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Reductive Ring-Opening 1,3-Difunctionalizations of Arylcyclopropanes with Sodium Metal

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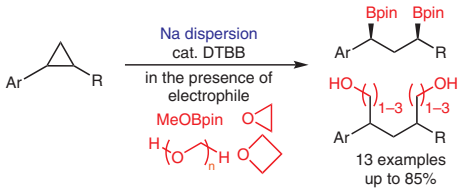

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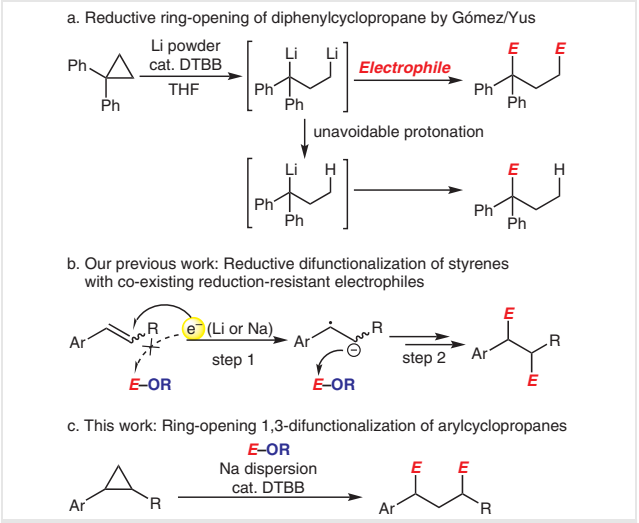
Abstract Sodium dispersion promotes reductive ring opening of arylcyclopropanes. The presence of a reduction-resistant electrophile, such as methoxypinacolatoborane, epoxide, oxetane, paraformaldehyde, or chlorotrimethylsilane, during the reductive ring opening event leads to the formation of 1,3-difunctionalized 1-arylalkanes by immediate trappings of the resulting two reactive carbanions. In particular, the ring-opening 1,3-diborylations of arylcyclopropanes afford 1,3-diborylalkanes with high *syn* selectivity.

Key words carbanions, cleavage, diastereoselectivity, electron transfer, metalation, reduction, ring opening, sodium

Ring-opening reactions of cyclopropanes have been recognized as attractive transformations in organic synthesis because the strained skeleton undergoes C–C bond cleavage that leads to a variety of characteristic 1,3-difunctionalizations, even without recourse to transition-metal catalysts.[1] A typical approach to such ring-opening 1,3-difunctionalizations of cyclopropanes is the use of donor–acceptor cyclopropanes to facilitate the heterolytic C–C bond cleavage.[2] Another useful strategy to achieve ring-opening functionalizations of cyclopropanes, especially without the donor–acceptor trick, is the electrophilic ring opening with reactive electrophiles[3] or electron-deficient radical species,[4] utilizing the known similarity between alkenes and cyclopropanes. Meanwhile, ring-opening 1,3-difunctionalizations that begin with a reductive process have scarcely been reported.[5] In particular, Gómes, Yus, and co-worker reported reductive ring opening of 1,1-diphenylcyclopropane using lithium and 4,4′-di-*tert*-butylbiphenyl (DTBB) as an electron-transfer catalyst (Scheme 1a).[5b] Subsequent addition of electrophiles such as chlorotrimethylsilane and carbonyl compounds to a mixture of the resulting 1,3-dianion provided the corresponding 1,3-difunctionalized products. However, the reactive and thus unstable 1,3-dianionic intermediates decomposed mainly via protonation by an ethereal solvent at the temperature where the ring opening occurred (0 °C), and very low yields of difunctionalized products were thus obtained. There are hence no reports about the reductive ring opening of cyclopropanes that is followed by efficient twofold trapping with electrophiles.



Scheme 1 Reductive transformations of cyclopropanes and styrenes with alkali metals

For the last few years, we have been interested in revisiting the use of alkali metals to develop new reductive transformations of unsaturated compounds for modern organic synthesis.[6] Very recently, we have developed sodium-promoted reductive 1,2-difunctionalization of styrenes in the presence of boron- and carbon-centered electrophiles such as $B(OMe)_3$, isobutylene oxide, and oxetane.[6c] The reduction-resistant nature of these alkoxy-substituted electrophiles allows us to achieve preferential single-electron injection to styrenes from sodium over that to the co-existing electrophiles (Scheme 1b, step 1) and to instantly trap the resulting unstable anionic species with the electro-

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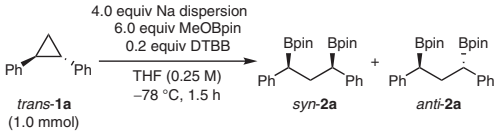
philes (Scheme 1b, step 2). With our strategy using reduction-resistant electrophiles, herein, we report sodium-metal-promoted reductive ring-opening 1,3-difunctionalization of arylcyclopropanes (Scheme 1c).

Our investigations began by evaluating the ring-opening diborylation of *trans*-1,2-diphenylcyclopropane (*trans*-**1a**) using alkoxyboranes and alkali metals to afford synthetically versatile 1,3-diborylalkane[7] **2a** (Table 1). After some experimentation, we found that the following procedure gave the best result: sodium dispersion (4.0 equiv) that has a large surface area (average particle size <10 μm)[6b–d,8] was added to a solution of *trans*-**1a** with MeOBpin (6.0 equiv) and DTBB (0.2 equiv) in THF at –78 °C (entry 1).[9] The starting cyclopropane **1a** was fully consumed within 1.5 h to provide 1,3-diborylated product **2a** in 97% NMR yield (81% isolated yield) with high *syn* selectivity (*syn*/*anti* = 89:11).[10] When the reaction was performed at 0 ℃, both the yield and diastereoselectivity decreased (entry 2). The use of cheaper $B(OMe)_3$ instead of MeOBpin followed by treatment with pinacol (6.0 equiv) also diminished both yield and diastereoselectivity (entry 3). This result suggests that the ligand exchange between the two methoxy and pinacol groups would not be perfect in efficiency and that the steric hindrance of the Bpin group plays a role in controlling the selectivity of the reaction. While the reaction proceeded without DTBB, a longer reaction time (4 h) was required for full conversion of **1a** (entry 4). When lithium powder (particle size: 120–250 μm)[6d] was employed instead of sodium dispersion, only a 30% yield of **2a** was obtained along with the formation of monoborylated product **2a′** in 51% yield (entry 5) and 17% recovery of starting **1a**. This method was applicable to the gram-scale synthesis of **2a** starting from 5.0 mmol of *trans*-**1a** (entry 6).

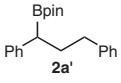
We next surveyed the scope with respect to arylcyclopropanes under the optimized reaction conditions (Table 2). Interestingly, the reaction of *cis*-**1a** also provided **2a** with the same *syn* selectivity (*syn*/*anti* = 89:11, entry 1), which shows the stereoconvergence of this protocol. A substrate having an electron-withdrawing fluoro or electron-donating methoxy group at the *para* position reacted to furnish a comparable yield of diborylated product **2b** or **2c** with similar diastereoselectivity (entries 2 and 3). In the case of *p*-methylsulfanyl-substituted **1d**, 2.8 equiv of Na dispersion was employed because overreduction of the methylsulfanyl group was observed under the optimized reaction conditions (entry 4). An electron-rich *p*-dimethylamino-substituted cyclopropane **1e** was unreactive at –78 ℃, and a higher temperature of 0 ℃ promoted the reductive diborylation (entry 5). Because the corresponding 1,3-diborylated product **2e** was found to be unstable, an initial diborylated product was converted into the corresponding 1,3-diol after oxidation by H_2O_2. Cyclopropane **1f** underwent the ring-opening borylation irrespective of the *ortho* substituent with comparable efficiency and diastereoselectivity (entry 6). 2-Thienyl-substituted cyclopropane **1g** was converted into the corresponding product **2g** in 40% yield (entry 7). The ring opening of pinacolatoboryl-substituted cyclopropane **1h** took place at 0 ℃ to give triborylalkane **2h** in 65% yield. Unfortunately, the reaction of 1,1-diphenylcyclopropane[5b] under the optimal reaction conditions resulted in no conversion.

Table 1 Optimization for Reductive Ring-Opening Diborylation of *trans*-**1a**



trans-**1a** (1.0 mmol) *syn*-**2a** *anti*-**2a**

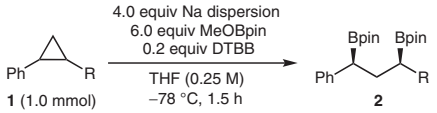
Entry	Deviations from the above conditions	NMR yield (%)	*syn*/*anti*[b]
1	none	97 (81)[a]	89:11
2	0 °C	87	75:25
3	$B(OMe)_3$ instead of MeOBpin, then 6.0 equiv pinacol, 0 °C to rt	71	86:14
4	without DTBB, 4 h	90	90:10
5	Li powder instead of Na dispersion	30	88:12
6	fivefold-larger scale	(74)[a]	91:9

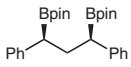
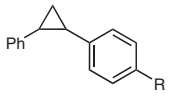
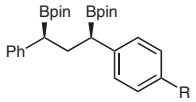
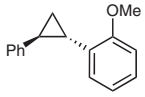
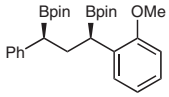
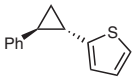
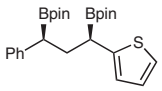
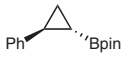
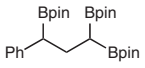


2a'

[a] Isolated yield.
[b] Determined by NMR analysis of an isolated mixture of *syn* and *anti* isomers.
[c] Monoborylated product **2a**′ was observed in a crude reaction mixture in <5% yield.

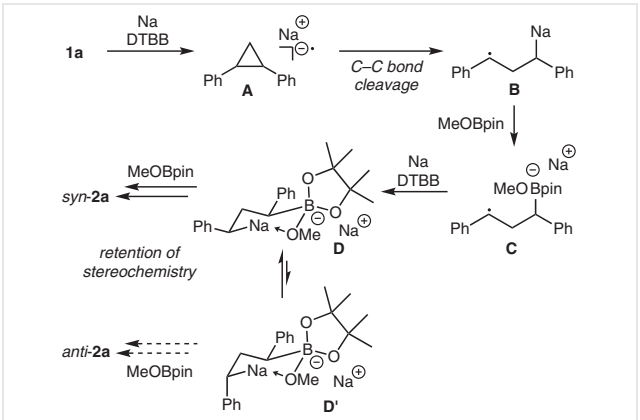
Table 2 Substrate Scope with Respect to Cyclopropanes **1**



Entry	**1** (*cis*/*trans*)	*cis*/*trans* ratio	**2**, Isolated yield (%)	*syn*/*anti* ratio[a]
				
1	*cis*-**1a**	99:1	**2a** 85	89:11
				
2	**1b** R = F	38:62	**2b** 84	92:8
3	**1c** R = OMe	3:97	**2c** 76	90:10
4[b]	**1d** R = SMe	38:62	**2d** 72	96:4
5[c]	**1e** R = NMe_2	2:98	**2e** 28[d]	67:33
				
6	**1f**	2:98	**2f** 83	87:13
				
7[e]	**1g**	0.5:99.5	**2g** 40	77:23
				
8[c]	*trans*-**1h**		**2h** 65	

[a] Determined by NMR analysis of an isolated mixture of *syn* and *anti* isomers. The relative stereochemistries of **2b**–**g**, except for **2e**, were tentatively assigned according to the comparisons of their NMR spectra with those of **2a**. For **2e**, the stereochemistry was unambiguously determined similarly as described in ref. 10.
[b] 2.8 equiv of Na dispersion for 1.0 h.
[c] At 0 °C.
[d] Isolated as the corresponding 1,3-diol after oxidation with H_2O_2. For details, see the Supporting Information.
[e] 3.0 equiv of Na dispersion.

We propose a reaction mechanism as shown in Scheme 2. Firstly, a single-electron transfer from sodium metal to cyclopropane **1a** would occur to generate radical anion **A**.[5] Subsequent carbon–carbon bond cleavage of **A** would generate benzylic anion **B** bearing a benzylic radical with the loss of the stereochemistry of starting cyclopropane **1a**. Radical anion **B** would be immediately trapped with MeOBpin to form borate **C**. The second single-electron reduction of **C** would afford putative six-membered carbanions **D** and **D′**, which are stabilized by the intramolecular coordination of the methoxy group on the boron atom to the sodium cation. Carbanion **D** that has two equatorial phenyl groups is considered to be more favorable than **D′** having one axial and one equatorial phenyl group. Finally, the preferential reaction of conformationally fixed **D** with MeOBpin would form the second C–B bond with retention of the stereochemistry,[6c,11] affording *syn*-**2a** as the major isomer. DTBB would promote the overall single-electron-transfer process.[5b]

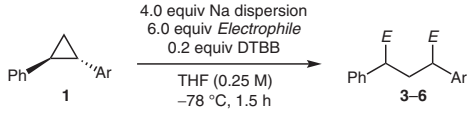


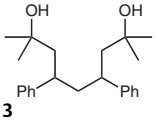
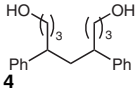
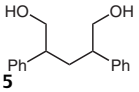
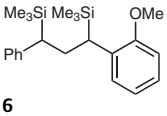
Scheme 2 Plausible reaction mechanism

Besides MeOBpin, we also attempted trapping with other electrophiles (Table 3). When isobutylene oxide and oxetane were used as electrophiles for the reaction of *trans*-**1a** (entries 1 and 2), the corresponding diols **3** and **4** were obtained in 77% and 85% yields, respectively. Gratifyingly, paraformaldehyde was found to serve as a reduction-resistant hydroxymethyl cation equivalent and to yield 1,5-pentanediol **5** albeit in moderate yield. Attempts to improve the efficiency of the trapping with paraformaldehyde at a higher temperature of 0 °C result in no conversion of **1a**, which indicates the preferential degradation of paraformaldehyde at the higher temperature. Surprisingly, chlorotrimethylsilane, which can undergo facile reductive dimerization into hexamethyldisilane,[12] also served as a reduction-resistant electrophile under the conditions to yield **6** in high yield. Again, the use of chlorotrimethylsilane at 0 °C inhibited the reductive ring opening, probably due to the preferential dimerization prior to the reduction of **1a**. In all these cases in Table 3, diastereoselectivity was not observed. The negligible diastereoselectivity highlights the characteristic advantage of the versatile alkoxyborane electrophiles (Table 1 and 2 and Scheme 2).

To validate the synthetic utility of this protocol, several transformations of diborylation product **2** were conducted (Scheme 3). The reductive diborylation of *trans*-**1a** with $B(OMe)_3$[13] followed by oxidation with H_2O_2 in the same pot afforded 1,3-diol **7** in good yield with high diastereoselectivity (Scheme 3a). According to the stereoretentive arylation of alkylboronates with aryllithiums reported by Aggarwal,[14] sequential treatment of **2a** (*syn*/*anti* = 91:9) with 4.0 equiv of 2-thienyllithium and of NBS provided doubly thie-

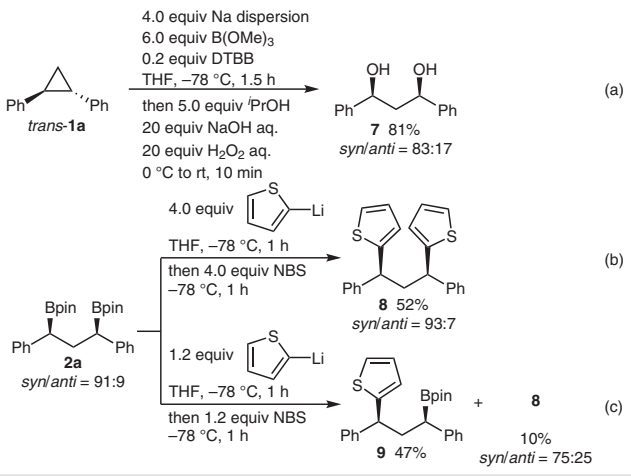
Table 3 Scope with Respect to Electrophiles



Entry	1	Electrophile	Product	Isolated yield (%)	dr [a]
1	*trans*-**1a**		 **3**	77	60:40
2	*trans*-**1a**		 **4**	85	66:34
3	*trans*-**1a**	$(HCHO)_n$	 **5**	37	57:43
4	**1f** (*cis*/*trans* = 2:98)	Me_3SiCl	 **6**	81	53:47

[a] Determined by NMR analysis of an isolated mixture of isomers.

nylated product **8** in 52% yield without a significant change of diastereoselectivity (Scheme 3b). When the amounts of 2-thienyllithium and NBS were decreased to 1.2 equiv, monothienylated product **9** was isolated in 47% yield as a single isomer,[15] along with a 10% yield of **8** (*syn*/*anti* = 75:25) (Scheme 3c).



Scheme 3 Derivatizations of diborylated products

In conclusion, we have developed a method for alkali-metal-promoted reductive ring-opening 1,3-difunctionalization of arylcyclopropanes, utilizing sodium dispersion as a reducing agent and reduction-resistant electrophiles. We succeeded in synthesizing 1,3-diborylalkanes with high *syn* selectivity and verifying their synthetic utility. Additionally, paraformaldehyde and chlorotrimethylsilane have proved to be available as reduction-resistant electrophiles at a low temperature. Further exploration on the reductive ring-opening functionalizations of small-ring compounds is currently in progress.

Funding Information

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1706538.

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(9) **Experimental Procedure**

An oven-dried 20 mL Schlenk tube was charged with 4,4′-di-*tert*-butylbiphenyl (DTBB, 53.3 mg, 0.200 mmol), THF (4.0 mL), and *trans*-**1a** (191 mg, 0.983 mmol). After the mixture was cooled to –78 °C, MeOBpin (0.97 mL, 6.0 mmol) was added. Sodium dispersion (10.0 M, 0.40 mL, 4.0 mmol) was then added dropwise, and the resulting suspension was stirred at –78 °C for 1.5 h. The resulting mixture was warmed to 0 °C, and the reaction was then quenched with *i*-PrOH (0.31 mL, 4.0 mmol) and then aqueous NH_4Cl (5 mL). The resulting biphasic solution was extracted with EtOAc (4 × 10 mL). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (hexane to hexane/EtOAc = 30:1) on silica gel to provide **2a** as a white solid (81% yield, 359 mg, 0.801 mmol, *syn*/*anti* = 89:11); mp 120–130 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.21 (dd, *J* = 7.5, 7.5 Hz, 0.89 × 4 H + m, 0.11 × 4 H), 7.13 (d, *J* = 7.5 Hz, 0.89 × 4 H + m, 0.11 × 4 H), 7.10 (t, *J* = 7.5 Hz, 0.89 × 2 H + m, 0.11 × 2 H), 2.36 (ddd, *J* = 14.4, 7.8, 7.8 Hz, 0.89 × 1 H), 2.30 (t, *J* = 7.8 Hz, 0.89 × 2 H), 2.25 (dd, *J* = 9.6, 6.6 Hz, 0.11 × 2 H), 2.21 (t, *J* = 6.6 Hz, 0.11 × 2 H), 2.02 (ddd, *J* = 14.4, 7.8, 7.8 Hz, 0.89 × 1 H), 1.20 (s, 0.89 × 12 H), 1.18 (s, 0.89 × 12 H), 1.15 (s, 0.11 × 12 H), 1.14 (s, 0.11 × 12 H). ^{13}C NMR (151 MHz, $CDCl_3$): δ (*syn* isomer) = 143.3, 128.6, 128.4, 125.3, 83.3, 35.2, 31.3 (br), 24.8. ^{11}B NMR (192 MHz, $CDCl_3$): δ = 33.1 (br). HRMS (APCI-MS, positive): *m*/*z* = 448.2957. Anal. Calcd for $C_{27}H_{38}B_2O_4$: 448.2960 $[M]^+$.

(10) The relative stereochemistry of **2a** was unambiguously assigned after oxidation to the corresponding diol with retention of the stereochemistry.

(11) Organolithium compounds can react with electrophiles with either retention or inversion of the stereochemistry of the nucleophilic carbon center, which depends on the electrophiles used. See: (a) Hoppe, D.; Hense, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2282. (b) Gawley, R. E. *Tetrahedron Lett.* **1999**, *40*, 4297. (c) Basu, A.; Thayumanavan, S. *Angew. Chem. Int. Ed.* **2002**, *41*, 716. (d) *The Chemistry of Organolithium Compounds*; Rappoport, Z.; Marek, I., Ed.; Wiley: New York, **2003**.

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(15) Although the *anti*-isomer of **8** is likely to be formed in less than 5% yield, we could not isolate the isomer.