J|A|C|S
COMMUNICATIONS

Published on Web 04/12/2002

Highly Effective Chiral Ortho-Substituted BINAPO Ligands (*o*-BINAPO): Applications in Ru-Catalyzed Asymmetric Hydrogenations of *β*-Aryl-Substituted *β*-(Acylamino)acrylates and *β*-Keto Esters

Yong-Gui Zhou, Wenjun Tang, Wen-Bo Wang, Wenge Li, and Xumu Zhang*

Department of Chemistry, The Pennsylvania State University, 152 Davey Laboratory, University Park, Pennsylvania 16802

Received January 23, 2002

During the last several decades, many effective chiral bisphosphines have been developed. However, there is no solution in dealing with many transition metal-catalyzed asymmetric transformations since enantioseletivities are often substrate-dependent. Subtle changes in conformational, steric, and electronic properties of chiral ligands can lead to dramatic variations of reactivities and enantioselectivities. Conformationally rigid and tunable chiral ligands offer a great advantage for optimizing the enantioselectivty of a reaction. Herein, we like to report ruthenium catalysts with a novel family of BINOL-derived phosphinite ligands for the first highly enantioselective hydrogenation of *β*-aryl-substituted *β*-(acylamino)acrylates. These catalysts are also effective for highly enantioselective hydrogenation of *β*-aryl-substituted *β*-keto esters.

Noyori and co-workers have demonstrated that highly skewed BINAP was an effective ligand for many asymmetric catalytic reactions.[1,2] A comparison of the structure of BINAP with the less-effective BINAPO ligands[3] reveals two possible reasons: (1) the oxygen atoms in the BINAPO increase the distance between the chiral binaphthyl moiety and PPh_2 groups and therefore decrease the influence of chiral binaphthyl on orientation of the phenyl groups of PPh_2 and (2) the presence of the C−O−P bond in BINAPO increases the flexibility of backbone. To develop highly effective BINAPO ligands, we have designed ligands **2a**−**d** by introducing groups into 3,3′-positions of the binaphthyl backbone (ortho-substituted BINAPO, abbreviated as *o*-BINAPO): introduction of 3,3′-R groups can restrict the orientation of Ar groups adjacent to phosphine atoms. In addition, tuning of the steric and electronic properties can be achieved by changing the R and Ar groups of ligands. These ligands can be synthesized from the corresponding diols [4] (Scheme 1).

Enantiomerically pure *β*-amino acids and their derivatives are important building blocks for the synthesis of *β*-peptides, *β*-lactam antibiotics, and many important drugs.[5] Recently, several synthetic methodologies have been developed to make *β*-amino acids by using stoichiometric chiral auxiliaries and catalytic methods,[6] Among these methods, straightforward asymmetric hydrogenation of *β*-aminoacrylic acid derivatives represents one of the simplest routes. Previous attempts at asymmetric hydrogenation of *β*-(acylamino)-acrylates using Ru[7] and Rh[8] catalysts led to moderate to good enantioselectivity. The main issue is that the different catalytic behaviors (ee values, catalytic activities) exist with *Z*- and *E*-isomeric substrates. For example, (*E*)-methyl 3-acetamido-2-butenoate gave 96% ee in Noyori's Ru-BINAP system,[7] while (*Z*)-methyl 3-acetamido-2-butenoate gave only 5% ee with the opposite configuration. So far, only moderate ee can be obtained with Rh-DuPhos[8c] and Ru-BINAP[7] systems for hydrogenation of *β*-aryl-substituted *β*-(acylamino)acrylates.

Scheme 1

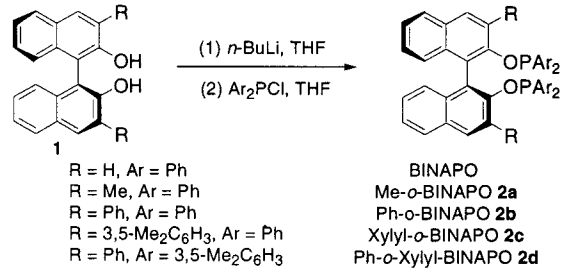
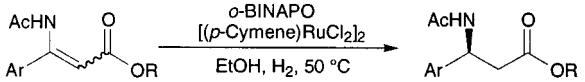


Table 1. Asymmetric Hydrogenation of *β*-Aryl-Substituted *β*-(Acylamino)acrylates **3**[a]



entry	ligands	Ar of **3**	R of **3**	ee (%)[b]	config.[c]
1	BINAPO	Ph	Me (**3a**)	2 (**5a**)	S
2	**2a**	Ph	Me (**3a**)	22 (**5a**)	S
3	**2b**	Ph	Me (**3a**)	98 (**5a**)	S
4	**2c**	Ph	Me (**3a**)	99 (**5a**)	S
5	**2d**	Ph	Me (**3a**)	97 (**5a**)	S
6	BINAP	Ph	Me (**3a**)	31 (**5a**)	S
7	MeO-Biphep	Ph	Me (**3a**)	39 (**5a**)	S
8	**2c**	*p*-F-C_6H_4	Me (**3b**)	99 (**5b**)	S
9	**2c**	*p*-Cl-C_6H_4	Me (**3c**)	97 (**5c**)	S
10	**2c**	*p*-Br-C_6H_4	Me (**3d**)	97 (**5d**)	S
11	**2c**	*p*-Me-C_6H_4	Me (**3e**)	99 (**5e**)	S
12	**2c**	*p*-MeO-C_6H_4	Me (**3f**)	99 (**5f**)	S
13	**2c**	*o*-Me-C_6H_4	Me (**3g**)	96 (**5g**)	S
14	**2c**	*o*-MeO-C_6H_4	Me (**3h**)	80 (**5h**)	S
15	**2c**	Ph	Et (**3i**)	98 (**5i**)	S
16	**2c**	*p*-F-C_6H_4	Et (**3j**)	98 (**5j**)	S
17	**2c**	*p*-Cl-C_6H_4	Et (**3k**)	95 (**5k**)	S
18	**2c**	*p*-Br-C_6H_4	Et (**3l**)	93 (**5l**)	S

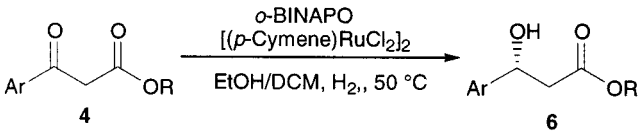
[a] The absolute configurations were determined by comparing optical rotations with reported values. The reaction was carried out under 80 psi of H_2 in EtOH at 50 °C for 20 h, substrate/[Ru(*p*-cymene)Cl_2]$_2$/ligand = 50/1/2.1. [b] The ee (%) values were determined by GC using a chiralselect 1000 column. [c] Determined by the sign of rotations.

To test the synthetic utility of bisphosphinite ligands **2**, we have explored the Ru-catalyzed asymmetric hydrogenation of *β*-aryl-substituted *β*-(acylamino)acrylates **3** (Table 1). Substrates **3a**−**l** (*E*/*Z* = 5/95 to 40/60) can be made from the *β*-keto esters **4** according to a literature procedure.[8c,9] The *E*/*Z* mixture of enamides **3a**−**l** cannot be separated by silica gel column chromatography. The Ru catalyst was prepared by mixing the [Ru(*p*-cymene)Cl_2]$_2$ and a

* Corresponding author. E-mail: xumu@chem.psu.edu.

10.1021/ja020121u CCC: $22.00

Table 2. Asymmetric Hydrogenation of β-Keto Esters **4**[a]



entry	ligand	Ar of **4**	R of **4**	ee (%) of **6**[b]	config.[c]
1	**2c**	Ph	Et (**4a**)	99 (**6a**)	R
2	**2c**	*p*-F-C_6H_4	Et (**4b**)	93 (**6b**)	R
3	**2c**	*p*-Cl-C_6H_4	Et (**4c**)	98 (**6c**)	R
4	**2c**	*p*-Br-C_6H_4	Et (**4d**)	96 (**6d**)	R
5	**2c**	*p*-Me-C_6H_4	Et (**4e**)	95 (**6e**)	R
6	**2c**	*p*-MeO-C_6H_4	Et (**4f**)	87 (**7f**)	R
7	**2c**	*o*-Me-C_6H_4	Et (**4g**)	90 (**6g**)	R
8	**2c**	*o*-MeO-C_6H_4	Et (**4h**)	98 (**6h**)	R
9	**2d**	Me	Me (**4i**)	96 (**6i**)	S
10	**2d**	Me	Et (**4j**)	96 (**6j**)	S
11	**2d**	$ClCH_2$	Et (**4k**)	98 (**6k**)	R

[a] The absolute configurations were determined by comparing optical rotations with reported values. The reaction was carried out under 80 psi of H_2 in EtOH/DCM (3/1) at 50 °C for 20 h, substrate/[Ru(*p*-cymene)Cl_2]$_2$/ligand = 200/1/2.1. [b] The ee (%) values were determined by GC using a chiralselect 1000 column or HPLC with Chiralpak AS column. [c] Determined by the sign of rotations.

bisphosphinite ligand **2** in situ in hot DMF.[10] The reaction was carried out under 80 psi of H_2 in EtOH at 50 °C for 20 h. Although ligands BINAPO and **2a**−**d** show similar reactivity, the enantioselectivity varied dramatically. For example, substrate **3a** was reduced with 2% ee using a Ru-BINAPO complex as the catalyst (entry 1). The enantioselectivity increased to 22% with Ru-Me-*o*-BINAPO (**2a**) (entry 2), Surprisingly, ee values increased dramatically when an aryl was introduced in the *o*-BINAPO ligand (entries 3−5). Up to 99% ee has been achieved with the Ru-**2c** catalyst (entry 4). This result is superior to ee values obtained with other phosphine ligands (entry 6, 31% ee with BINAP; entry 7, 39% ee with MeO-BIPHEP).

A variety of β-aryl-substituted β-(acylamino)acrylates were employed as substrates for the Ru-catalyzed hydrogenation reaction with **2c** as the ligand (Table 1). High enantiomerical excesses have been achieved with the exception of **3h** (entry 14). There is no major electonic effect on the substitution pattern of **3** (96−99% ee). A possible explanation of the low ee (80%) with *o*-methoxy-substituted enamide **3h** is that competing coordination of the *o*-methoxy group exists in the Ru system. In this catalytic system, methyl β-aryl-substituted β-(acylamino)acrylates gave slightly better enantioselectivities than the corresponding ethyl β-aryl-substituted β-(acylamino)acrylates.

It is noteworthy that *our catalytic system Ru-bisphosphinite can tolerate an E/Z mixture of substrates*. The ability to reduce the *E*/*Z* mixture of β-aryl-substituted β-(acylamino)acrylates **3** is crucial to practical synthesis of various β-aryl-substituted β-amino acids. To the best of our knowledge, *enantioselectivities achieved with Ru-**2c** as the catalyst for hydrogenation of **3** are the highest reported to date*.

In a related area, Ru-BINAP[1,2] and other Ru-phosphine systems[11] were efficient for reduction of β-alkyl-substituted β-keto esters, but only moderate to good enantioselectivities were obtained for hydrogenation of β-aryl-substituted β-keto esters.

To further expand the utility of the *o*-BINAPO ligands system, we have examined Ru-catalyzed enantioselective hydrogenation of β-aryl-substituted β-keto esters (Table 2). High enantioselectivities have been achieved with most substrates (93−99% ee) except for **4f** and **4g**. Under the same reaction conditions, we examined the enantioselectivties for hydrogenation of **4a**: BINAP (80% ee), MeO-BIPHEP (88%), BINAPO (29%), **2a** (29%), **2b** (94%), **2c** (99%), and **2d** (97%). *The enantioselectivities achieved with Ru-**2c** as the catalyst are the highest reported for substrate **4a***. For hydrogenation of β-alkyl-substituted β-keto esters, we found that *o*-BINAPO (**2d**) is a better ligand (entries 9−11).

In conclusion, we have developed a novel family of chiral bisphosphinite ligands for enantioselective Ru-catalyzed hydrogenation. These catalysts are especially effective for hydrogenation of β-aryl-substituted β-(acylamino)acrylates and β-aryl-substituted β-keto esters. The highly enantioselective hydrogenation provides a useful way to prepare β-aryl-substituted β-amino acids and β-hydroxyl acids. Further studies of other transition metal complexes of these ligands and their applications are in progress.

Acknowledgment. This work was supported by grants from National Institute of health.

Supporting Information Available: Full experimental procedure, GC, HPLC data, and $[\alpha]_D$ values of ligands **2** and hydrogenation products **5** and **6** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345.
(2) Ohta, T.; Takaya, H.; Noyori, R. *Inorg. Chem.* **1988**, *27*, 566.
(3) Grubbs, R.; DeVries, R. A. *Tetrahedron Lett.* **1977**, 1879.
(4) (a) Cox, P. J.; Wang, W.; Snieckus, V. *Tetrahedron Lett*. **1992**, *33*, 2253. (b) Huang, W. S.; Hu, Q. S.; Pu, L. *J. Org. Chem*. **1999**, *64*, 7940.
(5) (a) Hoekstra, W. J., Ed. The Chemistry and Biology of β-Amino Acids. *Curr. Med. Chem*. **1999**, *6*, 905. (b) *Enantioselective Synthesis of β-amino Acids*; Juaristi, E., Ed.; Wiley-VCH: New York, **1997**. (c) Guenard, D.; Guritte-Voegelein, R.; Potier, P. *Acc. Chem. Res.* **1993**, *26*, 160.
(6) (a) Boesch, H.; Cesco-Cancian, S.; Hecker, L. R.; Hoekstra, W. J.; Justus, M.; Mryanoff, C. A.; Scott, L.; Shah, R. D.; Solms, G.; Sorgi, K. L.; Stefanick, S. M.; Thurnheer, U.; Villani, F. J.; Walker, D. G. *Org. Process Res. Dev*. **2001**, *5*, 23. (b) Tang, T.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 12. (c) Hoekstra, W. J.; Maryanoff, B. E.; Damiano, B. P.; Andrade-Gordon, P.; Cohen, J. H.; Costanzo, M. J.; Haertlein, B. J.; Hecker, L. R.; Hulshizer, B. L.; Kauffman, J. A.; Keane, P.; McComsey, D. F.; Mitchell, J. A.; Scott, L.; Shah, R. D.; Yabut, S. C. *J. Med. Chem.* **1999**, *42*, 5254. (d) Sibi, M. P.; Shay, H. J.; Liu, M.; Jasperse, C. P. *J. Am. Chem. Soc*. **1998**, *120*, 6615. (e) Kobayashi, S.; Ishitani, H.; Ueno, M. *J. Am. Chem. Soc.* **1998**, *120*, 431. (f) Chung, X. X. *Tetrahedron: Asymmetry* **1997**, *8*, 5. (g) Dumas, F.; Mezrhab, B.; d'Angelo, J. *J. Org. Chem.* **1996**, *61*, 2293. (h) Davis, F. A.; Szewczyk, J. M.; Reddy, R. E. *J. Org. Chem.* **1996**, *61*, 2222. (i) Enders, D.; Wahl, H.; Bettray, W. *Angew. Chem., Int. Ed. Engl*. **1995**, *34*, 455. (j) Wang, Z. M.; Kolb, H. C.; Sharpless, K. B. *J. Org. Chem.* **1994**, *59*, 5104. (k) Hattori, K.; Miyata, M.; Yamamoto, H. *J. Am. Chem. Soc*. **1993**, *115*, 1151. (l) Bunnage, M. E.; Davies, S. G.; Goodwin, C. J. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1375. (m) Juaristi, E.; Escalante, J.; Lamatsch, B.; Seebach, D. *J. Org. Chem.* **1992**, *57*, 2396. (n) Deng, L.; Jacobsen, E. N. *J. Org. Chem.* **1992**, *57*, 4320. (o) Hawkins, J. M.; Fu, G. C. *J. Org. Chem.* **1986**, *51*, 2820.
(7) Lubell, W. D.; Kitamura, M.; Noyori, R. *Tetrahedron: Asymmetry* **1991**, *2*, 543.
(8) (a) Yasutake, M.; Gridnev, I. D.; Higashi, N.; Imamoto, T. *Org. Lett.* **2001**, *3*, 1701. (b) Heller, D.; Holz, J.; Drexler, H. J.; Lang, J.; Drauz, K.; Krimmer, H. P.; Borner, A. *J. Org. Chem*. **2001**, *66*, 6816. (c) Zhu, G.; Chen, Z.; Zhang, X. *J. Org. Chem.* **1999**, *64*, 6907. (d) Furukawa, M.; Okawara, T.; Noguchi, Y.; Terawaki, Y. *Chem. Pharm. Bull*. **1979**, *27*, 2223. (e) Achiwa, K.; Soga, T. *Tetrahedron Lett*. **1978**, 1119.
(9) For the detailed experimental procedure, please see the Supporting Information.
(10) Kitamura, M.; Tokunaga, M.; Ohkuma, T.; Noyori, R. *Org. Synth.* **1993**, *71*, 1.
(11) For TunaPhos: (a) Zhang, Z.; Qian, H.; Longmire, J.; Zhang, X. *J. Org. Chem*. **2000**, *65*, 6223. For BIPHEP and MeO-BIPHEP: (b) Schmid, R.; Cereghetti, M.; Heiser, B.; Schonhonlzer, P.; Hansen, H. J. *Helv. Chim. Acta* **1988**, *71*, 897. For BPE: (c) Burk, M. J.; Harper, T. G. P.; Kalberg, C. S. *J. Am. Chem. Soc.* **1995**, *117*, 4423. For **P**-Phos: (d) Pai, C. C.; Lin, C. W.; Lin, C. C.; Chen, C. C.; Chan, A. S. C. *J. Am. Chem. Soc.* **2000**, *122*, 11513. For BITIOP: (e) Benincori, T.; Cesarotti, E.; Piccolo, O.; Sannicolo, F. *J. Org. Chem*. **2000**, *65*, 2043.

JA020121U