Ruthenium/Me-BIPAM Catalyzed Asymmetric Addition of Arylboronic Acids to Carbonyl Compounds

A Thesis

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by

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Contents

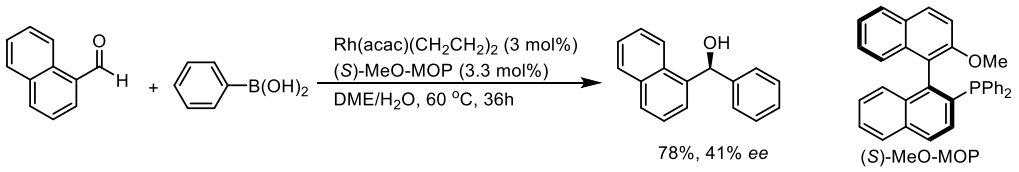
Chapter 1 Introduction

1.1 Asymmetric addition of arylboronic acids to aldehydes

The arylation of aldehydes with organolithium,[1] organomagnesium,[2] and organozinc[3,4] reagents are the traditional way in which to access diarylmethanols. But there has been recent interest in the transition-metal-catalyzed arylation using non-metallic boron[5–9] and silicon[10,11] compounds; such compounds are stable in air and water, are compatible with a broad range of functional groups, and have potential applications in asymmetric synthesis. In 1997, the basis of the chemistry involved can be found in early contributions by Oi, Inoue, and co-worker for rhodium-catalyzed arylation of aldehydes and ketones with arylstannanes.[12] In 1998, Miyaura and co-workers reported a rhodium-catalyzed addition of organoboronic acids to aldehydes using several ligands.[5a] This discovery was then followed by additions of organoboronic acids with rhodium[5], palladium[6], nickel[7], ruthenium[8], cobalt[9] catalysts.

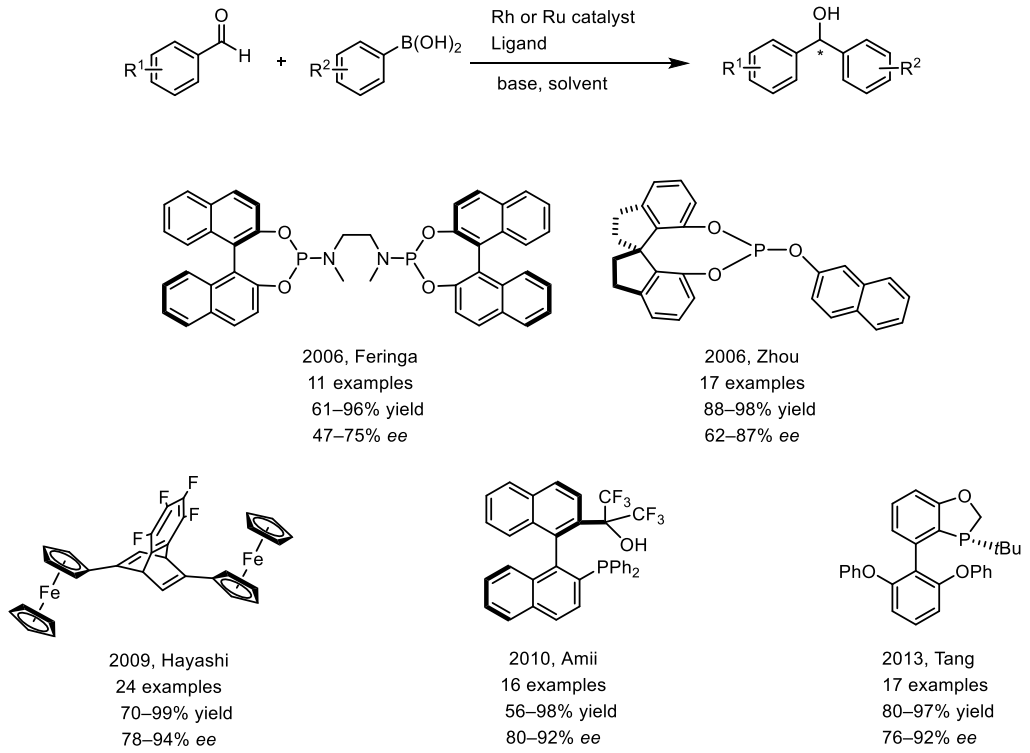
Optically active secondary alcohol derivatives are known as the attractive compounds, which are important family of biologically active molecules and synthetic materials of medicine. Especially, these compounds such as 3-substituted-isobenzofuranones are important structures in medicinal chemistry as well as in synthetic chemistry.[13,14] Recently, various methods for the synthesis of these chiral compounds have been developed.[15] Reported methods include lactonization followed by the hydrogenation of the corresponding ketones,[16] intramolecular ketone hydroacylation,[17] aldol reaction,[18] addition reaction,[19] and cyclization reaction.[20] Transition metal-catalyzed addition reactions of arylboronic acids with aldehydes and intramolecular cyclization also have become useful tools for accessing 3-aryl-isobenzofuranones.[21]

In 1998, Miyaura and co-workers first reported a rhodium-catalyzed arylation of arylboronic acids to aromatic aldehydes.[5a] In this report, the combination of $[Rh(acac)(CH_2CH_2)]$ (acac = acetylacetonato) and MeO-MOP could efficiently catalyze the asymmetric addition of phenylboronic acid to 1-naphthylaldehyde in aqueous dimethoxyethane (Scheme 1.1).



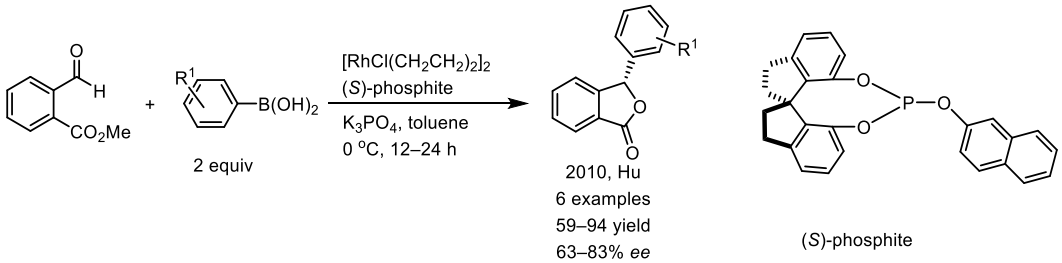
Scheme 1.1 Rhodium/MeO-MOP-catalyzed asymmetric addition of arylboronic acid to 2-naphthyl-aldehyde

There have been many attempts at arylation of aldehydes with arylboronic acids using chiral rhodium-catalysts. However, this protocol did not achieve high enantioselectivity with conventional bisphosphine ligands designed based on C2 symmetry. Recently, a variety of chiral ligands were developed and rhodium-catalyzed asymmetric addition to aldehyde has been investigated. In 2006, Feringa and co-workers reported that bidentate phosphoramidite is an effective chiral ligand in the rhodium-catalyzed asymmetric addition of arylboronic acids to aldehydes, providing chiral diarylmethanols in high yields and up to 75% *ee* (Scheme 1.2).[5g] In the same year, Zhou and co-workers reported that chiral spiro-phosphite ligand also proved to provide excellent yields and good enantiomeric excesses in addition reaction of arylboronic acids to aldehydes (62–87% *ee*).[5h] In 2009, Hayashi and co-workers developed a novel C2-symmetric tetrafluorobenzobarrelene ligand and applied it in the rhodium-catalyzed asymmetric addition reaction of arylboronic acids to aryl aldehydes, affording chiral diarylmethanols in high yields and high enantioselectivities (78–94% *ee*).[5j] In 2010, Amii and co-workers developed that chiral monophosphorus ligand bearing a di(trifluoromethyl)alcohol moiety has excellent catalytic activity for asymmetric 1,2-addition of arylboronic acids to aldehydes (80–92% *ee*).[5o] More recently, Tang and co-workers reported that a ruthenium catalyst on the basis of a chiral monophosphorus ligand was efficient for the asymmetric addition of arylboronic acids to aryl aldehydes, providing a series of chiral diarylmethanols in excellent yields and enantioselectivities (81–92% *ee*).[8e]



Scheme 1.2 Rhodium catalyzed asymmetric addition of arylboronic acids to aromatic aldehydes

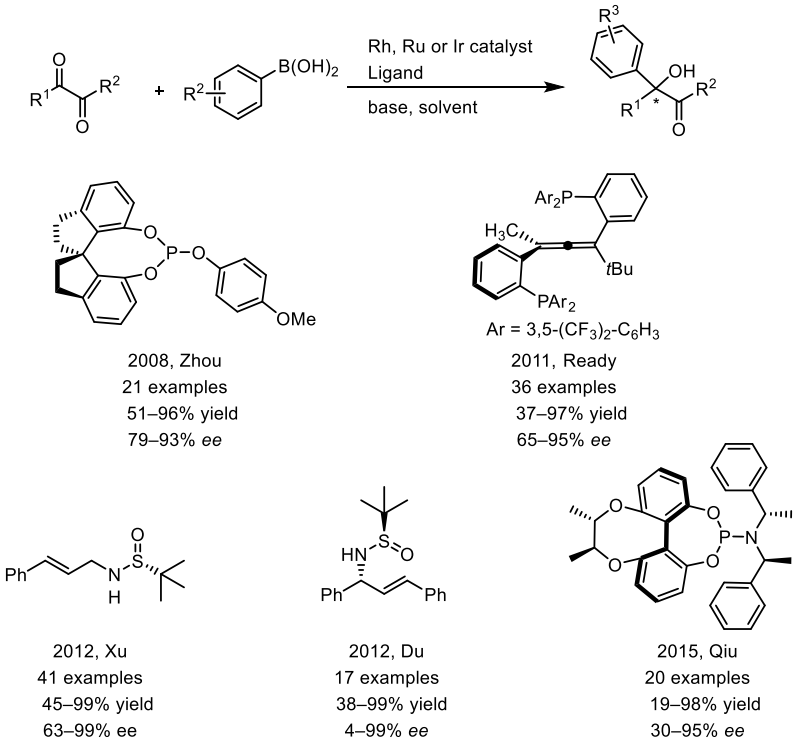
Recently, rhodium catalyzed asymmetric addition of arylboronic acids and cyclization strategy was developed for synthesis of 3-aryl-isobenzofuranones. In 2010, Hu and co-workers applied methyl 2-formylbenzoate in the rhodium catalyzed asymmetric addition with various arylboronic acids; a series of chiral 3-substituted phthalides (63–83% *ee*) were conveniently synthesized by using rhodium/SPINOL-based phosphite catalytic system (Scheme 1.3).[5m]



Scheme 1.3 Rhodium/phosphite catalyzed asymmetric addition of arylboronic acids to 2-formylbenzoate and cyclization

1.2 Asymmetric addition of arylboronic acids to ketones

Optically active 3-substituted tertiary alcohol derivatives are important structures in medicinal chemistry as well as in synthetic chemistry. Recently, rhodium catalyzed asymmetric addition of arylboronic acids to α-keto carbonyl compounds was developed for synthesis of optically active α-hydroxy carbonyl compounds.[22–24] In 2008, Zhou and co-workers reported that a chiral spiro-phosphite ligand is an effective chiral ligand in the rhodium-catalyzed asymmetric addition of arylboronic acids to α-ketoesters, providing chiral α-hydroxy esters in high yields and up to 93% *ee* (Scheme 1.4).[22a] In 2011, Ready and co-workers developed a novel chiral allene-containing bisphosphine ligand and applied it in the asymmetric addition of arylboronic acids to α-ketoesters, affording chiral α-hydroxy esters in high yields and high enantioselectivities (65–95% *ee*).[22b] In 2012, Xu and co-workers developed a chiral sulfinamide-based olefin ligand and applied it in the asymmetric addition of arylboronic acids to α-ketoesters and α-diketones, affording chiral α-hydroxy carbonyl compounds in high yields and high enantioselectivities (63–99% *ee*).[22d] In the same year, chiral sulfur-alkene hybrid ligand has excellent catalytic activity for asymmetric 1,2-addition

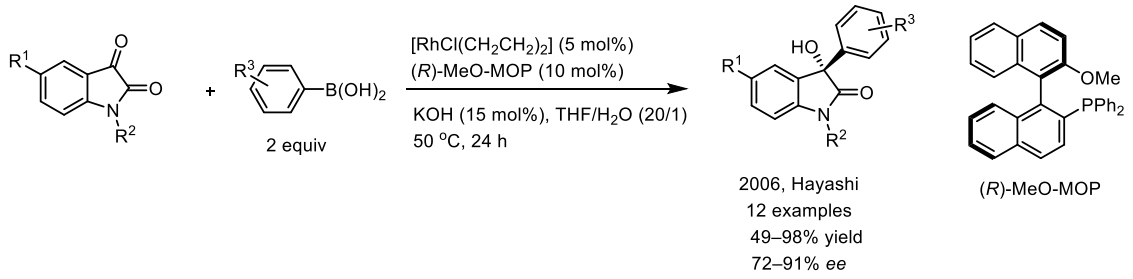


Scheme 1.4 Transition-metal-catalyzed asymmetric addition of arylboronic acids to α-keto carbonyl compounds

of arylboronic acids to α-diketones (4–99% *ee*).[24a] In 2015, Qiu and co-workers reported that a novel chiral phosphoramidite ligand based on chiral biphenyl backbones and this iridium-catalyst effectively the enantioselective arylation of α-ketoamide of isatins with arylboronic acids with high enantioselectivity (30–95% *ee*).[23h]

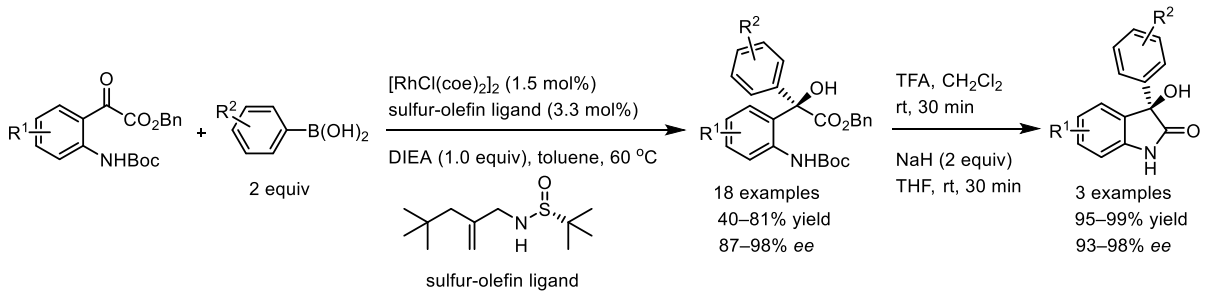
Especially, an optically active α-hydroxy carbonyl compounds such as 3-substituted-3-hydroxy-benzofuranones and 3-substituted-3-hydroxy-oxindoles are not only very important structural motifs in numerous biologically interesting compounds, but also serve as fundamental building blocks for a lot of applications in organic synthesis.[25,26] Over the past decades, various methods have been developed for the synthesis of these valuable chiral compounds.[27] Enantioselective Morita–Baylis–Hillman reactions,[28] aldol reactions,[29] asymmetric allylation of isatins,[30] Friedel–Crafts reactions,[31] direct hydroxylation,[32] and metal-catalyzed intramolecular coupling reactions have been reported.[33,34] In recent years, transition metal-catalyzed asymmetric nucleophilic addition of organoboronic compounds to α-keto carbonyl compounds is a particularly powerful and straightforward approach.[22–24]

In 2006, Hayashi and co-workers first reported a rhodium-catalyzed arylation of arylboronic acids to isatins.[23a] In this report, the combination of $[RhCl(CH_2CH_2)_2]_2$ and MeO-MOP could efficiently catalyze the asymmetric addition of phenylboronic acid to 1-naphthylaldehyde in aqueous THF (Scheme 1.5).



Scheme 1.5 Rhodium/MeO-MOP-catalyzed asymmetric addition of arylboronic acid to isatins

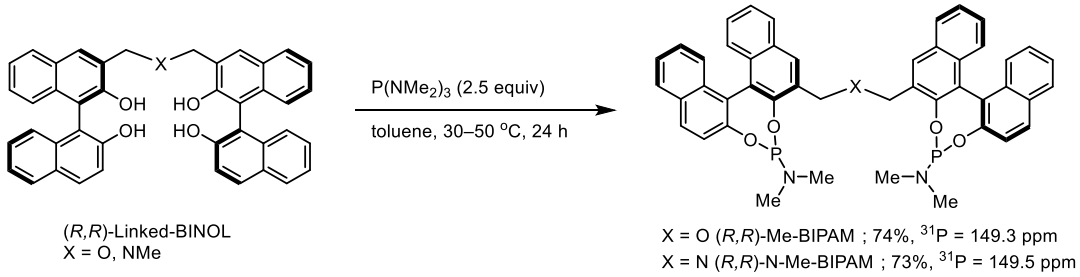
Recently, rhodium catalyzed asymmetric addition of arylboronic acids and cyclization strategy was developed for synthesis of 3-substituted-3-hydroxy-oxindoles. In 2013, Xu and co-workers reported that the reaction of *ortho*-substituted ketoesters with arylboronic acids and intramolecular lactonization afforded 3-aryl-3-hydroxy-oxindoles (Scheme 1.6).[22f] Xu and co-workers also reported that enantioselective addition of unsymmetrical α-diketones afforded the resulting α-hydroxy ketones and intramolecular etherification or esterification of the corresponding 3-tetrasubstituted isochromanones.[24b]



Scheme 1.6 Enantioselective synthesis of 3-aryl-3-hydroxy-oxindoles by rhodium catalyzed asymmetric addition and cyclization

1.3 Synthesis of Me-BIPAM and ruthenium/Me-BIPAM-catalyzed arylation of aldehydes and α-ketoesters with arylboronic acids

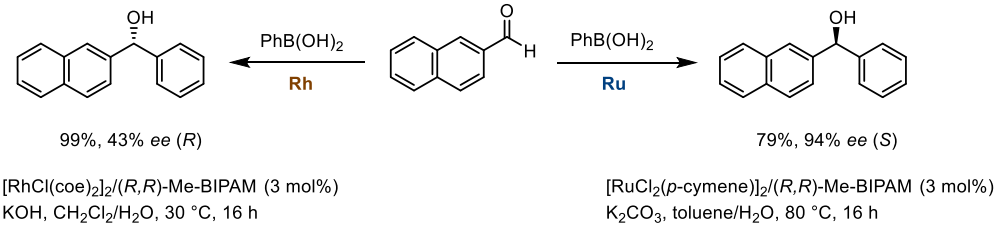
Our research group developed a chiral *O*- or *N*-linked C_2-symmetric bidentate phosphoramidite (Me-BIPAM or N-Me-BIPAM) having linked-BINOL unit in 2005.[35] In general, phosphoramidite ligand has both σ-donating ability derived from the inductive effect and π-accepting ability derived from the back donation which means electron flow the filled d-orbital of transition metal to anti-donating orbital of phosphine-heteroatom bond. Additionally, these ligands can be easily synthesized from commercially available 1,1'-bi-2-naphtol.



Scheme 1.7 Synthesis of Me-BIPAM

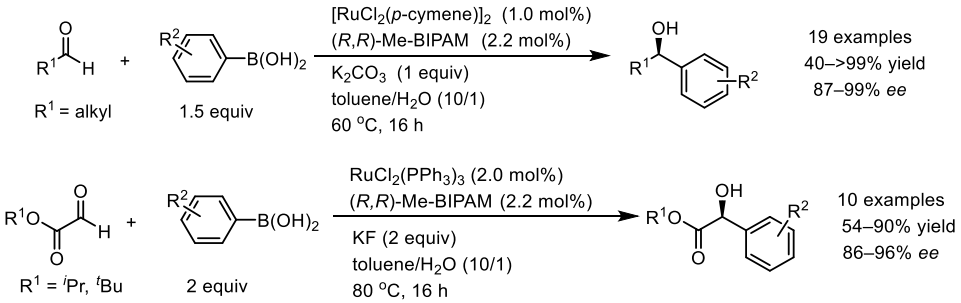
In this field, we have already reported enantioselective addition reactions using organoboron compounds under rhodium catalysis.[36] We previously developed bidentate chiral phosphoramidites (Me-BIPAM and *N*-Me-BIPAM),[35] derived from linked BINOL (BINOL = 1,1′-binaphthalene-2,2′-diol) units, for the enantioselective 1,4-addition of arylboronic acids to enones,[37] and arylation of aldimines.[38] However, rhodium(I) complexes were inefficient for the enantioselective arylation of aldehydes (Scheme1.8). In 2009, we have first reported that

a novel ruthenium(II) and a chiral *O*-linked C_2-symmetric bidentate phosphoramidite (Me-BIPAM) complex catalyzed effectively the enantioselective arylation of aldehydes with arylboronic acids with high enantioselectivity (82–99% *ee*) (Scheme1.8).[8a]



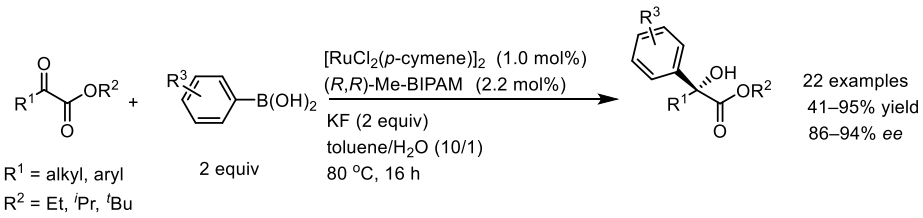
Scheme 1.8 Rhodium or ruthenium/Me-BIPAM catalysed asymmetric addition of arylboronic acids to aromatic aldehydes

$[RuCl_2(p\text{-cymene})]_2$/Me-BIPAM catalyzed the addition of arylboronic acids to aliphatic aldehydes and *tert*-butyl glyoxylate in high yields and enantioselectivities in the presence of bases such as K_2CO_3 and KF at 60–80 °C in toluene/H_2O.[8b,8c] A variety of aliphatic aldehydes underwent the arylation reaction (Scheme 1.9). The enantioselective synthesis of α-hydroxy esters by $RuCl_2(PPh_3)_3$/(*R,R*)-Me-BIPAM catalyzed addition of arylboronic acids to *tert*-butyl glyoxylate is achieved. The arylation products were gave up to 99% *ee*. Addition of a fluoride salt such as potassium fluoride (KF) or caesium fluoride (CsF) was effective for achieving high enantioselectivities.



Scheme 1.9 Ruthenium/Me-BIPAM-catalyzed asymmetric addition of arylboronic acids to aliphatic aldehydes and *tert*-butyl glyoxylate

In 2011, we have reported that a novel ruthenium(II) and a chiral *O*-linked C_2-symmetric bidentate phosphoramidite (Me-BIPAM) complex catalyzed effectively the enantioselective arylation of α-ketoesters with arylboronic acids with high enantioselectivities (82–99% *ee*) (Scheme 1.10).[8b]



Scheme 1.10 Ruthenium/Me-BIPAM-catalyzed asymmetric addition of arylboronic acids to α-ketoesters

The catalytic cycle of this reaction may involves (a) transmetalation between arylboronic acid and ruthenium(II) complex ([Ru] = Ru(II)L) to give an Ar–[Ru] complex, (b) insertion of an aldehyde C=O bond into the Ar–[Ru] bond, (c) formation of a diarylmethanol and [Ru]–OH complex through hydrolysis of the [Ru]–OCHAr^{1}Ar^2 intermediate with water, and finally (d) transmetalation between arylboronic acid and [Ru]–OH complex to give an Ar–[Ru] complex (Figure 1.1). The enantioselectivity are determined at insertion step of the C=O bond into an Ar–[Ru] intermediate.

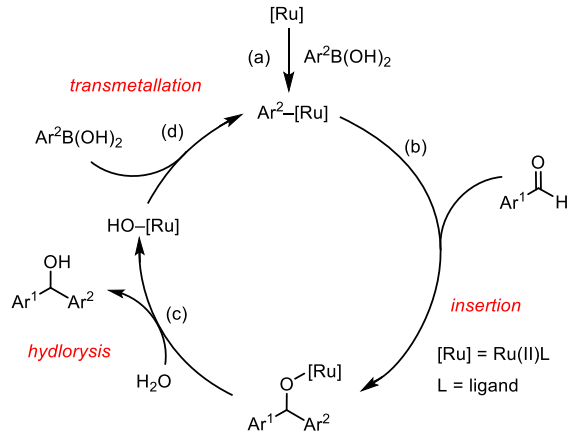
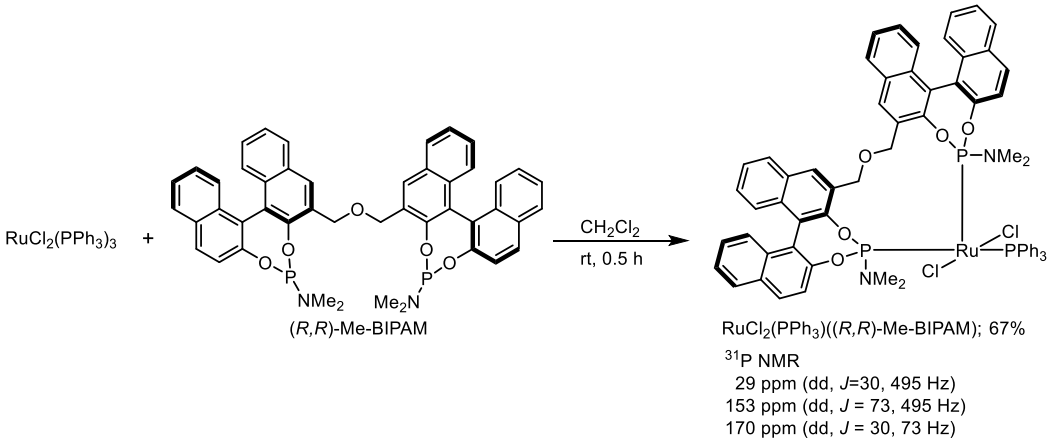


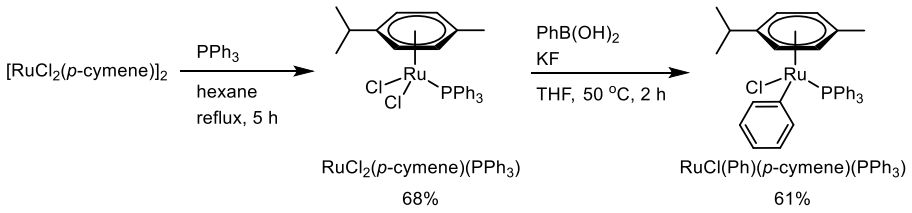
Figure 1.1 Proposed catalytic cycle for ruthenium-catalyzed addition to aldehyde

To determine the structure of the catalyst, we reacted $RuCl_2(PPh_3)_3$ with (*R,R*)-Me-BIPAM in CH_2Cl_2. This provided $RuCl_2(PPh_3)$((*R,R*)-Me-BIPAM) in 67% yield (Scheme 1.11).[8c] The transmetalation between $RuCl_2(PPh_3)$((*R,R*)-Me-BIPAM) and $ArBF_n(OH)$ generated by the reaction of $ArB(OH)_2$ and KF may provide the arylruthenium(II) intermediate $RuCl(Ar)(PPh_3)$((*R,R*)-Me-BIPAM), which is analogous to a Ph–Cl exchange between $PhB(OH)_2$ and [$RuCl_2$(*p*-cymene)(PPh_3)]. The reaction of

phenylboronic acid and $RuCl_2$(*p*-cymene)(PPh_3) in the presence of KF gave RuCl(Ph)(*p*-cymene)(PPh_3) in 61% yield (Scheme 1.11).[8c]

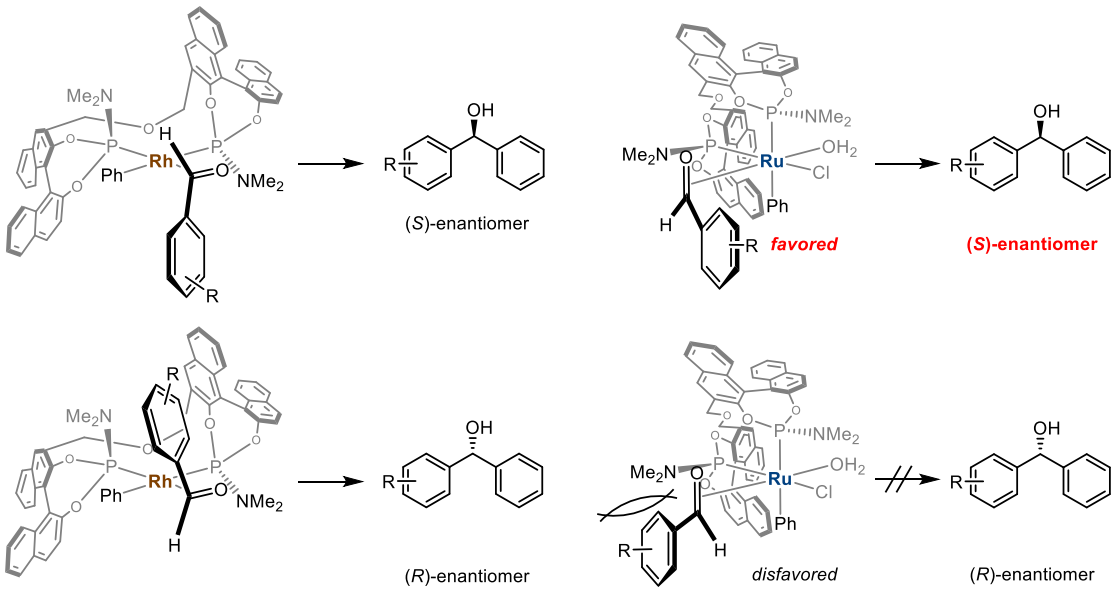


Scheme 1.11 Ruthenium/Me-BIPAM complex from the reaction of $RuCl_2(PPh_3)_3$ with (*R,R*)-Me-BIPAM



Scheme 1.12 Transmetalation between $PhB(OH)_2$ and [$RuCl_2$(*p*-cymene)(PPh_3)]

The enantioselectivity is determined at insertion of the C−O double bond into the C−Ru bond of RuCl(Ar)(H_2O)((*R,R*)-Me-BIPAM) complex. An enantioselection model which two dimethylamino groups of Me-BIPAM blocked one side of the complex was proposed in Scheme 1.13 to rationalize the absolute configuration of the products in the addition of arylboronic acids to aldehydes. The asymmetric environment of ruthenium(II)/(*R,R*)-Me-BIPAM complex is different from a *cis*-ligated square-planar rhodium complex. It can be seen from the model that the transfer of the phenyl group to the *Si*-face of aldehyde is much more favorable.

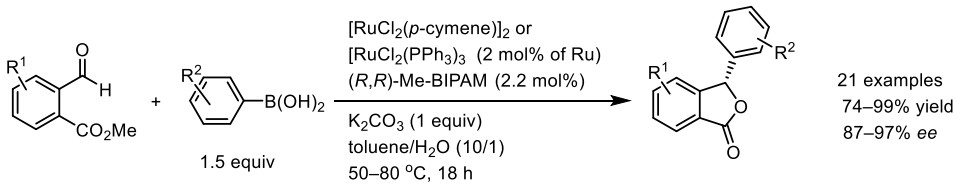


Scheme 1.13 Enantioselection model for the rhodium or ruthenium/(*R,R*)-Me-BIPAM catalysed asymmetric addition of arylboronic acids to aldehydes

1.4 Survey of this thesis

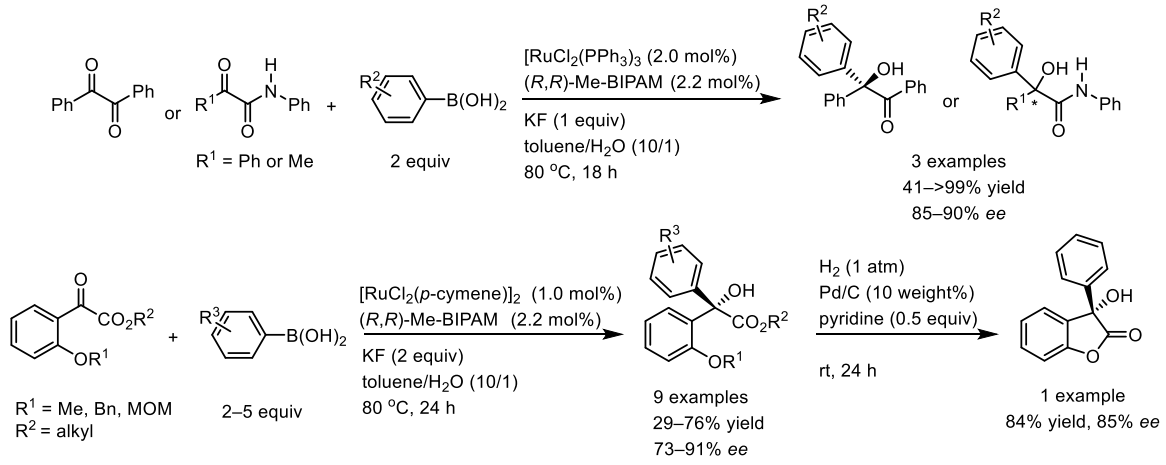
In this thesis, it was described that the enantioselective synthesis of 3-aryl-isobenzofuranones, 3-aryl-3-hydroxy-benzofuranones and 3-aryl-3-hydroxy-oxyindoles using ruthenium/Me-BIPAM-catalyzed addition reaction of arylboronic acids to methyl 2-formylbenzoates, phenylglyoxylate esters, benzofuran-2,3-diones and isatins.

In Chapter 2, Ruthenium/Me-BIPAM-catalyzed asymmetric addition of arylboronic acids to methyl 2-formylbenzoates afforded chiral 3-aryl-isobenzofuranones. $[RuCl_2(p\text{-cymene})]_2$/Me-BIPAM and $RuCl_2(PPh_3)_3$/Me-BIPAM catalyst systems tolerate a variety of functional groups and give high yields with high enantioselectivities. (Scheme 1.14)



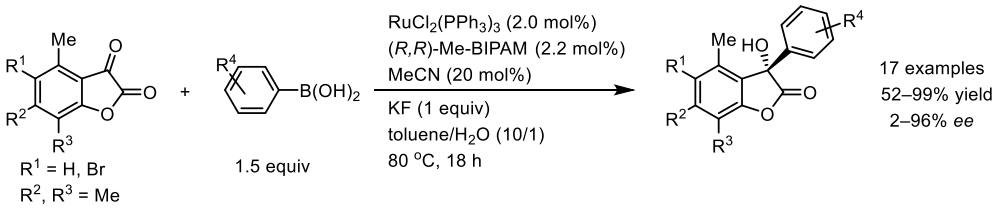
Scheme 1.14 Addition of arylboronic acids to methyl 2-formylbenzoates

In Chapter 3, Me-BIPAM was found to be efficient for the ruthenium-catalyzed addition of arylboronic acids to α-diketones, α-ketoamide and *ortho*-substituted phenylglyoxylate esters. $[RuCl_2(p\text{-cymene})]_2$ or $[RuCl_2(PPh_3)_3]$/(*R,R*)-Me-BIPAM and KF afforded α-hydroxy-ketone, -amide and -esters with α-quaternary carbon centers with high enantioselectivities up to 93% *ee*. It was found that the reaction with α-hydroxy ester product proceeds lactonization under basic condition with high yields and good enantioselectivities (Scheme 1.15).



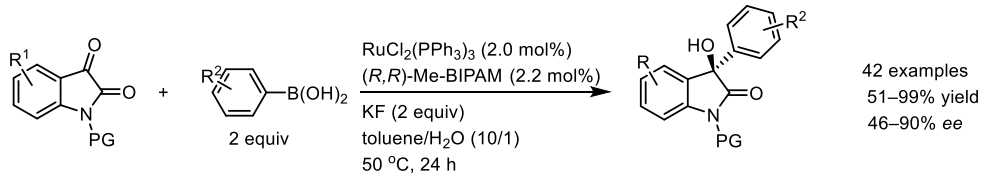
Scheme 1.15 Addition of arylboronic acids to α-keto carbonyl compounds

In Chapter 4, it was described that an enantioselective synthesis of 3-aryl-3-hydroxybenzofuran-2-ones by ruthenium-catalyzed 1,2-addition of arylboronic acids to benzofuran-2,3-diones. The use of $RuCl_2(PPh_3)_3$ with Me-BIPAM in the presence of a small amount of acetonitrile (20 mol%) gave optically active 3-aryl-3-hydroxybenzofuran-2-ones of up to 96% *ee*. This reaction is the first example of catalytic asymmetric 1,2-addition reaction of arylboronic acids to benzofuran-2,3-diones for highly efficient and enantioselective synthesis of quaternary carbon-containing benzofuran-2-ones (Scheme 1.16).



Scheme 1.16 Addition of arylboronic acids to 1-benzofuran-2,3-diones

In Chapter 5, Me-BIPAM was found to be efficient for the ruthenium-catalyzed addition of arylboronic acids to isatins. Asymmetric synthesis of 3-aryl-3-hydroxy-2-oxindoles by 1,2-addition of arylboronic acids to isatins was carried out in the presence of $RuCl_2(PPh_3)_3$/(*R,R*)-Me-BIPAM and KF, resulting in an enantioselectivity as high as 90 % *ee*. It was found that the reaction with *N*-protected isatins proceeds with high yields and good enantioselectivities. The best protective groups on the nitrogen atom were different depending on the substituents on the aromatic ring. The use of a *N*-benzyl group resulted in excellent enantioselectivities in many substrates compared with other groups. (Scheme 1.17)



Scheme 1.17 Addition of arylboronic acids to isatins.

1.5 References

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Chapter 2 Enantioselective Addition of Arylboronic Acids to Methyl 2-Formylbenzoates by using a Ruthenium/Me-BIPAM Catalyst for Synthesis of Chiral 3-Aryl-isobenzofuranones

Abstract: Ruthenium/Me-BIPAM-catalyzed asymmetric addition of arylboronic acids to methyl 2-formylbenzoates afforded chiral 3-aryl-isobenzofuranones. $[RuCl_2(p\text{-cymene})]_2$/Me-BIPAM and $RuCl_2(PPh_3)_3$/Me-BIPAM catalyst systems tolerate a variety of functional groups and give high yields with high enantioselectivities.

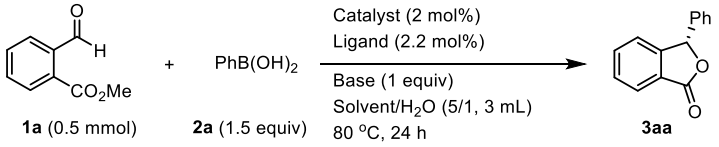
2.1 Introduction

Optically active 3-substituted isobenzofuranones are important structures in medicinal chemistry as well as in synthetic chemistry.[1,2] Recently, various methods for the synthesis of these chiral compounds have been developed.[3] Transition metal-catalyzed addition reactions of arylboronic acids with 2-formylbenzoates have become useful tools for accessing 3-aryl-isobenzofuranones.[4] However, to our knowledge, there have been only a few reports on the synthesis of optically active 3-aryl-isobenzofuranones using this strategy.[5] In this section, it is described that the synthesis of optically active 3-aryl-isobenzofuranones by using ruthenium/Me-BIPAM[6]-catalyzed enantioselective addition of arylboronic acids to methyl 2-formylbenzoates.

2.2 Results and discussion

Our initial investigation began by screening catalysts to evaluate their ability to promote enantioselective arylation of methyl 2-formylbenzoate with phenylboronic acid. As shown in Table 2.1, when $[RuCl_2(p\text{-cymene})]_2$, $RuCl_2(PPh_3)_3$ or $RuCl_2(nbd)(MeCN)_2$ with Me-BIPAM, which were used in our previous works, were used for this reaction, addition products were obtained in high yields with high enantioselectivities (entries 2, 7 and 8). Use of KOH and DCE resulted in lower yields (entries 4 and 5). Among the chiral ligands screened, the use of (*R*)-BINAP (entry 10) and monodentate phosphoramidite, (*R*)-MonoPhos (entry 11) resulted in lower enantioselectivities, 12% *ee* (*R*) and 78% *ee* (*S*), respectively.

Table 2.1 Reaction conditions[a]

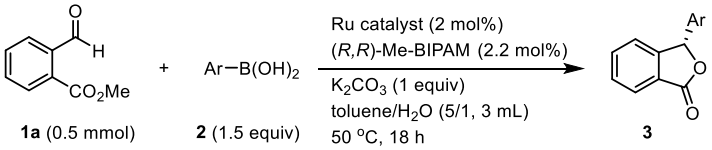


entry	catalyst	ligand	base	solvent	yield (%)[b]	*ee* (%)[c]
1	$[RuCl_2(p\text{-cymene})]_2$	(*R,R*)-Me-BIPAM	K_2CO_3	toluene	96	94 (*S*)
2[d]	$[RuCl_2(p\text{-cymene})]_2$	(*R,R*)-Me-BIPAM	K_2CO_3	toluene	96	97 (*S*)
3[d]	$[RuCl_2(p\text{-cymene})]_2$	(*R,R*)-Me-BIPAM	KF	toluene	99.5	97 (*S*)
4[d]	$[RuCl_2(p\text{-cymene})]_2$	(*R,R*)-Me-BIPAM	KOH	toluene	74	96 (*S*)
5[d]	$[RuCl_2(p\text{-cymene})]_2$	(*R,R*)-Me-BIPAM	K_2CO_3	DCE	52	93 (*S*)
6	$RuCl_2(PPh_3)_3$	(*R,R*)-Me-BIPAM	K_2CO_3	toluene	96	93 (*S*)
7[d]	$RuCl_2(PPh_3)_3$	(*R,R*)-Me-BIPAM	K_2CO_3	toluene	98	96 (*S*)
8	$RuCl_2(nbd)(MeCN)_2$	(*R,R*)-Me-BIPAM	K_2CO_3	toluene	96	93 (*S*)
9[e]	$RuCl_2(PPh_3)_3$	(*R,R*)-Me-BIPAM	K_2CO_3	toluene	67	91 (*S*)
10	$[RuCl_2(p\text{-cymene})]_2$	(*R*)-BINAP	K_2CO_3	toluene	26	12 (*R*)
11	$[RuCl_2(p\text{-cymene})]_2$	(*R*)-Monophos	K_2CO_3	toluene	70	78 (*S*)

[a] Reactions were carried out at 50–80 °C for 18 h by using methyl 2-formylbenzoates 1a (0.5 mmol), **2a** (0.75 mmol), Ru catalyst (0.01 mmol), ligand (0.011 mmol), K_2CO_3 (0.5 mmol) and toluene/H_2O (5/1, 3.0 mL). [b] Isolated yields. [c] The ee value of **3** was determined by chiral HPLC analysis. [d] 50 °C, 18 h. [e] MeCN (20 mol %) was added.

The substrate scope for various arylboronic acids with $[RuCl_2(p\text{-cymene})]_2$- or $RuCl_2(PPh_3)_3$-Me-BIPAM catalyst was then studied (Table 2.2). Arylboronic acids with electron-donating and -withdrawing groups at *para*- and *meta*-positions afforded 3-aryl-isobenzofuranones in high yields with high enantioselectivities in the range of 91–97% *ee*. The addition of *para*-biphenylboronic acid and 3-thienylboronic acid resulted in a high yield with high enantioselectivities when the temperature was increased and the solvent ratio of toluene/H_2O was changed (entries 5 and 12). The structure of **3al** was confirmed unequivocally by its X-ray crystal structure (entry 12). The absolute configuration of the product was assigned as *S* enantiomer from X-ray crystallographic analysis of the compound of **3al** (Figure 2.1).[7]

Table 2.2 Substrate scope for the arylboronic acids[a]



entry	Ar = (Ar-B(OH)$_2$)	catalyst	yield (%)[b]	*ee* (%)[c]
1	C_6H_5	[$RuCl_2$(*p*-cymene)]$_2$	96 (**3aa**)	97 (*S*)
2[d]	4-$MeOC_6H_4$	[$RuCl_2$(*p*-cymene)]$_2$	80 (**3ab**)	96 (*S*)
3[d]	4-MeC_6H_4	[$RuCl_2$(*p*-cymene)]$_2$	99 (**3ac**)	95 (*S*)
4	4-CH_2=CHC_6H_4	[$RuCl_2$(*p*-cymene)]$_2$	93 (**3ad**)	95 (+)
5[e]	4-PhC_6H_4	$RuCl_2(PPh_3)_3$	87 (**3ae**)	94 (+)
6	4-FC_6H_4	$RuCl_2(PPh_3)_3$	98 (**3af**)	95 (+)
7	4-ClC_6H_4	$RuCl_2(PPh_3)_3$	97 (**3ag**)	96 (*S*)
8	4-$CF_3C_6H_4$	$RuCl_2(PPh_3)_3$	74 (**3ah**)	91 (*S*)
9	2-naphthyl	$RuCl_2(PPh_3)_3$	92 (**3ai**)	93 (*S*)
10	3, 5-MeC_6H_4	$RuCl_2(PPh_3)_3$	99 (**3aj**)	96 (*S*)
11	3-ClC_6H_4	$RuCl_2(PPh_3)_3$	84 (**3ak**)	93 (*S*)
12[f]	3-thienyl	$RuCl_2(PPh_3)_3$	92 (**3al**)	91 (*S*)

[a] Reactions were carried out at 50–80 °C for 18 h by using methyl 2-formylbenzoates **1a** (0.5 mmol), **2** (0.75 mmol), Ru catalyst (0.01 mmol), (*R,R*)-Me-BIPAM (0.011 mmol), K_2CO_3 (0.5 mmol) and toluene/H_2O (5/1, 3.0 mL). [b] Isolated yields. [c] The *ee* value of **3** was determined by chiral HPLC analysis. [d] 6 h. [e] 80 °C, toluene/H_2O (20/1, 3 mL). [f] 80 °C, toluene/H_2O (10/1, 3 mL).

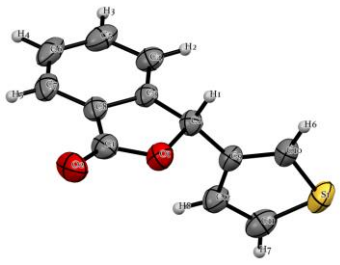


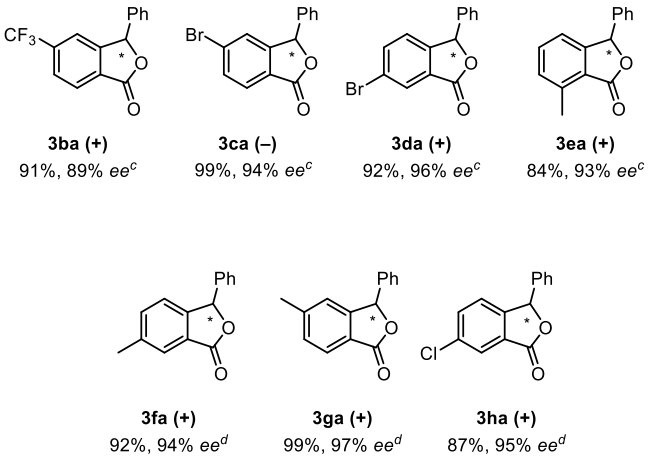
Figure 2.1 ORTEP diagram of **3al** (ORTEP drawing at 50% ellipsoid probability)

From the above results, [$RuCl_2$(*p*-cymene)]$_2$ with (*R,R*)-Me-BIPAM catalyst gave higher enantioselectivities for the electron-donating arylboronic acids, but $RuCl_2(PPh_3)_3$ with (*R,R*)-Me-BIPAM catalyst gave higher enantioselectivities for the

electron-withdrawing arylboronic acids. The structure of $[RuCl_2(p\text{-cymene})]_2$ with (*R,R*)-Me-BIPAM showed cationic complex,[8] but the structure of $RuCl_2(PPh_3)_3$ with (*R,R*)-Me-BIPAM complex showed neutral complex.[11c] It is considered that the reactivity of the ruthenium complex differences is correlated with the electronic nature of the arylboronic acids.

Next, the substrate scope with focus on substituents on the aromatic ring of methyl 2-formylbenzoates was investigated (Table 2.3). Arylation of methyl 2-formylbenzoates gave the corresponding products in high yields (84–99%) with excellent enantioselectivities (87–97% *ee*). This ruthenium/Me-BIPAM catalyzed asymmetric arylation was applied to the synthesis of (–)-5,6-desmethylenedioxy-5-methoxy-aglalactone (**3ib**). This product was isolated from the $CHCl_3$ soluble extract of the leaves and twigs of Aglaia ponapensis exhibit the NF-kB inhibitory activity.[9] As shown in Scheme 2.1, we converted commercial 2,4-dimethoxybenzoic acid **4** to methyl 2-formylbenzoate **1i** in 21% yield in 4 steps.[10] The reaction of 2-formylbenzoate **1i** and 4-methoxyphenylboronic acid **2b** was catalyzed by $[RuCl_2(p\text{-cymene})]_2$ and Me-BIPAM to provide **3ib (–)** in 85% yield and 87% *ee*, $[\alpha]_D^{25} = -13.0$ (*c* 0.50, $CHCl_3$) [lit. $[\alpha]_D^{22} = -13$ (*c* 1.1, $CHCl_3$)[9a]].

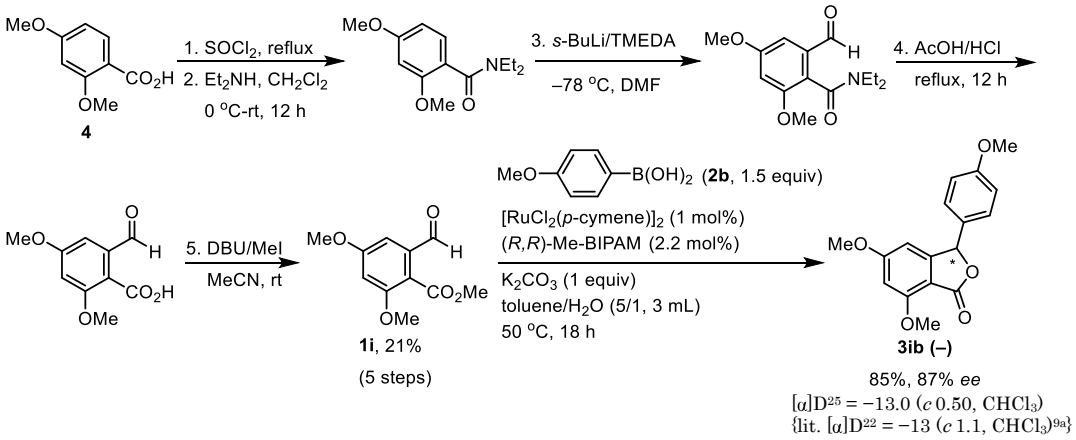
Table 2.3 Substrate scope for the methyl 2-formylbenzoates[a,b]



3ba (+) 91%, 89% *ee*[c] **3ca (–)** 99%, 94% *ee*[c] **3da (+)** 92%, 96% *ee*[c] **3ea (+)** 84%, 93% *ee*[c]

3fa (+) 92%, 94% *ee*[d] **3ga (+)** 99%, 97% *ee*[d] **3ha (+)** 87%, 95% *ee*[d]

[a] Isolated yield. [b] The *ee* value of **3** was determined by chiral HPLC analysis. [c] $[RuCl_2(p\text{-cymene})]_2$ was used. [d] $RuCl_2(PPh_3)_3$ was used.



Scheme 2.1 Total synthesis of (–)-5,6-desmethylenedioxy-5-methoxy-aglalactone (**3ib**).

2.3 Conclusions

In summary, a ruthenium/Me-BIPAM-catalyzed addition of arylboronic acids to methyl 2-formylbenzoates for enantioselective synthesis of 3-aryl-isobenzofuranones has been developed. Various substituted chiral 3-aryl-isobenzofuranones were obtained with excellent enantioselectivities (87–97 % *ee*).

2.4 Experimental section

2.4.1 General information.

^{1}H NMR spectra were recorded on a JEOL ECX-400 (400 MHz) or JEOL ECS-400 (400 MHz) in $CDCl_3$ with tetramethylsilane (δ = 0.00) as internal standard. Chemical shifts are reported in part per million (ppm), and signal are expressed as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (br). ^{13}C NMR spectra were recorded on a JEOL ECX-400 (100MHz) in $CDCl_3$ (δ = 77.00) with tetramethylsilane as an internal standard (δ = 0.0). Chemical shifts are reported in part per million (ppm). HPLC analysis was directly performed with chiral stationary phase column, CHIRALPAK AD-H or CHIRALCEL OD-H purchased from DAICEL Co., Ltd. High resolution mass spectra (HRMS) were recorded on a JEOL JMS 700TZ mass spectrometer at the Center for Instrumental Analysis, Hokkaido University. Optical rotations were measured on a HORIBA SEPA-300 digital polarimeter. Kanto Chemical silica gel 60N (particle size 0.063–0.210 mm) was used for flash column chromatography. $RuCl_3 \cdot xH_2O$ was purchased from Furuya Metal Co., Ltd. $[RuCl_2(p\text{-cymene})]_2$,[11] $RuCl_2(PPh_3)_3$[12] and $RuCl_2(nbd)(MeCN)_2$[13] were prepared by the literature procedure. BIPAM ligand (Me-BIPAM) were prepared according to our previous procedure.[14] Me-BIPAM was commercially available from Wako Pure Chemical Industries, Ltd. Phthalide was purchased from commercial source and substituted phthalides were synthesized according to known literature.[15]

2.4.2 Preparation of 2-formylbenzoates[16]

To a solution of phthalides (2.0 mmol) in 10 mL dry benzene was added NBS (0.41g, 2.2 mmol) and AIBN (16.4 mg, 0.1 mmol) was added at room temperature. Then the mixture was refluxed at 85 °C overnight. It was cooled to room temperature and purified by flash chromatograph (silica gel, petroleum ether and ethyl acetate as eluent). The product was then suspended in 20 mL of H_2O and heated to 100 °C. After 1 h, the mixture was cooled to room temperature and then extracted with EtOAc (3×30 mL). The combined extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a corresponding 2-formylbenzoic acid as a solid. To a solution of the corresponding 2-formylbenzoic acid in acetone were added Me_2SO_4 (0.126 g, 1 mmol) and K_2CO_3 (0.276 g, 2 mmol). After stirring for 2 h at room temperature, the mixture was refluxed for 1 h and cooled to ambient temperature, filtered and washed with acetone (3×15 mL). The combined filtrates were concentrated in vacuo and the residue was purified by flash chromatography (silica gel, eluent: petroleum/ethyl acetate = 20:1) to give methyl 2-formylbenzoate.

2.4.3 General procedure for ruthenium/Me-BIPAM catalyzed asymmetric arylation of 2-formylbenzoate with arylboronic acids

A flask was charged with Ruthenium catalyst (0.01 mmol, 2 mol%) and Me-BIPAM (0.011 mmol, 2.2 mol%) under nitrogen atmosphere. Toluene (2.5 ml) was added and the mixture was stirred at room temperature for 30 min. Phenylboronic acid (0.75 mmol), 2-formylbenzoate (0.5 mmol), K_2CO_3 (0.5 mmol) and H_2O (0.5 ml) were then added to this catalyst solution. The reaction mixture was then heated at 50 ºC for 18 h. The mixture was quenched with aqueous saturated NH_4Cl, extracted with AcOEt, dried over $MgSO_4$, filtered off, and the solvents were evaporated. The crude product was purified by flash column chromatography (Hexane/AcOEt = 7/1 to 5/1) to afford pure 3-aryl-ahydroxy-benzofuran-2-one.

(*S*)-3-Phenyl-1,3-dihydro-2-benzofuran-1-one (3aa).[5a] White solid; mp 151–153 ºC; 96% yield (103 mg); $[\alpha]_D^{24}$ = +43.0 (*c* 0.50, $CHCl_3$), 97% *ee* [lit. $[\alpha]_D$ = +45.3 (*c* 0.10, $CHCl_3$, 71% ee (*S*))[5a]], [HPLC condition: CHIRALCEL OD-H column, hexane/2-propanol = 90/10, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 23.4 min (major) and 30.9 min (minor)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.96 (d, *J* = 7.8 Hz, 1H), 7.64 (t, *J* = 7.3 Hz 7.8 Hz, 1H), 7.55 (t, *J* = 7.3 Hz 7.8 Hz, 1H), 7.36 (m, 2H), 7.33 (d, *J* = 7.3 Hz, 1H), 7.28 (m, 2H), 6.40 (s, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ = 170.42, 149.53, 136.25, 134.23, 129.23, 129.14, 128.82, 126.81, 125.41, 125.34, 122.76, 82.57; MS (EI) *m/z* 77.02 (30), 105.03 (100), 133.02 (12), 152.06 (12), 165.07 (34), 181.06 (16), 210.06 (78); HRMS (EI) *m/z* calcd for $C_{14}H_{10}O_2[M]^+$: 210.06808, found: 210.06768.

(*S*)-3-(4-Methoxyphenyl)-1,3-dihydro-2-benzofuran-1-one (3ab).[5a] White solid; mp 141–144 ºC; 80% yield (96 mg); $[\alpha]_D^{24}$ = −8.9 (*c* 0.50, $CHCl_3$), 96% *ee* [lit. $[\alpha]_D$ = -27.8 (*c* 0.10, $CHCl_3$, 67% *ee* (*S*))[5a]], [HPLC condition: CHIRALCEL OD-H column, hexane/2-propanol = 90/10, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 30.2 min (major) and 40.6 min (minor)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.96 (d, *J* = 7.3 Hz, 1H), 7.65 (t, *J* = 7.5 Hz, 1H), 7.55 (t, *J* = 7.3 Hz, 1H), 7.32 (d, *J* = 7.3 Hz, 2H), 7.17 (d, *J* = 8.7 Hz, 1H), 6.89 (d, *J* = 8.7 Hz, 2H), 6.37 (s, 1H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.43, 160.24, 149.63, 134.17, 129.17, 128.66, 128.11, 125.71, 125.35, 122.85, 114.17, 82.60, 55.19; MS (EI) *m/z* 43.98 (23), 77.02 (32), 104.01 (53), 135.02 (52), 152.03 (48), 165.04 (30), 181.03 (32), 195.05 (30), 209.02 (23), 240.03 (100); HRMS (EI) *m/z* calcd for $C_{15}H_{12}O_3$ [M]$^+$: 240.07864, found: 240.07806.

(*S*)-3-(4-Methylphenyl)-1,3-dihydro-2-benzofuran-1-one (3ac).[5a] White solid; mp 128–132 ºC; >99% yield (117 mg); $[\alpha]_D^{25}$ = +15.0 (*c* 0.50, $CHCl_3$), 95% *ee* [lit. $[\alpha]_D$ = +10.3 (*c* 0.10, $CHCl_3$, 77% *ee* (*S*))[5a]], [HPLC condition: CHIRALCEL OD-H column, hexane/2-propanol = 90/10, flow = 0.5 mL/min, wavelength = 230 nm, tR = 19.3 min (major) and 25.8 min (minor)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.96 (d, *J* = 7.8 Hz, 1H), 7.64 (t, *J* = 7.3 Hz 7.8 Hz, 1H), 7.55 (t, *J* = 7.3 Hz 7.8 Hz, 1H), 7.36 (m, 2H), 7.33 (d, *J* = 7.3 Hz, 1H), 7.28 (m, 2H), 6.40 (s, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ = 170.49, 149.68, 139.16, 134.18, 133.24, 129.48, 129.14, 126.89, 125.49, 125.36, 122.77, 82.63, 21.08; MS (EI) *m/z* 77.03 (22), 91.04 (20), 104.01 (37), 119.03 (65),

133.01 (12), 152.04 (20), 165.04 (60), 178.05 (18), 195.05 (7), 209.03 (100), 224.05 (84); HRMS (EI) *m/z* calcd for $C_{15}H_{12}O_2$ $[M]^+$: 224.08373, found: 224.08311.

(+)-3-(4-Ethenylphenyl)-1,3-dihydro-2-benzofuran-1-one (3ad). White solid; mp 139–142 °C; 93% yield (111 mg); $[\alpha]_D^{25}$ = +23.0 (*c* 0.50, $CHCl_3$), 95% *ee* [HPLC condition: CHIRALCEL OD-H column, hexane/2-propanol = 90/10, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 21.6 min (major) and 27.4 min (minor)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.96 (d, *J* = 7.3 Hz, 1H), 7.64 (t, *J* = 7.3 Hz, 1H), 7.55 (t, *J* = 7.3 Hz, 7.8 Hz, 1H), 7.41 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 7.8 Hz, 1H), 7.23 (d, *J* = 8.2 Hz, 2H), 6.70 (dd, *J* = 11.0 Hz 17.8 Hz, 1H), 6.39 (s, 1H), 5.76 (d, *J* = 17.8 Hz, 1H), 5.28 (d, *J* = 11.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.43, 149.49, 135.88, 135.61, 134.28, 129.29, 127.12, 126.63, 125.51, 125.42, 122.76, 114.93, 82.38; MS (EI) *m/z* 77.04 (27), 104.03 (43), 131.05 (38), 191.09 (20), 209.06 (10), 236.08 (100); HRMS (EI) *m/z* calcd for $C_{16}H_{12}O_2$ $[M]^+$: 236. 08373, found: 236.08326.

(+)-3-(4-Phenylphenyl)-1,3-dihydro-2-benzofuran-1-one (3ae). White solid; mp 249–251 °C; 87% yield (125 mg); $[\alpha]_D^{25}$ = +31.0 (*c* 0.50, $CHCl_3$), 94% *ee* [HPLC condition: CHIRALPAK AD-H column, hexane/2-propanol = 90/10, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 38.3 min (major) and 50.2 min (minor)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.99 (d, *J* = 7.8 Hz, 1H), 7.67 (t, *J* = 7.3 Hz 7.8 Hz, 1H), 7.62–7.55 (m, 5H), 7.44 (t, *J* = 7.3 Hz 7.8 Hz, 2H), 7.39–7.34 (m, 4H), 6.46 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.61, 149.71, 142.40, 140.36, 129.53, 128.95, 127.81, 127.58, 127.23, 125.81, 125.75, 123.00, 82.62; MS (EI) *m/z* 43.99 (13), 77.03 (22), 104.01 (43), 132.00 (9), 152.04 (26), 181.04 (39), 209.03 (9), 241.06 (35), 286.06 (100), 224.05 (xx); HRMS (EI) *m/z* calcd for $C_{20}H_{14}O_2$ $[M]^+$: 286.09938, found: 286.09876.

(+)-3-(4-Fluorophenyl)-1,3-dihydro-2-benzofuran-1-one (3af). White solid; mp 121–124 °C; 98% yield (112 mg); $[\alpha]_D^{25}$ = +18.0 (*c* 0.50, $CHCl_3$), 95% *ee* [HPLC condition: CHIRALCEL OD-H column, hexane/2-propanol = 90/10, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 21.1 min (major) and 25.9 min (minor)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.97 (d, *J* = 7.3 Hz, 1H), 7.68 (t, *J* = 7.3 Hz 7.8 Hz, 1H), 7.58 (t, *J* = 7.3 Hz 7.8 Hz, 1H), 7.32 (d, *J* = 7.8 Hz, 1H), 7.28–7.24 (m, 2H), 7.07 (t, *J* = 8.7 Hz, 1H), 6.40 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.19, 163.02 (d, $J_{C\text{-}F}$ = 247.5 Hz), 149.25, 134.36, 132.17, 129.40, 128.96 (d, $J_{C\text{-}F}$ = 8.8 Hz), 125.50, 125.41, 122.76, 115.85 (d, $J_{C\text{-}F}$ = 21.3 Hz), 81.87; MS (EI) *m/z* 77.04 (20), 105.03 (100), 123.02 (26), 133.03 (11), 170.05 (11), 183.06 (54), 199.05 (6), 228.06 (57); HRMS (EI) *m/z* calcd for $C_{14}H_9FO_2$ $[M]^+$: 228.05866, found: 228.05819.

(*S*)-3-(4-Chlorophenyl)-1,3-dihydro-2-benzofuran-1-one (3ag).[17] White solid; mp 156–159 °C; 97% yield (118 mg); $[\alpha]_D^{25}$ = +25.0 (*c* 0.5, $CHCl_3$), 96% *ee* [lit. $[\alpha]_D^{22}$ = −32.2 (*c* 0.72, $CHCl_3$, 88% *ee* (*R*))[17]] [HPLC condition: CHIRALCEL OD-H column, hexane/2-propanol = 90/10, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 22.0 min (major) and 26.8 min (minor)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.97 (d, *J* = 7.3 Hz, 1H), 7.67 (t, *J* = 7.3 Hz 7.8 Hz, 1H), 7.58 (t, *J* = 7.3 Hz 7.8 Hz, 1H), 7.37–7.31 (m, 3H), 7.24–7.21 (m, 2H), 6.38 (s, 1H); ^{13}C NMR (100 MHz,

$CDCl_3$) δ = 170.18, 149.11, 135.14, 134.85, 134.42, 129.49, 129.10, 128.28, 125.63, 125.33, 122.70, 81.74; MS (EI) *m/z* 43.99 (28), 77.04 (32), 105.03 (100), 133.03 (15), 138.99 (21), 165.07 (60), 199.03 (5), 209.06 (90), 244.03 (29); HRMS (EI) *m/z* calcd for $C_{14}H_9FO_2$ $[M]^+$: 244.02911, found: 244.02859.

(*S*)-3-[4-(Trifluoromethyl)phenyl]-1,3-dihydro-2-benzofuran-1-one (3ah).[18] White solid; mp 118–121 °C; 74% yield (103 mg); $[\alpha]_D^{24}$ = +47.0 (*c* 0.50, $CHCl_3$), 91% *ee* [lit. $[\alpha]_D^{27}$ = +34.0 (*c* 0.50, CH_2Cl_2, 70% ee (*S*))[18]] [HPLC condition: CHIRALCEL OD-H column, hexane/2-propanol = 90/10, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 22.5 min (major) and 26.2 min (minor)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.98 (d, *J* = 7.3 Hz, 1H), 7.70–7.64 (m, 3H), 7.59 (d, *J* = 7.3 Hz 7.8 Hz, 1H), 7.45 (d, *J* = 8.2 Hz, 2H), 7.36 (d, *J* = 7.8 Hz, 1H), 6.47 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.11, 148.90, 140.44, 134.57, 131.32 (q, $J_{C\text{-}F}$ = 32.9 Hz), 129.69, 127.05, 125.96 (q, $J_{C\text{-}F}$ = 3.8 Hz), 125.83, 125.17, 123.70 (q, $J_{C\text{-}F}$ = 271.5 Hz), 122.67, 81.50; MS (EI) *m/z* 77.04 (18), 105.03 (100), 133.02 (13), 145.02 (8), 165.06 (18), 201.04 (8), 209.05 (18), 278.05 (21); HRMS (EI) *m/z* calcd for $C_{15}H_9F_3O_2$ $[M]^+$: 278.05546, found: 278.05473.

(*S*)-3-(Naphthalen-2-yl)-1,3-dihydro-2-benzofuran-1-one (3ai).[5a] White solid; mp 184–187 °C; 92% yield (127 mg); $[\alpha]_D^{25}$ = +97.0 (*c* 0.50, $CHCl_3$), 93% *ee* [lit. $[\alpha]_D$ = +97.9 (*c* 0.10, $CHCl_3$, 83% ee (*S*))[5a]] [HPLC condition: CHIRALCEL OD-H column, hexane/2-propanol = 90/10, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 26.9 min (major) and 38.4 min (minor)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.0 (d, *J* = 7.3 Hz, 1H), 7.85–7.82 (m, 4H), 7.64 (t, *J* = 7.3 Hz, 1H), 7.58–7.49 (m, 3H), 7.34 (d, *J* = 7.8 Hz, 1H), 7.24–7.22 (m, 1H), 6.56 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.59, 149.69, 134.36, 133.65, 133.55, 133.04, 129.41, 129.05, 128.06, 127.78, 126.81, 126.68, 125.69, 125.58, 125.75, 122.90, 82.89; MS (EI) *m/z* 43.99 (6), 77.03 (15), 104.02 (41), 127.04 (24), 132.01 (6), 155.04 (29), 202.07 (15), 215.08 (50), 231.07 (15), 260.07 (100); HRMS (EI) *m/z* calcd for $C_{18}H_{12}O_2$ $[M]^+$: 260.08373, found: 260.08340.

(*S*)-3-(3,5-Dimethylphenyl)-1,3-dihydro-2-benzofuran-1-one (3aj).[5a] White solid; mp 91–93 °C; 99% yield (120 mg); $[\alpha]_D^{25}$ = +56.0 (*c* 0.50, $CHCl_3$), 96% *ee* [lit. $[\alpha]_D$ = +18.8 (*c* 0.07, $CHCl_3$, 67% ee (*S*)[5a]) [HPLC condition CHIRALCEL OD-H column, hexane/2-propanol = 90/10, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 14.7 min (major) and 17.4 min (minor)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.94 (d, *J* = 7.8 Hz, 1H), 7.63 (t, *J* = 7.3 Hz 7.8 Hz, 1H), 7.53 (t, *J* = 7.3 Hz 7.8 Hz, 1H), 7.33 (d, *J* = 7.8 Hz, 1H), 6.98 (s, 1H), 6.87 (s, 2H), 6.31 (s, 1H), 2.28 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.57, 149.79, 138.53, 136.14, 134.19, 130.80, 129.13, 125.40, 124.49, 122.77, 82.77, 21.82; MS (EI) *m/z* 43.99 (13), 77.03 (18), 104.02 (44), 133.05 (62), 152.05 (9), 165.05 (18), 179.07 (31), 195.06 (11), 215.08 (50), 223.05 (100), 238.08 (82); HRMS (EI) *m/z* calcd for $C_{16}H_{14}O_2$ $[M]^+$: 238.09938, found: 238.09888.

(*S*)-3-(3-Chlorophenyl)-1,3-dihydro-2-benzofuran-1-one (3ak). White solid; mp 118–121 °C; 84% yield (107 mg); $[\alpha]_D^{24}$ = +54.0 (*c* 0.50, $CHCl_3$), 93% *ee* [HPLC condition: CHIRALCEL OD-H column, hexane/2-propanol = 90/10, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 22.6

min (major) and 31.5 min (minor)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.96 (d, J = 7.8 Hz, 1H), 7.67 (d, J = 7.3 Hz 7.8 Hz, 1H), 7.58 (d, J = 7.3 Hz 7.8 Hz, 1H), 7.36–7.30 (m, 3H), 7.27–7.26 (m, 1H), 7.21–7.19 (m, 1H), 6.37 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.12, 148.95, 138.38, 134.82, 134.48, 130.25, 129.58, 129.38, 126.85, 125.72, 125.25, 124.99, 122.72, 81.60; MS (EI) *m/z* 77.03 (21), 105.02 (100), 133.01 (16), 152.05 (11), 165.05 (21), 209.04 (50), 244.01 (26); HRMS (EI) *m/z* calcd for $C_{14}H_9ClO_2$ $[M]^+$: 244.02911, found: 244.02872.

(*S*)-3-(Thiophen-3-yl)-1,3-dihydro-2-benzofuran-1-one (3al). White solid; mp 112–116 ºC; 92% yield (99 mg); $[\alpha]_D^{25}$ = −34.0 (*c* 0.50, $CHCl_3$), 91% *ee* [HPLC condition: CHIRALCEL OD-H column, hexane/2-propanol = 90/10, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 30.2 min (major) and 39.9 min (minor)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.96 (d, J = 7.3 Hz, 1H), 7.69 (t, J = 7.3 Hz, 1H), 7.58 (t, J = 7.5 Hz, 1H), 7.43 (d, J = 7.8 Hz, 1H), 7.36–7.33 (m, 2H), 6.96–6.34 (m, 1H), 6.52 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.15, 148.89, 137.06, 134.23, 129.37, 129.13, 125.79, 125.61, 125.57, 124.41, 122.77, 78.34; MS (EI) *m/z* 77.04 (20), 82.99 (2), 105.03 (59), 110.99 (37), 133.03 (7), 171.02 (59), 187.01 (10), 216.02 (100); HRMS (EI) *m/z* calcd for $C_{12}H_8O_2S$ $[M]^+$: 216.02450, found: 216.02450.

(+)-3-Phenyl-5-(trifluoromethyl)-1,3-dihydro-2-benzofuran-1-one (3ba). White solid; mp 152–155 ºC; 91% yield (127 mg); $[\alpha]_D^{25}$ = +29.0 (*c* 0.5, $CHCl_3$), 89% *ee* [HPLC condition: CHIRALCEL OD-H column, hexane/2-propanol = 90/10, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 18.9 min (major) and 29.1 min (minor)]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (d, J = 8.1 Hz, 1H), 7.83 (d, J = 8.1 Hz, 1H), 7.61 (s, 1H), 7.42–7.41 (m, 3H), 7.30–7.26 (m, 2H), 6.47 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.92, 149.99, 136.08 (q, $J_{C\text{-}F}$ = 32.9 Hz), 135.26, 129.70, 129.19, 128.74, 126.91, 126.70 (dd, $J_{C\text{-}F}$ = 2.8 Hz 3.8Hz), 126.39, 125.95 (q, $J_{C\text{-}F}$ = 273.4 Hz), 120.23 (q, $J_{C\text{-}F}$ = 3.8 Hz), 82.71; MS (EI) *m/z* 77.05 (34), 105.05 (93), 145.04 (34), 165.09 (47), 172.03 (75), 201.07 (19), 233.08 (12), 249.08 (12), 278.08 (100); HRMS (EI) *m/z* calcd for $C_{15}H_9F_3O_2$ $[M]^+$: 278.05546, found: 278.05451.

(–)-5-Bromo-3-phenyl-1,3-dihydro-2-benzofuran-1-one (3ca). White solid; mp 171–173 ºC; 99% yield (143 mg); $[\alpha]_D^{25}$ = −49.0 (*c* 0.50, $CHCl_3$), 94% *ee* [HPLC condition: CHIRALCEL OD-H column, hexane/2-propanol = 90/10, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 23.3 min (major) and 32.4 min (minor)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.82 (d, J = 8.2 Hz, 1H), 7.69 (d, J = 8.2 Hz, 1H), 7.49 (s, 1H), 7.41–7.39 (m, 3H), 7.29–7.24 (m, 2H), 6.37 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 169.38, 151.29, 135.53, 132.91, 129.49, 129.46, 129.02, 126.81, 126.78, 126.18, 124.34, 81.95; MS (EI) *m/z* 77.03 (14), 105.02 (100), 152.05 (9), 165.05 (23), 184.92 (16), 210.92 (3), 289.95 (23); HRMS (EI) *m/z* calcd for $C_{14}H_9BrO_2$ $[M]^+$: 287.97859, found: 287.97765.

(+)-6-Bromo-3-phenyl-1,3-dihydro-2-benzofuran-1-one (3da). White solid; mp 109–112 ºC; 92% yield (133 mg); $[\alpha]_D^{24}$ = +19.0 (*c* 0.50, $CHCl_3$), 96% *ee* [HPLC condition: CHIRALCEL OD-H column, hexane/2-propanol = 95/5, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 28.8

min (major) and 47.0 min (minor)]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (d, J = 1.4 Hz, 1H), 7.76 (dd, J = 1.83 Hz 8.2 Hz, 1H), 7.41–7.37 (m, 3H), 7.28–7.21 (m, 3H), 6.36 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.85, 148.29, 137.37, 135.67, 129.55, 129.07, 128.58, 127.67, 126.93, 124.46, 123.41, 82.63; MS (EI) *m/z* 43.99 (19), 75.01 (27), 105.02 (100), 152.05 (16), 165.05 (48), 184.92 (35), 210.92 (8), 289.95 (55); HRMS (EI) *m/z* calcd for $C_{14}H_9BrO_2$ $[M]^+$: 287.97859, found: 287.97776.

(+)-7-Methyl-3-phenyl-1,3-dihydro-2-benzofuran-1-one (3ea). Colorless oil; 84% yield (94 mg); $[\alpha]_D^{25}$ = +54.0 (*c* 0.50, $CHCl_3$), 93% *ee* [HPLC condition: CHIRALCEL OD-H column, hexane/2-propanol = 90/10, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 18.1 min (major) and 24.8 min (minor)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.49 (t, J = 7.2 Hz 7.6 Hz, 1H), 7.39–7.35 (m, 3H), 7.30–7.26 (m, 3H), 7.12 (d, J = 7.2 Hz, 1H), 6.33 (s, 1H), 2.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.67, 150.14, 139.54, 136.74, 133.96, 130.83, 129.07, 128.83, 126.87, 122.89, 120.13, 81.72, 17.32; MS (EI) *m/z* 77.05 (15), 91.07 (23), 119.06 (100), 147.06 (10), 165.09 (27), 224.11 (54); HRMS (EI) *m/z* calcd for $C_{15}H_{12}O_2$ $[M]^+$: 224. 08373, found: 224.08290.

(+)-6-Methyl-3-phenyl-1,3-dihydro-2-benzofuran-1-one (3fa). White solid; mp 103–106 °C; 92% yield (103 mg); $[\alpha]_D^{25}$ = +25.0 (*c* 0.50, $CHCl_3$), 95% *ee* [HPLC condition: CHIRALCEL OD-H column, hexane/2-propanol = 90/10, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 19.5 min (major) and 26.3 min (minor)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.75 (s, 1H), 7.46 (d, J = 7.8 Hz, 1H), 7.38–7.36 (m, 3H), 7.28–7.26 (m, 2H), 7.21 (d, J = 7.8 Hz, 1H), 6.37 (s, 1H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.61, 147.01, 139.55, 136.54, 135.42, 129.10, 128.81, 126.84, 125.59, 125.40, 122.47, 82.52, 21.16; MS (EI) *m/z* 41.04 (16), 91.05 (16), 105.02 (13), 119.04 (100), 147.03 (13), 165.05 (25), 178.06 (9), 224.06 (52); HRMS (EI) *m/z* calcd for $C_{15}H_{12}O_2$ $[M]^+$: 224. 08373, found: 224.08364.

(+)-5-Methyl-3-phenyl-1,3-dihydro-2-benzofuran-1-one (3ga). White solid; mp 138–141 °C; 99% yield (111 mg); $[\alpha]_D^{25}$ = +4.0 (*c* 0.50, $CHCl_3$), 97% *ee* [HPLC condition: CHIRALCEL OD-H column, hexane/2-propanol = 90/10, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 19.7 min (major) and 24.4 min (minor)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.84 (d, J = 7.8 Hz, 1H), 7.41–7.34 (m, 4H), 7.29–7.26 (m, 2H), 7.11 (s, 1H), 6.35 (s, 1H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.54, 150.18, 145.59, 136.52, 130.45, 129.11, 128.84, 126.82, 125.23, 123.01, 122.80, 82.35, 21.96; MS (EI) *m/z* 43.99 (16), 77.03 (14), 91.05 (20), 119.04 (100), 147.03 (12), 165.05 (26), 178.06 (9), 195.06 (6), 224.06 (45); HRMS (EI) *m/z* calcd for $C_{15}H_{12}O_2$ $[M]^+$: 224. 08373, found: 224.08364.

(+)-6-Chloro-3-phenyl-1,3-dihydro-2-benzofuran-1-one (3ha). White solid; mp 102–106 °C; 87% yield (106 mg); $[\alpha]_D^{25}$ = +17.0 (*c* 0.50, $CHCl_3$), 95% *ee* [HPLC condition: CHIRALCEL OD-H column, hexane/2-propanol = 90/10, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 25.5 min (major) and 43.5 min (minor)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.92 (d, J = 1.8 Hz, 1H),

7.61 (dd, J = 1.8 Hz 7.9 Hz, 1H), 7.39 (t, J = 3.1 Hz, 3H), 7.29–7.23 (m, 3H), 6.39 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 169.00, 147.79, 135.72, 134.62, 129.53, 129.07, 127.39, 126.92, 125.50, 124.18, 82.58; MS (EI) *m/z* 77.04 (25), 105.03 (100), 138.99 (27), 165.07 (31), 181.06 (7), 199.03 (5), 209.06 (5), 244.03 (67); HRMS (EI) *m/z* calcd for $C_{14}H_9ClO_2$ $[M]^+$: 244.02911, found: 244.02842.

(–)-5,7-Dimethoxy-3-(4-methoxyphenyl)-1,3-dihydro-2-benzofuran-1-one (3ib).[9a] White solid; mp 138–142 ºC; 85% yield (127 mg); $[\alpha]_D^{25}$ = −13.0 (*c* 0.50, $CHCl_3$), 87% *ee* [lit. $[\alpha]_D^{22}$ = −13 (*c* 1.1, $CHCl_3$)[9a]] [HPLC condition: CHIRALCEL OD-H column, hexane/2-propanol = 90/10, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 114.8 min (minor) and 127.6 min (major)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.26 (s, 1H), 7.19 (d, J = 8.7 Hz, 2H), 6.89 (d, J = 8.2 Hz, 2H), 6.43 (s, 1H), 6.26 (s, 1H), 6.18 (s, 1H), 3.98 (s, 3H), 3.81 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.16, 166.66, 159.97, 159.08, 154.64, 128.41, 113.98, 106.15, 98.76, 98.22, 81.08, 55.80, 55.71, 55.04; MS (EI) *m/z* 43.99 (35), 77.05 (13), 106.03 (14), 135.03 (23), 165.04 (67), 255.05 (33), 270.06 (51), 300.08 (100); HRMS (EI) *m/z* calcd for $C_{17}H_{16}O_5$ $[M]^+$: 300.09977, found: 300.09907.

2.4.4 X-ray crystal structure of compound 3al

Data collection

A colorless block crystal of $C_{12}H_8O_2S$ having approximate dimensions of 0.672 x 0.195 x 0.180 mm was mounted on a glass fiber. All measurements were made on a Rigaku R-AXIS RAPID diffractometer using graphite monochromated Mo-Kα radiation.

The crystal-to-detector distance was 127.40 mm.

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

a = 6.158(1) Å
b = 7.366(2) Å ß = 91.935(5)°
c = 11.253(2) Å
V = 510.2(2) Å^3

For Z = 2 and F.W. = 216.25, the calculated density is 1.408 g/cm^3. Based on the reflection conditions of:

0k0: k = 2n

Packing considerations, a statistical analysis of intensity distribution, and the successful solution and refinement of the structure, the space group was determined to be:

$P2_1$ (#4)

The data were collected at a temperature of -150 + 1° C to a maximum 2θ value of 54.9°. A total of 44 oscillation images were collected. A sweep of data was done using w scans from 130.0 to 190.0° in 5.0° step, at χ = 45.0° and φ = 0.0°. The exposure rate was 60.0 [sec./°]. A second sweep was performed using w scans from 0.0 to 160.0° in 5.0° step, at χ = 45.0° and φ = 180.0°. 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 4978 reflections that were collected, 2133 were unique (R_{int} = 0.0478); equivalent reflections were merged.

The linear absorption coefficient, μ, for Mo-Kα radiation is 2.899 cm^{-1}. An empirical absorption correction was applied which resulted in transmission factors ranging from 0.549 to 0.949. 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 2133 observed reflections and 140 variable parameters and converged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors of:

$$R1 = \Sigma \; | \; |Fo| - |Fc| \; | \; / \Sigma \; |Fo| = 0.0442$$

$$wR2 = [\Sigma (w (Fo^2 - Fc^2)^2) / \Sigma w(Fo^2)^2]^{1/2} = 0.1171$$

The standard deviation of an observation of unit weight was 1.00. Unit weights were used. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.18 and -0.40 $e^-/Å^3$, respectively. The absolute structure was deduced based on Flack parameter, 0.13(12), refined using 878 Friedel pairs.

Neutral atom scattering factors were taken from Cromer and Wabe Anomalous dispersion effects were included in Fcalc; 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 Crystal Structure crystallographic software package except for refinement, which was performed using SHELXL-97.

Experimental details

A. Crystal data

Empirical formula	$C_{12}H_8O_2S$
Formula weight	216.25
Crystal color, Habit	colorless, block
Crystal dimensions	0.672 X 0.195 X 0.180 mm
Crystal system	monoclinic
Lattice type	Primitive
Lattice parameters	a = 6.158(1) Å
	b = 7.366(2) Å
	c = 11.253(5) Å
	β = 91.935(5) °
	V = 510.2(2) Å^3
Space group	$P2_1$ (#4)
Z value	2
D_{calc}	1.408 g/cm^3
F_{000}	224.00
μ (MoKα)	2.899 cm^{-1}

B. Intensity measurements

Diffractometer	R-AXIS RAPID
Radiation	MoKα (λ = 0.71075 Å) graphite monochromated
Voltage, Current	50kV, 40mA
Temperature	-150.0°C
Detector Aperture	280 x 256 mm
Data images	44 exposures
ω oscillation range (χ=45.0, φ=0.0)	130.0 - 190.0°
Exposure rate	60.0 sec./°
ω oscillation range (χ=45.0, φ=180.0)	0.0 - 160.0°
Exposure rate	60.0 sec./°
Detector position	127.40 mm
Pixel size	0.100 mm
$2q_{max}$	54.9°
No. of reflections measured	Total: 4978 Unique: 2133 (R_{int} = 0.0478) Friedel pairs: 878
Corrections	Lorentz-polarization Absorption (trans. factors: 0.549 - 0.949)

C. Structure solution and refinement

Structure solution	Direct methods (SIR92)
Refinement	Full-matrix least-squares on F^2
Function minimized	$\Sigma w (Fo^2 - Fc^2)^2$
Least squares weights	$w = 1/ [\sigma^2(Fo^2) + (0.1070 . P)^2 + 1.6775 . P]$ where $P = (Max(Fo^2,0) + 2Fc^2)/3$
2θmax cut-off	54.9°
Anomalous dispersion	All non-hydrogen atoms
No. Observations (All reflections)	2133
No. Variables	140
Reflection/parameter ratio	15.24
Residuals: R1 (I>2.00σ(I))	0.0442
Residuals: R (All reflections)	0.0593
Residuals: wR2 (All reflections)	0.1171
Goodness of fit indicator	0.997
Flack parameter (Friedel pairs = 2836)	0.13(12)
Max shift/error in final cycle	0.000
Maximum peak in final diff. map	0.18 $e^-/Å^3$
Minimum peak in final diff. map	-0.40 $e^-/Å^3$

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Chapter 3 Ruthenium-Me-BIPAM-Catalyzed Addition Reaction of Aryl-boronic Acids to α-Keto Carbonyl Compounds and Asymmetric Synthesis of 3-Aryl-3-hydroxy-benzofuranones

Abstract: Ruthenium/Me-BIPAM-catalyzed addition of arylboronic acids to α-diketone, α-ketoamides and *ortho*-substituted phenylglyoxylate esters were developed. $[RuCl_2(p\text{-cymene})]_2$ or $RuCl_2(PPh_3)_3$/(*R,R*)-Me-BIPAM and KF afforded useful α-hydroxy carbonyl derivatives having α-quaternary carbon centers with high enantioselectivities up to 93% *ee*. Enantioselective synthesis of 3-aryl-3-hydroxy-benzofuranones was achieved by a cascade addition-lactonization strategy.

3.1 Introduction

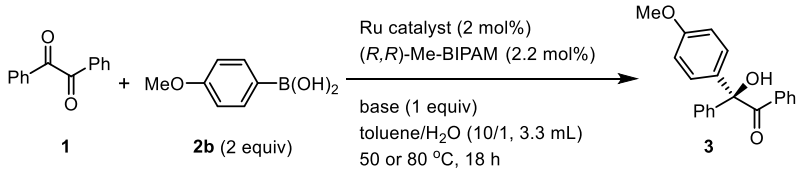
Over the past decades, transition-metal-catalyzed asymmetric addition of organometallic reagents to α-keto carbonyl compounds have been developed for the enantioselective synthesis of α-hydroxy carbonyl compounds.[1] Among these, the catalytic asymmetric addition of aryl boronic acids to α-keto carbonyl compounds has become a current focus for research.[2–4] Recently, we have first reported that ruthenium/Me-BIPAM catalyzed asymmetric arylation of α-ketoesters.[3c] However, ruthenium/Me-BIPAM catalyzed asymmetric arylation of α-diketones and α-ketoamides have not been developed.[2c,3f] In this section, it was described that a ruthenium/Me-BIPAM-catalyzed asymmetric addition reactions of arylboronic acids to α-diketones and α-ketoamides.

3.2 Asymmetric addition to α-diketone and α-ketoamide

We began our survey by examining the reaction of α-diketone **1** and α-ketoamide **4** with arylboronic acid **2** under the same conditions previously reported for arylation of α-ketoesters or isatins.[2c,3f] The results of asymmetric arylation of benzil as diketone are shown in Table 3.1. When $[RuCl_2(p\text{-cymene})]_2$ was used as precursor, the addition of phenylboronic acids to benzil gave the desired product with low yield (30%, entry 1). Finally, the reaction proceeded smoothly in toluene/H_2O (10/1) at 50 °C for 18 h in addition of KF as base by using $RuCl_2(PPh_3)_3$/Me-BIPAM catalyst (95% yield and 93% *ee*, entry 4).

Next, asymmetric addition of phenylboronic acid to α-ketoamide were tried (Scheme 3.1). The addition reaction to 2-pheny-2-oxo-N-phenylacetoamide with phenylboronic acid were carried out at 80 °C for 18 h in the presence of $RuCl_2(PPh_3)_3$/(*R,R*)- Me-BIPAM. The addition product **5a** was obtained in 94% yield and 89% *ee*. The addition reaction of phenylboronic acid to 2-oxo-N-phenylpropanamide under the same conditions furnished product **5b** in 41% yield and 87% *ee*.

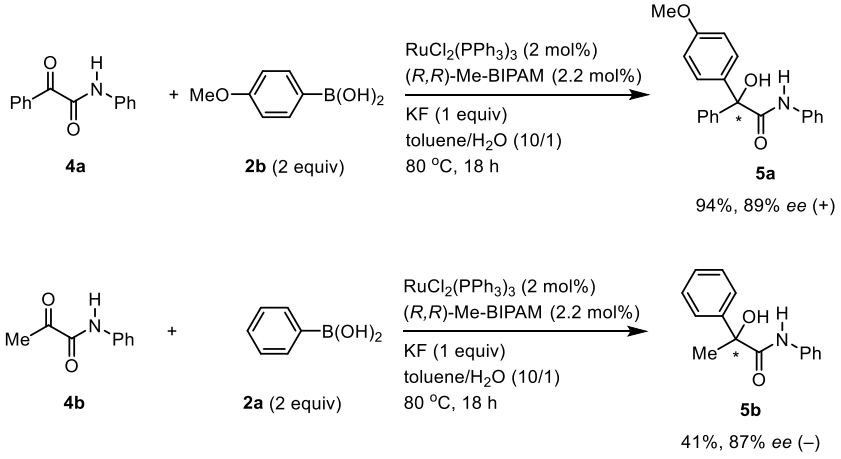
Table 3.1　Enantioselective arylation of benzil.



1　　**2b** (2 equiv)　　3

entry[a]	Ru catalyst	base	temp. (°C)	yield (%)	*ee* (%)
1	$[RuCl_2(p\text{-cymene})]_2$	KF	80	30	85 (*S*)
2	$RuCl_2(PPh_3)_3$	KF	80	>99	90 (*S*)
3	$RuCl_2(PPh_3)_3$	K_2CO_3	80	>99	89 (*S*)
4	$RuCl_2(PPh_3)_3$	KF	50	95	93 (*S*)
5	$RuCl_2(PPh_3)_3$	K_2CO_3	50	22	89 (*S*)

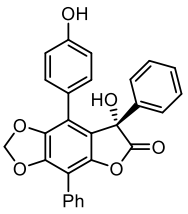
[a] Conditions: **1** (0.5 mmol), Ru catalyst (0.010 mmol), (*R,R*)-Me-BIPAM (0.011 mmol), base (0.5 mmol), toluene/H_2O (10/1, 3.3 mL), 2 equiv of boron reagent.



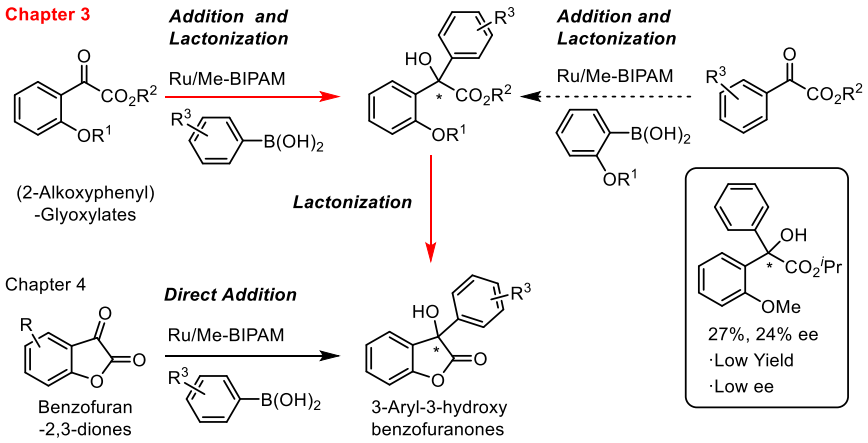
Scheme 3.1　Enantioselective arylation of α-ketoamide.

3.3 Asymmetric addition to *ortho*-alkoxy phenylglyoxylates

3-aryl-3-hydroxy-1-benzofuran-2-one derivative is reported that dragmacidol A was isolated from a specimen of the *marine sponge Dragmacidon australe*.[5] Therefore, I planned three synthesis methods of 3-aryl-3-hydroxy-1-benzofuran-2-ones as shown in Scheme 3.2. The first is enantioselective synthesis of these derivatives by a cascade addition-lactonization strategy involving transition metal-catalyzed asymmetric addition reaction of arylboronic acids to *ortho*-alkoxy phenylglyoxylate esters and lactonization.[2g] The second is an asymmetric addition reaction of *ortho*-alkoxyphenylboronic acids to phenylglyoxylate esters and lactonization strategy. The third is a ruthenium-catalyzed addition reaction of arylboronic acids to benzofuran-2,3-diones (Chapter 4). However, there have been no examples reported to date that employ these strategies. In this section, it was described that a ruthenium/Me-BIPAM-catalyzed asymmetric addition reactions of arylboronic acids to phenylglyoxylate esters followed by lactonization was gave optically active3-aryl-3-hydroxy-1-benzofuran-2-ones (Scheme 3.2).



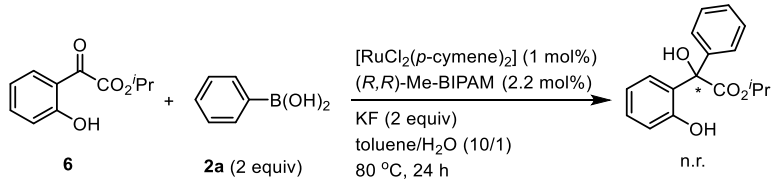
dragmacidol A



Scheme 3.2 Strategies to access optically active 3-aryl-3-hydroxy-1-benzofuran-2-ones

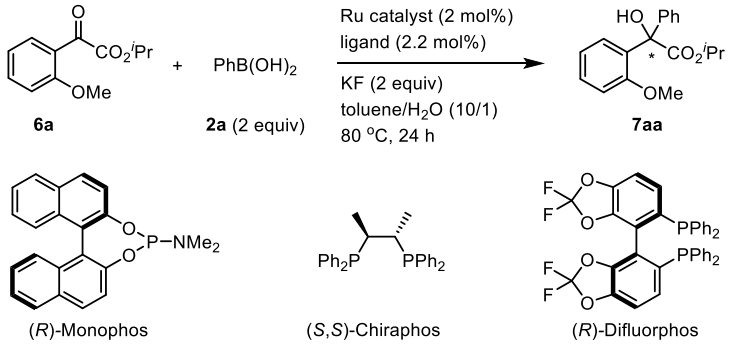
I have tried that the reaction of *ortho*-alkoxyphenylboronic acids to phenylglyoxylate esters and lactonization strategy. Unfortunately, the reaction resulted in low yield and low enantioselectivity (27% yield and 24% *ee*) (Scheme 3.2). So, I began survey by examining the reaction of *ortho*-hydroxy substituted isopropyl phenylglyoxylate with phenylboronic acid **2a** under the same conditions previously reported for arylation of α-ketoesters (Scheme 3.3).[2c] No reaction occurred when using 1.0 mol% of $[RuCl_2(p\text{-cymene})]_2$ and 2.2 mol% of Me-BIPAM in the presence of two equivalents of KF. Fortunately, *ortho*-methoxy substituted isopropyl

phenylglyoxylate **6a** with phenylboronic acid **2a** could furnish the expected addition product **7b** in 66 % yield, 86% *ee*. To attain higher reactivity and enantioselectivity, ruthenium precursors and chiral ligand were investigated (Table 3.2). When $[RuCl_2(benzene)]_2$ or $RuCl_2(PPh_3)_3$ with Me-BIPAM, which were used in our previous works, were used for this



Scheme 3.3 Enantioselective arylation of *ortho*-hydroxy substituted isopropyl phenylglyoxylate.

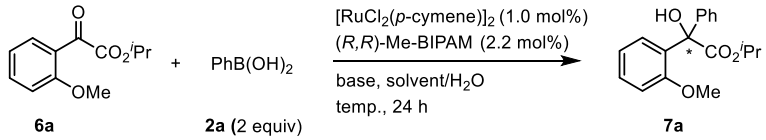
Table 3.2 Reaction conditions.



entry[a]	Ru catalyst	ligand	yield (%)[b]	*ee* (%)[c]
1	$[RuCl_2(p\text{-cymene})]_2$	(*R*,*R*)-Me-BIPAM	66	86 (–)
2	$[RuCl_2(benzene)]_2$	(*R*,*R*)-Me-BIPAM	58	85 (–)
3	$RuCl_2(PPh_3)_3$	(*R*,*R*)-Me-BIPAM	59	85 (–)
4	$[RuCl_2Cp^*]_2$	(*R*,*R*)-Me-BIPAM	26	50 (–)
5	$RuCl_2(nbd)(MeCN)_2$	(*R*,*R*)-Me-BIPAM	18	–
5	$[RuCl_2(p\text{-cymene})]_2$	(*R*)-Monophos	26	13 (–)
6	$[RuCl_2(p\text{-cymene})]_2$	(*S*,*S*)-Chiraphos	trace	–
7	$[RuCl_2(p\text{-cymene})]_2$	(*R*)-Difluorphos	trace	–

[a] Conditions: **1a** (0.5 mmol), Ru catalyst (0.010 mmol), ligand (0.011 mmol), KF (1.0 mmol), toluene /H_2O (10/1, 3.3 mL), **2a** (1.0 mmol). [b] Yield was determined by NMR analysis. [c] Determined by HPLC analysis.

Table 3.3 Reaction conditions.[a]



entry[a]	base	solvent	temp. (°C)	yield (%)[b]	*ee* (%)[c]
1	KF	toluene	80	66	86 (–)
2	K_2CO_3	toluene	80	67	82 (–)
3	K_3PO_4	toluene	80	54	82 (–)
4	LiF	toluene	80	33	86 (–)
5	CsF	toluene	80	44	84 (–)
6	KF	benzene	80	58	82 (–)
7	KF	mesitylene	80	64	86 (–)
8	KF	chlorobenzene	80	54	84 (–)
9	KF	DCE	80	36	77 (–)
10	KF	toluene	50	trace	–
11	KF	toluene	110	47	83 (–)

[a] Conditions: **6a** (0.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (0.010 mmol), (*R,R*)-Me-BIPAM (0.011 mmol), base (1.0 mmol), solvent/H_2O (10/1, 3.3 mL), **2a** (1.0 mmol). [b] Yield was determined by MNR analysis. [c] Determined by HPLC analysis.

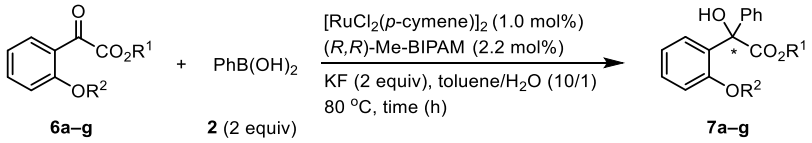
reaction, addition products were obtained in 66%, 86% *ee*, 58%, 85% *ee* and 59%, 85% *ee*, respectively (entries 1, 2 and 3). Furthermore, $RuCl_2Cp^*$ and $RuCl_2(nbd)(MeCN)_2$ gave low yields (entries 4 and 5). Among the chiral ligands screened, (*R*)-Monophos, (*S,S*)-Chiraphos and (*R*)-Difluorphos resulted in lower yields (entries 5–7). The highest efficiency to the reaction was observed when KF and K_2CO_3 were used for the arylation of **1a** with phenylboronic acid at 80 °C (Table 3.3, entries 1 and 2). K_3PO_4, LiF or CsF resulted in lower yields (Table 3.3, entries 3–5). In a survey of solvents, the use of benzene, mesitylene, chlorobenzene or DCE decreased yields (Table 3.3, entries 6–9).

Next, the effect of the ester group in *ortho*-methoxy substituted phenylglyoxylate was thoroughly explored (Table 3.4). Varying the ester substituent from isopropyl to methyl, ethyl, or tert-butyl decreased yields and did not improve the enantioselectivity of the reaction (entries 2–5). When *ortho*-substituents of phenylglyoxylate were changed, methoxymethyl ether and benzyl ether substituent of corresponding product was obtained with similar enantioselectivity (entries 6 and 7). By increasing amount of boronic acid to 5 equivalent, the

desired addition product was obtained in 51% yield, 84% *ee* (entry 8). Above the result, *ortho*-benzyl ether substituted phenylglyoxylate was determined, because benzyl ether is easy to deprotection.

Then the various arylboronic acids were used (Table 3.5). *Para*-methoxyphenyl, *para*-chlorophenyl, and 2-naphthylboronic acids afforded moderate yields of tertiary α-hydroxy-esters with good enantioselectivities.

Table 3.4 Reaction conditions.

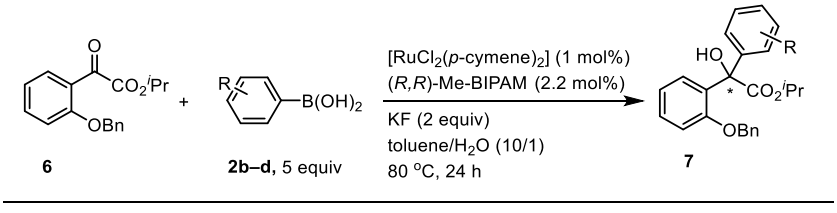


6a–g **2** (2 equiv) **7a–g**

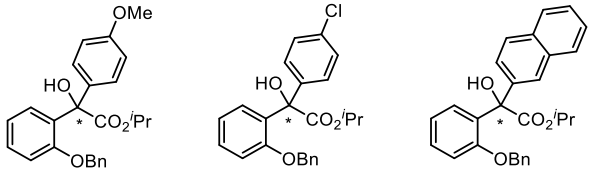
entry[a]	R^1 =	R^2 =	time (h)	product	yield (%)[b]	*ee* (%)[c]
1	^{i}Pr	Me	24	**7a**	66	86 (–)
2	Me	Me	24	**7b**	29	88 (–)
3	Et	Me	24	**7c**	42	88 (–)
4	^{t}Bu	Me	24	**7d**	trace	–
5	Me	MOM	24	**7e**	59	91 (–)
6	^{i}Pr	MOM	24	**7f**	49	88 (–)
7	^{i}Pr	Bn	24	**7g**	37	84 (–)
8[d]	^{i}Pr	Bn	72	**7g**	51	84 (–)

[a] Conditions: **6a–g** (0.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (0.005 mmol), Me-BIPAM (0.011 mmol), KF (1.0 mmol), toluene/H_2O (10/1, 3.3 mL), **2** (1.0 mmol). [b] Isolated yield. [c] Determined by HPLC analysis. [d] 5 equiv of $PhB(OH)_2$ was used.

Table 3.5 Addition of arylboronic acids to (2-benzyloxyphenyl)-glyoxylate



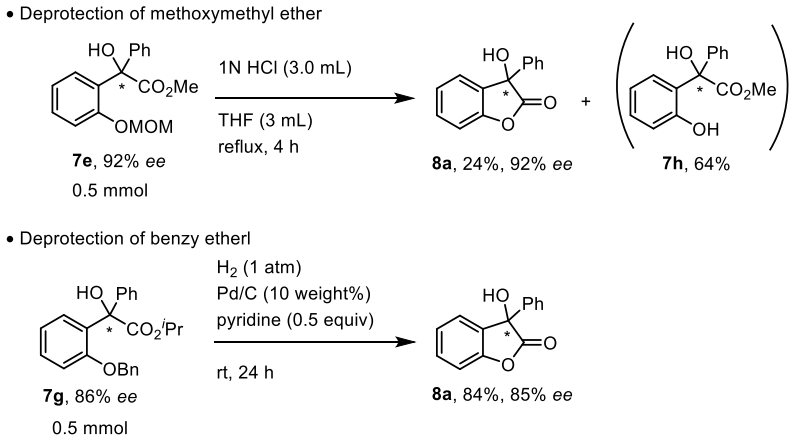
6 **2b–d,** 5 equiv **7**



7h 76%[a], 76% *ee* (–)[a] **7i** 61%[b], 73% *ee* (–) **7j** 53%[b], 79% *ee* (–)

[a] Isolated yield. [b] Determined by HPLC.

Finally, as shown in Scheme 3.4, the reaction of deprotection of alkoxy groups and intramolecular lactonization to construct 3-aryl-3-hydroxy-benzofuranone was tried. As a result, deprotection of methoxymethyl ether and lactonization under the acidic condition afforded desired product **8a** in 24% yield with 92% *ee*.[6] Deprotection of benzyl ether and lactonization under the hydrogen atmosphere with Pd/C afforded desired product **8a** in 84% yield with 85% *ee*.[7] It was found that catalytic asymmetric approaches to access such 3-aryl-3-hydroxy-benzofuranone derivatives remain considerably scarce. The current approach represents a new promising methodology to generate these interesting chiral compounds. In the next chapter, I will describe a third strategy that a ruthenium-catalyzed asymmetric addition reaction of arylboronic acids to benzofuran-2,3-diones.



Scheme 3.4 Deprotection of alkoxy group and lactonization.

3.4 Conclusion

In conclusion, ruthenium/Me-BIPAM-catalyzed addition of arylboronic acids to α-diketones, α-ketoamides and *ortho*-substituted phenylglyoxylate esters were developed. $[RuCl_2(p\text{-cymene})]_2$ or $RuCl_2(PPh_3)_3$/(*R,R*)-Me-BIPAM and KF afforded useful α-hydroxy carbonyl derivatives having α-quaternary carbon centers with high enantioselectivities up to 93% *ee*. Enantioselective synthesis of 3-aryl-3-hydroxy-benzofuranones was achieved by a cascade addition-lactonization strategy.

3.5 Experimental section

3.5.1 General information.

^{1}H NMR spectra were recorded on a JEOL ECX-400 (400 MHz) in $CDCl_3$ with tetramethylsilane as an internal standard. Chemical shifts are reported in part per million (ppm), and signal are expressed as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (br). ^{13}C NMR spectra were recorded on a JEOL ECX-400 (100MHz) in $CDCl_3$ (δ = 77.00) with tetramethylsilane as an internal standard (δ = 0.0) or CD_2Cl_2 (relative to residual CH_2Cl_2 δ = 53.84). Chemical shifts are reported in part per million (ppm). HPLC analysis was directly performed with chiral stationary phase column, CHIRALPAK AD-H or CHIRALCEL OD-H, purchased from DAICEL Co., Ltd. High resolution mass spectra (HRMS) were recorded on a JEOL JMS 700TZ mass spectrometer at the Center for Instrumental Analysis, Hokkaido University. Optical rotations were measured on a HORIBA SEPA-300 digital polarimeter. Kanto Chemical silica gel 60N (particle size 0.063–0.210 mm) was used for flash column chromatography. Glassware was oven dried at 130 ºC and allowed to cool under a stream of dry nitrogen. $RuCl_3 \cdot xH_2O$, (*R*)-Monophos, (*S,S*)-Chiraphos and (*R*)-BINAP were purchased from Strem Chemical, Inc. $[RuCl_2(p\text{-cymene})]_2$,[8] $RuCl_2(PPh_3)_3$,[9] $[Cp^*RuCl_2]_2$,[10] and $RuCl_2(nbd)(MeCN)_2$,[11] were prepared by the literature procedure. BIPAM ligands (Me-BIPAM, N-Me-BIPAM) were prepared according to our previous procedure.[12] Me-BIPAM was commercially available from Wako Pure Chemical Industries, Ltd. All chemicals were purchased from Aldrich, Wako, TCI, or Kanto chemicals and used as received. The spectra of compounds **3**,[2e] **6a**,[13] **6b**,[14] **6c**,[15] **6d**,[15] and **8a**[16] were identical to those reported in the literature.

3.5.2 General procedure for arylation of -diketones or α-ketoamides with arylboronic acids

A vial was charged with $RuCl_2(PPh_3)_3$ (0.005 mmol, 2 mol%) and (*R,R*)-Me-BIPAM (0.0055 mmol, 2.2 mol%) under a nitrogen atmosphere. Toluene (1.5 mL) was added to the vial and the mixture was then stirred at room temperature for 1 h. Substrate of α-diketone or α-ketoamide (0.25 mmol), arylboronic acid (0.5 mmol), KF (0.25 mmol), and H_2O (0.15 mL) were then added to the solution containing the catalyst. The reaction mixture was stirred at 50–80 °C for 18 h, at which time the crude reaction mixture was extracted using ethyl acetate and washed with saturated NH_4Cl. The extract was dried over $MgSO_4$, and was concentrated. The crude product was purified by silica gel column chromatography (hexane–AcOEt system). Enantiomeric excesses (*ee*) were determined by chiral HPLC analysis.

(*S*)-2-Hydroxy-2-(4-methoxyphenyl)-1,2-diphenylethan-1-one (3)[2e]: 95% yield. $[\alpha]_D^{23}$ = +11.2 (*c* 1.0, $CHCl_3$), 94% *ee*, [lit. $[\alpha]_D^{20}$ = +17.2 (*c* 1.0, CH_2Cl_2, 97% *ee*)[2e]], [HPLC condition:

CHIRALCEL OD-H column, hexane/2-propanol = 95/5, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 26.9 min (major) and 32.1 min (minor)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.71 (d, J = 8.5 Hz, 2H), 7.44–7.40 (m, 3H), 7.34–7.23 (m, 7H), 6.84 (d, J = 9.0 Hz, 2H), 5.0 (s, 1H), 3.77 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 200.8, 159.2, 142.0, 135.1, 133.9, 132.8, 130.8, 129.5, 128.3, 128.2, 128.0, 113.6, 84.6, 55.2.

(+)-2-Hydroxy-2-(4-methoxyphenyl)-N,2-diphenylacetamide (5a): 94% yield. $[\alpha]_D^{23}$ = +5.4 (*c* 1.0, $CHCl_3$), 89% *ee*, [HPLC condition: CHIRALPAK AD-H column, hexane/2-propanol = 80/20, flow = 1.0 mL/min, wavelength = 254 nm, t_R = 13.4 min (major) and 14.8 min (minor)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.55 (s), 7.54 (d, J = 8.5 Hz, 2H), 7.51–7.48 (m, 2H), 7.39–7.29 (m, 8H), 7.12 (d, J = 7.3, 7.8 Hz, 1H), 6.86 (t, J = 7.3, 7.8 Hz, 2H), 3.79 (s, 3H), 3.67 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 171.3, 159.4, 142.6, 137.2, 134.7, 129.0, 128.9, 128.3, 128.2, 127.5, 124.6, 119.7, 113.7, 81.6, 55.3; MS (ESI) *m/z* 65.05 (4), 77.05 (27), 92.05 (5), 105.05 (37), 135.06 (27), 213.12 (100), 214.13 (56), 277.15 (1), 286.20 (2), 316.20 (12); HRMS m/z calcd. for $C_{21}H_{19}NO_3Na$ $(M+Na)^+$: 356.12626, found 356.12571.

(–)-2-Hydroxy-N,2-diphenylpropanamide (5b): 41% yield. $[\alpha]_D^{23}$ = −14.0 (*c* 1.0, $CHCl_3$), 87% *ee*, [HPLC condition: CHIRALPAK AD-H column, hexane/2-propanol = 80/20, flow = 1.0 mL/min, wavelength = 254 nm, t_R = 6.2 min (minor) and 8.0 min (major)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.62 (s), 7.60 (t, J = 7.3 Hz, 2H), 7.49 (d, J = 7.3 Hz, 2H), 7.37–7.25 (m, 3H), 7.34–7.23 (m, 5H), 7.08 (t, J = 7.3, 7.8 Hz, 1H), 3.43 (s, 1H), 1.86 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 172.5, 142.8, 137.3, 128.9, 128.5, 128.0, 125.2, 124.4, 119.6, 76.8, 27.1; MS (EI) *m/z* 43.02 (53), 51.03 (5), 65.05 (5), 77.05 (15), 93.07 (25), 105.05 (6), 121.08 (100), 122.09 (13), 180.12 (1), 241.15 (2); HRMS m/z calcd. for $C_{15}H_{15}NO_2$ $[M]^+$: 241.11028, found 241.10950.

3.5.3 Preparation of isopropyl 2-(2-methoxyphenyl)-2-oxoacetate (6a) [13]

Under a nitrogen atmosphere, a solution of arylmagnesium bromide, prepared from 2-bromoanisole (5 mmol) and magnesium turning (0.17 g, 7 mmol) in anhydrous THF (5 ml), was added dropwise to a solution of di-isopropyl oxalate (1.42 g, 7 mmol) in anhydrous THF (10 ml) at −78 °C and the mixture was stirred at −78 °C for 2 h. After the addition of saturated NH_4Cl aq, the mixture was extracted with AcOEt three times. The combined organic extracts were washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane–AcOEt system) to give the following products.

Methyl 2-(2-methoxyphenyl)-2-oxoacetate (6b)[14]: **6b** was synthesized from 2-bromoanisole and di-methyl oxalate, following the procedure for **6a**.

Ethyl 2-(2-methoxyphenyl)-2-oxoacetate (6c)[15]: **6c** was synthesized from 2-bromoanisole and di-ethyl oxalate, following the procedure for **6a**.

tert-Butyl 2-(2-methoxyphenyl)-2-oxoacetate (6d)[15]: **6d** was synthesized from 2-bromoanisole and di-tert-butyl oxalate, following the procedure for **6a**.

Isopropyl 2-(2-hydroxyphenyl)-2-oxoacetate (6): *p*-TsOH monohydrate (65 mmol) was added to a solution of **6a** (3.46 g, 13 mmol) in CH_2Cl_2/MeOH (4:1, 50 ml) and the mixture was stirred at room temperature for 90 h. After addition of H_2O, the whole mixture was extracted with AcOEt three times. The combined organic extracts were washed with saturated $NaHCO_3$ aq and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/AcOEt = 20:1) to give the product. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 11.21 (s, 1H), 7.67 (dd, J = 1.4, 1.8, 8.0 Hz, 1H), 7.57 (td, J = 1.4, 1.8, 7.8, 8.0 Hz, 1H), 7.04 (dd, J = 0.9, 8.3 Hz, 1H), 6.96 (ddd, J = 0.9, 1.8, 7.1, 8.3 Hz, 1H), 5.34 (sept, J = 6.4 Hz, 1H), 1.43 (d, J = 6.4 Hz, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 191.16, 163.67, 162.16, 138.05, 132.02, 119.62, 118.51, 116.02, 71.15, 21.64; MS (ESI) *m/z* 179.06 (40), 207.07 (100), 208.07 (11); HRMS (ESI) *m/z* calcd for $C_{11}H_{11}O_4$ $(M-H)^-$: 207.06628, found: 207.06633.

Methyl 2-(2-(methoxymethoxy)phenyl)-2-oxoacetate (6e): **6e** was synthesized from 1-bromo-2-(methoxymethoxy)benzene and di-methyl oxalate, following the procedure for **6a**. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.88 (dd, J = 1.8, 7.8 Hz, 1H), 7.56 (td, J = 1.8, 7.8 Hz, 1H), 7.19 (d, J = 8.7 Hz, 1H), 7.12 (t, J = 7.3, 7.8 Hz, 1H), 5.20 (s, 2H), 3.92 (s, 3H), 3.48 (s, 3H); ^{3}C NMR (100 MHz, $CDCl_3$) δ = 186.23, 165.49, 157.77, 136.19, 130.53, 123.10, 122.13, 114.67, 94.76, 56.55, 52.30; MS (ESI) *m/z* 123.04 (13), 137.03 (31), 151.04 (70), 179.03 (100), 181.05 (74), 209.05 (19), 223.06 (45); HRMS (ESI) *m/z* calcd for $C_{11}H_{13}O_5$ $(M+H)^+$: 225.07575, found: 225.07594.

Isopropyl 2-(2-(methoxymethoxy)phenyl)-2-oxoacetate (6f): **6f** was synthesized from 1-bromo-2-(methoxymethoxy)benzene and di-isopropyl oxalate, following the procedure for **6a**. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.88 (dd, J = 1.8, 7.8 Hz, 1H), 7.55 (ddd, J = 1.8, 7.3, 8.3 Hz, 1H), 7.21(d, J = 8.3 Hz, 1H), 6.97 (td, J = 0.9, 7.3, 7.8 Hz, 1H), 5.32 (d, J = 6.5 Hz, 2H), 3.88 (m, 1H), 3.44 (s, 3H), 1.39 (d, J = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.86, 154.50, 129.26, 128.58, 127.88, 127.84, 121.54, 114.22, 94.22, 69.03, 55.66, 21.30, 21.06; MS (ESI) *m/z* 108.12 (11), 137.02 (27), 151.04 (19), 179.07 (100), 207.07 (47); HRMS (ESI) *m/z* calcd for $C_{13}H_{17}O_5$ $(M+H)^+$: 253.10705, found: 253.10706.

Isopropyl 2-(2-(benzyloxy)phenyl)-2-oxoacetate (6g): **6g** was synthesized from 1-(benzyloxy)-2-bromobenzene and di-isopropyl oxalate, following the procedure for **6a**. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.89 (dd, J = 1.8, 7.7 Hz, 1H), 7.52 (ddd, J = 1.8, 7.7, 8.2 Hz, 1H), 7.42–7.32 (m, 5H), 7.05 (ddd, J = 0.9, 7.3, 7.7 Hz, 1H), 7.00 (d, J = 8.6 Hz, 1H), 5.12 (s, 2H), 4.79 (sept, J = 6.3 Hz, 1H), 1.11 (d, J = 6.3 Hz, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 186.82, 164.61, 159.25, 136.02, 135.43, 130.99, 128.60, 128.35, 127.82, 122.95, 121.31, 112.92, 70.92, 69.85, 21.38; MS (ESI) *m/z* 137.03 (30), 179.07 (100), 198.07 (73), 207.07 (35), 241.09 (13), 269.12 (49), 297.11 (35); HRMS (ESI) *m/z* calcd for $C_{18}H_{19}O_4$ $(M+H)^+$: 299.12779, found: 299.12764.

3.5.4 General Procedure for Arylation of (2-Alchoxyphenyl)-Glyoxylate Derivatives with Arylboronic Acids

A vial was charged with $[RuCl_2(p\text{-cymene})]_2$ (0.005 mmol, 1 mol%) and (*R,R*)-Me-BIPAM (0.011 mmol, 2.2 mol%) under a nitrogen atmosphere. Toluene (3.0 mL) was added to the vial and the mixture was then stirred at room temperature for 1 h. (2-Alchoxyphenyl)-glyoxylate derivatives (0.5 mmol), arylboronic acid (1.0 mmol), KF (1.0 mmol), and H_2O (0.3 mL) were then added to the solution containing the catalyst. The reaction mixture was stirred at 80 °C for 24 h, at which time the crude reaction mixture was extracted using ethyl acetate and washed with saturated NH_4Cl. The extract was dried over $MgSO_4$, and was concentrated. The crude product was purified by silica gel column chromatography (hexane–AcOEt system). Enantiomeric excesses (*ee*) were determined by chiral HPLC analysis.

(–)-Methyl 2-hydroxy-2-(2-methoxyphenyl)-2-phenylacetate (7b): 29% yield. $[\alpha]_D^{23}$ = −60.9 (*c* 2.8, $CHCl_3$), 88% *ee* [HPLC condition: CHIRALPAK AD-H column, hexane/2-propanol = 9/1, flow = 1.0 mL/min, wavelength = 230 nm, t_R = 11.9 min (minor) and 22.6 min (major)]; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.71 (d, 2H), 7.43–7.28 (m, 4H), 6.94 (d, J = 8.2 Hz, 1H), 6.82 (m, 1H), 6.73 (dd, J = 7.7 Hz, 1.4 Hz, 1H), 4.39 (br s, 1H), 3.86 (s, 3H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 175.48, 157.24, 139.19, 132.22, 129.85, 129.43, 128.18, 127.29, 120.66, 111.40, 78.99, 55.85, 53.19; MS (ESI) *m/z* 199.13 (16), 227.15 (16), 255.23 (77); HRMS (ESI) *m/z* calcd for $C_{16}H_{16}O_4Na$ $(M+Na)^+$: 295.09408, found: 295.09384.

(–)-Ethyl 2-hydroxy-2-(2-methoxyphenyl)-2-phenylacetate (7c): 42% yield. $[\alpha]_D^{23}$ = −51.3 (*c* 1.5, $CHCl_3$), 88% *ee* [HPLC condition: CHIRALPAK AD-H column, hexane/2-propanol = 9/1, flow = 1.0 mL/min, wavelength = 230 nm, t_R = 13.1 min (minor) and 20.9 min (major)]; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.72 (d, 2H), 7.42–7.26 (m, 3H), 6.92 (d, 1H), 6.80 (m, 1H), 6.71 (dd, J = 7.7 Hz, 1.4 Hz, 1H), 4.39 (br s, 1H), 4.30–4.24 (m, 2H), 3.85 (s, 3H), 1.24 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 174.93, 157.24, 139.27, 132.24, 129.75, 129.49, 128.08, 127.33, 120.53, 111.20, 78.90, 62.25, 55.61, 14.21; MS (ESI) *m/z* 171.11 (100), 197.06 (52), 225.09 (53), 255.23 (69), 283.26 (62), 301.11 (37); HRMS (ESI) *m/z* calcd for $C_{17}H_{18}O_4Na$ $(M+Na)^+$: 309.10973, found: 309.10946.

(–)-Isopropyl 2-hydroxy-2-(2-methoxyphenyl)-2-phenylacetate (7a): 66% yield. $[\alpha]_D^{22}$ = −34.5 (*c* 5.0, $CHCl_3$), 86% *ee* [HPLC condition: CHIRALPAK AD-H column, hexane/2-propanol = 9/1, flow = 1.0 mL/min, wavelength = 230 nm, t_R = 12.8 min (minor) and 20.2 min (major)]; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.75–7.72 (m, 2H), 7.41–7.25 (m, 4H), 6.91 (dd, J = 8.2 Hz, 0.9 Hz, 1H), 6.79 (m, 1H), 6.71 (dd, J = 7.7 Hz, 1.4 Hz, 1H), 5.11 (quintet, J = 6.3 Hz, 1H), 4.4 (s, 1H), 3.84 (s, 3H), 1.22 (t, J = 5.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 174.45 157.25, 139.52, 132.20, 129.65, 129.56, 128.01, 127.98, 127.40, 120.36, 110.90, 78.80, 70.04, 55.38, 21.61 (d, J = 1.9 Hz); MS (ESI) *m/z* 197.06 (100), 231.02 (52), 233.03 (15), 300.11

(13), 315.12 (36); HRMS (ESI) *m/z* calcd for $C_{18}H_{20}O_4Na$ $(M+Na)^+$: 323.12538, found: 323.12494.

(–)-Methyl 2-hydroxy-2-(2-(methoxymethoxy)phenyl)-2-phenylacetate (7e): 59% yield. $[\alpha]_D^{21}$ = −38.1 (*c* 2.4, $CHCl_3$), 91% *ee* [HPLC condition: CHIRALPAK AD-H column, hexane/2-propanol = 95/5, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 33.2 min (minor) and 50.1 min (major)]; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.71–7.68 (m, 2H), 7.41–7.35 (m, 3H), 7.26–7.24 (m, 1H), 7.15 (dd, *J* = 8.2 Hz, 0.9 Hz, 1H), 6.88–6.83 (m, 1H), 6.75–6.73 (m, 1H), 5.18 (s, 2H), 4.37 (s, 1H), 3.80 (s, 3H), 3.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 175.38, 155.29, 139.33, 132.67, 129.90, 129.50, 128.16, 127.28, 127.28, 121.68, 114.84, 95.23, 78.99, 56.44, 55.38, 53.18; MS (ESI) *m/z* 197.06 (100), 198.06 (14), 271.10 (10); HRMS (ESI) *m/z* calcd for $C_{17}H_{18}O_5Na$ $(M+Na)^+$: 325.10464, found: 325.10427.

(–)-Isopropyl 2-hydroxy-2-(2-(methoxymethoxy)phenyl)-2-phenylacetate (7f): 49% yield. $[\alpha]_D^{22}$ = −29.4 (*c* 3.7, $CHCl_3$), 88% *ee* [HPLC condition: CHIRALPAK AD-H column, hexane/2-propanol = 95/5, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 29.3 min (minor) and 31.5 min (major)]; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.73 (dd, *J* = 8.2 Hz, 1.4 Hz, 2H), 7.42–7.35 (m, 3H), 7.27–7.23 (m, 1H), 7.15 (dd, *J* = 8.2 Hz, 0.9 Hz, 1H), 6.87–6.82 (m, 1H), 6.75–6.73 (m, 1H), 5.22–5.09 (m, 3H), 4.45 (br s, 1H), 1.22 (dd, *J* = 9.1 Hz, 6.3 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 174.33, 155.48, 139.58, 132.85, 129.76, 129.58, 128.07, 128.00, 127.38, 121.58, 114.98, 95.27, 78.88, 70.30, 56.43, 21.61 (d, *J* = 1.9 Hz); MS (ESI) *m/z* 197.06 (100), 198.06 (13), 255.23 (10), 283.26 (7); HRMS (ESI) *m/z* calcd for $C_{19}H_{22}O_5Na$ $(M+Na)^+$: 353.13594, found: 353.13545.

(–)-Isopropyl 2-(2-(benzyloxy)phenyl)-2-hydroxy-2-phenylacetate (7g): 51% yield. $[\alpha]_D^{22}$ = −6.4 (*c* 3.1, $CHCl_3$), 85% *ee* [HPLC condition: CHIRALPAK AD-H column, hexane/2-propanol = 95/5, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 98.5 min (minor) and 104.5 min (major)]; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.73–7.70 (m, 2H), 7.41–7.32 (m, 8H), 7.27–7.23 (m, 1H), 7.27–7.23 (m, 1H), 6.97 (d, *J* = 8.2 Hz, 1H), 6.83–6.79 (m, 1H), 6.74 (dd, *J* = 7.7 Hz, 1.8 Hz, 1H), 5.18 (d, *J* =11.8 Hz, 1H), 5.09 (d, *J* = 12.2 Hz, 1H), 4.93 (quintet, *J* = 6.3 Hz, 1H), 4.40 (br s, 1H), 1.08 (dd, *J* = 6.3 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.88, 156.54, 139.71, 136.47, 132.31, 129.74, 129.64, 128.68, 128.11, 128.02, 127.37, 127.29, 120.63, 112.33, 79.19, 70.70, 70.06, 21.48 (d, *J* = 9.5 Hz); MS (ESI) *m/z* 183.08 (100), 197.06 (93), 227.07 (19), 255.07 (37), 283.09 (43), 287.11 (98), 311.10 (77), 325.13 (43), 343.10 (22), 389.12(44); HRMS (ESI) *m/z* calcd for $C_{24}H_{24}O_4Na$ $(M+Na)^+$: 399.15668, found: 399.15603.

(–)-Isopropyl 2-(2-(benzyloxy)phenyl)-2-hydroxy-2-(4-methoxyphenyl) acetate (7h): 68% yield. $[\alpha]_D^{22}$ = −7.5 (*c* 5.1, $CHCl_3$), 77% *ee* [HPLC condition: CHIRALCEL OD-H column, hexane/2-propanol = 95/5, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 25.0 min (minor) and 28.1 min (major)]; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.64–7.61 (m, 2H), 7.41–7.22 (m, 6H), 6.96–6.90 (m, 3H), 6.83–6.75 (m, 2H), 5.18 (d, *J* =11.9 Hz, 1H), 5.08 (d, *J* = 11.9 Hz, 1H), 4.95–

4.89 (quintet, 1H), 4.45 (s, 1H), 3.83 (s, 3H), 1.09–1.04 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 174.05, 159.41, 156.51, 136.51, 131.66, 129.70, 129.60, 128.68, 128.53, 128.10, 127.37, 120.63, 113.38, 112.29, 78.85, 70.68, 69.95, 55.35, 21.51 (d, J = 7.6 Hz); MS (ESI) *m/z* 211.04 (34), 227.08 (100), 265.14 (21), 283.26 (15), 325.19 (16), 340.20 (12); HRMS (ESI) *m/z* calcd for $C_{25}H_{26}O_5Na$ $(M+Na)^+$: 429.16725, found: 429.16648.

(–)-Isopropyl 2-(2-(benzyloxy)phenyl)-2-(4-chlorophenyl)-2-hydroxyacetate (7i): 61% yield. $[\alpha]_D^{22}$ = −2.2 (*c* 4.3, $CHCl_3$), 73% *ee* [HPLC condition: CHIRALCEL OD-H column, hexane/2-propanol = 95/5, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 16.7 min (minor) and 20.5 min (major)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.67–7.63 (m, 2H), 7.38–7.24 (m, 9H), 6.97 (d, J = 8.2 Hz, 0.9 Hz, 1H), 6.84–6.80 (m, 1H), 6.74 (dd, J = 7.7 Hz, 1.4 Hz, 1H), 5.17 (d, J =11,8 Hz, 1H), 5.07 (d, J = 11.8 Hz, 1H), 4.94–4.88 (quintet, 1H), 4.49 (s, 1H), 3.83 (s, 3H), 1.10–1.04 (dd, J = 16.8 Hz, 6.3 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.54, 156.43, 138.37, 136.29, 134.01, 131.79, 129.84, 129.46, 127.57, 128.82, 128.69, 128.17, 127.40, 120.67, 112.41, 78.85, 70.71, 70.33, 21.46 (d, J = 9.5 Hz); MS (ESI) *m/z* 231.02 (100), 233.02 (30); HRMS (ESI) *m/z* calcd for $C_{24}H_{23}ClO_4Na$ $(M+Na)^+$: 433.11771, found: 433.11746.

(–)-Isopropyl 2-(2-(benzyloxy)phenyl)-2-hydroxy-2-(naphthalen-2-yl)acetate (7j): 53% yield. $[\alpha]_D^{22}$ = −20.7 (*c* 2.2, $CHCl_3$), 79% *ee* [HPLC condition: CHIRALCEL OD-H column, hexane/2-propanol = 95/5, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 22.1 min (minor) and 30.4 min (major)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.66–7.63 (m, 2H), 7.40–7.24 (m, 9H), 6.97 (d, J = 7.7 Hz, 1H), 6.84–6.80 (m, 1H), 6.73 (dd, J = 7.7 Hz, 1.8 Hz, 2H), 5.16 (d, J =11,8 Hz, 1H), 5.07 (d, J = 11.8 Hz, 1H), 4.94–4.88 (m, 1H), 4.48 (s, 1H), 3.83 (s, 3H), 1.09–1.04 (dd, J = 16.3 Hz, 6.3 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.84, 156.51, 137.17, 136.45, 133.14, 133.08, 132.08, 129.20, 129.74, 128.68, 128.14, 127.57, 127.39, 127.33, 126.39, 126.34, 120.66, 112.36, 79.28, 70.71, 70.23, 21.53 (d, J = 7.6 Hz); MS (ESI) *m/z* 153.02 (33), 227.19 (17), 242.09 (26), 247.08 (67), 255.23 (100), 283.26 (74), 285.10 (38), 297.12 (23), 325.18 (20), 379.15 (15), 409.16 (23); HRMS (ESI) *m/z* calcd for $C_{28}H_{26}O_4Na$ $(M+Na)^+$: 449.17233, found: 449.17163.

(+)-3-Hydroxy-3-phenylbenzofuran-2(3H)-one (8a)[16]: 84% yield. $[\alpha]_D^{22}$ = +6.0 (*c* 0.5, $CHCl_3$), 85% *ee* [HPLC condition: CHIRALPAK AD-H column, hexane/2-propanol = 95/5, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 34.7 min (minor) and 40.0 min (major)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.44–7.33 (m, 7H), 7.25–7.19 (m, 2H), 3.29 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 176.52, 153.66, 139.25, 131.50, 129.79, 129.38, 129.21, 125.76, 125.68, 125.57, 111.77, 77.41; MS (EI) *m/z* 51.03 (12), 65.05(11), 77.05 (36), 93.04 (7), 105.05 (29), 121.04 (55), 152.08 (18), 181.09 (20), 197.09 (100), 226.13(29).

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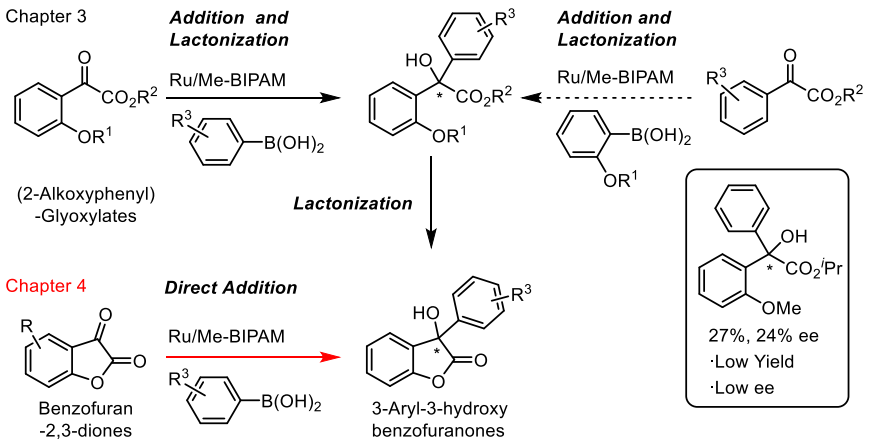
Chapter 4 Ruthenium/Me-BIPAM-Catalyzed Addition Reaction of Arylboronic Acids to Benzofuran-2,3-diones for Enantioselective Synthesis of 3-Aryl-3-hydroxybenzofuran-2-ones

Abstract: Enantioselective syntheses of 3-aryl-3-hydroxybenzofuran-2-ones by ruthenium-catalyzed 1,2-addition of arylboronic acids to benzofuran-2,3-diones have been developed. The use of $RuCl_2(PPh_3)_3$ with a chiral bidentate phosphoramidite ligand ((*R,R*)-Me-BIPAM) in the presence of a small amount of acetonitrile (20 mol%) gave optically active 3-aryl-3-hydroxybenzofuran-2-ones of up to 96% *ee*. This reaction is the first example of catalytic asymmetric 1,2-addition reaction of arylboronic acids to benzofuran-2,3-diones for highly efficient and enantioselective synthesis of quaternary carbon-containing benzofuran-2-ones.

4.1 Introduction

3-substituted-3-hydroxy-1-benzofuran-2-ones are also synthetic chemically important compounds,[1,2] and the approaches to these derivatives are limited to much compared with other derivatives.[3] In Chapter 3, cascade addition-lactonization strategy involving transition metal-catalyzed asymmetric addition reaction of arylboronic acids to *ortho*-alkoxy phenylglyoxylate esters and lactonization achieved enantioselective synthesis of 3-aryl-3-hydroxy-1-benzofuran-2-ones (Scheme 4.1). Although transition metal-catalyzed



Scheme 4.1 Strategies to access optically active 3-aryl-3-hydroxy-1-benzofuran-2-ones

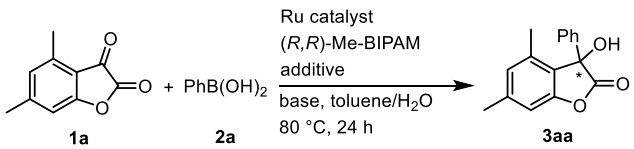
asymmetric addition reactions of organoboronic acids to benzofuran-2,3-diones are particularly powerful and straightforward approaches, benzofuran-2,3-diones have not been used in asymmetric addition reactions.[4–7] In this section, it is described that the asymmetric addition reactions of arylboronic acids to benzofuran-2,3-diones catalyzed by a ruthenium/Me-BIPAM complex (Scheme 4.1).

4.2 Results and discussion

As shown in Table 4.1, when $[RuCl_2(p\text{-cymene})]_2$ or $RuCl_2(PPh_3)_3$ with Me-BIPAM, which were used in our previous works, were used for this reaction, addition products were obtained in 29%, 34% *ee* and 27%, 54% *ee*, respectively (entries 1 and 2). Furthermore, $RuCl_2(nbd)(MeCN)_2$ and $RuCl_2(PPh_3)_2(MeCN)_2$ gave a moderate yield and high enantioselectivity (entries 3 and 4). We thought that both triphenylphosphine and acetonitrile inhibited the coordination to the ruthenium catalyst of benzofurandione.[8,9] We therefore confirmed the addition of triphenylphosphine or acetonitrile to the ruthenium precursor. $RuCl_2(PPh_3)_3$ with 20 mol% of acetonitrile afforded the desired product in 76% yield and with 91% *ee* (entry 6). By further investigation of the amount of base, the desired addition product was finally obtained in 87% yield and with 93% *ee* in the presence of 1.0 equivalent of KF (entries 7–10). The use of K_2CO_3 or K_3PO_4 resulted in lower yields (entries 12 and 13). KF play two roles. 1) The reaction of F^- with $ArB(OH)_2$ may be formed three species $ArBF_n(OH)_{3-n}$ (n = 1–3) and these species accelerate the transmetalation step.[10] 2) F^- is more suppressing the hydrolysis of 4,6-dimethyl-benzofuran-2,3-dione than OH^- (Table 4.1, entries 12 and 13). Among the chiral ligands screened, the use of bidentate phosphoramidite derived from N-linked BINOL (*R,R*)-N-Me-BIPAM, (*R*)-BINAP and monodentate phosphoramidite, (*R*)-Monophos, resulted in lower yields and enantioselectivities (entries 14–16).

Based on optimized reaction conditions, the substrate scope of asymmetric addition reactions of various arylboronic acids to 4,6-dimethyl-1-benzofuran-2,3-dione was examined (Table 4.2). *Para*- and *meta*-substituted arylboronic acids with an electron-donating group or electron-withdrawing group afforded 3-aryl-3-hydroxy-benzofuran-2-ones in good yields and enantioselectivities in the range of 87–96% *ee*. However, para-trifluoromethyl-phenylboronic acid gave a moderate yield with the use of 3 equivalent of boronic acid and changing the solvent ratio of toluene/H_2O (entry 7). *Ortho*-fluorophenylboronic acid can also be employed in the addition reaction with the use of 3 equivalent of arylboronic acid (entry 13).

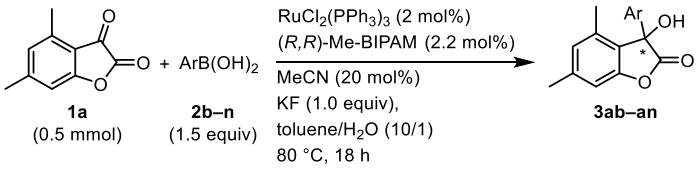
Table 4.1 Reaction conditions.[a]



entry	Ru catalyst	additive	base	yield (%)[b]	*ee* (%)[c]
1	$[RuCl_2(p\text{-cymene})]_2$	–	KF	29	34 (+)
2	$RuCl_2(PPh_3)_3$	–	KF	27	54 (+)
3	$RuCl_2(nbd)(MeCN)_2$	–	KF	39	81 (+)
4	$RuCl_2(PPh_3)_2(MeCN)_2$	–	KF	60	82 (+)
5[d]	$RuCl_2(nbd)(MeCN)_2$	PPh_3	KF	65	80 (+)
6[e]	$RuCl_2(PPh_3)_3$	MeCN	KF	76	91 (+)
7[e,f]	$RuCl_2(PPh_3)_3$	MeCN	KF	74	90 (+)
8[e,g]	$RuCl_2(PPh_3)_3$	MeCN	KF	82	92 (+)
9[e,g,h]	$RuCl_2(PPh_3)_3$	MeCN	KF	87	93 (+)
10[g,i]	$RuCl_2(PPh_3)_3$	MeCN	KF	48	86 (+)
11[g,j]	$RuCl_2(PPh_3)_3$	PhCN	KF	77	93 (+)
12[e,g,h]	$RuCl_2(PPh_3)_3$	MeCN	K_2CO_3	34	82 (+)
13[e,g,h]	$RuCl_2(PPh_3)_3$	MeCN	K_3PO_4	48	79 (+)
14[k]	$RuCl_2(PPh_3)_3$	MeCN	KF	46	91 (+)
15[l]	$RuCl_2(PPh_3)_3$	MeCN	KF	57	36 (+)
16[m]	$RuCl_2(PPh_3)_3$	MeCN	KF	51	61 (+)

[a] Conditions: a mixture of **1a** (0.5 mmol), **2a** (1 mmol), base (1 mmol), Ru catalyst (2 mol%) and (*R,R*)-Me-BIPAM (2.2 mol%) in toluene/H_2O (3 mL/0.3 mL) was stirred at 80 °C for 24 h. [b] Isolated yield. [c] Determined by HPLC analysis. [d] PPh_3 (6 mol%) was added. [e] MeCN (20 mol%) was added. [f] **2a** (0.75 mmol) and base (0.75 mmol) were used. [g] **2a** (0.75 mmol) and base (0.5 mmol) were used. [h] The mixture was stirred for 18 h. [i] **2a** (0.75 mmol) and base (0.25 mmol) were used. [j] PhCN (20 mol%) was added. [k] (*R,R*)-N-Me-BIPAM was used instead (*R,R*)-Me-BIPAM. [l] (*R*)-Monophos was used instead (*R, R*)-Me-BIPAM. [m] (*R*)-BINAP was used instead (*R,R*)-Me-BIPAM.

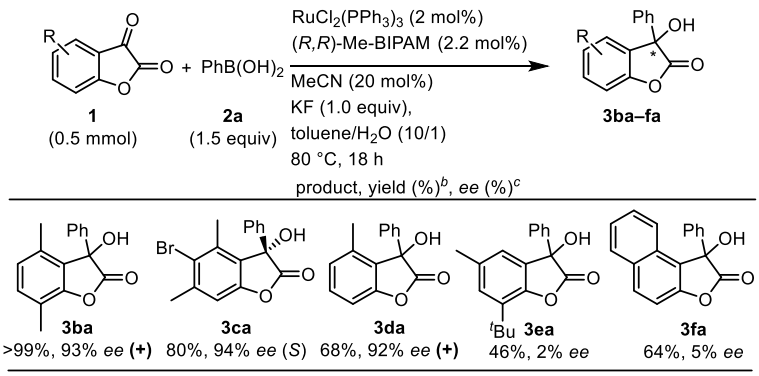
Table 4.2 Arylation of 4,6-dimethyl-1-benzofuran-2,3-dione.[a]



entry	Ar = (Ar-B(OH)$_2$)	product	yield (%)[b]	*ee* (%)[c]
1	4-PhOC$_6$H$_4$ (**2b**)	**3ab**	82	91 (+)
2	4-MeSC$_6$H$_4$ (**2c**)	**3ac**	75	90 (+)
3	4-MeC$_6$H$_4$ (**2d**)	**3ad**	85	91 (+)
4	4-PhC$_6$H$_4$ (**2e**)	**3ae**	81	95 (+)
5	4-ClC$_6$H$_4$ (**2f**)	**3af**	83	95 (+)
6	4-FC$_6$H$_4$ (**2g**)	**3ag**	96	94 (+)
7[d,e]	4-CF$_3$C$_6$H$_4$ (**2h**)	**3ah**	52	94 (+)
8	4-CH$_2$=CHC$_6$H$_4$ (**2i**)	**3ai**	86	94 (+)
9	2-naphthyl (**2j**)	**3aj**	86	96 (+)
10	3,4-(CH$_2$O$_2$)C$_6$H$_3$ (**2k**)	**3ak**	71	88 (+)
11	3,5-Me$_2$C$_6$H$_3$ (**2l**)	**3al**	96	92 (+)
12	3-ClC$_6$H$_4$ (**2m**)	**3am**	65	94 (+)
13[d]	2-FC$_6$H$_4$ (**2n**)	**3an**	78	87 (–)

[a] Conditions: a mixture of **1a** (0.5 mmol), **2b–n** (0.75 mmol), KF (0.5 mmol), MeCN (20 mol%), RuCl$_2$(PPh$_3$)$_3$ (2 mol%) and (*R,R*)-Me-BIPAM (2.2 mol%) in toluene/H$_2$O (3 mL/0.3 mL) was stirred at 80 °C for 18 h. [b] Isolated yield. [c] Determined by HPLC analysis. [d] ArB(OH)$_2$ (1.5 mmol) was used. [e] In toluene/H$_2$O (3 mL/0.15 mL).

Table 4.3 Ruthenium-catalyzed asymmetric addition of phenylboronic acid to 1-benzofuran-2,3-diones.[a]



[a] Conditions: a mixture of **1** (0.5 mmol), **2a** (0.75 mmol), KF (0.5 mmol), MeCN (20 mol%), $RuCl_2(PPh_3)_3$ (2 mol%) and (*R,R*)-Me-BIPAM (2.2 mol%) in toluene/H_2O (3 mL/0.3 mL) was stirred at 80 °C for 18 h. [b] Isolated yield. [c] Determined by HPLC analysis.

Next, the substrate scope of several substituted benzofuran-2,3-diones was investigated (Table 4.3). Arylation of benzofuran-2,3-diones with 4-methyl substituent proceeded efficiently to give the corresponding products in high yield and high enantioselectivity. But, **1e** and **1f** gave the corresponding products (**3ea** and **3fa**) in low enantioselectivity. From the above results, it was found that steric effects of 4-methyl substituent make the stability of the lactone ring against hydrolysis and give high enantioselectivities.[11]

The structure of **3ca** was confirmed unequivocally by X-ray crystal structure.[12] The absolute configuration of the product was assigned as *S* enantiomer from X-ray crystallographic analysis of the compound of **3ca** (Figure 4.1).

To determine the structure of the catalyst, I reacted $RuCl_2(PPh_3)_3$ with (*R,R*)-Me-BIPAM in CH_2Cl_2 with 20 mol % of acetonitrile could not obtain $RuCl_2(PPh_3)$((*R,R*)-Me-BIPAM) complex.[7c] I thought that a small amount of acetonitrile form $RuCl_2(MeCN)$((*R,R*)-Me-BIPAM) complex from ligand exchange between PPh_3 and MeCN.[13] The *re*-coordination of the substrate is preferred without significant steric interaction with two dimethylamino groups of the bis-phosphoramidite ligands to give the experimentally observed *S* enantiomer by parallel coordination of the C=O bond to the Ar–Ru bond for the subsequent insertion step.

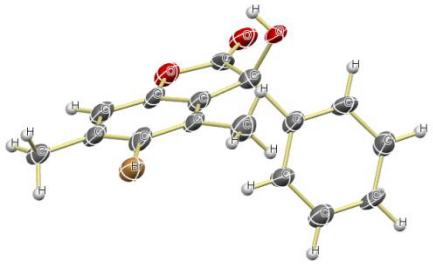


Figure 4.1　ORTEP diagram of **3ca** (ORTEP drawing at 50% ellipsoid probability)

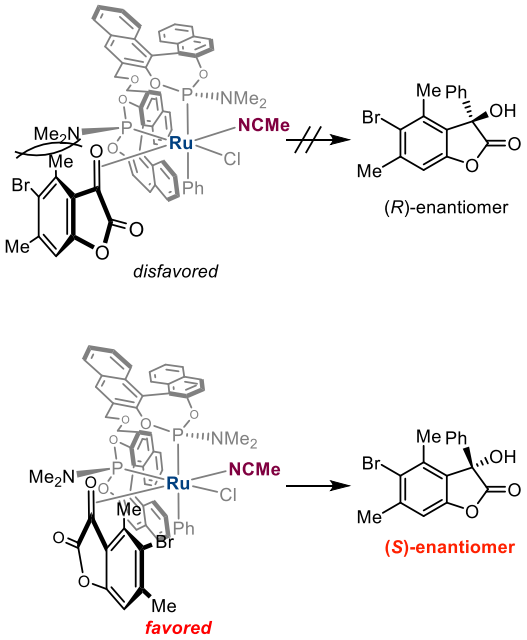


Figure 4.2　Proposed enantioselection models for $RuCl_2(MeCN)((R,R)$-Me-BIPAM) complex

4.3　Conclusion

In conclusion, an asymmetric arylation of benzofuran-2,3-diones with arylboronic acids using $[RuCl_2(PPh_3)_3]/(R,R)$-Me-BIPAM with an acetonitrile catalyst system has been developed. High performance of Me-BIPAM for enantioselective 1,2-addition to benzofuran-2,3-diones was demonstrated. A variety of chiral 3-aryl-3-hydroxybenzofuran-2-ones were obtained with good enantioselectivities for various substituted arylboronic acids (87–96 % *ee*). To our knowledge, this is the first example of catalytic asymmetric addition of arylboronic acids to benzofuran-2,3-diones.

4.4 Experimental section

4.4.1 General information.

^{1}H NMR spectra were recorded on a JEOL ECX-400 (400 MHz) or JEOL ECS-400 (400 MHz) in $CDCl_3$ with tetramethylsilane (δ = 0.00) as internal standard or CD_2Cl_2 (relative to residual CH_2Cl_2 δ = 5.32). Chemical shifts are reported in part per million (ppm), and signal are expressed as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (br). ^{13}C NMR spectra were recorded on a JEOL ECX-400 (100MHz) in $CDCl_3$ (δ = 77.00) with tetramethylsilane as an internal standard (δ = 0.0) or CD_2Cl_2 (relative to residual CH_2Cl_2 δ = 53.84) or acetone–d_6 (relative to residual acetone δ = 206.26). Chemical shifts are reported in part per million (ppm). HPLC analysis was directly performed with chiral stationary phase column, CHIRALPAK AD-H or CHIRALCEL OD-H purchased from DAICEL Co., Ltd. High resolution mass spectra (HRMS) were performed on an electron Ionization (EI) and electrospray ionization (ESI). Optical rotations were measured on a HORIBA SEPA-300 digital polarimeter. Kanto Chemical silica gel 60N (particle size 0.063–0.210 mm) was used for flash column chromatography. $RuCl_3 \cdot xH_2O$ was obtained from commercial source. $[RuCl_2(p\text{-cymene})]_2$,[14] $RuCl_2(PPh_3)_3$,[15] $RuCl_2(nbd)(MeCN)_2$,[16] $RuCl_2(PPh_3)_2(MeCN)_2$[17] and were prepared by the literature procedure. BIPAM ligand (Me-BIPAM) were prepared according to our previous procedure.[18]

4.4.2 Preparation of Benzofuran-2,3-diones (1a)[19]: A solution of the 3,5-xylenol (20 mmol), oxalyl chloride (36 mmol) and 4-(*N*,*N*-dimethylamino)-pyridine (0.1 g, 0.82 mmol) in chloroform (30 mL) was refluxed for 10 h. During the reaction the color changed from yellow to light yellow. After the reaction time to 10 h, the solution was concentrated. The oily residue was dissolved in 1,2-dichloroethane (20 mL) and at room temperature dropped into a suspension of aluminium chloride (50 mmol) in 1,2-dichloroethane (20 mL). After a reaction time of 10 h, the dark colored reaction mixture was hydrolysed cold water (50 mL). The yellow organic material was collected by extraction with chloroform, washed with brine. The extracted solution was dried with magnesium sulfoxide for 2 hours and concentrated. The yellow-red residue was purified by silica column chromatography. After evaporation of the chloroform, the residue was recrystallized from chloroform and hexane.

4.4.3 General procedure for ruthenium-catalyzed asymmetric additions of arylboronic acids to benzofuran-2,3-dione: A flask was charged with $RuCl_2(PPh_3)_2$ (0.01 mmol, 2 mol %) and (*R,R*)-Me-BIPAM (0.011 mmol, 2.2 mol %) under a nitrogen atmosphere. Subsequently, toluene (3.0 mL) and MeCN (0.1 mmol, 20 mol%) was added to the flask and the mixture was stirred at room temperature for 30 min to prepare the catalyst. Benzofuran-2,3-dine (0.5 mmol), arylboronic acid (0.75 mmol), KF (0.5 mmol), and H_2O (0.3 mL) were then added to

the catalyst solution. The reaction mixture was stirred at 80 °C for 18 h, at which time the crude reaction mixture was extracted using ethyl acetate, washed with saturated NH_4Cl and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (Hexane/EtOAc) to give 3-aryl-3-hydroxybenzofuran-2-one.

(+)-3-Hydroxy-4,6-dimethyl-3-phenylbenzofuran-2(3H)-one (3aa). Colorless oil: 87% yield (111 mg) and 93% *ee* [HPLC condition: CHIRALPAK AD-H column, hexane/2-propanol = 95/5, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 25.9 min (major) and 32.6 min (minor)]; $[\alpha]_D^{22}$ = +49.0 (*c* 0.5, $CHCl_3$), ^1H NMR (400 MHz, CD_2Cl_2): δ = 7.40–7.30 (br s, 5H), 6.87 (s, 1H), 6.83 (s, 1H), 3.48 (br s, 1H), 2.39 (s, 3H), 2.05 (s, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 176.9, 154.0, 142.2, 138.3, 137.2, 129.08, 129.05, 127.9, 125.6, 124.6, 109.5, 77.7, 21.9, 17.3; MS (ESI) m/z 237.09 (33), 272.13 (39), 277.08 (100); HRMS (ESI) m/z calcd for $C_{16}H_{14}O_3Na$ $(M+Na)^+$: 277.08352, found: 277.08343.

(+)-3-Hydroxy-3-(4-phenoxyphenyl)-4,6-dimethylbenzofuran-2(3H)-one (3ab). Colorless oil: 82% yield (142 mg) and 91% *ee* [HPLC condition: CHIRALPAK AD-H column, hexane/2-propanol = 95/5, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 50.7 min (major) and 58.5 min (minor)]; $[\alpha]_D^{23}$ = +68.0 (*c* 0.5, $CHCl_3$), ^1H NMR (400 MHz, $CDCl_3$) δ = 7.33–7.23 (m, 4H), 7.10 (t, *J* = 7.3 Hz, 1H), 6.99 (d, *J* = 8.2 Hz, 2H), 6.93 (d, *J* = 9.1 Hz, 2H), 6.80 (s, 1H), 6.78 (s, 1H), 3.56 (br s, 1H), 2.35 (s, 3H), 2.08 (s, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 177.0, 158.2, 156.9, 153.9, 142.2, 137.3, 132.7, 130.2, 128.0, 127.4, 124.4, 124.2, 119.7, 118.8, 109.5, 77.3, 21.9, 17.4; MS (EI) m/z 77.05 (53), 115.06 (21), 148.07 (57), 209.12 (24), 225.11 (100), 300.14(29), 317.14 (93), 346.15 (38); HRMS (EI) m/z calcd for $C_{22}H_{18}O_4$ (M): 346.12051, found: 346.12001

(+)-3-Hydroxy-3-(4-methylthiophenyl)-4,6-dimethylbenzofuran-2(3H)-one (3ac). Colorless oil: 75% yield (112 mg) and 90% *ee* [HPLC condition: CHIRALPAK AD-H column, hexane/2-propanol = 95/5, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 43.1 min (major) and 82.5 min (minor)]; $[\alpha]_D^{23}$ = +114.0 (*c* 0.5, $CHCl_3$), ^1H NMR (400 MHz, $CDCl_3$) δ = 7.23 (d, *J* = 8.7 Hz, 2H), 7.18 (d, *J* = 9.1 Hz, 2H), 6.81 (s, 1H), 6.78 (s, 1H), 3.49 (s, 1H), 2.44 (s, 3H), 2.36 (s, 3H), 2.05 (s, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 176.8, 153.9, 142.2, 140.1, 137.2, 134.7, 127.9, 126.5, 126.2, 124.3, 109.5, 77.3, 21.9, 17.3, 15.5; MS (EI) m/z 77.05 (14), 149.07 (20), 252.11 (100), 271.10 (37), 273.11 (32), 300.11 (58); HRMS (EI) m/z calcd for $C_{17}H_{16}O_3S$ (M): 300.08201, found: 300.08175.

(+)-3-Hydroxy-4,6-dimethyl-3-(p-tolyl)benzofuran-2(3H)-one (3ad). Colorless oil: 85% yield (114 mg) and 91% *ee* [HPLC condition: CHIRALPAK AD-H column, hexane/2-propanol = 95/5, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 27.7 min (major) and 44.9 min (minor)]; $[\alpha]_D^{23}$ = +83.3 (*c* 0.54, $CHCl_3$), ^1H NMR (400 MHz, $CDCl_3$) δ = 7.22 (d, *J* = 8.3 Hz, 2H), 7.16 (d, *J* = 8.3 Hz, 2H), 6.84 (s, 1H), 6.79 (s, 1H), 3.12 (s, 1H), 2.37 (s, 3H), 2.33 (s, 3H), 2.08 (s, 3H);

^{13}C NMR (100 MHz, acetone-d_6): δ = 176.9, 154.5, 141.9, 138.8, 137.5, 137.0, 129.9, 128.0, 126.4, 126.3, 109.5, 77.6, 21.7, 21.1, 17.3; MS (ESI) m/z 251.11 (36), 286.14 (39), 291.10 (100); HRMS (ESI) m/z calcd for $C_{17}H_{16}O_3Na$ $(M+Na)^+$: 291.09917, found: 291.09913.

(+)-3-Hydroxy-3-([1,1'-biphenyl]-4-yl)-4,6-dimethylbenzofuran-2(3H)-one (3ae). Colorless solid: 61–63 °C; 81% yield (134 mg) and 95% *ee* [HPLC condition: CHIRALPAK AD-H column, hexane/2-propanol = 95/5, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 65.6 min (major) and 88.0 min (minor)]; $[\alpha]_D^{23}$ = +69.0 (*c* 0.5, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.56–7.53 (m, 4H), 7.44–7.40 (m, 4H), 7.35 (t, *J* = 7.3 Hz, 1H), 6.87 (s, 1H), 6.82 (s, 1H), 3.23 (br s, 1H), 2.39 (s, 3H) , 2.11 (s, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ = 177.0, 154.0, 142.3, 141.9, 140.6, 137.3, 129.2, 128.0, 127.75, 127.44, 126.2, 124.6, 109.6, 77.7, 21.9, 17.4; MS (ESI) m/z: 313.12 (54), 353.11 (100); HRMS (ESI) m/z calcd for $C_{22}H_{18}O_3Na$ $(M+Na)^+$: 353.11482, found: 353.11435.

(+)-3-Hydroxy-3-(4-chlorophenyl)-4,6-dimethylbenzofuran-2(3H)-one (3af). Colorless oil: 83% yield (119 mg) and 95% *ee* [HPLC condition: CHIRALPAK AD-H column, hexane/2-propanol = 95/5, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 24.5 min (major) and 39.0 min (minor)]; $[\alpha]_D^{22}$ = +86.0 (*c* 0.5, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.34 (d, *J* = 8.7 Hz, 2H), 7.29 (d, *J* = 8.7 Hz, 2H), 6.86 (s, 1H), 6.82 (s, 1H), 3.05 (br s, 1H), 2.39 (s, 3H), 2.06 (s, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ = 176.3, 154.4, 142.2, 138.7, 137.4, 134.5, 129.3, 128.11, 128.06, 125.7, 109.6, 77.1, 21.6, 17.1; MS (ESI) m/z 271.05 (36), 311.05 (100); HRMS (ESI) m/z calcd for $C_{16}H_{13}ClO_3Na$ $(M+Na)^+$: 311.04454, found: 311.04458.

(+)-3-Hydroxy-3-(4-fluorophenyl)-4,6-dimethylbenzofuran-2(3H)-one (3ag). Colorless oil: 96% yield (131 mg) and 94% *ee* [HPLC condition: CHIRALPAK AD-H column, hexane/2-propanol = 95/5, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 23.7 min (major) and 35.2 min (minor)]; $[\alpha]_D^{23}$ = +69.0 (*c* 0.5, $CHCl_3$), 1H NMR (400 MHz, $CDCl_3$) δ = 7.34–7.31 (m, 2H), 7.03 (m, 2H), 6.84 (s, 1H), 6.80 (s, 1H), 3.30 (br s, 1H), 2.38 (s, 3H) , 2.06 (s, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ = 176.9, 163.3 (d, *J* = 247.0 Hz), 153.9, 142.4, 137.3, 134.2 (d, *J* = 2.9 Hz), 128.1, 127.9 (d, *J* = 8.6 Hz), 124.4, 116.0 (d, *J* = 21.9 Hz), 109.6, 77.2, 21.9, 17.3; MS (ESI) m/z 255.08 (27), 295.07 (100); HRMS (ESI) m/z calcd for $C_{16}H_{13}FO_3Na$ $(M+Na)^+$: 295.07409, found: 295.07422.

(+)-3-Hydroxy-3-(4-(trifluoromethyl)phenyl)-4,6-dimethyl-benzofuran-2(3H)-one (3ah). Yellow oil: 52% yield (84 mg) and 94% *ee* [HPLC condition: CHIRALPAK AD-H column, hexane/2-propanol = 95/5, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 17.7 min (major) and 29.7 min (minor)]; $[\alpha]_D^{23}$ = +57.0 (*c* 0.5, $CHCl_3$), ^{1}H NMR (400 MHz, CD_2Cl_2) δ = 7.64 (d, *J* = 8.7 Hz, 2H), 7.50 (d, *J* = 8.2 Hz, 2H), 6.89 (s, 1H), 6.84 (s, 1H), 3.65 (s, 1H), 2.39 (s, 3H) , 2.02 (s, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ = 176.3, 154.0, 142.8, 142.4, 137.3, 131.0 (q, *J* = 32.6 Hz), 128.2, 126.4, 126.1 (q, *J* = 2.9 Hz), 124.4 (q, *J* = 272.2 Hz), 124.1, 109.7, 77.4, 21.9, 17.3; MS (EI) m/z: 77.05 (15), 91.07 (14), 145.06 (29), 149.09 (39), 209.14 (26), 225.14 (100), 293.14 (75), 322.15 (14); HRMS (EI) m/z calcd for $C_{17}H_{13}F_3O_3$: 322.08168, found: 322.08254.

(+)-3-Hydroxy-3-(4-vinylphenyl)-4,6-dimethyl-benzofuran-2(3H)-one (3ai). Colorless oil: 86% yield (121 mg) and 94% *ee* [HPLC condition: CHIRALPAK AD-H column, hexane/2-propanol = 95/5, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 36.3 min (major) and 58.4 min (minor)]; $[\alpha]_D^{23}$ = +63.0 (*c* 0.5, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39 (d, *J* = 8.7 Hz, 2H), 7.29 (d, *J* = 8.7 Hz, 2H), 6.85 (s, 1H), 6.79 (s, 1H), 6.69 (dd, *J* = 11.0 Hz 17.4 Hz, 1H), 5.75 (d, *J* = 17.4 Hz, 1H), 5.27 (d, *J* = 11.0 Hz, 1H), 3.21 (br s, 1H), 2.38 (s, 3H) , 2.07 (s, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ = 176.6, 154.4, 141.9, 139.3, 138.4 137.4, 137.1, 127.9, 127.0, 126.5, 126.2, 114.8, 109.5, 77.5, 21.6, 17.2; MS (ESI) m/z 298.14 (28), 303.10 (100); HRMS (ESI) m/z calcd for $C_{18}H_{16}O_3Na$ $(M+Na)^+$: 303.09917, found: 303.09900.

(+)-3-Hydroxy-3-(naphthalen-2-yl)-4,6-dimethyl-benzofuran-2(3H)-one (3aj). Colorless solid: 56–58 ºC; 86% yield (130 mg) and 96% *ee* [HPLC condition: CHIRALPAK AD-H column, hexane/2-propanol = 95/5, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 60.2 min (major) and 68.6 min (minor)]; $[\alpha]_D^{23}$ = +37.0 (*c* 0.5, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.93 (s, 1H), 7.82 (m, 3H), 7.51 (d, *J* = 3.2 Hz, 1H), 7.49 (d, J = 3.2 Hz, 1H), 7.31 (d, *J* = 8.7 Hz, 1H), 6.90 (s, 1H), 6.81 (s, 1H), 3.22 (s, 1H), 2.40 (s, 3H) , 2.07 (s, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ = 176.9, 154.1, 142.3, 137.4, 135.7, 133.6, 133.4, 129.1, 128.7, 128.03, 128.00, 127.08, 126.96, 125.1, 124.7, 123.1, 109.6, 77.9, 22.0, 17.3; MS (ESI) m/z 287.11 (54), 327.10 (100); HRMS (ESI) m/z calcd for $C_{20}H_{16}O_3Na$ $(M+Na)^+$: 327.09917, found: 327.09869.

(+)-3-Hydroxy-3-(benzo[d][1,3]dioxol-5-yl)-4,6-dimethylbenzofuran-2(3H)-one (3ak). Colorless oil: 71% yield (106 mg) and 88% *ee* [HPLC condition: CHIRALPAK AD-H column, hexane/2-propanol = 95/5, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 59.0 min (major) and 78.6 min (minor)]; $[\alpha]_D^{23}$ = +100.0 (*c* 0.5, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.87–6.74 (m, 5H), 5.96 (dd, *J* = 3.6, 1.4 Hz, 2H), 3.07 (s, 1H), 2.38 (s, 3H) , 2.11 (s, 3H); ^{13}C NMR (100 MHz, acetone-d_6): δ = 176.7, 154.5, 149.0, 148.7, 142.0, 137.5, 133.7, 128.0, 126.1, 119.9, 109.6, 108.7, 107.0, 102.4, 77.3, 21.7, 17.3; MS (ESI) m/z: 281.08 (34), 316.12 (18), 321.07 (100); HRMS (ESI) m/z calcd for $C_{17}H_{14}O_5Na$ $(M+Na)^+$: 321.07334, found: 321.07293.

(+)-3-Hydroxy-3-(3,5-dimethylphenyl)-4,6-dimethylbenzofuran-2(3H)-one (3al). White solid: mp 162–164 ºC; 96% yield (135 mg) and 92% *ee* [HPLC condition: CHIRALPAK AD-H column, hexane/2-propanol = 95/5, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 23.8 min (major) and 25.6 min (minor)]; $[\alpha]_D^{23}$ = +63.0 (*c* 0.5, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.94–6.92 (m, 3H), 6.85 (s, 1H), 6.79 (s, 1H), 3.07 (br s, 1H), 2.38 (s, 3H), 2.28 (s, 6H), 2.08 (s, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ = 176.9, 154.5, 141.8, 139.8, 138.8, 137.4, 130.6, 128.0, 126.6, 124.0, 109.5, 77.6, 21.7, 21.4, 17.3; MS (ESI) m/z 265.12 (40), 300.16 (50), 305.11 (100); HRMS (ESI) m/z calcd for $C_{18}H_{18}O_3Na$ $(M+Na)^+$: 305.11482, found: 305.11486.

(+)-3-Hydroxy-3-(3-chlorophenyl)-4,6-dimethylbenzofuran-2(3H)-one (3am). Colorless oil: 65% yield (94 mg) and 94% *ee* [HPLC condition: CHIRALPAK AD-H column, hexane/2-propanol = 95/5, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 23.9 min (major) and

28.0 min (minor)]; $[\alpha]_D^{23}$ = +64.0 (*c* 0.5, $CHCl_3$), ^1H NMR (400 MHz, $CDCl_3$) δ = 7.39–7.18 (m, 4H), 6.87 (s, 1H), 6.82 (s, 1H), 3.11 (br s, 1H), 2.39 (s, 3H), 2.07 (s, 3H); ^{13}C NMR (100 MHz, acetone-d_6): δ = 176.2, 154.5, 142.5, 142.3, 137.4, 135.0, 131.1, 129.2, 128.2, 126.5, 125.7, 124.8, 109.7, 77.2, 21.7, 17.2; MS (ESI) m/z 271.05 (29), 306.09 (25), 311.05 (100); HRMS (ESI) m/z calcd for $C_{16}H_{13}ClO_3Na$ $(M+Na)^+$: 311.04454, found: 311.04471.

(–)-3-Hydroxy-3-(2-fluorophenyl)-4,6-dimethylbenzofuran-2(3H)-one (3an). Colorless oil: 78% yield (106 mg) and 87% *ee* [HPLC condition: CHIRALCEL OD-H column, hexane/2-propanol = 95/5, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 17.9 min (major) and 22.9 min (minor)]; $[\alpha]_D^{24}$ = −135.0 (*c* 0.5, $CHCl_3$), ^1H NMR (400 MHz, $CDCl_3$) δ = 7.83 (dt, *J* = 8.0, 1.7 Hz, 1H), 7.34–7.28 (m, 1H), 7.22–7.19 (m, 1H), 6.97–6.92 (m, 1H), 6.82 (s, 1H), 6.70 (s, 1H), 3.59 (br s, 1H), 2.33 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 176.3, 158.9 (d, *J* = 246 Hz), 153.9, 141.6, 136.3, 130.4 (d, *J* = 8.6 Hz), 127.7 (d, *J* = 2.9 Hz), 127.4, 125.8 (d, *J* = 11.5 Hz), 124.0 (d, *J* = 2.9 Hz), 122.9, 115.7 (d, *J* = 21.1 Hz), 109.1, 74.5, 21.7, 16.8; MS (EI) m/z 77.05 (27), 149.07 (22), 224.10 (36), 243.11 (100), 272.11 (23); HRMS (EI) m/z calcd for $C_{16}H_{13}FO_3$ (M): 272.08487, found: 272.08473.

(+)-3-Hydroxy-3-phenyl-4,7-dimethyl-benzofuran-2(3H)-one (3ba). Colorless oil: >99% yield (129 mg) and 93% *ee* [HPLC condition: CHIRALPAK AD-H column, hexane/2-propanol = 95/5, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 21.2 min (major) and 23.2 min (minor)]; $[\alpha]_D^{23}$ = +57.0 (*c* 0.5, $CHCl_3$), ^1H NMR (400 MHz, $CDCl_3$) δ = 7.35–7.30 (br s, 5H), 7.11 (d, *J* = 7.8 Hz, 1H), 6.86 (d, *J* = 8.2 Hz, 1H), 3.58 (s, 1H), 2.31 (s, 3H), 2.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 176.50, 151.74, 137.57, 134.14, 132.14, 128.65, 128.62, 126.59, 126.53, 125.21, 118.45, 77.77, 16.88, 14.59; MS (EI) m/z 77.05 (20), 149.07 (14), 208.10 (33), 225.11 (100), 254.12 (9); HRMS (EI) m/z calcd for $C_{16}H_{14}O_3$ (M): 254.09429, found: 254.09363.

(+)-3-Hydroxy-3-phenyl-5-bromo-4,6-dimethyl-benzofuran-2(3H)-one (3ca). White solid: mp 146–147 °C; 80% yield (133 mg) and 94% *ee* [HPLC condition: CHIRALPAK AD-H column, hexane/2-propanol = 95/5, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 20.9 min (minor) and 25.8 min (major)]; $[\alpha]_D^{23}$ = +86.0 (*c* 0.5, $CHCl_3$), ^1H NMR (400 MHz, $CDCl_3$) δ = 7.38–7.31 (m, 5H), 7.00 (s, 1H), 3.20 (s, 1H), 2.49 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ = 176.3, 152.5, 142.3, 138.0, 137.8, 129.3, 129.3, 126.5, 125.6, 124.1, 111.4, 78.0, 25.0, 19.1; MS (ESI) m/z 315.00 (5), 354.99 (28), 356.99 (28); HRMS (ESI) m/z calcd for $C_{16}H_{13}BrO_3Na$ $(M+Na)^+$: 354.99403, found: 354.99384.

(+)-3-Hydroxy-4-methyl-3-phenylbenzofuran-2(3H)-one (3da). Colorless oil: 68% yield (84 mg) and 92% *ee* [HPLC condition: CHIRALPAK AD-H column, hexane/2-propanol = 95/5, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 27.2 min (minor) and 30.0 min (major)]; $[\alpha]_D^{23}$ = +29.0 (*c* 0.5, $CHCl_3$), ^1H NMR (400 MHz, CD_2Cl_2): δ = 7.30–7.23 (m, 6H), 6.96 (d, *J* = 8.2 Hz, 1H), 6.92 (d, *J* = 7.8 Hz, 1H), 3.21 (br s, 1H), 2.00 (s, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 176.5, 153.9, 138.1, 137.8, 131.3, 129.2, 127.5, 127.3, 125.6, 109.0, 77.7, 17.4; MS (EI) m/z

77.05 (22), 105.04 (13), 135.05 (16), 194.09 (24), 211.10 (100), 240.10 (10); HRMS (EI) m/z calcd for $C_{15}H_{12}O_3$ (M): 240.07864, found: 240.07830.

3-Hydroxy-7-(tert-butyl)-5-methyl-3-phenylbenzofuran-2(3H)-one (3ea). White solid: 46% yield (68 mg) and 2% *ee* [HPLC condition: CHIRALPAK AD-H column, hexane/2-propanol = 95/5, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 19.5 min (minor) and 25.0 min (major)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.41–7.33 (m, 5H), 7.13 (s, 1H), 6.95 (s, 1H), 3.37 (br s, 1H), 2.31 (s, 3H), 1.42 (s. 9H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 176.8, 149.5, 139.7, 135.1, 134.8, 130.1, 129.2, 129.1, 125.7, 123.2, 77.0, 34.5, 29.7, 21.4.

Hydroxy-1-phenylnaphtho[2,1-b]furan-2(1H)-one (3fa). Yellow oil: 64% yield (89 mg) and 5% *ee* [HPLC condition: CHIRALPAK AD-H column, hexane/2-propanol = 95/5, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 50.6 min (major) and 63.7 min (minor)]; ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 8.02 (d, J = 8.7 Hz, 1H), 7.95–7.92 (m, 1H), 7.68–7.65 (m, 1H), 7.46–7.32 (m, 9H), 3.74 (br s, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ = 177.0, 151.9, 138.4, 133.0, 131.8, 129.6, 129.3, 129.2, 128.4, 125.7, 123.3, 121.5, 112.0, 78.3.

4.4.4 X-ray crystal structure of compound 3ca

Data collection

A colorless block crystal of $C_{16}H_{13}BrO_3$ having approximate dimensions of 0.254 x 0.250 x 0.176 mm was mounted on a glass fiber. All measurements were made on a Rigaku R-AXIS RAPID diffractometer using graphite monochromated Mo-Kα radiation.

The crystal-to-detector distance was 127.40 mm.

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

a = 10.997(2) Å
b = 10.587(2) Å ß = 101.316(4)°
c = 11.994(2) Å
V = 1369.3(3) Å^3

For Z = 4 and F.W. = 333.18, the calculated density is 1.616 g/cm^3. Based on the reflection conditions of:

0k0: k = 2n

packing considerations, a statistical analysis of intensity distribution, and the successful solution and refinement of the structure, the space group was determined to be:

$P2_1$ (#4)

The data were collected at a temperature of -150 + 1° C to a maximum 2θ value of 55.0°. A total of 44 oscillation images were collected. A sweep of data was done using w scans from 130.0 to 190.0° in 5.0° step, at χ = 45.0° and ϕ = 0.0°. The exposure rate was 60.0 [sec./°]. A second sweep was performed using w scans from 0.0 to 160.0° in 5.0° step, at χ = 45.0° and ϕ = 180.0°. 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 12860 reflections that were collected, 6146 were unique (R_{int} = 0.0633); equivalent reflections were merged.

The linear absorption coefficient, μ, for Mo-Kα radiation is 30.145 cm^{-1}. An empirical absorption correction was applied which resulted in transmission factors ranging from 0.291 to 0.588. The data were corrected for Lorentz and polarization effects. A correction for secondary extinction was applied (coefficient = 0.029070).

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 6146 observed reflections and 367 variable parameters and converged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors of:

$$R1 = \Sigma \; | \; |Fo| - |Fc| \; | \; / \Sigma \; |Fo| = 0.0722$$

$$wR2 = [\Sigma (w (Fo^2 - Fc^2)^2) / \Sigma \, w(Fo^2)^2]^{1/2} = 0.2226$$

The standard deviation of an observation of unit weight was 1.11. Unit weights were used. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.94 and -1.90 e/$Å^3$, respectively. The absolute structure was deduced based on Flack parameter, 0.01(2), refined using 2836 Friedel pairs.

Neutral atom scattering factors were taken from Cromer and Wabe[6] Anomalous dispersion effects were included in Fcalc; 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 Crystal Structure crystallographic software package except for refinement, which was performed using SHELXL-97.

Experimental details

A. Crystal data

Empirical formula	$C_{16}H_{13}BrO_3$
Formula weight	333.18
Crystal color, Habit	colorless, block
Crystal dimensions	0.254 X 0.250 X 0.176 mm
Crystal system	monoclinic
Lattice type	Primitive
Lattice parameters	a = 10.997(2) Å
	b = 10.587(2) Å
	c = 11.994(2) Å
	ß = 101.316(4) °
	V = 1369.3(3) $Å^3$
Space group	$P2_1$ (#4)
Z value	4
D_{calc}	1.616 g/cm^3
F_{000}	672.00
μ (MoKα)	30.145 cm^{-1}

B. Intensity measurements

Diffractometer	R-AXIS RAPID
Radiation	MoKα (λ = 0.71075 Å) graphite monochromated
Voltage, Current	50kV, 40mA
Temperature	-150.0°C
Detector aperture	280 x 256 mm
Data images	44 exposures
ω oscillation range (χ=45.0, ϕ=0.0)	130.0 – 190.0°
Exposure rate	60.0 sec./°
ω oscillation range (χ=45.0, ϕ=180.0)	0.0 – 160.0°
Exposure rate	60.0 sec./°
Detector position	127.40 mm
Pixel size	0.100 mm
$2q_{max}$	55.0°
No. of reflections measured	Total: 12860 Unique: 6146 (R_{int} = 0.0633) Friedel pairs: 2836
Corrections	Lorentz-polarization Absorption (trans. Factors: 0.291 – 0.588) Secondary Extinction (coefficient: 2.90700e-002)

C. Structure solution and refinement

Structure solution	Direct Methods
Refinement	Full-matrix least-squares on F^2
Function minimized	$\Sigma w (Fo^2 - Fc^2)^2$
Least Squares Weights	$w = 1/ [\sigma^2(Fo^2) + (0.1070 . P)^2 + 1.6775 . P]$ where $P = (Max(Fo^2,0) + 2Fc^2)/3$
2θmax cut-off	55.0^o
Anomalous dispersion	All non-hydrogen atoms
No. Observations (All reflections)	6146
No. Variables	367
Reflection/parameter ratio	16.75
Residuals: R1 (I>2.00σ(I))	0.0722
Residuals: R (All reflections)	0.1035
Residuals: wR2 (All reflections)	0.2226
Goodness of fit indicator	1.106
Flack parameter (Friedel pairs = 2836)	0.01(2)
Max shift/error in final cycle	0.000
Maximum peak in final diff. map	0.94 $e^-/Å^3$
Minimum peak in final diff. map	-1.90 $e^-/Å^3$

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Chapter 5 Me-BIPAM for the Synthesis of Optically Active 3-Aryl-3-hydroxy-2-oxindoles by Ruthenium-catalyzed Addition of Arylboronic Acids to Isatins

Abstract: A chiral bidentate phosphoramidite (Me-BIPAM) was found to be efficient for the ruthenium-catalyzed addition of arylboronic acids to isatins. Asymmetric synthesis of 3-aryl-3-hydroxy-2-oxindoles by 1,2-addition of arylboronic acids to isatins was carried out in the presence of $[RuCl_2(PPh_3)_3]$/(*R,R*)-Me-BIPAM and KF, resulting in an enantioselectivity as high as 90 % *ee*. It was found that the reaction with *N*-protected isatins proceeds with high yields and good enantioselectivities. The best protective groups on the nitrogen atom were different depending on the substituents on the aromatic ring. The use of a *N*-benzyl group resulted in excellent enantioselectivities in many substrates compared with other groups.

5.1 Introduction

Optically active 3-substituted 3-hydroxy-2-oxindoles are not only important structures in biologically active compounds but also serve as fundamental building blocks in organic synthesis.[1,2] For example, SM-130686 (**a**) is a potent growth hormone secretagogue,[3] and compounds **b** shows a high affinity for the arginine-vasopressin (AVP) V1b receptors and/or the ocytocin (OT) receptors (Fig. 5.1).[4]

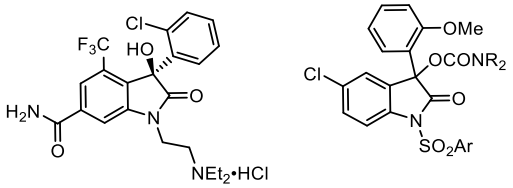
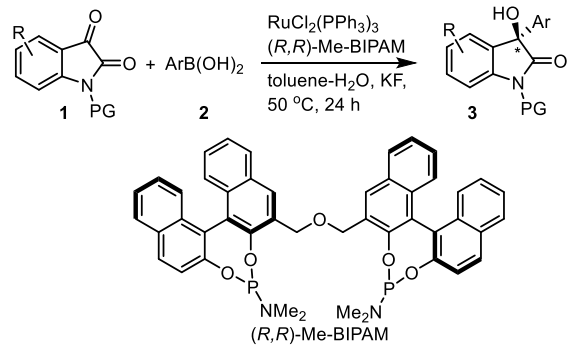


Figure 5.1 Pharmaceutical isatin derivatives.

In recent years, the use of stable, commercially available arylboronic acids in transition metal-catalyzed carbon–carbon bond-forming reactions has attracted considerable attention. Transition metal-catalyzed asymmetric nucleophilic addition of organoboronic compounds to isatins is a particularly powerful and straightforward approach. In 2006, the groups of Hayashi and Minnaard independently reported the addition of arylboronic acids to isatins by a rhodium-catalyzed reaction.[5,6] Since then, palladium-catalyzed addition reactions have

been developed.[7] In 2009, Shibasaki and co-workers reported the arylation of isatins in the presence of a chiral copper catalyst.[8] In 2010, Hayashi and co-workers reported a copper-catalyzed asymmetric addition reaction.[9] In 2015, Qiu and co-workers reported a iridium/monophosphoramidite catalyzed asymmetric addition reaction.[10] In this section, it is described that the asymmetric addition reactions of arylboronic acids to isatins catalyzed by a ruthenium/Me-BIPAM complex (Scheme 5.1).[11]



Scheme 5.1 Enantioselective addition of arylboronic acids to isatins.

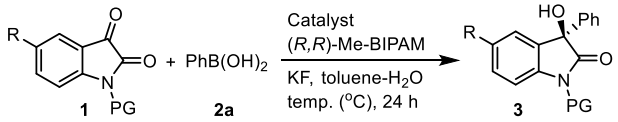
5.2 Results and discussion

Initially, the reaction of 5-chloroisatin with phenylboronic acid in the presence of KF (2 equiv) and ruthenium/(*R,R*)-Me-BIPAM complex was investigated (Table 5.1). Since the rhodium complex was inefficient (entry 1), the use of ruthenium as the central metal was critical for achieving high enantioselectivities. $[RuCl_2(p\text{-cymene})]_2$ and $[RuCl_2(benzene)]_2$ led to adducts in 72 % yield with 17 % *ee* (*N*-Bn isatin), 94 % yield with 49 % *ee* (*N*-Me isatin), and 94 % yield with 1 % *ee* (*N*-Bn isatin) (entries 2, 3, and 4). We already reported $RuCl_2(PPh_3)_3$/(*R,R*)-Me-BIPAM complex-catalyzed highly enantioselective arylation of glyoxylate.[11c] When $RuCl_2(PPh_3)_3$ was used as the precursor, the product was obtained in 99 % yield and 85 % *ee* (entry 6). The use of benzyl, *p*-fluorobenzyl (*p*-F-Bn), *p*-methoxybenzyl (PMB), and trityl (Tr) groups as protective groups on the nitrogen atom also resulted in similar yield and enantioselectivity under these conditions (entries 6–13). The best result was achieved when the reaction of *N*-*p*-methoxybenzyl isatin was carried out at 50 °C in toluene in the presence of KF and $RuCl_2(PPh_3)_3$/(*R,R*)-Me-BIPAM (entry 11 (97 % yield, 88 % *ee*)). Encouraged by these results, the reactions of 5-phenylisatin bearing methyl, benzyl, and PMB groups on the nitrogen atom with phenylboronic acid then were studied (entries 14–19). *N*-Methyl- and *N*-PMB-5-phenylisatin can be reacted effectively at 50 °C in 96 % yield with 90 % *ee* and 87 % yield with 90 % *ee*, respectively (entries 16 and 19).

Next, the substrate scope was investigated focusing on isatins bearing substituents on the aromatic ring. The arylation of isatins proceeded efficiently to give the corresponding products in yields of 92–99 % with 86–90 % *ee*. As shown in Table 5.2, the best protective groups on the nitrogen atom were different depending on the substituents on the aromatic ring. In addition to 5-bromo-, 5-methyl-, and non-substituted isatin, the *p*-methoxybenzyl group was the most effective (entries 3, 5, and 9). The *N*-benzyl group resulted in the best enantioselectivities for 5-fluoro- and 6-chloro isatins (entries 2 and 8).

Then the scope and limitations for various arylboronic acids were studied. Again, a difference in enantioselectivity was observed depending on the protecting group on the nitrogen atom (Table 5.3). The addition of 4-methoxyphenylboronic acid to *N*-Bn-5-chloroisatin resulted in better enantioselectivity than the use of other protective groups. When *p*-tolyl- and *p*-fluorophenylboronic acid were used, *N*-Me isatin yielded better selectivities as compared to *N*-Bn isatin. On the other hand, the addition of *p*-trifluoromethyl phenylboronic acid to *N*-*p*-fluorobenzyl isatin resulted in enantioselectivities higher than *N*-Bn- and *N*-*p*-CF_3-Bn isatins. The results of the arylation of 5-chloroisatin with other arylboronic acids are summarized in Table 5.4. *Para*- and *meta*- substituted arylboronic acids bearing electron-donating or electron-withdrawing substituents afforded 3-aryl-3-hydroxy-2-oxindole derivatives in good yields with good enantioselectivities in the range of 68–88 % *ee* (entries 1–5). However, since the steric hindrance was increased, (*R,R*)-Me-BIPAM was less effective for *ortho*-substituted arylboronic acids. The addition of *o*-methoxyphenyl-, *o*-fluorophenyl- and *o*-chlorophenylboronic acids resulted in 90% yield with 0% *ee*, >99 % yield with 51% *ee* and 57% yield with 20% *ee*, respectively (entries 6, 8 and 9). *Ortho*-substituted-3-aryl-3-hydroxy-2-oxindoles are containing pharmaceutical isatin derivatives. We hypothesized that the substituent on the phosphoramidite (Me-BIPAM) is effect on the enantioselectivity. When newly synthesized (*R,R*)-(Ph,H)-BIPAM was used instead of (*R,R*)-Me-BIPAM in the reaction of *ortho*-methoxyphenyl- and *ortho*-chlorophenylboronic acids, the absolute configuration reversed products were obtained with 56% *ee* and 58% *ee* (entries 7 and 10).

Table 5.1 Reaction conditions.[a]

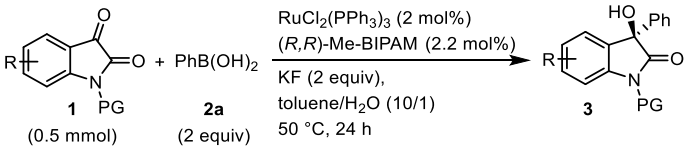


1a: R = Cl, PG = Me
1b: R = Cl, PG = Bn
1c: R = Cl, PG = PMB
1d: R = Cl, PG = *p*-F-Bn
1e: R = Cl, PG = Tr
1f: R = Ph, PG = Me
1g: R = Ph, PG = Bn
1h: R = Ph, PG = PMB

entry	catalyst	R	PG	product	temp. (°C)	yield (%)[b]	*ee* (%)[c]
1	$[Rh(acac)(CH_2CH_2)_2]$	Cl	Bn	**3ba**	50	>99	58 (*R*)[d]
2	$[RuCl_2(p\text{-cymene})]_2$	Cl	Bn	**3ba**	80	72	17 (*R*)
3	$[RuCl_2(p\text{-cymene})]_2$	Cl	Me	**3aa**	80	94	49 (*R*)
4	$[RuCl_2(benzene)]_2$	Cl	Bn	**3ba**	50	94	1
5	$[RuCl_2(PPh_3)_3]$	Cl	Me	**3aa**	80	>99	85 (*R*)
6	$[RuCl_2(PPh_3)_3]$	Cl	Bn	**3ba**	80	99	85 (*R*)
7	$[RuCl_2(PPh_3)_3]$	Cl	PMB	**3ca**	80	95	84 (*R*)
8	$[RuCl_2(PPh_3)_3]$	Cl	Me	**3aa**	50	>99	81 (*R*)
9	$[RuCl_2(PPh_3)_3]$	Cl	Bn	**3ba**	50	99	87 (*R*)
10	$[RuCl_2(PPh_3)_3]$	Cl	PMB	**3ca**	50	97	88 (*R*)
11	$[RuCl_2(PPh_3)_3]$	Cl	*p*-F-Bn	**3da**	50	>99	83 (+)
12	$[RuCl_2(PPh_3)_3]$	Cl	Tr	**3ea**	50	71	77 (–)
13	$[RuCl_2(p\text{-cymene})]_2$	Ph	Me	**3fa**	80	71	58 (–)
14	$[RuCl_2(PPh_3)_3]$	Ph	Me	**3fa**	80	94	88 (–)
15	$[RuCl_2(PPh_3)_3]$	Ph	Me	**3fa**	50	96	90 (–)
16	$[RuCl_2(PPh_3)_3]$	Ph	Me	**3fa**	30	88	90 (–)
17	$[RuCl_2(PPh_3)_3]$	Ph	Bn	**3ga**	50	90	86 (–)
18	$[RuCl_2(PPh_3)_3]$	Ph	PMB	**3ha**	50	87	90 (–)

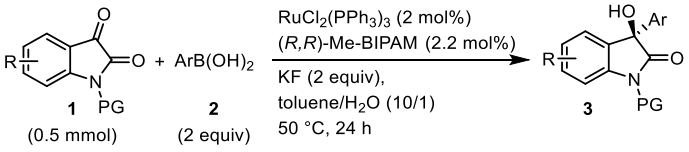
[a] Reaction conditions: A mixture of isatin (0.5 mmol), phenylboronic acid (1.0 mmol), KF (1.0 mmol), catalyst (2 mol %), and (*R*,*R*)-Me-BIPAM (2.2 mol %) in toluene (3 mL) and H_2O (0.3 mL) was stirred for 24 h. [b] Isolated yields. [c] Determined by HPLC analysis. [d] A mixture of isatin (0.5 mmol), phenylboronic acid (0.75 mmol), $Rh(acac)(CH_2CH_2)_2$ (3 mol %), and (*R*,*R*)-*N*-Me-BIPAM (3.3 mol %) in toluene/H_2O (20:1) was stirred at 50 °C for 16 h.

Table 5.2 Ruthenium-catalyzed asymmetric addition of phenylboronic acids to isatins.



entry	R	PG		product	yield (%)	*ee* (%)
1	5-F	PMB	**1i**	**3ia**	>99	87 (+)
2	5-F	Bn	**1j**	**3ja**	95	90 (*R*)
3	5-Br	PMB	**1k**	**3ka**	97	90 (–)
4	5-Br	Bn	**1l**	**3la**	96	86 (–)
5	5-Me	PMB	**1m**	**3ma**	97	90 (*R*)
6	5-Me	Bn	**1n**	**3na**	92	87 (*R*)
7	6-Cl	PMB	**1o**	**3oa**	97	88 (+)
8	6-Cl	Bn	**1p**	**3pa**	>99	89 (+)
9	H	PMB	**1q**	**3qa**	>99	89 (*R*)
10	4-Me	Bn	**1r**	**3ra**	75	87 (–)

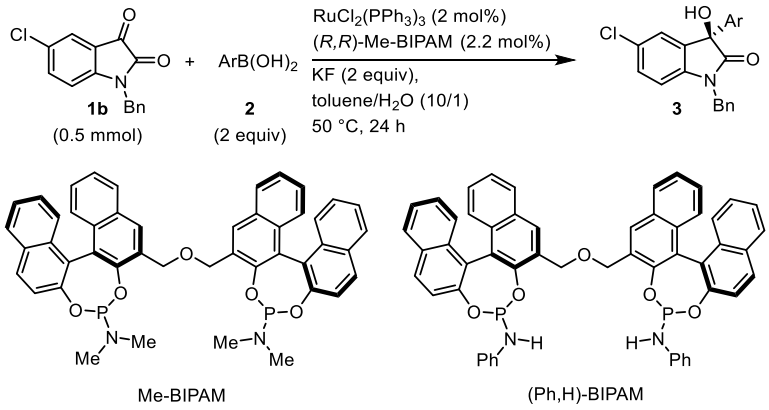
Table 5.3 Arylation of 5-chloroisatins.[a]



Ar	PG = Me (**1a**)	PG = Bn (**1b**)	PG = PMB (**1c**)	PG = *p*-F-Bn (**1d**)	PG = *p*-CF_3-Bn (**1s**)
4-$MeOC_6H_4$ (**2b**)	>99 %, 61 % *ee* (–) (**3ab**)	87 %, 78 % *ee* (*R*) (**3bb**)	78 %, 52 % *ee* (*R*) (**3cb**)	75 %, 64 % *ee* (–) (**3db**)	90 %, 60 % *ee* (–) (**3sb**)
4-MeC_6H_4 (**2c**)	>99 %, 83 % *ee* (–) (**3ac**)	>99 %, 81 % *ee* (*R*) (**3bc**)	93 %, 79 % *ee* (*R*) (**3cc**)	>99 %, 52 % *ee* (–) (**3dc**)	>99 %, 76 % *ee* (–) (**3sc**)
4-FC_6H_4 (**2d**)	>99 %, 83 % *ee* (–) (**3ad**)	97 %, 74 % *ee* (*R*) (**3bd**)	91 %, 77 % *ee* (*R*) (**3cd**)	99 %, 77 % *ee* (–) (**3dd**)	>99 %, 75 % *ee* (–) (**3sd**)
4-$CF_3C_6H_4$ (**2e**)	–	57 %, 74 % *ee* (+)[b] (**3be**)	–	74 %, 82 % *ee* (+)[b] (**3de**)	51 %, 69 % *ee* (+)[b] (**3se**)

[a] Reaction conditions: A mixture of isatin (0.5 mmol), phenylboronic acid (1.0 mmol), KF (1.0 mmol), ruthenium catalyst (2 mol %), and (*R*,*R*)-Me-BIPAM (2.2 mol %) in toluene (3 mL) and H_2O (0.3 mL) was stirred for 24 h. [b] The reaction was carried out at 80 °C.

Table 5.4 Arylation of *N*-benzyl 5-chloroisatin.



entry	Ar = (Ar–B(OH)$_2$)	product	yield (%)[a]	*ee* (%)[b]
1	4-PhC$_6$H$_4$ (**2f**)	**3bf**	>99	88 (–)
2	3-MeC$_6$H$_4$ (**2g**)	**3bg**	>99	87 (*R*)
3[c]	3-ClC$_6$H$_4$ (**2h**)	**3bh**	>99	72 (+)
4[c]	3-CF$_3$C$_6$H$_4$ (**2i**)	**3bi**	99	68 (+)
5	2-naphthyl (**2j**)	**3bj**	99	82 (–)
6[c]	2-MeOC$_6$H$_4$ (**2k**)	**3bk**	90	0
7[c,d]	2-MeOC$_6$H$_4$ (**2k**)	**3bk**	65	56 (+)
8[c]	2-FC$_6$H$_4$ (**2l**)	**3bl**	>99	51 (+)
9[c]	2-ClC$_6$H$_4$ (**2m**)	**3bm**	57	20 (–)
10[c,d]	2-ClC$_6$H$_4$ (**2m**)	**3bm**	59	58 (+)

[a] Isolated yield. [b] Determined by HPLC analysis. [c] The reaction was carried out at 80 °C. [d] Instead of (*R,R*)-Me-BIPAM, (*R,R*)-(Ph,H)-BIPAM was used.

The absolute configuration and enantioselectivity are determined at the insertion step of the C=O bond into the Ar–Ru bond of RuCl(Ar)(PPh$_3$)((*R,R*)-Me-BIPAM) complex (Figure 5.2).[11c] Thus, the *R* configuration in Tables 5.1, 5.2, and 5.3 caused by (*R,R*)-Me-BIPAM is rationalized by the coordination of an isatin with its *si*-face. Triphenylphosphine ligand blocked one side of the complex. The *si*-coordination of the substrate is preferred without significant steric interaction with two dimethylamino groups of the bis-phosphoramidite ligands to give the experimentally observed *R* enantiomer by parallel coordination of the C=O bond to the Ar–Ru bond for the subsequent insertion step. However, when newly synthesized (*R,R*)-(Ph,H)-BIPAM was used instead of (*R,R*)-Me-BIPAM in the reaction of *ortho*-substituted-phenylboronic acids, the coordination of an isatin with its *re*-face. In order to obtain the experimentally observed *S* enantiomer, it was thought that *re*-face orientation

where the N–H group of the BIPAM ligand had significant interaction with the amido carbonyl group of isatin occurred.

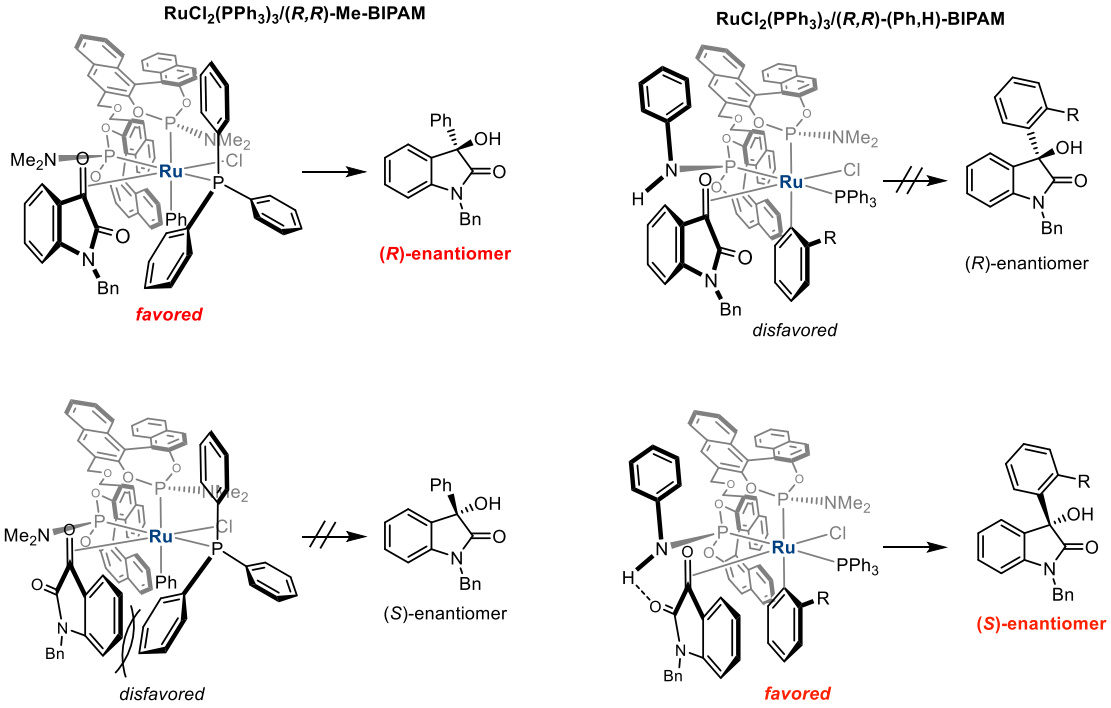


Figure 5. 2 Proposed enantioselection model for RuCl(Ar)(PPh_3)((*R,R*)-Me-BIPAM) complex and RuCl(Ar)(PPh_3)((*R,R*)-(Ph,H)-BIPAM) complex.

5.3 Conclusions

In conclusion, an asymmetric arylation of *N*-protected isatins with arylboronic acids using an $RuCl_2(PPh_3)_3$/(*R,R*)-Me-BIPAM catalyst system has been developed. High performance of Me-BIPAM for enantioselective 1,2-addition to *N*-protected isatins was demonstrated. A variety of chiral 3-aryl-3-hydroxy-2-oxindoles were obtained with good enantioselectivities for *para*- and *meta*-substituted arylboronic acids (68–90 % *ee*). When newly synthesized (*R,R*)-(Ph,H)-BIPAM was used instead of (*R,R*)-Me-BIPAM in the reaction of *ortho*-methoxyphenyl- and *ortho*-chlorophenylboronic acids, the absolute configuration reversed products were obtained with 56% *ee* and 58% *ee*, respectively

5.4 Experimental section

5.4.1 General information.

^{1}H NMR spectra were recorded on a JEOL ECX-400 (400 MHz) in $CDCl_3$ with tetramethylsilane as an internal standard. Chemical shifts are reported in part per million (ppm), and signal are expressed as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (br). ^{13}C NMR spectra were recorded on a JEOL ECX-400 (100 MHz) in $CDCl_3$ (δ = 77.0) with tetramethylsilane as an internal standard. Chemical shifts are reported in part per million (ppm). HPLC analysis was directly performed with chiral stationary phase column, CHIRALPAK AD-H, AS-H, and CHIRALCEL OD-H, purchased from DAICEL Co., Ltd. High resolution mass spectra (HRMS) were recorded on a JEOL JMS 700TZ mass spectrometer at the Center for Instrumental Analysis, Hokkaido University. Optical rotations were measured on a HORIBA SEPA-300 digital polarimeter. Kanto Chemical silica gel 60N (particle size 0.063–0.210 mm) was used for flash column chromatography. Glassware was oven dried at 130 °C and allowed to cool under a stream of dry nitrogen. $RuCl_3 \cdot xH_2O$ were purchased from Strem Chemical, Inc. $[RuCl_2(p\text{-cymene})]_2$,[12] $RuCl_2(PPh_3)_3$,[13] Me-BIPAM[14a] and N-Me-BIPAM[14b] were prepared according to our previous procedure. Me-BIPAM was commercially available from Wako Pure Chemical Industries, Ltd. All chemicals were purchased from Aldrich, Wako, TCI, or Kanto chemicals and used as received.

The spectra of compounds **1a**,[5a,15] **1b**,[5a] **1c**,[5a] **1j**,[16] **1l**,[16] **1m**,[5a] **1n**,[16] **1p**,[17] **1q**,[18] and **1r**[19] were identical to those reported in the literature.

5.4.2 Preparation of 5-Chloro-1-methylindoline-2,3-dione (1a):[5a,15] NaH (60 wt% in mineral oil, 16.5 mmol) was added portionwise to a solution of 5-chloroisatin (15 mmol) in DMF (40 ml) at 0 °C and the mixture was stirred for 20 min at room temperature. Then, MeI (16.5 mmol) was added and the mixture was stirred for 20 min at 50 °C After cooling to room temperature, the reaction mixture was extracted with chloroform, washed with water. The organic layer was dried over $MgSO_4$, filtered and concentrated to afford oil. Added Et_2O and hexane formed a desired product, and the solid was collected by filtration. 1a was dried under reduce pressure.

1-Benzyl-5-chloroindoline-2,3-dione (1b):[5a] **1b** was synthesized from 5-chloroisatin and benzyl bromide (room temperature, 20 min), following the procedure for **1a**. HRMS m/z calcd for $C_{15}H_{10}ClNO_2$ 271.04001, found 271.03961.

5-Chloro-1-(*p*-methoxybenzyl)indoline-2,3-dione (1c):[5a] **1c** was synthesized from 5-chloroisatin and *p*-methoxybenzyl chloride (50 °C, 20 min), following the procedure for **1a**. HRMS m/z calcd for $C_{16}H_{12}ClNO_3$ 301.05057, found 301.05031.

5-Chloro-1-(*p*-fluorobenzyl)indoline-2,3-dione (1d): **1d** was synthesized from 5-chloroisatin and *p*-fluorobenzyl bromide (30 °C, 2 h), following the procedure for **1a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.58 (d, 1H, J = 2.15 Hz), 7.46 (dd, 1H, J = 8.43, 2.15 Hz), 7.33–7.28 (m, 2H), 7.08–7.02 (m, 2H), 6.74 (d, 1H, J = 8.61 Hz), 4.90 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 182.06, 162.50 (d, J = 247 Hz), 157.62, 148.63, 137.67, 129.84, 129.20 (d, J = 8.46 Hz), 125.39, 118.43, 116.12 (d, J = 21.61 Hz), 112.08, 43.45; HRMS m/z calcd for $C_{15}H_9ClFNO_2$ 289.03058, found 289.03003.

5-Chloro-1-tritylindoline-2,3-dione (1e): **1e** was synthesized from 5-chloroisatin and trityl bromide (room temperature, 2.5 h), following the procedure for **1a**, and purified by silica gel chromatography (hexane/AcOEt = 7/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.54(d, 1H, J = 2.28 Hz), 7.40–7.43 (m, 6H), 7.22–7.31 (m, 9H), 7.14 (dd, 1H, J = 8.7, 2.28 Hz), 6.34(d, 1H, J = 9.12 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 182.07, 158.80, 150.59, 140.84, 136.22, 129.45, 129.26, 128.17, 127.63, 124.50, 119.98, 118.93, 76.82; HRMS m/z calcd for $C_{27}H_{18}O_2NClNa$ 446.09183, found 446.09137.

1-Methyl-5-phenylindoline-2,3-dione (1f): A 3L three-necked flask charged with $Pd(PPh_3)_4$ (0.367 mmol, 3 mol%), 5-iodoisatin (7.33 mmol), phenylboronic acid (14.7 mmol) was flush with nitrogen. DME (225 ml) and $NaHCO_3/H_2O$ (14.7 mmol/225 ml) were added successively and the mixture was heated at reflux for 2 h. After cooling to room temperature, the reaction mixture was treated with 1N HCl. The reaction mixture was extracted with AcOEt, washed with brine. The organic layer was dried over $MgSO_4$, filtered and concentrated to afford solid. Flash chromatography on silica gel (hexane/acetone = 2/1) gave the 5-phenylisatin (58%). Then, N-methyl-5-phenylisatin was synthesized from 5-phenylisatin and MeI (room temperature, 1.5 h), following the procedure for **1a**. ^{1}H NMR (400 MHz, DMSO) δ = 8.24 (d, 1H, J = 8.24 Hz), 7.81 (s, 1H), 7.69 (d, 2H, J = 7.36 Hz), 7.46 (t, 2H, J = 7.36 Hz), 7.37 (t, 1H, J = 7.32 Hz), 7.25 (d, 1H, J = 8.24 Hz), 3.18 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ = 183.94, 158.92, 151.15, 139.12, 136.66, 135.82, 129.57, 128.12, 126.84, 122.60, 118.58, 111.64, 26.71; HRMS m/z calcd. for $C_{15}H_{11}NO_2$ 237.07898, found 237.07878.

1-Benzyl-5-phenylindoline-2,3-dione (1g): *N*-benzyl-5-phenylisatin was synthesized from 5-phenylisatin and benzyl bromide (room temperature, 1 h), following the procedure for **1a.** ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.83 (d, 1H, J = 1.79 Hz), 7.70 (dd, 1H, J = 8.25, 1.79 Hz), 7.49–7.29 (m, 10H), 6.85 (d, 1H, J = 8.25 Hz), 4.97 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 183.33, 158.34, 149.66, 138.84, 137.37, 136.76, 134.41, 129.05, 129.02, 128.18, 127.86, 127.42, 126.49, 123.83, 118.03, 111.33, 44.11; HRMS m/z calcd for $C_{21}H_{15}NO_2$ 313.11028, found 313.11017.

1-(*p*-Methoxybenzyl)-5-phenylindoline-2,3-dione (1h): *N*-*p*-methoxybenzyl-5-phenylisatin was synthesized from 5-phenylisatin and p-methoxybenzyl chloride (50 °C, 2.5 h), following the procedure for **1a.** The crude product is dissolved in CH_2Cl_2/hexane and is allowed to cool

to -30 °C for 2 h. The resulting crystals are collected by filtration. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.83 (d, 1H, J = 1.84 Hz), 7.70 (dd, 1H, J = 8.46, 1.84 Hz), 7.49–7.28 (m, 7H), 6.87 (dd, 3H, J = 8.72, 4.36 Hz), 4.90 (s, 2H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ = 183.61, 159.57, 158.44, 149.87, 139.03, 137.46, 136.83, 129.16, 129.07, 127.98, 126.63, 126.53, 123.95, 118.20, 114.53, 111.46, 55.40, 43.76; HRMS m/z calcd for $C_{22}H_{17}NO_3$ 343.12084, found 343.11982.

5-Fluoro-1-(*p*-methoxybenzyl)-indoline-2,3-dione (1i): **1i** was synthesized from 5-fluoroisatin and *p*-methoxybenzyl chloride (50 °C, 4 h), following the procedure for **1a.** ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.32–7.17 (m, 4H), 6.88 (d, 2H, J = 8.61 Hz), 6.76 (dd, 1H, J = 8.61, 3.62 Hz), 4.87 (s, 2H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 182.79, 159.50, 159.23 (d, J = 254 Hz), 146.74, 128.86, 126.02, 124.54 (d, J = 23.84 Hz), 118.25 (d, J = 6.68 Hz), 114.44, 112.51, 112.24 (d, J = 4.77 Hz), 112.15, 55.27, 43.64; HRMS m/z calcd for $C_{16}H_{12}FNO_3$ 285.08012, found 285.07958.

1-Benzyl-5-fluoroindoline-2,3-dione (1j):[16] **1j** was synthesized from 5-fluoroisatin and benzyl bromide (room temperature, 1 h), following the procedure for **1a**.

5-Bromo-1-(*p*-methoxybenzyl)indoline-2,3-dione (1k): **1k** was synthesized from 5-bromoisatin and *p*-methoxybenzyl chloride (50 °C, 4 h), following the procedure for **1a.** The crude product is dissolved in CH_2Cl_2/hexane and is allowed to cool to -30 °C. The resulting crystals are collected by filtration.^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.68 (d, 1H, J = 2.28 Hz), 7.57 (dd, 1H, J = 8.48, 2.32 Hz), 7.23 (d, 2H, J = 8.68 Hz), 6.85 (d, 2H, J = 8.72 Hz), 6.69 (d, 1H, J = 8.72 Hz), 4.48 (s, 2H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 182.33, 154.64, 157.58, 149.50, 140.56, 128.56, 128.20, 126.02, 118.92, 116.77, 114.57, 112.86, 55.40, 43.74; HRMS m/z calcd for $C_{16}H_{12}BrNO_3$ 345.00006, found 345.99913.

1-Benzyl-5-bromoindoline-2,3-dione (1l):[16] **1l** was synthesized from 5-bromolisatin and benzyl bromide (room temperature, 1 h), following the procedure for **1a.**

1-(*p*-Methoxybenzyl)-5-methylindoline-2,3-dione (1m)[12a]: **1m** was synthesized from 5-methylisatin and *p*-methoxybenzyl chloride (50 °C, 1.5 h), following the procedure for **1a.** HRMS m/z calcd. for $C_{17}H_{15}NO_3$ 281.10519, found 281.10414.

1-Benzyl-5-methylindoline-2,3-dione (1n):[16] **1n** was synthesized from 5-methylisatin and benzyl bromide (room temperature, 20 min), following the procedure for **1a**.

6-Chloro-1-(*p*-methoxybenzyl)indoline-2,3-dione (1o): **1o** was synthesized from 6-chlorolisatin and *p*-methoxybenzyl chloride (50 °C, 4 h), following the procedure for **1a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.53 (d, 1H, J = 8.24 Hz), 7.25 (d, 2H, J = 8.68 Hz), 7.05 (dd, 1H, J = 8.24, 1.36 Hz), 6.88 (d, 2H, J = 8.72 Hz), 6.79 (d, 1H, J = 1.36 Hz), 4.84 (s, 2H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 181.94, 159.67, 158.28, 151.81, 144.77, 129.00, 126.50, 126.03, 124.16, 116.07, 114.62, 111.79, 55.40, 43.80; HRMS m/z calcd for $C_{16}H_{12}ClNO_3$ 301.05057, found 301.05009.

1-Benzyl-6-chloroindoline-2,3-dione (1p):[17] **1p** was synthesized from 6-chlorolisatin and benzylchloride (room temperature, 20 min), following the procedure for **1a.**

1-(4-Methoxybenzyl)indoline-2,3-dione (1q):[18] **1q** was synthesized from isatin and *p*-methoxybenzyl chloride (50 °C, 4 h), following the procedure for **1a**.

1-Benzyl-4-mehylindoline-2,3-dione (1r):[19] Under an air atmosphere, 4-methylindole (0.5 mmol), DMSO (1 mL) were added into a flask and vigorously stirred at 80 °C. Then the mixture of I_2 (0.6 mmol), TBHP (5 equiv), and DMSO (6 mL) was added to the flask dropwise. The reaction was stopped until N-methyl indole was completely consumed as monitored by TLC analysis. After the completion of reaction, 5% $Na_2S_2O_3$ solution (10 mL) was added to the mixture. The mixture was extracted with EtOAc (3×15 mL) and the organic layer was dried ($MgSO_4$) and evaporated. Then the crude product was purified by column chromatography on silica gel.

5-Chloro-1-(*p*-trifluoromethylbenzyl)indoline-2,3-dione (1s): **1r** was synthesized from 5-Chloroisatin and *p*-trifluoromethylbenzyl bromide (40 °C, 1 h), following the procedure for **1a**.^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.64–7.60 (m, 3H), 7.49–7.44 (m, 3H), 6.70 (d, 1H, J = 8.25 Hz), 5.00 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 181.80, 157.68, 148.42, 138.11, 137.81, 130.67 (d, J = 32.89 Hz), 130.08, 127.64, 126.16 (d, J = 3.76 Hz), 125.55, 123.75 (d, J = 272 Hz), 118.47, 43.67; HRMS m/z calcd for $C_{16}H_9ClF_3NO_2$ 339.02739, found 339.02661.

5.4.3 Typical procedure for ruthenium-catalyzed asymmetric additions of arylboronic acids to isatins: A flask was charged with $RuCl_2(PPh_3)_2$ (0.01 mmol, 2 mol%) and (*R,R*)-Me-BIPAM (0.011 mmol, 2.2 mol%) under a nitrogen atmosphere. Toluene (3.0 mL) was added to the flask and the mixture was then stirred at room temperature for 30 min to prepare the catalyst. Isatin (0.5 mmol), arylboronic acid (1.0 mmol), KF (1.0 mmol), and H_2O (0.3 mL) were then added to the catalyst solution. The reaction mixture was stirred at 50 °C for 24 h, at which time the crude reaction mixture was extracted using ethyl acetate, washed with saturated NH_4Cl and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel to give 3-aryl-3-hydroxy-2-oxindole.

(*R*)-5-Chloro-3-hydroxy-1-methyl-3-phenylindolin-2-one (3aa):[5a] >99% yield. $[\alpha]_D^{19}$ = +19.1492 (*c* 4.6, $CHCl_3$), 81% *ee* [lit. $[\alpha]_D^{20}$ = −13.1 (*c* 0.84, $CHCl_3$, 88% *ee* (*S*))[5a]], [HPLC condition: CHIRALPAK AD-H column, hexane/2-propanol = 9/1, flow = 1.0 mL/min, wavelength = 254 nm, t_R = 11.5 min (major) and 14.1 min (minor)]; HRMS m/z calcd for $C_{15}H_{12}ClNO_2$ 273.05566, found 273.05608.

(*R*)-1-Benzyl-5-chloro-3-hydroxy-3-phenylindolin-2-one. (3ba):[5a,6b] 99% yield. $[\alpha]_D^{19}$ = +15.3670 (*c* 3.9, $CHCl_3$), 87% *ee* [lit. $[\alpha]_D^{20}$ = −8.6 (*c* 0.92, $CHCl_3$, 89% *ee* (*S*)),[5a] $[\alpha]_D^{20}$ = +6 (*c* 0.1, $CHCl_3$, 90% ee (*R*))[6b]] [HPLC condition: CHIRALPAK AD-H column, hexane/2-propanol =

9/1, flow = 1.0 mL/min, wavelength = 254 nm, t_R = 23.7 min (major) and 30.0 min (minor)]; HRMS m/z calcd for $C_{21}H_{16}ClNO_2$ 349.08696, found 349.08585.

(*R*)-5-Chloro-3-hydroxy-1-(*p*-methoxybenzyl)-3-phenylindolin-2-one (3ca):[5a,6c] 97% yield. $[\alpha]_D^{19}$ = −9.4768 (*c* 5.1, $CHCl_3$), 88% ee [lit. $[\alpha]_D^{20}$ = +13.8 (*c* 0.70, $CHCl_3$, 90% ee (*S*)),[5a] $[\alpha]_D^{20}$ = −9.2 (*c* 0.74, $CHCl_3$, 76% ee (*R*))[6c]], [HPLC condition: CHIRALCEL OD-H column, hexane/2-propanol = 4/1, flow = 1.0 mL/min, wavelength = 254 nm, t_R = 17.3 min (minor) and 19.6 min (major)]; HRMS m/z calcd for $C_{22}H_{18}ClNO_3$ 379.09752, found 379.09675.

(+)-5-Chloro-1-(*p*-fluoromethylphenyl)-3-hydroxy-3-phenylindolin-2-one (3da): >99% yield. $[\alpha]_D^{21}$ = +15.0423 (*c* 0.94, $CHCl_3$), 83% *ee* (*R* enantiomer) [HPLC condition: CHIRALPAK AD-H column, hexane/2-propanol = 9/1, flow = 1.0 mL/min, wavelength = 254 nm, t_R = 23.6 min (major) and 34.6 min (minor)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.34 (s, 5H), 7.28–7.24 (m, 3H), 7.17 (dd, 1H, *J* = 8.25, 2.15 Hz), 7.01 (t, 2H, *J* = 8.43 Hz), 6.68 (d, 1H, *J* = 8.61 Hz), 4.95 (d, 1H, *J* = 15.78 Hz), 4.79 (d, 1H, *J* = 15.78 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 177.29, 162.33 (d, *J* = 246 Hz), 140.74, 139.36, 133.20, 130.65 (d, *J* = 2.82 Hz), 129.67, 129.15, 128.99 (d, *J* = 8.46 Hz), 128.83, 128.66, 125.61, 125.10, 115.93 (d, *J* = 21.61 Hz), 77.92, 43.44; HRMS m/z calcd for $C_{21}H_{15}ClFNO_2$ 367.07753, found 367.07770.

(–)-5-Chloro-3-hydroxy-3-phenyl-1-tritylindolin-2-one (3ea): 71% yield. $[\alpha]_D^{18}$ = −35.1488 (*c* 3.2, $CHCl_3$), 77% *ee* [HPLC condition: CHIRALCEL OD-H column, hexane/2-propanol = 4/1, flow = 1.0 mL/min, wavelength = 254 nm, t_R = 5.0 min (major) and 5.9 min (minor)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.43-7.37 (m, 11H), 7.26-7.19 (m, 10H), 6.92 (dd, 1H, *J* = 8.46, 1.84 Hz), 6.29 (d, 1H, *J* = 8.72 Hz), 3.25 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 179.05, 141.88, 141.50, 140.03, 133.47, 129.18, 128.98, 128.72, 128.40, 127.99, 127.28, 125.36, 124.87, 117.34, 77.62, 74.82; HRMS m/z calcd for $C_{33}H_{24}O_2NCl$ 524.13878, found 524.13794.

(–)-3-Hydroxy-1-methyl-3-phenyl-5-phenylindolin-2-one (3fa): 96% yield. $[\alpha]_D^{20}$ = −50.3393 (*c* 3.9, $CHCl_3$, 58% *ee*), $[\alpha]_D^{19}$ = −65.5050 (*c* 4.5 $CHCl_3$, 90% *ee*) [HPLC condition: CHIRALPAK AD-H column, hexane/2-propanol = 9/1, flow = 1.0 mL/min, wavelength = 254 nm, t_R = 24.1 min (major) and 32.3 min (minor)]; ^{1}H NMR (400 MHz, DMSO) δ = 7.68 (d, 1H, *J* = 8.24 Hz), 7.56 (d, 2H, *J* = 7.32 Hz), 7.42–7.27 (m, 9H), 7.19 (d, 1H, *J* = 8.24 Hz), 6.85 (s, 1H), 3.20 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ = 177.30, 143.48, 141.67, 135.48, 129.51, 128.74, 128.30, 128.19, 127.57, 126.73, 126.04, 123.08, 109.92, 77.71, 26.79; HRMS m/z calcd for $C_{21}H_{17}NO_2$ 315.12593, found 315.12555.

(–)-1-Benzyl-3-hydroxy-3-phenyl-5-phenylindolin-2-one (3ga): 90% yield. $[\alpha]_D^{22}$ = −54.6910 (*c* 0.87, $CHCl_3$), 86% *ee*. [HPLC condition: CHIRALPAK AD-H column, hexane/2-propanol = 95/5, flow = 1.0 mL/min, wavelength = 254 nm, t_R = 19.5 min (major) and 27.0 min (minor)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.51 (d, 1H, *J* = 1.79 Hz), 7.48–7.44 (m, 5H), 7.38–7.25 (m, 11H), 6.85 (d, 1H, *J* = 8.25 Hz), 5.09 (d, 1H, *J* = 15.78 Hz); 4.86 (d, 1H, *J* = 15.78 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 177.65, 141.91, 140.37, 140.01, 137.04, 135.32, 132.14,

128.94, 128.77, 128.76, 128.56, 128.43, 127.87, 127.32, 127.15, 126.78, 125.30, 123.94, 110.05, 78.13, 44.18; HRMS m/z calcd for $C_{27}H_{21}NO_2$ 391.15723, found 391.15735.

(–)-3-Hydroxy-1-(*p*-methoxybenzyl)-3-phenyl-5-phenylindolin-2-one (3ha): 87% yield, $[\alpha]_D^{19}$ = −49.1856 (*c* 4.6, $CHCl_3$), 90% *ee* [HPLC condition: CHIRALCEL OD-H column, hexane/2-propanol = 4/1, flow = 0.5 mL/min, wavelength = 254 nm, t_R = 26.3 min (major) and 51.7 min (minor)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.51–7.25 (m, 14H), 6.86 (dd, 3H, *J* = 8.24, 5.26 Hz), 5.00 (d, 1H, *J* = 15.56 Hz), 4.77 (d, 1H, *J* = 15.56 Hz), 3.89 (s, 1H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 177.78, 159.28, 142.04, 140.52, 140.23, 137.06, 132.48, 128.88, 128.81, 128.56, 128.45, 127.51, 127.24, 126.88, 125.45, 124.02, 114.39, 110.16, 78.26, 55.37, 43.75; HRMS m/z calcd for $C_{28}H_{23}NO_3$ 421.16779, found 421.16632.

(+)-5-Fluoro-3-hydroxy-1-(*p*-methoxybenzyl)-3-phenylindolin-2-one (3ia): >99% yield. $[\alpha]_D^{19}$ = +48.7115 (c4.4, $CHCl_3$), 87% *ee* [HPLC condition: CHIRALCEL OD-H column, hexane/2-propanol = 4/1, flow = 0.5 mL/min, wavelength = 254 nm, t_R = 21.0 min (minor) and 31.7 min (major)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.37–7.31 (m, 5H), 7.22 (d, 2H, *J* =8.8 Hz), 6.99 (dd, 1H, *J* = 7.68, 2.56 Hz), 6.91 (dt, 1H, *J* = 9.14, 2.6 Hz), 6.85 (d, 2H, *J* = 8.76 Hz), 6.71 (dd, 1H, *J* = 8.78, 4.04 Hz), 4.95 (d, 1H, *J* = 15.72 Hz), 4.75 (d, 1H, *J* = 15.76 Hz), 3.77 (s, 3H), 3.45 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 177.55, 159.68 (d, *J* = 246 Hz), 159.32, 139.77, 138.48, 133.35 (d, *J* = 7.63 Hz), 128.89, 128.77, 128.65, 127.15, 125.23, 116.13 (d, *J* = 23.84 Hz), 114.40, 113.17 (d, *J* = 24.8 Hz), 110.62 (d, *J* = 7.63 Hz), 78.21, 55.37, 43.80; HRMS m/z calcd for $C_{22}H_{18}FNO_3$ 363.12707, found 363.12857.

(*R*)-1-Benzyl-5-fluoro-3-hydroxy-3-phenylindolin-2-one (3ja):[6b] 95% yield. $[\alpha]_D^{21}$ = +75.9036 (*c* 0.83, $CHCl_3$), 90% *ee*, [lit. $[\alpha]_D^{20}$ = +57 (*c* 0.1, $CHCl_3$, 87% *ee*)[6b]], [HPLC condition: CHIRALPAK AD-H column, hexane/2-propanol = 9/1, flow = 1.0 mL/min, wavelength = 254 nm, t_R = 25.0 min (major) and 32.0 min (minor)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.38–7.25 (m, 10H), 7.01–6.98 (m, 1H), 6.92–6.87 (m, 1H), 6.69–6.65 (m, 1H), 5.02 (d, 1H, *J* = 15.6 Hz), 4.79 (d, 1H, *J* = 15.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 177.61, 159.61 (d, *J* = 242 Hz), 139.63, 138.27, 134.99, 133.32 (d, *J* = 7.63 Hz), 128.92, 128.74, 128.50, 127.87, 127.20, 125.16, 115.99 (d, *J* = 23.8 Hz), 113.08 (d, *J* = 24.8 Hz), 110.48 (d, *J* = 7.63 Hz), 78.13, 44.15; HRMS m/z calcd for $C_{21}H_{16}FNO_2$ 333.11651, found 333.11544.

(–)-5-Bromo-3-hydroxy-1-(*p*-methoxybenzyl)-3-phenylindolin-2-one (3ka): 97% yield, $[\alpha]_D^{19}$ = −5.8918 (*c* 4.3, $CHCl_3$), 90% *ee* [HPLC condition: CHIRALCEL OD-H column, hexane/2-propanol = 4/1, flow = 0.5mL/ min, wavelength = 254 nm, t_R= 23.7 min (minor) and 25.6 min (major)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.36–7.30 (m, 7H), 7.21 (d, 2H, *J* = 8.64 Hz), 6.84 (d, 2H, *J* = 8.72 Hz), 6.66 (d, 1H, *J* = 8.72 Hz), 4.93 (d,1H, *J* = 15.56 Hz), 4.74 (d, 1H, *J* = 15.56 Hz), 3.77 (s, 3H), 3.71 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 177.23, 159.36, 141.66, 139.62, 133.72, 132.64, 128.92, 128.78, 128.70, 128.32, 126.98, 125.24, 116.34, 114.43, 111.44, 77.99, 55.38, 43.74; HRMS m/z calcd for $C_{22}H_{18}BrNO_3$ 423.04701, found 423.04718.

(–)-1-Benzyl-5-bromo-3-hydroxy-3-phenylindolin-2-one (3la): 96% yield. $[\alpha]_D^{21}$ = −3.6344 (*c* 0.96, $CHCl_3$), 86% *ee* [HPLC condition: CHIRALPAK AD-H column, hexane/2-propanol = 95/5, flow = 1.0 mL/min, wavelength = 254 nm, t_R = 49.6 min (major) and 69.2 min (minor)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.43–7.20 (m, 12H), 6.69–6.56 (m, 1H), 5.00 (d, 1H, J = 12.38), 4.77 (d, 1H, J = 12.38 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 177.28, 141.43, 139.44, 134.81, 133.67, 132.47, 128.93, 128.76, 128.54, 128.21, 127.92, 127.18, 125.15, 116.30, 11.27, 77.92, 44.07; HRMS m/z calcd for $C_{21}H_{16}BrNO_2$ 393.03644, found 393.03639.

(*R*)-3-Hydroxy-1-(*p*-methoxybenzyl)-5-methyl-3-phenylindolin-2-one (3ma):[5a] 97% yield. $[\alpha]_D^{19}$ = +20.8922 (*c* 4.9, $CHCl_3$), 90% ee, [lit. $[\alpha]_D^{20}$ = −18.6 (*c* 0.93, $CHCl_3$, 87% ee (*S*))[5a]], [HPLC condition: CHIRALCEL OD-H column, hexane/2-propanol = 4/1, flow = 0.5 mL/min, wavelength = 254 nm, t_R= 19.9 min (minor) and 23.2 min (major)]; HRMS m/z calcd for $C_{23}H_{21}NO_3$ 359.15214, found 359.15205.

(*R*)-1-Benzyl-5-methyl-3-hydroxy-3-phenylindolin-2-one (3na):[6b] 92% yield. $[\alpha]_D^{22}$ = +30.3532 (*c* 0.91, $CHCl_3$), 87% *ee*, [lit. $[\alpha]_D^{20}$ = +17 (*c* 0.1, $CHCl_3$, 86% *ee*)[6b]], [HPLC condition: CHIRALPAK AD-H column, hexane/2-propanol = 95/5, flow = 1.0 mL/min, wavelength = 254 nm, t_R = 47.7 min (major) and 64.5 min (minor)]; ^{1}H NMR ($CHCl_3$, 400 MHz) δ = 7.52–7.21 (m, 10H), 7.17–6.94 (m, 2H), 6.76–6.60 (m, 1H), 5.02 (dd, 1H, J = 3.62, 15.29 Hz), 4.80 (dd, 1H, 3.62, 15.29 Hz); ^{13}C NMR ($CHCl_3$, 100 MHz) δ = 177.61, 140.30, 140.10, 135.46, 133.25, 131.64, 129.96, 128.80, 128.61, 128.21, 127.69, 127.24, 125.63, 125.25, 109.52, 78.05, 44.01, 20.97; HRMS m/z calcd for $C_{22}H_{19}NO_2$ 329.14158, found 329.14030.

(+)-6-Chloro-3-hydroxy-1-(*p*-methoxybenzyl)-3-phenylindolin-2-one (3oa): 97% yield. $[\alpha]_D^{19}$ = +51.6676 (*c* 5.1, $CHCl_3$), 88% *ee* [HPLC condition: CHIRALCEL OD-H column, hexane/2-propanol = 4/1, flow = 0.5 mL/min, wavelength = 254 nm, t_R = 18.3 min(minor) and 29.2 min(major)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.35–7.31 (m, 6H), 7.22 (d, 2H, J = 8.68 Hz), 7.15 (d, 1H, J = 8.24 Hz), 6.99 (dd, 1H, J = 8.23, 1.36 Hz), 6.85 (d, 2H, J = 8.68 Hz), 6.79 (d, 1H, J = 1.8 Hz), 4.93 (d, 1H, J = 15.56Hz), 4.70 (d, 1H, J = 15.56 Hz), 3.78 (s, 3H), 3.73 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 177.68, 159.39, 143.94, 139.78, 135,59, 130.20, 128.86, 128.79, 128.61, 126.96, 126.07, 125.28, 123.56, 114.48, 110.50, 77.70, 55.38, 43.74; HRMS m/z calcd for $C_{22}H_{18}ClNO_3$ 379.09752, found 379.09730.

(+)-1-Benzyl-6-chloro-3-hydroxy-3-phenylindolin-2-one (3pa): >99% yield. $[\alpha]_D^{21}$ = +69.7746 (*c* 0.98, $CHCl_3$), 89% *ee* [HPLC condition: CHIRALPAK AD-H column, hexane/2-propanol = 9/1, flow = 0.5 mL/min, wavelength = 254 nm, t_R = 39.2 min (major) and 46.0 min (minor)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.38–7.25 (m, 10H), 7.19–7.16 (m, 1H), 7.01 (dt, 1H, J = 7.89, 1.79 Hz), 6.77 (s, 1H), 5.01 (d, 1H, J = 15.78 Hz), 4.77 (d, 1H, J = 15.78 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 177.58, 143.78, 139.59, 135.52, 134.78, 129.96, 129.02, 128.76, 128.53, 128.00, 127.20, 125.98, 125.16, 123.51, 110.35, 77.57, 44.11; HRMS m/z calcd for $C_{21}H_{16}ClNO_2$ 349.08696, found 349.08774.

(*R*)-3-Hydroxy-1-(*p*-methoxybenzyl)-3-phenylindolin-2-one (3qa):[6b] >99% yield. $[\alpha]_D^{19}$ = +36.7314 (*c* 4.4, $CHCl_3$), 89% *ee* [lit. $[\alpha]_D^{20}$ = +37 (*c* 0.1, $CHCl_3$, 85% *ee*)[6b]], [HPLC condition: CHIRALCEL OD-H column, hexane/2-propanol = 4/1, flow = 0.5 mL/min, wavelength = 254 nm, t_R= 20.2 min (minor) and 27.7 min (major)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39–7.19 (m, 9H), 7.02 (t, 1H, *J* = 7.8 Hz), 6.84–6.78 (m, 3H), 4.95 (d, 1H, *J* = 15.56 Hz), 4.72 (d, 1H, *J* = 15.56 Hz), 4.13(s, 1H), 3.75 (s, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 177.83, 159.21, 142.69, 140.36, 132.02, 129.77, 128.84, 128.72, 128.34, 127.58, 125.48, 125.09, 123.64, 114.33, 109.88, 78.15, 55.37, 43.60; HRMS m/z calcd for$C_{22}H_{19}NO_3$ 345.13649, found 345.13604.

(–)-1-Benzyl-3-hydroxy-4-methyl-3-phenylindolin-2-one (3ra): 75% yield. $[\alpha]_D^{22}$ = −29.0999 (*c* 1.0, $CHCl_3$), 87% *ee* [HPLC condition: CHIRALPAK OD-H column, hexane/2-propanol = 90/10, flow = 0.5 mL/min, wavelength = 230 nm, t_R = 17.9 min (minor) and 19.7 min (major)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.34–7.22 (m, 11H), 7.12 (t, 11H, *J* = 7.8 Hz), 6.80 (d, 1H, *J* = 7.8 Hz), 6.62 (d, 1H, *J* = 7.8 Hz), 4.97 (d, 1H, *J* = 15.53 Hz); 4.73 (d, 1H, *J* = 15.53 Hz), 4.04 (s br, 1H), 2.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 177.70, 142.78, 138.94, 136.57, 135.46, 129.55, 129.34, 128.75, 128.48, 127.94, 127.64, 127.22, 125.62, 125.11, 107.13, 78.42, 43.93, 17.50; HRMS m/z calcd for $C_{22}H_{19}NO_2$ 329.14158, found 329.14137.

(–)-5-Chloro-3-hydroxy-3-(*p*-methoxylphenyl)-1-methyl-indolin-2-one (3ab): >99% yield. $[\alpha]_D^{20}$ = −25.3461 (*c* 0.94, $CHCl_3$), 61% *ee* [HPLC condition: CHIRALCEL OD-H column, hexane/2-propanol = 4/1, flow = 0.7 mL/min, wavelength = 254 nm, t_R = 11.2 min (major) and 13.6 min (minor)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.34–7.28 (m, 4H), 6.88–6.82 (m, 3H), 3.79 (s, 3H), 3.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.79, 141.90, 133.00, 131.37, 129.69, 128.86, 126.65, 125.42, 114.12, 109.68, 77.52, 55.30, 26.63; HRMS m/z calcd for $C_{16}H_{14}ClNO_3$ 303.06622, found 303.06553.

(*R*)-1-Benzyl-5-chloro-3-hydroxy-3-(*p*-methoxyphenyl)-indolin-2-one (3bb):[6b] 87% yield. $[\alpha]_D^{20}$ = −17.6411 (*c* 0.99, $CHCl_3$), 78% *ee*, [lit. $[\alpha]_D^{20}$ = −43 (*c* 0.1, $CHCl_3$, 85% *ee*)[6b]], [HPLC condition: CHIRALPAK AD-H column, hexane/2-propanol = 4/1, flow = 0.7 mL/min, wavelength = 254 nm, t_R = 26.4 min (major) and 35.8 min (minor)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.32–7.16 (m, 11H), 6.68 (d, 1H, *J* = 8.15 Hz), 5.03 (d, 1H, *J* = 15.86 Hz), 4.82 (d, 1H, *J* = 15.40 Hz), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 177.36, 140.97, 138.49, 136.55, 134.92, 133.32, 129.55, 129.48, 128.94, 127.91, 127.20, 125.44, 125.07, 110.76, 77.85, 44.10, 21.14; HRMS m/z calcd for $C_{22}H_{18}ClNO_3$ 379.09752, found 379.09715.

(*R*)-5-Chloro-3-hydroxy-3-(*p*-methoxylphenyl)-1-(*p*-methoxybenzyl)-indolin-2-one (3cb):[5a] 78% yield. $[\alpha]_D^{21}$ = −18.0084 (*c* 0.94, $CHCl_3$), 52% *ee*, [lit. $[\alpha]_D^{20}$ = +44.5 (*c* 0.83, $CHCl_3$, 91% *ee* (*S*))[5a]], [HPLC condition: CHIRALCEL OD-H column, hexane/2-propanol = 4/1, flow = 0.5 mL/min, wavelength = 254 nm, t_R = 24.5 min (minor) and 28.2 min (major)]; HRMS m/z calcd for $C_{23}H_{20}ClNO_4$ 409.10809, found 409.10578.

(–)-5-Chloro-1-(*p*-fluoromethylphenyl)-3-hydroxy-3-(*p*-methoxylphenyl)-indolin-2-one (3db): 75% yield. $[\alpha]_D^{21}$ = −12.4203 (*c* 0.94, $CHCl_3$), 64% *ee* [HPLC condition: CHIRALPAK AD-H column, hexane/2-propanol = 9/1, flow = 1.0 mL/min, wavelength = 254 nm, t_R = 42.5 min (major) and 50.6 min (minor)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.29–7.18 (m, 6H), 7.00 (t, 2H, *J* = 8.61 Hz), 6.85 (d, 2H, *J* = 8.97 Hz), 6.66 (d, 1H, *J* = 8.25 Hz), 4.93 (d, 1H, *J* = 15.42 Hz), 4.77 (d, 1H, *J* = 15.78 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 177.43, 162.29 (d, *J* = 246 Hz), 159.77, 140.63, 133.30, 131.34, 139.69 (d, *J* = 2.82 Hz), 129.54, 129.07, 128.96 (d, *J* = 8.46 Hz), 126.62, 125.55, 115.90 (d, *J* = 21.61 Hz), 114.14, 110.57, 77.57, 55.27, 43.37; HRMS m/z calcd for $C_{22}H_{17}ClFNO_3$ 397.08810, found 397.08703.

(–)-5-Chloro-3-hydroxy-3-(*p*-methoxylphenyl)-1-(*p*-trifluoromethylphenyl)-indolin-2-one (3sb): 90% yield. $[\alpha]_D^{20}$ = −17.6591 (*c* 0.97, $CHCl_3$), 60% *ee* [HPLC condition: CHIRALPAK AS-H column, hexane/2-propanol = 9/1, flow = 0.7 mL/min, wavelength = 254 nm, t_R = 27.6 min (major) and 34.6 min (minor)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.57 (d, 2H, *J* = 7.89 Hz), 7.36 (d, 2H, *J* = 7.89 Hz), 7.32–7.26 (m, 3H), 7.19 (dd, 1H, *J* = 8.61, 2.15 Hz), 6.89–6.85 (m, 2H), 6.61 (d, 1H, *J* = 8.25 Hz), 5.01 (d, 1H, *J* = 16.14 Hz), 4.85 (d, 1H, *J* = 16.14 Hz), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 177.53, 159.85, 140.43, 138.97, 133.24, 131.19, 130.23 (d, *J* = 32.89 Hz), 129.65, 129.28, 127.39, 126.67, 125.95 (d, *J* = 3.76 Hz), 125.70, 123.84 (d, *J* = 271 Hz), 114.20, 110.45, 77.61, 55.28, 43.56; HRMS m/z calcd for $C_{23}H_{17}ClF_3NO_3$ 447.08491, found 447.08530.

(–)-5-Chloro-3-hydroxy-3-(*p*-methylphenyl)-1-methyl-indolin-2-one (3ac): >99% yield. $[\alpha]_D^{21}$ = −5.8693 (*c* 0.90, $CHCl_3$), 83% *ee* [HPLC condition: CHIRALCEL OD-H column, hexane/2-propanol = 4/1, flow = 1.0 mL/min, wavelength = 254 nm, t_R = 14.9 min (major) and 16.8 min (minor)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.32 (dd, 1H, *J* = 8.15, 1.81 Hz), 7.26–7.24 (m, 3H), 7.17–7.15 (m, 2H), 6.83 (d, 1H, *J* = 8.61 Hz), 3.25 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 177.19, 141.93, 138.50, 136.46, 133.08, 129.68, 129.44, 128.88, 125.42, 125.07, 109.66, 77.78, 26.63, 21.12; HRMS m/z calcd for $C_{16}H_{14}ClNO_2$ 287.07131, found 287.07180.

(*R*)-1-Benzyl-5-chloro-3-hydroxy-3-(*p*-methylphenyl)-indolin-2-one (3bc):[6b] >99% yield. $[\alpha]_D^{21}$ = −8.4033 (*c* 0.95, $CHCl_3$), 81% *ee*, [lit. $[\alpha]_D^{20}$ = −22 (*c* 0.1, $CHCl_3$, 89% *ee*)[6b]], [HPLC condition: CHIRALPAK AD-H column, hexane/2-propanol = 4/1, flow = 1.0 mL/min, wavelength = 254 nm, t_R = 14.2 min (major) and 18.7 min (minor)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.34–7.26 (m, 8H), 7.17 (dd, 1H, *J* = 8.24, 2.15 Hz), 6.88 (d, 2H, *J* = 8.97 Hz), 6.67 (d, 1H, *J* = 8.61 Hz), 5.01 (d, 1H, *J* = 15.78 Hz), 4.80 (d, 1H, *J* = 15.78 Hz), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 177.37, 159.77, 140.90, 134.91, 133.19, 131.47, 129.55, 128.94, 127.91, 127.18, 126.63, 125.43, 114.16, 110.77, 77.58, 55.29, 44.08; HRMS m/z calcd for $C_{16}H_{23}Cl_2NO_4$ 363.10261, found 363.10144.

(*R*)-5-Chloro-3-hydroxy-3-(*p*-methylphenyl)-1-(*p*-methoxybenzyl)-indolin-2-one (3cc):[5a] 93% yield. $[\alpha]_D^{20}$ = −13.1894 (*c* 0.83, $CHCl_3$), 79% *ee*, [lit. $[\alpha]_D^{20}$ = +19.6 (*c* 0.70, $CHCl_3$, 89% *ee* (*S*)[5a]], [HPLC condition: CHIRALCEL OD-H column, hexane/2-propanol = 4/1, flow = 0.7 mL/min, wavelength = 254 nm, t_R = 11.8 min (minor) and 14.7 min (major)].

(–)-5-Chloro-1-(*p*-fluoromethylphenyl)-3-hydroxy-3-(*p*-methylphenyl)-indolin-2-one (3dc): >99% yield. $[\alpha]_D^{21}$ = −7.6252 (*c* 0.92, $CHCl_3$), 52% *ee* [HPLC condition: CHIRALPAK AD-H column, hexane/2-propanol = 4/1, flow = 0.7 mL/min, wavelength = 254 nm, t_R = 15.4 min (major) and 17.8 min (minor)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.24–7.00 (m, 10H), 6.67–6.65 (m, 1H), 4.93 (d, 1H, *J* = 15.42 Hz), 4.76 (d, 1H, *J* = 15.78 Hz), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 177.44, 162.28 (d, *J* = 246 Hz), 140.67, 138.49, 136.42, 133.39, 130.69, 129.47, 129.08, 128.96 (d, *J* = 7.52 Hz), 125.55, 125.05, 115.88 (d, *J* = 21.61 Hz), 110.55, 77.82, 43.37, 21.12; HRMS m/z calcd for $C_{22}H_{17}ClFNO_2$ 381.09318, found 381.09303.

(–)-5-Chloro-3-hydroxy-3-(*p*-methylphenyl)-1-(*p*-trifluoromethylphenyl)-indolin-2-one (3sc): >99% yield. $[\alpha]_D^{21}$ = −10.3806 (*c* 0.87, $CHCl_3$), 76% *ee* [HPLC condition: CHIRALPAK AS-H column, hexane/2-propanol = 9/1, flow = 0.4 mL/min, wavelength = 254 nm, t_R = 27.3 min (major) and 38.2 min (minor)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.57–7.55 (m, 2H), 7.37–7.35 (m, 2H), 7.25–7.14 (m, 6H), 6.61 (dd, 1H, *J* = 8.43, 3.41 Hz), 5.01 (dd, 1H, *J* = 16.14, 2.87 Hz), 4.85 (dd, 1H, *J* = 15.78, 2.87 Hz), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 177.51, 140.49, 138.97, 138.64, 136.29, 133.30, 130.23 (d, *J* = 32.89 Hz), 129.65, 129.53, 129.30, 127.40, 125.94 (d, *J* = 3.76 Hz), 125.70, 125.09, 123.84 (d, *J* = 272 Hz), 110.43, 77.86, 43.57, 21.13; HRMS m/z calcd for $C_{23}H_{17}ClF_3NO_2$ 431.08999, found 431.08945.

(–)-5-Chloro-3-(*p*-fluorophenyl)-3-hydroxy-1-methyl-indolin-2-one (3ad): >99% yield. $[\alpha]_D^{21}$ = −6.0639 (*c* 0.91, $CHCl_3$), 83% *ee* [HPLC condition: CHIRALCEL OD-H column, hexane/2-propanol = 4/1, flow = 0.5 mL/min, wavelength = 254 nm, t_R = 13.7 min (major) and 16.1 min (minor)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.35–7.30 (m, 3H), 7.24 (d, 1H, *J* = 2.27 Hz), 7.01 (t, 1H, *J* = 8.61 Hz), 6.84 (d, 1H, *J* = 8.15 Hz), 3.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 176.99, 141.79, 134.03 (d, *J* = 225 Hz), 129.89, 129.08, 127.21 (d, *J* = 7.63 Hz), 125.41, 115.64 (d, *J* = 20.98 Hz), 109.83, 77.45, 26.69; HRMS m/z calcd for $C_{15}H_{11}ClFNO_2$ 291.04623, found 29104605.

(*R*)-1-Benzyl-5-chloro-3-(*p*-fluorophenyl)-3-hydroxyindolin-2-one (3bd):[6b] 97% yield. $[\alpha]_D^{21}$ = −3.6764 (*c* 0.95, $CHCl_3$), 74% *ee*, [lit. $[\alpha]_D^{20}$ = −13 (*c* 0.1, $CHCl_3$, 88% *ee*)[6b]], [HPLC condition: CHIRALPAK AD-H column, hexane/2-propanol = 4/1, flow = 1.0 mL/min, wavelength = 254 nm, t_R = 10.5 min (major) and 13.3 min (minor)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.35–7.17 (m, 9H), 7.02 (t, 2H, *J* = 8.61 Hz), 6.69 (d, 1H, *J* = 8.61 Hz), 4.99 (d, 1H, *J* = 15.86 Hz), 4.78 (d, 1H, *J* = 15.40 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 177.21, 162.76 (d, *J* = 248 Hz), 140.81, 135.25 (d, *J* = 2.86 Hz), 134.74, 133.08, 129.77, 129.15, 128.98, 128.01, 127.24, 127.18, 125.43, 115.70

(d, J = 21.93 Hz), 110.92, 77.53, 44.15; HRMS m/z calcd for $C_{21}H_{15}ClFNO_2$ 367.07753, found 367.07595.

(*R*)-5-Chloro-3-hydroxy-3-(*p*-fluorophenyl)-1-(*p*-methoxybenzyl)-indolin-2-one (3cd)[5a]: 91% yield. $[\alpha]_D^{20}$ = −8.2159 (*c* 0.85, $CHCl_3$), 77% *ee*, [lit. $[\alpha]_D^{20}$ = +12.3 (*c* 0.87, $CHCl_3$, 82% *ee* (*S*))[5a]], [HPLC condition: CHIRALPAK AD-H column, hexane/2-propanol = 4/1, flow = 1.0 mL/min, wavelength = 254 nm, t_R = 15.0 min (major) and 18.9 min (minor)]; HRMS m/z calcd for $C_{22}H_{17}ClFNO_3$ 397.08810, found 397.08786.

(–)-5-Chloro-3-hydroxy-1,3-di(*p*-fluorophenyl)-indolin-2-one (3dd): 99% yield. $[\alpha]_D^{21}$ = −5.2915 (*c* 0.93, $CHCl_3$), 77% *ee* [HPLC condition: CHIRALPAK AD-H column, hexane/2-propanol = 4/1, flow = 0.7 mL/min, wavelength = 254 nm, t_R = 12.6 min (minor) and 14.6 min (major)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.33–7.28 (m, 2H), 7.26–7.19 (m, 4H), 7.03–6.97 (m, 4H), 6.78 (d, 1H, J = 8.25 Hz), 4.91 (d, 1H, J = 15.78 Hz), 4.77 (d, 1H, J = 15.78 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 177.22, 162.75 (d, J = 248 Hz), 162.33 (d, J = 247 Hz), 140.56, 135.14 (d, J = 2.82 Hz), 133.13, 130.52 (d, J = 2.82 Hz), 129.77, 129.28, 128.97 (d, J = 8.46 Hz), 127.18 (d, J = 8.46 Hz), 125.55, 115.88 (d, J = 21.61 Hz), 115.70 (d, J = 22.55 Hz), 110.72, 77.50, 43.43; HRMS m/z calcd for $C_{21}H_{14}ClF_2NO_2$ 385.06811, found 385.06695.

(–)-5-Chloro-3-(*p*-fluorophenyl)-3-hydroxy-1-(*p*-trifluoromethylphenyl)-indolin-2-one (3sd): >99% yield. $[\alpha]_D^{21}$ = −3.6687 (*c* 0.95, $CHCl_3$), 75% *ee* [HPLC condition: CHIRALPAK AS-H column, hexane/2-propanol = 9/1, flow = 0.4 mL/min, wavelength = 254 nm, t_R = 28.2 min (major) and 32.1 min (minor)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.57 (d, 2H, J = 7.89 Hz), 7.37–7.30 (m, 4H), 7.26–7.19 (m, 2H), 7.03 (dt, 2H, J = 8.61, 1.43 Hz), 6.64 (dd, 1H, J = 8.25, 1.08 Hz), 4.99 (d, 1H, J = 16.14 Hz), 4.87 (d, 1H, J = 15.78 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 177.26, 162.83 (d, J = 248 Hz), 140.38, 138.76, 134.98(d, J = 3.76 Hz), 132.98, 130.36 (d, J = 32.89 Hz), 129.92, 129.50, 127.39, 127.21 (d, J = 8.46 Hz), 125.99 (d, J = 3.76 Hz), 125.70, 123.79 (d, J = 272 Hz), 115.80 (d, J = 21.61 Hz), 110.61, 77.52, 43.64; HRMS m/z calcd for $C_{22}H_{14}ClF_4NO_2$ 435.06492, found 435.06346.

(+)-1-Benzyl-5-chloro-3-hydroxy-3-(*p*-trifluoromethylphenyl)-indolin-2-one (3be): 57% yield. $[\alpha]_D^{21}$ = +15.6250 (*c* 0.96, $CHCl_3$), 74% *ee* [HPLC condition: CHIRALPAK AD-H column, hexane/2-propanol = 95/5, flow = 0.5 mL/min, wavelength = 254 nm, t_R = 68.1 min (minor) and 74.1 min (major)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.59 (d, 2H, J = 7.89 Hz), 7.46 (d, 2H, J = 8.25 Hz), 7.49–7.19 (m, 6H), 6.73 (d, 1H, J = 7.89 Hz), 5.01 (d, 1H, J = 15.78 Hz), 4.80 (d, 1H, J = 15.78 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 176.94, 143.40, 140.80, 134.60, 132.86, 130.82, 130.50, 130.01, 129.36, 129.03, 128.11, 127.22, 125.72 (q, J = 3.76 Hz), 125.66, 125.44, 111.07, 77.78, 44.25; HRMS m/z calcd for $C_{22}H_{15}ClF_3NO_2$ 417.07434, found 417.07362.

(+)-5-Chloro-1-(*p*-fluorophenyl)-3-hydroxy-3-(*p*-trifluoromethylphenyl)-indolin-2-one (3de): 74% yield. $[\alpha]_D^{20}$ = +0.5208 (*c* 0.96, $CHCl_3$), 82% *ee* [HPLC condition: CHIRALPAK AD-H column, hexane/2-propanol = 9/1, flow = 1.0 mL/min, wavelength = 254 nm, t_R = 18.0

min (minor) and 20.5 min (major)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.58 (d, 2H, J = 7.53 Hz), 7.47–7.42 (m, 2H), 7.27–7.20 (m, 4H), 7.04–6.70 (m, 2H), 6.72 (d, 1H, J = 8.25 Hz), 4.93 (d, 1H, J = 15.78 Hz), 4.79 (d, 1H, J = 15.42 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 176.87, 162.41 (d, J = 248 Hz), 143.27, 140.59, 132.79, 130.76 (d, J = 31.95 Hz), 130.39 (d, J = 2.82 Hz), 130.09, 129.52, 129.04 (d, J = 8.46 Hz), 125.77 (d, J = 3.76 Hz), 125.63, 125.57, 123.80 (d, J = 272 Hz), 116.03 (d, J = 21.61 Hz), 110.91, 77.74, 43.58; HRMS m/z calcd for $C_{22}H_{14}ClF_4NO_2$ 435.06492, found 435.06399.

(+)-5-Chloro-3-hydroxy-1,3-di(*p*-trifluoromethylphenyl)-indolin-2-one (3se): 51% yield. $[\alpha]_D^{21}$ = +0.52633 (*c* 0.95, $CHCl_3$), 69% *ee* [HPLC condition: CHIRALPAK AD-H column, hexane/2-propanol = 9/1, flow = 1.0 mL/min, wavelength = 254 nm, t_R = 14.6 min (minor) and 21.8 min (major)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.62–7.59 (m, 4H), 7.50–7.46 (m, 2H), 7.39 (d, 2H, J = 7.89 Hz), 7.26–7.23 (m, 2H), 6.69 (d, 1H, J = 8.25 Hz), 5.02 (d, 1H, J = 15.78 Hz), 4.91 (d, 1H, J = 15.78 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 176.80, 143.10, 140.46, 138.63, 132.57, 130.71 (d, J = 9.40 Hz), 130.25, 129.71, 127.45, 126.08 (q, J = 2.82 Hz), 125.85 (q, J = 3.76 Hz), 125.74, 125.66, 123.77 (d, J = 272 Hz), 77.72, 43.77; HRMS m/z calcd for $C_{23}H_{14}ClF_6NO_2$ 485.06173, found 485.05977.

(–)-1-Benzyl-5-chloro-3-hydroxy-3-(*p*-phenylphenyl)-indolin-2-one (3bf): >99% yield. $[\alpha]_D^{22}$ = −16.3333 (*c* 0.9, $CHCl_3$), 88% *ee*. [HPLC condition: CHIRALPAK AD-H column, hexane/2-propanol = 4/1, flow = 0.5 mL/min, wavelength = 254 nm, t_R = 39.7 min (minor) and 49.1 min (major)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.60–7.31 (m, 5H), 7.22–7.20 (m, 1H), 6.72 (d, 1H, J = 8.61 Hz), 5.06 (d, 1H, J = 15.86 Hz), 4.86 (d, 1H, J = 15.40 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 177.31, 141.57, 140.99, 140.35, 138.38, 134.84, 133.10, 129.74, 128.99, 128.80, 128.30, 128.00, 127.58, 127.23, 127.10, 126.67, 125.61, 115.62, 110.90, 77.89, 44.19; HRMS m/z calcd for $C_{27}H_{20}ClNO_2$ 425.11826, found 425.1177.

(*R*)-1-Benzyl-5-chloro-3-hydroxy-3-(*m*-methylphenyl)-indolin-2-one (3bg):[6b] >99% yield. $[\alpha]_D^{21}$ = +15.1136 (*c* 0.88, $CHCl_3$), 87% *ee*, [lit. $[\alpha]_D^{20}$ = +9 (*c* 0.1, $CHCl_3$, 91% *ee*)[6b]], [HPLC condition: CHIRALPAK AD-H column, hexane/2-propanol = 4/1, flow = 0.5 mL/min, wavelength = 254 nm, t_R = 19.6 min (major) and 26.9 min (minor)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.35–7.12 (m, 11H), 6.68 (d, 1H, J = 8.25 Hz), 5.02 (, 1H, J = 15.78 Hz), 4.80 (d, 1H, J = 15.42 Hz), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 177.40, 140.94, 139.44, 138.55, 134.94, 133.37, 129.56, 129.38, 128.93, 128.69, 127.94, 127.25, 125.59, 125.43, 122.06, 110.75, 77.94, 44.09, 21.54; HRMS m/z calcd for $C_{22}H_{18}ClNO_2$ 363.10261, found 363.10136.

(+)-1-Benzyl-5-chloro-3-(*m*-chlorophenyl)-3-hydroxyindolin-2-one (3bh): >99% yield. $[\alpha]_D^{21}$ = +25.6250 (*c* 0.80, $CHCl_3$), 72% *ee*. [HPLC condition: CHIRALPAK AD-H column, hexane/2-propanol = 4/1, flow = 0.5 mL/min, wavelength = 254 nm, t_R = 18.2 min (major) and 22.5 min (minor)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.38-7.18 (m, 11H), 6.72-6.69 (m, 1H), 5.00 (d, 1H, J = 15.42 Hz), 4.80 (d, 1H, J = 15.78 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 176.90,

141.49, 140.80, 134.76, 134.68, 132.83, 130.07, 129.91, 129.23, 129.01, 128.77, 128.05, 127.24, 125.40, 123.28, 110.98, 77.58, 44.20; HRMS m/z calcd. for $C_{21}H_{15}ClNO_2$ 383.04798, found 383.04714.

(+)-1-Benzyl-5-chloro-3-hydroxy-3-(*m*-trifluoromethylphenyl)-indolin-2-one (3bi): 99% yield. $[\alpha]_D^{22}$ = +5.6818 (*c* 0.88, $CHCl_3$), 68% *ee*. [HPLC condition: CHIRALPAK AD-H column, hexane/2-propanol = 4/1, flow = 0.5 mL/min, wavelength = 254 nm, t_R = 24.3 min (major) and 30.9 min (minor)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.67–7.45 (m, 4H), 7.36–7.26 (m, 5H), 7.22–7.19 (m, 2H), 6.74 (d, 1H, J = 8.25 Hz), 5.05 (d, 1H, J = 15.42 Hz), 4.77 (d, 1H, J = 15.78 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 176.88, 140.73 (d, J = 19.73 Hz), 134.66, 132.78, 131.27, 130.93, 130.08, 129.32, 129.05, 128.52, 128.12, 127.22, 125.44, 125.38, 125.18, 122.42, 121.98 (q, J = 3.76 Hz), 111.08, 77.69, 44.23; HRMS m/z calcd for $C_{22}H_{15}ClF_3NO_2$ 417.07434, found 417.07326.

(–)-1-Benzyl-5-chloro-3-hydroxy-3-(2-naphthyl)-indolin-2-one (3bj): 99% yield. $[\alpha]_D^{21}$ = −18.6956 (*c* 0.92, $CHCl_3$), 82% *ee*. [HPLC condition: CHIRALPAK AD-H column, hexane/2-propanol = 4/1, flow = 0.5 mL/min, wavelength = 254 nm, t_R = 47.4 min (major) and 50.6 min (minor)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.92 (s, 1H), 7.81–7.78 (m, 2H), 7.50–7.48 (m, 2H), 7.37–7.19 (m, 9H), 6.74 (d, 1H, J = 8.25 Hz), 5.08 (d, 1H, J = 15.78 Hz), 4.86 (d, 1H, J = 15.78 Hz), 3.64 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 177.20, 141.03, 136.74, 134.93, 133.15, 133.08, 133.01, 129.77, 129.07, 129.00, 128.88, 128.26, 128.02, 127.62, 127.30, 126.58, 126.53, 125.56, 124.22, 122.64, 110.88, 78.12, 44.21; HRMS m/z calcd for $C_{25}H_{18}ClNO_2$ 399.10261, found 399.1026.

(+)-1-Benzyl-5-chloro-3-hydroxy-3-(*o*-methoxyphenyl)-indolin-2-one (3bk): 65% yield. $[\alpha]_D^{23}$ = +14.0000 (*c* 0.5, $CHCl_3$), 56% *ee*. [HPLC condition: CHIRALPAK IC column, hexane/2-propanol = 90/10, flow = 1.0 mL/min, wavelength = 254 nm, t_R = 18.0 min (minor) and 30.0 min (major)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.75 (d, 1H, J =7.53 Hz), 7.41–7.26 (m, 6H), 7.15–7.18 (m, 1H), 7.05–7.09 (m, 2H), 6.82 (d, 1H, J = 8.25 Hz), 6.71 (d, 1H, J = 8.61 Hz), 5.02 (d, 1H, J = 15.78 Hz), 4.85 (d, 1H, J = 15.42 Hz), 3.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 177.16, 155.92, 142.01, 135.47, 132.28, 129.83, 129.33, 128.79, 128.20, 127.80, 127.70, 136.75, 124.89, 121.05, 111.52, 109.99, 77.20, 76.22, 55.58, 44.11; HRMS m/z calcd for $C_{22}H_{18}ClNO_3$ 379.09752, found 379.09621.

(+)-1-Benzyl-5-chloro-3-(*o*-fluorophenyl)-3-hydroxyindolin-2-one (3bl): >99% yield. $[\alpha]_D^{21}$ = +27.8409 (*c* 0.88, $CHCl_3$), 51% *ee*. [HPLC condition: CHIRALCEL OD-H column, hexane/2-propanol = 4/1, flow = 0.5 mL/min, wavelength = 254 nm, t_R = 13.7 min (minor) and 15.3 min (major)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.93–7.85 (m, 1H), 7.40–7.06 (m, 9H), 6.99–6.94 (m, 1H), 6.65 (d, 1H, J = 8.25 Hz), 5.07 (d, 1H, J = 15.78 Hz), 4.84 (d, 1H, J = 15.78 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 176.60, 158.85 (d, J = 248 Hz), 141.39, 134.78, 131.76 (d, J = 4.7 Hz), 130.27 (d, J = 8.46 Hz), 129.77, 128.86, 128.72, 127.82, 127.36, 127.22, 126.84 (d, J =

13.15 Hz), 125.07, 124.46, 115.60 (d, J = 20.67 Hz), 110.82, 75.10, 44.29; HRMS m/z calcd for $C_{21}H_{15}ClFNO_2$ 367.07753, found 367.07770.

(+)-1-Benzyl-5-chloro-3-(*o*-chlorophenyl)-3-hydroxyindolin-2-one (3bm): 59% yield. $[\alpha]_D^{23}$ = +25.5000 (*c* 1.0, $CHCl_3$), 58% *ee*. [HPLC condition: CHIRALPAK IC column, hexane/2-propanol = 90/10, flow = 0.5 mL/min, wavelength = 254 nm, t_R = 20.8 min (minor) and 22.7 min (major)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.06 (d, 1H, J = 8.08 Hz), 7.38–7.24 (m, 8H), 7.18 (dd, 1H, J = 1.80, 2.24, 8.30 Hz), 6.93 (d, 1H, J = 1.80 Hz), 6.71 (d, 1H, J = 8.53 Hz), 5.02 (d, 1H, J = 15.26 Hz), 4.84 (d, 1H, J = 15.26 Hz), 4.03 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 176.08, 142.34, 136.60, 134.76, 131.25, 130.96, 130.19, 129.91, 129.83, 128.81, 128.64, 128.25, 127.90, 127.74, 126.97, 124.93, 110.57, 76.89, 44.48; HRMS m/z calcd for $C_{21}H_{15}Cl_2NO_2$ 383.04798, found 383.04733.

5.5 References

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List of Publications

1) 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. Miyaura, *Chem. Asian J.* **2012**, *7*, 2446–2449.

2) Enantioselective Addition of Arylboronic Acids to Methyl 2-Formylbenzoates by using a Ruthenium/Me-BIPAM Catalyst for Synthesis of Chiral 3-Aryl-isobenzofuranones
M. Yohda, Y. Yamamoto, *Org. Biomol. Chem.* **2015**, *13*, 10874–10880.

3) Ruthenium-Me-BIPAM-Catalyzed Addition Reaction of Aryl-boronic Acids to Benzofuran-2,3-diones for Enantioselective Synthesis of 3-Aryl-3-hydroxybenzofuran-2-ones
M. Yohda, Y. Yamamoto, *Tetrahedron: Asymmetry* **2015**, *26*, 1430–1435.

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