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Enantioselective Synthesis of Planar-Chiral 1,*n*-Dioxa[*n*]paracyclophanes via Catalytic Asymmetric *ortho*-Lithiation

Kazumasa Kanda, Kohei Endo, and Takanori Shibata*

Department of Chemistry and Biochemistry, School of Advanced Science and Engineering, Waseda University, Okubo, Shinjuku, Tokyo 169-8555, Japan

tshibata@waseda.jp

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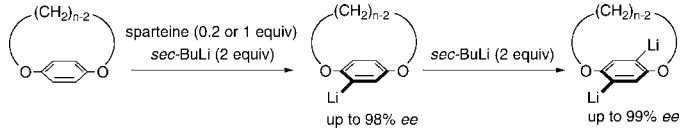
ABSTRACT



Highly enantioselective *ortho*-lithiation and dilithiation of 1,*n*-dioxa[*n*]paracyclophanes were realized with the use of *sec*-butyllithium and a catalytic or stoichiometric amount of sparteine. Quenching with various electrophiles, such as iodine, iodomethane, and chlorodiphenylphosphine, afforded chiral mono- and disubstituted paracyclophanes with good to excellent ee.

Planar-chiral paracyclophanes are interesting from a structural point of view and expected to be useful as a framework for functional materials,[1] such as chiral discriminators,[2a,b] chiral polymers,[2c,d] NADH models,[2e,f] or guest receptors.[2g] In particular, [2.2]paracyclophane derivatives including PHANEPHOS[3a] can be used as efficient chiral ligands.[3b] However, a major protocol for the synthesis of these planar-chiral paracyclophanes is the optical resolution of racemic compounds by chromatographic techniques or chiral reagents,[2,3] and there are few examples of the enantioselective synthesis of planar-chiral paracyclophanes. A pioneering study described intramolecular S_NAr etherification using a chiral quaternary ammonium salt, but the enantioselectivity was low.[4a] The chiral Rh-catalyzed coupling of dithiol and dibromide has been used to realize moderate enantioselectivity (up to 60% ee).[4b] We previously reported the chiral Pd-catalyzed asymmetric double Sonogashira coupling of diiodoparacyclophanes with up to 78% ee.[4c] Therefore, the development of a method for the facile and highly enantioselective synthesis of planar-chiral paracyclophanes is required.[5]

We report here a new approach to the highly enantioselective synthesis of planar-chiral paracyclophanes via catalytic asymmetric *ortho*-lithiation. Enantioselective syntheses of planar-chiral chromium-arene complexes[6] and ferrocene[7] via asymmetric lithiation have been reported previously;[8,9] however, there have been no examples of catalytic and enantioselective *ortho*-lithiation for the generation of planar

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

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(5) It is not an enantioselective synthesis, but enantiomerically pure paracyclophanes have been recently synthesized from hydrogen-bond controlled axially chiral substrates using metathesis: Mori, K.; Ohmori, K.; Suzuki, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 5638–5641.

(6) (a) Uemura, M.; Hayashi, Y.; Hayashi, Y. *Tetrahedron: Asymmetry* **1994**, *5*, 1427–1430. (b) Alexakis, A.; Kanger, T.; Mangeney, P.; Rose-Munch, F.; Perrotey, A.; Rose, E. *Tetrahedron: Asymmetry* **1995**, *6*, 2135–2138. (c) Pache, S.; Botuha, C.; Franz, R.; Kündig, P.; Einhorn, J. *Helv. Chim. Acta* **2000**, *83*, 2436–2451.

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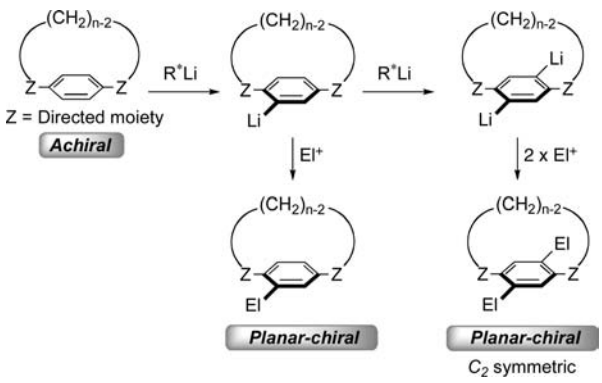
chirality.[10] We assumed that the enantioselective *ortho*-lithiation of an achiral [*n*]paracyclophane with directed moieties at the 1 and *n* positions of its ansa chain would

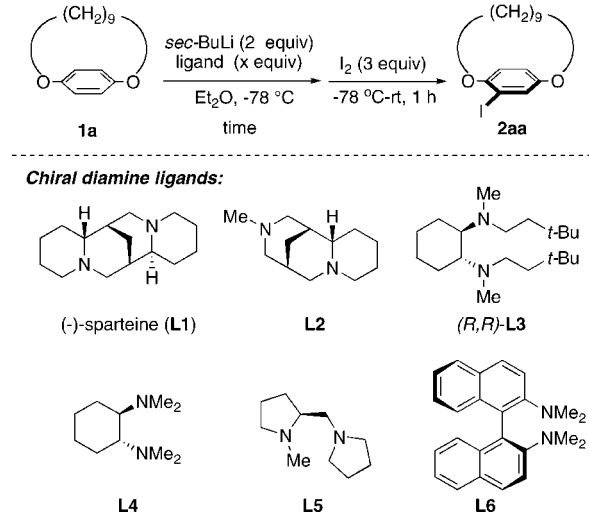
Scheme 1



proceed with a chiral lithium reagent. Furthermore, a second lithiation should be possible, which would give a C_2-symmetric dilithio paracyclophane. The consequent quenching of these aryllithiums with various electrophiles would afford mono- and disubstituted planar-chiral paracyclophanes (Scheme 1).

[11]Paracyclophanes ($n = 11$) are not flipped at room temperature.[11] Therefore, we chose an achiral 1,11-dioxa[11]paracyclophane **1a** as a model substrate, which has oxygen atoms as directed moieties. We examined asymmetric lithiation using a *sec*-butyllithium-(−)-sparteine (**L1**) system and quenched it with iodine as an electrophile. As a result, planar-chiral iodoparacyclophane (+)-**2aa** was obtained in high yield and excellent ee (Table 1, entry 1).[12] Sparteine surrogate **L2**[13a,b] induced the opposite enantiomer (−)-**2aa** (entry 2). Chiral diamine **L3**[13c] derived from cyclohexane-1,2-diamine gave good enantioselectivity (entries 3 and 4). Other chiral diamines, such as cyclohexane-1,2-diamine-derived **L4**,[13d] proline-derived **L5**,[13e] and 2,2′-diamino-1,1′-binaphtyl-derived **L6**[13f] also afforded the product but in poor ee (entries 5−7). An equivalent amount of **L1** is sufficient for high yield and excellent ee (entry 8), but a decrease of the amount of *s*-BuLi (1.2 equiv) slightly lowered the yield (entry 9). It is noteworthy that even a catalytic amount of **L1** and **L2** gave good yield and enantioselectivity (entries 11 and 12).[14]

Table 1. Optimization of Reaction Conditions



entry	ligand	x	time (h)	yield (%)	ee (%)[a]
1	**L1**	2	1	91	98 (+)
2	**L2**	2	1	82	91 (−)
3	(*R*,*R*)-**L3**	2	5	75	73 (+)
4	(*S*,*S*)-**L3**	2	5	77	74 (−)
5	**L4**	2	2	88	24 (+)
6	**L5**	2	2	87	13 (+)
7	**L6**	2	3	55	<1
8	**L1**	1	2	89	97 (+)
9[b]	**L1**	1	2	74	96 (+)
10	**L1**	0.5	3	87	93 (+)
11	**L1**	0.2	5	84	76 (+)
12	**L2**	0.2	4	79	74 (−)

[a] Signs of optical rotation are in parentheses. [b] *s*-BuLi (1.2 equiv) was used.

Under the optimal reaction conditions, we investigated the enantioselective lithiation of various 1,*n*-dioxa[*n*]paracyclophanes (Table 2). 1,10-Dioxa[10]paracyclophane **1b** with a shorter ansa chain also gave the corresponding iodo product **2ba** with excellent ee with the use of an equivalent amount

(7) (a) Nishibayashi, Y.; Aikawa, Y.; Ohe, K.; Uemura, S. *J. Org. Chem.* **1996**, *61*, 1172–1174. (b) Tsukazaki, M.; Tinkl, M.; Roglans, A.; Chapell, B. J.; Taylor, N. J.; Snieckus, V. *J. Am. Chem. Soc.* **1996**, *118*, 685–686. (c) Iftime, G.; Daran, J.-C.; Manoury, E.; Balavoine, G. G. A. *Angew. Chem., Int. Ed.* **1998**, *37*, 1698–1701. (d) Metallinos, C.; Szillat, H.; Taylor, N. J.; Snieckus, V. *Adv. Catal. Synth.* **2003**, *345*, 370–382.

(8) For examples of lithiation using a catalytic amount of chiral diamines, see: (a) Genet, C.; Canipa, S. J.; O'Brien, P.; Taylor, S. *J. Am. Chem. Soc.* **2006**, *128*, 9336–9337. (b) Gammon, J. J.; Canipa, S. J.; O'Brien, P.; Kelly, B.; Taylor, S. *Chem. Commun.* **2008**, 3750–3752. (c) Canipa, S. J.; O'Brien, P.; Taylor, S. *Tetrahedron: Asymmetry* **2009**, *20*, 2407–2412.

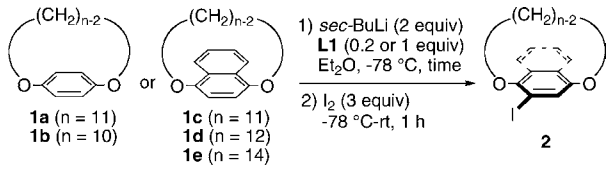
(9) For examples of enantioselective lithiation using a catalytic amount of chiral diamines and a stoichiometric amount of achiral amines including lithium amide, see: (a) Asami, M.; Ishizaki, T.; Inoue, S. *Tetrahedron: Asymmetry* **1994**, *5*, 793–796. (b) Yamashita, T.; Sato, D.; Kiyoto, T.; Kumar, A.; Koga, K. *Tetrahedron* **1997**, *33*, 16987–16998. (c) Södergren, M. J.; Andersson, P. G. *J. Am. Chem. Soc.* **1998**, *120*, 10760–10761. (d) Lill, S. O. N.; Pettersen, D.; Amedjkouh, M.; Ahlberg, P. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3054–3063. (e) Amedjkouh, M.; Pettersen, D.; Lill, S. O. N.; Davidsson, Ö.; Ahlberg, P. *Chem.—Eur. J.* **2001**, *7*, 4368–4377. (f) Pettersen, D.; Amedjkouh, M.; Ahlberg, P. *Tetrahedron* **2002**, *58*, 4669–4673. (g) Malhotra, S. V. *Tetrahedron: Asymmetry* **2003**, *14*, 645–647. (h) McGrath, M. J.; O'Brien, P. *J. Am. Chem. Soc.* **2005**, *127*, 16378–16379. (i) McGrath, M. J.; Bilke, J. L.; O'Brien, P. *Chem. Commun.* **2006**, 2607–2609. (j) Bilke, J. L.; O'Brien, P. *J. Org. Chem.* **2008**, *73*, 6452–6454. (k) Bilke, J. L.; Moore, S. P.; O'Brien, P.; Gilday, J. *Org. Lett.* **2009**, *11*, 1935–1938.

(10) Enantioselective synthesis of a planar-chiral ferrocene via asymmetric deprotonation using a catalytic amount of a chiral diamine was reported; see ref 8a.

(11) Enantiomeric resolution is accomplished in the case of monosubstituted [11]paracyclophanes at room temperature; see: (a) Hochmuth, D. H.; König, W. A. *Liebigs Ann.* **1996**, 947–951. (b) Hochmuth, D. H.; König, W. A. *Tetrahedron: Asymmetry* **1999**, *10*, 1089–1097. (c) Scharwächter, K. P.; Hochmuth, D. H.; Dittmann, H.; König, W. A. *Chirality* **2001**, *13*, 679–690.

(12) In the case of *n*-BuLi and *t*-BuLi, only a trace amount of **2aa** was obtained.

Table 2. Investigation of Various 1,*n*-Dioxa[*n*]paracyclophanes by Iodine Quenching

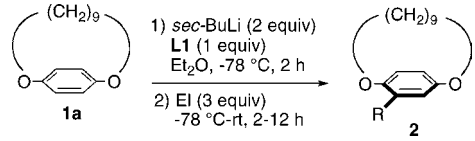


entry	1	**L1** (equiv)	time (h)	yield (%)	ee (%)
1	**1b**	1	2	81 (**2ba**)	97
2	**1b**	0.2	5	83 (**2ba**)	78
3	**1c**	1	2	95 (**2ca**)	97
4	**1c**	0.2	5	93 (**2ca**)	81
5	**1d**	1	10	82 (**2da**)	92
6	**1e**	1	10	84 (**2ea**)	92

of **L1** (entry 1) and with good ee with the use of a catalytic amount of **L1** (entry 2). 1,*n*-Dioxa[*n*](1,4)naphthalenophanes were also investigated. The catalytic lithiation of 1,11-dioxa[11](1,4)naphthalenophane **1c** was possible, and the corresponding planar-chiral 2′-iodo product **2ca** was obtained by quenching with iodine (entry 4). However, in the case of (1,4)naphthalenophanes **1d** and **1e**, an equivalent amount of **L1** was needed because lithiation was sluggish (entries 5 and 6).

We next examined various electrophiles (El) other than iodine (Table 3). Treatment with iodomethane, *N*,*N*-dimethylformamide, benzophenone, and chlorodiphenylphosphine gave methylated product **2ab**, formylated product **2ac**, tertiary alcohol **2ad**, and diphenylphosphine **2ae**, respectively (entries 1−4). In each case, excellent ee was achieved.

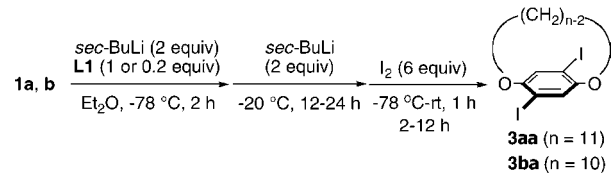
Table 3. Investigation of 1,11-Dioxa[*n*]paracyclophanes with Various Electrophiles



entry	electrophile	R	yield (%)	ee (%)
1	MeI	Me	74 (**2ab**)	95
2	DMF	CHO	70 (**2ac**)	97
3	benzophenone	$C(OH)Ph_2$	84 (**2ad**)	95
4	PPh_2Cl	PPh_2	58 (**2ae**)	98

We further investigated the enantioselective dilithiation of 1,*n*-dioxa[*n*]paracyclophanes for the synthesis of C_2-symmetric planar-chiral paracyclophanes (Table 4).[15] After the first lithiation at −78 °C, the second lithiation was examined by adding another 2 equiv of *s*-BuLi at −20 °C. Quenching with iodine provided diiododioxa[11]paracyclophane **3aa** with almost perfect ee from **1a** (entry 1) and [10]paracyclophane **3ba** with excellent ee from **1b** (entry 3). In the case of enantioselective dilithiation, even a catalytic amount of **L1** gave a high ee of around 90%, probably because kinetic resolution occurred on the second lithiation (entries 2 and 4).

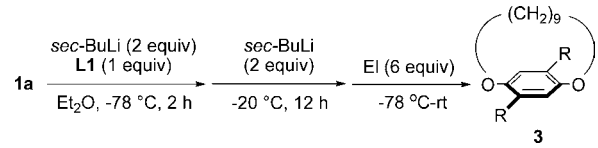
Table 4. Enantioselective Dilithiation of 1,*n*-Dioxa[*n*]paracyclophanes



entry	1	**L1** (equiv)	yield (%)	ee (%)
1	**1a**	1	79 (**3aa**)	99
2	**1a**	0.2	53 (**3aa**)	89
3	**1b**	1	91 (**3ba**)	98
4	**1b**	0.2	82 (**3ba**)	93

Also in the enantioselective dilithiation, quenching with various electrophiles was possible under the same reaction conditions (Table 5); the dimethylated product **3ab**, diformylated product **3ac**, diol **3ad**, and diphosphine **3ae** were afforded with almost perfect enantioselectivity.

Table 5. Enantioselective Synthesis of C_2-Symmetric Paracyclophanes Using Various Electrophiles



entry	electrophile	R	yield (%)	ee (%)
1	MeI	Me	76 (**3ab**)	99
2	DMF	CHO	44 (**3ac**)	99
3	benzophenone	$C(OH)Ph_2$	84 (**3ad**)	99
4	PPh_2Cl	PPh_2	55 (**3ae**)	99

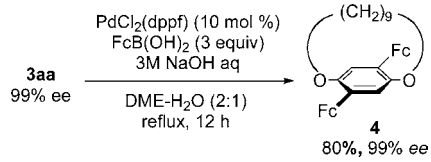
(13) (a) Dearden, M. J.; Firkin, C. R.; Hermet, J.-P. R.; O'Brien, P. *J. Am. Chem. Soc.* **2002**, *124*, 11870–11871. (b) Dixon, A. J.; McGrath, M. J.; O'Brien, P. *Org. Synth.* **2006**, *83*, 141–154. (c) Stead, D.; O'Brien, P.; Sanderson, A. *Org. Lett.* **2008**, *10*, 1409–1412. (d) Cole, A. P.; Mahadevan, V.; Mirica, L. M.; Ottenwaelder, X.; Stack, T. D. P. *Inorg. Chem.* **2005**, *44*, 7345–7364. (e) Hayashi, Y.; Tamura, T.; Shoji, M. *Adv. Synth. Catal.* **2004**, *346*, 1106–1110. (f) Benson, S. C.; Cai, P.; Colon, M.; Haiza, M. A.; Tokles, M.; Snyder, J. K. *J. Org. Chem.* **1988**, *53*, 5335–5341.

(14) **Typical Experimental Procedure (entry 10 in Table 1).** To a solution of **1a** (0.1 mmol) and **L1** (4.6 μL, 0.02 mmol) in Et_2O (0.5 mL) was added dropwise a 1.0 M cyclohexane-hexane solution of *sec*-butyllithium (0.2 mL, 0.2 mmol) at −78 °C, and the mixture was stirred for 5 h at −78 °C. To the mixture was added dropwise iodine (76.1 mg, 0.3 mmol) in Et_2O (0.6 mL) at −78 °C, and the resulting mixture was stirred for 1 h at room temperature. It was treated with saturated $Na_2S_2O_3$ aqueous solution and extracted with ethyl acetate. The organic layer was washed with water and brine. The extract was dried over Na_2SO_4 and evaporated under reduced pressure. The resulting residue was purified by PTLC to give **2aa**.

(15) The absolute configuration was determined by comparison of the sign of optical rotation of dibromodioxa[12]paracyclophane with that in the literature;[2d] see Supporting Information for details.

The resulting mono- and diiodo compounds may be precursors for the synthesis of various planar-chiral paracyclophanes. We describe Suzuki coupling as an example: chiral diiodo **3aa** was transformed into diferrocenyl product **4** with 99% ee by double coupling with ferroceneboronic acid ($FcB(OH)_2$) (Scheme 2).

Scheme 2



In conclusion, we have developed a new protocol for the highly enantioselective synthesis of planar-chiral paracyclophanes via asymmetric *ortho*-lithiation and dilithiation. This method gave various planar-chiral 1,*n*-dioxa[*n*]paracyclophane derivatives with excellent ee according to the choice of electrophiles. This is the first example of catalytic and enantioselective *ortho*-lithiation for the generation of planar chirality. We are now studying the application of these compounds as chiral ligands and host molecules.

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

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