A Facile One-Pot Synthesis of Chiral β-Amino Esters

Tanasri Bunlaksananusorn,* Florian Rampf

Lanxess Deutschland GmbH, Fine Chemicals Research & Development, 51369 Leverkusen, Germany
Fax +49(214)3095971322; E-mail: tanasri.bunlaksananusorn@lanxess.com

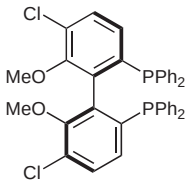
Received 16 August 2005

Abstract: We report a facile one-pot synthesis of chiral β-amino esters via direct reductive amination of β-keto esters with ammonium acetate (NH_4OAc) and H_2 in the presence of chiral Ru–ClMeOBIPHEP catalysts using 2,2,2-trifluoroethanol (TFE) as a solvent, leading to β-amino esters in high yields with high enantioselectivities (up to 99% ee).

Key words: reductive amination, β-amino esters, β-keto esters, Ru–ClMeOBIPHEP catalyst

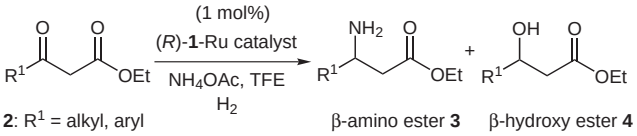
The preparation of chiral β-amino acid derivatives is an important task for the pharmaceutical industry, since they are chiral building blocks for the synthesis of numerous biologically active compounds such as β-peptides, β-lactam antibiotics and many chiral drugs.[1] From an industrial point of view, one of the most promising methods to prepare β-amino acid derivatives is the use of catalytic asymmetric hydrogenation. Recently, many groups have reported asymmetric hydrogenations of β-acetamido acrylates employing a catalytic amount of chiral Rh or Ru complexes. However, these methods require additional steps for the introduction and removal of a protecting group such as an acyl group. Additionally, mixtures of *E*- and *Z*-isomers are formed, which have sometimes dramatic differences in the enantioface-discriminating abilities.[2] Moreover, the removal of the acyl group requires harsh conditions (heating under strongly acidic or basic conditions). Very recently, two groups at Merck and Takasago described the enantioselective hydrogenation of unprotected β-enamine esters, which represents an important breakthrough in the synthesis of chiral β-amino esters.[3] Börner et al. have developed a direct reductive amination (DRA) of carbonyl compounds, catalyzed by homogeneous Rh(I)–diphosphane complexes, providing chiral amines with high enantioselectivities and chemoselectivities.[4] Over the last years, Bayer's central research department and then Lanxess have developed numerous applications of the chiral ClMeOBIPHEP ligand (Figure 1) in asymmetric hydrogenation of prochiral C=O or C=C bonds.[5]

Herein we report a facile one-pot synthesis of chiral β-amino esters via direct reductive amination of β-keto esters with NH_4OAc and H_2 in the presence of (*R*)-**1**-Ru catalysts (Scheme 1).



ClMeOBIPHEP (*R*)-**1**
(*Lanxess*)

Figure 1



2: R^1 = alkyl, aryl β-amino ester **3** β-hydroxy ester **4**

Scheme 1 Direct reductive amination of β-keto esters with (*R*)-**1**-Ru catalyst

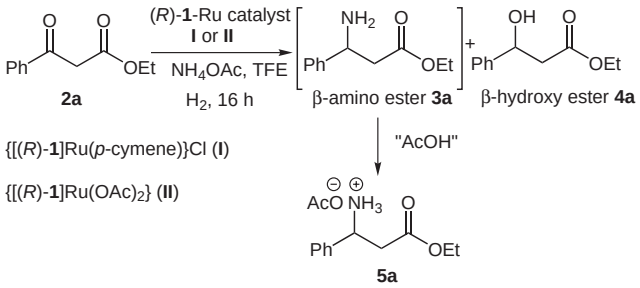
Initially, we examined the reductive amination of ethyl benzoyl acetate **2a** with NH_4OAc (5 equiv) in the presence of (*R*)-**1**-Ru catalyst **I** using TFE as a solvent[6] (Table 1). High chemoselectivity in terms of the **3a**/**4a**[7] ratio (≥ 99:1) was observed (entries 1–5, Table 1). It was found that the reductive amination of **2a** was performed efficiently by increasing the temperature from 60 °C to 80 °C under 10–30 bar of H_2, leading to full conversion and high enantioselectivity of **3a** (entries 1–3). Similar ee values were observed in the presence of (*R*)-**1**-Ru catalyst **II**[8] (entries 2 vs. 4). Increasing the substrate to catalyst (s/c) ratio from 100 to 1,000 led to 64% conversion (entries 4 vs. 5). Usually the product was formed as the ammonium salt **5a**, due to the excess of NH_4OAc, which generates acetic acid in situ and subsequently protonates the β-amino ester **3a**.

Under optimized conditions, a series of aryl-substituted β-keto esters was investigated using 1 mol% of the (*R*)-**1**-Ru catalyst **I**. Results are summarized in Table 2. In most cases, the corresponding ammonium salts **5**[9] were formed in good yields with high enantioselectivities (≥ 96% ee) and high chemoselectivities (≥ 99:1 of β-amino ester:β-hydroxy ester, see entries 1, 2 and 4–6, Table 2). However, a small amount of β-hydroxyester was formed, when *m*-methoxy substituted compound **2c** was employed (entry 3).

Reductive amination of alkyl β-keto esters like **2g** was also successful, yielding the ammonium salt **5g** with high enantioselectivity (96% ee, Scheme 2) and high chemoselectivity (≥ 99:1 of β-amino ester:β-hydroxy ester).

SYNLETT 2005, No. 17, pp 2682–2684
Advanced online publication: 05.10.2005
DOI: 10.1055/s-2005-917108; Art ID: G25805ST

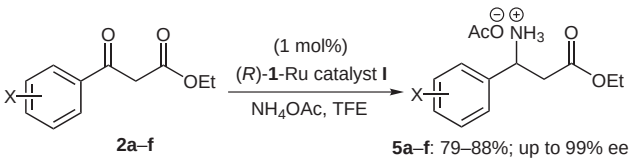
Table 1 Reductive Amination of β-Keto Ester **2a**[a]



Entry	[Ru]	S/C	H_2 (bar)	Temp (°C)	Conversion (%)[b]	ee (%)[c]
1	**I**	100	30	60	85	nd[d]
2	**I**	100	30	80	100	97 (*S*)
3	**I**	100	10	80	100	97 (*S*)
4	**II**	100	30	80	100	98 (*S*)
5	**II**	1000	30	80	64	nd

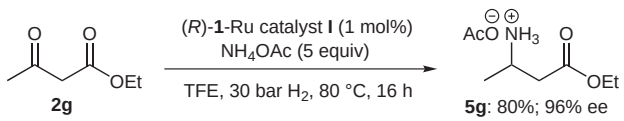
[a] Reaction conditions: 5 μmol (*R*)-**1**-Ru catalyst, 0.5 mmol **2a**, 2.5 mmol NH_4OAc, 4 mL TFE.
[b] Determined by GC.
[c] Determined by chiral GC.
[d] Not determined.

Table 2 Reductive Amination of Aryl-Substituted Keto Ester **2a–f** under Optimized Conditions[a]



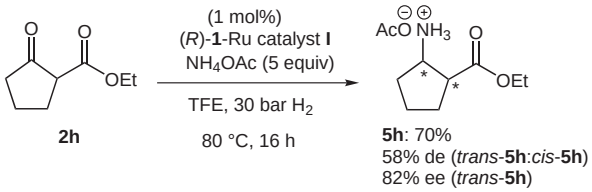
Entry	X	Yield (%)[b]	ee (%)[c]	Ratio of β-amino ester to β-hydroxy ester
1	**2a**: X = H	88	98	99:1
2	**2b**: X = *m*-Cl	81	98	99:1
3	**2c**: X = *m*-OMe	88	96	94:6[d]
4	**2d**: X = *p*-F	80	96	99:1
5	**2e**: X = *p*-OMe	83	98	99:1
6	**2f**: X = *p*-Cl	79	99	99:1

[a] Reaction conditions: 5 μmol (*R*)-**1**-Ru catalyst **I**, 0.5 mmol β-keto ester, 2.5 mmol NH_4OAc, 4 mL TFE, 30 bar of H_2, 80 °C, 16 h.
[b] Isolated yields of analytically pure products.
[c] Determined by chiral GC.
[d] Determined by GC.



Scheme 2 Reductive amination of ethyl acetylacetonate **2g**

For the reaction mechanism, we also believed that it might proceed via reduction of an imine intermediate as previously discussed by the Merck group.[3] Furthermore, our methodology could also be extended to the reductive amination of cyclic β-keto esters such as **2h**. Under non-optimized conditions, moderate diastereoselectivities (58% de) and enantioselectivity (82% ee) were obtained with high chemoselectivity (≥99:1 of β-amino ester:β-hydroxy ester, Scheme 3).



Scheme 3 Reducive amination of cyclic β-keto ester **2h**

In summary, we have demonstrated a facile one-pot synthesis of various chiral β-amino esters via reductive amination of β-keto esters. Optimization of the catalyst to substrate ratio and scale-up are currently being performed in our laboratories.

General Procedure for the Reductive Amination of β-Keto Esters

Preparation of Ethyl (*S*)-3-Amino-3-phenylpropanoate Acetate (5a)

(*R*)-**1**-Ru catalyst **I** (5 mg, 5 μmol), NH_4OAc (196 mg, 2.5 mmol), β-keto ester **2a** (100 mg, 0.5 mmol) and TFE (4 mL) were placed in an autoclave. The autoclave was sealed and pressurized to 30 bar H_2

and the mixture was stirred at 80 °C for 16 h. TFE was removed and the crude product was passed through a short silica gel column with *tert*-butylmethylether (TBME) as an eluent. After evaporation of the solvent, (*S*)-**5a** was obtained in 88% yield, 98% ee as a white solid; mp[10] 86–87 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.15 (m, 5 H), 5.97 (br s, 3 H), 4.40 (dd, *J* = 8.6, 5.1 Hz, 1 H), 4.05 (q, *J* = 7.1 Hz, 2 H), 2.77 (dd, *J* = 16.4, 8.6 Hz, 1 H), 2.67 (d, *J* = 16.4, 5.1 Hz, 1 H), 1.89 (s, 3 H), 1.15 (t, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.2, 170.5, 141.0, 127.7, 126.9, 125.5, 59.8, 51.3, 41.2, 20.7, 13.1 ppm.

References

(1) (a) *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley-VCH: New York, **1997**. (b) Gademann, K.; Hintermann, T.; Schreiber, J. V. *Curr. Med. Chem.* **1999**, *6*, 905. (c) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173.

(2) (a) Drexler, H.-J.; You, J.; Zhang, S.; Fischer, C.; Baumann, W.; Spannenberg, A.; Heller, D. *Org. Process Res. Dev.* **2003**, *7*, 355. (b) Zhou, Y.-G.; Tang, W.; Wang, W.-B.; Li, W.; Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 4952. (c) Pena, D.; Minnaard, A. J.; de Vries, J. G.; Feringa, B. L. *J. Am. Chem. Soc.* **2002**, *124*, 14552. (d) Heller, D.; Holz, J.; Komarov, I.; Drexler, H.-J.; You, J.; Drauz, K.; Börner, A. *Tetrahedron: Asymmetry* **2002**, *13*, 2735. (e) Heller, D.; Drexler, H.-J.; You, J.; Baumann, W.; Drauz, K.; Krimmer, H.-P.; Börner, A. *Chem.–Eur. J.* **2002**, *8*, 5196. (f) Lubell, W. D.; Kitamura, M.; Noyori, R. *Tetrahedron: Asymmetry* **1991**, *2*, 543.

(3) (a) Hsiao, Y.; Rivera, N. R.; Rosner, T.; Krska, S. W.; Njolito, E.; Wang, F.; Sun, Y.; Armstrong, J. D. III; Grabowski, E. J. J.; Tillyer, R. D.; Spindler, F.; Malan, C. *J. Am. Chem. Soc.* **2004**, *126*, 9918. (b) Rosner, T.; Dormer, P. G.; Hsiao, Y.; Rivera, N.; Krska, S.; Hansen, K.; Armstrong, J. D. III; Sun, Y.; Grabowski, E. J. J.; Volante, R. *OMCOS-13*, Poster, Geneva, Switzerland, **2005**. (c) Kazuhiko, M.; Xiaoyong, Z.; Takao, S. Eur. Pat. Appl. EP 1386901, **2004**.

(4) (a) Tararov, V. I.; Börner, A. *Synlett* **2005**, 203. (b) Kadyrov, R.; Riermeier, T. H. *Angew. Chem. Int. Ed.* **2003**, *42*, 5472. (c) Tararov, V. I.; Kadyrov, R.; Riermeier, T. H.; Fischer, C.; Börner, A. *Adv. Synth. Catal.* **2004**, *346*, 561. (d) Tararov, V. I.; Kadyrov, R.; Riermeier, T. H.; Börner, A. *Adv. Synth. Catal.* **2002**, *344*, 200. (e) Riermeier, T. H.; Haack, K.-J.; Dingerdissen, U.; Börner, A.; Tararov, V. I.; Kadyrov, R. Ger. Offen. DE 19933611, **2001**. (f) Kadyrov, R.; Riermeier, T. H.; Dingerdissen, U.; Tararov, V. I.; Börner, A. *J. Org. Chem.* **2003**, *68*, 4067.

(5) For (+)-ClMeOBIPHEP, see: (a) Laue, C.; Schroeder, G.; Arlt, D. Eur. Pat. Appl. EP 749973, **1996**. (b) Drießen-Hölscher, B.; Kralik, J.; Agel, F.; Steffens, C.; Hu, C. *Adv. Synth. Catal.* **2004**, *346*, 979. (c) Gerlach, A.; Scholz, U. *Speciality Chemicals Magazine* **2004**, *24*, 37. (d) Rampf, F. *Proc. Chiral USA* **2004**, Scientific update, Mayfield, UK.

(6) Using solvents such as EtOH, THF, CH_2Cl_2 or toluene led to the recovered starting material **2a**.

(7) For the reduction of β-keto esters, see: (a) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley and Sons: New York, **1994**. (b) Ojima, I. *Catalytic Asymmetric Synthesis*; VCH: Weinheim, **2000**. (c) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029. (d) Blaser, H.-U.; Pugin, B.; Spindler, F. *J. Mol. Catal. A: Chem.* **2005**, *231*, 1. (e) Ratovelomanana-Vidal, V.; Girard, C.; Touati, R.; Tranchier, J. P.; Hassine, B. B.; Genêt, J. P. *Adv. Synth. Catal.* **2003**, *345*, 261; and reference therein.

(8) Kitamura, M.; Tokunaga, M.; Noyori, R. *J. Org. Chem.* **1992**, *57*, 4053.

(9) The structure of ammonium salts of β-amino esters **5** were confirmed by ^{1}H NMR.

(10) Leflemme, N.; Dallemagne, P.; Rault, S. *Synthesis* **2002**, 1740.