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# Transition metal-catalyzed alkene hydroacylation and carboacylation

Kevin Leon Vickerman
*Iowa State University*

**Transition metal-catalyzed alkene hydroacylation and carboacylation**

by

**Kevin Leon Vickerman**

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Levi Stanley, Major Professor
George Kraus
Brett VanVeller
Javier Vela
Wenyu Huang

The student author, whose presentation of the scholarship herein was approved by the program of study committee, is 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 |
| BARF | tetrakis[3,5-bis(trifluoromethyl)phenyl]borate |
| $BF_4$ | tetrafluoroborate |
| Boc | *tert*-butoxycarbonyl |
| $Boc_2O$ | di-*tert*-butyldicarbonate |
| Bn | benzyl |
| Bz | benzoyl |
| cat. | catalytic |
| $CF_3$ | trifluoromethyl |
| $CHCl_3$ | chloroform |
| $CH_2Cl_2$ | dichloromethane |
| CHO | aldehyde |
| CN | cyano/nitrile |
| cod | 1,5-cyclooctadiene |
| d | doublet |
| dba | dibenzylideneacetone |
| dd | doublet of doublets |
| ddd | doublet of doublet of doublets |
| ddt | doublet of doublet of triplets |
| DCM | dichloromethane |
| DMAP | 4-dimethylaminopyridine |
| DMF | *N,N*-dimethylformamide |

| | |
|---|---|
| dq | doublet of quartets |
| dr | diastereomeric ratio |
| dt | doublet of triplets |
| dtd | doublet of triplets of doublets |
| DTBM | di-*tert*-butyl-4-methoxy |
| ee | enantiomeric excess |
| equiv | equivalents |
| ESI | electrospray ionization |
| Et | ethyl |
| $Et_2O$ | diethyl ether |
| EtOAc | ethyl acetate |
| h | hour |
| Hex | hexanes |
| HPLC | high performance liquid chromatography |
| HRMS | high resolution mass spectrometry |
| Hz | hertz |
| IPA | isopropanol |
| m | multiplet |
| M | molar |
| MHz | megahertz |
| mL | milliliter |
| NBS | *N*-bromosuccinimide |
| *n*Bu | butyl |

| | |
|---|---|
| NHC | *N*-heterocyclic carbene |
| NMR | nuclear magnetic resonance |
| $NO_2$ | nitro |
| OAc | acetate |
| OMe | methoxy |
| OTs | tosylate |
| PFTE | polytetrafluoroethylene |
| Ph | phenyl |
| Ppm | parts per million |
| rac | racemic |
| s | singlet |
| sat. | saturate |
| SM | startming material |
| t | triplet |
| *t*Butyl | *tert*-butyl |
| *tert* | tertiary |
| THF | tetrahydrofuran |
| TLC | thin layer chromatography |
| Tol | tolyl |
| $t_R$ | retention time |
| UV | ultraviolet |
| Xyl | xylyl |

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## ABSTRACT

This dissertation presents the development of new catalysts for enantioselective, rhodium-catalyzed alkene hydroacylation to form polycyclic heterocyclic ketones, the first examples of nickel-catalyzed alkene carboacylation via amide C−N bond activation, and the first examples of enantioselective, intermolecular palladium-catalyzed alkene carboacylation via ester C−O bond activation.

Chapter II describes the enantioselective synthesis of polycyclic nitrogen, oxygen, and sulfur heterocycles by rhodium-catalyzed intramolecular alkene hydroacylation. The intramolecular hydroacylation reactions generate 1,4-dihydrocyclopenta[*b*]indol-3(2*H*)-ones and 3,4-dihydrocyclopenta[*b*]indol-1(2*H*)-one in moderate-to-high yields (65-99%) with good-to-excellent enantioselectivities (84-99% ee). The catalyst system also promotes alkene hydroacylation of 3-vinylfuran-, 3-vinylbenzothiophene-, and 3-vinylthiophene-2-carboxaldehydes to generate the corresponding ketone products in moderate-to-high yields (71-91% yield) with excellent enantioselectivities (97-99% ee).

Chapter III discusses nickel-catalyzed formal carboacylation of *ortho*-allylbenzamides with arylboronic acid pinacol esters. The reaction is triggered by oxidative addition of an activated amide C−N bond to a Ni(0) catalyst and proceeds via alkene insertion into a Ni(II)-acyl bond. The *exo*-selective carboacylation reaction generates 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 show that amides are practical substrates for alkene carboacylation via amide C−N bond activation, and this approach bypasses challenges associated with alkene carboacylation triggered by C−C bond activation.

Chapter IV describes palladium-catalyzed formal intermolecular carboacylation of aryl benzoate esters with sodium tetraarylborates and norbornene. The reaction is triggered by oxidative addition of an activated amide C−O bond to a Pd(0) catalyst and proceeds via alkene insertion into a Pd(II)-acyl bond. The three-component intermolecular carboacylation reaction generates phenyl(3-phenylbicyclo[2.2.1]heptan-2-yl)methanones in up to 99% yield with 1:1 diastereomeric ratio and in moderate to high enantiomeric excess from a variety of aryl benzoate esters and sodium tetraarylborates. These results show that esters are practical substrates for enantioselective, intermolecular alkene carboacylation via ester C−O bond activation. This approach bypasses challenges associated with alkene carboacylation triggered by C−C bond activation and expands alkene carboacylation via carbon-heteroatom bond activation beyond twisted amides.

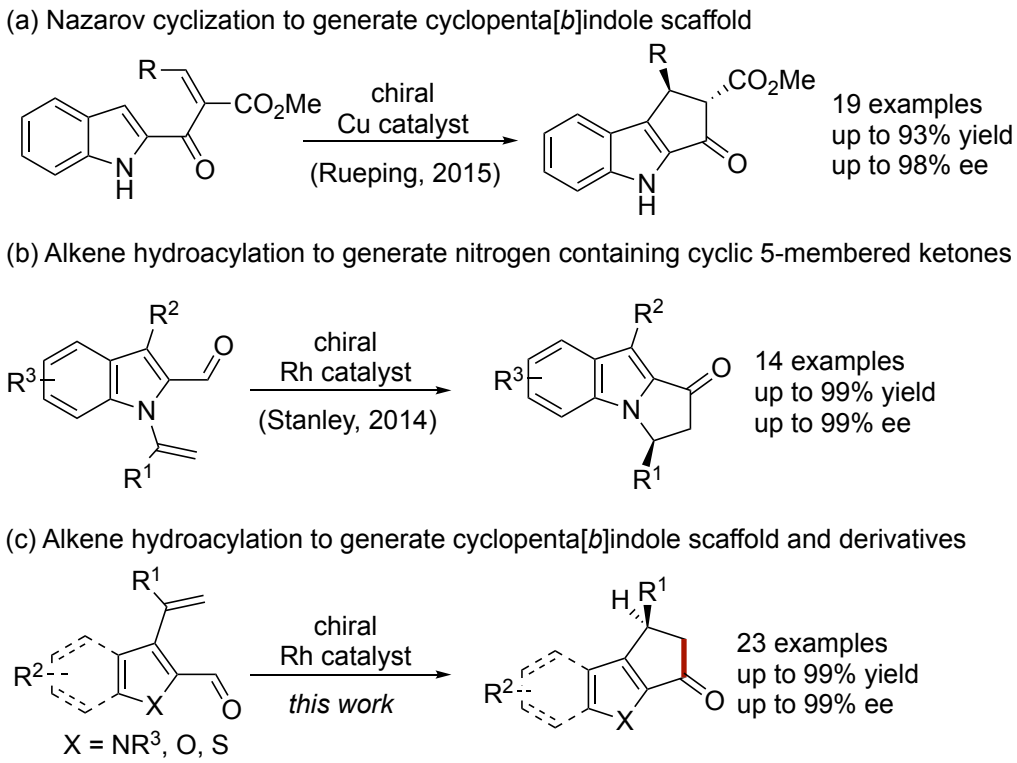
# CHAPTER 1. INTRODUCTION: THESIS FORMATTING

## General Introduction

Transition-metal catalysis has been established as an essential component of modern synthetic organic chemistry.[1] This broad research area encompasses reactions such as cross-coupling, C−H activation chemistry, hydrofunctionalization, and metathesis, among many others.[1] Vast amounts of insight have been gained through advances in transition metal-catalyzed processes and enabled both identification of novel and improved catalysts for a variety of chemical transformations. In this dissertation, fundamental principles of transition-metal catalysis is applied to the development of new catalysts for alkene difunctionalization reactions including an enantioselective, rhodium catalyst for the synthesis of polycyclic heterocycles, a nickel-NHC (*N*-heterocyclic carbene) catalyst for the formal alkene carboacylation of *ortho*-allylbenzamides via amide C−N bond activation, and a palladium catalyst for enantioselective, intermolecular formal alkene carboacylation of aryl benzoates via ester C−O bond activation.

Nitrogen- and oxygen-containing polycyclic heterocycles are common scaffolds present in many biologically active small molecules and natural products. The chiral cyclopenta[*b*]indole scaffold is present in a number of these biologically active compounds.[5-10] Therefore, the development of enantioselective methods to access this scaffold and its derivatives remains important.[11-17] However, limited enantioselective methods to access this scaffold have been reported. Rueping et al. developed a direct method to generate the cyclopenta[*b*]indole scaffold via enantioselective copper-catalyzed Nazarov Cyclizations (Scheme 1a).[12] Enantioselective intramolecular alkene hydroacylations in the presence of transition-metal catalysts are established processes to generate cyclic five-membered

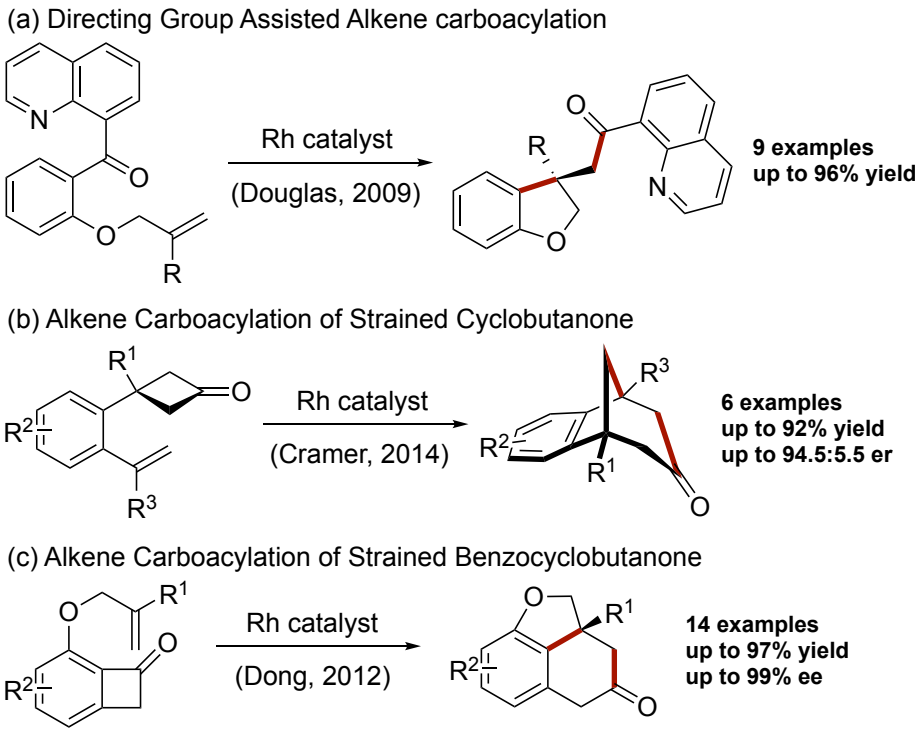
ketones.[18] The ability to generate heteroatom containing cycle five-membered ketones has been previously developed in our group (Scheme 1b).[19] This dissertation presents an enantioselective, catalytic method for the direct synthesis of the cyclopenta[*b*]indole scaffold in addition to oxygen- and sulfur-containing heterocyclic scaffolds (Scheme 1c).[20] The rhodium-catalyzed alkene hydroacylation reaction bypasses the requirement of activated alkenes in Nazarov cyclizations and enables rapid access into a library of enantioenriched polycyclic heterocycles.




**Scheme 1:** Catalytic, Enantioselective Synthesis of Nitrogen-Containing Heterocyclic Scaffolds

Similar to hydroacylation, alkene carboacylation enables the difunctionalization of an alkene. Carboacylation of alkenes in the presence of a transition-metal catalyst is an emerging reaction that enables the formation of two C−C σ bonds.[21-36] The most studied and developed approaches to alkene carboacylation are reactions triggered by the initial activation of a C−C

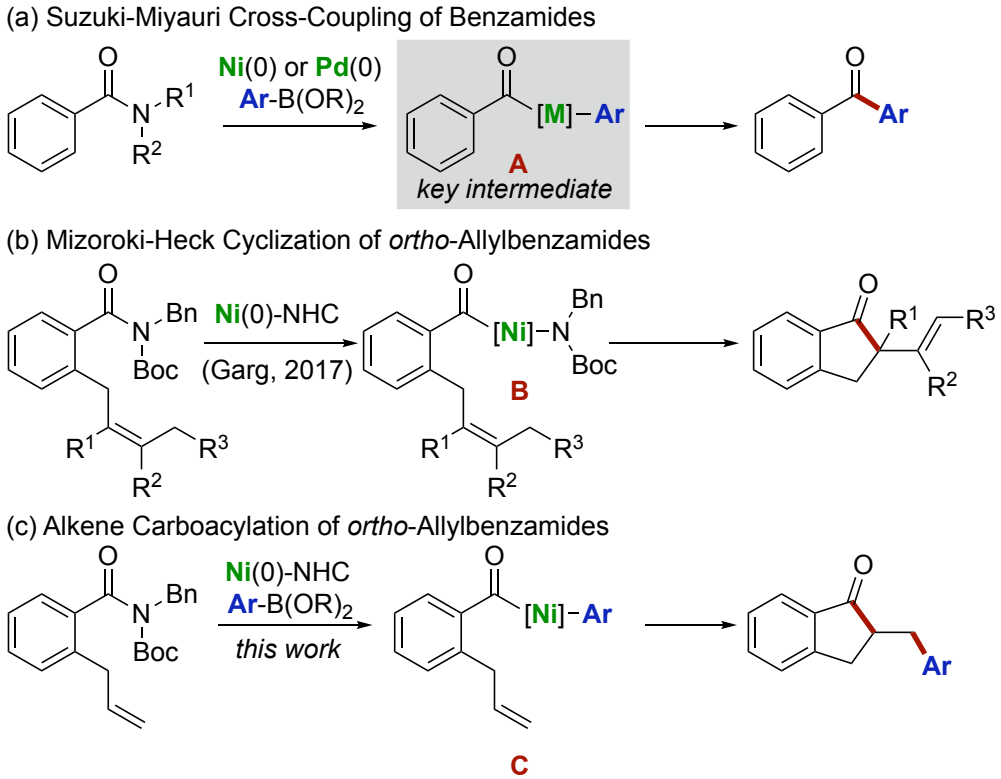
bond of a ketone (Scheme 2). Although much progress has been made to understand mechanistic pathways, the development and utility of alkene carboacylation is limited to substrates containing either a quinoline direction group[21-25] or a strained cyclic ketone.[26-32] The ability to bypass these limitations and perform alkene carboacylation reactions simple substrates has the potential to expand the utility of these reactions.[33-36,37-41]



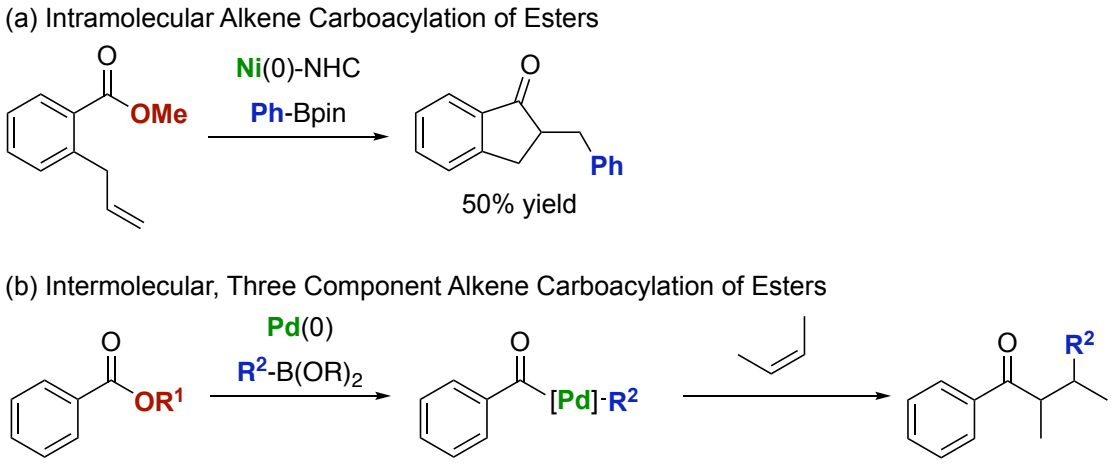

**Scheme 2.** Alkene Carboacylation via C−C σ Bond Activation

Recently, studies by a number of groups have demonstrated Suzuki-Miyaura coupling of benzamides with arylboron compounds to generate a variety of ketones.[42-53] The Suzuki-Miyaura coupling reactions are initiated by C−N bond activation of an activated twisted benzamide. The oxidative addition into the amide C−N bond and transmetalation with an arylboron compound generates a key acyl-metal-aryl intermediate **A**, and subsequent reductive elimination forms a diaryl ketone (Scheme 1a). The ability to intercept the key acy-metal-aryl intermediate **A** with alkenes offers the potential to develop a new class of alkene

functionalization reactions. During the course of our studies, Garg et al. developed Mizoroki-Heck cyclization of *ortho*-allylbenzamides that involved the insertion of the pendant alkene into acyl-Ni(II)-amido intermediate **B** (Scheme 1b).[54] Subsequent β-hydride elimination of intermeidate **B** forms 2-vinylindanones. This dissertation presents the first example of nickel-catalyzed formal alkene carboacylation reactions via activation of amide C−N bonds. The alkene carboacylation reaction is triggered by oxidative addition of the twisted amide C−N bond with a nickel(0) catalyst and subsequent transmetalation with an organoboron nucleophile forms the key acyl-Ni(II)-aryl intermediate. We envisioned intercepting the key intermediate generated from the readily accessible ortho-allylbenzamides with the pendant alkene to obtain *exo*-selective formal alkene carboacylation. The alkene carboacylation reactions demonstrate that amides are practical substrates for alkene carboacylation and this approach bypasses the challenges associated with carboacylation via C−C σ bond activation (Scheme 1c).[55]




**Scheme 3.** Ketone Synthesis via Transition Metal-Catalyzed Activation of Amide C−N Bonds




**Scheme 4.** Transition Metal-Catalyzed Alkene Carboacylation via Ester C−O Bond Activation

Transition metal-catalyzed oxidative addition into activated twisted amide C−N bonds is relatively well established.[42-53,56-61] Although there are a fewer examples, similar cross-coupling reactions have been developed with aryl benzoates and organometallic nucleophiles via ester C−O bond activation.[62-68] Our group previously reported one example of alkene carboacylation via ester C−O bond activation to generate an indanone in 50% yield (Scheme 4a).[55] To extend formal alkene carboacylation beyond activated amides we envisioned utilizing esters for the synthesis of ketones from esters, alkenes, and organoboron nucleophiles (Scheme 4b). This dissertation presents the first examples of enantioselective, intermolecular alkene carboacylation of esters via C−O bond activation. This palladium-catalyzed process generates phenyl(3-phenylbicyclo[2.2.1]heptan-2-yl)methanones products with high enantioselectivities. Continued efforts to mitigate epimerization and improve the diastereomeric ratios through catalyst design are ongoing in our lab.

**Dissertation Organization**

This dissertation is comprised of five chapters that contain work that has been published in peer-reviewed journals and research results that are in preparation for publication. Chapter I serves to introduce transition-metal catalysis and catalytic methods development in the

context of alkene hydroacylation and carboacylation reactions. Chapter II is adapted from a paper published in *Organic Letters*. Chapter III is adapated from a paper published in *Journal of the American Chemical Society*. Chapter IV discusses research results that are currently in preparation for submission. Chapter V serves as a general summary and conclusion of the presented research and provides a future outlook that proposes strategies to address the limitations that remain.

Chapter II describes the rhodium-catalyzed synthesis of cyclopenta[*b*]indoles and is a modified version from a paper published in *Organic Letters* in 2017. The work included in this chapter encompasses the development of an enantioselective, catalytic method for the synthesis of nitrogen-, oxygen-, and sulfur-containing polycyclic heterocycles. The catalytic method facilitates the synthesis of heterocycles with a range of electronic character and substitution. The author of this dissertation is responsible for all work reported in this chapter.

Chapter III describes the development of nickel-catalyzed formal alkene carboacylation of *ortho*-allylbenzamides via amide C−N bond activation. The chapter is a modified version from a published paper in *Journal of the American Chemical Society* in 2017. This chapter demonstrates new synthetic utility of amides in organic chemistry for their use in formal carboacylation reactions. The developed method also bypasses the current limitations of traditional alkene carboacylation via C−C σ bond activation. Mechanistic studies were conducted and a catalytic cycle was proposed for the new reaction. This work was accomplished in collaboration with James Walker who completed his PhD as a student of the Stanley group in 2017, and Jenna Humke, an undergraduate researcher. James Walker was responsible for the synthesis and characterization of *ortho*-allylbenzamides and the scope of *ortho*-allylbenzamides. Jenna Humke was responsible for assisting in the synthesis of *ortho*-

allylbenzamides. The author of this dissertation is responsible for the synthesis of the arylboronate esters, carboacylation scope involving the arylboron compounds, characterization of the products, and the competition experiments to gain mechanistic insight. The author of this dissertation and James Walker contributed equally to this publication.

Chapter IV describes the development of palladium-catalyzed formal carboacylation of aryl benzoates with alkenes via ester C−O bond activation. The chapter contains research results that will be utilized for a manuscript currently in preparation. This chapter discusses efforts towards the development of a palladium catalyst for enantioselective, intermolecular three component alkene hydroacylation of aryl benzoates with alkenes and organoboron nucleophiles. The catalyst system is able to generate highly enantioenriched ketone products and efforts are ongoing to improve the diastereomeric ratios in addition to simple alkenes. This work was accomplished in collaboration with Haley Banovetz, a graduate student of the Stanley group. Haley Banovetz was responsible for assisting in the development of reactions conditions. The author of this dissertation is responsible for the synthesis and characterization of aryl benzoates, development of reaction conditions, and control experiments to gain mechanistic insight.

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

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# CHAPTER 2.

# CATALYTIC, ENANTIOSELECTIVE SYNTHESIS OF POLYCYCLIC NITROGEN, OXYGEN, AND SULFUR HETEROCYCLES VIA RHODIUM-CATALYZED ALKENE HYDROACYLATION

Modified from a paper published in *Organic Letters*

Kevin L. Vickerman, Levi M. Stanley

*Department of Chemistry, Iowa State University, Ames, Iowa 50011-3111, United States*

**Abstract**

We report enantioselective synthesis of polycyclic nitrogen, oxygen, and sulfur heterocycles by rhodium-catalyzed intramolecular alkene hydroacylation. The intramolecular hydroacylation reactions generate 1,4-dihydrocyclopenta[*b*]indol-3(2*H*)-ones and 3,4-dihydrocyclopenta[*b*]indol-1(2*H*)-one in moderate-to-high yields (65-99%) with good-to-excellent enantioselectivities (84-99% ee). The catalyst system also promotes alkene hydroacylation of 3-vinylfuran-, 3-vinylbenzothiophene-, and 3-vinylthiophene-2-carboxaldehydes to generate the corresponding ketone products in moderate-to-high yields (71-91% yield) with excellent enantioselectivities (97-99% ee).

## Introduction

Polycyclic nitrogen-containing heterocycles are common structural motifs present in many biologically active natural products and small molecules.[1-3] Chiral cyclopenta[*b*]indoles are core architectures in a number of these biologically active compounds (Figure 1).[4-9] Thus, the development of new catalytic, enantioselective methods to generate chiral cyclopenta[*b*]indoles and derivatives remains important.[10-16]

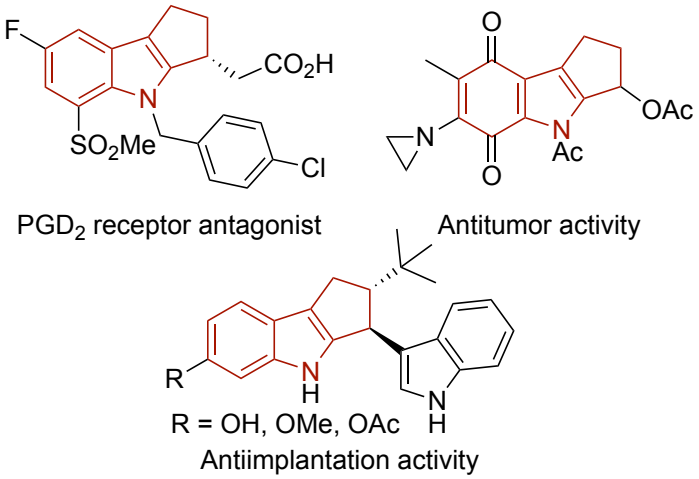
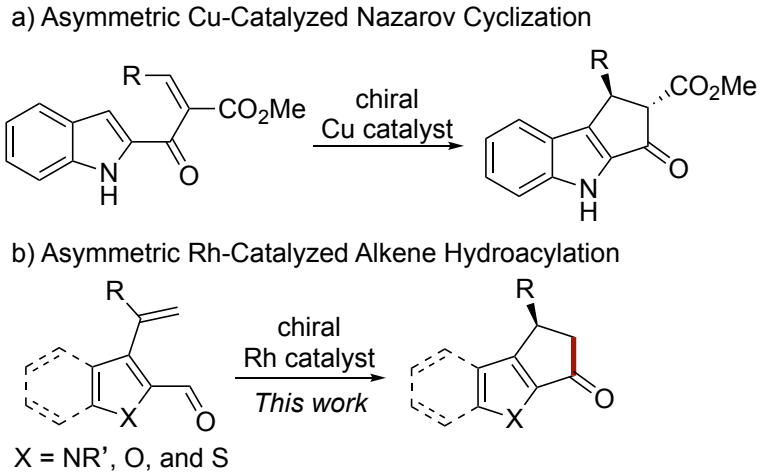



**Figure 1.** Biologically Active Cyclopenta[*b*]indoles

Recently, Rueping et al. reported a direct method to generate cyclopenta[*b*]indole derivatives via enantioselective copper-catalyzed Nazarov cyclizations involving activated alkenes (Scheme 1a).[11-14] Enantioselective, intramolecular alkene hydroacylations in the presence of transition-metal catalysts are established processes to generate cyclic five-membered ketones[17-35], including previous studies from our group on enantioselective, Rh-catalyzed hydroacylation of *N*-vinylindole-2-carboxaldehydes to generate 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indolones.[36] We envisioned that a related rhodium catalyst would promote intramolecular hydroacylation of 3-vinylindole-2-carboxaldehydes to allow rapid access to the cyclopenta[*b*]indole core and related polycyclic heterocycles (Scheme 1b). Herein, we report catalytic, enantioselective synthesis of a variety of polycyclic heterocycles through rhodium-catalyzed intramolecular alkene hydroacylation reactions.

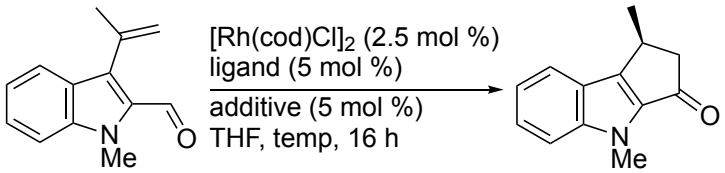


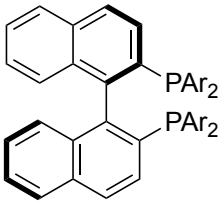

**Scheme 1. Catalytic, Enantioselective Synthesis of Dihydrocyclo-penta[*b*]indolones**

**Results and Discussion**

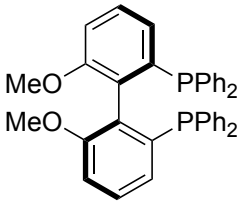
To assess the feasibility of Rh-catalyzed alkene hydroacylation to generate dihydrocyclopenta[*b*]indolones, we evaluated the reaction of 1-methyl-3-(prop-1-en-2-yl)-1*H*-indole-2-carboxaldehyde **1a** as a model substrate (Table 1). The hydroacylation of **1a** in the presence of a catalyst generated from $[Rh(cod)Cl]_2$, (*R*)-BINAP, and $AgBF_4$ formed the ketone product **2a** in 24-42% yield at temperatures ranging from rt to 100 °C (entries 1-4). When the active catalyst was generated from $[Rh(cod)_2]BF_4$ and (*R*)-BINAP in the absence of a silver salt, the hydroacylation of **1a** formed **2a** in 78% yield and 98% ee (entry 5). We observed an increase in the yield of ketone **2a** to 87% when the catalyst was generated from $[Rh(cod)Cl]_2$, (*R*)-BINAP, and sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaBARF) (entry 6). To evaluate the impact of steric and electronic properties of the ligand, we evaluated reactions in the presence of catalysts prepared from a series of chiral bisphosphines, $[Rh(cod)Cl]_2$ and NaBARF in THF at 60 °C (entries 6-10). A catalyst generated from $[Rh(cod)Cl]_2$, (*R*)-MeO-Biphep, and NaBARF provided the best combination of yield and enantioselectivity with the desired dihydrocyclopenta[*b*]indolone derivative formed in 94% yield and 99% ee (entry 9).

**Table 1. Identification of Catalysts for Rh-Catalyzed Hydroacylation of 1a**[a]

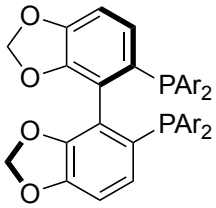


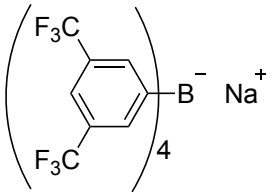

(*R*)-BINAP (Ar = Ph)
(*R*)-Tol-BINAP (Ar = 4-Me-$C_6H_4$)
(*R*)-Xyl-BINAP (Ar = 3.5-$Me_2$-$C_6H_3$)




(*R*)-MeO-Biphep




(*R*)-Segphos




NaBARF

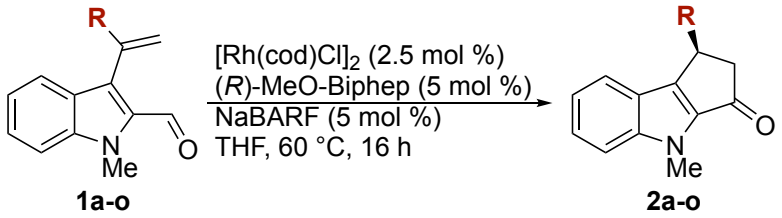
| entry | temp (°C) | ligand | additive | yield **2** (%)[b] | ee (%)[c] |
|---|---|---|---|---|---|
| 1 | rt | (*R*)-BINAP | $AgBF_4$ | 24 | - |
| 2 | 40 | (*R*)-BINAP | $AgBF_4$ | 28 | - |
| 3 | 60 | (*R*)-BINAP | $AgBF_4$ | 42 | - |
| 4[d] | 100 | (*R*)-BINAP | $AgBF_4$ | 39 | - |
| 5[e] | 60 | (*R*)-BINAP | - | 78 | 98 |
| 6 | 60 | (*R*)-BINAP | NaBARF | 87 | 98 |
| 7 | 60 | (*R*)-Tol-BINAP | NaBARF | 80 | 99 |
| 8 | 60 | (*R*)-Xyl-BINAP | NaBARF | 91 | 99 |
| 9 | 60 | (*R*)-MeO-Biphep | NaBARF | 94 | 99 |
| 10 | 60 | (*R*)-Segphos | NaBARF | 84 | 99 |

[a]Reaction conditions: **1** (0.10 mmol), $[Rh(cod)Cl]_2$ (0.0025 mmol), ligand (0.0050 mmol), additive (0.0050 mmol), THF (0.25 mL), 16 h. [b]Isolated yield of **2**. [c]Determined by chiral HPLC analysis. [d]1,4-dioxane (0.25 mL) used as solvent, [e]$[Rh(cod)_2]BF_4$ (0.0050 mmol) used as rhodium precatalyst.

With a practical catalyst system identified, we evaluated alkene hydroacylations of a variety of 1-methyl-3-vinyl-1*H*-indole-2-carboxaldehydes containing alkyl- and aryl-substituted vinyl units (Table 2). The hydroacylations of alkyl-substituted 1-methyl-3-vinyl-

1*H*-indole-2-carboxaldehydes **1a** (R = Me) and **1b** (R = cyclohexyl) occur to form polycyclic heterocyclic ketones **2a** and **2b** in 94% and 88% yields with 99% ee (entries 1 and 2). Hydroacylation of **1c** (R = Ph) generated the ketone **2c** in 99% yield and 99% ee (entry 3), and this reaction can be conducted on a 1.32 mmol scale without loss of enantioselectivity (entry 4).

**Table 2.** Rh-Catalyzed, Enantioselective Hydroacylation of **1a-1o**[a]



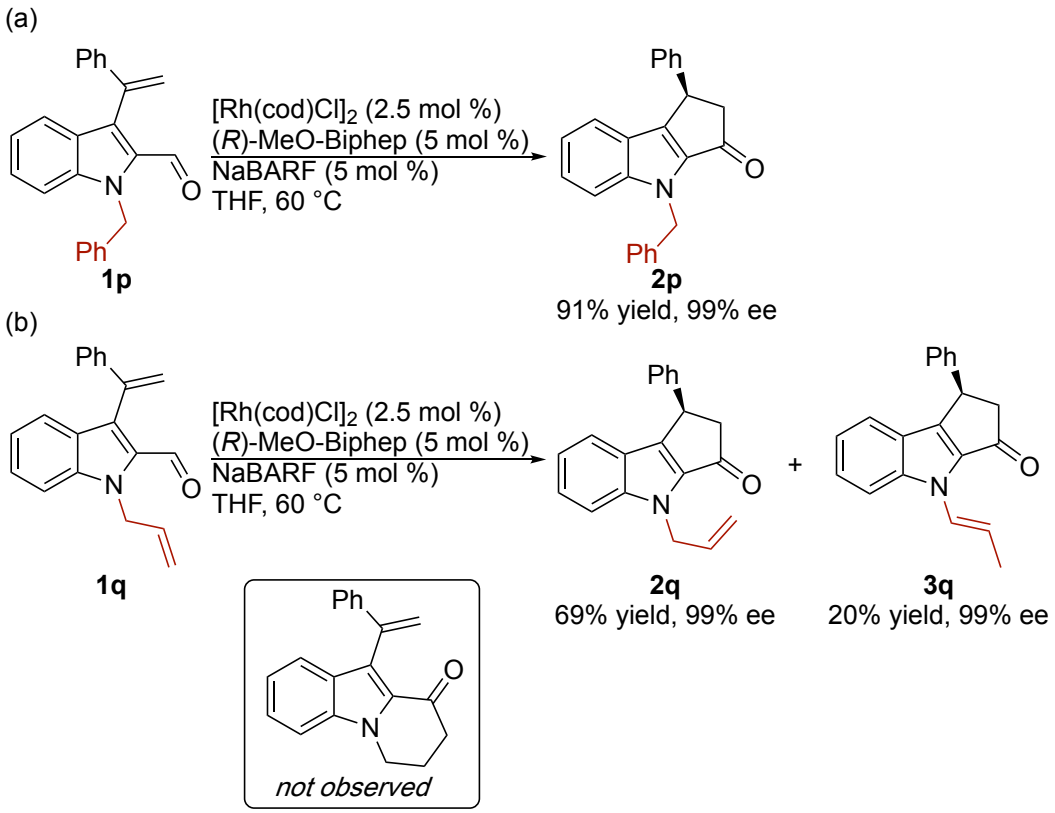

| entry | 1 | R | 2 | yield 2 (%)[b] | ee (%)[c] |
|---|---|---|---|---|---|
| 1 | **1a** | Me | **2a** | 94 | 99 |
| 2 | **1b** | Cy | **2b** | 88 | 99 |
| 3 | **1c** | Ph | **2c** | 99 | 99 |
| 4[d] | **1c** | Ph | **2c** | 83 | 99 |
| 5 | **1d** | 4-MeO-$C_6H_4$ | **2d** | 77 | 97 |
| 6 | **1e** | 4-F-$C_6H_4$ | **2e** | 72 | 98 |
| 7 | **1f** | 4-Cl-$C_6H_4$ | **2f** | 87 | 99 |
| 8 | **1g** | 3-MeO-$C_6H_4$ | **2g** | 91 | 99 |
| 9 | **1h** | 3-F-$C_6H_4$ | **2h** | 96 | 99 |
| 10 | **1i** | 3-$CF_3$-$C_6H_4$ | **2i** | 87 | 99 |
| 11 | **1j** | 2-F-$C_6H_4$ | **2j** | 77 | 98 |
| 12[e] | **1k** | 2-Me-$C_6H_4$ | **2k** | 95 | 84 |
| 13[e] | **1l** | 2-Cl-$C_6H_4$ | **2l** | 94 | 87 |
| 14 | **1m** | 2-furyl | **2m** | 65 | 98 |
| 15 | **1n** | 2-thienyl | **2n** | 71 | 99 |
| 16 | **1o** | $CO_2Me$ | **2o** | 88 | 99 |

[a]Reaction conditions: **1** (0.10 mmol), $[Rh(cod)Cl]_2$ (0.0025 mmol), (*R*)-MeO-Biphep (0.0050 mmol), NaBARF (0.0050 mmol), THF (0.25 mL), 60 °C, 16 h. [b]Isolated yield of **2**. [c]Determined by chiral HPLC analysis. [d]1.32 mmol scale based on **1c**. [e]Reaction performed with 1,4-dioxane as solvent at 100 °C.

Substrates containing electron-rich or electron-poor para-, meta-, and ortho-substituted aryl groups at the internal carbon of the vinyl unit are all suitable precursors for

hydroacylations to form dihydrocyclopenta[*b*]indolone products. The hydroacylation reactions of **1d**−**1j** occur to form 4-methyl-1-aryl-1,4-dihydrocyclopenta[*b*]indol-3-(*2*H)-ones **2d**−**2j** in 72−96% yield with excellent enantioselectivities (97−99%) (entries 5− 11). Substrates containing aryl groups with larger ortho-substituted aryl units (**1k** and **1l**) require reactions to be carried out at 100 °C in 1,4-dioxane to generate the corresponding heterocyclic ketones **2k** and **2l** in 95% and 94% yield with 84% and 87% ee (entries 12 and 13). Additionally, 1-methyl-3-vinyl-1*H*-indole-2-carboxaldehydes (**1m** and **1n**) with oxygen- and sulfur-containing heteroarene substitution on the vinyl moiety are tolerated. Hydroacylations of **1m** and **1n** generate the corresponding ketones **2m** and **2n** in 65% and 71% yield with 98% and 99% ee (entries 14 and 15). The hydroacylation of **1o** (R = $CO_2Me$), a substrate containing an electron-withdrawing group at the internal carbon of the vinyl unit, forms the corresponding heterocyclic ketone **2o** in 88% yield and 99% ee (entry 16).

The alkene hydroacylation reactions are not limited to 1-methyl-3-vinyl-1*H*-indole-2-carboxaldehydes. The hydroacylation of 1-benzyl-3-(1-phenylvinyl)-1*H*-indole-2-carboxaldehyde **1p** occurs to form 4-benzyl-1-phenyl-1,4-dihydrocyclopenta-[*b*]indol-3(2*H*)-one **2p** in 91% yield and 99% ee (Scheme 2a). The hydroacylation of 1-allyl-3-(1-phenylvinyl)-1*H*-indole-2- carboxaldehyde **1q** occurs to form ketones **2q** and **3q** in 69% and 20% yield with 99% ee (Scheme 2b). Ketone **3q** is generated through alkene hydroacylation of the vinyl group and alkene isomerization of the *N*-allyl unit to the internal alkene. We observed the hydroacylation of *N*-allyl substituted **1q** to be completely selective for the vinyl alkene to generate a five-membered ring over the allyl alkene, which would generate a six-membered ring.

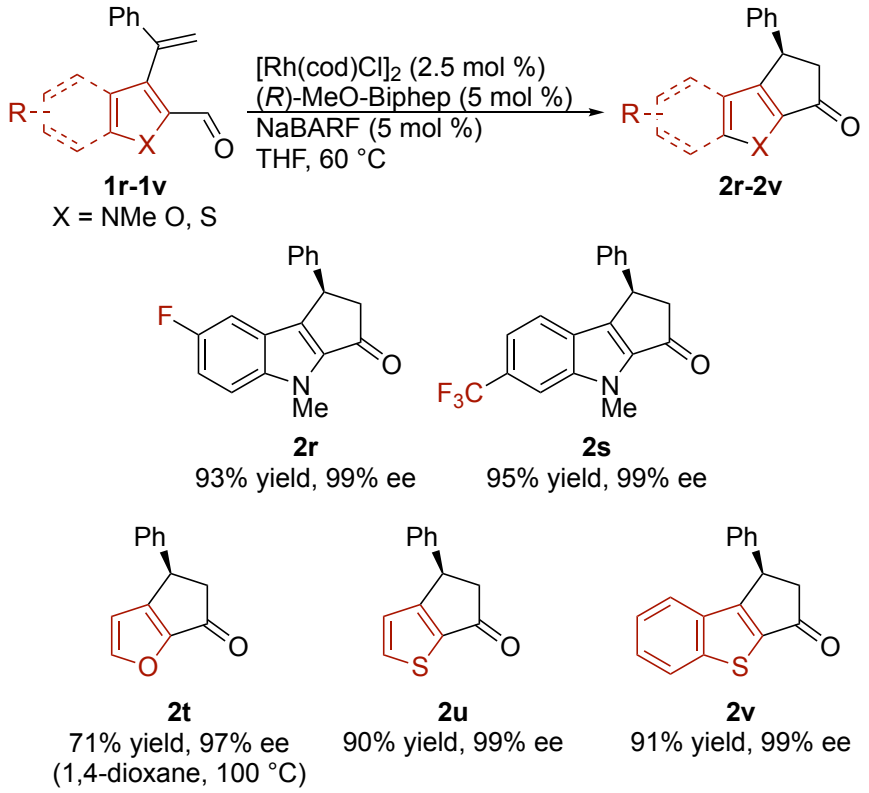



[a]Isolated yield of **2**. Enantiomeric excesses were determined by chiral HPLC analysis.

**Scheme 2.** Rh-Catalyzed Hydroacylation of *N*-Substituted 3-Vinyl-1*H*-indole-2-carboxaldehydes **1p**–**1q**[a]

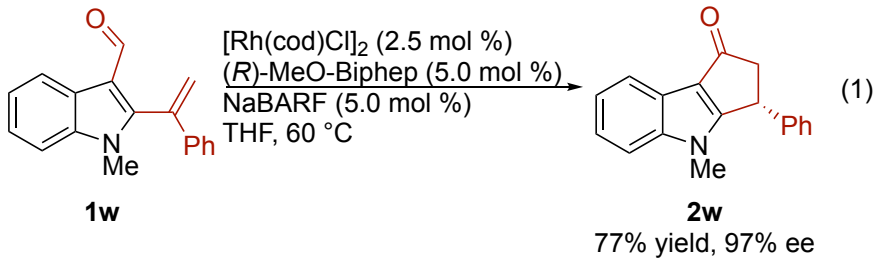
The alkene hydroacylation also occurs to generate polycyclic heterocycles containing oxygen, sulfur, and additional substituted indole derivatives (Scheme 3). The hydroacylations of 1-methyl-3-vinyl-1*H*-indole-2-carboxaldehydes with electron-withdrawing substituents on the indole backbone are promoted by our catalyst system. Hydroacylation of 5-fluoro-1-methyl-3-(1-phenylvinyl)-1*H*-indole-2-carboxaldehyde **1r** and 1-methyl-3-(1-phenylvinyl)-5-(trifluoromethyl)-1*H*-indole-2-carboxaldehyde **1s** generated the corresponding ketones **2r** and **2s** in high yields (93% and 95%) with excellent enantioselectivities (99% ee). The hydroacylation of an oxygen containing heterocycle, 3-(1-phenylvinyl)furan-2-carboxaldehyde **1t**, required the reaction to be carried out at 100 °C in 1,4-dioxane to form 4-phenyl-4,5-dihydro-6*H*-cyclopenta[*b*]furan-6-one **2t** in 71% yield with 97% ee. The absolute

configuration of **2t** was determined to be (*R*)-4-phenyl-4,5-dihydro-6*H*-cyclopenta[*b*]-furan-6-one by comparing the sign of the optical rotation with a literature value.[36] In addition, the hydroacylations of sulfur-containing heterocycles 3-(1-phenylvinyl)thiophene-2-carbaldehyde **1u** and 3-(1-phenylvinyl)benzo[*b*]thiophene-2-carbaldehyde **1v** generated the corresponding sulfur-containing polycyclic ketones **2u** and **2v** in 90% and 91% yield with 99% ee.

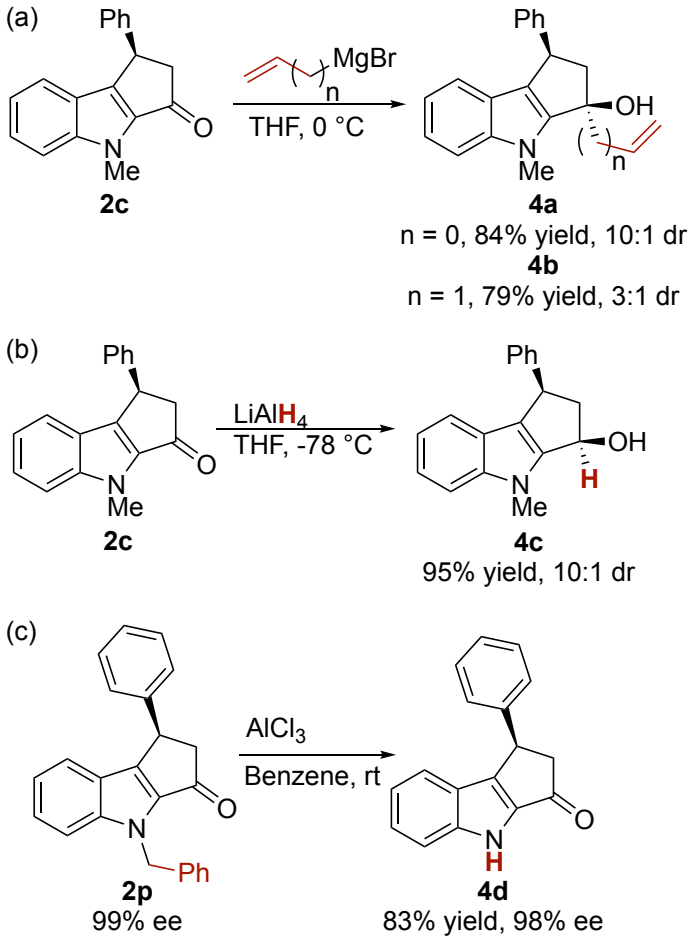



[a]Isolated yield of **2**. Enantiomeric excesses were determined by chiral HPLC analysis. [b]Reaction performed with 1,4-dioxane at 100 °C.

**Scheme 3.** Rh-Catalyzed Hydroacylation of Nitrogen, Oxygen, and Sulfur Containing Heterocycles[a]



To further evaluate the utility of the catalyst system for intramolecular alkene hydroacylation to form polycyclic heterocycles, we investigated exchanging the positions of the aldehyde and vinyl moieties on the indole core. The hydroacylation of 1-methyl-2-(1-phenylvinyl)-1*H*-indole-3-carboxaldehyde **1w** occurs to form 4-methyl-3-phenyl-3,4-dihydro-cyclopenta[*b*]indol-1(2*H*)-one **2w** in 77% yield and 97% ee (eq 1). The hydroacylation of **1w** allows access to a dihydrocyclopenta[*b*]indolone with the stereogenic carbon center and functional group handle in different positions relative to the indole core.[37]




**Scheme 4.** Synthetic Transformations of Dihydrocyclopenta[*b*]indolones

To demonstrate the utility of the ketone products generated from these hydroacylation reactions, we carried out select addition reactions to the carbonyl of

dihydrocyclopenta[*b*]indolone **2c** and a straightforward deprotection of dihydro-cyclopenta[*b*]indolone **2p** (Scheme 4). The addition of vinyl and allyl Grignard reagents to **2c** generated the corresponding alcohol products **4a** and **4b** in 84% and 79% yield with 10:1 and 3:1 diastereomeric ratios. Reduction of **2c** with lithium aluminum hydride formed the secondary alcohol product **4c** in 95% yield with 10:1 dr. Debenzylation of **2p** occurs in the presence of $AlCl_3$ to form **4d** in 83% yield without significant degradation of the optical purity.

**Conclusion**

In summary, we have developed a catalyst system for intramolecular hydroacylation of nitrogen, oxygen, and sulfur heterocycles to generate structurally complex polycyclic heterocycles in moderate-to-high yields and with excellent enantioselectivities. The rhodium-catalyzed alkene hydroacylation encompasses reactions of a range of nitrogen, oxygen, and sulfur heterocycles with a variety of alkyl, electron-rich and electron-poor aryl, and heteroaryl substitution on the alkene unit. Indoles with varied substitution at the nitrogen are also tolerated, and we observed complete selectivity for five-membered ring formation over the potential six-membered ring formation in the reaction of 1-allyl-3-(1-phenylvinyl)-1*H*- indole-2-carboxaldehyde. In addition, the catalyst system is active for intramolecular hydroacylation of 1-methyl-2-vinyl-1*H*-indole-3-carboxaldehydes to generate an additional dihydrocyclopenta[*b*]indolone scaffold. Further studies are ongoing in our laboratory to expand the breadth of enantioselective alkene hydroacylation reactions to access heterocyclic compounds.

**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 nitrogen unless otherwise stated. All glassware for moisture sensitive

reactions was dried in an oven at 140 ºC for at least two hours before use. THF, $Et_2O$, and DCM 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 and DMF were purchased from Sigma-Aldrich and used as received. Flash column chromatography was performed on SiliFlash® P60 silica gel (40-63µm, 60 Å) using hexanes, hexanes/ethyl acetate or hexanes/diethyl ether mixtures. 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. HPLC analyses were carried out on a Waters Alliance HPLC system with an e2695 separations module and a 2489 dual wavelength detector. Optical rotations were measured on an Atago AP-300 automatic polarimeter using a 0.5 dm cell. NMR spectra were acquired on Varian MR-400 and Bruker Avance III 600 spectrometers at the Iowa State University Chemical Instrumentation Facility. Chemicals shifts are reported in ppm relative to residual solvent peaks ($CDCl_3$ = 7.26 ppm for $^1H$ and 77.16 ppm for $^{13}C$). Coupling constants are reported in hertz. $^{19}F$ NMR shifts are reported based on indirect reference to $CDCl_3$.[38]

**Materials.** Tributyltin hydride, tributyltin chloride, diisopropylamine, bromine, sodium hydride, lithium aluminum hydride, manganese(IV) oxide, cesium fluoride, copper(I) iodide, magnesium, sodium sulfate, magnesium sulfate, 2-bromopropene, 2-furyl methyl ketone, 4'-methoxyacetophenone, 2'-methoxyacetophenone, and 2-acetylthiophene were purchased from Sigma-Aldrich and used without further purification. *n*-Butyllithium (2.5M in hexanes) was purchased from Sigma-Aldrich and titrated with recrystallized diphenylacetic acid prior to use. 3-Bromothiophene-2-carbaldehyde was purchased from Maybridge and used

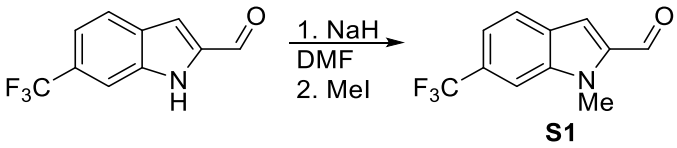
without further purification. Acetophenone, triethylamine and *p*-toluenesulfonic acid were purchased from Fisher Scientific and used without further purification. 3'-Methoxyacetophenone, 2'-chloroacetophenone, 3'-chloroacetophenone, and 3'-(trifluoromethyl)acetophenone were purchased from AK Scientific and used without further purification. Cyclohexyl methyl ketone was purchased from Alfa Aesar and used without further purification. Methyl iodide was purchased from Acros Organics and used without further purification.

$Pd(PPh_3)_4$, $[Rh(cod)Cl]_2$, $[Rh(cod)_2]BF_4$, *rac*-BINAP ((*rac*)-2,2'-bis(diphenylphosphino)-1,1'-binaphthalene), (*R*)-BINAP ((*R*)-2,2'-bis(diphenylphosphino)-1,1'-binaphthalene), (*R*)-Tol-BINAP ((*R*)-2,2'-bis(di-*p*-tolylphosphino)-1,1'-binaphthalene), (*R*)-Xyl-BINAP ((*R*)-2,2'-bis(di-3,5-dimethylphenylphosphino)-1,1'-binaphthalene), (*R*)-MeO-Biphep ((*R*)-2,2'-bis(diphenylphosphino)-1,1'-biphenyl), and (*R*)-Segphos ((*R*)-2,2'-bis(diphenylphosphino)-4,4'-bi-1,3-benzodioxole), and were purchased from Strem Chemicals and used without further purification.

NaBARF (sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate) was prepared according to a literature procedure.[39] 1*H*-Indole-2-methanol was prepared according to a literature procedure from ethyl 1*H*-indole-2-carboxylate.[30] 1*H*-Indole-2-carbaldehyde was prepared according to a literature procedure from 1*H*-indole-2-methanol.[30] 1-Methyl-1*H*-indole-2-carbaldehyde was prepared according to a literature procedure from 1*H*-indole-2-carbaldehyde.[40] 3-Bromo-1-methyl-1*H*-indole-2-carbaldehyde was prepared according to a literature procedure from 1-methyl-1*H*-indole-2-carbaldehyde.[41] Ethyl 5-fluoro-1*H*-indole-2-carboxylate was prepared according to a literature procedure from 2-bromo-5-fluorobenzaldehyde.[42] Organostannanes were prepared according to a literature procedure

from corresponding ketones and used as crude mixtures after filtration through a short plug of silica eluting with hexane.[43] Methyl 2-(tributylstannyl)acrylate was prepared according to a literature procedure from methyl propiolate.[44]

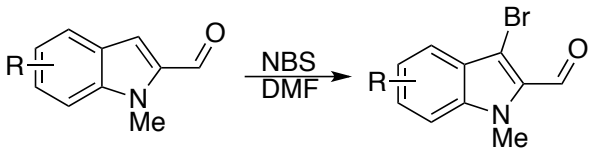
**Synthesis of 1-Methyl-6-(trifluoromethyl)-1*H*-indole-2-carbaldehyde S1**




**S1**

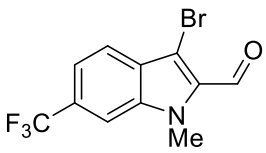
**1-Methyl-6-(trifluoromethyl)-1*H*-indole-2-carbaldehyde (S1):** In an oven dried round-bottom-flask, 6-(trifluoromethyl)-1*H*-indole-2-carbaldehyde (0.851 g, 4.00 mmol) was dissolved in DMF (20 mL, 0.20 M). The solution was then cooled to 0 °C and sodium hydride (0.239 g, 6.00 mmol) was added and stirred for 1 hour. Methyl iodide (0.37 mL, 6.0 mmol) was then added dropwise and the reaction was warmed to rt and stirred for 3 hours. After completion of the reaction, water was added to quench the reaction, and ether was added to the solution. The solution was washed three times with water and once with aq. $NH_4Cl$ (sat.), and then the organic layer was then dried with $MgSO_4$. The dried organic layer was concentrated under reduced pressure to yield the crude product. The crude product was purified by flash column chromatography (90:10 hexanes:EtOAc) to yield **S1** (470 mg, 2.07 mmol, 52% yield) as a white solid. **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 4.15 (s, 3H), 7.31 (s, 1H), 7.40 (d, $J$ = 8.0 Hz, 1H), 7.71 (s, 1H), 7.85 (d, $J$ = 8.0 Hz, 1H), 9.96 (s, 1H). **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 31.9, 108.4 (q, $J$ = 4.2 Hz, 1C), 116.7, 117.4 (q, $J$ = 3.3 Hz, 1C), 124.2, 124.7 (q, $J$ = 271 Hz, 1C), 128.4, 128.6 (q, $J$ = 31.9 Hz, 1C), 137.6, 139.6, 183.2. **$^{19}$F NMR** ($CDCl_3$, 376 MHz) δ -61.6 (s, 3F**). HRMS** (ESI) calcd. for $C_{11}H_9F_3NO^+$ ($M+H^+$) 228.0631, found 228.0633.

**General Procedure A: Synthesis of S2a-S2b**



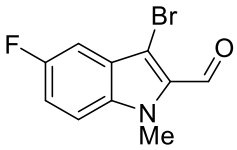

**S2a-B**
**S2a**: R = 6-$CF_3$
**S2b**: R = 5-F

In an oven dried round-bottom-flask, the corresponding indole (1.00 equiv) was dissolved in DMF (0.10 M). *N*-Bromosuccinimide (1.20 equiv) was then added to the solution and stirred at rt for 16 hours. After completion of the reaction, aqueous saturated $NH_4Cl$ solution was added to quench the reaction, and EtOAc was added to the solution. The solution was washed three times with water and once with aq. $NH_4Cl$ (sat.), and then the organic layer was then dried with $MgSO_4$. The dried organic layer was concentrated under reduced pressure to yield the crude product. The crude reaction mixtures were purified by flash column chromatography (90:10 hexanes:EtOAc) to yield **S2a-S2b**.




**S2a**

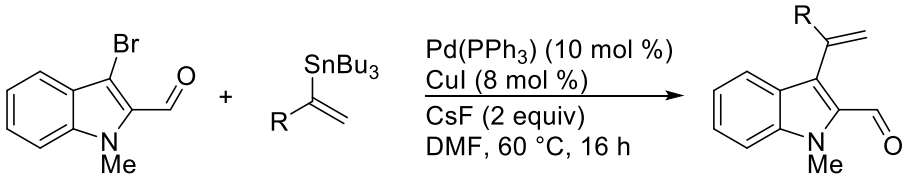
**3-Bromo-1-methyl-6-(trifluoromethyl)-1*H*-indole-2-carbaldehyde (S2a):** Prepared according to general procedure A from 1-methyl-6-(trifluoromethyl)-1*H*-indole-2-carbaldehyde (0.439 g, 1.93 mmol) (**S1**) and NBS (0.412 g, 2.32 mmol). The crude product was purified by flash column chromatography (90:10 hexanes:EtOAc) to yield **S2a** (556 mg, 1.82 mmol, 94% yield) as a white solid. **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 4.14 (s, 3H), 7.47 (d, $J$ = 8.0 Hz, 1H), 7.70 (s, 1H), 7.82 (d, $J$ = 8.0 Hz, 1H), 10.18 (s, 1H). **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 32.3, 105.3, 108.7 (q, $J$ = 4.8 Hz, 1C), 118.1 (q, $J$ = 3.0 Hz, 1C), 122.6, 124.4 (q, $J$ = 271 Hz, 1C), 128.1, 129.8 (q, $J$ = 32.3 Hz, 1C), 131.9, 138.2, 182.8. **$^{19}$F NMR** ($CDCl_3$, 376 MHz) δ -61.7 (s, 3F). **HRMS** (ESI) calcd. for $C_{11}H_8BrF_3NO^+$ ($M+H^+$) 305.9736, found 305.9735.



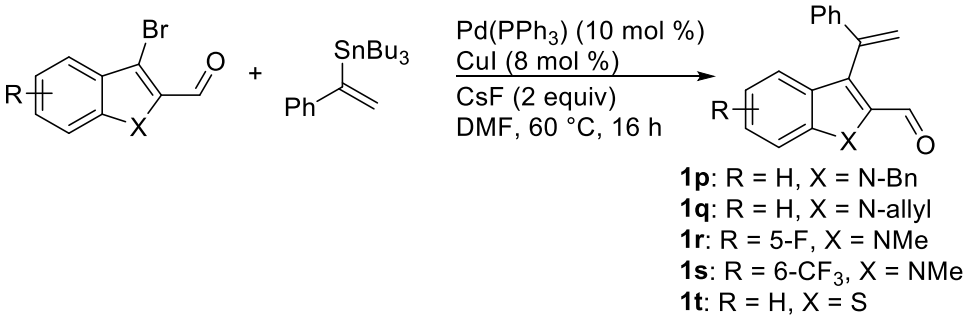
**S2b**

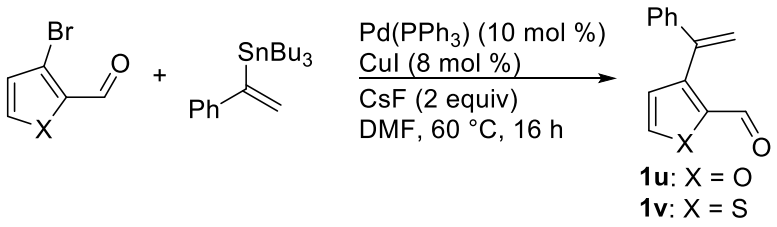
**3-Bromo-5-fluoro-1-methyl-1*H*-indole-2-carbaldehyde (S2b):** Prepared according to general procedure A from 5-fluoro-1-methyl-1*H*-indole-2-carbaldehyde (0.470 g, 2.65 mmol) and NBS (0.519 g, 2.92 mmol). The crude product was purified by flash column chromatography (90:10 hexanes:EtOAc) to yield **S2b** (576 mg, 2.25 mmol, 85% yield) as a white solid. **$^{1}$H NMR** ($CDCl_3$, 400 MHz): δ 4.06 (s, 3H), 7.22 (td, *J* = 8.0, 2.6 Hz, 1H), 7.30-7.33 (m, 2H), 10.10 (s, 1H). **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 32.0, 104.8 (d, *J* = 6.0 Hz, 1C), 105.7 (d, *J* = 24.6 Hz, 1C), 111.9 (d, *J* = 9.2 Hz, 1C), 117.5 (d, *J* = 27.3, 1C), 126.3 (d, *J* = 10.3 Hz, 1C), 131.0, 136.0, 158.5 (d, *J* = 239 Hz, 1C), 182.5. **$^{19}$F NMR** ($CDCl_3$, 376 MHz) δ -120.6 (m, 1F). **HRMS** (ESI) calcd. for $C_{10}H_8BrFNO^+$ ($M+H^+$) 255.9768, found 255.9770.

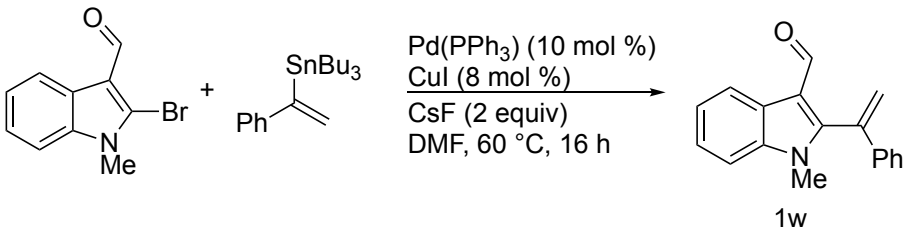
**General Procedure B: Synthesis of Indoles 1a-1u**



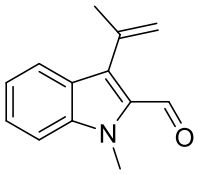

**1a**: R = Me
**1b**: R = Cy
**1c**: R = Ph
**1d**: R = 4-MeO-$C_6H_4$
**1e**: R = 4-F-$C_6H_4$
**1f**: R = 4-Cl-$C_6H_4$
**1g**: R = 3-MeO-$C_6H_4$
**1h**: R = 3-F-$C_6H_4$
**1i**: R = 3-$CF_3$-$C_6H_4$
**1j**: R = 2-F-$C_6H_4$
**1k**: R = 2-Me-$C_6H_4$
**1l**: R = 2-Cl-$C_6H_4$
**1m**: R = 2-furanyl
**1n**: R = 2-thienyl
**1o**: R = $CO_2Me$



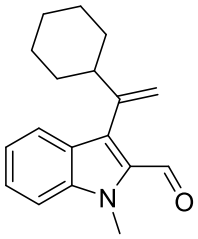




In a nitrogen-filled dry box, the appropriate arylbromide (1.00 equiv) was added to an oven dried round-bottom-flask and dissolved in DMF (0.20 M). The appropriate organostannane (1.10-1.50 equiv), CsF (2.00 equiv), tetrakis(triphenylphosphine)palladium(0) (10 mol %), and copper(I) iodide (8.0 mol %) were then added to the flask in the indicated order, and the flask was capped with a septum. The flask was removed from the dry box and stirred at 60 °C for 16 hours. The reaction mixture was cooled to room temperature, and EtOAc was added. This solution was then washed 3 times with water and once with aq. $NH_4Cl$ (sat.). The organic layer was dried over $MgSO_4$. The dried organic layer was filtered through a plug of celite, eluting with EtOAc, and concentrated under reduced pressure. The crude reaction mixtures were purified by flash column silica gel chromatography (100:0 to 90:10 gradient of hexanes:EtOAc) to yield **1a-1u**.



1a

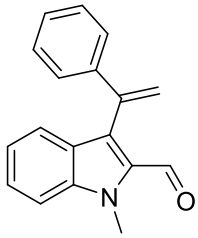
**1-Methyl-3-(prop-1-en-2-yl)-1*H*-indole-2-carbaldehyde (1a):** Prepared according to general procedure B starting from 3-bromo-1-methyl-1*H*-indole-2-carbaldehyde (0.357 g, 1.50 mmol), tributyl(prop-1-en-2-yl)stannane (0.546 g, 1.65 mmol), $Pd(PPh_3)_4$ (0.173 g, 0.150 mmol), CuI (22.9 mg, 0.120 mmol), and CsF (0.466 g, 3.00 mmol). The crude product was purified by flash column chromatography (100% hexanes then gradient to 90:10 hexanes:EtOAc) to yield **1a** (0.162 g, 0.811 mmol, 54% yield) as a white solid. **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 2.3 (dd, *J* = 1.4, 0.9 Hz, 3H), 4.09 (s, 3H), 5.11 (m, 1H), 5.49 (m, 1H), 7.18 (ddd, *J* = 8.0, 6.8, 1.1 Hz, 1H), 7.37 (d, *J* = 8.5 Hz, 1H), 7.43 (m, 1H), 7.75 (dt, *J* = 8.2, 0.9 Hz, 1H), 10.02 (s, 1H). **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 25.1, 31.8, 110.4, 119.7, 120.8, 122.6, 125.3, 127.2, 131.0, 133.7, 136.5, 139.6, 183.7. **HRMS** (ESI) calcd. for $C_{13}H_{14}NO^+$ ($M+H^+$) 200.1070, found 200.1068.



1b

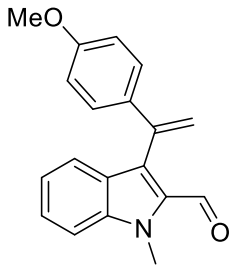
**3-(1-Cyclohexylvinyl)-1-methyl-1*H*-indole-2-carbaldehyde (1b):** Prepared according to general procedure B starting from 3-bromo-1-methyl-1*H*-indole-2-carbaldehyde (0.262 g, 1.10 mmol), tributyl(1-cyclohexylvinyl)stannane (0.879 g, 2.20 mmol), $Pd(PPh_3)_4$ (0.129 g, 0.110 mmol), CuI (16.8 mg, 0.088 mmol), and CsF (0.334 g, 2.20 mmol). The crude product was purified by flash column chromatography (100% hexanes then gradient to 90:10 hexanes:EtOAc) to yield **1b** (0.177 g, 0.663 mmol, 60% yield) as a pale yellow solid. **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 1.1 – 1.3 (m, 5H), 1.65 – 1.7 (m, 1H), 1.75 – 1.8 (m, 2H), 1.88 – 1.91 (m, 2H), 2.41 (m, 1H), 4.10 (s, 3H), 5.10 (m, 1H), 5.44 (m, 1H), 7.15 (ddd, *J* = 8.0, 6.8, 1.1 Hz, 1H), 7.37 (dt, *J* = 8.5, 0.9 Hz, 1H), 7.43 (m, 1H), 7.75 (dt, *J* = 8.1, 1.0 Hz, 1H), 9.90 (s, 1H). **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 26.3, 26.7, 31.7, 32.5, 45.5, 110.3, 116.6, 120.7, 122.6,

126.0, 127.2, 131.7, 133.8, 139.5, 146.3, 183.9. **HRMS** (ESI) calcd. for $C_{18}H_{22}NO^+$ ($M+H^+$) 268.1696, found 268.1694.



**1c**

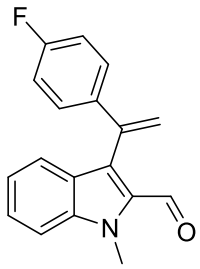
**1-Methyl-3-(1-phenylvinyl)-1*H*-indole-2-carbaldehyde (1c):** Prepared according to general procedure B starting from 3-bromo-1-methyl-1*H*-indole-2-carbaldehyde (0.478 g, 2.00 mmol), tributyl(1-phenylvinyl)stannane (0.881 g, 2.20 mmol), $Pd(PPh_3)_4$ (0.234 g, 0.200 mmol), CuI (51.9 mg, 0.160 mmol), and CsF (0.632 g, 4.00 mmol). The crude product was purified by flash column chromatography (100% hexanes then gradient to 90:10 hexanes:EtOAc) to yield **1c** (0.361 g, 1.38 mmol, 69% yield) as a pale yellow solid. **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 4.15 (s, 3H), 5.42 (d, $J$ = 0.9 Hz, 1H), 6.00 (d, $J$ = 0.9 Hz, 1H), 7.05 (ddd, $J$ = 5.3, 3.4, 1.8 Hz, 1H), 7.30 – 7.33 (m, 4H), 7.39 – 7.41 (m, 4H), 9.93 (s, 1H). **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 31.9, 110.4, 119.4, 121.0, 122.9, 126.1, 127.3, 127.3, 128.3, 128.6, 131.1, 132.5, 139.6, 140.1, 141.2, 183.9. **HRMS** (ESI) calcd. for $C_{18}H_{16}NO^+$ ($M+H^+$) 262.1226, found 262.1224.



**1d**

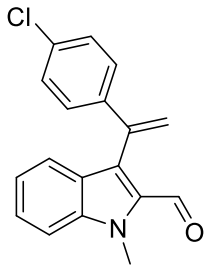
**3-(1-(4-Methoxyphenyl)vinyl)-1-methyl-1*H*-indole-2-carbaldehyde (1d):** Prepared according to general procedure B starting from 3-bromo-1-methyl-1*H*-indole-2-carbaldehyde (0.179 g, 0.750 mmol), tributyl(1-(4-methoxyphenyl)vinyl)stannane (0.351 g, 0.830 mmol), $Pd(PPh_3)_4$ (89.1 mg, 0.075 mmol), CuI (12.7 mg, 0.060 mmol), and CsF (0.270 g, 1.50 mmol). The crude product was purified by flash column chromatography (100% hexanes then gradient to 90:10 hexanes:EtOAc) to yield **1d** (45.1 mg, 0.155 mmol, 21% yield) as a white

solid. **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 3.82 (s, 3H), 4.15 (s, 3H), 5.31 (d, *J* = 1.4 Hz, 1H), 5.90 (d, *J* = 1.4 Hz, 1H), 6.85 (m, 2H), 7.05 (ddd, *J* = 8.0, 5.0, 2.8 Hz, 1H), 7.31 – 7.35 (m, 3H), 7.39 – 7.44 (m, 2H), 9.94 (s, 1H). **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 31.9, 55.4, 110.3, 113.9, 117.6, 120.9, 123.0, 126.1, 127.2, 128.6, 131.4, 132.5, 133.8, 139.3, 139.6, 159.8, 184.0. **HRMS** (ESI) calcd. for $C_{19}H_{18}NO_2^+$ ($M+H^+$) 292.1332, found 292.1333.



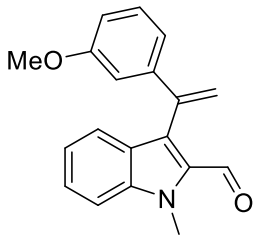

**1e**

**3-(1-(4-Fluorophenyl)vinyl)-1-methyl-1*H*-indole-2-carbaldehyde (1e):** Prepared according to general procedure B starting from 3-bromo-1-methyl-1*H*-indole-2-carbaldehyde (0.448 g, 2.00 mmol), tributyl(1-(4-fluorophenyl)vinyl)stannane (1.23 g, 3.00 mmol), $Pd(PPh_3)_4$ (0.231 g, 0.200 mmol), CuI (30.5 mg, 0.160 mmol), and CsF (0.608 g, 4.00 mmol). The crude product was purified by flash column chromatography (100% hexanes then gradient to 90:10 hexanes:EtOAc) to yield **1e** (0.221 g, 0.789 mmol, 39% yield) as a pale orange solid. **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 4.13 (s, 3H), 5.31 (d, *J* = 0.8 Hz, 1H), 5.91 (d, *J* = 0.8 Hz, 1H), 6.98 (m, 2H), 7.03 (ddd, *J* = 7.9, 5.0, 2.8 Hz, 1H), 7.24 (bs, 1H), 7.33 – 7.42 (m, 4H), 9.91 (s, 1H). **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 32.0, 110.5, 115.5, 115.6 (d, *J* = 22.0 Hz, 1C), 121.1, 122.8, 126.0, 127.4, 129.1 (d, *J* = 8.1 Hz, 1C), 130.8, 132.5, 137.3 (d, *J* = 3.3 Hz, 1C), 139.1, 139.6, 162.9 (d, *J* = 247 Hz, 1C), 183.7. **$^{19}$F NMR** ($CDCl_3$, 376 MHz) δ -113.8 (m, 1F). **HRMS** (ESI) calcd. for $C_{18}H_{15}FNO^+$ ($M+H^+$) 280.1132, found 280.1130.




**1f**

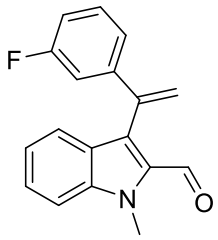
**3-(1-(4-Chlorophenyl)vinyl)-1-methyl-1*H*-indole-2-carbaldehyde (1f):** Prepared according to general procedure B starting from 3-bromo-1-methyl-1*H*-indole-2-carbaldehyde (0.417 g, 1.75 mmol), tributyl(1-(4-chlorophenyl)vinyl)stannane (0.973 g, 2.28 mmol), $Pd(PPh_3)_4$ (0.202 g, 0.175 mmol), CuI (26.7 mg, 0.140 mmol), and CsF (0.532 g, 3.50 mmol). The crude product was purified by flash column chromatography (100% hexanes then gradient to 90:10 hexanes:EtOAc) to yield **1f** (0.139 g, 0.471 mmol, 27% yield) as a yellow solid. **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 4.15 (s, 3H), 5.42 (d, *J* = 1.2 Hz, 1H), 5.98 (d, *J* = 1.2 Hz, 1H), 7.06 (ddd, *J* = 8.0, 5.1, 2.7 Hz, 1H), 7.25 – 7.30 (m, 3H), 7.32 – 7.35 (m, 2H), 7.39 – 7.44 (m, 2H), 9.92 (s, 1H). **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 31.9, 110.5, 119.7, 121.1, 122.8, 125.9, 127.4, 128.6, 128.8, 130.4, 132.5, 134.3, 139.0, 139.59, 139.60, 183.6. **HRMS** (ESI) calcd. for $C_{18}H_{15}ClNO^+$ ($M+H^+$) 296.0837, found 296.0836.




**1g**

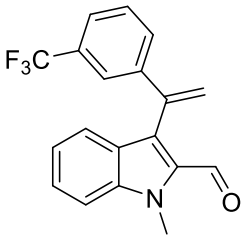
**3-(1-(3-Methoxyphenyl)vinyl)-1-methyl-1*H*-indole-2-carbaldehyde (1g):** Prepared according to general procedure B starting from 3-bromo-1-methyl-1*H*-indole-2-carbaldehyde (0.476 g, 2.00 mmol), tributyl(1-(3-methoxyphenyl)vinyl)stannane (1.69 g, 4.00 mmol), $Pd(PPh_3)_4$ (0.231 g, 0.200 mmol), CuI (30.5 mg, 0.160 mmol), and CsF (0.608 g, 4.00 mmol). The crude product was purified by flash column chromatography (100% hexanes then gradient to 90:10 hexanes:EtOAc) to yield **1g** (0.259 g, 0.890 mmol, 44% yield) as a white solid. **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 3.61 (s, 3H), 4.12 (s, 3H), 5.54 (d, *J* = 2.0 Hz, 1H), 5.89 (d, *J* = 2.0 Hz, 1H), 6.87 (d, *J* = 8.1 Hz, 1H), 6.95 (t, *J* = 7.5 Hz, 1H), 7.01 (ddd, *J* = 8.0, 5.4,

1.4 Hz, 1H), 7.27 – 7.39 (m, 5H), 10.02 (s, 1H). **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 31.9, 55.7, 110.2, 111.7, 120.7, 120.8, 122.8, 122.8, 125.9, 127.0, 129.5, 130.7, 131.2, 131.7, 132.9, 137.9, 139.5, 157.2, 184.4. **HRMS** (ESI) calcd. for $C_{19}H_{18}NO_2^+$ ($M+H^+$) 292.1332, found 292.1330.




**1h**

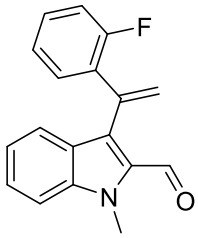
**3-(1-(3-Fluorophenyl)vinyl)-1-methyl-1*H*-indole-2-carbaldehyde (1h):** Prepared according to general procedure B starting from 3-bromo-1-methyl-1*H*-indole-2-carbaldehyde (0.357 g, 1.50 mmol), tributyl(1-(3-fluorophenyl)vinyl)stannane (0.832 g, 1.95 mmol), $Pd(PPh_3)_4$ (0.174 g, 0.150 mmol), CuI (22.9 mg, 0.120 mmol), and CsF (0.456 g, 3.00 mmol). The crude product was purified by flash column chromatography (100% hexanes then gradient to 90:10 hexanes:EtOAc) to yield **1h** (0.230 g, 0.825 mmol, 55% yield) as a white solid. **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 4.18 (s, 3H), 5.49 (d, $J$ = 1.1 Hz, 1H), 6.04 (d, $J$ = 1.2 Hz, 1H), 7.01 – 7.05 (m, 1H), 7.06 – 7.13 (m, 2H), 7.20 (ddd, $J$ = 7.8, 1.5, 1.1 Hz, 1H), 7.27 – 7.34 (m, 2H), 7.42 – 7.47 (m, 2H), 9.94 (s, 1H). **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 31.9, 110.5, 114.2 (d, $J$ = 22.1 Hz, 1C), 115.2 (d, $J$ = 21.2 Hz, 1C), 120.3, 121.2, 122.7, 123.0 (d, $J$ = 2.8 Hz, 1C), 126.0, 127.4, 130.1 (d, $J$ = 8.3 Hz, 1C), 130.2, 132.5, 139.1, 139.6, 143.5 (d, $J$ = 7.3 Hz, 1C), 163.1 (d, $J$ = 245 Hz, 1C), 183.6. **$^{19}$F NMR** ($CDCl_3$, 376 MHz) δ -113.1 (m, 1F). **HRMS** (ESI) calcd. for $C_{18}H_{15}FNO^+$ ($M+H^+$) 280.1132, found 280.1130.




**1i**

**1-Methyl-3-(1-(3-(trifluoromethyl)phenyl)vinyl)-1*H*-indole-2-carbaldehyde (1i):** Prepared according to general procedure B starting from 3-bromo-1-methyl-1*H*-indole-2-carbaldehyde (0.238 g, 1.00 mmol), tributyl(1-(3-(trifluoromethyl)phenyl)vinyl)stannane (0.922 g, 2.00

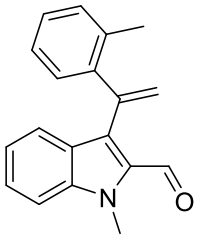
mmol), $Pd(PPh_3)_4$ (0.116 g, 0.100 mmol), CuI (15.2 mg, 0.080 mmol), and CsF (0.304 g, 2.00 mmol). The crude product was purified by flash column chromatography (100% hexanes then gradient to 90:10 hexanes:EtOAc) to yield **1i** (0.110 g, 0.333 mmol, 33% yield) as a pale yellow solid. **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 4.17 (s, 3H), 5.52 (bs, 1H), 6.06 (bs, 1H), 7.07 (ddd, *J* = 7.9, 4.2, 3.7 Hz, 1H), 7.24 – 7.26 (m, 1H), 7.41 – 7.45 (m, 3H), 7.53 (bd, *J* = 7.8 Hz, 1H), 7.58 (bd, *J* = 7.8 Hz, 1H), 7.72 (bs, 1H), 9.92 (s, 1H). **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 32.0, 110.1, 120.9, 121.3, 122.6, 123.8 (q, *J* = 3.8 Hz, 1C), 124.1 (q, *J* = 271 Hz, 1C), 125.2 (q, *J* = 3.7 Hz, 1C), 125.9, 127.5, 129.2, 129.8, 130.8, 131.2 (q, *J* = 32.1 Hz, 1C), 132.5, 139.0, 139.7, 142.0, 183.5. **$^{19}$F NMR** ($CDCl_3$, 376 MHz) δ -62.6 (s, 3F). **HRMS** (ESI) calcd. for $C_{19}H_{15}F_3NO^+$ ($M+H^+$) 330.1100, found 330.1099.




**1j**

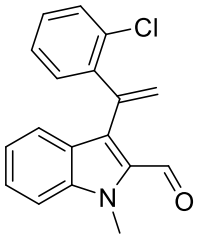
**3-(1-(2-fluorophenyl)vinyl)-1-methyl-1*H*-indole-2-carbaldehyde (1j):** Prepared according to general procedure B starting from 3-bromo-1-methyl-1*H*-indole-2-carbaldehyde (0.357 g, 1.50 mmol), tributyl(1-(2-fluorophenyl)vinyl)stannane (0.832 g, 1.95 mmol), $Pd(PPh_3)_4$ (0.173 g, 0.150 mmol), CuI (22.9 mg, 0.120 mmol), and CsF (0.456 g, 3.00 mmol). The crude product was purified by flash column chromatography (100% hexanes then gradient to 90:10 hexanes:EtOAc) to yield **1j** (0.230 g, 0.823 mmol, 55% yield) as a pale yellow solid. **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 4.14 (s, 3H), 5.63 (dd, *J* = 1.4, 0.8 Hz, 1H), 6.00 (dd, *J* = 1.4, 1.4 Hz, 1H), 7.03 – 7.11 (m, 3H), 7.26 – 7.32 (m, 3H), 7.37 – 7.43 (m, 2H), 10.00 (s, 1H). **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 31.9, 110.4, 116.3 (d, *J* = 22.4 Hz, 1C), 121.0, 122.4, 123.7, 123.8, 124.3 (d, *J* = 3.7 Hz, 1C), 125.8, 129.3 (d, *J* = 12.0 Hz, 1C), 129.9 (d, *J* = 8.4 Hz, 1C), 130.9 (d, *J* = 3.0 Hz, 1C), 131.2, 132.0, 134.8, 139.5, 160.2 (d, *J* = 249 Hz, 1C), 183.7. **$^{19}$F NMR** ($CDCl_3$,

376 MHz) δ -114.3 (m, 1F). **HRMS** (ESI) calcd. for $C_{18}H_{15}FNO^+$ ($M+H^+$) 280.1132, found 280.1131.



**1k**

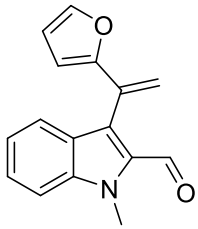
**1-methyl-3-(1-(o-tolyl)vinyl)-1*H*-indole-2-carbaldehyde (1k):** Prepared according to general procedure B starting from 3-bromo-1-methyl-1*H*-indole-2-carbaldehyde (0.357 g, 1.50 mmol), tributyl(1-(*o*-tolyl)vinyl)stannane (0.672 g, 1.65 mmol), $Pd(PPh_3)_4$ (0.173 g, 0.150 mmol), CuI (22.9 mg, 0.120 mmol), and CsF (0.456 g, 3.00 mmol). The crude product was purified by flash column chromatography (100% hexanes then gradient to 90:10 hexanes:EtOAc) to yield **1k** (0.267 g, 0.971 mmol, 65% yield) as a pale orange solid. **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 2.10 (s, 3H), 4.12 (s, 3H), 5.61 (d, $J$ = 1.9 Hz, 1H), 5.68 (d, $J$ = 1.9 Hz, 1H), 7.03 (ddd, $J$ = 8.0, 5.8, 2.0 Hz, 1H), 7.15 (m, 1H), 7.20 – 7.24 (m, 2H), 7.30 (dt, $J$ = 8.2, 1.0 Hz, 1H), 7.35 – 7.42 (m, 3H), 9.98 (s, 1H). **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 20.8, 32.0, 110.3, 121.1, 122.5, 122.8, 125.6, 126.2, 127.2, 128.2, 129.8, 130.9, 131.6, 131.7, 135.9, 139.6, 141.2, 142.1, 183.9. **HRMS** (ESI) calcd. for $C_{19}H_{18}NO^+$ ($M+H^+$) 276.1383, found 276.1381.



**1l**

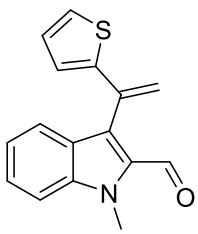
**3-(1-(2-chlorophenyl)vinyl)-1-methyl-1*H*-indole-2-carbaldehyde (1l):** Prepared according to general procedure B starting from 3-bromo-1-methyl-1*H*-indole-2-carbaldehyde (0.357 g, 1.50 mmol), tributyl(1-(2-chlorophenyl)vinyl)stannane (0.836 g, 1.95 mmol), $Pd(PPh_3)_4$ (0.173 g, 0.150 mmol), CuI (22.9 mg, 0.120 mmol), and CsF (0.456 g, 3.00 mmol). The crude product was purified by flash column chromatography (100% hexanes then gradient to 90:10 hexanes:EtOAc) to yield **1l** (0.262 g, 0.885 mmol, 59% yield) as a white solid. **$^1$H**

**NMR** ($CDCl_3$, 400 MHz): δ 4.12 (s, 3H), 5.66 (d, *J* = 1.0 Hz, 1H), 5.81 (d, *J* = 1.0 Hz, 1H), 7.04 (ddd, *J* = 5.4, 4.0, 1.2 Hz, 1H), 7.27 – 7.31 (m, 3H), 7.35 – 7.40 (m, 3H), 7.45 – 7.47 (m, 1H), 10.02 (s, 1H). **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 32.0, 110.5, 121.1, 122.6, 124.1, 125.7, 127.1, 127.2, 129.5, 130.5, 130.8, 131.3, 131.9, 133.2, 139.0, 139.6, 141.0, 184.1. **HRMS** (ESI) calcd. for $C_{18}H_{15}ClNO^+$ ($M+H^+$) 296.0837, found 296.0834.



**1m**

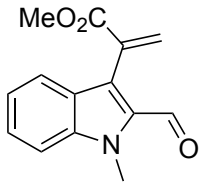
**3-(1-(furan-2-yl)vinyl)-1-methyl-1*H*-indole-2-carbaldehyde (1m):** Prepared according to general procedure B starting from 3-bromo-1-methyl-1*H*-indole-2-carbaldehyde (0.169 g, 1.30 mmol), tributyl(1-(furan-2-yl)vinyl)stannane (0.548 g, 1.43 mmol), $Pd(PPh_3)_4$ (0.150 g, 0.130 mmol), CuI (19.8 mg, 0.104 mmol), and CsF (0.395 g, 2.60 mmol). The crude product was purified by flash column chromatography (100% hexanes then gradient to 90:10 hexanes:EtOAc) to yield **1m** (0.169 g, 0.674 mmol, 52% yield) as a white solid. **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 4.15 (s, 3H), 5.29 (d, *J* = 1.4 Hz, 1H), 6.09 (bd, *J* = 3.3 Hz, 1H), 6.14 (d, *J* = 1.4 Hz, 1H), 6.37 (dd, *J* = 3.3, 1.8 Hz, 1H), 7.14 (ddd, *J* = 8.0, 6.2, 1.6 Hz, 1H), 7.40 – 7.47 (m, 3H), 7.59 (bd, *J* = 8.2 1H), 9.98 (s, 1H). **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 31.9, 109.9, 110.4, 111.7, 116.5, 121.0, 122.6, 126.0, 127.3, 128.4, 129.0, 132.2, 139.5, 142.8, 154.1, 185.6. **HRMS** (ESI) calcd. for $C_{16}H_{14}NO_2^+$ ($M+H^+$) 252.1019, found 252.1024.



**1n**

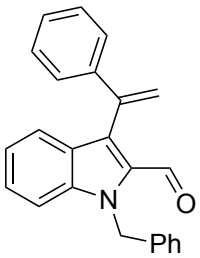
**1-methyl-3-(1-(thiophen-2-yl)vinyl)-1*H*-indole-2-carbaldehyde (1n):** Prepared according to general procedure B starting from 3-bromo-1-methyl-1*H*-indole-2-carbaldehyde (0.357 g, 1.50 mmol), tributyl(1-(thiophen-2-yl)vinyl)stannane (0.659 g, 1.65 mmol), $Pd(PPh_3)_4$ (0.173 g, 0.150 mmol),

CuI (22.9 mg, 0.120 mmol), and CsF (0.456 g, 3.00 mmol). The crude product was purified by flash column chromatography (100% hexanes then gradient to 90:10 hexanes:EtOAc) to yield **1n** (0.107 g, 0.401 mmol, 27% yield) as a white solid. **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 4.15 (s, 3H), 5.27 (d, *J* = 0.6 Hz, 1H), 6.01 (d, *J* = 0.7 Hz, 1H), 6.85 (dd, *J* = 3.6, 1.1 Hz 1H), 6.93 (dd, *J* = 5.1, 3.6 Hz 1H), 7.11 (ddd, *J* = 8.0, 6.0, 1.9 Hz, 1H), 7.25 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.40 – 7.46 (m, 2H), 7.52 (ddd, *J* = 8.2, 0.8, 0.8 Hz, 1H), 9.98 (s, 1H). **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 32.0, 110.4, 117.8, 121.1, 122.7, 125.7, 126.0, 126.9, 127.4, 127.7, 130.0, 132.1, 133.5, 139.5, 145.2, 186.6. **HRMS** (ESI) calcd. for $C_{16}H_{14}NOS^+$ ($M+H^+$) 268.0791, found 268.0796.



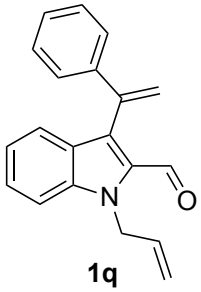

**1o**

**methyl 2-(2-formyl-1-methyl-1*H*-indol-3-yl)acrylate (1o):** Prepared according to general procedure B starting from 3-bromo-1-methyl-1*H*-indole-2-carbaldehyde (0.357 g, 1.50 mmol), methyl 2-(tributylstannyl)acrylate (0.619 g, 1.65 mmol), $Pd(PPh_3)_4$ (0.173 g, 0.150 mmol), CuI (22.9 mg, 0.120 mmol), and CsF (0.456 g, 3.00 mmol). The crude product was purified by flash column chromatography (100% hexanes then gradient to 80:20 hexanes:EtOAc) to yield a mixture of **1o** and 3-bromo-1-methyl-1*H*-indole-2-carbaldehyde (2.9:1 ratio) (0.100 g, 0.411 mmol, 27% yield) as a yellow oil. **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 3.81 (s, 3H), 4.12 (s, 3H), 5.97 (d, *J* = 1.6 Hz, 1H), 6.83 (d, *J* = 1.6 Hz, 1H), 7.19 (ddd, *J* = 8.0, 6.6, 1.3 Hz, 1H), 7.39 – 7.47 (m, 2H), 7.59 (ddd, *J* = 8.2, 1.0, 1.0 Hz, 1H), 9.91 (s, 1H). **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 31.9, 52.7, 110.6, 121.4, 122.0, 125.3, 126.1, 127.4, 127.8, 132.1, 132.5, 139.4, 166.9, 182.9. **HRMS** (ESI) calcd. for $C_{14}H_{14}NO_3^+$ ($M+H^+$) 244.0968, found 244.0971.



**1p**

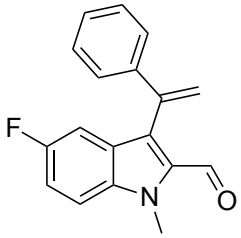
**1-benzyl-3-(1-phenylvinyl)-1*H*-indole-2-carbaldehyde (1p):** Prepared according to general procedure B starting from 1-benzyl-3-bromo-1*H*-indole-2-carbaldehyde (0.314 g, 1.00 mmol), tributyl(1-phenylvinyl)stannane (0.433 g, 1.10 mmol), $Pd(PPh_3)_4$ (0.116 g, 0.100 mmol), CuI (15.3 mg, 0.080 mmol), and CsF (0.304 g, 2.00 mmol). The crude product was purified by flash column chromatography (100% hexanes then gradient to 90:10 hexanes:EtOAc) to yield **1p** (0.193 g, 0.571 mmol, 57% yield) as a white solid. **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 5.48 (d, *J* = 1.4 Hz, 1H), 5.92 (s, 2H), 6.05 (d, *J* = 1.4 Hz, 1H), 7.07 (ddd, *J* = 8.0, 6.4, 1.4 Hz, 1H), 7.16 – 7.18 (m, 2H), 7.23 – 7.44 (m, 11H), 9.96 (s, 1H). **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 48.2, 111.1, 119.6, 121.3, 123.0, 126.4, 126.8, 127.3, 127.5, 127.6, 128.4, 128.7, 128.8, 131.9, 132.1, 138.0, 139.5, 140.0, 141.1, 183.5. **HRMS** (ESI) calcd. for $C_{24}H_{20}NO^+$ ($M+H^+$) 338.1539, found 338.1544.



**1q**

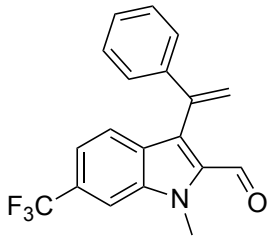
**1-allyl-3-(1-phenylvinyl)-1*H*-indole-2-carbaldehyde (1q):** Prepared according to general procedure B starting from 1-allyl-3-bromo-1*H*-indole-2-carbaldehyde (0.198 g, 0.750 mmol), tributyl(1-phenylvinyl)stannane (0.324 g, 0.825 mmol), $Pd(PPh_3)_4$ (86.7 mg, 0.075 mmol), CuI (11.3 mg, 0.060 mmol), and CsF (0.228 g, 1.50 mmol). The crude product was purified by flash column chromatography (100% hexanes then gradient to 90:10 hexanes:EtOAc) to yield **1q** (0.121 g, 0.422 mmol, 56% yield) as a white solid. **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 4.99 (ddd, *J* = 17.2, 2.9, 1.6 Hz, 1H), 5.16 (ddd, *J* = 17.2, 2.9, 1.6 Hz, 1H), 5.29 (ddd, *J* = 5.0, 1.6, 1.6 Hz, 2H), 5.44 (d, *J* = 1.4 Hz, 1H), 6.00 – 6.09 (m, 2H), 7.05 (m 1H), 7.30 – 7.33 (m, 4H), 7.39 – 7.41 (m, 4H), 9.92 (s, 1H). **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 47.1, 110.8, 116.5,

119.5, 121.2, 123.0, 126.3, 127.3, 127.4, 128.4, 128.7, 131.6, 131.9, 133.7, 139.2, 140.0, 141.1, 183.5. **HRMS** (ESI) calcd. for $C_{20}H_{18}NO^+$ ($M+H^+$) 288.1383, found 288.1386.




**1r**

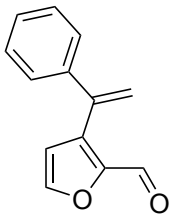
**5-fluoro-1-methyl-3-(1-phenylvinyl)-1*H*-indole-2-carbaldehyde (1r):** Prepared according to general procedure B starting from 3-bromo-5-fluoro-1-methyl-1*H*-indole-2-carbaldehyde (0.384 g, 1.50 mmol), tributyl(1-phenylvinyl)stannane (0.649 g, 1.65 mmol), $Pd(PPh_3)_4$ (0.173 g, 0.150 mmol), CuI (22.9 mg, 0.120 mmol), and CsF (0.456 g, 3.00 mmol). The crude product was purified by flash column chromatography (100% hexanes then gradient to 90:10 hexanes:EtOAc) to yield **1r** (0.252 g, 0.903 mmol, 60% yield) as a white solid. **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 4.14 (s, 3H), 5.40 (d, $J$ = 1.4 Hz, 1H), 5.99 (d, $J$ = 1.4 Hz, 1H), 6.92 (ddd, $J$ = 9.1, 2.5, 0.5 Hz, 1H), 7.17 (ddd, $J$ = 9.0, 9.0, 2.5 Hz, 1H), 7.31 – 7.41 (m, 6H), 9.92 (s, 1H). **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 32.1, 107.0 (d, $J$ = 23.0 Hz, 1C), 111.5 (d, $J$ = 9.3 Hz, 1C), 116.6 (d, $J$ = 27.2 Hz, 1C), 119.5, 126.2 (d, $J$ = 9.9 Hz, 1C), 127.3, 128.5, 128.7, 130.5 (d, $J$ = 5.9 Hz, 1C), 133.6, 136.3, 139.8, 140.8, 158.1 (d, $J$ = 237 Hz, 1C), 183.8. **$^{19}$F NMR** ($CDCl_3$, 376 MHz) δ -121.6 (m, 1F). **HRMS** (ESI) calcd. for $C_{18}H_{15}FNO^+$ ($M+H^+$) 280.1132, found 280.1135.




**1s**

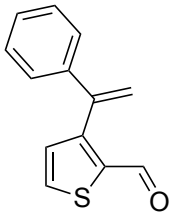
**1-methyl-3-(1-phenylvinyl)-6-(trifluoromethyl)-1*H*-indole-2-carbaldehyde (1s):** Prepared according to general procedure B starting from 3-bromo-1-methyl-6-(trifluoromethyl)-1*H*-indole-2-carbaldehyde (0.505 g, 1.65 mmol), tributyl(1-phenylvinyl)stannane (0.714 g, 1.82 mmol), $Pd(PPh_3)_4$ (0.191 g, 0.165 mmol), CuI (25.1 mg,

0.132 mmol), and CsF (0.501 g, 3.30 mmol). The crude product was purified by flash column chromatography (100% hexanes then gradient to 90:10 hexanes:EtOAc) to yield **1s** (0.390 g, 1.19 mmol, 72% yield) as a white solid. **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 4.20 (s, 3H), 5.44 (d, $J$ = 1.3 Hz, 1H), 6.04 (d, $J$ = 1.3 Hz, 1H), 7.25 – 7.27 (m, 1H), 7.32 – 7.42 (m, 6H), 7.71 (bs, 1H), 9.98 (s, 1H). **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 32.2, 108.3 (q, $J$ = 4.6 Hz, 1C), 117.4 (q, $J$ = 3.3 Hz, 1C), 119.9, 123.7, 124.6 (q, $J$ = 271 Hz, 1C), 127.3, 128.1, 128.6, 128.8, 128.9 (q, $J$ = 31.9 Hz, 1C), 130.5, 134.2, 138.4, 139.5, 140.8, 184.0. **$^{19}$F NMR** ($CDCl_3$, 376 MHz) δ -61.6 (s, 3F). **HRMS** (ESI) calcd. for $C_{19}H_{15}F_3NO^+$ ($M+H^+$) 330.1100, found 330.1104.



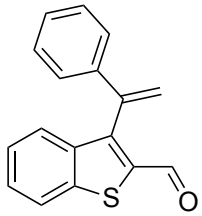
**1t**

**3-(1-phenylvinyl)furan-2-carbaldehyde (1t):** Prepared according to general procedure B starting from 3-bromofuran-2-carbaldehyde (0.263 g, 1.50 mmol), tributyl(1-phenylvinyl)stannane (0.649 g, 1.65 mmol), $Pd(PPh_3)_4$ (0.173 g, 0.150 mmol), CuI (22.9 mg, 0.120 mmol), and CsF (0.456 g, 3.00 mmol). The crude product was purified by flash column chromatography (100% hexanes then gradient to 90:10 hexanes:EtOAc) to yield **1t** (0.199 g, 1.00 mmol, 67% yield) as a pale yellow oil. **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 5.55 (d, $J$ = 1.0 Hz, 1H), 5.79 (d, $J$ = 1.0 Hz, 1H), 6.51 (d, $J$ = 1.8 Hz, 1H), 7.34 – 7.38 (m, 5H), 7.64 (dd, $J$ = 1.7, 0.8 Hz, 1H), 9.45 (s, 1H). **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 114.0, 119.2, 127.4, 128.80, 128.81, 139.0, 139.2, 139.7, 147.1, 149.2, 177.5. **HRMS** (ESI) calcd. for $C_{13}H_{11}O_2^+$ ($M+H^+$) 199.0754, found 199.0756.



**1u**

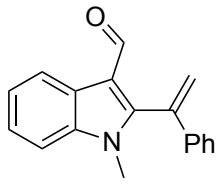
**3-(1-phenylvinyl)thiophene-2-carbaldehyde (1u):** Prepared according to general procedure B starting from 3-bromothiophene-2-carbaldehyde (0.287 g, 1.50 mmol), tributyl(1-phenylvinyl)stannane (0.649 g, 1.65 mmol), $Pd(PPh_3)_4$ (0.173 g, 0.150 mmol), CuI (22.9 mg, 0.120 mmol), and CsF (0.456 g, 3.00 mmol). The crude product was purified by flash column chromatography (100% hexanes then gradient to 90:10 hexanes:EtOAc) to yield **1u** (0.158 g, 0.735 mmol, 49% yield) as a pale yellow oil. **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 5.42 (d, $J$ = 1.0 Hz, 1H), 5.89 (d, $J$ = 1.0 Hz, 1H), 7.02 (d, $J$ = 5.0 Hz, 1H), 7.31 – 7.38 (m, 5H), 7.67 (dd, $J$ = 5.0, 1.2 Hz, 1H), 9.81 (s, 1H). **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 119.2, 127.3, 128.7, 128.8, 130.9, 133.7, 140.2, 140.7, 142.1, 151.3, 184.0. **HRMS** (ESI) calcd. for $C_{13}H_{11}OS^+$ ($M+H^+$) 215.0525, found 215.0527.



**1v**

**3-(1-phenylvinyl)benzo[*b*]thiophene-2-carbaldehyde (1v):** Prepared according to general procedure B starting from 3-bromobenzo[*b*]thiophene-2-carbaldehyde (0.362 g, 1.50 mmol), tributyl(1-phenylvinyl)stannane (0.649 g, 1.65 mmol), $Pd(PPh_3)_4$ (0.173 g, 0.150 mmol), CuI (22.9 mg, 0.120 mmol), and CsF (0.456 g, 3.00 mmol). The crude product was purified by flash column chromatography (100% hexanes then gradient to 90:10 hexanes:EtOAc) to yield **1v** (0.201 g, 0.759 mmol, 51% yield) as a white solid. **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 5.53 (d, $J$ = 0.7 Hz, 1H), 6.19 (d, $J$ = 0.8 Hz, 1H), 7.26 – 7.30 (m, 1H), 7.32 – 7.37 (m, 5H), 7.47 (ddd, $J$ = 8.1, 7.2, 1.0 Hz, 1H), 7.53 (bd, $J$ = 8.2 Hz, 1H), 7.90 (bd, $J$ = 8.2 Hz, 1H), 10.11 (s, 1H). **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 120.3, 123.3, 125.2, 125.8, 126.8, 128.4, 128.8, 128.9, 139.2,

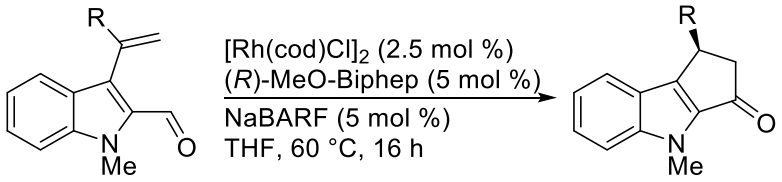
139.5, 140.4, 140.7, 141.9, 147.4, 185.7. **HRMS** (ESI) calcd. for $C_{17}H_{13}OS^+$ ($M+H^+$) 265.0682, found 265.0687.




**1w**

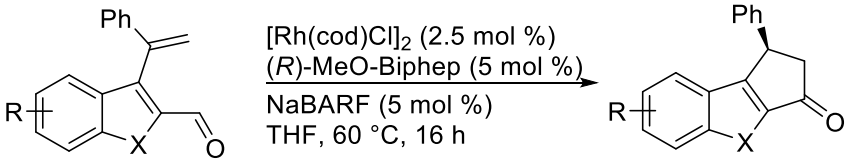
**1-methyl-2-(1-phenylvinyl)-1*H*-indole-3-carbaldehyde (1w):** Prepared according to general procedure B starting from 2-bromo-1-methyl-1*H*-indole-3-carbaldehyde (0.357 g, 1.50 mmol), tributyl(1-phenylvinyl)stannane (0.649 g, 1.65 mmol), $Pd(PPh_3)_4$ (0.173 g, 0.150 mmol), CuI (22.9 mg, 0.120 mmol), and CsF (0.456 g, 3.00 mmol). The crude product was purified by flash column chromatography (100% hexanes then gradient to 80:20 hexanes:EtOAc) to yield **1w** (0.251 g, 0.960 mmol, 64% yield) as a white solid. **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 3.46 (s, 3H), 5.62 (d, $J$ = 0.8 Hz, 1H), 6.28 (d, $J$ = 0.8 Hz, 1H), 7.26 – 7.32 (m, 2H), 7.33 – 7.40 (m, 6H), 8.44 – 8.48 (m, 1H), 9.96 (s, 1H). **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 31.0, 109.7, 116.9, 122.4, 122.6, 123.3, 124.2, 125.3, 126.5, 129.1, 129.2, 137.3, 137.4, 138.3, 151.0, 186.4. **HRMS** (ESI) calcd. for $C_{18}H_{16}NO^+$ ($M+H^+$) 262.1226, found 262.1230.

**General Procedure C: Hydroacylation to Form 2a-2v, 3p**



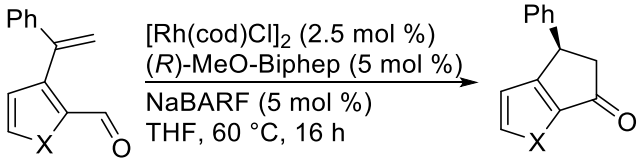

**1a**: R = Me
**1b**: R = Cy
**1c**: R = Ph
**1d**: R = 4-MeO-$C_6H_4$
**1e**: R = 4-F-$C_6H_4$
**1f**: R = 4-Cl-$C_6H_4$
**1g**: R = 3-MeO-$C_6H_4$
**1h**: R = 3-F-$C_6H_4$
**1i**: R = 3-$CF_3$-$C_6H_4$
**1j**: R = 2-F-$C_6H_4$
**1k**: R = 2-Me-$C_6H_4$
**1l**: R = 2-Cl-$C_6H_4$
**1m**: R = 2-furanyl
**1n**: R = 2-thienyl
**1o**: R = $CO_2Me$

**2a**: R = Me
**2b**: R = Cy
**2c**: R = Ph
**2d**: R = 4-MeO-$C_6H_4$
**2e**: R = 4-F-$C_6H_4$
**2f**: R = 4-Cl-$C_6H_4$
**2g**: R = 3-MeO-$C_6H_4$
**2h**: R = 3-F-$C_6H_4$
**2i**: R = 3-$CF_3$-$C_6H_4$
**2j**: R = 2-F-$C_6H_4$
**2k**: R = 2-Me-$C_6H_4$
**2l**: R = 2-Cl-$C_6H_4$
**2m**: R = 2-furanyl
**2n**: R = 2-thienyl
**2o**: R = $CO_2Me$




**1p**: R = H, X = N-Bn
**1q**: R = H, X = N-allyl
**1q**: R = H, X = N-allyl
**1r**: R = 5-F, X = NMe
**1s**: R = 6-$CF_3$, X = NMe
**1t**: R = H, X = S

**2p**: R = H, X = N-Bn
**2q**: R = H, X = N-allyl
**3q:** R = H, X = NCHCHCH$_3$
**2r**: R = 5-F, X = NMe
**2s**: R = 6-$CF_3$, X = NMe
**2t**: R = H, X = S

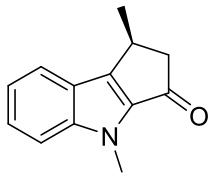



**1u**: X = O
**1v**: X = S

**2u**: X = O
**2v**: X = S

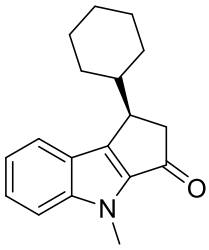
In a nitrogen-filled dry box, the appropriate substrate **1a-1v** (0.100 mmol, 1.00 equiv) was added to an oven dried 1 dram vial. [Rh(cod)Cl]$_2$ (1.2 mg, 0.0025 mmol, 2.5 mol %), (*R*)-MeOBiphep (2.9 mg, 0.005 mmol, 5.0 mol %), and NaBARF (4.4 mg, 0.005 mmol, 5.0 mol %) were then added to the vial and all components dissolved in tetrahydrofuran (0.25 mL, 0.40

M). The 1 dram vial was capped with a teflon-lined screw cap and removed from the dry box and stirred at 60 °C for 16 hours. The reaction mixture was cooled to room temperature and EtOAc was added. The reaction was filtered through a plug of celite and washed twice with EtOAc (2 mL) and twice with DCM (2 mL). The filtrate was concentrated under reduced pressure. The crude reaction mixtures were purified by flash column chromatography (hexanes:EtOAc) to yield **2a-2v, 3p**.



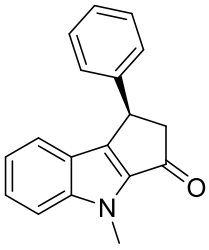

**2a**

**(*S*)-1,4-dimethyl-1,4-dihydrocyclopenta[*b*]indol-3(2*H*)-one (2a):** Prepared according to general procedure C starting from 1-methyl-3-(prop-1-en-2-yl)-1*H*-indole-2-carbaldehyde **1a** (19.9 mg, 0.100 mmol). The crude product was purified by flash column chromatography (100% hexanes to 90:10 hexanes:EtOAc) to yield **2a** (18.7 mg, 0.094 mmol, 94% yield) as a white solid. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) $t_R$ 9.10 min (major); $t_R$ 13.6 min (minor) [Chiracel AS-H (0.46cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/$^i$PrOH, 95:5, 1 mL/min] to be 99% ee. $[\alpha]_D^{22.4}$ = +60.4° (c 1.060, $CHCl_3$). **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 1.48 (d, *J* = 7.1 Hz, 3H), 2.54 (dd, *J* = 18.3, 2.0 Hz, 1H), 3.22 (dd, *J* = 18.3, 6.2 Hz, 1H), 3.53 (qdd, *J* = 7.1, 6.2, 2.0 Hz, 1H), 3.91 (s, 3H), 7.18 (ddd, *J* = 8.0, 6.8, 1.2 Hz, 1H), 7.35 – 7.44 (m, 2H), 7.72 (ddd, *J* = 8.1, 0.9, 0.9 Hz, 1H). **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 21.2, 28.2, 30.2, 50.8, 111.2, 120.3, 122.0, 122.7, 126.7, 138.3, 145.0, 149.5, 194.5. **HRMS** (ESI) calcd. for $C_{13}H_{14}NO^+$ ($M+H^+$) 200.1070, found 200.1066.



2b

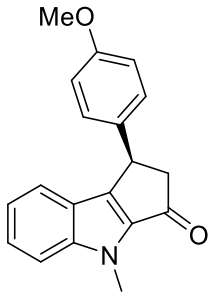
**(*R*)-1-cyclohexyl-4-methyl-1,4-dihydrocyclopenta[*b*]indol-3(2*H*)-one (2b):** Prepared according to general procedure C starting from 3-(1-cyclohexylvinyl)-1-methyl-1*H*-indole-2-carbaldehyde **1b** (26.7 mg, 0.100 mmol). The crude product was purified by flash column chromatography (100% hexanes to 90:10 hexanes:EtOAc) to yield **2b** (23.5 mg, 0.088 mmol, 88% yield) as a white solid. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) $t_R$ 13.7 min (major); $t_R$ 15.8 min (minor) [Chiracel OJ-H (0.46cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/$^i$PrOH, 95:5, 0.5 mL/min] to be 99% ee. $[\alpha]_D^{22.4}$ = +7.6° (c 1.315, $CHCl_3$). **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 1.06 – 1.29 (m, 5H), 1.52 – 1.56 (m, 1H), 1.63 – 1.86 (m, 5H), 2.75 (dd, *J* = 18.4, 1.8 Hz, 1H), 2.99 (dd, *J* = 18.4, 6.4 Hz, 1H), 3.53 (ddd, *J* = 6.4, 4.9, 1.5 Hz, 1H), 3.91 (s, 3H), 7.17 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H), 7.35 – 7.43 (m, 2H), 7.75 (ddd, *J* = 8.1, 0.9, 0.9 Hz, 1H). **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 26.6, 29.6, 30.2, 31.6, 39.9, 42.5, 45.8, 111.1, 120.3, 122.9, 123.5, 126.7, 139.0, 144.9, 146.9, 194.9. **HRMS** (ESI) calcd. for $C_{18}H_{22}NO^+$ ($M+H^+$) 268.1696, found 268.1694.



2c

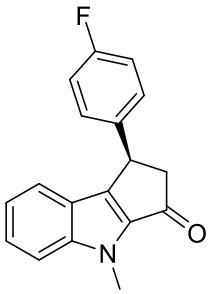
**(*R*)-4-methyl-1-phenyl-1,4-dihydrocyclopenta[*b*]indol-3(2*H*)-one (2c):** Prepared according to general procedure C starting from 1-methyl-3-(1-phenylvinyl)-1*H*-indole-2-carbaldehyde **1c** (26.1 mg, 0.100 mmol). The crude product was purified by flash column chromatography (100% hexanes to 90:10 hexanes:EtOAc) to yield **2c** (25.9 mg, 0.099 mmol, 99% yield) as a pale yellow solid. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) $t_R$ 14.0 min (minor); $t_R$ 16.6 min (major) [Chiracel AS-H (0.46cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/$^i$PrOH, 95:5, 1 mL/min] to be 99% ee. $[\alpha]_D^{22.4}$ = +118.6°

(c 1.315, $CHCl_3$). **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 2.89 (dd, *J* = 18.4, 2.4 Hz, 1H), 3.51 (dd, *J* = 18.4, 6.8 Hz, 1H), 3.99 (s, 3H), 4.65 (dd, *J* = 6.8, 2.4 Hz, 1H), 7.08 (ddd, *J* = 8.0, 5.0, 3.0 Hz, 1H), 7.22 – 7.26 (m, 3H), 7.22 – 7.26 (m, 2H), 7.35 – 7.41 (m, 3H). **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 30.3, 39.2, 52.3, 111.1, 120.6, 122.3, 122.8, 126.96, 126.96, 127.3, 128.9, 139.0, 143.0, 145.2, 146.5, 194.0. **HRMS** (ESI) calcd. for $C_{18}H_{16}NO^+$ ($M+H^+$) 262.1226, found 262.1225.



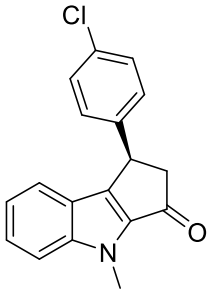
**2d**

**(*R*)-1-(4-methoxyphenyl)-4-methyl-1,4-dihydrocyclopenta[*b*]indol-3(2*H*)-one (2d):** Prepared according to general procedure C starting from 3-(1-(4-methoxyphenyl)vinyl)-1-methyl-1*H*-indole-2-carbaldehyde **1d** (29.1 mg, 0.100 mmol). The crude product was purified by flash column chromatography (100% hexanes to 90:10 hexanes:EtOAc) to yield **2d** (22.4 mg, 0.077 mmol, 77% yield) as a pale yellow solid. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) $t_R$ 13.7 min (major); $t_R$ 16.5 min (minor) [Chiracel OD-H (0.46cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/$^i$PrOH, 95:5, 1 mL/min] to be 97% ee. $[\alpha]_D^{22.3}$ = +98.3° (c 0.895, $CHCl_3$). **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 2.85 (dd, *J* = 18.4, 2.4 Hz, 1H), 3.49 (dd, *J* = 18.4, 6.7 Hz, 1H), 3.79 (s, 3H), 3.98 (s, 3H), 4.61 (dd, *J* = 6.7, 2.3 Hz, 1H), 6.82 – 6.85 (m, 2H), 7.08 (ddd, *J* = 8.0, 5.2, 2.8 Hz, 1H), 7.12 – 7.16 (m, 2H), 7.35 – 7.43 (m, 3H). **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 30.3, 33.4, 52.5, 55.4, 111.1, 114.3, 120.5, 122.4, 122.8, 126.9, 128.3, 135.1, 139.0, 145.2, 146.8, 158.6, 194.1. **HRMS** (ESI) calcd. for $C_{19}H_{18}NO_2^+$ ($M+H^+$) 292.1332, found 292.1329.




**2e**

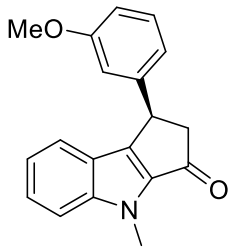
**(*R*)-1-(4-fluorophenyl)-4-methyl-1,4-dihydrocyclopenta[*b*]indol-3(2*H*)-one (2e):** Prepared according to general procedure C starting from 3-(1-(4-fluorophenyl)vinyl)-1-methyl-1*H*-indole-2-carbaldehyde **1e** (27.9 mg, 0.100 mmol). The crude product was purified by flash column chromatography (100% hexanes to 90:10 hexanes:EtOAc) to yield **2e** (20.1 mg, 0.072 mmol, 72% yield) as a white solid. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) $t_R$ 17.6 min (minor); $t_R$ 19.4 min (major) [Chiracel AS-H (0.46cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/$^i$PrOH, 95:5, 1 mL/min] to be 99% ee. $[\alpha]_D^{22.3}$ = +115.8° (c 1.105, $CHCl_3$). **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 2.83 (dd, *J* = 18.4, 2.4 Hz, 1H), 3.50 (dd, *J* = 18.4, 6.8 Hz, 1H), 3.98 (s, 3H), 4.63 (dd, *J* = 6.7, 2.3 Hz, 1H), 6.96 – 7.02 (m, 2H), 7.09 (ddd, *J* = 8.0, 5.3, 2.6 Hz, 1H), 7.16 – 7.21 (m, 2H), 7.34 (ddd, *J* = 8.1, 0.9, 0.9 Hz, 1H), 7.39 – 7.44 (m, 2H). **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 30.3, 38.4, 52.3, 111.2, 115.7 (d, *J* = 21.2 Hz, 1C), 120.7, 122.2, 122.7, 127.1, 128.8 (d, *J* = 8.0 Hz, 1C), 138.7 (d, *J* = 3.3 Hz, 1C), 139.0, 145.2, 146.1, 161.9 (d, *J* = 244 Hz, 1C), 193.7. **$^{19}$F NMR** ($CDCl_3$, 376 MHz) δ -116.1 (m, 1F). **HRMS** (ESI) calcd. for $C_{18}H_{15}FNO^+$ ($M+H^+$) 280.1132, found 280.1131.




**2f**

**(*R*)-1-(4-chlorophenyl)-4-methyl-1,4-dihydrocyclopenta[*b*]indol3(2*H*)-one (2f):** Prepared according to general procedure C starting from 3-(1-(4-chlorophenyl)vinyl)-1-methyl-1*H*-indole-2-carbaldehyde **1f** (29.6 mg, 0.100 mmol). The crude product was purified by flash column chromatography (100% hexanes to 90:10 hexanes:EtOAc) to yield **2f** (25.8

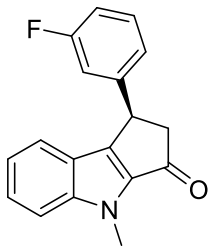
g, 0.087 mmol, 87% yield) as a white solid. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) $t_R$ 19.0 min (major); $t_R$ 22.4 min (minor) [Chiracel OJ-H (0.46cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/$^i$PrOH, 95:5, 1 mL/min] to be 99% ee. $[\alpha]_D^{23.1}$ = +108.4° (c 1.365, $CHCl_3$). **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 2.82 (dd, *J* = 18.4, 2.5 Hz, 1H), 3.50 (dd, *J* = 18.4, 6.8 Hz, 1H), 3.98 (s, 3H), 4.62 (dd, *J* = 6.8, 2.4 Hz, 1H), 7.09 (ddd, *J* = 8.0, 5.5, 2.5 Hz, 1H), 7.14 – 7.17 (m, 2H), 7.25 – 7.29 (m, 2H), 7.34 (ddd, *J* = 8.1, 0.9, 0.9 Hz, 1H), 7.39 – 7.44 (m, 2H). **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 30.3, 38.5, 52.1, 111.2, 120.7, 122.1, 122.6, 127.1, 128.7, 129.1, 132.7, 139.0, 141.5, 145.2, 145.8, 193.5. **HRMS** (ESI) calcd. for $C_{18}H_{15}ClNO^+$ ($M+H^+$) 296.08347, found 296.0834.




**2g**

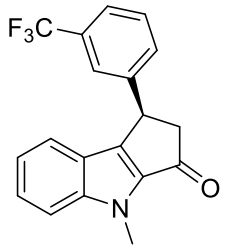
**(*R*)-1-(3-methoxyphenyl)-4-methyl-1,4-dihydrocyclopenta[*b*]indol-3(2*H*)-one (2g):** Prepared according to general procedure C starting from 3-(1-(3-methoxyphenyl)vinyl)-1-methyl-1*H*-indole-2-carbaldehyde **1g** (29.1 mg, 0.100 mmol). The crude product was purified by flash column chromatography (100% hexanes to 90:10 hexanes:EtOAc) to yield **2g** (26.5 g, 0.091 mmol, 91% yield) as a white solid. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) $t_R$ 12.9 min (major); $t_R$ 19.0 min (minor) [Chiracel OD-H (0.46cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/$^i$PrOH, 95:5, 1 mL/min] to be 99% ee. $[\alpha]_D^{23.1}$ = +248.1° (c 1.330, $CHCl_3$). **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 2.78 (dd, *J* = 18.6, 2.4 Hz, 1H), 3.55 (dd, *J* = 18.6, 6.7 Hz, 1H), 3.91 (s, 3H), 3.99 (s, 3H), 4.98 (dd, *J* = 6.7, 2.2 Hz, 1H), 6.81 (ddd, *J* = 8.4, 7.4, 0.9 Hz, 1H), 6.94 (dd, *J* = 8.2, 0.8 Hz, 1H), 6.99 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.11 (ddd, *J* = 8.0, 5.2, 2.8 Hz, 1H), 7.23 (ddd, *J* = 9.2, 8.2, 1.7 Hz, 1H), 7.39 – 7.46 (m, 3H). **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 30.3, 33.1, 51.2, 55.6, 110.5, 111.1, 120.4, 120.7,

122.6, 123.1, 126.8, 127.5, 127.9, 131.1, 139.3, 145.1, 145.8, 157.3, 194.6. **HRMS** (ESI) calcd. for $C_{19}H_{18}NO_2^+$ ($M+H^+$) 292.1332, found 292.1330.



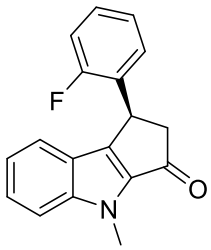

**2h**

**(*R*)-1-(3-fluorophenyl)-4-methyl-1,4-dihydrocyclopenta[*b*]indol-3(2*H*)-one (2h):** Prepared according to general procedure C starting from 3-(1-(3-fluorophenyl)vinyl)-1-methyl-1*H*-indole-2-carbaldehyde **1h** (27.9 mg, 0.100 mmol). The crude product was purified by flash column chromatography (100% hexanes to 90:10 hexanes:EtOAc) to yield **2h** (26.7 mg, 0.096 mmol, 96% yield) as a white solid. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) $t_R$ 10.0 min (minor); $t_R$ 13.9 min (major) [Chiracel OD-H (0.46cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/$^i$PrOH, 95:5, 1 mL/min] to be 99% ee. $[\alpha]_D^{23.1}$ = +109.9° (c 1.110, $CHCl_3$). **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 2.86 (dd, *J* = 18.4, 2.4 Hz, 1H), 3.51 (dd, *J* = 18.4, 6.8 Hz, 1H), 3.98 (s, 3H), 4.64 (dd, *J* = 6.8, 2.3 Hz, 1H), 6.89 – 6.96 (m, 2H), 7.02 (bd, *J* = 7.7 Hz, 1H), 7.10 (ddd, *J* = 8.0, 5.4, 2.6 Hz, 1H), 7.24 – 7.30 (m, 1H), 7.37 (ddd, *J* = 8.0, 0.9, 0.9 Hz, 1H), 7.39 – 7.42 (m, 2H). **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 30.3, 38.8, 52.0, 111.2, 114.0 (d, *J* = 21.0 Hz, 1C), 114.2 (d, *J* = 21.5 Hz, 1C), 120.8, 122.2, 122.7, 123.0 (d, *J* = 2.8 Hz, 1C), 127.1, 130.4 (d, *J* = 8.3 Hz, 1C), 139.0, 145.2, 145.6, 145.7 (d, *J* = 6.8 Hz, 1C), 163.3 (d, *J* = 245 Hz, 1C), 193.4. **$^{19}$F NMR** ($CDCl_3$, 376 MHz) δ -112.7 (m, 1F). **HRMS** (ESI) calcd. for $C_{18}H_{15}FNO^+$ ($M+H^+$) 280.1132, found 280.1130.




**2i**

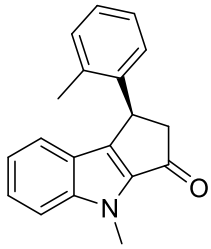
**(*R*)-4-methyl-1-(3-(trifluoromethyl)phenyl)-1,4-dihydrocyclopenta-[*b*]indol-3(2*H*)-one (2i):** Prepared according to general procedure C starting from 1-methyl-3-(1-(3-(trifluoromethyl)phenyl)vinyl)-1*H*-indole-2-carbaldehyde **1i** (32.9 mg, 0.100 mmol). The crude product was purified by flash column chromatography (100% hexanes to 90:10 hexanes:EtOAc) to yield **2i** (28.5 g, 0.087 mmol, 87% yield) as a white solid. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) $t_R$ 9.41 min (minor); $t_R$ 11.2 min (major) [Chiracel OD-H (0.46cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/$^{i}$PrOH, 95:5, 1 mL/min] to be 99% ee. $[\alpha]_D^{23.1}$ = +92.8° (c 1.465, $CHCl_3$). **$^{1}$H NMR** ($CDCl_3$, 400 MHz): δ 2.86 (dd, *J* = 18.4, 2.5 Hz, 1H), 3.54 (dd, *J* = 18.4, 6.8 Hz, 1H), 4.00 (s, 3H), 4.71 (dd, *J* = 6.8, 2.4 Hz, 1H), 7.10 (ddd, *J* = 8.0, 4.8, 3.1 Hz, 1H), 7.32 (ddd, *J* = 8.1, 0.9, 0.9 Hz, 1H), 7.37 – 7.45 (m, 4H), 7.51 – 7.53 (m, 2H). **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 30.4, 38.9, 51.9, 111.3, 120.9, 122.0, 122.8, 124.0 (q, *J* = 3.8 Hz, 1C), 124.2 (q, *J* = 271 Hz, 1C), 124.2 (q, *J* = 3.8 Hz, 1C), 127.2, 129.5, 130.6, 131.3 (q, *J* = 32.0 Hz, 1C), 139.1, 144.1, 145.2, 145.2, 193.2. **$^{19}$F NMR** ($CDCl_3$, 376 MHz) δ -62.5 (s, 3F). **HRMS** (ESI) calcd. for $C_{19}H_{15}F_3NO^+$ ($M+H^+$) 330.1100, found 330.1099.




**2j**

**(*S*)-1-(2-fluorophenyl)-4-methyl-1,4-dihydrocyclopenta[*b*]indol-3(2*H*)-one (2j):** Prepared according to general procedure C starting from 3-(1-(2-fluorophenyl)vinyl)-1-methyl-1*H*-indole-2-carbaldehyde **1j** (27.9 mg, 0.100 mmol). The crude product was purified by flash column chromatography (100% hexanes to 90:10 hexanes:EtOAc) to yield **2j** (21.4 g, 0.077 mmol, 77% yield) as a white solid. The enantiomeric excess was determined by HPLC

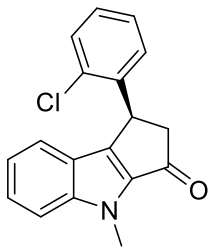
analysis (254 nm, 25 °C) $t_R$ 14.1 min (major); $t_R$ 18.9 min (minor) [Chiracel OJ-H (0.46cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/$^i$PrOH, 95:5, 1 mL/min] to be 98% ee. $[\alpha]_D^{23.0}$ = +179.8° (c 0.990, $CHCl_3$). **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 2.87 (dd, *J* = 18.4, 2.4 Hz, 1H), 3.56 (dd, *J* = 18.4, 7.4 Hz, 1H), 3.99 (s, 3H), 4.95 (dd, *J* = 6.8, 2.3 Hz, 1H), 6.98 – 7.14 (m, 4H), 7.20 – 7.26 (m, 1H), 7.40 – 7.43 (m, 3H). **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 30.3, 32.1 (d, *J* = 3.7 Hz, 1C), 50.8, 111.2, 115.6 (d, *J* = 21.6 Hz, 1C), 120.7, 122.2, 122.8, 124.5 (d, *J* = 3.6 Hz, 1C), 127.0, 128.3 (d, *J* = 4.2 Hz, 1C), 128.5, 128.6, 129.7 (d, *J* = 14.2 Hz, 1C), 139.1, 144.9 (d, *J* = 44.2 Hz, 1C), 161.0 (d, *J* = 245 Hz, 1C), 193.6. **$^{19}$F NMR** ($CDCl_3$, 376 MHz) δ -118.6 (m, 1F). **HRMS** (ESI) calcd. for $C_{18}H_{15}FNO^+$ ($M+H^+$) 280.1132, found 280.1130.




**2k**

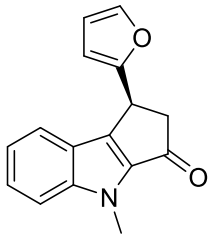
**(*R*)-4-methyl-1-(o-tolyl)-1,4-dihydrocyclopenta[*b*]indol-3(2*H*)-one (2k):** Prepared according to a modified general procedure C starting from 1-methyl-3-(1-(*o*-tolyl)vinyl)-1*H*-indole-2-carbaldehyde **1k** (27.5 mg, 0.100 mmol). The reaction was run at 100°C in 1,4-dioxane. The crude product was purified by flash column chromatography (100% hexanes to 90:10 hexanes:EtOAc) to yield **2k** (26.2 mg, 0.095 mmol, 95% yield) as a white solid. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) $t_R$ 16.2 min (minor); $t_R$ 26.3 min (major) [Chiracel AS-H (0.46cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/$^i$PrOH, 98:2, 1 mL/min] to be 84% ee. $[\alpha]_D^{23.0}$ = +272.9° (c 1.275, $CHCl_3$). **$^1$H NMR** ($CDCl_3$, 600 MHz): δ 2.49 (s, 3H), 2.75 (dd, *J* = 18.2, 2.5 Hz, 1H), 3.54 (dd, *J* = 18.1, 6.7 Hz, 1H), 4.00 (s, 3H), 4.81 (dd, *J* = 6.7, 2.4 Hz, 1H), 6.94 (bd, *J* = 7.7 Hz, 1H), 7.04 (bt, *J* = 7.6 Hz, 1H), 7.11 (ddd, *J* = 8.0, 5.3, 2.6 Hz, 1H), 7.15 (ddd, *J* = 8.5, 7.4, 1.1 Hz, 1H), 7.24 (bd, *J* = 7.5 Hz, 1H), 7.38 (bd, *J* = 8.1 Hz, 1H), 7.41 – 7.45 (m, 2H). **$^{13}$C NMR** ($CDCl_3$, 125 MHz):

δ 19.9, 30.3, 35.9, 51.0, 111.2, 120.6, 122.6, 123.0, 136.47, 126.51, 126.8, 127.0, 130.6, 135.7, 139.3, 140.9, 145.2, 146.0, 193.9. **HRMS** (ESI) calcd. for $C_{19}H_{18}NO^+$ ($M+H^+$) 276.1383, found 276.1381.



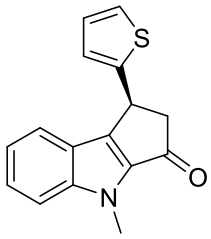

**2l**

**(*S*)-1-(2-chlorophenyl)-4-methyl-1,4-dihydrocyclopenta[*b*]indol-3(2*H*)-one (2l):** Prepared according to a modified general procedure C starting from 3-(1-(2-chlorophenyl)vinyl)-1-methyl-1*H*-indole-2-carbaldehyde **1l** (29.6 mg, 0.100 mmol). The reaction was run at 100°C in 1,4-dioxane. The crude product was purified by flash column chromatography (100% hexanes to 90:10 hexanes:EtOAc) to yield **2l** (27.7 g, 0.094 mmol, 94% yield) as a white solid. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) $t_R$ 9.98 min (minor); $t_R$ 16.6 min (major) [Chiracel AS-H (0.46cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/$^i$PrOH, 95:5, 1 mL/min] to be 87% ee. $[\alpha]_D^{23.0}$ = +243.0° (c 1.465, $CHCl_3$). **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 2.77 (dd, *J* = 18.5, 2.4 Hz, 1H), 3.64 (dd, *J* = 18.6, 6.8 Hz, 1H), 3.99 (s, 3H), 5.07 (dd, *J* = 6.8, 2.4 Hz, 1H), 7.00 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.08 – 7.14 (m, 2H), 7.19 (ddd, *J* = 9.1, 7.5, 1.7 Hz, 1H), 7.41 – 7.46 (m, 4H). **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 30.4, 36.1, 50.8, 111.2, 120.7, 122.5, 122.8, 127.1, 127.3, 128.15, 128.22, 129.8, 133.9, 139.4, 140.3, 144.7, 145.1, 193.6. **HRMS** (ESI) calcd. for $C_{18}H_{15}ClNO^+$ ($M+H^+$) 296.0837, found 296.0834.




**2m**

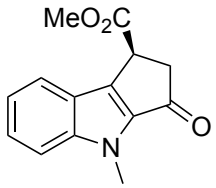
**(*S*)-1-(furan-2-yl)-4-methyl-1,4-dihydrocyclopenta[*b*]indol-3(2*H*)-one (2m):** Prepared according to general procedure C starting from 3-(1-(furan-2-yl)vinyl)-1-methyl-1*H*-indole-2-carbaldehyde **1m** (25.1 mg, 0.100 mmol). The crude product was purified by flash column chromatography (100% hexanes to 90:10 hexanes:EtOAc) to yield **2m** (16.4 mg, 0.065 mmol, 65% yield) as a yellow solid. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) $t_R$ 11.0 min (minor); $t_R$ 12.1 min (major) [Chiracel OD-H (0.46cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/$^i$PrOH, 95:5, 1 mL/min] to be 98% ee. $[\alpha]_D^{22.9}$ = +103.3° (c 0.91, $CHCl_3$). **$^1$H NMR** ($CDCl_3$, 600 MHz): δ 3.09 (dd, *J* = 18.2, 2.3 Hz, 1H), 3.40 (dd, *J* = 18.1, 6.7 Hz, 1H), 3.95 (s, 3H), 4.73 (d, *J* = 6.5 Hz, 1H), 6.08 (d, *J* = 3.1 Hz, 1H), 6.30 (dd, *J* = 1.6, 1.2 Hz, 1H), 7.17 (dd, *J* = 7.9, 7.0 Hz, 1H), 7.36 – 7.44 (m, 3H), 7.68 (d, *J* = 8.0 Hz, 1H). **$^{13}$C NMR** ($CDCl_3$, 150 MHz): δ 30.3, 32.6, 48.2, 105.4, 110.4, 111.2, 120.7, 122.4, 122.9, 127.0, 138.6, 143.0, 143.6, 145.1, 155.4, 193.0. **HRMS** (ESI) calcd. for $C_{16}H_{14}NO_2^+$ ($M+H^+$) 252.1019, found 252.1021.




**2n**

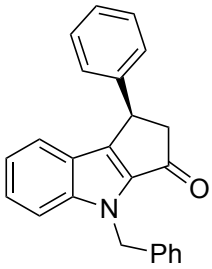
**(*S*)-4-methyl-1-(thiophen-2-yl)-1,4-dihydrocyclopenta[*b*]indol-3(2*H*)-one (2n):** Prepared according to general procedure C starting from 1-methyl-3-(1-(thiophen-2-yl)vinyl)-1*H*-indole-2-carbaldehyde **1n** (26.7 mg, 0.100 mmol). The crude product was purified by flash column chromatography (100% hexanes to 90:10 hexanes:EtOAc) to yield **2n** (18.9 mg, 0.071 mmol, 71% yield) as a pale orange solid. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) $t_R$ 20.0 min (minor); $t_R$ 22.2 min (major) [Chiracel OD-H (0.46cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/$^i$PrOH, 98:2, 1 mL/min] to be 99%

ee. $[\alpha]_D^{22.7}$ = +163.1° (c 0.895, $CHCl_3$). **$^1$H NMR** ($CDCl_3$, 600 MHz): δ 3.01 (dd, *J* = 18.2, 2.3 Hz, 1H), 3.53 (dd, *J* = 18.2, 6.8 Hz, 1H), 3.97 (s, 3H), 4.95 (dd, *J* = 6.5, 1.5 Hz, 1H), 6.92 – 6.94 (m, 2H), 7.13 (ddd, *J* = 7.9, 6.7, 1.5 Hz, 1H), 7.17 (dd, *J* = 5.0, 1.1 Hz, 1H), 7.39 – 7.44 (m, 2H), 7.55 (d, *J* = 8.1 Hz, 1H). **$^{13}$C NMR** ($CDCl_3$, 150 MHz): δ 30.3, 34.2, 52.6, 111.2, 120.7, 122.4, 122.7, 124.1, 124.3, 127.0, 127.1, 138.5, 145.1, 145.4, 146.7, 193.0. **HRMS** (ESI) calcd. for $C_{16}H_{14}NOS^+$ ($M+H^+$) 268.0791, found 268.0794.



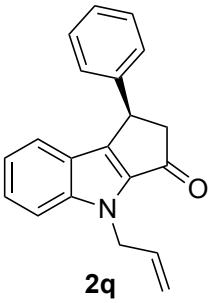

**2o**

**methyl (*S*)-4-methyl-3-oxo-1,2,3,4-tetrahydrocyclopenta[*b*]indole-1-carboxylate (2o):** Prepared according to general procedure C starting from a 2.9:1 mixture of methyl 2-(2-formyl-1-methyl-1*H*-indol-3-yl)acrylate **1o** (0.100 mmol) and 3-bromo-1-methyl-1*H*-indole-2-carbaldehyde. The crude product was purified by flash column chromatography (100% hexanes to 80:20 hexanes:EtOAc) to yield **2o** (21.4 mg, 0.088 mmol, 88% yield) as a white solid. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) $t_R$ 20.9 min (major); $t_R$ 23.2 min (minor) [Chiracel OD-H (0.46cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/$^i$PrOH, 90:10, 1 mL/min] to be 99% ee. $[\alpha]_D^{22.3}$ = +99.5° (c 1.055, $CHCl_3$). **$^1$H NMR** ($CDCl_3$, 600 MHz): δ 3.04 (dd, *J* = 18.4, 6.8 Hz, 1H), 3.42 (dd, *J* = 18.4, 2.3 Hz, 1H), 3.79 (s, 3H), 3.92 (s, 3H), 4.33 (dd, *J* = 6.8, 2.2 Hz, 1H), 7.22 (ddd, *J* = 8.0, 6.9, 1.0 Hz, 1H), 7.37 (d, *J* = 8.5, 1H), 7.43 (ddd, *J* = 8.4, 6.9, 1.1 Hz, 1H), 7.83 (d, *J* = 8.2 Hz, 1H). **$^{13}$C NMR** ($CDCl_3$, 150 MHz): δ 30.2, 38.7, 44.4, 52.6, 111.2, 121.0, 122.4, 122.8, 127.1, 138.3, 140.1, 145.0, 172.3, 192.4. **HRMS** (ESI) calcd. for $C_{14}H_{14}NO_3^+$ ($M+H^+$) 244.0968, found 244.0969.



**2p**

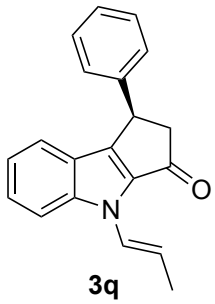
**(*R*)-4-benzyl-1-phenyl-1,4-dihydrocyclopenta[*b*]indol-3(2*H*)-one (2p):** Prepared according to general procedure C starting from 1-benzyl-3-(1-phenylvinyl)-1*H*-indole-2-carbaldehyde **1p** (33.7 mg, 0.100 mmol). The crude product was purified by flash column chromatography (100% hexanes to 90:10 hexanes:EtOAc) to yield **2p** (30.7 mg, 0.091 mmol, 91% yield) as a pale yellow solid. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) $t_R$ 31.2 min (major); $t_R$ 34.3 min (minor) [Chiracel AD-H (0.46cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/$^i$PrOH, 95:5, 0.5 mL/min] to be 99% ee. $[\alpha]_D^{22.8}$ = +61.9° (c 1.550, $CHCl_3$). **$^1$H NMR** ($CDCl_3$, 600 MHz): δ 2.89 (dd, *J* = 18.4, 2.0 Hz, 1H), 3.51 (dd, *J* = 18.4, 6.7 Hz, 1H), 4.65 (dd, *J* = 6.7, 1.9 Hz, 1H), 5.55 (d, *J* = 15.7 Hz, 1H), 5.59 (d, *J* = 15.7 Hz, 1H), 7.02 (t, *J* = 7.1 Hz, 1H), 7.20 – 7.35 (m, 13H). **$^{13}$C NMR** ($CDCl_3$, 150 MHz): δ 39.2, 47.7, 52.3, 112.0, 120.8, 122.4, 123.2, 127.0, 127.1, 127.3, 127.4, 127.8, 128.9, 128.9, 137.4, 138.8, 142.9, 144.6, 147.1, 193.7. **HRMS** (ESI) calcd. for $C_{24}H_{20}NO^+$ ($M+H^+$) 338.1539, found 338.1543.



**2q**

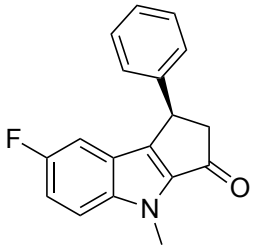
**(*R*)-4-allyl-1-phenyl-1,4-dihydrocyclopenta[*b*]indol-3(2*H*)-one (2q):** Prepared according to general procedure C starting from 1-allyl-3-(1-phenylvinyl)-1*H*-indole-2-carbaldehyde **1q** (28.7 mg, 0.100 mmol). The crude product was purified by flash column chromatography (100% hexanes to 90:10 hexanes:EtOAc) to yield **2q** (19.7 mg, 0.069 mmol, 69% yield) as a pale yellow solid. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) $t_R$ 14.4 min (minor); $t_R$ 15.9 min (major) [Chiracel OD-H (0.46cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/$^i$PrOH, 98:2, 1 mL/min] to be 99% ee. $[\alpha]_D^{22.7}$ = +66.7° (c

1.080, $CHCl_3$). **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 2.90 (dd, *J* = 18.5, 2.4 Hz, 1H), 3.52 (dd, *J* = 18.5, 6.8 Hz, 1H), 4.67 (dd, *J* = 6.8, 2.4 Hz, 1H), 5.03 – 5.05 (m, 2H), 5.10 (ddd, *J* = 17.1, 1.6, 1.2 Hz, 1H), 5.20 (ddd, *J* = 10.3, 1.4, 1.2 Hz, 1H), 6.04 (dddd, *J* = 17.0, 10.5, 5.4, 5.2 Hz, 1H), 7.07 (ddd, *J* = 8.1, 6.2, 1.7 Hz, 1H), 7.21 – 7.41 (m, 8H). **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 39.2, 46.3, 52.2, 111.9, 117.2, 120.7, 122.4, 123.1, 127.96, 126.98, 127.3, 128.9, 133.3, 138.6, 142.9, 144.6, 146.9, 193.6. **HRMS** (ESI) calcd. for $C_{20}H_{18}NO^+$ ($M+H^+$) 288.1383, found 288.1384.



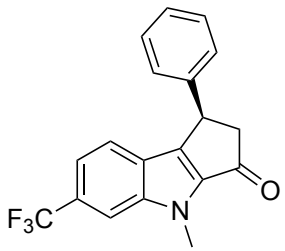
**3q**

**(*R*,*E*)-1-phenyl-4-(prop-1-en-1-yl)-1,4-dihydrocyclopenta[*b*]indol-3(2*H*)-one (3q):** Prepared according to general procedure C starting from 1-allyl-3-(1-phenylvinyl)-1*H*-indole-2-carbaldehyde **1q** (28.7 mg, 0.100 mmol). The crude product was purified by flash column chromatography (100% hexanes to 90:10 hexanes:EtOAc) to yield **3q** (5.8 mg, 0.02 mmol, 20% yield) as a pale yellow solid. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) $t_R$ 12.2 min (minor); $t_R$ 18.8 min (major) [Chiracel OD-H (0.46cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/$^i$PrOH, 98:2, 1 mL/min] to be 99% ee. $[\alpha]_D^{22.6}$ = +10.8° (c 0.37, $CHCl_3$). **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 1.95 (dd, *J* = 6.8, 1.7 Hz, 3H), 2.92 (dd, *J* = 18.4, 2.5 Hz, 1H), 3.54 (dd, *J* = 18.4, 6.8 Hz, 1H), 4.65 (dd, *J* = 6.8, 2.4 Hz, 1H), 6.45 (dq, *J* = 13.6, 6.8 Hz, 1H), 7.06 – 7.12 (m, 2H), 7.21 – 7.27 (m, 3H), 7.29 – 7.33 (m, 3 H), 7.37 – 7.42 (m, 1H), 7.61 (ddd, *J* = 8.6, 0.9, 0.9 Hz, 1H). **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 15.9, 39.2, 52.2, 116.4, 116.7, 121.3, 122.4, 123.0, 123.2, 127.3, 127.5, 128.9, 129.1, 138.2, 142.6, 143.6, 149.3, 192.7. **HRMS** (ESI) calcd. for $C_{20}H_{18}NO^+$ ($M+H^+$) 288.1383, found 288.1385.




**2r**

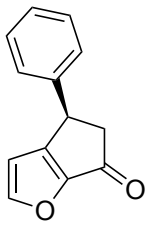
**(*R*)-7-fluoro-4-methyl-1-phenyl-1,4-dihydrocyclopenta[*b*]indol-3(2*H*)-one (2r):** Prepared according to general procedure C starting from 5-fluoro-1-methyl-3-(1-phenylvinyl)-1*H*-indole-2-carbaldehyde **1r** (27.9 mg, 0.100 mmol). The crude product was purified by flash column chromatography (100% hexanes to 90:10 hexanes:EtOAc) to yield **2r** (26.0 mg, 0.093 mmol, 93% yield) as a white solid. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) $t_R$ 14.9 min (minor); $t_R$ 18.4 min (major) [Chiracel OD-H (0.46cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/$^i$PrOH, 95:5, 1 mL/min] to be 99% ee. $[\alpha]_D^{22.6}$ = +103.9° (c 1.425, $CHCl_3$). **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 2.89 (dd, *J* = 18.6, 2.5 Hz, 1H), 3.50 (dd, *J* = 18.6, 6.8 Hz, 1H), 3.97 (s, 3H), 4.61 (dd, *J* = 6.7, 2.3 Hz, 1H), 6.99 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.16 (ddd, *J* = 9.0, 9.0, 2.5 Hz, 1H), 7.17 – 7.27 (m, 3H), 7.29 – 7.35 (m, 3H). **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 30.5, 39.0, 52.2, 106.7 (d, *J* = 23.1 Hz, 1C), 112.1 (d, *J* = 9.4 Hz, 1C), 115.8 (d, 26.8 Hz, 1C), 122.7 (d, *J* = 10.0 Hz, 1C), 127.1, 127.2, 129.0, 140.2, 141.8, 142.6, 145.6 (d, *J* = 5.5 Hz, 1C), 157.9 (d, *J* = 237 Hz, 1C), 194.0. **$^{19}$F NMR** ($CDCl_3$, 376 MHz) δ -122.5 (m, 1F). **HRMS** (ESI) calcd. for $C_{18}H_{15}FNO^+$ ($M+H^+$) 280.1132, found 280.1137.




**2s**

**(*R*)-4-methyl-1-phenyl-6-(trifluoromethyl)-1,4-dihydrocyclopenta[*b*]indol-3(2*H*)-one (2s):** Prepared according to general procedure C starting from 1-methyl-3-(1-phenylvinyl)-6-(trifluoromethyl)-1*H*-indole-2-carbaldehyde **1s** (32.9 mg, 0.100 mmol). The crude product was purified by flash column chromatography (100% hexanes to 90:10 hexanes:EtOAc) to yield **2s** (31.3 g, 0.095 mmol,

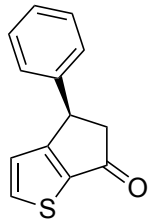
95% yield) as a yellow solid. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) $t_R$ 13.8 min (minor); $t_R$ 16.6 min (major) [Chiracel OD-H (0.46cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/$^i$PrOH, 95:5, 1 mL/min] to be 99% ee. $[\alpha]_D^{22.6}$ = +94.7° (c 1.710, $CHCl_3$). **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 2.92 (dd, *J* = 18.6, 2.4 Hz, 1H), 3.54 (dd, *J* = 18.6, 6.8 Hz, 1H), 4.03 (s, 3H), 4.68 (dd, *J* = 6.8, 2.4 Hz, 1H), 7.19 – 7.34 (m, 6H), 7.45 – 7.47 (m, 1H), 7.69 (m, 1H). **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 30.5, 39.0, 52.2, 108.9 (q, *J* = 4.4 Hz, 1C), 117.1 (q, *J* = 3.4 Hz, 1C), 122.9, 123.3, 126.4, 126.7 (q, *J* = 247 Hz, 1C), 127.2, 128.5 (q, *J* = 31.9 Hz, 1C), 129.1, 141.1, 142.5, 143.9, 145.5, 194.2. **$^{19}$F NMR** ($CDCl_3$, 376 MHz) δ -61.5 (s, 3F). **HRMS** (ESI) calcd. for $C_{19}H_{15}F_3NO^+$ ($M+H^+$) 330.1100, found 330.1104.



**2t**

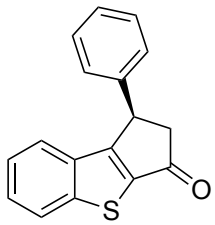
**(*R*)-4-phenyl-4,5-dihydro-6*H*-cyclopenta[*b*]furan-6-one (2t):** Prepared according to modified general procedure C starting from 3-(1-phenylvinyl)furan-2-carbaldehyde **1t** (19.8 mg, 0.100 mmol). The reaction was run at 100°C in 1,4-dioxane. The crude product was purified by flash column chromatography (100% hexanes to 90:10 hexanes:EtOAc) to yield **2t** (14.9 mg, 0.075 mmol, 75% yield) as a pale yellow solid. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) $t_R$ 22.9 min (minor); $t_R$ 25.7 min (major) [Chiracel OD-H (0.46cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/$^i$PrOH, 95:5, 1 mL/min] to be 95% ee. $[\alpha]_D^{22.4}$ = -25.7 ° (c 0.855, MeOH). The absolute configuration of compound **2t** was determined to be (*R*) by comparing the sign of the optical rotation with a literature value.[36] **$^1$H NMR** ($CDCl_3$, 600 MHz): δ 2.83 (dd, *J* = 18.4, 2.8 Hz, 1H), 3.43 (dd, *J* = 18.4, 6.7 Hz, 1H), 4.38 (dd, *J* = 6.6, 1.7 Hz, 1H), 6.45 (d, *J* = 1.4 Hz, 1H), 7.16 (d, *J* = 7.4 Hz, 2H), 7.27 (t, *J* = 7.3 Hz, 1H), 7.33 (t, *J* = 7.4 Hz, 2H), 7.80 (d, *J* = 1.5 Hz, 1H). **$^{13}$C NMR** ($CDCl_3$, 150 MHz): δ 38.0, 51.3, 110.1,

127.1, 127.4, 129.1, 141.6, 154.1, 155.2, 158.6, 187.4. **HRMS** (ESI) calcd. for $C_{13}H_{11}O_2^+$ ($M+H^+$) 199.0754, found 199.0754.



**2u**

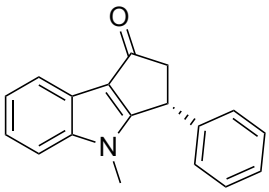
**(*R*)-4-phenyl-4,5-dihydro-6*H*-cyclopenta[*b*]thiophen-6-one (2u):** Prepared according to general procedure C starting from 3-(1-phenylvinyl)thiophene-2-carbaldehyde **1u** (21.4 mg, 0.100 mmol). The crude product was purified by flash column chromatography (100% hexanes to 90:10 hexanes:EtOAc) to yield **2u** (19.3 mg, 0.090 mmol, 90% yield) as a pale yellow solid. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) $t_R$ 12.5 min (minor); $t_R$ 16.2 min (major) [Chiracel OD-H (0.46cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/$^i$PrOH, 95:5, 1 mL/min] to be 99% ee. $[\alpha]_D^{22.5}$ = -44.4 ° (c 1.260, $CHCl_3$). **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 2.92 (dd, *J* = 18.6, 2.8 Hz, 1H), 3.49 (dd, *J* = 18.6, 7.2 Hz, 1H), 4.52 (dd, *J* = 7.2, 2.8 Hz, 1H), 6.89 (d, *J* = 4.8 Hz, 1H), 7.13 – 7.15 (m, 2H), 7.23 – 7.34 (m, 3H), 7.89 (d, *J* = 4.8 Hz, 1H). **$^{13}$C NMR** ($CDCl_3$, 150 MHz): δ 42.7, 51.6, 124.1, 127.3, 127.3, 129.1, 141.0, 141.4, 142.4, 171.2, 196.3. **HRMS** (ESI) calcd. for $C_{13}H_{11}OS^+$ ($M+H^+$) 215.0525, found 215.0527.



**2v**

**(*R*)-1-phenyl-1,2-dihydro-3*H*-benzo[*b*]cyclopenta[*d*]thiophen-3-one (2v):** Prepared according to general procedure C starting from 3-(1-phenylvinyl)benzo[*b*]thiophene-2-carbaldehyde **1v** (26.4 mg, 0.100 mmol). The crude product was purified by flash column chromatography (100% hexanes to 90:10 hexanes:EtOAc) to yield **2v** (24.1 mg, 0.091 mmol, 91% yield) as a white solid. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) $t_R$ 11.4 min (minor); $t_R$ 24.7 min (major) [Chiracel OD-H (0.46cm x 25 cm) (from Daicel Chemical Ind.,

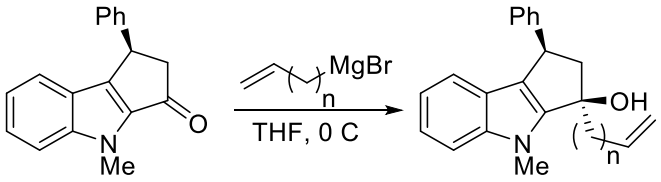
Ltd.) hexane/$^{i}$PrOH, 95:5, 1 mL/min] to be 99% ee. $[\alpha]_D^{22.5}$ = +12.2 ° (c 1.260, $CHCl_3$). **$^{1}$H NMR** ($CDCl_3$, 400 MHz): δ 2.96 (dd, *J* = 18.6, 2.6 Hz, 1H), 3.58 (dd, *J* = 18.6, 7.1 Hz, 1H), 4.73 (dd, *J* = 7.0, 2.6 Hz, 1H), 7.18 – 7.21 (m, 2H), 7.25 – 7.35 (m, 4H), 7.40 – 7.46 (m, 2H), 7.90 (d, *J* = 8.2 Hz, 1H). **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 42.8, 51.2, 124.60, 124.64, 125.2, 127.4, 127.5, 128.2, 129.2, 133.9, 141.59, 141.62, 148.7, 166.4, 197.8. **HRMS** (ESI) calcd. for $C_{17}H_{13}OS^+$ ($M+H^+$) 265.0682, found 265.0685.



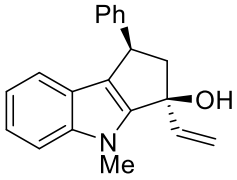

**2w**

**(*S*)-4-methyl-3-phenyl-3,4-dihydrocyclopenta[*b*]indol-1(2*H*)-one (2w):** Prepared according to general procedure C starting from 1-methyl-2-(1-phenylvinyl)-1*H*-indole-3-carbaldehyde **1w** (26.1 mg, 0.100 mmol). The crude product was purified by flash column chromatography (100% hexanes to 80:10 hexanes:EtOAc) to yield **2w** (18.6 mg, 0.0712 mmol, 71% yield) as a white solid. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) $t_R$ 27.1 min (minor); $t_R$ 32.0 min (major) [Chiracel OJ-H (0.46cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/$^{i}$PrOH, 90:10, 1 mL/min] to be 97% ee. $[\alpha]_D^{22.5}$ = -118.6° (c 0.995, $CHCl_3$). **$^{1}$H NMR** ($CDCl_3$, 600 MHz): δ 2.83 (dd, *J* = 17.8, 2.3 Hz, 1H), 3.36 (s, 3H), 3.49 (dd, *J* = 17.8, 7.3 Hz, 1H), 4.53 (dd, *J* = 7.1, 2.0 Hz, 1H), 7.12 (d, *J* = 7.2 Hz, 2H), 7.22 – 7.30 (m, 6H), 7.97 (d, *J* = 7.8 Hz, 1H). **$^{13}$C NMR** ($CDCl_3$, 150 MHz): δ 30.8, 40.3, 52.5, 110.2, 120.3, 121.2, 121.5, 122.7, 123.9, 127.3, 127.7, 129.4, 140.7, 143.4, 168.5, 194.5. **HRMS** (ESI) calcd. for $C_{18}H_{16}NO^+$ ($M+H^+$) 262.1226, found 262.1230.

**Grignard Addition to 2c to Form 4a-b**

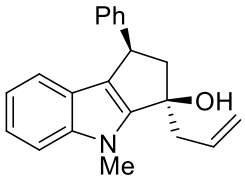



**2c** **4a-b**




**4a**

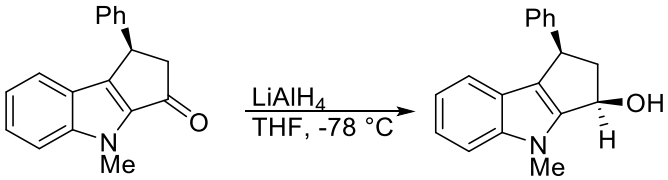
**(1*R*,3*S*)-4-methyl-1-phenyl-3-vinyl-1,2,3,4-tetrahydrocyclopenta-[*b*]indol-3-ol (4a): 2c** (30.5 mg, 0.115 mmol) was dissolved in ether in an oven dried round bottom flask under a $N_2$ environment. The solution was then cooled to 0 °C and a solution of vinylmagnesium bromide in THF (0.17 mL, 0.17 mmol, 1.0 M) was added dropwise. The reaction was warmed to rt and stirred for 1 h. The reaction was quenched with sat. aqueous $NH_4Cl$ and extracted three times with ether. The organic layer was dried with $MgSO_4$ and concentrated down. The crude product was purified by flash column chromatography (80:20 hexanes:EtOAc) to yield **4a** (28.1 mg, 0.097 mmol, 84% yield) as a white solid. The diastereomeric ratio was determined to be 10:1 and the major diastereomer is reported. **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 2.16 (s, 1H), 2.47 (dd, *J* = 13.3, 6.3 Hz, 1H), 3.28 (dd, *J* = 13.3, 7.7 Hz, 1H), 3.76 (s, 3H), 4.39 (dd, *J* = 7.6, 6.4 Hz, 1H), 5.20 (dd, *J* = 10.6, 1.2 Hz, 1H), 5.25 (dd, *J* = 17.2, 1.2 Hz, 1H), 6.20 (dd, *J* = 17.2, 10.6 Hz, 1H), 7.02 (m, 1H), 7.20 – 7.25 (m, 3H), 7.29 – 7.36 (m, 5 H). **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 30.1, 41.8, 58.5, 79.4, 109.9, 113.0, 119.4, 119.9, 121.1, 121.8, 123.4, 126.5, 127.5, 128.7, 140.9, 142.4, 144.8, 145.4. **HRMS** (ESI) calcd. for $C_{20}H_{20}NO^+$ ($M+H^+$) 290.1539, found 290.1538.



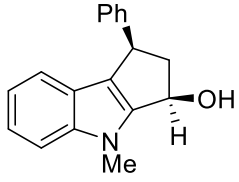
**4b**

**(1*R*,3*R*)-3-allyl-4-methyl-1-phenyl-1,2,3,4-tetrahydrocyclopenta-[*b*]indol-3-ol (4b): 2c** (30.5 mg, 0.115 mmol) was dissolved in ether in an oven dried round bottom flask under a $N_2$ environment. The solution was then cooled to 0 °C and a solution of allylmagnesium bromide in THF (0.09 mL, 0.17 mmol, 2.0 M) was added dropwise. The reaction was warmed to rt and stirred for 1 h. The reaction was quenched with sat. aqueous $NH_4Cl$ and extracted three times with ether. The organic layer was dried with $MgSO_4$ and concentrated down. The crude product was purified by flash column chromatography (80:20 hexanes:EtOAc) to yield **4b** (27.5 mg, 0.091 mmol, 79% yield) as a white solid. The diastereomeric ratio was determined to be 3:1 and the major diastereomer is reported. **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 2.12 (s, 1H), 2.32 (dd, *J* = 12.8, 6.0 Hz, 1H), 2.74 – 2.78 (m, 1H), 3.28 (dd, *J* = 13.2, 7.6 Hz, 1H), 3.87 (s, 3H), 4.30 (dd, *J* = 7.8, 7.8 Hz, 1H), 5.10 – 5.30 (m, 2H), 5.73 – 5.86 (m, 1H), 6.99 – 7.05 (m, 1H), 7.16 – 7.35 (m, 9H). **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 30.6, 42.0, 44.6, 56.6, 78.8, 109.8, 119.4, 119.4, 119.9, 120.8, 121.7, 123.4, 126.4, 127.5, 128.6, 133.2, 142.6, 145.0, 146.4. **HRMS** (ESI) calcd. for $C_{21}H_{22}NO^+$ ($M+H^+$) 304.1696, found 304.1670.

**Reduction of 2c to Form 4c**



**2c** **4c**

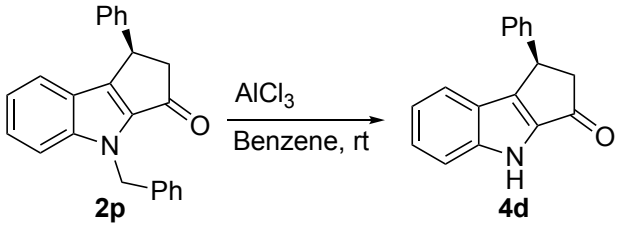


**4c**

**(1*R*,3*R*)-4-methyl-1-phenyl-1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-ol (4c): 2c** (30.5 mg, 0.115 mmol) was dissolved in THF in an oven dried round bottom flask under a $N_2$ environment, cooled to -78 °C and lithium

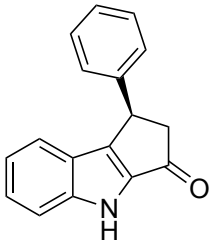
aluminum hydride (10.9 mg, 0.288 mmol) was added. The reaction was allowed to warm to rt and stirred for 3 h. The reaction was quenched with sat. rochelle salt and extracted three times with EtOAc. The organic layer was dried with $MgSO_4$ and concentrated down. The crude product was purified by flash column chromatography (80:20 hexanes:EtOAc) to yield **4c** (28.8 mg, 0.109 mmol, 95% yield) as a white solid. The diastereomeric ratio was determined to be 10:1 and the major diastereomer is reported. **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 1.78 (bs, 1H), 2.21 (ddd, *J* = 13.9, 4.5, 4.4 Hz, 1H), 3.51 (ddd, *J* = 13.8, 7.6, 7.6 Hz, 1H), 3.84 (s, 3H), 4.37 (dd, *J* = 8.1, 5.0 Hz, 1H), 5.38 (dd, *J* = 6.4, 3.9 Hz, 1H), 7.03 (dd, *J* = 7.6, 7.3 Hz, 1H), 7.21 – 7.35 (m, 8H). **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 30.5, 42.4, 51.4, 69.7, 110.0, 119.5, 120.0, 121.6, 121.9, 123.5, 126.4, 127.4, 128.7, 142.5, 145.6, 146.0. **HRMS** (ESI) calcd. for $C_{18}H_{18}NO^+$ ($M+H^+$) 264.1383, found 264.1378.

**Debenzylation of 2p to Form 4d**




**2p**
99% ee

**4d**
83% yield, 98% ee




**4d**

**(*R*)-1-phenyl-1,4-dihydrocyclopenta[*b*]indol-3(2*H*)-one (4d):** A solution of **2p** (30.0 mg, 0.090 mmol) dissolved in benzene (0.15 M) was added to a 1 dram vial containing $AlCl_3$ and stirred for 30 minutes at rt. The reaction was transferred and washed into a round bottom flask with benzene and concentrated down onto silica. The crude product was purified by flash column chromatography (80:20 hexanes:EtOAc) to yield **4d** (18.2 mg, 0.074 mmol, 83% yield) as a

white solid. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) $t_R$ 17.1 min (major); $t_R$ 20.2 min (minor) [Chiracel AD-H (0.46cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/$^i$PrOH, 90:10, 1 mL/min] to be 98% ee. $[\alpha]_D^{22.2}$ = +179.7° (c 0.935, $CHCl_3$). **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 2.97 (dd, *J* = 18.6, 2.3 Hz, 1H), 3.60 (dd, *J* = 18.6, 6.6 Hz, 1H), 4.72 (dd, *J* = 6.6, 2.1 Hz, 1H), 7.09 (ddd, *J* = 7.9, 7.2, 0.7 Hz, 1H), 7.24 – 7.28 (m, 3H), 7.31 – 7.34 (m, 2H), 7.38 – 7.42 (m, 2H), 7.61 (d, *J* = 8.32 Hz, 1H), 10.12 (s, 1H). **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 39.7, 51.9, 114.0, 121.0, 122.1, 123.2, 127.1, 127.3, 127.6, 129.0, 138.9, 142.7, 144.5, 149.1, 194.4. **HRMS** (ESI) calcd. for $C_{17}H_{14}NO^+$ ($M+H^+$) 248.1070, found 248.1073.

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# CHAPTER 3.

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

Modified from a paper published in *Journal of the American Chemical Society*

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

[†]J.A.W. Jr. and K.L.V. contributed equally to this work.

*Department of Chemistry, Iowa State University, Ames, Iowa 50011-3111, United States*

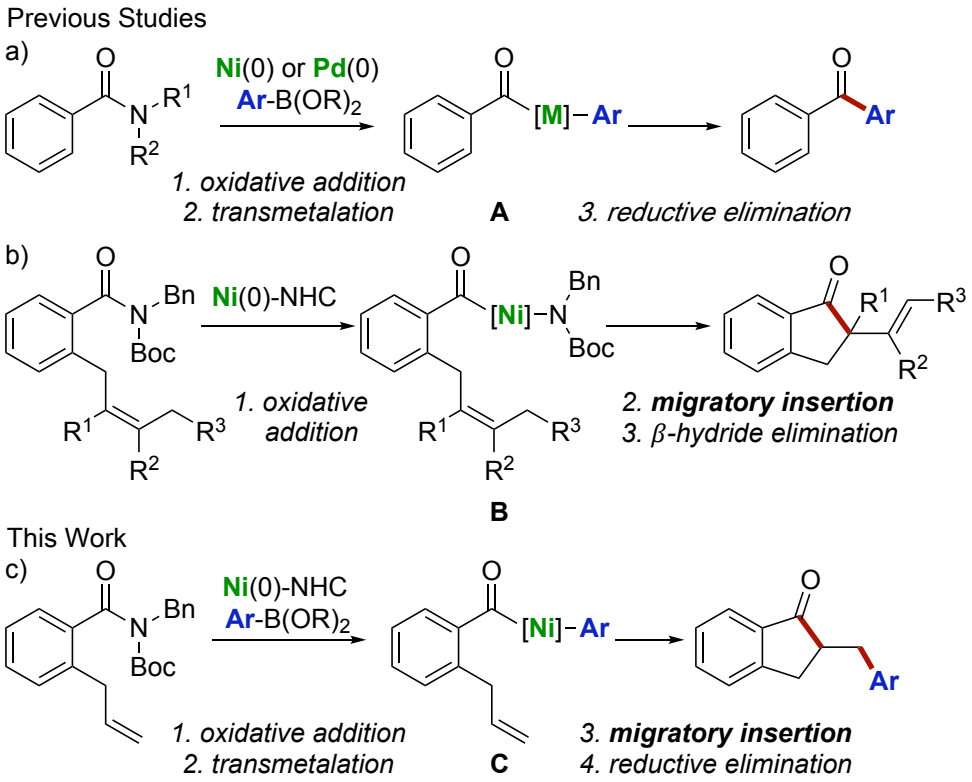
## Abstract

We report Ni-catalyzed formal carboacylation of *ortho*-allylbenzamides with arylboronic acid pinacol esters. The reaction is triggered by oxidative addition of an activated amide C−N bond to a Ni(0) catalyst and proceeds via alkene insertion into a Ni(II)-acyl bond. The *exo*-selective carboacylation reaction generates 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 show that amides are practical substrates for alkene carboacylation via amide C−N bond activation, 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 the formation of two C−C bonds.[1-16] Among the most studied and developed approaches to alkene carboacylation are reactions initiated by activation of a C−C 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[1-5] or a strained cyclic ketone.[6-12] The ability to perform alkene carboacylation reactions on substrates without a strained ketone or a directing group has the potential to expand the utility of these reactions with readily accessible substrates.[13-16,17-21]




**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 acylmetal intermediates with alkenes 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 acyl-Ni(II)-amido intermediate **B** (Scheme 1b).[34] Subsequent β-hydride elimination forms 2-vinylindanones containing a quaternary carbon center.

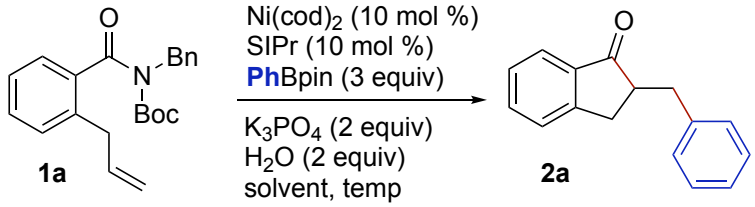
The potential to develop a new class of alkene carboacylation reactions via activation of amide C−N bonds[22-33,35-40] led us to investigate nickel-catalyzed carboacylations of *ortho*-allylbenzamides. We envisioned a process involving activation of the C−N bond of a benzamide via oxidative addition and transmetalation with an arylboron compound to generate acyl-Ni(II)-aryl intermediate **C** (Scheme 1c). Migratory insertion of the tethered alkene and reductive elimination would generate a 2-benzylindanone, 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 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 and 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 equivalents of PhBpin (entry 1). The yield of indanone **2a** increased to 30% when the reaction was run with 3.0 equivalents of PhBpin (entry 3). However, the major product of these reactions was 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 along with the isomerized starting material in 24% yield (entry 7).

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




| entry | temperature (°C) | solvent | conversion (%)[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 | 1,4-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) |

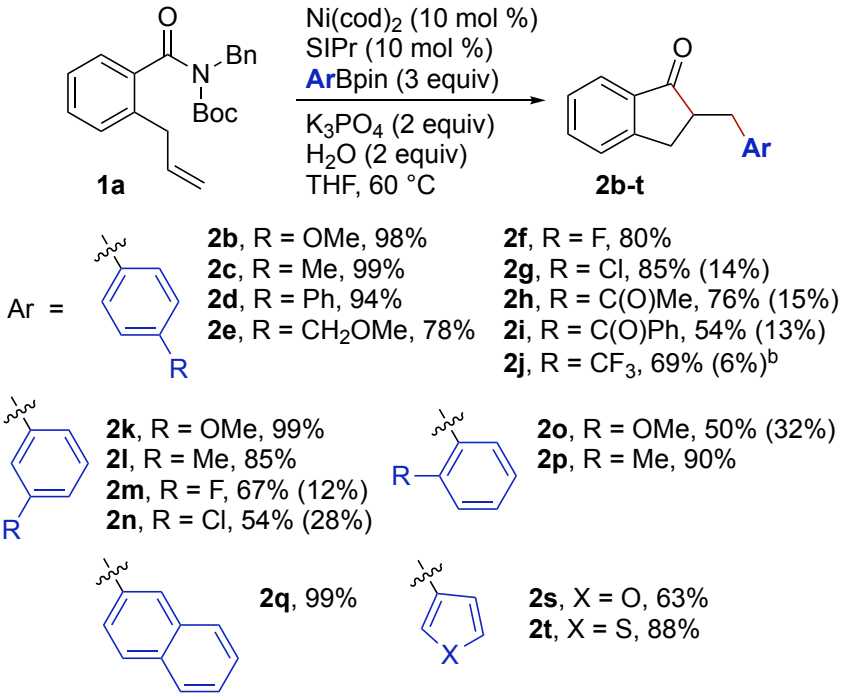
[a]Reaction conditions: **1a** (0.100 mmol), $Ni(cod)_2$ (0.010 mmol), SIPr (0.010 mmol), $K_3PO_4$ (0.200 mmol), $H_2O$ (0.200 mmol), solvent (1.0 M), 12 h. [b]Determined by $^1H$ NMR spectroscopy of the crude reaction mixture using dibromomethane as an internal standard. [c]$^1H$ NMR yields of the alkene isomerization product, *tert*-butyl (benzyl)(2-(prop-1-en-1-

yl)benzoyl)carbamate, are shown in parentheses. [d]PhBpin (1.2 equiv). [e]PhBpin (2 equiv). [f]Isolated yield of **2a**. [g]5 mol % $Ni(cod)_2$ and 5 mol % SIPr. [h]2.5 mol % $Ni(cod)_2$ and 2.5 mol % SIPr. [i]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 the 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** decreased as the number of equivalents of PhBpin was decreased when the reaction was run in THF at 60 °C (compare entry 10 with entries 12 and 13). The model reaction catalyzed with 5 mol % Ni catalyst formed **2a** in 95% yield (entry 14). However, decreasing the catalyst loading to 2.5 mol % led to incomplete conversion and formation of **2a** in only 38% yield (entry 15). The model reaction formed **2a** in 88% yield with 11% isomerization of **1a** when the nickel carbene catalyst was 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). Carboacylation of **1a** with a range of para-substituted, electron-rich ArBpin reagents generated ketones **2b**-**2e** 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%). Carboacylation of **1a** with ArBpin compounds containing electron-donating groups at the meta position formed ketones **2k** and **2l** in 85-99% yield, while meta-halogenated ArBpin compounds reacted with **1a** to form **2m** and **2n** in 54-67% yield. Reactions of **1a** with ArBpin reagents containing electron-donating groups at the *ortho* position 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** and **2s** in 63-88% yield. Reactions of **1a** with arylboronic acids and alkylboronic acid pinacol esters did not occur under our standard reaction conditions.

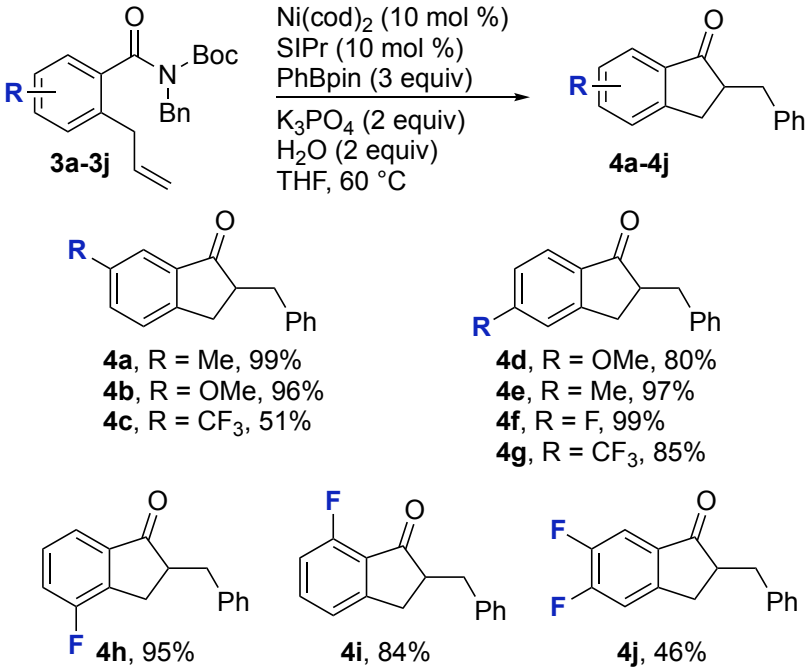



[a]Reaction conditions: **1a** (0.100 mmol), $Ni(cod)_2$ (0.010 mmol), SIPr (0.010 mmol), $K_3PO4$ (0.200 mmol), $H_2O$ (0.200 mmol), ArBPin (0.300 mmol), THF (0.100 mL), 16 h. Yields of **2b-2t** are isolated yields after column chromatography. $^1H$ NMR yields of the alkene isomerization product, *tert*-butyl (benzyl)(2-(prop-1-en-1-yl)benzoyl)carbamate, are shown in parentheses. [b]20 mol % $Ni(cod)_2$, 20 mol % SIPr, and 0.200 mL of THF.

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

With the scope of arylboronic acid pinacol esters established, we sought to evaluate Nickel-catalyzed carboacylations of a variety of substituted *ortho*-allylbenzamides **3a-3j** (Scheme 3). Reactions of PhBpin with **3a-3c** containing electron-donating and electron-

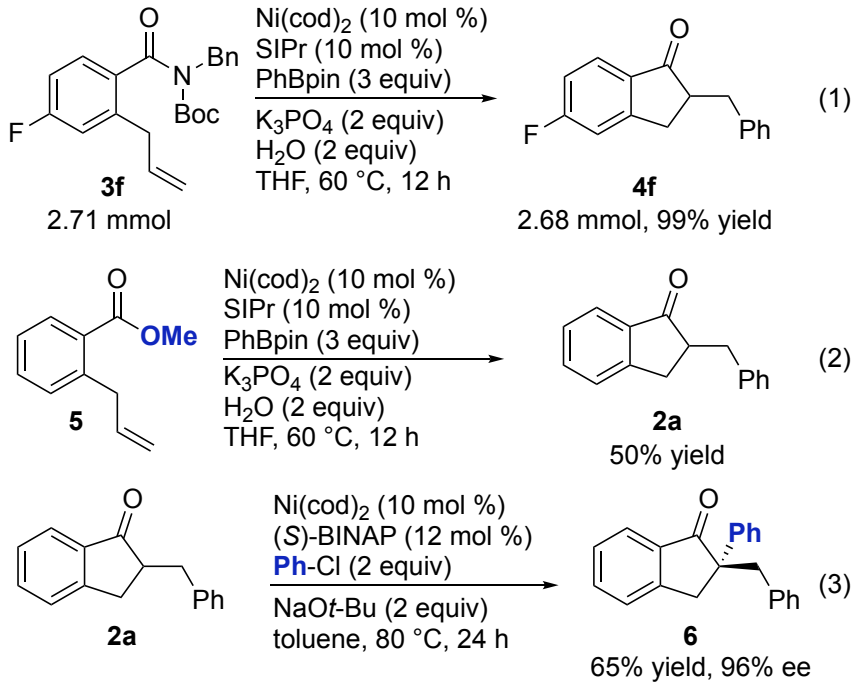
withdrawing groups at the 5-position formed indanones **4a**-**4c** in moderate-to-excellent yields (51-99%). Carboacylations of 4-substituted *ortho*-allylbenzamides containing either electron-donating or electron-withdrawing groups generated ketones **4d**-**4g** in 80-99% yield. Carboacylations of 3- and 6-fluorinated *ortho*-allylbenzamides generated indanones **4h** and **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. Carboacylation of the acyclic 5-hexenamide derivative, *tert*-butyl (benzyl)(hex-5-enoyl)carbamate, with PhBpin to form the corresponding cyclic ketone did not occur.



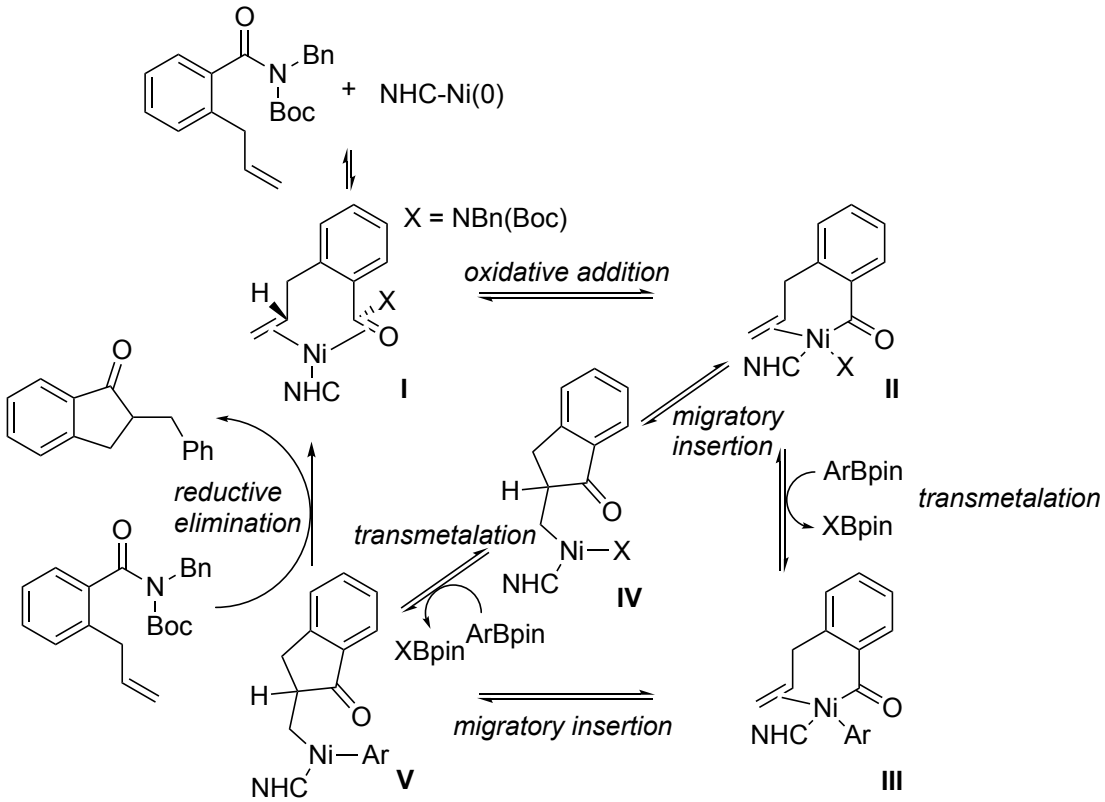

[a]Reaction conditions: **3a**–**3j** (0.100 mmol), $Ni(cod)_2$ (0.010 mmol), SIPr (0.010 mmol), $K_3PO_4$ (0.200 mmol), $H_2O$ (0.200 mmol), PhBpin (0.300 mmol), THF (0.100 mL), 12 h. Yields of **4a**–**4j** are isolated yields after column chromatography.

**Scheme 3.** Carboacylation of Benzamides **3a**–**3j**[a]

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 indanone derivatives 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, 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 with 98% ee (eq 3).

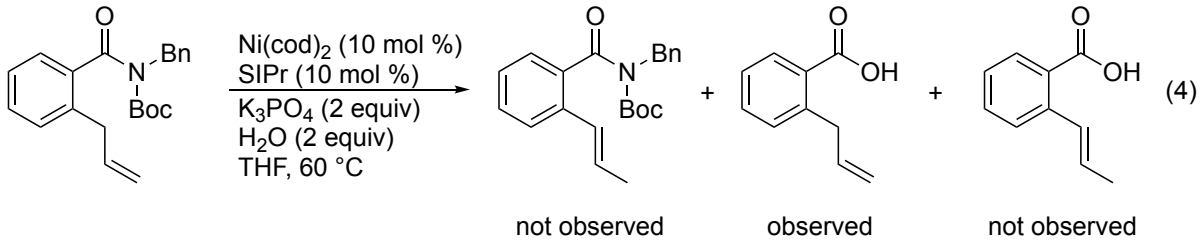


Two potential mechanistic pathways for the carboacylation of **1a** with ArBpin are presented in Scheme 4. After coordination of the NHC-Ni(0) catalyst to **1a** to form complex **I**, oxidative addition of the amide C−N bond to the Ni(0) center is likely to form the acyl-Ni(II)-amido complex **II**. At this stage, the mechanism of the formal carboacylation may diverge depending on the order of the subsequent transmetalation and migratory insertion events. If transmetalation of ArBpin with **II** occurs first, acyl-Ni(II)-aryl complex **III** would be generated. Subsequent migratory insertion of the tethered alkene into the Ni-C(acyl) bond would form alkyl-Ni(II)-aryl complex **V**. Reductive elimination of the indanone product **2a** from **V** and coordination of another molecule of **1a** would close the catalytic cycle. Alternatively, if migratory insertion precedes transmetalation, alkyl-Ni(II)-amido complex **IV** would be formed by insertion of the tethered alkene into the Ni-C(acyl) bond of **II**.[34] Transmetalation of ArBpin with **IV** would form **V** and indanone **2a** upon reductive elimination.




**Scheme 4.** Potential Mechanistic Pathways

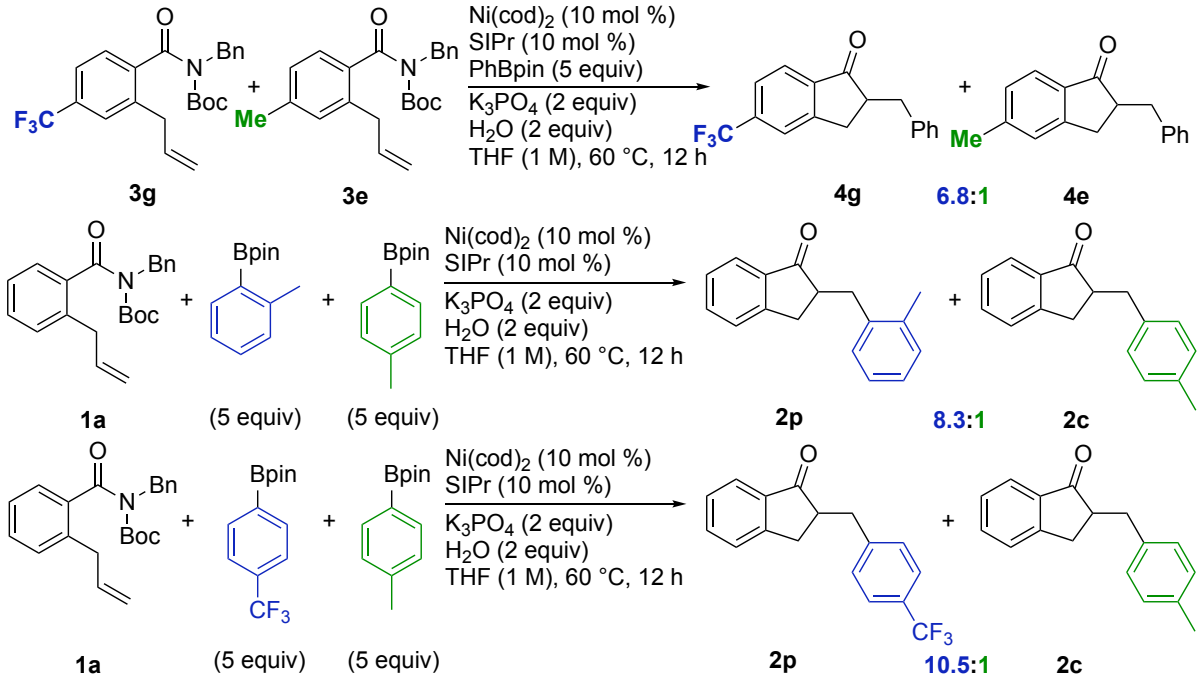
Our working hypothesis is that transmetalation of ArBpin with **II** precedes migratory insertion of the tethered alkene, on the basis of two observations. First, the identity of the ArBpin significantly impacts the amount of alkene isomerization observed under our reaction conditions (see Scheme 2). Second, alkene isomerization is not observed in the absence of ArBpin (eq 4). Taken together, these results are consistent with transmetalation of ArBpin with **II** occurring first to form **III** followed by migratory insertion to generate **V**.




(4)

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)benzamide **3g** and 4-methylbenzamide **3e** formed ketones **4g** and **4e** in a 6.8:1 ratio favoring the trifluoromethyl-substituted ketone **4g**. 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 with the more facile nature of oxidative addition into electron-rich benzamide **3e** versus electron-deficient benzamide **3g** due to the increased amidic resonance that would be expected for **3g** versus **3e**.[50] In addition, this result suggests that the ratio of products observed is not determined by the relative rates of oxidative addition of **3g** and **3e**. Competition experiments between the pinacol ester of 4-tolylboronic acid and the pinacol esters of 2-tolylboronic acid and 4-(trifluoromethyl)phenylboronic acid formed ketones **2p** and **2c** in an 8.3:1 ratio and ketones **2j** and **2c** in a 10.5:1 ratio, respectively. 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 that 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 **4g** and **4e** would be expected from the competition between **3g** and **3e** if reductive elimination were turnover-limiting, we propose that migratory insertion of the alkene into the Ni-C(acyl) bond is the elementary step critical to determining the product ratio.




**Scheme 5.** Competition Experiments

**Conclusion**

In summary, we have developed the first Ni-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 to further leverage the synthetic potential of this transformation and to gain additional mechanistic understanding of the nickel-catalyzed alkene carboacylation reaction are ongoing in our laboratory.

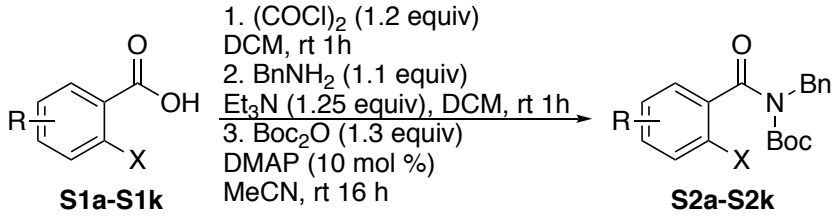
**Experimental**

**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 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* Gold™ 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. HPLC analyses were carried out on a Waters Alliance HPLC system with an e2695 separations module and a 2489 dual wavelength detector. NMR spectra were acquired on Varian MR-400 and Bruker Avance III 600 spectrometers at the Iowa State University Chemical Instrumentation Facility. Chemicals shifts are reported in ppm relative to residual solvent peaks ($CDCl_3$ = 7.26 ppm for $^1H$ and 77.16 ppm for $^{13}C$). Coupling constants are reported in hertz. $^{19}F$ 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:**



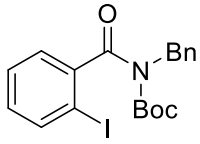

**S1a-S1k** **S2a-S2k**

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

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

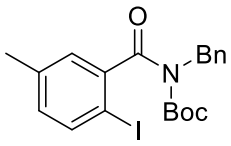
*ortho*-Halobenzamides (**S2a-S2k**) were prepared from the appropriate *ortho*-halobenzoic acid (**S1a-S1k**). To the appropriate *ortho*-halobenzoic acid (**S1a-S1k**) in anhydrous DCM (0.3 M) at 0 °C under $N_2$ was added 2 M oxalyl chloride (1.20 equiv) dropwise and a catalytic amount

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 three times with ethyl acetate. The organic layers were combined, dried over $Na_2SO_4$, filtered, and evaporated under reduced pressure. The resulting crude *ortho*-halobenzamides (**S2a-S2k**) were used directly in the next step without further purification.



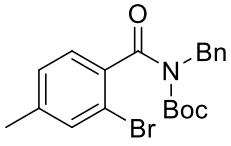
**S2a**

***tert*-butyl benzyl(2-iodobenzoyl)carbamate (S2a):** Prepared according to general procedure A from *ortho*-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.



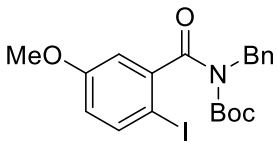

**S2b**

***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**

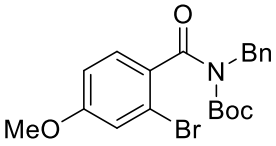
***tert*-butyl benzyl(2-bromo-4-methylbenzoyl)carbamate (S2c):** Prepared according to general procedure A from 2-bromo-4-methylbenzoic acid **S1c** (2.15 g, 10.0 mmol). The reactions afforded crude product **S2c** as a colorless oil in 83% yield (3.36 g, 8.32 mmol). **$^1$H NMR** (400 MHz, $CDCl_3$) 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**

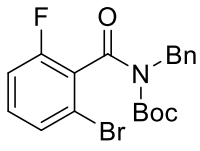
***tert*-butyl benzyl(2-iodo-5-methoxybenzoyl)carbamate (S2d):** Prepared according to general procedure A from 2-iodo-5-methoxybenzoic acid **S1d** (2.78 g, 10.0 mmol). The reactions afforded

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**

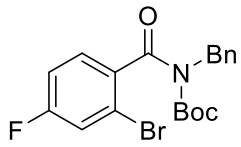
***tert*-butyl benzyl(2-bromo-4-methoxybenzoyl)carbamate (S2e):** Prepared according to general procedure A from 2-bromo-4-methoxybenzoic acid **S1e** (2.31 g, 10.0 mmol). The reactions afforded crude product **S2e** as a yellow oil in 90% yield (3.80 g, 9.00 mmol). **$^1$H NMR** (400 MHz, $CDCl_3$) 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**

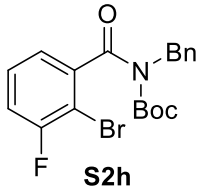
***tert*-butyl benzyl(2-bromo-6-fluorobenzoyl)carbamate (S2f):** Prepared according to general procedure A from 2-bromo-6-fluorobenzoic acid **S1f** (2.19 g, 10.0 mmol). The reactions afforded crude product **S2f** as a white solid in 75% yield (3.05 g, 7.50 mmol). **$^1$H NMR** (400 MHz, $CDCl_3$) δ 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**

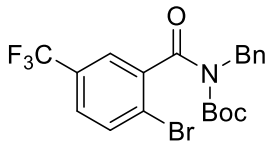
**tert-butyl benzyl(2-bromo-4-fluorobenzoyl)carbamate (S2g):** Prepared according to general procedure A from 2-bromo-4-fluorobenzoic acid **S1g** (2.19 g, 10.0 mmol). The reactions afforded crude product **S2g** as a white solid in 85% yield (3.47 g, 8.50 mmol). **$^1$H NMR** (400 MHz, $CDCl_3$) δ 1.20 (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**

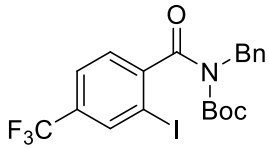
***tert*-butyl benzyl(2-bromo-3-fluorobenzoyl)carbamate (S2h):** Prepared according to general procedure A from 2-bromo-3-fluorobenzoic acid **S1h** (2.19 g, 10.0 mmol). The reactions afforded crude product **S2h** as a white solid in 84% yield (3.43 g, 8.40 mmol). **$^1$H NMR** (400 MHz, $CDCl_3$) δ 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**

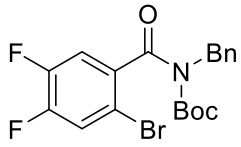
***tert*-butyl benzyl(2-bromo-5-(trifluoromethyl)benzoyl)carbamate (S2i):** Prepared according to general procedure A from 2-bromo-5-(trifluoromethyl)benzoic acid **S1i** (2.69 g, 10.0 mmol). The reactions afforded crude product **S2i** as a white solid in 88% yield (4.03 g, 8.80 mmol). **$^1$H NMR** (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

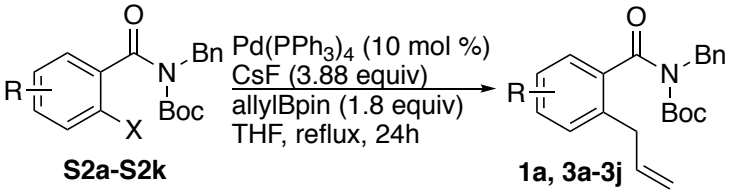
MHz): δ -62.8 (s, 3F). **HRMS** (ESI): Calcd. for $C_{20}H_{20}F_3INO_3^+$ ($[M+H]^+$): 506.0434, Found: 506.0450.




**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**

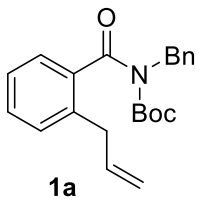



**S2a-S2k** **1a, 3a-3j**

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

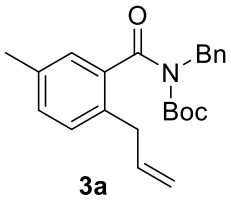
**1a**: R = H
**3a**: R = 5-Me
**3b**: R = 4-Me
**3c**: R = 5-MeO
**3d**: R = 4-MeO
**3e**: R = 6-F
**3f**: R = 4-F
**3g**: R = 3-F
**3h**: R = 5-$CF_3$
**3i**: R = 4-$CF_3$
**3j**: R = 4,5-F

*ortho*-Allylbenzamides (**1a, 3a-j**) were prepared according to the following procedure. A round-bottom flask was charged with 3.00 mmol of *ortho*-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 *ortho*-allylbenzamides **1a, 3a-j**.



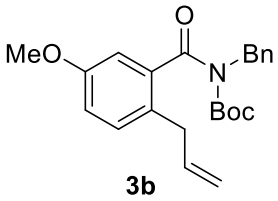
**1a**

***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.



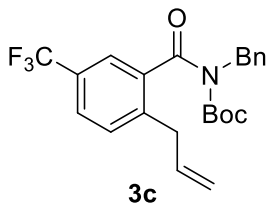
3a

***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.



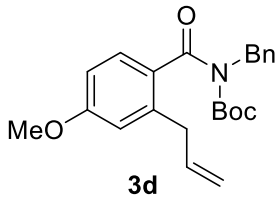
3b

***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**

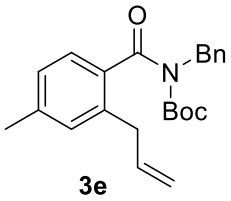
***tert*-butyl (2-allyl-5-(trifluoromethyl)benzoyl)(benzyl)carbamate (3c):** Prepared according to general procedure B from *tert*-butyl benzyl(2-bromo-5-(trifluoromethyl)benzoyl)carbamate **S2i** (1.37 g, 3.00 mmol). The crude reaction mixture was purified by flash column chromatography (100:0 hexanes:EtOAc 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**

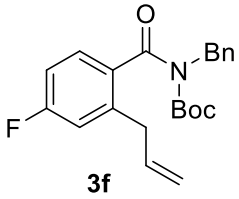
***tert*-butyl benzyl(2-allyl-4-methoxybenzoyl)carbamate (3d):** Prepared according to general procedure B from *tert*-butyl benzyl(2-bromo-4-methoxybenzoyl)carbamate **S2e** (1.26 g, 3.00 mmol). The crude reaction mixture was purified by flash column chromatography (100:0 hexanes:EtOAc to 90:10 hexanes:EtOAc) 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**

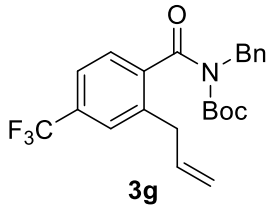
***tert*-butyl (2-allyl-4-methylbenzoyl)(benzyl)carbamate (3e):** Prepared according to general procedure B from *tert*-butyl benzyl(2-bromo-4-methylbenzoyl)carbamate **S2c** (1.21 g, 3.00 mmol). The crude reaction mixture was purified by flash column chromatography (100:0 hexanes:EtOAc to 90:10 hexanes:EtOAc) 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**

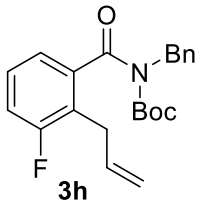
**tert-butyl (2-allyl-4-fluorobenzoyl)(benzyl)carbamate (3f):** Prepared according to general procedure B from *tert*-butyl benzyl(2-bromo-4-fluorobenzoyl)carbamate **S2g** (1.22 g, 3.00 mmol). The crude reaction mixture was purified by flash column chromatography (100:0 hexanes:EtOAc to 90:10 hexanes:EtOAc) 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**

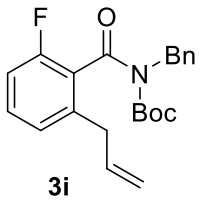
***tert*-butyl (2-allyl-4-(trifluoromethyl)benzoyl)(benzyl)carbamate (3g):** Prepared according to general procedure B from *tert*-butyl benzyl(2-iodo-4-(trifluoromethyl)benzoyl)carbamate **S2j** (1.52 g, 3.00 mmol). The crude reaction mixture was purified by flash column chromatography (100:0 hexnaes:EtOAc 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**

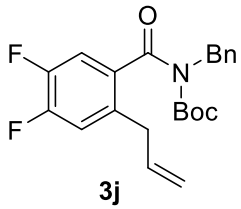
***tert*-butyl (2-allyl-3-fluorobenzoyl)(benzyl)carbamate (3h):** Prepared according to general procedure B from *tert*-butyl benzyl(3-fluoro-2-bromobenzoyl)carbamate **S2h** (1.22 g, 3.00 mmol). The crude reaction mixture was purified by flash column chromatography (100:0

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**

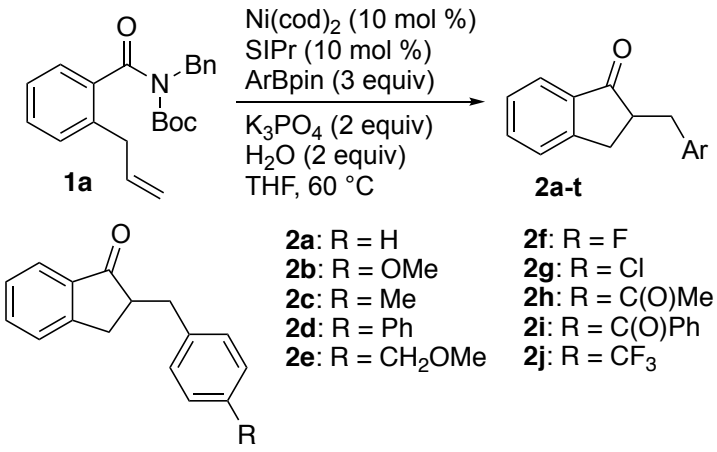
***tert*-butyl (2-allyl-6-fluorobenzoyl)(benzyl)carbamate (3i):** Prepared according to general procedure B from *tert*-butyl benzyl(2-bromo-6-fluorobenzoyl)carbamate **S2f** (1.22 g, 3.00 mmol). The crude reaction mixture was purified by flash column chromatography (100:0 hexanes:EtOAc to 90:10 hexanes:EtOAc) 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**

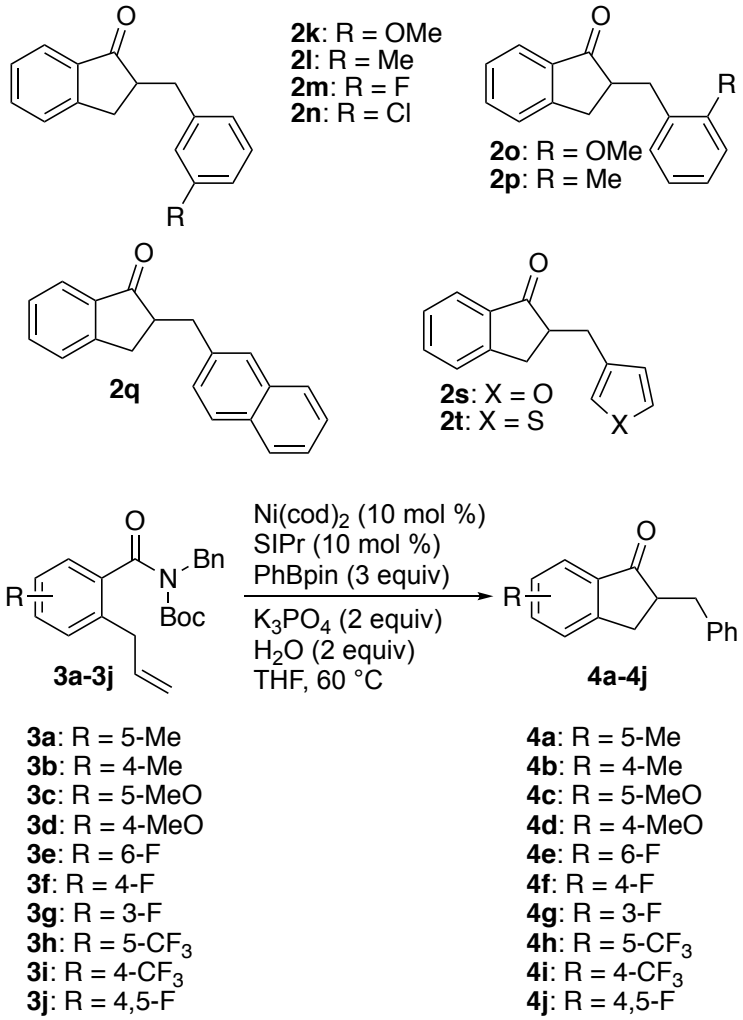
***tert*-butyl (2-allyl-4,5-difluorobenzoyl)(benzyl)carbamate (3j):** Prepared according to general procedure B from *tert*-butyl benzyl(4,5-difluoro-2-bromobenzoyl)carbamate **S2k** (1.28 g, 3.00 mmol). The crude reaction mixture was purified by flash column chromatography (100:0 DCM:EtOAc to 90:10 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**

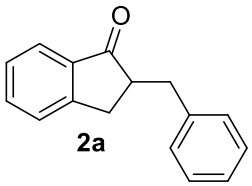


**1a** **2a-t**

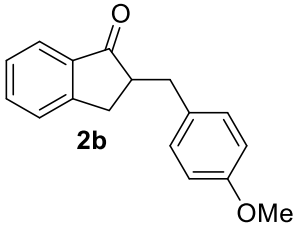
**2a**: R = H
**2b**: R = OMe
**2c**: R = Me
**2d**: R = Ph
**2e**: R = $CH_2OMe$
**2f**: R = F
**2g**: R = Cl
**2h**: R = C(O)Me
**2i**: R = C(O)Ph
**2j**: R = $CF_3$




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.

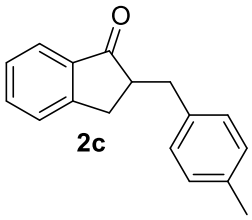



**2-benzyl-2,3-dihydro-1*H*-inden-1-one (2a):** Prepared according to general procedure C from *tert*-butyl (2-allylbenzoyl)(benzyl)carbamate **1a** (35.1 mg, 0.100 mmol) and phenylboronic acid pinacol ester (61.2 mg, 0.300 mmol). The crude reaction mixture was purified by flash column chromatography (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.

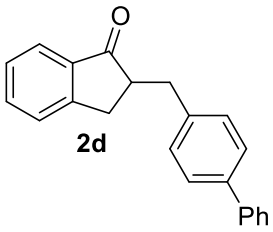



**2-(4-methoxybenzyl)-2,3-dihydro-1*H*-inden-1-one (2b):** Prepared according to general procedure C from *tert*-butyl (2-allylbenzoyl)(benzyl)carbamate **1a** (35.1 mg, 0.100 mmol) and 4-methoxyphenylboronic acid pinacol ester (70.2 mg, 0.300 mmol). The crude reaction mixture was purified by flash column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

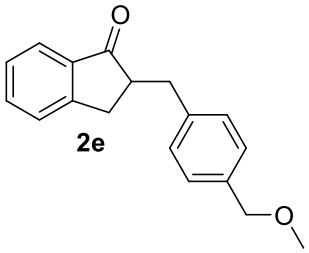



**2-(4-methylbenzyl)-2,3-dihydro-1*H*-inden-1-one (2c):** Prepared according to general procedure C from *tert*-butyl (2-allylbenzoyl)(benzyl)carbamate **1a** (35.1 mg, 0.100 mmol) and 4-tolylboronic acid pinacol ester (65.4 mg, 0.300 mmol). The crude reaction mixture was purified by flash column chromatography (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.

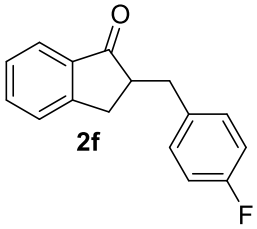



**2-([1,1'-biphenyl]-4-ylmethyl)-2,3-dihydro-1*H*-inden-1-one (2d):** Prepared according to general procedure C from *tert*-butyl (2-allylbenzoyl)(benzyl)carbamate **1a** (35.1 mg, 0.100 mmol) and 4-biphenylboronic acid pinacol ester (84.1 mg, 0.300 mmol). The crude reaction mixture was purified by flash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

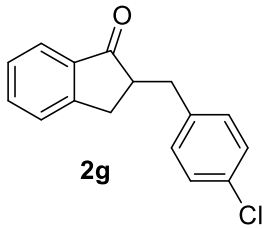



**2-(4-(methoxymethyl)benzyl)-2,3-dihydro-1*H*-inden-1-one (2e):** Prepared according to general procedure C from *tert*-butyl (2-allylbenzoyl)(benzyl)carbamate **1a** (35.1 mg, 0.100 mmol) and 4-(methoxymethyl)phenylboronic acid pinacol ester (74.4 mg, 0.300 mmol). The crude reaction mixture was purified 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.



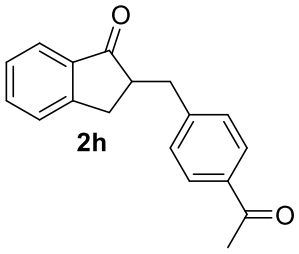

**2-(4-fluorobenzyl)-2,3-dihydro-1*H*-inden-1-one (2f):** Prepared according to general procedure C from *tert*-butyl (2-allylbenzoyl)(benzyl)carbamate **1a** (35.1 mg, 0.100 mmol) and 4-fluorophenylboronic acid pinacol ester (66.7 mg, 0.300 mmol). The

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.

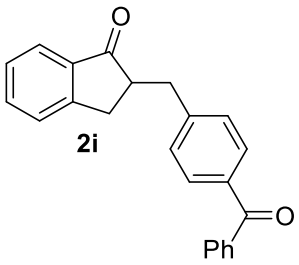


**2g**

**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.

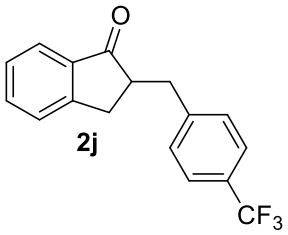



**2-(4-acetylbenzyl)-2,3-dihydro-1*H*-inden-1-one (2h):** Prepared according to general procedure C from *tert*-butyl (2-allylbenzoyl)(benzyl)carbamate **1a** (35.1 mg, 0.100 mmol) and 4-acetylboronic acid pinacol ester (73.8 mg, 0.300 mmol). The crude reaction mixture was purified by flash column chromatography (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.

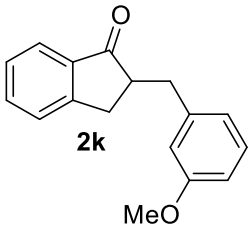



**2-(4-benzoylbenzyl)-2,3-dihydro-1*H*-inden-1-one (2i):** Prepared according to general procedure C from *tert*-butyl (2-allylbenzoyl)(benzyl)carbamate **1a** (35.1 mg, 0.100 mmol) and 4-benzoylphenylboronic acid pinacol ester (92.5 mg, 0.300 mmol). The crude reaction mixture was purified by flash column 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.

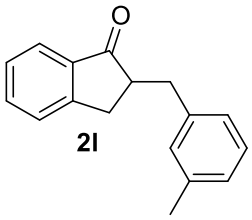



**2-(4-(trifluoromethyl)benzyl)-2,3-dihydro-1*H*-inden-1-one (2j):** Prepared according to general procedure C from *tert*-butyl (2-allylbenzoyl)(benzyl)carbamate **1a** (35.1 mg, 0.100 mmol) and 4-(trifluoromethyl)phenylboronic acid pinacol ester (81.6 mg, 0.300 mmol). The crude reaction mixture was 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.

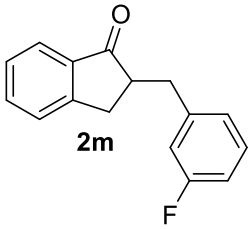



**2-(3-methoxybenzyl)-2,3-dihydro-1*H*-inden-1-one (2k):** Prepared according to general procedure C from *tert*-butyl (2-allylbenzoyl)(benzyl)carbamate **1a** (35.1 mg, 0.100 mmol) and 3-methoxyphenylboronic acid pinacol ester (70.2 mg, 0.300 mmol). The crude reaction mixture was purified by flash column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

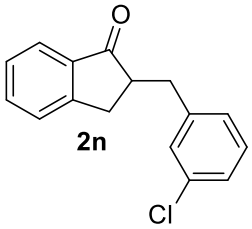



**2-(3-methylbenzyl)-2,3-dihydro-1*H*-inden-1-one (2l):** Prepared according to general procedure C from *tert*-butyl (2-allylbenzoyl)(benzyl)carbamate **1a** (35.1 mg, 0.100 mmol) and 3-tolylboronic acid pinacol ester (65.4 mg, 0.300 mmol). The crude reaction mixture was purified by flash column chromatography (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.

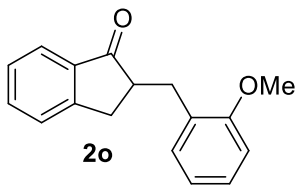



**2-(3-fluorobenzyl)-2,3-dihydro-1*H*-inden-1-one (2m):** Prepared according to general procedure C from *tert*-butyl (2-allylbenzoyl)(benzyl)carbamate **1a** (35.1 mg, 0.100 mmol) and 3-fluorophenylboronic acid pinacol ester (66.7 mg, 0.300 mmol). The

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.

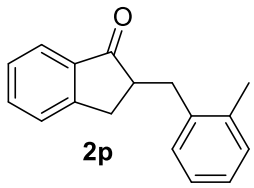



**2-(3-chlorobenzyl)-2,3-dihydro-1*H*-inden-1-one (2n):** Prepared according to general procedure C from *tert*-butyl (2-allylbenzoyl)(benzyl)carbamate **1a** (35.1 mg, 0.100 mmol) and 3-chlorophenylboronic acid pinacol ester (71.6 mg, 0.300 mmol). The crude reaction mixture was purified by flash column 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.



**2o**

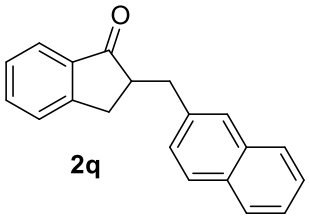
**2-(2-methoxybenzyl)-2,3-dihydro-1*H*-inden-1-one (2o):** Prepared according to general procedure C from *tert*-butyl (2-allylbenzoyl)(benzyl)carbamate **1a** (35.1 mg, 0.100 mmol) and 2-methoxyphenylboronic acid pinacol ester (70.2 mg, 0.300 mmol). The crude reaction mixture was purified by flash column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



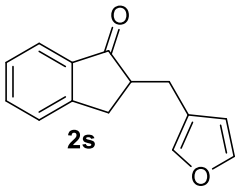
**2p**

**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.

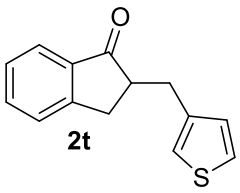



**2-(naphthalen-2-ylmethyl)-2,3-dihydro-1*H*-inden-1-one (2q):** Prepared according to general procedure C from *tert*-butyl (2-allylbenzoyl)(benzyl)carbamate **1a** (35.1 mg, 0.100 mmol) and 2-naphthylboronic acid pinacol ester (76.2 mg, 0.300 mmol). The crude reaction mixture was purified by flash 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.



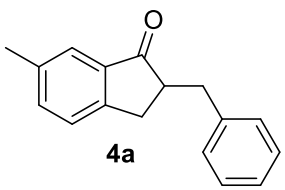

**2-(furan-3-ylmethyl)-2,3-dihydro-1*H*-inden-1-one (2s):** Prepared according to general procedure C from *tert*-butyl (2-allylbenzoyl)(benzyl)carbamate **1a** (35.1 mg, 0.100 mmol) and 3-furanylboronic acid pinacol ester (58.2 mg, 0.300 mmol). The crude reaction mixture was purified by flash column 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.



**2t**

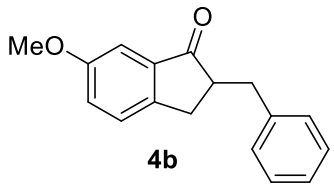
**2-(thiophen-3-ylmethyl)-2,3-dihydro-1*H*-inden-1-one (2t):** Prepared according to general procedure C from *tert*-butyl (2-allylbenzoyl)(benzyl)carbamate **1a** (35.1 mg, 0.100 mmol) and 3-thienylboronic acid pinacol ester (63.0 mg, 0.300 mmol). The crude reaction mixture was purified by flash column 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

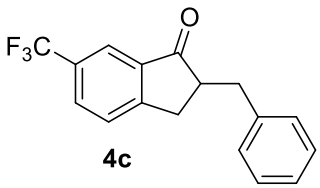
phenylboronic acid pinacol ester (61.2 mg, 0.300 mmol). The crude reaction mixture was purified by flash column chromatography (100:0 hexanes:EtOAc to 90:10 hexanes:EtOAc) to give **4a** as a colorless oil in 92% yield (21.7 mg, 0.092 mmol). **$^1$H NMR** (400 MHz, $CDCl_3$) δ 2.41 (s, 3H), 2.66 (dd, *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**

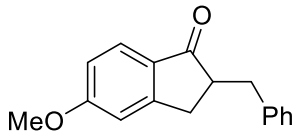
**2-benzyl-6-methoxy-2,3-dihydro-1*H*-inden-1-one (4b):** Prepared according to a modified version of general procedure C from *tert*-butyl (2-allyl-5-methoxy)(benzyl)carbamate **3b** (38.1 mg, 0.100 mmol) and phenylboronic acid pinacol ester (61.2 mg, 0.300 mmol). Upon completion of the reaction, the 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**

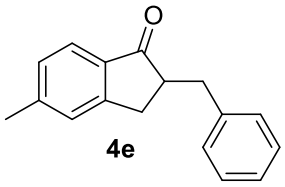
**2-benzyl-6-(trifuoromethyl)-2,3-dihydro-1*H*-inden-1-one (4c):** Prepared according to general procedure C from *tert*-butyl (2-allyl-5-(trifluoromethyl)benzoyl)(benzyl)carbamate **3c** (41.9 mg, 0.100 mmol) and phenylboronic acid pinacol ester (61.2 mg, 0.300 mmol). The crude reaction mixture was 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**

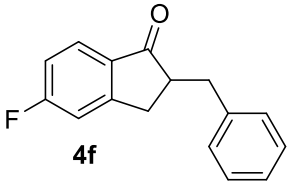
**2-benzyl-5-methoxy-2,3-dihydro-1*H*-inden-1-one (4d):** Prepared according to general procedure C from *tert*-butyl (2-allylbenzoyl)(benzyl)carbamate **3d** (38.1 mg, 0.100 mmol) and phenylboronic acid pinacol ester (61.2 mg, 0.300 mmol). The crude reaction mixture was purified by flash column chromatography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

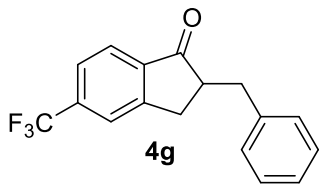
**2-benzyl-5-methyl-2,3-dihydro-1*H*-inden-1-one (4e):** Prepared according to general procedure C from *tert*-butyl (2-allyl-4-methylbenzoyl)(benzyl)carbamate **3e** (36.5 mg, 0.100 mmol) and phenylboronic acid pinacol ester (61.2 mg, 0.300 mmol). The crude reaction mixture was purified by flash column 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**

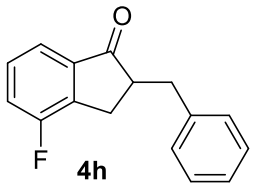
**2-benzyl-5-fluoro-2,3-dihydro-1*H*-inden-1-one (4f):** Prepared according to general procedure C from *tert*-butyl (2-allyl-4-fluorobenzoyl)(benzyl)carbamate **3f** (36.9 mg, 0.100 mmol) and phenylboronic acid pinacol ester (61.2 mg, 0.300 mmol). The crude reaction mixture was purified by flash column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



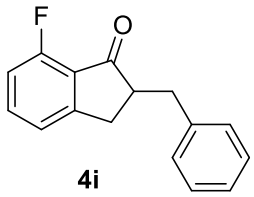
**4g**

**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**

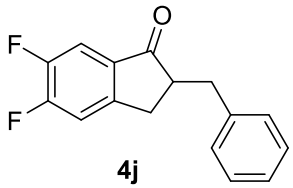
**2-benzyl-4-fluoro-2,3-dihydro-1*H*-inden-1-one (4h):** Prepared according to general procedure C from *tert*-butyl(2-allyl-3-fluorobenzoyl)(benzyl)carbamate **3h** (36.9 mg, 0.100 mmol) and phenylboronic acid pinacol ester (61.2 mg, 0.300 mmol). The crude reaction mixture was purified by flash column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

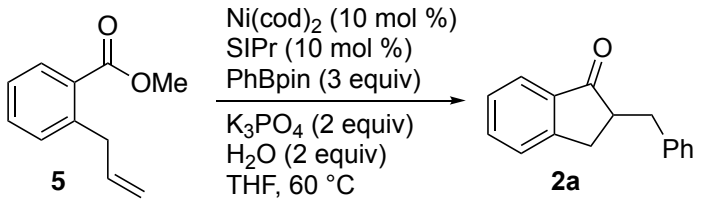
$CDCl_3$) δ 32.2, 37.0, 49.6, 114.4 (d, *J* = 19.2 Hz, 1C), 122.5 (d, *J* = 5.1 Hz, 1C), 124.5 (d, *J* = 13.1 Hz, 1C), 126.6, 128.7, 129.1, 136.7-136.9 (m, 1C), 139.4, 155.8 (d, *J* = 2.0 Hz, 1C), 159.2 (d, *J* = 265.6 Hz, 1C), 204.1 (d, *J* = 1.0 Hz, 1C). **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ -114.4 (m, 1F). **HRMS** (ESI): Calcd. for $C_{16}H_{14}FO^+$ ($[M+H]^+$): 241.1023, Found: 241.1018.



**4j**

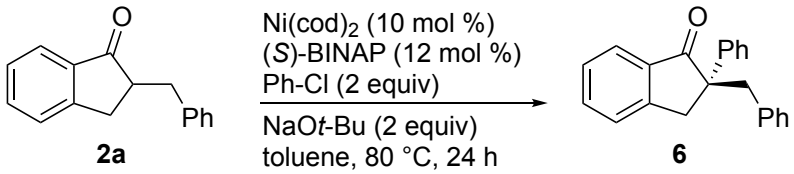
**2-benzyl-5,6-difluoro-2,3-dihydro-1*H*-inden-1-one (4j):** Prepared according to general procedure C from *tert*-butyl(2-allyl-4,5-difluorobenzoyl)(benyl)carbamate **3j** (38.7 mg, 0.100 mmol) and phenylboronic acid pinacol ester (61.2 mg, 0.300 mmol). The crude reaction mixture was purified by flash 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**



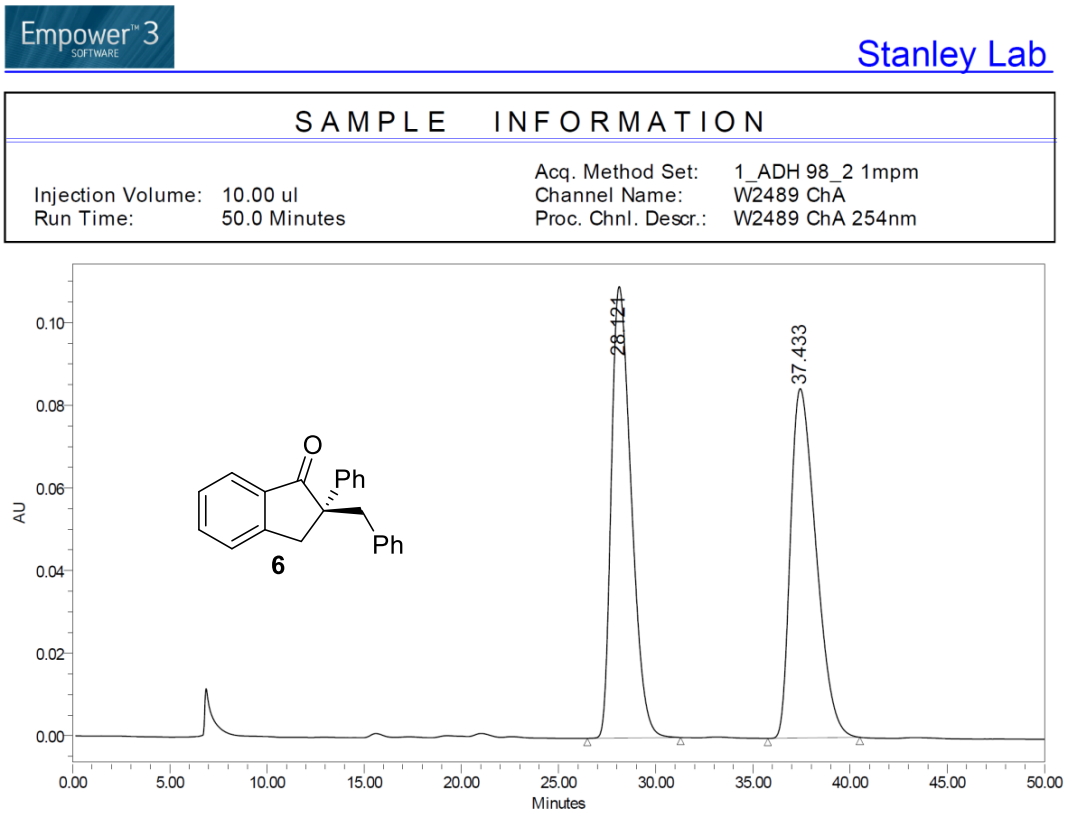

A 1-dram vial was charged with 0.100 mmol of methyl 2-allylbenzoate **5** (17.6 mg, 0.100 mmol), $Ni(cod)_2$ (2.8 mg, 0.010 mmol), SIPr (3.9 mg, 0.010 mmol), $K_3PO_4$ (42.5 mg, 0.200 mmol), $H_2O$ (3.6 μL, 0.20 mmol), phenylboronic acid pinacol ester (61.2 mg, 0.300 mmol), and THF (0.100 mL). The resulting 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 96% ee. NMR data are consistent with known literature values.[48]

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|---|---|---|---|---|---|
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| 2 | 37.433 | 7700176 | 49.72 | 84584 | bb |

Empower™ 3 SOFTWARE

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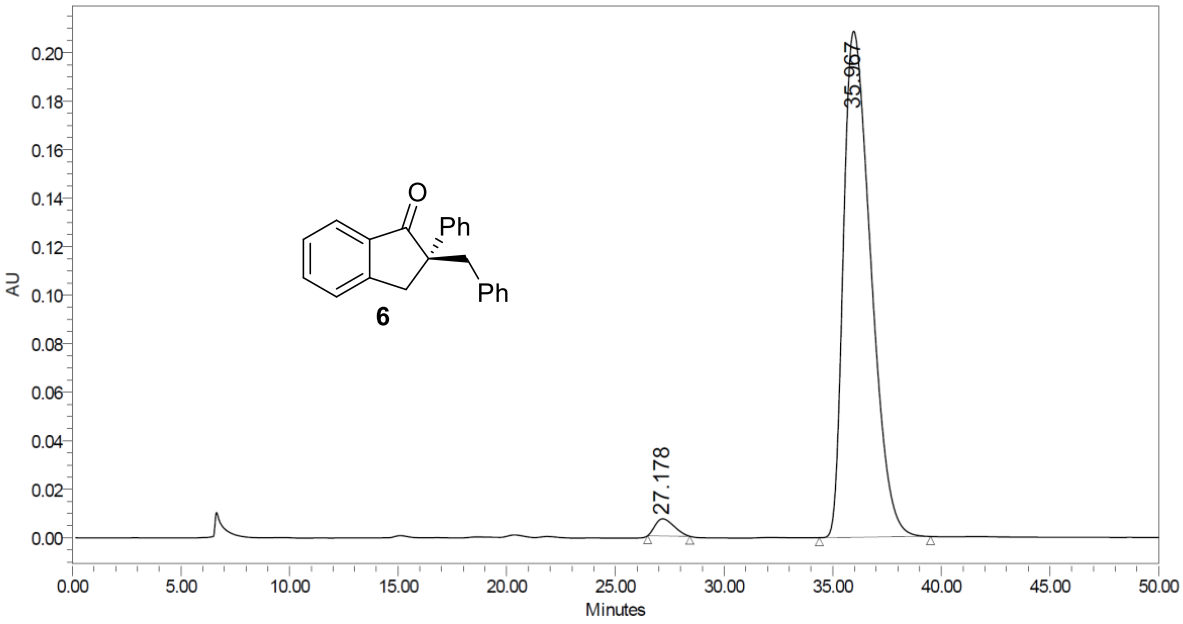
SAMPLE INFORMATION

| | | | |
|---|---|---|---|
| Injection Volume: | 10.00 ul | Acq. Method Set: | 1_ADH 98_2 1mpm |
| Run Time: | 50.0 Minutes | Channel Name: | W2489 ChA |
| | | Proc. Chnl. Descr.: | W2489 ChA 254nm |

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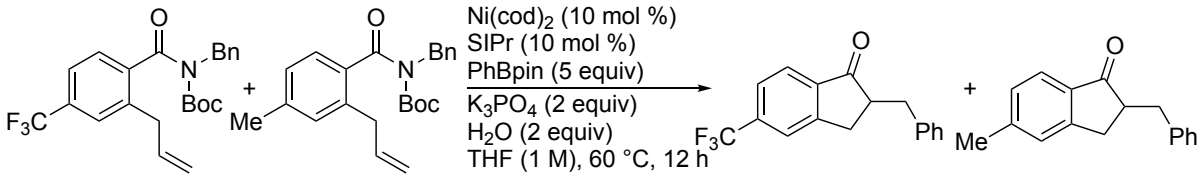
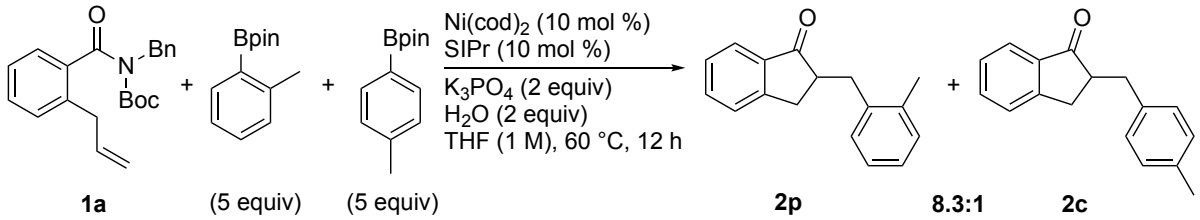
| 2 | 35.967 | 18255606 | 97.75 | 208617 | bb |

**Experimental Procedures for Competition Experiments:**

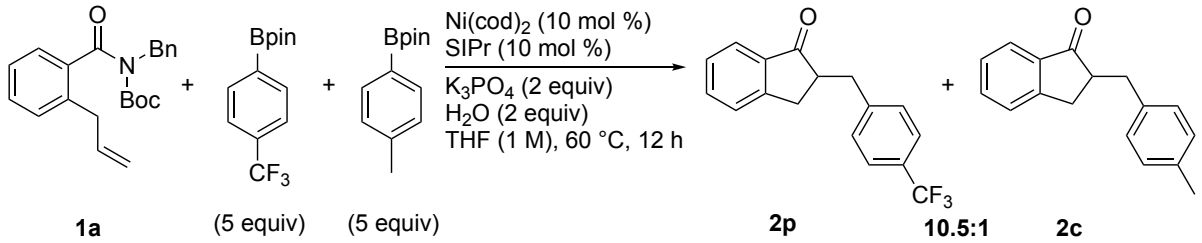



A competition experiment generating 2-benzyl-2,3-dihydro-1*H*-inden-1-ones **4b** and **4k** was carried out by the following procedure. A 1-dram vial was charged with *o*-allylbenzamides **3b**

(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 4.

# PALLADIUM-CATALYZED ALKENE CARBOACYLATION VIA ACTIVATION OF ESTER C−O BONDS

Modified from a manuscript in preparation

Kevin L. Vickerman, Haley K. Banovetz, and Levi M. Stanley

*Department of Chemistry, Iowa State University, Ames, Iowa 50011-3111, United States*

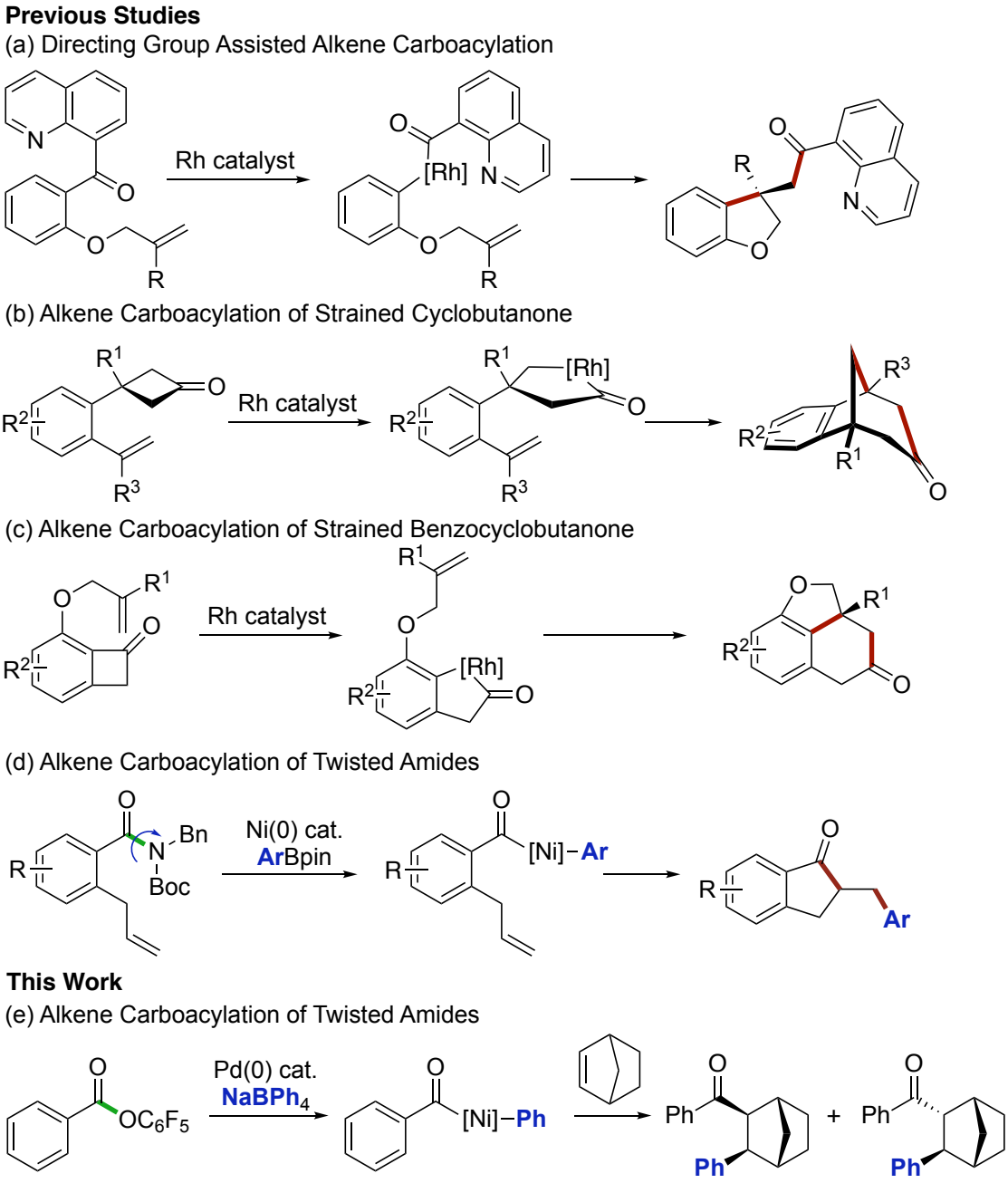
**Abstract**

We report palladium-catalyzed formal intermolecular carboacylation of norbornene with aryl benzoates and sodium tetraarylborates. The reaction is triggered by oxidative addition of an activated ester C−O bond to a Pd(0) catalyst. The three-component intermolecular carboacylation reaction generates phenyl(3-phenylbicyclo[2.2.1]heptan-2-yl)methanones in up to 99% yield with 1:1 diastereomeric ratio and in moderate-to-high enantiomeric excess from a variety of aryl benzoate esters and sodium tetraarylborates. The *cis*-carboacylation diastereomer can be converted to the *trans*-diastereomer in high yields with >20:1 dr under mild conditions. These results show that esters are practical substrates for enantioselective, intermolecular alkene carboacylation via ester C−O bond activation. This represents the first enantioselective, intermolecular carboacylation of esters, and bypasses the challenges associated with alkene carboacylation reactions triggered by C−C and C−N bond activation.

**Introduction**

Intermolecular and intramolecular alkene carbocylation in the presence of a transition-metal catalyst through the formation of two new C-C bonds is an emerging alkene difunctionalization reaction.[1-16] Alkene carboacylation reactions initiated by activation of a C−C bond of a ketone is the most common and established approach. While much progress has been made to demonstrate the utility of these carboacylation reactions, the development of these reactions is limited by the requirement for substrates to contain either a quinoline directing group[1-5] or a strained cyclic ketone (Scheme 1a-c).[6-12] The ability to perform alkene carboacylation reactions on additional classes of substrates has the potential to expand the utility of these reactions.[13-16,17-21]

Recently, studies by a number of groups have demonstrated Suzuki-Miyaura coupling of benzamides with arylboron compounds to generate a variety of aromatic ketones that occur through C−N bond activation.[22-33] Similar approaches have recently been reported utilizing aryl benzoates as suitable substrates for cross-coupling triggered via C−O bond activation.[34-40] Recently, we have reported formal intramolecular nickel-catalyzed carboacylation of *ortho*-allylbenzamides with PhBpin. Our approach demonstrated that the acyl-metal-aryl intermediate generated from oxidative addition into a carbon-heteroatom bond of an amide followed by transmetalation of an organometallic nucleophile can be intercepted by an alkene (Scheme 1d). The ability to intercept these acylmetal intermediates from C−X bond activation of carboxylic acid derivatives with alkenes offers the potential to expand alkene carboacylation beyond the current limitations of strained cyclic ketones, directing groups, or twisted amide substrates.




**Scheme 1.** Synthesis of Ketones via Transition-Metal Catalyzed Alkene Carboacylation

The potential to develop a new class of asymmetric, intermolecular alkene carboacylation reactions via activation of ester C−O bonds led us to investigate palladium-catalyzed carboacylations of aryl benzoates. We envisioned a process involving activation of the C−O bond of an ester via oxidative addition and transmetalation with an arylboron

nucleophile to generate acyl-Pd(II)-aryl intermediate (Scheme 1e). Migratory insertion of an alkene and reductive elimination would generate ketones, the product of a formal intermolecular alkene carboacylation reaction. The proposed formal carboacylation reactions involve difunctionalization of an alkene with the formation of two C−C σ bonds in an intermolecular and asymmetric fashion. We now report the first palladium-catalyzed asymmetric, intermolecular alkene carboacylations triggered by C−O bond activation of aryl benzoates to form phenyl(3-phenylbicyclo[2.2.1]heptan-2-yl)methanones in high yield and enantioselectivity.

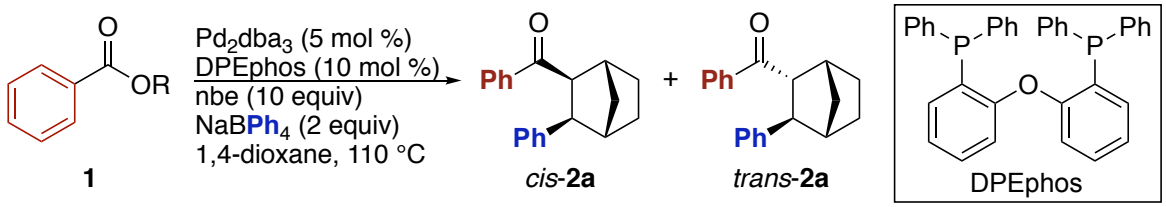
**Results and Discussion**

To identify reaction conditions for the palladium-catalyzed intermolecular carboacylation of aryl benzoates and alkenes, we first evaluated the identity of the aryl and alkyl benzoates, norbornene (nbe), and sodium tetraphenylborate ($NaBPh_4$) in the presence of a catalyst generated from tris(dibenzylideneacetone)dipalladium(0) and DPEphos (Table 1). Alkyl and simple aryl benzoates did not generate any of the desired carboacylation product (entries 1-5). When the reaction was run with pentafluorophenyl benzoate ($Ph(CO)OC_6F_5$) **1a**, norbornene, and sodium tetraphenylborate in the presence of the same catalyst the carboacylation product phenyl((1*R*,2*S*,3*R*,4*S*)-3-phenylbicyclo[2.2.1]heptan-2-yl)methanone *cis*-**2a** and epimerized product phenyl((1*R*,2*R*,3*R*,4*S*)-3-phenylbicyclo[2.2.1]heptan-2-yl)methanone *trans*-**2a** were formed in 54% yield with a 1.25:1 (*cis*:*trans*) diastereomeric ratio (entry 6).

With initial reactivity established using penatafluorophenyl benzoate **1a** to generate the desired ketone product **2a** in moderate yield, we next evaluated a variety of palladium precatalysts with DPEphos (Table 2). When the reaction of **1a**, nbe, and $NaBPh_4$ was conducted in the presence of palladium(II) precatalysts the conversion and yield of the model

reaction increased (entries 2-4). The yield of **2a** increased to 84% when the reaction was run in the presence of a catalyst generated from $[Pd(allyl)Cl]_2$ and DPEphos (entry 2). Similar diastereomeric ratios of **2a** were generated with each palladium precatalyst. With high yields of **2a** (84%) generated in the presence of an achiral DPEphos, we shifted our focus to evaluate chiral, non-racemic ligands.

**Table 1.** Identification of Reaction Conditions for Palladium-Catalyzed Intermolecular Carboacylation of **1** with nbe and $NaBPh_4$[a]



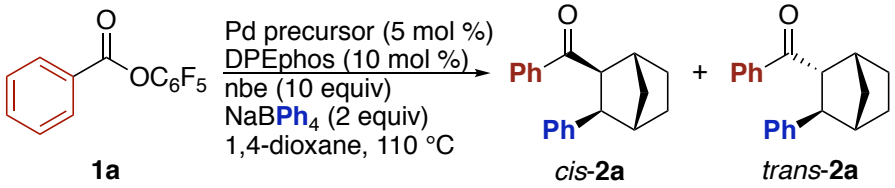

**1**

R = Me, $CH_2CF_3$, Bn, Ph

| entry | R | conversion (%) | yield **2a** (%)[b] | dr (*cis*:*trans*)[b] |
|---|---|---|---|---|
| 1 | Me | 0 | 0 | 0 |
| 2 | Bn | 0 | 0 | 0 |
| 3 | Ph | 0 | 0 | 0 |
| 4 | 2-F-$C_6F_5$ | 0 | 0 | 0 |
| 5 | 4-$CF_3$-$C_6H_4$ | 0 | 0 | 0 |
| 6 | $C_6F_5$ | 55 | 54 | 1.25:1 |

[a]Reaction conditions: **1** (0.100 mmol), $Pd_2dba_3$ (0.005 mmol), DPEphos (0.010 mmol), nbe (10 equiv), $NaBPh_4$ (0.200 mmol), solvent (0.33 M), 20 h. [b]Determined by $^1H$ NMR spectroscopy of the crude reaction mixture using dibromomethane as an internal standard.

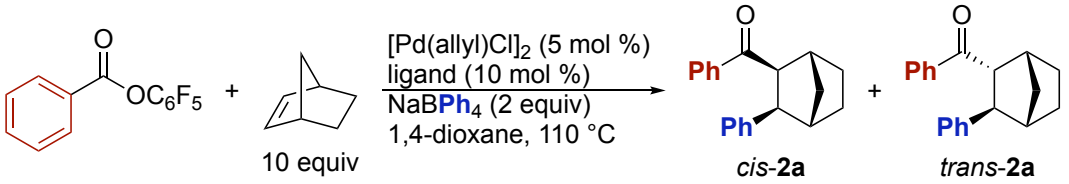
**Table 2.** Investigation of Palladium Precatalysts for Carboacylation of **1a**[a]

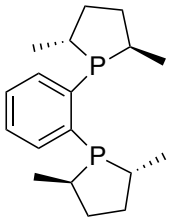



**1a**

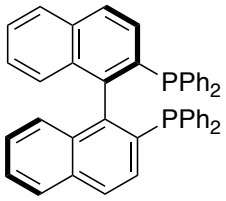
| entry | Pd precursor | conversion (%) | yield **2a** (%)[b] | dr (*cis*:*trans*)[b] |
|---|---|---|---|---|
| 1 | $Pd_2dba_3$ | 55 | 54 | 1.25:1 |
| 2 | $[Pd(allyl)Cl]_2$ | 91 | 84 | 1.27:1 |
| 3 | $[Pd(cinnamyl)Cl]_2$ | 75 | 53 | 1.12:1 |
| 4 | $[Pd(OAc)_2]_3$ | 75 | 71 | 1.37:1 |

[a]Reaction conditions: **1** (0.100 mmol), Pd precursor (0.005 mmol), DPEphos (0.010 mmol), nbe (10 equiv), $NaBPh_4$ (0.200 mmol), solvent (0.33 M), 20 h. [b]Determined by $^1H$ NMR spectroscopy of the crude reaction mixture using dibromomethane as an internal standard.

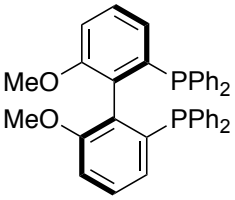


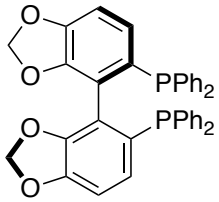
(*R*,*R*)-Me-Duphos
conversion: 99%
**A**: 83% yield, 56% ee
dr (*cis*:*trans*): 0.93:1



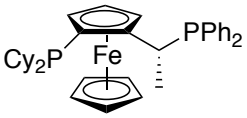
(*R*)-BINAP
conversion: 96%
**A**: 70% yield, 19% ee
dr (*cis*:*trans*): 1.19:1



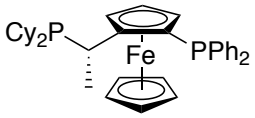
(*R*)-MeO-Biphep
conversion: 99%
**A**: 92% yield, 16% ee
dr (*cis*:*trans*): 1.56:1



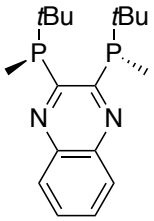
(*R*)-Segphos
conversion: 99%
**A**: 92% yield, 24% ee
dr (*cis*:*trans*): 1.19:1



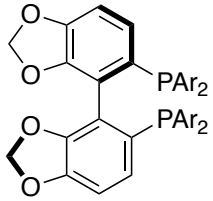
Josiphos SL-J004-1
conversion: 96%
**A**: 82% yield, 46% ee
dr (*cis*:*trans*): 0.90:1



Josiphos SL-J001-2
conversion: 97%
**A**: 83% yield, 58% ee
dr (*cis*:*trans*): 1.02:1



(*R*,*R*)-QuinoxP
conversion: 99%
**A**: 85% yield, 51% ee
dr (*cis*:*trans*): 0.98:1



(*R*)-DTBM-Segphos
Ar = 3,5-*t*Bu-4-MeO-$C_6H_2$
conversion: 99%
**A**: 99% yield, 49% ee
dr (*cis*:*trans*): 0.98:1

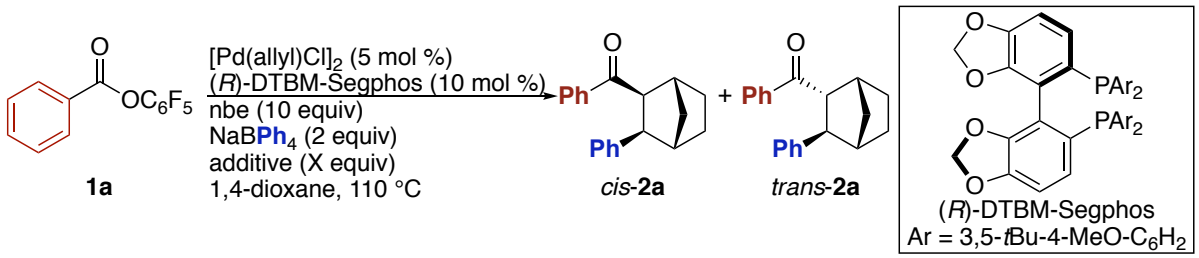
[a]Reaction conditions: **1a** (0.100 mmol), $[Pd(allyl)Cl]_2$ (0.005 mmol), ligand (0.010 mmol), nbe (10 equiv), $NaBPh_4$ (0.200 mmol), solvent (0.33 M), 20 h. Yields and dr determined by $^1H$ NMR spectroscopy of the crude reaction mixture using dibromomethane as an internal standard. Enantioselectivity determined by chiral HPLC analysis of isolated compounds.

**Scheme 2.** Identification of Asymmetric, Intermolecular Alkene Carboacylation of Esters Triggered by C-O Bond Activation[a]

A wide array of chiral, non-racemic bisphosphine ligands, monophosphine, phosphoramidite, and NHC ligands were examined under the carboacylation reaction conditions for ester C−O bond activation. Ligands that generated **2a** in moderate-to-high yields and moderate enantioselectivites are shown in Scheme 2. When the model reaction was run with catalysts generated from $[Pd(allyl)Cl]_2$ and (*R*)-BINAP, (*R*)-Segphos or (*R*)-MeO-Biphep, **2a** was generated in 96-99% yield with only 16-24% ee. When the reaction was run with (*R*)-DTBM-Segphos as the ligand ketone **2a** was formed in 99% yield with 49% ee. Similar yields

(96-99%) and enantioselectivities (46-58%) of **2a** were observed when (*R*,*R*)-MeDuphos, Josiphos SL-J004-1, Josiphos SL-J001-2, and (*R*,*R*)-QuinoxP were used as the ligand. Although these ligands increased the enantiomeric excess of **2a**, the diastereoselectivity for *cis*-**2a**:*trans*-**2a** were typically around 1:1 after the reaction was complete.

**Table 3.** Investigation of Additives for Carboacylation of **1a**[a]



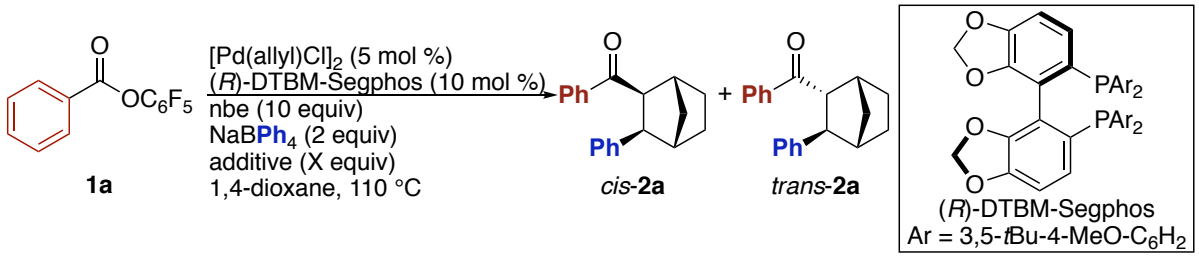

| entry | additive | conv. (%) | yield **2a** (%)[b] | ee **2a** (%)[c] | dr (*cis*:*trans*)[b] |
|---|---|---|---|---|---|
| 1 | none | 99 | 99 | 49 | 0.98:1 |
| 2 | $H_3BO_3$ (2 equiv) | 77 | 78 | 50 | 1:1 |
| 3 | $Mg(OTf)_2$ (0.3 equiv) | 64 | 56 | 79 | 0.75:1 |
| 4 | DIEA | 84 | 63 | 47 | 1.52:1 |

[a]Reaction conditions: **1** (0.100 mmol), Pd precursor (0.005 mmol), DPEphos (0.010 mmol), nbe (10 equiv), $NaBPh_4$ (0.200 mmol), solvent (0.33 M), 20 h. [b]Determined by $^1H$ NMR spectroscopy of the crude reaction mixture using dibromomethane as an internal standard. [c]Enantioselectivity determined by chiral HPLC analysis of isolated compounds.

To investigate the impact of additives on the dr of **2a**, we evaluated boric acid, magnesium(II) triflate, and Hünig's base (diisopropylethyl amine, DIEA) (Table 3). These additives were initially investigated due to their prominence in carbon-nitrogen bond activation of amides. The yield of **2a** decreased by 22-45% when the model reaction was run with an additive (entries 2-4). Combinations of each additive and utilizing all three additives at the same time did not improve the yield or dr. Interestingly, when $Mg(OTf)_2$ was used as an additive in the model reaction the enantiomeric excess of **2a** increased to 79%. The large improvement in enantioselectivity observed with $Mg(OTf)_2$ led us to evaluate a variety of other magnesium salts and metal triflates (Table 4). When the reaction was run in the presence of silver(I), sodium(I), bismuth(III), or samarium(III) triflate, ketone **2a** was generated in similar

yields and dr to the reaction with magnesium(II) triflate without any improvement of the ee (entries 2-5). The reaction of **1a** under the model reaction conditions with calcium(II) triflate generated **2a** in 70% yield with 70% ee (entry 4). When the equivalents of magnesium(II) triflate was increased from 0.1 to 2.0 equiv the ee of **2a** increased from 60 to 95% ee (entries 7-13). We observed the highest combination of yield and enantiomeric excess when **1a** was run with 1 equiv of magnesium(II) triflate, as an additive to generate **2a** in 67% yield and 92% ee.

**Table 4.** Investigation of Additives on the Enantioselective Carboacylation of **1a**[a]

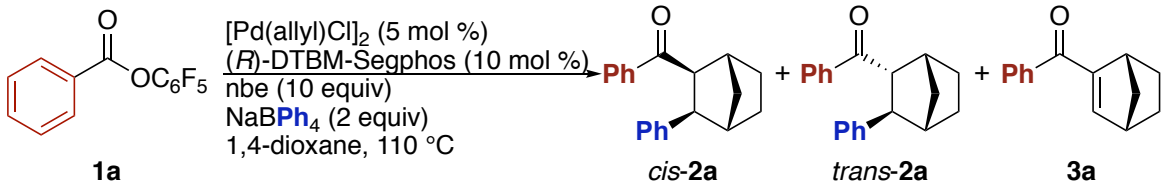



| entry | additive | X equiv | conv. (%) | yield **2a** (%)[b] | ee **2a** (%)[c] | dr (*cis*:*trans*)[b] |
|---|---|---|---|---|---|---|
| 1 | none | - | 99 | 99 | 49 | 0.98:1 |
| 2 | AgOTf | 0.3 | 99 | 95 | 50 | 0.98:1 |
| 3 | NaOTf | 0.3 | 97 | 75 | 51 | 0.94:1 |
| 4 | $Sm(OTf)_3$ | 0.3 | 87 | 57 | 47 | 1.19:1 |
| 5 | $Bi(OTf)_3$ | 0.3 | 75 | 71 | 50 | 0.78:1 |
| 6 | $Ca(OTf)_2$ | 0.3 | 69 | 70 | 70 | 0.79:1 |
| 7 | $Mg(OTf)_2$ | 0.1 | 60 | 51 | 60 | 0.76:1 |
| 8 | $Mg(OTf)_2$ | 0.3 | 67 | 56 | 79 | 0.75:1 |
| 9 | $Mg(OTf)_2$ | 0.5 | 79 | 58 | 85 | 0.81:1 |
| 10 | $Mg(OTf)_2$ | 1 | 78 | 67 | 92 | 0.72:1 |
| 11[d] | $Mg(OTf)_2$ | 1 | 99 | 73 | 82 | 0.46:1 |
| 13 | $Mg(OTf)_2$ | 2 | 72 | 45 | 95 | 0.88:1 |

[a]Reaction conditions: **1** (0.100 mmol), Pd precursor (0.005 mmol), DPEphos (0.010 mmol), nbe (10 equiv), $NaBPh_4$ (0.200 mmol), solvent (0.33 M), 20 h. [b]Determined by $^1H$ NMR spectroscopy of the crude reaction mixture using dibromomethane as an internal standard. [c]Enantioselectivity determined by chiral HPLC analysis of isolated compounds. [d]Reaction run at 120 ºC.

With a catalyst system identified for the intermolecular, asymmetric alkene carboacylation of pentafluorophenyl benzoate, we next investigated the role of each reaction

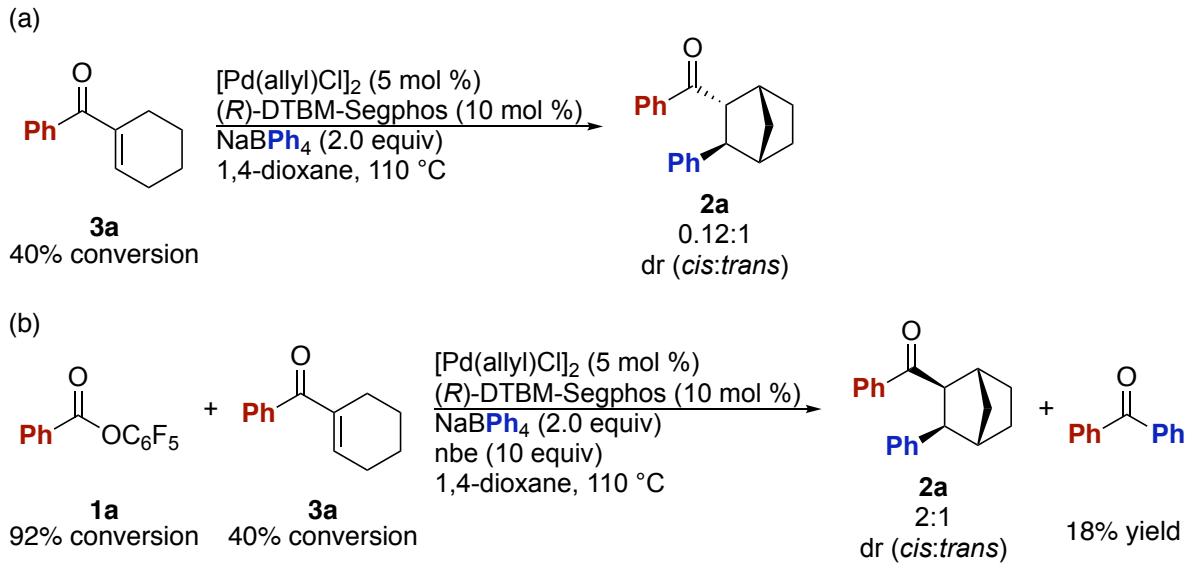
component in the generation of the *cis*-**2a** and *trans*-**2a** diastereomers. We monitored the reaction over time and observed the carboacylation product *cis*-**2a** being epimerized to *trans*-**2a** throughout the entire reaction (Scheme 3). Interestingly, we observed a steady 10-14% of the Heck coupling product **3a** during each time period analyzed.



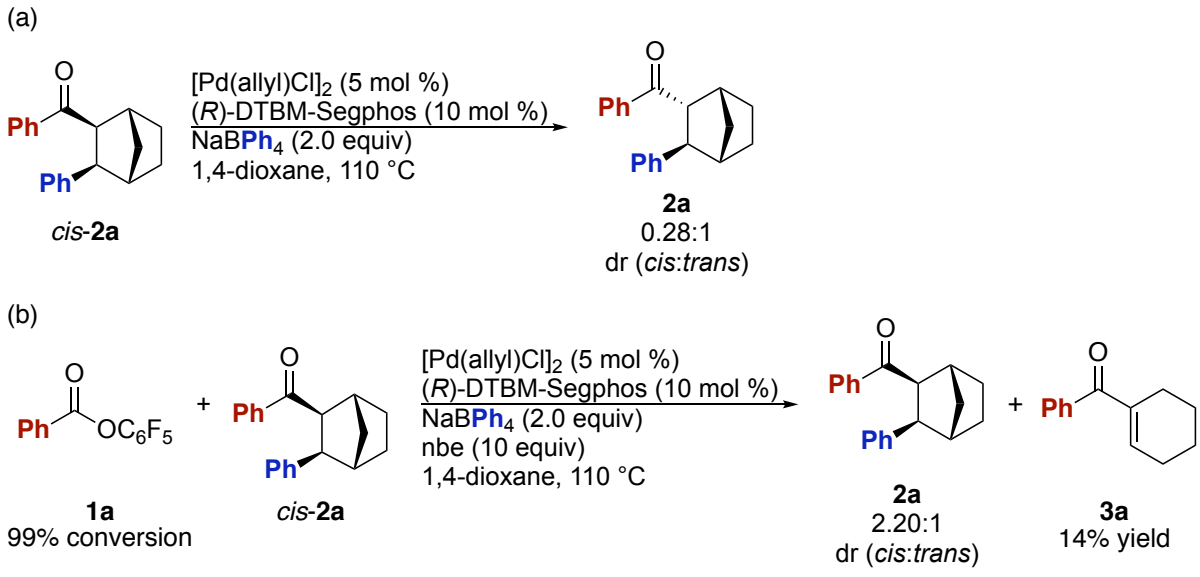

**Scheme 3.** Alkene Carboacylation Time Studies.

To identify whether *trans*-**2a** is generated primarily through epimerization of *cis*-**2a** or conjugate addition of $NaBPh_4$ to **3a** we conducted a series of control experiments (Scheme 4-6). When Heck product **3a** was run in the presence of $[Pd(allyl)Cl]_2$, (*R*)-DTBM-Segphos, and sodium tetraphenylborate, only 40% was converted into **2a** over a 20-hour period (Scheme 4a). The reaction of **1a** and one equivalent of **3a** was run in the presence of $[Pd(allyl)Cl]_2$, (*R*)-DTBM-Segphos, nbe, and sodium tetraphenylborate generated the ketone product with 2:1 dr (*cis*:*trans*), which signifies that conjugate addition to generate *trans*-**2a** is not a major contributor to the overall yield of **2a** (Scheme 4b). These control experiments in addition to the studies on reaction progress over time (Scheme 3) demonstrate that even though a small amount of **3a** is generated in the reaction, *trans*-**2a** is predominantly generated from the epimerization of *cis*-**2a**. When *cis*-**2a** was run in the presence of $[Pd(allyl)Cl]_2$, (*R*)-DTBM-Segphos, and sodium tetraphenylborate, a large amount of *cis*-**2a** was converted to *trans*-**2a** with a final dr of 0.12:1 (*cis*:*trans*) (Scheme 5a). The reaction of **1a** and one equivalent of *cis*-

**2a** run in the presence of $[Pd(allyl)Cl]_2$, (*R*)-DTBM-Segphos, nbe, and sodium tetraphenylborate generated ketone product **2a** with 2.20:1 dr (*cis*:*trans*) (Scheme 5b). This result is consistent with the *cis*-**2a** product being generated via carboacylation and epimerization over the course of the reaction to generate increasing amounts of *trans*-**2a**.

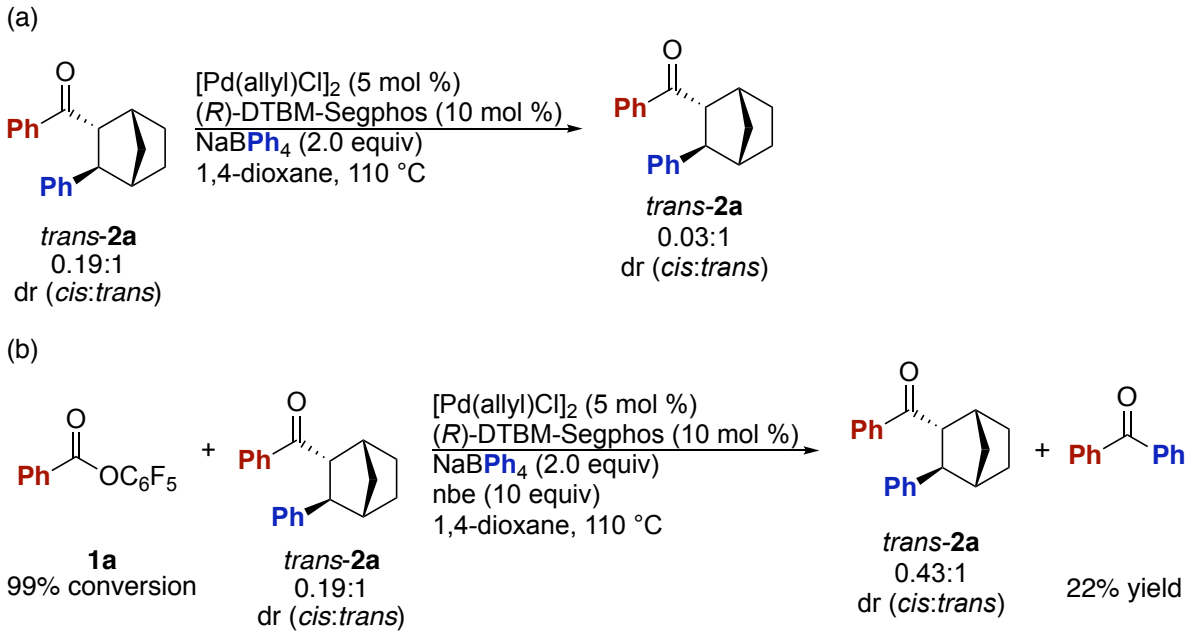



**Scheme 4.** Control Experiments from **3a**.




**Scheme 5.** Control Experiments from *cis*-**2a.**

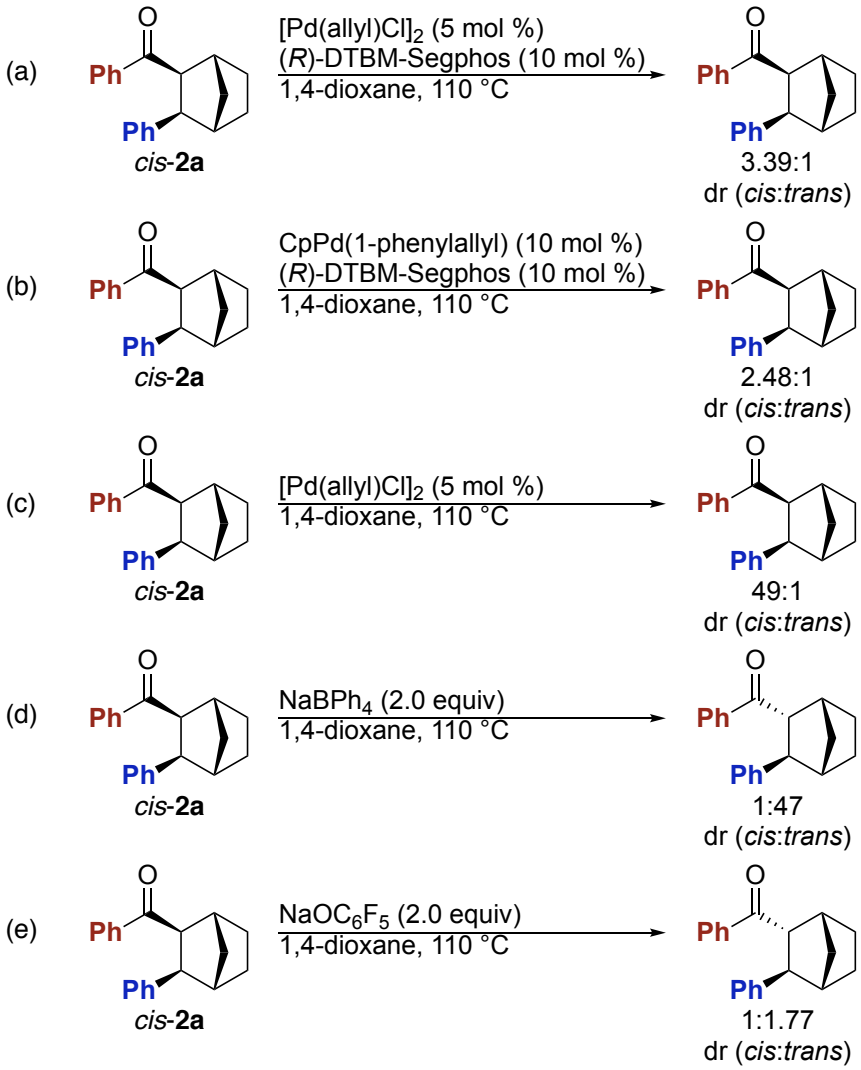
When predominantly *trans*-**2a** (0.19:1 dr *cis*:*trans*) was run in the presence of $[Pd(allyl)Cl]_2$, (*R*)-DTBM-Segphos, and sodium tetraphenylborate, we observed additional epimerization of the *cis*-**2a** ketone into *trans*-**2a** with a final dr of 0.03:1 *cis*:*trans*-**2a** (Scheme 6a). The reaction of **1a** and one equivalent of *trans*-**2a** (0.19:1 dr *cis*:*trans*) run in the presence of $[Pd(allyl)Cl]_2$, (*R*)-DTBM-Segphos, nbe, and sodium tetraphenylborate generated **2a** with a 0.43:1 dr (*cis*:*trans*) (Scheme 6b). This data also supports that the *trans*-**2a** ketone is generated through the epimerization of *cis*-**2a** under the reaction conditions.




**Scheme 6.** Control Experiments from *trans*-**2a.**

With a better understanding of the diastereomeric ratios generated from alkene carboacylation, we next sought to evaluate which components of the reaction are responsible for the epimerization of *cis*-**2a** to *trans*-**2a**. Control experiments with palladium precatalyst, palladium bisphosphine complex, $NaBPh_4$, and $NaOC_6F_5$ were conducted in the presence of *cis*-**2a** (Scheme 7). Based off these control experiments, the active palladium bisphosphine complex and palladium precursor are not major contributors to the epimerization of *cis*-**2a**

(Scheme 7a-c). Additionally, the pentafluorophenoxide byproduct from oxidative addition did not rapidly epimerize *cis*-**2a**, although over 16 hours more than 50% of the *cis*-**2a** diastereomer was converted (Scheme 7e). Interestingly, when *cis*-**2a** was stirred with $NaBPh_4$ we observed almost complete epimerization of *cis*-**2a** to *trans*-**2a** (Scheme 7d). Therefore, we hypothesize that $NaBPh_4$ is the component responsible for the majority of the epimerization under standard reaction conditions. This result also demonstrates the potential to convert the high yield, high ee, and low dr ketone products from this alkene carboacylation into the *trans*-diastereomer after the reaction is complete.




**Scheme 7.** Control Experiments from *trans*-**2a.**

**Conclusion**

In summary, we have developed the first palladium-catalyzed enantioselective, intermolecular alkene carboacylation reactions triggered via C−O bond activation of readily accessible esters. This reaction enables the three-component coupling of aryl benzoates, norbornene, and sodium tetraarylborates to form the corresponding ketone products in high yields, enantioselectivities, and diastereoselectivities. The ability to access acyl-metal-aryl intermediates via ester C−O bond activation and interception with an alkene demonstrates a new approach into carboacylation reactions and bypasses the limitations associated with C−C and C−N bond activation. Studies to expand the scope of alkenes and organometallic nucleophiles and to gain additional mechanistic understanding of the palladium-catalyzed alkene carboacylation reaction 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 were dried at 140 °C in an oven. Tetrahydrofuran, methylene chloride, benzene, and toluene 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* Gold™ 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. HPLC analyses were carried out on a Waters Alliance HPLC system with an e2695 separations module and a 2489 dual wavelength detector. NMR spectra were acquired on Varian MR-400 and Bruker Avance III 600 spectrometers at the Iowa State University Chemical Instrumentation Facility. Chemicals shifts are reported in ppm relative to residual solvent peaks ($CDCl_3$ = 7.26 ppm for $^{1}H$ and 77.16 ppm for $^{13}C$). Coupling constants are reported in hertz. $^{19}F$ NMR shifts are reported based on indirect reference to $CDCl_3$.[41]

**Materials.** Benzoyl chloride, methyl benzoate, benzyl benzoate, phenyl benzoate, norbornene, sodium tetraphenylborate, $[Pd(allyl)Cl]_2$, CpPd(1-phenylallyl), *rac*-BINAP ((*rac*)-2,2'-bis(diphenylphosphino)-1,1'-binaphthalene), (*R*)-BINAP ((*R*)-2,2'-bis(diphenylphosphino)-1,1'-binaphthalene), (*R*)-Tol-BINAP ((*R*)-2,2'-bis(di-*p*-tolylphosphino)-1,1'-binaphthalene), (*R*)-Xyl-BINAP ((*R*)-2,2'-bis(di-3,5-dimethylphenylphosphino)-1,1'-binaphthalene), (*R*)-MeO-Biphep ((*R*)-2,2'-bis(diphenylphosphino)-1,1'-biphenyl), (*R*)-Segphos ((*R*)-2,2'-bis(diphenylphosphino)-4,4'-bi-1,3-benzodioxole), DPEphos (Oxydi-2,1-phenylene)bis(diphenylphosphine), (*R,R*)-DIOP (−)-2,3-*O*-Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane, (*S,S*)-chiraphos (2*S*,3*S*)-(−)-Bis(diphenylphosphino)butane, (*R,R*)-QuinoxP (R,R)-(–)-2,3-Bis(tert-butylmethylphosphino)quinoxaline, CTH-(*R*)-P-Phos (*R*)-(+)-2,2',6,6'-Tetramethoxy-4,4'-bis(diphenylphosphino)-3,3'-bipyridine, dppf 1,1′-bis(diphenylphosphino)ferrocene, dcpb 1,4-bis(dicyclohexylphosphino)butane, magnesium(II) triflate, silver(I) triflate, sodium(I) triflate, magnesium(II) iodide, magnesium(II) carbonate, magnesium(II) perchlorate, magnesium(II) triflamide, scandium(III) triflate, zinc(II) triflate, silver nitrate, silver mesylate, silver

hexafluoroantimonate, silver tetrafluoroborate, silver hexafluorophosphate, silver perchlorate, bismith(III) triflate, yttrium(III) triflate, copper(II) triflate, samarium(III) triflate, *N,N*-dimethylaminopyriridine, diisopropylethylamine, sodium hydride, cesium fluoride, copper(I) iodide, magnesium, sodium sulfate, magnesium sulfate, were purchased from Sigma-Aldrich and used without further purification. Pentraflurophenol was purchased from Oakwood Chemical and used without further purification. Triethylamine was purchased from Fisher Scientific and used without further purification.

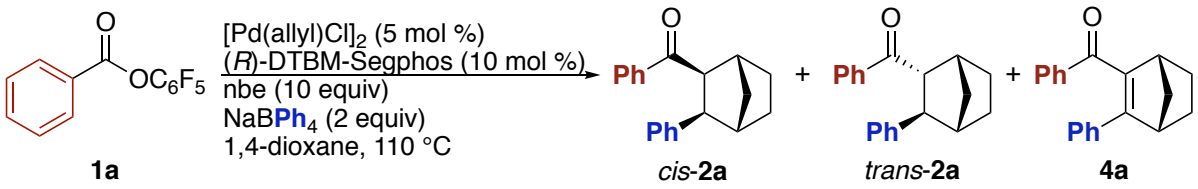
(*R*)-DTBM-Segphos (*R*)-(−)-5,5′-bis[di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-4,4′-bi-1,3-benzodioxole, (*R*)-DTBM-MeO-Biphep (*R*)-(-)-2,2'-bis[di(3,5-di-*t*-butyl-4-methoxyphenyl)phosphino]-6,6'-dimethoxy-1,1'-biphenyl, (*R*)-*t*Bu-MeO-Biphep (*R*)-(+)-2,2'-bis[di(3,5-di-*t*-butylphenyl)phosphino]-6,6'-dimethoxy-1,1'-biphenyl, (*S,S*)-BDPP (2*S*,4*S*)-2,4-bis(diphenylphosphino)pentane, Josiphos SL-J004-1 (*R*)-1-[($S_P$)-2-(dicyclohexylphosphino)ferrocenylethyl]diphenylphosphine, Josiphos SL-J009-1 (*R*)-1-[($S_P$)-2-(dicyclohexylphosphino)ferrocenyl]ethyldi-tert-butylphosphine, JoSPOphos SL-J681-2 ($R_P$)-1-[(*S*)-tert-butylphosphinoyl]-2-[(*S*)-1-(diphenylphosphino)ethyl]ferrocene, and Josiphos SL-J001-2 (*S*)-1-[($R_P$)-2-(diphenylphosphino)ferrocenyl]ethyldicyclohexylphosphine, were purchased from Strem Chemicals and used without further purification.

**Synthesis of Pentafluorophenyl benzoate 1a**.

**Pentrafluorophenyl benzoate 1a**: In an oven dried round-bottom-flask, pentafluorophenol (1.104 g, 6.00 mmol), triethylamine (1.05 mL, 7.50 mmol), and 4-dimethylaminopyridine (0.061g, 0.500 mmol), were dissolved in DCM (10 mL, 0.60 M). The solution was cooled to 0 °C and then a solution of benzoyl chloride (0.58 mL, 5.00 mmol) in

DCM (10 mL, 0.50 M) was added slowly. The reaction was allowed to warm to rt and stirred for 12 hours. After completion of the reaction, 1 N HCl was added to quench the reaction, and more DCM was added. The solution was washed with aq. $NaHCO_3$ (sat.), brine, and then the organic layer was dried with $MgSO_4$. The dried organic layer was concentrated under reduced pressure to yield the crude product. The crude product was purified by flash column chromatography (90:10 hexanes:EtOAc) to yield **1a** (1.124 g, 3.9 mmol, 78% yield) as a white solid. **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 7.45 - 7.58 (m, 2H), 7.69 - 7.73 (m, 1H), 8.20 - 8.22 (m, 2H), 9.96 (s, 1H). **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 127.1, 129.0, 130.9, 134.9, 136.7 - 137.1 (m), 138.3 - 138.6 (m), 139.2 - 141.1 (m), 142.7 - 142.9 (m), 162.8. **$^{19}$F NMR** ($CDCl_3$, 376 MHz) δ -162.5 (m, 2F), -158.1 (t, 1F), -152.6 (m, 2F).

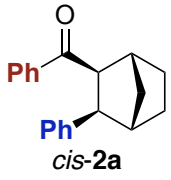
**General Procedure A for Alkene Carboacylation of 1a.**




**1a** *cis*-**2a** *trans*-**2a** **4a**

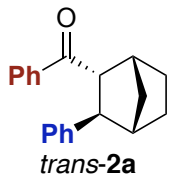
In a nitrogen-filled dry box, the palladium precatalyst (0.005 mmol dimer) and corresponding ligand (0.010 mmol) were stirred to precomplex for 30 minutes in 1,4-dioxane (0.30 mL). In an oven-dried 1-dram vial, **1a** (22.8 mg, 0.100 mmol), nbe (94.1 mg, 1.00 mmol), sodium tetraphenylborate (68.4 mg, 0.200 mmol), and additive (0.00 - 2.00 equiv, 0 - 0.200 mmol) were added with a magnetic stir bar. Then 0.30 mL of the precomplexed ligated-palladium solution was added to the 1-dram vial. The vial was capped with a teflon-lined screw cap and removed from the dry box and stirred at 110 °C for 16-24 hours. The reaction mixture was cooled to room temperature and DCM was added. The reaction was filtered through a plug of celite and washed 4x with DCM (2 mL). The filtrate was concentrated under reduced

pressure. The crude reaction mixtures were purified by flash column chromatography (hexanes:EtOAc) to yield **2a** (a mixture of *cis*-**2a** and *trans*-**2a**, and in some cases **3a**).



*cis*-**2a**

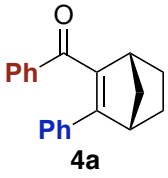
**phenyl((1*R*,2*S*,3*R*,4*S*)-3-phenylbicyclo[2.2.1]heptan-2-yl)methanone (*cis*-2a):** Prepared according to general procedure A starting from pentafluorophenyl benzoate **1a** (28.8 mg, 0.100 mmol), nbe (94.1 mg, 1.00 mmol), $NaBPh_4$ (68.4 mg, 0.200 mmol), $[Pd(allyl)Cl]_2$ (1.8 mg, 0.005 mmol), and (*R*)-DTBM-Segphos (11.8 mg, 0.010 mmol). After completion of the reaction the yield **2a** was determined to be 49% *cis*-**2a** and 50% *trans*-**2a** (0.98:1 dr), an overall 99% yield of **2a** based off dibromomethane internal standard. To isolate *cis*-**2a** and *trans*-**2a** the crude product was purified by flash column chromatography (100% hexanes to 91:9 hexanes:EtOAc) to yield *cis*-**2a** (13.1 mg, 0.047 mmol, 47% yield) as a white solid. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) $t_R$ 14.3 min (major); $t_R$ 16.6 min (minor) [Chiracel OJ-H (0.46cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/$^i$PrOH, 95:5, 1 mL/min] to be 49% ee. **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 1.39 -1.78 (m, 4H), 1.67 - 1.78 (m, 2H), 2.44 - 2.49 (m, 2H), 2.71 (s, 1H), 3.29 (d, *J* = 10.4 Hz, 1H), 3.84 (d, *J* = 10.2 Hz, 1H), 6.88 - 6.96 (m, 5H), 7.21 (t, *J* = 7.8 Hz, 1H), 7.34 (d, *J* = 6.9, 1H), 7.55 (d, *J* = 7.5 Hz, 1H). **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 29.1, 31.3, 37.6, 39.3, 43.7, 54.1, 56.4, 126.0, 127.8, 128.0, 128.1, 128.5, 132.1, 138.7, 141.9, 201.8.



*trans*-**2a**

**phenyl((1*R*,2*R*,3*R*,4*S*)-3-phenylbicyclo[2.2.1]heptan-2-yl)methanone (*trans*-2a):** Prepared according to general procedure A starting from pentafluorophenyl benzoate **1a** (28.8 mg, 0.100 mmol), nbe (94.1 mg, 1.00 mmol), $NaBPh_4$ (68.4 mg, 0.200 mmol), $[Pd(allyl)Cl]_2$ (1.8 mg, 0.005 mmol), and (*R*)-DTBM-Segphos (11.8 mg, 0.010 mmol). After completion of the reaction the yield **2a** was determined

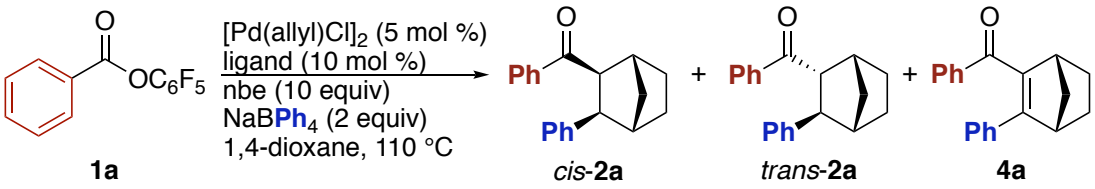
to be 49% *cis*-**2a** and 50% *trans*-**2a** (0.98:1 dr), an overall 99% yield of **2a** based off dibromomethane internal standard. To isolate *cis*-**2a** and *trans*-**2a** the crude product was purified by flash column chromatography (100% hexanes to 91:9 hexanes:EtOAc) to yield *trans*-**2a** (13.5 mg, 0.049 mmol, 49% yield) as a white solid. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) $t_R$ 28.6 min (major); $t_R$ 31.9 min (minor) [Chiracel OJ-H (0.46cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/$^i$PrOH, 95:5, 1 mL/min] to be 53% ee. **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 1.21 - 1.39 (m, 3H), 1.50 (d, $J$ = 9.9 Hz, 1H), 1.61 - 1.69 (m, 1H), 2.01 (d, $J$ = 9.6 Hz, 1H), 2.61 (d, $J$ = 3.7 Hz, 1H), 3.62 (d, $J$ = 5.4 Hz, 1H), 3.72 (dd, $J$ = 4.2, 4.2 Hz, 1H), 6.93 (d, $J$ = 8.6, 2H), 7.14 (t, $J$ = 6.8 Hz, 1H), 7.22 - 7.28 (m, 5H), 7.98 (d, $J$ = 8.6 Hz, 1H). **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 23.8, 30.1, 39.7, 42.5, 43.1, 55.6, 59.8, 113.8, 125.8, 127.0, 128.6, 130.8, 146.8, 163.4, 198.9.



**4a**

**phenyl((1*R*,4*S*)-3-phenylbicyclo[2.2.1]hept-2-en-2-yl)methanone (4a):** This compound was generated in varying amounts 0 to 15% yield as a byproduct of the general procedure A starting from pentafluorophenyl benzoate **1a** (28.8 mg, 0.100 mmol), nbe (94.1 mg, 1.00 mmol), $NaBPh_4$ (68.4 mg, 0.200 mmol), $[Pd(allyl)Cl]_2$ (1.8 mg, 0.005 mmol), and ligand (0.010 mmol). NMR yield of this byproduct was determined with dibromomethane internal standard. To isolate **4a** the crude product was purified by flash column chromatography (100% hexanes to 91:9 hexanes:EtOAc) to yield **4a** as a white solid. **$^1$H NMR** ($CDCl_3$, 400 MHz): δ 1.44 - 1.52 (m, 3H), 1.56 - 1.60 (m, 1H), 2.48 (d, $J$ = 10.0 Hz, 1H), 2.59 (d, $J$ = 2.4 Hz, 1H), 2.78 (d, $J$ = 3.2 Hz, 1H), 4.12 (d, $J$ = 1.7 Hz, 1H), 7.20 - 7.26 (m, 1H), 7.30 - 7.34 (m, 4H), 7.42 (t, $J$ = 7.8 Hz, 2H), 7.52 (t, $J$ = 7.5 Hz, 1H), 8.24 (d, $J$ = 7.2 Hz, 1H). **$^{13}$C NMR** ($CDCl_3$, 100 MHz): δ 22.4, 30.2, 38.2, 40.7, 47.6, 53.3, 89.4, 127.2, 128.2, 129.0, 129.2, 130.3, 132.7, 136.3, 138.2, 200.7.

**Table 5.** Investigation of Achiral and Chiral Ligands for Carboacylation of **1a**[a]



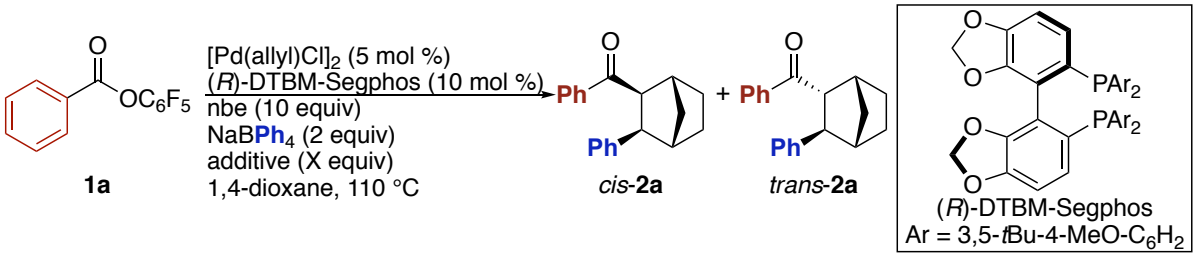

**1a** *cis*-**2a** *trans*-**2a** **4a**

| entry | ligand | conv. (%) | yield **2a** (%)[b] | ee **2a** (%)[c] | dr (*cis*:*trans*)[b] | yield **4a** (%) |
|---|---|---|---|---|---|---|
| 1 | DPEphos | 91 | 84 | - | 1.27:1 | 4 |
| 2 | Cy-DPEphos | 71 | 34 | - | 1.43:1 | 0 |
| 3 | dppf | 62 | 58 | - | 4.27:1 | 0 |
| 4 | dcpb | 46 | 17 | - | 0.89:1 | 0 |
| 5 | (*R*)-Segphos | 99 | 92 | 39 | 1.19:1 | 8 |
| 6 | (*R*)-DTBM-Segphos | 99 | 99 | 49 | 0.98:1 | <1 |
| 7 | (*R*)-MeO-Biphep | 99 | 92 | 16 | 1.56:1 | 6 |
| 8 | (*R*)-DTBM-MeO-Biphep | 93 | 80 | 29 | 1.86:1 | 8 |
| 9 | (*R*)-*t*Bu-MeO-Biphep | 88 | 70 | 41 | 0.84:1 | 17 |
| 10 | (*R*)-BINAP | 96 | 70 | 19 | 1.19:1 | 16 |
| 11 | (*R*)-tol-BINAP | 95 | 70 | 10 | 1.19:1 | 15 |
| 12 | (*R*)-xyl-BINAP | 96 | 91 | 16 | 1.12:1 | 9 |
| 13 | (*R*)-Monophos | 57 | 3 | - | 20:1 | 0 |
| 14 | (*S,S*)-BDPP | 96 | 75 | 7 | 1.14:1 | 13 |
| 15 | (*R,R*)-DIOP | 56 | 44 | 8 | 1.20:1 | 3 |
| 16 | (*S,S*)-Chiraphos | 54 | 52 | 36 | 1.48:1 | 6 |
| 17 | (*R,R*)-MeDuphos | 99 | 83 | 56 | 0.93:1 | 8 |
| 18 | (*R,R*)-QuinoxP | 99 | 85 | 51 | 0.98:1 | 18 |
| 19 | CTH-(*R*)-P-Phos | 68 | 69 | 9 | 1.56:1 | 0 |
| 20 | Josiphos SL-J004-1 | 96 | 82 | 46 | 1.05:1 | 11 |
| 21 | Josiphos SL-J009-1 | 0 | 0 | - | - | 0 |
| 22 | JoSPOphos SL-J681-2 | 98 | 91 | 13 | 1.12:1 | <1 |
| 23 | Josiphos SL-J001-2 | 97 | 93 | 58 | 1.02:1 | <1 |

[a]Reaction conditions: **1a** (0.100 mmol), $[Pd(allyl)Cl]_2$ (0.005 mmol), ligand (0.010 mmol), nbe (10 equiv), $NaBPh_4$ (0.200 mmol), solvent (0.33 M), 20 h. Yields and dr determined by $^1H$ NMR spectroscopy of the crude reaction mixture using dibromomethane as an internal standard. [c]Enantioselectivity determined by chiral HPLC analysis of isolated compounds.

A large amount of the bisphosphine ligands investigated generated **2a** in moderate-to-high yields, albeit in poor enantioselectivities. The ligands that generated high yields and moderate enantioselectivities for intermolecular alkene carboacylation were reported and discussed in scheme 2. There was an additional byproduct **4a** observed in trace to low yields in the majority of the reactions which was isolated and characterized (Table 5).

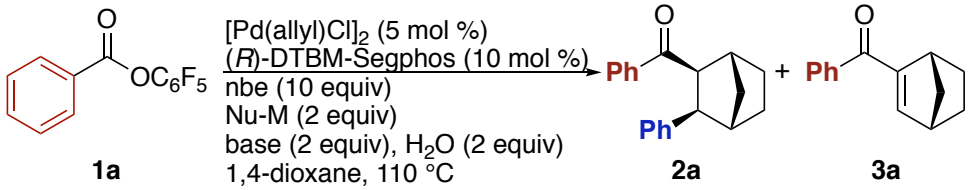
**Table 6.** Investigation of Additives on the Enantioselective Carboacylation of **1a**[a]




| entry | additive | X equiv | conv. (%) | yield **2a** (%)[b] | ee **2a** (%)[c] | dr (*cis*:*trans*)[b] |
|---|---|---|---|---|---|---|
| 1 | none | - | 99 | 99 | 49 | 0.98:1 |
| 2 | AgOTf | 0.3 | 99 | 95 | 50 | 0.98:1 |
| 3 | NaOTf | 0.1 | 96 | 74 | 49 | 0.95:1 |
| 4 | NaOTf | 0.3 | 97 | 75 | 51 | 0.94:1 |
| 5 | NaOTf | 0.5 | 93 | 65 | 55 | 1.24:1 |
| 6 | NaOTf | 1 | 93 | 55 | 54 | 1.39:1 |
| 7 | $Sm(OTf)_3$ | 0.3 | 87 | 57 | 47 | 1.19:1 |
| 8 | $Bi(OTf)_3$ | 0.3 | 75 | 71 | 50 | 0.78:1 |
| 9 | $Ca(OTf)_2$ | 0.3 | 69 | 70 | 70 | 0.79:1 |
| 10 | $Sc(OTf)_3$ | 0.3 | 24 | 26 | - | 1:1 |
| 11 | $Zn(OTf)_2$ | 0.3 | 98 | 47 | - | 0.24:1 |
| 12 | $Y(OTf)_3$ | 0.3 | 40 | 33 | - | 0.74:1 |
| 13 | $Mg(OTf)_2$ | 0.1 | 60 | 51 | 60 | 0.76:1 |
| 14 | $Mg(OTf)_2$ | 0.3 | 67 | 56 | 79 | 0.75:1 |
| 15 | $Mg(OTf)_2$ | 0.5 | 79 | 58 | 85 | 0.81:1 |
| 16 | $Mg(OTf)_2$ | 1 | 78 | 67 | 92 | 0.72:1 |
| 17[d] | $Mg(OTf)_2$ | 1 | 99 | 73 | 82 | 0.46:1 |
| 18 | $Mg(OTf)_2$ | 2 | 72 | 45 | 95 | 0.88:1 |
| 19 | $MgI_2$ | 0.3 | 47 | 22 | - | 1:20 |
| 20 | $MgCO_3$ | 0.3 | 82 | 79 | 48 | 1.19:1 |
| 21 | $Mg(ClO_4)_2$ | 0.3 | 25 | 14 | - | 20:1 |
| 22 | $Mg(NTf)_2$ | 0.3 | 29 | 15 | - | 20:1 |
| 23 | $AgNO_3$ | 0.3 | 76 | 44 | - | 0.91:1 |
| 24 | $AgSO_2Me$ | 0.3 | 63 | 36 | - | 0.80:1 |
| 25 | $AgSbF_6$ | 0.3 | 15 | 0 | - | - |
| 26 | $AgBF_4$ | 0.3 | 92 | 59 | - | 0.84:1 |
| 27 | $AgPF_6$ | 0.3 | 99 | 76 | 54 | 1.11:1 |
| 28 | $AgClO_4$ | 0.3 | 99 | 59 | 49 | 1.03:1 |

[a]Reaction conditions: **1a** (0.100 mmol), $[Pd(allyl)Cl]_2$ (0.005 mmol), (*R*)-DTBM-Segphos (0.010 mmol), nbe (10 equiv), $NaBPh_4$ (0.200 mmol), additive (X equiv), solvent (0.33 M), 20 h. [b]Determined by $^1H$ NMR spectroscopy of the crude reaction mixture using dibromomethane as an internal standard. [c]Enantioselectivity determined by chiral HPLC analysis of isolated compounds. [d]Reaction run at 120 ºC.

**Table 7.** Investigation of Organoboron Nucleophiles for Carboacylation of **1a**[a]



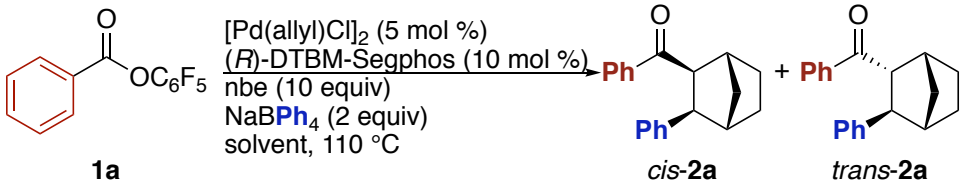

**1a** **2a** **3a**

| entry | Nu-M | base | conv. (%) | yield **2a** (%)[b] | yield **3a** (%)[c] |
|---|---|---|---|---|---|
| 1 | $NaBPh_4$ | - | 99 | 99 | 0 |
| 2[c] | $PhB(OH)_2$ | $Na_2CO_3$ | 99 | 0 | 48 |
| 3[c] | $PhB(OH)_2$ | CsF | 99 | 0 | 3 |
| 4[c,d] | $PhB(OH)_2$ | CsF | 84 | 0 | 18 |
| 5[c] | $PhB(OH)_2$ | $K_3PO_4$ | 99 | 0 | 24 |
| 6 | $PhB(OH)_2$ | $Na_2CO_3$ | 84 | 4 | 60 |
| 7 | - | $Na_2CO_3$ | 31 | 0 | 0 |
| 8 | $PhB(OH)_2$ | CsF | 99 | 0 | 31 |
| 9[d] | $PhB(OH)_2$ | CsF | 78 | 0 | 27 |
| 10 | $PhB(OH)_2$ | $K_3PO_4$ | 94 | 0 | 19 |
| 11[c] | PhBpin | $Na_2CO_3$ | 68 | 0 | 6 |
| 12[c] | PhBpin | CsF | 99 | 0 | 0 |
| 13[c] | PhBpin | $K_3PO_4$ | 99 | 0 | 3 |
| 14 | PhBpin | $Na_2CO_3$ | 43 | 0 | 2 |
| 15 | PhBpin | CsF | 99 | 0 | 10 |
| 16 | PhBpin | $K_3PO_4$ | 78 | 0 | 13 |
| 17[c] | $NaBPh_4$ | CsF | 55 | 0 | 8 |
| 18[c,d] | $NaBPh_4$ | CsF | 71 | 0 | 20 |

[a]Reaction conditions: **1a** (0.100 mmol), $[Pd(allyl)Cl]_2$ (0.005 mmol), (*R*)-DTBM-Segphos (0.010 mmol), nbe (10 equiv), Nu-M (0.200 mmol), base (0.200 mmol), water (0.00 or 0.200 mmol), solvent (0.33 M), 20 h. [b]Determined by $^1H$ NMR spectroscopy of the crude reaction mixture using dibromomethane as an internal standard. [c]Run with 2 equiv of water. [d]Reaction run with 10 mol % CuI

Attempts to utilize other organoboron nucleophiles were unsuccessful in the generation of the desired carboacylation product **2a**. Instead, we observed the formation of **3a**, the product of Heck coupling in low-to-moderate yields (0-60%) (Table 7).

**Table 8.** Investigation of Solvents on the Enantioselective Carboacylation of **1a**[a]

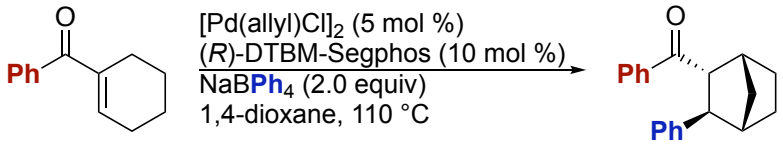



**1a** *cis*-**2a** *trans*-**2a**

| entry | solvent | conv. (%) | yield **2a** (%)[b] | ee **2a** (%)[c] | dr (*cis*:*trans*)[b] |
|---|---|---|---|---|---|
| 1 | 1,4-dioxane | 99 | 99 | 49 | 0.98:1 |
| 2 | benzene | 88 | 68 | 57 | 1.83:1 |
| 3 | toluene | 87 | 66 | 57 | 1.64:1 |
| 4 | $CF_3C_6H_5$ | 13 | 3 | - | 20:1 |
| 5 | cyclopentyl methyl ether | 99 | 71 | 52 | 1.29:1 |
| 6 | dibutyl ether | 87 | 68 | 51 | 3.53:1 |

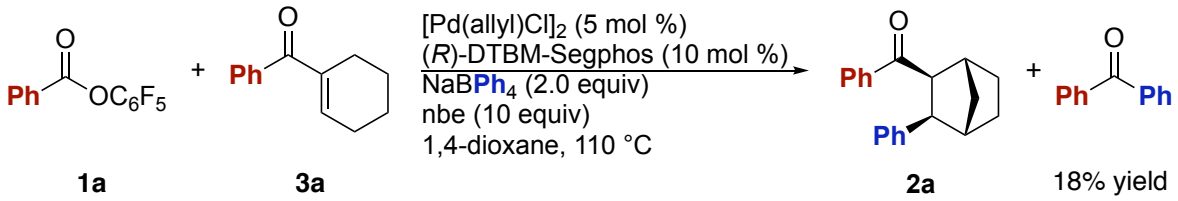
[a]Reaction conditions: **1a** (0.100 mmol), $[Pd(allyl)Cl]_2$ (0.005 mmol), (*R*)-DTBM-Segphos (0.010 mmol), nbe (10 equiv), $NaBPh_4$ (0.200 mmol), solvent (0.33 M), 20 h. [b]Determined by $^1H$ NMR spectroscopy of the crude reaction mixture using dibromomethane as an internal standard. [c]Enantioselectivity determined by chiral HPLC analysis of isolated compounds.

**Experimental Procedure for Control Experiments:**

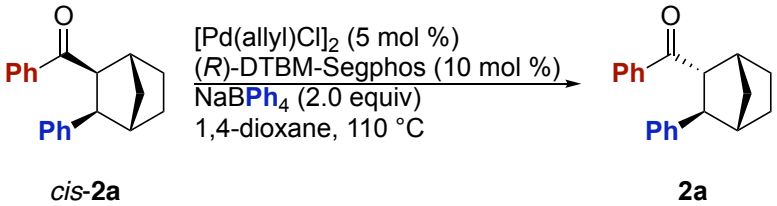



**3a** **2a**

A control experiment generating ketone **2a** was carried out by the following procedure. A 1-dram vial was charged with **3a** (19.8 mg, 0.100 mmol), $[Pd(allyl)Cl]_2$ (1.8 mg, 0.005 mmol), (*R*)-DTBM-Segphos (11.8 mg, 0.010 mmol), sodium tetraphenylborate (68.4 mg, 0.200 mmol), and 1,4-dioxane (0.30 mL). The vial was capped with a teflon-lined screw cap and stirred at 110 °C for 16 hours. The reaction mixture was cooled to room temperature and DCM was added. The reaction was filtered through a plug of celite and washed 4x with DCM (2 mL). The filtrate was concentrated under reduced pressure. The crude mixture was dissolved in $CDCl_3$ with $CH_2Br_2$ as internal standard. The diastereomeric ratio of *cis*-**2a**:*trans*-**2a** was determined to be 0.12:1 by $^1H$ NMR spectroscopy. The NMR yields of *cis*-**2a** and *trans*-**2a** were determined to be 3% and 16%, respectively with 40% conversion of **3a**.

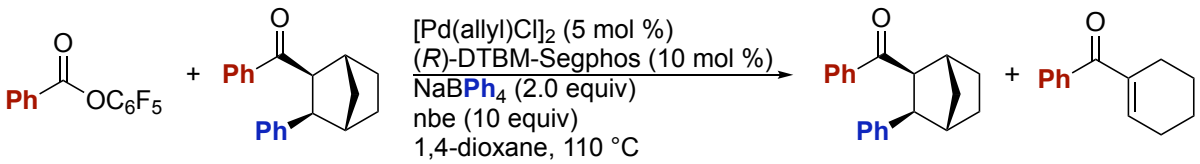



A control experiment generating ketone **2a** was carried out by the following procedure. A 1-dram vial was charged with **3a** (19.8 mg, 0.100 mmol), **1a** (28.8 mg, 0.100 mmol) $[Pd(allyl)Cl]_2$ (1.8 mg, 0.005 mmol), (*R*)-DTBM-Segphos (11.8 mg, 0.010 mmol), nbe (94.1 mg, 1.00 mmol), sodium tetraphenylborate (68.4 mg, 0.200 mmol), and 1,4-dioxane (0.30 mL). The vial was capped with a teflon-lined screw cap and stirred at 110 °C for 16 hours. The reaction mixture was cooled to room temperature and DCM was added. The reaction was filtered through a plug of celite and washed 4x with DCM (2 mL). The filtrate was concentrated under reduced pressure. The crude mixture was dissolved in $CDCl_3$ with $CH_2Br_2$ as internal standard. The diastereomeric ratio of *cis*-**2a**:*trans*-**2a** was determined to be 2.0:1 by $^1H$ NMR spectroscopy. The NMR yields of *cis*-**2a** and *trans*-**2a** were determined to be 40% and 20%, respectively with 40% conversion of **3a** and 92% conversion of **1a**.



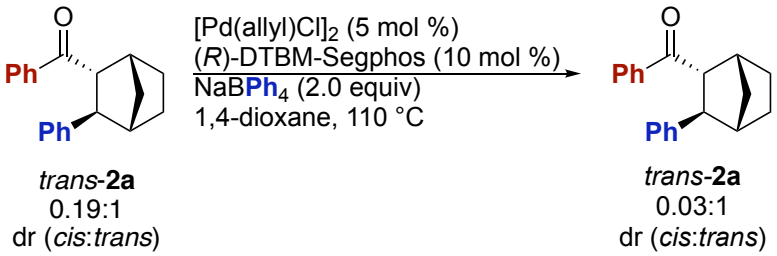

A control experiment generating ketone **2a** was carried out by the following procedure. A 1-dram vial was charged with *cis*-**2a** (27.6 mg, 0.100 mmol), $[Pd(allyl)Cl]_2$ (1.8 mg, 0.005 mmol), (*R*)-DTBM-Segphos (11.8 mg, 0.010 mmol), sodium tetraphenylborate (68.4 mg, 0.200 mmol), and 1,4-dioxane (0.30 mL). The vial was capped with a teflon-lined screw cap and stirred at 110 °C for 16 hours. The reaction mixture was cooled to room temperature and DCM was added. The reaction was filtered through a plug of celite and washed 4x with DCM

(2 mL). The filtrate was concentrated under reduced pressure. The crude mixture was dissolved in $CDCl_3$ with $CH_2Br_2$ as internal standard. The diastereomeric ratio of *cis*-**2a**:*trans*-**2a** was determined to be 0.28:1 by $^1H$ NMR spectroscopy. The NMR yields of *cis*-**2a** and *trans*-**2a** were determined to be 21% and 75%, respectively with 79% conversion of *cis*-**2a**.

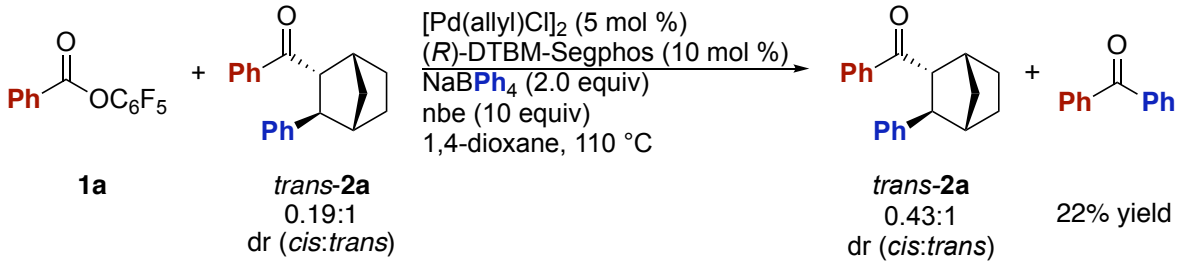



**1a** *cis*-**2a** **2a** **3a** 14% yield

A control experiment generating ketone **2a** was carried out by the following procedure. A 1-dram vial was charged with *cis*-**2a** (27.6 mg, 0.100 mmol), **1a** (28.8 mg, 0.100 mmol) $[Pd(allyl)Cl]_2$ (1.8 mg, 0.005 mmol), (*R*)-DTBM-Segphos (11.8 mg, 0.010 mmol), nbe (94.1 mg, 1.00 mmol), sodium tetraphenylborate (68.4 mg, 0.200 mmol), and 1,4-dioxane (0.30 mL). The vial was capped with a teflon-lined screw cap and stirred at 110 °C for 16 hours. The reaction mixture was cooled to room temperature and DCM was added. The reaction was filtered through a plug of celite and washed 4x with DCM (2 mL). The filtrate was concentrated under reduced pressure. The crude mixture was dissolved in $CDCl_3$ with $CH_2Br_2$ as internal standard. The diastereomeric ratio of *cis*-**2a**:*trans*-**2a** was determined to be 2.20:1 by $^1H$ NMR spectroscopy. The NMR yields of *cis*-**2a** and *trans*-**2a** were determined to be 62% and 28%, respectively with 84% conversion of **1a**.

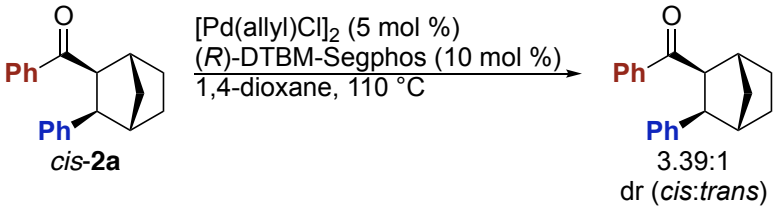



A control experiment generating ketone **2a** was carried out by the following procedure. A 1-dram vial was charged with *trans*-**2a** (0.19:1 dr *cis*:*trans*, 27.6 mg, 0.100 mmol), $[Pd(allyl)Cl]_2$ (1.8 mg, 0.005 mmol), (*R*)-DTBM-Segphos (11.8 mg, 0.010 mmol), sodium tetraphenylborate (68.4 mg, 0.200 mmol), and 1,4-dioxane (0.30 mL). The vial was capped with a teflon-lined screw cap and stirred at 110 °C for 16 hours. The reaction mixture was cooled to room temperature and DCM was added. The reaction was filtered through a plug of celite and washed 4x with DCM (2 mL). The filtrate was concentrated under reduced pressure. The crude mixture was dissolved in $CDCl_3$ with $CH_2Br_2$ as internal standard. The diastereomeric ratio of *cis*-**2a**:*trans*-**2a** was determined to be 0.03:1 by $^1H$ NMR spectroscopy. The NMR yields of *cis*-**2a** and *trans*-**2a** were determined to be 3% and 97%.

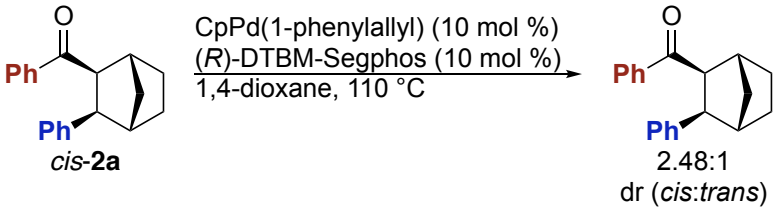



A control experiment generating ketone **2a** was carried out by the following procedure. A 1-dram vial was charged with *trans*-**2a** (0.19:1 dr *cis*:*trans*, 27.6 mg, 0.100 mmol), **1a** (28.8 mg, 0.100 mmol) $[Pd(allyl)Cl]_2$ (1.8 mg, 0.005 mmol), (*R*)-DTBM-Segphos (11.8 mg, 0.010 mmol), nbe (94.1 mg, 1.00 mmol), sodium tetraphenylborate (68.4 mg, 0.200 mmol), and 1,4-dioxane (0.30 mL). The vial was capped with a teflon-lined screw cap and stirred at 110 °C

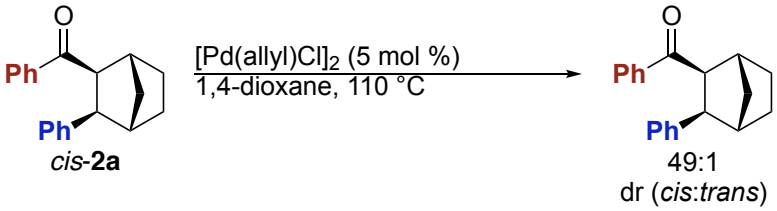
for 16 hours. The reaction mixture was cooled to room temperature and DCM was added. The reaction was filtered through a plug of celite and washed 4x with DCM (2 mL). The filtrate was concentrated under reduced pressure. The crude mixture was dissolved in $CDCl_3$ with $CH_2Br_2$ as internal standard. The diastereomeric ratio of *cis*-**2a**:*trans*-**2a** was determined to be 0.43:1 by $^1$H NMR spectroscopy. The NMR yields of *cis*-**2a** and *trans*-**2a** were determined to be 28% and 66%, respectively with 99% conversion of **1a**.




A control experiment generating ketone **2a** was carried out by the following procedure. A 1-dram vial was charged with *cis*-**2a** **(**27.6 mg, 0.100 mmol), $[Pd(allyl)Cl]_2$ (1.8 mg, 0.005 mmol), (*R*)-DTBM-Segphos (11.8 mg, 0.010 mmol), and 1,4-dioxane (0.30 mL). The vial was capped with a teflon-lined screw cap and stirred at 110 °C for 16 hours. The reaction mixture was cooled to room temperature and DCM was added. The reaction was filtered through a plug of celite and washed 4x with DCM (2 mL). The filtrate was concentrated under reduced pressure. The crude mixture was dissolved in $CDCl_3$ with $CH_2Br_2$ as internal standard. The diastereomeric ratio of *cis*-**2a**:*trans*-**2a** was determined to be 3.39:1 by $^1$H NMR spectroscopy. The NMR yields of *cis*-**2a** and *trans*-**2a** were determined to be 78% and 22%, respectively.

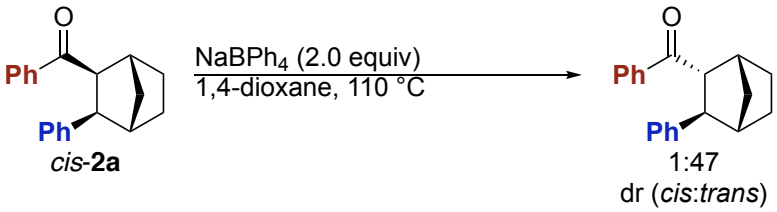



A control experiment generating ketone **2a** was carried out by the following procedure. A 1-dram vial was charged with *cis*-**2a** (27.6 mg, 0.100 mmol), CpPd(1-phenylallyl) (2.9 mg, 0.005 mmol), (*R*)-DTBM-Segphos (11.8 mg, 0.010 mmol), and 1,4-dioxane (0.30 mL). The vial was capped with a teflon-lined screw cap and stirred at 110 °C for 16 hours. The reaction mixture was cooled to room temperature and DCM was added. The reaction was filtered through a plug of celite and washed 4x with DCM (2 mL). The filtrate was concentrated under reduced pressure. The crude mixture was dissolved in $CDCl_3$ with $CH_2Br_2$ as internal standard. The diastereomeric ratio of *cis*-**2a**:*trans*-**2a** was determined to be 2.48:1 by $^1H$ NMR spectroscopy. The NMR yields of *cis*-**2a** and *trans*-**2a** were determined to be 71% and 29%, respectively.

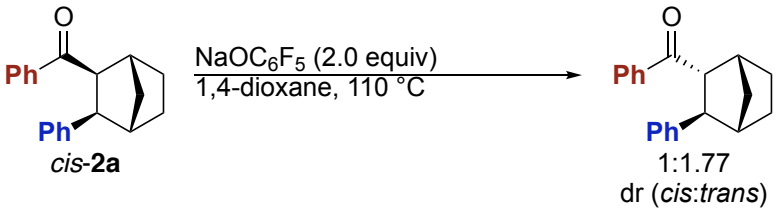



A control experiment generating ketone **2a** was carried out by the following procedure. A 1-dram vial was charged with *cis*-**2a** (27.6 mg, 0.100 mmol), $[Pd(allyl)Cl]_2$ (1.8 mg, 0.005 mmol), and 1,4-dioxane (0.30 mL). The vial was capped with a teflon-lined screw cap and stirred at 110 °C for 16 hours. The reaction mixture was cooled to room temperature and DCM was added. The reaction was filtered through a plug of celite and washed 4x with DCM (2 mL). The filtrate was concentrated under reduced pressure. The crude mixture was dissolved in $CDCl_3$ with $CH_2Br_2$ as internal standard. The diastereomeric ratio of *cis*-**2a**:*trans*-**2a** was

determined to be 49:1 by $^1$H NMR spectroscopy. The NMR yields of *cis*-**2a** and *trans*-**2a** were determined to be 98% and 2%, respectively.




A control experiment generating ketone **2a** was carried out by the following procedure. A 1-dram vial was charged with *cis*-**2a** (27.6 mg, 0.100 mmol), sodium tetraphenylborate (68.4 mg, 0.200 mmol), and 1,4-dioxane (0.30 mL). The vial was capped with a teflon-lined screw cap and stirred at 110 °C for 16 hours. The reaction mixture was cooled to room temperature and DCM was added. The reaction was filtered through a plug of celite and washed 4x with DCM (2 mL). The filtrate was concentrated under reduced pressure. The crude mixture was dissolved in $CDCl_3$ with $CH_2Br_2$ as internal standard. The diastereomeric ratio of *cis*-**2a**:*trans*-**2a** was determined to be 1:47 by $^1$H NMR spectroscopy. The NMR yields of *cis*-**2a** and *trans*-**2a** were determined to be 2% and 94%, respectively.




A control experiment generating ketone **2a** was carried out by the following procedure. A 1-dram vial was charged with *cis*-**2a** (27.6 mg, 0.100 mmol), sodium tetraphenylborate (68.4 mg, 0.200 mmol), and 1,4-dioxane (0.30 mL). The vial was capped with a teflon-lined screw cap and stirred at 110 °C for 16 hours. The reaction mixture was cooled to room temperature and DCM was added. The reaction was filtered through a plug of celite and washed 4x with DCM (2 mL). The filtrate was concentrated under reduced pressure. The crude mixture was dissolved

in $CDCl_3$ with $CH_2Br_2$ as internal standard. The diastereomeric ratio of *cis*-**2a**:*trans*-**2a** was determined to be 1:1.77 by $^1H$ NMR spectroscopy. The NMR yields of *cis*-**2a** and *trans*-**2a** were determined to be 62% and 36%, respectively.

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# CHAPTER 5.

# CONCLUSIONS

This thesis describes the development of new transition metal-catalyzed asymmetric hydroacylation, intramolecular alkene carboacylation, and asymmetric, intermolecular alkene carboacylation reactions. The synthesis of a variety of heterocyclic and carbocyclic ketone scaffolds is enabled through the methods developed for these alkene difunctionalization reactions. Experimental work contributes to fundamental understanding of catalytic principles that is the foundation for new alkene difunctionalization reactions.

The rhodium-catalyzed intramolecular hydroacylation of nitrogen, oxygen, and sulfur heterocycles provides a method for the synthesis of complex polycyclic heterocycle scaffolds. The rhodium-catalyzed alkene hydroacylation encompasses reactions of a variety of alkyl, electron-rich and electron-poor aryl, and heteroaryl substituted alkene units. Varied substitution at the nitrogen is also tolerated, and complete selectivity is observed for five-membered ring generation over six-membered ring generation in the reaction of 1-allyl-3-(1-phenylvinyl)-1*H*- indole-2-carboxaldehyde. In addition, the alkene hydroacylation reaction encompasses a variety of nitrogen, oxygen, and sulfur heterocycles to generate the corresponding polycyclic ketones.

The nickel-catalyzed alkene carboacylation reactions initiated by amide carbon-nitrogen bond activation demonstrates novel reactivity. The nickel-catalyzed alkene carboacylation encompasses reactions of a variety of *ortho*-allylbenzamides and arylboronic acid pinacol esters to generate indanone products through the formation of two new carbon-carbon bonds. This process bypasses the typical substrate requirements for alkene carboacylation that occur via carbon-carbon bond activation. The ability to bypass the

requirement of strained ketones and directing groups demonstrates amides as substrates in the new class of alkene difunctionalization reactions and as powerful building blocks in organic synthesis.

The palladium-catalyzed alkene carboacylation reaction initiated by ester carbon-oxygen bond activation demonstrates the first example of intermolecular, asymmetric alkene carboacylation of esters. The palladium-catalyzed alkene carboacylation encompasses reactions of norbornene, aryl benzoates, and sodium tetraarylborates to form ketone products and two new carbon-carbon bonds. This process bypasses substrate requirements for alkene carboacylation processes that proceed through carbon-nitrogen and carbon-carbon bond activation. With the foundation of alkene carboacylation of esters established, we aim to expand the scope of alkenes and organometallic nucleophiles that can be utilized in this three-component reaction.

Overall, the new alkene difunctionalized methods presented in this thesis occur with low catalyst loadings to generate a variety of ketone products with high levels of enantioselectivity and/or diastereoselectivity. Competition and control experiments contribute to a deeper understanding of the mechanisms for these processes. The new methods developed represents significant advancements for alkene difunctionalization reactions and highlights the utility of amides and esters as substrates in transition-metal catalysis.