

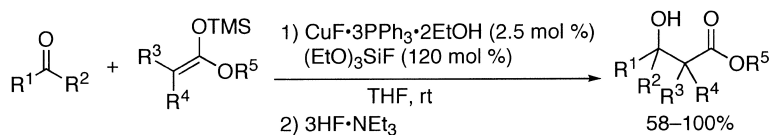
Communication

## A New Method for the Catalytic Aldol Reaction to Ketones

Kounosuke Oisaki, Yutaka Suto, Motomu Kanai, and Masakatsu Shibasaki

*J. Am. Chem. Soc.*, **2003**, 125 (19), 5644-5645 • DOI: 10.1021/ja034993n • Publication Date (Web): 22 April 2003

Downloaded from <http://pubs.acs.org> on March 26, 2009



### More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 13 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

[View the Full Text HTML](#)



## A New Method for the Catalytic Aldol Reaction to Ketones

Kounosuke Oisaki,<sup>†</sup> Yutaka Suto,<sup>†</sup> Motomu Kanai,<sup>†,‡</sup> and Masakatsu Shibasaki<sup>\*†</sup>

Graduate School of Pharmaceutical Sciences, The University of Tokyo, Tokyo 113-0033, Japan, and  
PRESTO, Japan Science and Technology Corporation, Japan

Received March 5, 2003; E-mail: mshibasa@mol.f.u-tokyo.ac.jp

The aldol reaction is one of the most versatile carbon–carbon bond-forming reactions. A number of excellent asymmetric catalyses have been developed for this important reaction using aldehydes as acceptors.<sup>1</sup> In contrast, only very few methodologies have been reported for the catalytic aldol reaction to ketones, even for cases of nonstereoselective reactions.<sup>2</sup> Specifically, there is only one example of a catalytic enantioselective aldol reaction to simple ketones, which was recently reported by Denmark.<sup>3</sup> This pioneering work, however, is still limited to reactions using the highly reactive trichlorosilyl enolate of methyl acetate as the nucleophile. The difficulty is partly due to the attenuated reactivity of ketones and the intrinsic reversibility of aldol additions to ketones. In this Communication, we report a new catalysis that can be applied to reactions between a wide range of ketones and trimethylsilyl enolates and can, in principle, be extended to catalytic enantioselective reactions.

We previously reported the CuCl–TBAT (tetrabutylammonium triphenyldifluorosilicate)-catalyzed allylation of carbonyl compounds (aldehydes and ketones) and imines using allyltrimethoxysilane as the nucleophile.<sup>4</sup> Although the detailed reaction mechanism is not clear, the initial generation of copper fluoride from CuCl and TBAT induces a dynamic ligand exchange between silicon and copper atoms, and this appears to be the key for generation of a highly active allylating nucleophile. These results prompted us to investigate whether the same catalyst could be applied to the aldol reaction of ketene silyl acetals to ketones.<sup>5</sup>

The conditions were first optimized for the reaction of acetophenone **1a** and the trimethylsilyl enolate of methyl isobutyrate **2f** (room temperature, 20 h). When 10 mol % CuCl–TBAT was used as the catalyst, enol trimethylsilyl ether formation of **1a** proceeded predominantly, and there was no aldol product formation. On the other hand, a trace amount of aldol product was produced when isolated and purified CuF·3PPh<sub>3</sub>·2EtOH complex (10 mol %)<sup>6</sup> was used as the catalyst. Encouraged by these results, we attempted the reaction in the presence of 20 mol % (EtO)<sub>3</sub>SiF, based on the findings of a previous study<sup>4</sup> that a catalytic amount of alkoxy-silyl fluoride acts as a ligand exchange mediator to generate the active allylating nucleophile. In the case of aldol reactions, aldol product **3af** was obtained in nearly 20% yield after deprotection with 3HF·NEt<sub>3</sub>. The product was mainly (>99%) trapped as the corresponding triethoxysilyl ether in the reaction mixture. Thus, the reaction was conducted in the presence of 120 mol % (EtO)<sub>3</sub>SiF, and the aldol product was obtained in quantitative yield (Table 1, entry 15). The aldol reaction did not proceed when only TBAT was used as a catalyst, even in the presence of 120 mol % (EtO)<sub>3</sub>SiF, indicating the essential role of the copper atom for the success of this reaction.

Using these optimized reaction conditions, we investigated the substrate generality. As shown in Table 1, the reaction proceeded

**Table 1.** Catalytic Aldol Reaction to Ketones<sup>a</sup>

entry	ketone	ketene silyl acetal	product	time (h)	yield (%) <sup>b</sup>
1					
2		X = H ( <b>1a</b> )	<b>3aa</b>	2	95
3		X = Cl ( <b>1b</b> )	<b>3ba</b>	4	85
3		X = OMe ( <b>1c</b> )	<b>3ca</b>	35	85
4		<b>2a</b>	<b>3da</b>	4	91
5		<b>2a</b>	<b>3ea</b>	4	90
6		<b>2a</b>	<b>3fa</b>	4	85
7		<b>2a</b>	<b>3ga</b>	1	88
8		<b>2a</b>	<b>3ha</b>	1	85
9		<b>2a</b>	<b>3ia</b>	3.5	85
10 <sup>c</sup>		<b>2b</b>	<b>3jb</b>	5	69 <sup>d</sup> (ca. 15:1)
11	<b>1a</b>	<b>2c</b> (5:1)	<b>3ac</b>	0.5	85 (1.6:1)
12	<b>1a</b>	<b>2d</b> (3:1)	<b>3ad</b>	1	90 (1.6:1)
13		<b>2c</b>	<b>3kc</b>	24	58
14		<b>2e</b>	<b>3le</b>	3	80
15 <sup>c</sup>	<b>1a</b>	<b>2f</b>	<b>3af</b>	20	100

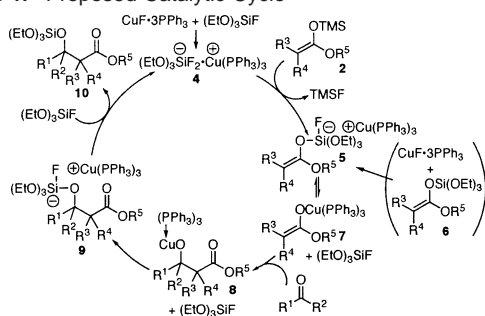
<sup>a</sup> For experimental procedures, see the Supporting Information (SI).  
<sup>b</sup> Isolated yield. <sup>c</sup> 10 mol % catalyst was used. <sup>d</sup> β-Attack was the major.

smoothly even in the presence of 2.5 mol % catalyst with a wide range of ketones and TMS enolates. In every case, the addition of (EtO)<sub>3</sub>SiF was essential for a smooth reaction and high yield of the aldol products.<sup>7</sup> α,β-Unsaturated ketones gave the corresponding 1,2-adducts as the sole constitutional isomer (entries 8 and 9). Using propionate-derived ketene silyl acetals **2c** and **2d**, we obtained the (2*R*\*,3*S*\*)-diastereomer as the preferred isomer (1.6:1) despite the geometry of the enolate (entries 11 and 12). The reaction could also be applied to a multifunctional substrate **1j**, which did not produce aldol product under conventional Lewis acid catalysis. Thus, the present reaction is advantageous for the synthesis of complex molecules.

To gain insight into the reaction mechanism, several experiments were performed, and the proposed catalytic cycle based on these studies is summarized in Scheme 1. First, when CuF·3PPh<sub>3</sub><sup>8</sup> and (EtO)<sub>3</sub>SiF were mixed in a 1:3 ratio in THF, the <sup>19</sup>F NMR peak corresponding to the copper fluoride completely disappeared, and a new peak appeared, corresponding to silicate **4** (−138.6 ppm, with a doublet satellite peak due to the coupling with <sup>29</sup>Si, *J* = 143 Hz).<sup>9</sup>

Ketene silyl acetal **2a** (1 equiv to copper) was added to this solution. The generation of TMSF was then confirmed (ca. 60%) on <sup>19</sup>F (−157.2 ppm) and <sup>1</sup>H NMR (0.20 ppm). These observations strongly suggested that the fluoride anion was transferred to the TMS group of **2** from silicate **4**, giving triethoxysilicate **5**.<sup>10</sup> The

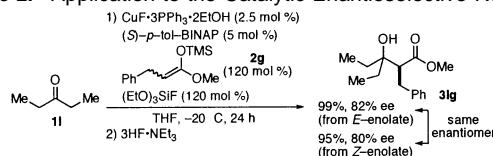
<sup>†</sup> The University of Tokyo.  
<sup>‡</sup> PRESTO.

**Scheme 1.** Proposed Catalytic Cycle

intermediary of **5** was also supported by the fact that the reaction between **1a** and triethoxysilyl enolate of ethyl acetate **6a** proceeded smoothly (room temperature, 25 min, 80% yield) in the presence of  $\text{CuF}\cdot 3\text{PPh}_3\cdot 2\text{EtOH}$  (2.5 mol %) and in the absence of  $(\text{EtO})_3\text{SiF}$ . Moreover, the  $^1\text{H}$  and  $^{19}\text{F}$  NMR spectra of a mixture of  $\text{CuF}\cdot 3\text{PPh}_3$ ,  $(\text{EtO})_3\text{SiF}$ , and **2a** (1:3:1) were almost identical to those of  $\text{CuF}\cdot 3\text{PPh}_3$  and **6a** (1:1), except for the presence of TMSF and excess  $(\text{EtO})_3\text{SiF}$  peaks. Thus, the copper silicate (**4**)-mediated conversion of trimethylsilyl enolate **2** to silicate **5** is the first key step in the catalytic cycle.

We next performed kinetic studies to address the question of whether the actual nucleophile was silicate **5** or copper enolate **7**, which was produced through further ligand exchange between silicon and copper atoms.<sup>11</sup> The order dependency of the initial reaction rate on  $[\text{CuF}\cdot 3\text{PPh}_3]$  and  $[\mathbf{6a}]$  was 1.5 and  $-0.8$ , respectively.<sup>12</sup> Although not conclusive, the results suggest that the actual nucleophile was copper enolate **7**.<sup>13</sup> The generation of highly nucleophilic copper enolate would be the second key for the catalytic cycle. When **7** reacts with a ketone, copper alkoxide **8** should be produced. To gain insight into the catalyst turnover step from **8**, we attempted the reaction of **1a** and **2a** using  $\text{CuO}\cdot\text{Bu}$ <sup>14</sup> as the catalyst (10 mol %) in the presence of  $(\text{EtO})_3\text{SiF}$  (1.2 equiv). Unexpectedly, the reaction did not proceed well, and the aldol product was obtained in only 29% yield after 20 h. When the same reaction was conducted in the presence of 30 mol %  $\text{PPh}_3$ , however, the reaction proceeded smoothly in 1.5 h, giving the product in 92% yield. These results indicated that the phosphine ligand was essential for the catalyst turnover from the copper alkoxide. Thus, the catalytic cycle for the present reaction is proposed in Scheme 1 as a working hypothesis. First, a dynamic ligand exchange between  $\text{CuF}\cdot 3\text{PPh}_3$ ,  $(\text{EtO})_3\text{SiF}$ , and **2** produces silicate **5** and copper enolate **7**, which reacts with a ketone to give copper alkoxide **8**. **8** then reacts with  $(\text{EtO})_3\text{SiF}$  to produce silicate **9**. Finally, fluoride exchange between **9** and  $(\text{EtO})_3\text{SiF}$  produces the triethoxysilyl-protected aldol product **10** and active silicate **4** to complete the catalytic cycle.<sup>15</sup>

This new methodology could, in principle, be extended to the catalytic enantioselective reaction, and the preliminary results are shown in Scheme 2. Thus, in the presence of 2.5 mol %  $\text{CuF}\cdot 3\text{PPh}_3\cdot 2\text{EtOH}$ -*(S)*-*p*-*tol*-BINAP complex, the aldol reaction between ketone **11** and silyl enolate **2g** gave the product with up to 82% ee. As expected, the sense of enantioselectivity was almost completely controlled by the asymmetric catalyst, and not by the geometry of the initial ketene silyl acetal.

**Scheme 2.** Application to the Catalytic Enantioselective Reaction

In summary, we developed a new methodology for the catalytic aldol reaction to ketones. The success of the reaction depended on a unique, dynamic ligand exchange between silicon and copper atoms. The method was applied to a catalytic enantioselective reaction. Detailed mechanistic studies, improvement of the enantioselectivity, and application of the present method to other important carbon–carbon bond-forming reactions are now in progress.

**Acknowledgment.** Financial support was provided by PRESTO of the Japan Science and Technology Corp. (JST).

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

## References

- (1) Carreira, E. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Heidelberg, 1999; Vol. III, Chapter 29.1.
- (2) For example, see: (a) Kobayashi, S.; Matsui, S.; Mukaiyama, T. *Chem. Lett.* **1988**, 1491. (b) Chen, J.; Sakamoto, K.; Orita, A.; Otera, J. *J. Org. Chem.* **1998**, *63*, 9739.
- (3) Denmark, S. E.; Fan, Y. *J. Am. Chem. Soc.* **2002**, *124*, 4233.
- (4) Yamasaki, S.; Fujii, K.; Wada, R.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2002**, *124*, 6536.
- (5) For a copper fluoride-catalyzed asymmetric aldol reaction of a silyl dienolate to aromatic and  $\alpha,\beta$ -unsaturated aldehydes, see: (a) Krüger, J.; Carreira, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 837. (b) Pagenkopf, B. L.; Krüger, J.; Stojanovic, A.; Carreira, E. M. *Angew. Chem., Int. Ed.* **1998**, *37*, 3124. Aliphatic substrates gave poor yields in those cases.
- (6) Gulliver, D. J.; Levason, W.; Webster, M. *Inorg. Chim. Acta* **1981**, *52*, 153.
- (7) For example, the reaction of aliphatic ketone **1g** produced multiple products, and **3ga** was obtained in only 28% yield after 74 h in the absence of  $(\text{EtO})_3\text{SiF}$ . See the Supporting Information (SI) for details.
- (8) To avoid the undesired solvolysis of the active species, EtOH was completely eliminated by azeotropic evaporation with toluene in the NMR studies. EtOH-free catalyst contained the same activity as  $\text{CuF}\cdot 3\text{PPh}_3\cdot 2\text{EtOH}$ .
- (9) There have been no reports on the  $^{19}\text{F}$  NMR chemical shift values of trialkoxydifluoro silicates. When TBAT was mixed with  $(\text{EtO})_3\text{SiF}$ , a peak at  $-130$  ppm (with a doublet satellite peak,  $J = 156$  Hz) was observed, which supports the assignment of **4**.
- (10) Peaks of **5** and **7** were not observed on  $^{19}\text{F}$  and  $^1\text{H}$  NMR, possibly due to the fast ligand exchange between silicon and copper atoms.
- (11) React IR did not provide any clear information in our case. A very small amount of  $(\text{EtO})_3\text{SiF}$  was observed on the  $^{19}\text{F}$  NMR of a  $\text{CuF}\cdot 3\text{PPh}_3$ -**6a** mixture, suggesting that **5** and **7** were in equilibrium.
- (12) **6a** was used for the kinetic studies to eliminate the effect of the complex initial ligand exchange process. The fractional order dependency might suggest that the overall reaction contains several rate-determining steps. The ligand-exchange step to generate the active nucleophile, the aldol addition step, and the catalyst turnover step are possible candidates. The inhibitory feature of the ketene silyl acetal (minus order dependency) might be due to the nonproductive fluoride exchange between silicon atoms (inhibition of the active nucleophile generation step).
- (13) The possibility that  $\text{Cu}^+$  acts as a Lewis acid cannot be completely excluded.
- (14) Tsuda, T.; Hashimoto, T.; Saegusa, T. *J. Am. Chem. Soc.* **1972**, *94*, 658.
- (15) The proposed mechanism is distinct from the silyl Lewis acid-catalyzed aldol reaction (Ishihara, K.; Hiraiwa, Y.; Yamamoto, H. *Chem. Commun.* **2002**, 1564) or the tin(II) triflate- and tin fluoride-mediated asymmetric aldol reaction (Kobayashi, S.; Uchiro, H.; Fujishita, Y.; Shiina, I.; Mukaiyama, T. *J. Am. Chem. Soc.* **1991**, *113*, 4247).

JA034993N