was purified by flash column silica gel chromatography (hexane:EtOAc) to give the appropriate 2-methyl-2,3-dihydro-1*H*-pyrrolizin-1-one (**2m**) and 2-benzyl-2,3-dihydro-1*H*-pyrrolizin-1-ones (**2n-p**).



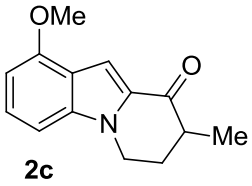
2a

2-Methyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-one (2a): Prepared according to the general procedure D from **1a** (19.0 mg, 0.103 mmol). The crude product was purified by silica gel chromatography with a CombiFlash system (4 g column, 100:0→95:5 hexanes/EtOAc) to give **2a** as a white solid in 70% yield (13.3 mg, 0.0718 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.44 (d, *J* = 7.4 Hz, 3H), 3.21 – 3.30 (m, 1H), 3.93 (dd, *J* = 10.8, 4.8 Hz, 1H), 4.62 (dd, *J* = 10.8, 8.0 Hz, 1H), 7.00 (s, 1H), 7.18 (ddd, *J* = 8.2, 6.6, 1.2 Hz, 1H), 7.32 – 7.40 (m, 2H), 7.75 (d, *J* = 8.2 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 15.8, 45.7, 48.1, 99.4, 110.8, 121.7, 124.4, 125.3, 132.3, 135.27, 135.35, 196.3. **HRMS** (ESI): Calcd. for $C_{12}H_{12}NO$ ($[M+H]^+$): 186.0919, Found: 186.0918.



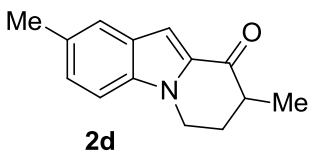
2b

8-Methyl-7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-one (2b): Prepared according to the general procedure C from **1b** (20.0 mg, 0.100 mmol). The mixture was purified by flash column chromatography (95:5 hexane:EtOAc) to give **2b** as a yellowish white solid in 95% yield (19.0 mg, 0.095 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.34 (d, *J* = 6.8 Hz, 3H), 2.15 (app qd, *J* = 11.2, 4.6 Hz, 1H), 2.41 (app dq, *J* = 13.6, 4.6 Hz, 1H), 2.67 – 2.76 (m, 1H), 4.11 (ddd, *J* = 11.2, 11.2, 3.8 Hz, 1H), 4.38 (ddd, *J* = 12.2, 3.8, 3.8 Hz, 1H), 7.16 (t, *J* = 7.2 Hz, 1H), 7.29 – 7.38 (m, 3H), 7.72 (d, *J* = 8.0 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 15.1, 31.2, 41.1, 41.3, 105.8, 110.5, 121.3, 123.6, 125.7, 127.2, 133.7, 137.4, 193.1. **HRMS** (ESI): Calcd. for $C_{13}H_{14}NO^+$ ($[M+H]^+$): 200.1070, Found: 200.1068.



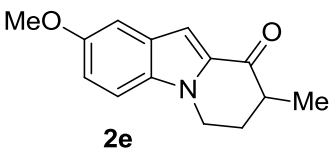
2c

1-Methoxy-8-methyl-7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-one (2c): Prepared according to the general procedure C from **1c** (23.0 mg, 0.100 mmol). The mixture was purified by flash column chromatography (95:5 hexane:EtOAc) to give **2c** as a yellow solid in 92% yield (21.2 mg, 0.092 mmol). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.34 (d, *J* = 6.8 Hz, 3H), 2.14 – 2.22 (m, 1H), 2.42 (app dq, *J* = 13.6, 4.2 Hz, 1H), 2.70 – 2.76 (m, 1H), 3.96 (s, 3H), 4.13 (ddd, *J* = 13.6, 11.0, 4.2 Hz, 1H), 4.37 (ddd, *J* = 12.0, 4.2, 4.2 Hz, 1H), 6.50 (d, *J* = 8.0 Hz, 1H), 6.94 (d, *J* = 8.0 Hz, 1H), 7.29 (t, *J* = 8.0 Hz, 1H), 7.42 (s, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 15.1, 31.4, 41.3, 41.4, 55.8, 100.2, 103.4, 103.9, 119.0, 127.0, 132.8, 139.0 155.6, 192.8. **HRMS** (ESI) Calcd. for $C_{14}H_{16}NO_2^+$ ($[M+H]^+$): 230.1176, Found: 230.1177.



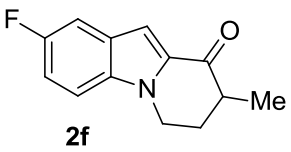
2d

2,8-Dimethyl-7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-one (2d): Prepared according to the general procedure C from **1d** (22.0 mg, 0.103 mmol). The mixture was purified by flash column chromatography (95:5 hexane:EtOAc) to give **2d** as a dark yellow solid in 88% yield (19.4 mg, 0.0910 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.34 (d, *J* = 6.9 Hz, 3H), 2.16 (app dtd, *J* = 13.6, 11.0, 4.8 Hz, 1H), 2.38 – 2.44 (m, 4H), 2.72 (app tt, *J* = 11.0, 6.8 Hz, 1H), 4.12 (ddd, *J* = 14.0, 11.0, 4.0 Hz, 1H), 4.37 (ddd, *J* = 12.2, 4.0, 4.0 Hz, 1H), 7.18 – 7.20 (m, 2H), 7.24 (d, *J* = 8.4 Hz, 1H), 7.48 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 15.2, 21.8, 31.4, 41.1, 41.3, 105.3, 110.2, 122.8, 127.5, 127.9, 130.7, 133.8, 136.1, 193.2. **HRMS** (ESI): Calcd. for $C_{14}H_{16}NO^+$ ($[M+H]^+$): 214.1226, Found: 214.1229.



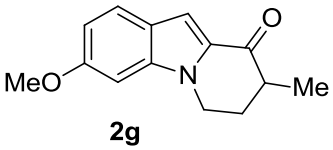
2e

2-Methoxy-8-methyl-7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-one (2e): Prepared according to the general procedure C from **1e** (23.0 mg, 0.100 mmol). The mixture was purified by flash column chromatography (95:5 hexane:EtOAc) to give **2e** as a light yellow solid in 90% yield (20.8 mg, 0.0907 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.34 (d, *J* = 6.9 Hz, 3H), 2.17 (app dtd, *J* = 13.8, 10.8, 4.8 Hz, 1H), 2.43 (app dq, *J* = 13.8, 4.4 Hz, 1H), 2.68 – 2.78 (m, 1H), 3.85 (s, 3H), 4.13 (ddd, *J* = 13.8, 10.8, 4.4 Hz, 1H), 4.37 (ddd, *J* = 12.2, 4.4, 4.4 Hz, 1H), 7.05 (dd, *J* = 9.0, 2.4 Hz, 1H), 7.08 (d, *J* = 2.4 Hz, 1H), 7.21 (s, 1H), 7.23 – 7.26 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 15.2, 31.4, 41.2, 41.2, 56.0, 102.9, 105.2, 111.5, 118.0, 127.5, 133.2, 134.1, 155.3, 192.9. **HRMS** (ESI) Calcd. for $C_{14}H_{16}NO_2^+$ ($[M+H]^+$): 230.1176, Found: 230.1179.



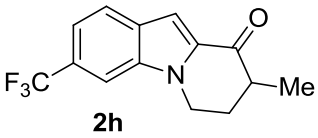
2f

2-Fluoro-8-methyl-7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-one (2f): Prepared according to the general procedure C from **1f** (22.0 mg, 0.101 mmol). The mixture was purified by flash column chromatography (95:5 hexane:EtOAc) to give **2g** as a yellowish white solid in 96% yield (21.2 mg, 0.097 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.35 (d, *J* = 6.9 Hz, 3H), 2.19 (app dtd, *J* = 13.8, 11.0, 4.8 Hz, 1H), 2.45 (app dq, *J* = 13.8, 4.0 Hz, 1H), 2.70 – 2.79 (m, 1H), 4.16 (ddd, *J* = 12.2, 11.0, 4.0 Hz, 1H), 4.40 (ddd, *J* = 12.2, 4.4, 4.4 Hz, 1H), 7.15 (app td, *J* = 9.0, 2.4 Hz, 1H), 7.24 (s, 1H), 7.295 (dd, *J* = 9.0, 4.4 Hz, 1H), 7.35 (dd, *J* = 9.0, 2.4 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 15.1, 31.3, 41.2, 41.4, 106.55 (d, *J* = 5.0 Hz, 1C), 107.6 (d, *J* = 23.2 Hz, 1C), 111.5 (d, *J* = 10.1 Hz, 1C), 115.1 (d, *J* = 27.3 Hz, 1C), 127.25 (d, *J* = 10.1 Hz, 1C), 134.2, 135.0, 158.6 (d, *J* = 238.4 Hz, 1C), 193.0. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -122.5 (m, 1F). **HRMS** (ESI) Calcd. for $C_{13}H_{13}FNO^+$ ($[M+H]^+$): 218.0976, Found: 218.0979.



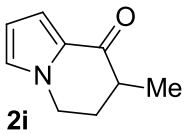
2g

3-Methoxy-8-methyl-7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-one (2g): Prepared according to the general procedure C from **1g** (23.0 mg, 0.100 mmol). The mixture was purified by flash column chromatography (95:5 hexane:EtOAc) to give **2f** as a light yellow solid in 91% yield (21.0 mg, 0.0916 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.34 (d, *J* = 6.8 Hz, 3H), 2.16 (app dtd, *J* = 13.8, 10.9, 4.4 Hz, 1H), 2.42 (app dq, *J* = 13.8, 4.0 Hz, 1H), 2.67 - 2.76 (m, 1H), 3.89 (s, 3H), 4.09 (ddd, *J* = 12.1, 10.9, 4.0 Hz, 1H), 4.33 (ddd, *J* = 12.1, 4.4, 4.4 Hz, 1H), 6.70 (d, *J* = 2.2 Hz, 1H), 6.83 (dd, *J* = 8.8, 2.2 Hz, 1H), 7.25 (s, 1H), 7.58 (d, *J* = 8.8 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 15.2, 31.3, 41.11, 41.13, 55.9, 92.1, 106.5, 113.2, 121.7, 124.5, 133.3, 138.6, 159.4, 192.5. **HRMS** (ESI) Calcd. for $C_{14}H_{16}NO_2^+$ ($[M+H]^+$): 230.1176, Found: 230.1178.



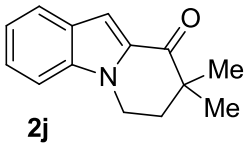
2h

8-Methyl-3-(trifluoromethyl)-7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-one (2h): Prepared according to the general procedure C from **1h** (27.0 mg, 0.101 mmol). The mixture was purified by flash column chromatography (92:8 hexane:EtOAc) to give **2h** as a white solid in 75% yield (20.3 mg, 0.0760 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.37 (d, *J* = 6.8 Hz, 3H), 2.22 (app dtd, *J* = 13.8, 11.2, 4.8 Hz, 1H), 2.49 (app dq, *J* = 13.8, 4.0 Hz, 1H), 2.74 – 2.83 (m, 1H), 4.22 (ddd, *J* = 13.8, 11.2, 4.0 Hz, 1H), 4.485 (ddd, *J* = 12.2, 4.0, 4.0 Hz, 1H), 7.31 (s, 1H), 7.38 (dd, *J* = 8.5, 1.0 Hz, 1H), 7.67 (s, 1H), 7.81 (d, *J* = 8.5 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 15.0, 31.2, 41.49, 41.54, 106.6, 108.4 (q, *J* = 5.05 Hz, 1C), 117.7 (q, *J* = 4.0 Hz, 1C), 124.3, 125.1 (q, *J* = 273.7 Hz, 1C), 127.4 (q, *J* = 32.3 Hz, 1C), 129.2, 135.8, 136.2, 193.0. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -61.5 (s, 3F). **HRMS** (ESI) Calcd $C_{14}H_{13}F_3NO^+$ ($[M+H]^+$): 268.0944, Found: 268.0940.



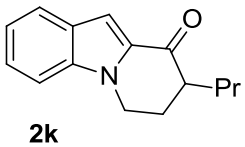
2i

7-Methyl-6,7-dihydroindolizin-8(5*H*)-one (2i): Prepared according to the general procedure D from **1k** (15.0 mg, 0.100 mmol). The mixture was purified by flash column chromatography (92:8 hexane:EtOAc) to give **2k** as a white solid in 80% yield (12.0 mg, 0.0800 mmol). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.29 (d, *J* = 6.8 Hz, 3H), 2.07 (qd, *J* = 10.8, 4.4 Hz, 1H), 2.28 – 2.31 (m, 1H), 2.57 – 2.60 (m, 1H), 4.10 (ddd, *J* = 12.4, 12.4, 3.4 Hz, 1H), 4.20 (ddd, *J* = 12.4, 4.4, 4.4 Hz, 1H), 6.25 (d, *J* = 1.2 Hz, 1H), 6.82 (m, 1H), 7.00 (d, *J* = 2.4 Hz, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 15.4, 31.8, 40.3, 44.6, 110.8, 114.3, 125.7, 130.7, 190.2. **HRMS** (ESI) Calcd $C_9H_{12}NO^+$ ($[M+H]^+$): 150.0913, Found: 150.0917.



2j

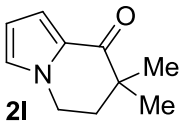
8,8-Dimethyl-7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-one (2j): Prepared according to the general procedure D from **1i** (22.0 mg, 0.103 mmol). The mixture was purified by flash column chromatography (90:10 hexane:EtOAc) to give **2i** as a yellow solid in 75% yield (16.5 mg, 0.077 mmol). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.32 (s, 6H), 2.25 (t, *J* = 6.0 Hz, 2H), 4.28 (t, *J* = 6.0 Hz, 2H), 7.17 (ddd, *J* = 8.0, 5.4, 2.4 Hz, 1H), 7.30 (s, 1H), 7.35 – 7.39 (m, 2H), 7.73 (d, *J* = 8.0 Hz, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 24.3, 36.9, 38.8, 41.6, 106.6, 110.6, 121.4, 123.6, 125.8, 127.5, 132.9, 137.5, 195.6. **HRMS** (ESI): Calcd. for $C_{14}H_{16}NO^+$ ($[M+H]^+$): 214.1226, Found: 214.1225.



2k

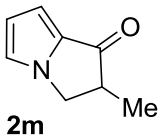
8-Propyl-7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-one (2k): Prepared according to a modified version of general procedure D from **1j** (68.0 mg, 0.299 mmol). The mixture was purified by flash column chromatography (80:20 hexane:EtOAc) to give **2j** as a yellow solid in 15% yield (10.5 mg, 0.0460 mmol). **^{1}H**

NMR (600 MHz, $CDCl_3$) δ 0.98 (t, *J* = 7.2 Hz, 3H), 1.41 – 1.58 (m, 3H), 1.98 – 2.04 (m, 1H), 2.19 (app dtd, *J* = 13.8, 9.4, 4.6 Hz, 1H), 2.48 (app dq, *J* = 13.8, 5.4 Hz, 1H), 2.62 – 2.66 (m, 1H), 4.16 (ddd, *J* = 12.4, 9.4, 4.2 Hz, 1H), 4.39 (ddd, *J* = 12.4, 5.4, 5.4 Hz, 1H), 7.16 (ddd, *J* = 8.0, 5.8, 2.0 Hz, 1H), 7.30 (s, 1H), 7.35 – 7.39 (m, 2H), 7.72 (d, *J* = 8.0 Hz, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 14.4, 20.5, 28.3, 31.3, 40.7, 46.1, 106.0, 110.6, 121.4, 123.7, 125.8, 127.3, 133.9, 137.5, 193.0. **HRMS** (ESI) Calcd $C_{15}H_{18}NO^+$ ($[M+H]^+$): 228.1383, Found: 228.1385.



2l

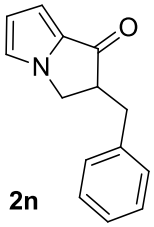
7,7-Dimethyl-6,7-dihydroindolizin-8(5*H*)-one (2l): Prepared according to a modified version of general procedure D from **1l** (49.0 mg, 0.300 mmol). The mixture was purified by flash column chromatography (90:10 hexane:EtOAc) to give **2l** as a white solid in 20% yield (10.0 mg, 0.0610 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.25 (s, 6H), 2.11 (t, *J* = 9.0 Hz, 2H), 4.14 (t, *J* = 9.0 Hz, 2H), 6.25 (dd, *J* = 6.0, 3.6 Hz, 1H), 6.80 – 6.81 (m, 1H), 7.00 (dd, *J* = 3.6, 1.6 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 24.6, 37.4, 40.6, 42.2, 111.0, 114.9, 125.5, 129.6, 192.6. **HRMS** (ESI) Calcd $C_{10}H_{14}NO^+$ ($[M+H]^+$): 164.1070, Found: 164.1068.



2m

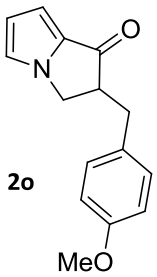
2-Methyl-2,3-dihydro-1*H*-pyrrolizin-1-one (2m): Prepared according to general procedure E from **1m** (27.0 mg, 0.200 mmol). The reaction mixture was stirred at 60 °C for 24 h. The mixture was purified by flash column chromatography (90:10 hexane:EtOAc) to give **2m** as a white solid in 80% yield (21.6 mg, 0.160 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.36 (d, *J* = 7.4 Hz, 3H), 3.10 - 3.18 (m, 1H), 3.85 (dd, *J* = 11.6, 4.6 Hz, 1H), 4.50 (dd, *J* = 11.6, 8.0 Hz, 1H), 6.50 (dd, *J* = 4.0, 2.4 Hz, 1H), 6.71 (dd, *J* = 4.0, 0.8 Hz, 1H),

7.00 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 15.9, 45.6, 50.3, 108.1, 117.1, 122.9, 132.2, 192.7. **HRMS** (ESI) Calcd $C_8H_{10}NO^+$ ($[M+H]^+$): 136.0757, found 136.0761.



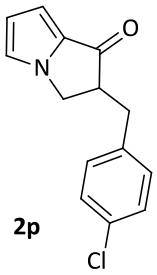
2n

2-Benzyl-2,3-dihydro-1*H*-pyrrolizin-1-one (2n): Prepared according to a general modified version of general procedure E from **1n** (42.0 mg, 0.199 mmol). The mixture was purified by flash column chromatography (90:10 hexane:EtOAc) to give **2n** as a yellow oil in 96% yield (40.3 mg, 0.191 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.79 (dd, *J* = 15.0, 12.0 Hz, 1H), 3.40 - 3.47 (m, 2H), 3.98 (dd, *J* = 12.0, 4.4 Hz, 1H), 4.26 (dd, *J* = 12.0, 7.6 Hz, 1H), 6.51 (dd, *J* = 4.0, 2.2 Hz, 1H), 6.75 (dd, *J* = 4.0, 0.6 Hz, 1H), 6.96 (m, 1H), 7.21 - 7.26 (m, 3H), 7.29 - 7.32 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 36.8, 47.9, 52.5, 108.4, 117.3, 123.2, 127.0, 129.08, 129.10, 132.5, 139.1, 191.0. **HRMS** (ESI): Calcd. for $C_{14}H_{14}NO^+$ ($[M+H]^+$): 212.1070, found 212.1072.



2o

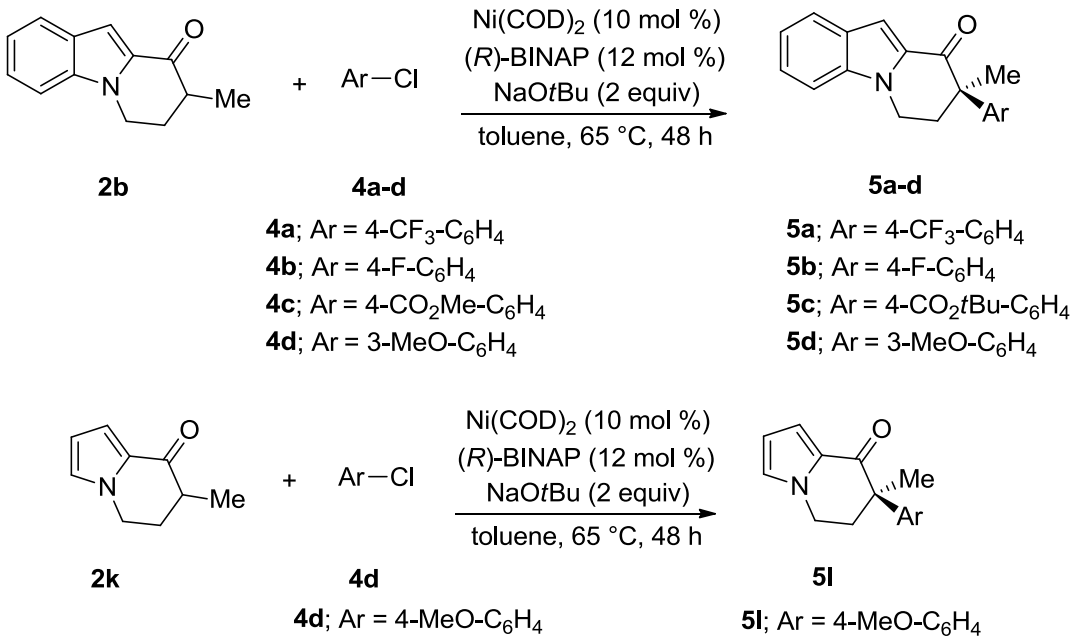
2-(4-Methoxybenzyl)-2,3-dihydro-1*H*-pyrrolizin-1-one (2o): Prepared according to a modified version of general procedure E from **1o** (48.0 mg, 0.199 mmol). The mixture was purified by flash column chromatography (90:10 hexane:EtOAc) to give **2o** as a white solid in 99% yield (47.6 mg, 0.197 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.77 (dd, *J* = 14.0, 10.2 Hz, 1H), 3.32 (dd, *J* = 14.0, 4.4 Hz, 1H), 3.37 - 3.43 (m, 1H), 3.78 (s, 3H), 3.97 (dd, *J* = 11.8, 4.4 Hz, 1H), 4.26 (dd, *J* = 11.8, 7.8 Hz, 1H), 6.50 (dd, *J* = 4.0, 2.2 Hz, 1H), 6.75 (dd, *J* = 4.0, 0.8 Hz, 1H), 6.83 (d, *J* = 8.6 Hz, 2H), 6.96 (m, 1H), 7.13 (d, *J* = 8.6 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 35.9, 47.8, 52.7, 55.6, 108.4, 114.4, 117.3, 123.2, 130.1, 130.9, 132.6, 158.7, 191.2. **HRMS** (ESI): Calcd. for $C_{15}H_{16}NO_2^+$ ($[M+H]^+$): 242.1176, found 242.1178.



2p

2-(4-Chlorobenzyl)-2,3-dihydro-1*H*-pyrrolizin-1-one (2p): Prepared according to a modified version of general procedure E from **1p** (49.0 mg, 0.199 mmol). The mixture was purified by flash column chromatography (90:10 hexane:EtOAc) to give **2p** as a white solid in 99% yield (48.5 mg, 0.197 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.75 (dd, *J* = 14.0, 9.8 Hz, 1H), 3.27 (dd, *J* = 14.0, 4.4 Hz, 1H), 3.31 - 3.37 (m, 1H), 3.87 (dd, *J* = 11.8, 4.4 Hz, 1H), 4.21 (dd, *J* = 11.8, 7.8 Hz, 1H), 6.44 (dd, *J* = 4.0, 2.2 Hz, 1H), 6.68 (dd, *J* = 4.0, 0.6 Hz, 1H), 6.89 (m, 1H), 7.08 (d, *J* = 8.4 Hz, 2H), 7.19 (d, *J* = 8.4 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 36.0, 47.7, 52.2, 108.6, 117.4, 123.4, 129.2, 130.5, 132.4, 132.9, 137.4, 190.6. **HRMS** (ESI): Calcd. for $C_{14}H_{13}ClNO^+$ ($[M+H]^+$): 246.0680, found 246.0791.

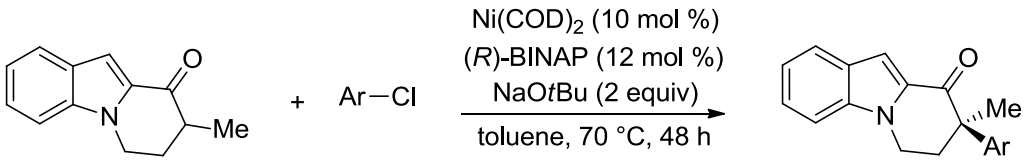
4.5.8 General Procedure F: Synthesis of (*R*)-8-Aryl-8-methyl-7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-ones (5a-d) and (*R*)-7-Aryl-7-methyl-6,7-dihydroindolizin-8(5*H*)-one (5l)



In a nitrogen-filled glovebox, 8-methyl-7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-one (**2b**) (0.100 mmol, 1.0 equiv) or 7-methyl-6,7-dihydroindolizin-8(5*H*)-one (**2k**) (0.100 mmol, 1.0 equiv), $Ni(COD)_2$ (2.8 mg, 0.0100 mmol, 0.10 equiv), (*R*)-BINAP (7.5 mg, 0.0120 mmol, 0.12 equiv), NaO*t*Bu (19.3 mg, 0.200 mmol, 2.0 equiv), the appropriate aryl chloride (0.200 mmol, 2.0 equiv), a magnetic stirring bar, and toluene (0.5 mL) were added to a 1-dram vial. The vial was sealed with a cap containing a PTFE septum and removed from the glovebox. The reaction mixture was stirred at 65 °C in an oil bath for 48 h. The vial was removed from the oil bath and allowed to cool to room temperature. The reaction mixture was filtered through short plug of silica gel (eluting with 20 mL of 3:2 hexanes:EtOAc). The crude reaction mixture was concentrated under reduced pressure. The crude product was purified with a CombiFlash system with 5-20% ethyl acetate in hexanes as eluent to give the appropriate (*R*)-8-aryl-8-methyl-7,8-

dihydropyrido[1,2-*a*]indol-9(6*H*)-ones (**5a-d**) and (*R*)-7-aryl-7-methyl-6,7-dihydroindolizin-8(5*H*)-one (**5l**).

4.5.9 General Procedure G: Synthesis of (*R*)-8-Aryl-8-methyl-7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-ones (5e-k)



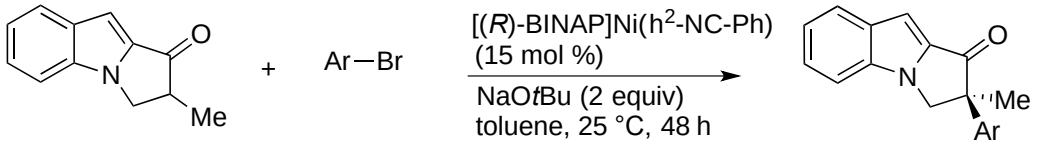
2b + **4e-k** → **5e-k**

4e; Ar = 4-Me-C_6H_4
4f; Ar = 4-MeO-C_6H_4
4g; Ar = 3-CF_3-C_6H_4
4h; Ar = 3-F-C_6H_4
4i; Ar = 3,4-(OCH_2O)-C_6H_3
4j; Ar = 2-napthyl
4k; Ar = C_6H_5

5e; Ar = 4-Me-C_6H_4
5f; Ar = 4-MeO-C_6H_4
5g; Ar = 3-CF_3-C_6H_4
5h; Ar = 3-F-C_6H_4
5i; Ar = 3,4-(OCH_2O)-C_6H_3
5j; Ar = 2-napthyl
5k; Ar = C_6H_5

In a nitrogen-filled glovebox, 8-methyl-7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-one (**2b**) (0.100 mmol, 1.0 equiv), $Ni(COD)_2$ (2.80 mg, 0.0100 mmol, 0.10 equiv), (*R*)-BINAP (7.5 mg, 0.0120 mmol, 0.12 equiv), NaO*t*Bu (19.3 mg, 0.200 mmol, 2.0 equiv), the appropriate aryl chloride **4e-k** (0.200 mmol, 2.0 equiv), a magnetic stirring bar, and toluene (0.5 mL) were added to a 1-dram vial. The vial was sealed with a cap containing a PTFE septum and removed from the glovebox. The reaction mixture was stirred at 70 °C in an oil bath for 48 h. The vial was removed from the oil bath and allowed to cool to room temperature. The reaction mixture was filtered through short plug of silica gel (eluting with 20 mL of 3:2 hexanes:EtOAc). The crude reaction mixture was concentrated under reduced pressure. The crude product was purified with a CombiFlash system with 5-20% ethyl acetate in hexanes as eluent to give the appropriate (*R*)-8-aryl-8-methyl-7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-ones (**5e-k**).

4.5.10 General Procedure H: Synthesis of (*S*)-2-Aryl-2-methyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-one (9a-c)



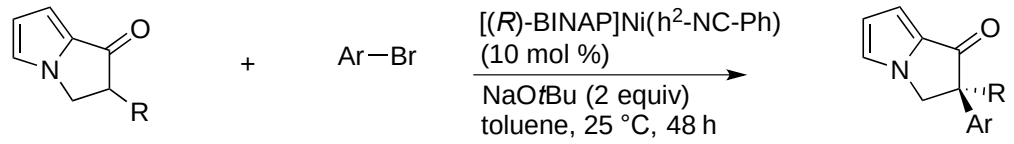
2a **8a-c** **9a-c**

8a; Ar = C_6H_5
8b; Ar = 3-MeO-C_6H_4
8c; Ar = 4-CF_3-C_6H_4

9a; Ar = C_6H_5
9b; Ar = 3-MeO-C_6H_4
9c; Ar = 4-CF_3-C_6H_4

In a nitrogen-filled glovebox, 2-methyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-one (**2a**) (0.200 mmol, 1.0 equiv), [(*R*)-BINAP]Ni(η^2-NC-Ph) (26.3 mg, 0.0300 mmol, 0.15 equiv), NaO*t*Bu (38.4 mg, 0.400 mmol, 2.0 equiv), the appropriate aryl bromide **8a-c** (0.400 mmol, 2.0 equiv), a magnetic stirring bar, and toluene (1.0 mL) were added to a 1-dram vial. The vial was sealed with a cap containing a PTFE septum and removed from the glovebox. The reaction mixture was stirred at 25 °C in for 48 h. The vial was removed from the oil bath and allowed to cool to room temperature. The reaction mixture was filtered through short plug of silica gel (eluting with 20 ml of 3:2 hexanes:EtOAc). The crude reaction mixture was concentrated under reduced pressure. The crude product was purified with a CombiFlash system with 5-20% ethyl acetate in hexanes as eluent to give the appropriate (*S*)-2-aryl-2-methyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-one (**9a-c**).

4.5.11 General Procedure I: Synthesis of (*S*)-2-Aryl-2-methyl-2,3-dihydro-1*H*-pyrrolizin-1-ones (9d-j) and (*S*)-2-Phenyl-2-benzyl-2,3-dihydro-1*H*-pyrrolizin-1-ones (9k-m)



2m-p

2m; R = Me
2n; R = CH_2-C_6H_4
2o; R = CH_2-(4-MeO)-C_6H_4
2p; R = CH_2-(4-Cl)-C_6H_4

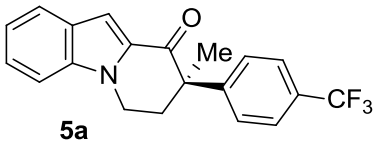
8a-g

8a; Ar = C_6H_5
8b; Ar = 4-CF_3-C_6H_4
8c; Ar = 3-MeO-C_6H_4
8d; Ar = 3-CF_3-C_6H_4
8e; Ar = 3-F-C_6H_4
8f; Ar = 4-MeO-C_6H_4
8g; Ar = napthyl

9d-m

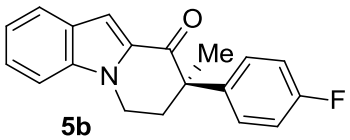
9d; R = Me, Ar = C_6H_5
9e; R = Me, Ar = 4-CF_3-C_6H_4
9f; R = Me, Ar = 3-CF_3-C_6H_4
9g; R = Me, Ar = 3-F-C_6H_4
9h; R = Me, Ar = 3-MeO-C_6H_4
9i; R = Me, Ar = 4-MeO-C_6H_4
9j; R = Me, Ar = napthyl
9k; R = CH_2-C_6H_4, Ar = C_6H_5
9l; R = CH_2-(4-MeO)-C_6H_4, Ar = C_6H_5
9m; R = CH_2-(4-Cl)-C_6H_4, Ar = C_6H_5

In a nitrogen-filled glovebox, 2-methyl-2,3,-dihydro-1*H*-pyrrolizin-1-one (**2m**) (0.200 mmol, 1.0 equiv) or 2-benzyl-2,3-dihydro-1*H*-pyrrolizin-1-ones (**2n-p**) (0.200 mmol, 1.0 equiv), [(*R*)-BINAP]Ni(η^2-NC-Ph) (17.5 mg, 0.0200 mmol, 0.10 equiv), NaO*t*Bu (38.4 mg, 0.400 mmol, 2.0 equiv), the appropriate aryl bromide **8a-g** (0.400 mmol, 2.0 equiv), a magnetic stirring bar, and toluene (1.0 mL) were added to a 1-dram vial. The vial was sealed with a cap containing a PTFE septum and removed from the glovebox. The reaction mixture was stirred at 25 °C for 48 h. The vial was removed from the oil bath and allowed to cool to room temperature. The reaction mixture was filtered through short plug of silica gel (eluting with 20 ml of 3:2 hexanes:EtOAc). The crude reaction mixture was concentrated under reduced pressure. The crude product was purified with a CombiFlash system with 5-20% ethyl acetate in hexanes as eluent to give the appropriate (*S*)-2-aryl-2-methyl-2,3-dihydro-1*H*-pyrrolizin-1-ones (**9d-j**) and (*S*)-2-aryl-2-benzyl-2,3-dihydro-1*H*-pyrrolizin-1-ones (**9k-m**).



5a

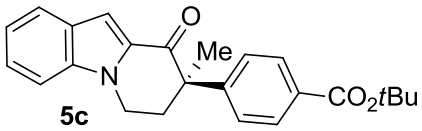
(*R*)-8-Methyl-8-(4-(trifluoromethyl)phenyl)-7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-one (5a): Prepared according to the general procedure F from **2b** (20.0 mg, 0.100 mmol) and 1-chloro-4-(trifluoromethyl)benzene **4a** (36.2 mg, 0.200 mmol). The crude product was purified by silica gel chromatography with a CombiFlash system (4 g column, 100:0→90:10 hexanes/EtOAc) to give **5a** as a light yellow solid in 99% yield (34.3 mg, 0.099 mmol). The enantiomeric excess was determined by HPLC analysis (220 nm, 25 °C) t_R 20.4 min (major); t_R 27.8 min (minor) [Chiracel AS-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 99:1, 1.0 mL/min] to be 99% ee. $[\alpha]_D^{24}$ = +99.2° (c 0.89, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.66 (s, 3H), 2.59 (ddd, *J* = 14.4, 11.2, 4.9 Hz, 1H), 2.83 (ddd, *J* = 14.4, 3.8, 3.8 Hz, 1H), 3.89 (ddd, *J* = 11.2, 11.2, 3.8 Hz, 1H), 4.30 (ddd, *J* = 11.2, 4.9, 3.8 Hz, 1H), 7.17 (ddd, *J* = 7.9, 7.0, 0.8 Hz, 1H), 7.26 – 7.28 (m, 1H), 7.36 (ddd, *J* = 8.2, 7.0, 0.8 Hz, 1H), 7.41 – 7.44 (m, 3H), 7.55 – 7.57 (m, 2H), 7.74 (d, *J* = 8.2 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 26.0, 36.7, 39.1, 50.3, 107.3, 110.6, 121.6, 123.8, 124.3 (q, *J* = 273.7 Hz, 1C), 126.1 (q, *J* = 4.0 Hz, 1C), 126.2, 127.1, 127.4, 129.7 (q, *J* = 33.3 Hz, 1C), 133.6, 137.6, 146.1, 192.8. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -62.9 (s, 3F). **HRMS** (ESI): Calcd. for $C_{20}H_{17}F_3NO^+$ ($[M+H]^+$): 344.1257, Found: 344.1265.



5b

(*R*)-8-(4-Fluorophenyl)-8-methyl-7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-one (5b): Prepared according to the general procedure F from **2b** (20.0 mg, 0.100 mmol) and 1-chloro-4-fluorobenzene **4b** (26.2 mg, 0.200 mmol). The crude product was purified by silica gel chromatography with a CombiFlash system (4 g column, 100:0→94:6 hexanes/EtOAc) to give

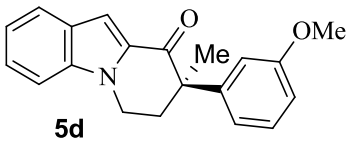
5b as a light yellow solid in 95% yield (28.0 mg, 0.0954 mmol). The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 28.6 min (major); t_R 38.2 min (minor) [Chiracel AS-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 99:1, 1.0 mL/min] to be 99% ee. $[\alpha]_D^{23}$ = +152.1° (c 0.53, $CHCl_3$). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.62 (s, 3H), 2.56 (ddd, *J* = 14.4, 11.4, 4.8 Hz, 1H), 2.76 (ddd, *J* = 14.4, 3.6, 3.6 Hz, 1H), 3.88 (ddd, *J* = 11.4, 11.4, 3.6 Hz, 1H), 4.27 (ddd, *J* = 11.4, 4.8, 3.6 Hz, 1H), 6.97 – 7.00 (m, 2H), 7.16 (ddd, *J* = 7.8, 6.6, 0.5 Hz, 1H), 7.24 – 7.27 (m, 3H), 7.35 (ddd, *J* = 8.1, 7.0, 0.8 Hz, 1H), 7.42 (s, 1H), 7.73 (d, *J* = 8.1 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 26.3, 36.9, 39.1, 49.8, 107.0, 110.6, 116.0 (d, *J* = 21.3 Hz, 1C), 121.5, 123.7, 126.1, 127.4, 128.3 (d, *J* = 7.9 Hz, 1C), 133.7, 137.489 (d, *J* = 3.4 Hz, 1C), 137.492, 162.0 (d, *J* = 247.5 Hz, 1C), 193.4. **^{19}F NMR** ($CDCl_3$, 565 MHz): δ -116.0 (s, 1F). **HRMS** (ESI): Calcd. for $C_{19}H_{17}FNO^+$ ($[M+H]^+$): 294.1289, Found: 294.1293.



5c

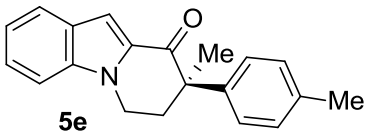
(*R*)-*tert*-Butyl 4-(8-methyl-9-oxo-6,7,8,9-tetrahydropyrido[1,2-*a*]indol-8-yl)benzoate (5c): Prepared according to the general procedure F from **2b** (20.0 mg, 0.100 mmol) and methyl 4-chlorobenzoate **4c** (34.2 mg, 0.200 mmol). The crude product was purified by silica gel chromatography with a CombiFlash system (4 g column, 100:0→85:15 hexanes/dichloromethane) to give **5c** as a light yellow solid in 85% yield (32.1 mg, 0.0855 mmol). The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 15.4 min (major); t_R 25.5 min (minor) [Chiracel OJ-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90:10, 1.0 mL/min] to be 99% ee. $[\alpha]_D^{25}$ = +63.2° (c 0.66, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.54 (s, 9H), 1.64 (s, 3H), 2.58 (ddd, *J* = 14.4, 11.6, 4.8 Hz, 1H), 2.82 (ddd, *J* = 14.4, 3.4, 3.4 Hz, 1H), 3.85 (ddd, *J* = 11.6, 11.6, 3.4 Hz, 1H), 4.27 (ddd, *J* = 11.6,

4.8, 3.4 Hz, 1H), 7.15 (ddd, *J* = 8.0, 6.7, 1.0 Hz, 1H), 7.22 – 7.26 (m, 1H), 7.31 – 7.35 (m, 3H), 7.42 (s, 1H), 7.72 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.94 – 7.87 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 26.0, 28.5, 36.7, 39.2, 50.5, 81.4, 107.1, 110.6, 121.5, 123.7, 126.1, 126.6, 127.4, 130.3, 131.2, 133.7, 137.5, 146.5, 165.6, 193.1. **HRMS** (ESI): Calcd. for $C_{24}H_{26}NO_3^+$ ($[M+H]^+$): 376.1907, Found: 376.1910.



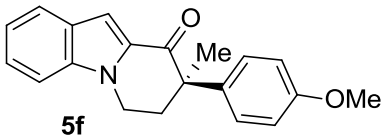
5d

(*R*)-8-(3-Methoxyphenyl)-8-methyl-7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-one (5d): Prepared according to general procedure F from **2b** (20.0 mg, 0.100 mmol) and 1-chloro-3-methoxybenzene **4d** (28.6 mg, 0.200 mmol). The crude product was purified by silica gel chromatography with a CombiFlash system (4 g column, 100:0→92:8 hexanes/EtOAc) to give **5d** as a light yellow solid in 93% yield (28.5 mg, 0.093 mmol). m.p. = 159 - 161 °C. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 30.6 min (major); t_R 41.2 min (minor) [Chiracel AS-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 99:1, 1.0 mL/min] to be 99% ee. $[\alpha]_D^{24}$ = +125.6° (c 0.61, $CHCl_3$). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.64 (s, 3H), 2.56 (ddd, *J* = 14.1, 11.6, 4.6 Hz, 1H), 2.81 (ddd, *J* = 14.1, 3.4, 3.4 Hz, 1H), 3.76 (s, 3H), 3.93 (ddd, *J* = 11.6, 11.6, 3.4 Hz, 1H), 4.26 – 4.28 (m, 1H), 6.77 (d, *J* = 6.1 Hz, 1H), 6.86 – 6.88 (m, 2H), 7.16 (t, *J* = 7.1 Hz, 1H), 7.23 (t, *J* = 7.9 Hz, 1H), 7.26 – 7.27 (m, 1H), 7.35 (t, *J* = 7.1 Hz, 1H), 7.43 (s, 1H), 7.74 (d, *J* = 7.9 Hz, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 26.3, 36.7, 39.2, 50.3, 55.5, 106.7, 110.6, 112.1, 113.2, 119.0, 121.4, 123.6, 125.8, 127.4, 130.1, 133.9, 137.5, 143.3, 160.2, 193.5. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -63.1. **HRMS** (ESI): Calcd. for $C_{20}H_{20}NO_2^+$ ($[M+H]^+$): 306.1489, Found: 306.1491.



5e

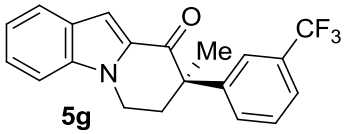
(*R*)-8-Methyl-8-(*p*-tolyl)-7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-one (5e): Prepared according to the general procedure G from **2b** (20.0 mg, 0.100 mmol) and 1-chloro-4-methylbenzene **4e** (25.4 mg, 0.200 mmol). The crude product was purified by silica gel chromatography with a CombiFlash system (4 g column, 100:0→90:10 hexanes/EtOAc) to give **5e** as a yellow solid in 83% yield (24.0 mg, 0.0829 mmol). The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 19.2 min (major); t_R 25.6 min (minor) [Chiracel AS-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 99:1, 1.0 mL/min] to be 99% ee. $[\alpha]_D^{23}$ = +115.8° (c 0.52, $CHCl_3$). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.61 (s, 3H), 2.28 (s, 3H), 2.54 (ddd, *J* = 14.3, 11.8, 4.9 Hz, 1H), 2.79 (ddd, *J* = 14.3, 3.4, 3.4 Hz, 1H), 3.90 (ddd, *J* = 11.8, 11.8, 3.4 Hz, 1H), 4.26 (ddd, *J* = 11.8, 4.9, 3.4 Hz, 1H), 7.09 – 7.10 (m, 2H), 7.13 – 7.17 (m, 3H), 7.24 – 7.25 (m, 1H), 7.33 (ddd, *J* = 8.2, 6.9, 1.0 Hz, 1H), 7.41 (s, 1H), 7.73 (dd, *J* = 8.2, 1.0 Hz, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 20.9, 26.1, 36.4, 38.9, 49.7, 106.3, 110.2, 121.0, 123.3, 125.5, 126.2, 127.1, 129.6, 133.7, 136.7, 137.2, 138.3, 193.5. **HRMS** (ESI): Calcd. for $C_{20}H_{20}NO^+$ ($[M+H]^+$): 290.1539, Found: 290.1545.



5f

(*R*)-8-(4-Methoxyphenyl)-8-methyl-7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-one (5f): Prepared according to the general procedure G from **2b** (20.0 mg, 0.100 mmol) and 1-chloro-4-methoxybenzene **4f** (28.6 mg, 0.200 mmol). The crude product was purified by silica gel chromatography with a CombiFlash system (4 g column, 100:0→90:10 hexanes/EtOAc) to give **5f** as a white solid in 92% yield (28.3 mg, 0.0927 mmol). The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 17.5 min (major); t_R 23.6 min (minor) [Chiracel AS-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 95:5, 1.0

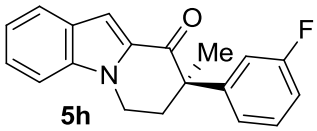
mL/min] to be 97% ee. $[\alpha]_D^{23}$ = +109.9° (c 0.56, $CHCl_3$). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.62 (s, 3H), 2.55 (ddd, *J* = 14.6, 11.8, 4.8 Hz, 1H), 2.77 (ddd, *J* = 14.6, 3.6, 3.6 Hz, 1H), 3.76 (s, 3H), 3.91 (ddd, *J* = 11.8, 11.8, 3.6 Hz, 1H), 4.28 (ddd, *J* = 11.8, 4.8, 3.6 Hz, 1H), 6.84 (d, *J* = 8.8 Hz, 2H), 7.16 (t, *J* = 7.4 Hz, 1H), 7.21 (d, *J* = 8.8 Hz, 2H), 7.27 – 7.28 (m, 1H), 7.35 (t, *J* = 7.4 Hz, 1H), 7.42 (s, 1H), 7.74 (d, *J* = 8.1 Hz, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 26.4, 36.8, 39.2, 49.7, 55.6, 106.7, 110.6, 114.6, 121.4, 123.6, 125.8, 127.4, 128.0, 133.6, 134.0, 137.5, 158.8, 193.9. **HRMS** (ESI): Calcd. for $C_{20}H_{20}NO_2^+$ ($[M+H]^+$): 306.1489, Found: 306.1499.



5g

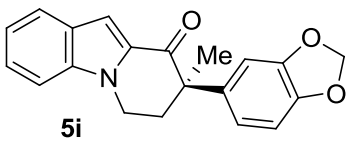
(*R*)-8-Methyl-8-(3-(trifluoromethyl)phenyl)-7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-one (5g): Prepared according to the general procedure G from **2b** (20.0 mg, 0.100 mmol) and 1-chloro-3-(trifluoromethyl)benzene **4g** (36.2 mg, 0.200 mmol). The crude product was purified by silica gel chromatography with a CombiFlash system (4 g column, 100:0→90:10 hexanes/EtOAc) to give **5g** as an orange solid in 90% yield (31.0 mg, 0.0903 mmol). The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 13.7 min (major); t_R 18.5 min (minor) [Chiracel AS-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 98:2, 1.0 mL/min] to be 99% ee. $[\alpha]_D^{24}$ = +119.6° (c 0.60, $CHCl_3$). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.66 (s, 3H), 2.59 (ddd, *J* = 14.6, 11.0, 4.8 Hz, 1H), 2.85 (ddd, *J* = 14.6, 3.8, 3.8 Hz, 1H), 3.93 (ddd, *J* = 12.4, 11.0, 3.8 Hz, 1H), 4.31 (ddd, *J* = 12.4, 4.8, 4.8 Hz, 1H), 7.17 (t, *J* = 7.8 Hz, 1H), 7.28 (d, *J* = 8.2 Hz, 1H), 7.40 (ddd, *J* = 7.8, 7.1, 0.7 Hz, 1H), 7.39 – 7.42 (m, 1H), 7.44 – 7.45 (m, 2H), 7.50 (d, *J* = 7.5 Hz, 1H), 7.61 (s, 1H), 7.74 (d, *J* = 8.2 Hz, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 26.1, 36.6, 39.1, 50.2, 107.5, 110.6, 121.6, 123.2 (q, *J* = 3.0, 1C), 123.8, 124.3 (q, *J* = 271.8, 1C), 124.4 (q, *J* = 4.5, 1C), 126.2, 127.4, 129.7, 130.4 (q, *J* = 3.0, 1C), 131.6 (q, *J* = 31.7, 1C), 133.5,

137.6, 143.1, 192.7. **^{19}F NMR** ($CDCl_3$, 565 MHz): δ -63.05 (s, 3F). **HRMS** (ESI): Calcd. for $C_{20}H_{17}F_3NO^+$ ($[M+H]^+$): 344.1257, Found: 344.1264.



5h

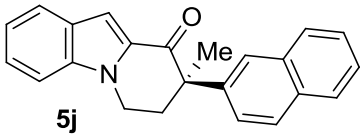
(*R*)-8-(3-Fluorophenyl)-8-methyl-7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-one (5h): Prepared according to the general procedure G from **2b** (20.0 mg, 0.100 mmol) and 1-chloro-3-fluorobenzene **4h** (26.2 mg, 0.200 mmol). The crude product was purified by silica gel chromatography with a CombiFlash system (4 g column, 100:0→94:6 hexanes/EtOAc) to give **5h** as a yellow oil in 75% yield (22.0 mg, 0.0750 mmol). The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 18.7 min (major); t_R 24.0 min (minor) [Chiracel AS-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 98:2, 1.0 mL/min] to be 99% ee. $[\alpha]_D^{23}$ = +148.6° (c 0.70, $CHCl_3$). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.63 (s, 3H), 2.57 (ddd, *J* = 14.4, 11.6, 4.8 Hz, 1H), 2.77 (ddd, *J* = 14.4, 3.6, 3.6 Hz, 1H), 3.91 (ddd, *J* = 11.6, 11.6, 3.6 Hz, 1H), 4.28 (ddd, *J* = 11.6, 4.8, 3.6 Hz, 1H), 6.90 – 6.93 (m, 1H), 7.00 – 7.04 (m, 2H), 7.16 (ddd, *J* = 8.2, 7.0, 1.0 Hz, 1H), 7.23 – 7.28 (m, 2H), 7.35 (ddd, *J* = 8.2, 1.0, 1.0 Hz, 1H), 7.43 (s, 1H), 7.73 (d, *J* = 8.2 Hz, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 26.2, 36.8, 39.1, 50.2, 107.2, 110.6, 113.9 (d, *J* = 22.6, 1C), 114.5 (d, *J* = 19.6, 1C), 121.5, 122.4 (d, *J* = 3.0, 1C), 123.8, 126.1, 127.4, 130.7 (d, *J* = 7.5, 1C), 133.7, 137.6, 144.5 (d, *J* = 6.0, 1C), 163.4 (d, *J* = 247.6, 1C), 192.9. **^{19}F NMR** ($CDCl_3$, 565 MHz): δ -112.3 (s, 1F). **HRMS** (ESI): Calcd. for $C_{19}H_{17}FNO^+$ ($[M+H]^+$): 294.1289, Found: 294.1293.



5i

(*R*)-8-(Benzo[*d*][1,3]dioxol-5-yl)-8-methyl-7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-one (5i): Prepared according to the general procedure G from **2b** (20.0 mg, 0.100 mmol) and 5-

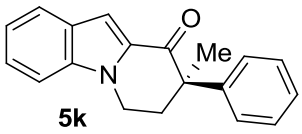
chlorobenzo[*d*][1,3]dioxole **4i** (31.4 mg, 0.200 mmol). The crude product was purified by silica gel chromatography with a CombiFlash system (4 g column, 100:0→85:15 hexanes/EtOAc) to give **5i** as a yellow solid in 82% yield (26.3 mg, 0.0823 mmol). The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 26.0 min (major); t_R 36.1 min (minor) [Chiracel AS-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 95:5, 1.0 mL/min] to be 99% ee. $[\alpha]_D^{23}$ = +132.2° (c 0.48, $CHCl_3$). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.59 (s, 3H), 2.53 (ddd, *J* = 14.2, 11.8, 4.8 Hz, 1H), 2.72 (ddd, *J* = 14.2, 3.2, 3.2 Hz, 1H), 3.94 (ddd, *J* = 11.8, 11.8, 3.2 Hz, 1H), 4.26 (ddd, *J* = 11.8, 4.8, 3.2 Hz, 1H), 5.90 (d, *J* = 9.7 Hz, 2H), 6.69 (s, 2H), 6.80 (s, 1H), 7.15 (t, *J* = 8.0 Hz, 1H), 7.26 – 7.27 (m, 1H), 7.34 (t, *J* = 7.4 Hz, 1H), 7.40 (s, 1H), 7.72 (d, *J* = 8.0 Hz, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 26.5, 36.9, 39.2, 50.1, 101.5, 106.9, 107.2, 108.7, 110.6, 120.0, 121.4, 123.7, 125.9, 127.4, 133.9, 135.5, 137.5, 146.9, 148.5, 193.5. **HRMS** (ESI): Calcd. for $C_{20}H_{18}NO_3^+$ ($[M+H]^+$): 320.1281, Found: 320.1287.



5j

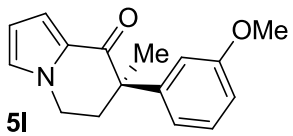
(*R*)-8-Methyl-8-(naphthalen-2-yl)-7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-one (5j): Prepared according to the general procedure G from **2b** (20.0 mg, 0.100 mmol) and 2-chloronaphthalene **4j** (32.6 mg, 0.200 mmol). The crude product was purified by silica gel chromatography with a CombiFlash system (4 g column, 100:0→85:15 hexanes/EtOAc) to give **5j** as a yellow solid in 95% yield (31.1 mg, 0.0956 mmol). The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 23.2 min (major); t_R 37.0 min (minor) [Chiracel AS-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 98:2, 1.0 mL/min] to be 99% ee. $[\alpha]_D^{24}$ = +24.4° (c 0.57, $CHCl_3$). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.72 (s, 3H), 2.62 (ddd, *J* = 14.6, 12.8, 4.5 Hz, 1H), 2.94 (ddd, *J* = 14.6, 3.6, 3.6 m, 1H), 3.90 (ddd, *J* = 12.2, 12.2, 3.6 Hz, 1H), 4.28 (ddd, *J* = 12.2, 4.5, 3.6 Hz,

1H), 7.14 (t, *J* = 7.4 Hz, 1H), 7.21 – 7.23 (m, 1H), 7.32 (t, *J* = 7.4 Hz, 1H), 7.42 – 7.49 (m, 4H), 7.65 (s, 1H), 7.71 – 7.78 (m, 3H), 7.83 (d, *J* = 8.6 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 26.2, 36.8, 39.3, 50.6, 106.9, 110.6, 121.4, 123.7, 124.3, 125.9, 125.9, 126.4, 126.6, 127.4, 127.7, 128.4, 129.1, 132.6, 133.6, 134.0, 137.5, 139.1, 193.7. **HRMS** (ESI): Calcd. for $C_{23}H_{20}NO^+$ ($[M+H]^+$): 326.1539, Found: 326.1543.



5k

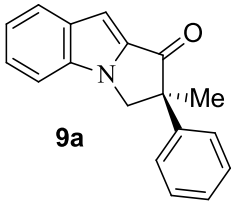
(*R*)-8-Methyl-8-phenyl-7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-one (5k): Prepared according to the general procedure G from **2b** (20.0 mg, 0.100 mmol) and chlorobenzene **4k** (22.6 mg, 0.200 mmol). The crude product was purified by silica gel chromatography with a CombiFlash system (4 g column, 100:0→95:5 hexanes/EtOAc) to give **5k** as a yellow solid in 99% yield (27.4 mg, 0.0995 mmol). The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 16.7 min (major); t_R 21.7 min (minor) [Chiracel AS-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 98:2, 1.0 mL/min] to be 98% ee. $[\alpha]_D^{23}$ = +148.7° (c 0.54, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.62 (s, 3H), 2.54 (ddd, *J* = 14.2, 12.0, 4.8 Hz, 1H), 2.79 (ddd, *J* = 14.2, 3.4, 3.4 Hz, 1H), 3.86 (ddd, *J* = 12.0, 12.0, 3.4 Hz, 1H), 4.24 (ddd, *J* = 12.0, 4.8, 3.4 Hz, 1H), 7.13 (t, *J* = 7.6 Hz, 1H), 7.18 – 7.34 (m, 7H), 7.41 (s, 1H), 7.72 (d, *J* = 8.1 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 26.3, 36.7, 39.2, 50.3, 106.7, 110.6, 121.4, 123.6, 125.9, 126.6, 127.3, 127.4, 129.2, 134.0, 137.4, 141.7, 193.7. **HRMS** (ESI): Calcd. for $C_{19}H_{18}NO^+$ ($[M+H]^+$): 276.1383, Found: 276.1388.



5l

(*R*)-7-(3-Methoxyphenyl)-7-methyl-6,7-dihydroindolizin-8(5*H*)-one (5l): Prepared according to the general procedure F from **2k** (30.0 mg, 0.201 mmol) and 1-chloro-3-methoxybenzene **4d** (57.3 mg, 0.402 mmol). The crude product was

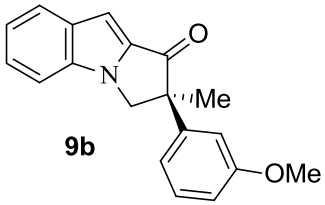
purified by silica gel chromatography with a CombiFlash system (4 g column, 100:0→90:10 hexanes/EtOAc) to give **5l** as a colorless oil in 70% yield (43.0 mg, 0.141 mmol). The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 27.2 min (major); t_R 31.7 min (minor) [Chiracel AS-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 98:2, 1.0 mL/min] to be 91% ee. $[\alpha]_D^{25}$ = +123.4° (c 0.87, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.56 (s, 3H), 2.44 (ddd, *J* = 14.2, 12.0, 4.6 Hz, 1H), 2.60 (ddd, *J* = 14.2, 3.4, 3.4 Hz, 1H), 3.76 (s, 3H), 3.86 (ddd, *J* = 12.0, 12.0, 3.4 Hz, 1H), 4.03 (ddd, *J* = 12.0, 4.6, 3.4 Hz, 1H), 6.25 (dd, *J* = 4.0, 2.4 Hz, 1H), 6.74 – 6.86 (m, 4H), 7.11 (dd, *J* = 4.0, 1.4 Hz, 1H), 7.22 (t, *J* = 8.0 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 26.3, 37.6, 42.6, 49.3, 55.5, 111.1, 112.0, 113.3, 115.2, 119.1, 125.8, 130.0, 130.8, 144.1, 160.1, 190.4. **HRMS** (ESI): Calcd. for $C_{16}H_{18}NO_2^+$ ($[M+H]^+$): 256.1332, Found: 256.1335.



9a

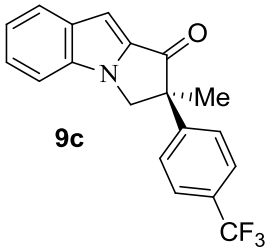
(*S*)-2-Methyl-2-phenyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-one (9a): Prepared according to the general procedure H from **2a** (37.0 mg, 0.200 mmol) and 1-chloro-3-methoxybenzene **8a** (63.0 mg, 0.399 mmol). The mixture was purified by flash column chromatography (98:2 hexane:EtOAc) to give **9a** as a white solid in 78% yield (40.7 mg, 0.156 mmol). The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 12.8 min (major); t_R 18.5 min (minor) [Chiracel (AS-H) (from Diacel Chemical Ind., Ltd.) hexane/*i*-PrOH 95:5, 1.0 ml/min] to be 99% ee. $[\alpha]_D^{24}$ = -228.9 ° (c 0.59, $CHCl_3$). The NMR data is consistent with the data available in literature.[32] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.84 (s, 3H), 4.48 (d, *J* = 11.0 Hz, 1H), 4.76 (d, *J* = 11.0 Hz, 1H), 7.14 (s, 1H), 7.21 - 7.30 (m, 2H), 7.31 - 7.35 (m, 4H), 7.38 - 7.46 (m, 2H), 7.81 (ddd, *J* = 8.4, 1.2, 1.2 Hz,

1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 22.6, 56.9, 57.5, 101.0, 111.0, 121.9, 124.6, 125.7, 126.2, 127.7, 129.2, 132.7, 132.8, 135.6, 142.5, 196.3.



9b

(*S*)-2-(3-Methoxyphenyl)-2-methyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-one (9b): Prepared according to the general procedure H from **2a** (37.0 mg, 0.199 mmol) and 1-bromo-3-methoxybenzene **8b** (74.7 mg, 0.399 mmol). The crude product was purified by silica gel chromatography with a CombiFlash system (4 g column, 100:0→92:8 hexanes/EtOAc) to give a mixture of **9b** and possibly, its rotameric isomer in 85:15 ratio, as a yellow solid in 44% combined yield (25.7 mg, 0.0882 mmol). The enantiomeric excess was determined by HPLC analysis (220 nm, 25 °C) t_R 32.7 min (major); t_R 50.0 min (minor) [Chiracel AS-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 98:2, 1.0 mL/min] to be 99% ee. $[\alpha]_D^{24}$ = -193.5° (c 0.15, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.81 (s, 3H), 3.77 (s, 3H), 4.47 (d, *J* = 11.0 Hz, 1H), 4.75 (d, *J* = 11.0 Hz, 1H), 6.79 – 6.81 (s, 1H), 6.88 – 6.90 (m, 2H), 7.12 (s, 1H), 7.20 – 7.26 (m, 2H), 7.37 – 7.45 (m, 2H), 7.80 (d, *J* = 8.4 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 23.6, 55.6, 56.9, 57.4, 101.1, 111.0, 112.5, 112.9, 118.6, 121.9, 124.6, 125.7, 130.2, 132.7, 134.8, 135.7, 144.1, 160.2, 196.2. **HRMS** (ESI): Calcd. for $C_{19}H_{18}NO_2^+$ ($[M+H]^+$): 292.1332, Found: 292.1334. The extra peaks in ^{1}H and ^{13}C NMR might have resulted due to the presence of rotameric isomer of **9b**.

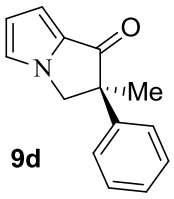


9c

(*S*)-2-Methyl-2-(4-(trifluoromethyl)phenyl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-one (9c): Prepared according to the general procedure H from **2a** (37.0 mg, 0.199 mmol) and 1-bromo-4-(trifluoromethyl)benzene **8c** (89.9 mg, 0.399 mmol). The crude product

was purified by silica gel chromatography with a CombiFlash system (4 g column, 100:0→90:10 hexanes/EtOAc) to give a mixture of **9c** and possibly its rotameric isomer in 86:14 ratio, as a light yellow solid in 68% combined yield (44.6 mg, 0.135 mmol). The enantiomeric excess was determined by HPLC analysis (220 nm, 25 °C) t_R 13.0 min (major); t_R 15.8 min (minor) [Chiracel AS-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 95:5, 1.0 mL/min] to be 99% ee. $[\alpha]_D^{25}$ = -133.3° (c 0.85, $CHCl_3$). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.86 (s, 3H), 4.52 (d, *J* = 11.0 Hz, 1H), 4.75 (d, *J* = 11.0 Hz, 1H), 7.15 (s, 1H), 7.24 (ddd, *J* = 8.2, 6.7, 1.1 Hz, 1H), 7.40 – 7.48 (m, 4H), 7.59 (d, *J* = 8.2 Hz, 2H), 7.82 (d, *J* = 8.2 Hz, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 23.8, 56.5, 57.5, 101.6, 111.0, 122.2, 124.3 (q, *J* = 271.8 Hz, 1C), 124.8, 126.1, 126.2 (q, *J* = 4.5 Hz, 1C), 126.8, 130.0 (q, *J* = 33.2 Hz, 1C), 132.8, 134.4, 135.8, 146.4 (q, *J* = 1.5 Hz, 1C), 195.3. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -62.9 (s, 3F). **HRMS** (ESI): Calcd. for $C_{19}H_{15}F_3NO^+$ ($[M+H]^+$): 330.1100, Found: 330.1107.

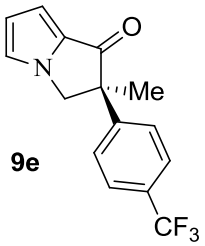
The extra peaks in ^{1}H and ^{13}C NMR might have resulted due to the presence of rotameric isomer of **9c**. Variable-temperature NMR measurements (Bruker 400 MHz) on a sample of **9c** in DMSO-d_6 at temperatures ranging from 20 °C to 135 °C, upper limit of the instrument, did not show coalescence of peaks. Additional NMR studies (1-D selective chemical-exchange NMR) were carried out to confirm the presence of rotameric isomer.[33] However, the results were inconclusive.



9d

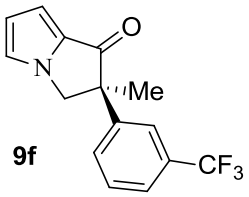
(*S*)-2-Methyl-2-phenyl-2,3-dihydro-1*H*-pyrrolizin-1-one (9d): Prepared according to the general procedure I from **2m** (27.0 mg, 0.200 mmol) and 1-bromobenzene **8a** (63.0 mg, 0.399 mmol). The crude product was purified by flash column chromatography (98:2 hexane:EtOAc) to give **9d** as a white solid in 80% yield

(33.8 mg, 0.160 mmol). The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 28.0 min (major); t_R 46.4 min (minor) [Chiracel OJ-H (0.46 cm x 25 cm) (from Diacel Chemical Ind., Ltd.) hexane/*i*-PrOH 80:20, 1.0 ml/min] to be 99% ee. $[\alpha]_D^{24}$ = -262.4° (c 0.78, $CHCl_3$). The NMR data is consistent with the data available in literature.[10] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.74 (s, 3H), 4.33 (d, *J* = 11.8 Hz, 1H), 4.56 (d, *J* = 11.8 Hz, 1H), 6.58 (dd, *J* = 4.0, 2.4 Hz, 1H), 6.82 (dd, *J* = 4.0, 0.6 Hz, 1H), 7.05 – 7.06 (m, 1H), 7.21 - 7.25 (m, 1H), 7.27 – 7.33 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 23.5, 57.3, 59.0, 109.5, 117.6, 123.3, 126.2, 127.5, 129.1, 131.6, 142.9, 192.9.



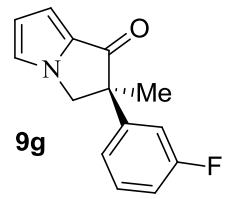
9e

(*S*)-2-Methyl-2-(4-(trifluoromethyl)phenyl)-2,3-dihydro-1*H*-pyrrolizin-1-one (9e): Prepared according to the general procedure I from **2m** (27.0 mg, 0.199 mmol) and 1-bromo-4-(trifluoromethyl)benzene **8b** (89.9 mg, 0.399 mmol). The crude product was purified by silica gel chromatography with a CombiFlash system (4 g column, 100:0→90:10 hexanes/EtOAc) to give **9e** as a light yellow solid in 90% yield (50.0 mg, 0.179 mmol). The enantiomeric excess was determined by HPLC analysis (220 nm, 25 °C) t_R 21.0 min (major); t_R 29.1 min (minor) [Chiracel AS-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 98:2, 1.0 mL/min] to be 99% ee. $[\alpha]_D^{23}$ = -68.0° (c 0.62, $CHCl_3$). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.78 (s, 3H), 4.38 (d, *J* = 11.8 Hz, 1H), 4.57 (d, *J* = 11.8 Hz, 1H), 6.62 (dd, *J* = 4.0, 2.2 Hz, 1H), 6.86 (dd, *J* = 4.0, 1.0 Hz, 1H), 7.10 (d, *J* = 2.2 Hz, 1H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.58 (d, *J* = 8.4 Hz, 2H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 23.6, 57.4, 58.6, 110.0, 118.1, 123.6, 124.3 (q, *J* = 271.8 Hz, 1C), 126.1 (q, *J* = 4.5 Hz, 1C), 126.8, 129.8 (q, *J* = 33.2 Hz, 1C), 131.3, 146.8, 191.5. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -62.9 (s, 3F). **HRMS** (ESI): Calcd. for $C_{15}H_{13}F_3NO^+$ ($[M+H]^+$): 280.0944, Found: 280.0949.



9f

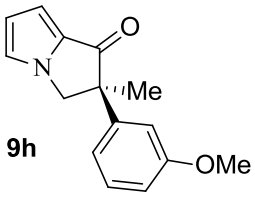
(*S*)-2-Methyl-2-(3-(trifluoromethyl)phenyl)-2,3-dihydro-1*H*-pyrrolizin-1-one (9f): Prepared according to the general procedure I from **2m** (27.0 mg, 0.199 mmol) and 1-bromo-3-(trifluoromethyl)benzene **8d** (89.9 mg, 0.399 mmol). The crude product was purified by silica gel chromatography with a CombiFlash system (4 g column, 100:0→90:10 hexanes/EtOAc) to give **9f** as a yellow oil in 88% yield (49.0 mg, 0.175 mmol). The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 17.5 min (major); t_R 25.0 min (minor) [Chiracel AS-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 98:2, 1.0 mL/min] to be 99% ee. $[\alpha]_D^{23}$ = -67.3° (c 0.74, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.78 (s, 3H), 4.39 (d, *J* = 11.8 Hz, 1H), 4.56 (d, *J* = 11.8 Hz, 1H), 6.62 (dd, *J* = 4.0, 2.0 Hz, 1H), 6.86 (dd, *J* = 4.0, 1.0 Hz, 1H), 7.10 (dd, *J* = 2.0, 1.0 Hz, 1H), 7.42 – 7.53 (m, 3H), 7.58 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 23.8, 57.3, 58.6, 110.0, 118.1, 123.1 (q, *J* = 4.0 Hz, 1C), 123.7, 124.3 (q, *J* = 273.7 Hz, 1C), 124.5 (q, *J* = 4.0 Hz, 1C), 129.7, 129.9 (q, *J* = 2.0 Hz, 1C), 131.3, 131.4 (q, *J* = 32.3 Hz, 1C), 143.8, 191.6. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -62.8 (s, 3F). **HRMS** (ESI): Calcd. for $C_{15}H_{13}F_3NO^+$ ($[M+H]^+$): 280.0944, Found: 280.0947.



9g

(*S*)-2-(3-Fluorophenyl)-2-methyl-2,3-dihydro-1*H*-pyrrolizin-1-one (9g): Prepared according to the general procedure I from **2m** (27.0 mg, 0.199 mmol) and 1-bromo-3-fluorobenzene **8e** (69.9 mg, 0.399 mmol). The crude product was purified by silica gel chromatography with a CombiFlash system (4 g column, 100:0→90:10 hexanes/EtOAc) to give **9g** as a light yellow oil in 92% yield (42.3 mg, 0.184 mmol). The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 25.2 min

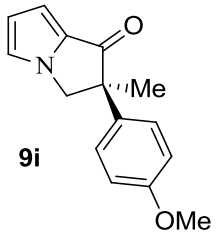
(major); t_R 35.5 min (minor) [Chiracel AS-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 98:2, 1.0 mL/min] to be 99% ee. $[\alpha]_D^{24}$ = -80.6° (c 0.84, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.74 (s, 3H), 4.35 (d, *J* = 11.8 Hz, 1H), 4.55 (d, *J* = 11.8 Hz, 1H), 6.60 (dd, *J* = 4.0, 2.4 Hz, 1H), 6.85 (dd, *J* = 4.0, 0.8 Hz, 1H), 6.92 – 6.97 (m, 1H), 7.01 – 7.09 (m, 3H), 7.27 – 7.31 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 23.5, 57.2, 58.8, 109.9, 113.6 (d, *J* = 23.2 Hz, 1C), 114.5 (d, *J* = 21.2 Hz, 1C), 117.9, 121.9 (d, *J* = 3.0 Hz, 1C), 123.5, 130.6 (d, *J* = 9.1 Hz, 1C), 131.4, 145.4 (d, *J* = 7.1 Hz, 1C), 163.3 (d, *J* = 247.4 Hz, 1C), 191.8. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -112.3 (m, 1F). **HRMS** (EI): Calcd. for $C_{14}H_{13}FNO^+$ ($[M+H]^+$): 230.0976, Found: 230.0979.



9h

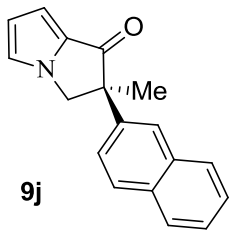
(*S*)-2-(3-Methoxyphenyl)-2-methyl-2,3-dihydro-1*H*-pyrrolizin-1-one (9h): Prepared according to the general procedure I from **2m** (27.0 mg, 0.199 mmol) and 1-bromo-3-methoxybenzene **8c** (74.7 mg, 0.399 mmol). The crude product was purified by silica gel chromatography with a CombiFlash system (4 g column, 100:0→90:10 hexanes/EtOAc) to give **9h** as a light yellow oil in 99% yield (48.0 mg, 0.199 mmol). The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 25.6 min (major); t_R 28.6 min (minor) [Chiracel AS-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 95:5, 1.0 mL/min] to be 98% ee. $[\alpha]_D^{24}$ = -95.1° (c 0.95, $CHCl_3$). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.74 (s, 3H), 3.77 (s, 3H), 4.33 (d, *J* = 11.6 Hz, 1H), 4.56 (d, *J* = 11.6 Hz, 1H), 6.59 (dd, *J* = 4.0, 2.2 Hz, 1H), 6.79 (ddd, *J* = 8.2, 2.2, 0.8 Hz, 1H), 6.83 (dd, *J* = 4.0, 0.8 Hz, 1H), 6.88 – 6.85 (m, 2H), 7.06 – 7.07 (m, 1H), 7.24 (t, *J* = 8.2 Hz, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 23.5, 55.6, 57.4, 59.0, 109.6, 112.3, 112.8, 117.7, 118.6, 123.3, 130.1, 131.7,

144.5, 160.2, 192.5. **HRMS** (ESI): Calcd. for $C_{15}H_{16}NO_2^+$ ($[M+H]^+$): 242.1176, Found: 242.1180.



9i

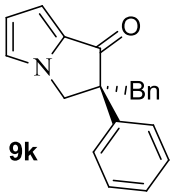
(*S*)-2-(4-Methoxyphenyl)-2-methyl-2,3-dihydro-1*H*-pyrrolizin-1-one (9i): Prepared according to the general procedure I from **2m** (27.0 mg, 0.199 mmol) and 1-bromo-4-methoxybenzene **8f** (74.2 mg, 0.399 mmol). The crude product was purified by silica gel chromatography with a CombiFlash system (4 g column, 100:0→90:10 hexanes/EtOAc) to give **9i** as a yellow oil in 52% yield (25.0 mg, 0.104 mmol). The enantiomeric excess was determined by HPLC analysis (220 nm, 25 °C) t_R 18.0 min (major); t_R 25.0 min (minor) [Chiracel AS-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90:10, 1.0 mL/min] to be 99% ee. $[\alpha]_D^{25}$ = -87.7° (c 0.36, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.73 (s, 3H), 3.78 (s, 3H), 4.33 (d, *J* = 11.6 Hz, 1H), 4.54 (d, *J* = 11.6 Hz, 1H), 6.59 (dd, *J* = 4.0, 2.2 Hz, 1H), 6.82 – 6.86 (m, 3H), 7.06 (m, 1H), 7.20 – 7.22 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 23.6, 55.6, 56.8, 59.1, 109.5, 114.5, 117.6, 123.2, 127.4, 131.7, 134.9, 158.9, 193.0. **HRMS** (ESI): Calcd. for $C_{15}H_{16}NO_2^+$ ($[M+H]^+$): 242.1176, Found: 242.1180.



9j

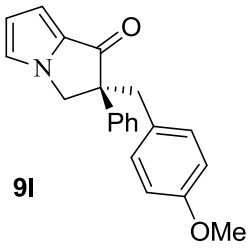
(*S*)-2-Methyl-2-(naphthalen-2-yl)-2,3-dihydro-1*H*-pyrrolizin-1-one (9j): Prepared according to the general procedure I from **2m** (27.0 mg, 0.199 mmol) and 2-bromonaphthalene **8g** (82.7 mg, 0.399 mmol). The crude product was purified by silica gel chromatography with a CombiFlash system (4 g column, 100:0→90:10 hexanes/EtOAc) to give **9j** as a light yellow solid in 96% yield (50.3 mg, 0.192 mmol). The enantiomeric excess was determined by HPLC analysis (220

nm, 25 °C) t_R 24.1 min (major); t_R 36.0 min (minor) [Chiracel AS-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 95:5, 1.0 mL/min] to be 99% ee. $[\alpha]_D^{23}$ = -287.1° (c 0.81, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.87 (s, 3H), 4.42 (d, *J* = 11.8 Hz, 1H), 4.66 (d, *J* = 11.8 Hz, 1H), 6.62 (dd, *J* = 4.0, 2.2 Hz, 1H), 6.88 (dd, *J* = 4.0, 1.0 Hz, 1H), 7.10 (dd, *J* = 2.2, 1.0 Hz, 1H), 7.31 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.43 – 7.50 (m, 2H), 7.77 – 7.82 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 23.6, 57.6, 58.9, 109.6, 117.8, 123.4, 124.4, 125.1, 126.4, 126.7, 127.8, 128.5, 129.1, 131.8, 132.7, 133.5, 140.1, 192.7. **HRMS** (ESI): Calcd. for $C_{18}H_{16}NO^+$ ($[M+H]^+$): 262.1226, Found: 262.1231.



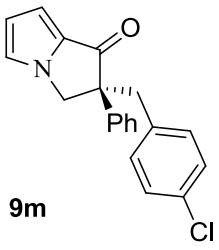
9k

(*S*)-2-Benzyl-2-phenyl-2,3-dihydro-1*H*-pyrrolizin-1-one (9k): Prepared according to the modified version of the general procedure I from **2n** (42.0 mg, 0.199 mmol) and bromobenzene **8a** (63.0 mg, 0.398 mmol) at 10 °C. The mixture was purified by flash column chromatography (98:2 hexane:EtOAc) to give **9k** as a white solid in 69% yield (39.6 mg, 0.138 mmol). The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 35.2 min (major); t_R 48.9 min (minor) [Chiracel OJ-H (0.46 cm x 25 cm) (from Diacel Chemical Ind., Ltd.) hexane/*i*-PrOH 80:20, 1.0 ml/min] to be 99% ee. $[\alpha]_D^{24}$ = -219.1° (c 0.78, $CHCl_3$). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 3.33 (d, *J* = 13.8 Hz, 1H), 3.63 (d, *J* = 13.8 Hz, 1H), 4.52 (d, *J* =12.0 Hz, 1H), 4.56 (d, *J* = 12.0 Hz, 1H), 6.45 (dd, *J* = 4.2, 2.4 Hz, 1H), 6.73 (dd, *J* = 4.2, 1.2 Hz, 1H), 6.91 (m, 1H), 7.07 – 7.08 (m, 2H), 7.16 – 7.19 (m, 3H), 7.26 – 7.28 (m, 1H), 7.34 (t, *J* = 8.0 Hz, 2H), 7.43 (d, *J* = 8.0 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 43.2, 53.5, 62.0, 109.3, 117.4, 123.3, 126.7, 127.2, 127.3, 128.3, 129.1, 130.5, 132.2, 136.7, 141.9, 191.3. **HRMS** (ESI): Calcd. for $C_{20}H_{18}NO^+$ ($[M+H]^+$): 288.1383, found 288.1390.



9l

(*S*)-2-(4-Methoxybenzyl)-2-phenyl-2,3-dihydro-1*H*-pyrrolizin-1-one (9l): Prepared according to the general procedure I from **2o** (48.0 mg, 0.199 mmol) and bromobenzene **8a** (63.0 mg, 0.398 mmol). The mixture was purified by flash column chromatography (98:2 hexane:EtOAc) to give **9l** as a white solid in 91% yield (57.6 mg, 0.181 mmol). $[\alpha]_D^{24}$ = -81.2° (c 1.22, $CHCl_3$) The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 29.4 min (major); t_R 42.1 min (minor) [Chiracel AD-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 95:5, 1.0 ml/min] to be 99%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.15 (d, *J* = 14.0 Hz, 1H), 3.51 (d, *J* = 14.0 Hz, 1H), 3.65 (s, 3H), 4.43 (d, *J* = 11.8 Hz, 1H), 4.48 (d, *J* = 11.8 Hz, 1H) 6.37 (dd, *J* = 4.0, 2.2 Hz, 1H), 6.61 - 6.65 (m, 3H), 6.82 – 6.83 (m, 1H), 6.89 (d, *J* = 8.6 Hz, 2H), 7.16 – 7.20 (m, 1H), 7.25 (t, *J* = 7.2 Hz, 2H), 7.34 (d, *J* = 8.6 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 42.4, 53.5, 55.5, 62.2, 109.2, 114.0, 117.4, 123.3, 126.7, 127.5, 128.6, 129.0, 131.5, 132.3, 142.1, 158.7, 191.5. **HRMS** (ESI) Calcd. for $C_{21}H_{20}NO_2^+$ ($[M+H]^+$): 318.1489, found 318.1494.

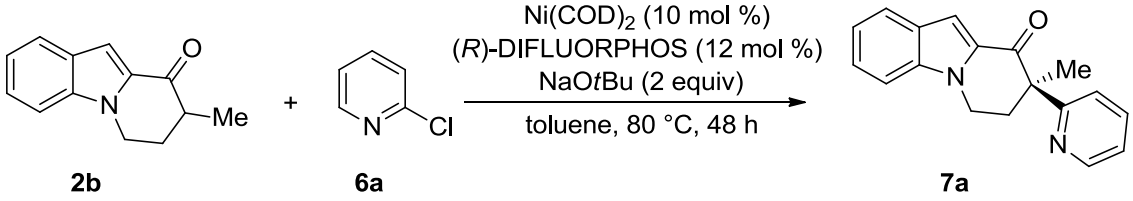


9m

(*S*)-2-(4-Chlorobenzyl)-2-phenyl-2,3-dihydro-1*H*-pyrrolizin-1-one (9m): Prepared according to the general procedure I from **2p** (49.0 mg, 0.199 mmol) and bromobenzene **8a** (63.0 mg, 0.399 mmol). The mixture was purified by flash column chromatography (98:2 hexane:EtOAc) to give **9m** as a white solid in 84% yield (54.0 mg, 0.168 mmol). The enantiomeric excess was determined by HPLC analysis (220 nm, 25 °C) t_R 25.7 min (major); t_R 30.6 min (minor) [Chiracel AS-H (0.46 cm x 25 cm) (from Diacel Chemical Ind., Ltd.) hexane/*i*-PrOH 95:5, 1.0 ml/min] to be 99%. $[\alpha]_D^{24}$ = -70.1° (c 0.68, $CHCl_3$). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 3.27 (d, *J* = 13.8 Hz, 1H), 3.60 (d, *J* = 13.8 Hz, 1H), 4.46 (d, *J* = 12.0 Hz, 1H), 4.59 (d, *J* = 12.0 Hz, 1H), 6.47 (dd, *J* = 3.6, 1.8 Hz, 1H),

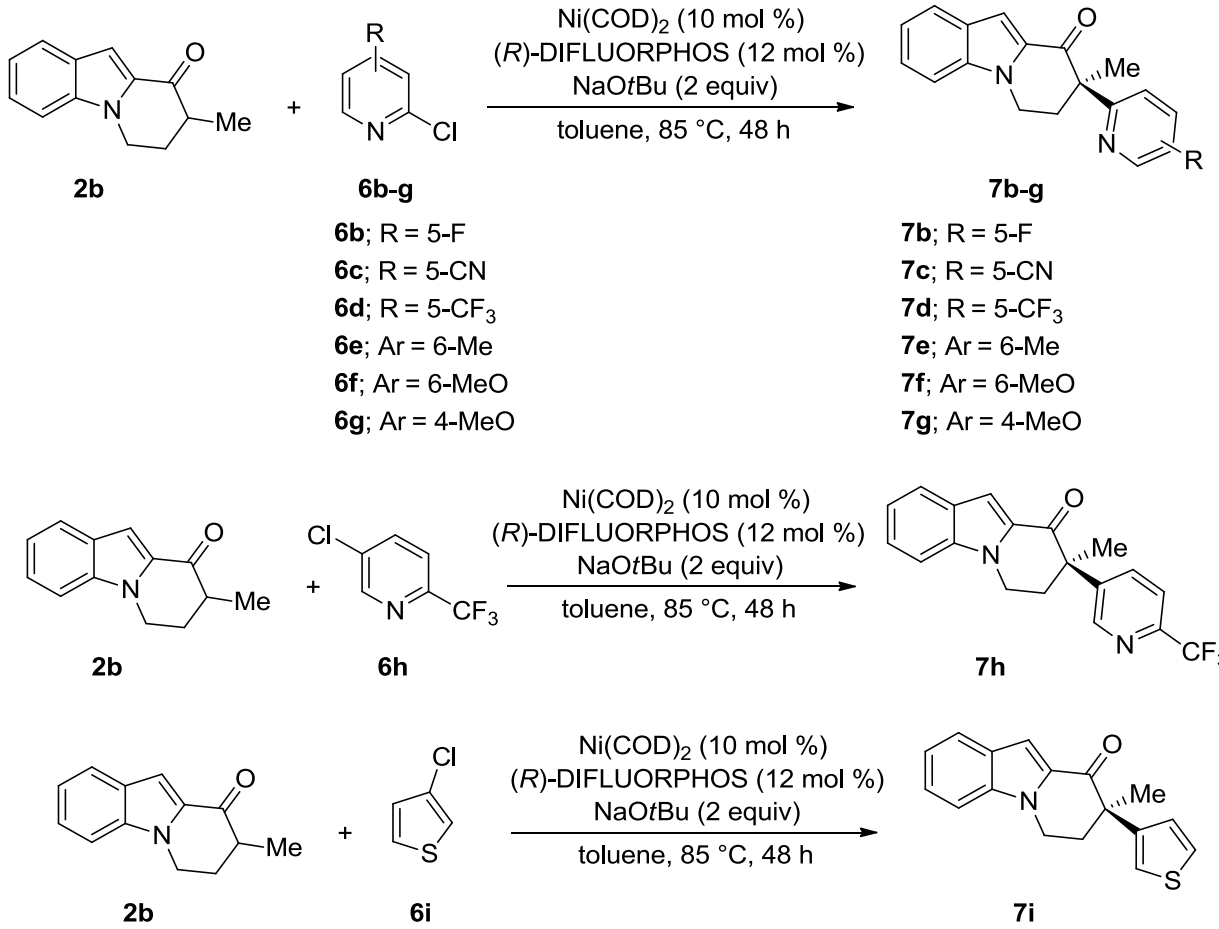
6.73 (d, *J* = 3.6 Hz, 1H), 6.93 (m, 1H), 6.99 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 7.27 - 7.28 (m, 1H), 7.34 (t, *J* = 7.8 Hz, 2H), 7.40 (d, *J* = 7.8 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 42.6, 53.4, 61.9, 109.5, 117.6, 123.4, 126.7, 127.7, 128.7, 129.2, 131.8, 132.1, 133.1, 135.1, 141.6, 191.0. **HRMS** (ESI) Calcd. for $C_{20}H_{17}ClNO^+$ ($[M+H]^+$): 322.0993, found 322.0998.

4.5.12 General Procedure J: Synthesis of (*R*)-8-Methyl-8-(pyridin-2-yl)-7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-one (7a)



In a nitrogen-filled glovebox, 8-methyl-7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-one (**2b**) (0.100 mmol, 1.0 equiv), $Ni(COD)_2$ (2.8 mg, 0.0100 mmol, 0.10 equiv), (*R*)-DIFLUORPHOS (9.2 mg, 0.0120 mmol, 0.12 equiv), NaO*t*Bu (19.3 mg, 0.200 mmol, 2.0 equiv), 2-chloropyridine **6a** (0.200 mmol, 2.0 equiv), a magnetic stirring bar, and toluene (0.5 mL) were added to a 1-dram vial. The vial was sealed with a cap containing a PTFE septum and removed from the glovebox. The reaction mixture was stirred at 80 °C in an oil bath for 48 h. The vial was removed from the oil bath and allowed to cool to room temperature. The reaction mixture was filtered through short plug of silica gel (eluting with 20 mL of 3:2 hexanes:EtOAc). The crude reaction mixture was concentrated under reduced pressure. The crude product was purified with a CombiFlash system with 5-20% ethyl acetate in hexanes as eluent to give (*R*)-8-methyl-8-(pyridin-2-yl)-7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-one (**7a**).

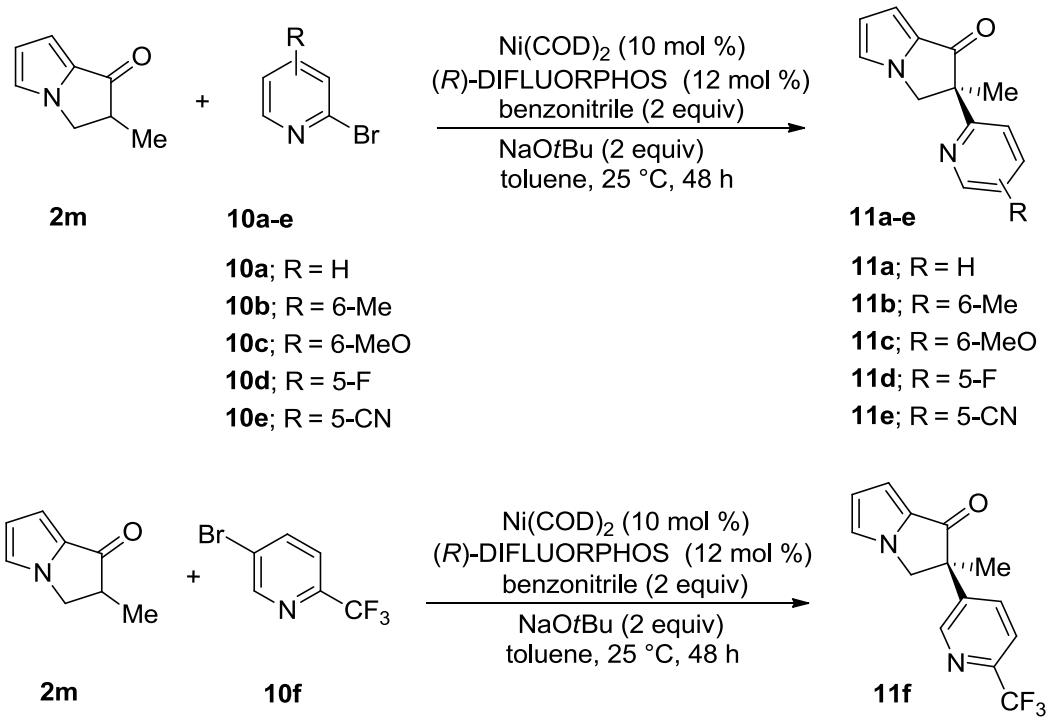
4.5.13 General Procedure K: Synthesis of (*R*)-8-Heteroaryl-8-methyl-7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-ones (7b-i)



In a nitrogen-filled glovebox, 8-methyl-7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-one (**2b**) (0.100 mmol, 1.0 equiv), $Ni(COD)_2$ (2.8 mg, 0.0100 mmol, 0.10 equiv), (*R*)-DIFLUORPHOS (9.2 mg, 0.0120 mmol, 0.12 equiv), NaO*t*Bu (19.3 mg, 0.200 mmol, 2.0 equiv), the appropriate heteroaryl chloride **6b-i** (0.200 mmol, 2.0 equiv), a magnetic stirring bar, and toluene (0.5 mL) were added to a 1-dram vial. The vial was sealed with a cap containing a PTFE septum and removed from the glovebox. The reaction mixture was stirred at 85 °C in an oil bath for 48 h. The vial was removed from the oil bath and allowed to cool to room temperature. The reaction mixture was filtered through short plug of silica gel (eluting with 20 mL of 3:2 hexanes:EtOAc).

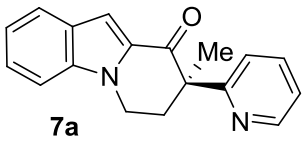
The crude reaction mixture was concentrated under reduced pressure. The crude product was purified with a CombiFlash system with 5-10% ethyl acetate in hexanes as eluent to give the appropriate (*R*)-8-heteroaryl-8-methyl-7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-ones (**7b-i**).

4.5.14 General Procedure L: Synthesis of (*R*)-2-Heteroaryl-2-methyl-2,3-dihydro-1*H*-pyrrolizin-1-one (11a-d) and (*S*)-2-Methyl-2-(6-(trifluoromethyl)pyridin-3-yl)-2,3-dihydro-1*H*-pyrrolizin-1-one (11f)



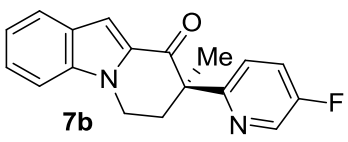
In a nitrogen-filled glovebox, 2-methyl-2,3-dihydro-1*H*-pyrrolizin-1-one (**2m**) (0.200 mmol, 1.0 equiv), $Ni(COD)_2$ (5.5 mg, 0.0200 mmol, 0.10 equiv), (*R*)-DIFLUORPHOS (18.4 mg, 0.0240 mmol, 0.12 equiv), NaO*t*Bu (38.4 mg, 0.400 mmol, 2.0 equiv), benzonitrile (41.2 mg, 0.400 mmol, 2.0 equiv), the appropriate heteroaryl bromide **10a-f** (0.400 mmol, 2.0 equiv), a magnetic stirring bar, and toluene (1.0 mL) were added to a 1-dram vial. The vial was sealed with a cap containing a PTFE septum and removed from the glovebox. The reaction mixture was stirred at 25 °C for 48 h. The vial was removed from the oil bath and allowed to cool to room temperature. The reaction mixture was filtered through short plug of silica gel (eluting with 20

mL of 3:2 hexanes:EtOAc). The crude reaction mixture was concentrated under reduced pressure. The crude product was purified with a CombiFlash system with 5-20% ethyl acetate in hexanes as eluent to give the appropriate (*R*)-2-heteroaryl-2-methyl-2,3-dihydro-1*H*-pyrrolizin-1-one (**11a-d**) and (*S*)-2-methyl-2-(6-(trifluoromethyl)pyridin-3-yl)-2,3-dihydro-1*H*-pyrrolizin-1-one (**11f**).



7a

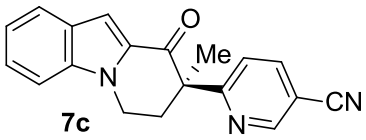
(*R*)-8-Methyl-8-(pyridin-2-yl)-7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-one (7a): Prepared according to the general procedure J from **2b** (20.0 mg, 0.100 mmol) and 2-chloropyridine **6a** (22.8 mg, 0.200 mmol). The crude product was purified by silica gel chromatography with a CombiFlash system (4 g column, 100:0→90:10 hexanes/EtOAc) to give **7a** as a light yellow solid in 72% yield (20.0 mg, 0.0724 mmol). The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 21.2 min (major); t_R 28.6 min (minor) [Chiracel AS-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 99:1, 1.0 mL/min] to be 99% ee. $[\alpha]_D^{23}$ = -79.2° (c 0.78, $CHCl_3$). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.66 (s, 3H), 2.49 (ddd, *J* = 13.8, 11.6, 5.0 Hz, 1H), 3.24 (ddd, *J* = 13.8, 3.2, 3.2 Hz, 1H), 4.01 (ddd, *J* = 11.6, 11.6, 3.2 Hz, 1H), 4.29 (ddd, *J* = 11.6, 5.0, 3.2 Hz, 1H), 7.12 – 7.15 (m, 2H), 7.25 – 7.28 (m, 2H), 7.33 (ddd, *J* = 8.4, 6.8, 1.2 Hz, 1H), 7.40 (s, 1H), 7.57 (ddd, *J* = 8.4, 8.4, 1.2 Hz, 1H), 7.71 (dt, *J* = 8.2, 0.8 Hz, 1H), 8.57 (m, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 25.4, 35.5, 39.5, 52.7, 106.8, 110.7, 121.4, 122.2, 122.5, 123.7, 125.9, 127.4, 133.8, 137.3, 137.6, 149.6, 160.7, 193.2. **HRMS** (ESI): Calcd. for $C_{18}H_{17}N_2O^+$ ($[M+H]^+$): 277.1335, Found: 277.1339.



7b

(*R*)-8-(5-Fluoropyridin-2-yl)-8-methyl-7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-one (7b): Prepared according to the general

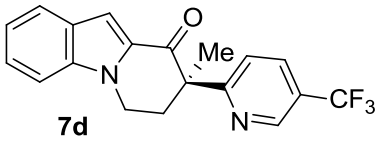
procedure K from **2b** (20.0 mg, 0.100 mmol) and 2-chloro-5-fluoropyridine (**6b**) (26.4 mg, 0.200 mmol). The crude product was purified by silica gel chromatography with a CombiFlash system (4 g column, 100:0→90:10 hexanes/EtOAc) to give **7b** as a yellow oil in 82% yield (24.2 mg, 0.0822 mmol). The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 20.0 min (major); t_R 26.1 min (minor) [Chiracel AS-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 99:1, 1.0 mL/min] to be 98% ee. $[\alpha]_D^{23}$ = +112.0° (c 0.52, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.64 (s, 3H), 2.48 (ddd, *J* = 13.9, 11.6, 5.0 Hz, 1H), 3.20 (ddd, *J* = 13.9, 3.6, 3.6 Hz, 1H), 4.03 (ddd, *J* = 11.6, 11.6, 3.6 Hz, 1H), 4.30 (ddd, *J* = 11.6, 5.0, 3.6 Hz, 1H), 7.14 (ddd, *J* = 8.0, 6.8, 1.0 Hz, 1H), 7.28 – 7.30 (m, 3H), 7.34 (ddd, *J* = 8.4, 6.8, 1.0 Hz, 1H), 7.40 (s, 1H), 7.72 (d, *J* = 8.0 Hz, 1H), 8.41 (t, *J* = 1.6 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 25.5, 35.4, 39.4, 52.2, 107.1, 110.7, 121.5, 123.1 (d, *J* = 4.2 Hz, 1C), 123.7, 124.0 (d, *J* = 18.3 Hz, 1C), 126.1, 127.4, 133.5, 137.6, 137.8, 156.7 (d, *J* = 3.7 Hz, 1C), 158.8 (d, *J* = 257.2 Hz, 1C), 193.0. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -129.4 (m, 1F). **HRMS** (ESI): Calcd. for $C_{18}H_{16}FN_2O^+$ ($[M+H]^+$): 295.1241, Found: 295.1243.



7c

(*R*)-6-(8-Methyl-9-oxo-6,7,8,9-tetrahydropyrido[1,2-*a*]indol-8-yl)nicotinonitrile (7c): Prepared according to the general procedure K from **2b** (20.0 mg, 0.100 mmol) and 6-chloronicotinonitrile **6c** (27.8 mg, 0.200 mmol). The crude product was purified by silica gel chromatography with a CombiFlash system (4 g column, 100:0→90:10 hexanes/EtOAc) to give **7c** as a light yellow solid in 93% yield (28.1 mg, 0.0932 mmol). The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 22.5 min (major); t_R 39.0 min (minor) [Chiracel AS-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90:10, 1.0 mL/min] to be 29% ee. $[\alpha]_D^{25}$ = +4.2° (c 0.95,

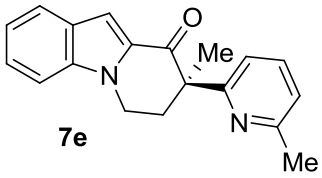
$CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.67 (s, 3H), 2.51 (ddd, *J* = 14.0, 11.0, 5.0 Hz, 1H), 3.24 (ddd, *J* = 14.0, 3.9, 3.9 Hz, 1H), 4.05 (ddd, *J* = 12.6, 11.0, 3.9 Hz, 1H), 4.32 (ddd, *J* = 12.6, 5.0, 3.9 Hz, 1H), 7.16 (ddd, *J* = 8.2, 6.9, 0.8 Hz, 1H), 7.29 (dd, *J* = 8.4, 0.8 Hz, 1H), 7.37 (ddd, *J* = 8.4, 6.9, 1.0 Hz, 1H), 7.41 (s, 1H), 7.46 (dd, *J* = 8.4, 0.8 Hz, 1H), 7.72 (ddd, *J* = 8.2, 0.8, 0.8 Hz, 1H), 7.86 (dd, *J* = 8.4, 2.2 Hz, 1H), 8.83 (dd, *J* = 2.2, 0.8 Hz, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 25.3, 35.0, 39.3, 53.0, 107.7, 108.8, 110.7, 116.8, 121.7, 122.4, 123.8, 126.4, 127.4, 133.2, 137.8, 140.2, 152.3, 165.5, 191.8. **HRMS** (ESI): Calcd. for $C_{19}H_{16}N_3O^+$ ($[M+H]^+$): 302.1288, Found: 302.1296.



7d

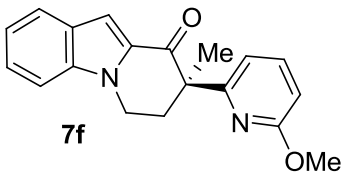
(*R*)-8-Methyl-8-(5-(trifluoromethyl)pyridin-2-yl)-7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-one (7d): Prepared according to the general procedure K from **2b** (20.0 mg, 0.100 mmol) and 2-chloro-5-(trifluoromethyl)pyridine **6d** (36.4 mg, 0.200 mmol). The crude product was purified by silica gel chromatography with a CombiFlash system (4 g column, 100:0→90:10 hexanes/EtOAc) to give **7d** as a yellow oil in 55% yield (19.0 mg, 0.0552 mmol). The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 17.4 min (major); t_R 19.7 min (minor) [Chiracel AS-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 98:2, 0.5 mL/min] to be 65% ee. $[\alpha]_D^{23}$ = +34.0° (c 0.76, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.68 (s, 3H), 2.51 (ddd, *J* = 13.9, 11.6, 5.0 Hz, 1H), 3.26 (ddd, *J* = 13.9, 3.8, 3.8 Hz, 1H), 4.05 (ddd, *J* = 12.2, 11.6, 3.8 Hz, 1H), 4.32 (ddd, *J* = 12.2, 5.0, 3.8 Hz, 1H), 7.15 (ddd, *J* = 8.0, 6.8, 0.8 Hz, 1H), 7.28 – 7.30 (m, 1H), 7.36 (ddd, *J* = 8.0, 6.8, 0.6 Hz, 1H), 7.41 (s, 1H), 7.43 – 745 (m, 1H), 7.72 (d, *J* = 8.4 Hz, 1H), 7.81 (dd, *J* = 8.4, 2.0 Hz, 1H), 8.83 (d, *J* = 2.0 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 25.4, 35.2, 39.4, 52.8, 107.4, 110.7, 121.6, 122.0, 123.7, 123.8

(q, *J* = 273.6 Hz, 1C), 125.5 (q, *J* = 33.3 Hz, 1C), 126.2, 127.4, 133.4, 134.3 (q, *J* = 4.0 Hz, 1C), 137.7, 146.5 (q, *J* = 4.0 Hz, 1C), 164.9 (q, *J* = 2.0 Hz, 1C), 192.3. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -62.7 (s, 3F). **HRMS** (ESI): Calcd. for $C_{19}H_{16}F_3N_2O^+$ ($[M+H]^+$): 345.1209, Found: 345.1218.



7e

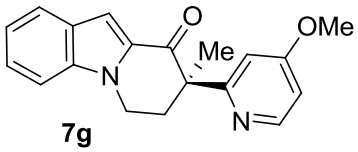
(*R*)-8-Methyl-8-(6-methylpyridin-2-yl)-7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-one (7e): Prepared according to the general procedure K from **2b** (20.0 mg, 0.100 mmol) and 2-chloro-6-methylpyridine **6e** (25.6 mg, 0.200 mmol). The crude product was purified by silica gel chromatography with a CombiFlash system (4 g column, 100:0→90:10 hexanes/EtOAc) to give **7e** as a yellow solid in 72% yield (21.0 mg, 0.0723 mmol). The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 12.2 min (major); t_R 17.6 min (minor) [Chiracel AS-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 99:1, 1.0 mL/min] to be 75% ee. $[\alpha]_D^{25}$ = +171.8° (c 0.74, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.63 (s, 3H), 2.43 (ddd, *J* = 13.8, 11.8, 5.2 Hz, 1H), 2.51 (s, 3H), 3.29 (ddd, *J* = 13.8, 3.8, 3.8 Hz, 1H), 4.04 (ddd, *J* = 11.8, 11.8, 3.8 Hz, 1H), 4.27 (ddd, *J* = 11.8, 5.2, 3.8 Hz, 1H), 6.96 – 7.03 (m, 2H), 7.13 (ddd, *J* = 7.8, 6.7, 1.2 Hz, 1H), 7.26 – 7.35 (m, 2H), 7.37 (s, 1H), 7.41 (t, *J* = 7.8 Hz, 1H), 7.71 (d, *J* = 8.0, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 25.0, 25.5, 35.2, 39.6, 52.6, 106.6, 110.6, 118.9, 121.3, 121.9, 123.6, 125.7, 127.3, 133.9, 137.2, 137.5, 158.4, 159.7, 193.6. **HRMS** (ESI): Calcd. for $C_{19}H_{19}N_2O^+$ ($[M+H]^+$): 291.1492, Found: 291.1495.



7f

(*R*)-8-(6-Methoxypyridin-2-yl)-8-methyl-7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-one (7f): Prepared according to the general procedure K from **2b** (20.0 mg, 0.100 mmol) and 2-chloro-6-

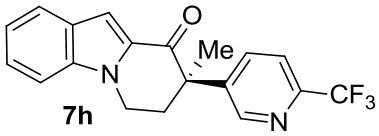
methoxypyridine **6f** (28.8 mg, 0.200 mmol). The crude product was purified by silica gel chromatography with a CombiFlash system (4 g column, 100:0→90:10 hexanes/EtOAc) to give **7f** as a light yellow solid in 75% yield (23.1 mg, 0.0754 mmol). The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 12.0 min (major); t_R 15.6 min (minor) [Chiracel AS-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 98:2, 1.0 mL/min] to be 95% ee. $[\alpha]_D^{23}$ = +183.8° (c 0.54, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.65 (s, 3H), 2.46 (ddd, *J* = 13.8, 12.0, 5.0 Hz, 1H), 3.14 (ddd, *J* = 13.8, 3.8, 3.0 Hz, 1H), 3.81 (s, 3H), 3.98 (ddd, *J* = 12.0, 12.0, 3.8 Hz, 1H), 4.29 (ddd, *J* = 12.0, 5.0, 3.0 Hz, 1H), 6.57 (dd, *J* = 8.2, 0.6 Hz, 1H), 6.78 (dd, *J* = 7.4, 0.6 Hz, 1H), 7.14 (ddd, *J* = 8.2, 6.8, 1.2 Hz, 1H), 7.26 – 7.36 (m, 2H), 7.38 (s, 1H), 7.43 (dd, *J* = 8.2, 7.4 Hz, 1H), 7.72 (ddd, *J* = 8.2, 1.2, 1.2 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 24.8, 35.8, 39.5, 52.4, 53.5, 106.4, 109.4, 110.6, 114.5, 121.3, 123.6, 125.8, 127.4, 134.1, 137.5, 139.6, 158.6, 163.8, 193.2. **HRMS** (ESI): Calcd. for $C_{19}H_{19}N_2O_2^+$ ($[M+H]^+$): 307.1441, Found: 307.1445.



7g

(*R*)-8-(4-Methoxypyridin-2-yl)-8-methyl-7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-one (7g): Prepared according to the general procedure K from **2b** (20.0 mg, 0.100 mmol) and 2-chloro-4-methoxypyridine **6g** (28.8 mg, 0.200 mmol). The crude product was purified by silica gel chromatography with a CombiFlash system (4 g column, 100:0→90:10 hexanes/EtOAc) to give **7g** as a white solid in 50% yield (15.3 mg, 0.0499 mmol). The enantiomeric excess was determined by HPLC analysis (220 nm, 25 °C) t_R 11.9 min (major); t_R 14.4 min (minor) [Chiracel AS-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 95:5, 1.0 mL/min] to be 86% ee. $[\alpha]_D^{25}$ = +17.2° (c 0.46, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.63 (s,

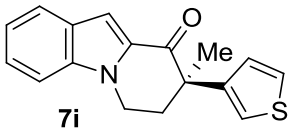
3H), 2.45 (ddd, *J* = 13.8, 11.8, 5.1 Hz, 1H), 3.23 (ddd, *J* = 13.8, 3.2, 3.2 Hz, 1H), 3.74 (s, 3H), 4.03 (ddd, *J* = 11.8, 11.8, 3.2 Hz, 1H), 4.28 (ddd, *J* = 11.8, 5.1, 3.2 Hz, 1H), 6.65 (dd, *J* = 5.8, 2.4 Hz, 1H), 6.76 (d, *J* = 2.4 Hz, 1H), 7.13 (ddd, *J* = 8.0, 7.0, 0.6 Hz, 1H), 7.28 – 7.35 (m, 2H), 7.39 (s, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 8.38 (d, *J* = 5.8 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 25.4, 35.4, 39.6, 52.7, 55.4, 106.8, 108.3, 108.6, 110.7, 121.3, 123.6, 125.9, 127.4, 133.8, 137.6, 150.8, 162.4, 166.6, 193.3. **HRMS** (ESI): Calcd. for $C_{19}H_{19}N_2O_2^+$ ($[M+H]^+$): 307.1441, Found: 307.1443.



7h

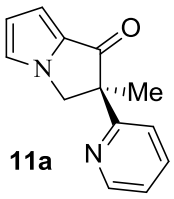
(*R*)-8-Methyl-8-(6-(trifluoromethyl)pyridin-3-yl)-7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-one (7h): Prepared according to the general procedure K from **2b** (20.0 mg, 0.100 mmol) and 5-chloro-2-(trifluoromethyl)pyridine **6h** (36.4 mg, 0.200 mmol). The crude product was purified by silica gel chromatography with a CombiFlash system (4 g column, 100:0→90:10 hexanes/EtOAc) to give **7h** as a yellow solid in 80% yield (27.7 mg, 0.0804 mmol). The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 16.1 min (major); t_R 33.5 min (minor) [Chiracel AS-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90:10, 1.0 mL/min] to be 99% ee. $[\alpha]_D^{23}$ = +65.7° (c 1.03, $CHCl_3$). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.72 (s, 3H), 2.63 (ddd, *J* = 14.6, 10.1, 4.8 Hz, 1H), 2.89 (ddd, *J* = 14.6, 4.8, 4.8 Hz, 1H), 3.99 (ddd, *J* = 12.5, 10.1, 4.8 Hz, 1H), 4.35 (ddd, *J* = 12.5, 4.8, 4.8 Hz, 1H), 7.18 (ddd, *J* = 8.4, 6.6, 0.6 Hz, 1H), 7.29 – 7.30 (m, 1H), 7.39 (ddd, *J* = 8.4, 6.6, 0.8 Hz, 1H), 7.46 (s, 1H), 7.61 (d, *J* = 8.4 Hz, 1H), 7.74 (d, *J* = 8.4 Hz, 1H), 7.78 (dd, *J* = 8.4, 2.0 Hz, 1H), 8.76 (d, *J* = 2.0 Hz, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 25.3, 36.4, 38.9, 48.9, 108.1, 110.6, 120.7 (q, *J* = 2.7 Hz, 1C), 121.7 (q, *J* = 274.0 Hz, 1C), 121.9, 123.9, 126.7, 127.4, 133.0, 136.4, 137.8, 141.2, 147.3 (q, *J* = 35.0 Hz, 1C),

148.6, 191.4. **^{19}F NMR** ($CDCl_3$, 565 MHz): δ -68.5 (s, 3F). **HRMS** (ESI): Calcd. for $C_{19}H_{16}F_3N_2O^+$ ($[M+H]^+$): 345.1209, Found: 345.1213.



7i

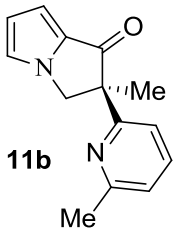
(*R*)-8-Methyl-8-(thiophen-3-yl)-7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-one (7i): Prepared according to the general procedure K from **2b** (20.0 mg, 0.100 mmol) and 3-chlorothiophene **6i** (23.8 mg, 0.200 mmol). The crude product was purified by silica gel chromatography with a CombiFlash system (4 g column, 100:0→90:10 hexanes/EtOAc) to give **7i** as a light yellow solid in 92% yield (27.2 mg, 0.0924 mmol). The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 23.0 min (major); t_R 27.9 min (minor) [Chiracel AS-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 98:2, 1.0 mL/min] to be 94% ee. $[\alpha]_D^{23}$ = +84.2° (c 0.55, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.63 (s, 3H), 2.55 (ddd, *J* = 14.0, 11.8, 4.6 Hz, 1H), 2.70 (ddd, *J* = 14.0, 3.6, 3.6 Hz, 1H), 3.94 (ddd, *J* = 11.8, 11.8, 3.6 Hz, 1H), 4.29 (ddd, *J* = 11.8, 4.6, 3.6 Hz, 1H), 6.96 (d, *J* = 1.4 Hz, 1H), 7.04 (dd, *J* = 5.0, 1.4 Hz, 1H), 7.15 (t, *J* = 7.4 Hz, 1H), 7.25 – 7.36 (m, 3H), 7.41 (s, 1H), 7.73 (d, *J* = 8.1 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 25.8, 37.1, 39.2, 48.1, 107.1, 110.6, 121.4, 121.6, 123.7, 126.0, 126.1, 126.7, 127.4, 133.5, 137.5, 142.6, 192.6. **HRMS** (ESI): Calcd. for $C_{17}H_{16}NOS^+$ ($[M+H]^+$): 282.0947, Found: 282.0951.



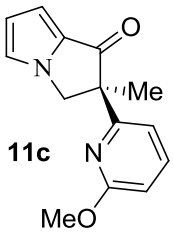
11a

(*R*)-2-Methyl-2-(pyridin-2-yl)-2,3-dihydro-1*H*-pyrrolizin-1-one (11a): Prepared according to the general procedure L from **2m** (27.0 mg, 0.199 mmol) and 2-bromopyridine **10a** (63.1 mg, 0.399 mmol). The crude product was purified by silica gel chromatography with a CombiFlash system (4 g column, 100:0→90:10 hexanes/EtOAc) to give **11a** as a light yellow oil in 99% yield (42.0 mg, 0.198 mmol). The

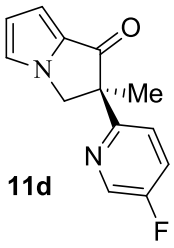
enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 10.6 min (major); t_R 13.7 min (minor) [Chiracel AS-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90:10, 1.0 mL/min] to be 97% ee. $[\alpha]_D^{25}$ = -136.8° (c 0.89, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.77 (s, 3H), 4.24 (d, *J* = 11.4 Hz, 1H), 5.31 (d, *J* = 11.4 Hz, 1H), 6.55 (dd, *J* = 4.0, 2.2 Hz, 1H), 6.78 (dd, *J* = 4.0, 1.0 Hz, 1H), 7.09 (m, 1H), 7.16 (ddd, *J* = 7.2, 4.8, 1.2 Hz, 1H), 7.61 – 7.69 (m, 2H), 8.51 (ddd, *J* = 4.8, 1.7, 1.2 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 24.6, 55.8, 60.0, 109.3, 117.5, 121.5, 122.5, 123.6, 131.4, 137.1, 149.3, 160.7, 191.9. **HRMS** (ESI): Calcd. for $C_{13}H_{13}N_2O^+$ ($[M+H]^+$): 213.1022, Found: 213.1024.



(*R*)-2-Methyl-2-(6-methylpyridin-2-yl)-2,3-dihydro-1*H*-pyrrolizin-1-one (11b): Prepared according to the general procedure L from **2m** (27.0 mg, 0.199 mmol) and 2-bromo-6-methylpyridine **10b** (68.7 mg, 0.399 mmol). The crude product was purified by silica gel chromatography with a CombiFlash system (4 g column, 100:0→90:10 hexanes/EtOAc) to give **11b** as a light yellow oil in 71% yield (32.0 mg, 0.141 mmol). The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 8.00 min (major); t_R 10.2 min (minor) [Chiracel AS-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90:10, 1.0 mL/min] to be 95% ee. $[\alpha]_D^{23}$ = -53.2° (c 0.53, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.74 (s, 3H), 2.47 (s, 3H), 4.20 (d, *J* = 11.4 Hz, 1H), 5.41 (d, *J* = 11.4 Hz, 1H), 6.54 (dd, *J* = 4.0, 2.2 Hz, 1H), 6.77 (dd, *J* = 4.0, 1.0 Hz, 1H), 7.00 – 7.01 (m, 1H), 7.08 (m, 1H), 7.41 – 7.43 (m, 1H), 7.53 (t, *J* = 7.6 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 24.89, 24.92, 55.6, 59.9, 109.0, 117.2, 118.3, 121.9, 123.4, 131.5, 137.2, 158.0, 159.8, 192.3. **HRMS** (ESI): Calcd. for $C_{14}H_{15}N_2O^+$ ($[M+H]^+$): 227.1179, Found: 227.1179.

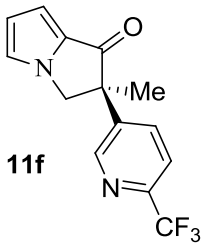


(*R*)-2-(6-Methoxypyridin-2-yl)-2-methyl-2,3-dihydro-1*H*-pyrrolizin-1-one (11c): Prepared according to the general procedure L from **2m** (27.0 mg, 0.199 mmol) and 2-bromo-6-methoxypyridine **10c** (75.1 mg, 0.399 mmol). The crude product was purified by silica gel chromatography with a CombiFlash system (4 g column, 100:0→90:10 hexanes/EtOAc) to give **11c** as a light yellow oil in 51% yield (24.8 mg, 0.102 mmol). The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 8.92 min (major); t_R 11.5 min (minor) [Chiracel AS-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90:10, 1.0 mL/min] to be 95% ee. $[\alpha]_D^{23}$ = -60.2° (c 0.80, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.74 (s, 3H), 3.77 (s, 3H), 4.21 (d, *J* = 11.2 Hz, 1H), 5.16 (d, *J* = 11.2 Hz, 1H), 6.55 (dd, *J* = 4.0, 2.2 Hz, 1H), 6.60 (dd, *J* = 8.2, 0.6 Hz, 1H), 6.78 (dd, *J* = 4.0, 1.0 Hz, 1H), 7.07 – 7.08 (m, 1H), 7.10 (dd, *J* = 7.4, 0.6 Hz, 1H), 7.54 (dd, *J* = 8.2, 7.4 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 23.4, 53.4, 56.1, 59.9, 109.1, 109.5, 113.7, 117.3, 123.2, 131.7, 139.6, 158.4, 163.5, 191.9. **HRMS** (ESI): Calcd. for $C_{14}H_{15}N_2O_2^+$ ($[M+H]^+$): 243.1128, Found: 243.1131.



(*R*)-2-(5-Fluoropyridin-2-yl)-2-methyl-2,3-dihydro-1*H*-pyrrolizin-1-one (11d): Prepared according to the general procedure L from **2m** (27.0 mg, 0.199 mmol) and 2-bromo-5-fluoropyridine **10d** (70.3 mg, 0.399 mmol). The crude product was purified by silica gel chromatography with a CombiFlash system (4 g column, 100:0→90:10 hexanes/EtOAc) to give **11d** as a colorless oil in 48% yield (22.0 mg, 0.0955 mmol). The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 10.1 min (major); t_R 12.9 min (minor) [Chiracel AS-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90:10, 1.0 mL/min] to be 95% ee. $[\alpha]_D^{25}$ = -113.6° (c 0.81, $CHCl_3$).

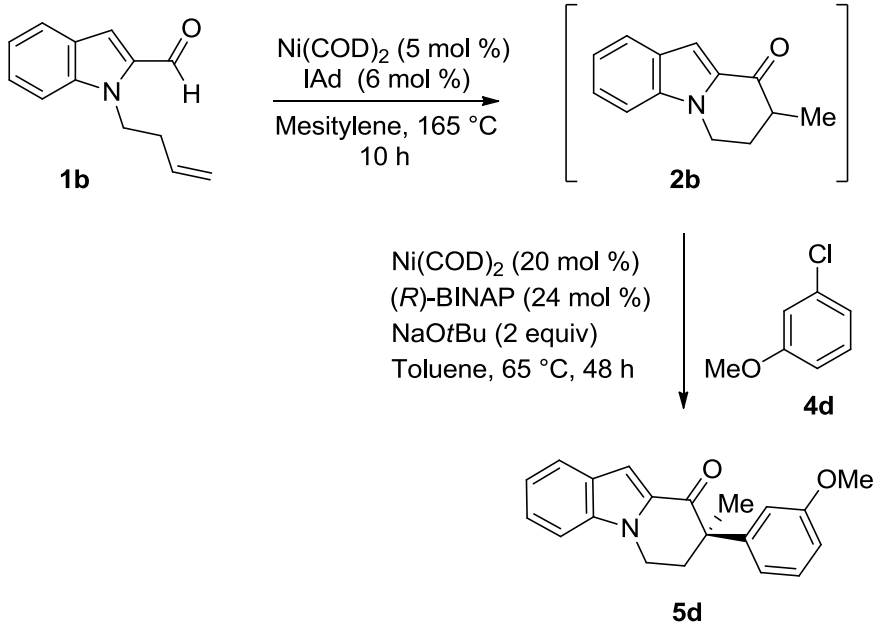
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.75 (s, 3H), 4.24 (d, *J* = 11.6 Hz, 1H), 5.29 (d, *J* = 11.6 Hz, 1H), 6.56 (dd, *J* = 4.0, 2.2 Hz, 1H), 6.79 (dd, *J* = 4.0, 1.0 Hz, 1H), 7.09 – 7.10 (m, 1H), 7.38 (ddd, *J* = 8.8, 8.2, 3.0 Hz, 1H), 7.66 (ddd, *J* = 8.8, 4.0, 0.4 Hz, 1H), 8.34 (d, *J* = 3.0 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 24.9, 55.7, 59.5 (d, *J* = 1.0 Hz, 1C), 109.5, 117.6, 122.5 (d, *J* = 5.0 Hz, 1C), 123.7 (d, *J* = 2.0 Hz, 1C), 123.9, 131.1, 137.3 (d, *J* = 24.2 Hz, 1C), 156.5 (d, *J* = 4.0 Hz, 1C), 158.9 (d, *J* = 257.5 Hz, 1C), 191.5. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -129.7 (s, 1F). **HRMS** (ESI): Calcd. for $C_{13}H_{12}FN_2O^+$ ($[M+H]^+$): 231.0928, Found: 231.0931.



11f

(*S*)-2-Methyl-2-(6-(trifluoromethyl)pyridin-3-yl)-2,3-dihydro-1*H*-pyrrolizin-1-one (11f): Prepared according to the general procedure L from **2m** (27.0 mg, 0.199 mmol) and 5-bromo-2-(trifluoromethyl)pyridine **10f** (90.3 mg, 0.399 mmol). The crude product was purified by silica gel chromatography with a CombiFlash system (4 g column, 100:0→90:10 hexanes/EtOAc) to give **11f** as a colorless oil in 23% yield (13.0 mg, 0.046 mmol). The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 21.7 min (major); t_R 26.2 min (minor) [Chiracel AS-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90:10, 1.0 mL/min] to be 92% ee. $[\alpha]_D^{25}$ = -51.9° (c 0.38, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.82 (s, 3H), 4.45 (d, *J* = 11.8 Hz, 1H), 4.62 (d, *J* = 11.8 Hz, 1H), 6.63 (dd, *J* = 4.0, 2.2 Hz, 1H), 6.88 (dd, *J* = 4.0, 0.6 Hz, 1H), 7.12 (m, 1H), 7.65 (d, *J* = 8.2 Hz, 1H), 7.89 (dd, *J* = 8.2, 2.0 Hz, 1H), 8.68 (d, *J* = 2.0 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 24.0, 55.9, 57.7, 110.6, 118.5, 120.7 (q, *J* = 2.7 Hz, 1C), 121.7 (q, *J* = 275.0 Hz, 1C), 124.0, 130.8, 135.5, 141.7, 147.4 (q, *J* = 35.1 Hz, 1C), 148.3, 190.2. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -68.2 (s, 3F). **HRMS** (ESI): Calcd. for $C_{14}H_{12}F_3N_2O^+$ ($[M+H]^+$): 281.0896, Found: 281.0896.

4.5.15 Procedure for One-pot Synthesis of (*R*)-8-(3-Methoxyphenyl)-8-methyl-7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-one (5d)



In a nitrogen-filled glovebox, 1-(but-3-en-1-yl)-1*H*-indole-2-carboxaldehyde (**1b**) (20.0 mg, 0.100 mmol, 1.0 equiv) was added to a 1-dram vial containing solution of $Ni(COD)_2$ (1.4 mg, 0.00500 mmol, 0.050 equiv) and IAd (2.0 mg, 0.00600 mmol, 0.060 equiv) in mesitylene (0.5 mL). The vial was sealed with a PTFE/silicone-lined septum cap and removed from the glovebox. The reaction mixture was stirred at 165 °C in an oil bath for 10 h. The vial was removed from the oil bath and allowed to cool to room temperature. The reaction mixture was allowed to stir in air at room temperature for 5-10 min. The vial was taken inside the glove box and $Ni(COD)_2$ (5.6 mg, 0.0200 mmol, 0.20 equiv), (*R*)-BINAP (15.0 mg, 0.0240 mmol, 0.24 equiv), NaO*t*Bu (19.3 mg, 0.200 mmol, 2.0 equiv), 1-chloro-3-methoxybenzene (**4d**) (28.6 mg, 0.200 mmol, 2.0 equiv), and toluene (0.5 mL) were added. The vial was sealed and removed from the glovebox. The reaction mixture was stirred at 65 °C in an oil bath for 48 h. The vial was removed from the oil bath and allowed to cool to room temperature. The reaction mixture was filtered through a short plug of silica

gel (eluting with 20 mL of 3:2 hexanes:EtOAc). The crude reaction mixture was concentrated under reduced pressure. The crude product was purified with a CombiFlash system with 10% ethyl acetate in hexanes as eluent to give (*R*)-8-(3-methoxyphenyl)-8-methyl-7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-one (5d) as a light yellow solid in 70% yield (21.5 mg, 0.0704 mmol). The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 30.6 min (major); t_R 41.2 min (minor) [Chiracel AS-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 99:1, 1.0 mL/min] to be 98% ee. $[\alpha]_D^{24}$ = +125.4° (c 0.92, $CHCl_3$).

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CHAPTER 5

NICKEL PHOSPHIDE (Ni_2P) NANOCRYSTAL CATALYZED HYDROGENATION OF PHENYLACETYLENE

Chapter would be modified for publication

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5.1 Abstract

Hydrogenation of phenylacetylene catalyzed by Ni_2P nanocrystals at 100 °C with 40 bar H_2 is reported. The model reaction is studied with both hollow and solid Ni_2P nanocrystals in two different solvents (1,4-dioxane and 1-propanol). Recycling studies in both solvents demonstrated increase in catalytic activity of Ni_2P nanocrystals over reaction cycles. Structural characterization of recycled Ni_2P nanocrystals via powder XRD, TEM and XPS analyses revealed reduction in the size of hollow nanoparticles along with the formation of Ni(II) species after the hydrogenation reaction. Systematic characterization of Ni_2P nanocrystals isolated after each reaction throughout the lifetime of the recycling study (in both 1,4-dioxane and 1-propanol) has been demonstrated using powder XRD, TEM and XPS analyses. Hydrogenation of phenylacetylene in 1,4-dioxane catalyzed by Ni_2P nanocrystal has been recycled up to 8 times without any significant loss in reactivity. However, hydrogenation of phenylacetylene in 1-propanol catalyzed by Ni_2P nanocrystal demonstrated steady drop in the yield of product over recycling. Use of $NiCl_2$ as precursor for synthesis of Ni_2P nanocrystal generated a mixture of solid and hollow Ni_2P nanocrystal, while $Ni(OAc)_2$ precursor exclusively forms hollow Ni_2P nanocrystal having smaller particle size as compared to the ones synthesized from $NiCl_2$. These smaller, hollow Ni_2P nanocrystals obtained from $Ni(OAc)_2$ as nickel precursor, has been shown to be catalytically

more active than the mixture of solid and hollow Ni_2P nanocrystals as synthesized from $NiCl_2$ as nickel precursor.

5.2 Introduction

Nanocatalysis has been a subject of extensive interest because of the novel catalytic properties associated with nanostructures, including highly enhanced reactivity and selectivity of nanoparticle catalysts as compared to their bulk counterparts.[1] The intrinsic properties of a metal nanoparticle are a function of its size, shape, composition, crystallinity, and structure.[2] In order to utilize the power of these nanocatalysts to their true potential, a detailed understanding of the origin of their enhanced performance is required. Many experimental studies on nanocatalysts have focused on correlating catalytic activity with particle size.[3] While particle size is an important consideration, many other factors such as geometry, composition, shape, oxidation state, and chemical/physical environment can play a role in determining nanocrystals reactivity.[4] However, the exact relationship between these parameters and nanocrystal catalytic performance may be system dependent, and is yet to be determined for many nanoscale catalysts. Thus, in the last two decades, considerable effort has been dedicated to the systematic investigation of the influence of the nanoparticle preparation method, size, shape, and nanoparticle-metal oxide support interaction on catalytic performance.[2, 3, 4]

Metal phosphides (MPs)[5] are a class of materials with various compositions and ratios that show fascinating properties in magnetic, electronic, and catalytic applications due to their specific structural properties. During last few decades, their catalytic properties have garnered extensive research interest. For instance, several studies have shown that transition metal

phosphides (e.g., MoP, CoP, Fe_2P, and Ni_2P) display high activity toward hydrodesulfurization (HDS)[6] and hydrodenitrogeneration (HDN) reactions.[4a]

The nickel-rich phosphides,[7] having a metallic character, have been used as heterogeneous catalysts mainly in hydrotreating reactions. An early use of bulk Ni_2P was reported for the reduction of nitrobenzene,[8] but was not studied further. Reports during the 1980s demonstrated that phosphorus-containing amorphous nickel catalysts exhibited attenuated hydrogenation activities compared with nickel, due to the electron-withdrawing effect of the phosphorus on the nickel. In the next decade, efforts concentrated on the crystallized phases, as a wide variety of nickel phosphides were constructed, with stoichiometry ranging from Ni_3P to NiP_3.[9] Their oxidation states and electronic properties strongly relied on the Ni/P ratio.[10] Among the Ni-rich phases (Ni_3P, $Ni_{12}P_5$, Ni_5P_4, and Ni_2P), the Ni_2P phase has been studied most extensively, particularly due its higher stability upon sulfur exposure, thus making it an efficient catalyst for hydrodesulfurization processes.[11]

Recently, Ni_2P nanocrystals have been studied in the context of selective hydrogenation of alkynes. Mezailles, Sanchez, Corma and coworkers in 2012 reported that well-defined 25 nm Ni_2P nanoparticles act as a colloidal catalyst for the chemoselective hydrogenation of terminal and internal alkynes.[12] In this study, *cis*-alkenes were obtained as products under mild reaction conditions (6 bar H_2, 85 °C) with good yield (up to 95%) and selectivity (up to 99%). The authors noted that the phosphorus inserted in the Ni-P nanoparticles was critical for the selectivity of the nanocatalyst.

Last year, He, Wei and coworkers reported a new synthetic strategy for the fabrication of various alumina supported nickel phosphides ($Ni_{12}P_5$, Ni_2P, and NiP_2) with particle size ranging from 5 to 15 nm via a two-step procedure: preparation of supported Ni particles from layered

double hydroxide precursors, followed by a further reaction with a certain amount of red phosphorus.[13] They evaluated the activity of these alumina supported metal phosphides toward selective hydrogenation of phenylacetylene and the Ni_2P/Al_2O_3 catalyst was found to exhibit higher selectivity to styrene (up to 88%) than $Ni_{12}P_5/Al_2O_3$ (48%), NiP_2/Al_2O_3 (66%), and Ni/Al_2O_3 (1%) catalysts. EXAFS and in situ IR measurements revealed that the incorporation of P increases the bond length of Ni−Ni, which imposes a key influence on the adsorption state of alkene intermediates: as the Ni−Ni bond length extends to 0.264 nm, the alkene intermediate undergoes di-π(C=C) adsorption, facilitating its desorption and the resulting enhanced selectivity. They further noted that electron transfer occurs from Ni to P, as confirmed by EXAFS, XPS, and in situ CO-IR experiment, in which the positively charged Ni reduces the desorption energy of alkene and thus improves the reaction selectivity.

In this study, we demonstrate a systematic study on the effects of phase, size, shape, oxidation state and preparation method of Ni_2P nanocrystals on its catalytic activity toward hydrogenation of phenylacetylene. We further discuss the effect of recycling on the catalyst surface through characterization of recycled Ni_2P nanocrystals via powder XRD, TEM AND XPS analyses.

5.3 Results and Discussion

5.3.1 Nanocrystalline Ni_2P synthesized from $NiCl_2$ and $Ni(OAc)_2$

Nanocrystalline Ni_2P was synthesized by injecting an organophosphite precursor into a solution containing a nickel(II) source (chloride and acetate) and oleylamine in 1-octadecene (ODE) at 275 °C.[9] The phase, size and shape of the isolated nickel phosphide nanocryatals were determined using powder X-ray diffraction (XRD) and transmission electron microscopy (TEM).

Nickel phosphide nanocrystals synthesized from both nickel chloride and nickel acetate showed formation of Ni_2P through XRD analysis (Table 5.1). TEM images revealed that Ni_2P obtained from nickel acetate are hollow particles with 29 ± 6 nm diameter and Ni_2P obtained from nickel chloride showed bimodal distribution with the presence of both solid (14 ± 3 nm) and hollow particles (58 ± 5 nm).

Figure 5.1 represents the unit cell of Ni_2P. The crystal structure of Ni_2P is similar to that of Fe_2P with space group P62m. The hexagonal unit cell contains two types of Ni atoms: Ni(I) of tetrahedral coordination and Ni(II) of square pyramidal coordination. There are two surfaces, Ni_3P_2 and Ni_3P_1 terminated.

Table 5.1 Selected properties of nanocrystalline Ni_2P synthesized from $NiCl_2$ and $Ni(OAc)_2$ as Ni(II) precursors

Entry	Ni(II) precursor	Shape	Size (nm)		XPS
			TEM	XRD	
1	$NiCl_2$	Solid	14 ± 3	17 ± 4	Ni_2P
		Hollow	58 ± 5		
2	$Ni(OAc)_2$	Hollow	29 ± 6	17 ± 2	Ni_2P

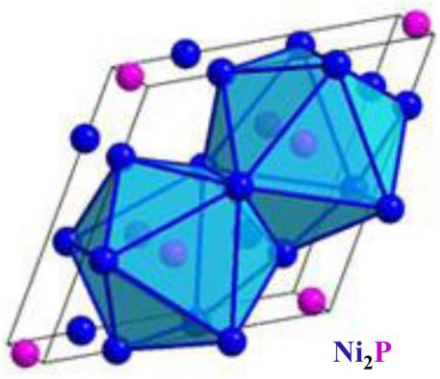


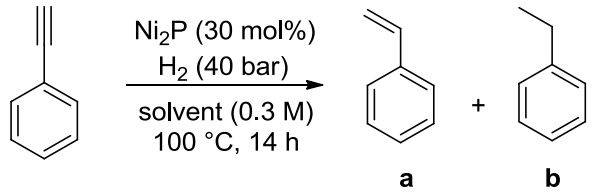
Figure 5.1 Unit cell of Ni_2P nanocrystal

5.3.2 Shape- and Size-dependant catalytic activity of Ni_2P nanocrystals toward hydrogenation of plenylacetylene

To test the catalytic activity of Ni_2P nanocrystals, we conducted hydrogenation reactions of phenylacetylene in presence of 30 mol% Ni_2P (solid+hollow nanocrystals, synthesized from $NiCl_2$) and 40 bar hydrogen pressure at 100 °C for 14 h in two different solvents (1,4-dioxane and 1-propanol) (Table 5.2). The hydrogenation reaction carried out in 1,4-dioxane formed 23% styrene and 5% ethylbenzene (28% total yield with 4.6:1 selectivity for styrene:ethylbenzene). To test if the Ni_2P nanocrystals used in trial 1 could be recycled for another reaction, we isolated the crystalline Ni_2P from the reaction mixture by centrifugation and subjected it to another hydrogenation reaction under identical reaction conditions. Trial 2 in 1,4-dioxane showed formation of 63% styrene and 7% ethylbenzene thus increasing the total yield (**a**+**b**) to 69% and selectivity towards styrene to 9:1. Due to the apparent increase in catalytic activity of Ni_2P on recycling, we further recycled the same Ni_2P for one more trial (trial 3). In trial 3, we observed formation of 47% styrene and 20% ethylbenzene thus reducing the selectivity toward formation of styrene to 2.3:1.

A similar trend in activity of Ni_2P was observed when the hydrogenation of phenylacetylene was carried out in 1-propanol as solvent under otherwise identical reaction conditions. While trial 1 in 1-propanol formed 34% styrene and 4% ethylbenzene (38% total yield with 8.5:1 selectivity for styrene:ethylbenzene), the total yield in trial 2 was increased to 71%. However, selectivity of the reaction decreased with formation of an almost equal mixture of styrene and ethylbenzene. Selectivity was completely lost in trial 3 as ethyl benzene was generated as the only product in 72% yield.

Table 5.2 Hydrogenation of phenylacetylene catalyzed by Ni_2P (solid+hollow)



Trial	1,4-Dioxane			1-Propanol		
	Conv (%)	Total yield (**a**+**b**) (%)	**a**:**b**	Conv (%)	Total yield (**a**+**b**) (%)	**a**:**b**
1	40	28	4.6:1	99	38	8.5:1
2	99	69	9:1	99	71	1:1.1
3	99	67	2.3:1	99	72	0:1

To confirm the integrity of the catalyst after three trials, XRD, TEM and XPS analyses of the isolated solid catalysts were performed and their results are tabulated in Table 5.3. Nanocrystals isolated after trial 3 in both 1,4-dioxane and 1-propanol were confirmed to be Ni_2P by XRD analyses (Figure 5.3). Analysis of TEM images still showed bimodal distribution comprised of solid and hollow particles in both cases (Figure 5.2). However, the hollow particles present in Ni_2P nanocrystals isolated from reactions in both 1,4-dioxane and 1-propanol showed reduced particle size (Table 5.3, compare entries 2 and 3 with entry 1). Moreover, XPS analyses (Figure 5.4, Table 5.4) indicated presence of Ni^{2+} species on the catalyst surface along with Ni_2P (Table 5.3, see entries 2 and 3).

Table 5.3 Selected properties of nanocrystalline Ni_2P before and after hydrogenation reaction of phenylacetylene

Entry	Ni_2P	Shape	Size (nm)		XPS (Oxidation state)
			TEM	XRD	
1	Before trial 1	Solid	14 ± 3	17 ± 4	Ni_2P
		Hollow	58 ± 5		
2	After trial 3 (1,4-dioxane)	Solid	17 ± 2	21 ± 2	Ni_2P, Ni^{2+}
		Hollow	37 ± 6		
3	After trial 3 (1-propanol)	Solid	16 ± 3	22 ± 6	Ni_2P, Ni^{2+}
		Hollow	40 ± 7		

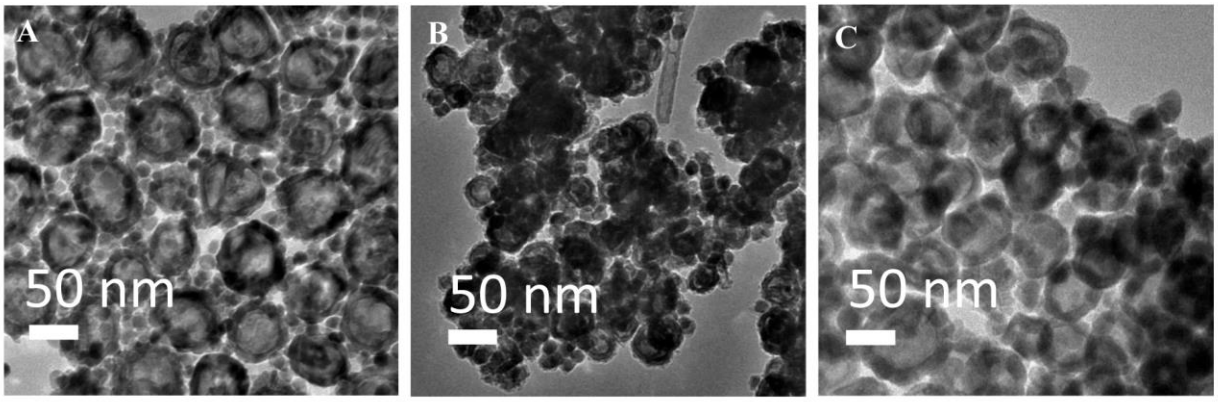


Figure 5.2 TEM images of A) Ni_2P B) Ni_2P after trial 3 in 1,4-dioxane C) Ni_2P after trial 3 in 1-propanol

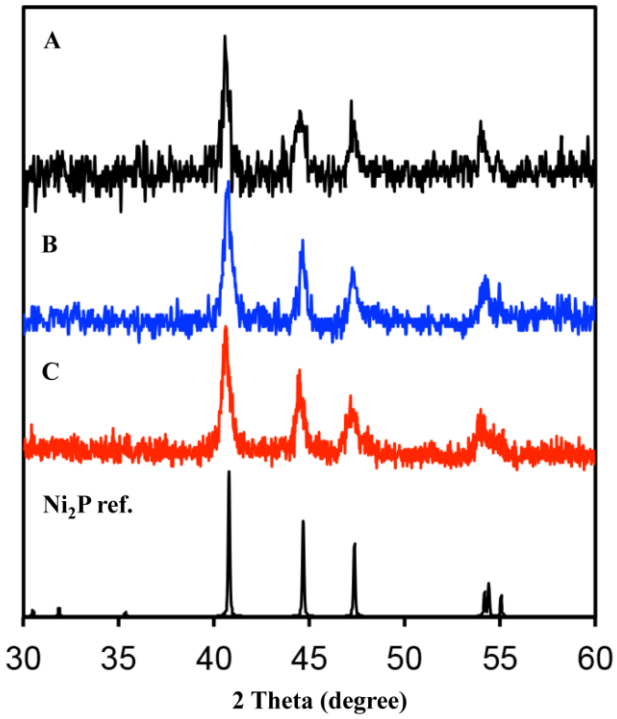


Figure 5.3 Powder XRD patterns of A) Ni_2P B) Ni_2P after trial 3 in 1,4-dioxane C) Ni_2P after trial 3 in 1-propanol

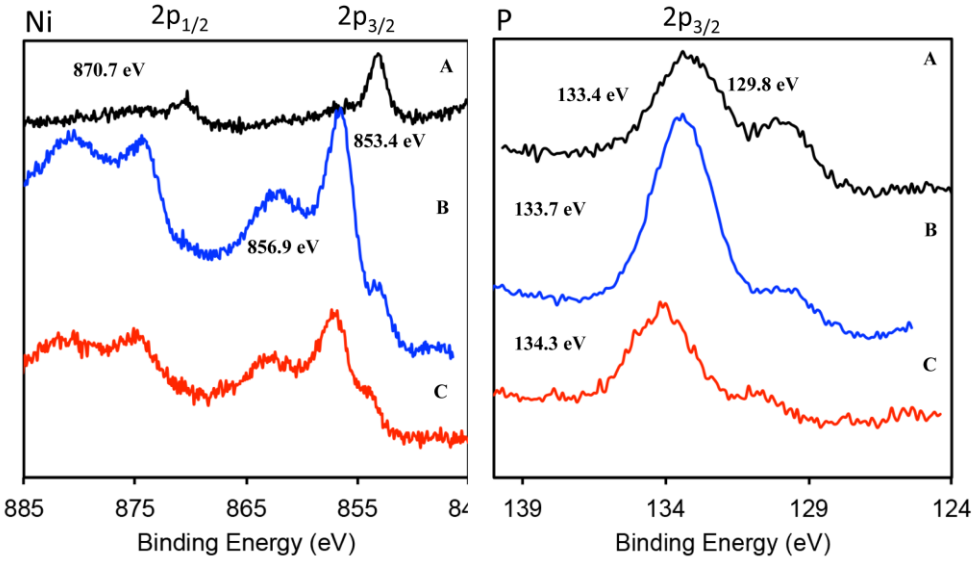


Figure 5.4 XPS of A) Ni_2P B) Ni_2P after trial 3 in 1,4-dioxane C) Ni_2P after trial 3 in 1-propanol

Table 5.4 Chemical state-Binding energy (eV) correlation chart

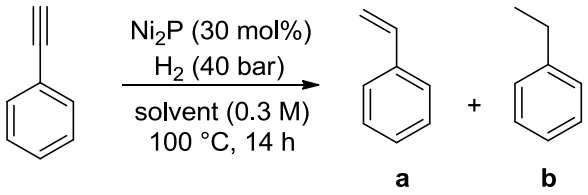
Chemical State	Binding Energy Ni $2p_{3/2}$ (eV)	Binding Energy P $2p_{3/2}$ (eV)
Ni_2P	852.9	--
NiO	853.7	--
$Ni(OH)_2$	855.6	--
Metal phosphide	--	~129
Metal phosphate	--	~133

5.3.3 Systematic study of Ni_2P nanocrystals through recycling reactions: Effect of recycling on shape, size and oxidation state of Ni_2P nanocrystals

To investigate the impact of shape of the Ni_2P nanocrystals on its catalytic activity, we conducted hydrogenation reactions of phenylacetylene in the presence of 30 mol% Ni_2P nanocrystals (hollow nanocrystals, synthesized from $Ni(OAc)_2$) and 40 bar hydrogen pressure at 100 °C for 14 h in two different solvents (1,4-dioxane and 1-propanol) (Table 5.5). In both solvents, 1,4-dioxane and 1-propanol, Ni_2P nanocrystal was recycled for 8 times.

Trials 1 and 2 of the hydrogenation of phenylacetylene in 1,4-dioxane generated a mixture of styrene and ethylbenzene (entries 1 and 2). While styrene was the major product in first trial, ethyl benzene was the major product (89% yield) in trial 2 (1:15 styrene: ethylbenzene). In trial 3 through trial 8, ethyl benzene was formed as the only product in consistently high yields (83-89% yields).

Table 5.5 Recyclability of Ni_2P nanocrystal (hollow nanocrystals, synthesized from $Ni(OAc)_2$) catalyst in hydrogenation of phenylacetylene



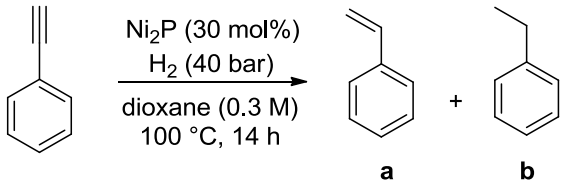
Trial	1,4-Dioxane			1-Propanol		
	Conv (%)	Total yield (**a**+**b**) (%)	**a**:**b**	Conv (%)	Total yield (**a**+**b**) (%)	**a**:**b**
1	99	55	6.9:1	99	58	3.8:1
2	99	95	1:15	99	96	0:1
3	99	87	0:1	99	77	0:1
4	99	86	0:1	99	68	0:1
5	99	85	0:1	99	68	0:1
6	99	83	0:1	99	63	0:1
7	99	83	0:1	99	55	0:1
8	99	89	0:1	99	59	0:1

Hydrogenation of phenylacetylene in 1-propanol in the presence of hollow, nanocrystalline Ni_2P generated 46% styrene and 12% ethylbenzene in the first trial (58% total yield, 3.8:1 styrene:ethylbenzene). In trial 2 through trial 8, the hydrogenation of phenylacetylene yielded ethylbenzene as the only product. While ethylbenzene was formed in 96% yield in trial 2, the yield of the product decreased progressively from 96% to 55% from trial 2 through trial 8.

To investigate any modification of the hollow, nanocrystalline catalyst surface during recycling, we conducted multiple identical hydrogenation reactions of phenylacetylene in

the presence of hollow Ni_2P catalysts in both 1,4-dioxane and 1-propanol. Nanocrystalline Ni_2P catalysts were isolated after each trial from trial 1 through trial 4 for reactions in both solvents (Table 5.6 & Table 5.8) and the isolated Ni_2P catalysts were subjected to XRD, TEM and XPS analyses. The results of TEM, PXRD, XPS analyses of Ni_2P nanocrystals isolated after trials 1 through 4 in 1,4-dioxane are tabulated in Table 5.7. The results of TEM, PXRD, XPS analyses of Ni_2P nanocrystals isolated after trials 1 through 4 in 1-propanol are tabulated in Table 5.9. Analysis of TEM images of Ni_2Ps isolated from reactions in both 1,4-dioxane and 1-propanol demonstrated sole presence of hollow Ni_2P (Figures 5.5 & 5.8, Tables 5.7 & 5.9). However, these hollow Ni_2P nanocrystals isolated after reactions in 1,4-dioxane and 1-propanol showed reduced particle size (Tables 5.7 & 5.9). Moreover, XPS analyses indicated presence of Ni^{2+} species along with Ni_2P in the nanocrystals isolated after hydrogenation reaction (Table 5.7, refer Table 5.4 for chemical state-binding energy correlation chart).

Table 5.6 Hydrogenation of phenyl acetylene in 1,4-dioxane



Entry	Trial	Conv (%)	**a** (%)	**b** (%)	Total Yield (%)	**a**:**b**
1	1	99	49	6	55	8.2:1

- Ni_2P isolated after trial 1 is subjected to PXRD, TEM and XPS analyses

Entry	Trial	Conv (%)	**a** (%)	**b** (%)	Total Yield (%)	**a**:**b**
2	1	99	67	3	70	22:1
	2	99	0	84	84	0:1

- Ni_2P isolated after trial 2 is subjected to PXRD, TEM and XPS analyses

Entry	Trial	Conv (%)	**a** (%)	**b** (%)	Total Yield (%)	**a**:**b**
3	1	99	46	16	62	2.9:1
	2	99	0	88	88	0:1
	3	99	0	86	86	0:1

- Ni_2P isolated after trial 3 is subjected to PXRD, TEM and XPS analyses

Entry	Trial	Conv (%)	**a** (%)	**b** (%)	Total Yield (%)	**a**:**b**
4	1	99	63	12	75	5.3:1
	2	99	0	89	89	0:1
	3	99	0	88	88	0:1
	4	99	0	85	85	0:1

- Ni_2P isolated after trial 4 is subjected to PXRD, TEM and XPS analyses

Table 5.7 Selected properties of nanocrystalline Ni_2P before and after hydrogenation reaction of phenylacetylene in 1,4-dioxane

Entry	Ni_2P	Shape	Size (nm)		XPS (Oxidation state)
			TEM	XRD	
1	Before trial 1	Hollow	29 ± 6	17 ± 2	Ni_2P
2	After trial 1	Hollow	27 ± 3	12 ± 1	Ni_2P, Ni^{2+}
3	After trial 2	Hollow	28 ± 4	15 ± 1	Ni_2P, Ni^{2+}
4	After trial 3	Hollow	22 ± 4	10 ± 1	Ni_2P, Ni^{2+}
5	After trial 4	Hollow	28 ± 5	12 ± 1	Ni_2P, Ni^{2+}

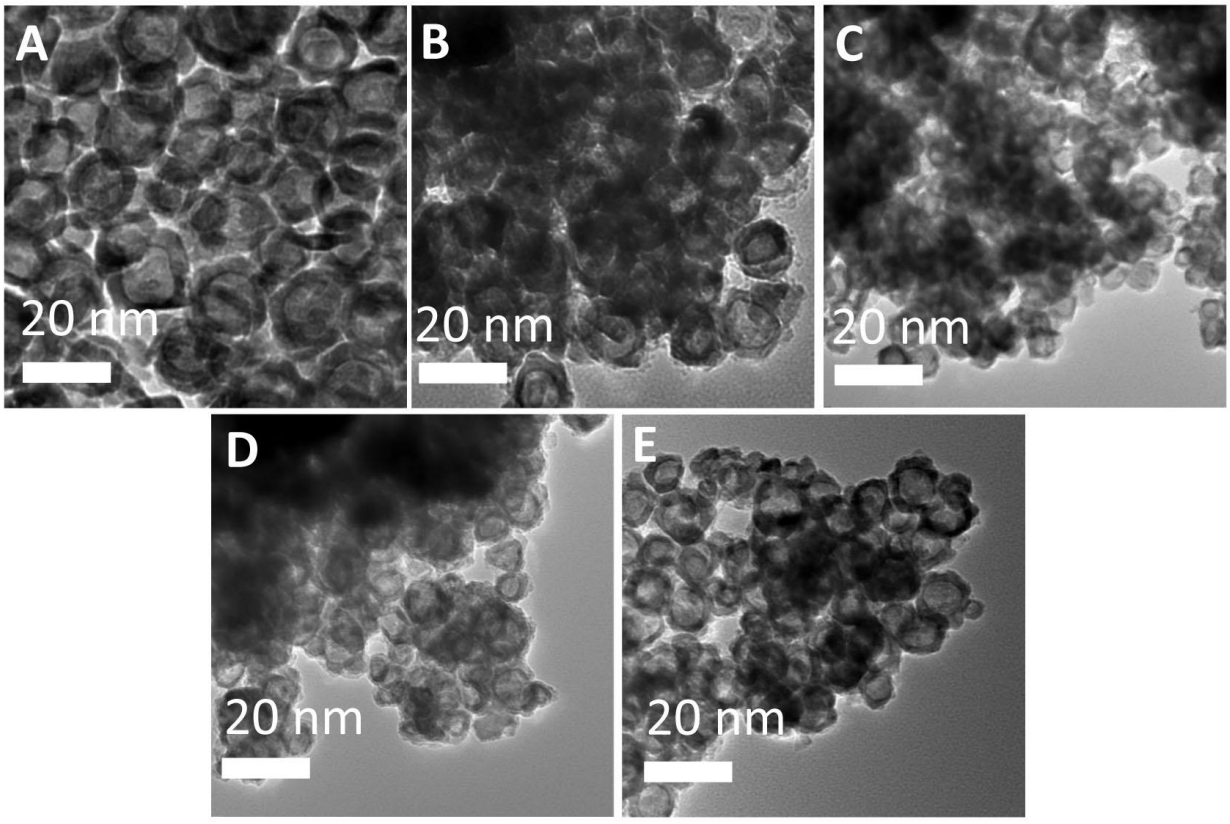


Figure 5.5 TEM images of A) Ni_2P B) Ni_2P after trial 1 C) Ni_2P after trial 2 D) Ni_2P after trial 3 E) Ni_2P after trial 4 in 1,4-dioxane

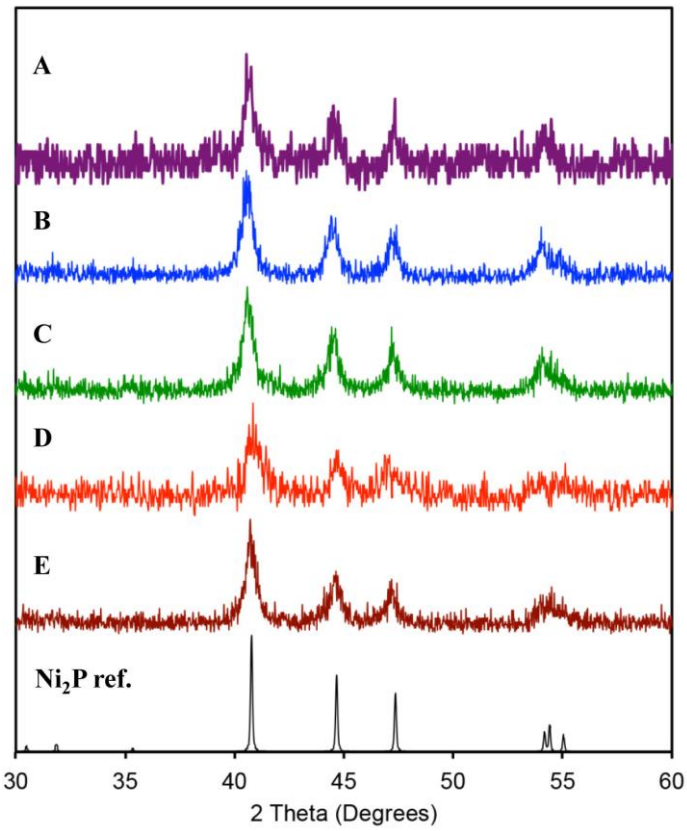


Figure 5.6 Powder XRD patterns of A) Ni_2P B) Ni_2P after trial 1 C) Ni_2P after trial 2 D) Ni_2P after trial 3 E) Ni_2P after trial 4 in 1,4-dioxane

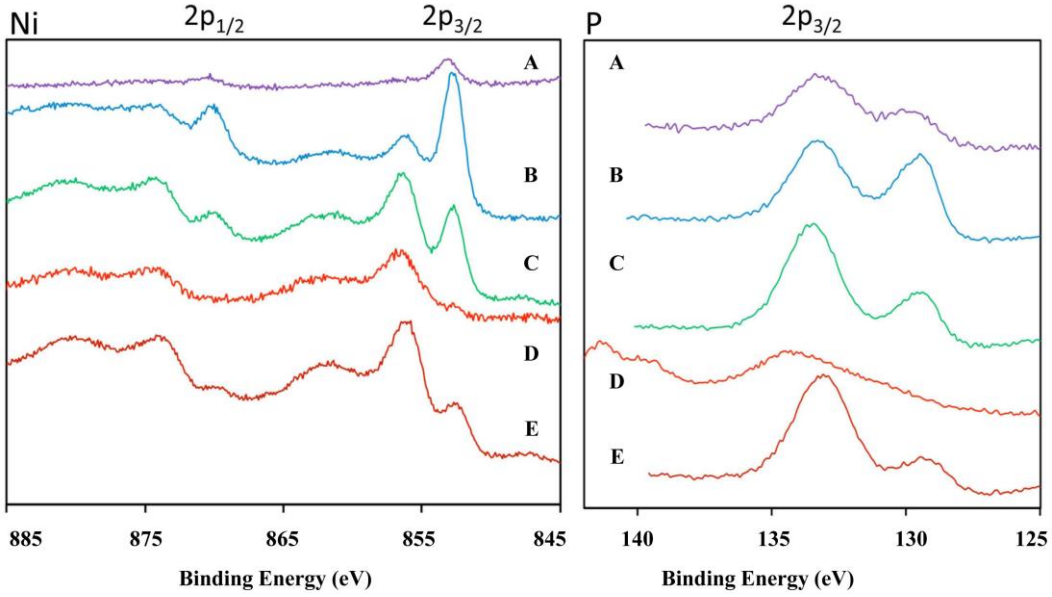
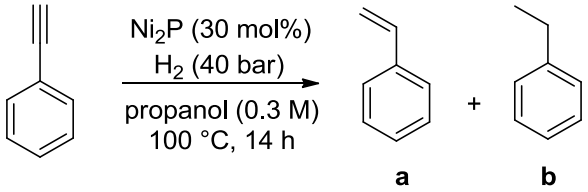


Figure 5.7 XPS of A) Ni_2P B) Ni_2P after trial 1 C) Ni_2P after trial 2 D) Ni_2P after trial 3 E) Ni_2P after trial 4 in 1,4-dioxane

Table 5.8 Hydrogenation of phenyl acetylene in 1-propanol



Entry	Trial	Conv (%)	**a** (%)	**b** (%)	Total Yield (%)	**a**:**b**
1	1	99	44	15	59	3:1

- Ni_2P isolated after trial 1 is subjected to PXRD, TEM and XPS analyses

Entry	Trial	Conv (%)	**a** (%)	**b** (%)	Total Yield (%)	**a**:**b**
2	1	99	41	25	66	1.6:1
	2	99	0	80	80	0:1

- Ni_2P isolated after trial 2 is subjected to PXRD, TEM and XPS analyses

Entry	Trial	Conv (%)	**a** (%)	**b** (%)	Total Yield (%)	**a**:**b**
3	1	99	45	8	53	5.6:1
	2	99	0	70	70	0:1
	3	99	0	66	66	0:1

- Ni_2P isolated after trial 3 is subjected to PXRD, TEM and XPS analyses

Entry	Trial	Conv (%)	**a** (%)	**b** (%)	Total Yield (%)	**a**:**b**
4	1	99	43	10	53	4.3:1
	2	99	0	81	81	0:1
	3	99	0	66	66	0:1
	4	99	0	62	62	0:1

- Ni_2P isolated after trial 1 is subjected to PXRD, TEM and XPS analyses

Table 5.9 Selected properties of nanocrystalline Ni_2P before and after hydrogenation reaction of phenylacetylene in 1-propanol

Entry	Ni_2P	Shape	Size (nm)		XPS (Oxidation state)
			TEM	XRD	
1	Before trial 1	Hollow	29 ± 6	17 ± 2	Ni_2P
2	After trial 1	Hollow	30 ± 7	15 ± 1	Ni_2P, Ni^{2+}
3	After trial 2	Hollow	28 ± 4	15 ± 2	Ni_2P, Ni^{2+}
4	After trial 3	Hollow	27 ± 4	13 ± 1	Ni_2P, Ni^{2+}
5	After trial 4	Hollow	24 ± 4	11 ± 2	Ni_2P, Ni^{2+}

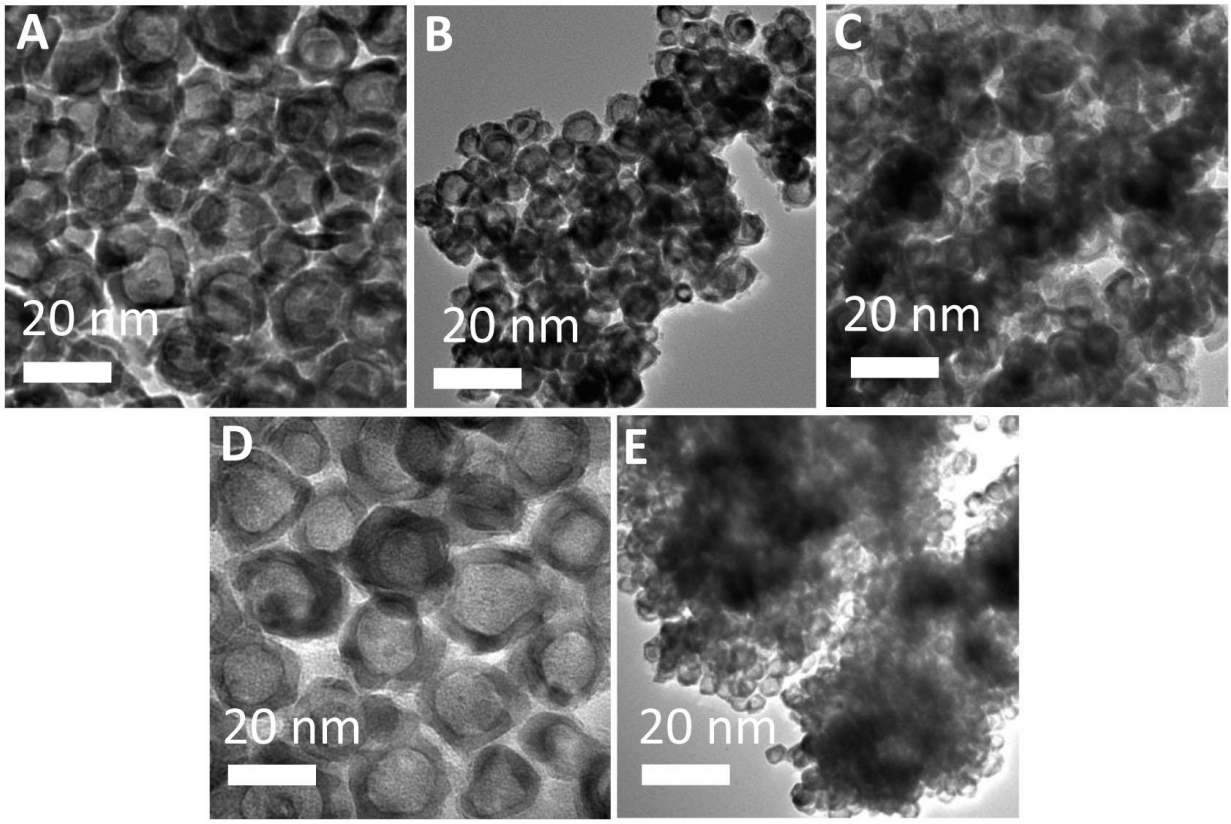


Figure 5.8 TEM images of A) Ni_2P B) Ni_2P after trial 1 C) Ni_2P after trial 2 D) Ni_2P after trial 3 E) Ni_2P after trial 4 in 1-propanol

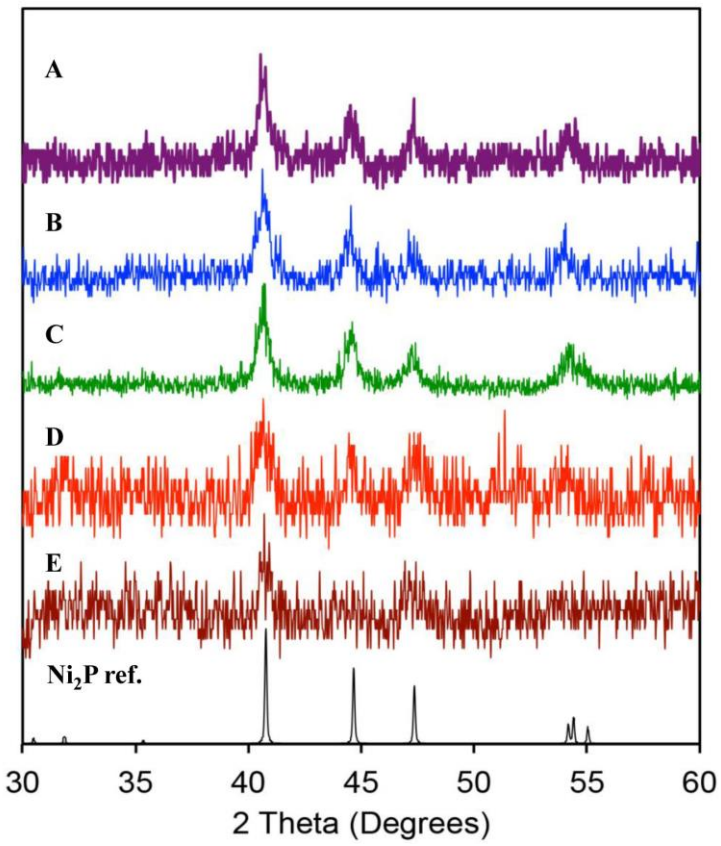


Figure 5.9 Powder XRD patterns of A) Ni_2P B) Ni_2P after trial 1 C) Ni_2P after trial 2 D) Ni_2P after trial 3 E) Ni_2P after trial 4 in 1-propanol

5.4 Conclusions

In conclusion, we have studied hydrogenation of phenylacetylene catalyzed by Ni_2P nanocrystals at 100 °C with 40 bar H_2 as a function of size and shape of Ni_2P nanocrystals in 1,4-dioxane and 1-propanol. Recycling studies in both solvents demonstrated an increase in catalytic activity of Ni_2P nanocrystals toward hydrogenation of phenylacetylene over reaction cycles. Structural characterization of recycled Ni_2P nanocrystals via powder XRD, TEM and XPS analyses revealed reduction in the size of hollow nanoparticles along with the formation of Ni(II) species after hydrogenation reaction. Systematic characterization of Ni_2P nanocrystals isolated after each reaction throughout the lifetime of the recycling study

(in both 1,4-dioxane and 1-propanol) has been completed using powder XRD, TEM and XPS analytical techniques and in most cases, reduction in size of the hollow Ni_2P nanocrystal has been observed after hydrogenation of phenylacetylene reactions. Hydrogenation of phenylacetylene in 1,4-dioxane catalyzed by Ni_2P nanocrystal has been recycled up to 8 times without any significant loss in reactivity. However, hydrogenation of phenylacetylene in 1-propanol catalyzed by Ni_2P nanocrystal demonstrated steady drop in the yield of product over recycling. Use of $NiCl_2$ as precursor for synthesis of Ni_2P nanocrystal generated a mixture of solid and hollow Ni_2P nanocrystal, while $Ni(OAc)_2$ precursor exclusively forms hollow Ni_2P nanocrystal having smaller particle size as compared to the ones synthesized from $NiCl_2$. These smaller, hollow Ni_2P nanocrystals obtained from $Ni(OAc)_2$ as nickel precursor, has been shown to be catalytically more active than the mixture of solid and hollow Ni_2P nanocrystals as synthesized from $NiCl_2$ as nickel precursor.

5.5 Experimental details

5.5.1 Materials

Nickel(II) chloride hexahydrate, triphenylphosphite were purchased from Strem chemicals; 1-octadecene (ODE, 90%) and oleylamine (80−90%) from Acros organics; and nickel(II) acetate, phenyl acetylene, styrene, ethyl benzene and dodecane from Sigma-Aldrich. All compounds were used as received and handled under an inert (dry N_2 or Ar) atmosphere inside a glovebox or with a Schlenk line.

5.5.2 Nanocrystal synthesis

5.5.2.1 *Phosphite addition solution.* Inside a glovebox filled with dry N_2, 0.11 mL of $P(OPh)_3$ was thoroughly dissolved in ODE (1.00 g, 1.27 mL).

5.5.2.2 *General procedure for nanocrystal synthesis*. Inside a three-neck flask, $NiCl_2 \cdot 6H_2O$ (26 mg, 0.10 mmol) or $Ni(OAc)_2$ (18 mg, 0.10 mmol), oleylamine (270 mg, 1.00 mmol, 0.33 mL), and ODE (5.00 g, 6.34 mL) were degassed under vacuum at 80 °C for 1 h, refilled with Ar, and heated to 275 °C. After 5 min, the organophosphite addition solution was quickly injected and stirred at this temperature for 1 h. The mixture was allowed to cool to room temperature, and nanocrystalline products were isolated by washing with toluene for two times and centrifugation at 4900 rpm for 5 min.

5.5.4 Structural characterization

Powder X-ray Diffraction (XRD) was measured using Cu Kα radiation on a Scintag XDS-2000 diffractometer. Transmission Electron Microscopy (TEM) was conducted on carbon-coated copper grids using a FEI Technai G2 F20 field emission scanning transmission electron microscope (STEM) at 200 kV (point-to-point resolution <0.25 nm, line to line resolution <0.10 nm). Particle dimensions were measured manually and/or with ImageJ for >50−100 particles. Averages are reported ± one standard deviation.

5.5.3 Procedure for hydrogenation of phenylacetylene catalyzed by Ni_2P nanocrystals

5.5.3.1 *General procedure*. In a nitrogen-filled glovebox, Ni_2P nanocrystals (13.4 mg, 0.090 mmol, 0.30 equiv), phenylacetylene (30.7 mg, 0.300 mmol, 1.00 equiv), a magnetic stirring bar, and 1,4-dioxane (1.0 mL) or 1-propanol (1.0 mL) were added to a 20 mL vial. The vial

was sealed with a PTFE septum and removed from the glovebox. The septum was pierced with a 20-gauge needle and quickly placed in a pressure reactor. The pressure reactor was sealed and pressurized with hydrogen gas at 40 bar. The pressure reactor was placed in a pre-heated oil bath at 100 °C and the reaction mixture was stirred at the same temperature for 14 h. The pressure reactor was removed from oil bath after 14 h of stirring and cooled to room temperature. Once it reached room temperature, the hydrogen gas was released and the reaction vial was removed from the reactor. Dodecane (22.6 µL, 0.30 mmol) was added to the reaction mixture as an internal standard. 3.0 mL 1,4-dioxane or 1-propanol was added to the reaction mixture and stirred at room temperature for 5 min. The reaction mixture was centrifuged for 15 min at 5000 rpm and the supernatant liquid was injected for gas chromatographic (GC) analysis. The conversion of phenylacetylene and yields of styrene and ethylbenzene were calculated from the relative area of dodecane and analyte using a GC calibration curve.

5.5.3.2 *Procedure for recycling reactions.* In a nitrogen-filled glovebox, Ni_2P nanocrystals (13.4 mg, 0.090 mmol, 0.30 equiv), phenylacetylene (30.7 mg, 0.300 mmol, 1.00 equiv), a magnetic stirring bar, and 1,4-dioxane (1.0 mL) or 1-propanol (1.0 mL) were added to a 20 mL vial. The vial was sealed with a PTFE septum and removed from the glovebox. The septum was pierced with a 20-gauge needle and quickly placed in a pressure reactor. The pressure reactor was sealed and pressurized with hydrogen gas at 40 bar. The pressure reactor was placed in a pre-heated oil bath at 100 °C and the reaction mixture was stirred at the same temperature for 14 h. The pressure reactor was removed from oil bath after 14 h of stirring and cooled to room temperature. Once it reached room temperature, the hydrogen

gas was released and the reaction vial was removed from the reactor. Dodecane (22.6 µL, 0.30 mmol) was added to the reaction mixture as an internal standard. 3.0 mL 1,4-dioxane or 1-propanol was added to the reaction mixture and stirred at room temperature for 5 min. The reaction mixture was centrifuged for 15 min at 5000 rpm and the supernatant liquid was injected for gas chromatographic (GC) analysis. The conversion of phenylacetylene and yields of styrene and ethylbenzene were calculated from the relative area of dodecane and analyte using a GC calibration curve. The solid catalyst was further washed with 3.0 mL solvent twice and isolated by centrifugation at 5000 rpm for 15 min. After removing the supernatant liquid, solid nanocrystals were used as catalyst for the next reaction in the same vial.

5.6 References

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CHAPTER 6

CONCLUSIONS AND OUTLOOK

About 59% of the U.S FDA approved unique small-molecule drugs possess nitrogen heterocycles. These nitrogen heterocycles are currently used to treat human disease ranging from cancer to diabetes to microbial infections. The prevalence of nitrogen heterocycles in medicinally important compounds continues to drive research into strategies to form new heterocyclic scaffolds and methods that streamline the syntheses of complex heterocycles.

To this end, we have developed catalytic, enantioselective intramolecular hydroacylation of *N*-vinylindole-2-carboxaldehydes in the presence of a readily accessible rhodium catalyst and form chiral, non-racemic dihydropyrroloindolones in high yields with excellent enantioselectivities. These reactions encompass a broad range of *N*-vinylindole-2-carboxaldehydes bearing a variety of aryl and alkyl substituents on the olefin moiety and substitution throughout the indole core. In addition, catalyst loadings can be lowered to 0.2 mol % with only modest impact on the yield and no impact on the enantioselectivity of the hydroacylations. This methodology could be extended to hydroacylations of *N*-allylindole- and *N*-allylpyrrole-2-carboxaldehydes in construction of six-membered rings that generates dihydropyridoindolones and dihydroindolizinones in moderate to high yields with excellent enantioselectivities. This study represents a rare example of alkene hydroacylation to generate nitrogen heterocycles and, to our knowledge, is only the first report of enantioselective alkene hydroacylation to generate chiral, non-racemic nitrogen heterocycles. More importantly, these hydroacylation reactions can be extended to the formation of six-membered nitrogen heterocycles in the absence of chelating functionality

within the substrates or introduced through additives. Additionally, these dihydropyrroloindolone and dihydropyridoindolone products can be readily transformed to dihydropyrroloindoles and dihydropyridoindoles that are core structures present in a variety of natural products and biologically relevant compounds. We believe the ability to form nitrogen heterocycles and medium-sized rings by alkene hydroacylation in the absence of chelation assistance will be of great interest to the chemistry community, and the knowledge gained on catalyst design principles will extend to additional systems and will significantly expand the classes of ketones accessible by alkene hydroacylation.

We have also demonstrated the first enantioselective model synthesis of the 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole core present in the putative structure of yuremamine. The 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole core containing three contiguous stereogenic centers was synthesized in 39% overall yield and 96% ee in 5 steps. The model synthesis leverages enantioselective, rhodium-catalyzed hydroacylation of an *N*-vinylindole-2-carboxaldehyde as the key step in the installation of the stereochemical triad. The ketone functionality present in the hydroacylation product served as a synthetic handle for the installation of additional stereogenic centers with precise control of absolute and relative stereochemistry. Progress toward enantioselective synthesis of the putative structure of yuremamine is also reported, and the enantioselective synthesis of a densely functionalized dihydropyrroloindolone core that maps onto its structure has been demonstrated in 26% yield and 97% ee over 8 steps. The synthetic strategy is likely to be amenable to synthesis of other natural products containing a 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]-indole core and

highlights the utility of enantioselective hydroacylation reactions in the construction of complex molecular scaffolds.

Despite many advances over the past decades, enantioselective synthesis of quaternary stereogenic centers remains a significant synthetic challenge. In 2011, 12% of the top 200 prescription drugs sold in United States contained quaternary stereogenic centers and majority of these compounds are synthesized from naturally occurring compounds (steroids, opioids, taxane and diterpenoids) with the natural product precursor providing the quaternary stereogenic centers. To this end, we have developed a catalytic strategy that combines alkene hydroacylation with enantioselective α-(hetero)arylation reactions that construct a wide variety of nitrogen-containing heterocyclic ketones bearing α-chiral quaternary stereogenic centers. The first step in the sequential protocol involves intramolecular nickel-catalyzed hydroacylations of *N*-homoallylindole- and *N*-homoallylpyrrole-2-carboxaldehydes to form α-substituted six-membered heterocyclic ketones or *N*-heterocyclic carbene (NHC)-catalyzed hydroacylations to form α-substituted five-membered heterocyclic ketones with absolute *exo*-selectivity. The racemic five- and six-membered products of Ni- and NHC-catalyzed hydroacylation reactions are readily transformed into heterocyclic ketones containing an α-chiral quaternary stereogenic center by enantioselective Ni-catalyzed α-(hetero)arylation reactions. The chiral, non-racemic products of sequential alkene hydroacylation and α-(hetero)arylation reactions are formed in moderate-to-high yields with excellent enantioselectivities. In contrast to the previous studies on nickel-catalyzed α-arylation involving carbocyclic ketone starting materials, the identity of the precatalyst for Ni-catalyzed α-(hetero)arylation is dictated by the identity of the α-substituted five- or six-membered heterocyclic ketone starting material. We also demonstrate a one-pot

protocol for sequential alkene hydroacylation and α-arylation that generates the heterocyclic ketone product in good yield and high enantioselectivity. Due to the potential to further functionalize the remaining carbonyl moiety, we believe that this sequence of reactions is poised to serve as a strategic approach to the synthesis of complex chiral heterocycles possessing benzylic quaternary stereocenters.

In the final chapter, we have outlined a systematic study on the effects of phase, size, shape, oxidation state and preparation method of Ni_2P nanocrystals on its catalytic activity toward hydrogenation of phenylacetylene. We have further discussed the effect of recycling on the catalyst surface through characterization of recycled Ni_2P nanocrystals via powder XRD, TEM and XPS analyses.