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Novel Axially Chiral Phosphine Ligand with a Fluoro Alcohol Moiety for Rh-Catalyzed Asymmetric Arylation of Aromatic Aldehydes

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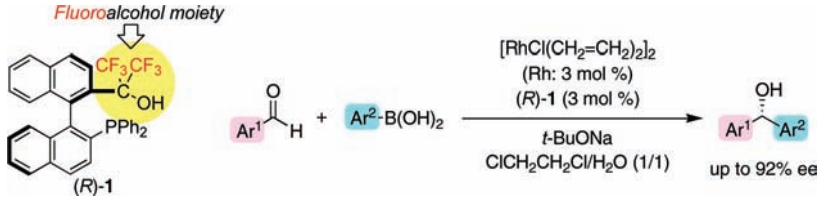
ABSTRACT



A new chiral phosphine ligand (*R*)-1 possessing a fluoroalcohol moiety was prepared. The (*R*)-1-coordinated Rh(I) complex showed an excellent catalytic activity for asymmetric 1,2-addition of arylboronic acids to aldehydes to afford highly enantioenriched diarylmethanols. The fluoroalcohol moiety in ligand (*R*)-1 plays a pivotal role for the high enantioselectivity of the present Rh(I)-catalyzed transformation.

Enantiopure diarylmethanols are important compounds because of the biological activity of their derivatives, such as neobenodine and orphenadrine.[1] Besides asymmetric hydrogenation of diarylketones,[2] catalytic asymmetric addition of carbon-based nucleophiles to carbonyl compounds provides a direct route for synthesis of enantiomerically enriched diarylmethanols.[3] Arylboronic acids are among the most convenient reagents because of their stability and easy handling, and therefore they have been used for a wide repertoire of organic transformations.[4,5] In 1998, Miyaura reported the first example of Rh-catalyzed asymmetric 1,2-addition of $PhB(OH)_2$ to 1-naphthaldehyde to give the diarylmethanol in 41% ee.[6] Despite the synthetic advantage to use arylboronic acids, the progress in catalytic enantioselective arylation reactions of aldehydes using $ArB(OH)_2$ has

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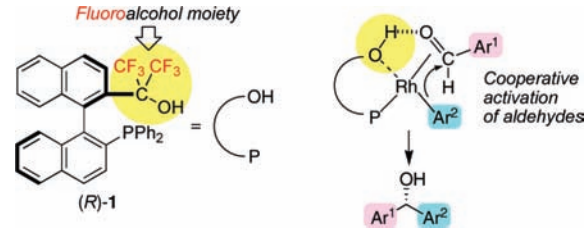
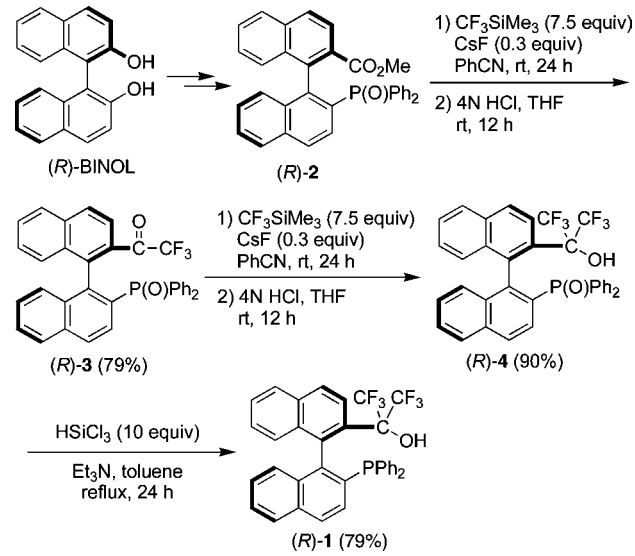
been slow as a result of their difficulty;[7−10] the lack of suitable catalyst systems has limited their further development during the past decade. Recently, excellent results on enantioselective carbonyl addition of arylboron reagents have been reported by several groups.[11−17] In particular, Yamamoto and Miyaura demonstrated highly enantioselective addition of arylboronic acids to aldehydes catalyzed by Ru(II)-bipam complexes.[17] For the investigation of a novel catalyst system,the design of a new chiral ligand is a key challenge to achieve highly stereocontrolled reactions. Using bifunctional molecular catalysts containing transition metals and ancillary ligands with hydrogen bond donor groups (so-called "concerto catalysis") is one of the most elegant and efficient methods for catalytic asymmetric transformation.[18−22] Herein, we report a preparation of a new chiral phosphine ligand (*R*)-**1** endowed with a fluoroalcohol moiety and its application to rhodium-catalyzed asymmetric 1,2-addition of arylboronic acids to aldehydes to give diarylmethanols with high enantioselectivities (Scheme 1).

Scheme 1



Enantiopure binaphthyl ligand (*R*)-**1** tethered to a fluoroalcohol moiety was synthesized via nucleophilic transformations of ester (*R*)-**2**,[23] which was readily prepared from (*R*)-BINOL (Scheme 2). Sequential introduction of trifluoromethyl

Scheme 2



groups to (*R*)-**2** by the use of CF_3SiMe_3[24] provided bis(trifluoromethyl)methanol (*R*)-**4**. Reduction of phosphine oxide (*R*)-**4** by $HSiCl_3$ afforded phosphine (*R*)-**1** without loss of enantiopurity.

Next, the new rhodium complex with chiral ligand (*R*)-**1** was used for the asymmetric arylation of aldehydes with arylboronic acids. A mixture of *p*-tolylaldehyde (**5a**) and phenylboronic acid (**6a**) in xylene/H_2O was heated at 60 °C for 24 h in the presence of *t*-BuONa (2 equiv) and a catalytic amount of Rh(I) complex prepared in situ by mixing dinuclear complex $[Rh(CH_2{=}CH_2)_2Cl]_2$ (1.5 mol %) with

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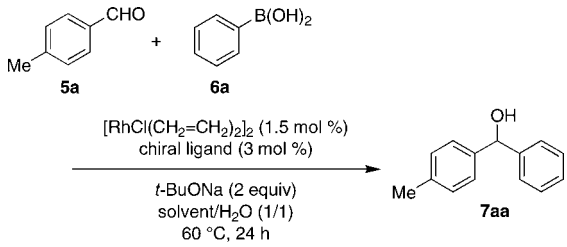
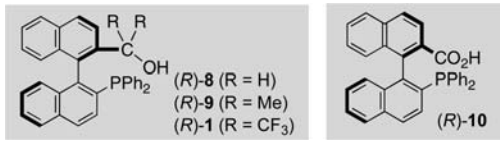
(*R*)-**1** (3 mol %) to afford diarylmethanol **7aa** in 83% yield with 69% ee (Table 1, entry 1). Enhancement of the

Table 1. Rh-Catalyzed Addition of Phenylboronic Acid to *p*-Tolylaldehyde: Screening of Ligands and Solvents



			7aa	
entry	chiral ligand	solvent	yield, %[a]	ee, %[b] (config)
1	(*R*)-**1**	xylene	83	69 (*R*)
2	(*R*)-**1**	$ClCH_2CH_2Cl$	78	82 (*R*)
3	(*R*)-**8**	xylene	9	0
4	(*R*)-**8**	$ClCH_2CH_2Cl$	0	*c*
5	(*R*)-**9**	xylene	41	16 (*S*)
6	(*R*)-**9**	$ClCH_2CH_2Cl$	<3	*c*
7	(*R*)-**10**	xylene	0	*c*
8	(*R*)-**10**	$ClCH_2CH_2Cl$	0	*c*

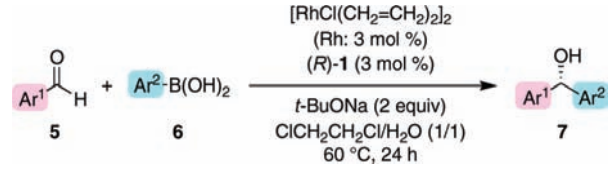
[a] Isolated yield. [b] Enantiomeric excesses were determined by HPLC analyses (Daicel Chiralcel OD-H). [c] Enantiomeric excesses were not determined.



enantioselectivity (82% ee) in arylation of aldehyde **5a** was observed employing a dichloroethane−H_2O solvent system (entry 2). On the other hand, phosphine ligands (*R*)-**8** and (*R*)-**9** with (nonfluorinated) alcohol moieties displayed lower catalytic activitities and enantioselectivities (entries 3−6). Furthermore, the use of a ligand possessing a carboxy group was not effective for the present Rh-catalyzed arylation (entries 7 and 8). Therefore, the presence of a weakly acidic fluoroalcohol moiety[25,26] in the ligand (*R*)-**1** leads to a significant increase of the product yield and enantioselectivity in 1,2-addition.

With the optimized reaction conditions (at 60 °C, in $ClCH_2CH_2Cl/H_2O$) asymmetric 1,2-addition reactions of arylboronic acids **6** to various aldehydes **5** were examined. Representative results are summarized in Table 2. To achieve

Table 2. Rh-Catalyzed 1,2-Addition of Arylboronic Acids to Aromatic Aldehydes



entry	Ar^1	Ar^2	yield, %[a]	ee, %[b]
1	4-MeC_6H_4 (**5a**)	Ph (**6a**)	78 (**7aa**)	82 (*R*)
2	2,4-$Me_2C_6H_3$ (**5b**)	Ph (**6a**)	75 (**7ba**)	82 (*R*)
3	4-^{i}PrC_6H_4 (**5c**)	Ph (**6a**)	96 (**7ca**)	80 (*R*)
4[c]	4-^{i}PrC_6H_4 (**5c**)	Ph (**6a**)	68 (**7ca**)	86 (*R*)
5	4-$MeOC_6H_4$ (**5d**)	Ph (**6a**)	99 (**7da**)	81 (*R*)
6[c]	4-$MeOC_6H_4$ (**5d**)	Ph (**6a**)	56 (**7da**)	90 (*R*)
7	3,4-$(OCH_2O)C_6H_3$ (**5e**)	Ph (**6a**)	96 (**7ea**)	81 (*R*)
8	4-MeC_6H_4 (**5a**)	4-AcC_6H_4 (**6b**)	57 (**7ab**)	80 (+)
9[c]	Ph (**5f**)	4-ClC_6H_4 (**6c**)	99 (**7 fc**)	87 (*S*)
10	4-MeC_6H_4 (**5a**)	4-ClC_6H_4 (**6c**)	99 (**7ac**)	80 (*S*)
11[c]	4-MeC_6H_4 (**5a**)	4-ClC_6H_4 (**6c**)	64 (**7ac**)	88 (*S*)
12	4-MeC_6H_4 (**5a**)	3-ClC_6H_4 (**6d**)	99 (**7ad**)	84 (*S*)
13[c]	4-$MeOC_6H_4$ (**5d**)	4-ClC_6H_4 (**6c**)	84 (**7dc**)	89 (*S*)
14[c]	4-$MeOC_6H_4$ (**5d**)	3-ClC_6H_4 (**6d**)	73 (**7dd**)	92 (*S*)
15[c]	2-thienyl (**5g**)	4-ClC_6H_4 (**6c**)	93 (**7gc**)	90 (*S*)
16[c]	2-thienyl (**5g**)	3-ClC_6H_4 (**6d**)	74 (**7gd**)	91 (*S*)

[a] Isolated yield. [b] Enantiomeric excesses were determined by HPLC analyses (Daicel Chiralcel OD-H, OB, Chiralpak AD-H, or AS). [c] These reactions were carried out at 30 °C for 24 h.

high enantioselectivities, several recent examples of catalytic arylation of aldehydes require the presence of *ortho* substituents on the benzene ring of aromatic aldehydes[9,16] or that of arylboronic acids.[11] In our case, the position of substituents of aldehydes **5** and arylboronic acids **6** is not restrictive for obtaining good enantioselectivities (entries 1−16). When the reactions were carried out at 30 °C, enantioselectivities were improved (entries 4, 6, 9, 11, 13, and 15). Furthermore, the present transformation is tolerant of functional groups of arylboronic acids **6** (entries 8−16). The combination of aromatic aldehydes **5a**−**g** bearing electron-donating groups on the aryl rings and arylboronic acids **6** possessing electron-withdrawing substituents on the aryl rings provided **7** with high enantioselectivities. In particular, the reactions of *p*-anisaldehyde (**5d**) and 2-thiophenecarboxaldehyde (**5g**) with 3-chlorophenylboronic acid (**6d**) afforded the adducts **7dd** and **7gd** in 73% isolated yield with 92% ee and in 74% isolated yield with 91% ee, respectively (entries 14 and 16).

A plausible mechanism for the present Rh(I)-catalyzed arylation is pictured in Scheme 3A. In the first step, transmetalation of arylboronic acids **4** with hydroxy rhodium(I) complex **11**, which is generated from $[Rh(CH_2{=}CH_2)_2Cl]_2$ and phosphine ligand (*R*)-**1** upon treatment with aqueous base, gives arylrhodium(I) species **12**. Next, coordination of **12** with aldehydes **5** provides the intermediates **13**, which undergo insertion of the C−O double

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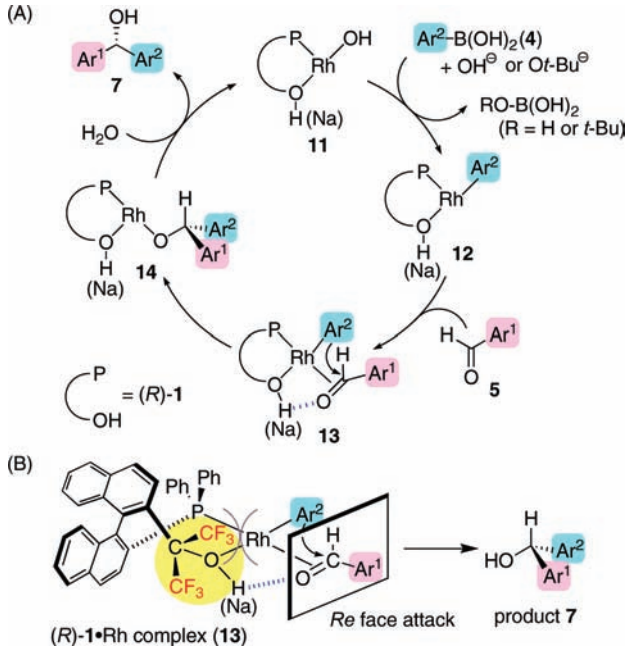
Scheme 3



bonds of aldehyde ligands into the C−Rh bonds in **13** to form alkoxyrhodium(I) complexes **14**.[27] The subsequent hydrolysis of **14** results in the liberation of diarylmethanols **7** and the regeneration of the active Rh(I) species **11** to make possible the reactions catalytic in rhodium. The enantioselectivity observed with the chiral ligand (*R*)-**1** suggests that high enantioface selection of the Rh-catalyzed arylation of aldehydes is achieved. As shown in Scheme 3B, addition of the aryl groups in **13** to the coordinated aldehydes from the *re* face leads to the formation of adduct **14** in a stereoselective manner. The chirality recognition ability is substantially high; the chiral coordination environment in the intermediate **13** would be created by the bulky trifluoromethyl groups of phosphine ligand (*R*)-**1**.

In summary, we have developed a new enantioselective transformation involving C−C bond formation. The axially chiral phosphine compound (*R*)-**1** tethered to a fluoroalcohol moiety was found to be an effective ligand for Rh(I)-catalyzed asymmetric arylation of aromatic aldehydes with arylboronic acids affording enantiomerically enriched diaryl methanols. Further investigation to expand the scope of the present protocol for the synthesis of bioactive diaryl methanols is in progress.

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Supporting Information Available: Details of experimental procedures and characterization data (^1H, ^{13}C and ^{19}F NMR, IR, and mass spectrometry) for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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