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C_2-Symmetric Bicyclo[3.3.1]nonadiene as a Chiral Ligand for Rhodium-Catalyzed Asymmetric Arylation of *N*-(4-Nitrobenzenesulfonyl)arylimines

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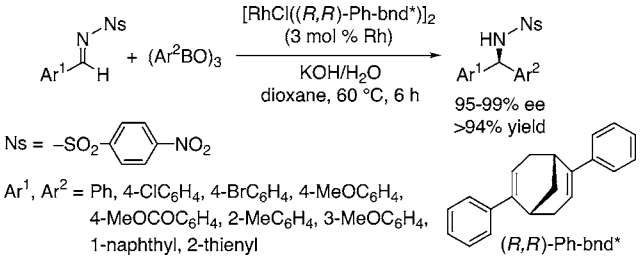
ABSTRACT



Asymmetric synthesis of diarylmethylamines with high enantioselectivity (95–99% ee) was realized by use of a new C_2-symmetric diene ligand, (1*R*,5*R*)-2,6-diphenylbicyclo[3.3.1]nona-2,6-diene (Ph-bnd*), for the rhodium-catalyzed asymmetric arylation of *N*-(4-nitrobenzenesulfonyl)arylimines with arylboroxines.

One of the recent topics in the field of asymmetric catalysis is the development of chiral diene ligands, which have been demonstrated to have advantages over other types of chiral ligands containing phosphorus and/or nitrogen atoms in some asymmetric reactions catalyzed by transition metal complexes.[1] The C_2-symmetric dienes based on a bicyclo[2.2.1]-heptadiene backbone (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] Carreira reported the preparation of several types of C_1-symmetric bicyclo[2.2.2]octadienes and their successful use for iridium-catalyzed kinetic resolution of allyl carbonates[4] and the rhodium-catalyzed asymmetric 1,4-addition.[5] Very recently, we reported[6] (*R*,*R*)-2,5-diphenylbicyclo[2.2.2]octa-2,5-diene (Ph-bod*) as a new type of C_2-symmetric chiral diene ligand and its application to rhodium-catalyzed asymmetric arylation of *N*-tosylarylimines with arylboroxines giving diarylmethylamines,[7,8] where high enantioselectivity (95−99% ee) was observed for a variety of substitution patterns on the aryl groups. One drawback in this report[6] is

(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) Defieber, C.; Paquin, J.-F.; Serna, S.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 3873.

(6) Tokunaga, N.; Otomaru, Y.; Okamoto, K.; Ueyama, K.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2004**, *126*, 13584.

(7) Other reports on the catalytic enantioselective arylation of arylimines giving enantiomerically enriched diarylmethylamines: (a) Hayashi, T.; Ishigedani, M. *J. Am. Chem. Soc.* **2000**, *122*, 976. (b) Hermanns, N.; Dahmen, S.; Bolm, C.; Bräse, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 3692. (c) Kuriyama, M.; Soeta, T.; Hao, X.; Chen, Q.; Tomioka, K. *J. Am. Chem. Soc.* **2004**, *126*, 8128. (d) Hayashi, T.; Kawai, M.; Tokunaga, N. *Angew. Chem., Int. Ed.* **2004**, *43*, 6125.

(8) Rhodium-catalyzed arylation of *N*-tosylimines with arylboron reagents was first reported by Miyaura: (a) Ueda, M.; Miyaura, N. *J. Organomet. Chem.* **2000**, *595*, 31. (b) Ueda, M.; Saito, A.; Miyaura, N. *Synlett* **2000**, 1637.

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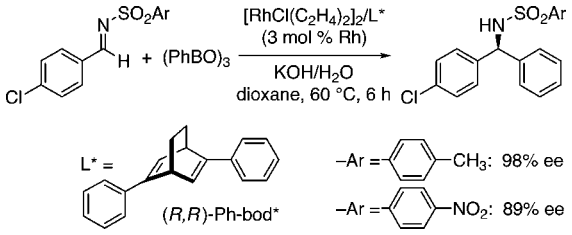
the difficulty in removing the tosyl group from nitrogen on the diarylmethylamines. Thus, reductive deprotection of phenyl(4-chlorophenyl)methylamine tosylamide with, for example, Li/NH_3 or SmI_2/HMPA resulted in the formation of a significant amount of diphenylmethylamine.[6,9] It is anticipated that the use of a 4-nitrobenzenesulfonyl group[10] in place of a tosyl group makes the deprotection much easier. Unfortunately, however, the enantioselectivity of the asymmetric arylation catalyzed by the rhodium/(*R*,*R*)-Ph-bod* complex was significantly lower for *N*-4-nitrobenzenesulfonylimines, as exemplified by the phenylation of the sulfonylimines of 4-chlorobenzaldehyde where the enantioselectivity was 98 and 89% ee for tosylimine and 4-nitrobenzenesulfonylimine, respectively (Scheme 1) (vide infra). Here we

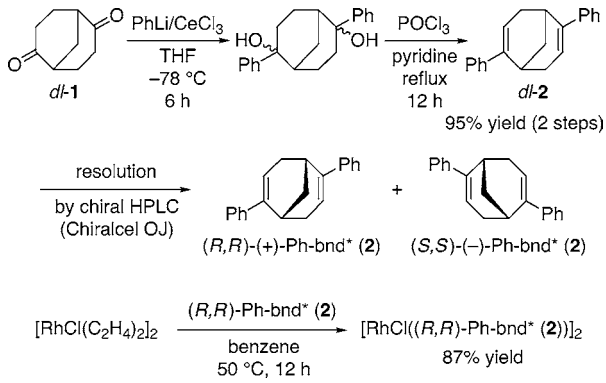
Scheme 1. Asymmetric Phenylation Catalyzed by Rhodium/Ph-bod*



report a new C_2-symmetric chiral diene, 2,6-diphenylbicyclo[3.3.1]nona-2,6-diene (Ph-bnd*), which is a chiral ligand suitable for the rhodium-catalyzed asymmetric arylation of *N*-4-nitrobenzenesulfonylimines.

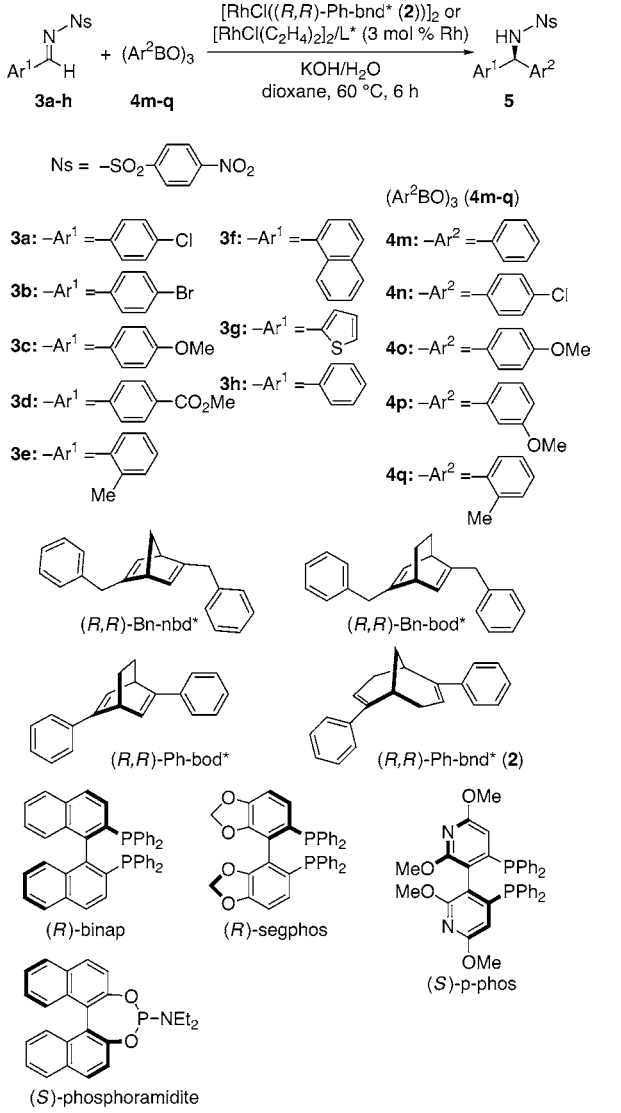
Scheme 2 shows the synthetic pathway to the 2,6-diphenylbicyclo[3.3.1]nona-2,6-diene (Ph-bnd*). Racemic

Scheme 2. Preparation of Ph-bnd* (**2**)



diketone, bicyclo[3.3.1]nonane-2,6-dione (**1**), prepared according to the procedures reported by Schaefer,[11] was treated

Scheme 3. Rhodium-Catalyzed Asymmetric Arylation of Imines **3** with Arylboroxines **4**



with a phenylcerium reagent generated from phenyllithium and cerium trichloride in THF followed by dehydration of the resulting diol with phosphoryl chloride and pyridine to give 95% yield of racemic 2,6-diphenylbicyclo[3.3.1]nona-2,6-diene (Ph-bnd* **2**). Resolution of *dl*-**2** was efficiently carried out by use of a chiral stationary phase column (Chiralcel OJ) to give both enantiomers, (+)-Ph-bnd* (**2**) and (−)-Ph-bnd* (**2**).[12] The absolute configuration of the (+)-isomer was assigned to be (*R*,*R*)- by consideration of the stereochemical reaction pathway in the catalytic asymmetric arylation shown in Schemes 3 (vide infra). Treatment of (*R*,*R*)-(+)-Ph-bnd* (**2**) with $[RhCl(C_2H_4)_2]_2$ in benzene at 50 °C for 12 h gave 87% yield of the diene−rhodium complex $[RhCl((R,R)\text{-Ph-bnd*}\ (\mathbf{2}))]_2$.[13]

(9) Loss of chloride was also observed during the reductive removal of 2,4,6-triisopropylbenzenesulfonyl group with SmI_2/HMPA: see ref 7d.

(10) (a) Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373. (b) Kan, T.; Fukuyama, T. *Chem. Commun.* **2004**, 353. (c) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999; p 609.

(11) Schaefer, J. P.; Honig, L. M. *J. Org. Chem.* **1968**, *33*, 2655. See also: Meerwein, H.; Schürmann, W. *Justus Liebigs Ann. Chem.* **1913**, *398*, 196.

(12) *R*,*R*)-(+)-Ph-bnd*: $[\alpha]^{20}_D$ +39 (*c* 0.58, $CHCl_3$).

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

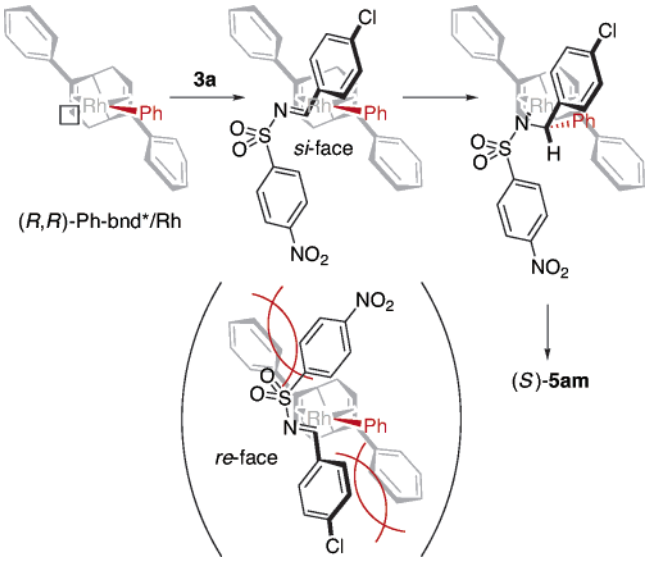
entry	imine **3**	boroxine **4**	ligand	yield (%)[b] of amine	% ee[c] of amine[d]
1	**3a**	**4m**	(*R*)-binap	15 (**5am**)	34 (*S*)
2	**3a**	**4m**	(*R*)-segphos	<5 (**5am**)	
3	**3a**	**4m**	(*S*)-p-phos	15 (**5am**)	49 (*R*)
4	**3a**	**4m**	(*S*)-phosphoramidite	68 (**5am**)	23 (*S*)
5	**3a**	**4m**	(*R*,*R*)-Bn-nbd*	88 (**5am**)	81 (*S*)
6	**3a**	**4m**	(*R*,*R*)-Bn-bod*	99 (**5am**)	70 (*S*)
7	**3a**	**4m**	(*R*,*R*)-Ph-bod*	96 (**5am**)	89 (*S*)
8	**3a**	**4m**	(*R*,*R*)-Ph-bnd* (**2**)	96 (**5am**)	98 (*S*)
9	**3b**	**4m**	(*R*,*R*)-Ph-bnd* (**2**)	98 (**5bm**)	98 (*S*)
10	**3c**	**4m**	(*R*,*R*)-Ph-bnd* (**2**)	98 (**5cm**)	99 (*S*)
11	**3d**	**4m**	(*R*,*R*)-Ph-bnd* (**2**)	95 (**5dm**)	95 (*S*)
12	**3e**	**4m**	(*R*,*R*)-Ph-bnd* (**2**)	95 (**5em**)	98 (*S*)
13[e]	**3f**	**4m**	(*R*,*R*)-Ph-bnd* (**2**)	94 (**5fm**)	96 (*S*)
14[e]	**3g**	**4m**	(*R*,*R*)-Ph-bnd* (**2**)	99 (**5gm**)	95 (*S*)
15	**3h**	**4n**	(*R*,*R*)-Ph-bnd* (**2**)	96 (**5hn**)[f]	99 (*R*)
16[g]	**3h**	**4o**	(*R*,*R*)-Ph-bnd* (**2**)	94 (**5ho**)[f]	98 (*R*)
17	**3h**	**4p**	(*R*,*R*)-Ph-bnd* (**2**)	99 (**5hp**)[f]	99 (*R*)
18[h]	**3h**	**4q**	(*R*,*R*)-Ph-bnd* (**2**)	98 (**5hq**)	99 (*R*)
19	**3b**	**4p**	(*R*,*R*)-Ph-bnd* (**2**)	99 (**5bp**)	98 (*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 % (Rh) of $[RhCl((R,R)\text{-Ph-bnd*}(\mathbf{2}))]_2$ or a 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 = 4/1 for **5am**, **5bm**, **5em**, **5hn**, and **5hp**; hexane/2-propanol = 2/1 for **5cm**, **5fm**, **5gm**, **5ho**, **5hq**, and **5bp**; hexane/2-propanol = 1/1 for **5dm**.). [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. [e] With 6 mol % catalyst, 2.4 equiv of **4m**, and 40 mol % KOH for 12 h. [f] Products **5hn**, **5ho**, and **5hp** are enantiomers of **5am**, **5cm**, and **5em**, respectively. [g] With 1.8 equiv of **4o** for 9 h. [h] With 2.4 equiv of **4q** for 12 h.

The results obtained for the asymmetric arylation of *N*-4-nitrobenzenesulfonylimines **3**[14] with arylboroxines **4** in the presence of $[RhCl((R,R)\text{-Ph-bnd*}(\mathbf{2}))]_2$ (3 mol % Rh) and aqueous potassium hydroxide in dioxane (Scheme 3) are summarized in Table 1, which also contains the data obtained with other chiral diene and chiral phosphorus ligands for comparison. Table 1 contains the following significant features. (1) Catalytic activity and enantioselectivity in the present arylation are very low with chiral phosphorus ligands,[15] binap,[16] segphos,[17] p-phos,[18] and a phosphoramidite[19] (entries 1−4), all of which have been reported to be highly effective for the rhodium-catalyzed asymmetric 1,4-addition to electron-deficient olefins.[20] (2) The rhodium complexes of the diene ligands are catalytically much more active than those of the phosphorus ligands for the addition of phenylboroxine (**4m**) to the *N*-4-nitrobenzenesulfonylimine of 4-chlorobenzaldehyde **3a**, the yields of the phenylation product **5am** all being higher than 95% with the diene ligands (entries 5−8). (3) Of the diene ligands, Ph-bnd* (**2**) is most enantioselective, giving (*S*)-**5am** with 98% ee (entry 8). (4) The additions of phenylboroxine (**4m**) to imines substituted with 4-bromo (**3b**), 4-methoxy (**3c**), 4-carbomethoxy (**3d**), and 2-methyl (**3e**) all proceeded with high enantioselectivity to give the corresponding *N*-sulfonylphenyl(aryl)methylamines with high (95−99% ee) enantioselectivity (entries 9−12). High enantioselectivity (95−96% ee) was also observed in the phenylation of imines **3f** and **3g**, which were derived from 1-naphthaldehyde and 2-thiophenecarboxaldehyde, respectively (entries 13 and 14). (5) The asymmetric arylation of benzaldehyde imine **3h** with substituted phenyl groups was also successful using arylboroxines containing 4-chloro (**4n**), 4-methoxy (**4o**), 3-methoxy (**4p**), and 2-methyl (**4q**) groups (entries 15−18). The arylation products **5hn**, **5ho**, and **5hp** obtained here are the enantiomers of **5am**, **5cm**, and **5em**, respectively, which were obtained by the asymmetric phenylation using phenylboroxine (**4m**).

The (*S*)-configuration of the arylation product **5am** obtained with (+)-Ph-bnd* (**2**) indicates that the absolute configuration of (+)-**2** is (*R*,*R*). Thus, the dienes, (*R*,*R*)-Bn-nbd*, (*R*,*R*)-Bn-bod*, and (*R*,*R*)-Ph-bod*, whose configura-

Scheme 4. Stereochemical Pathway of the Asymmetric Arylation



(13) ^1H NMR ($CDCl_3$): δ 1.28 (s, 4H), 2.24 (s, 4H), 2.29 (d, J = 15.1 Hz, 4H), 3.50 (dt, J = 15.1 and 3.7 Hz, 4H), 4.70 (d, J = 2.9 Hz, 4H), 7.22−7.29 (m, 12H), 7.50 (d, J = 7.2 Hz, 8H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 32.94, 34.61, 41.47, 72.68 (d, J = 11.4 Hz), 86.22 (d, J = 14.5 Hz), 126.54, 126.64, 127.77, 144.77 (d, J = 2.1 Hz).

(14) Prepared from aromatic aldehydes and 4-nitrobenzenesulfonamide in the presence of tetraethoxysilane: Love, B. E.; Raje, P. S.; Williams II, T. C. *Synlett* **1994**, 493.

(15) Low efficiency of the chiral phosphorus ligands has been also observed in the arylation of *N*-tosylimines: see ref 6.

(16) Takaya, H.; Mashima, K.; Koyano, K.; Yagi, M.; Kumobayashi, H.; Taketomi, T.; Akutagawa, S.; Noyori, R. *J. Org. Chem.* **1986**, *51*, 629.

(17) Saito, T.; Yokozawa, T.; Ishizaki, T.; Moroi, T.; Sayo, N.; Miura, T.; Kumobayashi, H. *Adv. Synth. Catal.* **2001**, *343*, 264.

(18) Shi, Q.; Xu, L.; Li, X.; Jia, X.; Wang, R.; Au−Yeng, T. T.-L.; Chan, A. S. C.; Hayashi, T.; Cao, R.; Hong, M. *Tetrahedron Lett.* **2003**, *44*, 6505.

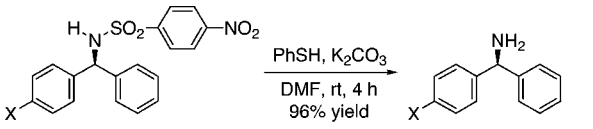
(19) Boiteau, J.-G.; Minnaard, A. J.; Feringa, B. L. *J. Org. Chem.* **2003**, *68*, 9481.

(20) 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.; Muniz, K.; Hermanns, N. *Angew. Chem., Int. Ed.* **2001**, *40*, 3284.

tions have been unambiguously determined, gave the phenylation product **5am** of (*S*)-configuration. The similarity in the structure of these dienes supports the assignment of the absolute configuration of diene **2**. The coordination of imine **3** with its *si*-face to the rhodium bearing (*R*,*R*)-Ph-bnd* (**2**) as a chiral ligand is much more favorable than the coordination with its *re*-face because of the steric repulsions shown in Scheme 4. The *si*-face coordination will lead to the phenylation products of (*S*)-configuration.

The 4-nitrobenzenesulfonyl group was readily removed from diarylmethylamines **5** without racemization or any side reactions in high yields. Thus, for example, treatment of the 4-nitrobenzenesulfonamide **5am** with benzenethiol and potassium carbonate in DMF[10] gave 96% yield of free amine

Scheme 5. Deprotection of 4-Nitrobenzenesulfonyl Group



5am: X = Cl (98% ee)
5bm: X = Br (98% ee)

(*S*)-**6a**: X = Cl (98% ee)
(*S*)-**6b**: X = Br (98% ee)

(*S*)-phenyl(4-chlorophenyl)methylamine (**6a**) (Scheme 5). The deprotection of **5bm**, which contains bromide on the phenyl ring, was also successful to give the corresponding free amine (*S*)-**6a** in 96% yield.

In summary, high enantioselectivity and high catalytic activity were observed in the rhodium-catalyzed asymmetric arylation of *N*-4-nitrobenzenesulfonylimines with arylboroxines by use of a C_2-symmetric new diene ligand, 2,6-diphenylbicyclo[3.3.1]nona-2,6-diene (Ph-bnd*), to give high yields of diarylmethylamines with 95−99% ee.

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

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