CHEMCOMM Communication
www.rsc.org/chemcomm

Catalytic asymmetric Henry reactions—a simple approach to optically active β-nitro α-hydroxy esters†

Christina Christensen, Karsten Juhl and Karl Anker Jørgensen*

Center for Metal Catalysed Reactions, Department of Chemistry, Aarhus University, DK-8000 Aarhus C, Denmark. E-mail: kaj@chem.au.dk

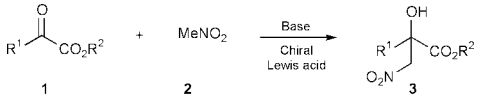
Received (in Cambridge, UK) 4th July 2001, Accepted 19th September 2001
First published as an Advance Article on the web 18th October 2001

The development and potential of a catalytic enantioselective Henry reaction of nitromethane with various α-keto esters catalyzed by chiral bisoxazoline–copper(II) complexes are presented.

The reaction between a carbonyl and a nitro compound, known as the Henry[1] or nitroaldol reaction, constitutes a fundamental carbon–carbon bond forming reaction in organic chemistry which has been applied for the construction of numerous natural products and other useful compounds.[2]

The catalytic asymmetric version of the Henry reaction has been successfully carried out in only a very few cases; Shibasaki *et al*. have in a series of papers shown that rare-earth–lithium–BINOL complexes can be applied as catalysts for the enantioselective reaction of aldehydes with nitroalkanes.[3,4]

This paper presents a new catalytic asymmetric Henry reaction of α-keto esters **1** with nitromethane **2** in the presence of easy-available chiral catalysts [eqn. (1)]. The present reaction is an important new development of the Henry reaction as it demonstrates (*i*) for the first time that ketones react in a catalytic highly enantioselective fashion, (*ii*) the products formed contain a chiral quaternary carbon center, the formation of which is a particularly demanding task in organic synthesis,[5] and (*iii*) highly attractive functionalized optically active β-nitro α-hydroxy esters **3** are formed.

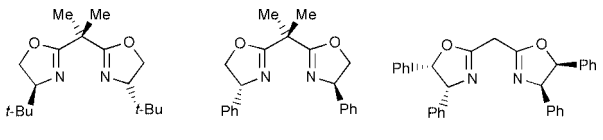


1 2 3

a: R^1 = Me, R^2 = Et
b: R^1 = Et, R^2 = Et
c: R^1 = Et, R^2 = Bn
d: R^1 = $PhCH_2CH_2$, R^2 = Et
e: R^1 = Ph, R^2 = Et
f: R^1 = p-$NO_2C_6H_4$, R^2 = Et

(1)

Different chiral ligands, Lewis acids and bases have been tested as catalyst for the enantioselective Henry reaction of ethyl pyruvate **1a** with nitromethane **2**. The most promising results were found when the chiral bisoxazoline ligands[6] (*S*)-*t*-Bu-BOX **4a**, (*R*)-Ph-BOX **4b** and (4*R*,5*S*)-DiPh-BOX **4c**, were used in combination with copper(II) as the Lewis acid.[7] Table 1 presents some representative results from the screening.



(*S*)-*t*-Bu-BOX **4a** (*R*)-Ph-BOX **4b** (4*R*,5*S*)-DiPh-BOX **4c**

Of the three chiral bisoxazoline–copper(II) catalysts presented for the reaction, the combination of (*S*)-*t*-Bu-BOX **4a** as ligand and $Cu(OTf)_2$ as the Lewis acid gave the most promising results with >95% conversion and 92% ee of the Henry adduct **3a** (entry 1) at rt, compared to >95% conversion and 14% ee for (*R*)-Ph-BOX–$Cu(OTf)_2$ and 11% conversion and 18% ee for (4*R*,5*S*)-DiPh-BOX–$Cu(OTf)_2$ (entries 2, 3). Reduction of the catalyst loading from 20 mol% to 10 mol% does not change the conversion and enantioselectivity of the reaction significantly when using (*S*)-*t*-Bu-BOX–$Cu(OTf)_2$ as the catalyst (entry 4). The conversion and enantioselectivity of the reaction of **1a** with **2** is also dependent on the amount of base relative to the catalyst. A reduction of the amount of Et_3N to 10 mol%, or an increase to 40 mol%, relative to the catalyst (20 mol%) gave a significant reduction in conversion and enantioselectivity for the first combination, and a high conversion and a racemic product **3a** for the latter combination (entries 5, 6). In the presence of NEt_3 and no chiral Lewis acid the reaction proceeds with full conversion (entry 7). The reaction also proceeds well in the presence of (*S*)-*t*-Bu-BOX–$Cu(SbF_6)_2$ as the catalyst: >95% conversion is found and **3a** is obtained with 81% ee (entry 8). Changing the Lewis acid from copper(II) to zinc(II) [(*S*)-*t*-Bu-BOX–$Zn(OTf)_2$] leads to a reaction with only 16% ee of the other enantiomer (entry 9).

Table 1 Some representative results from the screening of reaction conditions for the catalytic enantioselective Henry reaction of ethyl pyruvate **1a** with nitromethane **2** in the presence of Et_3N as the base at room temperature

Entry	Catalyst	Catalyst loading (%)	Base (%)	Conversion (%)[a]	Ee of **3a** (%)[b]
1	(*S*)-*t*-Bu-BOX–$Cu(OTf)_2$	20	20	>95	92
2	(*R*)-Ph-BOX–$Cu(OTf)_2$	20	20	>95	14
3	(4*R*,5*S*)-DiPh-BOX–$Cu(OTf)_2$	20	20	11	18
4	(*S*)-*t*-Bu-BOX–$Cu(OTf)_2$	10	10	84	81
5	(*S*)-*t*-Bu-BOX–$Cu(OTf)_2$	20	10	11	49
6	(*S*)-*t*-Bu-BOX–$Cu(OTf)_2$	20	40	>95	<5
7	—	—	20	>95	—
8	(*S*)-*t*-Bu-BOX–$Cu(SbF6)_2$	20	20	>95	81
9	(*S*)-*t*-Bu-BOX–$Zn(OTf)_2$	20	20	87	−16

[a] Determined by 1H-NMR spectroscopy. [b] Determined by chiral GC using a Chromopack CP-Chiracil (β-PM) column.

The reaction of **1a** with **2** catalyzed by (*S*)-*t*-Bu-BOX–$Cu(OTf)_2$ is base dependent. The results for some representative bases are: Hünigs base 31% conversion, 69% ee; dimethylaniline 14% conversion, 9% ee; *N*-methylmorpholine 65% conversion, 83% ee; Bn_3N 10% conversion, 14% ee, compared to >95% conversion and 92% ee applying Et_3N. It should also be noted that lowering the reaction temperature did not improve the enantioselectivity (at 0 °C: full conversion, 89% ee).

The potential of the reaction is demonstrated for the reaction of the α-keto esters **1a–f** with **2** catalyzed by (*S*)-*t*-Bu–BOX–$Cu(OTf)_2$ as shown in Table 2.‡

Ethyl pyruvate **1a** reacts with nitromethane **2** to give 2-hydroxy-2-methyl-3-nitropropanoic acid ethyl ester **3a** in 95% yield and with 92% ee (Table 2, entry 1). The corresponding ethyl analogue **1b** reacts in a similar way to give the Henry

† Electronic supplementary information (ESI) available: spectroscopic and analytical data. See http://www.rsc.org/suppdata/cc/b1/b105929g/

 DOI: 10.1039/b105929g

Table 2 Catalytic enantioselective addition of nitromethane to various α-keto esters catalyzed by (*S*)-*t*-Bu-BOX–$Cu(OTf)_2$ in the presence of Et_3N as the base

Entry	α-Keto ester	Yield (%)[a]	Ee (%)[b]
1[c]	**1a**	95	92
2[c]	**1b**	46	90
3[d]	**1b**	73	87
4[d]	**1c**	69	87
5[d]	**1d**	47	77
6[c]	**1e**	81	86
7[c]	**1f**	99	93

[a] Isolated yield. [b] Determined by chiral GC or HPLC. [c] Reaction performed at rt. [d] Reaction performed at 50 °C.

adduct **3b** in 46% yield and 90% ee at rt (entry 2). The yield of the Henry adduct is increased to 73% without significant loss in enantioselectivity by heating the reaction mixture to 50 °C (entry 3). In the same manner, the corresponding benzyl ester **1c** gives 69% yield of **3c** with 87% ee (entry 4). The α-keto ester **1d** reacts with **2** giving a moderate yield and enantioselectivty (entry 5) compared to the other reactions presented. The aromatic α-keto esters **1e**,**f** react with **2** in the presence of (*S*)-*t*-Bu-BOX–$Cu(OTf)_2$ as the catalyst to give the optically active Henry adducts in excellent yield and enantioselectivity as 81% and 86% ee of **3e**, and 99% yield and 93% ee of **3f**, respectively, are obtained (entries 6,7).

This new catalytic enantioselective Henry reaction leads to a simple synthetic approach to attractive functionalized optically active β-nitro α-hydroxy esters,[2] while reduction of the nitro functionality gives the corresponding optically active β-amino α-hydroxy esters which are highly attractive compounds in organic chemistry,[8] *e.g.* the side chain in taxol.

In summary, the first catalytic enantioselective addition reaction of α-keto esters with nitromethane has been developed. This approach shows for the first time that ketones undergo catalytic highly enantioselective Henry reactions giving attractive optically active β-nitro α-hydroxy esters having a chiral quaternary carbon center. Further work is in progress to develop, understand and apply this new type of catalytic enantioselective Henry reaction.

We are indebted to The Danish National Research Foundation for financial support.

Notes and references

‡ *Representative experimental procedure*. To a flame dried Schlenk tube $Cu(OTf)_2$ (36.2 mg, 0.100 mmol) and 2,2′-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline] (30.9 mg, 0.105 mmol) were added. The mixture was stirred under vacuum for 2 h and filled with N_2. Dry freshly distilled $MeNO_2$ (2 ml) was added and the solution was stirred for 1 h. Ethyl pyruvate **1a** (56 μl, 0.50 mmol) was added followed by the addition of Et_3N (14 μl, 0.1 mmol) and reacted for 16 h under N_2 at rt. The reaction mixture was filtered through a plug of silica with Et_2O. The solvent was removed *in vacuo* and the residue was purified by FC (silica: 10% Et_2O in CH_2Cl_2) to yield 2-hydroxy-2-methyl-3-nitropropanoic acid ethyl ester **3a** as a pale yellow oil (84 mg, 0.475 mmol, 95%) with 92% ee detected by chiral GC using a Chromopack CP-Chiracil (β-PM) column, $\tau_{(minor)}$ = 23.4 min, $\tau_{(major)}$ = 24.1 min, $[\alpha]_D^{23}$ = +10.2° (*c* = 1.19 g per 100 ml in CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 4.83 (d, *J* = 14 Hz, 1H), 4.55 (d, *J* = 14 Hz, 1H), 4.34 (m, 2H), 3.71 (s, 1H), 1.45 (s, 3H), 1.33 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 80.9, 72.3, 62.9, 23.7, 13.8; HRMS $[M + Na]^+$ calcd: $C_6H_{11}NO_5$, 200.0535; found: 200.0282.

1 L. C. Henry, *R. Hebd. Seances Acad. Sci.*, 1895, **120**, 1265.
2 See *e.g.*: D. Seebach, E. W. Lehr and T. Weller, *Chemia*, 1973, **33**, 1; G. Rosini, *Comprehensive Organic Synthesis*, ed. B. M. Trost and C. H. Heathcook, Pergamon Press, Oxford, 1991, Vol. 2, p. 321; M. Shibasaki and H. Gröger in *Comprehensive Asymmetric Catalysis I-III*, ed. E. N. Jacobsen, A. Pfaltz and H. Yamamoto, Springer-Verlag, Berlin–Heidelberg, 1999, Chapter 29.3; F. A. Luzzio, *Tetrahedron*, 2001, **57**, 915.
3 See *e.g.*: H. Sasai, T. Suzuki, S. Arai, T. Arai and M. Shibasaki, *J. Am. Chem. Soc.*, 1992, **114**, 4418; H. Sasai, T. Suzuki, N. Itoh and M. Shibasaki, *Tetrahedron Lett.*, 1993, **34**, 851; H. Sasai, T. Tokunaga, S. Watanabe, T. Suzuki, N. Itoh and M. Shibasaki, *J. Org. Chem.*, 1995, **60**, 7388; K. Iseki, S. Oishi, H. Sasai and M. Shibasaki, *Tetrahedron Lett.*, 1996, **37**, 9081; T. Arai, Y. M. A. Yamada, N. Yamamoto, H. Sasai and M. Shibasaki, *Chem. Eur. J.*, 1996, **2**, 1368.
4 See also: R. Chinchialla, C. Nájera and P. Sánches-Agulló, *Tetrahedron: Asymmetry*, 1994, **5**, 1393; A. P. Davis and K. J. Dempsey, *Tetrahedron: Asymmetry*, 1995, **6**, 2829.
5 For a review about the catalytic formation of molecules with quaternary carbon centers: E. J. Corey and A. Guzman-Perez, *Angew. Chem., Int. Ed.*, 1998, **37**, 388.
6 For recent reviews see: J. S. Johnson and D. A. Evans, *Acc. Chem. Res.*, 2000, **33**, 325; K. A. Jørgensen, M. Johannsen, S. Yao, H. Audrain and J. Thorhauge, *Acc. Chem. Res.*, 1999, **32**, 605; A. K. Ghosh, P. Mathivanan and L. Cappiello, *Tetrahedron: Asymmetry*, 1998, **9**, 1.
7 The chiral bisoxazoline–copper(II) complexes can also catalyze the highly enantioselective addition of nitro compounds to imines: N. Nishiwaki, K. R. Knudsen, K. V. Gothelf and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2001, **40**, 2992.
8 C. Cativiela, M. D. Diez-de-Villegas and J. A. Gálvez, *Tetrahedron: Asymmetry*, 1996, **7**, 529 and references therein.