JOC*Article*

Copper-Catalyzed Enantioselective Henry Reactions of α-Keto Esters: An Easy Entry to Optically Active *β*-Nitro-α-hydroxy Esters and *β*-Amino-α-hydroxy Esters

Christina Christensen, Karsten Juhl, Rita G. Hazell, and Karl Anker Jørgensen*

Center for Metal Catalyzed Reactions, Department of Chemistry, Aarhus University, DK-8000 Aarhus C, Denmark

kaj@chem.au.dk

Received March 7, 2002

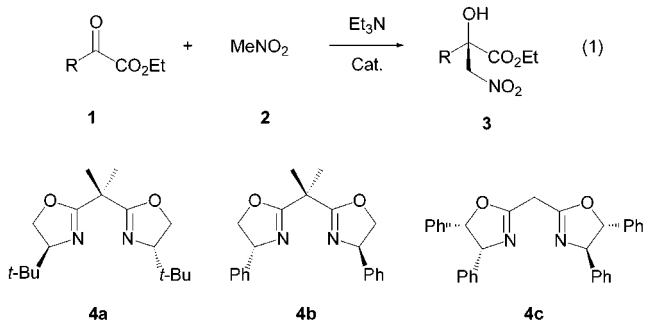
The catalytic enantioselective Henry reaction of α-keto esters with nitromethane has been developed. The reaction conditions have been optimized by the screening of different chiral Lewis acids, solvents, and bases, and it was found that the copper(II)−*tert*-butyl bisoxazoline complex in combination with triethylamine catalyzed a highly enantioselective reaction giving optically active *β*-nitro-α-hydroxy esters in high yields and with excellent enantiomeric excesses. The scope of the reaction is demonstrated by the reaction of a variety of different α-keto esters. The catalytic enantioselective Henry reaction of *β*,*γ*-unsaturated-α-keto esters proceeds as a 1,2-addition reaction exclusively, in contrast to the uncatalyzed reaction where both the 1,2- and 1,4-addition products are formed. It is demonstrated that the *β*-nitro-α-hydroxy esters can be converted into, e.g., Boc-protected *β*-amino-α-hydroxy esters in high yields and without loss of optical purity. The mechanism for the reaction is discussed, and it is postulated that both the α-keto ester and nitromethane/nitronate is coordinated to the metal center during the reaction course.

Introduction

The Henry[1] or nitroaldol reaction, which essentially is a coupling reaction between a carbonyl compound and a nitroalkane having α-hydrogen atoms, constitutes a fundamental synthetic tool for the construction of C−C bonds in organic chemistry.[2] The importance of the Henry reaction is typically further transformations involving the newly formed *β*-nitroalkanol functionality such as reduction, oxidation, or dehydration, depending on the requirements and overall goal of the multistep synthetic plan.[1,2]

In a more complex venture, the Henry reaction will facilitate the joining of two molecular fragments, under mild conditions, with the possible formation of one or two chiral centers at the new C−C bond. The catalytic enantioselective version of the Henry reaction[3] has only been reported for very few systems, and compared to the closely related catalytic asymmetric aldol reaction, it has been met with much lower interest. Shibasaki et al. were the first to report that rare-earth-lithium−BINOL complexes can be applied as catalysts for the enantioselective Henry reaction of aldehydes.[4,5] More recently, we communicated a new copper-catalyzed enantioselective Henry reaction of nitromethane and α-keto esters[6] using readily available bisoxazolines as the chiral ligand.[7,8]

In this paper, we disclose the development of the enantioselective Henry reaction of α-keto esters **1** with nitromethane **2** catalyzed by copper(II) salts in combination with chiral bisoxazoline ligands **4** in detail (eq 1).



The scope and generality of this reaction is demonstrated by the synthesis of several optically active *β*-nitro-α-hydroxy esters **3**, which are easily converted to, e.g., the corresponding *β*-amino-α-hydroxy esters. Another inter-

(1) Henry, L. *Hebd. CR Seances Acad. Sci.* **1895**, *120*, 1265; *Bull. Soc. Chim. Fr.* **1895**, *13*, 999.

(2) For recent reviews dealing with the Henry reaction and its use, see: (a) Luzzio, F. A. *Tetrahedron* **2001**, *57*, 915. (b) Rosini, G. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1999; Vol. 1, p 321. (c) Rosini, G.; Ballini, R. *Synthesis* **1988**, 833. (d) Pinnick, H. W. In *Organic Reactions*; Paquette, L. A., Ed.; Wiley: New York, 1990; Vol. 38, Chapter 3.

(3) Shibasaki, M.; Gröger, H. In *Comprehensive Asymmetric Catalysis I−IIII*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin-Heidelberg, 1999; Chapter 29.3.

(4) (a) Sasai, H.; Suzuki, T.; Arai, S.; Arai, T.; Shibasaki, M. *J. Am. Chem. Soc.* **1992**, *114*, 4418. (b) Sasai, H.; Suzuki, T.; Itoh, N.; Shibasaki, M. *Tetrahedron Lett.* **1993**, *34*, 851. (c) Sasai, H.; Tokunaga, T.; Watanabe, S.; Suzuki, T.; Itoh, N.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 7388. (d) Iseki, K.; Oishi, S.; Shibasaki, M. *Tetrahedron Lett.* **1996**, *37*, 9081. (e) Arai, T.; Yamada, Y. M. A.; Sasai, H.; Shibasaki, M. *Chem. Eur. J.* **1996**, *2*, 1368.

(5) See also: (a) Chinchialla, R.; Nájera, C.; Sánches-Agulló, P. *Tetrahedron: Asymmetry* **1994**, *5*, 1393. (b) Davis, A. P.; Dempsey, K. J. *Tetrahedron: Asymmetry* **1995**, *6*, 2829.

10.1021/jo025690z CCC: $22.00
Published on Web 05/23/2002

esting feature of this reaction is the formation of a chiral quaternary carbon center, a particularly demanding task in organic chemistry.[9] Furthermore, the mechanistic detail of the reaction will also be presented and discussed.

Results and Discussion

The initial studies of the catalytic asymmetric Henry reaction were performed on the reaction of ethyl pyruvate **1a** (R = Me) and nitromethane **2** in the presence of bisoxazoline ligands (**4a**−**c**) in combination with copper(II) and zinc(II) salts. The results from these studies are shown in Table 1.

Ethyl pyruvate **1a** reacted smoothly with nitromethane **2** in the presence of 20 mol % Et_3N at room temperature with formation of 2-hydroxy-2-methyl-3-nitropropanoic acid ethyl ester **3a** in more than 95% yield (Table 1, entry 1). A highly enantioselective reaction also proceeded at room temperature in the presence of 20 mol % of Et_3N and 20 mol % of the copper(II)−(*S*)-*tert*-butyl bisoxazoline complex ($Cu(OTf)_2$-**4a**) to give **3a** in quantitative yield and 92% ee (entry 2). Other chiral copper(II) and zinc(II) complexes were also tested as catalysts for the reaction; the application of the (*R*)-phenyl bisoxazoline ligand **4b** in combination with $Cu(OTf)_2$ did not affect the yield but led to significant loss in enantioselectivity (entry 3). With (4*R*,5*S*)-phenyl bisoxazoline **4c** as the ligand, only 11% yield and 18% ee of **3a** were obtained (entry 4). The enantioselectivity was dependent on the counterion, as application of the $Cu(SbF_6)_2$-**4a** complex resulted in 81% ee of **3a** (entry 5) compared with 92% ee using $Cu(OTf)_2$ as the Lewis acid. The zinc bisoxazoline complexes $Zn(OTf)_2$-**4a** and $Zn(OTf)_2$-**4b** could also catalyze the reaction; however, only minute or no enantioselectivity of **3a** was detected (entries 6, 7). In an attempt to suppress the Et_3N-initiated background reaction, the reaction temperature was lowered to 0 and −24 °C, respectively; however, this had little effect on the yield of the reaction, whereas the enantioselectivity dropped at −24 °C (entries 8, 9).

A series of Brønsted bases were also tested for the catalytic enantioselective Henry reaction of ethyl pyruvate **1a** with nitromethane **2**. The results of the base survey are shown in Table 2.

Of the different bases tested, Et_3N was clearly the base of choice for this reaction (Table 2, entry 1). The slightly less basic *N*-methyl morpholine gave lower yield and enantioselectivity (entry 2), while *N*,*N*-dimethyl aniline was not sufficiently basic to catalyze the reaction and only 14% yield of the Henry adduct **3a** was obtained (entry 3). The bases Bn_3N and Et(*i*-Pr)$_2$N (Hünig's base) were tested in the reaction, as these bases are much more bulky than Et_3N but have the same basicity. It was expected that the bulkiness of these bases would obstruct coordination to the chiral Lewis acid, giving more uncoordinated base and chiral catalyst and hopefully leading

TABLE 1. Optimization of the Catalytic Enantioselective Henry Reaction of Ethyl Pyruvate 1a and Nitromethane 2[a]

entry	catalyst (mol %)	Et_3N (mol %)	yield[b] (%)	ee[c] (%)
1	none	20	>95	0
2	$Cu(OTf)_2$-**4a** (20)	20	>95	92
3	$Cu(OTf)_2$-**4b** (20)	20	>95	14
4	$Cu(OTf)_2$-**4c** (20)	20	11	18
5	$Cu(SbF_6)_2$-**4a** (20)	20	>95	81
6	$Zn(OTf)_2$-**4a** (20)	20	87	−16
7	$Zn(OTf)_2$-**4b** (20)	20	>95	<5
8[d]	$Cu(OTf)_2$-**4a** (20)	20	>95	92
9[e]	$Cu(OTf)_2$-**4a** (20)	20	93	77
10[f]	$Cu(OTf)_2$-**4a** (20)	20	63	76

[a] Reaction was performed in 2 mL of dry $MeNO_2$ at room temperature (except entries 8−10) on a 0.5 mmol scale. [b] Determined by ^1H NMR spectroscopy with pentachlorobenzene as the internal standard. [c] Determined by chiral GC. [d] Reaction was performed at 0 °C. [e] Reaction was performed at −24 °C. [f] Reaction was performed in nondried $MeNO_2$.

TABLE 2. Enantioselective Henry Reaction of Ethyl Pyruvate 1a and Nitromethane 2 Catalyzed by 20 mol % $Cu(OTf)_2$-4a and 20 mol % Base[a]

entry	base	yield[b] **3** (%)	ee[c] (%)
1	Et_3N	>95	92
2	*N*-Me-morpholine	65	83
3	$PhNMe_2$	14	9
4	Bn_3N	10	14
5	Et(*i*-Pr)$_2$N	31	69
6	pyridine	6	13
7	K_2CO_3	>95	27

[a] Reaction performed in 2 mL of dry $MeNO_2$ at room temperature on a 0.5 mmol scale. [b] Determined by ^1H NMR spectroscopy with pentachlorobenzene as the internal standard. [c] Determined by chiral GC.

(6) Christensen, C.; Juhl, K.; Jørgensen, K. A. *Chem. Commun.* **2001**, 2222.

(7) For reviews of C_2-bisoxazoline−Lewis acid complexes as catalysts, see: (a) Ghosh, A. K.; Mathivanen, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1. (b) Jørgensen, K. A.; Johannsen, M.; Yao, S.; Audrain, H.; Thorhauge, J. *Acc. Chem. Res.* **1999**, *32*, 605. (c) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325.

(8) For recent examples of C_2-bisoxazoline−Lewis acid complexes as catalysts, see: (a) Evans, D. A.; Kozlowski, M. C.; Murry, J. A.; Burgey, C. S.; Campos, K. R.; Connell, B. T.; Staples R. J. *J. Am. Chem. Soc.* **1999**, *121*, 669 and references therein. (b) Evans, D. A.; Burgey, C. S.; Kozlowski, M. C.; Tregay, S. W. *J. Am. Chem. Soc.* **1999**, *121*, 686 and references therein. (c) Evans, D. A.; Scheidt, K. A.; Johnston, J. N.; Willis, M. C. *J. Am. Chem. Soc.* **2001**, *123*, 4480. (d) Evans, D. A.; Barnes, D. M.; Johnson, J. S.; Lectka, T.; von Matt, P.; Miller, S. J.; Norcross, R. D.; Shaughnessy, E. A.; Campos, K. R. *J. Am. Chem. Soc.* **1999**, *121*, 7582 and references therein. (e) Evans, D. A.; Miller, S. J.; Lectka, T.; von Matt, P. *J. Am. Chem. Soc.* **1999**, *121*, 7559 and references therein. (f) Aggarwal, V. K.; Jones, D. E.; Martin-Castro, A. M. *Eur. J. Org. Chem.* **2000**, 2939. (g) Jensen, K. B.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1999**, *64*, 2353. (h) Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Tedrow, J. S. *J. Am. Chem. Soc.* **1999**, *121*, 1994. (i) Evans, D. A.; Johnson, J. S.; Olhava, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 1635. (j) Audrain, H.; Thorhauge, J.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2000**, *65*, 4487. (k) Zhuang, W.; Thorhauge, J.; Jørgensen, K. A. *Chem. Commun.* **2000**, 459. (l) Evans, D. A.; Tregay, S. W.; Burgey, C. S.; Paras, N. A.; Vojkovsky, T. *J. Am. Chem. Soc.* **2000**, *122*, 7936 and references therein. (m) Reichel, F.; Fang, X.; Yao, S.; Ricci, M.; Jørgensen, K. A. *Chem. Commun.* **1999**, 1505. (n) Gathergood, N.; Jørgensen, K. A. *Chem. Commun.* **1999**, 1869. (o) Gathergood, N.; Zhuang, W.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2000**, *120*, 12517. (p) Zhuang, W.; Gathergood, N.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2001**, *66*, 1009. (q) Jensen, K. B.; Thorhauge, J.; Hazell, R. G.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 160. (r) Zhuang, W.; Hansen, T.; Jørgensen, K. A. *Chem. Commun.* **2001**, 347. (s) Juhl, K.; Gathergood, N.; Jørgensen, K. A. *Chem. Commun.* **2000**, 2211. (t) Audrain, H.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2000**, *122*, 11543. (u) Juhl, K.; Gathergood, N.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 2995. (v) Knudsen, K. R.; Risgaard, T.; Nishiwaki, N.; Gothelf, K. V.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2001**, *123*, 5843. (x) Nishiwaki, N.; Knudsen, K. R.; Gothelf, K.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 2992. (y) Juhl, K.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 2420. (z) Thorhauge, J.; Roberson, M.; Hazell, R. G.; Jørgensen, K. A. *Chem. Eur. J.* **2002**, *8*, 1888.

(9) For reviews concerning catalytic formation of molecules with quaternary carbon centers, see: (a) Corey E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388. (b) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591.

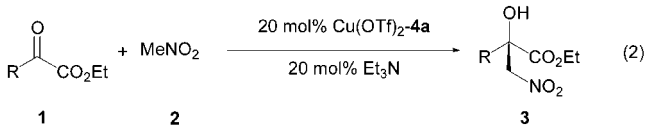
TABLE 3. Enantioselective Henry Reaction of α-Keto Esters 1a−l with Nitromethane 2 Catalyzed by $Cu(OTf)_2$-4a (20 mol %) in the Presence of Et_3N (20 mol %) as the Base[a]

entry	α-keto ester R	product	yield[b] (%)	ee[c] (%)
1	Me (**1a**)	**3a**	95	92
2[e]	Et (**1b**)	**3b**	46	90
3[d,e]	Et (**1b**)	**3b**	73	87
4[d,e]	$(CH_2)_2Ph$ (**1c**)	**3c**	47	77
5	hexyl (**1d**)	**3d**	91	93
6	but-3-enyl (**1e**)	**3e**	97	94
7	pent-4-enyl (**1f**)	**3f**	92	94
8	3-methyl-butyl (**1g**)	**3g**	90	94
9	*i*-Bu (**1h**)	**3h**	99	92
10	Ph (**1i**)	**3i**	81	86
11	*p*-ClC_6H_4 (**1j**)	**3j**	91	88
12	*p*-$NO_2C_6H_4$ (**1k**)	**3k**	99	93
13	*p*-$MeOC_6H_4$ (**1l**)	**3l**	68	57

[a] Reaction was performed in 2 mL of dry $MeNO_2$ at room temperature (except entries 3 and 4) on a 0.5 mmol scale for 24 h (except entries 2−4). [b] Yield of isolated product. [c] Determined by chiral GC or HPLC. [d] Reaction performed at 50 °C. [e] Reaction time = 48 h.

to lower catalyst loadings (vide infra). Unfortunately, this effect was not achieved, and instead lower yields and enantioselectivities were the results of applying these bases (entry 4, 5). Pyridine was also tested as a base in the catalytic enantioselective Henry reaction, but only 6% yield of **3a** was formed (entry 6); overly strong coordination of pyridine to the copper complex could be the explanation of this result. The inorganic base K_2CO_3 was a good base for the Henry reaction in terms of yield, but the enantioselectivity was significantly reduced compared to that achieved with Et_3N (entry 7).

The scope of the catalytic enantioselective Henry reaction is demonstrated by the reactions of the α-keto esters **1a**−**l** with nitromethane **2** catalyzed by 20 mol % $Cu(OTf)_2$-**4a** and 20 mol % Et_3N as shown in eq 2 and Table 3.



a: R = Me **g**: R = 3-methyl-butyl
b: R = Et **h**: R = *i*-Bu
c: R = $(CH_2)_2Ph$ **i**: R = Ph
d: R = hexyl **j**: R = *p*-ClC_6H_4
e: R = but-3-enyl **k**: R = *p*-$NO_2C_6H_4$
f: R = pent-4-enyl **l**: R = *p*-$MeOC_6H_4$

Ethyl pyruvate **1a** reacted with nitromethane **2** to give 2-hydroxy-2-methyl-3-nitropropanoic acid ethyl ester **3a** in 95% yield and with 92% ee (Table 3, entry 1). The catalytic enantioselective Henry reaction of the corresponding ethyl analogue **1b** proceeded in a similar way to give **3b** in 46% yield and 90% ee at room temperature (entry 2). The yield of the Henry adduct **3b** was increased to 73% without significant loss in enantioselectivity by heating the reaction mixture to 50 °C (entry 3). The α-keto ester **1c** reacted with **2** giving a moderate yield and enantioselectivity (entry 4) compared to the other reactions presented. A variety of other alkyl-substituted 2-keto esters **1d**−**h** smoothly underwent the catalytic enantioselective Henry reaction with excellent yields and enantioselectivities of **3d**−**h** (entries 5−9). The aryl-

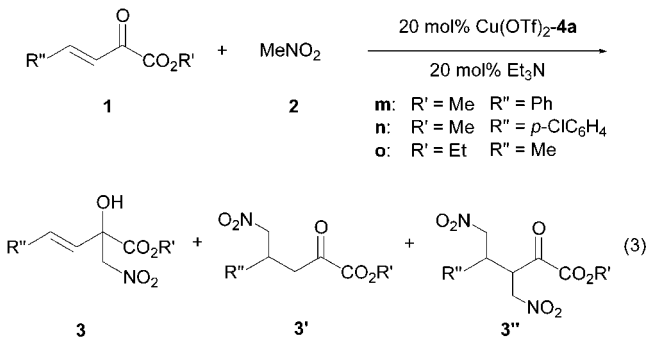
TABLE 4. Catalytic Enantioselective Henry Reaction of *β,γ*-Unsaturated α-Keto Esters 1m−o with Nitromethane 2 Catalyzed by $Cu(OTf)_2$-4a (20 mol %) in the Presence of Et_3N (20 mol %) as the Base[a]

	α-keto ester					
entry	R′	R″		product	yield[b] (%)	ee[c] (%)
1	Me	Ph	(**1m**)	**3m**	95	35
2	Me	*p*-ClC_6H_4	(**1n**)	**3n**	95	30
3	Et	Me	(**1o**)	**3o**	>96	60

[a] Reaction was performed in 2 mL of dry $MeNO_2$ at room temperature on a 0.5 mmol scale for 24 h. [b] Determined by ^1H NMR spectroscopy with pentachlorobenzene as the internal standard. [c] Determined by chiral GC or HPLC.

substituted α-keto esters **1i**−**l** also reacted with **2** in the presence of $Cu(OTf)_2$-**4a** as the catalyst to give the optically active Henry adducts **3i**−**l** in excellent yields and enantioselectivities (entries 10−12). The electron-donating methoxy group of ethyl (*p*-methoxy)phenyl glyoxylate (**1l**) caused a lower yield of the Henry adduct **3l**, as well as a lower enantioselectivity (entry 13).

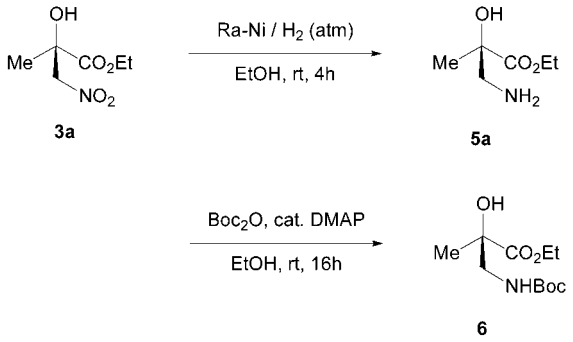
During the screening of different 2-keto esters as substrates for the catalytic enantioselective Henry reaction, the *β,γ*-unsaturated-α-keto esters **1m**−**o** were also tested (eq 3). The results are presented in Table 4.



Two different reactions can take place by the addition of nitromethane **2** to the *β,γ*-unsaturated α-keto esters **1m**−**o**, the 1,2-addition and/or 1,4-addition reaction, leading to **3m**−**o** (1,2-addition), **3′m**−**o** (1,4-addition), and **3″m**−**o** (both 1,4- and 1,2-addition) (eq 3). It is important to note that in the presence of 20 mol % of Et_3N and 20 mol % of $Cu(OTf)_2$-**4a**, the reaction of **1m**−**o** with **2** gave the 1,2-addition products **3m**−**o** exclusively. In the absence of the chiral Lewis acid, the Et_3N-induced reaction gives a mixture of 1,2-addition (**3m**−**o**) and 1,4-addition products (**3′m**−**o**) and products obtained from 1,4-addition followed by 1,2-addition (**3″m**−**o**, eq 3). The catalytic enantioselective reaction of **1m**−**o** with **2** proceeded with excellent yields and chemoselectivities as exclusively the 1,2-addition products **3m**−**o** were formed; however, the enantioselectivity was low with the exception of **3o**, which was formed with 60% ee (Table 3, entry 3). The selective 1,2-addition reaction in the presence of the chiral Lewis acid could indicate that nitromethane is coordinated to the metal before deprotonation by the base and that the nitronate is coordinated also to the metal when reacting with the keto functionality of the α-keto ester (vide infra).

Product Modification. The catalytic enantioselective Henry reaction gives an easy access to different *β*-nitro-

SCHEME 1



α-hydroxy esters. These *β*-nitro-α-hydroxy esters are readily transformed into Boc-protected *β*-amino-α-hydroxy esters by the procedure shown in Scheme 1 for the 2-hydroxy-2-methyl-3-nitropropanoic acid ethyl ester **3a**. Treatment of **3a** with a catalytic amount of Raney nickel under a hydrogen atmosphere in EtOH at room temperature for 4 h led to reduction of the nitro moiety. After addition of 3 equiv of di-*tert*-butyl dicarbonate and a catalytic amount of DMAP (20 mol %), the Boc-protected *β*-amino-α-hydroxy ester **6** was obtained in 76% yield based on *β*-nitro-α-hydroxy ester **3a** without a detectable loss of optical purity.

A similar procedure was applied to the chloro-substituted *β*-nitro-α-hydroxy ester **3j**. The *β*-amino-α-hydroxy ester **5j** was protected as oxazolidinone **7** by treatment with phosgene in toluene in 40% overall yield based on **3j** (Figure 1). The oxazolidinone **7** gave crystals suitable for X-ray crystallography, and due to the presence of the chlorine atom, the absolute configuration of the chiral center could be determined to have the (*R*)-configuration. Figure 1 also shows the X-ray structure of **7**.

Mechanistic Considerations. The chiral Lewis acid−Brønsted base ratio was very crucial to the outcome of the reaction. A lower concentration of Brønsted base relative to Lewis acid led to a significant drop in enantioselectivity and yield, whereas a higher concentration of Brønsted base gave a high yield of racemic Henry adduct.[10] The effect of the concentration of Brønsted base relative to Lewis acid was examined further, and the results are presented in Table 5. It appears from the results in Table 5 that both the yield and enantiomeric excess are dependent on the amount of base relative to the catalyst. Figure 2 shows the enantiomeric ratio of the two enantiomers of the Henry adduct (**3a**) as a function of the concentration of Et_3N in the presence of 20 mol % $Cu(OTf)_2$-**4a**. The graph in Figure 2 shows a clear maximum at 20 mol % Et_3N, indicating that equimolar amounts of chiral Lewis acid and Et_3N constitute the best catalytic system in terms of enantioselectivity.

The results of the catalytic enantioselective Henry reaction with various amounts of base can be rationalized as outlined in Scheme 2. The chiral Lewis acid ($Cu(OTf)_2$-**4a**) and Et_3N are in equilibrium with the inactive complex $Cu(Et_3N)(OTf)_2$-bisoxazoline, **8**. The Henry reaction proceeds when uncoordinated Et_3N is available to

(10) $Cu(OTf)_2$-**4a** (20 mol %) and Et_3N (10 mol %) gave 11% conversion and 49% ee. $Cu(OTf)_2$-**4a** (20 mol %) and Et_3N (40 mol %) gave full conversion to the racemic Henry adduct.

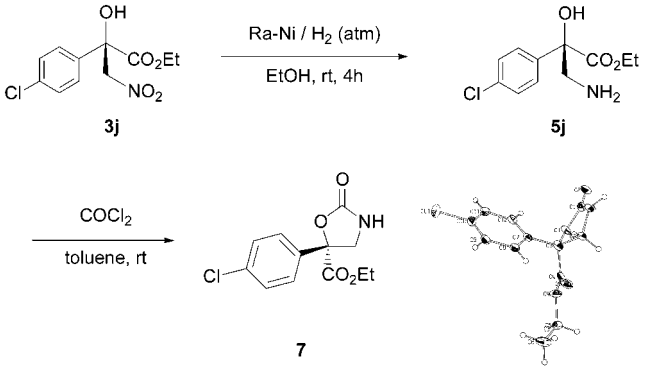


FIGURE 1. Reaction sequence leading to the oxazolidinone **7** and X-ray structure of **7**.

TABLE 5. Catalytic Enantioselective Henry Reaction of Ethyl Pyruvate 1a and Nitromethane 2 Catalyzed by $Cu(OTf)_2$-4a (20 mol %) in the Presence of Various Amounts of Et_3N[a]

Et_3N (mol %)	conversion[b] (%)	ee[c]	er[c]
5	<10	27	1.7:1
10	11	49	2.9:1
15	57	56	3.6:1
20	>95	92	24:1
25	>95	73	6.4:1
30	>95	26	1.7:1
35	>95	10	1.2:1
40	>95	4	1.1:1

[a] Reaction was performed in 2 mL of dry $MeNO_2$ at room temperature on a 0.5 mmol scale. [b] Determined by ^1H NMR spectroscopy. [c] Determined by chiral GC.

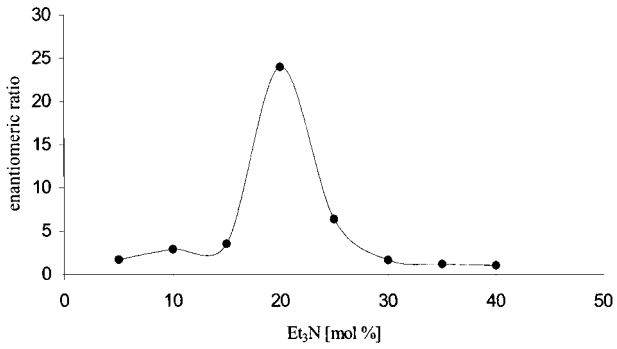
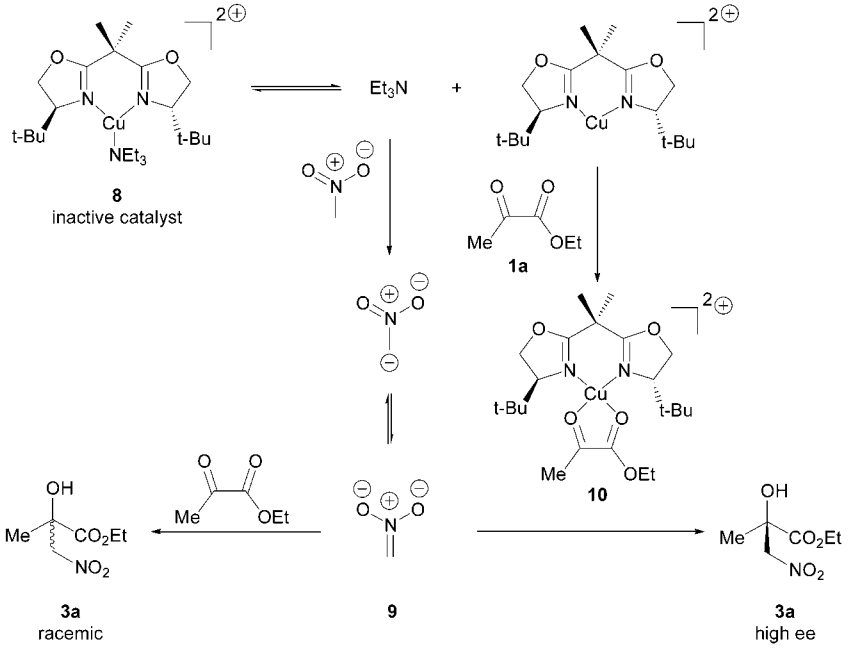


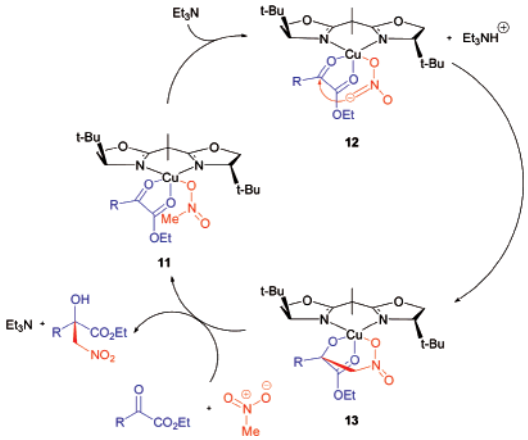
FIGURE 2. Enantiomeric ratio of Henry adduct **3a** as a function of the concentration of Et_3N relative to the $Cu(OTf)_2$-**4a** catalyst (20 mol %).

deprotonate nitromethane **2** to give the nitronate **9**. The nitronate can then undergo an enantioselective reaction with ethyl pyruvate **1a** activated by the chiral Lewis acid (vide infra) or a racemic reaction with uncoordinated **1a**. When the chiral Lewis acid is in excess compared to Et_3N, the equilibrium is shifted toward the inactive complex **8**. However, the Henry reaction still proceeds via a less effective reaction path giving lower conversion and poor enantioselectivity. When Et_3N is in excess compared to the chiral Lewis acid, the equilibrium is also shifted toward the inactive complex **8**, hence trapping the chiral Lewis acid. The remaining uncoordinated Et_3N then induces the racemic reaction path, affording only racemic **3a**. When equimolar amounts of the chiral Lewis acid and Et_3N are present, the Henry reaction proceeds by a nucleophilic attack of nitronate **9** (vide infra) on the

SCHEME 2



SCHEME 3



α-keto ester coordinated to the chiral catalyst, rather than on the uncoordinated α-keto ester, since the former is activated by the Lewis acid.

The absolute configuration of the oxazolidinone **7** showed that the chiral carbon atom formed in the catalytic enantioselective step has the (*R*)-configuration. This absolute configuration is in contrast to what has normally been found for enantioselective reactions catalyzed by $Cu(OTf)_2$-**4a** complexes.[11] Taking into account also the reactions of *β*,*γ*-unsaturated α-keto esters led us to propose the mechanism shown in Scheme 3 for the induction of enantioselectivity in the catalytic reaction.

When the chiral Lewis acid, $Cu(OTf)_2$-**4a**, is not blocked by the base, both the α-keto ester and nitromethane are coordinated to the copper-center-forming intermediate **11**. The α-keto functionality and the oxygen atom of nitromethane are in this intermediate coordinated to the metal center in the equatorial positions, while the ester carbonyl oxygen atom is coordinated to the metal center in the axial position leading to the proposed square pyramidal intermediate. Coordination of the α-keto functionality in the ligand plane affords maximum activation of the keto functionality. Deprotonation of nitromethane by the base gives the nitronate, and with the coordination pattern outlined, the *si*-face of the α-keto functionality of the α-keto ester is shielded by the *tert*-butyl substituent of the chiral bisoxazoline ligand. The *re*-face is thus available for approach by the nucleophilic carbon atom of the nitronate with a chairlike six-membered transition-state structure as outlined in **12** in Scheme 3. The enantioselective reaction then proceeds, giving the chiral Lewis acid product complex **13**. Protonation of the product and ligand exchange of the product and the two new reactants constitute the final step of the catalytic cycle.

In summary, a catalytic enantioselective Henry reaction of α-keto esters with nitromethane in the presence of Et_3N using copper(II)−(*S*)-*tert*-butyl bisoxazoline as the catalyst has been developed. The reaction gives optically active *β*-nitro-α-hydroxy esters in high yields and with excellent enantioselectivities. It is also demonstrated that the Henry adducts can be converted into optically active *β*-amino-α-hydroxy esters. On the basis of investigations of the reaction course and the absolute configuration of the optically active Henry adducts, a square pyramidal intermediate is postulated in which the α-keto functionality and the oxygen atom of nitromethane coordinate to copper(II) in the equatorial positions, while the ester carbonyl oxygen atom has an axial coordination.

General Methods

Commercially available compounds were used without further purification. Solvents were dried according to standard procedures. Flash chromatography (FC) was carried out using silica gel 60 (230−400 mesh). The ^1H NMR and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively. The chemical shifts are reported in ppm downfield to TMS ($\delta = 0$) for ^1H NMR and relative to the central $CDCl_3$ resonance ($\delta =$

(11) See refs 8a and 8z, and references therein, for a discussion of intermediate structures.

77.0) for ^{13}C NMR. The enantiomeric excess (ee) of the products was determined by chiral GC or HPLC (*i*-PrOH/hexane as the eluent).

Materials. 2,2′-Isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline], 2,2′-isopropylidenebis[(4*R*)-4-phenyl-2-oxazoline], methylenebis[(4*R*,5*S*)-4,5-diphenyl-2-oxazoline], $Cu(OTf)_2$, and $Zn(OTf)_2$ were purchased commercially and used without further purification. Ethyl pyruvate **1a**, 2-keto butyric acid, ethyl 2-oxo-4-phenylbutyrate **1c**, ethyl benzoylformate **1i**, ethyl 4-nitrophenylglyoxylate **1k**, Raney Ni, 4-(dimethylamino)-pyridine, di-*tert*-butyl dicarbonate, and the 20% phosgene solution in toluene were also purchased commercially. α-Keto ester **1b** was prepared by refluxing 2-keto-butyric acid in ethanol in the presence of a catalytic amount of HCl followed by distillation. α-Keto esters **1d**−**h** were prepared in a Grignard reaction of diethyl oxalate and the appropriate bromide following a literature procedure.[12] The bromides used are all commercially available. α-Keto esters **1j**,[13] **1l**,[14] **1m**,[8j] and **1n**,**o**[8q] were all prepared according to literature procedures.

General Procedure for Catalytic Asymmetric Henry Reactions of α-Keto Esters. To a flame-dried Schlenk tube equipped with a magnetic stirrer were added $Cu(OTf)_2$ (36.2 mg, 0.100 mmol) and 2,2′-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline] (30.9 mg, 0.105 mmol). 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. The α-keto ester (0.5 mmol) was added followed by the addition of triethylamine (14 μL, 0.1 mmol). The reaction mixture was stirred for 16 h under N_2 and then flushed through a plug of silica. Solvent was removed in vacuo, and the residue was purified by FC to give the *β*-nitro-α-hydroxy esters.

2-Hydroxy-2-methyl-3-nitro-propionic Acid Ethyl Ester (3a). Prepared according to the general procedure using 56 μL (0.5 mmol) of the commercially available α-keto ester **1a**. Purified by FC (10% Et_2O in CH_2Cl_2) to yield 84 mg (95%) of **3a** as a pale yellow oil. The ee of the product was determined by chiral GC, $\tau_{(minor)} = 23.4$ min, $\tau_{(major)} = 24.1$ min: $[\alpha]^{23}_D$ +10.2° (*c* 1.19, CH_2Cl_2, 92% ee); ^1H NMR *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 *δ* 173.4, 80.9, 72.3, 62.9, 23.7, 13.8; HRMS (TOF ES$^+$) calcd for $C_6H_{11}NO_5$ [M + Na]$^+$ 200.0535, found 200.0282.

2-Hydroxy-2-nitromethyl-butyric Acid Ethyl Ester (3b). Prepared according to the general procedure using 65.1 mg (0.5 mmol) of α-keto ester **1b.** The reaction proceeded for 48 h at room temperature, and the crude reaction mixture was purified by FC (gradient from CH_2Cl_2 to 10% Et_2O in CH_2Cl_2) to yield 44 mg (46%) of **3b** as a colorless oil. The ee of the product was determined by chiral GC, $\tau_{minor} = 9.1$ min, $\tau_{major} = 9.2$ min: $[\alpha]^{23}_D$ +20.9° (*c* 1.0, $CHCl_3$, 90% ee); ^1H NMR *δ* 4.81 (d, *J* = 13.6 Hz, 1H), 4.54 (d, *J* = 13.6 Hz, 1H), 4.32 (m, 2H), 3.72 (s, 1H), 1.68 (m, 2H), 1.30 (t, *J* = 6.8 Hz, 3H), 0.89 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR *δ* 172.8, 80.7, 75.5, 62.9, 29.7, 14.0, 6.9; HRMS (TOF ES$^+$) calcd for $C_7H_{13}NO_5$ [M + Na]$^+$ 214.0691, found 214.0536.

2-Hydroxy-2-nitromethyl-4-phenyl-butyric Acid Ethyl Ester (3c). Prepared according to the general procedure using 95 μL (0.5 mmol) of the commercially available α-keto ester **1c**. The reaction proceeded for 48 h at 50 °C. Purification was performed by FC (10% Et_2O in pentane) to yield 63 mg (47%) of **3c** as a colorless oil. The ee of the product was determined by HPLC (94/6 hexane/*i*-PrOH; flow rate = 1.0 mL/min; $\tau_{minor} = 13.1$ min; $\tau_{major} = 15.5$ min): $[\alpha]^{23}_D$ +16.5° (*c* 1.27, CH_2Cl_2, 77% ee); ^1H NMR *δ* 7.30−7.13 (m, 5H), 4.83 (d, *J* = 13.6 Hz, 1H), 4.58 (d, *J* = 13.6 Hz, 1H), 4.31 (m, 2H), 3.82 (s, 1H), 2.82 (m, 1H), 2.48 (m, 1H), 1.98 (m, 2H), 1.33 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR *δ* 172.6, 140.2, 128.6, 128.3, 126.4, 80.8, 75.0, 63.2, 38.2, 29.0, 14.1; HRMS (TOF ES$^+$) calcd for $C_{13}H_{17}NO_5$ [M + Na]$^+$ 290.1004, found 290.0999.

2-Hydroxy-2-nitromethyl-octanoic Acid Ethyl Ester (3d). Prepared according to the general procedure using 93.1 mg (0.5 mmol) of α-keto ester **1d**. Purification was performed by FC (CH_2Cl_2) to yield 113 mg (91%) of **3d** as a yellow oil. The ee was determined by chiral GC, $\tau_{minor} = 15.8$ min, $\tau_{major} = 16.0$ min: $[\alpha]^{23}_D$ +10.8° (*c* 1.11, CH_2Cl_2, 93% ee); ^1H NMR *δ* 4.79 (d, *J* = 13.6 Hz, 1H), 4.53 (d, *J* = 13.6 Hz, 1H), 4.30 (m, 2H), 3.74 (s, 1H), 1.61 (m, 2H), 1.42 (m, 1H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.22 (m, 6H), 1.10 (m, 1H), 0.83 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR *δ* 172.9, 80.8, 75.2, 62.9, 36.4, 31.3, 28.9, 22.4, 22.3, 13.9, 13.8; HRMS (TOF ES$^+$) calcd for $C_{11}H_{21}NO_5$ [M + Na]$^+$ 270.1317, found 270.1324.

2-Hydroxy-2-nitromethyl-hex-5-enoic Acid Ethyl Ester (3e). Prepared according to the general procedure using 78.1 mg (0.5 mmol) of α-keto ester **1e**. Purification was performed by FC (10% Et_2O in CH_2Cl_2) to yield 105 mg (97%) of **3e** as a pale yellow oil. The ee was determined by chiral GC, $\tau_{minor} = 14.7$ min, $\tau_{major} = 15.3$ min: $[\alpha]^{23}_D$ +11.7° (*c* 1.04, CH_2Cl_2, 94% ee); ^1H NMR *δ* 5.75 (m, 1H), 5.00 (m, 2H), 4.82 (d, *J* = 13.6 Hz, 1H), 4.57 (d, *J* = 13.6 Hz, 1H), 4.34 (m, 2H), 3.72 (s, 1H), 2.24 (m, 1H), 1.95 (m, 1H), 1.76 (m, 2H), 1.33 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR *δ* 172.6, 136.5, 115.7, 80.7, 74.9, 63.0, 35.5, 26.8, 13.9; HRMS (TOF ES$^+$) calcd for $C_9H_{15}NO_5$ [M + Na]$^+$ 240.0848, found 240.0851.

2-Hydroxy-2-nitromethyl-hept-6-enoic Acid Ethyl Ester (3f). Prepared according to the general procedure using 85.1 mg (0.5 mmol) of α-keto ester **1f**. Purification was performed by FC (10% Et_2O in CH_2Cl_2) to yield 106 mg (92%) of **3f** as a pale yellow oil. The ee was determined by chiral GC, $\tau_{minor} = 20.2$ min, $\tau_{major} = 21.0$ min: $[\alpha]^{23}_D$ +13.5° (*c* 1.09, CH_2Cl_2, 94% ee): ^1H NMR *δ* 5.73 (m, 1H), 4.98 (m, 2H), 4.81 (d, *J* = 13.6 Hz, 1H), 4.55 (d, *J* = 13.6 Hz, 1H), 4.34 (m, 2H), 3.69 (s, 1H), 2.05 (m, 2H), 1.64 (m, 3H), 1.33 (t, *J* = 7.2 Hz, 3H), 1,25 (m, 1H); ^{13}C NMR *δ* 172.8, 137.5, 115.3, 80.8, 75.1, 63.0, 35.7, 33.1, 21.7, 4.0;_HRMS (TOF ES$^+$) for $C_{10}H_{17}NO_5$ [M + Na]$^+$; calculated: 254.1004; found: 254.1010.

2-Hydroxy-5-methyl-2-nitromethyl-hexanoic Acid Ethyl Ester (3g). Prepared according to the general procedure using 86.1 mg (0.5 mmol) of α-keto ester **1g**. Purification was performed by FC (10% Et_2O in CH_2Cl_2) to yield 105 mg (90%) of **3g** as a pale yellow oil. The ee of the product was determined by chiral GC, $\tau_{minor} = 21.1$ min, $\tau_{major} = 21.6$ min: $[\alpha]^{23}_D$ +9.5° (*c* 1.11, CH_2Cl_2, 94% ee); ^1H NMR *δ* 4.81 (d, *J* = 13.6 Hz, 1H), 4.56 (d, *J* = 13.6 Hz, 1H), 4.34 (dk, *J* = 1.2, 7.2 Hz, 2H), 3.68 (s, 1H), 1.64 (m, 2H), 1.50 (m, 1H), 1.36 (m, 1H), 1.33 (t, *J* = 7.2 Hz, 3H), 0.97 (m, 1H), 0.87 (d, *J* = 6.8 Hz, 3H), 0.86 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR *δ* 172.9, 80.9, 75.2, 62.9, 34.4, 31.3, 27.8, 22.3, 22.2, 14.0; HRMS (TOF ES$^+$) calcd for $C_{10}H_{19}NO_5$ [M + Na]$^+$ 256.1161, found 256.1161.

2-Hydroxy-4-methyl-2-nitromethyl-pentanoic Acid Ethyl Ester (3h). Prepared according to the general procedure using 79.1 mg (0.5 mmol) of α-keto ester **1h**. Purification was performed by FC (10% Et_2O in CH_2Cl_2) to yield 109 mg (99%) of **3h** as a pale yellow oil. The ee of the product was determined by chiral GC, $\tau_{minor} = 16.1$ min, $\tau_{major} = 17.5$ min: $[\alpha]^{23}_D$ +21.1° (*c* 1.02, CH_2Cl_2, 92% ee); ^1H NMR *δ* 4.78 (d, *J* = 13.6 Hz, 1H), 4.53 (d, *J* = 13.6 Hz, 1H), 4.34 (m, 2H), 3.69 (s, 1H), 1.78 (m, 1H), 1.59 (m, 2H), 1.33 (t, *J* = 7.2 Hz, 3H), 0.97 (d, *J* = 6.4 Hz, 3H), 0.87 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR *δ* 173.2, 81.4, 75.3, 62.9, 44.4, 24.0, 23.7, 23.3, 13.9; HRMS (TOF ES$^+$) calcd for $C_9H_{17}NO_5$ [M + Na]$^+$ 242.1004, found 242.0997.

2-Hydroxy-3-nitro-2-phenyl-propionic Acid Ethyl Ester (3i). Prepared according to the general procedure using 79 μL (0.5 mmol) of the commercially available α-keto ester **1i**. The product was purified by FC (10% Et_2O in pentane) to yield 97 mg (81%) of **3i** as a colorless oil. The ee of the product was determined by HPLC (90/10 hexane/*i*-PrOH; flow rate = 1.0 mL/min; $\tau_{minor} = 11.0$ min; $\tau_{major} = 14.1$ min): $[\alpha]^{23}_D$ −16.2° (*c* 1.13, CH_2Cl_2, 86% ee): ^1H NMR *δ* 7.60 (dd, *J* = 2, 8.8 Hz, 2H), 7.42−7.36 (m, 3H), 5.25 (d, *J* = 14 Hz, 1H), 4.67 (d, *J* =

(12) Macritchie, J. A.; Sicock, A.; Willis, C. L. *Tetrahedron: Asymmetry* **1997**, *8*, 3895.
(13) Hu, S.; Neckers, D. C. *J. Org. Chem.* **1996**, *61*, 6407.
(14) Creary, X. *J. Org. Chem.* **1987**, *52*, 5026.

14 Hz, 1H), 4.36 (m, 2H), 4.21 (s, 1H), 1.33 (t, J = 7.2 Hz, 3H); ^{13}C NMR δ 171.6, 136.4, 129.0, 128.8, 125.2, 80.7, 75.9, 63.5, 13.8; HRMS (TOF ES$^+$) calcd for $C_{11}H_{13}NO_5$ [M + Na]$^+$ 262.0691, found 262.0691.

2-(4-Chloro-phenyl)-2-hydroxy-3-nitro-propionic Acid Ethyl Ester (3j). Prepared according to the general procedure using 106.3 mg (0.5 mmol) of α-keto ester **1j**. The product was purified by FC (10% Et_2O in pentane) to yield 125 mg (91%) of **3j** as a pale yellow oil. The ee of the product was determined by HPLC (90/10 hexane/*i*-PrOH; flow rate = 1.0 mL/min; τ_{minor} = 13.9 min; τ_{major} = 16.9 min): $[\alpha]^{23}_D$ −17.5° (*c* 1.02, CH_2Cl_2, 88% ee); ^{1}H NMR δ 7.55 (d, J = 8.8 Hz, 2H), 7.37 (d, J = 8.8 Hz, 2H), 5.21 (d, J = 14.0 Hz, 1H), 4.63 (d, J = 14.0 Hz, 1H), 4.37 (m, 2H), 4.23 (s, 1H), 1.33 (t, J = 7.2 Hz, 3H); ^{13}C NMR δ 171.2, 135.2, 134.9, 129.0, 126.7, 80.5, 75.6, 63.8, 13.8; HRMS (TOF ES$^+$) for $C_{11}H_{12}ClNO_5$ [M + Na]$^+$ 296.0302, found 296.0323.

2-Hydroxy-3-nitro-2-(4-nitro-phenyl)-propionic Acid Ethyl Ester (3k). Prepared according to the general procedure using 111.6 mg (0.5 mmol) of the commercially available α-keto ester **1k**. The product was purified by FC (CH_2Cl_2) to yield 141 mg (99%) of **3k** as an orange oil. The ee of the product was determined by HPLC (95/5 hexane/*i*-PrOH; flow rate = 1.0 mL/min; τ_{minor} = 47.9 min; τ_{major} = 50.7 min): $[\alpha]^{23}_D$ −15.1° (*c* 1.0, CH_2Cl_2, 93% ee); ^{1}H NMR δ 8.26 (d, = 8.8 Hz, 2H), 7.84 (d, = 9.2 Hz, 2H), 5.26 (d, = 14 Hz, 1H), 4.67 (d, = 14 Hz, 1H), 4.40 (m, 2H), 4.36 (s, 1H), 1.35 (t, J = 7.2 Hz, 3H); ^{13}C NMR δ 170.5, 148.2, 143.1, 126.7, 123.8, 80.2, 75.8, 64.2, 13.8; HRMS (TOF ES$^+$) calcd for $C_{11}H_{12}N_2O_7$ [M + Na]$^+$ 307.0542, found 307.0540.

2-Hydroxy-2-(4-methoxy-phenyl)-3-nitro-propionic Acid Ethyl Ester (3l). Prepared according to the general procedure using 104.1 mg (0.5 mmol) of α-keto ester **1l**. The product was purified by FC (gradient from 5% EtOAc in pentane to 10% EtOAc in pentane) to yield 91 mg (68%) of **3l** as a colorless oil. The ee of the product was determined by HPLC (90/10 hexane/*i*-PrOH; flow rate = 1.0 mL/min; τ_{major} = 38.8 min; τ_{minor} = 45.4 min): $[\alpha]^{23}_D$ −10.2° (*c* 1.16 g/100 mL, CH_2Cl_2, 88% ee); ^{1}H NMR δ 7.50 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 5.21 (d, J = 14.4 Hz, 1H), 4.64 (d, J = 14.4 Hz, 1H), 4.35 (m, 2H), 4.18 (s, 1H), 3.80 (s, 3H), 1.33 (t, J = 7.2 Hz, 3H); ^{13}C NMR δ 171.8, 160.1, 128.2, 126.6, 114.2, 80.8, 75.7, 63.5, 55.3, 14.0; HRMS (TOF ES$^+$) calcd for $C_{12}H_{15}NO_6$ [M + Na]$^+$ 292.0797, found 292.0796.

2-Hydroxy-2-nitromethyl-4-phenyl-but-3-enoic Acid Methyl Ester (3m). Prepared according to the general procedure using 95.1 mg (0.5 mmol) of β,γ-unsaturated α-keto ester **1m**. The crude reaction mixture was flushed through a plug of silica using Et_2O as the eluent, and the yield was determined by ^{1}H NMR with pentachlorobenzene as the internal standard. The ee of the product was determined by HPLC (90/10 hexane/*i*-PrOH; flow rate = 1.0 mL/min; τ_{minor} = 20.5 min; τ_{major} = 32.4 min): ^{1}H NMR δ 7.39−7.29 (m, 5H), 6.56 (d, J = 15.6 Hz, 1H), 6.10 (d, J = 15.6 Hz, 1H), 4.98 (d, J = 13.6 Hz, 1H), 4.57 (d, J = 13.6 Hz, 1H), 4.32 (s, 1H), 3.92 (s, 3H); ^{13}C NMR δ 171.9, 135.0, 133.6, 128.6, 126.9, 123.1, 79.8, 75.6, 54.0; HRMS (TOF ES$^+$) calcd for $C_{12}H_{13}NO_5$ [M + Na]$^+$ 274.0691, found 274.0692.

4-(4-Chloro-phenyl)-2-hydroxy-2-nitromethyl-but-3-enoic Acid Methyl Ester (3n). Prepared according to the general procedure using 112.3 mg (0.5 mmol) of β,γ-unsaturated α-keto ester **1n**. The crude reaction mixture was flushed through a plug of silica using Et_2O as the eluent, and the yield was determined by ^{1}H NMR with pentachlorobenzene as the internal standard. The ee of the product was determined by HPLC (90/10 hexane/*i*-PrOH; flow rate 1.0 mL/min; τ_{minor} = 41.9 min; τ_{major} = 52.8 min): ^{1}H NMR δ 7.30 (s, 4H), 6.98 (d, J = 15.6 Hz, 1H), 6.08 (d, J = 15.6 Hz, 1H), 4.97 (d, J = 14 Hz, 1H), 4.56 (d, J = 14 Hz, 1H), 4.33 (s, 1H), 3.93 (s, 3H); ^{13}C NMR δ 171.8, 134.3, 133.5, 132.5, 128.8, 128.1, 123.7, 79.8, 75.5, 54.1; HRMS (TOF ES$^+$) calcd for $C_{12}H_{12}ClNO_5$ [M + Na]$^+$ 308.0302, found 308.0295.

2-Hydroxy-2-nitromethyl-pent-3-enoic Acid Ethyl Ester (3o). Prepared according to the general procedure using 71.1 mg (0.5 mmol) of β,γ-unsaturated α-keto ester **1o**. The crude reaction mixture was flushed through a plug of silica using Et_2O as the eluent, and the yield was determined by ^{1}H NMR with pentachlorobenzene as the internal standard. The ee of the product was determined by chiral GC, τ_{minor} = 10.7 min, τ_{major} = 11.1 min: ^{1}H NMR δ 6.12 (dk, J = 6.8, 15.2 Hz, 1H), 5.43 (d, J = 15.2 Hz, 1H), 4.86 (d, J = 14 Hz, 1H), 4.47 (d, J = 14 Hz, 1H), 4.34 (m, 2H), 3.76 (s, 1H), 1.74 (d, J = 6.8 Hz, 3H), 1.33 (t, J = 7.2 Hz, 3H); ^{13}C NMR δ 171.8, 130.6, 125.6, 79.9, 75.0, 63.1, 17.5, 13.9; HRMS (TOF ES$^+$) calcd for $C_8H_{13}NO_5$ [M + Na]$^+$ 226.0691, found 226.0611.

3-*tert*-Butoxycarbonylamino-2-hydroxy-2-methyl-propionic Acid Ethyl Ester (6). Compound **3a** (177.2 mg, 1.0 mmol), prepared following the general procedure, was dissolved in EtOH (10 mL), and Raney nickel (400 mg in 5 mL EtOH) was added. The reaction mixture was stirred under H_2 at atmospheric pressure for 4 h at room temperature. Di-*tert*-butyl dicarbonate (655 mg, 3.0 mmol) was added followed by 4-*N*,*N*-(dimethylamino)pyridine (24 mg, 0.2 mmol). The reaction mixture was stirred at room temperature for an additional 16 h and then flushed through a plug of silica. Solvent was removed in vacuo, and the residue was purified by FC (gradient from 5% Et_2O in CH_2Cl_2 to 50% Et_2O in CH_2Cl_2) to yield 189 mg (76%) of **6** as a colorless oil, which became a solid upon standing (mp: 59−61 °C). The ee of the product was determined by chiral GC, τ_{major} = 11.7 min, τ_{minor} = 12.0 min: $[\alpha]^{23}_D$ −12.1° (*c* 1.05, CH_2Cl_2, 92% ee); ^{1}H NMR δ 5.00 (bs, 1H), 4.18 (m, 2H), 3.73 (s, 1H), 3.56 (dd, J = 8, 14 Hz, 1H), 3.15 (dd, J = 4.8, 14 Hz, 1H), 1.37 (s, 9H), 1.33 (s, 3H), 1.24 (t, J = 7.2 Hz, 3H); ^{13}C NMR δ 175.5, 155.9, 79.3, 74.6, 62.1, 48.3, 28.1, 23.0, 14.0; HRMS (TOF ES$^+$) calcd for $C_{11}H_{21}NO_5$ [M + Na]$^+$ 270.1317, found 270.1319.

5-(4-Chloro-phenyl)-2-oxo-oxazolidine-5-carboxylic Acid Ethyl Ester (7). Compound **3j** (137 mg, 0.5 mmol), prepared following the general procedure, was dissolved in EtOH (4 mL), and Raney nickel (200 mg in 3 mL of EtOH) was added. The reaction mixture was stirred under H_2 at atmospheric pressure for 4 h at room temperature. The reaction mixture was filtered through an HPLC filter, and the solvent was removed in vacuo. The residue was dissolved in a 20% solution of phosgene in toluene and left stirring for 16 h. The solvent was removed in vacuo, and the crude reaction mixture was purified by FC (gradient from CH_2Cl_2 to 10% Et_2O in CH_2Cl_2) to give 54 mg (40%) of **7** as a white powder. Recrystallization from CH_2Cl_2 in a hexane chamber afforded colorless needles for X-ray analysis (mp: 154−156 °C). The ee of the product was determined by HPLC (90/10 hexane/*i*-PrOH; flow rate = 1.0 mL/min; τ_{major} = 17.6 min; τ_{minor} = 19.4 min): $[\alpha]^{23}_D$ −49.6° (*c* 1.08, CH_2Cl_2, 92% ee); ^{1}H NMR δ 7.41 (d, J = 8.8 Hz, 2H), 7.35 (d, J = 8.8 Hz, 2H), 6.50 (bs, 1H), 4.40 (d, J = 9.6 Hz, 1H), 4.22 (k, J = 7.2 Hz, 2H), 3.74 (d, J = 8.8 Hz, 1H), 1.23 (t, J = 7.2 Hz, 3H); ^{13}C NMR δ 169.6, 158.0, 135.7, 135.1, 129.0, 126.1, 83.5, 63.0, 50.8, 13.8; HRMS (TOF ES$^+$) calcd for $C_{12}H_{12}ClNO_4$ [M + Na]$^+$ 292.0353, found 292.0352. See Supporting Information for X-ray data.

Acknowledgment. This work was made possible by a grant from The Danish National Research Foundation.

Note Added in Proof. Trost et al. have recently disclosed a catalytic enantioselective Henry reaction employing a bimetallic zinc complex.[15]

Supporting Information Available: Complete X-ray data for compound **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO025690Z

(15) Trost, B. M.; Yeh, V. S. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 861.