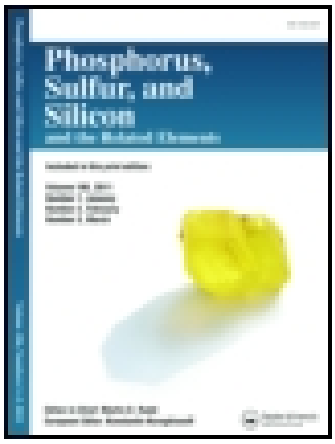

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A Convenient Stereoselective Reduction of gem-Dibromides with a Combination of Dimethyl Phosphite and Potassium Carbonate

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A Convenient Stereoselective Reduction of *gem*-Dibromides with a Combination of Dimethyl Phosphite and Potassium Carbonate

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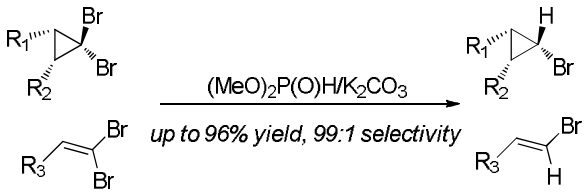
Abstract: *An efficient and highly stereoselective reduction of a gem-dibromocyclopropane to the corresponding monobromocyclopropane under mild reaction conditions was developed using a combination of dimethyl phosphite and potassium carbonate. This reaction provided a simple and practical way for the synthesis of the valuable monobromocyclopropanes and* β*-monobromoalkenes.*



Key words: Reduction; stereoselective; *gem*-dibromides; dimethyl phosphite; potassium carbonate

INTRODUCTION

The stereoselective reduction of a *gem*-dibromocyclopropane to a monobromocyclopropane is an important reaction in organic synthesis.[1,2] This transformation is closely related to the preparation of agrochemicals, pharmaceuticals and natural products, since many of these molecules hold cyclopropyl groups with defined *cis* or *trans* configurations.[1,2] Traditionally, such a stereoselective reduction was achieved by using metallic reagents. However, the hazardous condition, complicated manipulation and low functional-group tolerance limited the applications.[3] In 1981, Hirao et al. disclosed that a *gem*-dibromocyclopropane could be efficiently reduced to the corresponding bromocyclopropane with up to 88:12 (*cis*/*trans*) selectivity by using a combination of diethyl phosphite and triethylamine.[4]

This reduction system was later modified.[5-8] Meijs achieved up to >99:1 stereoselectivity with the reduction of dibromocyclopropyl compounds using an excess potassium dimethyl phosphate (6 eqs) in liquid NH_3.[6] A similar reduction was also observed by using a VCl_3-Zn-a secondary phosphite system (reaction time: 60h).[7] By applying the microwave irradiation technology, Tokuda et al. developed an efficient reduction of *gem*-dibromoalkenes using a combination of diethyl phosphite and EtONa in EtOH, but they did not tested the reactivity of dibromocyclopropyl compounds.[8]

An ongoing project on the study of biological activity of phosphorus compounds in this laboratory needs a rapid access to bromocyclopropanes. Although they had been prepared by the literature`s methods as mentioned above, the selectivity of the products was either not satisfactory or the reaction

required complicated manipulation. So we decided to reinvestigate Hirao`s method, in order to find out an easy-operating highly efficient practical reduction system.

Herein, we report a highly stereoselective reduction of *gem*-dibromocyclopropanes to the corresponding monobromocyclopropanes under mild reaction conditions using the readily available dimethylphosphite and potassium carbonate (Scheme 1). Monobromoalkenes could also be obtained similarly from the corresponding dibromoalkenes. Compared to the literature`s procedures, the present method does not use hazardous chemicals, and thus is simpler and more practical.

RESULTS AND DISCUSSION

As shown in Table 1, an extensive screening on the reaction conditions revealed that 2,2-dibromocyclopropylbenzene **1a** could be efficiently reduced to the corresponding monobromocyclopropane **2a** by a combination of dimethyl phosphite and potassium carbonate. Thus, it was found that heating a mixture of **1a**, $(MeO)_2P(O)H$ and K_2CO_3 in DMF at 100 ^oC overnight produced 89% yield of **2a** with 84% selectivity to the *cis*-isomer (Table 1, entry 1). The reduction also proceeded efficiently in propylene carbonate and acetonitrile with a slightly improved selectivity (entries 2 and 3). The selectivity could be improved to 97% when the reaction was conducted in toluene (entry 4), and a quantitative yield of **2a** was obtained in dioxane and THF (entries 5 and 6) with 96% selectivity to the *cis*-product. In addition to potassium carbonate, cesium carbonate also produced **2a** in an almost

quantitative yield with very high selectivity (entry 7). However, other bases such as Na_2CO_3, CsOAc, NaOAc, Na_2SiF_6 did not give satisfactory results (entries 7-11). As demonstrated by entry 12, this reaction also took place smoothly at 80 ^oC with two equivalents of $(MeO)_2P(O)H$ and 1 equivalent of K_2CO_3 to quantitatively produce **2a** highly selectively. Finally, even a stoichiometric amount of the chemicals could produce a good yield (75% yield) of the reduced product **2a** (entry 13).

By using the optimized reaction conditions described in Table 1, a variety of *gem*-dibromides could be stereoselectively reduced to the corresponding monobromides **2** in high yields. As shown in Table 2, all of the aromatic dibromocyclopropanes investigated could be converted stereoselectively to the corresponding monobromocyclopropanes in high yields under the reaction conditions (Table 2, entries 1-3). It is worth noting that the bromo atom bonded to benzene (entry 2) and the chloro atom at the benzyl position (entry 3) remained intact during the reduction. However, compared to the high reactivity of dibromocycopropanes, an analogue dichlorocyclopropane could not be reduced under the reaction conditions (entry 4). In addition to aromatic dibromocyclopropanes, aliphatic dibromocyclopropanes also served as good substrates in this reduction to produce the corresponding products in high yields with high *cis*-stereoselectivity (entries 5 and 6).

In addition to *gem*-dibromocyclopropyl compounds, the current reduction system could also be applicable to the selective reduction of *gem*-dibromoalkenes to produce the corresponding bromoalkenes selectively (entries 7-13). Thus, 83% yield of β-bromostyrene **2g** was obtained with 95% selectivity to

the *trans* form from β-dibromostyrene **1g** (entry 7). Similarly, both *gem*-dibromoalkenes with 1-naphthyl and 2-naphthyl substituent also served as good substrates in this reaction to produce the corresponding *trans*-β-monobromoalkenes in 92% and 86% yields, respectively (entries 8 and 9). Substrates bearing either an electron-donating group (MeO) or an electron-withdrawing group (NO_2) on the benzene ring were all applicable to this reaction to give the expected products in high yields with high *trans*-stereoselectivity (entries 10 and 11). Worth noting again is that even the easily reducible NO_2 group is tolerable under the current reduction conditions. Similarly, aliphatic *gem*-dibromoalkenes were efficiently reduced to the corresponding monobromoalkenes with a moderate stereoselectivity (entries 12 and 13).

On the basis of the experimental results and literature`s reports,[5-8] possible mechanisms were proposed as shown in Schemes 2 and 3. As shown in Table 1, the use of an alkali metal carbonate with a higher basicity is necessary for efficiently promoting the reaction (Cs_2CO_3 = K_2CO_3 > Na_2CO_3). In addition, it was known that an alkali metal phosphonate $MOP(OR)_2$ could reduce the dibromocompounds.[6] Therefore, it is rationally assumed that a potassium phosphonate $KOP(OMe)_2$ is involved in the current $(MeO)_2P(O)H/K_2CO_3$ system as shown in eq 1.

$$(MeO)_2P(O)H \xrightarrow{-KHCO_3} KOP(OMe)_2 \quad (1)$$

As for the reduction of dibromocyclopropyl compounds,[5,6] it was assumed that the halophilic attack of the resulting dimethyl phosphonate anion on the *gem*-dibromocylopropanes occurred

subsequently at the less hindered *trans*-site (Scheme 2). As a result, the *cis*- monobromocyclopropane was formed selectively.[6]

As for the reduction of *gem*-dibromoalkenes,[5,8] the addition of the resulting dimethyl phosphonate anion to the *gem*-dibromoalkene might take place first, generating anions **4** and **4'**. Protonation of **4** and **4'** afforded intermediates **5** and **5'**. The reduction product monobromides were produced by elimination of $(MeO)_2P(O)Br$ from **5** and **5'** (Scheme 3). It was proposed that the interaction of Br with the phosphoryl group generating four-membered rings in **5** and **5'** is the key factor determining the stereoselectivity.[8] Because of the repulsion between Br and the R group, the formation of **5** is more favorable than **5'**. Therefore, the formation of *trans*-monobromides is favored.[8]

CONCLUSION

In summary, by employing a combination of dimethyl phosphite with potassium carbonate, we have developed a very simple and practical system for the selectively reduction of *gem*-dibromides to the corresponding monobromides under mild reaction conditions. This reaction is applicable to the synthesis of a wide range of monobromocyclopropanes and β-monobromoalkenes in high yields with high stereoselectivity.

EXPERIMENTAL SECTION

General Information. Except where otherwise noted, all reactions were carried out in oven-dried

glass tubes under N_2 atmosphere with dry solvents under anhydrous conditions. Dry solvents were obtained by purification according to standard methods. Reagents were used as received unless otherwise noted. Column chromatography was performed using Silica Gel 60 (particle size 40-50 ε m) purchased from Kanto Chemical Co. Inc. All solvents and reagents were purchased from Wako Pure Chemical Industries Ltd. (Japan), Tokyo Chemical Industry Co. (Japan), and Aldrich Chemical Co. (USA) .The pure products were obtained by column chromatography or GPC (LC-908). NMR spectra were obtained on a JEOL ECX-400 instrument (400 MHz for ^{1}H, 100 MHz for ^{13}C NMR spectroscopy). $CDCl_3$, or C_6D_6 was used as the solvent. Chemical shifts for ^{1}H NMR are referred to internal Me_4Si (0 ppm) and reported as follows: chemical shift (ŭ ppm), multiplicity, integration and coupling constant (Hz). Data for ^{13}C NMR are reported in ppm relative to the center line of a triplet at 77.0 ppm for chloroform-*d*). ^{1}H and ^{13}C multiplicities are reported as follows: singlet (s), doublet (d), doublet of doublets (dd), quartet (q), multiplet (m), and broad resonance (br). Gas chromatographic (GC) analysis was acquired on a Shimadzu GC-2010 Series GC System equipped with a flame-ionization detector. The Supplemental Materials file contains characterization data of the known products, together with sample ^{1}H and ^{13}C NMR spectra for compounds 2a-2m (Figures S 1 ï S 24).

Typical Experimental Procedure

General procedure for Synthesis of *gem*-dibromocyclopropanes:

In a 100-mL three-necked round-bottomed flask equipped with a teflon-coated magnetic stir bar and a condenser, alkene (10 mmol), bromoform (40 mmol), and benzyltriethylammonium chloride (TEBA) (0.1 mmol) was added. The result mixture was placed in an ice bath, then, 2.4 g of a 50% aqueous solution of sodium hydroxide (NaOH) (1.2 g, 30 mmol in 1.2 mL of H_2O) was added dropwise by a syringe in 10 min. The reaction mixture is stirred vigorously at bath temperature (approximately 0 °C) for 2 h and at room temperature for 22 h, then cooled in an ice bath again and quenched by injecting 6 M hydrochloric acid (3 mL) dropwise over a 10 min period. The result mixture was extracted with dichloromethane, washed with water, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure, then distilled to afford the products.

General procedure for Synthesis of *gem*-dibromoalkenes:

To a solution of PPh_3 (20 mmol) and CBr_4 (10 mmol) in CH_2Cl_2 (20 mL) under N_2 atmosphere in 100mL round-bottomed flask at 0 ^oC was added R-CHO (10 mmol) dropwise, the result mixture was allowed to warm to room temperature and stirred for another 1h, then water (50 mL) was added and extracted with dichloromethane, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The products were purified by silica gel used hexane as eluent.

General Procedure for Reduction of *gem*-Dibromides with Dimethyl Phosphite and Potassium Carbonate:

General procedure: An oven-dried glass tube containing an Teflon-coated stir bar was charged with a mixture of dibromide (0.2 mmol), *(*$(MeO)_2P(O)H$ (0.4 mmol), and K_2CO_3 (0.2 mmol) in 0.4 mL of dioxane under N_2 atmosphere and stirred at 80 ^oC for 13h. After the reaction, Na_2CO_3 saturated solution (1 mL) was added to the reaction mixture, and extracted with ethyl acetate. The combined organic extracts were dried over anhydrous Na_2SO_4, concentrated in vacuum, and the resulting residue was purified by GPC to afford the pure products.

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REFERENCES

[1] For the application of monobromoalkenes in organic synthesis, please see, a) Gallagher, W. P.; Maleczka, Jr, R. E. *J. Org. Chem.* **2005**, 70, 841-846. b) Maleczka, Jr, R. E.; Gallagher, W. P.; Terstiege,I. *J. Am. Chem. Soc.* **2000**, 122, 384-385. c) Gallagher, W. P.; Terstiege, I.; Maleczka, Jr, R. E. *J. Am. Chem. Soc.* **2001**, 123, 3194-3204. d) Maleczka, Jr, R. E.; Gallagher, W. P. *Org. Lett.* **2001**, 3, 4173-4176. e) Ranu, B. C.; Chattopadhyay, K.; Banerjee, S. *J. Org. Chem.* **2006**, 71, 423-425. f) Sun, P.; Yan, H.; Lu, L.; Liu, D.; Rong, G.; Mao, J. *Tetrahedron*, **2013**, 69, 6969-6974. g) Saha, D.; Chatterjee, T.; Ranu, B. C.; Mukherjee, M. *J. Org. Chem.* 2012, 77, 9379-9383. h) Semmelhack, M. F.; Helquist, P.; Jones, L. D.; Keller, L.; Mendelson, L. *J. Am. Chem. Soc.* **1981**, 103, 6460-6471. i) Hirao, T.; Masunaga, T.; Ohshiro, Y.; Agawa, T. *Tetrahedron Lett.* **1980**, 21, 3595-3598. j) Reddy, C. R.; Urgaonkar, V. S.; Verkade, J. G. *Org. Lett.* **2005**, 7, 4427-4430. k) Hayford, A.; Kaloko, J. J.; EI-Kazaz, S.; Bass, G.; Harrison, C.; Corprew, T. *Org. Lett.* **2005**, 7, 2671-2673. l) Roberts, B.; Liptrot, D.; Alcaraz, L.; Luker, T.; Stocks, M. J. *Org. Lett.* **2010**, 12, 4280-4283. m) Davis, F. A.; Lal, G. S.; Wei, J. *Tetrahedron Lett.* **1988**, 29, 4269-4272. n) Duncton, M. A.; Pattenden, J. G.; *J. Chem. Soc., Perkin Trans. 1* **1999**, 1235-1242.

[2] For the application of monobromocyclopropanes in organic synthesis, please see, a) Porter, N. A.; Roberts, D. H.; Ziegler, C. B. *J. Am. Chem. Soc.* **1980**, 102, 5912-5913. b) Rauhut, C. B.; Cervino, C.; Krasovskiy, A.; Knochel, P. *Synlett.* **2009**, 67-70. c) Fox, M. A.; Chen, C.-C.; Campbell, K. A. *J.*

Org. Chem. **1983**, 48, 321-326. d) Porter, N. A.; Ziegler, C. B.; Khouri, F. F.; Roberts, D. H. *J. Org. Chem.* **1985**, 50, 2252-2258.

[3] a) Hofmann, K.; Orochena, S. F.; Sax, S. M.; Jeffrey, G. A. *J. Am. Chem. Soc.* **1959**, 81, 992-997. b) Nozaki, H.; Aratani, T.; Noyori, R. *Tetrahedron*, **1967**, 23, 3645-3648. c) Kulinkovich, O. G.; Astapovich, I. V.; Masalov, N. V.; *Russ. J. Org. Chem.* **1998**, 34, 1327-1329. d) Touster, J.; Fry, A. J. *Tetrahedron Lett.* 1997, 38, 6553-6556. e) Harada, T.; Katsuhira, T.; Hattori, K.; Oku, A. *Tetrahedron,* **1994**, 50, 7987-8002. f) Yanilkin, V. V.; Strunskaya, E. I.; Nastapova, N. V.; Maksimyuk, N. I.; Bredikhina, Z. A.; Sharafutdinova, D. R.; Bredikhin, A. A. *Russ. Chem. Bull.* **2003**, 52, 923-928. g) Tsang, D. S.; Yang, S.; Alphonse, F-A.; Yudin, A. K. *Chem. -Eur. J.* **2008**, 14, 886-894. h) Duddu, R.; Eckhardt, M.; Furlongl, M.; Knoess, H. P.; Berger, S.; Knochel, P. *Tetrahedron,* **1994**, 50, 2415-2432. i) Kulinkovich, O. G.; Astapovich, I. V.; Masalov, N. V. *Russ. J. Org. Chem.* **1998**, 34, 1266-1268. j) Uenishi, J.; Kawahama, R.; Yonemitsu, O. *J. Org. Chem.* **1998**, 63, 8965-8975. k) Wang, L.; Li, P.; Xie, Y.; Ding, Y. *Synlett.* **2003**, 8, 1137-1140. l) Ranu, B. C.; Samanta, S.; Guchhait, S. K. *J. Org. Chem.* **2001**, 66, 4102-4103. m) Fakhfakh, M. A.; Franck, X.; Hocquemiller, R.; Figadere, B. *J. Organomet. Chem.* **2001**, 624, 131-135.

[4] Hirao, T.; Masunaga, T.; Ohshiro, Y.; Agawa, T. *J. Org. Chem.* **1981**, 46, 3745-3747.

[5] a) Hirao, T.; Kohno, S.; Ohshiro, Y.; Agawa, T. *Bull. Chem. Soc. Jpn.* **1983**, 56, 1881-1882. b) Hirao, T.; Masunaga, T.; Hayashi, K.-I.; Ohshiro, Y.; Agawa. T. *Tetrahedron Lett.* **1983**, 24, 399-400. c)

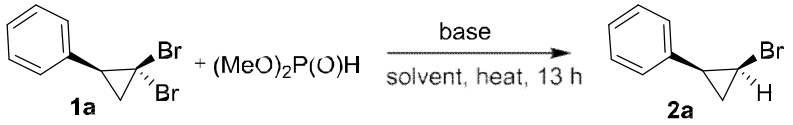
Abbas, S.; Hayes, C. J. *Synlett.* **1999**, 1124-1126. d) Dulayymi, J. R. A.; Baird, M. S.; Bolesov, I. G.; Tveresovsky, V.; Rubin, M. *Tetrahedron Lett.* **1996**, 37, 8933-8936. e) Meijs, G. F. *J. Org. Chem.* **1984**, 49, 3863-3865. f) Abbas, S.; Hayes, C. *Tetrahedron Lett.* **2000**, 41, 3215-3219.

[6] Meijs, G. F.; Doyle, L. R. *J. Org. Chem.* **1985**, 50, 3713-3716.

[7] Hirao, T.; Hirano, K.; Hasegawa, T.; Ohshiro, Y.; Ikeda, I. *J. Org. Chem.* **1993**, 58, 6529-6530.

[8] Kuang, C.; Senboku, H.; Tokuda, M. *Tetrahedron*, **2002**, 58, 1491-1496.

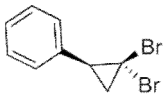
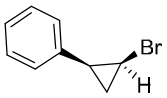
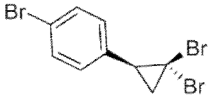
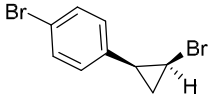
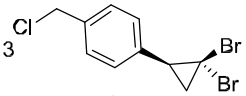
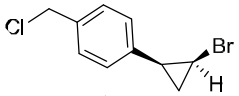
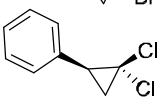
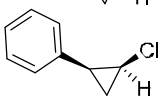
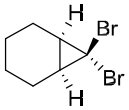
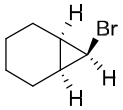
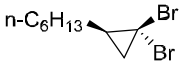
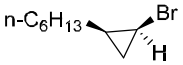
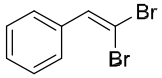
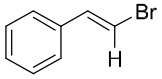
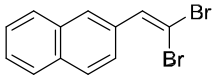
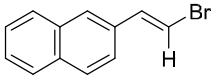
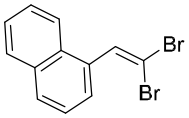
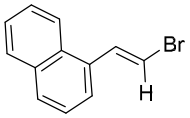
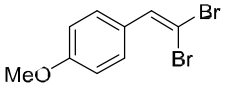
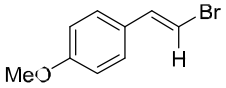
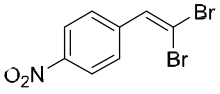
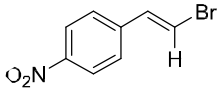
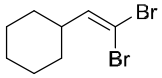
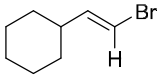
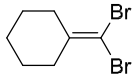
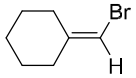
Table 1. Optimization of reaction conditions [a]



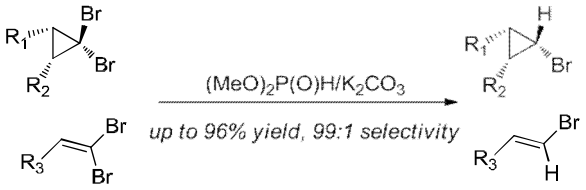
entry	$(MeO)_2P(O)H$	solv	base (equiv)	temp	yield(%)(*cis*/*trans*)[b]
1	4 equivs	DMF	K_2CO_3 (2)	100 °C	89 (84/16)
2	4 equivs	propylene carbonate	K_2CO_3 (2)	100 °C	90 (87/13)
3	4 equivs	MeCN	K_2CO_3 (2)	100 °C	100 (90/10)
4	4 equivs	toluene	K_2CO_3 (2)	100 °C	90 (97/3)
5	4 equivs	dioxane	K_2CO_3 (2)	100 °C	100 (96/4)
6	4 equivs	THF	K_2CO_3 (2)	100 °C	100 (96/4)
7	4 equivs	dioxane	Cs_2CO_3 (2)	100 °C	99 (97/3)
8	4 equivs	dioxane	Na_2CO_3 (2)	100 °C	44 (96/4)
9	4 equivs	dioxane	CsOAc (2)	100 °C	16 (91/9)
10	4 equivs	dioxane	NaOAc (2)	100 °C	7 (81/19)
11	4 equivs	dioxane	Na_2SiF_6 (2)	100 °C	trace (-/-)
12	**2 equivs**	**dioxane**	**K_2CO_3 (1)**	**80 °C**	**100 (97/3)**
13	1 equiv	dioxane	K_2CO_3 (1)	80 °C	75 (96/4)

[a]A mixture of **1a** (0.2 mmol), $(MeO)_2P(O)H$ and a base in a solvent (0.4 mL) was heated in a 10 mL glass tube. [b]GC yield using dodecane as an internal standard.

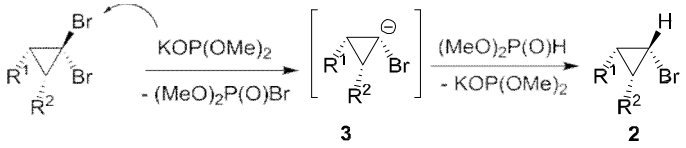
Table 2. Reduction of *gem*-Dibromides with Dimethylphosphite and Carbonates.[a]

entry	substrate	product	yield(%)(*cis*/*trans*)[b]
1	 **1a**		**2a**, 95 (97:3)
2	 **1b**		**2b**, 94 (95:5)
3	 **1c**		**2c**, 96 (92:8)
4	 **1d**		**2d**, 0 (-:-)
5	 **1e**		**2e**, 94 (99:1)
6	 **1f**		**2f**, 80 (92:8)
7	 **1g**		**2g**, 83 (5:95)
8	 **1h**		**2h**, 92 (8:92)
9	 **1i**		**2i**, 86 (8:92)
10	 **1j**		**2j**, 90 (7:93)
11	 **1k**		**2k**, 93 (7:93)
12	 **1l**		**2l**, 94 (30:70)
13	 **1m**		**2m**, 92

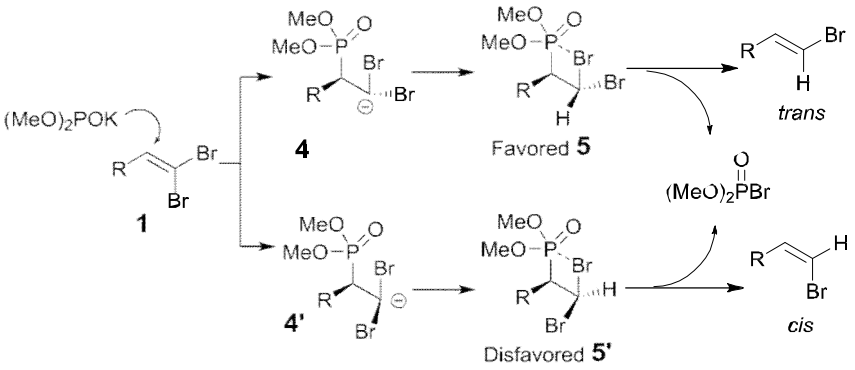
[a]Reaction conditions: *gem*-dibromide (0.2 mmol), $(MeO)_2P(O)H$ (2 equiv), K_2CO_3 (1 equiv), dioxane (0.4 mL), 80 ^{O}C, 13 h. [b]Isolated yield.



Scheme 1. Selective reduction of *gem*-dibromides with dimethylphosphite and potassium carbonate.



Scheme 2. A proposed mechanism for the reduction of *gem*-dibromocyclopropanes.



Scheme 3. A proposed mechanism for the reduction of *gem*-dibromoalkenes.