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A Chiral Chelating Diene as a New Type of Chiral Ligand for Transition Metal Catalysts: Its Preparation and Use for the Rhodium-Catalyzed Asymmetric 1,4-Addition

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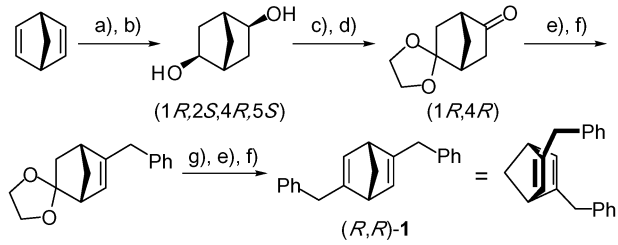
One of the significant subjects for developing catalytic asymmetric reactions is the design and preparation of a chiral ligand which will fit in with a given reaction efficiently in catalytic activity and enantioselectivity.[1] A number of chiral molecules containing phosphines and/or amines have been prepared and some of them have shown their utility as chiral ligands in the catalytic asymmetric reactions.[1] Although chelating dienes represented by 1,5-cyclooctadiene (cod) and norbornadiene (nbd) are known to be stable ligands for late transition metal complexes,[2,3] the use of their chiral version for asymmetric catalysis has never been reported to our best knowledge. Here we report the preparation of a C_2-symmetric chiral diene ligand and its successful use for the rhodium-catalyzed asymmetric 1,4-addition of organometallic reagents.

As a chiral diene framework, C_2-symmetric norbornadiene was chosen because the key intermediate, 2,5-dihydroxybicyclo[2.2.1]-heptane, can be readily obtained in an enantiomerically enriched form by the catalytic asymmetric hydrosilylation.[4] Thus, the hydrosilylation of norbornadiene with trichlorosilane in the presence of 0.1 mol % of a palladium/(*R*)-MeO-MOP catalyst followed by the hydrogen peroxide oxidation gave the diol of (1*R*,2*S*,4*R*,5*S*) configuration (>99% ee) (Scheme 1). Swern oxidation and acetal protection of one of the two carbonyl groups gave (1*R*,4*R*)-acetal-ketone.[5] The alkenyl triflate formation followed by cross-coupling with $PhCH_2MgBr$ in the presence of $PdCl_2(dppf)$[6] and its repetition for the other carbonyl group gave (1*R*,4*R*)-2,5-dibenzylbicyclo-[2.2.1]hepta-2,5-diene ((*R*,*R*)-**1**).[7]

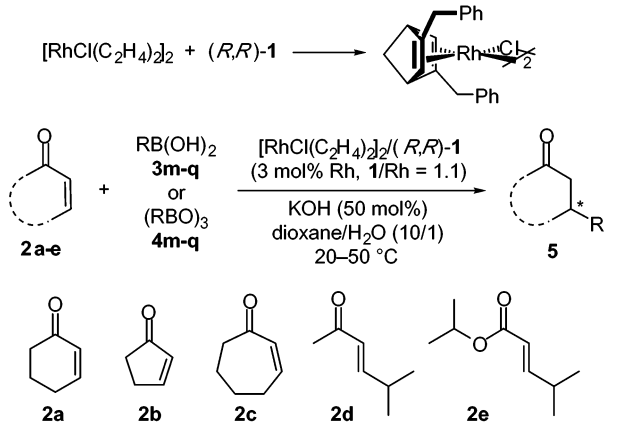
Scheme 1[a]



[a] Reagents and conditions: a) $HSiCl_3$, $[PdCl(\pi\text{-}C_3H_5)]_2$/(*R*)-MeO-MOP (0.1 mol % Pd), 0 °C. b) i) MeOH, Et_3N; ii) H_2O_2, KHF_2, THF/MeOH. c) Me_2SO, $(COCl)_2$, Et_3N, CH_2Cl_2. d) $HOCH_2CH_2OH$, TsOH. e) i) LDA, THF; ii) Tf_2Npy-2. f) $PhCH_2MgBr/Et_2O$, $PdCl_2(dppf)$ (1 mol %). g) dil HCl/THF.

Addition of 1.1 equiv (to Rh) of (*R*,*R*)-**1** to a $CDCl_3$ solution of $[RhCl(C_2H_4)_2]_2$ in an NMR sample tube showed the replacement of ethylene by the diene **1** forming chelating diene complex $[RhCl((R,R)\text{-}\mathbf{1})]_2$[8] at room temperature within 1 h. The rhodium complex in situ generated was used as a catalyst for the asymmetric 1,4-addition of organoboron reagents to α,β-unsaturated ketones and esters[9−11] (Scheme 2). The results summarized in Table 1 deserve the following comments: (1) The catalytic activity is the highest of the chiral rhodium catalysts used for the asymmetric 1,4-addition.

Scheme 2[a]



[a] R = Ph (**m**), 3-$MeOC_6H_4$ (**n**), 4-$MeOC_6H_4$ (**o**), 4-MeC_6H_4 (**p**), 3-ClC_6H_4 (**q**), 4-$CF_3C_6H_4$ (**r**), 4-FC_6H_4 (**s**), 2-naphthyl (**t**), (*E*)-*n*-$C_5H_{11}CH{=}CH$ (**u**).

Table 1. Asymmetric 1,4-Addition of Organoboron Reagents $RB(OH)_2$ (**3**) or $(RBO)_3$ (**4**) to α,β-Unsaturated Ketones and Esters **2** Catalyzed by $[RhCl(C_2H_4)_2]_2$/(*R*,*R*)-**1**[a]

entry	**2**	**3** or **4**	temp (°C)	time (h)	yield[b] (%) of **5**	% ee[c]
1	**2a**	**3m**	30	1	94 (**5am**)	96 (*R*)
2[d]	**2a**	**3m**	20	3	85 (**5am**)	96 (*R*)
3	**2a**	**3m**	40	1	94 (**5am**)	95 (*R*)
4	**2a**	**4n**	30	1	92 (**5an**)	97 (*R*)
5	**2a**	**4o**	30	1	89 (**5ao**)	95 (*R*)
6	**2a**	**4p**	30	1	88 (**5ap**)	96 (*R*)
7	**2a**	**4q**	50	1	92 (**5aq**)	93 (*R*)
8	**2a**	**3r**	50	1	90 (**5ar**)	99 (*R*)
9	**2a**	**4s**	50	1	91 (**5as**)	97 (*R*)
10	**2a**	**4t**	30	1	96 (**5at**)	96 (*R*)
11	**2a**	**3u**	50	1	73 (**5au**)	88 (*R*)
12	**2b**	**4m**	50	1	88 (**5bm**)	88 (*R*)
13[e]	**2b**	**3u**	50	1	78 (**5bu**)	96 (*R*)
14	**2c**	**3m**	50	1	81 (**5cm**)	90 (*R*)
15	**2d**	**3m**	30	3	81 (**5dm**)	97 (*R*)
16	**2e**	**4m**	50	1	73 (**5em**)	92 (*R*)

[a] The reaction was carried out with enone **2** (0.30 mmol), boron reagent **3** or **4** (0.60 mmol), $[RhCl(C_2H_4)_2]_2$ (3 mol % Rh), (*R*,*R*)-**1** (**1**/Rh = 1.1/1.0), and 1.5 M aq KOH (0.10 mL) in dioxane (1.0 mL). [b] Isolated yield by silica gel chromatography. [c] Determined by HPLC analysis with chiral stationary phase columns: Daicel Chiralcel OD-H for **5am**, **5an**, **5ar**, **5at**, **5cm**, **5dm**, and **5em**; OB−H for **5bm**; AD for **5ao**, **5ap**, **5aq**, and **5as**; and AS for **5au** and **5bu**. [d] The ratio of **3m**/**2a** is 1.3/1.0. [e] The amount of the rhodium catalyst is 10 mol %.

The addition of phenylboronic acid (**3m**) to 2-cyclohexenone (**2a**) took place at 20 or 30 °C in dioxane/H_2O in the presence of KOH[12] to give high yield of the 1,4-addition product **5am** (entries 1 and 2). (2) The enantioselectivities observed here are among the highest for the rhodium-catalyzed asymmetric 1,4-addition, the selectivity being over 90% ee in most of the reactions examined for several cyclic and linear enones and for aryl- and alkenylboron reagents.

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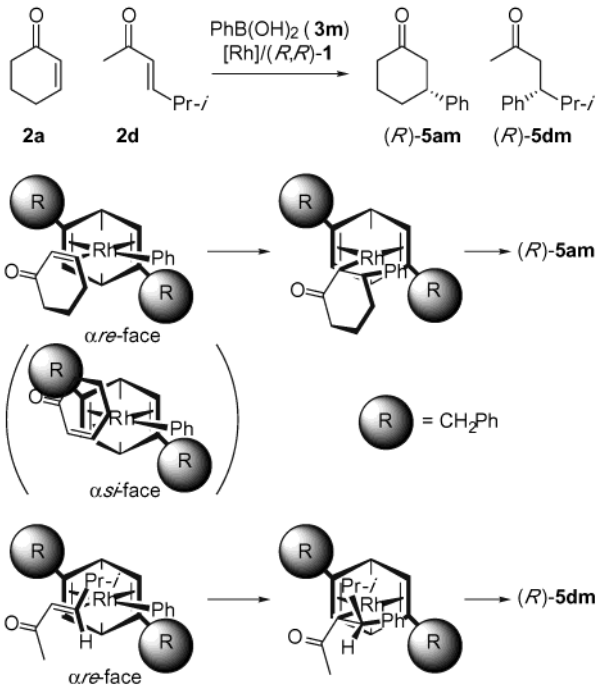
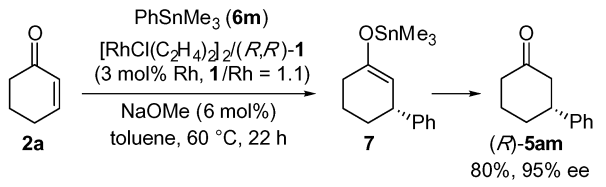
Scheme 3



(3) The absolute configuration of all the products obtained with (*R*,*R*)-**1** is (*R*). The (*R*,*R*)-**1**-rhodium complex recognizes the enantioface of the enones by the steric repulsions between the benzyl group on the diene and the carbonyl moiety, the coordination with the α*re*-face being favorable for both cyclic and linear enones, which leads to the products of (*R*) configuration (Scheme 3).

The diene (*R*,*R*)-**1** demonstrates its remarkable ability as a chiral ligand in the catalytic reactions where chiral phosphine ligands cannot be used because of the low catalytic activity of the phosphine complexes. The rhodium-catalyzed 1,4-addition of organostannanes is one of the typical examples.[13] The reaction of phenyltrimethylstannane (**6m**) with 2-cyclohexenone (**2a**) in the presence of 3 mol % of the (*R*,*R*)-**1**-rhodium catalyst and sodium methoxide in toluene at 60 °C for 22 h gave a high yield of the stannyl enol ether **7** (Scheme 4). On hydrolysis, (*R*)-**5am** of 95% ee was obtained in 80% yield. Under similar conditions, rhodium catalysts coordinated with binap ligand gave less than 10% yield of the 1,4-addition product.

Scheme 4



In summary, we have succeeded, for the first time, in the design and preparation of a chiral diene as a chiral ligand for asymmetric catalysis. The diene ligand demonstrated its high and unique ability in the rhodium-catalyzed asymmetric 1,4-addition of organoboron and -tin reagents. We are now in a position to be able to design new chiral diene ligands of higher ability and to apply them to a variety of catalytic asymmetric reactions, especially to those where the diene ligands are more suitable than other types of ligands in catalytic activity.

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Supporting Information Available: Experimental procedures, spectroscopic and analytical data for the products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) (*R*,*R*)-**1**: ^{1}H NMR ($CDCl_3$): δ 1.94 (t, J = 1.7 Hz, 2H), 3.14 (dt, J = 3.8, 1.7 Hz, 2H), 3.49 (s, 4H), 6.02 (dt, J = 3.8, 1.6 Hz, 2H), 7.09 (d, J = 7.2 Hz, 4H), 7.18 (tt, J = 7.2, 1.2 Hz, 2H), 7.26 (t, J = 7.2 Hz, 4H). $[\alpha]^{20}_D$ +217 (*c* 1.02, $CHCl_3$).

(8) $[RhCl(R,R\text{-}\mathbf{1})]_2$: ^{1}H NMR ($CDCl_3$): δ 0.76 (s, 4H), 3.07 (d, J = 14.4 Hz, 4H), 3.50 (s, 4H), 3.75 (d, J = 14.4 Hz, 4H), 3.79 (s, 4H), 7.17−7.47 (m, 20H).

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