Enantioselective Synthesis

Copper(II)-Catalyzed Highly Enantioselective Addition of Enamides to Imines: The Use of Enamides as Nucleophiles in Asymmetric Catalysis**

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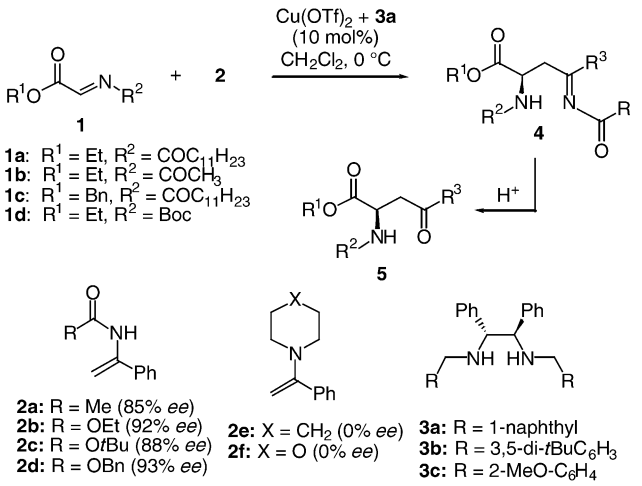
Enamides are potentially useful and atom-economical nucleophiles that contain amide or carbamate moieties after nucleophilic additions. While enamides can be easily prepared,[1] handled, and stored at room temperature, their use in organic synthesis is limited.[2] To the best of our knowledge, there have been no reports of using enamides as nucleophiles in asymmetric catalysis. We describe here the first example of the enantioselective addition of enamides to imines using a chiral copper catalyst.

Initially, we examined the reaction of enamide **2a** with imine **1a**[3,4] in the presence of a chiral copper catalyst (10 mol%) prepared from $Cu(OTf)_2$ and chiral diamine **3a** (Scheme 1).[4b,c] The addition reaction proceeded smoothly in dichloromethane at 0°C for 15 min to afford β-aminoimine **4aa**. The yield (83%) and enantioselectivity (85%) were determined after conversion of **4aa** to β-amino ketone **5aa** by treatment with acid (HBr in $EtOH/H_2O$).[5] Enamides **2b**, **2c**, and **2d** were also investigated in the reaction. The highest *ee* value (93%) was obtained with **2d**. Interestingly, enamines **2e** and **2f** reacted with **1a** under the same reaction conditions to afford **5aa** in high yields, but no asymmetric induction was observed.



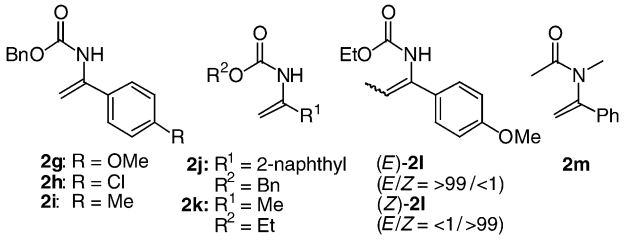
Scheme 1. The copper-catalyzed enantiomeric addition of an enamide **2** with an imine **1** to yield a β-aminoimine **4**, which on treatment with acid produces a β-amino ketone **5**. Boc = *tert*-butoxycarbonyl, Bn = benzyl, OTf = trifluoromethanesulfonate.

The results obtained employing other imines and enamides are summarized in Table 1. Several imines, including an *N*-carbamate-protected imine,[6] were treated with **2d** in the presence of the chiral copper catalyst (10 mol%) to afford the corresponding adducts in high yields with high enantiomeric excesses. It was also observed that the reaction proceeded efficiently when 5 mol% of the catalyst was employed. Enamides with aromatic substituents were as successful as substrates as those with alkyl substituents. The use of chiral diamine **3b** instead of **3a** was also effective. All the reactions proceeded smoothly at 0°C over 15 minutes, and high yields and high levels of enantioselectivity were attained with a wide range of substrates. We also conducted the reaction of (*E*)- and (*Z*)-2-methyl-substituted enamides (*E*)-**2l** and (*Z*)-**2l**[7] with imine **1a** in the presence of the chiral copper catalyst (10 mol%) in dichloromethane at 0°C for 30 min (Scheme 2). Enamide (*E*)-**2l** was treated with **1a** to give the adduct in a high yield with good *syn* selectivity (syn adduct: 94% *ee*). However, the reaction of (*Z*)-**2l** with **1a** also gave the *syn* adduct as the major product, but the yield and diastereo- and enantioselectivities were lower. It is noted that *syn*-

Table 1: Enantioselective addition of enamides to imines.

Entry	Imine	Enamide	Yield [%][a]	*ee* [%][b]
1	**1a**	**2d**	94 (91)[c]	93 (93)[c]
2[d]	**1a**	**2d**	92	93
3	**1b**	**2d**	72	94
4	**1c**	**2d**	89	91
5[e]	**1d**	**2d**	78	87
6	**1a**	**2g**	97	90
7	**1b**	**2g**	76	92
8	**1a**	**2h**	89	90
9	**1a**	**2i**	93	91
10	**1a**	**2j**	83	88
11	**1b**	**2j**	76	91
12	**1c**	**2k**	84	83
13[d]	**1c**	**2k**	81	84

[a] Yield of isolated product. [b] Determination by high-performance liquid chromatographic analysis. Details are given in the Supporting Information. [c] $Cu(OTf)_2$ (10 mol%) and **3a** (10 mol%). [d] Diamine **3b** was employed instead of **3a**. [e] Diamine **3c** was employed instead of **3a**.



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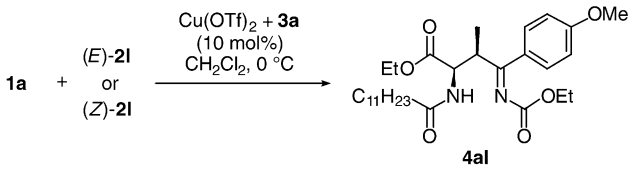
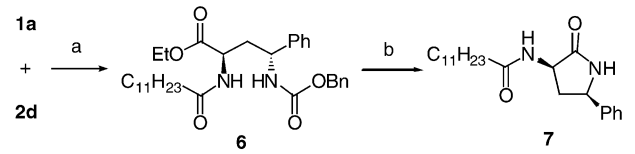


(*E*)-**2l**: 77%, *syn*/*anti* = 86/14, 94% *ee* (*syn*)
(*Z*)-**2l**: 63%, *syn*/*anti* = 68/32, 32% *ee* (*syn*)

Scheme 2. The reaction of (*E*)- and (*Z*)-2-methyl-substituted enamides (*E*)-**2l** and (*Z*)-**2l** with imine **1a** in the presence of a chiral copper catalyst.

adducts were obtained preferentially in both reactions in which the (*E*)- and (*Z*)-enamides were used.

A characteristic of addition reactions of enamides with imines is the formation of a β-aminoimine **4** as an end product. Although β-aminoimines are readily converted into β-amino ketones **5** after treatment with acid, the treatment of **1a** with **2d**, $LiAlH(OtBu)_3$, and LiI[8] in the same pot afforded a 1,3-diamine product **6** in an 87% yield with good diastereoselectivity (Scheme 2, *syn*:*anti* = 14:86; no epimerization was observed during the transformation). Diamine **6** was further transformed into lactam **7** in high yield (Scheme 3). Thus, these enantioselective reactions provide new routes to optically active 1,3-diamine derivatives, which are versatile chiral building blocks for the synthesis of natural products, drugs, ligands, etc.[9]



Scheme 3. a) 1. $Cu(OTf)_2$ (10 mol%), **3a** (11 mol%), CH_2Cl_2, 0°C, 2. $LiAlH(OtBu)_3$/LiI, Et_2O, −45°C (87% yield, *syn*:*anti* = 14:86). b) Pd/C (10 mol%), H_2, AcOEt, AcOH (71% yield).

A plausible mechanism of this reaction may include an aza-ene-type pathway via an acyclic transition state.[10] Preliminary kinetic studies using FT-IR spectroscopic analysis suggest direct formation of β-aminoimine **4** from imine **1**.[11] In addition, *N*-methyl-substituted enamide **2m** did not react with **1a** under the standard reaction conditions. The stereoselectivities observed for the reactions of (*E*)-**2l** and (*Z*)-**2l** with **1a** support the proposed acyclic transition states being formed during the reaction pathway. The catalyst was prepared by treating $Cu(OTf)_2$ with chiral diamine **3a** in CH_2Cl_2 to give a green color, and then adding water to form the dimeric copper species **8** (blue color). The X-ray structure of **8** is shown in Figure 1.[12,13] The coordination mode of **8** and that of the $Cu(ClO_4)_2$·diamine complex[4c] may help rationalize the reaction stereoselectivity. In addition, while **8** was found to be a less-effective catalyst for the addition of enamide **2d** to imine **1a**,[14] a blue-colored solution of **8** in CH_2Cl_2 turned green when **8** was treated with two equivalents of trifluoromethanesulfonic acid. Compounds **1a** and **2d** were

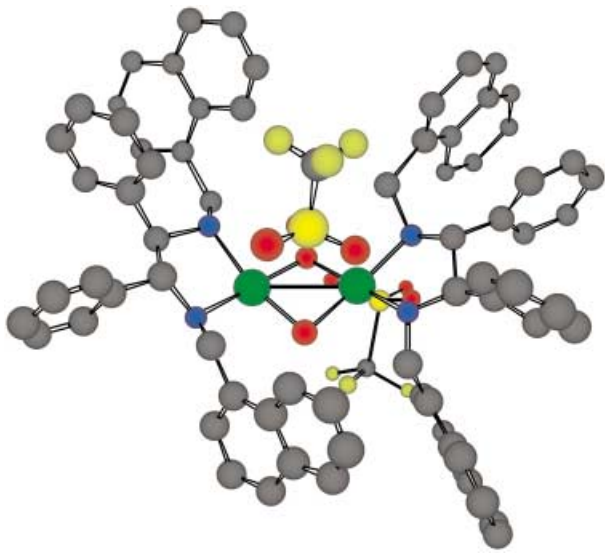


Figure 1. X-ray structure of **8**.

added to this green solution and the mixture stirred at 0°C for 15 min to afford the adduct **5aa** in a yield of 90% and 82% *ee*.

In summary, we have developed highly enantioselective reactions of enamides with imines using a chiral copper catalyst. This is the first example of the use of enamides as nucleophiles in asymmetric catalysis. The use of enamides has advantages over that of other nucleophilic enolate equivalents, such as silicon and tin enolates, enamines, etc., from an atom-economical point of view. From a synthetic standpoint, functional groups bearing nitrogen atoms have been successfully introduced by using enamides as nucleophiles, and efficient ways to optically active amino acid and 1,3-diamine derivatives have been developed. Further investigations into applying this reaction to preparing biologically interesting compounds, studying the reaction mechanism, and elucidating the structure of the chiral copper catalyst are in progress.

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[1] For example, a) Y. H. Suen, A. Horeau, H. B. Kagan, *Bull. Soc. Chim. Fr.* **1965**, *5*, 1454; b) S. Machida, I. Tanaka, *Kyoto Kogei Sen'i Daigaku Sen'igakubu Gakujutsu Ho* **1975**, *7*, 423; c) M. J. Burk, G. Casy, N. B. Johnson, *J. Org. Chem.* **1998**, *63*, 6084.

[2] a) L. Eberson, M. Malmberg, K. Nyberg, *Acta. Chem. Scand.* **1984**, *38*, 391; b) O. Meth-Cohn, K. T. Westwood, *J. Chem. Soc. Perkin Trans. 1* **1984**, 1173; c) T. Shono, Y. Matsumura, K. Tsubata, Y. Suihara, S. Yamane, T. Kanazawa, T. Aoki, *J. Am. Chem. Soc.* **1982**, *104*, 6697.

[3] a) R. Kober, K. Papadopoulos, E. Miltz, D. Enders, W. Steglich, H. Reuter, H. Puff, *Tetrahedron* **1985**, *41*, 1693. b) P. Münster, W. Steglich, *Synthesis* **1987**, 223.

[4] a) S. Kobayashi, H. Kitagawa, R. Matsubara, *J. Comb. Chem.* **2001**, *3*, 401; b) S. Kobayashi, R. Matsubara, H. Kitagawa, *Org.*

Lett. **2002**, *4*, 143; c) S. Kobayashi, R. Matsubara, Y. Nakamura, H. Kitagawa, M. Sugiura, *J. Am. Chem. Soc.* **2003**, *125*, 2507.
[5] The absolute configuration was determined to be the *R* enantiomer by comparison with the authentic sample.[4c]
[6] Y. Nakamura, R. Matsubara, H. Kiyohara, S. Kobayashi, *Org. Lett.* **2003**, *5*, 2481.
[7] The *E*- and *Z*-enamide isomers were separated and isolated by column chromatography.
[8] Y. Mori, M. Suzuki, *Tetrahedron Lett.* **1989**, *30*, 4383.
[9] For example, a) F. Cohen, L. E. Overman, *J. Am. Chem. Soc.* **2001**, *123*, 10782; b) C. F. Bigge, J.-P. Wu, J. T. Drummond, *Bioorg. Med. Chem. Lett.* **1992**, *2*, 207; c) F. R. Pfeiffer, T. W. Ku, D. C. Peterson, *J. Antibiot.* **1981**, *34*, 5; d) M. M. Kabat, *Tetrahedron Lett.* **2001**, *42*, 7521; e) A. R. Donovan, G. H. P. Roos, *Synth. Commun.* **1999**, *29*, 3685.
[10] An aza-ene-type reaction of enamines by a concerted pathway has been proposed: a) M. Nour, K. Tan, C. Cavé, D. Villeneuve, D. Desmaële, J. d'Angelo, C. Riche, *Tetrahedron: Asymmetry* **2000**, *11*, 995; however, copper-catalyzed asymmetric ene-type reactions of α-imino esters with alkenes have been reported. b) W. J. Drury III, D. Ferraris, C. Cox, B. Young, T. Lectka, *J. Am. Chem. Soc.* **1998**, *120*, 11006; c) S. Yao, X. Fang, K. A. Jørgensen, *Chem. Commun.* **1998**, 2547.
[11] Experimental details are given in the Supporting Information.
[12] **8:** [{Cu(OH)(OTf)(**3a**)}$_2$]. Elemental analysis (%) calcd for $C_{74}H_{66}Cu_2F_6N_4O_8S_2$: C 61.53, H 4.61, N 3.88; found: C 61.37, H 4.70, N 3.80. Further details are given in the Supporting Information. CCDC-224229 (**8**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from www.ccdc.cam.ac.uk/conts/retrieving.html, from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk.
[13] Several di-μ-hydrodicopper(II) complexes are already known. The aerobic oxidation of a catechol derivative to the corresponding quinone (achiral synthesis) using the dicopper catalyst was reported: M. Kodera, T. Kawata, K. Kano, Y. Tachi, S. Itoh, S. Kojo. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 1957.
[14] Enamide **2d** was treated with **1a** in dichloromethane at 0 °C for 15 min in the presence of **8** (10 mol %) to afford **5aa** in a yield of 78% and 8% *ee*.

