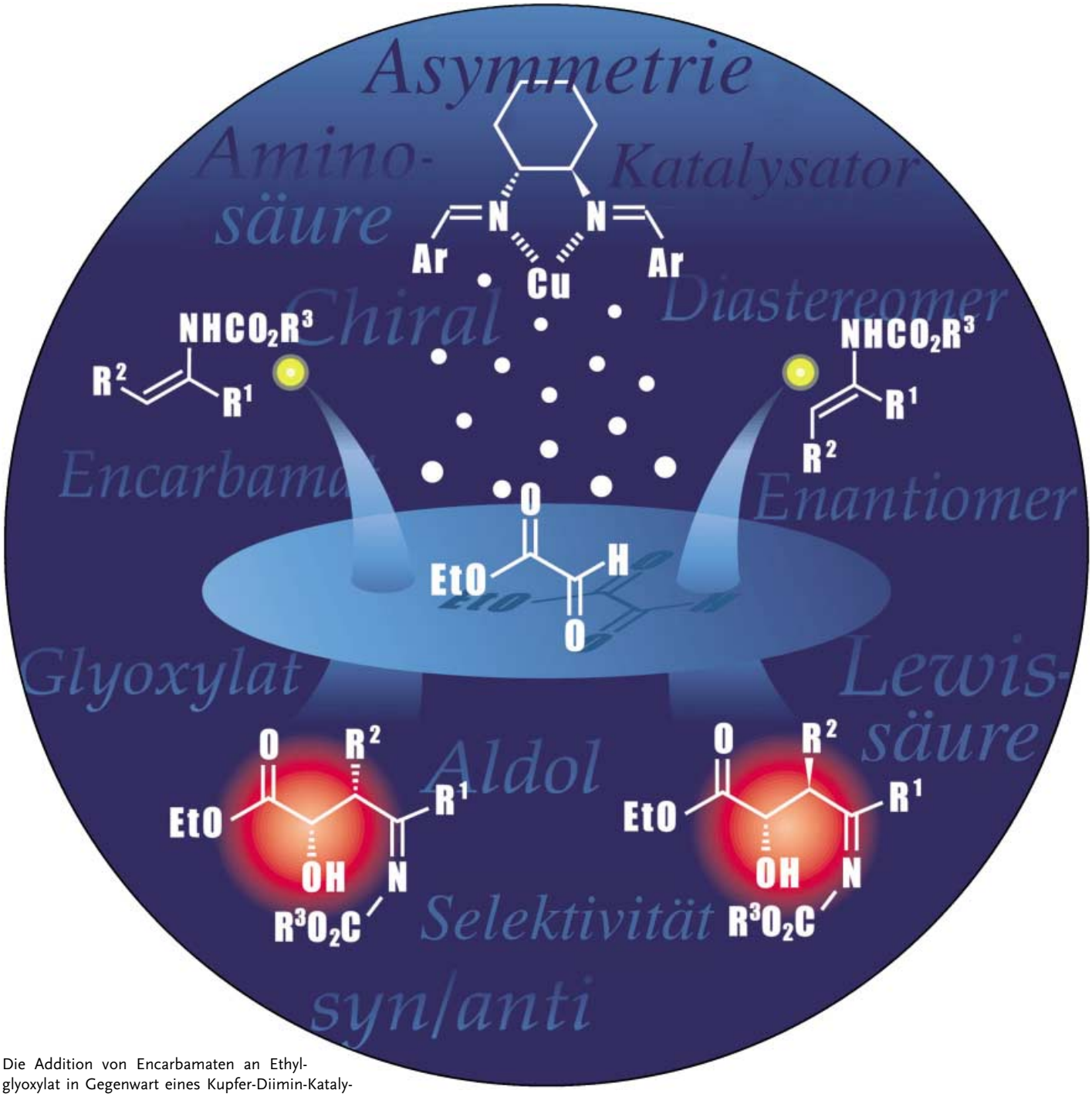
Zuschriften



Die Addition von Encarbamaten an Ethylglyoxylat in Gegenwart eines Kupfer-Diimin-Katalysators führt in hohen Ausbeuten und mit ausgezeichneten Enantioselektivitäten zu den entsprechenden Iminen. Aus (*E*)-Encarbamaten werden *anti*-Addukte, aus (*Z*)-Encarbamaten *syn*-Addukte erhalten. S. Kobayashi et al. beschreiben diese neuartige Reaktion auf den folgenden Seiten und erklären die bemerkenswerte Stereoselektivität mit einem konzertierten Aza-En-Mechanismus.

DOI: 10.1002/ange.200460165

Addition Reactions

Highly Diastereo- and Enantioselective Reactions of Enecarbamates with Ethyl Glyoxylate To Give Optically Active *syn* and *anti* α-Alkyl-β-Hydroxy Imines and Ketones**

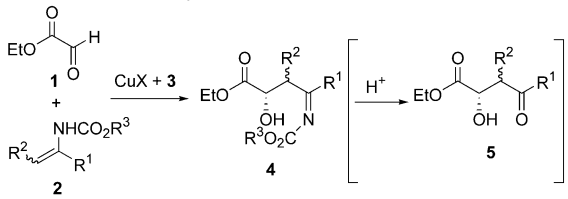
*Ryosuke Matsubara, Yoshitaka Nakamura, and Shū Kobayashi**

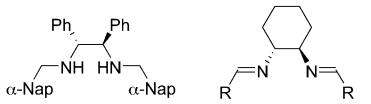
Control of the absolute configuration of two adjacent stereogenic centers that include alkyl and hydroxy groups is among the most important reactions for the synthesis of many biologically active compounds.[1] For the relative stereochemistry issue (*syn*/*anti*), aldol,[2] allylation,[3] and related reactions via six-membered transition states are powerful tools, and diastereoselective reactions with chiral auxiliaries have opened the way to optically active compounds. For asymmetric catalysis, on the other hand, Mukaiyama-type reactions of silicon reagents with chiral Lewis acids have been investigated extensively.[4] However, the reactions proceed via acyclic transition states to afford *syn* adducts in most cases, and control of the relative stereochemistry by geometrical isomers is difficult.

We recently investigated the use of enamides and enecarbamates as nucleophiles.[5] In spite of their importance in organic chemistry, examples of nucleophilic additions of enamides or enecarbamates are few,[6] whereas there are many reports on the use of enamines as nucleophiles.[7] Herein we report the first highly diastereo- and enantioselective addition reaction of enecarbamates with ethyl glyoxylate. This reaction proceeds smoothly in the presence of a Cu^{I}–chiral diimine complex, and α-monosubstituted enecarbamates provide the corresponding adducts stereospecifically; that is, *syn* products are obtained from *Z* enecarbamates and *anti* products are obtained from *E* enecarbamates with high diastereo- and enantioselectivities.

Initially, the reaction of ethyl glyoxylate (**1**), which was freshly distilled from a commercially available polymer-form solution in toluene, with enecarbamate **2a**[8] was investigated in the presence of various chiral Lewis acids. It was found that some Lewis acids were effective and afforded the corresponding imine-type adducts **4** in high yields. For determining the *ee* values of the products, **4** was converted into the corresponding ketones **5**.[9] Although some copper salts worked well in this reaction, Cu^{II}–diamine complexes,[10] which gave excellent results in Mannich-type reactions of *N*-acylimino esters with enamides and enecarbamates,[5] afforded the product with moderate enantioselectivity (Table 1, entry 1). On the other hand, it was revealed that much higher enantioselectivities were obtained when Cu^{I}–diimine complexes[11] were used (Table 1, entries 4 and 5). Among several chiral imines tested, Cu^{I}–diimine ligand **3c** gave the highest enantioselelctivity (97% *ee*). Furthermore, lower loading of the catalyst (2 mol%) gave the same level of reactivity and selectivity (96% yield, 95% *ee*; Table 1, entry 6).

Table 1: Catalyzed reactions of ethyl glyoxylate (**1**) with enecarbamate **2a** (R^1 = Ph, R^2 = H, R^3 = Bn).[a]





Entry	Ligand	CuX	Yield [%][b]	*ee* [%][c]
1	**3a**	$Cu(OTf)_2$	93	55[d]
2	**3b**	$Cu(OTf)_2$	65	70[d]
3	**3a**	$CuClO_4 \cdot 4CH_3CN$	90	35[d]
4	**3b**	$CuClO_4 \cdot 4CH_3CN$	94	93
5	**3c**	$CuClO_4 \cdot 4CH_3CN$	93	97
6[e]	**3c**	$CuClO_4 \cdot 4CH_3CN$	96	95

[a] All reactions were performed in CH_2Cl_2 at 0°C for 1 h in the presence of CuX (10 mol%) and **3**. [b] Yield of isolated **5a**. [c] Determined by HPLC (see Supporting Information). [d] The absolute configuration is *R*. [e] Catalyst: 2 mol%. Tf = trifluoromethanesulfonyl.

We then examined several other enecarbamates, and the results are summarized in Table 2. α-Unsubstituted enecarbamates **2b–e** reacted smoothly to afford the desired adducts in high yields with excellent enantioselectivities (Table 2, entries 1–4). For the reactions with α-substituted enecarbamates, remarkable results were obtained. The reactions proceeded stereospecifically: *E* enecarbamates gave *anti* adducts, whereas *Z* enecarbamates produced *syn* adducts with both excellent diastereo- and enantioselectivities in most cases. These selectivities are in contrast to Lewis acid catalyzed asymmetric aldol-type reactions of silicon enolates with aldehydes, which give mostly *syn* adducts, regardless of the geometry of the enolates.[4,12] The asymmetric reactions discussed herein also proceeded smoothly in the presence of 0.1 mol% of the Cu^{I} catalyst. Moreover, it was found that under the same conditions as those shown in Table 1, entry 5, comparable yield and enantioselectivity were obtained when using an undistilled polymer-form ethyl glyoxylate solution in

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[**] This work was partially supported by CREST, SORT, and ERATO, Japan Science Technology Agency (JST), and a Grand-in-Aid for Scientific Research from Japan Society for the Promotion of Sciences (JSPS). R.M. is grateful for a JSPS fellowship for Japanese Junior Scientists.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

  DOI: 10.1002/ange.200460165

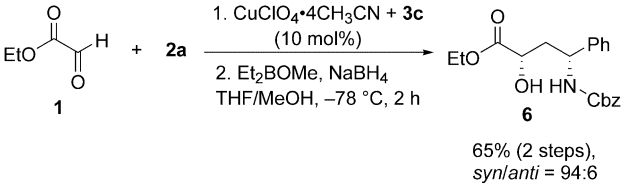
Table 2: Cu^{I}–**3c**-catalyzed reactions of **1** with **2** (R^3 = Bn).[a]

Entry	2	5	Yield [%][b]	*syn*/*anti*[c]	*ee* [%][d]
1	**2b** (R^1 = PMP, R^2 = H)	**5b**	94	–	93
2	**2c** (R^1 = PCP, R^2 = H)	**5c**	97	–	97
3	**2d** (R^1 = PMeP, R^2 = H)	**5d**	quant	–	96
4	**2e** (R^1 = 2-Nap, R^2 = H)	**5e**	91	–	96
5	(*E*)-**2f** (R^1 = Ph, R^2 = Me)	**5f**	83	1:99	98
6[e,f]	(*E*)-**2f**	**5f**	95	1:99	98
7	(*Z*)-**2f**	**5f**	82	98:2	98
8[f]	(*Z*)-**2f**	**5f**	96	98:2	98
9	(*E*)-**2g** (R^1 = PMP, R^2 = Me)	**5g**	96	2:98	98
10	(*Z*)-**2g**	**5g**	97	98:2	98
11	(*E*)-**2h** (R^1 = PMP, R^2 = Me)[g]	**5g**	82	3:97	96
12	(*Z*)-**2h**[g]	**5g**	96	99:1	98
13	(*E*)-**2i** (R^1 = PCP, R^2 = Me)	**5i**	85	2:98	98
14	(*Z*)-**2i**	**5i**	79	99:1	98
15	(*E*)-**2j** (R^1 = Ph, R^2 = Et)[h]	**5j**	58	1:99	98
16	(*Z*)-**2j**	**5j**	92	99:1	98
17[e]	(*E*)-**2k** (R^1 = Et, R^2 = Me)	**5k**	83	3:97[i]	97
18[e]	(*Z*)-**2k**	**5k**	89	92:8[i]	98
19	**2l** (R^1, R^2 = $-(CH_2)_4-$)	**5l**	85	16:84[i]	94

[a] All reactions were performed in CH_2Cl_2 at 0°C in the presence of the catalyst (10 mol%, unless otherwise noted). Reaction time was 0.5–2 h in most cases. [b] Yield of isolated product. [c] Determined by HPLC. [d] Major diastereomer, *ee* value determined by HPLC (see Supporting Information). [e] −20°C. [f] Catalyst: 0.1 mol%. [g] R^3 = Et. [h] **1** (1.0 equiv) and **2** (2.0 equiv). [i] Determined by NMR analysis. PMP = *p*-methoxyphenyl, PCP = *p*-chlorophenyl; PMeP = *p*-methylphenyl; 2-Nap = 2-naphthyl.

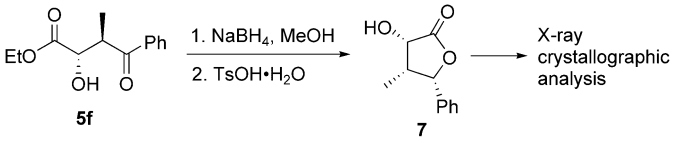
toluene, which indicates that the Cu^{I}–diimine complex both depolymerizes the glyoxylate as well as catalyzes the following asymmetric addition reaction.[13]

The reactions with enecarbamates are more atom economical than those with enolates; the initial imine-type products **4** contain all the atoms that compose both substrates (ethyl glyoxylate and enecarbamates). After the enecarbamate addition, the following diastereoselective reduction was conducted in the same pot to afford *N*-Cbz-protected α-hydroxy-γ-amino acid ester **6** with high selectivity (Scheme 1).[14] For *anti*-**5f** (d.r. = 99:1), the reduction of the



Scheme 1. Conversion into *N*-Cbz α-hydroxy γ-amino acid ester **6**. Cbz = benzyloxycarbonyl.

ketone moiety with $NaBH_4$ followed by cyclization gave lactone **7** as a diastereomeric mixture (Scheme 2).[15] One diastereomer of **7** was obtained as a crystalline compound, which was characterized by X-ray crystallography.[16] From the knowledge of the relative configuration of **7**, the relative configuration of **5f** was determined.



Scheme 2. Determination of the relative configuration of **5f**.

The fact that α-monosubstituted enecarbamates provided products stereospecifically led us to propose a concerted aza-ene-type reaction mechanism outlined in Figure 1.[17,18] This

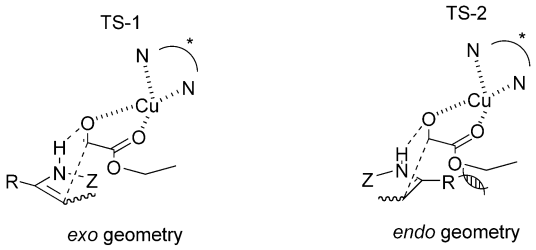


Figure 1. Proposed transition-state models.

proposed mechanism does not contradict the result that the reaction of *N*-methylated enecarbamate **2m** with ethyl glyoxylate gave no adduct with almost all the starting materials left unconverted. TS-1 should be a predominant transition state since the other candidate, TS-2, has unfavourable steric interaction between the bulky R group of the enecarbamate and the ester group of ethyl glyoxylate and/or the bulky copper catalyst. The TS-1 model would account for the stereochemical outcome of the reaction.

2m

In summary, novel highly enantioselective copper–diimine-catalyzed addition reactions of enecarbamates with ethyl glyoxylate have been developed. It was demonstrated that high yields and high enantioselectivities were obtained, even when using 0.1 mol% of the catalyst. α-Monosubstituted enecarbamates also reacted with glyoxylate stereospecifically to give the corresponding adducts in high yields with excellent diastereo- and enantioselectivities. Further investigations into the precise mechanism of this reaction as well as the use of enecarbamates as nucleophiles in other reactions are in progress.

Received: March 31, 2004 [Z460165]
Published Online: May 17, 2004

Keywords: asymmetric catalysis · aza-ene reaction · copper · N ligands · synthetic methods

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