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Enantioselective Synthesis of β-Hydroxy Acid Derivatives via a One-Pot Aldol Reaction–Dynamic Kinetic Resolution

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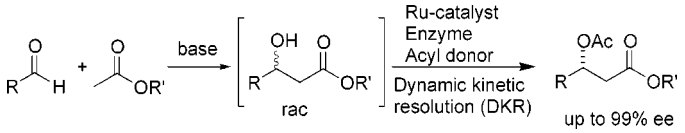
ABSTRACT

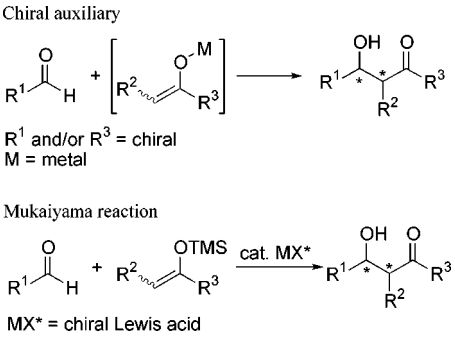


Combining dynamic kinetic resolution with an aldol reaction provides access to β-hydroxy ester derivatives with high enantiomeric purity (up to 99% ee) in a one-pot procedure. Only simple starting materials are required in this enantioselective process, and preformation of a silyl enol ether is not necessary.

The aldol reaction is one of the most important methods for the construction of new carbon−carbon bonds.[1] In these reactions, control of diastereo- and enantioselectivity has attracted much attention. There are two main routes for controlling the stereochemical outcome in the aldol reaction; the use of asymmetrically modified enolates or electrophiles (chiral auxiliary)[2] and the use of chiral Lewis acids (Scheme 1).[3] The former method relies on the use of stoichiometric amounts of chiral material, an obvious drawback due to the necessity of an additional step to recover the chiral auxiliary. In the latter method catalytic amounts of a chiral Lewis acid are sufficient to efficiently control diastereo- and enantioselectivity in the aldol process (Mukaiyama type reactions[4]). However, the enolate has to be preformed and isolated as a silyl enol ether prior to the reaction (Scheme 1).[4d,5]

Herein, we report on a novel combination of an aldol reaction and a dynamic kinetic resolution (DKR) of the corresponding adduct.[6] This one-pot tandem procedure allows the enantioselective synthesis of β-hydroxy acid derivatives from an aldehyde and a ketone and does not require the isolation of a preformed silyl enol ether (Scheme 2).

Scheme 1. Asymmetric Aldol Reactions



(1) Review: (a) Mahrwald, R. *Chem. Rev.* **1999**, *99*, 1095−1120. (b) Machajewski, T. D.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1352−1374. (c) Nelson, S. G. *Tetrahedron: Asymmetry* **1998**, *9*, 357−389. (d) Gröger, H.; Vogl, E. M.; Shibasaki, M. *Chem. Eur. J.* **1998**, *4*, 1137−1141.

(2) See, for example: (a) Solladié-Cavallo, A.; Csaky, A. G. *J. Org. Chem.* **1994**, *59*, 2585−2589. (b) Ahn, M.; Tanaka, K.; Fuji, K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 185−192.

(3) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; p 835.

(4) (a) Mukaiyama, T. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 817−826. (b) Kobayashi, S.; Uchiro, H.; Fujishita, I.; Shiina, I.; Mukaiyama, T. *J. Am. Chem. Soc.* **1991**, *113*, 4247−4252. (c) Kobayashi, S.; Horibe, M. *Chem. Eur. J.* **1997**, *3*, 1472−1481. (d) For an early report on direct catalytic asymmetric aldol reactions of aldehydes with isocyanoacetate giving high ee's, see: Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 6405−6406.

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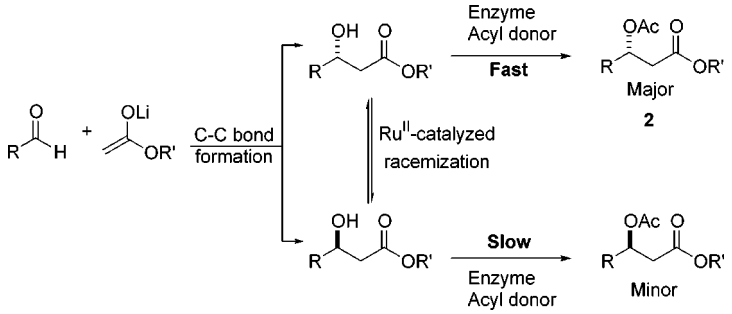
Scheme 2



To our knowledge, DKR of β-hydroxy esters has not been reported but their kinetic resolution (KR) is known.[7,8] This is mainly due to the problems of isomerizing chiral β-hydroxy esters. An obvious limitation with KR is that the maximum theoretical yield of one enantiomer is 50% vs 100% with DKR.[9] Preliminary experiments indicated that chiral β-hydroxy esters undergo slow ruthenium-catalyzed isomerization, and it was found that this isomerization could be combined with enzymatic acylation. Thus, racemic β-hydroxy ester **1a** was transformed to compound **2a** in 70% yield and 93% ee after 72 h using ruthenium catalyst **3**,[10] *Pseudomonas cepacia* lipase (PS-C type II from Amano), and *p*-chlorophenyl acetate[6b] as the acyl donor in cyclohexane at 60 °C (Scheme 3). This result prompted us to develop conditions for a one-pot synthesis of compound **2a** starting from the aldol precursors.

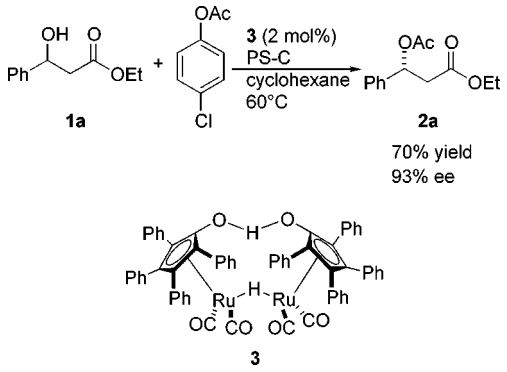
The desired coupled process in which the aldol adduct formed is continuously undergoing a dynamic kinetic resolution (DKR) seemed difficult due to incompatibility of the reagents and reaction conditions between the two processes. For example, the ruthenium catalyst **3** would interfere with the aldehyde, and the use of silyl enol ether would lead to a β-silylated adduct, which cannot racemize in the DKR (Scheme 2). We therefore focused on a one-pot procedure in which the aldol adduct is generated in situ and allowed to reach full conversion, followed by a DKR without prior isolation of the aldol adduct. For this purpose the best option is to run the aldol reaction under kinetic control using a strong base such as lithium diisopropylamine (LDA) to obtain complete enolate formation followed by reaction with the aldehyde. This suggests that polar solvents such as tetrahydrofuran (THF) or ethyl ether (Et_2O) have to be used at low temperature. On the other hand, the DKR works better in nonpolar solvents in a temperature range of 60−80 °C.

Another important factor is that, after the aldol reaction, the β-hydroxy ester has to be in its neutral form. Attempts to carry out the DKR reaction starting from the alkoxide resulted in low conversion and poor ee's; thus, a source of protons after the aldol coupling is needed.

Taking into account all these considerations, various solvents were tested in the aldol reaction (Table 1). The best results were obtained with either THF or Pr^i_2O as solvent, which gave full conversion to the desired compound (Table 1, entries 1 and 3). Et_2O gave a slightly lower conversion (entry 2). In the other cases (entries 4−6), the low conversion achieved in the coupling reaction made us reject the use of these solvents for the tandem process.

When combining the aldol reaction with the DKR, two additional problems have to be overcome: the DKR works

Scheme 3. Dynamic Kinetic Resolution of the β-Hydroxy Ester **1a**



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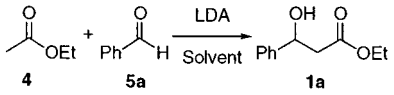
(8) Kazutoshi, M.; Naoyuki, Y. (Chisso Corp., Japan). Eur. Pat. Appl. EP 451668 A2 19911016, 1991, 12 pp.

(9) For reviews on DKR, see: (a) Ward, R. S. *Tetrahedron: Asymmetry* **1995**, *6*, 1475−1490. (b) Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36−56. (c) Caddick, S.; Jenkins, K. *Chem. Soc. Rev.* **1996**, *25*, 447−456. (d) Stecher, H.; Faber, K. *Synthesis* **1997**, 1−16. (e) El Gihani, M. T.; Williams, J. M. J. *Curr. Opin. Chem. Biol.* **1999**, *3*, 11−15. (f) Strauss, U. T.; Felfer, U.; Faber, K. *Tetrahedron: Asymmetry* **1999**, *10*, 107−117.

(10) (a) Blum, Y.; Czarkie, D.; Rahamim, Y.; Shvo, Y. *Organometallics* **1985**, *4*, 1459−1461. (b) Shvo, Y.; Czarkie, D.; Rahamin, Y. *J. Am. Chem. Soc.* **1986**, *108*, 7400−7402. (c) Menashe, N.; Shvo, Y. *Organometallics* **1991**, *10*, 3885−3891.

Table 1. Solvent Effect in the Synthesis of **1a**[a]

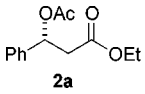


4 **5a** **1a**

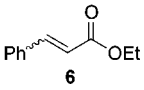
entry	solvent	convn (%)
1	THF	>99
2	Et_2O	95
3	Pr^i_2O	>99
4[b]	TBME	46
5[b]	$PhCH_3$	traces
6[b]	hexane	16

[a] Unless otherwise noted, all the reactions were carried out by adding ethyl acetate to a 0.3 M solution of LDA (1 equiv) at −78 °C. After 1 h, benzaldehyde (1 equiv) was added at the same temperature and the mixture was stirred for 0.5−1 h. [b] After the benzaldehyde addition, the reaction was allowed to reach rt over 2 h.

better in TBME (*tert*-butyl methyl ether)[11] as solvent, whereas the aldol reaction does not (Table 1, entry 4). Furthermore, the presence of diisopropylamine (DIPA) as a base after the deprotonation of the corresponding ester with LDA has a negative effect on the outcome of the reaction. Lipase-mediated acetylation of the aldol adduct leads to an acetate (**2a**), which is sensitive toward base-catalyzed β-elimination.[12] In fact, the aldol coupling in Pr^i_2O between ethyl acetate (**4**) and benzaldehyde (**5a**) followed by in situ DKR without neutralizing the base gave the olefin **6** as a single reaction product.



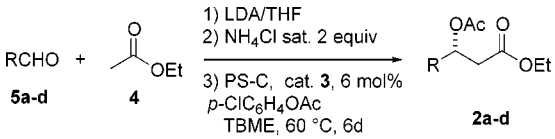
2a



6

Finally, the combined reaction was carried out by enolate formation and coupling with the corresponding aldehyde **5a** in THF at low temperature. Once the aldol adduct **1a** was formed, the THF was removed in vacuo and the residue dissolved in TBME and transferred to a suspension of lipase (PS-C), acyl donor, and ruthenium catalyst **3** in TBME (Scheme 4, Table 1).[13] Compound **2a** was isolated in 73% yield (from **5a**) and 95% ee. Both catalysts (PS-C lipase and

Scheme 4



5a-d **4** **2a-d**

3) were easily recovered. The lipase was filtered off and washed with TBME several times, without loss of activity.[14] The ruthenium catalyst **3** was recovered in 75% yield from the reaction mixture by crystallization from dichloromethane/Et_2O. This result provides a new and an economical alternative for the chemoenzymatic enantioselective synthesis of β-hydroxy esters. These compounds are versatile building blocks for chiral synthesis,[15,16] and compound **2a** is a progenitor for the antidepressant drugs tomoxetine and fluoxetine (Prozac, Eli Lilly Co.).[16]

This new one-pot tandem reaction was applied to different substrates (Scheme 4, Table 2). The success of the procedure

Table 2. One-Pot Aldol Coupling−DKR[a]

entry	R	aldol adduct	product	yield (%)[b]	ee (%)[c]
1	Ph	**1a**	**2a**	73 (76)	95
2	*p*-MeO-C_6H_4	**1b**	**2b**	69 (74)	99
3	$PhCH_2$	**1c**	**2c**	75 (80)	96
4	Cy	**1d**	**2d**	71 (82)[d]	70

[a] For a typical experiment, see ref 12. [b] Isolated yield with respect to **5**. In parentheses isolated yields obtained in the DKR from purified **1** are given. [c] The ee of product **2** was determined by GC equipped with a CP-Chirasil-Dex CB column. [d] Kinetic resolution of **1d** with PS-C (60 mg/mmol) and *p*-ClC_6H_4OAc (3 equiv) in TBME (8 mL/mmol) at 60 °C gave 22% yield after 48 h (calculated by ^1H NMR) and 70% ee.

is highly dependent on the enzymatic resolution. The substrate requirements for an efficient kinetic resolution are that there are two groups with different sizes next to the stereocenter.[17] Moreover, the size of these geminal groups cannot exceed the size of the active pocket in the enzyme. Considering these restrictions, several compounds, **2a**−**d**, were synthesized from ester **4** and aldehydes **5a**−**d** via the coupled aldol reaction−DKR process. The results of these one-pot tandem reactions are summarized in Table 2. Although the presence of electron-donating groups in the

(11) TBME was chosen as solvent for the DKR due to the high enantiomeric ratio (E > 200) obtained with the PS-C lipase for our model substrate in this solvent.

(12) In the case of benzylic acetates, the elimination leads to a highly conjugated double bond.

(13) In a typical experiment *n*-BuLi (1 equiv, 0.625 mL of 1.7 M solution in hexane) was added over DIPA (1 mmol, 0.166 mL) in THF (3 mL) in a Schlenk tube. The mixture was cooled to −78 °C, and ethyl acetate (1 equiv, 0.098 mL) was added dropwise. After 50 min benzaldehyde (0.8 equiv, 0.082 mL) was added dropwise to the solution and the reaction stirred for 30 min. Then, after hydrolysis with a saturated NH_4Cl solution at 0 °C (5.5 M solution, 2 equiv), the solvent was evaporated and the resulting reaction crude dissolved in TBME (6 mL) and transferred to another Schlenk containing a suspension of PS-C (48 mg, 60 mg/mmol), *p*-ClC_6H_4OAc (3 equiv, 0.409 g), and Ru catalyst **3** (6 mol %, 52 mg) in TBME (2 mL). The resulting mixture was stirred at 60 °C (bath temperature) during 6 d. The enzyme was filtered off from the reaction mixture and washed with TBME (3 × 10 mL), the solvent evaporated, and the catalyst **3** recovered by crystallization in CH_2Cl_2/Et_2O. **2a** was purified by flash chromatography (pentane/Et_2O).

(14) The kinetic resolution of compound **1a** with the recovered enzyme gave the same E value. ee = enantiomeric excess of substrate (S) or product (P) and E = enantiomeric ratio

$$E = \frac{\ln\frac{[ee_p\,(1 - ee_s)]}{(ee_p + ee_s)}}{\ln\frac{[ee_p\,(1 + ee_s)]}{(ee_p + ee_s)}}$$

(15) Rodríguez, S.; Schroeder, K. T.; Kayser, M. M.; Stewart, J. D. *J. Org. Chem.* **2000**, *65*, 2586−2587.

(16) (a) Boaz, N. W. *J. Org. Chem.* **1992**, *57*, 4289−4292 and references therein. (b) Kumar, A.; Ner, D. H.; Dike, S. Y. *Tetrahedron Lett.* **1991**, *32*, 1901−1904.

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aromatic ring has been observed previously to have a negative effect on the racemization process,[6c] the enantioselection in this particular case was excellent, >99% ee (entry 2), and compound **2b** was isolated in 69% yield (based on aldehyde **5b**). Attempts to obtain enantio- and diastereoselection in compounds **2** with a methyl group in the α-position have so far been fruitless, due to the increased bulkiness next to the stereocenter (vide supra).[7c,18] Substitution of the phenyl group in benzaldehyde (**5a**) with a benzyl group also resulted in an efficient DKR (entry 3). Cyclohexyl derivative **2d** (entry 4) gave a low ee compared to that of aryl compounds **2a**−**c**. Although the enantioselectivity can be slightly improved (80% ee) using less enzyme, the reaction time increased dramatically (50% conversion after 7 days). Comparing the result obtained by DKR with that obtained by KR of compound **1d** (22% yield and 70% ee), we can note the efficiency of the dynamic process vs the traditional kinetic resolution.

In summary, we have demonstrated that the ruthenium- and enzyme-catalyzed DKR in tandem with carbon−carbon bond-forming reactions such as the aldol addition reaction is a valuable tool for asymmetric synthesis. The procedure reported here should be a useful complement to previous methodology since enantiomerically pure aldol adducts lacking an α substituent (cf. **2a**−**d**) are difficult to obtain with catalytic asymmetric aldol reactions[19] and also because this procedure does not require access to preformed silyl enolates.[5] Moreover, the easy handling of the chemicals employed and recovery of both catalysts makes this system suitable for upscaling.

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