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Rhodium-catalyzed asymmetric addition of arylboroxines to β-alkoxyacrylate esters†

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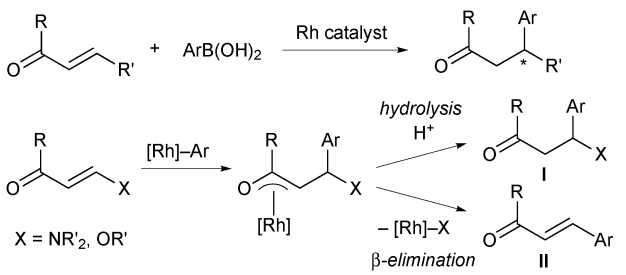
Asymmetric addition of arylboroxines to β-alkoxyacrylate esters proceeded in the presence of a rhodium complex coordinated with a chiral diene ligand to give high yields of β-alkoxy-β-arylcarboxylic acid esters with very high enantioselectivity.

Rhodium-catalyzed asymmetric addition of organoboron reagents to α,β-unsaturated carbonyl compounds is a powerful tool to construct a stereogenic carbon center,[1] because a wide variety of aryl- and alkenyl groups can be introduced into the β-position in high yields and high enantioselectivity.[2] Most studies so far have focused on the addition to α,β-unsaturated carbonyl compounds substituted with alkyl or aryl groups at the β-position, while the addition to those substituted with heteroatoms has been less developed.[3–5] The rhodium-catalyzed addition of arylboronic acids to α,β-unsaturated carbonyl compounds proceeds *via* an oxa-π-allylrhodium intermediate, which then undergoes hydrolysis to give a hydroarylation product **I** (Scheme 1).[6] On the other hand, in the addition to α,β-unsaturated carbonyl compounds bearing a strongly electronegative atom such as nitrogen or oxygen at the β-position, β-elimination from the oxa-π-allylrhodium intermediate giving a substitution product **II** becomes a problem as a competitive reaction,[7] and the preferential hydrolysis of the oxa-π-allylrhodium intermediate is important for the selective formation



Scheme 1 Rhodium-catalyzed addition to α,β-unsaturated carbonyl compounds.

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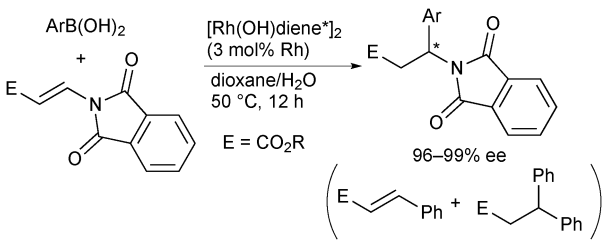


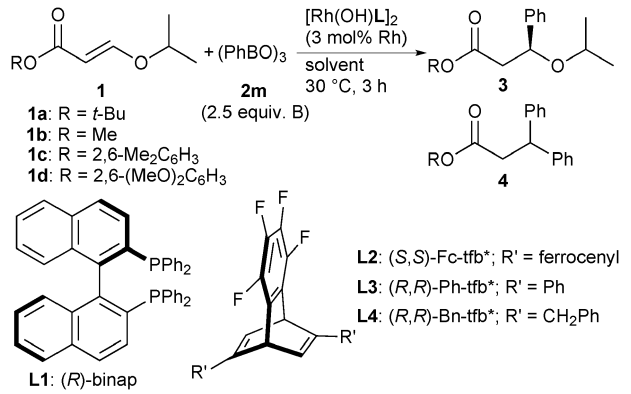
Scheme 2 Asymmetric addition to β-phthaliminoacrylate esters.

of the addition product. Recently, we reported rhodium-catalyzed asymmetric addition of arylboronic acids to β-phthaliminoacrylate esters (Scheme 2). The reaction was successfully carried out by use of a hydroxorhodium/chiral diene catalyst giving β-aryl-β-*N*-phthaloylamino acid esters in high yields with high enantioselectivity, while elimination of phthalimide was observed in the reaction with a bisphosphine ligand (binap) or KOH as a base.[8]

Chiral β-hydroxy- and β-alkoxy carboxylic acid derivatives are important structural components in natural products and pharmaceuticals, and a number of methods to access β-alkoxy carbonyl compounds in a stereoselective manner have been reported in the aldol reaction[9] and the oxa-Michael reaction.[10,11] Our straightforward approach to synthesize chiral β-alkoxy carboxylic acid derivatives is focusing on the rhodium-catalyzed asymmetric conjugate arylation of β-alkoxyacrylate esters. Here we report the asymmetric addition of arylboroxines to β-alkoxyacrylate esters, which are readily available from propiolic acid esters and alcohols.[12] The reaction giving chiral β-alkoxy-β-arylcarboxylic acid esters with extremely high enantioselectivity is realized by use of a rhodium/chiral diene catalyst.

We found that the catalytic activity of a rhodium complex for the reaction of β-alkoxyacrylate esters is higher with a diene ligand than with a bisphosphine ligand (Table 1). Thus, treatment of *tert*-butyl 3-isopropoxypropenoate (**1a**) with phenylboroxine (**2m**) (2.5 equiv. of B) in the presence of $[Rh(OH)((R)\text{-binap})]_2$[6] (3 mol% of Rh) in 1,4-dioxane/H_2O (9 : 1) at 30 °C for 3 h, which is one of the best catalytic conditions in the asymmetric addition of arylboronic acids to α,β-unsaturated carbonyl compounds,[6] gave the addition product **3am** in 6% yield, where most of the phenylboroxine (**2m**) was consumed to give benzene by protodeborylation (entry 1). The yield of the addition product **3am** was low (5%) even in the reaction in the presence of KOH (40 mol%)

Table 1 Rhodium-catalyzed addition of phenylboroxine (**2m**) to **1**[a]



Entry	1	L and conditions		Conv.[b] (%)	3[b] (%)	4[b] (%)	ee[c] (%)
1	**1a**	**L1**	A	8	6 (**3am**)	<1	—[d]
2[e]	**1a**	**L1**	A	19	5 (**3am**)	2 (6)[f]	—[d]
3	**1a**	cod	A	45	27 (**3am**)	12	—
4	**1a**	cod	B	25	18 (**3am**)	3	—
5	**1a**	cod	C	38	30 (**3am**)	2	—
6	**1a**	**L2**	C	92	82 (**3am**)	10	98
7	**1b**	**L2**	C	89	86 (**3bm**)	2	>99.5
8	**1c**	**L2**	C	100	90 (**3cm**)	10	>99.5
9	**1d**	**L2**	C	100	97 (**3dm**)	3	>99.5
10	**1d**	**L3**	C	91	78 (**3dm**)	11	99.2
11	**1d**	**L4**	C	87	77 (**3dm**)	9	94
12	**1d**	**L1**	C	<1	<1 (**3dm**)	0	—[d]
13[g]	**1d**	**L2**	C	100	96 (**3dm**)	3	>99.5

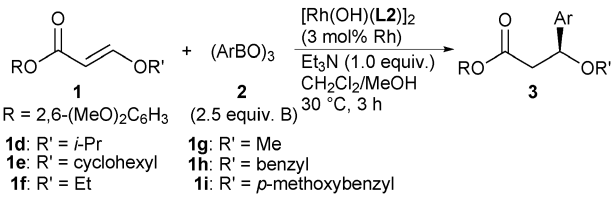
[a] Reaction conditions: **1** (0.200 mmol), $(PhBO)_3$ (**2m**) (0.167 mmol), $[Rh(OH)\mathbf{L}]_2$ (3 mol% of Rh) at 30 °C for 3 h. Conditions A: the reaction in dioxane/H_2O (9 : 1; 0.8 mL). Conditions B: the reaction in CH_2Cl_2/MeOH (1 : 1; 0.8 mL). Conditions C: the reaction in CH_2Cl_2/MeOH (1 : 1; 0.8 mL) in the presence of Et_3N (0.20 mmol). [b] A conversion of **1** and yields of **3** and **4** were determined by ^1H NMR. [c] The ee was determined by HPLC analysis with chiral stationary phase columns. [d] Not determined. [e] Performed in the presence of KOH (40 mol%) at 60 °C. [f] The value in parentheses is an yield of *t*-butyl cinnamate. [g] $PhB(OH)_2$ (0.50 mmol) was used instead of $(PhBO)_3$; cod: cycloocta-1,5-diene.

at 60 °C (entry 2). The β-alkoxyacrylate ester was prone to eliminate the alkoxy group during the present rhodium-catalyzed reaction to give *tert*-butyl cinnamate (6%) and *tert*-butyl 3,3-diphenylpropanoate (**4am**: 2%), which is the phenylation product of *tert*-butyl cinnamate formed by elimination of the isopropoxy group. On the other hand, the use of $[Rh(OH)(cod)]_2$ gave 27% yield of **3am** and 12% of **4am** (entry 3). The selectivity giving the addition product **3am** was higher in the solvent system of CH_2Cl_2/MeOH (1 : 1) (**3am**/**4am** = 18%/3%) (entry 4), and the addition of triethylamine (1.0 equiv.) increased the chemoselectivity (**3am**/**4am** = 30%/2%) (entry 5). Chiral diene ligands[13,14] based on tetrafluorobenzobarrelenes (tfb)[15] displayed a high catalytic activity and enantioselectivity. Thus, the reaction of **1a** in the presence of $[Rh(OH)((S,S)$-Fc-tfb* (**L2**))$]_2$ (Fc; ferrocenyl)[15a] (3 mol% of Rh) gave the 1,4-addition product **3am** in 82% yield, whose ee was 98% (entry 6). The formation of 10% yield of the diphenylation product **4am** was also observed. The ester group of **1** had a significant influence on both the reactivity and selectivity (entries 7–9). The addition to methyl ester **1b** gave the addition product **3bm** in 86% yield with over 99.5% ee and a small amount (2%) of methyl 3,3-diphenylpropanoate (**4bm**) (entry 7). The reactions of 2,6-dimethylphenyl ester **1c** and 2,6-dimethoxyphenyl ester **1d** proceeded with complete conversion to give the corresponding addition products **3cm** and **3dm** in 90 and 97% yield, respectively (entries 8 and 9), where the chemoselectivity was high in the reaction of **1d** (**3dm**/**4dm** = 97%/3%) (entry 9). The enantioselectivities observed for **3cm** and **3dm** were extremely high (>99.5% ee). The reaction was also catalyzed by rhodium complexes coordinated with Ph-tfb* (**L3**) or Bn-tfb* (**L4**), but their catalytic activities and stereoselectivities were lower than those observed with the ferrocene-substituted diene **L2** (entries 10 and 11). The reaction was not catalyzed at all by $[Rh(OH)(binap$ (**L1**))$]_2$ under the same reaction conditions (entry 12). Phenylboronic acid can be used as well as phenylboroxine (**2m**) to give **3dm** with the same high chemo- and enantioselectivity (entry 13). The absolute configuration of **3dm** obtained with (*S*,*S*)-**L2** was assigned to be *S* by analogy with (*S*)-**3im** (*vide infra*).

The present catalytic system can be applied to the asymmetric addition of several arylboroxines to β-alkoxyacrylates with all extremely high enantioselectivity (Table 2). Aryl groups (**2m–2t**) having a variety of substituents were successfully introduced at the β position of the β-isopropoxyacrylate **1d** giving the corresponding addition products (**3dm–3dt**) in high yields with over 99.5% ee (entries 1–8). The addition of phenylboroxine (**2m**) to β-alkoxyacrylates where the alkoxy groups are cyclohexyloxy (**1e**), ethoxy (**1f**), methoxy (**1g**), benzyloxy (**1h**), and *p*-methoxybenzyloxy (**1i**) gave the corresponding addition products **3em–3im** with over 99.5% ee (entries 9–13).[16]

The β-alkoxy-β-arylcarboxylic acid esters obtained here with almost perfect enantioselectivity can be converted into

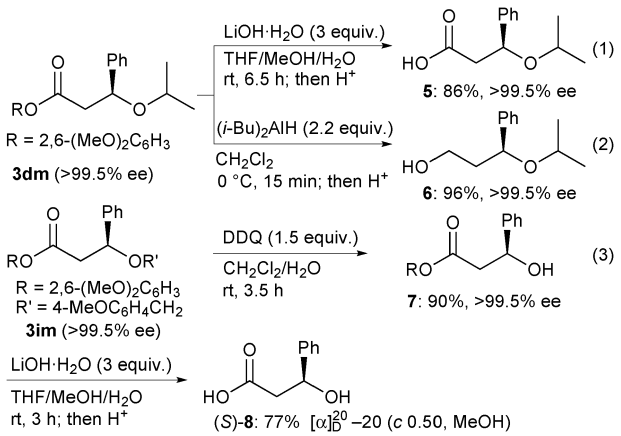
Table 2 Asymmetric addition of arylboroxine **2** to **1**[a]



Entry	1	Ar (2)	Yield[b] (%)	ee[c] (%)
1	**1d**	Ph (**2m**)	95 (**3dm**)	>99.5
2	**1d**	2-MeC_6H_4 (**2n**)	91 (**3dn**)	>99.5
3	**1d**	3-MeC_6H_4 (**2o**)	96 (**3do**)	>99.5
4	**1d**	4-MeC_6H_4 (**2p**)	94 (**3dp**)	>99.5
5[d]	**1d**	4-$MeOC_6H_4$ (**2q**)	91 (**3dq**)	>99.5
6[e]	**1d**	4-ClC_6H_4 (**2r**)	90 (**3dr**)	>99.5
7[f]	**1d**	4-$CF_3C_6H_4$ (**2s**)	68 (**3ds**)	>99.5
8	**1d**	2-Naphthyl (**2t**)	90 (**3dt**)	>99.5
9	**1e**	Ph (**2m**)	92 (**3em**)	>99.5
10	**1f**	Ph (**2m**)	87 (**3fm**)	>99.5
11	**1g**	Ph (**2m**)	75 (**3gm**)	>99.5
12	**1h**	Ph (**2m**)	88 (**3hm**)	>99.5
13	**1i**	Ph (**2m**)	88 (**3im**)	>99.5

[a] Reaction conditions: **1** (0.200 mmol), $(PhBO)_3$ (**2**) (0.167 mmol), $[Rh(OH)(\mathbf{L2})]_2$ (3 mol% of Rh), Et_3N (0.20 mmol), MeOH (0.40 mL), CH_2Cl_2 (0.40 mL) at 30 °C for 3 h. [b] Isolated yield of **3**. [c] Determined by HPLC analysis with chiral stationary phase columns. [d] Performed with $(4\text{-}MeOC_6H_4BO)_3$ (0.200 mmol). [e] For 12 h. [f] For 24 h.

some functionalized compounds without loss of their enantiomeric purity (eqn (1)–(3)). Thus, basic hydrolysis of **3dm** gave the corresponding β-isopropoxycarboxylic acid **5** in 86% yield (eqn (1)), and the reduction of **3dm** by treatment with $(i\text{-Bu})_2$AlH gave alcohol **6** in 96% yield (eqn (2)). Treatment of β-*p*-methoxybenzyloxycarboxylic acid ester **3im** with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ), followed by basic hydrolysis gave β-hydroxycarboxylic acid (*S*)-**8**, whose absolute configuration was determined by comparison of its specific rotation with the value reported previously (eqn (3)).[17]



In summary, we have developed a rhodium-catalyzed asymmetric addition of arylboroxines to β-alkoxyacrylate esters giving β-alkoxy-β-arylcarboxylic acid esters in high yields with very high enantioselectivity, which was realized by use of a rhodium/chiral diene catalyst.

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