Asymmetric Catalysis

Highly Chemo- and Enantioselective Arylative Cyclization of Alkyne-Tethered Electron-Deficient Olefins Catalyzed by Rhodium Complexes with Chiral Dienes**

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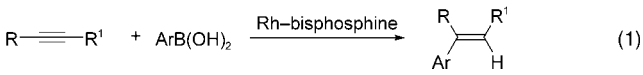
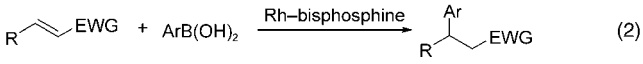
Multiple carbon–carbon bond-forming reactions catalyzed by transition metals are a powerful method for the construction of structurally complex molecules in a convergent manner from relatively simple precursors.[1] Compounds that bear two or more electrophilic sites at appropriate positions are potentially useful for the preparation of complex cyclic materials by sequential addition and cyclization of nucleophiles in a cascade manner.[2,3] However, if these electrophilic sites are all reactive toward the incoming nucleophile, chemoselectivity of the initial nucleophilic attack becomes an important issue. In this context, alkyne-tethered electron-deficient olefins should be an interesting class of substrates, as both internal alkynes[4] and electron-deficient olefins[5] are good electrophiles in a rhodium–bisphosphine-catalyzed addition of aryl boronic acids [Eq. (1) and Eq. (2); EWG = electron-withdrawing group]. Herein, we describe how a rhodium–diene catalyst, rather than a rhodium–bisphosphine catalyst, can effectively catalyze an arylative cyclization of alkyne-tethered electron-deficient olefins with high chemoselectivity, and that high enantioselectivity can also be attained by the use of chiral diene ligands in this process (Scheme 1).



(1)



(2)

In an initial investigation, we employed alkyne-tethered enoate **1a** as a model substrate in combination with $PhB(OH)_2$ to examine the effect of the ligand in the presence of 6 mol% rhodium (Table 1). Although the reaction proceeds smoothly when (*S*)-binap is used as a ligand, a mixture

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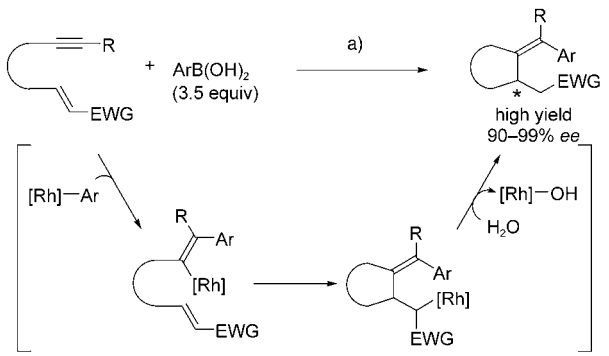
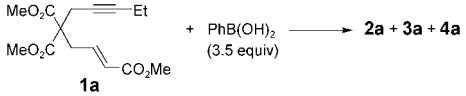


Scheme 1. a) [{RhCl(C_2H_4)$_2$}$_2$] (6 mol% Rh), (*S*,*S*)-Bn-bod* (6.5 mol%), KOH (0.3 equiv), dioxane/H_2O (10:1), 60°C, 4 h.

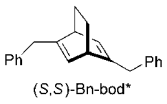
Table 1: Rhodium-catalyzed asymmetric arylative cyclization of model substrate **1a**: effect of the ligand.[a]



1a

	Yield [%]		
	2a	**3a**	**4a**
(*S*)-binap	23 (95% *ee*)	22	45
dppf	3	9	32
(*S*,*S*)-Bn-bod*	83 (99% *ee*)	5	5
cod	72	3	8

[a] Conditions: [{RhCl(C_2H_4)$_2$}$_2$] (6 mol% Rh), ligand (6.5 mol%), KOH (0.3 equiv), dioxane/H_2O (10:1), 60°C, 4 h. (*S*)-binap = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl, dppf = 1,1′-bis(diphenylphosphino)ferrocene, cod = cycloocta-1,5-diene.

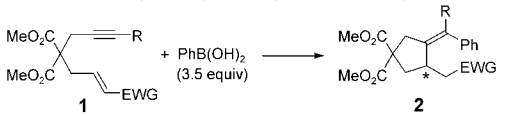


(*S*,*S*)-Bn-bod*

of three different phenylated products (**2a**, **3a**,[6] and **4a**) are obtained rather nonselectively (23, 22, and 45% yields, respectively). The use of other bisphosphine ligands such as dppf leads to somewhat lower reactivity (51% conversion), which tends to give 1,4-adduct **4a** as the major product. In contrast, the use of chiral diene ligand (*S*,*S*)-Bn-bod*[2f,7] dramatically changes the course of the reaction and preferentially leads to product **2a**, which is obtained in 83% yield and with 99% *ee* (compare with 95% *ee* when (*S*)-binap is used), with a small amount of **3a** and **4a** (5% yield for each) also formed. The employment of other diene ligands such as cod also provides compound **2a** as the major product.

Under these conditions with Rh(*S*,*S*)-Bn-bod* as a catalyst, several alkyne-tethered electron-deficient olefins can be successfully used as shown in Table 2. Thus, not only methyl or ethyl esters (entries 1–3) but also phenyl ketone (entry 4) can be employed as an electron-withdrawing group

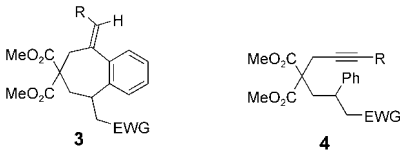
Table 2: Rhodium-catalyzed arylative cyclization: scope of substrate **1**.[a]



1 **2**

Entry	Substrate	R; EWG	Yield [%][b]	*ee* [%][c]	$[\alpha]_D^{20}$ (in $CHCl_3$)
1	**1a**	Et; CO_2Me	93	99	−65.8 (*c* = 0.97)
2	**1b**	Me; CO_2Me	86	99	−67.0 (*c* = 0.97)
3	**1c**	Et; CO_2Et	89	99	−73.5 (*c* = 1.02)
4	**1d**	Et; COPh	87	90	−90.2 (*c* = 1.45)

[a] Conditions: [{RhCl(C_2H_4)$_2$}$_2$] (6 mol% Rh), (*S*,*S*)-Bn-bod* (6.5 mol%), KOH (0.3 equiv), dioxane/H_2O (10:1), 60°C, 4 h. [b] Contaminated with up to 10% of **3** and **4** (≈1:1) in all cases. [c] *ee* values were determined by HPLC on a chiralpak AD-H column.

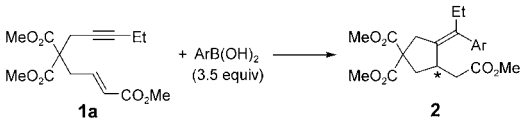


3 **4**

on the olefin to furnish five-membered carbocycles with high chemo- and enantioselectivities (90–99% *ee*).

With respect to the scope of the nucleophilic component, sterically and electronically diverse arrays of aryl boronic acids can be used under the same conditions to afford the five-membered products uniformly with high chemoselectivity and with excellent enantioselectivity (Table 3; 97–99% *ee*).

Table 3: Rhodium-catalyzed asymmetric arylative cyclization: scope of the aryl boronic acid.[a]

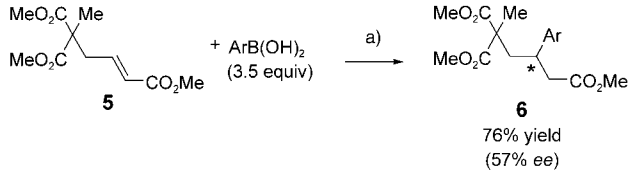


1a **2**

Entry	Ar	Yield [%][b]	*ee* [%][c]	$[\alpha]_D^{20}$ (in $CHCl_3$)
1	Ph	93	99	−65.8 (*c* = 0.97)
2	4-MeC_6H_4	87	99	−87.7 (*c* = 1.11)
3	4-$MeOC_6H_4$	86	99	−90.9 (*c* = 1.14)
4	4-FC_6H_4	88	97	−72.5 (*c* = 1.28)
5	3-ClC_6H_4	84	99	−77.4 (*c* = 1.29)
6	3,5-$Me_2C_6H_3$	83	99	−63.5 (*c* = 1.07)
7	2-naphthyl	80	98	−82.8 (*c* = 0.94)

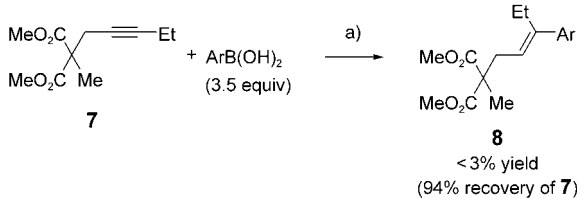
[a] Conditions: [{RhCl(C_2H_4)$_2$}$_2$] (6 mol% Rh), (*S*,*S*)-Bn-bod* (6.5 mol%), KOH (0.3 equiv), dioxane/H_2O (10:1), 60°C, 4 h. [b] Contaminated with 7–11% of **3**/**4** (≈1:1) in all cases. [c] *ee* values were determined by HPLC on a Chiralpak AD-H column.

To gain insight into the origin of the difference in chemoselectivity between rhodium–bisphosphine and rhodium–diene catalysts in these arylative cyclization reactions, we conducted the following experiments. Reaction of α,β-enoate **5** with an aryl boronic acid (Ar = 3,5-$Me_2C_6H_3$) in the presence of 6 mol% Rh–(*S*)-binap produced the corresponding 1,4-adduct **6** in 76% yield (Scheme 2). In contrast, the use of alkyne **7** as a substrate under Rh–(*S*)-binap catalysis resulted in 94% recovery of **7** with almost no formation of



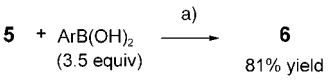
Scheme 2. a) [{RhCl(C_2H_4)$_2$}$_2$] (6 mol% Rh), (*S*)-binap (6.5 mol%), KOH (0.3 equiv), dioxane/H_2O (10:1), 60°C, 4 h.

arylated product **8** (Scheme 3). Compared to these results, both α,β-enoate **5** and alkyne **7** reacted with the aryl boronic acid (Ar = 3,5-$Me_2C_6H_3$) in the presence of 6 mol% Rh–cod

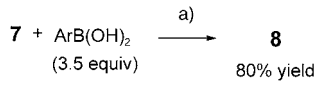


Scheme 3. a) [{RhCl(C_2H_4)$_2$}$_2$] (6 mol% Rh), (*S*)-binap (6.5 mol%), KOH (0.3 equiv), dioxane/H_2O (10:1), 60°C, 4 h.

catalyst to furnish the corresponding arylated products **6** and **8** in over 80% yield (Scheme 4 and Scheme 5). To distinguish the reactivity between the two, we conducted a competition

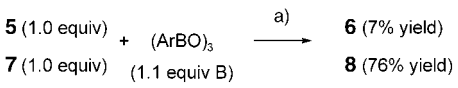


Scheme 4. a) [{RhCl(cod)}$_2$] (6 mol% Rh), KOH (0.3 equiv), dioxane/H_2O (10:1), 60°C, 4 h.



Scheme 5. a) [{RhCl(cod)}$_2$] (6 mol% Rh), KOH (0.3 equiv), dioxane/H_2O (10:1), 60°C, 4 h.

experiment using a 1:1 mixture of **5** and **7** with 1.1 equivalents of aryl boron species (Ar = 3,5-$Me_2C_6H_3$) in the presence of 6 mol% Rh–cod (Scheme 6). Under these conditions, α,β-enoate **5** was recovered in 90% yield and alkyne **7** was completely comsumed to give product **8** in 76% yield. These results indicate that a Rh–bisphosphine catalyzes the 1,4-addition of α,β-enoates more effectively than the arylation of alkynes, and that a Rh–diene catalyst displays higher activity



Scheme 6. a) [{RhCl(cod)}$_2$] (6 mol% Rh), KOH (0.3 equiv), dioxane/H_2O (10:1), 60°C, 4 h.

in the arylation of alkynes than in the 1,4-addition of α,β-enoates. This conclusion should partially explain the observed high chemoselectivity in the arylative cyclization of **1** with a rhodium–diene catalyst.[8]

In summary, we have developed a rhodium-catalyzed arylative cyclization of alkyne-tethered electron-deficient olefins with aryl boronic acids, and high chemo- and enantioselectivities have been observed by the use of a chiral diene ligand. We hope to further develop chiral diene ligands and their application to various transition-metal-catalyzed asymmetric processes.

Experimental Section

Procedure for Table 1: An aqueous solution of KOH (0.3 M in H_2O; 0.2 mL, 60 μmol) was added to a solution of [{RhCl(C_2H_4)$_2$}$_2$] (2.3 mg, 12 μmol Rh) and ligand (13 μmol) in 1,4-dioxane (1.0 mL), and the mixture was stirred for 5 min at room temperature. $PhB(OH)_2$ (85.4 mg, 0.70 mmol) and **1a** (59.3 mg, 0.20 mmol) were then added along with additional 1,4-dioxane (1.0 mL), and the resulting solution was stirred for 4 h at 60°C. The reaction mixture was directly passed through a pad of silica gel with Et_2O, and the solvent was removed under vacuum. The residue was purified by preparative TLC (silica gel) with a mixture of Et_2O/hexane (1:1) as eluent.

With (*S*)-binap as ligand, a mixture of **2a**, **3a**, and **4a** (26:24:50, as determined by ^{1}H NMR spectroscopy) was obtained as a pale yellow oil (67.7 mg, 90% combined yield). The *ee* value for **2a** was determined on a Daicel Chiralpak AD-H column with hexane/2-propanol (90:10) and a flow rate of 0.3 mL min^{-1}. Retention times: 29.8 min ((+)-enantiomer) and 33.5 min ((−)-enantiomer, 95% *ee*).

With (*S*,*S*)-Bn-bod* as ligand, a mixture of **2a**, **3a**, and **4a** (90:5:5, as determined by ^{1}H NMR spectroscopy) was obtained as a yellow oil (69.5 mg, 93% combined yield). **2a**: 99% *ee*; $[\alpha]_D^{20} = -65.8$ ($c = 0.97$, $CHCl_3$).

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[8] This conclusion does not necessarily fully explain the low chemoselectivity in the reaction of **1a** with phenylboronic acid in the presence of a Rh–bisphosphine catalyst (Table 1).

