Asymmetric Catalysis

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Chiral Tetrafluorobenzobarrelenes as Effective Ligands for Rhodium-Catalyzed Asymmetric 1,4-Addition of Arylboroxines to β,β-Disubstituted α,β-Unsaturated Ketones**

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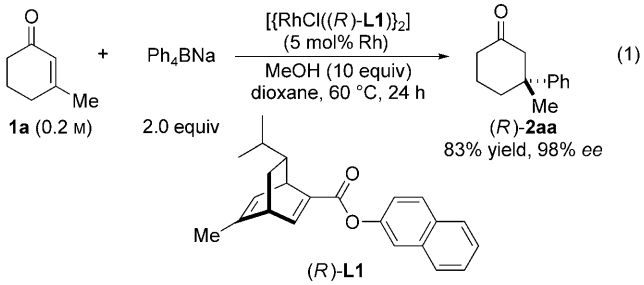
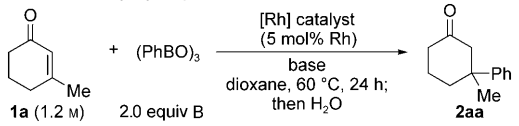
The catalytic asymmetric 1,4-addition of organometallic reagents to β,β-disubstituted α,β-unsaturated compounds offers a straightforward way of constructing all-carbon quaternary stereocenters.[1,2] Although some copper-catalyzed processes have appeared in combination with highly reactive nucleophiles, such as diorganozinc,[3] Grignard,[4] and triorganoaluminum reagents,[5] the use of air-stable, easily handled organoboronic acid derivatives would be desirable in view of the mildness of the reaction conditions. Unfortunately, however, applicable substrates have so far been limited to α,β-unsaturated pyridyl sulfones[6] and 3-substituted maleimides[7] under rhodium catalysis. Herein, we describe that simple β,β-disubstituted α,β-unsaturated ketones can now be employed as substrates for the rhodium-catalyzed 1,4-addition of arylboroxines (arylboronic acid anhydrides) and that highly efficient asymmetric catalysis can be realized by using a chiral tetrafluorobenzobarrelene as the ligand.

As a partial solution to the use of simple β,β-disubstituted α,β-enones in the asymmetric 1,4-addition of air-stable organoboron nucleophiles, we recently reported a rhodium-catalyzed asymmetric 1,4-addition of sodium tetraarylborates in the presence of chiral diene ligand (*R*)-**L1**,[8] as illustrated in Equation (1).[9] Although high yields and enantioselectivities were achieved, the synthetic drawback of this process was that tetraarylborates were required to promote the reaction, and more readily available organoboronic acids and organoboronates could not be effectively employed as the nucleophile.



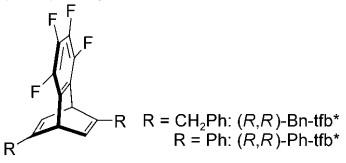
To solve this methodological problem, we decided to reinvestigate the reaction conditions for the phenylation of 3-methyl-2-cyclohexen-1-one (**1a**) and found that [{Rh(OH)(cod)}$_2$] (5 mol% Rh) could effectively catalyze the addition of air-stable and readily available phenylboroxine[10] at 60 °C in anhydrous dioxane to give 1,4-adduct **2aa** in 78% yield (1.2 M initial concentration of **1a**; Table 1, entry 1).[11] The use of [{RhCl(cod)}$_2$] in place of [{Rh(OH)(cod)}$_2$] as the catalyst did not promote the reaction (Table 1, entry 2), but the in situ generation of [{Rh(OH)(cod)}$_2$] from [{RhCl(cod)}$_2$] by treating it with KOH successfully produced **2aa** in 73% yield (Table 1, entry 3). Furthermore, no reaction was observed with a rhodium bis(phosphine) complex, such as

Table 1: Rhodium-catalyzed 1,4-addition of phenylboroxine to 3-methyl-2-cyclohexen-1-one (**1a**): Optimization.



Entry	Rhodium catalyst	Base (mol%)	Yield [%][a]	*ee* [%][b]
1	[{Rh(OH)(cod)}$_2$]	none	78	–
2	[{RhCl(cod)}$_2$]	none	0[c]	–
3	[{RhCl(cod)}$_2$]	KOH (7.5)	73	–
4	[{Rh(OH)(binap)}$_2$]	none	0[c]	–
5	[{RhCl((*R*)-**L1**)}$_2$]	KOH (7.5)	0[c]	–
6	[{RhCl((*R*)-**L1**)}$_2$]	Cs_2CO_3 (15)	10[c]	–[d]
7	[{RhCl((*R*)-**L1**)}$_2$]	Cs_2CO_3 (100)	48	90 (*R*)
8	[{Rh(OH)((*R*,*R*)-Bn-tfb*)}$_2$]	none	94	99 (*R*)
9	[{Rh(OH)((*R*,*R*)-Ph-tfb*)}$_2$]	none	99	99 (*R*)
10	[{RhCl((*R*,*R*)-Bn-tfb*)}$_2$]	KOH (7.5)	70	98 (*R*)
11	[{RhCl((*R*,*R*)-Ph-tfb*)}$_2$]	KOH (7.5)	92	97 (*R*)

[a] Yield of isolated product. [b] Determined by chiral HPLC on a Chiralcel OJ-H column with hexane/2-propanol = 95:5. [c] Determined by ^{1}H NMR spectroscopy of the crude material. [d] Not determined. cod = 1,5-cyclooctadiene, binap = 1,1′-binaphthalene-2,2′-diylbis(diphenylphosphine).



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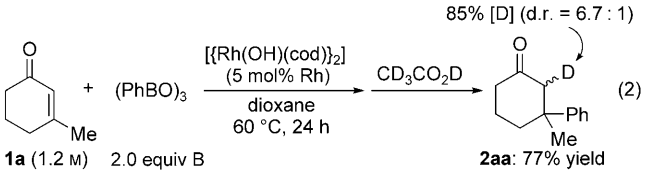
[{Rh(OH)(binap)}$_2$] as the catalyst (Table 1, entry 4). On the basis of these results and our previous success in the addition of sodium tetraarylborates, we attempted to develop its asymmetric analogue by using [{RhCl((*R*)-**L1**)}$_2$] as the catalyst; however, no **2aa** product was obtained with KOH as a base (Table 1, entry 5). Changing the base from KOH to Cs_2CO_3 afforded **2aa** in up to 48% yield with 90% *ee* (Table 1, entries 6 and 7), but further improvement could not be achieved with this rhodium complex.

We successively examined chiral tetrafluorobenzobarrelene (tfb*) ligands[12–15] because their hydroxorhodium complexes can be isolated as stable compounds[12e] and they are known to display high catalytic activity in other related asymmetric addition reactions.[12] To our delight, both [{Rh(OH)((*R*,*R*)-Bn-tfb*)}$_2$] and [{Rh(OH)((*R*,*R*)-Ph-tfb*)}$_2$] did effectively promote the reaction of **1a** with phenylboroxine to give **2aa** in 94 and 99% yield, respectively, with excellent enantioselectivity (99% *ee*; Table 1, entries 8 and 9). The reaction also proceeded well using catalysts generated in situ from reaction of their corresponding chlororhodium complexes with KOH, but the yields became somewhat lower (70–92%, 97–98% *ee*; Table 1, entries 10 and 11).

Various cyclic enones were then reacted with phenylboroxine using [{Rh(OH)((*R*,*R*)-Ph-tfb*)}$_2$] as the catalyst to give the corresponding β-phenylketones in high yields and enantioselectivities (70–99% yield, 98–99% *ee*; Table 2, entries 1–3). Furthermore, acyclic enones also reacted successfully under the same conditions (78–82% yield; Table 2, entries 4–6), although the enantioselectivities were somewhat lower (81–86% *ee*). It is worthy to note that (*E*) and (*Z*)-enones give the opposite enantiomers as the major product, which indicates that the catalyst efficiently recognizes the olefin geometry of the substrates (Table 2, entry 4 versus entry 6). With regard to the nucleophilic component, a sterically and electronically diverse array of aryl groups can be installed onto enone **1a** in uniformly high yield (81–97%) with excellent enantioselectivity (99%; Table 2, entries 7–12).

To gain some insight into the mechanism, we conducted a reaction of **1a** with phenylboroxine in the presence of [{Rh(OH)(cod)}$_2$] as the catalyst and the reaction was quenched with [D_4]acetic acid instead of water [Eq. (2)].



Under these conditions, product **2aa** was obtained in 77% yield with 85% deuterium incorporation only at the α-position adjacent to the quaternary carbon stereocenter (d.r. = 6.7:1); this result indicates that the primary product during the catalysis exists as a form of enolate, which is protonated upon aqueous work-up. On the basis of this result, a proposed catalytic cycle of the reaction of **1a** with phenylboroxine is illustrated in Figure 1.[1d] Thus, phenylrhodium

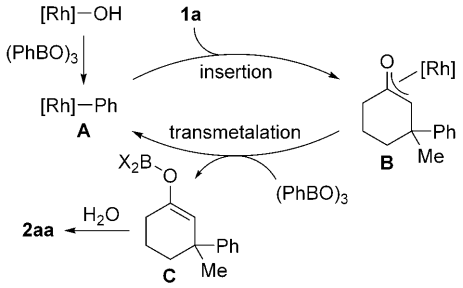
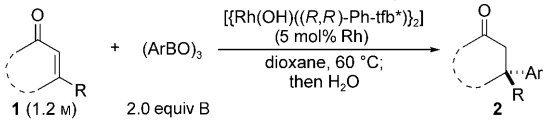


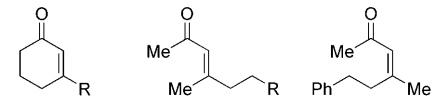
Figure 1. Proposed catalytic cycle for the rhodium-catalyzed 1,4-addition of phenylboroxine to **1a**. [Rh] = [{Rh(diene)}].

species **A**, initially generated by transmetalation between phenylboroxine and a hydroxorhodium complex, undergoes insertion of **1a** to give oxa-π-allylrhodium intermediate **B**. Direct transmetalation of this intermediate with phenylboroxine regenerates phenylrhodium **A** along with the formation of boron enolate **C**,[16] which becomes **2aa** after addition of water at the end of the reaction.

We also carried out the reaction of **1a** with phenylboroxine in the presence of both [{Rh(OH)(cod)}$_2$] and [{Rh(OH)((*R*,*R*)-Ph-tfb*)}$_2$] (2.5 mol% Rh for each), and found that product **2aa** was obtained in 90% yield with 79% *ee* (*R*) [Eq. (3)]. Because [{Rh(OH)(cod)}$_2$] gives racemic **2aa**, and [{Rh(OH)((*R*,*R*)-Ph-tfb*)}$_2$] gives **2aa** with 99% *ee* (*R*), the rhodium complex with the (*R*,*R*)-Ph-tfb* ligand is approximately four times more active than the complex with the cod ligand, assuming that these complexes work as

Table 2: Rhodium-catalyzed asymmetric 1,4-addition of arylboroxines to β,β-disubstituted α,β-unsaturated ketones **1**: Scope.





Entry	1	Ar	*t* [h]	Product	Yield [%][a]	*ee* [%][b]
1	**1a**	Ph	24	(*R*)-**2aa**	99	99
2	**1b**	Ph	48	(*R*)-**2ba**	88	99
3	**1c**	Ph	48	(*R*)-**2ca**	70	98
4	(*E*)-**1d**	Ph	60	(*S*)-**2da**	82	86
5	(*E*)-**1e**	Ph	60	(*S*)-**2ea**	80[c]	81
6	(*Z*)-**1d**	Ph	60	(*R*)-**2da**	78	86
7	**1a**	4-MeOC$_6$H$_4$	48	(*R*)-**2ab**	81	99
8	**1a**	4-FC$_6$H$_4$	24	(*R*)-**2ac**	94	99
9	**1a**	4-ClC$_6$H$_4$	24	(*R*)-**2ad**	97	99
10	**1a**	3-ClC$_6$H$_4$	24	(*R*)-**2ae**	85	99
11	**1a**	2-ClC$_6$H$_4$	24	(*R*)-**2af**	87	99
12	**1a**	2-naphthyl[d]	48	(*R*)-**2ag**	95	99

[a] Yield of isolated product. [b] Determined by chiral HPLC with hexane/2-propanol. [c] Determined by ^{1}H NMR spectroscopy against an internal standard after chromatographic purification. [d] 1.2 equivalents B.

catalysts independently. This high activity of [{Rh(OH)((*R*,*R*)-Ph-tfb*)}$_2$] could be attributed to the acceleration of transmetalation and insertion steps owing to the electron-withdrawing nature of (*R*,*R*)-Ph-tfb*.[17]

In summary, we have developed a rhodium-catalyzed 1,4-addition of arylboroxines to β,β-disubstituted α,β-unsaturated ketones. Highly efficient asymmetric catalysis has also been described to create quaternary carbon stereocenters by employing a chiral tetrafluorobenzobarrelene as the ligand. Future studies will explore further expansion of the substrate scope.

Experimental Section

General procedure for Table 2: A solution of [{Rh(OH)((*R*,*R*)-Ph-tfb*)}$_2$] (9.0 mg, 18 μmol Rh), enone **1** (0.36 mmol), and arylboroxine (0.72 mmol) in dioxane (0.30 mL) was stirred for 24–60 h at 60 °C, and the reaction was quenched with water (50 μL). The mixture was passed through a pad of silica gel with EtOAc and the solvent was removed under vacuum. The residue was purified by preparative TLC on silica gel to afford 1,4-adduct **2**.

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