Aldol Reactions with α-Trimethylsilyl Ketones. Dual Roles of the Trimethylsilyl Group for Regiospecific Generation of Enolate Equivalents[1]

Tan Inoue, Toshio Sato,[2] and Isao Kuwajima*

Department of Chemistry, Tokyo Institute of Technology, Meguro, Tokyo 152, Japan

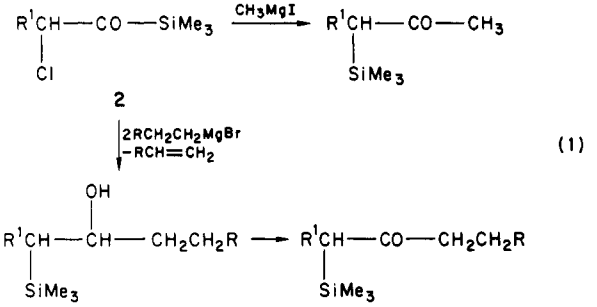
Received January 31, 1984

Aldol reactions of α-trimethylsilyl ketones, $R^1CH(SiMe_3)COCH_2R^2$, with aldehydes or acetals have been examined under Lewis acidic and basic conditions. In the presence of stannic chloride or boron trifluoride etherate, α-trimethylsilyl ketones react with aldehydes or acetals on the carbon bearing the silyl group exclusively to afford the corresponding addition products. On the other hand, lithium diisopropylamide usually deprotonates the opposite carbon atom to generate enolates, $R^1CH(SiMe_3)C(OLi)=CHR^2$, selectively, which yield another type of aldol product after removal of the silyl group. Thus, two types of aldols can be prepared regioselectively from common α-trimethylsilyl ketones.

Silyl enol ethers have now been employed as one of the most useful enolate equivalents in organic synthesis.[3] They usually react with various kinds of electrophiles regiospecifically, and several types of their aldol reactions have been extensively studied.[4-6] In contrast, the types of reactions and synthetic utilities of their structural isomers, α-trimethylsilyl ketones 1, have never been elucidated up to now. Several reports have also dealt with specific generation of enolates from 1 through selective removal of the silyl group with certain bases.[7] But, the regiochemical outcome of proton abstraction from 1 with bases has not been studied yet, although anion stabilizing effects of trialkylsilyl groups are well precedented on various organosilicon compounds.[8] Recently, several methods have been developed for regiospecific preparation of α-trialkylsilyl ketones 1 by us[9,10] and others.[11] By using these substrates as nucleophiles, we have examined aldol reactions under acidic and basic reaction conditions, which disclosed useful and interesting features of 1. In this paper, we describe characteristic roles of the trimethylsilyl group for specific generation of two types of enolates from α-trimethylsilyl ketones 1.

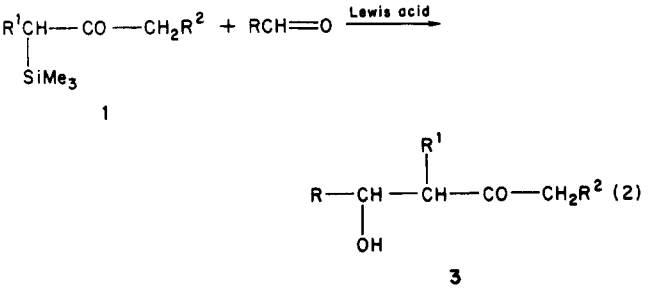
Results and Discussion

The requisite α-trimethylsilyl ketones 1 have been prepared as follows. As already described, treatment of an appropriate (α-chloroacyl)trimethylsilane 2 with methylmagnesium iodide gave the corresponding 3-(trimethylsilyl)-2-alkanones 1 (R^2 = H) in excellent yields.[8] Other ketones 1 (R^2 = alkyl) were prepared by treating 2 with 2 equiv of an appropriate Grignard reagent followed by Collins oxidation[12] of the resulting β-(trimethylsilyl)-alkanols[9] (eq 1).



(1)

Initially, the reaction of 1 with aldehydes was examined in the presence of a Lewis acid. Under such conditions, ketones 1 were found to act toward aldehydes in a similar manner with the corresponding silyl enol ethers, and the reaction proceeded on the carbon bearing the silyl group selectively to yield the corresponding aldol adducts 3. The



(2)

complete absence of the regioisomer was confirmed in the reaction mixture of 1 ($R^1 = C_6H_5CH_2$, R^2 = H) with benzaldehyde by comparison of its ^1H NMR spectrum with those of authentic samples of the corresponding 3 and its regioisomer. The Lewis acids $TiCl_4$, $SnCl_4$, and BF_3OEt_2 were examined. All of these effected the aldol reaction, but the last one appeared to be most efficient. Results are summarized in Table I.

Specific formation of 3 may be explicable by assuming an intermediary formation of enolates[13] or their keto isomers[14] through coordination of the Lewis acid followed by

(1) A preliminary report dealing with certain aspects of this work has appeared: Kuwajima, I.; Inoue, T.; Sato, T. *Tetrahedron Lett.* **1978**, 4887.
(2) Present address: Chemistry Department of Resources, Mie University, Tsu, Mie 514, Japan.
(3) (a) Colvin, E. W. "Silicon in Organic Synthesis"; Butterworths: London, 1981; Chapter 17. (b) Weber, W. P. "Silicon Reagents for Organic Synthesis"; Springer-Verlag: Berlin, 1983; Chapter 12. (c) Brownbridge, P. *Synthesis* **1983**, *85*, 1.
(4) Stork, G.; Hudrlik, P. F. *J. Am. Chem. Soc.* **1968**, *90*, 4464.
(5) Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503. Mukaiyama, T. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 817.
(6) Noyori, R.; Yokoyama, K.; Sakata, J.; Kuwajima, I.; Nakamura, E.; Shimizu, M. *J. Am. Chem. Soc.* **1977**, *99*, 1265. Nakamura, E.; Shimizu, M.; Kuwajima, I.; Sakata, J.; Yokoyama, K.; Noyori, R. *J. Org. Chem.* **1983**, *48*, 933.
(7) Eaborn, C.; Bott, R. W. "Organometallic Compounds of the Group IV Elements"; MacDiarmid, A. G., Ed; Marcel Dekker: New York, 1968; Vol 1, part 1.
(8) See, for example, ref 3a, Chapter 4.
(9) Sato, T.; Abe, T.; Kuwajima, I. *Tetrahedron Lett.* **1978**, 259. Sato, T.; Matsumoto, K.; Abe, T.; Kuwajima, I. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2167.
(10) Kuwajima, I.; Takeda, R. *Tetrahedron Lett.* **1982**, *23*, 403.
(11) Obayashi, M.; Utimoto, K.; Nozaki, H. *Tetrahedron Lett.* **1977**, 1805; *Bull. Chem. Soc. Jpn.* **1979**, *52*, 2646. Kowalski, C. J.; O'Dowd, M. L.; Burke, M. C.; Fields, K. W. *J. Am. Chem. Soc.* **1980**, *102*, 5471. Beisswenger, H.; Hanack, M. *Tetrahedron Lett.* **1982**, *23*, 403.
(12) Hudrlik, P. F.; Peterson, D. *J. Am. Chem. Soc.* **1975**, *97*, 1467.
(13) Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1983**, *24*, 3343.

0022-3263/84/1949-4671$01.50/0

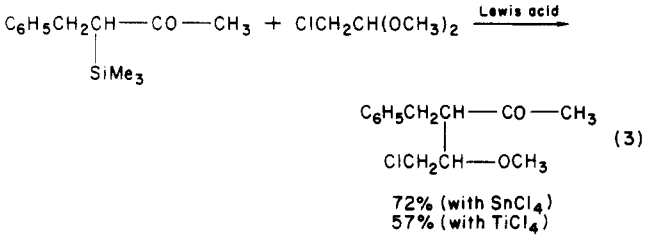
Table I. Aldol Reactions of 1 with Aldehydes Catalyzed by BF_3OEt_2

	R^1	R^2	R	yield of 3, %
a	$C_6H_5CH_2$	H	C_6H_5	87 (71,[a] 81[b])
b	$C_6H_5CH_2$	H	C_8H_{17}	78
c	CH_3	CH_3	C_6H_5	78
d	CH_3	CH_3	C_5H_{11}	78
e	CH_3CH_2	CH_3	C_6H_5	81
f	CH_3CH_2	CH_3	C_5H_{11}	76
g	$C_6H_5CH_2$	CH_3	C_6H_5	73

[a] Yield on using $TiCl_4$. [b] Yield on using $SnCl_4$.

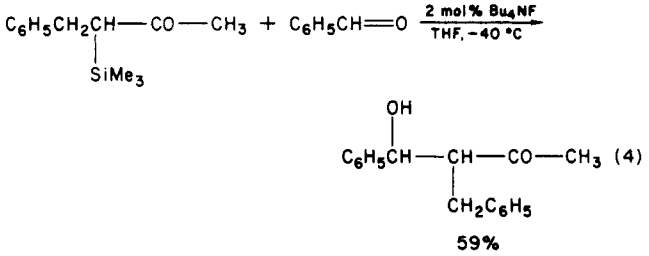
removal of the silyl group as suggested by analogy with silyl enol ethers.[15,16]

An acetal was found to react similarly with 1 in the presence of $SnCl_4$ or $TiCl_4$, but BF_3OEt_2 did not effect this type of condensation reaction (eq 3).



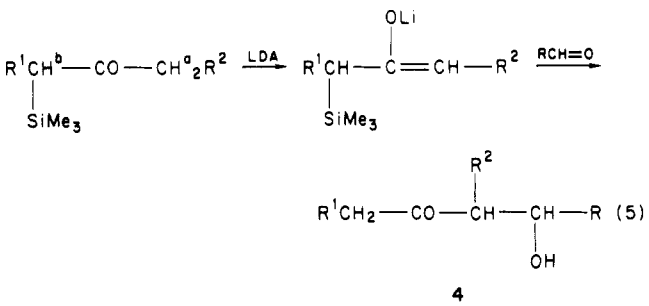
(3)

Fluoride anion also catalyzed the regioselective aldol reaction[6,17] of 1 with aldehydes but gave less satisfactory results (eq 4).



(4)

In connection with the well-documented anion stabilizing effect[8] of the silyl group, it seems to be quite interesting to clarify which proton, H^a or H^b of 1 (eq 5), is



(5)

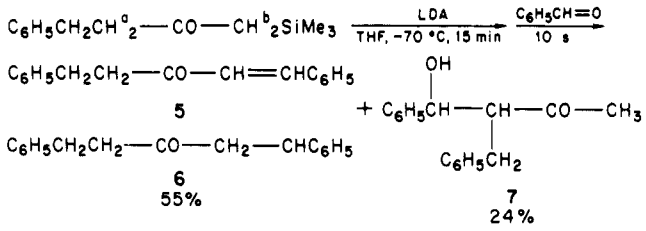
4

more kinetically acidic. In order to compare the relative acidities, methyl ketone 1 (R^1 = $C_6H_5CH_2$, R^2 = H) was treated with lithium diisopropylamide (LDA) at −78 °C for 15 min in tetrahydrofuran (THF), and the resulting solution was subsequently quenched with an equimolar amount of an aldehyde at −78 °C for 15 min. The usual acidic workup of the reaction mixture gave the aldol adduct 4, a regioisomer of 3. Interestingly this aldol reaction also proceeds regiospecifically, giving 4 as a sole aldol product without any formation of regioisomers 3. When a higher reaction temperature (−50 °C) and a prolonged period (3–4 h) for generation of enolates were used, ethyl ketones 1 (R^2 = CH_3) also underwent deprotonation of H^a selectively and afforded the corresponding aldol products 4 of the same type. The results are shown in Table II.

Table II. Aldol Reactions of 1 with Aldehydes under the Influence of LDA

	R^1	R^2	R	yield of 4, %
a	$C_6H_5CH_2$	H	C_6H_5	82
b	$C_6H_5CH_2$	H	C_8H_{17}	78
c	CH_3	CH_3	C_6H_5	95
d	CH_3	CH_3	C_5H_{11}	78
e	CH_3CH_2	CH_3	C_6H_5	87
f	CH_3CH_2	CH_3	C_5H_{11}	72
g	$C_6H_5CH_2$	CH_3	C_6H_5	95

These results raise the question of whether a trimethylsilyl group lowers the acidity of an α-proton or whether it arises from the structural features that H^a is a methyl or methylene proton, whereas H^b is that of a methyne, which surpasses the anion stabilizing effect of the silyl group. In order to compare the directing effect of the silyl group, 4-phenyl-1-(trimethylsilyl)-2-butanone was chosen and generation of the enolate was examined. Treatment of the ketone with LDA followed by quenching with benzaldehyde gave a mixture of three products 5 (48%), 6 (7%), and 7 (24%), the first and second ones forming from the enolate generated by deprotonation of H^b and the last one from the enolate resulting from H^a deprotonation.

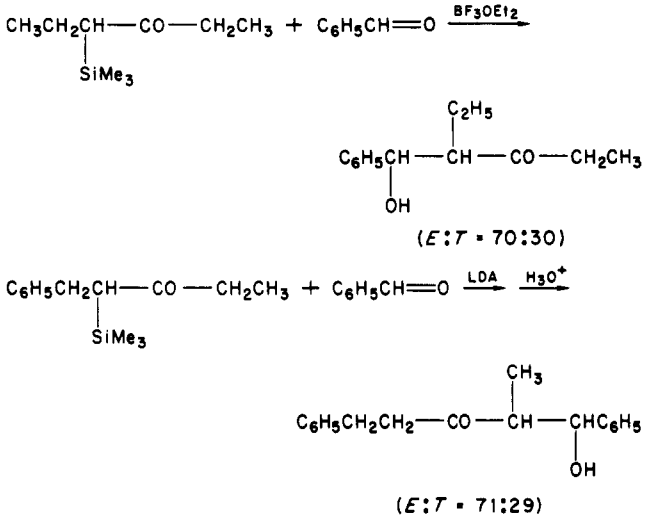


In comparison with the effect of an alkyl group, the trimethylsilyl group apparently favors deprotonation from the α-carbon as shown in the above experiment, but the selectivity is quite low (2.3:1) compared with the ratio of kinetic deprotonation from alkyl methyl ketones.[18] Thus, the silyl group of 1 acts as a blocking group rather than as an activating one, and kinetic deprotonation takes place selectively on the less substituted side of ketones 1 (R^1 = alkyl).

In summary, the trimethylsilyl group of 1 has been proven to play dual roles for specific generation of two types of enolates; under Lewis acidic conditions, α-trimethylsilyl ketones 1 behave similarly to the corresponding silyl enol ethers, whereas they are particularly useful for selective generation of another type of enolate under basic reaction conditions. This has made it possible to prepare two types of aldol adducts in a completely regiocontrolled manner just by choosing the reaction conditions. The only exceptional case is that of (trimethylsilyl)methyl ketones; use of LDA failed to generate the corresponding enolates regiospecifically and instead afforded a mixture of regioisomeric aldols. However, selective preparation of such kinds of aldols can be performed directly from the parent methyl ketones through kinetic deprotonation without any aid from the trimethylsilyl group.[19,20]

(14) Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1983**, *24*, 3347.
(15) Nakamura, E.; Shimada, J.; Horiguchi, Y.; Kuwajima, I. *Tetrahedron Lett.* **1983**, *24*, 3341.
(16) Nakamura, E.; Kuwajima, I. *Chem. Lett.* **1983**, 59.
(17) Nakamura, E.; Shimizu, M.; Kuwajima, I. *Tetrahedron Lett.* **1976**, 1699.
(18) House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1969**, *34*, 2324.
(19) Stork, G.; Kraus, G. A.; Garcia, G. A. *J. Org. Chem.* **1974**, *39*, 3459.
(20) Kuwajima, I.; Sato, T.; Arai, M.; Minami, N. *Tetrahedron Lett.* **1976**, 1817.

Finally, stereochemical results[21] have also been examined on these two types of aldol reactions, but, as shown below, only moderate erythro selectivities (ca. 70%) have been observed in the reactions of 1 with benzaldehyde both in the presence of boron trifluoride etherate and LDA.



Experimental Section

General Methods. Infrared (IR) spectra were recorded on a Hitachi EPI-G3 spectrometer; absorptions are given in reciprocal centimeters. Proton nuclear magnetic resonance spectra (^{1}H NMR) were obtained on a Hitachi R-24B spectrometer; chemical shifts (δ) are expressed in part per million downfield from internal tetramethylsilane. Microanalysis were performed with a Perkin Elmer 240 at the Microanalytical Laboratory, Tokyo Institute of Technology.

Reactions involving air- or moisture-sensitive compounds were carried out in appropriate round-bottomed flasks with magnetic stirring bars under nitrogen or argon atmosphere.

Preparative thin-layer chromatography (TLC) was carried out on glass plates (20 × 20 cm) coated with Merck silica gel PF 254 (1 mm thick). Column chromatography was performed on Merck Kieselgel or Wakogel C-200.

Materials. Methyl α-(trimethylsilyl)alkyl ketones were prepared by reaction of the corresponding (α-chloroacyl)trimethylsilanes with methylmagnesium iodide.[9] Other ketones were prepared by treating (α-chloroacyl)trimethylsilanes with 2 equiv of an appropriate Grignard reagent followed by Collins oxidation[12] of the resulting β-(trimethylsilyl)alkanols.[9] The following spectral data were obtained for each compound. **2-(Trimethylsilyl)-3-pentanone**: IR (neat) 1690; NMR (CCl_4) 0.20 (s, 9 H), 0.6-1.2 (m, 6 H), 1.8–2.4 (m, 3 H). **4-(Trimethylsilyl)-3-hexanone**: IR (neat) 1690; NMR (CCl_4) 0.20 (s, 9 H), 0.8–1.4 (m, 8 H), 2.0–2.5 (m, 3 H). **4-Phenyl-3-(trimethylsilyl)-2-butanone**: IR (neat) 1690; NMR (CCl_4) 0.20 (s, 9 H), 1.70 (s, 3 H), 2.2–3.2 (m, 3 H), 7.02 (s, 5 H). **1-Phenyl-2-(trimethylsilyl)-3-pentanone**: IR (neat) 1690; NMR (CCl_4) 0.10 (s, 9 H), 0.82 (t, J = 9 Hz, 3 H), 1.9–3.7 (m, 5 H), 7.00 (s, 5 H). **4-Phenyl-1-(trimethylsilyl)-2-butanone** was prepared by addition of [(trimethylsilyl)-methyl]lithium to 3-phenylpropanal followed by Collins oxidation of the resulting alcohol.[12]

The Reaction of 4-Phenyl-3-(trimethylsilyl)-2-butanone with Benzaldehyde in the Presence of BF_3OEt_2. A General Procedure for the Preparation of Aldols 3. A dichloromethane solution (1.5 mL) of the silyl ketone 1 (R^1 = $C_6H_5CH_2$, R^2 = H) (222 mg, 1 mmol) and benzaldehyde (108 mg, 1 mmol) was added to boron trifluoride etherate (146 mg, 1 mmol) in dichloromethane (0.5 mL) at −78 °C and it was stirred for 1 h at −78 °C and then for 30 min at −40 °C. The reaction mixture was quenched with saturated aqueous NaCl and washed with aqueous Na_2CO_3 solution. The aqueous layer was extracted with ether and the combined organic layers were dried over anhydrous $MgSO_4$. Removal of the solvent followed by purification with TLC afforded 3-benzyl-4-hydroxy-4-phenyl-2-butanone (**3a**) (215 mg, 86%), which was identified by comparison with the authentic sample prepared by the reported procedure.[22] Similarly, other aldol products **3** were obtained. **3-Benzyl-4-hydroxy-2-dodecanone (3b)** was identified by comparison with the authentic sample.[22] **1-Hydroxy-2-methyl-1-phenyl-3-pentanone (3c)**: IR (neat) 3405, 1695; NMR (CCl_4) 0.60–1.10 (m, 6 H), 1.78–2.95 (m, 3 H), 3.50–3.85 (b s, 1 H), 4.55 (d, J = 9 Hz, 0.3 H), 4.81 (d, J = 6 Hz, 0.7 H), 7.23 (s, 5 H). Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 75.03; H, 8.59. The erythro to threo ratio was determined by comparison of the ratio of benzylic proton appearing at 4.81 (erythro) and 4.55 (threo). **5-Hydroxy-4-methyl-3-decanone (3d)**: IR (neat) 3400, 1700; NMR (CCl_4) 0.6–1.7 (m, 17 H), 2.0–2.7 (m, 4 H), 3.2–3.9 (b s, 1 H). **1-Hydroxy-2-ethyl-1-phenyl-3-pentanone (3e)**: IR (neat) 3410, 1700; NMR (CCl_4) 0.5–1.1 (m, 6 H), 1.3–2.9 (m, 5 H), 3.1–3.6 (b s, 1 H), 4.42 (d, J = 7 Hz, 1 H), 7.00 (s, 5 H). Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.53; H, 8.95. **5-Hydroxy-4-ethyl-3-decanone (3f)**: IR (neat) 3400, 1700; NMR (CCl_4) 0.5–1.9 (m, 19 H), 2.2–2.7 (m, 3 H), 2.6–3.2 (b s, 1 H), 3.2–3.8 (m, 1 H). **2-Benzyl-1-hydroxy-1-phenyl-3-pentanone (3g)**: IR (neat) 3405, 1700; NMR (CCl_4) 0.70 (d, J = 6 Hz) and 1.00 (d, J = 10 Hz, 3 H), 2.2–3.9 (m, 4 H), 3.45 (q, J = 7 Hz, 1 H), 3.2–4.0 (b s, 1 H), 4.57 (d, J = 6 Hz) and 4.78 (d, J = 10 Hz, 1 H), 7.05 (s, 5 H), 7.12 (s, 5 H). Anal. Calcd for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.38; H, 7.72.

The Reaction of 4-Phenyl-3-(trimethylsilyl)-2-butanone with Chloroacetaldehyde Dimethyl Acetal in the Presence of $SnCl_4$. The reaction was performed by using an equimolar amount of $SnCl_4$ in a similar manner as above and 3-benzyl-5-chloro-4-methoxy-2-pentanone was obtained in 72% yield: IR (neat) 1710; NMR (CCl_4) 1.68 and 1.72 (s, 3 H), 2.5–4.1 (m, 6 H), 3.32 and 3.45 (s, 3 H), 7.15 (s, 5 H).

Fluoride Ion Catalyzed Aldol Reaction of 4-Phenyl-3-(trimethylsilyl)-2-butanone with Benzaldehyde. The silyl ketone 1 (222 mg, 1 mmol) and benzaldehyde (108 mg, 1 mmol) in THF (2 mL) were added to tetrabutylammonium fluoride (5.2 mg, 0.02 mmol) at −78 °C and the resulting solution was stirred for 3 h at −40 °C. Then, the solvent was removed and the residual oil was separated by TLC to give 3-benzyl-4-hydroxy-4-phenyl-2-butanone (150 mg, 59%).

The Reaction of 4-Phenyl-3-(trimethylsilyl)-2-butanone with Benzaldehyde in the Presence of LDA. A General Procedure for the Preparation of Aldols 4. Diisopropylamine (111 mg, 1.1 mmol) was treated with butyllithium (0.66 mL of 1.5 M hexane solution) in THF (2 mL) at 0 °C. To the resulting solution was added a THF (1.5 mL) solution of 4-phenyl-3-(trimethylsilyl)-2-butanone 1 (220 mg, 1 mmol) at −78 °C and it was stirred for 15 min at that temperature. Then, a THF (1 mL) solution of benzaldehyde (106 mg, 1 mmol) was added and the mixture kept stirring for 15 min at −78 °C. The reaction mixture was quenched with dilute HCl, the aqueous layer was extracted with ether, and the combined organic layer was dried over anhydrous $MgSO_4$. Removal of the solvent followed by purification with TLC gave 1,5-diphenyl-1-hydroxy-3-pentanone (**4a**) (203 mg, 82%). The product was identified by comparison with the authentic sample prepared by the reported procedure.[22]

Similarly, other aldol products **4** were obtained. When ethyl ketones were used, generation of enolates was performed at −50 °C for 3–4 h. **5-Hydroxy-1-phenyl-3-tridecanone (4b)**: IR (neat) 3400, 1705; NMR (CCl_4) 0.3–1.4 (m, 17 H), 2.20–2.72 (m, 6 H), 2.85–3.12 (b s, 1 H), 3.45–4.00 (m, 1 H), 7.10 (s, 5 H). Anal. Calcd for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.78; H, 10.14. The products **4c** and **4d** were identical with **3c** and **3d**, respectively.

1-Hydroxy-2-methyl-1-phenyl-3-hexanone (4e): IR (neat) 3400, 1700; NMR (CCl_4) 0.6–1.8 (m, 8 H), 2.0–2.9 (m, 3 H), 2.9–3.2 (b s, 1 H), 4.35–5.00 (m, 1 H), 7.04 (s, 5 H). Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.86; H, 8.71. **6-**

(21) For reviews on stereochemistry of aldol reaction: Evans, D. A.; Nelson, J. V.; Taber, T. R. "Topics in Stereochemistry"; John Wiley & Sons: New York, 1982; Vol. 13, p 1. Heathcock, C. H. "Asymmetric Synthesis"; Morrison, J. D., Ed; Academic Press: New York, 1983; Chapter 2.

(22) Inoue, T.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 174.

Hydroxy-5-methyl-4-undecanone (4f): IR (neat) 3400, 1700; NMR (CCl_4) 0.6–2.9 (m, 19 H), 2.0–2.5 (m, 3 H), 2.7–3.1 (b s, 1 H), 3.2–3.8 (m, 1 H).

1,5-Diphenyl-1-hydroxy-2-methyl-3-pentanone (4g): IR (neat) 3410, 1700; NMR (CCl_4) 0.70 (d, J = 6 Hz) and 1.05 (d, J = 10 Hz, 3 H), 2.2–3.9 (m, 4 H), 3.45 (m, 1 H), 3.2–4.0 (b s, 1 H), 4.53 (d, J = 6 Hz) and 4.76 (d, J = 10 Hz, 1 H), 7.05 (s, 5 H), 7.12 (s, 5 H). Anal. Calcd for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.77; H, 7.36. The erythro to threo ratio was determined by comparison of the ratio of benzylic protons appearing at 4.76 (erythro) and 4.53 (threo).

Registry No. **1a**, 66581-82-6; **1c**, 70280-36-3; **1e**, 70280-37-4; **1g**, 69583-57-9; **3a**, 62730-80-7; **3b**, 70280-44-3; **3c** (isomer 1), 71699-15-5; **3c** (isomer 2), 71699-16-6; **3d**, 70280-40-9; **3e**, 92694-77-4; **3f**, 92694-78-5; **3g**, 70280-45-4; **4a**, 62731-45-7; **4b**, 70280-38-5; **4e**, 70280-41-0; **4f**, 70280-42-1; **4g** (isomer 1), 77189-68-5; **4g** (isomer 2), 77189-62-9; **5**, 62510-08-1; LDA, 4111-54-0; BF_3OEt_2, 109-63-7; $TiCl_4$, 7550-45-0; $SnCl_4$, 7646-78-8; $C_6H_5CH{=}O$, 100-52-7; $C_8H_{17}CH{=}O$, 124-19-6; $C_5H_{11}CH{=}O$, 66-25-1; $ClCH_2CH(OCH_3)_2$, 97-97-2; $C_6H_5CH_2CH_2(CO)CH_2SiMe_3$, 92694-79-6; 5-chloro-4-methoxy-3-(phenylmethyl)pentan-3-one, 70280-48-7.

Hydrofluoric Acid Catalyzed Intramolecular Diels–Alder Reactions[1]

William R. Roush,*[2] Herbert R. Gillis, and Amy P. Essenfeld

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

Received October 20, 1983

Studies of catalysis of intramolecular Diels–Alder reactions of trienes activated with substituted 2-hydroxyethyl esters are described. Triene esters **1**, **11**, **22**, and **26** cyclize in moderate to good yield (44–78%) when exposed to aqueous HF in acetonitrile at 23 °C. These results appear not to be the consequence of simple protic acid catalysis since trienes **5**, **13**, **14**, and **33** fail to cyclize under analogous conditions. Rather, a mechanism involving the cyclization of a reversibly generated dioxolenium ion (e.g., **16**) is proposed. Although very little relative asymmetric induction was realized, these hydrofluoric acid promoted cyclizations proved to be highly stereoselective otherwise. Products of endo cycloaddition were obtained exclusively in the cyclizations of **11**, **26**, and **30**, and the cyclization of **22** was more selective (96:4 mixture of endo and exo cycloadducts) than the Lewis acid assisted cyclization of methyl ester **35** (88:12). The method at present is limited to intramolecular cases since the cyclization of crotonate **41** with cyclopentadiene proceeded in very poor yield. Trienes possessing diene allylic alkoxyl groups (e.g., **38**) and (*Z*)-α,β-unsaturated dienophiles (e.g., **39**) are also unsuited substrates for this reaction.

For several years we have been interested in synthetic applications of intramolecular Diels–Alder reactions.[3,4] We have studied the stereochemistry of the cyclizations of activated deca-2,7,9-trienes and undeca-2,8,10-trienes and have shown that in many cases the best product ratios are obtained when the cycloadditions are performed in the presence of Lewis acids.[5] Unfortunately, a number of substrates decompose and fail to cyclize when exposed to Lewis acidic reagents. In addition, our preliminary studies of enantioselective intramolecular cycloadditions (which require Lewis acid catalysis for maximal stereochemical induction)[5b] afforded results far short of expectations based on bimolecular Diels–Alder analogies.[6]

In an attempt to extend Lewis acid catalysis to recalcitrant triene systems and to improve the facial selectivity in cyclizations of trienes possessing chiral dienophiles, we have studied the Lewis acid catalyzed cyclizations of trienes activated with 2-hydroxyethyl esters (cf. **1a**).[7] We imagined that treatment of such systems with an appropriate organometallic reagent (e.g., $EtAlCl_2$, $MeTiCl_3$,[8] or $MeNbCl_4$[9]) would effect cyclization via an internally coordinated alkoxymetal halide complex (e.g., **1a** → **2** → **3a**).[10] In principle, this would enable reactive or unstable functional groups to be isolated from the Lewis acid and, at the same time, restrict the number of degrees of freedom

(1) Portions of this work are described in the Ph.D. Thesis of H. R. Gillis, Massachusetts Institute of Technology, Cambridge, MA 1982.

(2) Holder of the Roger and Georges Firmenich Career Development Chair in Natural Products Chemistry, 1981–84; Fellow of the Alfred P. Sloan Foundation, 1982–84.

(3) Reviews: (a) Fallis, A. G. *Can. J. Chem.* **1984**, *62*, 183. (b) Ciganek, B. *Org. React. (N.Y.)*, in press. (c) Brieger, G.; Bennett, J. N. *Chem. Rev.* **1980**, *80*, 63. (d) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 10.

(4) See, for example: (a) Hall, S. E.; Roush, W. R. *J. Org. Chem.* **1982**, *47*, 4611. (b) Roush, W. R.; Peseckis, S. M. *Tetrahedron Lett.* **1982**, *23*, 4879. (c) Roush, W. R.; Myers, A. G. *J. Org. Chem.* **1981**, *46*, 1509. (d) Roush, W. R. *J. Am. Chem. Soc.* **1980**, *102*, 1390. (e) Roush, W. R.; Peseckis, S. M.; Walts, A. E. *J. Org. Chem.* **1984**, *49*, 3429.

(5) For leading references, see: (a) Roush, W. R.; Gillis, H. R. *J. Org. Chem.* **1982**, *47*, 4825. (b) Roush, W. R.; Gillis, H. R.; Ko, A. I. *J. Am. Chem. Soc.* **1982**, *104*, 2269. For other recent examples of catalyzed intramolecular Diels–Alder reactions, see: (c) Stork, G.; Clark, G.; Shiner, C. S. *J. Am. Chem. Soc.* **1981**, *103*, 4948. (d) Funk, R. L.; Zeller, W. E. *J. Org. Chem.* **1982**, *47*, 180. (e) Sternbach, D. D.; Rossana, D. M. *J. Am. Chem. Soc.* **1982**, *104*, 5853. (f) Bailey, M. S.; Brisdon, B. J.; Brown, D. W.; Stark, K. M. *Tetrahedron Lett.* **1983**, *24*, 3037. (g) Sakan, K.; Craven, B. M. *J. Am. Chem. Soc.* **1983**, *105*, 3732. (h) Shea, K. J.; Gilman, J. W. *Tetrahedron Lett.* **1983**, *24*, 657. (i) Attah-Poku, S. K.; Gallacher, G.; Ng, A. S.; Taylor, L. E. B.; Alward, S. J.; Fallis, A. G. *Ibid.* **1983**, *24*, 677. (j) See also the literature cited in ref 11.

(6) (a) Ensley, H. E.; Parnell, C. A.; Corey, E. J. *J. Org. Chem.* **1978**, *43*, 1610. (b) Boeckman, R. K., Jr.; Naegely, P. C.; Arther, S. D. *Ibid.* **1980**, *45*, 752. (c) Oppolzer, W.; Kurth, M.; Reichlin, D.; Moffatt, F. *Tetrahedron Lett.* **1981**, *22*, 2545. (d) Oppolzer, W.; Chapuis, C.; Dao, G. M.; Reichlin, D.; Godel, T. *Ibid* **1982**, *23*, 4781. (e) Oppolzer, W.; Kurth, M.; Reichlin, D.; Chapuis, C.; Mohnhaupt, M.; Moffatt, F. *Helv. Chim. Acta* **1981**, *64*, 2802. (f) Oppolzer, W.; Chapuis, C.; Kelly, M. *Ibid.* **1983**, *66*, 2358. (g) Helmchen, G.; Schmierer, R. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 208. (h) Choy, W.; Reed, L. A., III; Masamune, S. *J. Org. Chem.* **1983**, *48*, 1137. (i) Masamune, S.; Reed, L. A., III; Davis, J. T.; Choy, W. *J. Org. Chem.* **1983**, *48*, 4441. (j) Note added in proof. See also: Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1984**, *106*, 4261.

(7) These studies are decribed fully in ref 1.

(8) DeVries, H. *Recl. Chim.* **1961**, *80*, 866.

(9) Santini-Scampucci, C.; Riess, J. G. *J. Chem. Soc., Dalton Trans.* **1973**, 2436; **1974**, 1433.

(10) Alkoxyaluminum dichlorides are excellent catalyst for Diels–Alder reactions: see ref 5a,b and Hashimoto, S.-I.; Komeshima, N.; Koga, K. *J. Chem. Soc., Chem. Commun.* **1979**, 437.

0022-3263/84/1949-4674$01.50/0