J|A|C|S
COMMUNICATIONS

Published on Web 10/05/2004

C_2-Symmetric Bicyclo[2.2.2]octadienes as Chiral Ligands: Their High Performance in Rhodium-Catalyzed Asymmetric Arylation of *N*-Tosylarylimines

Norihito Tokunaga, Yusuke Otomaru, Kazuhiro Okamoto, Kazuhito Ueyama, Ryo Shintani, and Tamio Hayashi*

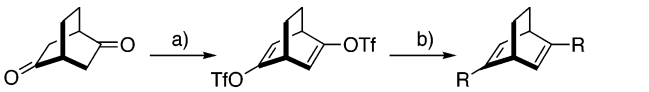
Department of Chemistry, Graduate School of Science, Kyoto University, Sakyo, Kyoto 606-8502, Japan

Received August 29, 2004; E-mail: thayashi@kuchem.kyoto-u.ac.jp

Recent developments on the chiral diene ligands have opened the door to an exciting new research area of catalytic asymmetric reactions.[1] The C_2-symmetric bicyclo[2.2.1]heptadienes (nbd*), which we have reported in 2003,[2] are highly enantioselective chiral ligands for rhodium-catalyzed asymmetric addition of organoboronic acids to α,β-unsaturated ketones[2] and fumaric and maleic compounds.[3] More recently, Carreira reported C_1-symmetric bicyclo[2.2.2]octadienes and their successful use for iridium-catalyzed kinetic resolution of allyl carbonates.[4] We have continued our studies on the preparation of new chiral diene ligands and their application to catalytic asymmetric reactions. Here we wish to report our new C_2-symmetric bicyclo[2.2.2]octadienes (bod*), which have a clear superiority over chiral phosphorus ligands in both enantioselectivity and catalytic activity in the rhodium-catalyzed arylation of *N*-tosylarylimines giving diarylmethylamines.

The synthetic pathway to the C_2-symmetric bicyclo[2.2.2]-octadienes is straightforward as shown in Scheme 1. Enantiomerically pure (1*R*,4*R*)-bicyclo[2.2.2]octa-2,5-dione ((*R*,*R*)-**1**)[5] was obtained by optical resolution of racemic diketone **1** through fractional recrystallization of its dihydrazone of (*R*)-5-(1-phenylethyl)semioxamazide.[6] Ditriflate formation with excess LDA and *N*-(2-pyridyl)triflimide followed by cross-coupling of (*R*,*R*)-ditriflate **2** with $PhCH_2MgBr$ and PhMgBr in the presence of $PdCl_2$(dppf) as a catalyst[7] gave the 2,5-disubstituted (1*R*,4*R*)-bicyclo[2.2.2]-octadienes, (*R*,*R*)-Bn-bod* and (*R*,*R*)-Ph-bod*, respectively.[8] It should be noted that the 2,5-diphenyl diene, Ph-bod*, is a stable compound, while its [2.2.1] (nbd) analogue readily undergoes decomposition in the air under light.

Scheme 1[a]



(*R*,*R*)-diketone (**1**) (*R*,*R*)-ditriflate (**2**) R = $PhCH_2$: (*R*,*R*)-Bn-bod* R = Ph: (*R*,*R*)-Ph-bod*

[a] Reagents and conditions: (a) (i) LDA/THF, −78 °C; (ii) Tf_2Npy-2, −78 °C→rt. Yield = 70%. (b) RMgBr, $PdCl_2$(dppf) (1 mol %), Et_2O reflux. Yield = 59% for R = $PhCH_2$. Yield = 78% for R = Ph.

The asymmetric synthesis of diarylmethylamines by the catalytic asymmetric arylation[9,10] has attracted growing attention due to their importance in biological activity.[11] Unfortunately, however, enantioselectivity as high as 95% has not been reported yet for the asymmetric synthesis of phenyl(4-chlorophenyl)methylamine, which is a potential key intermediate to Cetirizine hydrochloride,[11] although considerable efforts have been made, for example, by steric tuning of aryl groups in arenesulfonamides of arylimines.[9b,c]

It was found that the enantioselectivity as high as 98% was readily attained by use of chiral diene ligand (*R*,*R*)-Ph-bod* for the reaction of 4-chlorobenzaldehyde *N*-tosylimine **3a** with phenylboroxine (**4m**).[12] Thus, a rhodium catalyst[13] generated from $[RhCl(C_2H_4)]_2]_2$ (3 mol % Rh), Ph-bod* (1.1 equiv with respect to Rh), and aqueous KOH (20 mol %) in dioxane was added to a solution of imine **3a** and boroxine **4m** (1.2 equiv with respect to **3a**) in dioxane, and the mixture was heated at 60 °C for 6 h. Chromatography on silica gel gave phenyl(4-chlorophenyl)methylamine tosylamide **5am** in 96% yield, whose enantiomeric purity was determined to be 98% ee by HPLC analysis with a chiral stationary phase column (entry 1 in Table 1). Deprotection of tosylamide **5am** with SmI_2 in HMPA gave free amine (*S*)-phenyl-(4-chlorophenyl)methylamine in 64% yield as a mixture with 14% of diphenylmethylamine (not optimized). The enantioselectivity was still high but a little lower with benzyl-disubstituted diene ligands, Bn-bod* and Bn-nbd*, which gave a high yield of tosylamide **5am** in 94 and 92% ee, respectively (entries 2 and 3). On the contrary, (*R*)-binap, which is a chiral bisphosphine ligand successfully used for the rhodium-catalyzed asymmetric 1,4-addition to electron-deficient olefins,[14] was a poor ligand in terms of both enantioselectivity and catalytic activity in the present arylation reaction[15] (entry 4). Low efficiency was also observed with segphos[16] and a phosphoramidite[17] as a ligand (entries 5 and 6).

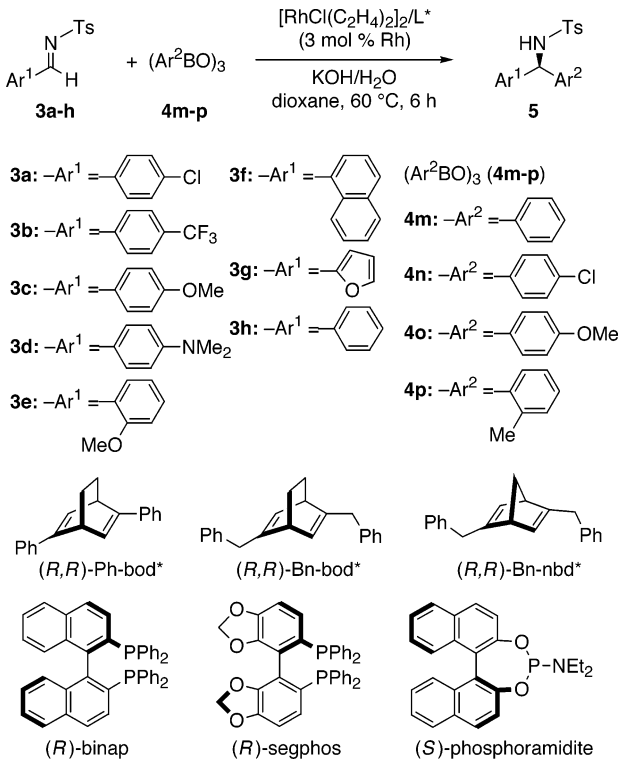
Table 1. Rhodium-Catalyzed Asymmetric Arylation of Imines **3** with Arylboroxines **4**[a]

entry	imine **3**	boroxine **4**	ligand	yield (%)[b] of amine	% ee[c] of amine[d]
1	**3a**	**4m**	(*R*,*R*)-Ph-bod*	96 (**5am**)	98 (*S*)
2	**3a**	**4m**	(*R*,*R*)-Bn-bod*	98 (**5am**)	94 (*S*)
3	**3a**	**4m**	(*R*,*R*)-Bn-nbd*	98 (**5am**)	92 (*S*)
4	**3a**	**4m**	(*R*)-binap	28 (**5am**)	31 (*S*)
5	**3a**	**4m**	(*R*)-segphos	30 (**5am**)	70 (*S*)
6	**3a**	**4m**	(*S*)-phosphoramidite	44 (**5am**)	6 (*S*)
7	**3b**	**4m**	(*R*,*R*)-Ph-bod*	97 (**5bm**)	95 (*S*)
8	**3c**	**4m**	(*R*,*R*)-Ph-bod*	96 (**5cm**)	99 (*S*)
9	**3d**	**4m**	(*R*,*R*)-Ph-bod*	94 (**5dm**)	98 (*S*)
10	**3e**	**4m**	(*R*,*R*)-Ph-bod*	98 (**5em**)	99 (*S*)
11	**3f**	**4m**	(*R*,*R*)-Ph-bod*	95 (**5fm**)	98 (*S*)
12	**3g**	**4m**	(*R*,*R*)-Ph-bod*	99 (**5gm**)	99 (*S*)
13	**3h**	**4n**	(*R*,*R*)-Ph-bod*	99 (**5hn**)	99 (*R*)
14	**3h**	**4o**	(*R*,*R*)-Ph-bod*	97 (**5ho**)	96 (*R*)
15	**3h**	**4p**	(*R*,*R*)-Ph-bod*	96 (**5hp**)	99 (*R*)
16	**3c**	**4n**	(*R*,*R*)-Ph-bod*	98 (**5cn**)	99 (*R*)

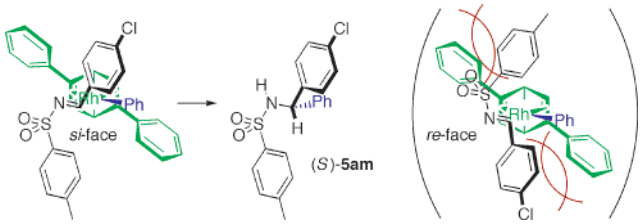
[a] Reaction was carried out in dioxane at 60 °C for 6 h with 1.2 equiv of boroxine **4** in the presence of 20 mol % KOH, 1 equiv (with respect to boron) of H_2O, and 3 mol % the catalyst generated from $[RhCl(C_2H_4)_2]_2$ and a chiral ligand. [b] Isolated yields by column chromatography on silica gel (hexane/ethyl acetate = 2/1). [c] Determined by HPLC analysis with a chiral stationary phase column (Chiralcel OD-H: hexane/2-propanol = 80/20 for **5am**, **5bm**, **5cm**, **5dm**, **5em**, **5fm**, **5hn**, **5ho**, **5hp**, and **5cn**; hexane/2-propanol = 90/10 for **5gm**). [d] Absolute configuration of **5am** was determined by conversion into known free amine (*S*)-phenyl(4-chlorophenyl)methylamine. The configurations of other amines were assigned by consideration of the stereochemical reaction pathway.

10.1021/ja044790e CCC: $27.50

Scheme 2



Scheme 3



The high enantioselectivity observed with chiral diene ligands, especially Ph-bod*, demonstrates that the chirality recognition ability brought about by two phenyl groups at the 2- and 5-positions of the diene is substantially high and is higher for the *N*-tosylarylimine than the ability brought about by the face-and-edge orientation of four phenyl groups[18] on the chelating bisphosphine ligands represented by binap. The *S* configuration of the arylation product **5am** obtained with (*R*,*R*)-dienes is rationalized by the coordination of imine **3a** to a rhodium with its *si*-face.[19] The coordination with the other face is much less favorable due to the steric repulsions caused by both of two phenyl groups on the diene ligand (Scheme 3).

The scope of the present rhodium-catalyzed asymmetric arylation using Ph-bod* as a chiral ligand is limited to aryl-derived imines but is tolerant of a range of functional groups. Phenylation of the aromatic imines substituted with trifluoromethyl (**3b**), methoxy (**3c**), and dimethylamino (**3d**) at the 4-position of phenyl gave the corresponding sulfonamides of aryl(phenyl)methylamines (*S*)-**5** in high yields with over 95% enantioselectivity (entries 7−9 in Table 1). High enantioselectivity (98−99% ee) was also observed in the phenylation of imines **3e**, **3f**, and **3g**, which were derived from 2-methoxybenzaldehyde, 1-naphthaldehyde, and 2-furaldehyde, respectively (entries 10−12). The asymmetric arylation of benzaldehyde imine **3h** with substituted phenyl groups was also successful using arylboroxines where the aryl groups are 4-chloro (**4n**), 4-methoxy (**4o**), and 2-methyl (**4p**) phenyls (entries 13−15). The diarylmethylamines where both of the aryl groups are substituted phenyls can be prepared as well by combination of substituted arylimines and substituted arylboroxines. One example giving (*R*)-4-chlorophenyl(4-methoxyphenyl)methylamine (**5cn**) with 99% enantioselectivity is shown in entry 16.

In summary, asymmetric synthesis of diarylmethylamines with high enantioselectivity (95−99% ee) was realized for the first time by use of a C_2-symmetric diene ligand, Ph-bod*, for the rhodium-catalyzed asymmetric arylation of *N*-tosylarylimines.

Acknowledgment. This work has been supported in part by a Grant-in-Aid for Scientific Research, the Ministry of Education, Culture, Sports, Science and Technology, Japan (21 COE on Kyoto University Alliance for Chemistry). N.T. thanks the Japan Society for the Promotion of Science for the award of a fellowship for graduate students.

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

References

(1) For a short review: Glorius, F. *Angew. Chem., Int. Ed.* **2004**, *43*, 3364.
(2) Hayashi, T.; Ueyama, K.; Tokunaga, N.; Yoshida, K. *J. Am. Chem. Soc.* **2003**, *125*, 11508.
(3) Shintani, R.; Ueyama, K.; Yamada, I.; Hayashi, T. *Org. Lett.* **2004**, *6*, 3425.
(4) Fischer, C.; Defieber, C.; Suzuki, T.; Carreira, E. M. *J. Am. Chem. Soc.* **2004**, *126*, 1628.
(5) Some other methods for the optical resolution have been reported: (a) Hill, R. K.; Morton, G. H.; Peterson, J. R.; Walsh, J. A.; Paquette, L. A. *J. Org. Chem.* **1985**, *50*, 5528. (b) Naemura, K.; Takahashi, N.; Tanaka, S.; Ida, H. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2337. (c) Kinoshita, T.; Haga, K.; Ikai, K.; Takeuchi, K.; Okamoto, K. *Tetrahedron Lett.* **1990**, *31*, 4057. (d) Almqvist, F.; Ekman, N.; Frejd, T. *J. Org. Chem.* **1996**, *61*, 3794 and references therein.
(6) Optical resolution of ketones using (*R*)-5-(1-phenylethyl)semioxamazide has been reported: Leonard, N. L.; Boyer, J. H. *J. Org. Chem.* **1950**, *15*, 42.
(7) Hayashi, T.; Konishi, M.; Kobori, Y.; Kumada, M.; Higuchi, T.; Hirotsu, K. *J. Am. Chem. Soc.* **1984**, *106*, 158.
(8) (*R*,*R*)-Bn-bod*: $[\alpha]^{20}_D$ +86 (*c* 0.71, $CHCl_3$). (*R*,*R*)-Ph-bod*: $[\alpha]^{20}_D$ −30 (*c* 0.72, $CHCl_3$).
(9) Rhodium-catalyzed arylation. (a) With arylstannane: Hayashi, T.; Ishigedani, M. *J. Am. Chem. Soc.* **2000**, *122*, 976. (b) With arylboroxine: Kuriyama, M.; Soeta, T.; Hao, X.; Chen, Q.; Tomioka, K. *J. Am. Chem. Soc.* **2004**, *126*, 8128. (c) With aryltitanium: Hayashi, T.; Kawai, M.; Tokunaga, N. *Angew. Chem., Int. Ed.* **2004**, *43*, in press.
(10) Addition of phenylzinc catalyzed by a chiral ketimine: Hermanns, N.; Dahmen, S.; Bolm, C.; Bräse, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 3692.
(11) For examples: (a) Bishop, M. J.; McNutt, R. W. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1311. (b) Spencer, C. M.; Foulds, D.; Peters, D. H. *Drugs* **1993**, *46*, 1055. (c) Sakurai, S.; Ogawa, N.; Suzuki, T.; Kato, K.; Ohashi, T.; Yasuda, S.; Kato, H.; Ito, Y. *Chem. Pharm. Bull.* **1996**, *44*, 765. (d) Cetirizine is currently prepared as a racemate via an alkylation of a piperazine derivative with a benzhydryl chloride derivative: Baltes, E.; De Lannoy, J.; Rodriguez, L. Eur. Patent Appl. 58146, 1982.
(12) Rhodium-catalyzed arylation of *N*-tosylimines with arylboron reagents has been reported by Tomioka (ref 9b) and by Miyaura: (a) Ueda, M.; Miyaura, N. *J. Organomet. Chem.* **2000**, *595*, 31. (b) Ueda, M.; Saito, A.; Miyaura, N. *Synlett* **2000**, 1637.
(13) We presume the formation of $[Rh(OH)(Ph\text{-}bod^*)]_2$ as an active catalyst.
(14) For reviews: (a) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829. (b) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169. (c) Bolm, C.; Hildebrand, J. P.; Muñiz, K.; Hermanns, N. *Angew. Chem., Int. Ed.* **2001**, *40*, 3284.
(15) Low enantioselectivity of binap in the rhodium-catalyzed asymmetric arylation of imines has been reported in refs 9b and 9c.
(16) Saito, T.; Yokozawa, T.; Ishizaki, T.; Moroi, T.; Sayo, N.; Miura, T.; Kumobayashi, H. *Adv. Synth. Catal.* **2001**, *343*, 264.
(17) Boiteau, J.-G.; Minnaar, A. J.; Feringa, B. L. *J. Org. Chem.* **2003**, *68*, 9481.
(18) Ozawa, F.; Kubo, A.; Matsumoto, Y.; Hayashi, T. *Organometallics* **1993**, *12*, 4188, and references therein.
(19) Insertion of imine into an aryl-rhodium bond forming an amido complex has been reported: Krug, C.; Hartwig, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 2694.

JA044790E