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# Dynamic kinetic resolution: an efficient route to *anti* α-amino-β-hydroxy esters *via* Ru-SYNPHOS® catalyzed hydrogenation†

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**The Ru(II)-catalyzed hydrogenation of α-amino-β-keto esters as their hydrochloride salts affords preparation of the corresponding *anti* α-amino-β-hydroxy esters under mild conditions with high diastereoselectivities and enantioselectivities *via* dynamic kinetic resolution.**

Ruthenium-promoted hydrogenation *via* Dynamic Kinetic Resolution (DKR) has turned out to be an elegant and powerful method of simultaneously controlling two adjacent stereogenic centers with high levels of selectivity in a single chemical operation.[1] This reaction was first reported independently by Noyori *et al.*[2] and Genet *et al.*[3] in 1989 for the synthesis of threonine. The hydrogenation of α-acetamido-β-keto esters and more generally of non-cyclic α-amido-β-keto esters[4] with Ru(II)-catalysts affords, under optimized conditions, the corresponding *syn* β-hydroxy esters with excellent diastereoisomeric and enantiomeric excesses. The stereochemical course of the hydrogenation reaction is highly dependent on the nature of the configurationally labile group borne at the α-position of the β-keto ester. α-Chloro-[5] or cyclic α-alkyl[1,2,6]-β-keto esters were reduced to the *anti* α-substituted β-hydroxy esters. The first example of an efficient DKR of an α-alkyl-β-keto ester was observed by our group during preliminary studies on Dolastatin 10:[7] the *anti* β-hydroxy-α-methyl ester was isolated with high stereoselectivity after hydrogenation under mild conditions of the β-keto ester derived from the hydrochloride salt of (*S*)-proline.

Inspired by these encouraging results and as part of our continuing interest in stereoselective hydrogenation, we set out to achieve high *anti* diastereoselectivity by asymmetric Ru(II)-promoted hydrogenation of a β-keto ester α-substituted by a $NH_2$.HCl group displaying non-chelating properties towards the metal.

Moreover, this 'α-amino-β-hydroxy' fragment can be found in numerous natural or synthetic molecules with an *anti* configuration. For example, 3-hydroxyleucine methyl ester is a key unit of many peptide antibiotics such as (+)-lactacystin (Fig. 1), a neurotrophic agent,[8] while D-*erythro*-dihydrosphingosine constitutes the amino portion of symbioramide, a ceramide, which exhibits antileukemic activity.[9] Thus, for all organic chemists, it remains a challenge to synthesize one specific isomer of medically important compounds.

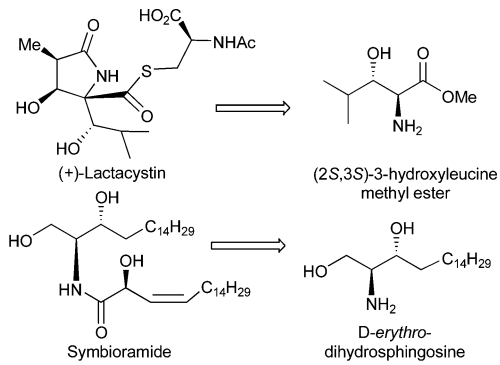
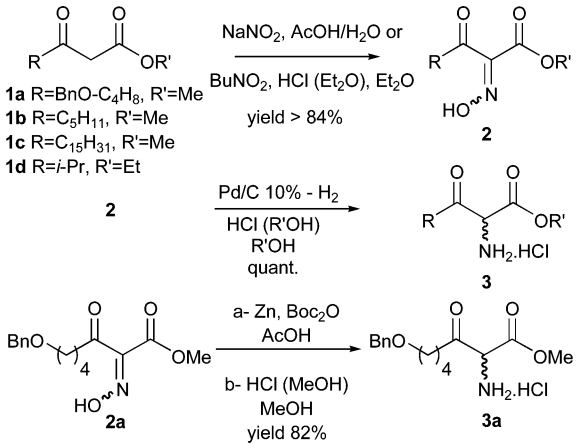



**Fig. 1** Examples of molecules with *anti* α-amino-β-hydroxy fragment.

In this paper, we wish to report a straightforward and efficient synthesis of *anti* α-amino-β-hydroxy esters based on the DKR of the hydrochloride salts of α-amino-β-keto esters, which, until very recently, has not been reported.[10] In this context, we examined the ruthenium-mediated hydrogenation of a few substrates of synthetic interest. The hydrogenation substrates were easily prepared according to the general scheme depicted below (Scheme 1). The α-amino-β-keto ester hydrochloride salts **3** were obtained from the corresponding α-hydroxyimino-β-keto esters **2**, in turn prepared from β-keto esters **1** according to classic procedures. The reduction of **2** with Pd/C in the presence of a methanolic or ethanolic solution of hydrochloric acid under atmospheric pressure of hydrogen led to the hydrochloride salts **3** (except **3a**) in quantitative yields. Because of the benzyloxy function of the substrate **2a**, the hydrochloride salt **3a** was formed by adding hydrochloric acid to the intermediate α-*tert*-butoxycarbonyl-β-keto ester.




**Scheme 1** Synthesis of the hydrogenation substrates **3**.

Following our previous results obtained with the β-keto-α-methyl ester derived from (*S*)-proline hydrochloride,[7] the preliminary hydrogenation reactions were run in an alcoholic solvent (R′OH) with compounds **3c** and **3d** as representative precursors of 3-hydroxyleucine and dihydrosphingosine, respectively. The trials were performed under mild conditions: 12 bar of hydrogen at 50 °C for 24 h (Table 1, entries 1 and 4), in the presence of the *in situ* generated chiral catalyst[11] [Ru(MeO–BIPHEP)$Br_2$]. The *anti* configuration of the resulting α-amino-β-hydroxy ester, isolated with good yield after reprotection of the crude hydrogenated product with benzoic anhydride, was determined by comparison with the well-known *syn* products and authentic samples.[12] The main results are summarized in Table 1.

For substrate **3d**, an excellent diastereoselectivity (98%) and a significant level of enantioselectivity (87%) were observed in ethanol (entry 1). These results remained unchanged regardless of the hydrogen pressure (50 or 100 bar, entries 2 and 3). The hydrogenation proceeded smoothly with high diastereoselectivity (93%) even with the long-chain substrate **3c** though the enantioselectivity was poor (39%, entry 4). Higher hydrogen pressure (50

† Electronic supplementary information (ESI) available: experimental details for the preparation of compounds **1**–**4**. See http://www.rsc.org/suppdata/cc/b4/b401631a/

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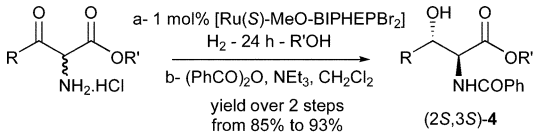
bar, entry 5) did not improve the e.e. (36%) and only a small increase in enantioselectivity (52%) was observed when the hydrogenation was carried out at 100 °C (entry 6).

**Table 1** Hydrogenation reaction[a] of compounds **3c** and **3d** in alcoholic solvent

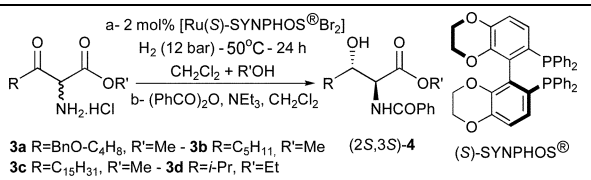



| Entry | Substrate | Solvent (R′OH) | $P(H_2)$/ bar | $T$/°C | *d.e.*[b] (%) *anti* | *e.e.*[b] (%) (2*S*,3*S*) |
|---|---|---|---|---|---|---|
| 1 | **3d** R=*i*Pr | EtOH | 12 | 50 | 98 | 87 |
| 2 | **3d** R=*i*Pr | EtOH | 50 | 50 | 98 | 87 |
| 3 | **3d** R=*i*Pr | EtOH | 100 | 50 | 98 | 87 |
| 4 | **3c** R=$C_{15}H_{31}$ | MeOH | 12 | 50 | 93 | 39 |
| 5 | **3c** R=$C_{15}H_{31}$ | MeOH | 50 | 50 | 90 | 36 |
| 6 | **3c** R=$C_{15}H_{31}$ | MeOH | 12 | 100 | 93 | 52 |

[a] Conversions rates were determined by $^1$H NMR (MeOD) spectroscopy before reprotection; all reactions were complete. [b] *d.e.* and *e.e.* were determined by HPLC analysis after reprotection.

Based on these first results, the reaction solvent was changed to slow down the reaction rate in order to favor a better discrimination by the catalyst and improve the chiral induction. All hydrogenations of the hydrochloride salts **3** were then conducted in dichloromethane with a small percentage of alcoholic solvent (9%) to maintain homogeneity. 2 mol% of catalyst [Ru(diphosphine)$Br_2$] were required to ensure complete conversions, the other conditions remaining unchanged (*i.e.* under 12 bar of hydrogen at 50 °C for 24 h). This combination turned out to be the most appropriate to achieve high *anti* diastereoselectivity and enantioselectivity for both linear and branched α-amino-β-keto ester hydrochloride salts **3**, regardless of the length or the hindrance of the side chain and with good to excellent yields (Table 2). In all experiments, the Ru(II)-catalysts were prepared *in situ* from (cod)Ru(2-methylallyl)$_2$, SYNPHOS® ligand recently developed by our group[13,14] and methanolic HBr according to our convenient procedure.[11] As shown in Table 2, the Ru(II)-catalyst containing SYNPHOS®

**Table 2** Hydrogenation of compounds **3** in optimized conditions[a]




| Entry | Substrate | Yield[b] (%) | *d.e.*[c] (%) *anti* | *e.e.*[c] (%) (2*S*,3*S*) |
|---|---|---|---|---|
| 1 | **3a** R=BnO-$C_4H_8$ | 94 | 92 | 92 |
| 2 | **3b** R=$C_5H_{11}$ | 85 | 93 | 91 |
| 3 | **3c** R=$C_{15}H_{31}$ | 83 | 96 | 96 |
| 4 | **3d** R=*i*Pr | 90 | 99 | 97 |
| 5[d] | **3d** R=*i*Pr | 96 | 98 | 96[d] |

[a] Reaction conditions: 0.5 mmol of substrate in 2 mL of $CH_2Cl_2$ and 200 μL of R′OH. [b] Yield over two steps. [c] *d.e.* and *e.e.* were determined by HPLC analysis after reprotection. [d] Reaction conducted with (*R*)-SYNPHOS®, *e.e.* of (2*R*,3*R*)-isomer.

displayed, under these optimized reaction conditions, an excellent catalytic activity for all the substrates **3** considered, with high levels of *anti* diastereoselectivity (86–99%) and enantioselectivity (91–97%). Both *anti* (2*S*,3*S*)- and (2*R*,3*R*)-α-amino-β-hydroxy esters could be easily synthesized with high diastereoisomeric and enantiomeric excesses by judicious choice of the ligand configuration. It is noteworthy that the diastereoisomeric excesses observed seem linked to the nature of the side chain. The best results were obtained with a long or ramified chain in the β-position (**3c** and **3d**, respectively).

In conclusion, the SYNPHOS® catalyzed hydrogenation affords a general and efficient access to *anti* α-amino-β-hydroxy esters by using configurationally labile α-$NH_2$.HCl-β-keto esters. High levels of enantiomeric and diastereoisomeric excesses are obtained for a variety of alkyl β-keto esters under mild conditions *via* dynamic kinetic resolution. This convenient method complements the well-known hydrogenation of α-amido-β-keto esters which provides the *syn* isomers as major products. This reaction is still under investigation and the application of this strategy to the synthesis of natural products and their analogues is currently underway in our group.

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