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Catalytic Asymmetric Desymmetrization of *meso*-Diamide Derivatives through Enantioselective *N*-Allylation with a Chiral π-Allyl Pd Catalyst: Improvement and Reversal of the Enantioselectivity

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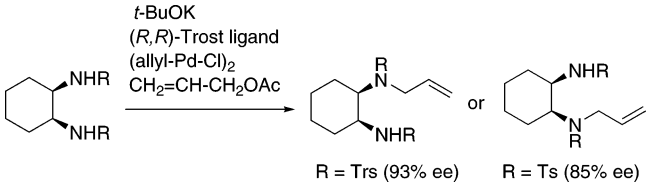
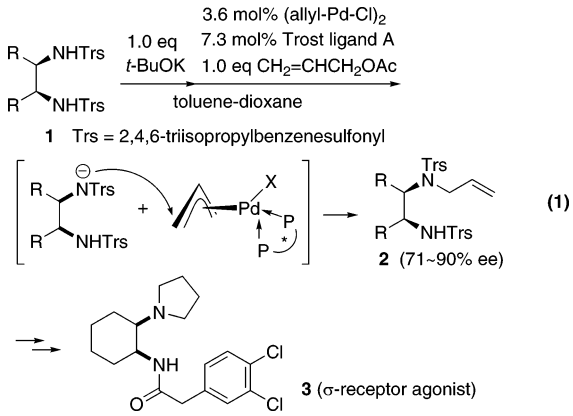


In the presence of the Trost ligands−Pd catalysts, *N*-monoallylation of bis(2,4,6-triisopropylbenzne)sulfonylamides derived from *meso*-1,2-diamines proceeds with good to excellent enantioselectivity (85−96% ee) to give asymmetric desymmetrization products. Under the same conditions, in the reaction with *meso*-bistolunesulfonylamide derivatives, reversal of the enantioselectivity is observed.

Organic compounds possessing a diamine functionality have played an important role in the field of medicinal and synthetic chemistry.[1] Various optically active synthetic diamine derivatives have been employed as chemotherapeutic agents or as chiral ligands for asymmetric reaction.[1] Accordingly, numerous synthetic methods for optically active diamine derivatives have been developed,[1] while the asymmetric synthesis of these diamine derivatives through a catalytic enantioselective reaction has been limited to only a few examples.[2] Especially, until now catalytic asymmetric synthesis of chiral cyclic *syn*-diamines such as unsymmetrical *cis*-1,2-diaminocycloalkanes has been uncommon. It is also noted that chiral compounds possessing a *cis*-1,2-diaminocyclohexane and -cyclopentane skeleton have received attention as potent medicinal agents.[3]

Recently, we found a new method for the preparation of optically active unsymmetrical *cis*-1,2-diaminocycloalkane derivatives through enantioselective *N*-monoallylation of *meso*-1,2-diamine bistrisylamides **1** using a chiral π-allyl Pd catalyst (eq 1).[4,5] This reaction proceeded in the presence of (allyl-Pd-Cl)$_2$ and (*R*,*R*)-Trost ligand to give *N*-monoallylated (asymmetric desymmetrization) products **2** in 71−90% ee. We also succeeded in the conversion of asymmetric desymmetrization product **2a** [R = R = $(CH_2)_4$] to σ-receptor agonist **3** (eq 1).[3a] The present reaction is the first example of asymmetric desymmetrization with *meso*-diamine derivatives.[6,7] In addition, it should be noteworthy that among transition metal-catalyzed N−C bond-forming reactions, this reaction is a rare example of asymmetric induction at the nitrogen nucleophile site (enantiocontrol of prochiral nitrogen nucleophile).[8] In this paper, we report the improvement of the enantioselectivity by screening the Trost



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(6) To the best of our knowledge, there has been no report on asymmetric desymmetrization of *meso*-diamine derivatives. In the reaction with diamine substrates, the enantiocontrol may be difficult because of high nucleophilicity of the amino group and the strong ability to chelate with transition metal, which may result in dissociation of the chiral ligand from the catalytic center and deactivation of the catalyst.

(7) In contrast to diamine derivatives, catalytic asymmetric desymmetrization of *meso*-diols has been well-known. (a) Vedejs, E.; Daugulis, O.; Diver, S. T. *J. Org. Chem*. **1996**, *61*, 430. (b) Oriyama, T.; Imai, K.; Sano, T.; Hosoya, T. *Tetrahedron Lett*. **1998**, *39*, 397. (c) Kawabata, T.; Stragies, R.; Fukuya, T.; Nagaoka, Y.; Schedel, H.; Fuji, K. *Tetrahedron Lett*. **2003**, *44*, 1545. (d) Matsumura, Y.; Maki, T.; Murakami, S.; Onomura, O. *J. Am. Chem. Soc*. **2003**, *125*, 2052. (e) Trost, B. M.; Mino, T. *J. Am. Chem. Soc*. **2003**, *125*, 2410. (f) Shimizu, H.; Katsuki, T. *Chem. Lett*. **2003**, *32*, 480. (g) Mizuta, S.; Sadamori, M.; Fujimoto, T.; Yamamoto, I. *Angew. Chem., Int. Ed*. **2003**, *42*, 3383. (h) Mandal, S. K.; Jensen, D. R.; Pugsley, J. S.; Sigman, M. S. *J. Org. Chem*. **2003**, *68*, 4600. (i) Mizuta, S.; Tsuzuki, T.; Fujimoto, T.; Yamamoto, I. *Org. Lett*. **2005**, *7*, 3633. (j) For a review see: Willis, M. C. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1765.

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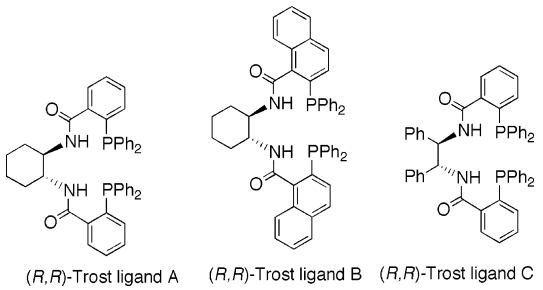
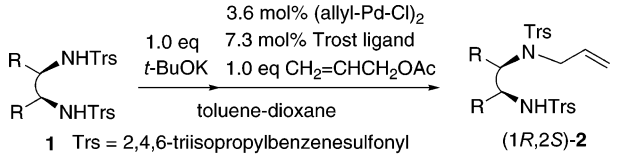
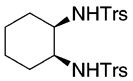
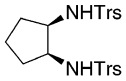
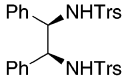
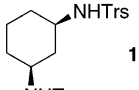
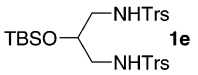


FIGURE 1. Several types of Trost ligand.

TABLE 1. Asymmetric Desymmetrization of Various *meso*-Diamides through Catalytic Enantioselective *N*-Allylation



entry	1	ligand A-C	temp (°C)	2	yield (%)[a]	ee (%)[b]
1		A	-15 to -10		70	90
2	**1a**	B	-15 to -10	**2a**	85	93
3		C	-15 to -10		81	71
4		A	-15 to -10		85	71
5	**1b**	B	-15 to -10	**2b**	84	85
6[c]		A	-15 to +4		63	90
7[c]	**1c**	B	-15 to +4	**2c**	65	96
8		A	-15 to -10		53	18
9	**1d**	B	-15 to -10	**2d**[d]	61	57
10		C	-15 to rt		37	47
11		A	-15 to -10		69[e]	27[e]
12	**1e**	B	-15 to -10	**2e**[d]	78[e]	18[e]

[a] Isolated yield. [b] The ee was determined by HPLC analysis with use of a chiral column. [c] CH_2Cl_2 was used as a solvent. [d] The absolute configuration of the major enantiomer was not determined. [e] The ee and the chemical yield of a hydroxy derivative that was obtained after removal of the TBS group are shown.

ligands, and the reversal of the enantioselectivity by a sulfonyl substituent on a nitrogen atom.

As described in our previous paper,[4] the use of Trost ligand as a chiral phosphine and trisyl (2,4,6-triisopropylbenznesulfonyl = Trs) group as a sulfonyl substituent on a nitrogen atom was essential for the achievement of good enantioselectivity. For example, in the presence of the standard Trost ligand (0.073 equiv, Trost ligand A in Figure 1), $(allyl\text{-}PdCl)_2$ (0.036 equiv), allyl acetate (1 equiv), and *t*-BuOK (1 equiv), the reaction with bistrisylamides **1a** and **1c** of *meso*-1,2-diaminocyclohexane and *meso*-1,2-diphenylethylenediamine gave the desymmetrization products **2a** and **2c** with good enantioselectivity (both 90% ee, entries 1 and 6 in Table 1).[4] On the other hand, under the same conditions, with 1,2-diaminocyclopentane **1b** and 1,3-diamine derivatives **1d** and **1e**, moderate or poor enantioselectivity was observed (**2b** 71% ee, **2d** 18% ee, **2e** 27% ee, entries 4, 8, and 11 in Table 1).[4]

We found that the enantioselectivity can be improved by further survey of the Trost ligands (A−C, Figure 1).[9] That is, the reaction of cyclohexanediamide **1a** with Trost ligand B having a phosphinonaphthyl group gave *N*-monoallylated product **2a** in higher enantioselectivity (93% ee, entry 2 in Table 1), while in the case of ligand C possessing a 1,2-diphenylethylenediamine skeleton, a considerable decrease in the enantioselectivity was observed (71% ee, entry 3). The improvement of the enantioselectivity by using Trost ligand B was also realized in the reaction with other *meso*-1,2-diamide derivatives **1b** and **1c** (entry 4 vs 5, entry 6 vs 7). In these reactions, the products **2b** and **2c** were obtained in 85% ee and 96% ee, respectively (entries 5 and 7). Although the ee was not high with cyclohexane-1,3-diamide **1d** (57% ee, entry 9), the increase in the enantioselectivity was clearly remarkable (entry 8 vs 9). Unfortunately, in the reaction of 2-siloxy-1,3-diaminopropane **1e**, the use of Trost ligand B was not effective. In this case, in comparison with Trost ligand A, a slight decrease in the enantioselectivity was observed (entry 11 vs 12). Since the enantioselectivity was strongly influenced by the reaction temperature, the temperature control shown in Table 1 was required.

Next, we investigated the reversal of the enantioselectivity by a sulfonyl substituent on a nitrogen atom. The *N*-monoallylaion of bistrisylamides **1a**−**1c** with (*R*,*R*)-Trost ligands A−C gave (1*R*,2*S*)-**2a**−**c** as major enantiomers (entries 1−7 in Table 1). Contrary to these, under similar conditions with (*R*,*R*)-Trost ligand A, in the reaction of 4-tosylamide **1f** and 2-nosylamide **1g**, (1*S*,2*R*)-isomeres of **2f** and **2g** were obtained as the major enantiomers (**2f** 52% ee, **2g** 69% ee, entries 1 and 4 in Table 2).[4] To elucidate the origin of the difference of the enantioselectivity by the sulfonyl substituent, the reactions with several sulfonylamide derivatives were further examined with (*R*,*R*)-Trost ligand A (entries 6, 8, and 10 in Table 2). The reaction of benznensulfonylamide **1h** gave the product **2h** with the same enantioselectivity (1*S*,2*R*) and similar ee (50% ee) as in the case of 4-tosyl derivative **1f** (entry 6). With 2-tosyl derivative **1i**, (1*S*,2*R*)-**2i** was obtained in poor enantioselectivity (7% ee, entry 8). The reaction of mesityl derivative **1j** proceeded in the opposite enantioselectivity from those of **1f**−**i** (same enantioselectivity as that of trisyl derivative **1a**) to give (1*R*,2*S*)-**2j** in 26% ee (entry 10). Although the effect of the 2-nosyl group in the reaction of **1g** is still obscure, these results may indicate the importance of an *o*-alkyl substituent for (1*R*,2*S*)-selectivity.

The best (1*S*,2*R*)-selectivity was obtained through the reaction of 4-tosyl derivative **1f** with Trost ligand B (entry 2 in Table 2). In this case, the desymmetrization product (1*S*,2*R*)-**2f** was obtained in 73% ee (at room temperature). Furthermore, when the reaction was conducted at lower temperature (−15 to −10 °C), the ee of the desymmetrization product **2f** increased to 85% (eq 2). Both trisyl-product **2a** and tosyl-product **2f** can be converted to optically active *N*-allyl-1,2-diaminocyclohexane **4** (Scheme 1) by desulfonylation with use of Birch reduction.[4,10] Therefore, both enantiomers of **4** with high enantioselectivity (93% ee and 85% ee) can be obtained through the reaction of **1a** and **1f** with use of the same chiral ligand (avoiding the use of both enantiomers of the chiral ligand).[11] Such reversal of

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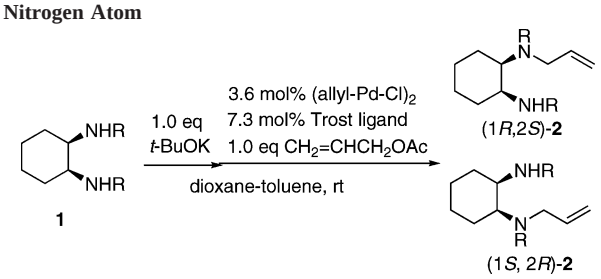
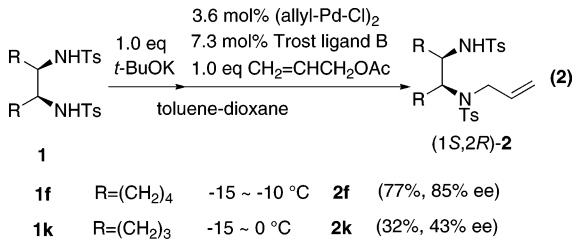
(10) Neipp, C. E.; Humphrey, J. M.; Martin, S. F. *J. Org. Chem.* **2001**, *66*, 531.

TABLE 2. Substituent Effect of the Sulfonyl Group on the Nitrogen Atom

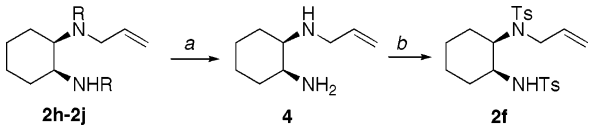


entry	R	1	ligand A-C	2	yield (%)[a]	ee (%)[b]	absolute
1			A		68	52	(1*S*, 2*R*)
2	Me-C6H4-SO2-	1f	B	2f	74	73	(1*S*, 2*R*)
3			C		69	52	(1*S*, 2*R*)
4	NO2-C6H4-SO2-	1g	A	2g	74	69	(1*S*, 2*R*)
5			B		74	53	(1*S*, 2*R*)
6	C6H5-SO2-	1h	A	2h	73	50	(1*S*, 2*R*)
7			B		86	44	(1*S*, 2*R*)
8	Me-C6H4-SO2-	1i	A	2i	73	7	(1*S*, 2*R*)
9			B		75	19	(1*S*, 2*R*)
10	Me2-C6H3-SO2-	1j	A	2j	82	26	(1*R*, 2*S*)
11			B		75	24	(1*R*, 2*S*)

[a] Isolated yield. [b] The ee was determined by HPLC analysis with use of a chiral column.



SCHEME 1. Determination of Absolute Configuration of 2h−2j[a]

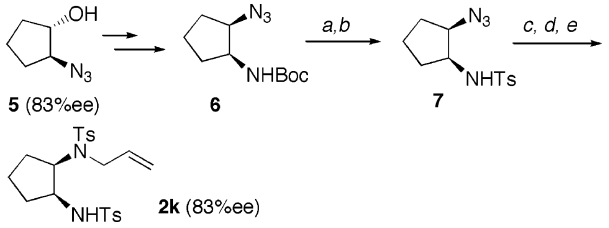


[a] Reagents and conditions: (a) Na, liquid NH_3; (b) Ts-Cl, Et_3N, THF, 60 °C, 9−21% (2 steps).

the enantioselectivity was also observed in the reaction with 1,2-diaminocyclopentane derivatives. That is, the reaction of **1b** and **1k** with (*R*,*R*)-Trost ligand B gave (1*R*,2*S*)-**2b** and (1*S*,2*R*)-**2k** in 85% ee and 43% ee, respectively (entry 5 in Table 1, eq 2), while the ee values are lower than those of cyclohexane derivatives **2a** and **2f**. Unfortunately, the reaction with bistosylamide of 1,2-diphenylethylenediamine failed because of its extremely low solubility in various organic solvents.

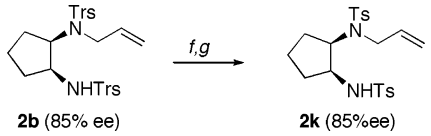
The stereochemical assignment of the products **2a**, **2f**, and **2g** was already described in the previous paper.[4] The absolute configurations of **2h−j** were determined by the conversion to

SCHEME 2. Determination of Absolute Configuration of 2k[a]



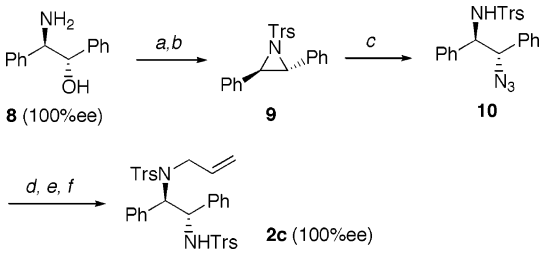
[a] Reagents and conditions: (a) CF_3COOH, CH_2Cl_2, rt; (b) Ts-Cl, Et_3N, THF, rt, 63% (2 steps); (c) 10% Pd−C/H_2, CH_3OH, rt; (d) allyl bromide, K_2CO_3, THF, 60 °C; (e) Ts-Cl, Et_3N, THF, 60 °C, 25% (3 steps).

SCHEME 3. Determination of Absolute Configuration of 2b[a]



[a] Reagents and conditions: (f) Na, liquid NH_3; (g) Ts-Cl, Et_3N, THF, 60 °C, 16% (2 steps).

SCHEME 4. Determination of Absolute Configuration of 2c[a]



[a] Reagents and conditions: (a) Trs-Cl, Et_3N, THF, rt, 75%; (b) NaH, Ms-Cl, THF, rt, 69%; (c) TMS-N_3, TBAF, THF, 50 °C, 97%; (d) *t*-BuOK, (allyl-Pd-Cl)$_2$, dppe, allyl acetate, toluene−dioxane, 0 °C, 72%; (e) Ph_3P, H_2O, THF, rt, 36%; (f) Trs-Cl, Et_3N, dioxane, 100 °C, 26%.

tosyl derivative **2f** (Scheme 1).[12] Those of cyclopentane derivatives **2b** and **2k** and 1,2-diphenylethylenediamine derivative **2c** were confirmed by the direct comparison with authentic samples prepared from the known azide alcohol **5** and amino alcohol **8**, respectively (Schemes 2,[3f] 3,[12] and 4).

In conclusion, we have succeeded in the improvement of the enantioselectivity in the catalytic asymmetric *N*-monoallylation of *meso*-bissulfonamides by screening the Trost ligands. Furthermore, we found a remarkable reversal of the enantioselectivity by the sulfonyl substituent on the nitrogen atom. The present reaction should provide a new methodology for the preparation of optically active unsymmetrical *cis*-1,2-diaminocycloalkane derivatives. In addition, the present reaction should be notable as a rare example of asymmetric induction at the nitrogen nucleophile site in transition metal-catalyzed

(11) For recent examples in relation to the switch of enantioselectivity by the use of the same chiral ligand, see: (a) Sibi, M. P.; Shay, J. J.; Liu, M.; Jasperse, C. P. *J. Am. Chem. Soc*. **1998**, *120*, 6615. (b) Kobayashi, S.; Kusakabe, K.; Komiyama, S.; Ishitani, H. *J. Org. Chem*. **1999**, *64*, 4220. (c) Yabu, K.; Masumoto, S.; Yamasaki, S.; Hamashima, Y.; Kanai, M.; Du, W.; Curran, D. P.; Shibasaki, M. *J. Am. Chem. Soc*. **2001**, *123*, 9908. (d) Wilkinson, J. A.; Rossington, S. B.; Leonard, J.; Hussein, N. *Tetrahedron Lett*. **2004**, *45*, 1191. (e) Du, D.; Lu, S.; Fang, T.; Xu, J. *J. Org. Chem*. **2005**, *70*, 3712. (f) Desimoni, G.; Faita, G.; Guala, M.; Laurenti, A.; Mella, M. *Chem. Eur. J*. **2005**, *11*, 3816.

(12) The reaction conditions in the conversion of Schemes 1 and 3 were not optimized, while as described in our previous paper,[4] similar conversion with trisyl derivative **2a** gave **4f** in 46% yield.

N−C coupling and as the first example of asymmetric desymmetrization with *meso*-diamine derivative.

Experimental Section

General Procedure of Catalytic Asymmetric *N*-Allylation with (*R*,*R*)-Trost Ligand−Pd Catalyst. Under Ar atmosphere, to a suspension of *t*-BuOK (34 mg, 0.3 mmol) in toluene (1.5 mL) was added diamide **1a** (194 mg, 0.3 mmol). After the solution was stirred for 5 min at room temperature, allylpalladium chloride dimer (4 mg, 0.011 mmol), (*R*,*R*)-Trost ligand B (17 mg, 0.022 mmol), and allyl acetate (33 μL, 0.3 mmol) in 1,4-dioxane (1.5 mL) were added to the mixture at −15 °C, and then the reaction mixture was stirred for 14 h from −15 to −10 °C. The mixture was poured into 2% HCl solution and extracted with AcOEt. The AcOEt extracts were washed with brine, dried over $MgSO_4$, and evaporated to dryness. Purification of the residue by column chromatography (hexane/AcOEt = 30) gave **2a** (175 mg, 85%). The ee (93% ee) of **2a** was determined by HPLC analysis, using a CHIRALCEL OD-H column [25 cm × 0.46 cm i.d.; 1% *i*-PrOH in hexane; flow rate, 0.5 mL/min; (+)-**2a** (minor), t_R = 11.8 min; (−)-**2a** (major), t_R = 14.4 min]. ^{1}H NMR data for **2a** coincided with those reported in our previous paper.[4]

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Supporting Information Available: Experimental procedures and spectral data for all new compounds; ^{1}H and ^{13}C NMR spectra of new compounds (**2j**, **2k**, **7**) with no elemental analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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