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

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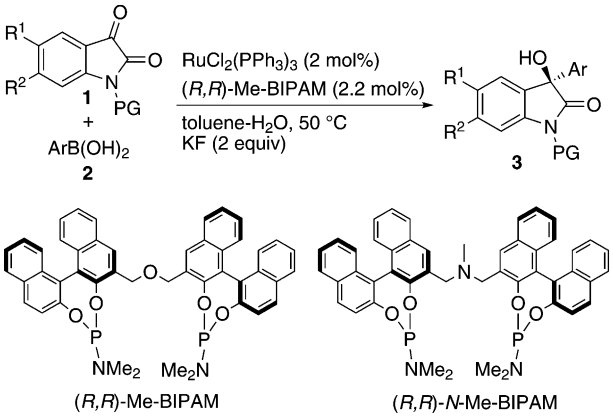
Abstract: A chiral *O*-linked C_2-symmetric bidentate phosphoramidite (Me-BIPAM) was found to be efficient for the ruthenium-catalyzed addition of arylboronic acids to isatins. Asymmetric synthesis of 3-aryl-3-hydroxy-2-oxindoles by 1,2-addition of arylboronic acids to isatins was carried out in the 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.

Keywords: 1,2-addition · 3-substituted-3-hydroxy-2-oxindole · boron · isatin · ruthenium

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] Over the past decade, various methods for the synthesis of these chiral compounds have been developed. Enantioselective Morita–Baylis–Hillman reactions,[3] aldol reactions,[4] asymmetric allylation of isatins,[5] Friedel–Crafts reactions,[6] direct hydroxylation,[7] and metal-catalyzed intramolecular coupling reactions have been reported.[8,9] In recent years, the use of stable, commercially available aryl boronic 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.[10,11] Since then, palladium-catalyzed addition reactions have been developed.[12] In 2009, Shibasaki and co-workers reported the arylation of isatins in the presence of a chiral copper catalyst.[13] In 2010, Hayashi et al. reported a copper-catalyzed asymmetric addition reaction.[14] In this field, we have already reported enantioselective addition reactions using organoboron compounds under rhodium, palladium, and ruthenium catalysis.[15] We previously developed bidentate chiral phosphoramidites (Me-BIPAM and *N*-Me-BIPAM), derived from linked BINOL (BINOL = 1,1′-binaphthalene-2,2′-diol) units, for the enantioselective 1,4-addition of arylboronic acids to enones,[16] arylation of aldimines,[17] and hydrogenation of alkenes.[18] These ligands were also found to be highly efficient for ruthenium-catalyzed enantioselective arylation of aldehydes, ketoesters, and glyoxylate.[19] In the course of our study on bisphosphoroamidites as a chiral auxiliary for enantioselective bond-forming reactions, we report here on the asymmetric addition of aryl boronic acids to isatins catalyzed by a Ru/Me-BIPAM complex (Scheme 1).



Scheme 1. Enantioselective addition of arylboronic acids to isatins.

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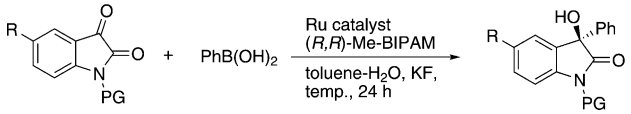
Results and Discussion

Initially, we utilized the reaction of 5-chloroisatin with phenyl boronic acid in the presence of KF (2 equiv) and ruthenium/(*R,R*)-Me-BIPAM complex (Table 1). Since the rhodium complex was inefficient, the use of ruthenium as the central metal was critical for achieving high enantioselectivities (entry 1). $[RuCl_2(p\text{-cymene})]_2$ and $[RuCl(C_6H_6)]_2$ 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) (Table 1, entries 2, 3, and 5). The use of *N*-Me-BIPAM as a ligand resulted in lower selectivity than that when Me-BIPAM was used (entries 3 and 4). We already reported $[RuCl_2(PPh_3)_3]$/(*R,R*)-Me-BIPAM complex-catalyzed highly enantioselective arylation of glyoxylate.[19c] When $[RuCl_2(PPh_3)_3]$ was used as the precursor, the product was obtained in 99% yield and 85% *ee* (Table 1, 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 (Table 1, entries 6–13). The best result was achieved when the reaction of *N*-*p*-methoxybenzyl isatin was controlled at 50°C in toluene in the presence of KF and $[RuCl_2(PPh_3)_3]$/(*R,R*)-Me-BIPAM (Table 1, entry 11 (97% yield, 88% *ee*)). Encouraged by these results, we then studied the reactions of 5-phenyl isatin bearing methyl, benzyl, and PMB groups on the nitrogen atom with phenyl boronic acid (Table 1, entries 14–19). *N*-Methyl- and *N*-PMB-5-phenyl isatin 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, we investigated the substrate scope 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 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).

We then studied the scope and limitations for various arylboronic acids. Again, a difference in enantioselectivity was observed depending on the protecting group on the nitrogen atom (Table 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*-trifluoromethylphenyl boronic 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 4. *Para*- and *meta*-

Table 1. Reaction conditions.[a]



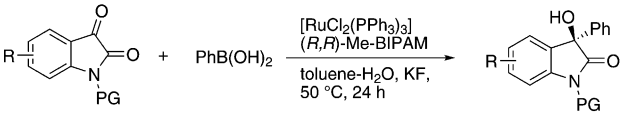
1 2a 3

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	3	*T* [°C]	Yield[b] [%]	*ee*[c] [%]
1	$[Rh(acac)(C_2H_4)_2]$	Cl	Bn	**3ba**	50	>99	58[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	$[RuCl_2(p\text{-cymene})]_2$	Cl	Me	**3aa**	80	78	24[e]
5	$[RuCl_2(benzene)]_2$	Cl	Bn	**3ba**	50	94	1
6	$[RuCl_2(PPh_3)_3]$	Cl	Me	**3aa**	80	>99	85 (*R*)
7	$[RuCl_2(PPh_3)_3]$	Cl	Bn	**3ba**	80	99	85 (*R*)
8	$[RuCl_2(PPh_3)_3]$	Cl	PMB	**3ca**	80	95	84 (*R*)
9	$[RuCl_2(PPh_3)_3]$	Cl	Me	**3aa**	50	>99	81 (*R*)
10	$[RuCl_2(PPh_3)_3]$	Cl	Bn	**3ba**	50	99	87 (*R*)
11	$[RuCl_2(PPh_3)_3]$	Cl	PMB	**3ca**	50	97	88 (*R*)
12	$[RuCl_2(PPh_3)_3]$	Cl	*p*-F-Bn	**3da**	50	>99	83
13	$[RuCl_2(PPh_3)_3]$	Cl	Tr	**3ea**	50	71	77
14	$[RuCl_2(p\text{-cymene})]_2$	Ph	Me	**3fa**	80	71	58
15	$[RuCl_2(PPh_3)_3]$	Ph	Me	**3fa**	80	94	88
16	$[RuCl_2(PPh_3)_3]$	Ph	Me	**3fa**	50	96	90
17	$[RuCl_2(PPh_3)_3$	Ph	Me	**3fa**	30	88	90
18	$[RuCl_2(PPh_3)_3$	Ph	Bn	**3ga**	50	90	86
19	$[RuCl_2(PPh_3)_3$	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), Ru 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. [d] A mixture of isatin (0.5 mmol), phenylboronic acid (0.75 mmol), $Rh(acac)(C_2H_4)_2$ (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. [e] (*R,R*)-*N*-Me-BIPAM was used as ligand.

Table 2. Ruthenium-catalyzed asymmetric addition of phenylboronic acids to isatins.



1 2a 3

Entry	1	R	PG	3	Yield[a] [%]	*ee*[b] [%]
1	**1i**	5-F	PMB	**3ia**	>99	87
2	**1j**	5-F	Bn	**3ja**	95	90 (*R*)
3	**1k**	5-Br	PMB	**3ka**	97	90
4	**1l**	5-Br	Bn	**3la**	96	86
5	**1m**	5-Me	PMB	**3ma**	97	90 (*R*)
6	**1n**	5-Me	Bn	**3na**	92	87 (*R*)
7	**1o**	6-Cl	PMB	**3oa**	97	88
8	**1p**	6-Cl	Bn	**3pa**	>99	89
9	**1q**	H	PMB	**3qa**	>99	89 (*R*)

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

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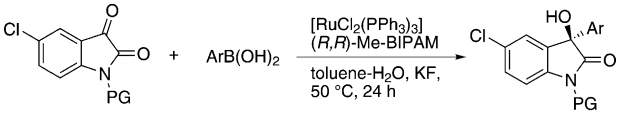
Table 3. Arylation of 5-chloroisatins.[a]

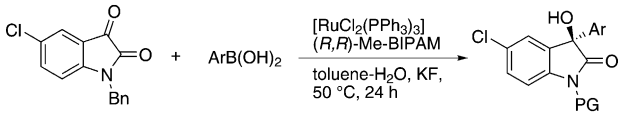


1 2 3

Ar	PG =	Me (**1a**)	Bn (**1b**)	PMB (**1c**)	*p*-F-Bn (**1d**)	*p*-CF_3-Bn (**1r**)
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* (**3rb**)
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* (**3rc**)
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* (**3rd**)
4-$CF_3C_6H_4$ (**2e**)		–	57%, 74% *ee*[b] (**3be**)	–	74%, 82% *ee*[b] (**3de**)	51%, 69% *ee*[b] (**3re**)

[a] Reaction conditions: A mixture of isatin (0.5 mmol), phenylboronic acid (1.0 mmol), KF (1.0 mmol), Ru 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 4. Arylation of *N*-benzyl 5-chloroisatin.



1b 2 3

Entry	Ar	3	Yield[a] [%]	*ee*[b] [%]
1	4-PhC_6H_4 (**2f**)	**3bf**	>99	88
2	3-MeC_6H_4 (**2g**)	**3bg**	>99	87 (*R*)
3	3-ClC_6H_4 (**2h**)	**3bh**	>99	72[c]
4	3-$CF_3C_6H_4$ (**2i**)	**3bi**	99	68[c]
5	2-naphthyl (**2j**)	**3bj**	99	82
6	2-$MeOC_6H_4$ (**2k**)	**3bk**	97	46
7	2-FC_6H_4 (**2l**)	**3bl**	>99	51[c]

[a] Isolated yields. [b] Determined by HPLC. [c] The reaction was carried out at 80°C.

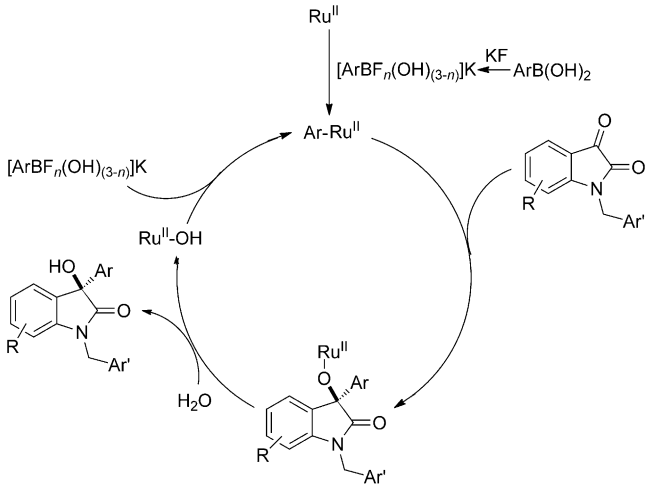


Figure 1. Proposed catalytic cycle.

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, the catalyst was less effective for *ortho*-substituted arylboronic acids. The addition of *o*-methoxyphenyl- and *o*-fluorophenyl boronic acids resulted in 97% yield with 46% *ee* and >99% yield with 51% *ee*, respectively (entries 6 and 7).

The catalytic cycle involves 1) transmetalation of an arylboronic acid to a Ru/Me-BIPAM complex giving an Ar–[Ru] species, 2) insertion of the C=O bond of isatin into the Ar–Ru bond, and finally 3) formation of a 3-aryl-3-hydroxy-2-oxindole through hydrolysis of the Ru–O intermediate with water (Figure 1). The absolute configuration and enantioselectivity are determined at the insertion step of the C=O bond into an arylruthenium intermediate (Figure 2). Thus, the *R* configuration in Tables 1–3 caused by (*R*,*R*)-Me-BIPAM is rationalized by the coordination of an isatin with its *si*-face. The *si*-coordination of the substrate is preferred without significant steric interaction 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.

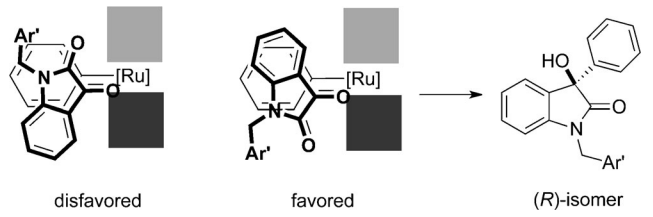


Figure 2. Proposed coordination modes.

Conclusions

In conclusion, we have developed asymmetric arylation of *N*-protected isatins with arylboronic acids using an [$RuCl_2(PPh_3)_3$]/(*R*,*R*)-Me-BIPAM catalyst system. 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*). The mechanisms underlying enantioselection will be reported elsewhere.

Experimental Section

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. Subsequently, toluene (3.0 mL) was added to the flask and the mixture was 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 (EtOAc/$CHCl_3$) to give 3-aryl-3-hydroxy-2-oxindole.

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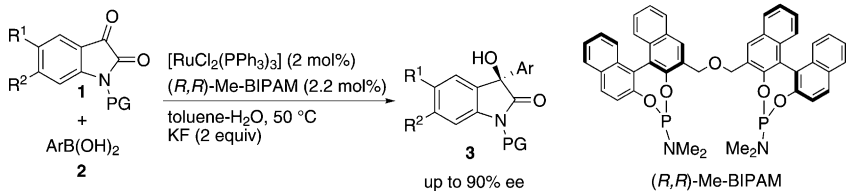

Add it up: A chiral *O*-linked C_2-symmetric bidentate phosphoramidite (Me-BIPAM) was found to be efficient for the ruthenium-catalyzed addition of arylboronic acids to isatins. Asymmetric synthesis of 3-aryl-3-hydroxy-2-oxindoles by 1,2-addition of arylboronic acids to isatins was carried out in the presence of $[RuCl_2(PPh_3)_3]$/(*R,R*)-Me-BIPAM and KF, resulting in an enantioselectivity as high as 90% *ee*.

Asymmetric Synthesis

Yasunori Yamamoto, Masaaki Yohda, Tomohiko Shirai, Hajime Ito, Norio Miyaura* ———— ■■■■–■■■■

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

