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ON THE ORDER OF ADDITION OF SODIUM DISPERSION IN REDUCTIVE DIBORATIONS OF STILBENE AND 1,2-DIPHENYLCYCLOPROPANE

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Abstract –Two extreme methods to add sodium dispersion were investigated in the 1,2-diboration of stilbene and the ring-opening 1,3-diboration of 1,2-diphenylcyclopropane on a 20-mmol scale. Method 1 denotes that a substrate is added to a mixture of sodium dispersion and a boron electrophile. Method 2 denotes that sodium dispersion is slowly added to a mixture of a substrate and a boron electrophile. In these four cases, no significant differences were observed in the yields of the products and their *syn*/*anti* ratios, except for the diboration of stilbene by Method 1, wherein aggregation of sodium dispersion in the flask and 5% recovery of stilbene were observed. This information would be helpful in performing sodium-dispersion-mediated transformations on a large scale.

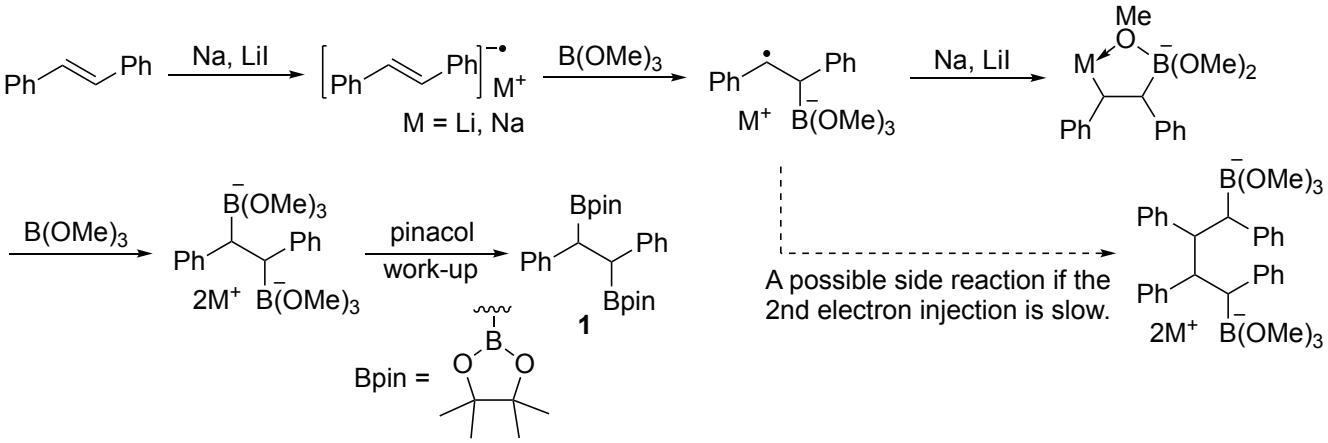
* Dedicated to Professor Yasuyuki Kita on the occasion of his 77th birthday

Reduction by alkali metal is a classical important synthetic methodology to reduce multiple bonds and strained bonds.[1] These transformations generally lead to construction of C–H bonds via protonation of the resulting carbanions *in situ*, as represented by *trans*-hydrogenation of alkynes. Trapping the anions with aprotic electrophiles has been underdeveloped despite its potent utility to synthesize highly functionalized molecules. This immaturity would be due to the incompatibility of common aprotic electrophiles, such as haloalkanes and carbonyls, with the reduction by alkali metals.

We have been interested in methodologies for the activations of unsaturated molecules by using alkali metals and development of reduction-resistant aprotic electrophiles that are applicable to reductive difunctionalization of unsaturated compounds.[2] Among these, diboration reactions of unsaturated compounds by means of rapid and powerful electron injection from sodium dispersion[3] are expected to be

practical because they provide diborylated intermediates of synthetic use from simple starting materials.[2b–e]

Scheme 1 exemplifies our proposed mechanism for the diboration of stilbene with sodium.[2c] Single electron injection from sodium dispersion to stilbene occurs to yield the radical anion of stilbene. Co-existing trimethoxyborane immediately traps the radical anion to generate the corresponding carbon-centered radical bearing a borate group. The benzylic radical undergoes the second single electron injection from sodium dispersion to afford the corresponding benzylic anion. The benzylic anion is trapped by another trimethoxyborane to result in the diboration.



Scheme 1. A proposed mechanism for the diboration of stilbene with sodium

Rapid electron injection from very fine sodium dispersion is extremely important. Especially, unless the second single electron injection is sufficiently fast, undesired side reactions including dimerization of the benzylic radicals might occur to decrease the yield of the diboration product. In our previous experiments on a 1.0-mmol scale,[2c] sodium dispersion was added to a solution of stilbene and trimethoxyborane over only a few second to realize a high concentration of sodium in the reaction flask. However, if this protocol is applied to a large-scale diboration reaction, methods of adding sodium dispersion, i.e., the order or the speed of the addition, may affect the product yield. The effect of the methods of adding sodium dispersion on the reaction should be investigated in order to establish the transformations of unsaturated compounds by using sodium dispersion as a practical methodology for organic synthesis.

Here, we report investigations on two extreme methods to add sodium dispersion (Figure 1). Method 1 denotes that a substrate is added to a mixture of sodium dispersion and a boron electrophile, representing a system where a sufficient amount of sodium exists throughout in a reaction flask. Method 2 denotes that sodium dispersion is slowly added to a mixture of a substrate and a boron electrophile, representing a system that maintains a much lower concentration of sodium. We chose the 1,2-diboration of stilbene[2c]

and the ring-opening 1,3-diboration of 1,2-diphenylcyclopropane[2e] as model reactions to investigate the effect of the methods of adding sodium dispersion.

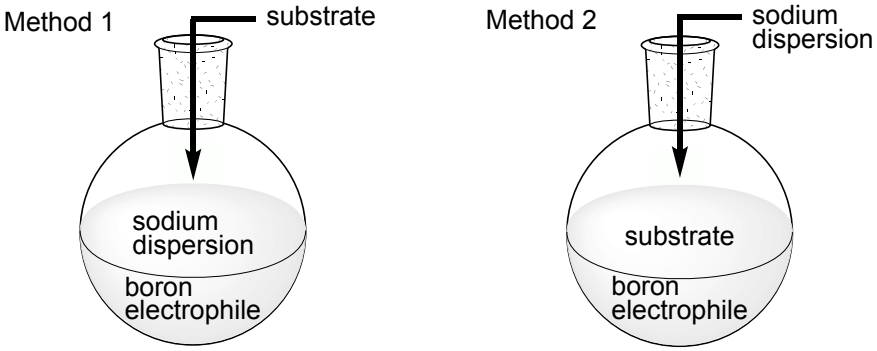
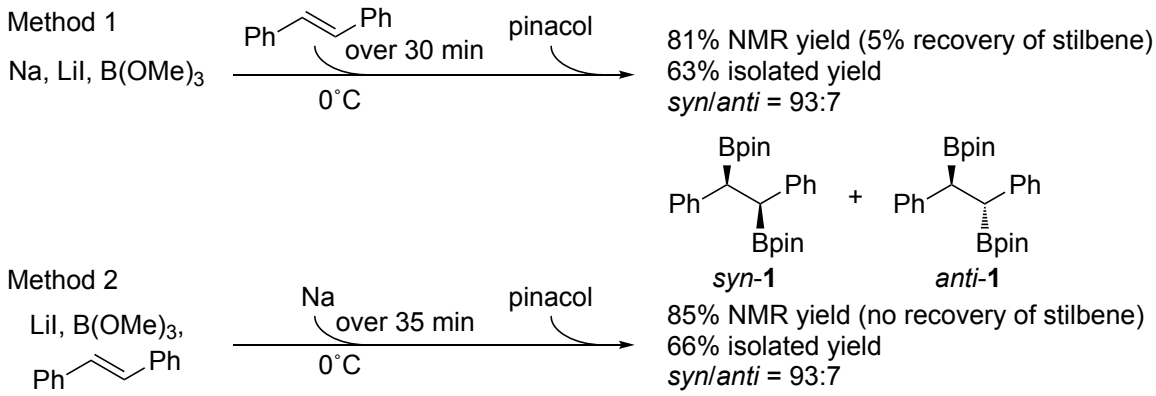


Figure 1. Two extreme methods to treat a substrate with sodium dispersion

The diboration of *trans*-stilbene was firstly examined on a 20-mmol scale (Scheme 2), a larger scale compared to our previous work (1–5 mmol).[2c] According to Method 1, stilbene (20 mmol) was added dropwise over 30 min to a mixture of sodium dispersion (50 mmol), lithium iodide (50 mmol), and trimethoxyborane ($B(OMe)_3$, 120 mmol) in THF/TMEDA at 0 ºC with stirring. Notably, sodium dispersion aggregated during the addition of stilbene and the aggregation was gradually dissolved as the reaction proceeded. After an additional 30-min stirring, pinacol was added to protect the boron moieties as pinacolatoboryl groups. Usual aqueous work-up followed by chromatographic purification on silica gel afforded 12.5 mmol of **1** in 63% isolated yield (81% NMR yield) in a *syn*/*anti* ratio of 93:7, along with 5% recovery of stilbene. Even when the stirring continued for 1 h, the aggregation remained in the flask and the recovery of stilbene was observed again. These observations indicate that the aggregation would trap active sodium metal inside and that Method 1 would be inappropriate in this case from the viewpoints of reaction efficiency and safety.

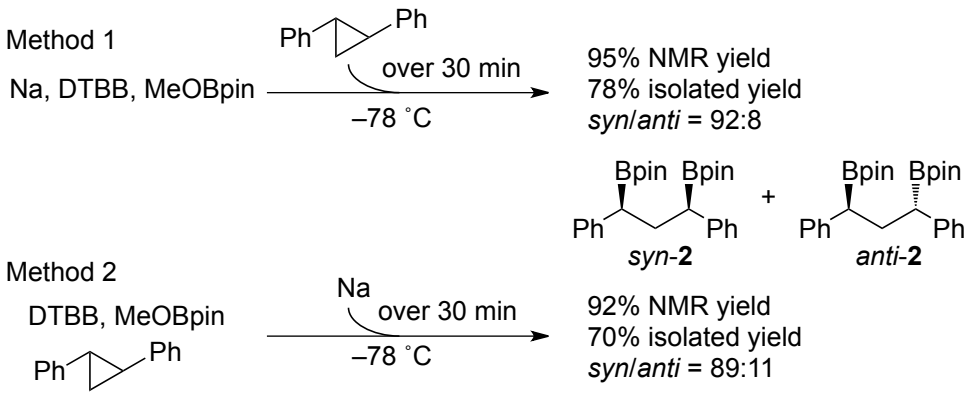
The reverse addition of sodium dispersion was then examined according to Method 2, which is in analogy to that of the previous report.[2c] Sodium dispersion (50 mmol) was added dropwise over 35 min to a THF/TMEDA solution of stilbene (20 mmol), lithium iodide (50 mmol), and $B(OMe)_3$ (120 mmol) at 0 ºC. After 30 min, the same treatment with pinacol, aqueous work-up, and purification as described above afforded **1** in 66% isolated yield (85% NMR yield) in a *syn*/*anti* ratio of 93:7. None of the remaining stilbene was observed. The yield and stereoselectivity are similar to those on a 1.0-mmol scale in the previous report[2c] (68% isolated yield, *syn*/*anti* ratio of 94:6). When the same 20-mmol-scale reaction was performed by adding sodium dispersion over a shorter time of 10 min, similar yield and selectivity were observed (67% isolated yield, 87% NMR yield, *syn*/*anti* ratio of 94:6). These results indicate that the diboration of stilbene by Method 2 is robust.



Scheme 2. Diboration reactions of stilbene according to Method 1 and 2

The ring-opening diboration of *trans*-1,2-diphenylcyclopropane was then investigated, again on a 20-mmol scale (Scheme 3). According to Method 1, the cyclopropane (19.7 mmol) was added dropwise over 30 min to a mixture of sodium dispersion (80 mmol), 4,4'-di-*tert*-butylbiphenyl (DTBB, 4.0 mmol), and methoxypinacolatoborane (MeOBpin, 120 mmol) in THF at –78 ºC. In contrast to the reaction of stilbene by Method 1, no aggregation was likely to occur during the addition of the cyclopropane, probably because of the lower temperature and the presence of DTBB. After the mixture was stirred for an additional 1.5 h, aqueous work-up and subsequent silica gel column chromatography afforded 15.5 mmol of **2** in 78% isolated yield (95% NMR yield) in a *syn*/*anti* ratio of 92:8.

Method 2 was also applied to the reaction of the cyclopropane, which is equivalent to a large-scale reaction of the previous report.[2e] Sodium dispersion (80 mmol) was added dropwise over 30 min to a THF solution of the cyclopropane (20.0 mmol), DTBB (4.0 mmol), and MeOBpin (120 mmol) at –78 ºC. After 1.5 h, aqueous work-up and purification afforded 15.9 mmol of **2** in 70% isolated yield (92% NMR yield) in a *syn*/*anti* ratio of 89:11. The yield and stereoselectivity are similar to those on a 1.0-mmol scale in the previous report[2e] (81% isolated yield, *syn*/*anti* ratio of 89:11). When the same 20-mmol-scale reaction was performed by adding sodium dispersion over a shorter time of 10 min, a similar yield and the same selectivity were observed (78% isolated yield, 94% NMR yield, *syn*/*anti* ratio of 89:11).



Scheme 3. Ring-opening diboration reactions of 1,2-diphenylcyclopropane according to Method 1 and 2

The methods of adding sodium dispersion as well as the scale of the reactions had no significant influences on the yields of **1** and **2** and their *syn*/*anti* ratios. However, the diboration of stilbene by Method 1 showed different appearance in the reaction flask and resulted in the recovery of a small amount of stilbene. As sodium dispersion is stabilized in mineral oil, placing and using sodium dispersion in THF/TMEDA at 0 ºC in the reaction flask would change the form of sodium particles. The particles would aggregate into larger particles, which lowers the efficiency of electron injection.

The negligible influence of the slow additions of sodium dispersion by Method 2 suggests that the two sequential single electron injection events should proceed rapidly even at a low concentration of sodium, maybe on the same particle of sodium, to suppress undesired side reactions of unstable benzylic radicals such as the homo-dimerization described in Scheme 1.

These are important information in scaling up reductive transformations of unsaturated compounds by means of the electron injection from sodium dispersion.

EXPERIMENTAL

All non-aqueous reactions were carried out under an inert atmosphere of N_2 gas in oven-dried glassware. Dehydrated THF was purchased from Kanto Chemical Co., Inc. and stored under nitrogen atmosphere. Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. $B(OMe)_3$ and MeOBpin were purchased from commercial suppliers and distilled prior to use. Sodium dispersion (ca. 10 M suspension in mineral oil) was provided by KOBELCO ECO-Solutions Co., Ltd.[4] and stored under nitrogen in a freezer. The concentration of the Na dispersion was determined by acid-base titration.[2d,e] 1,2-Diphenylcyclopropane was prepared according to the literature.[2e] Preparative flash chromatography was performed using Silica Gel 60N, spherical neutral, particle size 100-210 μm, purchased from Kanto Chemical Co., Inc. ^{1}H NMR (600 MHz) and ^{13}C NMR (151 MHz) spectra were recorded on a JEOL ECZ-600 spectrometer at 25 ºC. The NMR yields were determined by using crude samples before purification. The structure, purity, and diastereomeric ratio of the products after purification were identified by ^{1}H NMR analysis.[2c,e]

Synthesis of 1 from Stilbene by Method 1

LiI (6.69 g, 50 mmol), THF (52 mL), TMEDA (8.0 mL), and $B(OMe)_3$ (13.4 mL, 120 mmol) were placed in an oven-dried 300-mL two-necked flask at 0 ºC. Sodium dispersion (10.3 M, 4.9 mL, 50 mmol) was then added dropwise via a syringe at 0 ºC over 10 min. *trans*-Stilbene (3.61 g, 20.0 mmol) in THF (20 mL) was added dropwise via a syringe over 30 min, and the resulting suspension was stirred at 0 ºC for an additional 30 min. Pinacol (14.2 g, 120 mmol) was then added portionwise over 1 min, and the resulting mixture was stirred at 0 ºC for 10 min before an addition of aqueous HCl (1 M, 140 mL). The resulting biphasic solution was extracted with EtOAc (100 mL × 4). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was dissolved in $CHCl_3$

(100 mL) and stirred at 40 ºC for 2 h to complete protection of the boron moieties with pinacol. After $CHCl_3$ was removed under reduced pressure, the residue was purified by column chromatography on silica gel (hexane to hexane/EtOAc = 15:1) to provide **1** as a white solid (63% yield, 5.44 g, 12.5 mmol, *syn*/*anti* = 93:7).

Synthesis of 1 from Stilbene by Method 2

LiI (6.69 g, 50 mmol), *trans*-stilbene (3.61 g, 20.0 mmol), $B(OMe)_3$ (13.4 mL, 120.0 mmol), THF (72 mL), and TMEDA (8.0 mL) were placed in an oven-dried 300-mL two-necked flask at 0 ºC. Sodium dispersion (10.3 M, 4.9 mL, 50 mmol) was added dropwise via a syringe over 35 min, and the resulting suspension was stirred at 0 ºC for an additional 30 min. The same treatment with pinacol, extractive work-up, and chromatographic purification provided **1** as a white solid (66% yield, 5.73 g, 13.2 mmol, *syn*/*anti* = 93:7).

Synthesis of 2 from *trans*-1,2-Diphenylcyclopropane by Method 1

An oven-dried 300-mL two-necked flask was charged with DTBB (1.07 g, 4.00 mmol) and THF (80 mL). After the mixture was cooled to −78 ºC, MeOBpin (20.2 mL, 120 mmol) was added. Sodium dispersion (10.3 M, 7.7 mL, 80 mmol) was added dropwise over 10 min. *trans*-1,2-Diphenylcyclopropane (3.86 g, 19.9 mmol) was then added dropwise via a syringe over 30 min, and the resulting suspension was stirred at −78 ºC for an additional 1.5 h. The resulting mixture was warmed to 0 ºC, and *i*PrOH (6.17 mL, 80 mmol, via a syringe over 30 s) and aqueous NH_4Cl (80 mL) were sequentially added. The resulting biphasic solution was extracted with EtOAc (100 mL × 4). 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 = 15:1) on silica gel to yield **2** as a white solid (78% yield, 6.96 g, 15.5 mmol, *syn*/*anti* = 92:8).

Synthesis of 2 from *trans*-1,2-Diphenylcyclopropane by Method 2

An oven-dried 300-mL two-necked flask was charged with DTBB (1.07 g, 4.00 mmol), THF (80 mL), and *trans*-1,2-diphenylcyclopropane (3.88 g, 20.0 mmol). After the mixture was cooled to −78 °C, MeOBpin (20.2 mL, 120 mmol) was added. Sodium dispersion (10.1 M, 7.9 mL, 80 mmol) was then added dropwise via a syringe over 30 min with stirring, and the resulting suspension was stirred at −78 °C for an additional 1.5 h. The same termination with *i*PrOH, extractive work-up, and chromatographic purification (hexane to hexane/EtOAc = 30:1) afforded **2** as a white solid (70% yield, 6.23 g, 13.9 mmol, *syn*/*anti* = 89:11).

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4. The sodium dispersion is also commercially available as SD Super Fine™ from FUJIFILM Wako Pure Chemical Corporation and Tokyo Chemical Industry Co., Ltd.