Methods for alkene difunctionalizations: hydroacylation & carboacylation

by

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The student author and the program of study committee are solely responsible for the content of this dissertation. The Graduate College will ensure this dissertation is globally accessible and will not permit alterations after a degree is conferred.

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NOMENCLATURE

Ar	Aryl
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
Boc_2O	Di-*tert*-butyldicarbonate
CF_3	Trifluoromethyl
$CHCl_2$	Dichloromethane
CN	Cyano/nitrile
COD	1,5-cyclooctadiene
DBU	1,8-Diazabicyclo(5.4.0)undec-7-ene
DCM	Dichloromethane
dd	Doublet of Doublets
ddd	Doublet of Doublet of Doublets
ddt	Doublet of Doublet of Triplets
DMAP	Dimethylaminepyridine
DME	Dimethoxyethane
DMSO	Dimethyl Sulfoxide
DMF	Dimethyl Formamide
dq	Doublet of Quartets
dt	Doublet of Triplets
dtd	Doublet of Triplets of Doublets
EtOAc	Ethyl Acetate
HPLC	High Performance Liquid Chromatography

HRMS	High Resolution Mass Spectroscopy
IAD	1,3-Bis(1-adamantyl)imidazolium
IMes	1,3-Bis(2,4,6-trimethylphenyl)imidazolium
i-PrOH	*iso*-Propanol
I*t*Bu	1,3-Di-*t*-Butylimidazol-2-ylidene
m	Multiplet
MHz	Megahertz
NHC	*N*-heterocyclic Carbene
NMR	Nuclear Molecular Resonance
OTs	Tosylate
Ph	Phenyl
Pr	Propyl
q	Quartet
rac	Racemic
s	Singlet
t	Triplet
tBu	*tert*-Butyl
td	Triplet of Doublets
THF	Tetrahydrofuran
TLC	Thin-Layer Chromatography
tt	Triplet of Triplets
UV	Ultra-violet

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ABSTRACT

This thesis presents the development of new catalyst for the coupling of alkene hydroacylation and enantioselective *α*-arylation to form heterocyclic ketones containing *α*-chiral quarternary stereocenters, the *N*-heterocyclic carbene-catalyzed intramolecular hydroacylation to form basic nitrogen-containing heterocycles, and the first examples of nickel-catalyzed alkene carboacylation triggered by amide C-N bond activation.

Chapter II discusses a strategy that combines alkene hydroacylation and enantioselective *α*-arylation to form a wide variety of nitrogen-containing heterocyclic ketones bearing *α*-chiral quarternary stereogenic centers. *Exo*-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 quarternary stereogenic center by enantioselective Ni-catalyzed *α*-arylation and *α*-(hetero)arylation reactions. The chiral, nonracemic products formed through a combination of 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.

Chapter III describes the intramolecular hydroacylations of *N*-allylimidazole- 2-carboxaldehydes and *N*-allylbenzimidazole-2-carboxaldehydes. These *exo*-selective hydroacylations occur in the presence of a *N*-heterocyclic carbene catalyst to generate 5,6-dihydro-7*H*-pyrrolo[1,2-α]imidazol-7-ones and 1,2-dihydro-3*H*-benzo[*d*] pyrrolo[1,2-α]imidazol-2-ones in high yields (66–99%). In addition, hydroacylations of *N*-allylimidazole-2-carboxaldehydes in the presence of a chiral, non-racemic NHC catalyst occur, forming 5,6- dihydro-7*H*-pyrrolo[1,2-α]imidazol-7-ones in moderate-to-high yields (39–98%) with modest enantioselectivities (56–79% ee).

Chapter IV discusses nickel-catalyzed formal carboacylation of *ortho*-allylbenzamides with arylboronic acid pinacol esters. These carboacylation reactions are triggered by the oxidative addition of an activated amide C-N bond to a nickel(0) catalyst and proceed via alkene insertion into a nickel(II)-acyl bond. The *exo*-selective carboacylation reactions generate 2-benzyl-2,3-dihydro-1*H*-inden-1-ones in moderate-to-high yields (46-99%) from a variety of arylboronic acid pinacol esters and substituted *ortho*-allylbenzamides. These results demonstrate that amides are practical substrates for alkene carboacylation via activation of an amide C-N bond, and this approach bypasses challenges associated with alkene carboacylation triggered by C-C bond activation.

CHAPTER I

INTRODUCTION

Transition-metal catalyzed olefin functionalizations has been an important and essential component of modern synthetic organic chemistry.[1-6] This broad area of research encompasses reactions such as hydroacylation, carboacylation, polymerizations, metathesis, among many others.[1-6] In this thesis, fundamental principles of transition-metal catalysts and organocatalysts will be applied to the development of processes for the *endo*- and *exo-selective* hydroacylation of nitrogen-containing heterocycles and sequential enantioselective α-arylation, *N*-heterocylcic carbene catalyzed hydroacylation or *N*-allylimidazolecarboxaldehydes and *N*-allylbenzimidazolecarboxaldehyes and a new method for the formal carboacylation of *ortho*-allylbenzamides triggered by nickel-catalyzed activation of amide C-N bonds.

Nitrogen-containing heterocycles possessing quarternary stereogenic centers are common structural motifs present in biologically active natural products and small molecules.[7-18] Despite many advances over the past decades, enantioselective synthesis of quarternary stereogenic centers remain a significant synthetic challenge.[19-27] In 2011, 12% of the top 200 prescription drugs sole in the United States contained quarternary stereogenic centers.[27-28] However, the majority of these compounds are synthesized from naturally occurring compounds (steroids, opioids, taxane, and diterpenoids) with the natural product precursor providing the quarternary stereogenic centers.[27,29]

To address this issue we have developed a strategy to generate racemic five- and six-membered products of Ni- and NHC-catalyzed hydroacylation reactions. The generated products are readily transformed into heterocyclic ketones containing an α-chiral quarternary stereogenic center by enantioselective Ni-catalyzed α-arylation and α-(hetero)arylation reactions (Figure 1.) This thesis presents a method of sequential hydroacylation and α-arylation to generate nitrogen-

containing heterocycle containing all-carbon quaternary stereocenters in high yields (up to 99%) and enantioselectivities (typically >95% ee).

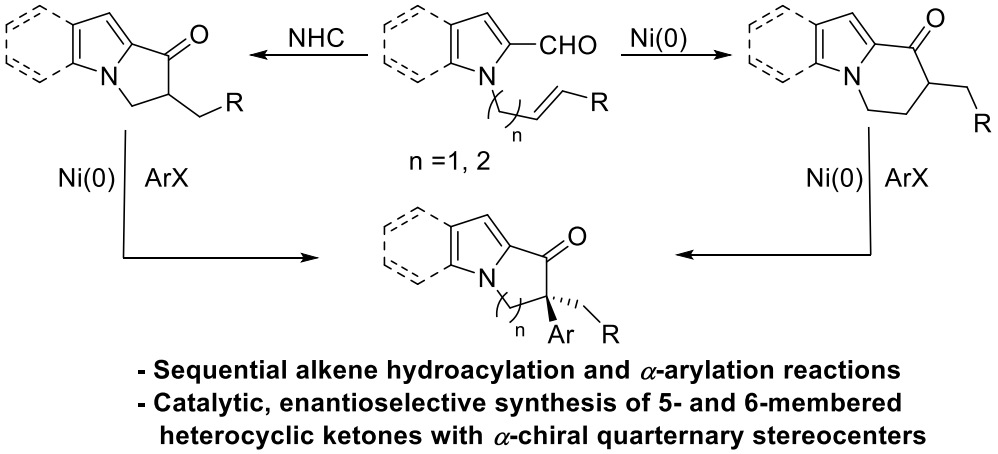


Figure 1. Coupling catalytic alkene hydroacylation and α-arylation reactions.

Intramolecular hydroacylation of alkenes in the presence of transition-metal catalysts are well-known processes to generate a variety of valuable cyclic ketones.[30-35] Transition metal-catalysed alkene hydroacylations to form and functionalize nitrogen-containing heterocycles, in many cases with high yields and enantioselectivities, have been the focus of recent studies to improve the synthetic utility of these important C-C bond forming processes.[36-40] However, alkene hydroacylations to form nitrogen heterocycles containing a basic nitrogen atom often do not occur in the presence of rhodium, cobalt, and nickel complexes that are excellent catalysts for alkene hydroacylation due to inhibition of the catalyst in the presence of basic nitrogen atoms.[36]

N-Heterocyclic carbenes (NHCs)[41-45] are a widely utilized class of organocatalysts and offer a promising alternative to transition-metal catalsyts for alkene hydroacylation reactions.[46-49] Key to our studies, NHCs have been shown to tolerate additives containing basic nitrogen atoms.[50] Building on reports from Glorius and co-workers (Figure 2.)[50-53] and a recent study from our laboratory[54] on NHC-catalyzed intramolecular hydroacylations of unactivated alkenes, this thesis describes the *exo*-selective intramolecular hydroacylation of basic nitrogen-containing

heterocycles. This NHC-catalyzed process generates 5,6-dihydro-7*H*-pyrrolo[1,2-α]imidazol-2-ones in high yields (66-99%). Additionally, hydroacylations of *N*-allylimidazole-2-carboxaldehydes in the presence of a chiral, non-racemic NHC catalyst occur, forming 5,6-dihydro-7*H*-pyrrolo[1,2-α]imidazol-7-ones in moderate-to-high yields (39-98%) with modest enantioselectivities (56-79% ee).

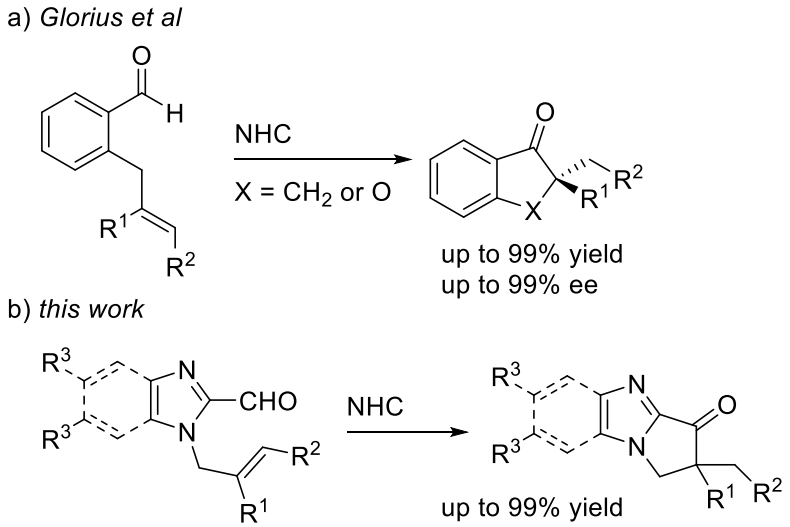
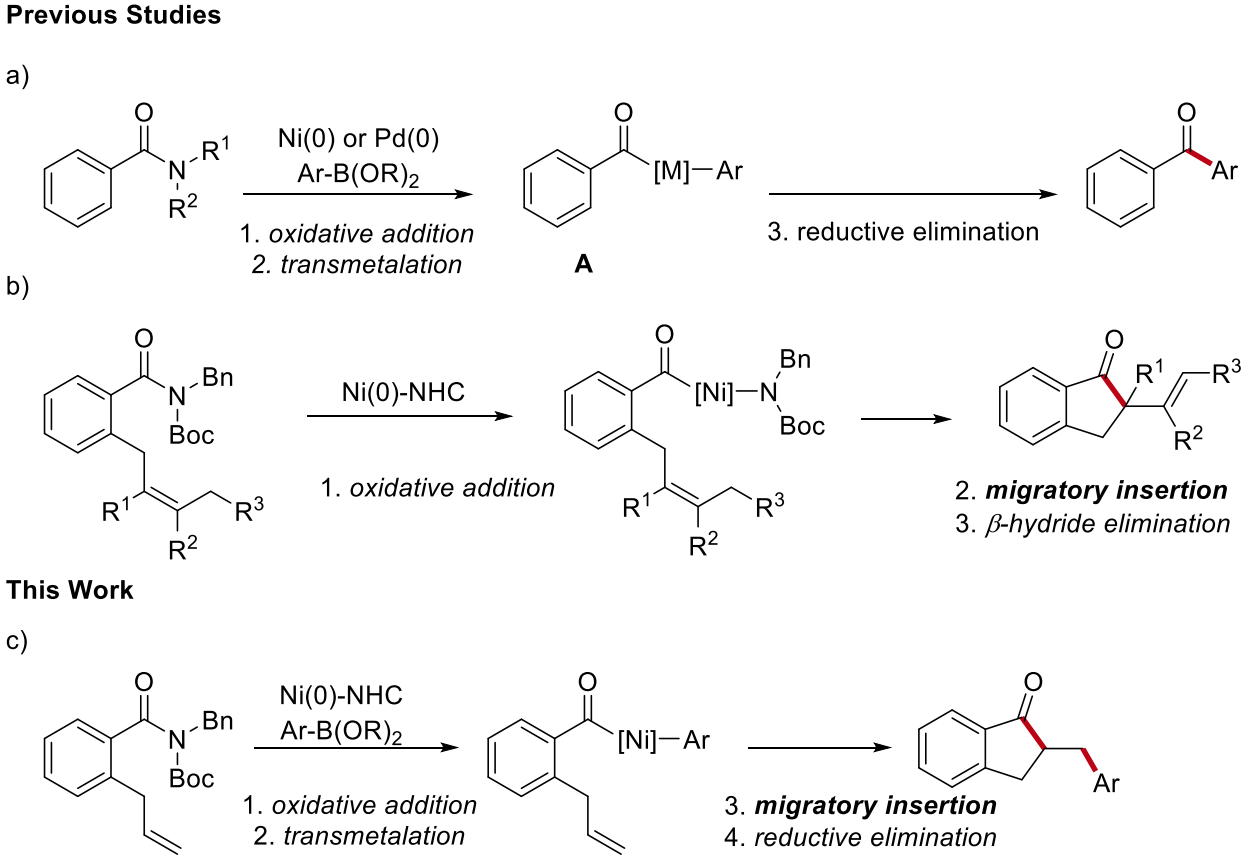


Figure 2. (a) NHC-catalyzed enantioselective intramolecular hydroacylations of unactivated alkenes and (b) NHC-catalyzed, exo-selective hydroacylation of *N*-allylimidazole and *N*-allylbenzimidazole-2-carboxaldehydes.

Carboacylation of alkenes in the presence of a transition-metal catalyst is an emerging reaction that enables the difunctionalization of an alkene with formation of two C-C σ-bonds.[55-70] Among the most studies and developed approaches to alkene carboacylation are reactions initiated by activation of a C-C σ-bond of a ketone. However, current methods are limited by the requirement of substrates containing either a quinolone directing group[56-57, 59, 61, 65] or a strained cyclic ketone.[60, 63-64, 66-69] The ability to perform alkene carboacylation reactions without a requirement for strained ketone substrates or substrates containing directing groups has the potential to expand the utility of these reactions with readily accessible substrates.[55, 58, 62, 70-75]

Scheme 1. Synthesis of Ketones via Transition Metal-Catalyzed Activation of Amide C-N Bonds



Recently, studies by a number of groups have demonstrated Suzuki-Miyaura coupling of benzamides with arylboron compounds to generate a variety of aromatic ketones.[76-87] The Suzuki-Miyaura-Type coupling reactions involve C-N activation of an activated benzamide via oxidative addition and transmetalation with an arylboron compound to generate acyl-metal-aryl intermediate **A** (Scheme 1a.). Subsequent reductive elimination forms a diary ketone. The ability to intercept acyl-metal intermediates with an alkene offers the potential to develop a new class of alkene functionalization reactions. During the course of our studies, Garg and co-workers reported Mizoroki-Heck cyclizations of *ortho*-allylbenzamides that involve insertation of an alkene into an acyl-nickel(II)-amido intermediate **B** (Scheme 1b).[88] Subsequent β-hydride elimination forms 2-vinylindanones containing a quarternary carbon center. This thesis describes carboacylation

reactions triggered by the oxidative addition of an activated amide C-N bond[76-87, 89-94] to a nickel (0) catalyst that proceed via alkene insertions into a nickel(II)-acyl bond (Scheme 1c). The *exo*-selective carboacylation reactions generate 2-benzyl-2,3-dihydro-1*H*-1-ones in moderate-to-high yields (46-99%) from a variety of arylboronic acid pinacol esters and substituted *ortho*-allylbenzamides. These results demonstrate that amides are practical substrates for alkene carbazcylaion via activation of an amide C-N bond, and this approach bypasses challenges associated with alkene carboacylation triggered by C-C bond activation.

Thesis Organization

This thesis is comprised of five chapters that contain work that has been published in peer-reviewed journals. Chapter I serves to introduce transition metal-catalyzed and organo catalytic methods development in the context of hydroacylation and carboacylation reactions. Chapter II is adapted from a paper published in *ACS* catalysis. Chapter III is adapted from a paper published in *Organic & Biomolecular Chemistry*. Chapter IV is adapted from a paper published in the *Journal of the American Chemical Society*. Chapter V serves as a general summary and conclusion of the presented research and proposes strategies to address the limitations that remain in some of the research projects described.

Chapter II describes the *exo*-selective, intramolecular nickel-catalyzed hydroacylation of *N*-homoallylindole- and *N*-homoallylpyrrole-2-carboxaldehydes and *N*-heterocyclic carbene-catalyzed hydroacylations of *N*-allylindole- and *N*-allylpyrrole-2-carboxaldehydes. In addition, the racemic five- and six-membered products of Ni- and NHC-catalyzed hydroacylation reactions were readily transformed into heterocyclic ketones containing an α-chiral quarternary stereogenic center by enantioselective Ni-catalyzed α-arylation and α-(hetero)arylation reactions. Chapter II is adapted from a paper published in *ACS Catalysis* in 2016. This work was accomplished in

collaboration with Avipsa Ghosh, also of the Stanley group. The author of this thiesis is responsible for the synthesis of indole substrates **1a**, **1c**, **1e**, **1h**, and pyrrole substrates **1m-p**. Additionally, the development of reaction conditions and scope of NHC-catalyzed hydroacylation of *N*-allylindole-2-carboxaldehyde and *N*-allylpyrrole-2-carboxaldehyde was completed by the author of this thesis. The screening of reaction conditions for the α-arylation of dihydropyrroloindolones and evaluation of the scope was completed by the author of this thesis. Avipsa Ghosh was responsible for the screening of reaction conditions for the nickel-catalyzed of hydroacylation *N*-homoallylindole-2-carboxaldehyde to generate dihydropyridoindolones, and the synthesis of compounds of **1b**, **1d**, **1f-g**, **1i-l**, and scope of the nickel-catalyzed hydroacylation. Additionally, Avipsa Ghosh was responsible for the screening of reaction conditions for Ni-catalyzed α-arylation of dihydropyridoindolones and the scope of the reactions. Lastly, Avipsa Ghosh screened reaction conditions for the α-heteroarylation of dihydropyrroloindolone, dihydropyridoindolone, dihydropyrrolizinone, and dihydroindolizinone, and the corresponding scope of the reaction.

Chapter III describes the NHC-catalyzed hydroacylation of *N*-allylimidazole-2-carboxaldehydes and *N*-allylbenzimidazole-2-carboxaldehydes, and is adapted from a paper published in *Organic and Biomolecular Chemistry* in 2016. This details the development of a intramolecular hydroacylation of basic nitrogen-containing heterocycles *N*-allylimidazole and *N*-allylbenzimidazole to generate 5,6-dihydro-7*H*-pyrrolo[1,2-α]imidazol-7-ones and 1,2-dihydro-3*H*-pyrrolo[1,2-α]imidazol-2-ones in high yields. Additionally, hydroacylations of *N*-allylimidazole-2-carboxaldehydes in the presence of a chiral, non-racemic NHC catalyst occur, forming 5,6-dihydro-7*H*-pyrrolo[1,2-α]imidazol-7-ones in moderate-to-high yields with modest enantioselectivities. The author of this thesis is responsible for all work reported in this chapter.

Chapter IV details the development of nickel-catalyzed formal carboacylation of *ortho*-allylbenzamides triggered by activation of amide C-N bond. The chapter is adapted from a paper published in the *Journal of the American Chemical Society* in 2017. This chapter demonstrates a new utility of amides for use in formal carboacylation reactions. Additionally, this demonstrates how this new method bypasses the limitations of traditional carboacylation reactions. We also propose a mechanistic cycle for the new reaction that is well supported by experimental data detailed in the manuscript. This work was accomplished in collaboration with Kevin Vickerman, a graduate student of the Stanley group, and Jenna Humke, an undergraduate researcher. Kevin Vickerman is responsible for the synthesis of arylboronate esters, and the carboacylation scope involving the arylboron compounds and characterization of products formed. Jenna Humke is responsible for assisting in the initial development of reaction conditions, and development of procedures to synthesize *ortho*-allylbenzamides. The author of this thesis is responsible for the synthesis and characterization of all *ortho*-allylbenzamides, development of reaction conditions, scope of *ortho*-allylbenzamides and characterization of products. The author of the thesis and Kevin Vickerman contributed equally to this published paper.

Chapter V discusses general conclusions from the work presented and proposes new directions for the continuation of this research in the Stanley lab.

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CHAPTER II

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

Modified from *ACS Catalysis* **2016**, 6, 2673-2680.

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

Abstract

We report a strategy that combines alkene hydroacylation and enantioselective *α*-(hetero)arylation reactions to form a wide variety of nitrogen-containing heterocyclic ketones bearing *α*-chiral quarternary stereogenic centers. *Exo*-selective, intramolecular Ni-catalyzed hydroacylation of *N*-homoallylindole- and *N*-homoallylpyrrole-2-carboxaldehydes from *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 quarternary stereogenic center by enantioselective Ni-catalyzed *α*-arylation and *α*-(hetero)arylation reactions. The chiral, nonracemic products formed through a combination of 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.

Introduction

Nitrogen-containing heterocycles possessing quarternary stereogenic centers are common structural motifs present in biologically active natural products and small molecules.[1-12] Despite many advances over the past decades, enantioselective synthesis of quarternary stereogenic centers remains a significant synthetic challenge.[13-21] The composition of current pharmaceutical agents provides a snapshot into this challenge. In 2011, 12% of the top 200 prescription drugs sold in the United States contained quaternary stereogenic centers.[21-22] 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.[21, 23] 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 α to a carbonyl group.[24] However, the majority of the metal-catalyzed, enantioselective α-arylation studies have focused on reactions of ketones with carbocyclic backbones[25-31] or lactones.[31-32] 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.[33-36] We focused our studies on 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[37-41] and polycyclic indoles with antiandrogenic,[42] antiarrhythmic,[43] and antihypertensive[44-45] activities (Figure 1).

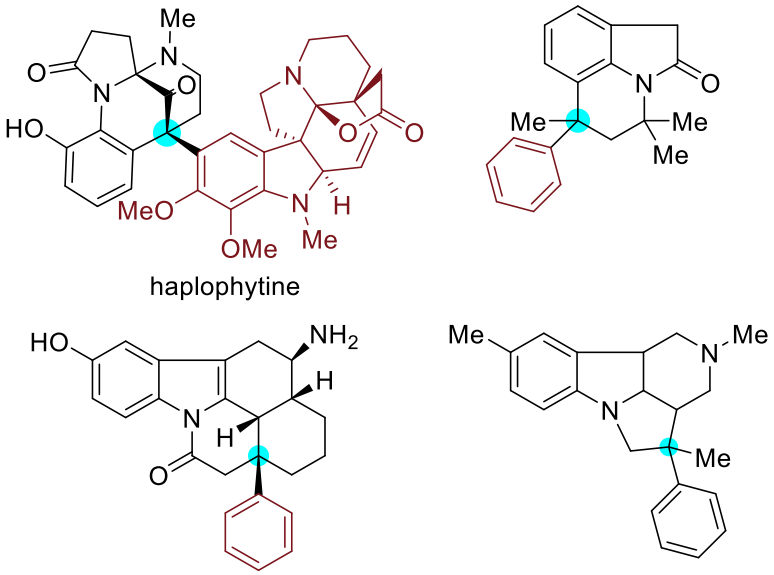


Figure 1. Biologically active indole derivatives containing benzylic quaternary stereogenic centers

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.[46] They reported the formation of chiral, nonracemic 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-economical transformation to generate a wide variety of carbocyclic and heterocyclic ketones.[47-50] 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[51] and *N*-allylindole- and *N*-allylpyrrole-2-carboxaldehydes to form *β*-substituted dihydropyridoindolones and dihydroindolizinones that occur exclusively with *endo* selectivity.[52] 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.[53-65] 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 the 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 chiral heterocycles possessing benzylic quaternary stereocenters.[66]

Herein, we report a strategy that combines catalytic alkene hydroacylation and *α*-arylation to generate five- and six-membered nitrogen-containing heterocyclic ketones bearing *α*-chiral quaternary stereocenters (Figure 2). We have identified a Ni(0)-NHC complex that catalyzes *exo*-selective hydroacylations of *N*-homoallylindole-2-carboxaldehydes to form six-membered heterocyclic ketones in high yields. This reactivity increases the scope of Ni-catalyzed hydroacylation beyond the formation of carbocyclic ketones and is complementary to NHC-catalyzed hydroacylations which are known to form five-membered nitrogen-containing, *α*-substituted heterocyclic ketones in excellent yields.[46, 64] Our studies reveal that nitrogen-containing five- and six-membered heterocyclic ketones exhibit significantly different reactivity toward Ni-

catalyzed, enantioselective α-arylations in comparison to previously studied carbocyclic ketones.[29] 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.

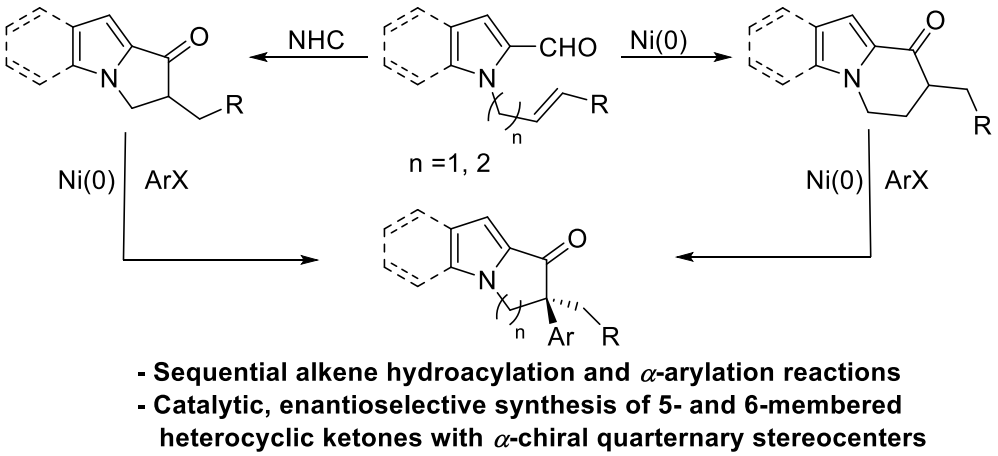


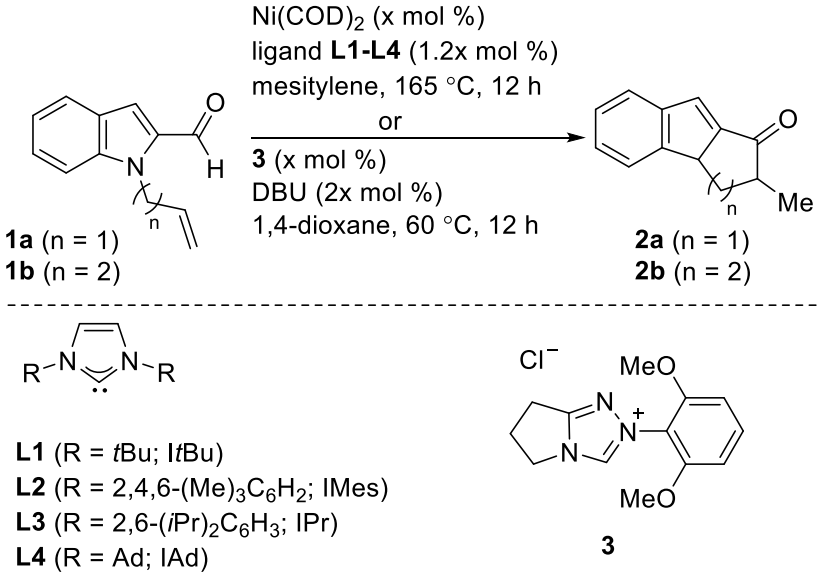
Figure 2. Coupling catalytic alkene hydroacylation and α-arylation reactions.

Results and Discussion

***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.[60] To test whether hydroacylation of *N*-allylindole-2-carboxaldehyde (**1a**) could occur under reaction conditions similar 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 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 1, entries 5 and 6). In contrast, an NHC catalyst, generated in situ from 10 mol % of 3 and 20 mol % of 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 1, entry 7).[67]

Table 1. Identification of Catalysts for Exo-Selective Hydroacylation of *N*-allyl- and *N*-Homoallylindole-2-carboxaldehyde[a,b]



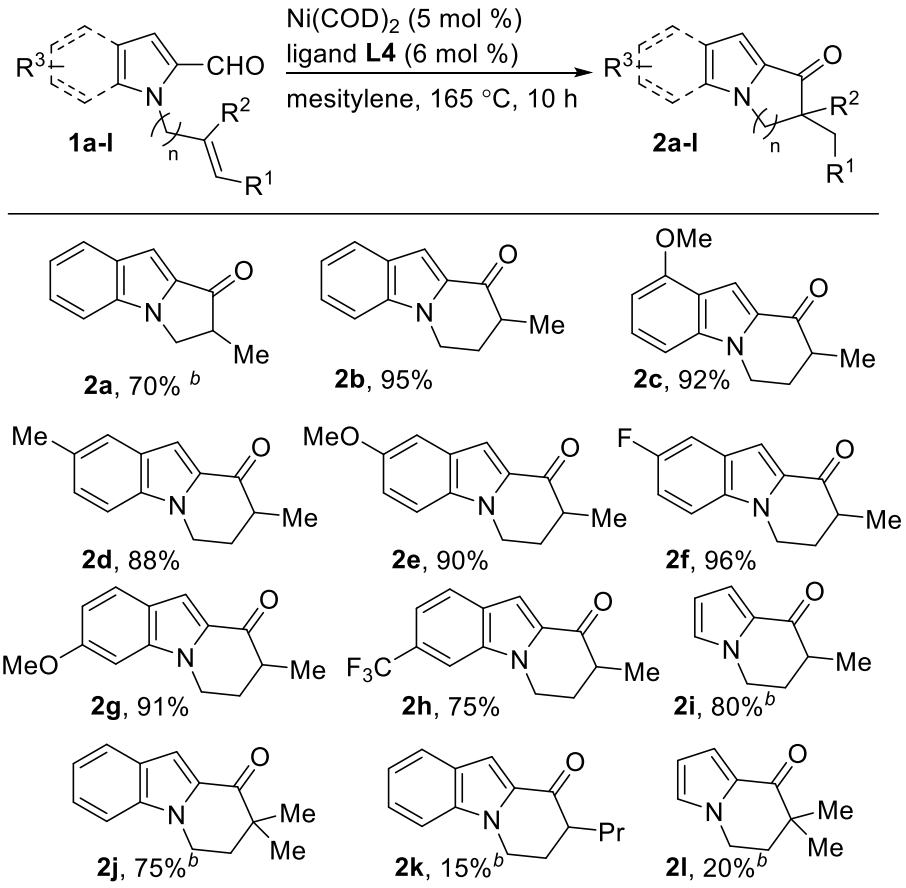
entry	**1**	precatalyst	precatalyst (mol %)	ligand	temp (°C)	Yield (%)[c]
1	**1a**	$Ni(COD)_2$	10	**L1**	130	16
2	**1a**	$Ni(COD)_2$	10	**L2**	130	8
3	**1a**	$Ni(COD)_2$	10	**L3**	130	9
4	**1a**	$Ni(COD)_2$	10	**L4**	130	34(30)
5	**1a**	$Ni(COD)_2$	10	**L4**	165	60(60)
6	**1a**	$Ni(COD)_2$	15	**L4**	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 mesitylne (1.0 mL). [b]Reaction conditions for NHC0catalyzed hydroacylations **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; the isolated yield of **2a** or **2b** is shown in parentheses.

In general, the formation of six-membered rings by transition-metal-catalyzed intramolecular hydroacylation reactions is challenging in comparison to the formation of five-

membered rings.[68-73] 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 % of Ni catalyst (Table 1, entry 8). However, a catalyst generated in situ from 10 mol % of **3** and 20 mol % of DBU at 60 °C forms **2b** in only 30% yield (Table 1, entry 9).

Scheme 1. Intramolecular Exo-Selective Ni-Catalyzed Hydroacylation[a]



[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 % of $Ni(COD)_2$ and 18 mol % of ligand **L4**.

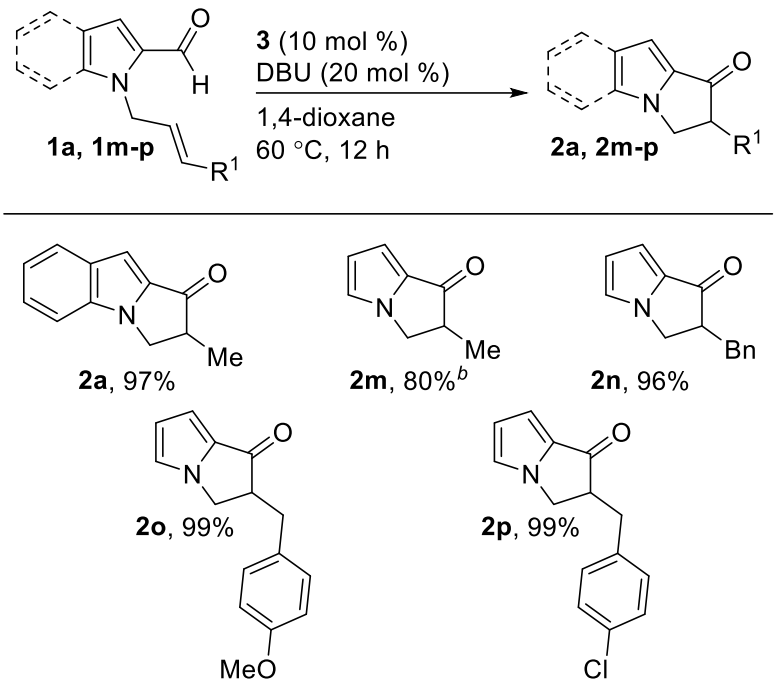
With a practical Ni catalyst system in hand, we evaluated the hydroacylations of various *N*-homoallylindole-2-carboxaldehydes containing substitution at the 4-, 5-, and 6-positions on the indole backbone (Scheme 1). A variety of *N*-homoallylindole-2-carboxaldehydes containing

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-, and 6-MeO-substituted *N*-homoallylindole-2-carboxaldehydes occur with 5 mol % of Ni catalyst and form dihydropyridoindolones **2c**−**e**,**g** in 88−92% yields. Hydroacylations of electron-deficient 5-F- and 6-CF_3-substituted *N*-homoallylindole-2-carboxaldehydes also form dihydropyridoindolones **2f**,**h** in 96% and 75% yields. Intramolecular hydroacylation of *N*-homoallylpyrrole-2- carboxaldehyde (**1i**) forms the product **2i** in 80% yield with 15 mol % of Ni catalyst.

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 % of 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 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 2. Intramolecular Exo-Selective NHC-Catalyzed Hydroacylation[a]



[a]Reaction conditions: **1a,m-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.

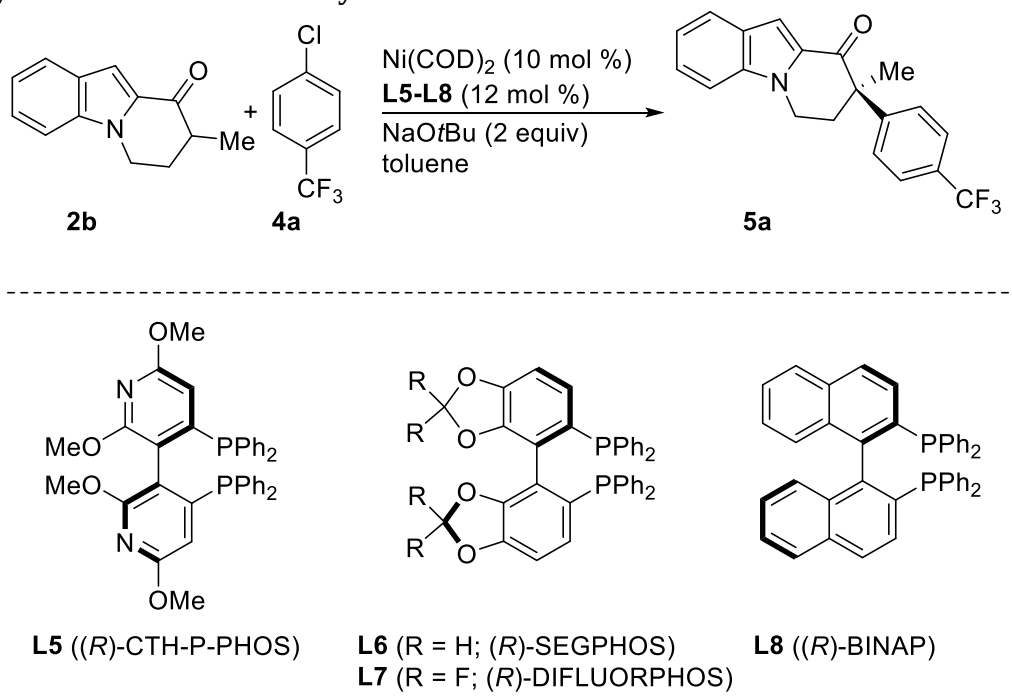
***α*-Arylation of Nitrogen-Containing Six-Membered Heterocyclic Ketones**. Initial studies to develop catalytic, enantioselective *α*-arylations of *α*-methyl dihydropyridoindolones were guided by *α*-arylations of 2-methyl-1-indanones and 2-methyl-1-tetralones catalyzed by a Ni(0) complex of BINAP.[29] 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 2, entries 1−4). 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 to 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% and 99% as the temperature of the reaction decreased from 80 to 70 and 65 °C (compare entries 4−6; see the Experimental section for additional entries) 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** (see the Experimental section), which leads to the pronounced influence of temperature on the yield of **5a**.[29, 74]

Scheme 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 the tert-butyl ester **5c** as the only *α*-arylated product, presumably due to complete transesterification in the presence of NaOtBu. 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**,**k** 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.

The absolute configuration of the quaternary stereocenter in **5d** was unambiguously determined by X-ray crystallographic analysis to be *R* (see the Experimental section for details). Thus, the catalyst generated from (*R*)-BINAP leads to the formation of (*R*)-**5d** (Figure 3).

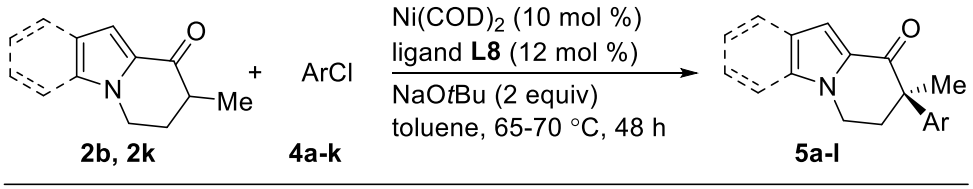
Table 2. Identification of Catalyst for Ni-Catalyzed *α*-Arylation of Dihydropyridoindolone and Dihydroindolizinone with Aryl Chlorides[a,b]



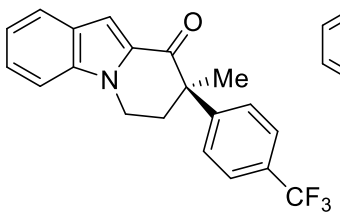
entry	ligand	temp (°C)	time (h)	conversion[b] (%)	yield[c] (%)	ee[d] (%)
1	**L5**	80	48	99	77	95
2	**L6**	80	48	99	72	97
3	**L7**	80	48	80	45	97
4	**L8**	80	48	99	60	97
5	**L8**	70	48	99	72	98
6	**L8**	65	48	99	99	99
7	**L8**	65	24	75	60	98

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

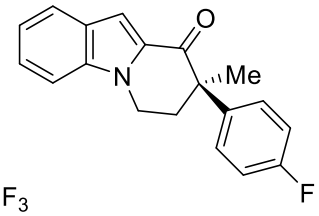
Scheme 3. Ni-Catalyzed Enantioselective *α*-Arylation of Dihydropyridoindolone and Dihydroindolizinone with Aryl Chlorides[a,b]



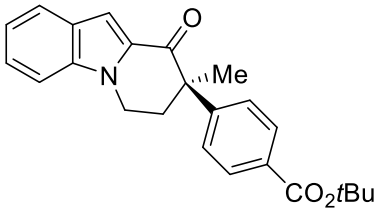
2b, 2k **4a-k** **5a-l**



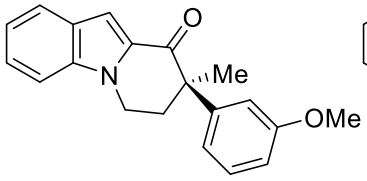
5a, 99%, 99% ee, 65 °C



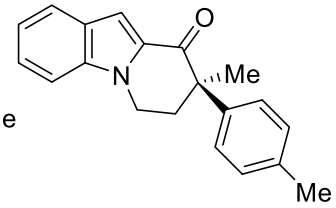
5b, 95%, 99% ee, 65 °C



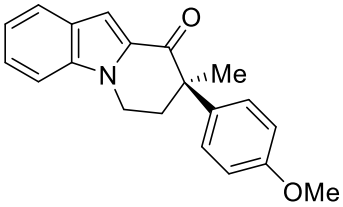
5c, 85%, 99% ee, 65 °C



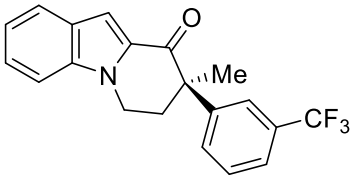
5d, 93%, 99% ee, 65 °C



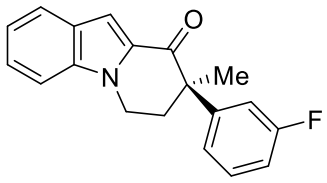
5e, 83%, 99% ee, 70 °C



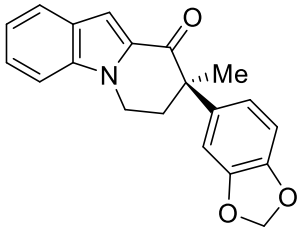
5f, 92%, 97% ee, 70 °C



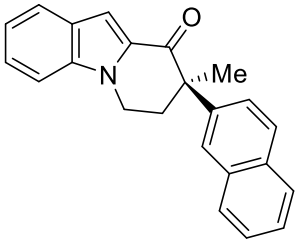
5g, 90%, 99% ee, 70 °C



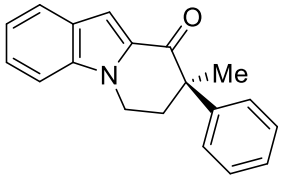
5h, 75%, 99% ee, 70 °C



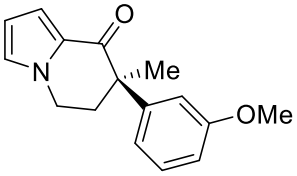
5i, 82%, 99% ee, 70 °C



5j, 95%, 99% ee, 70 °C



5k, 99%, 98% ee, 70 °C



5l, 70%, 91% ee, 65 °C

[a]Reaction conditions: **2b,k** (0.100 mmol), **4a-k** (0.200 mmol), NaO*t*Bu (0.200 mmol), $Ni(COD)_2$ (0.010 mmol), ligand **L8** (0.012 mmol), and toluene (0.5 mL).

***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).

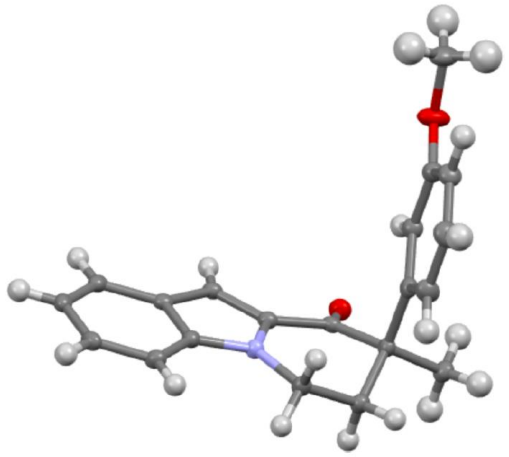
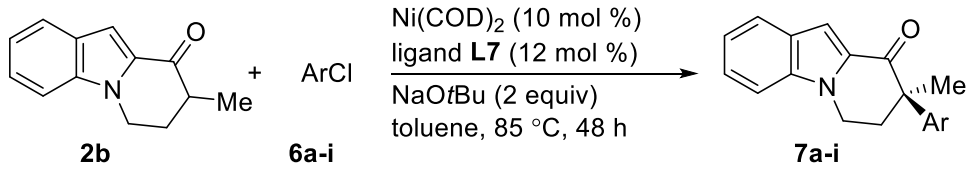
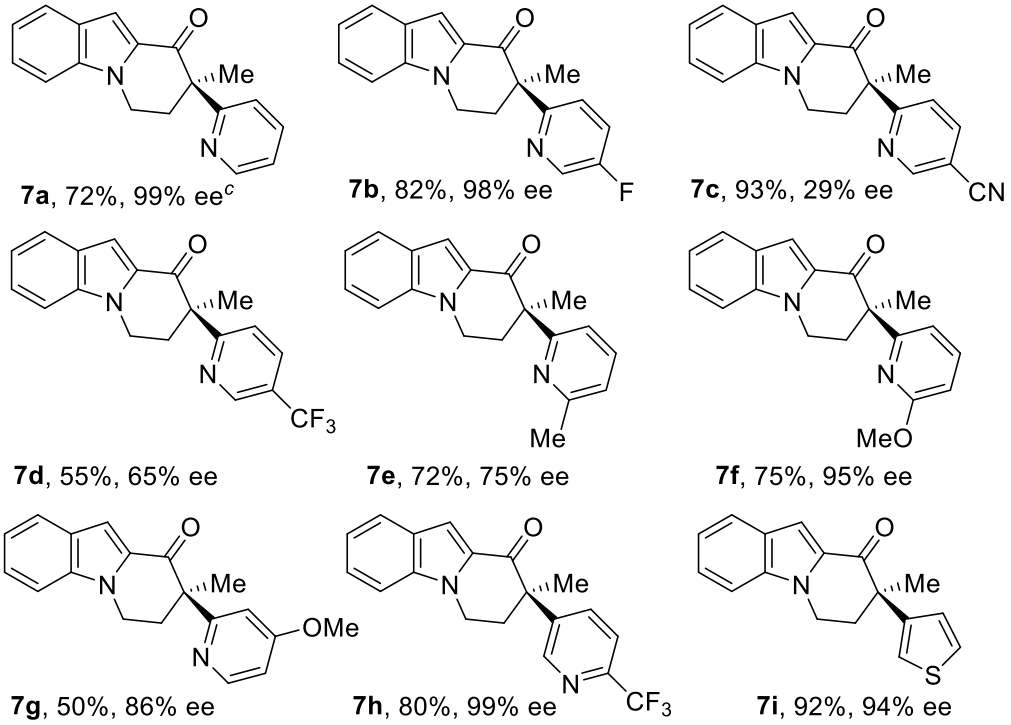


Figure 3. Determination of the absolute stereochemistry of 5d by X-ray crystallographic analysis.

Scheme 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 with 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-(trifluoromethyl)pyridine (**6d**) generated the heteroarylated products **7c**,**d** 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**,**d** at 85 °C in the absence of catalyst formed the α-arylated products **7c**,**d** in 42% and 22% yields by ^{1}H NMR analysis.

Scheme 4. Ni-Catalyzed Enantioselective *α*-Heteroarylation of Dihydropyridoindolone with Heteroaryl Chlorides[a,b]





[a]Reaction conditions: **2b** (0.100 mmol), **6a-I** (0.200 mmol), NaO*t*Bu (0.200 mmol), $Ni(COD)_2$ (0.010 mmol), ligand **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.

α-Heteroarylation of **2b** with the 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**,**i** in high yields (80−92%) with excellent enantioselectivities (94−99%).

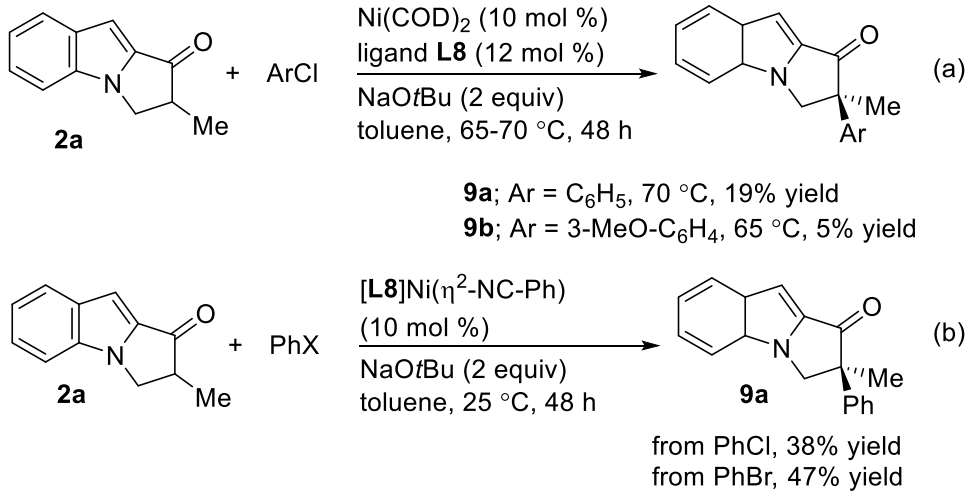
***α*-Arylation of Nitrogen-Containing Five-Membered Heterocyclic Ketones**. The ability to form a range of dihydropyridoindolones with *α*-chiral quaternary stereocenters in high yield with excellent stereocontrol led us to investigate Ni-catalyzed *α*-arylation reactions of five-membered heterocyclic ketones. Surprisingly, *α*-arylation of **2a** with chlorobenzene at 70 °C 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 °C generated a 5% yield of the coupled product **9b** (Scheme 5a). 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 that is known to oxidatively add aryl halides at 25 °C and attenuate decomposition of the oxidative addition product [**L8**]Ni(Ar)(Cl).[29, 74-75] The reactions of **2a** with chlorobenzene and bromobenzene formed **9a** in 38% and 47% yields, respectively, when the reactions were performed at 25 °C in the presence of 10 mol % of [**L8**]Ni(η^2 -NC-Ph) (Scheme 5b).

α-Arylations of dihydropyrroloindolone **2a** occurred in the highest yields when they were performed at 25 °C in the presence of 15 mol % of [**L8**]Ni(η^2 -NC-Ph) (Scheme 6). *α*-Arylations of **2a** with bromobenzene, 3-methoxybromobenzene, and 4-(trifluoromethyl)bromobenzene formed **9a**−**c** in 44−78% yield and 99% ee.

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**). 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 % of [**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-Bromonaphthalene also reacted with **2m** to form **9j** in 96% yield and 99% ee.

Scheme 5. Reactivity of Dihydropyrroloindolone 2a with Aryl Halides in Ni-Catalyzed α-Arylations[a,b]



[a]Reaction conditions: **2a** (0.200 mmol), **4d,k** and **8a** (0.400 mmol), NaO*t*Bu (0.400 mmol), $Ni(COD)_2$ (0.020 mmol), ligand **L8** (0.024 mmol), [**L8**]Ni(η^2-NC-Ph) (0.020 mmol), and toluene (1.0 mL). [b]Yields of **9a** are isolated yields after column chromatography.

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 6, dihydropyrrolizinones **2n**−**p** with substituted and unsubstituted benzyl groups at the α-position reacted with bromobenzene in the presence of 10 mol % of [**L8**]Ni(η^2 -NC-Ph) to form α-arylated ketones **9k**−**m** in 69−91% yield and 99% ee. The chemoselectivity of the α-arylation is highlighted by the reaction of dihydropyrrolizinone **2p** (R = 4-ClC6H4CH2). Dihydropyrrolizinone **2p** reacted exclusively with bromobenzene to form α-arylated ketone **9m** in high yield and ee.

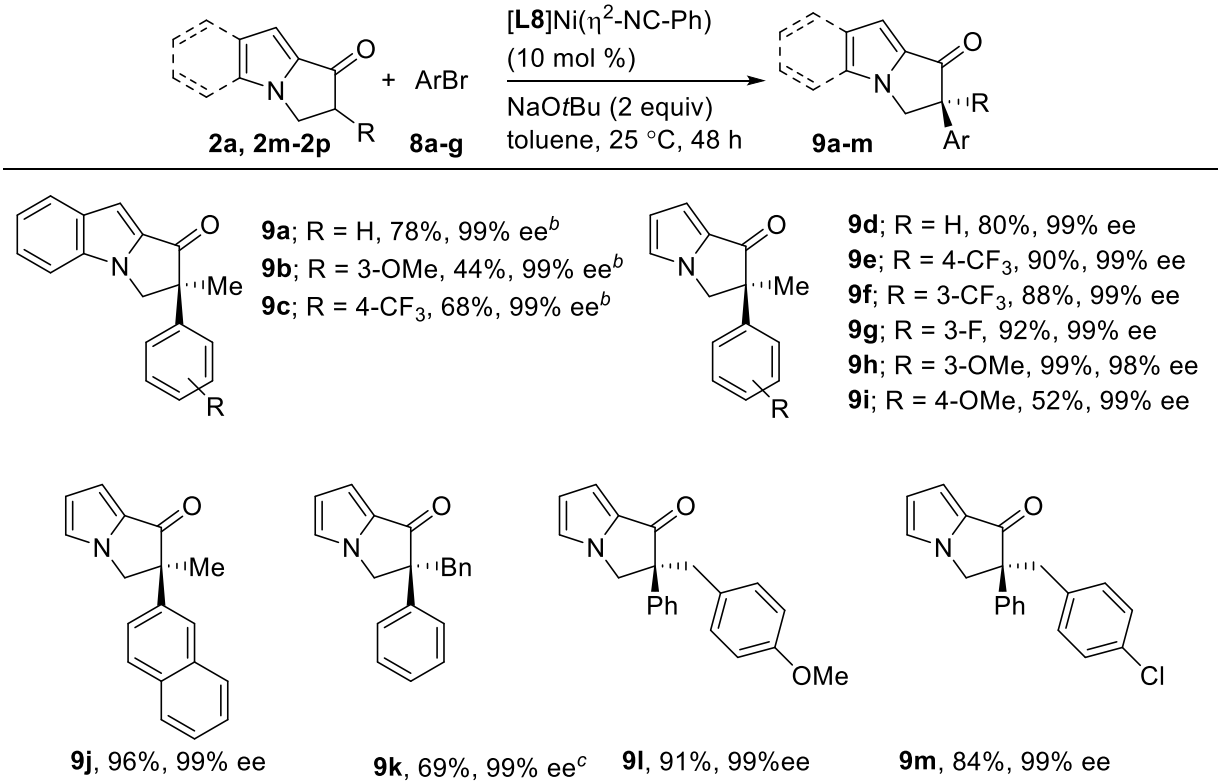
***α*-Heteroarylation of Nitrogen-Containing Five-Membered Heterocyclic Ketones**. After successfully demonstrating *α*-arylations of dihydropyrrolizinones with aryl bromides in the presence of the benzonitrile-ligated Ni(0)-**L8** complex, we sought to identify the benzonitrile-ligated Ni(0)-**L7** 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 % of $Ni(COD)_2$, 12 mol % of ligand **L7**, and 2 equiv of benzonitrile (Scheme 7). 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** formed **11f** in low yield, but the enantioselectivity of the *α*-heteroarylation remained high (92% ee).

A One-Pot Sequential Alkene Hydroacylation and α- Arylation Process. One-pot multicatalytic transformations are attractive processes for sustainable chemical synthesis because these processes improve efficiency and eliminate waste and labor associated with the 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.[76-77]

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 (see the Experimental section). In a typical sequence, $Ni(COD)_2$, (*R*)-BINAP,

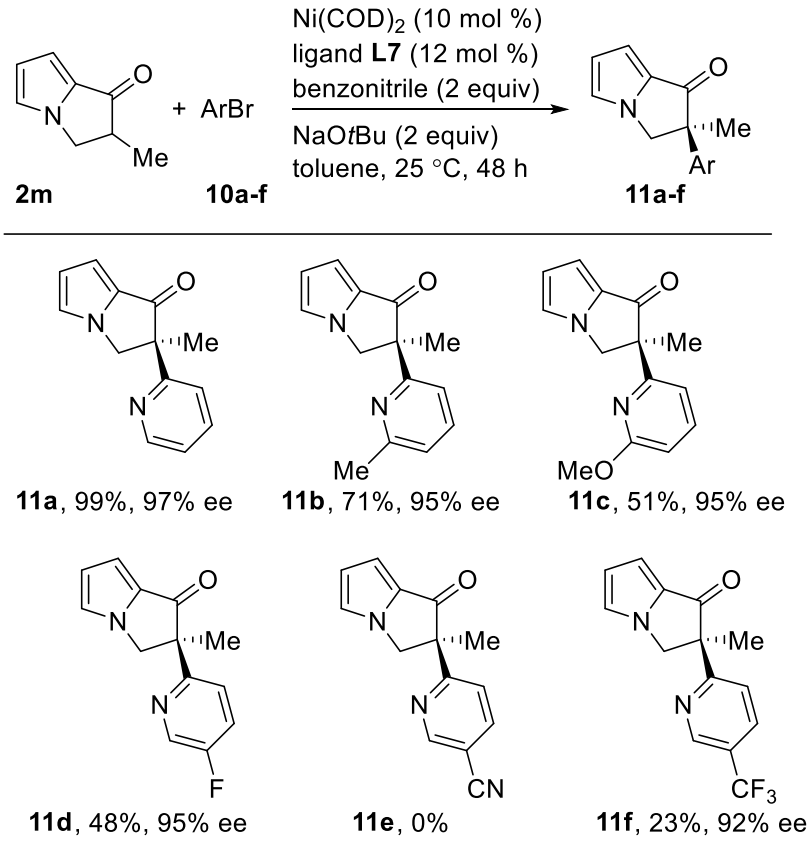
NaO*t*Bu, 1-chloro-3-methoxybenzene, and toluene were added to the reaction mixture under a nitrogen atmosphere upon completion of the hydroacylation reaction. The enantioselectivity of these sequential reactions was high (>95% ee), but the yield of *α*-arylated ketone **5d** was low (30−40%). However, the yield of the sequential hydroacylation and *α*-arylation could be improved significantly by exposing the reaction mixture to air for 5−10 min before addition of the 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 8).

Scheme 6. Ni-Catalyzed Enantioselective *α*-Arylation of Dihydropyrroloindolone and Dihydropyrrolizinones with Aryl Bromides[a]



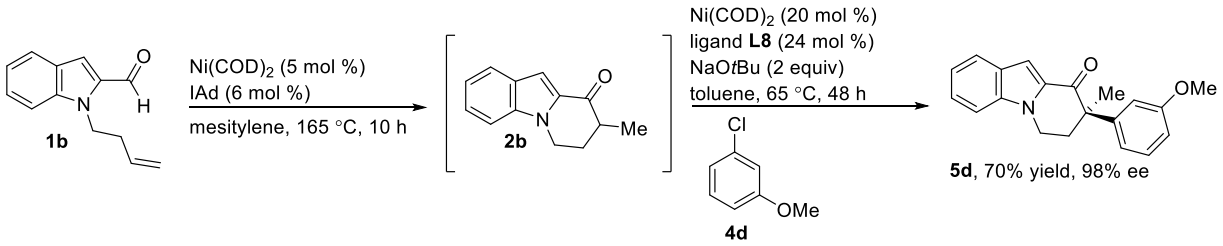
[a]Reaction conditions: **2a,m-p** (0.200 mmol), **8a-g** (0.400 mmol), NaO*t*Bu (0.400 mmol), [**L8**]Ni(η^2-NC-Ph) (0.020-0.030 mmol), and toluene (1.0 mL). Yields of **9** are isolated yields after column chromatography; enantiomeric excesses of **9** were determined by chiral HPLC analysis. [b]Reaction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

Scheme 7. Ni-Catalyzed Enantioselective *α*-Heteroarylation of Dihydropyrrolizinone with Heteroaryl Bromides[a,b]



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

Scheme 8. One-Pot Sequential Hydroacylation and *α*-Arylation Reaction[a,b]



[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), ligand **L8** (0.024 mmol), and toluene (0.5 mL). [b]The yield of **5d** is the isolated yield after column chromatography; the enantiomeric excess of **5d** was determined by chiral HPLC analysis.

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 nonracemic, *α*-chiral quaternary stereocenters. The potential to further functionalize the remaining carbonyl moiety makes this sequential reaction an attractive strategy to access a wide range of complex chiral heterocycles having benzylic quaternary stereocenters. This sequential alkene hydroacylation/*α*-arylation protocol can also be performed in a 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.

Experimental

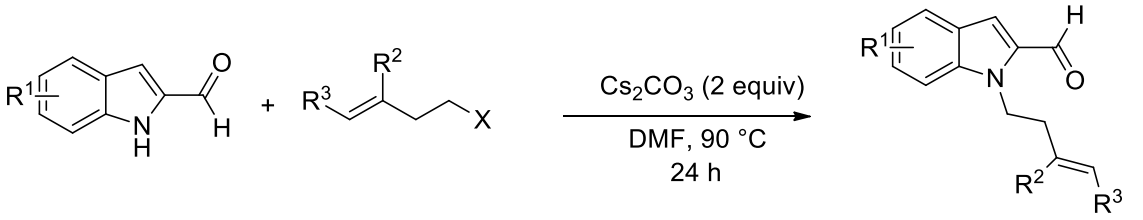
General synthetic details. All air-sensitive procedures were conducted under inert atmosphere in a nitrogen-filled dry box or by standard Schlenk techniques. All reactions were performed under an atmosphere of nitrogen unless otherwise stated. All glassware for moisture sensitive reactions was dried 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.

Instrumentation. 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.

Materials. 5-Methylindole-2-carboxaldehyde, 5-methoxyindole-2-carboxaldehyde, and 6-methoxyindole-2-carboxaldehyde were synthesized according to reported literature procedures.[78-82] 4-Methoxyindole-2-carboxaldehyde and 6-trifluoromethylindole-2-carboxaldehyde were synthesized according to the known literature procedure.[82-84] 5-Fluoroindole-2-carboxaldehyde was synthesized according to a literature procedure.[82, 85] Indole-2-carboxaldehyde was synthesized from ethyl indole-2-carboxylate according to a known literature procedure.[82] 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.[86] (*E*)-Hex-3-en-1-yl 4-methylbenzenesulfonate **S2c** was synthesized from (*E*)-hex-3-en-1-ol according to a known literature procedure.[87] Substituted cinnamyl bromides **S2d** and **S2e** were synthesized according to the known literature procedure.[78, 88-89] **1a**, **1m**, **1n** were synthesized according to the known literature procedure.[82] Organocatalyst **3** was synthesized according to the known literature procedure.[90] IAd, I*t*Bu, IMes, IPr were synthesized according to the known literature procedure.[91-92] 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.[93]

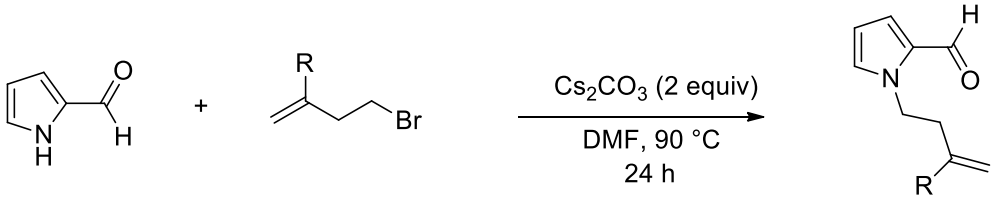
General Procedure A: Synthesis of *N*-Homoallylindole-2-carboxaldehydes (1b-h, 1j-k) and *N*-Homoallylpyrrole-2-carboxaldehydes (1i, 1l)



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



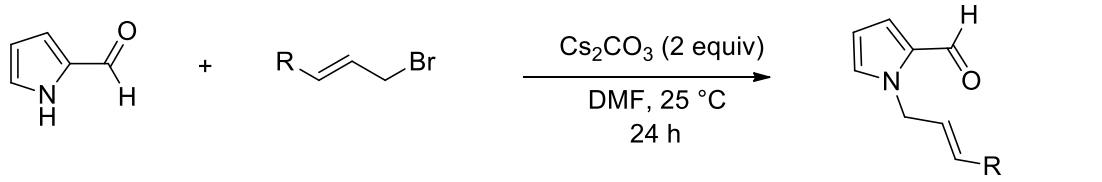
S1h

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**).

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



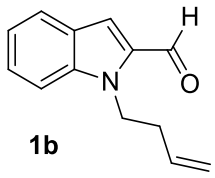
S1h

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

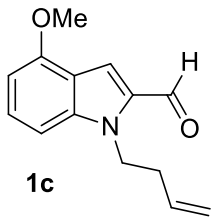
1-Cinnamyl-1*H*-pyrrole-2-carboxaldehydes (**1o-p**) were prepared according to a modified literature procedure from the appropriate cinnamyl bromides (**S2d-e)** and pyrrole-2-carboxaldehyde (**S1h)**.[82] To the pyrrole-2-carboxaldehyde (1.0 equiv) and Cs_2CO_3 (1.2 equiv) was added DMF (0.27 M **S1h**). 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**).



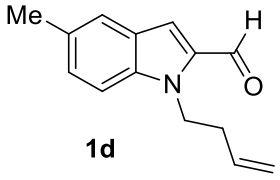
1b

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.



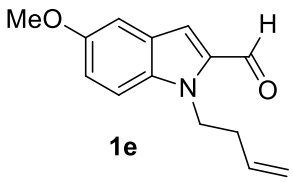
1c

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.



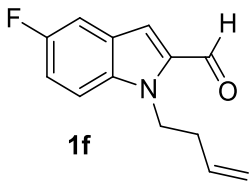
1d

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

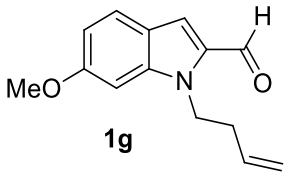
1-(But-3-en-1-yl)-5-methoxy-1*H*-indole-2-carboxaldehyde (1e): Prepared according to the general procedure A from **S1d** (0.343 g, 1.96 mmol) and **S2a** (0.317 g, 2.35 mmol). The mixture was purified by flash column chromatography (90:10 hexanes:EtOAc) to give **1e** as yellow solid in 60% yield (0.270 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

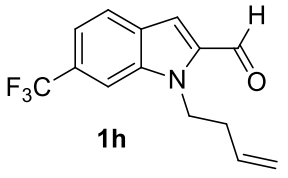
1-(But-3-en-1-yl)-5-fluoro-1*H*-indole-2-carboxaldehyde (1f): Prepared according to the general procedure A from **S1e** (0.136 g, 0.834 mmol) and **S2a** (0.135 g, 1.00 mmol). The mixture was purified by column chromatography (95:5 hexanes:EtOAc) to give **1f** as yellow oil in 55% yield (0.100 g, 0.460

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

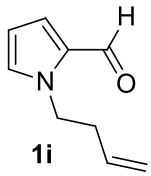
1-(But-3-en-1-yl)-6-methoxy-1*H*-indole-2-carboxaldehyde (1g): Prepared according to the general procedure A from **S1f (**0.283 g, 1.62 mmol) and **S2a** (0.262 g, 1.94 mmol). The mixture was purified by flash column chromatography (90:10 hexane:EtOAc) to give **1g** as a dark yellow oil in 57% yield (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

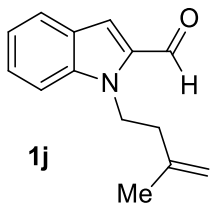
1-(But-3-en-1-yl)-6-(trifluoromethyl)-1*H*-indole-2-carboxaldehyde (1h): Prepared according to the general procedure A from **S1g** (0.512 g, 2.40 mmol) and **S2a** (0.389 g, 2.88 mmol). The mixture was purified by column chromatography (90:10 hexanes:EtOAc) to give **1h** as yellow oil in 17% yield (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.



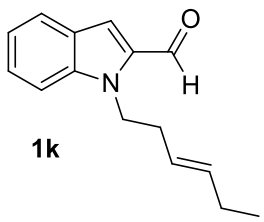
1i

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 (90:10 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.



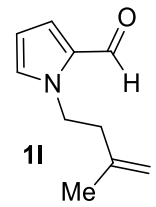
1j

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.



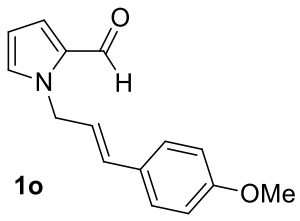
1k

(*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.



1l

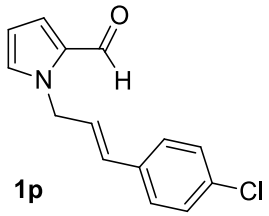
1-(3-Methylbut-3-en-1-yl)-1*H*-pyrrole-2-carboxaldehyde (1l): Prepared according to the general procedure A from **S1h** (1.000 g, 10.52 mmol) and 17% solution of **S2b** (11.06 g, 12.62 mmol) in THF. The mixture was purified by flash column chromatography (90:10 hexane:EtOAc) to give **1l** as a dark 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.



1o

(*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,

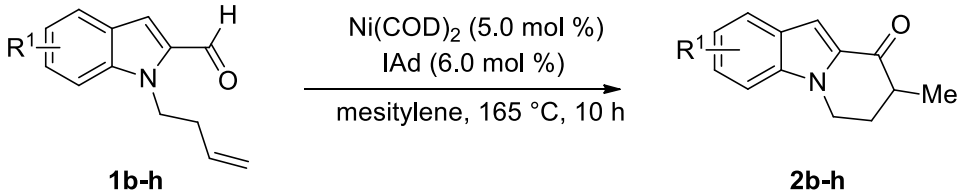
1.0 Hz, 2H), 6.19 (ddd, *J* = 15.8, 6.4, 6.4 Hz, 1H), 6.26 (dd, *J* = 4.0, 2.6 Hz, 1H), 6.43 (d, *J* = 15.8 Hz, 1H), 6.83 (d, *J* = 8.8 Hz, 2H), 6.96 (dd, *J* = 4.0, 1.7 Hz, 1H), 7.03 (m, 1H), 7.28 (d, *J* = 8.8 Hz, 2H), 9.57 (s, 1H). **^{13}C NMR** (101 MHz $CDCl_3$) δ 51.0, 55.6, 110.3, 114.3, 123.1, 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.

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



1b-h

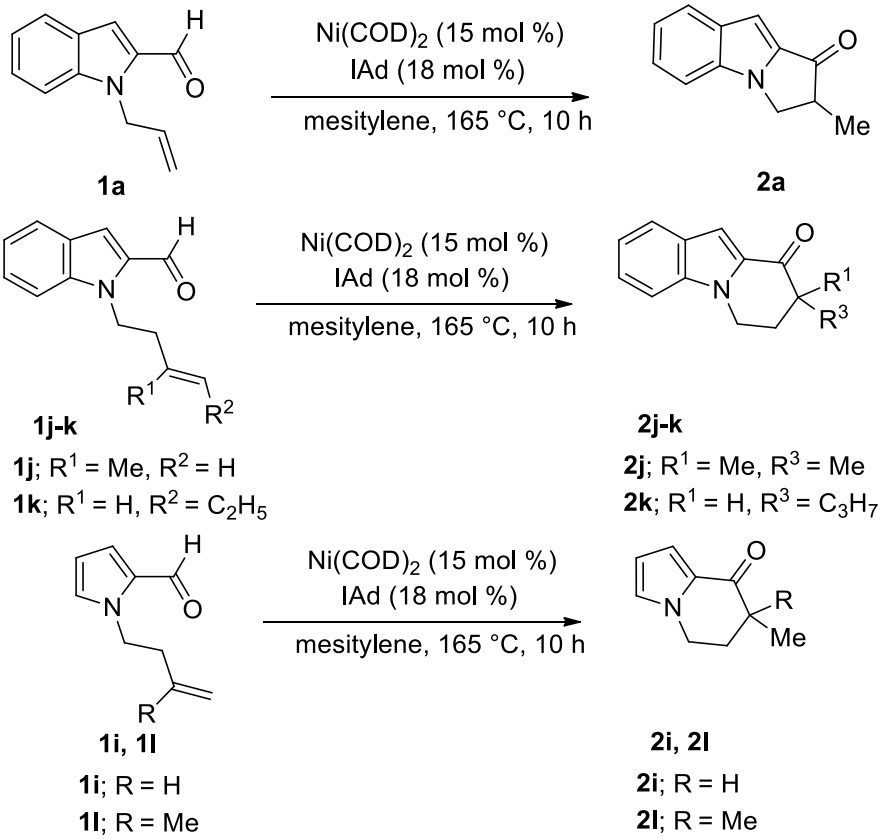
1b; R^1 = H
1c; R^1 = 4-MeO-C_6H_4
1d; R^1 = 5-Me-C_6H_4
1e; R^1 = 5-MeO-C_6H_4
1f; R^1 = 5-F-C_6H_4
1g; R^1 = 6-MeO-C_6H_4
1h; R^1 = 6-CF_3-C_6H_4

2b-h

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

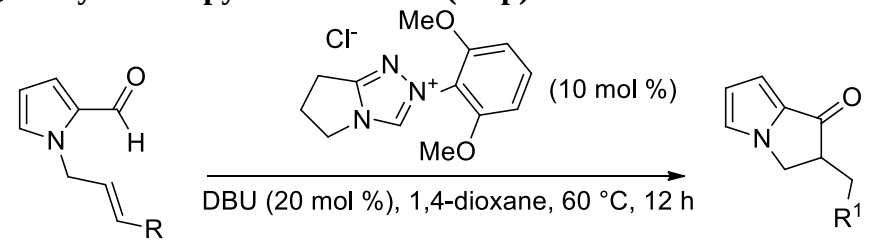
In a nitrogen-filled glovebox, the appropriate *N*-homoallylindole-2-carboxaldehyde (**1b-h**) (0.100 mmol, 1.0 equiv) was added to a 1-dram vial containing $Ni(COD)_2$ (1.4 mg, 0.00500 mmol, 0.050 equiv) and IAd (2.0 mg, 0.00600 mmol, 0.060 equiv) in mesitylene (0.5 mL). The vial was sealed with a PTFE/silicone-lined 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**).

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**).

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)

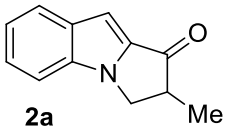


1m; R = H
1n; R = C_6H_5
1o; R = 4-OMe-C_6H_4
1p; R= 4-Cl-C_6H_4

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

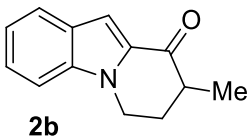
2-methyl-2,3-dihydro-1*H*-pyrrolizin-1-one (**2m**) and 2-benzyl-2,3-dihydro-1*H*-pyrrolizin-1-one (**2n-p**) were prepared according to a modified literature procedure from the appropriate 1-allyl-1*H*-pyrrole-2-carboxaldehyde (**1m-p**).[90] In a nitrogen-filled glovebox, to a 1-dram vial was added 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

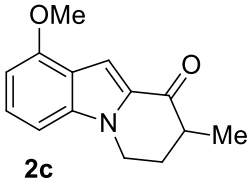
2-Methyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-one (2a): Prepared according to the general procedure D from **1a** (19.0 mg, 0.103 mmol). The crude product was purified by silica gel chromatography with a CombiFlash system (4 g column, 100:0→90:10 hexanes/EtOAc) to give **2a** as a white solid in 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

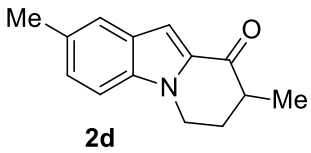
8-Methyl-7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-one (2b): Prepared according to the general procedure C from **1b** (20.0 mg, 0.100 mmol). The mixture was purified by flash column chromatography (90:10 hexane:EtOAc) to give **2b** as a yellowish white solid in 95% yield (19.0 mg, 0.095 mmol). **^{1}H 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.



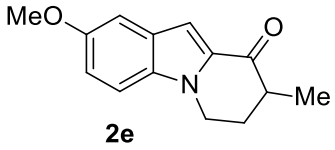
2c

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 (90:10 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.



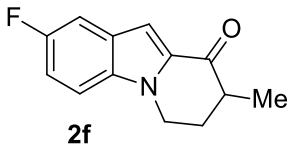
2d

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 (90:10 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.



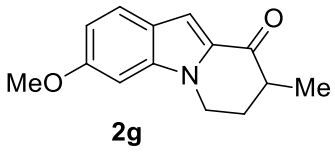
2e

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 (90:10 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.



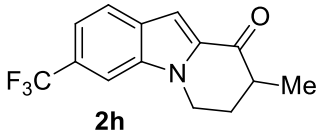
2f

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 (90:10 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.



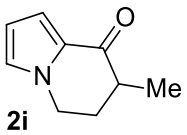
2g

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 (90:10 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.



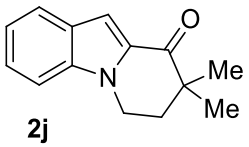
2h

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 (90:10 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.



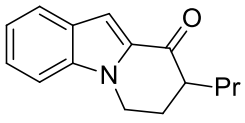
2i

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 (90:10 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

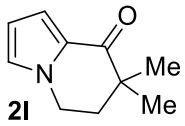
8,8-Dimethyl-7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-one (2j): Prepared according to the general procedure D from **1i** (22.0 mg, 0.103 mmol). The mixture was purified by flash column chromatography (80:20 hexane:EtOAc) to give **2i** as a yellow solid in 75% yield (16.5 mg, 0.077 mmol). **^{1}H NMR** (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

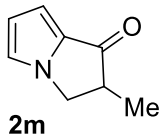
8-Propyl-7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-one (2k): Prepared according to a modified version of general procedure D from **1j** (68.0 mg, 0.299 mmol). The mixture was purified by flash column chromatography (80:20 hexane:EtOAc) to give **2j** as a yellow solid in 15% yield (10.5 mg, 0.0460 mmol).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



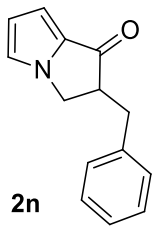
2l

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

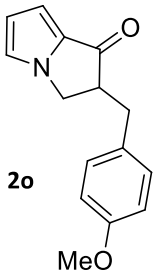
2-Methyl-2,3-dihydro-1*H*-pyrrolizin-1-one (2m): Prepared according to general procedure E from **1m** (27.0 mg, 0.200 mmol). The reaction mixture was stirred at 60 °C for 24 h. The mixture was purified by flash column chromatography (90:10 hexane:EtOAc) to give **2m** as a white solid in 80% yield (21.6 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

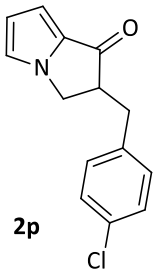
2-Benzyl-2,3-dihydro-1*H*-pyrrolizin-1-one (2n): Prepared according to a general modified version of general procedure E from **1n** (42.0 mg, 0.199 mmol). The mixture was purified by flash column chromatography (90:10 hexane:EtOAc) to give **2n** as a yellow oil in 96% yield (40.3 mg, 0.191 mmol). **^{1}H 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

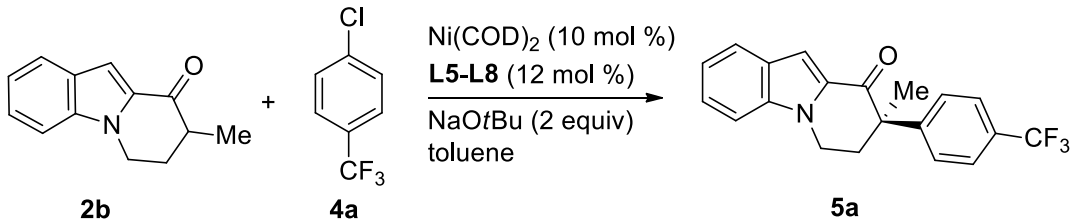
2-(4-Methoxybenzyl)-2,3-dihydro-1*H*-pyrrolizin-1-one (2o): Prepared according to a modified version of general procedure E from **1o** (48.0 mg, 0.199 mmol). The mixture was purified by flash column chromatography (90:10 hexane:EtOAc) to give **2o** as a white solid in 99% yield (47.6 mg, 0.197 mmol). **^{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.

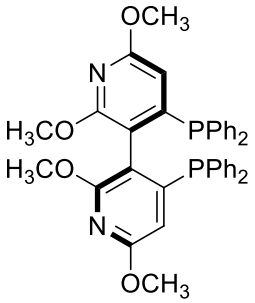


2p

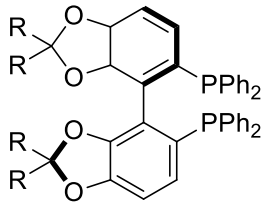
2-(4-Chlorobenzyl)-2,3-dihydro-1*H*-pyrrolizin-1-one (2p): Prepared according to a modified version of general procedure E from **1p** (49.0 mg, 0.199 mmol). The mixture was purified by flash column chromatography (90:10 hexane:EtOAc) to give **2p** as a white solid in 99% yield (48.5 mg, 0.197 mmol). **^{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.

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

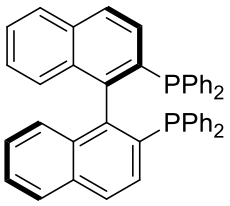




L5: (*R*)-CTH-P-PHOS



R = H; **L6**: (*R*)-SEGPHOS
R = F; **L7**: (*R*)-DIFLUORPHOS

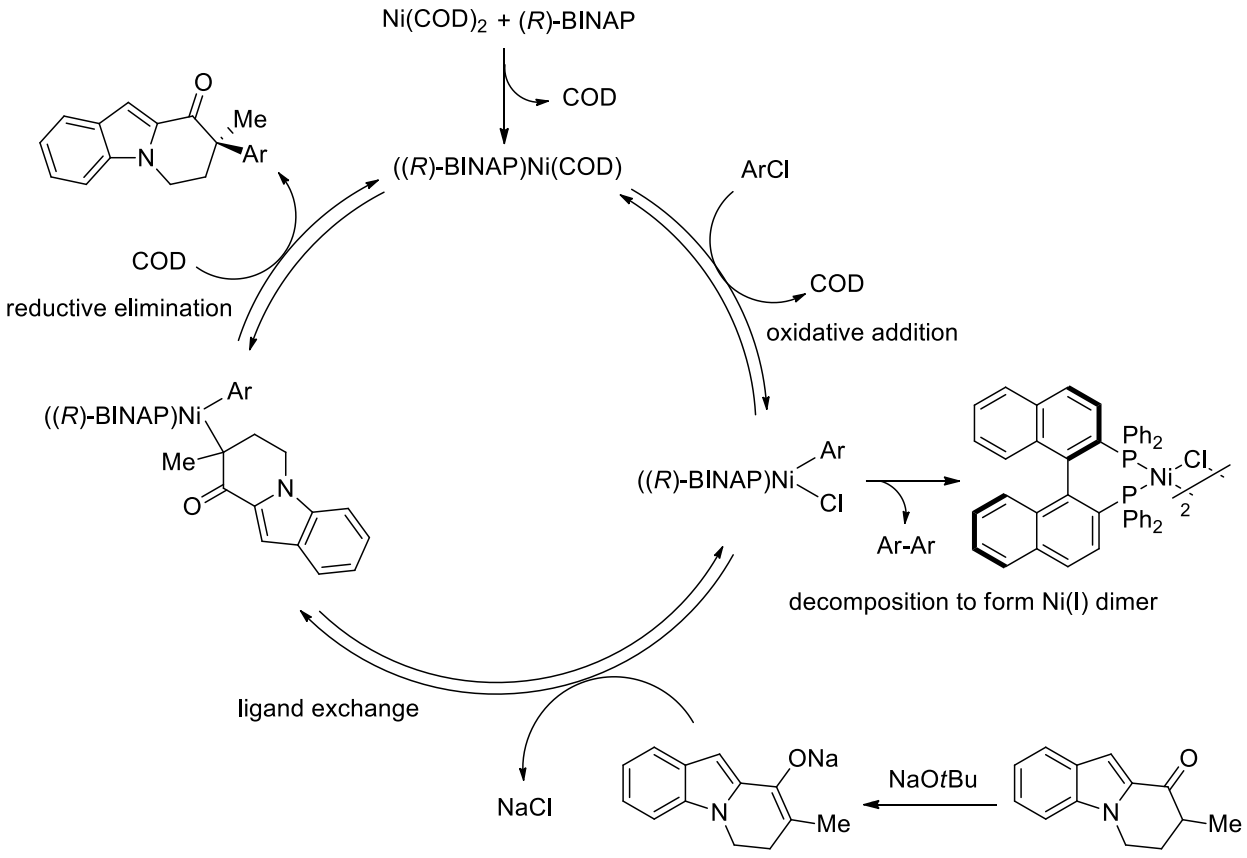


L8: (*R*)-BINAP

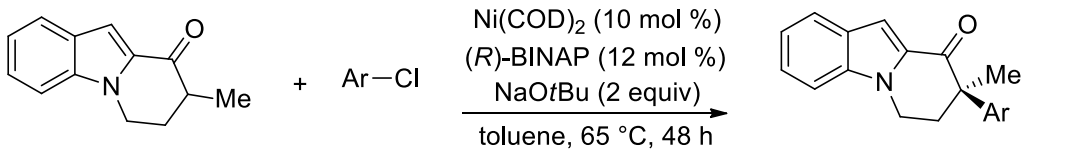
entry	ligand	temp (°C)	time (h)	conv[a] (%)	yield[b] (%)	ee[c] (%)
1	**L5**	80	48	99	77	95
2	**L6**	80	48	99	72	97
3	**L7**	80	48	80	45	97
4	**L7**	70	48	75	42	99
5	**L7**	60	48	75	69	99
6	**L8**	80	48	99	60	97
7	**L8**	70	48	99	72	98
8	**L8**	65	48	99	99	99
9	**L8**	65	24	75	60	98
10	**L8**	60	48	60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

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). [a] Conversion of **2b** was determined by ^1H NMR spectroscopy. [b] Isolated yield after column chromatography. [c] Determined by chiral HPLC analysis.

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

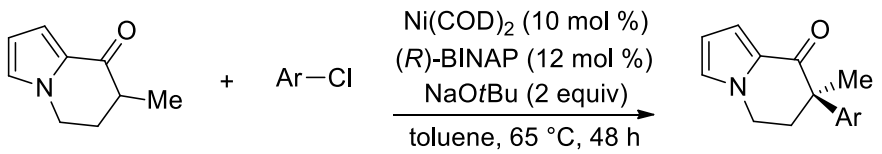


General Procedure F: Synthesis of (*R*)-8-Aryl-8-methyl-7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-ones (5a-d) and (*R*)-7-Aryl-7-methyl-6,7-dihydroindolizin-8(5*H*)-one (5l)



2b **4a-d** **5a-d**

4a; Ar = 4-CF_3-C_6H_4 **5a**; Ar = 4-CF_3-C_6H_4
4b; Ar = 4-F-C_6H_4 **5b**; Ar = 4-F-C_6H_4
4c; Ar = 4-CO_2Me-C_6H_4 **5c**; Ar = 4-CO_2tBu-C_6H_4
4d; Ar = 3-MeO-C_6H_4 **5d**; Ar = 3-MeO-C_6H_4

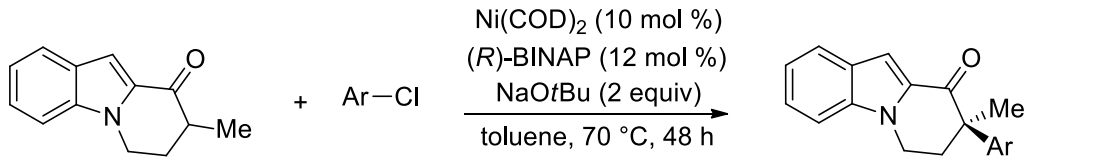


2k **4d** **5l**

4d; Ar = 4-MeO-C_6H_4 **5l**; Ar = 4-MeO-C_6H_4

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**).

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



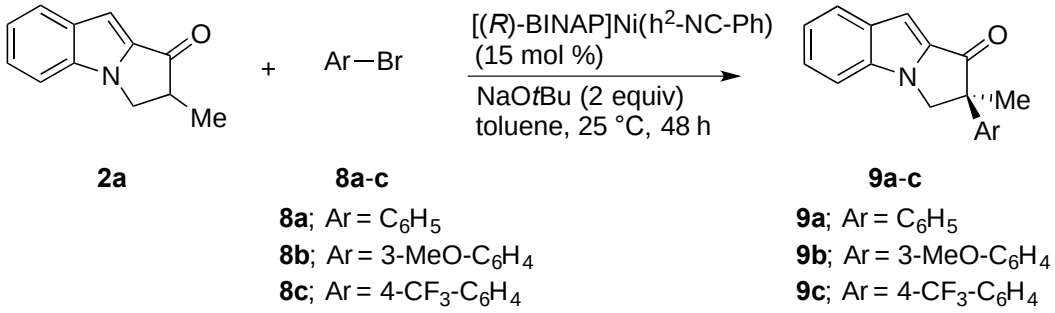
2b **4e-k** **5e-k**

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**).

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



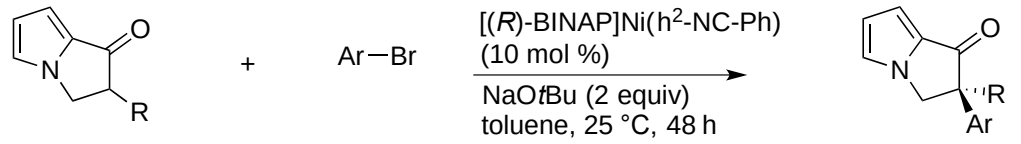
2a **8a-c** **9a-c**

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**).

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

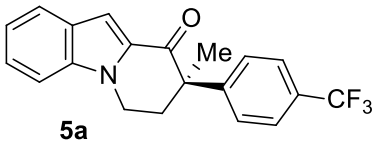
8a-g

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

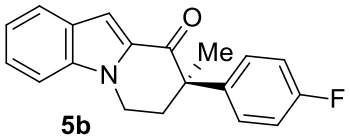
9d; R = Me, Ar = C_6H_5
9e; R = Me, Ar = 4-CF_3-C_6H_4
9f; R = Me, Ar = 3-CF_3-C_6H_4
9g; R = Me, Ar = 3-F-C_6H_4
9h; R = Me, Ar = 3-MeO-C_6H_4
9i; R = Me, Ar = 4-MeO-C_6H_4
9j; R = Me, Ar = napthyl
9k; R = CH_2-C_6H_4, Ar = C_6H_5
9l; R = CH_2-(4-MeO)-C_6H_4, Ar = C_6H_5
9m; R = CH_2-(4-Cl)-C_6H_4,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

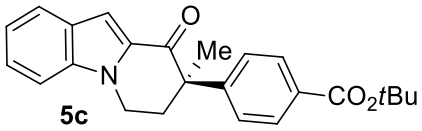
(*R*)-8-Methyl-8-(4-(trifluoromethyl)phenyl)-7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-one (5a): Prepared according to the general procedure F from **2b** (20.0 mg, 0.100 mmol) and 1-chloro-4-(trifluoromethyl)benzene **4a** (36.2 mg, 0.200 mmol). The crude product was purified by silica gel chromatography with a CombiFlash system (4 g column, 100:0→80:20 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→80:20 hexanes/EtOAc) to give **5b** as a light yellow solid in 85% yield (25.0 mg, 0.085 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

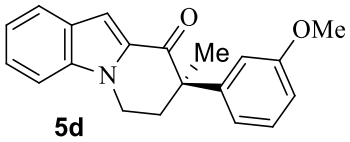
AS-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 99:1, 1.0 mL/min] to be 99% ee. $[\alpha]_D^{23}$ = +152.1° (c 0.53, $CHCl_3$). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.62 (s, 3H), 2.56 (ddd, *J* = 14.4, 11.4, 4.8 Hz, 1H), 2.76 (ddd, *J* = 14.4, 3.6, 3.6 Hz, 1H), 3.88 (ddd, *J* = 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

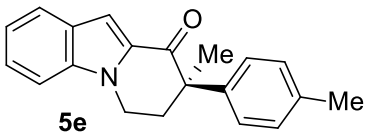
(*R*)-*tert*-Butyl 4-(8-methyl-9-oxo-6,7,8,9-tetrahydropyrido[1,2-*a*]indol-8-yl)benzoate (5c): Prepared according to the general procedure F from **2b** (20.0 mg, 0.100 mmol) and methyl 4-chlorobenzoate **4c** (34.2 mg, 0.200 mmol). The crude product was purified by silica gel chromatography with a CombiFlash system (4 g column, 100:0→80:20 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

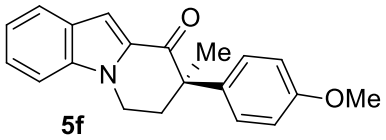
(*R*)-8-(3-Methoxyphenyl)-8-methyl-7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-one (5d): Prepared according to general procedure F from **2b** (20.0 mg, 0.100 mmol) and 1-chloro-3-methoxybenzene **4d** (28.6 mg, 0.200 mmol). The crude product was purified by silica gel chromatography with a CombiFlash system (4 g column, 100:0→80:20 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→80:20 hexanes/EtOAc) to give **5e** as a yellow solid in 83% yield (24.0 mg, 0.0829 mmol).

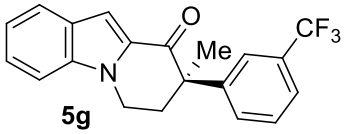
The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 19.2 min (major); t_R 25.6 min (minor) [Chiracel AS-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 99:1, 1.0 mL/min] to be 99% ee. $[\alpha]_D^{23}$ = +115.8° (c 0.52, $CHCl_3$). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.72 (s, 3H), 2.39 (s, 3H), 2.65 (ddd, *J* = 14.3, 11.8, 4.9 Hz, 1H), 2.89 (ddd, *J* = 14.3, 3.4, 3.4 Hz, 1H), 4.00 (ddd, *J* = 11.8, 11.8, 3.4 Hz, 1H), 4.36 (ddd, *J* = 11.8, 4.9, 3.4 Hz, 1H), 7.26 – 7.18 (m, 2H), 7.29 – 7.23 (m, 3H), 7.38 – 7.33 (m, 1H), 7.43 (ddd, *J* = 8.2, 6.9, 1.0 Hz, 1H), 7.51 (s, 1H), 7.83 (dd, *J* = 8.2, 1.0 Hz, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 21.2, 26.4, 36.7, 39.2, 50.0, 106.7, 110.6, 121.3, 123.6, 125.8, 126.5, 127.4, 129.9, 134.0, 137.1, 137.5, 138.6, 193.8. **HRMS** (ESI): Calcd. for $C_{20}H_{20}NO^+$ ([M+H]$^+$): 290.1539, Found: 290.1545.



5f

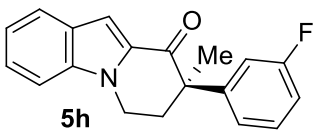
(*R*)-8-(4-Methoxyphenyl)-8-methyl-7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-one (5f): Prepared according to the general procedure G from **2b** (20.0 mg, 0.100 mmol) and 1-chloro-4-methoxybenzene **4f** (28.6 mg, 0.200 mmol). The crude product was purified by silica gel chromatography with a CombiFlash system (4 g column, 100:0→80:20 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 98% ee. $[\alpha]_D^{23}$ = +109.9° (c 0.56, $CHCl_3$). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.60 (s, 3H), 2.53 (ddd, *J* = 14.6, 11.8, 4.8 Hz, 1H), 2.75 (ddd, *J* = 14.6, 3.6, 3.6 Hz, 1H), 3.74 (s, 3H), 3.89 (ddd, *J* = 11.8, 11.8, 3.6 Hz, 1H), 4.26 (ddd, *J* = 11.8, 4.8, 3.6 Hz, 1H), 6.82 (d, *J* = 8.8 Hz, 2H), 7.14 (t, *J* = 7.4 Hz, 1H), 7.19 (d, *J* = 8.8 Hz, 2H), 7.25 – 7.26 (m, 1H), 7.33 (t, *J* = 7.4 Hz, 1H), 7.40 (s, 1H), 7.72 (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

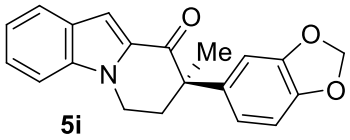
(*R*)-8-Methyl-8-(3-(trifluoromethyl)phenyl)-7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-one (5g): Prepared according to the general procedure G from **2b** (20.0 mg, 0.100 mmol) and 1-chloro-3-(trifluoromethyl)benzene **4g** (36.2 mg, 0.200 mmol). The crude product was purified by silica gel chromatography with a CombiFlash system (4 g column, 100:0→80:20 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 18.4 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→80:20 hexanes/EtOAc) to give **5h** as a yellow oil in 75% yield (22.0 mg, 0.0750 mmol).

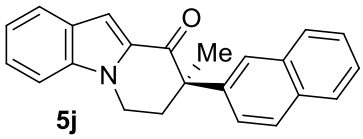
The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 18.7 min (major); t_R 24.0 min (minor) [Chiracel AS-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 98:2, 1.0 mL/min] to be 99% ee. $[\alpha]_D^{23}$ = +148.6° (c 0.70, $CHCl_3$). **^{1}H NMR** (600 MHz, $CDCl_3$) 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

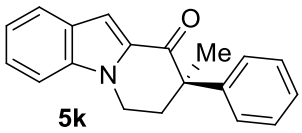
(*R*)-8-(Benzo[*d*][1,3]dioxol-5-yl)-8-methyl-7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-one (5i): Prepared according to the general procedure G from **2b** (20.0 mg, 0.100 mmol) and 5-chlorobenzo[*d*][1,3]dioxole **4i** (31.4 mg, 0.200 mmol). The crude product was purified by silica gel chromatography with a CombiFlash system (4 g column, 100:0→80:20 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

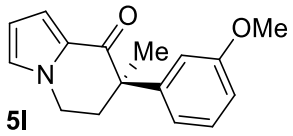
(*R*)-8-Methyl-8-(naphthalen-2-yl)-7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-one (5j): Prepared according to the general procedure G from **2b** (20.0 mg, 0.100 mmol) and 2-chloronaphthalene **4j** (32.6 mg, 0.200 mmol). The crude product was purified by silica gel chromatography with a CombiFlash system (4 g column, 100:0→80:20 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** (151 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

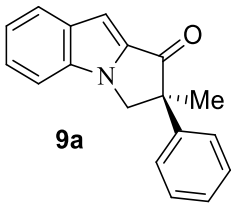
(*R*)-8-Methyl-8-phenyl-7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-one (5k): Prepared according to the general procedure G from **2b** (20.0 mg, 0.100 mmol) and chlorobenzene **4k** (22.6 mg, 0.200 mmol). The crude product was purified by silica gel chromatography with a CombiFlash system (4 g column, 100:0→80:20 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.



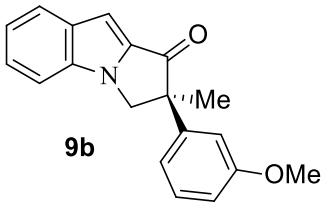
5l

(*R*)-7-(3-Methoxyphenyl)-7-methyl-6,7-dihydroindolizin-8(5*H*)-one (5l): Prepared according to the general procedure F from **2k** (20.0 mg, 0.134 mmol) and 1-chloro-3-methoxybenzene **4d** (38.2 mg, 0.268 mmol). The crude product was purified by silica gel chromatography with a CombiFlash system (4 g column, 100:0→80:20 hexanes/EtOAc) to give **5l** as a colorless oil in 70% yield (28.7 mg, 0.0939 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

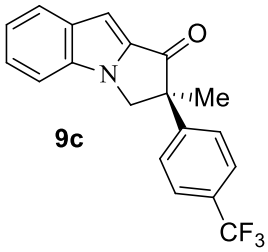
(*S*)-2-Methyl-2-phenyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-one (9a): Prepared according to the general procedure H from **2a** (37.0 mg, 0.200 mmol) and 1-chloro-3-methoxybenzene **8a** (63.0 mg, 0.399 mmol). The mixture was purified by flash column chromatography (98:2 hexane:EtOAc) to give **9a** 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 12.82 min (major); t_R 18.51 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.[94] **^{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→80:20 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**.

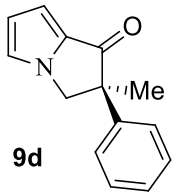


9c

(*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→80:20 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.

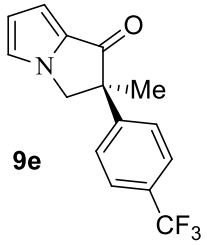
The extra peaks in ^{1}H and ^{13}C NMR might have resulted due to the presence of rotameric isomer of **9c**. Variable-temperature NMR measurements (Bruker 400 MHz) on a sample of **9c** in DMSO-d_6 at temperatures ranging from 20 °C to 135 °C, upper limit of the instrument, did not show

coalescence of peaks. Additional NMR studies (1-D selective chemical-exchange NMR) were carried out to confirm the presence of rotameric isomer.[95] However, the results were inconclusive.



9d

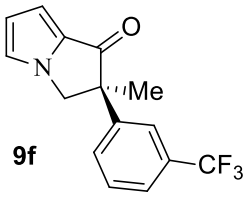
(*S*)-2-Methyl-2-phenyl-2,3-dihydro-1*H*-pyrrolizin-1-one (9d): Prepared according to the general procedure I from **2m** (27.0 mg, 0.200 mmol) and 1-bromobenzene **8a** (63.0 mg, 0.399 mmol). The crude product was purified by flash column chromatography (98:2 hexane:EtOAc) to give **9d** as a white solid in 80% yield (33.8 mg, 0.160 mmol). The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 28.04 min (major); t_R 46.36 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.[94] **^{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 23.2, 57.1, 58.7, 109.2, 117.3, 123.0, 125.9, 127.2, 128.8, 131.3, 142.6, 192.6.



9e

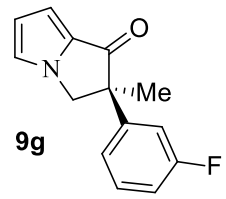
(*S*)-2-Methyl-2-(4-(trifluoromethyl)phenyl)-2,3-dihydro-1*H*-pyrrolizin-1-one (9e): Prepared according to the general procedure I from **2m** (27.0 mg, 0.199 mmol) and 1-bromo-4-(trifluoromethyl)benzene **8b** (89.9 mg, 0.399 mmol). The crude product was purified by silica gel chromatography with a CombiFlash system (4 g column, 100:0→80:20 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

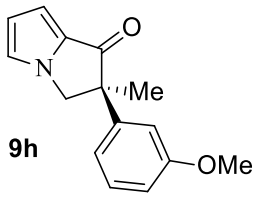
(*S*)-2-Methyl-2-(3-(trifluoromethyl)phenyl)-2,3-dihydro-1*H*-pyrrolizin-1-one (9f): Prepared according to the general procedure I from **2m** (27.0 mg, 0.199 mmol) and 1-bromo-3-(trifluoromethyl)benzene **8d** (89.9 mg, 0.399 mmol). The crude product was purified by silica gel chromatography with a CombiFlash system (4 g column, 100:0→80:20 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

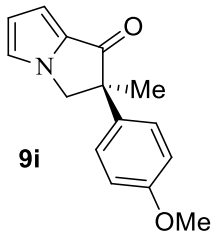
(*S*)-2-(3-Fluorophenyl)-2-methyl-2,3-dihydro-1*H*-pyrrolizin-1-one (9g): Prepared according to the general procedure I from **2m** (27.0 mg, 0.199 mmol) and 1-bromo-3-fluorobenzene **8e** (69.9 mg, 0.399 mmol). The crude product was purified by silica gel chromatography with a CombiFlash system (4 g column, 100:0→80:20 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.



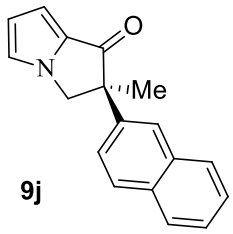
9h

(*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→80:20 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

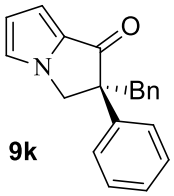
(*S*)-2-(4-Methoxyphenyl)-2-methyl-2,3-dihydro-1*H*-pyrrolizin-1-one (9i): Prepared according to the general procedure I from **2m** (27.0 mg, 0.199 mmol) and 1-bromo-4-methoxybenzene **8f** (74.2 mg, 0.399 mmol). The crude product was purified by silica gel chromatography with a CombiFlash system (4 g column, 100:0→80:20 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

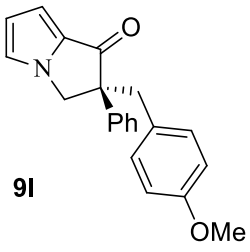
(*S*)-2-Methyl-2-(naphthalen-2-yl)-2,3-dihydro-1*H*-pyrrolizin-1-one (9j): Prepared according to the general procedure I from **2m** (27.0 mg, 0.199 mmol) and 2-bromonaphthalene **8g** (82.7 mg, 0.399 mmol). The crude product was purified by silica gel chromatography with a CombiFlash system (4 g column, 100:0→80:20 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

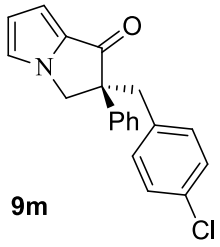
(*S*)-2-Benzyl-2-phenyl-2,3-dihydro-1*H*-pyrrolizin-1-one (9k): Prepared according to the modified version of the general procedure I from **2n** (42.0 mg, 0.199 mmol) and bromobenzene **8a** (63.0 mg, 0.398 mmol) at 10 °C. The mixture was purified by flash column chromatography (98:2 hexane:EtOAc) to 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 35.24 min (major); t_R 48.92 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), 4.53 (d, *J* =12.0 Hz, 1H), 4.57 (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), 6.90 (m, 1H), 7.05 – 7.08 (m, 2H), 7.14 – 7.20 (m, 3H), 7.25 – 7.29 (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 29.37 min (major); t_R 42.10 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),

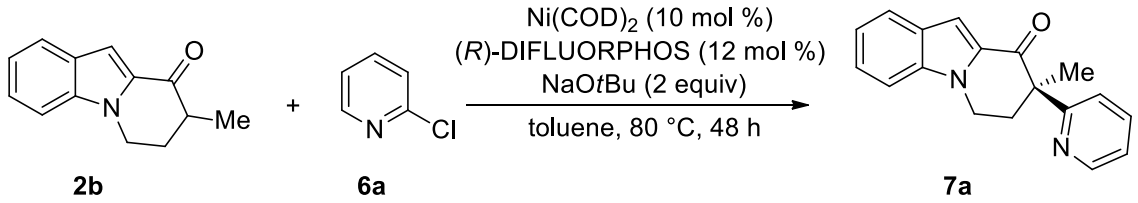
3.51 (d, *J* = 14.0 Hz, 1H), 3.65 (s, 3H), 4.43 (d, *J* = 11.8 Hz, 1H), 4.48 (d, *J* = 11.8 Hz, 1H) 6.37 (dd, *J* = 4.0, 2.2 Hz, 1H), 6.61 - 6.65 (m, 3H), 6.82 – 6.83 (m, 1H), 6.89 (d, *J* = 8.6 Hz, 2H), 7.16 – 7.20 (m, 1H), 7.25 (t, *J* = 7.2 Hz, 2H), 7.34 (d, *J* = 8.6 Hz, 2H). **^{13}C NMR** (101 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

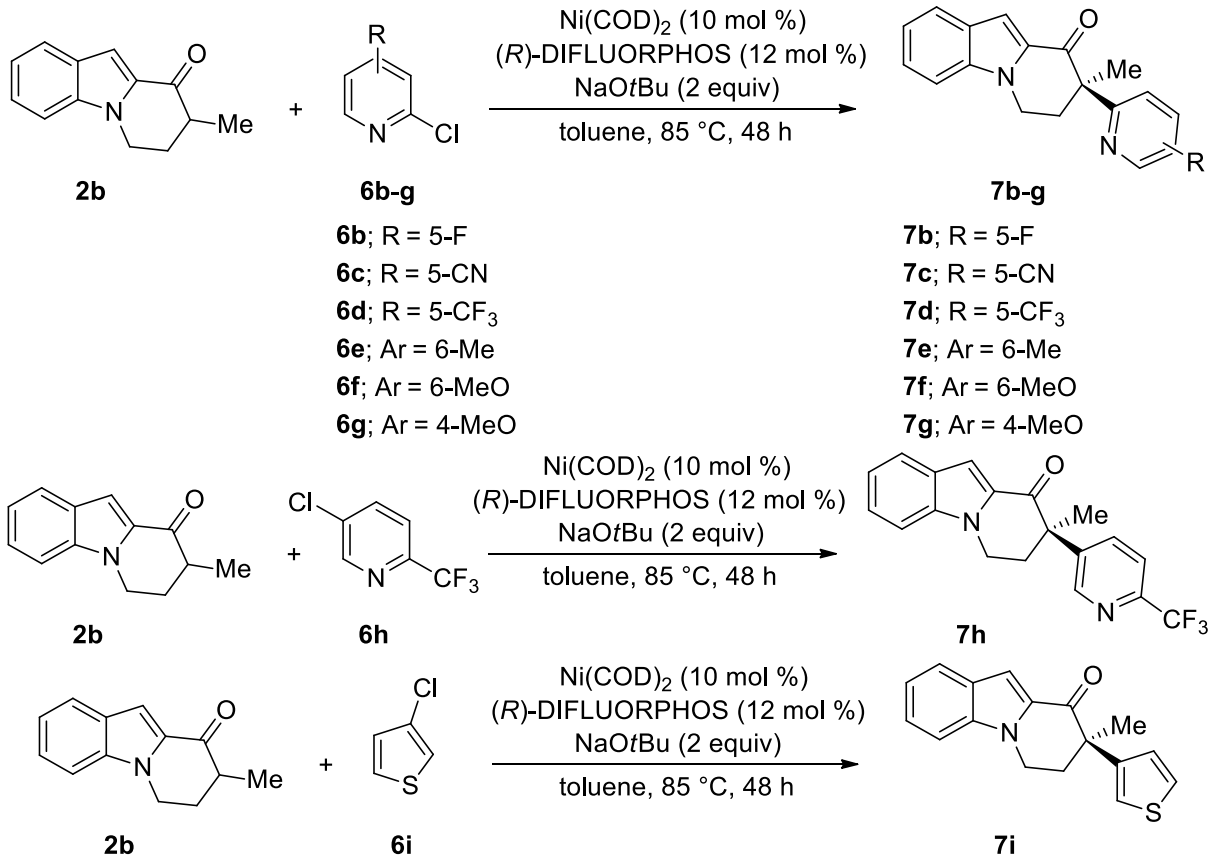
(*S*)-2-(4-Chlorobenzyl)-2-phenyl-2,3-dihydro-1*H*-pyrrolizin-1-one (9m): Prepared according to the general procedure I from **2p** (49.0 mg, 0.199 mmol) and bromobenzene **8a** (63.0 mg, 0.399 mmol). The mixture was purified by flash column chromatography (98:2 hexane:EtOAc) to give **9m** as a white solid in 84% yield (54.0 mg, 0.168 mmol). The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 21.01 min (major); t_R 24.97 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 3.28 (d, *J* = 13.8 Hz, 1H), 3.58 (d, *J* = 13.8 Hz, 1H), 4.47 (d, *J* = 12.0 Hz, 1H), 4.57 (d, *J* = 12.0 Hz, 1H), 6.47 (dd, *J* = 3.6, 1.8 Hz, 1H), 6.73 (d, *J* = 3.6 Hz, 1H), 6.92 (m, 1H), 6.99 (d, *J* = 8.0 Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 7.24 - 7.29 (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.

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



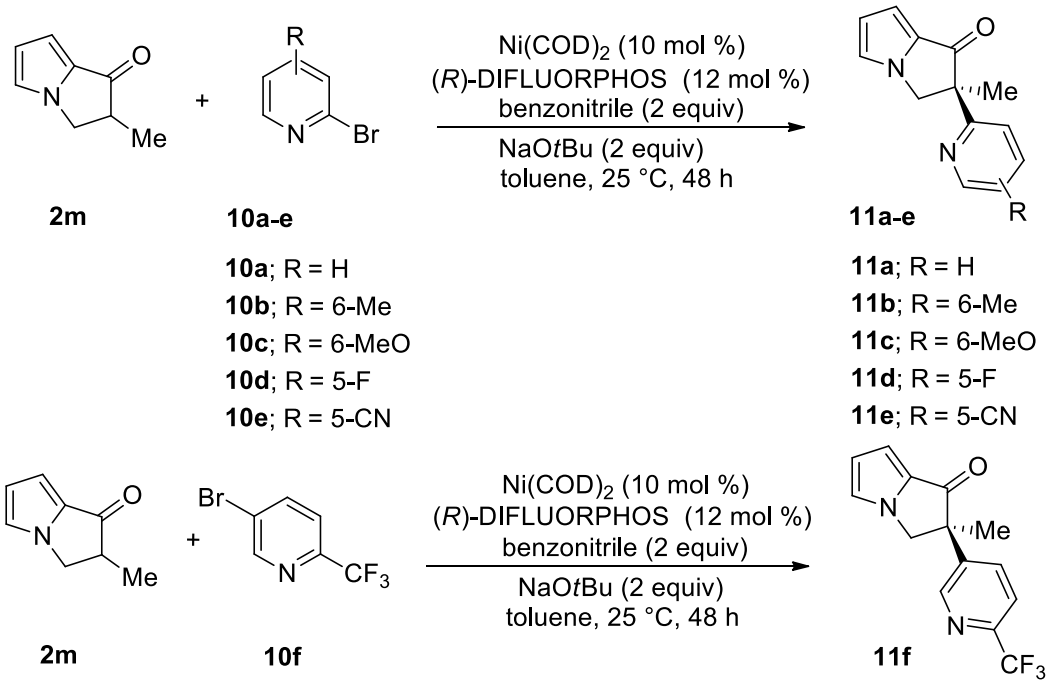
In a nitrogen-filled glovebox, 8-methyl-7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-one (**2b**) (0.100 mmol, 1.0 equiv), $Ni(COD)_2$ (2.8 mg, 0.0100 mmol, 0.10 equiv), (*R*)-DIFLUORPHOS (9.2 mg, 0.0120 mmol, 0.12 equiv), NaO*t*Bu (19.3 mg, 0.200 mmol, 2.0 equiv), 2-chloropyridine **6a** (0.200 mmol, 2.0 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**).

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

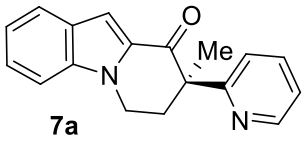


In a nitrogen-filled glovebox, 8-methyl-7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-one (**2b**) (0.100 mmol, 1.0 equiv), $Ni(COD)_2$ (2.8 mg, 0.0100 mmol, 0.10 equiv), (*R*)-DIFLUORPHOS (9.2 mg, 0.0120 mmol, 0.12 equiv), NaO*t*Bu (19.3 mg, 0.200 mmol, 2.0 equiv), the appropriate heteroaryl chloride **6b-i** (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**).

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)

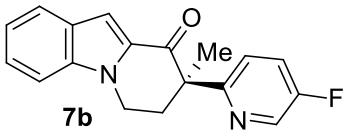


In a nitrogen-filled glovebox, 2-methyl-2,3-dihydro-1*H*-pyrrolizin-1-one (**2m**) (0.200 mmol, 1.0 equiv), $Ni(COD)_2$ (5.5 mg, 0.0200 mmol, 0.10 equiv), (*R*)-DIFLUORPHOS (18.4 mg, 0.0240 mmol, 0.12 equiv), NaO*t*Bu (38.4 mg, 0.400 mmol, 2.0 equiv), benzonitrile (41.2 mg, 0.400 mmol, 2.0 equiv), the 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

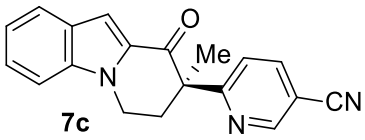
(*R*)-8-Methyl-8-(pyridin-2-yl)-7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-one (7a): Prepared according to the general procedure J from **2b** (20.0 mg, 0.100 mmol) and 2-chloropyridine **6a** (22.8 mg, 0.200 mmol). The crude product was purified by silica gel chromatography with a CombiFlash system (4 g column, 100:0→80:20 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 28.5 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

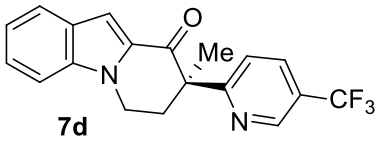
(*R*)-8-(5-Fluoropyridin-2-yl)-8-methyl-7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-one (7b): Prepared according to the general procedure K from **2b** (20.0 mg, 0.100 mmol) and 2-chloro-5-fluoropyridine (**6b**) (26.4 mg, 0.200 mmol). The crude product was purified by silica gel chromatography with a CombiFlash system (4 g column, 100:0→80:20 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.



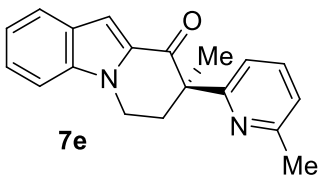
7c

(*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→80:20 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 38.9 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 33% 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

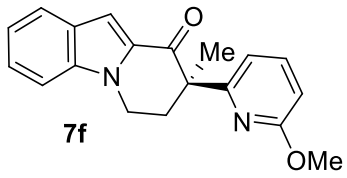
(*R*)-8-Methyl-8-(5-(trifluoromethyl)pyridin-2-yl)-7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-one (7d): Prepared according to the general procedure K from **2b** (20.0 mg, 0.100 mmol) and 2-chloro-5-(trifluoromethyl)pyridine **6d** (36.4 mg, 0.200 mmol). The crude product was purified by silica gel chromatography with a CombiFlash system (4 g column, 100:0→80:20 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 17.5 min (major); t_R 19.9 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→80:20 hexanes/EtOAc) to give **7e** as a yellow solid in

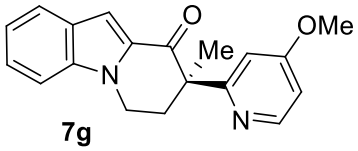
72% yield (21.0 mg, 0.0723 mmol). The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 12.2 min (major); t_R 17.6 min (minor) [Chiracel AS-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 99:1, 1.0 mL/min] to be 75% ee. $[\alpha]_D^{25}$ = +171.8° (c 0.74, $CHCl_3$). **^{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

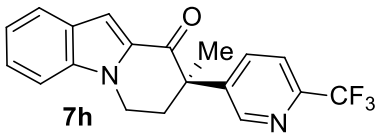
(*R*)-8-(6-Methoxypyridin-2-yl)-8-methyl-7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-one (7f): Prepared according to the general procedure K from **2b** (20.0 mg, 0.100 mmol) and 2-chloro-6-methoxypyridine **6f** (28.8 mg, 0.200 mmol). The crude product was purified by silica gel chromatography with a CombiFlash system (4 g column, 100:0→80:20 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

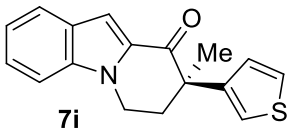
(*R*)-8-(4-Methoxypyridin-2-yl)-8-methyl-7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-one (7g): Prepared according to the general procedure K from **2b** (20.0 mg, 0.100 mmol) and 2-chloro-4-methoxypyridine **6g** (28.8 mg, 0.200 mmol). The crude product was purified by silica gel chromatography with a CombiFlash system (4 g column, 100:0→80:20 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→80:20 hexanes/EtOAc) to give **7h** as a yellow solid in 80% yield (27.7 mg, 0.0804 mmol). The enantiomeric excess was

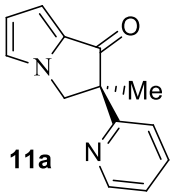
determined by HPLC analysis (254 nm, 25 °C) t_R 16.1 min (major); t_R 33.5 min (minor) [Chiracel AS-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90:10, 1.0 mL/min] to be 99% ee. $[\alpha]_D^{23}$ = +65.7° (c 1.03, $CHCl_3$). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.72 (s, 3H), 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

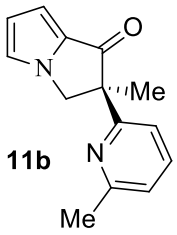
(*R*)-8-Methyl-8-(thiophen-3-yl)-7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-one (7i): Prepared according to the general procedure K from **2b** (20.0 mg, 0.100 mmol) and 3-chlorothiophene **6i** (23.8 mg, 0.200 mmol). The crude product was purified by silica gel chromatography with a CombiFlash system (4 g column, 100:0→80:20 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

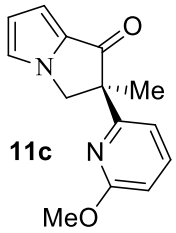
(*R*)-2-Methyl-2-(pyridin-2-yl)-2,3-dihydro-1*H*-pyrrolizin-1-one (11a): Prepared according to the general procedure L from **2m** (27.0 mg, 0.199 mmol) and 2-bromopyridine **10a** (63.1 mg, 0.399 mmol). The crude product was purified by silica gel chromatography with a CombiFlash system (4 g column, 100:0→80:20 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.



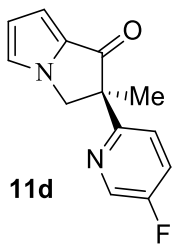
11b

(*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→80:20 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.

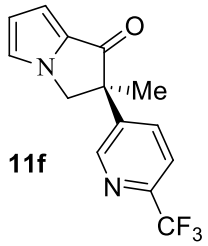


(*R*)-2-(6-Methoxypyridin-2-yl)-2-methyl-2,3-dihydro-1*H*-pyrrolizin-1-one (11c): Prepared according to the general procedure L from **2m** (27.0 mg, 0.199 mmol) and 2-bromo-6-methoxypyridine **10c** (75.1 mg, 0.399 mmol). The crude product was purified by silica gel chromatography with a CombiFlash system (4 g column, 100:0→80:20 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→80:20 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.

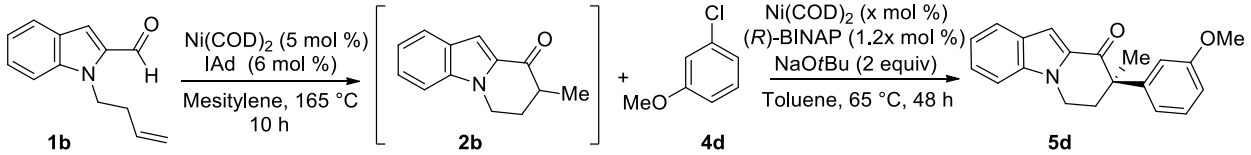


11f

(*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→80:20 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.

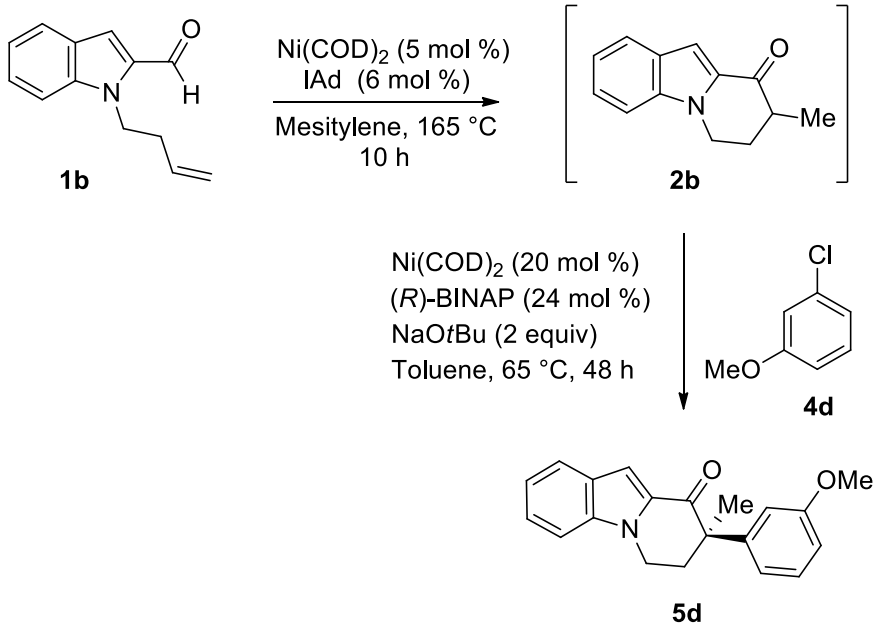
Identification of Reaction Conditions for One-pot Synthesis of (*R*)-8-(3-Methoxyphenyl)-8-methyl-7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-one (5d) via Sequential Hydroacylation/α-Arylation



	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	n.d
2[f]	0.50	99	10	0.50	0.10	22	19	n.d
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	n.d
6	0.13	99	10	0.50	0.16	50	40	n.d
7	0.25	99	10	0.25	0.20	30	10	n.d
8	0.13	99	10	0.37	0.20	50	30	n.d
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. n.d = Not determined

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

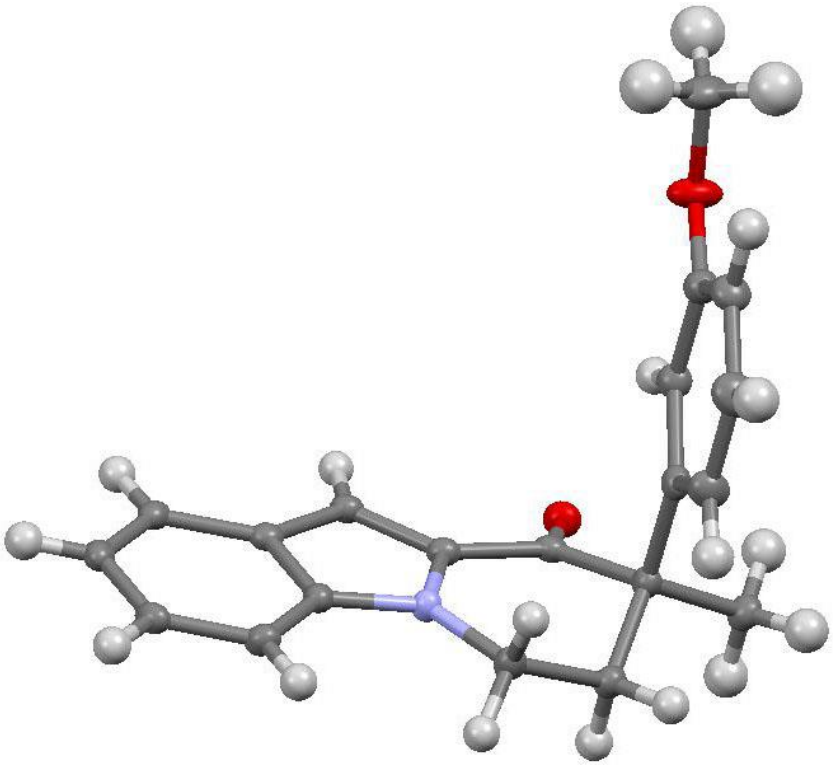


In a nitrogen-filled glovebox, 1-(but-3-en-1-yl)-1*H*-indole-2-carboxaldehyde (**1b**) (20.0 mg, 0.100 mmol, 1.0 equiv) was added to a 1-dram vial containing solution of $Ni(COD)_2$ (1.4 mg, 0.00500 mmol, 0.050 equiv) and IAd (2.0 mg, 0.00600 mmol, 0.060 equiv) in mesitylene (0.5 mL). The vial was sealed 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, $CHCl_3$).

Absolute Stereochemistry and Structure of 5d

Single crystal X-ray structure determination of **5d** was performed 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. 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.



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CHAPTER III

N-HETEROCYCLIC CARBENE-CATALYSED INTRAMOLECULAR HYDROACYLATION TO FORM BASIC NITROGEN-CONTAINING HETEROCYCLES

Modified from *Organic & Biomolecular Chemistry* **2016**, 14, 9981-9984.

James A. Walker Jr. and Levi Stanley

Abstract

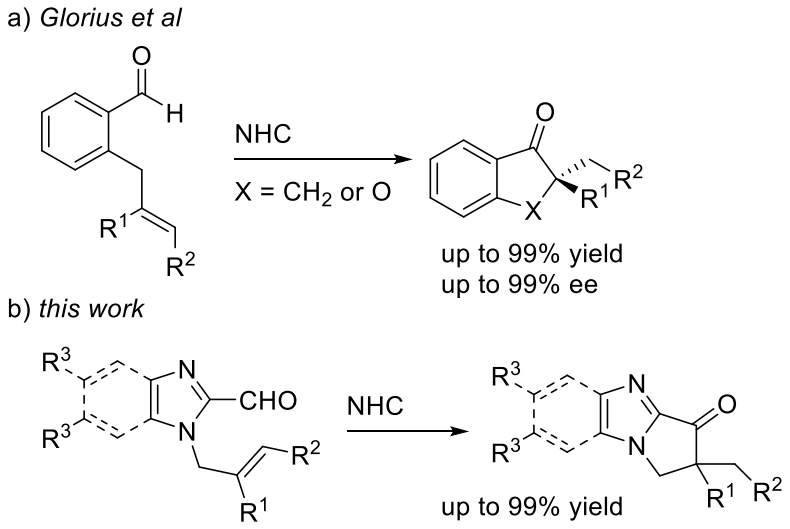
We report catalytic, intramolecular hydroacylations of *N*-allylimidazole-2-carboxaldehydes and *N*-allylbenzimidazole-2-carboxaldehydes. These *exo*-selective hydroacylations occur in the presence of a *N*-heterocyclic carbene catalyst to generate 5,6-dihydro-7*H*-pyrrolo[1,2-α]imidazol-7-ones and 1,2-dihydro-3*H*-benzo[*d*]pyrrolo[1,2-α]imidazol-2-ones in high yields (66–99%). In addition, hydroacylations of *N*-allylimidazole-2-carboxaldehydes in the presence of a chiral, non-racemic NHC catalyst occur, forming 5,6-dihydro-7*H*-pyrrolo[1,2-α]imidazol-7-ones in moderate-to-high yields (39–98%) with modest enantioselectivities (56–79% ee)

Introduction

Intramolecular hydroacylations of alkenes in the presence of transition-metal catalysts are well-known processes to generate a variety of valuable cyclic ketones.[1-6] Transition metal-catalysed alkene hydroacylations to form and functionalize nitrogen-containing heterocycles, in many cases with high yields and enantioselectivities, have been the focus of recent studies to improve the synthetic utility of these important C–C bond forming processes.[7-11] However, alkene hydroacylations to form nitrogen heterocycles containing a basic nitrogen atom often do not occur

in the presence of rhodium, cobalt, and nickel complexes that are excellent catalysts of alkene hydroacylation due to inhibition of the catalyst in the presence of basic nitrogen atoms.[7]

N-Heterocyclic carbenes (NHCs)[12-16] are a widely utilized class of organocatalysts and offer a promising alternative to transition-metal catalysts for alkene hydroacylation reactions.[17-20] Key to our studies, NHCs have been shown to tolerate additives containing basic nitrogen atoms.[21]

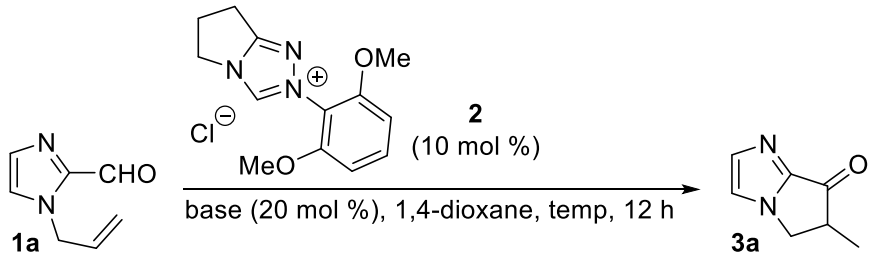


Scheme 1. (a) NHC-catalyzed enantioselective intramolecular hydroacylations of unactivated alkenes and (b) NHC-catlyzed, exo-selective hyddroacylation of *N*-allylimidazole and *N*-allylbenzimidazole-2-carboxaldehydes.

The potential to further develop alkene hydroacylation reactions as a platform to generate polycyclic nitrogen heterocycles led us to investigate NHC-catalysed intramolecular hydroacylations of *N*-allylimidazole-2-carboxaldehydes and *N*-allylbenzimidazole-2-carboxaldehydes. The development of such reactions offers the potential to rapidly generate dihydropyrroloimidazolone[22-23] and dihydrobenzopyrroloimidazolone[24-25] derivatives through *exo*-selective hydroacylations. Building on reports from Glorius and co-workers (Scheme 1a)[21, 26-28] and a recent study from our laboratory[29] on NHC-catalysed intramolecular hydroacylations of unactivated alkenes, we now report NHC-catalysed, *exo*-selective hydroacylations of *N*-allylimidazole- and *N*-allylbenzimidazole-2-carboxaldehydes to a form a variety of

dihydropyrroloimidazolones and dihydrobenzopyrroloimidazolones in moderate to high yields (Scheme 1b).

Table 1. Identification of reaction conditions for NHC-catalysed hydroacylation of *N*-allylimidazole-2-carboxaldehyde 1a[a]



entry	base	temp. (°C)	conv.[b] (%)	yield **3a**[c] (%)
1	DBU	25	100	14
2	DBU	60	100	96
3	DBU	80	100	95
4	DBU	100	100	45
5	DBU	120	100	0
6[d]	DBU	60	100	21
7[e]	DBU	60	82	81
8[d,e]	DBU	60	70	33
9	Et_3N	60	100	0
10	NaOAc	60	100	7
11	KOAc	60	100	18
12	K_3PO_4	60	100	99

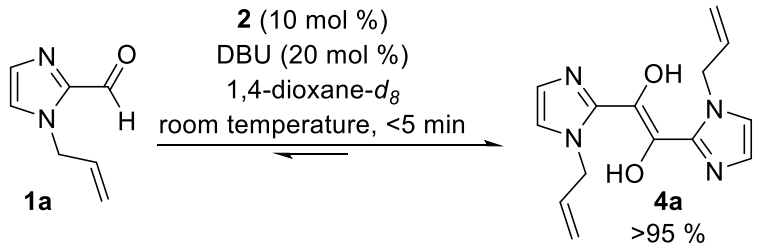
[a]Reaction conditions: **1a** (0.20 mmol), **2** (0.02 mmol), base (0.04 mmol), 1,4-dioxane (0.4 mL), 12 h. [b]Determined by ^{1}H NMR spectroscopy of the crude reaction mixture using dibromomethane as an internal standard. [c]Isolated yield of **3a**. [d]Reaction run in the presence of 10 mol % DBU. [e]Reaction run in the presence of 5 mol % **2**.

Results & Discussion

To identify general reaction conditions for the NHC-catalysed hydroacylation of *N*-allylimidazole- and *N*-allylbenzimidazole-2-carboxaldehydes, we evaluated the model reaction of *N*-allylimidazole-2-carboxaldehyde **1a** in the presence of triazolium chloride **2**[30] and a variety of organic and inorganic bases (Table 1). An initial survey of reaction conditions showed that reaction temperature dramatically impacts the yield of dihydropyrroloimidazolone **3a** (entries 1–5). Reactions of **1a** run at 60 or 80 °C formed **3a** in 96% and 95% yield when 20 mol% DBU was

employed as the base (entries 2 and 3). In contrast, reactions of **1a** carried out at room temperature and at or above 100 °C led to the formation of **3a** in low-to-moderate yield (entries 1, 4 and 5).

The low yields of ketone **3a** in reactions conducted at room temperature and at or above 100 °C result from a benzoin condensation that is the primary reaction pathway at room temperature and deactivation of the NHC catalyst at or above 100 °C.[27] The reaction of **1a** conducted at room temperature leads to the nearly quantitative formation of benzoin condensation product **4a** within minutes (Scheme 2). Heating the reaction mixture containing benzoin condensation product **4a** to 60 °C in the presence of the NHC catalyst generated from triazolium chloride **2** leads to high yield of ketone **3a** (see Fig. S2 in the Experimental section) In contrast, heating the reaction mixture containing **4a** at 100 or 120 °C in the presence of the NHC catalyst generated from triazolium chloride **2** did not lead to high yields of **3a**, likely because the NHC catalyst decomposes at these temperatures. The balance of the mass in these reactions is composed of the benzoin condensation product which is readily oxidized to the corresponding diketone upon exposure of the reaction mixture to air (see synthesis of S1 in the Experimental section).[31]

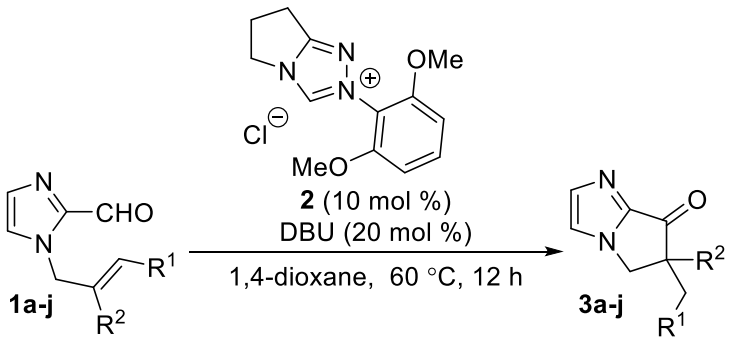


Scheme 2. Rapid NHC-catalysed benzoin condensation of **1a** at room temperature

The loading of catalyst and base and the identity of the base are also important reaction variables that must be controlled to generate **3a** in high yield (Table 1, entries 6–12). Lowering the loading of DBU to 10 mol% (entry 6), triazolium chloride 2 to 5 mol% (entry 7) or both (entry 8) was detrimental to the yield of **3a**. The model reaction formed **3a** in low yield when we replaced DBU with a relatively weak organic or inorganic base, such as triethylamine, sodium acetate, or

potassium acetate (entries 9–11). However, the identity of the base is not limited to DBU. The model reaction generates the hydroacylation product **3a** in nearly quantitative yield when tribasic potassium phosphate is used as the base (entry 12).

Table 2. NHC-catalyzed hydroacylation of *N*-allylimidazole-2-carboxaldehydes 1a-j[a]

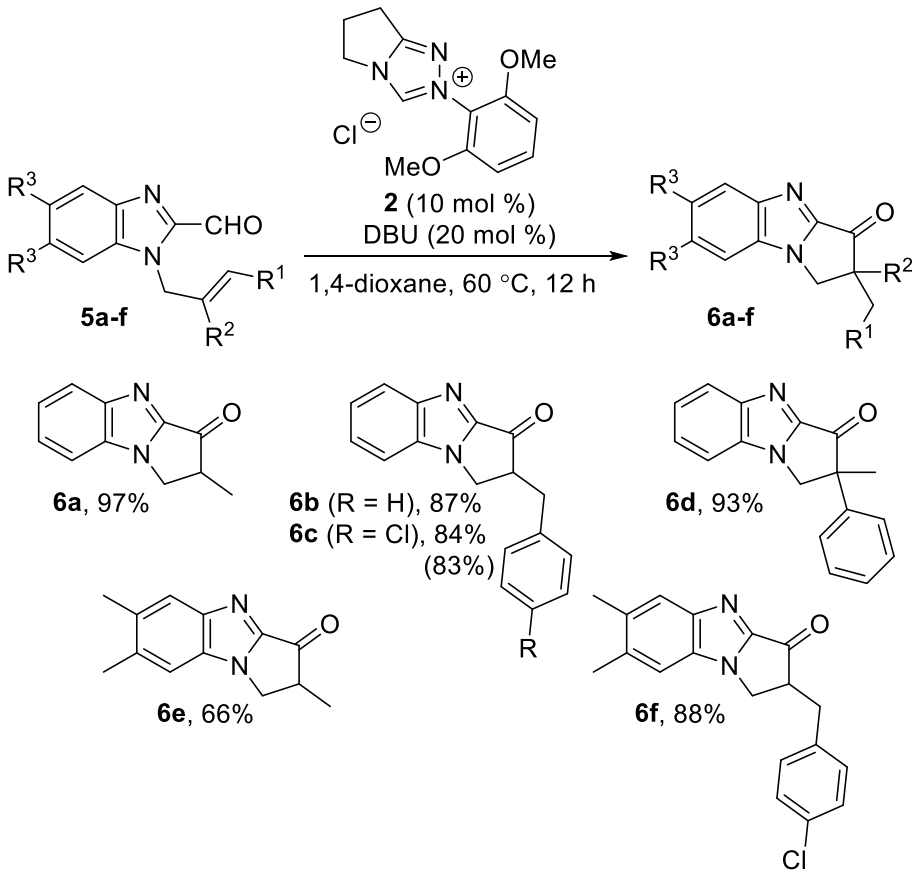


entry	**1**	R^1	R^2	yield 3[b] (%)
1	**1a**	H	H	96(99)[c]
2	**1b**	C_6H_5	H	96
3	**1c**	4-MeO-C_6H_4	H	85
4	**1d**	4-Cl-C_6H_4	H	99
5	**1e**	H	C_6H_5	99
6	**1f**	H	4-MeO-C_6H_4	99(88)[c]
7	**1g**	H	4-Cl-C_6H_4	95(81)[c]
8	**1h**	H	4-F-C_6H_4	99
9	**1i**	H	3-F-C_6H_4	99
10	**1j**	H	2-F-C_6H_4	99

[a]Reaction conditions: **1a-j** (0.20 mmol), triazolium **2** (0.02 mmol), DBU (0.04 mmol) and 1,4-dioxane (0.4 mL). [b]Isolated yield of **3** after column chromatography. [c]Reaction run in the presence of 10 mol % **2** and 20 mol % K_3PO_4.

A summary of NHC-catalysed intramolecular hydroacylations of *N*-allylimidazole-2-carboxaldehydes containing a range of substituted allyl units is shown in Table 2. The hydroacylation of *N*-allylimidazole-2-carboxaldehyde forms **3a** in high yield when either DBU or K_3PO_4 is used as the base (Table 2, entry 1). Reactions of *N*-allylimidazole-2-carboxaldehydes containing electron-neutral, electron-rich, or electron-deficient aryl groups at the terminal position of the allyl unit formed heterocyclic ketones **3b–3d** in good to excellent yields (85–99%, entries 2–4). Aryl substitution at the internal position of the allyl unit is also well tolerated.

Hydroacylations of *N*-allylimidazole-2-carboxaldehydes containing aryl groups with a variety of electronic properties and substitution patterns at the internal position of the allyl unit occur to form heterocyclic ketones **3e–3j** containing a quaternary carbon center in high yields (95–99%, entries 5–10).

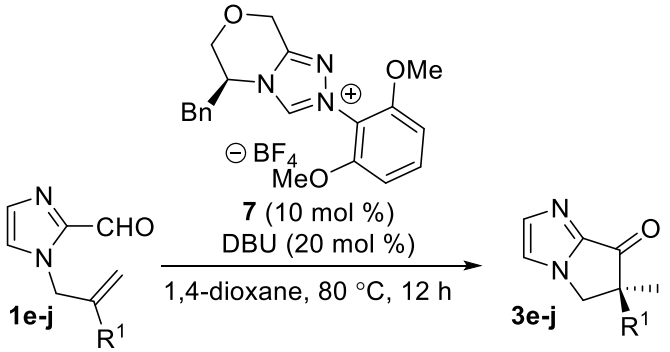


Scheme 3. NHC-catalysed hyddroacylation of *N*-allylbenzimidazole-2-carboxaldehydes. Reaction conditions: **5a-g** (0.20 mmol), triazolium **2** (0.02 mmol), DBU (0.04 mmol) and 1,4-dioxane (0.4 mL). Yields of **3** are isolated after column chromatography. Yields in parentheses correspond to reactions run in the presence of 10 mol % **2** and 20 mol % K_3PO_4.

The NHC-catalysed hydroacylations of *N*-allylbenzimidazole- 2-carboxaldehydes **5a–f** also occur to form heterocyclic ketone products **6a–f** in moderate-to-high yields (59–97%, Scheme 3). *N*-Allylbenzimidazole-2-carboxaldehydes containing unsubstituted allyl units, allyl units with terminal or internal aryl substitution, and 5,6-dimethylbenzimidazole units are all suitable substrates for the NHC-catalysed hydroacylation reaction. The NHC-catalysed hydroacylation of

N-allylbenzimidazole-2-carboxaldehyde **5a** formed the corresponding ketone **6a** in 97% yield. Hydroacylations of **5b–c**, substrates containing aryl substitution at the terminal position of the allyl unit, generated ketones **6b–c** in 83–87% yield. Intramolecular hydroacylations of *N*-allylbenzimidazole-2-carboxaldehydes **5d–f** containing substitution at the internal position of the allyl unit and on the benzimidazole backbone formed ketones **6d–f** in 66–93% yield.

Table 3. Enantioselective NHC-catalysed hydroacylation of *N*-allylimidazole-2-carboxaldehydes **1e-j**[a]



entry	**1**	R	yield 3[b] (%)	ee[c] (%)
1	**1e**	C_6H_5	90	71
2	**1f**	4-MeO-C_6H_4	98	79
3	**1g**	4-Cl-C_6H_4	96	67
4	**1h**	4-F-C_6H_4	81	75
5	**1i**	3-F-C_6H_4	93	67
6	**1j**	2-F-C_6H_4	39	56

[a]Reaction conditions: **1e-j** (0.10 mmol), triazolium **7** (0.01 mmol), DBU (0.02 mmol) and 1,4-dioxane (0.2 mL). [b]Isolated yield of **3** after column chromatography. [c]Determined by chiral HPLC analysis.

In addition to hydroacylations of *N*-allylimidazole-2-carboxaldehydes and *N*-allylbenzimidazole-2-carboxaldehydes conducted in the presence of an achiral NHC catalyst, we investigated enantioselective hydroacylations of *N*-allylimidazole-2-carboxaldehydes **1e–j** catalyzed by the chiral, non-racemic NHC derived from triazolium tetrafluoroborate **7** (Table 3). The hydroacylations of *N*-allylimidazole-2-carboxaldehydes **1e–i** occur to form heterocyclic ketone products **3e–i** in high yields (81–98%, entries 1–5) with modest enantioselectivities (67–79% ee). However, the hydroacylation of *N*-allylimidazole-2-carboxaldehyde **1j** (R = 2-F-C_6H_4)

generated heterocyclic ketone **3j** in 39% yield with 56% ee (entry 6). The absolute configuration of chiral, non-racemic heterocyclic ketones **3e**–**j** was assigned as (S) based on analogy with a previous report by Glorius and coworkers.[21]

Conclusions

In conclusion, we have established *exo*-selective NHC-catalyzed intramolecular hydroacylation of *N*-allylimidazoleand *N*-allylbenzimidazole-2-carboxaldehydes as a practical approach to generate 5,6-dihydro-7*H*-pyrrolo[1,2-α]imidazol-7- ones and 1,2-dihydro-3*H*-benzo[*d*]pyrrolo[1,2-α]imidazol-2- ones in high yields. This synthetic methodology represents a new example of NHC-catalysed hydroacylation of unactivated alkenes that enables efficient hydroacylations of nitrogen heterocycles containing basic nitrogen atoms.

Experimental

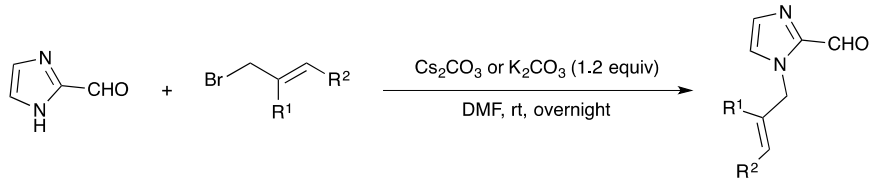
General Experimental. All air-sensitive procedures were conducted under inert atmosphere in a nitrogen-filled dry box or by standard Schlenk techniques. All reactions were performed under an atmosphere of nitrogen unless otherwise stated. All glassware for moisture sensitive reactions was dried at 140 °C in an oven. Tetrahydrofuran, methylene chloride and *N*,*N*-dimethylformamide 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 Aldrich. Flash column chromatography was performed on SiliFlash® P60 silica gel (40-63 μm, 60Å) or using a Teledyne Isco Combiflash® R*f* system with Redi*Sep* GoldTM columns using hexanes/ethyl acetate or dichloromethane/methanol mixtures as eluents. Reactions products were visualized on TLC by UV light or by staining with $KMnO_4$.

Instrumentation. HRMS (ESI) analysis was performed at the Iowa State University Chemical Instrumentation Facility on an Agilent 6540 QTOF spectrometer. 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, 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 reporting in hertz

Materials. (*E*)-1-(3-Bromoprop-1-en-1yl)-4-methoxybenzene (**S1c**), (*E*)-1-(3-Bromoprop-1-en-2-yl)-4-chlorobenzene (**S1d**) were synthesized according to reported literature procedures.[32] 1-(3-Bromoprop-1-en-2-yl)-4-fluorobenzene (**S1h**), 1-(3-bromoprop-1-en-2yl)-4-chlorobenzene (**S1g**), 1-(3-bromoprop-1-en-2-yl)-4-methoxybenzene (**S1f**), 1-(3-bromoprop-1-en-2-yl)-3-fluorobenzene (**S1i**), 1(3-bromoprop-1-en-2-yl)-2-fluorobenzene (**S1j**), and (3-bromoprop-1-en-2-yl)benzene (**S1e**) were synthesized according to a literature procedure.[33] (1*H*-Benzo[*d*]imidazol-2-yl)methanol and (5,6-dimethyl-1*H*-benzo[*d*]imidazol-2-yl)methanol were synthesized according to a literature procedure.[34] Cinnamyl bromide (**S1b**), allyl bromide (**S1a**), activated manganese dioxide, anhydrous 1,4-dioxane, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were purchased from Aldrich and used without further purification. Imidazole-2-carboxaldehyde was purchased from AK Scientific and used without further purification. Triazolium chloride **2** was synthesized according to a literature procedure.[26] Triazolium tetrafluoroborate **7** was synthesized according to a literature procedure.[35]

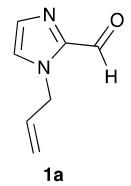
General Procedure A: Synthesis of *N*-allylimdazole-2-carboxaldehydes (1a-j):



S1a; R^1 = H, R^2 = H
S1b; R^1 = H, R^2 = Ph
S1c; R^1 = H, R^2 = 4-OMe-C_6H_4
S1d; R^1 = H, R^2 = 4-Cl-C_6H_4
S1e; R^1 = Ph, R^2 = H
S1f; R^1 = 4-MeO-C_6H_4, R^2 = H
S1g; R^1 = 4-Cl-C_6H_4, R^2 = H
S1h; R^1 = 4-F-C_6H_4, R^2 = H
S1i; R^1 = 3-F-C_6H_4, R^2 = H
S1j; R^1 = 2-F-C_6H_4, R^2 = H

1a; R^1 = H, R^2 = H
1b; R^1 = H, R^2 = Ph
1c; R^1 = H, R^2 = 4-OMe-C_6H_4
1d; R^1 = H, R^2 = 4-Cl-C_6H_4
1e; R^1 = Ph, R^2 = H
1f; R^1 = 4-MeO-C_6H_4, R^2 = H
1g; R^1 = 4-Cl-C_6H_4, R^2 = H
1h; R^1 = 4-F-C_6H_4, R^2 = H
1i; R^1 = 3-F-C_6H_4, R^2 = H
1j; R^1 = 2-F-C_6H_4, R^2 = H

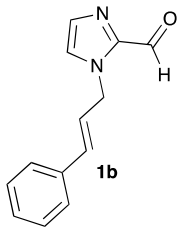
N-Allylimidazole-2-carboxaldehydes (**1a-j**) were prepared according to a modified literature procedure from the appropriate allyl bromides (**S1a-j**) and imidazole-2-carboxaldehyde.[36] To the appropriate *N*-allylimidazole-carboxaldehyde (1.0 equiv) and Cs_2CO_3 or K_2CO_3 (1.2 equiv) was added DMF (0.27 M). The resulting mixture was stirred at room temperature for 0.5 h. The appropriate allyl 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 and 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 *N*-allylimidazole-2-carboxaldehyde (**1a-j**).



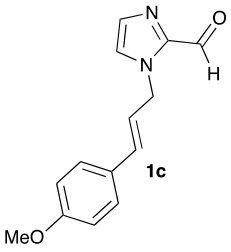
1a

1-allyl-1*H*-imidazole-2-carboxaldehyde (1a): Prepared according to general procedure A from imidazole-2-carboxaldehyde (0.500 g, 5.20 mmol) and allyl bromide **S1a** (0.674 mL, 7.80 mmol). The crude reaction mixture was purified by flash column chromatography (90:10 hexane:EtOAc) to give **1a** as a brown oil in 49% yield (350 mg, 2.54 mmol) **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.96 (d, *J* = 6.0 Hz, 2H), 5.02 (dd, *J* = 16.0, 0.8 Hz, 1H), 5.17 (dd, *J* = 10.4, 0.8 Hz, 1H), 5.89 (ddt, *J* = 16.0, 10.4, 6.0 Hz, 1H), 7.11 (app s, 1H),

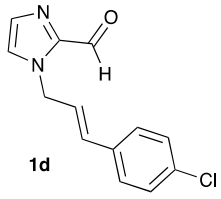
7.21 (app s, 1H), 9.72 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 49.7, 118.5, 126.0, 131.6, 132.4, 143.1, 181.9. **HRMS** (ESI): Calcd. for $C_7H_9N_2O^+$ ($[M+H]^+$): 137.0709, Found: 137.0718.



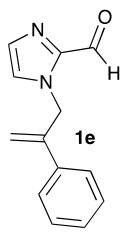
1-cinnamyl-1*H*-imidazole-2-carboxaldehyde (1b): Prepared according to general procedure A from imidazole-2-carboxaldehyde (1.44 g, 15.0 mmol) and cinnamyl bromide **S1b** (3.31 mL, 22.5 mmol). The crude reaction mixture was purified by flash column chromatography (70:30 hexanes:EtOAc) to give **1b** as a light yellow solid in 51% yield (1.63 g, 7.68 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.12 (dd, *J* = 6.4, 1.2 Hz, 2H), 6.22 (dt, *J* = 15.6, 6.4 Hz, 1H), 6.47 (d, *J* = 15.6 Hz, 1H), 7.16 (app s, 1H), 7.18-7.30 (m, 6H), 9.77 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 49.5, 123.3, 126.0, 126.7, 128.4, 128.8, 131.9, 134.4, 135.8, 143.3, 182.3. **HRMS** (ESI): Calcd. for $C_{13}H_{13}N_2O^+$ ($[M+H]^+$): 213.1022, Found: 213.1026.



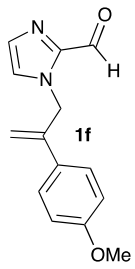
(*E*)-1-(3-(4-methoxyphenyl)allyl)-1*H*-imidazole-2-carboxaldehyde (1c): Prepared according to general procedure A from imidazole-2-carbaldehyde (62.0 mg, 0.640 mmol), and *trans*-*p*-methoxycinnamyl bromide **S1c** (0.219 g, 0.970 mmol). The crude reaction mixture was purified by flash column chromatography (100:0 hexanes:EtOAc to 90:10 hexanes:EtOAc) to give **1c** as a brown oil in 39% yield (0.060 g, 0.25 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.73 (s, 3H), 5.09 (d, *J* = 6.0 Hz, 2H), 6.09 (dt, *J* = 15.6, 6.0 Hz, 1H), 6.44 (d, *J* = 15.6 Hz, 1H), 6.78 (d, *J* = 8.0 Hz, 2H), 7.14-7.30 (m, 4H), 9.77 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 49.7, 55.4, 114.2, 120.9, 125.9, 128.0, 128.5, 131.9, 134.0, 143.3, 159.9, 182.3. **HRMS** (ESI): Calcd. for $C_{14}H_{15}N_2O_2^+$ ($[M+H]^+$): 243.1128, Found: 243.1135.



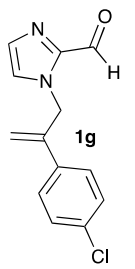
(*E*)-1-(3-(4-chlorophenyl)allyl)-1*H*-imidazole-2-carboxaldehyde (1d): Prepared according to general procedure A from imidazole-2-carboxaldehyde (0.140 g, 1.44 mmol) and *trans*-*p*-chlorocinnamyl bromide **S1d** (0.500 g, 2.16 mmol). The crude reaction mixture was purified by flash column chromatography (100:0 hexanes:EtOAc to 90:10 hexanes:EtOAc) to give **1d** as an off-white solid in 23% yield (0.082 g, 0.33 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.11 (d, *J* = 8.0 Hz, 2H), 6.18 (dt, *J* = 16.0, 8.0 Hz, 1H), 6.38 (d, *J* = 16.0 Hz, 1H), 7.15 (app s, 1H), 7.17-7.22 (m, 4H), 7.25 (app s, 1H), 9.77 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 49.4, 124.1, 126.0, 127.9, 129.0, 132.0, 132.9, 134.1, 134.3, 143.3, 182.3. **HRMS** (ESI): Calcd. for $C_{13}H_{12}ClN_2O^+$ ($[M+H]^+$): 247.0633, Found: 247.0642.



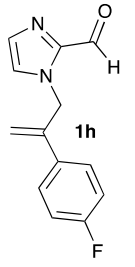
1-(2-phenylallyl)-1*H*-imidazole-2-carboxaldehyde (1e): Prepared according to general procedure A from imidazole-2-carboxaldehyde (0.200 g, 2.08 mmol) and 2-phenylallyl bromide **S1e** (0.615 g, 3.12 mmol). The crude reaction mixture was purified by flash column chromatography (100:0 hexanes:EtOAc to 90:10 hexanes:EtOAc) to give **1e** as a brown oil in 65% yield (0.286 g, 1.35 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.81 (s, 1H), 5.38 (app s, 3H), 7.05 (app s, 1H), 7.16 (app s, 1H), 7.18-7.28 (m, 1H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.31 (dd, *J* = 8.0, 1.2 Hz, 2H), 9.74 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 50.8, 115.2, 126.2, 126.3, 128.5, 128.7, 131.8, 137.8, 143.3, 143.6, 182.2. **HRMS** (ESI): Calcd. for $C_{13}H_{13}N_2O^+$ ($[M+H]^+$): 213.1022, Found: 213.1020



1-(2-(4-methoxyphenyl)allyl)-1*H*-imidazole-2-carboxaldehyde (1f): Prepared according to general procedure A from imidazole-2-carbaldehyde (0.455 g, 4.74 mmol) and 1-(3-bromoprop-1-en-2-yl)-4-methoxybenzene **S1f** (1.29g, 5.68 mmol). The crude reaction mixture was purified by flash column chromatography (100:0 hexanes:EtOAc to 90:10 hexanes:EtOAc) to give **1f** as a light-brown solid in 12% yield (0.138 g, 0.570 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.79 (s, 3H), 4.85 (s, 1H), 5.41 (s, 1H), 5.44 (s, 2H), 6.84 (d, *J* = 8.4 Hz, 2H), 7.13 (app s, 1H), 7.24 (app s, 1H), 7.33 (d, *J* = 8.4 Hz, 2H), 9.83 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 51.0, 55.4, 114.0, 114.1, 126.3, 127.4, 130.2, 131.8, 142.9, 143.4, 159.9, 182.3. **HRMS** (ESI): Calcd. for $C_{14}H_{15}N_2O_2^+$ ($[M+H]^+$): 243.1128, Found:243.1127

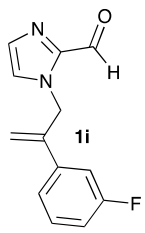


1-(2-(4-chlorophenyl)allyl)-1*H*-imidazole-2-carboxaldehyde (1g): Prepared according to general procedure A from imidazole-2-carboxaldehyde (0.390 g, 4.11 mmol) and 1-(3-bromoprop-1-en-2-yl)-4-chlorobenzene **S1g** (1.14 g, 4.93 mmol). The crude reaction mixture was purified by flash column chromatography (100:0 hexanes:EtOAc to 90:10 hexanes:EtOAc) to give **1g** as a off-white solid in 30% yield (0.300 g, 1.23 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.94 (s, 1H), 5.45 (s, 2H), 5.47 (s, 1H), 7.14 (app s, 1H), 7.27 (d, *J* = 8.4 Hz, 2H), 7.27 (app s, 1H), 7.46 (d, *J* = 8.4 Hz, 2H), 9.82 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 50.7, 115.9, 122.7, 126.3, 127.9, 131.9, 132.0, 136.8, 142.8, 143.3, 182.3. **HRMS** (ESI): Calcd. for $C_{13}H_{12}ClN_2O^+$ ($[M+H]^+$): 247.0633, Found: 247.0624

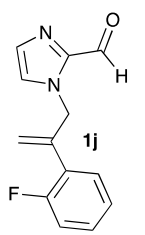


1-(2-(4-fluorophenyl)allyl)-1*H*-imidazole-2-carboxaldehyde (1h): Prepared according to general procedure A from imidazole-2-carboxaldehyde (0.306 g, 3.19 mmol) and 1-(3-bromoprop-1-en-2-yl)-4-fluorobenzene **S1h** (0.823 g, 3.83 mmol). The crude reaction mixture was purified by flash column chromatography (100:0

hexanes:EtOAc to 90:10 hexanes:EtOAc) to give **1h** as a brown amorphous solid in 23% yield (0.168 g, 0.730 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.88 (s, 1H), 5.40 (s, 1H), 5.43 (s, 2H), 7.00 (dd, *J* = 8.8, 8.8 Hz, 2H), 7.13 (app s, 1H), 7.25 (d, *J* = 0.8 Hz, 1H), 7.35 (dd, *J* = 8.8, 5.2 Hz, 2H), 9.81 (d, *J* = 1.2 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 50.9, 115.3 (d, *J* = 1.2 Hz, 2C), 115.7 (d, *J* = 21.8 Hz, 2C), 126.3, 128.0 (d, *J* = 8 Hz, 1C), 131.9, 133.9 (d, *J* = 3.4 Hz, 1C), 142.8, 143.3, 162.9 (d, *J* = 249.5 Hz, 1C), 182.3. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -113.48 (m, 1F). **HRMS** (ESI): Calcd. for $C_{13}H_{12}FN_2O^+$ ($[M+H]^+$): 231.0928, Found: 231.0922



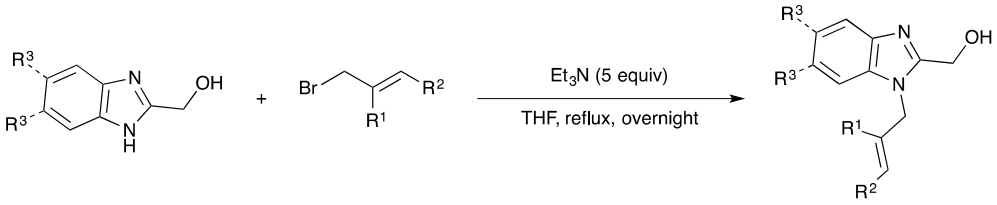
1-(2-(3-fluorophenyl)allyl)-1*H*-imidazole-2-carboxaldehyde (1i): Prepared according to general procedure A from imidazole-2-carboxaldehyde (0.291 g, 3.03 mmol) and 1-(3-bromoprop-1-en-2-yl)-3-flurobenzene **S1i** (0.784 g, 3.64 mmol). The crude reaction mixture was purified by flash column chromatography (100:0 hexanes:EtOAc to 90:10 hexanes:EtOAc) to give **1i** as a brown oil in 28% yield (0.195 g, 0.846 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.94 (s, 1H), 5.46 (s, 2H), 5.50 (s, 1H), 7.00 (m, 1H), 7.10 (app dt, *J* = 15.6, 2.4 Hz, 1H), 7.15 (app s, 1H), 7.18(ddd, *J* = 7.6, 1.6, 0.8 Hz, 1H), 7.28 (d, *J* = 0.8 Hz, 1H), 7.28-7.34 (m, 1H), 9.83 (d, *J* = 0.8 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 50.6, 113.4 (d, *J* = 22.2 Hz, 1C), 115.4 (d, *J* = 21.2 Hz, 1C), 116.1, 121.9 (d, *J* = 3.0 Hz, 1C), 126.3, 130.3 (d, *J* = 8.4 Hz, 1C), 131.9, 140.1 (d, *J* = 7.6 Hz, 1C), 142.7 (d, *J* = 2.2 Hz, 1C), 143.3, 162.9 (d, *J* = 247.6 Hz, 1C), 182.2. **^{19}F NMR** ($CDCl_3$ 376 MHz): δ -112.71 (m, 1F). **HRMS** (ESI): Calcd. for $C_{13}H_{12}FN_2O^+$ ($[M+H]^+$): 231.0928, Found: 231.0922



1(2-(2-fluorophenyl)allyl)-1*H*-imidazole-2-carbaldehyde (1j): Prepared according to general procedure A from imidazole-2-carbaldehyde (0.570 g, 5.88 mmol) and 1-(3-bromoprop-1-en-2-yl)-2-fluorobenzene **S1j** (1.52 g, 7.01 mmol). The crude

reaction mixture was purified by flash column chromatography (100:0 hexanes:EtOAc to 90:10 hexanes:EtOAc) to give **1j** as a brown oil in 15% yield (0.200 g, 0.866 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.12 (s, 1H), 5.38 (s, 1H), 5.42 (s, 2H), 7.02-7.12 (m, 2H), 7.14 (s, 1H), 7.20-7.32 (m, 3H), 9.80 (d, *J* = 0.8 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 51.4, 115.9 (d, *J* = 22.4 Hz, 1C), 118.6 (d, *J* = 2.2 Hz, 1C), 124.5 (d, *J* = 3.4 Hz, 1C), 126.2 (d, *J* = 14.4 Hz, 1C), 126.6, 130.1 (d, *J* = 8.4 Hz, 1C), 130.2 (d, *J* = 3.8 Hz, 1C), 131.7, 140.0, 143.4, 159.9 (d, *J* = 248.6 Hz, 1C), 181.9. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -115.31 (m, 1F). **HRMS** (ESI): Calcd. for $C_{13}H_{12}FN_2O^+$ ($[M+H]^+$): 231.0928, Found: 231.0926.

General Procedure B: Synthesis of *N*-allylbenzimidazole-2-carboxaldehyde (5a-f)



S1a; R^1 = H, R^2 = H
S1b; R^1 = H, R^2 = Ph
S1c; R^1 = H, R^2 = 4-Cl-C_6H_4
S1d; R^1 = Ph, R^2 = H

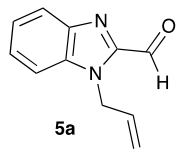
S2a; R^1 = H, R^2 = H, R^3 = H
S2b; R^1 = H, R^2 = Ph, R^3 = H
S2c; R^1 = H, R^2 = 4-Cl-C_6H_4, R^3 = H
S2d; R^1 = Ph, R^2 =H, R^3 = H
S2e; R^1 = H, R^2 = H, R^3 = CH_3
S2f; R^1= H, R^2 = 4-Cl-C_6H_4, R^3 = CH_3

S2a; R^1 = H, R^2 = H, R^3 = H
S2b; R^1 = H, R^2 = Ph, R^3 = H
S2c; R^1 = H, R^2 = 4-Cl-C_6H_4, R^3 = H
S2d; R^1 = Ph, R^2 =H, R^3 = H
S2e; R^1 = H, R^2 = H, R^3 = CH_3
S2f; R^1= H, R^2 = 4-Cl-C_6H_4, R^3 = CH_3

5a; R^1 = H, R^2 = H, R^3 = H
5b; R^1 = H, R^2 = Ph, R^3 = H
5c; R^1 = H, R^2 = 4-Cl-C_6H_4, R^3 = H
5d; R^1 = Ph, R^2 =H, R^3 = H
5e; R^1 = H, R^2 = H, R^3 = CH_3
5f; R^1= H, R^2 = 4-Cl-C_6H_4, R^3 = CH_3

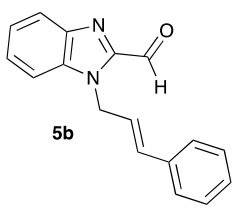
N-allylbenzimidazole-2-carboxaldehydes (**5a-f**) were prepared according to a modified literature procedure from (1*H*-benzo[*d*]imidazol-2-yl)methanol or (5,6-dimethyl-1*H*-

benzo[*d*]imidazol-2-yl)methanol.[37] To a solution of (1*H*-benzo[*d*]imidazol-2-yl)methanol or (5,6-dimethyl-1*H*-benzo[*d*]imidazol-2-yl)methanol in THF (0.3M) was added Et_3N (5 equiv). The solution was refluxed for 1 h. The appropriate allyl bromide (1.2-5.0 equiv)(**S1a-d**) was added, and the mixture refluxed overnight. Water was added to the cooled reaction mixture. The resulting mixture was extracted with Et_2O (3x). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to afford the appropriate crude *N*-allylbenzimidazol-2-methanol (**S2a-f**). To a solution of the crude *N*-allylbenzimidazol-2-methanol (1.00 equiv) in DCM (4 mM) was added activated MnO_2 (30.0 equiv). The resulting mixture was refluxed overnight. The cooled reaction mixture was filtered through a plug of celite. The combined organic layers were concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (DCM:EtOAc or hexanes:EtOAc) to give the appropriate *N*-allylbenzimidazole-2-carboxaldehyde (**5a-f**).

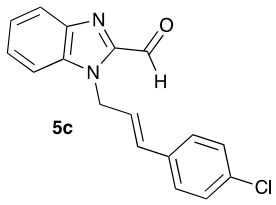


5a

1-allyl-1*H*-benzo[*d*]imidazole-2-carboxaldehyde (5a): Prepared according to general procedure B from (1*H*-benzo[*d*]imidazol-2-yl)methanol (0.500 g, 3.37 mmol) and allyl bromide **S1a** (291 μL, 3.37 mmol) to give the crude product **S2a** (0.201 g, 1.06 mmol). Oxidation with MnO_2 (0.929 mg, 10.69 mmol) generated crude **5a**. The crude reaction mixture was purified by flash column chromatography (100:0 hexanes:EtOAc to 90:10 hexanes EtOAc) to give **5a** as an orange solid in 20% yield over two-steps (0.128 g, 0.687 mmol). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.03 (dd, *J* = 16.8, 0.6 Hz, 1H), 5.19 (dd, *J* = 10.2, 0.6 Hz, 1H), 5.25 (app dt, *J* = 5.4, 1.2 Hz, 2H), 5.98 (ddt, *J* = 16.8, 10.2, 5.4 Hz, 1H), 7.37-7.40 (m, 1H), 7.45-7.46 (m, 2H), 7.93 (d, *J* = 8.4 Hz, 1H), 10.10 (s, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 46.9, 111.2, 117.8, 122.5, 124.3, 127.0, 132.1, 136.4, 143.0, 145.8, 184.9 **HRMS** (ESI): Calcd. for $C_{11}H_{11}N_2O^+$ ($[M+H]^+$): 187.0866, Found: 187.0872

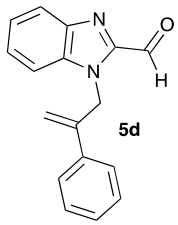


1-cinnamyl-1*H*-benzo[*d*]imidazole-2-carboxaldehyde (5b): Prepared according to general procedure B from (1*H*-benzo[*d*]imidazol-2-yl)methanol (0.801 g, 5.41 mmol) and **S1b** (4.00 mL, 27.0 mmol) to give the crude product **S2b** (0.258 g, 0.980 mmol). Oxidation with MnO_2 (2.55 g, 29.3 mmol) generated crude **5b**. The crude reaction mixture was purified by flash column chromatography (100:0 DCM:EtOAc to 95:5 DCM:EtOAc) to give **5b** as a light-orange solid in 9% yield over two-steps (0.132 g, 0.500 mmol). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.43 (dd, *J* = 6.0, 1.2, Hz, 2H), 6.34 (dt, *J* = 16.2, 6.0 Hz, 1H), 6.56 (d, *J* = 16.2 Hz, 1H), 7.25 (t, *J* = 7.2 Hz, 1H), 7.30 (t, *J* = 7.2 Hz, 2H), 7.33 (d, *J* = 7.2 Hz, 2H), 7.44 (ddd, *J* = 15.6, 8.4, 1.2 Hz, 1H), 7.50 (ddd, *J* = 15.6, 8.4, 1.2 Hz, 1H), 7.56 (d, *J* = 8.4 Hz, 1H), 7.99 (d, *J* = 8.4 Hz, 1H), 10.17 (s, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 46.7, 111.2, 122.5, 123.2, 124.3, 126.6, 127.1, 128.2, 128.6, 133.4, 135.8, 136.3, 143.0, 145.8, 184.9. **HRMS** (ESI): Calcd. for $C_{17}H_{15}N_2O^+$ ($[M+H]^+$): 263.1179, Found: 263.1181.

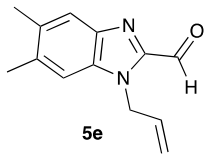


(*E*)-1-(3-(4-chlorophenyl)allyl)-1*H*-benzo[*d*]imidazole-2-carboxaldehyde (5c): Prepared according to general procedure B from (1*H*-benzo[*d*]imidazol-2-yl)methanol (0.452 g, 3.05 mmol) and **S1c** (3.53 g, 15.2 mmol) to give the crude product **S2c** (0.227 g, 0.765 mmol). Oxidation with MnO_2 (1.98 g, 22.8 mmol) generated crude **5c**. The crude reaction mixture was purified by flash column chromatography (100:0 hexanes:EtOAc to 85:15 hexanes:EtOAc) to give **5c** as a white solid in 7% yield over two-steps (0.059 g, 0.20 mmol). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.40 (dd, *J* = 6.0, 1.2 Hz, 2H), 6.29 (dt, *J* = 15.6, 6.0 Hz, 1H), 6.46 (d, *J* = 15.6 Hz, 1H), 7.20-7.24 (m, 4H), 7.41 (ddd, *J* = 15.0, 8.4, 1.2 Hz, 1H), 7.48, (ddd, *J* = 15.0, 8.4, 1.2 Hz, 1H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.96 (d, *J* = 8.4 Hz, 1H), 10.13 (s, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 46.5, 111.1, 122.7, 123.9,

124.4, 127.2, 127.9, 128.9, 132.1, 133.9, 134.4, 136.4, 143.0, 145.8, 185.1. **HRMS** (ESI): Calcd. for $C_{17}H_{14}ClN_2O^+$ ($[M+H]^+$): 297.0789, Found: 297.0789.

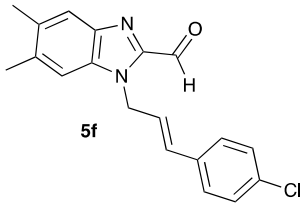


1-(2-phenylallyl)-1*H*-benzo[d]imidazole-2-carboxaldehyde (5d): Prepared according to general procedure B from (1*H*-benzo[*d*]imidazol-2-yl)methanol (0.725 g, 4.89 mmol) and **S1d** (4.82 g, 24.5 mmol) to give the crude product **S2d** (0.437 g, 1.65 mmol), Oxidation with MnO_2 (4.31 g, 49.6 mmol) generate crude **5d**. The crude reaction mixture was purified by flash column chromatography (100:0 hexanes:EtOAc to 90:10 hexanes:EtOAc) to give **5d** as an orange solid in 16% yield over two-steps (0.210 g, 0.801 mmol). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 4.51 (s, 1H), 5.33 (s, 1H), 5.67 (s, 2H), 7.30-7.38 (m, 3H), 7.38-7.42 (m, 1H), 7.43-7.48 (m, 4H), 7.94 (d, *J* = 8.4 Hz, 1H), 10.11 (s, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 48.2, 111.6, 113.1, 122.5, 124.4, 126.4, 127.2, 128.5, 128.7, 136.7, 138.5, 142.9, 143.3, 146.0, 184.9. **HRMS** (ESI): Calcd. for $C_{17}H_{15}N_2O^+$ ($[M+H]^+$): 263.1179, Found: 263.1184.



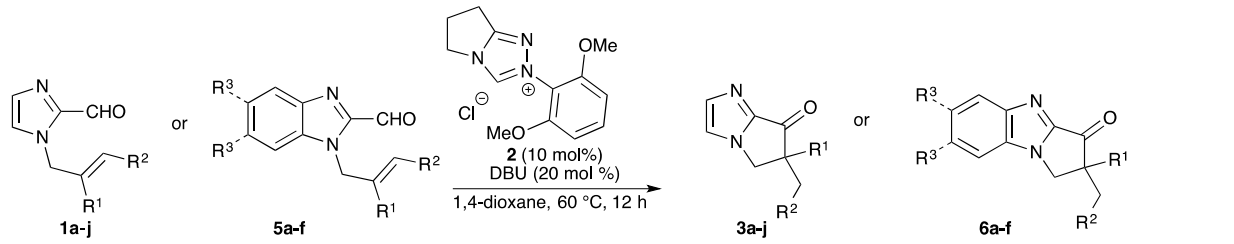
1-allyl-5,6-dimethyl-1*H*-benzo[*d*]imidazole-2-carboxaldehyde (5e): Prepared according to general procedure B from (5,6-dimethyl-1*H*-benzo[*d*]imidazol-2-yl)methanol (1.00 g, 5.67 mmol) and **S1a** (0.589 ml, 6.81 mmol) to give the crude product **S2e** (0.289 g, 1.35 mmol). Oxidation with MnO_2 (3.55 g, 41.9 mmol) generated crude **5e**. The crude reaction mixture was purified by flash column chromatography (100:0 DCM:EtOAc to 90:10 DCM:EtOAc) to give **5e** as a white solid in 4% yield over two-steps (0.047 g, 0.22 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.39 (s, 3H), 2.42 (s, 3H), 5.00 (dd, *J* = 17.2, 0.8 Hz, 1H), 5.18 (dd, *J* = 10.4, 0.8 Hz, 1H), 5.21 (m, 2H), 5.93-6.02 (m, 1H), 7.20 (s, 1H), 7.66 (s, 1H), 10.05 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 20.6, 21.2, 46.9,

110.9, 117.5, 121.9, 132.3, 134.0, 135.2, 137.5, 141.9, 145.4, 184.7. **HRMS** (ESI): Calcd. for $C_{13}H_{15}N_2O^+$ ($[M+H]^+$): 215.1179, Found: 215.1184.



(*E*)-1-(3-(4-chlorophenyl)allyl)-5,6-dimethyl-1*H*-benzo[*d*]imidazole-2-carboxaldehyde (5f): Prepared according to general procedure B from (5,6-dimethyl-1*H*-benzo[*d*]imidazol-2-yl)methanol (1.00 g, 5.74 mmol) and **S1c** (1.58 g, 6.81 mmol) to give the crude product **S2f** (0.330 g, 1.01 mmol). Oxidation with MnO_2 (2.65 g, 30.5 mmol) generated crude **5f**. The crude reaction mixture was purified by flash column chromatography (100:0 DCM:EtOAc to 90:10 DCM:EtOAc) to give **5f** as a yellow oil in 3% yield over two-steps (0.050 g, 0.15 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.40 (s, 3H), 2.42 (s, 3H), 5.34 (d, *J* = 5.6 Hz, 2H), 6.28 (dt, *J* = 16.0, 5.6 Hz, 1H), 6.41 (d, *J* = 16 Hz, 1H), 7.18-7.23 (m, 4H), 7.25 (s, 1H), 7.68 (s, 1H), 10.07 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 20.6, 21.3, 46.3, 110.7, 122.0, 124.2, 127.8, 128.8, 131.7, 133.8, 134.1, 134.5, 135.1, 137.6, 141.9, 145.3, 184.7. **HRMS** (ESI): Calcd. for $C_{19}H_{18}ClN_2O^+$ ($[M+H]^+$): 325.1102, Found: 325.1093

General Procedure C: Synthesis of dihydropyrroloimidazolones (3a-j), dihydrobenzopyrroloimidazolones (6a-f)



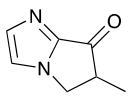
1a; R^1 = H, R^2 = H
1b; R^1 = H, R^2 = Ph
1c; R^1 = H, R^2 = 4-OMe-C_6H_4
1d; R^1 = H, R^2 = 4-Cl-C_6H_4
1e; R^1 = Ph, R^2 = H
1f; R^1 = 4-MeO-C_6H_4, R^2 = H
1g; R^1 = 4-Cl-C_6H_4, R^2 = H
1h; R^1 = 4-F-C_6H_4, R^2 = H
1i; R^1 = 3-F-C_6H_4, R^2 = H
1j; R^1 = 2-F-C_6H_4, R^2 = H

5a; R^1 = H, R^2 = H, R^3 = H
5b; R^1 = H, R^2 = Ph, R^3 = H
5c; R^1 = H, R^2 = 4-Cl-C_6H_4, R^3 = H
5d; R^1 = Ph, R^2 =H, R^3 = H
5e; R^1 = H, R^2 = H, R^3 = CH_3
5f; R^1= H, R^2 = 4-Cl-C_6H_4, R^3 = CH_3

3a; R^1 = H, R^2 = H
3b; R^1 = H, R^2 = Ph
3c; R^1 = H, R^2 = 4-OMe-C_6H_4
3d; R^1 = H, R^2 = 4-Cl-C_6H_4
3e; R^1 = Ph, R^2 = H
3f; R^1 = 4-MeO-C_6H_4, R^2 = H
3g; R^1 = 4-Cl-C_6H_4, R^2 = H
3h; R^1 = 4-F-C_6H_4, R^2 = H
3i; R^1 = 3-F-C_6H_4, R^2 = H
3j; R^1 = 2-F-C_6H_4, R^2 = H

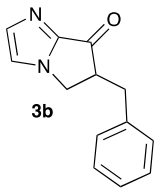
6a; R^1 = H, R^2 = H, R^3 = H
6b; R^1 = H, R^2 = Ph, R^3 = H
6c; R^1 = H, R^2 = 4-Cl-C_6H_4, R^3 = H
6d; R^1 = Ph, R^2 =H, R^3 = H
6e; R^1 = H, R^2 = H, R^3 = CH_3
6f; R^1= H, R^2 = 4-Cl-C_6H_4, R^3 = CH_3

Dihydropyrroloimidazolones (**3a-j**) and dihydrobenzopyrroloimidazolones (**6a-f**) were prepared according to a modified literature procedure from the appropriate carboxaldehyde (**1a-j**) or (**5a-f**).[26] In a nitrogen-filled glovebox, to a 1-dram vial was added triazolium **2** (0.020 mmol, 0.10 equiv), the appropriate carboxaldehyde **1a-j** or **5a-f** (0.20 mmol, 1.0 equiv), DBU (6 μL, 0.04 mmol, 0.2 equiv), and 1,4-dioxane (0.4 mL, 0.5 M). 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 dihydropyrroloimidazolones (**3a-j**) and dihydrobenzopyrroloimidazolones (**6a-f**).

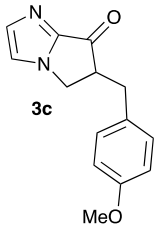

3a

6-methyl-5,6-dihydro-7*H*-pyrrolo[1,2-a]imidazole-7-one (3a): Prepared according to general procedure C from 1-allyl-1*H*-imidazole-2-carbaldehyde **1a** (0.041 g, 0.30 mmol), DBU (9 μL, 0.06 mmol) and triazolium **2** (9.0 mg, 0.030 mmol). The crude reaction

mixture was purified by column chromatography (100:0 hexane:EtOAc to 90:10 hexane:EtOAc) to afford **3a** in 96% yield (0.039 g, 0.29 mmol) as a yellow oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.40 (d, *J* = 7.8 Hz, 3H), 3.19-3.24 (m, 1H), 3.92 (dd, *J* = 12.0, 3.6 Hz, 1H), 4.58 (dd, *J* = 12.0, 7.8 Hz, 1H), 7.23 (app s, 1H), 7.57 (app s, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 15.4, 44.9, 48.7, 120.0, 139.4, 146.5, 190.3. **HRMS** (ESI): Calcd. for $C_7H_9N_2O^+$ ($[M+H]^+$): 137.0709, Found 137.0716.

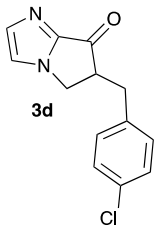


6-benzyl-5,6-dihydro-7*H*-pyrrolo[1,2-a]imidazole-7-one (3b): Prepared according to general procedure C from 1-cinnamyl-1*H*-imidazole-2-carbaldehyde **1b** (0.064 g, 0.30 mmol), DBU (8.97 μL, 0.0600 mmol) and triazolium **2** (9.0 mg, 0.030 mmol). The crude reaction mixture was purified by flash column chromatography (90:10 hexanes:EtOAc) to afford **3b** in 96% yield (0.061 mg, 0.29 mmol) as an off-white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.82 (dd, *J* = 14.0, 10.4 Hz, 1H), 3.35 (dd, *J* = 14.0, 4.4 Hz, 1H), 3.45 (dddd, *J* = 10.4, 7.6, 4.4, 4.0 Hz, 1H), 3.98 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.28 (dd, *J* = 12.0, 7.6 Hz, 1H), 7.11 (app s, 1H), 7.12-7.27 (m, 5H), 7.52 (app s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 36.1, 46.1, 51.5, 120.2, 127.1, 128.9, 129.0, 137.7, 139.5, 146.7, 188.8. **HRMS** (ESI): Calcd. for $C_{13}H_{13}N_2O^+$ ($[M+H]^+$): 213.1022, Found: 213.1019.

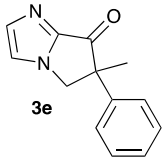


6-(4-methoxybenzyl)-5,6-dihydro-7*H*-pyrrolo[1,2-a]imidazole-7-one (3c): Prepared according to general procedure C from (*E*)-1-(3-(4-methoxyphenyl)allyl)-1*H*-imidazole-2-carbaldehyde **1c** (0.048 g, 0.20 mmol), DBU (6 μL, 0.04 mmol) and triazolium **2** (6 mg, 0.02 mmol). The crude reaction mixture was purified by column chromatography (90:10 hexanes:EtOAc) to afford **3c** in 85% yield (0.041 g, 0.17 mmol) as an off-white solid. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 2.87 (dd, *J* = 14.4, 9.6 Hz, 1H), 3.32 (dd, *J* = 14.4, 4.8 Hz, 1H), 3.43-3.49 (m, 1H), 3.77 (s, 3H), 4.03 (dd, *J* = 12.0, 3.6 Hz, 1H), 4.33 (dd, *J* =

12.0, 7.8 Hz, 1H), 6.82 (d, *J* = 7.8 Hz, 2H), 7.11 (d, *J* = 7.8 Hz, 2H), 7.16 (app s, 1H), 7.57 (app s, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 35.2, 46.0, 51.7, 55.4, 114.4, 120.1, 129.5, 129.9, 139.5, 146.8, 158.7, 188.9. **HRMS** (ESI): Calcd. for $C_{14}H_{15}N_2O_2^+$ ($[M+H]^+$): 243.1128, Found 243.1121.

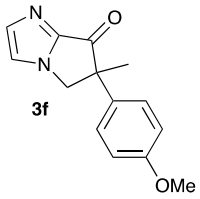


6-(4-chlorobenzyl)-5,6-dihydro-7*H*-pyrrolo[1,2-a]imidazole-7-one (3d): Prepared according to general procedure C from (*E*)-1-(3-(4-chlorophenyl)allyl)-1*H*-imidazole-2-carbaldehyde **1d** (0.049 g, 0.20 mmol), triazolium **2** (6 mg, 0.02 mmol) and DBU (6 μL, 0.04 mmol). The crude reaction mixture was purified by flash column chromatography with (100:0 hexanes:EtOAc to 90:10 hexanes:EtOAc) to afford **3d** in 99% yield (0.049 g, 0.20 mmol) as an off-white solid. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 2.88 (dd, *J* = 14.4, 10.2 Hz, 1H), 3.32 (dd, *J* = 14.4, 4.2 Hz, 1H), 3.43-3.49 (m, 1H), 4.00 (dd, *J* = 12.0, 4.2 Hz, 1H), 4.36 (dd, *J* = 12.0, 7.8 Hz, 1H), 7.13 (d, *J* = 7.8 Hz, 2H), 7.17 (app s, 1H), 7.24 (d, *J* = 7.8 Hz, 2H), 7.54 (app s, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 35.3, 46.0, 51.2, 120.3, 129.1, 130.2, 132.9, 136.1, 139.5, 146.5, 188.4. **HRMS** (ESI): Calcd. for $C_{13}H_{12}ClN_2O^+$ ($[M+H]^+$): 247.0633, Found 247.0632.

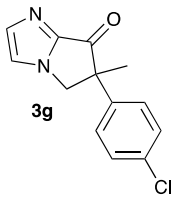


6-methyl-6-phenyl-5,6-dihydro-7*H*-pyrrolo[1,2-a]imidazole-7-one (3e): Prepared according to general procedure C from 1-(2-phenylallyl)-1*H*-imidazole-2-carbaldehyde **1e** (0.042 g, 0.20 mmol), triazolium **2** (6 mg, 0.02 mmol) and DBU (6 μL, 0.04 mmol). The crude reaction mixture was purified by flash column chromatography with (90:10 hexanes:EtOAc) to afford **3e** in 99% yield (0.042 g, 0.20 mmol) as an off white solid. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.78 (s, 3H), 4.42 (d, *J* = 12.0 Hz, 1H), 4.66 (d, *J* = 12.0 Hz, 1H), 7.25-7.37 (m, 6H), 7.69 (app s, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 23.7, 56.7, 57.2, 120.2, 125.9,

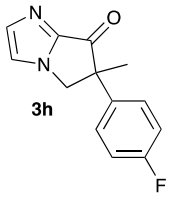
127.7, 129.1, 139.9, 141.3, 145.9, 190.3. **HRMS** (ESI): Calcd. for $C_{13}H_{13}N_2O^+$ ($[M+H]^+$): 213.1022, Found: 213.1029.



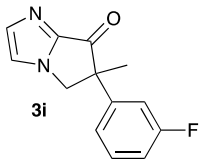
6-(4-methoxyphenyl)-6-methyl-5,6-dihydro-7*H*-pyrrolo[1,2-a]imidazole-7-one (3f): Prepared according to general procedure C from 1-(2-(4-methoxyphenyl)allyl)-1*H*-imidazole-2-carbaldehyde **1f** (0.048 g, 0.20 mmol), triazolium **2** (6 mg, 0.02 mmol), and DBU (6 μL, 0.04 mmol). The crude reaction mixture was purified by flash column chromatography with (90:10 hexanes:EtOAc) to afford **3f** in 99% yield (0.048 g, 0.20 mmol) as an off white solid. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.73 (s, 3H), 3.76 (s, 3H), 4.37 (d, *J* = 12.0 Hz, 1H), 4.61 (d, *J* = 12.0 Hz, 1H), 6.84 (d, *J* = 9.0 Hz, 2H), 7.19 (d, *J* = 9.0 Hz, 2H), 7.27 (d, *J* = 0.6 Hz,, 1H), 7.65 (d, *J* = 0.6 Hz, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 23.8, 55.4, 56.1, 57.2, 114.5, 120.1, 127.1, 133.3, 139.8, 146.0, 159.1, 190.6. **HRMS** (ESI): Calcd. for $C_{14}H_{15}N_2O_2^+$ ($[M+H]^+$): 243.1128, Found: 243.1123.



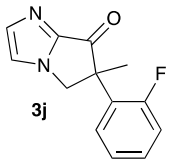
6-(4-chlorophenyl)-6-methyl-5,6-dihydro-7*H*-pyrrolo[1,2-a]imidazole-7-one (3g): Prepared according to general procedure C from 1-(2-(4-chlorophenyl)allyl)-1*H*-imidazole-2-carbaldehyde **1g** (0.049 g, 0.20 mmol), triazolium **2** (6 mg, 0.02 mmol) and DBU (6 μL, 0.04 mmol). The crude reaction mixture was purified by flash column chromatography with (90:10 hexanes:EtOAc) to afford **3g** 95% yield (0.047 g, 0.19 mmol) as an off white solid. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.73 (s, 3H), 4.41 (d, *J* = 12.0 Hz, 1H), 4.60 (d, *J* = 12.0 Hz, 1H), 7.16 (d, *J* = 8.4 Hz, 2H), 7.30 (app s, 1H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.67 (app s, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) 23.8, 56.3, 56.8, 120.4, 121.8, 127.8, 132.2, 140.2, 140.3, 145.6, 189.7. **HRMS** (ESI): Calcd. for $C_{13}H_{12}ClN_2O^+$ ($[M+H]^+$): 247.0633, Found: 247.0638.



6-(4-fluorophenyl)-6-methyl-5,6-dihydro-7*H*-pyrrolo[1,2-a]imidazole-7-one (3h): Prepared according to general procedure C from 1-(2-(4-fluorophenyl)allyl)-1*H*-imidazole-2-carbaldehyde **1h** (0.046 g, 0.20 mmol), triazolium **2** (6 mg, 0.02 mmol) and DBU (6 μL, 0.04 mmol). The crude reaction mixture was purified by flash column chromatography with (90:10 hexanes:EtOAc) to afford **3h** in 99% yield (0.046 g, 0.20 mmol) as an orange oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.77 (s, 3H), 4.45 (d, *J* = 12.0 Hz, 1H), 4.64 (d, *J* = 12.0 Hz, 1H), 7.03 (dd, *J* = 9.0, 9.0 Hz, 2H), 7.28 (dd, *J* = 9.0, 5.4 Hz, 2H), 7.33 (app s, 1H), 7.69 (app s, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 23.7, 56.1, 57.1, 115.9 (d, *J* = 21.4 Hz, 2C), 120.3, 127.7 (d, *J* = 8.2 Hz, 2C), 137.0 (d, *J* = 3.2 Hz, 1C), 140.1, 145.7, 162.1 (d, *J* = 247.2 Hz, 1C), 190.1. **^{19}F NMR** ($CDCl_3$, 565 MHz): δ -115.08 (s, 1F) **HRMS** (ESI): Calcd. for $C_{13}H_{12}FN_2O^+$ ($[M+H]^+$): 231.0928, Found: 231.0923.

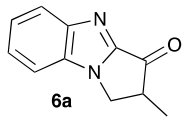


6-(3-fluorophenyl)-6-methyl-5,6-dihydro-7*H*-pyrrolo[1,2-a]imidazole-7-one (3i): Prepared according to general procedure C from 1-(2-(3-fluorophenyl)allyl)-1*H*-imidazole-2-carbaldehyde **1i** (0.046 g, 0.20 mmol), triazolium **2** (6 mg, 0.02 mmol) and DBU (6 μL, 0.04 mmol). The crude reaction mixture was purified by flash column chromatography with (90:10 hexanes:EtOAc) to afford **3i** in 99% yield (0.046 g, 0.20 mmol) as an orange oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.78 (s, 3H), 4.45 (d, *J* = 12.0 Hz, 1H), 4.66 (d, *J* = 12.0 Hz, 1H), 6.95-7.01 (m, 1H), 7.03-7.07 (m, 2H), 7.32 (ddd, 12, 10.2, 3.6 Hz, 1H), 7.35 (app s, 1H), 7.71 (app s, 1H). **^{13}C NMR** (151 MHz,$CDCl_3$) δ 23.7, 56.4 (d, *J* = 1.66 Hz, 1C), 56.9, 113.4 (d, *J* = 22.6 Hz, 1C), 114.7 (d, *J* = 19.6 Hz, 1C), 120.4, 121.6 (d, *J* = 3.0 Hz, 1C), 130.7 (d, *J* = 8.2 Hz, 1C), 140.2, 143.7 (d, *J* = 6.0 Hz, 1C), 145.7, 163.1 (d, *J* = 247.0 Hz, 1C), 189.6. **^{19}F NMR** ($CDCl_3$, 565 MHz): δ -111.98 (s, 1F). **HRMS** (ESI): Calcd. for $C_{13}H_{12}FN_2O^+$ ($[M+H]^+$): 231.0928, Found: 231.0929.



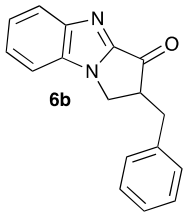
3j

6-(2-fluorophenyl)-6-methyl-5,6-dihydro-7*H*-pyrrolo[1,2-a]imidazole-7-one (3j): Prepared according to general procedure C from 1-(2-(2-fluorophenyl)allyl)-1*H*-imidazole-2-carbaldehyde **1j** (0.046 g, 0.20 mmol), triazolium **2** (6 mg, 0.02 mmol) and DBU (6 μL, 0.04 mmol). The crude reaction mixture was purified by flash column chromatography with (90:10 hexanes:EtOAc) to afford **3j** in 99% yield (0.046 g, 0.20 mmol) as an off-white solid. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.74 (s, 3H), 4.39 (d, *J* = 12.0 Hz, 1H), 4.53 (d, *J* = 12.0 Hz, 1H), 7.03 (dd, *J* = 12.0, 7.8 Hz, 1H), 7.15 (t, *J* = 7.8 Hz, 1H), 7.25 (app s, 1H), 7.29 (m, 1H), 7.48 (t, *J* = 7.8 Hz, 1H), 7.64 (s, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 23.2, 54.1, 56.2 (d, *J* = 4.6 Hz, 1C), 116.2 (d, *J* = 21.6 Hz, 1C), 119.9, 124.5 (d, *J* = 3.2 Hz, 1C), 128.1 (d, *J* = 12.8 Hz, 1C), 128.2 (d, *J* = 4.0 Hz, 1C), 129.9 (d, *J* = 8.8 Hz, 1C), 139.6, 145.5, 160.7 (d, *J* = 246.8 Hz, 1C), 189.9. **^{19}F NMR** ($CDCl_3$, 565 MHz): δ -113.05 (s, 1F). **HRMS** (ESI): Calcd. for $C_{13}H_{12}FN_2O^+$ ($[M+H]^+$): 231.0928, Found: 231.0928.

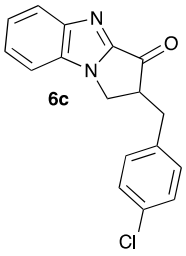


6a

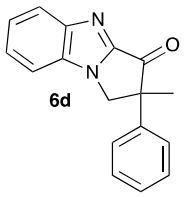
2-methyl-1,2-dihydro-3*H*-benzo[*d*]pyrrolo[1,2-a]imidazol-3-one (6a): Prepared according to general procedure C from 1-allyl-1*H*-benzo[*d*]-imidazole-2-carbaldehyde **5a** (0.037 g, 0.20 mmol), triazolium **2** (6 mg, 0.02 mmol) and DBU (6 μL, 0.04 mmol). The crude reaction mixture was purified by flash column chromatography (90:10 hexanes:EtOAc) to afford **6a** in 97% yield (0.036 g, 0.19 mmol) as a white solid. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.47 (d, *J* = 7.2 Hz, 3H), 3.33 (m, 1H), 4.03 (dd, *J* = 11.4, 4.2 Hz, 1H), 4.71 (dd, *J* = 11.4, 7.8 Hz, 1H), 7.38 (ddd, *J* = 7.8, 7.2, 1.2, Hz, 1H), 7.41 (ddd, *J* = 7.8, 7.2, 1.2 Hz, 1H), 7.48 (d, *J* = 7.8 Hz, 1H), 7.92 (d, *J* = 7.8 Hz, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 15.4, 45.0, 47.0, 111.0, 123.21, 124.8, 125.6, 132.8, 149.1, 149.4, 193.7. **HRMS** (ESI): Calcd. for $C_{11}H_{11}N_2O^+$ ($[M+H]^+$): 187.0866, Found: 187.0866.



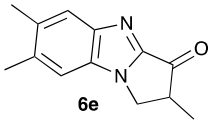
2-benzyl-1,2-dihydro-3*H*-benzo[*d*]pyrrolo[1,2-a]imidazol-3-one (6b): Prepared according to general procedure C from 1-cinnamyl-1*H*-benzo[*d*]imidazole-2-carbaldehyde **5b** (0.052 g, 0.20 mmol), triazolium **2** (6 mg, 0.02 mmol) and DBU (6 μL, 0.04 mmol). The crude reaction mixture was purified by flash column chromatography with (100:0 hexanes:EtOAc to 90:10 hexanes:EtOAc) to afford **6b** in 87% yield (0.045 g, 0.17 mmol) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.96 (dd, *J* = 14.0, 10.0 Hz, 1H), 3.51 (dd, *J* = 14.0, 4.4 Hz, 1H), 3.61-3.70 (m, 1H), 4.18 (dd, *J* = 11.6, 4.0 Hz, 1H), 4.51 (dd, *J* = 11.6, 7.6 Hz, 1H), 7.24-7.30 (m, 3H), 7.31-7.37 (m, 2H), 7.38-7.49 (m, 3H), 7.94 (dd, *J* = 6.8, 2.8 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 36.1, 44.6, 51.6, 111.1, 123.4, 125.0, 125.8, 127.3, 128.9, 129.1, 132.9, 137.6, 149.2, 149.5, 192.2. **HRMS** (ESI): Calcd. for $C_{17}H_{15}N_2O^+$ ($[M+H]^+$): 263.1179, Found: 263.1177.



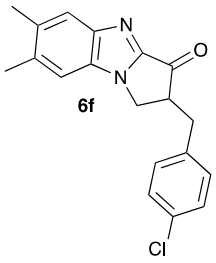
2-(4-chlorobenzyl)-1,2-dihydro-3*H*-benzo[*d*]pyrrolo[1,2-a]imidazol-3-one (6c): Prepared according to general procedure C from (*E*)-1-(3-(4-chlorophenyl)allyl)-1*H*-benzo[*d*]imidazole-2-carbaldehyde **5c** (0.059 g, 0.20 mmol), triazolium **2** (6 mg, 0.02 mmol) and DBU (6 μL, 0.04 mmol). The crude reaction mixture was purified by flash column chromatography with (100:0 hexanes:EtOAc to 90:10 hexanes:EtOAc) as eluent to afford **6c** in 84% yield (0.050 g, 0.17 mmol). **^{1}H NMR** (600 MHz, d6-DMSO) δ 3.00 (dd, *J* = 14.4, 10.8 Hz, 1H), 3.28 (dd, *J* = 14.4, 4.8 Hz, 1H), 3.75-3.82 (m, 1H), 4.21 (dd, *J* = 11.4, 4.2 Hz, 1H), 4.56 (dd, *J* = 11.4, 7.8 Hz, 1H), 7.35-7.41 (m, 5H), 7.42-7.45 (m, 1H), 7.76 (d, *J* = 8.4 Hz, 1H), 7.85 (d, *J* = 8.4 Hz, 1H). **^{13}C NMR** (101 MHz, d6-DMSO) δ 34.1, 44.6, 50.8, 112.3, 122.0, 124.3, 124.9, 128.5, 130.8, 131.3, 132.7, 137.6, 148.5, 149.6, 193.5. **HRMS** (ESI): Calcd. for $C_{17}H_{14}ClN_2O^+$ ($[M+H]^+$): 297.0789, Found: 297.0789.



2-methyl-2-phenyl-1,2-dihydro-3*H*-benzo[*d*]pyrrolo[1,2-a]imidazol-3-one (6d): Prepared according to general procedure C from 1-(2-phenylallyl)-1*H*-benzo[*d*]imidazole-2-carbaldehyde **5d** (0.052 g, 0.20 mmol), triazolium **2** (6 mg, 0.02 mmol) and DBU (6 μL, 0.04 mmol). The crude reaction mixture was purified by flash column chromatography with (100:0 hexanes:EtOAc to 90:10 hexanes:EtOAc) as eluent to afford **6d** in 93% yield (0.048 g, 0.19 mmol) as a white solid. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.86 (s, 3H), 4.57 (d, *J* = 11.4 Hz, 1H), 4.84 (d, *J* = 11.4 Hz, 1H), 7.25-7.36 (m, 5H), 7.45 (ddd, *J* = 8.4, 7.8, 1.2 Hz, 1H), 7.48 (ddd, *J* = 8.4, 7.8, 1.2 Hz, 1H), 7.57 (dd, *J* = 7.8, 1.2 Hz, 1H), 8.01 (dd, *J* = 7.8, 1.2 Hz, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 23.8, 55.5, 56.7, 111.2, 123.4, 125.0, 125.9, 125.93, 127.9, 129.2, 132.8, 140.9, 148.6, 149.8, 193.8. **HRMS** (ESI): Calcd. for $C_{17}H_{15}N_2O^+$ ($[M+H]^+$): 263.1179, Found: 263.1181.

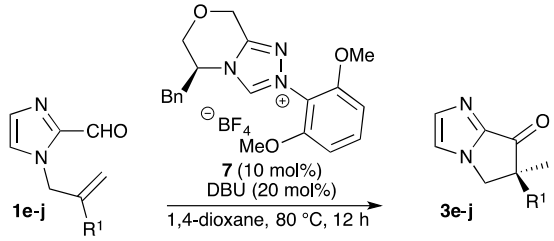


2,6,7-trimethyl-1,2-dihydro-3*H*-benzo[*d*]pyrrolo[1,2-a]imidazol-3-one (6e): Prepared according to general procedure C from 1-allyl-5,6-dimethyl-1*H*-benzo[*d*]imidazole-2-carbaldehyde **5e** (0.021 g, 0.10 mmol), triazolium **2** (3 mg, 0.01 mmol) and DBU (2.9 μL, 0.020 mmol). The crude reaction mixture was purified by flash column chromatography with (100:0 hexanes:EtOAc to 90:10 hexanes:EtOAc) to afford **6e** in 66% yield (0.014 g, 0.066 mmol) as a white solid. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 1.48 (d, *J* = 7.2 Hz, 3H), 2.39 (s, 3H), 2.41 (s, 3H), 3.29-3.35 (m, 1H), 3.99 (dd, *J* = 11.4, 4.2 Hz, 1 H), 4.67 (dd, *J* = 11.4, 7.8 Hz, 1H), 7.26 (s, 1H), 7.68 (s, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 1.1, 15.5, 20.7, 20.9, 45.0, 47.0, 110.7, 122.6, 131.6, 134.6, 135.9, 148.5, 193.4. **HRMS** (ESI): Calcd. for $C_{13}H_{15}N_2O^+$ ($[M+H]^+$): 215.1179, Found: 215.1178.



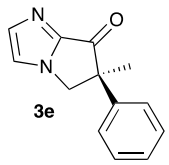
2-(4-chlorobenzyl)-6,7-dimethyl-1,2-dihydro-3*H*-benzo[*d*]pyrrolo[1,2-a]imidazol-3-one (6f): Prepared according to general procedure C (*E*)-1-(3-(4-chlorophenyl)allyl)-5,6-dimethyl-1*H*-benzo[*d*]imidazole-2-carbaldehyde **5f** (0.032 g, 0.10 mmol), triazolium **2** (3 mg, 0.01 mmol) and DBU (3 μL, 0.02 mmol). The crude reaction mixture was purified by column chromatography with (100:0 hexanes:EtOAc to 90:10 hexanes:EtOAc) to afford **6f** in 88% yield (0.028 g, 0.088 mmol) as a white solid. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 2.38 (app s, 6H), 2.95 (dd, *J* = 14.4, 10.2 Hz, 1H), 3.41 (dd, *J* = 14.4, 4.2 Hz, 1H), 3.54-3.60 (m, 1H), 4.05 (dd, *J* = 11.4, 3.6 Hz, 1H), 4.44 (dd, *J* = 11.4, 7.2 Hz, 1H), 7.18 (d, *J* = 7.8 Hz, 2H), 7.20 (s, 1H), 7.28 (d, *J* = 7.8 Hz, 2H), 7.66 (s, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 20.8, 21.0, 35.5, 44.3, 51.4, 110.7, 122.7, 129.2, 130.3, 130.8, 131.6, 133.1, 134.9, 136.2, 148.3, 148.4, 191.5. **HRMS** (ESI): Calcd. for $C_{19}H_{18}ClN_2O^+$ ($[M+H]^+$): 325.1102, Found: 325.1103.

General Procedure D: Enantioselective synthesis of 3e-j

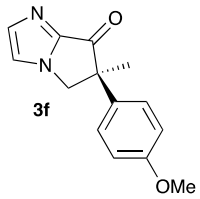


In a nitrogen-filled glovebox, to a 1-dram vial was added triazolium **7** (0.010 mmol, 0.10 equiv), the appropriate *N*-allyimidazole-2-carboxaldehyde **1e-j** (0.10 mmol, 1.0 equiv), DBU (3 μL, 0.02 mmol, 0.2 equiv), and 1,4-dioxane (0.2 mL, 0.5 M). The vial was sealed with a teflon-lined septum cap. The reaction vessel was removed from the glovebox and the reaction mixture was stirred at 80 °C for 12 h. The reaction was cooled to room temperature and filtered through a

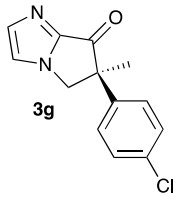
plug of silica gel with EtOAc as eluent. The filtrate was concentrated under reduced pressure. The crude product was purified by flash column silica gel chromatography (hexane:EtOAc) to give the appropriate dihydropyrroloimidazolones (**3e-j**).



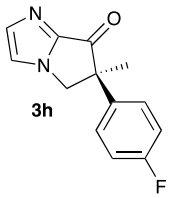
(*S*)-6-methyl-6-phenyl-5,6-dihydro-7*H*-pyrrolo[1,2-a]imidazole-7-one (3e): Prepared according to general procedure D from 1-(2-phenylallyl)-1*H*-imidazole-2-carbaldehyde **1e** (0.021 g, 0.10 mmol), triazolium **7** (4 mg, 0.01 mmol) and DBU (3 μL, 0.02 mmol). The crude reaction mixture was purified by flash column chromatography with (90:10 hexanes:EtOAc) to afford **3e** in 90% yield (0.019 g, 0.090 mmol) as an off white solid. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 27.1 min (major); t_R 32.4 min (minor) [Chiracel AD-H (0.46 cm x 25 cm)(from Daicel Chemical Ind., hexane/*i*-PrOH, 90:10, 1.0 mL/min] to be 71% ee. $[\alpha]_D^{24}$ = -188.8° (c 0.63, $CHCl_3$). NMR spectra are consistent with racemic spectra above.



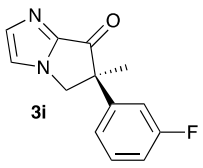
(*S*)-6-(4-methoxyphenyl)-6-methyl-5,6-dihydro-7*H*-pyrrolo[1,2-a]imidazole-7-one (3f): Prepared according to general procedure D from 1-(2-(4-methoxyphenyl)allyl)-1*H*-imidazole-2-carbaldehyde **1f** (0.024 g, 0.10 mmol), triazolium **7** (4 mg, 0.01 mmol), and DBU (3 μL, 0.02 mmol). The crude reaction mixture was purified by flash column chromatography with (90:10 hexanes:EtOAc) to afford **3f** in 98% yield (0.024 g, 0.097 mmol) as an off white solid. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 44.3 min (major); 56.9 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 79% ee. $[\alpha]_D^{23}$ = -84.9° (c 1.06, $CHCl_3$). NMR spectra are consistent with racemic spectra above.



(*S*)-6-(4-chlorophenyl)-6-methyl-5,6-dihydro-7*H*-pyrrolo[1,2-a]imidazole-7-one (3g): Prepared according to general procedure D from 1-(2-(4-chlorophenyl)allyl)-1*H*-imidazole-2-carbaldehyde **1g** (0.025 g, 0.10 mmol), triazolium **7** (4 mg, 0.01 mmol) and DBU (3 μL, 0.02 mmol). The crude reaction mixture was purified by flash column chromatography with (90:10 hexanes:EtOAc) to afford **3g** 96% yield (0.024 g, 0.096 mmol) as an off white solid. The enantiomeric excess was determinded by HPLC analysis (254 nm, 25 °C) t_R 36.1 min (major); 45.7 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 67% ee. $[\alpha]_D^{22}$ = -156.9° (c 1.02, $CHCl_3$). NMR spectra are consistent with racemic spectra above.

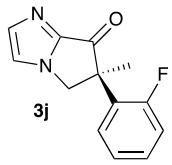


(*S*)-6-(4-fluorophenyl)-6-methyl-5,6-dihydro-7*H*-pyrrolo[1,2-a]imidazole-7-one (3h): Prepared according to general procedure D from 1-(2-(4-fluorophenyl)allyl)-1*H*-imidazole-2-carbaldehyde **1h** (0.023 g, 0.10 mmol), triazolium **7** (4 mg, 0.01 mmol) and DBU (3 μL, 0.02 mmol). The crude reaction mixture was purified by flash column chromatography with (90:10 hexanes:EtOAc) to afford **3h** in 81% yield (0.019 g, 0.083 mmol) as an orange oil. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 33.3 min (major); t_R 39.8 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 75% ee. $[\alpha]_D^{23}$ = -40.5° (c 0.84, $CHCl_3$). NMR spectra are consistent with racemic spectra above.



(*S*)-6-(3-fluorophenyl)-6-methyl-5,6-dihydro-7*H*-pyrrolo[1,2-a]imidazole-7-one (3i): Prepared according to general procedure D from 1-(2-(3-fluorophenyl)allyl)-1*H*-imidazole-2-carbaldehyde **1i** (0.023 g, 0.10 mmol), triazolium **7** (4 mg, 0.01 mmol) and DBU (3 μL, 0.02 mmol). The crude reaction mixture was

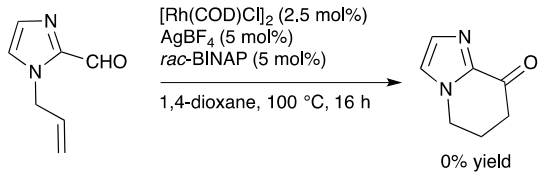
purified by flash column chromatography with (90:10 hexanes:EtOAc) to afford **3i** in 93% yield (0.021 g, 0.093 mmol) as an orange oil. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 29.2 min (major); t_R 33.5 min (minor) [Chiracel AD-H (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90:10, 1.0 mL/min] to be 67% ee. $[\alpha]_D^{23}$ = -51.2° (c 1.01, $CHCl_3$). NMR spectra are consistent with racemic spectra above.



3j

(*S*)-6-(2-fluorophenyl)-6-methyl-5,6-dihydro-7*H*-pyrrolo[1,2-a]imidazole-7-one (3j): Prepared according to general procedure D from 1-(2-(2-fluorophenyl)allyl)-1*H*-imidazole-2-carbaldehyde **1j** (0.023 g, 0.10 mmol), triazolium **7** (4 mg, 0.01 mmol) and DBU (3 μL, 0.02 mmol). The crude reaction mixture was purified by flash column chromatography with (90:10 hexanes:EtOAc) to afford **3j** in 39% yield (0.089 g, 0.038 mmol) as an off-white solid. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 29.0 min (major); t_R 35.4 min (minor) [Chiracel AD-H (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexaes/*i*-PrOH, 90:10, 1.0 mL/min] to be 56% ee. $[\alpha]_D^{23}$ = +28.6° (c 0.35, $CHCl_3$). NMR spectra are consistent with racemic spectra above.

Representative Procedure for Rhodium-Catalysed Hydroacylation of 1a



0% yield

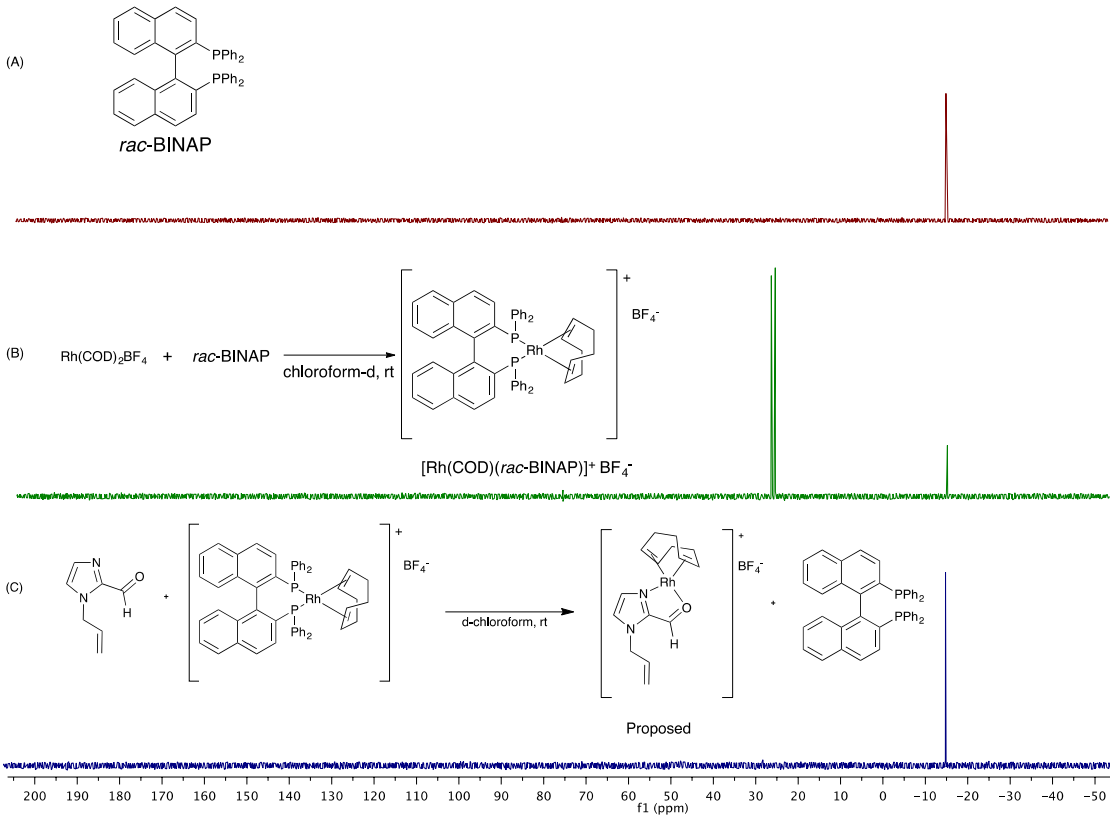
In a nitrogen-filed glovebox, 1-allyl-1*H*-imidazole-2-carboxaldehyde (13.6 mg, 0.100 mmol, 1.00 equiv), $[Rh(COD)Cl]_2$ (1.2 mg, 0.0025 mmol, 0.025 equiv), racemic-BINAP (3.1 mg, 0.0050 mmol, 0.050 equiv), $AgBF_4$ (1.0 mg, 0.0050 mmol, 0.050 equiv) and 1,4-dioxane (0.25 mL, 0.40M) were added to 1-dram vial. The vial was sealed with a Teflon-lined septum cap and

removed from the glovebox. The reaction mixture was stirred at 100 °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 a short plug of silica gel with 100% EtOAc as eluent. The crude reaction mixture was concentrated under reduced pressure. The crude residue was analyzed by ^{1}H NMR spectroscopy with dibromomethane as the internal standard. Only unreacted starting material was observed by ^{1}H NMR spectroscopy.

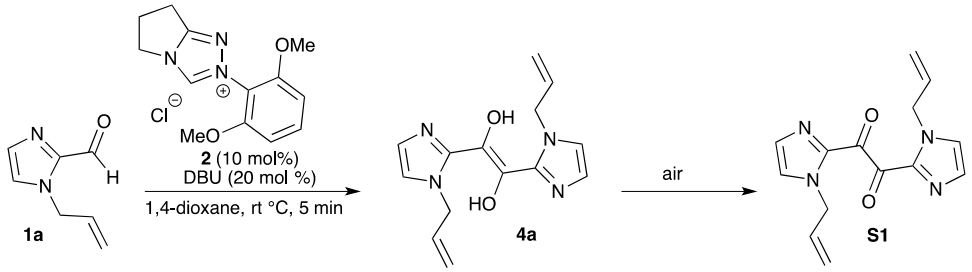
Evaluation of Rhodium-Catalysed Hydroacylation of 1a by ^{31}P NMR Spectroscopy

In a nitrogen-filled glovebox, *rac*-BINAP (6.2 mg, 0.010 mmol, 0.050 equiv) and $CDCl_3$ (0.5 mL) was added to 1-dram vial and stirred until *rac*-BINAP fully dissolved. The reaction mixture was then transferred to an NMR tube and sealed. A ^{31}P spectrum was obtained to give spectrum A in Figure S1. The sealed NMR tube was returned to the glovebox. To a 1-dram vial was added $Rh(COD)_2BF_4$ (4.1 mg, 0.010 mmol, 0.050 equiv) and the solution containing *rac*-BINAP in $CDCl_3$, and the resulting solution was stirred for 15 minutes at room temperature. After stirring, the solution was returned to the NMR tube, sealed, and spectrum B in Figure S1 was obtained, showing that the formation of [Rh(COD)(*rac*-BINAP)]$^{+}BF_4^{-}$. The NMR tube was returned to the nitrogen-filled glovebox. To a 1-dram vial containing 1-allyl-1*H*-imidazole-2-carboxaldehyde **1a** (27.2 mg, 0.200 mmol, 1.00 equiv) was added the solution containing [Rh(COD)(*rac*-BINAP)]$^{+}BF_4^{-}$, and the resulting solution was stirred for 15 minutes. After stirring, the solution was returned to the NMR tube, sealed, and spectrum C in Figure S1 was obtained, showing the displacement of *rac*-BINAP from the rhodium.

Figure S1



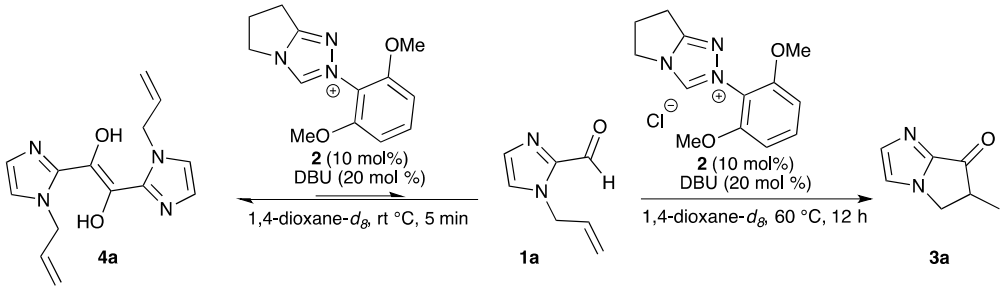
Synthesis of Diketone S1



1,2-Bis(1-allyl-1*H*-imidazol-2-yl)ethane-1,2-dione was prepared according to the following procedure from carboxaldehyde **1a.** In a nitrogen-filled glovebox, to a 1-dram vial was added triazolium **2** (9.0 mg, 0.030 mmol, 0.10 equiv), 1-allyl-1*H*-imidazole-2-carboxaldehyde **1a** (0.041 g, 0.30 mmol, 1.0 equiv), DBU (9 μL, 0.06 mmol, 0.2 equiv), and 1,4-dioxane (0.6 mL, 0.5

M). 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 rt for 5 minutes. The reaction was cooled to room temperature, exposed to air, and filtered through a plug of silica gel with EtOAc as eluent. The filtrate was concentrated under reduced pressure. The reaction mixture was purified by column chromatography (100% DCM) to afford diketone **S1** in 90% yield (0.037 g, 0.13 mmol) as an off-white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.08 (d, *J* = 6.0 Hz, 4H), 5.17 (dd, *J* = 17.2, 1.2 Hz, 2H), 5.24 (dd, *J* = 10.4, 1.2 Hz, 2H), 5.93-6.04 (m, 2H), 7.14 (d, *J* = 0.8 Hz, 2H), 7.20 (d, *J* = 0.8 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 50.7, 119.5, 126.3, 132.1, 132.2, 140.3, 183.2. **HRMS** (ESI): Calcd. for $C_{14}H_{15}N_4O_2^+$ ([M+H]$^+$): 271.1190, Found: 271.1194.

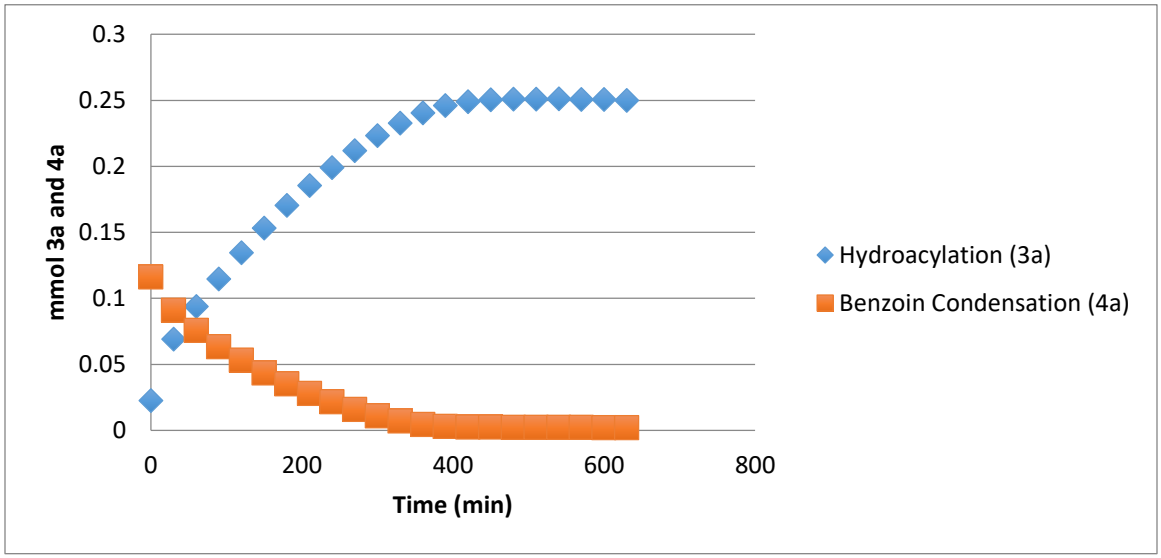
Evaluation of NHC-Catalysed Hydroacylation of 1a by ^{1}H NMR Spectroscopy



In a nitrogen-filled glovebox, to a 1-dram vial was added triazolium **2** (7.1 mg, 0.025 mmol, 0.10 equiv), 1-allyl-1*H*-imidazole-2-carboxaldehyde **1a** (34.0 mg, 0.250 mmol, 1.0 equiv), 1,4-dioxane-d_8 (0.5 mL, 0.5 M), and finally DBU (7.5 μL, 0.050 mmol, 0.20 equiv). The reaction mixture was immediately added to a NMR tube and sealed with a teflon-lined septum cap. The reaction vessel was removed from the glovebox and immediately inserted into the Bruker Avance III 600 that was preheated to 60 °C. Spectra were collected every 10 seconds for the first 42 minutes, every 27 seconds for the following 112 minutes, every 57 seconds for the next 237 minutes, and every 117 seconds for the remainder of the reaction time. Within the time taken to

prepare the sample, **1a** is converted to **4a** at room temperature. Upon heating the mixture containing **4a** at 60 °C in the NMR spectrometer, **4a** is converted to hydroacylation product **3a** over the course of the experiment as shown in Figure S2. Upon completion of the NMR experiment, 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 (90:10 hexane:EtOAc) to give **3a** in 96% yield (32 mg, 0.24 mmol).

Figure S2



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CHAPTER IV

NICKEL-CATALYZED ALKENE CARBOACYLATION VIA ACTIVATION OF AMIDE C-N BONDS

Modified from the *Journal of the American Chemical Society* **2017**, *139*, 10228-10231

James A. Walker Jr., Kevin L. Vickerman, Jenna N. Humke, and Levi M. Stanley

Abstract

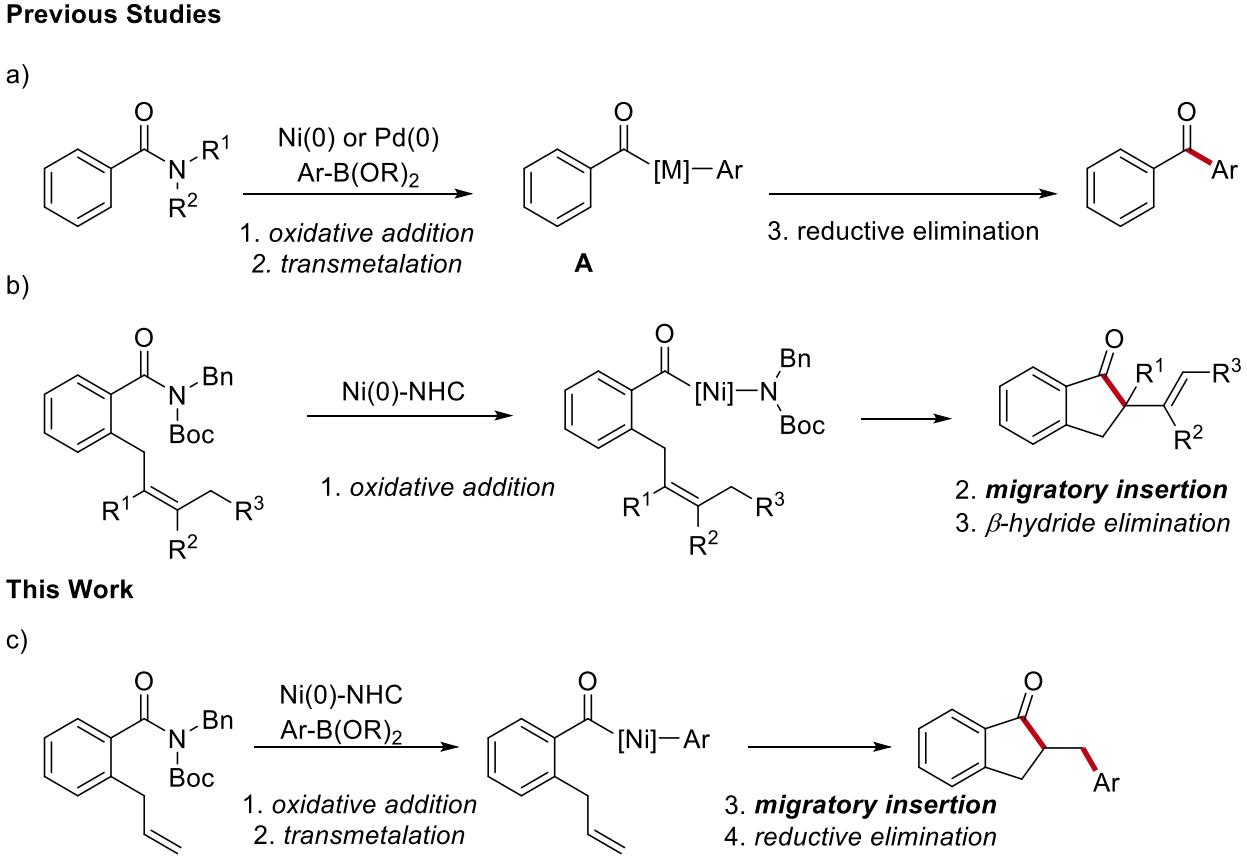
We report nickel-catalyzed formal carboacylation of *ortho*-allylbenzamides with arylboronic acid pinacol esters. These carboacylation reactions are triggered by the oxidative addition of an activated amide C-N bond to a nickel(0) catalyst and proceed via alkene insertion into a nickel(II)-acyl bond. The *exo*-selective carboacylation reactions generate 2-benzyl-2,3-dihydro-1*H*-inden-1-ones in moderate-to-high yields (46-99%) from a variety of arylboronic acid pinacol esters and substituted *ortho*-allylbenzamides. These results demonstrate that amides are practical substrates for alkene carboacylation via activation of an amide C-N bond, and this approach bypasses challenges associated with alkene carboacylation triggered by C-C bond activation.

Introduction

Carboacylation of alkenes in the presence of a transition-metal catalyst is an emerging reaction that enables the difunctionalization of an alkene with formation of two C-C σ-bonds.[1-16] Among the most studied and developed approaches to alkene carboacylation are reactions initiated by activation of a C-C σ-bond of a ketone. While much progress has been made to understand the mechanistic pathways and utility of these carboacylation reactions, the development of alkene carboacylation reactions is limited by the requirement for substrates containing either a quinoline

directing group[2-3, 5, 7, 11] or a strained cyclic ketone.[6, 9-10, 12-15] The ability to perform alkene carboacylation reactions without a requirement for strained ketone substrates or substrates containing directing groups has the potential to expand the utility of these reactions with readily accessible substrates.[1, 4, 8, 16-21]

Scheme 1. Synthesis of Ketones via Transition Metal-Catalyzed Activation of Amide C-N Bonds



Recently, studies by a number of groups have demonstrated Suzuki-Miyaura coupling of benzamides with arylboron compounds to generate a variety of aromatic ketones.[22-33] The Suzuki-Miyaura-type coupling reactions involve C-N activation of an activated benzamide via oxidative addition and transmetalation with an arylboron compound to generate acyl-metal-aryl intermediate **A** (Scheme 1a). Subsequent reductive elimination forms a diaryl ketone. The ability to intercept

acyl-metal intermediates with an alkene offers the potential to develop a new class of alkene functionalization reactions. During the course of our studies, Garg and co-workers reported Mizoroki-Heck cyclizations of *ortho*-allylbenzamides that involve insertion of an alkene into an acyl-nickel(II)-amido intermediate **B** (Scheme 1b).[34] Subsequent β-hydride elimination forms 2-vinylindanones containing a quaternary carbon center.

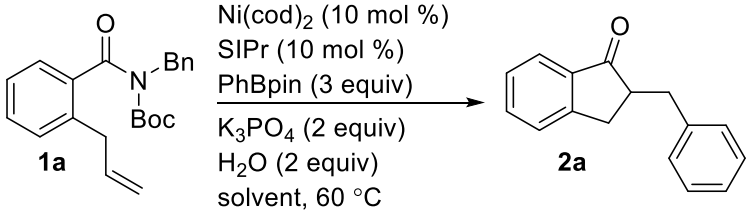
The potential to develop a new class of alkene carboacylation reactions via activation of amide C-N bonds[22-33, 35-40] led us to investigate nickel-catalyzed carboacylations of *ortho*-allylbenzamides. We envisioned a process involving activation of the C-N bond of a benzamide via oxidative addition and transmetalation with an arylboron compound to generate acyl-nickel(II)-aryl intermediate **C** (Scheme 1c). Migratory insertion of the tethered alkene and reductive elimination would generate 2-benzylindanones, the product of a formal alkene carboacylation reaction. In contrast to the recently reported Mizoroki-Heck cyclization reactions which involve the formation of a single C-C σ-bond, the proposed formal carboacylation reactions involve difunctionalization of an alkene with the formation of two C-C σ-bonds. The development of this approach to alkene carboacylation offers the potential to expand these reactions beyond strained cyclic ketones and ketones containing a quinoline directing group. We now report the first nickel-catalyzed carboacylations triggered by C-N bond activation of *ortho*-allylbenzamides to form a variety of 2-benzyl-2,3-dihydro-1*H*-inden-1-ones in up to 99% yield.

Results & Discussion

To identify reaction conditions for the nickel-catalyzed carboacylation of *ortho*-allylbenazamides, we evaluated the model reaction of *tert*-butyl(2-allylbenzoyl)(benzyl)carbamate (**1a**) with phenylboronic acid pinacol ester (PhBpin) in the presence of a catalyst generated from $Ni(cod)_2$ and 1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidine (SIPr) (Table 1). The

nickel carbene complex catalyzed the model reaction to form indanone **2a** in 20% yield when the reaction was conducted in toluene at 90 °C with 1.2 equiv of PhBpin (entry 1). The yield of indanone **2a** increased to 30% when the reaction was run with 3.0 equiv of PhBpin (entry 3). However, the major product of these reactions is generated from isomerization of the *ortho*-allylbenzamide starting material. To further improve the yield of the model reaction and minimize alkene isomerization, we investigated the impact of the identity of the solvent (entries 3-7). When the model reaction was carried out in THF, indanone **2a** was generated in 75% yield with the formation of 24% yield of the isomerized starting material (entry 7).

Table 1. Identification of Reaction Conditions for Ni-Catalyzed Carboacylation of 1a with PhBpin[a]



entry	temp (°C)	solvent	conv. (%)[b]	yield (%)[b,c]
1[d]	90	toluene	67	20(35)
2[e]	90	toluene	49	21(27)
3	90	toluene	100	30(43)
4	90	benzene	70	27(45)
5	90	dioxane	84	26(46)
6[f]	90	DME	82	46(9)
7[f]	90	THF	99	75(24)
8[f]	80	THF	100	78(9)
9[f]	70	THF	100	83(4)
10[f]	60	THF	100	97(0)
11	40	THF	48	39(0)
12[e]	60	THF	65	55(0)
13[d]	60	THF	39	39(0)
14[f,g]	60	THF	100	95(0)
15[h]	60	THF	40	38(0)
16[i]	60	THF	100	88(11)

[a]Reaction conditions: **1a** (0.100 mmol), $Ni(cod)_2$ (0.010 mmol), SIPr = 1,3-bis-(2,6-diisopropylphenyl)imidazolidin-2-ylidene (0.010 mmol), K_3PO_4 (0.200 mmol), solvent (1.0 M), 12 h. [b]Determinded by ^1H NMR spectroscopy of the crude reaction mixture using dibromomethane as an internal standard. [c]Yields of alkene isomerization product *tert*-butyl benzyl(2-(prop-1-en-1-yl)benzoyl)carbamate determined by ^1H NMR spectroscopy are shown in parentheses. [d]PhBpin

(1.2 equiv). [e]PhBpin (2 equiv). [f]isolated yields of **3a**. [g]5 mol % $Ni(cod)_2$ and 5 mol % SIPr. [h]2.5 mol % $Ni(cod)_2$ and 2.5 mol % SIPr. [i]Reaction run with SIPr·HCl (0.010 mmol) in place of SIPr

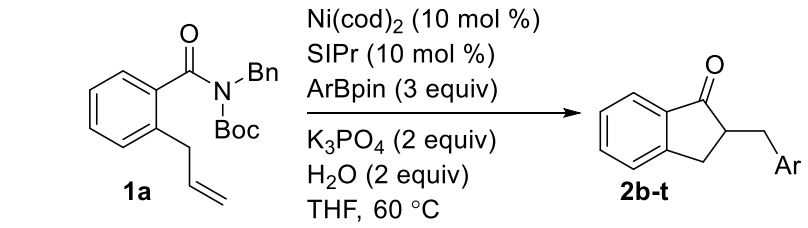
To further increase the ratio of indanone **2a** relative to the isomerized starting material, we investigated the impact of reaction temperature (entries 7-11). Lowering the reaction temperature to 60 °C led to the formation of indanone **2a** in 97% yield without observable isomerization of the *ortho*-allylbenzamide (entry 10). Consistent with our observations of reactions run in toluene (entries 1-3), the yield of indanone **2a** decreases upon lowering the nymber of equivalents of PhBpin when the reaction is run in THF at 60 °C (compare entry 10 with entries 12 and 13). The model reaction catalyzed by 5 mol % of the nickel catalyst formed **2a** in 95% yield (entry 14). However, decreasing the catalyst loading to 2.5 mol % led incomplete conversion and formation of **2a** in only 38% yield (entry 15). The model reaction occurs to form **2a** in 88% yield with 11% isomerization of **1a** when the nickel carbene catalyst is generated *in situ* from $Ni(cod)_2$ and SIPr·HCl (entry 16).

With a practical catalyst system identified for the model reaction of **1a** with PhBpin, we next evaluated carboacylation reactions of **1a** with a broad range of arylboronic acid pinacol esters (ArBpin) (Scheme 2). The carboacylation of **1a** with a range of *para*-substituted, electron-rich ArBpin reagents generated ketones **2b**-**e** in good-to-excellent yields (78-99%). The reaction of **1a** with *para*-substituted electron-deficient ArBpin reagents formed indanones **2f**-**2j** in moderate-to-high yields (54-85%). The carboacylation of **1a** with ArBpin compounds containing electron-donating groups at the *meta*-position formed ketones **2k**-**2l** in 85-99% yield, while *meta*-halogenated ArBpin compunds reacted with **1a** to form **2m**-**2n** in 54-67% yield. Reactions of ArBpin reagents containing electron-donating groups at the *ortho*-position with **1a** were also possible and generated the carboacylation products **2o** and **2p** in 50% and 90% yield. However, reactions of **1a** with *ortho*-halogenated ArBpin reagents did not occur under our reaction

conditions. The scope of alkene carboacylation is not limited to substituted ArBpin compounds but also includes boronic acid pinacol esters of polycyclic arenes and heteroarenes. The carboacylation reactions of **1a** with heteroarylboronic acid pinacol esters formed ketone products **2r**-**2s** in 63-88% yields. Reactions of **1a** with arylboronic acids and alkylboronic acid pinacol esters did not occur under our standard reaction conditions.

With the scope of arylboronic acid pinacol esters established, we sought to evaluate nickel-catalyzed carboacylations of a variety of substituted *ortho*-allylbenzamides **3a**-**j** (Scheme 3). Reactions of PhBpin with **3a**-**3c** containing electron-donating and electron-withdrawing groups at the 5-position occur to form indanones **4a**-**4c** in moderate-to-excellent yields (51-99%). Carboacylations of 4-substituted *ortho*-allylbenzamides containing either electron-donating or electron-withdrawing groups occur to generate ketones **4d**-**4g** in 80-99% yield. Carboacylations of 3- and 6-fluorinated *ortho*-allylbenzamides generated indanones **4h**-**4i** in excellent yields (84-95%), while the reaction of a 4,5-difluorinated *ortho*-allylbenzamide formed indanone **4j** in 46% yield. *ortho*-Allylbenzamides containing substituted allyl units were unreactive under our standard reaction conditions, and reactions conducted at elevated temperatures led exclusively to isomerization of the alkene. The carboacylation of the acyclic 5-hexenamide derivative, *tert*-butyl benzyl(hex-5-enoyl)carbamate, with PhBpin did not form the corresponding cyclic ketone.

Scheme 2. Scope of Arylboronic Acid Pinacol Esters[a]

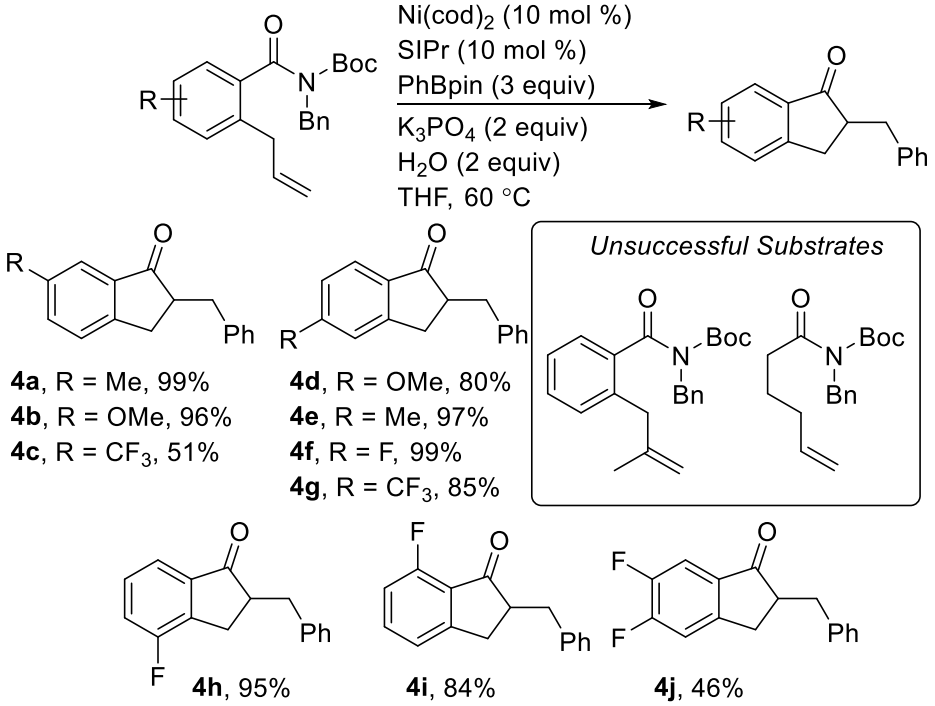


[a]Reaction conditions: **1a** (0.100 mmol), $Ni(cod)_2$ (0.010 mmol), SIPr (0.010 mmol), K_3PO_4 (0.200 mmol), H_2O (0.200 mmol), ArBpin (0.300 mmol), THF (0.100 mL), 16 h. Yields of **2b-t** are isolated yields after column chromatography. Yields of alkene isomerization product *tert*-butyl benzyl(2-(prop-1-en-1-yl)benzoyl)carbamate determined by ^{1}H NMR spectroscopy are shown in parnetheses. [b]20 mol % $Ni(cod)_2$, 20 mol %, SIPr, and 0.20 mL THF.

To highlight the utility of our alkene carboacylation reaction, we conducted a series of experiments to show that the carboacylation reaction 1) can be conducted on the gram scale, 2) encompasses an *ortho*-allylbenzoate ester, and 3) can be sequenced with nickel-catalyzed, enantioselective α-arylation to form an indanone derivative containing a quaternary stereogenic center. The reaction of 4-fluorinated *ortho*-allylbenzamide **3f** with PhBpin can be conducted on a gram scale to form the product **4f** in nearly quantitative yield (eq 1). In addition, the carboacylation of methyl 2-allylbenzoate **5** with PhBpin forms indanone **2a** in 50% yield (eq 2).[41-47] The modest yield of **2a** can be attributed to alkene isomerization of **5** to form methyl 2-(prop-1-en-1-

yl)benzoate in 25% yield. Highly enantioenriched indanone derivatives containing a quaternary stereogenic center are readily prepared by nickel-catalyzed α-arylation of the racemic 2-benzylindanones generated from our carboacylation reactions.[48] For example, the α-arylation of **2a** occurs in the presence of a catalyst generated from $Ni(cod)_2$ and (*S*)-BINAP to form indanone **6** in 65% yield and 98% ee (eq 3).

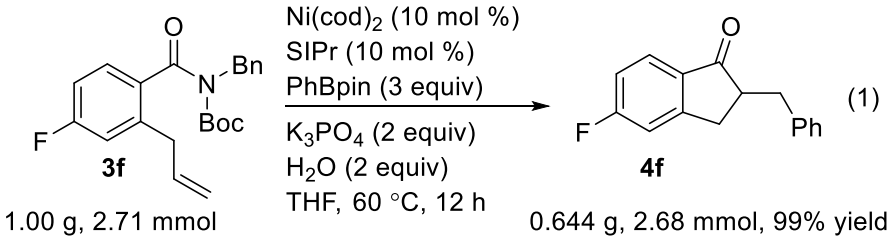
Scheme 3. Carboacylation of Benzamides 3a-j[a]

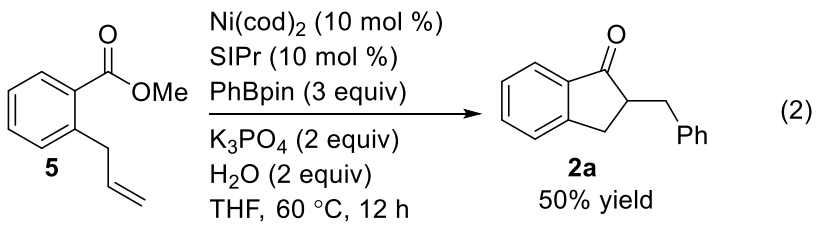


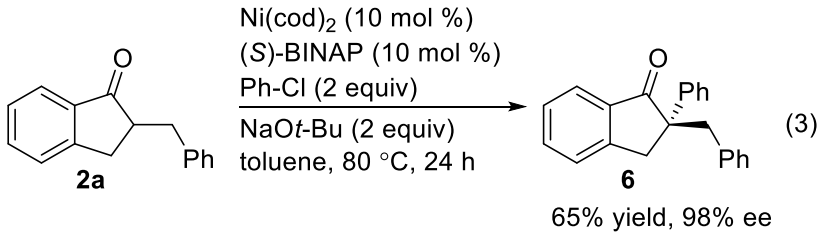
[a]Reaction conditions: **3a-j** (0.100 mmol), $Ni(cod)_2$, SIPr (0.010 mmol), K_3PO_4 (0.200 mmol), H_2O (0.200 mmol), PhBpin (0.300 mmol), THF (0.100 mL), 12 h. Yields of **4a-j** are isolated yields after column chromatography.

Two potential mechanistic pathways for the carboacylation of **1a** with ArBpin are presented in Scheme 4. After coordination of the NHC-Ni(0) catalyst to **1a** to form complex **I**, oxidative addition of the amide C-N bond to the Ni(0) center is likely to form the acyl-nickel(II)-amido complex **II**. At this stage, the mechanism of the formal carboacylation may diverge based on the ordering of the subsequent transmetalation and migratory insertion events. If transmetalation of ArBpin with complex **II** occurs first, acyl-nickel(II)-aryl complex **III** would be

generated. Subsequent migratory insertion of the tethered alkene into the Ni-C(acyl) bond would form alkyl-nickel(II)-aryl complex **V**. Reductive elimination of the indanone product **2** from **V** and coordination of another molecule of **1a** would close the catalytic cycle. Alternatively, if migratory insertion precedes transmetallation, alkyl-nickel(II)-amido complex **IV** would be formed by insertion of the tethered alkene into the Ni-C(acyl) bond of complex **II**.[34] Subsequent transmetalation of ArBpin with complex **IV** would form complex **V** and the indanone **2** upon reductive elimination.



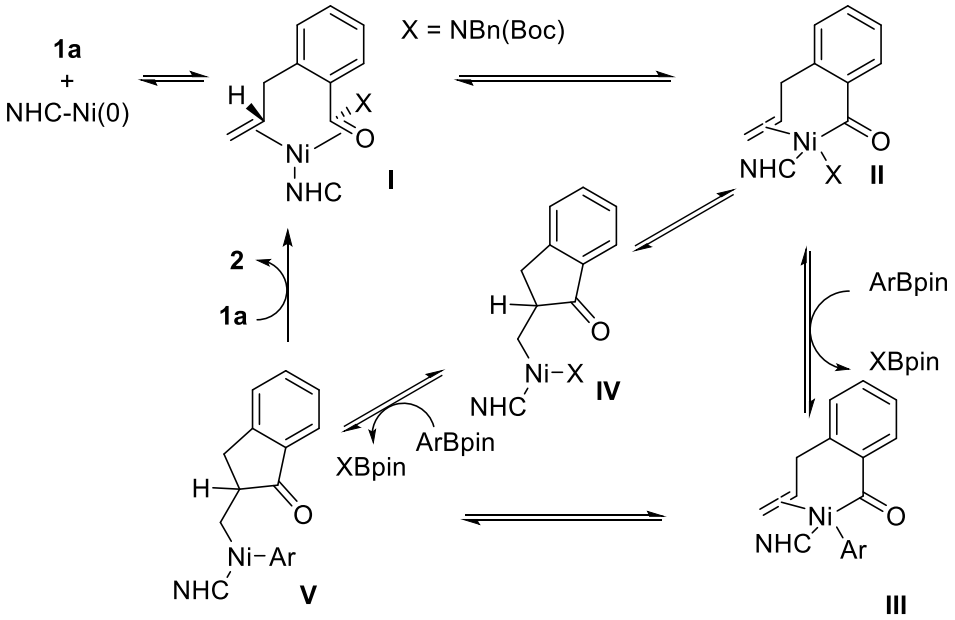




Our working hypothesis is that transmetalation of ArBpin with complex **II** precedes migratory insertion of the tethered alkene based on two observations. First, the identity of the ArBpin significantly impacts the amount of alkene isomerization observed under our reaction conditions (see Scheme 2). Second, alkene isomerization is not observed in the absence of ArBpin.

Taken together, these results are consistent with transmetalation of ArBpin with complex **II** occurring first to form complex **III** followed by migratory insertion to generate complex **V**.

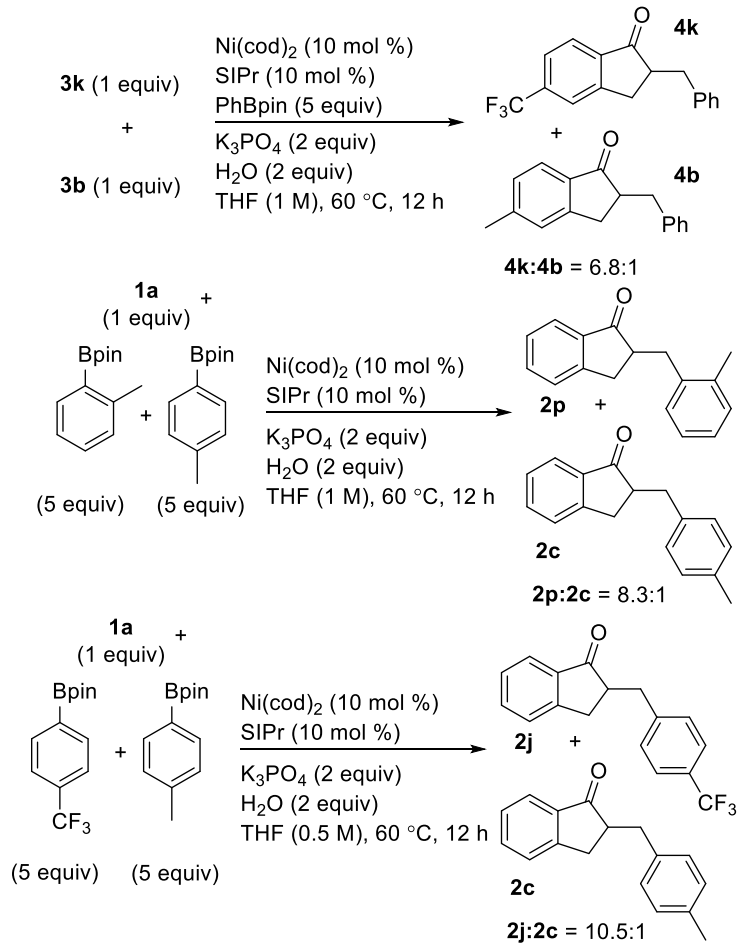
Scheme 4. Potential Mechanistic Pathways for Ni-Catalyzed Carboacylation via Amide C-N Activation



To gain additional insight into the mechanism of the formal carboacylation reaction, we conducted a series of competition experiments (Scheme 5). The competition experiment between 4-(trifluoromethyl)- and 4-methylbenzamides **3k** and **3b** formed ketones **4k** and **4b** in a 6.8:1 ratio favoring the trifluoromethyl-substituted ketone **4k**. Although this result is consistent with the relative reactivity of electron-deficient and electron-rich benzamides in the context of Suzuki-Miyaura and Negishi coupling,[23, 49] it contrasts the more facile nature of oxidative addition into electron-rich benzamide **3b** versus electron-deficient benzamide **3k** due to the increased amidic resonance that would be expected for **3k** versus **3b**.[50] In addition, this result suggests that the ratio of products observed is not determined by the relative rates of oxidative addition of **3k** and **3b**. Competition experiments between the pinacol ester of 4-tolylboronic acid with the pinacol esters

of 2-tolylboronic acid or 4-(trifluoromethyl)pheylboronic acid formed ketones **2p** and **2c** in an 8.3:1 ratio and ketones **2j** and **2c** in a 10.5:1 ratio. The observation that ketones derived from reactions with sterically hindered and electron-deficient arylboron nucleophiles are favored suggests that transmetalation is fast relative to reductive elimination and the ratio of products is determined by the relative rates of either reductive elimination or migratory insertion into the Ni-C(acyl) bond of complex **III**. Given that a nearly equimolar ratio of **4k** and **4b** would be expected from the competition between **3k** and **3b** if reductive elimination was turnover-limiting, we propose that migratory insertion of the alkene into the Ni-C(acyl) bond is the elementary step critical to determining product ratios.

Scheme 5. Competition Experiments between Substituted Benzamides or ArBpin



Conclusion

In summary, we have developed the first nickel-catalyzed alkene carboacylation reactions initiated by activation of amide C-N bonds. These processes enable coupling of a variety of *ortho*-allylbenzamides and arylboronic acid pinacol esters to form two new C-C bonds and the indanone products in up to 99% yield. Moreover, the development of this approach to alkene carboacylation bypasses challenges associated with related alkene carboacylation reactions that rely on C-C bond activation and further demonstrates the utility of amides as powerful building blocks in organic synthesis. Studies are ongoing in our laboratory to further leverage the synthetic potential of this transformation and to gain additional mechanistic understanding of the nickel-catalyzed alkene carboacylation reaction.

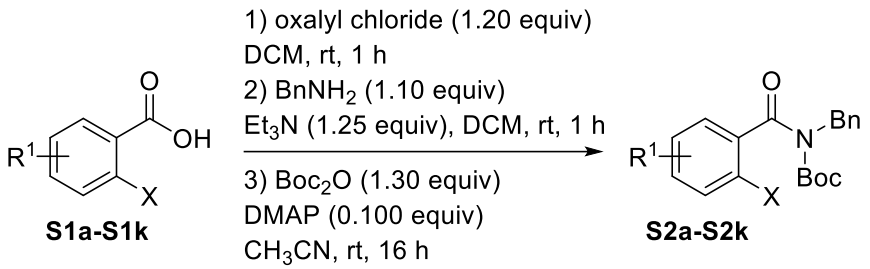
Experimental

General Experimental. 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 were dried at 140 °C in an oven. Tetrahydrofuran, methylene chloride and *N*,*N*-dimethylformamide 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. Flash column chromatography was performed on SiliFlash® P60 silica gel (40-63 μm, 60Å) or using a Teledyne Isco Combiflash® R*f* system with Redi*Sep* GoldTM columns using hexanes/ethyl acetate, dichloromethane/methanol, or pentane/ether mixtures as eluents. Reactions products were visualized on TLC by UV light or by staining with $KMnO_4$.

Instrumentation. HRMS (ESI) analysis was performed at the Iowa State University Chemical Instrumentation Facility on an Agilent 6540 QTOF spectrometer. 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 ^{1}H and 77.16 ppm for ^{13}C). ^{19}F NMR shifts are reported based on indirect reference to $CDCl_3$.[51]

Materials. 2-iodobenzoic acid (**S1a**) was purchased from Sigma Aldrich. 2-Iodo-5-methylbenzoic acid (**S1b**), 2-bromo-4-methylbenzoic acid (**S1c**), 2-iodo-5-methoxybenzoic acid (**S1d**), 2-bromo-4-methoxybenzoic acid (**S1e**), 2-bromo-6-fluorobenzoic acid (**S1f**), 2-bromo-4-fluorobenzoic acid (**S1g**), 2-bromo-3-fluorobenzoic acid (**S1h**), 2-bromo-5-(trifluoromethyl)benzoic acid (**S1i**), 2-iodo-4-(trifluoromethyl)benzoic acid (**S1j**), and 2-bromo-4,5-difluorobenzoic acid (**S1k**) were purchased from Combi-Blocks. Arylboronic acid pinacol esters were synthesized according to known a literature procedure.[52] Tetrakis(triphenylphosphine), cesium fluoride, and di-*tert*-butyl dicarbonate were purchased from Ak Scientific. Tribasic potassium phosphate was purchased from Sigma Aldrich. Bis(1,5-cyclooctadiene)nickel(0), and 1,3-bis(2,6-di-i-propylphenyl)-4,5-dihydroimidazol-2-ylidine were purchased from Strem Chemicals.

General Procedure A: Synthesis of *o*-Halobenzamides S2a-S2k:

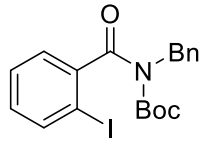


S1a; R^1 = H, X = I
S1b; R^1 = 5-Me, X = I
S1c; R^1 = 4-Me, X= Br
S1d; R^1 = 5-MeO, X= I
S1e; R^1 = 4-MeO, X = Br
S1f; R^1 = 6-F, X = Br
S1g; R^1 = 4-F, X= Br
S1h; R^1 = 3-F, X= Br
S1i; R^1 = 5-CF_3, X= Br
S1j; R^1 = 4-CF_3, X = I
S1k; R^1 = 4,5-F, X = Br

S2a; R^1 = H, X= I
S2b; R^1 = 5-Me, X = I
S2c; R^1 = 4-Me, X = Br
S2d; R^1 = 5-MeO, X = I
S2e; R^1 = 4-MeO, X = Br
S2f; R^1 = 6-F, X = Br
S2g; R^1 = 4-F, X = Br
S2h; R^1 = 3-F, X = Br
S2i; R^1 = 5-CF_3, X = Br
S2j; R^1 = 4-CF_3, X = I
S2k; R^1 = 4,5-F, X = Br

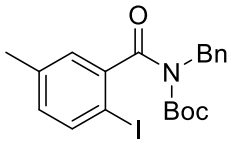
o-Halobenzamides (**S2a-S2k**) were prepared from the appropriate *o*-halobenzoic acid (**S1a-S1k**). To the appropriate *o*-halobenzoic acid (**S1a-S1k**) in anhydrous DCM (0.3 M) at 0 °C under N_2 was added 2M oxalyl chloride (1.20 equiv) dropwise and a catalytic amount of DMF (1-2 drops). The reaction was allowed to warm to room temperature and stirred for 1 h. The solvent was removed under reduced pressure to afford the corresponding crude acid chloride. To the crude acid chloride was added DCM (0.9 M) and triethylamine (1.25 equiv). Next, a solution of benzylamine (1.10 equiv) in DCM (0.5 M) was added dropwise. The reaction mixture was stirred at room temperature for 1 h, then diluted with ethyl acetate, and washed successively with 1M HCl and brine. The organic layer was dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The resulting crude material was used directly in the next step. To the round-bottom flask containing the crude benzamide was added DMAP (0.10 equiv), acetonitrile (0.2 M)

and Boc_2O (1.30 equiv). The reaction flask was then flushed with N_2 and allowed to stir at room temperature for 16 h. The reaction was quenched by addition of water, and extracted with ethyl acetate (3x). The organic layers were combined, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The resulting crude *o*-halobenzamides (**S2a-S2k**) were used directly in the next step without further purification.



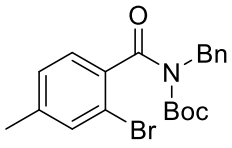
S2a

***tert*-butyl benzyl(2-iodobenzoyl)carbamate (S2a):** Prepared according to general procedure A from *o*-iodobenzoic acid **S1a** (7.61 g, 30.7 mmol). The reactions afforded crude product **S2a** as white solid in 80% yield (10.7 g, 24.7 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.14 (s, 9H), 5.05 (s, 2H), 7.07 (td, *J* = 7.1, 1.5 Hz, 1H), 7.17 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.29 (d, *J* = 7.2 Hz, 1H), 7.31-7.38 (m, 3H), 7.47 (d, *J* = 8.0 Hz, 2H), 7.80 (d, *J* = 8.0 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 27.5, 47.6, 83.9, 91.7, 127.0, 127.6, 127.9, 128.5, 128.6, 130.3, 137.5, 139.2, 144.6, 15.1, 171.6. **HRMS** (ESI): Calcd. for $C_{19}H_{21}INO_3^+$ ($[M+H]^+$): 438.0561, Found: 438.0556.



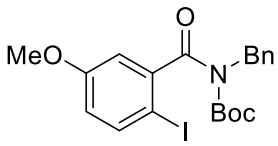
S2b

***tert*-butyl benzyl(2-iodo-5-methylbenzoyl)carbamate (S2b):** Prepared according to general procedure A from 2-iodo-5-methylbenzoic acid **S1b** (2.62 g, 10.0 mmol). The reactions afforded crude product **S2b** as a colorless oil in 91% yield (4.01 g, 9.10 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.16 (s, 9H), 2.30 (s, 3H), 5.05 (s, 2H), 6.90 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.01 (d, *J* = 1.5 Hz, 1H), 7.28 (t, *J* = 7.2 Hz, 1H), 7.32-7.38 (m, 2H), 7.48 (d, *J* = 7.2 Hz, 2H), 7.66 (d, *J* = 8.1 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 21.0, 27.5, 48.0, 83.7, 87.5, 127.5, 127.9, 128.5, 128.6, 131.3, 137.5, 138.1, 138.9, 144.3, 152.1, 171.8. **HRMS** (ESI): Calcd. for $C_{20}H_{23}INO_3^+$ ($[M+H]^+$): 452.0717, Found: 452.0720.



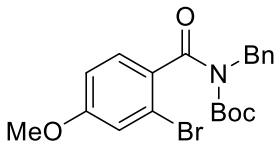
S2c

***tert*-butyl benzyl(2-bromo-4-methylbenzoyl)carbamate (S2c):** Prepared according to general procedure A from 2-bromo-4-methylbenzoic acid **S1c** (2.15 g, 10.0 mmol). The reactions afforded crude product **S2c** as a colorless oil in 83% yield (3.36 g, 8.32 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.17 (s, 9H), 2.35 (s, 3H), 5.05 (s, 2H), 7.12-7.18 (m, 2H), 7.26-7.30 (m, 1H), 7.32-7.37 (m, 3H), 7.45-7.47 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 27.5, 48.0, 83.6, 118.5, 127.4, 127.7, 128.0, 128.4, 128.5, 133.0, 133.1, 137.5, 137.6, 140.9, 152.3, 170.5. **HRMS** (ESI): Calcd. for $C_{20}H_{23}BrNO_3^+$ ($[M+H]^+$): 404.0856, Found: 404.0828.



S2d

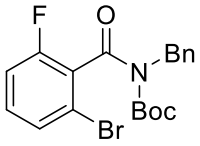
***tert*-butyl benzyl(2-iodo-5-methoxybenzoyl)carbamate (S2d):** Prepared according to general procedure A from 2-iodo-5-methoxybenzoic acid **S1d** (2.78 g, 10.0 mmol). The reactions afforded crude product **S2d** as a colorless oil in 81% yield (3.79 g, 8.10 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.17 (s, 9H), 3.75 (s, 3H), 5.04 (s, 2H), 6.67 (dd, *J* = 8.7, 3.0 Hz, 1H) 6.74 (d, *J* = 3.0 Hz, 1H), 7.28 (d, *J* = 7.3 Hz, 1H), 7.31-7.37 (m, 2H), 7.47 (d, *J* = 7.3 Hz, 2H), 7.63 (d, *J* = 8.7 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 27.5, 48.0, 55.6, 80.1, 83.8, 112.9, 116.9, 127.5, 128.5, 128.6, 137.4, 139.8, 145.2, 152.0, 159.7, 171.3. **HRMS** (ESI): Calcd. for $C_{20}H_{23}INO_4^+$ ($[M+H]^+$): 468.0666, Found: 468.0665.



S2e

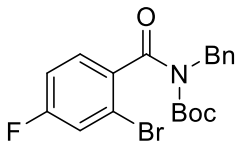
***tert*-butyl benzyl(2-bromo-4-methoxybenzoyl)carbamate (S2e):** Prepared according to general procedure A from 2-bromo-4-methoxybenzoic acid **S1e** (2.31 g, 10.0 mmol). The reactions afforded crude product **S2e** as a yellow oil in 90% yield (3.80 g, 9.00 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.19 (s, 9H), 3.81 (s, 3H), 5.03 (s, 2H), 6.86 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.07 (d, *J* = 2.4 Hz, 1H), 7.21 (d, *J* = 8.6 Hz, 1H), 7.26-7.29 (m, 1H), 7.31-7.35 (m, 2H), 7.42-7.46 (m, 2H). **^{13}C NMR** (101

MHz, $CDCl_3$) δ 27.6, 48.2, 53.6, 55.8, 83.5, 113.2, 118.1, 119.7, 127.5, 128.5, 129.2, 132.6, 137.7, 152.4, 160.7, 170.5. **HRMS** (ESI): Calcd. for $C_{20}H_{22}BrNO_4^+Na$ ($[M+Na]^+$): 442.0624, Found: 442.0587.



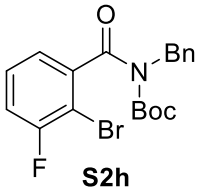
S2f

***tert*-butyl benzyl(2-bromo-6-fluorobenzoyl)carbamate (S2f):** Prepared according to general procedure A from 2-bromo-6-fluorobenzoic acid **S1f** (2.19 g, 10.0 mmol). The reactions afforded crude product **S2f** as a white solid in 75% yield (3.05 g, 7.50 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.18 (s, 9H), 5.10 (s, 2H), 7.04-7.08 (m, 1H), 7.21 (m, 1H), 7.24-7.30 (m, 1H), 7.31-7.37 (m, 3H), 7.41-7.45 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 27.5, 47.6, 84.2, 114.6 (d, *J* = 21.2 Hz, 1C), 119.2 (d, *J* = 5.05 Hz, 1C), 127.5, 128.1, 128.3 (d, *J* = 4.04 Hz, 1C), 128.5, 129.7, (d, *J* = 21.2 Hz, 1C), 130.6 (d, *J* = 8.08 Hz, 1C), 137.2, 151.6, 158.4 (d *J* = 252.5 Hz, 1C), 165.4. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -114.1 (m, 1F). **HRMS** (ESI): Calcd. for $C_{19}H_{19}BrFNO_3^+Na$ ($[M+Na]^+$): 430.0425, Found: 430.0387.



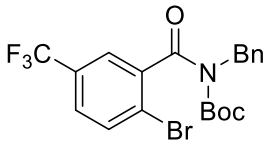
S2g

tert-butyl benzyl(2-bromo-4-fluorobenzoyl)carbamate (S2g): Prepared according to general procedure A from 2-bromo-4-fluorobenzoic acid **S1g** (2.19 g, 10.0 mmol). The reactions afforded crude product **S2g** as a white solid in 85% yield (3.47 g, 8.50 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.20 (s, 9H), 5.04 (s, 2H), 7.06 (td, *J* = 8.0, 2.5 Hz, 1H), 7.24-7.36 (m, 5H), 7.43-7.45 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 27.6, 48.1, 84.0. 114.7 (d, *J* = 21.2, 1C), 119.3 (d, *J* = 9.09 Hz, 1C), 120.0 (d, *J* = 13.1 Hz, 1C), 120.2 (d, *J* = 14.1 Hz, 1C), 127.6, 128.5, 129.2, 136.7 (d, *J* = 4.04 Hz, 1C), 137.4, 152.1, 162.5 (d, *J* = 254.5 Hz, 1C), 169.6. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -109.4 (m, 1F). **HRMS** (ESI): Calcd. for $C_{19}H_{19}BrFNO_3^+Na$ ($[M+Na]^+$): 430.0425, Found: 430.0384.



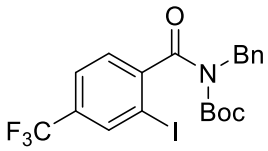
S2h

***tert*-butyl benzyl(2-bromo-3-fluorobenzoyl)carbamate (S2h):** Prepared according to general procedure A from 2-bromo-3-fluorobenzoic acid **S1h** (2.19 g, 10.0 mmol). The reactions afforded crude product **S2h** as a white solid in 84% yield (3.43 g, 8.40 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.17 (s, 9H), 5.06 (s, 2H), 7.04 (dt, *J* = 7.6, 1.0 Hz, 1H), 7.14 (td, *J* = 8.4, 1.4 Hz, 1H), 7.27-7.37 (m, 4H), 7.42-7.47 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 27.5, 47.9, 84.1, 106.4 (d, *J* = 23.2 Hz, 1C), 116.7 (d, *J* = 22.2 Hz, 1C), 122.8 (d, *J* = 3.0 Hz, 1C), 127.7, 128.5, 128.6, 128.9 (d, *J* = 8.1 Hz, 1C), 137.3, 142.6, 151.9, 159.0 (d, *J* = 248.5 Hz, 1C), 169.1. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -106.1 (m, 1F). **HRMS** (ESI): Calcd. for $C_{19}H_{19}BrFNO_3^+Na$ ($[M+Na]^+$): 430.0425, Found: 430.0393.



S2i

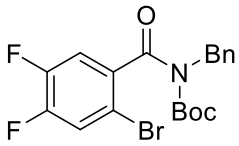
***tert*-butyl benzyl(2-bromo-5-(trifluoromethyl)benzoyl)carbamate (S2i):** Prepared according to general procedure A from 2-bromo-5-(trifluoromethyl)benzoic acid **S1i** (2.69 g, 10.0 mmol). The reactions afforded crude product **S2i** as a white solid in 88% yield (4.03 g, 8.80 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.16 (s, 9H), 5.07 (s, 2H), 7.28-7.38 (m, 3H), 7.45-7.51 (m, 4H), 7.67 (d, *J* = 8.2 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 27.5, 48.0, 84.4, 122.5, 124.7 (q, *J* = 3.8 Hz, 1C), 126.1 (q, *J* = 274.0 Hz, 1C), 126.8 (q, *J* = 3.7 Hz, 1C), 127.7, 128.6, 128.6, 130.3, 133.3, 137.1, 141.4, 151.7, 168.9. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -62.9 (s, 3F). **HRMS** (ESI): Calcd. for $C_{20}H_{19}BrF_3NO_3^+Na$ ($[M+Na]^+$): 480.0393, Found: 480.0344.



S2j

***tert*-butyl benzyl(2-iodo-4-(trifluoromethyl)benzoyl)carbamate (S2j):** Prepared according to general procedure A from 2-iodo-4-(trifluoromethyl)benzoic acid **S1j** (3.16 g, 10.0 mmol). The reactions afforded crude product **S2j** as a colorless oil in 91% yield (4.60 g, 9.10 mmol). **^{1}H NMR** (400

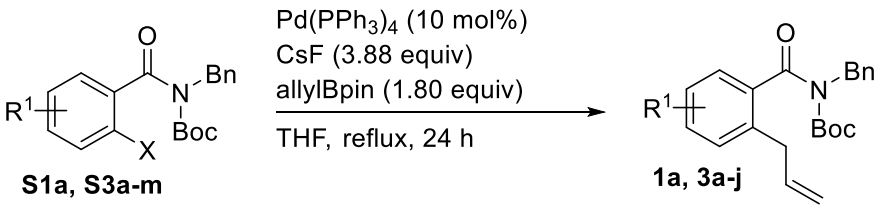
MHz, $CDCl_3$) δ 1.19 (s, 9H), 5.08 (s, 2H), 7.27-7.38 (m, 4H), 7.49 (d, *J* = 8.0 Hz, 2H), 7.64 (dd, *J* = 8.0, 0.9 Hz, 1H), 8.06 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 27.6, 47.8, 84.5, 91.1, 122.7 (q, *J* = 274.7, 1C), 124.5 (d, *J* = 22.2 Hz, 1C), 126.9 (d, *J* = 11.1 Hz, 1C), 127.7 (q, *J* = 6.1 Hz, 1C), 128.6 (m, 1C), 128.7 (d, *J* = 9.1 Hz, 1C), 132.0 (q, *J* = 33.3 Hz, 1C), 135.9 (dd, *J* = 15.2, 4.0 Hz, 1C), 137.1, 148.1, 151.6, 170.5. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -62.8 (s, 3F). **HRMS** (ESI): Calcd. for $C_{20}H_{20}F_3INO_3^+$ ($[M+H]^+$): 506.0434, Found: 506.0450.



S2k

***tert*-butyl benzyl(2-bromo-4,5-difluorobenzoyl)carbamate (S2k):** Prepared according to general procedure A from 2-bromo-4,5-difluorobenzoic acid **S1k** (2.37 g, 10.0 mmol). The reactions afforded crude product **S2k** as a white solid in 74% yield (3.16 g, 7.40 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.24 (s, 9H), 5.03 (s, 2H), 7.14 (dd, *J* = 9.8, 7.9 Hz, 1H), 7.27-7.43 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 27.6, 48.1, 84.4, 112.6 (dd, *J* = 7.4, 4.1 Hz, 1C), 116.9, 117.1 (d, *J* = 2.0 Hz, 1C), 127.7, 128.5, 128.6 (d, *J* = 2.0 Hz, 1C), 137.0 (dd, *J* = 6.1, 5.1 Hz, 1C), 137.1, 149.7 (dd, *J* = 252.5, 13.1 Hz, 1C), 150.4 (dd, *J* = 257.6, 14.1 Hz, 1C), 151.9, 168.4. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -137.8 (m, 1F), -133.4 (m, 1F). **HRMS** (ESI): Calcd. for $C_{19}H_{19}BrF_2NO_3^+$ ($[M+H]^+$): 426.0511, Found: 426.0502.

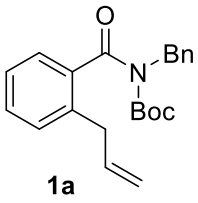
General Procedure B: Synthesis of *o*-Allylbenzamides 1a, 3a-j



S2a; R^1 = H, X = I
S2b; R^1 = 5-Me, X = I
S2c; R^1 = 4-Me, X = Br
S2d; R^1 = 5-MeO, X = I
S2e; R^1 = 4-MeO, X = Br
S2f; R^1 = 6-F, X = Br
S2g; R^1 = 4-F, X= Br
S2h; R^1 = 3-F, X = Br
S2i; R^1 = 5-CF_3, X = Br
S2j; R^1 = 4-CF_3, X = I
S2k; R^1 = 4,5-F, X = Br

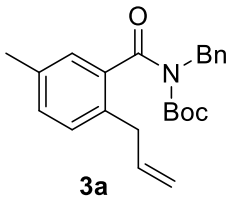
1a; R^1 = H
3a; R^1 = 5-Me
3b; R^1 = 5-MeO
3c; R^1 = 5-CF_3
3d; R^1 = 4-MeO
3e; R^1 = 4-Me
3f; R^1 = 4-F
3g; R^1 = 4-CF_3
3h; R^1 = 3-F
3i; R^1 = 6-F
3j; R^1 = 4,5-F

o-Allylbenzamides (**1a, 3a-j**) were prepared according to the following procedure. A round-bottom flask was charged with 3.00 mmol of *o*-iodobenzamide (**S2a-S2k**), CsF (1.77 g, 11.6 mmol), $Pd(PPh_3)_4$ (0.347 g, 0.300 mmol), and THF (37.5 mL). The resulting solution was stirred at room temperature for 30 minutes. Then 2-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (allylBpin) (0.907 g, 5.40 mmol) in THF (37.5 mL) was added. The resulting solution was stirred at reflux for 24 hours. The reaction mixture was diluted with hexanes (100 mL) followed by water (100 mL). The layers were separated, and the organic layer extracted with hexanes (2 x 100 mL). The combined organic layers were washed with water (200 mL) and brine (200 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purifications of the crude products were carried out by flash column chromatography to give *o*-allylbenzamides **1a, 3a-j**.



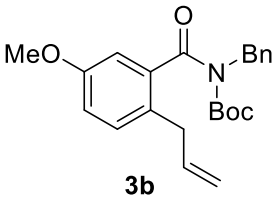
1a

***tert*-butyl (2-allylbenzoyl)(benzyl)carbamate (1a):** Prepared according to general procedure B from *tert*-butyl benzyl(2-iodobenzoyl)carbamate **S2a** (1.31 g, 3.00 mmol). The crude reaction mixture was purified by flash column chromatography (100:0 hexanes:EtOAc to 90:10 hexanes EtOAc) to give **1a** as a colorless oil in 79% yield (0.830 g, 2.37 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.08 (s, 9H), 3.45 (d, *J* = 6.8 Hz, 1H), 5.03 (s, 2H), 5.03-5.10 (m, 2H), 5.92 (ddt, *J* = 17.0, 10.0, 6.8 Hz, 1H), 7.12 (d, *J* = 7.6 Hz, 1H), 7.19 (t, *J* = 7.6 Hz, 1H), 7.22-7.37 (m, 5H), 7.45 (d, *J* = 7.4 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 27.5, 37.6, 48.1, 83.4, 116.6, 125.9, 126.1, 127.5, 128.4, 128.6, 129.6, 129.8, 136.6, 137.3, 137.9, 138.2, 153.0, 172.4. **HRMS** (ESI): Calcd. for $C_{22}H_{26}NO_3^+$ ($[M+H]^+$): 352.1907, Found: 352.1883.



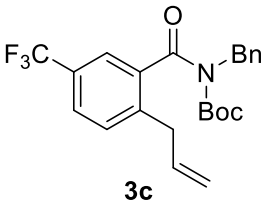
3a

***tert*-butyl (2-allyl-5-methylbenzoyl)(benzyl)carbamate (3a):** Prepared according to general procedure B from *tert*-butyl (2-iodo-5-methylbenzoyl)(benzyl)carbamate **S2b** (1.35 g, 3.00 mmol). The crude reaction mixture was purified by flash column chromatography (100:0 hexanes:EtOAc to 90:10 Hexanes:EtOAc) to give **3a** as a colorless oil in 78% yield (0.856 g, 2.34 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.09 (s, 9H), 2.30 (s, 3H), 3.41 (d, *J* = 8.0 Hz, 2H), 5.03 (s, 2H), 5.01-5.08 (m, 2H), 5.91 (ddt, *J* = 17.0, 10.0, 8.0 Hz, 1H), 6.96 (s, 1H), 7.11-7.16 (m, 2H), 7.26-7.30 (m, 1H), 7.33-7.37 (m, 2H), 7.45-7.47 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 20.9, 27.4, 37.2, 48.1, 83.3, 116.2, 126.7, 127.5, 128.4, 128.5, 129.8, 130.3, 134.3, 135.4, 136.81, 137.9, 137.9, 153.1, 172.5. **HRMS** (ESI): Calcd. for $C_{23}H_{28}NO_3^+$ ($[M+H]^+$): 366.2064, Found: 366.2024.



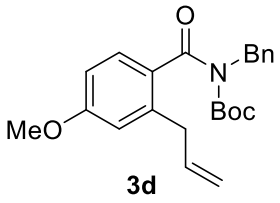
3b

***tert*-butyl (2-allyl-5methoxybenzoyl)(benzyl)carbamate (3b):** Prepared according to general procedure B from *tert*-butyl benzyl(2-iodo-5-methoxybenzoyl)carbamate **S2d** (1.40 g, 3.00 mmol). The crude reaction mixture was purified by flash column chromatography (100:0 hexanes:EtOAc to 90:10 hexanes:EtOAc) to give **3b** as a dark-green oil in 61% yield (0.698 g, 1.83 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.14 (s, 9H), 3.38 (d, *J* = 6.8 Hz, 2H), 3.76 (s, 3H), 5.02-5.08 (m, 2H), 5.04 (s, 2H), 5.91 (ddt, *J* = 17.0, 10.1, 6.8 Hz, 1H), 6.69 (d, *J* = 2.8 Hz, 1H), 6.89 (dd, *J* = 8.5, 2.8 Hz, 1H), 7.16 (d, *J* = 8.5 Hz, 1H), 7.28-7.31 (m, 1H), 7.34-7.38 (m, 2H), 7.46-7.48 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 27.5, 36.7, 48.1, 55.5, 83.4, 111.5, 115.4, 116.1, 127.5, 128.4, 128.5, 129.2, 130.9, 136.9, 137.8, 138.9, 152.9, 157.6, 172.1. **HRMS** (ESI): Calcd. for $C_{23}H_{27}NO_4^+Na$ ($[M+Na]^+$): 404.1832, Found: 404.1786.



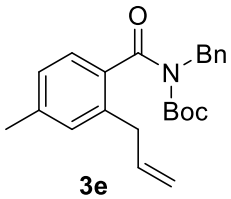
3c

***tert*-butyl (2-allyl-5-(trifluoromethyl)benzoyl)(benzyl)carbamate (3c):** Prepared according to general procedure B from *tert*-butyl benzyl(2-bromo-5-(trifluoromethyl)benzoyl)carbamate **S2i** (1.37 g, 3.00 mmol). The crude reaction mixture was purified by flash column chromatography (100:0 hexanes:EtOAc to 95:5 hexanes:EtOAc) to give **3c** as a colorless oil as an 84:16 mixture of **3c** and the olefin isomerization product in 70% yield (0.879 g, 2.10 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.10 (s, 9H), 3.46 (d, *J* = 6.8 Hz, 2H), 5.05 (s, 2H), 5.06-5.11 (m, 2H), 5.81-5.93 (m, 1H), 7.27-7.40 (m, 5H), 7.45 (d, *J* = 7.2 Hz, 2H) 7.58 (dd, *J* = 7.9, 3.1 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 27.3, 37.3, 48.0, 83.9, 117.4, 122.9 (q, *J* = 3.7 Hz, 1C), 125.9 (q, *J* = 3.8 Hz, 1C), 127.0 (q, *J* = 273.4 Hz, 1C), 127.6, 128.3, 128.5, 128.7, 130.2, 131.5, 135.2, 137.3, 138.7, 141.0, 152.3, 170.8,. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -62.6 (m, 1F). **HRMS** (ESI): Calcd. for $C_{23}H_{25}F_3NO_3^+$ ($[M+H]^+$): 420.1781, Found: 420.1720.



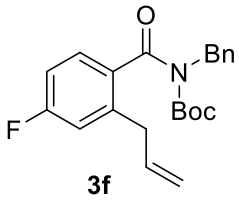
3d

***tert*-butyl benzyl(2-allyl-4-methoxybenzoyl)carbamate (3d):** Prepared according to general procedure B from *tert*-butyl benzyl(2-bromo-4-methoxybenzoyl)carbamate **S2e** (1.26 g, 3.00 mmol). The crude reaction mixture was purified by flash column chromatography (100:0 hexanes:EtOAc to 90:10 hexanes:EtOAc) to give **3d** as a colorless oil in 34% yield (0.386 g, 1.01 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.13 (s, 9H), 3.48 (d, *J* = 6.8 Hz, 2H), 3.80 (s, 3H), 4.99 (s, 2H), 5.04-5.12 (m, 2H), 5.92 (ddt, *J* = 17.2, 10.0, 6.8 Hz, 1H), 6.70 (dd, *J* = 8.5, 2.4 Hz, 1H), 6.78 (d, *J* = 2.4 Hz, 1H), 7.12 (d, *J* = 8.5 Hz, 1H), 7.24-7.29 (m, 1H), 7.31-7.35 (m, 2H), 7.42-7.44 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 27.6, 37.7, 48.4, 55.4, 83.1, 110.9, 115.5, 116.6, 127.5, 128.3, 128.4, 128.5, 130.5, 136.5, 138.0, 140.2, 153.3, 160.8, 172.4. **HRMS** (ESI): Calcd. for $C_{23}H_{27}NO_4^+Na$ ($[M+Na]^+$): 404.1832, Found: 404.1782.



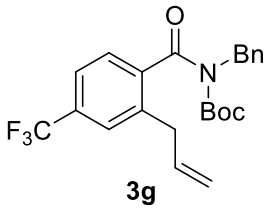
3e

***tert*-butyl (2-allyl-4-methylbenzoyl)(benzyl)carbamate (3e):** Prepared according to general procedure B from *tert*-butyl benzyl(2-bromo-4-methylbenzoyl)carbamate **S2c** (1.21 g, 3.00 mmol). The crude reaction mixture was purified by flash column chromatography (100:0 hexanes:EtOAc to 90:10 hexanes:EtOAc) to give **3e** as a colorless oil in 28% yield (0.310 g, 0.848 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.11 (s, 9H), 2.34 (s, 3H), 3.44 (d, *J* = 8.0 Hz, 2H), 5.01 (s, 2H), 5.05-5.10 (m, 2H), 5.93 (ddt, *J* = 17.0, 10.0, 6.9 Hz, 1H), 6.99 (d, *J* = 8.0 Hz, 1H), 7.05 (d, *J* = 8.0 Hz, 1H), 7.05-7.07 (m, 1H), 7.24-7.30 (m, 1H), 7.30-7.37 (m, 2H), 7.44 (d, *J* = 8.0 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 21.5, 27.5, 37.6, 48.2, 83.2, 116.3, 126.4, 126.5, 127.5, 128.3, 128.5, 130.6, 135.3, 136.8 137.5, 138.0, 139.8, 153.1, 172.6. **HRMS** (ESI): Calcd. for $C_{23}H_{28}NO_3^+$ ($[M+H]^+$): 366.2064, Found: 366.2027.



3f

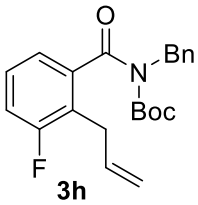
tert-butyl (2-allyl-4-fluorobenzoyl)(benzyl)carbamate (3f): Prepared according to general procedure B from *tert*-butyl benzyl(2-bromo-4-fluorobenzoyl)carbamate **S2g** (1.22 g, 3.00 mmol). The crude reaction mixture was purified by flash column chromatography (100:0 hexanes:EtOAc to 90:10 hexanes:EtOAc) to give **3f** as a colorless oil in 51% yield (0.568 g, 1.54 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.14 (s, 9H), 3.44 (d, *J* = 6.9 Hz, 2H), 5.01 (s, 2H), 5.06-5.12 (m, 2H), 5.89 (ddt, *J* = 17.4, 9.6, 6.9 Hz, 1H), 6.89 (td, *J* = 8.5, 2.4 Hz, 1H), 6.97 (dd, *J* = 9.8, 2.4 Hz, 1H), 7.12 (dd, *J* = 8.5, 5.7 Hz, 1H), 7.26-7.30 (m, 1H), 7.32-7.36 (m, 2H), 7.42-7.44 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 27.6, 37.4, 48.2, 83.6, 112.8 (d, *J* = 21.2 Hz, 1C), 116.7 (d, *J* = 22.2 Hz, 1C), 117.4, 127.61, 128.1 (d, *J* = 9.1 Hz, 1C), 128.4, 128.6, 134.3 (d, *J* = 3.0 Hz, 1C), 135.6, 137.7 140.6 (d, *J* = 7.1 Hz, 1C), 152.9, 163.3 (d, *J* = 250.5 Hz, 1C), 171.6. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -110.9 (m, 1F). **HRMS** (ESI): Calcd. for $C_{22}H_{24}FNO_3^+Na$ ($[M+Na]^+$): 392.1632, Found: 392.1596.



3g

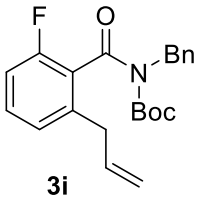
***tert*-butyl (2-allyl-4-(trifluoromethyl)benzoyl)(benzyl)carbamate (3g):** Prepared according to general procedure B from *tert*-butyl benzyl(2-iodo-4-(trifluoromethyl)benzoyl)carbamate **S2j** (1.52 g, 3.00 mmol). The crude reaction mixture was purified by flash column chromatography (100:0 hexnaes:EtOAc to 90:10 hexanes:EtOAc) to give **3g** as a colorless oil in 81% yield (1.02 g, 2.43 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.12 (s, 9H), 3.45 (d, *J* = 6.8 Hz, 2H), 5.05 (s, 2H), 5.06-5.12 (m, 2H), 5.89 (ddt, *J* = 16.8, 10.3, 6.8 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 1H), 7.27-7.32 (m, 1H), 7.34-7.38 (m, 2H), 7.43-7.51 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 22.5, 37.4, 47.9, 84.1, 117.7, 122.9 (q, *J* = 3.75 Hz, 1C), 126.1, 126.5 (q, *J* = 4.0 Hz, 1C), 127.0 (q, *J* = 274.1 Hz, 1C), 127.7, 128.5, 128.6, 131.2,

135.2, 137.5, 137.9, 141.8, 152.4, 171.1. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -62.6 (s, 3F). **HRMS** (ESI): Calcd. for $C_{23}H_{24}F_3NO_3^+Na$ ($[M+Na]^+$): 442.1600, Found: 442.1550.



3h

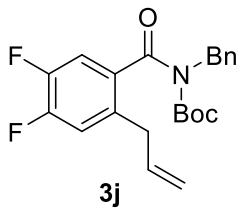
***tert*-butyl (2-allyl-3-fluorobenzoyl)(benzyl)carbamate (3h):** Prepared according to general procedure B from *tert*-butyl benzyl(3-fluoro-2-bromobenzoyl)carbamate **S2h** (1.22 g, 3.00 mmol). The crude reaction mixture was purified by flash column chromatography (100:0 hexanes:EtOAc to 90:10 hexanes:EtOAc) to give **3h** as a colorless oil in 71% yield (0.787 g, 2.13 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.12, (s, 9H), 3.43 (d, *J* = 6.0 Hz, 2H), 4.97-5.05 (m, 2H), 5.03 (s, 2H), 5.89 (ddt, *J* = 17.1, 10.0, 6.6 Hz, 1H), 6.93 (dd, *J* = 7.6, 0.6 Hz, 1H), 7.05-7.09 (m, 1H), 7.18 (m, 1H), 7.27-7.30 (m, 1H), 7.33-7.37 (m, 2H), 7.43-7.45 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 27.5, 30.7, 48.0, 83.8, 116.27, 116.3, 116.5, 121.7 (d, *J* = 3.0 Hz, 1C), 124.6 (d, *J* = 17.2 Hz, 1C), 127.4 (d, *J* = 9.1 Hz, 1C), 127.6, 128.5 (d, *J* = 15.2 Hz, 1C), 135.2, 137.7, 140.4 (d, *J* = 5.1 Hz, 1C), 152.7, 161.4 (d, *J* = 248.5 Hz, 1C), 170.9 (d, *J* = 3.0 Hz, 1C). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -116.6 (m, 1F). **HRMS** (ESI): Calcd. for $C_{22}H_{24}FNO_3^+Na$ ($[M+Na]^+$): 392.1632, Found: 392.1587.



3i

***tert*-butyl (2-allyl-6-fluorobenzoyl)(benzyl)carbamate (3i):** Prepared according to general procedure B from *tert*-butyl benzyl(2-bromo-6-fluorobenzoyl)carbamate **S2f** (1.22 g, 3.00 mmol). The crude reaction mixture was purified by flash column chromatography (100:0 hexanes:EtOAc to 90:10 hexanes:EtOAc) to give **3i** as a colorless oil in 89% yield (0.984 g, 2.66 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.16 (s, 9H), 3.37 (dd, *J* = 22.6, 7.2 Hz, 2H), 4.99-5.05 (m, 2H), 5.09 (d, *J* = 4.6 Hz, 2H), 5.86 (ddt, *J* = 17.6, 9.6, 6.8 Hz, 1H), 6.91 (t, *J* = 9.6 Hz, 1H), 7.03 (d, *J* = 7.6 Hz, 1H), 7.24-7.30 (m, 2H), 7.32-7.36 (m, 2H), 7.42-7.44 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 27.4 (d, *J* = 4.0 Hz, 1C), 37.4,

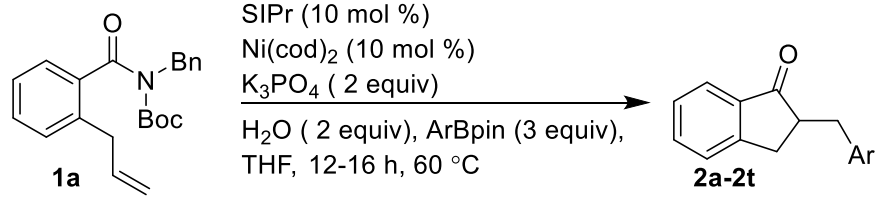
47.6, 83.7, 112.9, 113.1, 116.9, 125.3 (d, *J* = 2.0 Hz, 1C), 126.9 (d, *J* = 17.2 Hz, 1C), 127.8 (d, *J* = 74.7 Hz, 1C), 128.5, 130.1 (d, *J* = 8.1 Hz, 1C), 135.8 (d, *J* = 6.1 Hz, 1C), 137.6, 139.1 (d, *J* = 3.0 Hz, 1C), 152.1, 158.3 (d, *J* = 247.5 Hz, 1C), 167.25. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -117.7 (m, 1F). **HRMS** (ESI): Calcd. for $C_{22}H_{24}FNO_3^+Na$ ([M+Na]$^+$): 392.1632, Found: 392.1598.

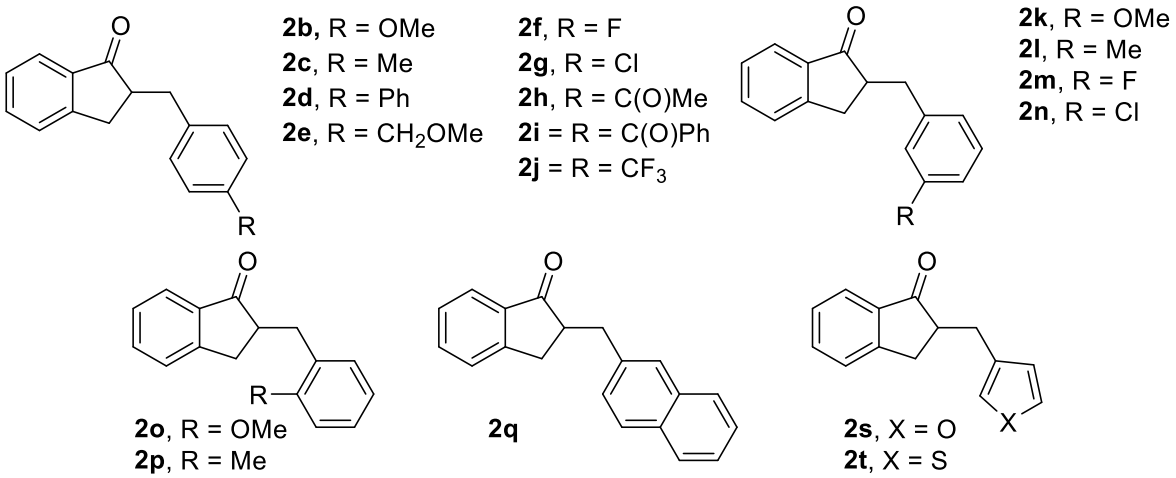


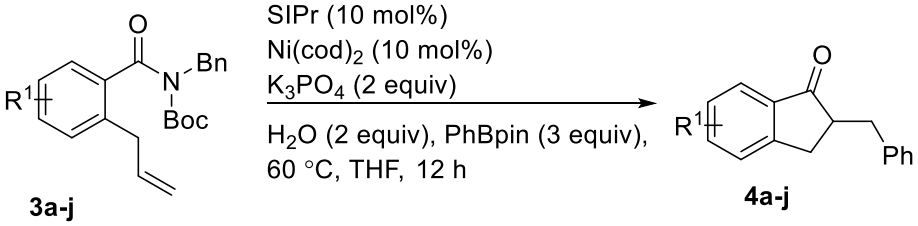
3j

***tert*-butyl (2-allyl-4,5-difluorobenzoyl)(benzyl)carbamate (3j):** Prepared according to general procedure B from *tert*-butyl benzyl(4,5-difluoro-2-bromobenzoyl)carbamate **S2k** (1.28 g, 3.00 mmol). The crude reaction mixture was purified by flash column chromatography (100:0 DCM:EtOAc to 90:10 DCM:EtOAc) to give **3j** as a colorless oil in 61% yield (0.709 g, 1.83 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.19 (s, 9H), 3.36 (d, *J* = 6.8 Hz, 2H), 5.00 (s, 2H), 5.03-5.10 (m, 2H), 5.84 (ddt, *J* = 16.9, 10.2, 6.8 Hz, 1H), 6.97 (dd, *J* = 10.2, 7.8 Hz, 1H), 7.06 (dd, *J* = 11.2, 7.6 Hz, 1H), 7.27-7.31 (m, 1H), 7.33-7.38 (m, 2H), 7.39-7.43 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 27.5, 36.6, 48.1, 83.9, 115.3 (d, *J* = 19.2 Hz, 1C), 117.4, 118.5 (d, *J* = 18.2 Hz, 1C), 127.6, 128.36 (d, *J* = 29.3 Hz, 1C), 128.37 (d, *J* = 10.1 Hz, 1C), 134.2 (dd, *J* = 5.1 Hz, 1C), 134.5 (dd, *J* = 5.1 Hz, 1C), 135.3, 137.3, 148.2 (dd, *J* = 249.6, 13.2 Hz, 1C), 150.5 (dd, *J* = 248.2, 12.6 Hz, 1C), 152.4, 170.1. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -141.3 (m, 1F) -135.8 (m, 1F). **HRMS** (ESI): Calcd. for $C_{22}H_{23}F_2NO_3^+Na$ ([M+Na]$^+$): 410.1538, Found: 410.1492.

General Procedure C: Synthesis of 2-Benzyl-2,3-dihydro-1*H*-inden-1-ones 2a-2t, 4a-4j





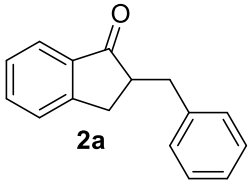


3a; R^1 = 5-Me
3b; R^1 = 5-MeO
3c; R^1 = 5-CF_3
3d; R^1 = 4-MeO
3e; R^1 = 4-Me
3f; R^1 = 4-F
3g; R^1 = 4-CF_3
3h; R^1 = 3-F
3i; R^1 = 6-F
3j; R^1 = 4,5-F

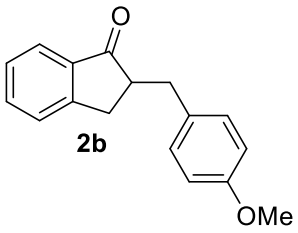
4a; R^1 = 5-Me
4b; R^1 = 5-MeO
4c; R^1 = 5-CF_3
4d; R^1 = 4-MeO
4e; R^1 = 4-Me
4f; R^1 = 4-F
4g; R^1 = 4-CF_3
4h; R^1 = 3-F
4i; R^1 = 6-F
4j; R^1 = 4,5-F

2-benzyl-2,3-dihydro-1*H*-inden-1-ones **2a-2t, 4a-4j** were prepared by the following procedure. A 1-dram vial was charged with 0.100 mmol of the appropriate *o*-allylbenzamide **1a,**

3a-3j, $Ni(cod)_2$ (2.8 mg, 0.010 mmol), SIPr (3.9 mg, 0.010 mmol), K_3PO_4 (42.5 mg, 0.200 mmol), H_2O (3.6 µL, 0.20 mmol), the appropriate ArBpin (0.300 mmol), and THF (0.10-0.20 mL, 0.50-1.0 M). The resulting solution stirred at 60 °C for 12-16 hours. Upon completion of the reaction, the reaction mixture was filtered through a short plug of silica gel eluting with 70:30 hexanes:EtOAc and concentrated under reduced pressure. The crude product was purified by column chromatography with a gradient of 100:0 hexanes:EtOAc to 90:10 hexanes:EtOAc over a 25 minute period on a Combiflash system.

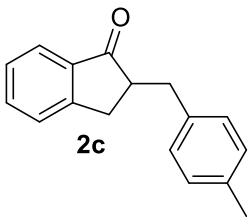


2-benzyl-2,3-dihydro-1*H*-inden-1-one (2a): Prepared according to general procedure C from *tert*-butyl (2-allylbenzoyl)(benzyl)carbamate **1a** (35.1 mg, 0.100 mmol) and phenylboronic acid pinacol ester (61.2 mg, 0.300 mmol). The crude reaction mixture was purified by flash column chromatography (100:0 hexanes:EtOAc to 90:10 hexanes:EtOAc) to give **2a** as a colorless oil in 97% yield (21.6 mg, 0.097 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.68 (dd, *J* = 14.0, 10.4 Hz, 1H), 2.88 (dd, *J* = 17.2, 4.0 Hz, 1H), 2.97-3.06 (m, 1H), 3.18 (dd, *J* = 17.2, 7.8 Hz, 1H), 3.42 (dd, *J* = 14.0, 4.2 Hz, 1H), 7.20-7.34 (m, 5H), 7.35-7.43 (m, 2H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.80 (d, *J* = 7.6 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 32.3, 37.1, 49.1, 124.1, 126.5, 126.7, 127.5, 128.6, 129.0, 134.9, 136.7, 139.8, 153.7, 207.9. **HRMS** (ESI): Calcd. for $C_{16}H_{14}O^+Na$ ($[M+Na]^+$): 245.0937, Found: 245.0902.

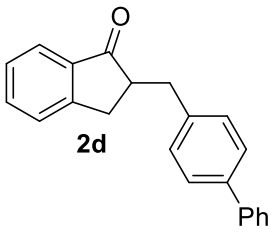


2-(4-methoxybenzyl)-2,3-dihydro-1*H*-inden-1-one (2b): Prepared according to general procedure C from *tert*-butyl (2-allylbenzoyl)(benzyl)carbamate **1a** (35.1 mg, 0.100 mmol) and 4-methoxyphenylboronic acid pinacol ester (70.2 mg, 0.300 mmol). The crude reaction mixture was purified by flash column chromatography (100:0 hexanes:EtOAC to

90:10 hexanes:EtOAc) to give **2b** as a colorless oil in 98% yield (24.8 mg, 0.098 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.65 (dd, *J* = 14.0, 10.1 Hz, 1H), 2.86 (dd, *J* = 17.2, 4.0 Hz, 1H), 2.93-3.00 (m, 1H), 3.17 (dd, *J* = 17.2, 7.7 Hz, 1H), 3.31 (dd, *J* = 14.0, 4.3 Hz, 1H), 3.79 (s, 3H), 6.84 (ddd, *J* = 8.7, 3.0, 2.1 Hz, 2H), 7.16 (ddd, *J* = 8.7, 3.0, 2.0 Hz, 2H), 7.35-7.41 (m, 2H), 7.57 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 32.2, 36.2, 49.3, 55.4, 114.0, 124.1, 126.7, 127.5, 130.0, 131.7, 134.9, 136.7, 153.8, 158.3, 208.1. **HRMS** (ESI): Calcd. for $C_{17}H_{17}O_2^+$ ($[M+H]^+$): 253.1223, Found: 253.1225.

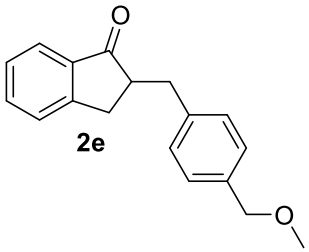


2-(4-methylbenzyl)-2,3-dihydro-1*H*-inden-1-one (2c): Prepared according to general procedure C from *tert*-butyl (2-allylbenzoyl)(benzyl)carbamate **1a** (35.1 mg, 0.100 mmol) and 4-tolylboronic acid pinacol ester (65.4 mg, 0.300 mmol). The crude reaction mixture was purified by flash column chromatography (100:0 hexanes:EtOAc to 90:10 hexanes:EtOAc) to give **2c** as a colorless oil in 99% yield (23.4 mg, 0.099 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.33 (s, 3H), 2.64 (dd, *J* = 14.0, 10.4 Hz, 1H), 2.86 (dd, *J* = 17.2, 3.9 Hz, 1H), 2.95-3.02 (m, 1H), 3.17 (dd, *J* = 17.2, 7.8 Hz, 1H), 3.36 (dd, *J* = 14.0, 4.2 Hz, 1H), 7.10-7.15 (m, 4H), 7.35-7.41 (m, 2H), 7.57 (ddd, *J* = 7.6, 7.6, 1.1 Hz, 1H), 7.78 (d, *J* = 7.7 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 21.3, 32.3, 36.7, 49.2, 124.1, 126.6, 127.5, 128.9, 129.3, 134.8, 136.0, 136.66, 136.73, 153.8, 208.1. **HRMS** (ESI): Calcd. for $C_{17}H_{17}O^+$ ($[M+H]^+$): 237.1274, Found: 237.1272.



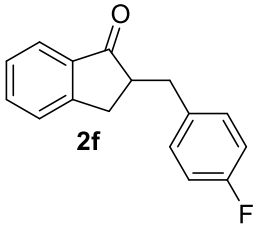
2-([1,1'-biphenyl]-4-ylmethyl)-2,3-dihydro-1*H*-inden-1-one (2d): Prepared according to general procedure C from *tert*-butyl (2-allylbenzoyl)(benzyl)carbamate **1a** (35.1 mg, 0.100 mmol) and 4-biphenylboronic acid pinacol ester (84.1 mg, 0.300 mmol). The crude

reaction mixture was purified by flash column chromatography (100:0 hexanes:EtOAc to 90:10 hexanes:EtOAc) to give **2d** as a colorless oil in 94% yield (27.9 mg, 0.094 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.73 (dd, *J* = 14.0, 10.4 Hz, 1H), 2.91 (dd, *J* = 17.2, 4.0 Hz, 1H), 3.02-3.08 (m, 1H), 3.23 (dd, *J* = 17.2, 7.8 Hz, 1H), 3.44 (dd, *J* = 14.0, 4.3 Hz, 1H), 7.32-7.46 (m, 7H), 7.53-7.60 (m, 5H), 7.81 (d, *J* = 7.5 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 32.4, 36.8, 49.0, 124.2, 126.7, 127.1, 127.3, 127.4, 127.6, 128.9, 129.5, 135.0, 136.7, 138.9, 139.4, 141.0, 153.8, 207.9. **HRMS** (ESI): Calcd. for $C_{22}H_{19}O^+$ ($[M+H]^+$): 299.1430, Found: 299.1433.



2e

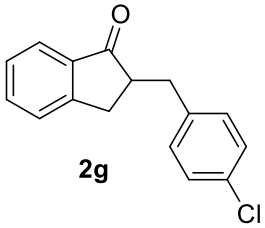
2-(4-(methoxymethyl)benzyl)-2,3-dihydro-1*H*-inden-1-one (2e): Prepared according to general procedure C from *tert*-butyl (2-allylbenzoyl)(benzyl)carbamate **1a** (35.1 mg, 0.100 mmol) and 4-(methoxymethyl)phenylboronic acid pinacol ester (74.4 mg, 0.300 mmol). The crude reaction mixture was purified by flash column chromatography (100:0 hexanes:EtOAc to 90:10 hexanes:EtOAc) to give **2e** as a colorless oil in 78% yield (20.7 mg, 0.078 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.68 (dd, *J* = 13.8, 11.0 Hz, 1H), 2.84 (dd, *J* = 17.2, 3.8 Hz, 1H), 2.96-3.03 (m, 1H), 3.16 (dd, *J* = 17.1, 7.8 Hz, 1H), 3.36-3.40 (m, 4H), 4.42 (s, 2H), 7.22-7.28 (m, 4H), 7.34-7.40 (m, 2H), 7.56 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.78 (d, *J* = 7.7 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 32.3, 36.8, 49.0, 58.3, 74.6, 124.2, 126.7, 127.6, 128.2, 129.1, 134.9, 136.4, 136.8, 138.2, 153.8, 207.91. **HRMS** (ESI): Calcd. for $C_{18}H_{19}O_2^+$ ($[M+H]^+$): 267.1380, Found: 267.1383.



2f

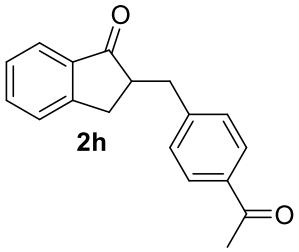
2-(4-fluorobenzyl)-2,3-dihydro-1*H*-inden-1-one (2f): Prepared according to general procedure C from *tert*-butyl (2-allylbenzoyl)(benzyl)carbamate **1a** (35.1 mg, 0.100 mmol) and 4-fluorophenylboronic acid pinacol ester

(66.7 mg, 0.300 mmol). The crude reaction mixture was purified by flash column chromatography (100:0 hexanes:EtOAc to 90:10 hexanes:EtOAc) to give **2f** as a colorless oil in 98% yield (23.6 mg, 0.098 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.70 (dd, *J* = 14.0, 10.0 Hz, 1H), 2.83 (dd, *J* = 17.1, 4.0 Hz, 1H), 2.93-3.00 (m, 1H), 3.18 (dd, *J* = 17.1, 7.8 Hz, 1H), 3.33 (dd, *J* = 14.0, 4.3 Hz, 1H), 6.95-7.00 (m, 2H), 7.18-7.21 (m, 2H), 7.35-7.41 (m, 2H), 7.57 (ddd, *J* = 7.7, 7.7, 1.0 Hz, 1H), 7.77 (d, *J* = 7.6 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 32.2, 36.2, 49.0, 115.4 (d, *J* = 21.0 Hz), 124.2, 126.7, 127.6, 130.5 (d, *J* = 7.8 Hz), 135.0, 135.3 (d, *J* = 3.2 Hz), 136.6, 153.6, 161.6 (d, *J* = 243 Hz), 207.7. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -116.9 (m, 1F). **HRMS** (ESI): Calcd. for $C_{16}H_{14}FO^+$ ($[M+H]^+$): 241.1023, Found: 241.1023.

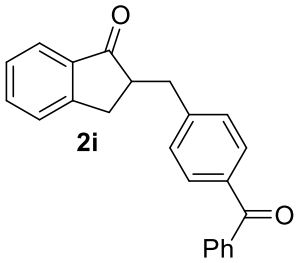


2g

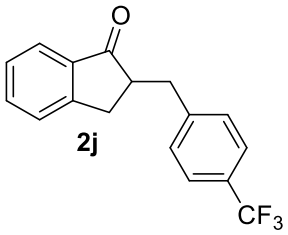
2-(4-chlorobenzyl)-2,3-dihydro-1*H*-inden-1-one (2g): Prepared according to general procedure C from *tert*-butyl (2-allylbenzoyl)(benzyl)carbamate **1a** (35.1 mg, 0.100 mmol) and 4-chlorophenylboronic acid pinacol ester (71.5 mg, 0.300 mmol). The crude reaction mixture was purified by flash column chromatography (100:0 hexanes:EtOAc to 90:10 hexanes:EtOAc) to give **2g** as a colorless oil in 85% yield (21.8 mg, 0.085 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.70 (dd, *J* = 14.0, 10.0 Hz, 1H), 2.83 (dd, *J* = 17.2, 4.2 Hz, 1H), 2.94-3.00 (m, 1H), 3.18 (dd, *J* = 17.1, 7.8 Hz, 1H), 3.34 (dd, *J* = 14.0, 4.4 Hz, 1H), 7.18 (d, *J* = 8.5, 2H), 7.26 (d, *J* = 8.5 Hz, 2H), 7.36-7.42 (m, 2H), 7.58 (td, *J* = 7.6, 1.2 Hz, 1H), 7.78 (d, *J* = 7.7 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 32.2, 36.4, 48.8, 124.3, 126.7, 127.7, 128.8, 130.4, 132.3, 135.1, 136.6, 138.1, 153.6, 207.6. **HRMS** (ESI): Calcd. for $C_{16}H_{14}ClO^+$ ($[M+H]^+$): 257.0728, Found: 257.0726.



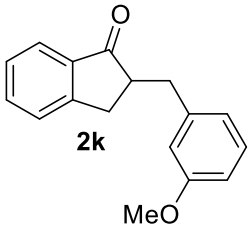
2-(4-acetylbenzyl)-2,3-dihydro-1*H*-inden-1-one (2h): Prepared according to general procedure C from *tert*-butyl (2-allylbenzoyl)(benzyl)carbamate **1a** (35.1 mg, 0.100 mmol) and 4-acetylboronic acid pinacol ester (73.8 mg, 0.300 mmol). The crude reaction mixture was purified by flash column chromatography (100:0 hexanes:EtOAc to 90:10 hexanes:EtOAc) to give **2h** as a white solid in 76 % yield (20.1 mg, 0.076 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.58 (s, 3H), 2.75-2.85 (m, 2H), 2.98-3.05 (m, 1H), 3.18 (dd, *J* = 17.1, 7.9 Hz, 1H), 3.42 (dd, *J* = 14.0, 4.4 Hz, 1H), 7.34 (d, *J* = 8.1 Hz, 2H), 7.39 (dd, *J* = 7.5., 7.5 Hz, 2H), 7.58 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.78 (d, *J* = 7.6 Hz, 1H), 7.90 (d, *J* = 7.7 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 23.7, 32.2, 37.0, 48.6, 124.2, 126.7, 127.7, 128.8, 129.3, 135.1, 135.7, 136.5, 145.5, 153.5, 197.9, 207.4. **HRMS** (ESI): Calcd. for $C_{18}H_{17}O_2^+$ ($[M+H]^+$): 265.1223, Found: 265.1226.



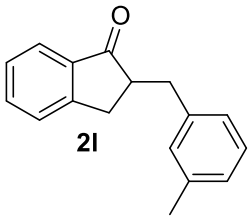
2-(4-benzoylbenzyl)-2,3-dihydro-1*H*-inden-1-one (2i): Prepared according to general procedure C from *tert*-butyl (2-allylbenzoyl)(benzyl)carbamate **1a** (35.1 mg, 0.100 mmol) and 4-benzoylphenylboronic acid pinacol ester (92.5 mg, 0.300 mmol). The crude reaction mixture was purified by flash column chromatography (100:0 hexanes:EtOAc to 80:20 hexanes:EtOAc) to give **2i** as a white solid in 54% yield (17.5 mg, 0.054 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.80 (dd, *J* = 14.0, 10.2 Hz, 1H), 2.87 (dd, *J* = 17.1, 3.9 Hz, 1H), 3.02-3.08 (m, 1H), 3.22 (dd, *J* = 17.0, 7.8 Hz, 1H), 3.47 (dd, *J* = 17.0, 4.3 Hz, 1H), 7.36-7.43 (m, 4H), 7.47-7.50 (m, 2H), 7.57-7.61 (m, 2H), 7.75-7.80 (m, 5H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 32.3, 37.1, 48.7, 124.2, 126.7, 127.7, 128.4, 129.0, 130.1, 130.6, 132.4, 135.1, 135.9, 136.5, 137.8, 144.9, 153.5, 196.5, 207.4. **HRMS** (ESI): Calcd. for $C_{23}H_{19}O_2^+$ ($[M+H]^+$): 327.1380, Found: 327.1382.



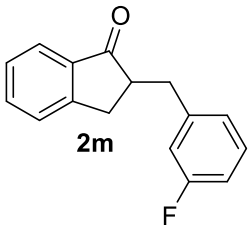
2-(4-(trifluoromethyl)benzyl)-2,3-dihydro-1*H*-inden-1-one (2j): Prepared according to general procedure C from *tert*-butyl (2-allylbenzoyl)(benzyl)carbamate **1a** (35.1 mg, 0.100 mmol) and 4-(trifluoromethyl)phenylboronic acid pinacol ester (81.6 mg, 0.300 mmol). The crude reaction mixture was purified by flash column chromatography (100:0 hexanes:EtOAc to 90:10 hexanes:EtOAc) to give **2j** as colorless oil in 69% yield (19.9 mg, 0.069 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.74-2.85 (m, 2H), 2.93-3.00 (m, 1H), 3.20 (dd, *J* = 17.0, 7.8 Hz, 1H), 3.43 (dd, *J* = 14.0, 4.3 Hz, 1H), 7.35-7.42 (m, 4H), 7.55-7.61 (m, 3H), 7.79 (d, *J* = 7.7 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 32.3, 36.9, 48.7, 110.2, 124.3, 125.6 (q, *J* = 3.8 Hz), 126.7, 127.8, 129.1 (q, *J* = 235 Hz), 129.4, 132.6, 135.2, 136.5, 143.9, 207.31. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -62.4 (s, 1F). **HRMS** (ESI): Calcd. for $C_{17}H_{14}F_3O^+$ ($[M+H]^+$): 291.0991, Found: 291.0992.



2-(3-methoxybenzyl)-2,3-dihydro-1*H*-inden-1-one (2k): Prepared according to general procedure C from *tert*-butyl (2-allylbenzoyl)(benzyl)carbamate **1a** (35.1 mg, 0.100 mmol) and 3-methoxyphenylboronic acid pinacol ester (70.2 mg, 0.300 mmol). The crude reaction mixture was purified by flash column chromatography (100:0 hexanes:EtOAc to 90:10 hexanes:EtOAc) to give **2k** as a colorless oil in 96% yield (24.3 mg, 0.096 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.64 (dd, *J* = 13.9, 10.5 Hz, 1H), 2.87 (dd, *J* = 17.2, 4.0 Hz, 1H), 2.96-3.03 (m, 1H), 3.18 (dd, *J* = 17.2, 7.8 Hz, 1H), 3.38 (dd, *J* = 14.0, 4.2 Hz, 1H), 3.79 (s, 3H), 6.75-6.85 (m, 3H), 7.22 (dd, *J* = 7.9, 7.9 Hz, 1H), 7.35-7.42 (m, 2H), 7.57 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H), 7.78 (d, *J* = 7.7 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 32.4, 37.2, 49.0, 55.3, 111.8, 114.7, 121.4, 124.2, 126.7, 127.6, 129.6, 135.0, 136.7, 141.4, 153.8, 160.0, 207.9. **HRMS** (ESI): Calcd. for $C_{17}H_{17}O_2^+$ ($[M+H]^+$): 253.1223, Found: 253.1227.

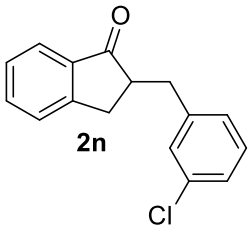


2-(3-methylbenzyl)-2,3-dihydro-1*H*-inden-1-one (2l): Prepared according to general procedure C from *tert*-butyl (2-allylbenzoyl)(benzyl)carbamate **1a** (35.1 mg, 0.100 mmol) and 3-tolylboronic acid pinacol ester (65.4 mg, 0.300 mmol). The crude reaction mixture was purified by flash column chromatography (100:0 hexanes:EtOAc to 90:10 hexanes:EtOAc) to give **2l** as a white solid in 85% yield (20.0 mg, 0.085 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.34 (s, 3), 2.61 (dd, *J* = 13.9, 10.6 Hz, 1H), 2.86 (dd, *J* = 17.2, 3.9 Hz, 1H), 2.96-3.03 (m, 1H), 3.17 (dd, *J* = 17.2, 7.7 Hz, 1H), 3.38 (dd, *J* = 13.9, 4.1 Hz, 1H), 7.03-7.07 (m, 3H), 7.19 (dd, *J* = 7.5 Hz, 1H), 7.36-7.42 (m, 2H), 7.58 (d, *J* = 7.7 Hz, 1H) 7.79 (d, *J* = 7.6 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 21.5, 32.4, 37.1, 49.1, 124.1, 126.0, 126.8, 127.2, 127.6, 128.6, 129.8, 134.8, 136.7, 138.3, 139.8, 153.8, 208.0. **HRMS** (ESI): Calcd. for $C_{17}H_{17}O^+$ ($[M+H]^+$): 237.1274, Found: 237.1276.

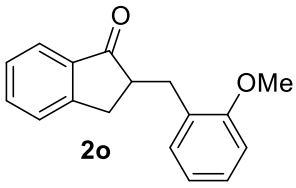


2-(3-fluorobenzyl)-2,3-dihydro-1*H*-inden-1-one (2m): Prepared according to general procedure C from *tert*-butyl (2-allylbenzoyl)(benzyl)carbamate **1a** (35.1 mg, 0.100 mmol) and 3-fluorophenylboronic acid pinacol ester (66.7 mg, 0.300 mmol). The crude reaction mixture was purified by flash column chromatography (100:0 hexanes:EtOAc to 90:10 hexanes:EtOAc) to give **2m** as a colorless oil in 67% yield (16.1 mg, 0.067 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.68 (dd, *J* = 14.0, 10.3 Hz, 1H), 2.84 (dd, *J* = 17.1, 4.1 Hz, 1H), 2.95-3.02 (m, 1H), 3.20 (dd, *J* = 17.2, 7.8 Hz, 1H), 3.38 (dd, *J* = 14.0, 4.3 Hz, 1H), 6.89-6.97 (m, 2H), 7.02 (d, *J* = 7.6 Hz, 1H), 7.23-7.28 (m, 1H), 7.36-7.42 (m, 2H), 7.58 (ddd, *J* = 7.7, 7.7, 1.1 Hz, 1H), 7.78 (d, *J* = 7.7 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 32.3, 36.8, 48.8, 113.4 (d, *J* = 21.0 Hz), 115.9 (d, *J* = 21.0 Hz), 124.2, 124.7 (d, *J* = 2.8 Hz), 126.7, 127.7, 130.1 (d, *J* = 8.3 Hz), 135.6, 136.6, 142.3

(d, *J* = 7.2 Hz), 153.6, 163.0 (d, *J* = 245 Hz), 207.5. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -113.3 (m, 1F). **HRMS** (ESI): Calcd. for $C_{16}H_{14}FO^+$ ($[M+H]^+$): 241.1023, Found: 241.1023.

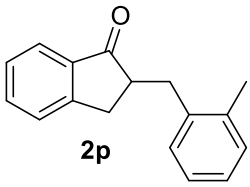


2-(3-chlorobenzyl)-2,3-dihydro-1*H*-inden-1-one (2n): Prepared according to general procedure C from *tert*-butyl (2-allylbenzoyl)(benzyl)carbamate **1a** (35.1 mg, 0.100 mmol) and 3-chlorophenylboronic acid pinacol ester (71.6 mg, 0.300 mmol). The crude reaction mixture was purified by flash column chromatography (100:0 hexanes:EtOAc to 90:10 hexanes:EtOAc) to give **2n** as a colorless oil in 54% yield (13.9 mg, 0.054 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.65 (dd, *J* = 14.0, 10.4 Hz, 1H), 2.84 (dd, *J* = 17.0, 4.1 Hz, 1H), 2.95-3.01 (m, 1H), 3.20 (dd, *J* = 17.2, 7.7 Hz, 1H), 3.37 (dd, *J* = 14.1, 4.2 Hz, 1H), 7.13 (ddd, *J* = 7.0, 1.7, 1.7 Hz, 1H), 7.18-7.25 (m, 3H), 7.36-7.43 (m, 2H), 7.58 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H), 7.78 (d, *J* = 7.7 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 32.3, 36.8, 48.8, 124.2, 126.74, 126.75, 127.2, 127.7, 129.1, 130.0, 134.4, 135.1, 136.6, 141.9, 153.5, 207.4. **HRMS** (ESI): Calcd. for $C_{16}H_{14}ClO^+$ ($[M+H]^+$): 257.0728, Found: 257.0725.

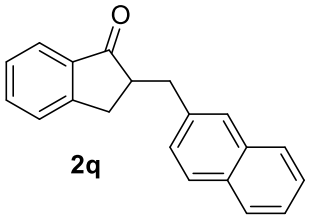


2-(2-methoxybenzyl)-2,3-dihydro-1*H*-inden-1-one (2o): Prepared according to general procedure C from *tert*-butyl (2-allylbenzoyl)(benzyl)carbamate **1a** (35.1 mg, 0.100 mmol) and 2-methoxyphenylboronic acid pinacol ester (70.2 mg, 0.300 mmol). The crude reaction mixture was purified by flash column chromatography (100:0 hexanes:EtOAc to 90:10 hexanes:EtOAc) to give **2o** as a colorless oil in 50% yield (12.6 mg, 0.050 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.63 (dd, *J* = 13.6, 9.9 Hz, 1H), 2.86 (dd, *J* = 20.5, 7.2 Hz, 1H), 3.07-3.16 (m, 2H), 3.42 (dd, *J* = 13.6, 4.2 Hz, 1H), 3.82 (s, 3H), 6.86-6.92 (m, 2H), 7.17-7.24 (m, 2H), 7.34-7.40 (m, 2H), 7.56 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H) 7.78 (d, *J* = 7.9 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 31.9, 32.5, 47.7,

55.3, 110.4, 120.6, 124.1, 126.7, 127.4, 127.8, 128.3, 130.6, 134.7, 136.9, 154.0, 157.9, 208.5. **HRMS** (ESI): Calcd. for $C_{17}H_{17}O_2^+$ ($[M+H]^+$): 253.1223, Found: 253.1221.

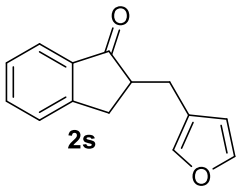


2-(2-methylbenzyl)-2,3-dihydro-1*H*-inden-1-one (2p): Prepared according to general procedure C from *tert*-butyl (2-allylbenzoyl)(benzyl)carbamate **1a** (35.1 mg, 0.100 mmol) and 2-tolylboronic acid pinacol ester (65.4 mg, 0.300 mmol). The crude reaction mixture was purified by flash column chromatography (100:0 hexanes:EtOAc to 90:10 hexanes:EtOAc) to give **2p** as a colorless oil in 90% yield (21.3 mg, 0.090 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.38 (s, 3H), 2.59 (dd, *J* = 14.5, 11.1 Hz, 1H), 2.87 (dd, *J* = 17.2, 4.0 Hz, 1H), 2.99-3.06 (m, 1H), 3.21 (dd, *J* = 17.2, 7.8 Hz, 1H), 3.49 (dd, *J* = 14.5, 4.1 Hz, 1H), 7.14-7.21 (m, 4H), 7.37-7.44 (m, 2 H), 7.59 (ddd, *J* = 7.6, 7.6, 1.1 Hz, 1H) 7.81 (d, *J* = 7.6 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 19.6, 32.8, 34.6, 47.7, 124.1, 124.3, 126.1, 126.6, 126.8, 127.5, 129.1, 130.6, 135.0, 136.6, 138.1, 153.7, 208.1. **HRMS** (ESI): Calcd. for $C_{17}H_{17}O^+$ ($[M+H]^+$): 237.1274, Found: 237.1273.

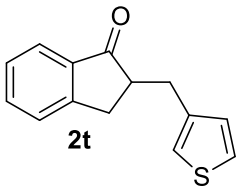


2-(naphthalen-2-ylmethyl)-2,3-dihydro-1*H*-inden-1-one (2q): Prepared according to general procedure C from *tert*-butyl (2-allylbenzoyl)(benzyl)carbamate **1a** (35.1 mg, 0.100 mmol) and 2-naphthylboronic acid pinacol ester (76.2 mg, 0.300 mmol). The crude reaction mixture was purified by flash column chromatography (100:0 DCM:EtOAc to 90:10 DCM:EtOAc) to give **2q** as a white solid in 99% (27.0 mg, 0.099 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.84 (dd, *J* = 14.1, 10.0 Hz, 1H), 2.92 (dd, *J* = 16.5, 3.2 Hz, 1H), 3.06-3.23 (m, 2H), 3.57 (dd, *J* = 14.1, 4.1 Hz, 1H), 7.34-7.50 (m, 5H), 7.57 (dt, *J* = 7.7, 1.2 Hz, 1H), 7.68 (broad s, 1H), 7.76-7.84 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 32.3, 37.3, 49.0, 124.2, 125.6, 126.2, 126.7,

127.4, 127.5, 127.6, 127.61, 127.8, 128.4, 132.3, 133.7, 135.0, 136.7, 137.3, 153.8, 208.0. **HRMS** (ESI): Calcd. for $C_{20}H_{16}O^{+}Na$ ($[M+Na]^{+}$): 295.1093, Found: 295.1057.

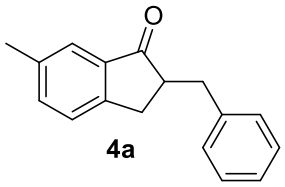


2-(furan-3-ylmethyl)-2,3-dihydro-1*H*-inden-1-one (2s): Prepared according to general procedure C from *tert*-butyl (2-allylbenzoyl)(benzyl)carbamate **1a** (35.1 mg, 0.100 mmol) and 3-furanylboronic acid pinacol ester (58.2 mg, 0.300 mmol). The crude reaction mixture was purified by flash column chromatography (100:0 hexanes:EtOAc to 90:10 hexanes:EtOAc) to give **2s** as a colorless oil in 63% yield (13.4 mg, 0.063 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.67 (dd, *J* = 14.2, 8.8 Hz, 1H), 2.89 (dd, *J* = 16.6, 4.2 Hz, 1H), 2.87-2.95 (m, 2H), 3.08 (dd, *J* = 14.2, 3.7 Hz, 1H), 3.26 (dd, *J* = 16.6, 7.2 Hz, 1H), 6.27 (s, 1H), 7.32 (t, *J* = 1.6 Hz, 1H), 7.36 (t, *J* = 7.8 Hz, 1H), 7.42 (d, *J* = 7.7 Hz, 1H), 7.57 (td, *J* = 7.6, 1.2 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 26.2, 32.4, 47.8, 111.3, 122.3, 124.1, 126.7, 127.6, 135.0, 136.8, 139.8, 143.1, 153.8, 208.0. **HRMS** (ESI): Calcd. for $C_{14}H_{13}O_2^{+}$ ($[M+H]^{+}$): 213.0910, Found: 213.0916.



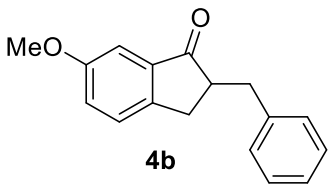
2-(thiophen-3-ylmethyl)-2,3-dihydro-1*H*-inden-1-one (2t): Prepared according to general procedure C from *tert*-butyl (2-allylbenzoyl)(benzyl)carbamate **1a** (35.1 mg, 0.100 mmol) and 3-thienylboronic acid pinacol ester (63.0 mg, 0.300 mmol). The crude reaction mixture was purified by flash column chromatography (100:0 hexanes:EtOAc to 90:10 hexanes:EtOAc) to give **2t** as a white solid in 88% yield (20.1 g, 0.088 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.82 (dd, *J* = 14.4, 9.8 Hz, 1H), 2.88 (dd, *J* = 17.2, 4.0 Hz, 1H), 2.96-3.02 (m, 1H), 3.25 (dd, *J* = 17.2, 7.7 Hz, 1H), 3.33 (dd, *J* = 14.4, 4.1 Hz, 1H), 6.98 (dd, *J* = 4.9, 1.2 Hz, 1H), 7.00-7.02 (m, 1H), 7.25 (dd, *J* = 4.9, 3.0 Hz, 1H), 7.37 (t, *J* = 7.8 Hz, 1H), 7.41 (d, *J* = 7.7 Hz, 1H), 7.57 (td, *J* = 7.6, 1.2 Hz, 1H), 7.77 (d, *J* = 7.7 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 31.5, 32.5, 48.3, 121.5, 124.1, 125.8,

126.7, 127.5, 128.4, 134.9, 136.7, 139.8, 153.8, 207.9. **HRMS** (ESI): Calcd. for $C_{14}H_{13}OS^+$ ($[M+H]^+$): 229.0682, Found: 222.0684.



4a

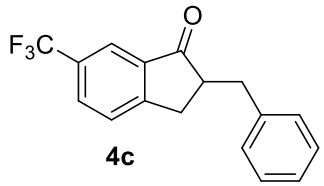
2-benzyl-6-methyl-2,3-dihydro-1*H*-inden-1-one (4a): Prepared according to general procedure C from *tert*-butyl (2-allyl-5-methyl)(benzyl)carbamate **3a** (36.5 mg, 0.100 mmol) and phenylboronic acid pinacol ester (61.2 mg, 0.300 mmol). The crude reaction mixture was purified by flash column chromatography (100:0 hexanes:EtOAc to 90:10 hexanes:EtOAc) to give **4a** as a colorless oil in 92% yield (21.7 mg, 0.092 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.41 (s, 3H), 2.66 (dd, *J* = 14.0, 10.4 Hz, 1H), 2.81 (dd, *J* = 17.0, 3.8 Hz, 1H), 2.97-3.04 (m, 1H), 3.13 (dd, *J* = 17.0, 7.8 Hz, 1H), 3.40 (dd, *J* = 14.0, 4.2 Hz, 1H), 7.21-7.36 (m, 6H), 7.40 (dd, *J* = 7.8. 1.1 Hz, 1H), 7.59 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 21.2, 32.0, 37.2, 49.4, 124.1, 126.4, 126.4, 128.6, 129.0, 136.2, 136.8, 137.5, 139.9, 151.1, 208.1. **HRMS** (ESI): Calcd. for $C_{17}H_{17}O^+$ ($[M+H]^+$): 237.1274, Found: 237.1270.



4b

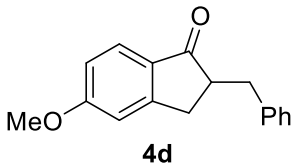
2-benzyl-6-methoxy-2,3-dihydro-1*H*-inden-1-one (4b): Prepared according to a modified version of general procedure C from *tert*-butyl (2-allyl-5-methoxy)(benzyl)carbamate **3b** (38.1 mg, 0.100 mmol) and phenylboronic acid pinacol ester (61.2 mg, 0.300 mmol). Upon completion of the reaction, the reaction mixture was filtered through a short plug of silica gel. The filtrate was concentrated under reduced pressure. To the crude product was dissolved in DCM (2.0 mL). The resulting solution was cooled to 0 °C, and TFA (0.400 mL) was added slowly. The mixture was allowed to warm to room temperature and stirred for 1 h. The reaction was concentrated under reduced pressure. The crude reaction mixture was purified by flash column chromatography (100:0 hexanes:EtOAc to

90:10 hexanes:EtOAc) to give **4b** as a white solid in 96% yield (24.0 mg, 0.096 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.66 (dd, *J* = 14.0, 10.2 Hz, 1H), 2.78 (dd, *J* = 16.4, 3.2 Hz, 1H), 2.97-3.07 (m, 1H), 3.09 (dd, *J* = 16.4, 7.6 Hz, 1H), 3.39 (dd, *J* = 14.0, 4.2 Hz, 1H), 3.84 (s, 3H), 7.17 (dd, *J* = 8.3, 2.5 Hz, 1H), 7.19-7.33 (m, 6H) **^{13}C NMR** (101 MHz, $CDCl_3$) δ 31.6, 37.2, 49.8, 55.7, 105.2, 124.4, 126.5, 127.4, 128.6, 129.0, 137.8, 139.8, 146.6, 159.5, 208.0 **HRMS** (ESI): Calcd. for $C_{17}H_{17}O_2^+$ ($[M+H]^+$): 253.1223, Found: 253.1226.



4c

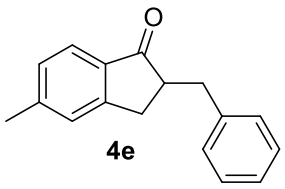
2-benzyl-6-(trifuoromethyl)-2,3-dihydro-1*H*-inden-1-one (4c): Prepared according to general procedure C from *tert*-butyl (2-allyl-5-(trifluoromethyl)benzoyl)(benzyl)carbamate **3c** (41.9 mg, 0.100 mmol) and phenylboronic acid pinacol ester (61.2 mg, 0.300 mmol). The crude reaction mixture was purified by flash column chromatography (100:0 hexanes:EtOAc to 90:10 hexanes:EtOAc) to give **4c** as a white solid in 51% yield (14.8 mg, 0.051 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.73 (dd, *J* = 14.0, 10.1 Hz, 1H), 2.93 (dd, *J* = 17.6, 4.0 Hz, 1H), 3.05-3.12 (m, 1H), 3.24 (dd, *J* = 17.6, 7.9 Hz, 1H), 3.40 (dd, *J* = 14.0, 4.4 Hz, 1H), 7.21-7.25(m, 3H), 7.28-7.34 (m, 2H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.81 (dd, *J* = 8.0, 1.3 Hz, 1H), 8.04 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 32.3, 36.9, 49.4, 121.4 (q, *J* = 4.0 Hz, 1H), 126.6 (q, *J* = 274 Hz, 1C), 126.7, 127.5, 128.8, 129.0. 130.5 (q, *J* = 33.3 Hz, 1C), 131.4 (q, *J* = 3.0 Hz, 1C), 137.1, 139.2, 156.9, 206.6. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -62.5 (s, 1F). **HRMS** (ESI): Calcd. for $C_{17}H_{14}F_3O^+$ ($[M+H]^+$): 291.0991, Found: 291.0995.



4d

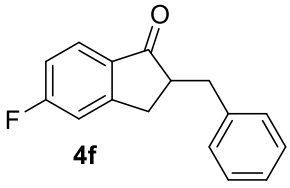
2-benzyl-5-methoxy-2,3-dihydro-1*H*-inden-1-one (4d): Prepared according to general procedure C from *tert*-butyl (2-allylbenzoyl)(benzyl)carbamate **3d** (38.1 mg, 0.100 mmol) and phenylboronic acid pinacol ester (61.2 mg, 0.300 mmol). The crude reaction mixture was purified

by flash column chromatography (100:0 hexanes:EtOAc to 90:10 hexanes:EtOAc) to give **4d** as a white solid in 88% yield (22.2 mg, 0.088 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.65 (dd, *J* = 14.0, 10.4 Hz, 1H), 2.80 (dd, *J* = 17.2, 3.8 Hz, 1H), 2.96-3.02 (m, 1H), 3.11 (dd, *J* = 17.2, 7.8 Hz, 1H), 3.39 (dd, *J* = 14.0, 4.2 Hz, 1H), 3.86 (s, 3H), 6.82 (s, 1H), 6.90 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.19-7.32 (m, 5H), 7.72 (d, *J* = 8.5 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 32.3, 37.3, 49.2, 55.7, 109.8, 115.5, 125.8, 126.4, 128.6, 129.0, 129.9, 139.9, 156.7, 165.5, 206.1. **HRMS** (ESI): Calcd. for $C_{17}H_{17}O_2^+$ ($[M+H]^+$): 253.1223, Found: 253.1226.



4e

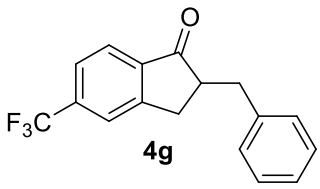
2-benzyl-5-methyl-2,3-dihydro-1*H*-inden-1-one (4e): Prepared according to general procedure C from *tert*-butyl (2-allyl-4-methylbenzoyl)(benzyl)carbamate **3e** (36.5 mg, 0.100 mmol) and phenylboronic acid pinacol ester (61.2 mg, 0.300 mmol). The crude reaction mixture was purified by flash column chromatography (100:0 hexanes:EtOAc to 90:10 hexanes:EtOAc) to give **4e** as a colorless oil in 97% yield (22.9 mg, 0.097 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.42 (s, 3H), 2.65 (dd, *J* = 14.0, 10.5 Hz, 1H), 2.81 (dd, *J* = 17.1, 3.7 Hz, 1H), 2.95-3.02 (m, 1H), 3.11 (dd, *J* = 17.1, 7.7 Hz, 1H), 3.39 (dd, *J* = 13.9, 4.1 Hz, 1H), 7.17-7.32 (m, 7H), 7.68 (d, *J* = 7.8 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 22.2, 32.1, 37.3, 49.2, 123.9, 126.4, 127.0, 128.6, 128.8, 129.1, 134.4, 139.9, 146.1, 154.3, 207.4. **HRMS** (ESI): Calcd. for $C_{17}H_{17}O^+$ ($[M+H]^+$): 237.1274, Found: 237.1276.



4f

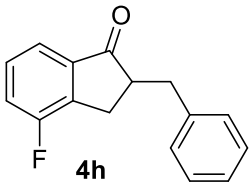
2-benzyl-5-fluoro-2,3-dihydro-1*H*-inden-1-one (4f): Prepared according to general procedure C from *tert*-butyl (2-allyl-4-fluorobenzoyl)(benzyl)carbamate **3f** (36.9 mg, 0.100 mmol) and phenylboronic acid pinacol ester (61.2 mg, 0.300 mmol). The crude reaction mixture was purified

by flash column chromatography (100:0 hexanes:EtOAc to 90:10 hexanes:EtOAc) to give **4f** as a yellow oil in 99% yield (23.8 mg, 0.099 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.69 (dd, *J* = 14.0, 10.2 Hz, 1H), 2.85 (dd, *J* = 17.3, 3.8 Hz, 1H), 2.98-3.07 (m, 1H), 3.15 (dd, *J* = 17.3, 7.8 Hz, 1H), 3.38 (dd, *J* = 14.0, 4.3 Hz, 1H), 7.02-7.95 (m, 2H), 7.19-7.25 (m, 3H), 7.27-7.33 (m, 2H), 7.78 (dd, *J* = 8.2, 5.3 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 32.2 (d, *J* = 2.0 Hz, 1C), 37.1, 49.3, 113.3 (d, *J* = 22.2 Hz, 1C), 115.9 (d, *J* = 24.2 Hz, 1C), 126.4 (d, *J* = 11.1 Hz, 1C), 126.6, 128.7, 129.0, 133.1 (d, *J* = 2.0 Hz, 1C), 139.4, 156.6 (d, *J* = 10.1 Hz, 1C), 167.3 (d, *J* = 257.6 Hz, 1C), 206.0. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -102.7 (m, 1F). **HRMS** (ESI): Calcd. for $C_{16}H_{14}FO^+$ ($[M+H]^+$): 241.1023, Found: 241.1027.



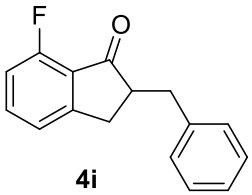
4g

2-benzyl-5-(trifluoromethyl)-2,3-dihydro-1*H*-inden-1-one (4g): Prepared according to general procedure C from *tert*-butyl(2-allyl-4-(trifluoromethyl)(benzyl)carbamate **3g** (41.9 mg, 0.100 mmol) and phenylboronic acid pinacol ester (61.2 mg, 0.300 mmol). The crude reaction mixture was purified by flash column chromatography (100:0 hexanes:EtOAc to 90:10 hexanes:EtOAc) to give **4g** as a white solid in 85% yield (24.7 mg, 0.085 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.73 (dd, *J* = 14.0, 10.1 Hz, 1H), 2.93 (dd, *J* = 17.4, 4.0 Hz, 1H), 3.03-3.11 (m, 1H), 3.24 (dd, *J* = 17.4, 7.8 Hz, 1H), 3.39 (dd, *J* = 14.0, 4.4 Hz, 1H), 7.20-7.25 (m, 3H), 7.28-7.34 (m, 2H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.67 (s, 1H), 7.88 (d, *J* = 8.0 Hz, 1H) **^{13}C NMR** (101 MHz, $CDCl_3$) δ 32.2, 36.9, 49.4, 123.9 (q, *J* = 4.0 Hz, 1C), 124.7, 125.2 (q, *J* = 4.0 Hz, 1C), 126.5 (q, *J* = 274.7 Hz, 1C), 126.7, 128.8, 129.0, 136.2 (q, *J* = 31.3 Hz, 1C), 139.2, 139.31-139.35 (m, 1C), 153.8, 206.9. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -62.9 (s, 3F). **HRMS** (ESI): Calcd. for $C_{17}H_{14}F_3O^+$ ($[M+H]^+$): 291.0991, Found: 291.0978.



4h

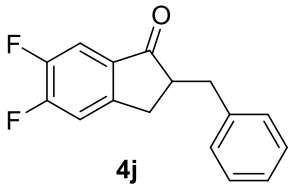
2-benzyl-4-fluoro-2,3-dihydro-1*H*-inden-1-one (4h): Prepared according to general procedure C from *tert*-butyl(2-allyl-3-fluorobenzoyl)(benzyl)carbamate **3h** (36.9 mg, 0.100 mmol) and phenylboronic acid pinacol ester (61.2 mg, 0.300 mmol). The crude reaction mixture was purified by flash column chromatography (100:0 hexanes:EtOAc to 90:10 hexanes:EtOAc) to give **4h** as a yellow oil in 95% yield (22.8 mg, 0.095 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.71 (dd, *J* = 14.0, 10.2 Hz, 1H), 2.85 (dd, *J* = 17.5, 4.0 Hz, 1H), 3.00-3.06 (m, 1H), 3.20 (dd, *J* = 17.5, 7.8 Hz, 1H), 3.39 (dd, *J* = 14.0, 4.3 Hz, 1H), 7.21-7.27 (m, 4H), 7.29-7.33 (m, 2H), 7.34-7.39 (m, 1H), 7.58 (d, *J* = 7.5 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 28.0, 37.0, 49.0, 119.9, 121.0 (d, *J* = 20.2 Hz, 1C), 126.6, 128.7, 129.0, 129.5 (d, *J* = 6.1 Hz, 1C), 139.3, 139.5 (d, *J* = 8.1 Hz, 1C), 139.6 (d, *J* = 8.1 Hz, 1C), 160.2 (d, *J* = 251.5 Hz, 1C), 206.6. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -118.9 (m, 1F). **HRMS** (ESI): Calcd. for $C_{16}H_{14}FO^+$ ($[M+H]^+$): 241.1023, Found: 241.1019.



4i

2-benzyl-4-fluoro-2,3-dihydro-1*H*-inden-1-one (4i): Prepared according to general procedure C from *tert*-butyl(2-allyl-6-fluorobenzoyl)(benyl)carbamate **3i** (36.9 mg, 0.100 mmol) and phenylboronic acid pinacol ester (61.2 mg, 0.300 mmol). The crude reaction mixture was purified by flash column chromatography (100:0 hexanes:EtOAc to 90:10 hexanes:EtOAc) to give **4i** as a yellow oil in 84% yield (20.2 mg, 0.084 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.70 (dd, *J* = 14.0, 10.2 Hz, 1H), 2.87 (dd, *J* = 17.3, 4.2 Hz, 1H), 3.00-3.06 (m, 1H), 3.17 (dd, *J* = 17.3, 7.9 Hz, 1H), 3.39 (dd, *J* = 14.0, 4.3 Hz, 1H), 6.97 (t, *J* = 9.0 Hz, 1H), 7.16 (d, *J* = 7.3 Hz, 1H), 7.19-7.33 (m, 5H), 7.54 (m, 1H) **^{13}C NMR** (101 MHz, $CDCl_3$) δ 32.2, 37.0, 49.6, 114.4 (d, *J* = 19.2 Hz, 1C), 122.5 (d, *J* = 5.1 Hz, 1C), 124.5 (d, *J* = 13.1 Hz, 1C), 126.6, 128.7, 129.1, 136.7-136.9 (m, 1C),

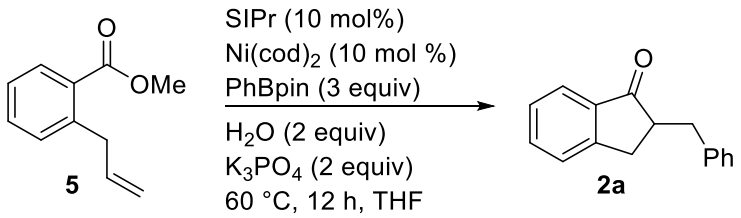
139.4, 155.8 (d, *J* = 2.0 Hz, 1C), 159.2 (d, *J* = 265.6 Hz, 1C), 204.1 (d, *J* = 1.0 Hz, 1C). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -114.4 (m, 1F). **HRMS** (ESI): Calcd. for $C_{16}H_{14}FO^+$ ($[M+H]^+$): 241.1023, Found: 241.1018.



4j

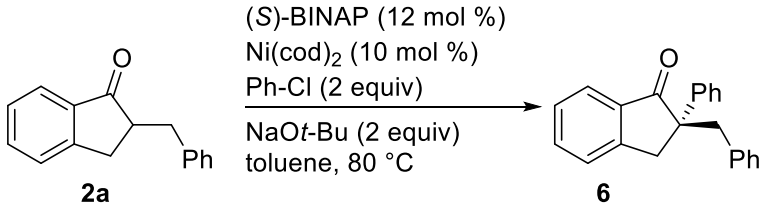
2-benzyl-5,6-difluoro-2,3-dihydro-1*H*-inden-1-one (4j): Prepared according to general procedure C from *tert*-butyl(2-allyl-4,5-difluorobenzoyl)(benyl)carbamate **3j** (38.7 mg, 0.100 mmol) and phenylboronic acid pinacol ester (61.2 mg, 0.300 mmol). The crude reaction mixture was purified by flash column chromatography (100:0 hexanes:EtOAc to 90:10 hexanes:EtOAc) to give **4j** as a off-white solid in 46% yield (11.9 mg, 0.046 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.70 (dd, *J* = 14.0, 10.0 Hz, 1H), 2.82 (dd, *J* = 17.0, 1.2 Hz, 1H), 2.99-3.08 (m, 1H), 3.13 (ddd, *J* = 17.0, 7.7, 0.6 Hz, 1H), 3.36 (dd, *J* = 14.0, 4.3 Hz, 1H), 7.17 (dd, *J* = 9.4, 6.7 Hz, 1H), 7.20-7.24 (m, 3H), 7.27-7.33 (m, 2H), 7.54 (dd, *J* = 8.2, 0.4 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 31.8 (d, *J* = 1.0 Hz, 1C), 40.0, 49.4 (d, *J* = 1.0 Hz, 1C), 112.2 (dd, *J* = 17.2, 2.0 Hz, 1C), 114.9 (d, *J* = 18.2 Hz, 1C), 126.7, 128.7, 129.0, 133.0 (dd, *J* = 6.1, 3.0 Hz, 1C), 139.1, 150.3 (dd, *J* = 8.1, 3.0 Hz, 1C), 150.8 (dd, *J* = 252.5, 14.1 Hz, 1C), 155.4 (dd, *J* = 260.6, 14.1 Hz, 1C), 205.7 (d, *J* = 2.0 Hz, 1C). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -136.8 (m, 1F), -125.2 (m, 1F). **HRMS** (ESI): Calcd. for $C_{16}H_{13}F_2O^+$ ($[M+H]^+$): 259.0929, Found: 259.0918.

Nickel-Catalyzed Carboacylation of Methyl-2-Allylbenzoate 5



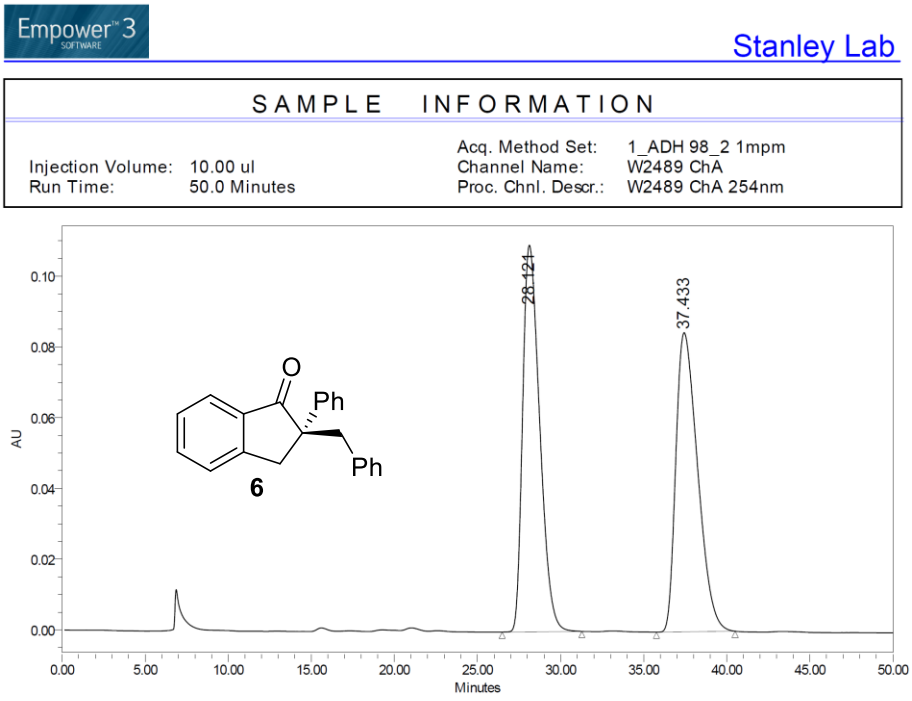
A 1-dram vial was charged with 0.100 mmol of methyl 2-allylbenzoate **5** (17.6 mg, 0.100 mmol), $Ni(cod)_2$ (2.8 mg, 0.010 mmol), SIPr (3.9 mg, 0.010 mmol), K_3PO_4 (42.5 mg, 0.200 mmol), H_2O (3.6 μL, 0.20 mmol), phenylboronic acid pinacol ester (61.2 mg, 0.300 mmol), and THF (0.100 mL). The resulting solution stirred at 60 °C for 12 hours. Upon completion of the reaction, the reaction mixture was filtered through a plug of silica with 70:30 hexanes:EtOAc. The crude product was purified by column chromatography with a gradient of 100:0 hexanes:EtOAc to 90:10 hexanes:EtOAc over a 25 minute period on a Combiflash system to **2a** as colorless oil in 50% yield (11.0 mg, 0.049 mmol). NMR data match those reported for synthesis of **2a** from benzamide **1a**.

Enantioselective α-Arylation of 2a to Form (*S*)-2-Benzyl-2-phenyl-2,3-dihydro-1*H*-inden-1-one 6

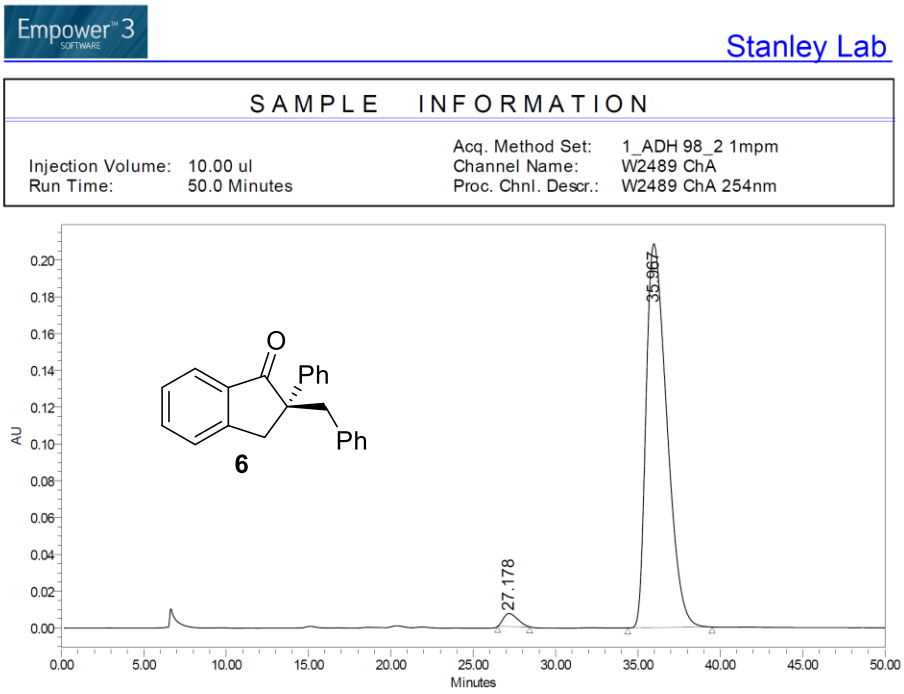


2-Benzyl-2-phenyl-2,3-dihydro-1*H*-inden-1-one **6** was prepared according to a known literature procedure.[48] Inside of a glovebox, to a 1-dram vial containing a magnetic stir bar was added $Ni(cod)_2$ (5.5 mg, 0.020 mmol), (*S*)-BINAP (14.9 mg, 0.024 mmol), NaO*t*Bu (38.4 mg,

0.400 mmol), chlorobenzene (40.5 μL, 0.400 mmol), **2a** (44.5 mg, 0.200 mmol), and toluene (1.00 mL). The vial was sealed with a cap containing a PTFE septum and removed from the glovebox. The reaction was stirred at 80 °C for 36 h. Upon completion, the reaction was cooled to room temperature. The reaction was quenched with a saturated aqueous NH_4Cl solution and extracted with Et_2O (2 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (98:2, hexanes:EtOAc) to give **6** as a white solid in 65% yield (39.0 mg, 0.130 mmol). The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 27.2 min (minor); t_R 36.0 min (major) [Chiracel AD-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. NMR data are consistent with known literature values.[48]

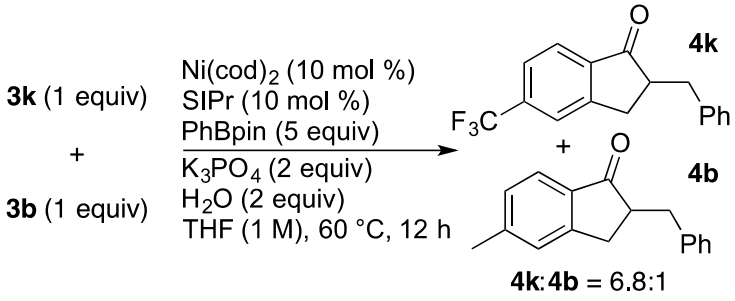


	RT	Area	% Area	Height	Int Type
1	28.121	7785708	50.28	109316	bb
2	37.433	7700176	49.72	84584	bb



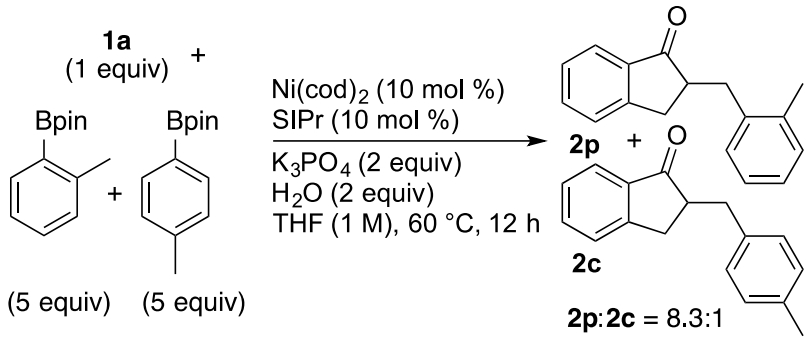
	RT	Area	% Area	Height	Int Type
1	27.178	420907	2.25	7035	bb
2	35.967	18255606	97.75	208617	bb

Experimental Procedures for Competition Experiments:

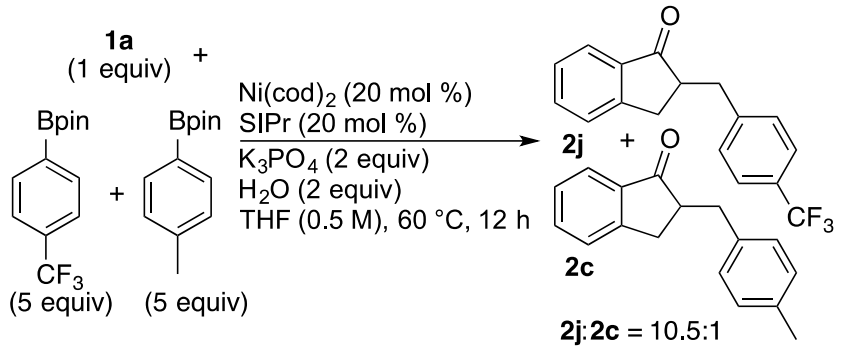


A competition experiment generating 2-benzyl-2,3-dihydro-1*H*-inden-1-ones **4b** and **4k** was carried out by the following procedure. A 1-dram vial was charged with *o*-allylbenzamides **3b** (36.5 mg, 0.100 mmol) and **3k** (41.9 mg, 0.100 mmol), $Ni(cod)_2$ (2.8 mg, 0.010 mmol), SIPr (3.9 mg, 0.010 mmol), K_3PO_4 (42.4 mg, 0.200 mmol), H_2O (3.6 μL, 0.20 mmol), phenylboronic acid

pinacol ester (102 mg, 0.500 mmol), and THF (0.10 mL). The resulting solution was stirred at 60 °C for 12 hours. Upon completion of the reaction, the reaction mixture was filtered through a plug of silica with hexanes:EtOAc (70:30), and concentrated under reduced pressure. The crude mixture was dissolved in $CDCl_3$ with CH_2Br_2 as internal standard. The ratio of products **4k:4b** was determined to be 6.8:1 by ^1H NMR spectroscopy. The NMR yields of **4k** and **4b** were determined to be 75% and 11%, respectively.



A competition experiment generating 2-benzyl-2,3-dihydro-1*H*-inden-1-ones **2p** and **2c** was carried out by the following procedure. A 1-dram vial was charged with *o*-allylbenzamide **1a** (35.1 mg, 0.100 mmol), $Ni(cod)_2$ (2.8 mg, 0.010 mmol), SIPr (3.9 mg, 0.010 mmol), K_3PO_4 (42.5 mg, 0.200 mmol), H_2O (3.6 μL, 0.20 mmol), 4-tolylboronic acid pinacol ester (109 mg, 0.500 mmol), 2-tolylboronic acid pinacol ester (109 mg, 0.500 mmol), and THF (0.10 mL). The resulting solution was stirred at 60 °C for 12 hours. Upon completion of the reaction, the reaction mixture was filtered through a plug of silica with hexanes:EtOAc (70:30), and concentrated under reduced pressure. The crude mixture was dissolved in $CDCl_3$ with CH_2Br_2 as internal standard. The ratio of products **2p:2c** was determined to be 8.3:1 by ^1H NMR spectroscopy. The NMR yields of **2p** and **2c** were determined to be 58% and 7%, respectively.



A competition experiment generating 2-benzyl-2,3-dihydro-1*H*-inden-1-ones **2j** and **2c** was carried out by the following procedure. A 1-dram vial was charged with *o*-allylbenzamide **1a** (35.1 mg, 0.100 mmol), $Ni(cod)_2$ (2.8 mg, 0.010 mmol), SIPr (3.9 mg, 0.010 mmol), K_3PO_4 (42.5 mg, 0.200 mmol), H_2O (3.6 μL, 0.20 mmol), 4-tolylboronic acid pinacol ester (109 mg, 0.500 mmol), 4-(trifluoromethyl)phenylboronic acid pinacol ester (136 mg, 0.500 mmol), and THF (0.10 mL). The resulting solution was stirred at 60 °C for 12 hours. Upon completion of the reaction, the reaction mixture was filtered through a plug of silica with hexanes:EtOAc (70:30), and concentrated under reduced pressure. The crude mixture was dissolved in $CDCl_3$ with CH_2Br_2 as internal standard. The ratio of products **2j:2c** was determined to be 10.5:1 by ^1H NMR spectroscopy. The NMR yields of **2j** and **2c** were determined to be 84% and 8%, respectively.

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CHAPTER V

CONCLUSION

Summary

This thesis describes the development of new transition metal- and NHC-catalyzed alkene hydroacylation and enantioselective α-arylation reactions. Additionally, the development of a new nickel-catalyzed formal alkene carboacylation is discussed. The catalytic methods discussed enabled access to a wide variety of carbocyclic and heterocyclic molecular scaffolds, and in some cases access to all-carbon quarternary stereocenters. The experimental work detailed contributes to the fundamental understanding of the mechanistic principles that control these reactions and opens the door for many new developments.

This thesis presents the first nickel-catalyzed alkene carboacylation reactions initiated by activation of amide C-N bonds. These processes enable coupling of a wide variety of *o*-allylbenzmides with arylboronic acid pinacol esters to form two new C-C bonds and the indanone products in up to 99% yield. Additionally, experimental results have given insight into the mechanism of this new reaction. The development of this approach to alkene carboacylation bypasses the challenges associated with related alkene carboacylation reactions that rely on the use of non-removable directing groups or ring-strain release to facilitate the C-C bond activation. This method also demonstrates the utility of amides as powerful building blocks in organic synthesis and is an early example of the potential of activation of amide C-N bonds in the development of new classes of reactions.

The utilization of amide C-N bond activation has the potential to allow innovation of existing and development of new reactions. Currently, developments to further expand the utility of this process have led to the studies of intramolecular boroacylation to form a new carbon-carbon

and carbon-boron bond in a single transformation that could later be used for further functionalization for more complex molecular scaffolds. Additionally, the investigation of a transition-metal catalyzed system that will catalyze the asymmetric intramolecular carboacylation of *ortho*-allylbenzaldehyde and *ortho*-vinylbenzaldehyde is ongoing in our lab. The development of the racemic, three-component, intermolecular carboacylation of benzamides with norbornene has shown early promise and further being leveraged as a preliminary result to the study and develop intermolecular carboacylation of simple alkenes via amide C-N bond activation.

Conclusion

In conclusion, the synthetic methods detailed in this thesis demonstrates a variety of methods to functionalize alkenes to generate a wide variety of products with excellent yields, enantio- and regioselectivities. These new catalytic methods represent substantial advancement in terms of alkene hydroacylation, and a new class of reaction for the formal alkene carboacylation triggered by amide C-N bond activation. Additionally, the utilization of amide C-N bond activation has led to a variety of new developments in the areas of boroacylation and the development of asymmetric intra- and intermolecular carboacylation reactions.