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Enamides and Enecarbamates as Nucleophiles in Stereoselective C–C and C–N Bond-Forming Reactions

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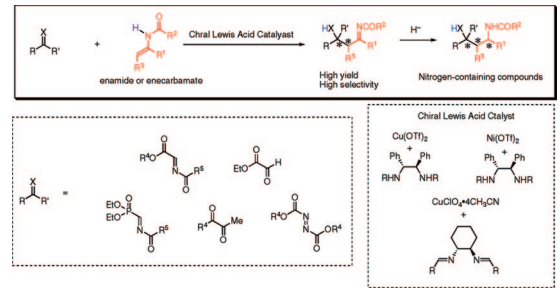
CONSPECTUS



Because the backbone of most of organic compounds is a carbon chain, carbon–carbon bond-forming reactions are among the most important reactions in organic synthesis. Many of the carbon–carbon bond-forming reactions so far reported rely on nucleophilic attack of enolates or their derivatives, because those nucleophiles can be, in general, readily prepared from the corresponding carbonyl compounds. In this Account, we summarize the recent development of reactions using enamide and enecarbamate as a novel type of nucleophile. Despite their ready availability and their intrinsic attraction as a synthetic tool that enables us to introduce a protected nitrogen functional group, enamide and enecarbamate have rarely been used as a nucleophile, since their nucleophilicity is low compared with the corresponding metal enolates and enamines. A characteristic of enamides and enecarbamates is that those bearing a hydrogen atom on nitrogen are relatively stable at room temperature, while enamines bearing a hydrogen atom on nitrogen are likely to tautomerize into the corresponding imine form. Enamides and enecarbamates can be purified by silica gel chromatography and kept for a long time without decomposition.

During the investigation of nucleophilic addition reactions using enamides and enecarbamates, it has been revealed that enamides and enecarbamates bearing a hydrogen atom on nitrogen react actually as a nucleophile with relatively reactive electrophiles, such as glyoxylate, *N*-acylimino ester, *N*-acylimino phosphonate, and azodicarboxylate, in the presence of an appropriate Lewis acid catalyst. Those bearing no hydrogen atom on nitrogen did not react at all. The products initially obtained from the nucleophilic addition of enamides and enecarbamates are the corresponding N-protected imines, which can be readily transformed to important functional groups, such as ketones by hydrolysis and N-protected amines by reduction or nucleophilic alkylation.

In the nucleophilic addition reactions of enamides and enecarbamates to aldehydes, it was unveiled that the reaction proceeds stereospecifically, that is, (*E*)-enecarbamate gave *anti* product and (*Z*)-enecarbamate afforded *syn* product with high diastereoselectivity (>97/3). This fact can be rationalized by consideration of a concerted reaction pathway via a hydrogen-involved cyclic six-membered ring transition state. In the addition reactions to *N*-acylimino phosphonates, much higher turnover frequency was observed when enamides and enecarbamates were used as a nucleophile than was observed when silicon enolates were used. When silicon enolates were used, the intermediates bearing a strong affinity for the catalyst inhibited catalyst turnover, resulting in low enantioslectivity because of the dominance of the uncatalyzed racemic pathway. In the case of nucleophilic addition of enamides and enecarbamate, however, a fast intramolecular hydrogen transfer from the enecarbamate nitrogen may prevent the intermediate from trapping the catalyst for a long time, to afford the product with a high enantioselectivity.

In conclusion, enamides and enecarbamates, although originally employed as just N-analogues to silicon enolates, have emerged as remarkably useful nucleophiles in a variety of Lewis acid-catalyzed reactions.

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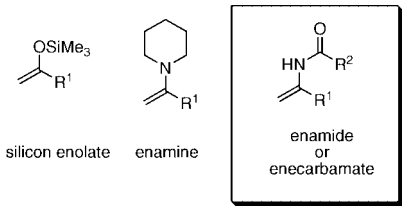
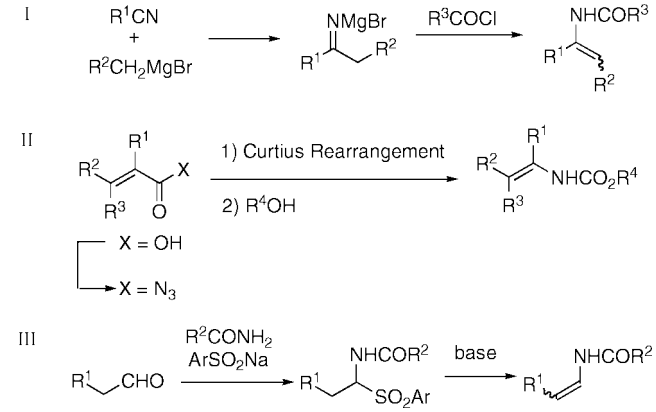
Introduction

Carbon−carbon bond-forming reactions are among the most important reactions in organic synthesis. Many of the carbon−carbon bond-forming reactions so far reported rely on nucleophilic attack of enolates or their derivatives, because those nucleophiles can be, in general, readily prepared from the corresponding carbonyl compounds. There have been many useful enolates developed to date including silicon enolates.



Enamines are also useful reagents since following completion of the reaction they give imine or iminium species, which may be converted to the corresponding carbonyl compounds. While enamines have been used widely as powerful nucleophiles since their synthetic utility was discovered by Stork,[1] enamides and enecarbamates, which have electron-withdrawing groups on nitrogen, have rarely been used as nucleophiles.[2] The high nucleophilicity of enamines can be ascribed to the electron-donating ability of the nitrogen lone pair to C=C double bond, increasing its electron density. The nitrogen lone pair of enamides and enecarbamates, however, conjugates with the neighboring carbonyl group, leading to decreasing electron density of the C=C double bond and diminishing the nucleophilic ability of C=C double bond. Enamides and enecarbamates are intrinsically useful as synthetic tools since many acyl and alkoxycarbonyl groups known to be protecting groups of amino groups can be introduced in structures of enamides and enecarbamates, and as a result after the reactions of enamides and enecarbamates, the products bear protected amino groups. Products thus obtained can be employed in the next transformation as N-protected compounds and also can be converted to free amine compounds after deprotection. Despite the attractive potential of enamides and enecarbamates as described above, they have rarely been used systematically as substrates except in asymmetric hydrogenation reactions using transition metal catalysts such as Rh(I).[3] Encouraged by the potential usefulness of enamides and enecarbamates, we set about investigating the nucleophilic reactions of enamides and enecarbamates.

SCHEME 1



Nature and Synthetic Methods of Enamides and Enecarbamates

Shortly after starting our study, our interest was directed to enamides and enecarbamates bearing a hydrogen atom on nitrogen since enamides and enecarbamates bearing no hydrogen on nitrogen were found not to react with any electrophiles studied at all (*vide infra*). A majority of enamides and enecarbamates bearing hydrogen on nitrogen are stable under air, are solid at rt, and can be purified by chromatography on silica gel.[5] This stability contrasts with the corresponding enamines bearing hydrogen on nitrogen. Such enamines are known to exist in equilibrium with the imine at rt.[6] Under acidic conditions such as TfOH or Lewis acid having TfO^- as a counteranion, enamides and enecarbamates are rather unstable and readily isomerized to N-acyl and alkoxycarbonyl imines, respectively. However, in the presence of some appropriate ligands for metal salts, the isomerization to imines is suppressed, and this fact allows the realization of catalytic asymmetric reactions of enamides and enecarbamates by using chiral Lewis acid catalysts.

Several synthetic methods for enamides and enecarbamates have been reported, and we followed or adapted them (Scheme 1). One of the methods starts from nitriles, which are subjected to a Grignard reagent followed by treatment with acyl or alkoxy carbonyl cation equivalents (method I).[7] This method can be used for the syntheses of aromatic ketone-derived enamides and enecarbamates. Another method starts from α,β-unsaturated carboxylic acids, which are converted to acid azides followed by Curtius rearrangement to give isocyanates, which are treated with alcohols (method II).[8] Most enecarbamates can be prepared via this method, although some of the corresponding α,β-unsaturated carboxylic acids are troublesome to synthesize. An alternative method starts

TABLE 1. Enamides and Enecarbamates[4]

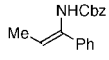
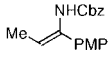
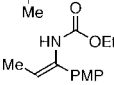
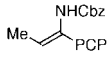
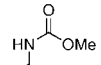
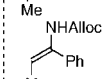
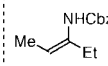
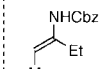
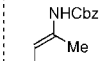
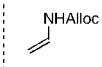
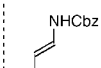
Structure	No.	Mp.	Method
	**1a**	90.0 – 91.0	I
	**1b**	92.8 – 93.0	I
	**1c**	130.5 – 131.1	I
	**1d**	72.1 – 72.4	I
	**2a**	69.4 – 69.5	I
	**2b**	54.7 – 54.8	I
	**2c**	79.0 – 79.1	I
	**2d**	52.3 – 53.0	I
	**2e**	100.3 – 101.5	I
	**2f**		L I
	**2g**		L I
	**2h**		L I
	***Z*-2i**	73.5 – 74.0	I
	***E*-2i**	63.9 – 64.0	I
	***Z*-2j**	110.0 – 110.5	I
	***E*-2j**	66.0 – 66.5	I
	***Z*-2k**	57.1 – 57.2	I
	***E*-2k**		L I
	***Z*-2l**	95.2 – 95.3	I
	***E*-2l**	71.2 – 71.3	I
	***E*-2m**	29.0 – 30.0	I
	***E*-2n**		L I
	***E*-2o**		L I
	***E*-2p**		L I
	***E*-2q**	64.0 – 64.5	I
	***E*-2r**		L I
	***Z*-2s**	60.3 – 60.8	I
	***E*-2s**		L I
	***Z*-2t**	53.0 – 54.0	II
	***E*-2t**	33.0 – 33.5	II
	**2u**	49.0 – 50.0	II
	***E*-2v**		L I
	**3a**	41.0 – 42.0	II
	**3b**		L II
	***Z*-3c**	32.0 – 33.0	III
	***E*-3c**	55.0 – 56.0	II
	***Z*-3d**		L III
	***E*-3d**	34.5 – 35.0	II
	***Z*-3e**	25.0 – 26.0	III
	***E*-3e**	110.0 – 111.0	III
	3f	38.5 – 39.0	III

FIGURE 1. N-Protected iminoester and HPA-12.

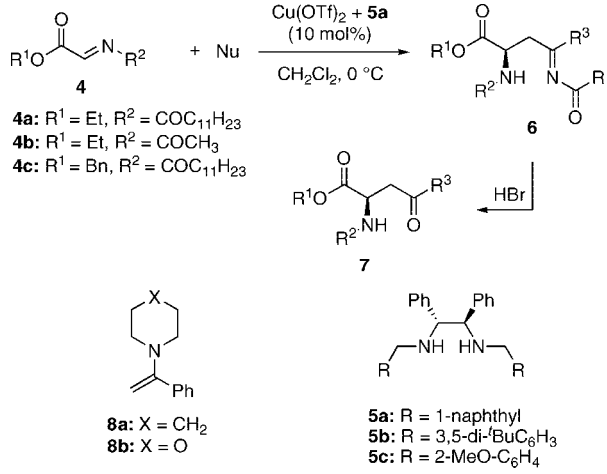
from the corresponding aldehydes, which are converted to *N*,*S*-acetals, followed by desulfonylation by treatment with bases (method III).[9] Most of all aldehyde-derived enecarbamates were synthesized via this method. It is noted that *Z*-enecarbamates are dominantly formed via method III. Other miscellaneous synthetic pathways for enamides and enecarbamates have been reported so far.[10] All the enamides and enecarbamates synthesized and studied in our group are summarized in Table 1.

Reactions of Enamides and Enecarbamates with *N*-Acylimino Esters[11]

N-Protected iminoesters are not only highly reactive electrophiles but also precursors of α-amino acids (Figure 1). Moreover, iminoesters bear imine functional groups adjacent to the carbonyl group which coordinate to a metal strongly in a bidentate fashion. The synthetic utility of these systems prompted us to investigate their catalytic asymmetric reactions, and several successful examples were reported.[12] Our group focused on the reaction of *N*-acylimino esters with silicon enolates since the procedure provides a facile way to enantio-enriched *N*-(3-hydroxy-1-hydroxymethyl-3-phenylpropyl)dodecanamide (HPA-12) (Figure 1).[13] This has been reported by our group to be a new type of inhibitor of ceramide trafficking from endoplasmic reticulum to the site of sphingomyelin synthesis.[14] The best catalyst for the reaction of *N*-acylimino esters with silicon enolates was found to be $Cu(OTf)_2$–diamine **5a** complex, which afforded the desired adducts with up to 94% ee.

Our initial investigation revealed that enamide **1a** reacted with *N*-acylimino ester **4a** to produce the adduct with 85% ee, while the corresponding enamines **8a** and **8b** gave the racemic product. The initially formed product was acylimine **6**, which could be observed by ^{1}H NMR spectroscopy. All the trials to purify and isolate the acylimine **6** failed; acylimine **6** was observed to isomerize to the corresponding enamide during the isolation process. It was found that hydrolysis of acylimine **6** by a treatment with acid (HBr in EtOH/H_2O particularly works well) furnished the corresponding ketone **7** in good yield. Further studies employing a variety of enamides and enecarbamates showed that enecarbamates were superior to enamides in this Mannich-type reaction as to enantioselectivity. Enecar-

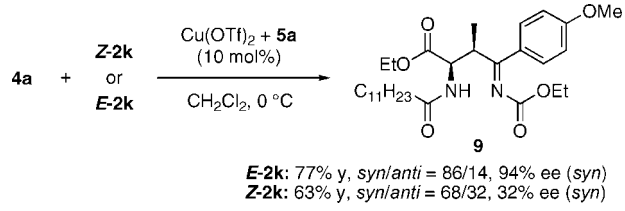
TABLE 2. Reactions of *N*-Acylimino Esters with Enamides and Enecarbamates



entry	imine	enamide	yield (%)[a]	ee (%)[b]
1	**4a**	**2a**	94	93
2[c]	**4a**	**2a**	92	93
3	**4b**	**2a**	72	94
4	**4c**	**2a**	89	91
5[d]	**4d**	**2a**	78	87
6	**4a**	**2b**	97	90
7	**4b**	**2b**	76	92
8	**4a**	**2c**	89	90
9	**4a**	**2d**	93	91
10	**4a**	**2e**	83	88
11	**4b**	**2e**	76	91
12	**4c**	**2h**	84	83
13[c]	**4c**	**2h**	81	84

[a] Isolated yield. [b] Determined by HPLC analysis. [c] Diamine **5b** was used instead of **5a**. [d] Diamine **5c** was used instead of **5a**.

SCHEME 2



***E*-2k:** 77% y, *syn*/*anti* = 86/14, 94% ee (*syn*)
***Z*-2k:** 63% y, *syn*/*anti* = 68/32, 32% ee (*syn*)

bamates **2a** bearing a typical nitrogen-protecting group, benzyloxycarbonyl (Cbz), proved to react with *N*-acylimino ester **4a** to afford the product with higher enantioselectivity (up to 94% ee). The results of investigation of the substrate generality for this Cu-catalyzed addition reaction of enecarbamates are summarized in Table 2. Aromatic and aliphatic ketone-derived enecarbamates afforded the desired products in good yields with high enantioselectivities. The use of monosubstituted enecarbamate resulted in the formation of the corresponding acylimine, which was found to be relatively stable under purification conditions (chromatography on silica gel, Scheme 2). Both *E*- and *Z*-enecarbamates **2k** were subjected to the reaction, and *syn*-

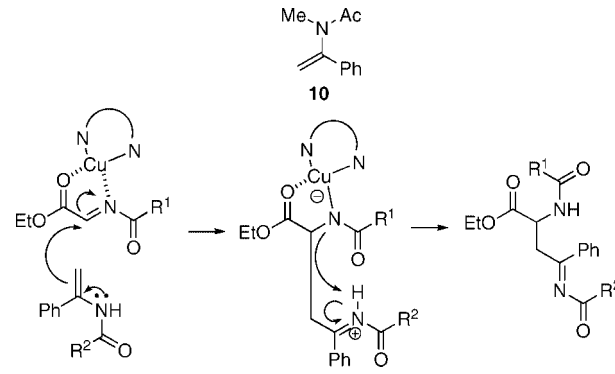
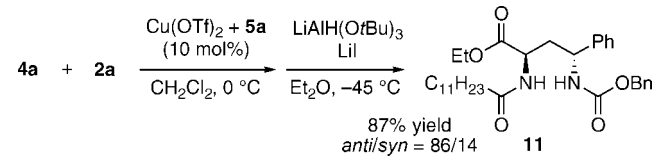


FIGURE 2. Proposed reaction mechanism of catalytic asymmetric reaction of *N*-acylimino ester with enamide.

SCHEME 3



adduct was obtained as a major product in both cases. The ee of the *syn* adduct obtained from ***E*-2k** was high (94% ee), while that of the *syn*-adduct obtained from ***Z*-2k** was 32% ee.

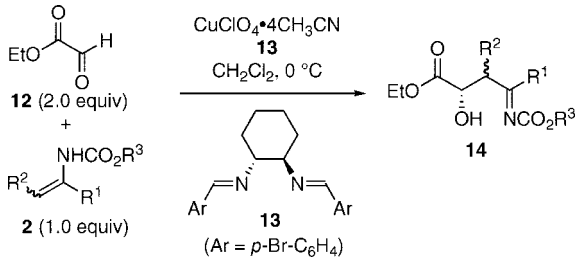
It is worth noting that enecarbamate **10** bearing no hydrogen on nitrogen does not react with *N*-acylimino ester **4a** at all and that only starting material was recovered. This fact indicates that hydrogen on nitrogen plays a significant role in reaction progress, although steric reasons cannot be denied completely. Judging from the results mentioned above, we now consider that this reaction proceeds via a nonconcerted aza–ene-type pathway, which is illustrated in Figure 2.

An end product, acylimine **6**, is subjected to further transformation as electrophilic imine is included in the molecule. Instead of hydrolysis, reduction of the imine group gave 1,3-diamine derivatives, which are versatile chiral building blocks for the synthesis of natural products, drugs, ligands, etc. It was found that LiAlH(O*t*-Bu)$_3$ in the presence of LiI reduced the acylimine to afford 1,3-diamine derivative **11** in good yield with good diastereoselectivity (Scheme 3). We can regard enamides and enecarbamates as reagents for the introduction of C2 and protected nitrogen units in a stereoselective manner.

Reactions of Enecarbamates with Ethyl Glyoxylate[15]

Having shown enamides and enecarbamates to be prominent nucleophiles, we started to see which electrophile can react

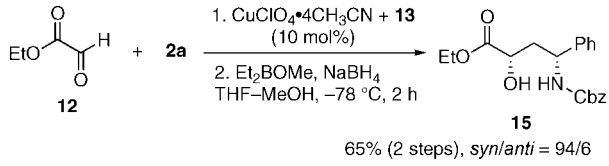
TABLE 3. Catalytic Asymmetric Reactions of Ethyl Glyoxylate with Enecarbamates[a]



entry	2	yield (%)[b]	*syn*/*anti*[c]	ee (%)[d]
1	**2a**	93		97
2	**2b**	94		93
3	**2c**	97		97
4	**2d**	quant		96
5	**2e**	91		96
6	***E*-2i**	83	1/99	98
7[e,f]	***E*-2i**	95	1/99	98
8	***Z*-2i**	82	98/2	98
9[f]	***Z*-2i**	96	98/2	98
10	***E*-2j**	96	2/98	98
11	***Z*-2j**	97	98/2	98
12	***E*-2k**	82	3/97	96
13	***Z*-2k**	96	99/1	98
14	***E*-2l**	85	2/98	98
15	***Z*-2l**	79	99/1	98
16	***E*-2s**	58	1/99	98
17[g]	***Z*-2s**	92	99/1[h]	98
18[e]	***E*-2t**	89	8/92[h]	98
19[e]	***Z*-2t**	83	97/3[h]	97
20	**2u**	85	16/84	94

[a] All reactions were performed in the presence of the catalyst (10 mol%, unless otherwise noted). [b] Isolated yield. [c] Determined by HPLC. [d] Ee of the major diastereomer. Determined by HPLC. [e] −20 °C. [f] 0.1 mol % of catalyst was used. [g] **12** (1.0 equiv) and **2** (2.0 equiv) were used. [h] Determined by NMR analysis.

SCHEME 4



with enamides and enecarbamates. Although general aldehydes such as benzaldehyde failed to react with enamides or enecarbamates in the absence or presence of catalysts, ethyl glyoxylate (**12**) reacted with enamides and enecarbamates in the presence of catalysts. After screening a wide range of catalysts, mainly copper catalysts, we found that a copper complex prepared from Cu(I) salt and diimine ligand **13**, which has a 1,2-cyclohexanediamine backbone, was pre-eminent for enantioselectivity (Table 3).

We then examined several enecarbamates including aromatic ketones, aliphatic ketone-derived enecarbamates, and enecarbamates bearing substituents at the olefin terminus. Unsubstituted enecarbamates reacted smoothly to afford the desired adducts in high yields with a high degree of enantioselectivity. The adduct acylimine thus obtained can be converted to γ-amino alcohol **15** highly *anti* selectively (*anti*/*syn* = 94/6) by treatment of the crude acylimine product with $NaBH_4$ in the presence of $Et_2B(OMe)$ (Scheme 4). It should be stressed that the reactions of enecarbamates are more atom economical than those of metal enolates since all the atoms of the starting materials (aldehyde and enecarbamate) are included in the end product. Remarkable results were obtained in the reactions of substituted enecarbamates. *E*-Enecarbamates gave *anti* adducts, and *Z*-enecarbamates gave *syn* adducts stereospecifically. The diastereoselectivity is in general excellent, and the enantioselectivity of the major diastereomer is quite high. This result is in contrast to Mukaiyama-type aldol reactions using silicon enolates, which usually proceed via an acyclic transition state, leading to the formation of *syn* adducts. It is noted that 0.1 mol % of the catalyst is sufficient to make the reaction proceed; almost the same results are observed only if the reaction is prolonged. Enecarbamate, which bears no hydrogen on nitrogen, such as **16**, again fails to react.

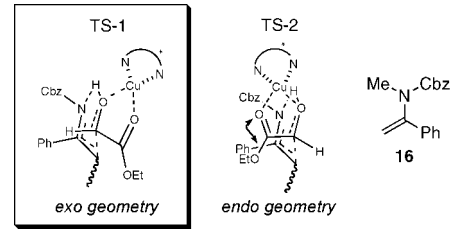


FIGURE 3. Plausible reaction mechanism of addition reaction of enecarbamate to ethyl glyoxylate.

We inferred from the diastereoselection outcome that this reaction proceeded via a cyclic transition state and proposed a concerted aza−ene-type mechanism (Figure 3). In this compact transition state, the interaction between a substituent of enecarbamate and the ester part of ethyl glyoxylate disfavors *endo* geometry, so the reaction proceeds via an *exo* geometry in both cases of *E*- and *Z*-enecarbamates, leading to the formation of *anti* and *syn* adduct, respectively. The hydrogen atom on the nitrogen of enecarbamate has proved to be requisite for both reaction progress and selectivity induction.[16] Considering that few enamines that have hydrogen on nitrogen have been reported (this does not mean that enamines cannot have hydrogen on nitrogen but that enamines are in an equilibrium between enamines and imines), enecarbamates are marked by the fact that enecarbamates bearing hydrogen on nitrogen are easy to isolate (stable even on silica gel) and store.

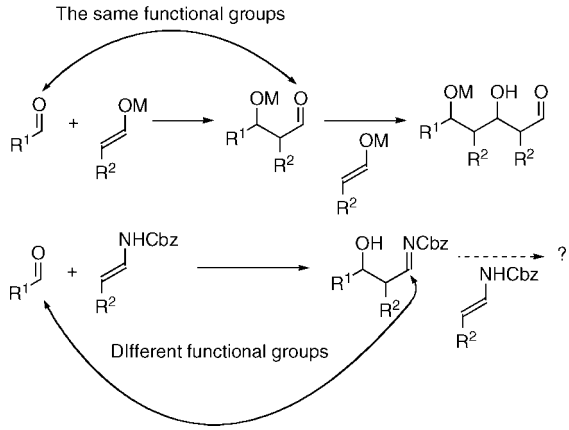
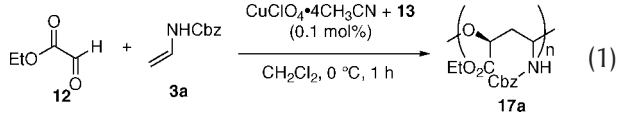


FIGURE 4. Reaction of aldehyde-derived nucleophile with aldehyde.

Aldehyde-Derived Enecarbamates[17]

A majority of aldol or aldol-type reactions reported so far employ nucleophiles derived from ketones and esters, and the use of aldehyde-derived nucleophiles remains a challenging endeavor. A complicating factor when carrying out reactions involving aldehyde-derived nucleophiles is the tendency of the latter to undergo further reaction with the aldehyde formed as the product of the reaction (upper equation in Figure 4). Only a few examples on catalytic asymmetric reactions using aldehyde-derived nucleophiles have been reported to date.[18]

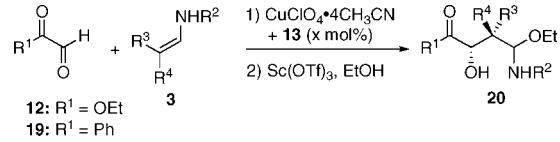
Aldehyde-derived enecarbamate as typified by enecarbamate **3a** has been reported to be stable and easy to handle and synthesize,[19] which prompted us to develop the reaction of aldehyde-derived enecarbamates. The expected feature of this chemistry is demonstrated in the lower equation of Figure 4. Enecarbamates react with aldehydes to give *N*-acylimines. Because *N*-acylimines and aldehydes have different reactivities, it is expected that we can control over-reaction in some way. We soon discovered that starting enecarbamate **3a** was consumed in the presence of the copper(I) catalyst, but that ^{1}H NMR spectroscopy of the crude product showed a complex mixture to be formed (eq 1). A number of experiments were carried out, revealing this complex mixture to be a compound of the structure **17a**. The fact that the treatment of the compound with EtOH in the presence of a catalytic amount of $Sc(OTf)_3$ gives N,O-acetal **18** supports this postulate (eq 2).



(1)

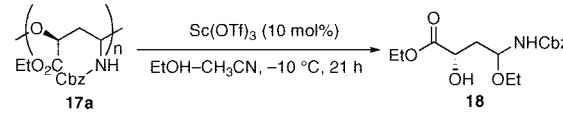
Having established a method for isolation of the products, we used a variety of enecarbamates as summarized in Table 4. In almost all the cases, *N*,*O*-acetals **20** were furnished in high yields with excellent enantioselectivities. A similar tendency to the reactions of ketone-derived enecarbamates is observed: (1) *E*-encarbamates give *anti* products, while *Z*-enecarbamates give *syn* products, selectively. (2) Catalyst loading can be decreased to 0.1 mol % in some cases. (3) Enecarbamates bearing no hydrogen on nitrogen such as **3g** fail to react.

TABLE 4. Catalytic Asymmetric Reactions of Aldehyde-Derived Enecarbamates



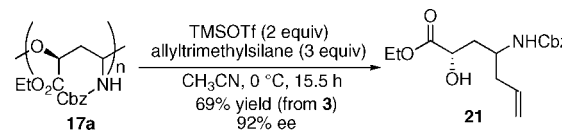
entry	R^1	**3**	*x*	time (h)	yield (%)[a]	*syn*/*anti*[b]	ee (%)[c]
1[d]	OEt	**3a**	0.1	1	80		92
2[e]	Ph	**3a**	1	1.5	54		88
3	OEt	**3b**	0.1	1	50		96
4[e]	Ph	**3b**	1	1.5	58		91
5	OEt	***E*-3c**	1	5.5	84	12/88	97
6	OEt	***Z*-3c**	1	28	79	92/8	95
7	OEt	***E*-3d**	1	5.5	87	9/91	98
8	OEt	***Z*-3d**	1	28	79	82/18	94
9	OEt	***E*-3e**	1	24	50	5/95	96
10	OEt	***Z*-3e**	1	24	0		
11	OEt	**3f**	5	18	81		70
12	OEt	**3f**	1	28	39		78
13	OEt	**3g**[f]	5	24	0		

[a] Yield of isolated compound **20** unless otherwise noted. [b] Dr ratio was determined after reduction of **20**. [c] Ee of the major diastereomer. [d] *i*-PrOH (1 equiv) was added in the copper-catalyzed reaction. [e] **3** was slowly added over 2 h. [f] **3g** is N-methylated **3a**.



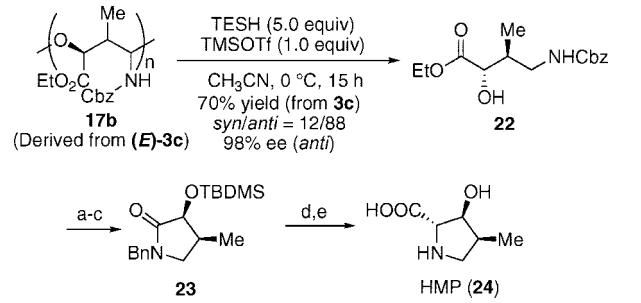
(2)

We can expect a broad range of applications of developed reactions because the *N*,*O*-acetal moiety can be transformed readily into other functional groups. For example, the polymeric or oligomeric compound **17a** obtained as an adduct from this reaction can be allylated under Lewis acidic conditions in good yield (eq 3). Reduction of the polymeric or oligomeric compound **17b** by using triethylsilyl hydride and trimethylsilyl triflate furnished the compound **22**, which was successfully transformed to (2*S*,3*S*,4*S*)-3-hydroxy-4-methylproline (HMP, **24**), one of the nonproteinogenic amino acids (Scheme 5).[20]



(3)

SCHEME 5[a]



[a] Reaction conditions: (a) TBDMSOTf, 2.6-lutidine, 93%; (b) Pd/C, H_2, AcOH, 87%; (c) BnBr, KOH, 18-crown-6, 86%; (d) DIBAL; KCN, 78%; (e) cHCl; Pd/C, H_2, H_2O, 88%.

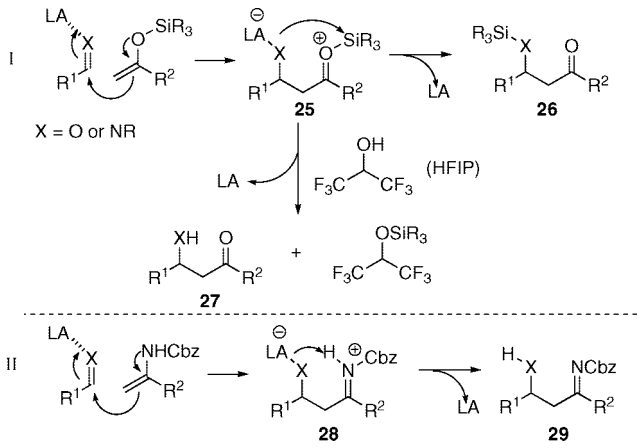


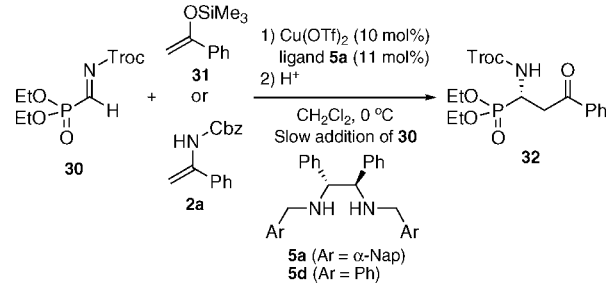
FIGURE 5. Lewis acid-mediated nucleophilic addition.

Identification of Advantageous Aspects of Enamide and Enecarbamate Nucleophilic Reactions

Although much attention has been paid recently to the catalytic asymmetric direct nucleophilic addition reaction of ketones and aldehydes,[21] the use of silicon enolates is still among the most reliable methods since they are highly reactive and relatively stable, facilitating their purification and isolation. In the Lewis acid-catalyzed nucleophilic addition reactions of silicon enolates to, for example, aldehydes, the catalytic process is completed by the transfer of a silicon cation from the nucleophile oxygen to the aldehyde one, resulting in the cleavage of the newly formed O–M bond to liberate the catalyst (Figure 5, reaction I). Some reports suggest that silicon transfer is slow and becomes the catalyst-turnover-limiting step.[22] If a reaction proceeds even in the absence of the catalyst (there is a competition between catalyzed and uncatalyzed pathways), low turnover frequency leads to a drop of enantioselectivity.

In 2004, we reported catalytic asymmetric reactions of silicon enolates with *N*-acyl-α-iminophosphonates (Table 5, entries 1–3).[23] A drawback of this method is low turnover frequency and slow addition of substrates (entry 1 vs entry 3 in Table 5), or addition of proton source such as hexafluoroisopropanol (HFIP) is necessary (entry 2 vs entry 4 in Table 5) so as to obtain high enantioselectivity. Nucleophilic attack of silicon enolate to *N*-acyl-α-iminophosphonate occurs even in the absence of the catalyst (0 °C, 1 min, 78% yield), which causes detrimental erosion of enantioselectivity when catalyst turnover frequency is low. This latter phenomena is ascribed to the inhibition of the catalyst by the intermediates such as **25** to which slow silicon transfer gives a longer life. In this case, a delay in the reaction cycle is required while the intermediate is released from the catalyst, before another molecule of the substrate is added. HFIP supplies a proton to the nitrogen of the intermediate, resulting in the cleavage of the N–M bond without silicon transfer and so improves catalyst turnover (Figure 5, reaction I).[24]

TABLE 5. Reactions of Iminophosphonate **30** with Silyl Enolate **31** or Enecarbamate **2a**

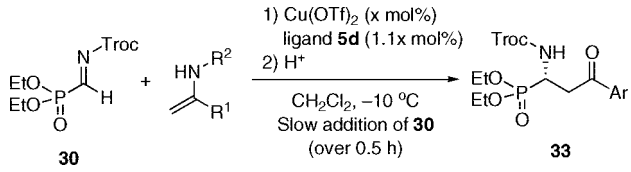


entry	nucleophile	addition time (h)[a]	yield (%)	ee (%)
1	**31**	0.5	78	49
2	**31**	8	81	73
3	**31**	48	79	90
4[b]	**31**	8	81	89
5	**2a**	0.05	72	89

[a] Iminophosphonate **30** was slowly added. [b] 1.0 equiv of HFIP was added. Troc = 2,2,2-trichloroethoxycarbonyl.

In the reaction of enamides and enecarbamates, it is a proton that transfers after the nucleophilic addition, which would not cause prevention of catalyst turnover (Figure 5, reaction II). Indeed, slow addition of substrates is no longer necessary for high enantioselectivity. Addition of iminophosphonate over as short a time as 3 min in the reaction of enecarbamate is enough to obtain the same level of enantioselectivity (entry 5 in Table 5) as is observed in the reaction of silicon enolate in which the iminophosphonate is slowly added over 48 h (entry 3 in Table 5). The catalyst loading can be reduced to 1.5 mol % in some cases (Table 6), while 10 or 15 mol % of the catalyst is needed in the reaction of iminophosphonates with silicon enolates. The catalytic cycle is demonstrated in Figure 6. Iminophosphonate coordinated by copper catalyst **32** reacts with enecarbamate **2a** or silicon enolate **31** to afford zwitterionic intermediate **33**, which

TABLE 6. Catalytic Asymmetric Reactions of Iminophosphonate **30** with Enecarbamates



entry	nucleophile	*x*	yield (%)	ee (%)
1	**1b**	1.5	81	85
2	**1c**	2.0	72	86
3	**1d**	1.5	83	86
4	**2a**	5.0	77	89
5	**2b**	5.0	77	94
6	**2c**	5.0	78	87
7	**2d**	5.0	77	93
8	**2e**	5.0	66	89

can be directly converted through a M^+ transfer mechanism to the compound **35**, which has less coordinating ability. Alternatively, the intermediate **33** may be converted to **34a** via M^+ transfer. The intermediate **34a** is transformed to **35** via M^+ transfer from carbamate oxygen to carbamate nitrogen. We cannot deny the third possibility of six-membered ring formation and nucleophilic attack by carbamate oxygen to C=X double bond

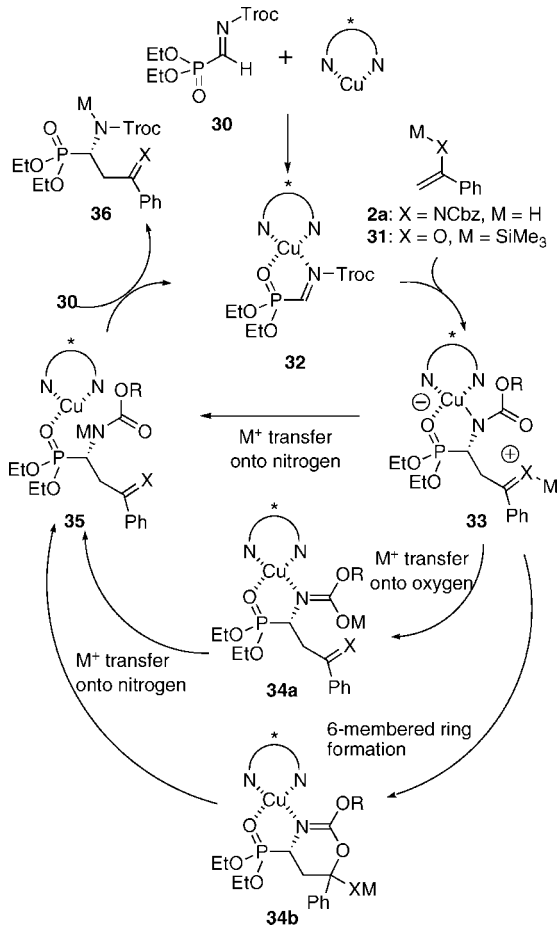


FIGURE 6. Rationale for high turnover frequency in the reaction of iminophosphonate **30** with enecarbamates.

SCHEME 6

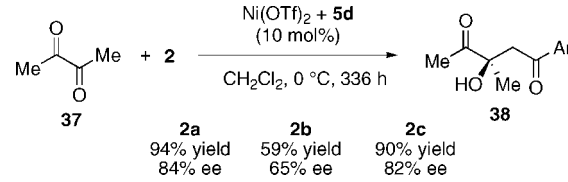
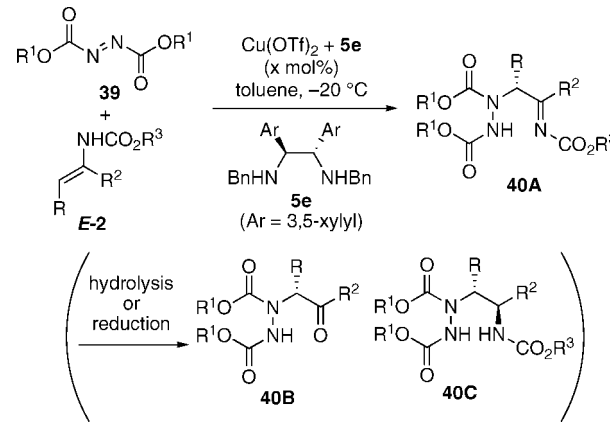


TABLE 7. Reactions of Azodicarboxylates **39** with Enecarbamates



entry	R^1	***E*-2**	*x*	time (h)	yield (%)	ee (%)	product[f]
1[a]	*i*-Pr	**2i**	0.2	22	84	98	**40C**
2	*i*-Pr	**2m**	1	25	90	92	**40B**
3	*i*-Pr	**2n**	1	24	87	84	**40B**
4	*i*-Pr	**2o**	1	24	62	83	**40B**
5	Me	**2i**	3	24	83	82	**40B**
6	Et	**2i**	3	24	91	84	**40B**
7[b]	Bn	**2i**	10	6	99	85	**40B**
8	*i*-Pr	**2p**	5	20	84	96	**40A**
9	*i*-Pr	**2q**	1	24	93	97	**40B**
10	*i*-Pr	**2r**	5	10	90	94	**40B**
11	*i*-Pr	**2j**	3	6	81	90	**40C**
12	*i*-Pr	**2l**	0.2	24	79	96	**40C**
13[c]	*i*-Pr	**2t**	2	6	82[e]	82	**40C**
14[d]	*i*-Pr	**2v**	5	4	70	86	**40C**
15[c]	*i*-Pr	**3c**	5	26	82	67	**40C**

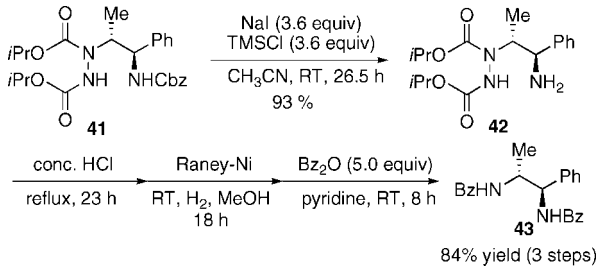
Reactions conducted with 1.1 equiv of **39** relative to **2** in toluene (0.067 M in substrate). [a] −10 °C. [b] MS 3A was added (100 mg/mmol). [c] Ligand **5a** was used instead of **5e**. [d] MS 3A was added (50 mg/mmol). [e] *syn/anti* = 28:72. [f] **A** = acylimine (no treatment); **B** = ketone by hydrolysis; **C** = 1,2-diamino derivative by reduction (*syn/anti* = <5:>95).

in **33**, furnishing **34b**. The intermediates **33**, **34a**, and **34b**[25] may inhibit the catalyst turnover because they have strong coordinating ability to the catalyst. Proton transfer is faster than silicon transfer; therefore, catalyst turnover is faster overall in the case of enecarbamate addition than that in the case of silicon enolate addition.

Miscellaneous Reactions of Enamides and Enecarbamates

Diketone **37** reacts with enecarbamates to afford stereogenic *t*-alcohols **38** in the presence of a nickel(II) triflate complex (Scheme 6).[26] Reactions of enecarbamates with azodicarboxylates **39** are catalyzed by a copper(II)−diamine **5e** complex, leading to the formation of the adducts **40**, with a high level of enantioselectivity

SCHEME 7



(Table 7).[27] The initially formed acylimines **40A** were readily converted into ketone products **40B** after hydrolysis or 1,2-diamine derivatives **40C** after highly stereoselective reduction by $NaBH_4$. N–N bond cleavage could be achieved using Raney–Ni, which enabled us to make unsymmetrical *trans*-1,2-diamine derivatives such as compound **43** (Scheme 7).

Conclusion

Enamides and enecarbamates, although originally employed as just N-analogues to silicon enolates, have emerged as remarkably useful nucleophiles in a variety of Lewis acid-catalyzed reactions. This system displays a number of unique characteristics: (1) Initially formed products are acylimines, which are easily transformed to other nitrogen-containing products. (2) Reactions of enamides and enecarbamates are atom economical. All atoms composing starting materials are included in the end products. (3) In aldol-type reactions, stereospecific transformation occurs via a concerted aza–ene-type mechanism. (4) Catalyst turnover frequency is improved in comparison with silicon enolate addition since a proton should be transferred after a nucleophilic addition. Current efforts are directed to developing additional applications of enamides and enecarbamates as nucleophiles as well as designing novel types of nucleophiles based on a proton transfer mechanism.

We thank the graduate students, postdocs, and undergraduates at the university of Tokyo who participated in this project. In particular, we are grateful to Hiroshi Kiyohara, Dr. Yoshitaka Nakamura, Dr. Nobuyuki Kawai, Dr. John S. Fossey, and Dr. Paulo Vital for their contributions, that made this Account possible. Financial support by CREST, SORT, ERATO, Japan Science and Technology Corporation (JST), and a Grant-in-Aid for Scientific Research from Japan Society is also acknowledged.

BIOGRAPHICAL INFORMATION

Ryosuke Matsubara was born in Chiba, Japan, in 1978. He studied chemistry at the University of Tokyo and received a Ph.D. in 2007 with a thesis on study of catalytic asymmetric reactions using enamides and enecarbamates as nucleophiles (supervisor Shū Kobayashi). In the period 2003–2005, he received the Japan Society of the Promotion of Sciences (JSPS) fellowship for Japanese junior scientists. He started his academic career as an assistant professor in 2005 at the University of Tokyo. His current research interest lies in the development of new reactions taking advantage of hydrogen atoms.

Shū Kobayashi studied at the University of Tokyo, receiving his Ph.D. in 1988 working under the direction of Professor T. Mukaiyama. Following an initial period as assistant professor, he was promoted to lecturer then associate professor at the Science University of Tokyo. In 1998, he moved to the Graduate School of Pharmaceutical Sciences, The University of Tokyo, as full professor. In April 2007, he was appointed to his current position as professor of organic chemistry in the Department of Chemistry, within the Faculty of Science of The University of Tokyo. Professor Kobayashi is also director of the ERATO project of the Japan Science Agency (JST). He has held various visiting professorships, including the Universite Louis Pasteur, Strasbourg (1993), Kyoto University (1995), Nijmegen University (1996), and Philipps-University of Marburg (1997).

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4 PCP = *p*-chlorophenyl; PMP = *p*-MeO-phenyl; OMeP = *o*-Me-phenyl; MMeP = *m*-Me-phenyl; PMeP = *p*-Me-phenyl; α-Nap = α-Naphthyl; β-Nap = β-Naphthyl; Alloc = allyloxycarbonyl; L = liquid.

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