nistic details, dioxirane oxyfunctionalization of vitamin D_3 metabolite precursors shows promise of considerable practical value because of its efficiency and simplicity of approach.

Acknowledgment. We thank the Board of Progetto Finalizzato C.F.-II of the CNR (Rome, Italy) and the Ministry of University, Scientific and Technological Research (MURST 40) of Italy for partial support.

How Can High Diastereoselectivity Be Attained in the Michael Addition of Ketene Silyl Acetals?

Junzo Otera,* Yukihiro Fujita, Tsuneo Sato, and Hitosi Nozaki

Department of Applied Chemistry, Okayama University of Science, Ridai-cho, Okayama 700, Japan

Shunichi Fukuzumi* and Morifumi Fujita

Department of Applied Chemistry, Faculty of Engineering, Osaka University, Suita, Osaka 565, Japan

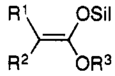
Received July 6, 1992

Summary: Criteria for attaining high diastereoselectivity in the title reaction are elucidated in terms of suppressing an electron-transfer process.

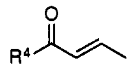
Michael addition of ketene silyl acetals to α-enones (Mukaiyama–Michael reaction) is a powerful means for carbon–carbon bond formation.[1] Stereocontrol of this reaction would be highly desired in the context of "acyclic stereoselection".[2] Nonetheless, it has been generally accepted that the reaction is virtually nonstereoselective, in particular, with regard to the relative topicity between two prochiral centers (simple diastereoselection).[3] Recently, we disclosed that this reaction, especially when β-substituted acetals were employed, involved an electron-transfer process which necessarily gave rise to loss of the stereoselectivity as a consequence of double-bond isomerization of the reactants.[4] In other words, the high stereoselectivity may be achievable if the electron transfer is suppressed and the transition-state geometry of an alternative nucleophilic reaction is sterically controlled. This hypothesis has prompted us to address the entitled problem.

The only precedent of the high stereoselection was put forth by Heathcock et al.[5] $TiCl_4$-promoted reaction between ketene silyl acetal **1b** and enone **2a** resulted in an exceptionally high syn/anti ratio (99:1 simple diastereoselection) (see Table I, entry 1), a very promising clue to the present subject. The *E* isomer **1c** provides the same outcome (entry 2).[6] Accordingly, we have begun with the scrutiny of this reaction.

One of the grounds on which we advanced the electron-transfer mechanism lies in unexpected competition reaction where β-substituted ketene silyl acetals react in preference to the corresponding less substituted ones.



1a R^1 = Me R^2 = Me Sil = TBS R^3 = ^{t}Bu
b = Me = H = TBS = ^{t}Bu
c = H = Me =TBS = ^{t}Bu
d = H = H = TBS = ^{t}Bu
e = Me = Me = TBS = bornyl
f = H = Me = TBS = bornyl
g = H = H = TBS = bornyl
h = H = Me = TMS = bornyl
i = H = Me = TES = ^{t}Bu
j = H = Me = TBS = $CH_2{}^t$Bu
k = H = Me = TBS = Me



2a R^4 = ^{t}Bu
b = 2,4,6-$Me_3C_6H_2$
c = 4-$MeOC_6H_4$

When a similar competition is run employing *tert*-butyldimethylsilyl (TBS) enolates of *tert*-butyl esters, **1a**, **1c**, and **1d**, the preference is completely opposite from that of conventional less bulky ketene silyl acetals such as triethylsilyl (TES) enolates of ethyl esters.[4] The less sterically crowded products always predominate, suggesting that the electron-transfer process is unlikely (Scheme I). Apparently, incorporation of TBS and *tert*-butoxy groups dramatically changes the reactivity of the ketene silyl acetals. The PM_3 semiempirical molecular orbital calculations[7,8] demonstrate that introduction of these elec-

---

(1) Saigo, K., Osaki, M.; Mukaiyama, T. *Chem. Lett.* **1976**, 163. Kobayashi, S.; Mukaiyama, T. *Chem. Lett.* **1986**, 1805. Kobayashi, S.; Mukaiyama, T. *Chem. Lett.* **1987**, 1183. Hashimoto, Y.; Sugumi, H.; Okauchi, T.; Mukaiyama, T. *Chem. Lett.* **1987**, 1691. Minowa, N.; Mukaiyama, T. *Chem. Lett.* **1987**, 1719. Kobayashi, S.; Tamura, M.; Mukaiyama, T. *Chem. Lett.* **1988**, 91.

(2) Oare, D. A.; Heathcock, C. H. In *Topics in Stereochemistry*; Eliel, E. L., Wilen, S. H., Eds.; Wiley: New York, 1991; Vol. 20, p 87.

(3) Recently, Danishefsky disclosed γ-substituent-induced diastereoselection for cyclic α-enones: Danishefsky, S. J.; Simoneau, B. *J. Am. Chem. Soc.* **1989**, *111*, 2599. Danishefsky, S. J.; Cabal, M. P.; Chow, K. *J. Am. Chem. Soc.* **1989**, *111*, 3456. Jeroncic, L.; Cabal, M.-P.; Danishefsky, S. J.; Shulte, G. M. *J. Org. Chem.* **1991**, *56*, 387.

(4) Sato, T.; Wakahara, Y.; Otera, J.; Nozaki, H.; Fukuzumi, S. *J. Am. Chem. Soc.* **1991**, *113*, 4028.

(5) Heathcock, C. H.; Norman, M. H.; Uehling, D. E. *J. Am. Chem. Soc.* **1985**, *107*, 2797.

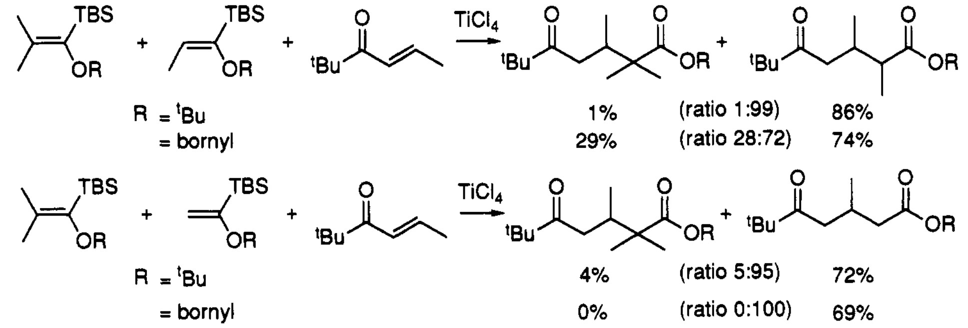
(6) Heathcock reported that reaction of **1c** with (*E*)-2,2,6-trimethyl-4-hepten-3-one gave rise to a 98:2 syn/anti ratio.[5]

(7) (a) Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 209, 221. (b) The PM_3 MO calculations were performed by using the MOPAC program (QCPE No. 455), which was revised as OS/2 Version 5.01 to adapt for the use on a NEC PC computer: Toyoda, J. *JCPE News Lett.* **1990**, *2*, 37.

(8) Final geometries and energetics were obtained by optimizing the total molecular energy with respect to all structural variables. The geometries of the radical cations were optimized using the unrestricted Hartree–Fock (UHF) formalism.

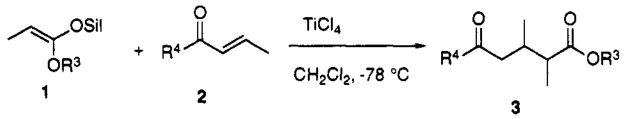
0022-3263/92/1957-5054$03.00/0

Scheme I^{a}



^{a}Reaction conditions: acetal:acetal:enone:TiCl$_4$ = 1:1:1:1, CH$_2$Cl$_2$, −78 °C, 1 h; the product ratio was determined by GLC.

Table I. Diastereoselective Michael Reaction of Ketene Silyl Acetals



entry	1	2	3 yield	3 syn:anti
1	**1b**	**2a**	84^{a}	>99:1^{a}
2	**1c**	**2a**	85^{a}	>99:1^{a}
3	**1f**	**2a**	84	97:3^{b}
4	**1h**	**2a**	74	90:10^{b}
5	**1i**	**2a**	86	90:10^{c}
6	**1j**	**2a**	90	92:8^{b}
7	**1k**	**2a**	93	71:29
8	**1c**	**2b**	99	91:9^{a}
9	**1j**	**2b**	93	90:10^{d}
10	**1c**	**2c**	63	52:48^{c}

^{a}Determined as methyl ester since the product is a mixture of *tert*-butyl and TBS ester (see ref 5). ^{b}Determined as 5-oxo-2,3,6,6-tetramethylheptyl benzoate by HPLC. ^{c}Determined as methyl ester after hydrolysis of *tert*-butyl ester. ^{d}Determined as 2,3-dimethyl-4-(mesitylcarbonyl)butyl benzoate by HPLC.

Table II. Rate Constants (k_{et}) of Photoinduced Electron Transfer from Ketene Silyl Acetals to the Singlet Excited State of Pyrene in MeCN at 298 K and the Adiabatic Ionization Potentials (I_a) Calculated by the PM$_3$ Method

ketene silyl acetal	k_{et}, M^{-1} s^{-1}	I_a,^{a} eV
Me$_2$C=C(OMe)OTMS	1.3×10^9	7.25
Me$_2$C=C(O^{t}Bu)OTBS	2.7×10^8	7.09
Me(H)C=C(OEt)OTES	1.0×10^9	7.44^{b}
Me(H)C=C(O^{t}Bu)OTBS	4.9×10^8	7.24

^{a}I_a values were calculated as the difference in the heat of formation (ΔH_f) between the radical cation and the parent neutral molecule. ^{b}Calculated for Me(H)C=C(OMe)OTMS.

tron-releasing groups results in the decrease of the adiabatic ionization potentials of these compounds in the gas phase as expected (Table II). Nevertheless, the one-electron oxidation potentials of these compounds *in solution* may be higher than those of less bulky ketene silyl acetals, since the rate constants of photoinduced electron transfer to the singlet excited state of pyrene becomes smaller by the introduction of bulky substituents[9] (Table II). These results lead us to postulate that incorporation of bulky groups should retard the electron transfer. Indeed, TBS enolates of bornyl esters, **1e**, **1f**, and **1g**, exhibit the analogous reactivity profiles (Scheme I). Of more importance is the high diastereoselectivity displayed by **1f** in the reaction with **2a** (Table I, entry 3). A few more comments are worthy of note with regard to the simple diastereoselection. Incorporation of a bornyl group is enough to suppress the electron transfer since the corresponding trimethylsilyl (TMS) enolate **1h** also shows satisfactory stereoselectivity (entry 4). Effectiveness of the bulky esters is evident from the results with *tert*-butyl and neopentyl esters (entries 5,6) while the TBS group alone does not suffice for this purpose (entry 7).

The enone partner also plays an important part. Heathcock's protocol was found to be stereoselective only when *tert*-butyl enone **2a** was employed.[5] The roles of the *tert*-butyl group seem to be 2-fold: (1) increasing donor property of carbonyl oxygen through inductive effect causing strong complexation of the α-enone with TiCl$_4$ and (2) biasing the transition-state geometry of nucleophilic reaction favoring the syn-product for steric reasons. In relation to these aspects, two α-enones, **2b** and **2c**, have been brought to the test. The mesityl group has proved to be effective (entries 8,9) whereas the anisyl group is not (entry 10). It follows that both requirements above need to be satisfied for gaining the high selectivity.

In addition, proper choice of Lewis acid is crucial as well. Use of Lewis acids other than TiCl$_4$ gave somewhat lower selectivities: the syn/anti ratios were 86:14 and 92:8 with SnCl$_4$ (57% yield) and TESClO$_4$, (63% yield), respectively, for the reaction between **1c** and **2a**. TiCl$_4$ is a strong oxygenophile, and hence, reduction potential of this Lewis acid is diminished upon tight complexation with α-enone.

We conclude that suppression of the electron-transfer process makes the Mukaiyama–Michael reaction of ketene silyl acetals stereoselective to a practical level. The following conditions must be fulfilled to this end. (1) Ketene silyl acetals should involve bulky silyl and/or alkoxy groups. These groups increase the ionization potential of the acetals in solution. (2) α-Enones should involve a bulky acyl moiety which is effective for enhancing the donor property of carbonyl oxygen and for increasing the steric demand of the transition state.[10] (3) Lewis acids should be strongly oxygenophilic so that reduction of these reagents by ketene silyl acetal is retarded. In addition, strong complexation renders the α-enone more susceptible to nucleophilic attack by ketene silyl acetal. These criteria no doubt serve for designing stereoselective reactions.

Supplementary Material Available: Procedures and compound characterization data (4 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.

---

(9) Increase of the ionization potential is interpreted in terms of less effective solvation for a cation radical of bulkier ketene silyl acetals.

(10) Discussion of the transition-state geometry will be given in a full paper.