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Sequential and Highly Stereoselective Intermolecular Radical Additions of 2,3-*cis*-Disubstituted 1,1-Dibromo- and 1-Bromocyclopropanes to Electron-Deficient Olefins

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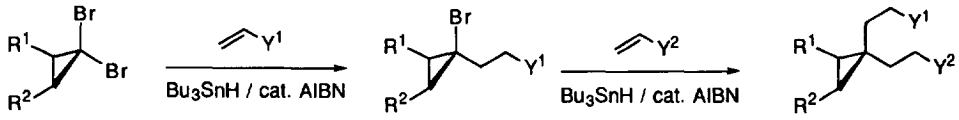
Abstract: Novel and sequential intermolecular radical additions of 2,3-*cis*-disubstituted 1,1-dibromo- and 1-bromocyclopropanes to electron-deficient olefins proceeded with high stereoselectivity, i.e., in an *exo*-face addition manner. This highly stereoselective addition was also applied to an intramolecular cyclization.

The synthetic protocol of radical types of carbon-carbon bond formations has attained a significant position in organic syntheses.[1] The intermolecular additions of radical species to substituted olefins, pioneered by Giese *et al.*, are recognized as representative and are useful two or three carbon-elongation reactions.[2] The stereochemical mode is currently a highlighted feature of these reactions. Vicinal substituents of five- or six-membered ring radical systems influence the stereoselectivity during *anti*-selective intermolecular olefin additions and reductions.[3] However, the facial selectivities are generally moderate or poor except in cases using specific substrates.

Meanwhile, the mono- or di-dehalogenation of *gem*-dihalocyclopropanes using Bu_3SnH/cat. azobisisobutyronitrile (AIBN) or benzoyl peroxide is a representative and practical example of radical reductions.[4] Other reductive debrominations use other metal hydrides and reagents.[5] On the other hand, stereoselective carbon-carbon bond formations utilizing metalate complexes of 1,1-dibromocyclopropanes have also been reported.[6] Despite this extensive research, no report has appeared concerning the intermolecular radical addition of *gem*-dihalocyclopropanes to olefins. Against this prior background, recent studies[7] on the regioselective, intramolecular radical cyclization of *gem*-dihalo substituted substrates prompted us to investigate the intermolecular additions of radicals on cyclopropane derivatives, focusing our attention on the stereochemical mode of reaction. In the course of our studies on the utilization of halocyclopropanes,[8] we described here that the sequential intermolecular radical additions of various *gem*-dibromocyclopropanes **1** and monobromocyclopropanes **2** to olefins proceeded in a highly stereoselective *exo*-face attack manner.

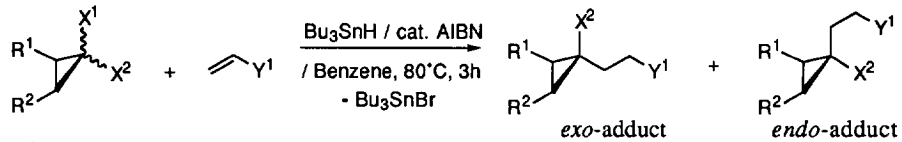


1 **2** **3**

Table 1 lists the results of the first-step intermolecular radical addition of 2,3-*cis*-disubstituted 1,1-dibromocyclopropanes **1** and their analogs **4** and **6-9**. 7,7-Dibromobicyclo[4.1.0]heptane (**1a**), a type of 2,3-*cis*-disubstituted 1,1-dibromocyclopropane, is known as the standard model compound for debromination reactions. However, all of these methods resulted in moderate stereoselectivity (For example, using a Bu_3SnH

system: *exo*-reduction/*endo*-reduction = ca. 2.5/1). In clear contrast, all the present intermolecular reactions proceeded with high stereoselectivities to give the *exo*-adducts **2a-n**.[9] Several cyclic and acyclic substrates are applicable. While the olefins, acrylonitrile and methyl acrylate gave fairly good yields, however, electron-rich butyl vinyl ether resulted in a poor yield. Substrates containing functionalities such as an olefin, ether, alcohol, ester, and trimethylsilane could tolerate these reaction conditions. Although *gem*-bromochlorocyclopropanes **4a** and **4b** similarly underwent stereoselective addition to give the *exo*-chlorocyclopropyl adducts **2k** and **2l**, *gem*-dichlorocyclopropane **5** did not give the desired product at all. The use of bromocyclopropane **6** gave cyclopropane **2n** in low yield, but with high selectivity. As for the substrate of monosubstituted cyclopropanes **7** and **8**, the stereoselectivities were moderate. It should be noted that the addition of the trimethylsilyl substrate **9** showed high stereoselectivity, which is a specific example of monosubstituted cyclopropanes.

Table 1



1, 4, 6-9 *exo*-adduct **2** *endo*-adduct

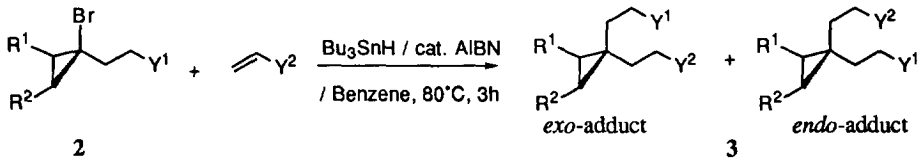
Entry	Substrate	X^1	X^2	R^1 R^2	Y^1	Product	Yield/%	*exo*-add.:*endo*-add.[a]
1	**1a**	Br	Br	$-(CH_2)_4-$	CN	**2a**	59	99.5:0.5
2					CO_2Me	**2b**	35	99.5:0.5
3					OBu	**2c**	17	>99:1
4	**1b**	Br	Br	$-CH_2CH=CHCH_2-$	CN	**2d**	46	>99:1
5					CO_2Me	**2e**	37	99.5:0.5
6	**1c**	Br	Br	$-(CH_2)_3O-$	CN	**2f**	47[b]	>99:1
7	**1d**	Br	Br	$-(CH_2)_6-$	CN	**2g**	52	97:3
8					CO_2Me	**2h**	40	97:3
9	**1e**	Br	Br	Et CH_2CH_2OH	CN	**2i**	42	>99:1
10	**1f**	Br	Br	CO_2Me CO_2Me	CN	**2j**	29	>99:1
11	**4a**[c]	Br	Cl	$-(CH_2)_4-$	CN	**2k**	67	>99:1
12	**4b**[c]	Br	Cl	$-(CH_2)_6-$	CN	**2l**	58	97:3
13					CO_2Me	**2m**	48	97:3
14	**5**	Cl	Cl	$-(CH_2)_4-$	CN		0[d]	---
15	**6**[e]	Br	H	$-(CH_2)_4-$	CN	**2n**	10[d]	>99:1
16	**7**	Br	Br	Ph H	CN	**2o**	49	5:1
17					CO_2Me	**2p**	43	6:1
18	**8**	Br	Br	CH_2OH H	CN	**2q**	45	1.5:1
19	**9**	Br	Br	$SiMe_3$ H	CN	**2r**	35	>99:1

a) These ratios were determined by integration of methylene-protons adjacent to the bridgehead carbon using ^1H NMR (400 MHz).[9] b) Reaction time was 1 h. c) Diastereomixtures of *exo*-Br and *endo*-Br. d) Hydrostannylation of acrylonitrile mainly occurred. e) Diastereomixtures of *exo*-Br and *endo*-Br (1:3) substrates.

The second-step addition was investigated as follows. As a preliminary experiment, the radical debromination of 3-(7-bromobicyclo[4.1.0]heptan-7-yl)propionitrile (**2a**) with Bu_3SnH/cat.AIBN was examined to check the stereochemical behavior of the bridgehead carbon (7-position). This radical reduction (86% yield) showed poor selectivity; **2n**-*exo*-product (with retention): **2n**-*endo*-product (with inversion) ratio = 1:1.5. Nevertheless, the radical addition of **2a**, **2b**, **2e**, and **2h**, obtained by the first-step addition, to

acrylonitrile and methyl acrylate took place accompanied by *nearly complete inversion* (**3**-*exo*-adduct : **3**-*endo*-adduct = >95:5)[10] as shown in Table 2.

Table 2[a)]

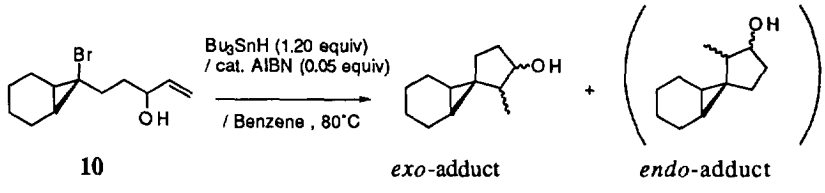


2 **3**

Entry	Substrate	R^1 R^2	Y^1	Y^2	Product	Yield/%	*exo*-add.:*endo*-add.[b)]
1	**2a**	$-(CH_2)_4-$	CN	CO_2Me	**3a**	30	95:5
2	**2b**	$-(CH_2)_4-$	CO_2Me	CN	**3b**	51	98:2
3	**2e**	$-CH_2CH=CHCH_2-$	CO_2Me	CN	**3c**	27	98:2
4	**2h**	$-(CH_2)_6-$	CO_2Me	CN	**3d**	68	96:4

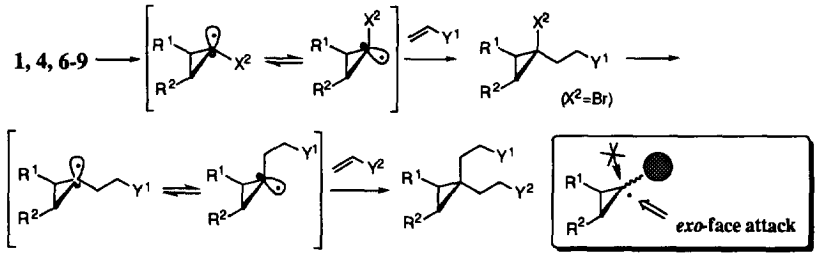
a) Optimized molar ratio of **2**:Bu_3SnH:olefin = 1:4.5:20. b) These ratios were determined by integration of methylene-protons adjacent to the bridgehead carbon using ^1H NMR (400 MHz).[10]

Finally, we attempted the intramolecular addition (cyclization) as a further extension of the second-step reaction. This cyclization using bromocyclopropane **10**[11] also proceeded with *complete inversion* to give spiro compound **11** (*exo*-adduct:*endo*-adduct = >99:1)[10] in 75% yield. It should be pointed out that the initial radical flipped (equilibrated) very rapidly prior to the intramolecular cyclization despite the short life of the radicals.



10 *exo*-adduct *endo*-adduct

11



Scheme

In conclusion, the present inter- and intramolecular additions utilizing radicals on a cyclopropane ring bearing a 2,3-*cis*-disubstituent system involved unequivocal stereoselective *exo*-face attack of olefins as illustrated in the scheme. This method would provide not only a new process of stereo-controlled radical addition but a new entry for the stereoselective construction of cyclopropane derivatives. Computational calculation to support this mechanism is now under progress.

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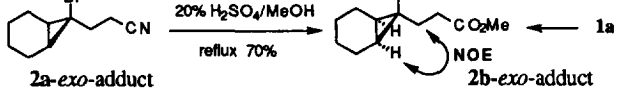
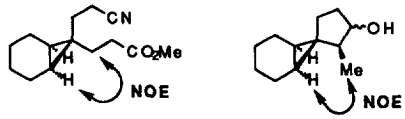
9. Due to the sequential rule of stereochemistry, reverse configuration (*exo*-adducts are *endo*-halocyclopropanes, and vice versa) is indicated. A typical procedure is exemplified by the preparation of **2a**: To a stirred solution of 7,7-dibromobicyclo[4.1.0]heptane (**1a**; 254 mg, 1.0 mmol) and acrylonitrile (531 mg, 10.0 mmol) in benzene (2.4 ml) was successively added AIBN (8 mg, 0.05 mmol) and Bu_3SnH (437 mg, 1.5 mmol) at 65 °C under N_2 and the mixture was kept at 80 °C for 3 h. Usual work up of the mixture gave **2a** (135 mg, 59%) as colorless crystals. mp 44.5-45.5 °C; ^{1}H-NMR (400 MHz) δ 0.99-1.10 (2H, m), 1.17-1.30 (2H, m), 1.35-1.46 (2H, m), 1.47-1.61 (2H, m), 1.95-2.09 (2H, m), 2.02 (2H, t, J = 7.1 Hz), 2.64 (2H, t, J = 7.1 Hz). IR (neat) 2934, 2247, 1439 cm^{-1}. The relative configuration was determined by a NOESY experiment of **2b**, which was derived from **2a** and was prepared directly from **1a** by the present first-step reaction.



2a-*exo*-adduct 2b-*exo*-adduct

10. In a similar procedure for preparing **2** except the molar ratio (see text), **3a-d** and **11** were obtained. **3a**: Colorless oil; ^{1}H-NMR (400 MHz) δ 0.70-0.77 (2H, m), 1.14-1.38 (6H, m), 1.49 (2H, t, J = 7.8 Hz), 1.75 (2H, t, J = 8.1 Hz), 1.85-1.97 (2H, m), 2.32 (2H, t, J = 7.8 Hz), 2.40 (2H, t, J = 8.1 Hz), 3.66 (*exo*-adduct ; 3Hx95/100, s), 3.69 (*endo*-adduct; 3Hx5/100, s). IR (neat) 2930, 2247, 1739, 1439 cm^{-1}. **11**-*exo*-adduct contained diastereomixtures **a** and **b** (=1:1.1). **a**: Colorless oil; ^{1}H-NMR (400 MHz) δ 0.51-0.60 (1H, m), 0.72 (3H, d, J = 7.2 Hz), 0.82-0.91 (1H, m), 1.00-1.12 (2H, m), 1.12-1.24 (2H, m), 1.25-1.50 (3H, m), 1.56-1.66 (1H, m), 1.70-1.96 (5H, m), 4.10-4.17 (1H, m). IR (neat) 1448, 2854, 2928, 3373 cm^{-1}. **b**: Colorless oil; ^{1}H NMR (400 MHz) δ 0.62-0.71 (1H, m), 0.72 (3H, d, J = 7.4 Hz), 0.82-0.88 (1H, m), 0.96-1.24 (4H, m), 1.24-1.34 (1H, m), 1.34-1.70 (5H, m), 1.71-1.89 (2H, m), 2.01-2.13 (1H, m), 3.72-3.81 (1H, m). IR (neat) 1448, 2866, 2929 and 3356 cm^{-1}. These relative configurations were determined by NOESY experiments.



3a-*exo*-adduct 11-*exo*-a or b adduct

11. DIBAL reduction of **2a** gave the corresponding aldehyde, which was coupled with vinylmagnesium bromide to afford bromocyclopropane **10** in 44% overall yield.

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