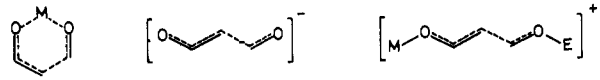
A Stereoselective Aldol-Type Condensation of Enol Silyl Ethers and Acetals Catalyzed by Trimethylsilyl Trifluoromethanesulfonate[1]

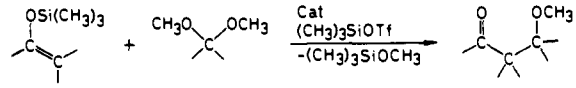
Sir:

Aldol-type reactions[2] in aprotic organic solvents are divided into three classes depending on the method of activation of the enolates and carbonyl substrates. Most reactions are achieved with enolates possessing a Lewis acidic metal counterion[3-6] that can accept the two oxygen atoms as ligands. Such reactions proceed via a six-membered chelate transition state of type I (M = metallic species) assembled by the metal enolate and carbonyl compound. The second type is the combination of a nucleophilically activated, naked enolate and unactivated carbonyl compound.[7] Yet unknown is the reaction of an unactivated enolate and an electrophilically activated carbonyl substrate. The latter two reactions would proceed through acyclic transition states of type II and III (E = cationic activating species), respectively, and consequently could exhibit unique selectivities not observable in aldol reactions by way of I. Disclosed herein is a new, highly selective reaction which is categorized into the third, unexplored class of condensation.



I II III

The reaction of enol silyl ethers (**1**) and acetals (**2**) or certain ortho esters, giving the aldol products (**3**), is accomplished by

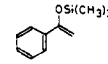
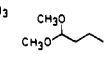
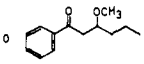
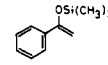
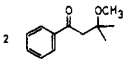
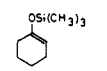
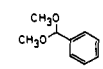
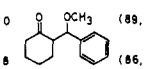
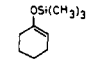
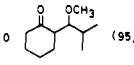
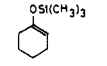
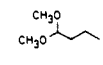
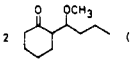
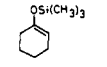
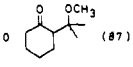
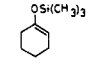
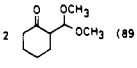
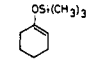
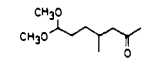
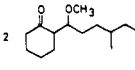
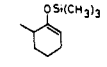
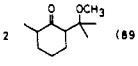
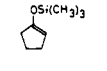
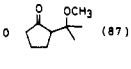
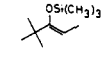
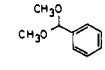
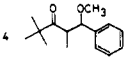
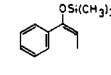
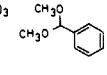
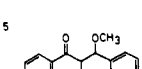
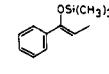
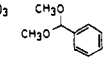
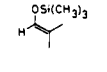


1 2 3

the use of trimethylsilyl trifluoromethanesulfonate (**4**) as the catalyst (1–5 mol %). The examples are given in Table I. The typical experimental procedure is provided by the reaction of 1-trimethylsiloxycyclohexene (**5**) and benzaldehyde dimethyl acetal (**6**) (entry 3). A mixture of **5** (0.873 g, 5.12 mmol) and **6** (0.833 g, 5.47 mmol) in dry dichloromethane (15 mL) placed under argon was cooled at −78 °C, and to this was added a 0.1 M dichloromethane solution of **4** (0.5 mL, 0.05 mmol). The mixture was stirred at −78 °C for 8 h and quenched by adding water at the same temperature. The product was extracted with dichloromethane and worked up in a usual manner. The crude oil, consisting of a 93:7 mixture of *erythro*- and *threo*-2-(methoxyphenylmethyl)-1-cyclohexanone (**7** and **8**), was chromatographed on silica gel (20 g, 10:1 mixture of petroleum ether and ether as eluant) to give pure **7** (less polar; 0.920 g, 82% yield) and **8** (more polar; 0.097 g, 6.7% yield) as oils. No polycondensation product, self-condensation product, or α,β-unsaturated carbonyl compound was formed by this reaction. The stereochemistries of the diastereomers **7** and **8** were determined by comparison with the authentic samples prepared stereospecifically from the corresponding aldols[8] by treatment with butyllithium (1 equiv, THF–ether, −78 °C) and then methyl fluorosulfate (1 equiv, −78 °C) (20–30% yield).

The characteristic features of the conceptually new aldol reaction follow. (1) The reaction conditions are extremely mild (low temperatures, aprotic, nonbasic, and only very weak nucleophiles present). (2) The reaction is irreversible and the adducts are kinetically determined. (3) The absence of equilibrium (double-bond migration) in enol silyl ethers allows for the regiospecific aldol reaction (entry 10). (4) Crossed and directed reactions between aldehydes and ketones, in a formal sense, are possible. The example of entry 16 can be viewed as the otherwise difficult combination of an aldehyde enolate and a ketone.[9] (5) The easiness with which the reaction occurs is sensitive to steric environment of double bonds in enol silyl ethers.[10] (6) Acetals are highly reactive receptors of enol silyl ethers but, remarkably, the parent aldehydes and ketones *do not* react with enol silyl ethers. Attempted reaction of the enol silyl ether **5** and benzaldehyde, isobutyraldehyde, benzophenone, or cyclohexanone under comparable catalytic conditions resulted in recovery of the starting materials. Reaction of **5** with a 1:1 mixture of butanal dimethyl acetal and pentanal produced only the acetal condensation product leaving the aldehyde intact (see also entry 9 of Table I). Thus the acetal function has proved to act as an activating group, rather than protecting group, in this aldol-type reaction.[11] (7) In the re-

Table I. Condensation of Enol Silyl Ethers with Acetals or Ortho Esters Catalyzed by Trimethylsilyl Trifluoromethanesulfonate

entry	enol silyl ether	acetal or orthoester	conditions: catalyst, mol %	temp, °C	time, h	product[a] (% yield,[b] erythro/threo)
1			5	−78	10	 (75)
2			5	−78	12	 (96)
3			1	−78	10	 (89, 93:7[c])
4			5	−90	8	(86, 92:8[c])
	5	6				7 (erythro) 8 (threo)
5			1	−78	10	 (95, 86:14[d])
6			1	−78	12	 (91, 89:11[d])
7			5	−78	10	 (87)
8		$(CH_3O)_3CH$	5	−78	12	 (89)
9			5	−78	12	 (92)[e]
10			5	−78	12	 (89)[f]
11			5	−78	10	 (87)
12			5	−78	4	 (94, 95:5[c])
13			5	−78	5	 (83, 71:29[c])
14			5	−78	4	(97, 84:16[c])
15			5	−78	4	(89)
16			5	−78	4	(85)
17			5	−78	4	(87)

[a] All products were identified by ^1H NMR and IR spectra. All new compounds gave satisfactory elemental analyses. The stereochemistries (threo or erythro) were determined by independent synthesis of the methyl ethers. [b] Isolated yield. [c] Determined by ^1H NMR analysis. [d] Isolated ratio. [e] A mixture of diastereomers. [f] A mixture of cis and trans isomers.

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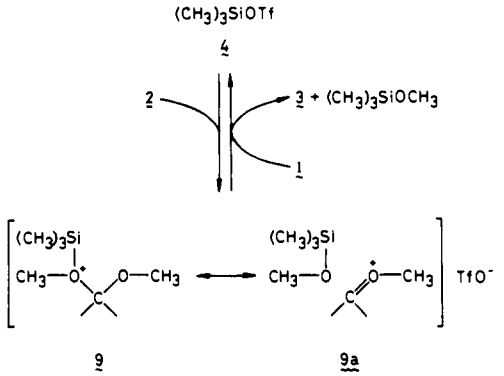
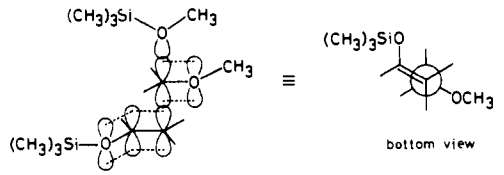
action creating new chiral centers, a high to moderate degree (depending on the systems) of stereoselectivity is obtained. Both (*E*)- and (*Z*)-enol silyl ethers give the erythro adducts selectively (entries 3–6 and 12–14), in sharp contrast to the stereoselection observed in ordinary aldol reaction.[3-5,6a]

The use of trimethylsilyl moiety as both protecting group of enolates and initiator of the reaction allows this group serving as the chain carrier of the catalytic cycle involving supercationic species.[12] Electrophilic attack of the silyl triflate **4** on an oxygen atom of the acetal **2** generates the reactive oxonium intermediate **9**[13] that is in resonance with a methylcarboxonium ion/methoxytrimethylsilane contact pair, **9a**.[14]



9 9a

Subsequent nucleophilic displacement by the enol silyl ether **1** gives rise to the condensation product **3** and methoxytrimethylsilane, accompanied by regeneration of the catalyst **4**.[15] The observed stereoselection is best accounted for in terms of the acyclic extended transition states of type **10** in which



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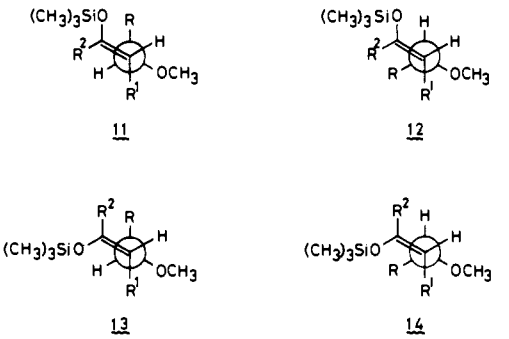
electrostatic repulsion is minimized. In the reaction of enol silyl ethers possessing *E* configuration, the transition state **11** (R = phenyl or alkyl; R^1 and R^2 = alkyl) leading to the erythro isomer is sterically favored over the diastereomeric transition state **12** affording the threo adduct, in accord with the experimental findings (entries 3–6 and 13). In a like manner, the erythro transition state **13** (R = phenyl; R^1 = alkyl; R^2 = phenyl or alkyl) resulting from (*Z*)-enol silyl ethers is preferable to the alternative threo transition state **14** (entries 12 and 14).



11 12

13 14

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Supplementary Material Available: Spectral and analytical data for new compounds (4 pages). Ordering information is given on any current masthead page.

References and Notes

(1) Trialkylsilyl Triflates. 5. Part 4: Murata, S.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 767.
(2) Reviews: Nielsen, A. T.; Houlihan, W. J. *Org. React.* **1968**, *16*, 1. House, H. O. "Modern Synthetic Reactions", 2nd ed.; Benjamin: Menlo Park, 1972, pp 629–682.
(3) (a) Li^+: Kleschick, W. A.; Buse, C. T.; Heathcock, C. H. *J. Am. Chem. Soc.* **1977**, *99*, 247. (b) Li^+: Dubois, J. E.; Fellmann, P. *Tetrahedron Lett.* **1975**, 1225. Buse, C. T.; Heathcock, C. H. *J. Am. Chem. Soc.* **1977**, *99*, 8109. Meyers, A. I.; Reider, P. J. *Ibid.* **1979**, *101*, 2501. Heathcock, C. H.; White, C. T. *Ibid.* **1979**, *101*, 7076. Heathcock, C. H.; Pirrung, M. C.; Buse, C. T.; Hagen, J. P.; Young, S. D.; Sohn, J. E. *Ibid.* **1979**, *101*, 7077. (c) Li^+, Mg^{2+}, Zn^{2+}: House, H. O.; Crumrine, D. S.; Teranishi, A. Y.; Olmstead, H. D. *Ibid.* **1973**, *95*, 3310.
(4) B^{3+}: Mukaiyama, T.; Inoue, T. *Chem. Lett.* **1976**, 559. Inoue, T.; Uchimaru, T.; Mukaiyama, T. *Ibid.* **1977**, 153. Fenzl, W.; Köster, R.; Zimmerman, H.-J. *Justus Liebigs Ann. Chem.* **1975**, 2201. Masamune, S.; Van Horn, D.; Brooks, D. W. *Tetrahedron Lett.* **1979**, 1665. Van Horn, D. E.; Masamune, S. *Ibid.* **1979**, 2229. Hirama, M.; Garvey, D. S.; Lu, L. D.-L.; Masamune, S. *Ibid.* **1979**, 3937. Evans, D. A.; Vogel, E.; Nelson, J. V. *J. Am. Chem. Soc.* **1979**, *101*, 6120. Inoue, T.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 174.
(5) Al^{3+}: Jeffery, E. A.; Meisters, A.; Mole, T. *J. Organomet. Chem.* **1974**, *74*, 373. Maruoka, K.; Hashimoto, S.; Kitagawa, Y.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 7705. Nozaki, H.; Oshima, K.; Takai, K.; Ozawa, S. *Chem. Lett.* **1979**, 379.
(6) Ti^{4+}: (a) Mukaiyama, T.; Narasaka, K.; Banno, K. *Chem. Lett.* **1973**, 1011. Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503. (b) Chan, T. H.; Aida, T.; Lau, P. W. K.; Gorys, V.; Harpp, D. N. *Tetrahedron Lett.* **1979**, 4029.
(7) Quaternary ammonium enolates: Noyori, R.; Yokoyama, K.; Sakata, J.; Kuwajima, I.; Nakamura, E.; Shimizu, M. *J. Am. Chem. Soc.* **1977**, *99*, 1265. See also ref 3a.
(8) Isomerically pure *erythro*- and *threo*-2-(hydroxyphenylmethyl)-1-cyclohexanone were obtained by chromatographic separation of the mixture obtained by reaction of cyclohexanone lithium enolate and benzaldehyde.[3c]
(9) For directed aldol and related reactions, see ref 6 and the following: Wittig, G.; Frommeld, H.-D. *Chem. Ber.* **1964**, *97*, 3548. Wittig, G.; Suchanek, P. *Tetrahedron, Suppl.* **1966**, No. 8, Part I, 347. Corey, E. J.; Enders, D. *Tetrahedron Lett.* **1976**, 3. Corey, E. J.; Enders, D.; Bock, M. G. *Ibid.* **1976**, 7.
(10) Reaction of a 1:1 mixture of **5** and its 2-methylated derivative with acetone dimethyl acetal (2 equiv) in the presence of **4** (5 mol %) produced only the adduct of **5** in 90% yield.
(11) Reaction of enol silyl ethers and acetals or carbonyl compounds using a stoichiometric amount of $TiCl_4$ is known (ref 6 and Mukaiyama, T.; Hayashi, M. *Chem. Lett.* **1974**, 15). Stereoselectivity of the $TiCl_4$-promoted reaction of acetals is lower than that of the present reaction. For instance, the reaction of 1-trimethylsiloxycyclohexene and isobutyraldehyde dimethyl acetal gave the erythro:threo ratio of 55:45.
(12) The cationic intermediates under such conditions have only negligible interactions with the counter anion (triflate) or solvents and, consequently, display strong electrophilic behavior. The silyl triflate **4**, though having a covalent Si–O bond, affords the lowest ^{29}Si NMR chemical shift among various trimethylsilyl derivatives: Marsmann, H. C.; Horn, H.-G. *Z. Naturforsch. B.* **1972**, *27*, 1448.
(13) Murata, S.; Suzuki, M.; Noyori, R. *J. Am. Chem. Soc.* **1979**, *101*, 2738.
(14) In view of the lack of reactivity of carbonyl compounds, free methylcarboxonium ions are unlikely to be involved as the reactive species.
(15) Reaction of acetals and alkenyl alkyl ethers promoted by BF_3 may be mechanistically related: Isler, O.; Lindlar, H.; Montavon, M.; Ruegg, R.; Zeller, P. *Helv. Chim. Acta* **1956**, *39*, 249.

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^{13}C NMR Spectra of Cellulose Polymorphs

Sir:

We report high resolution ^{13}C NMR spectra of the two major crystalline polymorphs of cellulose and an amorphous sample, recorded using the cross polarization/magic angle spinning (CP/MAS) technique. The spectra provide important new evidence concerning the basic structure of cellulose; they demonstrate nonequivalence of adjacent anhydroglucose units and are consistent with conformational differences between the polymorphs.

Cellulose, which is the primary constituent of plant cell walls, is the β-1,4 polymer of anhydroglucose. Its two most common polymorphs, celluloses I and II, are usually identified with the native and the mercerized or regenerated forms, re-

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