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**Development of Asymmetric Hydroarylation
of Unsaturated Bond *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

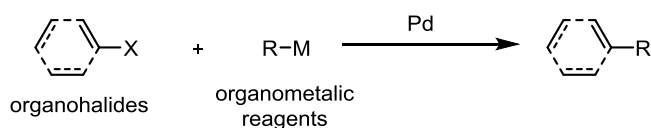
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Chapter 1 Introduction

Organometallic chemistry has contributed to remarkable industrial development for over sixty years since the discovery of polymerization catalyst by Ziegler.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 Nobel 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.

● *cross-coupling reaction*

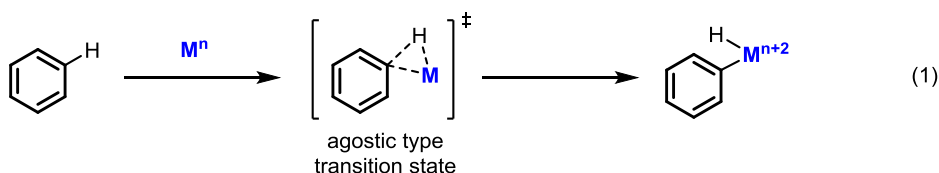


Meanwhile, regioselective cleavage and functionalization of stable and abundant C–H bond were recognized as an intriguing research subject in the field of organometallic chemistry. However, C–H covalent bond shows low reactivity because of the large bond dissociation energy compared with carbon-halogen bond (105 kcal/mol for H–CH₃, and 110 kcal/mol for H–C₆H₅). Murahashi group and Dubek group have been reported cyclometalation reaction of azobenzene with Co₂(CO)₈ or Cp₂Ni respectively as the first examples of intramolecular oxidative addition of C(sp²)–H bond.²⁾ Besides, the first intermolecular oxidative addition of C(sp²)–H bond was discovered by Chatt and Davidson with ruthenium complex in 1965.³⁾ These discoveries established the foundation of following studies clearly.

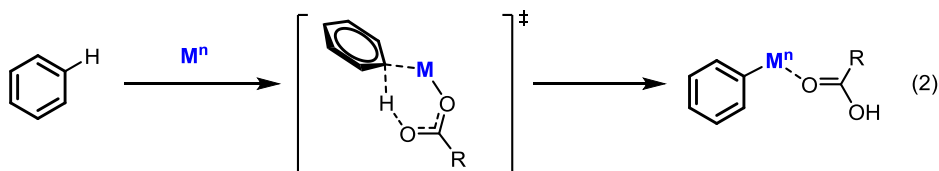
In general, transition metal-catalyzed C–H bond cleavage can be classified into four types;⁴⁾ oxidative addition (Scheme 1.1 (1)), concerted metalation/deprotonation process (CMD) (Scheme 1.1 (2)), σ -bond metathesis (Scheme 1.1 (3)), aromatic electrophilic substitution (Friedel-Crafts type reaction) (Scheme 1.1 (4)). In case of (1), the transition-metal hydride intermediates are formed by oxidative addition *via* agostic type transition state. In contrast, M–C bond forms simultaneously

with abstraction of proton by acetate ligand in CMD mechanism. σ -bond metathesis occurs in four-membered ring transition state consisting of metal-X σ -bond and the arene C-H σ -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.

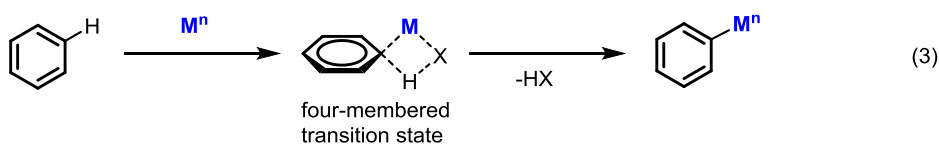
• *oxidative addition*



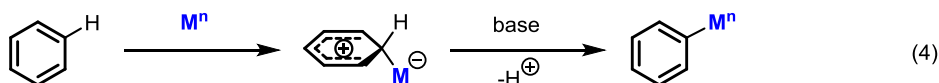
• *concerted metalation / deprotonation (CMD)*



• *σ -bond metathesis*



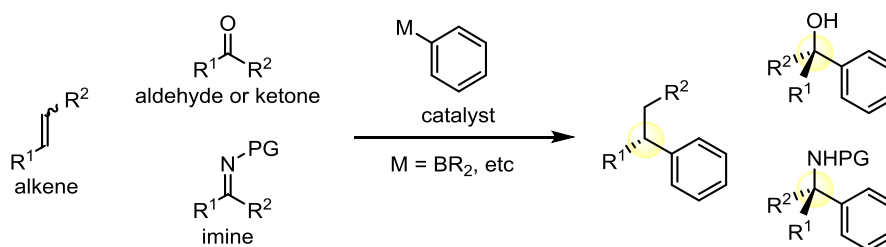
• *aromatic electrophilic substitution (Friedel-Crafts type)*



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=N⁶⁾ and C=C⁷⁾ 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.



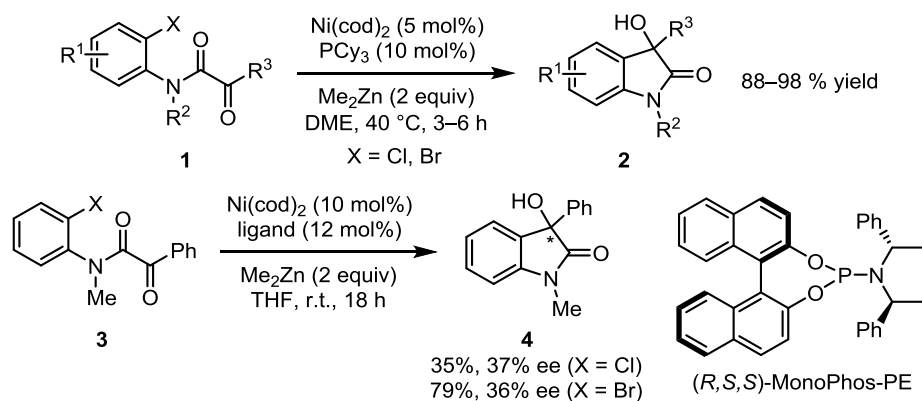
Scheme 1.2 Asymmetric hydroarylation of unsaturated compounds

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

1.1.1.1 Addition to C–O double bond

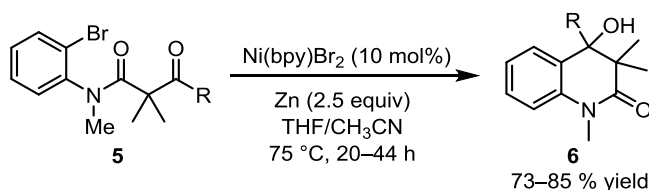
The addition of aryl halides to carbonyl groups is an atom-economical synthetic method compared with the transformation employing an organometallic reagent, to give the benzylic alcohol derivatives.⁸⁾

Gao and co-workers achieved the Nickel-catalyzed addition of aryl chlorides to α -ketoamides **1** through C(sp²)–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 PCy₃ catalyst, a series of α -ketoamides **1** was hydroarylated to give oxindole products **2** in high yields (Scheme 1.3).^{8a)} 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

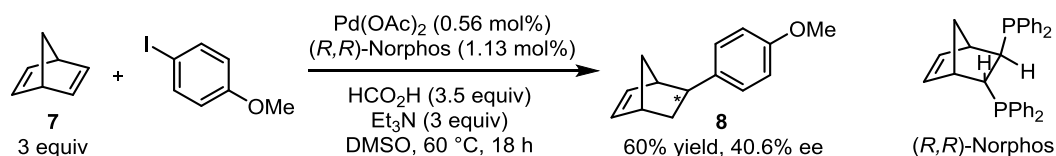
They have also reported the six-membered ring formation reaction by C–Br bond activation/insertion strategy (Scheme 1.4).^{8b)} As mentioned in this section, there are only limited examples in this research field.



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

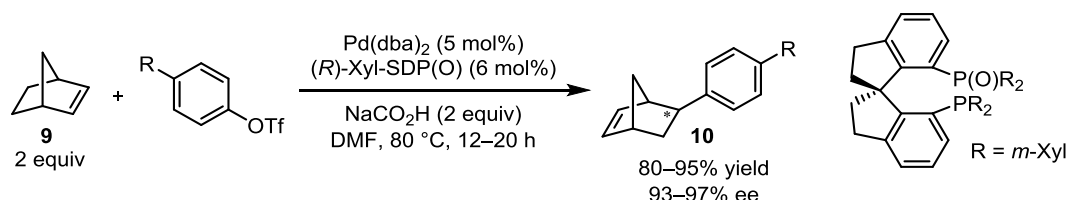
1.1.1.2 Addition to C–C double bond

There are several reports for a palladium-catalyzed Heck-type hydroarylation of alkenes to date and selected examples were shown in this section.⁹⁾ In 1991, Brunner and Kramler developed the first asymmetric hydroarylation of norbornadiene **7** in the presence of Pd(II)/norphos catalyst.^{9a)} 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).



Scheme 1.5 Palladium-catalyzed addition of aryl halides to β -ketoamides

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).⁹ⁱ⁾



Scheme 1.6 Palladium-catalyzed asymmetric hydroarylation of bicyclic olefins

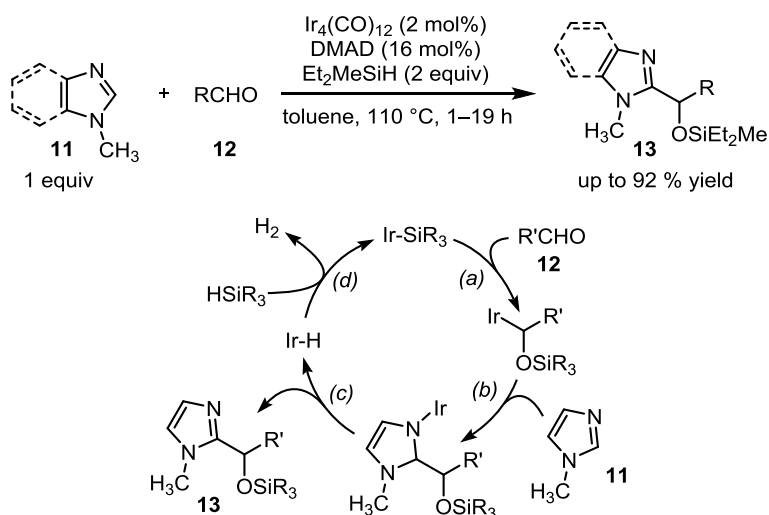
1.1.2 Transition-metal-catalyzed direct addition of aryl C(sp²)-H bond to double bond

1.1.2.1 Direct addition to C–O double bond

The catalytic C(sp²)-H bond functionalization is one of the key strategies in the field of transition-metal chemistry.¹⁰⁾ 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.

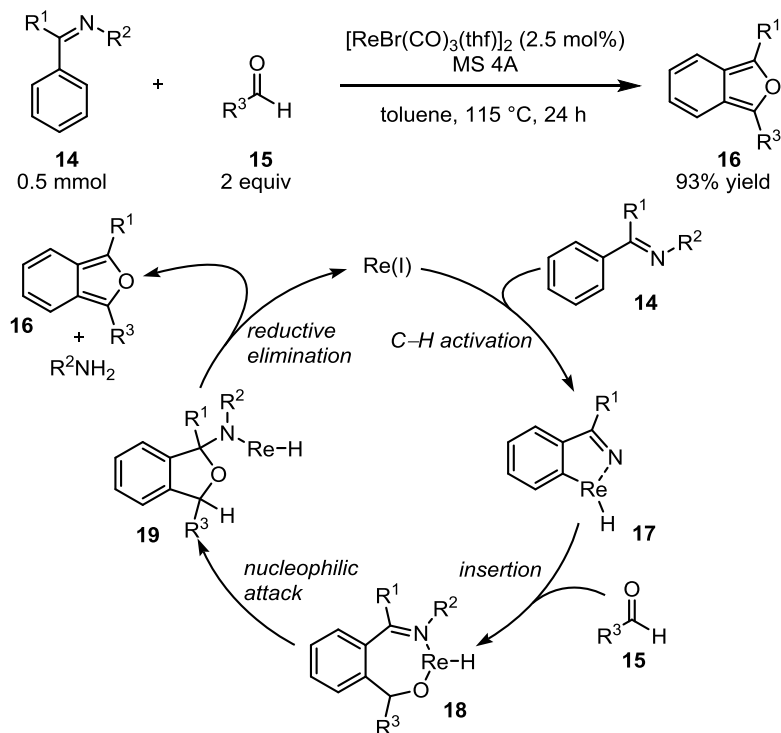
In 2002, Murai and co-workers discovered the Ir-catalyzed coupling reactions of imidazoles **11** with aldehydes **12** (Scheme 1.7).¹¹⁾ In the presence of [Ir₄(CO)₁₂], DMAD and hydrosilane, various aliphatic or aryl aldehydes underwent a coupling reaction at 110 °C to give 2-alkylimidazoles **13**. 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.



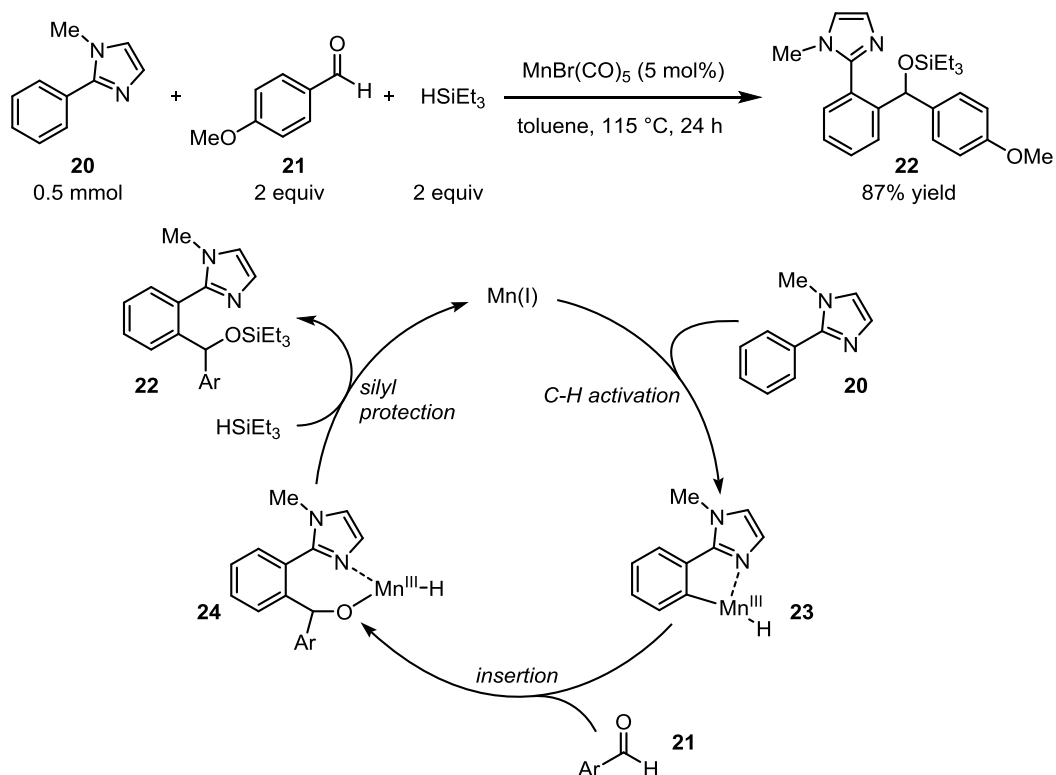
Scheme 1.7 Iridium-catalyzed coupling reaction of imidazoles with aldehydes

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).¹²⁾ In the reaction of ketimine **14** with aldehyde **15** in the presence of a rhenium catalyst, $[\text{ReBr}(\text{CO})_3(\text{thf})]_2$, 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**.



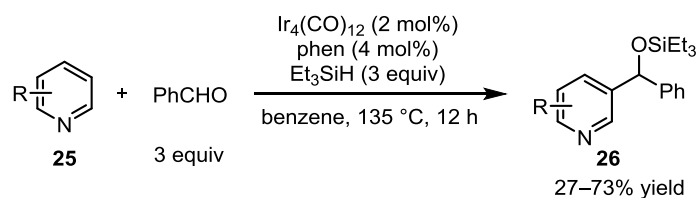
Scheme 1.8 Rhenium-catalyzed insertion of aldehydes into a C-H bond

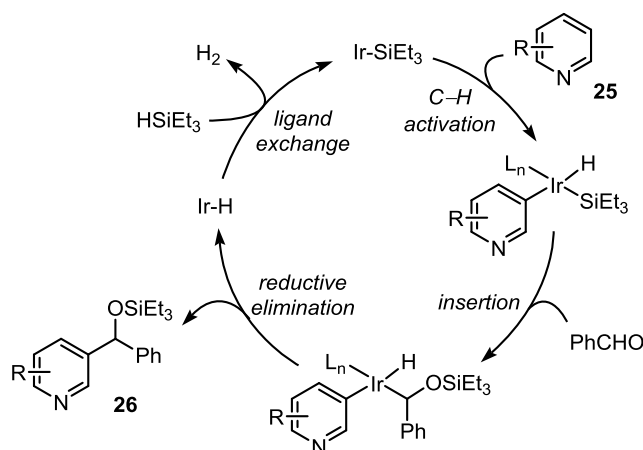
In 2007, Takai and co-workers also reported Manganese-catalyzed insertion of aldehydes into a C-H bond (Scheme 1.9).¹³⁾ They found that a mixture of 1-methyl-2-phenyl-1*H*-imidazole **20**, and aryl aldehyde **21** and triethylsilane in the presence of 5.0 mol% of $\text{MnBr}(\text{CO})_5$ in toluene 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^{I} complex to give the $\text{Ar-Mn}^{\text{III}}\text{-H}$ 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.¹⁴⁾



Scheme 1.9 Manganese-catalyzed insertion of aldehydes into a C–H bond

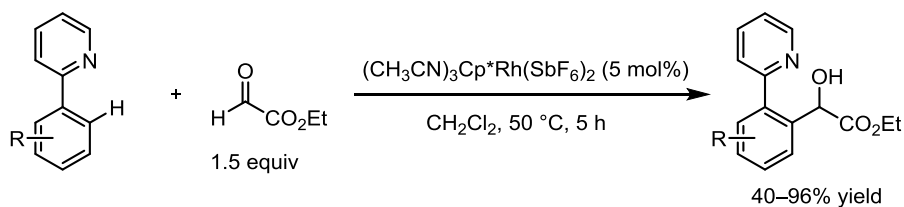
In addition, Ir-catalyzed direct addition of pyridyl $\text{C}(\text{sp}^2)\text{--H}$ bond to aldehydes was reported by Shi and co-workers in 2011 (Scheme 1.10).¹⁵ Using 2 mol% of Ir/phen catalyst, a series of pyridines **25** was alkylated selectively at 3-position. The plausible mechanism including 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.

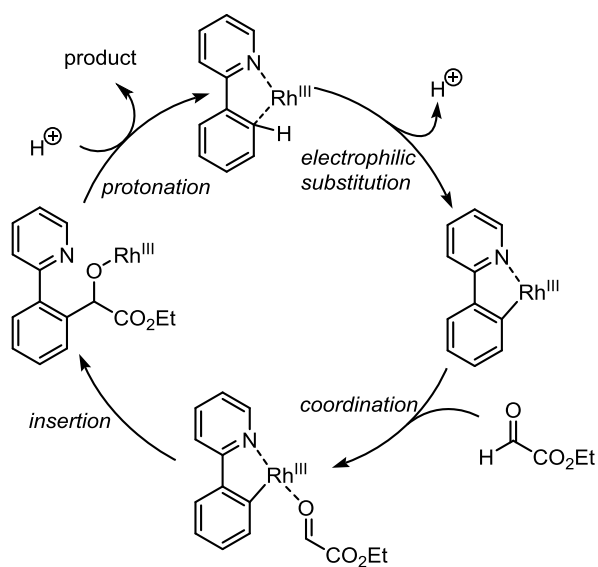




Scheme 1.10 Iridium-catalyzed direct addition of pyridyl C-H bond to aldehydes

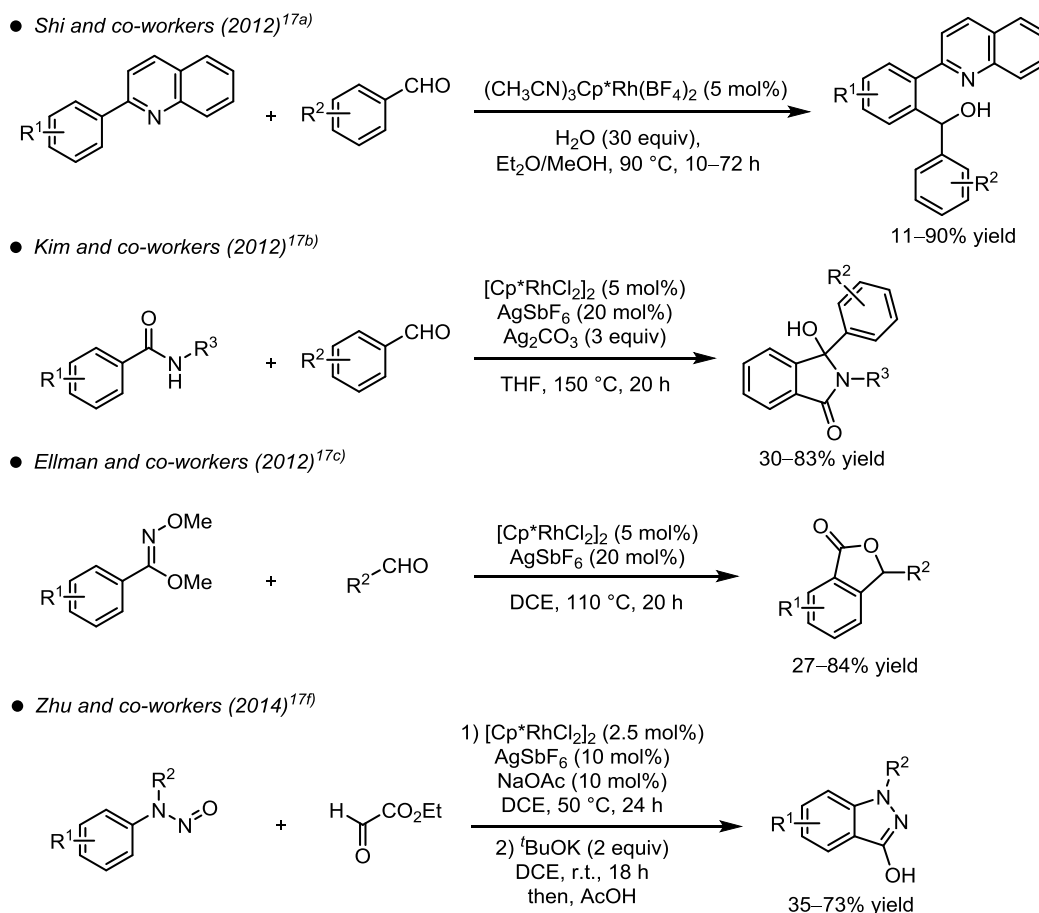
Li and co-workers established similar type of C-H bond addition reaction in mild conditions catalyzed by a cationic cyclopentadienyl rhodium complex (Scheme 1.11).¹⁶⁾ They pointed to cationic catalyst to increase its Lewis acidity because a low Lewis acidic neutral complex displayed no catalytic activity. The screening of counter anion of catalyst revealed that SbF₆ is best one while BF₄ and PF₆ 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 CF₃, NO₂, CO₂Me 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.





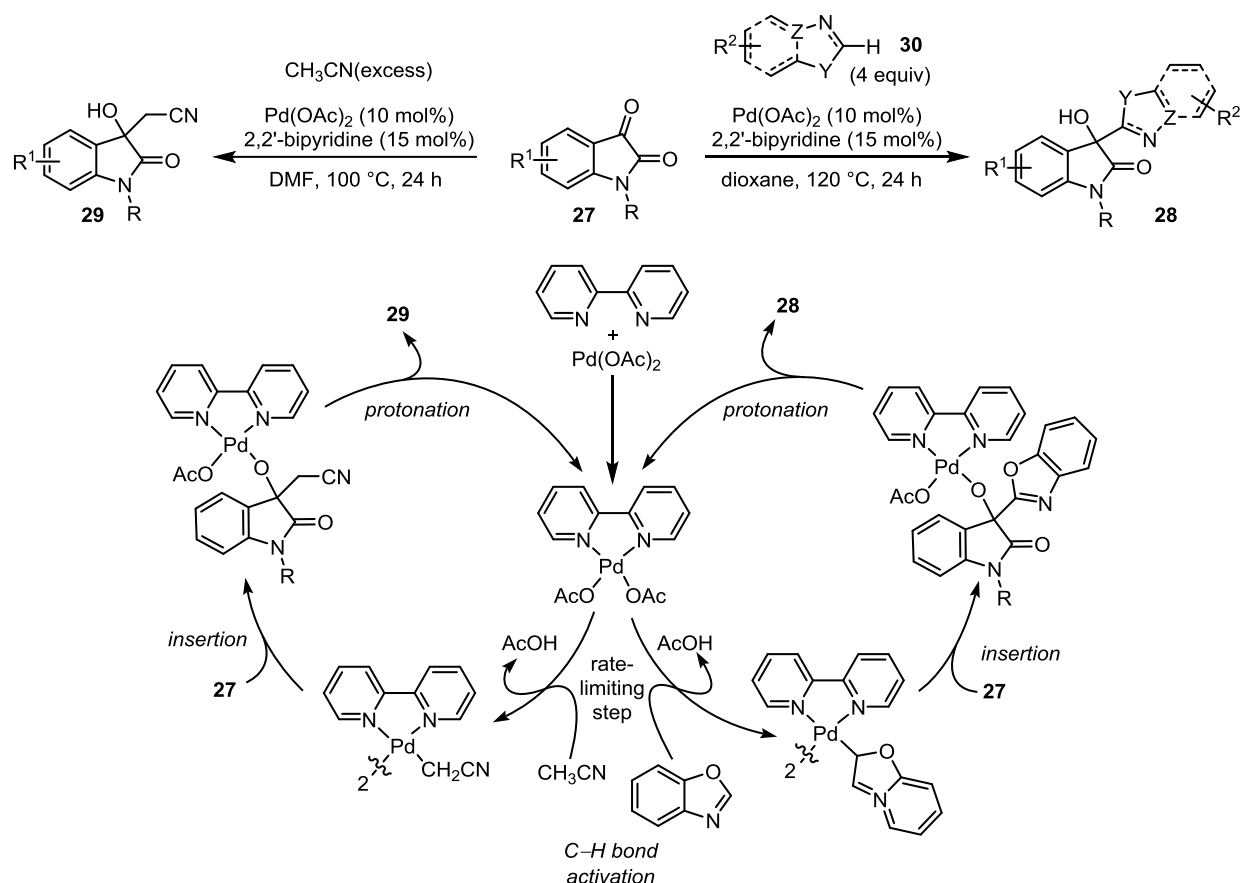
Scheme 1.11 Cationic Cp^*Rh -catalyzed hydroarylation of glyoxylates

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 1.12.¹⁷⁾



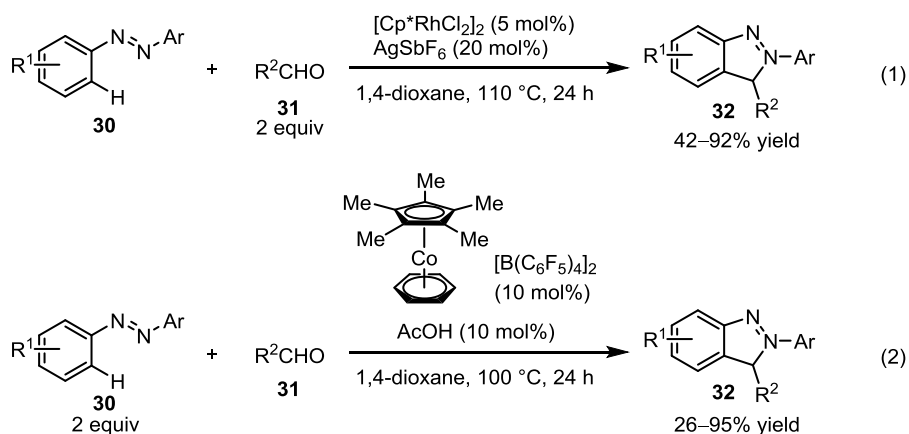
Scheme 1.12 Cationic Cp*Rh-catalyzed hydroarylation

Yang et al. successfully achieved the development of first Pd^{II}-catalyzed C(sp²)-H or C(sp³)-H addition to isatins through direct C-H bond activation for the synthesis of 3-substituted 3-hydroxy-2-oxindoles (Scheme 1.13).¹⁸⁾ They have also clarified that the newly synthesized 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.



Scheme 1.13 Palladium-catalyzed C(sp²)-H or C(sp³)-H bond addition to isatin

Very Recently, Ellman and co-workers reported the Rh^{III}-catalyzed indazole synthesis by C-H bond addition/cyclization cascades (Scheme 1.14 (1)).^{17e} In this reaction, various aldehydes **31** and azobenzenes **30** were found to be good substrate to give N-aryl-2H-indazoles **32**. Subsequently, they have successfully extended to the similar strategy with Co^{III} catalyst that is abundant on the earth (Scheme 1.14 (2)).¹⁹ The B(C₆F₅)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.

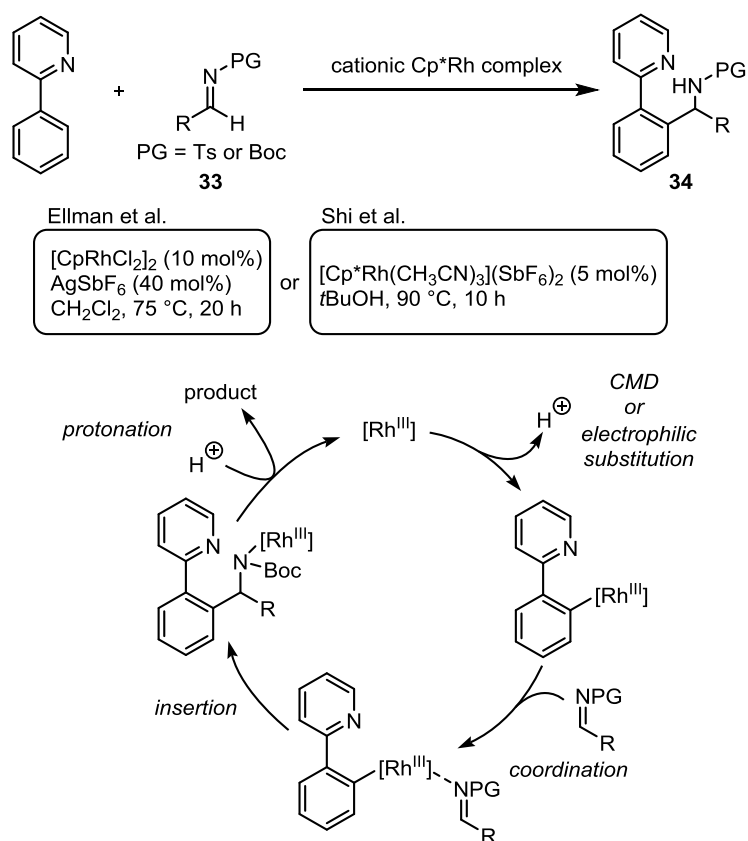


Scheme 1.14 First cobalt-catalyzed direct C–H bond addition to various aldehydes

1.1.2.2 Direct addition to C–N double bond

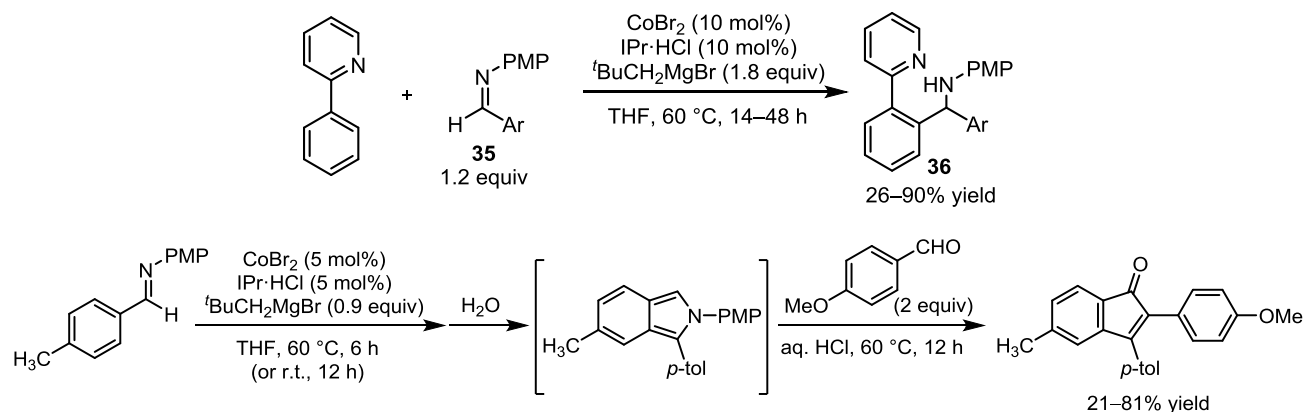
As shown in section 1.1, hydroarylation of carbon–nitrogen double bonds through C–H bond functionalization became a useful transformation to make the beneficial amine derivatives. Rh^{III} complex system is currently the most commonly used as active catalyst.²⁰⁾ Some selected examples are given below.

In 2011, Ellman^{20a)} and Shi^{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*RhCl₂]₂ and AgSbF₆, a variety of N-protected aldimines **33** underwent the hydroarylation at 75–90 °C to provide a branched amine products **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^{III} catalyst were triggered by Ellman and Shi's brilliant works.



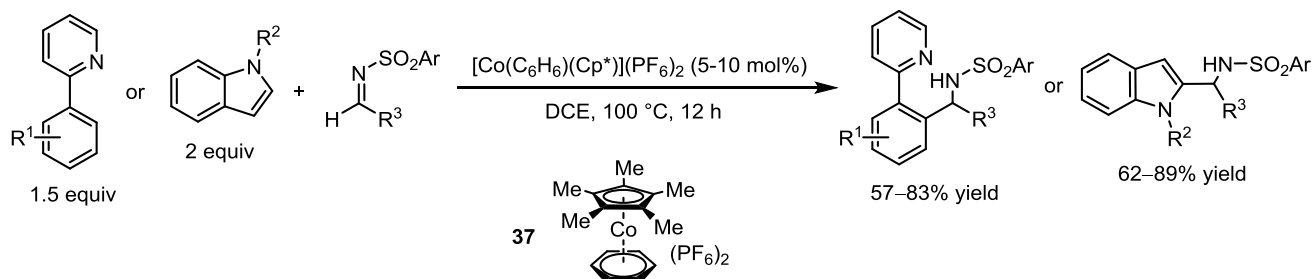
Scheme 1.15 First transition-metal-catalyzed direct C–H bond addition to aldimines

In 2012, Yoshikai and co-workers investigated the cobalt-catalyzed similar type of reaction *via* C–H bond functionalization (Scheme 1.16).²¹⁾ They described an effective hydroarylation and self-coupling of N-aryl aldimine **35** catalyzed by 10 mol% of $CoBr_2$ and $IPr \cdot HCl$.



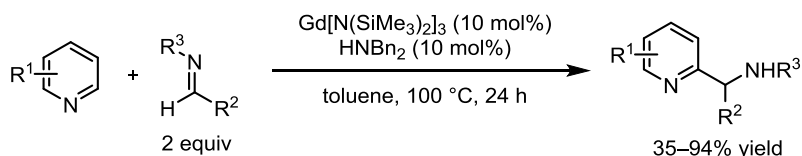
Scheme 1.16 Cobalt-catalyzed direct C–H bond addition to aldimines and application

Similar works with high-valent cationic Cp*Co complex were demonstrated by Kanai and co-workers in 2013 (Scheme 1.17).²²⁾ They found that the hydroarylation of aldimine via arene C–H bond cleavage or pyridyl C–H bond cleavage proceeded smoothly when using the $[\text{Co}(\text{C}_6\text{H}_6)(\text{Cp}^*)](\text{PF}_6)_2$ **37** as the catalyst, giving the desired alkylated product in moderate to good yields.



Scheme 1.17 Cobalt-catalyzed direct C–H bond addition to aldimines

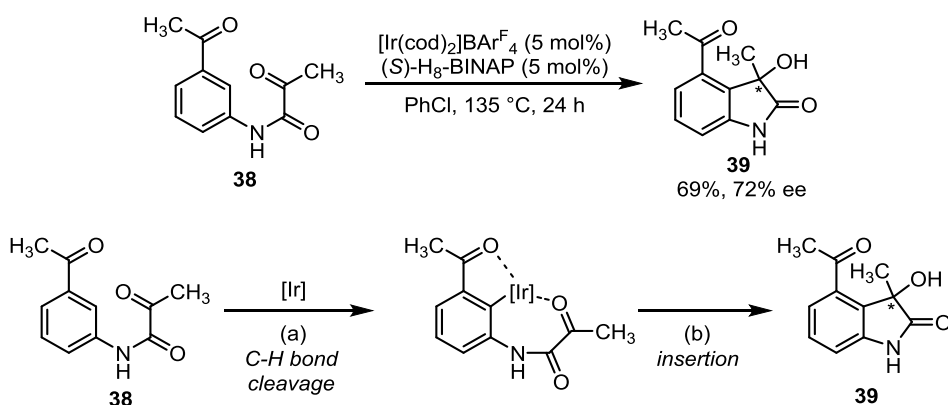
Very recently, it is first demonstrated by Mashima et al. that the rare-earth metal such as Gd, Y, and Nd that has the catalytic activity for pyridyl C(sp²)–H bond addition to aldimines (Scheme 1.18).²³⁾ In this methodology, the catalytic amount of dibenzylamine plays an important role in catalytic cycle to generate the active species.



Scheme 1.18 Rare-earth-catalyzed pyridyl C–H bond addition to aldimines

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 **38** was reported by Shibata and co-workers (Scheme 1.19).²⁴⁾ In this case, C–H bond at most congested position was selectively cleaved by cationic iridium/ H_8 -BINAP complex at 135 °C to generate Aryl–M specie. It should be noted that this is the first example of enantioselective C(sp²)–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 **39**.

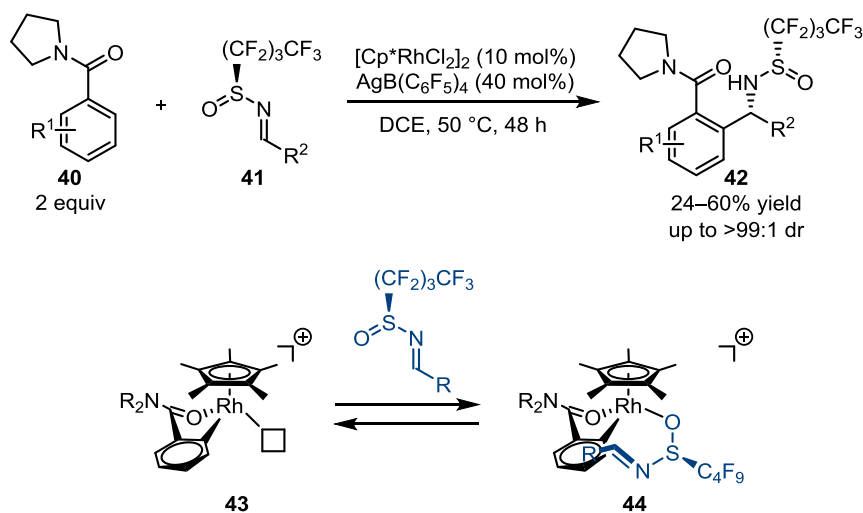


Scheme 1.19 Cationic iridium-catalyzed asymmetric C–H bond addition to carbonyl groups

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(sp²)–H bond addition to imines by asymmetric catalysis. In 2014, Ellman et al. reported the first diastereoselective intermolecular addition of C(sp²)–H bonds of benzamides **40** to N-perfluorobutanesulfinyl aldimines **41**.²⁵⁾ 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.



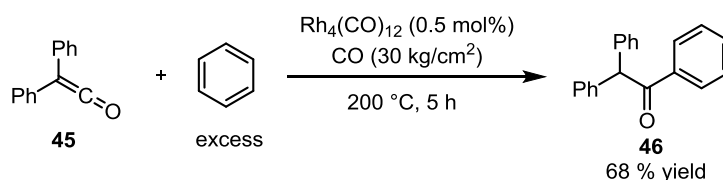
Scheme 1.20 Cp*Rh^{III}-catalyzed asymmetric direct addition to aldimine

1.1.2.5 Direct addition to C–C double bonds

Transition-metal-catalyzed aryl C(sp²)–H addition to alkenes, also known as hydroarylation,

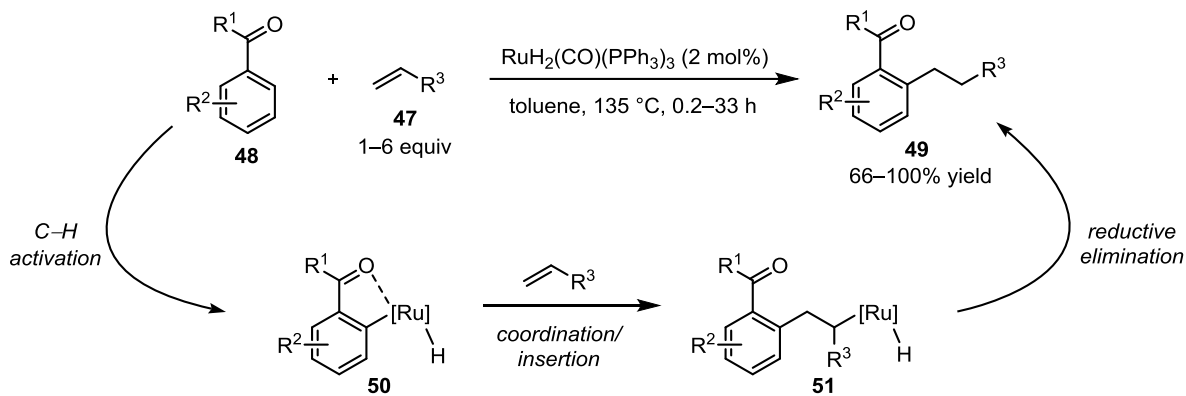
offers a straightforward route to alkylated arene without pre-activation such as an use of organometallic reagents. There are many examples in this research area compared with the direct addition to C–O and C–N double bonds to date.²⁶⁾ In this section, pioneering works and selected examples are shown below.

In 1978, Hong et al. reported the rhodium carbonyl cluster-catalyzed addition of arene to diphenylketene (Scheme 1.21).^{26a)} 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 $\text{Rh}_4(\text{CO})_{12}$, the hydroarylation of diphenylketene **45** with benzene proceeds to give α,α -diphenylacetophenone **46**.



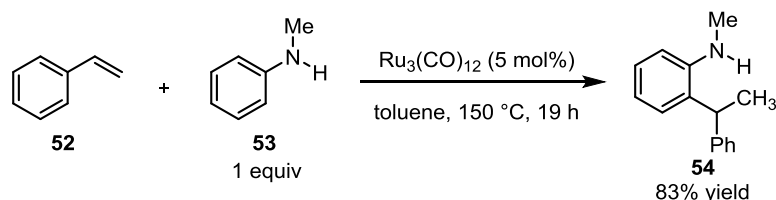
Scheme 1.21 Rhodium cluster-catalyzed C(sp²)–H addition to diphenylketene

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).^{26b)} They found that a mixture of olefin **47**, such as vinylsilane or styrene or ethylene derivatives, and aromatic ketone **48** in the presence of 2.0 mol% of $\text{RuH}_2(\text{CO})(\text{PPh}_3)_3$ in toluene at 135 °C provides the corresponding alkylated product **49** in high yields. In this report, C–H activation is occurred selectively in *ortho*-position of directing group to form intermediate **50**. Then, product was obtained by insertion of alkene and C–H forming reductive elimination from specie **51**. Since this report, similar type of addition reactions with chelation-assisted methodology has been reported.

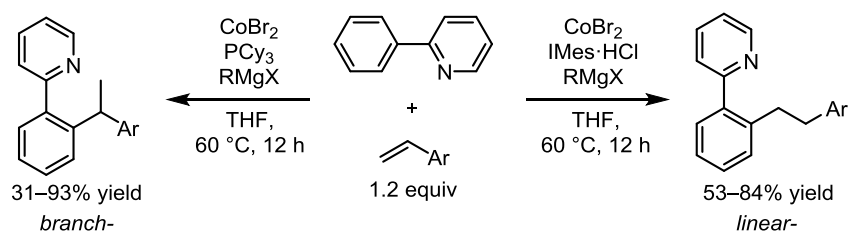


Scheme 1.22 Ruthenium-catalyzed direct hydroarylation of various alkenes

In addition, Uchimaru developed the ruthenium-catalyzed first branch-selective hydroarylation of alkene **52** with N-methylaniline **53** in 1999 (Scheme 1.23).^{26e)} 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).^{26g)} Using 10 mol% of $\text{CoBr}_2/\text{PCy}_3$, 80 mol% of $\text{Me}_3\text{SiCH}_2\text{MgBr}$ 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 $\text{CoBr}_2/\text{IMes}$ 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.

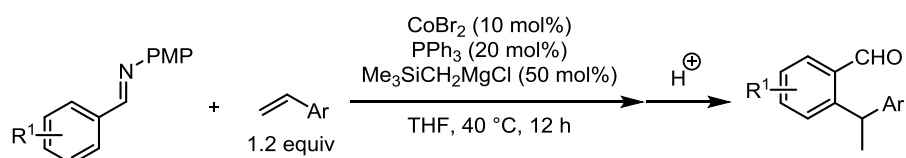


Scheme 1.23 Ruthenium-catalyzed first branch selective hydroarylation of styrene



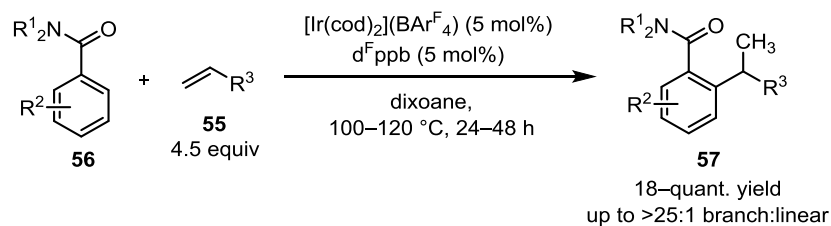
Scheme 1.24 Cobalt-catalyzed ligand-controlled branch selective hydroarylation of styrene

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).^{26h)} Treatment of imine group in crude product with acid produces the useful formyl functionality.



Scheme 1.25 Cobalt-catalyzed aldimine-directed branch selective hydroarylation of styrene

Recently, Bower and co-workers established the cationic iridium-catalyzed branch selective hydroarylation of alkenes **55** with benzamides **56** (Scheme 1.26).^{26i, 26l)} In this case, [Ir(cod)₂](BAr^F₄)/d^Fppb is most effective catalyst under the optimized condition, and mono-hydroarylation products **57** were solely produced with high yields and excellent branch selectivities.

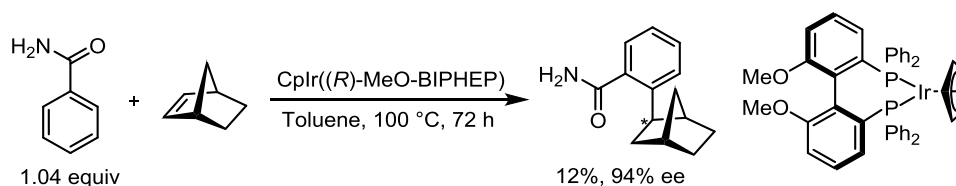


Scheme 1.26 Cationic iridium-catalyzed-branch selective hydroarylation

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.^{26m, 26n)} Further development of new hydroarylation and hydroheteroarylation reactions of alkenes is continuing.

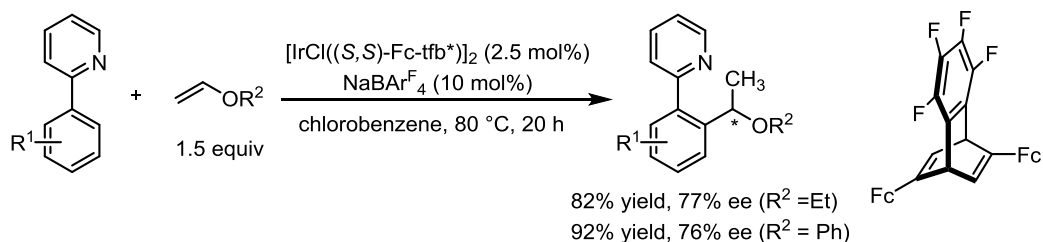
1.1.2.6 Direct asymmetric addition to C–C double bonds

Transition-metal-catalyzed asymmetric intramolecular C(sp²)-H addition to alkenes has been well studied by Ellman group²⁷⁾ and Cramer group.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.²⁹⁾ In 2000, Togni and co-workers developed the first iridium-catalyzed asymmetric intermolecular hydroarylation of 2-norbornene with benzamide (Scheme 1.27).^{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.



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).^{29d)} 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.

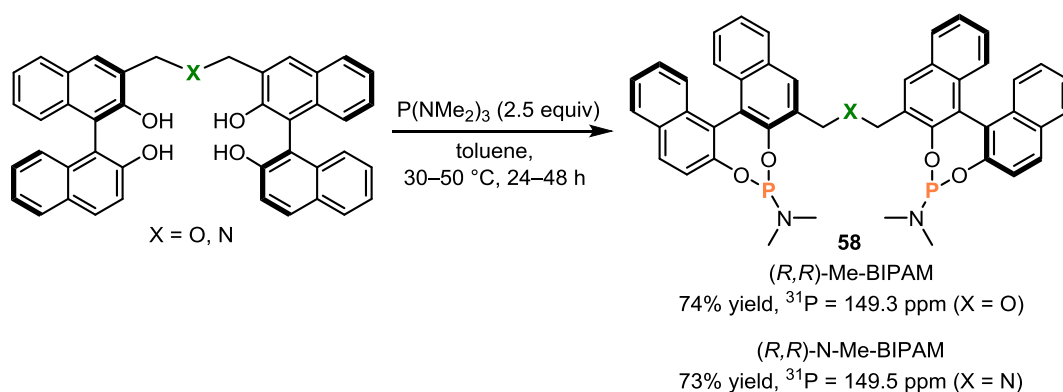


Scheme 1.28 Cationic iridium-catalyzed asymmetric hydroarylation of vinyl ethers

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).³⁰⁾ In general, phosphoramidite ligand has both a σ -donating ability derived from the inductive effect and π -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-naphthol.

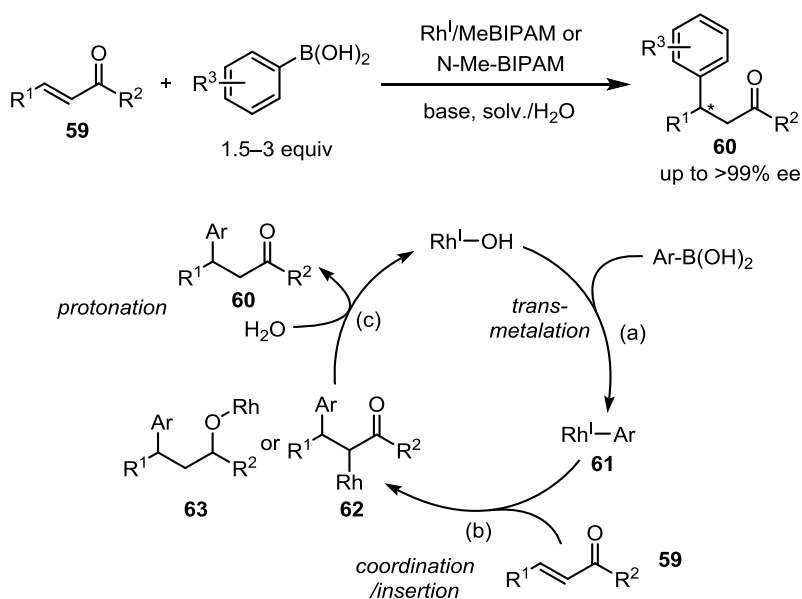


Scheme 1.29 Synthesis of Me-BIPAM ligands

1.2.2 Asymmetric hydroarylations of various unsaturated bonds with arylboronic acids

1.2.2.1 Asymmetric hydroarylation of electron-deficient olefins

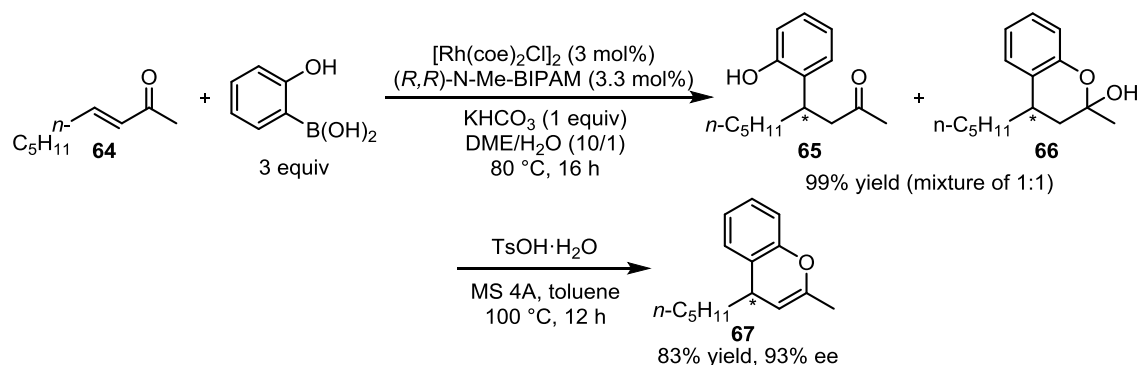
Transition-metal-catalyzed asymmetric hydroarylation of electron-deficient olefins, called as 1,4-addition or conjugate addition, is known as one of the most practical method to form an carbon–carbon bond in the field of synthetic organic chemistry.³¹⁾ Our group has already reported the rhodium/Me-BIPAM-catalyzed 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

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 $[\text{Rh}(\text{coe})_2\text{Cl}]_2$ 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

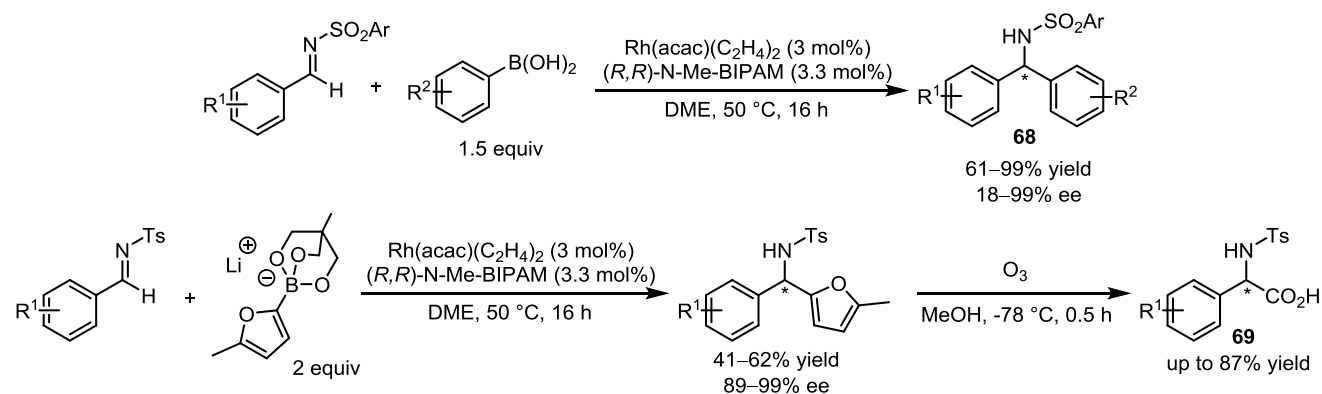
with TsOH to give the desired 2-methyl-4-pentyl-4H-chromene **67** with 83%, 93% ee.



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**^{32a)} and arylglycine **69**^{32b)} derivatives by Rh/*N*-Me-BIPAM-catalyzed asymmetric hydroarylation, called as 1,2-addition, with arylboronic reagents (Scheme 1.32). The amine products are produced with moderate to high yields and excellent enantioselectivities.



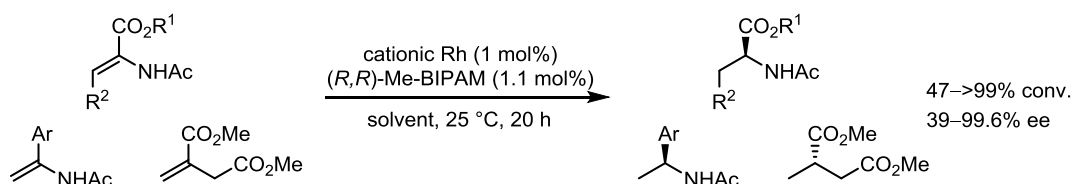
Scheme 1.32 Asymmetric 1,2-addition to aldimines with arylboronic reagents

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).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.

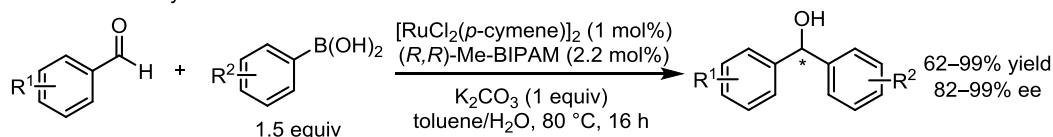
1.2.3 Asymmetric hydrogenation of α -dehydroamino esters, enamides, and dimethyl itaconates

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).³⁴⁾

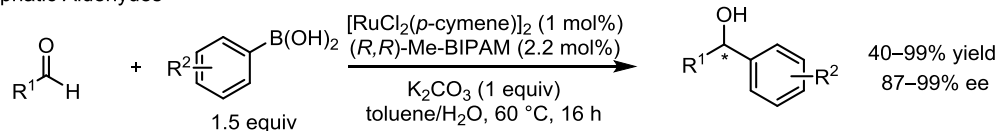


Scheme 1.34 Asymmetric hydrogenation catalyzed by cationic Rh/Me-BIPAM complex

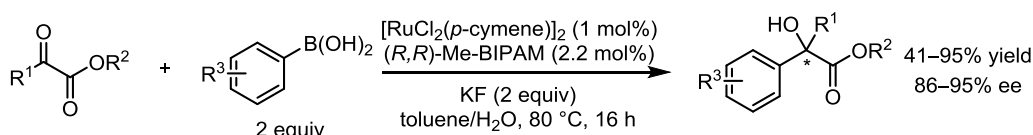
● Aromatic Aldehydes^{33a)}



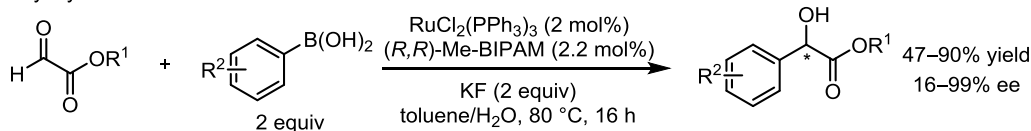
● Aliphatic Aldehydes^{33b)}



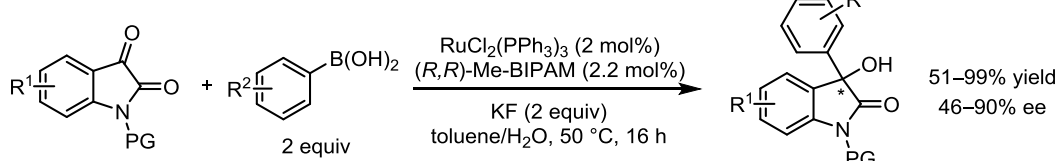
● α -Ketoesters^{33b)}



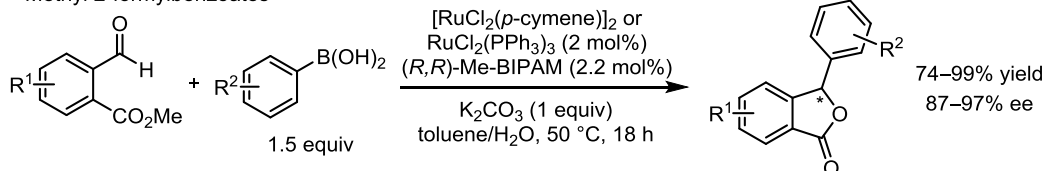
● Glyoxylates^{33c)}



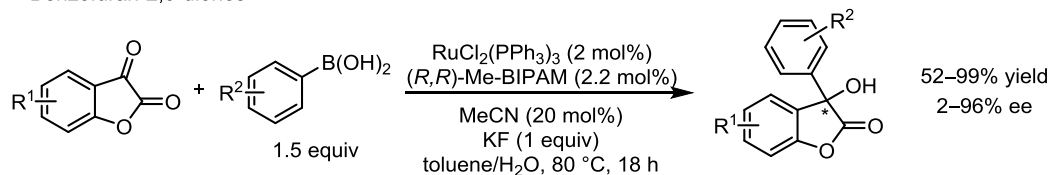
● Isains^{33d)}



● Methyl 2-formylbenzoates^{33e)}



● Benzofuran-2,3-diones^{33f)}

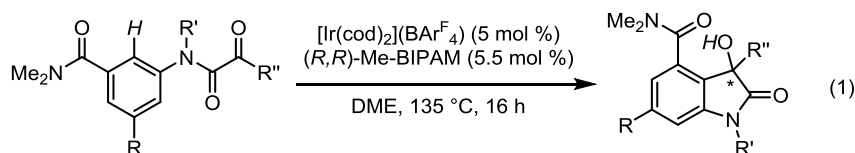


Scheme 1.33 Asymmetric 1,2-addition to carbonyl compounds with arylboronic acids

1.3 Survey of this thesis

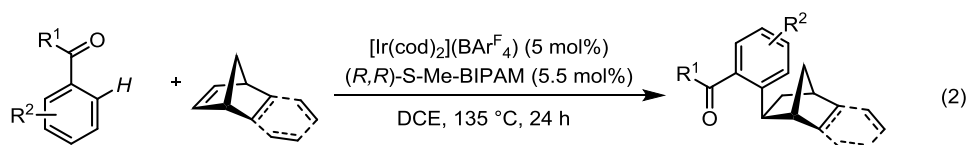
As described in previous sections, transition-metal-catalyzed C–H functionalization has emerged in recent years as a powerful tool for the formation of carbon–carbon bonds from simple starting materials. Very recently, it was shown that direct hydroarylation of imines, carbonyls and olefins through catalytic C–H bond activation provides a concise and highly efficient pathway to synthesize various building blocks. By contrast, only a few examples 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 α -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 $[\text{Ir}(\text{cod})_2](\text{BARF}_4)$ and the chiral O-linked bidentate phosphoramidite (*R,R*)-Me-BIPAM (eq. 1).



In Chapter 3, the detailed mechanism for asymmetric intramolecular hydroarylation of α -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 ^1H 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)



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Chapter 2

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

Abstract: Asymmetric intramolecular direct hydroarylation of α -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 $[\text{Ir}(\text{cod})_2](\text{BAr}^{\text{F}}_4)$ and the chiral O-linked bidentate phosphoramidite (*R,R*)-Me-BIPAM.

2.1 Introduction

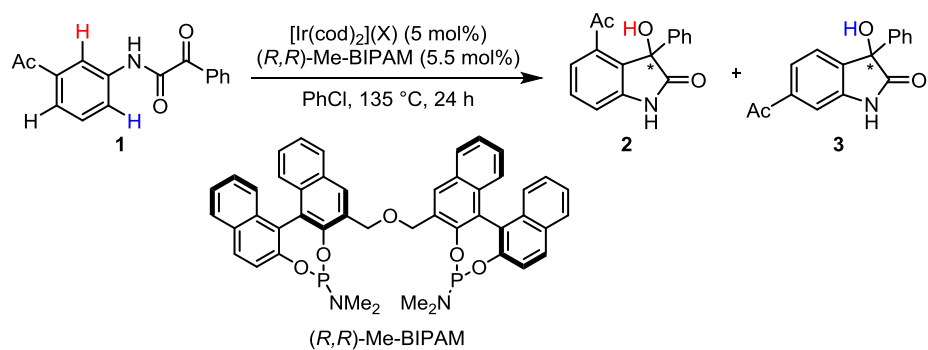
Oxindoles containing a chiral tetrasubstituted carbon at the 3-position are common structural motifs in many biologically active compounds.¹⁾ Among them, 3-substituted 3-hydroxy-2-oxindoles are particularly noteworthy, and various methods for the synthesis of these chiral compounds have been developed in the past decade.^{2–6)} Transition-metal-catalyzed asymmetric nucleophilic addition reactions of organoboronic acid derivatives to isatins are powerful and straightforward approaches.⁷⁾ 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,⁸⁾ the arylation of imines⁹⁾ and carbonyl compounds,¹⁰⁾ and the hydrogenation of α -dehydroaminoesters,¹¹⁾ was efficient for ruthenium-catalyzed addition reactions of arylboronic acids to isatins.^{10d)} 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.^{12,13)} 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.^{14–17)} Intramolecular cyclizations by C–H bond activation have been reported for the synthesis of oxindoles.¹⁸⁾ Iridium complexes have also been shown to be efficient catalysts for C–H bond functionalization.^{13e, 19, 20)} In 2009, Shibata and co-workers reported cationic

Ir/(*S*)-H₈-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.^{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^F₄) (cod = 1,5-cyclooctadiene, BAr^F₄ = tetrakis(3,5-bis(trifluoromethyl)phenyl)borate) complex would be more favorable than other counter anions (BF₄[−], SbF₆[−], TfO[−], ClO₄[−], 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^F₄). 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).

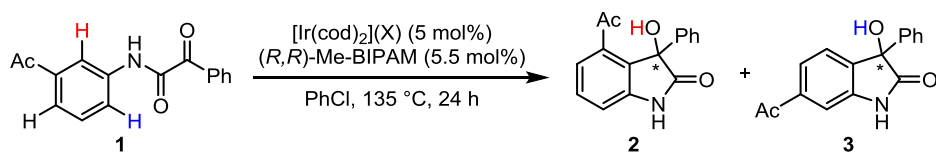
Table 2.1 Screening of counter anions^[a]



Entry	Catalyst (mol%)	Yield of 2/3 [%]	ee of 2/3 [%]
1	[Ir(cod)₂](BARF₄) (5)	62 / trace	71 / –
2	[Ir(cod) ₂](BF ₄) (5)	37 / trace	53 / –
3	[Ir(cod) ₂](SbF ₆) (5)	12 / trace	38 / –
4	[Ir(cod) ₂](OTf) (5)	15 / trace	29 / –
5	[Ir(cod) ₂](ClO ₄) (5)	3 / trace	29 / –
6	[Ir(cod) ₂]Cl (5)	n.r.	n.r.

[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]



Entry	Solvent	Yield of 2/3 [%]	ee of 2/3 [%]
1	PhCl	62 / trace	71 / –
2	DMF	n.r.	–
3	DMSO	n.r.	–
4	DMA	n.r.	–
5	THF	94 / trace	66 / –
6	DME	90 / trace	88 / –
7	DEE	33 / trace	86 / –
8	Dioxane	28 / trace	77 / –
9	Diglyme	19 / trace	58 / –
10 ^[b]	Diglyme	21 / 27	57 / 20
11	toluene	51 / trace	75 / –
12	mesitylene	25 / trace	68 / –

[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]

1: DG = Ac
 4: DG = Bz
 5: DG = CO₂Me
 6a: DG = CONMe₂
 7: DG = NHAc
 8: DG = H

2: DG = Ac
 9: DG = Bz
 10: DG = CO₂Me
 11a: DG = CONMe₂
 12: DG = NHAc
 13: DG = H

Entry	DG	Ir precatalyst (mol%)	Ligand	Yield [%]	ee ^[b] [%]
1	Ac	[Ir(cod) ₂](BARF ₄) (5)	(<i>R,R</i>)-Me-BIPAM	90	88
2	Bz	[Ir(cod) ₂](BARF ₄) (5)	(<i>R,R</i>)-Me-BIPAM	90	88
3	CO ₂ Me	[Ir(cod) ₂](BARF ₄) (5)	(<i>R,R</i>)-Me-BIPAM	37	95
4	CONMe ₂	[Ir(cod) ₂](BARF ₄) (5)	(<i>R,R</i>)-Me-BIPAM	>99	98 (S)
5 ^[c]	CONMe₂	[Ir(cod)₂](BARF₄) (5)	(<i>R,R</i>)-Me-BIPAM	>99	98 (S)
6	CONMe ₂	[Ir(cod) ₂](BARF ₄) (3)	(<i>R,R</i>)-Me-BIPAM	96	97 (S)
7	NHAc	[Ir(cod) ₂](BARF ₄) (5)	(<i>R,R</i>)-Me-BIPAM	63	82
8	H	[Ir(cod) ₂](BARF ₄) (5)	(<i>R,R</i>)-Me-BIPAM	n.r.	—
9	CONMe ₂	[Ir(cod) ₂](BARF ₄) (5)	(<i>R</i>)-BINAP	91	49
10	CONMe ₂	[Ir(cod) ₂](BARF ₄) (5)	(<i>R</i>)-MONOPHOS	32	45

[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).²¹⁾

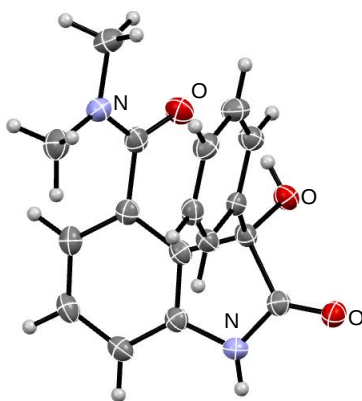


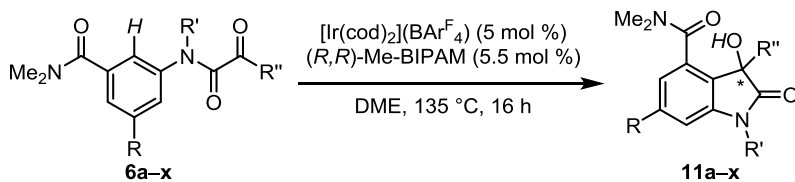
Figure 2.1 ORTEP diagram of 11a, with thermal ellipsoids set at 50%

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 α -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 $[\text{Ir}(\text{cod})((R,R)\text{-Me-bipam})](\text{BAr}^{\text{F}}_4)$. These phenomena indicated that the cationic iridium catalyst precursor, $[\text{Ir}(\text{cod})_2](\text{BAr}^{\text{F}}_4)$, sometimes slightly catalyzed this chemical transformation under our standard conditions.

Furthermore, in the reaction of α -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 α -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 α -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).

Table 2.4

Asymmetric intramolecular direct hydroarylation of α -ketoamides^[a]

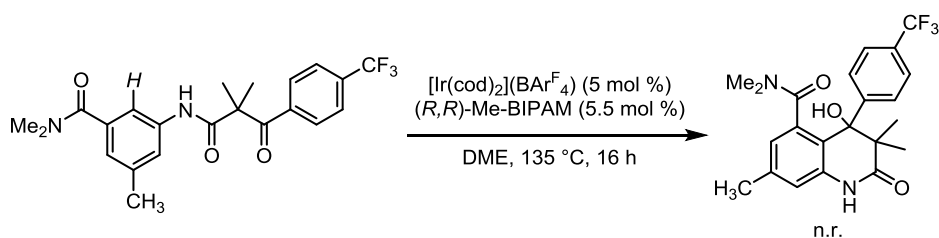
Entry	R	R'	R''	Yield [%]	ee ^[b] [%]
1	H	H	C ₆ H ₅ (6a)	>99 (11a)	98 (<i>S</i>)
2	H	H	4-CF ₃ C ₆ H ₄ (6b)	98 (11b)	98
3	H	H	4-FC ₆ H ₄ (6c)	99 (11c)	90
4	H	H	4-BrC ₆ H ₄ (6d)	80 (11d)	98
5	H	H	4-PhC ₆ H ₄ (6e)	94 (11e)	91
6	H	H	4-MeC ₆ H ₄ (6f)	93 (11f)	91
7	H	H	4-PhOC ₆ H ₄ (6g)	73 (11g)	84
8 ^[c]	H	H	4-PhOC ₆ H ₄ (6g)	97 (11g)	84
9	H	H	3-CF ₃ C ₆ H ₄ (6h)	97 (11h)	97
10	H	H	3-CH ₃ C ₆ H ₄ (6i)	98 (11i)	86
11 ^[c]	H	H	3-CH ₃ C ₆ H ₄ (6i)	90 (11i)	92
12	H	H	2-FC ₆ H ₄ (6j)	87 (11j)	97
13	H	H	2-naphthyl (6k)	91 (11k)	88
14 ^[c]	H	H	2-naphthyl (6k)	88 (11k)	94
15	H	H	3,5-(CF ₃) ₂ C ₆ H ₃ (6l)	97 (11l)	98
16	H	H	3,4-(CH ₂ O ₂)C ₆ H ₃ (6m)	69 (11m)	84
17 ^[c]	H	H	3,4-(CH ₂ O ₂)C ₆ H ₃ (6m)	85 (11m)	80
18	CH ₃	H	C ₆ H ₅ (6n)	90 (11n)	93
19	CF ₃	H	C ₆ H ₅ (6o)	96 (11o)	91
20	Cl	H	C ₆ H ₅ (6p)	85 (11p)	95
21	H	H	CH ₃ (6q)	96 (11q)	94
22	H	H	CH ₂ CH ₃ (6r)	95 (11r)	92
23	H	H	CH(CH ₃) ₂ (6s)	93 (11s)	90
24	H	CH ₃	C ₆ H ₅ (6t)	85 (11t)	92
25	H	CH ₃	4-CF ₃ C ₆ H ₄ (6u)	92 (11u)	87
26	H	CH ₃	4-FC ₆ H ₄ (6v)	95 (11v)	86
27	H	CH ₃	4-CH ₃ C ₆ H ₄ (6w)	86 (11w)	90
28	H	CH ₃	4-CH ₃ OC ₆ H ₄ (6x)	66 (11x)	70

[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 16 h at 135 °C.

[b] The absolute configuration of the chiral center within the product is given in parentheses.

[c] 5 mol % of [Ir(cod)]((*R,R*)-Me-bipam)](BARF₄) was used as the catalyst.

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.^{3c, 20a)} First, $[\text{Ir}((R,R)\text{-Me-bipam})](\text{BAR}^{\text{F}}_4)$ ($[\text{Ir}]$, **14**) is formed by an iridium catalyst precursor, $[\text{Ir}(\text{cod})_2](\text{BAR}^{\text{F}}_4)$, and $(R,R)\text{-Me-BIPAM}$ 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**.

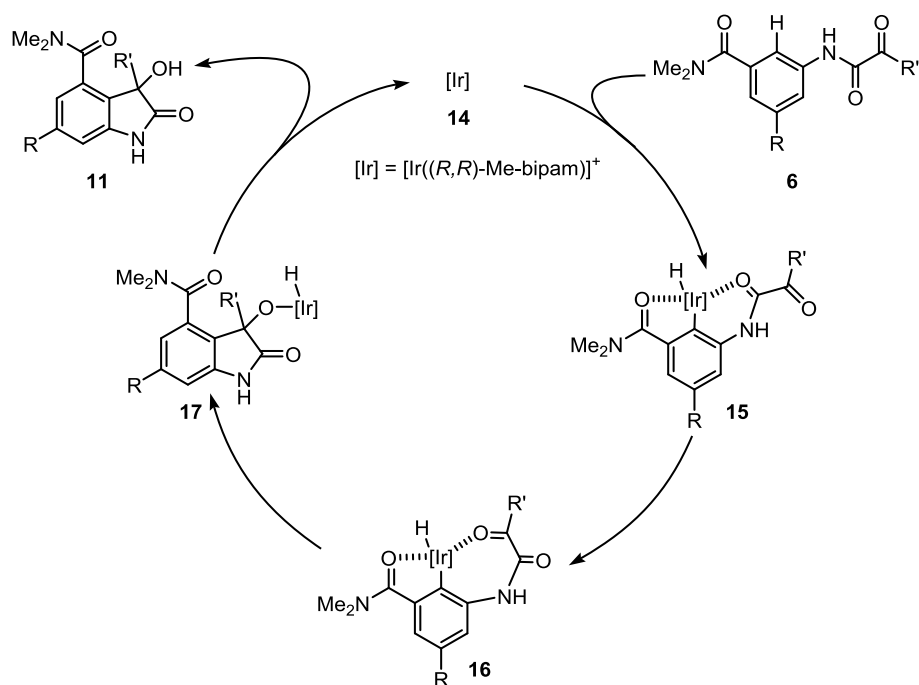


Figure 2.2 Proposed catalytic cycle

On the basis of a previous report,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.

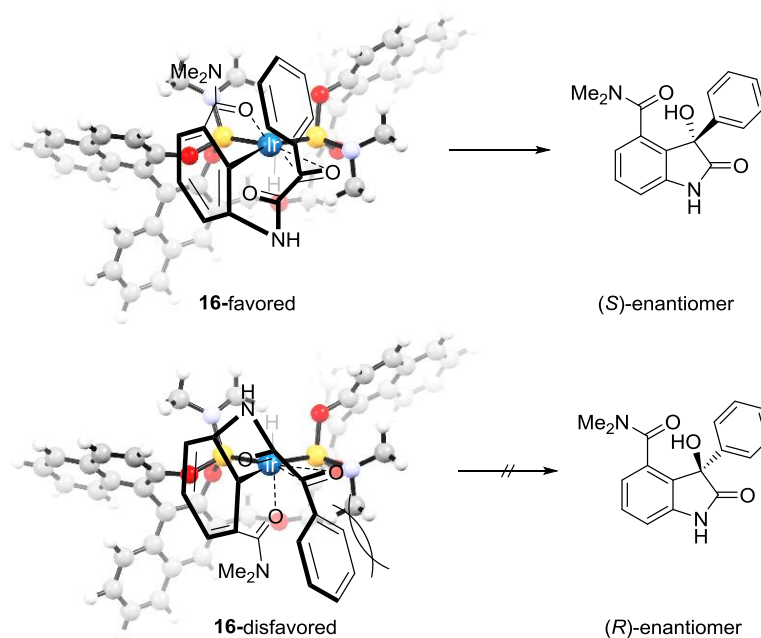


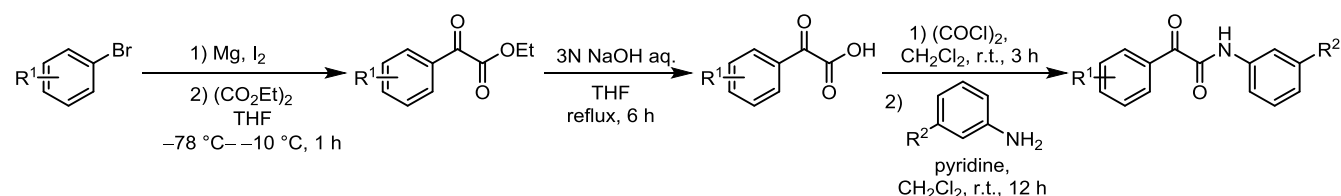
Figure 2.3 Plausible models for enantioselection

2.4 Conclusion

In conclusion, we have developed a cationic iridium/(*R,R*)-Me-BIPAM-catalyzed highly enantioselective intramolecular direct hydroarylation of α -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



Synthesis of α -ketoesters

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 °C. After 1 h at -78 °C, the mixture was warmed to -10 °C. The mixture was quenched with aqueous saturated NH₄Cl, extracted with Et₂O, washed with brine, dried over MgSO₄, 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 α -ketoesters.

Synthesis of glyoxylic acids

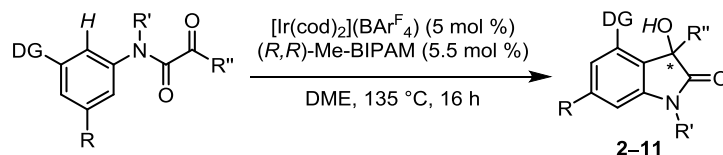
The α -ketoester was hydrolyzed upon being stirred with 3N NaOH (50 mL) in THF (50 mL) at reflux temperature for 6 h. Then, THF was evaporated, and the aqueous residue was cooled to 0 °C and acidified with 6N HCl. The mixture was extracted with AcOEt. The combined extracts were washed with brine and dried over MgSO₄. The solvent was removed in vacuo to afford glyoxylic acid as a brown solid.

Synthesis of α -ketoamides

To a CH₂Cl₂ solution (20 mL) of glyoxylic acid (6.0 mmol) were added catalytic amount of DMF (5

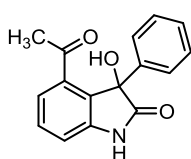
drops) and oxalyl chloride (6.6 mmol). The reaction mixture was stirred at room temperature until generation of gasses was stopped (commonly for 3 h). Then, reaction flask was cooled to 0 °C. A solution of aniline (6.0 mmol) and pyridine (15.0 mmol) were added and stirred at room temperature for 12 h. 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



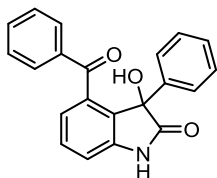
To a flame-dried flask, $[\text{Ir}(\text{cod})_2](\text{BAR}^{\text{F}_4})$ (0.0125 mmol, 5 mol%) and (R,R) -Me-BIPAM (0.0138 mmol, 5.5 mol%) and dry 1,2-dimethoxyethane (1.0 mL) were added under an N_2 atmosphere. The solution was stirred at room temperature for 30 min, followed by the addition of 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)



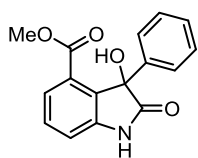
88% ee [HPLC condition: Chiralcel OD-H column, hexane/2-propanol = 9/1, flow = 1.0 mL/min, wavelength = 230 nm, t_{R} = 29.3 min (minor) and 40.8 min (major)]; $[\alpha]_{\text{D}}^{21} = +105.3$ (*c* 0.35, DMSO); ^1H NMR (400 MHz, $[\text{D}_6]\text{DMSO}$): δ = 7.50–7.47 (m, 2H), 7.29–7.20 (m, 6H), 6.30 (s, 1H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $[\text{D}_6]\text{DMSO}$): 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 $\text{C}_{16}\text{H}_{13}\text{O}_3\text{NNa}$ ($\text{M}+\text{Na}$) $^+$: 290.07876, found: 290.07866.

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



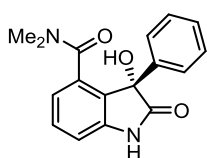
88% ee [HPLC condition: Chiralcel OD-H column, hexane/2-propanol = 9/1, flow = 1.0 mL/min, wavelength = 230 nm, t_{R} = 25.0 min (minor) and 36.5 min (major)]; $[\alpha]_{\text{D}}^{21} = +94.0$ (*c* 0.34, DMSO); ^1H NMR (400 MHz, $[\text{D}_6]\text{DMSO}$): δ = 10.66 (br s, NH), 7.55 (t, J = 7.7 Hz, 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, $[\text{D}_6]\text{DMSO}$): 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 $\text{C}_{21}\text{H}_{15}\text{O}_3\text{NNa}$ ($\text{M}+\text{Na}$) $^+$: 352.09441, found: 352.09419.

3-Hydroxy-4-(methoxycarbonyl)-3-phenyl-indolin-2-one (10)



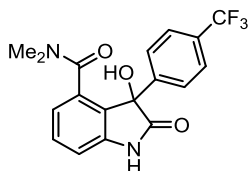
95% ee [HPLC condition: Chiralcel AD-H column, hexane/2-propanol = 9/1, flow = 1.0 mL/min, wavelength = 230 nm, t_R = 19.7 min (minor) and 34.3 min (major)]; $[\alpha]_D^{20}$ = +75.0 (c 0.14, DMSO); ^1H NMR (400 MHz, $[\text{D}_6]\text{DMSO}$): δ = 10.62 (s, NH), 7.48–7.43 (m, 2H), 7.28–7.14 (m, 6H), 6.17 (s, 1H), 3.46 (s, 3H); ^{13}C NMR (100 MHz, $[\text{D}_6]\text{DMSO}$): δ = 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 $\text{C}_{16}\text{H}_{13}\text{O}_4\text{NNa}$ ($\text{M}+\text{Na}$) $^+$: 306.07368, found: 306.07308.

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



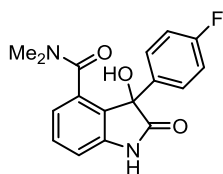
98% ee [HPLC condition: Chiralcel OD-H column, hexane/2-propanol = 6/1, flow = 1.0 mL/min, wavelength = 230 nm, t_R = 26.6 min (major) and 37.8 min (minor)]; $[\alpha]_D^{20}$ = +72.1 (c 0.30, DMSO); ^1H NMR (400 MHz, $[\text{D}_6]\text{DMSO}$): δ = 10.63 (br s, NH), 7.32–7.18 (m, 6H), 6.97 (dd, J = 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, $[\text{D}_6]\text{DMSO}$): δ = 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 $\text{C}_{17}\text{H}_{16}\text{O}_3\text{N}_2\text{Na}$ ($\text{M}+\text{Na}$) $^+$: 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); ^1H NMR (400 MHz, CD_2Cl_2): δ = 9.13 (br s, NH), 7.58 (d, J = 8.3 Hz, 2H), 7.48 (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_2Cl_2): δ = 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 $\text{C}_{18}\text{H}_{15}\text{O}_3\text{N}_2\text{F}_3\text{Na}$ ($\text{M}+\text{Na}$) $^+$: 387.09270, found: 387.09225.

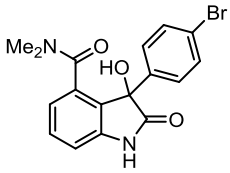
3-(4-Fluorophenyl)-3-hydroxy-4-(*N,N*-dimethylaminocarbonyl)-indolin-2-one (11c)



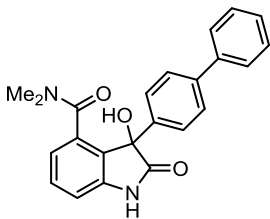
90% ee [HPLC condition: Chiralcel AD-H column, hexane/2-propanol = 9/1, flow = 1.0 mL/min, wavelength = 230 nm, t_R = 33.4 min (minor) and 44.2 min (major)]; $[\alpha]_D^{22}$ = +204.8 (c 0.34, CHCl_3); ^1H NMR (400 MHz, CD_2Cl_2): δ = 8.29 (br s, NH), 7.36–7.29 (m, 3H), 7.06–6.97 (m, 4H), 6.15 (s, 1H), 2.74 (s, 3H), 2.69 (s, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 177.3, 170.0, 162.9 (d, J = 245.2 Hz), 142.1, 135.7, 132.9, 132.3, 129.5, 127.7 (d, J = 8.5 Hz), 121.1, 115.3 (d, J = 21.6 Hz), 112.0,

77.1, 39.0, 34.8; HRMS (ESI) m/z calc for $C_{17}H_{15}O_3N_2FNa$ ($M+Na$)⁺: 337.09589, found: 337.09543.

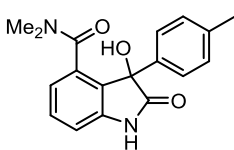
3-(4-Bromophenyl)-3-hydroxy-4-(*N,N*-dimethylaminocarbonyl)-indolin-2-one (11d)

 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)]; $[\alpha]_D^{23}$ = +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); ^{13}C 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 $C_{17}H_{15}O_3N_2BrNa$ ($M+Na$)⁺: 397.01583, found: 397.01537.

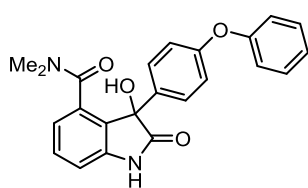
3-Hydroxy-4-(*N,N*-dimethylaminocarbonyl)-3-(4-phenylphenyl)-indolin-2-one (11e)

 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)]; $[\alpha]_D^{22}$ = +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); ^{13}C 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 $C_{23}H_{20}O_3N_2Na$ ($M+Na$)⁺: 395.13661, found: 395.13610.

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

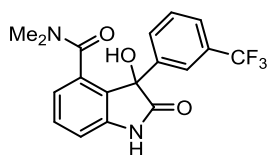
 91% ee [HPLC condition: Chiralcel OD-H column, hexane/2-propanol = 9/1, flow = 1.0 mL/min, wavelength = 230 nm, t_R = 44.7 min (major) and 62.9 min (minor)]; $[\alpha]_D^{21}$ = +197.3 (*c* 2.6, $CHCl_3$); 1H NMR (400 MHz, $[D_6]DMSO$): δ = 10.56 (br s, NH), 7.29 (t, J = 7.6 Hz, 1H), 7.09 (d, J = 8.5 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); ^{13}C 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 $C_{18}H_{18}O_3N_2Na$ ($M+Na$)⁺: 333.12096, found: 333.12115.

3-Hydroxy-4-(*N,N*-dimethylaminocarbonyl)-3-(4-phenoxyphenyl)-indolin-2-one (11g)



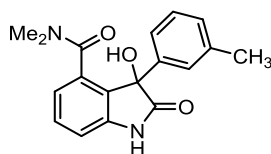
84% ee [HPLC condition: Chiralcel AD-H column, hexane/2-propanol = 9/1, flow = 2.0 mL/min, wavelength = 230 nm, t_R = 29.4 min (minor) and 57.3 min (major)]; $[\alpha]_D^{22} = +169.2$ (c 0.30, CHCl₃); ^1H NMR (400 MHz, CD₂Cl₂): δ = 9.07 (br s, NH), 7.36–7.28 (m, 5H), 7.11 (t, J = 7.7 Hz, 1H), 7.06 (d, J = 7.7 Hz, 1H), 6.99–6.92 (m, 5H), 6.12 (s, 1H), 2.79 (s, 3H), 2.70 (s, 3H); ^{13}C NMR (100 MHz, CD₂Cl₂): 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 C₂₃H₂₀O₄N₂Na (M+Na)⁺: 411.13153, found: 411.13088.

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



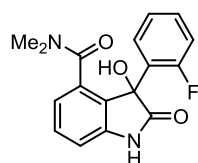
97% ee [HPLC condition: Chiralcel AD-H column, hexane/2-propanol = 9/1, flow = 1.0 mL/min, wavelength = 230 nm, t_R = 25.6 min (minor) and 31.5 min (major)]; $[\alpha]_D^{23} = +197.4$ (c 0.30, CHCl₃); ^1H NMR (400 MHz, CD₂Cl₂): δ = 8.97 (br s, NH), 7.62 (d, J = 7.7 Hz, 1H), 7.57 (d, J = 7.7 Hz, 1H), 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); ^{13}C NMR (100 MHz, CD₂Cl₂): δ = 177.0, 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 C₁₈H₁₅O₃N₂F₃Na (M+Na)⁺: 387.09270, found: 387.09256.

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



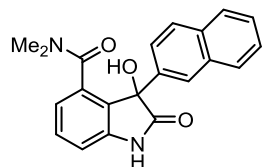
92% ee [HPLC condition: Chiralcel AD-H column, hexane/2-propanol = 9/1, flow = 1.0 mL/min, wavelength = 230 nm, t_R = 34.7 min (minor) and 52.7 min (major)]; $[\alpha]_D^{22} = +201.4$ (c 0.33, CHCl₃); ^1H NMR (400 MHz, CD₂Cl₂): δ = 9.23 (br s, NH), 7.29 (t, J = 7.7 Hz, 1H), 7.18 (t, J = 7.7 Hz, 1H), 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); ^{13}C NMR (100 MHz, CD₂Cl₂): 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 C₁₈H₁₈O₃N₂Na (M+Na)⁺: 333.12096, found: 333.12048.

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



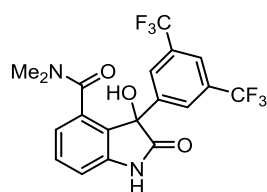
97% ee [HPLC condition: Chiralcel AD-H column, hexane/2-propanol = 9/1, flow = 1.0 mL/min, wavelength = 230 nm, t_R = 36.0 min (minor) and 70.4 min (major)]; $[\alpha]_D^{21} = -8.0$ (c 0.32, DMSO); ^1H NMR (400 MHz, CDCl_3): δ = 9.64 (br s, NH), 7.99 (ddd, J = 1.8, 7.5, 7.6 Hz, 1H), 7.31–7.22 (m, 3H), 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): δ = 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 $\text{C}_{17}\text{H}_{15}\text{O}_3\text{N}_2\text{FNa}$ ($\text{M}+\text{Na}$) $^+$: 337.09589, found: 337.09555.

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



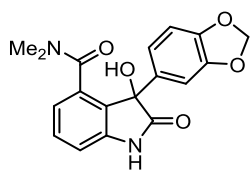
94% ee [HPLC condition: Chiralcel AD-H column, hexane/2-propanol = 9/1, flow = 2.0 mL/min, wavelength = 230 nm, t_R = 36.1 min (major) and 47.7 min (minor)]; $[\alpha]_D^{23} = +190.0$ (c 0.31, CHCl_3); ^1H NMR (400 MHz, CD_2Cl_2): δ = 8.76 (br s, NH), 7.93 (s, 1H), 7.82 (m, 2H), 7.75 (d, J = 8.6 Hz, 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_2Cl_2): δ = 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 $\text{C}_{21}\text{H}_{18}\text{O}_3\text{N}_2\text{Na}$ ($\text{M}+\text{Na}$) $^+$: 369.12096, found: 369.12029.

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



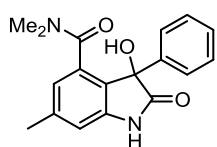
98% ee [HPLC condition: Chiralcel AD-H column, hexane/2-propanol = 9/1, flow = 1.0 mL/min, wavelength = 230 nm, t_R = 8.8 min (minor) and 12.5 min (major)]; $[\alpha]_D^{23} = +71.3$ (c 0.34, DMSO); ^1H NMR (400 MHz, $[\text{D}_6]\text{DMSO}$): δ = 10.83 (br s, NH), 8.06 (s, 1H), 7.75 (s, 2H), 7.38 (t, 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, $[\text{D}_6]\text{DMSO}$): δ = 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 $\text{C}_{19}\text{H}_{14}\text{O}_3\text{N}_2\text{F}_6\text{Na}$ ($\text{M}+\text{Na}$) $^+$: 455.08008, found: 455.07974.

3-Hydroxy-4-(*N,N*-dimethylaminocarbonyl)-3-(3,4-methylenedioxyphenyl)-indolin-2-one (11m)



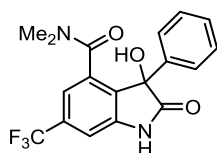
84% ee [HPLC condition: Chiralcel AD-H column, hexane/2-propanol = 9/1, flow = 2.0 mL/min, wavelength = 230 nm, t_R = 34.6 min (minor) and 42.2 min (major)]; $[\alpha]_D^{23} = +186.7$ (c 0.19, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ = 9.81 (br s, NH), 7.29–7.25 (m, 1H), 7.04 (d, J = 7.9 Hz, 1H), 6.97 (d, 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 C₁₈H₁₆O₅N₂Na (M+Na)⁺: 363.09514, found: 363.09467.

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



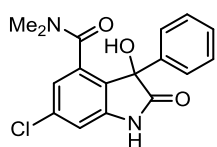
93% ee [HPLC condition: Chiralpak AD-H column, hexane/2-propanol = 9/1, flow = 1.0 mL/min, wavelength = 254 nm, t_R = 45.8 min (minor) and 77.7 min (major)]; $[\alpha]_D^{22} = +187.6$ (c 3.3, CHCl₃); ¹H NMR (400 MHz, [D₆]DMSO): δ = 10.56 (br s, NH), 7.29–7.17 (m, 5H), 6.78 (s, 1H), 6.63 (s, 1H), 6.21 (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 C₁₈H₁₈O₃N₂Na (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)]; $[\alpha]_D^{21} = +153.8$ (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 C₁₈H₁₅O₃N₂F₃Na (M+Na)⁺: 387.09270, found: 387.09222.

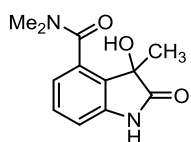
6-Chloro-3-hydroxy-4-(*N,N*-dimethylaminocarbonyl)-3-phenyl-indolin-2-one (11p)



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)]; $[\alpha]_D^{23} = +13.1$ (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,

33.7; HRMS (ESI) m/z calc for $C_{17}H_{15}O_3N_2ClNa$ ($M+Na$)⁺: 353.06634, found: 353.06696.

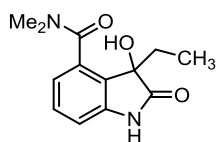
3-Hydroxy-3-methyl-4-(*N,N*-dimethylaminocarbonyl)-indolin-2-one (11q)



94% ee [HPLC condition: Chiralcel AD-H column, hexane/2-propanol = 9/1, flow = 1.0 mL/min, wavelength = 230 nm, t_R = 24.5 min (minor) and 31.9 min (major)]; $[\alpha]_D^{23}$ = -39.8 (c 0.31, DMSO); 1H NMR (400 MHz, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{12}H_{14}O_3N_2Na$ ($M+Na$)⁺: 257.08966, found: 257.08934.

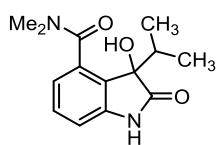
3-Ethyl-3-hydroxy-4-(*N,N*-dimethylaminocarbonyl)-indolin-2-one (11r)



92% ee [HPLC condition: Chiralcel AD-H column, hexane/2-propanol = 9/1, flow = 1.0 mL/min, wavelength = 230 nm, t_R = 26.2 min (minor) and 35.0 min (major)]; $[\alpha]_D^{22}$ = +114.3 (c 0.30, $CHCl_3$); 1H NMR (400 MHz, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{13}H_{16}O_3N_2Na$ ($M+Na$)⁺: 271.10531, found: 271.10506.

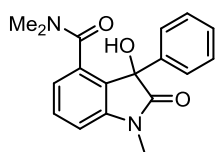
3-Hydroxy-3-isopropyl-4-(*N,N*-dimethylaminocarbonyl)-indolin-2-one (11s)



90% ee [HPLC condition: Chiralcel AD-H column, hexane/2-propanol = 9/1, flow = 1.0 mL/min, wavelength = 230 nm, t_R = 31.9 min (minor) and 59.2 min (major)]; $[\alpha]_D^{23}$ = +87.1 (c 0.32, $CHCl_3$); 1H NMR (400 MHz, $CDCl_3$): δ = 9.70 (br s, NH), 7.23 (t, J = 7.9

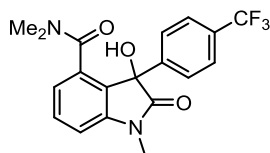
Hz, 1H), 7.01 (d, J = 7.9 Hz, 1H), 6.93 (d, J = 7.9 Hz, 1H), 5.78 (s, 1H), 3.13 (s, 6H), 2.20 (sep, J = 6.8 Hz, 1H), 1.10 (d, J = 6.8 Hz, 3H), 0.81 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.0, 171.2, 142.5, 131.9, 130.1, 128.7, 121.0, 112.0, 79.7, 39.9, 36.3, 35.5, 16.7, 15.6; HRMS (ESI) m/z calc for $C_{14}H_{18}O_3N_2Na$ ($M+Na$)⁺: 285.12096, found: 285.12081.

3-Hydroxy-1-methyl-4-(*N,N*-dimethylaminocarbonyl)-3-phenyl-indolin-2-one (2t)



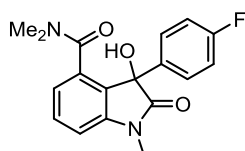
92% ee [HPLC condition: Chiralpak AD-H column, hexane/2-propanol = 4/1, flow = 1.0 mL/min, wavelength = 230 nm, t_R = 18.0 min (minor) and 22.0 min (major)]; $[\alpha]_D^{20}$ = +234.3 (*c* 3.6, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ = 7.37 (t, *J* = 8.1 Hz, 1H), 7.32–7.21 (m, 5H), 6.98 (d, *J* = 8.1 Hz, 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, [D₆]DMSO): 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 C₁₈H₁₈O₃N₂Na (M+Na)⁺: 333.12096, found: 333.12135.

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



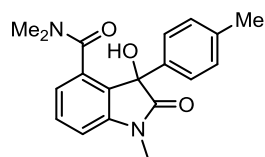
87% ee [HPLC condition: Chiralpak AD-H column, hexane/2-propanol = 4/1, flow = 1.0 mL/min, wavelength = 230 nm, t_R = 11.8 min (major) and 13.9 min (minor)]; $[\alpha]_D^{22}$ = +240.8 (*c* 2.3, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ = 7.55 (d, *J* = 8.2 Hz, 2H), 7.47 (d, *J* = 8.2 Hz, 2H), 7.42 (dd, *J* = 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), 3.26 (s, 3H), 2.73 (s, 3H), 2.69 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): 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 C₁₉H₁₇O₃N₂F₃Na (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)]; $[\alpha]_D^{22}$ = +264.6 (*c* 2.1, CHCl₃); ¹H NMR (400 MHz, CDCl₃): 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, CDCl₃): 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 C₁₈H₁₇O₃N₂FNa (M+Na)⁺: 351.11154, found: 351.11173.

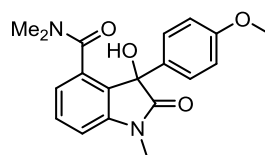
3-Hydroxy-1-methyl-3-(4-methylphenyl)-4-(*N,N*-dimethylaminocarbonyl)-indolin-2-one (2w)



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); ^1H NMR (400 MHz, CDCl_3): δ = 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): δ = 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 $\text{C}_{19}\text{H}_{20}\text{O}_3\text{N}_2\text{Na}$ ($\text{M}+\text{Na}$) $^+$: 347.13661, found: 347.13667.

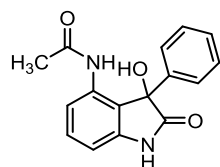
3-Hydroxy-3-(4-methoxyphenyl)-1-methyl-4-(*N,N*-dimethylaminocarbonyl)-indolin-2-one (2x)



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); ^1H NMR (400 MHz, CDCl_3): δ = 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): δ = 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 $\text{C}_{19}\text{H}_{20}\text{O}_4\text{N}_2\text{Na}$ ($\text{M}+\text{Na}$) $^+$: 363.13153, found: 363.13158.

4-(Acetylamino)-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), ^1H NMR (400 MHz, $[\text{D}_6]\text{DMSO}$): δ = 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, $[\text{D}_6]\text{DMSO}$): δ =

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 $\text{C}_{16}\text{H}_{14}\text{O}_3\text{N}_2\text{Na}$ ($\text{M}+\text{Na}$) $^+$: 305.08966, found: 305.08899.

X-ray Crystal Structure of Compound 11a

Data Collection

A colorless block crystal of $C_{17}H_{16}N_2O_3$ 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-K α 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:

$$\begin{aligned}a &= 10.8424(3) \text{ \AA} \\c &= 12.2648(5) \text{ \AA} \\V &= 1441.81(8) \text{ \AA}^3\end{aligned}$$

For $Z = 4$ and F.W. = 296.32, the calculated density is 1.365 g/cm³. Based on the reflection conditions of:

$$00l: \quad l = 4n$$

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

$$P41 \text{ (#76)}$$

The data were collected at a temperature of $-150 \pm 1^\circ\text{C}$ 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 $\chi = 54.0^\circ$ and $\phi = 0.0^\circ$. The exposure rate was 50.0 [sec./ $^\circ$]. A second sweep was performed using ω scans from 80.0 to 260.0° in 30.0° step, at $\chi = 54.0^\circ$ and $\phi = 90.0^\circ$. The exposure rate was 50.0 [sec./ $^\circ$]. Another sweep was performed using ω scans from 80.0 to 260.0° in 30.0° step, at $\chi = 54.0^\circ$ and $\phi = 180.0^\circ$. The exposure rate was 50.0 [sec./ $^\circ$]. Another sweep was performed using ω scans from 80.0 to 260.0° in 30.0° step, at $\chi = 54.0^\circ$ and $\phi = 270.0^\circ$. The exposure rate was 50.0 [sec./ $^\circ$].

Another sweep was performed using ω scans from 80.0 to 260.0° in 30.0° step, at $\chi = 0.0^\circ$ and $\phi = 0.0^\circ$. The exposure rate was 50.0 [sec./°]. 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, μ , for Cu-K α 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:

$$R1 = \Sigma ||F_o| - |F_c|| / \Sigma |F_o| = 0.0291$$

$$wR2 = [\Sigma (w (F_o^2 - F_c^2)^2) / \Sigma w(F_o^2)^2]^{1/2} = 0.0756$$

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 /Å³, 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_{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

Empirical Formula	$\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_3$
Formula Weight	296.32
Crystal Color, Habit	colorless, block
Crystal Dimensions	0.553 X 0.372 X 0.242 mm
Crystal System	tetragonal
Lattice Type	Primitive
Lattice Parameters	$a = 10.8424(3) \text{ \AA}$ $c = 12.2648(5) \text{ \AA}$ $V = 1441.81(8) \text{ \AA}^3$
Space Group	$P4_1$ (#76)
Z value	4
D_{calc}	1.365 g/cm ³
F_{000}	624.00
μ (CuK α)	7.774 cm ⁻¹

B. Intensity Measurements

Diffractometer	R-AXIS RAPID
Radiation	CuK α ($\lambda = 1.54187 \text{ \AA}$)
	Graphite monochromator
Voltage, Current	50kV, 40mA
Temperature	-150.0°C
Detector Aperture	460 x 256 mm
Data Images	30 exposures
ω oscillation Range ($\chi=54.0, \phi=0.0$)	80.0 - 260.0°
Exposure Rate	50.0 sec./°
ω oscillation Range ($\chi=54.0, \phi=90.0$)	80.0 - 260.0°
Exposure Rate	50.0 sec./°
ω oscillation Range ($\chi=54.0, \phi=180.0$)	80.0 - 260.0°
Exposure Rate	50.0 sec./°
ω oscillation Range ($\chi=54.0, \phi=270.0$)	80.0 - 260.0°
Exposure Rate	50.0 sec./°
ω oscillation Range ($\chi=0.0, \phi=0.0$)	80.0 - 260.0°
Exposure Rate	50.0 sec./°
Detector Position	127.40 mm
Pixel Size	0.100 mm
$2\theta_{\text{max}}$	136.4°
No. of Reflections Measured	Total: 14905
	Unique: 2623 ($R_{\text{int}} = 0.0345$)
	Friedel pairs: 1237
Corrections	Lorentz-polarization
	Absorption
	(Trans. factors: 0.684 - 0.829)
	Secondary Extinction
	(Coefficient: 2.55000e-003)

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SHELX97)
Refinement	Full-matrix least-squares on F^2
Function Minimized	$\Sigma w (F_o^2 - F_c^2)^2$
Least Squares Weights	$w = 1 / [\sigma^2(F_o^2) + (0.0392 \cdot P)^2 + 0.1950 \cdot P]$ where $P = (\text{Max}(F_o^2, 0) + 2F_c^2)/3$
2 θ max cutoff	136.4°
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (All reflections)	2623
No. Variables	228
Reflection/Parameter Ratio	11.50
Residuals: R1 ($I > 2.00\sigma(I)$)	0.0291
Residuals: R (All reflections)	0.0361
Residuals: wR2 (All reflections)	0.0756
Goodness of Fit Indicator	1.057
Flack Parameter (Friedel pairs = 1237)	0.00(19)
Max Shift/Error in Final Cycle	0.000
Maximum peak in Final Diff. Map	0.13 e-/Å ³
Minimum peak in Final Diff. Map	-0.15 e-/Å ³

2.6 References

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- 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

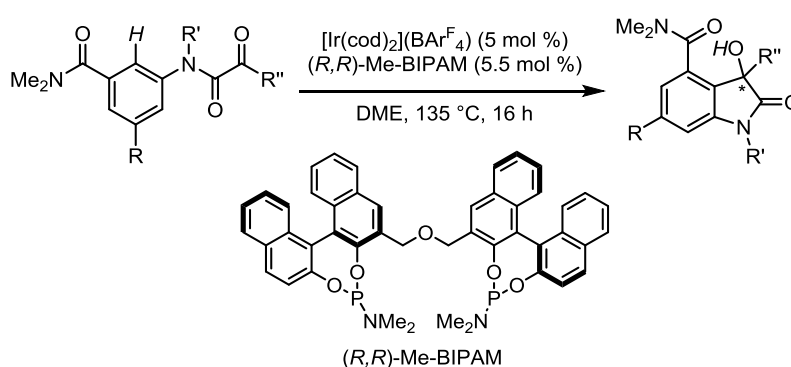
Mechanistic Studies of the Cationic Ir/Me-BIPAM-Catalyzed Asymmetric Intramolecular Direct Hydroarylation Reaction

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 addition¹⁾ of aryl boron reagents to C=O or C=N double bonds such as ketones²⁾ and ketimines³⁾ 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

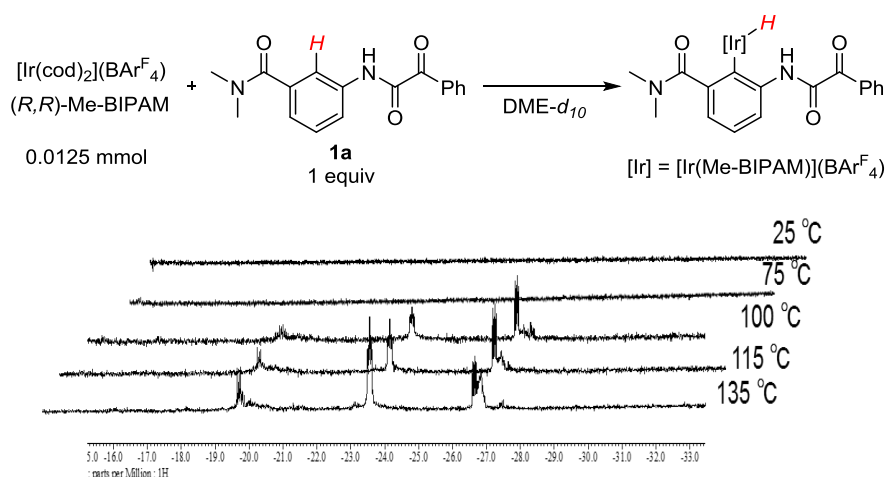
desirable in terms of the atom and synthetic step economy. However, there have been few reports on asymmetric nucleophilic addition of a C–H bond to the carbonyl group by a transition metal catalyst.⁴⁾ As described in Chapter 2, authors recently developed cationic Ir/Me-BIPAM-catalyzed enantioselective intramolecular direct hydroarylation of α -ketoamides (Scheme 1).⁵⁾ This transformation provides a convenient synthetic route for chiral 3-substituted 3-hydroxy-2-oxindole derivatives with asymmetric induction. While some pioneering works have been reported,⁶⁾ only limited mechanistic information is available for aryl C(sp²)–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.



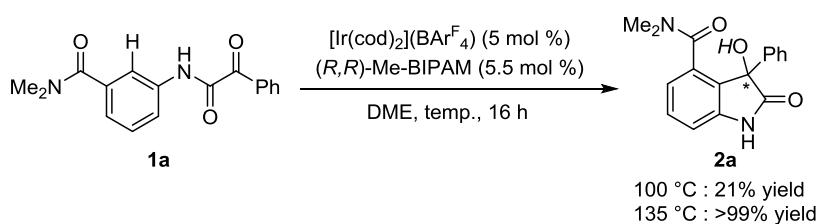
Scheme 3.1 Cationic Ir/Me-BIPAM-catalyzed enantioselective intramolecular direct hydroarylation

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 ^1H NMR spectra of a mixture of Ir/Me-BIPAM complex and **1a** in DME- d_{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 $100\text{ }^\circ\text{C}$. While iridium hydride was detected at $100\text{ }^\circ\text{C}$, the product **2a** was obtained in only 21% yield for catalytic reaction conditions (Scheme 3.3). These results clearly demonstrate that a high temperature ($135\text{ }^\circ\text{C}$) is essential for the steps except for C–H bond cleavage in the catalytic cycle.

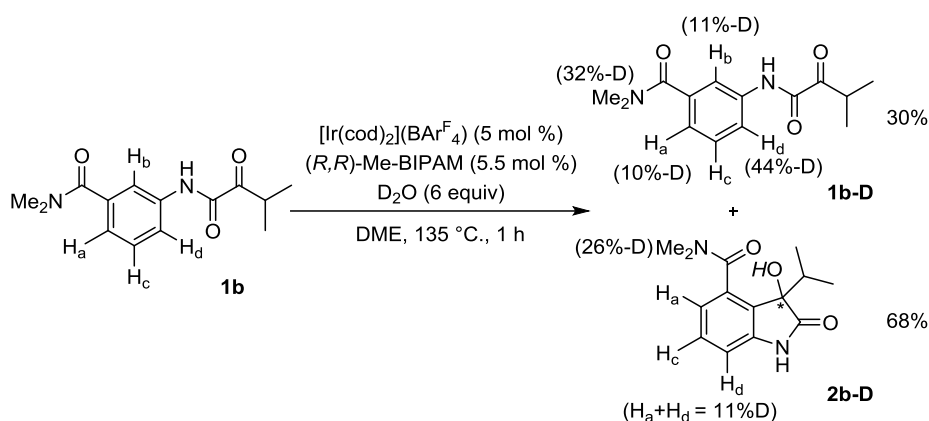


Scheme 3.2 Formation of iridium hydride species



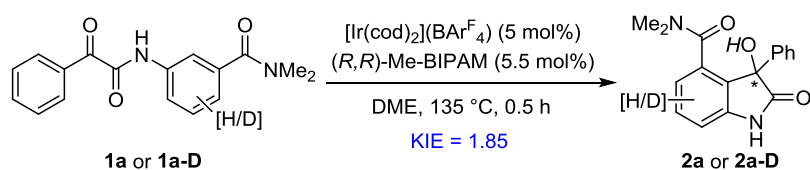
Scheme 3.3 Effect of temperature

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 H_b and 44%-D at H_d), the *ortho* position of the N,N-dimethyl carbamoyl group (10%-D at H_a) in the substrate, and the 5- and 7-positions of the product (11%-D at H_a and H_d) 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), 7)} In addition, deuterium incorporation was also observed at the N,N-dimethyl carbamoyl group in both the substrate (**1s-D**) and (**2s-D**).



Scheme 3.4 Deuterium labeling experiment

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).⁸ These experimental observations for the C–H bond cleavage step suggest that C–H bond cleavage occurs before the turnover-limiting step in the catalytic cycle (secondary isotope effect can be observed) (Figure 3.1).⁹ In Figure 3.1, the turnover-limiting 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 ($100\text{ }^\circ\text{C}$), the reaction only proceeded smoothly at a high temperature ($135\text{ }^\circ\text{C}$) 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.



Scheme 3.5 Kinetic isotope effect

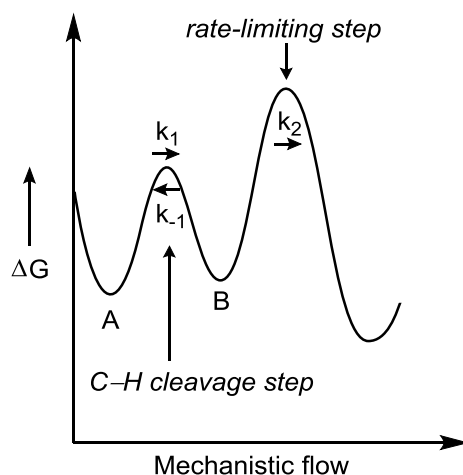


Figure 3.1 **Proposed energy diagram**

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 (**1a**, **1n–1p**) provided a linear relationship in a plot of $\log(k_X/k_H)$ versus σ , where ρ 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 $\text{Ar}[\text{Ir}]^+$ intermediate (an electron-donating substituent increase the nucleophilicity of the aryl-iridium species).

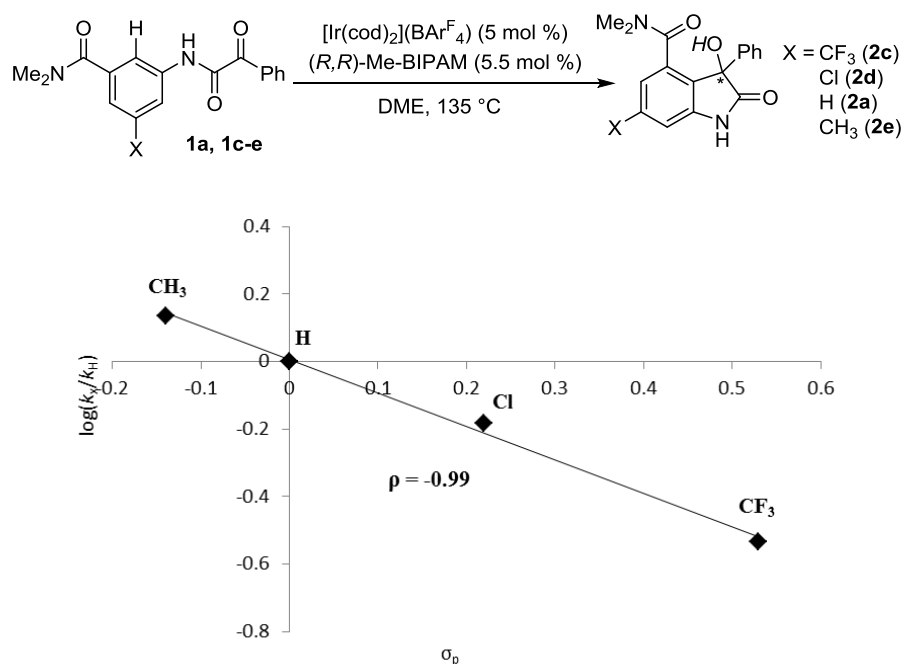


Figure 3.2 Hammett plot using substrates **1a** and **1c-e**

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 σ , resulting in a small ρ 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 ρ 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.

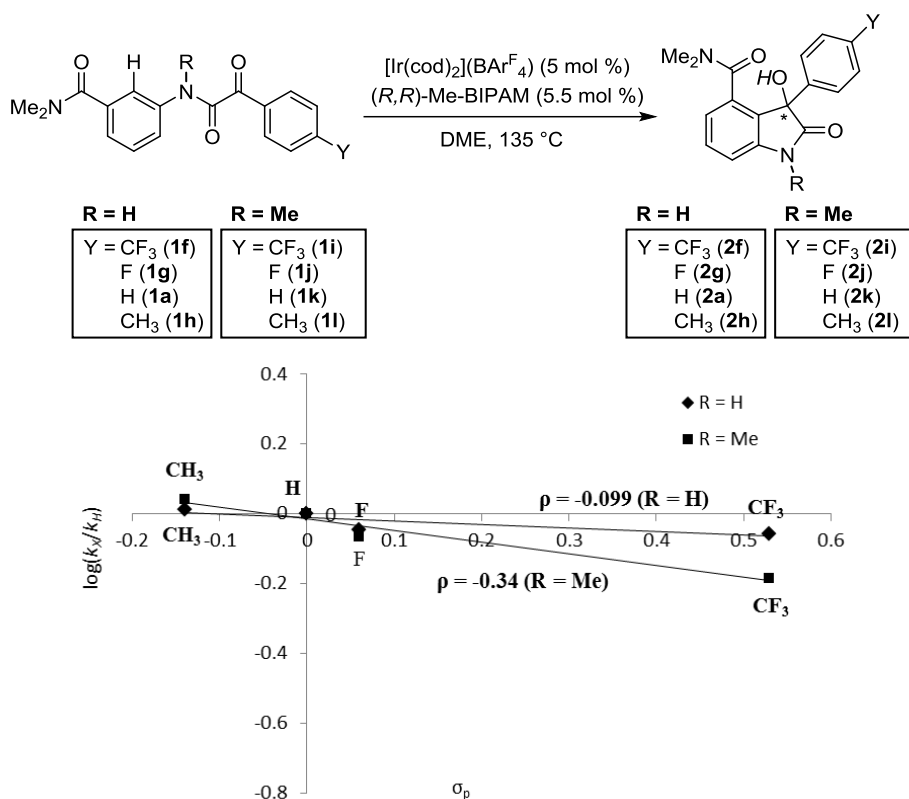
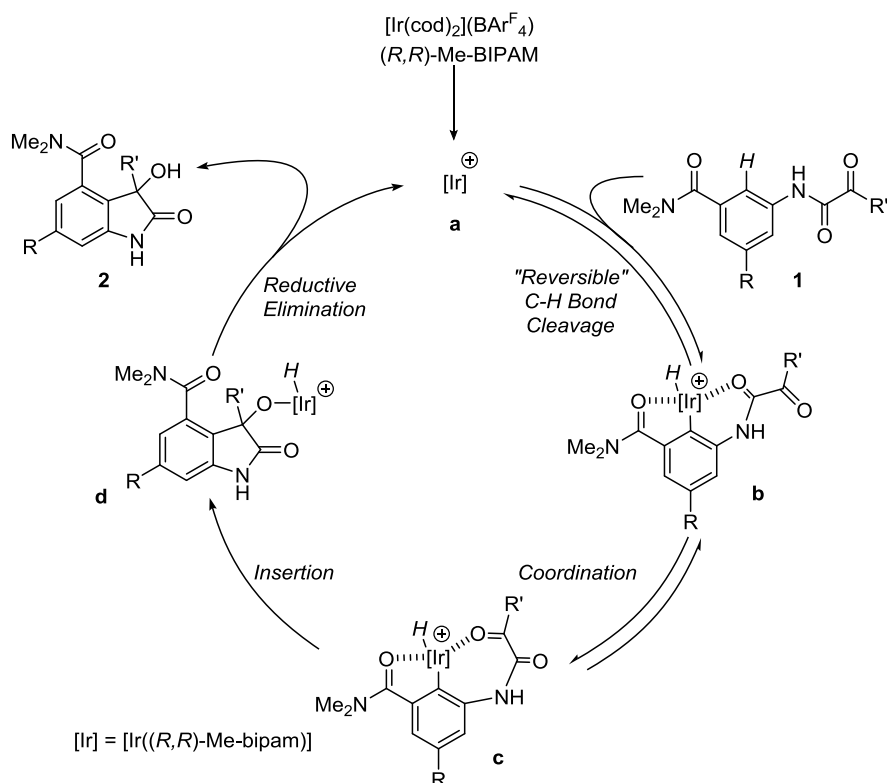


Figure 3.3 Hammett plot using substrates **1a** and **1f–h** (NH) or **1i–1l** (NMe)

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 $[\text{Ir}(\text{cod})_2](\text{BAr}^{\text{F}}_4)$ 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.



Scheme 3.6 **Proposed catalytic cycle**

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 Ar-[Ir((*R,R*)-Me-BIPAM)]-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**) ($\Delta E_{\text{c1-c2}} = 3.10$ kcal/mol). Thus, the enantioselective insertion to *Si*-face of the carbonyl group can be rationalized by less steric congestion intermediate **c2**.

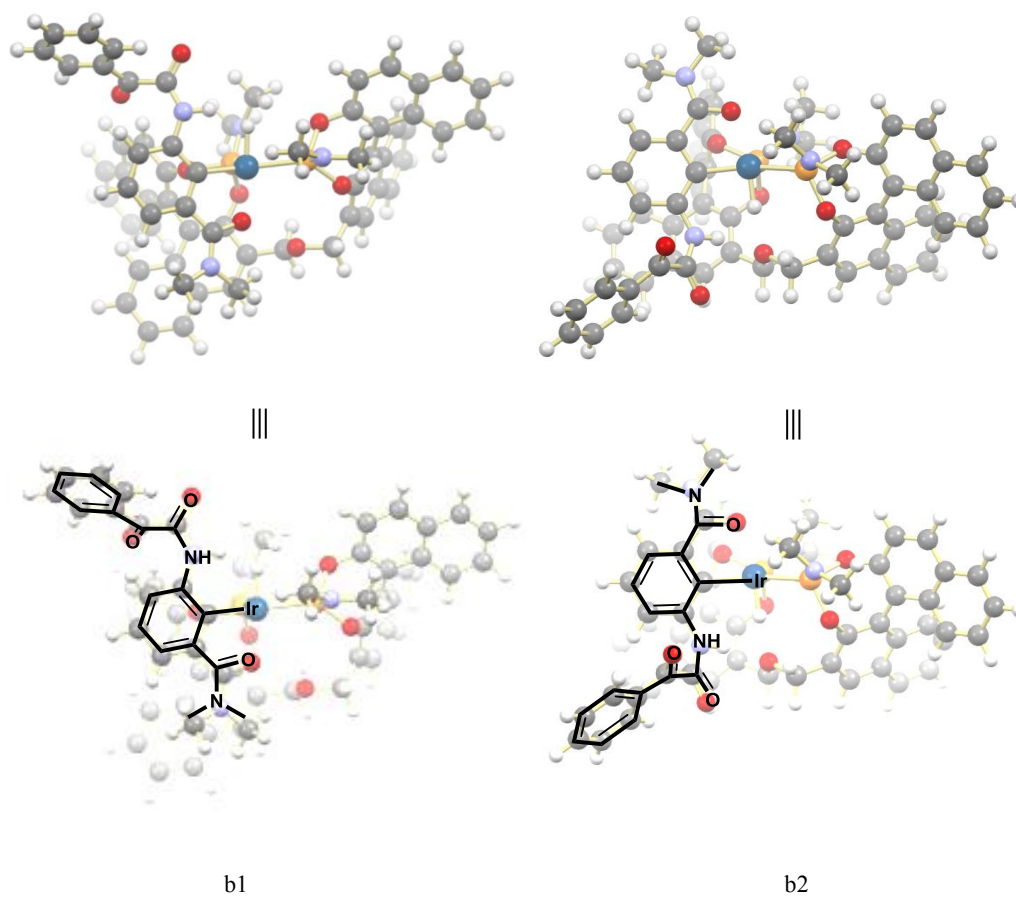


Figure 3.4 DFT calculations of aryl-iridium intermediate optimized at the B3LYP/LANL2DZ

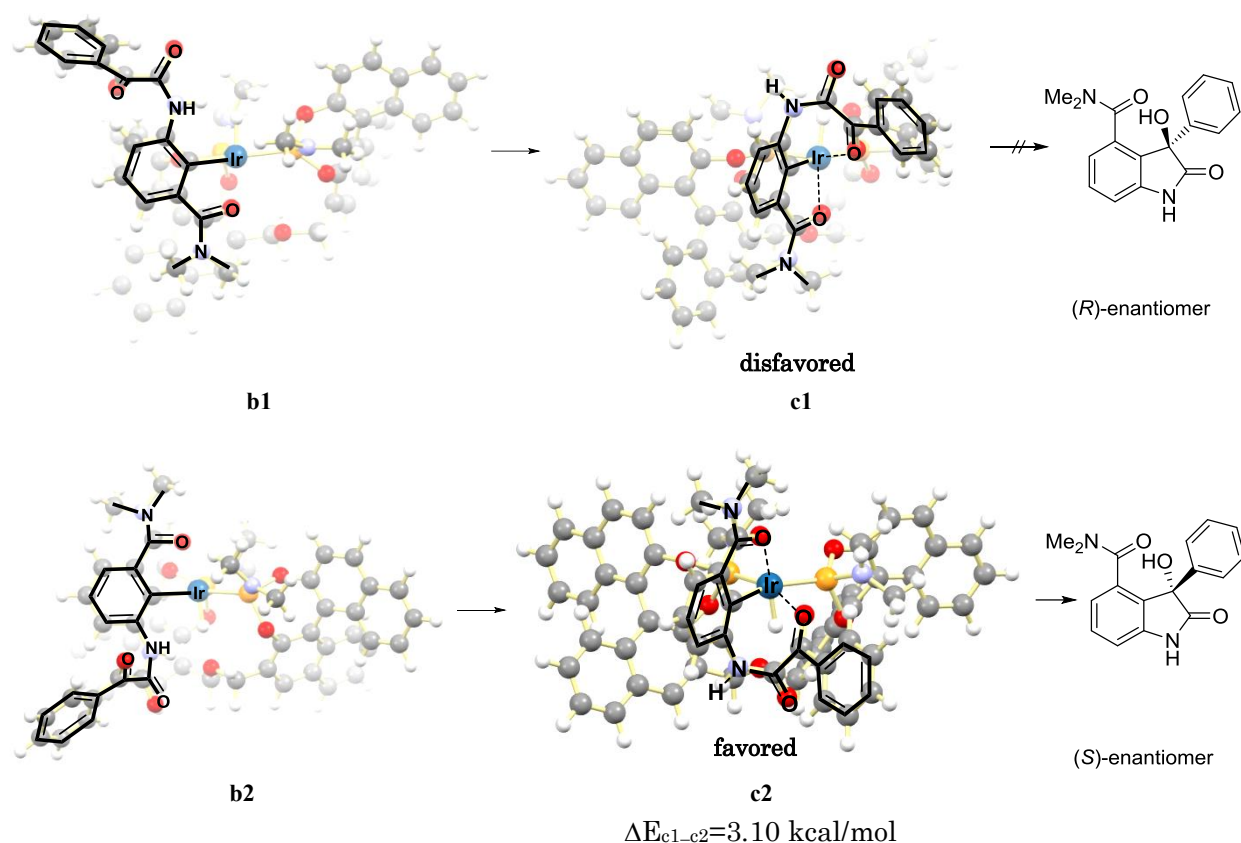


Figure 3.5 DFT calculations of enantioselection models at the B3LYP/LANL2DZ

3.3 Conclusion

In conclusion, the detailed mechanism for enantioselective intramolecular direct hydroarylation of α -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 ^1H 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 $\text{C}(\text{sp}^2)\text{--H}$ bond.

3.4 Experimental section

Mechanistic Studies

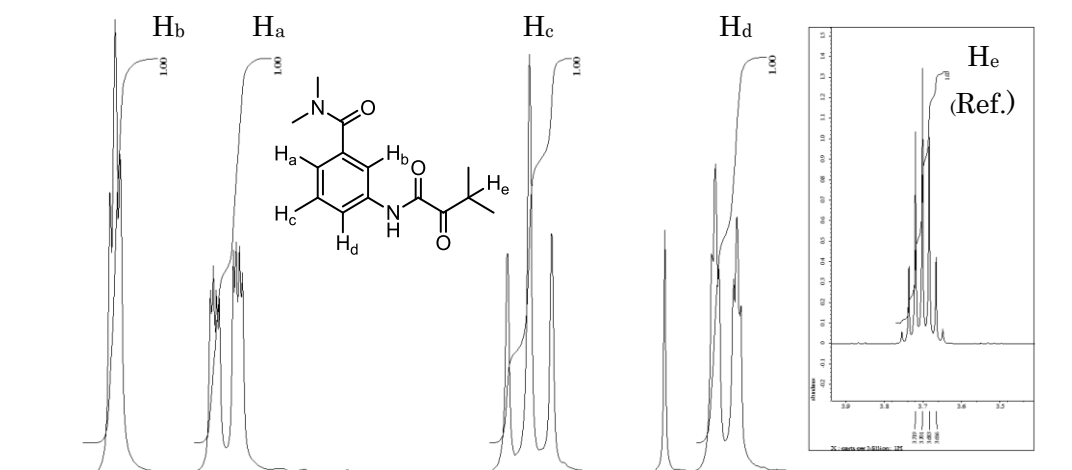
3.4.1 General procedures for NMR experiments of Iridium-hydride species

To a flame-dried NMR sample tube, $[\text{Ir}(\text{cod})_2](\text{BAr}^{\text{F}}_4)$ (0.00125 mmol) and (*R,R*)-Me-BIPAM (0.00125 mmol) and 1,2-dimethoxyethane-*D*₁₀ (1.0 mL) were added under an N₂ 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 α -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, ¹H NMR spectra were measured.

3.4.2 General procedures for deuterium labeling experiment

To a flame-dried NMR sample tube, $[\text{Ir}(\text{cod})_2](\text{BAr}^{\text{F}}_4)$ (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 N₂ atmosphere. The solution was stirred at room temperature for 30 min, followed by the addition of α -keto amide (0.25 mmol) and D₂O (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)

^1H NMR spectrum of original substrate



^1H NMR spectrum of recovered substrate

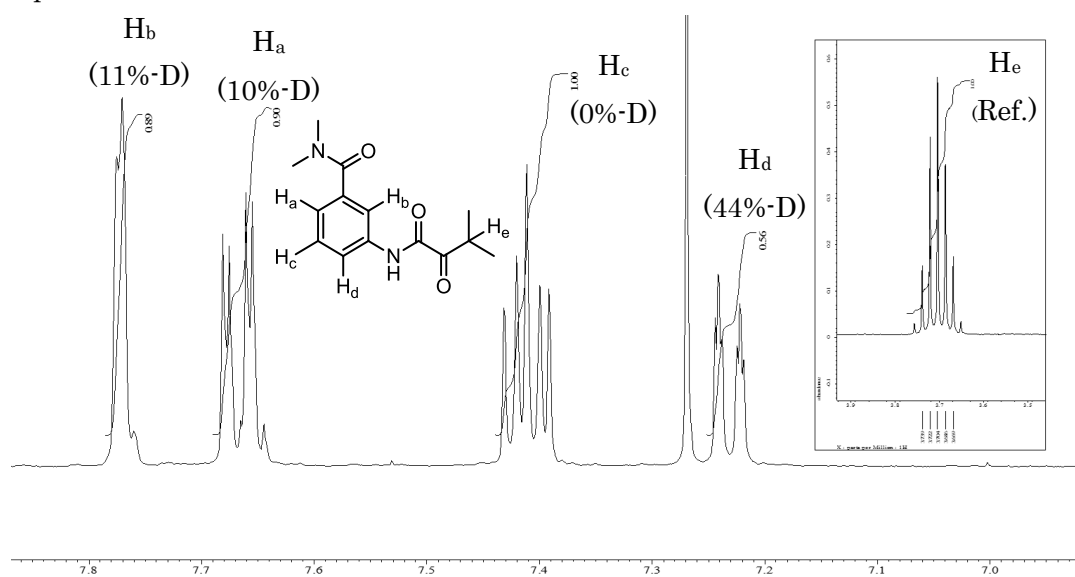
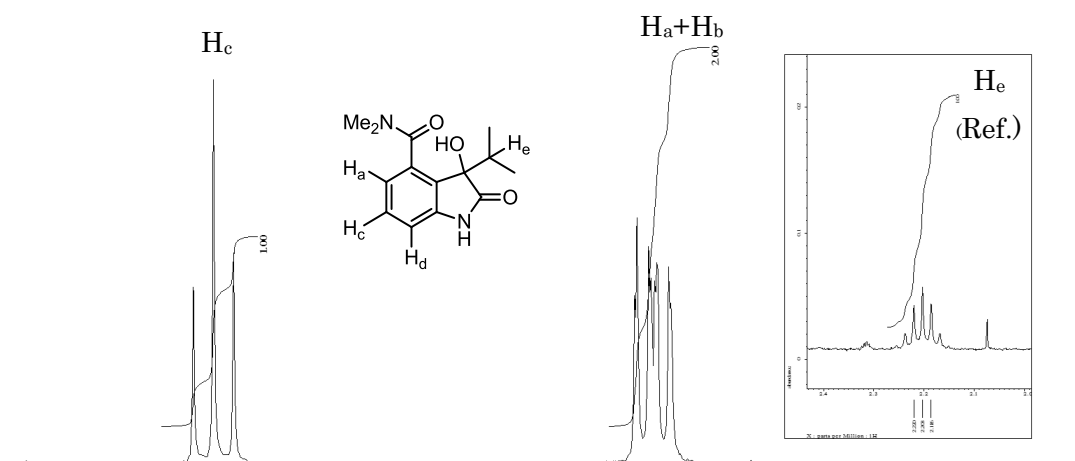


Figure 3.6 ^1H NMR Spectra of recovered substrate

^1H NMR spectrum of pure product



^1H NMR spectrum of product in the presence of D_2O

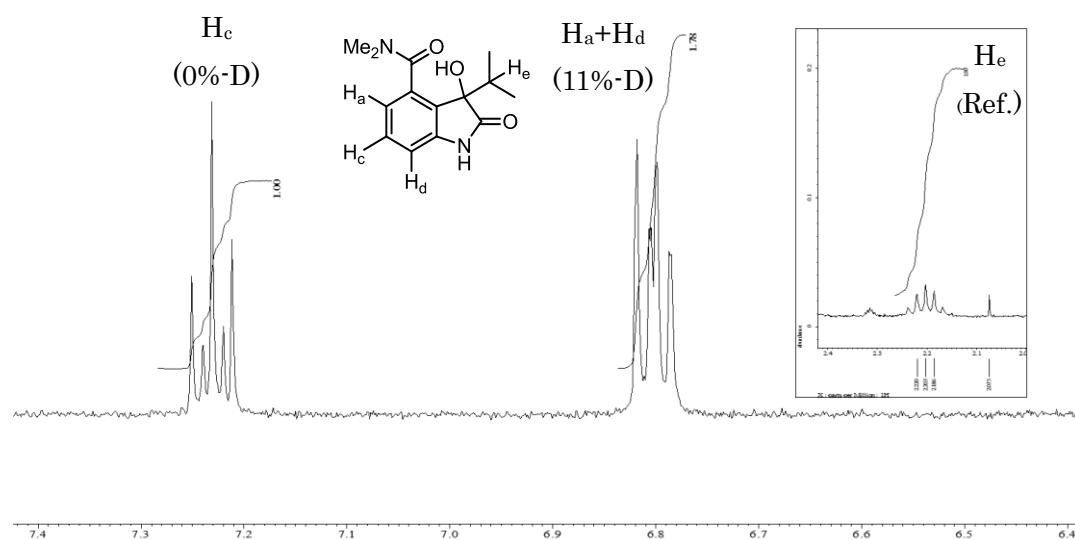
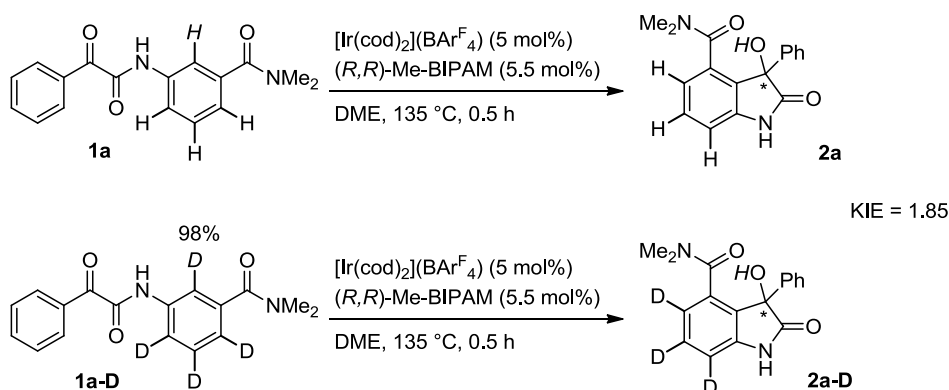


Figure 3.7 ^1H NMR spectra of product

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.



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*-CF₃ (**1c**), *p*-H (**1a**) vs *p*-CF₃ (**1c**), and *p*-Me (**1e**) vs *p*-Cl (**1d**)), respectively. To a flame-dried flask, $[\text{Ir}(\text{cod})_2](\text{BARF}_4)$ (0.0125 mmol, 5 mol%) and $(R,R)\text{-Me-BIPAM}$ (0.0138 mmol, 5.5 mmol%) and dry 1,2-dimethoxyethane (1.0 mL) were added under an N₂ 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

	k_X^a	k_X/k_H	$\log(k_X/k_H)$	σ
CH ₃	95.6	1.365714	0.13535985	-0.14
H	70	1	0	0
Cl	46	0.657143	-0.1823402	0.22
CF ₃	20.5	0.292857	-0.5333442	0.53

^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*-CF₃ (**1f**), and H (**1a**) vs *p*-Me (**1h**)), respectively. To a flame-dried flask, [Ir(cod)₂](BAr^F₄) (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 N₂ 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

	k_X^a	k_X/k_H	$\log(k_X/k_H)$	σ
CH ₃	82.4	1.024876	0.01067116	-0.14
H	80.4	1	0	0
F	72.4	0.900498	-0.0455175	0.06
CF ₃	70.1	0.871891	-0.059538	0.53

^aThe 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*-CF₃ (**1i**), *p*-Me (**1l**) vs *p*-F (**1j**), and H (**1k**) vs *p*-CF₃ (**1i**)), respectively. To a flame-dried flask, [Ir(cod)₂](BAr^F₄) (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 N₂ 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*-CF₃ (**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.

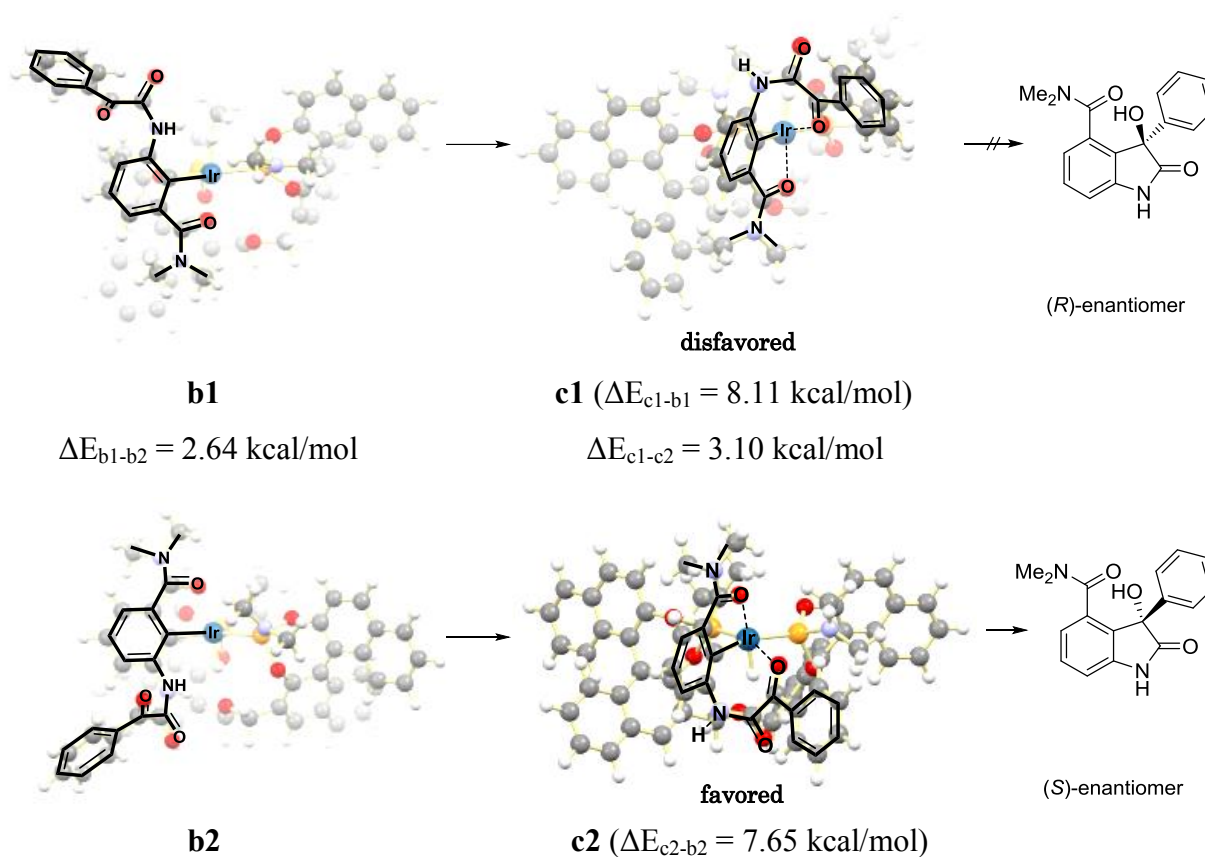
Plot data for Hammett correlation study

	k_X^a	k_X/k_H	$\log(k_X/k_H)$	σ
CH ₃	14.667	1.100053	0.0414134	-0.14
H	13.333	1	0	0
F	11.454	0.859071	-0.065971	0.06
CF ₃	8.6667	0.650019	-0.187074	0.53

^aThe 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.^{5,6} The basis sets were described using an effective core potential (LANL2DZ) for all atoms.⁷ The structures at the stationary points were fully optimized at the B3LYP/LANL2DZ level of theory.



DFT Calculations of Enantioselection Models at the B3LYP/LANL2DZ Level

The total energies and relative energies calculated at the B3LYP/LANL2DZ level of $[C_{63}H_{54}IrN_4O_8P_2(1+)]$ in gas-phase.

Intermediate	E (A.U.)		ΔE (A.U.)	ΔE (kcal/mol)
b1	-3371.11601922	ΔE_{b1-b2}	0.00421404	2.64
c1	-3371.10310293	ΔE_{c1-b1}	0.012916290	8.11
b2	-3371.12023326	ΔE_{c2-b2}	0.012196420	7.65
c2	-3371.10803684	ΔE_{c1-c2}	0.004933910	3.10

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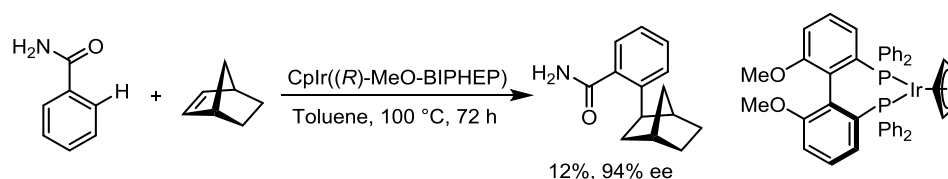
Chapter 4

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-economical 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,¹⁾ C=N,²⁾ and C=C,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.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.^{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).



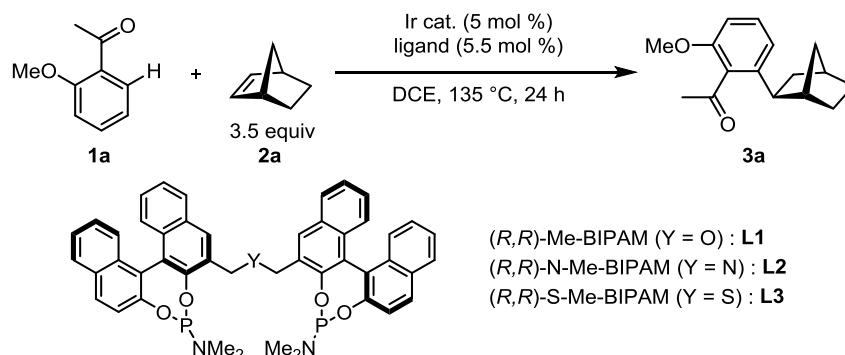
Scheme 4.1 Amide-assisted asymmetric hydroarylation

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.⁷⁾ 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](BAR^F₄)/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].⁸⁾ 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^[a]

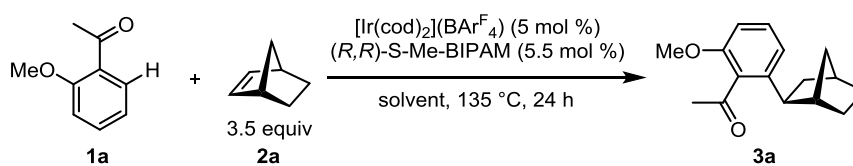


Entry	Precursor	Ligand	Yield ^[b] [%]	ee [%]
1	[Ir(cod) ₂](BARF ₄)	L1	93	52
2	[Ir(cod) ₂](BARF ₄)	L2	35	73
3	[Ir(cod) ₂](BARF ₄)	L3	82	88
4	[Ir(cod) ₂](BARF ₄)	BINAP	44	13
5	[Ir(cod) ₂](BARF ₄)	MonoPhos	96	21
6	[Ir(cod) ₂](SbF ₆)	L3	79	87
7	[Ir(cod) ₂](BF ₄)	L3	trace	–
8	[Ir(cod)Cl] ₂	L3	n.r.	–

[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.

[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-dioxa-4-phosphacyclohepta[2,1a;3,4-*a'*]dinaphthalen-4-yl)-dimethylamine.

Table 4.2 Optimization of solvents^[a]



Entry	Solvent	Yield ^[b] [%]	ee [%]
1	DCE	82	88
2	toluene	87	86
3	DME	58	89
4	THF	71	84
5	PhCl	71	80
6	DMF	trace	–

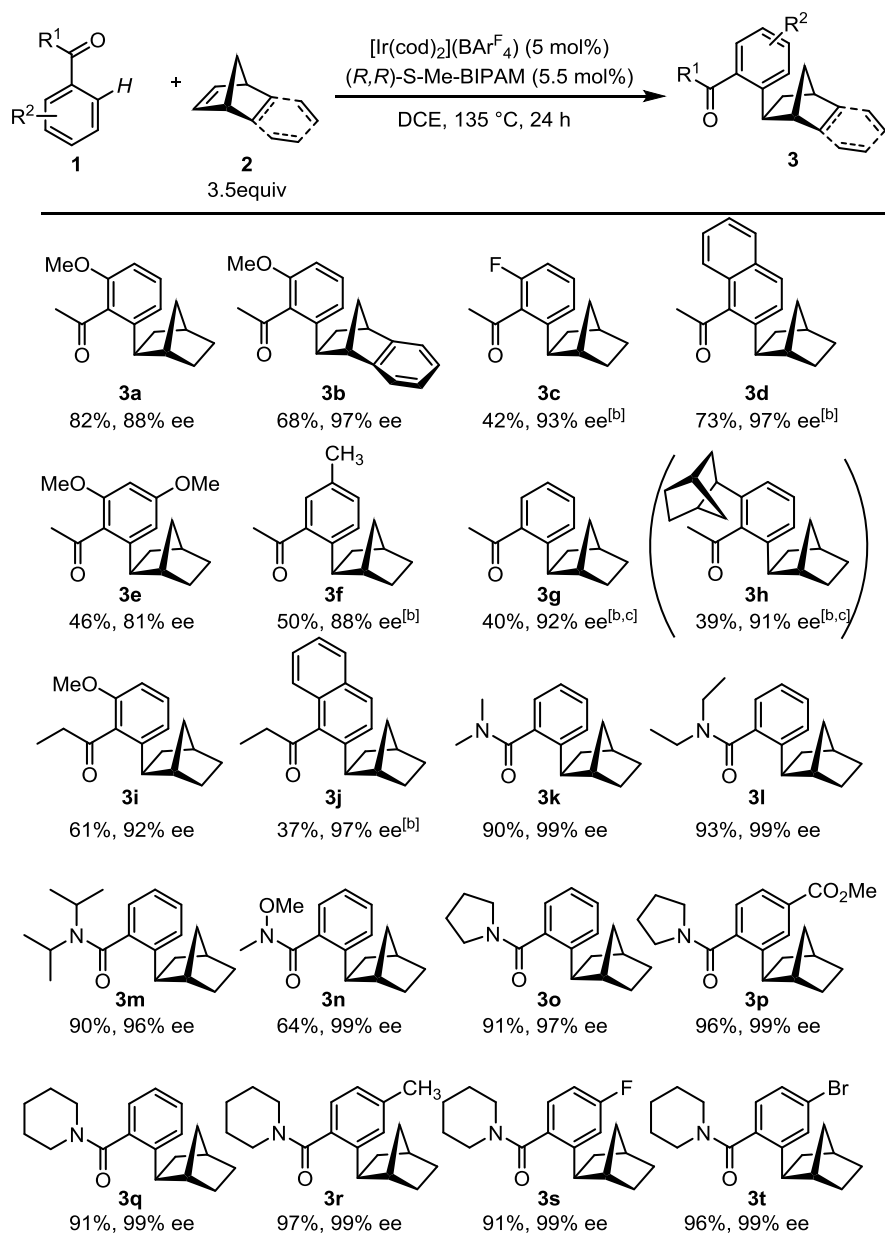
[a] Reaction conditions: arene (0.25 mmol), iridium catalyst (5 mol %), and ligand (1.1 equiv to Ir) in solvent (1 mL) was stirred for 24 h at 135 °C.

[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^[a]



[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.

[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.

[c] 0.5 mL of DCE was used as solvent.

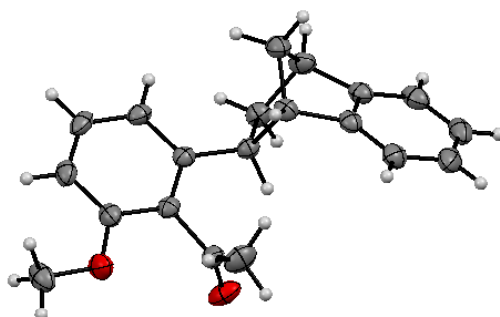


Figure 4.1 ORTEP diagram of **3b** with thermal ellipsoids set at 50%

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.

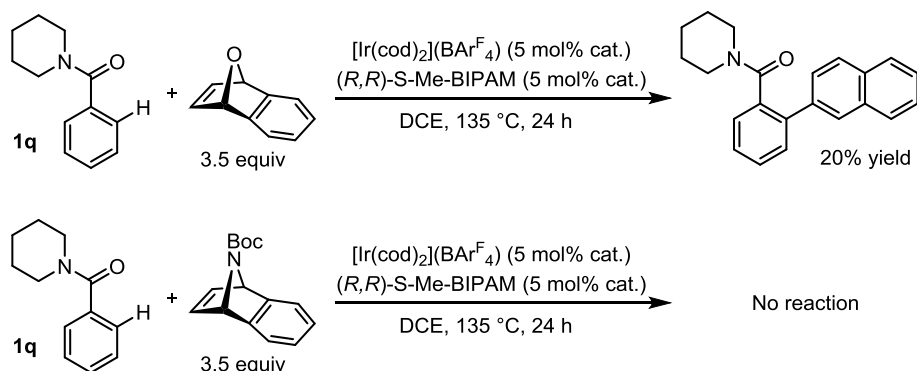
Table 4.4 Substituent effect of benzamides^[a]

Entry	R	R'		yield [%], ee [%] mono-	di-
1	H	H	(1u)	trace	-
2	Me	H	(1v)	23%, 99% ee	72%, 99% ee
3	Me	Me	(1k)	90%, 99% ee	-

[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.

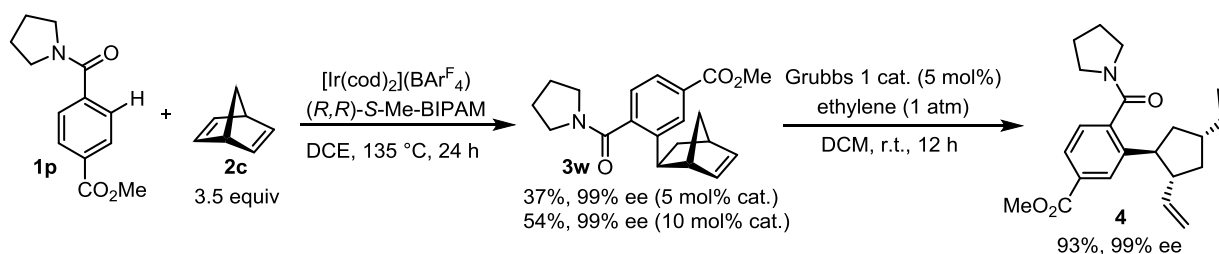
In addition, we carried out the reactions of oxygen- or nitrogen-containing bicyclic alkenes with benzamide **1q** (Scheme 4.2). Unfortunately, hydroarylation of heteroatom-containing bicyclic alkenes did not proceed in most cases. In the reaction of 1,4-dihydro-1,4-epoxynaphthalene, biaryl compound 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

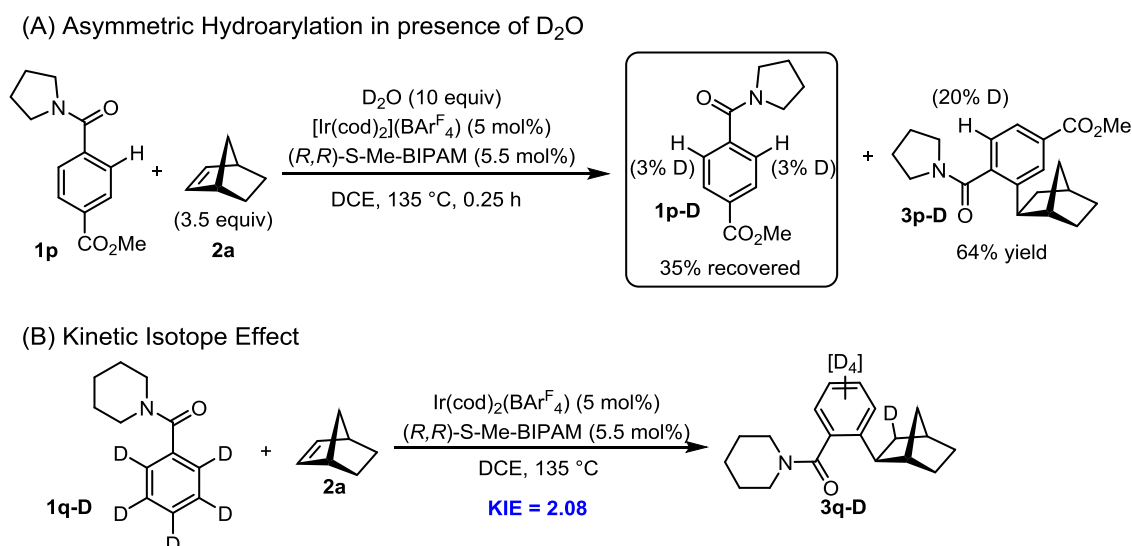
To demonstrate the synthetic utility of this protocol, we further transformed the products of asymmetric hydroarylation of bicycloalkenes. Enantioenriched norbornene could be used as a building block in organic synthesis for the preparation of functionalized chiral compounds. The highly functionalized 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 D_2O 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.^{1h, 1j, 4e)}



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 species¹¹⁾.

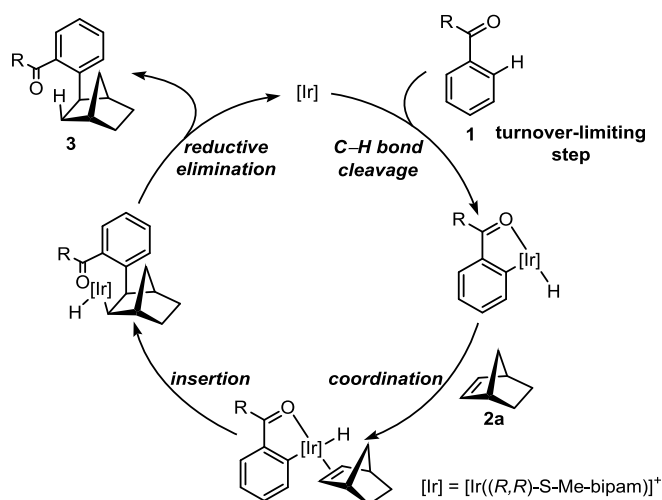


Figure 4.2 Proposed catalytic cycle

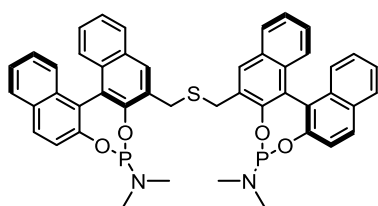
4.4 Conclusion

In this Chapter, we described the first highly enantioselective intermolecular hydroarylation of bicycloalkene through arene C–H bond cleavage catalyzed by a cationic iridium/(*R,R*)-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*)-S-Me-BIPAM (L3):

To a toluene solution (10 mL) of (*R,R*)-S-linked-BINOL (3.17 mmol) was added P(NMe₂)₃ (2.5 equiv) under N₂ 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 Et₃N) short column chromatography (hexane/AcOEt = 6/1) to afford desired (*R,R*)-S-linked bis(phosphoramidite) ((*R,R*)-S-Me-BIPAM) (L3) as pure white solid (63% yield).



¹H NMR (400 MHz, CD₂Cl₂): δ = 8.04-7.83 (m, 7H), 7.51-7.13 (m, 15H),

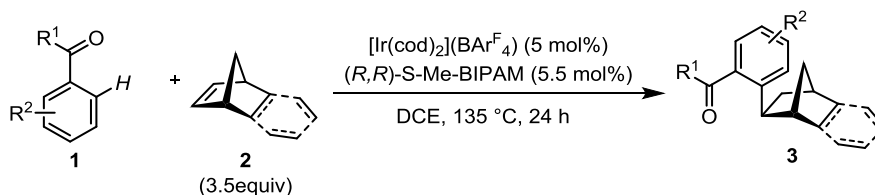
4.26 (d, *J* = 13.8 Hz, 2H), 3.96 (d, *J* = 13.8 Hz, 2H), 2.51-2.37 (m, 12H);

¹³C NMR (100 MHz, CD₂Cl₂): δ = 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,

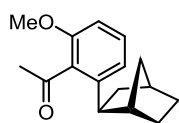
126.4, 126.2, 125.1, 124.9, 122.1, 35.8, 35.6, 32.4; ³¹P NMR (161.7 MHz, CD₂Cl₂) δ = 149.6; HRMS (APCI) *m/z* calc for C₄₆H₃₈O₄N₂NaP₂S (M+Na)⁺: 799.19197, found: 799.19160.

General procedure and NMR spectra of products



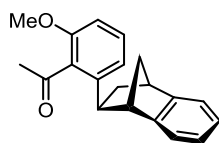
To a flame-dried sealed tube, [Ir(cod)₂](BARF₄) (0.0125 mmol, 5 mol%) and (*R,R*)-S-Me-BIPAM (0.0138 mmol, 5.5 mol%) and dry 1,2-dichloroethane (1.0 mL) were added under an N₂ atmosphere. The solution was stirred at room temperature for 30 min, followed by the addition of arene (0.25 mmol) and bicycloalkene (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)



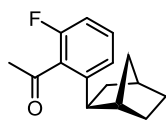
88% ee [HPLC condition: Chiralpak AS-H column, hexane/2-propanol = 200/1, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 16.9 min (minor) and 21.1 min (major)]; $[\alpha]_D^{20}$ = +54.5 (c 2.0, CHCl_3); ^1H NMR (400 MHz, CDCl_3): δ = 7.26 (t, J = 8.2 Hz, 1H), 6.93 (d, J = 8.2 Hz, 1H), 6.74 (d, J = 8.2 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); ^{13}C 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 $\text{C}_{16}\text{H}_{20}\text{O}_2\text{Na}$ ($\text{M}+\text{Na}$) $^+$: 267.13555, found: 267.13531.

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



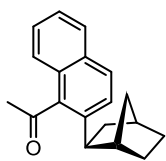
97% ee [HPLC condition: Chiralpak AD-3 column, hexane/2-propanol = 200/1, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 37.7 min (minor) and 46.6 min (major)]; $[\alpha]_D^{20}$ = + (c , CHCl_3); ^1H NMR (400 MHz, CDCl_3): δ = 7.32 (t, J = 8.1 Hz, 1H), 7.23–7.14 (m, 2H), 7.10–7.05 (m, 3H), 6.80 (d, J = 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); ^{13}C 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 $\text{C}_{20}\text{H}_{20}\text{O}_2\text{Na}$ ($\text{M}+\text{Na}$) $^+$: 315.13555, found: 315.13530.

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



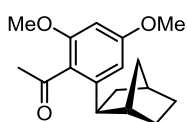
93% ee [HPLC condition: Chiralpak AD-H column, hexane/2-propanol = 200/1, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 10.3 min (minor) and 10.8 min (major)]; $[\alpha]_D^{20}$ = +78.0 (c 1.0, CHCl_3); ^1H NMR (400 MHz, CDCl_3): δ = 7.31–7.26 (m, 1H), 7.13 (d, J = 8.2 Hz, 1H), 6.90 (t, J = 8.6 Hz, 1H), 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); ^{13}C 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 $\text{C}_{15}\text{H}_{17}\text{OFNa}$ ($\text{M}+\text{Na}$) $^+$: 255.11556, found: 255.11551.

1-[2-(Exo-bicyclo[2.2.1]heptan-2-yl)naphthalen-1-yl]ethan-1-one (3d)



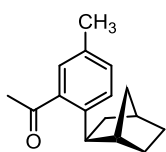
97% ee [HPLC condition: Chiralpak AS-H column, hexane/2-propanol = 200/1, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 19.3 min (minor) and 24.3 min (major)]; $[\alpha]_D^{20}$ = +54.6 (*c* 1.5, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ = 7.84–7.79 (m, 2H), 7.58–7.42 (m, 4H), 2.75 (dd, *J* = 8.5, 6.3 Hz, 1H), 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-dimethoxyphenyl]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, t_R = 18.4 min (minor) and 23.6 min (major)]; $[\alpha]_D^{20}$ = +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.

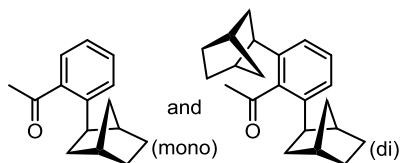
1-[2-(Exo-bicyclo[2.2.1]heptan-2-yl)-5-methylphenyl]ethan-1-one (3f)



88% ee [HPLC condition: Chiralpak AS-H column, hexane/2-propanol = 200/1, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 12.5 min (minor) and 15.3 min (major)]; $[\alpha]_D^{20}$ = +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)

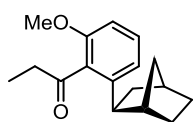


92% ee (mono), 91% ee (di) [HPLC condition: Chiralcel OJ-H column, hexane/2-propanol = 100/1, flow = 0.5 mL/min, wavelength = 230 nm, $t_{R(\text{mono})}$ = 10.8 min (minor) and 11.8 min (major), $t_{R(\text{di})}$ =

8.8 min (minor) and 9.2 min (major)]; $[\alpha]_{D^{20}} = +69.2$ (c 1.7, CHCl_3).

The ^1H 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)

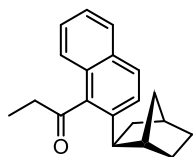


92% ee [HPLC condition: Chiralpak AD-3 column, hexane/2-propanol = 200/1, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 16.3 min (minor) and 17.7 min (major)];

$[\alpha]_{D^{20}} = +40.8$ (c 2.1, CHCl_3); ^1H NMR (400 MHz, CDCl_3): δ = 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): δ = 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 $\text{C}_{17}\text{H}_{22}\text{O}_2\text{Na}$ ($\text{M}+\text{Na}$) $^+$: 281.15120, found: 281.15085.

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

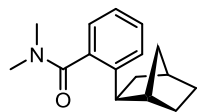


97% ee [HPLC condition: Chiralpak AD-3 column, hexane/2-propanol = 200/1, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 37.2 min (minor) and 40.9 min (major)];

$[\alpha]_{D^{20}} = +36.5$ (c 2.6, CHCl_3); ^1H NMR (400 MHz, CDCl_3): δ = 7.81 (d, J = 8.6 Hz, 2H),

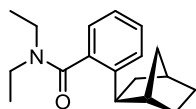
7.51–7.40 (m, 4H), 2.90 (q, J = 7.3 Hz, 2H), 2.67–2.63 (m, 1H), 2.41 (br s, 1H), 2.35 (br s, 1H), 1.82–1.54 (m, 5H), 1.34–1.24 (m, 3H), 1.30 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ = 211.8, 139.7, 138.5, 131.6, 129.0, 128.8, 128.1, 126.7, 125.4, 124.1, 123.9, 44.5, 43.8, 40.6, 39.3, 37.1, 36.6, 31.3, 28.4, 7.8; HRMS (ESI) m/z calc for $\text{C}_{20}\text{H}_{22}\text{ONa}$ ($\text{M}+\text{Na}$) $^+$: 301.15629, found: 301.15618.

2-(Exo-bicyclo[2.2.1]heptan-2-yl)-N,N-dimethylbenzamide (3k)



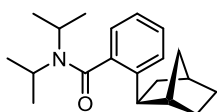
99.6% ee [HPLC condition: Chiralpak AD-3 column, hexane/2-propanol = 200/1, flow = 1.3 mL/min, wavelength = 230 nm, t_R = 54.5 min (minor) and 55.6 min (major)]; $[\alpha]_D^{20}$ = +49.8 (c 2.0, CHCl_3); ^1H NMR (400 MHz, CDCl_3): δ = 7.36–7.27 (m, 2H), 7.17 (t, J = 7.2 Hz, 1H), 7.13–7.08 (m, 1H), 3.14 (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); ^{13}C NMR (100 MHz, CDCl_3): 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 $\text{C}_{16}\text{H}_{21}\text{ONNa}$ ($\text{M}+\text{Na}$) $^{+}$: 266.15154, found: 266.15137.

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



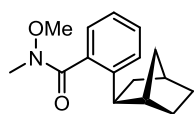
99.1% ee [HPLC condition: Chiralpak AD-3 column, hexane/2-propanol = 200/1, flow = 1.3 mL/min, wavelength = 230 nm, t_R = 53.4 min (minor) and 55.9 min (major)]; $[\alpha]_D^{20}$ = +22.8 (c 2.1, CHCl_3); ^1H NMR (400 MHz, TCE-D_2): δ = 7.32–7.26 (m, 2H), 7.19–7.12 (m, 1H), 7.10–7.06 (m, 1H), 3.90–3.72 (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); ^{13}C NMR (100 MHz, TCE-D_2): 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 $\text{C}_{18}\text{H}_{25}\text{ONNa}$ ($\text{M}+\text{Na}$) $^{+}$: 294.18284, found: 294.18224.

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



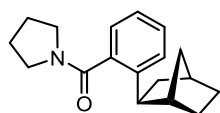
96% ee [HPLC condition: Chiralpak AD-3 column, hexane/2-propanol = 200/1, flow = 1.3 mL/min, wavelength = 230 nm, t_R = 33.1 min (minor) and 38.2 min (major)]; $[\alpha]_D^{20}$ = +9.6 (c 1.4, CHCl_3); ^1H NMR (400 MHz, TCE-D_2): δ = 7.32–7.25 (m, 2H), 7.15 (t, J = 6.8 Hz, 1H), 7.03 (t, J = 6.8 Hz, 1H), 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); ^{13}C NMR (100 MHz, TCE-D_2): 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 $\text{C}_{20}\text{H}_{29}\text{ONNa}$ ($\text{M}+\text{Na}$) $^{+}$: 322.21414, found: 322.21377.

2-(Exo-bicyclo[2.2.1]heptan-2-yl)-N-methoxy-N-methylbenzamide (3n)



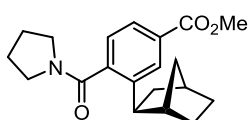
99.0% ee [HPLC condition: Chiralpak AD-3 column, hexane/2-propanol = 200/1, flow = 1.3 mL/min, wavelength = 230 nm, t_R = 45.4 min (minor) and 46.9 min (major)]; $[\alpha]_D^{20}$ = +40.4 (*c* 2.6, CHCl₃); ¹H NMR (400 MHz, DMSO-*D*₆ at 353 K): δ = 7.38–7.30 (m, 2H), 7.23–7.17 (m, 2H), 3.51 (s, 3H), 3.19 (s, 3H), 2.75 (t, *J* = 7.7 Hz, 1H), 2.32 (br s, 1H), 2.27 (br s, 1H), 1.68–1.48 (m, 5H), 1.30–1.14 (m, 3H); ¹³C NMR (100 MHz, DMSO-*D*₆ at 353 K): δ = 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 C₁₆H₂₁O₂NNa (M+Na)⁺: 282.14645, found: 282.14620.

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



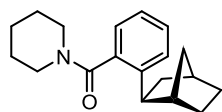
97% ee [HPLC condition: Chiralpak AD-3 column, hexane/2-propanol = 200/1, flow = 1.3 mL/min, wavelength = 230 nm, t_R = 50.4 min (minor) and 52.3 min (major)]; $[\alpha]_D^{20}$ = +54.4 (*c* 1.6, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ = 7.35–7.27 (m, 2H), 7.19–7.14 (m, 2H), 3.71–3.60 (m, 2H), 3.20–3.08 (m, 2H), 2.89 (br s, 1H), 2.43–2.31 (m, 2H), 2.00–1.47 (m, 9H), 1.33–1.20 (m, 3H); ¹³C NMR (100 MHz, CDCl₃): δ = 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 C₁₈H₂₃ONNa (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, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ = 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); ¹³C NMR (100 MHz, CDCl₃): δ = 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 C₂₀H₂₅O₃NNa (M+Na)⁺: 350.17266, found: 350.17231.

1-[(2-(Exo-bicyclo[2.2.1]heptan-2-yl)phenyl)carbonyl]piperidine (3q)

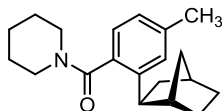


99.0% ee [HPLC condition: Chiralpak AD-3 column, hexane/2-propanol = 200/1,

flow = 1.3 mL/min, wavelength = 230 nm, t_R = 40.3 min (minor) and 45.4 min (major)]; $[\alpha]_D^{20}$ = +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), 7.11–7.09 (m, 1H), 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, 14H); ^{13}C 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 $\text{C}_{19}\text{H}_{25}\text{ONNa}$ ($\text{M}+\text{Na}$) $^+$: 306.18284, found: 306.18266.

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

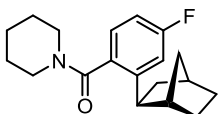


99.3% ee [HPLC condition: Chiralpak AD-3 column, hexane/2-propanol = 200/1,

flow = 1.3 mL/min, wavelength = 230 nm, t_R = 76.6 min (minor) and 94.7 min (major)]; $[\alpha]_D^{20}$ = +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, 14H); ^{13}C 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 $\text{C}_{20}\text{H}_{27}\text{ONNa}$ ($\text{M}+\text{Na}$) $^+$: 320.19849, found: 320.19803.

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

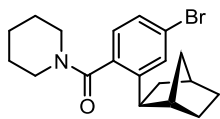


99.9% ee [HPLC condition: Chiralpak AD-3 column, hexane/2-propanol = 200/1,

flow = 1.3 mL/min, wavelength = 230 nm, t_R = 57.0 min (minor) and 58.0 min (major)]; $[\alpha]_D^{20}$ = +35.5 (c 2.0, CHCl_3); ^1H NMR (400 MHz, TCE-D_2): δ = 7.06–6.98

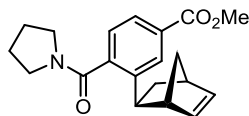
(m, 2H), 6.89–6.81 (m, 1H), 3.80–3.50 (m, 2H), 3.16–3.02 (m, 2H), 2.80 (dd, J = 8.5, 5.8 Hz, 1H), 2.41–2.10 (m, 2H), 1.77–1.21 (m, 14H); ^{13}C NMR (100 MHz, TCE-D_2): δ = 170.7, 170.6, 164.2 (d, J = 246 Hz), 149.2, 148.5, 134.4, 133.9, 129.0 (d, J = 8.6 Hz), 114.9, 114.7, 114.5, 113.8 (d, J = 21.9 Hz), 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 $\text{C}_{19}\text{H}_{24}\text{ONFNa}$ ($\text{M}+\text{Na}$) $^+$: 324.17341, found: 324.17330.

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



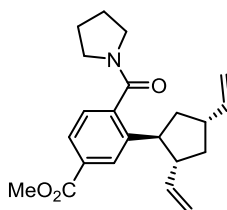
99.3% ee [HPLC condition: Chiralpak AD-3 column, hexane/2-propanol = 200/1, flow = 1.3 mL/min, wavelength = 230 nm, t_R = 59.1 min (minor) and 69.0 min (major)]; $[\alpha]_D^{20}$ = +25.8 (c 1.0, CHCl_3); ^1H NMR (400 MHz, CDCl_3): δ = 7.46 (t, J = 2.3 Hz, 1H), 7.33–7.29 (m, 1H), 6.98 (d, J = 8.2 Hz, 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); ^{13}C NMR (100 MHz, CDCl_3): δ = 169.2, 169.1, 146.5, 146.2, 135.5, 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 $\text{C}_{19}\text{H}_{24}\text{ONBrNa}$ ($\text{M}+\text{Na}$) $^+$: 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: Chiralpak AD-3 column, hexane/2-propanol = 200/1, flow = 1.3 mL/min, wavelength = 230 nm, t_R = 126.4 min (minor) and 164.2 min (major)]; $[\alpha]_D^{20}$ = +49.5 (c 2.8, CHCl_3); ^1H NMR (400 MHz, CDCl_3): 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); ^{13}C NMR (100 MHz, CDCl_3): 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 $\text{C}_{20}\text{H}_{23}\text{O}_3\text{NNa}$ ($\text{M}+\text{Na}$) $^+$: 348.15701, found: 348.15677.

Methyl 3-[(1*S*,2*R*,4*R*)-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 N_2 atmosphere. The resulting solution was sparged with ethylene gas. A Grubbs 1st generation catalyst (5 mol%) in dichloromethane (5 mL) 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: Chiralpak AD-3 column, hexane/2-propanol = 200/1, flow = 1.3 mL/min, wavelength = 230 nm, t_R = 116.4 min (minor) and 141.5 min (major)]; $[\alpha]_D^{20}$ = +9.58 (c 2.0, CHCl_3); ^1H NMR (400 MHz, CDCl_3): 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); ^{13}C NMR (100 MHz, CDCl_3): 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 $\text{C}_{22}\text{H}_{27}\text{O}_3\text{NNa}$ ($\text{M}+\text{Na}$) $^{+}$: 376.18831, found: 376.18801.

X-ray Crystal Structure of Compound 3b

Data Collection

A colorless block crystal of $C_{20}H_{20}O_2$ 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-K α 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:

$$a = 7.16564(15) \text{ \AA}$$

$$b = 12.5866(2) \text{ \AA}$$

$$c = 17.3312(4) \text{ \AA}$$

$$V = 1563.11(6) \text{ \AA}^3$$

For $Z = 4$ and F.W. = 292.38, the calculated density is 1.242 g/cm³. The reflection conditions of:

$$h00: h = 2n$$

$$0k0: k = 2n$$

$$00l: l = 2n$$

uniquely determine the space group to be:

$$P2_12_12_1 \text{ (\#19)}$$

The data were collected at a temperature of $-150 \pm 1^\circ\text{C}$ to a maximum 2θ value of 136.5° . A total of 30 oscillation images were collected. A sweep of data was done using ω scans from 80.0 to 260.0° in 30.00° step, at $\phi = 54.0^\circ$ and $\chi = 0.0^\circ$. The exposure rate was 60.0 [sec./ $^\circ$]. A second sweep

was performed using ω scans from 80.0 to 260.0° in 30.00° step, at $c=54.0^\circ$ and $\phi = 90.0^\circ$. The exposure rate was 60.0 [sec./°]. Another sweep was performed using ω scans from 80.0 to 260.0° in 30.00° step, at $c=54.0^\circ$ and $\phi = 195.0^\circ$. The exposure rate was 60.0 [sec./°]. Another sweep was performed using ω scans from 80.0 to 260.0° in 30.00° step, at $c=54.0^\circ$ and $\phi = 270.0^\circ$. The exposure rate was 60.0 [sec./°]. Another sweep was performed using ω scans from 80.0 to 260.0° in 30.00° step, at $c=0.0^\circ$ and $\phi = 0.0^\circ$. The exposure rate was 60.0 [sec./°]. 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, μ , for Cu-K α 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:

$$R_1 = \sum ||F_o| - |F_c|| / \sum |F_o| = 0.0360$$

$$wR_2 = [\sum (w (F_o^2 - F_c^2)^2) / \sum w(F_o^2)^2]^{1/2} = 0.0994$$

The goodness of fit was 0.78. Unit weights were used. Plots of $\sum w (|F_o| - |F_c|)^2$ 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 F_{calc}; the values for D_f' and D_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 SHELXL2013.

EXPERIMENTAL DETAILS

A. Crystal Data

Empirical Formula	C ₂₀ H ₂₀ O ₂
Formula Weight	292.38
Crystal Color, Habit	colorless, block
Crystal Dimensions	0.627 X 0.438 X 0.374 mm
Crystal System	orthorhombic
Lattice Type	Primitive
Lattice Parameters	a = 7.16564(15) Å b = 12.5866(2) Å c = 17.3312(4) Å V = 1563.11(6) Å ³
Space Group	P2 ₁ 2 ₁ 2 ₁ (#19)
Z value	4
D _{calc}	1.242 g/cm ³
F ₀₀₀	624.00
m(CuKα)	6.200 cm ⁻¹

B. Intensity Measurements

Diffractometer	R·AXIS RAPID
Radiation	CuK α ($\lambda = 1.54187 \text{ \AA}$)
	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
2 θ_{max}	136.5°
No. of Reflections Measured	Total: 15757
	Unique: 2857 ($R_{\text{int}} = 0.0433$)
	Parsons quotients (Flack x parameter): 992
Corrections	Lorentz·polarization
	Absorption
	(trans. factors: 0.697 - 0.793)

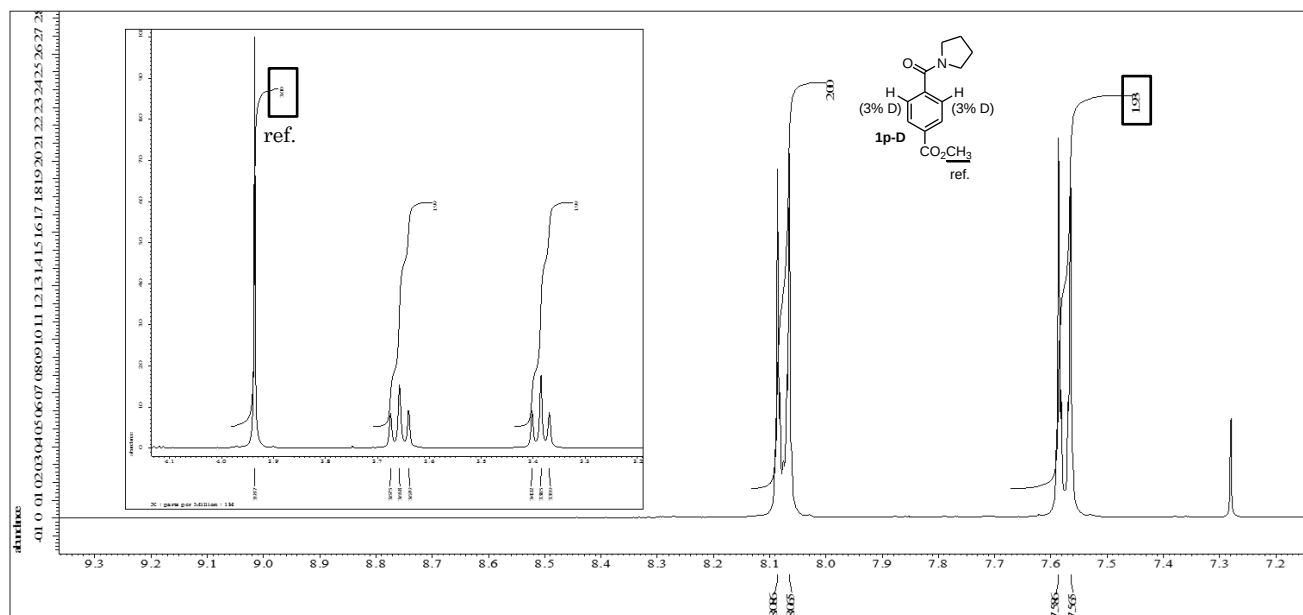
C. Structure Solution and Refinement

Structure Solution	Direct Methods (SHELXS2013)
Refinement	Full-matrix least-squares on F^2
Function Minimized	$\sum w (F_o^2 - F_c^2)^2$
Least Squares Weights	$w = 1 / [\sigma^2(F_o^2) + (0.1000 \cdot P)^2 + 0.0000 \cdot P]$ where $P = (\text{Max}(F_o^2, 0) + 2F_c^2)/3$
$2\theta_{\text{max}}$ cutoff	136.5°
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (All reflections)	2857
No. Variables	201
Reflection/Parameter Ratio	14.21
Residuals: R_1 ($I > 2.00\sigma(I)$)	0.0360
Residuals: R (All reflections)	0.0386
Residuals: wR_2 (All reflections)	0.0994
Goodness of Fit Indicator	0.784
Flack parameter (Parsons' quotients = 992)	0.01(10)
Max Shift/Error in Final Cycle	0.067
Maximum peak in Final Diff. Map	0.12 e ⁻ /Å ³
Minimum peak in Final Diff. Map	-0.18 e ⁻ /Å ³

Deuterium labeling experiments

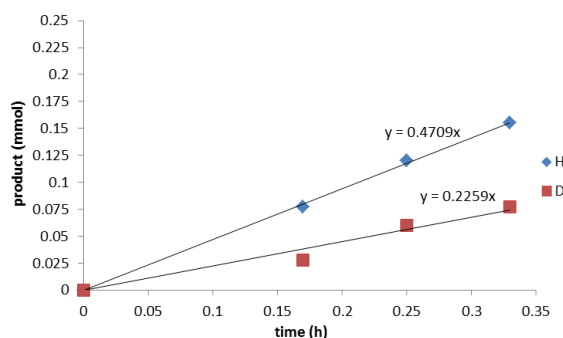
General procedures of hydroarylation in presence of D₂O

To a flame-dried sealed tube, [Ir(cod)₂](BAr^F₄) (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 N₂ 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 D₂O (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 ¹H 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, $[\text{Ir}(\text{cod})_2](\text{BAr}^{\text{F}}_4)$ (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

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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
T. Shirai, H. Ito, Y. Yamamoto, *Angew. Chem. Int. Ed.* **2014**, *53*, 2658–2661.
Selected as “Back Cover”
Highlighted in Synfacts **2014**, *10*, 493.
- (2) Cationic Iridium/S-Me-BIPAM-Catalyzed Direct Asymmetric Intermolecular Hydroarylation of Bicycloalkenes
T. Shirai, Y. Yamamoto, *Angew. Chem. Int. Ed.* **2015**, *54*, 9894–9897.
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 Furyl Ring with Ozone
X.-Q. Yu, **T. Shirai**, Y. Yamamoto, N. Miyaoura, *Chem. Asian J.* **2011**, *6*, 932–937.
Selected as “New Synthetic Methods” in J. Synth. Org. Chem. Jpn. **2011**, *69*, 727.
- (2) Ru/Me-BIPAM-Catalyzed Asymmetric Addition of Arylboronic Acids to Aliphatic Aldehydes and α -Ketoesters
Y. Yamamoto, **T. Shirai**, M. Watanabe, K. Kurihara, N. Miyaoura, *Molecules* **2011**, *16*, 5020-5034.
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
Y. Yamamoto, **T. Shirai**, N. Miyaoura, *Chem. Commun.* **2012**, *48*, 2803–2805.
Highlighted in Synfacts **2012**, *8*, 516.
- (4) Me-BIPAM for the Synthesis of Optically Active 3-Aryl-3-Hydroxy-2-Oxindoles by Ruthenium-Catalyzed Addition of Arylboronic Acids to Isatins
Y. Yamamoto, M. Yohda, **T. Shirai**, H. Ito, N. Miyaoura, *Chem. Asian J.* **2012**, *7*, 2446–2449.

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Tomohiko Shirai

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