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Highly enantioselective synthesis of anti aryl β-hydroxy α-amino esters via DKR transfer hydrogenation

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ABSTRACT

An efficient preparation of highly enantiomerically enriched aryl β-hydroxy α-amino esters via dynamic kinetic resolution (DKR), asymmetric transfer hydrogenation of α-amino β-keto esters is described. The *anti* β-hydroxyl α-amino esters were obtained both in high yields and high diasteroselectivity. The observed high *anti* selectivity is inconsistent with the previous results in literature. The absolute stereochemistry of the aryl β-hydroxy α-amino esters was unambiguously confirmed via chemical derivatization as well as Vibrational Circular Dichroism (VCD) techniques.

1. Introduction

Recently, asymmetric hydrogenation via dynamic kinetic resolution (DKR) has received significant attention in both industry and academia, due to its attractive capability to simultaneously set up two adjacent stereogenic centers in a single transformation from racemic substrates.[1] The use of chiral ruthenium catalysts for DKR asymmetric hydrogenation of α-amino β-keto esters was first reported by Noyori.[2] High diastereo- and enantio-selectivities of *syn* β-hydroxyl α-amino esters were obtained under these conditions; however, prolonged reaction time and high pressure were required.[2] Since then, a number of modified conditions applying transition metal catalysts for DKR asymmetric hydrogenation of α-amino β-keto esters have been developed.[3] Despite these efforts, only a few asymmetric transfer hydrogenation reactions of α-amino β-keto esters have been reported to date.[4]

During our course of studies on the synthesis of amino alcohols, we became interested in preparing amino alcohol esters such as **2** via DKR asymmetric transfer hydrogenation. Treatment of ketone **1** with $(RuCl_2C_6H_6)_2$/(−)-pseudoephedrine/HCO_2H/NEt_3 in *i*-PrOH led to a complete conversion and afforded **3** in 85% ee and 14:1 diastereoselectivity; similarly 15:1 diastereoselectivity was observed when Ts-DPEN-Ru/HCO_2H/NEt_3 system was applied without optimization (Scheme 1). Surprisingly, the preliminary data showed the relative stereochemistry observed was inconsistent with the results reported in prior publications,[4a,c] where *syn* β-hydroxyl α-amino ester **2** was claimed to form under similar conditions.

Thus, studies on elucidation of the relative stereochemistry of product **3** via derivatization and alternative synthesis were initiated. Product **3**, obtained from transfer hydrogenation, was converted into alcohol **5** by protection with 2,2-dimethoxypropane in the presence of $BF_3{\cdot}Et_2O$ followed by a reduction of the corresponding ester **4** with lithium borohydride in THF. The observed NOE effect between the aromatic protons and CH_2 protons in **5** clearly showed an *anti* relationship of benzyl alcohol and NHBoc amine, which confirmed the *anti* relative stereochemistry of the DKR reduction product **3**.[5]

To further verify the *anti* stereochemistry of **3** by eliminating a concern about the possibility of epimerization during the formation of **4** under acidic conditions, ester **3** was reduced to amino diol **6** by $LiAlH_4$ in tetrahydrofuran at 0 °C (Scheme 2). However, diol **6** did not match either with *tert*-butyl[((1*S*,2*S*)-1,3-dihydroxy-1-phenylpropan-2-yl)]carbamate (**7**) or its enantiomer *ent*-**7** on achiral HPLC (see Supplementary data), both of which were prepared from commercially available (1*R*,2*R*)-2-amino-1-phenylpropan-1,3-diol,

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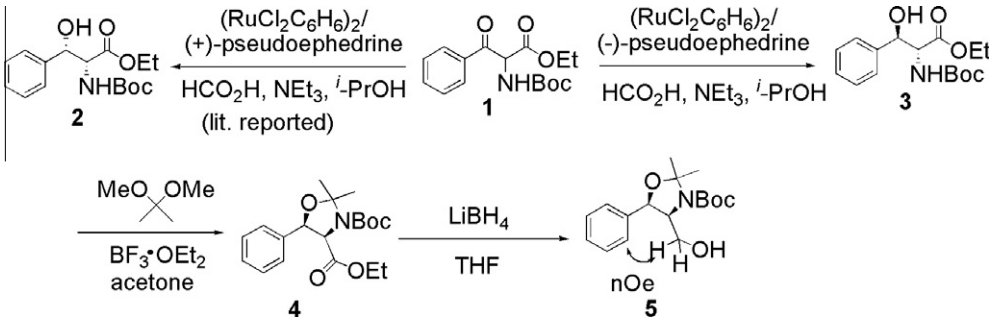
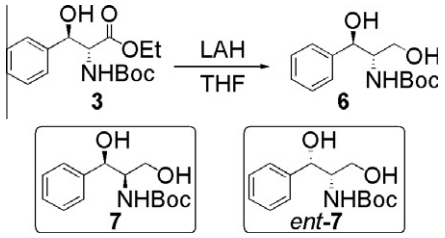


Scheme 1.



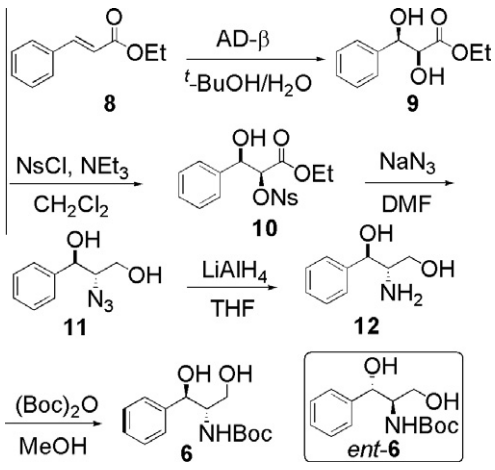
Scheme 2.

or its corresponding enantiomer, in the presence of $(Boc)_2O$ in methanol, respectively. The mismatch of **6** to *syn* **7** and *ent*-**7** is in agreement with the *anti* stereochemistry assignment for **3**.[6]

At this point, studies were required to unambiguously determine the absolute stereochemistry of **3**. Due to difficulties encountered from attempts to obtain X-ray quality single crystals of derivatives of **3**, we decided to correlate the absolute stereochemistry of **3** to alcohol **6**, which could be synthesized alternatively by applying the well-established Sharpless dihydroxylation protocol.[7] Therefore, treatment of (*E*)-ethyl cinnamate with AD-mix β led to the formation of *syn*-diol **9**, which was transformed into amino diol **12** following Halies's procedure (Scheme 3).[8,9] Selective reaction of diol **9** with nosyl chloride afforded nosylate **10**, which was then treated with sodium azide and provided azide **11** through S_N2 displacement. Reduction of azide **11** with lithium aluminum hydride gave fully reduced amino diol **12**, which was protected with $(Boc)_2O$ to afford NHBoc diol **6**. Similarly, *ent*-**6** was synthesized starting with the treatment of the corresponding (*E*)-ethyl cinnamate with AD-mix α. With all four diastereomers **6**, *ent*-**6**, **7,** and *ent*-**7** in hand, a chiral Supercritical Fluid Chromatography (SFC) assay to separate these isomers was developed. Clearly, the diol **6** prepared from derivatization of the transfer hydrogenation product co-eluted with **6** prepared from AD-mix β (see Supplementary data). In conclusion, the absolute stereochemistry of the *anti* β-hydroxyl α-amino ester **3** obtained under our DKR transfer hydrogenation conditions was (2*R*,3 *R*). This is inconsistent with the previously reported assignment of stereochemistry of **2**.t[4a] In that publication the stereochemistry of **2** was assigned by the comparison of optical rotation, a method that has some limitations in determining the absolute stereochemistry of substrates containing more than one stereogenic center.

To further confirm the absolute stereochemical assignment, Vibrational Circular Dichroism (VCD) measurements were applied on ester **3**.[10a] VCD is a useful method for determining the absolute configuration of chiral molecules.[10b] As a result, VCD measurements also confirmed the assignments of absolute stereochemistry from chemical derivation (Fig. 1).

With the establishment of the absolute stereochemistry of the transfer hydrogenation product **3**, we turned our attention to optimization of the reaction conditions. Thus, the Ts-DPEN-$RuCl_2$/HCO_2H/NEt_3 system was applied.[4b,c] We were pleased to find that significant improvement of the ee from our initial results with the Ts-DPEN-Ru/HCO_2H/NEt_3 system were achieved by using CH_2Cl_2 as a co-solvent, although the diastereoselectivity eroded slightly to ca. 8:1 (Table 1, entry 3). However, the diastereoselectivity could be remedied by either changing the ratio of HCO_2H:NEt_3 to 1:3 (Table 1, entry 4) or by performing a slow addition of formic acid over 5 h (Table 1, entry 5). It was believed that the slow addition



Scheme 3.

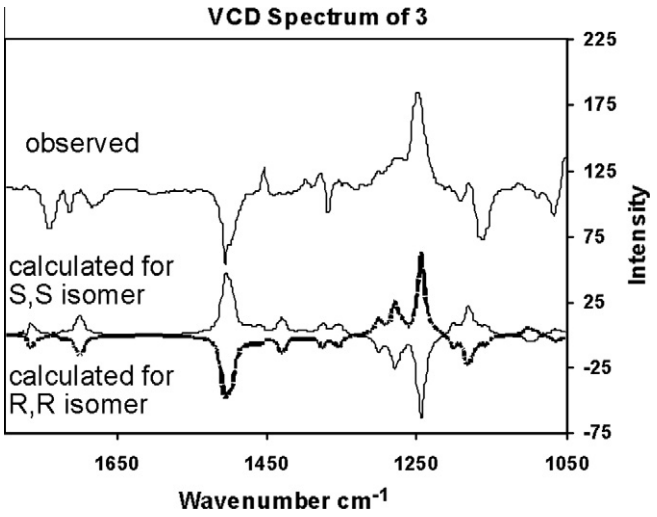


Figure 1. Measured and calculated VCD spectra for **3**.

Table 1
Optimization of dynamic kinetic resolution (DKR) transfer hydrogenation of **1**

Entries	Ligand	Solvent	Conditions	Conv (%)	dr[a]	ee (anti)[a]
1	Ts-DPEN	HCO_2H:NEt_3 (5:2)		100	15:1	45%
2	Ts-DPEN	HCO_2H:NEt_3 (3:4)		100	21:1	42%
3	Ts-DPEN	CH_2Cl_2	HCO_2H:NEt_3 (5:2)	77	8:1	75%
4	Ts-DPEN	CH_2Cl_2	HCO_2H:NEt_3 (1:3)	100	28:1	80%
5	Ts-DPEN	CH_2Cl_2	Addition of HCO_2H over 5 h HCO_2H:NEt_3 (5:2)	100	31:1	82%
6	F_5PhSO_2DPEN	CH_2Cl_2	HCO_2H:NEt_3 (5:2)	100	40:1	73%
7	F_5PhSO_2DPEN	CH_2Cl_2	Addition of HCO_2H over 5 h HCO_2H:NEt_3 (5:2)	100	42:1	91%

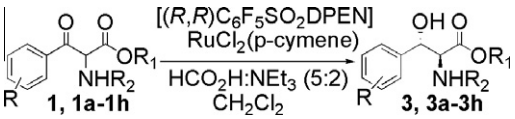
[a] SFC conditions: Chiralpak IC column, 250 × 4.6 mm, 5 μm particle size, modified with MeOH, 2 mL/min, 35 °C, 200 bar, UV detector: λ 210 nm.

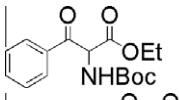
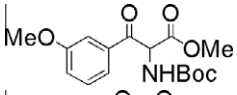
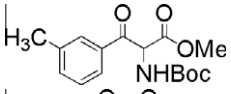
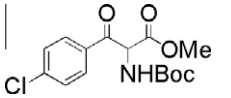
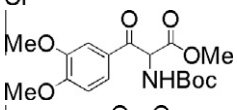
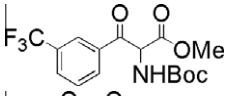
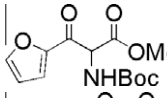
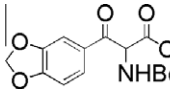
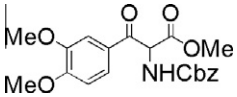
of formic acid or the use of more NEt_3 allowed better balancing of the kinetics of the epimerization vs. the enantioselective reduction in this DKR process. Finally, we found that utilization of the more electron deficient perfluorophenyl ligand gave an even further boost in selectivity (entry 7) under our optimized conditions.[4b,c]

With the optimized reaction conditions in hand, we further explored the generality of the reaction scope. A variety of different substrates were studied (Table 2). The reaction proceeded smoothly for substrates with both electron donating (Table 2, entries 2, 5, and 8), and electron withdrawing groups (Table 2, entries 4 and 6) with excellent ee and diastereoselectivity. Moderate enantio- and diastereo-selectivities were obtained when the phenyl group was replaced with a furyl group (Table 2, entry 7). In addition, the sense of asymmetric induction was not affected when Boc protection on nitrogen was replaced with a Cbz group (Table 2, entries 5 and 9).[11] The absolute stereochemistry of the product **3h** from entry 9 (Table 2) was also confirmed on chiral SFC after converting it to the corresponding Boc protected product **3d** through hydrogenation and Boc protection with Pd/C in MeOH in the presence of $(Boc)_2O$.

In summary, an asymmetric method for the preparation of *anti* β-hydroxyl α-amino esters via DKR transfer hydrogenation is reported. Our results showed that *anti* β-hydroxyl α-amino esters were obtained from performing DKR asymmetric transfer hydrogenation on α-amino β-keto esters under these conditions. The absolute stereochemistry of the products was unambiguously elucidated by both chemical derivatization and VCD spectroscopy.

Table 2
Exploration of substrate scope



Entry	Substrate	Yield[a] (%)	dr[b]	ee[b] (%)
1		90	41.3:1	91
2		89	24.2	92
3		90	23.7	84
4		96	23.1	97
5		87	27.0	90
6		89	>99:1	80
7		99	6:1	72
8		80	28.9:1	92
9		82	24.7	83

[a] See typical reaction procedures.
[b] dr and ee were determined by SFC.

2. Typical experimental procedures

To a N_2 degassed solution of α-amino β-keto ester **1** (200 mg, 0.65 mmol) and $[(R,R)\text{-}C_6F_5SO_2DPEN]RuCl_2(p\text{-cymene})_2$ (6.9 mg, 0.00976 mmol) in dichloromethane (1 mL) was added triethylamine (0.09 mL, 0.65 mmol). The reaction solution was heated to 35 °C and a N_2 degassed solution of formic acid (0.06 mL, 1.63 mmol) in dichloromethane (1 mL) was added via syringe pump over 5 h. The resulting reaction solution was agitated for additional 13–17 h at 35 °C. The crude mixture was purified by silica gel chromatography eluting with Hex/EtOAc (5:1–2:1) to afford **3** (181 mg, 90%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.35–7.21 (m, 5H), 5.37 (d, J = 8.0 Hz, 1H), 5.14 (br s, 1H), 4.65 (br s, 1H), 4.09 (dd, J = 14.2, 7.1 Hz, 2H), 1.41 (s, 9H), 1.11 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 156.4, 139.5, 128.3, 128.0, 126.2, 80.6, 75.0, 74.0, 61.7, 61.0, 60.5, 59.9, 28.4, 14.0; HRMS m/z: Calcd for $C_{16}H_{23}NaNO_5$: 332.1474; found: 332.1473.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.01.146.

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3. For recent examples, see: (a) Makato, H.; Tetsuro, S.; Yasufumi, O. *Org. Lett.* **2009**, *11*, 4664; (b) Tone, H.; Buchotte, M.; Mordant, C.; Guittet, E.; Ayad, T.; Ratovelomanana-vidal, V. *Org. Lett.* **2009**, *11*, 1995; (c) Makino, K.; Goto, T.;

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5. Determination of the relative stereochemistry of compound **4** by NOE effects was not conclusive.
6. cf. Ref. 4e, the assignment of an *anti* stereochemistry of β-hydroxy-α-amino esters were also obtained through coupling constants comparison of corresponding cyclic carbamate after the removal of Boc group followed by treatment of the corresponding product with triphosgene. However, absolute stereochemistry assignment was not determined.
7. Sharpless, K. B.; Amberg, W.; Youssef, L. B.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768.
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9. Even though a small amount of epimerization may happen at the α-position of ester, it is unlikely to epimerize the stereogenic center at the benzylic position. Therefore, we can correlate four isomers with ester **3** for a comparison to assign the absolute stereochemistry.
10. For VCD method and recently applications, see: (a) Nafie, L. A.; Diem, M.; Vidrine, D. W. *J. Am. Chem. Soc.* **1979**, *101*, 496; (b) Yang, G.; Tran, H.; Shi, W.; Lowary, T. L.; Xu, Y. *Chirality* **2010**, *22*, 734. and the references cited therein.
11. cf. Refs. 4b and 4c, *syn* β-hydroxyl α-amino esters were reported when Cbz protected substrate **1h** was used under similar conditions.