Chiral Tetrafluorobenzobarrelenes as Highly Efficient Ligands for the Rhodium-catalyzed Asymmetric 1,4-Addition of Arylboronic Acids

Takahiro Nishimura,* Makoto Nagaosa, and Tamio Hayashi*
Department of Chemistry, Graduate School of Science, Kyoto University, Kyoto 606-8502

(Received May 26, 2008; CL-080531; E-mail: thayashi@kuchem.kyoto-u.ac.jp)

New C_2-symmetric chiral diene ligands bearing a tetrafluorobenzobarrelene framework and (−)-menthyl groups as chiral auxiliaries were prepared through [4 + 2] cycloaddition of 1,4-bis((−)-menthoxymethyl)benzene with tetrafluorobenzyne. The diene ligands realized the rhodium-catalyzed asymmetric addition of arylboronic acids to α,β-unsaturated carbonyl compounds giving β-arylcarbonyl compounds in high yields with high enantioselectivity.

Recent progress in rhodium-catalyzed asymmetric reactions using chiral diene ligands has opened up new possibilities for designing ligands for transition metals.[1–4] The chiral diene ligands developed by us[2] and other groups[3] have frequently displayed higher activity and enantioselectivity than chiral phosphine ligands in catalytic asymmetric reactions. Enantiomerically pure dienes have been prepared by use of commercially available chiral building blocks,[3a–3d] by asymmetric synthesis of chiral intermediates,[2a,3f–3h] or by resolution using chiral HPLC.[2b–2i] Those ligands generally require multistep synthesis and thus, the development of readily accessible chiral diene ligands is highly desirable. Here, we wish to report the new C_2-symmetric tetrafluorobenzo[2.2.2]octatrienes (tetrafluorobenzobarrelenes; tfb) **1**[5] as chiral diene ligands, which are prepared in two steps from commercially available reagents (Chart 1). Diastereo- and enantiomerically pure dienes substituted with (−)-menthoxymethyl groups as chiral auxiliaries, are isolated by column chromatography on silica gel. Their application to rhodium-catalyzed asymmetric conjugate arylation, which displays very high enantioselectivity, is also described.

The C_2-symmetric tfb ligands were prepared through a straightforward pathway (Scheme 1). 1,4-Bis((−)-menthoxymethyl)benzene (**2**)[6] was prepared in 72% yield by the etherification of 1,4-bis(chloromethyl)benzene with (−)-menthol. The [4 + 2] cycloaddition of **2** with tetrafluorobenzyne according to a known procedure[5b,5c] gave a 1 to 1 mixture of diastereomers, (*R*,*R*)-**1** and (*S*,*S*)-**1**. It should be noted that these dienes were prepared in only two steps and that each diastereomer was isolated by column chromatography on silica gel, although their yields were not satisfactory. Treatment of $[RhCl(coe)_2]_2$[7] with (*R*,*R*)-**1** or (*S*,*S*)-**1** in hexane at 50 °C for 2 h gave high yields of the corresponding diene–rhodium complexes, $[RhCl((R,R)\text{-}\mathbf{1})]_2$ or $[RhCl((S,S)\text{-}\mathbf{1})]_2$.[8] The hydroxorhodium complex $[Rh(OH)((R,R)\text{-}\mathbf{1})]_2$ was also prepared by the reaction of $[RhCl((R,R)\text{-}\mathbf{1})]_2$ with aqueous KOH in acetone at room temperature for 1 h. The X-ray crystal structure of the rhodium complex $[RhCl((R,R)\text{-}\mathbf{1})]_2$ determined the relative and absolute configuration of the diene (1*R*,4*R*)-**1** as shown in Figure 1.[9] The steric difference between a bulky menthoxymethyl group and a small hydrogen atom creates a good chiral environment around the rhodium.

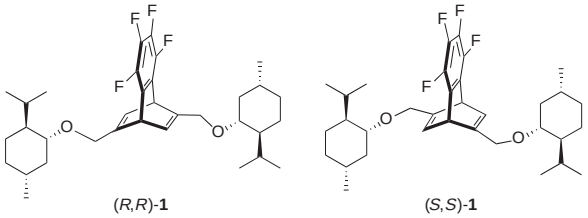
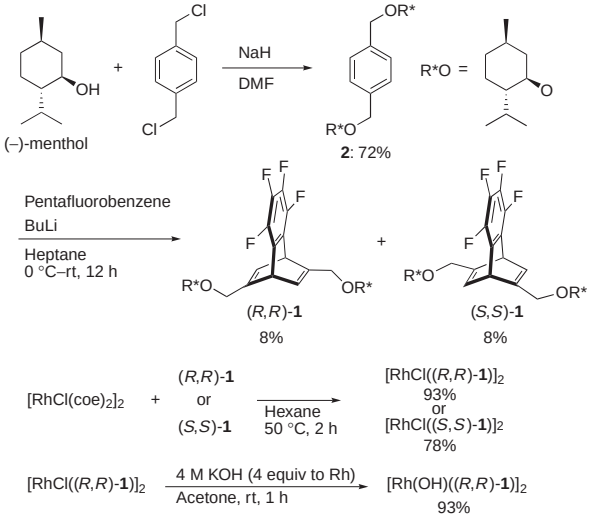


Chart 1.



Scheme 1. Synthesis of chiral tfb ligands.

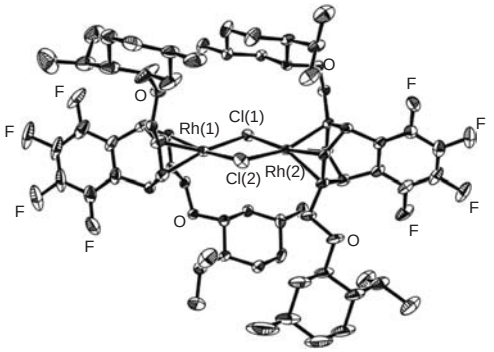
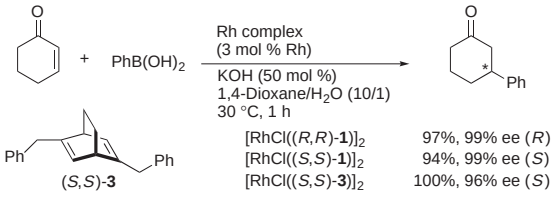
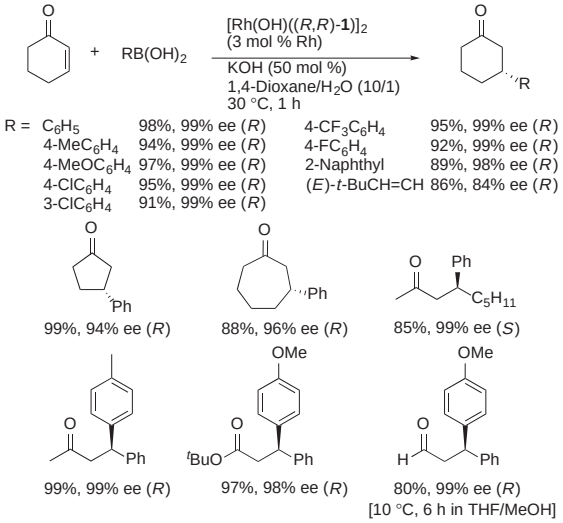


Figure 1. ORTEP illustration of complex $[RhCl((R,R)\text{-}\mathbf{1})]_2$ with thermal ellipsoids drawn at the 50% probability level.

The new tfb–rhodium complexes displayed very high catalytic activity and enantioselectivity in asymmetric 1,4-addition.[10] Thus, treatment of 2-cyclohexen-1-one with phenylboronic acid (2 equiv) and KOH (50 mol %) in 1,4-dioxane/H_2O in the presence of $[RhCl((R,R)\text{-}\mathbf{1})]_2$ (3 mol % of Rh) at 30 °C



Scheme 2. Rhodium-catalyzed asymmetric 1,4-addition of phenylboronic acid to 2-cyclohexen-1-one.



Scheme 3. Asymmetric 1,4-addition catalyzed by [Rh(OH)-((*R*,*R*)-**1**)]$_2$.

for 1 h gave (*R*)-3-phenylcyclohexanone in 97% yield with 99% ee (Scheme 2). The use of [RhCl((*S*,*S*)-**1**)]$_2$ gave the 1,4-addition product of opposite absolute configuration (*S*) with the same high enantioselectivity (99%), indicating that the stereochemical pathway is decided mainly by the chiral diene moiety with little influence of the (−)-menthyl group. The enantioselectivity observed with (*R*,*R*)-**1** or (*S*,*S*)-**1** is higher than that with 2,5-dibenzylbicyclo[2.2.2]octadiene [(*S*,*S*)-**3**],[2b–2f] which is one of the most effective diene ligands for rhodium-catalyzed asymmetric reactions. The high enantioselectivity of **1** may be ascribed to the steric bulkiness of menthoxymethyl group.

The reaction scope of the present enantioselective arylation catalyzed by rhodium/(*R*,*R*)-**1** is broad (Scheme 3). For example, in the presence of [Rh(OH)((*R*,*R*)-**1**)]$_2$ (3 mol % of Rh), the 1,4-addition of arylboronic acids substituted with several functional groups to 2-cyclohexen-1-one gave the corresponding 3-arylcyclohexanones in high yields with excellent enantioselectivity (98–99% ee). The addition of (*E*)-3,3-dimethyl-1-butenylboronic acid gave the corresponding 3-alkenylcyclohexanone in 86% yield with 84% ee. The asymmetric addition of phenylboronic acid to 2-cyclopenten-1-one, 2-cyclohepten-1-one, and 3-nonen-2-one is also catalyzed by rhodium/(*R*,*R*)-**1** with high enantioselectivity. The introduction of a 4-methylphenyl or 4-methoxyphenyl group onto the β-phenyl-substituted enone, enoate, and enal[2d] all proceeded with high enantioselectivity (98–99% ee) to give the corresponding arylation products which contain the diaryl-substituted stereogenic carbon center. These results demonstrate that the tfb **1** presented here is not less enantioselective than other chiral ligands in the rhodium-catalyzed asymmetric 1,4-addition of arylboronic acids to α,β-unsaturated carbonyl compounds.

In summary, we have developed new C_2-symmetric diene ligands having a tetrafluorobenzobarrelene framework, which were prepared in two steps from commercially available reagents. Two diastereomers bearing (−)-menthyl groups as chiral auxiliaries were separated by a simple column chromatography on silica gel. These ligands realized the rhodium-catalyzed highly enantioselective 1,4-addition of arylboronic acids to α,β-unsaturated carbonyl compounds.[11]

References and Notes

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11 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/.

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