

# High Turnover Frequency Observed in Catalytic Enantioselective Additions of Enecarbamates and Enamides to Iminophosphonates

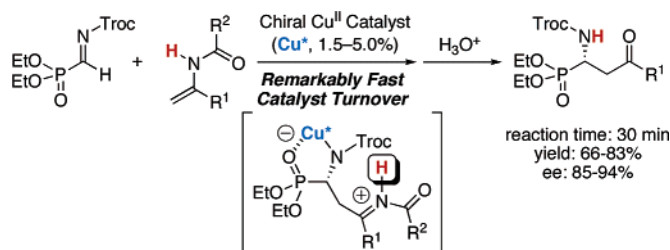
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## ABSTRACT



In addition reactions of enecarbamates and enamides, extremely high turnover frequency of the catalyst was observed in comparison with that of silicon enolate addition reactions. This is presumably due to fast transfer of the proton that locates on the nucleophiles.

Catalytic asymmetric reactions provide some of the most important methods for the synthesis of optically active molecules. Although great efforts to develop C–C bond-forming reactions have been made by using chiral Lewis acids, it is still difficult and a challenging issue to achieve high catalyst turnover compared to late transition-metal-catalyzed reactions such as hydrogenation of olefins. The lower catalyst turnover is mainly ascribed to product or intermediate inhibition, instability of Lewis acids toward moisture and oxygen, and slow rates of metal transfer steps. In Lewis acid catalyzed addition reactions of silicon enolates to C=O or C=N electrophiles, which are among the most important C–C bond-forming reactions in organic synthesis, fast silicon transfer from enolate components to newly generated O–M or N–M (M = metal) moieties is required, but those steps are often slow and catalyst turnover is limited significantly.<sup>1</sup> Herein, we report observation of high turnover frequency that is realized by using enamides or enecarbamates as nucleophiles instead of silicon enolates.

$\alpha$ -Amino phosphonic acids are established as analogues of  $\alpha$ -amino acids in medicinal and pharmaceutical science.<sup>2</sup> While many methods to synthesize enantiomerically enriched  $\alpha$ -amino acids have been developed up to now, asymmetric synthesis of  $\alpha$ -amino phosphonic acids has been a challenging topic due to limited synthetic schemes.<sup>3</sup> Recently, we reported catalytic asymmetric synthesis of  $\alpha$ -amino phosphonates using enantioselective addition of silicon enolates to iminophosphonates.<sup>4</sup> In that report, we showed that a wide range of  $\alpha$ -amino phosphonic acid derivatives could be synthesized in good yields with high enantioselectivities (in

(1) For turnover acceleration examples by Brønsted acid as an additive, see: (a) Dosa, P. I.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 445. (b) Takamura, M.; Hamashima, Y.; Usuda, H.; Kanai, M.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 1650. (c) Yamasaki, S.; Fujii, K.; Wada, R.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2002**, *124*, 6536. (d) Wadamoto, M.; Yamamoto, H. *J. Am. Chem. Soc.* **2005**, *127*, 14556. (e) Wada, R.; Shibuguchi, T.; Makino, S.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 7687.

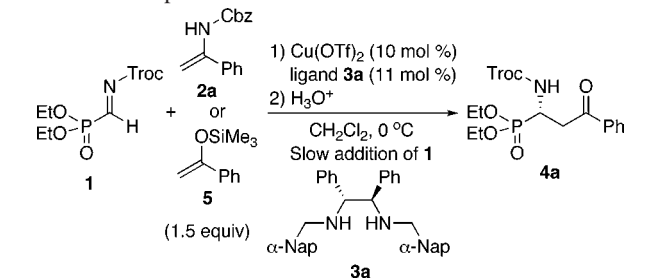
(2) For reviews on enantioselective  $\alpha$ -amino acid synthesis, see: (a) Gröger, H. *Chem. Rev.* **2003**, *103*, 2795. (b) Burk, M. J. *Acc. Chem. Res.* **2000**, *33*, 363.

general over 90% ee). On the other hand, a drawback of this method was the inevitably slow addition of substrates to a catalyst or addition of hexafluoroisopropyl alcohol (HFIP) in order to obtain high selectivities. We reasoned that low selectivity obtained without slow addition of substrates or addition of HFIP was ascribed to strong coordination of the intermediate to the catalyst,<sup>5</sup> which led to a background reaction without chiral catalyst involvement.

Our group has also recently revealed enecarbamates and enamides to be useful nucleophiles in several reactions with aldehydes and imines.<sup>6</sup> The products are reactive acylimines, which can be further converted into complicated target molecules. We assume that the reaction of enecarbamates occurs via an aza-ene type pathway, in which the hydrogen on the nitrogen atoms of enecarbamates and enamides plays an important role for reaction acceleration and stereoselective outcome. Based on these findings and the fact that addition of HFIP accelerated dissociation of the catalyst from the intermediate, we assumed that the use of enecarbamates and enamides could solve the catalyst-trapping problems in the reactions of iminophosphonates.

First, we conducted the reaction of iminophosphonate **1** with enecarbamate **2a** in the presence of Cu(OTf)<sub>2</sub> and chiral diamine **3a**<sup>6a,7</sup> in dichloromethane at 0 °C. To our delight, the product **4a** was obtained with high enantioselectivity even when the iminophosphonate **4a** was added to the catalyst over 30 min (Table 1, entry 1).

**Table 1.** Comparison of Enecarbamate vs Silicon Enolate

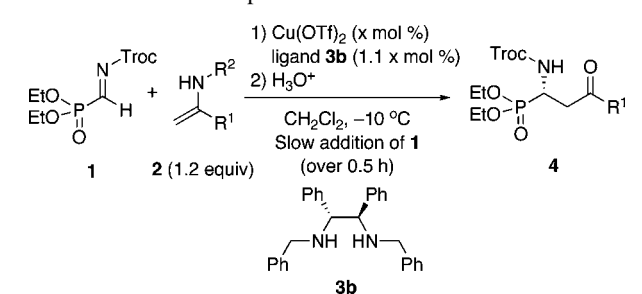


entry	nucleophile	addition time (h)	yield (%)	ee (%)
1	<b>2a</b>	0.5	86	89
2	<b>2a</b>	0.05	72	89
3	<b>5</b>	0.5	78	49
4	<b>5</b>	8.0	81	73
5	<b>5</b>	48.0	79	90
6 <sup>a</sup>	<b>5</b>	0.5	87	65
7 <sup>a</sup>	<b>5</b>	4.0	84	86
8 <sup>a</sup>	<b>5</b>	8.0	81	89

<sup>a</sup> HFIP (1.0 equiv) was employed.

It is noted that much lower enantioselectivity was obtained when silicon enolate **5** was employed instead of **2a** under the same reaction conditions (entry 3). Furthermore, no erosion of enantioselectivity was observed when the iminophosphonate **1** was added over just 3 min (entry 2). The same level of the enantioselectivity was observed using silicon

**Table 2.** Substrate Scope



entry	R <sup>1</sup>	R <sup>2</sup>	x	product	yield (%)	ee (%)
1	Ph ( <b>2a</b> )	Cbz	5.0	<b>4a</b>	77	89
2	Ph ( <b>2b</b> )	Bz	1.5	<b>4a</b>	81	85
3	4-MeC <sub>6</sub> H <sub>4</sub> ( <b>2c</b> )	Cbz	5.0	<b>4b</b>	77	93
4	4-ClC <sub>6</sub> H <sub>4</sub> ( <b>2d</b> )	Cbz	5.0	<b>4c</b>	78	87
5 <sup>a</sup>	4-ClC <sub>6</sub> H <sub>4</sub> ( <b>2e</b> )	Bz	2.0	<b>4c</b>	72	86
6	4-MeOC <sub>6</sub> H <sub>4</sub> ( <b>2f</b> )	Cbz	5.0	<b>4d</b>	77	94
7	$\beta$ -Nap ( <b>2g</b> )	Cbz	5.0	<b>4e</b>	66	89
8 <sup>a</sup>	3-MeC <sub>6</sub> H <sub>4</sub> ( <b>2h</b> )	Bz	1.5	<b>4f</b>	83	86

<sup>a</sup> 1.5 equiv of enamide was employed.

enolate **5** when **1** was added over 48 h (entry 5). From these results, it was approximately estimated that turnover frequency (TOF) of the reaction of **2a** with **1** was ca. 1000 times higher than that of the reaction of **5** with **1**. In the reaction using **5**, the use of HFIP (1 equiv) was not so effective (entries 6–8). In addition, it is remarkable that the reaction of **2a** with **1** in the absence of the catalyst completes at 0 °C in 1.5 min to afford the product **4a** in 86% yield.

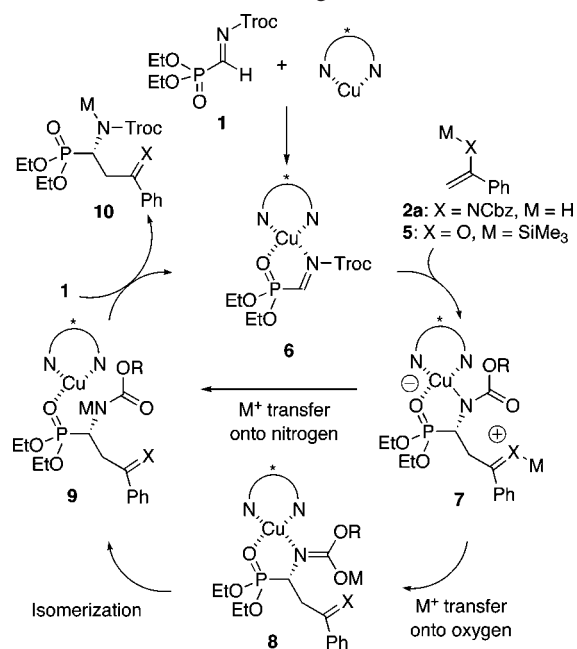
Encouraged by this remarkably high TOF thus observed in the presence of 10 mol % of catalyst, we then tried to decrease the catalyst loading. As ligand **3b** was found to be superior to **3a** for enantioselectivity, the following investigations were conducted using **3b**. When 5 mol % of the catalyst was employed in the reaction of **2a** with **1**, the desired product **4a** was obtained in 77% yield with 89% ee (Table 2, entry 1). The advantage of using enecarbamate **2a** instead

(3) For examples of carbon–phosphorus bond-forming reactions, see: (a) Sasai, H.; Arai, S.; Tahara, Y.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 6656. (b) Gröger, H.; Saida, Y.; Arai, S.; Martens, J.; Sasai, H.; Shibasaki, M. *Tetrahedron Lett.* **1996**, *37*, 9291. (c) Gröger, H.; Saida, Y.; Sasai, H.; Yamaguchi, K.; Martens, J.; Shibasaki, M. *J. Am. Chem. Soc.* **1998**, *120*, 3089. (d) Schlemminger, I.; Saida, Y.; Gröger, H.; Maison, W.; Durot, N.; Sasai, H.; Shibasaki, M.; Martens, J. *J. Org. Chem.* **2000**, *65*, 4818. (e) Joly, G. D.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 4102. (f) Akiyama, T.; Morita, H.; Itoh, J.; Fuchibe, K. *Org. Lett.* **2005**, *7*, 2583. (g) Pettersen, D.; Marcolini, M.; Bernardi, L.; Fini, F.; Herrera, R. P.; Sgarzani, V.; Ricci, A. *J. Org. Chem.* **2006**, *71*, 6269. For examples of enamide hydrogenation, see: (h) Schöllkopf, U.; Hoppe, I.; Thiele, A. *Liebigs Ann. Chem.* **1985**, 555. (i) Schmidt, U.; Oehme, G.; Krause, H. W. *Synth. Commun.* **1996**, *26*, 777. (j) Schmidt, U.; Krause, H. W.; Oehme, G.; Michalik, M.; Fischer, C. *Chirality* **1998**, *10*, 564. (k) Burk, M. J.; Stammers, T. A.; Straub, J. A. *Org. Lett.* **1999**, *1*, 387. For examples of carbon–carbon bond-forming reactions, see: (l) Sawamura, M.; Ito, Y.; Hayashi, T. *Tetrahedron Lett.* **1989**, *30*, 2247. (m) Kuwano, R.; Nishio, R.; Ito, Y. *Org. Lett.* **1999**, *1*, 837. For examples of carbon–nitrogen bond-forming reactions to give quaternary carbon centers, see: (n) Bernardi, L.; Zhuand, W.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 5772. (o) Kim, S. M.; Kim, H. R.; Kim, D. Y. *Org. Lett.* **2005**, *7*, 2309. See also: (p) Kitamura, M.; Tokunaga, M.; Pham, T.; Lubell, W. D.; Noyori, R. *Tetrahedron Lett.* **1995**, *36*, 5769.

of silicon enolate **5** was obvious since the product **4a** was obtained with lower enantioselectivity in the case of using silicon enolate **5**. After minor changes of the nitrogen protecting group, we have found that the reaction of enamide **2b** with **1** proceeded smoothly to afford **4a** with acceptable ee (85% ee) in the presence of 1.5 mol % of the catalyst (Table 2, entry 2). We evaluated other aromatic ketone-derived enecarbamates and enamides, and high yields and high enantioselectivities were obtained (Table 2).

We assume the catalytic cycle of this reaction is as shown in Scheme 1. The catalyst-coordinated iminophosphonate **6**

**Scheme 1.** Assumed Catalytic Cycle and Rationalization of Observed High TOF



is attacked by nucleophile **2a** (X = NCbz, M = H) to generate zwitterionic species **7**. Efficient chiral induction occurs at this stage. Conversion of **7** to **9** occurs via  $M^+$  transfer, and we assume **8** as a possible precursor of **9**. Proton, which is supposed to transfer more readily than silicon cation, accelerates dissociation of the catalyst from the product, leading to high turnover frequency (TOF).

In summary, we have achieved high turnover frequency in the reactions of enamides or enecarbamates with iminophosphonates. A copper complex prepared from  $Cu(OTf)_2$  and chiral diamine **3b** efficiently catalyzed nucleophilic addition of enecarbamates or enamides to iminophosphonates to provide the acylimine products in high yields with high enantioselectivities. In this reaction, remarkably high turnover frequency was observed, and we ascribed it to fast proton transfer leading to quick dissociation of the catalyst from the adducts. There are several issues to be addressed to attain really high catalyst turnover in chiral Lewis acid catalysis. This report has solved one of the most difficult issues, and it should be noted that this is the first example to demonstrate that proton transfer is much faster than silicon transfer in enolate-addition reactions. Further investigations to apply this new concept to other reactions as well as to elucidate a precise reaction mechanism are now in progress.

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**Supporting Information Available:** Experimental procedures and spectral data for synthesized compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(4) Kobayashi, S.; Kiyohara, H.; Nakamura, Y.; Matsubara, R. *J. Am. Chem. Soc.* **2004**, *126*, 6558.

(5) For examples of the use of HFIP for turnover acceleration, see: (a) Kitajima, H.; Ito, K.; Katsuki, T. *Tetrahedron* **1997**, *53*, 17015. (b) Evans, D. A.; Willis, M. C.; Johnston, J. N. *Org. Lett.* **1999**, *1*, 865. (c) Evans, D. A.; Johnson, D. S. *Org. Lett.* **1999**, *1*, 595. (d) Evans, D. A.; Scheidt, K. A.; Johnston, J. N.; Wills, M. C. *J. Am. Chem. Soc.* **2001**, *123*, 4480. (e) Takita, R.; Ohshima, T.; Shibasaki, M. *Tetrahedron Lett.* **2002**, *43*, 4661. (f) Majima, K.; Takita, R.; Okada, A.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 15837.

(6) (a) Matsubara, R.; Nakamura, Y.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 1679. (b) Matsubara, R.; Nakamura, Y.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3258. (c) Matsubara, R.; Vital, P.; Nakamura, Y.; Kiyohara, H.; Kobayashi, S. *Tetrahedron* **2004**, *60*, 9769. (d) Fossey, J. S.; Matsubara, R.; Vital, P.; Kobayashi, S. *Org. Biomol. Chem.* **2005**, *3*, 2910. (e) Matsubara, R.; Kawai, N.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 3814. After our reports, other groups also used enecarbamates as nucleophiles. See, for example: (f) Terada, M.; Machioka, K.; Sorimachi, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 2254.

(7) (a) Kobayashi, S.; Matsubara, R.; Kitagawa, H. *Org. Lett.* **2002**, *4*, 143. (b) Kobayashi, S.; Matsubara, R.; Nakamura, Y.; Kitagawa, H.; Sugiura, M. *J. Am. Chem. Soc.* **2003**, *125*, 2507.