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北海道大学 COLLECTION OF SCHOLARLY AND ACADEMIC PAPERS : HUSCAP
Development of Asymmetric Hydroarylation
of Unsaturated Bond \textit{via} Direct C–H Functionalization
by Cationic Iridium/Bisphosphoramidite Catalyst

A Thesis
Submitted to Graduate School of Chemical Sciences and Engineering,
Hokkaido University for the Degree of Doctor of Engineering

by
Tomohiko Shirai
2016
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Chapter 1 Introduction

Organometallic chemistry has contributed to remarkable industrial development for over sixty years since the discovery of polymerization catalyst by Ziegler.\textsuperscript{1} For example, transition-metal-catalyzed cross-coupling reaction is most important chemical transformation to construct C–C bond in the areas of fine chemicals, liquid materials and polymer materials. Suzuki, Negishi and Heck were given the Novel Prize in 2010 for the great achievement in palladium-catalyzed-cross-coupling reaction. In addition, various efficient catalyst systems for C–C bond formation have been developed to date, and catalytic C–C bond formation plays a key role in modern organic synthesis.

Meanwhile, regioselective cleavage and functionalization of stable and abundant C–H bond were recognized as an intriguing research subject in the field of organometallic chemistry. However, C–H covalent bond shows low reactivity because of the large bond dissociation energy compared with carbon-halogen bond (105 kcal/mol for H–CH\textsubscript{3}, and 110 kcal/mol for H–C\textsubscript{6}H\textsubscript{5}). Murahashi group and Dubek group have been reported cyclometalation reaction of azobenzene with Co\textsubscript{2}(CO)\textsubscript{8} or Cp\textsubscript{2}Ni respectively as the first examples of intramolecular oxidative addition of C(sp\textsuperscript{2})–H bond.\textsuperscript{2} Besides, the first intermolecular oxidative addition of C(sp\textsuperscript{2})–H bond was discovered by Chatt and Davidson with ruthenium complex in 1965.\textsuperscript{3} These discoveries established the foundation of following studies clearly.

In general, transition metal-catalyzed C–H bond cleavage can be classified into four types:\textsuperscript{4} oxidative addition (Scheme 1.1 (1)), concerted metalation/deprotonation process (CMD) (Scheme 1.1 (2)), \(\sigma\)-bond metathesis (Scheme 1.1 (3)), aromatic electrophilic substitution (Friedel-Crafts type reaction) (Scheme 1.1 (4)). In case of (1), the transition-metal hydride intermediates are formed by oxidative addition \textit{via} agostic type transition state. In contrast, M–C bond forms simultaneously
with abstraction of proton by acetate ligand in CMD mechanism. \(\sigma\)-bond metathesis occurs in four-membered ring transition state consisting of metal–X \(\sigma\)-bond and the arene C–H \(\sigma\)-bond. Aromatic electrophilic substitution involves two steps, which are a metalation step and followed deprotonation step by base, thus, forming an M–C bond. However, it should be noticed that generation of M–C bond in (4) occurs without direct involvement of metal complex. In most cases, regioselectivity of cleaved C–H bond can be controlled by a directing group, which has coordinating ability to metal center. A series of carbonyl groups such as ketone, aldehyde, amide, carboxylic acid and so on, are commonly used as directing group in catalytic C–H functionalization. Other nitrogen contained functional groups such as pyridine-2-yl, oxazolin-2-yl and pyrazol-1-yl groups are also effective in directed C–H bond cleavage. In addition, these directing groups are recognized as the important functionalities in organic molecules, and can be converted to other functional groups.

- **oxidative addition**

  \[
  \text{H} \quad \xrightarrow{\text{M}^n} \quad \text{agostic type transition state} \quad \xrightarrow{\text{H}^+} \quad \text{H}^{M^{n+2}}
  \]

- **concerted metalation / deprotonation (CMD)**

  \[
  \text{H} \quad \xrightarrow{\text{M}^n} \quad \xrightarrow{\text{OH}^-} \quad \text{H}^{M^n} \quad \xrightarrow{-\text{HX}} \quad \text{H}^{M^n}
  \]

- **\(\sigma\)-bond metathesis**

  \[
  \text{H} \quad \xrightarrow{\text{M}^n} \quad \text{four-membered transition state} \quad \xrightarrow{\text{base}} \quad \text{H}^{M^n}
  \]

- **aromatic electrophilic substitution (Friedel-Crafts type)**

  \[
  \text{H} \quad \xrightarrow{\text{M}^n} \quad \xrightarrow{\text{base}} \quad \text{H}^{M^n}
  \]

**Scheme 1.1** Mechanisms of C–H bond cleavage
1.1 Transition-metal-catalyzed addition reaction

As described in previous paragraph, transition-metal-catalyzed C–C bond forming reaction, which provides important tools for synthesis of carbon skeleton, is a principal technology in organic synthesis. In particular, the asymmetric hydroarylation of unsaturated double bonds such as C=O,\(^5\) C=N\(^6\) and C=C\(^7\) is most efficient method to prepare chiral alcohols, amines and alkylarenes (Scheme 1.2). A variety of asymmetric catalytic system using organometallic reagents such as organoboron reagent has been developed to date. However, this approach has the disadvantage in terms of step and atom-economy to require the preparation of organometallic reagents.

![Scheme 1.2: Asymmetric hydroarylation of unsaturated compounds](image)

1.1.1 Transition-metal-catalyzed addition of aryl halides to double bond

1.1.1.1 Addition to C–O double bond

The addition of aryl halides to carbonyl groups is an atom-economical synthetic method compared with the transformation employing an organometallic reagent, to give the benzylic alcohol derivatives.\(^8\)

Gao and co-workers achieved the Nickel-catalyzed addition of aryl chlorides to \(\alpha\)-ketoamides 1 through C(sp\(^3\))–Cl bond activation in 2011 as the first report for the addition of organohalides to carbonyl moieties. Using 5 mol\% of Ni(cod)\(_2\) and PCy\(_3\) catalyst, a series of \(\alpha\)-ketoamides 1 was hydroarylated to give oxindole products 2 in high yields (Scheme 1.3).\(^8\) In addition, they also described an asymmetric hydroarylation in the presence of 10 mol\% of Ni(cod)\(_2\) and (\(R,S,S\))-MonoPhos·PE, but product 4 was obtained with only 37% ee.
Scheme 1.3  Nickel-catalyzed addition of aryl halides to α-ketoamides

They have also reported the six-membered ring formation reaction by C–Br bond activation/insertion strategy (Scheme 1.4). As mentioned in this section, there are only limited examples in this research field.

Scheme 1.4  Nickel-catalyzed addition of aryl halides to β-ketoamides

1.1.1.2 Addition to C–C double bond

There are several reports for a palladium-catalyzed Heck-type hydroarylation of alkenes to date and selected examples were shown in this section. In 1991, Brunner and Kramler developed the first asymmetric hydroarylation of norbornadiene 7 in the presence of Pd(II)/norphos catalyst. Although this study is a primary report for the asymmetric Heck-type hydroarylation of olefins, aryl norbornene products 8 were obtained with low enantioselectivities (up to 40.6% ee).
Recently, Zhou and co-workers reported the first Pd-catalyzed highly enantioselective hydroarylation of bicyclic olefins. In this study, enantiomerically enriched exo-products 10 were produced in up to 97% ee with high yields in the presence of 5 mol% of Pd(dba)$_2$ and ($R$)-Xyl-SDP(O) (Scheme 1.6).

1.1.2 Transition-metal-catalyzed direct addition of aryl C(sp$^2$)–H bond to double bond

1.1.2.1 Direct addition to C–O double bond

The catalytic C(sp$^2$)–H bond functionalization is one of the key strategies in the field of transition-metal chemistry. Hydroarylation of carbonyl compounds by C–H bond cleavage offers the highly desirable method to prepare alcohols, which are frequently used in drugs and materials.

In 2002, Murai and co-workers discovered the Ir-catalyzed coupling reactions of imidazoles 11 with aldehydes 12 (Scheme 1.7). In the presence of [Ir$_4$(CO)$_{12}$], DMAD and hydrosilane, various aliphatic or aryl aldehydes underwent a coupling reaction at 110 °C to give 2-alkylimidazoles 13. While this report is the first elegant example of formal direct C–H bond addition to carbonyl compounds, the C–H bond activation step is not involved in the mechanism they proposed. The
possible catalytic cycle including (a) insertion of aldehyde to Ir–Si bond, (b) carboiridation of C–N double bond of the imidazole, (c) β-hydride elimination to give desired product 13, and (d) regeneration of the active specie by hydrosilane was proposed.

Scheme 1.7 Iridium-catalyzed coupling reaction of imidazoles with aldehydes

In 2006, Takai and co-workers reported Rhenium-catalyzed insertion of aldehydes into a C–H bond to synthesize the isobenzofuran derivatives as pioneering system for insertion of C–O double bond to C(sp²)–Metal bond (Scheme 1.8). In the reaction of ketimine 14 with aldehyde 15 in the presence of a rhenium catalyst, [ReBr(CO)₃(thf)]₂, the isobenzofuran derivative 16 was obtained in 93% yield. The proposed catalytic cycle is illustrated in Scheme 1.8. First, aryl hydride rhenium complex 17 is formed by C–H bond activation. Insertion of the carbonyl group into the C–Re bond produced the intermediate 18. Intramolecular nucleophilic attack of the alkoxy–rhenium moiety to the imine occurs, affording the rhenium species 19. Finally, N–H bond formation through reductive elimination and elimination of aniline led to the product 16.
In 2007, Takai and co-workers also reported Manganese-catalyzed insertion of aldehydes into a C–H bond (Scheme 1.9). They found that a mixture of 1-methyl-2-phenyl-1H-imidazole 20, and aryl aldehyde 21 and triethylsilane in the presence of 5.0 mol% of MnBr(CO)₅ in toluene provide the corresponding silyl ether 22 in 87% isolated yield. The proposed mechanism is as follows. In this reaction, C–H bond is first activated by Mn⁺ complex to give the Ar–Mn³⁺–H complex 23. Then, complex 23 undergoes an insertion reaction of aryl aldehyde to form the alkoxo-species 24. Desired product 22 is finally obtained by silyl protection with triethylsilane that is essential to recycle the manganese catalyst. In addition, they have been also examined the asymmetric reaction using chiral imidazoline as auxiliary. The corresponding chiral silyl ethers were obtained with moderate to high diastereomeric excess. Very recently, Wang et al. reported catalytic direct C–H bond addition to various aldehydes by dual activation strategy that includes the C–H activation by manganese catalyst and C–X multiple bond activation by Lewis acidic compounds.\textsuperscript{14}
Scheme 1.9 Manganese-catalyzed insertion of aldehydes into a C–H bond

In addition, Ir-catalyzed direct addition of pyridyl C(sp²)–H bond to aldehydes was reported by Shi and co-workers in 2011 (Scheme 1.10). Using 2 mol% of Ir/phen catalyst, a series of pyridines was alkylated selectively at 3-position. The plausible mechanism including the oxidative addition of pyridyl C–H bond to low valent Ir/phen complex, C=O insertion into the Ir–Si bond, C–C forming reductive elimination to give product 26, and regeneration of active complex with hydrosilane is shown below.
Li and co-workers established similar type of C–H bond addition reaction in mild conditions catalyzed by a cationic cyclopentadienyl rhodium complex (Scheme 1.11). They pointed to cationic catalyst to increase its Lewis acidity because a low Lewis acidic neutral complex displayed no catalytic activity. The screening of counter anion of catalyst revealed that SbF$_6$ is best one while BF$_4$ and PF$_6$ were also effective. In this reaction, Ar–Rh specie was generated by electrophilic aromatic substitution, followed by coordination of aldehyde and insertion sequence. Surprisingly, this transformation was not affected by water and oxygen. Additionally, excellent functional group tolerance including electron deficient functionalities such as CF$_3$, NO$_2$, CO$_2$Me and CHO was observed. These advantages make this methodology more practical and attractive for C–C bond forming reaction. This study first indicated that the cationic Cp*Rh complex work as efficient catalyst in direct hydroarylation of carbonyl compounds.
Since this discovery, similar direct hydroarylation reactions or hydroarylation/cyclization reactions catalyzed by Cp*Rh complex have been developed. Representative examples are shown in Scheme 1.12.\textsuperscript{17}
Yang et al. successfully achieved the development of first Pd$^{II}$-catalyzed C(sp$^2$)–H or C(sp$^3$)–H addition to isatins through direct C–H bond activation for the synthesis of 3-substituted 3-hydroxy-2-oxindoles (Scheme 1.13). They have also clarified that the newly synthesize compound, 3-(5-chlorobenzoxazole) 3-hydroxy-N-benzyl-2-oxindole, has the antitumor potential on the cellular level by the preliminary bioassay. In this transformation, 2,2'-bipyridine ligand plays a key role and strongly promote this reaction. Besides, mechanistic studies indicate that the turnover-limiting step in proposed catalytic cycle includes the C–H bond cleavage.
Very Recently, Ellman and co-workers reported the Rh\textsuperscript{III}-catalyzed indazole synthesis by C–H bond addition/cyclization cascades (Scheme 1.14 (1)).\textsuperscript{17e} In this reaction, various aldehydes \textsuperscript{31} and azobenzenes \textsuperscript{30} were found to be good substrate to give N-aryl-2H-indazoles \textsuperscript{32}. Subsequently, they have successfully extended to the similar strategy with Co\textsuperscript{III} catalyst that is abundant on the earth (Scheme 1.14 (2)).\textsuperscript{19} The B(C\textsubscript{6}F\textsubscript{5})\textsubscript{4} is most effective as counter anion of Co catalyst. A wide range of aryl, heteroaryl, and aliphatic aldehydes can be applicable to this transformation to give convenient access to highly substituted indazoles.
1.1.2.2 Direct addition to C–N double bond

As shown in section 1.1, hydroarylation of carbon–nitrogen double bonds through C–H bond functionalization became a useful transformation to make the beneficial amine derivatives. Rh\textsuperscript{III} complex system is currently the most commonly used as active catalyst.\textsuperscript{20} Some selected examples are given below.

In 2011, Ellman\textsuperscript{20a} and Shi\textsuperscript{20b} and co-workers reported almost simultaneously the first rhodium-catalyzed arylation of N-Boc/sulfonyl aldimine via C–H functionalization (Scheme 1.15). In the presence of a catalytic amount of [Cp*RhCl\textsubscript{2}]\textsubscript{2} and AgSbF\textsubscript{6}, a variety of N-protected aldimines \textsuperscript{33} underwent the hydroarylation at 75–90 °C to provide a branched amine products \textsuperscript{34} in good yields. In addition, same groups also investigated mechanistic studies. Ellman et al. proposed that the C–M specie might generate by concerted metalation deprotonation process. In contrast, Shi et al. speculated that the C–H bond was cleaved by electrophilic substitution to give the C–M specie and clarified the insertion of C=N into the C–Rh bond is responsible for the rate-limiting step. It is noteworthy that the many successful studies for direct C–H bond addition to N-protected aldimine with Rh\textsuperscript{III} catalyst were triggered by Ellman and Shi’s brilliant works.
In 2012, Yoshikai and co-workers investigated the cobalt-catalyzed similar type of reaction via C–H bond functionalization (Scheme 1.16).\textsuperscript{21} They described an effective hydroarylation and self-coupling of N-aryl aldimine 35 catalyzed by 10 mol% of CoBr\textsubscript{2} and IPr·HCl.
Similar works with high-valent cationic Cp*Co complex were demonstrated by Kanai and co-workers in 2013 (Scheme 1.17).\textsuperscript{23} They found that the hydroarylation of aldimine via arene C–H bond cleavage or pyridyl C–H bond cleavage proceeded smoothly when using the [Co(C6H6)(Cp*)(PF6)2] as the catalyst, giving the desired alkylated product in moderate to good yields.

Very recently, it is first demonstrated by Mashima et al. that the rare-earth metal such as Gd, Y, and Nd that has the catalytic activity for pyridyl C(sp\textsuperscript{2})–H bond addition to aldimines (Scheme 1.18).\textsuperscript{23} In this methodology, the catalytic amount of dibenzylamine plays an important role in catalytic cycle to generate the active species.
1.1.2.3 Asymmetric direct addition to C–O double bonds

As mentioned above, there are a number of reports on racemic direct addition to C–O double bonds. In contrast, asymmetric addition reaction by C–H functionalization remains underexplored, and only a very limited example is reported. In 2009, a pioneering work on asymmetric intramolecular direct addition of α-ketoamides was reported by Shibata and co-workers (Scheme 1.19). In this case, C–H bond at most congested position was selectively cleaved by cationic iridium/H8-BINAP complex at 135 °C to generate Aryl–M specie. It should be noted that this is the first example of enantioselective C(sp3)–H addition to carbonyl groups but the 3-hydroxy-2-oxindole product is obtained with only moderate enantioselectivity (72% ee). The proposed mechanism involved (a) C–H bond cleavage or an electrophilic metalation, (b) intramolecular insertion of carbonyl moiety into C–Ir bond to give useful oxindole compounds.

Scheme 1.19  Cationic iridium-catalyzed asymmetric C–H bond addition to carbonyl groups
This asymmetric synthetic methodology has strong impact in the field of synthetic chemistry due to their significance in the construction of chiral alcohols without preparation of highly reactive organometallic reagents and in the view of step and atom economy. Consequently, the development of more highly active catalyst system is greatly desired.

### 1.1.2.4 Asymmetric direct addition to C–N double bonds

There is no reports for enantioselective aryl C(sp^2)–H bond addition to imines by asymmetric catalysis. In 2014, Ellman et al. reported the first diastereoselective intermolecular addition of C(sp^2)–H bonds of benzamides 40 to N-perfluorobutanesulfinyl aldimines 41. Under the optimized conditions described in Scheme 1.20, the branched amines 42 were produced in moderate yields and excellent diastereoselectivities. The chiral sulfonyl group can be removed in good yields by treatment with HCl to give the highly enantiomerically enriched amine hydrochlorides. The diastereoselection model is also depicted in Scheme 1.20. They assumed that the reaction proceeds through 44 to avoid the steric repulsion between C₄F₉ moiety and the reaction center.

![Scheme 1.20](image)

**Scheme 1.20**  \( \text{Cp}^*\text{Rh}^{\text{III}} \)-catalyzed asymmetric direct addition to aldimine

### 1.1.2.5 Direct addition to C–C double bonds

Transition-metal-catalyzed aryl C(sp^2)–H addition to alkenes, also known as hydroarylation,
offers a straightforward route to alkylated arene without pre-activation such as an use of organometallic reagents. There are many examples in this research area compared with the direct addition to C–O and C–N double bonds to date. In this section, pioneering works and selected examples are shown below.

In 1978, Hong et al. reported the rhodium carbonyl cluster-catalyzed addition of arene to diphenylketene (Scheme 1.21). This study showed the first catalytic direct addition reaction to alkenes, and the corresponding ketone compounds were obtained with moderate yields. In the presence of Rh₄(CO)₁₂, the hydroarylation of diphenylketene with benzene proceeds to give α,α-diphenylacetophenone.

![Scheme 1.21 Rhodium cluster-catalyzed C(sp²)–H addition to diphenylketene](image)

In 1993, Murai and co-workers established a novel ruthenium-catalyzed hydroarylation of various C–C double bonds with a linear selectivity, which is a very important study of a highly efficient regioselective C–H bond functionalization (Scheme 1.22). They found that a mixture of olefin, such as vinylsilane or styrene or ethylene derivatives, and aromatic ketone in the presence of 2.0 mol% of RuH₂(CO)(PPh₃)₃ in toluene at 135 °C provides the corresponding alkylated product in high yields. In this report, C–H activation is occurred selectively in ortho position of directing group to form intermediate. Then, product was obtained by insertion of alkene and C–H forming reductive elimination from specie. Since this report, similar type of addition reactions with chelation-assisted methodology has been reported.
In addition, Uchimaru developed the ruthenium-catalyzed first branch-selective hydroarylation of alkene 52 with N-methylaniline 53 in 1999 (Scheme 1.23). Although this is the pioneering work of transition-metal-catalyzed hydroarylation with branch selectivity, the reaction was limited to only one compound. In 2011, Yoshikai and co-worker reported the ligand-controlled hydroarylation of styrenes (Scheme 1.24). Using 10 mol% of CoBr$_2$/PCy$_3$, 80 mol% of Me$_3$SiCH$_2$MgBr in THF, the branch-selective hydroarylation of styrene derivatives proceeded to provide alkylation product with good to high yields. In this paper, they estimated that the branch selectivity is caused by preference of benzylcobalt intermediate that have thermodynamic stability. In the case of CoBr$_2$/IMes catalyst system, the linear-product was mainly produced to avoid steric repulsion at the reaction center. 2-Phenylpyridine is most suitable substrate for the hydroarylation, but pyridine moiety has no synthetic utility because of the difficulty of transformation.

Scheme 1.22  Ruthenium-catalyzed direct hydroarylation of various alkenes

Scheme 1.23  Ruthenium-catalyzed first branch selective hydroarylation of styrene
To resolve this theme, Yoshikai et al. also reported the cobalt-catalyzed aldimine-directed branch selective hydroarylation reaction of styrene derivatives under mild conditions in 2013 (Scheme 1.25). Treatment of imine group in crude product with acid produces the useful formyl functionality.

Recently, Bower and co-workers established the cationic iridium-catalyzed branch selective hydroarylation of alkenes with benzamides (Scheme 1.26). In this case, [Ir(cod)2](BARF4)/d^3ppb is most effective catalyst under the optimized condition, and mono-hydroarylation products were solely produced with high yields and excellent branch selectivities.

18 quant. yield up to >25:1 branch:linear
In addition, transition-metal-catalyzed hydroheteroarylation of olefins is also desired process to construct the functionalized heteroarene skeletons, and various reports have been reported to date. Some selected examples are listed in references.\textsuperscript{26m, 26n} Further development of new hydroarylation and hydroheteroarylation reactions of alkenes is continuing.

1.1.2.6 Direct asymmetric addition to C–C double bonds

Transition-metal-catalyzed asymmetric intramolecular C(sp\textsuperscript{2})–H addition to alkenes has been well studied by Ellman group\textsuperscript{27} and Cramer group.\textsuperscript{28} In contrast, only limited examples have been reported for asymmetric intermolecular addition of C–H bond to alkenes, while such transformations are the efficient method to construct a chiral carbon center.\textsuperscript{29} In 2000, Togni and co-workers developed the first iridium-catalyzed asymmetric intermolecular hydroarylation of 2-norbornene with benzamide (Scheme 1.27).\textsuperscript{29a} In their report, enantiomerically enriched exo-adduct was produced in 94\% ee with only 12\% yield in the presence of CpIr((R)-MeOBIPHEP) complex.

\textbf{Scheme 1.27}  
Iridium-catalyzed asymmetric hydroarylation of 2-norbornene

Very recently, Nishimura and co-worker reported the cationic iridium-catalyzed asymmetric hydroarylation of vinyl ethers (Scheme 1.28).\textsuperscript{29b} Although products were obtained with high yields, enantioselectivities are still low. Despite the some efforts for asymmetric hydroarylation, reports were extremely limited as described in this section.
1.2 Bidentate phosphoramidite ligands (Me*-BIPAM ligands)

1.2.1. Synthesis of Me*-BIPAM ligands

Our research group developed a bidentate phosphoramidite ligands 58 having linked-BINOL unit in 2005 (Scheme 1.29). In general, phosphoramidite ligand has both a $\sigma$-donating ability derived from the inductive effect and $\pi$-accepting ability derived from the back donation which means electron flow from the filled d orbital of transition metal to antibonding orbital of phosphine–heteroatom bond. Additionally, these ligands can be easily synthesized from commercially available 1,1’-bi-2-naphtol.
1.2.2 Asymmetric hydroarylations of various unsaturated bonds with arylboronic acids

1.2.2.1 Asymmetric hydroarylation of electron-deficient olefins

Transition-metal-catalyzed asymmetric hydroarylation of electron-deficient olefins, called as 1,4-addition or conjugate addition, is known as one of the most practical method to form an carbon–carbon bond in the field of synthetic organic chemistry. Our group has already reported the rhodium/Me-BIPAM-catalyzed asymmetric 1,4-addition to various enones 59 with arylboronic acids (Scheme 1.30). This method can be extended to wide range of substrates to provide various β-aryl-carbonyl compounds 60. The mechanism involving (a) transmetalation between Ar–B(OH)_2 and Rh^I to give an aryl–Rh specie 61, (b) insertion of olefin to C–Rh intermediate to form C-enolate 62 or O-enolate 63, and (c) hydrolysis with H_2O to regenerate an active Rh^I complex was proposed.

![Scheme 1.30 Asymmetric hydroarylation of electron-deficient olefin](image)

Then, we also demonstrated that this reaction can be applied to synthesize chiral chromene derivatives as the key step (Scheme 1.31). In the presence of catalytic amount of [Rh(coe)_2Cl]_2 and N-Me-BIPAM, 1 equiv of KHCO_3, 3-nonene-2-one 64 underwent the asymmetric 1,4-addition at 80 °C to provide a mixture of ketone 65 and hemiacetal 66 in 99% yield, which was followed by treatment
with TsOH to give the desired 2-methyl-4-pentyl-4H-chromene 67 with 83%, 93% ee.

Scheme 1.31  Synthetic application of asymmetric 1,4-addition

1.2.2.2 Asymmetric hydroarylation of N-protected aldimines

We also reported the enantioselective synthesis of diarylamine 68\textsuperscript{32a)} and arylglycine 69\textsuperscript{32b)} derivatives by Rh/I\textsubscript{N}-Me\textbullet-BIPAM\textsuperscript{-}catalyzed asymmetric hydroarylation, called as 1,2\textsuperscript{-}addition, with arylboronic reagents (Scheme 1.32). The amine products are produced with moderate to high yields and excellent enantioselectivities.

Scheme 1.32  Asymmetric 1,2-addition to aldimines with arylboronic reagents
1.2.2.3 Asymmetric hydroarylation of carbonyl compounds

The chiral alcohols are known as the attractive compounds, which are important family of biologically active molecules and synthetic materials of medicine. We have found that a ruthenium(II)/Me-BIPAM complex catalyzes effectively the enantioselective arylation of various carbonyl compounds with arylboronic acids (Scheme 1.33). This catalytic system shows wide substrate scope and functional tolerance. In particular, asymmetric arylation of ketones is one of the most important transformations because the tertiary alcohols cannot be produced by general asymmetric hydrogenation reaction of carbonyl compounds. All examples are displayed in Scheme 1.26.

1.2.3 Asymmetric hydrogenation of α-dehydroamino esters, enamides, and dimethyl itaconates

In addition, cationic rhodium/Me-BIPAM catalyst is also effective in asymmetric hydrogenation of α-dehydroamino esters, enamides, and dimethyl itaconates to give β-aryl-α-amino esters up to 99% ee, 1-arylethylamines up to 97% ee, and diester with 97% ee, respectively (Scheme 1.34).
Scheme 1.33  Asymmetric 1,2-addition to carbonyl compounds with arylboronic acids
1.3 Survey of this thesis

As described in previous sections, transition-metal-catalyzed C–H functionalization has emerged in recent years as a powerful tool for the formation of carbon–carbon bonds from simple starting materials. Very recently, it was shown that direct hydroarylation of imines, carbonyls and olefins through catalytic C–H bond activation provides a concise and highly efficient pathway to synthesize various building blocks. By contrast, only a few example of enantioselective direct asymmetric hydroarylation reaction is reported. In this thesis, the author has developed asymmetric hydroarylation reaction of unsaturated compounds by transition-metal-catalyzed C–H functionalization.

In Chapter 2, the first successful asymmetric intramolecular direct hydroarylation of \(\alpha\)-ketoamides is described. This reaction gives various types of chiral 3-substituted 3-hydroxy-2-oxindoles in high yields with complete regioselectivity and high enantioselectivities (70–98% ee) This is realized by the use of the cationic iridium complex \([\text{Ir(cod)}_2](\text{BARF}_4)\) and the chiral O-linked bidentate phosphoramidite \((R,\bar{R})\text{-Me-BIPAM}\) (eq. 1).

\[
\begin{align*}
\begin{array}{c}
\text{Me}_2\text{N} \quad \text{H} \\
\text{R} \\
\text{O} \\
\text{N} \\
\text{O} \\
\text{R}^* \\
\end{array}
\quad \xrightarrow{[\text{Ir(cod)}_2](\text{BARF}_4) \ (5 \text{ mol } \%)} \\
\quad \xrightarrow{(R,\bar{R})\text{-Me-BIPAM} \ (5.5 \text{ mol } \%)}
\begin{array}{c}
\text{Me}_2\text{N} \\
\text{H} \\
\text{R} \\
\text{O} \\
\text{N} \\
\text{O} \\
\text{R}^* \\
\text{R}^* \\
\end{array}
\end{align*}
\]

In Chapter 3, the detailed mechanism for asymmetric intramolecular hydroarylation of \(\alpha\)-ketoamides is discussed. The turnover-limiting step in the catalytic cycle was determined to be the carbonyl insertion step to the aryl-iridium bond by \(^1\text{H}\) NMR experiments, kinetic isotope effect studies, and Hammett studies.
In Chapter 4, the author shows the first highly enantioselective asymmetric intermolecular direct hydroarylation of bicycloalkenes. This transformation was accomplished using a newly synthesized sulfur-linked bis(phosphoramidite) ligand (S-Me-BIPAM). The reaction provides alkylated acetophenone or benzamide derivatives in moderate to excellent yields and good to excellent enantioselectivities. (eq. 2)
1.4 References


7) Recent examples and reviews for asymmetric arylation of olefins with organoboron reagents, see:


Chapter 2

Cationic Ir/Me-BIPAM-Catalyzed Asymmetric Intramolecular Direct Hydroarylation of $\alpha$-Ketoamides

Abstract: Asymmetric intramolecular direct hydroarylation of $\alpha$-ketoamides gives various types of optically active 3-substituted 3-hydroxy-2-oxindoles in high yields with complete regioselectivity and high enantioselectivities (70–98% ee). This is realized by the use of the cationic iridium complex $[\text{Ir(cod)}_2](\text{BArF}_4)$ and the chiral O-linked bidentate phosphoramidite ($R,R\text{-Me-BIPAM}$).

2.1 Introduction

Oxindoles containing a chiral tetrasubstituted carbon at the 3-position are common structural motifs in many biologically active compounds. Among them, 3-substituted 3-hydroxy-2-oxindoles are particularly noteworthy, and various methods for the synthesis of these chiral compounds have been developed in the past decade. Transition-metal-catalyzed asymmetric nucleophilic addition reactions of organoboronic acid derivatives to isatins are powerful and straightforward approaches. In this field, we have already reported that a chiral bidentate phosphoramidite ligand (Me-BIPAM), previously developed for the enantioselective 1,4-addition of arylboronic acid to enones, the arylation of imines and carbonyl compounds, and the hydrogenation of $\alpha$-dehydroaminoesters, was efficient for ruthenium-catalyzed addition reactions of arylboronic acids to isatins. As described in chapter 1, transition-metal-catalyzed C–H functionalization has emerged in recent years as a powerful tool for the formation of C–C bonds from simple starting materials. Very recently, it was shown that direct nucleophilic addition to imines or carbonyls through transition-metal-catalyzed C–H bond activation provides a concise and highly efficient pathway to synthesize amines and alcohols. Intramolecular cyclizations by C–H bond activation have been reported for the synthesis of oxindoles. Iridium complexes have also been shown to be efficient catalysts for C–H bond functionalization. In 2009, Shibata and co-workers reported cationic...
Ir/(S)-H$_8$-BINAP-catalyzed enantioselective synthesis of a chiral 4-acetyl-3-hydroxy-3-methyl-2-oxindole with 72% ee using the method of direct C–H bond functionalization.\textsuperscript{20a)} Although this reaction is the first example of enantioselective direct addition of a C–H bond to ketones, there is still room for improvement in terms of the enantioselectivity. In Chapter 2, the Author describes a direct synthesis of chiral 3-substituted 3-hydroxy-2-oxindoles through a highly enantioselective intramolecular hydroarylation reaction of α-ketoamides by the use of a cationic iridium and chiral O-linked bidentate phosphoramidite ((R,R)-Me-BIPAM).

2.2 Optimization of reaction conditions

We first examined the use of an α-ketoamide (1) for the asymmetric intramolecular direct hydroarylation reaction in the presence of a cationic iridium complex with (R,R)-Me-BIPAM as the catalyst. Our initial screening of counter anions for the cationic iridium complex indicated that the [Ir(cod)$_2$](BAr$_4$)$_4$ (cod = 1,5-cyclooctadiene, BAr$_4$ = tetrakis(3,5-bis(trifluoromethyl)phenyl)borate) complex would be more favorable than other counter anions (BF$_4^-$, SbF$_6^-$, TfO$^-$, ClO$_4^-$, and Cl$^-$), although the yield and enantioselectivity were moderate (62%, 71% ee; entry 1) (Table 2.1). All reactions selectively gave 4-acetyl-3-hydroxy-3-phenyl-2-oxindole (2) with complete regioselectivity by enantioselective direct addition at the C–H bond in the more hindered ortho position to a carbonyl group. Further optimization of reaction conditions was performed using [Ir(cod)$_2$](BAr$_4$)$_4$. As a result of screening several solvents, the highest efficiency with regard to the reaction was observed in 1,2-dimethoxyethane (DME) at 135 °C (90%, 88% ee; entry 6) (Table 2.2). When the reaction carried out at 150 °C in diglyme, the corresponding 3-hydroxy-3-phenyl-2-oxindole 2 and 3 were obtained as a mixture of two regioisomers (entry 10).
Table 2.1  Screening of counter anions\[a]\n
<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (mol%)</th>
<th>Yield of 2/3 [%]</th>
<th>ee of 2/3 [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><a href="BAF$_2$">Ir(cod)$_2$</a> (5)</td>
<td>62 / trace</td>
<td>71 / --</td>
</tr>
<tr>
<td>2</td>
<td><a href="BF$_4$">Ir(cod)$_2$</a> (5)</td>
<td>37 / trace</td>
<td>53 / --</td>
</tr>
<tr>
<td>3</td>
<td><a href="SbF$_5$">Ir(cod)$_2$</a> (5)</td>
<td>12 / trace</td>
<td>38 / --</td>
</tr>
<tr>
<td>4</td>
<td><a href="OTf">Ir(cod)$_2$</a> (5)</td>
<td>15 / trace</td>
<td>29 / --</td>
</tr>
<tr>
<td>5</td>
<td><a href="ClO$_4$">Ir(cod)$_2$</a> (5)</td>
<td>3 / trace</td>
<td>29 / --</td>
</tr>
<tr>
<td>6</td>
<td>[Ir(cod)$_2$]Cl (5)</td>
<td>n.r.</td>
<td>n.r.</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: α-ketoamide (0.25 mmol), iridium catalyst (5 mol%), and (R,R)-Me-BIPAM (1.1 equiv to Ir) in solvent (1 mL), stirred for 24 h at 135 °C

Table 2.2  Screening of solvents and temperatures\[a]\n
<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Yield of 2/3 [%]</th>
<th>ee of 2/3 [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhCl</td>
<td>62 / trace</td>
<td>71 / --</td>
</tr>
<tr>
<td>2</td>
<td>DMF</td>
<td>n.r.</td>
<td>--</td>
</tr>
<tr>
<td>3</td>
<td>DMSO</td>
<td>n.r.</td>
<td>--</td>
</tr>
<tr>
<td>4</td>
<td>DMA</td>
<td>n.r.</td>
<td>--</td>
</tr>
<tr>
<td>5</td>
<td>THF</td>
<td>94 / trace</td>
<td>66 / --</td>
</tr>
<tr>
<td>6</td>
<td>DME</td>
<td>90 / trace</td>
<td>88 / --</td>
</tr>
<tr>
<td>7</td>
<td>DCEE</td>
<td>33 / trace</td>
<td>86 / --</td>
</tr>
<tr>
<td>8</td>
<td>Dioxane</td>
<td>28 / trace</td>
<td>77 / --</td>
</tr>
<tr>
<td>9</td>
<td>Diglyme</td>
<td>19 / trace</td>
<td>58 / --</td>
</tr>
<tr>
<td>10$^{[b]}$</td>
<td>Diglyme</td>
<td>21 / 27</td>
<td>57 / 20</td>
</tr>
<tr>
<td>11</td>
<td>toluene</td>
<td>51 / trace</td>
<td>75 / --</td>
</tr>
<tr>
<td>12</td>
<td>mesitylene</td>
<td>25 / trace</td>
<td>68 / --</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: α-ketoamide (0.25 mmol), iridium catalyst (5 mol%), and (R,R)-Me-BIPAM (1.1 equiv to Ir) in solvent (1 mL), stirred for 24 h at 135 °C [b] Run at 150 °C.
We next examined the directing group attached to the aromatic ring of the aniline side (Table 2.3). The dimethyl amino carbonyl group was most effective and the enantioselectivity additionally improved to 98% ee (entry 4). The reaction with substrate 8 gave no desired product, suggesting that a directing group is indispensable in this reaction. When the reaction time was 16 h, there was no change in yield and selectivity (entry 5). Moreover, it is notable that catalyst loading can be reduced to 3 mol% without loss of enantioselectivity (entry 6). Among the chiral ligands screened, the use of analogous C2-symmetric (R)-BINAP (entry 9) and monodentate phosphoramidite, (R)-MONOPHOS resulted in lower selectivities, 49% ee and 45% ee, respectively.

Table 2.3  Optimization of directing groups[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>DG</th>
<th>Ir precatalyst (mol%)</th>
<th>Ligand</th>
<th>Yield [%]</th>
<th>ee[β] [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ac</td>
<td><a href="BARF$_2%5E4$">Ir(cod)2</a> (5)</td>
<td>(R,R)-Me-BIPAM</td>
<td>90</td>
<td>88</td>
</tr>
<tr>
<td>2</td>
<td>Bz</td>
<td><a href="BARF$_2%5E4$">Ir(cod)2</a> (5)</td>
<td>(R,R)-Me-BIPAM</td>
<td>90</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>CO$_2$Me</td>
<td><a href="BARF$_2%5E4$">Ir(cod)2</a> (5)</td>
<td>(R,R)-Me-BIPAM</td>
<td>37</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>CONMe$_2$</td>
<td><a href="BARF$_2%5E4$">Ir(cod)2</a> (5)</td>
<td>(R,R)-Me-BIPAM</td>
<td>&gt;99</td>
<td>98 (S)</td>
</tr>
<tr>
<td>5[a]</td>
<td>CONMe$_2$</td>
<td><a href="BARF$_2%5E4$">Ir(cod)2</a> (5)</td>
<td>(R,R)-Me-BIPAM</td>
<td>&gt;99</td>
<td>98 (S)</td>
</tr>
<tr>
<td>6</td>
<td>CONMe$_2$</td>
<td><a href="BARF$_2%5E4$">Ir(cod)2</a> (3)</td>
<td>(R,R)-Me-BIPAM</td>
<td>96</td>
<td>97 (S)</td>
</tr>
<tr>
<td>7</td>
<td>NHAc</td>
<td><a href="BARF$_2%5E4$">Ir(cod)2</a> (5)</td>
<td>(R,R)-Me-BIPAM</td>
<td>63</td>
<td>82</td>
</tr>
<tr>
<td>8</td>
<td>H</td>
<td><a href="BARF$_2%5E4$">Ir(cod)2</a> (5)</td>
<td>(R,R)-Me-BIPAM</td>
<td>n.r.</td>
<td>–</td>
</tr>
<tr>
<td>9</td>
<td>CONMe$_2$</td>
<td><a href="BARF$_2%5E4$">Ir(cod)2</a> (5)</td>
<td>(R)-BINAP</td>
<td>91</td>
<td>49</td>
</tr>
<tr>
<td>10</td>
<td>CONMe$_2$</td>
<td><a href="BARF$_2%5E4$">Ir(cod)2</a> (5)</td>
<td>(R)-MONOPHOS</td>
<td>32</td>
<td>45</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: α-ketoamide (0.25 mmol), iridium catalyst (5 mol%), and (R,R)-Me-BIPAM (1.1 equiv to Ir) in solvent (1 mL), stirred for 24 h at 135 °C.
[b] The absolute configuration of the chiral center within the product is given in parentheses.
[c] Reaction mixture was stirred at 135 °C, 16 h

The absolute configuration of the product was assigned as the $S$ enantiomer based on X-ray crystallographic analysis of the compound of 11a (Figure 2.1).
2.3 Substrate scope

With these optimized conditions established, we next investigated the substrate scope of this reaction using 5 mol% of catalyst. As shown in Table 2.4, the reactions are applicable to a variety of \(\alpha\)-ketoamides. In most cases, complete regioselectivity, high yield, and excellent ee value were obtained. Both electron-donating and electron-withdrawing substituents on the aromatic ring at the ketone side of the substrates were tolerated. In some cases (entries 9 and 12), the enantioselectivity decreased slightly. However, the enantioselectivity was improved by using preformed [Ir(cod)((\(R,R\)-Me-bipam))(BARF)\(_4\)]. These phenomena indicated that the cationic iridium catalyst precursor, [Ir(cod)]\(_2\)(BARF)\(_4\), sometimes slightly catalyzed this chemical transformation under our standard conditions.

Furthermore, in the reaction of \(\alpha\)-ketoamides having a disubstituted aromatic ring at the ketone side, the corresponding 3-aryl-3-hydroxy-2-oxindoles were also obtained with high enantioselectivities (entries 13–17). High enantioselectivity was maintained even when the aromatic ring of the aniline side has a substituent, such as a CH\(_3\), Cl or CF\(_3\) group (entries 18–20). The method was easily extended to a variety of aliphatic \(\alpha\)-ketoamides and afforded the corresponding 3-alkyl-3-hydroxy-2-oxindoles in high enantioselectivities (90–94% ee; entries 21–23). In addition, the reaction of \(\alpha\)-ketoamides bearing a methyl group on the nitrogen atom was also attempted. In most cases, desired products were obtained with good yields and enantioselectivities (entries 24–27), but a moderate result was observed only in the case of electron-donating methoxy-bearing substrate (entry 28).
Although we have also investigated for 6-membered ring formation, no reaction occurred under optimized conditions (Scheme 2.1).
Scheme 2.1  Asymmetric direct hydroarylation of β-ketoamide

Finally, a plausible catalytic cycle and enantioselection mechanisms are proposed in Figure 2.2 and 2.3, based on the X-ray structure of 11a (Figure 2.1) and previous reports.\textsuperscript{3c, 20a} First, [Ir((R,R)-Me·bipam)(BAR\(_4\)) ([Ir], 14) is formed by an iridium catalyst precursor, [Ir(cod)\(_2\)](BAR\(_4\)), and (R,R)-Me·BIPAM in situ. Subsequently, 14 reacts with substrate 6 to afford aryl iridium complex 15, which is coordinated with the two carbonyl groups of the amide. Asymmetric hydroarylation of the ketone carbonyl group would proceed from 16, thus producing enantiomerically enriched iridium alkoxide species 17. Finally, reductive elimination to product 11 from 17 occurs and regenerates the active iridium catalyst 14.

Figure 2.2  Proposed catalytic cycle
On the basis of a previous report,\textsuperscript{9} the enantioselective insertion can be rationalized by intermediate 16-favored, which exhibits less steric congestion (Figure 2.3), and thus explains why the carbonyl group is attacked preferentially on its $si$ face to produce the ($S$)-enantiomer.

![Figure 2.3 Plausible models for enantioselection](image)

### 2.4 Conclusion

In conclusion, we have developed a cationic iridium/(R,R)-Me-BIPAM-catalyzed highly enantioselective intramolecular direct hydroarylation of $\alpha$-ketoamides through C–H functionalization. (R,R)-Me-BIPAM gave various types of optically active 3-substituted 3-hydroxy-2-oxindoles in high yields with complete regioselectivity and excellent enantioselectivities by enantioselective direct addition at the C–H bond in the more hindered $ortho$ position to a carbonyl group. Further studies of this method toward expansion of the substrate scope are in progress.
2.5 Experimental section

Synthesis of substrates

Magnesium (11.0 mmol) was heated at reduced pressure for 10 min in a three neck round flask with condenser and dropping funnel. THF (20 mL) was added after cooling to room temperature and aryl bromide (10 mmol) in THF (10 mL) was dropwised and stirred for 1 h. Grignard reagent was added over 1 h to a solution of diethyl oxalate (10.0 mmol) in THF (10 mL) at $-78^\circ$C. After 1 h at $-78^\circ$C, the mixture was warmed to $-10^\circ$C. The mixture was quenched with aqueous saturated NH$_4$Cl, extracted with Et$_2$O, washed with brine, dried over MgSO$_4$, filtered off, and the solvents were evaporated. The crude product was purified by flash column chromatography (Hexane/AcOEt = 20/1 to 10/1) to afford pure $\alpha$-ketoesters.

Synthesis of $\alpha$-ketoesters

The $\alpha$-ketoester was hydrolyzed upon being stirred with 3N NaOH (50 mL) in THF (50 mL) at reflux temperature for 6 h. Then, THF was evaporated, and the aqueous residue was cooled to 0 °C and acidified with 6N HCl. The mixture was extracted with AcOEt. The combined extracts were washed with brine and dried over MgSO$_4$, filtered off, and the solvent was removed in vacuo to afford glyoxylic acid as a brown solid.

Synthesis of glyoxylic acids

The $\alpha$-ketoester was hydrolyzed upon being stirred with 3N NaOH (50 mL) in THF (50 mL) at reflux temperature for 6 h. Then, THF was evaporated, and the aqueous residue was cooled to 0 °C and acidified with 6N HCl. The mixture was extracted with AcOEt. The combined extracts were washed with brine and dried over MgSO$_4$. The solvent was removed in vacuo to afford glyoxylic acid as a brown solid.

Synthesis of $\alpha$-ketoamides

To a CH$_2$Cl$_2$ solution (20 mL) of glyoxylic acid (6.0 mmol) were added catalytic amount of DMF (5
drops) and oxalyl chloride (6.6 mmol). The reaction mixture was stirred at room temperature until generation of gasses was stopped (commonly for 3 h). Then, reaction flask was cooled to 0 °C. A solution of aniline (6.0 mmol) and pyridine (15.0 mmol) were added and stirred at room temperature for 12 h. Next, the reaction was quenched by adding water and organic phase were extracted with AcOEt. The combined extracts were washed with brine and dried over MgSO₄. The solvent was removed in vacuo, and the resulting crude material was subjected to flash column chromatography (Hexane/AcOEt = 3/2 to 2/3) to afford desired α-ketoamides.
General procedure and NMR spectra of products

To a flame-dried flask, [Ir(cod)](BArF$_4$) (0.0125 mmol, 5 mol%) and (R,R)-Me-BIPAM (0.0138 mmol, 5.5 mol%) and dry 1,2-dimethoxyethane (1.0 mL) were added under an N$_2$ atmosphere. The solution was stirred at room temperature for 30 min, followed by the addition of α-ketoamide (0.25 mmol). The reaction mixture was then heated at 135 °C. After being stirred for 16 h, the mixture was purified with silica gel column chromatography (eluent: n-hexane/ethyl acetate) to afford pure 3-substituted 3-hydroxy-2-oxindole.

4-Acetyl-3-hydroxy-3-phenyl-indolin-2-one (2)

88% ee [HPLC condition: Chiralcel OD-H column, hexane/2-propanol = 9/1, flow = 1.0 mL/min, wavelength = 230 nm, t$_R$ = 29.3 min (minor) and 40.8 min (major); [α]$_D^{21}$ = +105.3 (c 0.35, DMSO); $^1$H NMR (400 MHz, [D$_6$]DMSO): δ = 7.50–7.47 (m, 2H), 7.29–7.20 (m, 6H), 6.30 (s, 1H), 2.33 (s, 3H); $^{13}$C NMR (100 MHz, [D$_6$]DMSO): δ = 201.2, 176.7, 143.2, 140.4, 135.6, 131.4, 130.2, 128.1, 127.5, 124.9, 123.4, 114.1, 77.8, 29.1 HRMS (ESI) m/z calc for C$_{16}$H$_{13}$O$_3$Na (M+Na)$^+$: 290.07876, found: 290.07866.

4-Benzoyl-3-hydroxy-3-phenyl-indolin-2-one (9)

88% ee [HPLC condition: Chiralcel OD-H column, hexane/2-propanol = 9/1, flow = 1.0 mL/min, wavelength = 230 nm, t$_R$ = 25.0 min (minor) and 36.5 min (major); [α]$_D^{21}$ = +94.0 (c 0.34, DMSO); $^1$H NMR (400 MHz, [D$_6$]DMSO): δ = 10.66 (br s, NH), 7.55 (t, J = 7.7 Hz, 1H), 7.48-7.35 (m, 5H), 7.16-7.07 (m, 6H), 6.93 (d, J = 7.7 Hz, 1H), 6.26 (s, 1H); $^{13}$C NMR (100 MHz, [D$_6$]DMSO): δ = 196.1, 177.7, 143.0, 140.0, 136.5, 136.0, 133.2, 131.8, 129.6, 129.4, 128.3, 127.8, 127.2, 124.9, 122.4, 112.3, 77.6; HRMS (ESI) m/z calc for C$_{21}$H$_{15}$O$_3$Na (M+Na)$^+$: 352.09441, found: 352.09419.
3-Hydroxy-4-(methoxycarbonyl)-3-phenyl-indolin-2-one (10)

95% ee [HPLC condition: Chiralcel AD-H column, hexane/2-propanol = 9/1, flow = 1.0 mL/min, wavelength = 230 nm, $t_R = 19.7$ min (minor) and 34.3 min (major)]; $[\alpha]D^{20} = +75.0$ (c 0.14, DMSO); $^1$H NMR (400 MHz, [D$_6$]DMSO): $\delta = 10.62$ (s, NH), 7.48–7.43 (m, 2H), 7.28–7.14 (m, 6H), 6.17 (s, 1H), 3.46 (s, 3H); $^{13}$C NMR (100 MHz, [D$_6$]DMSO): $\delta = 177.3, 166.0, 143.6, 141.0, 133.2, 130.0, 127.8, 127.5, 127.0, 124.6, 123.3, 114.2, 78.1, 51.7$; HRMS (ESI) $m/z$ calc for C$_{16}$H$_{13}$O$_4$NNa (M+Na)$^+$: 306.07368, found: 306.07308.

(S)-3-Hydroxy-4-(N,N-dimethylaminocarbonyl)-3-phenyl-indolin-2-one (11a)

98% ee [HPLC condition: Chiralcel OD-H column, hexane/2-propanol = 6/1, flow = 1.0 mL/min, wavelength = 230 nm, $t_R = 26.6$ min (major) and 37.8 min (minor)]; $[\alpha]D^{20} = +72.1$ (c 0.30, DMSO); $^1$H NMR (400 MHz, [D$_6$]DMSO): $\delta = 10.63$ (br s, NH), 7.32–7.18 (m, 6H), 6.97 (dd, $J = 0.7, 7.9$ Hz, 1H), 6.82 (dd, $J = 0.7, 7.9$ Hz, 1H), 6.30 (s, 1H), 2.64 (s, 3H), 2.22 (s, 3H); $^{13}$C NMR (100 MHz, [D$_6$]DMSO): $\delta = 177.5, 168.2, 142.5, 140.0, 133.9, 130.2, 129.5, 127.8, 127.4, 125.1, 119.8, 110.6, 77.2, 37.8, 33.8$; HRMS (ESI) $m/z$ calc for C$_{17}$H$_{16}$O$_3$N$_2$Na (M+Na)$^+$: 319.10531, found: 319.10512.

3-(4-Trifluoromethylphenyl)-3-hydroxy-4-(N,N-dimethylaminocarbonyl)-indolin-2-one (11b)

98% ee [HPLC condition: Chiralcel AD-H column, hexane/2-propanol = 9/1, flow = 1.0 mL/min, wavelength = 230 nm, $t_R = 21.9$ min (major) and 25.2 min (minor)]; $[\alpha]D^{23} = +194.3$ (c 0.30, CHCl$_3$); $^1$H NMR (400 MHz, CD$_2$Cl$_2$): $\delta = 9.13$ (br s, NH), 7.58 (d, $J = 8.3$ Hz, 2H), 7.32 (t, $J = 7.9$ Hz, 1H), 7.06 (d, $J = 7.9$ Hz, 1H), 6.97 (d, $J = 7.9$ Hz, 1H), 6.32 (s, 1H), 2.72 (s, 3H), 2.62 (s, 3H); $^{13}$C NMR (100 MHz, CD$_2$Cl$_2$): $\delta = 177.3, 168.2, 142.5, 140.0, 133.9, 130.2, 129.5, 127.8, 127.4, 125.1, 119.8, 110.6, 77.2, 37.8, 33.8$; HRMS (ESI) $m/z$ calc for C$_{18}$H$_{15}$O$_3$F$_3$Na (M+Na)$^+$: 387.09270, found: 387.09225.

3-(4-Fluorophenyl)-3-hydroxy-4-(N,N-dimethylaminocarbonyl)-indolin-2-one (11c)

90% ee [HPLC condition: Chiralcel AD-H column, hexane/2-propanol = 9/1, flow = 1.0 mL/min, wavelength = 230 nm, $t_R = 33.4$ min (minor) and 44.2 min (major)]; $[\alpha]D^{22} = +204.8$ (c 0.34, CHCl$_3$); $^1$H NMR (400 MHz, CD$_2$Cl$_2$): $\delta = 8.29$ (br s, NH), 7.36–7.29 (m, 3H), 7.06–6.97 (m, 4H), 6.15 (s, 1H), 2.74 (s, 3H); $^{13}$C NMR (100 MHz, CD$_2$Cl$_2$): $\delta = 177.3, 170.1, 144.3, 142.5, 133.1, 132.1, 130.3$ (q, $J = 32.0$ Hz), 130.1, 126.4, 125.4, 124.4 (q, $J = 271.5$ Hz), 121.5, 112.6, 77.8, 39.2, 35.0; HRMS (ESI) $m/z$ calc for C$_{16}$H$_{15}$O$_3$F$_3$Na (M+Na)$^+$: 387.09270, found: 387.09225.
77.1, 39.0, 34.8; HRMS (ESI) m/z calc for C_{17}H_{15}O_{3}N_{2}FNa (M+Na)^+ : 337.09589, found: 337.09543.

3-(4-Bromophenyl)-3-hydroxy-4-(N,N-dimethylaminocarbonyl)-indolin-2-one (11d)

98% ee [HPLC condition: Chiralcel AD-H column, hexane/2-propanol = 9/1, flow = 1.0 mL/min, wavelength = 230 nm, t_R = 41.2 min (major) and 46.0 min (minor)]; [a]_D^{23} = +197.6 (c 0.32, CHCl_3); ^1H NMR (400 MHz, CD_2Cl_2): δ = 9.04 (br s, NH), 7.43 (d, J = 8.6 Hz, 2H), 7.30 (t, J = 7.9 Hz, 1H), 7.20 (d, J = 8.6 Hz, 2H), 7.02 (d, J = 7.9 Hz, 1H), 6.95 (d, J = 7.9 Hz, 1H), 6.21 (s, 1H), 2.74 (s, 3H), 2.66 (s, 3H); ^13C NMR (100 MHz, CD_2Cl_2): δ = 177.4, 170.2, 142.5, 139.3, 133.1, 132.2, 131.5, 129.9, 127.7, 122.4, 121.5, 112.5, 77.6, 39.3, 35.1; HRMS (ESI) m/z calc for C_{17}H_{15}O_{3}N_{2}FNa (M+Na)^+ : 397.01583, found: 397.01537.

3-Hydroxy-4-(N,N-dimethylaminocarbonyl)-3-(4-phenylphenyl)-indolin-2-one (11e)

91% ee [HPLC condition: Chiralcel AD-H column, hexane/2-propanol = 4/1, flow = 1.0 mL/min, wavelength = 230 nm, t_R = 17.3 min (major) and 25.6 min (minor)]; [a]_D^{22} = +195.5 (c 0.24, CHCl_3); ^1H NMR (400 MHz, CD_2Cl_2): δ = 9.37 (br s, NH), 7.59–7.54 (m, 4H), 7.45–7.29 (m, 6H), 7.08 (d, J = 7.5 Hz, 1H), 6.95 (d, J = 7.5 Hz, 1H), 6.15 (s, 1H), 2.73 (s, 3H), 2.60 (s, 3H); ^13C NMR (100 MHz, CD_2Cl_2): δ = 178.0, 170.4, 142.5, 141.1, 140.8, 139.1, 133.3, 132.7, 129.7, 129.1, 127.8, 127.3, 127.0, 126.2, 121.2, 112.4, 77.8, 39.3, 35.0; HRMS (ESI) m/z calc for C_{23}H_{20}O_{3}N_{2}Na (M+Na)^+ : 395.13661, found: 395.13610.

3-Hydroxy-4-(N,N-dimethylaminocarbonyl)-3-(4-methylphenyl)-indolin-2-one (11f)

91% ee [HPLC condition: Chiralcel OD-H column, hexane/2-propanol = 9/1, flow = 1.0 mL/min, wavelength = 230 nm, t_R= 44.7 min (major) and 62.9 min (minor)]; [a]_D^{21} = +197.3 (c 2.6, CHCl_3); ^1H NMR (400 MHz, [D_6]DMSO): δ = 10.56 (br s, NH), 7.29 (t, J = 7.6 Hz, 1H), 7.09 (d, J = 8.5 Hz, 2H), 7.05 (d, J = 8.5 Hz, 2H), 6.95 (d, J = 7.6 Hz, 1H), 6.82 (d, J = 7.6 Hz, 1H), 6.23 (s, 1H), 2.66 (s, 3H), 2.28 (s, 3H), 2.25 (s, 3H); ^13C NMR (100 MHz, CD_2Cl_2): δ = 178.3, 170.4, 142.5, 138.2, 136.9, 133.2, 132.7, 129.5, 129.0, 125.5, 121.1, 112.3, 77.8, 39.2, 34.9, 21.1; HRMS (ESI) m/z calc for C_{18}H_{15}O_{3}N_{2}Na (M+Na)^+ : 333.12096, found: 333.12115.
3-Hydroxy-4-(N,N-dimethylaminocarbonyl)-3-(4-phenoxyphenyl)-indolin-2-one (11g)

84% ee [HPLC condition: Chiralcel AD-H column, hexane/2-propanol = 9/1, flow = 2.0 mL/min, wavelength = 230 nm, t_R = 29.4 min (minor) and 57.3 min (major)]; [α]_D^22 = +169.2 (c 0.30, CHCl_3); ^1H NMR (400 MHz, CD_2Cl_2): δ = 9.07 (br s, NH), 7.36–7.28 (m, 5H), 7.11 (t, J = 7.7 Hz, 1H), 7.06 (d, J = 7.7 Hz, 1H), 6.99–6.92 (m, 5H), 6.12 (s, 1H), 2.79 (s, 3H), 2.70 (s, 3H); ^13C NMR (100 MHz, CD_2Cl_2): δ = 178.0, 170.4, 157.5, 157.3, 142.4, 134.8, 133.2, 132.7, 130.1, 129.7, 127.4, 123.7, 121.3, 119.1, 118.7, 112.4, 77.6, 39.4, 35.1; HRMS (ESI) m/z calc for C_{23}H_{20}O_4N_2Na (M+Na)^+: 411.13153, found: 411.13088.

3-(3-Trifluoromethylphenyl)-3-hydroxy-4-(N,N-dimethylaminocarbonyl)-indolin-2-one (11h)

97% ee [HPLC condition: Chiralcel AD-H column, hexane/2-propanol = 9/1, flow = 1.0 mL/min, wavelength = 230 nm, t_R = 25.6 min (minor) and 31.5 min (major)]; [α]_D^23 = +197.4 (c 0.30, CHCl_3); ^1H NMR (400 MHz, CD_2Cl_2): δ = 8.97 (br s, NH), 7.62 (d, J = 7.7 Hz, 1H), 7.57 (d, J = 7.7 Hz, 1H), 7.54 (s, 1H), 7.48 (t, J = 7.7 Hz, 1H), 7.34 (t, J = 7.7 Hz, 1H), 7.07 (dd, J = 0.9, 7.7 Hz, 1H), 6.98 (dd, J = 0.9, 7.7 Hz, 1H), 6.33 (s, 1H), 2.71 (s, 3H), 2.65 (s, 3H); ^13C NMR (100 MHz, CD_2Cl_2): δ = 178.1, 170.1, 142.5, 141.4, 132.2, 132.0, 130.5 (q, J = 32.4 Hz), 130.1, 129.9, 129.2, 125.2, 124.5 (q, J = 272.8 Hz), 122.4, 121.6, 112.6, 77.5, 39.2, 35.0; HRMS (ESI) m/z calc for C_{18}H_{15}O_3F_3Na (M+Na)^+: 387.09270, found: 387.09256.

3-Hydroxy-4-(N,N-dimethylaminocarbonyl)-3-(3-methylphenyl)-indolin-2-one (11i)

92% ee [HPLC condition: Chiralcel AD-H column, hexane/2-propanol = 9/1, flow = 1.0 mL/min, wavelength = 230 nm, t_R = 34.7 min (minor) and 52.7 min (major)]; [α]_D^22 = +201.4 (c 0.33, CHCl_3); ^1H NMR (400 MHz, CD_2Cl_2): δ = 9.23 (br s, NH), 7.29 (t, J = 7.7 Hz, 1H), 7.18 (t, J = 7.7 Hz, 1H), 7.15 (s, 1H), 7.10–7.03 (m, 3H), 6.92 (d, J = 7.7 Hz, 1H), 5.96 (s, 1H), 2.71 (s, 1H), 2.56 (s, 3H), 2.29 (s, 3H); ^13C NMR (100 MHz, CD_2Cl_2): δ = 178.1, 170.4, 142.4, 139.8, 138.3, 133.3, 132.9, 129.6, 129.1, 128.3, 126.2, 122.8, 121.1, 112.2, 77.8, 39.1, 34.9, 21.5; HRMS (ESI) m/z calc for C_{18}H_{15}O_3Na (M+Na)^+: 333.12096, found: 333.12048.
3-(2-Fluorophenyl)-3-hydroxy-4-(N,N-dimethylaminocarbonyl)-indolin-2-one (11j)

\[
\begin{align*}
\text{Me}_2N-OH & \quad \text{F} \\
\text{H} & \quad \text{N}
\end{align*}
\]

97% ee [HPLC condition: Chiralcel AD-H column, hexane/2-propanol = 9/1, flow = 1.0 mL/min, wavelength = 230 nm, \(t_R = 36.0\) min (minor) and 70.4 min (major)]; \([\alpha]_D^{21} = -8.0\) (c 0.32, DMSO); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 9.64\) (br s, NH), 7.99 (ddd, \(J = 1.8, 7.5, 7.6\) Hz, 1H), 7.31–7.22 (m, 3H), 7.00 (d, \(J = 7.2\) Hz, 1H), 6.91–6.86 (m, 1H), 6.82 (d, \(J = 7.5\) Hz, 1H), 5.79 (s, 1H), 2.70 (s, 3H), 2.47 (s, 3H); \(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 177.1, 169.9, 158.8\) (d, \(J = 247.1\) Hz), 142.1, 132.4, 130.7, 129.8, 129.4, 129.0, 126.4, 123.7 (d, \(J = 2.8\) Hz), 119.9, 114.8 (d, \(J = 20.7\) Hz), 111.7, 74.7, 38.7, 34.6; HRMS (ESI) \(m/z\) calc for C\(_{17}\)H\(_{15}\)O\(_3\)N\(_2\)FNa (M+Na): 337.09589, found: 337.09555.

3-Hydroxy-4-(N,N-dimethylaminocarbonyl)-3-(2-naphthyl)-indolin-2-one (11k)

\[
\begin{align*}
\text{Me}_2N-OH & \quad \text{O} \\
\text{H} & \quad \text{N}
\end{align*}
\]

94% ee [HPLC condition: Chiralcel AD-H column, hexane/2-propanol = 9/1, flow = 2.0 mL/min, wavelength = 230 nm, \(t_R = 36.1\) min (major) and 47.7 min (minor)]; \([\alpha]_D^{23} = +190.0\) (c 0.31, CHCl\(_3\)); \(^1\)H NMR (400 MHz, CD\(_2\)Cl\(_2\)): \(\delta = 8.76\) (br s, NH), 7.93 (s, 1H), 7.82 (m, 2H), 7.75 (d, \(J = 8.6\) Hz, 1H), 7.48 (d, \(J = 6.5\) Hz, 1H), 7.47 (d, \(J = 6.5\) Hz, 1H), 7.32 (t, \(J = 7.9\) Hz, 1H), 7.28 (dd, \(J = 1.8, 8.6\) Hz, 1H), 7.07 (d, \(J = 7.9\) Hz, 1H), 6.95 (d, \(J = 7.9\) Hz, 1H), 6.21 (s, 1H), 2.56 (s, 3H), 2.50 (s, 3H); \(^13\)C NMR (100 MHz, CD\(_2\)Cl\(_2\)): \(\delta = 177.4, 170.3, 142.3, 137.3, 133.5, 133.4, 133.3, 132.6, 129.7, 128.4, 128.3, 127.9, 126.7, 126.5, 124.8, 123.5, 121.3, 112.2, 77.9, 39.2, 34.9; HRMS (ESI) \(m/z\) calc for C\(_{21}\)H\(_{18}\)O\(_3\)N\(_2\)Na (M+Na): 369.12096, found: 369.12029.

3-(3,5-Bis(trifluoromethyl)phenyl)-3-hydroxy-4-(N,N-dimethylaminocarbonyl)-indolin-2-one (11l)

\[
\begin{align*}
\text{Me}_2N-OH & \quad \text{CF}_3 \\
\text{H} & \quad \text{N}
\end{align*}
\]

98% ee [HPLC condition: Chiralcel AD-H column, hexane/2-propanol = 9/1, flow = 1.0 mL/min, wavelength = 230 nm, \(t_R = 8.8\) min (minor) and 12.5 min (major)]; \([\alpha]_D^{23} = +71.3\) (c 0.34, DMSO); \(^1\)H NMR (400 MHz, [D\(_6\)]DMSO): \(\delta = 10.83\) (br s, NH), 8.06 (s, 1H), 7.75 (s, 2H), 7.38 (t, \(J = 7.7\) Hz, 1H), 7.03 (s, 1H), 7.02 (d, \(J = 7.7\) Hz, 1H), 6.89 (d, \(J = 7.7\) Hz, 1H), 2.67 (s, 3H), 2.47 (s, 3H); \(^13\)C NMR (100 MHz, [D\(_6\)]DMSO): \(\delta = 176.8, 167.4, 143.6, 142.7, 134.3, 130.5, 130.0\) (q, \(J = 32.4\) Hz), 127.7, 126.0, 123.2 (q, \(J = 272.8\) Hz), 121.7, 120.1, 111.0, 76.7, 38.1, 33.6; HRMS (ESI) \(m/z\) calc for C\(_{19}\)H\(_{14}\)O\(_3\)F\(_6\)Na (M+Na): 455.08008, found: 455.07974.
3-Hydroxy-4-(N,N-dimethylaminocarbonyl)-3-(3,4-methylenedioxyphenyl)-indolin-2-one (11m)

84% ee [HPLC condition: Chiralcel AD-H column, hexane/2-propanol = 9/1, flow = 2.0 mL/min, wavelength = 230 nm, t_R = 45.8 min (minor) and 77.7 min (major)]; [α]_D^{23} = +186.7 (c 0.19, CHCl₃); ^1H NMR (400 MHz, CDCl₃): δ = 9.81 (br s, NH), 7.29–7.25 (m, 1H), 7.04 (d, J = 7.9 Hz, 1H), 6.97 (d, J = 1.4 Hz, 1H), 6.93 (d, J = 7.9 Hz, 1H), 6.74–6.69 (m, 2H), 6.12 (s, 1H), 5.92–5.91 (m, 2H), 2.82 (s, 3H), 2.75 (s, 3H); ^13C NMR (100 MHz, CDCl₃): δ = 178.3, 170.2, 147.7, 142.1, 133.3, 132.7, 132.5, 132.3, 129.3, 120.9, 118.6, 112.3, 107.7, 106.4, 101.0, 77.4, 39.2, 35.0; HRMS (ESI) m/z calc for C_{18}H_{16}O_{3}N_{2}Na (M+Na)^+: 363.09514, found: 363.09467.

3-Hydroxy-6-methyl-4-(N,N-dimethylaminocarbonyl)-3-phenyl-indolin-2-one (11n)

93% ee [HPLC condition: Chiralpak AD-H column, hexane/2-propanol = 9/1, flow = 1.0 mL/min, wavelength = 254 nm, t_R = 45.8 min (minor) and 77.7 min (major)]; [α]_D^{22} = +187.6 (c 3.3, CHCl₃); ^1H NMR (400 MHz, [D₆]DMSO): δ = 10.56 (br s, NH), 7.29–7.17 (m, 5H), 6.78 (s, 1H), 6.63 (s, 1H), 6.21 (s, 1H), 2.64 (s, 3H), 2.30 (s, 3H), 2.25 (s, 3H); ^13C NMR (100 MHz, [D₆]DMSO): δ = 177.8, 168.3, 142.5, 140.3, 139.4, 133.7, 127.8, 127.5, 127.3, 125.1, 120.1, 111.2, 77.1, 37.9, 33.8, 21.2; HRMS (ESI) m/z calc for C_{18}H_{18}O_{3}N_{2}Na (M+Na)^+: 333.12096, found: 333.12133.

6-Trifluoromethyl-3-hydroxy-4-(N,N-dimethylaminocarbonyl)-3-phenyl-indolin-2-one (11o)

91% ee [HPLC condition: Chiralcel AD-H column, hexane/2-propanol = 9/1, flow = 1.0 mL/min, wavelength = 230 nm, t_R = 19.4 min (minor) and 30.6 min (major)]; [α]_D^{21} = +153.8 (c 0.32, CHCl₃); ^1H NMR (400 MHz, CD₂Cl₂): δ = 9.64 (br s, NH), 7.31 (s, 5H), 7.28 (s, 1H), 7.16 (s, 1H), 6.02 (s, 1H), 2.74 (s, 3H), 2.46 (s, 3H); ^13C NMR (100 MHz, CD₂Cl₂): δ = 178.0, 168.9, 143.3, 138.7, 136.1, 133.9, 131.8 (q, J = 33.4 Hz), 128.7, 128.6, 125.5, 123.7 (q, J = 272.8 Hz), 117.9, 109.2, 77.7, 38.9, 34.9; HRMS (ESI) m/z calc for C_{18}H_{15}O_{3}N_{2}F_{3}Na (M+Na)^+: 387.09272, found: 387.09222.

6-Chloro-3-hydroxy-4-(N,N-dimethylaminocarbonyl)-3-phenyl-indolin-2-one (11p)

95% ee [HPLC condition: Chiralpak AD-H column, hexane/2-propanol = 4/1, flow = 1.0 mL/min, wavelength = 230 nm, t_R = 12.6 min (minor) and 18.2 min (major)]; [α]_D^{23} = +13.1 (c 1.8, DMSO); ^1H NMR (400 MHz, [D₆]DMSO): δ = 10.77 (br s, NH), 7.31–7.18 (m, 5H), 6.97 (d, J = 1.8 Hz, 1H), 6.88 (d, J = 1.8 Hz, 1H), 6.40 (s, 1H), 2.64 (s, 3H), 2.15 (s, 3H); ^13C NMR (100 MHz, [D₆]DMSO): δ = 177.9, 166.2, 144.1, 139.5, 135.6, 133.7, 128.6, 127.9, 127.6, 125.0, 119.2, 110.4, 76.9, 37.6,
3-Hydroxy-3-methyl-4-(N,N-dimethylaminocarbonyl)-indolin-2-one (11q)

94% ee [HPLC condition: Chiralcel AD-H column, hexane/2-propanol = 9/1, flow = 1.0 mL/min, wavelength = 230 nm, tR = 24.5 min (minor) and 31.9 min (major)]; [α]D^21 = -39.8° (c 0.31, DMSO); ^1H NMR (400 MHz, CDCl3): δ = 9.78 (br s, NH), 7.22 (t, J = 7.9 Hz, 1H), 7.00 (d, J = 7.9 Hz, 1H), 6.92 (d, J = 7.9 Hz, 1H), 5.54 (s, 1H), 3.16 (s, 3H), 3.06 (s, 3H), 1.56 (s, 3H); ^13C NMR (100 MHz, CDCl3): δ = 179.8, 170.4, 141.3, 131.8, 130.9, 128.9, 120.8, 112.1, 73.7, 39.7, 35.4, 23.3; HRMS (ESI) m/z calc for C_{17}H_{15}O_{3}N_{2}Na (M+Na)^+: 353.06634, found: 353.06696.

3-Ethyl-3-hydroxy-4-(N,N-dimethylaminocarbonyl)-indolin-2-one (11r)

92% ee [HPLC condition: Chiralcel AD-H column, hexane/2-propanol = 9/1, flow = 1.0 mL/min, wavelength = 230 nm, tR = 26.2 min (minor) and 35.0 min (major)]; [α]D^22 = +114.3° (c 0.30, CHCl3); ^1H NMR (400 MHz, CDCl3): δ = 9.71 (br s, NH), 7.24 (t, J = 6.8 Hz, 1H), 7.02 (d, J = 6.8 Hz, 1H), 6.94 (d, J = 6.8 Hz, 1H), 5.54 (s, 1H), 3.15 (s, 3H), 3.09 (s, 3H), 2.19-2.05 (m, 1H), 1.98-1.85 (m, 1H), 0.67 (t, J = 6.8 Hz, 3H); ^13C NMR (100 MHz, CDCl3): δ = 179.2, 170.5, 142.2, 132.0, 129.5, 128.9, 120.9, 112.0, 77.7, 39.7, 35.4, 30.4, 8.0; HRMS (ESI) m/z calc for C_{13}H_{16}O_{3}N_{2}Na (M+Na)^+: 271.10531, found: 271.10506.

3-Hydroxy-3-isopropyl-4-(N,N-dimethylaminocarbonyl)-indolin-2-one (11s)

90% ee [HPLC condition: Chiralcel AD-H column, hexane/2-propanol = 9/1, flow = 1.0 mL/min, wavelength = 230 nm, tR = 31.9 min (minor) and 59.2 min (major)]; [α]D^23 = +87.1° (c 0.32, CHCl3); ^1H NMR (400 MHz, CDCl3): δ = 9.70 (br s, NH), 7.23 (t, J = 7.9 Hz, 1H), 7.01 (d, J = 7.9 Hz, 1H), 6.93 (d, J = 7.9 Hz, 1H), 5.78 (s, 1H), 3.13 (s, 6H), 2.20 (sep, J = 6.8 Hz, 1H), 1.10 (d, J = 6.8 Hz, 3H), 0.81 (d, J = 6.8 Hz, 3H); ^13C NMR (100 MHz, CDCl3): δ = 179.0, 171.2, 142.5, 131.9, 130.1, 128.7, 121.0, 112.0, 79.7, 39.9, 36.3, 35.5, 16.7, 15.6; HRMS (ESI) m/z calc for C_{14}H_{18}O_{3}N_{2}Na (M+Na)^+: 285.12096, found: 285.12081.
3-Hydroxy-1-methyl-4-(N,N-dimethylaminocarbonyl)-3-phenylindolin-2-one (2t)

92% ee [HPLC condition: Chiralpak AD-H column, hexane/2-propanol = 4/1, flow = 1.0 mL/min, wavelength = 230 nm, t_r = 18.0 min (minor) and 22.0 min (major)]; [α]_D^{20} = +234.3 (c 3.6, CHCl_3); ¹H NMR (400 MHz, CDCl_3): δ = 7.37 (t, J = 8.1 Hz, 1H), 7.32–7.21 (m, 5H), 6.98 (d, J = 8.1 Hz, 1H), 6.94 (d, J = 8.1 Hz, 1H), 5.94 (s, 1H), 3.25 (s, 3H), 2.71 (s, 3H), 2.60 (s, 3H); ¹³C NMR (100 MHz, CDCl_3): δ = 175.9, 168.0, 143.9, 139.8, 133.5, 129.6, 129.4, 127.8, 127.5, 125.1, 120.4, 109.6, 77.0, 37.7, 33.8, 26.3; HRMS (ESI) m/z calc for C_{18}H_{18}O_3N_2Na (M+Na)^+: 333.12096, found: 333.12135.

3-(4-Trifluorophenyl)-3-hydroxy-1-methyl-4-(N,N-dimethylaminocarbonyl)indolin-2-one (2u)

87% ee [HPLC condition: Chiralpak AD-H column, hexane/2-propanol = 4/1, flow = 1.0 mL/min, wavelength = 230 nm, t_r = 11.8 min (major) and 13.9 min (minor)]; [α]_D^{22} = +240.8 (c 2.3, CHCl_3); ¹H NMR (400 MHz, CDCl_3): δ = 7.55 (d, J = 8.2 Hz, 2H), 7.47 (d, J = 8.2 Hz, 2H), 7.42 (dd, J = 7.7, 8.2 Hz, 1H), 7.02 (d, J = 7.7 Hz, 1H), 7.00 (d, J = 8.2 Hz, 1H), 6.21 (s, 3H), 2.73 (s, 3H), 2.69 (s, 3H); ¹³C NMR (100 MHz, CDCl_3): δ = 174.4, 169.8, 144.8, 143.7, 132.4, 131.6, 130.1 (q, J = 32 Hz), 129.6, 126.0, 124.9, 123.9 (q, J = 272 Hz), 121.1, 110.0, 76.9, 39.0, 34.9, 26.6; HRMS (ESI) m/z calc for C_{19}H_{17}O_3F_3Na (M+Na)^+: 401.10835, found: 401.10849.

3-(4-Fluorophenyl)-3-hydroxy-1-methyl-4-(N,N-dimethylaminocarbonyl)indolin-2-one (2v)

86% ee [HPLC condition: Chiralpak AD-H column, hexane/2-propanol = 4/1, flow = 1.0 mL/min, wavelength = 230 nm, t_r = 16.0 min (minor) and 18.9 min (major)]; [α]_D^{22} = +264.6 (c 2.1, CHCl_3); ¹H NMR (400 MHz, CDCl_3): δ = 7.39 (t, J = 8.1 Hz, 1H), 7.33–7.29 (m, 2H), 7.00-6.96 (m, 4H), 6.06 (s, 1H), 3.26 (s, 1H), 2.77 (s, 3H), 2.72 (s, 3H); ¹³C NMR (100 MHz, CDCl_3): δ = 174.8, 169.9, 162.4 (d, J = 246 Hz), 144.6, 135.3, 132.4, 131.8, 129.4, 127.3, 121.0, 114.8 (d, J = 22 Hz), 109.8, 76.6, 39.0, 34.9, 26.4; HRMS (ESI) m/z calc for C_{18}H_{17}O_3F_3Na (M+Na)^+: 351.11154, found: 351.11173.
3-Hydroxy-1-methyl-3-(4-methylphenyl)-4-(N,N-dimethylaminocarbonyl)-indolin-2-one (2w)

90% ee [HPLC condition: Chiralpak AD-H column, hexane/2-propanol = 4/1, flow = 1.0 mL/min, wavelength = 230 nm, $t_R$ = 35.2 min (minor) and 36.7 min (major)]; $[\alpha]_D^{23} = +269.3$ ($c$ 2.3, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 7.36 (t, $J$ = 8.1 Hz, 1H), 7.19 (d, $J$ = 8.1 Hz, 1H), 7.08 (d, $J$ = 8.1 Hz, 1H), 6.96 (d, $J$ = 8.1 Hz, 1H), 6.95 (d, $J$ = 8.1 Hz, 1H), 5.92 (s, 1H), 3.24 (s, 3H), 2.74 (s, 3H), 2.65 (s, 3H), 2.29 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 175.2, 170.1, 144.7, 137.6, 136.4, 132.6, 132.2, 129.1, 128.6, 125.2, 120.7, 109.5, 76.9, 39.0, 34.8, 26.4, 21.0; HRMS (ESI) $m/z$ calc for C$_{19}$H$_{20}$O$_3$Na (M+Na)$^+$: 347.13661, found: 347.13667.

3-Hydroxy-3-(4-methoxyphenyl)-1-methyl-4-(N,N-dimethylaminocarbonyl)-indolin-2-one (2x)

70% ee [HPLC condition: Chiralcel OD-H column, hexane/2-propanol = 4/1, flow = 1.0 mL/min, wavelength = 230 nm, $t_R$ = 55.5 min (minor) and 62.2 min (major)]; $[\alpha]_D^{23} = +178.0$ ($c$ 2.5, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 7.37 (t, $J$ = 7.7 Hz, 1H), 7.24 (d, $J$ = 8.8 Hz, 2H), 6.96 (d, $J$ = 7.7 Hz, 2H), 6.81 (d, $J$ = 8.8 Hz, 2H), 5.96 (s, 1H), 3.77 (s, 3H), 3.23 (s, 3H), 2.76 (s, 3H), 2.70 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 175.2, 170.1, 159.3, 144.7, 132.5, 132.1, 131.5, 129.1, 126.7, 120.8, 113.4, 109.6, 76.7, 55.2, 39.1, 34.9, 26.4; HRMS (ESI) $m/z$ calc for C$_{19}$H$_{20}$O$_3$Na (M+Na)$^+$: 363.13153, found: 363.13158.

4-(Acetamino)-3-hydroxy-3-phenyl-indolin-2-one (12)

82% ee [HPLC condition: Chiralcel OD-H column, hexane/2-propanol = 9/1, flow = 1.0 mL/min, wavelength = 230 nm, $t_R$ = 26.5 min (minor) and 33.5 min (major)]; $[\alpha]_D^{21} = +43.6$ ($c$ 0.30, DMSO); $^1$H NMR (400 MHz, [D$_6$]DMSO): $\delta$ = 10.50 (s, NH), 8.30 (s, 1H), 7.37–7.22 (m, 7H), 7.12 (s, 1H), 6.70 (d, $J$ = 7.5 Hz, 1H), 1.78 (s, 3H); $^{13}$C NMR (100 MHz, [D$_6$]DMSO): $\delta$ = 177.4, 168.4, 142.4, 139.2, 134.8, 130.1, 128.3, 127.8, 125.1, 122.2, 115.8, 106.3, 77.1, 23.6; HRMS (ESI) $m/z$ calc for C$_{16}$H$_{14}$O$_3$Na (M+Na)$^+$: 305.08966, found: 305.08899.
X-ray Crystal Structure of Compound 11a

Data Collection

A colorless block crystal of C\textsubscript{17}H\textsubscript{16}N\textsubscript{2}O\textsubscript{3} having approximate dimensions of 0.553 x 0.372 x 0.242 mm was mounted on a glass fiber. All measurements were made on a Rigaku R-AXIS RAPID diffractometer using graphite monochromator Cu-Kα radiation.

The crystal-to-detector distance was 127.40 mm.

Cell constants and an orientation matrix for data collection corresponded to a primitive tetragonal cell (Laue class: 4/m) with dimensions:

\[
\begin{align*}
\text{a} &= 10.8424(3) \text{ Å} \\
\text{c} &= 12.2648(5) \text{ Å} \\
\text{V} &= 1441.81(8) \text{ Å}^3
\end{align*}
\]

For Z = 4 and F.W. = 296.32, the calculated density is 1.365 g/cm\textsuperscript{3}. Based on the reflection conditions of:

\[00l: \ l = 4n\]

and the successful solution and refinement of the structure, the space group was determined to be:

P41 (#76)

The data were collected at a temperature of -150 + 1°C to a maximum 2θ value of 136.4°. A total of 30 oscillation images were collected. A sweep of data was done using ω scans from 80.0 to 260.0° in 30.0° step, at χ = 54.0° and ϕ = 0.0°. The exposure rate was 50.0 [sec./°]. A second sweep was performed using ω scans from 80.0 to 260.0° in 30.0° step, at χ = 54.0° and ϕ = 90.0°. The exposure rate was 50.0 [sec./°]. Another sweep was performed using ω scans from 80.0 to 260.0° in 30.0° step, at χ = 54.0° and ϕ = 180.0°. The exposure rate was 50.0 [sec./°]. Another sweep was performed using ω scans from 80.0 to 260.0° in 30.0° step, at χ = 54.0° and ϕ = 270.0°. The exposure rate was 50.0 [sec./°].
Another sweep was performed using \( \omega \) scans from 80.0 to 260.0\(^\circ\) in 30.0\(^\circ\) step, at \( \chi = 0.0^\circ \) and \( \phi = 0.0^\circ \). The exposure rate was 50.0 [sec./\( \theta \)]. The crystal-to-detector distance was 127.40 mm. Readout was performed in the 0.100 mm pixel mode.

Data Reduction

Of the 14905 reflections that were collected, 2623 were unique (\( R_{\text{int}} = 0.0345 \)).

The linear absorption coefficient, \( \mu \), for Cu-K\( \alpha \) radiation is 7.774 cm\(^{-1}\). An empirical absorption correction was applied which resulted in transmission factors ranging from 0.684 to 0.829. The data were corrected for Lorentz and polarization effects. A correction for secondary extinction was applied (coefficient = 0.002550).

Structure Solution and Refinement

The structure was solved by direct methods and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. Some hydrogen atoms were refined isotropically and the rest were refined using the riding model. The final cycle of full-matrix least-squares refinement on \( F^2 \) was based on 2623 observed reflections and 228 variable parameters and converged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors of:

\[
R1 = \Sigma |{Fo} - |Fc|/\Sigma |Fo| = 0.0291
\]

\[
wR2 = [\Sigma (w(Fo^2 - Fc^2)^2)/\Sigma w(Fo^2)]^{1/2} = 0.0756
\]

The standard deviation of an observation of unit weight was 1.06. Unit weights were used. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.13 and -0.15 e/\( \AA^3 \), respectively. The absolute structure was deduced based on Flack parameter, 0.00(19), using 1237 Friedel pairs.
Neutral atom scattering factors were taken from Cromer and Waber. Anomalous dispersion effects were included in $F_{\text{calc}}$; the values for $\Delta f'$ and $\Delta f''$ were those of Creagh and McAuley. The values for the mass attenuation coefficients are those of Creagh and Hubbell. All calculations were performed using the CrystalStructure crystallographic software package except for refinement, which was performed using SHELXL-97.
**EXPERIMENTAL DETAILS**

A. Crystal Data

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<td>c = 12.2648(5) Å</td>
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C. Structure Solution and Refinement

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<tr>
<td></td>
<td>where P = (Max(Fo^2,0) + 2Fc^2)/3</td>
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2.6 References


21) Crystallographic data of 11a can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. (CCDC 980114)
Chapter 3

Mechanistic Studies of the Cationic Ir/Me-BIPAM-Catalyzed Asymmetric Intramolecular Direct Hydroarylation Reaction

Abstract: Results of mechanistic studies on asymmetric hydroarylation of α-ketoamides via direct C–H bond addition to a carbonyl group catalyzed by a cationic Ir/Me-BIPAM complex are presented in this chapter. A catalytic cycle involving C–H bond cleavage to give an Ar–[Ir]+ intermediate, insertion of a carbonyl group into the aryl-iridium bond, giving iridium alkoxide, and finally reductive elimination to reproduce active [Ir]+ species is proposed. The mechanistic insight for the iridium hydride species indicated that the C–H bond cleavage is caused in a reversible manner. Furthermore, the kinetic isotope effect was measured by product analysis of the reaction to compare H/D, and it was determined that $k_H/k_D$ was 1.85. These experimental results suggest that the C–H bond cleavage step is not included in the turnover-limiting step. In addition, Hammett studies of substrates ($\sigma = -0.99$) demonstrated that electron-donating groups at the para position to the reactive C–H bond accelerate the reaction rate. This linear relationship obtained in the Hammett plot indicates that the nucleophilicity of the Ar–[Ir]+ intermediate is an important factor in this reaction. All of the data indicate that carbonyl insertion into Ar–[Ir]+ is included in the turnover-limiting step of the catalytic cycle.

3.1 Introduction

Asymmetric control in the construction of quaternary carbon centers is an important methodology to synthesize various pharmaceuticals and natural products. The asymmetric addition\(^1\) of aryl boron reagents to C–O or C–N double bonds such as ketones\(^2\) and ketimines\(^3\) is a general synthetic route for tertiary alcohols or amines having chiral quaternary carbon skeletons. However, these methods generate stoichiometric metal salt wastes as byproducts. Thus, an enantioselective direct C–H bond addition reaction that does not require an organometallic reagent is highly
desirable in terms of the atom and synthetic step economy. However, there have been few reports on asymmetric nucleophilic addition of a C–H bond to the carbonyl group by a transition metal catalyst.\textsuperscript{4} As described in Chapter 2, authors recently developed cationic Ir/Me\textendash BIPAM\textendash catalyzed enantioselective intramolecular direct hydroarylation of $\alpha$-ketoamides (Scheme 1).\textsuperscript{5} This transformation provides a convenient synthetic route for chiral 3\textendash substituted 3\textendash hydroxy\textendash 2-oxindole derivatives with asymmetric induction. While some pioneering works have been reported,\textsuperscript{6} only limited mechanistic information is available for aryl C(sp\textsuperscript{2})\textendash H bond addition to carbonyl groups. In this chapter, the author describes the results of mechanistic studies of our newly developed intramolecular enantioselective hydroarylation reaction.

\begin{scheme}
  \centering
  \includegraphics[width=\textwidth]{scheme31}
  \caption{Cationic Ir/Me\textendash BIPAM\textendash catalyzed enantioselective intramolecular direct hydroarylation}
\end{scheme}

3.2 Mechanistic studies

For mechanistic investigations, we first observed iridium hydride species that form via C–H bond cleavage (Scheme 3.2). In order to ascertain the C–H bond cleavage step, monitoring of $^1$H NMR spectra of a mixture of Ir/Me\textendash BIPAM complex and 1a in DME\textendash d\textsubscript{10} at various temperatures was conducted. As a result, some signals, such as those for iridium hydride species, were observed between −20 to −30 ppm at temperatures over 100 °C. While iridium hydride was detected at 100 °C, the product 2a was obtained in only 21% yield for catalytic reaction conditions (Scheme 3.3). These results clearly demonstrate that a high temperature (135 °C) is essential for the steps except for C–H bond cleavage in the catalytic cycle.
To obtain additional data for the reaction mechanism, we carried out an asymmetric hydroarylation reaction of substrate 1b in the presence of D₂O (6 equiv) under our optimized conditions (Scheme 3.4). The reaction was quenched in 1 h, and the mixture was purified to produce the unreacted substrate 1b-D (30%) and product 2b-D (68%). Deuterium incorporation was observed at the ortho position of the ketoamide group (11%-D at H₉ and 44%-D at H₆), the ortho position of the N,N-dimethyl carbamoyl group (10%-D at H₆) in the substrate, and the 5- and 7-positions of the product (11%-D at H₆ and H₉) on the integration ratio of the ¹H NMR spectra of 1b-D and 2b-D. These results may arise from the fact that the C–H bond cleavage occurs in a fast and reversible manner prior to the carbonyl insertion.⁴ In addition, deuterium incorporation was also observed at the N,N-dimethyl carbamoyl group in both the substrate (1s-D) and (2s-D).
Next, isotope labeling studies were undertaken, with separate rate constants being measured for reactions. The intermolecular kinetic isotope effect (KIE) of the reaction employing substrates 1a and 1a-D was found to be 1.85 at the early stage of the reaction (Scheme 3.5). These experimental observations for the C–H bond cleavage step suggest that C–H bond cleavage occurs before the turnover-liming step in the catalytic cycle (secondary isotope effect can be observed) (Figure 3.1). In Figure 3.1, the turnover-liming step is the second step, and the reaction rate is shown as \( k_2[B] \).

The concentration of B depends on the equilibrium of reversible C–H bond cleavage/formation having rate constants \( k_1 \) and \( k_1^- \), respectively. Due to the deuterium substitution, the equilibrium is greatly affected, and thus the concentration of B is reduced. As explained above, although iridium hydride species formed easily at a low temperature (100 °C), the reaction only proceeded smoothly at a high temperature (135 °C) to give the desired product, and H/D scrambling was observed in the deuterium labeling experiment. These results indicated that the \( k_1 \) step is much faster than the \( k_2 \) step, and the obtained value of the kinetic isotope effect (1.85) results from an equilibrium isotope effect on the C–H bond cleavage step.
To finally determine the turnover-limiting step of this reaction, a Hammett study was performed. The investigation focused on insertion of a carbonyl group into the aryl-iridium bond. First, substrates having an electron-donating or electron-withdrawing substituent (X) at the para position to the reactive C–H bond were subjected to competing reactions. Hammett plot analysis using substrates \( \textbf{1a, 1n–1p} \) provided a linear relationship in a plot of \( \log(k_X/k_H) \) versus \( \sigma \), where \( \rho \) was determined to be \(-0.99\) (Figure 3.2). This result shows that the reaction rate of a substrate having an electron-donating substituent at the para position to the reactive C–H bond is faster than that of a substrate having an electron-withdrawing substituent, and it can be considered that this relationship displays the reactivity for insertion of a carbonyl group into the Ar–[Ir]\(^+\) intermediate (an electron-donating substituent increase the nucleophilicity of the aryl-iridium species).
Next, the Hammett plot for substituents (Y) at the para position to the ketone group was also attempted to confirm the hypothesis as mentioned above (Figure 3.3). If the Hammett plot shown in Figure 2 displays reactivity for carbonyl insertion into aryl-iridium, a linear relationship having a positive gradient should be obtained in Figure 3. Unfortunately, a clear substituent effect was not observed. The Hammett plot displayed a linear relationship between \( \log(k_\text{X}/k_\text{H}) \) and \( \sigma \), resulting in a small \( \rho \) value of \(-0.099\). This result is probably due to a ketoamide skeleton being activating by the electron-withdrawing amide group, and the substituent effect was thus neutralized. In other words, the reactivity for the insertion step is determined by nucleophilicity of the aryl-iridium intermediate. In order to ascertain the effect by the electron-withdrawing amide group, we further tested by changing the electronic nature of the amide moiety. The Hammett plot using N–Me substrates displayed an insufficient \( \rho \) value of \(-0.34\). These experiments demonstrate the strong activation of amide group. In our developed reaction, the electronic effect of the substituent X in Figure 3.2 plays a key role in control of reactivity.
These experimental and kinetic data suggest that the turnover-limiting step in this reaction is more closely related to the insertion of a carbonyl group into the aryl-iridium intermediate than to the C–H bond cleavage step.8)

We propose a catalytic cycle for the cationic Ir/Me-BIPAM-catalyzed enantioselective intramolecular direct hydroarylation (Scheme 3.6). First, the precatalyst mixture of [Ir(cod)₂](BAR₄) and (R,R)-Me·BIPAM forms active complex a. Subsequently, a cationic active species reacts with substrate 1 to afford aryl-iridium intermediate b, which is coordinated with the two carbonyl groups of the amides. In this state, an equilibrium exist between complex b and c. Asymmetric hydroarylation of the ketone carbonyl group would proceed from c, thus producing enantiomerically enriched iridium alkoxide species d. Finally, reductive elimination occurs to give product 2 and regenerate the active species.
The absolute configuration of oxindole product 2a was established to be $S$ by X-ray analysis. However, no X-ray structure of an active chiral catalyst is yet available because of the difficulty in synthesizing a single crystal of the cationic Ir/Me-BIPAM complex. To further investigate the carbonyl insertion process (intermediate $c$ in Scheme 3.6), DFT calculations were performed with B3LYP/LANL2DZ level of theory. At first, the two minimum energy modes of $\text{Ar-}[\text{Ir}((R,R)-\text{Me-BIPAM})-\text{H}$ (intermediate $b$ in Scheme 3.6) were calculated (Figure 3.4). Next, the turnover-limiting and stereo-determining step, which is coordinated with the two carbonyl groups (the aryl-iridium intermediate $c$ in Scheme 3.6) were calculated (Figure 3.5). The conformation $c2$ giving the experimentally observed $S$ product has a low energy for reaction from the intermediate in which the carbonyl oxygen is coordinated to the iridium center at the $Si$-face after the C–H bond cleavage process. Conversely, coordination at the $Re$-face of the carbonyl group ($c1$) has a higher energy than $Si$-face coordination ($c2$) ($\Delta E_{c1-c2} = 3.10 \text{ kcal/mol}$). Thus, the enantioselective insertion to $Si$-face of the carbonyl group can be rationalized by less steric congestion intermediate $c2$. 

Scheme 3.6  Proposed catalytic cycle
Figure 3.4  DFT calculations of aryl–iridium intermediate optimized at the B3LYP/LANL2DZ
Figure 3.5 DFT calculations of enantioselection models at the B3LYP/LANL2DZ

3.3 Conclusion

In conclusion, the detailed mechanism for enantioselective intramolecular direct hydroarylation of $\alpha$-ketoamides catalyzed by a cationic iridium/Me·BIPAM complex was described in this Chapter. The turnover-limiting step in the catalytic cycle was determined to be the carbonyl insertion step to the aryl-iridium bond by $^1$H NMR experiments, kinetic isotope effect studies, and Hammett studies. On the basis of our conducted mechanistic studies, author expects the further development of other reactions which have a broader substrate applicability for enantioselective direct addition of C(sp$^2$)–H bond.
3.4 Experimental section

**Mechanistic Studies**

3.4.1 General procedures for NMR experiments of Iridium-hydride species

To a flame-dried NMR sample tube, $[\text{Ir(cod)}_2](\text{BAr}_4^\text{F})$ (0.00125 mmol) and $(R,R)$-Me·BIPAM (0.00125 mmol) and 1,2-dimethoxyethane-$D_{10}$ (1.0 mL) were added under an N$_2$ atmosphere (1,2-dimethoxyethane-$D_{10}$ was purchased from Wako Pure Chemical Industries, Ltd.). The solution was shaken at room temperature for 1 min, followed by the addition of $\alpha$-ketoamides (0.25 mmol). The reaction mixture was stirred for 1 min at various temperatures (25 °C, 75 °C, 100 °C, 115 °C, 135 °C). Then, $^1$H NMR spectra were measured.

3.4.2 General procedures for deuterium labeling experiment

To a flame-dried NMR sample tube, $[\text{Ir(cod)}_2](\text{BAr}_4^\text{F})$ (0.0125 mmol, 5 mol%) and $(R,R)$-Me·BIPAM (0.0138 mmol, 5.5 mmol%) and 1,2-dimethoxyethane (1.0 mL) were added under an N$_2$ atmosphere. The solution was stirred at room temperature for 30 min, followed by the addition of $\alpha$-keto amide (0.25 mmol) and D$_2$O (6 equiv). The reaction mixture was then heated at 135 °C. After being stirred for 1 h, the mixture was purified with silica gel column chromatography (eluent: $n$-Hexane/AcOEt) to afford recovered substrate and oxindole product. (Figure 3.6 and 3.7)
$^1$H NMR spectrum of original substrate

$^1$H NMR spectrum of recovered substrate

Figure 3.6  $^1$H NMR Spectra of recovered substrate
$^1$H NMR spectrum of pure product

$^1$H NMR spectrum of product in the presence of D$_2$O

Figure 3.7 $^1$H NMR spectra of product
3.4.3 General procedures for KIE experiment

Two separate rate constants were measured for two reactions that were conducted separately under 135 °C, 0.5 h (41% conversion for C–H substrate), one with a substrate containing a C–H bond and one with a substrate containing an analogous C–D bond.

![Diagram of reactions]

3.4.4 General procedures for Hammett correlation study

[Hammett plot using substrates 1a and 1c–e]

Ratio of rate constants (k_x/k_H) was determined by competitive reaction of two substrates (p-Me (1e) vs p-CF_3 (1c), p-H (1a) vs p-CF_3 (1c), and p-Me (1e) vs p-Cl (1d)), respectively. To a flame-dried flask, [Ir(cod)](BAr_F_4) (0.0125 mmol, 5 mol%) and (R,R)-Me-BIPAM (0.0138 mmol, 5.5 mol%) and dry 1,2-dimethoxyethane (1.0 mL) were added under an N_2 atmosphere. The solution was stirred at room temperature for 30 min, followed by the addition of para-substituted α-ketoamides (0.25 mmol). The reaction mixture was then heated at 135 °C for 0.5 h. After being stirred, the mixture was purified with silica gel column chromatography (eluent: n-hexane/ethyl acetate) to afford oxindole products. Then, the products were subjected to NMR analysis to determine the each yield.

Plot data for Hammett correlation study

<table>
<thead>
<tr>
<th>Substrate</th>
<th>k_x</th>
<th>k_x/k_H</th>
<th>log(k_x/k_H)</th>
<th>σ</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH_3</td>
<td>95.6</td>
<td>1.365714</td>
<td>0.13535985</td>
<td>-0.14</td>
</tr>
<tr>
<td>H</td>
<td>70</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cl</td>
<td>46</td>
<td>0.657143</td>
<td>-0.1823402</td>
<td>0.22</td>
</tr>
<tr>
<td>CF_3</td>
<td>20.5</td>
<td>0.292857</td>
<td>-0.5333442</td>
<td>0.53</td>
</tr>
</tbody>
</table>

a The average value.
[Hammett plot using substrates 1a, 1f–h]

Ratio of rate constants ($k_X/k_H$) was determined by competitive reaction of two substrates ($p$-Me (1h) vs $p$-F (1g), $p$-F (1g) vs $p$-CF$_3$ (1f), and H (1a) vs $p$-Me (1h)), respectively. To a flame-dried flask, [Ir(cod)$_2$(BArF$_4$)] (0.0125 mmol, 5 mol%) and ($R$,$R$)-Me-BIPAM (0.0138 mmol, 5.5 mmol%) and dry 1,2-dimethoxyethane (1.0 mL) were added under an N$_2$ atmosphere. The solution was stirred at room temperature for 30 min, followed by the addition of para-substituted α-ketoamides (0.25 mmol). The reaction mixture was then heated at 135 °C for 0.5 h. After being stirred, the solvents were evaporated. Then, dimethyl terephthalate was added as internal standard, the crude product was subjected to NMR analysis to determine the each yield.

Plot data for Hammett correlation study

<table>
<thead>
<tr>
<th></th>
<th>$k_X$</th>
<th>$k_X/k_H$</th>
<th>log($k_X/k_H$)</th>
<th>$\sigma$</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH$_3$</td>
<td>82.4</td>
<td>1.024876</td>
<td>0.01067116</td>
<td>−0.14</td>
</tr>
<tr>
<td>H</td>
<td>80.4</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>F</td>
<td>72.4</td>
<td>0.900498</td>
<td>−0.0455175</td>
<td>0.06</td>
</tr>
<tr>
<td>CF$_3$</td>
<td>70.1</td>
<td>0.871891</td>
<td>−0.059538</td>
<td>0.53</td>
</tr>
</tbody>
</table>

The average value.

[Hammett plot using substrates 1i–1l]

Ratio of rate constants ($k_X/k_H$) was determined by competitive reaction of two substrates ($p$-Me (1l) vs $p$-CF$_3$ (1i), $p$-Me (1l) vs $p$-F (1j), and H (1k) vs $p$-CF$_3$ (1i)), respectively. To a flame-dried flask, [Ir(cod)$_2$(BArF$_4$)] (0.0125 mmol, 5 mol%) and ($R$,$R$)-Me-BIPAM (0.0138 mmol, 5.5 mmol%) and dry 1,2-dimethoxyethane (1.0 mL) were added under an N$_2$ atmosphere. The solution was stirred at room temperature for 30 min, followed by the addition of para-substituted N-Me-α-ketoamides ($p$-Me (1l), H (1k), $p$-F (1j), $p$-CF$_3$ (1i)) (0.25 mmol). The reaction mixture was then heated at 135 °C for 1.5 h. After being stirred, the solvents were evaporated. Then, dimethyl terephthalate was added as internal standard, the crude product was subjected to NMR analysis to determine the each yield.

Plot data for Hammett correlation study

<table>
<thead>
<tr>
<th></th>
<th>$k_X$</th>
<th>$k_X/k_H$</th>
<th>log($k_X/k_H$)</th>
<th>$\sigma$</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH$_3$</td>
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<tr>
<td>H</td>
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<td>0</td>
</tr>
<tr>
<td>F</td>
<td>11.454</td>
<td>0.859071</td>
<td>−0.065971</td>
<td>0.06</td>
</tr>
<tr>
<td>CF$_3$</td>
<td>8.6667</td>
<td>0.650019</td>
<td>−0.187074</td>
<td>0.53</td>
</tr>
</tbody>
</table>

$^a$The average value.
3.4.5 **Computational details**

All calculations were performed by means of the density functional theory method, the hybrid Becke3LYP functional with a hybrid Becke exchange functional and a Lee–Yang–Parr correlation functional as implemented in Gaussian 03.\textsuperscript{5,6} The basis sets were described using an effective core potential (LANL2DZ) for all atoms.\textsuperscript{7} The structures at the stationary points were fully optimized at the B3LYP/LANL2DZ level of theory.

\[
\begin{align*}
\Delta E_{b1-b2} &= 2.64 \text{ kcal/mol} \\
\Delta E_{c1-c2} &= 3.10 \text{ kcal/mol} \\
\Delta E_{c2-b2} &= 7.65 \text{ kcal/mol}
\end{align*}
\]

**DFT Calculations of Enantioselection Models at the B3LYP/LANL2DZ Level**

The total energies and relative energies calculated at the B3LYP/LANL2DZ level of [C\textsubscript{63}H\textsubscript{54}IrN\textsubscript{4}O\textsubscript{8}P\textsubscript{2}(1\textsuperscript{+})] in gas-phase.

<table>
<thead>
<tr>
<th>Intermediate</th>
<th>E (A.U.)</th>
<th>$\Delta E_{b1-b2}$ (E (A.U.))</th>
<th>$\Delta E$ (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>b1</td>
<td>-3371.11601922</td>
<td>0.00421404</td>
<td>2.64</td>
</tr>
<tr>
<td>c1</td>
<td>-3371.10310293</td>
<td>0.012916290</td>
<td>8.11</td>
</tr>
<tr>
<td>b2</td>
<td>-3371.12023326</td>
<td>0.012196420</td>
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<tr>
<td>c2</td>
<td>-3371.10803684</td>
<td>0.004933910</td>
<td>3.10</td>
</tr>
</tbody>
</table>
3.5 References


2) Asymmetric arylation of various carbonyl compounds with organoboron reagents.


Chapter 4

Cationic Ir/S-Me-BIPAM-Catalyzed Asymmetric Intermolecular Direct Hydroarylation of Bicycloalkenes

Abstract: Highly enantioselective cationic iridium-catalyzed hydroarylation of bicycloalkenes, by carbonyl-directed C–H bond cleavage, was accomplished using a newly synthesized sulfur-linked bis(phosphoramidite) ligand (S-Me-BIPAM). The reaction provides alkylated acetophenone or benzamide derivatives in moderate to excellent yields and good to excellent enantioselectivities. Notably, the hydroarylation reaction of 2-norbornene with N,N-dialkylbenzamide proceeds with excellent enantioselectivity (up to 99% ee) and high selectivity for the mono-ortho-alkylation product.

4.1 Introduction

Transition-metal-catalyzed C–C bond-forming reactions by C–H bond activation are the ultimate atom-economic processes which feature high cost-efficiency and environmental harmony as also described in Chapter 1. In particular, direct additions of arenes to multiple bonds such as C=O,\textsuperscript{1} C=N,\textsuperscript{2} and C=C,\textsuperscript{3} called hydroarylation reactions, are highly desirable because of their complete atom economy. Recently, highly enantioselective hydroheteroarylation reactions by a C–H activation/migratory insertion sequence have been developed.\textsuperscript{4} Although some effort has been made to develop efficient catalytic systems for direct asymmetric intermolecular additions of arenes to alkenes, there have been no reports showing high levels of enantioselectivity, catalytic activity, and generality.\textsuperscript{5,6} In 2000, Togni et al. reported cyclopentadienyl iridium(I)-catalyzed asymmetric hydroarylation of 2-norbornene with benzamide (Scheme 4.1). Their study was a pioneering work on the direct intermolecular asymmetric addition of an arene C–H bond to alkenes. Although the reaction provides the hydroarylated product with 94% ee, their system displayed a very low catalytic activity and lack of substrate generality (12% yield, only one example).
4.2 Optimization of reaction conditions

As described in previous chapters, we recently developed a cationic iridium/Me-BIPAM catalyst system for a direct enantioselective intramolecular hydroarylation reaction of α-ketoamides as one of the rare examples of asymmetric hydroarylation of ketones by a C–H bond cleavage/migratory insertion sequence. Thus we became interested in developing asymmetric hydroarylation of alkenes. In Chapter 4, the author describes the highly enantioselective intermolecular hydroarylation of bicycloalkenes with high enantioselectivity by directed C–H bond cleavage of arenes.

Our initial studies were focused on the development of reaction conditions, including the iridium precursor and chiral ligand for the asymmetric hydroarylation of 2-norbornene (2a) with 2'-methoxyacetophenone (1a), thus giving the ortho-alkylated product 3a (Table 4.1). Because our previously developed asymmetric hydroarylation of ketones was effectively catalyzed by an [Ir(cod)₂][BARF₄]/bidentate bis(phosphoramidite) (Me-BIPAM) complex, we examined several chiral BIPAM ligands (entries 1–3). The use of (R,R)-Me-BIPAM (L1) as the ligand gave 3a in 93% yield with 52% ee, and a higher ee value was achieved by changing the linker atom of the linked BINOL unit from oxygen to nitrogen [(R,R)-N-Me-BIPAM (L2); entry 2]. Substantial improvement of the enantioselectivity was achieved by using a sulfur-linked bis(phosphoramidite) ligand [(R,R)-S-Me-BIPAM (L3); entry 3]. Among the chiral ligands screened, the use of (R)-BINAP (entry 4) and the monodentate phosphoramidite (R)-MonoPhos (entry 5) resulted in lower selectivities of 13 and 21% ee, respectively. Further optimization showed that the counter anion of the cationic iridium complex significantly affected the product yield (entries 6 and 7). A neutral iridium complex did not promote the hydroarylation reaction (entry 8). While the solvent had some influence on both the yield and enantioselectivity, no reaction occurs in the case of DMF (Table 4.2).
Table 4.1  Optimization of precursors and ligands\textsuperscript{[a]}

\[
\begin{align*}
\text{MeO-} & \quad \text{H} \quad + \quad \begin{tikzpicture}
\node [shape=circle,draw,inner sep=0.5mm] (a) at (0,0) {1a};
\node [shape=circle,draw,inner sep=0.5mm] (b) at (1,0) {2a};
\draw (a) -- (b);\end{tikzpicture} \quad \text{Ir cat. (5 mol \%)} \\
& \quad \text{ligand (5.5 mol \%)} \\
& \quad \text{DCE, 135 °C, 24 h} \\
\end{align*}
\]

\begin{align*}
& \quad \text{MeO-} \\
& \quad \text{H} \quad + \quad \begin{tikzpicture}
\node [shape=circle,draw,inner sep=0.5mm] (a) at (0,0) {1a};
\node [shape=circle,draw,inner sep=0.5mm] (b) at (1,0) {2a};
\draw (a) -- (b);\end{tikzpicture} \quad \text{Ir cat. (5 mol \%)} \\
& \quad \text{ligand (5.5 mol \%)} \\
& \quad \text{DCE, 135 °C, 24 h} \\
\end{align*}

\begin{tabular}{llllll}
\hline
Entry & Precursor & Ligand & Yield\textsuperscript{[b]} [%] & ee [%] \\
\hline
1 & \text{[Ir(cod)]}\text{(BF\textsubscript{3})} & L1 & 93 & 52 \\
2 & \text{[Ir(cod)]}\text{(BF\textsubscript{3})} & L2 & 35 & 73 \\
3 & \text{[Ir(cod)]}\text{(BF\textsubscript{3})} & L3 & 82 & 88 \\
4 & \text{[Ir(cod)]}\text{(BF\textsubscript{3})} & BINAP & 44 & 13 \\
5 & \text{[Ir(cod)]}\text{(BF\textsubscript{3})} & MonoPhos & 96 & 21 \\
6 & \text{[Ir(cod)]}\text{(BF\textsubscript{3})} & L3 & 79 & 87 \\
7 & \text{[Ir(cod)]}\text{(BF\textsubscript{3})} & L3 & trace & – \\
8 & \text{[Ir(cod)]}\text{(BF\textsubscript{3})} & L3 & n.r. & – \\
\hline
\end{tabular}

\textsuperscript{[a]} Reaction conditions: arene (0.25 mmol), iridium catalyst (5 mol\%), and ligand (1.1 equiv to Ir) in solvent (1 mL) was stirred for 24 h at 135 °C.

\textsuperscript{[b]} Yield of isolated product. BINAP = (+)-(R)-2,2’-bis(diphenylphosphanyl)-1,1’-binaphthyl, cod = 1,5-cyclooctadiene, DCE = 1,2-dichloroethane, DME = 1,2-dimethoxyethane, MonoPhos = (-)-(R)-(3,5-dioxo-4-phosphacyclohepta[2,1,3,4-\text{a}’]dinaphthalene-4-yl)-dimethylamine.

Table 4.2  Optimization of solvents\textsuperscript{[a]}

\[
\begin{align*}
\text{MeO-} & \quad \text{H} \quad + \quad \begin{tikzpicture}
\node [shape=circle,draw,inner sep=0.5mm] (a) at (0,0) {1a};
\node [shape=circle,draw,inner sep=0.5mm] (b) at (1,0) {2a};
\draw (a) -- (b);\end{tikzpicture} \quad \text{[Ir(cod)]}\text{(BF\textsubscript{3})} (5 mol \%) \\
& \quad \text{(R,R)-S-Me-BIPAM (5.5 mol \%)} \\
& \quad \text{solvent, 135 °C, 24 h} \\
\end{align*}
\]

\begin{tabular}{llllll}
\hline
Entry & Solvent & Yield\textsuperscript{[b]} [%] & ee [%] \\
\hline
1 & DCE & 82 & 88 \\
2 & toluene & 87 & 86 \\
3 & DME & 58 & 89 \\
4 & THF & 71 & 84 \\
5 & PhCl & 71 & 80 \\
6 & DMF & trace & – \\
\hline
\end{tabular}

\textsuperscript{[a]} Reaction conditions: arene (0.25 mmol), iridium catalyst (5 mol%), and ligand (1.1 equiv to Ir) in solvent (1 mL) was stirred for 24 h at 135 °C.

\textsuperscript{[b]} Yield of isolated product.
4.3 Substrate scope

With the optimized catalytic conditions (Table 4.1, entry 3) in hand, we next explored the substrate scope for asymmetric hydroarylation (Table 4.3). Various substituents including, OMe, F, and Me, on the arene moiety were tolerated (3a–3f). The hydroarylated products were obtained in moderate to good yields with high enantioselectivities. Furthermore, hydroarylation of the benzene-fused bicyclic alkene 2b with 1a proceeded to produce 3b in a synthetically useful yield with excellent enantioselectivity (97% ee). In the case of hydroarylation with unfunctionalized acetophenone as a substrate, a mixture of mono- (3g) and di-ortho-alkylated products (3h) was formed. Both products were characterized by GC-MS and 1H NMR analysis. Propiophenone could also be used as a viable directing group, and the products (3i, 3j) were isolated with high enantioselectivities, albeit in moderate yields. In some cases for the ketone-directed hydroarylation, it was necessary to adjust the reaction conditions (3c, 3d, 3f, 3g, and 3j). Next, the hydroarylation reaction of 1a with various benzamides was examined under the optimized reaction conditions. The protocol tolerates a range of amide-based directing groups, including a diethyl amide (3l) and diisopropyl amide (3m). A Weinreb amide, which is a synthon for the formyl group, was also tolerated and gave the hydroarylated product 3n in 64% yield. Pyrrolidine and piperidine-derived amides were also used as directing groups to form the desired products 3o and 3q, respectively. We also examined the substituent effects using a range of substituted benzamides. Substituents para to the directing group are well-tolerated (3p, 3r–t). In addition, potentially reactive functional groups such as an aryl ester (3p) and bromide (3t) were applicable to this transformation. Gratifyingly, only the mono-ortho-alkylated products were obtained in the amide-directed hydroarylation. X-ray diffraction analysis of a single crystal of 3b revealed that the absolute configuration of 3b is R at C1 and S at C8 and C9 (Figure 4.1).9) The acetyl group of 3b is orthogonal to the phenyl ring, probably because of steric hindrance. This observation suggests that the bond rotation of a directing group is limited by a congested environment. Therefore, the mono-ortho-alkylated products may predominate in the hydroarylation with benzamides that have more hindered substituents.10)
Table 4.3  Substrate scope of enantioselective hydroarylation\textsuperscript{[a]}

\[
\begin{align*}
R^1 & \quad O \\
R^2 & \quad H
\end{align*}
\]

\[\text{[Ir(cod)}_2\text{](BA}_{x_4}\text{)(5 mol\%)} \text{, (R,R)-S-Me-BIPAM (5.5 mol\%)}, \text{DCE, 135 °C, 24 h} \]

\[\text{3.5equiv} \]

<table>
<thead>
<tr>
<th>R\textsuperscript{2}</th>
<th>3a</th>
<th>3b</th>
<th>3c</th>
<th>3d</th>
<th>3e</th>
<th>3f</th>
<th>3g</th>
<th>3h</th>
<th>3i</th>
<th>3j</th>
<th>3k</th>
<th>3l</th>
<th>3m</th>
<th>3n</th>
<th>3o</th>
<th>3p</th>
<th>3q</th>
<th>3r</th>
<th>3s</th>
<th>3t</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeO \quad OMe</td>
<td>82%, 88% ee</td>
<td>68%, 97% ee</td>
<td>42%, 93% ee\textsuperscript{[b]}</td>
<td>73%, 97% ee\textsuperscript{[b]}</td>
<td>46%, 81% ee</td>
<td>50%, 88% ee\textsuperscript{[b]}</td>
<td>40%, 92% ee\textsuperscript{[bc]}</td>
<td>39%, 91% ee\textsuperscript{[bc]}</td>
<td>61%, 92% ee</td>
<td>37%, 97% ee\textsuperscript{[b]}</td>
<td>90%, 99% ee</td>
<td>93%, 99% ee</td>
<td>90%, 96% ee</td>
<td>64%, 99% ee</td>
<td>91%, 97% ee</td>
<td>96%, 99% ee</td>
<td>91%, 99% ee</td>
<td>97%, 99% ee</td>
<td>91%, 99% ee</td>
<td>96%, 99% ee</td>
</tr>
</tbody>
</table>

\textsuperscript{[a]} Reaction conditions: 1 (0.25 mmol), 2 (3.5 equiv), iridium catalyst (5 mol\%), and (R,R)-S-BIPAM (1.1 equiv to Ir) in DCE (1 mL) was stirred for 24 h at 135 °C.

\textsuperscript{[b]} Reaction conditions: 1 (2 equiv), 2 (0.25 mmol), iridium catalyst (5 mol\%), and (R,R)-S-Me-BIPAM (1.1 equiv to Ir) in DCE (1 mL) was stirred for 24 h at 135 °C.

\textsuperscript{[c]} 0.5 mL of DCE was used as solvent.
Figure 4.1  ORTEP diagram of 3b with thermal ellipsoids set at 50%

Next, substituent effect of amides is investigated under optimized conditions (Table 4.4). In the case of primary benzamide 1u, no reaction occurred. In addition, the mixtures of mono- and di-hydroarylated product were obtained when secondary benzamide 1v is subjected to the reaction with 2-norbornene. As a result, tertiary benzamides is most suitable for mono-ortho-selective hydroarylation.

Table 4.4  Substituent effect of benzamides^[a]^  

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R’</th>
<th>yield [%]</th>
<th>ee [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>H</td>
<td>trace</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>H</td>
<td>23%, 99% ee</td>
<td>72%, 99% ee</td>
</tr>
<tr>
<td>3</td>
<td>Me</td>
<td>Me</td>
<td>90%, 99% ee</td>
<td>-</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: 1 (0.25 mmol), 2 (3.5 equiv), iridium catalyst (5 mol%), and (R,R)-S-BIPAM (1.1 equiv to Ir) in DCE (1 mL) was stirred for 24 h at 135 °C.

In addition, we carried out the reactions of oxygen- or nitrogen-containing bicyclic alkenes with benzamide 1q (Scheme 4.2). Unfortunately, hydroarylation of heteroatom-containing bicyclic alkenes did not proceed in most cases. In the reaction of 1,4-dihydro-1,4-epoxynaphthalene, biaryl compound was exceptionally obtained in 20% yield through rapid β-heteroatom elimination of the alkyl iridium intermediate and dehydration. These results show the narrow substrate scope compatibility and the
need of further improvement of our developed catalytic system.

Scheme 4.2  hydroarylation of heteroatom-contained bicyclic compounds

To demonstrate the synthetic utility of this protocol, we further transformed the products of asymmetric hydroarylation of bicycloalkenes. Enantioenriched norbornene could be used as a building block in organic synthesis for the preparation of functionalized chiral compounds. The highly functionalized cyclopentane (5) was successfully obtained, as a single diastereomer, by ring-opening metathesis of 3w with ethylene and with no erosion of enantioselectivity (Scheme 4.3).

Scheme 4.3  Ring-opening metathesis of 3w with ethylene

To obtain data for the reaction mechanism, we carried out an asymmetric hydroarylation of the substrate 1p in the presence of D₂O under the optimized reaction conditions (Scheme 4.4(A)). The reaction was quenched after 0.25 hours, and the mixture was purified to obtain the unreacted substrate [D]-1p (35%) and product [D]-3p (64%). Deuterium incorporation was not observed at the ortho position of the amide group (3% D) in the substrate. This result may arise from the fact that C–H bond cleavage occurs in a non-reversible manner prior to the alkene insertion. In addition,
Deuterium-labeling studies were undertaken (Scheme 4.4(B)). Comparison of the initial rate constants for the addition of normal (1q) and deuterated N,N-piperidylbenzamide ([D]-1q) to 1a in separate vessels revealed a kinetic isotope effect (KIE) of 2.08. These results indicate that the turnover-limiting step in our developed asymmetric hydroarylation includes the C–H bond cleavage step.\textsuperscript{1h, 1j, 4e}

\begin{itemize}
\item[(A)] Asymmetric Hydroarylation in presence of D\textsubscript{2}O
\begin{equation}
\text{D}_2\text{O} \text{(10 equiv)} \stackrel{[\text{Ir}\text{-cod}]_2[\text{BAR}_4]_2 \text{(5 mol\%)} \ (R,R)-\text{S-Me-BIPAM (5.5 mol\%)}}{\text{DCE, 135°C, 0.25 h}} \text{1p-D}\text{CO}_2\text{Me} \ (35\% \text{ recovered}) + \text{3p-D} \text{CO}_2\text{Me} \ (64\% \text{ yield})
\end{equation}

\item[(B)] Kinetic Isotope Effect
\begin{equation}
\text{Ir}\text{-cod}[\text{BAR}_4]_2 \text{(5 mol\%)} \ (R,R)-\text{S-Me-BIPAM (5.5 mol\%)} \ \text{DCE, 135°C} \ \text{KIE = 2.08}
\end{equation}
\end{itemize}

**Scheme 4.4  Deuterium-labeling experiments**

Finally, a plausible catalytic cycle is shown in Figure 4.2. We propose a catalytic cycle involving chelation-assisted C–H bond cleavage, migratory insertion of a bicycloalkene into the Ir–C bond, and C–H bond-forming reductive elimination of the resulting organoiridium species\textsuperscript{11}.
4.4 Conclusion

In this Chapter, we described the first highly enantioselective intermolecular hydroarylation of bicycloalkene through arene C–H bond cleavage catalyzed by a cationic iridium/(\textit{R,R}-\textit{S}-Me-BIPAM) catalyst. Efforts to extend the scope of the enantioselective hydroarylation for other unstrained alkenes and mechanistic studies for the enantioselection are in progress.
4.5 Experimental section

Synthesis of \((R,R)-\text{S-Me-BIPAM (L3)}\):

To a toluene solution (10 mL) of \((R,R)-\text{S-linked-BINOL (3.17 mmol)}\) was added \(\text{P(NMe}_2\text{)}_3\) (2.5 equiv) under \(\text{N}_2\) gas atmosphere. The reaction mixture was then heated at 50 °C. After being stirred for 24h, the mixture was purified with silica gel (neutralized with \(\text{Et}_3\text{N}\)) short column chromatography (hexane/AcOEt = 6/1) to afford desired \((R,R)-\text{S-linked bis(phosphoramidite)}\) ((\(R,R)-\text{S-Me-BIPAM (L3)}) as pure white solid (63% yield).

\[\text{\Herz{H NMR (400 MHz, C}_2\text{Cl}_2): } \delta = 8.04-7.83 (m, 7H), 7.51-7.13 (m, 15H), 4.26 (d, J = 13.8 Hz, 2H), 3.96 (d, J = 13.8 Hz, 2H), 2.51-2.37 (m, 12H); \]

\[\text{\Herz{C NMR (100 MHz, C}_2\text{Cl}_2): } \delta = 150.3, 149.7, 148.6, 132.2, 131.7, 130.8, 130.7, 130.6, 130.1, 128.6, 128.5, 128.4, 127.1, 126.9, 126.8, 126.4, 126.2, 125.1, 124.9, 122.1, 35.8, 35.6, 32.4; \]

\[\text{\Herz{P NMR (161.7 MHz, C}_2\text{Cl}_2) : } \delta = 149.6; \text{HRMS (APCI) } m/z \text{ calc for C}_{46}\text{H}_{38}\text{O}_4\text{N}_2\text{P}_2\text{S (M+Na)^+: 799.19197, found: 799.19160.}\]

General procedure and NMR spectra of products

To a flame-dried sealed tube, \([\text{Ir(cod)}_2](\text{BARF}_4)\) (0.0125 mmol, 5 mol\%) and \(\text{(R,R)-S-Me-BIPAM (0.0138 mmol, 5.5 mol\%)}\) and dry 1,2-dichloroethane (1.0 mL) were added under an \(\text{N}_2\) atmosphere. The solution was stirred at room temperature for 30 min, followed by the addition of arene (0.25 mmol) and bicycloalkene (3.5 equiv). The reaction mixture was then heated at 135 °C. After being stirred for 24 h, the mixture was purified by silica gel column chromatography (eluent: hexane/AcOEt) to afford a pure hydroarylated product.
1-[2-Exo-bicyclo[2.2.1]heptan-2-yl]-6-methoxyphenyl]ethan-1-one (3a)

88% ee [HPLC condition: Chiralpak AS-H column, hexane/2-propanol = 200/1, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 16.9 min (minor) and 21.1 min (major)]; [α]_D^20 = +54.5 (c 2.0, CHCl_3); 1H NMR (400 MHz, CDCl_3): δ = 7.26 (t, J = 8.2 Hz, 1H), 6.93 (d, J = 8.2 Hz, 1H), 6.74 (d, J = 8.2 Hz, 1H), 3.80 (s, 3H), 2.66–2.63 (m, 1H), 2.50 (s, 3H), 2.33 (m, 2H), 1.73–1.68 (m, 1H), 1.63–1.49 (m, 4H), 1.30–1.19 (m, 3H); 13C NMR (100 MHz, CDCl_3): δ = 206.7, 155.6, 144.9, 131.2, 129.6, 118.0, 108.0, 55.5, 43.4, 42.7, 40.3, 36.7, 36.6, 32.7, 30.5, 28.4; HRMS (ESI) m/z calc for C_{16}H_{20}O_2 Na (M+Na)^+: 267.13555, found: 267.13531.

1-[2-Methoxy-6-[(1R, 8S, 9S)-tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-trien-9-yl]phenyl]ethan-1-one (3b)

97% ee [HPLC condition: Chiralpak AD-3 column, hexane/2-propanol = 200/1, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 37.7 min (minor) and 46.6 min (major)]; [α]_D^20 = + (c, CHCl_3); 1H NMR (400 MHz, CDCl_3): δ = 7.32 (t, J = 8.1 Hz, 1H), 7.23–7.14 (m, 2H), 7.10–7.05 (m, 3H), 6.80 (d, J = 8.1 Hz, 1H), 3.81 (s, 3H), 3.42 (br s, 2H), 2.69 (dd, J = 8.5, 5.2 Hz, 1H), 2.43 (s, 3H), 2.02–1.91 (m, 2H), 1.82–1.71 (m, 2H); 13C NMR (100 MHz, CDCl_3): δ = 206.2, 155.8, 148.6, 148.2, 143.2, 131.9, 129.8, 125.8, 125.7, 120.6, 118.1, 108.5, 55.6, 49.9, 46.8, 44.2, 42.1, 36.7, 32.6; HRMS (ESI) m/z calc for C_{20}H_{20}O_2 Na (M+Na)^+: 315.13555, found: 315.13530.

1-[2-Exo-bicyclo[2.2.1]heptan-2-yl]-6-fluorophenyl]ethan-1-one (3c)

93% ee [HPLC condition: Chiralpak AD-H column, hexane/2-propanol = 200/1, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 10.3 min (minor) and 10.8 min (major)]; [α]_D^20 = +78.0 (c 1.0, CHCl_3); 1H NMR (400 MHz, CDCl_3): δ = 7.31–7.26 (m, 1H), 7.13 (d, J = 8.2 Hz, 1H), 6.90 (t, J = 8.6 Hz, 1H), 2.80 (dd, J = 8.6, 6.0 Hz, 1H), 2.55 (d, J = 2.3 Hz, 3H), 2.38–2.31 (m, 2H), 1.77–1.71 (m, 1H), 1.62–1.46 (m, 4H), 1.33–1.20 (m, 3H); 13C NMR (100 MHz, CDCl_3): δ = 202.7, 159.3 (d, J = 246 Hz), 147.0 (d, J = 2.9 Hz), 130.5 (d, J = 8.6 Hz), 129.1 (d, J = 16.2 Hz), 121.4 (d, J = 2.9 Hz), 112.7 (d, J = 21.9 Hz), 43.4, 42.4, 40.3, 36.9, 36.6, 32.9, 30.4, 28.5; HRMS (ESI) m/z calc for C_{15}H_{17}OFNa (M+Na)^+: 255.11556, found: 255.11551.
1-[2-(Exo-bicyclo[2.2.1]heptan-2-yl)naphthalen-1-yl]ethan-1-one (3d)

97% ee [HPLC condition: Chiralpak AS-H column, hexane/2-propanol = 200/1, flow = 0.5 mL/min, wavelength = 230 nm, tR = 19.3 min (minor) and 24.3 min (major); [α]D20 = +54.6 (c 1.5, CHCl3); 1H NMR (400 MHz, CDCl3): δ = 7.84–7.79 (m, 2H), 7.58–7.42 (m, 4H), 2.75 (dd, J = 8.5, 6.3 Hz, 1H), 2.66 (s, 3H), 2.43–2.38 (m, 2H), 1.87–1.78 (m, 2H), 1.72–1.53 (m, 3H), 1.40–1.22 (m, 3H); 13C NMR (100 MHz, CDCl3): δ = 209.1, 139.5, 138.4, 131.5, 128.8, 128.6, 128.1, 126.7, 125.4, 124.0, 123.9, 44.3, 43.5, 40.6, 37.1, 36.6, 33.7, 31.1, 28.3; HRMS (ESI) m/z calc for C19H20ONa (M+Na)+: 287.14064, found: 287.14053

1-[2-(Exo-bicyclo[2.2.1]heptan-2-yl)-4,6-dimethoxypheny]ethan-1-one (3e)

81% ee [HPLC condition: Chiralpak AS-H column, hexane/2-propanol = 200/1, flow = 0.5 mL/min, wavelength = 230 nm, tR = 18.4 min (minor) and 23.6 min (major); [α]D20 = +44.6 (c 1.3, CHCl3); 1H NMR (400 MHz, CDCl3): δ = 6.47 (d, J = 2.3 Hz, 1H), 6.29 (d, J = 2.3 Hz, 1H), 3.82 (s, 3H), 3.79 (s, 3H), 2.73 (dd, J = 9.1, 5.9 Hz, 1H), 2.47 (s, 3H), 2.35–2.29 (m, 2H), 1.75–1.68 (m, 1H), 1.62–1.45 (m, 4H), 1.32–1.18 (m, 3H); 13C NMR (100 MHz, CDCl3): δ = 206.1, 160.9, 157.5, 146.7, 124.1, 103.2, 95.0, 55.5, 55.3, 43.4, 42.5, 40.4, 36.9, 36.7, 32.9, 30.5, 28.4; HRMS (ESI) m/z calc for C17H22O3Na (M+Na)+: 297.14612, found: 297.14585.

1-[2-(Exo-bicyclo[2.2.1]heptan-2-yl)-5-methylpheny]ethan-1-one (3f)

88% ee [HPLC condition: Chiralpak AS-H column, hexane/2-propanol = 200/1, flow = 0.5 mL/min, wavelength = 230 nm, tR = 12.5 min (minor) and 15.3 min (major); [α]D20 = +68.3 (c 2.4, CHCl3); 1H NMR (400 MHz, CDCl3): δ = 7.31–7.27 (m, 2H), 7.21–7.18 (m, 1H), 3.13 (dd, J = 8.6, 6.0 Hz, 1H), 2.55 (s, 3H), 2.35–2.29 (m, 2H), 2.34 (s, 3H), 1.83–1.77 (m, 1H), 1.61–1.20 (m, 7H); 13C NMR (100 MHz, CDCl3): δ = 204.0, 143.2, 139.3, 134.5, 131.4, 128.5, 126.3, 43.1, 42.7, 40.2, 36.9, 36.6, 30.7, 30.4, 28.7, 20.8; HRMS (ESI) m/z calc for C16H20ONa (M+Na)+: 251.14064, found: 251.14046.
1-[2-(Exo-bicyclo[2.2.1]heptan-2-yl)phenyl]ethan-1-one (3g) and 1-[2,6-bis(bicyclo[2.2.1]heptan-2-yl)phenyl]ethan-1-one (3h)

92% ee (mono), 91% ee (di) [HPLC condition: Chiralcel OJ-H column, hexane/2-propanol = 100/1, flow = 0.5 mL/min, wavelength = 230 nm, \( t_R \) (mono) = 10.8 min (minor) and 11.8 min (major), \( t_R \) (di) = 8.8 min (minor) and 9.2 min (major)]; \([\alpha]D^20 = +69.2 \ (c \ 1.7, \text{CHCl}_3)\).

The \(^1\)H NMR spectrum showed agreement with the literature data [6]. The mono/di ratio determined by GC-MS (EI) analysis.

1-[2-(Exo-bicyclo[2.2.1]heptan-2-yl)-6-methoxyphenyl]propan-1-one (3i)

92% ee [HPLC condition: Chiralpak AD-3 column, hexane/2-propanol = 200/1, flow = 0.5 mL/min, wavelength = 230 nm, \( t_R \) = 16.3 min (minor) and 17.7 min (major)]; \([\alpha]D^20 = +40.8 \ (c \ 2.1, \text{CHCl}_3)\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta = 7.25 \) (t, \( J = 7.7 \) Hz, 1H), 6.92 (d, \( J = 7.7 \) Hz, 1H), 6.73 (d, \( J = 8.2 \) Hz, 1H), 3.77 (s, 3H), 2.86–2.67 (m, 2H), 2.55 (dd, \( J = 8.6, 6.1 \) Hz, 1H), 2.31 (br s, 2H), 1.71–1.50 (m, 5H), 1.28–1.19 (m, 3H), 1.18 (t, \( J = 7.3 \) Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta = 209.5, 155.6, 144.9, 131.3, 129.5, 118.0, 108.0, 55.5, 43.6, 43.0, 40.2, 38.2, 36.7, 36.6, 30.7, 28.4, 7.7\); HRMS (ESI) \( m/z \) calc for C\(_{17}\)H\(_{22}\)O\(_2\)Na (M+Na): 281.15120, found: 281.15085.

1-[2-(Exo-bicyclo[2.2.1]heptan-2-yl)naphthalen-1-yl]propan-1-one (3j)

97% ee [HPLC condition: Chiralpak AD-3 column, hexane/2-propanol = 200/1, flow = 0.5 mL/min, wavelength = 230 nm, \( t_R \) = 37.2 min (minor) and 40.9 min (major)]; \([\alpha]D^20 = +36.5 \ (c \ 2.6, \text{CHCl}_3)\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta = 7.81 \) (d, \( J = 8.6 \) Hz, 2H), 7.51–7.40 (m, 4H), 2.90 (q, \( J = 7.3 \) Hz, 2H), 2.67–2.63 (m, 1H), 2.41 (br s, 1H), 2.35 (br s, 1H), 1.82–1.54 (m, 5H), 1.34–1.24 (m, 3H), 1.30 (t, \( J = 7.3 \) Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta = 211.8, 139.7, 138.5, 131.6, 129.0, 128.8, 128.1, 126.7, 125.4, 124.1, 123.9, 44.5, 43.8, 40.6, 39.3, 37.1, 36.6, 31.3, 28.4, 7.8\); HRMS (ESI) \( m/z \) calc for C\(_{20}\)H\(_{22}\)ONa (M+Na): 301.15629, found: 301.15618.
2-(Exo-bicyclo[2.2.1]heptan-2-yl)-N,N-dimethylbenzamide (3k)

99.6% ee [HPLC condition: Chiralpak AD-3 column, hexane/2-propanol = 200/1, flow = 1.3 mL/min, wavelength = 230 nm, tR = 54.5 min (minor) and 55.6 min (major); [α]D20 = +49.8 (c 2.0, CHCl3); 1H NMR (400 MHz, CDCl3): δ = 7.36–7.27 (m, 2H), 7.17 (t, J = 7.2 Hz, 1H), 7.13–7.08 (m, 1H), 3.14 (s, 3H), 2.87–2.62 (m, 2H), 2.81 (s, 3H), 2.47–2.22 (m, 2H), 1.84–1.42 (m, 5H), 1.36–1.18 (m, 3H); 13C NMR (100 MHz, CDCl3): δ = 171.7, 143.8, 143.6, 136.5, 136.3, 128.6, 125.8, 125.7, 125.6, 125.3, 43.7, 43.2, 42.8, 41.8, 40.4, 39.2, 38.9, 38.7, 36.9, 36.7, 36.4, 34.4, 31.1, 30.4, 28.4, 28.3; HRMS (ESI) m/z calc for C16H21ONa (M+Na)+: 266.15154, found: 266.15137.

2-(Exo-bicyclo[2.2.1]heptan-2-yl)-N,N-diethylbenzamide (3l)

99.1% ee [HPLC condition: Chiralpak AD-3 column, hexane/2-propanol = 200/1, flow = 1.3 mL/min, wavelength = 230 nm, tR = 53.4 min (minor) and 55.9 min (major); [α]D20 = +22.8 (c 2.1, CHCl3); 1H NMR (400 MHz, TCE-D2): δ = 7.32–7.26 (m, 2H), 7.19–7.12 (m, 1H), 7.10–7.06 (m, 1H), 3.90–3.72 (m, 1H), 3.29–2.95 (m, 3H), 2.76 (dd, J = 8.5, 6.0 Hz, 1H), 2.40–2.12 (m, 1H), 1.75–1.45 (m, 5H), 1.30–1.13 (m, 6H), 1.04–0.97 (m, 3H); 13C NMR (100 MHz, TCE-D2): δ = 172.3, 145.3, 145.1, 138.6, 138.4, 130.2, 127.7, 127.4, 127.0, 126.9, 126.8, 45.0, 44.7, 44.6, 44.5, 44.2, 43.9, 41.6, 40.9, 40.0, 39.7, 38.5, 38.1, 32.6, 32.1, 30.2, 30.1, 15.4, 14.3; HRMS (ESI) m/z calc for C18H25ONa (M+Na)+: 294.18284, found: 294.18224.

2-(Exo-bicyclo[2.2.1]heptan-2-yl)-N,N-diisopropylbenzamide (3m)

96% ee [HPLC condition: Chiralpak AD-3 column, hexane/2-propanol = 200/1, flow = 1.3 mL/min, wavelength = 230 nm, tR = 33.1 min (minor) and 38.2 min (major); [α]D20 = +9.6 (c 1.4, CHCl3); 1H NMR (400 MHz, TCE-D2): δ = 7.32–7.25 (m, 2H), 7.15 (t, J = 6.8 Hz, 1H), 7.03 (t, J = 6.8 Hz, 1H), 3.69–3.56 (m, 1H), 3.50–3.39 (m, 1H), 2.86–2.78 (m, 1H), 2.35 (br s, 2H), 1.80–1.44 (m, 11H), 1.30–1.04 (m, 9H); 13C NMR (100 MHz, TCE-D2): δ = 172.1, 145.2, 145.1, 140.0, 139.9, 129.8, 129.7, 127.7, 127.6, 126.9, 126.3, 126.1, 52.2, 52.0, 47.0, 45.0, 44.9, 42.1, 40.5, 38.4, 38.3, 38.2, 37.5, 32.9, 32.1, 30.4, 30.1, 22.3, 22.2, 22.1, 21.9; HRMS (ESI) m/z calc for C20H29ONa (M+Na)+: 322.21414, found: 322.21377.
2-(Exo-bicyclo[2.2.1]heptan-2-yl)-N-methoxy-N-methylbenzamide (3n)

99.0% ee [HPLC condition: Chiralpak AD-3 column, hexane/2-propanol = 200/1, flow = 1.3 mL/min, wavelength = 230 nm, \( t_R = 45.4 \) min (minor) and 46.9 min (major)]; \([\alpha]_D^{20} = +40.4 \) (c 2.6, CHCl\(_3\)); \(^1\)H NMR (400 MHz, DMSO-D\(_6\)) at 353 K: \( \delta = 7.38-7.30 \) (m, 2H), 7.23–7.17 (m, 2H), 3.51 (s, 3H), 3.19 (s, 3H), 2.75 (t, \( J = 7.7 \) Hz, 1H), 2.32 (br s, 1H), 2.27 (br s, 1H), 2.27 (br s, 1H), 2.27 (br s, 1H), 1.68–1.48 (m, 5H), 1.30–1.14 (m, 3H); \(^{13}\)C NMR (100 MHz, DMSO-D\(_6\)) at 353 K: \( \delta = 143.1, 135.5, 128.5, 125.4, 124.9, 124.7, 60.1, 43.0, 42.1, 38.6, 35.8, 35.5, 32.9, 30.0, 27.8 \); HRMS (ESI) \( m/z \) calc for C\(_{16}\)H\(_{21}\)O\(_2\)NNa (M+Na): 282.14645, found: 282.14620.

1-[(2-(Exo-bicyclo[2.2.1]heptan-2-yl)phenyl)carbonyl]pyrrolidine (3o)

97% ee [HPLC condition: Chiralpak AD-3 column, hexane/2-propanol = 200/1, flow = 1.3 mL/min, wavelength = 230 nm, \( t_R = 50.4 \) min (minor) and 52.3 min (major)]; \([\alpha]_D^{20} = +54.4 \) (c 1.6, CHCl\(_3\)); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta = 7.35-7.27 \) (m, 2H), 7.19–7.14 (m, 2H), 3.71–3.60 (m, 2H), 3.20–3.08 (m, 2H), 2.89 (br s, 1H), 2.43–2.31 (m, 2H), 2.00–1.47 (m, 9H), 1.33–1.20 (m, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta = 170.2, 143.6, 137.5, 128.7, 125.7, 125.5, 125.4, 48.6, 45.2, 43.3, 42.2, 39.7, 36.7, 36.6, 30.7, 28.4, 25.8, 24.5 \); HRMS (ESI) \( m/z \) calc for C\(_{18}\)H\(_{23}\)ONa (M+Na): 292.16719, found: 292.16692.

Methyl 3-(exo-bicyclo[2.2.1]heptan-2-yl)-4-[(pyrrolidin-1-yl)carbonyl]benzoate (3p)

99.3% ee [HPLC condition: Chiralpak AD-3 column, hexane/2-propanol = 200/1, flow = 1.3 mL/min, wavelength = 230 nm, \( t_R = 133.9 \) min (minor) and 169.4 min (major)]; \([\alpha]_D^{20} = +41.3 \) (c 2.4, CHCl\(_3\)); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta = 8.03 \) (s, 1H), 7.86 (dd, \( J = 7.7, 1.4 \) Hz, 1H), 7.24 (d, \( J = 7.7 \) Hz, 1H), 3.92 (s, 3H), 3.67 (dt, \( J = 6.8, 3.2 \) Hz, 2H), 3.15–3.09 (m, 2H), 2.89 (br s, 1H), 2.37 (br s, 2H), 2.05–1.58 (m, 9H), 1.34–1.23 (m, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta = 169.2, 166.7, 144.1, 141.8, 130.2, 127.1, 126.8, 125.7, 52.1, 48.5, 45.3, 43.3, 42.3, 39.6, 36.7, 36.6, 30.7, 28.3, 25.8, 24.4 \); HRMS (ESI) \( m/z \) calc for C\(_{20}\)H\(_{25}\)O\(_3\)NNa (M+Na): 350.17266, found: 350.17231.
1-[(2-Exo-bicyclo[2.2.1]heptan-2-yl)phenyl]carbonyl]piperidine (3q)

99.0% ee [HPLC condition: Chiralpak AD-3 column, hexane/2-propanol = 200/1, flow = 1.3 mL/min, wavelength = 230 nm, t_R = 40.3 min (minor) and 45.4 min (major)]; [α]_D^{20} = +30.6 (c 1.4, CHCl_3); ^1H NMR (400 MHz, CDCl_3): δ = 7.36–7.27 (m, 2H), 7.19–7.14 (m, 2H), 3.91–3.59 (m, 2H), 3.22–3.07 (br s, 1H), 2.61 (dd, J = 9.0, 5.8 Hz, 1H), 2.48–2.18 (m, 2H), 1.84–1.20 (m, 1H); ^13C NMR (100 MHz, CDCl_3): δ = 170.2, 144.0, 143.7, 136.7, 136.4, 128.6, 128.5, 126.0, 125.7, 125.5, 125.4, 125.3, 48.2, 48.1, 43.7, 43.3, 43.2, 42.3, 42.2, 41.9, 40.4, 39.7, 37.0, 36.7, 36.5, 31.2, 30.5, 28.6, 28.3, 26.3, 26.1, 25.7, 25.6, 24.5; HRMS (ESI) m/z calc for C_{19}H_{25}ONa (M+Na)^+: 306.18284, found: 306.18266.

1-[(2-Exo-bicyclo[2.2.1]heptan-2-yl)-4-methylphenyl]carbonyl]piperidine (3r)

99.3% ee [HPLC condition: Chiralpak AD-3 column, hexane/2-propanol = 200/1, flow = 1.3 mL/min, wavelength = 230 nm, t_R = 89.3 min (minor) and 89.8 min (major)]; [α]_D^{20} = +29.9 (c 1.4, CHCl_3); ^1H NMR (400 MHz, TCE-D_2): δ = 7.12–7.08 (m, 1H), 6.99–6.93 (m, 2H), 3.78–3.53 (m, 2H), 3.20–3.02 (m, 2H), 2.80 (dd, J = 9.0, 5.8 Hz, 1H), 2.46–2.08 (m, 2H), 2.34 (s, 3H), 1.71–1.16 (m, 1H); ^13C NMR (100 MHz, TCE-D_2): δ = 171.7, 171.6, 145.8, 145.2, 139.9, 135.6, 135.1, 128.3, 127.9, 127.7, 127.4, 127.0, 49.8, 49.7, 45.2, 45.1, 44.4, 43.9, 43.8, 43.0, 41.6, 41.4, 38.7, 38.4, 38.1, 32.8, 32.0, 30.2, 30.0, 27.9, 27.7, 27.4, 27.3, 26.1, 23.3; HRMS (ESI) m/z calc for C_{20}H_{27}ONa (M+Na)^+: 320.19849, found: 320.19803.

1-[(2-Exo-bicyclo[2.2.1]heptan-2-yl)-4-fluorophenyl]carbonyl]piperidine (3s)

99.9% ee [HPLC condition: Chiralpak AD-3 column, hexane/2-propanol = 200/1, flow = 1.3 mL/min, wavelength = 230 nm, t_R = 57.0 min (minor) and 58.0 min (major)]; [α]_D^{20} = +35.5 (c 2.0, CHCl_3); ^1H NMR (400 MHz, TCE-D_2): δ = 7.06–6.98 (m, 2H), 6.89–6.81 (m, 1H), 3.80–3.50 (m, 2H), 3.16–3.02 (m, 2H), 2.80 (dd, J = 8.5, 5.8 Hz, 1H), 2.41–2.10 (m, 2H), 1.77–1.21 (m, 1H); ^13C NMR (100 MHz, TCE-D_2): δ = 170.7, 170.6, 164.2 (d, J = 246 Hz), 149.2, 148.5, 134.4, 133.9, 129.0 (d, J = 8.6 Hz), 114.9, 114.7, 114.5, 113.8 (d, J = 21.9 Hz), 49.8, 49.7, 45.2, 45.0, 44.5, 44.0, 43.1, 41.7, 41.5, 38.6, 38.2, 38.1, 32.7, 31.9, 30.1, 29.9, 27.9, 27.7, 27.4, 27.2, 26.1; HRMS (ESI) m/z calc for C_{19}H_{24}ONFNa (M+Na)^+: 324.17341, found: 324.17330.
1-[(2-Exo-bicyclo[2.2.1]heptan-2-yl)-4-bromophenyl]carbonyl]piperidine (3t)

99.3% ee [HPLC condition: Chirapak AD-3 column, hexane/2-propanol = 200/1, flow = 1.3 mL/min, wavelength = 230 nm, tR = 59.1 min (minor) and 69.0 min (major)]; [α]D20 = +25.8 (c 1.0, CHCl3); 1H NMR (400 MHz, CDCl3): δ = 7.46 (t, J = 2.3 Hz, 1H), 7.33–7.29 (m, 1H), 6.98 (d, J = 8.1 Hz, 1H), 3.89–3.57 (m, 2H), 3.22–3.06 (m, 2H), 2.81 (dd, J = 9.1, 5.9 Hz, 1H), 2.46–2.19 (m, 2H), 1.84–1.20 (m, 14H); 13C NMR (100 MHz, CDCl3): δ = 169.2, 169.1, 146.5, 146.2, 135.2, 129.3, 129.1, 128.6, 128.4, 127.2, 127.0, 122.8, 122.7, 48.2, 48.0, 43.7, 43.2, 43.1, 42.3, 41.8, 40.4, 39.6, 36.9, 36.7, 36.4, 31.1, 30.3, 28.4, 28.2, 26.3, 26.1, 25.7, 25.6, 24.4; HRMS (ESI) m/z calc for C19H24ONBrNa (M+Na)+: 384.09335, found: 384.09306.

Methyl 3-(bicyclo[2.2.1]hept-5-en-2-yl)-4-[(pyrrolidin-1-yl)carbonyl]benzoate (3w)

99.3% ee [HPLC condition: Chirapak AD-3 column, hexane/2-propanol = 200/1, flow = 1.3 mL/min, wavelength = 230 nm, tR = 126.4 min (minor) and 164.2 min (major)]; [α]D20 = +49.5 (c 2.8, CHCl3); 1H NMR (400 MHz, CDCl3): δ = 8.05 (s, 3H), 7.89 (dd, J = 7.9, 1.8 Hz, 1H), 7.26 (d, J = 8.3 Hz, 1H), 6.25–6.21 (m, 2H), 6.16–6.12 (m, 2H), 3.93 (s, 3H), 3.68–3.59 (m, 2H), 3.21–3.06 (m, 2H), 3.03–2.95 (m, 2H), 2.88–2.75 (m, 1H), 2.01–1.80 (m, 4H), 1.71–1.49 (m, 4H); 13C NMR (100 MHz, CDCl3): δ = 169.1, 166.8, 142.9, 142.6, 137.4, 130.4, 127.1, 125.8, 52.2, 48.5, 47.3, 46.1, 45.3, 42.4, 40.0, 34.1, 25.9, 24.5; HRMS (ESI) m/z calc for C20H23O3NNa (M+Na)+: 348.15701, found: 348.15677.

Methyl 3-[(1S,2R,4R)-2,4-diethenylcyclopentyl]-4-[(pyrrolidin-1-yl)carbonyl]benzoate (5)

To a flame-dried round-bottom flask (100 ml), 3w (0.25 mmol) and dichloromethane (10 mL) were added under an N2 atmosphere. The resulting solution was sparged with ethylene gas. A Grubbs 1st generation catalyst (5 mol%) in dichloromethane (5mL) was syringed into a round-bottom flask. After being stirred for 12 h at ambient temperature, the solvents were removed by rotary evaporation, and the crude material was purified by silica gel column chromatography (eluent: hexane/AcOEt = 2/1). The solvent was evaporated to yield the pure compound 5.

99.4% ee [HPLC condition: Chirapak AD-3 column, hexane/2-propanol = 200/1, flow = 1.3 mL/min, wavelength = 230 nm, tR = 116.4 min (minor) and 141.5 min (major)]; [α]D20 = +9.58 (c 2.0, CHCl3); 1H NMR (400 MHz, CDCl3): δ = 8.08 (d, J = 1.2 Hz, 1H), 7.87 (dd, J = 8.1, 1.4 Hz, 1H), 7.23 (d, J = 8.1 Hz,
1H), 5.83 (ddd, J = 17.2, 9.9, 7.2 Hz, 1H), 5.70–5.57 (m, 1H), 5.02 (dt, J = 17.2, 1.4 Hz, 1H), 4.94–4.79 (m, 3H), 3.94 (s, 3H), 3.65 (t, J = 7.2 Hz, 2H), 3.15–3.03 (m, 3H), 2.96–2.76 (m, 2H), 2.18–1.78 (m, 7H), 1.45 (dd, J = 22.9, 11.2 Hz, 1H); 13C NMR (100 MHz, CDCl3): δ = 168.7, 166.7, 142.6, 142.2, 140.3, 130.8, 128.5, 127.1, 125.6, 114.6, 112.8, 53.0, 52.2, 48.7, 47.3, 45.4, 42.6, 41.4, 40.5, 25.9, 24.5: HRMS (ESI) m/z calc for C22H27O3NNa (M+Na)+: 376.18831, found: 376.18801.
X-ray Crystal Structure of Compound 3b

Data Collection

A colorless block crystal of $\text{C}_2\text{H}_2\text{O}_2$ having approximate dimensions of 0.627 x 0.438 x 0.374 mm was mounted on a glass fiber. All measurements were made on a Rigaku R-AXIS RAPID diffractometer using graphite monochromator Cu-Kα radiation.

The crystal-to-detector distance was 127.40 mm.

Cell constants and an orientation matrix for data collection corresponded to a primitive orthorhombic cell with dimensions:

\[
a = 7.16564(15) \, \text{Å} \\
b = 12.5866(2) \, \text{Å} \\
c = 17.3312(4) \, \text{Å} \\
V = 1563.11(6) \, \text{Å}^3
\]

For $Z = 4$ and F.W. = 292.38, the calculated density is 1.242 g/cm$^3$. The reflection conditions of:

- $h00$: $h = 2n$
- $0k0$: $k = 2n$
- $00l$: $l = 2n$

uniquely determine the space group to be:

$P2_12_12_1$ (#19)

The data were collected at a temperature of $-150 \pm 1^\circ\text{C}$ to a maximum $2\theta$ value of 136.5$^\circ$. A total of 30 oscillation images were collected. A sweep of data was done using $w$ scans from 80.0 to 260.0$^\circ$ in 30.00$^\circ$ step, at $c=54.0^\circ$ and $f = 0.0^\circ$. The exposure rate was 60.0 [sec/\(^\circ\)]. A second sweep...
was performed using \( \omega \) scans from 80.0 to 260.0\(^\circ\) in 30.00\(^\circ\) step, at \( c = 54.0^\circ \) and \( f = 90.0^\circ \). The exposure rate was 60.0 \([\text{sec./}^\circ]\). Another sweep was performed using \( \omega \) scans from 80.0 to 260.0\(^\circ\) in 30.00\(^\circ\) step, at \( c = 54.0^\circ \) and \( f = 195.0^\circ \). The exposure rate was 60.0 \([\text{sec./}^\circ]\). Another sweep was performed using \( \omega \) scans from 80.0 to 260.0\(^\circ\) in 30.00\(^\circ\) step, at \( c = 54.0^\circ \) and \( f = 270.0^\circ \). The exposure rate was 60.0 \([\text{sec./}^\circ]\). Another sweep was performed using \( \omega \) scans from 80.0 to 260.0\(^\circ\) in 30.00\(^\circ\) step, at \( c = 0.0^\circ \) and \( f = 0.0^\circ \). The exposure rate was 60.0 \([\text{sec./}^\circ]\). The crystal-to-detector distance was 127.40 mm. Readout was performed in the 0.100 mm pixel mode.

**Data Reduction**

Of the 15757 reflections were collected, where 2857 were unique (\( R_{\text{int}} = 0.0433 \)); equivalent reflections were merged.

The linear absorption coefficient, \( m \), for Cu-Ka radiation is 6.200 cm\(^{-1}\). An empirical absorption correction was applied which resulted in transmission factors ranging from 0.697 to 0.793. The data were corrected for Lorentz and polarization effects.

**Structure Solution and Refinement**

The structure was solved by direct methods and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined using the riding model. The final cycle of full-matrix least-squares refinement on \( F^2 \) was based on 2857 observed reflections and 201 variable parameters and converged (largest parameter shift was 0.07 times its esd) with unweighted and weighted agreement factors of:

\[
R1 = \frac{\sum |F_o| - |F_c|}{\sum |F_o|} = 0.0360
\]

\[
wR2 = \frac{\sum (w(F_o^2 - F_c^2)^2)}{\sum w(F_o^2)^2}^{1/2} = 0.0994
\]

The goodness of fit was 0.78. Unit weights were used. Plots of \( S \cdot w(\sum (|F_o| \cdot |F_c|)^2) \) versus \( |F_o| \), reflection order in data collection, \( \sin \theta/\lambda \) and various classes of indices showed no unusual
trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.12 and -0.18 e/Å³, respectively. The final Flack parameter was 0.01(10), indicating that the present absolute structure is correct.

Neutral atom scattering factors were taken from International Tables for Crystallography (IT), Vol. C, Table 6.1.1.4. Anomalous dispersion effects were included in Fcalc; the values for Df and Df'' were those of Creagh and McAuley. The values for the mass attenuation coefficients are those of Creagh and Hubbell. All calculations were performed using the CrystalStructure crystallographic software package except for refinement, which was performed using SHELXL2013.
### EXPERIMENTAL DETAILS

#### A. Crystal Data

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>Empirical Formula</td>
<td>C$<em>{20}$H$</em>{20}$O$_2$</td>
</tr>
<tr>
<td>Formula Weight</td>
<td>292.38</td>
</tr>
<tr>
<td>Crystal Color, Habit</td>
<td>colorless, block</td>
</tr>
<tr>
<td>Crystal Dimensions</td>
<td>0.627 X 0.438 X 0.374 mm</td>
</tr>
<tr>
<td>Crystal System</td>
<td>orthorhombic</td>
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<tr>
<td>Lattice Type</td>
<td>Primitive</td>
</tr>
<tr>
<td>Lattice Parameters</td>
<td></td>
</tr>
<tr>
<td>a</td>
<td>7.16564(15) Å</td>
</tr>
<tr>
<td>b</td>
<td>12.5866(2) Å</td>
</tr>
<tr>
<td>c</td>
<td>17.3312(4) Å</td>
</tr>
<tr>
<td>V</td>
<td>1563.11(6) Å$^3$</td>
</tr>
<tr>
<td>Space Group</td>
<td>P2$_1$2$_1$2$_1$ (#19)</td>
</tr>
<tr>
<td>Z value</td>
<td>4</td>
</tr>
<tr>
<td>D$_{calc}$</td>
<td>1.242 g/cm$^3$</td>
</tr>
<tr>
<td>F$_{000}$</td>
<td>624.00</td>
</tr>
<tr>
<td>m(CuKa)</td>
<td>6.200 cm$^{-1}$</td>
</tr>
</tbody>
</table>
B. Intensity Measurements

Diffractometer

R-AXIS RAPID

Radiation

CuKa (λ = 1.54187 Å)

Graphite monochromator

Voltage, Current

40kV, 40mA

Temperature

-150.0°C

Detector Aperture

460.0 x 256.0 mm

Data Images

30 exposures

w oscillation Range (c=54.0, f=0.0) 80.0 - 260.0°

Exposure Rate

60.0 sec./°

w oscillation Range (c=54.0, f=90.0) 80.0 - 260.0°

Exposure Rate

60.0 sec./°

w oscillation Range (c=54.0, f=195.0) 80.0 - 260.0°

Exposure Rate

60.0 sec./°

w oscillation Range (c=54.0, f=270.0) 80.0 - 260.0°

Exposure Rate

60.0 sec./°

w oscillation Range (c=0.0, f=0.0) 80.0 - 260.0°

Exposure Rate

60.0 sec./°

Detector Position

127.40 mm

Pixel Size

0.100 mm

2θ max

136.5°

No. of Reflections Measured

Total: 15757

Unique: 2857 (Rint = 0.0433)

Parsons quotients (Flack x parameter): 992

Corrections

Lorentz polarization

Absorption

(trans. factors: 0.697 - 0.793)
C. Structure Solution and Refinement

<table>
<thead>
<tr>
<th>Structure Solution</th>
<th>Direct Methods (SHELXS2013)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refinement</td>
<td>Full-matrix least-squares on F^2</td>
</tr>
<tr>
<td>Function Minimized</td>
<td>S w (Fo^2 · Fc^2)^2</td>
</tr>
<tr>
<td>Least Squares Weights</td>
<td>w = 1/ [ s^2(Fo^2) + (0.1000 · P)^2 + 0.0000 · P ]</td>
</tr>
<tr>
<td></td>
<td>where P = (Max(Fo^2,0) + 2Fc^2)/3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2q_{max} cutoff</th>
<th>136.5°</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anomalous Dispersion</td>
<td>All non-hydrogen atoms</td>
</tr>
<tr>
<td>No. Observations (All reflections)</td>
<td>2857</td>
</tr>
<tr>
<td>No. Variables</td>
<td>201</td>
</tr>
<tr>
<td>Reflection/Parameter Ratio</td>
<td>14.21</td>
</tr>
<tr>
<td>Residuals: R1 (I&gt;2.00s(I))</td>
<td>0.0360</td>
</tr>
<tr>
<td>Residuals: R (All reflections)</td>
<td>0.0386</td>
</tr>
<tr>
<td>Residuals: wR2 (All reflections)</td>
<td>0.0994</td>
</tr>
<tr>
<td>Goodness of Fit Indicator</td>
<td>0.784</td>
</tr>
<tr>
<td>Flack parameter (Parsons' quotients = 992)</td>
<td>0.01(10)</td>
</tr>
<tr>
<td>Max Shift/Error in Final Cycle</td>
<td>0.067</td>
</tr>
<tr>
<td>Maximum peak in Final Diff. Map</td>
<td>0.12 e^-/Å^3</td>
</tr>
<tr>
<td>Minimum peak in Final Diff. Map</td>
<td>-0.18 e^-/Å^3</td>
</tr>
</tbody>
</table>
Deuterium labeling experiments

General procedures of hydroarylation in presence of $\text{D}_2\text{O}$

To a flame-dried sealed tube, $[\text{Ir(cod)}]_2(\text{BARF}_4)$ (0.0125 mmol, 5 mol%) and $(R,R)$-$\text{S}$-$\text{Me}$-$\text{BIPAM}$ (0.0138 mmol, 5.5 mmol%) and 1,2-dichloroethane (1.0 mL) were added under an N$_2$ atmosphere. The solution was stirred at room temperature for 30 min, followed by the addition of arene (0.25 mmol), bicycloalkene (3.5 equiv) and $\text{D}_2\text{O}$ (10 equiv). The reaction mixture was then heated at 135 °C. After being stirred for 0.25 h, the mixture was purified by silica gel column chromatography (eluent: $n$-Hexane/AcOEt) to afford recovered substrate and hydroarylated product. Deuterium incorporation was confirmed on the integration ratio of the $^1\text{H}$ NMR spectra.

General procedures for KIE experiment

Two separate rate constants were determined by measuring formation of product at early stage of two reactions that were conducted separately, one with a substrate containing a C–H bond and one with a substrate containing an analogous C–D bond. To a
flame-dried sealed tube, [Ir(cod)]_2(BAr^F) (0.0125 mmol, 5 mol%) and \( (R,R^-S^-Me^-BIPAM) \) (0.0138 mmol, 5.5 mmol%) and 1,2-dichloroethane (1.0 mL) were added under an \( N_2 \) atmosphere. The solution was stirred at room temperature for 30 min, followed by the addition of arene (0.25 mmol), bicycloalkene (3.5 equiv). The reaction mixture was then heated at 135 °C. After being stirred for several minutes, the mixture was purified by silica gel column chromatography (eluent: \( n^-Hexane/AcOEt \)) to afford hydroarylated product.
4.6 References


9) Crystallographic data of 3b can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. (CCDC 1400933)


11) Reductive eliminations to form C–C bonds from the iridium center are rare or unknown. See Ref. 4e)
Conclusion

As described in this doctoral thesis, the author has demonstrated that a cationic iridium/Me·BIPAM complexes can serve as unique catalyst for the asymmetric direct hydroarylation of unsaturated compounds such as ketones and alkenes via C(sp²)–H bond activation. This means that cationic iridium/Me·BIPAM catalysts have activity not only for “the asymmetric insertion of double bonds” but also for “the directed C(sp²)–H bond activation”. In Chapter 2, the author described the convenient synthesis of 3·aryl·3·hydroxy·2·oxindole derivatives via the direct intramolecular hydroarylation of α·ketoamides and this reaction proceeds with high yields and high enantioselectivities. In Chapter 3, the detailed mechanism for asymmetric intramolecular hydroarylation of α·ketoamides is discussed. In Chapter 4, the author mentions the enantioselective asymmetric intermolecular direct hydroarylation of bicycloalkenes. This transformation was realized by using a newly developed sulfur-linked bis(phosphoramidite) ligand (S·Me·BIPAM). To our knowledge, these reactions are the first reports for highly enantioselective hydroarylation of unsaturated compounds. In addition, our developed reactions have a potential which can apply for the synthesis of chiral building blocks of medicines. However, “intermolecular” direct asymmetric hydroarylation of carbonyl compounds and imines is a very challenging and important task that remains to be addressed. Therefore, the author believes that our achievement contribute for the further development of this research areas.
List of Publications

(1) Cationic Ir/Me-BIPAM-Catalyzed Asymmetric Intramolecular Direct Hydroarylation of α-Ketoamides


*Selected as “Back Cover”*

*Highlighted in Synfacts 2014, 10, 493.*

(2) Cationic Iridium/S-Me-BIPAM-Catalyzed Direct Asymmetric Intermolecular Hydroarylation of Bicycloalkenes


*Highlighted in Synfacts 2015, 11, 1067.*

*Highlighted in Advances in Engineering.*

(3) Scope and Mechanistic Studies of the Cationic Ir/Me-BIPAM-Catalyzed Asymmetric Intramolecular Direct Hydroarylation Reaction

**T. Shirai, Y. Yamamoto, Organometallics 2015, 34, 3459–3463.**
Other Publications

(1) Rhodium-Catalyzed 1,4-Addition of Lithium 2-Furyltriolborates to Unsaturated Ketones and Esters for Enantioselective Synthesis of γ-Oxo-carboxylic Acids by Oxydation of the Furryl Ring with Ozone

(2) Ru/Me-BIPAM-Catalyzed Asymmetric Addition of Arylboronic Acids to Aliphatic Aldehydes and α-Ketoesters
*Selected as “Molecules Best Paper Award 2015” in Molecules** **2015**, *20*, 1751–1754.

(3) Asymmetric Addition of Arylboronic Acids to Glyoxylate Catalyzed by a Ruthenium/Me-BIPAM Complex

(4) Me-BIPAM for the Synthesis of Optically Active 3-Aryl-3-Hydroxy-2-Oxindoles by Ruthenium-Catalyzed Addition of Arylboronic Acids to Isatins
Acknowledgements

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Tomohiko Shirai
March, 2016