CHEMISTRY
A EUROPEAN JOURNAL

FULL PAPER

DOI: 10.1002/chem.201103739

Enantioselective Synthesis of *anti*-β-Hydroxy-α-Amido Esters by Asymmetric Transfer Hydrogenation in Emulsions

Brinton Seashore-Ludlow,[a] Piret Villo,[a, b] and Peter Somfai*[a, b]

Abstract: Herein, we present two methods for an asymmetric transfer hydrogenation through the dynamic kinetic resolution of α-amido-β-ketoesters. These procedures yield the corresponding *anti*-β-hydroxy-α-amido esters in good yields and with good diastereo- and enantioselectivities. First, the scope of the reduction of α-amido-β-ketoesters by using triethylammonium formate azeotrope is examined. Then, an emulsion technology with sodium formate is explored, which allows for broader substrate scope, faster reaction times, and lower catalyst loading. Furthermore, these reactions are operationally simple and can be set up in air.

Keywords: amino acids · asymmetric synthesis · emulsions · kinetic resolution · transfer hydrogenation

Introduction

β-Hydroxy-α-amino acids and their corresponding vicinal amino alcohols are important chiral building blocks because this particular motif is embedded in numerous natural products and biologically relevant compounds, including the thiopeptide antibiotic GE2270A,[1] the papuamides,[2] cyclomarin C,[3] sphingosine,[4] and the muraymycins.[5] This molecular scaffold is also readily transformed into a variety of catalysts, ligands, and other essential synthons.[6] Given the prevalence of this type of architecture, it is then not surprising that the stereoselective synthesis of β-hydroxy-α-amino acids and their derivatives has received extensive examination.[7]

Asymmetric hydrogenation has emerged as a reliable and efficient technique for the enantioselective synthesis of α-amino acid derivatives.[8] Of particular importance for the stereoselective synthesis of β-hydroxy-α-amino acids is the use of asymmetric hydrogenation in conjunction with dynamic kinetic resolution (DKR).[9] In this sequence, two contiguous stereocenters are constructed in a single operation and, due to the stereomutation of the starting material under the reaction conditions, it is possible to produce a single diastereomer in 100% yield from a racemic starting material. Key discoveries in this area by Noyori et al.[10] and Genet et al.[11] have led to the *syn*-selective synthesis of β-hydroxy-α-amino esters from α-amido-β-ketoesters. More recently, Hamada and co-workers[12] and Genet and co-workers[13] have reported access to diastereomeric *anti*-β-hydroxy-α-amino esters from the corresponding α-amino-β-ketoester hydrochloride salts. Zhang and co-workers have also reported two examples of *anti*-selective asymmetric hydrogenation through DKR of α-phthalidamido-β-ketoesters.[14] Recently, the asymmetric hydrogenation and DKR of α-amino ketones to yield the corresponding amino alcohols has also been explored.[15]

However, the asymmetric transfer hydrogenation (ATH) through DKR of similar substrates has received much less attention. The ATH provides several advantages over traditional hydrogenation methods, because there is no need for flammable gas or high-pressure reactors. Therefore, we became interested in further exploring the ATH through DKR of α-amido-β-ketoesters. Prior to our work,[16] only two disclosures of the stereoselective ATH of α-amido-β-ketoesters through DKR leading to amino alcohols had been reported, and both indicated that the major diastereomer obtained was the *syn* isomer.[17] Herein, we further detail the scope and limitations of our previously disclosed "solvent-free" approach to *anti*-β-hydroxy-α-amino acids by using triethylammonium formate (TEAF) and disclose a new methodology with sodium formate in H_2O–CH_2Cl_2 emulsions. Importantly, this new emulsion-based approach is operationally simple because the reactions are set up in air and it allows for decreased reaction times and catalyst loadings relative to the TEAF conditions. Moreover, the emulsion conditions provide a significantly broader reaction scope, including aryl-, heteroaryl-, alkenyl-, and even alkyl-substituted α-amido-β-ketoesters.

[a] B. Seashore-Ludlow, P. Villo, Prof. P. Somfai
Organic Chemistry, Department of Chemical Science and Engineering, KTH Royal Institute of Technology
Teknikringen 36, 10044 Stockholm, Sweden
Fax: (+46) 8-791-2233
E-mail: somfai@kth.se

[b] P. Villo, Prof. P. Somfai
Institute of Technology, University of Tartu
Nooruse 1, 50411 Tartu (Estonia)

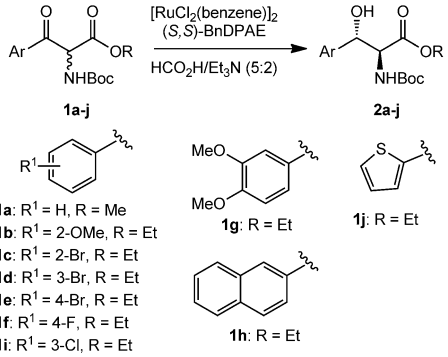
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201103739.

Results and Discussion

ATH through DKR with TEAF: Our investigations of the DKR of α-amido-β-ketoesters under transfer-hydrogenation conditions began by subjecting β-ketoester **1a** to TEAF (5:2 azeotrope) in the presence of $[RuCl_2(p\text{-cymene})]_2$ and the (*S,S*)-*N*-(*p*-toluenesulfonyl)-1,2-diphenylethanediamine ((*S,S*)-TsDPEN) ligand of Noyori and co-workers.[18] As previous reports had indicated that the major diastereomer was the *syn* isomer,[17] we were surprised to obtain the *anti*-β-hydroxy-α-amido ester **2a** in good yield and with good diastereoselectivity but low enantioselectivity.[19,20] On the basis that the synthesis of *anti*-β-hydroxy-α-amido esters by using ATH accompanied by DKR was previously unexplored, we opted to further optimize this reaction. Toward this end, a series of vicinal amino alcohol ligands was screened in the reaction in the hope that they would impart a higher enantioselectivity.[21] The optimal conditions used the less sterically encumbered $[RuCl_2(benzene)]_2$ with (1*S*,2*S*)-2-(benzylamino)-1,2-diphenylethanol ((*S,S*)-BnDPAE) as the ligand.[22]

With these conditions in hand, we then surveyed a variety of aromatic ketone substrates, **1a–j**, to determine the scope of the reaction. A wide variety of substitution patterns were tolerated on the aromatic moiety (Table 1, entries 1–8), including *ortho* subsituents, which had not been previously reported for this type of substrate (Table 1, entries 2 and 3). Both electron-rich and electron-poor aromatic substrates gave high yields and enantioselectivities (Table 1, entries 6 and 7). However, the 3-chloro substrate **1i** gave low enantioselectivity and low yield (Table 1, entry 9), which is surprising because the 3-bromo substrate **1d** gave notably higher yield and enantioselectivity (Table 1, entry 4). Heteroaromatics also performed poorly, as demonstrated by thiophene **1j**, which gave both low diastereoselectivity and enantioselectivity (Table 1, entry 10). Despite these drawbacks, the procedure remains useful for most aromatic substrates, because it is both operationally simple with no requirement for rigorous degassing procedures and it uses only the reducing agent and *i*PrOH as the solvent.

Table 1. Exploration of substrate scope.[a]



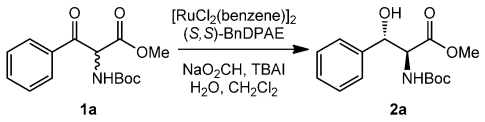
Entry	1/2	Yield[b] [%]	e.r.[c]
1	**a**	95	97:3
2	**b**	83	99:1
3	**c**	76	99:1
4	**d**	94	96:4
5	**e**	81	98:2
6	**f**	89	96:4
7	**g**	95	97:3
8	**h**	93	95:5
9	**i**	69	66:34
10	**j**	75[d]	76:24

[a] Reactions performed by heating $[RuCl_2(benzene)]_2$ (0.10 equiv) and (*S,S*)-BnDPAE (0.2 equiv) in 2-propanol ($c = 0.1$ M) at 80 °C for 1 h. After cooling, the catalyst was then added to the β-ketoester **1** (1 equiv) with HCOOH/Et_3N (5:2) complex ($c = 0.2$ M), and the mixture was stirred for 5–7 days at ambient temperature. Only a single diastereomer was visible in the ^1H NMR spectrum of the crude reaction mixture. [b] Yield of isolated product. [c] Determined by chiral HPLC. [d] Isolated as an 80:20 mixture of diastereomers.

ATH through DKR by using sodium formate in emulsions: Although the traditional conditions for ATH involve *i*PrOH or triethylammonium formate azeotropes as reducing agents in a variety of organic solvents, the performance of ATH in water or other environmentally benign reaction media has recently received more attention.[23] This is in part due to the considerable interest in greener reactions conditions, but it is also attributable to the particular effects of using water as the reaction medium,[24] including increased reaction rates.[25] However, many of the methodologies focus on the reduction of aromatic ketones or quinolines and, to our knowledge, there have been no disclosures of DKR combined with ATH in aqueous media. We were interested in improving upon our previous conditions for the synthesis of *anti*-β-hydroxy-α-amino esters, specifically in decreasing the reaction time, decreasing the catalyst loading, and widening the substrate scope, so we thought to examine aqueous reaction media for this transformation.

To this end, we began by testing the reported conditions for the ATH of aromatic ketones in water on substrate **1a**.[25] However, this resulted only in aggregation of the starting material and ligand in the aqueous media. In order to circumvent this, we explored the use of a CH_2Cl_2–water emulsion.[26] This yielded the desired product in 12 h in good yield and with good enantioselectivity, but lower diastereoselectivity (Table 2, entry 1). Encouraged by the significantly decreased reaction time (relative to 5–7 days, Table 1), we then wanted to improve the diastereoselectivity. It has been shown that the pH value can affect ATH.[27] The emulsion conditions in entry 1 in Table 2 have pH 7 and the previous conditions with TEAF, which led to excellent diastereoselectivity, proceeded at pH 4. Therefore, we first tried lowering the pH value. However, only traces of the desired product were observed at pH 5 (Table 2, entry 2). Also, an increase in the amount of Et_3N to five equivalents, effectively raising the pH value to 9, led to no increase in diastereoselectivity (Table 2, entry 3). Thus, we tried cooling the reaction in order to improve the diastereoselectivity (Table 2, entry 4). This lengthened the reaction time to three days but led to excellent yield and diastereo- and enantioselectivities.[28]

Table 2. Optimization of emulsion conditions.[a]

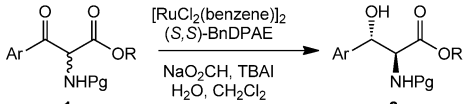


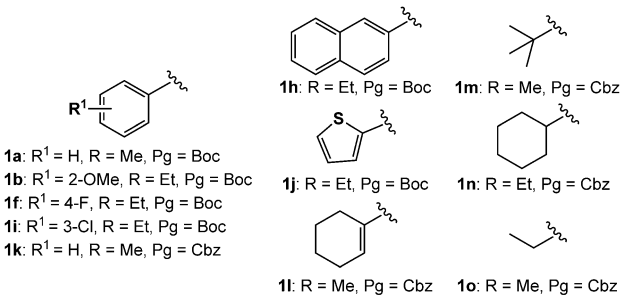
Entry	Other conditions	Yield[b] [%]	d.r.[c]	e.r.[d]
1	pH 7	97	92:8	96:4
2	pH 5	trace	–	–
3	pH 9	95	92:8	n.d.[e]
4	pH 7, −5 °C	92	>95:5	97:3

[a] Reactions performed by heating $[RuCl_2(benzene)]_2$ (0.05 equiv) and (*S*,*S*)-BnDPAE (0.1 equiv) with Et_3N (0.2 equiv) at 40 °C. When the catalyst mixture had cooled, it was added to β-ketoester **1** (1 equiv) and tetrabutylammonium iodide (TBAI; 2 equiv). An emulsion in 5 M aq. HCO_2Na (1 mL for 0.15 mmol) and CH_2Cl_2 (0.4 mL for 0.15 mmol) was formed by sonication. Reactions at room temperature were run overnight; reactions at −5 °C were run for three days. [b] Yield of isolated product. [c] Determined by ^1H NMR analysis. [d] Determined by chiral HPLC. [e] n.d.: not determined.

With competent conditions in hand, we then surveyed a range of aromatic ketones (Table 3). Again, *ortho* substituents are tolerated, as are electron-rich and electron-poor aromatics (Table 3, entries 3-5). The results under these conditions proved comparable to those with our previous TEAF method, with the advantage being that both the catalyst loading and the reaction time are reduced. More importantly, the 3-chloro substrate **1i** gave improved yield and enantioselectivity, as compared with the results under TEAF conditions (Table 3, entry 5; compare with Table 1, entry 9), and the hetereoaromatic substrate **1j** was now reduced with good enantioselectivity and diastereoselectivity as well (Table 3, entry 7; compare Table 1, entry 10). Notably, a comparison between entries 6 and 7 in Table 3 also demonstrates the improvement in enantioselectivity and diastereoselectivity that can be obtained for more recalcitrant substrates by simply decreasing the temperature. The 2-naphthyl substrate **1h** gave high enantio- and diastereoselectivities (Table 3, entry 4; compare Table 1, entry 8). We also examined the use of the CBz protecting group for the aryl substrates, but this led to a decrease in enantioselectivity, although the yield and diastereoselectivity were not diminished.[29] However, the CBz protecting group proved to be effective for alkenyl substrate **1l** and *t*Bu substrate **1m** (Table 3, entries 9 and 10). Both of these substrates were reduced in good yield and with good enantio- and diastereoselectivities. This is the first report of the synthesis of alkenyl *anti*-β-hydroxy-α-amino esters through hydrogenation in conjunction with DKR. Inspired by the encouraging results from the *t*Bu substrate **1m** and the cyclohexenyl substrate **1l**, we investigated the scope of other alkyl substrates. Unfortunately, the BnDPAE ligand in combination with $[RuCl_2(benzene)]_2$ did not impart high diastereoselectivity (Table 3, entry 11). However, when a racemic assay was conducted with $[RuCl_2(p\text{-cymene})]_2$ and the TsDPEN ligand, an excellent diastereoselectivity was observed. Thus, this ligand was employed for substrates **1n** and **1o** under the emulsion conditions, and

Table 3. Scope of the emulsion-based methodology for the ATH through DKR of α-amido-β-ketoesters.[a]



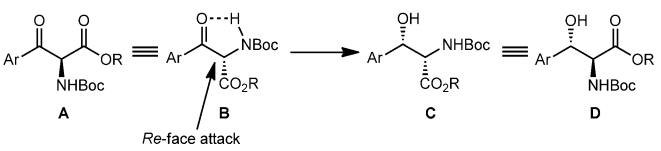


Entry	**1/2**	*T* [°C]	Yield[b] [%]	d.r.[c]	e.r.[d]
1	**a**	−5	92	>95:5	97:3
2	**b**	RT	88	94:6	97:3
3	**f**	−5	85	>95:5	98:2
4	**h**	−5	87	>95:5	96:4
5	**i**	RT	85	94:6	96:4
6	**j**	RT	79	86:14	88:12
7	**j**	−5	86	91:9	95:5
8	**k**	−5	86	>95:5	89:11
9	**l**	−5	90	95:5	97:3
10	**m**	−5	95	>95:5	99:1[e]
11	**n**	−5	93	60:40	n.d.
12[f]	**n**	−5	92	95:5	97:3
13[f]	**o**	−5	97	92:8	94:6

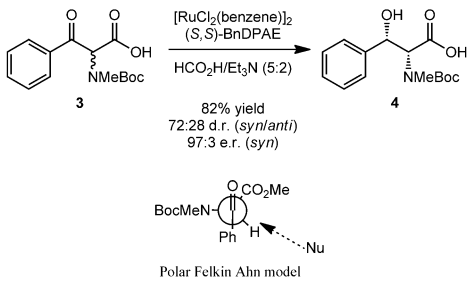
[a] Reactions performed by heating $[RuCl_2(benzene)]_2$ (0.05 equiv) and (*S*,*S*)-BnDPAE (0.1 equiv) with Et_3N (0.2 equiv) at 40 °C. When the catalyst mixture had cooled, it was added to β-ketoester **1** (1 equiv) and TBAI (2 equiv). An emulsion in 5 M aq. HCO_2Na (1 mL for 0.15 mmol) and CH_2Cl_2 (0.4 mL for 0.15 mmol) was formed by sonication. Reactions were run for 3–5 days. [b] Yield of isolated product. [c] Determined by ^1H NMR analysis. [d] Determined by chiral HPLC. [e] Determined by Mosher ester analysis. [f] Reactions run with $[RuCl_2(p\text{-cymene})]_2$ (0.05 equiv) and (*S*,*S*)-TsDPEN (0.1 equiv).

this reaction resulted in excellent yields, diastereoselectivities, and enantioselectivities (Table 3, entries 12 and 13).

As the diastereoselectivity of these reactions differs from that in the previous reports of ATH[17] and traditional hydrogenation reactions[10,13b] of similar substrates, we were also interested in determining the origin of the observed diastereofacial selectivity. We believe that the diastereofacial discrimination can be rationalized by invoking a cyclic intermediate **B**, in which a hydrogen bond exists between the N–H and the carbonyl moiety (Scheme 1).[30] Hydride addition from the least hindered face of the carbonyl group then



Scheme 1. Rationalization for the observed diastereoselectivity.



Scheme 2. Reduction of *N*-Me,*N*-Boc-protected substrate **3** and a model for the observed diastereoselectivity.

leads to the observed diastereomer **C**. To corroborate this proposal the *N*-Me,*N*-Boc substrate **3** was also synthesized and subjected to ATH conditions with TEAF (Scheme 2). This yielded amino alcohol **4** in 82% yield (72:28 d.r.), with the *syn* diastereomer (97:3 e.r.) as the major diastereomer.[31] Previous reports of the ATH in conjunction with DKR of α-methoxy-β-ketoesters[32] and *N*-Me,*N*-Cbz-protected α-amido-β-ketoesters[17b] also yield the *syn* diastereomer as the major diastereomer. In all of these substrates, the capacity for intramolecular hydrogen bonding between a proton on the α heteroatom and the carbonyl O atom is precluded; thus, the polar Felkin–Anh model can be used to accurately predict the observed *syn* selectivity.[33]

Conclusion

In conclusion, we have developed two different methods for the reduction of α-amido-β-ketoesters to yield *anti*-β-hydroxy-α-amino esters in good yields and with good diastereo- and enantioselectivities. The first method uses TEAF as the reducing agent and works well for aryl substrates. We then explored an emulsion-based method for the ATH in conjunction with DKR and with water as a solvent. This technique gave a wider substrate scope, including aryl, heteroaryl, alkenyl, and alkyl substrates. This breadth of reaction scope for such substrates has not been detailed before, as previous methods require separate conditions for alkyl and aryl substrates. To our knowledge, this is the first synthesis of alkenyl *anti*-β-hydroxy-α-amino esters by using hydrogenation combined with DKR. We were able to reduce both the catalyst loading and the reaction time from those in our previous report. Notably, both techniques discussed herein are operationally simple because they avoid the use of flammable hydrogen gas and can be run in air without rigorous degassing of the solvent.

Experimental Section

General procedure for the asymmetric transfer hydrogenation procedure with the azeotrope: First, the catalyst was prepared by stirring $[RuCl_2(benzene)]_2$ (0.1 equiv) and the (*S,S*)-BnDPAE ligand (0.2 equiv) in *i*PrOH (200 μL for 0.17 mmol substrate) at 80 °C for 1 h. After the catalyst mixture had been allowed to cool to ambient temperature, the catalyst was transferred into a vial containing the transfer-hydrogenation substrate (1 equiv) and the $HCOOH/Et_3N$ (5:2) complex (800 μL for 0.17 mmol substrate). The mixture was then stirred at room temperature for 7 days. (No other solvent was used.) The mixture was purified by flash chromatography over silica (10–20% EtOAc/hexanes as the eluent) to give the product.

For the synthesis of the racemic amino alcohols for the *ee* assay, the TsDPEN ligand (0.2 equiv) and $[RuCl_2(p\text{-cymene})]_2$ (0.1 equiv) were used as the catalyst precursors and the reaction was run at 45 °C by following the procedure outlined above.

General procedure for the asymmetric transfer hydrogenation under emulsion conditions: First, the catalyst was prepared by stirring the ruthenium dimer ($[RuCl_2(benzene)]_2$ or $[RuCl_2(p\text{-cymene})]_2$; 0.05 equiv) and the ligand (*S,S*-BnDPAE or *S,S*-TsDPEN; 0.1 equiv) in CH_2Cl_2 (0.25 mL) with Et_3N (0.2 equiv) at 40 °C for 1 h. The catalyst was then transferred into a precooled (0 °C) vial containing the substrate (1 equiv, 0.15 mmol) and tetrabutylammonium iodide (2 equiv). Additional CH_2Cl_2 (0.25 mL) was used to quantitatively transfer the catalyst. A 5 M sodium formate solution (1 mL) was then added to the vial. The vial was sonicated (the sonicator bath was precooled to 0 °C) and then set to stir in a cryostat bath at −5 °C. The reaction was monitored by TLC and stirred until consumption of the starting material (3–5 days). The reaction mixture was diluted with CH_2Cl_2 and water, and the layers were separated. The aqueous layer was extracted three times with CH_2Cl_2, and then the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude residue was then subjected to column chromatography.

Acknowledgements

The authors would like to thank the Knut and Alice Wallenberg Foundation, the Swedish Research Council, and the Estonian Science Foundation (grant no. 7808) for funding.

[1] K. C. Nicolaou, D. H. Dethe, G. Y. C. Leung, B. Zou, D. Y.-K. Chen, *Chem. Asian J.* **2008**, *3*, 413–429.
[2] P. W. Ford, K. R. Gustafson, T. C. McKee, N. Shigematsu, L. K. Maurizi, L. K. Pannell, D. E. Williams, E. Dilip de Silva, P. Lassota, T. M. Allen, R. Van Soest, R. J. Andersen, M. R. Boyd, *J. Am. Chem. Soc.* **1999**, *121*, 5899–5909.
[3] Y. Hamada, T. Shioiri, *Chem. Rev.* **2005**, *105*, 4441–4482, and references therein.
[4] R. J. B. H. N. van den Berg, H. van den Elst, C. G. N. Korevaar, J. M. F. G. Aerts, G. A. van der Marel, H. S. Overkleeft, *Eur. J. Org. Chem.* **2011**, *2011*, 6685–6689, and references therein.
[5] L. A. McDonald, L. R. Barbieri, G. T. Carter, E. Lenoy, J. Lotvin, P. J. Petersen, M. M. Siegel, G. Singh, R. T. Williamson, *J. Am. Chem. Soc.* **2002**, *124*, 10260–10261.
[6] a) D. J. Ager, I. Prakash, D. R. Schaad, *Chem. Rev.* **1996**, *96*, 835–876; b) M. T. Reetz, *Angew. Chem.* **1991**, *103*, 1559–1573; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1531–1546.
[7] a) R. M. Williams, C. M. Burnett in, *Asymmetric Synthesis and Application of α-Amino Acids, Vol. 1009*, American Chemical Society, **2009**, pp. 420–442; b) C. Nájera, J. M. Sansano, *Chem. Rev.* **2007**, *107*, 4584–4671; c) S. C. Bergmeier, *Tetrahedron* **2000**, *56*, 2561–2576.
[8] a) H. Shimizu, I. Nagasaki, N. Sayo, T. Saito in *Asymmetric Synthesis and Application of α-Amino Acids, Vol. 1009*, American Chemical Society, **2009**, pp. 203–226; b) T. Ohkuma, R. Noyori in *Transition Metals for Organic Synthesis*, 2nd ed. (Eds.: M. Beller, C. Bolm), **2008**, pp. 29–113; c) V. Ratovelomanana-Vidal, J.-P. Genêt, *Can. J. Chem.* **2000**, *78*, 846–851.
[9] a) E. Vedejs, M. Jure, *Angew. Chem.* **2005**, *117*, 4040–4069; *Angew. Chem. Int. Ed.* **2005**, *44*, 3974–4001; b) H. Pellissier, *Tetrahedron*

2003, *59*, 8291–8327; c) R. Noyori, M. Tokunaga, M. Kitamura, *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36–55.

[10] R. Noyori, T. Ikeda, T. Ohkuma, M. Widhalm, M. Kitamura, H. Takaya, S. Akutagawa, N. Sayo, T. Saito, *J. Am. Chem. Soc.* **1989**, *111*, 9134–9135.

[11] J. P. Genet, C. Pinel, S. Mallart, S. Juge, S. Thorimbert, J. A. Laffitte, *Tetrahedron: Asymmetry* **1991**, *2*, 555–567.

[12] a) T. Maeda, K. Makino, M. Iwasaki, Y. Hamada, *Chem. Eur. J.* **2010**, *16*, 11954–11962; b) Y. Hamada, K. Makino in *Asymmetric Synthesis and Application of α-Amino Acids, Vol. 1009*, American Chemical Society, **2009**, pp. 227–238; c) K. Makino, T. Goto, Y. Hiroki, Y. Hamada, *Tetrahedron: Asymmetry* **2008**, *19*, 2816–2828; d) K. Makino, M. Iwasaki, Y. Hamada, *Org. Lett.* **2006**, *8*, 4573–4576; e) K. Makino, T. Goto, Y. Hiroki, Y. Hamada, *Angew. Chem.* **2004**, *116*, 900–902; *Angew. Chem. Int. Ed.* **2004**, *43*, 882–884.

[13] a) C. Mordant, P. Dunkelmann, V. Ratovelomanana-Vidal, J.-P. Genet, *Chem. Commun.* **2004**, 1296–1297; b) C. Mordant, P. Dünkelmann, V. Ratovelomanana-Vidal, J.-P. Genet, *Eur. J. Org. Chem.* **2004**, 3017–3026.

[14] A. Lei, S. Wu, M. He, X. Zhang, *J. Am. Chem. Soc.* **2004**, *126*, 1626–1627.

[15] J.-H. Xie, S. Liu, W.-L. Kong, W.-J. Bai, X.-C. Wang, L.-X. Wang, Q.-L. Zhou, *J. Am. Chem. Soc.* **2009**, *131*, 4222–4223.

[16] B. Seashore-Ludlow, P. Villo, C. Häcker, P. Somfai, *Org. Lett.* **2010**, *12*, 5274–5277.

[17] a) L. H. Bourdon, D. J. Fairfax, G. S. Martin, C. J. Mathison, P. Zhichkin, *Tetrahedron: Asymmetry* **2004**, *15*, 3485–3487; b) B. Mohar, A. Valleix, J.-R. Desmurs, M. Felemez, A. Wagner, C. Mioskowski, *Chem. Commun.* **2001**, 2572–2573.

[18] T. Ikariya, K. Murata, R. Noyori, *Org. Biomol. Chem.* **2006**, *4*, 393–406.

[19] The relative stereochemistry was determined by conversion into the corresponding oxazolidinone and ^{1}H NMR analysis of the relevant *J*-coupling values. The absolute stereochemistry was determined by optical rotation. See the Supporting Information for details. This was further corroborated in reference [20].

[20] Z. Liu, C. S. Shultz, C. A. Sherwood, S. Krska, P. G. Dormer, R. Desmond, C. Lee, E. C. Sherer, J. Shpungin, J. Cuff, F. Xu, *Tetrahedron Lett.* **2011**, *52*, 1685–1688.

[21] a) K. Everaere, A. Mortreux, M. Bulliard, J. Brussee, A. van der Gen, G. Nowogrocki, J.-F. Carpentier, *Eur. J. Org. Chem.* **2001**, 275–291; b) K. Everaere, J.-F. Carpentier, A. Mortreux, M. Bulliard, *Tetrahedron: Asymmetry* **1999**, *10*, 4083–4086.

[22] See reference [16] for further details on the optimization and on the synthesis of (*S*,*S*)-BnDPAE.

[23] a) X. Wu, J. Xiao, *Chem. Commun.* **2007**, 2449–2466; b) K. Ahlford, H. Adolfsson, *Catal. Commun.* **2011**, *12*, 1118–1121; c) H. Lundberg, H. Adolfsson, *Tetrahedron Lett.* **2011**, *52*, 2754–2758; d) O. Soltani, M. A. Ariger, H. Vázquez-Villa, E. M. Carreira, *Org. Lett.* **2010**, *12*, 2893–2895; e) Y. Ma, H. Liu, L. Chen, X. Cui, J. Zhu, J. Deng, *Org. Lett.* **2003**, *5*, 2103–2106; f) U. M. Lindström, *Chem. Rev.* **2002**, *102*, 2751–2772.

[24] R. N. Butler, A. G. Coyne, *Chem. Rev.* **2010**, *110*, 6302–6337.

[25] X. Wu, X. Li, W. Hems, F. King, J. Xiao, *Org. Biomol. Chem.* **2004**, *2*, 1818–1821.

[26] W. Wang, Z. Li, W. Mu, L. Su, Q. Wang, *Catal. Commun.* **2010**, *11*, 480–483.

[27] X. Wu, X. Li, F. King, J. Xiao, *Angew. Chem.* **2005**, *117*, 3473–3477; *Angew. Chem. Int. Ed.* **2005**, *44*, 3407–3411.

[28] The reaction has been run on the 1.4 mmol scale with **1a** to yield **2a** in 89% yield after isolation and with >95:5 d.r. and 97:3 e.r.

[29] A similar observation is found in reference [20].

[30] a) P. Restorp, P. Somfai, *Org. Lett.* **2005**, *7*, 893–895; b) S.-i. Kiyooka, Y. Shiomi, H. Kira, Y. Kaneko, S. Tanimori, *J. Org. Chem.* **1994**, *59*, 1958–1960.

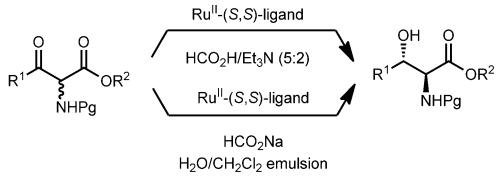
[31] The relative stereochemistry was determined by removal of the *N*-Boc protecting group and subsequent conversion into the oxazolidinone. See the Supporting Information for details. The absolute stereochemistry has not been determined.

[32] D. Cartigny, K. Püntener, T. Ayad, M. Scalone, V. Ratovelomanana-Vidal, *Org. Lett.* **2010**, *12*, 3788–3791.

[33] V. J. Cee, C. J. Cramer, D. A. Evans, *J. Am. Chem. Soc.* **2006**, *128*, 2920–2930.

Received: November 28, 2011
Published online: ■■ ■■, 2012

Asymmetric Synthesis



Emulsions do the trick! A new method is disclosed for an asymmetric transfer hydrogenation combined with a dynamic kinetic resolution of α-amido-β-ketoesters to yield the corresponding *anti*-β-hydroxy-α-amido esters (see scheme). This reaction has a broad substrate scope, including alkyl, alkenyl, and aryl substrates, and is performed in aqueous media.