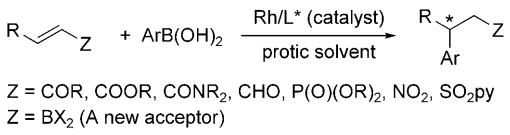
Rhodium Catalysis

DOI: 10.1002/ange.201004980

Rhodium-Catalyzed Asymmetric Conjugate Addition of Arylboroxines to Borylalkenes: Asymmetric Synthesis of β-Arylalkylboranes**

*Keigo Sasaki and Tamio Hayashi**

The transition-metal-catalyzed asymmetric conjugate addition of organometallic reagents to electron-deficient olefins provides a powerful tool for carbon–carbon bond formation with the simultaneous introduction of a new stereogenic carbon center at the β position,[1] and the use of chiral rhodium catalysts for the asymmetric addition of arylboron reagents has developed rapidly[2] since it was first reported in 1998 where the acceptors were β-substituted α,β-unsaturated ketones.[3] This asymmetric catalysis by rhodium has been successfully extended to the addition to olefins bearing ester,[4] amide,[5] aldehyde,[6] phosphonate,[7] nitro,[8] and sulfone[9] groups (Scheme 1). Herein, we wish to report that olefins substituted with a boryl group are good substrates for

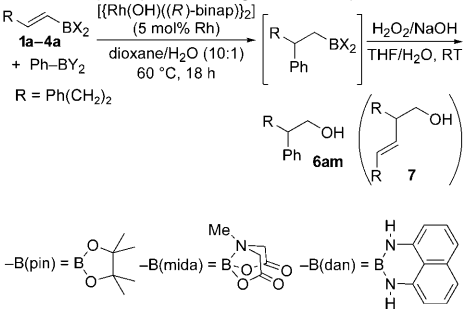


Scheme 1. Rhodium-catalyzed asymmetric conjugate addition to carbon–carbon double bonds.

the rhodium-catalyzed asymmetric addition reaction, thus giving chiral β-arylalkylboranes with high enantioselectivities. The high efficiency of the reaction was achieved by use of the 1,8-naphthalenediaminatoboryl group, B(dan), as a masking group for alkenylboronic acids, which has recently been developed by Suginome and co-workers.[10,11]

Considering that the rhodium-catalyzed conjugate addition has wide applicability for a variety of functionalized carbon–carbon multiple bonds[2] and that alkenylboron derivatives are reactive substrates, for example, as dienophiles in Diels–Alder reactions,[12] we anticipated that alkenylboron derivatives would be capable of being Michael acceptors in the rhodium-catalyzed reactions. First, we examined 4-phenyl-1-butenylboronic acid (**1a**) for the addition of phenylboroxine (**5m**, 3 equiv B) in the presence of [{Rh(OH)((*R*)-binap)}$_2$] as a catalyst (5 mol% Rh) in dioxane/H_2O (10:1) at 60 °C for 18 hours (Table 1), which is one of our sets of standard reaction conditions for the rhodium-catalyzed asymmetric addition reactions.[13] The crude reaction mixture was subjected to oxidation with H_2O_2 and NaOH

Table 1: Addition of phenylboron reagents to borylalkenes.[a]



Entry	BX_2 in borylalkene	Ph–BY_2 (**5**)	Yield [%][b]
1	$B(OH)_2$ (**1a**)	$(PhBO)_3$ (**5m**)	4[c]
2	B(pin) (**2a**)	$(PhBO)_3$ (**5m**)	9[c]
3	B(mida) (**3a**)	$(PhBO)_3$ (**5m**)	0
4	B(dan) (**4a**)	$(PhBO)_3$ (**5m**)	77
5	B(dan) (**4a**)	$PhB(OH)_2$	75
6	B(dan) (**4a**)	PhB(pin)	26
7	B(dan) (**4a**)	$PhBF_3K$	0
8	B(dan) (**4a**)	Ph_4BNa	0

[a] Reaction conditions: borylalkene (0.20 mmol), Ph–BY_2 (0.60 mmol B), catalyst (10 mmol Rh, 5 mol%), dioxane/H_2O (10:1, 1.1 mL). [b] Yield of isolated alcohol **6am**. [c] 6-Phenyl-2-(2-phenylethyl)-3-hexenol (**7**) was formed in 3% yield in both entries 1 and 2.

to give a 4% yield of 2,4-diphenyl-1-butanol (**6am**) as the desired conjugate-addition product together with 3% yield of 6-phenyl-2-(2-phenylethyl)-3-hexenol (**7**), which resulted from the homo addition of **1a** (Table 1, entry 1). The low yield of alcohols **6am** and **7** is due in part to decomposition of the alkylboronic acids, which are generated by cross and homo addition, probably through transmetalation to rhodium(I) under the reaction conditions. In order to inhibit the homo addition and the decomposition of the cross-addition product, the alkenylboronic acid derivatives **2a**–**4a**, which are expected to be less reactive than **1a** in the transmetalation to rhodium(I), were examined under similar conditions. The reaction of pinacol ester[14] **2a** gave a slightly improved yield of **6am**, but mida boronate[15] **3a** did not produce **6am**

[*] K. Sasaki, Prof. Dr. T. Hayashi
Department of Chemistry, Graduate School of Science
Sakyo, Kyoto 606-8502 (Japan)
Fax: (+81) 75-753-3988
E-mail: thayashi@kuchem.kyoto-u.ac.jp

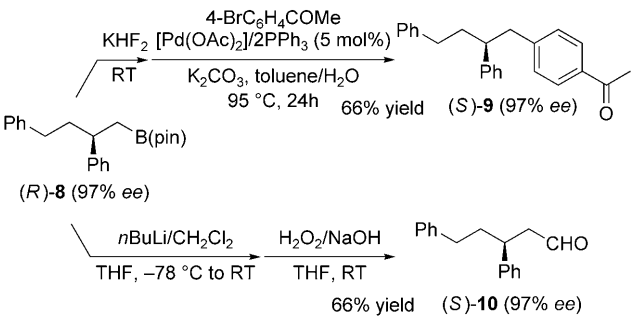
[**] This work has been supported by a Grant-in-Aid for Scientific Research (S) (19105002) from the MEXT (Japan). K.S. thanks the JSPS for Young Scientists for a research fellowship. We thank Takasago International Corporation for the gift of (*R*)-DTBM-segphos.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201004980.

(Table 1, entries 2 and 3). The use of RCH=CHB(dan)[10] (**4a**) greatly improved the selectivity giving the cross-addition product **6am**. Thus, the reaction of **4a** with **5m** gave, after oxidation, 77% yield (based on **4a**) of the alcohol **6am** with no formation of **7** (Table 1, entry 4). The use of $PhB(OH)_2$ in place of boroxine **5m** gave a slightly lower yield of **6am** (Table 1, entry 5). PhB(pin) did not improve the yield of alcohol **6am**, and the addition was not observed at all with $PhBF_3K$[16] or Ph_4BNa[17] (Table 1, entries 6–8).

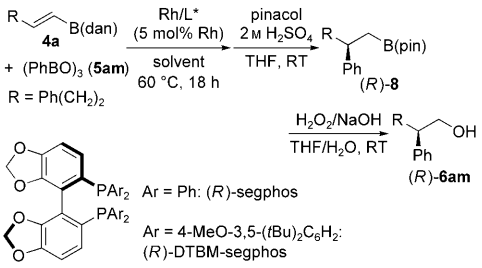
In the reaction of **4a** with **5m**, the conjugate-addition product before oxidation was isolated as a pinacol borane **8** in high yield by treatment of the crude reaction product with pinacol under acidic conditions, and the oxidation of isolated pinacol borane **8** gave a higher yield of alcohol **6am** than the direct oxidation of crude alkylB(dan). Thus, the rhodium-catalyzed addition under the same conditions as in Table 1, entry 4, followed by pinacol borane formation, gave 93% yield of **8** and 87% yield of **6am** (based on **4a**; Table 2, entry 1). The enantioselectivity of the present asymmetric addition to alkenylB(dan) **4a** is strongly dependent on the solvent and chiral ligand employed (Table 2). Although the yield was high in the reaction with $[\{Rh(OH)((R)\text{-binap})\}_2]$ as catalyst in dioxane/H_2O, the enantiomeric purity was not particularly high (77% *ee*; Table 2, entry 1). Of the alcohols examined as solvent, *t*BuOH gave the best results (89% yield, 87% *ee*) with $[\{Rh(OH)((R)\text{-binap})\}_2]$ as a catalyst (Table 2, entries 2–5). The in situ generation of the Rh/(*R*)-binap catalyst from $[Rh(acac)(C_2H_4)_2]$ and (*R*)-binap provided essentially the same result (Table 2, entry 6). The enantioselectivity was a little higher (90% *ee*) with (*R*)-segphos[18] as a ligand (Table 2, entry 7), and (*R*)-DTBM-segphos[18] showed the highest selectivity (97% *ee*) although the yields are lower because of incomplete conversion of starting **4a** (Table 2, entries 8 and 9). The absolute configuration of **6am** was determined to be *R* by comparison of its optical rotation with the reported value.[19]

In addition to the oxidation into alcohol **6am**, the pinacol borane (*R*)-**8** obtained here with high *ee* (97%) was readily applied to C–C bond-forming reactions by taking advantage of the wide synthetic utility of alkylboronates (Scheme 2).



Scheme 2. Synthetic reactions of chiral alkylborane (*R*)-**8**.

Table 2: Asymmetric addition of phenylboroxine (**5m**) to alkenylborane **4a**.[a]



Entry	Catalyst	Solvent	Yield [%][b]	*ee* [%][c]
1	$[\{Rh(OH)((R)\text{-binap})\}_2]$	dioxane/H_2O (10:1)	87 (93)[d]	77
2	$[\{Rh(OH)((R)\text{-binap})\}_2]$	MeOH	50	89
3	$[\{Rh(OH)((R)\text{-binap})\}_2]$	EtOH	37	81
4	$[\{Rh(OH)((R)\text{-binap})\}_2]$	*i*PrOH	61	72
5	$[\{Rh(OH)((R)\text{-binap})\}_2]$	*t*BuOH	89	87
6	$[Rh(acac)(C_2H_4)_2]$/(*R*)-binap	*t*BuOH	84	87
7	$[Rh(acac)(C_2H_4)_2]$/(*R*)-segphos	*t*BuOH	82	90
8	$[Rh(acac)(C_2H_4)_2]$/(*R*)-DTBM-segphos	*t*BuOH	56	97
9[e]	$[Rh(acac)(C_2H_4)_2]$/(*R*)-DTBM-segphos	*t*BuOH	77 (82)[d]	97

[a] Reaction conditions: alkenylborane **4a** (0.20 mmol), boroxine **5m** (0.20 mmol, 3 equiv of B), catalyst (10 mmol Rh, 5 mol%), solvent (1.0 mL). [b] Yield of isolated alcohol **6am** (based on **4a**). [c] Determined by HPLC analysis (Chiralpak AS-H) of **6am**. [d] Yield of isolated alkylboronic acid pinacol ester **8**. [e] Reaction with 0.40 mmol of **5m** and 10 mol% of the catalyst for 40 h. binap = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl.

Thus, for example, the alkyltrifluoroborate generated from **8** was subjected to the palladium-catalyzed cross-coupling reaction under Molander conditions[20] to give a 66% yield (based on **8**) of (*S*)-**9** without loss of enantiomeric purity. One-carbon homologation with a lithium carbenoid according to Matteson's protocol[21] followed by the oxidation gave aldehyde (*S*)-**10** with the same *ee*.

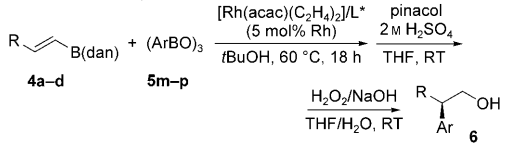
Table 3 summarizes the results obtained for the asymmetric addition of arylboroxines **5** to alkenylB(dan) **4**. Aryl groups (**5n**–**5p**) having electronically different substituents were successfully introduced onto **4a** to give, after oxidation, the corresponding alcohols **6** with high enantioselectivity (93–97% *ee*) using segphos or DTBM-segphos (Table 3, entries 2–4). Conjugate addition to RCH=CHB(dan)'s **4b**–**4d**, which possess other arylalkyl or alkyl substituents at the β position, also proceeded with high selectivity to give the corresponding alcohols **6bm**, **6cm**, and **6do** with the selectivity around 90% (entries 5–7).

In summary, we have described the development of a rhodium-catalyzed asymmetric addition of arylboroxines to borylalkenes giving β-arylated alkylboron compounds with high enantioselectivity, which was realized by use of B(dan) as a boryl group in the borylalkenes.

Experimental Section

A solution of $[Rh(acac)(C_2H_4)_2]$ (5.2 mg, 20 mmol Rh, 10 mol% Rh) and (*R*)-DTBM-segphos (25.9 mg, 22 mmol) in CH_2Cl_2 (0.50 mL) was stirred at room temperature for 10 min. The solvent was removed under vacuum, and 4-phenyl-1-butenylB(dan) (**4a**) (59.6 mg, 0.20 mmol), phenylboroxine (**5m**) (125 mg, 0.40 mmol, 1.2 mmol of

Table 3: Asymmetric addition to alkenylboranes **4**.[a]



Entry	R (**4**)	Ar (**5**)	Chiral ligand	Yield [%][b]	*ee* [%][c]
1[d]	$Ph(CH_2)_2$ (**4a**)	Ph (**5m**)	(*R*)-DTBM-segphos	77 (**6am**)	97 (*R*)
2[d]	$Ph(CH_2)_2$ (**4a**)	4-MeC_6H_4 (**5n**)	(*R*)-DTBM-segphos	74 (**6an**)	97 (*R*)
3	$Ph(CH_2)_2$ (**4a**)	4-ClC_6H_4 (**5o**)	(*R*)-segphos	70 (**6ao**)	94 (*R*)
4	$Ph(CH_2)_2$ (**4a**)	4-FC_6H_4 (**5p**)	(*R*)-segphos	85 (**6ap**)	93 (*R*)
5[d]	$Ph(CH_2)_3$ (**4b**)	Ph (**5m**)	(*R*)-DTBM-segphos	65 (**6bm**)	95 (*R*)
6	$PhCH_2$ (**4c**)	Ph (**5m**)	(*R*)-segphos	70 (**6cm**)	93 (*R*)
7	*n*-C_5H_{11} (**4d**)	4-ClC_6H_4 (**5o**)	(*R*)-segphos	86 (**6do**)	87 (*R*)

[a] Reaction conditions: alkenylborane **4** (0.20 mmol), boroxine **5** (0.20 mmol, 3 equiv B), [Rh(acac)-$(C_2H_4)_2$] (10 μmol, 5 mol%), chiral ligand (11 μmol), *t*BuOH (1.0 mL). [b] Yield of isolated alcohol **6**. [c] Determined by HPLC analysis. The absolute configuration *R* for **6am** and **6cm** was determined from their optical rotations, and that for other alcohols **6** was assigned by analogy of the stereochemical pathway. [d] Reaction with 0.40 mmol of **5** and 10 mol% of the catalyst for 40 h.

B), and *tert*-butyl alcohol (1.0 mL) were added successively. The mixture was stirred at 60°C for 40 h. The reaction mixture was directly passed through a pad of silica gel with hexane/EtOAc (3:1) and the solvent was removed under vacuum. 2 M H_2SO_4 (1.0 mL) and pinacol (118 mg, 1.0 mmol) were added to a solution of the crude alkylB(dan) obtained above in tetrahydrofuran (2.0 mL). The mixture was stirred at room temperature overnight, before it was diluted with H_2O and the aqueous layer was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was subjected to column chromatography on silica gel (hexane/EtOAc = 20:1) to give (*R*)-2,4-diphenylbutylboronic acid pinacol ester (**8**; 55.1 mg, 82% yield, 97% *ee*).

Received: August 10, 2010
Published online: September 20, 2010

Keywords: alkylboranes · asymmetric catalysis · borylalkenes · conjugate addition · rhodium

[1] For reviews, see: a) M. P. Sibi, S. Manyem, *Tetrahedron* **2000**, *56*, 8033; b) N. Krause, A. Hoffmann-Röder, *Synthesis* **2001**, 171; c) J. Christoffers, G. Koripelly, A. Rosiak, M. Rössle, *Synthesis* **2007**, 1279; d) A. Alexakis, J. E. Bäckvall, N. Krause, O. Pàmies, M. Diéguez, *Chem. Rev.* **2008**, *108*, 2796; e) S. R. Harutyunyan, T. den Hartog, K. Geurts, A. J. Minnaard, B. L. Feringa, *Chem. Rev.* **2008**, *108*, 2824; f) T. Jerphagnon, M. G. Pizzuti, A. J. Minnaard, B. L. Feringa, *Chem. Soc. Rev.* **2009**, *38*, 1039; g) *Catalytic Asymmetric Conjugate Reactions* (Ed.: A. Córdova), Wiley-VCH, Weinheim, **2010**.

[2] For reviews, see: a) C. Bolm, J. P. Hildebrand, K. Muñiz, N. Hermanns, *Angew. Chem.* **2001**, *113*, 3382; *Angew. Chem. Int. Ed.* **2001**, *40*, 3284; b) T. Hayashi, K. Yamasaki, *Chem. Rev.* **2003**, *103*, 2829; c) S. Darses, J.-P. Genet, *Eur. J. Org. Chem.* **2003**, 4313; d) K. Fagnou, M. Lautens, *Chem. Rev.* **2003**, *103*, 169; e) T. Hayashi, *Bull. Chem. Soc. Jpn.* **2004**, *77*, 13; f) G. Berthon, T. Hayashi in *Catalytic Asymmetric Conjugate Reactions* (Ed.: A. Córdova), Wiley-VCH, Weinheim, **2010**, p. 1.

[3] a) Y. Takaya, M. Ogasawara, T. Hayashi, M. Sakai, N. Miyaura, *J. Am. Chem. Soc.* **1998**, *120*, 5579; b) M. Sakai, H. Hayashi, N. Miyaura, *Organometallics* **1997**, *16*, 4229.

[4] a) Y. Takaya, T. Senda, H. Kurushima, M. Ogasawara, T. Hayashi, *Tetrahedron: Asymmetry* **1999**, *10*, 4047; b) S. Sakuma, M. Sakai, R. Itooka, N. Miyaura, *J. Org. Chem.* **2000**, *65*, 5951.

[5] a) T. Senda, M. Ogasawara, T. Hayashi, *J. Org. Chem.* **2001**, *66*, 6852; b) S. Sakuma, N. Miyaura, *J. Org. Chem.* **2001**, *66*, 8944.

[6] J.-F. Paquin, C. Defieber, C. R. J. Stephenson, E. M. Carreira, *J. Am. Chem. Soc.* **2005**, *127*, 10850.

[7] T. Hayashi, T. Senda, Y. Takaya, M. Ogasawara, *J. Am. Chem. Soc.* **1999**, *121*, 11591.

[8] T. Hayashi, T. Senda, M. Ogasawara, *J. Am. Chem. Soc.* **2000**, *122*, 10716.

[9] P. Mauleón, J. C. Carretero, *Org. Lett.* **2004**, *6*, 3195.

[10] a) H. Noguchi, K. Hojo, M. Suginome, *J. Am. Chem. Soc.* **2007**, *129*, 758; b) N. Iwadate, M. Suginome, *Org. Lett.* **2009**, *11*, 1899.

[11] Recently, copper-catalyzed asymmetric conjugate addition of Grignard reagents to a β-boryl acrylate has been reported: J. C. H. Lee, D. G. Hall, *J. Am. Chem. Soc.* **2010**, *132*, 5544.

[12] For a pertinent review on the reaction of alkenylboronic acids, see: B. Carboni, F. Carreaux, in *Boronic Acids* (Ed.: D. G. Hall), Wiley-VCH, Weinheim, **2005**, p. 343.

[13] T. Hayashi, M. Takahashi, Y. Takaya, M. Ogasawara, *J. Am. Chem. Soc.* **2002**, *124*, 5052. Binap: 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl.

[14] For a review on boronic acid esters, see: D. G. Hall, in *Boronic Acids* (Ed.: D. G. Hall), Wiley-VCH, Weinheim, **2005**, p. 1.

[15] E. P. Gillis, M. D. Burke, *Aldrichimica Acta* **2009**, *42*, 17.

[16] a) R. A. Batey, A. N. Thadani, D. V. Smil, *Org. Lett.* **1999**, *1*, 1683; b) M. Pucheault, S. Darses, J.-P. Genet, *Tetrahedron Lett.* **2002**, *43*, 6155.

[17] a) M. Ueda, N. Miyaura, *J. Organomet. Chem.* **2000**, *595*, 31; b) K. Ueura, S. Miyamura, T. Satoh, M. Miura, *J. Organomet. Chem.* **2006**, *691*, 2821.

[18] T. Saito, T. Yokozawa, T. Ishizaki, T. Moroi, N. Sayo, T. Miura, H. Kumobayashi, *Adv. Synth. Catal.* **2001**, *343*, 264.

[19] Y. Kiyotsuka, Y. Katayama, H. P. Acharya, T. Hyodo, Y. Kobayashi, *J. Org. Chem.* **2009**, *74*, 1939.

[20] a) G. A. Molander, D. E. Petrillo, *Org. Synth.* **2007**, *84*, 317; b) G. A. Molander, T. Ito, *Org. Lett.* **2001**, *3*, 393; c) G. A. Molander, B. Canturk, *Angew. Chem.* **2009**, *121*, 9404; *Angew. Chem. Int. Ed.* **2009**, *48*, 9240.

[21] a) D. S. Matteson, *Chem. Rev.* **1989**, *89*, 1535; b) D. S. Matteson, H.-W. Man, O. C. Ho, *J. Am. Chem. Soc.* **1996**, *118*, 4560. Also see: c) Y. Fujioka, H. Amii, *Org. Lett.* **2008**, *10*, 769.

