Rhodium-Catalyzed Asymmetric Arylation of Imines with Organostannanes. Asymmetric Synthesis of Diarylmethylamines

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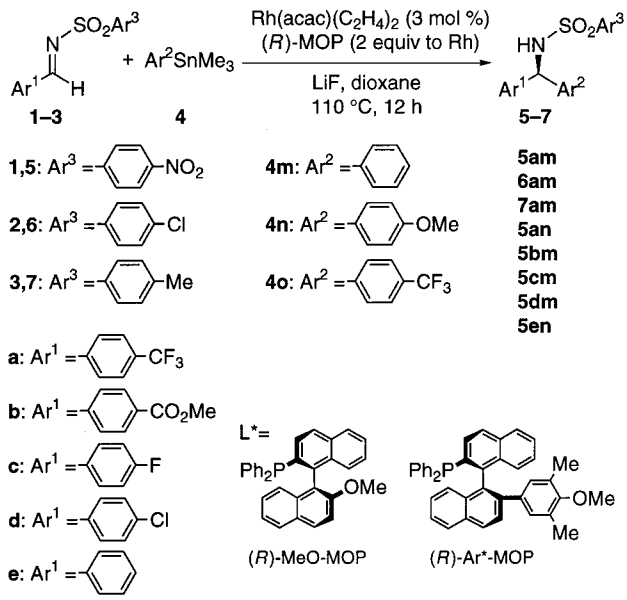
Although enantiomerically pure diarylmethylamines constitute many biologically important compounds,[1] their preparation by asymmetric synthesis has not been well developed.[2] Especially, the synthesis by asymmetric catalysis is a formidable challenge in synthetic organic chemistry. To our knowledge, there have been no successful reports on catalytic asymmetric synthesis of diarylmethylamines either by asymmetric reduction of imines of diaryl ketones or by asymmetric arylation of aldehyde imines.[3,4] We have made efforts to find a new chiral catalyst system for the asymmetric addition of arylmetal reagents to imines derived from aromatic aldehydes and found that some rhodium complexes coordinated with chiral monodentate phosphine ligands, MOP's,[5] catalyze the addition of arylstannanes to *N*-alkylidenesulfonamides to give sulfonamide of diarylmethylamines with high enantioselectivity (up to 96% ee). Here we wish to report the preliminary results of the new catalytic asymmetric addition reaction.

In numerous studies carried out in this laboratory, we have found that *N*-alkylidenesulfonamides ($Ar^1CH{=}NSO_2Ar^3$), readily accessible by condensation of aromatic aldehydes ($Ar^1CH{=}O$) with arenesulfonamides ($H_2NSO_2Ar^3$) in the presence of triethoxysilane,[6] undergo asymmetric arylation with arylstannanes under the catalysis by a rhodium complex coordinated with a chiral monodentate phosphine ligand (Scheme 1). The reactivity of sulfonamides **1**−**3** toward the rhodium-catalyzed arylation is dependent on the substituents at the 4 position on the phenyl ring Ar^3 of sulfonamides. Sulfonamide **1a** containing nitro group at the 4 position gave higher yields of arylation product **5am** in the reaction with phenyltrimethylstannane (**4m**) than that containing 4-chloro (**2a**) or 4-methyl (**3a**). The enantioselectivity is also higher with the 4-nitro group than with the 4-chloro or 4-methyl group. Thus, for example, the reaction of **1a** with **4m** in the presence of 3 mol % of a rhodium catalyst, generated from Rh(acac)$(C_2H_4)_2$ and (*R*)-MeO-MOP[5] (Rh/P = 1/2), and lithium

Scheme 1



fluoride[7] in dioxane at 110 °C for 12 h gave 82% yield of (+)-[*N*-(4-trifluoromethylphenyl)phenylmethyl]-4-nitrobenzenesulfonamide (**5am**) ($[\alpha]^{20}_D$ +7.2 (*c* 1.00, chloroform)), whose enantiomeric purity was determined to be 92% by HPLC analysis with a chiral stationary phase column (entry 1 in Table 1). On the other hand, the reaction of **2a** and **3a** with **4m** gave the corresponding arylation products **6am** and **7am**, in 66% yield (87% ee) and 64% yield (75% ee), respectively (entries 2 and 3). In addition to the higher reactivity and higher enantioselectivity, 4-nitrobenzenesulfonamide has another important advantage over others in that it is readily removed from diarylmethylamine moiety without loss of enantiomeric purity. Treatment of (+)-**5am** (92% ee) with benzenethiol and potassium carbonate in DMF[8] gave (+)-(4-trifluoromethylphenyl)phenylmethylamine (**8am**)[9] of 92% ee ($[\alpha]^{20}_D$ +13.4 (*c* 1.00, ethanol)) in 80% yield. The enantiomeric purity was determined by the HPLC analysis of toluenesulfonamide **7am** obtained by treatment of **8am**[9] with toluenesulfonyl chloride, triethylamine, and 4-(dimethylamino)pyridine (Scheme 2).

The choice of the MOP ligand is essential for the present catalytic asymmetric arylation. With chelating bisphosphine ligands the arylation was very slow, the yields of **5am** being 6% and 10%, with rhodium catalysts of binap[10] and diop,[11] respectively (entries 5 and 6). Higher yield and enantioselectivity were observed with newly developed MOP ligand, (*R*)-Ar*-MOP,[12] which gave 90% yield of **5am** with 96% ee (entry 4).

The present catalytic asymmetric arylation was also successful for the reaction of imines derived from benzaldehyde **1e** and aromatic aldehydes substituted with electron-withdrawing groups, methoxycarbonyl (**1b**), fluoro (**1c**), and chloro (**1d**), on the phenyl.

(1) 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.

(2) For recent examples of asymmetric synthesis of diarylmethylamines: (a) Corey, E. J.; Helal, C. J. *Tetrahedron Lett*. **1996**, *37*, 4837. (b) Delorme, D.; Berthelette, C.; Lavoie, R.; Roberts, E. *Tetrahedron Asym.* **1998**, *9*, 3963. (c) Pridgen, L. N.; Mokhallalati, M. K.; Wu, M. J. *J. Org. Chem*. **1992**, *57*, 1237.

(3) For a recent pertinent review on catalytic enantioselective addition to imines: Kobayashi, S.; Ishitani, H. *Chem. Rev*. **1999**, *99*, 1069.

(4) Catalytic asymmetric alkylation and allylation of imines and Mannich-type reaction have been reported. For recent examples: (a) Inoue, I.; Shindo, M.; Koga, K.; Kanai, M.; Tomioka, K. *Tetrahedron Asym.* **1995**, *6*, 2527. (b) Denmark, S. E.; Nakajima, N.; Nicaise, O. J.-C. *J. Am. Chem. Soc*. **1994**, *116*, 8797. (c) Gittins née Jones, C. A.; North, M. *Tetrahedron Asym.* **1997**, *8*, 3789. (d) Guijarro, D.; Pinho, P.; Andersson, P. G. *J. Org. Chem.* **1998**, *63*, 2530. (e) Nakamura, H.; Nakamura, K.; Yamamoto, Y. *J. Am. Chem. Soc*. **1998**, *120*, 4242. (f) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc*. **1997**, *119*, 7153. (g) Fujiidera, H.; Kanai, M.; Kambara, T.; Iida, A.; Tomioka, K. *J. Am. Chem. Soc*. **1997**, *119*, 2060. (h) Hagiwara, E.; Fujii, A.; Sodeoka, M. *J. Am. Chem. Soc*. **1998**, *120*, 2474. (i) Ferraris, D.; Young, B.; Dudding, T.; Lectka, T. *J. Am. Chem. Soc*. **1998**, *120*, 4548.

(5) (a) Uozumi, Y.; Hayashi, T. *J. Am. Chem. Soc.* **1991**, *113*, 9887. (b) Uozumi, Y.; Tanahashi, A.; Lee, S.-Y.; Hayashi, T. *J. Org. Chem.* **1993**, *58*, 1945. (c) Uozumi, Y.; Suzuki, N.; Ogiwara, A.; Hayashi, T. *Tetrahedron* **1994**, *50*, 4293.

(6) Love, B. E.; Raje, P. S.; Williams, T. C., II *Synlett* **1994**, 493.

(7) The present arylation was found to proceed with high reproducibility on addition of LiF though the addition is not essential.

(8) Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett*. **1995**, *36*, 6373.

(9) Diarylmethylamines **8** undergo slow decomposition on exposure to the air or silica gel. Attempts to determine the enantiomeric purity of amines **8** themselves were not successful.

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

(11) Kagan, H. B.; Dang, T. P. *J. Am. Chem. Soc*. **1972**, *94*, 6429.

(12) (*R*)-Ar*-MOP was prepared in 58% yield by cross-coupling of (*R*)-2′-(trifluoromethanesulfonyloxy)-2-diphenylphosphino-1,1′-binaphthyl with 3,5-dimethyl-4-methoxyphenylmagnesium bromide catalyzed by $NiCl_2$(dppe): $[\alpha]_D^{20}$ +183 (*c* 1.00, chloroform).

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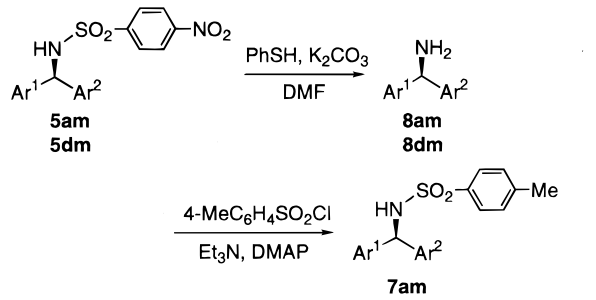
Table 1. Catalytic Asymmetric Arylation of Imines **1**−**3** with Arylstannanes **4** Catalyzed by Rhodium/(*R*)-MOP Complexes[a]

entry	imine	Ar^2SnMe_3 (**4**)	ligand	yield (%)[b] of amine	% ee[c] of amine[d,e]
1	**1a**	**4m**	(*R*)-MeO-MOP	82 (**5am**)	92 (+)−(*S*)
2	**2a**	**4m**	(*R*)-MeO-MOP	66 (**6am**)	87 (+)−(*S*)
3	**3a**	**4m**	(*R*)-MeO-MOP	64 (**7am**)	75 (+)−(*S*)
4	**1a**	**4m**	(*R*)-Ar*-MOP	90 (**5am**)	96 (+)−(*S*)
5	**1a**	**4m**	(*R*)-binap	6 (**5am**)	91 (+)−(*S*)
6	**1a**	**4m**	(+)-diop	10 (**5am**)	40 (−)−(*R*)
7	**1b**	**4m**	(*R*)-MeO-MOP	75 (**5bm**)	89 (+)−(*S*)
8	**1b**	**4m**	(*R*)-Ar*-MOP	90 (**5bm**)	92 (+)−(*S*)
9	**1c**	**4m**	(*R*)-MeO-MOP	61 (**5 cm**)	90 (+)−(*S*)
10	**1c**	**4m**	(*R*)-Ar*-MOP	69 (**5 cm**)	92 (+)−(*S*)
11	**1d**	**4m**	(*R*)-MeO-MOP	68 (**5dm**)	83 (+)−(*S*)
12	**1d**	**4m**	(*R*)-Ar*-MOP	83 (**5dm**)	92 (+)−(*S*)
13	**1a**	**4n**	(*R*)-MeO-MOP	82 (**5an**)	92 (+)−(*R*)
14	**1a**	**4n**	(*R*)-Ar*-MOP	89 (**5an**)	96 (+)−(*R*)
15	**1e**	**4n**	(*R*)-MeO-MOP	77 (**5en**)	91 (+)−(*R*)
16	**1e**	**4n**	(*R*)-Ar*-MOP	86 (**5en**)	92 (+)−(*R*)
17	**1e**	**4o**	(*R*)-MeO-MOP	31 (**5eo**)[f]	82 (−)−(*R*)

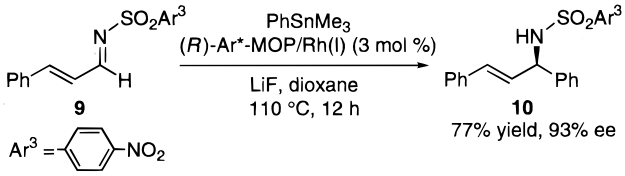
[a] The reaction was carried out in dioxane at 110 °C for 12 h with 5 equiv of **4** in the presence of LiF (10 equiv to imine) and 3 mol % of the catalyst generated from $Rh(acac)(C_2H_4)_2$ and (*R*)-MOP. [b] Isolated yields by column chromatography on silica gel (pretreated with methanol and dried) using ethyl acetate as an eluent. [c] Determined by HPLC analysis with a chiral stationary phase column (Daicel Chiralcel OD-H, hexane/2-propanol = 80/20). [d] Specific rotations ($[\alpha]^{20}_D$ (*c* 0.5−1.0, chloroform)) of the products, **6am** (entry 2), **7am** (entry 3), **5am** (entry 4), **5bm** (entry 8), **5cm** (entry 9), **5dm** (entry 12), **5an** (entry 14), and **5en** (entry 16) are +9.4, +8.0, +7.6, +6.4, +2.4, +0.4, +18.6, and +15.9, respectively. [e] The absolute configuration of **5dm** was determined to be (+)−(*S*) by comparison of the specific rotation of free amine **8dm** (see text). For other products, the configurations were assigned by consideration of the stereochemical reaction pathway. [f] Enantiomer of **5am**.

The phenylation with phenyltrimethylstannane (**4m**) gave high yields of the corresponding sulfonamide of aryl(phenyl)methylamines (+)-**5bm**, **5cm**, and **5dm** with 92% enantioselectivity in the reaction catalyzed by the rhodium-(*R*)-Ar*-MOP complex (entries 8, 10, and 12). Addition of the 4-methoxyphenyl group to **1a** and **1e** also proceeded with high enantioselectivity to give (+)-**5an** (96% ee) and (+)-**5en** (92% ee), respectively (entries 14 and 16). The reaction of imine **1e** with 4-trifluoromethylphenyltrimethylstannane (**4o**), which is a reverse combination of the reaction of **1a** with **4m**, gave a lower yield of product (−)-**5eo** that is an enantiomer of (+)-**5am** (entry 17). Absolute configuration of **5** produced here in the asymmetric arylation with (*R*)-MOP ligands was determined to be (*S*)-(+) for **5dm**, which is assigned by comparison of the specific rotation ($[\alpha]^{20}_D$ +10.4 (*c* 1.00, ethanol)) of (*S*)-(+)-4-chlorophenyl(phenyl)methylamine (**8dm**), obtained by the deprotection of the sulfonamide of (+)-**5dm** (Scheme 2), with the reported value.[2a,13] Considering the similarity in the stereochemical pathway where the *si* face of the imine was attacked by an aryl group, other diarylamines obtained with (*R*)-MOP ligands should have the same absolute configuration as **5dm**, which is depicted in Scheme 1.

Scheme 2



Scheme 3



The present catalytic asymmetric arylation can be applied to sulfonamide of an α,β-unsaturated aldehyde, the phenylation of **9** catalyzed by rhodium-(*R*)-Ar*-MOP complex giving allylic amine **10** of 93% ee[14] (Scheme 3). The catalytic cycle of the present asymmetric arylation probably involves a rhodium−aryl species generated from arylstannane and its enantioselective addition to the carbon−nitrogen double bond of imine. Mechanistic studies are now in progress.

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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.

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(13) For (*S*)-**8dm**: $[\alpha]_D^{20}$ +10.8 (*c* 2.18, ethanol). (a) Clemo, G. R.; Gardner, C.; Raper, R. *J. Chem. Soc.* **1939**, 1958. (b) Opalka, C. J.; D'Ambra, T. E.; Faccone, J. J.; Bodson, G.; Cossement, E. *Synthesis* **1995**, 766.

(14) **10** of 93% ee: $[\alpha]_D^{20}$ +7.4 (*c* 0.5, chloroform).