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Asymmetric Arylation

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Hydroxorhodium/Chiral Diene Complexes as Effective Catalysts for the Asymmetric Arylation of 3-Aryl-3-hydroxyisoindolin-1-ones**

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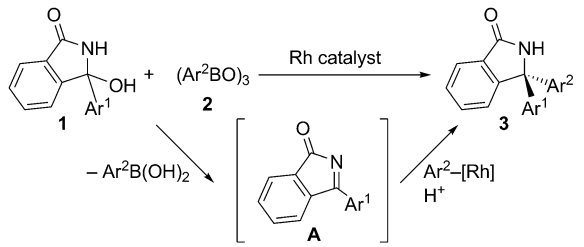
The transition-metal-catalyzed enantioselective alkylation and arylation of imines is a versatile means of accessing α-chiral amines, which are important structural components of a number of biologically active compounds, and there have been many reports of the successful catalytic enantioselective addition of organometallic reagents to imines derived from aldehydes.[1] In contrast, the asymmetric addition of organometallic reagents to ketimines, which provides chiral α-tertiary amines, remains less developed.[2–4] In this context, we have reported that rhodium/chiral diene complexes efficiently catalyze the asymmetric addition of arylboron reagents to *N*-sulfonyl ketimines with high enantioselectivity.[5,6] Herein, we report the rhodium-catalyzed asymmetric arylation of cyclic *N*-carbonyl ketimines, which are generated in situ by the dehydration of 3-aryl-3-hydroxyisoindolin-1-ones with arylboroxines, resulting in isoindolin-1-ones bearing a triaryl-substituted stereogenic carbon center.

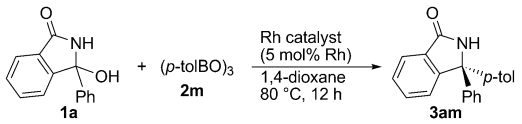
The stability of imines towards hydrolysis depends on the substituent on the imine nitrogen. For example, *N*-sulfonyl imines are sufficiently stable to be isolated and they are often used in the addition of organometallic reagents. On the other hand, when the imines are highly sensitive to hydrolysis, benzotriazole[7] or sulfinic acid imine adducts,[8] or hemiaminals[9b] have been often used as stable imine precursors. We focused on the use of 3-aryl-3-hydroxyisoindolin-1-ones[9] **1** as stable precursors for the generation of cyclic *N*-carbonyl ketimines bearing a diaryl-substituted azomethine moiety, which can be used in the rhodium-catalyzed asymmetric arylation reaction to produce chiral isoindolin-1-ones, which are structurally important core unit found in many biologically active compounds and natural products (Scheme 1).[10,11] We also decided to use arylboroxines **2**, which are dehydrated analogues of arylboronic acids, because they would be expected to work as dehydrating reagents to generate ketimine **A**, as well as arylating reagents for a subsequent arylation by a rhodium catalyst.



Scheme 1. Asymmetric arylation of isoindolin-1-ones **1**.

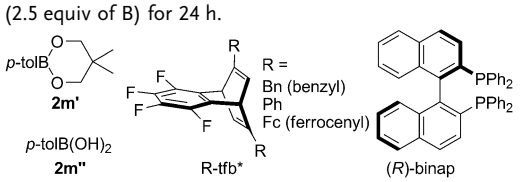
It was found that a hydroxorhodium complex was effective in catalyzing the arylation of 3-phenyl-3-hydroxyisoindolin-1-one (**1a**) with arylboroxines **2** (Table 1). Thus, treatment of hemiaminal **1a** with *p*-tolylboroxine (**2m**; 2 equiv of B) in the presence of a hydroxorhodium complex [{Rh(OH)(cod)}$_2$] (5 mol% of Rh; cod = 1,5-cyclooctadiene) at 80°C for 12 h gave 3-phenyl-3-(*p*-tolyl)isoindolin-1-one (**3am**) in 87% yield (entry 1). The arylating reagent *p*-tolylboronate **2m′** is also effective, giving **3am** in 85%

Table 1: Rhodium-catalyzed asymmetric arylation of 3-hydroxyisoindolin-1-one **1a**.[a]



Entry	Catalyst	*p*-tol[B]	Yield [%][b]	*ee* [%][b]
1	[{Rh(OH)(cod)}$_2$]	**2m**	87	–
2	[{Rh(OH)(cod)}$_2$]	**2m′**	85	–
3	[{Rh(OH)(cod)}$_2$]	**2m″**	7	–
4[c]	[{RhCl(cod)}$_2$]/KOH (aq)	**2m**	0	–
5[d]	[{RhCl(cod)}$_2$]/K_3PO_4	**2m**	7	–
6	[{Rh(OH)[(*R*,*R*)-Bn-tfb*]}$_2$]	**2m**	50	33
7	[{Rh(OH)[(*R*,*R*)-Ph-tfb*]}$_2$]	**2m**	79	87
8	[{Rh(OH)[(*S*,*S*)-Fc-tfb*]}$_2$]	**2m**	90[e]	95
9[f]	[{Rh(OH)[(*S*,*S*)-Fc-tfb*]}$_2$]	**2m**	96[e]	95
10	[{Rh(OH)[(*R*)-binap]}$_2$]	**2m**	44	63

[a] Reaction conditions: **1a** (0.10 mmol), *p*-tol[B] **2** (0.20 mmol of B), rhodium catalyst (5 mol% of Rh), 1,4-dioxane (0.4 mL) at 80°C for 12 h. [b] Yield of **3am** determined by ^{1}H NMR spectroscopy. [c] Performed with aq. KOH (1 M, 20 mol%). [d] Performed with K_3PO_4 (1 equiv). [e] Yield of isolated product. [f] Performed with 0.083 mmol of **2m** (2.5 equiv of B) for 24 h.



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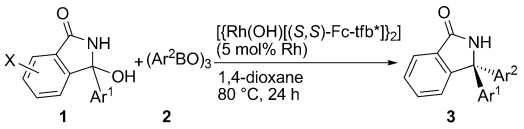
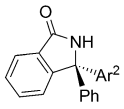
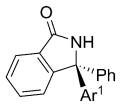
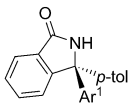
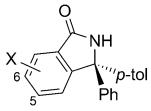
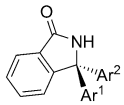
yield (entry 2). In sharp contrast, the reaction of **1a** with *p*-tolylboronic acid (**2m″**) gave only 7% yield of **3am**, although the formation of imines from 3-hydroxyisoindolin-1-ones has been reported to be accelerated by a Brønsted acid (entry 3).[9] The low yield of product **3am** when *p*-tolylboronic acid is used is probably due to the faster hydrolysis of a *p*-tolylrhodium intermediate, which leads to toluene rather than reaction with the imine. The combined use of a chlororhodium complex [{RhCl(cod)}$_2$] and bases such as KOH and K_3PO_4, which are often used in the rhodium-catalyzed addition of arylboron reagents,[12] provided very low catalytic activity in the present arylation; this was probably due to inhibition of imine formation by the bases (entries 4 and 5). These results prompted us to use hydroxorhodium catalysts coordinated with chiral diene ligands[13] for the development of an asymmetric variant of the present arylation. We have recently developed stable hydroxorhodium complexes coordinated with chiral tetrafluorobenzobarrelene (tfb*) ligands,[14] and thus they were tested in the reaction of **1a** (entries 6–8). The substituents on the tfb ligands significantly affected the catalytic activity and enantioselectivity. The use of benzyl-substituted tfb (Bn-tfb*) gave 50% yield of **3am** with 33% *ee* (entry 6). Higher catalytic activity was observed for phenyl-substituted tfb (Ph-tfb*), which gave **3am** in 79% yield with 87% *ee* (entry 7). The ligand Fc-tfb*, which is substituted with ferrocenyl groups, displayed the highest enantioselectivity (95% *ee*) and gave **3am** in 90% yield (entry 8), and in a reaction with **2m** (2.5 equiv of B) for a prolonged reaction time (24 h) it gave **3am** in 96% yield with 95% *ee* (entry 9). The same reaction was also catalyzed by a hydroxorhodium complex coordinated with (*R*)-binap, which is one of the most active catalysts for the 1,4-addition of arylboronic acids,[15] but the yield and *ee* of **3am** was only moderate (44% yield, 63% *ee*; entry 10).

Table 2 summarizes the results obtained for the reaction of 3-aryl-3-hydroxyisoindolin-1-ones **1** with arylboroxines **2** catalyzed by [{Rh(OH)[(*S*,*S*)-Fc-tfb*]}$_2$]. Aryl groups having a variety of electron-donating and -withdrawing substituents at the *ortho*, *meta*, and *para* positions of the phenyl substituent were successfully introduced onto the azomethine carbon of **1a** to give the corresponding addition products **3am**–**3au** in high yields with over 94% *ee* (entries 1–9). The present catalytic system can also be applied to the asymmetric arylation of several 3-aryl-3-hydroxyisoindoline-1-ones **1** with high enantioselectivity (entries 10–21). The addition of phenylboroxine (**2v**) to **1b**, which is substituted with a *p*-tolyl group, and thus is the reverse of the combination in the reaction of **1a** with **2m**, gave the opposite enantiomer ((−)-**3bv**) vs. (+)-**3am** in 95% yield with 94% *ee* (entry 10). The addition of *p*-tolylboroxine (**2m**) to ketimines **1c**–**1g**, which possess several aromatic rings substituted with both electron-donating (Me, MeO) and -withdrawing groups (Cl, CF_3) proceeded to give the corresponding isoindolin-1-ones **3cm**–**3gm** with high enantioselectivity (entries 11–15). Substrates that include heteroaromatic rings, such as 2-furyl (**1h**) and 2-thienyl (**1i**) 3-hydroxyisoindolin-1-ones, are also good substrates and give the corresponding isoindolin-1-ones **3hm** and **3im** with 96% and 93% *ee*, respectively (entries 16 and 17). The present catalytic system provides a general method for the preparation of enantioenriched isoindolin-1-ones substituted with a variety of aromatic groups (entries 18–21).

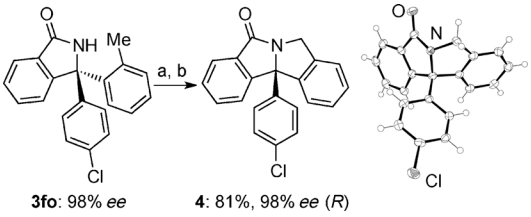
Table 2: Rhodium-catalyzed asymmetric arylation of 3-hydroxyisoindolin-1-ones **1**.[a]



Entry	Product	Ar^1 or Ar^2	Yield [%][b]	*ee* [%][c]
1		**3am**: Ar^2 = 4-MeC_6H_4	98	95
2		**3an**: Ar^2 = 3-MeC_6H_4	99	95
3		**3ao**: Ar^2 = 2-MeC_6H_4	94	98
4		**3ap**: Ar^2 = 4-$MeOC_6H_4$	94	94
5		**3aq**: Ar^2 = 3,4-$(OCH_2O)C_6H_3$	93	96
6		**3ar**: Ar^2 = 2-naphthyl	91	97
7		**3as**: Ar^2 = 4-FC_6H_4	87	96
8[d]		**3at**: Ar^2 = 4-ClC_6H_4	98	97
9[d]		**3au**: Ar^2 = 4-$CF_3C_6H_4$	96	97
10		**3bv**: Ar^1 = 4-MeC_6H_4	95	94
11		**3cm**: Ar^1 = 3-MeC_6H_4	94	95
12		**3dm**: Ar^1 = 4-$MeOC_6H_4$	99	97
13		**3em**: Ar^1 = 2-$MeOC_6H_4$	94	98
14		**3fm**: Ar^1 = 4-ClC_6H_4	82	94
15[d]		**3gm**: Ar^1 = 4-$CF_3C_6H_4$	65	91
16		**3hm**: Ar^1 = 2-furyl	87	96
17		**3im**: Ar^1 = 2-thienyl	89	93
18		**3jm**: X = 6-MeO	89	95
19		**3km**: X = 5-MeO	89	95
20		**3fr**: Ar^1 = 4-ClC_6H_4, Ar^2 = 2-naphthyl	95	96
21		**3fo**: Ar^1 = 4-ClC_6H_4, Ar^2 = 2-MeC_6H_4	82	98

[a] Reaction conditions: **1** (0.20 mmol), **2** (0.17 mmol), [{Rh(OH)[(*S*,*S*)-Fc-tfb*]}$_2$] (5 mol% of Rh), 1,4-dioxane (0.8 mL) at 80°C for 24 h. [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase. [d] Performed with 0.33 mmol of **2** (5 equiv of B) for 48 h.

The absolute configuration of isoindolin-1-one **3fo** was determined to be *R* by X-ray crystallographic analysis of **4**,[16] which was derived from **3fo** in 81% yield without loss in its enantiomeric purity by treatment with *N*-bromosuccinimide (NBS) in the presence of $ZrCl_4$,[17] followed by NaH (Scheme 2). The absolute configuration is in good agreement



Scheme 2. Transformation of **3fo** into **4**. a) *N*-bromosuccinimide, cat. $ZrCl_4$. b) NaH.

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with the stereochemical model previously proposed for the addition to *N*-tosylimines by use of C_2-symmetric chiral diene ligands.[18]

In summary, we have developed an asymmetric synthesis of isoindoline-1-ones bearing an α-triaryl-substituted stereogenic center through the enantioselective addition of arylboroxines to 3-hydroxyisoindolin-1-ones catalyzed by a hydroxorhodium/chiral diene complex, wherein cyclic *N*-carbonyl ketimines were generated in situ by dehydration.

Experimental Section

[{Rh(OH)[(*S*,*S*)-Fc-tfb*]}$_2$] (7.1 mg, 0.010 mmol of Rh), 3-hydroxy-3-phenylisoindolin-1-one (**1a**; 45.1 mg, 0.200 mmol), and *p*-tolylboroxine (**2m**; 59.0 mg, 0.167 mmol) were placed in a Schlenk tube under nitrogen. 1,4-Dioxane (0.80 mL) was added and the mixture was stirred at 80 °C for 24 h. The mixture was passed through a short column of alumina with EtOAc as eluent. The solvent was removed on a rotary evaporator and the residue was subjected to preparative TLC on silica gel with EtOAc/*n*-hexane (1:1) to give **3am** (58.5 mg, 0.195 mmol, 98 % yield).

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