Asymmetric Amination

Catalytic, Highly Enantioselective, Direct Amination of β-Ketoesters**

*Mauro Marigo, Karsten Juhl, and Karl Anker Jørgensen**

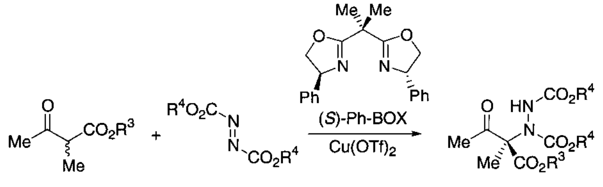
Optically active α-amino acid derivatives are fundamental constituents of numerous natural products and of other highly valuable compounds of importance for our daily life. Many different approaches for the synthesis of optically active α-amino acids are available.[1] However, the development of stereoselective transformations for the synthesis of optically active non-natural α-amino acid derivatives from simple and readily available starting compounds in the presence of a chiral catalyst is an ongoing challenge for chemists. The importance of these molecules has led to extensive development of synthetic methods that use catalytic enantioselective reactions. The majority of the procedures developed for the formation of optically active α-amino acid derivatives are C–C-bond-forming reactions and include catalytic enantioselective addition to imines using Strecker[2] and Mannich[3] reactions.

The synthesis of optically active α-amino acid derivatives by a catalytic, enantioselective, direct C–N-bond-forming reaction is probably among the simplest procedures for the formation of an asymmetric carbon center attached to a nitrogen atom.[4] Recently, we presented the first direct enantioselective α-amination of 2-ketoesters catalyzed by chiral copper(II)–bisoxazoline complexes,[5,6] and later both List and we developed the first direct organocatalytic α-amination of aldehydes[7,8] and ketones.[9] These developments led to simple procedures for the synthesis of optically active *syn*-β-amino-α-hydroxy esters, α-amino acid derivatives, α-amino aldehydes and ketones, and α-amino alcohols.

Herein we present the first direct α-amination of α-substituted β-ketoesters[10] **1** catalyzed by a chiral copper(II)–bisoxazoline (BOX)[11] complex with azodicarboxylates **2** as the nitrogen fragment source. This new reaction gives access to β-hydroxy-α-amino acids such as oxazolidinone derivatives. Some representative screening results for the catalytic enantioselective α-amination of the β-ketoester **1a** with the azodicarboxylates **2a** and **2b** in the presence of [(*S*)-Ph-BOX–Cu(OTf)$_2$] as the catalyst (10 mol%) are presented in Table 1.

The ethyl β-ketoester **1a** reacted with dibenzyl azodicarboxylate (**2a**) under the catalysis of [(*S*)-Ph-BOX–Cu(OTf)$_2$] (10 mol%) to give the α-aminated product **3a** in high yield with excellent enantioselectivity (97–98% *ee*) in a variety of solvents (Table 1, entries 1–3). The catalyst loading is remarkable for this direct α-amination reaction, which proceeds in excellent yield and enantioselectivity in the presence of just 0.2 mol% of catalyst (Table 1, entry 5). When diethyl azodi-

Table 1: Enantioselective direct α-amination of **1a** with **2a** and **2b**, catalyzed by [(*S*)-Ph-BOX–Cu(OTf)$_2$].[a]



1a: R^3 = Et
2a: R^4 = Bn
2b: R^4 = Et
3a: R^3 = Et, R^4 = Bn
3ab: R^3 = Et, R^4 = Et

Entry	R^3	R^4	Catalyst loading [%]	Solvent	Product	Yield[b] [%]	*ee*[c] [%]
1	Et (**1a**)	Bn (**2a**)	10	CH_2Cl_2	**3a**	98	98
2	Et (**1a**)	Bn (**2a**)	10	Et_2O	**3a**	90	97
3	Et (**1a**)	Bn (**2a**)	10	THF	**3a**	82	97
4	Et (**1a**)	Bn (**2a**)	1	CH_2Cl_2	**3a**	92	98
5	Et (**1a**)	Bn (**2a**)	0.2	CH_2Cl_2	**3a**	91	96
6	Et (**1a**)	Bn (**2a**)	0.05	CH_2Cl_2	**3a**	65	55
7	Et (**1a**)	Et (**2b**)	10	CH_2Cl_2	**3ab**	87	>95

[a] Experimental conditions: Cu(OTf)$_2$ (9 mg, 25 μmol) and (*S*)-(−)-2,2′-isopropylidene-bis(4-phenyl-2-oxazoline) (9.2 mg, 26 μmol) were stirred under vacuum in an oven-dried Schlenk tube for 2 h. The tube was then filled with N$_2$, dry CH$_2$Cl$_2$ (2 mL) was added, and the resulting solution was stirred for 1 h. The β-ketoester **1a** (0.25 mmol) was then added, followed by dibenzyl azodicarboxylate (**2a**) (90 mg, 0.30 mmol), and the product **3a** was isolated by flash chromatography after 16 h (see Supporting Information). [b] Yield of isolated product. [c] Chiral HPLC with AD or AS Daicel Chiralpack columns was used to determine the *ee* value.

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[*] Dr. K. A. Jørgensen, M. Marigo, Dr. K. Juhl
The Danish National Research Foundation: Center for Catalysis
Department of Chemistry, Aarhus University
DK-8000 Aarhus C (Denmark)
Fax: (+45) 8919-6199
E-mail: kaj@chem.au.dk

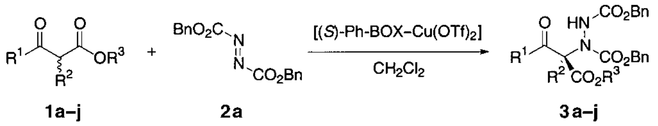
[**] This work was made possible by a grant from The Danish National Research Foundation and the EU: HMPT-CT-2001-00317. We are grateful to Dr. R. G. Hazell for X-ray crystallographic analysis.

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

carboxylate (**2b**) was used, the α-aminated adduct **3ab** was also produced in high yield and with >95% *ee* (Table 1, entry 7). The use of other β-ketoesters is also possible. The phenyl ester ($R^3 = Ph$) reacted highly enantioselectively with **2b**, and the corresponding α-aminated adduct was isolated in 91% yield and with 96% *ee*. Catalysts containing other chiral bisoxazoline ligands gave rise to lower yields and enantiomeric excesses of the α-aminated adducts than did the [(*S*)-Ph-BOX–Cu(OTf)$_2$] catalyst.

The excellent catalytic enantioselective direct α-amination properties of [(*S*)-Ph-BOX–Cu(OTf)$_2$] were demonstrated for a series of acyclic and cyclic β-ketoesters. The β-ketoesters **1a–j** were all treated with dibenzyl azodicarboxylate (**2a**) under the catalysis of [(*S*)-Ph-BOX–Cu(OTf)$_2$] (10 mol% and 0.5 mol%) in CH_2Cl_2 at room temperature to show the scope of the reaction (Table 2).

Table 2: Catalytic enantioselective direct α-amination of **1a–j** with **2a**, catalyzed by [(*S*)-Ph-BOX–Cu(OTf)$_2$].[a]



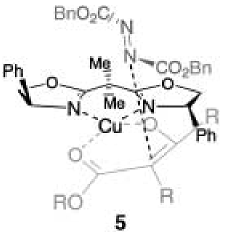
Entry	β-Ketoester R^1	R^2	R^3	Product	Catalyst loading 10 mol% Yield[b] [%]	10 mol% *ee*[c] [%]	0.5 mol% Yield[b] [%]	0.5 mol% *ee*[c] [%]
1	Me	Me	Et (**1a**)	**3a**	98	98	91	96[d]
2	Et	Me	Et (**1b**)	**3b**	94	98	98	98
3	Ph	Me	Et (**1c**)	**3c**	85	95	81	87
4	*i*Pr	Me	*t*Bu (**1d**)	**3d**	96	98	89	98
5	Bn	Me	*t*Bu (**1e**)	**3e**	84	98	79	98
6	Me	allyl	*t*Bu (**1f**)	**3f**	–	–	80	98
7	Me	Me	*t*Bu (**1g**)	**3g**	86	98	–	–
8	(CH$_2$)$_3$		Et (**1h**)	**3h**	98	99	96	99
9	(CH$_2$)$_4$		Et (**1i**)	**3i**	98	99	96	99
10	(CH$_2$)$_5$		Et (**1j**)	**3j**	76	98	70	99

[a] Experimental conditions (0.5 mol% of catalyst): A mixture of Cu(OTf)$_2$ (9 mg, 25 μmol) and (*S*)-(−)-2,2′-isopropylidene-bis(4-phenyl-2-oxazoline) (9.2 mg, 26 μmol) was stirred under vacuum in an oven-dried Schlenk tube for 2 h. The tube was then filled with N_2, dry CH_2Cl_2 (10 mL) was added, and the solution was stirred for a further 1 h. An aliquot of the solution (1 mL) was transferred to another oven-dried Schlenk tube and dry CH_2Cl_2 (1 mL) was added. The β-ketoester **1b** (0.50 mmol) was then added, followed by dibenzyl azodicarboxylate (**2a**) (180 mg, 0.60 mmol). After 16 h the product **3b** was isolated by flash chromatography (see Supporting Information). [b] Yield of isolated product. [c] Chiral HPLC with AD or AS Daicel Chiralpack or OD-Daicel Chiralgel columns was used to determine the *ee* value. [d] Reaction performed with 0.2 mol% catalyst loading.

This catalytic enantioselective direct α-amination of the α-substituted β-ketoesters is remarkable in that there is virtually no change in yield or enantioselectivity when the loading of the [(*S*)-Ph-BOX–Cu(OTf)$_2$] catalyst is decreased from 10 to 0.5 mol%. Acyclic β-ketoesters with alkyl, branched alkyl, benzyl, or phenyl substituents as R^1 (**1a–e**, and **1g**) all reacted with dibenzyl azodicarboxylate (**2a**) to give the corresponding α-aminated adducts **3a–e**, and **3g** in high yields with excellent enantioselectivity (Table 2, entries 1–5,7). The enantiomeric excesses observed were generally >95% *ee*, with the exception of **1c** in the presence of 0.5 mol% of the catalyst, in which case 87% *ee* was found. However, an improvement to 95% *ee* occurred when 10 mol% of the catalyst was used. The α-allyl-β-ketoester **1f** reacted with **2a** in the presence of 0.5 mol% of the catalyst and the α-aminated adduct **3f** was formed in 80% yield and 98% *ee* (Table 2, entry 6). The cyclic β-ketoesters **1h–j** underwent a particularly highly enantioselective α-amination reaction. For all three ring sizes (five-, six-, and seven-membered) 99% *ee* was observed when only 0.5 mol% of the catalyst was used (Table 2, entries 7–9). Furthermore, the α-aminated adducts were isolated in excellent yields. The catalytic enantioselective α-amination reaction of α-substituted β-ketoesters with dibenzyl azodicarboxylate as the nitrogen fragment source and catalyzed by [(*S*)-Ph-BOX–Cu(OTf)$_2$] seems to be a general reaction and gives the desired products in high yield with excellent enantioselectivity.

The absolute configuration of the α-aminated adducts was solved by X-ray crystal-structure analysis of a derivative of **3a** and showed that the stereogenic carbon center formed in the reaction is of *R* stereochemistry.[12] On the basis of the absolute configuration of the products and the results we have obtained in our investigations to date, we propose a reaction mechanism that involves the approach of dibenzyl azodicarboxylate to the catalyst-coordinated β-ketoester, as outlined in **5**.[13]

A variety of possible product modifications can be envisaged, for example, as shown in the reaction sequence in Scheme 1: Reduction of the β-keto functionality in **3a** proceeded in a highly diastereoselective manner and the *N*-amino oxazolidinone **6** was formed with a d.r. of 24:1. Cleavage of the N–N bond gave the oxazolidinone derivative **7** in an overall yield of 25% (unoptimized conditions). Thus, this direct α-amination reaction can be used as a new synthetic procedure for the formation of optically active β-hydroxy-α-amino acid derivatives.



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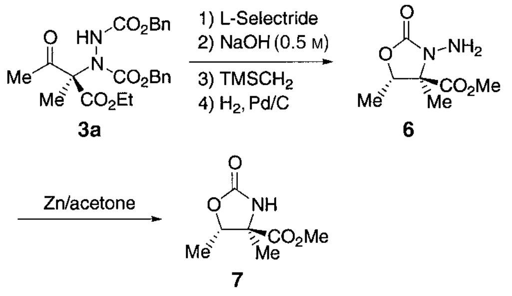
In conclusion, the first direct α-amination of α-substituted β-ketoesters with dibenzyl azodicarboxylate as the nitrogen fragment source has been developed. The reactions are catalyzed by [Ph-BOX–Cu(OTf)$_2$] and proceed with only 0.2–0.5 mol% of the catalyst to give the desired products in high yields and excellent enantiomeric excesses. Both acyclic and cyclic β-ketoesters undergo this highly selective α-amination reaction and the products obtained can be converted, for



Scheme 1. Reduction of the β-keto functionality in **3a** and conversion into the optically active β-hydroxy-α-amino acid derivative **7**. TMS = trimethylsilyl.

example, into optically active functionalized oxazolidinone derivatives by standard chemistry.

Received: November 28, 2002 [Z50655]

Keywords: β-ketoesters · amination · asymmetric catalysis · copper · synthetic methods

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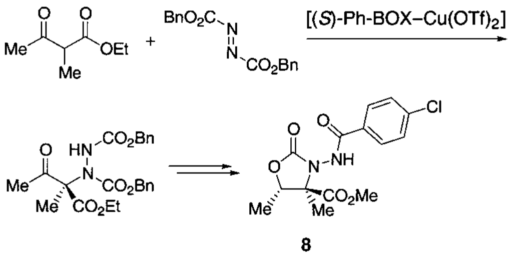

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