Asymmetric Catalysis

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Enantioselective Rhodium-Catalyzed Addition of Arylboronic Acids to α-Ketoesters**

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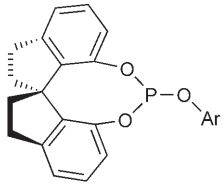
The transition-metal-catalyzed asymmetric addition of organometallic reagents to carbonyl compounds to produce enantiomer-enriched secondary or tertiary alcohols is a powerful tool for the construction of carbon–carbon bonds. Many organometallic reagents have been successfully used in this addition reaction.[1] However, a drawback for most organometallic reagents is their sensitivity to moisture and air, both of which impede the practical applications of these asymmetric carbon–carbon bond-forming reactions. As an exception, arylboronic acids are very stable to air and moisture. The catalytic enantioselective addition of arylboronic acids to carbonyl compounds has became a current focus for research,[1d] and a number of efficient chiral catalysts have been developed for the catalytic asymmetric addition of arylboronic acids to aldehydes[2] and aldimines.[3] However, the catalytic asymmetric addition of arylboronic acids to ketones, which are less active relative to aldehydes and aldimines, is more difficult, and only limited progress has been achieved. In 2006, Hayashi et al. reported the asymmetric addition of arylboronic acids to isatins, cyclic α-ketoamides, catalyzed by a rhodium/MeO-Mop (MeO-Mop = 2-methoxy-2′-diphenylphosphino-1,1′-binaphthyl) complex in high enantioselectivities (72–91 % *ee*).[4] By using a chiral phosphoramidite ligand derived from H_8-binol (binol = 2,2′-dihydroxy-1,1′-binaphthyl), de Vries, Minnard, Feringa and et al. obtained 55 % *ee* in the same reaction.[5] The chiral phosphoramidite ligand was also used in the asymmetric addition of arylboronic acids to trifluoromethyl ketones with good enantioselectivities (50–83 % *ee*).[6] The intramolecular asymmetric addition of arylboronic acids to ketones catalyzed by a cationic palladium complex of binap (binap = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl) to give cyclic tertiary alcohols in high enantioselectivities (53–96 % *ee*) was reported by Lu et al.[7] To the best of our knowledge, the catalytic enantioselective addition of arylboronic acids to α-ketoesters to provide tertiary α-hydroxyesters has not yet been reported.[8]

In the search for highly efficient methods to construct chiral 2-hydroxydiarylacetates, desirable chiral intermediates for the synthesis of antagonists of muscarinic receptors,[9] we became interested in the enantioselective addition of arylboronic acids to the α-aryl- and α-alkenyl-α-ketoesters. The Rh^I/ShiP (ShiP = aryl(1,1′-spirobiindane-7,7′-diyl)phosphite) catalysts (**1**) recently developed by us[2c,3b] were found to be highly efficient for this addition reaction to provide chiral tertiary α-hydroxyesters[10] in good yields and high enantiomeric excesses (up to 93 % *ee*).

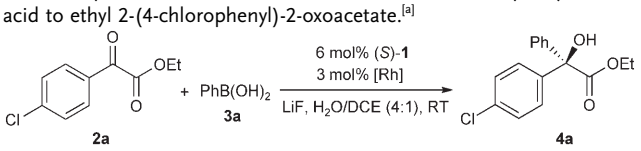


(*S*)-ShiP **1**

1a: Ar = C_6H_5
1b: Ar = 4-$CF_3C_6H_4$
1c: Ar = 4-$MeOC_6H_4$
1d: Ar = 3,5-(tBu)$_2C_6H_3$
1e: Ar = 2-naphthyl

Preliminary experiments were carried out in H_2O with catalyst generated in situ from 1.5 mol % [{RhCl(CH_2CH_2)$_2$}$_2$][11] and 6 mol % (*S*)-**1a** in the presence of two equivalents of LiF.[12] The addition of phenylboronic acid to ethyl 2-(4-chlorophenyl)-2-oxoacetate (**2a**) at room temperature for 48 hours afforded tertiary α-hydroxyester **4a** in 59 % yield with 70 % *ee* (Table 1, entry 1). The low solubility of the 2-oxoacetate substrate in H_2O was responsible for the long

Table 1: Optimization of the enantioselective addition of phenylboronic acid to ethyl 2-(4-chlorophenyl)-2-oxoacetate.[a]



2a 4a

Entry	ShiP	Solvent[b]	*t* [h]	Yield [%][c]	*ee* [%][d]
1	(*S*)-**1a**	H_2O	48	59	70
2	(*S*)-**1a**	H_2O/Tol	15	92	69
3	(*S*)-**1a**	H_2O/DME	15	71	72
4	(*S*)-**1a**	H_2O/EtOH	15	75	71
5	(*S*)-**1a**	H_2O/DCE	10	99	72
6	(*S*)-**1b**	H_2O/DCE	12	87	32
7	(*S*)-**1c**	H_2O/DCE	12	96	77
8	(*S*)-**1d**	H_2O/DCE	24	25	61
9	(*S*)-**1e**	H_2O/DCE	12	94	68

[a] **2a**/**3a**/LiF/[{RhCl(CH_2CH_2)$_2$}$_2$]/(*S*)-**1** = 1:2:2:0.015:0.06. [b] H_2O/solvent = 4:1 v/v (2 mL). [c] Yield of the isolated product. [d] Determined by chiral HPLC analysis by using a Daicel Chiralpak AD-H column.

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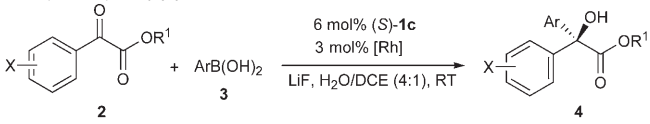
reaction time and low yield. When a small amount of organic solvent, such as toluene, dimethoxyethane (DME), EtOH, or 1,2-dichloroethane (DCE) was added (H_2O/organic solvent = 4:1), the reaction proceeded much faster and produced **4a** in higher yields (Table 1, entries 2–5). The H_2O/DCE solvent mixture is optimal as it gave the highest yield (99%) and good enantioselectivity (72% *ee*; Table 1, entry 5). A comparison of ligands showed that spirophosphite **1c**, having a *para*-OMe group on the phenyl ring, afforded product **4a** with the highest *ee* value (Table 1, entry 7). The LiF functions as a Lewis base, promoting the transfer of the phenyl group of the phenylboronic acid to rhodium by binding to the B atom and accelerating the reaction rate.[13]

The scope of the reaction was investigated under the optimal reaction conditions. From the results listed in Table 2, we can see that the ester group in the substrate imposed a notable effect on both the yield and the enantioselectivity. The best result was obtained with the benzyl ester (Table 2, entry 5). Lowering the reaction temperature to 0°C improved the enantioselectivity to 90% *ee*, but diminished the yield of reaction to 81%. The electronic properties of the substituents on the α-oxo(aryl)acetates had a limited influence on the enantiomeric excess of the products, but it markedly affected the reaction rate. For example, the reactions of benzyl α-oxo(aryl)acetates with an electron-withdrawing group, such as Cl, F, or CF_3, at the *para*-position can be performed at 0°C (Table 2, entries 6–8). However, room temperature (20–25°C) is necessary for the reaction of α-oxo(aryl)acetates with an electron-donating group such as Me and MeO at the *para*-position (Table 2, entries 9 and 10). The addition reaction is sensitive to the steric effect of the substrates and the reagents; for example, when an *ortho* or *meta* substituent was introduced onto the aryl ring of α-oxo(aryl)acetate **2** or onto the aryl ring of arylboronic acid **3**, the addition reaction became very slow. Only a trace amount of the product was observed at 40°C after 48 hours (results not shown). The absolute configuration of addition products can be changed by simply exchanging the aryl groups of the α-oxoester and the boronic acid, for instance, the additions of 4-methyl- and 4-methoxyphenylboronic acids to 2-phenyl-2-oxoacetate afforded α-hydroxyesters **4h** and **4i** in 80 and 83% *ee*, respectively, but with opposite configurations (Table 2, entries 12 and 13).

Except for α-oxo(aryl)acetate, the less hindered (*E*)-benzyl 2-oxo-4-phenylbut-3-enoate (**5**) is also a suitable substrate for the arylation reaction with arylboronic acids catalyzed by Rh^I/(*S*)-**1c**. A variety of arylboronic acids can undergo the enantioselective addition to compound **5** to produce tertiary α-hydroxyacetates **6** (Table 3). All *meta*- and *para*-substituted arylboronic acids, with electron-donating or electron-withdrawing substituents gave good yields and high enantioselectivities (90–93% *ee*), showing that the electronic properties of the arylboronic acids has a negligible effect on the enantioselectvity of the addition reaction (Table 3, entries 2–7). However, the fact that the *ortho*-methylphenylboronic acid afforded a lower enantioselectivity (75% *ee*) indicated that the steric hindrance has a negative influence on the enantioselectivity of the reaction (Table 3, entry 8). The 2-naphthyl- and 2-thiopheneboronic acids can also be used in the addition reaction with α-ketoester **5** to produce corresponding tertiary α-hydroxyesters **6i** and **6j**, respectively (Table 3, entries 9 and 10).

The ester group of the addition products can be converted into other functional groups by simple operations. For example, the benzyl 2-hydroxy-2-phenyl-4-phenylbut-3-enoate (**6a**) was hydrolyzed by aqueous NaOH to afford tertiary α-hydroxy acid **7** in 94% yield with complete retention of the optical purity. Furthermore, the chiral 1,2-dihydroxy compound **8** was easily obtained in 83% yield by

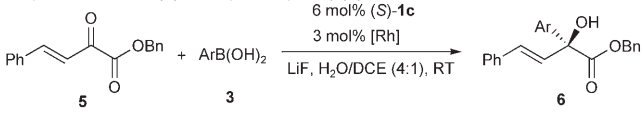
Table 2: Asymmetric addition of arylboronic acids **3** to α-ketoesters **2** catalyzed by Rh^I/(*S*)-**1c**.[a]



Entry	R^1	X	Ar	Prod.	*t* [h]	Yield [%][b]	*ee* [%][c]
1	Et	4-Cl	C_6H_5	**4a**	12	96	77
2	*i*Pr	4-Cl	C_6H_5	**4b**	12	93	80
3	*t*Bu	4-Cl	C_6H_5	**4c**	12	51	70
4	Ph	4-Cl	C_6H_5	**4d**	12	90	72
5	Bn	4-Cl	C_6H_5	**4e**	12	95	84
6[d]	Bn	4-Cl	C_6H_5	**4e**	48	81	90
7[d]	Bn	4-F	C_6H_5	**4f**	48	84	88
8[d]	Bn	4-CF_3	C_6H_5	**4g**	48	93	91
9	Bn	4-Me	C_6H_5	**4h**	36	96	84 (*R*)[e]
10	Bn	4-MeO	C_6H_5	**4i**	36	93	86
11[d]	Bn	3,4-$(CH)_4$-	C_6H_5	**4j**	60	78	80
12	Bn	H	4-MeC_6H_4	**4h**	36	85	80 (*S*)[e]
13	Bn	H	4-$MeOC_6H_4$	**4i**	36	80	83 (−)

[a] **2**/**3**/LiF/[{$RhCl(CH_2CH_2)_2$}$_2$]/ligand = 1:2:2:0.015:0.06. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis (see the Supporting Infomation). [d] 0°C. [e] Determined by comparing the measured optical rotation with the reported data.[14]

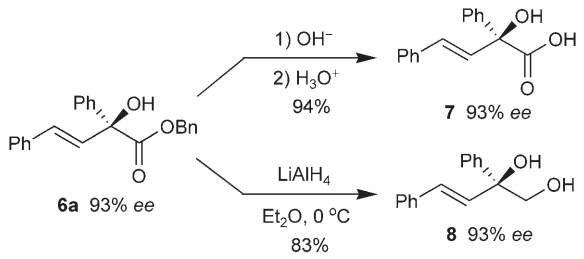
Table 3: Asymmetric addition of arylboronic acids **4** to benzyl 2-phenylvinyl-2-ketoester (**3**) catalyzed by Rh^I/(*S*)-**1c**.[a]



Entry	Ar	**6**	*t* [h]	Yield [%][b]	*ee* [%][c]
1[d]	C_6H_5	**6a**	60	70	93
2[d]	4-MeC_6H_4	**6b**	60	77	93
3[d]	4-$MeOC_6H_4$	**6c**	60	75	90
4	4-FC_6H_4	**6d**	32	93	92
5	4-$CF_3C_6H_4$	**6e**	32	61	90
6[d]	3-MeC_6H_4	**6f**	60	75	91
7[d]	3-$MeOC_6H_4$	**6g**	60	70	93
8	2-MeC_6H_4	**6h**	32	92	75
9	2-naphthyl	**6i**	24	89	90
10	2-thiophene	**6j**	24	91	88

[a] **5**/**3**/LiF/[{$RhCl(CH_2CH_2)_2$}$_2$]/ligand = 1:2:2:0.015:0.06. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis (see the Supporting Infomation). [d] 0°C.

reducing compound **6a** with $LiAlH_4$ in Et_2O. Both compounds **7**[15] and **8**[16] are important intermediates in the synthesis of biologically active molecules (Scheme 1).



Scheme 1. Conversion of ester **6a** to the acid and the diol.

In summary, the first asymmetric addition of arylboronic acids to α-ketoesters was developed by using rhodium catalysts bearing spirophosphite ligands. This protocol provides a new enantioselective approach to the synthesis of 2-hydroxydiarylacetates and alkenylarylacetates, as well as related α-hydroxy acids and vicinal diols that have a tertiary chiral center. This method was performed in aqueous media, which is benign to the environment.

Experimental Section

Typical procedure: A Schlenk tube was charged with [{RhCl-$(CH_2CH_2)_2\}_2$] (1.2 mg, 0.006 mmol) and (*S*)-**1c** (4.8 mg, 0.012 mmol) under a nitrogen atmosphere. DCE (0.4 mL) and water (1.6 mL) were then added, and the mixture was stirred at room temperature for 10 min. $PhB(OH)_2$ (49 mg, 0.4 mmol), LiF (13 mg, 0.4 mmol), and benzyl 2-(4-chlorophenyl)-2-oxoacetate (42 mg, 0.2 mmol) were added sequentially to the reaction mixture, which was then stirred at 0 °C for 48 h. The mixture was extracted with CH_2Cl_2, dried over $MgSO_4$, and purified by chromatography on silica gel with petroleum ether/ethyl acetate (8:1) to give product **4e** in 81 % yield as a white solid, mp 61–62 °C. The Enantiomeric excess (90 % *ee*) was determined by chiral HPLC analysis using a Daicel Chiralpak AS column.

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