SmI₂-Promoted Reformatsky-Type Reaction and Acylation of Alkyl 1-Chlorocyclopropanecarboxylates
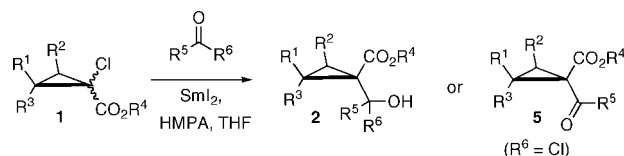
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ABSTRACT

In the presence of HMPA in THF, highly stereoselective SmI₂-promoted substitutions of alkyl 1-chlorocyclopropanecarboxylates 1 using various ketones, aldehydes (Reformatsky-type reaction), and acyl chlorides (acylation) proceeded to give *trans*-adducts (2 or 5) in good to high yield with excellent *trans*-stereoselectivity (*trans*-add/*cis*-add = > 99/1). The Reformatsky-type reaction of 1 with aldehydes and unsymmetrical ketones proceeded with moderate diastereoselectivity (*re*-face-adduct/*si*-face-adduct = 60/40–75/25).

The Reformatsky reaction, which involves the zinc-promoted addition of α-halo esters to ketones or aldehydes, has been recognized as a fundamental and useful C−C bond-forming reaction in organic synthesis.[1] Recently, various efficient Reformatsky-type reactions have been reported.[2,3] Among them, most of the SmI₂-promoted Reformatsky-type reactions of α-halo esters have been applied to intramolecular cyclizations.[3c−j] SmI₂ has found little use in intermolecular Reformatsky-type reactions due to numerous side reactions,

such as self-coupling of aldehyde or ketone,[4] self-Claisen condensation,[5a,b] and self-coupling of α-halo esters.[5c]

On the other hand, stepwise or sequential double transformation of the two carbon−halogen bonds of *gem*-dihalocyclopropanes into carbon−carbon bonds is useful for

(1) (a) Reformatsky, S. *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 1210. For a recent review of Reformatsky reactions, see: (b) Fürstner, A. *Synthesis* **1989**, 571. (c) Ocampo, R.; Dolbier, W. R., Jr. *Tetrahedron* **2004**, *60*, 9325. (d) Orsini, F.; Sello, G. *Curr. Org. Synth.* **2004**, *1*, 111. (e) Cozzi, P. G. *Angew. Chem., Int. Ed.* **2007**, *46*, 2568.

(2) (a) Wessjohann, L.; Gabriel, T. *J. Org. Chem.* **1997**, *62*, 3772. (b) Kanai, K.; Wakabayashi, H.; Honda, T. *Org. Lett.* **2000**, *2*, 2549. (c) Kakiya, H.; Nishimae, S.; Shinokubo, H.; Oshima, K. *Tetrahedron* **2001**, *57*, 8807. (d) Durandetti, M.; Meignein, C.; Périchon, J. *Org. Lett.* **2003**, *5*, 317. (e) Yanagisawa, A.; Takahashi, H.; Arai, T. *J. Chem. Soc., Chem. Commun.* **2004**, 580–581. (f) Babu, S. A.; Yasuda, M.; Shibata, I.; Baba, A. *J. Org. Chem.* **2005**, *70*, 10408. (g) Durandetti, M.; Gosmini, C.; Perichon, J. *Tetrahedron* **2007**, *63*, 1146. (h) Lombardo, M.; Gualandi, A.; Pasi, F.; Trombini, C. *Adv. Synth. Catal.* **2007**, *349*, 465. (i) Cozzi, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 2951. (j) Fernández-Ibáñez, M. Á.; Maciá, B.; Minnaard, A. J.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1317, and references cited therein.

(3) SmI₂-promoted Reformatsky-type reaction of Evans amide: (a) Fukuzawa, S.; Matsuzawa, H.; Yoshimitsu, S. *J. Org. Chem.* **2000**, *65*, 1702. (b) Sparling, B. A.; Moslin, R. M.; Jamison, T. F. *Org. Lett.* **2008**, *10*, 1291. For recent reviews of SmI₂-promoted reactions, see: (c) Molander, G. A.; Harris, C. H. *Chem. Rev.* **1996**, *96*, 307–338. (d) Kagan, H. B.; Namy, J. L. *Top. Organomet. Chem.* **1999**, *2*, 155. (e) Krief, A.; Laval, A.-M. *Chem. Rev.* **1999**, *99*, 745. (f) Kagan, H. B.; Namy, J. L. *Tetrahedron* **1986**, *42*, 6573. (g) Steel, P. G. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2727–2751. (h) Berndt, M.; Gross, S.; Hemann, A.; Reissig, H.-U. *Synlett* **2004**, 422. (i) Concell, J. M.; Rodriguez-Solla, H. *Chem. Soc. Rev.* **2004**, *33*, 599. (j) Edmonds, D. J.; Johnston, D.; Procter, D. *J. Chem. Rev.* **2004**, *104*, 3371.

(4) SmI₂-promoted self-coupling of α-bromo ester in THF−HMPA: (a) Balaux, E.; Ruel, R. *Tetrahedron Lett.* **1996**, *37*, 801. SmI₂-promoted self-Claisen condensation of α-bromo ester: (b) Park, H. S.; Lee, I. S.; Kim, Y. H. *Tetrahedron Lett.* **1995**, *36*, 1673. (c) Utimoto, K.; Matsui, T.; Takai, T.; Matsubara, S. *Chem. Lett.* **1995**, 197.

(5) For a discussion of SmI₂-promoted self-coupling of ketones and aldehydes, see: (a) Namy, J. L.; Souppe, J.; Kagan, H. B. *Tetrahedron Lett.* **1983**, *24*, 765. (b) Fürstner, A.; Csuk, R.; Rohrer, C.; Weidmann, H. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1729. (c) Akane, N.; Kanagawa, Y.; Nishiyama, Y.; Ishii, Y. *Chem. Lett.* **1992**, 2431. (d) Shiue, J.-S.; Lin, C.-C.; Fang, J.-M. *Tetrahedron Lett.* **1993**, *34*, 335. (e) Aspinall, H. C.; Greeves, N.; Valla, C. *Org. Lett.* **2005**, *7*, 1919.

the synthesis of functionalized cyclopropanes because of the preparative accessibility of *gem*-dihalocyclopropanes (Scheme 1).[6,7] However, most of the efficient methods have been
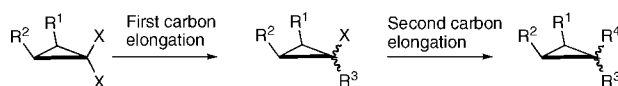
applied to *gem*-dibromo derivatives, which have a higher reactivity than *gem*-dichloro derivatives during such reactions.

As part of our ongoing synthetic studies on the transformation of *gem*-dihalocyclopropanes,[8] we have recently reported highly stereoselective radical-type carbonylations of *gem*-dichlorocyclopropane derivatives with CO using Bu$_3$SnH or Bu$_3$Sn(CH$_2$CH=CH$_2$).[8c] To complete the second carbon elongation from *gem*-dichlorocyclopropane, we disclose herein a highly stereoselective SmI$_2$-promoted Reformatsky-type intermolecular reaction of **1** with aldehydes, ketones, and acyl chlorides.

Alkyl 1-chlorocyclopropanecarboxylates **1** were derived from *gem*-dichlorocyclopropanes in three steps: (i) radical-type carbonylation[8c] (formylation), (ii) Jones oxidation, and (iii) alkylation (Scheme 2, eq 1). Ester **1** can be prepared by
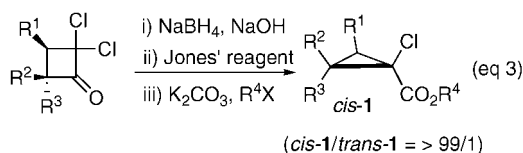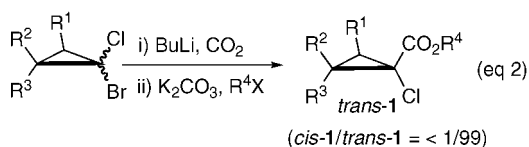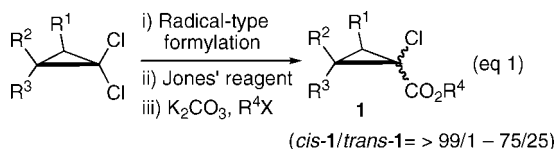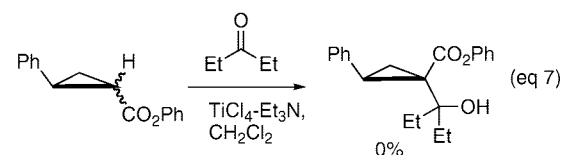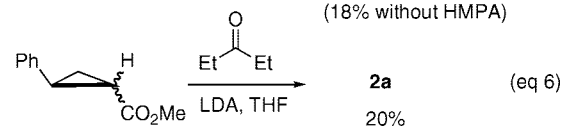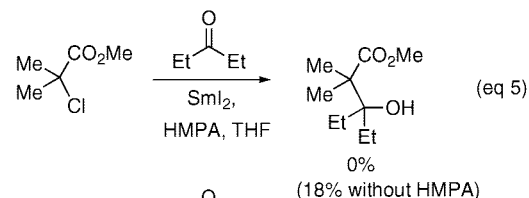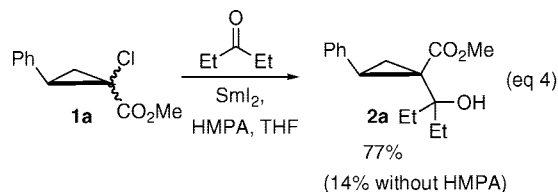
using other methods. *trans*-**1** (in this case, *trans* means *trans*-Cl) can be prepared via anionic carboxylation of bromochlorocyclopropanes (eq 2).[8c] On the other hand, *cis*-**1** can be prepared via rearrangement of 2,2-dichlorocyclobutanols which are generated by reducing 2,2-dichlorocyclobutanones with NaBH$_4$ (eq 3).[9]

(6) For a recent review, see: Fedorynski, M. *Chem. Rev.* **2003**, *103*, 1099, and references cited therein.

The initial investigation was guided by the reaction of methyl 1-chlorocyclopropanecarboxylate **1a** with diethyl ketone (Scheme 3, eq 4). The SmI$_2$-promoted Reformatsky-

type reaction of **1a** with diethyl ketone at rt gave *β*-hydroxy ester **2a** (14% yield) along with a pinacol (75% yield), which is afforded due to self-coupling of the ketone. The reaction in the presence of HMPA (4.0 equiv) proceeded to give **2a** in high yield (77%). Self-coupling of the ester did not occur under the reaction conditions. In the case of methyl α-chloro isobutyrate, the presence of HMPA adversely affected the Reformatsky-type reaction, causing the competitive self-coupling of ketones and hydrodechlorination of α-chloro esters to occur (Scheme 3, eq 5). The cyclopropyl case was successful unlike the acyclic case, which would have been caused by the difference between the reaction on the highly strained sp^3 carbon of cyclopropane ring and that on normal sp^3 carbon.[10] Hydroxyalkylation of methyl cyclopropanecar-

(7) (a) Vu, V. A.; Marek, I.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 351. (b) Inoue, R.; Shinokubo, H.; Oshima, K. *Tetrahedron Lett.* **1996**, *37*, 5377. (c) Harada, T.; Kastuhira, T.; Hattori, K.; Oku, A. *J. Org. Chem.* **1993**, *58*, 2958. (d) Danheiser, R. L.; Savoca, A. C. *J. Org. Chem.* **1985**, *50*, 2401. (e) Kitatani, K.; Hiyama, T.; Nozaki, H. *J. Am. Chem. Soc.* **1975**, *97*, 949; *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1600. (f) Scott, F.; Mafunda, B. G.; Normant, J. F.; Alexakis, A. *Tetrahedron Lett.* **1983**, *24*, 5767. (g) Corey, E. J.; Posner, G. H. *J. Am. Chem. Soc.* **1967**, *89*, 3911; **1968**, *90*, 5615.

(8) (a) Nishii, Y.; Wakasugi, K.; Koga, K.; Tanabe, Y. *J. Am. Chem. Soc.* **2004**, *126*, 5358. (b) 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. (c) Nishii, Y.; Nagano, T.; Gotoh, H.; Nagase, R.; Motoyoshiya, J.; Aoyama, H.; Tanabe, Y. *Org. Lett.* **2007**, *9*, 563, and references cited therein.

(9) Verniest, G.; Bombeke, F.; Kulinkovich, O. G.; Kimpe, N. D. *Tetrahedron Lett.* **2002**, *43*, 599.

boxylate using LDA gave β-hydroxy ester **2a** in low yield (20%) because retro-aldol reaction, self-Claisen condensation, and further side reaction occurred (Scheme 3, eq 6).[11] A similar reaction of phenyl cyclopropanecarboxylate using TiCl$_4$–Et$_3$N did not proceed to give a β-hydroxy ester, but instead, the self-aldol reaction of ketone mainly occurred (Scheme 3, eq 7).[12] This result means that the Ti-enolate is not generated under the reaction conditions. Thus, the SmI$_2$-promoted Reformatsky-type reaction of **1a** in the presence of HMPA was found to be the most efficient method for the synthesis of **2a**. Next, we investigated the generality of the reaction.

Table 1 lists the results of the Reformatsky-type reaction of **1** with various ketones and aldehydes. The salient features

Table 1. Stereoselective SmI$_2$-Promoted Reformatsky-Type Reaction of Alkyl 1-Chlorocyclopropanecarboxylates **1**[a]

$trans$-add/cis-add = > 99/1 [b]
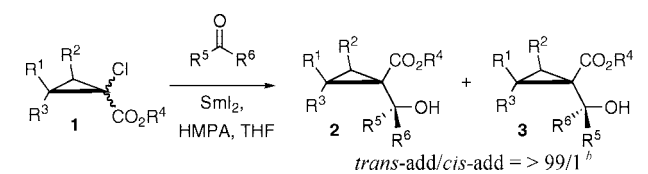
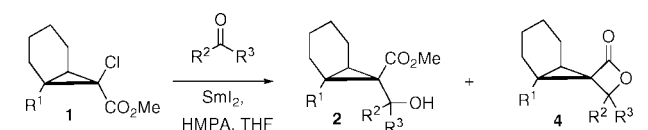| entry	substrate[c]	R^1	R^2	R^3	R^4	R^5	R^6	product	yield[d] (%)	ratio[e] of 2/3
1	**1a**	Ph	H	H	Me	Et	Et	**2a**	77	
2	**1a**					i-Pr	i-Pr	**2b**	95	
3	**1a**					—(CH$_2$)$_4$—		**2c**	82	
4	**1a**					Me	Ph	**2d, 3d**	82	67/34
5	**1a**					Me	t-Bu	**2e, 3e**	93	75/25
6	**1a**					H	t-Bu	**2f, 3f**	82	75/25
7	**1b**	Hex	H	H	Me	Et	Et	**2g**	90	
8	**1c**	—(CH$_2$)$_4$—		H	Me	Et	Et	**2h**	83	
9	**1c**					i-Pr	i-Pr	**2i**	68	
10	**1c**					—(CH$_2$)$_4$—		**2j**	71	
11	**1c**					H	Hept	**2k**	78	
12	**1c**					H	Ph	**2l**	81	
13	**1c**					H	t-Bu	**2m**	82	
14	**1d**	—(CH$_2$)$_6$—		H	Me	Et	Et	**2n**	86	
15	**1d**					—(CH$_2$)$_4$—		**2o**	87	
16	**1e**	Ph	H	H	Et	Et	Et	**2p**	91	
17	**1f**					i-Pr		**2q**	83	
18	**1g**					Bn		**2r**	80	
19	**1h**	—(CH$_2$)$_4$—		H	Et			**2s**	86	
20	**1i**					i-Pr		**2t**	77	
21	**1j**					Bn		**2u**	79	
22	**1k**	Ph	H	Me	Me	Et	Et	**2v**	79	
23	**1k**					H	Hept	**2w, 3w**	88	75/25
24	**1l**	—(CH$_2$)$_4$—		Me	Me	H	Hept	**2x, 3x**	72	60/40

[a] Reactions were carried out under an Ar atmosphere at rt (using ketones: entries 1–5, 7–10, and 14–22) or −78 °C (using aldehydes: entries 6, 11–13, 23, and 24). [b] Determined by using ^{1}H NMR spectroscopy. In this case, $trans$-add means $trans$-adduct. [c] A 3/1 mixture of cis-**1** and $trans$-**1** (in this case, cis means cis-Cl) was used for the reaction of **1a**, **1b**, whereas cis-**1** was used for the reaction of **1c**, **1d**, and **1e**–**l**. [d] Isolated. [e] Determined by using ^{1}H NMR spectroscopy.

were as follows: (i) R^1-monosubstituted-1-chlorocyclopropanecarboxylates **1a,b,e–g** underwent the desired Reformatsky-type addition with ketones and aldehydes to give $trans$-adducts **2a,b,e–g**, respectively, with excellent stereoselectivity ($trans$-add/cis-add = >99/1) (entries 1–7 and 16–18). The relative configuration of **2b** was unambiguously determined by using

X-ray crystallographic analysis. The structures ($trans$-adduct) of β-hydroxy esters **2a** and **2c**–**x** were determined by analogy with **2b** on the basis of their spectral data. (ii) Similar reactions of 2,3-cis-disubstituted cyclic substrates **1c**, **d,h–j** also gave the corresponding $trans$-adducts ($trans$-add/cis-add = >99/1) (entries 8–15 and 19–21). In these cases, cis-**1** was used for the reactions because the preparative method (radical formylation) afforded only the cis-isomer. Thus, $trans$-addition occurred with almost complete inversion. (iii) In the case of 2,2-disubstituted substrate **1k** and 2,2,3-trisubstituted substrate **1l**, both reactions proceeded with excellent $trans$-selectivity, avoiding the stereocongestion between the larger substituent R^1 (and/or R^2) on the cyclopropane ring and ketone or aldehyde (entries 22–24). (iv) Reactions with aldehydes or unsymmetrically substituted ketones also proceeded in high yield with excellent $trans$-selectivity ($trans$-add/cis-add = >99/1) at the α-position and moderate to good diastereoselectvity[13] [**2** (re-face-adduct)/**3** (si-face-adduct) = 60/40–75/25] at the β-position (entries 4–6, 23, and 24). (v) The main side reaction was a competitive self-coupling of aldehydes or ketones, which caused a decrease in the yields. (vi) The reaction with ketone was carried out at rt, whereas the reaction with aldehyde at −78 °C. In the case of aldehydes, at rt, a competitive self-coupling reaction of the aldehydes mainly occurred.

An increase in the stereocongestion around the newly formed C–C bond caused lactonization to give β-lactones **4**, instead of the retro-aldol reaction[14] (Table 2). The reaction

Table 2. Stereoselective SmI$_2$-Promoted Reformatsky-Type Reaction of Methyl 1-Chlorocyclopropanecarboxylates **1** To Afford β-Lactones **4**[a]

entry	substrate	R^1	R^2	R^3	T (°C)	product	yield[b] (%) 2	yield[b] (%) 4
1	**1c**	H	Me	t-Bu	rt	**4y**	0	80
2	**1l**	Me	Et	Et	rt	**2z,4z**	25	63
3	**1l**				−78	**4z**	0	84
4	**1l**		iPr	iPr	−78	**4α**	0	73

[a] Reactions were carried out under an Ar atmosphere. [b] Isolated.

of α-chloro ester **1c** with diisopropyl ketone and pivalaldehyde occurred to give β-hydroxy esters **2i** and **2m** in good to high yield, respectively (Table 1, entry 9, and 13). Notably,

(10) The reactivity of C–Cl on the cyclopropane ring is higher than that on the normal sp^3-carbon of methyl α-chloro isobutyrate. The stereocongestion around the newly formed C–C bond of **2** is less than that of acyclic α,α-dimethyl β-hydroxy ester because of the strained angle of the cyclopropane ring.

(11) For discussion of side reactions, see: (a) Pinnick, H. W.; Chang, Y.-H.; Foster, S. C.; Govindan, M. *J. Org. Chem.* **1980**, *45*, 4505. (b) Kai, Y.; Knochel, P.; Kwiatkowski, S.; Dunitz, J. D.; Oth, J. F. M.; Seebach, D.; Kalinowski, H. O. *Helv. Chim. Acta* **1982**, *65*, 137. For a similar reaction of siloxy-substituted derivatives, see: (f) Brückner, C.; Reissig, H.-U. *J. Org. Chem.* **1988**, *53*, 2440.

a similar reaction of **1c** with *t*-butyl methyl ketone gave only *β*-lactone **4y** (Table 2, entry 1). The reaction of **1l** with diethylketone at rt proceeded to give a mixture of *β*-hydroxy ester **2z** and *β*-lactone **4z** (Table 2, entry 2). Treatment of **2z** with NaH gave **3z** in quantitative yield.[15] The yield of **4z** increased at −78 °C (Table 2, entry 3). A similar reaction of **1l** with diisopropyl ketone also proceeded smoothly to give *β*-lactone **4α** (Table 2, entry 4).

These successful results led us to investigate the SmI$_2$-promoted acylation of methyl 1-chlorocyclopropanecarboxy-lates with acyl chlorides. As expected, acylation of **1a** and **1c** proceeded smoothly (Table 3). It should be noted that

Table 3. Stereoselective SmI$_2$-Promoted Acylation of Methyl 1-Chlorocyclopropanecarboxylates **1**[a,b]

trans-add/*cis*-add = > 99/1[c]
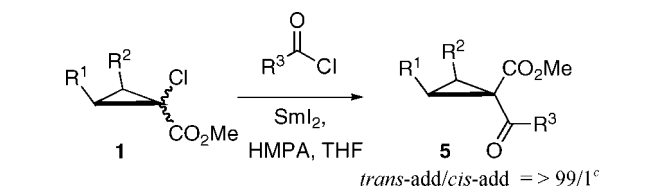
entry	substrate[d]	R[1]	R[2]	R[3]	product	yield[e] (%)
1	**1a**	Ph	H	Hept	**5a**	88
2	**1a**			*t*-Bu	**5b**	89
3	**1a**			Ph	**5c**	92
5	**1c**	−(CH$_2$)$_4$−		Hept	**5d**	89
6	**1c**			*t*-Bu	**5e**	78
7	**1c**			Ph	**5f**	82

[a] Reactions were carried out at −78 °C under an Ar atmosphere. [b] Acylchloride was added after generation of Sm-enolate. [c] In this case, *trans* means *trans*-adduct. Ratios were determined from ^{1}H NMR spectra. [d] A mixture of *cis*-**1a** and *trans*-**1a** (*cis*/*trans* = 3/1) was used for the reaction of **1a**, whereas *cis*-**1c** was used for the reaction of **1c**. [e] Isolated.

the reactions proceeded with nearly complete *trans*-selectivity (*trans*-add/*cis*-add = >99/1) for every case examined. Under the reaction conditions, self-coupling or self-Claisen con-densation of esters **1** did not occur.[4]

Due to the high *trans*-selectivity of the present reactions, we believe that the reaction proceeds via a samarium enolate

intermediate,[11a,16] which reacts with carbonyl compounds on only the *trans*-face because of the stereocongestion between R[1] (and/or R[2]) and the carbonyl compounds (ketones, aldehydes, or acyl chlorides) (Scheme 4). Detailed studies on the reaction mechanism are now being performed.

Scheme 4. Proposed Mechanism of the SmI$_2$-Promoted Reformatsky-Type Reaction
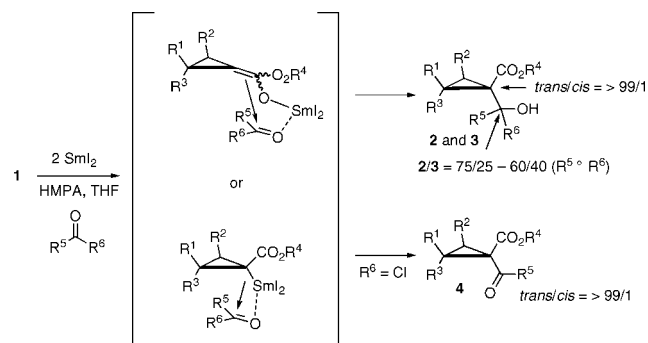
In conclusion, we developed a stereoselective synthesis of cyclopropane derivatives utilizing a highly stereoselective SmI$_2$-promoted Reformatsky-type reaction and acylation of 1-chlorocyclopropanecarboxylic esters. The present method is a new avenue for the stereoselective synthesis of highly substituted cyclopropylcarbonyl compounds. Utilizing radical formylation and the present protocols, we achieved a highly stereoselective double-carbon elongation on the dichloro-carbon of *gem*-dichlorocyclopropanes.

Note Added after ASAP Publication. The version published ASAP on November 7, 2008 contained errors in Table 1; the corrected version was published ASAP on November 11, 2008.

Supporting Information Available: Experimental details, analytical and crystallographic data, and characterization 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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(12) The use of phenyl esters has an advantage over that of methyl esters under the reaction condition, see: Nagase, R.; Matsumoto, N.; Hosomi, K.; Higashi, T.; Funakoshi, S.; Misaki, T.; Tanabe, Y. *Org. Biomol. Chem.* **2007**, *5*, 151.

(13) The relative structure of **2/3** (*re*-face-add/*si*-face-add) was assigned on the basis of the typical selectivity of SmI$_2$-promoted Reformatsky reaction (see ref 3) and Shuto's report of highly stereoselective reduction of *trans*-substituted cyclopropanes; see: Kazuta, Y.; Abe, H.; Yamamoto, T.; Matsuda, A.; Shuto, S. *J. Org. Chem.* **2003**, *68*, 3511.

(14) For discussion of the retro-aldol reaction, see: (a) *March's Advanced Organic Chemistry*, 5th ed.; Smith, M. B., March, J., Eds.; Wiley-Interscience: New York, 2001; p 1220. (b) Murakami, K.; Ohmiya, H.; Yorimitsu, H.; Oshima, K. *Tetrahedron Lett.* **2000**, *49*, 2388. (c) Houminer, Y.; Kao, J.; Seeman, J. I. *J. Chem. Soc., Chem. Commun.* **1984**, 1608. (d) Hatano, M.; Takagi, E.; Ishihara, K. *Org. Lett.* **2007**, *9*, 4527.

(15) In contrast, in the similar treatment of **2h** with NaH, a retro-aldol reaction occurred to give methyl bicyclo[4.1.0]heptane-7-carboxylate in 87% yield.

(16) (a) Molander, G. A.; Etter, J. B.; Harring, L. S.; Thorel, P.-J. *J. Am. Chem. Soc.* **1991**, *113*, 8036. (b) Utimoto, K.; Matsui, T.; Takai, T.; Matsubara, S. *Chem. Lett.* **1995**, 197. For a discussion of the pyramidal enolate of cyclopropanecarboxylate, see: (c) Reissig, H.-U.; Böhm, I. *J. Am. Chem. Soc.* **1982**, *104*, 1735.