Rhodium-Catalyzed Asymmetric 1,4-Addition to 1-Alkenylphosphonates

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Optically active phosphonic acid derivatives are important compounds because of their synthetic utility as chiral building blocks[1] as well as their potential biological activity.[2] Asymmetric 1,4-addition of organometallic reagents to α,β-unsaturated compounds is a powerful tool for carbon−carbon bond formation with simultaneous introduction of a new stereogenic carbon center at the β-position. Although many papers have appeared on the topic of catalytic asymmetric 1,4-addition to α,β-unsaturated carbonyl compounds with high enantioselectivity,[3] to our best knowledge the enantioselective reaction to α,β-unsaturated phosphonates has not been reported yet,[4,5] probably due to their low reactivity toward the 1,4-addition. Recently, we found asymmetric 1,4-addition of aryl- and alkenylboronic acids to α,β-unsaturated ketones which proceeds with high enantioselectivity under catalysis by a chiral phosphine−rhodium complex.[6] Here we report that the rhodium-catalyzed asymmetric 1,4-addition is successfully applied to α,β-unsaturated phosphonates[7] by use of triarylcyclotriboroxanes as arylating reagents in place of arylboronic acids.

We prepared geometrically pure diethyl (*E*)- and (*Z*)-1-propenylphosphonates (**1a**) by the palladium-catalyzed cross-coupling type reaction[8] of diethyl phosphite with (*E*)- and (*Z*)-1-propenyl bromide, respectively. Treatment of the α,β-unsaturated phosphonate with phenylboronic acid under the conditions previously reported[6] for α,β-unsaturated ketones gave a poor yield of diethyl 2-phenylpropylphosphonate (**3am**, Scheme 1). For example, the reaction of (*E*)-**1a** with phenylboronic acid in the presence of 3 mol % of the catalyst generated from Rh(acac)-$(C_2H_4)_2$ and (*S*)-binap in dioxane/H_2O (10/1) at 100 °C for 5 h gave **3am** (84% ee) only in 44% yield (entry 1 in Table 1). It was found that the rhodium catalyst loses its catalytic activity within 30 min under the conditions described above and that the presence of a large amount of water as a cosolvent causes the catalyst deactivation. The asymmetric 1,4-addition was greatly improved by carrying out the reaction with triphenylcyclotriboroxane (phenylboroxine, $(PhBO)_3$)[9] (**2m**) in place of phenylboronic acid (entry 2). Thus, the reaction of (*E*)-**1a** with phenylboroxine (**2m**) and 1 equiv (to boron) of water in dioxane at 100 °C for 3 h gave 94% yield of **3am** ($[\alpha]^{20}_D$ −19 (*c* 0.93, chloroform)), whose enantiomeric purity was determined to be 96% ee by HPLC analysis with a chiral stationary phase column (entry 2). The absolute configuration of (−)-**3am** was assigned to be *S* by correlation with (+)-(*R*)-1,3-diphenyl-1-butene (**4**)[10]

Scheme 1

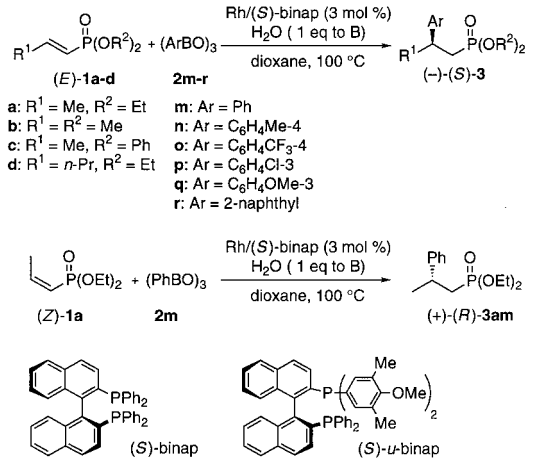

Table 1. Asymmetric 1,4-Addition of Arylboroxines **2** to 1-Alkenylphosphonates **1** Catalyzed by (*S*)-binap-Rhodium(I)[a]

entry	phosphonate **1**	$(ArBO)_3$ **2**	yield[b] (%) of **3**	% ee[c]	$[\alpha]^{20}_D$ (*c* in $CHCl_3$)
1[d]	(*E*)-**1a**	$PhB(OH)_2$	44 (**3am**)	84 (*S*)	
2	(*E*)-**1a**	**2m**	94 (**3am**)	96 (*S*)	−19 (0.93)
3[e]	(*E*)-**1a**	**2m**	5 (**3am**)		
4[d]	(*E*)-**1a**	*p*-$TolB(OH)_2$	43 (**3an**)	86	
5	(*E*)-**1a**	**2n**	84 (**3an**)	95	−23 (0.98)
6[f]	(*E*)-**1a**	**2n**	88 (**3an**)	96	
7	(*E*)-**1a**	**2o**	64 (**3ao**)	96	−25 (0.86)
8	(*E*)-**1a**	**2p**	61 (**3ap**)	96	−24 (0.72)
9	(*E*)-**1a**	**2q**	81 (**3aq**)	95	−21 (0.92)
10	(*E*)-**1a**	**2r**	89 (**3ar**)	89	−21 (1.01)
11[f]	(*E*)-**1a**	**2r**	92 (**3ar**)	90	
12	(*E*)-**1b**	**2m**	96 (**3bm**)	94	−25 (1.07)
13	(*E*)-**1c**	**2m**	95 (**3cm**)	91 (*S*)	−16 (1.10)
14[f]	(*E*)-**1c**	**2m**	99 (**3cm**)	94 (*S*)	
15	(*E*)-**1d**	**2m**	39 (**3dm**)	99	−10 (1.03)
16	(*Z*)-**1a**	**2m**	96 (**3am**)	89 (*R*)	+18 (1.13)
17[g]	(*Z*)-**1a**	**2m**	23 (**3am**)	97 (*R*)	
18[f]	(*Z*)-**1a**	**2m**	98 (**3am**)	92 (*R*)	

[a] The reaction was carried out with phosphonate **1** (0.20 mmol), arylboroxine **2** (0.67 mmol), and H_2O (2.0 mmol) in dioxane (0.8∼1.0 mL) at 100 °C for 3 h in the presence of 3 mol % of the catalyst generated from Rh(acac)$(C_2H_4)_2$ and (*S*)-binap unless otherwise noted. [b] Isolated yield by silica gel chromatography. [c] Determined by HPLC analysis with chiral stationary phase columns: Daicel Chiralcel AD (**3am**, **3an**, **3ao**, **3ap**, **3aq**, **3ar**, **3bm**) (eluent, hexane/2-propanol = 98/2), OD-H (**3cm**) (eluent, hexane/2-propanol = 90/10), and OJ (**3dm**) (eluent, hexane/2-propanol = 98/2). [d] Reaction of $ArB(OH)_2$ in dioxane/H_2O (10/1). [e] Reaction without addition of H_2O. [f] As a chiral ligand, (*S*)-*u*-binap was used in place of (*S*)-binap. [g] Reaction was stopped at the reaction period of 3 min.

(1) For a review on the use of phosphonates for alkene synthesis, see: Kelly, S. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 1, Chapter 3.1.

(2) For examples of asymmetric synthesis of biologically active phosphonates, see: (a) Blazis, V. J.; Koeller, K. J.; Spilling, C. D. *J. Org. Chem.* **1995**, *60*, 931. (b) Arai, T.; Bougauchi, M.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1996**, *61*, 2926 and references therein. (c) Nagaoka, Y.; Tomioka, K. *J. Org. Chem*. **1998**, *63*, 6428.

(3) For reviews, see: (a) Schmalz, H.-G. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 4, Chapter 1.5. (b) Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771. (c) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley and Sons: New York, 1994; pp 207−212. (d) Nógrádi, M. *Stereoselective Synthesis*; VCH Publishers: New York, 1995; pp 213−224. (e) Seyden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; John Wiley and Sons: New York, 1995.

(4) For a review on 1,4-addition reactions, see: Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1992.

(5) For an example of nonasymmetric addition of alkyl- and vinylcopper reagents to α,β-unsaturated phosphonates, see: Nicotra, F.; Panza, L.; Russo, G. *J. Chem. Soc., Chem. Commun*. **1984**, 5.

(6) (a) Takaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, N. *J. Am. Chem. Soc*. **1998**, *120*, 5579. (b) Takaya, Y.; Ogasawara, M.; Hayashi, T. *Tetrahedron Lett.* **1998**, *39*, 8479.

(7) For a review on vinylphosphonates in organic synthesis, see: Minami, T.; Motoyoshiya, J. *Synthesis* **1992**, 333.

(8) Hirao, T.; Masunaga, T.; Yamada, N.; Ohshiro, Y.; Agawa, T. *Bull. Chem. Soc. Jpn*. **1982**, *55*, 909.

(9) Arylboroxines are readily obtained by dehydration of arylboronic acids by azeotropic removal of water from their xylene solution or heating at 300 °C in vacuo. For a pertinent review, see: Lappert, M. F. *Chem. Rev*. **1956**, *56*, 959.

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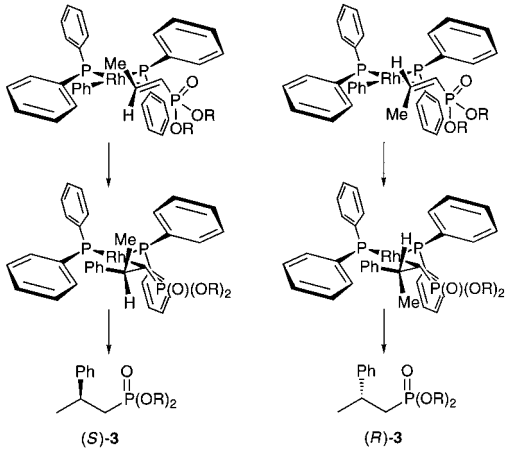
(vide infra). The addition of 1 equiv of water is essential for the high yield,[11] almost no reaction taking place in the absence of water (entry 3).

Under similar reaction conditions, diethyl (*E*)-1-propenylphosphonate ((*E*)-**1a**) underwent asymmetric arylation with some other arylboroxines (**2n**−**2r**) to give the corresponding diethyl 2-arylpropylphosphonates (**3an**−**3ar**) in good yields with high enantioselectivity (entries 5, and 7−10). Here, again, the yield of **3an** was much lower in the reaction with *p*-tolylboronic acid than with *p*-tolylboroxine (entries 4 and 5). The asymmetric phenylation was also successful for dimethyl and diphenyl esters of (*E*)-1-propenylphosphonate ((*E*)-**1b,c**) (entries 12 and 13). The enantioselectivities and chemical yields were slightly higher in the reaction catalyzed by rhodium complex coordinated with unsymmetrically substituted binap ligand, (*S*)-*u*-binap,[12] which has diphenylphosphino and bis(3,5-dimethyl-4-methoxyphenyl)phosphino groups at the 2 and 2′ positions on the 1,1′-binaphthyl skeleton (entries 6, 11, and 14).

The rhodium-catalyzed asymmetric phenylation of the *Z* isomer of diethyl 1-propenylphosphonate (*Z*)-**1a** with phenylboroxine **2m** for 3 h gave the *R* isomer of **3am** with 89% ee (entry 16). The observation of the opposite absolute configuration of **3am** for (*E*)-**1a** and (*Z*)-**1a** indicates that the dialkoxyphosphinyl moiety on the 1-alkenylphosphonate plays a key role in the enantioface selection (Scheme 2). The (*S*)-binap-rhodium catalyst recognizes the enantioface of 1-propenylphosphonate by the steric bulkiness of the phosphinyl group; both (*E*)-**1a** and (*Z*)-**1a** phenylated on the rhodium from the 1*si* face irrespective of the *E*,*Z* geometry of the 1-propenyl moiety.[13] The *Z* isomer (*Z*)-**1a** was found to undergo slow isomerization into the *E* isomer under these reactions conditions, resulting in the loss of enantioselectivity. This was demonstrated by stopping the reaction at the reaction period of 3 min, which gave **3am** of 97% ee (entry 17).

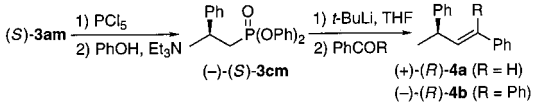
The optically active alkylphosphonates **3**, containing the stereogenic carbon center at the β-position, can be used as chiral building blocks for the synthesis of optically active alkenes by the Horner−Emmons type reaction (Scheme 3). The olefination of carbonyl compounds with diphenyl phosphonates proceeded without loss of enantiomeric purity. Unfortunately, the elimination forming alkenes did not take place from the β-hydroxyphosphonate intermediates in the reaction of diethyl phosphonates,[14] but diethyl esters were readily converted into diphenyl esters by way of dichlorides.[15] For example, the ester substitution of (−)-**3am** (91% ee) from ethyl to phenyl followed by treatment of the resulting diphenyl ester (−)-**3cm** with *tert*-butyllithium and benzaldehyde gave (+)-(*R*)-(*E*)-1,3-diphenyl-1-butene (**4a**)[10] of 92% ee,[16] together with a minor amount of (*Z*)-isomer (*E*/*Z* = 82/18), indicating that the absolute configuration of **3am** and **3cm** is (−)-(*S*). Similarly, the reaction of (−)-**3cm** with benzophenone gave (−)-(*R*)-1,1,3-triphenyl-1-butene (**4b**)[17] of 91% ee.[16]

Scheme 2[a]



[a] The binaphthylene moiety in (*S*)-binap is omitted for clarity.

Scheme 3



To summarize, we have realized, for the first time, the catalytic asymmetric 1,4-addition to 1-alkenylphosphonates, forming 2-arylalkylphosphonates in high yields with high enantioselectivity, by use of a new catalytic system consisting of a chiral phosphine−rhodium catalyst and arylboroxines as arylating reagents.

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Supporting Information Available: Experimental procedures and spectroscopic and analytical data for the substrates and products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Hayashi, T.; Konishi, M.; Fukushima, M.; Mise, T.; Kagotani, M.; Tajika, M.; Kumada, M. *J. Am. Chem. Soc*. **1982**, *104*, 180.

(11) Interestingly, the rhodium-catalyzed reaction of (*E*)-**1a** with phenylboronic acid in nonaqueous dioxane, namely, in the absence of water, resulted in a lower yield (67%) of **3am** (88% ee), though a boronic acid is known to be in equilibrium with a boroxine and water (ref 9). Methanol can also be used in place of water as a protic additive to phenylboroxine (85% yield of **3am**), while the reaction with dimethyl ester ($PhB(OMe)_2$) did not take place (<2% yield).

(12) The new chiral bisphosphine (*S*)-*u*-binap was prepared starting from (*S*)-binaphthol ditriflate by a sequence of reactions consisting of palladium-catalyzed monophosphinylation with bis[(3,5-dimethyl-4-methoxy)phenyl]-phosphine oxide, reduction of the phosphine oxide with trichlorosilane and triethylamine, and nickel-catalyzed cross-coupling of the remaining triflate with diphenylphosphine in 74% overall yield: $[\alpha]^{20}_D$ −103 (*c* 1.08, chloroform).

(13) For the highly skewed structure of transition metal complexes coordinated with a binap ligand, see: Ozawa, F.; Kubo, A.; Matsumoto, Y.; Hayashi, T. *Organometallics* **1993**, *12*, 4188 and references therein.

(14) Corey, E. J.; Kwiatkowski, G. T. *J. Am. Chem. Soc*. **1966**, *88*, 5654.

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(16) The enantiomeric purities of (*E*)-**4a** and -**4b** were determined by GLC analysis with CP-Chirasil-dex CB (25 m).

(17) $[\alpha]^{20}_D$ −73 (*c* 0.52, chloroform). The absolute configuration was assigned by the correlation with the starting (−)-(*S*)-3cm.