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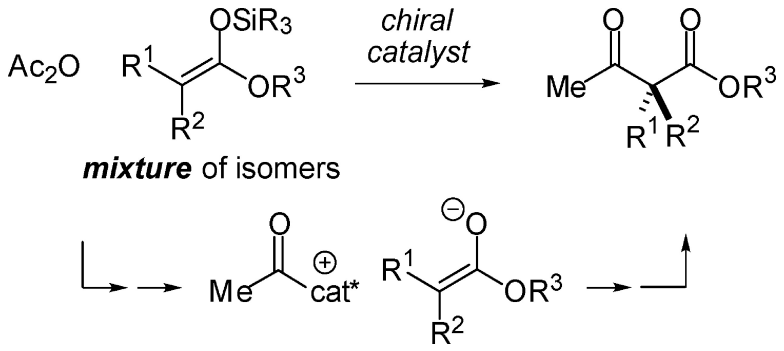

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Catalytic Enantioselective Construction of All-Carbon Quaternary Stereocenters: Synthetic and Mechanistic Studies of the C-Acylation of Silyl Ketene Acetals

Ara H. Mermerian and Gregory C. Fu*

Contribution from the Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

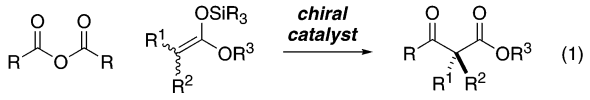
Received October 10, 2004; E-mail: gcf@mit.edu

Abstract: With the aid of an appropriate chiral catalyst, acyclic silyl ketene acetals react with anhydrides to furnish 1,3-dicarbonyl compounds that bear all-carbon quaternary stereocenters in good ee and yield. Mechanistic studies provide strong support for a catalytic cycle that involves activation of both the electrophile (anhydride → acylpyridinium) and the nucleophile (silyl ketene acetal → enolate).

Introduction

Within the area of asymmetric synthesis, the enantioselective construction of all-carbon quaternary stereocenters ($C^*R^1R^2R^3R^4$) is a particularly difficult challenge.[1] One obstacle is low reactivity, due to steric congestion, which discourages the targeted carbon−carbon bond formation from occurring. Of course, even if this reactivity problem can be overcome, there is yet another formidable barrier to success: high enantioselectivity requires that, in the transition state for the formation of a new $C-R^4$ bond, the three groups (R^1, R^2, and R^3) already attached to the central carbon must be very effectively distinguished.[2]

An even more daunting challenge is the development of *catalytic* processes that generate highly enantioenriched all-carbon quaternary stereocenters. As Overman summarized in a recent review, few chiral catalysts have yet been able to accomplish this difficult objective.[1b] In this report we establish that a chiral nucleophilic catalyst can efficiently achieve the asymmetric acylation of acyclic silyl ketene acetals to produce all-carbon quaternary stereocenters (eq 1). Furthermore, we describe mechanistic studies that elucidate the pathway and origin of stereoselection for this process.[3]

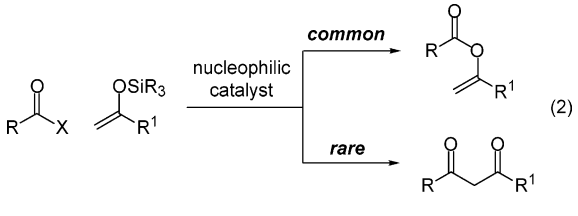


(1)

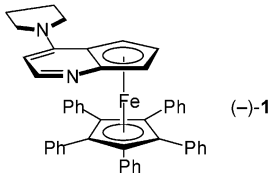
Results and Discussion

Catalytic asymmetric reactions of enolate derivatives with aldehydes have been very extensively investigated by a large number of groups.[4] In contrast, to the best of our knowledge, prior to our initial work in this area[3a] there had been no reports of corresponding processes wherein an acyl compound such as a halide or an anhydride had been employed as the electrophile.[5]

Attempts to employ nucleophiles to catalyze the acylation of silylated enolates have nearly always resulted in the formation of the O-acylated product (eq 2).[6] Nevertheless, we decided to explore the potential of planar-chiral DMAP and PPY derivatives (e.g., **1**; DMAP = 4-(dimethylamino)pyridine; PPY = 4-(pyrrolidino)pyridine)[7] as catalysts for enolate C-acylation. This decision was motivated in part by our realization that, even if the O-acylated compound is formed initially, complex **1** might catalyze subsequent migration of the acyl group from oxygen to carbon, thereby furnishing the target 1,3-dicarbonyl compound.[8]



(2)



(−)-**1**

We therefore initiated an investigation of the utility of chiral DMAP and PPY derivatives as catalysts for the enantioselective C-acylation of silyl ketene acetals with anhydrides.[3a,9] The

(1) For very recent reviews with leading references, see: (a) Denissova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105−10146. (b) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363−5367.

(2) Clearly, not all processes fall within this analysis (e.g., asymmetric cyclopropanations of olefins).

(3) (a) For a preliminary communication, see: Mermerian, A. H.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 4050−4051. (b) For a study of the catalytic asymmetric acylation of silyl ketene imines, see: Mermerian, A. H.; Fu, G. C. *Angew. Chem., Int. Ed.* **2005**, *44*, 949−952.

(4) For reviews of catalytic asymmetric aldol reactions, see: (a) Carreira, E. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; Chapter 29.1. (b) Machajewski, T. D.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1352−1374.

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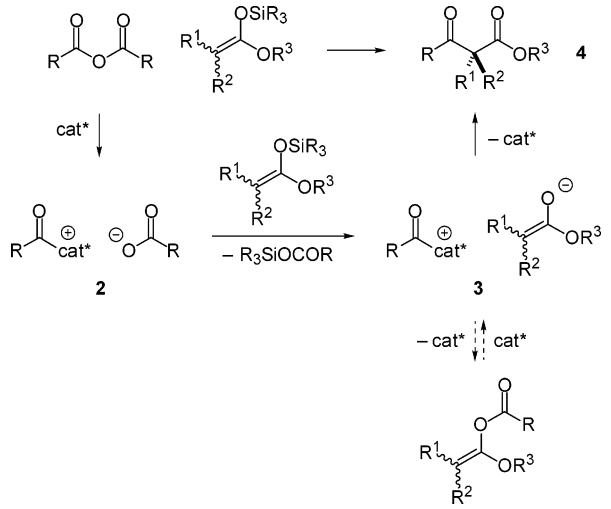
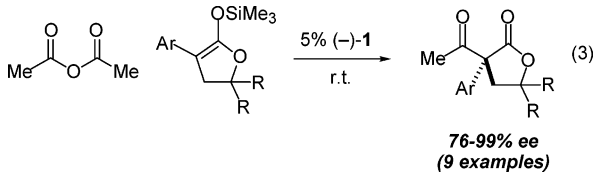


Figure 1. Possible Pathway for the Catalytic Asymmetric C−Acylation of Silyl Ketene Acetals: Dual Activation of the Nucleophile and the Electrophile.

mechanism that we envisioned for this process, which generates an all-carbon quaternary stereocenter (**4**), is outlined in Figure 1.[10] Of course, in order for this C-acylation to be highly enantioselective, the ester enolate must react with much greater facility with its chiral acylpyridinium counterion (see **3**) than with the much more abundant achiral anhydride.

For our initial study[3a] we chose to focus on acylations of silyl ketene acetals that are derived from lactones, since this avoids potential complications arising from the use of an *E*/*Z* isomeric mixture of a silyl ketene acetal. For the (admittedly limited) range of substrates depicted in eq 3, we were able to provide proof-of-principle for our approach—complex **1** not only catalyzes the C-acylation of these silyl ketene acetals but does so with good enantioselectivity. In addition, our preliminary mechanistic work was consistent with the pathway outlined in Figure 1.



76-99% ee
(9 examples)

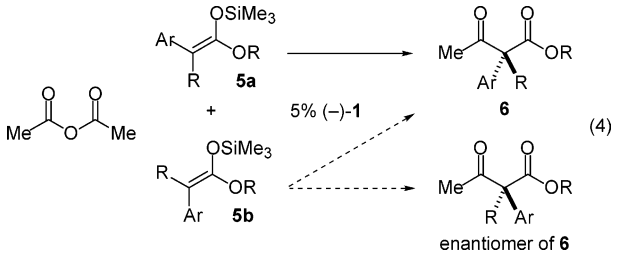
At this stage we were pleased that we had accomplished our objective of effecting catalytic asymmetric C-acylations of silyl ketene acetals to generate all-carbon quaternary stereocenters. On the other hand, we were not satisfied with the scope of the process since (five-membered) lactone-derived silyl ketene acetals comprise only a very small subset of the substrates of interest. Consequently, we decided to investigate the enantioselective acylation of silyl ketene acetals derived from acyclic esters.

Table 1. Catalytic Asymmetric C-Acylations of Acyclic Silyl Ketene Acetals: Effect of the R Group of the Ester on Enantioselectivity[a]

entry	R	isomer ratio	% ee	% yield
1	Me	1.5/1	70	87
2	CH_2CMe_3	1.1/1	79	75
3	*i*-Pr	1.8/1	85	92
4	*i*-Bu	1.5/1	93	47

[a] All data are the average of two runs.

There is a lack of general methods for producing geometrically pure silyl ketene acetals from α,α-disubstituted esters, and we were initially pessimistic about the prospects of obtaining highly enantioenriched 1,3-dicarbonyl compounds from C-acylations of *E*/*Z* mixtures of silyl ketene acetals. Thus, as illustrated in eq 4, whereas silyl ketene acetal **5a** *might* be predicted, in analogy with the results outlined in eq 3, to furnish 1,3-dicarbonyl **6** with good enantioselectivity, the stereochemical outcome of the acylation of **5b** was more uncertain.



Fortunately, we determined that isomeric mixtures of acyclic silyl ketene acetals do in fact undergo C-acylation to afford 1,3-dicarbonyl compounds with good enantioselectivity in the presence of catalyst **1** and Ac_2O (Table 1).[11] In contrast to silyl ketene acetals that are derived from lactones, for silyl ketene acetals that are generated from acyclic esters, the R group of the ester represents a parameter that can be varied in order to enhance enantioselectivity (Table 1). We established that the choice of R does indeed have a significant impact on stereoselection; specifically, as R becomes larger, the ee increases (entries 1−4). Unfortunately, in the case of the very bulky *tert*-

(5) The effective use of covalently bound chiral auxiliaries to achieve the asymmetric acylation of enolates has been described. For pioneering studies, see: (a) Evans, D. A.; Ennis, M. D.; Le, T., Mandel, N.; Mandel, G. *J. Am. Chem. Soc.* **1984**, *106*, 1154−1156. (b) Ito, Y.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1984**, *25*, 6015−6016.

(6) At the outset of our investigation, we were aware of only one example of a nucleophile-catalyzed C-acylation: the TBAF-catalyzed C-acylation of silyl enol ethers with acyl cyanides. See: Wiles, C.; Watts, P.; Haswell, S. J.; Pombo-Villar, E. Tet*rahedron Lett.* **2002**, *43*, 2945−2948.

(7) For an overview and leading references, see: Fu, G. C. *Acc. Chem. Res.* **2004**, *37*, 542−547.

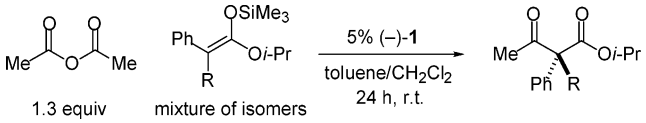
(8) For examples of O-to-C rearrangements catalyzed by such complexes, see: (a) Hills, I. D.; Fu, G. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 3921−3924. (b) Ruble, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 11532−11533.

(9) For examples of other methods for the catalytic asymmetric synthesis of β-ketoesters that contain an all-carbon quaternary stereocenter in the α position, see: (a) Nemoto, T.; Matsumoto, T.; Masuda, T.; Hitomi, T.; Hatano, K.; Hamada, Y. *J. Am. Chem. Soc.* **2004**, *126*, 3690−3691. (b) Ooi, T.; Miki, T.; Taniguchi, M.; Shiraishi, M.; Takeuchi, M.; Maruoka, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 3796−3798. (c) Hamashima, Y.; Hotta, D.; Sodeoka, M. *J. Am. Chem. Soc.* **2002**, *124*, 11240−11241. (d) Yang, D.; Gu, S.; Yan, Y.-L.; Zhu, N.-Y.; Cheung, K.-K. *J. Am. Chem. Soc.* **2001**, *123*, 8612−8613. (e) Trost, B. M.; Radinov, R.; Grenzer, E. M. *J. Am. Chem. Soc.* **1997**, *119*, 7879−7880.

(10) For a recent review of catalytic asymmetric processes that exploit dual activation of the electrophile and the nucleophile, see: Ma, J.-A.; Cahard, D. *Angew. Chem., Int. Ed.* **2004**, *43*, 4566−4583.

(11) (a) One preliminary example of an asymmetric C-acylation of an acyclic ketene acetal was described in our initial report (20% catalyst loading; ref 3a). (b) The ee of the product does not erode upon exposure to the catalyst for an extended period of time, which establishes that C-acylation is irreversible. (c) Silyl ketene acetals in which the aryl group is replaced with an alkyl substituent are not suitable substrates, presumably due to a reluctance to participate in acetate-induced desilylation to form an ester enolate (vide infra).

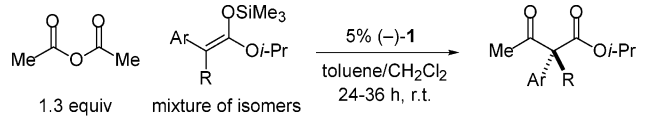
Table 2. Catalytic Asymmetric C-Acylations of Acyclic Silyl Ketene Acetals: Scope with Respect to the Alkyl Substituent[a]

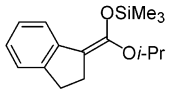


entry	R	isomer ratio	% ee	% yield
1	Me	1.8/1	69	54
2	Et	1.8/1	85	92
3	*i*-Bu	3.3/1	85	82
4	*i*-Pr	1.7/1	97	45

[a] All data are the average of two runs.

Table 3. Catalytic Asymmetric C-Acylations of Acyclic Silyl Ketene Acetals: Scope with Respect to the Aryl Substituent[a]



entry	Ar	R	isomer ratio	% ee	% yield
1	Ph	Et	1.8/1	85	92
2	6-(MeO)-2-naphthyl	Me	1.5/1	90	92
3	4-(MeO)C_6H_4	Et	1.4/1	90	83
4	4-(F_3C)C_6H_4	Et	2.1/1	92	96
5[b]	2-thienyl	Et	10/1	73	68
6[c]			1.4/1	81	82

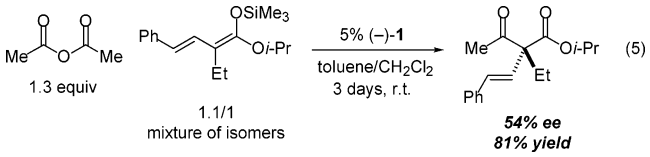
[a] All data are the average of two runs. [b] The TBS-substituted silyl ketene acetal was employed. [c] CH_2Cl_2 was employed as the solvent.

butyl group, high enantioselectivity is achieved at the price of lower yield (entry 4; a high yield can be achieved by using 20% catalyst or a longer reaction time). Taking into consideration both ee and reactivity, we chose to employ isopropyl-substituted silyl ketene acetals for our subsequent investigations.

In our initial studies of the scope of this catalytic asymmetric C-acylation of acyclic silyl ketene acetals we varied the bulk of the alkyl substituent on the olefin. As illustrated in Table 2, an array of *E*/*Z* mixtures of silyl ketene acetals react to generate all-carbon quaternary stereocenters in good to excellent ee. An increase in the steric demand of the alkyl group leads to higher enantioselectivity.

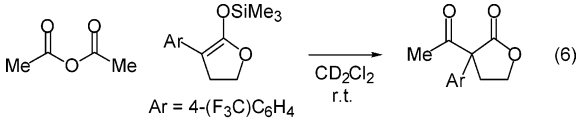
We also examined the scope of these catalytic asymmetric C-acylations with respect to the aromatic substituent on the olefin (Table 3).[12] For electron-rich (entries 2 and 3), electron-poor (entry 4), and heteroaryl (entry 5) groups, PPY derivative **1** furnishes the desired quaternary stereocenter in good ee. Significantly, a conformationally constrained indane-derived silyl ketene acetal is also a suitable substrate (entry 6). Furthermore, this nucleophile-catalyzed C-acylation process is not limited to aryl-substituted compounds—an alkenyl-substituted silyl ketene acetal can also be acylated regioselectively, albeit in modest ee (eq 5).[13] The catalyst may generally be recovered in high (>90%) yield at the end of these reactions.

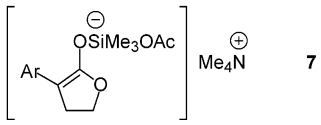
In addition to the synthetically oriented studies described above, we pursued investigations directed at determining the



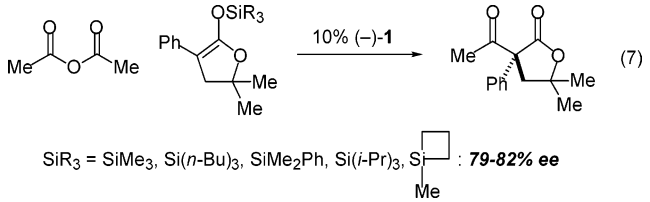
viability of the mechanism postulated in Figure 1. The first step in this proposed catalytic cycle, the reaction of a pyridine derivative with an anhydride to generate an acylpyridinium salt, is well precedented in transformations such as the DMAP-catalyzed acylation of alcohols.[14]

In the second step of the suggested catalytic cycle (Figure 1) a carboxylate anion desilylates a silyl ketene acetal to produce an ester enolate.[15] Although we do not expect this elementary step to be thermodynamically favorable, we anticipate that it may be kinetically accessible. Relevant to this suggestion, we observed that the C-acylation of silyl ketene acetals by anhydrides is catalyzed by $[Me_4N]OAc$ (eq 6).[3a] Since it is less clear how $[Me_4N]OAc$ might activate Ac_2O, we believe that the rate acceleration is likely due to activation of the silyl ketene acetal through the generation of either an enolate (see ion pair **3** in Figure 1) or a hypervalent silicate (**7**).[16,17]





With regard to distinguishing between these two possibilities, we observed that the enantioselectivity for C-acylations catalyzed by PPY derivative **1** is essentially independent of the choice of the SiR_3 group of the silyl ketene acetal (eq 7). This observation is more readily accommodated by a mechanism that involves a free enolate rather than a hypervalent silicate as an intermediate.



With respect to the final step in the postulated catalytic cycle, we generated the key intermediates (acylpyridinium and enolate) independently and allowed them to react (eq 8). Acylation on carbon does indeed occur, and the ee of the product is very similar to the catalytic asymmetric process.[18] It is worth noting that the acylpyridinium salt depicted in eq 8 does not react with

(12) The presence of a bulky aryl group (e.g., 1-naphthyl) leads to significant (sometimes exclusive) O-acylation, presumably due to steric hindrance to acylation at carbon.

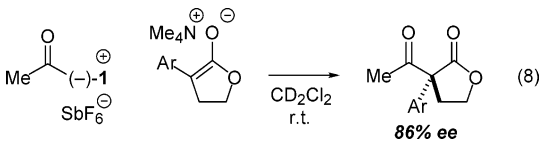
(13) We have not pursued a separate optimization of the ee for this family of substrates.

(14) For leading references to the chemistry of DMAP, see: Spivey, A. C.; Arseniyadis, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 5436−5441.

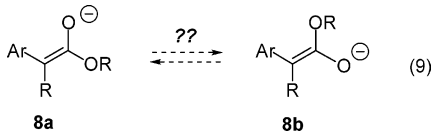
(15) The presence of an α-aryl substituent facilitates this process, since the aryl group allows delocalization of the enolate anion.

(16) For a closely related process, see: Pfaltz, A.; Lautens, M. In *Comprehensive Asymmetric Catalysis;* Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; pp 858−859.

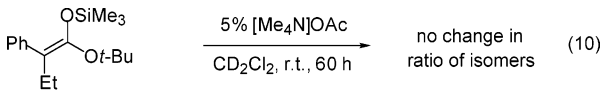
a silyl ketene acetal at room temperature, establishing that activation of the electrophile alone is not sufficient to achieve effective C-acylation. Thus, all of the mechanistic data that we accumulated are consistent with the dual-activation pathway illustrated in Figure 1.[19]



C-Acylations of *E*/*Z* mixtures of acyclic silyl ketene acetals proceed in high ee and yield (e.g., Tables 1−3), which establishes that both isomers of the substrate are transformed into the same enantiomer of the product with good selectivity. Two of the scenarios by which this could occur are: (1) enolates **8a** and **8b** each undergo C-acylation with a strong preference for generating the same enantiomer of the product or (2) enolates **8a** and **8b** interconvert under the reaction conditions[20] and the product arises primarily from the enantioselective acylation of the more reactive enolate.



To distinguish between these two possibilities, we investigated whether a carboxylate anion can induce the interconversion of silyl ketene acetals. As illustrated in eq 10, treatment of two separate isomeric mixtures of silyl ketene acetals with $[Me_4N]$-OAc does not lead to equilibration. Thus, it is likely that the high ee's that are obtained in C-acylations of acyclic silyl ketene acetals catalyzed by **1** are due to stereoselective reactions of both enolate isomers, presumably through an open transition state in which the relative position of the O^- vs the OR is inconsequential (eq 9).[21]



Experiment 1: 1.6/1 mixture of isomers
Experiment 2: 2.6/1 mixture of isomers

Finally, we established that the minor isomer of the silyl ketene acetal is more reactive than the major isomer and that the ee of the product is essentially constant throughout the course of the reaction, suggesting that the two enolates are reacting with virtually identical enantioselectivity.

Conclusions

With the aid of a chiral catalyst an array of *E*/*Z* isomeric mixtures of acyclic silyl ketene acetals react with an anhydride to generate all-carbon quaternary stereocenters in good ee and yield. Mechanistic studies provide strong support for a catalytic cycle that involves activation of both the electrophile (anhydride → acylpyridinium) and the nucleophile (silyl ketene acetal → enolate).

Acknowledgment. Support has been provided by the National Institutes of Health (National Institute of General Medical Sciences: R01-GM57034; National Cancer Institute: training grant CA009112), Merck, and Novartis. Funding for the MIT Department of Chemistry Instrumentation Facility has been furnished in part by NSF CHE-9808061 and NSF DBI-9729592.

Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

JA043832W

(17) For early studies of fluoride-catalyzed aldol reactions of silyl enol ethers, see: (a) Noyori, R.; Yokoyama, K.; Sakata, J.; Kuwajima, I.; Nakamura, E.; Shimizu, M. *J. Am. Chem. Soc.* **1977**, *99*, 1265−1267. (b) Nakamura, E.; Shimizu, M.; Kuwajima, I.; Sakata, J.; Yokoyama, K.; Noyori, R. *J. Org. Chem.* **1983**, *48*, 932−945. (c) Nakamura, E.; Yamago, S.; Machii, D.; Kuwajima, I. *Tetrahedron Lett.* **1988**, *29*, 2207−2210. (d) Yamago, S.; Machii, D.; Nakamura, E. *J. Org. Chem.* **1991**, *56*, 2098−2106. (e) Denmark, S. E.; Lee, W. *J. Org. Chem.* **1994**, *59*, 707−709.

(18) A control experiment has established that the presence of $[Me_4N]SbF_6$ does not affect the enantioselectivity of C-acylations of silyl ketene acetals catalyzed by **1**.

(19) A ^1H NMR study has shown that the resting state of the catalyst during the catalytic cycle is the unacylated species (i.e., structure **1**).

(20) The aromatic substituent is expected to lower the barrier to interconversion, relative to an enolate that bears only alkyl groups.

(21) For a discussion of open transition states in the context of Mukaiyama aldol reactions, see ref 4a.