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Catalytic Asymmetric Direct α-Amination Reactions of 2-Keto Esters: A Simple Synthetic Approach to Optically Active *syn*-β-Amino-α-hydroxy Esters

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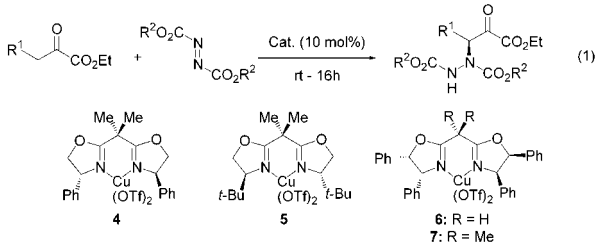
The direct catalytic enantioselective reaction of an electrophilic nitrogen source constitutes a fundamental challenge in chemistry. One of these reactions is the electrophilic amination of enols and enolates, which has received considerable interest in recent years.[1] Optically active α-amino acids have been obtained through this reaction by amination of chiral ketene acetals with dialkyl azo dicarboxylates.[2] Asymmetric catalytic amination reactions of silyl enol ethers have also been developed,[3] and to our knowledge only one example of a direct asymmetric catalytic α-amination reaction is known—that is, a reaction without prior silyl enol ether or silyl ketene acetal formation.[4]

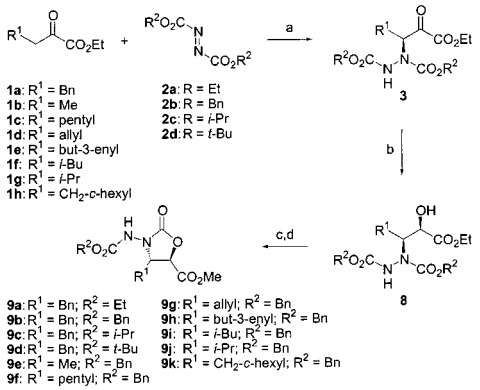
In this Communication we present the first direct asymmetric catalytic α-amination reaction of 2-keto esters with commercially available azo dicarboxylates (eq 1). This new catalytic enantioselective reaction provides an easy entry to optically active *syn*-β-amino-α-hydroxy esters, known as the chiral fragments of many important molecules.



Recently, we reported a catalytic asymmetric direct homoaldol reaction of pyruvate[5] and a catalytic asymmetric direct Mannich reaction of 2-keto esters with α-imino esters.[6] In these reactions we have proposed[7] a new property of chiral bisoxazoline−copper(II) complexes:[6,8] first to promote the keto to enol tautomerization, and then to catalyze the enantioselective C−C bond formation. The crucial step in these reactions is the formation of the nucleophilic enol form and we anticipated that this methodology could be extended to azo dicarboxylates.

The reaction of ethyl 2-keto-4-phenylbutyrate **1a** with various azo dicarboxylates was chosen as a test reaction for the chiral Lewis acid-catalyzed direct α-amination reaction. In the presence of the copper catalyst (*R*)-**4**, the 2-keto ester **1a** reacted smoothly with diethyl azodicarboxylate **2a** (DEAD) in CH_2Cl_2 at room temperature to give product **3a**. The measured ee values were low to moderate and decreased to racemic after normal flash chromatography purification. Clearly the acidity of the α-proton next to the ketone moiety[9] did not allow purification of **3a** at this stage without loss of enantioselectivity. This problem could be circumvented by a stereoselective reduction (>90% de) of the keto functionality by L-Selectride[3,10] prior to removal of the copper catalyst (Scheme 1). By quenching the reaction with aqueous NaOH, alcohol **8** was cyclized and the ester moiety was hydrolyzed. Reesterification with trimethylsilyl diazomethane gave the *N*-amino oxazolidinone **9a**.

Scheme 1 [a]



[a] Key: (a) chiral copper complex **4**−**7**; (b) L-Selectride, −78 °C to room temperature; (c) 0.5 N NaOH, 2 h; (d) $TMSCHN_2$ in MeOH/toluene.

Some representative results using this procedure from the screening of the different chiral Lewis acids **4**−**7** for the reaction of **1a** with the azo dicarboxylates **2a**−**d** are presented in Table 1.

The first four entries in Table 1 show the reaction of **1a** with the different azo dicarboxylates **2a**−**d** in the presence of (*S*)-**4** as the catalyst in CH_2Cl_2. Only DEAD **2a** and dibenzyl azodicarboxylate **2b** reacted with **1a** under these reaction conditions, and for **2a** and **2b**, 55% yield and 68% ee, and 39% yield and 90% ee of **9a** and **9b**, respectively, were obtained. Changing the solvent to THF improved the yield of the α-aminated product and the use of **2b** resulted in 60% yield of **9b** with 82% ee (entry 6). Several other chiral bisoxazoline−copper(II) complexes have also been tested for the reaction of **1a** with **2b** and under these conditions catalyst (4*R*,5*S*)-**6** gave the highest enantioselectivity as 89% ee of **9b** was obtained (entry 8).

The enantioselective direct α-amination turned out to be a general reaction for 2-keto esters using especially dibenzyl azodicarboxylate as the nitrogen source and chiral bisoxazoline−copper(II) complexes **4**, **6**, and **7** as the catalyst. Table 2 shows the results for the direct α-amination of different 2-keto esters **1a**−**h**.

Ethyl 2-keto-4-phenylbutyrate **1a** reacted with dibenzyl azodicarboxylate **2b** in both THF and CH_2Cl_2 as the solvents using the chiral bisoxazoline−copper(II) complexes **4**, **6**, and **7** as the catalysts to give *after four reaction steps* the α-aminated product **9b** in good yield and up to 90% ee (Table 2, entries 1−3). Reaction of ethyl 2-keto butyrate **1b** with **2b** led to a smooth reaction applying **4**, **6**, and **7** as the catalysts and **9e** was formed with up to 92% ee and isolated in moderate yields (entries 4−6). Prolongation of the alkyl chain of the 2-keto ester to pentyl (compound **1c**) also gave a smooth reaction and the α-aminated product **9f** could be isolated in up to 78% yield and 97% ee with use of the different chiral catalysts (entry 7−9). The last five entries (entry 10−14) demonstrate the potential of the direct α-amination reaction: the 2-keto

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Table 1. Enantioselective α-Aminiation Reaction of 2-Keto Ester **1a** with Azo Dicarboxylates **2a**−**d** Catalyzed by Copper Complexes **4**−**7**

entry	azo dicarboxylate	cat.	solvent	product	yield[a] (%)	ee[b] (%)
1	**2a** (R^2 = Et)	**4**	CH_2Cl_2	**9a**	55	68
2	**2b** (R^2 = Bn)	**4**	CH_2Cl_2	**9b**	39	90
3	**2c** (R^2 = *i*-Pr)	**4**	CH_2Cl_2	**9c**	n.d.[c]	n.d.[c]
4	**2d** (R^2 = *t*-Bu)	**4**	CH_2Cl_2	**9d**	n.d.[c]	n.d.[c]
5	**2a** (R^2 = Et)	**4**	THF	**9a**	47	35
6	**2b** (R^2 = Bn)	**4**	THF	**9b**	60	82
7	**2b** (R^2 = Bn)	**5**	THF	**9b**	31	7
8	**2b** (R^2 = Bn)	**6**	THF	**9b**	57	89
9	**2b** (R^2 = Bn)	**7**	THF	**9b**	58	88

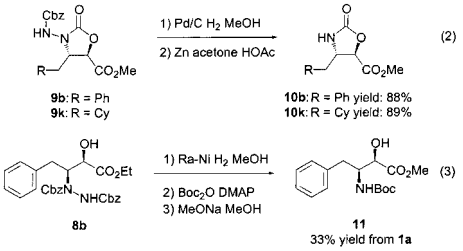
[a] Isolated yield after 4 reaction steps (see Scheme 1). [b] Ee determined by chiral HPLC. [c] Not determined

Table 2. Direct Enantioselective α-Aminiation Reaction of 2-Keto Esters **1a**−**h** with Dibenzyl Azodicarboxylate **2b** Catalyzed by Chiral Copper Complexes **4**, **6**, and **7** in THF and CH_2Cl_2

entry	2-keto ester R^1	cat.	product	THF[a] yield/ee	CH_2Cl_2[a] yield/ee
1	benzyl (**1a**)	**4**	**9b**	60/82	39/90
2	benzyl (**1a**)	**6**	**9b**	57/89	55/77
3	benzyl (**1a**)	**7**	**9b**	58/88	50/70
4	methyl (**1b**)	**4**	**9e**	44/86	33/78
5	methyl (**1b**)	**6**	**9e**	29/90	45/90
6	methyl (**1b**)	**7**	**9e**	44/92	36/78
7	pentyl (**1c**)	**4**	**9f**	78/92	40/93
8	pentyl (**1c**)	**6**	**9f**	48/97	63/93
9	pentyl (**1c**)	**7**	**9f**	50/95	52/85
10	allyl (**1d**)	**6**	**9g**	38/90	62/93
11	but-3-enyl (**1e**)	**6**	**9h**	36/94	52/92
12	isobutyl (**1f**)	**6**	**9i**	51/95	53/96
13	isopropyl (**1g**)	**6**	**9j**	60/95[b]	78/95[b]
14	*c*-hexylmethyl (**1h**)	**6**	**9k**	72/96	54/96

[a] Yield and ee in %; ee determined by chiral HPLC. [b] Ee determined by chiral-GC after removal of the Cbz group.

Scheme 2



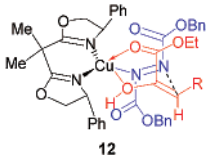
esters substituted with allyl (**1d**), but-3-enyl (**1e**), isobutyl (**1f**), isopropyl (**1g**), and cyclohexyl methyl (**1h**) all reacted with **2b** in the presence of **6** as the catalyst to give the corresponding α-aminated products **9g**−**k** in moderate to high yields and excellent enantioselectivities.

An important application of this direct α-amination reaction is the formation of *syn*-*β*-amino-α-hydroxy esters. Treatment of the *N*-amino oxazolidinones **9b**,**k** with first H_2−Pd/C, followed by treatment with Zn−acetone in acetic acid shows the scope of this direct α-amination reaction as the *syn*-*β*-amino-α-hydroxy esters masked as oxazolidinones **10b**,**k** are formed in 88% and 89% yield, respectively, and without detectable decrease in enantiomeric excess (Scheme 2, eq 2).

The *N*-Boc protected *syn*-*β*-amino-α-hydroxy ester **11** can be formed directly from **8**: Both the Cbz groups and the nitrogen−nitrogen bond are easily cleaved and reduced, respectively, by H_2-Raney-Ni and subsequent protection of the amino group by Boc_2O-DMAP gives **11** in good yield (Scheme 2, eq 3). It should be noted that the enantiomeric excess of **8b** is maintained during the reaction sequence.

The easy accessibility of both masked *syn*-*β*-amino-α-hydroxy esters **10** and the *N*-Boc protected *syn*-*β*-amino-α-hydroxy ester **11**, formed by the present catalytic enantioselective direct α-amination methodology, shows the applicability of this new reaction. These *syn*-*β*-amino-α-hydroxy ester fragments are present in many different important compounds of pharmaceutical interest such as Bestatin and Valinoctin A,[11] and the side chain of Taxol analogues.[12]

The formation of **10b**,**k** and **11** leads to an assignment of the chiral carbon atom formed in the catalytic enantioselective reaction as the (*S*)-enantiomer.[13] The absolute configuration leads us to propose transition state **12** to account for the enantioselectivity of



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the reactions. The first step in the reaction is the generation of the enol (red in **12**) from the 2-keto ester. This reaction is suggested to be copper-catalyzed and leads to the enol, which is coordinated to the metal either in a mono- or bidentate fashion. It is proposed that the azo dicarboxylate also coordinates to the chiral catalyst (blue in **12**) and that a six-membered chairlike transition state is formed, with the R-substituent of the enol-form of the 2-keto ester in the less crowded pseudoequatorial position.

In conclusion we have developed a catalytic highly enantioselective direct α-amination of 2-keto esters catalyzed by chiral bisoxazoline−copper(II) complexes. The reaction gives an easy entry to optically active masked *syn*-*β*-amino-α-hydroxy esters. Further work utilizing this new concept is in progress.

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Supporting Information Available: Complete experimental procedure and characterization (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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