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The concise synthesis of chiral tfb ligands and their application to the rhodium-catalyzed asymmetric arylation of aldehydes†‡

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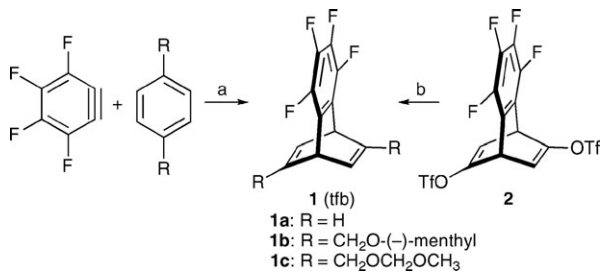
New C_2-symmetric tetrafluorobenzobarrelene ligands were prepared and applied successfully to the rhodium-catalyzed asymmetric addition of arylboronic acids to aromatic aldehydes giving chiral diarylmethanols in high yield with high enantioselectivity.

Chiral dienes have recently been developed as a new class of chiral ligands for transition metals, realizing highly efficient and enantioselective reactions.[1] Of diene ligands bearing diverse bicyclic skeletons, tetrafluorobenzobicyclo[2.2.2]octatriene (tetrafluorobenzobarrelene; tfb; **1a**) and its derivatives[2] are attractive compounds because of their high coordination ability toward transition metals due to their small bite angle and electron-deficient character.[3] In addition, the synthesis of tfb dienes is easy; *e.g.* tfb **1a** is prepared in one step by the formal [4 + 2]-cycloaddition of benzene with tetrafluorobenzyne generated from pentafluorophenyl-lithium or -magnesium (Scheme 1, route a).[2] The use of 1,4-disubstituted benzenes provides chiral tfb dienes. Recently, we reported the synthesis of enantiomerically-pure disubstituted tfb dienes (**1b** and **1c**) *via* the cycloaddition of tetrafluorobenzyne with 1,4-disubstituted benzenes, and their application to rhodium- and iridium-catalyzed asymmetric additions of arylboronic acids.[4] One drawback of the direct preparation of chiral tfb dienes is the difficulty of synthesizing tfbs **1** substituted with aromatic groups. Provided that enantiopure ditriflate **2** is obtained, it is possible to prepare diverse chiral tfb dienes by transition metal-catalyzed cross-coupling reactions (route b). Here, we report the development of C_2-symmetric disubstituted tetrafluorobenzobicyclo[2.2.2]octatrienes **1** and their successful application to the rhodium-catalyzed asymmetric arylation of aldehydes with arylboronic acids.



Scheme 1 Tetrafluorobenzobarrelenes (tfbs).

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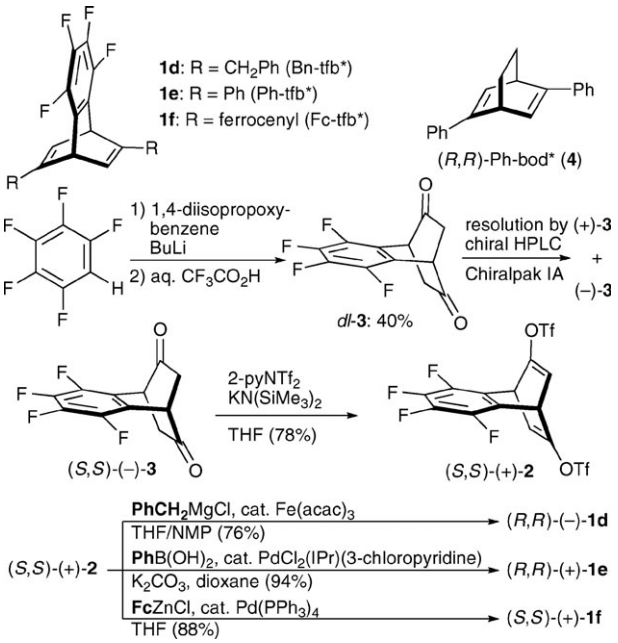
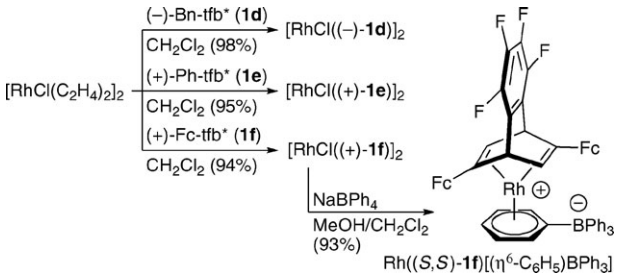
‡ Electronic supplementary information (ESI) available: Experimental procedures and compound characterization data. CCDC 734763. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b911118b



Scheme 2 Synthesis of C_2-symmetric tetrafluorobenzobarrelenes (tfb*).

Chiral ditriflate **2** and tfb ligands **1d–f** were prepared through straightforward pathways (Scheme 2). The [4 + 2]-cycloaddition of 1,4-diisopropoxybenzene to tetrafluorobenzyne, followed by hydrolysis, gave *dl*-**3** in 40% yield.[5] The resolution of diketone *dl*-**3** by the use of a chiral stationary phase column (Chiralpak IA)[6] gave both enantiomers (+)-**3** and (−)-**3**, which were transformed into ditriflate **2**.[7] Enantiopure ditriflate **2** was subjected to cross-coupling reactions with benzylmagnesium chloride,[8] phenylboronic acid[9] and ferrocenylzinc chloride,[10] leading to **1d**, **1e** and **1f**, respectively, in good yields. The reaction of chiral dienes **1d–f** with $[RhCl(C_2H_4)_2]_2$ gave rhodium complexes $[RhCl(\mathbf{1})]_2$ in high yields (Scheme 3). The absolute configuration of (*S*,*S*)-**1f** was assigned by the X-ray crystallographic analysis of its rhodium complex Rh(**1f**)[(η^6-C_6H_5)BPh_3] (Scheme 3, Fig. 1).[11]

The asymmetric synthesis of diarylmethanols by the enantioselective arylation of aldehydes remains a very important objective in organic synthesis.[12] A successful development has been achieved in the asymmetric addition of arylzinc reagents to aldehydes by the use of chiral ligands.[13]



Scheme 3 Synthesis of rhodium complexes.

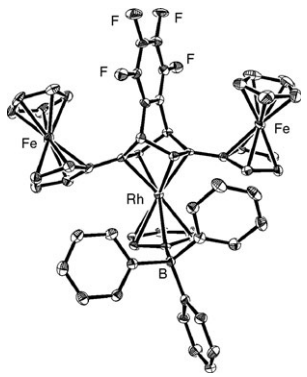
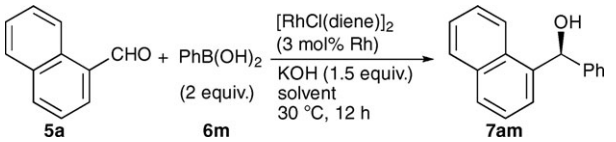


Fig. 1 ORTEP illustration of Rh((*S*,*S*)-**1f**)[(η^6-C_6H_5)BPh_3] with thermal ellipsoids drawn at the 50% probability level. The solvent molecule (CH_2Cl_2) and hydrogens are omitted for clarity.

The transition metal-catalyzed asymmetric addition of organometallic reagents to aldehydes is another useful method for the synthesis of chiral diarylmethanols, where arylboronic acids are used as attractive arylating reagents. Since the first report of the rhodium-catalyzed asymmetric arylation of aldehydes by Miyaura *et al*. in 1998,[14a] Rh,[1k,14] Ni[15] and Ru[16]-catalyzed reactions have been developed.

The new rhodium complexes with tfb ligands, **1d–1f**, were tested in the asymmetric arylation of aldehydes with arylboronic acids. Ligands **1b**, **1c** and Ph-bod **4**[1c,d] were also used for comparison. The treatment of 1-naphthaldehyde (**5a**) with phenylboronic acid (**6m**) in the presence of [RhCl(**1b**)]$_2$ (3 mol% of Rh) and KOH (1.5 equiv.) in 1,4-dioxane/H_2O (4 : 1) at 30 °C for 12 h gave diarylmethanol **7am** in low yield and ee (25%, 16% ee) (Table 1, entry 1). The yields of **7am** were also low in the reaction when tfb ligands substituted with alkyl groups were used (**1c** and **1d**; Table 1, entries 2 and 3). On the other hand, Ph-tfb* **1e** displayed a higher catalytic activity and enantioselectivity, giving **7am** in 94% yield with 49% ee (Table 1, entry 4). The same yield and enantioselectivity were observed in the reaction using Ph-bod* **4**, which has phenyl groups on a bicyclo[2.2.2]octadiene skeleton (Table 1, entry 5). These results imply that the electron-deficient character of the diene substituted with phenyl groups improves the catalytic activity. A higher enantioselectivity was obtained with the tfb ligand **1f** (Fc-tfb*) substituted with ferrocenyl groups, where the ee of **7am** was 72% (Table 1, entry 6). The reaction solvents had a significant influence on the enantioselectivity. Thus, reactions in protic solvents improved the ee of **7am** (Table 1, entries 7–9), and the highest enantioselectivity (86% ee) was observed in *tert*-butyl alcohol (Table 1, entry 9). The reaction with a catalyst loading of

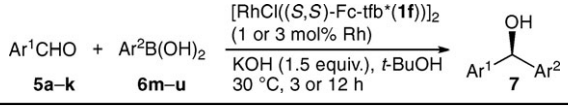
Table 1 The asymmetric addition of **6m** to **5a**[a]



Entry	Ligand	Solvent	Yield (%)[b]	ee (%)[c]
1	**1b**	1,4-Dioxane/H_2O (4 : 1)	25[d]	16 (*S*)
2	**1c**	1,4-Dioxane/H_2O (4 : 1)	30[d]	43 (*S*)
3	**1d**	1,4-Dioxane/H_2O (4 : 1)	49[d]	27 (*S*)
4	**1e**	1,4-Dioxane/H_2O (4 : 1)	94	49 (*S*)
5	**4**	1,4-Dioxane/H_2O (4 : 1)	94	49 (*S*)
6	**1f**	1,4-Dioxane/H_2O (4 : 1)	94	72 (*S*)
7	**1f**	Methanol	99	78 (*S*)
8	**1f**	2-Propanol	99	84 (*S*)
9	**1f**	*tert*-Butyl alcohol	94	86 (*S*)
10[e]	**1f**	*tert*-Butyl alcohol	95	86 (*S*)

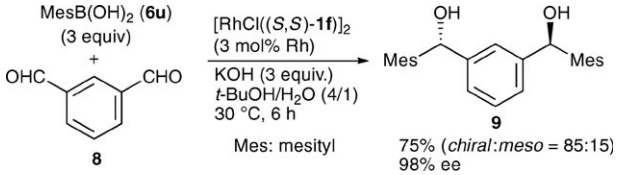
[a] Reaction conditions: [RhCl(diene)]$_2$ (3.75 μmol, 3 mol% of Rh), **5a** (0.25 mmol), **6m** (0.50 mmol), KOH (0.38 mmol), solvent (1.0 mL), 30 °C, 12 h. [b] Isolated yield. [c] Determined by HPLC analysis with a chiral stationary phase column (Chiralcel OD-H). [d] Unreacted **5a** was observed. [e] Performed with [RhCl((*S*,*S*)-**1f**)]$_2$ (1 mol% of Rh) for 3 h.

Table 2 The asymmetric addition of arylboronic acids (**6**) to aromatic aldehydes **5**[a]



Entry	Ar^1	Ar^2	Yield (%)[b]	ee (%)[c]
1	1-Naphthyl (**5a**)	Ph (**6m**)	95 (**7am**)	86 (*S*)
2	2-ClC_6H_4 (**5b**)	Ph (**6m**)	97 (**7bm**)	84 (*S*)
3	2-BrC_6H_4 (**5c**)	Ph (**6m**)	95 (**7cm**)	84 (*S*)
4	2-$MeOC_6H_4$ (**5d**)	Ph (**6m**)	99 (**7dm**)	85 (*S*)
5	2-MeC_6H_4 (**5e**)	Ph (**6m**)	98 (**7em**)	86 (*S*)
6	3-MeC_6H_4 (**5f**)	Ph (**6m**)	96 (**7fm**)	80 (*S*)
7	4-MeC_6H_4 (**5g**)	Ph (**6m**)	99 (**7gm**)	78 (*S*)
8	4-BrC_6H_4 (**5h**)	Ph (**6m**)	85 (**7hm**)	78 (*S*)
9	2-Naphthyl (**5i**)	Ph (**6m**)	93 (**7im**)	82 (*S*)
10	3,4-(OC_2H_4O)C_6H_3 (**5j**)	Ph (**6m**)	94 (**7jm**)	79 (*S*)
11	Ferrocenyl (**5k**)	Ph (**6m**)	94 (**7km**)	85 (*S*)
12	1-Naphthyl (**5a**)	3,5-$Me_2C_6H_3$ (**6n**)	90 (**7an**)	87 (*S*)[d]
13[e]	1-Naphthyl (**5a**)	4-MeC_6H_4 (**6o**)	90 (**7ao**)	85 (*S*)
14	1-Naphthyl (**5a**)	3-MeC_6H_4 (**6p**)	93 (**7ap**)	87 (*S*)[d]
15[e]	1-Naphthyl (**5a**)	2-MeC_6H_4 (**6q**)	87 (**7aq**)	91 (*S*)
16[e]	1-Naphthyl (**5a**)	2-ClC_6H_4 (**6r**)	91 (**7ar**)	86 (*R*)[d]
17[e]	1-Naphthyl (**5a**)	2-MeO-5-MeC_6H_3 (**6s**)	97 (**7as**)	85 (*R*)[d]
18[e]	1-Naphthyl (**5a**)	2,6-$(MeO)_2C_6H_3$ (**6t**)	80 (**7at**)	84 (*R*)[d]
19[e]	1-Naphthyl (**5a**)	Mesityl (**6u**)	87 (**7au**)	94 (*R*)
20[e]	2-ClC_6H_4 (**5b**)	Mesityl (**6u**)	70 (**7bu**)	94 (*S*)[d]
21[e]	2-MeC_6H_4 (**5e**)	Mesityl (**6u**)	87 (**7eu**)	93 (*R*)[d]
22[e]	2-BrC_6H_4 (**5c**)	2-MeC_6H_4 (**6q**)	87 (**7cq**)	86 (*S*)[d]
23[e]	Ferrocenyl (**5k**)	Mesityl (**6u**)	85 (**7ku**)	84 (*S*)[d]
24[e]	Ferrocenyl (**5k**)	2-MeC_6H_4 (**6q**)	98 (**7kq**)	86 (*S*)

[a] Reaction conditions: [RhCl((*S*,*S*)-**1f**)]$_2$ (1 mol% of Rh), Ar^1CHO (0.25 mmol), $Ar^2B(OH)_2$ (0.50 mmol), KOH (0.38 mmol), *t*-BuOH (1.0 mL), 30 °C, 3 h. [b] Isolated yield. [c] Determined by HPLC analysis. [d] The absolute configuration was assigned by analogy with entry 1. [e] Performed with [RhCl((*S*,*S*)-**1f**)]$_2$ (3 mol% of Rh) for 12 h.



Scheme 4 The asymmetric double arylation of **8**.

1 mol% rhodium was complete within 3 h (Table 1, entry 10). The absolute configuration of **7am**, produced by the use of (*S*,*S*)-**1f**, was determined to be (*S*) by comparisons of its specific rotation and retention time in chiral HPLC with those values reported previously.[14]

Table 2 summarizes the results obtained for the reactions of several aldehydes **5** with arylboronic acids **6**, which were carried out in the presence of [RhCl((*S*,*S*)-Fc-tfb*(**1f**))]$_2$ (1 or 3 mol% of Rh). The scope of the aldehydes was broad, examples variously substituted with electron-withdrawing groups and electron-donating groups were good substrates and produced diarylmethanols in high yields (Table 2, entries 1–11). Enantioselectivities in the phenylation of aldehydes having *ortho*-substituents (Table 2, entries 1–5) on the benzene ring were higher than those obtained with *meta*- or *para*-substituted aromatic aldehydes (Table 2, entries 6–9). The scope of arylboronic acids was also broad (Table 2, entries 12–24), where the use of *ortho*-substituted arylboronic acids displayed higher enantioselectivities of diarylmethanols **7** (Table 2, entries 13–15 for $MeC_6H_4B(OH)_2$). Thus, the present catalytic system is effective for the asymmetric synthesis of diarylmethanols having *ortho*-substituents on both aromatic rings, the enantioselectivity ranging between 84 and 94% ee (Table 2, entries 15–22). The asymmetric double arylation of isophthalaldehyde (**8**) was also successful, using mesitylboronic acid (**6u**) to give a 98% ee of chiral diol **9** (75% yield, *chiral* : *meso* = 85 : 15) (Scheme 4).[17]

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