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Synthesis of Planar-Chiral Paracyclophanes via Samarium(II)-Catalyzed Intramolecular Pinacol Coupling

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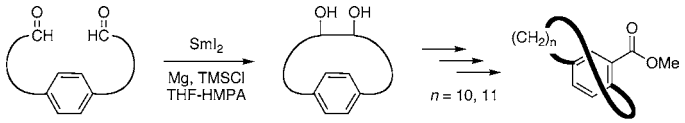
ABSTRACT



[*n*]Paracyclophanediol (*n* = 8–12)

A series of [*n*]paracyclophanediols (*n* = 8–12) was synthesized by samarium-catalyzed pinacol coupling for their ansa-bridge formation. Enantiomerically pure [*n*]paracyclophane esters were derived from the diols in a several steps via chiral resolution (for *n* = 10) or via crystallization-induced asymmetric transformation (for *n* = 11) by using amino alcohol auxiliaries and their selective cleavages.

Planar-chiral paracyclophanes are increasingly recognized as attractive chiral sources for various stereoselective reactions because of their unique structure and functionality.[1−3] We have previously reported that biomimetic reactions, where bridged NADH models having a chiral [10]parapyridinophane skeleton reduce pyruvate analogues with high enantioselectivity, are a successful application of pyridine-type of cyclophanes to asymmetric induction.[4] Although many synthetic routes are known to [*n*]paracyclophanes and their related compounds,[5] only limited approaches by intramolecular cyclization of functionalized disubstituted aromatics have been reported despite their direct and wide applicability.[6,7] Recently, Sm^{2+}-mediated pinacol coupling has been proven to be a most versatile and useful C−C bond formation reaction[8,9] and, therefore, seems to be a potent tool for ansa-bridge construction in cyclophane syntheses. In

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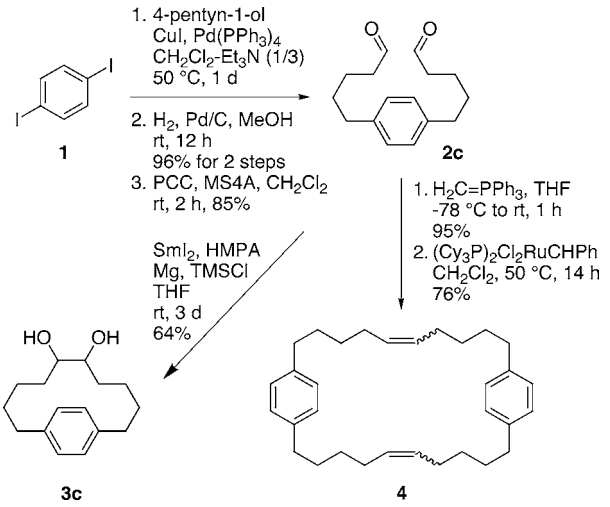
particular, the high Lewis acidity of Sm^{3+} generated in such reactions is known to exhibit heteroatom affinity and, therefore, seems to be useful for ring closure reactions via chelated intermediates.[10] We further anticipated that catalytic use of samarium, or its limited concentration, should prefer intramolecular cyclization to intermolecular oligomerization. We describe here a novel synthetic method for planar-chiral paracyclophanes via intramolecular ansa-bridge construction by SmI_2-catalyzed pinacol coupling under mild conditions and their application to planar-chiral cyclophane synthesis.

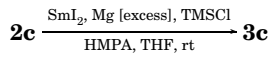
Scheme 1 outlines our synthetic route for a representative

Scheme 1. Synthesis of [10]Paracyclophanediol (**3c**) via SmI_2-Catalyzed Pinacol Coupling Cyclization



[10]paracyclophanediol (**3c**). The synthesis began with a double Sonogashira reaction[11] of 1,4-diiodobenzene (**1**) with 4-pentyn-1-ol to give diyne products in a quantitative yield. Hydrogenation and the following oxidation with PCC produced dialdehyde **2c** in 82% yield (three steps from **1**). The ansa-bridge formation reaction, a key step in this synthesis, was achieved by Sm^{2+}-mediated pinacol cyclization of **2c** in the presence of HMPA. Endo et al. previously reported that a novel SmI_2-catalyzed pinacol coupling of some aromatic and phenethyl aldehydes by using magnesium metal as co-reductant gave the corresponding diols in 23−81% yields.[9a] We initially followed Endo's protocol for the cyclization of **2c** without HMPA, but the yield of [10]-paracyclophanediol (**3c**) was poor (see entry 1 in Table 1). Then we found the cyclization proceeded efficiently in the presence of HMPA,[12] which is often used to activate various

Table 1. SmI_2-Catalyzed Pinacol Cyclization of **2c**[a]



entry	addition of **2c**	SmI_2 [equiv]	HMPA [equiv]	TMSC [equiv]	yield [%][b]
1	24 h	5.0	0	50	14
2	6 h	5.0	10	50	33
3	24 h	2.0	4.0	20	54
4	24 h	2.0	4.0	0	13
5	24 h	1.0	2.0	10	46
6	72 h	1.0	2.0	10	59
7	72 h	0.6	1.2	6.0	64
8	72 h	0.4	0.8	4.0	49
9	24 h	0	4.0	20	0

[a] All the reactions were carried out in the presence of a 50 equiv amount of magnesium for regenerating Sm^{2+}. [b] Isolated yields.

Sm^{2+}-promoted reactions, to give the desired **3c** in 64% yield as a 1/1 mixture of erythro and threo diols. It is worth mentioning that the ring-closing metathesis (RCM) of the corresponding diene derived from **2c** furnished undesired dimer **4** as a less strained product under reversible RCM conditions.[7]

Table 1 indicates the results for opimizing the SmI_2-catalyzed pinacol cyclization from **2c** to **3c**. We found that the pinacol cyclization was best accomplished in THF at room temperature in the presence of SmI_2, HMPA, TMSCl, and magnesium in a ratio of 1:2:10:50, respectively. We have carried out these reactions with various amounts of SmI_2 (entries 1−8), and the best result was obtained with 0.6 equiv of the Sm^{2+} catalyst for the synthesis of **3c** (entry 7). Reactions in the absence of HMPA or TMSCl resulted in low yields (entries 1 and 4). No reaction took place without SmI_2 (entry 9), which rules out the pathway through the known pinacol coupling by the TMSCl−Mg system in the presence of HMPA.[13]

The postulated reaction pathway is shown in Scheme 2. Single electron transfer from SmI_2 reduces a formyl group of dialdehyde **2c** in THF−HMPA to form a samarium(III) alkoxy radical **A**, which undergoes the C−C bond formation, and the subsequent reduction with the second SmI_2 gave the alcoholate **B**. The alcoholate **B** was then trapped with TMSCl to give the corresponding silyl ether and Sm^{3+}. Finally, the divalent samarium species such as SmI_2 or SmClI is regenerated by electron transfer from magnesium.

This method was found to be useful for the preparation of a series of [*n*]paracyclophanediols **3a**−**h** ($n = 8$−12) from the corresponding dialdehydes **2a**−**h**[14] (Table 2). As expected, yields of **3a**−**h** are dependent on the length of their oligomethylene bridges (entries 1−5), and the present method is evidently applicable for synthesis of [*n*]paracyclophanes

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(14) The compounds **2b**, **2d**, and **2h** ($x \neq y$) were synthesized via stepwise Sonogashira reactions of 1-bromo-4-iodobenzene with appropriate alkynols.

Scheme 2. Postulated Reaction Pathways of Pinacol Cyclization Catalyzed by Sm^{2+}

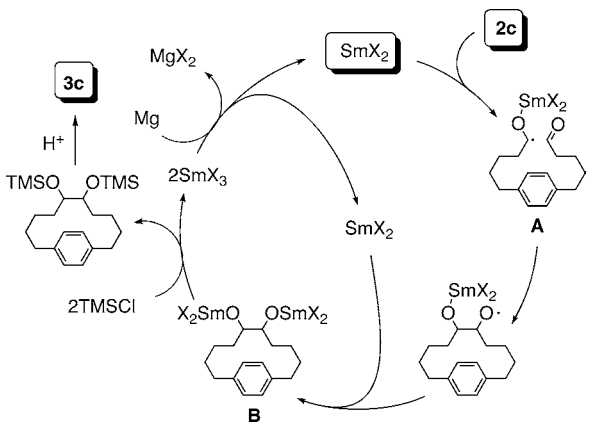
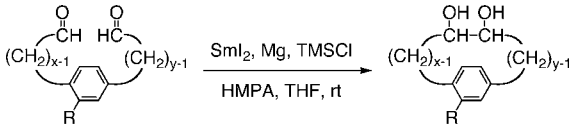


Table 2. Synthesis of [*n*]Paracyclophanediols (**3a**−**h**) by SmI_2-Catalyzed Pinacol Cyclization[a]



2a-h — [*n*]Paracyclophanediol **3a-h** ($n = x + y$)

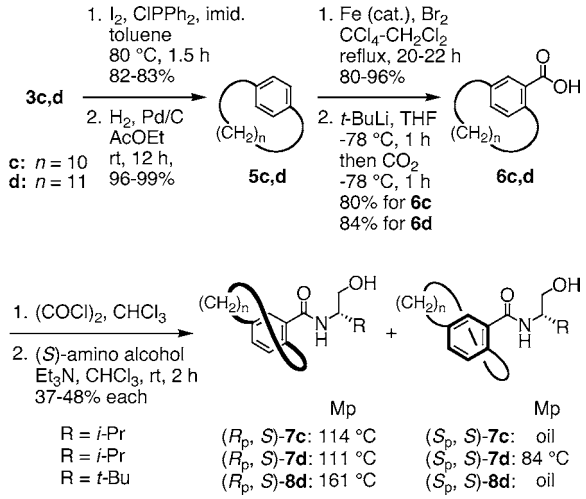
	aldehyde				SmI_2	product		yield
entry	**2**	R	*x*	*y*	[equiv]	**3**	*n*	[%][b]
1	**2a**	H	4	4	0.6	**3a**	8	11
2	**2b**	H	4	5	0.6	**3b**	9	47
3	**2c**	H	5	5	0.6	**3c**	10	64
4	**2d**	H	5	6	0.6	**3d**	11	63
5	**2e**	H	6	6	0.6	**3e**	12	57
6	**2f**	$CH_2OTBDPS$	5	5	0.8	**3f**	10	57
7[c]	**2g**	CH_2OBn	5	5	2.0	**3g**	10	51
8	**2h**	H	4	6	2.0	**3h**	10	18

[a] All the reactions were carried out in the presence of SmI_2, HMPA, TMSCl, and magnesium in 1/2/10/50 ratio unless otherwise specified. [b] Isolated yields. [c] 140 equiv of magnesium was used.

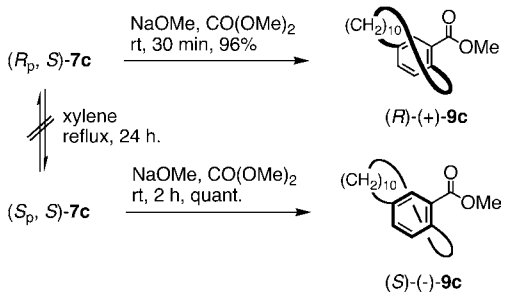
3b−**e** with middle-size ansa-bridges (n = 9−12) (entries 2−5). Substituted derivatives **2f**,**g** are also good substrates (entries 6 and 7), but [4+6]-type pinacol cyclization of **2h** was less effective than [5+5] cyclization for the synthesis of **3c** (entries 3 and 8; see also entry 3 in Table 1).

One most remarkable feature of cyclophanes having an appropriate length of ansa-bridge is their thermodynamic flexibility,[15] as we have previously reported spontaneous dynamic stereocontrol of planar-chiral nicotinamides having [10]parapyridinophane skeletons by crystallization- or adsorption-induced asymmetric transformations (CIAT and AIAT, respectively).[16] For studying the synthetic and thermodynamic aspects of the corresponding chiral cyclophanes, [10]- and [11]-paracyclophanediols (**3c**,**d**) were derived to diastereomeric mixtures of **7c**,**d** (n = 10, 11; R = *i*-Pr) and **8d** (n = 11; R = *t*-Bu), as shown in Scheme 3. Conversion

Scheme 3. Transformation of **3c**,**d** to Bridged Benzamides **7c**,**d** and **8d**



Scheme 4. Syntheses of Planar-Chiral [10]Paracyclophanecarboxylates (*R*)-(+)- and (*S*)-(−)-**9c**



of **3c**,**d** to the parent [10]- and [11]-paracyclophanes (**5c**[17] and **5d**[15b]) was done by Garegg−Samuelsson olefination[18,19] followed by hydrogenation. The known carboxylation[20] to **6c**[20a,21] and **6d** and the subsequent introducion of (*S*)-valinol or (*S*)-*tert*-leucinol auxiliary afforded **7c**,**d** and **8d**, respectively. Further transformation to enantiomerically pure [10]- and [11]-paracyclophane esters are summarized in Schemes 4 and 5.

(15) Thermodynamic studies regarding rope-skipping isomerization of paracyclophanes were reported: (a) Eberhardt, H.; Schlögl, K. *Liebigs Ann. Chem.* **1972**, *760*, 157−170. (b) Hochmuth, D. H.; König, W. A. *Tetrahedron: Asymmetry* **1999**, *10*, 1089−1097.

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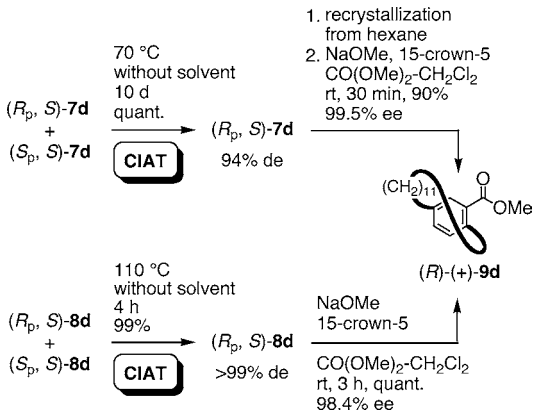
(18) (a) Garegg, P. J.; Samuelsson, B. *Synthesis* **1979**, 469−470. (b) Liu, Z.; Classon, B.; Samuelsson, B. *J. Org. Chem.* **1990**, *55*, 4273−4275. (c) Luzzio, F. A.; Menes, M. E. *J. Org. Chem.* **1994**, *59*, 7267−7272.

(19) The Corey−Winter reaction was not so successful in the case of **3c**, because the alkene product was obtained only in 36% yield: Corey, E. J.; Hopkins, B. *Tetrahedron Lett.* **1982**, *23*, 1979−1982.

(20) (a) Oi, S.; Miyano, S. *Chem. Lett.* **1992**, 987−990. (b) Cram, D. J.; Day, A. C. *J. Org. Chem.* **1966**, *31*, 1227−1232.

(21) Harada, N.; Soutome, T.; Nehira, T.; Uda, H.; Oi, S.; Okamura, A.; Miyano, S. *J. Am. Chem. Soc.* **1993**, *115*, 7547−7548.

Scheme 5. Stereocontrol to Planar-Chiral [11]Paracyclophane (*R*)-(+)-**9d** via CIAT Methods



As for planar-chiral [10]paracyclophanes, Hochmuth and König reported their GLC-based thermodynamic studies showed that the decamethylene ansa-bridge is not large enough to flip over the benzene ring.[15b] Indeed, planar-chiral cyclophanes **7c** were found to be thermodynamically quite stable molecules because neither (R_p,*S*)- nor (S_p,*S*)-**7c** exhibited thermal loss of their planar-chirality in refluxing xylene for a prolonged reaction time up to 24 h. Enantiomerically pure and stable carboxylic esters (*R*)-(+)-**9c**[15a] and (*S*)-(−)-**9c**[21] were cleanly obtained in high yields by transesterification of the hydroxyethylamide moieties in our methoxide-carbonate systems.[22] The absolute configuration of (*R*)-(+)- and (*S*)-(−)-**9c** thus obtained was unambiguously confirmed by further chemical correlation to the known (*S*)-(−)-[10]paracyclophane-12-carboxylic acid, namely (*S*)-(−)-**6c**.[20a,21]

On the other hand, [11]paracyclophanes are recognized as thermally metastable molecules[15b] and the compounds (R_p,*S*)-**7d** and (R_p,*S*)-**8d** have significantly higher melting points as compared to their diastereomeric (S_p,*S*)-isomers (see Scheme 3), as well as the case for the corresponding planar-chiral pyridinophanes.[16] In each case, CIAT of **7d** (70 °C for 10 days) and **8d** (110 °C for 4 h) proceeded well via rope-skipping isomerization to accumulate (*R*)-planar chirality to afford the (R_p,*S*)-form of **7d** (94% de) and **8d** (>99% de) almost quantitatively. Obviously, the CIAT of **8d** is much more efficient than that of **7d** due to the larger difference in the melting points between its diastereoisomers. Transesterification was also complete within 3 h successfully by methoxide−carbonate reaction in the presence of 15-crown-5 to give planar-chiral (*R*)-(+)-**9d** with up to 99.5% ee. Figure 1 depicts the CD spectra of (*R*)-(+)-**9c**,**d**, whose similarity suggests that these two compounds have the same configuration for their planar-chirality.

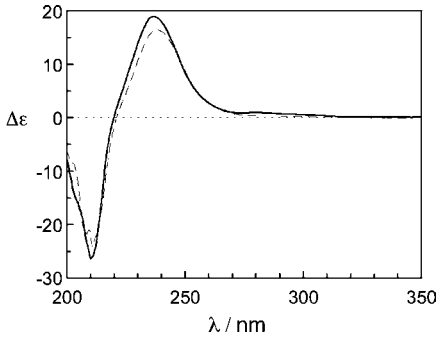


Figure 1. CD spectra of [10]paracyclophane (*R*)-(+)-**9c** (broken line) and [11]paracyclophane (*R*)-(+)-**9d** (solid line).

Consequently, we have achieved a facile and convenient synthetic method for [*n*]paracyclophanes (*n* = 8−12) by samarium iodide-catalyzed intramolecular pinacol coupling and its application to planar-chiral cyclophane synthesis in a preparative scale (see Supporting Information). Although several synthetic methods of paracyclophaenes with intramolecular ring-closure reactions have been reported, this method is probably simpler than any other procedure for synthesizing them. The present method developed here would be widely applicable for the preparation of various cyclophane systems.

Acknowledgment. We greatly acknowledge JSPS Grant-in-Aid for Scientific Research (B) (14350479) and Nagase Science and Technology Foundation for financial support of this work.

Supporting Information Available: Full experimental procedures, characterization data of all new compounds, ^{1}H and ^{13}C NMR spectra of **2a**−**h**, **3a**−**h**, **4**, **5c**,**d**, **6c**,**d**, (R_p,*S*)- and (S_p,*S*)-**7c**,**d**, (R_p,*S*)- and (S_p,*S*)-**8d**, and (*R*)-(+)-**9d**, and ^{1}H NMR spectra of (*R*)-(+)- and (*S*)-(−)- **9c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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