Tetrahedron Letters 51 (2010) 1860–1862

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Copper–bipyridine-catalyzed enantioselective α-amination of β-keto esters

Subrata Ghosh, Mecheril Valsan Nandakumar, Harald Krautscheid, Christoph Schneider *

Institut für Organische Chemie, Universität Leipzig, Johannisallee 29, 04103 Leipzig, Germany
Institut für Anorganische Chemie, Universität Leipzig, Johannisallee 29, 04103 Leipzig, Germany

ARTICLE INFO

Article history:
Received 21 December 2009
Revised 28 January 2010
Accepted 1 February 2010
Available online 6 February 2010

Keywords:
Asymmetric catalysis
Amination
β-Ketoester
Copper(II)-catalyzed
Bipyridine
Diethyl azodicarboxylate

ABSTRACT

The $Cu(OTf)_2$-bipyridine-catalyzed, enantioselective, direct α-amination of β-keto esters and β-diketones with diethyl azodicarboxylate (DEAD) has been studied. Exceptionally high enantioselectivities of up to 99% ee were found for 1-indanone-based β-keto esters in particular even for substrates and reagents carrying conventional ester groups such as methyl and ethyl.

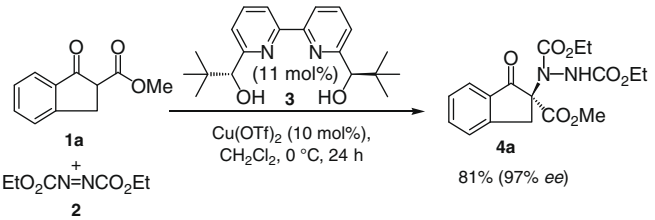
The direct α-amination of β-keto esters provides an excellent route for the synthesis of non-natural α,α-disubstituted α-amino acid derivatives through the construction of stereogenic carbon center attached to the nitrogen atom.[1] Optically active amino acids are broadly utilized with application in pharmaceuticals, agrochemicals, and after all they are the fundamental building blocks for various natural products and biologically active molecules.[2] Therefore, catalytic enantioselective α-amination of β-keto esters with azodicarboxylates has gained huge attention for the preparation of optically active non-natural amino acid derivatives. Some of the catalytic enantioselective systems that have been employed for this purpose with varying degrees of success include Cu(II)-Ph-box,[3] cinchonidine and cinchonine,[4] β-isocupreidine,[5] Cu(II)-Ph-trisox,[6] chiral urea,[7] chiral guanidine,[8] Pd-complexes,[9] Eu(III)-*ip*-pybox,[10] La–amide complex[11] quaternary phosphonium salts,[12] amine–thiourea bifunctional organocatalysts,[13] quaternary ammonium bromide,[14] and Ni(II)-complexes.[15]

One of the major limitations associated with most of these catalytic systems is the requirement to use bulky and less convenient β-keto esters and/or bulky azodicarboxylates such as the corresponding di*iso*propyl and di*tert*-butyl derivatives in order to achieve high enantioselectivities. Therefore, there is still a need for the development of convenient enantioselective methods which use synthetically more easily accessible β-keto methyl esters and the commercially available and cheap reagent diethyl azodicarboxylate (DEAD).

Jørgensen and co-workers established the high catalytic efficiency of $Cu(OTf)_2$ in the α-amination of β-keto esters.[3a] With (*S*)-Ph-box as chiral ligand they were able to isolate the α-aminated product with high enantiomeric excess. More recently, additional enantioselective methods have been reported based on the use of a combination of $Cu(OTf)_2$ and various chiral ligands.[3b,c] Based upon our recent experience with chiral bipyridine **3**[16] in metal-catalyzed epoxide-opening reactions[17] we envisioned that a metal–bipyridine complex might be a good chiral catalyst for the highly enantioselective α-amination of β-keto esters.

In this Letter, we wish to report the enantioselective direct α-amination of cyclic β-keto esters **1** with diethyl azodicarboxylate (DEAD) **2** catalyzed by an in situ-generated chiral Cu(II)–bipyridine **3**-complex.[18]

Initially we studied various metal triflates in combination with bipyridine **3** as chiral catalysts for the α-amination of β-keto ester **1a** with DEAD (Scheme 1). While, for example, $Sc(OTf)_3$, $Y(OTf)_3$,



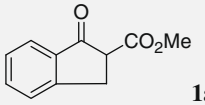
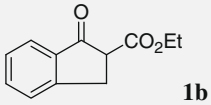
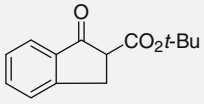
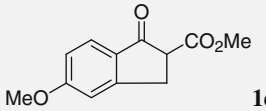
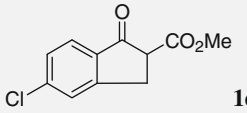
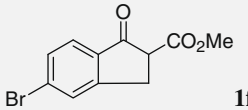
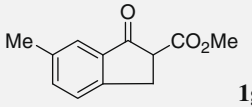
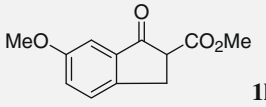
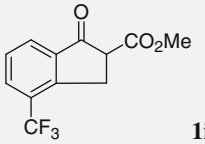
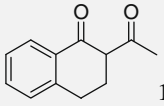
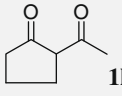
Scheme 1. Reaction between 1-indanone-based β-keto ester **1a** and diethyl azodicarboxylate (DEAD) **2** in the presence of $Cu(OTf)_2$ and chiral 2,2′-bipyridine **3**.

* Corresponding author. Tel./fax: +49 341 9736559.
E-mail address: schneider@chemie.uni-leipzig.de (C. Schneider).

0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.02.007

and $Yb(OTf)_3$ each were capable of catalyzing the model reaction with full conversion, the enantioselectivities remained poor to moderate and did not improve beyond 72% ee. On the other hand, the $Cu(OTf)_2$–bipyridine-catalyst (10 mol %) furnished α-aminated product **4a** in 84% yield and with 94% ee after stirring for 12 h at rt in CH_2Cl_2. Lowering the temperature to 0 °C further increased the enantioselectivity to 97% ee with almost identical chemical yield (Scheme 1).[19] Interestingly, when the temperature was further decreased to −55 °C, the selectivity dropped significantly to 85% ee.

Table 1
Enantioselective amination of β-keto esters and 1,3-dicarbonyl compounds **1a–l** catalyzed by $Cu(OTf)_2$-chiral bipyridine **3**[a]

Entry	Substrate	Product	Yield[b] (%)	Ee[c] (%)
1	 **1a**	**4a**	81	97
2	 **1b**	**4b**	82	97
3	 **1c**	**4c**	80	99
4	 **1d**	**4d**	86	>99
5	 **1e**	**4e**	78	93
6	 **1f**	**4f**	81	93
7	 **1g**	**4g**	79	98
8	 **1h**	**4h**	82	97
9	 **1i**	**4i**	74	79[d]
10	 **1j**	**4j**	66	45
11	 **1k**	**4k**	68	47

[a] Typical reaction conditions: 0.2 M in CH_2Cl_2 at 0 °C for 24 h.
[b] Isolated yield.
[c] The ee was determined by chiral HPLC analysis using a Daicel Chiracel OD-column and hexane–isopropanol mixtures as solvent.
[d] The reaction was carried out at room temperature.
[e] The assignment of absolute configuration is based upon the comparison of optical rotation with the literature values.[12]

Having identified optimal conditions we studied the scope of this reaction over a series of cyclic β-keto esters and β-diketones (Table 1). In general, 1-indanone-based β-keto esters gave excellent enantioselectivities for almost all substrates investigated (entries 1–9). Both electron-rich and electron-poor β-keto esters performed equally well and delivered the products with up to 99% ee. Substitution at both the 5- and 6-positions of the indanone backbone was possible without seriously affecting the enantioselectivitty of the reaction. Solely the 4-CF_3-substituted indanone gave rise to only 79% ee in this reaction (entry 9).

More importantly, the use of *tert*-butyl esters and/or di*iso*propyl or di*tert*-butyl azodicarboxylates proved to be not mandatory for a highly enantioselective amination reaction although the use of *tert*-butyl ester **1c** actually further enhanced the selectivity (entry 3, 99% ee). In general, we employed the more conventional and easily prepared β-keto methyl esters **1a** and **1d–i** as substrates which furnished the amination products with high enantioselectivity as well (entries 1 and 4–9).

Changing the substrate backbone to a 1-tetralone-based or a non-aromatic β-dicarbonyl compound significantly deteriorated the enantioselectivity of the reaction and furnished the products with only 45–47% ee (entries 10 and 11).

A single crystal of the chiral copper(II)–bipyridine-complex coordinated to β-keto ester **1d** suitable for X-ray diffraction analysis was obtained from dichloromethane–pentane solution (Fig. 1).[20] The structure of the complex displays a distorted square-pyramidal geometry around the Cu(II)-center. The two bipyridyl nitrogen atoms N1 and N2 as well as the ketone oxygen atom O1 and one of the hydroxyl oxygen atoms O5 are attached in the square plane and the ester oxygen atom O2 is located in the apical position of the complex. The β-keto ester is positioned almost orthogonal relative to the square plane of the complex (80°). Interestingly, the bipyridine ligand **3** binds to the copper atom only in a three-coordinate fashion leaving one of the hydroxyl groups free. The enantiofacial differentiation in the amination event is now most likely the result of hydrogen bonding of the more acidic hydroxyl proton attached to the copper-bound oxygen atom O5 to the basic azodicarboxylate which is thereby activated toward nucleophilic attack and directed to the open *si*-face of the enolate.

In conclusion, we have developed a chiral copper–bipyridine catalyst for the highly enantioselective α-amination of β-keto esters which gives rise to non-natural α,α-disubstituted α-amino acid derivatives. 1-Indanone-based β-keto esters proved to be excellent substrates for this process which were aminated with

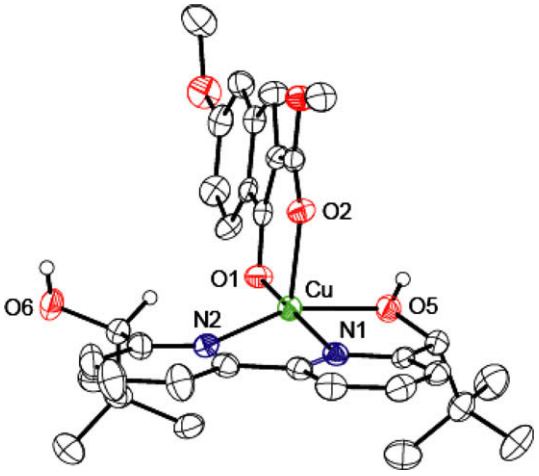


Figure 1. ORTEP (50% ellipsoid) of $Cu(OTf)_2$–bipyridine–**1d** complex. Hydrogen atoms as well as the non-coordinating triflate anions have been omitted for clarity.

up to 99% ee in good yields whereas other 1,3-dicarbonyl compounds gave rise to only moderate enantioselectivity. A crystal structure of the substrate-bound catalyst provides information related to the origin of enantiofacial discrimination.

Acknowledgments

We thank the Deutsche Forschungsgemeinschaft for generous financial support of this work and the Alexander von Humboldt foundation for a postdoctoral fellowship awarded to S.G.

References and notes

1. (a) Diels, O. *Justus Liebigs Ann. Chem.* **1922**, *429*, 1–55; (b) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539–1650; (c) Arend, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 2873–2874; (d) Kotha, S. *Acc. Chem. Res.* **2003**, *36*, 342–351; (e) Genet, J.-P.; Greck, C.; Lavergne, D. In *Modern Amination Methods*; Ricci, A., Ed.; Wiley-VCH: Weinheim, 2000; (f) Duthaler, R. O. *Angew. Chem., Int. Ed.* **2003**, *42*, 975–978; (g) Greck, C.; Drouillat, B.; Thomassigny, C. *Eur. J. Org. Chem.* **2004**, 1377–1385; (h) Erdik, E. *Tetrahedron* **2004**, *60*, 8747–8782; (i) Janey, J. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4292–4300; (j) Nájera, C.; Sansano, J. M. *Chem. Rev.* **2007**, *107*, 4584–4671.
2. Williams, R. M. *Synthesis of Optically Active a-Amino Acids*; Oxford: Pergamon, 1989; (b) Heimgartner, H. *Angew. Chem., Int. Ed.* **1991**, *30*, 238–264; (c) Williams, R. M.; Hendrix, J. A. *Chem. Rev.* **1992**, *92*, 889–917; (d) Bergmeier, S. C. *Tetrahedron* **2000**, *56*, 2561–2576; (e) Yet, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 875–877.
3. (a) Marigo, M.; Juhl, K.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1367–1369; (b) Ma, S.; Jiao, N.; Zheng, Z.; Ma, Z.; Lu, Z.; Ye, L.; Deng, Y.; Chen, G. *Org. Lett.* **2004**, *6*, 2193–2196; (c) Huber, D. P.; Stanek, K.; Togni, A. *Tetrahedron: Asymmetry* **2006**, *17*, 658–664; (d) Ghosh, A. K.; Bilcer, G.; Schiltz, G. *Synthesis* **2001**, 2203–2229; (e) List, B.; Castello, C. *Synlett* **2001**, 1687–1689.
4. Pihko, P. M.; Pohjakallio, A. *Synlett* **2004**, 2115–2118.
5. Saaby, S.; Bella, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 8120–8121.
6. Foltz, C.; Stecker, B.; Marconi, G.; Bellemin-Laponnaz, S.; Wadepohl, H.; Gade, L. H. *Chem. Commun.* **2005**, 5115–5117.
7. Xu, X.; Yabuta, T.; Yuan, P.; Takemoto, Y. *Synlett* **2006**, 137–140.
8. Terada, M.; Nakano, M.; Ube, H. *J. Am. Chem. Soc.* **2006**, *128*, 16044–16045.
9. Kang, Y. K.; Kim, D. Y. *Tetrahedron Lett.* **2006**, *47*, 4565–4568.
10. Comelles, J.; Pericas, Á.; Moreno-Mañas, M.; Vallribera, A.; Drudis-Solé, G.; Lledos, A.; Parella, T.; Roglans, A.; García-Granda, S.; Roces-Fernández, L. *J. Org. Chem.* **2007**, *72*, 2077–2087.
11. Mashiko, T.; Hara, K.; Tanaka, D.; Fujiwara, Y.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2007**, *129*, 11342–11343.
12. He, R.; Wang, X.; Hashimoto, T.; Maruoka, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 9466–9468.
13. (a) Jung, S. H.; Kim, D. Y. *Tetrahedron Lett.* **2008**, *49*, 5527–5530; (b) Mang, J. Y.; Kim, D. Y. *Bull. Korean Chem. Soc.* **2008**, *29*, 2091–2092.
14. Lan, Q.; Wang, X.; He, R.; Ding, C.; Maruoka, K. *Tetrahedron Lett.* **2009**, *50*, 3280–3282.
15. Mang, J. Y.; Kwon, D. G.; Kim, D. Y. *Bull. Korean Chem. Soc.* **2009**, *30*, 249–252.
16. (a) Bolm, C.; Zehnder, M.; Bur, D. *Angew. Chem., Int. Ed.* **1990**, *29*, 205–207; (b) Bolm, C.; Ewald, M.; Felder, M.; Schlingloff, G. *Chem. Ber.* **1992**, *125*, 1169–1190.
17. (a) Schneider, C.; Sreekanth, A. R.; Mai, E. *Angew. Chem., Int. Ed.* **2004**, *43*, 5691–5694; (b) Mai, E.; Schneider, C. *Chem. Eur. J.* **2007**, *13*, 2729–2741; (c) Tschöp, A.; Marx, A.; Sreekanth, A. R.; Schneider, C. *Eur. J. Org. Chem.* **2007**, 2318–2327; (d) Nandakumar, M. V.; Tschöp, A.; Krautscheid, H.; Schneider, C. *Chem. Commun.* **2007**, 2756–2758; (e) Mai, E.; Schneider, C. *Synlett* **2007**, 2136–2138; (f) Tschöp, A.; Nandakumar, M. V.; Pavlyuk, O.; Schneider, C. *Tetrahedron Lett.* **2008**, *49*, 1030–1033.
18. We have recently found that a novel copper–phenanthroline-complex catalyzes the amination of a narrow range of β-keto esters with good enantioselectivity, see: Nandakumar, M. V.; Ghosh, S.; Schneider, C. *Eur. J. Org. Chem.* **2009**, 6393–6398.
19. *Typical experimental procedure*: A solution of $Cu(OTf)_2$ (1.8 mg, 10 mol %) and chiral 2,2′-bipyridine **3** (1.8 mg, 11 mol %) in dry CH_2Cl_2 (1 mL) was stirred under argon atmosphere for 1 h at room temperature. Subsequently the respective β-keto ester (0.05 mmol) and DEAD (9.57 mg, 0.055 mmol) were added and the solution was stirred for 24 h at 0 °C. After completion of the reaction (as judged by TLC), the crude product was purified by flash chromatography over silica gel affording the desired α-aminated products. Authentic racemic samples were prepared by the same reaction using $Cu(OTf)_2$ without the chiral ligand. All the products gave satisfactory spectral and analytical data. Some characteristic data: Product **4c** (Table 1, entry 3): 99% ee (HPLC on a Daicel Chiracel OD-phase, 95:5 *n*-hexane/isopropanol, flow rate 1 mL/min), t_R (major) 10.95 min, t_R (minor) 16.07 min; $[\alpha]_D^{23}$ +164 (*c* 0.52, $CHCl_3$); IR (KBr): *ν* 3311, 2981, 2934, 2359, 1720, 1608, 1591, 1466, 1377, 1338, 1305, 1237, 1152, 1081, 1061, 1044, 905, 845, 824, 787, 761, 694, 618, 462 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 1.15–1.31 (m, 6H, CH_3), 1.39 (s, 9H, CH_3), 3.73–4.24 (m, 6H, CH_2, OCH_2), 6.99 (br s, 1H, NH), 7.37 (t, *J* = 7.5 Hz, 1H, ArH), 7.47 (d, *J* = 7.5 Hz, 1H, ArH), 7.62 (t, *J* = 7.5, Hz, 1H, ArH), 7.74–7.76 (m, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 14.2, 27.6, 39.3, 62.1, 62.9, 83.0, 125.0, 126.2, 127.5, 133.5, 135.5, 136.1, 155.9; HRMS-ESI: *m/z* calcd for $[C_{20}H_{26}N_2O_7Na]^+$; 429.16322; found 429.16339. Product **4e** (Table 1, entry 5): 93% ee (HPLC on a Daicel Chiracel OD-phase, 95:5 *n*-hexane/isopropanol, flow rate 1 mL/min), t_R (minor) 19.97, t_R (major) 24.29 min; $[\alpha]_D^{23}$ +163 (*c* 0.51, $CHCl_3$); IR (KBr): *ν* 3314, 2983, 1731, 1600, 1579, 1467, 1419, 1377, 1338, 1317, 1238, 1183, 1095, 1069, 1042, 902, 833, 788, 762, 617 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 1.17 (br s, 6H, CH_3), 3.72 (s, 3H, OCH_3), 3.80 (br s, 1H, CH_2), 4.14 (br s, 5H, CH_2, OCH_2), 7.05 (br s, 1H, NH), 7.33 (d, *J* = 8.1 Hz, 1H, ArH), 7.46 (br s, 1H, ArH), 7.65–7.68 (m, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 14.2, 36.4, 38.3, 53.6, 62.3, 63.3, 77.9, 126.2, 128.6, 131.5, 142.2, 142.9, 153.2, 155.3, 155.9, 166.9, 191.8; HRMS-ESI: *m/z* calcd. for $[C_{17}H_{20}ClN_2O_7]^+$; 399.09536; found 399.09526.
20. Crystal structure data for the copper(II)–bipyridine–**1d**-complex: $C_{33}H_{39}CuF_3N_2O_9S$; Stoe IPDS-2T diffractometer, Mo-Kα radiation, λ = 71.073 pm, *T* = 180(2) K, *MW* = 760.26, orthorhombic, space group $P2_12_12_1$ (no. 19), *a* = 1132.24(8), *b* = 1201.75(7), *c* = 2548.2(2) pm, *V* = 3467.2(4) 10^6 pm^3, *Z* = 4, $\rho_{cal.}$ = 1.456 g cm^{-3}, μ = 0.762 mm^{-1}, $2\Theta_{max}$ = 52°, 16572 measured reflections, 6737 unique (R_{int} = 0.059), 5287 observed, 450 parameters, H atom parameters of OH groups (O5, O6) refined, all other H atoms included in idealized positions, *R*1 = 0.037 (observed reflections) and *wR*2 = 0.060 (all data), Flack parameter—0.015(10); programs: SHELXS-97, SHELXL-97. CCDC 753510 contains the supplementary crystallographic data for this Letter.