Synthesis and Lewis Acid-Catalyzed Nucleophilic Substitution of Chiral 1-Alkoxyalkyl Carboxylates

Hiroshi Matsutani, Satsuki Ichikawa, Jayamma Yaruva, Tetsuo Kusumoto,* and Tamejiro Hiyama[†]

Sagami Chemical Research Center
Nishiohnuma, Sagamihara, Kanagawa 229, Japan
Research Laboratory of Resources Utilization
Tokyo Institute of Technology
Nagatsuta, Yokohama, Kanagawa 226, Japan

Chiral acetals are versatile building blocks for the synthesis of biologically active agents and functional materials.[1] The acetal is usually rendered chiral due to the dissymmetric environment induced by a stereogenic center near the acetal carbon or by a chiral glycol moiety.[1] In contrast, few optically pure acetals are known whose acetal carbon only is chiral.[2] The mechanism of the Lewis acid-mediated nucleophilic substitution of acetals is also a recent topic of interest.[3] Denmark reported that sterically unhindered aliphatic acetals underwent intramolecular S_N2-type substitution with the aid of a mild Lewis acid.[3a] In contrast, Sammakia observed that dimethyl acetals underwent intermolecular allylation *via* an oxocarbenium ion using any kind of Lewis acid.[3c] We report herein that the Baeyer–Villiger reaction of optically active α-alkoxy ketones **1** affords optically active 1-alkoxyalkyl carboxylates **2**. The resulting acetals **2** undergo substitution with lithium dialkylcuprate(I) in the presence of boron trifluoride etherate[4] to give optically active alkoxyalkane **3** with inversion of configuration.

The syntheses of optically active 1-alkoxyalkyl carboxylates **2a–g**[5] were readily achieved by the Baeyer–Villiger oxidation of optically active α-alkoxy ketones **1a–g**[6] shown in Table 1. The reaction proceeded smoothly in good yields (46–92%) from ketones **1a–g** (84–100% ee), and the resulting acetals **2a–g** had high anantiomeric excess (ee) (81–97%).[7] Due to the steric effect of the *t*-Bu group, longer reaction time was needed for **1g** to give **2g** and the yield was rather low (Table 1, entry 7).

[†] Tokyo Institute of Technology.

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(2) Synthesis of an optically active 1-alkoxy-2,2,2-trichloroethyl ester is achieved enzymatically: Chênevert, R.; Desjardins, M.; Gagnon, R. *Chem. Lett.* **1990**, 33–34.

(3) For the mechanism on the Lewis acid-catalyzed nucleophilic substitution of acetals, see: (a) Denmark, S. E.; Almstead, N. G. *J. Am. Chem. Soc.* **1991**, *113*, 8089–8110. (b) Denmark, S. E.; Almstead, N. G. *J. Org. Chem.* **1991**, *56*, 6485–6487. (c) Sammakia, T.; Smith, R. S. *J. Am. Chem. Soc.* **1994**, *116*, 7915–7616. (d) Sammakia, T.; Smith, R. S. *J. Am. Chem. Soc.* **1992**, *114*, 10998–10999. (e) Mori, I.; Ishihara, K.; Flippin, L. A.; Nozaki, K.; Yamamoto, H.; Bartlett, P. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 6107–6115. (f) Alexakis, A.; Mangeney, P. *Tetrahedron: Asymmetry* **1990**, *1*, 477–511.

(4) Organocopper or cuprate reagents associated with boron trifluoride cleave acetals: Ghribi, A.; Alexakis, A.; Normat, J. F. *Tetrahedron Lett.* **1984**, *25*, 3075–3078.

(5) To a dichloromethane solution of **1** were added sodium hydrogen carbonate (1.3 equiv) and *m*-chloroperbenzoic acid (*m*-CPBA, 1.5 equiv). The resulting mixture was stirred at 0 °C to room temperature. Excess *m*-CPBA was quenched with aqueous sodium sulfite solution, and the resulting mixture was extracted with chloroform. Organic layer was separated, washed first with aqueous sodium hydrogen carbonate and then with aqueous sodium chloride, dried, and concentrated. The residue was distilled to give **2**. Upon standing in a glass tube for several days or upon silica gel chromatography, **2** racemized gradually. Thus, **2** was used for further reaction immediately after isolation by distillation.

(6) Ketone **1a** was obtained from (2*R*,3*R*)-2,3-butanediol, **1b–f** were synthesized from α-amino acids, and **1g** was prepared from L-lactic acid. Details of the synthesis and spectral data are listed in Supporting Information.

Table 1. Bayer–Villiger Reaction of Optically Active α-Alkoxy Ketones

entry	ketone **1** (% *ee*)	time (h)	acetal **2** (% *ee*)	yield (%)
1	PhCH₂O—C(Me)(H)—COMe **1a** (98)	1	PhCH₂O—C(Me)(H)—OCOMe **2a** (94)	71
2	4-BrC₆H₄CH₂O—C(Me)(H)—COMe **1b** (85)	0.5	4-BrC₆H₄CH₂O—C(Me)(H)—OCOMe **2b** (85)	90
3	PhCH₂CH₂O—C(Me)(H)—COMe **1c** (93)	0.5	PhCH₂CH₂O—C(Me)(H)—OCOMe **2c** (91)	89
4	PhO—C(Me)(H)—COMe **1d** (100)	0.5	PhO—C(Me)(H)—OCOMe **2d** (97)	92
5	PhCH₂O—C(*i*-Bu)(H)—COMe **1e** (97)	0.5	PhCH₂O—C(*i*-Bu)(H)—OCOMe **2e** (95)	76
6	PhCH₂O—C(Me)(H)—COEt **1f** (94)	0.5	PhCH₂O—C(Me)(H)—OCOEt **2f** (92)	91
7	PhCH₂O—C(Me)(H)—CO*t*-Bu **1g** (84)	72	PhCH₂O—C(Me)(H)—OCO*t*-Bu **2g** (81)	46

It is worth noting that the oxidation is highly regioselective; the regioisomeric α-alkoxyalkanoate was not produced in the oxidation. Thus, the migratory aptitude is demonstrated to be 1-alkoxyalkyl ≫ alkyl, in accord with the order recently disclosed.[8] In line with well-established results,[9] we can state that the stereochemical course of the Baeyer–Villiger reaction is retention. This conclusion is substantiated by further elaboration (*vide infra*).

We next studied the stereochemical course of the Lewis acid-catalyzed C–C bond-forming reactions, using the optically active 1-alkoxyalkyl carboxylates **2**. The chiral acetals **2** should be advantageous reagents over cyclic diastereomeric acetals,[1,3,10] since their structure is simple and the stereochemical outcome is easily assayed. In our preliminary experiments, the reaction of **2a** with allyltrimethylsilane in the presence of boron
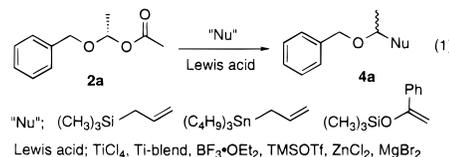
trifluoride etherate[10b,d] gave a homoallylic ether, with the acyloxy group behaving as the leaving group, but with complete racemization. All attempts to prevent the racemization by tuning the Lewis acid catalyst (TiCl₄, Ti-blend,[11] TMSOTf, ZnCl₂, or

(7) Enantiomeric excess (ee) was analyzed by HPLC with CHIRALCEL or CHIRALPAK (Daicel columns).

(8) (a) The migratory aptitude of a substituent in a pyranose system is reported to be C-OCH₂Ph > C-OMe > C(OR)₂ ≫ C-OCOR ~ C-CH₃ > C-H. Chida, N.; Tobe, T.; Ogawa, S. *Tetrahedron Lett.* **1994**, *35*, 7249–7252. (b) Only cyclic ketones were used as the substrate. Tsang, R.; Fraser-Reid, B. *J. Org. Chem.* **1992**, *57*, 1065–1067.

(9) Krow, G. R. In *Organic Reactions*; John Wiley & Sons: New York, 1993; Vol. 43, pp 251–798.

(10) For studies on the reaction of cyclic diastereomeric 1-alkoxyalkyl carboxylates, see: (a) Seebach, D.; Imwinkelried, R.; Stucky, G. *Ang. Chem., Int. Ed. Engl.* **1986**, *25*, 178–180. (b) Seebach, D.; Imwinkelried, R.; Stucky, G. *Helv. Chim. Acta* **1987**, *70*, 448–464. (c) Schreiber, S. L.; Reagan, J. *Tetrahedron Lett.* **1986**, *27*, 2945–2948. (d) Boons, G.-J.; Eveson, R.; Smith, S.; Stauch, T. *Synlett* **1996**, 536–538. (e) Dahanukar, V. H.; Rychnovsky, S. D. *J. Org. Chem.* **1996**, *61*, 8317–8320.

Table 2. Nucleophilic Substitution of Optically Active 1-Alkoxyalkyl Carboxylates Using Organocopper Reagents

entry	acetal 2 (% ee)	R^4_2CuLi (R^4)	$BF_3 \cdot OEt_2$ (equiv)	yield (%)	ether 3[12] % ee[7] (inversion ratio)
1	2a — 92	n-Bu	3.0	53	Me / PhCH$_2$O—*—n-Bu (S)-3a[a,b] — 86 (93)
2	2a — 94	n-Bu	1.5	51	83 (88)
3	2a — 94	Et	1.5	52	Me / PhCH$_2$O—*—Et (S)-3b[a,c] — 78 (83)
4	2b — 85	n-Bu	1.5	62	Me / 4-BrC$_6$H$_4$CH$_2$O—*—n-Bu (S)-3c[a,d] — 65 (76)
5	2c — 91	n-Bu	1.5	65	Me / PhCH$_2$CH$_2$O—*—n-Bu (S)-3d[e] — 81 (89)
6	2d — 97	n-Bu	3.0		no reaction
7	2e — 94	n-Bu	3.0	51	i-Bu / PhCH$_2$O—*—n-Bu (R)-3e[e] — 65 (69)
8	2e — 92	n-Bu	1.5	64	58 (63)
9	2e — 85	Me	3.0	68	i-Bu / PhCH$_2$O—*—Me (R)-3f[e] — 47 (55)
10	2e — 92	Me	1.5	70	83 (90)
11	2f — 92	n-Bu	1.5	75	Me / PhCH$_2$O—*—n-Bu (S)-3a[a,f] — 77 (84)
12[g]	2g — 80	n-Bu	3.0	79	Me / PhCH$_2$O—*—n-Bu (dl)-3a — 0 (0)

[a] The absolute configuration was assigned on the basis of the optical rotation of the corresponding authentic sample. [b] $[\alpha]^{20}_D = +19°$ (c 1.0, CHCl$_3$). The (R)-isomer, prepared by benzylation of commercially available (R)-2-hexanol, showed $[\alpha]^{20}_D = -21°$ (c 1.1, CHCl$_3$). [c] $[\alpha]^{20}_D = +23°$ (c 1.0, CHCl$_3$). The (S)-isomer prepared from commercially available (S)-2-butanol showed $[\alpha]^{20}_D = +25°$ (c 1.0, CHCl$_3$). [d] $[\alpha]^{20}_D = +14°$ (c 1.0, CHCl$_3$). The (S)-isomer derived from commercially available (S)-2-hexanol showed $[\alpha]^{20}_D = +17°$ (c 1.0 CHCl$_3$). [e] The absolute configuration was estimated on the analogy of entries 1–4 and 11. [f] $[\alpha]^{20}_D = +17°$ (c 1.0, CHCl$_3$). [g] Reaction at −78 to −30 °C for 1.5 h.

MgBr$_2 \cdot$OEt$_2$) failed. The racemic products resulted again with allyltributyltin[3b,10e] or enol sillyl ether[10d] (eq 1).

We then studied the reaction with an organocopper reagent. Treatment of **2a** with lithium dibutylcuprate(I) (Bu$_2$CuLi·LiI) afforded 2-(benzyloxy)hexane in only 12% yield. However, use of Bu$_2$CuLi·LiI and boron trifluoride etherate (BF$_3 \cdot$OEt$_2$) gave (S)-2-(benzyloxy)hexane[12] (**3a**, 69% yield, 48% ee) starting with 77% ee of (S)-1-(benzyloxy)ethyl acetate (**2a**). We were delighted to find that, by slow addition of BF$_3 \cdot$OEt$_2$ to a mixture of **2a** (92% ee) and Bu$_2$CuLi·LiI, ether **3a** was obtained in 53% yield with 86% ee (Table 2, entry 1).[13] Thus, the BF$_3 \cdot$OEt$_2$-aided alkylation of **2a** with Bu$_2$CuLi·LiI proceeds with inversion of configuration. In addition, the yield of **3a** was markedly suppressed by using BuCu·LiI/BF$_3 \cdot$OEt$_2$, and racemic **3a** resulted by using Bu$_2$CuLi·LiI/AlCl$_3$. Alkylation of various acetals **2** with lithium dialkylcuprate(I) and boron trifluoride etherate is summarized in Table 2. The inversion ratio, (% ee of **3**)/(% ee of **2**), is shown in parentheses. Noteworthy is that

Scheme 1
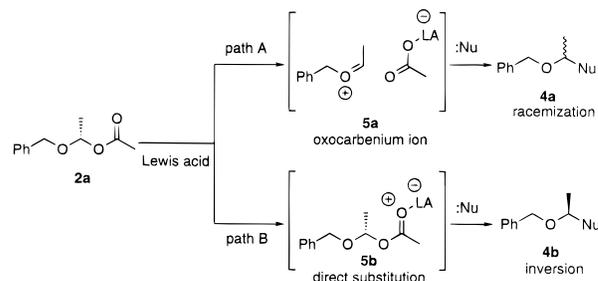
the reaction proceeded with high stereospecificity. Although we attempted to reduce the amount of BF$_3 \cdot$OEt$_2$ to 1.5 equiv (entry 2), the observed ee of **3a** was not improved. A similar reaction was performed using Et$_2$CuLi·LiI instead of Bu$_2$CuLi·LiI to give **3b** with a slightly reduced ee as compared with **3a** (entry 3). To demonstrate the generality and scope of this reaction, various 1-alkoxyalkyl carbonates were used as the substrate. An acetal **2b** gave ether **3c** (entry 4) with inversion ratio of 76%. Although **2c** reacted smoothly to give the corresponding ether **3d** (entry 5), (S)-1-phenoxyethyl acetate (**2d**) proved to be inert (entry 6). The acetal **2e** in which an isobutyl moiety is attached at the acetal carbon (R^2) gave **3e** (65% ee) by the reaction with Bu$_2$CuLi·LiI. The lower ee might be attributed to the steric hindrance of the isobutyl group (entries 7 and 8). The same substrate, upon reaction with Me$_2$CuLi·LiI/BF$_3 \cdot$OEt$_2$, gave **3f** with high inversion ratio, particularly when the amount of BF$_3 \cdot$OEt$_2$ was reduced (entry 10). Whereas the reaction of propanoate **2f** also proceeded stereospecifically (entry 11), pivalate **2g** reacted with Bu$_2$CuLi·LiI with complete loss of stereochemical integrity. Thus, the steric bulk of the leaving group affects significantly the stereochemical course of the reaction.

A plausible reaction pathway follows.[3c] The Lewis acid-aided reactions of acetal **2a** with allyltrimethylsilane should produce an oxocarbenium ion (**5a**), which then reacts with a nucleophile to give racemic **4a** (Scheme 1, path A). In contrast, BF$_3 \cdot$OEt$_2$-aided alkylation of **2a** with a cuprate reagent should proceed *via* a Lewis acid-substrate complex **5b** (Scheme 1, path B) that is responsible for the stereochemical course of the reaction *via* S$_N$2-like displacement. The reaction through an alternative path involving the oxocarbenium ion intermediate **5a** should be limited but not negligible. Our data show that S$_N$2 type nucleophilic substitution of chiral acetal derivatives can be realized by an appropriate combination of substrate, nucleophile, and the Lewis acid.

We have reported herein that the Baeyer−Villiger oxidation of optically active α-alkoxyalkyl ketones **1a**−**g** enables us to obtain chiral 1-alkoxyalkyl carboxylates **2a**−**g** of high optical purity. The alkylation with lithium dialkylcuprate(I) and boron trifluoride etherate gave stereospecifically alkylated products with a high degree of inversion of configuration. This process provides us with a new synthetic method for the synthesis of optically active secondary alcohols and their derivatives.

(11) Johnson, W. S.; Crackett, P. H.; Elliott, J. D.; Jagodzinski, J. J.; Lindell, S. D.; Natarajan, S. *Tetrahedron Lett.* **1984**, *25*, 3951−3954. Allylation of **1a** with "Ti-blend" as a catalyst according to the procedure reported by Denmark[3a] gave a racemic allylated product.

(12) The absolute configuration of **3a**−**c** was assigned by comparison of the sign of the optical rotation with the those of the corresponding authentic sample which was prepared by benzylation of the commercially available optically active 2-alkanol. The absolute configuration of **3d**−**f** was estimated on the analogy of **3a**−**c** in entries 1−4 and 11 of Table 2. See Supporting Information for details.

(13) Butyllithium (6 equiv) in hexane was added at −30 °C to the suspension of copper(I) iodide (3 equiv) in diethyl ether to prepare lithium dibutylcuprate(I). To the reaction mixture were added dropwise the ester **2a** at −78 °C and then an ethereal solution of boron trifluoride etherate (3 equiv). The reaction mixture was stirred at −78 °C for 0.5 h, and the reaction was quenched with aqueous ammonium chloride. The insoluble material was filtered through Celite, and the filtrate was extracted with diethyl ether. The organic layer was separated, washed with aqueous sodium chloride solution, dried, and concentrated. The residue was purified by silica gel column chromatography.