JOC*Note*

1,2-Acyl Transfer Reaction for the Construction of Multiple Carbonyl-Functionalized Architecture by Sm(II)-Induced Tandem Formation and Breaking of Cyclopropanol

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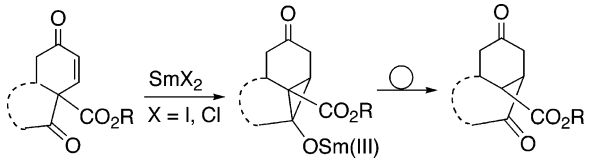

An efficient 1,2-acyl group migration reaction based on contiguous formation and breaking tactics of 1-oxycyclopropane-2-carboxylate as an intermediate is developed. Thus, the reduction of 2-cyclohexenones, bearing *gem*-acyl/alkoxycarbonyl groups at the C4 position, with Sm(II) reagent leads to 2-acyl-4-oxycyclohexanecarboxylates via cyclization followed by retro-aldol cleavage of the resulting donor/acceptor cyclopropane. Mechanistic insights and the scope of the reaction are described.

Michael addition of a masked acyl anion equivalent to the conjugated enone followed by revival of the carbonyl function is commonly used to construct an alkanoyl (acyl) group at the β-position of the carbonyl function.[1] However, the 1,4-addition reaction of the carbanion reagents is limited by functional group tolerance and hampered by steric hindrance with a decrease of efficiency. In contrast, 1,2-acyl group migration,[2] if achieved in a ring system, is considered to be a powerful tactic for construction of the carbonyl-functionalized architecture in a stereoselective manner. We envisioned that the 1,2-acyl group migration would be achieved by use of the breaking tendency of 2-oxycyclopropanecarboxylates to 4-oxoalkanoates.[3] Accordingly, we developed a new method to construct 2-oxy-1-carboxycyclopropane system **ii** on the cyclohexane via the radical ion cyclization of 4-acyl-2-cyclohexenone **i**, which would spontaneously undergo ring cleavage to regenerate the acyl function, giving the 1,2-acyl group-shifted **iii**, a potent intermediate for the synthesis of perhydroindanones (Scheme 1).

Thus far, intermolecular and intramolecular addition of a radical ion species, generated by the reduction of carbonyl compounds including enones and enoates with SmI_2, to C=C and C=O multiple bonds has been extensively studied.[4] However, cyclization to form the corresponding cycloporpanols has scarcely been realized.[5] We have therefore explored the radical ion cyclizaton of the 4-acyl-2-enone system of **i** to form **ii** and studied the relative stereochemistry of the migrated acyl group to a substituent Y on **iii**.

We employed 1-acyl-4-oxo-2-cyclohexene-1-carboxylate **1** as the substrate that can easily be obtained by the Lewis acid-catalyzed Diels−Alder reaction of alkylidene- or arylideneacetoacetates and activated dienes.[6] As shown in Table 1, the treatment of **1a** with a THF solution of SmI_2 (4−6 equiv) in the presence of *tert*-butyl acetoacetate as a proton donor[7] smoothly produced the desired 2-acyl-4-oxocyclohexanecarboxylate **2a** as a separable 1:1 diastereomeric mixture in 73% yield (run 1). The yields were easily improved to 88−90% by adding 1,3-dimethyl-2-imidazolidinone (DMI) to the reaction media (runs 2 and 3).[8] A similar additive effect was also found with HMPA and DMPU.[9a,b] A higher yield (93%) of **2a** than that of the above was obtained by using $SmCl_2$, generated in situ by mixing SmI_2 with LiCl in THF,[10] in the presence of *t*-BuOH (run 4).[9c] Our attempts with other reducing reagents such as sodium naphthalenide or lithium di-*tert*-butylbiphenylide (LDBB) were unsuccessful; no distinct products were characterized.

Isomers separated by column chromatography were tentatively assigned as the indicated structures, *cis*/*trans*-**2a** and *trans*/*cis*-**2a**, which were the stereoisomers at the C1 carbon. The trans and cis stereochemistry of the

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SCHEME 1

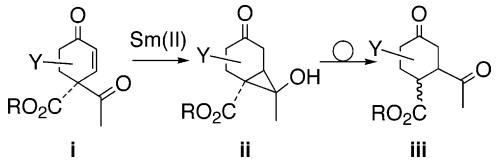
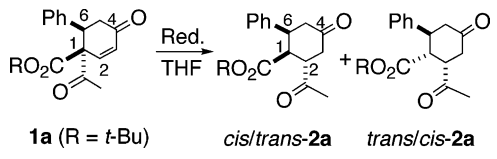
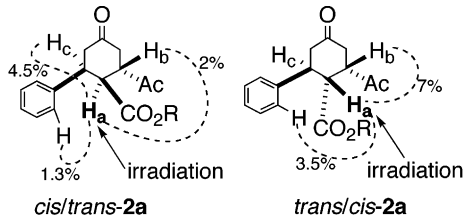


TABLE 1. Effect of Reagents and Additives for the Reduction of 1a to 2a with SmI_2 or $SmCl_2$[a]



run	reagents−additives	yield/% (cis/trans:trans/cis)[b]
1	SmI_2−$AcCH_2CO_2Bu^t$	73 (1:1)
2	SmI_2−DMI−$AcCH_2CO_2Bu^t$	88 (1:1.3)
3	SmI_2−DMI−*t*-BuOH	90 (1.1:1)
4[c]	$SmCl_2$−*t*-BuOH	93 (1:1.4)

[a] Carried out by using **1a** (0.1−0.3 mmol) and SmI_2 or $SmCl_2$ (4−6 equiv) in THF at 0−4 °C in the presence of 1,3-dimethyl-2-imidazolidinone (DMI, 20−30 equiv) and proton donor (1 equiv) under Ar for 10−30 min. [b] Yields are based on isolated products and diastereomer ratios were determined by isolated isomers or ^{1}H NMR. [c] Carried out at −65 to −50 °C.

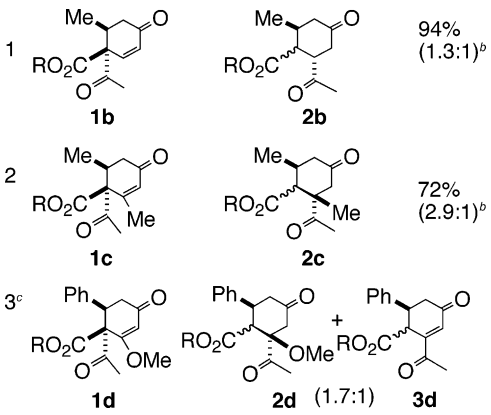


compds **2a**	H_a, δ, ppm	J_{ac} and J_{ab}, Hz
cis/trans	3.41	4.88 and 9.76
trans/cis	3.32	5.8 and 4.27

FIGURE 1. Characteristic ^{1}H NMR data and observed NOE of **2a** (R = *t*-Bu).

substituents (Ph, CO_2Bu^t, and Ac) at the C-6, C-1, and C-2 positions of **2a** was elucidated on the basis of ^{1}H NMR data. As indicated in Figure 1, the *cis/trans*-**2a** (less polar component on chromatography) showed an absorption at δ 3.41 ppm, due to the proton at the C1, with a splitting pattern of d,d with the coupling constants of J_{ac} = 4.88 Hz and J_{ab} = 9.76 Hz, indicating the cis stereochemistry between an ester and a phenyl group and the trans relationship between an ester and an acetyl group. The isomer, *trans/cis*-**2a**, on the other hand, showed an absorption at δ 3.32 ppm due to a proton on the same carbon, with a d,d splitting pattern with the coupling constants of J_{ac} = 5.8 Hz and J_{ab} = 4.27 Hz; the decreased value of J_{ab} in comparison with that of *cis/trans*-**2a** is consistent with the assigned stereochemistry as 1,2-cis. The NOE data observed are shown in the structures (Figure 1), which are in accordance with the proposed structures. Thus, the present Sm(II)-induced acyl transfer to the neighboring position on the cyclohexane proceeded stereospecifically with retention of the configuration. This stereospecificity was further confirmed by

TABLE 2. Sm(II)-Promoted 1,2-Acyl Transfer Reactions: Effect of Substitutions on the β-Position of Enone[a]



[a] Carried out by using **1** (R = *t*-Bu, 0.2−0.4 mmol) and $SmCl_2$ (4−6 equiv) in THF in the presence of *t*-BuOH under Ar for 10−30 min. [b] Yields are based on isolated products and diastereomer ratios were determined by isolation or ^{1}H NMR. [c] A 1.7:1 unseparable mixture of the methylcyclohexanone **2d** and the enone **3d**; ca. 30% yield, conversion 36%.

the acyl group migration in the system freed from the possibility of epimerization of the acetyl group at the C2 carbon, i.e. the case of compound **1c** to **2c** (Table 2, vide infra).

We next attempted the Sm(II)-reduction of the other keto esters **1b**, **1c**, and **1d** and the effect of a substituent such as a methyl or methoxy group on the C2 position was investigated. As shown in Table 2, upon treatment with SmI_2, the keto ester **1b** with no substituent on the C2 position gave the desired acyl transfer product **2b** in good yield (run 1). The yield of the acyl transfer reaction of **1c** bearing a methyl group on the C2 position decreased slightly (run 2), but it was demonstrated that the present reaction is viable in constructing an acyl group on the quaternary carbon. The SmI_2 reduction of the compound **1d**[11,12] substituted with a methoxy group produced, though in low yield, the desired acyl transferred **2d**, contaminated with the enone **3d** owing to elimination of methanol as an inseparable mixture. This low conversion of **1d** in the SmI_2 reduction may be ascribable to steric and electronic reasons.

As shown in Scheme 2, it is conceived that the present acyl transfer reaction was initiated by the reduction of the enone moiety of **1** with SmX_2 (X = I, Cl), generating the anion radical **A**,[13] since reduction of the saturated derivative **4a**, obtained by hydrogenation of **1a** on Pd/C (Scheme 3), with SmI_2−DMI led mainly to the recovery of the starting **4a** along with unidentified products. The anion radical **A** thus formed would be trapped with the internal acyl group to form the cyclopropylcarbinyl radi-

(11) Prepared by the Eu(fod)$_3$-catalyzed Diels−Alder reactions of 1,1-dimethoxy-3-trimethylsiloxybuta-1,3-diene[12a] and alkylideneacetoacetates as a dienophile. See the Supporting Information for experimental details.

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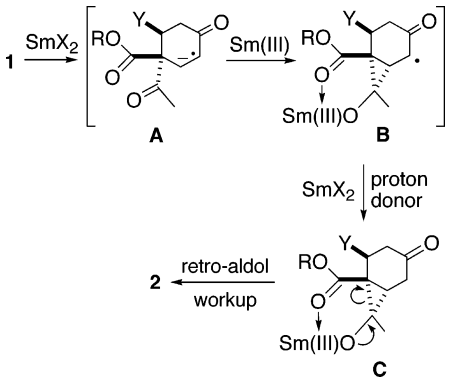
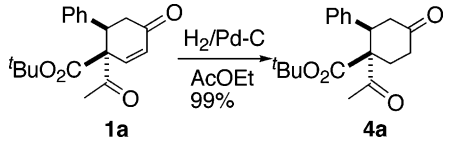
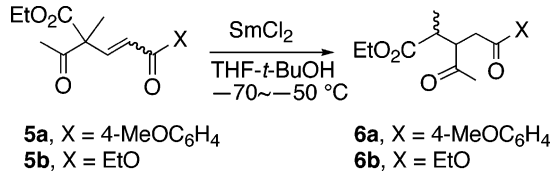
SCHEME 2. Proposed Mechanistic Pathway for 1,2-Acyl Transfer Reaction of 1 with Sm(II)



SCHEME 3



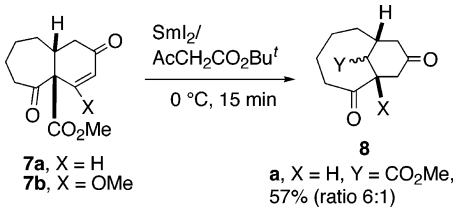
SCHEME 4



cal **B**, in which Sm(III)-alkoxide may be stabilized by coordination with an alkoxycarbonyl group.[14] Subsequently, further one-electron reduction of **B** was followed by protonation to produce the 2-oxycyclopropanecarboxylate **C**. Finally, the intermediate **C** would spontaneously undergo retro-aldol reaction due to the donor/acceptor cyclopropane structure,[15] affording **2**. However, the reaction path initiated by the ketyl radical by the reduction of the β-keto ester moiety of **1** with Sm(II) followed by an ensuing cyclization, one-electron reduction, protonation, and the cleavage of cyclopropane is also a likely mechanism in this system.[16]

We applied the 1,2-acyl transfer reaction to the acyclic enone **5a** and enoate **5b** (Scheme 4), which are easily available by Michael addition of ethyl 2-methylacetoacetate to the corresponding ynone and ynoate using a catalytic amount of NaH in THF.[17] The treatment of **5a** with $SmCl_2$ at −70 °C in the presence of *tert*-butyl alcohol afforded the desired 1,4-dicarbonyl compound **6a** as an ca. 4:1 diasteromeric mixture, a useful intermediate for

SCHEME 5



five-membered heteroaromatics,[18] in 52% yield. On the other hand, the same treatment of the enoate **5b** mostly resulted in reduction of the acyl group to the corresponding carbinols as well as recovery of the starting material. It is apparent that the present method is feasible in the 4-acyl-2-alkenone system, but not in the 2-alkenoate system.

Furthermore, we applied the present method to the ring enlargement of the bicyclic keto ester **7a**, accessible by the $Yb(OTf)_3$-catalyzed Diels−Alder reaction of 2-methoxycarbonyl-2-cycloheptenone and Danishefsky's diene.[6a] To our delight, the reduction of **7a** with SmI_2 in the presence of *tert*-butyl acetoacetate as a proton donor produced the desired bicyclo[5.3.1]undecane derivative **8a** in 57% yield as a ca. 6:1 inseparable stereoisomeric mixture (Scheme 5). However, the same treatment of **7b**,[11,12] bearing a methoxy group, with SmI_2 as above resulted in complete recovery of the starting material; our attempt to synthesize the bridgehead double bond[19] in the bicyclo[5.3.1] system was unsuccessful at present.

In summary, the 1,2-acyl group migration reaction occurred in the 4-acyl-4-alkoxycarbonyl-2-alkenone system when reduced with SmI_2 or $SmCl_2$. The present method allows construction of the δ-keto ester unit assembled in the acyclic, carbocyclic, and bicyclo[5.3.1]-nonane structures. This 1,2-acyl transfer reaction occurs stereospecifically with retention of configuration and permits introduction of an alkanoyl group even onto the quaternary carbon center.

Experimental Section

General Procedure for Sm(II)-Induced Acyl Transfer Reactions. Preparation of 6-Phenyl-2-acyl-4-oxocarboxylates 2a. To a mixture of **1a** (32 mg, 0.1 mmol), *t*-BuOH (10 μL), and DMI (0.3 mL) in THF (5 mL) was added with cooling at 0−4 °C a cooled solution of 0.1 M SmI_2 (5 mL) in THF over 5 min until a deep blue color of SmI_2 slightly persisted. The mixture was stirred at the same temperature for 30 min and the reaction was quenched with a mixture of hexane−AcOEt (1:1) and SiO_2. The suspension was passed through a short SiO_2 pad eluting with hexane−AcOEt (1:1) and the crude product was analyzed with GC (Methyl Silicone (MS), raised from 150 to 220 °C at a gradient rate of 10 °C/min after 10 min of isothermal analysis). The filtrate was concentrated and purified by column chromatography (SiO_2, hexane−AcOEt 7:1, 5:1, 3:1, and 2:1) to give 15 mg (47%) of *cis*/*trans*-**2a** (R_t 10.62 min) and 13 mg (41%) of *trans*/*cis*-**2b** (R_t 11.33 min). *cis*/*trans*-**2a** (R_f 0.53, hexane−AcOEt 2:1): mp 125−126 °C (from hexane−AcOEt); IR (KBr) 3066, 1718, 1703, 1604, 1456, 1367, 1278, 1220, 1166, 846, 702 cm^{-1}; ^1H NMR (500 MHz) δ 1.28 (s, 9H), 2.21 (s, 3H), 2.38 (d, d, d, J = 15.26, 11.3, 0.92 Hz, 1H), 2.73−2.81 (m, 2H), 2.84 (d, d, d, J = 10.68, 4.58, 1.83 Hz, 1H), 3.32 (d, d, d, J = 11.29, 9.765,

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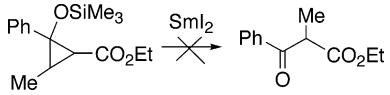
(15) Siloxycyclopropylcarboxylate was inert to SmI_2.



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5.18 Hz, 1H), 3.41 (d, d, J = 9.76, 4.88 Hz, 1H), 3.84 (m, 1H), 7.07−7.10 (m, 2H), 7.23−7.30 (m, 3H); ^{13}C NMR (75.5 MHz) δ 27.8 (3C), 29.2, 41.3, 42.0, 44.6, 46.8, 48.1, 81.7, 127.4, 128.2 (2C), 128.4 (2C), 140.1, 171.0, 208.3, 208.4. HRMS (EI) calcd for $C_{19}H_{24}O_4$ 316.1675, found 316.1665. *trans*/*cis*-**2a** (R_f 0.43): mp 106−107 °C (from hexane−AcOEt); IR (KBr) 3072, 3043, 1722, 1716, 1604, 1456, 1417, 1213, 1143, 981, 837, 769, 744, 703 cm^{-1}; ^{1}H NMR (500 MHz) δ 1.36 (s, 9H), 2.13 (s, 3H), 2.59−2.67 (m, 2H), 2.72 (d, d, d, J = 16.02, 9.46, 1.22 Hz, 1H), 2.85 (d, d, d, J = 16.17, 6.1, 1.22 Hz, 1H), 2.96 (m, 1H), 3.32 (d, d, J = 5.8, 4.27 Hz, 1H), 3.85 (m, 1H), 7.21−7.27 (m, 2H), 7.30−7.34 (m, 3H); ^{13}C NMR (75.5 MHz) δ 27.8 (3C), 29.0, 40.3, 41.4, 43.5, 47.2, 49.6, 82.3, 127.1, 127.4 (2C), 128.8 (2C), 142.2, 171.1, 207.4, 208.7. HRMS (EI) calcd for $C_{19}H_{24}O_4$ 316.1675, found 316.1627.

Reduction of 1a with $SmCl_2$. Anhydrous LiCl (24 mg, 0.56 mmol) was dried by heating under vacuum, back flushed with Ar, and dissolved in THF (5 mL). To this solution was added at 0−4 °C a cooled solution of 0.1 M SmI_2 in THF (5.6 mL) and the resulting solution was stirred at the same temperature for 30 min. Upon cooling to −70 °C, this $SmCl_2$ solution was added dropwise to a cooled (−70 °C) mixture of **1a** (34 mg, 0.11 mmol) and *t*-BuOH (11 μL) in THF (5 mL) over 5 min until a deep blue color of $SmCl_2$ slightly persisted. The mixture was worked up and the crude products were purified in the same manner as above to give a 1:1.46 mixture of *cis*/*trans*-**2a** and *trans*/*cis*-**2a** (32 mg, 93%), the ratio of which was determined on the basis of ^{1}H NMR data.

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Supporting Information Available: Preparative procedures, characterization data, and spectra (IR, ^{1}H NMR, and ^{13}C NMR spectra) for compounds **1d**, *cis*/*trans*- and *trans*/*cis*-**2a**−**c**, a mixture of **2d** and **3d**, **5a**, **6a**, **7b**, and **8a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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