Asymmetric 1,4-Addition of Arylboronic Acids to α,β-Unsaturated Aldehydes Catalyzed by a Chiral Diene–Rhodium Complex

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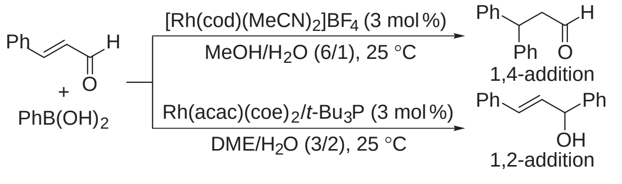
Asymmetric 1,4-addition of arylboronic acids to α,β-unsaturated aldehydes proceeded in the presence of a rhodium catalyst (3 mol %) coordinated with a chiral diene ligand ((*R*,*R*)-Bn-bod*) to give the corresponding β-arylaldehydes with perfect 1,4-selectivity and with 88–97% enantioselectivity.

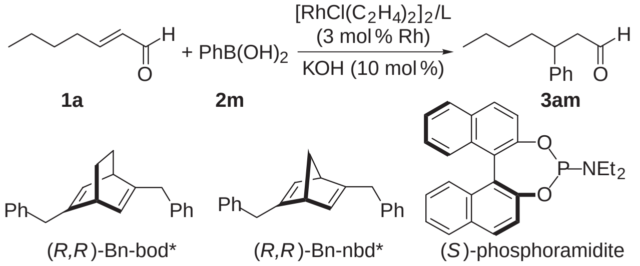
Chiral diene ligands have found wide applications in catalytic asymmetric reactions, especially in rhodium-catalyzed carbon–carbon bond forming reactions.[1,2] The chiral diene–rhodium catalysts have been demonstrated to possess advantages over the chiral phosphine–rhodium catalysts in that they have higher catalytic activity as well as higher enantioselectivity in asymmetric arylation of imines with arylboronic acids[3] and in asymmetric 1,4-addition to some α,β-unsaturated carbonyl compounds.[4] In the rhodium-catalyzed asymmetric addition of arylboronic acids to alkynals and alkyne-enoates, the diene ligand showed unique chemoselectivity leading to preferential formation of arylative cyclization products.[5] On the other hand, Miyaura reported in 2000[6] that the selectivity in giving 1,4-addition product or 1,2-addition product can be switched by a proper choice of reaction conditions in rhodium-catalyzed addition of phenylboronic acid to cinnamaldehyde (Scheme 1).[7] It is significant that an exclusive 1,4-addition was realized in the presence of a cationic rhodium catalyst coordinated with cod in aqueous methanol as a solvent. Based on this report, we have studied rhodium-catalyzed asymmetric 1,4-addition of arylboronic acids to α,β-unsaturated aldehydes by use of the chiral diene ligands. The asymmetric 1,4-addition to enals has been reported[8] to be catalyzed by $[Rh((R)\text{-binap})(nbd)]BF_4$, but the selectivity giving the 1,4-addition products is not high. A recent communication by Carreira[9] prompted us to report our own results.



Scheme 1. 1,4-Addition vs 1,2-addition reported by Miyaura.

In the first set of experiment, addition of phenylboronic acid (**2m**) to 2-heptenal (**1a**) was examined under several reaction conditions (Table 1). The 1,4-addition giving 3-phenylheptanal (**3am**) proceeded smoothly in the presence of 3 mol % of $[Rh(OH)(cod)]_2$ in a mixed solvent consisting of MeOH/THF/H_2O (12/3/2) at 30 °C (Entry 1). This is in good agreement with the Miyaura's report[6] that the 1,4-addition takes place in the presence of a rhodium/diene catalyst in aqueous methanol. A lower yield of the 1,4-addition product **3am** was observed in the reaction carried out in dioxane/H_2O (10/1) (Entry 2), which is a solvent system often used for rhodium-catalyzed 1,4-addition reactions.[10] The 1,4-addition catalyzed by $[Rh(OH)(cod)]_2$ was found to be accelerated by addition of a catalytic amount (10 mol %) of potassium hydroxide (Entries 3 and 4). Confirming that a rhodium/diene complex catalyzes the selective 1,4-addition to enal, chiral diene ligands (*R*,*R*)-Bn-bod*[1b] and Bn-nbd*[1a] were examined for their enantioselectivity. In the reaction at 30 °C, both of the two dienes gave (*S*)-**3am** with around 90% ee (Entries 5 and 6). The best result was obtained in the reaction with (*R*,*R*)-Bn-bod* at 10 °C, which gave 88% yield of (*S*)-**3am** with 93% ee[11,12] (Entry 7). Under otherwise the same reaction conditions, the rhodium complexes of a phosphoramidite[13] and binap[14] did not catalyze the asymmetric 1,4-addition efficiently (Entries 8 and 9).

Table 1. Rhodium-catalyzed addition of phenylboronic acid (**2m**) to 2-heptenal (**1a**)[a]

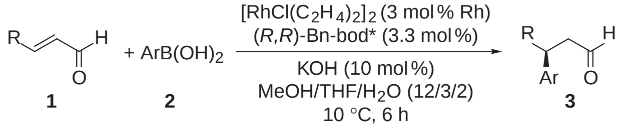


Entry	Ligand on Rh	Solvent	Temp /°C	Time /h	Yield[b] /%	% ee[c]
1	cod[d,e]	MeOH/THF/H_2O[f]	30	1	88	—
2	cod[d,e]	Dioxane/H_2O[g]	30	1	35	—
3	cod[d,e]	MeOH/THF/H_2O[f]	10	1	64	—
4	cod[d]	MeOH/THF/H_2O[f]	10	1	91	—
5	(*R*,*R*)-Bn-bod*	MeOH/THF/H_2O[f]	30	1	85	90 (*S*)
6	(*R*,*R*)-Bn-nbd*	MeOH/THF/H_2O[f]	30	1	82	89 (*S*)
7	(*R*,*R*)-Bn-bod*	MeOH/THF/H_2O[f]	10	6	88	93 (*S*)
8	Phosphoramidite[h]	MeOH/THF/H_2O[f]	30	1	58	26 (*R*)
9	(*R*)-binap	MeOH/THF/H_2O[f]	30	1	<3[i]	—

[a] The reaction was carried out with enal **1a** (0.20 mmol), arylboronic acid **2m** (0.40 mmol), KOH (0.02 mmol), $[RhCl(C_2H_4)_2]_2$ (0.0060 mmol Rh), and a ligand (0.0066 mmol) unless otherwise noted. [b] Isolated yield after silica gel chromatography. [c] Determined by HPLC analysis with a chiral stationary phase column (Chiralpak AS) after reduction into 3-phenylheptanol. [d] $[Rh(OH)(cod)]_2$ was used. [e] In the absence of KOH. [f] The ratio is 12/3/2. [g] The ratio is 10/1. [h] 0.0132 mmol. [i] Starting enone **1a** was recovered in a high yield.

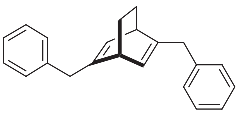
As illustrated in Table 2, the present asymmetric 1,4-addition is applicable to a broad range of arylboronic acids and α,β-unsaturated aldehydes. In the presence of 3 mol % of the rhodium/(*R*,*R*)-Bn-bod* catalyst, 2-heptenal (**1a**) underwent the addition of a variety of arylboronic acids (Entries 2–5). Phenylboronic acids substituted with 4-methoxy, 4-chloro, and

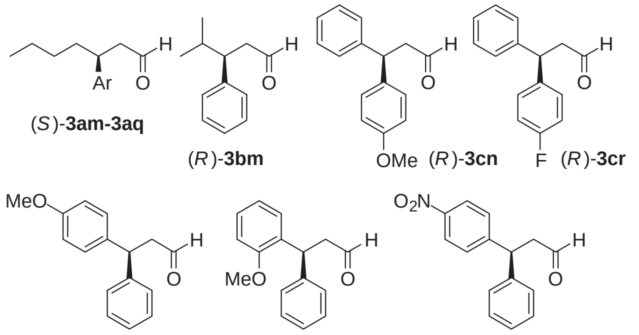
Table 2. Asymmetric 1,4-addition of arylboronic acids **2** to enals **1** catalyzed by Rh/(R,R)-Bn-bod*[a]



1a: R = n-Bu
1b: R = i-Pr
1c: R = Ph
1d: R = 4-MeOC$_6$H$_4$
1e: R = 2-MeOC$_6$H$_4$
1f: R = 4-NO$_2$C$_6$H$_4$

2m: Ar = Ph
2n: Ar = 4-MeOC$_6$H$_4$
2o: Ar = 4-ClC$_6$H$_4$
2p: Ar = 2-MeC$_6$H$_4$
2q: Ar = 2-naphthyl
2r: Ar = 4-FC$_6$H$_4$
2q: Ar = 2-MeOC$_6$H$_4$


(R,R)-Bn-bod*



(S)-**3am**-**3aq** (R)-**3bm** (R)-**3cn** (R)-**3cr**

(S)-**3dm** (S)-**3em** (S)-**3fm**

Entry	R in Enal **1**	Ar in ArB(OH)$_2$ **2**	Yield[b] /%	% ee[c]
1	n-Bu (**1a**)	Ph (**2m**)	88 (**3am**)	93 (S)
2	n-Bu (**1a**)	4-MeOC$_6$H$_4$ (**2n**)	94 (**3an**)	88 (S)
3	n-Bu (**1a**)	4-ClC$_6$H$_4$ (**2o**)	88 (**3ao**)	97 (S)
4	n-Bu (**1a**)	2-MeC$_6$H$_4$ (**2p**)	95 (**3ap**)	90 (S)
5	n-Bu (**1a**)	2-naphthyl (**2q**)	90 (**3aq**)	88 (S)
6[d]	i-Pr (**1b**)	Ph (**2m**)	83 (**3bm**)	92 (R)
7	Ph (**1c**)	4-MeOC$_6$H$_4$ (**2n**)	88 (**3cn**)	90 (R)
8	Ph (**1c**)	4-FC$_6$H$_4$ (**2r**)	84 (**3cr**)	90 (R)
9	4-MeOC$_6$H$_4$ (**1d**)	Ph (**2m**)	86 (**3dm**)[e]	90 (S)
10	2-MeOC$_6$H$_4$ (**1e**)	Ph (**2m**)	93 (**3em**)	90 (S)
11[f]	4-NO$_2$C$_6$H$_4$ (**1f**)	Ph (**2m**)	92 (**3fm**)	91 (S)

[a]The reaction was carried out at 10 °C for 6 h with enal **1** (0.20 mmol), arylboronic acid **2** (0.40 mmol), KOH (0.02 mmol), [RhCl(C$_2$H$_4$)$_2$]$_2$ (0.0060 mmol Rh), and (R,R)-Bn-bod* (0.0066 mmol) in a mixed solvent consisting of MeOH (0.60 mL), THF (0.15 mL), and H$_2$O (0.10 mL). [b]Isolated yield after silica gel chromatography. [c]Determined by HPLC analysis with a chiral stationary phase column after reduction into alcohols (See Supporting Information). [d]Reaction with 0.80 mmol of PhB(OH)2. [e]Enantiomer of **3cn**. [f]For 3 h.

2-methyl, all gave high yields of the corresponding (S)-3-arylheptanals with high enantioselectivity. Asymmetric addition to 4-methyl-2-pentenal (**1b**) proceeded as well, giving (R)-**3bm**[15] of 92% ee (Entry 6). Asymmetric synthesis of 3,3-diarylpropanals is also possible by the rhodium-catalyzed 1,4-addition of arylboronic acids to 3-arylpropenals (**1c**–**1f**). Thus, the reaction of cinnamaldehyde (**1c**) with both electron-rich boronic acid [4-MeOC$_6$H$_4$B(OH)$_2$ **2n**] and electron-poor boronic acid [4-FC$_6$H$_4$B(OH)$_2$ **2r**] proceeded smoothly to give the corresponding 3-phenyl-3-(substituted phenyl)propanals with 90% ee (Entries 7 and 8). The chiral 3,3-diarylpropanals of around 90% ee were also obtained by the other combination, that is, the addition of phenylboronic acid (**2m**) to 3-(substituted phenyl)propenals (**1d**–**1f**) (Entries 9–11). Both enantiomers of a 3,3-diarylpropanal ((R)-**3cn** and (S)-**3dm**) were readily obtained by varying the combination for a single enantiomer of the chiral diene ligand (R,R)-Bn-bod* (see Entries 7 and 9).

In summary, we have shown that asymmetric 1,4-addition of arylboronic acids to α,β-unsaturated aldehydes is efficiently catalyzed by a rhodium complex coordinated with a chiral diene ligand.

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