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Catalytic methods for alkene functionalization reactions

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Catalytic methods for alkene functionalization reactions

by

Abhishek Ashok Kadam

A dissertation submitted to the graduate faculty

in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

Major: Organic Chemistry

Program of Study Committee:

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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.

Iowa State University

Ames, Iowa

2019

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Dedicated to my mother and father

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NOMENCLATURE

Ar	aryl
equiv	equivalent
DCM	dichloromethane
THF	tetrahydrofuran
Et ₂ O	diethylether
CPME	cyclopentylmethylether
COD	1,5-cyclooctadiene
DMAP	dimethylaminopyridine
Et ₃ N	triethylamine
DMSO	dimethylsulfoxide
DMF	dimethylformamide
EtOAc	ethylacetate
NMR	Nuclear Magnetic Resonance
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
ESI	Electrospray Ionization
Pr	propyl
Bu	butyl
TLC	Thin Layer Chromatography
UV	Ultra-violet
h	Hours
ee	enantiomeric excess

GC	Gas Chromatography
TFA	trifluoroacetate
MHz	Megahertz
dr	diastereomeric ratio
<i>o</i>	ortho
<i>m</i>	meta
<i>p</i>	para
sat	saturated
M	molar
mL	milliliter
calcd	calculated
cat	catalyst

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ABSTRACT

This thesis presents the efforts towards developing transition metal-catalyzed protocols for rapid functionalization of alkenes. These protocols include – 1) enantioselective, palladium-catalyzed conjugate additions of arylboronic acids to generate compounds containing bis-benzylic quaternary stereocenter; 2) nickel-catalyzed three-component alkene carboacylation via activation of amide C-N bonds; 3) palladium-catalyzed intermolecular, acylative Heck reaction using amides as acyl electrophiles.

Chapter II discusses a strategy to access cyclic ketones containing bis-benzylic quaternary stereocenters through enantioselective palladium-catalyzed conjugate additions of arylboronic acids to β -aryl β,β -disubstituted cyclic enones. The catalyst generated from palladium trifluoroacetate and a chiral, non-racemic (*S*)-4-*tert*-butyl-2-(2-pyridyl)oxazoline ligand allows conjugate addition of a wide range arylboronic acids to a variety of β -aryl β,β -disubstituted cyclic enones to generate ketones containing bis-benzylic quaternary stereocenters in up to 92% yield and up to 93% ee. This protocol uses iterative addition strategy to minimize unproductive protodeboronation of arylboronic acid and leads to the formation of compounds containing bis-benzylic quaternary stereocenters.

Chapter III describes the nickel-catalyzed intermolecular alkene carboacylation via activation of amide C-N bonds. The developed method allows rapid functionalization of bicyclic alkenes with a variety of *N*-benzoyl, *N*-phenylbenzamides, and triarylboranes to synthesize ketone products in up to 91% yield. Preliminary mechanistic analysis of the method reveals that migratory insertion precedes transmetalation and that reductive elimination is likely the rate-limiting step.

Chapter IV discusses palladium-catalyzed intermolecular acylative Heck reaction using amides as acyl electrophiles. The catalyst generated from $[\text{Pd}(\text{allyl})\text{Cl}]_2$ and DPEphos promotes reaction between a wide range of *N*-aroylglutarimides and bicyclic alkenes to form α,β -unsaturated ketones in moderate to high yields (25-82%). This work represents the first examples of transition metal-catalyzed intermolecular acylative Heck reaction using amides as acyl electrophiles.

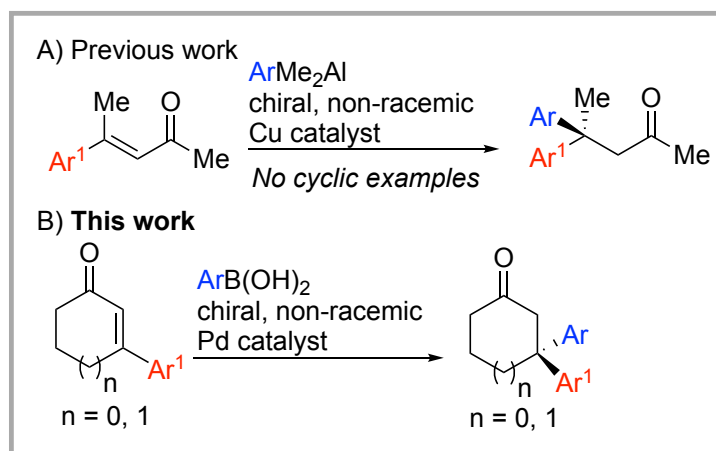
CHAPTER 1. INTRODUCTION

General Introduction

Alkenes are abundant starting materials due to enormity of the global natural gas deposits.¹ Transition metal-catalyzed processes that functionalize alkenes become an attractive platform to access a variety of compounds containing complex architecture.^{1a, 2-5} Since the discovery of Wacker process at Wacker Chemie in 1959,^{4, 6-7} researchers have developed numerous alkene functionalization reactions that allow rapid construction of C–H, C–C, C–N, and C–X bonds.^{1a, 2-5} These reactions include but are not limited to – hydrofunctionalization reactions such as hydroformylation,⁸ hydroboration,^{1a} hydrosilylation,^{1a} hydroamination,⁹ hydroarylation,^{3, 10} hydroacylation;¹¹⁻¹² carbonyl functionalization² reactions such as carboamination,¹³⁻¹⁷ carboxygenation,¹⁸⁻²³ carboacylation,²⁴⁻³² acylborylation,³³⁻³⁴ and Heck type reactions.³⁵⁻³⁹ This thesis will include a detailed account of the basic principles of transition-metal catalysis used to develop catalytic methods for conjugate addition of arylboronic acids to enones (or hydroarylation) reaction, carboacylation of alkenes, and acylative Heck reaction.

Enantioselective, transition metal-catalyzed additions of organometallic nucleophiles to enones constitutes a major subset of conjugate addition reactions.⁴⁰⁻⁴¹ Asymmetric conjugate additions of organometallic nucleophiles allow rapid synthesis of compounds containing quaternary stereocenter.⁴⁰⁻⁴¹ Over the years, new catalysts developed by various research groups have allowed synthesis of compounds containing quaternary stereocenters using arylzinc,⁴²⁻⁴³ arylmagnesium,⁴⁴⁻⁴⁵ and arylaluminum⁴⁶⁻⁴⁷ nucleophiles. However, the use of these organometallic nucleophiles is limited due to their sensitivity towards air and/or moisture.

Hayashi⁴⁸⁻⁴⁹ and Glorius⁵⁰ independently developed rhodium catalysts that catalyze additions of air stable and easily handled arylboron nucleophiles to β,β -disubstituted enones to generate compounds containing quaternary stereocenters. However, these reactions are not efficient for additions of commercially available arylboronic acids. Later, seminal work from Stoltz⁵¹⁻⁵⁵ and Minnaard⁵⁶⁻⁵⁷ showed that palladium catalysts of chiral bidentate nitrogen containing ligands can be used for conjugate additions of commercially available arylboronic acids to β,β -disubstituted enones to generate compounds containing quaternary stereocenters in high yields and enantioselectivities. However, to this point, there were no examples of enantioselective, palladium-catalyzed conjugate additions of arylboronic acids to β -aryl β,β -disubstituted enones to generate compounds containing bis-benzylic quaternary stereocenters.



Scheme 1. Enantioselective, Conjugate Additions of Aryl Nucleophiles to β -aryl β,β -disubstituted enones

In 2013, Hoveyda revealed enantioselective, copper-catalyzed conjugate additions of arylaluminum compounds to β -aryl β,β -disubstituted enones (Scheme 1A).⁵⁸ The copper catalyst generated from $\text{Cu}(\text{Otf})_2$ and a chiral *N*-heterocyclic ligand, catalyzed additions of

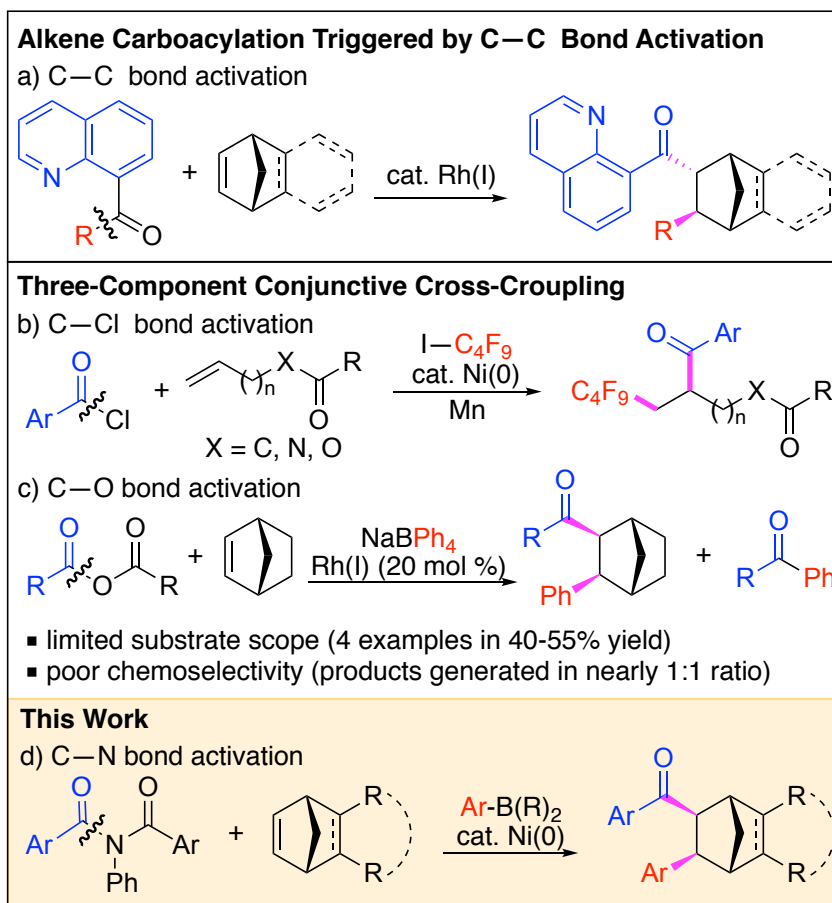
arylaluminum compounds to form bis-benzylic quaternary stereocenters in up to 81% yield and 98% ee. However, since these reactions use air and/or moisture sensitive arylaluminum nucleophiles, these reactions have low functional group tolerance. In addition, there are no examples of additions of arylaluminum nucleophiles to β -aryl β,β -disubstituted cyclic enones in this work.

In order to address these limitations, we developed a protocol for enantioselective, palladium-catalyzed conjugate additions of arylboronic acids to β -aryl, β,β -disubstituted enones to bis-benzylic quaternary stereocenters (Scheme 1B).

Alkene carboacylation is an emerging class of an alkene difunctionalization reactions.²⁴⁻³² It allows for rapid functionalization of alkenes to form two new C–C bonds. In 2017, our research group reported nickel-catalyzed intramolecular alkene carboacylation of *o*-allylbenzamides via activation of amide C–N bonds.⁵⁹ Current catalytic methods for intermolecular alkene carboacylation include conjunctive cross-coupling between a carboxylic acid derivative, an alkyl radical or organometallic nucleophile and an alkene.^{31, 60-61}

Douglas and coworkers revealed a Rh-catalyzed intermolecular alkene carboacylation reaction of 8-acylquinolines with strained bicyclic alkenes (Scheme 2a).³¹ However, these reactions require the use of non-removable quinoline directing group to facilitate C–C bond activation. An alternate approach involves three-component alkene carboacylation by Ni-catalyzed reductive radical relay mechanism (Scheme 2b).⁶¹ These reactions involve addition of a radical to terminal alkene followed by chelation-assisted alkyl radical capture of an acyl–nickel(II)–chloride intermediate. However, these reactions are limited to the use of perfluoroalkyl iodides. In 2002, Miura and coworkers reported a Rh-catalyzed conjunctive cross-coupling of an acid anhydride, tetraphenylborate, and norbornene (Scheme 2c).⁶⁰ The

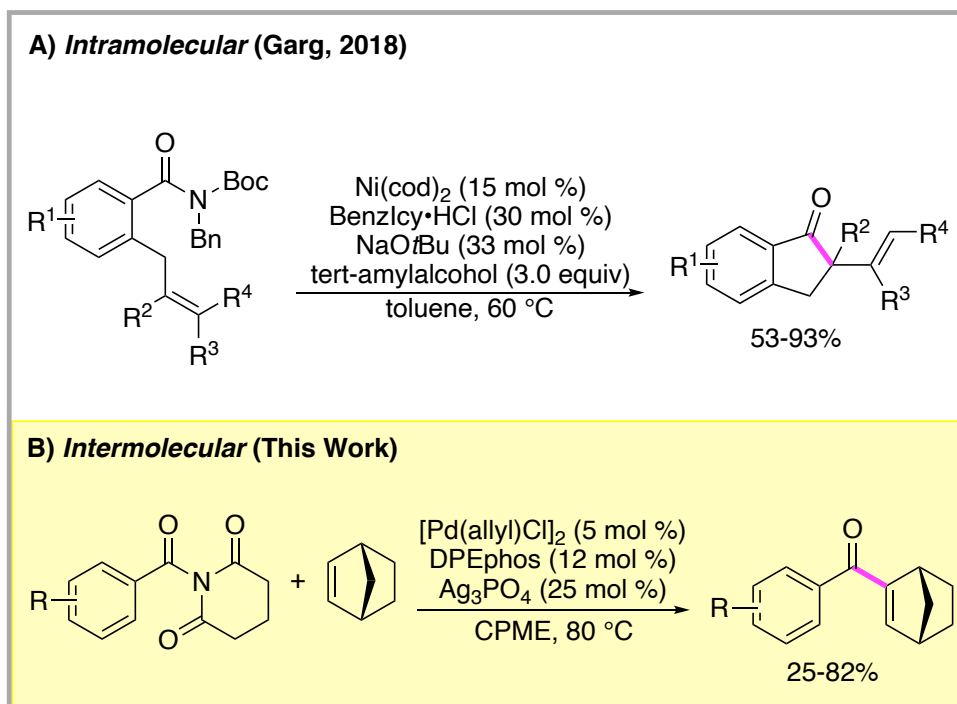
reaction, however, suffers from limited substrate scope (4 examples in 43-55% yield) and occurs with poor chemoselectivity. Despite these advances, more robust methods for intermolecular three-component alkene carboacylation of alkenes are needed.



Scheme 2. Current Strategies for Transition Metal-Catalyzed Intermolecular Alkene Carboacylation

In pursuit of addressing these limitations, we developed nickel-catalyzed three-component alkene carboacylation via activation of amide C–N bonds. This work represents first examples of nickel-catalyzed intermolecular, three-component alkene carboacylation through activation of amide C–N bonds (Scheme 2d).

Heck reaction is a great tool to rapidly construct C–C bonds.³⁵ Since the discovery of the Heck reaction, various efforts have been made to develop acylative Heck reaction using carbon monoxide.⁶²⁻⁶³ To bypass the need of using toxic carbon monoxide, many research groups have reported methods for intramolecular acylative Heck reaction using carboxylic acid derivatives such as acid chlorides,⁶⁴ anhydrides,³⁸ thioesters,³⁹ and carboxylic phosphoric anhydrides³⁷ as acyl electrophiles. However, reports of intermolecular acylative Heck reaction using carboxylic acid derivatives is limited to palladium-catalyzed acylative Heck reaction between acid chlorides and activated alkenes such as vinyl ethers.³⁶ Recently, Garg and co-workers reported a nickel-catalyzed intramolecular Heck reaction of *o*-allylbenzamides to generate indanone compounds containing quaternary center at α -position (Scheme 3A).⁶⁵ The Chapter IV will discuss efforts towards developing intermolecular palladium-catalyzed acylative Heck reaction using amides as acyl electrophiles (Scheme 3B).



Scheme 3. TM-catalyzed, acylative Heck reactions using amides as acyl electrophiles

Thesis Organization

This thesis is comprised of five chapters that describes research work that is published in peer reviewed journals and is in preparation for publication in a peer reviewed journal. Chapter I serves to introduce the general idea of the thesis. It introduces transition metal-catalyzed methods to functionalize alkenes with focus on conjugate addition reactions of arylboronic acids, intermolecular alkene carboacylation reactions, and intermolecular acylative Heck reaction of amides. Chapter II is adapted from a research article published by the author of this thesis in *Organic Letters*. Chapter II is adapted from a paper published in *ACS Catalysis*. Chapter III contains the detailed discussion on the research work towards development of the palladium-catalyzed acylative Heck reaction and will be modified for publication in a peer reviewed journal. Chapter IV serves as a general summary and conclusion of the presented research.

Chapter II describes the enantioselective, palladium-catalyzed conjugate additions of arylboronic acids to β -aryl, β,β -disubstituted enones to bis-benzylic quaternary stereocenters. This protocol described in this chapter allowed additions of a wide range of arylboronic to a variety of β -aryl, β,β -disubstituted enones to generate ketones containing bis-benzylic quaternary stereocenters in up to 92% yield and up to 93% ee. The work described in this chapter is a modified version of a paper published in *Organic Letters*.

Chapter III details the nickel-catalyzed three-component alkene carboacylation via activation of amide C–N bonds. This work is the first examples of nickel-catalyzed intermolecular alkene carboacylation via activation of amide C–N bonds. The developed protocol allowed for rapid functionalization of bicyclic alkenes with a variety of *N*-benzoyl-*N*-phenylbenzamides and triarylboranes, which are generated *in situ* from the corresponding

tetraarylborates, to synthesize ketone products in up to 91% yield. This chapter also discusses preliminary mechanistic studies on nickel-catalyzed intermolecular alkene carboacylation. The work described in this chapter was done in collaboration with Tanner Metz who was a graduate student in the Stanley Group. Yiqiu Qian was an undergraduate student who also worked on this project and helped in synthesizing amide substrates. The described work in Chapter III is a modified version of a paper published in *ACS Catalysis*.

Chapter IV discusses research findings on the palladium-catalyzed, intermolecular acylative Heck reaction using amides as electrophiles. This chapter will be modified for publication in a peer reviewed journal. Colton David, who is an undergraduate student in the Stanley group, is responsible for amide synthesis and has contributed towards reaction development. The discussion in this chapter includes development, substrate scope, and plausible mechanism of the palladium-catalyzed, intermolecular acylative Heck reaction. The developed method allowed for Heck reaction between a wide array of *N*-benzoylglutarimide bearing electron-donating, halogenated, and electro-withdrawing substituents and a bicyclic alkene, norbornene, to generate α,β -unsaturated ketones in up to 82% yield.

Chapter V describes a general summary and conclusion of the research findings described in Chapters II-IV.

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**CHAPTER 1. ENANTIOSELECTIVE, PALLADIUM-CATALYZED CONJUGATE
ADDITIONS OF ARYLBORONIC ACIDS TO β -ARYL, β,β -
DISUBSTITUTED ENONES TO BIS-BENZYLIC QUATERNARY
STEREOCENTERS**

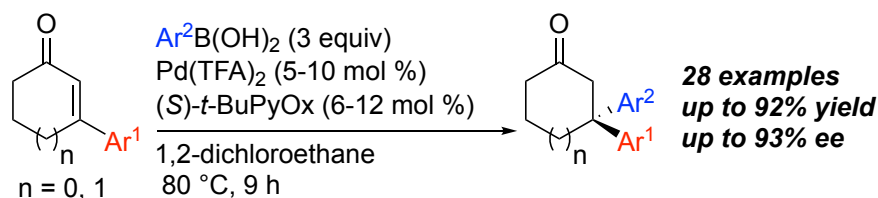
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Abstract



We report enantioselective, palladium-catalyzed conjugate additions of arylboronic acids to β -aryl, β,β -disubstituted enones to generate ketones containing bis-benzylic quaternary stereocenters. A catalyst generated from palladium trifluoroacetate and a chiral, non-racemic (*S*)-4-*tert*-butyl-2-(2-pyridyl)oxazoline ligand ((*S*)-*t*-BuPyOx) promotes conjugate additions of a wide range of arylboronic acids to a variety of β -aryl, β,β -disubstituted enones. Iterative addition of the arylboronic acid nucleophile to minimize undesired protodeboronation pathways leads to efficient formation of the corresponding ketones containing bis-benzylic quaternary stereocenters in up to 92% yield with up to 93% enantioselectivity.

Introduction

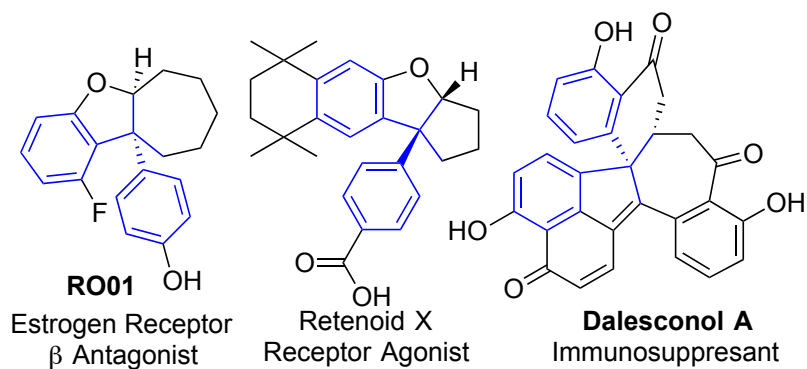
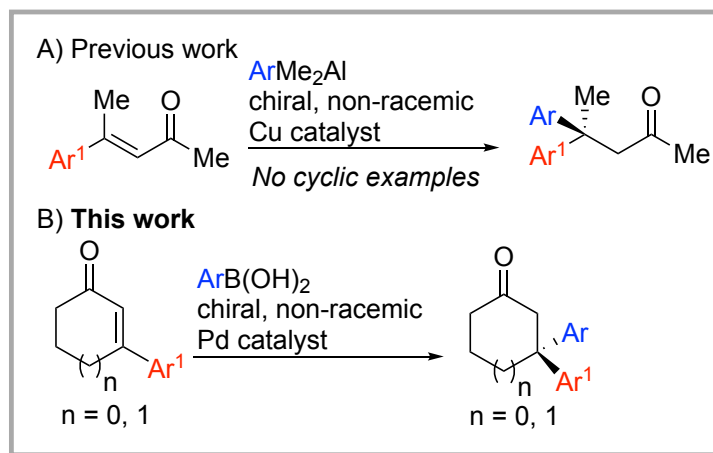


Figure 1. Biologically active compounds containing bis-benzylic quaternary centers.

Compounds containing bis-benzylic quaternary centers are present in an array of biologically active compounds¹ (Figure 1) and are a structural motif found in the cardo class of polymers.² Enantioselective, transition metal-catalyzed conjugate addition reactions of organometallic nucleophiles to β,β -disubstituted enones are a powerful approach to form quaternary stereocenters.³ Despite recent advances in enantioselective, transition metal-catalyzed conjugate additions of organometallic nucleophiles, asymmetric additions to β -aryl β,β -disubstituted enones to form bis-benzylic quaternary stereocenters remain challenging.

Over the past decades, enantioselective conjugate additions of arylzinc,⁴ arylaluminum,⁵ arylmagnesium,⁶ and arylboron⁷ nucleophiles to β,β -disubstituted enones in the presence of chiral copper, rhodium, and palladium catalysts have been developed as practical methods to synthesize compounds containing benzylic quaternary stereocenters. In particular, Stoltz and co-workers developed enantioselective conjugate additions of arylboronic acids to a variety of β -substituted cyclic enones to form quaternary stereocenters in the presence of Pd(II) complexes of a chiral, nonracemic pyridine-oxazoline ligand ((*S*)-*t*-BuPyOx).^{7d,f,h-k} However, examples of enantioselective, transition metal-catalyzed conjugate additions of aryl organometallic nucleophiles to β -aryl β,β -disubstituted enones to generate compounds

containing bis-benzylic quaternary stereocenters are limited to copper-catalyzed additions to acyclic electrophiles.



Scheme 1. Enantioselective, Conjugate Additions of Aryl Nucleophiles to β -aryl β,β -disubstituted enones

In 2013, Hoveyda and coworkers reported copper-catalyzed conjugate additions of arylaluminum compounds to β -aryl β,β -disubstituted acyclic enones to form acyclic ketones containing bis-benzylic quaternary stereocenters with good-to-excellent enantioselectivity (Scheme 1A).^{5c} In this report, however, there are no examples of additions of arylaluminum nucleophiles to β -aryl β,β -disubstituted cyclic enones. In addition, these copper-catalyzed conjugate addition reactions use air and moisture sensitive arylaluminum nucleophiles and have low functional group compatibility.

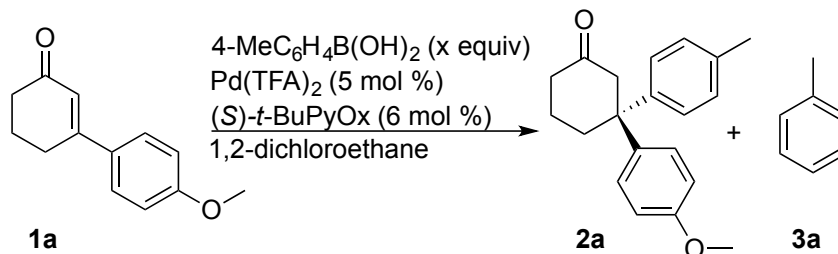
We recently reported palladium-catalyzed conjugate additions of bench stable and commercially available arylboronic acids to β,β -disubstituted enones in aqueous media to form an array of ketones with bis-benzylic quaternary centers in moderate-to-high yields (54-74%).^{8,9} However, efforts from our group and others to develop enantioselective variants of these reactions have been limited by modest enantioselectivity in aqueous media, poor

reactivity in organic solvents,⁷ⁱ and competing decomposition of the arylboronic acid nucleophile. We now report catalytic, enantioselective additions of arylboronic acids to β -aryl β,β -disubstituted cyclic enones that occur in up to 92% yield with high enantioselectivity and minimize undesired pathways for nucleophile decomposition (Scheme 1B).

Results and Discussion

Early efforts to identify an enantioselective catalyst for conjugate addition of phenylboronic acid to 3-(4-methoxyphenyl)-cyclohexen-2-one in aqueous reaction media led to modest yields of the corresponding ketone product and relatively low enantioselectivity (see Table S1 in General Experiment Details). After an initial evaluation of palladium(II) catalysts generated from chiral, non-racemic pyridine-oxazoline and bisoxazoline ligands, we identified reactions conducted in 1,2-dichloroethane and a catalyst generated *in situ* from palladium trifluoroacetate ($\text{Pd}(\text{TFA})_2$) and (*S*)-*t*-BuPyOx^{7k} as leads for further reaction optimization.^{7d,f,h-k}

We then selected the addition of 4-tolylboronic acid to 3-(4-methoxyphenyl)-cyclohex-2-enone **1a** in the presence of 5 mol % of the catalyst generated from $\text{Pd}(\text{TFA})_2$ and (*S*)-*t*-BuPyOx as a model reaction (Table 1) that would facilitate straightforward analysis of reaction products and byproducts. The addition of 4 equiv of 4-tolylboronic acid to **1a** at 90 °C formed 3-(4-methoxyphenyl)-3-(4-tolyl)cyclohexanone **2a** in 46% yield with 89% ee (entry 1). Palladium-catalyzed conjugate additions of arylboronic acids are often plagued by protodeboronation reactions that can occur through multiple pathways^{7g,10} and have hindered the development of conjugate additions to form bis-benzylic quaternary stereocenters.

Table 1. Identification of Reaction Conditions^a

Entry	temp (° C)	x	yield 2a (%) ^b	yield 3a (%) ^c	ee (%) ^d
1 ^e	90	4	46	43	89
2	90	1	45	25	89
3	80	1	42	10	89
4	60	1	42	9	91
5	40	1	24	6	94
6 ^f	60	1	49	10	91
7 ^{f,g}	60	1	55	12	92
8 ^{g,h}	60	2	70	11	91
9 ^{g,h}	60	3	82	14	91
10 ^{g,i}	60	3	64	9	91
11 ^{g,i}	80	3	83	21	89
12 ^{g,j}	80	3	80	nd ^k	87

^aReaction conditions: **1a** (1.0 equiv), 4-tolylboronic acid (x equiv) Pd(TFA)₂ (5 mol %), (S)-*t*-BuPyOx (6 mol %), 1,2-dichloroethane (0.5 M), 3 h. ^bIsolated yields. ^cGC yield, calculated based on the total number of equiv of 4-tolylboronic acid. ^dDetermined by chiral HPLC analysis. ^eReaction time = 24 h. ^fReaction time = 6 h. ^g[**1a**] = 2 M. ^hAddition of 4-tolylboronic at 6 h intervals. ⁱAddition of 4-tolylboronic at 3 h intervals. ^jReaction run in the presence of 10 mol % 2,6-di-*tert*-butylpyridine. ^knd = not determined.

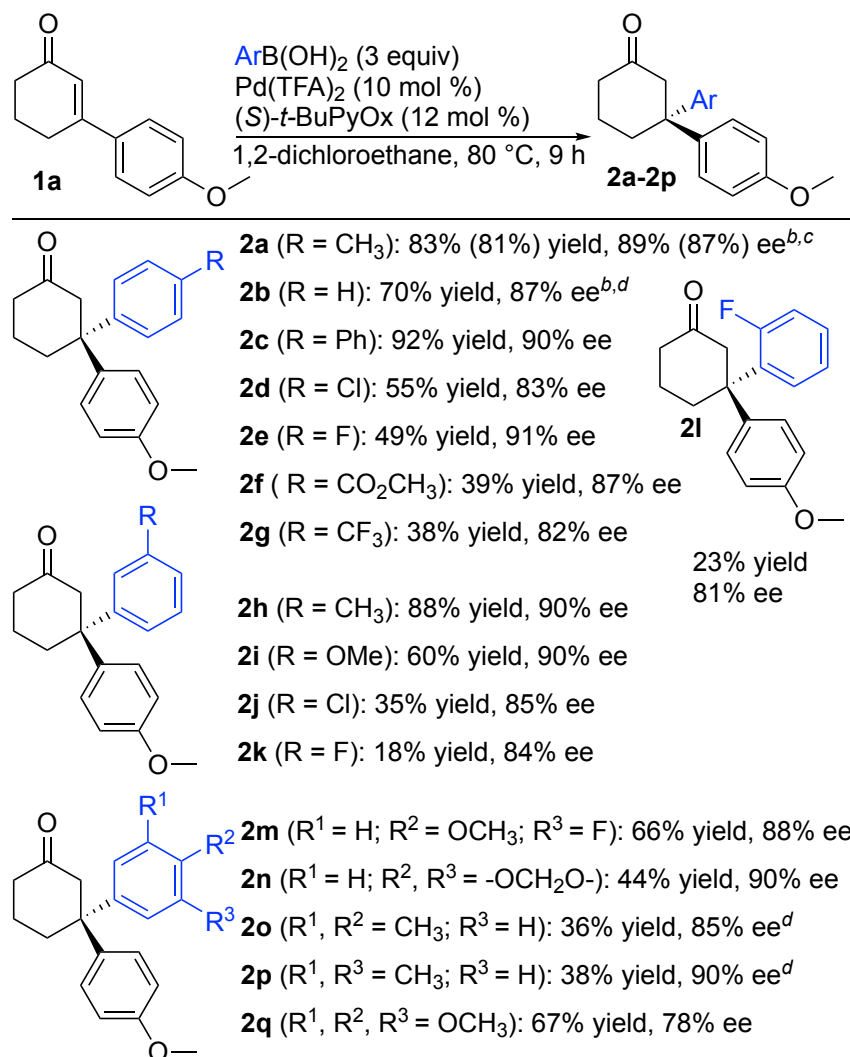
The addition of 4 equiv of 4-tolylboronic acid to **1a** led to protodeboronation of 43% of the total tolylboronic acid, formation of 2% of the homocoupling byproduct 4,4'-dimethyl-1,1'-

biphenyl, and oxidation of **1a** to form 4% 3-(4-methoxyphenyl)phenol. When the model reaction was conducted with 1 equiv of 4-tolylboronic acid, the reaction generated **2a** in 45% yield and 89% ee. The formation of 25% toluene through protodeboronation and small amounts (<5%) of 4,4'-dimethyl-1,1'-biphenyl and 3-(4-methoxyphenyl)-phenol were also observed.

The absolute configuration of ketone **2a** was determined after conversion to the corresponding 2,4-dinitrophenylhydrazone. The absolute configuration was determined to be *3S* by X-ray crystallographic analysis (see General Experimental Details).

We next studied the impact of reaction temperature on the relative rate of protodeboronation to conjugate addition (Table 1, entries 2-5). The amount of toluene generated decreases with lower reaction temperature. The best ratios of ketone **2a**/toluene **3a** (4.2-4.7:1) is observed at 60-80 °C, and the reactions generate **2a** in 42% yield and 89-91% ee (entries 3-4). Increasing the reaction time (entry 6) and the reaction concentration (entry 7) led to modest improvement in the yield of **2a** without increasing the rate of protodeboronation. To increase the yield of **2a**, we adopted an iterative addition strategy to maintain low concentrations of tolylboronic acid and hence a low rate of protodeboronation (entries 8-11). These reactions were conducted by starting the reaction with 1 equiv of 4-tolylboronic acid and adding additional equivalent(s) at 3 or 6 h intervals. This approach to arylboronic acid addition led to significantly higher yields of ketone **2a** (64-83%) and high enantioselectivities without a dramatic increase in the rate of protodeboronation. The model reaction occurs to form **2a** with similar yields and enantioselectivities in the presence and absence of 2,6-di-*tert*-butylpyridine (compare entries 11 and 12) suggesting that residual TFA is not required for product formation. We chose to evaluate the scope of the conjugate addition reaction using the

conditions identified in entry 11 as a practical combination of reactivity, enantioselectivity, and relative rates of productive versus unproductive reaction pathways.



^aReaction conditions: **1a** (1.0 equiv), arylboronic acid (3.0 equiv), Pd(TFA)₂ (10 mol %), (S)-*t*-BuPyOx (12 mol %), 1,2-dichloroethane (2 M). ^bReaction run in the presence of 5 mol % of the palladium catalyst. ^cValues in parentheses are for a 1.00 mmol scale experiment in the presence of 5 equiv of water. ^dReaction performed in the presence of 5 equiv of water.

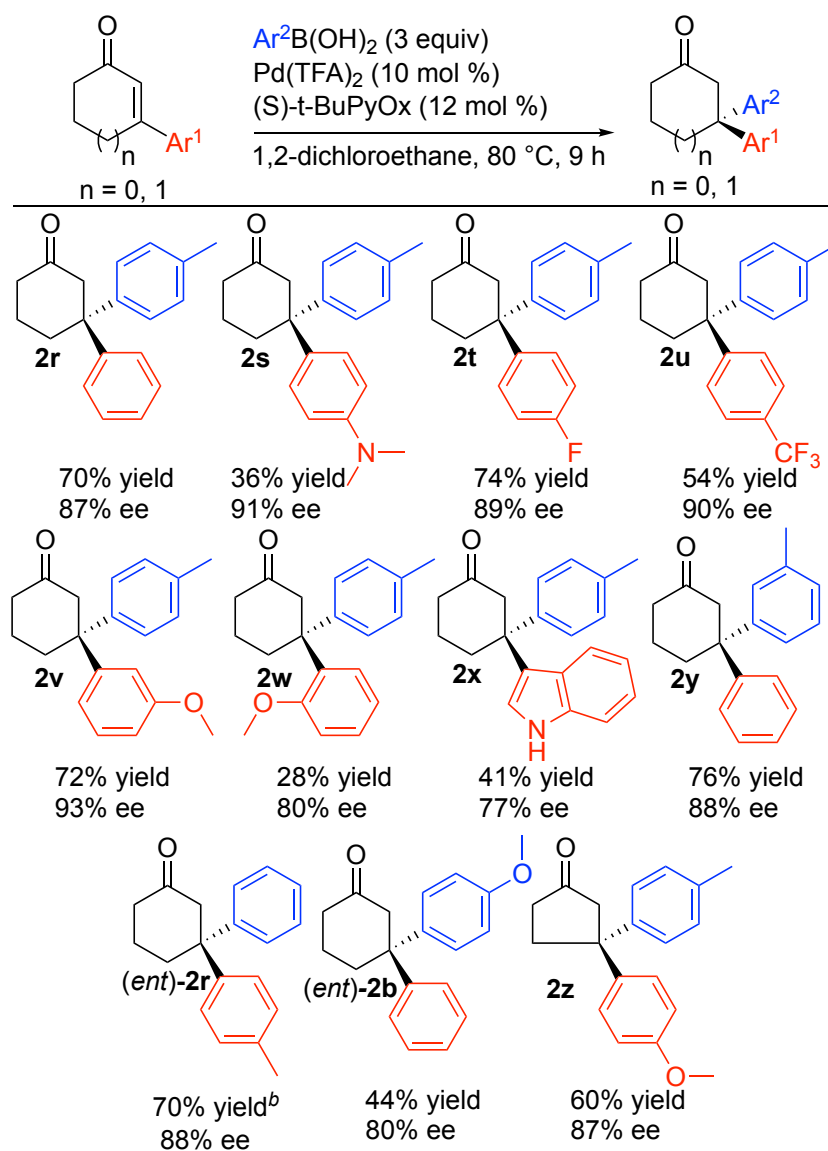
Scheme 2. Enantioselective, Pd-Catalyzed Conjugate Additions of Arylboronic Acids to **1a**^a

Studies to establish the scope of additions of a variety of arylboronic acids to 3-(4-methoxyphenyl)-cyclohex-2-enone **1a** are summarized in Scheme 2. Additions of electronically diverse, *para*- and *meta*-substituted arylboronic acids occurred to generate the corresponding ketone products **2a-2k** in 18-92% yields with 82-91% enantioselectivities. Additions of *para*-substituted electron-rich, electron-neutral, and halogenated arylboronic acids to **1a** formed ketones **2a-2e** in moderate-to-high yields (49-92%) with high enantioselectivities (82-91% ee). However, the addition of electron-deficient arylboronic acids, which are less nucleophilic, generated **2f** and **2g** in 39% and 38% yields. Additions of electron-rich *meta*-substituted arylboronic acids to **1a** formed **2h** and **2i** in 60% and 88% yield with 90% ee. In contrast, additions of *meta*- and *ortho*-halogenated arylboronic acids generate ketones **2j-2l** in low yields but with good enantioselectivities (81-84% ee).

These reactions also encompass additions of a variety of di- and tri-substituted arylboronic acids. The corresponding ketone products **2m-2q** are generated in moderate-to-good yields (36-67%) with good-to-high enantioselectivities (78-90%). However, additions of 2-methoxyphenylboronic acid, 3-furylboronic acid and 6-indolylboronic acid, which are more susceptible to protodeboronation,^{10a,11} were unsuccessful.

To further expand the scope of these reactions, we studied additions of arylboronic acids to a variety of β -aryl β,β -disubstituted enones. These results are summarized in Scheme 3. Additions of 4-tolylboronic acid to 3-arylcyclohex-2-enones containing electron-neutral, halogenated, electron-deficient, and electron-rich aryl groups generated **2r-2v** in moderate-to-good yields (36-74%) with high enantioselectivities (87-93%). The additions of 4-tolyl boronic acid to β,β -disubstituted enones containing either an *ortho*-substituted aryl unit or a heteroarene

enables the formation of ketones **2w** and **2x**, products that cannot be formed by addition of the corresponding *ortho*-substituted arylboronic acid or heteroarylboronic acid.



^aReaction conditions: 3-arylcyclohex-2-enone (1.0 equiv), arylboronic acid (3.0 equiv), Pd(TFA)_2 (10 mol %), $(S)\text{-}t\text{-BuPyOx}$ (12 mol %), 1,2-dichloroethane (2 M). ^bReaction performed in the presence of 5 equiv of water.

Scheme 3. Enantioselective Pd-Catalyzed Conjugate Additions of Arylboronic Acids to β -Aryl β,β -Disubstituted Enones^a

To demonstrate the addition of *meta*-substituted arylboronic acids to an additional enone, we conducted the reaction of 3-methylphenylboronic acid with 3-phenylcyclohex-2-enone to generate **2y** in 76% yield with 88% ee. The addition of phenylboronic acid to 3-(4-methylphenyl)cyclohex-2-enone, and 4-methoxyphenylboronic acid to 3-phenylcyclohex-2-enone generated (*ent*)-**2r** and (*ent*)-**2b** in 40-77% yield and 80-88% ee. We also studied the addition of 4-tolylboronic acid to cyclic enones with different ring sizes and to an acyclic enone. Addition of 4-tolylboronic acid to 3-(4-methoxyphenyl)cyclopent-2-enone generated **2z** in 60% yield and 91% ee. However, addition of 4-tolylboronic acid to 3-phenylcyclohept-2-enone and (*E*)-4-phenylpent-3-en-2-one generated the corresponding ketone products in less than 15% yield.

Conclusion

In summary, we have developed the first examples of enantioselective, palladium-catalyzed conjugate additions of arylboronic acids to β -aryl β,β -disubstituted cyclic enones. A catalyst generated *in situ* from Pd(TFA)₂ and (*S*)-*t*-BuPyOx catalyzes enantioselective conjugate additions of electronically and structurally diverse arylboronic acids to a variety of β -aryl β,β -disubstituted enones. These reactions generate cyclic ketone products containing bis-benzylic quaternary carbon stereocenters in up to 92% yield and up to 93% ee by iterative addition of the arylboronic acid nucleophile to minimize protodeboronation.

Experimental

General Details. All reactions were conducted under air unless otherwise noted. Reactions involving air-sensitive reagents were conducted under inert atmosphere in a nitrogen-filled dry box or by standard Schlenk techniques. Moisture sensitive reaction were performed using glassware which were dried at 140 °C in an oven overnight prior to use. Flash

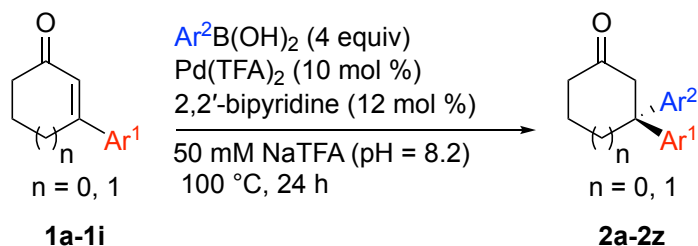
column chromatography was performed on Siliflash® P60 silica gel (230-400 mesh) or using a Teledyne Isco Combiflash® Rf system with RediSep Gold™ columns using hexane/ethyl acetate mixtures as the eluent. Products were visualized on TLC by UV light and/or by staining with 2,4-dinitrophenylhydrazine.

HRMS (ESI) analysis was performed at the Iowa State Chemical Instrumentation Facility on an Agilent 6540 QTOF spectrometer. Optical rotations were measured on an Atago AP-300 automatic polarimeter. HPLC analyses were carried out on a Water Alliance HPLC system with an e2695 Separations Module and a 2489 (UV/Vis) dual wavelength detector. NMR spectra were acquired on Varian MR-400 and Bruker Avance III 600 spectrometers at the Iowa State Chemical Instrumentation Facility. Chemical shifts are reported relative to a residual solvent peak ($\text{CDCl}_3 = 7.26$ ppm for ^1H , and 77.16 ppm for ^{13}C). ^{19}F NMR shifts are reported based on indirect reference to CDCl_3 .¹² Coupling constants are reported in hertz.

Materials. 3-(4-Methoxyphenyl)-cyclohex-2-enone **1a**, 3-phenylcyclohex-2-enone **1b**, 3-(4-fluorophenyl)-cyclohex-2-enone **1d**, 3-(4-trifluoromethylphenyl)-cyclohex-2-enone **1e**, 3-(3-methoxyphenyl)-cyclohex-2-enone **1f**, 3-(2-methoxyphenyl)-cyclohex-2-enone **1g**, and 3-(4-methylphenyl)-cyclohex-2-enone **1i**, and 3-(4-methoxyphenyl)-cyclopent-2-enone **1j** were prepared according to a literature procedure.¹³ Characterization data for 3-(4-methoxyphenyl)-cyclohex-2-enone **1a**,¹⁴ 3-phenylcyclohex-2-enone **1b**,¹³ 3-(4-fluorophenyl)-cyclohex-2-enone **1d**,^{7c} 3-(4-trifluoromethylphenyl)-cyclohex-2-enone **1e**,¹⁵ 3-(3-methoxyphenyl)-cyclohex-2-enone **1f**,^{7c} 3-(2-methoxyphenyl)-cyclohex-2-enone **1g**,^{7c} and 3-(4-methylphenyl)-cyclohex-2-enone **1i**,¹⁴ and 3-(4-methoxyphenyl)-cyclopent-2-enone **1j**¹⁶ matched previously reported data. 3-(1H-indol-3-yl)cyclohex-2-en-1-one **1h**,¹⁷ (*E*)-4-phenylcyclohept-2-enone **1k**,¹⁵ (*E*)-4-phenylpent-3-en-2-one **1l**^{5c} were synthesized according

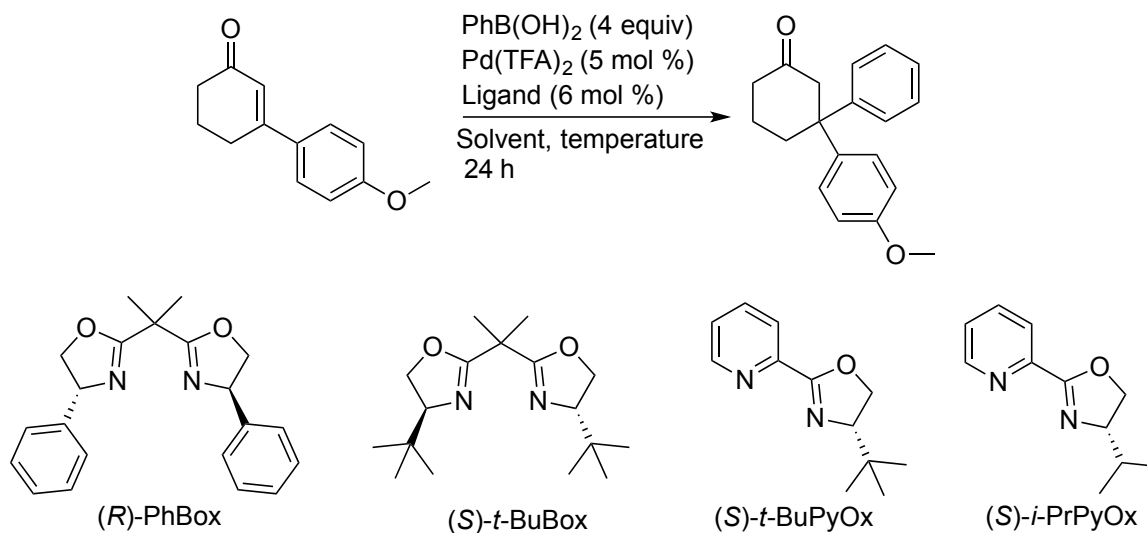
to reported literature procedures. (4*R*,4'*R*)-2,2'-(propane-2,2-diyl)bis(4-phenyl-4,5-dihydrooxazole) ((*R*)-PhBox),¹⁸ (*S*)-4-(*tert*-butyl)-2-(pyridin-2-yl)-4,5-dihydrooxazole ((*S*)-*t*-BuPyOx),¹⁹ and (*S*)-4-isopropyl-2-(pyridin-2-yl)-4,5-dihydrooxazole ((*S*)-*i*-PrPyOx)²⁰ were prepared according to previously reported literature procedures. Palladium trifluoroacetate, (4*S*,4'*S*)-2,2'-(propane-2,2-diyl)bis(4-(*tert*-butyl)-4,5-dihydrooxazole) ((*S*)-*t*-BuBox), 3,5-dimethylphenylboronic acid, 4-methoxycarbonylphenylboronic acid and 2,4-dinitrophenylhydrazine were purchased from Sigma-Aldrich and used without further purification. 2,2'-Bipyridine was purchased from Fisher Scientific and used without further purification. 4-Methylphenylboronic acid, phenylboronic acid, 4-methoxyphenylboronic acid, 4-fluorophenylboronic acid, 3-methoxyphenylboronic acid, 3-chlorophenylboronic acid, 3-fluorophenylboronic acid, 2-fluorophenylboronic acid and 4-trifluoromethylphenylbromide were purchased from AK Scientific and used without further purification. 4-Biphenylboronic acid, 4-trifluoromethylphenylboronic acid, 2-methoxyphenylboronic acid, 3-fluoro-4-methoxyphenylboronic acid, 3,4-methylenedioxyphenylboronic acid, 3,4-dimethylphenylboronic acid, 3,4,5-trimethoxyphenylboronic acid, 2-furanylboronic acid and 6-indolylboronic acid were purchased from Frontier Scientific, Inc. and used without further purification. 4-Chlorophenylboronic acid was purchased from Combi-Blocks, Inc. and used without further purification. 3-Methylphenylboronic acid was purchased from Ark Pharm, Inc. and used without further purification. Dibromomethane was purchased from Acros and used without further purification.

General Procedure A: Pd-Catalyzed Conjugate Additions of Arylboronic Acids to β -Aryl, β , β -Disubstituted Enones to Access Racemic Ketones 2a-2a



To a 1 dram vial were added Pd(TFA)_2 (10 mg, 0.030 mmol), 2,2'-bipyridine (5.6 mg, 0.036 mmol), the appropriate enone (0.300 mmol), arylboronic acid (1.20 mmol, 4.00 equiv) and 50 mM aqueous sodium trifluoroacetate solution (0.10 mL, pH = 8.2). The vial was sealed with a PTFE/silicone-lined septum cap. The reaction mixture was then stirred at 100 °C for 24 h. The reaction mixture was filtered through a short plug of magnesium sulfate (top) and silica gel (bottom) (eluting with 20 mL of ethyl acetate) and then concentrated under vacuum. The crude reaction mixture was dissolved in CDCl_3 (1 mL) and CH_2Br_2 (10.5 μL , 0.150 mmol) was added as an internal standard. NMR yields were determined by ^1H NMR spectroscopy of the crude reaction mixture. The crude reaction mixture was purified by flash column silica gel chromatography or using a Teledyne Isco Combiflash® Rf system with RediSep Gold™ columns (hexane:ethyl acetate) to give corresponding ketones. Racemic ketones **2a-2z** were isolated in 18-85% yields.

Table S1. Catalyst Identification for Pd-catalyzed Conjugate Additions of Phenylboronic Acid to 3-(4-Methoxyphenyl)-cyclohex-2-enone **1a^a**



Entry	temp (°C)	ligand	solvent	product ^b	% ee ^c
1	80	(<i>R</i>)-PhBox	aq. NaTFA (pH = 8.2)	0	-
2	80	(<i>S</i>)- <i>t</i> -BuBox	aq. NaTFA (pH = 8.2)	0	-
3	80	(<i>S</i>)- <i>t</i> -BuPyOx	aq. NaTFA (pH = 8.2)	17	77
4	80	(<i>S</i>)- <i>i</i> -PrPyOx	aq. NaTFA (pH = 8.2)	21	49
5	100	(<i>S</i>)- <i>t</i> -BuPyOx	aq. NaTFA (pH = 8.2)	8 ^d	-
6	60	(<i>S</i>)- <i>t</i> -BuPyOx	aq. NaTFA (pH = 8.2)	4	71
7	80	(<i>S</i>)- <i>t</i> -BuPyOx	1,2-dichloroethane	34	88
8 ^e	80	(<i>S</i>)- <i>t</i> -BuPyOx	1,2-dichloroethane	34	91
9 ^e	80	(<i>S</i>)- <i>t</i> -BuPyOx	methanol	36	84
10 ^{e,f}	80	(<i>S</i>)- <i>t</i> -BuPyOx	1,2-dichloroethane	30	91
11 ^e	90	(<i>S</i>)- <i>t</i> -BuPyOx	1,2-dichloroethane	39	91

^aReaction conditions: 3-(4-methoxyphenyl)-cyclohex-2-enone **1a** (0.300 mmol), phenylboronic acid (1.20 mmol), Pd(TFA)₂ (0.015 mmol), ligand (0.018 mmol), solvent (0.1 mL), 24 h. ^bIsolated yield. ^cDetermined by chiral HPLC analysis. ^dYield determined by ¹H

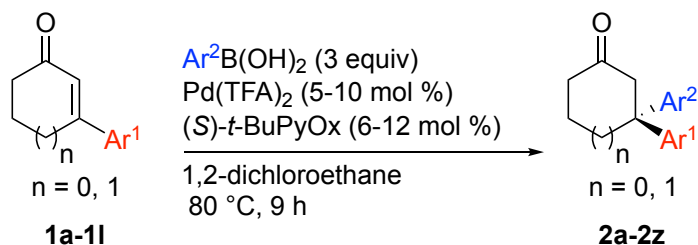
NMR using dibromomethane as an internal standard. ^eReaction run in 0.6 mL of solvent.

^fReaction run in the presence of 30 mol % NH₄PF₆ and 5 equiv. of water.

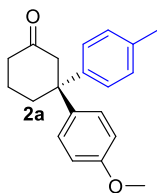
General Procedure B: Catalyst Identification by Conjugate Addition of Phenylboronic Acid to 3-(4-Methoxyphenyl)-cyclohex-2-enone 1a

To a 1 dram vial were added Pd(TFA)₂ (5.0 mg, 0.015 mmol), ligand (0.018 mmol), 3-(4-methoxyphenyl)-cyclohex-2-enone **1a** (60.7 mg, 0.300 mmol), phenylboronic acid (146 mg, 1.20 mmol), and solvent (0.1 mL). The vial was sealed with a PTFE/silicone-lined septum cap. The reaction mixture was then stirred at 60-100 °C for 24 h. The reaction mixture was filtered through a short plug of magnesium sulfate (top) and silica gel (bottom) (eluting with 20 mL of ethyl acetate) and then concentrated under vacuum. The crude reaction mixture was dissolved in CDCl₃ (1 mL) and CH₂Br₂ (10.5 μL, 0.15 mmol) was added as an internal standard. NMR yields were determined by ¹H NMR spectroscopy of the crude reaction mixture. The crude product was purified by silica gel column chromatography with a CombiFlash system (4 g column, 100:0 to 90:10 hexane: EtOAc) to give **2b** as a colorless oil. The enantiomeric excess was determined by HPLC analysis (220 nm, 25 °C) t_R 21.1 min (minor); t_R 34.8 min (major) [Chiracel AS-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 80:20, 1.0 mL/min].

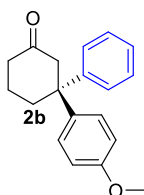
General Procedure C: Enantioselective, Pd-Catalyzed Conjugate Additions of Arylboronic Acids to β -Aryl, β,β -Disubstituted Enones to Access Ketones 2a-2z



To a 1 dram vial were added Pd(TFA)_2 (10 mg, 0.030 mmol), $(S)\text{-}t\text{-BuPyOx}$ (7.4 mg, 0.036 mmol), the appropriate enone (0.300 mmol), arylboronic acid (0.300 mmol, 1.00 equiv) and 1,2-dichloroethane (0.15 mL). The vial was sealed with a PTFE/silicone-lined septum cap. The reaction mixture was then stirred at 80 °C for 3 h. After 3 h, another equivalent of arylboronic acid (0.300 mmol, 1.00 equiv) was added and the reaction mixture was stirred for another 3 h. The same procedure was followed for a third equiv of arylboronic acid (0.300 mmol, 1.00 equiv). The reaction mixture was filtered through a short plug of silica gel (eluting with 20 mL of ethyl acetate) and then concentrated under vacuum. The crude reaction mixture was dissolved in CDCl_3 (1 mL) and CH_2Br_2 (10.5 μL , 0.15 mmol) was added as an internal standard. NMR yields were determined by ^1H NMR spectroscopy of the crude reaction mixture. The crude reaction mixture was purified by flash column silica gel chromatography or using a Teledyne Isco Combiflash® Rf system with RediSep Gold™ columns (hexane: ethyl acetate) to yield the corresponding ketone. **Note:** for synthesis of ketones **2a** and **2b**, Pd(TFA)_2 (5.0 mg, 0.015 mmol) and $(S)\text{-}t\text{-BuPyOx}$ (3.7 mg, 0.018 mmol) were used to generate the catalyst.

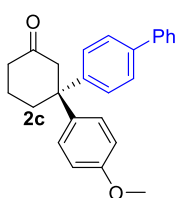


(S)-3-(4-methoxyphenyl)-3-(p-tolyl)cyclohexan-1-one (2a): Prepared according to General Procedure C from 3-(4-methoxyphenyl)cyclohex-2-en-1-one **1a** (60.7 mg, 0.300 mmol) and 4-tolylphenylboronic acid (122 mg, 0.900 mmol) using palladium trifluoroacetate (5.0 mg, 0.015 mmol) and (*S*)-*t*-BuPyOX (3.7 mg, 0.018 mmol). The crude product was purified by flash chromatography (90:10 hexane: EtOAc) to give **2a** (72.4 mg, 0.246 mmol, 83%) as a colorless oil. The enantiomeric excess was determined by HPLC analysis (220 nm, 25 °C) t_R 34.2 min (minor); t_R 40.8 min (major) [Chiracel OJ-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90:10, 1.0 mL/min] to be 89% ee. $[\alpha]_D^{22} = +10.2^\circ$ (*c* 0.78, CHCl₃). **¹H NMR** (400 MHz, CDCl₃): δ 1.65-1.74 (m, 2H), 2.30 (s, 3H), 2.34 (t, $J = 6.8$ Hz, 2H), 2.52 (d, $J = 7.2$ Hz, 1H), 2.53 (d, $J = 7.2$ Hz, 1H), 2.90 (d, $J = 15.6$ Hz, 1H), 2.94 (d, $J = 15.6$ Hz, 1H), 3.77 (s, 3H), 6.81 (ddd, $J = 8.8, 3.2, 2.0$ Hz, 2H), 7.08 (s, 4H), 7.12 (ddd, $J = 8.8, 3.2, 2.0$ Hz, 2H). **¹³C NMR** (101 MHz, CDCl₃): δ 21.0, 21.3, 36.0, 40.9, 49.6, 54.1, 55.3, 113.8, 126.9, 128.1, 129.2, 135.8, 129.6, 144.8, 157.9, 211.1. **HRMS** (ESI): Calcd. for C₂₀H₂₃O₂⁺ ([M+H]⁺): 295.1693 Found: 295.1689.



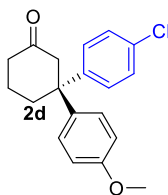
(S)-3-(4-methoxyphenyl)-3-phenylcyclohexan-1-one (2b): Prepared according to General Procedure C from 3-(4-methoxyphenyl)cyclohex-2-en-1-one **1a** (60.7 mg, 0.300 mmol) and phenylboronic acid (110 mg, 0.900 mmol) using palladium trifluoroacetate (5.0 mg, 0.015 mmol) and (*S*)-*t*-BuPyOX (3.7 mg, 0.018 mmol). The crude product was purified with a CombiFlash system (4 g column, 100:0 to 90:10 hexane: EtOAc) to give **2b** (58.8 mg, 0.210 mmol, 70%) as a colorless oil. The enantiomeric excess was determined by HPLC analysis (220 nm, 25 °C) t_R 21.1 min (minor); t_R 34.8 min (major) [Chiracel AS-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 80:20,

1.0 mL/min] to be 87% ee. $[\alpha]_D^{26} = +17.5$ (c 0.80, CHCl_3). **$^1\text{H NMR}$** (400 MHz, CDCl_3): δ 1.66-1.72 (m, 2H), 2.35 (t, $J = 6.8$ Hz, 2H), 2.55 (d, $J = 7.2$ Hz, 1H), 2.56 (d, $J = 7.2$ Hz, 1H), 2.91 (d, $J = 15.6$ Hz, 1H), 2.96 (d, $J = 15.6$ Hz, 1H), 3.77 (s, 3H), 6.81 (d, $J = 8.8$ Hz, 2H), 7.12 (d, $J = 8.8$ Hz, 2H), 7.17 (t, $J = 7.2$ Hz, 1H), 7.20 (d, $J = 7.2$ Hz, 2H), 7.27 (t, $J = 7.2$ Hz, 2H). **$^{13}\text{C NMR}$** (101 MHz, CDCl_3): δ 21.2, 35.9, 40.9, 49.9, 54.0, 55.3, 113.8, 126.3, 127.0, 128.2, 128.5, 139.4, 147.8, 157.9, 211.0. **HRMS** (ESI): Calcd. for $\text{C}_{19}\text{H}_{21}\text{O}_2^+$ ($[\text{M}+\text{H}]^+$): 281.1536 Found: 281.1539.



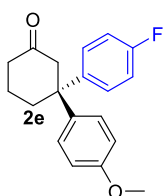
(S)-3-([1,1'-biphenyl]-4-yl)-3-(4-methoxyphenyl)cyclohexan-1-one (2c):

Prepared according to General Procedure C from 3-(4-methoxyphenyl)cyclohex-2-en-1-one **1a** (60.7 mg, 0.300 mmol) and [1,1'-biphenyl]-4-ylboronic acid (178 mg, 0.900 mmol). The crude product was purified with a CombiFlash system (4 g column, 100:0 to 95:5 hexane: EtOAc) to give **2c** (98.4 mg, 0.276 mmol, 92%) as a yellow solid. The enantiomeric excess was determined by HPLC analysis (220 nm, 25 °C) t_R 25.3 min (minor); t_R 29.7 min (major) [Chiracel AS-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 80:20, 1.0 mL/min] to be 90% ee. $[\alpha]_D^{26} = +11.0^\circ$ (c 0.73, CHCl_3). **$^1\text{H NMR}$** (400 MHz, CDCl_3): δ 1.66-1.81 (m, 2H), 2.38 (t, $J = 6.8$ Hz, 2H), 2.54-2.64 (m, 2H), 2.97 (d, $J = 15.2$, 1H), 3.01 (d, $J = 15.2$, 1H), 3.79 (s, 3H), 6.86 (ddd, $J = 8.8, 3.2, 2.0$ Hz, 2H), 7.19 (ddd, $J = 8.8, 3.2, 2.0$ Hz, 2H), 7.30 (d, $J = 8.4$ Hz, 2H), 7.34 (td, $J = 8.4, 7.2$ Hz, 1H), 7.44 (dd, $J = 8.4, 7.2$ Hz, 2H), 7.53 (d, $J = 8.4$ Hz, 2H), 7.58 (d, $J = 7.2$ Hz, 2H). **$^{13}\text{C NMR}$** (101 MHz, CDCl_3): δ 21.3, 36.0, 40.9, 49.8, 54.0, 55.3, 113.9, 127.1, 127.2, 127.3, 127.4, 128.2, 128.9, 139.0, 139.2, 140.6, 146.8, 157.9, 210.9. **HRMS** (ESI): Calcd. for $\text{C}_{25}\text{H}_{25}\text{O}_2^+$ ($[\text{M}+\text{H}]^+$): 357.1849 Found: 357.1826.



(R)-3-(4-chlorophenyl)-3-(4-methoxyphenyl)cyclohexan-1-one (2d):

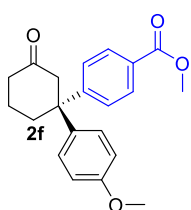
Prepared according to General Procedure C from 3-(4-methoxyphenyl)cyclohex-2-en-1-one **1a** (60.7 mg, 0.300 mmol) and 4-chlorophenylboronic acid (141 mg, 0.900 mmol). The crude product was purified with a CombiFlash system (4 g column, 100:0 to 95:5 hexane: EtOAc) to give **2d** (51.9 mg, 0.165 mmol, 55%) as a colorless oil. The enantiomeric excess was determined by HPLC analysis (220 nm, 25 °C) t_R 19.4 min (minor); t_R 36.6 min (major) [Chiracel AS-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 80:20, 1.0 mL/min] to be 83% ee. $[\alpha]_D^{22} = +8.0^\circ$ (c 1.00, CHCl₃). **¹H NMR** (400 MHz, CDCl₃): δ 1.65-1.71 (m, 2H), 2.34 (t, $J = 6.4$ Hz, 2H), 2.50-2.53 (m, 2H), 2.86 (d, $J = 15.2$ Hz, 1H), 2.92 (d, $J = 15.2$ Hz, 1H), 3.77 (s, 3H), 6.81 (d, $J = 8.4$ Hz, 2H), 7.09 (d, $J = 8.4$ Hz, 2H), 7.12 (d, $J = 8.4$ Hz, 2H), 7.23 (d, $J = 8.4$ Hz, 2H). **¹³C NMR** (101 MHz, CDCl₃): δ 21.2, 35.9, 40.8, 49.6, 53.9, 55.3, 114.0, 128.1, 128.4, 128.6, 132.1, 138.8, 146.3, 158.0, 210.6. **HRMS** (ESI): Calcd. for C₁₉H₂₀ClO₂⁺ ([M+H]⁺): 315.1146 Found: 315.1138.



(R)-3-(4-fluorophenyl)-3-(4-methoxyphenyl)cyclohexan-1-one (2e):

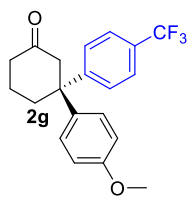
Prepared according to General Procedure C from 3-(4-methoxyphenyl)cyclohex-2-en-1-one **1a** (60.7 mg, 0.300 mmol) and 4-fluorophenylboronic acid (126 mg, 0.900 mmol). The crude product was purified with a CombiFlash system (4 g column, 100:0 to 95:5 hexane: EtOAc) to give **2e** (43.9 mg, 0.147 mmol, 49%) as a colorless oil with approximately 5% (calculated by ¹H NMR spectroscopy) of 4'-methoxy-3-methyl-1,1'-biphenyl as an inseparable impurity. The enantiomeric excess was determined by HPLC analysis (220 nm, 25 °C) t_R 22.9 min (minor); t_R 44.7 min (major) [Chiracel AS-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 80:20,

1.0 mL/min] to be 91% ee. $[\alpha]_D^{26} = +23.1^\circ$ (*c* 0.61, CHCl₃) **¹H NMR** (400 MHz, CDCl₃): δ 1.65-1.71 (m, 2H), 2.34 (t, *J* = 6.4 Hz, 2H), 2.51 (d, *J* = 7.2 Hz, 1H), 2.52 (d, *J* = 7.2 Hz, 1H), 2.87 (d, *J* = 15.2 Hz, 1H), 2.93 (d, *J* = 15.2 Hz, 1H), 3.77 (s, 3H), 6.81 (d, *J* = 8.4 Hz, 2H), 6.94 (d, *J* = 8.8 Hz, 1H), 6.96 (d, *J* = 8.4 Hz, 1H), 7.09 (d, *J* = 8.8 Hz, 2H), 7.15 (d, *J* = 8.4 Hz, 1H), 7.16 (d, *J* = 8.4 Hz, 1H). **¹³C NMR** (101 MHz, CDCl₃): δ 21.2, 36.1, 40.8, 49.6, 54.2, 55.3, 114.0, 115.3 (d, *J* = 21.1 Hz, 2C), 128.1, 128.6 (d, *J* = 7.9 Hz, 2C), 139.2, 143.5 (d, *J* = 3.3 Hz, 1C), 158.0, 161.2 (d, *J* = 246.6 Hz, 1C), 162.4, 210.7. **¹⁹F NMR** (376 MHz, CDCl₃): δ -116.9 (m, 1F). **HRMS** (ESI): Calcd. for C₁₉H₂₀FO₂⁺ ([M+H]⁺): 299.1442 Found: 299.1438.

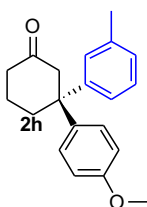


Methyl (S)-4-(1-(4-methoxyphenyl)-3-oxocyclohexyl)benzoate (2f):

Prepared according to General Procedure C from 3-(4-methoxyphenyl)cyclohex-2-en-1-one **1a** (60.7 mg, 0.300 mmol) and 4-methoxycarbonylphenylboronic acid (162 mg, 0.900 mmol). The crude product was purified by flash chromatography (50:50 hexane: diethylether) to give **2f** (39.6 mg, 0.117 mmol, 39%) as a white solid. The enantiomeric excess was determined by HPLC analysis (220 nm, 25 °C) t_R 33.4 min (minor); t_R 50.2 min (major) [Chiracel AS-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 80:20, 1.0 mL/min] to be 87% ee. $[\alpha]_D^{22} = 8.0^\circ$ (*c* 1.00, CHCl₃). **¹H NMR** (400 MHz, CDCl₃): δ 1.65-1.71 (m, 2H), 2.35 (t, *J* = 6.8 Hz, 2H), 2.54-2.57 (m, 2H), 2.89 (d, *J* = 15.2 Hz, 1H), 2.96 (d, *J* = 15.2 Hz, 1H), 3.77 (s, 3H), 3.88 (s, 3H), 6.81 (ddd, *J* = 8.8, 3.2, 2.0 Hz, 2H), 7.08 (ddd, *J* = 8.8, 3.2, 2.0 Hz, 2H), 7.27 (d, *J* = 8.4 Hz, 2H), 7.93 (d, *J* = 8.4 Hz, 2H). **¹³C NMR** (101 MHz, CDCl₃): δ 21.2, 35.9, 40.8, 50.2, 52.2, 53.7, 55.3, 114.0, 127.1, 128.2, 128.3, 129.9, 138.5, 153.1, 158.1, 166.9, 210.4. **HRMS** (ESI): Calcd. for C₂₁H₂₃O₄⁺ ([M+H]⁺): 339.1598 Found: 339.1591.

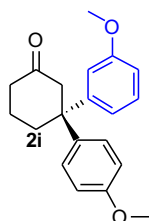


(S)-3-(4-methoxyphenyl)-3-(4-(trifluoromethyl)phenyl)cyclohexan-1-one (2g): Prepared according to General Procedure C from 3-(4-methoxyphenyl)cyclohex-2-en-1-one **1a** (60.7 mg, 0.300 mmol) and 4-trifluoromethylphenylboronic acid (171 mg, 0.900 mmol). The crude product was purified with a CombiFlash system (4 g column, 100:0 to 90:10 hexane: EtOAc) to give **2g** (39.7 mg, 0.114 mmol, 38%) as a colorless oil. The enantiomeric excess was determined by HPLC analysis (220 nm, 25 °C) t_R 23.2 min (minor); t_R 27.3 min (major) [Chiracel OJ-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90:10, 1.0 mL/min] to be 82% ee. $[\alpha]_D^{19} = +12.3^\circ$ (*c* 0.98, CHCl₃) **¹H NMR** (400 MHz, CDCl₃): δ 1.66-1.73 (m, 2H), 2.31-2.42 (m, 2H), 2.56 (d, *J* = 8.0 Hz, 1H), 2.57 (d, *J* = 8.0 Hz, 1H), 2.89 (d, *J* = 15.2 Hz, 1H), 2.97 (d, *J* = 15.2 Hz, 1H), 3.78 (s, 3H), 6.82 (ddd, *J* = 8.8, 3.6, 2.0 Hz, 2H), 7.09 (ddd, *J* = 8.8, 3.6, 2.0 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.52 (d, *J* = 8.4 Hz, 2H). **¹³C NMR** (151 MHz, CDCl₃): δ 21.2, 35.9, 40.8, 50.1, 53.8, 55.4, 114.1, 123.7 (q, *J* = 238.0 Hz, 1C), 125.6 (q, *J* = 5.6 Hz, 1C), 127.4, 128.2, 128.6 (q, *J* = 48.9 Hz, 1C), 138.4, 151.9, 158.2, 210.3. **¹⁹F NMR** (376 MHz, CDCl₃): δ -62.5 (s, 3F). **HRMS** (ESI): Calcd. for C₂₀H₂₀F₃O₂⁺ ([M+H]⁺): 349.1410 Found: 349.1385.



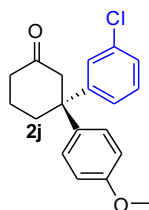
(R)-3-(4-methoxyphenyl)-3-(m-tolyl)cyclohexan-1-one (2h): Prepared according to General Procedure C from 3-(4-methoxyphenyl)cyclohex-2-en-1-one **1a** (60.7 mg, 0.300 mmol) and 3-tolylboronic acid (122 mg, 0.900 mmol). The crude product was purified with a CombiFlash system (4 g column, 100:0 to 95:5 hexane: EtOAc) to give **2h** (77.7 mg, 0.264 mmol, 88%) as a colorless oil. The enantiomeric excess was determined by HPLC analysis (220 nm, 25 °C) t_R 21.1 min (minor); t_R 25.8 min (major) [Chiracel OJ-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 80:20, 1.0 mL/min] to be 90% ee. $[\alpha]_D^{22} = +126.3^\circ$ (*c* 0.97, CHCl₃). **¹H NMR** (400 MHz, CDCl₃): δ

1.62-1.74 (m, 2H), 2.29 (s, 3H), 2.34 (t, $J = 6.4$ Hz, 2H), 2.48-2.58 (m, 2H), 2.89 (d, $J = 15.6$ Hz, 1H), 2.94 (d, $J = 15.6$ Hz, 1H), 3.77 (s, 3H), 6.81 (d, $J = 7.2$ Hz, 2H), 6.99 (d, $J = 7.2$ Hz, 2H), 7.00 (s, 1H), 7.12 (d, $J = 7.2$ Hz, 2H), 7.16 (t, $J = 7.2$ Hz, 1H). ^{13}C NMR (101 MHz, CDCl_3): δ 21.2, 21.8, 35.9, 40.9, 49.8, 54.0, 55.3, 113.8, 124.1, 127.0, 127.6, 128.2, 128.4, 138.0, 139.5, 147.7, 157.8, 211.1. **HRMS** (ESI): Calcd. for $\text{C}_{20}\text{H}_{23}\text{O}_2^+$ ($[\text{M}+\text{H}]^+$): 295.1693 Found: 295.1694.



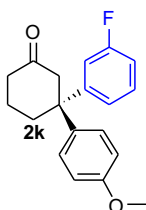
(R)-3-(3-methoxyphenyl)-3-(4-methoxyphenyl)cyclohexan-1-one (2i):

Prepared according to General Procedure C from 3-(4-methoxyphenyl)cyclohex-2-en-1-one **1a** (60.7 mg, 0.300 mmol) and 3-methoxyphenylboronic acid (137 mg, 0.900 mmol). The crude product was purified with a CombiFlash system (4 g column, 100:0 to 90:10 hexane: EtOAc) to give **2i** (55.9 mg, 0.180 mmol, 60%) as a colorless oil. The enantiomeric excess was determined by HPLC analysis (220 nm, 25 °C) t_{R} 42.5 min (major); t_{R} 63.9 min (minor) [Chiracel AS-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 80:20, 1.0 mL/min] to be 90% ee. $[\alpha]_{\text{D}}^{26} = +10.2^\circ$ (c 0.79, CHCl_3). ^1H NMR (400 MHz, CDCl_3): δ 1.61-1.76 (m, 2H), 2.34 (t, $J = 6.8$ Hz, 2H), 2.51 (d, $J = 6.0$ Hz, 1H), 2.53 (d, $J = 6.0$ Hz, 1H), 2.89 (d, $J = 15.2$ Hz, 1H), 2.94 (d, $J = 15.2$ Hz, 1H), 3.74 (s, 3H), 3.77 (s, 3H), 6.71 (dd, $J = 7.6, 2.0$ Hz, 1H), 6.75-6.82 (m, 4H), 7.12 (ddd, $J = 8.8, 3.2, 2.0$ Hz, 2H), 7.19 (t, $J = 8.0$ Hz, 1H). ^{13}C NMR (101 MHz, CDCl_3): δ 21.2, 35.9, 40.8, 49.9, 54.0, 55.2, 55.3, 111.0, 113.5, 113.8, 119.4, 128.1, 129.5, 139.2, 149.5, 157.9, 159.6, 210.9. **HRMS** (ESI): Calcd. for $\text{C}_{20}\text{H}_{23}\text{O}_3^+$ ($[\text{M}+\text{H}]^+$): 311.1642 Found: 311.1649.



(R)-3-(3-chlorophenyl)-3-(4-methoxyphenyl)cyclohexan-1-one (2j): Prepared according to General Procedure C from 3-(4-methoxyphenyl)cyclohex-2-en-1-one **1a** (60.7 mg, 0.300 mmol) and 3-chlorophenylboronic acid (141 mg, 0.900

mmol). The crude product was purified with a CombiFlash system (4 g column, 100:0 to 90:10 hexane: EtOAc) to give **2j** (33.1 mg, 0.105 mmol, 35%) as a colorless oil. The enantiomeric excess was determined by HPLC analysis (220 nm, 25 °C) t_R 18.1 min (minor); t_R 29.7 min (major) [Chiracel AS-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 80:20, 1.0 mL/min] to be 85% ee. $[\alpha]_D^{26} = +35.4^\circ$ (*c* 0.57, CHCl₃). **¹H NMR** (400 MHz, CDCl₃): δ 1.60-1.77 (m, 2H), 2.35 (t, *J* = 6.8 Hz, 2H), 2.47-2.57 (m, 2H), 2.85 (d, *J* = 15.2 Hz, 1H), 2.96 (d, *J* = 15.2 Hz, 1H), 3.78 (s, 3H), 6.82 (ddd, *J* = 9.2, 3.2, 2.4 Hz, 2H), 7.07 (ddd, *J* = 7.6, 2.4, 1.2 Hz, 1H), 7.09 (ddd, *J* = 9.2, 3.2, 2.4 Hz, 2H), 7.15 (ddd, *J* = 7.6, 2.4, 1.2 Hz, 1H), 7.16-7.22 (m, 2H). **¹³C NMR** (101 MHz, CDCl₃): δ 21.2, 35.9, 40.8, 49.9, 53.8, 55.3, 114.0, 125.3, 126.6, 127.1, 128.2, 129.8, 134.5, 138.4, 150.1, 158.1, 210.4. **HRMS** (ESI): Calcd. for C₁₉H₂₀ClO₂⁺ ([M+H]⁺): 315.1146 Found: 315.1138.

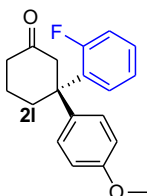


(R)-3-(3-fluorophenyl)-3-(4-methoxyphenyl)cyclohexan-1-one (2k): Prepared

according to General Procedure C from 3-(4-methoxyphenyl)cyclohex-2-en-1-one **1a** (60.7 mg, 0.300 mmol) and 3-fluorophenylboronic acid (126 mg, 0.900 mmol).

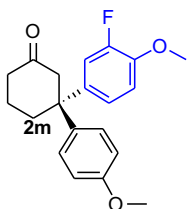
The crude product was purified with a CombiFlash system (4 g column, 100:0 to 95:5 hexane: EtOAc) to give **2k** (16.1 mg, 0.054 mmol, 35%) as a colorless oil. The enantiomeric excess was determined by HPLC analysis (220 nm, 25 °C) t_R 21.1 min (minor); t_R 29.6 min (major) [Chiracel AS-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 80:20, 1.0 mL/min] to be 84% ee. $[\alpha]_D^{21} = -319.2^\circ$ (*c* 0.31, CHCl₃). **¹H NMR** (400 MHz, CDCl₃): δ 1.65-1.76 (m, 2H), 2.35 (t, *J* = 6.8 Hz, 2H), 2.47-2.57 (m, 2H), 2.87 (d, *J* = 15.2 Hz, 1H), 2.95 (d, *J* = 15.2 Hz, 1H), 3.77 (s, 3H), 6.82 (ddd, *J* = 8.4, 3.2, 2.4 Hz, 2H), 6.83-6.91 (m, 2H), 6.97-7.00 (m, 1H), 7.10 (ddd, *J* = 8.4, 3.2, 2.4 Hz, 2H), 7.20-7.25 (m, 1H). **¹³C NMR** (151 MHz, CDCl₃): δ 21.2, 36.0, 40.9, 49.9 (d, *J* = 1.4 Hz, 1C), 53.9, 55.4, 113.3 (d,

$J = 21.1$ Hz, 1C), 114.1, 114.2 (d, $J = 20.1$ Hz, 1C), 122.7 (d, $J = 2.6$ Hz, 1C), 128.2, 130.0 (d, $J = 8.3$ Hz, 1C), 138.6, 150.7 (d, $J = 6.5$ Hz, 1C), 158.2, 163.1 (d, $J = 245.7$ Hz, 1C), 210.4. ^{19}F NMR (376 MHz, CDCl_3): δ -112.5 (m, 1F). HRMS (ESI): Calcd. for $\text{C}_{19}\text{H}_{20}\text{FO}_2^+$ ($[\text{M}+\text{H}]^+$): 299.1442 Found: 299.1446.



(R)-3-(2-fluorophenyl)-3-(4-methoxyphenyl)cyclohexan-1-one (2I): Prepared

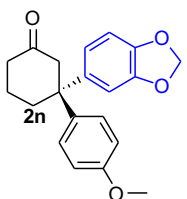
according to General Procedure C from 3-(4-methoxyphenyl)cyclohex-2-en-1-one **1a** (60.7 mg, 0.300 mmol) and 2-fluorophenylboronic acid (126 mg, 0.900 mmol). The crude product was purified with a CombiFlash system (4 g column, 100:0 to 95:5 hexane: EtOAc) to give **2I** (20.6 mg, 0.069 mmol, 23%) as a colorless oil. The enantiomeric excess was determined by HPLC analysis (220 nm, 25 °C) t_{R} 39.4 min (major); t_{R} 45.6 min (minor) [Chiracel OJ-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 75:25, 1.0 mL/min] to be 81% ee. $[\alpha]_{\text{D}}^{21} = -173.2^\circ$ (c 0.64, CHCl_3). ^1H NMR (400 MHz, CDCl_3): δ 1.57-1.67 (m, 1H), 1.69-1.79 (m, 1H), 2.36 (t, $J = 6.8$ Hz, 2H), 2.47 (ddd, $J = 12.4, 9.2, 2.4$ Hz, 1H), 2.75 (ddd, $J = 12.4, 9.2, 2.4$ Hz, 1H), 2.94 (d, $J = 15.6$ Hz, 1H), 3.01 (d, $J = 15.6$ Hz, 1H), 3.77 (s, 3H), 6.81 (ddd, $J = 8.8, 3.2, 2.0$ Hz, 2H), 6.91 (ddd, $J = 8.0, 4.4, 1.2$ Hz, 1H), 7.09-7.14 (m, 3H), 7.19 (m, 1H), 7.40 (td, $J = 8.4, 2.0$ Hz, 1H). ^{13}C NMR (151 MHz, CDCl_3): δ 21.2, 34.5 (d, $J = 3.5$ Hz, 1C), 41.0, 48.6 (d, $J = 1.2$ Hz, 1C), 53.2 (d, $J = 2.1$ Hz, 1C), 55.3, 113.8, 116.9 (d, $J = 23.3$ Hz, 1C), 124.1 (d, $J = 3.5$ Hz, 1C), 127.6, 128.4 (d, $J = 4.4$ Hz, 1C), 128.8 (d, $J = 8.9$ Hz, 1C), 134.3 (d, $J = 10.4$ Hz, 1C), 138.5, 158.0, 160.8 (d, $J = 249.5$ Hz, 1C), 210.8. ^{19}F NMR (376 MHz, CDCl_3): δ -108.5 (m, 1F). HRMS (ESI): Calcd. for $\text{C}_{19}\text{H}_{20}\text{FO}_2^+$ ($[\text{M}+\text{H}]^+$): 299.1442 Found: 299.1441.



(R)-3-(3-fluoro-4-methoxyphenyl)-3-(4-methoxyphenyl)cyclohexan-1-one

(2m): Prepared according to General Procedure C from 3-(4-methoxyphenyl)cyclohex-2-en-1-one **1a** (60.7 mg, 0.300 mmol) and 3-fluoro-

4-methoxyphenylboronic acid (153 mg, 0.900 mmol). The crude product was with a CombiFlash system (4 g column, 100:0 to 95:5 hexane: EtOAc) to give **2m** (65.0 mg, 0.198 mmol, 66%) as a colorless oil. The enantiomeric excess was determined by HPLC analysis (220 nm, 25 °C) t_R 40.2 min (major); t_R 53.3 min (minor) [Chiracel AS-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 80:20, 1.0 mL/min] to be 88% ee. $[\alpha]_D^{26} = +2.2^\circ$ (*c* 0.90, CHCl₃). **¹H NMR** (400 MHz, CDCl₃): δ 1.65-1.71 (m, 2H), 2.33 (t, *J* = 6.8 Hz, 2H), 2.43-2.54 (m, 2H), 2.85 (d, *J* = 15.6 Hz, 1H), 2.90 (d, *J* = 15.6 Hz, 1H), 3.77 (s, 3H), 3.84 (s, 3H), 6.81 (ddd, *J* = 8.8, 3.2, 2.0 Hz, 2H), 6.83-6.90 (m, 2H), 6.92 (ddd, *J* = 8.4, 2.4, 0.8 Hz, 1H), 7.09 (ddd, *J* = 8.8, 3.2, 2.0 Hz, 2H). **¹³C NMR** (101 MHz, CDCl₃): δ 21.2, 36.0, 40.8, 49.3 (d, *J* = 1.7 Hz, 1C), 54.0, 55.3, 56.3, 113.0 (d, *J* = 2.1 Hz, 1C), 113.9, 115.0 (d, *J* = 19.0 Hz, 1C), 122.5 (d, *J* = 3.3 Hz, 1C), 128.0, 138.9, 140.9 (d, *J* = 5.1 Hz, 1C), 145.9 (d, *J* = 10.8 Hz, 1C), 152.2 (d, *J* = 246.8 Hz, 1C), 157.9, 210.6. **¹⁹F NMR** (376 MHz, CDCl₃): δ -134.4 (m, 1F). **HRMS** (ESI): Calcd. for C₂₀H₂₂FO₃⁺ ([M+H]⁺): 329.1547 Found: 329.1553.

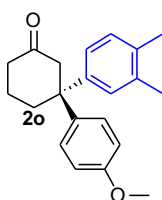


(R)-3-(benzo[d][1,3]dioxol-5-yl)-3-(4-methoxyphenyl)cyclohexan-1-one

(2n): Prepared according to General Procedure C from 3-(4-methoxyphenyl)cyclohex-2-en-1-one **1a** (60.7 mg, 0.300 mmol) and

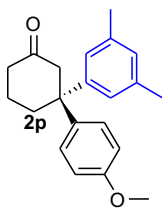
benzo[d][1,3]dioxol-5-ylboronic acid (149 mg, 0.900 mmol). The crude product was purified with a CombiFlash system (4 g column, 100:0 to 95:5 hexane: EtOAc) to give **2n** (42.8 mg, 0.132 mmol, 44%) as a colorless oil. The enantiomeric excess was determined by HPLC analysis (220 nm, 25 °C) t_R 22.8 min (minor); t_R 36.2 min (major) [Chiracel AS-H (0.46 cm x

25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 80:20, 1.0 mL/min] to be 90% ee. $[\alpha]_D^{26} = +16.3^\circ$ (*c* 0.74, CHCl₃). **¹H NMR** (400 MHz, CDCl₃): δ 1.63-1.73 (m, 2H), 2.33 (t, *J* = 6.8 Hz, 2H), 2.42-2.53 (m, 2H), 2.87 (s, 2H), 3.77 (s, 3H), 5.89 (s, 2H), 6.59-6.60 (m, 1H), 6.71 (m, 2H), 6.81 (ddd, *J* = 8.8, 3.2, 2.0 Hz, 2H), 7.11 (ddd, *J* = 8.8, 3.2, 2.0 Hz, 2H). **¹³C NMR** (101 MHz, CDCl₃): δ 21.2, 36.1, 40.8, 49.7, 54.3, 55.3, 101.1, 107.8, 107.9, 113.9, 119.9, 128.0, 139.5, 141.8, 145.9, 148.0, 157.9, 210.9. **HRMS** (ESI): Calcd. for C₂₀H₂₁O₄⁺ ([M+H]⁺): 325.1434 Found: 325.1424.



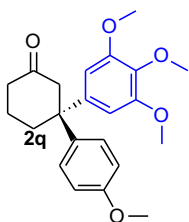
(R)-3-(3,4-dimethylphenyl)-3-(4-methoxyphenyl)cyclohexan-1-one (2o):

Prepared according to General Procedure C from 3-(4-methoxyphenyl)cyclohex-2-en-1-one **1a** (60.7 mg, 0.300 mmol) and 3,4-dimethylphenylboronic acid (135 mg, 0.900 mmol). The crude product was purified by flash chromatography (90:10 hexane: EtOAc) to give **2o** (33.3 mg, 0.108 mmol, 36%) as a colorless oil. The enantiomeric excess was determined by HPLC analysis (220 nm, 25 °C) *t_R* 18.6 min (minor); *t_R* 68.8 min (major) [Chiracel AS-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90:10, 1.0 mL/min] to be 85% ee. $[\alpha]_D^{22} = -94.4^\circ$ (*c* 0.98, CHCl₃). **¹H NMR** (400 MHz, CDCl₃): δ 1.61-1.76 (m, 2H), 2.20 (s, 6H), 2.33 (t, *J* = 6.8 Hz, 2H), 2.47-2.57 (m, 2H), 2.89 (d, *J* = 15.2 Hz, 1H), 2.94 (d, *J* = 15.2 Hz, 1H), 3.77 (s, 3H), 6.82 (ddd, *J* = 8.8, 3.2, 2.0 Hz, 2H), 6.91-6.94 (m, 2H), 7.03 (d, *J* = 8.0 Hz, 1H), 7.12 (ddd, *J* = 8.8, 3.2, 2.0 Hz, 2H). **¹³C NMR** (101 MHz, CDCl₃): δ 19.4, 20.2, 21.3, 36.0, 40.9, 49.5, 54.1, 55.3, 113.8, 124.4, 128.16, 128.20, 129.7, 134.5, 136.6, 139.6, 142.2, 157.8, 211.2. **HRMS** (ESI): Calcd. for C₂₁H₂₅O₂⁺ ([M+H]⁺): 309.1849 Found: 309.1846.



(R)-3-(3,5-dimethylphenyl)-3-(4-methoxyphenyl)cyclohexan-1-one (2p):

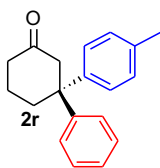
Prepared according to General Procedure C from 3-(4-methoxyphenyl)cyclohex-2-en-1-one **1a** (60.7 mg, 0.300 mmol) and 3,5-dimethylphenylboronic acid (135 mg, 0.900 mmol). The crude product was purified by flash chromatography (90:10 hexane: EtOAc) to give **2p** (35.2 mg, 0.114 mmol, 38%) as a colorless oil. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 19.8 min (minor); t_R 22.4 min (major) [Chiracel OJ-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90:10, 1.0 mL/min] to be 90% ee. $[\alpha]_D^{26} = -6.1^\circ$ (c 0.66, CHCl₃). **¹H NMR** (400 MHz, CDCl₃): δ 1.60-1.76 (m, 2H), 2.25 (s, 6H), 2.33 (t, $J = 6.8$ Hz, 2H), 2.47-2.57 (m, 2H), 2.88 (d, $J = 15.6$ Hz, 1H), 2.93 (d, $J = 15.2$ Hz, 1H), 3.78 (s, 3H), 6.79-6.83 (m, 5H), 7.12 (ddd, $J = 8.8, 3.2, 2.0$ Hz, 2H). **¹³C NMR** (101 MHz, CDCl₃): δ 21.3, 21.7, 36.0, 40.9, 49.7, 54.1, 55.3, 113.8, 124.8, 128.0, 128.2, 137.9, 139.6, 147.7, 157.8, 211.1. **HRMS** (ESI): Calcd. for C₂₁H₂₅O₂⁺ ([M+H]⁺): 309.1849 Found: 309.1848.



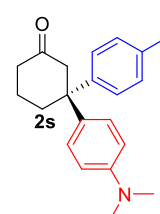
(R)-3-(4-methoxyphenyl)-3-(3,4,5-trimethoxyphenyl)cyclohexan-1-one (2q):

Prepared according to General Procedure C from 3-(4-methoxyphenyl)cyclohex-2-en-1-one **1a** (60.7 mg, 0.300 mmol) and 3,4,5-trimethoxyphenylboronic acid (191 mg, 0.900 mmol). The crude product was purified with a CombiFlash system (4 g column, 100:0 to 98:2 hexane: EtOAc) to give **2q** (74.5 mg, 0.201 mmol, 67%) as a colorless oil. The enantiomeric excess was determined by HPLC analysis (220 nm, 25 °C) t_R 22.8 min (minor); t_R 36.2 min (major) [Chiracel AS-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 80:20, 1.0 mL/min] to be 78% ee. $[\alpha]_D^{20} = -33.7^\circ$ (c 1.07, CHCl₃). **¹H NMR** (400 MHz, CDCl₃): δ 1.62-1.75 (m, 2H), 2.34 (t, $J = 6.4$ Hz, 2H), 2.45-2.56 (m, 2H), 2.85 (d, $J = 15.6$ Hz, 1H), 2.94 (d, $J = 15.2$ Hz, 1H), 3.76 (s, 6H), 3.77

(s, 3H), 3.81 (s, 3H), 6.39 (s, 2H), 6.81 (d, $J = 8.8$ Hz, 2H), 7.12 (d, $J = 8.8$ Hz, 2H). ^{13}C NMR (101 MHz, CDCl_3): δ 21.3, 36.2, 40.9, 50.3, 54.4, 55.3, 56.2, 60.9, 104.7, 113.8, 127.9, 136.3, 139.5, 143.1, 153.0, 158.0, 211.0. **HRMS** (ESI): Calcd. for $\text{C}_{22}\text{H}_{27}\text{O}_5^+$ ($[\text{M}+\text{H}]^+$): 325.1434 Found: 325.1436.

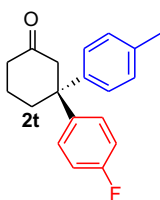


(R)-3-phenyl-3-(p-tolyl)cyclohexan-1-one (2r): Prepared according to General Procedure C from 3-phenylcyclohex-2-en-1-one **1b** (51.6 mg, 0.300 mmol) and 4-methylphenylboronic acid (122 mg, 0.900 mmol). The crude product was purified by flash chromatography (90:10 hexane: EtOAc) to give **(R)-2r** (55.5 mg, 0.210 mmol, 70%) as a colorless oil. The enantiomeric excess was determined by HPLC analysis (220 nm, 25 °C) t_{R} 48.9 min (minor); t_{R} 57.8 min (major) [Chiracel AS-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 99:01, 1.0 mL/min] to be 87% ee. $[\alpha]_{\text{D}}^{22} = -3.7$ (c 1.09, CHCl_3). ^1H NMR (400 MHz, CDCl_3): δ 1.66-1.72 (m, 2H), 2.30 (s, 3H), 2.35 (t, $J = 6.4$ Hz, 2H), 2.55-2.58 (m, 2H), 2.92 (d, $J = 15.2$ Hz, 1H), 2.98 (d, $J = 15.2$ Hz, 1H), 7.06-7.11 (m, 4H), 7.15-7.22 (m, 3H), 7.25-7.29 (m, 2H). ^{13}C NMR (101 MHz, CDCl_3): δ 21.0, 21.2, 35.9, 40.9, 50.2, 53.9, 126.3, 126.96, 127.01, 128.5, 129.3, 135.9, 144.4, 147.6, 210.9. **HRMS** (ESI): Calcd. for $\text{C}_{19}\text{H}_{21}\text{O}^+$ ($[\text{M}+\text{H}]^+$): 265.1587 Found: 265.1593.



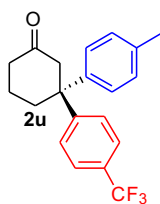
(S)-3-(4-(dimethylamino)phenyl)-3-(p-tolyl)cyclohexan-1-one (2s): Prepared according to General Procedure C from 3-[4-(dimethylamino)phenyl]cyclohex-2-en-1-one **1c** (64.6 mg, 0.300 mmol) and 4-methylphenylboronic acid (122 mg, 0.900 mmol). The crude product was purified with a CombiFlash system (4 g column, 100:0 to 90:10 hexane: EtOAc) to give **2s** (33.2 mg, 0.108 mmol, 36%) as a yellow oil. The enantiomeric excess was determined by HPLC analysis (220 nm, 25 °C) t_{R} 14.0 min (minor); t_{R} 24.1 min (major) [Chiracel AS-H (0.46 cm x 25 cm) (from

Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 80:20, 1.0 mL/min] to be 91% ee. $[\alpha]_D^{22} = +12.2^\circ$ (*c* 0.82, CHCl₃). **¹H NMR** (400 MHz, CDCl₃): δ 1.67-1.73 (m, 2H), 2.29 (s, 3H), 2.33 (t, *J* = 6.8 Hz, 2H), 2.50-2.53 (m, 2H), 2.87-2.96 (m, 8H), 6.65 (d, *J* = 8.8 Hz, 2H), 7.05-7.11 (m, 6H). **¹³C NMR** (101 MHz, CDCl₃): δ 21.0, 21.4, 36.0, 40.6, 40.9, 49.4, 54.1, 112.5, 126.9, 127.7, 129.2, 135.2, 135.6, 145.2, 148.8, 211.4. **HRMS** (ESI): Calcd. for C₂₁H₂₆NO⁺ ([M+H]⁺): 308.2135 Found: 308.2144.



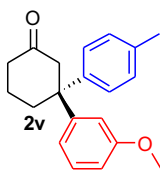
(S)-3-(4-fluorophenyl)-3-(p-tolyl)cyclohexan-1-one (2t): Prepared according to General Procedure C from 3-(4-fluorophenyl)-cyclohex-2-en-1-one **1d** (57.0 mg, 0.300 mmol) and 4-methylphenylboronic acid (122 mg, 0.900 mmol). The

crude product was purified with a CombiFlash system (4 g column, 100:0 to 90:10 hexane: EtOAc) to give **2t** (62.7 mg, 0.222 mmol, 74%) as a colorless oil. The enantiomeric excess was determined by HPLC analysis (220 nm, 25 °C) *t_R* 36.8 min (major); *t_R* 50.4 min (minor) [Chiracel OJ-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 99:01, 1.0 mL/min] to be 89% ee. $[\alpha]_D^{22} = +124.1^\circ$ (*c* 1.05, CHCl₃). **¹H NMR** (400 MHz, CDCl₃): δ 1.63-1.74 (m, 2H), 2.30 (s, 3H), 2.35 (t, *J* = 6.8 Hz, 2H), 2.49-2.59 (m, 2H), 2.90 (d, *J* = 15.2 Hz, 1H), 2.92 (d, *J* = 15.2 Hz, 1H), 6.94 (ddd, *J* = 8.8, 3.2, 2.0 Hz, 1H), 6.96 (ddd, *J* = 8.8, 3.2, 2.0 Hz, 1H), 7.07 (d, *J* = 8.4 Hz, 2H), 7.10 (d, *J* = 8.4 Hz, 2H), 7.16 (ddd, *J* = 8.8, 3.2, 2.0 Hz, 1H), 7.18 (ddd, *J* = 8.8, 3.2, 2.0 Hz, 1H). **¹³C NMR** (101 MHz, CDCl₃): δ 21.0, 21.2, 36.0, 40.8, 49.8, 54.0, 115.3 (d, *J* = 21.2 Hz, 1C), 126.8, 128.6 (d, *J* = 7.9 Hz, 1C), 129.3, 136.1, 143.4 (d, *J* = 3.3 Hz, 2C), 144.2, 160.0 (d, *J* = 246.6 Hz, 2C), 210.7. **¹⁹F NMR** (376 MHz, CDCl₃): δ -116.8 (m, 1F). **HRMS** (ESI): Calcd. for C₁₉H₂₀FO⁺ ([M+H]⁺): 283.1493 Found: 283.1496.



(S)-3-(p-tolyl)-3-(4-(trifluoromethyl)phenyl)cyclohexan-1-one (2u):

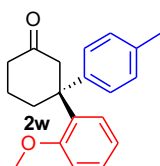
Prepared according to General Procedure C from 3-(4-trifluoromethylphenyl)-cyclohex-2-en-1-one **1e** (72.1 mg, 0.300 mmol) and 4-methylphenylboronic acid (122 mg, 0.900 mmol). The crude product was purified with a CombiFlash system (4 g column, 100:0 to 90:10 hexane: EtOAc) to give **2u** (53.8 mg, 0.162 mmol, 54%) as a colorless oil. The enantiomeric excess was determined by HPLC analysis (220 nm, 25 °C) t_R 37.0 min (major); t_R 50.4 min (minor) [Chiracel OJ-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 99.5:0.5, 1.0 mL/min] to be 90% ee. $[\alpha]_D^{26} = -398.8^\circ$ (*c* 0.64, CHCl₃). **¹H NMR** (400 MHz, CDCl₃): δ 1.62-1.76 (m, 2H), 2.30 (s, 3H), 2.37 (t, *J* = 6.8 Hz, 2H), 2.53-2.63 (m, 2H), 2.91 (d, *J* = 15.2 Hz, 1H), 2.98 (d, *J* = 15.2 Hz, 1H), 7.06 (d, *J* = 8.4 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.53 (d, *J* = 8.0 Hz, 2H). **¹³C NMR** (151 MHz, CDCl₃): δ 21.0, 21.2, 35.8, 40.8, 50.3, 53.6, 124.2 (q, *J* = 272.1 Hz, 1C), 125.5 (q, *J* = 3.8 Hz, 1C), 126.9, 127.4, 128.6 (q, *J* = 32.3 Hz, 1C), 129.5, 136.4, 143.4, 151.8, 210.2. **¹⁹F NMR** (376 MHz, CDCl₃): δ -62.5 (s, 3F). **HRMS** (ESI): Calcd. for C₂₀H₂₀F₃O⁺ ([M+H]⁺): 333.1461 Found: 333.1462.



(S)-3-(3-methoxyphenyl)-3-(p-tolyl)cyclohexan-1-one (2v):

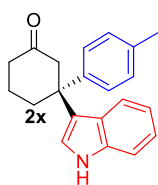
Prepared according to General Procedure C from 3-(3-methoxyphenyl)-cyclohex-2-en-1-one **1f** (60.7 mg, 0.300 mmol) and 4-methylphenylboronic acid (122 mg, 0.900 mmol). The crude product was purified with a CombiFlash system (4 g column, 100:0 to 90:10 hexane: EtOAc) to give **2v** (63.6 mg, 0.216 mmol, 72%) as a colorless oil. The enantiomeric excess was determined by HPLC analysis (220 nm, 25 °C) t_R 91.7 min (major); t_R 106.1 min (minor) [Chiracel OJ-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 98:2, 1.0 mL/min] to be 93% ee. $[\alpha]_D^{22} = -143.8^\circ$ (*c* 0.67, CHCl₃). **¹H NMR** (400 MHz, CDCl₃):

δ 1.66-1.72 (m, 2H), 2.30 (s, 3H), 2.34 (t, $J = 6.8$ Hz, 2H), 2.53 (d, $J = 6.0$ Hz, 1H), 2.55 (d, $J = 6.0$ Hz, 1H), 2.91 (d, $J = 15.6$ Hz, 1H), 2.95 (d, $J = 15.6$ Hz, 1H), 3.75 (s, 3H), 6.72 (ddd, $J = 8.4, 2.4, 0.8$ Hz, 1H), 6.77-6.80 (m, 2H), 7.07-7.11 (m, 4H), 7.19 (t, $J = 8.4$ Hz, 1H). ^{13}C NMR (101 MHz, CDCl_3): δ 21.0, 21.2, 35.9, 40.9, 50.2, 53.9, 55.2, 111.0, 113.6, 119.5, 126.9, 129.3, 129.5, 135.9, 144.2, 149.3, 159.7, 210.9. HRMS (ESI): Calcd. for $\text{C}_{20}\text{H}_{23}\text{O}_2^+$ ($[\text{M}+\text{H}]^+$): 295.1693 Found: 295.1691.



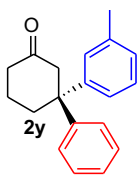
(S)-3-(2-methoxyphenyl)-3-(p-tolyl)cyclohexan-1-one (2w): Prepared according to General Procedure C from 3-(2-methoxyphenyl)-cyclohex-2-en-1-one **1g** (60.7 mg, 0.300 mmol) and 4-methylphenylboronic acid (122 mg, 0.900

mmol). The crude product was purified with a CombiFlash system (4 g column, 100:0 to 95:5 hexane: EtOAc) to give **2w** (24.7 mg, 0.084 mmol, 28%) as a colorless oil. The enantiomeric excess was determined by HPLC analysis (220 nm, 25 °C) t_{R} 16.2 min (minor); t_{R} 17.7 min (major) [Chiracel AS-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 80:20, 1.0 mL/min] to be 80% ee. $[\alpha]_{\text{D}}^{19} = -175.6^\circ$ (c 0.68, CHCl_3). ^1H NMR (400 MHz, CDCl_3): δ 1.59-1.68 (m, 2H), 2.28 (s, 3H), 2.33 (t, $J = 6.8$ Hz, 2H), 2.36-2.42 (m, 1H), 2.78-2.84 (m, 1H), 2.82, (d, $J = 16.0$ Hz, 1H), 3.15 (d, $J = 16.0$ Hz, 1H), 3.37 (s, 3H), 6.78 (d, $J = 7.6$ Hz, 1H), 6.96 (t, $J = 7.6$ Hz, 1H), 7.01 (d, $J = 9.2$ Hz, 2H), 7.04 (d, $J = 9.2$ Hz, 2H), 7.22 (t, $J = 7.6$ Hz, 1H), 7.39 (d, $J = 7.6$ Hz, 1H). ^{13}C NMR (101 MHz, CDCl_3): δ 21.0, 21.1, 34.5, 41.0, 49.3, 52.9, 55.4, 113.2, 120.6, 126.4, 127.7, 128.2, 128.6, 135.0, 135.8, 144.9, 157.7, 212.0. HRMS (ESI): Calcd. for $\text{C}_{20}\text{H}_{23}\text{O}_2^+$ ($[\text{M}+\text{H}]^+$): 295.1693 Found: 295.1694.



(S)-3-(1H-indol-3-yl)-3-(p-tolyl)cyclohexan-1-one (2x): Prepared according to General Procedure C from 3-(1H-indol-3-yl)cyclohex-2-en-1-one **1h** (63.3 mg, 0.300 mmol) and 4-methylphenylboronic acid (122 mg, 0.900 mmol). The

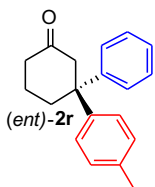
crude product was purified with a CombiFlash system (4 g column, 100:0 to 80:20 hexane: EtOAc) to give **2x** (37.3 mg, 0.123 mmol, 41%) as a white solid. The enantiomeric excess was determined by HPLC analysis (220 nm, 25 °C) t_R 28.8 min (minor); t_R 37.5 min (major) [Chiracel AS-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90:10, 1.0 mL/min] to be 77% ee. $[\alpha]_D^{22} = -25.1^\circ$ (*c* 1.12, CHCl₃). **¹H NMR** (400 MHz, CDCl₃): δ 1.44-1.55 (m, 1H), 1.79-1.88 (m, 1H), 2.29 (s, 3H), 2.35-2.40 (m, 2H), 2.54-2.61 (m, 1H), 2.76-2.79 (m, 1H), 2.82 (d, *J* = 15.2 Hz, 1H), 3.03 (d, *J* = 15.2 Hz, 1H), 6.89 (ddd, *J* = 8.4, 6.8, 0.8 Hz, 1H), 7.07 (d, *J* = 8.4 Hz, 2H), 7.10-7.13 (m, 2H), 7.16 (d, *J* = 2.4 Hz, 1H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.33 (dd, *J* = 8.4, 0.8 Hz, 1H), 8.13 (bs, 1H). **¹³C NMR** (101 MHz, CDCl₃): δ 21.0, 21.8, 34.1, 41.1, 46.6, 55.5, 111.3, 119.2, 121.1, 121.3, 122.1, 123.5, 125.3, 126.4, 129.2, 136.8, 137.2, 144.3, 212.2. **HRMS** (ESI): Calcd. for C₂₁H₂₂NO⁺ ([M+H]⁺): 304.1696 Found: 304.1696.



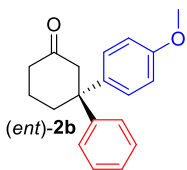
(R)-3-phenyl-3-(m-tolyl)cyclohexan-1-one (2y): Prepared according to General Procedure C from 3-phenylcyclohex-2-en-1-one **1b** (51.6 mg, 0.300 mmol) and 3-methylphenylboronic acid (122 mg, 0.900 mmol). The crude product was purified

with a CombiFlash system (4 g column, 100:0 to 90:10 hexane: EtOAc) to give **2v** (60.3 mg, 0.228 mmol, 76%) as a colorless oil. The enantiomeric excess was determined by HPLC analysis (220 nm, 25 °C) t_R 28.4 min (minor); t_R 32.4 min (major) [Chiracel OJ-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 95:05, 1.0 mL/min] to be 88% ee. $[\alpha]_D^{22} = +122.4^\circ$ (*c* 0.92, CHCl₃). **¹H NMR** (400 MHz, CDCl₃): δ 1.65-1.72 (m, 2H), 2.30 (s, 3H), 2.34-2.37 (t, *J* = 6.8 Hz, 2H), 2.57 (d, *J* = 6.0 Hz, 1H), 2.59 (d, *J* = 6.0 Hz, 1H), 2.96 (s, 2H), 7.00-7.02 (m, 3H), 7.15-7.23 (m, 4H), 7.26-7.30 (m, 2H).

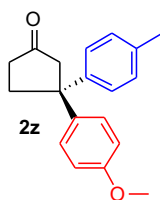
^{13}C NMR (101 MHz, CDCl_3): δ 21.2, 21.8, 35.8, 40.9, 50.3, 53.8, 124.2, 126.3, 127.0, 127.1, 127.7, 128.4, 128.5, 138.1, 147.3, 147.5, 211.0. HRMS (ESI): Calcd. for $\text{C}_{19}\text{H}_{20}\text{O}^+$ ($[\text{M}+\text{H}]^+$): 265.1587 Found: 265.1590.



(S)-3-phenyl-3-(p-tolyl)cyclohexan-1-one ((ent)-2r): Prepared according to General Procedure C from 3-(4-methylphenyl)-cyclohex-2-en-1-one **1i** (55.8 mg, 0.300 mmol) and phenylboronic acid (110 mg, 0.900 mmol). The crude product was purified by flash chromatography (90:10 hexane: EtOAc) to give *(ent)*-**2r** (55.5 mg, 0.210 mmol, 70%) as a colorless oil. The enantiomeric excess was determined by HPLC analysis (220 nm, 25 °C) t_{R} 44.6 min (major); t_{R} 59.4 min (minor) [Chiracel AS-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 99:01, 1.0 mL/min] to be 88% ee. $[\alpha]_{\text{D}}^{22} = +11.6^\circ$ (c 0.86, CHCl_3). ^1H and ^{13}C NMR data matched NMR data for **(R)-2q**. HRMS (ESI): Calcd. for $\text{C}_{19}\text{H}_{21}\text{O}^+$ ($[\text{M}+\text{H}]^+$): 265.1587 Found: 265.1584.



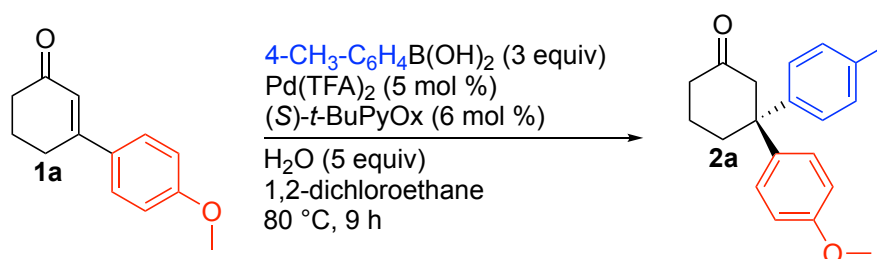
(R)-3-(4-methoxyphenyl)-3-phenylcyclohexan-1-one ((ent)-2b): Prepared according to General Procedure C from 3-phenylcyclohex-2-en-1-one **1b** (51.6 mg, 0.300 mmol) and 4-methoxyphenylboronic acid (137 mg, 0.900 mmol). The crude product was purified with a CombiFlash system (4 g column, 100:0 to 90:10 hexane: EtOAc) to give *(ent)*-**2b** (37.0 mg, 0.132 mmol, 44%) as a colorless oil. The enantiomeric excess was determined by HPLC analysis (220 nm, 25 °C) t_{R} 21.7 min (major); t_{R} 36.4 min (minor) [Chiracel OJ-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 75:25, 1.0 mL/min] to be 80% ee. $[\alpha]_{\text{D}}^{22} = -8.3^\circ$ (c 0.24, CHCl_3). ^1H and ^{13}C NMR data matched NMR data for **(S)-2b**. HRMS (ESI): Calcd. for $\text{C}_{19}\text{H}_{21}\text{O}_2^+$ ($[\text{M}+\text{H}]^+$): 281.1536 Found: 281.1526.



(S)-3-(4-methoxyphenyl)-3-(p-tolyl)cyclopentan-1-one (2z): Prepared according to General Procedure C from 3-(4-methoxyphenyl)-cyclopent-2-en-1-one **1j** (56.4 mg, 0.300 mmol) and 4-methylphenylboronic acid (122 mg, 0.900 mmol). The crude product was purified with a CombiFlash system (4 g column, 100:0 to 90:10 hexane: EtOAc) to give **2z** (50.5 mg, 0.180 mmol, 60%) as a colorless oil. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 22.9 min (minor); t_R 25.5 min (major) [Chiracel AS-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 80:20, 1.0 mL/min] to be 87% ee. $[\alpha]_D^{21} = -53.9^\circ$ (c 1.06, CHCl_3). **$^1\text{H NMR}$** (400 MHz, CDCl_3): δ 2.28 (t, $J = 7.6$ Hz, 2H), 2.31 (s, 3H), 2.66 (d, $J = 7.6$ Hz, 1H), 2.68 (d, $J = 7.6$ Hz, 1H), 2.93 (d, $J = 17.6$ Hz, 1H), 2.98 (d, $J = 17.6$ Hz, 1H), 3.77 (s, 3H), 6.83 (ddd, $J = 9.2, 2.8, 2.4$ Hz, 2H), 7.10 (d, $J = 8.4$ Hz, 2H), 7.15 (d, $J = 8.4$ Hz, 2H), 6.83 (ddd, $J = 9.2, 2.8, 2.4$ Hz, 2H). **$^{13}\text{C NMR}$** (101 MHz, CDCl_3): δ 21.0, 35.6, 36.7, 51.0, 52.2, 55.3, 113.9, 126.6, 127.8, 129.3, 136.0, 139.0, 144.1, 158.0, 217.8. **HRMS** (ESI): Calcd. for $\text{C}_{19}\text{H}_{21}\text{O}_2^+$ ($[\text{M}+\text{H}]^+$): 281.1536 Found: 281.1542.

Experimental Procedure for 1.0 mmol Scale, Enantioselective, Pd-Catalyzed Conjugate

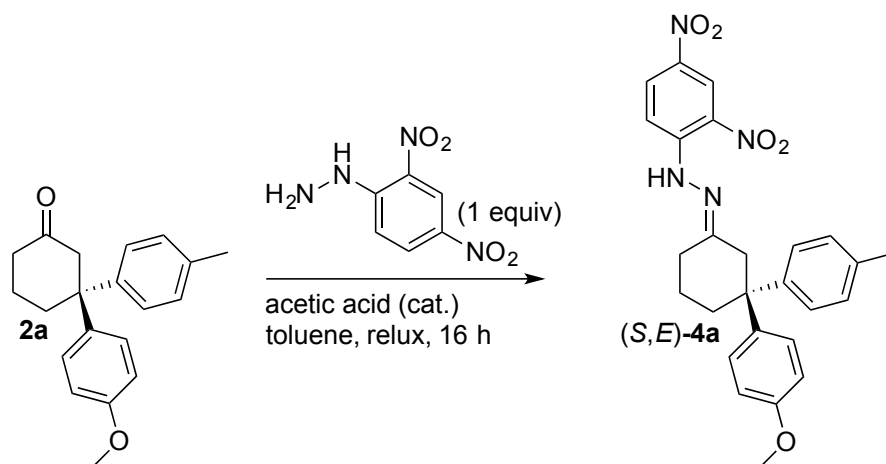
Addition of 4-Tolylphenylboronic Acid to **1a**



To a 20 mL scintillation vial were added Pd(TFA)₂ (16.6 mg, 0.0500 mmol), (*S*)-*t*-BuPyOx (12.3 mg, 0.0600 mmol), 3-(4-methoxyphenyl)cyclohex-2-en-1-one (202 mg, 1.00 mmol), 4-tolylboronic acid (1.00 mmol, 1.00 equiv), water (90.0 μL , 5.00 equiv) and 1,2-dichloroethane

(0.50 mL). The reaction mixture was stirred at 80 °C for 3 h. After 3 h, another equivalent of 4-tolylboronic acid (1.00 mmol, 1.00 equiv) was added and the reaction mixture was stirred for another 3 h. The same procedure was followed for a third equiv of 4-tolylboronic acid (1.00 mmol, 1.00 equiv). The reaction mixture was filtered through a short plug of silica gel (eluting with 50 mL of ethyl acetate) and concentrated under vacuum. The crude product was purified with a CombiFlash system (12 g column, 100:0 to 90:10 hexane: EtOAc) to give **2a** (238 mg, 0.0810 mmol, 81%) as a colorless oil. The enantiomeric excess was determined by HPLC analysis (220 nm, 25 °C) t_R 34.2 min (minor); t_R 40.8 min (major) [Chiracel OJ-H (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90:10, 1.0 mL/min] to be 87% ee.

Synthesis of (*S,E*)-1-(2,4-dinitrophenyl)-2-(3-(4-methoxyphenyl)-3-(*p*-tolyl)cyclohexylidene)hydrazine ((*S,E*)-4a)



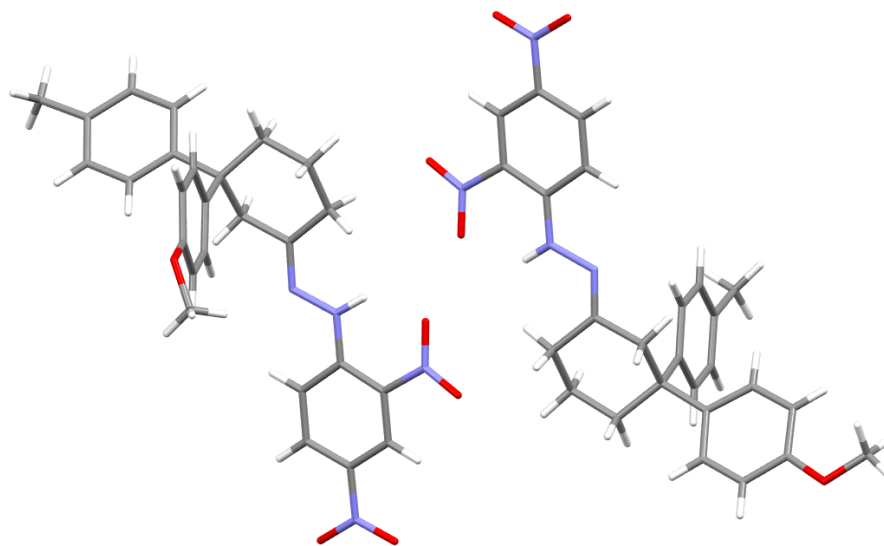
To an oven dried round bottom flask was added (*S*)-3-(4-methoxyphenyl)-3-(*p*-tolyl)cyclohexan-1-one **2a** (0.181 g, 0.614 mmol, 89% ee), 2,4-dinitrophenylhydrazine (0.122 g, 0.614 mmol) and 20 mL of anhydrous toluene. A drop of acetic acid was added to the reaction mixture and the resulting solution was refluxed with a Dean-Stark trap for 16 h. The reaction mixture was then concentrated under vacuum. The crude reaction mixture was purified with flash silica gel chromatography using dichloromethane:hexane (6:4) as an eluent to give

a mixture of (*S,E*)-1-(2,4-dinitrophenyl)-2-(3-(4-methoxyphenyl)-3-(p-tolyl)cyclohexylidene)hydrazine (*S,E*)-**4a** and (*S,Z*)-1-(2,4-dinitrophenyl)-2-(3-(4-methoxyphenyl)-3-(p-tolyl)cyclohexylidene)hydrazine (*S,Z*)-**4a** in 80 % yield with 3.3:1.0 dr. The resulting mixture was recrystallized from methanol to obtain yellow single crystals of (*S,E*)-**4a** for single crystal XRD analysis. $[\alpha]_D^{24} = +334.0^\circ$ (*c* 1.0, CHCl₃). ¹H NMR of (*S,E*)-**4a** (400 MHz, CDCl₃): δ 1.67-1.73 (m, 2H), 2.29 (s, 3H), 2.46-2.54 (m, 4H), 3.10 (d, *J* = 15.2 Hz, 1H), 3.14 (d, *J* = 15.2 Hz, 1H), 3.76 (s, 3H), 6.81 (d, *J* = 8.4 Hz, 2H), 7.09 (d, *J* = 8.4 Hz, 2H), 7.18 (d, *J* = 8.4 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 8.07 (d, *J* = 9.6 Hz, 1H), 8.35 (dd, *J* = 9.6, 2.4 Hz, 1H), 9.13 (d, *J* = 2.4 Hz, 1H), 11.21 (s, 1H). ¹³C NMR of (*S,E*)-**4a** (101 MHz, CDCl₃): 20.9, 21.0, 26.3, 36.1, 47.0, 47.6, 55.3, 113.8, 116.4, 123.8, 127.1, 128.3, 129.3, 130.2, 131.2, 135.8, 137.7, 139.5, 144.7, 145.4, 157.8, 159.66, 159.68. HRMS (ESI): Calcd. for C₂₆H₂₇N₄O₅⁺ ([M+H]⁺): 475.1976 Found: 475.1968.

Absolute stereochemistry and structure of (*S,E*)-4a**:**

Single crystal X-ray structure determination of **4a** was performed using Cu radiation to determine the absolute configuration of the molecule. The systematic absences in the diffraction data were consistent with the P1 space group. The position of almost all non-hydrogen atoms were found by direct methods. The remaining atoms were located in an alternating series of least-squares cycles on difference Fourier maps. All non-hydrogen atoms were refined in full-matrix anisotropic approximation. All hydrogen atoms were placed in the structure factor calculation at idealized positions and were allowed to ride on the neighboring atoms with relative isotropic displacement coefficients. Flack, Hooft, and Parsons parameters calculated with PLATON software (as 0.06(8), 0.08(8), and 0.07(7) respectively) are consistent with our assignment of the absolute configuration. CCDC 1544809 contains the

supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.



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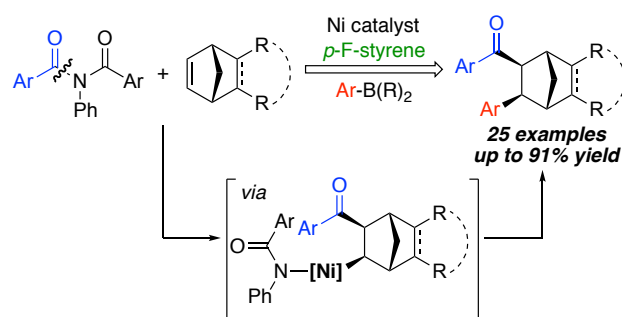
CHAPTER 3. NICKEL-CATALYZED THREE-COMPONENT ALKENE CARBOACYLATION VIA ACTIVATION OF AMIDE C-N BONDS

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Abhishek A. Kadam, Tanner Metz, Yiqiu Qian, and Levi M. Stanley*

Abstract



The nickel-catalyzed intermolecular carboacylation of alkenes with amides and tetraarylborates is presented. Bicyclic alkenes are readily functionalized with a variety of *N*-benzoyl-*N*-phenylbenzamides and triarylboranes, which are generated *in situ* from the corresponding tetraarylborates, to synthesize ketone products in up to 91% yield. Preliminary mechanistic studies suggest that migratory insertion precedes transmetalation, and that reductive elimination is the turnover-limiting step. These reactions occur with excellent chemoselectivity and diastereoselectivity in the absence of a directing/chelating group and further demonstrate amides as practical acyl electrophiles for alkene dicarbofunctionalization reactions.

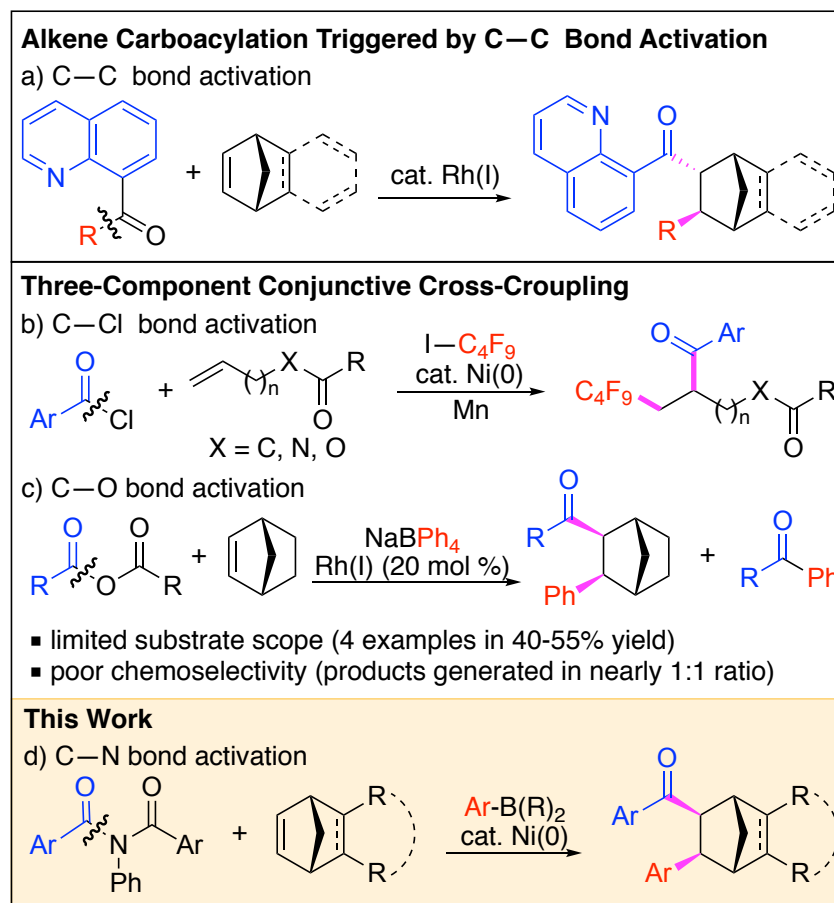
Introduction

Transition metal-catalyzed cross-coupling reactions constitute an integral toolkit for the construction of new C–C bonds.¹ Recently, cross-coupling reactions involving alkenes as ambiphilic conjunctive reagents have emerged as a promising platform for alkene dicarbofunctionalization reactions,² such as arylalkylation,^{2c} diarylation,^{2d-g} and dialkylation.^{2h} Carboacylation of alkenes is an important subset of these dicarbofunctionalization reactions,³⁻⁴ which results in the introduction of an acyl electrophile and an aryl or alkyl nucleophile into readily accessible alkene frameworks.

To date, most alkene carboacylation reactions proceed in an intramolecular fashion, delivering cyclized products from preassembled starting materials.³ As a consequence of their intramolecular nature, these processes are restricted to substrates bearing tethered alkenes. We envisioned the development of an intermolecular, three-component alkene carboacylation reaction, which would enable the synthesis of complex molecular scaffolds from readily accessible starting materials. Current approaches to intermolecular alkene carboacylation encompass (1) reactions triggered by the directed activation of a C–C bond,^{3a-h,4a} and (2) three-component conjunctive cross-coupling reactions between a carboxylic acid derivative, an alkyl radical or organometallic nucleophile, and an alkene.^{4b-c}

Douglas and co-workers reported a Rh-catalyzed intermolecular alkene carboacylation reaction of 8-acylquinolines with strained bicyclic alkenes (Scheme 1a).^{4a} A limitation of this approach is that it requires the use of a non-removable quinoline directing group to facilitate C–C bond scission. An alternative approach to three-component carboacylation of alkenes occurring by Ni-catalyzed reductive radical relay was recently reported (Scheme 1b).^{4b} This reaction involves radical addition to a terminal alkene followed by chelation-assisted alkyl

radical capture of an acyl–nickel(II)–chloride intermediate. While this report provides a practical entry into three-component alkene carboacylation reactions, the reaction is limited to the addition of perfluoroalkyl radicals to terminal alkenes. The ability to incorporate common organometallic nucleophiles, such as organoboron reagents, into this type of conjunctive three-component cross-coupling reaction is underdeveloped.



Scheme 1. Current Strategies for Transition Metal-Catalyzed Intermolecular Alkene Carboacylation

A mechanistically distinct approach to intermolecular three-component alkene carboacylation involves Rh-catalyzed conjunctive cross-coupling of an acid anhydride, tetraphenylborate, and norbornene (Scheme 1c).^{4c} This method begins to set the stage for

highly modular three-component alkene carboacylation; however, this reaction suffers from limited substrate scope (4 examples in 43-55% yield), occurs with poor chemoselectivity, and requires high loading (20 mol %) of a precious metal catalyst. Despite the significant advances outlined above, more robust methods for intermolecular three-component alkene carboacylation of alkenes are needed. Based on our previous report of nickel-catalyzed intramolecular alkene carboacylation of *o*-allylbenzamides, we sought to employ amides as acyl electrophiles⁵ in intermolecular alkene carboacylation reactions.³ⁱ This advance would enable coupling of bench stable amides with readily accessible alkene and arylboron reagents (Scheme 1d) to generate highly functionalized ketone products. Herein, we disclose a Ni-catalyzed three-component alkene carboacylation of alkenes with amides and tetraarylboron reagents.

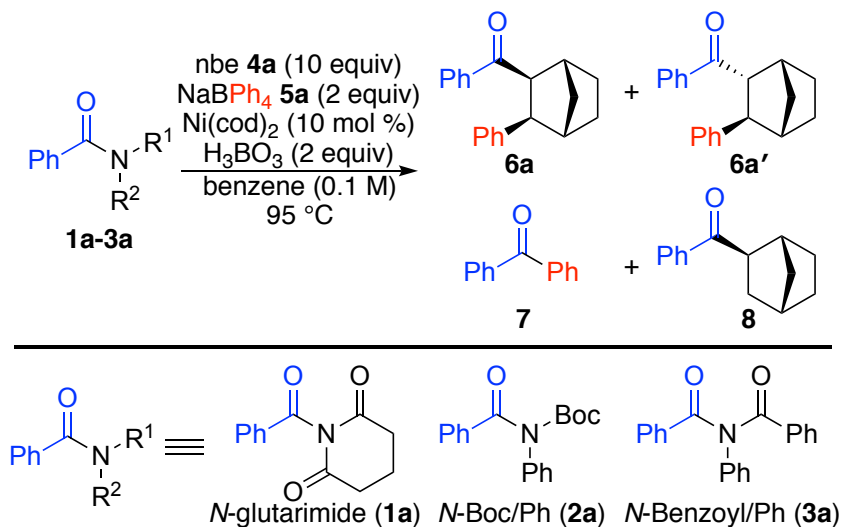
Results and Discussions:

Initially, we chose to evaluate the reaction of *N*-glutarimidebenzamide **1a**, norbornene **4a**, and sodium tetraphenylborate **5a** as a means to identify practical catalysts and reaction conditions (Table 1). We began our studies by investigating nickel complexes of *N*-heterocyclic carbene or monophosphine ligands that have previously been shown to readily activate amide C–N bonds.⁵ Nickel complexes generated from Ni(cod)₂ and a variety of *N*-heterocyclic carbene or monophosphine ligands catalyzed the model reaction to form the desired *cis*-diastereomer **6a** in 8-25% yield and the *trans*-diastereomer **6a'** in 0-16% yield (see Table S1 in General Experimental Details). We also observed the formation of the Suzuki-Miyaura coupling product **7** and the formal hydroacylation product **8** in low yields.

When the alkene carboacylation reaction was catalyzed by Ni(cod)₂ in the absence of an exogenous ligand, the reaction formed the *cis*-diastereomer **6a** in 29% yield with excellent

diastereoselectivity (Table 1, entry 1). In the presence of boric acid, the model reaction formed the carboacylation product **6a** in 48% yield (Table 1, entry 2). We initially hypothesized that boric acid could serve to activate the amide starting material and/or react with sodium tetraphenylborate to generate triphenylborane.⁶

Table 1. Identification of Reaction Conditions



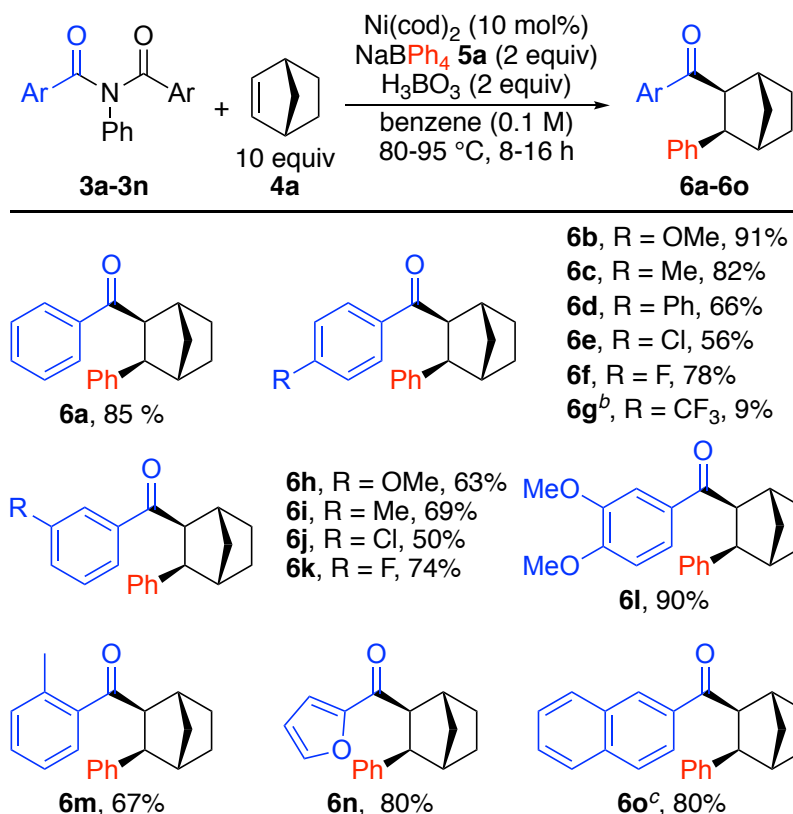
entry	amide	conv. (%) ^b	yield (%) ^b			
			6a	6a'	7	8
1 ^c	1a	70	29	1	4	2
2	1a	96	48	0	7	3
3	2a	99	60	3	2	5
4	3a	99	83	9	4	4
5 ^d	3a	99	84	3	5	2
6 ^{d,e}	3a	99	85	0	6	3
7 ^f	3a	99	65	0	6	4
8 ^{c,e,g}	3a	99	75	0	8	2
9 ^{e,g,h}	3a	99	87	0	5	5

^aReaction conditions: **1a-3a** (0.100 mmol), norbornene **4a** (1.00 mmol), NaBPh₄ **5a** (0.200 mmol), Ni(cod)₂ (0.010 mmol), H₃BO₃ (0.200 mmol), benzene (1 mL), 16 h. ^bDetermined by ¹H NMR spectroscopy of the crude reaction mixture using dibromomethane as an internal

standard. ^cReaction run in absence of boric acid. ^dReaction run for 8 h. ^eReaction run at 80 °C. ^fReaction run with 5 equiv of norbornene **4a**. ^gReaction run with 2 equiv of triphenylborane instead of sodium tetraphenylborate **5a**. ^hReaction run with 0.5 equiv of boric acid.

To improve the yield of the model alkene carboacylation reaction, we investigated the impact of amide identity. The reaction of *N*-phenyl-*N*-Boc-benzamide **2a** with norbornene and tetraphenylborate formed the carboacylation product **6a** in 60% yield (Table 1, entry 3). However, the yield is modest due to the formation of benzanilide in 30% yield. We initially hypothesized that benzanilide is formed from the acid-catalyzed deprotection of the Boc carbamate. Several attempts to mitigate the formation of benzanilide utilizing a variety of *N*-aryl-*N*-carbamate substituted benzamides were unsuccessful, and benzanilide formation is likely the result of carbamate C–N bond activation (see Table S2 in General Experimental Details).⁷

To mitigate the potential for undesired C–N bond activation, we evaluated reactions of the symmetrical *N*-benzoyl-*N*-phenylbenzamide **3a**.⁸ The reaction of **3a** with norbornene and tetraphenylborate generated the alkene carboacylation products in 92% yield with 9.2:1 dr (Table 1, entry 4). When the reaction time was reduced to 8 h, the reaction formed alkene carboacylation products in 87% yield with >20:1 dr (Table 1, entry 5). Running the reaction at 80 °C for 8 h led to the formation of product **6a** as a single diastereomer in 85% yield (Table 1, entry 6). We observed that high concentrations of norbornene were required to obtain product **6a** in high yields. The carboacylation reaction between amide **3a**, sodium tetraphenylborate and 5 equivalents of norbornene generated product **6a** in 65% yield (Table 1, entry 7).



^aReaction conditions: **3** (0.100 mmol), **4a** (1.00 mmol), **5a** (0.200 mmol), $\text{Ni}(\text{cod})_2$ (0.010 mmol), H_3BO_3 (0.200 mmol), benzene (1 mL), 80-95 °C, 8-16 h. ^bDetermined by ^1H NMR spectroscopy of the crude reaction mixture using dibromomethane as an internal standard.

^cReaction run using 1-(2-naphthoyl)piperidine-2,6-dione as the acyl electrophile.

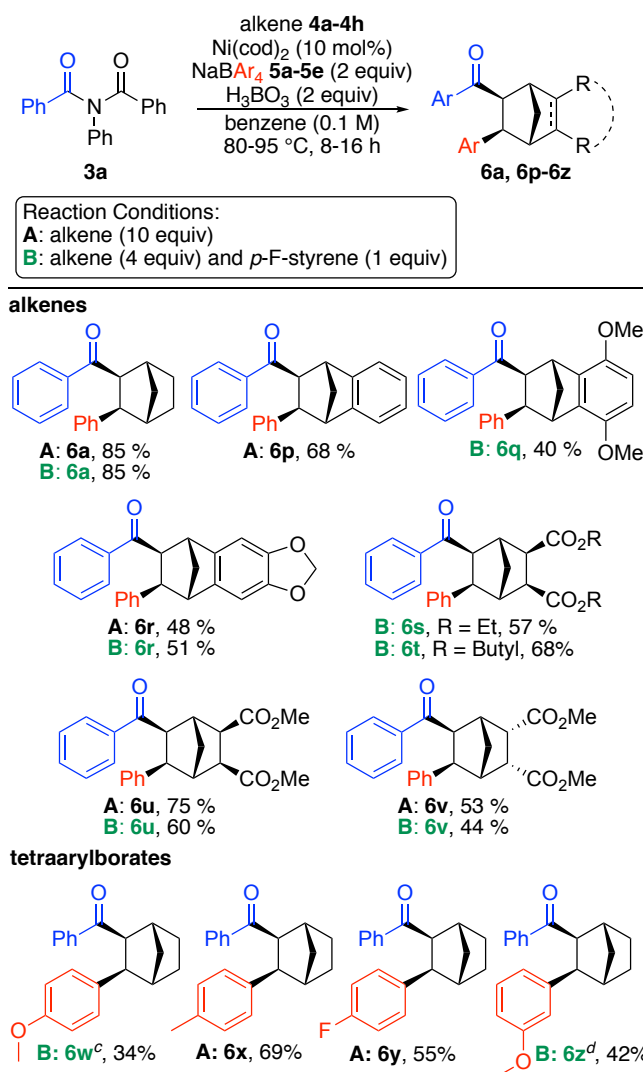
Scheme 2. Scope of Amides^a

We conducted control experiments to probe the role boric acid serves in our model carboacylation reaction. To probe whether boric acid reacts with sodium tetraphenylborate to generate triphenylborane, we evaluated the reaction of norbornene, *N*-benzoyl-*N*-phenylbenzamide **3a**, and triphenylborane. This reaction formed the ketone product **6a** in 75% yield (Table 1, entry 8). We hypothesized that the lower yield observed in entry 8 is due to the

absence of boric acid which can also facilitate amide activation.⁹ To investigate this hypothesis, we conducted the carboacylation reaction of norbornene, amide **3a**, and triphenylborane in the presence of 50 mol% boric acid. This reaction formed the carboacylation product **6a** in 87% yield (Table 1, entry 9). These results suggest that boric acid reacts with sodium tetraphenylborate to generate triphenylborane, which is the reactive organometallic nucleophile in these reactions, and that boric acid also serves as a Brønsted acid to activate the amide electrophile.

With a practical catalyst system identified for the model reaction between amide **3a**, norbornene **4a**, and tetraphenylborate **5a**, we evaluated intermolecular alkene carboacylation reactions with a variety of *N*-benzoyl-*N*-phenylbenzamides (Scheme 2). Carboacylation of norbornene with sodium tetraphenylborate and *N*-benzoyl-*N*-phenylbenzamides **3a-3f** containing electron-donating, electron-neutral, or halogenated *para*-substituents formed ketone products **6a-6f** in 56-91% yield. However, the reaction of a *N*-benzoyl-*N*-phenylbenzamide bearing an electron-deficient *p*-trifluoromethyl substituent occurs to form ketone product **6g** in <10% yield under our standard reaction conditions. Reactions of *N*-benzoyl-*N*-phenylbenzamides with electron-donating and halogenated *meta*-substituents occur to form the corresponding ketone products **6h-6k** in moderate-to-good yields (50-74%). The reaction of 3,4-dimethoxy substituted *N*-benzoyl-*N*-phenylbenzamide led to the formation of ketone product **6l** in 90% yield. The reaction of a *N*-benzoyl-*N*-phenylbenzamide containing an *ortho*-methyl substituent generated the ketone product **6m** in 67%. A heteroaromatic amide, *N*-phenyl-*N*-(furan-2-carbonyl)furan-2-carboxamide, is also a suitable electrophile for the alkene carboacylation. The carboacylation reaction of norbornene with *N*-phenyl-*N*-(furan-2-

carbonyl)furan-2-carboxamide and sodium tetraphenylborate forms the ketone product **6n** in 80% yield. Although we focused on developing alkene carboacylation reactions using *N*-



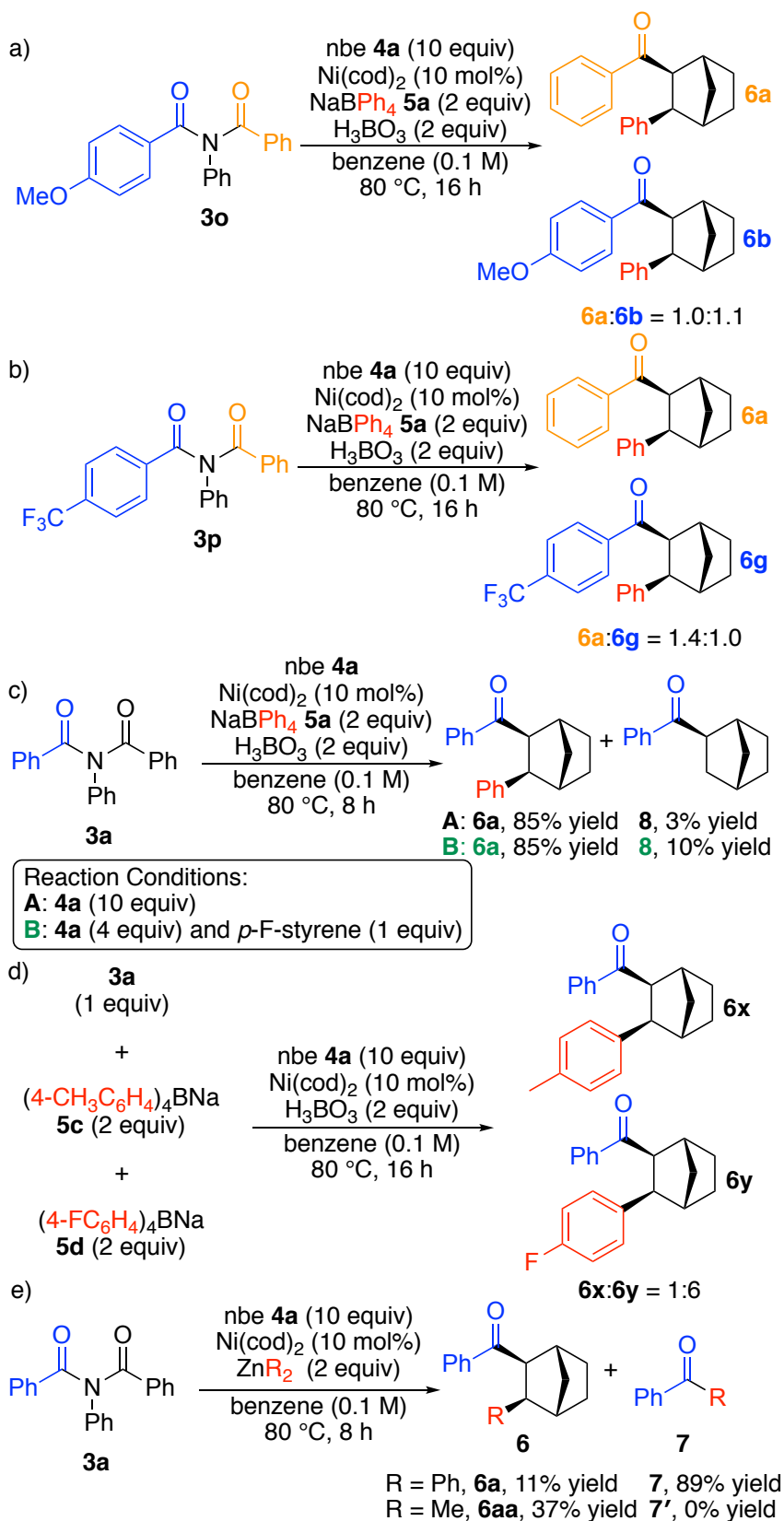
^aReaction conditions **A:** **3a** (0.100 mmol), **4** (1.00 mmol), **5** (0.200 mmol), Ni(cod)_2 (0.010 mmol), H_3BO_3 (0.200 mmol), benzene, 80-95 °C, 8-16 h. ^bReaction conditions **B:** **3a** (0.100 mmol), **4** (0.400 mmol), **5** (0.200 mmol), Ni(cod)_2 (0.010 mmol), H_3BO_3 (0.200 mmol), *p*-F-styrene (0.100 mmol) benzene, 80-95 °C, 8-16 h. ^cReaction run with 10 equiv of norbornene **4a**. ^dReaction run in the absence of H_3BO_3 .

Scheme 3. Scope of Alkenes and Tetraarylborates^{a,b}

benzoyl-*N*-phenylbenzamides, the reactions of amides derived from glutarimide were also successful.^{5b,9} For example, the reaction of 1-(2-naphthoyl)piperidine-2,6-dione forms the ketone product **6o** in 80% yield.

We then evaluated Ni-catalyzed alkene carboacylation with a range of bicyclic alkenes **4a-4h** and sodium tetraarylborates (Scheme 3). Carboacylations of benzonorbornadienes with amide **3a** and sodium tetraphenylborate **5a** generate ketone products **6p** and **6r** in 68% and 48% yield. Reactions of dimethyl (*exo,exo*)-5-nobornene-2,3-dicarboxylate and dimethyl (*endo,endo*)-5-nobornene-2,3-dicarboxylate generated carboacylation products **6u** and **6v** in 75% and 53% yield. We recognized the impracticality of establishing an alkene scope which requires a large excess of non-commercially available alkene coupling partners. We discovered that the presence of 1 equivalent of *p*-F-styrene enabled us to reduce the loading of the bicyclic alkenes to 4 equivalents without impacting the yield of ketone product **6a**.¹⁰⁻¹¹ Encouraged by this result, we continued our study of alkene scope using 4 equivalents of alkene in the presence of 1 equivalent of *p*-F-styrene. Carboacylation reactions of benzonorbornadienes formed ketone products **6q** and **6r** in 40% and 51% yield. In addition, reactions of dialkyl (*exo,exo*)-5-nobornene-2,3-dicarboxylates and dimethyl (*endo,endo*)-5-nobornene-2,3-dicarboxylate generated carboacylation products **6s-6v** in 44-68% yield.

Sodium tetraphenylborates **5b-5d** with electron-donating, electron-neutral and halogenated *para*-substituents reacted with *N*-benzoyl-*N*-phenylbenzamide **3a** and norbornene to form the corresponding ketone products **6w-6y** in 34-69% yields. The reaction of sodium tetrakis(4-trifluoromethylphenyl)borate, which contains electron-deficient aryl groups, did not form the corresponding carboacylation product. The reaction of sodium tetrakis(3-methoxyphenyl)borate **5e** occurred to form the ketone product **6z** in 42% yield.

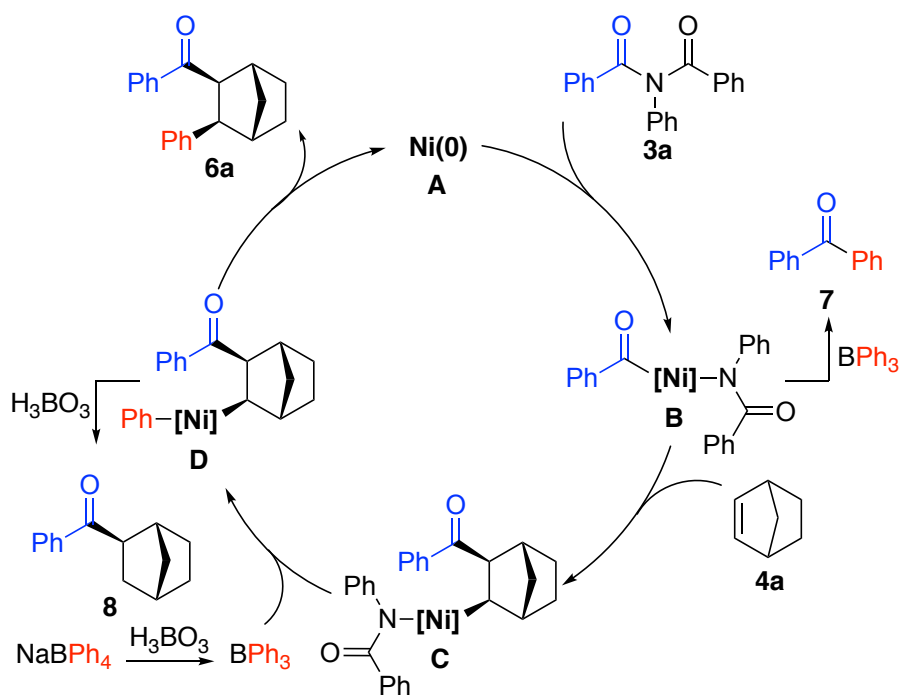


Scheme 4. Mechanistic Studies

We conducted a series of preliminary experiments to provide insight into the mechanism of the intermolecular alkene carboacylation reaction (Scheme 4). The carboacylation reactions with unsymmetrical amides, *N*-benzoyl-4-methoxy-*N*-phenylbenzamide **3o** or *N*-benzoyl-*N*-phenyl-4-(trifluoromethyl)benzamide **3p**, generated a mixture of ketone products **6a** and **6b** or **6a** and **6g** in nearly a 1:1 ratio (Scheme 4a and 4b). These results suggest it is unlikely that oxidative addition is the turnover-limiting step in these catalytic reactions.¹² As we have noted in our discussion of alkene scope (Scheme 3), the concentration of alkene can be significantly reduced when running the model reaction in the presence of *p*-F-styrene (Scheme 4c). The addition of *p*-F-styrene has been reported to facilitate reductive elimination for nickel-catalyzed cross-coupling reactions.^{10-11,2e} Additionally, the competition experiment between sodium tetra-*p*-tolylborate **5c** and sodium tetrakis(4-fluorophenyl)borate **5d** formed carboacylation products **6x** and **6y** in 1:6 ratio with the major product formed selectively from the relatively electron-deficient arylboron reagent (Scheme 4d). On the basis of these results, our working hypothesis is that reductive elimination is the turnover-limiting step for the intermolecular alkene carboacylation reaction.

After oxidative addition, we envisioned two potential pathways for our model reaction to proceed depending on the ordering of the subsequent transmetalation and migratory insertion steps. If transmetalation with triphenylborane occurs first, the corresponding acyl-nickel(II)-aryl complex would be generated as an on cycle intermediate. However, if migratory insertion precedes transmetalation, an alkyl-nickel(II)-amido complex would be formed. In this scenario, the acyl-nickel(II)-aryl complex would be an off-cycle intermediate with the potential to lead to the formation of benzophenone **7**, the product of Suzuki-Miyaura cross-coupling.

In an effort to determine the order of elementary steps we evaluated the three-component alkene carboacylation reaction between amide **3a**, norbornene and diphenylzinc (Scheme 4e). We postulated that in the presence of diphenylzinc, transmetalation will precede migratory insertion due to the relatively rapid rates of transmetalation with diarylzinc reagents and selectively generate the acyl-nickel(II)-aryl intermediate.¹³ This reaction generated benzophenone **7**, the product of Negishi coupling in 89% yield, and the desired carboacylation product **6a** was formed in only 11% yield. The formation of benzophenone **7** as the major product suggests that the acyl-nickel(II)-aryl complex is an off cycle intermediate and that migratory insertion precedes transmetalation for our model reaction. Interestingly, the reaction of dimethylzinc with amide **3a** and norbornene **4a** selectively formed the alkylacylation product **6aa**, albeit in modest yield (37%).



Scheme 5. Proposed Catalytic Cycle

Building upon these observations, we propose the catalytic cycle shown in Scheme 5. Oxidative addition of the active Ni(0) catalyst to amide **3a** affords acyl–Ni(II)–amido intermediate **B**. Migratory insertion of bicyclic alkene **4a** into the Ni–C(acyl) bond generates alkyl–Ni(II)–amido complex **C**. Subsequent transmetalation with triphenylborane forms the alkyl–Ni(II)–aryl intermediate **D**, which undergoes reductive elimination to form the carboacylation product **6a** and regenerates the active Ni(0) catalyst **A**.

Conclusion

In summary, we have developed a nickel-catalyzed intermolecular, three-component alkene carboacylation reaction triggered by activation of an amide C–N bond. This nickel-catalyzed conjunctive cross-coupling encompasses reactions of a variety of bicyclic alkenes, amides, and tetraarylborates to generate highly functionalized ketone products in high yields and excellent diastereoselectivities. In addition, preliminary mechanistic studies suggest that reductive elimination is the turnover-limiting step, and that migratory insertion precedes transmetalation. Studies to further leverage the synthetic potential of amides as acyl electrophiles in three-component conjunctive cross-coupling reactions are ongoing in our laboratory.

Experimental

General 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. Benzene, toluene, dichloromethane (DCM), diethylether (Et₂O), and tetrahydrofuran (THF) 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 dimethylformamide (DMF) were purchased

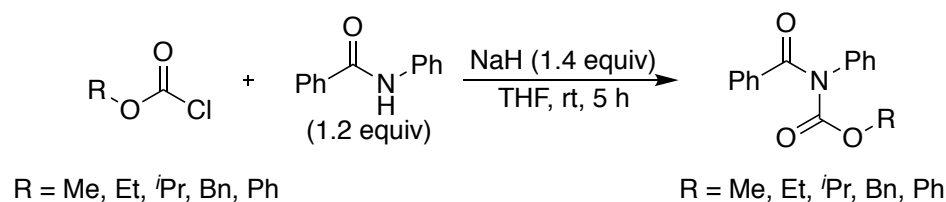
from Sigma-Aldrich and used as received. Flash column chromatography was performed on SiliFlash® P60 silica gel (40-63µm, 60Å) or using a Teledyne Isco Combiflash® Rf system with RediSep Gold™ columns using hexane/ethyl acetate or hexane/Et₂O or and pentane/Et₂O. Reaction products were visualized on TLC under UV light or by staining with KMnO₄.

HRMS (ESI) analysis was performed at the Iowa State University Chemical Instrumentation Facility on an Agilent 6540 QTOF spectrometer. Elemental analysis was performed at the Iowa State University Chemical Instrumentation Facility on the Perkin Elmer 2100 Series II CHN/S Analyzer. NMR spectra were acquired on Varian MR-400 and Bruker Avance III 600 spectrometers at the Iowa State University Chemical Instrumentation Facility. Chemical shifts are reported in ppm relative to a residual solvent peak (CDCl₃ = 7.26 ppm for ¹H and 77.16 ppm for ¹³C). ¹⁹F NMR shifts are reported based on indirect reference to CDCl₃. Coupling constants are reported in hertz.¹⁴

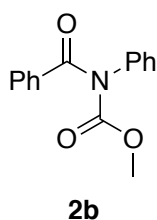
Materials. Sodium tetraphenylborate, norbornene, methylchloroformate, ethylchloroformate, isopropylchloroformate, phenylchloroformate, benzylchloroformate, 4-methoxybenzoic acid, 4-methylbenzoic acid, 4-phenylbenzoic acid, 4-chlorobenzoic acid, 4-fluorobenzoic acid, 3-chlorobenzoic acid, 3-fluorobenzoic acid, 2-thiophenecarboxylic acid, 2-furoic acid, magnesium triflate, anhydrous methanol, anhydrous ethanol, anhydrous *n*-butanol, dimethylzinc, benzoyl chloride, 2.0 M oxalyl chloride solution in DCM, and 2.5 M *n*-BuLi solution in hexanes were purchased from Sigma Aldrich. 3-Methylbenzoic acid was purchased from Lancaster Synthesis. 3-Methoxybenzoic acid was purchased from Eastman Organic Chemicals. Dicyclopentadiene and triphenylborane were purchased from Alfa Aesar. 4-Methoxybenzoyl chloride, and 4-(trifluoromethyl)benzoyl chloride were purchased from

TCI America. Carbic anhydride and benzanilide were purchased from AK Scientific. Ni(cod)₂ was purchased from Strem Chemical and Sigma Aldrich. Amides **1a**,¹⁵ **1b**,¹⁵ **2a**,¹⁶ **3a**^{17a} and **3aa**^{17b} were synthesized according to literature procedures. Alkene **4b**,¹⁸ **4c**,¹⁹ **4d**,²⁰ **4e**,²¹ **4f**,²¹ **4g**,²¹ and **4h**²¹ were synthesized according to literature procedures. Sodium tetraarylborates **5b**,²² **5c**,²² **5d**,²³ and **5e**²³ were prepared according to literature procedures.

General Procedure A for synthesis of amides **2b-2f**:

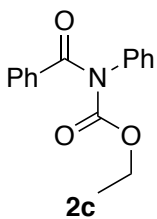


An oven dried flask was charged with a solution of NaH (1.4 equiv) in THF (0.60 M) at 0 °C under N₂. A solution of benzanilide (1.2 equiv) in THF (0.25 M) was added to the reaction flask. The resulting mixture was then stirred at 0 °C for 1 h. A solution of alkyl or aryl chloroformate (1.0 equiv) in THF (0.42 M) was added slowly to the reaction flask. The resulting mixture was stirred at room temperature for 5 h. The reaction mixture was then quenched with sat. NH₄Cl. The aqueous layer was separated and extracted with DCM (15 mL X 3). The combined organic layer was washed with brine, dried over MgSO₄ and concentrated under vacuum. The crude reaction mixture was then purified by flash column chromatography to give amides **2b-2f** in 61-99% yield.



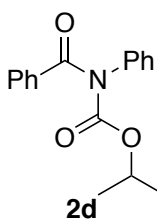
methyl benzoyl(phenyl)carbamate 2b: Prepared according to the general procedure A from benzanilide (0.500 g, 2.54 mmol) and methyl chloroformate (0.199 g, 2.11 mmol) to yield **2b** as a white solid in 73% yield (0.394 g, 1.54 mmol). ¹H NMR (400 MHz, CDCl₃): δ 3.68 (s, 3H), 7.24-7.27 (m, 2H), 7.36 (tt, *J* = 7.6, 1.2 Hz, 1H), 7.40-7.44 (m, 4H), 7.51 (tt, *J* = 7.6, 1.2 Hz, 1H), 7.70-7.73 (m, 2H). ¹³C

NMR (100 MHz, CDCl_3): 53.9, 128.1, 128.2, 128.4, 128.5, 129.4, 132.1, 135.7, 138.7, 155.3, 172.2. **HRMS** (ESI): Calcd. for $\text{C}_{15}\text{H}_{14}\text{NO}_3^+$ ($[\text{M}+\text{H}]^+$): 256.0968, Found: 256.0972.



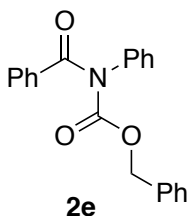
ethyl benzoyl(phenyl)carbamate 2c: Prepared according to the general procedure **A** from benzanilide (0.500 g, 2.54 mmol) and ethyl chloroformate (0.229 g, 2.11 mmol) to yield **2c** as a white solid in 99% yield (0.565 g, 2.09 mmol). $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 1.03 (t, $J = 7.2$ Hz, 3H), 4.12 (q, $J = 7.2$

Hz, 2H), 7.27 (dd, $J = 7.6, 1.2$ Hz, 2H), 7.35 (tt, $J = 7.6, 1.2$ Hz, 1H), 7.40-7.45 (m, 4H), 7.52 (tt, $J = 7.6, 1.2$ Hz, 1H), 7.71-7.73 (m, 2H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3): 13.9, 63.3, 128.1, 128.1, 128.3, 128.4, 129.4, 132.0, 136.2, 138.9, 154.9, 172.4. **HRMS** (ESI): Calcd. for $\text{C}_{16}\text{H}_{16}\text{NO}_3^+$ ($[\text{M}+\text{H}]^+$): 270.1125, Found: 270.1129.



isopropyl benzoyl(phenyl)carbamate 2d: Prepared according to the general procedure **A** from benzanilide (0.500 g, 2.54 mmol) and isopropyl chloroformate (0.259 g, 2.11 mmol) to yield **2d** as a white solid in 67% yield (0.405 g, 1.41 mmol). $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 1.04 (d, $J = 6.4$ Hz, 6H),

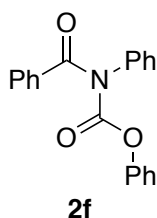
4.88 (sep, $J = 6.4$ Hz, 1H), 7.27 (dd, $J = 7.6, 1.2$ Hz, 2H), 7.35 (tt, $J = 7.6, 1.2$ Hz, 1H), 7.40-7.46 (m, 4H), 7.52 (tt, $J = 7.6, 1.2$ Hz, 1H), 7.72-7.74 (m, 2H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3): 21.4, 71.55, 71.62, 128.0, 128.3, 128.4, 129.3, 131.9, 136.6, 139.0, 154.4, 172.6. **HRMS** (ESI): Calcd. for $\text{C}_{17}\text{H}_{18}\text{NO}_3^+$ ($[\text{M}+\text{H}]^+$): 284.1281, Found: 284.1279



benzyl benzoyl(phenyl)carbamate 2e: Prepared according to the general procedure **A** from benzanilide (0.500 g, 2.54 mmol) and benzyl chloroformate (0.360 g, 2.11 mmol) to yield **2e** as a colorless oil in 65% yield (0.453g, 1.37 mmol). $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 5.10 (s, 2H), 7.03 (dd, $J = 7.6, 1.6$

Hz, 2H), 7.24-7.29 (m, 5H), 7.33-7.44 (m, 5H), 7.50 (tt, $J = 7.6, 1.2$ Hz, 1H), 7.68-7.71 (m,

2H). ^{13}C NMR (100 MHz, CDCl_3): 68.8, 128.1, 128.2, 128.46, 128.50, 128.52, 128.54, 128.57, 129.4, 132.2, 134.8, 135.9, 138.8, 154.8, 172.3. **HRMS** (ESI): Calcd. for $\text{C}_{21}\text{H}_{18}\text{NO}_3^+$ ($[\text{M}+\text{H}]^+$): 332.1281, Found: 332.1281.

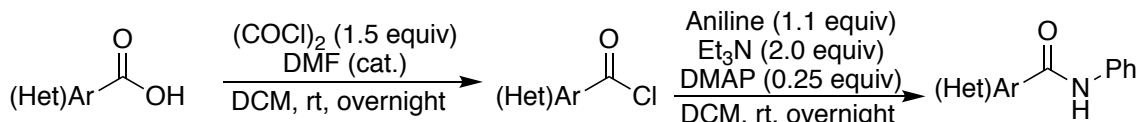


phenyl benzoyl(phenyl)carbamate 2f: Prepared according to the general procedure A from benzanilide (0.500 g, 2.54 mmol) and phenyl chloroformate

(0.331 g, 2.11 mmol) to yield **2f** as a white solid in 61% yield (0.409 g, 1.29

mmol). ^1H NMR (400 MHz, CDCl_3): δ 6.95-6.98 (m, 2H), 7.18 (tt, 7.6, 1.2 Hz, 1H), 7.30 (tt, 8.0, 2.0 Hz, 2H), 7.37-7.42 (m, 3H), 7.45-7.50 (m, 4H), 7.55 (tt, $J = 7.6, 1.2$ Hz, 1H), 7.84-7.87 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3): 121.0, 126.2, 128.0, 128.4, 128.67, 128.71, 129.5, 129.6, 132.5, 135.6, 138.6, 150.5, 153.2, 172.2. **HRMS** (ESI): Calcd. for $\text{C}_{20}\text{H}_{16}\text{NO}_3^+$ ($[\text{M}+\text{H}]^+$): 318.1125, Found: 318.1127.

General Procedure B for synthesis of amides 3a-3p:



Ar = C_6H_5
 Ar = 4- $\text{OCH}_3\text{C}_6\text{H}_4$
 Ar = 4- $\text{CH}_3\text{C}_6\text{H}_4$
 Ar = biphenyl
 Ar = 4- ClC_6H_4
 Ar = 4- FC_6H_4
 Ar = 3- $\text{OCH}_3\text{C}_6\text{H}_4$
 Ar = 3- $\text{CH}_3\text{C}_6\text{H}_4$
 Ar = 3- ClC_6H_4
 Ar = 3- FC_6H_4
 Ar = 3,4- $(\text{OCH}_3)_2\text{C}_6\text{H}_3$
 Ar = 2- $\text{CH}_3\text{C}_6\text{H}_4$
 HetAr = 2-furan

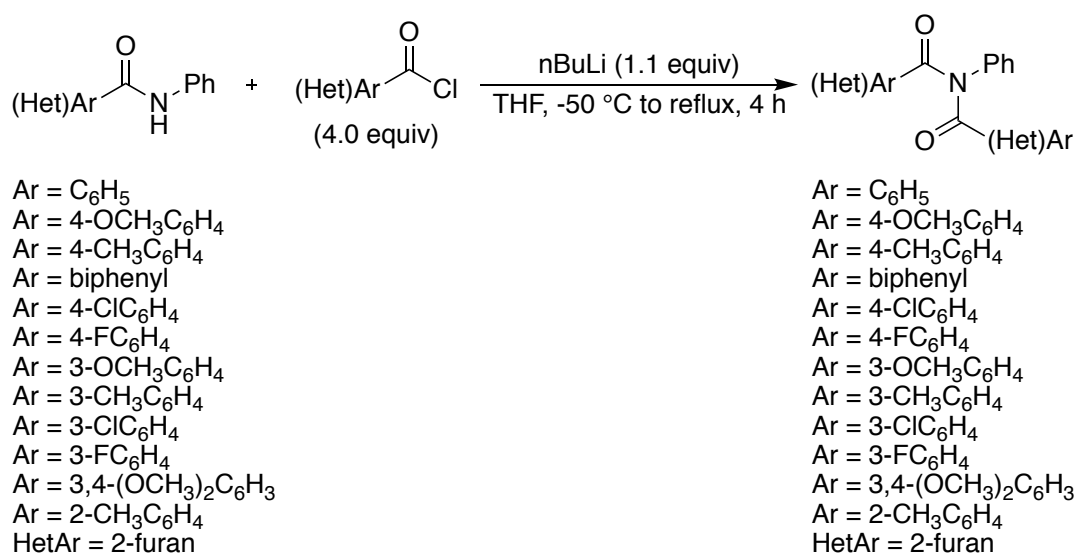
Ar = C_6H_5
 Ar = 4- $\text{OCH}_3\text{C}_6\text{H}_4$
 Ar = 4- $\text{CH}_3\text{C}_6\text{H}_4$
 Ar = biphenyl
 Ar = 4- ClC_6H_4
 Ar = 4- FC_6H_4
 Ar = 3- $\text{OCH}_3\text{C}_6\text{H}_4$
 Ar = 3- $\text{CH}_3\text{C}_6\text{H}_4$
 Ar = 3- ClC_6H_4
 Ar = 3- FC_6H_4
 Ar = 3,4- $(\text{OCH}_3)_2\text{C}_6\text{H}_3$
 Ar = 2- $\text{CH}_3\text{C}_6\text{H}_4$
 HetAr = 2-furan

To the appropriate benzoic acid in anhydrous DCM (0.3 M) at 0 °C under N_2 was added a catalytic amount of DMF (1-2 drops) followed by 2.0 M solution of oxalyl chloride in DCM (1.2 equiv) dropwise and. The reaction was allowed to warm to room temperature and stirred

overnight. The solvent was removed under vacuum to afford the corresponding acid chloride.

The acid chloride was used in the next step without further purification.

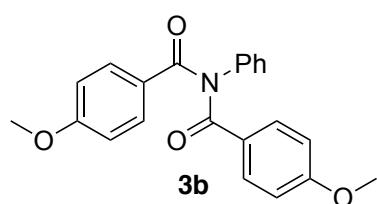
To a dry flask, aniline (1.1 equiv), triethylamine (2.0 equiv) and *N,N*-dimethylaminopyridine (0.25 equiv) were added in DCM (1.5 M). A solution of an appropriate acid chloride in DCM (0.30 M) was added slowly to the reaction flask at 0 °C under N₂. The reaction was allowed to warm to room temperature and stirred overnight. The reaction mixture was then quenched with 1N HCl and layers were separated. The aqueous layer was extracted with EtOAc (15 mL X 3). The organic layers were combined, washed with brine, dried over MgSO₄, and concentrated under vacuum to yield corresponding benzanilide (or *N*-phenylbenzamide). The benzanilide was used in the next step without further purification.



To an oven dried flask, a cold solution of benzanilide (or *N*-phenylbenzamide) (1.0 equiv) in THF (0.30 M) at -50 °C under N₂ was added. A solution of 2.5 M nBuLi in hexane (1.1 equiv) was added dropwise to the reaction flask. The resulting mixture was stirred at room temperature for 1 h. Acid chloride (4.0 equiv) was then added slowly under vigorous stirring. The resulting mixture was then refluxed for 4 h. The reaction mixture was then quenched with

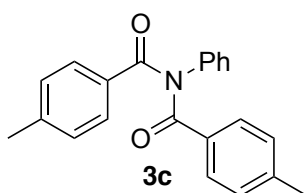
1 N HCl and layers were separated. The aqueous layer was then extracted with EtOAc (20 mL X 3). The combined organic layer was then washed with brine, dried over MgSO₄, and concentrated under vacuum. The crude reaction mixture was then purified by flash column chromatography using Hexane:EtOAc to afford corresponding amides. All the amides were then recrystallized from methanol or methanol:chloroform (1:1) to give pure amides **3a-3p** in 20-75% yields.

Characterization data for amides 3b-3p:



4-methoxy-*N*-(4-methoxybenzoyl)-*N*-phenylbenzamide

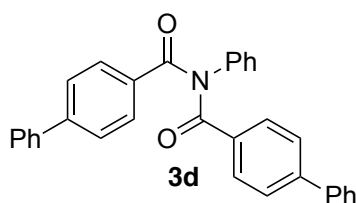
3b: Prepared according to general procedure **B** from 4-methoxy-*N*-phenylbenzamide (1.00 g, 4.40 mmol) and 4-methoxybenzoyl chloride (3.00 g, 17.6 mmol) to yield **3b** as a white solid in 64% yield (1.02 g, 2.82 mmol). ¹H NMR (400 MHz, CDCl₃): δ 3.81 (s, 6H), 6.82 (ddd, *J* = 8.8, 2.8, 2.0 Hz, 4H), 7.16 (d, *J* = 7.2 Hz, 2H), 7.25 (dd, *J* = 7.6, 7.2 Hz, 1H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.73 (ddd, *J* = 8.8, 2.8, 2.0 Hz, 4H). ¹³C NMR (100 MHz, CDCl₃): δ 55.6, 113.9, 127.2, 127.4, 127.7, 129.6, 131.8, 141.0, 163.0, 173.1. HRMS (ESI): Calcd. for C₂₂H₂₀NO₄⁺ ([M+H]⁺): 362.1387, Found: 362.1385.



4-methyl-*N*-(4-methylbenzoyl)-*N*-phenylbenzamide **3c:**

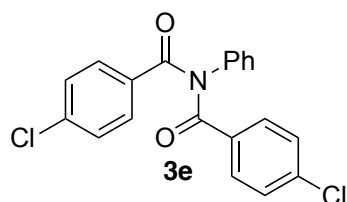
Prepared according to general procedure **B** from 4-methyl-*N*-phenylbenzamide (1.00 g, 4.73 mmol) and 4-methylbenzoyl chloride (2.93 g, 18.9 mmol) to yield **3c** as a white solid in 51% yield (0.793 g, 2.41 mmol). ¹H NMR (400 MHz, CDCl₃): δ 2.34 (s, 6H), 7.13 (d, *J* = 8.0 Hz, 4H), 7.17 (d, *J* = 8.4 Hz, 2H), 7.25 (t, *J* = 7.2 Hz, 1H), 7.34 (d, *J* = 8 Hz, 2H), 7.64 (d, *J* = 8.0 Hz, 4H).

^{13}C NMR (100 MHz, CDCl_3): δ 21.8, 127.5, 127.8, 129.3, 129.61, 129.64, 132.1, 140.7, 143.2, 173.6. **HRMS** (ESI): Calcd. for $\text{C}_{22}\text{H}_{20}\text{NO}_2^+$ ($[\text{M}+\text{H}]^+$): 330.1489, Found: 330.1466.



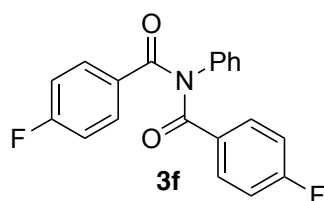
N*-([1,1'-biphenyl]-4-carbonyl)-*N*-phenyl-[1,1'-biphenyl]-4-carboxamide **3d*: Prepared according to general procedure **B** from *N*-phenyl-[1,1'-biphenyl]-4-carboxamide (0.740 g, 2.70

mmol) and 4-phenylbenzoyl chloride (2.35 g, 10.8 mmol) to yield **3d** as a white solid in 51% yield (0.624 g, 1.38 mmol). ^1H NMR (400 MHz, CDCl_3): δ 7.23-7.26 (m, 2H), 7.29 (tt, $J = 7.4, 1.29$ Hz, 1H), 7.35-7.41 (m, 4H), 7.44 (tdd, $J = 7.1, 1.8, 1.2$ Hz, 4H), 7.55-7.60 (m, 8H), 7.85 (ddd, $J = 8.6, 1.9, 1.8$ Hz, 4H). ^{13}C NMR (100 MHz, CDCl_3): δ 127.3, 127.4, 127.8, 127.9, 128.3, 129.1, 129.8, 130.1, 133.5, 139.9, 140.4, 145.3, 173.4. **HRMS** (ESI): Calcd. for $\text{C}_{32}\text{H}_{24}\text{NO}_2^+$ ($[\text{M}+\text{H}]^+$): 454.1802, Found: 454.1808.



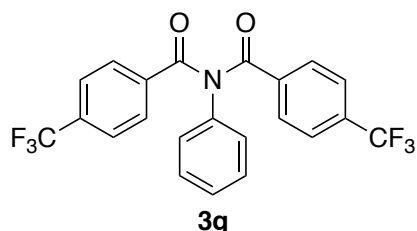
4-chloro-*N*-(4-chlorobenzoyl)-*N*-phenylbenzamide **3e**: Prepared according to general procedure **B** from 4-chloro-*N*-phenylbenzamide (1.00 g, 4.32 mmol) and 4-chlorobenzoyl

chloride (3.02 g, 17.3 mmol) to yield **3e** as a white solid in 40% yield (0.639 g, 1.73 mmol). ^1H NMR (400 MHz, CDCl_3): δ 7.14 (ddd, $J = 7.6, 1.6, 1.2$ Hz, 2H), 7.26-7.39 (m, 7H), 7.67 (ddd, $J = 8.0, 2.0, 2.0$ Hz, 4H). ^{13}C NMR (100 MHz, CDCl_3): δ 127.8, 128.1, 129.1, 129.9, 130.8, 132.9, 139.0, 139.8, 172.4. **HRMS** (ESI): Calcd. for $\text{C}_{22}\text{H}_{14}\text{Cl}_2\text{NO}_2^+$ ($[\text{M}+\text{H}]^+$): 370.0396, Found: 370.0387.



4-fluoro-*N*-(4-fluorobenzoyl)-*N*-phenylbenzamide **3f**: Prepared according to general procedure **B** from 4-fluoro-*N*-phenylbenzamide (1.20 g, 5.57 mmol) and 4-fluorobenzoyl chloride (3.52 g, 22.3 mmol) to yield **3f** as a white solid in 63% yield (1.18 g, 3.51 mmol). ^1H

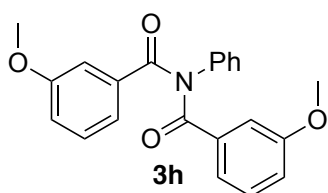
NMR (400 MHz, CDCl₃): δ 7.03 (dd, $J = 7.6, 5.2$ Hz, 4H), 7.16 (d, $J = 8.0$ Hz, 2H), 7.29 (t, $J = 8.0$ Hz, 1H), 7.37 (t, $J = 8.0$ Hz, 2H), 7.77 (dd, $J = 7.6, 5.2$ Hz, 4H). **¹³C NMR** (100 MHz, CDCl₃): δ 116.0 (d, $J = 22.0$ Hz, 4C), 127.8, 128.0, 129.8, 130.8 (d, $J = 3.1$ Hz, 2C), 132.0 (d, $J = 9.2$ Hz, 4C), 140.1, 165.2 (d, $J = 253.5$ Hz, 2C), 172.3. **¹⁹F NMR** (376 MHz, CDCl₃): δ -105.27 (m, 2F). **HRMS** (ESI): Calcd. for C₂₂H₁₄F₂NO₂⁺ ([M+H]⁺): 338.0987, Found: 338.0995.



***N*-phenyl-4-(trifluoromethyl)-*N*-(4-**

(trifluoromethyl)benzoyl)benzamide 3g: Prepared according to general procedure **B** from *N*-phenyl-4-(trifluoromethyl)benzamide (2.65 g, 10.0 mmol) and 4-

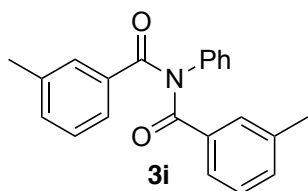
(trifluoromethyl)benzoyl chloride (4.17 g, 20.0 mmol) to yield **3g** as a white solid in 35% yield (1.53 g, 3.50 mmol). **¹H NMR** (400 MHz, CDCl₃): δ 7.15-7.18 (m, 2H), 7.32 (tt, $J = 7.2, 1.2$ Hz, 1H), 7.36-7.41 (m, 2H), 7.63 (d, $J = 8.4$, 4H), 7.84 (d, $J = 8.4$, 4H). **¹³C NMR** (100 MHz, CDCl₃): δ 126.0 (q, $J = 3.7$ Hz, 1C), 128.2, 128.8, 129.8, 130.3, 134.1, 134.4, 137.8, 139.3, 172.3. **¹⁹F NMR** (376 MHz, CDCl₃): δ -63.2 (s, 6F). **HRMS** (ESI): Calcd. for C₂₂H₁₄F₆NO₂⁺ ([M+H]⁺): 438.0923 Found: 438.0920.



3-methoxy-*N*-(3-methoxybenzoyl)-*N*-phenylbenzamide 3h:

Prepared according to general procedure **B** from 3-methoxy-*N*-phenylbenzamide (1.00 g, 4.41 mmol) and 3-methoxybenzoyl chloride (3.01 g, 17.6 mmol) to yield **3h** as a white solid in 42% yield (0.669 g, 1.85 mmol). **¹H NMR** (400 MHz, CDCl₃): δ 3.76 (s, 6H), 6.98 (dt, $J = 7.1, 2.4$ Hz, 2H), 7.17-7.39 (m, 11H).

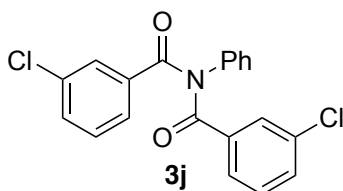
^{13}C NMR (100 MHz, CDCl_3): δ 55.5, 114.2, 118.9, 121.7, 127.76, 127.78, 129.6, 129.7, 136.2, 140.3, 159.7, 173.4. **HRMS** (ESI): Calcd. for $\text{C}_{22}\text{H}_{20}\text{NO}_4^+$ ($[\text{M}+\text{H}]^+$): 362.1387, Found: 362.1381.



3-methyl-N-(3-methylbenzoyl)-N-phenylbenzamide 3i: Prepared according to general procedure **B** from 3-methyl-N-phenylbenzamide (1.00 g, 4.74 mmol) and 3-methylbenzoyl

chloride (2.93 g, 19.0 mmol) to yield **3i** as a white solid in 44% yield (0.688 g, 2.09 mmol).

^1H NMR (400 MHz, CDCl_3): δ 2.31 (s, 6H), 7.17 -7.28 (m, 7H), 7.36 (t, $J = 7.4$ Hz, 2H), 7.50 (d, $J = 7.4$ Hz, 2H), 7.55 (s, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ 21.4, 126.4, 127.7, 127.9, 128.4, 129.6, 130.1, 133.2, 135.0, 138.5, 140.4, 173.8. **HRMS** (ESI): Calcd. for $\text{C}_{22}\text{H}_{20}\text{NO}_2^+$ ($[\text{M}+\text{H}]^+$): 330.1489, Found: 330.1476.

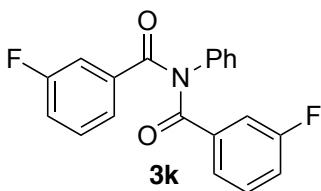


3-chloro-N-(3-chlorobenzoyl)-N-phenylbenzamide 3j:

Prepared according to general procedure **B** from 3-chloro-N-phenylbenzamide (1.00 g, 4.32 mmol) and 3-chlorobenzoyl

chloride (3.02 g, 17.3 mmol) to yield **3j** as a white solid in 43% yield (0.687 g, 1.86 mmol).

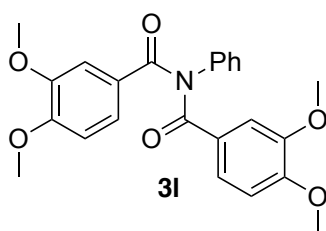
^1H NMR (400 MHz, CDCl_3): δ 7.16 (d, $J = 8.1$ Hz, 2H), 7.26-7.33 (m, 3H), 7.37-7.44 (m, 4H), 7.58 (d, $J = 7.8$ Hz, 2H), 7.71 (s, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ 127.3, 127.9, 128.3, 129.5, 129.95, 129.96, 132.6, 134.9, 136.3, 139.5, 172.0. **HRMS** (ESI): Calcd. for $\text{C}_{22}\text{H}_{14}\text{Cl}_2\text{NO}_2^+$ ($[\text{M}+\text{H}]^+$): 370.0396, Found: 370.0395.



3-fluoro-N-(3-fluorobenzoyl)-N-phenylbenzamide 3k: Prepared according to general procedure **B** from 3-fluoro-N-phenylbenzamide (0.982 g, 4.25 mmol) and 3-fluorobenzoyl

chloride (2.27 g, 12.8 mmol) to yield **3k** as a white solid in 75% yield (1.08 g, 3.19 mmol). ^1H

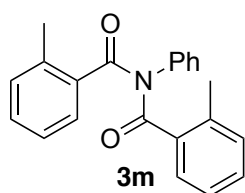
NMR (400 MHz, CDCl₃): δ 7.14-7.19 (m, 4H), 7.28-7.40 (m, 5H), 7.42 (dt, $J = 8.9, 2.5$ Hz, 2H), 7.51 (dt, $J = 7.8, 1.5$ Hz, 2H). **¹³C NMR** (100 MHz, CDCl₃): δ 116.4 (d, $J = 23.2$ Hz, 2C), 119.7 (d, $J = 21.2$ Hz, 2C), 125.0 (d, $J = 3.2$ Hz, 2C), 127.9, 128.3, 129.9, 130.4 (d, $J = 7.8$ Hz, 2C), 136.7 (d, $J = 6.9$ Hz, 2C), 139.6, 162.6 (d, $J = 247.2$ Hz, 2C), 172.1 (d, $J = 2.9$ Hz, 2C). **¹⁹F NMR** (376 MHz, CDCl₃): δ -111.39 (m, 2F). **HRMS** (ESI): Calcd. for C₂₂H₁₄F₂NO₂⁺ ([M+H]⁺): 338.0987, Found: 338.0991.



***N*-(3,4-dimethoxybenzoyl)-3,4-dimethoxy-*N*-phenylbenzamide**

3I: Prepared according to general procedure **B** from 3,4-dimethoxy-*N*-phenylbenzamide (1.00 g, 3.89 mmol) and 3,4-dimethoxybenzoyl chloride (2.34 g, 11.7 mmol) to yield **3I** as a

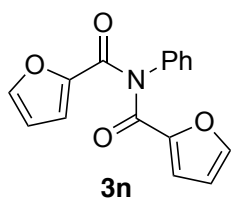
white solid in 31% yield (0.508 g, 1.21 mmol). **¹H NMR** (400 MHz, CDCl₃): δ 3.82 (s, 6H), 3.88 (s, 6H), 6.77 (d, $J = 8.5$ Hz, 2H), 7.18 (d, $J = 7.3$ Hz, 2H), 7.26 (t, $J = 8.3$ Hz, 1H), 7.32 (d, $J = 2.0$ Hz, 2H), 7.36 (t, $J = 8.0$ Hz, 2H), 7.40 (dd, $J = 8.4, 2.0$ Hz, 2H). **¹³C NMR** (100 MHz, CDCl₃): δ 56.0, 56.1, 110.3, 112.4, 123.8, 127.2, 127.4, 127.5, 129.7, 141.2, 148.9, 152.7, 173.1. **HRMS** (ESI): Calcd. for C₂₄H₂₄NO₆⁺ ([M+H]⁺): 422.1598, Found: 422.1601.



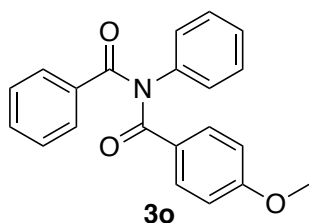
2-methyl-*N*-(2-methylbenzoyl)-*N*-phenylbenzamide **3m:** Prepared

according to general procedure **B** from 2-methyl-*N*-phenylbenzamide (1.48 g, 7.00 mmol) and 2-methylbenzoyl chloride (2.16 g, 14.0 mmol)

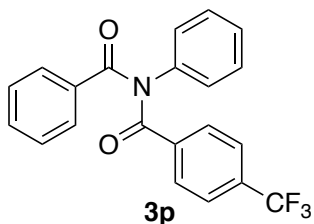
to yield **3m** as a white solid in 50% yield (1.16 g, 3.50 mmol). **¹H NMR** (400 MHz, CDCl₃): δ 2.40 (s, 6H), 7.05-7.13 (m, 4H), 7.20 (td, $J = 7.6, 1.2$ Hz, 2H), 7.27-7.32 (m, 3H), 7.38-7.43 (m, 2H), 7.50 (dd, $J = 7.6, 1.2$ Hz, 2H). **¹³C NMR** (100 MHz, CDCl₃): δ 20.1, 125.5, 127.7, 127.96, 128.01, 129.6, 130.9, 131.3, 136.0, 138.0, 139.6, 173.5. **HRMS** (ESI): Calcd. for C₂₂H₂₀NO₃⁺ ([M+H]⁺): 330.1489, Found: 330.1488.



***N*-(furan-2-carbonyl)-*N*-phenylfuran-2-carboxamide 3n:** ^1H NMR (400 MHz, CDCl_3): Prepared according to general procedure **B** from *N*-phenylfuran-2-carboxamide (2.00 g, 10.7 mmol) and 2-furoyl chloride (5.58 g, 40.8 mmol) to yield **3n** as a white solid in 70% yield (2.11 g, 7.49 mmol). ^1H NMR (400 MHz, CDCl_3): δ 6.44 (dd, $J = 3.6, 1.7$ Hz, 2H), 6.99 (dd, $J = 3.6, 0.7$ Hz, 2H), 7.24-7.27 (m, 2H), 7.35 (tt, $J = 7.4, 1.3$ Hz, 1H), 7.39-7.43 (m, 2H), 7.45 (dd, $J = 1.7, 0.7$ Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ 112.3, 119.6, 128.0, 128.4, 129.7, 139.1, 146.4, 147.7, 161.4. HRMS (ESI): Calcd. for $\text{C}_{16}\text{H}_{12}\text{NO}_4^+$ ($[\text{M}+\text{H}]^+$): 282.0791, Found: 282.0770.



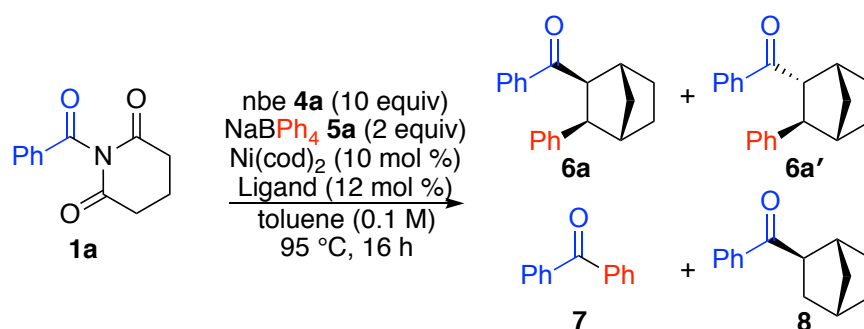
***N*-benzoyl-4-methoxy-*N*-phenylbenzamide 3o:** Prepared according to general procedure **B** from benzanilide (1.38 g, 7.00 mmol) and 4-methoxybenzoyl chloride (2.38 g, 14.0 mmol) to yield **3o** as a white solid in 21% yield (0.503 g, 1.47 mmol). ^1H NMR (400 MHz, CDCl_3): δ 3.81 (s, 3H), 6.82-6.84 (ddd, $J = 9.6, 4.8, 2.8$ Hz, 2H), 7.17 (ddd, $J = 7.6, 3.6, 1.2$ Hz, 2H), 7.26 (tt, $J = 7.6, 1.2$ Hz, 1H), 7.31-7.38 (m, 4H), 7.44 (tt, $J = 7.6, 1.2$ Hz, 1H), 7.74 (ddd, $J = 9.6, 4.8, 2.8$ Hz, 4H). ^{13}C NMR (100 MHz, CDCl_3): δ 55.6, 114.0, 126.8, 127.6, 127.8, 128.6, 129.2, 129.6, 132.1, 132.3, 135.3, 140.7, 163.2, 172.9, 173.7. HRMS (ESI): Calcd. for $\text{C}_{21}\text{H}_{18}\text{NO}_3^+$ ($[\text{M}+\text{H}]^+$): 332.1281, Found: 332.1277.



***N*-benzoyl-*N*-phenyl-4-(trifluoromethyl)benzamide 3p:** Prepared according to general procedure **B** from benzanilide (2.11 g, 10.0 mmol) and 4-(trifluoromethyl)benzoyl chloride (4.17 g, 20.0 mmol) to yield **3p** as a white solid in 30% yield (1.10 g, 3.00 mmol). ^1H NMR (400 MHz, CDCl_3): δ 7.16-7.20 (m, 2H), 7.27-7.40 (m, 5H), 7.47 (tt, $J = 7.6, 1.2$ Hz, 1H), 7.62 (d, $J = 8.0$ Hz, 2H), 7.73-7.75 (m, 2H), 7.85 (d, $J = 8.0$ Hz, 2H). ^{13}C NMR

(100 MHz, CDCl₃): δ 123.6 (d, J = 273 Hz, 1C), 125.7 (q, J = 4 Hz, 1C), 127.9, 128.1, 128.8, 129.4, 129.7, 129.9, 130.7, 132.9, 133.7 (d, J = 33 Hz, 1C), 134.2, 139.7, 172.4, 173.3. **¹⁹F NMR** (376 MHz, CDCl₃): δ -63.16 (s, 3F). **HRMS** (ESI): Calcd. for C₂₁H₁₅F₃NO₂⁺ ([M+H]⁺): 370.1049, Found: 370.1051.

Table S1. Catalyst Identification for Ni-catalyzed alkene carboacylation of norbornene **4a** with *N*-glutarimidebenzamide **1a** and sodium tetraphenylborate **5a**^a



Entry	ligand	conver. (%) ^b	yield (%) ^b			
			6a	6a'	7	8
1	SIPr	92	25	16	0	3
2	IMes	84	8	0	0	2
3 ^c	ICy·HCl	48	18	0	6	2
4	PCy ₃	89	15	6	7	0
5	P ^t Bu ₃	42	14	0	7	3
6	none	80	19	1	4	2
7 ^d	none	80	29	1	4	2

^aReaction conditions: *N*-glutarimidebenzamide **1a** (0.100 mmol), norbornene **4a** (1.00 mmol), NaBPh₄ **5a** (0.200 mmol), Ni(cod)₂ (0.010 mmol), ligand (0.012 mmol), toluene (1 mL) at 95 °C for 16 h. ^bDetermined by ¹H NMR spectroscopy of the crude reaction mixture using

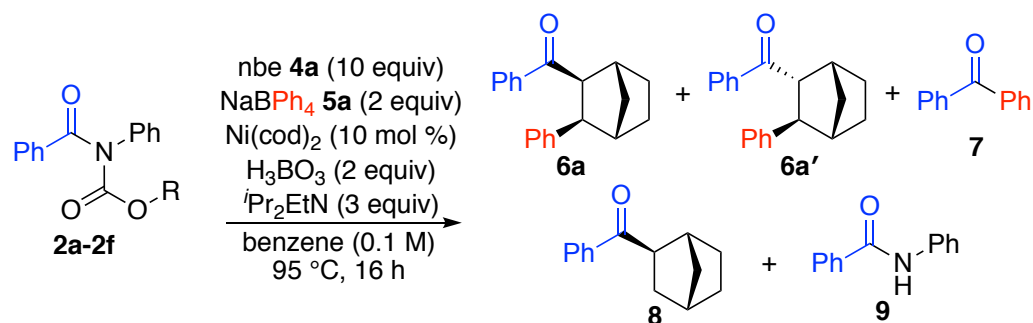
dibromomethane as an internal standard. ^cReaction run in the presence of 12 mol % NaO^tBu.

^dReaction run in benzene (0.1M) instead of toluene (0.1M).

Procedure for Catalyst Identification for Ni-catalyzed Alkene Carboacylation of Norbornene **4a with *N*-glutarimidebenzamide **1a** and Sodium tetraphenylborate **5a**:**

An oven dried 1-dram vial was charged with Ni(cod)₂ (2.8 mg, 0.010 mmol), ligand (0.012 mmol), *N*-glutarimidebenzamide **1a** (21.7 mg, 0.100 mmol), NaBPh₄ **5a** (68.4 mg, 0.200 mmol), norbornene **4a** (92.1 mg, 1.00 mmol), and toluene (1.00 mL, 0.100 M). The resulting solution was stirred at 95 °C for 16 h. Upon completion of the reaction, the reaction was cooled to room temperature and was filtered through a short plug of silica gel eluting with 50:50 hexanes:EtOAc and concentrated under vacuum. The crude reaction mixture was dissolved in CDCl₃ (0.700 mL) and CH₂Br₂ (3.51 μL, 0.050 mmol) was added as an internal standard. NMR yields were determined by ¹H NMR spectroscopy of the crude reaction mixture.

Table S2. Investigation of Ni-catalyzed Alkene Carboacylation of Norbornene **4a** with Amides **2a-2f** and Sodium tetraphenylborate **5a^a**



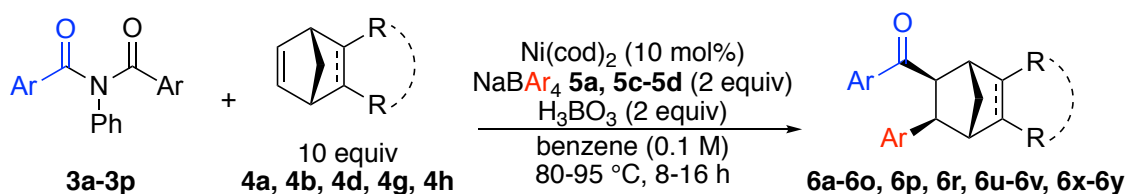
Entry	R	conver. (%) ^b	yield (%) ^b				
			6a	6a'	7	8	9
1	Me	99	54	6	2	5	33
2	Et	99	53	9	2	4	31
3	<i>i</i> Pr	99	54	12	2	6	15
4	<i>t</i> Bu	99	65	5	2	5	15
5	Bn	99	39	34	5	8	14
6	Ph	99	10	15	1	3	73

^aReaction conditions: Amide **2a-2f** (0.100 mmol), norbornene **4a** (1.00 mmol), NaBPh₄ **5a** (0.200 mmol), Ni(cod)₂ (0.010 mmol), H₃BO₃ (0.200 mmol), *i*Pr₂EtN (0.300 mmol), benzene (1 mL) at 95 °C for 16 h. ^bDetermined by ¹H NMR spectroscopy of the crude reaction mixture using dibromomethane as an internal standard.

Procedure for Investigation of Ni-catalyzed Alkene Carboacylation of Norbornene **4a with Amides **2a-2f** and Sodium tetraphenylborate **5a**^a**

An oven dried 1-dram vial was charged with Ni(cod)₂ (2.80 mg, 0.010 mmol), appropriate amide **2** (0.100 mmol), H₃BO₃ (12.4 mg, 0.200 mmol) NaBPh₄ **5a** (68.4 mg, 0.200 mmol), norbornene **4a** (92.1 mg, 1.00 mmol), ⁱPr₂EtN (52.2 μL, 0.300 mmol), and benzene (1.00 mL, 0.100 M). The resulting solution was stirred at 95 °C for 16 h. Upon completion of the reaction, the reaction was cooled to room temperature and was filtered through a short plug of silica gel eluting with 50:50 hexanes:EtOAc and concentrated under vacuum. The crude reaction mixture was dissolved in CDCl₃ (0.700 mL) and CH₂Br₂ (3.51 μL, 0.050 mmol) was added as an internal standard. NMR yields were determined by ¹H NMR spectroscopy of the crude reaction mixture.

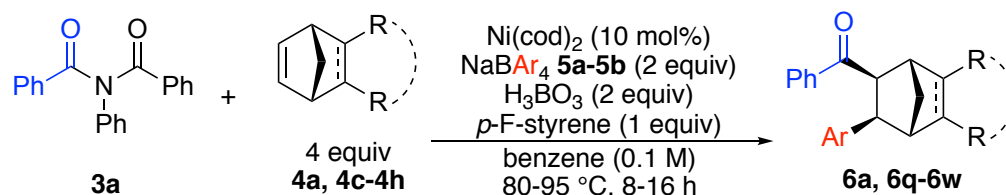
General Procedure C for Synthesis of Carboacylation Products **6a-6o, **6p**, **6r**, **6u-6v**, and **6x-6y**:**



An oven dried 1-dram vial was charged with 0.100 mmol of the appropriate amide **3a-3p**, **1b**, Ni(cod)₂ (2.80 mg, 0.010 mmol), H₃BO₃ (12.4 mg, 0.200 mmol), NaBAr₄ **5a, 5c-5d** (0.200 mmol), alkene **4a, 4b, 4d, 4g, 4h** (1.00 mmol), and benzene (1.0 mL, 0.1 M). The resulting solution was stirred at 80-95 °C for 8-16 h. Upon completion of the reaction, the reaction was cooled to room temperature and was filtered through a short plug of silica gel eluting with 50:50 hexanes:EtOAc and concentrated under reduced pressure. The crude product was

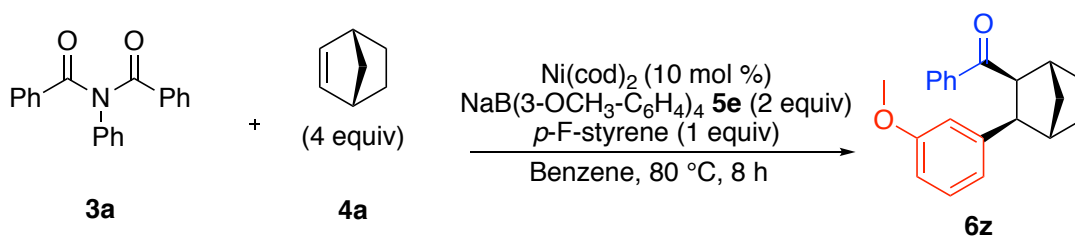
purified by flash column chromatography to give carboacylation products **6a-6o**, **6p**, **6r**, **6u-6v**, and **6x-6y**.

General Procedure D for Synthesis of Carboacylation Products 6a and 6q-6w:



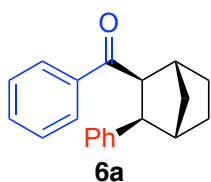
An oven dried 1-dram vial was charged with 0.100 mmol of *N*-benzoyl-*N*-phenylbenzamide **3a** (30.1 mg, 0.100 mmol), $\text{Ni}(\text{cod})_2$ (2.80 mg, 0.010 mmol), H_3BO_3 (12.4 mg, 0.200 mmol), NaBAr_4 **5a-5b** (0.200 mmol), alkene **4a, 4c-4h** (0.400 mmol), *p*-F-styrene (11.9 μL , 0.100 mmol) and benzene (1.0 mL, 0.1 M). The resulting solution was stirred at 80-95 °C for 8-16 h. Upon completion of the reaction, the reaction was cooled to room temperature and was filtered through a short plug of silica gel eluting with 50:50 hexanes:EtOAc and concentrated under reduced pressure. The crude product was purified by flash column chromatography to give carboacylation products **6a** and **6q-6w**.

General Procedure E for Synthesis of Carboacylation Product 6z:



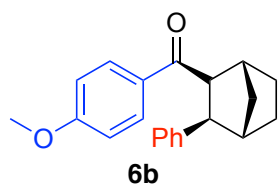
An oven dried 1-dram vial was charged with 0.100 mmol of *N*-benzoyl-*N*-phenylbenzamide **3a**, $\text{Ni}(\text{cod})_2$ (2.80 mg, 0.010 mmol), $\text{NaB}(\text{3-OCH}_3\text{-C}_6\text{H}_4)_4$ **5e** (92.4 mg, 0.200 mmol), norbornene **4a** (37.6 mg, 0.400 mmol), *p*-F-styrene (11.9 μL , 0.100 mmol) and benzene (1.0 mL, 0.1 M). The resulting solution was stirred at 80 °C for 8 h. Upon completion of the

reaction, the reaction was cooled to room temperature and was filtered through a short plug of silica gel eluting with 50:50 hexanes:EtOAc and concentrated under reduced pressure. The crude reaction mixture was purified by flash column chromatography (100:0→92:8 pentane:Et₂O) to give **6z** as a colorless oil in 42% yield (12.9 mg, 0.042 mmol).



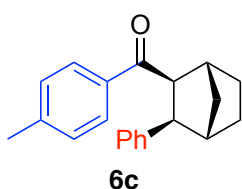
phenyl(3-phenylbicyclo[2.2.1]heptan-2-yl)methanone 6a: Prepared according to general procedure **C** from *N*-benzoyl-*N*-phenylbenzamide **3a** (30.1 mg, 0.100 mmol, 1.00 equiv), norbornene **4a** (94.2 mg, 1.00 mmol,

10.0 equiv), and sodium tetraphenylborate **5a** (68.4 mg, 0.200 mmol, 2.00 equiv) at 80°C in 8 h. The crude reaction mixture was purified by flash column chromatography (100:0 hexanes:EtOAc) to (91:9 hexanes:EtOAc) to yield **6a** as a white solid in 85% yield (25.5 mg, 0.085 mmol). Or prepared according to general procedure **D** from *N*-benzoyl-*N*-phenylbenzamide **3a** (30.1 mg, 0.100 mmol, 1.00 equiv), norbornene **4a** (37.7 mg, 1.00 mmol, 10.0 equiv), and sodium tetraphenylborate **5a** (68.4 mg, 0.200 mmol, 2.00 equiv) at 80°C in 8 h. The crude reaction mixture was purified by flash column chromatography (100:0→91:9 hexanes:EtOAc) to yield **6a** as a white solid in 85% yield (25.5 mg, 0.085 mmol). ¹H NMR (400 MHz, CDCl₃): δ 1.36-1.75 (m, 5H), 2.43-2.50 (m, 2H), 2.71 (m, 1H), 3.29 (d, *J* = 10.4 Hz, 1H), 3.85 (d, *J* = 10.4 Hz, 1H), 6.88-6.97 (m, 5H), 7.21 (t, *J* = 7.6 Hz, 2H) 7.32-7.36 (m, 1H), 7.53-7.56 (m, 2H), ¹³C NMR (100 MHz, CDCl₃): 29.1, 31.3, 37.6, 39.3, 43.7, 54.0, 56.4, 126.0, 127.8, 128.0, 128.1, 128.5, 132.1, 138.6, 141.9, 201.8. HRMS (ESI): Calcd. for C₂₀H₂₁O⁺ ([M+H]⁺): 277.1587, Found: 277.2202.



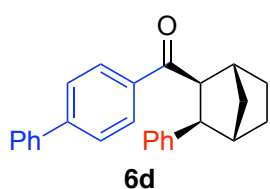
(4-methoxyphenyl)(3-phenylbicyclo[2.2.1]heptan-2-yl)methanone 6b: Prepared according to general procedure **C** from 4-methoxy-*N*-(4-methoxybenzoyl)-*N*-phenylbenzamide **3b** (36.1 mg,

0.100 mmol, 1.00 equiv), norbornene **4a** (94.2 mg, 1.00 mmol, 10.0 equiv), and sodium tetrphenylborate **5a** (68.4 mg, 0.200 mmol, 2.00 equiv) at 80°C in 8 h. The crude reaction mixture was purified by flash column chromatography (100:0→91:1 hexane:EtOAc) to give **6b** as a white solid in 91% yield (27.9 mg, 0.091 mmol). **¹H NMR** (400 MHz, CDCl₃): δ 1.36-1.51 (m, 3H), 1.66-1.76 (m, 2H), 2.42 (app. s, 1H), 2.48 (dp, *J* = 10.2, 1.7 Hz, 1H), 2.67 (app. s, 1H), 3.28 (d, *J* = 9.9 Hz, 1H), 3.78 (s, 3H), 3.79 (d, *J* = 9.9 Hz, 1H), 6.70 (ddd, *J* = 9.0, 2.8, 2.1 Hz, 2H), 6.88-6.99 (m, 5H), 7.57 (ddd, *J* = 9.0, 2.8, 2.1 Hz, 2H). **¹³C NMR** (100 MHz, CDCl₃): δ 29.2, 31.3, 37.5, 39.4, 43.6, 54.2, 55.4, 55.9, 113.2, 125.9, 127.7, 128.5, 130.4, 131.7, 142.1, 162.7, 200.2. **HRMS** (ESI): Calcd. for C₂₁H₂₃O₂⁺ ([M+H]⁺): 307.1693, Found: 307.1697.



(3-phenylbicyclo[2.2.1]heptan-2-yl)(*p*-tolyl)methanone **6c**: Prepared according to general procedure C from 4-methyl-*N*-(4-methylbenzoyl)-*N*-phenylbenzamide **3c** (32.9 mg, 0.100 mmol, 1.00 equiv), norbornene

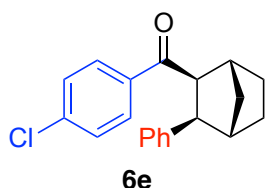
4a (94.2 mg, 1.00 mmol, 10.0 equiv), and sodium tetrphenylborate **5a** (68.4 mg, 0.200 mmol, 2.00 equiv) at 80°C in 8 h. The crude reaction mixture was purified by flash column chromatography (100:0→96:4 hexane: EtOAc) to give **6c** as a white solid in 82% yield (23.8 mg, 0.082 mmol). **¹H NMR** (400 MHz, CDCl₃): δ 1.37-1.51 (m, 3H), 1.66-1.76 (m, 2H), 2.30 (s, 3H), 2.43 (app. s, 1H), 2.48 (dp, *J* = 10.2, 1.8 Hz, 1H), 2.68 (app. s, 1H), 3.29 (d, *J* = 10.1 Hz, 1H), 3.81 (d, *J* = 10.1 Hz, 1H), 6.88-6.99 (m, 5H), 7.02 (d, *J* = 8.0 Hz, 2H), 7.48 (d, *J* = 8.0 Hz, 2H). **¹³C NMR** (100 MHz, CDCl₃): δ 21.6, 29.2, 31.3, 37.5, 39.5, 43.6, 54.1, 56.1, 125.9, 127.7, 128.3, 128.5, 128.7, 136.1, 142.0, 142.7, 201.4. **HRMS** (ESI): Calcd. for C₂₁H₂₃O⁺ ([M+H]⁺): 291.1743, Found: 291.1746.



[1,1'-biphenyl]-4-yl(3-phenylbicyclo[2.2.1]heptan-2-yl)methanone

6d: Prepared according to general procedure C from *N*-([1,1'-biphenyl]-4-carbonyl)-*N*-phenyl-[1,1'-biphenyl]-4-carboxamide **3d**

(45.3 mg, 0.100 mmol, 1.00 equiv), norbornene **4a** (94.2 mg, 1.00 mmol, 10.0 equiv), and sodium tetrphenylborate **5a** (68.4 mg, 0.200 mmol, 2.00 equiv) at 95°C in 8 h. The crude reaction mixture was purified by flash column chromatography (100:0→94:6 pentane:Et₂O) to give **6d** as a white solid in 66% yield (23.3 mg, 0.066 mmol). **¹H NMR** (400 MHz, CDCl₃): δ 1.38-1.54 (m, 3H), 1.69-1.79 (m, 2H), 2.46 (app. s, 1H), 2.51 (dt, *J* = 10.2, 1.8 Hz, 1H), 2.73 (app. s, 1H), 3.33 (d, *J* = 10.2 Hz, 1H), 3.88 (d, *J* = 10.2 Hz, 1H), 6.89-7.01 (m, 5H), 7.37 (t, *J* = 7.1 Hz, 1H), 7.42-7.46 (m, 4H), 7.55-7.57 (m, 2H), 7.63 (d, *J* = 8.4 Hz, 2H). **¹³C NMR** (100 MHz, CDCl₃): δ 29.1, 31.3, 37.6, 39.4, 43.6, 54.1, 56.4, 126.0, 126.7, 127.3, 127.8, 128.1, 128.6, 128.7, 129.0, 137.4, 140.2, 142.0, 144.6, 201.5. **HRMS** (ESI): Calcd. for C₂₆H₂₅O⁺ ([M+H]⁺): 353.1900, Found: 353.1900.

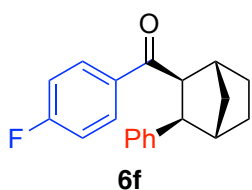


(4-chlorophenyl)(3-phenylbicyclo[2.2.1]heptan-2-yl)methanone

6e: Prepared according to general procedure C from 4-chloro-*N*-(4-chlorobenzoyl)-*N*-phenylbenzamide **3e** (37.0 mg, 0.100 mmol, 1.00

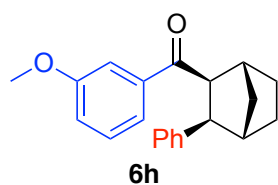
equiv), norbornene **4a** (94.2 mg, 1.00 mmol, 10.0 equiv), and sodium tetrphenylborate **5a** (68.4 mg, 0.200 mmol, 2.00 equiv) at 95°C in 8 h. The crude reaction mixture was purified by flash column chromatography (100:0→94:6 pentane:Et₂O) to give **6e** as a white solid in 56% yield (17.4 mg, 0.056 mmol). **¹H NMR** (400 MHz, CDCl₃): δ 1.37-1.53 (m, 3H), 1.66-1.74 (m, 2H), 2.42-2.47 (m, 2H), 2.70 (app. s, 1H), 3.28 (dd, *J* = 10.3, 0.5 Hz, 1H), 3.77 (dd, *J* = 10.3, 1.0 Hz, 1H), 6.90-6.98 (m, 5H), 7.18 (ddd, *J* = 8.7, 2.4, 2.0 Hz, 2H), 7.47 (ddd, *J* = 8.7, 2.4, 2.0 Hz, 2H). **¹³C NMR** (100 MHz, CDCl₃): δ 29.0, 31.3, 37.6, 39.2, 43.8, 54.0, 56.5, 126.2,

127.9, 128.3, 128.5, 129.5, 136.9, 138.4, 141.8, 200.7. **HRMS** (ESI): Calcd. for $C_{20}H_{20}ClO^+$ ($[M+H]^+$): 311.1197, Found: 311.1194.



(4-fluorophenyl)(3-phenylbicyclo[2.2.1]heptan-2-yl)methanone 6f:

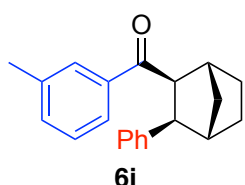
Prepared according to general procedure **C** from 4-fluoro-*N*-(4-fluorobenzoyl)-*N*-phenylbenzamide **3f** (33.7 mg, 0.100 mmol, 1.00 equiv), norbornene **4a** (94.2 mg, 1.00 mmol, 10.0 equiv), and sodium tetrphenylborate **5a** (68.4 mg, 0.200 mmol, 2.00 equiv) at 95°C in 8 h. The crude reaction mixture was purified by flash column chromatography (100:0→96:4 hexane:EtOAc) to give **6f** as a white solid in 78% yield (23.0 mg, 0.078 mmol). **¹H NMR** (400 MHz, $CDCl_3$): δ 1.37-1.53 (m, 3H), 1.66-1.78 (m, 2H), 2.42-2.47 (m, 2H), 2.70 (d, $J = 1.2$ Hz, 1H), 3.28 (dd, $J = 10.2, 0.8$ Hz, 1H), 3.78 (dd, $J = 10.2, 1.2$ Hz, 1H), 6.85-6.97 (m, 7H), 7.54-7.59 (m, 2H). **¹³C NMR** (100 MHz, $CDCl_3$): δ 29.0, 31.3, 37.6, 39.1, 43.8, 54.1, 56.4, 115.0 (d, $J = 21.6$ Hz, 2C), 126.1, 127.8, 128.5, 130.6 (d, $J = 9.2$ Hz, 2C), 135.0 (d, $J = 3.0$ Hz, 1C), 142.8, 165.1 (d, $J = 252.0$ Hz, 1C), 200.2. **¹⁹F NMR** (376 MHz, $CDCl_3$): δ -107.02 (m, 1F). **HRMS** (ESI): Calcd. for $C_{20}H_{20}FO^+$ ($[M+H]^+$): 295.1493, Found: 295.1491.



(3-methoxyphenyl)(3-phenylbicyclo[2.2.1]heptan-2-

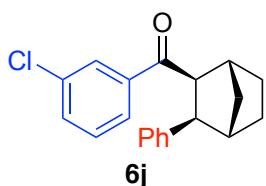
yl)methanone 6h: Prepared according to general procedure **C** from 3-methoxy-*N*-(3-methoxybenzoyl)-*N*-phenylbenzamide **3h** (36.1 mg, 0.100 mmol, 1.00 equiv), norbornene **4a** (94.2 mg, 1.00 mmol, 10.0 equiv), and sodium tetrphenylborate **5a** (68.4 mg, 0.200 mmol, 2.00 equiv) at 95°C in 8 h. The crude reaction mixture was purified by flash column chromatography (100:0→96:4 hexane:Et₂O) to give **6h** as a white solid in 63% yield (19.3 mg, 0.063 mmol). **¹H NMR** (400 MHz, $CDCl_3$): δ 1.35-1.53 (m, 3H), 1.65-1.78 (m, 2H), 2.44-2.49 (m, 2H), 2.69 (d, $J = 1.5$ Hz, 1H), 3.28 (dd, $J =$

10.2, 0.7 Hz, 1H), 3.71 (s, 3H), 3.82 (dd, $J = 10.2, 1.5$ Hz, 1H), 6.88-6.97 (m, 7H), 7.15 (t, $J = 7.8$ Hz, 1H), 7.22 (dt, $J = 7.8, 1.4$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 29.1, 31.3, 37.5, 39.4, 43.5, 54.0, 55.4, 56.6, 112.2, 118.8, 120.8, 125.9, 127.8, 128.6, 128.9, 140.3, 142.0, 159.4, 201.8. HRMS (ESI): Calcd. For $\text{C}_{21}\text{H}_{23}\text{O}_2^+$ ($[\text{M}+\text{H}]^+$): 307.1693, Found: 307.1695.



(3-phenylbicyclo[2.2.1]heptan-2-yl)(*m*-tolyl)methanone 6i: Prepared

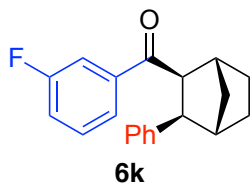
according to general procedure C from 3-methyl-*N*-(3-methylbenzoyl)-*N*-phenylbenzamide **3i** (32.9 mg, 0.100 mmol, 1.00 equiv), norbornene **4a** (94.2 mg, 1.00 mmol, 10.0 equiv), and sodium tetrphenylborate **5a** (68.4 mg, 0.200 mmol, 2.00 equiv) at 80°C in 8 h. The crude reaction mixture was purified by flash column chromatography (100:0→96:4 hexane:EtOAc) to give **6i** as a white solid in 69% yield (20.0 mg, 0.069 mmol). ^1H NMR (400 MHz, CDCl_3): δ 1.38-1.52 (m, 3H), 1.65-1.79 (m, 2H), 2.26 (s, 3H), 2.44-2.50 (m, 2H), 2.69 (d, $J = 1.3$ Hz, 1H), 3.29 (d, $J = 10.2$ Hz, 1H), 3.83 (dd, $J = 10.2, 1.3$ Hz, 1H), 6.89-6.97 (m, 5H), 7.09-7.16 (m, 2H), 7.28 (s, 1H), 7.37 (d, $J = 7.4$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 21.3, 29.1, 31.3, 37.6, 39.4, 43.6, 54.0, 56.5, 125.3, 125.9, 127.7, 127.8, 128.5, 128.7, 132.8, 137.6, 138.8, 142.0, 202.2. HRMS (ESI): Calcd. for $\text{C}_{21}\text{H}_{23}\text{O}^+$ ($[\text{M}+\text{H}]^+$): 291.1743, Found: 291.1746.



(3-chlorophenyl)(3-phenylbicyclo[2.2.1]heptan-2-yl)methanone 6j:

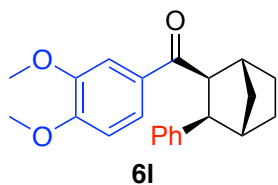
Prepared according to general procedure C from 3-chloro-*N*-(3-chlorobenzoyl)-*N*-phenylbenzamide **3j** (37.0 mg, 0.100 mmol, 1.00 equiv), norbornene **4a** (94.2 mg, 1.00 mmol, 10.0 equiv), and sodium tetrphenylborate **5a** (68.4 mg, 0.200 mmol, 2.00 equiv) at 95°C in 11 h. The crude reaction mixture was purified by flash column chromatography (100:0→98:2 hexane:EtOAc) to give **6j** as a white solid in 50% yield (15.5 mg, 0.050 mmol). ^1H NMR (400 MHz, CDCl_3): δ 1.38-1.53 (m, 3H), 1.66-

1.78 (m, 2H), 2.41-2.44 (m, 2H), 2.71 (app. s, 1H), 3.28 (d, $J = 10.2$ Hz, 1H), 3.76 (d, $J = 10.2$ Hz, 1H), 6.90-6.98 (m, 5H), 7.14 (t, $J = 7.9$ Hz, 1H), 7.30 (d, $J = 7.9$ Hz, 1H), 7.39 (d, $J = 7.9$ Hz, 1H), 7.43 (s, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 28.9, 31.3, 37.6, 39.1, 43.8, 53.9, 56.8, 126.1, 126.2, 127.9, 128.3, 128.5, 129.3, 131.9, 134.2, 140.2, 141.7, 200.7. HRMS (ESI): Calcd. for $\text{C}_{20}\text{H}_{20}\text{ClO}^+$ ($[\text{M}+\text{H}]^+$): 311.1197, Found: 311.1198.



(3-fluorophenyl)(3-phenylbicyclo[2.2.1]heptan-2-yl)methanone 6k:

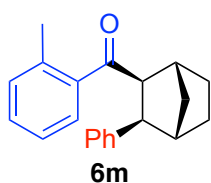
Prepared according to general procedure C from 3-fluoro-*N*-(3-fluorobenzoyl)-*N*-phenylbenzamide **3k** (33.7 mg, 0.100 mmol, 1.00 equiv), norbornene **4a** (94.2 mg, 1.00 mmol, 10.0 equiv), and sodium tetrphenylborate **5a** (68.4 mg, 0.200 mmol, 2.00 equiv) at 95°C in 11 h. The crude reaction mixture was purified by flash column chromatography (100:0→98:2 hexane:EtOAc) to give **6k** as a white solid in 74% yield (21.8 mg, 0.074 mmol). ^1H NMR (400 MHz, CDCl_3): δ 1.38-1.1.54 (m, 3H), 1.67-1.78 (m, 2H), 2.42-2.47 (m, 2H), 2.71-2.72 (m, 1H), 3.29 (d, $J = 10.3$, 1.0 Hz, 1H), 3.78 (d, $J = 10.3$, 1.2 Hz, 1H), 6.90-6.97 (m, 5H), 7.03 (tdd, $J = 8.2$, 2.6, 0.9 Hz, 1H), 7.14-7.22 (m, 2H), 7.35 (dt, $J = 7.8$, 1.2 Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 28.9, 31.3, 37.6, 39.1, 43.8, 54.0, 56.7, 114.8 (d, $J = 22.2$ Hz, 1C), 119.0 (d, $J = 21.4$ Hz, 1C), 123.8 (d, $J = 2.9$ Hz, 1C), 126.1, 127.9, 128.5, 129.6 (d, $J = 7.6$ Hz, 1C), 140.8 (d, $J = 6.0$ Hz, 1C), 141.7, 162.5 (d, $J = 245.6$ Hz, 1C), 200.6 (d, $J = 2.0$ Hz, 1C). ^{19}F NMR (376 MHz, CDCl_3): δ -113.01 (m, 1F). HRMS (ESI): Calcd. for $\text{C}_{20}\text{H}_{20}\text{FO}^+$ ($[\text{M}+\text{H}]^+$): 295.1493, Found: 295.1493.



(3,4-dimethoxyphenyl)(3-phenylbicyclo[2.2.1]heptan-2-

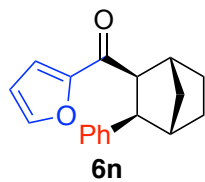
yl)methanone 6l: Prepared according to general procedure C from *N*-(3,4-dimethoxybenzoyl)-3,4-dimethoxy-*N*-phenylbenzamide **3l** (42.1 mg, 0.100 mmol, 1.00 equiv), norbornene **4a** (94.2 mg, 1.00 mmol, 10.0 equiv), and sodium

terraphenylborate **5a** (68.4 mg, 0.200 mmol, 2.00 equiv) at 80°C in 8 h. The crude reaction mixture was purified by flash column chromatography (100:0→90:10 hexane:EtOAc) to give **6l** as a white solid in 90% yield (30.3 mg, 0.090 mmol). **¹H NMR** (400 MHz, CDCl₃): δ 1.37-1.51 (m, 3H), 1.66-1.75 (m, 2H), 2.43 (app. s, 1H), 2.48 (dt, *J* = 10.2, 1.7 Hz, 1H), 2.67 (app. s, 1H), 3.26 (d, *J* = 10.0 Hz, 1H), 3.76 (s, 3H), 3.79 (d, *J* = 10.0 Hz, 1H), 3.87 (s, 3H), 6.71 (d, *J* = 8.4 Hz, 1H), 6.89-6.97 (m, 6H), 7.35 (dd, *J* = 8.4, 1.9 Hz, 1H). **¹³C NMR** (100 MHz, CDCl₃): δ 29.1, 31.2, 37.5, 39.5, 43.5, 54.2, 54.88, 54.94, 55.0, 109.4, 110.3, 122.6, 125.9, 127.7, 128.5, 132.2, 142.1, 148.5, 152.5, 200.5. **HRMS** (ESI): Calcd. for C₂₂H₂₅O₃⁺ ([M+H]⁺): 337.1798, Found: 337.1811.

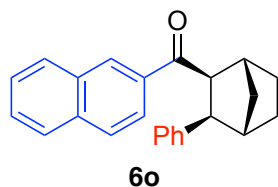


(3-phenylbicyclo[2.2.1]heptan-2-yl)(*o*-tolyl)methanone **6m**: Prepared according to according to general procedure **C** from 2-methyl-*N*-(2-methylbenzoyl)-*N*-phenylbenzamide **3m** (32.9 mg, 0.100 mmol, 1.00 equiv),

norbornene **4a** (94.2 mg, 1.00 mmol, 10.0 equiv), and sodium tetraphenylborate **5a** (68.4 mg, 0.200 mmol, 2.00 equiv) at 80°C in 8 h. The crude reaction mixture was purified by flash column chromatography (100:0→96:4 hexanes:EtOAc) to yield **6m** as a white solid in 67% yield (19.4 mg, 0.067 mmol). **¹H NMR** (400 MHz, CDCl₃): δ 1.36-1.75 (m, 5H), 1.86 (s, 3H), 2.49 (m, 2H), 2.69 (m, 1H), 3.23 (d, *J* = 10.0 Hz, 1H), 3.84 (d, *J* = 10.0 Hz, 1H), 6.93-7.02 (m, 5H), 7.15 (td, *J* = 7.6, 0.8 Hz, 1H), 7.21 (td, *J* = 7.6, 1.2 Hz, 1H), 7.25-7.29 (m, 1H), 7.52 (dd, *J* = 7.6, 1.2 Hz, 1H). **¹³C NMR** (100 MHz, CDCl₃): 20.8, 29.2, 31.2, 37.5, 40.0, 42.9, 53.5, 57.7, 125.2, 126.0, 127.9, 128.5, 128.8, 130.8, 131.8, 139.0, 139.3, 141.8, 204.9. **HRMS** (ESI): Calcd. for C₂₁H₂₃O⁺ ([M+H]⁺): 291.1743, Found: 291.1744.

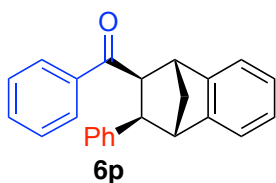


furan-2-yl(3-phenylbicyclo[2.2.1]heptan-2-yl)methanone 6n: Prepared according to general procedure **C** from *N*-(furan-2-carbonyl)-*N*-phenylfuran-2-carboxamide **3n** (28.1 mg, 0.100 mmol, 1.00 equiv), norbornene **4a** (94.2 mg, 1.00 mmol, 10.0 equiv), and sodium tetrphenylborate **5a** (68.4 mg, 0.200 mmol, 2.00 equiv) at 80°C in 8 h. The crude reaction mixture was purified by flash column chromatography (100:0→90:10 pentane:Et₂O) to give **6n** as a white solid in 80% yield (21.3 mg, 0.080 mmol). ¹H NMR (600 MHz, CDCl₃): δ 1.35-1.51 (m, 3H), 1.66-1.73 (m, 2H), 2.44-2.46 (m, 2H), 2.65 (app. s, 1H), 3.33 (d, *J* = 10.1 Hz, 1H), 3.71 (dd, *J* = 10.1, 0.9 Hz, 1H), 6.30 (dd, *J* = 3.5, 1.6 Hz, 1H), 6.74 (d, *J* = 3.5 Hz, 1H), 6.95-7.03 (m, 5H), 7.39 (d, *J* = 0.9 Hz, 1H). ¹³C NMR (150 MHz, CDCl₃): δ 29.0, 31.2, 37.8, 39.0, 42.9, 53.8, 56.4, 112.2, 115.9, 126.0, 127.8, 128.1, 141.7, 145.1, 153.7, 190.7. HRMS (ESI): Calcd. for C₁₈H₁₉O₂⁺ ([M+H]⁺): 267.1380, Found: 267.1385.



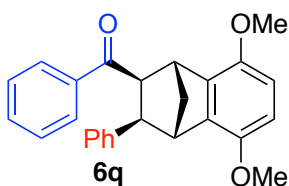
naphthalen-2-yl(3-phenylbicyclo[2.2.1]heptan-2-yl)methanone 6o: Prepared according to general procedure **C** from 1-(2-naphthoyl)piperidine-2,6-dione **1b** (26.7 mg, 0.100 mmol, 1.00 equiv), norbornene **4a** (94.2 mg, 1.00 mmol, 10.0 equiv), and sodium tetrphenylborate **5a** (68.4 mg, 0.200 mmol, 2.00 equiv) at 95°C in 16 h. The crude reaction mixture was purified by flash column chromatography (100:0→94:6 pentane:Et₂O) to give **6o** as a white solid in 80% yield (26.1 mg, 0.080 mmol). ¹H NMR (400 MHz, CDCl₃): δ 1.45-1.57 (m, 3H), 1.69-1.82 (m, 2H), 2.48 (app. s, 1H), 2.54 (dp, *J* = 10.0, 1.8 Hz, 1H), 2.76 (app. s, 1H), 3.38 (d, *J* = 10.3, 1H), 4.01 (d, *J* = 10.3, 1H), 6.80-6.88 (m, 3H), 6.94-6.98 (m, 2H), 7.47-7.56 (m, 3H), 7.64 (d, *J* = 8.7 Hz, 1H), 7.77 (d, *J* = 7.8 Hz, 1H), 7.87 (d, *J* = 7.8 Hz, 1H), 8.15 (s, 1H). ¹³C NMR (100 MHz, CDCl₃): δ 29.2, 31.3, 37.6, 39.5, 43.6, 54.2, 56.4, 124.3, 126.0, 126.5, 127.7, 127.8, 127.9,

128.0, 128.5, 129.50, 129.53, 132.4, 135.1, 136.1, 142.0, 201.8. **HRMS** (ESI): Calcd. for $C_{24}H_{23}O^+$ ($[M+H]^+$): 327.1743, Found: 327.1748.



phenyl(3-phenyl-1,2,3,4-tetrahydro-1,4-methanonaphthalen-2-yl)methanone 6p: Prepared according to general procedure **C** from *N*-benzoyl-*N*-phenylbenzamide **3a** (30.1 mg, 0.100 mmol, 1.00 equiv),

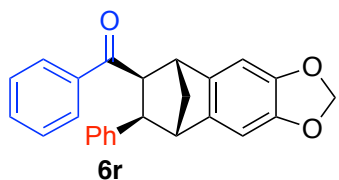
benzonorbornadiene **4b** (142.2 mg, 1.00 mmol, 10.0 equiv), and sodium tetraphenylborate **5a** (68.4 mg, 0.200 mmol, 2.00 equiv) at 95°C in 12 h. The crude reaction mixture was purified by flash column chromatography (100:0→90:10 hexanes:EtOAc) to yield **6p** as a white solid in 68% yield (22.0 mg, 0.068 mmol). **¹H NMR** (400 MHz, CDCl₃): δ 2.06-2.10 (m, 1H), 2.90 (dt, *J* = 9.6, 1.2 Hz, 1H), 3.36 (dd, 10.0, 1.2 Hz, 1H), 3.49 (m, 1H), 3.73 (m, 1H), 3.86 (dd, *J* = 10.0, 1.2 Hz, 1H), 6.96-7.01 (m, 5H), 7.16-7.23 (m, 4H), 7.27-7.32 (m, 2H), 7.36 (tt, *J* = 7.2, 1.2 Hz, 1H), 7.52 (m, 2H). **¹³C NMR** (100 MHz, CDCl₃): 46.8, 47.5, 50.8, 52.0, 52.8, 120.8, 121.4, 126.1, 126.2, 126.4, 128.0, 128.1, 128.2, 128.7, 132.4, 138.4, 140.7, 148.6, 150.6, 202.6. **HRMS** (ESI): Calcd. for $C_{24}H_{21}O^+$ ($[M+H]^+$): 325.1587, Found: 325.1592.



5,8-dimethoxy-3-phenyl-1,2,3,4-tetrahydro-1,4-methanonaphthalen-2-yl(phenyl)methanone 6q: Prepared according to general procedure **D** from *N*-benzoyl-*N*-phenylbenzamide **3a** (30.1 mg, 0.100 mmol, 1.00 equiv), 5,8-dimethoxy-1,4-dihydro-1,4-

methanonaphthalene **4c** (80.9 mg, 0.400 mmol, 4.0 equiv), and sodium tetraphenylborate **5a** (68.4 mg, 0.200 mmol, 2.00 equiv) at 95°C in 12 h. The crude reaction mixture was purified by flash column chromatography (100:0→90:10 hexanes:EtOAc) to yield **6q** as a white solid in 40% yield (15.4 mg, 0.040 mmol). **¹H NMR** (600 MHz, CDCl₃): δ 2.01 (dt, *J* = 9.6, 1.8 Hz, 1H), 2.84 (dt, 9.6, 1.8 Hz, 1H), 3.34 (dd, *J* = 10.0, 1.2 Hz, 1H), 3.71 (d, *J* = 1.2 Hz, 1H), 3.78

(s, 3H), 3.81 (s, 3H), 3.84 (dd, $J = 10.0, 1.2$ Hz, 1H), 3.93 (d, 1.2 Hz, 1H), 6.67 (s, 2H), 6.94-7.00 (m, 5H), 7.19-7.21 (m, 2H), 7.34 (tt, $J = 7.2, 1.2$ Hz, 1H), 7.53 (dd, $J = 8.4, 1.2$ Hz, 2H). ^{13}C NMR (150 MHz, CDCl_3): 43.4, 47.0, 47.2, 51.5, 52.1, 56.18, 56.20, 109.7, 109.9, 126.3, 127.9, 128.1, 128.2, 128.8, 132.3, 137.6, 138.5, 139.7, 140.8, 147.7, 148.2, 202.6. **HRMS** (ESI): Calcd. for $\text{C}_{26}\text{H}_{25}\text{O}_3^+$ ($[\text{M}+\text{H}]^+$): 385.1798, Found: 385.1799.

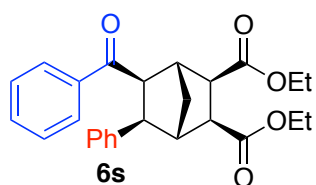


phenyl(7-phenyl-5,6,7,8-tetrahydro-5,8-

methanonaphtho[2,3-*d*][1,3]dioxol-6-yl)methanone 6r:

Prepared according to general procedure **C** from *N*-benzoyl-*N*-phenylbenzamide **3a** (30.1 mg, 0.100 mmol, 1.00 equiv), 5,8-dihydro-5,8-methanonaphtho[2,3-*d*][1,3]dioxole **4d** (186.2 mg, 1.00 mmol, 10.0 equiv), and sodium tetraphenylborate **5a** (68.4 mg, 0.200 mmol, 2.00 equiv) at 95°C in 12 h. The crude reaction mixture was purified by flash column chromatography (100:0→90:10 hexanes:EtOAc) to yield **6r** as a white solid in 48% yield (17.7 mg, 0.048 mmol). *Or* prepared according to general procedure **D** from *N*-benzoyl-*N*-phenylbenzamide **3a** (30.1 mg, 0.100 mmol, 1.00 equiv), 5,8-dihydro-5,8-methanonaphtho[2,3-*d*][1,3]dioxole **4d** (74.5 mg, 0.400 mmol, 4.00 equiv), and sodium tetraphenylborate **5a** (68.4 mg, 0.200 mmol, 2.00 equiv) at 95°C in 12 h. The crude reaction mixture was purified by flash column chromatography (100:0 hexanes:EtOAc) to (90:10 hexanes:EtOAc) to yield **6r** as a white solid in 51% yield (18.8 mg, 0.051 mmol). ^1H NMR (400 MHz, CDCl_3): δ 2.03-2.07 (m, 1H), 2.85 (dt, $J = 9.6, 1.6$ Hz, 1H), 3.30 (d, $J = 9.6, 1.2$ Hz, 1H), 3.39 (m, 1H), 3.63 (m, 1H), 3.80 (dd, $J = 10.0, 1.2$ Hz, 1H), 5.93 (d, $J = 1.2$ Hz, 1H), 5.95 (d, $J = 1.2$ Hz, 1H), 6.81 (s, 1H), 6.83 (s, 1H), 6.95-6.99 (m, 5H), 7.21 (t, $J = 7.6$ Hz, 2H), 7.36 (tt, $J = 7.6, 1.2$ Hz, 1H), 7.52 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3): 29.9, 46.9, 47.7, 50.9, 52.4, 53.2, 100.8, 103.2, 103.7, 126.4, 128.0, 128.10, 128.14, 128.6, 132.4, 138.4,

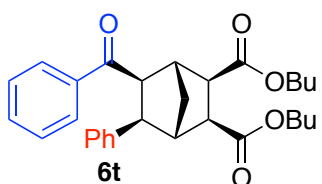
140.7, 141.9, 144.0, 145.7, 202.7. **HRMS** (ESI): Calcd. for $C_{25}H_{21}O_3^+$ ($[M+H]^+$): 369.1485, Found: 369.1481.



diethyl-5-benzoyl-6-phenylbicyclo[2.2.1]heptane-2,3-dicarboxylate 6w: Prepared according to general procedure **D** from *N*-benzoyl-*N*-phenylbenzamide **3a** (30.1 mg, 0.100 mmol,

1.00 equiv), diethyl-(*exo,exo*)-5-nobornene-2,3-dicarboxylate **4e** (117.8 mg, 0.400 mmol, 4.00 equiv), and sodium tetraphenylborate **5a** (68.4 mg, 0.200 mmol, 2.00 equiv) at 95°C in 12 h.

The crude reaction mixture was purified by flash column chromatography (90:10→70:30 hexanes:EtOAc) to yield **6s** as a white solid in 57% yield (24.0 mg, 0.057 mmol). **¹H NMR** (400 MHz, $CDCl_3$): 1.22-1.29 (m, 6H), 2.38 (dt, $J = 11.2$, 1.2 Hz, 1H), 2.52 (dt, $J = 11.2$, 1.2 Hz, 1H), 2.76-2.80 (m, 1H), 2.97 (qd, $J = 10.0$, 1.6 Hz, 2 H), 3.03-3.06 (m, 1H), 3.30 (dd, $J = 10.0$, 0.8 Hz, 1H), 3.85 (dd, $J = 10.0$, 0.8 Hz, 1H), 4.07-4.17 (m, 4H), 6.89-6.96 (m, 5H), 7.22 (t, 7.6 Hz, 2H), 7.35 (tt, $J = 7.6$, 1.2 Hz, 1H), 7.51 (m, 2H). **¹³C NMR** (100 MHz, $CDCl_3$): 14.29, 14.31, 35.5, 43.0, 46.8, 50.6, 52.5, 53.2, 55.1, 60.8, 60.9, 126.5, 128.0, 128.1, 128.2, 128.5, 132.5, 138.2, 140.3, 172.5, 172.7, 200.5. **HRMS** (ESI): Calcd. for $C_{26}H_{29}O_5^+$ ($[M+H]^+$): 421.2010, Found: 421.2011.

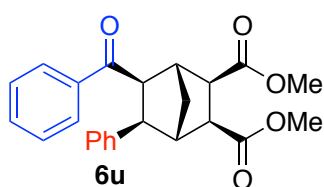


dibutyl-5-benzoyl-6-phenylbicyclo[2.2.1]heptane-2,3-dicarboxylate 6t: Prepared according to general procedure **D** from *N*-benzoyl-*N*-phenylbenzamide **3a** (30.1 mg, 0.100 mmol, 1.00

equiv), dibutyl-(*exo,exo*)-5-nobornene-2,3-dicarboxylate **4f** (117.8 mg, 0.400 mmol, 4.00 equiv), and sodium tetraphenylborate **5a** (68.4 mg, 0.200 mmol, 2.00 equiv) at 95°C in 12 h.

The crude reaction mixture was purified by flash column chromatography (90:10→70:30 hexanes:EtOAc) to yield **6t** as a white solid in 68% yield (32.4 mg, 0.068 mmol). **¹H NMR**

(400 MHz, CDCl₃): 0.90-0.96 (m, 6H), 1.32-1.44 (m, 4H), 1.55-1.65 (m, 4H), 2.37 (dt, $J = 11.2, 1.6$ Hz, 1H), 2.52 (dt, $J = 11.2, 1.5$ Hz, 1H), 2.78 (m, 1H), 2.93-3.01 (m, 2H), 3.03 (m, 1H), 3.31 (d, $J = 10.0$ Hz, 1H), 3.85 (d, $J = 10.0$ Hz, 1H), 3.96-4.12 (m, 4H), 6.90-6.95 (m, 5H), 7.21 (t, $J = 7.6$ Hz, 2H), 7.36 (tt, $J = 7.6, 1.2$ Hz, 1H), 7.52 (m, 2H). ¹³C NMR (100 MHz, CDCl₃): 13.9, 19.3, 19.4, 30.8, 35.4, 43.0, 46.8, 50.7, 52.6, 53.2, 53.3, 55.1, 55.2, 64.8, 64.9, 126.5, 128.0, 128.1, 128.2, 128.5, 132.5, 138.2, 140.3, 172.6, 172.7, 200.5. HRMS (ESI): Calcd. for C₃₀H₃₇O₅⁺ ([M+H]⁺): 477.2636, Found: 477.2633.

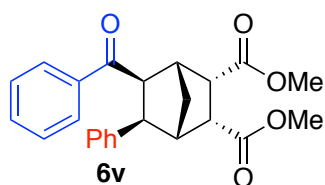


methyl-5-benzoyl-6-phenylbicyclo[2.2.1]heptane-2,3-

dicarboxylate 6u: Prepared according to general procedure C from *N*-benzoyl-*N*-phenylbenzamide **3a** (30.1 mg, 0.100 mmol, 1.00 equiv), dimethyl-(*exo,exo*)-5-nobornene-2,3-dicarboxylate **4g** (210.2 mg, 1.00 mmol, 10.0 equiv), and sodium tetraphenylborate **5a** (68.4 mg, 0.200 mmol, 2.00 equiv) at 95°C in 8 h.

The crude reaction mixture was purified by flash column chromatography (90:10→70:30 hexanes:EtOAc) to yield **6u** as a white solid in 75% yield (29.4 mg, 0.075 mmol). Or Prepared according to general procedure D from *N*-benzoyl-*N*-phenylbenzamide **3a** (30.1 mg, 0.100 mmol, 1.00 equiv), dimethyl-(*exo,exo*)-5-nobornene-2,3-dicarboxylate **4g** (84.1 mg, 0.400 mmol, 4.00 equiv), and sodium tetraphenylborate **5a** (68.4 mg, 0.200 mmol, 2.00 equiv). The crude reaction mixture was purified by flash column chromatography (90:10 hexanes:EtOAc) to (70:30 hexanes:EtOAc) to yield **6u** as a white solid in 60% yield (23.5 mg, 0.060 mmol). ¹H NMR (400 MHz, CDCl₃): 2.35 (dt, $J = 11.2, 1.6$ Hz, 1H), 2.53 (dd, $J = 11.2, 1.6$ Hz, 1H), 2.77-2.78 (m, 1H), 2.95-3.05 (m, 2H), 3.05 (m, 1H), 3.31 (d, $J = 10.4$ Hz, 1H), 3.65 (s, 3H), 3.68 (s, 3H), 3.85 (d, $J = 10.4$ Hz, 1H), 6.90-6.95 (m, 5H), 7.22 (t, $J = 7.6$ Hz, 2H), 7.36 (tt, $J = 7.6, 1.2$ Hz, 1H), 7.51-7.52 (m, 2H). ¹³C NMR (100 MHz, CDCl₃): 33.5, 42.9, 46.8, 50.4,

52.0, 52.1, 52.4, 53.1, 55.0, 126.5, 128.0, 128.1, 128.2, 128.4, 132.5, 138.1, 140.2, 172.9, 173.1, 200.4. **HRMS** (ESI): Calcd. for $C_{24}H_{25}O_5^+$ ($[M+H]^+$): 393.1697, Found: 393.1698.



methyl-5-benzoyl-6-phenylbicyclo[2.2.1]heptane-2,3-

dicarboxylate 6v: Prepared according to general procedure **C** from

N-benzoyl-*N*-phenylbenzamide **3a** (30.1 mg, 0.100 mmol, 1.00

equiv), dimethyl-(*endo,endo*)-5-nobornene-2,3-dicarboxylate **4h** (210.2 mg, 1.00 mmol, 10.0

equiv), and sodium tetraphenylborate **5a** (68.4 mg, 0.200 mmol, 2.00 equiv) at 95°C in 12 h.

The crude reaction mixture was purified by flash column chromatography (90:10→70:30

hexanes:EtOAc) to yield **6v** as a white solid in 53% yield (20.8 mg, 0.053 mmol). *Or* Prepared

according to general procedure **D** from *N*-benzoyl-*N*-phenylbenzamide **3a** (30.1 mg, 0.100

mmol, 1.00 equiv), dimethyl-(*endo,endo*)-5-nobornene-2,3-dicarboxylate **4h** (84.1 mg, 0.400

mmol, 4.00 equiv), and sodium tetraphenylborate **5a** (68.4 mg, 0.200 mmol, 2.00 equiv). The

crude reaction mixture was purified by flash column chromatography (90:10 hexanes:EtOAc)

to (70:30 hexanes:EtOAc) to yield **6v** as a white solid in 44% yield (17.2 mg, 0.044 mmol). **¹H**

NMR (400 MHz, CDCl₃): 1.67 (dt, *J* = 10.8, 1.6 Hz, 1H), 2.69 (dt, *J* = 10.8, 1.6 Hz, 1H), 2.74-

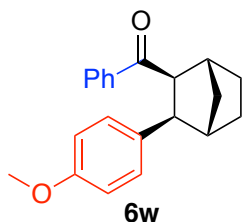
2.75 (m, 1H), 3.19-3.20 (m, 2H), 3.71 (s, 3H), 3.72 (s, 3H), 3.94 (dd, *J* = 10.4, 1.6 Hz, 1H),

4.63 (dd, *J* = 10.4, 1.6 Hz, 1H), 6.93-6.96 (m, 5H), 7.22 (t, *J* = 7.6 Hz, 2H), 7.35 (tt, *J* = 7.6,

1.2 Hz, 1H), 7.58-7.60 (m, 2H). **¹³C NMR** (100 MHz, CDCl₃): 38.8, 42.9, 46.2, 46.9, 47.0,

48.3, 49.3, 51.82, 51.84, 126.3, 128.0, 128.1, 128.4, 128.7, 132.4, 138.4, 141.0, 172.7, 173.2,

201.6. **HRMS** (ESI): Calcd. for $C_{24}H_{25}O_5^+$ ($[M+H]^+$): 393.1697, Found: 393.1700.

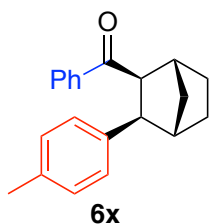


(3-(4-methoxyphenyl)bicyclo[2.2.1]heptan-2-

yl)(phenyl)methanone 6w: Prepared according to general procedure **D**

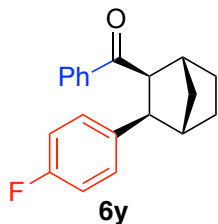
from *N*-benzoyl-*N*-phenylbenzamide **3a** (30.1 mg, 0.100 mmol, 1.00

equiv), norbornene **4a** (94.2 mg, 1.00 mmol, 10.0 equiv), and sodium tetrakis(4-methoxyphenyl)borate **5b** (92.4 mg, 0.200 mmol, 2.00 equiv) at 80°C in 8 h. The crude reaction mixture was purified by flash column chromatography (100:0→92:8 pentane:Et₂O) to give **6w** as a white solid in 34% yield (10.1 mg, 0.034 mmol). ¹H NMR (400 MHz, CDCl₃): δ 1.33-1.51 (m, 3H), 1.65-1.76 (m, 2H), 2.38 (app. s, 1H), 2.45 (dp, *J* = 10.2, 1.8 Hz, 1H), 2.69 (d, *J* = 1.3 Hz, 1H), 3.26 (d, *J* = 10.2 Hz, 1H), 3.63 (s, 3H), 3.81 (dd, *J* = 10.2, 1.3 Hz, 1H), 6.47 (ddd, *J* = 8.8, 3.1, 2.1 Hz, 2H), 6.87(ddd, *J* = 8.8, 3.1, 2.1 Hz, 2H), 7.21-5.25 (m, 2H), 7.35 (tt, *J* = 7.4, 1.3 Hz, 1H), 7.55-7.58 (m, 2H). ¹³C NMR (100 MHz, CDCl₃): δ 29.1, 31.2, 37.5, 39.2, 43.9, 53.2, 55.2, 56.4, 113.1, 128.0, 128.1, 129.5, 132.1, 134.1, 138.7, 157.6, 202.1. HRMS (ESI): Calcd. for C₂₁H₂₃O₂⁺ ([M+H]⁺): 307.1693, Found: 307.1693.



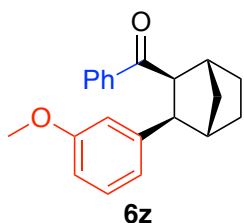
phenyl(3-(*p*-tolyl)bicyclo[2.2.1]heptan-2-yl)methanone 6x: Prepared according to general procedure C from *N*-benzoyl-*N*-phenylbenzamide **3a** (30.1 mg, 0.100 mmol, 1.00 equiv), norbornene **4a** (94.2 mg, 1.00 mmol, 10.0 equiv), and sodium tetra-*p*-tolylborate **5c** (79.6 mg, 0.200 mmol, 2.00

equiv) at 80°C in 8 h. The crude reaction mixture was purified by flash column chromatography (100:0→96:4 hexanes:EtOAc) to yield **6x** as a white solid in 69% yield (20.0 mg, 0.069 mmol). ¹H NMR (400 MHz, CDCl₃): δ 1.38-1.73 (m, 5H), 2.12 (s, 3H), 2.41 (m, 1H), 2.44-2.49 (m, 1H), 2.68 (m, 1H), 3.27 (d, *J* = 10.4 Hz, 1H), 3.82 (d, *J* = 10.4 Hz, 1H), 6.74 (d, *J* = 8.0 Hz, 2H), 6.85 (d, *J* = 8.0 Hz, 2H), 7.23 (t, *J* = 7.6, 2H), 7.35 (tt, *J* = 7.6, 1.2, 1H), 7.56 (m, 2H). ¹³C NMR (100 MHz, CDCl₃): 20.9, 29.2, 31.2, 37.5, 39.4, 43.7, 53.7, 56.4, 128.0, 128.1, 128.3, 128.4, 132.1, 135.3, 138.7, 138.9, 202.0. HRMS (ESI): Calcd. for C₂₁H₂₃O⁺ ([M+H]⁺): 291.1743, Found: 291.1745.



(3-(4-fluorophenyl)bicyclo[2.2.1]heptan-2-yl)(phenyl)methanone 6y:

Prepared according to general procedure C from *N*-benzoyl-*N*-phenylbenzamide **3a** (30.1 mg, 0.100 mmol, 1.00 equiv), norbornene **4a** (94.2 mg, 1.00 mmol, 10.0 equiv), and sodium tetrakis(4-fluorophenyl)borate **5d** (94.5 mg, 0.200 mmol, 2.00 equiv) at 80°C in 8 h. The crude reaction mixture was purified by flash column chromatography (100:0→95:5 hexane:EtOAc) to give **6y** as a white solid in 55% yield (16.2 mg, 0.055 mmol). ¹H NMR (400 MHz, CDCl₃): δ 1.35-1.52 (m, 3H), 1.65-1.77 (m, 2H), 2.39 (app. s, 1H), 2.43 (d, *J* = 10.3 Hz, 1H), 2.70 (app. s, 1H), 3.27 (d, *J* = 10.1 Hz, 1H), 3.84 (d, *J* = 10.1 Hz, 1H), 6.61 (t, *J* = 8.6 Hz, 2H), 6.90 (dd, *J* = 8.6, 5.7 Hz, 2H), 7.24 (t, *J* = 7.8 Hz, 2H), 7.37 (t, *J* = 7.8 Hz, 1H), 7.55 (d, *J* = 7.8 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃): δ 29.0, 31.3, 37.4, 39.3, 43.7, 53.2, 56.2, 114.5 (d, *J* = 20.9 Hz, 2C), 128.06, 128.14, 129.9 (d, *J* = 7.74 Hz, 2C), 132.3, 137.6 (d, *J* = 3.2 Hz, 1C), 138.5, 161.1 (d, *J* = 243.1 Hz, 1C), 201.8. ¹⁹F NMR (376 MHz, CDCl₃): δ -117.44 (m, 1F). HRMS (ESI): Calcd. for C₂₀H₁₉FO⁺ ([M+H]⁺): 295.1493, Found: 295.1494.

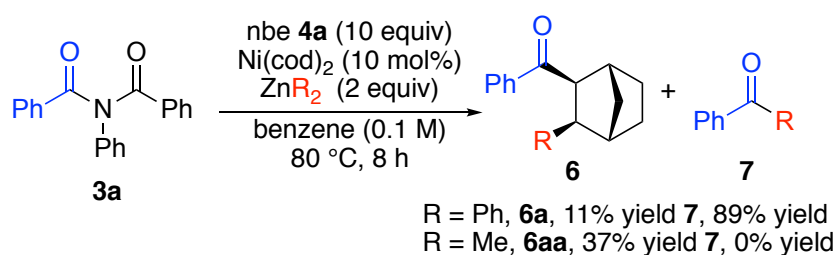


(3-(3-methoxyphenyl)bicyclo[2.2.1]heptan-2-yl)(phenyl)methanone 6z:

Prepared according to general procedure E from *N*-benzoyl-*N*-phenylbenzamide **3a** (30.1 mg, 0.100 mmol, 1.00 equiv), norbornene **4a** (94.2 mg, 1.00 mmol, 10.0 equiv), and sodium tetrakis(3-methoxyphenyl)borate **5e** (92.4 mg, 0.200 mmol, 2.00 equiv) at 80°C in 8 h. The crude reaction mixture was purified by flash column chromatography (100:0→92:8 pentane:Et₂O) to give **6z** as a colorless oil in 42% yield (12.9 mg, 0.042 mmol). ¹H NMR (400 MHz, CDCl₃): δ 1.34-1.52 (m, 3H), 1.67-1.77 (m, 2H), 2.43-2.47 (m, 2H), 2.70 (d, *J* = 1.2 Hz, 1H), 3.27 (d, *J* = 10.1 Hz, 1H), 3.52 (s, 3H), 3.84 (dd, *J* = 10.1, 1.2 Hz, 1H), 6.45-6.47 (m, 2H), 6.59 (d, *J* = 7.7 Hz,

1H), 6.85-6.89 (m, 1H), 7.24 (t, $J = 7.4$ Hz, 2H), 7.36 (tt, $J = 7.4, 1.2$ Hz, 1H), 7.56-7.58 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ 29.07, 31.2, 37.6, 39.3, 43.5, 54.0, 55.0, 56.2, 111.8, 114.3, 120.8, 128.0, 128.1, 128.8, 132.1, 138.8, 143.5, 158.9, 201.8. HRMS (ESI): Calcd. for $\text{C}_{21}\text{H}_{23}\text{O}_2^+$ ($[\text{M}+\text{H}]^+$): 307.1693, Found: 307.1696.

General Procedure F for Synthesis of Carboacylation Products **6a** and **6aa** Using Organozinc Nucleophiles



An oven dried 1-dram vial was charged with amide **3a** (30.1 mg, 0.100 mmol), $\text{Ni}(\text{cod})_2$ (2.80 mg, 0.010 mmol), ZnR_2 (0.200 mmol), norbornene **4a** (94.2 mg, 1.00 mmol), and benzene (1.0 mL, 0.1 M). The resulting solution was stirred at 80 °C for 8 h. Upon completion of the reaction, the reaction was cooled to room temperature and was filtered through a short plug of silica gel eluting with 50:50 hexanes:EtOAc and concentrated under reduced pressure. ^1H NMR yields were determined for the correspond crude reaction mixtures using dibromomethane as an internal standard.

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CHAPTER 4. PALLADIUM-CATALYZED, INTERMOLECULAR ACYLATIVE HECK REACTION USING AMIDES AS ACYL ELECTROPHILES

Chapter would be modified for publication

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Abstract

This chapter outlines the detailed discussion on the development of palladium-catalyzed, intermolecular acylative Heck reactions of amides. The developed palladium-catalyst system allows for Heck reaction between a wide array of *N*-benzoylglutarimides bearing electron-donating, halogenated, and electro-withdrawing substituents and a bicyclic alkene, norbornene, to generate α,β -unsaturated ketones in moderate to high yields (25-82%).

Introduction

Heck (or Heck-Mizoroki) reaction, discovered simultaneously by Heck and Mizoroki, is a powerful technique to rapidly construct C–C bonds.¹ The Heck reaction has been implemented to construct C–C bonds in the synthesis of a wide array of biologically active compounds such as Taxol,² (-)-Eptazocine,³ DG-041,⁴ CP-724,714,⁵ and Chantix® (Figure 1).⁶ In the late 1960s, Richard Heck discovered a protocol to synthesize functionalized olefins using arylmercuric compounds and either stoichiometric or catalytic amounts of palladium salts.⁷ Later on, independent and pioneering work from Heck⁸⁻¹¹ and Mizoroki¹² laboratories revealed the use of less toxic, commercially available, and more stable arylhalides as an arylating agent in the Heck-Mizoroki reaction. For his contribution in developing palladium-catalyzed cross-coupling reactions, Heck received the Nobel Prize in Chemistry in 2010 along

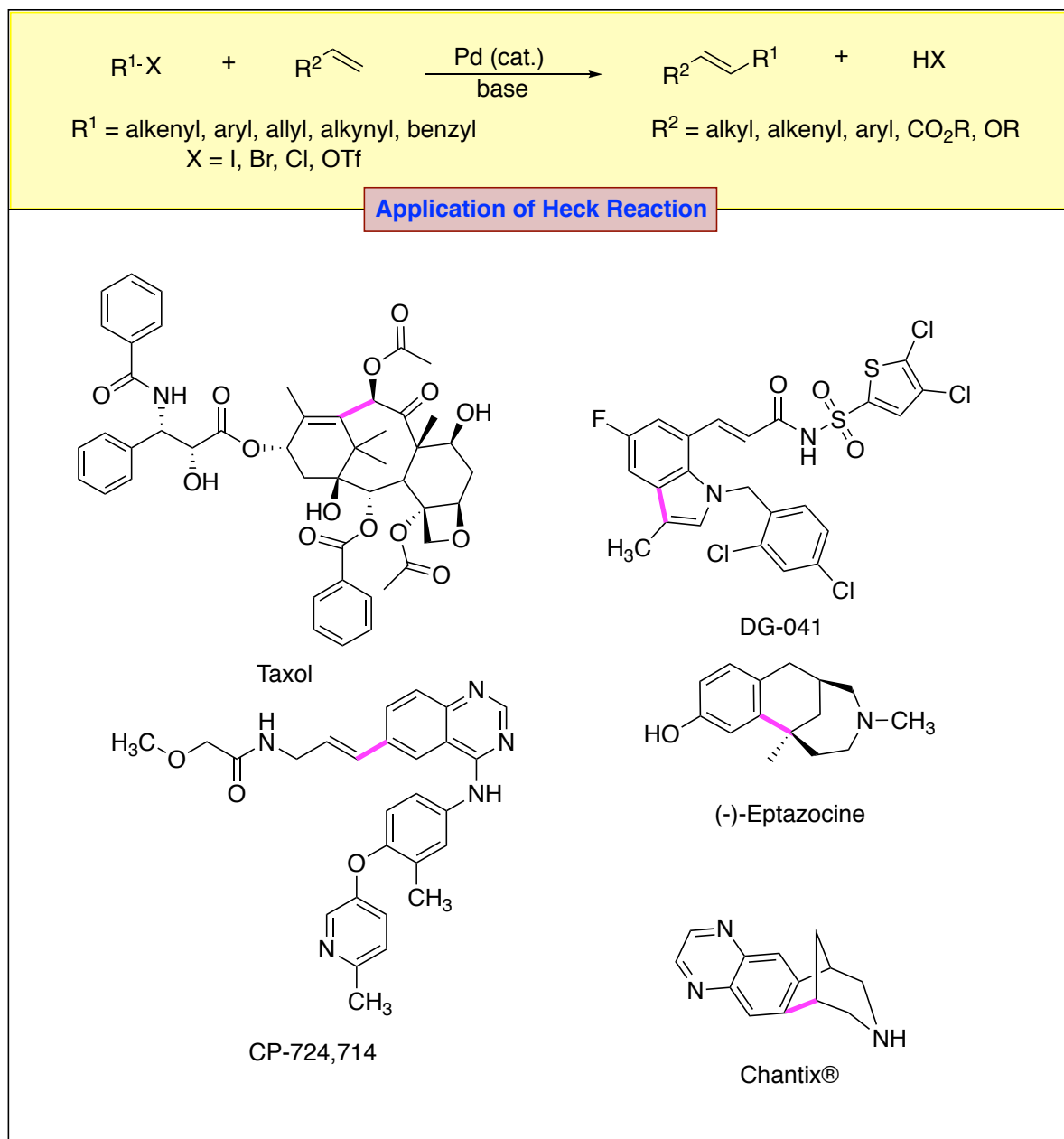
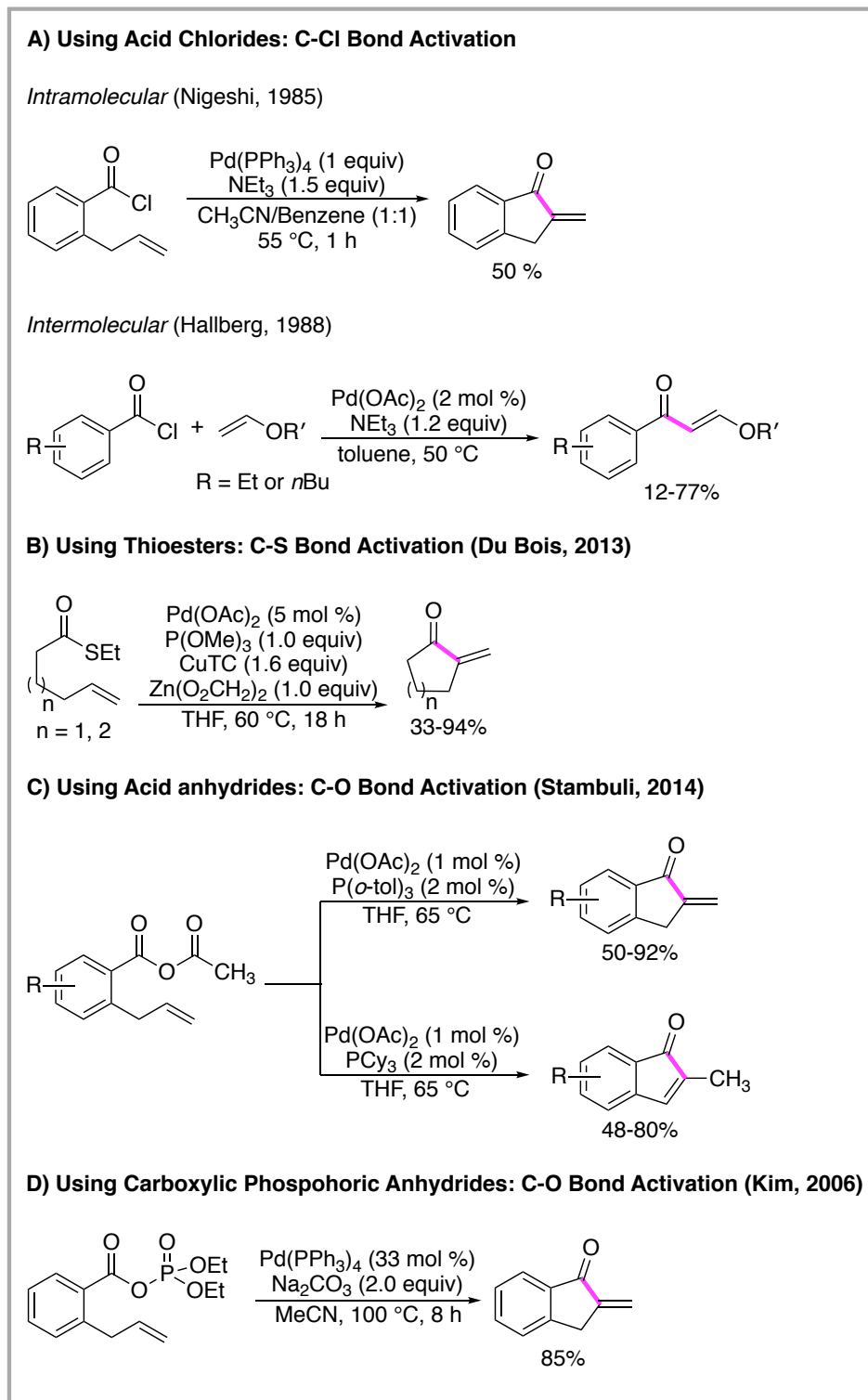


Figure 1. Heck-Mizoroki Reaction and its application in synthesis of biologically active compounds

with Japanese chemists Akira Suzuki and Ei-chi Negishi. Over the years, the chemistry scientific community has witnessed a continuous development of the Heck reaction using various aryl electrophiles and improved palladium catalyst systems including design of new ligands.¹

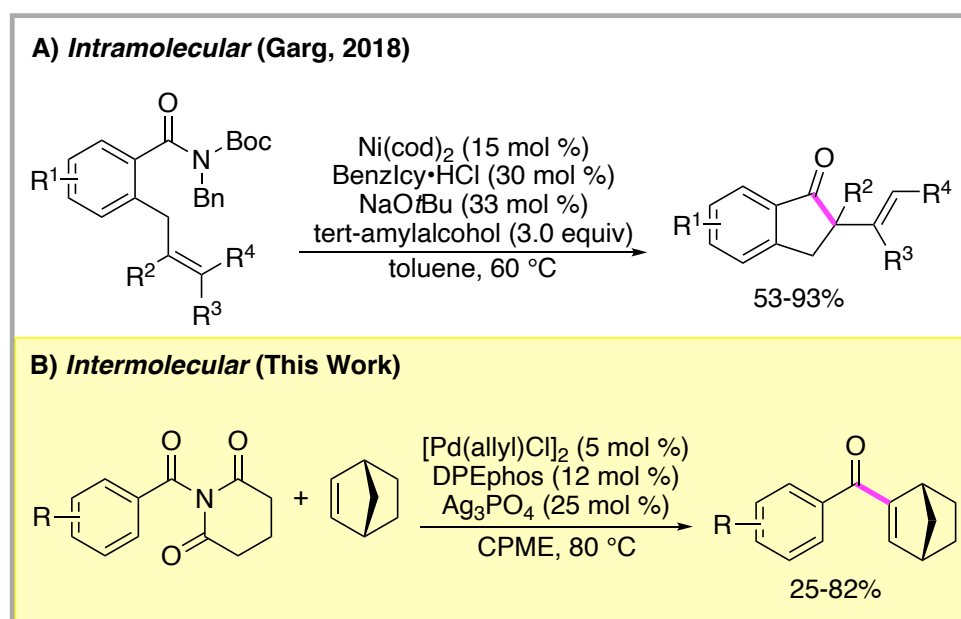
In 1974, in a series of scientific reports, Heck and co-workers revealed protocols for carbonylative Heck reaction.⁸⁻¹¹ These reports described palladium-catalyzed carboalkoxylation, amidation, and formylation of aryl, vinyl, and heteroaryl halides using carbon monoxides to access esters, amides, and aldehydes. However, these reactions needed to use toxic carbon monoxide as a C1 building block to introduce a carbonyl group. In 1985, Negishi and coworkers discovered intermolecular acylative Heck reaction of *o*-allylbenzoyl chloride using stoichiometric amounts of palladium to form 2-methylene-2,3-dihydro-inden-1-one in 50% yield (Scheme 2A).¹³ This reaction was the first example of acylative Heck reaction using carboxylic acid derivative as an acyl electrophile. The development of acylative Heck reaction using carboxylic acid derivatives gives an alternative to carbonylative Heck reaction using toxic carbon monoxide.

Following the discovery of acylative Heck reaction by Negishi in 1985, various research groups developed intra- and intermolecular acylative Heck reactions using carboxylic acid derivatives such as acid chlorides,¹⁴ thioesters,¹⁵ acid anhydrides,¹⁶ and carboxylic phosphoric anhydrides¹⁷ via activation of C-Cl, C-S and C-O bonds (Scheme 2). In a 1988 report, Hallberg and coworkers reported Pd-catalyzed Heck reaction between aryl chlorides and vinyl ethers to form corresponding products in 12-77% yields (Scheme 2A).¹⁴ Later, in 2013, Du Bois and coworkers revealed an intramolecular Heck reaction using thioesters to form cyclic ketones with exocyclic alkenes (Scheme 2B).¹⁵ Kim¹⁷ and Stambuli¹⁶ independently reported Pd-catalyzed methods for acylative Heck reactions of other carboxylic acid derivatives, such as acid anhydrides and phosphoric anhydrides, to form cyclic ketones in good to excellent yields (Scheme 2C and 2D). Recently, Garg and coworkers reported the first



Scheme 2. Pd-catalyzed, acylative Heck reactions of carboxylic acid derivatives

examples of nickel-catalyzed, intramolecular Heck reaction of *o*-allylbenzamides via activation of amide C-N bonds (Scheme 3A).¹⁸ The Ni-catalyst generated from Ni(cod)₂ and a *N*-heterocyclic carbene ligand, BenzIcy, allows access to ketones with α -quaternary center in good to excellent yields (53-93%). However, there are no reports of transition metal-catalyzed intermolecular acylative Heck reaction using amides acyl electrophiles. This chapter discusses our efforts to develop palladium-catalyzed, intermolecular acylative Heck reaction using amides as acyl electrophiles.

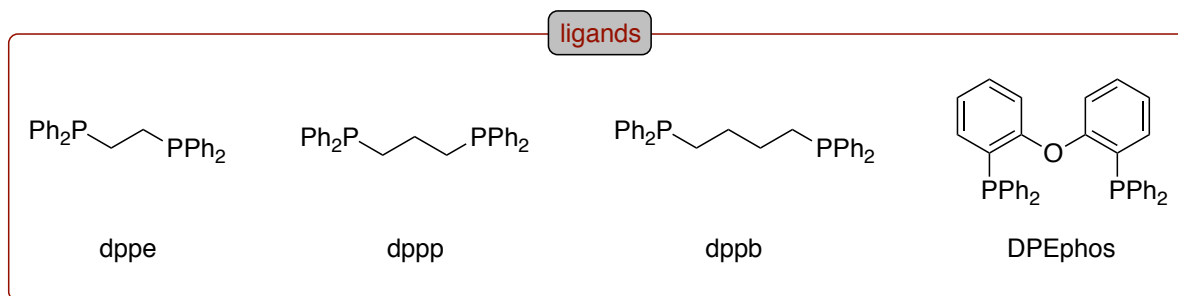
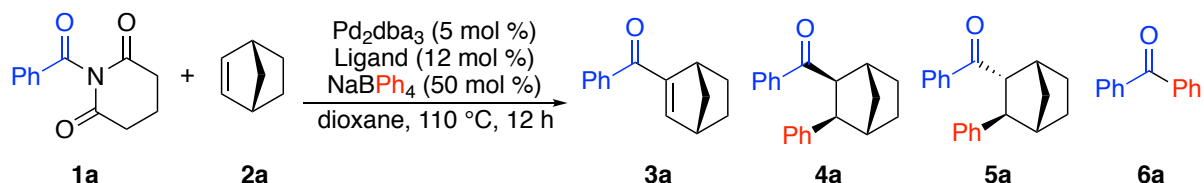


Scheme 3. TM-catalyzed, acylative Heck reactions using amides as acyl electrophiles

Results and Discussion

Ligand studies:

Table 1. Ligand studies for Pd-catalyzed acylative Heck reaction of *N*-benzoylglutarimide **1a** and norbornene **2a**



Entry	ligand	conv.	3a (%)	4a (%)	5a (%)	6a (%)
1	dppe	20	3	0	0	3
2	dppp	76	8	0	0	1
d	dppb	95	25	13	0	4
4	DPEphos	91	60	4	2	2
5 ^a	DPEphos	55	40	3	3	2
6 ^b	DPEphos	87	61	4	2	2
7 ^c	DPEphos	0	0	-	-	-
8 ^d	DPEphos	99	1	-	-	-
9 ^e	DPEphos	23	4	-	-	-

^aReaction run using 200 mol % of NaBPh₄; ^bReaction run using 25 mol % of NaBPh₄;

^cReaction run without NaBPh₄; ^dReaction run using 200 mol % of NaBF₄; ^eReaction run using

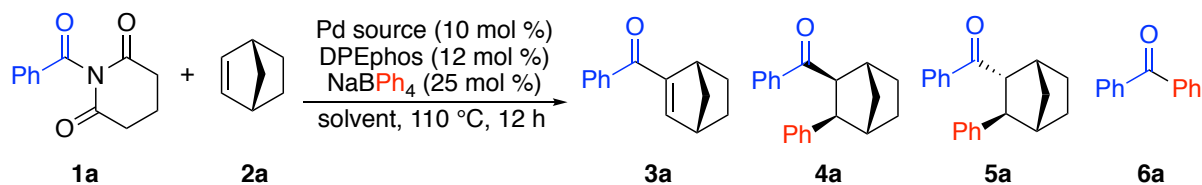
200 mol % NaBAr^F

To identify reaction conditions, we chose *N*-benzoylgularimide **1a** and norbornene **2a** as our model substrates. We investigated an array of Pd(0) complexes generated from Pd₂dba₃ and bisphosphine ligands containing various bite angles (Table 1, entries 1-4). We observed that the yield of the model reaction improved with increase in the bite angle of bisphosphine ligands. Reactions of palladium catalyst generated from Pd₂dba₃ and dppe (1,2-Bis(diphenylphosphino)-ethane, bite angle 86°) and dppp (1,3-Bis(diphenylphosphino)-propane, 91°) formed the bicyclo[2.2.1]hept-2-en-2-yl(phenyl)methanone **3a** in <10% yield with benzophenone **6a**, a product of Suzuki-Miyaura reaction, in <5% yield. The reaction conducted using a catalyst generated from Pd₂dba₃ and dppb (1,4-Bis(diphenylphosphino)-butane, bite angle 94°) formed bicyclo[2.2.1]hept-2-en-2-yl(phenyl)methanone **3a** in 25% yield (Table 1, entry 3). The reaction also formed formal carboacylation product **4a** in 13% yield and benzophenone **6a** in 4% yield. We next investigated complexes generated from Pd₂dba₃ and bisphosphine ligand containing ether backbone. When we conducted the model reaction using a catalyst generated from Pd₂dba₃ and DPEphos, the reaction formed bicyclo[2.2.1]hept-2-en-2-yl(phenyl)methanone **3a** in 60% yield with formal carboacylation products **4a** and **5a** in total 6% yield and benzophenone **6a** in 2% yield (Table 1, entry 4). We then studied the effect of the loading of sodium tetraphenylborate (NaBPh₄) on the yield of the model reaction. Increasing the loading of NaBPh₄ did not lead to improvement in the yield of the reaction (Table 1, entry 5). We also observed that lowering the loading of NaBPh₄ did not lower the yield of the model reaction (Table 1, entry 6). Control experiment showed that the reaction did not occur to form the product **3a** in the absence of NaBPh₄. We hypothesized that the NaBPh₄ was involved in generating cationic palladium intermediates. We next studied the impact of other sodium additives on the yield of the model reaction (Table 1, entries 8-9).

However, the reactions conducted in the presence of NaBF₄ and non-coordinating NaBAR^F formed the product **3a** in <5% yield.

Impact of palladium precursors and solvents:

Table 2. Impact of palladium precursors and solvents on Pd-catalyzed acylative Heck reaction of *N*-benzoylglutarimide **1a** and norbornene **2a**



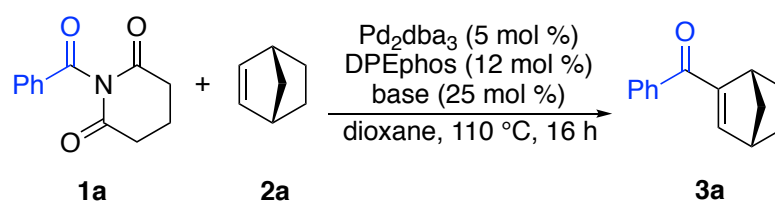
Entry	Pd source	(mol %)	solvent	conv.	3a (%)	4a (%)	5a (%)	6a (%)
1	Pd ₂ dba ₃	5	dioxane	87	61	2	4	2
2	[Pd(allyl)Cl] ₂	5	dioxane	69	48	0	2	3
3	[Pd(cinnamyl)Cl] ₂	5	dioxane	96	49	1	0	6
4	Pd ₂ dba ₃	5	CPME	74	61	2	7	3
5	Pd ₂ dba ₃	5	THF	86	66	1	3	1
6	Pd ₂ dba ₃	5	benzene	96	69	1	1	5

We next studied the impact of palladium precursors on the yield of the model reaction (Table 2, entries 1-3). When conducted using [Pd(allyl)Cl]₂ and [Pd(cinnamyl)Cl]₂, instead of Pd₂dba₃ as palladium precursors, the model reaction formed bicyclo[2.2.1]hept-2-en-2-yl(phenyl)methanone **3a** in 48 and 49% yields (Table 2, entries 2-3). The reactions also formed byproducts **4a**, **5a**, and **6a** in <10% yields. These results suggest that the active catalyst can be accessed by using other Pd(II) precursors. We then studied the impact of solvent on the model reaction. When we conducted the model reaction in other ethereal solvents such as

cyclopentylmethyl ether (CPME) and tetrahydrofuran (THF), the reaction formed the product **3a** in 61-66% yields (Table 2, entries 4-5). The yield of the reaction increased slightly (69% yield) when the reaction was conducted in benzene (Table 2, entry 6).

Impact of base:

Table 3. Impact of base on Pd-catalyzed acylative Heck reaction of *N*-benzoylglutarimide **1a** and norbornene **2a**



Entry	base	conv. (%)	3a (%)
1	none	0	0
2	LiO ^t Bu	72	0
3	K ₃ PO ₄	81	0
4	Ag ₂ CO ₃	56	17
5	K ₂ CO ₃	1	1
6	Cs ₂ CO ₃	0	0
7	NaOH	10	0
8	CsF	26	0
9	Et ₃ N	0	0
10	ⁱ Pr ₂ EtN	0	0
11 ^a	Ag ₂ CO ₃	99	47
12 ^b	Ag ₂ CO ₃	99	49
13 ^b	Ag ₃ PO ₄	93	55

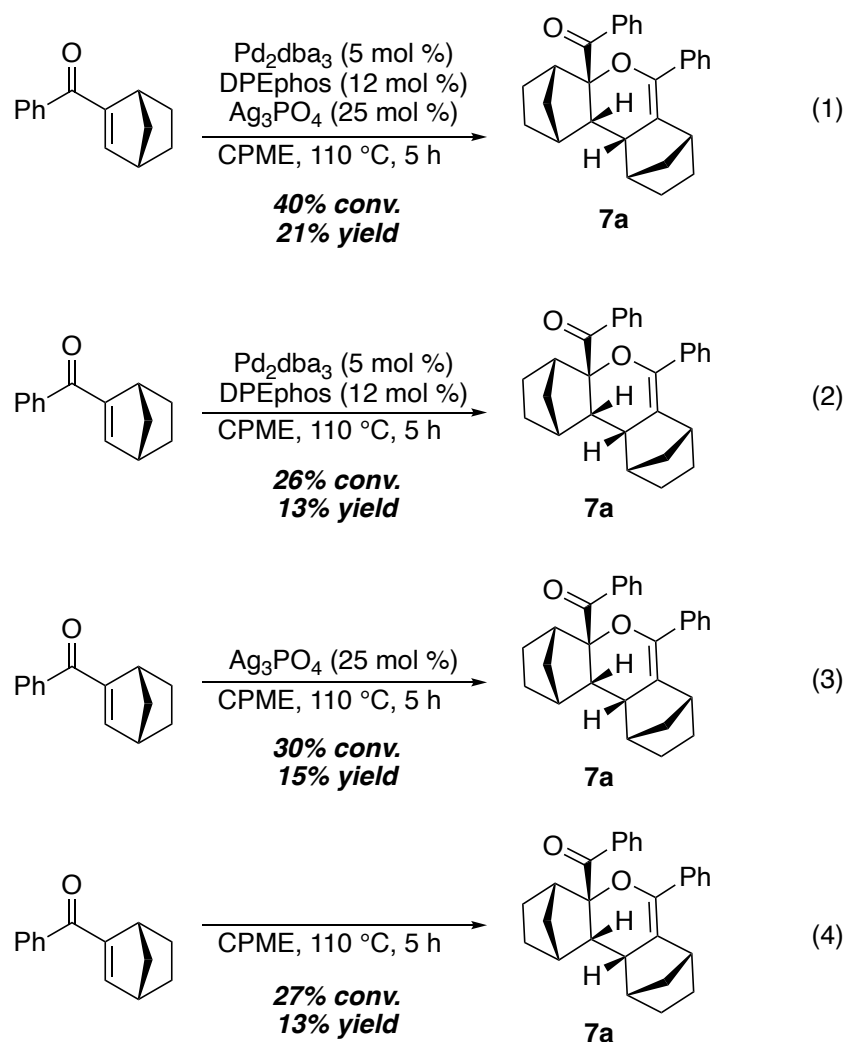
^aReaction run using benzene as solvent; ^bReaction run using CPME as solvent.

We hypothesized that besides serving as a non-coordinating counter ion, NaBPh₄ could also be involved in either β -hydride elimination after migratory insertion and/or in generating active catalyst back from palladium hydride intermediate after product formation. We recognized by eliminating NaBPh₄, we would also eliminate other byproducts, such as formal carboacylation and Suzuki-Miyaura byproducts, that resulted from using NaBPh₄. Based on this hypothesis, we sought to investigate the impact of bases on the model reaction. We examined the impact of a wide range of bases including inorganic and organic bases (Table 3, entries 2-10). The model reaction formed the product **3a** in 17% and 1% yield, when the reaction was conducted in the presence of Ag₂CO₃ and K₂CO₃ (Table 3, entries 4-5). The reaction did not form the product **3a** when other bases were used. We also observed formation of a byproduct in 6% yield generated from [4+2] cycloaddition reaction between two molecules of product **3a**. When the reaction was run conducted benzene and CPME, the model reaction formed the product **3a** in 47% and 49% yields with cycloaddition byproduct in 9% and 10% yields (Table 3, entries 11-12). The yield of the reaction improved to 55%, when the reaction was conducted using Ag₃PO₄ in CPME (Table 3, entries 13). The reaction also formed the cycloaddition byproduct in 12% yield.

Investigation of the byproduct:

In order to investigate the formation of the cycloaddition byproduct, we conducted various control experiments (Scheme 4). We exposed the Heck reaction product **3a** to the reaction conditions. When we reacted the product **3a** in the presence of palladium catalyst and silver phosphate, the reaction formed the cycloaddition product **7a** in 21% yield by consuming 40% of the enone **3a**. (Note: The relative stereochemistry of the cycloaddition product **7a** is temporarily assigned using molecular model kit. The relative stereochemistry will be

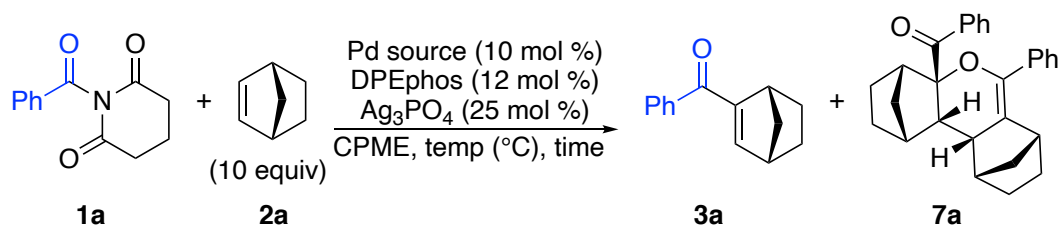
determined using spectrochemical analysis and/or by single-crystal X-ray diffraction) We also observed that when the enone was exposed to the reaction conditions in the absence of palladium catalyst and silver phosphate separately, the reactions formed the cycloaddition product **7a** in 13-15% yield (Scheme 4, eq 2 and 3). However, when the product **3a** was heated at 110 °C in CPME in the absence of palladium catalyst and silver phosphate, the reaction generated the product **7a** in 13% yield in 5 h (Scheme 4, eq 4). These results suggest that the enone product **3a** undergoes thermal [4+2] cycloaddition reaction to form **7a**.



Scheme 4. Control experiments to investigate the formation of Diels Alder product **7a**

Impact of palladium precursors and temperature:

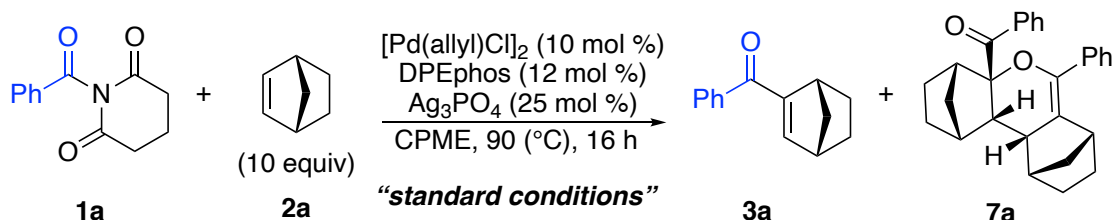
Table 4. Impact of palladium precursors and temperature on Pd-catalyzed acylative Heck reaction of *N*-benzoylglutarimide **1a** and norbornene **2a**



Entry	Pd source	time (h)	temp (°C)	conv. (%)	3a (%)	7a (%)
1	Pd ₂ dba ₃	3	110	3	1	0
2	Pd ₂ dba ₃	6	110	15	7	1
3	Pd ₂ dba ₃	12	110	93	55	12
4	Pd(OAc) ₂	5	110	96	55	9
5	[Pd(cinnamyl)Cl] ₂	5	110	49	48	1
6	[Pd(allyl)Cl] ₂	5	110	44	40	0
7	Pd(OAc) ₂	12	110	99	46	14
8	[Pd(cinnamyl)Cl] ₂	12	110	99	59	14
9	[Pd(allyl)Cl] ₂	12	110	99	65	18
11	[Pd(allyl)Cl] ₂	12	90	83	75	4
13	[Pd(allyl)Cl] ₂	16	90	99	84	5

We next sought to investigate the impact of palladium precursor, temperature, and time on the model reaction. These results are summarized in Table 4. We observed that when the model reaction was conducted using Pd₂dba₃ as Pd(0) source, the reaction goes through an induction period (Table 4, entries 1-3). After 6 h, the model reaction formed the enone product **3a** in 7% yield and the byproduct **7a** in 1% yield (Table 4, entry 2). The model reaction, when

conducted using Pd₂dba₃, formed the enone **3a** in 55% yield and the byproduct **7a** in 12% yield after 12 h (Table 4, entry 3). However, when Pd(II) precursors were used in the reaction, the rate of the reaction improved (Table 4, entries 1-6). When the model reaction was conducted using Pd(OAc)₂, [Pd(cinnamyl)Cl]₂, and [Pd(allyl)Cl]₂ as precursors, the reactions formed the enone product in 46%, 59%, and 65% yield at 110 °C in 12 h (Table 4, entries 7-9). These reactions also formed the byproduct **7a** in 14-18% yield. We then studied impact of temperature and time using [Pd(allyl)Cl]₂ as the precursor of choice. Lowering the temperature of the reaction and running the reaction longer improved the ratio of **3a**:**7a** from 3.6:1.0 to 16:1.0 (Table 4, entries 9-13). When the model reaction was conducted at 90 °C, the reaction formed enone **3a** in 84% yield and byproduct **7a** in 5% yield (Table 4, entry 13).

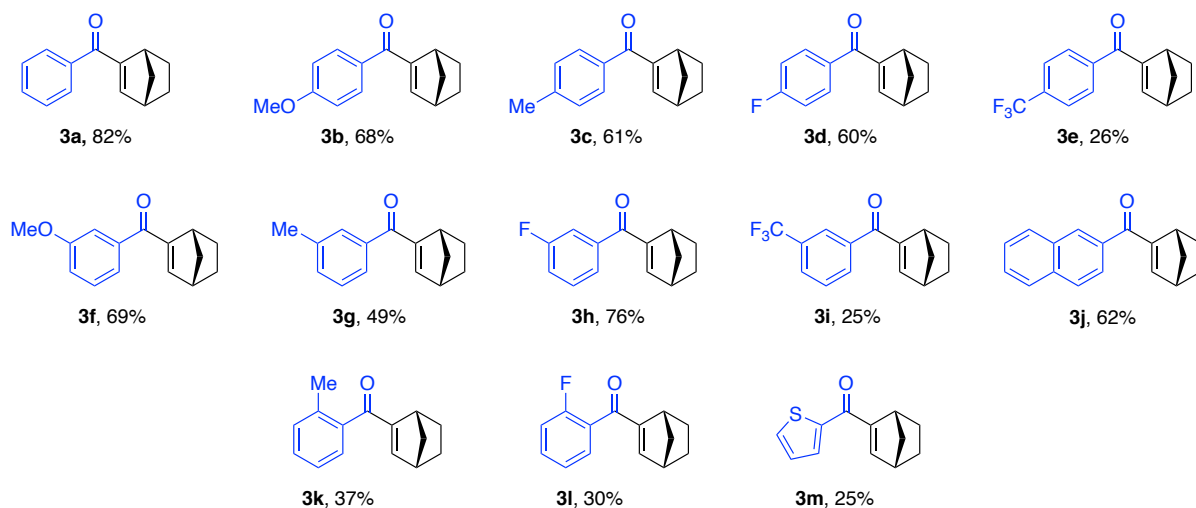
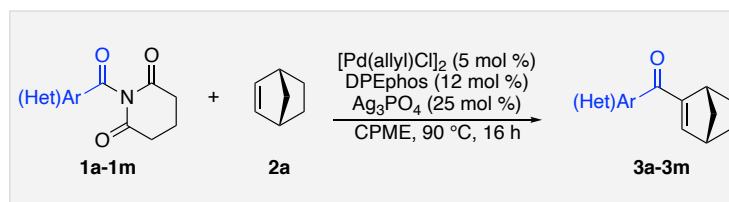
Identification of reaction conditions:**Table 5.** Identification of reaction conditions for Pd-catalyzed acylative Heck reaction of *N*-benzoylglutarimide **1a** and norbornene **2a**

Entry	Deviation from the standard conditions	conv. (%)	3a (%)	7a (%)
1	none	99	84	5
2	Pd ₂ dba ₃ (5 mol %)	73	59	3
3	K ₃ PO ₄ (25 mol %)	10	8	1
4	Ag ₃ PO ₄ (15 mol %)	1	1	0
5	no Ag ₃ PO ₄	0	0	0
6	nbe (5 equiv)	90	68	6
7	dioxane	96	61	5
8	THF	41	34	0

We identified reaction conditions mentioned in Table 5, entry 1 as the optimized reaction conditions. When the model reaction was conducted using a Pd(0) source, Pd₂(dba)₃, the reaction formed Heck product **3a** in 59% yield and Diels Alder byproduct **7a** in 3% yield (Table 5, entry 2). When the model reaction was conducted using K₃PO₄ instead of Ag₃PO₄, the reaction formed the enone product **3a** in 8% yield (Table 5, entry 3). Lowering the Ag₃PO₄ loading to 15 mol % significantly lowered the yield of the reaction (Table 5, entry 4). No product was observed when the model reaction was conducted in the absence of Ag₃PO₄ (Table

5, entry 5). These results show the importance of silver(I) additives in Pd-catalyzed acylative Heck reactions of amides. We hypothesize that Ag_3PO_4 helps in generating cationic palladium intermediate that facilitates migratory insertion. Lowering the loading of norbornene to from 10 to 5 equivalents led to the formation of Heck product **3a** in 68% yield. The model reaction formed the Heck product **3a** in 61% and 34% yields, when the reaction was conducted in dioxane and THF as solvents instead of cyclopentylmethyl ether (Table 5, entries 7-8).

Substrate Scope:

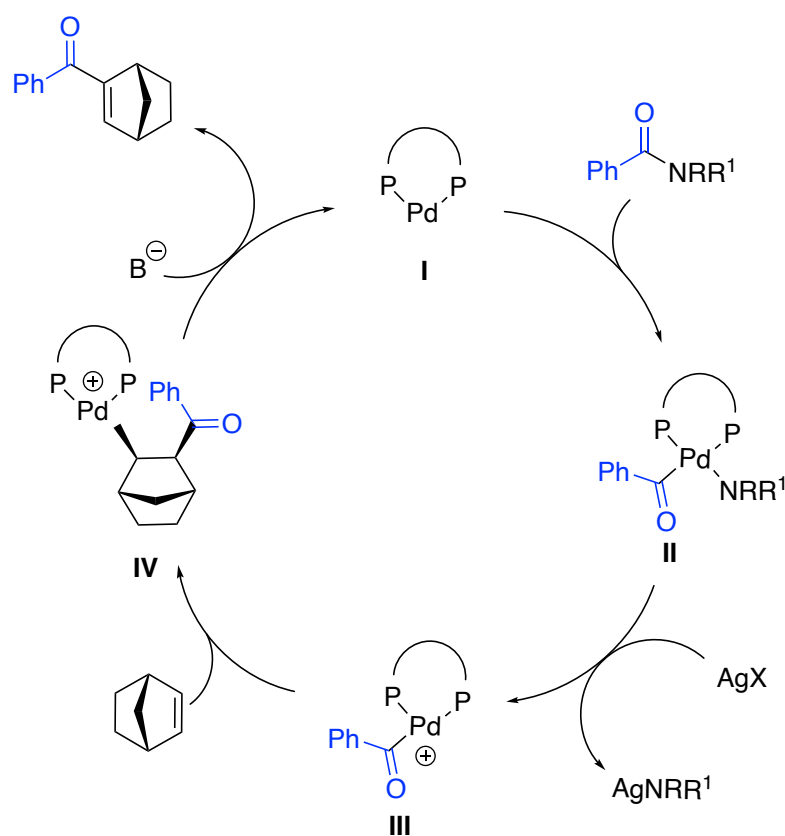


Scheme 5. Substrate scope of Pd-catalyzed acylative Heck reaction of amides **1a-1m** and norbornene **2a**

With a catalyst system identified for the model reaction between *N*-benzoylglutarimide **1a** and norbornene **2a**, we next evaluated the scope of amides for Pd-catalyzed acylative Heck reaction of amides (Scheme 5). Heck reaction between *para*-, *meta*-, and *ortho*-substituted *N*-benzoylglutarimide derivatives **1a-1l** and norbornene **2a** formed the corresponding Heck products **3a-3l** in 25-82% yields. Pd-catalyzed acylative Heck reaction between amides containing electron-donating, halogenated, and electron-withdrawing *para*-substituents and norbornene formed Heck products **3b-3e** in moderate to good yields (25-68%). Amides bearing electron-donating, halogenated, and electron-withdrawing *meta*-substituents formed products

3f-3i in 25-76% yields. Heck reaction between 1-(2-naphthoyl)piperidine-2,6-dione **1j** and norbornene **2a** formed product **3j** in 62% yield. Reactions of amides containing *ortho*-methyl and *ortho*-fluoro substituents formed the Heck products **3k** and **3l** in 30-37% yields. A heteroaromatic amide, 1-(thiophene-2-carbonyl)piperidine-2,6-dione **1m**, was also a suitable electrophile for Pd-catalyzed acylative Heck reaction. The reaction between 1-(thiophene-2-carbonyl)piperidine-2,6-dione **1m** and norbornene **2a** formed the corresponding Heck product **3m** in 25% yield.

Proposed Catalytic Cycle:



Scheme 6. Proposed catalytic cycle

We propose a classical Pd(0)/Pd(II) cycle for Pd-catalyzed acylative Heck reactions using amides as acyl electrophiles as depicted in Scheme 6. In this catalytic cycle, the active Pd(0) catalyst undergoes oxidative addition into the C–N bond of the amide to form acyl–

Pd(II)–amido complex **II**. Upon reaction of the complex **II** with Ag(I) salt, a cationic acyl–Pd(II) complex **III** is formed. Migratory insertion of alkene into Pd–C(O) bond of complex **III** generates cationic alkyl–Pd(II) complex **IV**. The alkyl–Pd(II) complex **IV** then undergoes non-classical β -hydride elimination in the presence of a base to give the desired enone product.

Although we propose a classical Pd(0)/Pd(II) cycle for the Heck reaction, a non-classical, rare Pd(II)/Pd(IV) pathway cannot be ruled out.¹⁹⁻²¹ We observe an induction period when the model reaction is conducted using a Pd(0) pre-catalyst (Pd₂dba₃) (Table 4, entries 1-3). This induction period could result from either the slow displacement of dibenzylideneacetone ligands by DPEphos ligand or oxidation of Pd(0) to Pd(II) by Ag(I) additive. When we conducted the model reaction using Pd(OAc)₂ precatalyst, the reaction formed the product **2a** in 55% yield in 5 h (Table 4, entry 4). These results together allude to Pd(II)/Pd(IV) cycle, however more experiments are needed to support the catalytic Pd(II)/Pd(IV) pathway.

Conclusion:

In summary, we have developed a palladium-catalyzed acylative Heck reaction using amides as electrophiles. The products of these reactions form α,β -unsaturated ketone products from simple starting materials such as amides and alkenes. These products can undergo a rapid Diels-Alder reaction to form compounds containing complex architectures. Studies to further expand the scope of the reaction and utility of these products are on-going in our laboratory.

Experimental

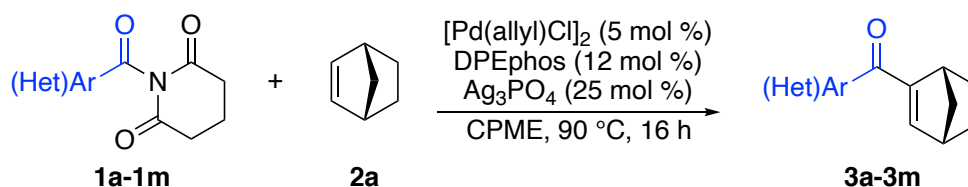
General Details. All air-sensitive procedures were conducted under inert atmosphere in a nitrogen-filled dry box or by standard Schlenk techniques. All reactions were performed under nitrogen unless otherwise stated. Benzene, toluene, dichloromethane (DCM), diethylether (Et₂O), and tetrahydrofuran (THF) 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 cyclopentyl methyl ether (CPME) were purchased from Sigma-Aldrich and used as received. Flash column chromatography was performed on SiliFlash® P60 silica gel (40-63µm, 60Å) or using a Teledyne Isco Combiflash® Rf system with RediSep Gold™ columns using hexane/ethyl acetate or hexane/Et₂O or and pentane/Et₂O. Reaction products were visualized on TLC under UV light or by staining with KMnO₄.

HRMS (ESI) analysis was performed at the Iowa State University Chemical Instrumentation Facility on an Agilent 6540 QTOF spectrometer. Elemental analysis was performed at the Iowa State University Chemical Instrumentation Facility on the Perkin Elmer 2100 Series II CHN/S Analyzer. NMR spectra were acquired on Varian MR-400 and Bruker Avance III 600 spectrometers at the Iowa State University Chemical Instrumentation Facility. Chemical shifts are reported in ppm relative to a residual solvent peak (CDCl₃ = 7.26 ppm for ¹H and 77.16 ppm for ¹³C). ¹⁹F NMR shifts are reported based on indirect reference to CDCl₃.²² Coupling constants are reported in hertz.

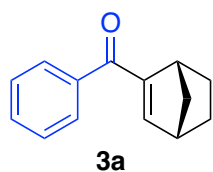
Materials. Sodium tetraphenylborate, norbornene, 4-methoxybenzoic acid, 4-methylbenzoic acid 4-trifluoromethylphenylbenzoic acid, 4-fluorobenzoic acid, 3-

trifluoromethylphenylbenzoic acid, 2-fluorobenzoic acid, 2-methylbenzoic acid, 2-thiophenecarboxylic acid, silver phosphate, benzoyl chloride, and $[\text{Pd}(\text{cinnamyl})\text{Cl}]_2$ were purchased from Sigma Aldrich. $[\text{Pd}(\text{allyl})\text{Cl}]_2$ and DPEphos were purchased from Strem Chemicals. 3-Methylbenzoic acid was purchased from Lancaster Synthesis. 3-Methoxybenzoic acid was purchased from Eastman Organic Chemicals. 4-Methoxybenzoyl chloride, and 4-(trifluoromethyl)benzoyl chloride were purchased from TCI America. Amides **1a-1m** were synthesized according to literature procedures.²³⁻²⁵

General Procedure A for Synthesis of Heck Products



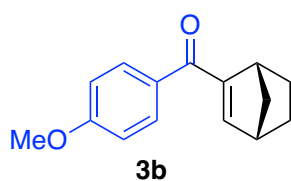
An oven-dried 1-dram vial was charged with $[\text{Pd}(\text{allyl})\text{Cl}]_2$ (1.80 mg, 0.005 mmol), DPEphos (6.50 mg, 0.012 mmol), alkene (1.00 mmol), and cyclopentyl methyl ether (0.333 M, 0.300 mL). The reaction mixture was stirred at 80-90 °C for 16 h. Upon completion of the reaction, the reaction mixture was filtered through a short plug of silica using ethyl acetate (20 mL) and concentrated under reduced pressure. The crude product was purified by flash column chromatography to give Heck products **3a-3m**.



(bicyclo[2.2.1]hept-2-en-2-yl)(phenyl)methanone **3a**: Prepared according to General Procedure A from 1-benzoylpiperidine-2,6-dione (21.7 mg, 0.100 mmol, 0.100 equiv) and norbornene (94.2 mg, 1.00 mmol, 10.0 equiv)

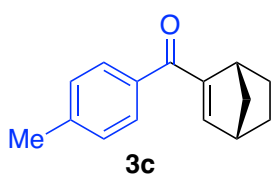
at 90 °C in 16 h. The crude reaction mixture was purified using flash chromatography (100:0 → 94:7 hexane:diethyl ether) to yield (bicyclo[2.2.1]hept-2-en-2-yl)(phenyl)methanone **3a** as

a white solid in 82 % yield (16.2 mg, 0.082 mmol). **¹H NMR** (400 MHz, CDCl₃): δ 1.05-1.12 (m, 1H), 1.18-1.24 (m, 1H), 1.27 (d, *J* = 8.7 Hz, 1H), 1.55-1.59 (m, 1H), 1.77-1.86 (m, 2H), 3.12 (s, 1H), 3.47 (s, 1H), 6.65 (d, *J* = 3.0 Hz, 1H), 7.42 (t, *J* = 7.2 Hz, 2H), (t, *J* = 7.2 Hz, 1H), 7.75 (d, *J* = 7.2 Hz, 2H). **¹³C NMR** (100 MHz, CDCl₃): δ 24.8, 25.5, 42.6, 44.5, 47.2, 128.3, 129.0, 132.0, 138.4, 148.7, 149.9, 192.9. **HRMS** (ESI): Calcd. for C₁₄H₁₅O⁺ ([M+H]⁺): 199.1117, Found: 199.1119.



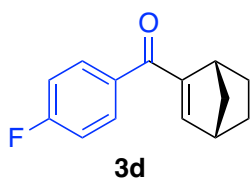
(bicyclo[2.2.1]hept-2-en-2-yl)(4-methoxyphenyl)methanone **3b**:

Prepared according to General Procedure A from 1-(4-methoxybenzoyl)piperidine-2,6-dione (24.7 mg, 0.100 mmol, 0.100 equiv) and norbornene (94.2 mg, 1.00 mmol, 10.0 equiv) at 90 °C in 16 h. The crude reaction mixture was purified using flash chromatography (100:0 → 94:6 hexane:diethyl ether) to yield (bicyclo[2.2.1]hept-2-en-2-yl)(4-methoxyphenyl)methanone **3b** as a white solid in 68% yield (15.5 mg, 0.068 mmol). **¹H NMR** (400 MHz, CDCl₃): δ 1.05-1.12 (m, 1H), 1.19-1.27 (m, 2H), 1.53-1.58 (m, 1H), 1.76-1.85 (m, 2H), 3.11 (s, 1H), 3.43 (s, 1H), 3.86 (s, 3H), 6.60 (d, *J* = 3.12 Hz, 1H), 6.91 (ddd, *J* = 8.92, 2.76, 2.08 Hz, 2H), 7.78 (ddd, *J* = 8.92, 2.76, 2.08 Hz, 2H). **¹³C NMR** (100 MHz, CDCl₃): δ 24.9, 25.6, 43.0, 44.5, 47.2, 55.6, 113.5, 113.16, 113.23, 148.2, 148.7, 162.9, 191.8. **HRMS** (ESI): Calcd. for C₁₅H₁₇O₂⁺ ([M+H]⁺): 229.1223, Found: 229.1227.



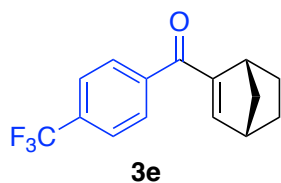
(bicyclo[2.2.1]hept-2-en-2-yl)(*p*-tolyl)methanone **3c**: Prepared according to General Procedure A from 1-(4-methylbenzoyl)piperidine-2,6-dione (23.1 mg, 0.100 mmol, 0.100

equiv) and norbornene (94.2 mg, 1.00 mmol, 10.0 equiv) at 90 °C in 16 h. The crude reaction mixture was purified using flash chromatography (100:0 → 93:7 hexane:diethyl ether) to yield (bicyclo[2.2.1]hept-2-en-2-yl)(*p*-tolyl)methanone **3c** as a white solid in 61% yield (12.9 mg, 0.061 mmol). **¹H NMR** (400 MHz, CDCl₃): δ 1.04-1.12 (m, 1H), 1.181.23 (m, 1H), 1.24-1.28 (m, 1H), 1.54-1.58 (m, 1H), 1.76-1.85 (m, 1H), 2.40 (s, 3H), 3.11 (s, 1H), 3.45 (s, 1H), 6.63 (d, *J* = 3.12 Hz, 1H), 7.22 (d, *J* = 7.92 Hz, 2H), 7.67 (d, *J* = 7.92 Hz, 2H). **¹³C NMR** (100 MHz, CDCl₃): δ 21.7, 24.8, 25.5, 42.7, 44.5, 47.2, 129.0, 129.2, 135.7, 142.7, 148.7, 149.1, 192.7. **HRMS** (ESI): Calcd. for C₁₄H₁₇O⁺ ([M+H]⁺): 213.1274, Found: 213.1278.



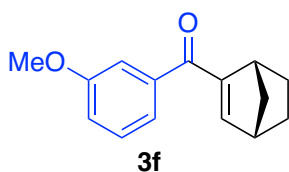
(bicyclo[2.2.1]hept-2-en-2-yl)(4-fluorophenyl)methanone **3d**: Prepared according to General Procedure A from 1-(4-fluorobenzoyl)piperidine-2,6-dione (23.5 mg, 0.100 mmol, 0.100 equiv) and norbornene (94.2 mg,

1.00 mmol, 10.0 equiv) at 90 °C in 16 h. The crude reaction mixture was purified using flash chromatography (100:0 → 92:8 hexane:diethyl ether) to yield (bicyclo[2.2.1]hept-2-en-2-yl)(4-fluorophenyl)methanone **3d** as a white solid in 60% yield (13.0 mg, 0.060 mmol). **¹H NMR** (400 MHz, CDCl₃): δ 1.05-1.12 (m, 1H), 1.17-1.29 (m, 2H), 1.54-1.58 (m, 1H), 1.77-1.87 (m, 2H), 3.11-3.14 (m, 1H), 3.45 (s, 1H), 6.63 (d, *J* = 3.16 Hz, 1H), 7.09 (t, *J* = 8.842 Hz, 2H), (dd, *J* = 8.84, 5.52 Hz, 2H). **¹³C NMR** (100 MHz, CDCl₃): δ 24.8, 25.5, 42.8, 44.5, 47.2, 115.4 (d, *J* = 21.6 Hz, 2C), 131.4 (d, *J* = 9.0 Hz, 2C), 134.6 (d, *J* = 3.0 Hz, 1C), 148.6, 149.6, 165.3 (d, *J* = 251.5 Hz, 1C), 191.4. **¹⁹F NMR** (376 MHz, CDCl₃): δ -107.28 (m, 1F). **HRMS** (ESI): Calcd. for C₁₄H₁₄FO⁺ ([M+H]⁺): 217.1023, Found: 217.1025.



(bicyclo[2.2.1]hept-2-en-2-yl)(4-(trifluoromethyl)phenyl)methanone

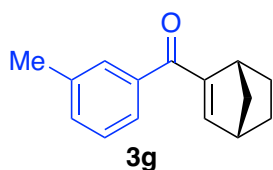
3e: Prepared according to General Procedure A from 1-(4-trifluoromethylbenzoyl)piperidine-2,6-dione (28.5 mg, 0.100 mmol, 0.100 equiv) and norbornene (94.2 mg, 1.00 mmol, 10.0 equiv) at 90 °C in 16 h. The crude reaction mixture was purified using flash chromatography (100:0 → 96:4 hexane:diethyl ether) to yield (bicyclo[2.2.1]hept-2-en-2-yl)(4-(trifluoromethyl)phenyl)methanone **3e** as a white solid in 26% yield (6.9 mg, 0.026 mmol). **¹H NMR** (400 MHz, CDCl₃): δ 1.05-1.13 (m, 1H), 1.16-1.25 (m, 1H), 1.30 (dd, *J* = 8.80, 0.840 Hz, 1H), 1.57-1.61 (m, 1H), 1.79-1.89 (m, 2H), 3.15 (d, *J* = 1.28 Hz, 1H), 3.49 (s, 1H), 6.68 (d, *J* = 3.12 Hz, 1H), 7.69 (d, *J* = 8.12 Hz, 2H), 7.83 (d, *J* = 8.12 Hz, 2H). **¹³C NMR** (100 MHz, CDCl₃): δ 24.7, 25.5, 42.4, 44.7, 47.3, 123.9 (q, *J* = 271.7 Hz, 1C), 125.3 (q, *J* = 3.7 Hz, 2C), 129.2, 133.4 (q, *J* = 32.4 Hz, 1C), 141.3 (q, *J* = 1.32 Hz, 2C), 148.6, 151.2, 191.6. **¹⁹F NMR** (376 MHz, CDCl₃): δ -62.96 (s, 3F). **HRMS** (ESI): Calcd. for C₁₅H₁₄F₃O⁺ ([M+H]⁺): 267.0991, Found: 267.0991.



(bicyclo[2.2.1]hept-2-en-2-yl)(3-methoxyphenyl)methanone **3f:**

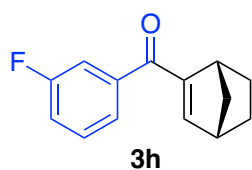
Prepared according to General Procedure A from 1-(3-methoxybenzoyl)piperidine-2,6-dione (24.7 mg, 0.100 mmol, 0.100 equiv) and norbornene (94.2 mg, 1.00 mmol, 10.0 equiv) at 90 °C in 16 h. The crude reaction mixture was purified using flash chromatography (100:0 → 92:8 hexane:diethyl ether) to yield (bicyclo[2.2.1]hept-2-en-2-yl)(3-methoxyphenyl)methanone **3f** as a white solid in 69% yield (15.7 mg, 0.069 mmol). **¹H NMR** (400 MHz, CDCl₃): δ 1.05-1.12 (m, 1H), 1.17-1.28 (m, 3H), 1.55-1.59 (m, 1H), 1.76-1.86 (m, 2H), 3.12 (s, 1H), 3.46 (s, 1H), 3.84 (s, 3H), 6.68 (d, *J* = 3.16 Hz, 1H), 7.04-7.09 (m, 1H), 7.27-7.34 (m, 3H). **¹³C NMR** (100 MHz, CDCl₃): δ 24.8, 25.5,

42.6, 44.5, 47.2, 55.5, 113.5, 118.3, 121.7, 129.2, 139.7, 148.7, 149.9, 159.6, 192.6. **HRMS** (ESI): Calcd. for $C_{15}H_{17}O_2^+$ ($[M+H]^+$): 229.1223, Found: 229.1228.



(bicyclo[2.2.1]hept-2-en-2-yl)(*m*-tolyl)methanone **3g**: Prepared according to General Procedure A from 1-(3-methylbenzoyl)piperidine-2,6-dione (23.1 mg, 0.100 mmol, 0.100

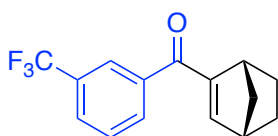
equiv) and norbornene (94.2 mg, 1.00 mmol, 10.0 equiv) at 90 °C in 16 h. The crude reaction mixture was purified using flash chromatography (100:0 → 92:8 hexane:diethyl ether) to yield (bicyclo[2.2.1]hept-2-en-2-yl)(*m*-tolyl)methanone **3g** as a white solid in 49% yield (10.4 mg, 0.049 mmol). **¹H NMR** (400 MHz, $CDCl_3$): δ 1.04-1.12 (m, 1H), 1.17-1.28 (m, 2H), 1.55-1.59 (m, 1H), 1.76-1.86 (m, 2H), 2.39 (s, 3H), 3.12 (s, 1H), 3.46 (s, 1H), 6.64 (d, $J = 3.12$ Hz, 1H), 7.30 (t, $J = 7.44$ Hz, 1H), 7.31-7.34 (m, 1H), 7.52-7.56 (m, 2H). **¹³C NMR** (100 MHz, $CDCl_3$): δ 21.5, 24.8, 25.5, 42.5, 44.5, 47.2, 126.3, 128.1, 129.4, 132.8, 138.1, 138.4, 148.8, 149.8, 193.2. **HRMS** (ESI): Calcd. for $C_{14}H_{17}O^+$ ($[M+H]^+$): 213.1274, Found: 213.1280.



(bicyclo[2.2.1]hept-2-en-2-yl)(3-fluorophenyl)methanone **3h**: Prepared according to General Procedure A from 1-(3-fluorobenzoyl)piperidine-2,6-dione (23.5 mg, 0.100 mmol, 0.100 equiv) and norbornene (94.2 mg,

1.00 mmol, 10.0 equiv) at 90 °C in 16 h. The crude reaction mixture was purified using flash chromatography (100:0 → 92:8 hexane:diethyl ether) to yield (bicyclo[2.2.1]hept-2-en-2-yl)(3-fluorophenyl)methanone **3h** as a white solid in 76% yield (16.4 mg, 0.076 mmol). **¹H NMR** (400 MHz, $CDCl_3$): δ 1.05-1.12 (m, 1H), 1.15-1.29 (m, 2H), 1.55-1.59 (m, 1H), 1.77-1.87 (m, 2H), 3.14 (s, 1H), 3.46 (s, 1H), 6.69 (d, $J = 3.08$ Hz, 1H), 7.21 (td, $J = 8.20, 2.32$ Hz,

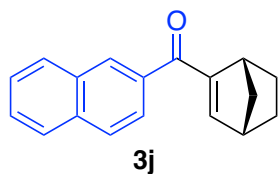
1H), 7.37-7.45 (m, 2H), 7.53 (d, $J = 7.68$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 24.7, 25.5, 42.6, 44.6, 47.2, 115.8 (d, $J = 22.3$ Hz, 1C), 119.0 (d, $J = 21.3$ Hz, 1C), 124.7 (d, $J = 3.0$ Hz, 1C), 130.0 (d, $J = 7.7$ Hz, 1C), 140.4 (d, $J = 6.2$ Hz, 1C), 148.5, 150.4, 162.6 (d, $J = 247.5$ Hz, 1C), 191.4 (d, $J = 2.0$ Hz, 1C). ^{19}F NMR (376 MHz, CDCl_3): δ -112.49 (m, 1F). HRMS (ESI): Calcd. for $\text{C}_{14}\text{H}_{14}\text{FO}^+$ ($[\text{M}+\text{H}]^+$): 217.1023, Found: 217.1023.

**3i**

(bicyclo[2.2.1]hept-2-en-2-yl)(3-(trifluoromethyl)phenyl)methanone

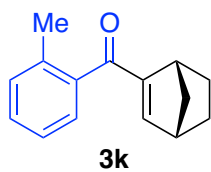
3i: Prepared according to General Procedure A from 1-(3-trifluoromethylbenzoyl)piperidine-2,6-dione (28.5 mg, 0.100 mmol,

0.100 equiv) and norbornene (94.2 mg, 1.00 mmol, 10.0 equiv) at 90 °C in 16 h. The crude reaction mixture was purified using flash chromatography (100:0 \rightarrow 96:4 hexane:diethyl ether) to yield (bicyclo[2.2.1]hept-2-en-2-yl)(3-(trifluoromethyl)phenyl)methanone **3i** as a white solid in 25% yield (6.7 mg, 0.025 mmol). ^1H NMR (400 MHz, CDCl_3): δ 1.05-1.13 (m, 1H), 1.16-1.25 (m, 1H), 1.30 (d, $J = 8.76$ Hz, 1H), 1.60 (d, $J = 8.72$ Hz, 1H), 1.78-1.88 (m, 2H), 3.16 (s, 1H) 3.48 (s, 1H), 6.67 (d, $J = 2.84$ Hz, 1H), 7.56 (t, $J = 7.80$ Hz, 1H), 7.77 (d, $J = 7.80$ Hz, 1H), 7.92 (d, $J = 7.80$ Hz, 1H), 7.99 (s, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 24.7, 25.5, 42.5, 44.7, 47.2, 123.9 (q, $J = 272.6$ Hz, 1C), 125.8 (q, $J = 3.8$ Hz, 1C), 128.5 (q, $J = 3.7$ Hz, 1C), 128.96, 130.91 (q, $J = 32.7$ Hz, 1C), 132.1 (q, $J = 1.6$ Hz, 1C), 138.9, 148.5, 150.9, 191.3. ^{19}F NMR (376 MHz, CDCl_3): δ -62.74 (s, 3F). HRMS (ESI): Calcd. for $\text{C}_{15}\text{H}_{14}\text{F}_3\text{O}^+$ ($[\text{M}+\text{H}]^+$): 267.0991, Found: 267.1004.



(bicyclo[2.2.1]hept-2-en-2-yl)(naphthalen-2-yl)methanone **3j**:

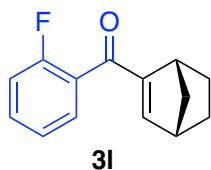
Prepared according to General Procedure A from 1-(2-naphthoyl)piperidine-2,6-dione (26.7 mg, 0.100 mmol, 0.100 equiv) and norbornene (94.2 mg, 1.00 mmol, 10.0 equiv) at 90 °C in 16 h. The crude reaction mixture was purified using flash chromatography (100:0 → 96:4 hexane:ethyl acetate) to yield (bicyclo[2.2.1]hept-2-en-2-yl)(naphthalen-2-yl)methanone **3j** as a white solid in 62% yield (15.4 mg, 0.062 mmol). ¹H NMR (400 MHz, CDCl₃): δ 1.08-1.15 (m, 1H), 1.23-1.33 (m, 2H), 1.65 (dp, *J* = 8.72, 1.92 Hz, 1H), 1.80-1.89 (m, 2H), 3.17 (s, 1H), 3.52 (s, 1H), 6.72 (d, *J* = 3.16 Hz, 1H), 7.52-7.60 (m, 2H), 7.84-7.90 (m, 3H), 7.93-7.95 (m, 1H), 8.26 (s, 1H). ¹³C NMR (100 MHz, CDCl₃): δ 24.8, 25.6, 42.8, 44.6, 47.2, 125.3, 126.7, 127.9, 128.0, 128.3, 129.4, 130.2, 132.5, 135.2, 135.6, 148.9, 149.8, 1912.9. HRMS (ESI): Calcd. for C₁₈H₁₇O⁺ ([M+H]⁺): 249.1274, Found: 149.1277.



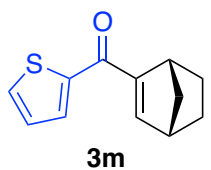
(bicyclo[2.2.1]hept-2-en-2-yl)(*o*-tolyl)methanone **3k**: Prepared according

to General Procedure A from 1-(2-methylbenzoyl)piperidine-2,6-dione (23.1 mg, 0.100 mmol, 0.100 equiv) and norbornene (94.2 mg, 1.00 mmol, 10.0 equiv) at 90 °C in 16 h. The crude reaction mixture was purified using flash chromatography (100:0 → 96:4 hexane:diethyl ether) to yield (bicyclo[2.2.1]hept-2-en-2-yl)(*o*-tolyl)methanone **3k** as a white solid in 37% yield (7.84 mg, 0.037 mmol). ¹H NMR (400 MHz, CDCl₃): δ 1.06-1.20 (m, 2H), 1.29 (dd, *J* = 8.72, 0.88 Hz, 1H), 1.57 (dp, *J* = 8.72, 1.96 Hz, 1H), 1.78-1.86 (m, 2H), 2.30 (s, 3H), 3.06 (d, *J* = 1.32 Hz, 1H), 3.51 (s, 1H), 6.51 (d, *J* = 3.24 Hz, 1H), 7.15-7.22 (m, 2H), 7.24-7.26 (m, 1H), 7.30 (td, *J* = 7.48, 1.40 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃): δ 19.8, 24.8, 25.3, 41.1, 44.3, 47.8, 125.0, 128.1, 129.8, 131.0, 136.1,

139.2, 150.5, 151.8, 185.3. **HRMS** (ESI): Calcd. for $C_{14}H_{17}O^+$ ($[M+H]^+$): 213.1274, Found: 213.1268.



(bicyclo[2.2.1]hept-2-en-2-yl)(2-fluorophenyl)methanone **3l**: Prepared according to General Procedure A from 1-(2-fluorobenzoyl)piperidine-2,6-dione (23.5 mg, 0.100 mmol, 0.100 equiv) and norbornene (94.2 mg, 1.00 mmol, 10.0 equiv) at 90 °C in 16 h. The crude reaction mixture was purified using flash chromatography (100:0 → 95:5 hexane:diethyl ether) to yield (bicyclo[2.2.1]hept-2-en-2-yl)(2-fluorophenyl)methanone **3l** as a white solid in 30% yield (6.48 mg, 0.030 mmol). **¹H NMR** (400 MHz, $CDCl_3$): δ 1.07-1.22 (m, 2H), 1.29 (dd, $J = 8.72$, 0.680 Hz, 1H), 1.59 (dp, $J = 8.72$, 1.92 Hz, 1H), 1.77-1.86 (m, 2H), 3.09 (d, $J = 1.44$ Hz, 1H), 3.51 (s, 1H), 6.67 (s, 1H), 7.09 (t, $J = 8.80$ Hz, 1H), 7.17 (td, $J = 7.56$, 0.72 Hz, 1H), 7.40-7.45 (m, 2H). **¹³C NMR** (100 MHz, $CDCl_3$): δ 24.7, 25.2, 41.3, 44.4, 47.8, 116.3 (d, $J = 22.1$ Hz, 1C), 124.0 (d, $J = 3.7$ Hz, 1C), 127.8 (d, $J = 15.0$ Hz, 1C), 130.2 (d, $J = 3.1$ Hz, 1C), 132.3 (d, $J = 8.3$ Hz, 1C), 149.9 (d, $J = 1.0$ Hz), 151.85 (d, $J = 2.2$ Hz), 159.82 (d, $J = 251.8$ Hz), 189.58. **¹⁹F NMR** (376 MHz, $CDCl_3$): δ -113.45 (m, 1F). **HRMS** (ESI): Calcd. for $C_{14}H_{14}FO^+$ ($[M+H]^+$): 217.1023, Found: 217.1018.



(bicyclo[2.2.1]hept-2-en-2-yl)(thiophen-2-yl)methanone **3m**: Prepared according to General Procedure A from 1-(thiophene-2-carbonyl)piperidine-2,6-dione (22.3 mg, 0.100 mmol, 0.100 equiv) and norbornene (94.2 mg, 1.00 mmol, 10.0 equiv) at 90 °C in 16 h. The crude reaction mixture was purified using flash chromatography (100:0 → 96:4 hexane:diethyl ether) to yield (bicyclo[2.2.1]hept-2-en-2-

yl)(thiophen-2-yl)methanone **3m** as a white solid in 25% yield (5.10 mg, 0.025 mmol). ^1H NMR (600 MHz, CDCl_3): δ 1.14-1.18 (m, 1H), 1.25-1.29 (m, H), 1.57 (dp, $J = 8.70, 1.98$ Hz, 1H), 1.81-1.89 (m, 2H), 3.16-3.17 (m, 1H), 3.47 (s, 1H), 6.91 (d, $J = 3.12$ Hz, 1H), 7.13 (dd, $J = 4.98, 3.78$ Hz, 1H), 7.62 (dd, $J = 4.98, 1.14$ Hz, 1H), 7.71 (dd, $J = 3.78, 1.14$ Hz, 1H). ^{13}C NMR (150 MHz, CDCl_3): δ 24.9, 25.5, 43.2, 44.4, 47.1, 127.8, 132.1, 132.7, 143.9, 147.6, 148.8, 184.2. HRMS (ESI): Calcd. for $\text{C}_{12}\text{H}_{13}\text{SO}^+$ ($[\text{M}+\text{H}]^+$): 205.0682, Found: 205.0681.

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CHAPTER 5. CONCLUSION

Summary

This thesis describes the first examples of enantioselective, palladium-catalyzed conjugate additions of arylboronic acids to β -aryl β,β -disubstituted cyclic enones. A catalyst generated *in situ* from Pd(TFA)₂ and (*S*)-*t*-BuPyOx catalyzes enantioselective conjugate additions of electronically and structurally diverse arylboronic acids to a variety of β -aryl β,β -disubstituted enones. These reactions generate cyclic ketone products containing bis-benzylic quaternary carbon stereocenters in up to 92% yield and up to 93% ee by iterative addition of the arylboronic acid nucleophile to minimize protodeboronation.

This thesis discusses nickel-catalyzed intermolecular, three-component alkene carboacylation reaction triggered by activation of an amide C–N bond. This nickel-catalyzed conjunctive cross-coupling encompasses reactions of a variety of bicyclic alkenes, amides, and tetraarylborates to generate highly functionalized ketone products in high yields and excellent diastereoselectivities. In addition, preliminary mechanistic studies suggest that reductive elimination is the turnover-limiting step, and that migratory insertion precedes transmetalation.

The research findings of the work described in the Chapter III has led to various new avenues that are further being explored in our laboratory. Efforts for the development nickel-catalyzed intermolecular alkyne carboacylation to synthesize tetrasubstituted alkenes are currently on-going and have shown promising results. The discovery of new class of imides that can be activated using nickel-catalyst has led to the development of nickel-catalyzed alkene carboacylation reactions that allow synthesis of γ -amino ketones. Efforts to develop enantioselective alkene carboacylation reactions are also currently on-going in our laboratory.

This thesis describes the first examples of palladium-catalyzed intermolecular acylative Heck reaction using amides as acyl electrophiles. This catalyst system allows reaction between a wide range of electronically and sterically diverse amides and bicyclic alkene to form α,β -unsaturated ketone products in up to 82% yield. This work shows that amides can be used as acyl electrophiles for palladium-catalyzed intermolecular Heck reaction.

Conclusions

In conclusion, the methods developed in this thesis allow rapid functionalization of alkenes to access various enantio-enriched and racemic products. The new catalytic methods represent advancement in the fields of transition metal-catalyzed conjugate addition reactions, alkene carboacylation, and acylative Heck reactions. Additionally, the work described in this thesis reveals that amides can be used as acyl electrophiles for alkene functionalization reactions.