ORGANIC LETTERS

2003
Vol. 5, No. 21
3831−3834

Synthesis of New Chiral Monodentate Phosphite Ligands and Their Use in Catalytic Asymmetric Hydrogenation

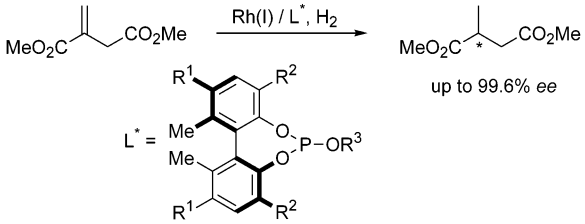
Zihao Hua, Victor C. Vassar, and Iwao Ojima*

Department of Chemistry, State University of New York at Stony Brook, Stony Brook, New York 11794-3400

iojima@notes.cc.sunysb.edu

Received July 19, 2003

ABSTRACT



New monodentate phosphite ligands have been developed from axially chiral biphenols, which show excellent enantioselectivity in the Rh-(I)-catalyzed hydrogenation of dimethyl itaconate. The new chiral ligand system is suitable to create libraries and possesses fine-tuning capability.

Recently, a number of monodentate phosphorus ligands has been developed for metal-catalyzed asymmetric reactions such as hydrogenation,[1] 1,4-addition to enones,[2] hydrovinylation,[3] hydrosilylation,[4] intramolecular Heck reaction,[5] allylic alkylation,[6] amination[7] and etherification.[8] The previously reported monodentate ligands are mostly based on enantiopure BINOL[2b,9] or TADDOL.[10] However, no monodentate phosphite ligands from enantiopure axially chiral biphenols have been reported. We describe here the development of a new class of readily accessible biphenol-based chiral monophosphite ligands **1** (Figure 1) and their application to the Rh(I)-catalyzed asymmetric hydrogenation of dimethyl itaconate.

One of the salient and practical features of these chiral monophosphite ligands is the fine-tuning capability with modifiable substituents R^1, R^2, and R^3 in structure **1**.

This fine-tuning capability will play a crucial role in the forthcoming applications of these new ligands to a variety of catalytic asymmetric reactions. Another advantage of these chiral monophosphite ligands is the fact that the 6,6′-dimethyl groups make the biphenol more configurationally stable as compared to the corresponding chiral BINOLs.

The enantiopure biphenols (*S*)-**2a** and (*R*)-**2a** were prepared following the literature procedure.[11] The *tert*-butyl groups at the 3 and 3′ positions of **2a** can be removed by treating with $AlCl_3$ in $MeNO_2$−benzene via a Friedel−Crafts

(1) For review: Komarov, I. V.; Börner, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 1197.; For recent examples: (a) Peña, D.; Minnaard, A. J.; de Vries, J. G.; Feringa, B. L. *J. Am. Chem. Soc.* **2002**, *124*, 14552. (b) Hu, A.-G.; Fu, Y.; Xie, J.-H.; Zhou, H.; Wang, L.-X.; Zhou, Q.-L. *Angew. Chem., Int. Ed.* **2002**, *41*, 2348. (c) Reetz, M, T.; Sell, T.; Meiswinkel, A.; Mehler, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 790. (d) Hannen, P.; Militzer, H.-C.; Vogl, E. M.; Rampf, F. A. *Chem. Commun.* **2003**, 2210.

(2) (a) For reviews, see: Krause, N. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 283. (b) Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346. (c) Alexakis, A.; Rosset, B. S.; Human, M. *J. Am. Chem. Soc.* **2002**, *124*, 5262.

(3) Francio, G.; Faraone, F.; Leitner, W. *J. Am. Chem. Soc.* **2002**, *124*, 736.

(4) Jensen, J. F.; Svendsen, B. Y.; la Cour, T. V.; Pedersen, H. L.; Johannsen, M. *J. Am. Chem. Soc.* **2002**, *124*, 4558.

(5) Imbos, R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2002**, *124*, 184.

(6) (a) Bartels, B,; Helmchen, G. *Chem. Commun.* **1999**, 741. (b) Malda, H.; van Zijl, A. W.; Arnold, L. A.; Feringa, B. L. *Org. Lett.* **2001**, *3*, 1169.

(7) Ohmura, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 15164.

(8) López, F.; Ohmura, T. Hartwig, J. F *J. Am. Chem. Soc.* **2003**, *125*, 3426.

(9) (a) Reetz, M. T.; Mehler, G. *Angew. Chem., Int. Ed.* **2000**, *39*, 3889. (b) Reetz, M. T.; Sell, T. *Tetrahedron Lett.* **2000**, *41*, 6333.

(10) Alexakis, A.; Vastra, J.; Burton, J.; Benhaim C.; Mangeney P. *Tetrahedron Lett.* **1998**, *39*, 7869.

(11) Alexander, J. B.; Schrock, R. R.; Davis, W. M.; Hultzsch, K. C.; Hoveyda, A. H.; Houser, J. H. *Organometallics* **2000**, *19*, 3700.

10.1021/ol035343r CCC: $25.00
Published on Web 09/18/2003

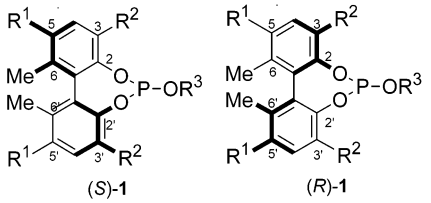
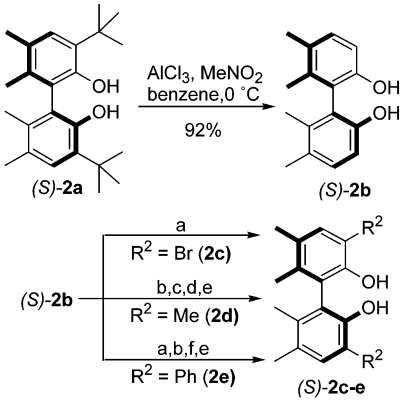


Figure 1. General structures of new monophosphite ligands.

transfer reaction to provide biphenol **2b** without any loss of enantiopurity.[12] The biphenols (*S*)-**2c**−**e** (R^2 = Br, Me, Ph) were synthesized from (*S*)-**2b** as shown in Scheme 1 (only the *S* series is shown).[13]

Scheme 1. Synthesis of Biphenols (*S*)-**2b**−**e**[a]



[a] Key: (a) Br_2, $CHCl_3$; (b) Me_2SO_4, Bu_4NI, KOH, CH_2Cl_2; (c) H_3PO_4, HCl, AcOH, CH_2O; (d) $LiAlH_4$, THF; (e) BBr_3, CH_2Cl_2; (f) $Pd(PPh_3)_4$, $C_6H_5B(OH)_2$, $NaHCO_3$, DME−H_2O.

Then, a small library of new monophosphite ligands **4**−**9** (Figure 2) was synthesized from the enantiopure biphenols (S)-**2a**−**e** or (*R*)-**2a**,**b** thus obtained, achiral hydroxyarenes (**4** and **5**) or chiral secondary alkanols (**6**−**9**), and phosphorus trichloride. A general procedure for the synthesis of these new monophosphite ligands is shown in Scheme 2, wherein an enantiopure biphenol **2** and a phosphorodichloridite **3** were reacted at ambient temperature in the presence of Et_3N to give the corresponding phosphite in good to high yields. Phosphorodichloridite **3** (R^3 = alkyl) was prepared by adding a secondary alkanol to PCl_3 (2 equiv) in CH_2Cl_2 and subsequent removal of excess PCl_3, while **3** (R^3 = aryl) was obtained in good yield by reacting $(ArO)_3P$ or ArOH with PCl_3 followed by distillation under reduced pressure.[14]

The efficacy of the new monophosphite ligands **4**−**9** was evaluated in the Rh(I)-catalyzed asymmetric hydrogenation

(12) For example, Yamato, T.; Hasegawa, K.; Saruwatari, Y.; Doamekpor, L. K. *Chem. Ber.* **1993**, *126*, 1435.

(13) For details of the synthesis of biphenols (*S*)-**2b**−**e**, see the Supporting Information.

(14) For preparation of $ArOPCl_2$, see: (a) Conant, J. B.; Wallngford, V. H.; Gandheker, S. S. *J. Am. Chem. Soc.* **1923**, *45*, 762. (b) Barinov, I. V.; Rode, D. D.; Rafikov, S. R. *J. Gen. Chem. USSR* **1967**, *37*, 432.

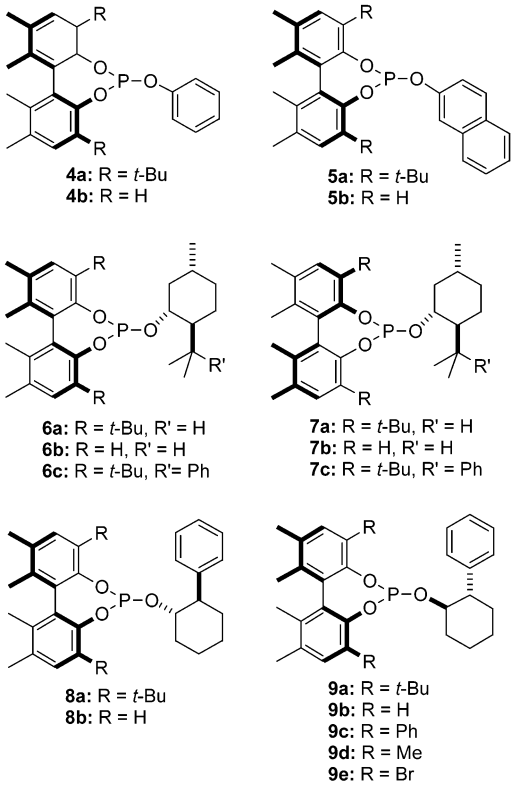


Figure 2. Ligand list.

of dimethyl itaconate. The catalyst was formed in situ by mixing a cationic Rh complex, $[Rh(COD)_2]BF_4$ or $[Rh(COD)_2]SbF_6$, with 2 equiv of a chiral ligand in a solvent at ambient temperature under nitrogen.

First, the reactions were carried out using ligands **4**−**9** having H or *tert*-butyl at the 3 and 3′ positions (R^2 = H or *t*-Bu) at ambient temperature and 100 psi (6.8 atm) of H_2 in CH_2Cl_2. Results are summarized in Table 1.

As Table 1 shows, the Rh catalysts with ligands bearing a *tert*-butyl group at the 3 and 3′ positions (**4a**−**9a**, **6c**, and **7c**) exhibited poor to excellent catalyst activity and low to moderate enantioselectivity (entries 1, 3, 5, 7, 9−11, and 13). In contrast, the Rh catalysts with ligands **4b**−**7b** (R^2 = H) showed excellent enantioselectivity (92−96.5% ee) with complete conversion (entries 2, 4, 6, and 8), which is comparable to that obtained by using the corresponding BINOL-based monophosphite ligands.[9a] The introduction of a chiral secondary alkoxy moiety to the ligands **6b** and **7b**

Scheme 2. Synthesis of Monophosphite Ligands

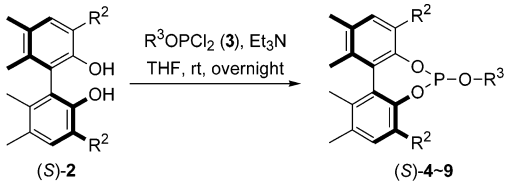


Table 1. Asymmetric Hydrogenation of Dimethyl Itaconate Using $[Rh(COD)_2]BF_4$ with Monophosphite Ligands[a]

entry	ligand	conv[b] (%)	% ee[b,c]
1	**4a**	90	14.0 (*R*)
2	**4b**	100	96.5 (*S*)
3	**5a**	97	19.0 (*R*)
4	**5b**	100	96.4 (*S*)
5	**6a**	100	25.0 (*R*)
6	**6b**	100	92.0 (*S*)
7	**7a**	100	44.0 (*S*)
8	**7b**	100	93.0 (*R*)
9	**6c**	3.5	24.3 (*R*)
10	**7c**	4.3	32.0 (*S*)
11	**8a**	<1	n.a.
12	**8b**	<1	n.a.
13	**9a**	<1	n.a.

[a] The reaction was performed in CH_2Cl_2 at 23 °C and 100 psi (6.8 atm) of H_2 for 20 h [substrate (0.5 mmol, 0.1 M)/$Rh(COD)_2BF_4$/ligand = 200:1:2]. [b] Conversion and enantiopurity were determined by GC on a Supelco Beta Dex-225 column. [c] The absolute configuration was determined by comparing the GC spectra with those of authentic samples.

Table 2. Asymmetric Hydrogenation of Dimethyl Itaconate Using $[Rh(COD)_2]SbF_6$ with Monophosphite Ligands[a]

entry	ligand	solvent	conv[b] (%)	% ee[b,c]
1	**4a**	CH_2Cl_2	100	16.4 (*R*)
2	**5a**	CH_2Cl_2	100	22.5 (*R*)
3	**6a**	CH_2Cl_2	100	14.5 (*R*)
4	**7a**	CH_2Cl_2	100	9.3 (*S*)
5	**6c**	CH_2Cl_2	100	94.4 (*R*)
6	**6c**	$ClCH_2CH_2Cl$	100	98.9 (*R*)
7	**7c**	CH_2Cl_2	100	97.6 (*S*)
8	**7c**	$ClCH_2CH_2Cl$	100	98.7 (*S*)
9	**8a**	CH_2Cl_2	100	97.8 (*R*)
10	**8a**	$ClCH_2CH_2Cl$	100	99.6 (*R*)
11	**9a**	CH_2Cl_2	100	99.0 (*R*)
12	**9a**	$ClCH_2CH_2Cl$	100	99.1 (*R*)

[a] The reaction was performed at 50 °C and 100 psi (6.8 atm) of H_2 for 20 h [substrate (0.5 mmol, 0.1 M)/$Rh(COD)_2SbF_6$/ligand = 200:1:2]. [b] Conversion and enantiopurity were determined by GC on a Supelco Beta Dex-225 column. [c] The absolute configuration was determined by comparing GC spectra with those of authentic samples.

did not further improve the enantioselectivity as compared to that achieved by the ligands with an achiral aryloxy moiety (**4b** and **5b**) (entries 2, 4, 6, and 8).

The reactions using **6b** (*S*-biphenyl) and **7b** (*R*-biphenyl), which have the same (−)-menthyloxy moiety, gave (*S*)-methylsuccinate (92% ee) and (*R*)-methylsuccinate (93% ee), respectively (entries 6 and 8). Thus, the influence of the chiral alkoxy moiety of the ligand on enantioselectivity is found to be almost negligible.

It is worth mentioning that the substituents at the 3 and 3′ positions (R^2 = H or *t*-Bu) exert marked differences in the direction and the extent of asymmetric induction. Thus, the ligands with a hydrogen at the 3 and 3′ positions (**4b**, **5b**, **6b**, and **7b**) uniformly show excellent enantioselectivity, giving (*S*)-methylsuccinate [(*R*) for **7b**], while those with a *tert*-butyl group at the 3 and 3′ positions afford (*R*)-methylsuccinate [(*S*) for **7a**] with only 14−44% ee.

The ligands bearing a bulky chiral secondary alkoxy group on the phosphorus (**8a**, **8b**, and **9a**) virtually do not show any appreciable activity under the same conditions, although the ligands with a (−)-phenylmenthyloxy group (**6c** and **7c**) show very low conversion and low to moderate enantioselectivity (entries 9−13).

Next, we switched the Rh-catalyst precursor from $[Rh(COD)_2]BF_4$ to $[Rh(COD)_2]SbF_6$ and carried out the reactions at 50 °C and 100 psi (6.8 atm) of H_2 in CH_2Cl_2. Results are summarized in Table 2. As Table 2 shows, the bulky ligands (**6c**, **7c**, **8a**, and **9a**), which gave rather poor results or did not show catalytic activity under the conditions summarized in Table 1, have achieved excellent enantioselectivity (up to 99.6% ee) and 100% conversion (entries 5−12). Thus, a remarkable effect of the counteranion on the catalytic activity as well as enantioselectivity is observed. However, it should be noted that the remarkable improvement in enantioselectivity is observed only for the ligands bearing very bulky chiral alkoxy moieties (**6c**, **7c**, **8a**, and **9a**), and the ligands bearing aryloxy moieties (**4a** and **5a**) (entries 1 and 2) or (−)-menthyloxy moieties (**6a** and **7a**) (entries 3 and 4) do not show any improvement. Nevertheless, the catalytic activity of these ligands (**4a**−**7a**) is greatly improved, giving the product in quantitative yield in each case.

Solvents used in this reaction exerted dramatic effects on the enantioselectivity. For example, when THF, MeOH, EtOAc, or $CHCl_3$ was used as the solvent, no enantioselectivity was observed. Similar results have recently been reported by van der Berg et al. for their BINOL-based phosphoramidite ligand.[15] Appropriate solvents for this hydrogenation reaction so far appear to be dichloromethane and 1,2-dichloroethane, and the use of 1,2-dichloroethane has achieved the best enantioselectivity in all cases examined (entries 6, 8, 10, and 12).

It is believed that two molecules of a monophosphite ligand will coordinate with a Rh metal to form an active catalyst species.[1b,16] However, the reaction using only 1 equiv of ligand **7b** to Rh under the conditions in Table 1 gave (*R*)-methylsuccinate with the same enantiopurity (93% ee) in quantitative yield. In turn, the conversion and enantioselectivity significantly decreased (7.0% conversion, 58% ee) when the ligand/Rh ratio was increased to 3. A similar phenomenon has recently been reported in the reaction of a dehydroamino acid using a monophosphoramidite ligand.[16] More interestingly, the ligand/Rh ratio did not make any difference in the conversion and enantioselectivity when using bulky ligands such as **7c** under the conditions in Table 2. Thus, the reactions using **7c** in 1,2-dichloroethane gave (*S*)-methylsuccinate in complete conversion and 98.7% ee with the ligand/Rh ratio of 1, 2, or 3. Detailed mechanistic

(15) van den Berg, M.; Minnaard, A. J.; Haak, R. M.; Leeman, M.; Schudde, E. P.; Meetsma, A.; Feringa, B. L.; de Vries, A. H. M.; Maljaars, C. E. P.; Willans, C. E.; Hyett, D.; Boogers, J. A. F.; Henderickx, H. J. W.; de Vries, J. G. *Adv. Synth. Catal.* **2003**, 308.

(16) Claver, C.; Fernandez, E.; Gillon, A.; Heslop, K.; Hyett, D. J.; Martorell, A.; Orpen, A. G.; Pringle, P. G. *Chem. Commun.* **2000**, 961.

Table 3. Asymmetric Hydrogenation of Dimethyl Itaconate Using $[Rh(COD)_2]SbF_6$ with Ligands **9a**−**e**[a]

entry	ligand	R^2	conv[b] (%)	% ee[b,c]
1	**9a**	*t*-Bu	100	99.0 (*R*)
2	**9b**	H	81	2.7 (*S*)
3	**9c**	C_6H_5	100	97.8 (*R*)
4	**9d**	CH_3	100	76.9 (*R*)
5	**9e**	Br	100	97.1 (*R*)

[a] The reaction was performed at 50 °C and 100 psi (6.8 atm) of H_2 for 20 h [substrate (0.5 mmol, 0.1 M)/$Rh(COD)_2SbF_6$/ligand = 200:1:2]. [b] Conversion and enantiopurity were determined by GC on a Supelco Beta Dex-225 column. [c] The absolute configuration was determined by comparing GC spectra with those of authentic samples.

work on the structure(s) of active catalyst species is clearly warranted.

The effects of the 3- and 3′-substituents (i.e., R^2) on the asymmetric induction were examined by introducing a hydrogen, phenyl, methyl, and bromine as R^2 to the ligand **9** in addition to a *tert*-butyl group (**9a**). Results of the asymmetric hydrogenation of dimethyl itaconate under the same reaction conditions as those shown in Table 2, except for using only dichloromethane as the solvent, are listed in Table 3. As Table 3 shows, the bulkiness of R^2 has critical influence on the extent and direction of asymmetric induction. Thus, the enantioselectivity decreases in the order *t*-Bu, Ph, Br, Me, and H as R^2, which is in accordance with the decrease in the size of this substituent. When R^2 is hydrogen (**9b**), the reaction did not complete and gave the product of the opposite configuration with only 2.7% ee. These results clearly indicate that the fine-tuning of this series of chiral ligands is possible by systematic modification of the substituent R^2, as originally designed, besides the obvious variations of the substituent R^3.

In conclusion, a library of new monophosphite ligands from biphenols with axial chirality has been developed. These new ligands have achieved excellent enantioselectivity (up to 99.6% ee) when used in the Rh(I)-catalyzed asymmetric hydrogenation of dimethyl itaconate. The substituents (R^2) at the 3 and 3′ positions exert dramatic effects on the catalyst activity as well as enantioselectivity of the reaction. The nature of the substituent (R^3) of the alkoxy or aryloxy moiety also exhibited substantial effects on enantioselectivity. Thus, it is obvious that this type of new monophosphite ligands possess fine-tuning capability, which would play a crucial role in achieving high enantioselectivity in the asymmetric hydrogenation of different substrate types. Applications of these biphenol-based monophosphite ligands to a variety of catalytic asymmetric transformations as well as detailed mechanistic studies are actively underway in these laboratories.

Acknowledgment. This work was supported by a grant from the Mitsubishi Chemical Corporation and in part by grants from the National Institutes of Health (NIGMS) and the National Science Foundation.

Supporting Information Available: Experimental procedures and the characterization data of all the ligands and new biphenols (*S*)-**2b**−**e**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL035343R