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Diastereocontrol in Lewis Acid-Catalyzed Michael Reactions of 4-Siloxycyclopentenone with Ketene Silyl Acetals: Stereoelectronic vs. Steric Effect

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Abstract: *The title reactions are shown to proceed with sterically unfavorable syn preference (to the siloxy group) when steric demand of the acetals is trivial, whereas β-substitution of acetals results in reversal of diastereoselection. These results are discussed in terms of the stereoelectronic vs. steric effect.*

In 1989, Danishefsky et al. disclosed a unique diastereoselection in the HgI_2-catalyzed Michael reaction of 4-*t*-butyldimethylsiloxy-2-cyclopentenone (**1**), wherein ketene silyl acetal **2a** approaches the enone face preferentially from the side syn to the bulky TBSO group (eq. 1).[1,2] Since this outcome is not compatible with the usual steric control, they interpreted it in terms of stereoelectronic effect based on the Cieplak model.[2f] The σ* orbital of the incipient bond is stabilized by interaction with the σ orbital of the more electron-donating C-H bond that is located anti to the incoming nucleophile. As part of our continuing studies on stereocontrol in Sn (IV)[3]- and Eu (III)[4]-catalyzed aldol and Michael reactions, we have thoroughly investigated this sort of reaction. Reported herein are the preliminary results.

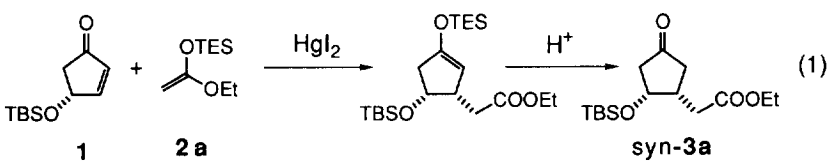
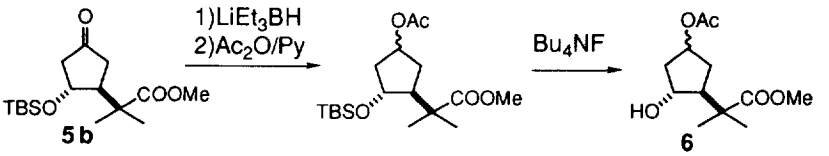


Table 1 summarizes the stereochemical results in the reaction of **1** with unsubstituted ketene silyl acetals **2** using various Lewis acids. All the Lewis acids employed result in syn preference, although the selectivities are slightly lower than that with HgI_2. Remarkably, however, the selectivity is reversed in the tris(diethylamino)sulfonium difluorotrimethylsilicate (TASF)-promoted reaction (entry 7): the 'normal' anti-isomer is a sole product. These results unambigously indicate that the Lewis acids play a key role for the unique syn diastereoselection.

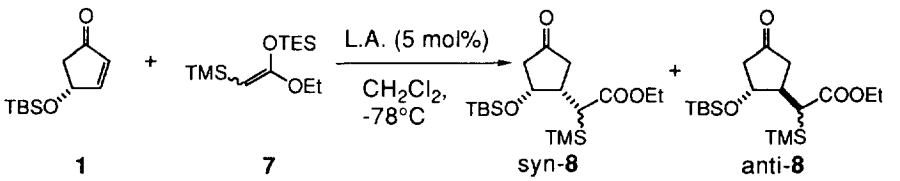
A dramatic changeover of the stereochemistry was observed when β,β-disubstituted ketene acetals **4** were subjected to the reaction (Table 2). The anti product was obtained exclusively or predominantly in every case, yet no reaction was induced by $Eu(fod)_3$. The anti stereochemistry of **5** is evident from the successful isolation of hydroxy ester **6**: no lactone is formed (Scheme 1). Note that syn-**3a** was found to afford the corresponding lactone under the same conditions.[2f,5] Apparently, the β,β-dimethyl groups of **4** experience severe steric interactions with the TBSO group in the case of the syn approach. Thus the steric hindrance prevails over the stereoelectronic effect on this occasion.

Scheme 1.



The improtance of such steric demand is also exemplified by use of β-trimethylsilyl-substituted ketene acetal **7** which leads predominantly to the anti-product (Scheme 2). The stereochemistry of **8** was assigned by its conversion to **3a** via protiodesilylation (KF, aq. MeOH).

Scheme 2.



L.A. = TMSOTf: 96%; syn:anti = 35:65
= TBSOTf: 95%; syn:anti = 29:71

Of more significance is the specific role of the 4-substituent on the enone ring in the stereocontrol concerned. The TMSOTf-catalyzed reaction of the 4-siloxymethyl analog **9**[7] with **2b** was found to provide the anti adduct almost exclusively (Scheme 3). The configuration of anti-**10** was assigned through comparison with the authentic syn-**10**, prepared from diketone **11** as depicted below. The stereochemical reversal on

Scheme 3.

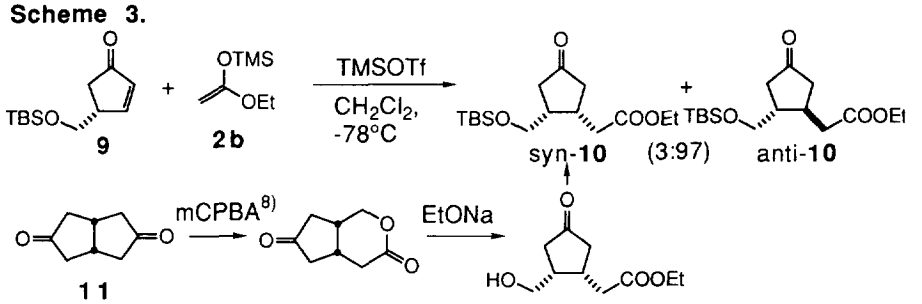
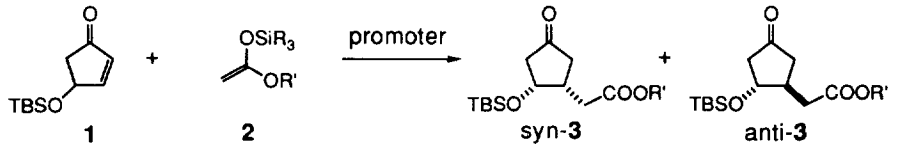


Table 1. syn-Preference of Unsubstituted Ketene Silyl Acetals.[a)]

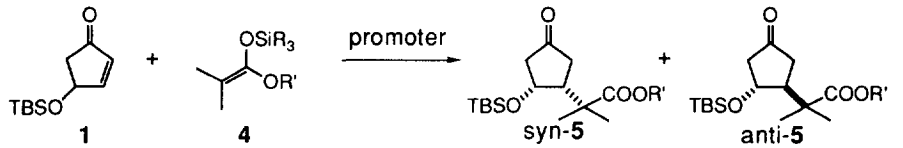


1 2 syn-3 anti-3

entry	2	R_3	R'	promoter (equivalent to 1)	yield (%)[b)]	syn:anti[c)]
1	**2a**	Et_3	Et	HgI_2 (0.1)[d)]	74	95:5[e)]
2				$TiCl_4$ (1.0)	70	76:24
3				$SnCl_4$ (0.1)	53	72:28
4	**2b**	Me_3	Et	$Eu(fod)_3$ (0.1)[f)]	99	74:26
5				TMSOTf (0.05)	72	76:24
6				TBSOTf (0.05)	56	80:20
7				TASF (0.05)[g)]	87	0:100
8	**2c**	*t*-$BuMe_2$	Me	$TiCl_4$ (1.0)	61	89:11
9	**2d**	*t*-$BuMe_2$	Et	$Bu_2Sn(OTf)_2$ (0.1)	92	60:40
10				$LiClO_4$ (5.0)[d,h)]	94	85:15

[a)] Reaction conditions: **1**:**2** = 1.0:1.2, CH_2Cl_2, -78 °C, 6 - 12 h, then hydrolysis. [b)] Isolated yield after column chromatography. [c)] Determined by ^1H NMR or GLC. [d)] In ether. [e)] Cited from ref. 1. [f)] At -78 °C - r.t. [g)] In THF. [h)] See ref. 6.

Table 2. anti-Preference of Disubstituted Ketene Silyl Acetals.[a)]



1 4 syn-5 anti-5

entry	4	R_3	R'	promoter (equivalent to 1)	yield (%)[b)]	syn:anti[c)]
1	**4a**	Et_3	Et	HgI_2 (0.1)[d)]	94	0:100
2				$TiCl_4$ (1.0)	90	0:100
3				$Bu_2Sn(OTf)_2$ (0.1)	86	0:100
4				TMSOTf (0.05)	91	12:88
5				TASF (0.05)[e)]	55	0:100
6	**4b**	*t*-$BuMe_2$	Me	$TiCl_4$ (1.0)	70	0:100

[a)] Reaction conditions: **1**:**4** = 1.0:1.2, CH_2Cl_2, -78 °C, 6 - 12 h, then hydrolysis. [b)] Isolated yield after column chromatography. [c)] Determined by ^1H NMR or GLC. [d)] In ether. [e)] In THF.

going from 4-siloxy (**1**) to 4-siloxymethyl (**9**) no doubt supports that a certain stereoelectronic effect does work in the present reaction of **1**, especially with less hindered ketene silyl acetals since electronic natures of the C-C and C-O bonds are substantially different.

In summary, we have shown that the stereochemical course of Lewis acid-catalyzed Michael reaction of 4-siloxycyclopentenone with ketene silyl acetals is governed basically by the contrasteric origin while the sterically favored course prevails in the reaction with β-substituted ketene acetals, or even with less sterically demanding nucleophiles in the cases where any Lewis acid is absent. It follows therefore that the electronic environments of the enone are significantly altered upon addition of Lewis acid. Accordingly the reaction should be regarded entirely different depending on the presence or absence of Lewis acid and hence the exact origin of the syn-preference should be elucidated along this line. Further studies are in progress in our laboratories in the hope of getting better insights into this issue.

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(5) The stereochemical assignment of **5** given here finds further support by comparison with **3** in terms of NMR spectra: the coupling constants between H_3 and H_4 of **5b** are 5.0 Hz for the anti isomer and 2.3 Hz for the syn counterpart whereas syn-**3c** that has been unequivocally assigned gives rise to 2.1 Hz.

(6) Michael addition by $LiClO_4$/ether: Grieco, P. A.; Cooke, R. J.; Henry, K. J.; VanderRoest, J. M. *Tetrahedron Lett.* **1991**, *32*, 4665.

(7) Prepared from 4-hydroxymethyl-2-cyclopenten-1-ol which was obtained from **1** according to our method: Tomooka, K.; Ishikawa, K.; Al-Masum, M.; Nakai, T. *Synlett* **1993**, 645.

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