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Communications

Boron Trifluoride Promoted Aldol Reaction of Silyl Ketene Acetals with the Intermediate Generated by the DIBALH Reduction of Carboxylic Acid Esters

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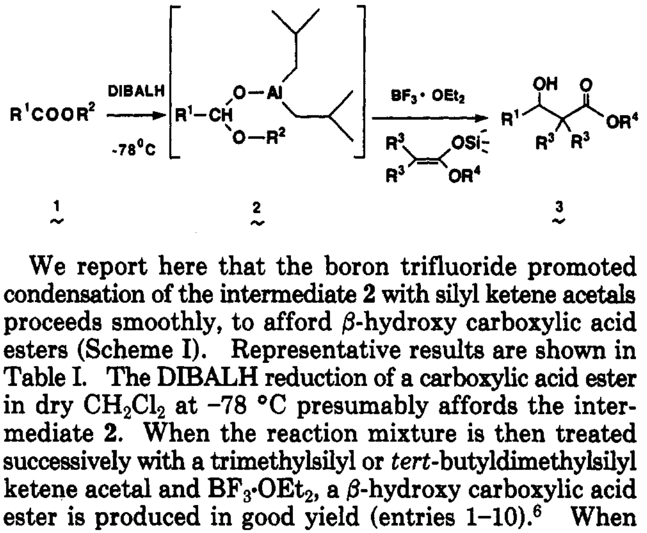
Summary: The intermediate generated by the DIBALH reduction of carboxylic acid esters undergoes a boron trifluoride promoted aldol reaction with silyl ketene acetals to afford the corresponding β-hydroxy carboxylic acids esters in good yield.

The low-temperature DIBALH reduction of carboxylic acid esters is of enormous synthetic value because it permits a one-step conversion of such esters to aldehydes.[1] One reason that overreduction is not a problem may be that the strength of the Al–O bond inhibits expulsion of alkoxide ion from the intermediate **2**.[2] Of the intermediates that are generated by DIBALH reductions apparently only such species as the vinylaluminums generated by the reduction of the carbon–carbon triple bond of alkynes[3] and the iminoaluminums generated by the reduction of the carbon–nitrogen triple bonds of nitriles[4] have subsequently been utilized as reagents in reactions that form carbon–carbon single bonds. It occurred to us that, under suitable reaction conditions, the alkyl diisobutylaluminum acetal intermediate **2**, which is presumably generated by the DIBALH reduction of a carboxylic acid ester, might similarly be utilized. Although, in general, acetals do undergo a Lewis acid promoted reaction with a variety of silylated nucleophiles,[5] if and how species like **2** would react were, to our knowledge, not known.

Scheme I



We report here that the boron trifluoride promoted condensation of the intermediate **2** with silyl ketene acetals proceeds smoothly, to afford β-hydroxy carboxylic acid esters (Scheme I). Representative results are shown in Table I. The DIBALH reduction of a carboxylic acid ester in dry CH_2Cl_2 at −78 °C presumably affords the intermediate **2**. When the reaction mixture is then treated successively with a trimethylsilyl or *tert*-butyldimethylsilyl ketene acetal and $BF_3{\cdot}OEt_2$, a β-hydroxy carboxylic acid ester is produced in good yield (entries 1–10).[6] When $BF_3{\cdot}OEt_2$ is introduced into the reaction mixture before the trialkylsilyl ketene acetal, the yield of β-hydroxy carboxylic acid ester drops slightly. Other solvents, e.g., THF, toluene, can also be used, but the β-hydroxy carboxylic acid ester is then formed in only moderate yield. The reaction

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[1] Winterfeldt, E. *Synthesis* **1975**, 617. Maruoka, K.; Yamamoto, H. *Tetrahedron* **1988**, *44*, 5001.

[2] Mudryk, B.; Shook, C. A.; Cohen, T. *J. Am. Chem. Soc.* **1990**, *112*, 6389.

[3] Zweifel, G.; Steele, R. B. *J. Am. Chem. Soc.* **1967**, *89*, 2754. Zeifel, G.; Miller, R. L. *Ibid.* **1970**, *92*, 6678. Newman, H. *Tetrahedron Lett.* **1971**, 4571.

[4] Goering, H. L.; Tseng, C. C. *J. Org. Chem.* **1981**, *46*, 5250. Cainelli, G.; Mezzina, E.; Panunzio, M. *Tetrahedron Lett.* **1990**, *31*, 3481.

[5] Mukaiyama, T.; Murakami, M. *Synthesis* **1987**, 1043.

[6] **General Procedures.** To a stirred solution of the ester (2 mmol) and anhyd CH_2Cl_2 (10 mL) at −78 °C under Ar was added, drop-by-drop, DIBALH (2.2 mmol; 2.2 mL of a 1.0 M solution in toluene). The mixture was stirred at −78 °C for 1 h, whereupon a solution of the trialkylsilyl ketene acetal (3 mmol) in CH_2Cl_2 (2 mL) and neat $BF_3{\cdot}OEt_2$ (2.5 mmol) were added. The mixture was stirred at −78 °C for 1 h and was then allowed to warm to rt, whereupon the reaction was quenched by the introduction of 10% aqueous HCl. The two liquid layers were separated. The aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography on silica gel.

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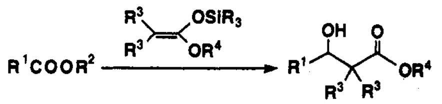
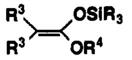
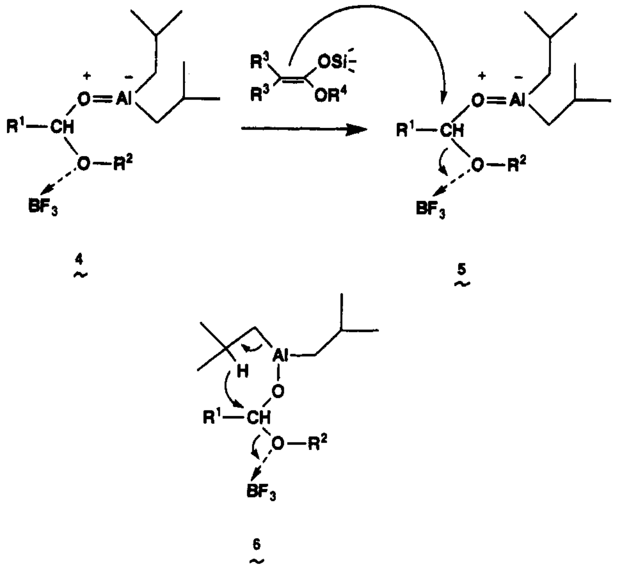
Table I. Boron Trifluoride Mediated Aldol Reaction of Trialkylsilyl Ketene Acetals with the Intermediate Generated by the DIBALH Reduction of Carboxylic Acid Esters



entry	R′COOR² R¹	R²	 R³	R⁴	R(Si)	β-hydroxy ester product[a] (% yield)
1	Me	Me	H	Ph	TMS	**3a** (65)
2	Me	Me	Me	Et	TMS	**3b** (70)
3	*i*-Pr	Et	H	Ph	TMS	**3c** (69)
4	*i*-Pr	Et	Me	Et	TMS	**3d** (77)
5	*s*-Bu	Me	H	Ph	TMS	**3e** (75)
6	*s*-Bu	Me	Me	Et	TMS	**3f** (66)
7	Bn	Me	H	Et	TBDMS	**3g** (85)
8	Bn	Me	Me	Et	TMS	**3h** (70)
9	Ph_2CH	Me	H	Et	TBDMS	**3i** (60)
10	Ph_2CH	Me	Me	Et	TMS	**3j** (86)
11	Ph	Me	H	Et	TBDMS	**3k** (5)
12	Ph	Me	Me	Et	TMS	**31** (31)

[a] Aliphatic esters (entries 1–10) gave products of overreduction, i.e., the alcohols derived from the acyl fragment of the ester starting material, in yields of 5–10%, whereas methyl benzoate (entries 11 and 12) gave benzyl alcohol in ca. 50% yield.

Scheme II



is very clean, and the only byproduct is the alcohol (5–10% yield) that results from overreduction of the starting ester. The less reactive allylsilane produced only a 25% yield under the BF_3 conditions; however, the performance of other Lewis acids in the reaction has not been examined for purposes of optimizing the yield. Thus, the one-pot conversion of a carboxylic acid ester to a β-hydroxy carboxylic acid ester of greater chain length has been achieved.[7] *What is described here is therefore of considerable synthetic value.* Unfortunately, esters of aromatic acids do not give aldol adducts in sufficiently high yields. For example, methyl benzoate (entries 11 and 12) gives the expected adduct in only low yield, along with a large amount of benzyl alcohol (ca. 50%). α,β-Unsaturated esters like methyl acrylate also give low yield of the desired products.

The reaction seems to occur when species **2** is activated by preferential coordination of BF_3 with the oxygen atom of the alkoxy group. Coordination of BF_3 with the oxygen atom of the carbon–oxygen–aluminum linkage is not favored because the basicity of that oxygen atom is lowered by the development of Al–O double bond character (Scheme II).[8] The alcohol byproduct is obviously the result of a BF_3-assisted Meerwein–Ponndorf–Verley reduction, which probably takes place in the manner indicated in structure **6**.

The details of the mechanism of the reaction are still being elucidated. Nevertheless, effects directed toward the asymmetric synthesis of β-hydroxy carboxylic acid esters by way of the reaction of esters which incorporate a chiral alcohol moiety are now in progress.

Supplementary Material Available: Additional experimental details section and the ¹H NMR, ¹³C NMR, and IR spectra of **3a–31** and **7** (7 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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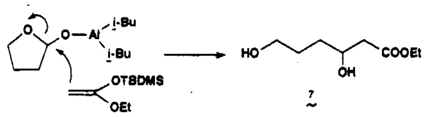
[7] The reaction of γ-butyrolactone under the conditions described here yields the dihydroxy carboxylic acid **7** (30%) as a major product.



What is unusual about this result is that it was reported that the BF_3-promoted reaction of γ-lactols with silylated nucleophiles gives the corresponding substituted tetrahydrofurans. No products of ring opening were detected. See: Schmitt, A; Reissig, H. -U. *Synlett* **1990**, 40.

[8] A reviewer has suggested that the structure of the complex **4** might be better represented as an oxygen-bridged dimer rather than as a monomer which processses an aluminum–oxygen double bond.

Regioselective Incorporation of CO into Enamines by Rhodium-Catalyzed Reaction with a Hydrosilane and CO

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Summary: In the presence of $[RhCl(CO)_2]_2$, the reaction of enamines with a hydrosilane and carbon monoxide (140 °C, 50 atm of CO) resulted in regioselective incorporation of CO into the α-carbon atom to give α-(siloxymethylene)amines, which can be easily converted into α-siloxy ketones by hydrolysis.

In a series of studies on new catalytic reactions of

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