Part I: Asymmetric intermolecular Heck reaction
of aryl halides.

Part II: Asymmetric addition of organoboroxines
to common enones and imines using copper
catalysts

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**NANYANG
TECHNOLOGICAL
UNIVERSITY**

**Part I: Asymmetric Intermolecular Heck Reaction of Aryl
Halides**

**Part II: Asymmetric Addition of Organoboroxines to Common
Enones and Imines Using Copper Catalysts**

Wu Chunlin

SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCE

**A thesis submitted to the Nanyang Technological University in
fulfillment of the requirement for the degree of Doctor of Philosophy
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Abstract

We developed a mild reaction for asymmetric Heck reaction of aryl bromides and chlorides with cyclic olefins. This is the first time that asymmetric intermolecular Heck reactions of aryl halides were realized in high *ee*. Ammonium salts and alcohol solvent were employed as hydrogen-bonding donors to permit the dissociation of halides from neutral palladium complex, so as to open the door to the enantioselective cationic pathway.

We developed a mild reaction for enantioselective conjugate addition of organoboron reagents to acyclic enones. A diverse set of acyclic enones bearing alkyl, aryl and heteroaryl groups produced the conjugate adducts in high yields and enantioselectivities. Furthermore, a rare 1,4-insertion pathway through a six-membered cyclic transition state was identified, which was supported by both DFT calculation and natural-abundance C13 KIE experiments. We then successfully applied the reaction system to the enantioselective addition of organoboron reagents to aldimines. The products of chiral amines are important structures in many drugs and drug candidates. The scope of aryl aldimines and arylboroxines were satisfactory and in most cases, >90% *ee* was obtained.

ABBREVIATIONS

°C	degree centigrade
Ac	acetate
AIBN	2,2'-azo <i>bisisobutyronitrile</i>
Ar	aryl (substituted aromatic ring)
(<i>R</i>)-BINAP	(<i>R</i>)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Boc	<i>tert</i> -butyloxycarbonyl
<i>t</i> Bu	<i>t</i> -butyl
Bu	butyl
Bn	benzyl
Bz	benzoyl
conv.	conversion
dba	dibenzylideneacetone
DCM	dichloromethane
DFT	density functional theory
DMA	<i>N,N</i> -dimethylacetamide
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMSO	Dimethylsulfoxide
ee	enantiomeric excess
Equiv	equivalent
ESI	electrospray ionization
GC	gas chromatography

h	hour
HRMS	high-resolution mass spectrometry
HPLC	high performance liquid chromatography
Hz	hertz
IPA	isopropyl alcohol
ⁱ Pr	Isopropyl
<i>J</i>	coupling constant
KIE	kinetic isotope effect
LDA	lithium diisopropylamide
<i>m</i> -CPBA	<i>meta</i> -chloroperbenzoic acid
mg	milligram
mL	millilitre
mmol	millimole
Ms	mesyl (methanesulfonyl)
NBS	<i>N</i> -bromosuccinimide
NMR	nuclear magnetic resonance
OAc	acetocy
OTf	trifluoromethanesulfonate
Ph	phenyl
<i>p</i> -TsOH	<i>p</i> -toluenesulfonic acid
PhMe / Tol.	toluene
proton sponge	1,8-Bis(dimethylamino)naphthalene
SET	single electron transfer
TBAB	tetra- <i>n</i> -butylammonium bromide
THF	tetrahydrofuran

Ts	<i>p</i> -toluenesulfonyl
TLC	thin layer chromatography
TMS	trimethylsilyl
α	alpha
β	beta
γ	gamma
μ	micro
π	pi
η	eta
ω	omega
σ	sigma

Chapter 1

Asymmetric Intermolecular Heck Reaction of Aryl Halide

1.1 Introduction of Heck reaction

Palladium-catalyzed Heck reaction is widely used in synthetic chemistry.¹⁻⁷ In the reaction, aryl or alkenyl halides and sulfonates couple with alkenes in the presence of palladium catalysts to form new C-C bonds. It can tolerate water and functional groups such as alcohols, aldehydes, ketones and amides. The reaction is not only limited to activated olefins. Some simple olefins also react under the Heck condition. It was used in total syntheses of several natural products and drug candidates.^{8,9} For example, Waite and Mason at Pfizer used two Heck reactions in their synthesis of a potent thromboxane receptor antagonist for the treatment of asthma, unstable angina, deep vein thrombosis, and coronary atherosclerosis (Scheme 1.1).¹⁰

Scheme 1.1 Example of Heck reaction in large-scale application

Since the first report in 1989, asymmetric Heck reaction has been well developed and used in the synthesis of some natural products.^{2,3,8,11} Chiral supporting ligands, such as BINAP, PHOX and bisphosphine monoxides, were successfully applied in asymmetric Heck reaction.

1.1.1 Mechanism of asymmetric Heck reaction

The catalytic cycle of asymmetric Heck reaction is shown in Scheme 1.2, including

oxidative addition, olefin insertion, β -hydride elimination and deprotonation of palladium hydride.^{12,13}

The first step is oxidative addition of an aryl or alkenyl triflate to a Pd(0) complex. On aryl group, electron-donating groups slow down oxidative addition, while electron-withdrawing groups accelerate this step.

Olefin binding to the vacant site and insertion follows oxidative addition. *Syn* insertion generates an alkylpalladium species.

Scheme 1.2 A catalytic cycle of the Heck reaction of ArOTf

The insertion step can proceed through a neutral or cationic pathway, depending on different reaction conditions.¹⁴ The cationic pathway begins with dissociation of weakly coordinating ligand X⁻ (such as triflate ion) from ArPdX complex, and then the alkene can coordinate to the cationic complex and undergo migratory insertion to form the alkyl palladium complex.

When the ligand X is a halide ion, it is possible to use silver and thallium salts to promote halide ionization and generate cationic arylpalladium complexes.¹⁵⁻¹⁸ The silver salts may cause oxidation of phosphine or compete with palladium for binding of phosphines. The thallium salts were extremely neurologically toxic. It is not advisable to use them in general.

The third step of the catalytic cycle is *syn* β -hydride elimination. One issue is competing β -hydride elimination at different positions. However, in cyclic alkenes, anti β -hydride elimination at the benzylic position is impossible in general.

The last step of the catalytic cycle is the deprotonation of the palladium hydride species.

The acidity of the palladium hydride decreases as more electron-donating phosphine coordinates to the palladium center. If the palladium hydride is not quickly cleared by the base, it can cause extensive olefin isomerization in Heck products.

1.1.2 Intermolecular asymmetric Heck reaction

Hayashi and co-workers reported the first example of intermolecular asymmetric Heck reaction between phenyl triflate and 2,3-dihydrofuran using (*R*)-BINAP ligand.^{19,20} However, the major isomer was derived from olefin isomerization of the initial Heck product. In the last two decades, many phosphorus ligands were developed and tested in search of a general ligand for the Heck reaction.

Scheme 1.3 Asymmetric Heck reaction catalyzed by (*R*)-BINAP

It is worthwhile to point out that under the conditions in Scheme 1.3, the palladium hydride complex of BINAP cannot be removed quickly by the base in the reaction mixture, which thus caused extensive isomerization of the C=C bond towards a more stable position.²¹⁻²³ The asymmetric Heck reaction of other olefins has also been catalyzed by this Pd/BINAP system.²⁴⁻²⁹ Many chiral biphosphine ligands have been used as chiral ligands in the asymmetric Heck reaction.³⁰⁻⁴³

Scheme 1.4 Product isomerization in the asymmetric Heck reaction

In 1996, Pfaltz group applied a mixed phosphine-oxazoline ligand (*t*-Bu-PHOX) to asymmetric Heck reaction of 2,3-dihydrofuran and phenyl triflate.⁴⁴ They obtained the immediate Heck product in good yield and excellent enantioselectivity (97%). Unfortunately, the catalytic turnover was very low and usually several days were needed to reach good conversion. Later, the *t*-Bu-PHOX ligand was applied to more challenging substrates such as cyclohexene and 3,4-dihydropyran, but only around 80% *ee* was obtained.^{27,28,45}

Later, many related *P,N*-mixed ligands were developed, but few have been widely used in the asymmetric Heck reaction.⁴⁶⁻⁵⁵

Scheme 1.5 Asymmetric Heck reaction catalyzed by ligand *t*-Bu-PHOX

Hou group performed DFT calculation and compared the olefin insertion step of both

cis and *trans* complexes ligated by a phosphine-oxazoline ligand.⁴⁸ The *trans* insertion pathway, wherein the phosphine ligand is *trans* to the *Pd*-aryl ligand, was found to be energetically more favorable than the *cis* pathway because of the lower energy gap between corresponding precursor complex (CP) and transition states (TS). The *trans* CP was destabilized, as compared to the *cis* complex, because the *Pd*-aryl bond in the former was weakened by *trans* influence of the phosphine. At the same time, the *trans* mode of the TS is much more stable than the *cis* mode.

Scheme 1.6 Reaction pathway to the *P,N*-ligand catalyzed asymmetric Heck reaction

Pàmies and Diéguez group developed phosphite-oxazoline ligands for metal catalysis.⁴⁶ These catalysts were much more active than phosphine-oxazoline catalysts. High *ee* was often secured by empirical change of ligand structure. When the reactions were set up under microwave conditions at *higher temperature*, the reaction time decreased significantly and excellent *ee* was still obtained.

Scheme 1.7 Asymmetric Heck reaction catalyzed by phosphite-oxazoline ligands

In 2011, Oestreich group reported a new type of chiral ligand, BINAP monoxide, BINAP(O) in the intermolecular Heck reaction.⁵⁶ Under these conditions,

2,3-dihydrofuran coupled with phenyl triflate to give a product in 92% *ee*, however, the BINAP(O) ligand did not generally give high *ee* for other substrates. For example, 84% *ee* was obtained in the reaction with cyclopentene.

Scheme 1.8 Asymmetric Heck reaction catalyzed by (R)-BINAP(O)

Around the same time, Dr. Jian Hu in our group also discovered that BINAP(O) was much more active than the parent bisphosphine itself. We also noticed that the *ee* was not high generally when Pd/ BINAP(O) catalyst was applied to other aryl triflates and other cyclic olefins.

Later, Dr. Hu found that another chiral bisphosphine monoxide, (R)-Xyl-SDP(O), built on a spiro-diindanyl backbone, catalyzed the Heck reaction with generality.⁵⁷ The reaction was applied to various olefins, even the less reactive ones such as cyclohexene and 3,4-dihydro-pyran. The bisphosphine monoxides are less donating than corresponding bisphosphines. As a result, the palladium complexes are more electron-deficient, which accelerates both insertion of olefins and deprotonation of the palladium hydride. The latter helped to minimize the double bond migration.

Scheme 1.9 Asymmetric Heck reaction catalyzed by spiro-bisphosphine monoxide ligand

The X-ray diffractational study of an arylpalladium halide ligated with (R)-Xyl-SDP(O), *P,O*-chelation of the ligand was observed.⁵⁷ Based on DFT calculations on olefin insertion of the cationic arylpalladium(II) complex, they deduced that the *P,O*-chelation was crucial to creating good chiral environment for highly asymmetric olefin insertion.^{57,58} BINAP oxide, BINAP(O) binds to Pd(0) centers via both monodentate mode and *P,arene*-chelation in complex [BINAP(O)]₂Pd(0), as reported by Grushin et al.⁵⁹ These alternative bonding modes afforded much less stable arylpalladium(II) complexes than the *P,O*-chelation in our DFT calculations due to Lewis acidic nature of palladium(II) centers.⁵⁷ They thus do not propose a possibility that the bisphosphine oxide ligand binds to the Lewis acidic arylpalladium(II) center in a hemilabile manner.

Figure 1.1 Left: ORTEP of *cis*-complex $\{[(R)\text{-Xyl-SDP(O)}](p\text{-CF}_3\text{-Phenyl})(\text{I})\text{Pd}^{\text{II}}\}$ with 50% thermal ellipsoid probability and hydrogen omitted for clarity. Right: front view of the complex with bisphosphine oxide in a space-filling model⁵⁷

Dr Yunpeng Lu at NTU conducted DFT calculation of insertion pathways of the Heck reaction. Ground states in *trans* pathways were 7-9 kcal/mol higher in energy than *cis* complexes, depending on the orientation of the olefin. The *trans* complexes were destabilized by *trans* positioning of two strongly σ -donating phosphine and an anionic aryl group (*trans* influence). In addition, the *trans* pathway would lead to the “wrong” (*R*)-isomer as the major. In comparison, the *cis* pathways were consistent with experimental results. An energy gap of 2.6 kcal/mol between two insertion transition states **TS(a)** and **TS(b)** agreed well with observed 99% *ee*. In the unfavorable transition state **TS(b)** in the *cis* pathway, close contact between the bound olefin and the phosphine oxide fragment was identified.⁵⁷

Figure 1.2 Calculated transition states, **TS(a)** (left) and **TS(b)** (right), for insertion of 2,3-dihydrofuran into cationic *cis*-complex $\{[(R)\text{-Xyl-SDP(O)}](p\text{-CF}_3\text{-Phenyl})\text{Pd}^{\text{II}}\}$. The B3LYP method was used and a polarizable continuum model accounted for the solvent effect in 1,4-dioxane⁵⁷

In 2012, Correia group developed the first enantioselective Heck-Matsuda reaction using aryldiazonium salts as electrophiles.⁶⁰ A chiral bisoxazoline ligand catalyzed the model reaction to produce the product in 84% *ee*. Phosphine ligands cannot be used due to its side reaction with aryldiazonium salts.

Scheme 1.10 Enantioselective Heck-Matsuda reaction developed by Correia group

In 2015, Correia group applied the Heck-Matsuda reaction and produced the quaternary stereogenic centers.⁶¹ The new type of ligand, pyrimidine-oxazoline was applied to

synthesis of a calcium channel blocker, (*R*)-verapamil.

Scheme 1.11 Formation of quaternary stereogenic centers through enantioselective Heck-Matsuda reaction

In 2012, Sigman group used a chiral pyridine-oxazoline ligand in asymmetric Heck reaction of aryl diazonium salts and acyclic alkenyl alcohols (Scheme 1.12).⁶² The mixed *N,N*-ligands are less donating than bisoxazolines ligands which helped to promote olefin insertion step and clearing of palladium hydride. The regioselective insertion of the olefin was caused by inductive effect of the oxygen atom of the alcohol. It polarized the C=C bond, so that the distant carbon of the olefin can better stabilize the partial positive charge in the insertion transition state.

Scheme 1.12 Enantioselective Matsuda- Heck reaction

Although asymmetric Heck reactions of aryl and vinyl triflates were well studied, there

was no example of asymmetric Heck reaction with other carbon electrophiles such as benzylic ones. In 2012, Dr. Zhigang Yang in our group solved this problem by using phosphoramidite ligands.⁶³ Excellent *ee* values were obtained under mild conditions. 2,3-Dihydrofuran, cyclopentene and *N*-Boc-2,3-dihydropyrrole reacted smoothly with the benzyl electrophile. He found that it was crucial to use trifluoroacetate as a leaving group to obtain high *ee*, because it can dissociate from the palladium center to generate a cationic benzylpalladium species. We believe two monodentate ligands bind in a *cis* fashion to create a good chiral pocket for asymmetric insertion of olefin.

Scheme 1.13 Asymmetric Heck reaction of benzylic electrophiles

1.1.3. Asymmetric intramolecular Heck reaction of aryl and alkenyl halides

In 1989, Shibasaki et al. reported the first intramolecular asymmetric Heck reaction of alkenyl iodides to form chiral decalin derivatives.⁶⁴ Around 80% *ee* values were obtained in the presence of silver salts. The latter acted as halide abstractors to promote the cationic pathway.⁶⁵

Scheme 1.14 Intramolecular asymmetric Heck reaction

In 1992, Shibasaki applied the cyclization reaction to asymmetric synthesis of hydrindans.⁶⁶ Ag_3PO_4 was used and 83% *ee* was obtained. The Heck product can be transformed to (-)-Oppositol and (-)-Prepinnaterpene.⁶⁷

Scheme 1.15 Intramolecular asymmetric Heck reaction to synthesize hydrindans

Overman group reported intramolecular asymmetric Heck reaction can be applied to *ortho*-iodoanilide bearing a cyclohexenyl ring on the amide. The cyclized product was obtained in moderate *ee* value (71% *ee*) in the presence of a silver salt. Notably, the reaction gave the opposite enantiomer when 1,2,2,6,6-pentamethylpiperidine (PMP) was used as the base.^{68,69} In 2006, Curran group pointed out an additional complication in the cyclization. Slow rotation of the C-N bond of aryl amides may give products of opposite configuration under different conditions and temperature.

Scheme 1.16 Intermolecular asymmetric Heck reaction to synthesize quaternary carbon centers molecules

1.2 Use of hydrogen bonding in regioselective Heck reaction of aryl halides

In common organic solvents, neutral arylpalladium halides ligated by a bisphosphine tend to dissociate one arm of a bisphosphine under forcing conditions. Subsequent insertion of aliphatic terminal olefins and vinyl ethers was not regioselective at all.^{19,65}

In 2006, Xiao's group found that aryl bromide and aryl chloride reacted smoothly with electron-rich vinyl esters and gave branched Heck products in the presence of trialkylammonium salts.⁷⁰ The salt $[\text{HNEt}_3][\text{BF}_4]$ was crucial for high yield and high selectivity. It promoted the dissociation of bromide ion from the neutral complex $[\text{Pd}(\text{dppp})(\text{Ph})\text{Br}]$ to produce a cationic palladium complex for insertion.

Scheme 1.17 $[\text{HNEt}_3][\text{BF}_4]$ acts as hydrogen-bonding donor in the Heck reaction.

When the reaction was performed in ethylene glycol, the salt $[\text{HNEt}_3][\text{BF}_4]$ was unnecessary. The hydrogen bonding offered by ethylene glycol can also promote the reaction via the cationic pathway.⁷¹ Even unactivated aryl chlorides reacted well under the reaction condition.

Scheme 1.18 ethylene glycol acts as hydrogen-bonding donor in Heck reaction

Liena Qin in our group in 2012 adopted Xiao's hydrogen bonding strategy and applied in selective Heck reaction of aliphatic olefins and aryl halides.^{72,73} Both alcohol solvents and alkylammonium salts were necessary to promote halide dissociation from neutral

arylpalladium complexes. The hypothesis was confirmed by DFT calculation performed by Prof. Hajime Hirao at NTU.

Scheme 1.19 MeOH and R_3NH^+ act as hydrogen-bonding donors in Heck reaction

1.3 Intermolecular asymmetric Heck reaction of aryl halide

Intermolecular asymmetric Heck reaction of aryl and alkenyl triflates and cyclic olefins was well studied. However, aryl and alkenyl triflates are very expensive to make. It will be desirable from a practical standpoint if the halides can be directly used as electrophiles in asymmetric Heck reaction. Prior to our study, no example of intermolecular asymmetric Heck reactions of aryl halides was reported.

As mentioned above, in asymmetric Heck reaction, the cationic pathway is required to obtain high enantioselectivity. In the neutral pathway, the dissociation of one arm of a bisphosphine is more likely in common organic solvent than dissociation of halide ions. It makes it difficult to achieve asymmetric insertion of olefin in common organic solvents. In our experience, common halide abstractors, silver and thallium salts did not give satisfactory results. Silver salts can cause oxidation of phosphine ligands. Plus, thallium salts are extremely toxic. We proposed to add hydrogen bonding donors, such as alkylammonium salts and use alcoholic solvents, so as to promote dissociation of halides

from neutral complex $[\text{Pd}(\text{L})_2(\text{Aryl})\text{X}]$ to form cationic palladium complex.

Scheme 1.20 A proposed pathway for asymmetric Heck reaction of aryl halides

1.3.1 Condition optimization

We chose 4-bromotoluene and 2,3-dihydrofuran as model substrates for the intermolecular Heck reaction to optimize the reaction condition. We studied different types of ligands in Table 1.1. According to our hypothesis, we chose ethylene glycol as the alcoholic solvent. Three equivalents of *N,N*-diisopropylethylamine was used as base and one equivalent *p*-nitrobenzoic acid was used to react with the base to in situ generate trialkylammonium salt. The latter can act as a hydrogen bond donor.

Scheme 1.21 Effect of ligand

When chiral *P,N*-ligands (*S*)-*t*Bu-PHOX and (*S*)-Ph-PHOX were used, low yield and olefinic selectivity (*s*) were obtained. (*R*)-BINAP, showed low activity (20% GC yield) and very low enantioselectivity (<5% *ee*). Similar results were obtained when another bisphosphine (*R*)-Xyl-SDP was used. When (*R*)-BINAP oxide, (*R*)-BINAP(O) was used as the ligand, the yield was increased from 20% to 73% while the enantioselectivity was greatly raised from <5% to 73%. It is noteworthy that the major product was the immediate Heck product, 2-phenyl-2,5-dihydrofuran when (*R*)-BINAP(O) was used. When a spiro-bisphosphine monoxide (*R*)-SDP(O) was used, 92% *ee* was obtained along with isomeric selectivity of 5:1. (*R*)-Xyl-SDP(O) proved to be the best ligand. 95% yield and 96% enantioselectivity were obtained. The selectivity was increased to 11:1 when the reaction time was shortened to 6 hours.

With the best ligand in hand, we studied the effect of solvents. In the alcohol solvents, the desired product was obtained in high enantioselectivity. Among them, ethylene glycol proved to be the best. As expected, no desired product was observed in THF and

1,4-dioxane.

Table 1.1 Effect of solvents

<div style="display: flex; align-items: center; justify-content: space-around;"> <div style="text-align: center;"> 2 equiv </div> <div style="text-align: center;"> 2 equiv </div> <div style="text-align: center;"> $\xrightarrow[\text{solvent}]{\begin{array}{l} \text{Pd(dba)}_2 \text{ (2.5 mol\%)} \\ \text{(R)-Xyl-SDP(O)} \text{ (3 mol\%)} \\ \text{iPr}_2\text{NEt} \text{ (3 equiv.)} \\ \text{p-NO}_2\text{C}_6\text{H}_4\text{CO}_2\text{H (1 equiv.)} \end{array}}$ </div> <div style="text-align: center;"> major </div> <div style="text-align: center;"> minor </div> </div> <p style="text-align: center;">80 °C, 12 h</p>					
Entry	Solvent	Conv (%)	GC yield (%)	Selectivity s	Ee (%)
1	ethylene glycol (6 h)	100	95	11	96
2	ethylene glycol (12 h)	100	93	7	95
3	MeOH	75	67	8	96
4	EtOH	60	47	7	96
5	iPrOH	35	30	5	95
6	nBuOH	45	33	7	96
7	THF	10	0	-	-
8	1,4-Dioxane	10	0	-	-

Also, we studied the effect of palladium salts and complexes. No desired product was observed when no palladium salt was added. Among them, Pd(dba)₂ proved to be the best palladium source in terms of yield, selectivity and enantioselectivity.

Table 1.2 Effect of palladium sources

<div style="display: flex; align-items: center; justify-content: space-around;"> <div style="text-align: center;"> 2 equiv </div> <div style="text-align: center;"> 2 equiv </div> <div style="text-align: center;"> $\xrightarrow[\text{ethylene glycol}]{\begin{array}{l} [\text{Pd}] \text{ (2.5 mol\%)} \\ \text{(R)-Xyl-SDP(O)} \text{ (3 mol\%)} \\ \text{iPr}_2\text{NEt} \text{ (3 equiv.)} \\ \text{p-NO}_2\text{C}_6\text{H}_4\text{CO}_2\text{H (1 equiv.)} \end{array}}$ </div> <div style="text-align: center;"> major </div> <div style="text-align: center;"> minor </div> </div> <p style="text-align: center;">80 °C, 12 h</p>					
Entry	Pd source	Conv (%)	GC yield (%)	Selectivity s	Ee (%)
1	Pd(dba) ₂ (6 h)	100	95	11	96
2	Pd(dba) ₂ (12 h)	100	93	7	95
3	Pd(OAc) ₂	92	65	5	90
4	PdBr ₂	60	36	7	90
5	Pd(CF ₃ CO ₂) ₂	100	45	1	93
6	PdMe ₂ (TMEDA)	90	80	10	96
7	None	0	-	-	-

We studied the effect of bases and the results are shown in Table 1.3. We found N,

N-diisopropylethylamine was the best base with respect to the yield, selectivity and enantioselectivity. Triethylamine also afforded good yield of the product (entry 5).

Table 1.3 Effect of bases

Entry	Base	Conv (%)	GC yield (%)	Selectivity s	<i>Ee</i> (%)
1	<i>i</i> Pr ₂ NEt (6 h)	100	93	11	96
2	<i>i</i> Pr ₂ NEt (12 h)	100	93	7	95
3	Cy ₂ NMe	98	67	4	96
4	<i>n</i> Bu ₃ N	50	40	8	95
5	Et ₃ N	85	80	5	96
6	Proton sponge	50	37	8	93
7	PhNHMe	30	0	-	-
8	No base	10	0	-	-

Under our conditions, the added acids formed alkylammonium salts with the alkylamines. When the reaction was performed in the absence of any acid additive, 56% GC yield and 94% *ee* were obtained, but the selectivity was only 3:1. When benzoic acids were used as additives, the reactions proceeded smoothly as shown in Table 1.4. *p*-Nitrobenzoic acid proved to be the best acid. When some selected silver salts were added, the reactions also proceeded smoothly in ethylene glycol. Notably, other silver salts gave inferior results in alcohols and the results from reactions of silver salts in THF and dioxane were much worse.

Table 1.4 Effect of additives

Entry	Additive	Conv. (12h)	GC Yield (%)	Selectivity s	<i>Ee</i> (%)
1	<i>p</i> -NO ₂ C ₆ H ₄ CO ₂ H (6 h)	100	95	11	96
2	<i>p</i> -NO ₂ C ₆ H ₄ CO ₂ H (12 h)	100	93	7	95
3	PhCO ₂ H	88	73	7	94
4	<i>p</i> - <i>t</i> BuC ₆ H ₄ CO ₂ H	86	67	9	90

5	PhCH ₂ CO ₂ H	80	64	8	94
6	MeCO ₂ H	60	20	37	96
7	<i>i</i> Pr ₂ NEt·HCl	80	73	8	96
8	<i>i</i> Pr ₂ NEt·HOTf	90	67	3	95
9	No additive	80	56	3	94
10	AgOTf	100	80	9	97
11	AgOBz	95	84	24	96
12	Ag ₂ CO ₃	90	78	13	97

We also found that when iodobenzene was used in place of bromobenzene, rather unsatisfactory results were obtained. Only 50% yield was obtained with the olefinic selectivity of 1:2 and 80% *ee*.

1.3.2 Asymmetric Heck reaction of 2,3-dihydrofuran

With the optimal conditions in hand, 2,3-dihydrofuran was used to react with various aryl bromides. As shown in Figure 1.3, most aryl bromides reacted smoothly and gave high selectivity of isomers (>10:1) and high enantioselectivity (>90%). Both aryl bromides with electron-withdrawing *p*-fluoro and electron-donating *p*-methoxy group reacted efficiently. Heteroaromatic bromides also reacted well. When (*E*)- β -bromostyrene was used as the substrate, the reaction at 40 °C gave 70% yield, 88% *ee* and 11:1 olefinic selectivity. When some aryl chlorides were in reactions with 2,3-dihydrofuran, good yield and *ee* values were obtained, although higher catalyst loadings and longer reaction times were needed to have good conversion. As one limitation, we found electron-poor (hetero)aryl halides gave low conversion or remained unreactive. This can be understood by considering relative low stability of cationic arylpalladium intermediates derived from these aryl groups, which is critical for the asymmetric insertion.

Figure 1.3 Asymmetric Heck reaction of aryl bromides and aryl chlorides with 2,3-dihydrofuran

1.3.3 Asymmetric Heck reaction of cyclopentene

When the optimal conditions were used in asymmetric Heck reaction of aryl bromides and cyclopentene, the results were not good (30% yield, 26% GC yield, 3:1 olefinic selectivity after 14 h). However, when the solvent was changed to methanol and the catalyst loading was increased to 5 mol%, the model reaction of *p*-bromotoluene was completed in 12 h with good results (93% GC yield, 42:1 olefinic selectivity and 96% *ee*).

Figure 1.4 Asymmetric Heck reaction of aryl bromide and aryl chloride with cyclopentene

As shown in Figure 1.4, most of aryl bromides reacted with cyclopentene smoothly under the modified conditions, with >20:1 olefinic selectivity and >90% enantioselectivity. Both electron-rich and electron-poor aryl bromides reacted well with cyclopentene. When an alkenyl bromide derived from 1,2-dihydro-4-oxa-naphthalene was used, satisfactory result was obtained (75% yield, 89% *ee*). When some aryl chlorides were used, longer reaction times and ethylene glycol solvent were needed to reach good conversion. When iodobenzene was used instead of bromobenzene, only 20% yield was obtained with 90% *ee*. We also noticed that some other examples of organic halides failed to react under the optimal condition in Figure 1.4.

1.3.4 Asymmetric Heck reaction of dihydropyrrole derivatives

The asymmetric Heck reaction of phenyl bromide and *N*-Boc-2,3-dihydropyrrole also proceeded smoothly under standard conditions and gave the desired product in 84% yield,

91% *ee* and 9:1 selectivity of isomers. Other aryl bromides with different electronic and steric properties also proceeded well in high *ee* values. Aryl chlorides can be used when the reactions were conducted at higher reaction temperature and over longer reaction times. When iodobenzene was used instead of bromobenzene, only 67% yield was obtained along with an olefinic selectivity of 21:1 and 66% *ee*.

Previously, Dr. Jian Hu reported derivatization of asymmetric Heck products to some bioactive compounds.⁵⁷ (+)-Preclamol proved to be promising for treatment to the schizophrenia.⁷⁴⁻⁷⁷ Its enantiomer can be obtained from our enantioselective Heck product of cyclopentene. As another example, *p*-fluorophenyl bromide coupled with *N*-Boc-2,3-dihydropyrrole in 93% *ee*. The resulting azacycle can be used to prepare BMS-394136,⁵⁷ which was developed for the treatment for cardiac arrhythmia.⁷⁸

Figure 1.5 Asymmetric Heck reaction of aryl bromides and chlorides with *N*-Boc-2,3-dihydropyrrole

Figure 1.6 Synthetic applications of asymmetric Heck reaction

1.3.5 Mechanism study

The (*S*)-configuration of major products and high *ee* in this study mirrored to our previous results from asymmetric Heck reaction of aryl triflates using the same chiral ligand, (*R*)-Xyl-SDP(O).⁵⁷ The similarity suggested that in our reactions of aryl halides, aryl insertion also proceeded via a cationic complex of (L)Pd(aryl)(olefin), after halide dissociation in alcohols.

I prepared a neutral arylpalladium bromide complex **A** from Pd(dba)₂, *p*-F-phenyl bromide and (*R*)-Xyl-SDP(O). When complex **A** was treated with cyclopentene in the presence of *i*Pr₂NEt and *p*-NO₂C₆H₄CO₂H in methanol, olefin insertion occurred at 50 °C and gave the Heck product in 94% *ee* and 28:1 isomeric selectivity. If no *p*-NO₂PhCO₂H was added, the yield decreased to 40% and the *ee* to 67%. Moreover, if 1,4-dioxane was used as the solvent, no Heck product was observed. The results proved that both the MeOH solvent was crucial for the product formation and the additive was crucial for the good results. The results were fitted with our proposed roles of the solvent and additive.

Scheme 1.22 Stoichiometric olefin insertion of neutral Pd complex **A**

1.4 Summary

We developed a mild reaction for asymmetric Heck reaction of aryl bromides and chlorides with cyclic olefins. This is the first time that asymmetric intermolecular Heck reactions of aryl halides were realized in high *ee*. Ammonium salts and alcohol solvent were employed as hydrogen-bonding donors to permit the dissociation of halides from neutral palladium complex, so as to open the door to the enantioselective cationic pathway.

1.5 Experiment section

1.5.1 Genral

All NMR spectra were acquired on Bruker BBFO1 400 MHz NMR spectrometers and Bruker AV 500 MHz NMR spectrometers. ¹H NMR (400 MHz) and ¹H NMR (500MHz) chemical shifts were recorded relative to SiMe₄ (δ 0.00) or residual protiated solvents (CDCl₃: δ 7.26; CD₂Cl₂: δ 5.32). Multiplicities were given as: s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). The number of protons (n) for a given resonance was indicated by nH. Coupling constants were reported as a *J* value in Hz. ¹³C NMR (100 MHz) chemical shifts were recorded relative to solvent resonance (CDCl₃: δ 77.16; CD₂Cl₂: δ 53.84). ¹⁹F NMR (376 MHz) chemical shifts were recorded relative to an external standard (BF₃·OEt₂: δ 153.0). ³¹P NMR (126 MHz) chemical shifts were relative to an external standard (85% H₃PO₄: δ 0.00). Proof of purity of new compounds was demonstrated with copies of ¹H, ¹³C, ³¹P and ¹⁹F NMR spectra.

Glassware was dried at 120 °C for at least 3 h before use. Methanol was distilled over CaH₂ under argon. Dry toluene, hexane, diethyl ether and dichloromethane were collected

from a solvent purification system containing a column of activated alumina (1 m x 2) under argon. Dry THF was freshly distilled from sodium/benzophenone under argon. *N*-Ethyldiisopropylamine (Hünig's base) was distilled from CaH₂ under argon before use. Methanol was distilled from sodium under argon before use. All anhydrous solvents were stored in Schlenk tubes in the glove box. Unless noted otherwise, commercially available chemicals were used as received without purification. The GC internal standard, *n*-C₁₂H₂₆ and *n*-C₁₄H₃₀ was degassed with argon and dried over activated 4 Å molecular sieve beads before use. Flash chromatography was performed using Merck 40-63D 60 Å silica gel. Gas chromatography (GC) analysis was performed on a Shimadzu GC-2010 instrument with Agilent J & W GC column DB-5MS-UI. GC/MS analysis was conducted on a Thermo Scientific DSQ II single quadrupole GC/MS instrument with Agilent J & W GC column DB-5MS-UI. ESI/MS analysis was conducted on a ThermoFinnigan LCQ Fleet MS spectrometer.

Chiral HPLC analysis was performed on a Shimadzu LC-20AD instrument using Daicel Chiralcel columns at 25°C and a mixture of HPLC-grade hexane and isopropanol as eluent. Optical rotation was measured using a JASCO P-1030 Polarimeter equipped with a sodium vapor lamp at 589 nm and the concentration of samples was denoted as *c*.

1.5.2 Isolation of Heck products

General procedure for asymmetric Heck reactions of 2,3-dihydrofuran:

In an argon-filled glove box, Pd(dba)₂ (7.2 mg, 0.013 mmol) and (*R*)-Xyl-SDP(O) (10.8 mg, 0.015 mmol) were stirred in ethylene glycol (1.0 mL) for 10-20 min in a 10-mL reaction tube, followed by successive addition of aryl bromide (0.50 mmol), *N*-ethyldiisopropylamine (255 μ L, 1.5 mmol, 3 equiv), *p*-nitrobenzoic acid (83.6 mg, 0.5 mmol, 1 equiv) and 2,3-dihydrofuran (1.0 mmol, 2 equiv). The mixture was vigorously stirred in a preheated oil bath at a set temperature (80 °C), until the aryl bromide was fully consumed (monitored by GC). The reaction mixture was cooled to room temperature and subjected to flash chromatography (pentane/Et₂O) to give the purified product. The olefinic selectivity *s* of product isomers in the crude mixture was determined by GC in most cases. The enantioselectivity (*ee*) of the purified product was determined by chiral HPLC analysis with Daicel Chiralcel columns.

General procedure for asymmetric Heck reactions of cyclopentene:

In an argon-filled glove box, Pd(dba)₂ (14.4 mg, 0.025 mmol) and (*R*)-Xyl-SDP(O) (21.6 mg, 0.030 mmol) were stirred in methanol (1.0 mL) for 10-20 min in a 10-mL reaction tube, followed by successive addition of aryl bromide (0.50 mmol),

N-ethyldiisopropylamine (255 μ L, 1.5 mmol, 3 equiv), *p*-nitrobenzoic acid (83.6 mg, 0.5 mmol, 1 equiv) and cyclopentene (2.0 mmol, 4 equiv). The mixture was vigorously stirred in a preheated oil bath (80 $^{\circ}$ C) at a set temperature until the aryl bromide was fully consumed (monitored by GC). The reaction mixture was cooled to room temperature and subjected to flash chromatography (pentane/Et₂O) to give the purified product. The olefinic selectivity of product in the crude mixture was determined by GC in most cases.

General procedure for asymmetric Heck reactions of *N*-Boc-2,3-dihydro-1*H*-pyrrole:

In an argon-filled glove box, Pd(dba)₂ (14.4 mg, 0.025 mmol) and (*R*)-Xyl-SDP(O) (21.6 mg, 0.030 mmol) were stirred in ethylene glycol (1.0 mL) for 10 min in a 10-mL reaction tube, followed by the successive addition of aryl bromide (0.50 mmol), *N*-ethyldiisopropylamine (255 μ L, 1.5 mmol, 3 equiv), *p*-nitrobenzoic acid (83.6 mg, 0.5 mmol, 1 equiv) and olefin (1.0 mmol, 2 equiv). The mixture was vigorously stirred in a preheated oil bath at a set temperature (70 $^{\circ}$ C) until the aryl bromide was fully consumed (monitored by GC). The reaction mixture was cooled to room temperature and subjected to flash chromatography (pentane/Et₂O) to give the purified product. The olefinic selectivity of product isomers in the crude mixture was determined by GC in most cases. The enantioselectivity (*ee*) of the purified product was determined by chiral HPLC analysis with Daicel Chiralcel columns.

(*S*)-3-(1-Naphthyl)cyclopentene [CAS 1461737-02-9] . Pd(dba)₂ (14.4 mg, 0.025 mmol), (*R*)-Xyl-SDP(O) (21.6 mg, 0.030 mmol), methanol (1.0 mL), 1-naphthyl bromide (103.5 mg, 0.50 mmol), *N*-ethyldiisopropylamine (255 μ L, 1.5 mmol), *p*-nitrobenzoic acid (83.6 mg, 0.5 mmol) and cyclopentene (180 μ L, 2.0 mmol) were used. The reaction completed in 32 h at 80 $^{\circ}$ C. The product was isolated by flash chromatography (pentane) as colorless oil. Yield: 94 mg, 95%. Olefinic selectivity in the crude product: >50:1. $[\alpha]_D^{23} = +98.1^{\circ}$ ($c = 0.78$, CHCl₃).

GC-MS (EI): Calcd for C₁₅H₁₄ M⁺: 194.11, Found: 194.1.

Ee: 98%. Daicel Chiralcel OJ-H, 98:2 hexane/isopropanol, flow rate = 0.5 mL/min.

PDA Ch1 214nm 4nm

Peak#	Ret. Time	Area	Area %
1	11.431	10810172	51.071
2	12.472	10356960	48.929
Total		21167133	100.000

PDA Ch1 214nm 4nm

Peak#	Ret. Time	Area	Area %
1	11.738	10069174	98.804
2	12.596	121862	1.196
Total		10191036	100.000

^1H NMR (400 MHz, CDCl_3): δ 8.16 (d, $J = 8.3$ Hz, 1H), 7.86-7.84 (m, 1H), 7.70 (d, $J = 8.1$ Hz, 1H), 7.53-7.45 (m, 2H), 7.41-7.38 (m, 1H), 7.31 (dd, $J = 7.1, 0.76$ Hz, 1H), 6.07-6.04 (m, 1H), 5.96-5.93 (m, 1H), 4.68-4.63 (m, 1H), 2.66-2.57 (m, 1H), 2.52-2.46 (m, 2H), 1.82-1.74 (m, 1H).

(S)-3-(2-Naphthyl)cyclopentene [CAS 1461737-03-0] $\text{Pd}(\text{dba})_2$ (14.4 mg, 0.025 mmol), (*R*)-Xyl-SDP(O) (21.6 mg, 0.030 mmol), methanol (1.0 mL), 2-naphthyl bromide (103.5 mg, 0.50 mmol), *N*-ethyldiisopropylamine (255 μL , 1.5 mmol), *p*-nitrobenzoic acid (83.6mg, 0.5mmol) and cyclopentene (180 μL , 2.0 mmol) were used. The reaction completed in 12 h at 80 $^\circ\text{C}$. The product was isolated by flash chromatography with pentane as colorless oil. Yield: 89 mg, 91%. Olefinic selectivity in the crude product: 21:1.

$[\alpha]_{\text{D}}^{23} = -199.9^\circ$ ($c = 0.78$, CHCl_3).

GC-MS (EI): Calcd for $\text{C}_{15}\text{H}_{14}$ M^+ : 194.11, Found: 194.1.

Ee: 97%. Daicel Chiralcel OJ-H, 98:2 hexane/isopropanol, flow rate = 0.5 mL/min.

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Area %
1	14.890	2338062	50.254
2	16.298	2314400	49.746
Total		4652462	100.000

PDA Ch1 214nm 4nm

Peak#	Ret. Time	Area	Area %
1	15.023	292458	1.533
2	16.546	18788682	98.467
Total		19081140	100.000

^1H NMR (400 MHz, CDCl_3): δ 7.79-7.75 (m, 3H), 7.60 (s, 1H), 7.44-7.37 (m, 2H), 7.32 (dd, $J = 8.4, 1.0$ Hz, 1H), 6.00-5.98 (m, 1H), 5.86-5.82 (m, 1H), 4.07-4.03 (m, 1H), 2.60-2.39 (m, 3H), 1.85-1.75 (m, 1H).

(S)-3-Phenylcyclopentene [CAS 38941-68-3] Pd(dba)₂ (14.4 mg, 0.025 mmol), (*R*)-Xyl-SDP(O) (21.6 mg, 0.030 mmol), methanol (1.0 mL), bromobenzene (78.5mg, 0.50 mmol), *N*-ethyl-diisopropylamine (170 μL, 1.5 mmol), *p*-nitrobenzoic acid (83.6 mg, 0.5 mmol) and cyclopentene (180 μL, 2.0 mmol) were used. The reaction completed in 15 h at 80 °C. The product was isolated by flash chromatography (silica gel, pentane) as colorless oil. Yield: 62.5 mg, 85%. Olefinic selectivity in the crude product: 43:1.

$[\alpha]_D^{23} = -170.9^\circ$ ($c = 0.62$, CHCl₃).

GC-MS (EI): Calcd for C₁₁H₁₂ M⁺: 144.09, Found: 144.1.

Ee: 92%. Daicel Chiralcel OJ-H, 98:2 hexane/isopropanol, flow rate = 0.5 mL/min

PDA Ch1 214nm 4mm

Peak#	Ret. Time	Area	Area %
1	9.335	771241	50.418
2	9.807	758464	49.582
Total		1529706	100.000

PDA Ch1 214nm 4mm

Peak#	Ret. Time	Area	Area %
1	9.323	6542995	95.893
2	9.789	280241	4.107
Total		6823237	100.000

¹H NMR (400 MHz, CDCl₃): δ 7.30-7.27 (m, 2H), 7.20-7.16 (m, 3H), 5.95-5.92 (m, 1H), 5.79-5.76 (m, 1H), 3.91-3.87 (m, 1H), 2.56-2.35 (m, 3H), 1.77-1.69 (m, 1H).

(S)-1-(cyclopent-2-en-1-yl)-4-methylbenzene [CAS 38805-99-1] Pd(dba)₂ (14.4 mg, 0.025 mmol), (*R*)-Xyl-SDP(O) (21.6 mg, 0.030 mmol), methanol (1.0 mL), 4-bromotoluene (85.5 mg, 0.50 mmol), *N*-ethyl-diisopropylamine (255 μL, 1.5 mmol), *p*-nitrobenzoic acid (83.6 mg, 0.5 mmol) and cyclopentene (180 μL, 2.0 mmol) were used. The reaction was complete in 12 h at 80 °C. The product was isolated by flash chromatography with pentane as colorless oil. Yield: 74 mg, 92%. Olefinic selectivity in the crude product: 42:1.

$[\alpha]_D^{23} = -174.2^\circ$ ($c = 0.90$, CHCl₃).

GC-MS (EI): Calcd for C₁₂H₁₄ M⁺: 158.11, Found: 158.1.

Ee: 96%. Daicel Chiralcel OJ-H, 98:2 n-hexane/isopropanol, flow rate = 0.5 mL/min.

PeakTable			
Peak#	Ret. Time	Area	Area %
1	10.298	1023996	48.915
2	11.026	1069403	51.085
Total		2093399	100.000

PeakTable			
Peak#	Ret. Time	Area	Area %
1	10.289	6938998	98.218
2	11.020	125922	1.782
Total		7064920	100.000

$\text{Pd}(\text{dba})_2$ (14.4 mg, 0.025 mmol), (*R*)-Xyl-SDP(O) (21.6 mg, 0.030 mmol), ethylene glycol (1.0 mL), 4-chlorotoluene (63.3 mg, 0.50 mmol), *N*-ethyl-diisopropylamine (255 μL , 1.5 mmol), *p*-nitrobenzoic acid (83.6 mg, 0.5 mmol) and cyclopentene (180 μL , 2.0 mmol) were used. The reaction was complete in 120 h at 80 °C. The product was isolated by flash chromatography with pentane as colorless oil. Yield: 60 mg, 75%. Olefinic selectivity in the crude product: 38:1.

Ee: 85%. Daicel Chiralcel OJ-H, 99:1 *n*-hexane/isopropanol, flow rate = 0.5 mL/min.

PeakTable			
Peak#	Ret. Time	Area	Area %
1	10.696	987188	49.888
2	11.904	991633	50.112
Total		1978821	100.000

PeakTable			
Peak#	Ret. Time	Area	Area %
1	10.658	12330595	92.331
2	11.859	1024197	7.669
Total		13354793	100.000

^1H NMR (400 MHz, CDCl_3): δ 7.16-7.06 (m, 4H), 5.92-5.90 (m, 1H), 5.77-5.75 (m, 1H), 3.88-3.83 (m, 1H), 2.54-2.45 (m, 1H), 2.43-2.36 (m, 2H), 2.31 (s, 3H), 1.74-1.66 (m, 1H)
 ^{13}C NMR (100 MHz, CDCl_3): δ 143.5, 135.4, 134.5, 131.7, 129.0, 127.1, 127.3, 50.9, 33.9, 32.5, 21.0.

(*S*)-3-(4-Methoxyphenyl)cyclopentene [CAS 1462335-55-2]

$\text{Pd}(\text{dba})_2$ (14.4 mg, 0.025 mmol), (*R*)-Xyl-SDP(O) (21.6 mg, 0.030 mmol), methanol (1.0 mL), 4-bromoanisole (93.5 mg, 0.50 mmol), *N*-ethyl-diisopropylamine (255 μL , 1.5 mmol), *p*-nitrobenzoic acid (83.6 mg, 0.5 mmol) and cyclopentene (180 μL , 2.0 mmol) were used. The reaction was complete in 9 h at 80 °C. The product was isolated by flash chromatography with pentane/ Et_2O (10:0 to 10:1) as a colorless liquid. Yield: 82 mg, 93%.

Olefinic selectivity in the crude product: 32:1.

$[\alpha]_D^{23} = -177.8^\circ$ ($c = 0.94$, CHCl_3).

GC-MS (EI): Calcd for $\text{C}_{12}\text{H}_{14}\text{O}$ M^+ : 174.10, Found: 174.1.

Ee: 93%. Daicel Chiralcel OJ-H, 98:2 hexane/isopropanol, flow rate = 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 7.12-7.11 (m, 1H), δ 7.10-7.08 (m, 1H), 6.85-6.81(m, 2H), 5.92-5.89 (m, 1H), 5.76-5.73 (m, 1H), 3.87-3.81 (m, 1H), 3.78 (s, 3H), 2.54-2.43 (m, 1H), 2.43-2.32 (m, 2H), 1.74-1.62 (m, 1H).

(S)-1-(cyclopent-2-en-1-yl)-4-fluorobenzene [CAS for racemate 78135-03-2]

$\text{Pd}(\text{dba})_2$ (14.4 mg, 0.025 mmol), (*R*)-Xyl-SDP(O) (21.6 mg, 0.030 mmol), methanol (1.0 mL), 1-bromo-4-fluorobenzene (87.5 mg, 0.50 mmol), *N*-ethyldiisopropylamine (255 μL , 1.5 mmol), *p*-nitrobenzoic acid (83.6 mg, 0.5 mmol) and cyclopentene (180 μL , 2.0 mmol) were used. The reaction was complete in 26 h at 80 $^\circ\text{C}$. The product was isolated by flash chromatography with pentane as colorless oil. Yield: 68 mg, 82%. Olefinic selectivity in the crude product: 28:1.

^1H NMR (400 MHz, CDCl_3): δ 7.16-7.11 (m, 2H), δ 6.99-6.93 (m, 2H), 6.95-6.92 (m, 1H), 5.76-5.73 (m, 1H), 3.90-3.85 (m, 1H), 2.55-2.45 (m, 1H), 2.44-2.34 (m, 2H), 1.71-1.63 (m, 1H).

(S)-3-(2-Methylphenyl)cyclopentene [CAS 1461737-06-3] $\text{Pd}(\text{dba})_2$ (14.4 mg, 0.025 mmol), (*R*)-Xyl-SDP(O) (21.6 mg, 0.030 mmol), methanol (1.0 mL), 2-bromotoluene (85.5 mg, 0.50 mmol), *N*-ethyldiisopropylamine (255 μL , 1.5 mmol), *p*-nitrobenzoic acid (83.6 mg, 0.5 mmol) and cyclopentene (180 μL , 2.0 mmol) were used. The reaction was

complete in 30 h at 80 °C. The product was isolated by flash chromatography with pentane as colorless oil. Yield: 75 mg, 93%. Olefinic selectivity in the crude product: 50:1.

$[\alpha]_D^{23} = -72.0^\circ$ ($c = 1.01$, CHCl_3).

GC-MS (EI): Calcd for $\text{C}_{12}\text{H}_{14}$ M^+ : 158.11, Found: 158.1.

Ee: 92%. BPH isothermal at 90°C, then 15 deg/min.

$\text{Pd}(\text{dba})_2$ (14.4 mg, 0.025 mmol), (*R*)-Xyl-SDP(O) (21.6 mg, 0.030 mmol), ethylene glycol (1.0 mL), 2-chlorotoluene (63.3 mg, 0.50 mmol), *N*-ethyldiisopropyl-amine (255 μL , 1.5 mmol), *p*-nitrobenzoic acid (83.6 mg, 0.5 mmol) and cyclopentene (180 μL , 2.0 mmol) were used. The reaction was complete in 120 h at 80 °C. The product was isolated by flash chromatography with pentane as colorless oil. Yield: 60 mg, 74%. Olefinic selectivity in the crude product: 50:1.

Ee: 82%. BPH isothermal at 90°C, then 15 deg/min.

^1H NMR (400 MHz, CDCl_3): δ 7.15-7.07 (4H), 5.98-5.96 (m, 1H), 5.79-5.77 (m, 1H), 4.12-4.07 (m, 1H), 2.51-2.38 (m, 3H), 2.37 (s, 3H), 1.65-1.57 (m, 1H).

(*S*)-3-(2-Methoxyphenyl)cyclopentene [CAS 1461737-07-4] $\text{Pd}(\text{dba})_2$ (14.4 mg, 0.025 mmol), (*R*)-Xyl-SDP(O) (21.6 mg, 0.030 mmol), methanol (1.0 mL),

2-bromoanisole (93.5 mg, 0.50 mmol), *N*-ethyldiisopropylamine (255 μ L, 1.5 mmol), *p*-nitrobenzoic acid (83.6 mg, 0.5 mmol) and cyclopentene (180 μ L, 2.0 mmol) were used. The reaction completed in 7 h at 80 $^{\circ}$ C. The product was isolated by flash chromatography with pentane/Et₂O (10:1) as colorless oil. Yield: 75 mg, 85%. Olefinic selectivity in the crude product: 39:1.

$[\alpha]_D^{23} = -68.5^{\circ}$ ($c = 1.00$, CHCl₃).

GC-MS (EI): Calcd for C₁₂H₁₄O M⁺: 174.10, Found: 174.1.

ee: 96%. BPH 90 $^{\circ}$ C 100 min then 15 deg/min.

¹H NMR (400 MHz, CDCl₃): δ 7.19-7.15 (m, 1H), 7.13-7.10 (m, 1H), 6.89 (t, $J = 7.4$, 1H), 6.86 (d, $J = 8.2$ Hz, 1H), 5.94-5.92 (m, 1H), 5.77-5.76 (m, 1H), 4.27-4.27 (m, 1H), 3.83 (s, 3H), 2.48-2.33 (m, 3H), 1.67-1.57 (m, 1H).

(S)-3-(cyclopent-2-en-1-yl)benzo[b]thiophene [NO CAS] Pd(dba)₂ (14.4 mg, 0.025 mmol), (*R*)-Xyl-SDP(O) (21.6 mg, 0.030 mmol), methanol (3.0 mL), 3-Bromothianaphthene (106.5 mg, 0.50 mmol), *N*-ethyldiisopropylamine (255 μ L, 1.5 mmol), *p*-nitrobenzoic acid (167.1 mg, 1.0 mmol) and cyclopentene (180 μ L, 2.0 mmol) were used. The reaction completed in 27 h at 80 $^{\circ}$ C. The product was isolated by flash chromatography with pentane as colorless oil. Yield: 87 mg, 86%. Olefinic selectivity in the crude product: 50:1. When 1.0 equiv *p*-nitrobenzoic acid and 1.0 mL MeOH were used, only 84% *ee* was obtained.

GC-MS (EI): Calcd for C₁₃H₁₂S M⁺: 200.07, Found: 200.0.

Ee: 96%, Daicel Chiralcel OJ-H, 90:10 hexane/isopropanol, flow rate = 1.0 mL/min.

PDA Ch1 214nm 4nm

Peak#	Ret. Time	Area	Area %
1	5.114	916190	50.603
2	5.696	894357	49.397
Total		1810547	100.000

PDA Ch1 214nm 4nm

Peak#	Ret. Time	Area	Area %
1	5.107	2890366	97.991
2	5.690	59248	2.009
Total		2949614	100.000

^1H NMR (400 MHz, CDCl_3): δ 7.85-7.80 (m, 2H), 7.38-7.30 (m, 2H), 7.03 (s, 1H), 6.01-5.98 (m, 1H), 5.94-5.91 (m, 1H), 4.27-4.22 (m, 1H), 2.54-2.41 (m, 3H), 1.91-1.80 (m, 1H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 141.0, 140.7, 138.7, 132.7, 132.4, 124.2, 123.8, 122.9, 122.1, 120.2, 44.8, 32.3, 31.3.

(S)-5-(Cyclopent-2-en-1-yl)-2-methylbenzothiazole. [CAS 1461737-12-1] $\text{Pd}(\text{dba})_2$ (14.4 mg, 0.025 mmol), (*R*)-Xyl-SDP(O) (21.6 mg, 0.030 mmol), methanol (3.0 mL), 5-Bromo-2-methyl-1,3-benzothiazole (114.1 mg, 0.50 mmol), *N*-ethyldiisopropylamine (255 μL , 1.5 mmol), *p*-nitrobenzoic acid (83.6 mg, 0.5 mmol) and cyclopentene (180 μL , 2.0 mmol) were used. The reaction was complete in 40 h at 80 $^\circ\text{C}$. The product was isolated by flash chromatography (silica gel, 10:1 hexane/Ethyl Ether) as colorless oil. Yield: 87 mg, 80%. Olefinic selectivity in the crude product: 50:1. When 1.0 equiv *p*-nitrobenzoic acid and 1.0 mL MeOH were used, only 50% *ee* was obtained. GC-MS (EI): Calcd for $\text{C}_{13}\text{H}_{13}\text{NS}$ M^+ : 245.08, Found: 215.0. $[\alpha]_{\text{D}}^{23} = -151.5^\circ$ ($c = 0.82$, CHCl_3).

Ee: 88%. Daicel Chiralcel IC, 95:5 hexane/isopropanol, flow rate = 0.5 mL/min.

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Area %
1	13.394	555955	49.530
2	16.379	566513	50.470
Total		1122469	100.000

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Area %
1	13.351	132600	5.964
2	16.330	2090756	94.036
Total		2223356	100.000

^1H NMR (400 MHz, CDCl_3): δ 7.77 (d, $J = 1.6$ Hz, 1H), 7.71 (d, $J = 8.2$ Hz, 1H), 7.20 (dd, $J = 8.2, 1.6$ Hz, 1H), 5.99-5.96 (m, 1H), 5.83-5.80 (m, 1H), 4.05-4.00 (m, 1H), 2.81

(s, 3H), 2.59-2.37 (m, 3H), 1.81-1.72 (m, 1H).

(S)-3-(*m*-Anisyl)cyclopentene [CAS 1461737-14-3] Pd(dba)₂ (28.8 mg, 0.050 mmol), (*R*)-Xyl-SDP(O) (43.2 mg, 0.060 mmol), methanol (2.0 mL), 3-bromoanisole (187 mg, 1.00 mmol), *N*-ethyl-diisopropylamine (510 μ L, 3.0 mmol), *p*-nitrobenzoic acid (167.1 mg, 1.0 mmol) and cyclopentene (360 μ L, 4.0 mmol) were used. The reaction completed in 12 h at 80 °C. The product was isolated by flash chromatography with pentane/Et₂O (10:1) as colorless oil. Yield: 163 mg, 92%. Olefinic selectivity in the crude product: >50:1

GC-MS (EI): Calcd for C₁₂H₁₄O M⁺: 174.10, Found: 174.1.

Ee: 87%. Daicel Chiralcel OJ-H, 99.8:0.2 hexane/isopropanol, flow rate = 0.5 mL/min.

¹H NMR (500 MHz, CDCl₃): δ 7.22-7.19 (m, 1H), 6.80-6.78 (m, 1H), 6.74-6.72 (m, 2H), 5.95-5.92 (m, 1H), 5.78-5.76 (m, 1H), 3.89-3.84 (m, 1H), 3.79 (s, 3H), 2.54-2.44 (m, 1H), 2.43-2.35 (m, 2H), 1.76-1.68 (m, 1H).

(S)-2-(1-Naphthyl)-2,5-dihydrofuran [CAS 131516-16-0] Pd(dba)₂ (7.2 mg, 0.013 mmol), (*R*)-Xyl-SDP(O) (10.8 mg, 0.015 mmol), ethylene glycol (1.0 mL), 1-bromonaphthalene (103.5 mg, 0.50 mmol), *N*-ethyl-diisopropylamine (255 μ L, 1.5 mmol), *p*-nitrobenzoic acid (83.6 mg, 0.5 mmol) and 2,3-dihydrofuran (75 μ L, 1.0 mmol) were used. The reaction was complete in 10 h at 80 °C. The product was isolated by flash chromatography (10:1 to 3:1 pentane/Et₂O) as colorless oil. Yield: 90 mg, 92%. Olefinic selectivity in the crude product: 12:1.

$[\alpha]_D^{23} = -162.3^\circ$ ($c = 0.72$, CHCl₃).

GC-MS (EI): Calcd for C₁₄H₁₂O M⁺: 196.09, Found: 196.0.

Ee: 97%. Daicel Chiralcel OD-H, 98:2 *n*-hexane/isopropanol.

PeakTable			
Peak#	Ret. Time	Area	Area %
1	29.385	43719213	49.722
2	34.982	44208666	50.278
Total		87927879	100.000

PeakTable			
Peak#	Ret. Time	Area	Area %
1	29.367	161016	1.727
2	34.973	9165143	98.273
Total		9326159	100.000

^1H NMR (400 MHz, CDCl_3): δ 8.11 (d, $J = 8.3$ Hz, 1H), 7.86-7.84 (m 1H), 7.76 (d, $J = 8.1$ Hz, 1H), 7.53-7.42 (m, 4H), 6.56-6.53 (m, 1H), 6.13-6.10 (m, 1H), 6.06-6.03 (m, 1H), 4.95-4.83 (m, 2H).

(S)-2-(2-Naphthyl)-2,5-dihydrofuran [CAS 131516-16-0] $\text{Pd}(\text{dba})_2$ (7.2 mg, 0.013 mmol), (*R*)-Xyl-SDP(O) (10.8 mg, 0.015 mmol), ethylene glycol (1.0 mL), bromonaphthalene (103.5 mg, 0.50 mmol), *N*-ethyldiisopropylamine (255 μL , 1.5 mmol), *p*-nitrobenzoic acid (83.6mg, 0.5mmol) and 2,3-dihydrofuran (75 μL , 1.0 mmol) were used. The reaction was complete in 6 h at 80 $^\circ\text{C}$. The product was isolated by flash chromatography (10:1 to 3:1 pentane/ Et_2O) as colorless oil. Yield: 85 mg, 86%. Olefinic selectivity in the crude product: 12:1.

$[\alpha]_{\text{D}}^{23} = -195.0^\circ$ ($c = 0.58$, CHCl_3).

GC-MS (EI): Calcd for $\text{C}_{14}\text{H}_{12}\text{O}$ M^+ : 196.09, Found: 196.0.

Ee: 96%. Daicel Chiralcel OD-H, *n*-hexane/isopropanol 98/2, flow rate = 0.5 mL/min.

PeakTable			
Peak#	Ret. Time	Area	Area %
1	20.324	27658075	50.051
2	24.163	27601659	49.949
Total		55259734	100.000

PeakTable			
Peak#	Ret. Time	Area	Area %
1	20.366	3722488	97.889
2	24.261	80286	2.111
Total		3802775	100.000

^1H NMR (400 MHz, CDCl_3): δ 7.84-7.80 (m, 3H), 7.76 (s, 1H), 7.48-7.44 (m, 2H), 7.41 (dd, $J = 8.5, 1.9$ Hz, 1H), 6.09-6.06 (m, 1H), 5.96-5.93 (m, 2H), 4.98-4.92 (m, 1H), 4.85-4.80 (m, 1H).

(S)-2-phenyl-2,5-dihydrofuran [CAS 131516-10-4] Pd(dba)₂ (7.2 mg, 0.013 mmol), (*R*)-Xyl-SDP(O) (10.8 mg, 0.015 mmol), ethylene glycol (1.0 mL), bromobenzene (78.5 mg, 0.50 mmol), *N*-ethyldiisopropylamine (255 μ L, 1.5 mmol), *p*-nitrobenzoic acid (83.6 mg, 0.5 mmol) and 2,3-dihydrofuran (75 μ L, 1.0 mmol) were used. The reaction completed in 6 h at 80 °C. The product was isolated by flash chromatography with pentane/Et₂O (10:1 to 5:1) as colorless oil. Yield: 62 mg, 84%. Olefinic selectivity in the crude product: 11:1.

$[\alpha]_D^{23} = -236.3^\circ$ ($c = 0.80$, CHCl₃).

GC-MS (EI): Calcd for C₁₀H₁₀O M⁺: 146.07, Found: 146.0

Ee: 97%. Daicel Chiralcel OJ-H, 98:2 *n*-hexane/isopropanol, flow rate = 0.5 mL/min.

¹H NMR (400 MHz, CDCl₃): δ 7.36-7.25 (m, 5H), 6.05-6.02 (m, 1H), 5.90-5.87 (m, 1H), 5.80-5.77 (m, 1H), 4.90-4.84 (m, 1H), 4.79-4.74 (m, 1H).

(S)-2-(*p*-Anisyl)-2,5-dihydrofuran [CAS 131516-15-9] Pd(dba)₂ (7.2 mg, 0.013 mmol), (*R*)-Xyl-SDP(O) (10.8 mg, 0.015 mmol), ethylene glycol (1.0 mL), 4-bromoanisole (93.5 mg, 0.50 mmol), *N*-ethyldiisopropylamine (255 μ L, 1.5 mmol), *p*-nitrobenzoic acid (83.6mg, 0.5mmol) and 2,3-dihydrofuran (75 μ L, 1.0 mmol) were used. The reaction was complete in 3h at 80°C. The product was isolated by flash chromatography (10:1 to 5:1 pentane/Et₂O) as colorless liquid. Yield: 82 mg, 93%. Olefinic selectivity in the crude product: 14:1.

$[\alpha]_D^{22} = -208.9^\circ$ ($c = 0.70$, CHCl₃).

GC-MS (EI): Calcd for C₁₁H₁₂O₂ M⁺: 176.08, Found: 176.0.

Ee: 98%. Daicel Chiralcel OD-H, 98:2 *n*-hexane/isopropanol, flow rate = 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 7.24-7.20 (m, 2H), 6.89-6.86 (m, 2H), 6.04-6.02 (m, 1H), 5.87-5.84 (m, 1H), 5.76-5.72 (m, 1H), 4.87-4.81 (m, 1H), 4.75-4.70 (m, 1H), 3.79 (s, 3H).

(S)-2-(p-tolyl)-2,5-dihydrofuran [CAS 1041861-52-2] $\text{Pd}(\text{dba})_2$ (7.2 mg, 0.013 mmol), (*R*)-Xyl-SDP(O) (10.8 mg, 0.015 mmol), ethylene glycol (1.0 mL), 4-bromotoluene (85.5 mg, 0.50 mmol), *N*-ethyl-diisopropylamine (255 μL , 1.5 mmol), *p*-nitrobenzoic acid (83.6 mg, 0.5 mmol) and 2,3-dihydrofuran (75 μL , 1.0 mmol) were used. The reaction was complete in 6 h at 80 $^\circ\text{C}$. The product was isolated by flash chromatography (10:1 to 5:1 pentane/ Et_2O) as a colorless liquid. Yield: 68 mg, 85%. Olefinic selectivity in the crude product: 10:1.

GC-MS (EI): Calcd for $\text{C}_{11}\text{H}_{12}\text{O}$ M^+ : 160.09, Found: 160.1.

Ee: 96%. Daicel Chiralcel IC-H, 98:2 *n*-hexane/isopropanol, flow rate = 0.5 mL/min.

$\text{Pd}(\text{dba})_2$ (14.4 mg, 0.025 mmol), (*R*)-Xyl-SDP(O) (21.6 mg, 0.030 mmol), ethylene glycol (1.0 mL), 4-chlorotoluene (63.3 mg, 0.50 mmol), *N*-ethyl-diisopropylamine (255 μL , 1.5 mmol), *p*-nitrobenzoic acid (83.6 mg, 0.5 mmol) and 2,3-dihydrofuran (150 μL , 2.0 mmol) were used. The reaction was complete in 55 h at 80 $^\circ\text{C}$. The product was isolated by flash chromatography (10:1 to 5:1 pentane/ Et_2O) as a colorless liquid. Yield: 64 mg, 80%. Olefinic selectivity in the crude product: 7:1.

Ee: 95%. Daicel Chiralcel IC-H, 99:1 *n*-hexane/isopropanol, flow rate = 0.5 mL/min.

PDA Ch1 214nm 4nm			
Peak#	Ret. Time	Area	Area %
1	27.798	1069137	50.171
2	29.733	1061850	49.829
Total		2130987	100.000

PDA Ch1 214nm 4nm			
Peak#	Ret. Time	Area	Area %
1	27.449	13746905	97.537
2	29.432	347198	2.463
Total		14094103	100.000

^1H NMR (400 MHz, CDCl_3): δ 7.20-7.14 (m, 4H), 6.03-6.00 (m, 1H), 5.88-5.85 (m, 1H), 5.77-5.75 (m, 1H), 4.88-4.82 (m, 1H), 4.77-4.72 (m, 1H).

(S)-2-(4-fluorophenyl)-2,5-dihydrofuran [CAS 184047-35-6] $\text{Pd}(\text{dba})_2$ (7.2 mg, 0.013 mmol), (*R*)-Xyl-SDP(O) (10.8 mg, 0.015 mmol), ethylene glycol (0.50 mL), 1-bromo-4-fluorobenzene (87.5 mg, 0.50 mmol), *N*-ethyldiisopropylamine (255 μL , 1.5 mmol), *p*-nitrobenzoic acid (83.6 mg, 0.5 mmol) and 2,3-dihydrofuran (75 μL , 1.0 mmol) were used. The reaction was complete in 19 h at 70 $^\circ\text{C}$. The product was isolated by flash chromatography (10:1 to 5:1 pentane/ Et_2O) as colorless oil. Yield: 68 mg, 82%.

Olefinic selectivity in the crude product: 13:1.

$[\alpha]_D^{22} = -187.3^\circ$ ($c = 1.00$, CHCl_3).

GC-MS (EI): Calcd for $\text{C}_{10}\text{H}_9\text{FO}$ M^+ : 164.06, Found: 164.0.

Ee: 98%. Daicel Chiralcel OJ-H, 99:1 *n*-hexane/isopropanol, flow rate = 0.5 mL/min.

PDA Ch1 200nm 4nm			
Peak#	Ret. Time	Area	Area %
1	26.711	339789	49.431
2	27.836	347618	50.569
Total		687407	100.000

PDA Ch1 200nm 4nm			
Peak#	Ret. Time	Area	Area %
1	26.570	108937	0.775
2	27.666	1395278	99.225
Total		14064216	100.000

$^{79}\text{Pd}(\text{dba})_2$ (14.4 mg, 0.025 mmol), (*R*)-Xyl-SDP(O) (21.6 mg, 0.030 mmol), ethylene glycol (1.0 mL), 1-bromo-4-fluorobenzene (87.5 mg, 0.50 mmol), *N*-ethyldiisopropylamine (255 μL , 1.5 mmol), *p*-nitrobenzoic acid (83.6 mg, 0.5 mmol) and 2,3-dihydrofuran (150 μL , 2.0 mmol) were used. The reaction was complete in 45 h at 80 $^\circ\text{C}$. The product was isolated by flash chromatography (10:1 to 5:1 pentane/ Et_2O) as a colorless liquid. Yield: 62 mg, 75%. Olefinic selectivity in the crude product: 7:1.

ee: 94%. Daicel Chiralcel OJ-H, 99:1 *n*-hexane/isopropanol, flow rate = 0.5 mL/min.

⁸⁵ [CAS 1461737-18-7] Pd(dba)₂ (7.2 mg, 0.013 mmol), (*R*)-Xyl-SDP(O) (10.8 mg, 0.015 mmol), ethylene glycol (0.50 mL), 2-bromoanisole (93.5 mg, 0.50 mmol), *N*-ethyldiisopropylamine (255 μL, 1.5 mmol), *p*-nitrobenzoic acid (83.6 mg, 0.5 mmol) and 2,3-dihydrofuran (75 μL, 1.0 mmol) were used. The reaction completed in 3 h at 80 °C. The product was isolated by flash chromatography (10:1 to 5:1 pentane/Et₂O) as colorless oil. Yield: 76 mg, 86%. Olefinic selectivity in the crude product: 28:1

GC-MS (EI): Calcd for $C_{11}H_{12}O_2 M^+$: 176.08, Found: 176.0.

Chromatogram showing two peaks at 16.928 and 18.588 minutes. The y-axis is mAU (0 to 250) and the x-axis is PeakTable (15.0 to 20.0). A label '1PDA' is at the bottom right.

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(S)-5-(2,5-dihydrofuran-2-yl)-2-methylbenzo[d]thiazole

Pd(dba)₂ (7.2 mg, 0.013 mmol), (*R*)-Xyl-SDP(O) (10.8 mg, 0.015 mmol), ethylene glycol (1.0 mL), 5-bromo-2-methylbenzo[d]thiazole (114.1 mg, 0.50 mmol), *N*-ethyldiisopropylamine (255 μ L, 1.5 mmol), *p*-nitrobenzoic acid (83.6 mg, 0.5 mmol) and 2,3-dihydrofuran (75 μ L, 1.0 mmol) were used. The reaction completed in 7 h at 80 °C. The product was isolated by flash chromatography (10:1 to 1:1 pentane/Et₂O) as colorless oil. Yield: 87 mg, 80%. Olefinic selectivity in the crude product: 10:1.

GC-MS (EI): Calcd for C₁₂H₁₁NOS M⁺: 217.06, Found: 217.0.

Ee: 95%. Daicel Chiralcel AS-H, 95:5 *n*-hexane/isopropanol, flow rate = 0.5 mL/min.

PDA Ch1 254nm 4nm			
Peak#	Ret. Time	Area	Area %
1	15.727	1456459	50.215
2	18.985	1444012	49.785
Total		2900471	100.000

PDA Ch1 254nm 4nm			
Peak#	Ret. Time	Area	Area %
1	15.732	2587945	97.421
2	19.033	68506	2.579
Total		2656452	100.000

¹H NMR (500 MHz, CDCl₃): δ 7.88 (d, *J* = 1.4 Hz, 1H), 7.78 (d, *J* = 8.3 Hz, 1H), 7.30 (dd, *J* = 8.3, 1.6 Hz, 1H), 6.07-6.05 (m, 1H), 5.93-5.91 (m, 1H), 4.93-4.89 (m, 1H), 4.82-4.78 (m, 1H), 2.82 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 167.4, 153.7, 140.5, 135.0, 129.9, 126.9, 123.3, 121.4, 120.2, 87.8, 75.9, 20.2.

(S)-3-(2,5-dihydrofuran-2-yl)benzofuran [NO CAS] Pd(dba)₂ (7.2 mg, 0.013 mmol), (*R*)-Xyl-SDP(O) (10.8 mg, 0.015 mmol), ethylene glycol (3.0 mL), 3-bromobenzofuran (98.5 mg, 0.50 mmol), *N*-ethyldiisopropylamine (255 μ L, 1.5 mmol), *p*-nitrobenzoic acid (167.1 mg, 1.0 mmol) and 2,3-dihydrofuran (75 μ L, 1.0 mmol) were used. The reaction completed in 27 h at 50 °C. The product was isolated by flash chromatography (10:1 to 5:1 pentane/Et₂O) as colorless oil. Yield: 75 mg, 80%. Olefinic selectivity in the crude

product: 8:1. When 1.0 equiv *p*-nitrobenzoic acid and 1.0 mL ethylene glycol were used, only olefinic selectivity is 7:1.

$[\alpha]_{\text{D}}^{22} = -163.2^\circ$ ($c = 0.92$, CHCl_3).

GC-MS (EI): Calcd for $\text{C}_{12}\text{H}_{10}\text{O}_2 \text{M}^+$: 186.07, Found: 186.0.

Ee: 97%. Daicel Chiralcel OD-H, 99:1 *n*-hexane/isopropanol, flow rate = 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 7.58 (dd, $J=7.5$, 0.72HZ 1H), 7.56 (s, 1H), 7.46 (d, $J=8.2$ HZ 1H), 7.30-7.26 (m, 1H), 7.24-7.20 (m, 1H), 6.13-6.10 (m, 1H), 6.04-6.00 (m, 1H), 6.00-5.97 (m, 1H), 4.92-4.86 (m, 1H), 4.82-4.77 (m, 1H)

^{13}C NMR (100 MHz, CDCl_3): δ 155.9, 142.1, 128.1, 127.8, 126.2, 124.5, 122.7, 121.3, 120.3, 111.6, 79.9, 75.5.

(S)-2-(benzo[b]thiophen-3-yl)-2,5-dihydrofuran. [NO CAS] $\text{Pd}(\text{dba})_2$ (7.2 mg, 0.013 mmol), (*R*)-Xyl-SDP(O) (10.8 mg, 0.015 mmol), ethylene glycol (3.0 mL), 3-bromobenzo[b]thiophene (106.5 mg, 0.50 mmol), *N*-ethyldiisopropylamine (255 μL , 1.5 mmol), *p*-nitrobenzoic acid (167.1 mg, 1.0 mmol) and 2,3-dihydrofuran (75 μL , 1.0 mmol) were used. The reaction completed in 30 h at 50 $^\circ\text{C}$. The product was isolated by flash chromatography (10:1 to 5:1 pentane/ Et_2O) as colorless oil. Yield: 86 mg, 85%. Olefinic selectivity in the crude product: 20:1. When 1.0 equiv *p*-nitrobenzoic acid and 1.0 mL ethylene glycol was used, only olefinic selectivity is 5:1.

$[\alpha]_{\text{D}}^{22} = -151.8^\circ$ ($c = 0.97$, CHCl_3).

GC-MS (EI): Calcd for $\text{C}_{12}\text{H}_{10}\text{OS} \text{M}^+$: 202.05, Found: 202.0.

Ee: 98%. Daicel Chiralcel OD-H, 98:2 *n*-hexane/isopropanol, flow rate = 0.5 mL/min.

PDA Ch1 214nm 4nm			
Peak#	Ret. Time	Area	Area %
1	24.795	593564	49.826
2	27.835	597699	50.174
Total		1191263	100.000

PDA Ch1 214nm 4nm			
Peak#	Ret. Time	Area	Area %
1	24.537	112485	1.001
2	27.537	11121980	98.999
Total		11234465	100.000

^1H NMR (400 MHz, CDCl_3): δ 7.86-7.83 (m, 2H), 7.40-7.33 (m, 3H), 6.17-6.14 (m, 1H), 6.13-6.10 (m, 1H), 6.09-6.05 (m, 1H), 6.17-6.14 (m, 1H), 6.13-6.10 (m, 1H), 6.09-6.05 (m, 1H), 4.92-4.86 (m, 1H), 4.84-4.79 (m, 1H)

^{13}C NMR (100 MHz, CDCl_3): δ 141.1, 137.5, 136.8, 128.3, 127.7, 124.4, 124.1, 123.3, 122.9, 122.2, 83.0, 75.5.

(S)-2-(thiophen-2-yl)-2,5-dihydrofuran [CAS 1335151-41-1] $\text{Pd}(\text{dba})_2$ (7.2 mg, 0.013 mmol), (*R*)-Xyl-SDP(O) (10.8 mg, 0.015 mmol), ethylene glycol (1.0 mL), 2-bromothiophene (81.5 mg, 0.50 mmol), *N*-ethyldiisopropylamine (255 μL , 1.5 mmol), *p*-nitrobenzoic acid (83.6 mg, 0.5 mmol) and 2,3-dihydrofuran (75 μL , 1.0 mmol) were used. The reaction completed in 24 h at 50 $^\circ\text{C}$. The product was isolated by flash chromatography (10:1 to 5:1 pentane/ Et_2O) as colorless oil. Yield: 61 mg, 80%. Olefinic selectivity in the crude product: 9:1.

GC-MS (EI): Calcd for $\text{C}_8\text{H}_8\text{OS}$ M^+ : 152.03, Found: 152.0.

$[\alpha]_D^{22} = -147.8^\circ$ ($c = 1.28$, CHCl_3).

Ee: 90%. Daicel Chiralcel OD-H, 98:2 *n*-hexane/isopropanol, flow rate = 0.5 mL/min.

PDA Ch1 214nm 4nm			
Peak#	Ret. Time	Area	Area %
1	14.809	405211	50.263
2	16.121	400976	49.737
Total		806187	100.000

PDA Ch1 214nm 4nm			
Peak#	Ret. Time	Area	Area %
1	14.803	8708871	94.983
2	16.123	460034	5.017
Total		9168905	100.000

^1H NMR (400 MHz, CDCl_3): δ 7.27-7.25 (m, 1H), 7.00-7.00 (m, 1H), 6.98-6.96 (m, 1H), 6.10-6.07 (m, 1H), 6.06-6.03 (m, 1H), 5.95-5.92 (m, 1H), 4.86-4.80 (m, 1H), 4.73-4.68

(m, 1H).

^{13}C NMR (100 MHz, CDCl_3): δ 145.9, 129.1, 127.7, 126.8, 125.5, 124.6, 82.8, 75.1.

(*R,E*)-2-styryl-2,5-dihydrofuran [CAS for Racemate: 119946-59-7] $\text{Pd}(\text{dba})_2$ (7.2 mg, 0.013 mmol), (*R*)-Xyl-SDP(O) (10.8 mg, 0.015 mmol), ethylene glycol (3.0 mL), 2-bromothiophene (91.5 mg, 0.50 mmol), *N*-ethyldiisopropylamine (255 μL , 1.5 mmol), *p*-nitrobenzoic acid (83.6 mg, 0.5 mmol) and 2,3-dihydrofuran (75 μL , 1.0 mmol) were used. The reaction completed in 9 h at 40 $^\circ\text{C}$. The product was isolated by flash chromatography (10:1 to 5:1 pentane/ Et_2O) as colorless oil. Yield: 61 mg, 70%. Olefinic selectivity in the crude product: 11:1.

GC-MS (EI): Calcd for $\text{C}_{12}\text{H}_{12}\text{O M}^+$: 172.09, Found: 172.0.

$[\alpha]_{\text{D}}^{22} = -200.0^\circ$ ($c = 0.97$, CHCl_3).

Ee: 88%. Daicel Chiralcel OD-H, 98:2 *n*-hexane/isopropanol, flow rate = 0.5 mL/min.

PDA Ch1 254nm 4mm

Peak#	Ret. Time	Area	Area %
1	17.908	639260	49.156
2	29.354	661204	50.844
Total		1300464	100.000

PDA Ch1 254nm 4mm

Peak#	Ret. Time	Area	Area %
1	17.681	11541022	94.000
2	28.504	736693	6.000
Total		12277715	100.000

^1H NMR (400 MHz, CDCl_3): δ 7.40-7.35 (m, 2H), 7.32-7.28 (m, 2H), 7.26-7.21 (m, 1H), 6.60 (d, $J = 15.8$, 1H), 6.16 (dd, $J = 15.8$, 7.2 1H), 5.99-5.96 (m, 1H), 5.83-5.80 (m, 1H), 5.41-5.37 (m, 1H), 4.80-4.75 (m, 1H), 4.71-4.66 (m, 1H).

^{13}C NMR (100 MHz, CDCl_3): δ 136.7, 130.9, 129.3, 128.9, 128.5, 127.7, 127.1, 126.6, 86.8, 75.3.

(*S*)-2-(*o*-Tolyl)-2,5-dihydrofuran [CAS 1361252-01-8] $\text{Pd}(\text{dba})_2$ (14.4 mg, 0.025 mmol), (*R*)-Xyl-SDP(O) (21.6 mg, 0.030 mmol), ethyl glycol (1.0 mL), 2-chlorotoluene (63.3 mg, 0.50 mmol), *N*-ethyldiisopropylamine (255 μL , 1.5 mmol) *p*-nitrobenzoic acid (83.6mg, 0.5 mmol) and 2,3-dihydrofuran (150 μL , 2.0 mmol) were used. The reaction

was complete in 55 h at 80 °C. The product was isolated by flash chromatography (10:1 to 5:1 pentane/Et₂O) as colorless oil. Yield: 67 mg, 81%. Olefinic selectivity in the crude product: 5:1.

GC-MS (EI): Calcd for C₁₁H₁₂O M⁺: 160.09, Found: 160.1.

[α]_D²² = -205.0° (*c* = 0.89, CHCl₃).

Ee: 97%. Daicel Chiralcel OD-H, 98:2 *n*-hexane/isopropanol, flow rate = 0.5 mL/min.

¹H NMR (500 MHz, CDCl₃): δ 7.31-7.29 (m, 1H), 7.21-7.13 (m, 3H), 6.04-6.02 (m, 2H), 5.93-5.90 (m, 1H), 4.89-4.85 (m, 1H), 4.80-4.76 (m, 1H), 2.39 (s, 3H).

(*S*)-*N*-Boc-2-Phenyl-2,5-dihydropyrrole [CAS 316813-68-0] Pd(dba)₂ (14.4 mg, 0.025 mmol), (*R*)-Xyl-SDP(O) (21.6 mg, 0.030 mmol), ethylene glycol (1.00 mL), bromobenzene (78.5 mg, 0.50 mmol), *N*-ethyldiisopropylamine (255 μL, 1.5 mmol), *p*-nitrobenzoic acid (83.6 mg, 0.5 mmol) and *N*-Boc-2,3-dihydro-1*H*-pyrrole (169 mg, 1.0 mmol) were used. The reaction completed in 36 h at 70 °C. The product was isolated by flash chromatography (silica gel, pentane/Et₂O) as pale yellow solid. Yield: 103 mg, 84%. Olefinic selectivity in the crude product: 9:1.

GC-MS (EI): Calcd for C₁₅H₁₉NO₂ M⁺: 245.14, Found: 245.1.

[α]_D²³ = -141.2° (*c* = 0.85, CHCl₃).

Ee: 91%. Daicel Chiralcel IC-H, 95:5 *n*-hexane/isopropanol, flow rate = 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 7.32-7.18 (m, 5H), 5.91-5.84 (m, 1H), 5.77-5.71 (m, 1H), 5.53-5.52 (br, 0.3H), 5.37 (br, 0.7H), 4.35-4.27 (m, 1H), 1.43 (br, s, 2.6H), 1.21 (br, s, 6.4H)

(Two rotamers are observed in 3:7 ratio.)

(S)-N-Boc-2-(p-Tolyl)-2,5-dihydropyrrole [NO CAS] $\text{Pd}(\text{dba})_2$ (14.4 mg, 0.025 mmol), (*R*)-Xyl-SDP(O) (21.6 mg, 0.030 mmol), ethylene glycol (1.0 mL), 4-bromotoluene (85.5 mg, 0.50 mmol), *N*-ethyl-diisopropylamine (255 μL , 1.5 mmol), *p*-nitrobenzoic acid (83.6 mg, 0.5 mmol) and *N*-Boc-2,3-dihydro-1*H*-pyrrole (169 mg, 1.0 mmol) were used. The reaction completed in 16 h at 70 $^\circ\text{C}$. The product was isolated by flash chromatography (silica gel, pentane/ Et_2O) as colorless oil. Yield: 119 mg, 92%. Olefinic selectivity in the crude product: 32:1.

GC-MS (EI): Calcd for $\text{C}_{16}\text{H}_{21}\text{NO}_2$ M^+ : 259.16, Found: 259.1.

$[\alpha]_D^{23} = -224.9^\circ$ ($c = 1.00$, CHCl_3).

Ee: 94%. Daicel Chiralcel OJ-H, 98:2 *n*-hexane/isopropanol, flow rate = 0.5 mL/min.

$\text{Pd}(\text{dba})_2$ (14.4 mg, 0.025 mmol), (*R*)-Xyl-SDP(O) (21.6 mg, 0.030 mmol), ethylene glycol (1.0 mL), 4-chlorotoluene (63.0 mg, 0.50 mmol), *N*-ethyl-diisopropylamine (255 μL , 1.5 mmol), *p*-nitrobenzoic acid (83.6 mg, 0.5 mmol) and

N-Boc-2,3-dihydro-1*H*-pyrrole (169 mg, 1.0 mmol) were used. The reaction completed in 60 h at 80 °C. The product was isolated by flash chromatography (silica gel, pentane/Et₂O) as colorless oil. Yield: 122 mg, 94%. Olefinic selectivity in the crude product: 48:1. *Ee*: 94%. Daicel Chiralcel OJ-H, 99:1 *n*-hexane/isopropanol, flow rate = 0.5 mL/min.

¹H NMR (400 MHz, CDCl₃): δ 7.16-7.06 (m, 4H), 5.88-5.81 (m, 1H), 5.74-5.68 (m, 1H), 5.49 (br, 0.31H), 5.35-5.34 (br, 0.68H), 4.33-4.25 (m, 2H), 2.32 (br, s, 2H), 2.31 (br, s, 0.9H), 1.43 (br, s, 2.9H), 1.23 (br, s, 6.2H) (Two rotamers are observed in 2.2:1 ratio.)
¹³C NMR (100 MHz, CDCl₃): δ 154.2, 153.9, 139.4, 138.8, 136.8, 131.4, 131.3, 129.2, 128.8, 126.6, 126.5, 124.4, 79.5, 79.4, 77.4, 77.1, 76.7, 67.8, 67.6, 54.0, 53.6, 28.5, 28.2, 21.1. (Two rotamers are observed.)

(*S*)-*N*-Boc-2-(*p*-Anisyl)-2,5-dihydropyrrole [NO CAS] Pd(dba)₂ (14.4 mg, 0.025 mmol), (*R*)-Xyl-SDP(O) (21.6 mg, 0.030 mmol), ethylene glycol (1.0 mL), 4-bromoanisole (93.5mg, 0.50 mmol), *N*-ethyldiisopropylamine (255 μL, 1.5 mmol), *p*-nitrobenzoic acid (83.6 mg, 0.5 mmol) and *N*-Boc-2,3-dihydro-1*H*-pyrrole (169 mg, 1.0 mmol) were used. The reaction completed in 16 h at 70 °C. The product was isolated by flash chromatography (silica gel, pentane/Et₂O) as colorless oil. Yield: 113 mg, 82%. Olefinic selectivity in the crude product: 11:1.

GC-MS (EI): Calcd for C₁₆H₂₁NO₃ M⁺: 275.15, Found: 275.1.

[α]_D²³ = -203.5.0° (*c* = 1.56, CHCl₃).

Ee: 97%. Daicel Chiralcel OJ-H, 98:2 *n*-hexane/isopropanol, flow rate = 0.5 mL/min.

Peak#	Ret. Time	Area	Area %
1	23.510	4607806	50.106
2	28.031	4588373	49.894
Total		9196179	100.000

Peak#	Ret. Time	Area	Area %
1	23.441	1522100	98.490
2	27.899	23329	1.510
Total		1545429	100.000

^1H NMR (400 MHz, CDCl_3): δ 7.20-7.10 (m, 2H), 6.85-6.82 (m, 2H), 5.89-5.82 (m, 1H), 5.74-5.68 (m, 1H), 5.48 (br, 0.32H), 5.34-5.33 (br, 0.68H), 4.32-4.24 (m, 2H), 3.79 (br, s, 2H), 3.77 (br, s, 1.0H), 1.43 (br, s, 2.8H), 1.24 (br, s, 6.2H) (Two rotamers are observed in 32:68 ratio.)

^{13}C NMR (100 MHz, CDCl_3): δ 158.8, 154.2, 153.9, 134.6, 133.9, 131.3, 128.0, 127.9, 124.5, 124.4, 113.8, 113.5, 79.5, 79.4, 77.4, 77.1, 76.8, 67.5, 67.2, 55.2, 53.9, 53.5, 28.5, 28.2. (Two rotamers are observed.)

(S)-N-Boc-2-(*o*-Anisyl)-2,5-dihydropyrrole [NO CAS]

$\text{Pd}(\text{dba})_2$ (14.4 mg, 0.025 mmol), (*R*)-Xyl-SDP(O) (21.6 mg, 0.030 mmol), ethylene glycol (1.0 mL), 2-bromoanisole (93.5 mg, 0.50 mmol), *N*-ethyldiisopropylamine (255 μL , 1.5 mmol), *p*-nitrobenzoic acid (83.6 mg, 0.5 mmol) and *N*-Boc-2,3-dihydro-1*H*-pyrrole (169 mg, 1.0 mmol) were used. The reaction completed in 16 h at 70 $^\circ\text{C}$. The product was isolated by flash chromatography (silica gel, pentane/ Et_2O) as colorless oil. Yield: 124 mg, 90%. Olefinic selectivity in the crude product: 45:1.

GC-MS (EI): Calcd for $\text{C}_{16}\text{H}_{21}\text{NO}_3$ M^+ : 275.15, Found: 275.1.

Ee: 96%. Daicel Chiralcel OJ-H, 98:2 *n*-hexane/isopropanol, flow rate = 0.5 mL/min.

Peak#	Ret. Time	Area	Area %
1	16.166	5941396	49.935
2	21.191	5956931	50.065
Total		11898327	100.000

Peak#	Ret. Time	Area	Area %
1	16.112	141024	1.982
2	20.955	6975084	98.018
Total		7116108	100.000

^1H NMR (500 MHz, CDCl_3): δ 7.21-7.16 (m, 1H), 7.09-7.08 (m, 1H), 6.90 (pseudo t, $J = 7.5$ Hz), 6.84 (d, $J = 8.2$ Hz, 1H), 5.91-5.79 (m, 2H), 5.77-5.70 (m, 1H), 4.34-4.25 (m, 2H), 3.83 (s, 3H), 1.47 (br, s, 2.8H), 1.19 (br, s, 6.4H). (Two rotamers are observed in 2.3:1 ratio.)

^{13}C NMR (100 MHz, CDCl_3): δ 158.8, 154.2, 153.9, 134.6, 133.9, 131.3, 128.0, 127.9, 124.5, 124.4, 113.8, 113.5, 79.5, 79.4, 77.4, 77.1, 76.8, 67.5, 67.2, 55.2, 53.9, 53.5, 28.5, 28.2. (Two rotamers are observed.)

(S)-N-Boc-2-(1-methyl-1H-pyrrole)-2,5-dihydropyrrole [NO CAS] $\text{Pd}(\text{dba})_2$ (14.4 mg, 0.025 mmol), (*R*)-Xyl-SDP(O) (21.6 mg, 0.030 mmol), ethylene glycol (1.0 mL), 2-bromo-1-methyl-1H-pyrrole (93.5 mg, 0.50 mmol), *N*-ethyldiisopropylamine (255 μL , 1.5 mmol), *p*-nitrobenzoic acid (83.6 mg, 0.5 mmol) and *N*-Boc- 2,3-dihydro-1H-pyrrole (169 mg, 1.0 mmol) were used. The reaction completed in 12 h at 50 $^\circ\text{C}$. The product was isolated by flash chromatography (silica gel, pentane/ Et_2O) as colorless oil. Yield: 114 mg, 92%. Olefinic selectivity in the crude product: >50:1.

GC-MS (EI): Calcd for $\text{C}_{14}\text{H}_{20}\text{N}_2\text{O}_2$ M^+ : 248.15, Found: 248.0.

$[\alpha]_{\text{D}}^{23} = -194.7^\circ$ ($c = 0.75$, CHCl_3).

Ee: 96%. Daicel Chiralcel OJ-H, 95:5 *n*-hexane/isopropanol, flow rate = 0.5 mL/min.

1 PDA Multi 2 / 214nm 4nm

PeakTable

Peak#	Ret. Time	Area	Area %
1	15.369	828438	50.116
2	21.357	824602	49.884
Total		1653041	100.000

1 PDA Multi 2 / 214nm 4nm

PeakTable

Peak#	Ret. Time	Area	Area %
1	15.200	155539	1.985
2	21.136	7680039	98.015
Total		7835578	100.000

^1H NMR (400 MHz, CDCl_3): δ 6.51-6.48 (m, 1H), 6.03-5.97 (m, 1H), 5.86 (m, 1H), 5.74-5.69 (m, 1H), 5.58-5.53 (m, 1H), 4.28-4.13 (m, 2H), 3.72 (br, s, 1.3H), 3.53 (br, s, 1.9H), 1.43 (br, s, 3.8H), 1.27 (br, s, 6.1H). (Two rotamers are observed in 1.6:1 ratio.)

^{13}C NMR (125 MHz, CDCl_3): δ 154.3, 154.1, 131.8, 131.6, 129.6, 124.9, 124.6, 122.6, 122.4, 108.1, 107.4, 106.7, 106.6, 79.7, 79.4, 77.4, 77.1, 76.9, 61.1, 59.7, 53.2, 34.1, 33.8, 28.9, 28.5, 28.2, 25.8, 25.4. (Two rotamers are observed)

(S)-N-Boc-2-(p-fluorophenyl)-2,5-dihydropyrrole [NO CAS] Pd(dba)₂ (28.8 mg, 0.050 mmol), (R)-Xyl-SDP(O) (43.2 mg, 0.060 mmol), ethylene glycol (1.0 mL), 1-bromo-4-fluorobenzene (87.5 mg, 0.50 mmol), N-ethyldiisopropylamine (255 µL, 1.5 mmol), p-nitrobenzoic acid (83.6 mg, 0.5 mmol) and N-Boc-2,3-dihydro-1H-pyrrole (169 mg, 1.0 mmol) were used. The reaction completed in 22 h at 70 °C. The product was isolated by flash chromatography (silica gel, pentane/Et₂O) as colorless oil. Yield: 92 mg, 70%. Olefinic selectivity in the crude product: 8:1.

GC-MS (EI): Calcd for C₁₅H₁₈FNO₂ M⁺: 263.13, Found: 263.1.

Ee: 93%. Daicel Chiralcel OJ-H, 98:2 n-hexane/isopropanol, flow rate = 0.5 mL/min.

¹H NMR (400 MHz, CDCl₃): δ 7.27-7.15 (m, 2H), 7.01-6.96 (m, 2H), 5.92-5.85 (m, 1H), 5.74-5.68 (m, 1H), 5.51-5.50 (m, 0.32 H), 5.37-5.36 (m, 0.67H), 4.33-4.22 (m, 2H), 1.43 (br, s, 2.9H), 1.27 (br, s, 6.1H). (Two rotamers are observed in 2.1:1 ratio.)

¹³C NMR (125 MHz, CDCl₃): δ 163.2, 160.8, 138.3, 137.5, 131.0, 128.4, 128.3, 124.9, 115.3, 115.1, 115.1, 114.9, 79.7, 67.4, 67.1, 54.0, 53.6, 28.5, 28.2. (Two rotamers are observed)

(S)-N-Boc-2-(p-Tolyl)-2,5-dihydropyrrole [NO CAS] Pd(dba)₂ (14.4 mg, 0.025 mmol), (R)-Xyl-SDP(O) (21.6 mg, 0.030 mmol), ethylene glycol (1.0 mL), 2-chlorotoluene (63.0 mg, 0.50 mmol), N-ethyldiisopropylamine (255 µL, 1.5 mmol), p-nitrobenzoic acid (83.6 mg, 0.5 mmol) and N-Boc-2,3-dihydro-1H-pyrrole (169 mg, 1.0 mmol) were used. The reaction completed in 42 h at 80 °C. The product was isolated by flash chromatography

(silica gel, pentane/Et₂O) as colorless oil. Yield: 121 mg, 93%. Olefinic selectivity in the crude product: 48:1.

Ee: 90%. Daicel Chiralcel OJ-H, 99:1 *n*-hexane/isopropanol, flow rate = 0.5 mL/min.

¹H NMR (500 MHz, CDCl₃): δ 7.16-7.08 (m, 4H), 5.86-5.65 (m, 3H), 4.42-4.28 (m, 2 H), 2.43 (br, s, 0.8H), 2.37 (br, s, 2.3H), 1.45 (br, s, 2.4H), 1.16 (br, s, 6.8H) (Two rotamers are observed in 2.8:1 ratio.)

¹³C NMR (125 MHz, CDCl₃): δ 154.0, 140.9, 139.9, 134.5, 134.3, 130.5, 130.4, 130.4, 130.0, 126.9, 126.8, 126.4, 126.3, 126.1, 125.4, 124.4, 124.3, 79.4, 65.0, 64.9, 54.2, 53.8, 28.5, 28.1, 19.1. (Two rotamers are observed)

(*S,Z*)-3-(2-methoxyphenyl)cyclooct-1-ene [CAS] Pd(dba)₂ (14.4 mg, 0.025 mmol), (*R*)-Xyl-SDP(O) (21.6 mg, 0.030 mmol), methanol (1.0 mL), 2-bromoanisole (93.5 mg, 0.50 mmol), *N*-ethyldiisopropylamine (255 μL, 1.5 mmol), *p*-nitrobenzoic acid (83.6 mg, 0.5 mmol) and *cis*-cyclooctene (260 μL, 2.0 mmol) were used. The reaction completed in 18 h at 80 °C. The product was isolated by flash chromatography with pentane as colorless oil. Yield: 92 mg, 85%. Olefinic selectivity in the crude product: 11:1.

GC-MS (EI): Calcd for C₁₅H₂₀O M⁺: 216.15, Found: 216.0.

Ee: 84%. Daicel Chiralcel OJ-H, 99.5:0.5 *n*-hexane/isopropanol, flow rate = 0.5 mL/min.

PDA Ch1 214nm 4nm

Peak#	Ret. Time	Area	Area %
1	9.892	1502961	49.577
2	10.695	1528637	50.423
Total		3031598	100.000

PDA Ch1 214nm 4nm

Peak#	Ret. Time	Area	Area %
1	9.793	387519	7.811
2	10.615	4573874	92.189
Total		4961393	100.000

^1H NMR (400 MHz, CDCl_3): δ 7.28 (dd, $J=7.5$, 1.5Hz 1H), 7.18-7.14 (m, 1H), 6.93 (t, J = 7.4, 1H), 6.85 (d, J = 8.2 Hz, 1H), 5.71-5.59 (m, 1H), 4.24-4.18 (m, 1H), 3.81 (s, 3H), 2.50-2.41 (m, 1H), 2.15-2.08 (m, 1H), 1.79-1.69 (m, 4H), 1.67-1.60 (m, 2H), 1.58-1.50 (m, 1H), 1.44-1.35 (m, 1H).

^{13}C NMR (100 MHz, CDCl_3): δ 156.9, 134.9, 133.8, 128.9, 127.5, 126.7, 120.7, 110.8, 55.6, 36.6, 35.2, 29.8, 26.7, 26.4, 26.3.

Chapter 2

Asymmetric Conjugate Addition of Organoboroxines to Common Enones Using Copper Catalysts

2.1 Introduction

Transition metal-catalyzed enantioselective conjugate addition of activated alkenes has been extensively developed as a promising approach to access optically enriched chiral building blocks.⁷⁹⁻⁸⁴ In the reaction, activated alkenes react with reactive organometallic reagents or organoboron reagents. It tolerates functional groups such as alcohols, amides and aryl halides. It was used in synthesis of several natural products and bioactive moieties.^{80,85} For example, Hayashi group developed an efficient route to synthesize a series of β -amino acid derivatives via a rhodium-catalyzed addition of an arylboron reagent.⁸⁶ Minnaard and Feringa et al. used copper-catalyzed conjugate addition of organozinc reagents to synthesize (-)-Pumiliotoxin C, a potent neurotoxin that acts as a noncompetitive blocker for acetylcholine receptor channels.⁸⁷

Scheme 2.1 Application of asymmetric conjugate addition

Scheme 2.2 Synthesize (-)-Pumiliotoxin C

2.2 Rhodium-catalyzed conjugate addition of organoboron reagents

In 1997, Miyaura group reported the first example of conjugate addition of aryl- and alkenylboronic acids to enones using rhodium/dppb catalyst. They obtained racemic products in good yield and both the cyclic and acyclic enones reacted well.⁸⁸ Miyaura group also conducted DFT calculation and established that the 1,2-insertion pathway formed an η^3 -bound rhodium enolate as the immediate product from insertion.⁸⁹ Since then, enantioselective conjugate addition of arylboronic acids to enones has been extensively developed by using many types of chiral supported ligand.

Scheme 2.3 1,2-Insertion pathway in rhodium-catalyzed conjugate addition

2.2.1 Rhodium catalyst of bisphosphine ligands

In 1998, Hayashi group developed the first version for enantioselective conjugate addition of aryl- and alkenylboronic acids to cyclic enones. $\text{Rh}(\text{acac})(\text{C}_2\text{H}_4)_2$ and (*S*)-BINAP were used as the catalyst combination and the reaction produced high *ee*.⁹⁰ Both cyclic enones and some acyclic enones were suitable substrates.

Scheme 2.4 Rhodium-catalyzed enantioselective conjugate addition using $(S)\text{-BINAP}$ ligand

Later in 2002, Hayashi group studied the mechanism of the rhodium catalysis.⁹¹ They found that after insertion, the enolate was bound to rhodium in an η^3 -manner and that the transmetalation of dimeric rhodium complex $[\text{Rh}(\text{OH})(\text{BINAP})]_2$ with arylboronic acid was fast at 25 °C.

In 2009, Korenaga group modified the *P*-phenyl groups on BINAP by introducing larger and more electron-withdrawing aryl groups which led to highly stereoselective ligands for the addition reaction.⁹²

2.2.2 Rhodium catalysts of diene ligands

In 2001, Miyaura group found that a small and weak-donating diene, 1,5-cyclooctadiene (cod) was more active as a supporting ligand in catalyzing conjugate reaction, than a common biphosphine BINAP.⁹³

Scheme 2.5 Rhodium/cod-catalyzed conjugate addition

In 2003, Hayashi group invented the first chiral diene ligands based on a norbornadiene skeleton.⁹⁴ The chiral dienes were able to catalyze enantioselective conjugate addition in higher activity and higher enantioselectivity than bisphosphine ligands. Both cyclic and acyclic enones reacted well. Hayashi group later conducted kinetic studies and found that the higher catalytic activity of the Rh/cod complex, as compared with Rh/BINAP complex, can be attributed to much faster transmetalation to the former.⁹⁵ In subsequent

years, many structurally diverse chiral dienes were invented for the conjugate addition.^{94,96-120}

Scheme 2.6 Rhodium-catalyzed enantioselective conjugate addition using a diene ligand

Scheme 2.7 Results using diene ligands in the model conjugate addition

2.2.3 Rhodium catalysts of other types of ligands

In 2003, Vries and Feringa et al. applied monodentate phosphoramidite ligands to conjugate addition of arylboronic acids to cyclic enones and obtained excellent results.^{121,122} They proposed that two phosphoramidite ligands bind to the rhodium center in *cis* positions to form a good chiral pocket.

Scheme 2.8 Rhodium-catalyzed enantioselective conjugate addition using a phosphoramidite ligand

In 2003, Andrus group used an *N*-heterocyclic carbenes (NHC) ligand bearing chiral cyclophane groups in the addition reaction.¹²³ Cyclic enones gave high *ee*, but acyclic enones gave only moderate 78-91% *ee*.

Scheme 2.9 Rhodium-catalyzed enantioselective conjugate addition using an NHC ligand

In 2007, Dorta group developed the first chiral disulfoxide ligand, *p*-tol-Binaso, based on a binaphthyl backbone.¹²⁴ Excellent results were obtained from reactions of cyclic enones.¹²⁵ However, when Me-BIPHESO was applied to acyclic enones such as *trans*-1,3-diphenyl-2-propenone, only 20% *ee* was obtained.

Scheme 2.10 Rhodium-catalyzed enantioselective conjugate addition using a disulfoxide ligand

Tomioka group developed a Proline-derived amidophosphine to catalyze the conjugate

addition.^{126,127} It also gave good *ee*. In 2005, Helmchen group also successfully used a mixed NHC-phosphine ligand in this conjugate addition.¹²⁸

Scheme 2.11 Rhodium-catalyzed enantioselective conjugate addition using an amidophosphine ligand

Scheme 2.12 Rhodium-catalyzed enantioselective conjugate addition using an NHC-phosphine ligand

Interestingly, in 2005 Hayashi group designed a phosphine-alkene mixed ligand which catalyzed the conjugate addition of cyclic enones and phenylboronic acids in good results.¹²⁹ The ligand was also applied to reactions of other activated alkenes, such as maleimides.

Scheme 2.13 Enantioselective conjugate addition of arylboronic acid to enones using a phosphine-alkene hydrid ligand

2.3 Palladium-catalyzed enantioselective conjugate addition of arylboronic acids to enones

In 1995, Uemura group developed the first palladium-catalyzed, nonstereoselective

conjugate addition of arylboronic acid to enones in the presence of a Lewis acid.¹³⁰ However, the palladium catalysis remained dormant in subsequent years. In 2005, Minnaard group discovered that $\text{Pd}(\text{TFA})_2$ and (*R,R*)-Me-Duphos catalyzed the reaction of phenylboronic acid to 2-cyclohexenone in excellent *ee*.¹³¹ However, when the reaction was applied to other enones, both the yields and *ee* decreased significantly.

Scheme 2.14 Enantioselective conjugate addition of arylboronic acid to enones catalyzed by $\text{Pd}(\text{OCOCF}_3)_2$ and (*R,R*)-Me-Duphos

In 2011, Stoltz group developed pyridine-oxazoline ligands for enantioselective conjugate addition of arylboronic acids to β -substituted cyclic enones which formed all-carbon quaternary stereocenters.¹³² High *ee* values were obtained for these challenging Michael acceptors. They later conducted DFT calculation and concluded that the insertion step took place via 1,2-insertion of enones to produce η^3 -bound palladium enolate directly.¹³³ M. Shi et al. also published on asymmetric conjugate addition of acyclic enones using chiral Pd/NHC complexes with good *ee*.^{134,135}

Scheme 2.15 Palladium-catalyzed enantioselective conjugate addition of arylboronic acids to cyclic enones and DFT simulation of the insertion step

2.4 Copper-catalyzed enantioselective conjugate addition of enones

2.4.1 Copper-catalyzed conjugate addition of organometallic reagents to enones

Copper-catalyzed enantioselective conjugate addition of organozinc reagents to enones was a common reaction to test new chiral ligands and was extensively developed by many groups. In the late 1990s, Feringa et al. reported the use of monodendate phosphoramidite ligands in this reaction and obtained high *ee* in addition to 2-cyclohexenone.^{136,137} Later in 2003, Qi-Lin Zhou group also successfully applied their spiro-phosphoramidite ligands in this reaction.¹³⁸ However, results for acyclic enones remained unsatisfactory.

Some representative examples are listed in Scheme 2.16 and more detailed discussion on the topic can be found in recent reviews.^{79,80,139} In 2001, Hoveyda group invented peptide-linked phosphine ligands.¹⁴⁰⁻¹⁴² Both cyclic and acyclic enones gave high *ee* values and the reaction was applied to asymmetric synthesis of natural products, for example, Clavularin B and Erogorgiaene.^{140,143} In 2006, Hoveyda group reported chiral NHC-copper catalysts for asymmetric addition to challenging β -substituted enones.¹⁴⁴

In 2003, Leighton group used a *tert*-leucine-derived phosphine which showed generality with cyclic enones.¹⁴⁵

Scheme 2.16 Copper-catalyzed conjugate addition of organozinc reagents to enones

2.4.2 Copper-catalyzed conjugate addition of air-stable organoboron reagents to Michael acceptors

Compared to addition reactions of reactive organozinc reagents, only limited success was met in similar addition processes of less reactive organoboron reagents. The latter are often stable to air and moisture and thus have great advantages in terms of practical applications.

In 2011, Hayashi group reported the first example of copper-catalyzed enantioselective conjugate addition of organoboronates.¹⁴⁶ In their reaction, highly activated α -cyanoacrylates were used as substrates and a bidentate NHC ligand was used. Various aryl, heteroaryl, and alkenyl groups can be present at the β position of Michael acceptors, but only around 1:1 diastereoselectivity was seen at α position of the products.

Scheme 2.17 Copper-catalyzed enantioselective conjugate addition of organoboronates to α -cyanoacrylates

Scheme 2.18 A proposed mechanism of copper-catalyzed enantioselective conjugate addition of organoboronate to α -cyanoacrylate

A proposed mechanism is showed in Scheme 2.18. First, copper alkoxide **A** undergoes

transmetalation with arylboron reagents to produce arylcopper(I) **B**. α -Cyanoacrylate inserts into **B** to produce enolate **C**, followed by ligand exchange with KO t Bu to produce product **D** and regenerate the catalyst. The oxidation state of copper(I) did not change in the catalytic cycle, which is different from the copper-catalyzed enantioselective conjugate addition of Grignard and organozinc reagents where organocopper(III) intermediates were involved. Copper enolate **C** and potassium enolate **D** have been detected by NMR spectroscopy.

In 2012, Sawamura group developed an enantioselective conjugate addition of alkyl-(9-BBN) to α,β -unsaturated ketones that were activated by imidazole and benzimidazole rings. Moderate to good *ee* values were obtained.¹⁴⁷

Scheme 2.19 Copper-catalyzed enantioselective conjugate addition of alkylboranes to activated enones

2.5 Organocatalyst-catalyzed conjugate addition of organoboron reagents to enones

Chong group reported enantioselective conjugate addition of alkenylboronates to acyclic enones using a modified BINOL as a chiral catalyst. Products were obtained in >90% *ee*.¹⁴⁸ However when arylboronic acid esters were used, the reaction proceeded in around 80% *ee*.¹⁴⁹ The organoboronates may undergo transesterification with the catalyst to produce chiral organoboronates which were responsible for the asymmetric bond formation.

Scheme 2.20 Organocatalytic conjugate addition of organoboron reagents to enones

Sugiura group also reported similar conjugate addition of alkenylboronic acid to enones using *o*-monoacyltartaric acid as a catalyst.¹⁵⁰ However, only four examples of alkenylboronic acids were used.

Scheme 2.21 Enantioselective conjugate addition of boronic acids to enones catalyzed by *o*-monoacyltartaric acid

2.6 Our work on asymmetric conjugate addition of organoboron reagents to common enones using copper/phosphoramidite catalysts.

Although Hayashi and Sawamura groups reported enantioselective conjugate addition to the enones, good results were limited to highly activated Michael acceptors. We decided to investigate the addition of arylboron reagents to common unactivated enones in 2014.

2.6.1 Catalyst and condition optimization

We first chose a model conjugate addition of phenylboronic acid and cyclohexenone to search for copper catalysts. We found that cyclohexenone was consumed in the presence of various ligands under many conditions. However, no desired product was detected while many minor byproducts were detected by GC and GCMS.

We then turned our attention to chalcone as the model enone. After many trials of conditions, we found that when CuCl was used as copper source and KO*t*Bu was base, about 37% of the desired product was obtained. When phenylboroxine was changed to its esters of diols, no desired product was obtained. Among many different bases, KOAc

proved to be the suitable base for the conjugate addition, while strong bases such as NaOH and alkoxides inhibited the process. We also found that H₂O and alcohol inhibited the reaction. Later, we found out that Hu group also reported conjugate addition of phenylboroxine with enones in year 2011 using simple copper salts as the catalyst. No asymmetric version was reported by Hu group.¹⁵¹

Scheme 2.22 Conditions for the copper-catalyzed conjugate addition to enones

We chose conjugate addition of phenylboroxine to *trans*-4-methylchalcone as the model reaction to find suitable ligands for the copper catalysts and to optimize conditions. We started with the solvent screening using Feringa ligand and KOAc as base. The results are presented in Table 2.1. The best result was obtained when the reaction was set up in toluene. When the reactions were set up in THF, dioxane and 1,2-dimethoxybenzene, the products were obtained in lower yields. The reaction did not proceed when other polar solvent such as ACN, DMF and DMSO were used.

Table 2.1 Effect of solvents

Entry	Solvent	Conv (%) 12h	GC yield (%)	ee (%)
1	Toluene	85	79	46
2	1,2-Dimethoxybenzene	50	41	45
3	Dioxane	65	62	43
4	THF	45	38	40
5	1,2-Dichloroethane	40	35	33
6	MeCN	0	0	-
7	DMF	0	0	-
8	DMSO	0	0	-
9	NMP	0	0	-

The effect of different copper salts is shown in Table 2.2. Both copper(I) and copper(II) salts catalyzed the addition in good yields and in similar *ee*. CuOTf•(0.5 toluene) was chosen as the best copper salt in the later studies.

Table 2.2 Effect of copper salts using Feringa ligand

Entry	Cu sources	Conv (%)	GC yield (%)	ee (%)
1	CuCl	85	79	46
2	CuBr	75	73	45
3	CuOAc	90	83	45
5	CuCN	0	0	-
6	CuOTf•(0.5 toluene)	86	82	46
7	Cu(acac) ₂	90	63	46
8	Cu(OTf) ₂	90	81	45
9	Cu(OAc) ₂	93	77	45

The effect of different ligands is shown in Table 2.3. BINAP and other bisphosphines did not catalyze the reaction. Then we focused on phosphoramidite ligands during the ligand screening. By comparing entries 4 and 8, it is clear that phosphoramidites with a spiro-biindanyl backbone catalyzed the reaction in higher *ee* value than BINOL derivatives. Among several structural derivatives of the spiro phosphoramidites including home-made ones, we found that Qilin Zhou's ligand gave the highest *ee* in the reaction.

Table 2.3 Effect of chiral ligands

Entry	Ligand	Conv (%) (12h)	GC yield (%)	ee (%)
1		35	31	-30
2		100	94	-15

3		100	94	-17
4		85	84	46
5		80	70	66
6		95	85	51
7		100	95	57
8	(<i>R_a</i> , <i>R</i> , <i>R</i>)- L1	100	95	-89
9	(<i>S_a</i> , <i>R</i> , <i>R</i>)	90	85	74

10		90	85	-76
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However, when the condition was applied to other acyclic ketones, only 80-89% *ee* was obtained to most of the substrates. A new ligand was necessary to increase the enantioselectivity. Since the result of *trans*-4-methylchalcone was not typical, we turned to 1-naphthyl- chalcone as the model substrate to test the ligand in the reaction. The results are presented in Scheme 2.23. When phosphoramidites based on BINOL structure were used, products in low yields and enantioselectivities were obtained. When the ligand **L1** was used, the product was obtained in 87% *ee*. When changing one α -methyl benzyl group to the tetrahydronaphthalene group (**L3** versus **L1**), the *ee* value increased to 91%. When keeping the tetrahydronaphthalene group and changing another α -methyl benzyl group to the bulky cyclododecane group (**L4** versus **L3**), the *ee* value remained the same while the reactivity increased. When keeping the tetrahydronaphthalene group and changing the phenyl ring from the α -methyl benzyl group to cyclohexyl group, (**L5** versus **L3**) the *ee* was increased to 94%. We tried to "invert" the configuration of cyclohexylethylamine in **L5**, and the resulting ligand **L7** was slightly less selective (88% *ee*). We also tried to "mutate" the spiro chirality in **L5**. The new ligand **L6** led to the opposite enantiomer as the major product in the model reaction. Thus, the spiro chirality had dominant influence on the absolute configuration of the product. We also checked the new ligand **L9** based on BINOL, but only moderate enantioselectivity was obtained. We chose ligand **L5** as the best ligand.

The effect of different copper salts is shown in Table 2.4. We found that CuOTf.(0.5toluene) was the best copper salt for the reaction. Other copper salts, such as

Cu(OAc), CuCl and Cu(OAc)₂ also catalyzed the reaction in high yield and in the same enantioselectivities.

When KOAc was absent (entry 9 and entry 11), almost no product was detected. When 20 mol% of KOAc was used (entry 8 and 10), only 50-55% yields were obtained. However, by increasing the catalyst loading to 10 mol% and prolonging the reaction time to 72 h, we obtained 86% yield of the product at 20 mol% KOAc (entry 12 and 13). This suggested that KOAc was not consumed in the reaction. Most likely it was inverted to produce active species (L)CuOAc.

Table 2.4 Effect of copper salts and amounts of KOAc in screening using ligand **L5**

Entry	Copper source	KOAc	Conv (%)	GC yield (%)	ee (%)
1	CuCl	2	91	87	95
2	CuBr	2	85	78	95
3	CuI	2	15	10	--
4	Cu(OTf) ₂	2	60	54	94
5	CuOTf•(0.5 tol)	2	100	95	95
6	Cu(OAc)	2	90	87	95
7	Cu(OAc) ₂	2	90	84	94
8	CuOTf•(0.5 tol)	0.2	50	50	95
9	CuOTf•(0.5 tol)	0	0	0	--
10	Cu(OAc)	0.2	55	53	95
11	Cu(OAc)	0	5	2	--
12	Cu(OAc) 10 % L5 12% 72 h	0.2	90	86	95
13	Cu(OAc) 20 % L5 24% 72 h	0.2	98	95	95

When the ratio of copper to the ligand was 1:1 or 1:2 (Table 2.5, entry 2 and 4), very similar result was seen. However, when the ratio was reduced to 1:0.5 (with less ligand), catalytic activity decreased significantly. This suggested that the active catalyst most likely had one ligand on the copper.

Table 2.5. Effect of copper and ligand **L5** ratio under optimized conditions

Entry	Ratio of x : y	GC yield (%) (5 h)	GC yield (%) (24 h)	<i>Ee</i> (%)
1	5 : 2.5	35	73	94
2	5 : 5	70	93	94
3	5 : 6	70	98	95
4	5 : 10	70	93	95

Thus our optimal conditions were included CuOTf.(0.5toluene) (5 mol%), ligand **L5** (6 mol%), KOAc (2.0 equiv) as base in toluene solvent, and the reaction temperature was around 70 °C.

2.6.2 Examples of enantioselective conjugate addition of phenylboroxine to acyclic enones

We successfully applied the optimal condition to other enones. When enones carried β -aryl groups in electron-withdrawing groups and electron-donating groups, both reacted well to give > 90% ee. We also found that enones carrying β -heteroaryl rings including thienyl, benzothienyl, benzofuryl and ferrocenyl, high ee values were obtained.

Scheme 2.24 Examples of enantioselective conjugate addition of phenylboroxine to β -aryl-substituted enones

Two examples of conjugated dienones were tested and only the 1,4-adducts were formed (by GC and GC-MS). No trace amount of 1,6-adducts were detected in crude reaction mixture. The terminal groups in the dienones can be both aryl and alkyl groups.

When the enones carried β -alkyl groups, the reactions required higher catalyst loading

(10 mol%). The β groups can be *n*-propyl, isopropyl and cyclohexyl with *ee* ranging from 80-94%.

Scheme 2.25 Examples of enantioselective conjugate addition of phenylboroxine to α' -aryl-substituted enones

When enones have different α' -aryl and heteroaryl groups, all the reaction completed in 30 hours under the optimal condition (5 mol% Cu), and products were obtained in good yield and > 90% *ee*. As shown in Scheme 2.25, the enones also tolerated α' -alkyl groups, including isopropyl and *t*-butyl groups. However, for enones carrying α' -methyl or ethyl group, the materials was consumed, but no desired product was detected by GC and GCMS. It is possible that the latter enones undergoes enolization which caused oligomerization or polymerization of the enones.

The reaction can be scaled up to give a gram of the product in the presence of 1 mol% of the catalyst at 110 °C. When the reaction was opened to air before heating and then sealed up, the product was obtained in 70% yield with 78% conversion and 91% *ee* at 70 °C.

We also tested activated Michael acceptors which were used in Hayashi and Sawamura's work with our catalyst. For an α -cyanoacrylate, less than 10% yield product was obtained with low conversion. For *N*-methyl-2-croylimidazole, 50% conversion and 30% yield were obtained at 10 mol% catalyst loading. The enantioselectivity was only 13% *ee*.

Scheme 2.26 Results from reactions of activated Michael acceptors

Different arylboroxines were tested under our optimal condition as shown in the Scheme 2.27. In general, electron-withdrawing groups in arylboron reagents accelerated the reaction while electron-donating groups caused slower reactions. For the *p*-anisylboroxine, the reaction gave only 65% yield after 30 hours with a partial conversion. For a more hindered *o*-tolylboroxine, the reaction completed in 36 hours when the catalyst loading was increased to 10 mol% at 100 °C. For 2-thienylboroxine, the reaction did not complete in 36 hours at 10 mol% catalyst loading. The product was obtained in only 50% yield (about 80% conversion) and 82% *ee*. To phenylvinylboroxine, the reaction gave only 50% yield and around 50% *ee*.

Scheme 2.27 Examples of enantioselective conjugate addition of arylboroxines to chalcone

The ketone group in the model product can be readily converted to other functional groups, such as esters and amides. It was also deoxygenated by Pd/C catalyzed hydrogenolysis. The enantioselectivity did not change in all the cases.

Scheme 2.28 Product derivatization

We tested some cyclic enones with phenylboroxine under the optimal condition. Cyclohexenone, cyclopentenone and 1-indenone were consumed, but no desired product was detected. α , β -Unsaturated esters, same as ethyl cinnamate, no conversion of esters was seen.

Scheme 2.29 Unsuccessful examples under the optimal conditions

2.6.3 Mechanistic study of copper-catalyzed enantioselective conjugate addition reaction

We considered several possible pathways for the conjugate addition. In copper-catalyzed conjugate addition of Grignard and organozinc reagents to enones, most pathways likely involved oxidative addition to form a copper(III) intermediates and subsequent reductive elimination to form copper enolates.¹⁵²⁻¹⁵⁵ In these reactions, Lewis acidic metal ions, such as lithium, zinc, magnesium and aluminum were critical for stabilization of enolate intermediate. However, in our reaction, the potassium ion is not sufficiently Lewis acidic to play this role. Furthermore, the boron centers of organoboroxines are too hindered to bind to the carbonyl group of enones.

Scheme 2.30 Proposed mechanistic pathway for the 1,4-addition of organocuprates

Professor Hajime Hirao's group performed DFT calculation on the insertion step of our model reaction. To our surprise, classical 1,2-insertion of the C=C bond was not found. Instead 1,4-insertion was identified as the preferred mode of the insertion. The conjugate addition proceeded through a six-membered cyclic transition state and formed an *O*-bound copper enolate directly.

Scheme 2.31 1,4-Insertion of phenylcopper(I) to chalcone

In 1989, Mookuma et al. suggested that nucleophilic addition of methylcopper to acrolein proceeded in 1,4-insertion rather than 1,2-insertion.¹⁵⁶ In their calculation, in the gas phase, the activation energy for 1,4-addition was 34 kcal/mol, compared to 48 kcal/mol for 1,2-addition. Although the calculation is in the gas phase, the big gap between the energies still suggests the 1,4-addition is the preferred pathway for the addition at the standard reaction conditions.

From the calculation results of our reaction system, the energy gap between the two transition states, TS-*R* and TS-*S*, was 2.3 kcal/mol. This was in good agreement with the results 94% ee in the model reaction. The structures in two ground states can interconvert easily, so the activation energy leading to the major (*R*)-enantiomer was 13.6 kcal/mol as shown in Scheme 2.32.

Scheme 2.32 Reaction energy profiles (in kcal/mol) for conjugate addition via 1,4-insertion

In the calculated 1,4-insertion pathway, only the *s*-cisoid conformation of enones are in the reactive conformation. This was confirmed by our experiments that cyclohexenone

and 1-indenone did not give conjugate adducts. The calculated 1,4-insertion pathway predicted a C12/C13 KIE value of 1.02 at β carbon of chalcone, which was confirmed by our natural-abundance C13 KIE experiments.¹⁵⁷

Scheme 2.33 KIE at natural-abundance for the conjugate addition

By inspecting the calculated transition states, we concluded that the factor of the chiral ligand contributed to the high enantioselectivity of the reaction. The chiral ligand adopts a special conformation to minimize the steric interaction of two large groups on the nitrogen atom. In the TS-*R* transition state (left), one indanyl group shielded the bottom-left space while the *N*-cyclohexyl group blocked the top-right quadrant. Moreover, the bottom-right quadrant is slightly more hindered than the top-left. Therefore the dominate TS had the bond forming occurring in the top-left quadrant.

Scheme 2.34 Transition states TS-*R* (left) and TS-*S* (right) for 1,4-insertion of (L)phenylcopper(I) to *p*-methylchalcone. Ligand is shown in a space-filling model and reacting ligands and copper are represented by ball-and-stick. Copper is blue while Cu-bound phenyl ring is pink. The carbon atoms in chalcone are green while its oxygen is red

One interesting aspect of TS-*R* is the weak hydrogen bonding between two aromatic C-Hs of the ligand and the carbonyl group of *p*-methylchalcone. Such hydrogen bonding is not observed in TS-*S*. Each of the hydrogen atoms involved in the hydrogen bonding

has a partial positive charge of + 0.2. The attraction between the ligand and carbonyl group provides an additional stabilization of the copper *O*-bound enolate during the insertion step. The weak hydrogen bonding offers stabilization energy of 0.5-4 kcal/mol, depending on the acidity of the aromatic CH bonds and topology of the atoms involved.^{133,158,159}

Mechanistic studies on transmetalation of the copper enolate to the boron enolate have not been studied by others. Dr. Hajime conducted DFT calculation on the transmetalation of (L)copper(I) enolate with phenylboroxine and a high energy transition state was identified (23-25 kcal/mol). This suggested that the transmetalation of the copper enolate is the rate-determining step in the catalytic cycle. When phenylboronic acid and its pinacol ester were used in the reaction, no conjugate adducts was obtained. This is because much higher activation energy was identified (27-30 kcal/mol) for transmetalation or it is because phenylboronic acid can cause protonation of the copper enolate intermediate and cause a problem in catalyst turnover.

Scheme 2.35 Transmetalation of copper enolate with phenylboroxine

2.8 Summary

We developed a mild reaction for enantioselective conjugate addition of organoboron reagents to acyclic enones. A diverse set of acyclic enones bearing alkyl, aryl and heteroaryl groups produced the conjugate adducts in high yields and enantioselectivities.

Furthermore, a rare 1,4-insertion pathway through a six-membered cyclic transition state was identified, which was supported by both DFT calculation and natural-abundance C13 KIE experiments.

2.9 Experiment section

2.9.1 General

All NMR spectra were acquired on Bruker BBFO1 400 MHz and Bruker AV 300 MHz NMR spectrometers. ¹H NMR (400 MHz) chemical shifts were recorded relative to SiMe₄ (δ 0.00) or residual protiated solvents (CDCl₃: δ 7.26). Multiplicities were given as: s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). The number of protons (n)

for a given resonance was indicated by nH. Coupling constants were reported as a *J* value in Hz. ¹³C NMR (100 MHz) chemical shifts were recorded relative to solvent resonance (CDCl₃; δ 77.16). ¹⁹F NMR (376 MHz) chemical shifts were recorded relative to an external standard (BF₃·OEt₂; δ 153.0). ³¹P NMR (126 MHz) chemical shifts were relative to an external standard (85% H₃PO₄; δ 0.00). Proof of purity of new compounds was demonstrated with copies of ¹H, ¹³C, ³¹P and ¹⁹F NMR spectra.

Glassware was dried at 120 °C for at least 1 h before use. Dry toluene, hexane, diethyl ether and dichloromethane were collected from a solvent purification system containing a column of activated alumina (1 m x 2) under argon. Dry THF was freshly distilled from sodium/benzophenone under argon. All anhydrous solvents were stored in Schlenk tubes in the glove box. Unless noted otherwise, commercially available chemicals were used as received without purification. The GC internal standard, *n*-C₁₂H₂₆ and *n*-C₁₄H₃₀ was degassed with argon and dried over activated 4 Å molecular sieve beads before use. Flash chromatography was performed using Merck 40-63D 60 Å silica gel. Gas chromatography (GC) analysis was performed on a Shimadzu GC-2010 instrument with Agilent J & W GC column DB-5MS-UI. GC/MS analysis was conducted on a Thermo Scientific DSQ II single quadrupole GC/MS instrument with Agilent J & W GC column DB-5MS-UI. ESI/MS analysis was conducted on a ThermoFinnigan LCQ Fleet MS spectrometer.

Chiral HPLC analysis was performed on a Shimadzu LC-20AD instrument using Daicel Chiracel columns at 25 °C and a mixture of HPLC-grade hexane and isopropanol as eluent. Optical rotation was measured using a JASCO P-1030 Polarimeter equipped with a sodium vapor lamp at 589 nm and the concentration of samples was denoted as *c*.

2.9.2 Synthesis of chiral phosphoramidites

(1*S*,1*S*)-*N*-(1-Cyclohexylethyl)-1-tetralinylamine and (1*S*,1*R*)-isomer.

In an argon-filled glove box, (1*S*)-1,2,3,4-tetrahydro-1-naphthylamine (10 mmol, 1.47 g) and cyclohexyl methyl ketone (10 mmol, 1.26 g) were added to 120-mL Parr bomb. Then Ti(*Oi*-Pr)₄ (9 mL, 30.6 mmol) was added via syringe. The reaction mixture was stirred at RT over 30 min before addition of 10% Pd/C (60 mg, 0.05 mmol). The reaction mixture was pressurized with H₂ gas (3 bar) and then stirred at RT for 48 h. When the reaction was completed, the reaction mixture was cooled in an ice bath and quenched with 10% aq NaOH (50 mL). This crude mixture was extracted with EtOAc (100 mL x 3). The combined organic layers and were washed with water, brine and then dried with

anhydrous Na₂SO₄. The diastereoselectivity of the crude product was determined to be around 3:2 by GC. Removal of the solvent by rotary evaporator and the residue was purified by flash column chromatography over silica gel using 50:1 hexane/EtOAc to obtain 1*S*,1*S* and 1*S*,1*R* isomers as colorless oil. (1*S*,1*S*)- isomer: 1.00 g and isomeric purity 99.5% judged by GC.

(1*S*,1*R*)- isomer: 0.75 g and isomeric purity 99.5% judged by GC.

(1*S*,1*S*)-*N*-(1-Cyclohexylethyl)-1-tetralinylamine.

The absolute structure of the amine was confirmed by X-ray diffraction of the hydrochloride salt by solvent evaporation of a solution of in MeOH and ether at RT.

$[\alpha]_D^{22} = 30.8^\circ$ ($c = 1.17$ in CHCl₃).

¹H NMR (400 MHz, CDCl₃): 7.34-7.32 (m, 1H), 7.16-7.09 (m, 2H), 7.07-7.04 (m, 1H), 3.78 (t, $J = 4.4$ Hz, 1H), 2.83-2.76 (m, 1H), 2.73-2.66 (m, 1H), 2.61-2.55 (m, 1H), 2.04-1.96 (m, 1H), 1.82-1.63 (m, 8H), 1.26-1.12 (m, 4H), 1.10 (d, $J = 6.4$ Hz, 3H), 1.07-0.92 (m, 2H), 0.84 (br s, 1H).

¹³C NMR (100 MHz, CDCl₃): δ 140.4, 137.5, 129.1, 128.9, 126.4, 125.8, 55.1, 52.3, 44.2, 29.6, 29.5, 29.1, 28.2, 26.8, 26.62, 26.60, 18.6, 17.5.

(1*S*,1*R*)-*N*-(1-Cyclohexylethyl)-1-tetralinylamine.

$[\alpha]_D^{22} = -12.1^\circ$ ($c = 1.70$ in CHCl₃).

¹H NMR (400 MHz, CDCl₃): δ 7.44-7.42 (m, 1H), 7.19-7.13 (m, 2H), 7.09-7.08 (m, 1H), 3.81 (ψt, $J = 4.4$ Hz, 1H), 2.88-2.81 (m, 1H), 2.76-2.70 (m, 2H), 2.03-1.88 (m, 2H), 1.82-1.70 (m, 7H), 1.52-1.44 (m, 1H), 1.34-1.07 (m, 5H), 1.04 (d, $J = 6.6$ Hz, 3H), 0.99 (br s, 1H).

¹³C NMR (100 MHz, CDCl₃): δ 140.6, 137.2, 129.0, 128.8, 126.4, 125.7, 55.4, 53.3, 42.4, 30.3, 29.5, 29.4, 27.5, 27.0, 26.9, 26.7, 19.1, 18.3.

(*Ss*,1*S*,1'*S*)-*N*-(1-Cyclohexylethyl)-*N*-(1-tetralinyl)-1,1'-spirobiindan-2,2'-diylphosphoramidite (Ligand L1)

Under argon, dry triethylamine (1.03 mL, 7.4 mmol, 5 equiv) was added dropwise to a solution of fresh phosphorus trichloride (129 μ L, 1.48 mmol, 1.0 equiv) in dry dichloromethane (20 mL) at 0 °C. The solution was warmed to RT and a solution of the chiral amine (0.38 g, 1.48 mmol, 1.0 equiv) in 5 mL of dry dichloromethane was added. After the reaction mixture was stirred at RT for 5 hours, (*Ss*)-1,1'-spirobiindane-2,2'-diol (0.37 g, 1.48 mmol, 1.0 equiv) was added as solid in one portion against an argon flow and the mixture was stirred at RT for 12 hours. At the end of the reaction, the suspension was concentrated on a rotary evaporator and the crude product was directly purified by flash chromatography using 100:1 hexane/EA to give the desired compound (0.50 g, 63%) as white foam.

$$[\alpha]_D^{22} = -143.0 \ (c = 1.12 \text{ in } \text{CHCl}_3).$$

^1H NMR (400 MHz, CDCl_3): δ 7.65 (d, $J = 8.0$ Hz, 1H), 7.28-7.06 (m, 4H), 7.02-6.93 (m, 4H), 6.83 (br s, 1H), 4.29 (br s, 1H), 3.08-2.98 (m, 2H), 2.83-2.73 (m, 3H), 2.68-2.58 (m, 2H), 2.33-2.12 (m, 3H), 2.03-1.43 (m, 11H), 1.26-0.67 (m, 8H).

^{13}C NMR (100 MHz, CDCl_3): δ 149.4 (d, $J = 7.1$ Hz), 147.2, 145.7 (d, $J = 1.6$ Hz), 144.9, 141.6 (d, $J = 3.5$ Hz), 140.0, 139.9, 138.2, 128.9 (2 overlapping signals), 128.4 (d, $J = 8.0$ Hz), 127.9, 126.3, 125.5, 121.8, 121.4 (d, $J = 5.4$ Hz), 120.9 (d, $J = 1.9$ Hz), 120.3, 58.9, 55.7, 54.1, 53.9, 44.5, 38.4, 38.0, 32.0, 30.8, 30.5, 29.9, 28.7, 26.8, 26.5, 26.4, 22.3, 18.8.

^{31}P { ^1H } NMR (162 MHz, CDCl_3): δ 133.0.

ESI-MS: Calcd for $\text{C}_{35}\text{H}_{41}\text{NO}_2\text{P}$ ($\text{M}+\text{H}$) $^+$: 538.29. Found: 538.37.

(*Rs*,1*S*,1*S*)-*N*-(1-Cyclohexylethyl)-*N*-(1-tetralinyl)-1,1'-spirobiindane-2,2'-diylphosphoramidite.

Under argon, triethylamine (175 μ L, 1.25 mmol, 5.0 equiv) was added dropwise to a solution of fresh phosphorus trichloride (22 μ L, 0.25 mmol, 1.0 equiv) in dry dichloromethane (5 mL) at 0 $^{\circ}$ C. The solution was warmed to RT and a solution of the amine (64 mg, 0.25 mmol, 1.0 equiv) in 5 mL of dry dichloromethane was added. After the reaction mixture was stirred at RT for 5 hours, (*Rs*)-1,1'-spirobiindane-2,2'-diol (63 mg, 0.25 mmol, 1.0 equiv) was added as solid in one portion and the mixture was stirred for 12 hours. At the end of the reaction, the suspension was concentrated on a rotary evaporator and the crude product was directly purified by flash chromatography using 100:1 hexane/EA to give the desired compound (50.0 mg, 40%) as white foam.

$[\alpha]_D^{22} = 102.1$ ($c = 1.36$ in CHCl_3).

^1H NMR (400 MHz, CDCl_3): δ 7.68 (d, $J = 7.8$ Hz, 1H), 7.20-7.13 (m, 2H), 7.08 (ψt, $J = 7.4$ Hz, 1H), 7.04-6.93 (m, 4H), 6.89 (d, $J = 7.2$ Hz, 1H), 6.84 (d, $J = 7.9$, 1H), 4.05-4.04 (m, 1H), 3.05-2.97 (m, 2H), 2.85-2.64 (m, 4H), 2.60-2.55 (m, 1H), 2.23-2.19 (m, 1H), 2.15-2.11 (m, 2H), 2.02-1.98 (m, 2H), 1.92-1.62 (m, 7H), 1.46-1.18 (m, 7H), 1.11-0.84 (m, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 149.4 (d, $J = 6.6$ Hz), 146.5 (d, $J = 11.2$ Hz), 145.6 (d, $J = 2.1$ Hz), 144.9, 141.6 (d, $J = 3.8$ Hz), 139.9 (d, $J = 1.3$ Hz), 138.8, 138.4, 128.9, 128.7, 128.4 (d, $J = 1.6$ Hz), 127.8, 126.1, 124.7, 122.0, 121.3 (d, $J = 5.5$ Hz), 120.9 (d, $J = 1.9$ Hz), 120.4, 58.9, 56.7 (d, $J = 7.6$ Hz), 56.3 (d, $J = 15.7$ Hz), 45.1 (d, $J = 4.3$ Hz), 38.3, 38.2, 33.0 (d, $J = 6.3$ Hz), 32.5, 30.8, 30.4, 29.8, 29.1 (d, $J = 6.7$ Hz), 26.9, 26.8, 26.5, 22.6, 19.2 (d, $J = 12.1$ Hz).

^{31}P $\{^1\text{H}\}$ NMR (162 MHz, CDCl_3): δ 137.7.

ESI-MS: Calcd for $\text{C}_{35}\text{H}_{41}\text{NO}_2\text{P}$ ($\text{M}+\text{H}$) $^+$: 538.29. Found: 538.31.

(*Ss*,1*S*,1*R*)-*N*-(1-Cyclohexylethyl)-*N*-(1-tetralinyl)-1,1'-spirobiindane-2,2'-diylphosphoramidite.

Under argon, dry triethylamine (175 μ L, 1.25 mmol, 5.0 equiv) was added dropwise to a solution of phosphorus trichloride (22 μ L, 0.25 mmol, 1.0 equiv) in dry dichloromethane (5 mL) at 0 $^{\circ}$ C. The solution was warmed to RT and a solution of the amine (64 mg, 0.25 mmol, 1.0 equiv) in 5 mL of dry dichloromethane was added. After the reaction mixture was stirred at RT for 5 hours, (*Ss*)-1,1'-spirobiindane-2,2'-diol (63 mg, 0.25 mmol, 1.0 equiv) was added as solid in one portion and the mixture was stirred for 12 hours. At the end of the reaction, the suspension was concentrated on a rotary evaporator and the crude product was directly purified by flash chromatography using 100:1 hexane/EA to give the desired compound (68 mg, 51%) as white foam.

$$[\alpha]_D^{22} = -156.3 \text{ (} c = 1.28 \text{ in CHCl}_3 \text{)}.$$

^1H NMR (400 MHz, CDCl_3): δ 7.67 (d, $J = 7.8$ Hz, 1H), 7.21-7.13 (m, 3H), 7.08 (t, $J = 7.3$ Hz, 1H), 7.03-6.96 (m, 4H), 6.87 (d, $J = 7.8$ Hz, 1H), 4.00-3.97 (m, 1H), 3.06-2.97 (m, 2H), 2.79-2.66 (m, 4H), 2.60-2.55 (m, 1H), 2.34-2.30 (m, 1H), 2.18-2.10 (m, 2H), 1.98-1.86 (m, 3H), 1.77-1.66 (m, 4H), 1.64-1.60 (m, 1H), 1.52-1.43 (m, 2H), 1.37-1.24 (m, 5H), 1.16-1.03 (m, 3H), 1.01-0.94 (m, 1H).

^{13}C NMR (100 MHz, CDCl_3): δ 149.3 (d, $J = 7.3$ Hz), 146.5 (d, $J = 9.8$ Hz), 145.7 (d, $J = 1.9$ Hz), 144.9, 141.7 (d, $J = 3.6$ Hz), 140.4 (d, $J = 1.3$ Hz), 138.8, 138.5 (d, $J = 1.2$ Hz), 128.73, 128.66, 128.4 (d, $J = 1.8$ Hz), 127.9, 126.2, 125.2, 121.6, 121.4 (d, $J = 5.5$ Hz), 120.9 (d, $J = 2.1$ Hz), 120.4, 58.8, 57.0 (d, $J = 24.1$ Hz), 55.9 (d, $J = 4.5$ Hz), 45.7, 38.5, 37.7, 31.7, 30.79, 30.72, 30.4, 29.9, 27.2, 26.9, 26.7 (d, $J = 7.2$ Hz), 26.9, 22.8, 16.8 (d, $J = 26.2$ Hz).

^{31}P $\{^1\text{H}\}$ NMR (162 MHz, CDCl_3): δ 127.6.

ESI-MS: Calcd for $\text{C}_{35}\text{H}_{41}\text{NO}_2\text{P}$ ($\text{M}+\text{H}$) $^+$: 538.29. Found: 538.33.

(*Ss*,1*S*)-*N*-1-Cyclododecyl-*N*-(1-tetralinyl)-1,1'-spirobiindane-2,2'-diylphosphoramidite.

Under argon, triethylamine (175 μ L, 1.25 mmol, 5.0 equiv) was added dropwise to a

solution of phosphorus trichloride (22 μ L, 0.25 mmol, 1.0 equiv) in dry dichloromethane (5 mL) at 0 °C. The solution was warmed to RT and a solution of the amine (78 mg, 0.25 mmol, 1.0 equiv) in 5 mL of dry dichloromethane was added. After the reaction mixture was stirred at RT for 5 hours, (*Ss*)-1,1'-spirobiindane-2,2'-diol (63 mg, 0.25 mmol, 1.0 equiv) was added as solid in one portion and the mixture was stirred for 12 hours. At the end of the reaction, the suspension was concentrated on a rotary evaporator and the crude product was directly purified by flash chromatography using 100:1 hexane/EA to give the desired compound (40 mg, 27%) as white foam.

^1H NMR (400 MHz, CDCl_3): δ 7.63-7.62 (m, 1H), 7.19-7.07 (m, 4H), 7.00-6.92 (m, 5H), 4.11 (br s, 1H), 3.08-2.98 (m, 3H), 2.78-2.72 (m, 3H), 2.66-2.62 (m, 1H), 2.23-2.18 (m, 1H), 2.15-2.10 (m, 1H), 2.01-1.94 (m, 2H), 1.91-1.84 (m, 3H), 1.63-1.48 (m, 4H), 1.29-1.17 (m, 19H).

^{13}C NMR (100 MHz, CDCl_3): δ 149.2 (d, $J = 7.7$ Hz), 146.7 (d, $J = 9.6$ Hz), 145.7, 144.9, 141.5, 140.2, 139.2, 138.5, 128.7 (2 overlapping signals), 128.4, 128.0, 126.2, 125.5, 121.5, 121.4 (d, $J = 5.5$ Hz), 120.9 (d, $J = 1.8$ Hz), 120.6, 58.9, 38.5, 37.8, 32.8, 30.7, 30.4, 30.0, 29.7, 24.4 (overlapping signals), 23.3, 23.0, 22.9, 22.7, 22.2 (overlapping signals).

^{31}P $\{^1\text{H}\}$ NMR (162 MHz, CDCl_3): δ 129.9.

(*Ss*,1*R*,1'*S*)-*N*-(1-Phenylethyl)-*N*-(1,2,3,4-tetrahydro-1-naphthyl)-1,1'-spirobiindane-2,2'-diylphosphoramidite.

Under argon, triethylamine (175 μ L, 1.25 mmol, 5.0 equiv) was added dropwise to a solution of phosphorus trichloride (22 μ L, 0.25 mmol, 1.0 equiv) in dry dichloromethane (5 mL) at 0 °C. The solution was warmed to RT and a solution of the amine (70 mg, 0.25 mmol, 1.0 equiv) in 5 mL of dry dichloromethane was added. After the reaction mixture was stirred at RT for 5 hours, (*Rs*)-1,1'-spirobiindane-2,2'-diol (63 mg, 0.25 mmol, 1.0 equiv) was added as solid in one portion and the mixture was stirred for 12 hours. At the end of the reaction, the suspension was concentrated on a rotary evaporator and the crude product was directly purified by flash chromatography using 100:1 hexane/EA to give the

desired compound (65.0 mg, 49%) as white foam.

$[\alpha]_D^{22} = 205.2$ ($c = 2.02$ in CHCl_3).

^1H NMR (400 MHz, CDCl_3): δ 7.44-7.42 (m, 2H), 7.26-7.18 (m, 4H), 7.08-6.92(m, 6H), 6.82 (vt, $J = 7.5$ Hz, 1H), 6.63 (d, $J = 7.6$ Hz, 1H), 6.37 (br s, 1H), 4.45-4.40 (m, 1H), 4.18-4.14 (m, 1H), 3.11-2.99 (m, 2H), 2.87-2.72 (m, 3H), 2.68-2.63 (m, 1H), 2.30-2.26 (m, 2H), 2.19-2.09 (m, 4H), 1.93-1.85 (m, 1H), 1.80-1.69 (m, 1H), 1.44-1.28 (m, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 149.0 (d, $J = 7.1$ Hz), 147.1 (d, $J = 8.9$ Hz), 145.7 (d, $J = 2.0$ Hz), 145.1, 143.1, 141.6 (d, $J = 3.5$ Hz), 140.2, 139.1 (d, $J = 6.7$ Hz), 137.8, 128.70, 128.65, 128.5, 128.3, 128.1 (2 overlapping signals), 127.1, 126.3, 125.6, 122.0, 121.4 (d, $J = 5.4$ Hz), 121.0 (d, $J = 2.0$ Hz), 120.7, 59.0, 53.5, 52.5 (d, $J = 25.0$ Hz), 38.5, 38.3, 35.2, 30.8, 30.6, 29.8, 21.9, 20.0.

^{31}P $\{^1\text{H}\}$ NMR (162 MHz, CDCl_3): δ 129.2.

ESI-MS: Calcd for $\text{C}_{35}\text{H}_{35}\text{NO}_2\text{P}$ ($\text{M}+\text{H}$) $^+$: 532.24. Found: 532.22.

2.9.3 Procedures and isolation of asymmetric conjugate adducts

A general procedure. In an argon-filled glove box, $\text{CuOTf}\cdot(0.5 \text{ toluene})$ (6.5 mg, 0.025 mmol) and (S,S,S)-ligand **L5** (16 mg, 0.03 mmol) were added to a 10-mL dry Schlenk tube, followed by addition of KOAc (98 mg, 1.0 mmol, 2.0 equiv), phenylboroxine (77 mg, 0.25 mmol, 0.5 equiv), *trans*-enones (0.5 mmol, 1 equiv) and dry toluene (2.0 mL). The mixture was vigorously stirred in a preheated oil bath at 70 °C for 30 h until >80% conversion by GC. The reaction mixture was cooled to room temperature, diluted by EtOAc and passed through a short plug of silical gel with diethyl ether washing. The filtrate was concentrated and purified by flash chromatography. The enantioselectivity (ee) of the purified product was determined by chiral HPLC analysis using Daicel Chiralcel columns. The reaction can be set up with a Schlenk tube and a vacuum manifold without using a glove box to give similar results. The racemic samples were made using the racemic ligand.

(*R*)-3-(1-Naphthyl)-1,3-diphenylpropan-1-one [1160606-15-4].

The reaction was complete in 30 h at 70 °C. The product was isolated by flash chromatography (30:1 to 10:1 hexane/EtOAc) as white solid. Yield: 158 mg, 94%.

GC-MS (EI): Calcd for C₂₅H₂₀O: 336.2. Found: 336.1.

$[\alpha]_D^{22} = -8.2$ ($c = 1.10$ in CHCl₃).

93% ee. Daicel Chiralcel IC-H, 95:5 *n*-hexane/isopropanol, flow rate: 0.5 mL/min.

¹H NMR (400 MHz, CDCl₃): δ 8.20-8.17 (m, 1H), 7.96-7.94 (m, 2H), 7.85-7.83 (m, 1H), 7.74 (d, $J = 7.9$ Hz, 1H), 7.57-7.53 (m, 1H), 7.48-7.36 (m, 6H), 7.31-7.29 (m, 2H), 7.26-7.22 (m, 2H), 7.17-7.13 (m, 1H), 5.69-5.66 (m, 1H), 3.92-3.80 (m, 2H).

¹³C NMR (400 MHz, CDCl₃): δ 198.0, 143.9, 139.7, 137.1, 134.2, 133.1, 131.6, 128.9, 128.63, 128.57, 128.1, 127.3, 126.4, 126.2, 125.6, 124.4, 123.9, 45.1, 41.4.

1 PDA Ch1 214nm 4nm

Peak#	Ret. Time	Area	Area %
1	15.702	344593	49.639
2	19.423	349604	50.361
Total		694198	100.000

1 PDA Ch1 214nm 4nm

Peak#	Ret. Time	Area	Area %
1	15.662	523952	3.445
2	19.364	14686001	96.555
Total		15209953	100.000

(R)-3-(p-Anisyl)-1,3-diphenylpropan-1-one [1020172-02-4].

The reaction stopped in 30 h at 70 °C. The product was isolated by flash chromatography (30:1 to 10:1 hexane/EtOAc) as white solid. Yield: 145 mg, 92%.

GC-MS (EI): Calcd for C₂₂H₂₀O₂: 316.2. Found: 316.1.

$[\alpha]_D^{22} = -2.7^\circ$ ($c = 1.22$ in CHCl₃) for a sample of 97% ee. Compare with reported $[\alpha]_D^{20} = +2.4^\circ$ ($c = 0.35$ in CHCl₃) for a sample of 98% ee (*S*) (*cf.* Chen, G.; Xing, J.; Cao, P.; Liao, J. *Tetrahedron* **2012**, 68, 5908).).

ee: 97%. Daicel Chiralcel ID-H, 95:5 *n*-hexane/isopropanol, flow rate: 0.5 mL/min.

¹H NMR (400 MHz, CDCl₃): δ 7.92-7.90 (m, 2H), 7.53-7.49 (m, 1H), 7.43-7.39 (m, 2H), 7.25-7.23 (m, 4H), 7.19-7.12 (m, 3H), 6.81-6.77 (m, 2H), 4.77 (ψt, $J = 7.4$ Hz, 1H), 3.72 (s, 3H), 3.69 (ψd, $J = 7.3$ Hz, 2H).

¹³C NMR (100 MHz, CDCl₃): δ 198.2, 158.1, 144.6, 137.2, 136.3, 133.1, 128.8, 128.64,

128.59, 128.1, 127.8, 126.4, 114.0, 55.2, 45.2, 45.0.

(R)-3-(p-Tolyl)-1,3-diphenylpropan-1-one [1020172-01-3].

The reaction stopped in 30 h at 70 °C. The product was isolated by flash chromatography (30:1 to 10:1 hexane/EtOAc) as white solid. Yield: 142 mg, 95%.

GC-MS (EI): Calcd for C₂₂H₂₀O: 300.2. Found: 300.1.

$[\alpha]_D^{22} = -8.6^\circ$ ($c = 1.43$ in CHCl₃) for a sample of 95% ee. Compare with reported $[\alpha]_D^{20} = -11^\circ$ ($c = 0.11$ in CHCl₃) for a sample of 95% ee (*R*) (*cf.* Chen, G.; Xing, J.; Cao, P.; Liao, J. *Tetrahedron* **2012**, 68, 5908).

95% ee. Daicel Chiralcel OD-H, 99:1 *n*-hexane/isopropanol, flow rate: 0.8 mL/min.

¹H NMR (400 MHz, CDCl₃): δ 7.93-7.91 (m, 2H), 7.54-7.50 (m, 1H), 7.43-7.39 (m, 2H), 7.26-7.24 (m, 4H), 7.17-7.14 (m, 3H), 7.06-7.06 (m, 2H), 4.79 (ψt, $J = 7.3$ Hz, 1H), 3.71 (ψd, $J = 7.3$ Hz, 2H), 2.27 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 198.1, 144.5, 141.2, 137.2, 135.9, 133.1, 129.3, 128.63, 128.59, 128.1, 127.8, 127.7, 126.3, 45.6, 44.9, 21.0.

A gram-scale procedure. Under argon, CuOTf•(0.5 toluene) (13 mg, 0.05 mmol) and (*S,S,S,S*)-ligand **L5** (32 mg, 0.06 mmol) were added to a dry 25-mL Schlenk tube, followed

by addition of KOAc (980 mg, 10 mmol, 2.0 equiv), phenylboroxine (770 mg, 2.5 mmol, 0.5 equiv), *trans*-enones (5 mmol, 1 equiv) and dry toluene (10 mL). The mixture was vigorously stirred in a preheated oil bath at 110 °C for 36 h until about 80% conversion as judged by GC. The reaction mixture was purified by flash chromatography to give off-white solid. Yield 79%, 1.18 gram. 91% ee. After recrystallized from EtOH, 99% ee product would obtained.

A procedure with exposure to air before heating. CuOTf•(0.5 toluene) (2.6 mg, 0.01 mmol) and (*S,S,S,S*)-ligand **L5** (6.4 mg, 0.012 mmol) were added to a 10-mL dry Schlenk tube, followed by addition of KOAc (196 mg, 2.0 mmol, 2.0 equiv), phenylboroxine (156 mg, 0.5 mmol, 0.5 equiv), the *trans*-enone (222 mg, 1.0 mmol, 1 equiv), GC standard *n*-dodecane (50 uL) and dry toluene (2.0 mL). *The mixture was opened to air for 5 minutes* and then capped tightly. It was vigorously stirred in a preheated oil bath at 110 °C for 48 h to give 78% GC conversion, 70% yield of product in 91% ee (chiral HPLC analysis using a Daicel Chiralcel column).

(*R*)-3-(*o*-Tolyl)-1,3-diphenylpropan-1-one [1338350-55-2].

The reaction was stopped in 30 h at 70 °C. The product was isolated by flash chromatography (30:1 to 10:1 hexane/EtOAc) as yellow oil. Yield: 127 mg, 85%.

GC-MS (EI): Calcd for C₂₂H₂₀O: 300.2. Found: 300.1.

$[\alpha]_D^{22} = -52.9^\circ$ ($c = 0.90$ in CHCl₃).

98% ee. Daicel Chiralcel ID-H, 95:5 *n*-hexane/isopropanol, flow rate: 0.5 mL/min.

¹H NMR (400 MHz, CDCl₃): δ 7.94-7.91 (m, 2H), 7.55-7.51 (m, 1H), 7.45-7.41 (m, 2H), 7.27-7.20 (m, 5H), 7.18-7.08 (m, 4H), 5.02 (vt, $J = 7.3$ Hz, 1H), 3.77-3.64 (m, 2H), 2.32 (s, 3H).

¹³C NMR (400 MHz, CDCl₃): δ 198.1, 143.8, 141.8, 137.1, 136.5, 133.1, 130.8, 128.6, 128.5, 128.09, 128.05, 126.4, 126.2, 126.0, 45.1, 41.9, 19.9.

1 PDA Ch1 214nm 4nm

Peak#	Ret. Time	Area	Area %
1	18.327	4373697	49.807
2	20.220	4407540	50.193
Total		8781237	100.000

2 PDA Ch1 250nm 4nm

Peak#	Ret. Time	Area	Area %
1	18.200	8527	0.915
2	20.064	923773	99.085
Total		932300	100.000

(R)-3-(2-Naphthyl)-1,3-diphenylpropan-1-one [1198215-04-1 for a racemate].

The reaction was stopped in 30 h at 70 °C. The product was isolated by flash chromatography (30:1 to 10:1 hexane/EtOAc) as white solid. Yield: 123 mg, 73%.

GC-MS (EI): Calcd for C₂₅H₂₁O: 336.2. Found: 336.0.

$[\alpha]_D^{22} = -29.8^\circ$ ($c = 1.16$ in CHCl₃).

99% ee. Daicel Chiralcel OD-H, 95:5 *n*-hexane/isopropanol, flow rate: 0.5 mL/min.

¹H NMR (400 MHz, CDCl₃): δ 7.96-7.93 (m, 2H), 7.76-7.71 (m, 4H), 7.55-7.51 (m, 1H), 7.44-7.36 (m, 5H), 7.32-7.24 (m, 4H), 7.19-7.15 (m, 1H), 5.00 (ψt, $J = 7.3$ Hz, 1H), 5.02-3.82 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): δ 198.0, 144.1, 141.7, 137.2, 133.6, 133.2, 128.7 (overlapping signals), 128.4, 128.14, 128.06, 127.9, 127.6, 126.8, 126.5, 126.1, 125.9, 125.6, 46.1, 44.7.

1 PDA Ch1 214nm 4nm

Peak#	Ret. Time	Area	Area %
1	23.615	593271	47.856
2	24.778	646430	52.144
Total		1239701	100.000

2 PDA Ch1 214nm 4nm

Peak#	Ret. Time	Area	Area %
1	23.624	11273169	99.997
2	24.672	374	0.003
Total		11273543	100.000

(R)-3-(p-N-Dimethylaminophenyl)-1,3-diphenylpropan-1-one [200130-95-6 for a racemate].

The reaction was stopped in 30 h at 70 °C. The product was isolated by flash chromatography (30:1 to 10:1 hexane/EtOAc) as brown solid. Yield: 140 mg, 85%.

GC-MS (EI): Calcd for C₂₃H₂₃NO: 329.2. Found: 329.1.

$[\alpha]_D^{22} = +0.4^\circ$ ($c = 1.64$ in CHCl₃).

94% ee. Daicel Chiralcel IC-H, 95:5 *n*-hexane/isopropanol, flow rate: 0.5 mL/min.

¹H NMR (400 MHz, CDCl₃): δ 7.93-7.92 (m, 2H), 7.52-7.48 (m, 1H), 7.42-7.38 (m, 2H), 7.26-7.19 (m, 4H), 7.15-7.10 (m, 3H), 6.66-6.62 (m, 2H), 4.73 (ψt, $J = 7.3$ Hz, 1H), 3.68 (ψd, $J = 7.4$ Hz, 2H), 2.86 (s, 6H).

¹³C NMR (100 MHz, CDCl₃): δ 198.4, 149.2, 145.0, 137.3, 133.0, 132.2, 128.6, 128.5, 128.5, 128.1, 127.8, 126.2, 112.9, 45.2, 45.1, 40.7.

1 PDA Ch1 200nm 4nm

Peak#	Ret. Time	Area	Area %
1	37.245	1410902	50.294
2	39.499	1394388	49.706
Total		2805290	100.000

PDA Ch1 200nm 4nm

Peak#	Ret. Time	Area	Area %
1	36.405	840150	3.243
2	38.594	25068266	96.757
Total		25908416	100.000

(R)-1,3-Diphenyl-3-(2-thienyl)propan-1-one [1383843-88-6].

The reaction finished in 30 h at 70 °C. The product was isolated by flash chromatography (30:1 to 10:1 hexane/EtOAc) as white solid. Yield: 131 mg, 90%.

GC-MS (EI): Calcd for C₁₉H₁₆OS: 292.1. Found: 292.0.

$[\alpha]_D^{21} = -12.4^\circ$ ($c = 1.2$ in CHCl₃) for a sample of 94% ee. Compare with reported $[\alpha]_D^{20} = -11^\circ$ ($c = 0.25$ in CHCl₃) for a sample of 81% ee (*R*) (*cf*: Chen, G.; Xing, J.; Cao, P.; Liao, J. *Tetrahedron* **2012**, 68, 5908).

94% ee. Daicel Chiralcel IC-H, 95:5 *n*-hexane/isopropanol, flow rate: 0.5 mL/min.

¹H NMR (400 MHz, CDCl₃): δ 7.95-7.93 (m, 2H), 7.57-7.53 (m, 1H), 7.47-7.42 (m, 2H), 7.36-7.31 (m, 2H), 7.30-7.27 (m, 2H), 7.23-7.19 (m, 1H), 7.13 (dd, *J* = 3.9, 1.2 Hz, 1H), 5.06 (ψt, *J* = 7.2 Hz, 1H), 3.81 (dd, *J* = 17.2, 7.1 Hz, 1H), 3.71 (dd, *J* = 17.2, 7.1 Hz, 1H).

¹³C NMR (400 MHz, CDCl₃): δ 197.5, 148.4, 143.9, 137.0, 133.2, 128.71, 128.68, 128.1, 127.8, 126.9, 126.7, 124.3, 123.9, 46.2, 41.7.

(R)-1,3-Diphenyl-3-(3-thienyl)propan-1-one.

The reaction was stopped in 30 h at 70 °C. The product was isolated by flash chromatography (30:1 to 10:1 hexane/EtOAc) as white solid. Yield: 102 mg, 70%.

GC-MS (EI): Calcd for C₁₉H₁₆OS: 292.1. Found: 292.0.

[α]_D²¹ = -25.5° (*c* = 1.49 in CHCl₃).

93% ee. Daicel Chiralcel IC-H, 98:2 *n*-hexane/isopropanol, flow rate: 0.5 mL/min.

¹H NMR (400 MHz, CDCl₃): δ 7.93-7.90 (m, 2H), 7.55-7.50 (m, 1H), 7.44-7.40 (m, 2H), 7.29-7.25 (m, 4H), 7.22-7.15 (m, 2H), 6.97-6.95 (m, 1H), 6.91 (dd, *J* = 5.0, 1.3 Hz, 1H), 4.87 (ψt, *J* = 7.2 Hz, 1H), 3.73 (dd, *J* = 17.0, 7.1 Hz, 1H), 3.64 (dd, *J* = 17.0, 7.1 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ 198.0, 145.0, 144.0, 137.1, 133.2, 128.7, 128.6, 128.1, 127.9, 127.8, 126.6, 125.8, 120.5, 45.3, 41.9.

1 PDA Ch1 214nm 4nm

Peak#	Ret. Time	Area	Area %
1	20.572	269995	49.943
2	21.471	270612	50.057
Total		540607	100.000

2 PDA Ch1 214nm 4nm

Peak#	Ret. Time	Area	Area %
1	20.474	4120185	96.667
2	21.379	142066	3.333
Total		4262251	100.000

(R)-3-Ferrocenyl-1,3-diphenylpropan-1-one.

The reaction was stopped in 30 h at 70 °C. The product was isolated by flash chromatography (10:1 to 3:1 hexane/DCM) as yellow solid. Yield: 187 mg, 95%.

GC-MS (EI): Calcd for $C_{25}H_{22}FeO$: 394.1. Found: 394.0.

$[\alpha]_D^{22} = +14.8^\circ$ ($c = 1.44$ in $CHCl_3$).

ee: 92%. Daicel Chiralcel IC-H, 95:5 *n*-hexane/isopropanol, flow rate: 0.5 mL/min.

1H NMR (400 MHz, $CDCl_3$): δ 7.90-7.88 (m, 2H), 7.54-7.49 (m, 1H), 7.43-7.39 (m, 2H), 7.28-7.21 (m, 4H), 7.15-7.11 (m, 1H), 4.54 (dd, $J = 5.4, 2.9$ Hz, 1H), 4.18-4.18 (m, 1H), 4.12-4.10 (m, 1H), 4.08-4.05 (m, 6H), 4.00-3.99 (m, 1H), 3.70-3.58 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 198.5, 144.9, 137.3, 133.0, 128.6, 128.3, 128.1, 127.9, 126.4, 93.4, 68.7, 68.0, 67.8, 67.3, 67.0, 46.4, 40.9.

1 PDA Ch1 214nm 4nm

Peak#	Ret. Time	Area	Area %
1	16.228	102130	51.213
2	17.961	97294	48.787
Total		199424	100.000

2 PDA Ch1 214nm 4nm

Peak#	Ret. Time	Area	Area %
1	16.221	2655218	95.976
2	17.976	111325	4.024
Total		2766543	100.000

(R)-3-(3-Benzothieryl)-1,3-diphenylpropan-1-one.

The reaction was stopped in 30 h at 70 °C. The product was isolated by flash chromatography (10:1 to 3:1 hexane/DCM) as white solid. Yield: 161 mg, 94%.

GC-MS (EI): Calcd for C₂₃H₁₈OS: 342.1. Found: 342.0.

$[\alpha]_D^{22} = -71.6^\circ$ ($c = 1.57$ in CHCl₃).

97% ee. Daicel Chiralcel IC-H, 95:5 *n*-hexane/isopropanol, flow rate: 0.5 mL/min.

¹H NMR (400 MHz, CDCl₃): δ 7.91-7.89 (m, 2H), 7.80-7.76 (m, 1H), 7.69-7.65 (m, 1H), 7.52-7.48 (m, 1H), 7.41-7.37 (m, 2H), 7.32-7.29 (m, 2H), 7.26-7.21 (m, 4H), 7.16-7.12 (m, 2H), 5.18 (ψt, $J = 7.1$ Hz, 1H), 3.81 (dd, $J = 17.1, 7.1$ Hz, 1H), 3.73 (dd, $J = 17.1, 7.1$ Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ 197.8, 142.9, 140.7, 138.6, 138.4, 137.0, 133.3, 128.7, 128.1, 128.0, 126.8, 124.5, 124.1, 122.9, 122.5, 121.7, 45.0, 40.4.

1 PDA Ch1 214nm 4nm

Peak#	Ret. Time	Area	Area %
1	16.535	88241	48.503
2	19.673	93689	51.497
Total		181930	100.000

PDA Ch1 214nm 4nm

Peak#	Ret. Time	Area	Area %
1	16.530	40202	1.356
2	19.656	2924306	98.644
Total		2964508	100.000

(R)-3-(2-Benzothiophenyl)-1,3-diphenylpropan-1-one.

The reaction was stopped in 30 h at 70 °C. The product was isolated by flash chromatography (10:1 to 3:1 hexane/DCM) as off-yellow solid. Yield: 153 mg, 89%.

GC-MS (EI): Calcd for C₂₃H₁₈OS: 342.1. Found: 342.1.

$[\alpha]_D^{22} = -31.2^\circ$ ($c = 1.54$ in CHCl₃).

97% ee. Daicel Chiralcel IC-H, 98:8 *n*-hexane/isopropanol, flow rate: 0.5 mL/min.

¹H NMR (400 MHz, CDCl₃): δ 7.93 (d, $J = 7.3$ Hz, 2H), 7.67 (d, $J = 8.0$ Hz, 1H), 7.60 (d,

$J = 7.6$ Hz, 1H), 7.42-7.34 (m, 4H), 7.31-7.17 (m, 5H), 7.04 (s, 1H), 5.12 (ψt, $J = 7.1$ Hz, 1H), 3.87 (dd, $J = 17.3$, 7.1 Hz, 1H), 3.73 (dd, $J = 17.3$, 7.1 Hz, 1H).

^{13}C NMR (100 MHz, CDCl_3): δ 197.2, 149.3, 143.2, 139.8, 139.5, 136.9, 133.3, 128.8, 128.7, 128.2, 127.9, 127.1, 124.3, 123.9, 123.2, 122.2, 120.9, 45.6, 42.3.

1 PDA Ch1 200nm 4nm

Peak#	Ret. Time	Area	Area %
1	25.536	1391511	49.961
2	26.931	1393693	50.039
Total		2785203	100.000

PDA Ch1 200nm 4nm

Peak#	Ret. Time	Area	Area %
1	25.506	235251	1.596
2	26.842	14501371	98.404
Total		14736622	100.000

(R)-3-(2-Benzofuryl)-1,3-diphenylpropan-1-one.

The reaction was stopped in 30 h at 70 °C. The product was isolated by flash chromatography (10:1 to 3:1 hexane/DCM) as yellow solid. Yield: 134 mg, 82%.

$[\alpha]_D^{22} = -40.0^\circ$ ($c = 1.26$ in CHCl_3).

95% ee. Daicel Chiralcel IC-H, 95:5 *n*-hexane/isopropanol, flow rate: 0.5 mL/min.

^1H NMR (300 MHz, CDCl_3): δ 8.20-8.16 (m, 1H), 7.90 (d, $J = 7.4$ Hz, 2H), 7.81-7.78 (m, 1H), 7.71-7.68 (m, 1H), 7.51-7.35 (m, 7H), 7.30-7.27 (m, 2H), 7.23-7.17 (m, 2H), 7.14-7.09 (m, 1H), 5.67 (ψt, $J = 7.1$ Hz, 1H), 3.90-3.74 (m, 2H).

^{13}C NMR (75 MHz, CDCl_3): δ 198.1, 144.0, 139.8, 137.1, 134.3, 133.2, 131.7, 128.7, 128.7, 128.1, 128.1, 127.4, 126.5, 126.3, 125.6, 125.3, 124.5, 123.9, 45.2, 41.5.

1 PDA Ch1 200nm 4nm

Peak#	Ret. Time	Area	Area %
1	15.403	473699	49.635
2	20.929	480656	50.365
Total		954356	100.000

PDA Ch1 200nm 4nm

Peak#	Ret. Time	Area	Area %
1	15.901	621580	2.505
2	19.681	24187938	97.495
Total		24809519	100.000

(R)-3-(1,3-Benzodioxol-5-yl)-1,3-diphenylpropan-1-one.

The reaction was stopped in 30 h at 70 °C. The product was isolated by flash chromatography (10:1 to 3:1 hexane/DCM) as white solid. Yield: 119 mg, 72%.

GC-MS (EI): Calcd for C₂₂H₁₈O₃: 330.1. Found: 330.1.

$[\alpha]_D^{22} = -1.2^\circ$ ($c = 1.61$ in CHCl₃).

98% ee. Daicel Chiralcel IC-H, 95:5 *n*-hexane/isopropanol, flow rate: 0.5 mL/min.

¹H NMR (400 MHz, CDCl₃): δ 7.91 (d, $J = 7.2$ Hz, 2H), 7.53-7.49 (m, 1H), 7.42-7.38 (m, 2H), 7.28-7.20 (m, 4H), 7.17-7.13 (m, 1H), 6.73-6.71 (m, 2H), 6.69-6.67 (m, 1H), 5.83 (s, 2H), 4.74 (ψt, $J = 7.3$ Hz, 1H), 3.72-3.61 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): δ 198.0, 147.8, 146.1, 144.3, 138.2, 137.1, 133.2, 128.7, 128.7, 128.1, 127.7, 126.5, 120.7, 108.5, 108.3, 100.9, 45.7, 44.8.

1 PDA Ch1 214nm 4nm

Peak#	Ret. Time	Area	Area %
1	25.089	631166	49.949
2	26.959	632456	50.051
Total		1263622	100.000

PDA Ch1 214nm 4nm

Peak#	Ret. Time	Area	Area %
1	25.115	95851	1.216
2	26.946	7789222	98.784
Total		7885073	100.000

(R)-3-(p-Fluorophenyl)-1,3-diphenylpropan-1-one [683816-03-7 for a racemate].

CuOTf•(0.5 toluene) (6.5 mg, 0.025 mmol), (*S,S,S*)-Ligand **1** (16 mg, 0.03 mmol), *trans*-enone (113 mg, 0.5 mmol), phenylboroxine (77 mg, 0.25 mmol), KOAc (98 mg, 1.0 mmol) and dry toluene (2.0 mL) were used. The reaction was stopped after 30 h at 70 °C. The product was isolated by flash chromatography (50:1 to 30:1 hexane/EA) as white solid. Yield: 129 mg, 84%.

GC-MS (EI): Calcd for C₂₁H₁₇FO: 304.1. Found: 304.1.

96% ee. Daicel Chiralcel IC-H, 98:2 *n*-hexane/isopropanol, flow rate: 0.5 mL/min.

¹H NMR (400 MHz, CDCl₃): δ 7.94-7.91 (m, 2H), 7.55 (t, $J = 7.4$ Hz, 1H), 7.46-7.42 (m, 2H), 7.30-7.16 (m, 7H), 6.97-6.92 (m, 2H), 4.81 (ψt, $J = 7.3$ Hz, 1H), 3.76-3.66 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): δ 197.8, 161.4 (d, $J_{\text{C-F}} = 254.6$ Hz), 144.0, 139.8 (d, $J_{\text{C-F}} = 3.2$ Hz), 137.0, 133.2, 129.3 (d, $J_{\text{C-F}} = 7.8$ Hz), 128.7 (2 overlapping signals), 128.1, 127.7, 126.5, 115.3 (d, $J_{\text{C-F}} = 21.1$ Hz), 45.2, 44.8.

^{19}F NMR (377 MHz, CDCl_3): δ : -116.8.

(R)-3-(p-Trifluoromethylphenyl)-1,3-diphenylpropan-1-one [1020172-03-5].

$\text{CuOTf} \cdot (0.5 \text{ toluene})$ (6.5 mg, 0.025 mmol), (S_S, S_S)-Ligand **1** (16 mg, 0.03 mmol), *trans*-enone (138 mg, 0.5 mmol), phenylboroxine (77.3 mg, 0.25 mmol), KOAc (98 mg, 1.0 mmol) and dry toluene (2.0 mL) were used. The reaction was stopped after 30 h at 70 °C. The product was isolated by flash chromatography (50:1 to 30:1 hexane/EA) as white solid. Yield: 154 mg, 87%.

GC-MS (EI): Calcd for $\text{C}_{22}\text{H}_{17}\text{F}_3\text{O}$: 354.1. Found: 354.1.

$[\alpha]_{\text{D}}^{22} = -0.10^\circ$ ($c = 1.25$ in CHCl_3).

97% ee. Daicel Chiralcel IC-H, 98:2 *n*-hexane/isopropanol, flow rate: 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 7.94-7.92 (m, 2H), 7.56-7.50 (m, 3H), 7.45-7.41 (m, 2H), 7.38 (d, $J = 8.2$ Hz, 2H), 7.31-7.24 (m, 4H), 7.22-7.17 (m, 1H), 4.89 (q, $J = 7.2$ Hz, 1H), 3.81-3.69 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): δ 197.5, 148.2, 143.3, 136.9, 133.4, 128.8, 128.5, 128.3, 128.2 (an overlapping quartet), 128.07, 127.8, 126.8, 125.6 (q, $J = 3.8$ Hz), 124.2 (q, $J = 271.9$ Hz), 45.7, 44.4.

(3*S*,4*E*)-1,3,5-Triphenylpent-4-en-1-one [937805-64-6]. CuOTf•(0.5 toluene) (6.5 mg, 0.025 mmol), (*S_S,S_S*)-Ligand **1** (16 mg, 0.03 mmol), *trans*-enone (117 mg, 0.5 mmol), phenylboroxine (124 mg, 0.40 mmol), KOAc (98 mg, 1.0 mmol) and dry toluene (2.0 mL) were used. The reaction was stopped after 30 h at 80 °C (about 80% conversion by GC). The product was isolated by flash chromatography (30:1 to 10:1 hexane/EtOAc) as white solid. Yield: 101 mg, 65%. When 10 mol% CuOTf•(0.5 toluene) and 12 mol% Ligand **1** were used in the reaction, 127 mg, 82% yield product was obtained after 30 h at 80 °C (incomplete conversion). No 1,6-addition product was detected in the reaction mixtures by GC and GCMS.

GC-MS (EI): Calcd for C₂₃H₂₀O: 312.2. Found: 312.1.

$[\alpha]_D^{22} = 2.0^\circ$ ($c = 1.20$ in CHCl₃).

90% ee. Daicel Chiralcel OD-H, 95:5 *n*-hexane/isopropanol, flow rate: 0.5 mL/min.

¹H NMR (400 MHz, CDCl₃): δ 7.93-7.91 (m, 2H), 7.52-7.48 (m, 1H), 7.42-7.38 (m, 2H), 7.32-7.27 (m, 6H), 7.45-7.13 (m, 4H), 6.40-6.39 (m, 2H), 4.30 (ψq, $J = 7.0$ Hz, 1H), 3.53-3.42 (m, 2H).

¹³C NMR (400 MHz, CDCl₃): δ 198.2, 143.4, 137.3, 137.2, 133.2, 132.7, 130.2, 128.8, 128.7, 128.5, 128.2, 127.9, 127.3, 126.7, 126.3, 44.6, 44.0.

(3*S*,4*E*)-1,3-Diphenyloct-4-en-1-one. CuOTf•(0.5 toluene) (13.0 mg, 0.050 mmol), (*S_S,S_S,S_S*)-Ligand **1** (32 mg, 0.06 mmol), *trans*-enone (100 mg, 0.5 mmol), phenylboroxine (124 mg, 0.40 mmol), KOAc (98 mg, 1.0 mmol) and dry toluene (2.0 mL) were used. The reaction was stopped after 30 h at 80 °C (about 85 % conversion). No 1,6-addition product was detected in the mixture by GC and GCMS. The product was isolated by flash chromatography (30:1 to 10:1 hexane/EtOAc) as white solid. Yield: 101 mg, 73%.

GC-MS (EI): Calcd for C₂₀H₂₂O: 278.2. Found: 278.1.

$[\alpha]_D^{22} = 16.4^\circ$ ($c = 1.30$ in CHCl₃).

88% ee. Daicel Chiralcel OJ-H, 98:2 *n*-hexane/isopropanol, flow rate: 0.5 mL/min.

¹H NMR (400 MHz, CDCl₃): δ 7.93-7.90 (m, 2H), 7.55-7.50 (m, 1H), 7.44-7.41 (m, 2H), 7.31-7.23 (m, 4H), 7.20-7.15 (m, 1H), 5.65-5.60 (m, 1H), 5.46-5.39 (m, 1H), 4.07 (ψq, $J = 7.2$ Hz, 1H), 3.42-3.29 (m, 2H), 1.97-1.91 (m, 2H), 1.36-1.27 (m, 2H), 0.82 (t, $J = 7.4$ Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 198.6, 144.2, 137.4, 132.9, 132.4, 130.9, 128.6, 128.5, 128.1, 127.6, 126.4, 44.9, 44.0, 34.6, 22.5, 13.6.

(*S*)-4-Methyl-1-phenyl-1-(*p*-tolyl)pentan-3-one. CuOTf •(0.5 toluene) (13 mg, 0.050 mmol), (*S_S,S_S,S_S*)-Ligand **1** (32 mg, 0.06 mmol), *trans*-enone (87 mg, 0.5 mmol), *p*-tolylboroxine (88 mg, 0.25 mmol), KOAc (98 mg, 1.0 mmol) and dry toluene (2.0 mL)

were used. The reaction was stopped after 30 h at 70 °C. The product was isolated by flash chromatography (30:1 to 10:1 hexane/EtOAc) as white solid. Yield: 110 mg, 82%.

GC-MS (EI): Calcd for C₁₉H₂₂O: 266.2. Found: 266.1.

$[\alpha]_D^{22} = +5.1^\circ$ ($c = 1.07$ in CHCl₃).

94% ee. Daicel Chiralcel IC-H, 95:5 *n*-hexane/isopropanol, flow rate: 0.5 mL/min.

¹H NMR (400 MHz, CDCl₃): δ 7.26-7.20 (m, 4H), 7.16-7.10 (m, 3H), 7.07-7.05 (m, 2H), 4.59 (q, $J = 7.4$ Hz, 1H), 3.17 (qd, $J = 7.4$ Hz, 2H), 2.53-2.43 (pseudoheptet, $J = 6.9$ Hz, 1H), 2.27 (s, 3H), 0.972 (d, $J = 6.9$ Hz, 3H), 0.965 (d, $J = 6.9$ Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 144.4, 141.1, 135.8, 129.2, 128.5, 127.7, 127.6, 126.3, 46.7, 45.4, 41.4, 21.0, 17.9.

(S)-4,4-Dimethyl-1-phenyl-1-(*p*-tolyl)pentan-3-one.

CuOTf•(0.5 toluene) (13 mg, 0.050 mmol, 10 mol%), (*S,S,S,S*)-Ligand **1** (32 mg, 0.06 mmol), *trans*-enone (107 mg, 0.5 mmol), *p*-tolylboroxine (88 mg, 0.25 mmol), KOAc (98 mg, 1.0 mmol) and dry toluene (2.0 mL) were used.

The reaction was stopped after 30 h at 70 °C. The product was isolated by flash chromatography (30:1 to 10:1 hexane/EtOAc) as white solid. Yield: 127 mg, 91%.

$[\alpha]_D^{22} = +6.1^\circ$ ($c = 1.08$ in CHCl₃).

96% ee. Daicel Chiralcel IC-H, 95:5 *n*-hexane/isopropanol, flow rate: 0.5 mL/min.

¹H NMR (400 MHz, CDCl₃): δ 7.26-7.20 (m, 4H), 7.13-7.05 (m, 4H), 4.63-4.60 (m, 1H), 3.22-3.20 (m, 2H), 2.28 (s, 3H), 1.03 (s, 9H).

¹³C NMR (100 MHz, CDCl₃): δ 213.3, 144.6, 141.4, 135.8, 129.2, 128.9, 128.5, 127.8,

127.7 45.2, 44.2, 43.1, 26.2, 21.0.

1 PDA Ch1 214nm 4nm

Peak#	Ret. Time	Area	Area %
1	9.585	348237	50.046
2	10.024	347597	49.954
Total		695834	100.000

PDA Ch1 214nm 4nm

Peak#	Ret. Time	Area	Area %
1	9.586	4780611	98.079
2	10.023	93610	1.921
Total		4874222	100.000

(S)-3-Cyclohexyl-1,3-diphenylpropan-1-one [1313404-65-7].

CuOTf•(0.5 toluene) (13 mg, 0.050 mmol, 10 mol%), (*S,S,S*)-Ligand **L5** (32 mg, 0.06 mmol), enone (107 mg, 0.5 mmol), phenylboroxine (77 mg, 0.25 mmol), KOAc (98 mg, 1.0 mmol) and dry toluene (2.0 mL) were used.

The reaction was stopped in 30 h at 70 °C. The product was isolated by flash chromatography (30:1 to 10:1 hexane/EtOAc) as white solid. Yield: 132 mg, 90%.

GC-MS (EI): Calcd for C₂₁H₂₄O: 292.2. Found: 292.1.

94% ee. Daicel Chiralcel IC-H, 95:5 *n*-hexane/isopropanol, flow rate: 0.5 mL/min.

$[\alpha]_D^{22} = -6.4^\circ$ ($c = 1.07$ in CHCl₃).

¹H NMR (400 MHz, CDCl₃): δ 7.88-7.85 (m, 2H), 7.53-7.49 (m, 1H), 7.43-7.38 (m, 2H), 7.26-7.21 (m, 2H), 7.17-7.12 (m, 3H), 3.44-3.26 (m, 2H), 3.21-3.16 (m, 1H), 1.86-1.82 (m, 1H), 1.77-1.71 (m, 1H), 1.65-1.48 (m, 4H), 1.28-0.95 (m, 4H), 0.89-0.79 (m, 1H).

¹³C NMR (100 MHz, CDCl₃): δ 199.5, 143.9, 137.4, 132.8, 128.5, 128.4, 128.1, 128.0, 126.1, 47.1, 43.1, 42.5, 31.4, 30.8, 26.6, 26.4, 26.4.

1 PDA Ch1 214nm 4nm

Peak#	Ret. Time	Area	Area %
1	11.202	545379	50.608
2	12.757	532279	49.392
Total		1077658	100.000

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Area %
1	11.195	354709	96.854
2	12.745	11521	3.146
Total		366230	100.000

(S)-4-Methyl-1,3-diphenylpentan-1-one.

CuOTf•(0.5 toluene) (13 mg, 0.050 mmol, 10 mol%), (*S,S,S,S*)-ligand **L5** (32 mg, 0.06 mmol), *trans*-enone (87 mg, 0.5 mmol), phenylboroxine (77 mg, 0.25 mmol), KOAc (98 mg, 1.0 mmol) and dry toluene (2.0 mL) were used. The reaction was stopped in 30 h at 80 °C. The product was isolated by flash chromatography (30:1 to 10:1 hexane/EtOAc) as white solid. Yield: 107 mg, 85%.

GC-MS (EI): Calcd for C₁₈H₂₀O: 252.2. Found: 252.1.

83% ee. Daicel Chiralcel IC-H, 95:5 *n*-hexane/isopropanol, flow rate: 0.5 mL/min.

¹H NMR (300 MHz, CDCl₃): δ 7.91-7.85 (m, 2H), 7.55-7.48 (m, 1H), 7.43-7.37 (m, 2H), 7.26-7.11 (m, 5H), 3.35 (ψd, *J* = 7.0 Hz, 2H), 3.20-3.13 (m, 1H), 2.02-1.86 (m, 1H), 0.96 (d, *J* = 6.7 Hz, 3H), 0.79 (d, *J* = 6.7 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃): δ 199.5, 143.6, 137.4, 132.8, 128.5, 128.5, 128.4, 128.1, 128.0, 126.1, 47.9, 42.6, 33.3, 21.0, 20.4.

(R)-1,3-Diphenylhexan-1-one.

CuOTf•(0.5 toluene) (13 mg, 0.050 mmol), (*S,S,S,S*)-Ligand **L5** (32 mg, 0.06 mmol), *trans*-enone (87 mg, 0.5 mmol), phenylboroxine (77 mg, 0.25 mmol), KOAc (98 mg, 1.0 mmol) and dry toluene (2.0 mL) were used. The reaction was stopped in 30 h at 80 °C. The product was isolated by flash chromatography (30:1 to 10:1 hexane/EtOAc) as white solid. Yield: 108 mg, 86%.

GC-MS (EI): Calcd for C₁₈H₂₀O: 252.2. Found: 252.0.

82% ee. Daicel Chiralcel IC-H, 95:5 *n*-hexane/isopropanol, flow rate: 0.5 mL/min.

¹H NMR (300 MHz, CDCl₃): δ 7.91-7.88 (m, 2H), 7.56-7.50 (m, 1H), 7.45-7.39 (m, 2H),

7.31-7.14 (m, 5H), 3.33-3.30 (m, 1H), 3.27-3.18 (m, 2H), 1.76-1.55 (m, 2H), 1.29-1.10 (m, 2H), 0.85 (t, $J = 6.7$ Hz, 3H).

^{13}C NMR (75 MHz, CDCl_3): δ 199.2, 145.0, 137.3, 132.9, 128.5, 128.4, 128.1, 127.6, 126.2, 46.0, 41.1, 38.6, 20.6, 14.0.

(R)-3-Phenyl-1,3-di-*p*-tolylpropan-1-one.

$\text{CuOTf} \cdot (0.5 \text{ toluene})$ (6.5 mg, 0.025 mmol), (S,S,S)-Ligand **L5** (16 mg, 0.03 mmol), trans-enone (118 mg, 0.5 mmol), phenylboroxine (77 mg, 0.25 mmol), KOAc (98 mg, 1.0 mmol) and dry toluene (2.0 mL) were used. The reaction was stopped in 30 h at 70 °C. The product was isolated by flash chromatography (10:1 to 3:1 hexane/DCM) as white solid. Yield: 147 mg, 94%.

GC-MS (EI): Calcd for $\text{C}_{23}\text{H}_{22}\text{O}$: 314.2. Found: 314.0.

$[\alpha]_{\text{D}}^{22} = -4.3^\circ$ ($c = 1.04$ in CHCl_3).

98% ee. Daicel Chiralcel IC-H, 98:2 *n*-hexane/isopropanol, flow rate: 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 7.83 (d, $J = 6.7$ Hz, 2H), 7.25-7.20 (m, 6H), 7.14 (m, 3H), 7.06 (d, $J = 8.0$ Hz, 2H), 4.78 (ψt , $J = 7.3$ Hz, 1H), 3.68 (ψd , $J = 7.3$ Hz, 2H), 2.37 (s, 3H), 2.64 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 197.7, 144.6, 143.9, 141.3, 135.9, 134.7, 129.3, 129.3, 128.6, 128.3, 127.9, 127.7, 126.3, 45.7, 44.7, 21.7, 21.0.

(R)-1-(4-Fluorophenyl)-3-phenyl-3-p-tolylpropan-1-one.

CuOTf• (0.5 toluene) (6.5 mg, 0.025 mmol), (*S,S,S*)-Ligand **L5** (16 mg, 0.03 mmol), *trans*-enone (120 mg, 0.5 mmol), phenylboroxine (77 mg, 0.25 mmol), KOAc (98 mg, 1.0 mmol) and dry toluene (2.0 mL) were used. The reaction was stopped in 30 h at 70 °C. The product was isolated by flash chromatography (10:1 to 3:1 hexane/DCM) as white solid. Yield: 141 mg, 89%.

GC-MS (EI): Calcd for C₂₂H₁₉FO: 318.4. Found: 318.0.

[α]_D²² = -7.1° (*c* = 2.78 in CHCl₃).

95% ee. Daicel Chiralcel OD-H, 95:5 *n*-hexane/isopropanol, flow rate: 0.8 mL/min.

¹H NMR (400 MHz, CDCl₃): δ 7.95-7.91 (m, 2H), 7.25-7.23 (m, 4H), 7.17-7.13 (m, 3H), 7.09-7.05 (m, 4H), 4.76 (ψt, *J* = 7.3 Hz, 1H), 3.67 (ψd, *J* = 7.3 Hz, 2H), 2.27 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 196.5, 165.8 (d, *J*_{C-F} = 254.5 Hz), 144.3, 141.1, 136.0, 133.6 (d, *J*_{C-F} = 3.2 Hz), 130.7 (d, *J*_{C-F} = 9.7 Hz), 129.3, 128.6, 127.8, 127.7, 126.4, 115.7 (d, *J*_{C-F} = 21.8 Hz), 45.7, 44.7, 21.0.

¹⁹F NMR (377 Hz, CDCl₃): δ -105.2.

(R)-3-Phenyl-1-(2-thiophenyl)-3-p-tolylpropan-1-one.

CuOTf• (0.5 toluene) (6.5 mg, 0.025 mmol), (*S,S,S,S*)-Ligand **L5** (16 mg, 0.03 mmol), trans-enone (114 mg, 0.5 mmol), phenylboroxine (77 mg, 0.25 mmol), KOAc (98 mg, 1.0 mmol) and dry toluene (2.0 mL) were used. The reaction was stopped in 30 h at 70 °C. The product was isolated by flash chromatography (10:1 to 3:1 hexane/DCM) as white solid. Yield: 129 mg, 84%.

GC-MS (EI): Calcd for C₂₀H₁₈OS: 306.1. Found: 306.0.

[α]_D²² = -5.0° (*c* = 1.54 in CHCl₃).

95% ee. Daicel Chiralcel OD-H, 95:5 *n*-hexane/isopropanol, flow rate: 0.5 mL/min.

¹H NMR (400 MHz, CDCl₃): δ 7.67 (dd, *J* = 3.8, 0.9 Hz, 1H), 7.54 (dd, *J* = 4.9, 0.9 Hz, 1H), 7.26-7.12 (m, 4H), 7.20-7.12 (m, 3H), 7.07-7.04 (m, 3H), 4.77 (ψ t, *J* = 7.4 Hz, 1H), 3.62 (ψ d, *J* = 7.4 Hz, 2H), 2.26 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 191.0, 144.5, 144.2, 141.0, 136.0, 133.7, 131.9, 129.3, 128.6, 128.1, 127.8, 127.7, 126.4, 45.8, 45.6, 21.0.

(R)-1-(2-Benzofuranyl)-3-phenyl-3-(p-tolyl)propan-1-one.

CuOTf•(0.5 toluene) (6.5 mg, 0.025 mmol), (*S,S,S,S*)-Ligand **L5** (16 mg, 0.03 mmol), trans-enone (131 mg, 0.5 mmol), phenylboroxine (77.3 mg, 0.25 mmol), KOAc (98 mg, 1.0 mmol) and dry toluene (2.0 mL) were used. The reaction was stopped in 30 h at 70 °C. The product was isolated by flash chromatography (10:1 to 3:1 hexane/DCM) as white solid. Yield: 160 mg, 94%.

GC-MS (EI): Calcd for C₂₄H₂₀O₂: 340.2. Found: 340.1.

$[\alpha]_D^{22} = -9.6^\circ$ ($c = 1.02$ in CHCl₃).

95% ee. Daicel Chiralcel IC-H, 98:2 *n*-hexane/isopropanol, flow rate: 0.5 mL/min.

¹H NMR (400 MHz, CDCl₃): δ 7.65 (d, $J = 7.8$ Hz, 1H), 7.54 (d, $J = 8.4$ Hz, 1H), 7.46-7.41 (m, 2H), 7.30-7.23 (m, 5H), 7.21-7.12 (m, 3H), 7.06 (d, $J = 8.0$ Hz, 2H), 4.82 (ψ t, $J = 7.6$ Hz, 1H), 3.70 (ψ d, $J = 7.6$ Hz, 2H), 2.26 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 189.3, 155.6, 152.8, 144.1, 140.8, 136.0, 129.3, 128.6, 128.3, 127.8, 127.8, 127.1, 126.5, 123.9, 123.4, 112.8, 112.5, 45.5, 45.0, 21.0.

(R)-1-(2-Naphthyl)-3-phenyl-3-(*p*-tolyl)propan-1-one.

CuOTf • (0.5 toluene) (6.5 mg, 0.025 mmol), (*S,S,S*)-Ligand **L5** (16 mg, 0.03 mmol), trans-enone (136 mg, 0.5 mmol), phenylboroxine (77 mg, 0.25 mmol), KOAc (98 mg, 1.0 mmol) and dry toluene (2.0 mL) were used. The reaction was stopped in 30 h at 70 °C. The product was isolated by flash chromatography (10:1 to 3:1 hexane/DCM) as white solid. Yield: 156 mg, 89%.

GC-MS (EI): Calcd for C₂₆H₂₂O: 350.2. Found: 350.1.

$[\alpha]_D^{22} = -8.6^\circ$ ($c = 1.58$ in CHCl₃).

95% ee. Daicel Chiralcel OD-H, 95:5 *n*-hexane/isopropanol, flow rate: 0.8 mL/min.

¹H NMR (400 MHz, CDCl₃): δ 8.42 (s, 1H), 7.96 (dd, $J = 8.6, 1.6$ Hz, 1H), 7.87 (d, $J = 8.0$ Hz, 1H), 7.80 (d, $J = 8.8$ Hz, 2H), 7.54-7.46 (m, 2H), 7.29-7.22 (m, 4H), 7.19-7.12 (m, 3H), 7.06 (d, $J = 8.0$ Hz, 2H), 4.85 (ψ t, $J = 7.3$ Hz, 1H), 3.82 (ψ d, $J = 7.4$ Hz, 2H), 2.25 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 198.1, 144.6, 141.3, 136.0, 135.7, 134.5, 132.6, 129.8, 129.7, 129.4, 128.7, 128.5, 128.0, 127.9, 126.9, 126.4, 124.0, 45.9, 45.0, 21.1.

(R)-3-Phenyl-1-o-tolyl-3-(p-tolyl)propan-1-one.

CuOTf •(0.5 toluene) (6.5 mg, 0.025 mmol), (*S,S,S*)-Ligand **L5** (16 mg, 0.03 mmol), trans-enone (118 mg, 0.5 mmol), phenylboroxine (77 mg, 0.25 mmol), KOAc (98 mg, 1.0 mmol) and dry toluene (2.0 mL) were used. The reaction was stopped in 30 h at 70 °C. The product was isolated by flash chromatography (10:1 to 3:1 hexane/DCM) as white solid. Yield: 148 mg, 94%.

GC-MS (EI): Calcd for C₂₃H₂₂O: 314.2. Found: 314.1.

$[\alpha]_D^{22} = -12.3^\circ$ (*c* = 2.13 in CHCl₃).

94% ee. Daicel Chiralcel AD-H, 95:5 *n*-hexane/isopropanol, flow rate: 0.5 mL/min.

¹H NMR (400 MHz, CDCl₃): δ 7.52 (d, *J* = 7.1 Hz, 1H), 7.33-7.29 (m, 1H), 7.26-7.11 (m, 9H), 7.07-7.05 (m, 2H), 4.70 (ψt, *J* = 7.7 Hz, 1H), 3.61 (ψd, *J* = 7.7 Hz, 2H), 2.27 (s, 3H), 2.21 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 202.7, 144.2, 141.0, 138.5, 138.0, 136.0, 131.9, 131.1, 129.3, 128.6, 128.0, 127.9, 127.7, 126.4, 125.6, 48.0, 46.2, 21.0, 20.7.

(S)-3-(p-Tolyl)-1,3-diphenylpropan-1-one [1005391-52-5].

CuOTf• (0.5 toluene) (6.5 mg, 0.025 mmol), (*S,S,S,S*)-Ligand **L5** (16 mg, 0.03 mmol), *trans*-chalcone (104 mg, 0.5 mmol), *p*-tolylboroxine (88 mg, 0.25 mmol), KOAc (98 mg, 1.0 mmol) and dry toluene (2.0 mL) were used. The reaction was stopped in 30 h at 70 °C. The product was isolated by flash chromatography (30:1 to 10:1 hexane/EtOAc) as white solid. Yield: 142 mg, 95%. The ¹³C NMR data of its enantiomer is provided elsewhere in the supporting information.

GC-MS (EI): Calcd for C₂₂H₂₀O: 300.2. Found: 300.1.

[α]_D²² = +2.1° (*c* = 1.81 in CHCl₃).

94% ee. Daicel Chiralcel OD-H, 99:1 *n*-hexane/isopropanol, flow rate: 0.8 mL/min.

¹H NMR (400 MHz, CDCl₃): δ 7.93-7.91 (m, 2H), 7.54-7.50 (m, 1H), 7.43-7.39 (m, 2H), 7.26-7.24 (m, 4H), 7.17-7.14 (m, 3H), 7.06-7.06 (m, 2H), 4.79 (ψt, *J* = 7.3 Hz, 1H), 3.71 (ψd, *J* = 7.3 Hz, 2H), 2.27 (s, 3H).

(S)-1,3-Diphenyl-3-(o-tolyl)propan-1-one [1050676-32-8]. CuOTf•(0.5 toluene) (7.8 mg, 0.03 mmol, 10 mol%), (*S,S,S,S*)-Ligand **L5** (19 mg, 0.036 mmol), *trans*-chalcone (63 mg, 0.3 mmol), *o*-tolylboroxine (85 mg, 0.24 mmol, 0.8 equiv), KOAc (59 mg, 0.6 mmol) and dry toluene (1.2 mL) were used. The reaction was stopped after 34 h at 100 °C.

The product was isolated by flash chromatography (30:1 to 10:1 hexane/EtOAc) as white solid. Yield: 76 mg, 84% (88% conversion of chalcone). The ^{13}C NMR data of its enantiomer is provided elsewhere in the supporting information.

92% ee. Daicel Chiralcel ID-H, 95:5 *n*-hexane/isopropanol, flow rate: 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 7.94-7.91 (m, 2H), 7.55-7.51 (m, 1H), 7.45-7.41 (m, 2H), 7.27-7.20 (m, 5H), 7.18-7.08 (m, 4H), 5.02 (ψt, $J = 7.3$ Hz, 1H), 3.77-3.64 (m, 2H), 2.32 (s, 3H).

1 PDA Ch1 200nm 4nm

Peak#	Ret. Time	Area	Area %
1	12.704	893058	49.101
2	13.733	925773	50.899
Total		1818832	100.000

1 PDA Ch1 200nm 4nm

Peak#	Ret. Time	Area	Area %
1	12.680	3018354	96.065
2	13.709	123648	3.935
Total		3142001	100.000

(S)-3-(*p*-Fluorophenyl)-1,3-diphenylpropan-1-one [683816-03-7 for a racemate].

$\text{CuOTf} \cdot (0.5 \text{ toluene})$ (6.5 mg, 0.025 mmol), (S_S, S_S, S_S)-Ligand **L5** (16 mg, 0.03 mmol), *trans*-chalcone (104 mg, 0.5 mmol), *p*-fluorophenylboroxine (92 mg, 0.25 mmol), KOAc (98 mg, 1.0 mmol) and dry toluene (2.0 mL) were used.

The reaction was stopped after 30 h at 70 °C. The product was isolated by flash chromatography (30:1 to 10:1 hexane/EtOAc) as white solid. Yield: 142 mg, 93%. The NMR data of its enantiomer is provided elsewhere in the supporting information.

$[\alpha]_D^{22} = -1.3^\circ$ ($c = 1.66$ in CHCl_3).

94% ee. Daicel Chiralcel IC-H, 98:2 *n*-hexane/isopropanol, flow rate: 0.5 mL/min.

1 PDA Ch1 214nm 4nm

Peak#	Ret. Time	Area	Area %
1	18.286	162146	50.155
2	19.206	161142	49.845
Total		323288	100.000

PDA Ch1 214nm 4nm

Peak#	Ret. Time	Area	Area %
1	18.221	791899	3.016
2	19.094	25467419	96.984
Total		26259318	100.000

(S)-3-[p-(Trifluoromethyl)phenyl]-1,3-diphenylpropan-1-one [1383843-82-0].

CuOTf•(0.5 toluene) (6.5 mg, 0.025 mmol), (*S,S,S,S*)-Ligand **L5** (16 mg, 0.03 mmol), *trans*-chalcone (104 mg, 0.5 mmol), *p*-trifluoromethylphenylboroxine (129 mg, 0.25 mmol), KOAc (98 mg, 1.0 mmol) and dry toluene (2.0 mL) were used. The reaction was stopped after 30 h at 70 °C. The product was isolated by flash chromatography (30:1 to 10:1 hexane/EtOAc) as white solid. Yield: 154 mg, 87%. The ¹³C NMR data of its enantiomer is provided elsewhere in the supporting information.

GC-MS (EI): Calcd for C₂₂H₁₇F₃O: 354.1. Found: 354.0.

82% ee. Daicel Chiralcel IC-H, 98:2 *n*-hexane/isopropanol, flow rate: 0.5 mL/min.

¹H NMR (400 MHz, CDCl₃): δ 7.94-7.92 (m, 2H), 7.56-7.50 (m, 3H), 7.45-7.41 (m, 2H), 7.38 (d, *J* = 8.2 Hz, 2H), 7.31-7.24 (m, 4H), 7.22-7.17 (m, 1H), 4.89 (ψt, *J* = 7.2 Hz, 1H), 3.81-3.69 (m, 2H).

1 PDA Ch1 200nm 4nm

Peak#	Ret. Time	Area	Area %
1	12.804	2132768	49.845
2	13.390	2146030	50.155
Total		4278797	100.000

PDA Ch1 230nm 4nm

Peak#	Ret. Time	Area	Area %
1	12.789	136781	9.034
2	13.371	1377221	90.966
Total		1514002	100.000

(S)-3-[3,5-Bis(trifluoromethyl)phenyl]-1,3-diphenylpropan-1-one.

CuOTf•(0.5 toluene) (6.5 mg, 0.025 mmol), (*S,S,S*)-Ligand **L5** (16 mg, 0.03 mmol), *trans*-chalcone (104 mg, 0.5 mmol), 3,5-bis(trifluoromethyl)phenyl boroxine (180 mg, 0.25 mmol), KOAc (98 mg, 1.0 mmol) and dry toluene (2.0 mL) were used. The reaction was stopped after 30 h at 70 °C. The product was isolated by flash chromatography (30:1 to 10:1 hexane/EtOAc) as white solid. Yield: 204 mg, 91% yield.

GC-MS (EI): Calcd for C₂₃H₁₆F₆O: 422.1. Found: 422.0.

$[\alpha]_D^{22} = 14.5^\circ$ ($c = 1.01$ in CHCl₃).

95% ee. Daicel Chiralcel IC-H, 98:2 *n*-hexane/isopropanol, flow rate: 0.5 mL/min.

¹H NMR (400 MHz, CDCl₃): δ 7.95-7.92 (m, 2H), 7.71 (ψd, $J = 9.2$ Hz, 3H), 7.59-7.55 (m, 1H), 7.48-7.44 (m, 2H), 7.34-7.31 (m, 2H), 7.26-7.22 (m, 3H), 4.96 (ψt, $J = 7.3$ Hz, 1H), 3.82 (dd, $J = 17.5, 7.3$ Hz, 1H), 3.75 (dd, $J = 17.5, 7.3$ Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ 197.0, 146.9, 142.3, 136.7, 133.5, 131.8 (q, $J_{C-F} = 33.1$ Hz), 129.1, 128.8, 128.1 (q, $J_{C-F} = 2.7$ Hz), 128.05, 127.8, 127.2, 123.4 (q, $J_{C-F} = 272.8$ Hz), 120.6 (hept, $J_{C-F} = 3.8$ Hz), 45.7, 44.3.

¹⁹F NMR (377 MHz, CDCl₃): δ -62.7.

PDA Ch1 200nm 4nm				PDA Ch1 200nm 4nm			
Peak#	Ret. Time	Area	Area %	Peak#	Ret. Time	Area	Area %
1	8.821	2569978	49.822	1	8.832	180359	2.531
2	9.430	2588330	50.178	2	9.440	6945887	97.469
Total		5158308	100.000	Total		7126246	100.000

(S)-3-(p-Anisyl)-1,3-diphenylpropan-1-one [1338350-59-6].

CuOTf• (0.5 toluene) (6.5 mg, 0.025 mmol), (*S,S,S,S*)-Ligand **L5** (16 mg, 0.03 mmol), *trans*-enone (104 mg, 0.5 mmol), *p*-anisylboroxine (100 mg, 0.25 mmol), KOAc (98 mg, 1.0 mmol) and dry toluene (2.0 mL) were used. The reaction was stopped after 30 h at 80 °C. The product was isolated by flash chromatography (30:1 to 10:1 hexane/EtOAc) as white solid. Yield: 102 mg, 65%. The ¹³C NMR data of its enantiomer is provided elsewhere in the supporting information.

$[\alpha]_D^{22} = 1.1^\circ$ ($c = 1.37$ in CHCl₃).

95% ee. Daicel Chiralcel ID-H, 95:5 *n*-hexane/isopropanol, flow rate: 0.5 mL/min.

GC-MS (EI): Calcd for C₂₂H₂₀O₂: 316.2. Found: 316.1.

¹H NMR (400 MHz, CDCl₃): δ 7.92-7.90 (m, 2H), 7.53-7.49 (m, 1H), 7.43-7.39 (m, 2H), 7.25-7.23 (m, 4H), 7.19-7.12 (m, 3H), 6.81-6.77 (m, 2H), 4.77 (ψt, $J = 7.4$ Hz, 1H), 3.72 (s, 3H), 3.69 (ψd, $J = 7.4$ Hz, 2H).

(*S*)-1,3-Diphenyl-3-(2-thienyl)propan-1-one [2691-13-6 for racemate].

CuOTf•(0.5 toluene) (7.8 mg, 0.03 mmol), (*S,S,S,S*)-ligand **L5** (19 mg, 0.036 mmol), *trans*-chalcone (62 mg, 0.53 mmol), 2-thienylboroxine (80 mg, 0.24 mmol, 0.8 equiv), KOAc (59 mg, 0.6 mmol) and dry toluene (1.2 mL) were used. The reaction stopped after 30 h at 110 °C (about 65% conversion). The product was isolated by flash chromatography (30:1 to 10:1 hexane/EtOAc) as white solid. Yield: 44 mg, 50% yield (about 60 % conversion of chalcone). The ¹³C NMR data of its enantiomer is provided elsewhere in the supporting information.

GC-MS (EI): Calcd for C₁₉H₁₆OS: 292.1. Found: 292.0.

82% ee. Daicel Chiralcel IC-H, 98:2 *n*-hexane/isopropanol, flow rate: 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 7.95-7.93 (m, 2H), 7.57-7.53 (m, 1H), 7.47-7.42 (m, 2H), 7.36-7.31 (m, 2H), 7.30-7.27 (m, 2H), 7.23-7.19 (m, 1H), 7.13 (dd, $J = 3.9, 1.2$ Hz, 1H), 5.06 (vt, $J = 7.2$ Hz, 1H), 3.81 (dd, $J = 17.2, 7.1$ Hz, 1H), 3.71 (dd, $J = 17.2, 7.1$ Hz, 1H).

(R)-1,3-Diphenyl-1-p-tolylpropane. In an argon-filled glove box, an 8-mL vial was charged with (*R*)-3-*p*-tolyl-1,3-diphenylpropan-1-one (99% *ee*, 90 mg, 0.30 mmol), analytical-grade ethyl acetate (2 mL) and 5% Pd/C (32 mg, 0.015 mmol). The vial was placed in a 125-mL Parr bomb and pressurized with 30 psi of H_2 gas. The mixture was stirred at 25 °C for 48 hours until completion as monitored by TLC. The mixture was passed through a pad of Celite with ethyl acetate washing (5 mL). After concentration of the filtrate, the residue was purified by flash chromatography (hexane) to afford the titled compound as colorless oil (74 mg, 86% yield).

GC-MS (EI): Calcd for $\text{C}_{22}\text{H}_{22}$: 286.2. Found: 286.0.

$[\alpha]_{\text{D}}^{21} = -1.5^\circ$ ($c = 1.60$ in CHCl_3).

99% *ee*. Daicel Chiralcel AD-H, 99.5:0.5 *n*-hexane/isopropanol, flow rate: 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 7.27-7.21 (m, 6H), 7.17-7.11 (m, 6H), 7.09-7.07 (m, 2H), 3.87 (vt, $J = 7.7$ Hz, 1H), 2.58-2.54 (m, 2H), 2.38-2.32 (m, 2H), 2.28 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 145.2, 142.3, 141.9, 135.7, 129.3, 128.6 (2 overlapping signals), 128.4, 127.9, 127.9, 126.2, 125.9, 50.4, 37.5, 34.2, 21.1.

1 PDA Ch1 200nm 4nm

Peak#	Ret. Time	Area	Area %
1	12.201	5067695	52.233
2	12.800	4634454	47.767
Total		9702149	100.000

1 PDA Ch1 200nm 4nm

Peak#	Ret. Time	Area	Area %
1	12.362	19303925	100.000
Total		19303925	100.000

(*R,E*)-1,3-Diphenyl-3-(*p*-tolyl)propan-1-one oxime. Under argon, to a 10-mL Schlenk tube was added (*R*)-3-*p*-tolyl-1,3-diphenylpropan-1-one (99% *ee*, 150 mg, 0.50 mmol). Sodium acetate (50 mg, 0.60 mmol, 1.2 equiv) and hydroxylamine hydrochloride (42 mg, 0.60 mmol, 1.2 equiv) and MeOH (2 mL) were added and the mixture was heated to reflux. After refluxing for 2 h, the reaction mixture was allowed to cool down to RT and diluted with toluene (5 mL). 2 N NaOH (0.3 mL) was added and the solvent was removed in vacuo. Water (3 mL) was added and the crude product was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (5 mL) and dried over anhydrous Na₂SO₄. The filtration was concentrated on a rotary evaporator and the residue was purified by flash chromatography (EtOAc/hexane 1:4) to afford the pure (*E*)-isomer as white solid (128 mg, 81% yield). The *E/Z* ratio of oxime isomers in the crude mixture was determined to be 5.7:1 by proton NMR spectroscopy.

ESI-MS: Calcd for C₂₂H₂₂NO (M+H)⁺: 316.2. Found: 316.9.

99% *ee*. Daicel Chiralcel OJ-H, 90:10 *n*-hexane/isopropanol, flow rate: 1.0 mL/min.

¹H NMR (400 MHz, CDCl₃): δ 9.59 (br s, 1H), 7.28-7.23 (m, 5H), 7.17-7.13 (m, 4H), 7.11-7.06 (m, 3H), 7.00-7.6.98 (m, 2H), 4.36 (t, *J* = 8.0 Hz, 1H), 3.53 (d, *J* = 8.0 Hz, 2H), 2.24 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 158.8, 144.1, 140.9, 136.1, 135.9, 129.1, 129.0, 128.4, 128.4, 128.0, 127.9, 126.9, 126.4, 47.2, 32.9, 21.1.

(R)-N-Phenyl-3-phenyl-3-*p*-tolylpropanamide. Under argon, to a 10-mL Schlenk tube was added (*R,E*)-1,3-diphenyl-3-*p*-tolylpropan-1-one oxime (99% *ee*, 94.5 mg, 0.30 mmol), TsOH·H₂O (6.0 mg, 0.03 mmol), ZnCl₂ powder (4.8 mg, 0.036 mmol) and dry acetonitrile (2.0 mL). The reaction mixture was refluxed for 5 h and then cooled to room temperature. 2N NaOH (2 mL) was added to quench the reaction and the solvent was removed under reduced pressure. Water (10 mL) was added and the aqueous phase was extracted with EtOAc (3 x 40 mL). The combined organic layers were washed with brine (2 x 10 mL) and then dried over anhydrous Na₂SO₄. After the evaporation of the solvent, the residue was purified via flash column chromatography (EtOAc/hexane 1:4) to give the desired product as white solid (86 mg, 91% yield).

GC-MS (EI): Calcd for C₂₂H₂₁NO: 315.2. Found: 315.1.

$[\alpha]_D^{21} = -2.4^\circ$ ($c = 2.54$ in CHCl₃).

99% *ee*. Daicel Chiralcel OD-H, 80:20 *n*-hexane/isopropanol, flow rate: 1.0 mL/min.

¹H NMR (400 MHz, CDCl₃): δ 7.59 (s, 1H), 7.29-7.27 (m, 2H), 7.24-7.13 (m, 7H), 7.10-7.08 (m, 2H), 7.05-6.99 (m, 3H), 4.57 (ψt, $J = 7.7$ Hz, 1H), 3.00 (ψd, $J = 7.8$ Hz, 2H), 2.26 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 170.0, 143.9, 140.6, 137.8, 136.2, 129.4, 128.9, 128.7, 127.75, 127.65, 126.6, 124.3, 120.3, 47.1, 44.1, 21.0.

(R)-Phenyl 3-phenyl-3-*p*-tolylpropanoate [1092118-46-1 for racemate]. A 10-mL Schlenk tube was charged with (*R*)-3-*p*-tolyl-1,3-diphenylpropan-1-one (99% *ee*, 90 mg, 0.30 mmol), *m*CPBA (273 mg, 1.2 mmol, about 70% purity, Aldrich), trifluoroacetic acid (48 μ L, 0.60 mmol) and in CH_2Cl_2 (2.4 mL). The solution was stirred with refluxing for 48 h. The organic phase was washed with saturated aqueous NaHCO_3 (3 x 20 mL), extracted with CH_2Cl_2 , dried over Na_2SO_4 and filtered. The filtrate was concentrated in vacuo and the residue was purified by flash column chromatography (hexane/EA 4:1) to afford the product as colorless oil (62 mg, 65% yield).

GC-MS (EI): Calcd for $\text{C}_{22}\text{H}_{20}\text{O}_2$: 316.2. Found: 316.1.

$[\alpha]_{\text{D}}^{22} = -1.9^\circ$ ($c = 1.25$ in CHCl_3).

99% *ee*. Daicel Chiralcel AD-H, 98:2 *n*-hexane/isopropanol, flow rate: 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 7.30-7.25 (m, 6H), 7.22-7.10 (m, 6H), 6.79-6.77 (m, 2H), 4.62 (q, $J = 8.2$ Hz, 1H), 3.27 (qd, $J = 8.2$ Hz, 2H), 2.30 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 170.5, 150.7, 143.4, 140.2, 136.3, 129.40, 129.26, 128.7, 127.8, 127.7, 126.7, 125.8, 121.5, 47.0, 41.1, 21.0.

2.9.4 Determination of natural-abundance C^{13} KIE value

A procedure for conjugate addition of *p*-methylchalcone with phenylboroxine. In an

argon-filled glove box, to a 100-mL Schlenk tube, *p*-methylchalcone (9.99 g, 45.0 mmol), GC standard 1-dodecane (2.0 mL) and 70 mL of dry toluene were added. The mixture was stirred for 20 minutes at RT until the solid was completely dissolved. Aliquots were taken for GC analysis. Then to the mixture was added CuOTf •(0.5 toluene) (117 mg, 0.45 mmol, 1 mol%), (*S,S,S,S*)-ligand **L5** (290 mg, 0.54 mmol, 1.2 mol%), KOAc (8.82 g, 90 mmol) and phenylboroxine (6.95 g, 22.5 mmol). The reaction mixture was heated with stirring in a pre-warmed 110 °C oil bath for 42 h. After cooling to room temperature, aliquots of the crude mixture were analyzed by GC to determine the conversion of chalcone by GC (81.1(1.5)%). Most unreacted *p*-methylchalcone was recovered by flash chromatography with 10:1 hexane/DCM.

Determination of ¹²C/¹³C KIE values. The samples were prepared by dissolving around 450 mg of material in powder form in 0.6 mL of CDCl₃ in J. Young tubes with 0.5 mm OD. Note: too concentrate samples led to crystal formation during NMR experiment. The NMR spectra were recorded on a same Bruker BBF-O 400 NMR spectrometer. The ¹³C NMR spectra were obtained with inverse gate decoupling with a delay time of > 5T₁ (55 s) and calibrated π/4 pulses were used. The longest T₁ for the sample was determination with inversion-recovery method. 262144 points were collected, which was zero-filled to 512K points before Fourier transformation. Zeroth-order baseline correction was applied. Integration was determined by using a constant range of ± 5 Hz around each peak. The signal at 129.75 ppm, which corresponds to two meta/ortho hydrogens of an aryl ring, was chosen as an internal standard for integration and its integration value was set as 2. We assumed that its isotopic content was the least affected by the reaction amongst carbon signals in the material.

The ¹³C KIE values were calculated according to the equation below. F is the fraction conversion and R₀ and R are integration values of standard and recovered starting materials, respectively.

$$\text{KIE}_{\text{calcd}} = \ln(1-F)/\ln[(1-F)R/R_0]$$

Table 2.6. Average C13 integration values for standard and unrecovered methylchalcone, R/R₀ values and KIE values (standard deviation in the last digits are shown in parentheses)

	C	C	C(=O)
Standard material	1.001(2)	1.029(1)	1.039(2)

Recovered material	1.003(1)	1.068(1)	1.041(4)
R/R ₀ ratio	1.002(2)	1.038(2)	1.001(4)
Expt. KIE value	1.001(1)	1.023 (1)	1.001 (1)
Calc. KIE value using (L5)phenylcopper	1.00	1.02	1.00

Chapter 3

Asymmetric Addition of Organoboron Reagents to Aldimines Using Copper Catalysts

3.1 Introduction

Chiral amines are important motifs in many drugs and drug candidates.¹⁶⁰⁻¹⁶³ Therefore, methods that produce chiral amines are extensively studied. One of the most common methods is chiral resolution.^{164,165} This method is cost-effective, but it wastes half of the material. Another widely used method is asymmetric synthesis of chiral amines using chiral auxiliaries.¹⁶⁶⁻¹⁶⁹ The auxiliaries are often expensive, which limits the use of this method. A third approach, asymmetric reduction of corresponding ketimines is potentially very useful to produce chiral amines.¹⁷⁰⁻¹⁷⁴ However, high stereoselectivity is limited to ketimines carrying two very different groups such as phenyl and methyl groups. A fourth method, catalytic asymmetric nucleophilic addition to imines, in comparison, can provide amines carrying similar groups in high *ee*, for example, diarylmethylamines bearing two similar aryl rings.

Scheme 3.1 Chiral amines used in drugs

3.2 Copper-catalyzed asymmetric addition of organometallic reagents to imines

Copper-catalyzed asymmetric addition of reactive organometallic reagents such as Grignard and organozinc reagents, to imines has been extensively developed by many groups and many catalysts were tested. For example, in 2000, Tomioka group reported asymmetric addition of diethyl zinc to the imines using a Proline-derived amidophosphine.¹⁷⁵ Later, Charette group used (*R,R*)-Me-DuPhos and Me-DuPhos monoxide in the reaction and gave good results.^{84,176} In 2008, Minnaard and Feringa et al. successfully applied phosphoramidite ligands on a binaphthyl skeleton in the addition of *N*-formylimines.¹⁷⁷

Scheme 3.2 Copper-catalyzed asymmetric addition of organozinc reagents to imines

3.3 Rhodium-catalyzed asymmetric arylation of imines

In 2000, Hayashi group reported rhodium-catalyzed asymmetric arylation of imines using arylstannanes, using a chiral biarylphosphine as a supporting ligand. However, organostannanes are not commercially available and highly toxic.¹⁷⁸

Scheme 3.3 Rhodium-catalyzed asymmetric arylation of imines using organostannanes reagents

Aryltitanium reagents are more reactive, although they are sensitive to water. They

have also been used in rhodium-catalyzed arylation of imines.¹⁷⁹

Scheme 3.4 Rhodium-catalyzed asymmetric arylation of imines using organotitanium reagents

The breakthrough for asymmetric arylation of imines using air-stable, nontoxic organometallic reagents was reported by Tomioka group in 2004.¹⁸⁰ Commercially available and air-stable arylboronic acids were used in the reaction. Under the optimal conditions, an *N*-Boc-valine-derived amidophosphine was used as the ligand. Aromatic aldimines with large *ortho* groups reacted well in high enantioselectivity. For less hindered substrates, the enantioselectivities were only moderate. In comparison, a common chiral ligand (*S*)-BINAP gave only 34% *ee*. The pioneering work of Tomioka group encouraged others to try different types of ligands for the asymmetric arylation of imines.

Scheme 3.5 Rhodium-catalyzed asymmetric arylation of imines using amidomonophosphane ligand

In 2004, Hayashi group applied C_2 -symmetric bicyclo[2.2.2]octadienes in the asymmetric arylation of *N*-tosylaldimine and obtained good enantioselectivities (95-99% *ee*).¹⁸¹ Substrates with different electron density and steric property reacted smoothly to give the products in good results.

Scheme 3.6 Rhodium-catalyzed asymmetric arylation of imine using (*R, R*)-Ph-Bod* ligand

In 2010, Hayashi group extended the reactivity to arylation of more challenging ketimines.¹⁸² Good yield was obtained only when sodium tetraphenylborate was used as the reagent, which is a main limitation. Phenylboronic acid, its boroxine and neopentylglycol ester gave low yields.

Scheme 3.7 Rhodium-catalyzed asymmetric arylation of ketimine using *C*₂-symmetric diene ligand

In 2012, Hayashi group expanded the scope of imines to cyclic benzosultams.¹⁸³ The enantioenriched products could be converted to chiral (triaryl)methylamines after transformation, which are difficult to obtain from methods. Later, rhodium-catalyzed asymmetric addition of organoboron reagents was also realized with other cyclic *N*-sulfonylketimines by others.¹⁸⁴⁻¹⁸⁶

Scheme 3.8 Rhodium-catalyzed asymmetric arylation of *N*-sulfonylketimines using a *C*₂-symmetric diene ligand

In 2007, Lin group in China successfully applied *C*₂-symmetric tetrahydropentalenes based on two *cis*-fused cyclopentene rings in asymmetric arylation of imines.¹¹⁷ Notably, sterically encumbered *ortho*-substituted imines reacted to produce the products in good

enantioselectivities.

α -Aryl alkylamines are prevalent in biologically active molecules.¹⁸⁷ The development of new methods for asymmetric synthesis of α -aryl alkylamines is important in organic synthesis. In 2012, the tetrahydropentalenes diene was successfully used in arylation of the aliphatic aldimines.¹⁸⁸ It is remarkable that diverse aliphatic imines, including 1°, 2° and 3° aliphatic ones, reacted to give high enantioselectivity.

Scheme 3.9 Rhodium-catalyzed asymmetric arylation of imines using a C_2 -symmetric diene ligand

Other types of phosphorus ligands were also successfully applied in asymmetric arylation of imines. For example, in 2006, Zhou Qilin's group reported (*S*)-ShiP in this reaction.¹⁸⁹ The phosphite ligand was based on a spirobiindane structure and has been used in other metal-catalyzed reactions.¹⁹⁰

Scheme 3.10 Rhodium-catalyzed asymmetric arylation of imines using (*S*)-ShiP ligand

In 2006, Feringa group reported the use of a phosphoramidite ligand in asymmetric addition of arylboronic acids to *N*-sulfamoylimines.¹⁹¹ The phosphoramidite ligands are cheap to make and readily available. Chiral phosphoramidite ligands previously proved to be effective in rhodium-catalyzed asymmetric addition of arylboronic acids to enones.^{121,192-195}

Scheme 3.11 Rhodium-catalyzed asymmetric arylation of imines using a phosphoramidite ligand

In 2008, Ellman group used a special bisphosphine, (*R,R*)-deguphos in arylation of aryl aldimines.¹⁹⁶ The imines were generated in situ from α -carbamoylsulfones and provided *N*-Boc-protected products. Many other methods gave *N*-tosyl amines as products which are difficult to cleave later. Aliphatic *N*-tosyl aldimines were also suitable substrates.¹⁹⁷

Scheme 3.12 Rhodium-catalyzed asymmetric arylation of imines using deguphos ligand

In 2014, Sieber group invented a mixed phosphine-olefin ligand, JoshPhos for asymmetric arylation of imines.¹⁹⁸ The *P*-chiral phosphine and the olefin unit can bind to the rhodium center to form a chiral pocket.

Scheme 3.13 Rhodium-catalyzed asymmetric arylation of imines using JoshPhos ligand

In 2016, Dorta group successfully applied a chiral disulfoxide ligand in asymmetric addition of arylboronic acids to imines.¹⁹⁹ The same type of ligands were efficient in rhodium-catalyzed asymmetric addition of arylboronic acids to unsaturated

ketones.^{124,125,200,201}

Scheme 3.14 Rhodium-catalyzed asymmetric arylation of imines using a chiral disulfoxide ligand

3.4 Palladium-catalyzed asymmetric addition of organoboron reagents to imines

In 2009, Shi group invented the first example of palladium-catalyzed asymmetric addition of arylboronic acids to imines.²⁰² Chiral bis-NHC ligand base on a binaphthyl motif was used to produce good yields and enantioselectivities. The reaction was applied to different arylboronic acids and both aryl and aliphatic aldimines reacted efficiently.

Scheme 3.15 asymmetric addition of arylboronic acids to imines catalyzed by a Pd/NHC complex

In 2015, Peters group reported a more efficient palladium catalyst. The ferrocene-imidazoline palladacycle (FIP) was converted to the palladacycle acetate by the reactions of AgOAc in situ.²⁰³ For most of substrates, >99% ee was obtained.

Scheme 3.16 Palladium catalyzed asymmetric addition of arylboronic acids to imines using a palladacycle complex

In 2014, Hayashi group reported palladium-catalyzed asymmetric addition of organoboron reagents to benzoxathiazine-2,2-dioxides.²⁰⁴ The carbamate group in products can be easily cleared by LiAlH_4 without *ee* erosion. A cationic aryl palladium was crucial for the good activity and enantioselectivity. Some additional works on palladium-catalyzed asymmetric addition of arylboronic acids to benzosultams and benzoxathiazine-2,2-dioxides have emerged since then.²⁰⁵⁻²⁰⁷

Scheme 3.17 Palladium-catalyzed asymmetric addition of arylboronic acids to cyclic *N*-sulfonylketimines

3.5 Organocatalytic asymmetric addition of imines

Recently, some organocatalysts have been developed for asymmetric addition of organoboron reagents to imines.^{208,209} The organoboronic acid underwent exchange with the BINOL fragment of the catalyst. The hydrogen bonding between the thiourea group and phenolate ion docked the imine substrate on the catalyst, so that the asymmetric aryl transfer was an intramolecular event. However, the substrates scope of the reaction was limited and moderate enantioselectivities were obtained in most cases.

Scheme 3.18 Organocatalyst activated asymmetric addition of organoboron reagents to imines

3.6 Our work on copper-catalyzed asymmetric addition of arylboronic reagents to imines

Although the asymmetric addition of imines using air-stable organoboron reagents was extensively studied in the past decade and great progress has been achieved, most catalysts used expensive and toxic noble metals, especially, rhodium and palladium. We decided to examine whether similar addition reactions can be realized by using cheap and much less toxic copper catalysts.

We started by studying copper-catalyzed addition of *p*-tolylboroxine to *N*-*p*-methoxyphenyl benzaldimine. No reactivity was observed under numerous conditions initially. When *N*-tosyl benzaldimine was used as the imine substrate, good yield was obtained, however, the enantioselectivity was low even in the presence of many phosphorus and nitrogen ligands. When we tried 3-methyl-2-pyridyl as the activating group on benzaldimine, the desired product was obtained in good yield and moderate *ee* in the presence of Feringa ligand. We chose the addition of *p*-tolylboroxine to the latter imine as a model reaction to optimize catalysts and conditions.

Scheme 3.19 Copper-catalyzed asymmetric addition of organoboroxine to a model imine using a phosphoramidite ligand

Initially, we screened the different bases. The results are in Table 3.1. The reactions proceeded smoothly to give good yields when many bases were used, for example, alkoxides, hydroxides, carbonates and acetates. We chose KOAc as the best base for the further study. When K₃PO₄ was used, low conversion and low yield were obtained. When the reaction was set up in the absence of the base, no reaction happened.

Table 3.1 Effect of bases

Entry	Base	Conv (%)	GC yield (%)	Ee (%)
1	LiOtBu	90	75	-55
2	LiOMe	90	80	-53
3	LiOH	80	70	-51
4	NaOAc	90	85	-55
5	KOAc	95	90	-54
6	K ₃ PO ₄	45	30	-54
7	KF	90	85	-55
8	K ₂ CO ₃	90	80	-54
9	None	0	0	-

Next, we tried different phosphoramidite ligands in the model reaction. The results are presented in Table 3.2. The ligands based on a spiro-biindanyl backbone catalyzed the reaction in much higher enantioselectivity, compared to BINOL derivatives (entry 1 versus 6). In particular, a spiro-phosphoramidite ligand (*R_a,R,R*)-SIPHOS-PE bearing a bis-2-phenylethylamine fragment proved to be the best ligand and afforded good *ee*. Further modification of the chiral amine groups did not lead to better results. We found that the spiro chirality had dominant influence on the absolute configuration of the product (entry 6 versus 7). Thus, (*R_a,R,R*)-SIPHOS-PE, which was invented by Qilin Zhou et al., was chosen as the optimal ligand for our study.

Table 3.2 Effect of chiral phosphoramidite ligands

Entry	Ligand	Conv. (%) (12h)	GC yield (%)	<i>Ee</i> (%)
1		95	90	-55
2		85	80	-55
3		100	90	74
4		100	85	-56
5		100	90	-65
6		100	90	90

7		100	80	-84
8		100	90	60
9		90	80	56
10		100	90	85
11		100	92	-83
12		100	90	-65
13		100	85	77

14		100	90	82
15		100	90	-84

The effect of the solvents was also tested in the model reaction. In many common solvents, satisfactory yield and *ee* were obtained, for example, toluene, THF and dioxane, but poor conversion and poor yield were obtained in acetonitrile (Table 3.3)

Table 3.3 Effect of solvents

Entry	Solvent	Conv (%) 24 h	GC yield (%)	<i>Ee</i> (%)
1	Toluene	100	90	89
2	PhCF ₃	100	89	89
3	Dioxane	100	90	86
4	THF	100	84	90
6	NMP	100	90	79
5	MeCN	60	20	-

When the ratio of copper and ligand was varied, almost identical results were seen (Table 3.4). We thus used 10 mol% copper and 12 mol% ligand in later studies.

Table 3.4 Effect of the ratio of copper and ligand

Entry	Ratio of X : Y	GC yield (%)	GC yield (%)	Ee (%)
1	10 : 10	90	75	88
2	10 : 12	100	87	89
3	10 : 15	96	80	89
4	10 : 20	100	90	89

Later, when we lowered reaction temperature from 110 °C to 80 °C, the model reaction also proceeded efficiently in the presence of many copper salts (Table 3.5). 0.5 equivalent of phenylboroxines was sufficient to obtain 85% yield of the product (entry 5).

Table 3.5 Effect of copper source and reaction temperature

Entry	Cu sources/temp.	Conv (%)	GC yield (%)	Ee (%)
1	CuCl	88	80	92
2	CuBr	80	70	92
3	CuTC	80	72	93
4	Cu(OAc) ₂	78	70	93
5	Cu(OAc)	88	85	93
6	CuCl 0.7 equiv boroxine	88	83	93
7	Cu(OAc) 0.7 equiv boroxine	100	95	93

We applied the optimal conditions to different aldimines and the results are presented in Scheme 3.20. Both *para*-methoxy and *para*-trifluoromethyl substituted arylimines proceeded smoothly in high *ee*. We found that some *ortho*-substituted arylimines afforded only moderate *ee* values which requires further optimization of chiral ligands. When the reaction was set up at a gram scale, 2.5 mol% of copper catalyst can yield the product in 93% yield and 92% *ee* after 48 hours at 100 °C.

examples that gave unsatisfactory results

Scheme 3.20 Asymmetric addition of phenylboroxine to aldimines using a copper catalyst

Scheme 3.21 X-ray structure of one product and its absolute configuration

We also tested different arylboroxines and the results are presented in Scheme 3.22. In most cases, high yield and good enantioselectivity were obtained. However, more hindered *ortho*-tolylboroxine gave only 68% yield and 68% *ee* under the same conditions

Scheme 3.22 Asymmetric addition of arylboroxines to benzaldehydes using a copper catalyst

3.7 Summary

Chiral amines are important structures in many drugs and drug candidates. We developed the first copper-catalyzed enantioselective addition of organoboron reagents to aldimines. The scope of aryl aldimines and arylboroxines were satisfactory and in most cases, >90% *ee* was obtained. In future, we will test whether aliphatic aldimines and alkenylboroxines can react under the copper/phosphoramidite catalysis.

3.8 Experiment section

3.8.1. General

All NMR spectra were acquired on Bruker BBFO1 400 MHz and Bruker AV 300 MHz

NMR spectrometers. ^1H NMR (400 MHz) chemical shifts were recorded relative to SiMe_4 (δ 0.00) or residual protiated solvents (CDCl_3 : δ 7.26). Multiplicities were given as: s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). The number of protons (n) for a given resonance was indicated by $n\text{H}$. Coupling constants were reported as a J value in Hz. ^{13}C NMR (100 MHz) chemical shifts were recorded relative to solvent resonance (CDCl_3 : δ 77.16). ^{19}F NMR (376 MHz) chemical shifts were recorded relative to an external standard ($\text{BF}_3\cdot\text{OEt}_2$: δ 153.0). ^{31}P NMR (126 MHz) chemical shifts were relative to an external standard (85% H_3PO_4 : δ 0.00). Proof of purity of new compounds was demonstrated with copies of ^1H , ^{13}C , ^{31}P and ^{19}F NMR spectra.

Glassware was dried at 120 $^\circ\text{C}$ for at least 1 h before use. Dry toluene, hexane, diethyl ether and dichloromethane were collected from a solvent purification system containing a column of activated alumina (1 m x 2) under argon. Dry THF was freshly distilled from sodium/benzophenone under argon. All anhydrous solvents were stored in Schlenk tubes in the glove box. KOAc was dried for 48 hours at 220 $^\circ\text{C}$ under vacuum pressure. Unless noted otherwise, commercially available chemicals were used as received without purification. The GC internal standard, $n\text{-C}_{12}\text{H}_{26}$ was degassed with argon and dried over activated 4 Å molecular sieve beads before use. Flash chromatography was performed using Merck 40-63D 60 Å silica gel. Gas chromatography (GC) analysis was performed on a Shimadzu GC-2010 instrument with Agilent J & W GC column DB-5MS-UI. GC/MS analysis was conducted on a Thermo Scientific DSQ II single quadrupole GC/MS instrument with Agilent J & W GC column DB-5MS-UI. ESI/MS analysis was conducted on a ThermoFinnigan LCQ Fleet MS spectrometer. The starting materials of imine were purified by Buchi glass oven B-585 Kugelrohr. Chiral HPLC analysis was performed on a Shimadzu LC-20AD instrument using Daicel Chiracel columns at 25 $^\circ\text{C}$ and a mixture of HPLC-grade hexane and isopropanol as eluent. Optical rotation was measured using a JASCO P-1030 Polarimeter equipped with a sodium vapor lamp at 589 nm and the concentration of samples was denoted as c .

3.8.2. Procedures and isolation of arylaldimines

The aldimines used in this study were prepared from the corresponding aldehydes and 2-amino-3-picoline according to the literature procedure.²¹⁰ The aldimines were stored in the fridge in glovebox.

***N*-Benzylidene-*N*-(3-methylpyridin-2-yl)amine [36952-37-1].**

Yellow oil. ^1H NMR (400 MHz, CDCl_3): δ 9.07 (s, 1H), 8.31 (dd, $J = 4.8, 1.3$ Hz, 1H), 8.02-7.99 (m, 2H), 7.53-7.52 (m, 1H), 7.49-7.43 (m, 3H), 7.07 (dd, $J = 7.4, 4.8$ Hz, 1H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 161.7, 159.6, 146.1, 138.9, 136.3, 131.7, 129.4, 128.8, 128.7, 121.8, 17.4.

***N*-(*p*-Methylbenzylidene)-*N*-(3-methylpyridin-2-yl)amine [415901-35-8].**

Yellow solid. ^1H NMR (400 MHz, CDCl_3): δ 9.02 (s, 1H), 8.30 (dd, $J = 4.7, 1.5$ Hz, 1H), 7.90 (d, $J = 8.1$ Hz, 2H), 7.52 (d, $J = 7.4$ Hz, 1H), 7.28-7.26 (m, 2H), 7.06 (dd, $J = 7.4, 4.8$ Hz, 1H), 2.45 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 161.5, 159.8, 146.1, 142.2, 138.8, 133.8, 129.5, 129.4, 128.6, 121.6, 21.7, 17.4.

***N*-(*o*-Methylbenzylidene)-*N*-(3-methylpyridin-2-yl)amine [117487-01-1].**

Yellow solid. ^1H NMR (400 MHz, CDCl_3): δ 9.35 (s, 1H), 8.32 (d, $J = 4.1$ Hz, 1H), 8.15 (d, $J = 7.6$ Hz, 1H), 7.55-7.53 (m, 1H), 7.39-7.35 (m, 1H), 7.32-7.28 (m, 1H), 7.24 (d, $J = 8.1$ Hz, 1H), 7.08 (dd, $J = 7.4, 4.8$ Hz, 1H), 2.68 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 160.7, 160.0, 146.2, 139.6, 138.8, 134.2, 131.2, 131.1, 129.1, 128.7, 126.2, 121.7, 19.9, 17.5.

***N*-(*p*-Methoxybenzylidene)-*N*-(3-methylpyridin-2-yl)amine [36952-41-7].**

Yellow solid. ^1H NMR (400 MHz, CDCl_3): δ 9.00 (s, 1H), 8.29 (dd, $J = 4.7, 1.3$ Hz, 1H), 7.97-7.94 (m, 2H), 7.52 (d, $J = 7.4$ Hz, 1H), 7.05 (dd, $J = 7.4, 4.8$ Hz, 1H), 6.99-6.96 (m, 2H), 3.86 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 162.6, 160.8, 159.9, 146.1, 138.7, 131.2, 129.4, 128.5, 121.4, 114.1, 55.4, 17.4.

***N*-(*o*-Methoxybenzylidene)-*N*-(3-methylpyridin-2-yl)amine [1273592-79-2].**

Yellow solid. ^1H NMR (400 MHz, CDCl_3): δ 9.49 (s, 1H), 8.31 (dd, $J = 4.8, 1.3$ Hz, 1H), 8.27 (dd, $J = 7.7, 1.8$ Hz, 1H), 7.51 (dd, $J = 7.4, 0.9$ Hz, 1H), 7.46-7.42 (m, 1H), 7.06-7.02 (m, 2H), 6.94 (d, $J = 8.4$, 1H), 3.89 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 160.4, 160.2, 157.7, 146.2, 138.6, 133.1, 128.4, 127.9, 124.9, 121.4, 120.7, 111.2, 55.5, 17.5.

***N*-(*p*-Trifluoromethylbenzylidene)-*N*-(3-methylpyridin-2-yl)amine [850132-21-7]**

Yellow solid. ^1H NMR (400 MHz, CDCl_3): δ 9.14 (s, 1H), 8.31 (dd, $J = 4.8, 1.6$ Hz, 1H), 8.10 (d, $J = 8.1$ Hz, 2H), 7.71 (d, $J = 8.2$ Hz, 2H), 7.56-7.54 (m, 1H), 7.11 (dd, $J = 7.4, 4.8$ Hz, 1H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 159.9, 158.7, 146.2, 139.4, 139.1, 132.9 (q, $J = 32.4$ Hz), 129.5, 129.3, 126.6 (q, $J = 272.5$ Hz), 125.6 (q, $J = 3.8$ Hz), 122.4, 17.3; ^{19}F NMR (376 MHz, CDCl_3): δ -62.9.

***N*-(*o*-Trifluoromethylbenzylidene)-*N*-(3-methylpyridin-2-yl)amine.**

Yellow solid. ^1H NMR (400 MHz, CDCl_3): δ 9.46 (s, 1H), 8.53 (d, $J = 7.8$ Hz, 1H), 8.33 (dd, $J = 4.7, 1.4$ Hz, 1H), 7.73 (d, $J = 7.8$ Hz, 1H), 7.64 (t, $J = 7.7$ Hz, 1H), 7.56 (t, $J = 8.1$ Hz, 2H), 7.10 (dd, $J = 7.5, 4.8$ Hz, 1H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 159.1, 157.8, 146.3, 139.0, 134.3, 132.0, 130.9, 130.3 (q, $J = 31.0$ Hz), 129.0, 128.9, 125.8 (q, $J = 5.8$ Hz), 124.2 (q, $J = 274.1$ Hz), 122.4, 17.3.

***N*-(*p*-Fluorobenzylidene)-*N*-(3-methylpyridin-2-yl)amine [676159-42-5].**

Yellow solid. ^1H NMR (400 MHz, CDCl_3): δ 9.04 (s, 1H), 8.30 (dd, $J = 4.7, 1.4$ Hz, 1H), 8.02-7.98 (m, 2H), 7.75-7.53 (m, 1H), 7.17-7.13 (m, 2H), 7.08 (dd, $J = 7.5, 4.8$ Hz, 1H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 165.0 (d, $J = 252.6$ Hz), 160.1, 159.3, 146.1, 138.9, 132.7 (d, $J = 3.0$ Hz), 131.4 (d, $J = 8.7$ Hz), 128.8, 121.9, 115.9 (d, $J = 21.8$ Hz), 17.4; ^{19}F NMR (376 MHz, CDCl_3): δ -107.6.

***N*-(*m,m*-Difluorobenzylidene)-*N*-(3-methylpyridin-2-yl)amine.**

Yellow solid. ^1H NMR (400 MHz, CDCl_3): δ 9.02 (s, 1H), 8.29 (dd, $J = 4.4, 1.3$ Hz, 1H), 7.54-7.52 (m, 1H), 7.51-7.47 (m, 2H), 7.09 (dd, $J = 7.5, 4.8$ Hz, 1H), 6.90 (tt, $J = 8.6, 2.3$ Hz, 1H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 164.4 (d, $J = 12.2$ Hz), 161.9 (d, $J = 12.3$ Hz), 158.8 (t, $J = 3.2$ Hz), 158.2, 146.1, 139.6 (t, $J = 8.8$ Hz), 139.1, 129.4, 122.6, 111.7 (q, $J = 11.7$ Hz), 111.7 (q, $J = 25.8$ Hz), 106.7 (t, $J = 20.6$ Hz), 17.2; ^{19}F NMR (376

MHz, CDCl₃): δ -109.1.

***N*-(*p*-Bromobenzylidene)-*N*-(3-methylpyridin-2-yl)amine [117487-00-0].**

Yellow solid. ¹H NMR (400 MHz, CDCl₃): δ 9.02 (s, 1H), 8.28 (d, *J* = 4.7 Hz, 1H), 7.84 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 7.4 Hz, 2H), 7.06 (dd, *J* = 7.4, 4.8 Hz, 1H), 2.43 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 160.2, 159.0, 146.2, 139.0, 135.2, 132.0, 130.7, 129.0, 126.3, 122.1, 17.4.

***N*-(*p*-Chlorobenzylidene)-*N*-(3-methylpyridin-2-yl)amine [69556-14-5].**

Yellow solid. ¹H NMR (400 MHz, CDCl₃): δ 9.05 (s, 1H), 8.30-8.29 (m, 1H), 7.94-7.89 (m, 2H), 7.55-7.53 (m, 1H), 7.46-7.39 (m, 2H), 7.10-7.04 (m, 1H), 2.45 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 160.1, 159.1, 146.2, 139.0, 137.7, 134.8, 130.5, 129.03, 128.96, 122.1, 17.4.

***N*-(*o*-Chlorobenzylidene)-*N*-(3-methylpyridin-2-yl)amine.**

Yellow solid. ¹H NMR (400 MHz, CDCl₃): δ 9.52 (s, 1H), 8.36-8.32 (m, 2H), 7.54 (d, *J* = 7.4 Hz, 1H), 7.44-7.33 (m, 3H), 7.11-7.08 (m, 1H), 2.45 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 159.4, 158.4, 146.3, 138.9, 137.0, 133.4, 132.4, 130.0, 129.0, 128.9, 127.0, 122.1, 17.4.

***N*-(2-Naphthylidene)-*N*-(3-methylpyridin-2-yl)amine [415901-38-1].**

Yellow solid. ^1H NMR (400 MHz, CDCl_3): δ 9.23 (s, 1H), 8.33 (dd, $J = 4.7, 1.3$ Hz, 1H), 8.28-8.26 (m, 2H), 7.94-7.85 (m, 3H), 7.56-7.49 (m, 3H), 7.09 (dd, $J = 7.4, 4.8$ Hz, 1H), 2.50 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 161.6, 159.6, 146.2, 138.9, 135.3, 134.1, 133.2, 132.3, 129.0, 128.9, 128.6, 127.9, 127.7, 126.6, 124.2, 121.9, 17.5.

***N*-(1-Naphthylidene)-*N*-(3-methylpyridin-2-yl)amine [1273592-81-6].**

Yellow solid. ^1H NMR (400 MHz, CDCl_3): δ 9.74 (s, 1H), 9.38 (d, $J = 8.6$ Hz, 1H), 8.40-8.38 (m, 1H), 8.22 (dd, $J = 7.2, 1.0$ Hz, 1H), 7.98 (d, $J = 8.2$ Hz, 1H), 7.92 (d, $J = 8.2$ Hz, 1H), 7.68-7.64 (m, 1H), 7.60-7.55 (m, 3H), 7.11 (dd, $J = 7.4, 4.8$ Hz, 1H), 2.56 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 161.8, 159.9, 146.3, 138.9, 134.0, 132.4, 131.8, 131.63, 131.57, 129.0, 128.7, 127.6, 126.3, 125.3, 125.0, 121.9, 17.8.

***N*-(1,3-Benzodioxo-5-ylidene)-*N*-(3-methylpyridin-2-yl)amine.**

Yellow solid. ^1H NMR (400 MHz, CDCl_3): δ 8.95 (s, 1H), 8.27 (dd, $J = 4.7, 1.3$ Hz, 1H), 7.62 (d, $J = 1.5$ Hz, 1H), 7.50 (dd, $J = 7.4, 0.9$ Hz, 1H), 7.36 (dd, $J = 8.0, 1.6$ Hz, 1H), 7.03 (dd, $J = 7.4, 4.8$ Hz, 1H), 6.86 (d, $J = 7.9$ Hz, 1H), 6.00 (s, 2H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 160.5, 159.5, 150.8, 148.3, 146.1, 138.8, 131.3, 128.7, 126.8, 121.5, 108.2, 107.2, 101.6, 17.4.

***N*-(3-Thienylidene)-*N*-(3-methylpyridin-2-yl)amine [1701462-96-5].**

Yellow oil. ^1H NMR (400 MHz, CDCl_3): δ 9.07 (s, 1H), 8.29 (dd, $J = 4.7, 1.2$ Hz, 1H), 7.88 (dd, $J = 2.9, 0.9$ Hz, 1H), 7.75 (d, $J = 5.1$ Hz, 1H), 7.53 (d, $J = 6.6$ Hz, 1H), 7.37 (dd, $J = 5.0, 3.0$ Hz, 1H), 7.07 (dd, $J = 7.4, 4.8$ Hz, 1H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 159.6, 155.6, 146.1, 141.1, 138.8, 131.5, 128.7, 126.5, 126.2, 121.7, 17.4.

***N*-(2-Thienylidene)-*N*-(3-methylpyridin-2-yl)amine [327973-86-4].**

Yellow oil. ^1H NMR (400 MHz, CDCl_3): δ 9.23 (s, 1H), 8.28 (dd, $J = 4.7, 1.3$ Hz, 1H), 7.57 (d, $J = 3.5$ Hz, 1H), 7.54-7.52 (m, 2H), 7.14 (dd, $J = 5.0, 3.7$ Hz, 1H), 7.06 (dd, $J = 7.4, 4.8$ Hz, 1H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 158.8, 154.2, 146.1, 143.3, 138.9, 133.4, 130.9, 129.0, 127.9, 121.8, 17.3.

***N*-(2-Furylidene)-*N*-(3-methylpyridin-2-yl)amine [59374-26-4].**

Brown oil. ^1H NMR (400 MHz, CDCl_3): δ 8.95 (s, 1H), 8.28 (dd, $J = 4.7, 1.3$ Hz, 1H), 7.64 (d, $J = 1.5$ Hz, 1H), 7.53 (d, $J = 7.4$ Hz, 1H), 7.07 (dd, $J = 7.4, 4.8$ Hz, 1H), 7.04 (d, $J = 3.4$ Hz, 1H), 6.56 (dd, $J = 3.4, 1.8$ Hz, 1H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 159.1, 152.6, 149.2, 146.1 (overlap), 139.0, 129.0, 121.9, 117.9, 112.3, 17.4.

***N*-(2-Benzofurylidene)-*N*-(3-methylpyridin-2-yl)amine.**

Yellow solid. ^1H NMR (400 MHz, CDCl_3): δ 9.11 (s, 1H), 8.32 (dd, $J = 4.7, 1.3$ Hz, 1H), 7.67 (d, $J = 7.8$ Hz, 1H), 7.63 (d, $J = 8.4$ Hz, 1H), 7.57 (d, $J = 7.4$ Hz, 1H), 7.44-7.40 (m, 1H), 7.36 (s, 1H), 7.30-7.26 (m, 1H), 7.11 (dd, $J = 7.5, 4.8$ Hz, 1H), 2.53 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 158.8, 156.1, 153.6, 150.1, 146.2, 139.2, 129.4, 127.9, 127.2, 123.5, 122.4, 122.3, 114.7, 112.3, 17.5.

***N*-Benzylidene-*N*-(6-methylpyridin-2-yl)amine [83053-89-8].**

Colorless solid. ^1H NMR (400 MHz, CDCl_3): δ 9.06 (s, 1H), 7.98 (dd, $J = 7.2, 1.6$ Hz, 2H), 7.64-7.60 (m, 1H), 7.51-7.39 (m, 3H), 7.09 (d, $J = 7.8$ Hz, 1H), 7.02 (d, $J = 7.5$ Hz, 1H), 2.57 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 162.8, 161.0, 157.9, 138.3, 136.0, 131.8, 129.5, 128.7, 121.3, 115.8, 24.3.

***N*-Benzylidene-*N*-(pyridin-2-yl)-amine [1883-96-1].**

Yellow oil. ^1H NMR (400 MHz, CDCl_3): δ 9.15 (s, 1H), 8.52-8.50 (m, 1H), 8.01-7.98 (m, 2H), 7.78-7.73 (m, 1H), 7.53-7.46 (m, 3H), 7.33 (d, $J = 8.0$ Hz, 1H), 7.20-7.16 (m, 1H).

3.8.3 Procedures and isolation of conjugate addition products

A general procedure. In an argon-filled glove box, CuOAc (6.2 mg, 0.05 mmol) and (*R*_S,*R*,*R*)- SIPHOS-PE (30.3 mg, 0.06 mmol) were added to a 10-mL dry Schlenk tube, followed by addition of KOAc (98 mg, 1.0 mmol, 2.0 equiv), phenylboroxine (108 mg, 0.35 mmol, 0.7 equiv), arylaldehydes (0.5 mmol, 1 equiv) and dry toluene (2.0 mL). The mixture was vigorously stirred in a preheated oil bath at 80 °C for 48 h. The reaction mixture was cooled to room temperature, diluted by EtOAc and passed through a short plug of silica gel with diethyl ether washing. The filtrate was concentrated and purified by flash chromatography. The enantioselectivity (ee) of the purified product was

determined by chiral HPLC analysis using Daicel Chiralcel columns.

(S)-N-(3-Methylpyridin-2-yl)-1-(p-tolyl)benzylamine [1376412-39-7 for racemate].

The reaction was complete in 48 h at 80 °C. The product was isolated by flash chromatography (30:1 hexane/EtOAc) as white solid. Yield: 133.1 mg, 93%.

GC-MS (EI): Calcd for C₂₀H₂₀N₂: 288.2. Found: 288.1.

93% ee. Daicel Chiralcel IC-H, 98:2 *n*-hexane/isopropanol, flow rate: 0.5 mL/min.

¹H NMR (400 MHz, CDCl₃): δ 7.95 (d, *J* = 3.7 Hz, 1H), 7.33-7.25 (m, 4H), 7.21-7.16 (m, 4H), 7.09 (d, *J* = 7.9 Hz, 2H), 6.50-6.47 (m, 2H), 4.62 (d, *J* = 6.8 Hz, 1H), 2.29 (s, 3H), 2.09 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 155.8, 145.8, 143.8, 140.7, 136.9, 136.7, 129.3, 128.5, 127.62, 127.57, 127.0, 116.3, 113.1, 58.3, 21.2, 17.1.

1 PDA Ch1 200nm 4nm			
Peak#	Ret. Time	Area	Area %
1	13.915	770964	50.390
2	14.956	759032	49.610
Total		1529996	100.000

1 PDA Ch1 200nm 4nm			
Peak#	Ret. Time	Area	Area %
1	13.892	243321	3.516
2	14.902	6677013	96.484
Total		6920334	100.000

A gram-scale procedure. In an argon-filled glove box, CuOAc (12.4 mg, 0.10 mmol, 2.5 mol%) and (*R*_S,*R*,*R*)-SIPHOS-PE (60.6 mg, 0.12 mmol) were added to a 25-mL dry Schlenk tube, followed by addition of KOAc (784 mg, 8.0 mmol, 2.0 equiv), phenylboroxine (865 mg, 2.8 mmol, 0.7 equiv), aldimine (4.0 mmol, 1 equiv) and dry toluene (10.0 mL). The mixture was vigorously stirred in a preheated oil bath at 100 °C for 48 h. The reaction mixture was cooled to room temperature, and purified by flash column chromatography to give the white solid. Yield: 1.07 g, 93% yield and 92% ee. The product with 99% ee was obtained after recrystallization from EtOAc/Hexane.

(S)-N-(3-Methylpyridin-2-yl)-1-(*o*-tolyl)benzylamine [1388624-26-7 for racemate].

The reaction was complete in 48 h at 80 °C. The product was isolated by flash chromatography (30:1 hexane/EtOAc) as white solid. Yield: 121.6 mg, 85%.

GC-MS (EI): Calcd for C₂₀H₂₀N₂: 288.2. Found: 288.1.

97% ee. Daicel Chiralcel OJ-H, 98:2 *n*-hexane/isopropanol, flow rate: 0.5 mL/min.

¹H NMR (400 MHz, CDCl₃): δ 7.94 (d, *J* = 3.6 Hz, 1H), 7.30-7.25 (m, 4H), 7.23-7.18 (m, 2H), 7.17-7.12 (m, 4H), 6.71 (d, *J* = 7.2 Hz, 1H), 6.48 (dd, *J* = 7.1, 5.1 Hz, 1H), 4.55 (d, *J* = 7.0 Hz, 1H), 2.35 (s, 3H), 2.10 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 155.7, 145.8, 142.9, 141.6, 136.9, 136.7, 130.7, 128.5, 127.7, 127.11, 127.10, 126.9, 126.0, 116.1, 113.0, 55.4, 19.7, 17.1.

1 PDA Ch1 214nm 4nm

Peak#	Ret. Time	Area	Area %
1	16.412	433459	50.589
2	18.144	423370	49.411
Total		856829	100.000

1 PDA Ch1 214nm 4nm

Peak#	Ret. Time	Area	Area %
1	16.369	23560	1.571
2	18.060	1476112	98.429
Total		1499673	100.000

(S)-N-(3-Methylpyridin-2-yl)-1-(*p*-anisyl)benzylamine [1370412-41-1 for racemate].

The reaction was complete in 48 h at 80 °C. The product was isolated by flash chromatography (20:1 hexane/EtOAc) as white solid. Yield: 143 mg, 94%.

GC-MS (EI): Calcd for C₂₀H₂₀N₂O: 304.2. Found: 304.1.

93% ee. Daicel Chiralcel IC-H, 98:2 *n*-hexane/isopropanol, flow rate: 0.5 mL/min.

¹H NMR (400 MHz, CDCl₃): δ 7.94 (d, *J* = 3.7 Hz, 1H), 7.32-7.25 (m, 4H), 7.22-7.18 (m, 4H), 6.84-6.80 (m, 2H), 6.50-6.46 (m, 2H), 4.62 (d, *J* = 6.9 Hz, 1H), 3.73 (s, 3H), 2.10 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 158.7, 155.8, 145.6, 143.7, 137.0, 135.8, 128.8, 128.5, 127.5, 127.0, 116.4, 114.0, 113.1, 58.0, 55.3, 17.1.

(S)-N-(3-Methylpyridin-2-yl)-1-(o-anisyl)benzylamine.

The reaction was complete in 48 h at 80 °C. The product was isolated by flash chromatography (30:1 hexane/EtOAc) as white solid. Yield: 137 mg, 90%.

GC-MS (EI): Calcd for $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}$: 304.2. Found: 304.1.

59% ee. Daicel Chiralcel OJ-H, 90:10 *n*-hexane/isopropanol, flow rate: 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 7.95 (d, J = 3.6 Hz, 1H), 7.36 (dd, J = 7.5, 1.9 Hz 1H), 7.30-7.28 (m, 2H), 7.24-7.18 (m, 3H), 7.17-7.12 (m, 2H), 6.93-6.89 (m, 1H), 6.84 (d, J = 8.2 Hz, 1H), 6.76 (d, J = 8.3 Hz, 1H), 6.44 (dd, J = 7.1, 5.1 Hz, 1H), 5.40 (d, J = 8.3 Hz, 1H), 3.68 (s, 3H), 2.10 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 157.5, 156.2, 145.7, 143.7, 136.9, 131.3, 129.3, 128.5, 128.1, 127.0, 126.5, 120.9, 116.3, 112.7, 111.6, 55.5, 55.3, 17.0.

(S)-N-(3-Methylpyridin-2-yl)-1-(p-trifluoromethylphenyl)benzylamine [1370412-44-4 for racemate].

The reaction was complete in 48 h at 80 °C. The product was isolated by flash chromatography (30:1 hexane/EtOAc) as colorless oil. Yield: 147 mg, 86%.

GC-MS (EI): Calcd for C₂₀H₁₇F₃N₂: 342.1. Found: 342.1.

[α]_D²² = 69.2 (*c* = 1.62 in CHCl₃).

94% ee. Daicel Chiralcel OJ-H, 98:2 *n*-hexane/isopropanol, flow rate: 0.5 mL/min.

¹H NMR (400 MHz, CDCl₃): δ 7.93 (d, *J* = 4.1 Hz, 1H), 7.53 (d, *J* = 8.2 Hz 2H), 7.44 (d, *J* = 8.2 Hz, 2H), 7.32-7.27 (m, 4H), 7.26-7.16 (m, 2H), 6.55 (d, *J* = 6.5 Hz, 1H), 6.51 (dd, *J* = 7.1, 5.1 Hz, 1H), 4.63 (d, *J* = 6.5 Hz, 1H), 2.10 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 155.5, 147.7, 145.7, 142.9, 137.2, 129.1 (q, *J*_{C-F} = 32.3 Hz), 128.9, 127.9, 127.8, 127.7, 125.4 (q, *J*_{C-F} = 3.7 Hz), 124.4 (q, *J*_{C-F} = 272.0 Hz), 116.6, 113.7, 58.6, 17.0.

¹⁹F NMR (377 MHz, CDCl₃): -62.2.

PDA Ch1 200nm 4nm

Peak#	Ret. Time	Area	Area %
1	14.358	5187838	50.198
2	15.750	5146903	49.802
Total		10334742	100.000

PDA Ch1 200nm 4nm

Peak#	Ret. Time	Area	Area %
1	14.328	9844055	97.203
2	15.725	283298	2.797
Total		10127353	100.000

(S)-N-(3-Methylpyridin-2-yl)-1-(*m,m*-difluorophenyl)benzylamine.

The reaction was complete in 48 h at 90 °C. The product was isolated by flash chromatography (30:1 hexane/EtOAc) as colorless solid. Yield: 133 mg, 86%.

GC-MS (EI): Calcd for C₁₉H₁₆F₂N₂: 310.1. Found: 310.1.

$[\alpha]_D^{22} = 108.3^\circ$ ($c = 1.52$ in CHCl₃).

95% ee. Daicel Chiralcel IC-H, 95:5 *n*-hexane/isopropanol, flow rate: 0.5 mL/min.

¹H NMR (400 MHz, CDCl₃): δ 8.03 (d, $J = 4.1$ Hz, 1H), 7.42-7.35 (m, 5H), 7.32-7.28 (m, 1H), 6.97-6.94 (m, 2H), 6.72 (tt, $J = 8.8, 2.3$ Hz, 1H), 6.62 (dd, $J = 7.2, 5.1$ Hz, 1H), 6.53 (d, $J = 6.4$ Hz, 1H), 4.66 (d, $J = 6.2$ Hz, 1H), 2.19 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 163.1 (dd, $J_{C-F} = 248.2, 12.5$ Hz), 155.3, 148.0 (t, $J_{C-F} = 8.0$ Hz), 145.6, 142.5, 137.2, 129.0, 127.8, 116.6, 113.8, 110.21 (d, $J_{C-F} = 25.4$ Hz), 110.20 (d, $J_{C-F} = 12.0$ Hz), 102.3 (t, $J_{C-F} = 25.5$ Hz), 58.4, 17.0.

¹⁹F NMR (377 MHz, CDCl₃): -109.8.

PDA Ch1 200nm 4nm

Peak#	Ret. Time	Area	Area %
1	8.436	3212945	50.140
2	8.880	3194963	49.860
Total		6407908	100.000

PDA Ch1 200nm 4nm

Peak#	Ret. Time	Area	Area %
1	8.443	567521	2.478
2	8.883	22331639	97.522
Total		22899160	100.000

(S)-N-(3-Methylpyridin-2-yl)-1-(2-thienyl)benzylamine.

The reaction was stopped in 48 h at 80 °C. The product was isolated by flash chromatography (30:1 hexane/EtOAc) as colorless solid. Yield: 113 mg, 81%.

GC-MS (EI): Calcd for C₁₇H₁₆N₂S: 280.1. Found: 280.1.

$[\alpha]_D^{23} = 17.9^\circ$ ($c = 1.60$ in CHCl₃).

90% ee. Daicel Chiralcel OJ-H, 90:10 *n*-hexane/isopropanol, flow rate: 0.5 mL/min.

¹H NMR (400 MHz, CDCl₃): δ 8.07 (d, $J = 4.9$ Hz, 1H), 7.53-7.51 (m, 2H), 7.43-7.39 (m, 2H), 7.36-7.34 (m, 1H), 7.32-7.28 (m, 2H), 7.00-6.98 (m, 1H), 6.91-6.88 (m, 2H), 6.61 (dd, $J = 7.0, 5.1$ Hz, 1H), 4.88 (d, $J = 7.4$ Hz, 1H), 2.20 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 155.4, 148.4, 145.6, 143.1, 137.1, 128.6, 127.5, 127.3, 126.9, 125.4, 124.6, 116.6, 113.6, 54.5, 17.0.

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Area %
1	25.793	708621	50.154
2	33.825	704261	49.846
Total		1412881	100.000

PDA Ch1 200nm 4nm

Peak#	Ret. Time	Area	Area %
1	25.735	144457	5.230
2	33.619	2617447	94.770
Total		2761904	100.000

(S)-N-(3-Methylpyridin-2-yl)-1-(3-thienyl)benzylamine.

The reaction was stopped in 48 h at 80 °C. The product was isolated by flash chromatography (30:1 hexane/EtOAc) as colorless solid. Yield: 120 mg, 86%.

GC-MS (EI): Calcd for C₁₇H₁₆N₂S: 280.1. Found: 280.1.

[α]_D²³ = -0.22° (c = 1.90 in CHCl₃).

94% ee. Daicel Chiralcel AD-H, 99:1 *n*-hexane/isopropanol, flow rate: 0.5 mL/min.

¹H NMR (400 MHz, CDCl₃): δ 7.97 (d, *J* = 4.9 Hz, 1H), 7.37-7.35 (m, 2H), 7.32-7.28 (m, 2H), 7.24-7.19 (m, 3H), 6.99-6.97 (m, 2H), 6.60 (d, *J* = 4.9 Hz, 1H), 6.50 (dd, *J* = 6.8, 5.2 Hz, 1H), 4.67 (d, *J* = 7.4 Hz, 1H), 2.09 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 155.7, 145.7, 145.0, 143.3, 137.0, 128.6, 127.5, 127.4, 127.2, 126.0, 122.1, 116.4, 113.3, 54.7, 17.1.

PDA Ch1 200nm 4nm

Peak#	Ret. Time	Area	Area %
1	17.728	3030271	50.188
2	19.479	3007625	49.812
Total		6037896	100.000

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Area %
1	17.911	2775779	97.038
2	19.631	84722	2.962
Total		2860501	100.000

(S)-N-(3-Methylpyridin-2-yl)-1-(2-furyl)benzylamine.

The reaction was stopped in 48 h at 80 °C. The product was isolated by flash chromatography (20:1 hexane/EtOAc) as colorless solid. Yield: 106 mg, 80%.

GC-MS (EI): Calcd for C₁₇H₁₆N₂O: 264.1. Found: 264.1.

[α]_D²³ = -24.1° (*c* = 1.80 in CHCl₃).

78% ee. Daicel Chiralcel IC-H, 90:10 *n*-hexane/isopropanol, flow rate: 0.5 mL/min.

¹H NMR (400 MHz, CDCl₃): δ 8.07 (d, *J* = 4.5 Hz, 1H), 7.48-7.43 (m, 3H), 7.41-7.38 (m, 2H), 7.34-7.28 (m, 2H), 6.76 (d, *J* = 7.9 Hz, 1H), 6.60 (m, dd, *J* = 7.1, 5.1 Hz, 1H), 6.39-6.37 (m, 1H), 4.90 (d, *J* = 7.8 Hz, 1H), 2.19 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 155.6, 155.5, 145.6, 142.2, 141.4, 137.1, 128.5, 127.4, 127.2, 116.5, 113.5, 110.2, 107.2, 52.6, 17.0.

(S)-N-(3-Methylpyridin-2-yl)-1-(2-naphthyl)benzylamine.

The reaction was stopped in 48 h at 80 °C. The product was isolated by flash chromatography (30:1 hexane/EtOAc) as colorless solid. Yield: 106 mg, 95%.

GC-MS (EI): Calcd for C₂₃H₂₀N₂: 324.2. Found: 324.1.

95% ee. Daicel Chiralcel IC-H, 99:1 *n*-hexane/isopropanol, flow rate: 0.5 mL/min.

¹H NMR (400 MHz, CDCl₃): δ 7.96 (d, *J* = 4.8 Hz, 1H), 7.81-7.75 (m, 4H), 7.45-7.42 (m, 3H), 7.37-7.35 (m, 2H), 7.33-7.29 (m, 2H), 7.27-7.24 (m, 2H), 6.70 (d, *J* = 6.9 Hz, 1H),

6.54-6.51 (m, 1H), 4.73 (d, $J = 6.6$ Hz, 1H), 2.16 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 155.7, 145.7, 143.4, 140.9, 137.0, 133.4, 132.7, 128.6, 128.3, 128.0, 127.8, 127.6, 127.2, 126.13, 126.05, 125.9, 125.7, 116.4, 113.2, 58.6, 17.1.

PDA Ch1 200nm 4nm

Peak#	Ret. Time	Area	Area %
1	21.278	7317600	50.064
2	23.798	7298823	49.936
Total		14616423	100.000

PDA Ch1 200nm 4nm

Peak#	Ret. Time	Area	Area %
1	21.453	160364	2.494
2	23.821	6269447	97.506
Total		6429811	100.000

(S)-N-(3-Methylpyridin-2-yl)-1-(1,3-benzodioxo-5-yl)benzylamine.

The reaction was stopped in 48 h at 80 °C. The product was isolated by flash chromatography (20:1 hexane/EtOAc) as colorless solid. Yield: 148 mg, 93%.

GC-MS (EI): Calcd for $\text{C}_{20}\text{H}_{18}\text{N}_2\text{O}_2$: 318.1. Found: 318.1.

$[\alpha]_D^{23} = -11.4^\circ$ ($c = 2.73$ in CHCl_3).

94% ee. Daicel Chiralcel IC-H, 95:5 *n*-hexane/isopropanol, flow rate: 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 7.94 (d, $J = 4.2$ Hz, 1H), 7.31-7.25 (m, 4H), 7.21-7.17 (m, 2H), 6.79-6.78 (m, 2H), 6.70 (d, $J = 8.0$ Hz, 1H), 6.49-6.46 (m, 1H), 6.43-6.41 (m, 1H), 5.82 (s, 2H), 4.59 (d, $J = 5.3$ Hz, 1H), 2.16 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 155.7, 147.9, 146.6, 145.7, 143.6, 137.7, 137.0, 128.6, 127.5, 127.1, 120.8, 116.5, 113.3, 108.3, 108.2, 101.0, 58.4, 17.1.

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Area %
1	16.323	145886	50.202
2	17.737	144714	49.798
Total		290601	100.000

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Area %
1	16.307	21077	2.847
2	17.704	719223	97.153
Total		740300	100.000

(S)-N-(3-Methylpyridin-2-yl)-1-(p-fluorophenyl)benzylamine [1370412-42-2 for racemate].

The reaction was stopped in 48 h at 80 °C. The product was isolated by flash chromatography (30:1 hexane/EtOAc) as colorless solid. Yield: 128 mg, 88%.

GC-MS (EI): Calcd for C₁₉H₁₇FN₂: 292.1. Found: 292.1.

[α]_D²³ = 21.6° (c = 1.75 in CHCl₃).

95% ee. Daicel Chiralcel OJ-H, 90:10 *n*-hexane/isopropanol, flow rate: 0.5 mL/min.

¹H NMR (400 MHz, CDCl₃): δ 7.94 (d, *J* = 4.8 Hz, 1H), 7.29-7.25 (m, 6H), 7.23-7.18 (m, 2H), 6.97-6.92 (m, 2H), 6.51-6.47 (m, 2H), 4.59 (d, *J* = 6.7 Hz, 1H), 2.08 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 161.9 (d, *J*_{C-F} = 245.1 Hz), 155.7, 145.7, 143.5, 139.4 (d, *J*_{C-F} = 3.1 Hz), 137.1, 129.2 (d, *J*_{C-F} = 3.1 Hz), 128.7, 127.7, 127.3, 116.5, 115.3 (d, *J*_{C-F} = 21.4 Hz), 113.4, 58.0, 17.1.

PDA Ch1 200nm 4nm

Peak#	Ret. Time	Area	Area %
1	14.768	4728811	50.116
2	16.787	4706864	49.884
Total		9435676	100.000

PDA Ch1 200nm 4nm

Peak#	Ret. Time	Area	Area %
1	14.767	6979810	97.585
2	16.805	172730	2.415
Total		7152540	100.000

(S)-N-(3-Methylpyridin-2-yl)-1-(p-chlorophenyl)benzylamine [1370412-43-3 for racemate].

The reaction was stopped in 48 h at 80 °C. The product was isolated by flash chromatography (30:1 hexane/EtOAc) as colorless solid. Yield: 129 mg, 84%.

GC-MS (EI): Calcd for C₁₉H₁₇ClN₂: 308.1. Found: 308.1.

95% ee. Daicel Chiralcel IC-H, 99:1 *n*-hexane/isopropanol, flow rate: 0.5 mL/min.

¹H NMR (400 MHz, CDCl₃): δ 7.94 (d, *J* = 4.8 Hz, 1H), 7.32-7.27 (m, 4H), 7.25-7.21 (m, 6H), 6.53-6.50 (m, 1H), 6.47 (d, *J* = 4.8 Hz, 1H), 4.58 (d, *J* = 6.2 Hz, 1H), 2.11 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 155.6, 145.7, 143.1, 142.1, 137.1, 132.7, 128.9, 128.7, 128.6, 127.7, 127.4, 116.4, 113.4, 58.1, 17.1.

PDA Ch1 200nm 4mm

Peak#	Ret. Time	Area	Area %
1	13.117	2419650	49.806
2	13.927	2438530	50.194
Total		4858179	100.000

PDA Ch1 200nm 4mm

Peak#	Ret. Time	Area	Area %
1	13.141	77380	2.264
2	13.931	3339885	97.736
Total		3417266	100.000

(S)-N-(3-Methylpyridin-2-yl)-1-(2-benzofuryl)benzylamine.

The reaction was stopped in 48 h at 110 °C. The product was isolated by flash chromatography (20:1 hexane/EtOAc) as colorless solid. Yield: 129 mg, 65%.

GC-MS (EI): Calcd for C₂₁H₁₈N₂O: 314.1. Found: 314.1.

[α]_D²³ = -33.2° (*c* = 1.25 in CHCl₃).

74% ee. Daicel Chiralcel IC-H, 90:10 *n*-hexane/isopropanol, flow rate: 0.5 mL/min.

¹H NMR (400 MHz, CDCl₃): δ 7.99 (d, *J* = 4.4 Hz, 1H), 7.49-7.48 (m, 1H), 7.45-7.40 (m, 3H), 7.35-7.31 (m, 2H), 7.29-7.27 (m, 1H), 7.2-7.15 (m, 3H), 6.79 (d, *J* = 7.8 Hz, 1H), 6.59 (s, 1H), 6.54 (dd, *J* = 7.0, 5.2 Hz, 1H), 4.88 (d, *J* = 7.8 Hz, 1H), 2.15 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 158.4, 155.4, 155.1, 145.6, 140.7, 137.2, 128.7, 128.4, 127.7, 127.4, 123.9, 122.7, 120.9, 116.6, 113.7, 111.3, 104.1, 53.0, 17.0.

PDA Ch1 200nm 4nm

Peak#	Ret. Time	Area	Area %
1	9.719	7672257	50.224
2	10.628	7603754	49.776
Total		15276011	100.000

PDA Ch1 200nm 4nm

Peak#	Ret. Time	Area	Area %
1	9.732	632176	12.990
2	10.679	4234294	87.010
Total		4866470	100.000

(S)-N-(3-Methylpyridin-2-yl)-1-(1-naphthyl)benzylamine [1498343-08-0 for racemate].

The reaction was stopped in 48 h at 100 °C. The product was isolated by flash chromatography (30:1 hexane/EtOAc) as colorless solid. Yield: 149 mg, 92%.

GC-MS (EI): Calcd for C₂₃H₂₀N₂: 324.2. Found: 324.1.

$[\alpha]_D^{23} = -15.2^\circ$ ($c = 2.80$ in CHCl₃).

90% ee. Daicel Chiralcel IC-H, 98:2 *n*-hexane/isopropanol, flow rate: 0.5 mL/min.

¹H NMR (400 MHz, CDCl₃): δ 8.14-8.12 (m, 1H), 7.99 (d, $J = 5.0$ Hz, 1H), 7.88-7.85 (m, 1H), 7.78 (d, $J = 8.2$ Hz, 1H), 7.48-7.41 (m, 2H), 7.41-7.36 (m, 3H), 7.33-7.29 (m, 4H), 7.27-7.23 (m, 2H), 6.53 (dd, $J = 7.1, 5.1$ Hz, 1H), 4.71 (d, $J = 7.0$ Hz, 1H), 2.08 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 155.6, 145.9, 143.1, 139.2, 137.0, 134.1, 131.7, 128.7, 128.5, 128.1, 127.8, 127.0, 126.4, 125.7, 125.6, 125.3, 124.3, 116.2, 113.1, 55.2, 17.1.

PDA Ch1 200nm 4nm

Peak#	Ret. Time	Area	Area %
1	14.114	2335358	49.256
2	15.336	2405901	50.744
Total		4741259	100.000

PDA Ch1 200nm 4nm

Peak#	Ret. Time	Area	Area %
1	14.090	8053279	95.227
2	15.352	403635	4.773
Total		8456914	100.000

(S)-N-(3-Methylpyridin-2-yl)-1-(p-bromophenyl)benzylamine.

The reaction was stopped in 48 h at 80 °C. The product was isolated by flash chromatography (30:1 hexane/EtOAc) as colorless solid. Yield: 129 mg, 81%.

GC-MS (EI): Calcd for C₁₉H₁₇BrN₂: 352.1. Found: 352.0.

95% ee. Daicel Chiralcel IC-H, 99:1 *n*-hexane/isopropanol, flow rate: 0.5 mL/min.

The absolute structure of the product was confirmed by X-ray diffraction by vapor diffusion of hexane into a solution in ethyl acetate at room temperature.

¹H NMR (400 MHz, CDCl₃): δ 7.94 (d, *J* = 4.2 Hz, 1H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.31-7.26 (m, 4H), 7.25-7.18 (m, 4H), 6.50 (dd, *J* = 7.1, 5.2 Hz, 1H), 6.46 (d, *J* = 6.7 Hz, 1H), 4.58 (d, *J* = 6.6 Hz, 1H), 2.09 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 155.6, 145.7, 143.1, 142.7, 137.1, 131.6, 129.3, 128.8, 127.8, 127.4, 120.9, 116.5, 113.5, 58.2, 17.1.

(R)-N-(3-Methylpyridin-2-yl)-1-(p-tolyl)benzylamine [1376412-39-7 for racemate].

The reaction was complete in 48 h at 80 °C. The product was isolated by flash chromatography (30:1 hexane/EtOAc) as white solid. Yield: 130 mg, 90%.

GC-MS (EI): Calcd for C₂₀H₂₀N₂: 288.2. Found: 288.1.

$[\alpha]_D^{23} = 33.2^\circ$ ($c = 1.36$ in CHCl_3).

95% ee. Daicel Chiralcel IC-H, 98:2 *n*-hexane/isopropanol, flow rate: 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 7.96 (d, $J = 4.0$ Hz, 1H), 7.33-7.27 (m, 4H), 7.25-7.19 (m, 4H), 7.11 (d, $J = 8.0$ Hz, 2H), 6.52-6.47 (m, 2H), 4.63 (d, $J = 6.8$ Hz, 1H), 2.32 (s, 3H), 2.13 (s, 3H). See above for ^{13}C NMR data of its enantiomer.

PDA Ch1 200nm 4nm

Peak#	Ret. Time	Area	Area %
1	13.915	770964	50.390
2	14.956	759032	49.610
Total		1529996	100.000

PDA Ch1 200nm 4nm

Peak#	Ret. Time	Area	Area %
1	13.929	3255287	97.596
2	14.973	80182	2.404
Total		3335469	100.000

(*R*)-*N*-(3-Methylpyridin-2-yl)-1-(*p*-anisyl)benzylamine [1370412-41-1 for racemate].

The reaction was finished in 48 h at 80 °C. The product was isolated by flash chromatography (20:1 hexane/EtOAc) as white solid. Yield: 138 mg, 91%.

GC-MS (EI): Calcd for $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}$: 304.2. Found: 304.1.

$[\alpha]_D^{23} = 37.4^\circ$ ($c = 1.48$ in CHCl_3).

92% ee. Daicel Chiralcel IC-H, 98:2 *n*-hexane/isopropanol, flow rate: 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 7.95 (d, $J = 5.0$ Hz, 1H), 7.32-7.27 (m, 4H), 7.25-7.21 (m, 4H), 6.86-6.82 (m, 2H), 6.51 (dd, $J = 7.1, 5.1$ Hz, 1H), 6.47 (d, $J = 6.9$ Hz, 1H), 4.61 (d, $J = 6.8$ Hz, 1H), 3.77 (s, 3H), 2.12 (s, 3H). See above for ^{13}C NMR data of its enantiomer.

PDA Ch1 200nm 4nm

Peak#	Ret. Time	Area	Area %
1	21.611	4574492	49.712
2	22.569	4627504	50.288
Total		9201997	100.000

PDA Ch1 200nm 4nm

Peak#	Ret. Time	Area	Area %
1	21.629	8604142	96.059
2	22.660	353010	3.941
Total		8957153	100.000

(R)-N-(3-Methylpyridin-2-yl)-1-(*m,m*-difluorophenyl)benzylamine.

The reaction was finished in 48 h at 80 °C. The product was isolated by flash chromatography (30:1 hexane/EtOAc) as colorless solid. Yield: 133 mg, 86%.

GC-MS (EI): Calcd for C₁₉H₁₆F₂N₂: 310.1. Found: 310.1.

92% ee. Daicel Chiralcel IC-H, 98:2 *n*-hexane/isopropanol, flow rate: 0.5 mL/min.

¹H NMR (400 MHz, CDCl₃): δ 7.96 (d, *J* = 5.0 Hz, 1H), 7.37-7.33 (m, 2H), 7.31-7.26 (m, 4H), 6.88-6.85 (m, 2H), 6.66 (tt, *J* = 8.8, 2.3 Hz, 1H), 6.57 (dd, *J* = 7.2, 5.1 Hz, 1H), 6.43 (d, *J* = 6.4 Hz, 1H), 4.57 (d, *J* = 6.1 Hz, 1H), 2.14 (s, 3H). See above for ¹³C NMR data of its enantiomer.

(R)-N-(3-Methylpyridin-2-yl)-1-[*m,m*-bis(trifluoromethyl)phenyl]benzylamine.

The reaction was finished in 48 h at 80 °C. The product was isolated by flash chromatography (30:1 hexane/EtOAc) as colorless solid. Yield: 174 mg, 85%.

GC-MS (EI): Calcd for C₂₁H₁₆F₆N₂: 410.1. Found: 410.1.

[α]_D²⁴ = -86.8° (*c* = 2.76 in CHCl₃).

93% ee. Daicel Chiralcel OJ-H, 98:2 *n*-hexane/isopropanol, flow rate: 0.5 mL/min.

¹H NMR (400 MHz, CDCl₃): δ 7.93 (d, *J* = 5.0 Hz, 1H), 7.83 (s, 2H), 7.75 (s, 1H),

7.37-7.33 (m, 2H), 7.31-7.27 (m, 3H), 7.26-7.24 (m, 1H), 6.57-6.54 (m, 2H), 4.64 (d, $J = 5.8$ Hz, 1H), 2.13 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3): 155.3, 146.5, 145.6, 142.1, 137.3, 131.6 (q, $J = 33.1$ Hz), 129.2, 128.1, 127.9, 127.6, 127.8 (t, $J_{\text{C-F}} = 124.5$ Hz), 127.55, 127.52, 123.5 (q, $J_{\text{C-F}} = 272.7$ Hz), 121.0 (heptet, $J_{\text{C-F}} = 4.1$ Hz), 116.8, 114.1, 58.6, 16.9.

^{19}F NMR (377 MHz, CDCl_3): -62.7.

Peak#	Ret. Time	Area	Area %
1	9.910	3849379	49.638
2	11.081	3905536	50.362
Total		7754915	100.000

Peak#	Ret. Time	Area	Area %
1	9.902	811173	3.563
2	11.032	21955777	96.437
Total		22766950	100.000

(*R*)-*N*-(3-Methylpyridin-2-yl)-1-(2-naphthyl)benzylamine.

The reaction was finished in 48 h at 80 °C. The product was isolated by flash chromatography (30:1 hexane/EtOAc) as colorless solid. Yield: 141 mg, 87%.

GC-MS (EI): Calcd for $\text{C}_{23}\text{H}_{20}\text{N}_2$: 324.2. Found: 324.1.

$[\alpha]_{\text{D}}^{24} = 22.7^\circ$ ($c = 1.65$ in CHCl_3).

94% ee. Daicel Chiralcel IC-H, 98:2 *n*-hexane/isopropanol, flow rate: 0.5 mL/min.

^1H NMR (400 MHz, CDCl_3): δ 7.96 (d, $J = 4.9$ Hz, 1H), 7.81-7.76 (m, 4H), 7.46-7.43 (m, 3H), 7.38-7.35 (m, 2H), 7.34-7.30 (m, 2H), 7.28-7.26 (m, 2H), 6.69 (d, $J = 7.0$ Hz, 1H), 6.53 (dd, $J = 7.1, 5.1$ Hz, 1H), 4.73 (d, $J = 7.0$ Hz, 1H), 2.16 (s, 3H).

Peak#	Ret. Time	Area	Area %
1	15.680	8589219	49.934
2	17.548	8612061	50.066
Total		17201279	100.000

Peak#	Ret. Time	Area	Area %
1	15.724	7518665	96.964
2	17.501	235426	3.036
Total		7754091	100.000

(R)-N-(3-Methylpyridin-2-yl)-1-(p-fluorophenyl)benzylamine [1370412-42-2 for racemate].

The reaction was finished in 48 h at 80 °C. The product was isolated by flash chromatography (30:1 hexane/EtOAc) as colorless solid. Yield: 133 mg, 91%.

GC-MS (EI): Calcd for C₁₉H₁₇FN₂: 292.1. Found: 292.1.

[α]_D²⁴ = -27.1° (c = 1.43 in CHCl₃).

95% ee. Daicel Chiralcel OJ-H, 90:10 *n*-hexane/isopropanol, flow rate: 0.5 mL/min.

¹H NMR (400 MHz, CDCl₃): δ 7.96 (d, *J* = 5.0 Hz, 1H), 7.32-7.23 (m, 8H), 7.01-6.95 (m, 2H), 6.53 (dd, *J* = 7.1, 5.1 Hz, 1H), 6.49 (d, *J* = 6.8 Hz, 1H), 4.59 (d, *J* = 6.6 Hz, 1H), 2.13 (s, 3H). See above for ¹³C NMR data of its enantiomer.

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Area %
1	14.648	754871	49.934
2	16.633	756874	50.066
Total		1511745	100.000

1 PDA Ch1 200nm 4nm

Peak#	Ret. Time	Area	Area %
1	14.659	115007	3.698
2	16.640	2995323	96.302
Total		3110330	100.000

(R)-N-(3-Methylpyridin-2-yl)-1-(p-chlorophenyl)benzylamine [1370412-43-3 for racemate].

The reaction was stopped in 48 h at 80 °C. The product was isolated by flash chromatography (30:1 hexane/EtOAc) as colorless solid. Yield: 124 mg, 81%.

GC-MS (EI): Calcd for C₁₉H₁₇ClN₂: 308.1. Found: 308.1.

[α]_D²⁴ = -15.3° (c = 1.40 in CHCl₃).

90% ee. Daicel Chiralcel IC-H, 99:1 *n*-hexane/isopropanol, flow rate: 0.5 mL/min.

¹H NMR (400 MHz, CDCl₃): δ 7.92 (d, *J* = 4.9 Hz, 1H), 7.29-7.27 (m, 4H), 7.23-7.18 (m, 6H), 6.51-6.47 (m, 2H), 4.58 (d, *J* = 6.6 Hz, 1H), 2.08 (s, 3H). See above for ¹³C NMR data of its enantiomer.

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Area %
1	13.148	411449	49.967
2	13.964	411992	50.033
Total		823441	100.000

PDA Ch1 200nm 4nm

Peak#	Ret. Time	Area	Area %
1	13.157	5850463	95.091
2	13.991	302008	4.909
Total		6152470	100.000

(*R*)-*N*-(3-Methylpyridin-2-yl)-1-(*p*-bromophenyl)benzylamine.

The reaction was stopped in 48 h at 80 °C. The product was isolated by flash chromatography (30:1 hexane/EtOAc) as colorless solid. Yield: 163 mg, 93%.

GC-MS (EI): Calcd for C₁₉H₁₇BrN₂: 352.1. Found: 352.0.

[α]_D²⁴ = -13.1° (*c* = 1.26 in CHCl₃).

93% ee. Daicel Chiralcel OJ-H, 98:2 *n*-hexane/isopropanol, flow rate: 0.5 mL/min.

¹H NMR (400 MHz, CDCl₃): δ 7.94 (d, *J* = 4.2 Hz, 1H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.31-7.26 (m, 4H), 7.25-7.18 (m, 4H), 6.50 (dd, *J* = 7.1, 5.2 Hz, 1H), 6.46 (d, *J* = 6.7 Hz, 1H), 4.58 (d, *J* = 6.6 Hz, 1H), 2.09 (s, 3H). See above for ¹³C NMR data of its enantiomer.

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Area %
1	24.017	218760	49.047
2	25.586	227265	50.953
Total		446025	100.000

PDA Ch1 200nm 4nm

Peak#	Ret. Time	Area	Area %
1	24.136	273794	3.354
2	25.598	7890147	96.646
Total		8163941	100.000

(R)-N-(3-Methylpyridin-2-yl)-1-(p-trifluoromethylphenyl)benzylamine.

The reaction was complete in 48 h at 80 °C. The product was isolated by flash chromatography (30:1 hexane/EtOAc) as colorless oil. Yield: 149 mg, 87%.

90% ee. Daicel Chiralcel OJ-H, 98:2 *n*-hexane/isopropanol, flow rate: 0.5 mL/min.

¹H NMR (400 MHz, CDCl₃): δ 7.93 (d, *J* = 4.1 Hz, 1H), 7.53 (d, *J* = 8.2 Hz 2H), 7.44 (d, *J* = 8.2 Hz, 2H), 7.32-7.27 (m, 4H), 7.26-7.16 (m, 2H), 6.55 (d, *J* = 6.5 Hz, 1H), 6.51 (dd, *J* = 7.1, 5.1 Hz, 1H), 4.63 (d, *J* = 6.5 Hz, 1H), 2.10 (s, 3H). See above for ¹³C NMR data of its enantiomer.

PDA Ch1 200nm 4mm

Peak#	Ret. Time	Area	Area %
1	14.166	3016728	49.538
2	15.519	3073025	50.462
Total		6089753	100.000

PDA Ch1 200nm 4mm

Peak#	Ret. Time	Area	Area %
1	14.207	415529	4.990
2	15.506	7912010	95.010
Total		8327540	100.000

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