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Enantioselective synthesis of compounds containing bis-benzylic quaternary stereocenters through palladium-catalyzed conjugate additions of arylboronic acids

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Enantioselective synthesis of compounds containing bis-benzylic quaternary stereocenters through palladium-catalyzed conjugate additions of arylboronic acids

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Keith Woo
Aaron Sadow
Wenyu Huang

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DEDICATION

This thesis is dedicated to my family and friends who have supported me throughout my life to reach here.

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List of Abbreviations

$Pd(TFA)_2$	Palladium trifluoroacetate
AgTFA	Silver trifluoroacetate
NMR	Nuclear Magnetic Resonance
HPLC	High Performance Liquid Chromatography
ee	Enantiomeric excess
GC	Gas chromatography
ESI	Electrospray Ionization
HRMS	High Resolution Mass Spectrometry
NaTFA	Sodium trifluoroacetate
t_R	Retention Time
tert	Tertiary
BuPyOx	Butylpyridinooxazoline
Pd	Palladium

ACKNOWLEDGMENTS

I would like to take this opportunity to thank all the individuals who have supported me throughout the journey of graduate school. First and foremost, I thank my major advisor Dr. Levi M. Stanley, whose constant support in last three years have been vital to bring out the best in me. I deeply admire his critical thinking, perseverance, patience and hard work. I am grateful to my committee members, Dr. George Kraus, Dr. Keith Woo, Dr. Aaron Sadow and Dr. Wenyu Huang, for their constant guidance throughout my graduate studies.

I would like to thank my parents for all the hard work and sacrifice they have made to provide me the education I wanted. I thank all my family members who have always believed in me. I would also like to thank my friends here and back in India. They have always managed to find time for me whenever I needed them. I thank all the current and past members of Stanley research group who have made my time here enjoyable.

In addition, I would like to thank Iowa State University for giving me a chance to groom myself with a wonderful research experience.

ABSTRACT

This thesis describes development of a catalyst system that allows formation of compounds containing bis-benzylic quaternary stereocenters. The work presented herein describes studies towards development of 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 *in situ* 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 electronically and structurally diverse arylboronic acids to a variety of β-aryl, β,β-disubstituted enones. In this work, we have used iterative addition of the arylboronic acids as a strategy to minimize undesired protodeboronation pathways that leads to efficient formation of the corresponding ketones containing bis-benzylic quaternary stereocenters in up to 92% yield with up to 93% enantioselectivity.

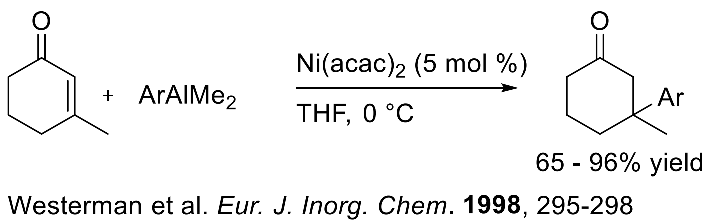
CHAPTER I

INTRODUCTION

A Brief Overview of Development of Transition Metal-Catalyzed Conjugate Additions of Organometallic Nucleophiles to Access Benzylic and Bis-Benzylic Quaternary Stereocenters

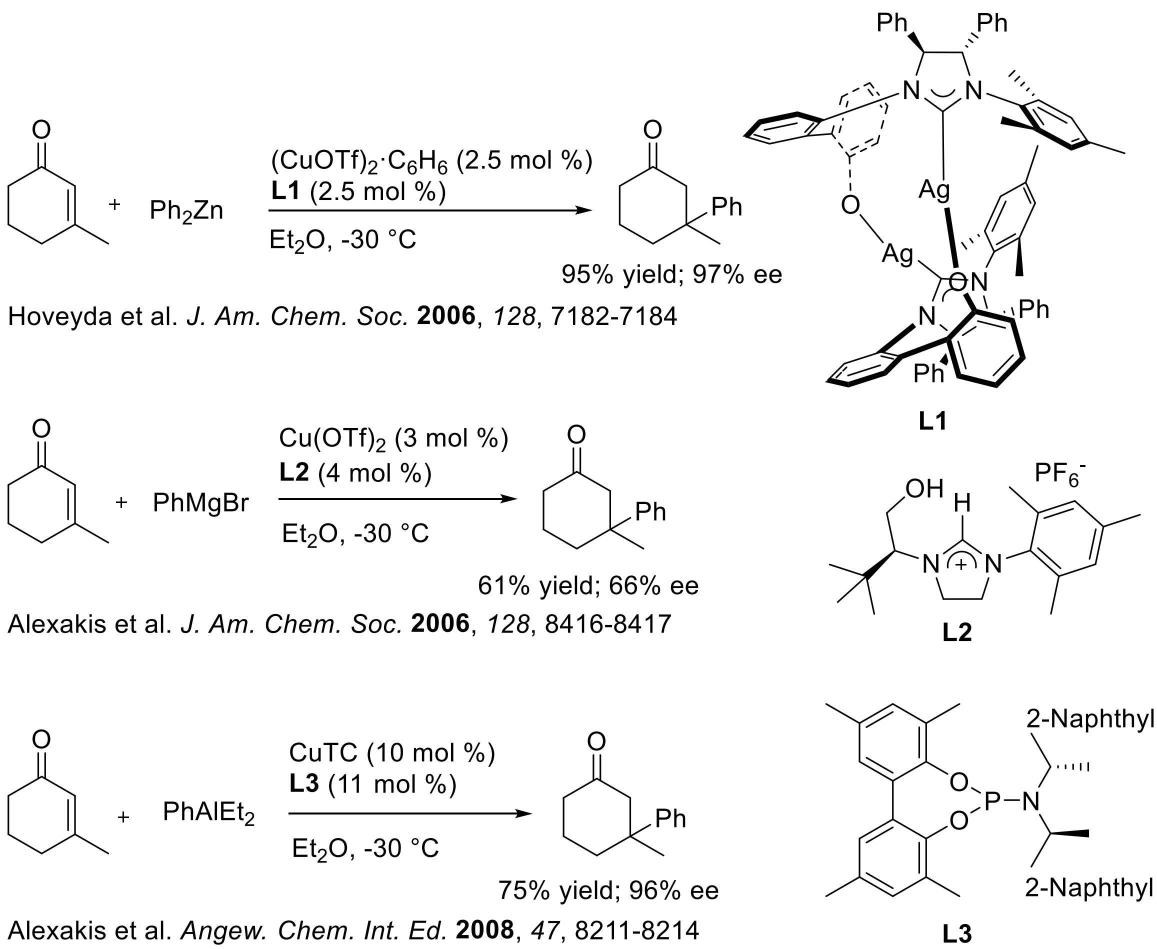
Transition metal-catalyzed conjugate addition of organometallic nucleophiles is a reliable and practical approach to form benzylic quaternary centers.[1] Over the past decades, many research groups have developed enantioselective, transition metal-catalyzed conjugate addition reactions of various organometallic aryl nucleophiles using nickel, copper, rhodium and palladium catalysts.[2]

Nickel-catalyzed conjugate additions of arylaluminum compounds represent an early example of transition metal-catalyzed conjugate additions of organometallic nucleophiles to generate compounds containing benzylic quaternary centers (Scheme 1).[3]



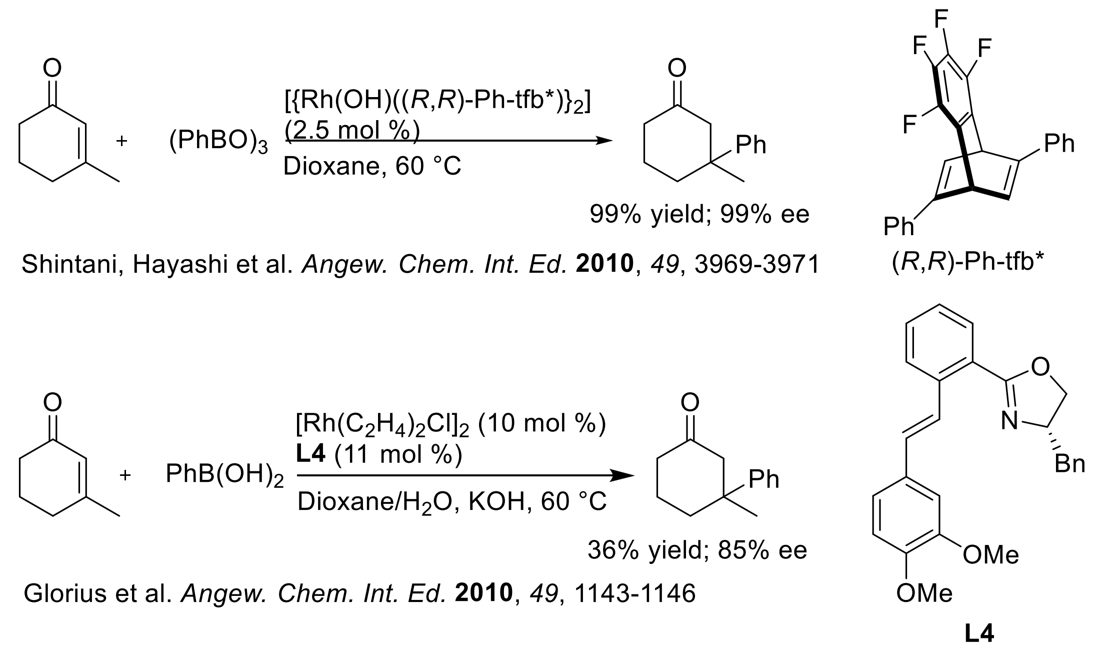
Scheme 1. Nickel-catalyzed conjugate additions of arylaluminum compounds to generate compounds containing benzylic quaternary centers

Pioneering work by Hoveyda and Alexakis led to the development of enantioselective, copper-catalyzed conjugate additions of arylzinc,[4] arylmagnesium,[5] and arylaluminum[6] nucleophiles to *β*,*β*-disubstituted enones to access benzylic quaternary stereocenters (Scheme 2). However, these nickel- and copper-catalyzed conjugate addition reactions involve use of highly reactive, air and/or moisture sensitive organometallic nucleophiles. Thus, they have limited functional group tolerance.



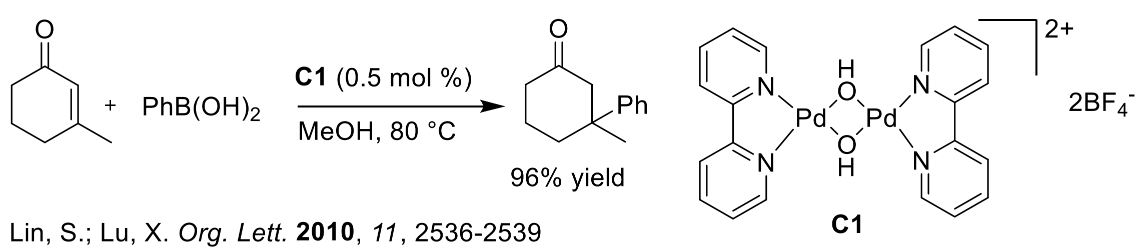
Scheme 2. Enantioselective, copper-catalyzed conjugate additions of aryl nucleophiles to generate compounds containing benzylic quaternary stereocenters

Hayashi and Glorius have independently developed enantioselective conjugate addition reactions catalyzed by rhodium catalysts that use air stable and easily handled arylboron nucleophiles to generate compounds containing benzylic quaternary sterocenters in high yields and enantioselectivities (Scheme 3).[7] However, rhodium-catalyzed additions of commercially available arylboronic acids are not efficient in these systems.



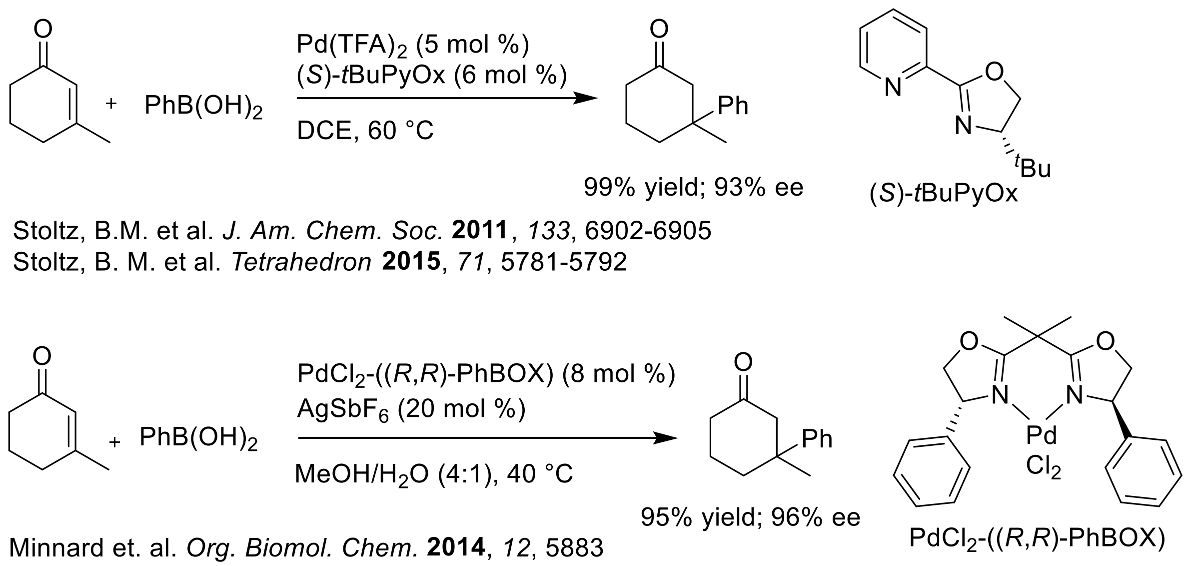
Scheme 3. Enantioselective, rhodium-catalyzed conjugate additions of arylboron compounds to generate compounds containing benzylic quaternary stereocenters

Lu and coworkers reported first examples of palladium-catalyzed conjugate additions of arylboronic acids to generate compounds containing benzylic quaternary centers (Scheme 4). In this work, Lu and coworkers use a cationic bipyridine ligated palladium complex to catalyze additions of arylboronic acids to β,β-disubstituted enones to form compounds containing benzylic quaternary centers in high yields.[8]



Scheme 4. Palladium-catalyzed conjugate additions of arylboronic acids to generate compounds containing benzylic quaternary centers

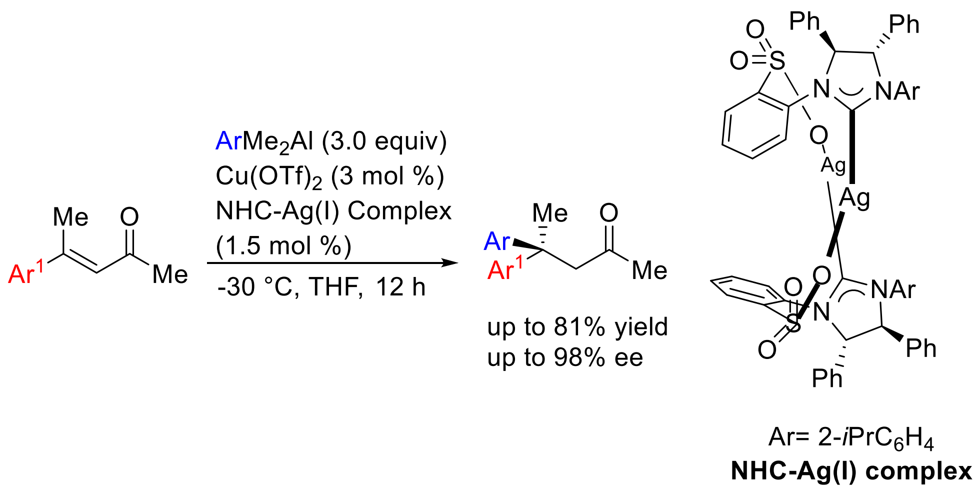
Stoltz and Minnaard have independently developed chiral palladium catalysts that catalyze additions of arylboronic acids to generate compounds containing benzylic stereocenters (Scheme 5).[9] These reactions use complexes generated *in situ* from palladium trifluoroacetate and chiral, non-racemic bidentate nitrogen-containing ligands, such as chiral pyridine-oxazolines and bisoxazolines, that catalyze additions of a wide array of arylboronic acids to generate ketones containing benzylic quaternary stereocenters in high yields and enantioselectivities.



Scheme 5. Enantioselective, palladium-catalyzed conjugate additions of arylboronic acids to generate compounds containing benzylic quaternary stereocenters

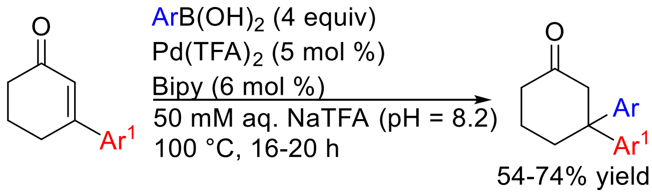
However, there are no examples of enantioselective, palladium-catalyzed conjugate additions of arylboronic acids to generate compounds containing bis-benzylic quaternary stereocenters. In fact, previous attempts to generate compounds containing bis-benzylic quaternary stereocenters using chiral palladium catalyst have been unsuccessful.[9d]

In 2013, Hoveyda reported copper-catalyzed conjugate additions of arylaluminum compounds to β-aryl, β,β-disubstituted acyclic enones to generate acyclic ketones containing bis-benzylic quaternary stereocenters (Scheme 6).[10] However, these reactions use air and/or moisture sensitive arylaluminum nucleophiles and thus, have low functional group tolerance. In addition, no examples of additions to *β*-aryl, *β*,*β*-disubstituted cyclic enones have been reported in this work.



Scheme 6. Enantioselective, copper-catalyzed conjugate additions of arylaluminum compounds to generate compounds containing bis-benzylic quaternary stereocenters

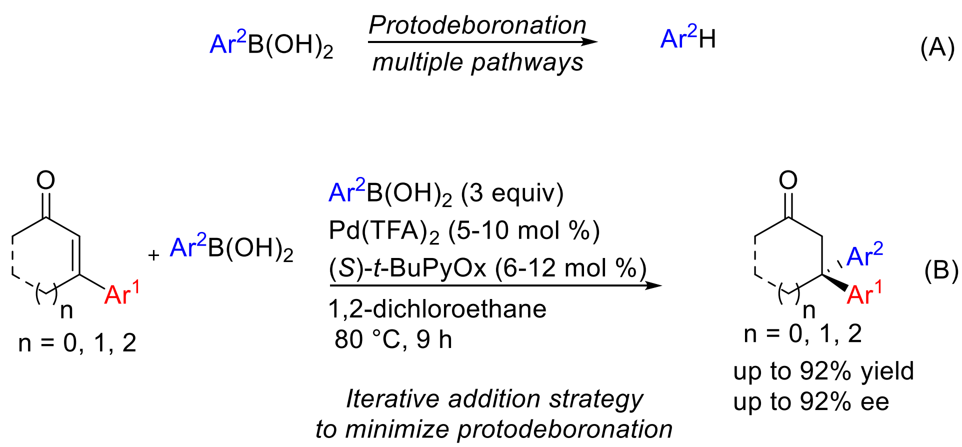
Our recent development of palladium-catalyzed conjugate additions of arylboronic acids to *β*-aryl, *β*,*β*-disubstituted enones in an aqueous media to access bis-benzylic quaternary centers prompted us to develop an enantioselective variant of this method (Scheme 7).[11]



Van Zeeland, R., Stanley, L. M., *ACS Catal.* **2015**, *5*, 5203-5206

Scheme 7. Palladium-catalyzed conjugate additions of arylboronic acids in aqueous media to generate compounds containing bis-benzylic quaternary centers

This thesis details the work towards development of enantioselective, palladium-catalyzed conjugate additions of arylboronic acids to β-aryl, β,β-disubstituted enones. In this work, we have used iterative addition of arylboronic acids as a strategy to minimize protodeboronation of arylboronic acids (Scheme 8, A), which is a major unproductive pathway in pd-catalyzed conjugate additions of arylboronic acids, that led to efficient formation of compounds containing bis-benzylic quaternary stereocenters in up to 92% yield and 93% enantioselectivities (Scheme 8, B).



Scheme 8. Enantioselective, palladium-catalyzed conjugate additions of arylboronic acids to β-aryl β,β-disubstituted enones

Thesis organization

This thesis contains three chapters. Chapter 1 is a general introduction to the chemistry described in the thesis. Chapter 2 describes research work that has not been submitted for publication at this time. Chapter 3 is a conclusion chapter for the thesis.

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CHAPTER 2

ENANTIOSELECTIVE, PALLADIUM-CATALYZED CONJUGATE ADDITIONS OF ARYLBORONIC ACIDS TO FORM BIS-BENZYLIC QUATERNARY STEREOCENTERS

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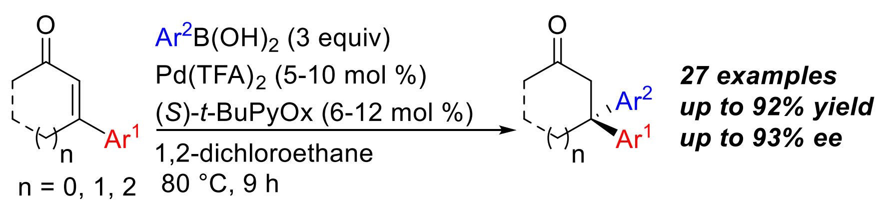
Abstract



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 92% enantioselectivity.

General Introduction

Compounds containing bis-benzylic quaternary centers are present in an array of biologically active compounds[1] (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 compounds containing quaternary stereocenters.[3] Despite recent advances in enantioselective, transition metal-catalyzed conjugate additions of organometallic nucleophiles, analogous asymmetric additions to *β*-aryl *β*,*β*-disubstituted enones to form bis-benzylic quaternary stereocenters remain challenging.

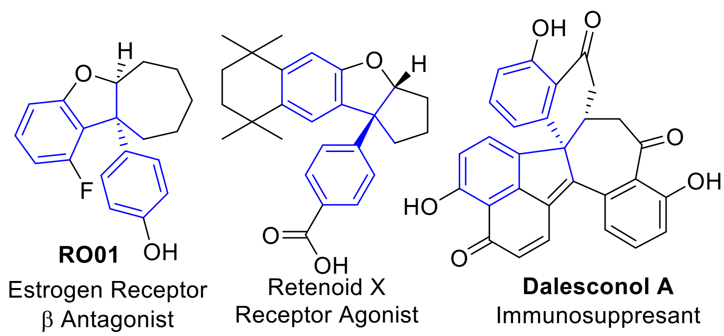
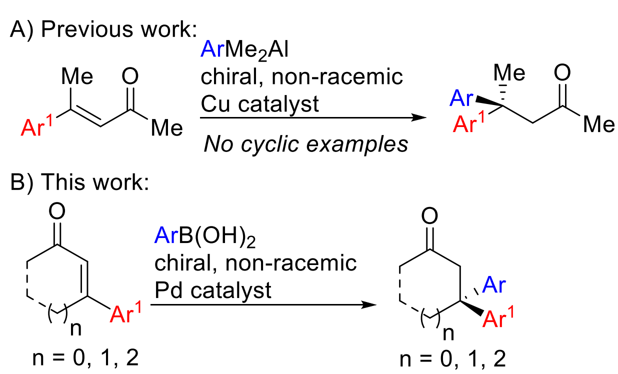


Figure 1. Biologically active compounds containing bis-benzylic quaternary stereocenters

Over the past decades, enantioselective conjugate additions of arylzinc,[4] arylaluminum,[5] arylmagnesium,[6] and arylboron[7] 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. 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 currently limited to copper-catalyzed additions to acyclic electrophiles. 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).[5a] 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 highly air and/or moisture sensitive arylaluminum nucleophiles and thus, have low functional group tolerance.



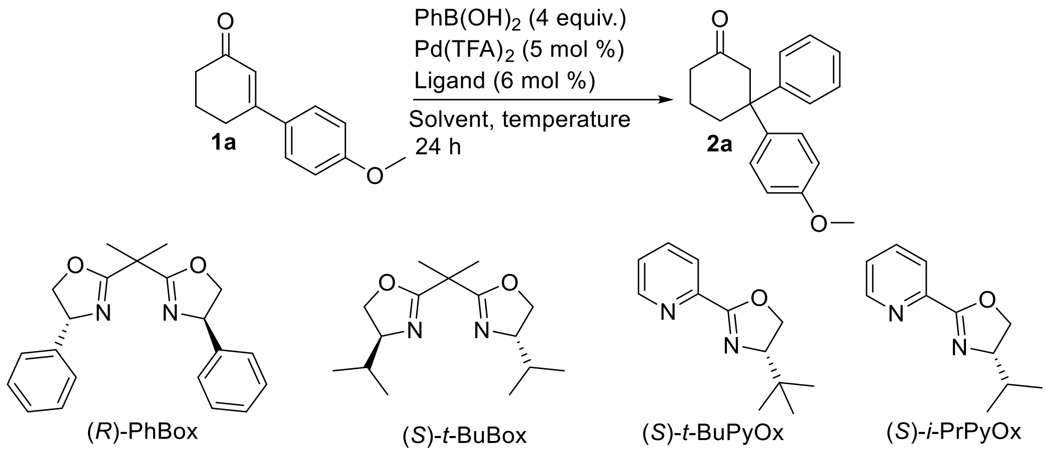
Scheme 1. Enantioselective, transition-metal catalyzed conjugate additions of aryl nucleophiles to *β*-aryl, *β*,*β*-disubstituted enones

We recently reported palladium-catalyzed conjugate additions of bench stable and commercially available arylboronic acids to *β*,*β*-disubstituted enones in aqueous media.[8] This approach enables additions of arylboronic acids to *β*-aryl *β*,*β*-disubstituted cyclic enones to form an array of ketones with bis-benzylic quaternary centers in moderate-to-high yields (54-74%). However, efforts from our group and others[7d] to develop enantioselective variants of these reactions have been limited by modest enantioselectivity in aqueous media, poor reactivity in organic solvents, 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:

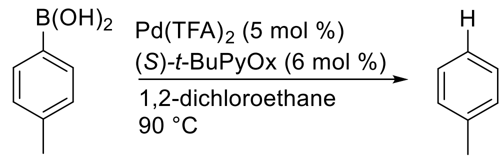
At the outset of our studies, we chose 3-(4-methoxyphenyl)-cyclohexen-2-one **1a** and phenylboronic acid as our model substrates to optimize palladium-catalyzed conjugate addition reactions. Evaluation of chiral, non-racemic pyridine-oxazoline and bisoxazoline ligands showed that reactions conducted in the presence of palladium trifluoroacetate and (*S*)-*t*-BuPyOx formed the ketone product with highest ee (Table 1, entries 1-6) at 80 °C in aq. NaTFA solution. However, when these reactions were conducted in organic solvents, yield and enantioselectivity of the reaction increased (Table 1, entries 7-9). Addition of 4 equiv of phenylboronic acid to **1a** at 90 °C formed 3-(4-methoxyphenyl)-3-(4-phenyl)cyclohexanone **2a** in 39% yield with 91% ee (Table 1, entry 10). However, when the same reaction was conducted in the presence of 1 equiv of phenylboronic acid, the reaction generated the ketone product **2a** in nearly identical 38% yield and 91% ee in 3 h (Table 1, entry 11). This result suggests that there are potential unproductive pathways involved in this reaction. Palladium-catalyzed conjugate additions of arylboronic acids are often plagued by protodeboronation of arylboronic acid that can occur through multiple pathways.[9] To investigate formation of byproducts in this reaction, we conducted control experiments using 4-tolylboronic acid. Indeed, when 4-tolylboronic acid was exposed to the reaction conditions in the absence of enone **1a**, toluene was formed in nearly 75% yield in the presence of the catalyst. However, in the absence of the catalyst, <5% toluene formation of observed (Figure 2).

Table 1. Initial optimization studies



Entry	Temp (°C)	Ligand	Solvent	Yield **2a**[b]	% ee[c]
1	80	(*R*)-PhBox	aq. NaTFA (pH = 8.2)	0	-
2	80	(*S*)-*t*-BuBox	aq. NaTFA (pH = 8.2)	0	-
3	80	(*S*)-*t*-BuPyOx	aq. NaTFA (pH = 8.2)	17	77
4	80	(*S*)-*i*-PrPyOx	aq. NaTFA (pH = 8.2)	21	49
5	100	(*S*)-*t*-BuPyOx	aq. NaTFA (pH = 8.2)	8[d]	-
6	60	(*S*)-*t*-BuPyOx	aq. NaTFA (pH = 8.2)	4	71
7	80	(*S*)-*t*-BuPyOx	1,2-Dichloroethane	34	88
8[e]	80	(*S*)-*t*-BuPyOx	1,2-Dichloroethane	34	91
9[e]	80	(*S*)-*t*-BuPyOx	Methanol	36	84
10[e]	90	(*S*)-*t*-BuPyOx	1,2-Dichloroethane	39	91
11[f]	90	(*S*)-*t*-BuPyOx	1,2-Dichloroethane	38	91

[a]Reaction conditions: 3-(4-Methoxyphenyl)-cyclohex-2-enone (0.30 mmol), phenylboronic acid (1.2 mmol), $Pd(TFA)_2$ (0.015 mmol), ligand (0.018 mmol) run in 0.1 mL of solvent for 24 h. [b]Isolated yields. [c]Determined by chiral HPLC analysis. [d]Yield determined by ^1H NMR using dibromomethane as an internal standard. [e]Reaction run in 0.6 mL of solvent. [f]Reaction conducted with 1 equiv of phenylboronic acid, time = 3 h.



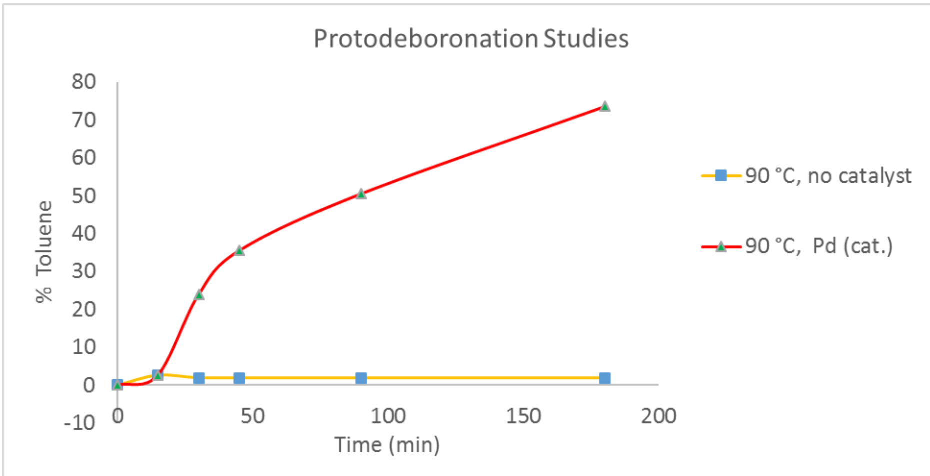


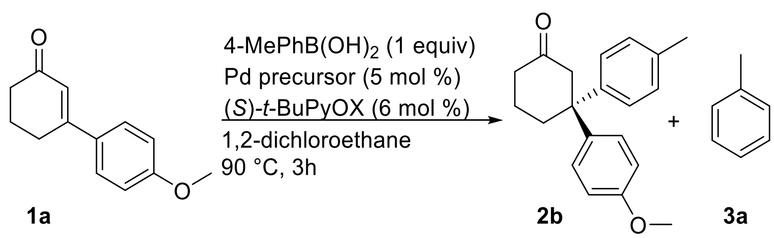
Figure 2. Control experiments: Protodeboronation studies

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 Pd(TFA)$_2$ and (*S*)-*t*-BuPyOx as a model reaction that would facilitate straightforward analysis of reaction products and byproducts. To this point, the addition of 4 equiv of 4-tolyboronic 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 **2b** in nearly identical 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. We further optimized the reaction using 1 equiv of 4-tolylboronic acid.

Evaluation of palladium precursors:

We next evaluated the effect of different palladium precursors on our model reaction. Reactions conducted with $PdCl_2$ and $Pd(CH_3CN)_2Cl_2$ did not form the ketone product **2b**. However, when 12 mol % of AgTFA was added to these reactions, the reactions formed product **2b** in identical yields and ee along with 16-19% toluene. However, reactions conducted with $Pd(TFA)_2$ generated the ketone product in 45% yield and 89% ee along with 26% toluene. Reactions conducted with $Pd(OAc)_2$ generated 7% yield of **2b** and 48% yield of toluene. Thus, we decided to carry out further optimization studies with $Pd(TFA)_2$ as a palladium(II) precursor of choice. Less than 5% of 4,4′-dimethyl-1,1′-biphenyl and 3-(4-methoxyphenyl)-phenol were observed in these reactions.

Table 2. Evaluation of palladium precursors



Entry	pd precursor	yield **2b**[b]	yield **3a**[c]	**2b**/**3a**	% ee[d]
1	$PdCl_2$	0	2	0	-
2	$Pd(CH_3CN)_2Cl_2$	0	4	0	-
3[e]	$PdCl_2$, AgTFA	34	16	2.1:1.0	89
4[e]	$Pd(CH_3CN)_2Cl_2$, AgTFA	35	19	1.8:1.0	90
5	$Pd(TFA)_2$	45	26	1.7:1.0	89
6	$Pd(OAc)_2$	7[b]	48	0.1:1.0	-

[a]Reaction conditions: **1a** (1.0 equiv), Pd precursor (5 mol %), (*S*)-*t*-BuPyOx (6 mol %), 1,2-dichloroethane (0.5 M), 3 h. [b]Isolated yields. [c]Yield determined by gas chromatography. [d]Determined by chiral HPLC analysis. [e]12 mol% AgTFA was used.

Impact of water:

We then studied the impact of water on protodeboronation of arylboronic acids. In the absence of enone **1a** and any external water (neglecting the water present in the moisture in air and from glassware), protodeboronation of 4-tolylboronic acid occurred to form 75% yield of toluene when exposed to the catalyst. We observed a decrease in protodeboronation of 4-tolylboronic acid when additional water was added to the control reaction. When 4-tolylboronic acid was exposed to the catalyst and 5 equiv of water, protodeboronation decreased by nearly 35%. The reaction formed only 14% toluene when 15 equiv of water was used.

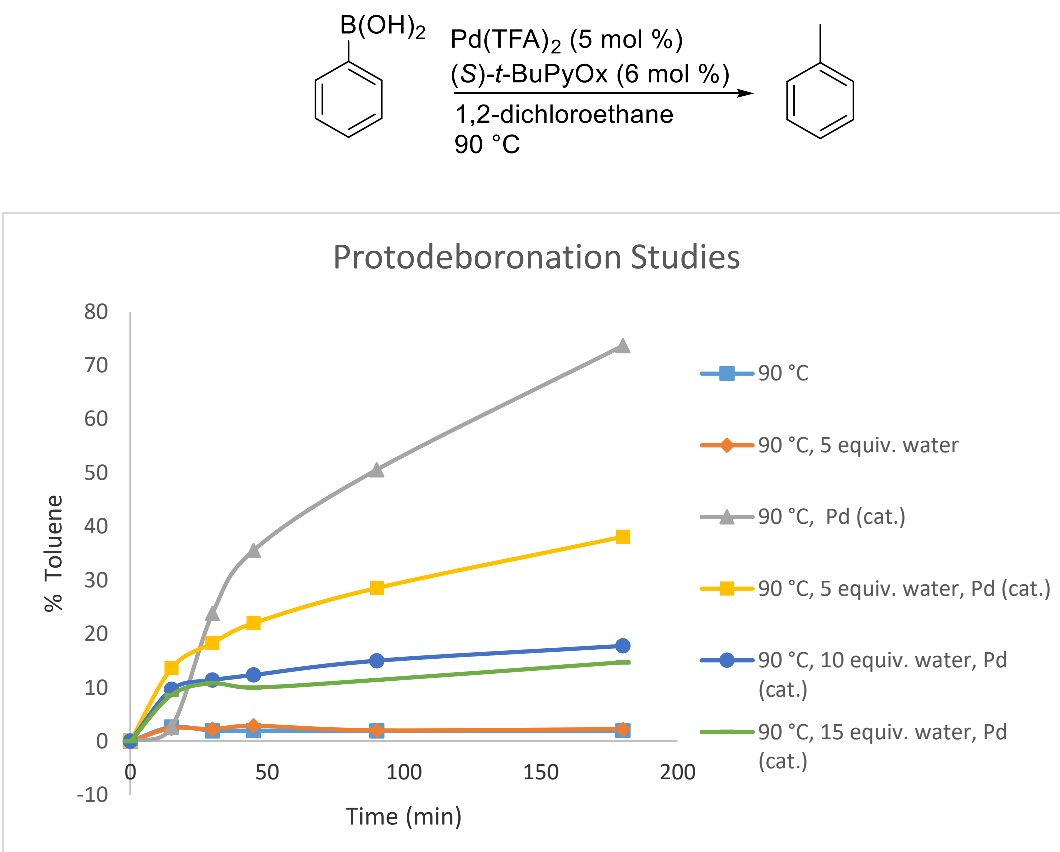
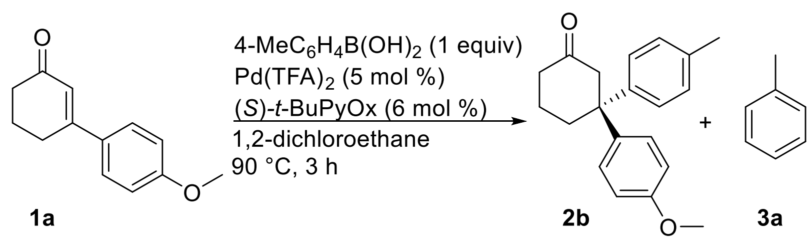


Figure 3. Control experiments: Impact of water on protodeboronation

We then set out to the study palladium-catalyzed conjugate additions of 4-tolylboronic acid to enone **1a** in the presence of water. The results of these experiments are summarized in Table 3. The reaction generated ketone product **2b** in nearly identical yields and ee when the reaction was conducted in the absence of any additional water and in the presence of 5 equiv of water (Entries 1 & 2). We presume the water present in the air and from glassware is sufficient to turn over the active catalyst. This is in accordance with previously reported palladium-catalyzed conjugate addition studies.[7e] A decrease in yield of **2b** and **3a** was observed when the reaction was conducted in the presence of 10 and 15 equiv of water. Less than 5% of 4,4′-dimethyl-1,1′-biphenyl and 3-(4-methoxyphenyl)-phenol were observed in these reactions.

Table 3. Impact of water



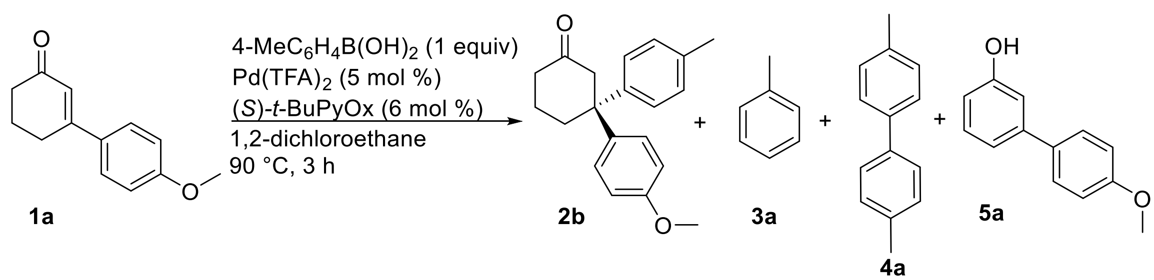
Entry	water (equiv.)	yield **2b**[b]	yield **3a**[c]	**2b**/**3a**	% ee[d]
1	-	45	26	1.7:1.0	89
2	5	47	27	1.7:1.0	87
3	10	26	18	1.4:1.0	87
4	15	28	17	1.6:1.0	87

[a]Reaction conditions: **1a** (1.0 equiv), 4-tolylboronic acid (1.0 equiv), Pd(OTFA)$_2$ (5.0 mol %), (*S*)-*t*-BuPyOx (6.0 mol %), 1,2-dichloroethane (0.5 M), 3 h. [b]Isolated yields. [c]Yield determined by gas chromatography. [d]Determined by chiral HPLC analysis.

Impact of oxygen:

Pd(0) species are known to be inactive towards conjugate additions of arylboronic acids. Formation of Pd(0) species through homocoupling of 4-tolylboronic acid to 4,4′-dimethyl-1,1′-biphenyl **4a** and oxidation of **1a** to 3-(4-methoxyphenyl)-phenol **5a** can have deleterious effect on the efficiency of palladium-catalyzed conjugate addition reactions of arylboronic acids. Our data supports that the oxygen present in the air is sufficient to oxidize Pd(0) back to active Pd(II) catalyst. This is supported by the results presented in Table 4. Reactions conducted in the presence of 1 atm of oxygen and air formed the ketone product **2b** and toluene in nearly identical yields (Entries 1 and 2). However, when the reaction was conducted in an oxygen free environment, the yield of the reaction decreased. The reaction formed the ketone product **2b** in 25% yield (Entry 3).

Table 4. Impact of oxygen



Entry	reaction atmosphere	yield **2b**[b]	yield **3a**[c]	**2b**/**3a**	yield **4a**[c]	yield **5a**[c]	% ee[d]
1	O_2 (1 atm)	42	12	3.2:1.0	1	4	89
2	Air	40	10	3.3:1.0	1	4	89
3[e]	O_2 free	25	8	2.9:1.0	1	2	91

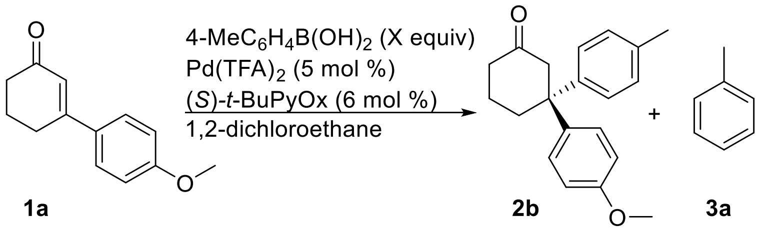
[a]Reaction conditions: **1a** (1.0 equiv), 4-tolylboronic acid (1.0 equiv), $Pd(OTFA)_2$ (5.0 mol %), (*S*)-*t*-BuPyOx (6.0 mol %), 1,2-dichloroethane (0.5 M), 3 h. [b]Isolated yields. [c]Yield determined by gas chromatography. [d]Determined by chiral HPLC analysis. [e]Reaction set up in the glovebox, 1,2-dichloroethane was degassed using freeze-pump-thaw technique before use.

Identification of reaction conditions:

We next studied the impact of reaction temperature on the relative rate of protodeboronation to conjugate addition (Table 5, entries 1-5). The amount of toluene generated decreases with lower reaction temperature. The best ratios of ketone **2b**: toluene **3a** (4.2-4.7:1) are observed at 60-80 °C, and the reactions generate **2b** in 42% yield and 89-91% ee (entries 2-3). Increasing the reaction time (entry 5) and the reaction concentration (entry 6) led to modest improvement in the yield of **2b** without increasing the rate of protodeboronation.

To increase the yield of **2b** to synthetically useful levels, we adopted an iterative addition strategy to maintain low concentrations of tolylboronic acid and hence a low rate of protodeboronation (entries 7-10). 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 **2b** (64-83%) and high enantioselectivities without a dramatic increase in the rate of protodeboronation. We chose to evaluate the scope of the conjugate addition reaction using the conditions identified in entry 10 as a practical combination of reactivity, enantioselectivity, and relative rates of productive versus unproductive reaction pathways.

Table 5. Identification of reaction conditions



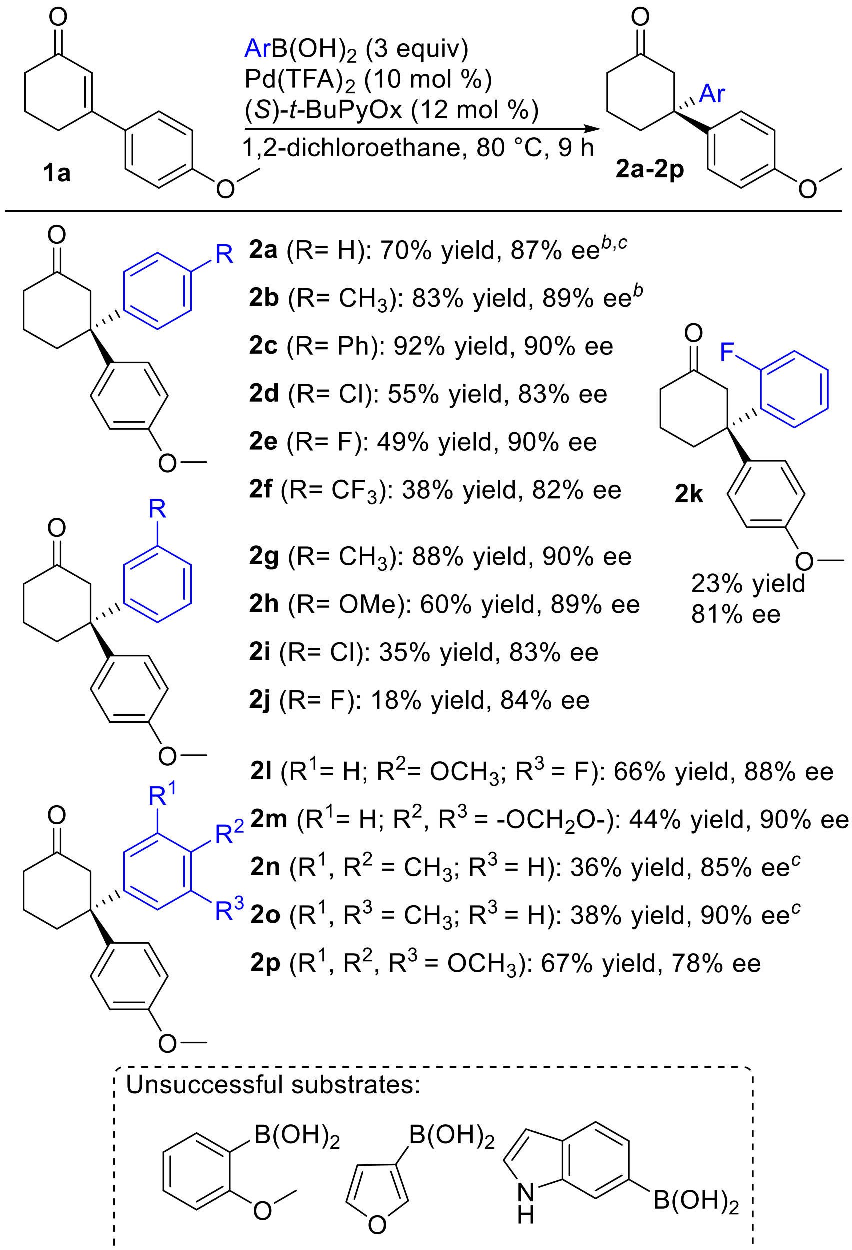
Entry	temp (° C)	X	yield **2b** (%)[b]	yield **3a** (%)[c]	ee (%)[d]
1	90	1	45	25	89
2	80	1	42	10	89
3	60	1	42	9	91
4	40	1	24	6	94
5[e]	60	1	49	10	91
6[e,f]	60	1	55	12	92
7[f,g]	60	2	70	11	91
8[f,g]	60	3	82	14	91
9[f,h]	60	3	64	9	91
10[f,h]	80	3	83	21	89

[a]Reaction conditions: **1a** (1.0 equiv), $Pd(TFA)_2$ (5 mol %), (*S*)-*t*-BuPyOx (6 mol %), 1,2-dichloroethane (0.5 M), 3 h. [b]Isolated yields. [c]GC yield, calculated based on the total number of equiv of tolylboronic acid. [d]Determined by chiral HPLC analysis. [e]Reaction time = 6 h. [f][**1a**] = 2 M. [g]Addition of 4-$MeC_6H_4B(OH)_2$ at 6 h intervals. [h]Addition of 4-$MeC_6H_4B(OH)_2$ at 3 h intervals.

Scope of arylboronic acid:

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 3. Additions of electronically diverse, *para*- and *meta*-substituted arylboronic acids occurred to generate the corresponding ketone products **2a**-**2j** in 18-92% yields with 82-90% enantioselectivities. Additions of *para*-substituted electron-rich, electron-neutral, and halogenated arylboronic acids to **1a** formed ketones **2a**-**e** in moderate-to-high yields (49-92%) with high enantioselectivities (82-90% ee). However, the addition of electron-deficient 4-trifluoromethylphenylboronic acid, which is less nucleophilic, generated **2f** in only 38% yield. Additions of electron-rich *meta*-substituted arylboronic acids to **1a** formed **2g** and **2h** in 60-88% yield with 89-90% ee. In contrast, additions of *meta*- and *ortho*-halogenated arylboronic acids generate the corresponding ketones **2i**-**k** in low yields (18-35%) 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 **2l**-**2p** 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, were unsuccessful under our reaction conditions.[10]

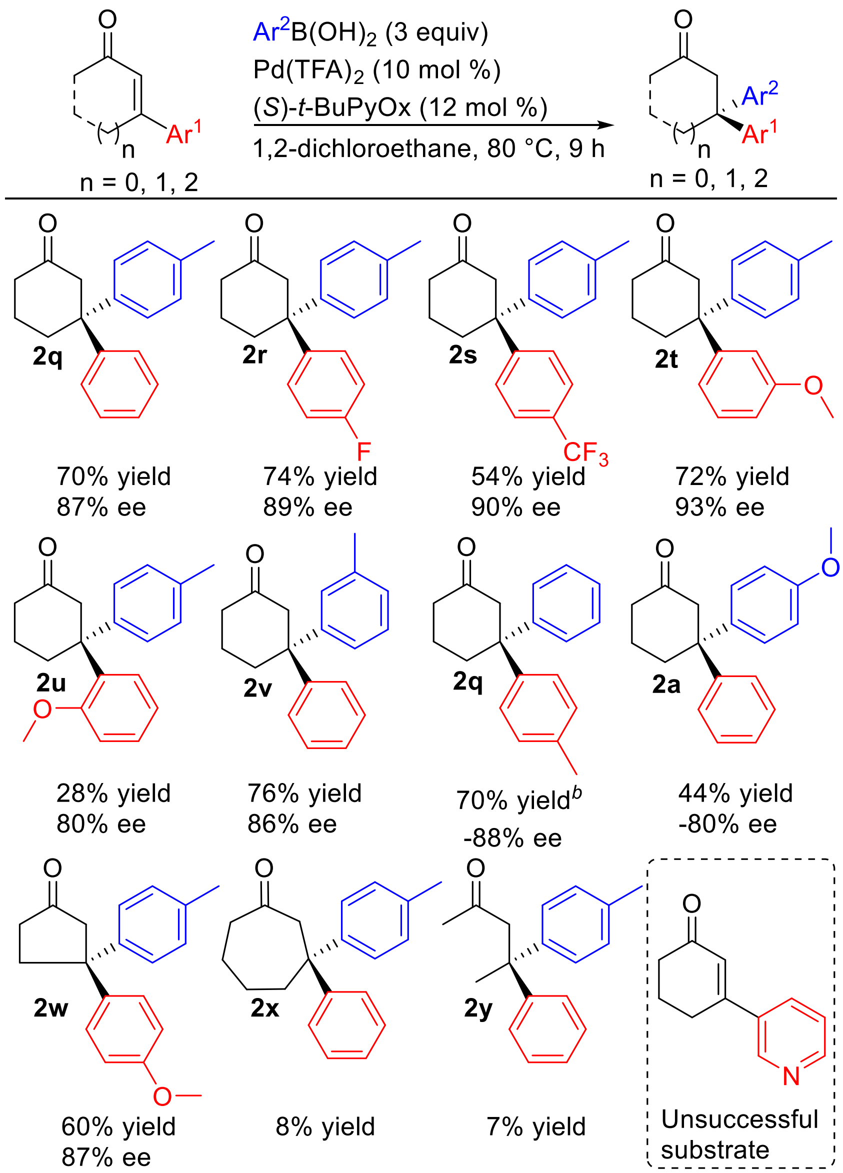


[a]Reaction conditions: **1a** (1 equiv), arylboronic acid (3 equiv), Pd(TFA)$_2$ (10 mol %), (*S*)-*t*-BuPyOx (12 mol %), 1,2-dichloroethane (2 M). [b]Reaction run in the presence of 5 mol % of the palladium catalyst. [c]Reaction performed in the presence of 5 equiv of water.

Scheme 3. Enantioselective Pd-Catalyzed Conjugate Additions of Arylboronic Acids to 3-(4-Methoxyphenyl)-cyclohex-2-enone 1a[a]

Scope of β-aryl β,β-disubstituted enones:

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 4. Additions of 4-tolylboronic acid to 3-arylcyclohex-2-enones containing electron-neutral, halogenated, electron-deficient, and electron-rich aryl groups generated **2q-2t** in good yields (54-74%) with high enantioselectivities (87-93%). Successful formation of **2u** demonstrates that this method allows access to products that are otherwise difficult to access when the same aryl unit is present in arylboronic acid. To demonstrate that *meta*-substituted arylboronic acids can be added to other enones, 3-methylphenylboronic acid was added to 3-phenylcyclohex-2-enone to generate **2v** in 76% yield with 86% ee. Addition of phenylboronic acid to 3-(4-methylphenyl)cyclohex-2-enone, and 4-methoxyphenylboronic acid to 3-phenylcyclohex-2-enone generated enantiomers of **2q** and **2b** in 40-77% yield and 81-88% ee. We then studied 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 **2w** 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 **2x** and **2y** in low yields (7-8%). Addition of 4-tolylboronic acid to 3-pyridylcyclohex-2-enone was unsuccessful. In this reaction, 48% of total 4-tolylboronic acid underwent homocoupling to form 4,4′-dimethyl-1,1′-biphenyl **4a**. The low yield likely results from catalyst deactivation by coordination of the pyridyl nitrogen of enone to the active catalyst.



[a]Reaction conditions: 3-arylcyclohex-2-enone (1 equiv), arylboronic acid (3 equiv), $Pd(TFA)_2$ (10 mol %), (*S*)-*t*-BuPyOx (12 mol %), 1,2-dichloroethane (2 M). [b]Reaction performed in the presence of 5 equiv of water.

Scheme 4. Enantioselective Pd-catalyzed conjugate additions of arylboronic acid to *β*-aryl *β*,*β*-disubstituted enones[a]

Conclusion

In conclusion, we have developed the first example of enantioselective, palladium-catalyzed conjugate additions of arylboronic acids to *β*-aryl *β*,*β*-disubstituted cyclic enones. A palladium(II) catalyst generated *in situ* from $Pd(TFA)_2$ and (*S*)-*t*-BuPyOx catalyzes enantioselective conjugate additions of electronically and structurally different arylboronic acids to a variety of *β*-aryl *β*,*β*-disubstituted enones. We have employed the strategy of iterative addition of arylboronic acid that leads to low rate of protodeboronation which allows additions of a wide array of arylboronic acids to a variety of enones in up to 92% yield and 93% enantioselectivity.

Experimental 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® R*f* system with Redi*Sep* GoldTM 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.

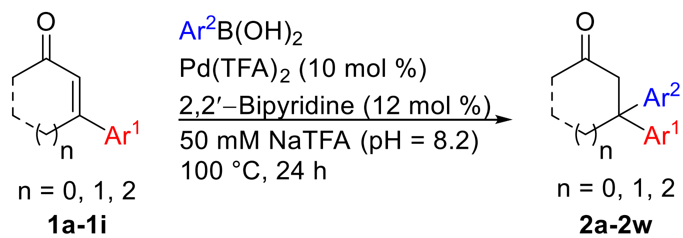
HRMS (ESI) analysis was performed at the Iowa State Chemical Instrumentation Facility on an Agilent 6540 QTOF spectrometer. Optical rotations were measured on an Atago AP-300 automatic polarimeter. HPLC analyses were carried out on a Water Alliance HPLC system with an e2695 Separations Module and a 2489 (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 ($CDCl_3$ = 7.26 ppm for ^1H, and 77.16 ppm for ^{13}C). ^{19}F NMR shifts are reported based on indirect reference to $CDCl_3$.[17] 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 **1c**, 3-(4-methylphenyl)-cyclohex-2-enone **1d**, 3-(4-methoxyphenyl)-cyclopent-2-enone **1e**, 3-(4-trifluoromethylphenyl)-cyclohex-2-enone **1f**, 3-(3-methoxyphenyl)-cyclohex-2-enone **1g**, and 3-(2-methoxyphenyl)-cyclohex-2-enone **1h** were prepared according to a literature procedure.[18] Characterization data for 3-(4-

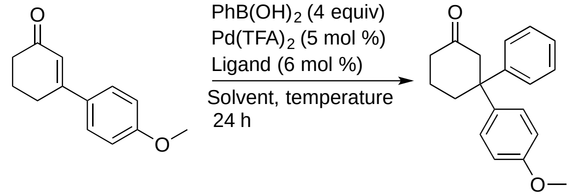
methoxyphenyl)-cyclohex-2-enone **1a**,[19] 3-phenylcyclohex-2-enone **1b**,[18] 3-(4-fluorophenyl)-cyclohex-2-enone **1c**,[20] 3-(4-methylphenyl)-cyclohex-2-enone **1d**,[19] 3-(4-methoxyphenyl)-cyclopent-2-enone **1e**,[21] 3-(4-trifluoromethylphenyl)-cyclohex-2-enone **1f**,[22] 3-(3-methoxyphenyl)-cyclohex-2-enone **1g**,[20] and 3-(2-methoxyphenyl)-cyclohex-2-enone **1h**[20] matched previously reported data. 3-(3-Pyridyl)-cyclohex-2-enone **1i**,[23] (*E*)-4-phenylcyclohept-2-enone **1j**,[22] (*E*)-4-phenylpent-3-en-2-one **1k**[24] 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),[25] (*S*)-4-(*tert*-butyl)-2-(pyridin-2-yl)-4,5-dihydrooxazole ((*S*)-*t*-BuPyOx),[26] and (*S*)-4-isopropyl-2-(pyridin-2-yl)-4,5-dihydrooxazole ((*S*)-*i*-PrPyOx)[27] 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 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.

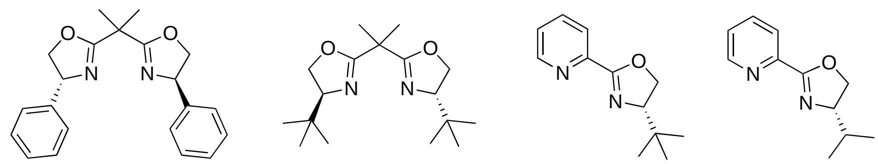
General Procedure A: Pd-Catalyzed Conjugate Additions of Arylboronic Acids to *β*-Aryl, *β*, *β*-Disubstituted Enones to Access Racemic Ketones 2a-2w



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® R*f* system with Redi*Sep* GoldTM columns (hexane:ethyl acetate) to give corresponding ketones. Racemic ketones **2a-2w** were isolated in 18-85% yield.

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





(*R*)-PhBox (*S*)-*t*-BuBox (*S*)-*t*-BuPyOx (*S*)-*i*-PrPyOx

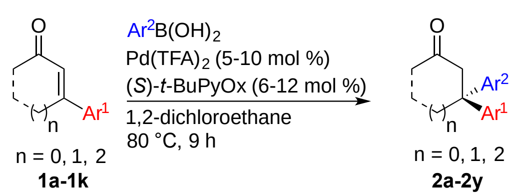
Entry	temp (°C)	ligand	solvent	product[b]	% ee[c]
1	80	(*R*)-PhBox	aq. NaTFA (pH = 8.2)	0	-
2	80	(*S*)-*t*-BuBox	aq. NaTFA (pH = 8.2)	0	-
3	80	(*S*)-*t*-BuPyOx	aq. NaTFA (pH = 8.2)	17	77
4	80	(*S*)-*i*-PrPyOx	aq. NaTFA (pH = 8.2)	21	49
5	100	(*S*)-*t*-BuPyOx	aq. NaTFA (pH = 8.2)	8[d]	-
6	60	(*S*)-*t*-BuPyOx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

[a]Reaction 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. [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]Yield determined by ^1H NMR using dibromomethane as an internal standard. [e]Reaction run in 0.6 mL of solvent. [f]Reaction run in the presence of 30 mol % NH_4PF_6 and 5 equiv. of water.

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

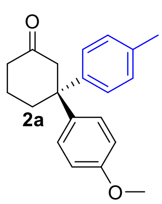
To a 1 dram vial were added $Pd(TFA)_2$ (5.0 mg, 0.015 mmol), ligand (0.018 mmol), 3-(4-methoxyphenyl)-cyclohex-2-enone **1a** (60.7 mg, 0.300 mmol), phenylboronic acid (146 mg, 1.20 mmol), and solvent (0.1 mL). The vial was sealed with a PTFE/silicone-lined septum cap. The reaction mixture was then 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 $CDCl_3$ (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 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-2y



To a 1 dram vial were added $Pd(TFA)_2$ (10 mg, 0.030 mmol), (*S*)-*t*-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 mixed 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 ^{1}H 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® R*f* system with Redi*Sep* GoldTM 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*)-*t*-BuPyOx (3.7 mg, 0.018 mmol) were used to generate the catalyst.

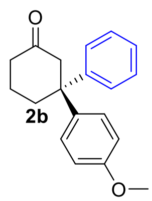
Characterization Data for Ketones 2a-2w



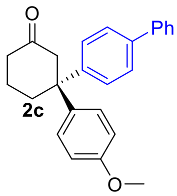
2a

(*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, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): 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*

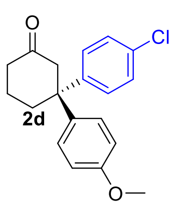
= 7.2 Hz, 1H), 2.90 (d, *J* = 15.6 Hz, 1H), 2.94 (d, *J* = 15.6 Hz, 1H), 3.77 (s, 3H), 6.81 (ddd, *J* = 8.8, 3.2, 2.0 Hz, 2H), 7.08 (s, 4H), 7.12 (ddd, *J* = 8.8, 3.2, 2.0 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 21.0, 21.3, 36.0, 40.9, 49.6, 54.1, 55.3, 113.8, 126.9, 128.1, 129.2, 135.8, 129.6, 144.8, 157.9, 211.1. **HRMS** (ESI): Calcd. for $C_{20}H_{23}O_2^+$ ($[M+H]^+$): 295.1693 Found: 295.1689.



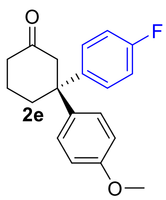
(*S*)-3-(4-methoxyphenyl)-3-phenylcyclohexan-1-one (2b): Prepared according to General Procedure C from 3-(4-methoxyphenyl)cyclohex-2-en-1-one **1a** (60.7 mg, 0.300 mmol) and phenylboronic acid (110 mg, 0.900 mmol) using palladium trifluoroacetate (5.0 mg, 0.015 mmol) and (*S*)-*t*-BuPyOX (3.7 mg, 0.018 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}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}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 $C_{19}H_{21}O_2^+$ ($[M+H]^+$): 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 colorless oil. 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° (*c* 0.73, $CHCl_3$). **^{1}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}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 $C_{25}H_{25}O_2^+$ ($[M+H]^+$): 357.1849 Found: 357.1826.

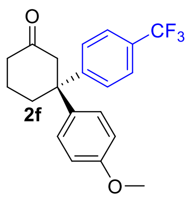


(*R*)-3-(4-chlorophenyl)-3-(4-methoxyphenyl)cyclohexan-1-one (2d): Prepared according to General Procedure C from 3-(4-methoxyphenyl)cyclohex-2-en-1-one **1a** (60.7 mg, 0.300 mmol) and 4-chlorophenylboronic acid (141 mg, 0.900 mmol). The crude product was purified with a CombiFlash system (4 g column, 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° (*c* 1.00, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): 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). **^{13}C NMR** (101 MHz, $CDCl_3$): 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 $C_{19}H_{20}ClO_2^+$ ($[M+H]^+$): 315.1146 Found: 315.1138.

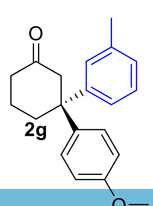

2e

(*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 ^{1}H 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° (*c* 0.61, $CHCl_3$) **^{1}H NMR** (400 MHz, $CDCl_3$): 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). **^{13}C NMR** (101 MHz, $CDCl_3$): 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. **^{19}F NMR** (376 MHz, $CDCl_3$): δ -116.9 (m, 1F). **HRMS** (ESI): Calcd. for $C_{19}H_{20}FO_2^+$ ($[M+H]^+$): 299.1442 Found: 299.1438.

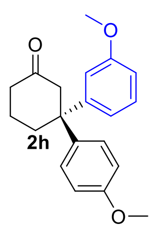


(*S*)-3-(4-methoxyphenyl)-3-(4-(trifluoromethyl)phenyl)cyclohexan-1-one (2f): Prepared according to General Procedure C from 3-(4-methoxyphenyl)cyclohex-2-en-1-one **1a** (60.7 mg, 0.300 mmol) and 4-trifluoromethylphenylboronic acid (171 mg, 0.900 mmol). The crude product was purified with a CombiFlash system (4 g column, 100:0 to 90:10 hexane: EtOAc) to give **2f** (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° (*c* 0.98, $CHCl_3$) **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.66-173 (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). **^{13}C NMR** (151 MHz, $CDCl_3$): 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. **^{19}F NMR** (376 MHz, $CDCl_3$): δ -62.5 (s, 3F). **HRMS** (ESI): Calcd. for $C_{20}H_{20}F_3O_2^+$ ($[M+H]^+$): 349.1410 Found: 349.1385.

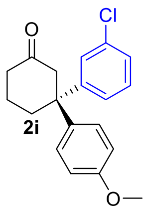


(*R*)-3-(4-methoxyphenyl)-3-(m-tolyl)cyclohexan-1-one (2g): Prepared according to General Procedure C from 3-(4-methoxyphenyl)cyclohex-2-en-1-

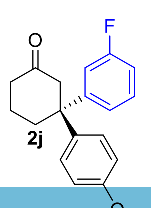
one **1a** (60.7 mg, 0.300 mmol) and 3-tolylboronic acid (122 mg, 0.900 mmol). The crude product was purified with a CombiFlash system (4 g column, 100:0 to 95:5 hexane: EtOAc) to give **2g** (77.7 mg, 0.264 mmol, 88%) as a colorless oil. The enantiomeric excess was determined by HPLC analysis (220 nm, 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° (*c* 0.97, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): 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 $C_{20}H_{23}O_2^+$ ($[M+H]^+$): 295.1693 Found: 295.1694.



(*R*)-3-(3-methoxyphenyl)-3-(4-methoxyphenyl)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-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 **2h** (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. $[\alpha]_D^{26}$ = +10.2° (*c* 0.79, $CHCl_3$). **^{1}H 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 $C_{20}H_{23}O_3^+$ ($[M+H]^+$): 311.1642 Found: 311.1649.

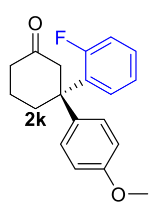


(*R*)-3-(3-chlorophenyl)-3-(4-methoxyphenyl)cyclohexan-1-one (2i): Prepared according to General Procedure C from 3-(4-methoxyphenyl)cyclohex-2-en-1-one **1a** (60.7 mg, 0.300 mmol) and 3-chlorophenylboronic acid (141 mg, 0.900 mmol). The crude product was purified with a CombiFlash system (4 g column, 100:0 to 90:10 hexane: EtOAc) to give **2i** (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° (*c* 0.57, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): 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). **^{13}C NMR** (101 MHz, $CDCl_3$): 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 $C_{19}H_{20}ClO_2^+$ ($[M+H]^+$): 315.1146 Found: 315.1138.



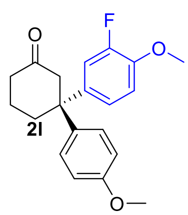
(*R*)-3-(3-fluorophenyl)-3-(4-methoxyphenyl)cyclohexan-1-one (2j): Prepared according to General Procedure C from 3-(4-methoxyphenyl)cyclohex-2-en-1-

one **1a** (60.7 mg, 0.300 mmol) and 3-fluorophenylboronic acid (126 mg, 0.900 mmol). The crude product was purified was purified with a CombiFlash system (4 g column, 100:0 to 95:5 hexane: EtOAc) to give **2j** (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° (*c* 0.31, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): 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). **^{13}C NMR** (151 MHz, $CDCl_3$): 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 $C_{19}H_{20}FO_2^+$ ($[M+H]^+$): 299.1442 Found: 299.1446.

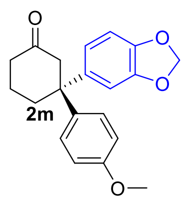


(*R*)-3-(2-fluorophenyl)-3-(4-methoxyphenyl)cyclohexan-1-one (2k): Prepared according to General Procedure C from 3-(4-methoxyphenyl)cyclohex-2-en-1-one **1a** (60.7 mg, 0.300 mmol) and 2-fluorophenylboronic acid (126 mg, 0.900 mmol). The crude product was purified with a CombiFlash system (4 g column, 100:0 to 95:5 hexane: EtOAc) to give **2k** (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. $[\alpha]_D^{21}$ =

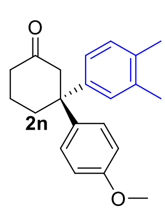
-173.2° (c 0.64, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.57-1.67 (m, 1H), 1.69-1.79 (m, 1H), 2.36 (t, J = 6.8 Hz, 2H), 2.47 (ddd, J = 12.4, 9.2, 2.4 Hz, 1H), 2.75 (ddd, J = 12.4, 9.2, 2.4 Hz, 1H), 2.94 (d, J = 15.6 Hz, 1H), 3.01 (d, J = 15.6 Hz, 1H), 3.77 (s, 3H), 6.81 (ddd, J = 8.8, 3.2, 2.0 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 $C_{19}H_{20}FO_2^+$ ($[M+H]^+$): 299.1442 Found: 299.1441.



(*R*)-3-(3-fluoro-4-methoxyphenyl)-3-(4-methoxyphenyl)cyclohexan-1-one (2l): 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 **2l** (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° (c 0.90, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): 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). **^{13}C NMR** (101 MHz, $CDCl_3$): 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. **^{19}F NMR** (376 MHz, $CDCl_3$): δ -134.4 (m, 1F). **HRMS** (ESI): Calcd. for $C_{20}H_{22}FO_3^+$ ($[M+H]^+$): 329.1547 Found: 329.1553.

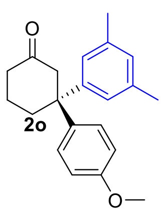

2m

(*R*)-3-(benzo[d][1,3]dioxol-5-yl)-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 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 **2m** (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° (*c* 0.74, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): 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). **^{13}C NMR** (101 MHz, $CDCl_3$): 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 $C_{20}H_{21}O_4^+$ ($[M+H]^+$): 325.1434 Found: 325.1424.


2n

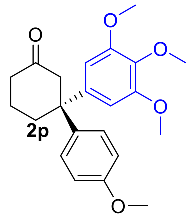
(*R*)-3-(3,4-dimethylphenyl)-3-(4-methoxyphenyl)cyclohexan-1-one (2n): Prepared according to General Procedure C from 3-(4-methoxyphenyl)cyclohex-2-en-1-one **1a** (60.7 mg, 0.300 mmol) and 3,4-

dimethylphenylboronic acid (135 mg, 0.900 mmol). The crude product was purified by flash chromatography (90:10 hexane: EtOAc) to give **2n** (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° (*c* 0.98, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): 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). **^{13}C NMR** (101 MHz, $CDCl_3$): 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 $C_{21}H_{25}O_2^+$ ($[M+H]^+$): 309.1849 Found: 309.1846.

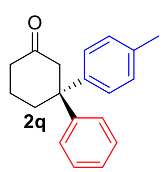


2o

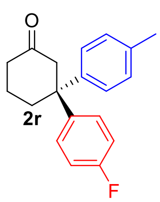
(*R*)-3-(3,5-dimethylphenyl)-3-(4-methoxyphenyl)cyclohexan-1-one (2o): Prepared according to General Procedure C from 3-(4-methoxyphenyl)cyclohex-2-en-1-one **1a** (60.7 mg, 0.300 mmol) and 3,5-dimethylphenylboronic acid (135 mg, 0.900 mmol). The crude product was purified by flash chromatography (90:10 hexane: EtOAc) to give **2o** (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° (*c* 0.66, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): 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). **^{13}C NMR** (101 MHz, $CDCl_3$): 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 $C_{21}H_{25}O_2^+$ ($[M+H]^+$): 309.1849 Found: 309.1848.



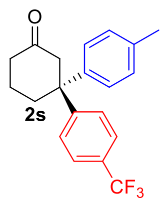
(*R*)-3-(4-methoxyphenyl)-3-(3,4,5-trimethoxyphenyl)cyclohexan-1-one (2p): Prepared according to General Procedure C from 3-(4-methoxyphenyl)cyclohex-2-en-1-one **1a** (60.7 mg, 0.300 mmol) and 3,4,5-trimethoxyphenylboronic acid (191 mg, 0.900 mmol). The crude product was purified with a CombiFlash system (4 g column, 100:0 to 98:2 hexane: EtOAc) to give **2p** (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° (*c* 1.07, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): 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 $C_{22}H_{27}O_5^+$ ($[M+H]^+$): 325.1434 Found: 325.1436.



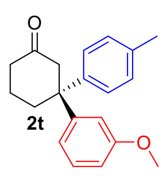
(*R*)-3-phenyl-3-(p-tolyl)cyclohexan-1-one (2q): Prepared according to General Procedure C from 3-phenylcyclohex-2-en-1-one **1b** (51.6 mg, 0.300 mmol) and 4-methylphenylboronic acid (122 mg, 0.900 mmol). The crude product was purified by flash chromatography (90:10 hexane: EtOAc) to give **(*R*)-2q** (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. $[\alpha]_D^{22}$ = -3.7 (*c* 1.09, $CHCl_3$). **^{1}H 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 $C_{19}H_{21}O^+$ ($[M+H]^+$): 265.1587 Found: 265.1593.



(*S*)-3-(4-fluorophenyl)-3-(p-tolyl)cyclohexan-1-one (2r): Prepared according to General Procedure C from 3-(4-fluorophenyl)-cyclohex-2-en-1-one **1c** (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 **2r** (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° (*c* 1.05, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): 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). **^{13}C NMR** (101 MHz, $CDCl_3$): 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. **^{19}F NMR** (376 MHz, $CDCl_3$): δ -116.8 (m, 1F). **HRMS** (ESI): Calcd. for $C_{19}H_{20}FO^+$ ($[M+H]^+$): 283.1493 Found: 283.1496.

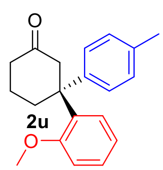


(*S*)-3-(*p*-tolyl)-3-(4-(trifluoromethyl)phenyl)cyclohexan-1-one (2s): Prepared according to General Procedure C from 3-(4-trifluoromethylphenyl)-cyclohex-2-en-1-one **1f** (72.1 mg, 0.300 mmol) and 4-methylphenylboronic acid (122 mg, 0.900 mmol). The crude product was purified with a CombiFlash system (4 g column, 100:0 to 90:10 hexane: EtOAc) to give **2s** (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° (*c* 0.64, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): 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). **^{13}C NMR** (151 MHz, $CDCl_3$): 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. **^{19}F NMR** (376 MHz, $CDCl_3$): δ -62.5 (s, 3F). **HRMS** (ESI): Calcd. for $C_{20}H_{20}F_3O^+$ ($[M+H]^+$): 333.1461 Found: 333.1462.



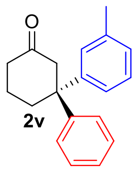
(*S*)-3-(3-methoxyphenyl)-3-(p-tolyl)cyclohexan-1-one (2t): Prepared according to General Procedure C from 3-(3-methoxyphenyl)-cyclohex-2-en-1-one **1g** (60.7 mg, 0.300 mmol) and 4-methylphenylboronic acid (122 mg, 0.900 mmol). The crude product was purified with a CombiFlash system (4 g column, 100:0

to 90:10 hexane: EtOAc) to give **2t** (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° (*c* 0.67, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): 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 $C_{20}H_{23}O_2^+$ ($[M+H]^+$): 295.1693 Found: 295.1691.

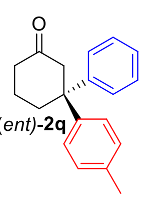


(*S*)-3-(2-methoxyphenyl)-3-(p-tolyl)cyclohexan-1-one (2u): Prepared according to General Procedure C from 3-(2-methoxyphenyl)-cyclohex-2-en-1-one **1h** (60.7 mg, 0.300 mmol) and 4-methylphenylboronic acid (122 mg, 0.900 mmol). The crude product was purified with a CombiFlash system (4 g column, 100:0 to 95:5 hexane: EtOAc) to give **2u** (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. $[\alpha]_D^{19}$ = -175.6° (*c* 0.68, $CHCl_3$). **^{1}H 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

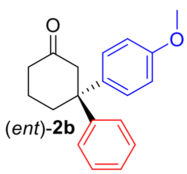
21.0, 21.1, 34.5, 41.0, 49.3, 52.9, 55.4, 113.2, 120.6, 126.4, 127.7, 128.2, 128.6, 135.0, 135.8, 144.9, 157.7, 212.0. **HRMS** (ESI): Calcd. for $C_{20}H_{23}O_2^+$ ($[M+H]^+$): 295.1693 Found: 295.1694.


2v

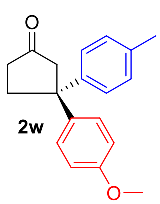
(*R*)-3-phenyl-3-(m-tolyl)cyclohexan-1-one (2v): Prepared according to General Procedure C from 3-phenylcyclohex-2-en-1-one **1b** (51.6 mg, 0.300 mmol) and 3-methylphenylboronic acid (122 mg, 0.900 mmol). The crude product was purified with a CombiFlash system (4 g column, 100:0 to 90:10 hexane: EtOAc) 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° (*c* 0.92, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$): 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 $C_{19}H_{20}O^+$ ($[M+H]^+$): 265.1587 Found: 265.1590.


(*ent*)-2q

(*S*)-3-phenyl-3-(p-tolyl)cyclohexan-1-one (*ent*-2q): Prepared according to General Procedure C from 3-(4-methylphenyl)-cyclohex-2-en-1-one **1d** (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*)-**2q** (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. $[\alpha]_D^{22}$ = +11.6° (*c* 0.86, $CHCl_3$). **^{1}H** and **^{13}C NMR** data matched NMR data for **(*R*)-2q**. **HRMS** (ESI): Calcd. for $C_{19}H_{21}O^+$ ($[M+H]^+$): 265.1587 Found: 265.1584.



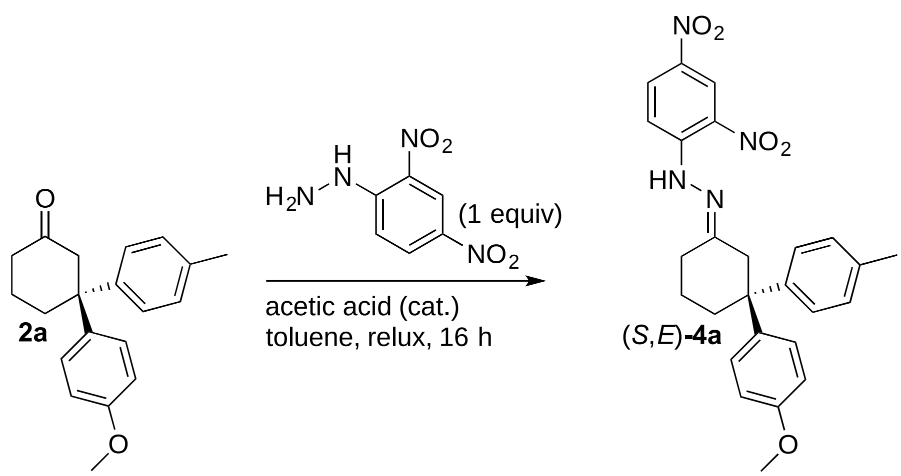
(*R*)-3-(4-methoxyphenyl)-3-phenylcyclohexan-1-one (*ent*-2a): Prepared according to General Procedure C from 3-phenylcyclohex-2-en-1-one **1b** (51.6 mg, 0.300 mmol) and 4-methoxyphenylboronic acid (137 mg, 0.900 mmol). The crude product was purified with a CombiFlash system (4 g column, 100:0 to 90:10 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. $[\alpha]_D^{22}$ = -8.3° (*c* 0.24, $CHCl_3$). **^{1}H** and **^{13}C** NMR data matched NMR data for **(*S*)-2b**. **HRMS** (ESI): Calcd. for $C_{19}H_{21}O_2^+$ ($[M+H]^+$): 281.1536 Found: 281.1526.



(*S*)-3-(4-methoxyphenyl)-3-(p-tolyl)cyclopentan-1-one (2w): Prepared according to General Procedure C from 3-(4-methoxyphenyl)-cyclopent-2-en-1-one **1e** (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 **2w** (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° (*c* 1.06, $CHCl_3$). **^{1}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}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 $C_{19}H_{21}O_2^+$ ($[M+H]^+$): 281.1536 Found: 281.1542.

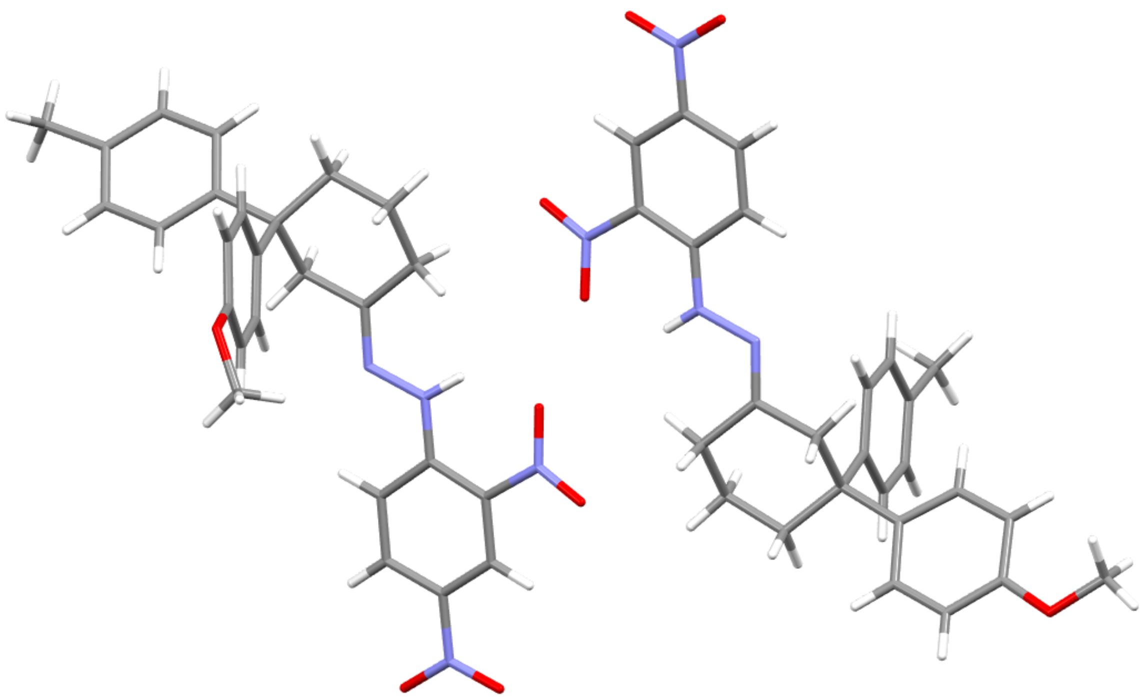
Synthesis of (*S*,*E*)-1-(2,4-dinitrophenyl)-2-(3-(4-methoxyphenyl)-3-(*p*-tolyl)cyclohexylidene)hydrazine ((*S*,*E*)-4a)



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, $CHCl_3$). **^{1}H NMR** of (*S*,*E*)-**4a** (400 MHz, $CDCl_3$)**:** 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). **^{13}C NMR** of (*S*,*E*)-**4a** (101 MHz, $CDCl_3$)**:** 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 $C_{26}H_{27}N_4O_5^+$ ($[M+H]^+$): 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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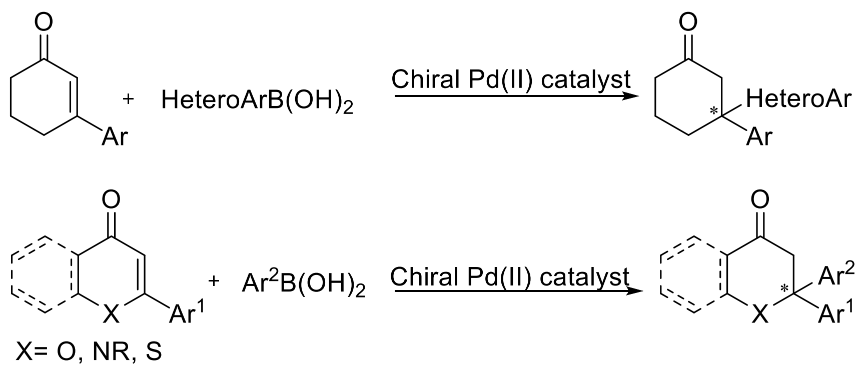
CHAPTER 3

CONCLUSION

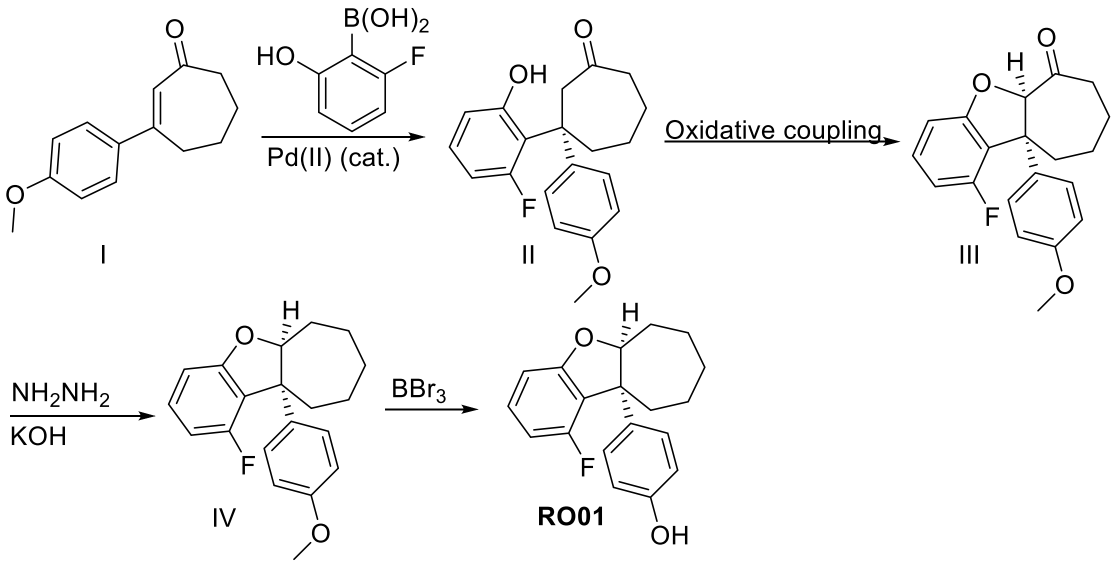
In conclusion, this thesis describes the development of enantioselective, palladium(II)-catalyzed conjugate additions of arylboronic acids to form compounds containing bis-benzylic quaternary stereocenters. Prior to this work, enantioselective, palladium-catalyzed conjugate additions of arylboronic acids to *β*-aryl *β*,*β*-disubstituted cyclic enones were unsuccessful. The thesis describes the studies involved in the development of enantioselective, palladium-catalyzed conjugate additions of arylboronic acids to *β*-aryl *β*,*β*-disubstituted cyclic enones. This includes identification of reaction conditions by studying impact of chiral ligands, solvents, reaction atmosphere and temperature on palladium-catalyzed conjugate additions of arylboronic acids to *β*-aryl *β*,*β*-disubstituted enones. We also studied impact of water, reaction atmosphere and temperature on protodeboronation of arylboronic acids which is a major undesired pathway in palladium-catalyzed conjugate additions of arylboronic acids. We adopted iterative addition strategy to maintain low concentration of arylboronic acids and hence a low rate of protodeboronation. This strategy allows us to access different ketone products containing bis-benzylic quaternary stereocenters by additions of a wide array of arylboronic acids to a variety of *β*-aryl *β*,*β*-disubstituted enones in up to 92% yield and 93% enantioselectivity.

However, the method developed has some limitations. Additions of *ortho*-substituted arylboronic acids and heteroarylboronic acids, which are more susceptible to protodeboronation, were usually low yielding and unsuccessful in some cases. This method, however, allows access to ketone products containing *ortho*-substitution on aryl groups by additions of arylboronic acids to *ortho*-substituted *β*-aryl *β*,*β*-disubstituted enones. Additions of arylboronic acid to *β*-aryl *β*,*β*-disubstituted cyclohepten-2-one and acyclic enone were low yielding. Further work should be done to overcome these limitations. A catalyst system which allows faster conjugate addition reactions and suppresses protodeboronation pathways is desirable to allow additions of challenging substrates such as *ortho*-substituted arylboronic acids and heteroarylboronic acids. Future plan involves studies towards development of enantioselective additions of arylboronic acids to heterocyclic electrophiles containing aryl substitution at 2-position.



Scheme 1. Future directions

Future plan includes synthesis of estrogen receptor *β* antagonist **RO01**. After enantioselective, palladium-catalyzed conjugate additions of *ortho*-substituted arylboronic acids to *β*-aryl *β*,*β*-disubstituted cyclohepten-2-one are developed, the reaction can be used as a key step to access ketone product II. Current development in photoredox catalysis involving nickel-mediated alcohol coupling allows bond formation between arylbromides and aliphatic alcohols.[1] However, oxidative coupling between aryl alcohols and enolates is unprecedented. We propose to develop a diastereoselective, photoredox, nickel-mediated oxidative coupling between aryl alcohols and enolates to give dihydrobenzofuarn fused ketone III. A sequence of Wolff Kishner reduction of III, followed by demethylation of IV can yield **RO01**.



Scheme 2: Proposed synthetic route for synthesis of **RO01**

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