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# Rhodium-Catalyzed Reactions of Dithiols and 1,4-Bis(bromomethyl)benzenes Leading To Enantioenriched Dithiaparacyclophanes

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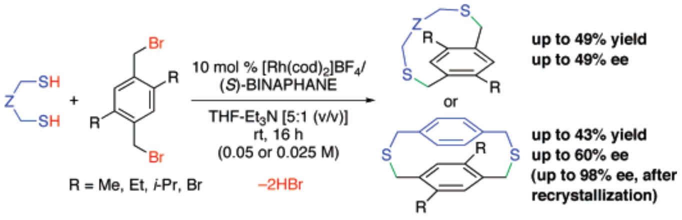
## ABSTRACT



**We have achieved the first catalytic enantioselective synthesis of planar-chiral dithiaparacyclophanes by means of cationic rhodium(I)/(*S*)-BINAPHANE complex-catalyzed reactions of dithiols and 1,4-bis(bromomethyl)benzenes. The present method represents the first example of asymmetric synthesis of planar-chiral cyclophanes through catalytic enantioselective construction of the ansa chains.**

Planar-chiral paracyclophanes have received much attention as attractive chiral sources for chiral reagents and functional materials.[1] However, their previously reported syntheses are mainly based on the redundant optical resolution of racemic compounds.[2,3] Recently, Kanomata and co-workers reported stereocontrol of cyclophane-type planar chirality by crystallization-induced[4a,b] or adsorption-induced[4c] dynamic resolution of diastereomeric mixtures of paracyclophanes. However, the straightforward catalytic enantioselective synthesis of planar-chiral paracyclophanes has not been realized. In the course of our studies on cationic rhodium(I)/$H_8$-BINAP-catalyzed alkyne cyclotrimerization, we found that paracyclophanes can be obtained in good yield by catalytic aromatization through partial intramolecular cyclotrimerization of terminal $\alpha,\omega$-diynes and dimethyl acetylenedicarboxylate (Scheme 1).[5,6] Recently, we have successfully applied this methodology to the first enantioselective synthesis of planar-chiral metacyclophanes, although the enantioselective synthesis of planar-chiral paracyclophanes has

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(1) For reviews of cyclophanes, see: (a) *Modern Cyclophane Chemistry*; Gleither, R., Hopf, H., Eds.; Wiley: Chichester, 2004. (b) *Cyclophane Chemistry*; Vögtle, F., Ed.; Wiley: Chichester, 1993.

(2) For a review of the cyclophane synthesis, see: Kane, V. V.; De Wolff, W. H.; Bickelhaupt, F. *Tetrahedron* **1994**, *50*, 4574.

(3) For recent examples of synthesis and optical resolution of planar-chiral paracyclophanes, see: (a) Kanomata, N.; Yamada, S.; Ohhama, T.; Fusano, A.; Ochiai, Y.; Oikawa, J.; Yamaguchi, M.; Sudo, F. *Tetrahedron* **2006**, *62*, 4128. (b) Kanomata, N.; Nakata, T. *J. Am. Chem. Soc.* **2000**, *122*, 4563. (c) Sato, M.; Uehara, F.; Sato, K.; Yamaguchi, M.; Kabuto, C. *J. Am. Chem. Soc.* **1999**, *121*, 8270. (d) Kanomata, N.; Nakata, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1207. (e) Pischel, I.; Nieger, M.; Archut, A.; Vögtle, F. *Tetrahedron* **1996**, *52*, 10043.

(4) (a) Kanomata, N.; Ochiai, Y. *Tetrahedron Lett.* **2001**, *42*, 1045. (b) Ueda, T.; Kanomata, N.; Machida, H. *Org. Lett.* **2005**, *7*, 2365. (c) Kanomata, N.; Oikawa, J. *Tetrahedron Lett.* **2003**, *44*, 3625.

(5) For our synthesis of cyclophanes via cationic rhodium(I)/$H_8$-BINAP-catalyzed [2 + 2 + 2] cycloadditions, see: (a) Tanaka, K.; Shirasaka, K. *Org. Lett.* **2003**, *5*, 4697. (b) Tanaka, K.; Toyoda, K.; Wada, A.; Shirasaka, K.; Hirano, M. *Chem.—Eur. J.* **2005**, *11*, 1145. (c) Tanaka, K.; Sagae, H.; Toyoda, K.; Noguchi, K. *Eur. J. Org. Chem.* **2006**, 3575.

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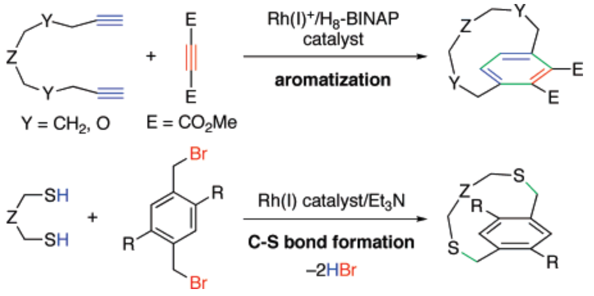
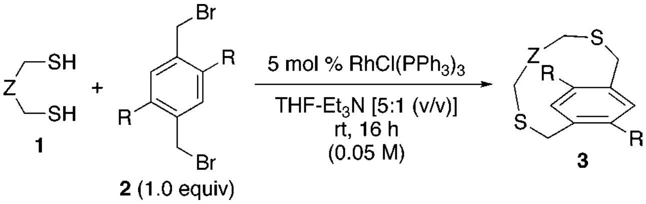
**Scheme 1.** Rh(I)-Catalyzed Synthesis of Paracyclophanes



not been reported yet.[7] An alternative approach to the synthesis of paracyclophanes is construction of the ansa chain, such as double C−S bond formation leading to dithiaparacyclophanes (Scheme 1).[8,9] We have previously reported $RhCl(PPh_3)_3$-catalyzed C−S bond formation of thiols and alkyl bromides in the presence of $Et_3N$.[10,11] In this paper, we report the first catalytic enantioselective synthesis of planar-chiral dithiaparacyclophanes by means of cationic rhodium(I)/(*S*)-BINAPHANE complex-catalyzed reactions of dithiols and 1,4-bis(bromomethyl)benzenes.

We first examined the reaction of 1,5-pentanedithiol (**1a**) and 1,4-bis(bromomethyl)-2,5-dimethylbenzene (**2a**, 1.0 equiv) using 5 mol % of $RhCl(PPh_3)_3$ in THF−$Et_3N$ at room temperature and various concentrations.[12] In the conventional double C−S bond formation of dithiols and 1,4-bis(halomethyl)benzenes leading to dithiaparacyclophanes, high dilution conditions and/or slow addition of substrates are necessary.[8] On the contrary, after examining the effect of concentrations, the $RhCl(PPh_3)_3$-catalyzed double C−S bond formation between dithiol **1a** and dibromide **2a** furnished the desired dithia[9]paracyclophane **3aa** in good yield even at high concentration without slowly adding the substrates (0.10 M: 39%, 0.05 M: 50%, 0.025 M: 51%, 0.0125 M: 25%). Thus, we explored the scope of this process with respect to dibromides and dithiols (Table 1). Not only dimethyl-substituted dibromide (**2a**, entry 1) but diethyl- (**2b**, entry 2), diisopropyl- (**2c**, entry 3), and dibromo- (**2d**, entry 4) substituted dibromides could also participate in this reaction. With regard to dithiols, the use of commercially available 1,6-hexanedithiol (**1b**) and 1,8-octanedithiol (**1c**) could furnish the desired dithia[10]paracyclophane **3ba** and dithia[12]paracyclophane **3ca**, respectively (entries 5 and 6).

**Table 1.** $RhCl(PPh_3)_3$-Catalyzed Synthesis of Racemic Dithia[9], [10], and [12]paracyclophanes **3**[a]



| entry | 1 | Z | 2 | R | 3 | yield[b] (%) |
|---|---|---|---|---|---|---|
| 1 | **1a** | $(CH_2)_3$ | **2a** | Me | **3aa** | 50 |
| 2 | **1a** | $(CH_2)_3$ | **2b** | Et | **3ab** | 42 |
| 3 | **1a** | $(CH_2)_3$ | **2c** | *i*-Pr | **3ac** | 54 |
| 4 | **1a** | $(CH_2)_3$ | **2d** | Br | **3ad** | 32 |
| 5 | **1b** | $(CH_2)_4$ | **2a** | Me | **3ba** | 40 |
| 6 | **1c** | $(CH_2)_6$ | **2a** | Me | **3ca** | 29 |

[a] Dithiol (0.25 mmol), dibromide (0.25 mmol), $RhCl(PPh_3)_3$ (0.0125 mmol), and THF−$Et_3N$ [5:1 (v/v), 5.0 mL] were employed. [b] Isolated yield.

The successful synthesis of dithia[*n*]paracyclophanes prompted our investigation into the synthesis of dithia[3.3]-paracyclophanes.[8] Unfortunately, the reactions of dithiol **1d** with dibromides **2a** and **2d** at 0.025 M concentration furnished the corresponding dithia[3.3]paracyclophanes **3da** and **3dd** in low yields (Scheme 2).

Next, we investigated the asymmetric variant of this reaction by employing chiral rhodium(I) catalysts.[13] However, the use of conventional chiral monodentate or bidentate phosphine ligands furnished dithia[9]paracyclophane **3aa**

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(6) For syntheses of cyclophanes via transition-metal-catalyzed or mediated macrocyclization, see: Cobalt-catalyzed [2 + 2 + 2] cycloaddition: (a) Boñaga, L. V. R.; Zhang, H.-C.; Moretto, A. F.; Ye, H.; Gautheir, D. A.; Li, J.; Leo, G. C.; Maryanoff, B. E. *J. Am. Chem. Soc.* **2005**, *127*, 3473. (b) Boñaga, L. V. R.; Zhang, H.-C.; Maryanoff, B. E. *Chem. Commun.* **2004**, 2394. (c) Boñaga, L. V. R.; Zhang, H.-C.; Gautheir, D. A.; Reddy, I.; Maryanoff, B. E. *Org. Lett.* **2003**, *5*, 4537. (d) Moretto, A. F.; Zhang, H.-C.; Maryanoff, B. E. *J. Am. Chem. Soc.* **2001**, *123*, 3157. $RhCl(PPh_3)_3$-catalyzed [2 + 2 + 2] cycloaddition: (e) Kinoshita, H.; Shinokubo, H.; Oshima, K. *J. Am. Chem. Soc.* **2003**, *125*, 7784. Palladium-catalyzed coupling of enynes: (f) Weibel, D.; Gevorgyan, V.; Yamamoto, Y. *J. Org. Chem.* **1998**, *63*, 1217. (g) Saito, S.; Tsuboya, N.; Yamamoto, Y. *J. Org. Chem.* **1997**, *62*, 5042. Cycloaddition of Fischer chromium carbenes with alkynes: (h) Wang, H.; Wulff, D. W.; Rheingold, L. A. *J. Am. Chem. Soc.* **2003**, *125*, 8980. (i) Wang, H.; Wulff, D. W.; Rheingold, L. A. *J. Am. Chem. Soc.* **2000**, *122*, 9862. (j) Dötz, H. K.; Gerhardt, A. *J. Organomet. Chem.* **1999**, *578*, 223. Intramolecular addition of rhodium carbenes: (k) Doyle, M. P.; Hu, W. *Synlett* **2001**, 1364. (l) Doyle, M. P.; Hu, W.; Chapman, B.; Marnett, A. B.; Peterson, C. S.; Viatale, P. J.; Stanley, S. A. *J. Am. Chem. Soc.* **2000**, *122*, 5718. Heck reaction: (m) Dyker, G.; Kadzimirsz, D.; Henkel, G. *Tetrahedron Lett.* **2003**, *44*, 7905. (n) Geng, X.; Miller, M. L.; Lin, S.; Ojima, I. *Org. Lett.* **2003**, *5*, 3733.

(7) Tanaka, K.; Sagae, H.; Toyoda, K.; Noguchi, K.; Hirano, M. *J. Am. Chem. Soc.* **2007**, *129*, 1522.

(8) For selected examples, see: (a) Grimme, S.; Pischel, F.; Vögtle, F.; Nieger, M. *J. Am. Chem. Soc.* **1995**, *117*, 157. (b) Chiu, J.-J.; Hart, H.; Ward, D. L. *J. Org. Chem.* **1993**, *58*, 964. (c) Takeshita, M.; Tsuzuki, H.; Tashiro, M. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 2076. (d) Rossa, L.; Vögtle, F. *Top. Curr. Chem.* **1983**, *113*, 1. (e) See also ref 3e.

(9) For synthesis of dithiaparacyclophanes by transacetalization, see: (a) Ellis-Holder, K. K.; Peppers, B. P.; Kovalevsky, A. Y.; Diver, S. T. *Org. Lett.* **2006**, *8*, 2511. (b) Ellis, K. K.; Wilke, B.; Zhang, Y.; Diver, S. T. *Org. Lett.* **2000**, *2*, 3785.

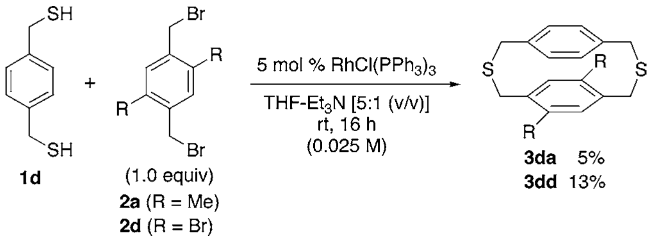
(10) (a) Tanaka, K.; Ajiki, K. *Org. Lett.* **2005**, *7*, 1537. For rhodium-catalyzed reductive coupling of disulfides with alkyl halides using hydrogen as a reducing agent, see: (b) Ajiki, K.; Hirano, M.; Tanaka, K. *Org. Lett.* **2005**, *7*, 4193.

(11) For pioneering work on a metal-catalyzed coupling reaction of thiols and alkyl iodides using a platinum complex as a catalyst, see: (a) Page, P. C. B.; Klair, S. S.; Brown, M. P.; Harding, M. M.; Smith, C. S.; Maginn, S. J.; Mulley, S. *Tetrahedron Lett.* **1988**, *29*, 4477. (b) Page, P. C. B.; Klair, S. S.; Brown, M. P.; Smith, C. S.; Maginn, S. J.; Mulley, S. *Tetrahedron* **1992**, *48*, 5933.

(12) Increasing the reaction temperature decreased the yields of dithiaparacyclophanes.

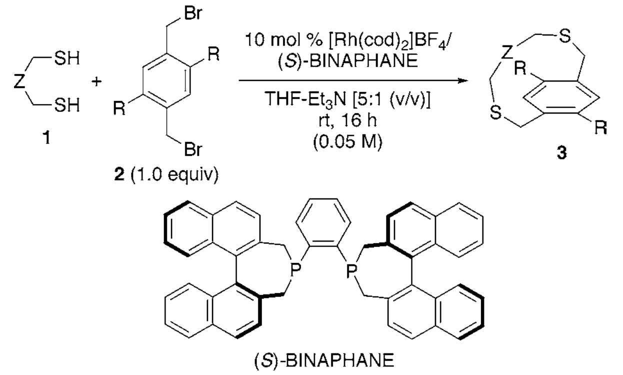
(13) Synthesis and chiroptical properties of planar-chiral dithia[*n*]cyclophanes were reported. For dithia[*n*]paracyclophanes, see ref 3e. For dithia[*n*]metacyclophanes, see ref 8a.

**Scheme 2.** $RhCl(PPh_3)_3$-Catalyzed Reactions of Dithiol **1d** and Dibromides **2a** and **2d**



with very low ee's [e.g., (*R*)-MOP[14] (<2% ee), (*R*)-BINAP (4% ee), (*R*)-tol-BINAP (4% ee), (*S*,*S*)-Chiraphos[14] (8% ee), (*R*,*R*)-DIOP[14] (<2% ee), and (*R*,*R*)-*i*-Pr-Duphos[14] (<2% ee)]. Fortunately, the use of (*S*)-BINAPHANE as a ligand significantly improved the ee to 49% (Table 2, entry 1).

**Table 2.** Rh(I)$^+$/(*S*)-BINAPHANE-Catalyzed Synthesis of Enantioenriched Dithia[9], [10], and [12]paracyclophanes **3**[a]



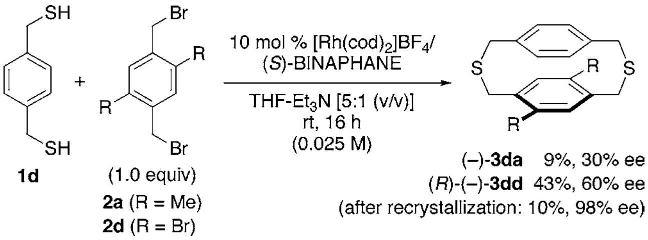
| entry | 1 | Z | 2 | R | 3 | yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|---|---|---|
| 1 | **1a** | $(CH_2)_3$ | **2a** | Me | (−)-**3aa** | 45 | 49 |
| 2 | **1a** | $(CH_2)_3$ | **2b** | Et | (−)-**3ab** | 41 | 36 |
| 3 | **1a** | $(CH_2)_3$ | **2c** | *i*-Pr | (−)-**3ac** | 49 | 37 |
| 4 | **1a** | $(CH_2)_3$ | **2d** | Br | (−)-**3ad** | 43 | 27 |
| 5 | **1b** | $(CH_2)_4$ | **2a** | Me | **3ba** | 39 | <2 |
| 6 | **1c** | $(CH_2)_6$ | **2a** | Me | (−)-**3ca** | 11 | 20 |

[a] Dithiol (0.25 mmol), dihalide (0.25 mmol), $[Rh(cod)_2]BF_4$ (0.025 mmol), (*S*)-BINAPHANE (0.025 mmol), and THF−$Et_3N$ [5:1 (v/v), 5.0 mL] were employed. [b] Isolated yield. [c] Enantiomeric excess was determined by chiral stationary phase HPLC analysis.

Although the enantioselectivity decreased, diethyl- (**3ab**), diisopropyl- (**3ac**), and dibromo- (**3ad**) substituted dithia[9]paracyclophanes could be obtained with 27−37% ee (entries 2−4). Not only enantioselective synthesis of dithia[9]paracyclophanes but also that of dithia[10] and [12]paracyclophanes was also investigated by employing the above optimal reaction conditions, but the desired dithia[10] and [12]paracyclophanes **3ba** and **3ca** were obtained with lower ee's (entries 5 and 6).

The cationic rhodium(I)/(*S*)-BINAPHANE complex could be applied to the synthesis of enantioenriched dithia[3.3]paracyclophanes. The reaction of dithiol **1d** and dibromide **2a** furnished dimethyl-substituted cyclophane (−)-**3da** in 9% yield with 30% ee (Scheme 3). Further improved yield (43%) and ee (60%) were observed in the synthesis of dibromo-substituted cyclophane (−)-**3dd**, and highly enantioenriched (−)-**3dd** (98% ee) could be readily obtained by recrystallization (Scheme 3). Interestingly, compared with the synthesis of dithia[3.3]paracyclophanes using $RhCl(PPh_3)_3$ catalyst, the use of the cationic rhodium(I)/(*S*)-BINAPHANE catalyst significantly improved the yields of cyclophanes.[15] The chiral dibromocyclophane (−)-**3dd** would be a useful compound for further functionalization and polymer synthesis through metal-catalyzed coupling reactions.[16]

**Scheme 3.** Rh(I)$^+$/(*S*)-BINAPHANE-Catalyzed Synthesis of Enantioenriched Dithia[3.3]paracyclophanes **3da** and **3dd**



The enantiopure crystals of (−)-**3dd** were subjected to X-ray crystallographic analysis, which determined the absolute configuration to be *R* (Figure 1). There are two crystallographically independent molecules (Mol A and B) in an asymmetric unit. The molecular structures of Mol A and B are almost identical to each other. The rms difference calculated after least-square fitting of independent molecules is 0.041 Å. As shown in Figure 1, one phenyl ring in the molecule largely overlaps the other. Intramolecular distances between mean planes of two phenyl rings (stacking distance)

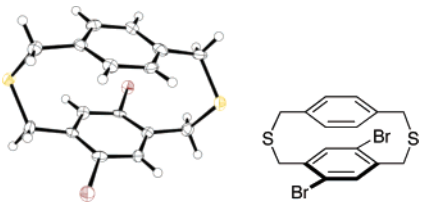


**Figure 1.** ORTEP diagram of (*R*)-(−)-**3dd** (Mol A).

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[14] MOP: 2-(diphenylphosphino)-2′-methoxy-1,1′-binaphthyl. Chiraphos: 2,3-bis(diphenylphosphino)butane. DIOP: 4,5-bis(diphenylphosphinomethyl)-2,2-dimethyl-1,3-dioxolane. *i*-Pr-Duphos: 1,2-bis(2,5-di-*i*-propylphospholano)benzene.

(15) In the reactions of dithiols and dibromides shown in Tables 1 and 2 and Schemes 1 and 2, the starting materials were not recovered and insoluble oligomers were obtained as byproducts.

(16) For synthesis of fluorenedithia[3.3]paracyclophane copolymers, see: Wang, W.; Xu, J.; Lai, Y.-H. *Org. Lett.* **2003**, *5*, 2765.

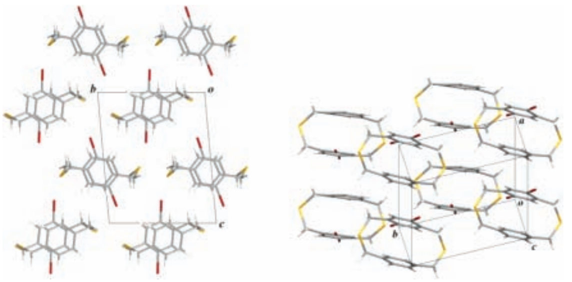

**Figure 2.** Packing diagram of (*R*)-(−)-**3dd** projected along the *a*-axis (left) and the *ab*-projection (right).

and between ring centroids projected to one of the mean planes of phenyl rings (slippage distance) in Mol A and B are 3.237 and 0.687 Å, and 3.190 and 0.739 Å, respectively. In addition, intermolecular stacking and slippage distances between the adjacent molecules for Mol A and B are 3.509 and 1.138 Å, and 3.289 and 1.469 Å, respectively. These observations indicate that crystals of (−)-**3dd** are stabilized by $\pi/\pi$-stacking interaction along the crystallographic *a*-axis (Figure 2).

In conclusion, the first catalytic enantioselective synthesis of planar-chiral dithiaparacyclophanes was achieved by cationic rhodium(I)/(*S*)-BINAPHANE complex-catalyzed reactions of dithiols and 1,4-bis(bromomethyl)benzenes. The present new method represents the first example of asymmetric synthesis of planar-chiral cyclophanes through catalytic enantioselective construction of the ansa chains.

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**Supporting Information Available:** Experimental procedures, compound characterization data, and an X-ray crystallographic information file (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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