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Highly Stereoselective Radical Carbonylations of *gem*-Dihalocyclopropane Derivatives with CO

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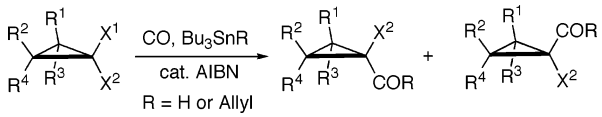
ABSTRACT



A couple of radical carbonylations of *gem*-dihalocyclopropanes 1 using CO and Bu_3SnH (formylation) or $Bu_3Sn(CH_2CH{=}CH_2)$ (allylacylation) successfully proceeded to give trans and cis adducts (2 and 3) with good to excellent stereoselectivity (trans/cis = >99/1–75/25 or 17/83–1/99). The formylation of 2,3-cis-disubstituted 1,1-dihalocyclopropanes enhanced trans selectivity (trans/cis = >99/1–95/5), whereas both 2,3-cis-disubstituted and 2-monosubstituted 1,1-dihalocyclopropanes underwent allylacylation with nearly complete trans selectivity (trans/cis = >99/1). Inherently less reactive *gem*-dichloro- and bromochlorocyclopropanes than *gem*-dibromocyclopropanes served as favorable substrates.

Intermolecular carbonylation of various organic radical intermediates using CO is recognized as a useful transformation.[1] The addition of certain radical species to CO generates the corresponding acyl radicals, which undergo hydroformylation (−CHO) or acylation through the consecutive trap with olefins (−COR).[2] Recently, Zard's group reported that cyclopropylacyl radicals derived from *S*-cyclopropylacylxanthates add to external olefins without loss of the labile cyclopropane ring.[3]

Cyclopropyl carbonyls and methanols are an important chemical class in organic synthesis due to their widespread occurrence in nature and potential synthetic utility.[4] Transformations of *gem*-dihalocyclopropanes into functionalized cyclopropanes are useful because of the preparative accessibility of *gem*-dihalocyclopropanes and the unique reaction mode.[5] Several efficient methods have been exploited for the carbon elongation on the *gem*-dihalogenocarbons,[6] but

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(1) For reviews of radical reactions of CO, see: (a) Ryu, I.; Sonoda, N. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1050. (b) Ryu, I.; Sonoda, N.; Curran, D. P. *Chem. Rev.* **1996**, *96*, 177. (c) Ryu, I. *Chem. Soc. Rev.* **2001**, *30*, 16. For a review of acyl radicals, see: (d) Chatgilialogu, C.; Crich, D.; Komatsu, M.; Ryu, I. *Chem. Rev.* **1999**, *99*, 1991.

(2) (a) Ryu, I.; Kusano, K.; Ogawa, A.; Kambe, N.; Sonoda, N. *J. Am. Chem. Soc.* **1990**, *112*, 1295. (b) Ryu, I.; Yamazaki, H.; Kusano, K.; Ogawa, A.; Sonoda, N. *J. Am. Chem. Soc.* **1991**, *113*, 8558. (c) Ryu, I.; Yamazaki, H.; Ogawa, A.; Kambe, N.; Sonoda, N. *J. Am. Chem. Soc.* **1993**, *115*, 1187.

(3) Heinrich, M. R.; Zard, S. Z.; *Org. Lett.* **2004**, *6*, 4969.

(4) (a) Patai, S.; Rappoport, Z. *The Chemistry of the Cyclopropyl Group*; Wiley: London, 1987. (b) Reissig, H.-U. *Top. Curr. Chem.* **1988**, *144*, 73. (c) Wong, H. N. C.; Hon, M.-Y.; Tse, C.-Y.; Yip, Y.-C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165. For recent reviews: (d) Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977. (e) Reissig, H.-U.*; Zimmer, R. Chem. Rev.* **2003**, *103*, 1151. (f) Wessjohann, L. A.; Brandt, W. *Chem. Rev.* **2003**, *103*, 1625. (g) Liu, X.; Fox, J. *M. J. Am. Chem. Soc.* **2006**, *128*, 5600.

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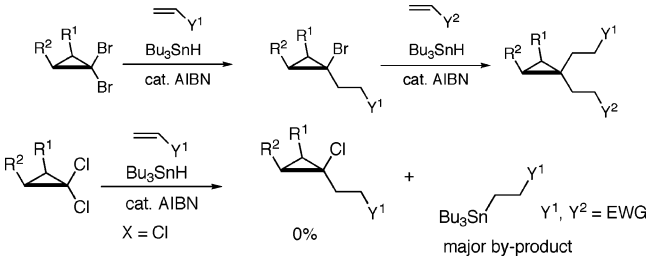
most of them were applied to *gem*-dibromo derivatives, which have higher reactivity than *gem*-dichloro derivatives during such reactions. For example, a Giese-type radical-mediated reaction of 2,3-disubstituted *gem*-dibromocyclopropanes successfully proceeds with electron-deficient olefins such as acrylonitrile and methyl acrylate, whereas the related reaction using less reactive *gem*-dichlorocyclopropanes gave a disappointing result: a competitive hydrostannylation of olefins with Bu_3SnH mainly occurred (Scheme 1).[7a]

Scheme 1

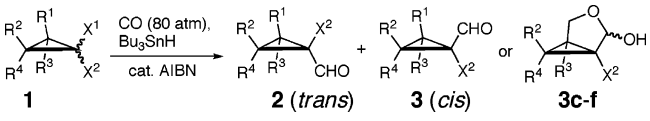


Consistent with our ongoing study on useful transformations of *gem*-dihalocyclopropanes,[7–9] we disclose herein a few highly stereoselective radical-type carbonylations of *gem*-dihalocyclopropane derivatives with CO, utilizing Bu_3SnH or $Bu_3Sn(CH_2CH{=}CH_2)$/catalytic AIBN.

The initial investigation was guided by the formylation of inherently less reactive, but synthetically more accessible, *gem*-dichlorocyclopropanes **1a**−**h** (Table 1).[10a] The salient features are as follows. (i) R^1-Monosubstituted 1,1-dichlorocyclopropanes **1a** and **b** underwent the desired formylation to give trans and cis adducts **2a**,**b** and **3a**,**b**, respectively, with moderate stereoselectivity (t/c = 75/25) (entries 1, 2). (ii) Surprisingly, although the reaction using **1c** bearing the CH_2OH group (R^1) showed moderate trans selectivity (t/c = 75/25) (entry 3), Me (R^3) and/or Ph (R^4) substituted analogues **1d**−**f** resulted in an apparent switch of the stereoselectivity to give lactols **3d**−**f** that were derived from *cis*-formyl radicals (t/c = 17/83 to <1/99) (entries 4−6). (iii) Note that similar reactions of 2,3-cis-disubstituted cyclic substrates **1g**,**h** gave almost the corresponding trans adduct (t/c = >99/1−95/5) (entries 7 and 8). This result is consistent with that of a relevant radical addition.[7a] (iv) Unexpectedly, inherently higher reactive dibromocyclopropane **1i** underwent mainly an undesirable (competitive) side hydrodebromination (entry 9). (v) Notably, the use of *gem*-bromochloro analogues **1j**−**o** consistently increased the reactivity and yield while maintaining the stereoselectivity spectrum (entries 10−15).[10b] (vi) The main side reaction was a competitive hydrodehalogenation of substrates by Bu_3SnH, which may somewhat decrease the yields. (vii) The *gem*-dichloro substrate required 0.4 equiv of AIBN catalyst, whereas only 0.2 equiv of AIBN was required for the *gem*-bromochloro substrate. We speculate that the rate-determining step is not the initial debromination, but rather the second carbonylation: the α-chlorocyclopropyl radical is more reactive than the α-boromocyclopropyl radical.

These successful results led us to investigate the reaction utilizing $Bu_3Sn(CH_2CH{=}CH_2)$ instead of Bu_3SnH. As ex-

Table 1. Stereoselective Radical-Type Formylation of *gem*-Dihalocyclopropanes **1**[a]



1 **2** (*trans*) **3** (*cis*) **3c-f**

entry	substrate	X^1	X^2	R^1	R^2	R^3	R^4	yield[b] (%)	ratio[c] of **2**/**3**
1	**1a**	Cl	Cl	Ph	H	H	H	51	75:25
2	**1b**	Cl	Cl	Hex	H	H	H	48	75:25
3	**1c**	Cl	Cl	CH_2OH	H	H	H	54	75:25
4	**1d**	Cl	Cl	CH_2OH	H	Me	H	60	17:83
5	**1e**	Cl	Cl	CH_2OH	H	H	Ph	48	20:80
6	**1f**	Cl	Cl	CH_2OH	H	Me	Ph	42	<1:99
7	**1g**	Cl	Cl	$-(CH_2)_4-$		H	H	55	>99:1
8	**1h**	Cl	Cl	$-(CH_2)_6-$		H	H	47	95:5
9	**1i**	Br	Br	$-(CH_2)_4-$		H	H	14	>99:1
10	**1j**	Br	Cl	Ph	H	H	H	60	75:25
11	**1k**	Br	Cl	Hex	H	H	H	63	75:25
12	**1l**	Br	Cl	$-(CH_2)_4-$		H	H	73	>99:1
13	**1m**	Br	Cl	$-(CH_2)_6-$		H	H	67	95:5
14	**1n**	Br	Cl	CH_2OH	H	Me	H	62	17:83
15	**1o**	Br	Cl	CH_2OH	H	Me	Ph	41	<1:99

[a] Reactions were carried out under CO pressure (80 atm) at 80 °C. 0.4 equiv (0.2 equiv added twice) of AIBN was used for **1a**−**h**, 0.2 equiv (added once) for **1i**−**o**. [b] Isolated. [c] Determined by ^1H NMR measurement.

(7) Radical type reactions: (a) Tanabe, Y.; Wakimura, K.; Nishii, Y. *Tetrahedron Lett.* **1996**, *37*, 1837.(b) Tanabe, Y.; Nishii, Y.; Wakimura, K. *Chem. Lett*. **1994**, 1757. (c) Nishii, Y.; Fujiwara, A.; Wakasugi, K.; Miki, M.; Yanagi, K.; Tanabe, Y. *Chem. Lett*. **2002**, 30.

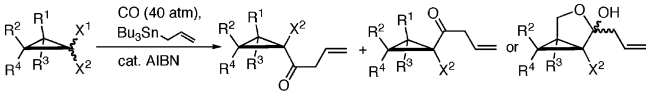
(8) Cationic-type reactions: (a) Tanabe, Y.; Seko, S.; Nishii, Y.; Yoshida, T.; Utsumi, N.; Suzukamo, G. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2157. (b) Nishii, Y.; Tanabe, Y. *J. Chem. Soc., Perkin Trans. 1* **1997**, 477. (c) Nishii, Y.; Wakasugi, K.; Koga, K.; Tanabe, Y. *J. Am. Chem. Soc.* **2004**, *126*. 5358. (d) Nishii, Y.; Yoshida, T.; Asano, H.; Wakasugi, K.; Morita, J.; Aso, Y.; Yoshida, E.; Motoyoshiya, J.; Aoyama, H.; Tanabe, Y. *J. Org. Chem*. **2005**, *70*, 2667 and other references cited therein.

(9) Anionic-type reactions and their application: (a) Nishii, Y.; Wakasugi, K.; Tanabe, Y. *Synlett* **1998**, 67. (b) Nishii, Y.; Wakimura, K.; Tsuchiya, T.; Nakamura, S.; Tanabe, Y. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1243. (c) Nishii, Y.; Maruyama, N.; Wakasugi, K.; Tanabe, Y. *Bioorg. Med. Chem.* **2001**, *9*, 33.

(10) **Typical Procedure.** (a) 7,7-Dichlorobicyclo[4.1.0]heptane (**1g**) (165 mg, 1.00 mmol), AIBN (33 mg, 0.20 mmol), Bu_3SnH (349 mg, 1.20 mmol), and benzene (50 mL) were placed in a 100-mL stainless steel autoclave with a inserted glass tube. The mixture was stirred under CO pressure (80 atm) at 80 °C for 3 h. After temporary release of CO pressure, AIBN (33 mg, 0.20 mmol) was added to the mixture. Then, the mixture was stirred under CO pressure (80 atm) at 80 °C for 3 h. After evacuation of excess CO at room temperature, benzene was removed under reduced pressure. The residue was stirred for 1 h with Et_2O (10 mL) and aqueous satd KF solution (10 mL). After Celite filtration, the separated organic phase was washed with water and brine, dried (Na_2SO_4), and concentrated. The obtained crude product was purified by SiO_2 column chromatography (hexane) to give the desired product **2g** (87 mg, 55 %). (b) Following the procedure mentioned above, the reaction of 1-bromo-1-chlorobicyclo[4.1.0]-heptane (**1l**) (210 mg, 1.00 mmol) with 0.2 equiv of AIBN (33 mg, 0.20 mmol, added once) instead of the procedure using 0.2 equiv added twice gave the desired product **2g** (108 mg, 73%): ^1H NMR (400 MHz, $CDCl_3$) δ 1.24−1.35 (m, 2H), 1.39−1.47 (m, 2H), 1.62−1.69 (m, 2H), 1.90−1.94 (m, 2H), 1.97−2.06 (m, 2H), 9.43 (s, 1H, CHO); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.7, 20.8, 25.9, 58.7, 198.5; IR (neat) 2939, 2858, 1709, 1447 cm^{-1}; HRMS (EI) calcd for $C_8H_{11}ClO$ (M^+) 158.0498, found 158.0498.

pected, allylacylation (sequential carbonylation and allylation) proceeded smoothly using **1a**,**b**,**d**,**g**,**h**−**o** (Table 2).[11]

Table 2. Stereoselective Radical-Type Allylacylation of *gem*-Dihalocyclopropanes **1**[a]



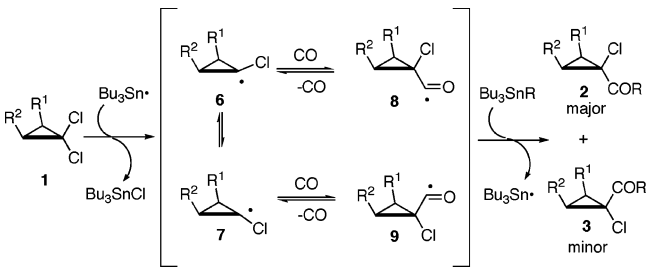
1 **4** (*trans*) **5** (*cis*) **5c, n, o**

entry	substrate	X^1	X^2	R^1	R^2	R^3	R^4	yield[b] (%)	ratio[c] of **4**/**5**
1	**1a**	Cl	Cl	Ph	H	H	H	51	>99:1
2	**1b**	Cl	Cl	Hex	H	H	H	47	>99:1
3	**1d**	Cl	Cl	CH_2OH	H	Me	H	38	<1:99
4	**1g**	Cl	Cl	$-(CH_2)_4-$	H	H		54	>99:1
5	**1h**	Cl	Cl	$-(CH_2)_6-$	H	H		48	>99:1
6	**1i**	Br	Br	$-(CH_2)_4-$	H	H		17[d]	>99:1
7	**1j**	Br	Cl	Ph	H	H	H	58	>99:1
8	**1k**	Br	Cl	Hex	H	H	H	53	>99:1
9	**1l**	Br	Cl	$-(CH_2)_4-$	H	H		64	>99:1
10	**1m**	Br	Cl	$-(CH_2)_6-$	H	H		54	>99:1
11	**1n**	Br	Cl	CH_2OH	H	Me	H	68	<1:99
12	**1o**	Br	Cl	CH_2OH	H	Me	Ph	35	<1:99

[a] Reactions were carried out under CO pressure (40 atm) at 80 °C. 0.4 equiv (0.2 equiv added twice) of AIBN was used for **1a**−**h**, 0.2 equiv (added once) for **1j**−**o**. [b] Isolated yield. [c] Determined by ^{1}H NMR measurement. [d] An unidentified complex byproduct was obtained.

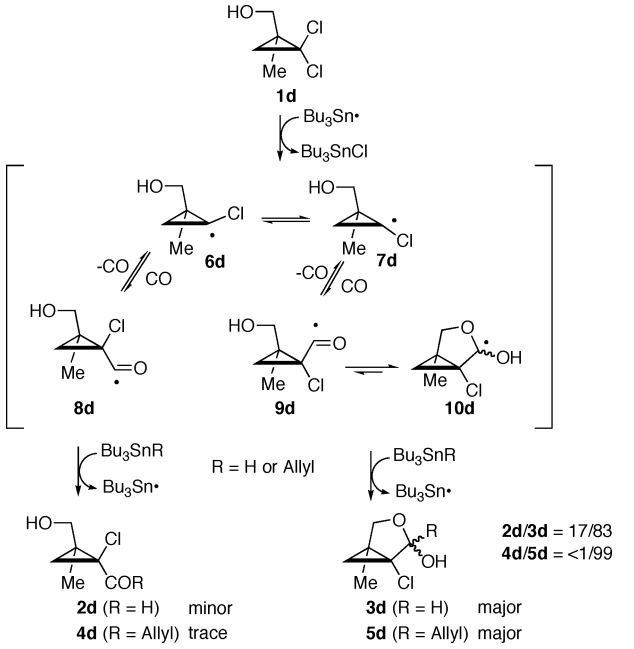
The most notable feature is that the present reaction was performed with nearly complete trans as well as cis selectivity (t/c = >99/1 for **1a**,**b**,**d**,**g**−**m** and t/c = <1/99 for **1d**,**n**,**o**) for every case examined. The present protocol can be applied for not only 2,3-disubstituted substrates but also 2-monosubstituted analogues, which are unfavorable substrates with regard to stereoselectivity.[7a] On this exclusive selectivity switch, we speculate that the final allylation step markedly enhances the trans selectivity. Similar to the preceding formylation, bromochloro analogues **1j**−**n** underwent the allylacylation more smoothly than the dichloro analogues (entries 1−5,7−11).

Scheme 2



We propose the following mechanism to explain the stereoselectivity issue (Schemes 2 and 3). Initially generated trans radical **6** more preferentially adds to CO than cis radical **7** to give mainly **2** because of the stereocongestion between R^1 (and/or R^2) and CO. Hydroxymethyl substrate **1d** undergoes cyclization to give *cis*-lactol **3d** through sterically unfavorable cis radical **9d** and stable lactol radical **10d**. This irreversible process from **9d** to **10d** drives an equilibrium shift from **6d** to **7d**, eventually giving **3d** as the major product.[12,13] The case of allylacylation amplifies the stereoselectivity due to the additional stereocongestion in the final product-determining allylation step.

Scheme 3



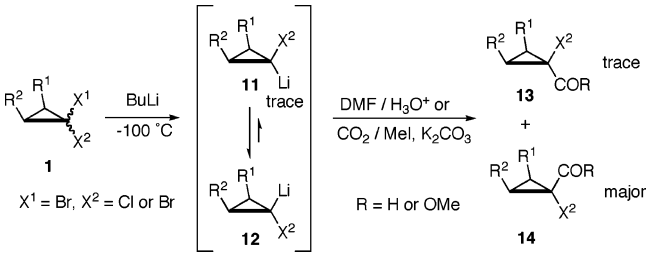
As the literature showed, lithium halocarbenoid on 2,3-cis disubstituted or 2-monosubstituted cyclopropane rings favors conformation **12** rather than **11**, wherein lithium

(11) **Typical Procedure.** (a) 1,1-Dichloro-2-phenylcyclopropane (**1a**) (187 mg, 1.00 mmol), AIBN (33 mg, 0.20 mmol), $Bu_3Sn(CH_2CH{=}CH_2)$ (662 mg, 2.00 mmol), and benzene (30 mL) were placed in a 100-mL stainless steel autoclave with a insert glass tube. The mixture was stirred under CO pressure (40 atm) at 80 °C for 12 h. After temporary release of CO pressure, AIBN (33 mg, 0.20 mmol) was added to the mixture. Then, the mixture was stirred under CO pressure (40 atm) at 80 °C for 12 h. After evacuation of excess CO at room temperature, benzene was removed under reduced pressure. The residue was stirred for 1 h with Et_2O (10 mL) and aqueous satd KF solution (10 mL). The residue was stirred for 1 h with Et_2O (10 mL) and aqueous satd KF solution (10 mL). After Celite filtration, the separated organic phase was washed with water and brine, dried (Na_2SO_4), and concentrated. The obtained crude product was purified by SiO_2 column chromatography (hexane/EtOAc = 3/1) to give the desired product **4a** (113 mg, 51%). (b) Following the procedure mentioned above, the reaction of 1-bromo-1-chloro-2-phenylcyclopropane (**1j**) (210 mg, 1.00 mmol) with 0.2 equiv of AIBN (33 mg, 0.20 mmol, added once) instead of the procedure using 0.2 equiv added twice gave the desired product **4a** (126 mg, 58%). **4a**: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.73 (dd, J = 7.0 Hz, J = 10.1 Hz, 1H), 2.21 (dd, J = 7.0 Hz, J = 10.1 Hz 1H), 3.01 (dd, J = 7.0 Hz, J = 10.1 Hz, 1H) 3.68 (m, 2H), 5.16−5.26 (m, 2H), 5.94−6.04 (m, 1H), 7.20−7.24 (m, 2H), 7.29−7.37 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.0, 36.3, 44.8, 52.5, 119.0, 127.6, 128.1, 129.3, 130.2, 134.6, 204.5; IR (neat) 2843, 1716, 1640, 1497 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{13}ClO$ (M^+) 220.0655, found 220.0656.

(12) Intra- and intermolecular traps of acyl radicals by amino groups were reported: (a) Tojino, M.; Uenoyama, Y.; Fukuyama, T.; Ryu, I. *Chem. Commun*. **2004**, 2482. (b) Uenoyama, Y.; Fukuyama, T.; Nobuta, O.; Matsubara, H.; Ryu, I. *Angew. Chem., Int. Ed.* **2005**, *44*, 1075.

(13) Baird, M. S.; Huber, F. A. M. *Tetrahedron Lett.* **1998**, *39*, 9081.

Scheme 4



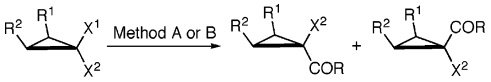
locates in the concave site (Scheme 4).[14] Therefore, this anionic carbonylation (method A) and carboxylation (method B) is anticipated to proceed to give cis adduct **14** more preferentially than trans adduct **13**. Indeed, either method (A or B) utilizing the BuLi−DMF reagent or the BuLi−CO_2 reagent (followed by methylation using MeI−K_2CO_3) successfully afforded the desired product **14** with nearly complete selectivity in every case examined (Table 3).

The stereocomplemented result of the present radical carbonylations vs the reported anionic method demonstrates the utility from a synthetic viewpoint.

In conclusion, we developed a few stereoselective syntheses of cyclopropane derivatives utilizing highly stereoselective radical carbonylations (formylation and allylacylation) of *gem*-dihalocyclopropanes. The present method is a new avenue for the stereoselective synthesis of cyclopropylcarbonyl compounds.

(14) (a) Oku, A.; Harada, T.; Homoto, Y.; Iwamoto, M. *J. Chem. Soc., Chem. Commun*. **1988**, 1490. (b) Seyferth, D.; Lambert, R. L.; Massol, M. *J. Organomet. Chem*. **1975**, *88*, 255. (c) Banwell, M. G.; Reumin, M. E. *Advances in Strain in Organic Chemistry*; Halton. B., Ed.; JAI Press: Greenwich, CT, 1991; Vol. 1, p 19.

Table 3. Stereoselective Anionic Carbonylation and Carboxylation of *gem*-Dihalocyclopropanes **1**[a]



entry	substrate	method[a]	X^1	X^2	R^1	R^2	R	yield (%)
1	**1i**	A	Br	Br	$-(CH_2)_4-$		H	65
2	**1i**	B	Br	Br	$-(CH_2)_4-$		OMe	64
3	**1l**	A	Br	Cl	$-(CH_2)_4-$		H	43
4	**1l**	B	Br	Cl	$-(CH_2)_4-$		OMe	47
5	**1p**	A	Br	Br	Ph	H	H	64
6	**1p**	B	Br	Br	Ph	H	OMe	57
7	**1q**	B	Br	Br	Bu	H	OMe	36

[a] Method A: BuLi, DMF. Method B: (i) BuLi, CO_2, (ii) K_2CO_3, MeI.

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Supporting Information Available: Experimental details, analytical data, and characterization data for reactions in Tables 1−3. This material is available free of charge via the Internet at http://pubs.acs.org.

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