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COMMUNICATIONS

Published on Web 03/15/2003

Catalytic Enantioselective Synthesis of Quaternary Stereocenters via Intermolecular C-Acylation of Silyl Ketene Acetals: Dual Activation of the Electrophile and the Nucleophile

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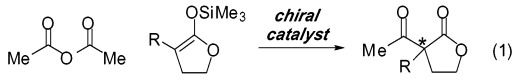
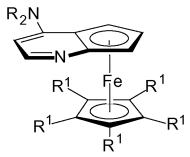
Received September 16, 2002; E-mail: gcf@mit.edu

Catalytic enantioselective reactions of enolates or enol ethers with aldehydes (i.e., aldol reactions) have been intensively investigated, and remarkable success has been reported in recent years.[1] In contrast, corresponding catalytic asymmetric processes in which acyl derivatives (acid halides or anhydrides) serve as the electrophilic component have not yet been described (eq 1).[2] With respect to non-asymmetric catalysis of these transformations, achiral Lewis acids such as $ZnBr_2$ have been shown to be effective;[3] to date, however, Lewis bases (e.g., fluoride) have not proved to be useful, leading instead to undesired O-acylation.[4]



(1)

During the past several years, we have been pursuing the development of planar-chiral derivatives of DMAP (for example, **1**−**4**) as enantioselective nucleophilic catalysts.[5] As part of this program, we decided to explore the possibility that these complexes could serve as effective catalysts for asymmetric intermolecular C-acylation processes (eq 1).[6,7]



NR_2 =	R^1 =	
dimethylamino	Me	(–)-**1**
pyrrolidino	Me	(–)-**2**
dimethylamino	Ph	(–)-**3**
pyrrolidino	Ph	(–)-**4**

A pathway by which this objective might be achieved is outlined in Figure 1 for the acylation of a silyl ketene acetal by acetic anhydride. Initially, the catalyst reacts with the anhydride to generate an acylpyridinium ion, which should be a more active acylating agent than acetic anhydride itself, along with an acetate counterion (**5**).[8] The Lewis-basic acetate then complexes to the Lewis-acidic silicon of the silyl ketene acetal, affording an enolate.[9] The activated components of this new ion pair (**6**) then couple to furnish the desired product (**7**), which bears a new carbon−carbon bond and a quaternary stereocenter,[10] and to regenerate the catalyst.

In early studies of the process illustrated in eq 2,[11] we determined that, in the absence of a catalyst, there is no reaction between the silyl ketene acetal and acetic anhydride after 60 h at room temperature. However, we were pleased to discover that, in the presence of 5% of complexes **1**−**4**, acylation on carbon can be achieved, proceeding to completion within 24 h (eq 2). Furthermore, we obtain very good ee's for reactions catalyzed by C_5Ph_5-bound **3** and **4**, with PPY derivative **4** furnishing the highest enantioselectivity (90% ee).

We have established that complex **4** effectively catalyzes the asymmetric intermolecular C-acylation of a range of silyl ketene

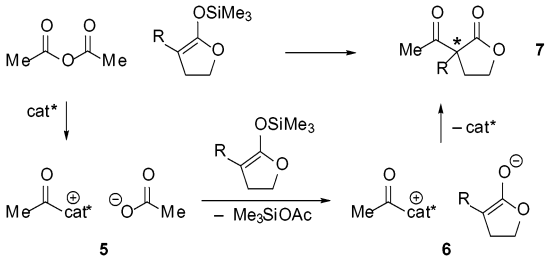
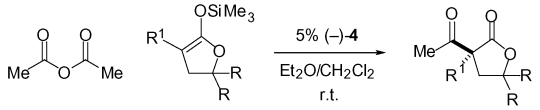


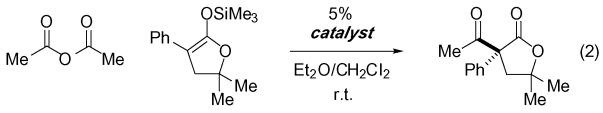
Figure 1. Possible pathway for nucleophile-catalyzed asymmetric C-acylation.

Table 1. Catalytic Enantioselective Intermolecular C-Acylation of Silyl Ketene Acetals



entry	R^1	R	% ee[a]	% yield[a]
1	Ph	Me	90	80
2	4-(MeO)C_6H_4	Me	95	78
3	4-(F_3C)C_6H_4	H	90	84
4	o-tolyl	Me	95	89
5	1-naphthyl	Me	99	82
6	2-thienyl	Me	76	84
7	3-thienyl	Me	87	86
8	3-thienyl	H	80	73
9	3-(*N*-methylindolyl)	Me	94	92

[a] Average of two runs.



(2)

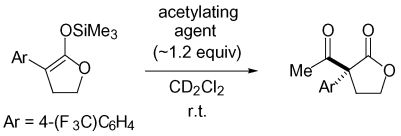
catalyst: (–)-**1** 40% ee
(–)-**2** 33% ee
(–)-**3** 87% ee
(–)-**4** 90% ee

acetals, providing new quaternary stereocenters in good enantiomeric excess (Table 1).[12] The method accommodates an electronically (entries 1−3) and sterically (entries 4 and 5) diverse array of aromatic substituents (R^1). In addition, heteroaromatic groups are tolerated (entries 6−9). At the end of the reaction, the catalyst can be recovered in essentially quantitative yield.

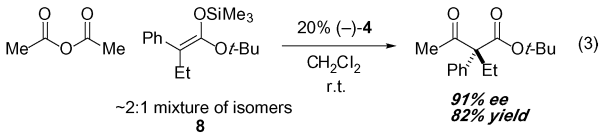
This new catalytic asymmetric process is not limited to acylations of silyl ketene acetals derived from lactones. For example, PPY derivative **4** catalyzes the C-acylation of silyl ketene acetal **8** (2:1 mixture of olefin isomers) with excellent enantiomeric excess (eq 3). Obtaining high ee and high yield establishes that both the *E* and the *Z* isomers of substrate **8** are being converted efficiently into the same enantiomer of the product.[13]

10.1021/ja028554k CCC: $25.00

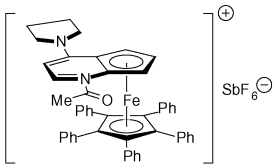
Table 2. Evidence for Dual Activation: Reactivity of a Silyl Ketene Acetal toward Several Potential Acetylating Agents



entry	acetylating agent	$t_{1/2}$ for reaction
1	Ac_2O	<2% conversion (60 h)
2	Ac_2O; 5% (−)-**4**	0.3 h
3	(+)-**9**	<2% conversion (60 h)
4	Ac_2O; 5% $[Me_4N]OAc$	<0.1 h



We have begun to pursue experiments designed to test the mechanistic hypothesis outlined in Figure 1. Thus, we have examined the reactivity of a silyl ketene acetal toward the various acetylating systems illustrated in Table 2.[14] In the absence of a catalyst, treatment of the silyl ketene acetal with acetic anhydride results in no detectable reaction after 60 h at room temperature (entry 1). In contrast, the addition of 5% of catalyst **4** leads to very rapid acetylation ($t_{1/2}$ = 0.3 h; entry 2). Activation of the electrophile ($Ac_2O \rightarrow$ acylpyridinium) is not sufficient for achieving efficient acylation − the silyl ketene acetal does not react with salt **9** at room temperature (entry 3). On the other hand, $Me_4N[OAc]$ is an effective (non-enantioselective) catalyst for the reaction (entry 4). Taken together, the data provided in Table 2 indicate that it is the *combination* of the acylpyridinium ion and the acetate ion that is responsible for the dramatic rate acceleration and high enantioselectivity that we observe in the presence of catalyst **4**.[15]



In conclusion, we have developed a new process − a nucleophile-catalyzed intermolecular C-acylation of silyl ketene acetals by anhydrides. Through mechanistic studies, we have provided support for the hypothesis that the reaction involves activation of both the anhydride (formation of an acylpyridinium ion) and the silyl ketene acetal (generation of an enolate). Furthermore, we have demonstrated that a catalytic asymmetric variant of this new transformation can be achieved, furnishing a new carbon−carbon bond and a quaternary stereocenter with very good enantioselection. Additional synthetic and mechanistic studies are underway.

Acknowledgment. We thank Ivory D. Hills for assistance with X-ray crystallography. Support has been provided by the National Institutes of Health (National Institute of General Medical Sciences, R01-GM57034) and Novartis.

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

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(6) The synthesis of related β-ketoesters has been achieved by: (a) catalytic asymmetric alkylation: Trost, B. M.; Radinov, R.; Grenzer, E. M. *J. Am. Chem. Soc.* **1997**, *119*, 7879−7880. (b) catalytic asymmetric Michael reaction: Hamashima, Y.; Hotta, D.; Sodeoka, M. *J. Am. Chem. Soc.* **2002**, *124*, 11240−11241.

(7) For an enantioselective rearrangement reaction catalyzed by **2**, see: Ruble, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 11532−11533.

(8) For overviews of the chemistry of DMAP, see: (a) Scriven, E. F. V. *Chem. Soc. Rev.* **1983**, *12*, 129−161. (b) Hassner, A.; Krepski, L. R.; Alexanian, V. *Tetrahedron* **1978**, *34*, 2069−2076. (c) Höfle, G.; Steglich, W.; Vorbrüggen, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569−583.

(9) For an example of another reaction that is initiated by complexation of acetate to a $SiMe_3$ group, see: Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1979**, *101*, 6432−6433.

(10) For a recent review of catalytic asymmetric methods that generate quaternary stereocenters, see: Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388−401. See also: Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591−4597.

(11) Gem-dimethyl substitution is present for ease of synthesis (double deprotonation of an arylacetic acid, followed by trapping with isobutylene oxide). As shown in Table 1, these groups are not necessary for high enantioselectivity.

(12) (a) DMAP derivative **4** also catalyzes the C-acylation of silyl ketene acetals by reagents such as acid chlorides, albeit in lower enantiomeric excess. (b) Use of isobutyric, rather than acetic, anhydride as the acylating agent for the silyl ketene acetal illustrated in Table 1, entry 1, provides the desired product in 83% ee, but the reaction is quite slow. (c) The enantioselectivity is not very sensitive to temperature. (d) We observe none of the product derived from O-acylation of the silyl ketene acetal. (e) Currently, silyl ketene acetals in which the aryl group is replaced with an alkyl or alkenyl substituent are not suitable substrates (low conversion).

(13) We have established through ^{1}H NMR studies that the minor isomer of **8** is more reactive than the major isomer.

(14) Because these reactions were monitored by ^{1}H NMR, CD_2Cl_2, rather than a mixture of d_{10}-Et_2O/CD_2Cl_2, was employed. In CD_2Cl_2, the intermolecular C-acylation that is illustrated in Table 2 proceeds in 87% ee (vs 90% ee in Et_2O/CH_2Cl_2).

(15) Consistent with the hypothesis that a silicon-free enolate is a key reactive intermediate in these catalytic asymmetric acylations, the sense and level of enantioselectivity is independent of the silyl group of the silyl ketene acetal (e.g., $SiMe_3$, $SiMe_2Ph$, and $Si(i\text{-}Pr)_3$).

JA028554K