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Enantioselective Synthesis of *syn*- and *anti*-1,3-Aminoalcohols via β-Aminoketones and Subsequent Reduction/Dynamic Kinetic Asymmetric Transformation

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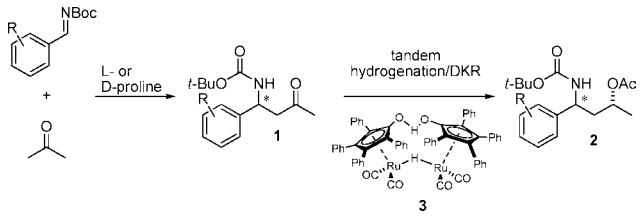
Abstract: β-Aminoketones obtained from imines in an organocatalytic Mannich reaction were transformed to enantio- and diastereomerically pure 1,3-aminoalcohols with two stereogenic centers via a combined reduction/dynamic kinetic asymmetric transformation. Both syn and anti diastereomers were obtained in high yield, dr, and *ee*.

Acyclic chiral 1,3-aminoalcohols with two stereogenic centers are structural motifs in many natural products and biologically active compounds.[1] They are also useful building blocks in asymmetric synthesis.[2] Various methods for their preparation have been developed, but most of these methods are based on diastereoselective reduction,[3] and only a few describe enantioselective preparations. There is therefore a demand for new and efficient methods for the enantio- and diastereoselective preparation of acyclic 1,3-aminoalcohols.

During the past decade, the combination of metal catalysis and enzymatic resolution has emerged as a powerful tool for the synthesis of enantiopure esters and amides via dynamic kinetic resolution (DKR).[4] Although enzymatic kinetic resolution of racemic mixtures is a useful tool for obtaining enantiopure compounds, it is limited by a theoretical yield of 50%. To overcome this problem, the slow-reacting enantiomer can be converted into the other one by a racemization catalyst, allowing a yield of 100% to be obtained via DKR. The same approach has been employed to form diastereo- and enantiomerically pure 1,3-diols via a dynamic kinetic asymmetric transformation (DYKAT).[5]

Herein we report our strategy based on a two-step procedure combining organo-, organometallic, and enzymatic catalysis (Scheme 1).[6] The enantiopure β-aminoketones **1**, which were available via organocatalysis, were subjected to reduction and subsequent DYKAT to give enantio- and diastereomerically pure 1,3-aminoacetates **2**.

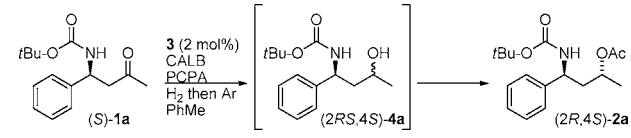
Scheme 1. Two-Step Synthesis of Protected 1,3-Aminoalcohols



β-Aminoketones **1** were synthesized through an enantioselective proline-catalyzed Mannich reaction.[7] A wide range of electron-rich and electron-deficient β-aminoketones **1** were obtained in >98% *ee* in moderate to good yields.[8] It was shown that reduction of **1a** using sodium borohydride or hydrogenation with catalyst **3** led to poor diastereoselectivty in favor of the anti diastereomer (dr = 2:1 and 2.8:1, respectively). Similar reduction by L-selectride showed a selectivity for the syn diastereomer, but again, the diastereomeric ratio was low (dr = 1:3). The enantiomeric and diastereomeric excess of 1,3-aminoalcohols therefore had to be introduced through a second asymmetric transformation. Taking advantage of the high enantioselectivity shown by lipases in transesterification reactions of secondary alcohols would give an amplification of the second stereocenter. However, the ketone first had to be reduced to the corresponding alcohol. The Shvo complex **3**[9] can act as a dual catalyst for both reduction of the ketone and epimerization of the alcohol, and thus, a one-pot procedure for transforming the ketone to the enantiomerically pure aminoalcohol derivative via DYKAT could be realized.[10,11]

The reaction conditions for the reduction/DYKAT were optimized. CALB was chosen as a suitable lipase because of its thermostability, wide substrate scope, and high enantioselectivity for secondary alcohols. *N*-Boc-protected β-aminoketone (*S*)-**1a** was used as a standard substrate, and the previously described *p*-chlorophenyl acetate (PCPA) was employed as the acyl donor.[12]

Table 1. Combined Reduction/DKR of (*S*)-**1a**[a]



entry	equiv of PCPA[b]	*T* (°C)	conv. (%)[c]	dr[c]	*ee* (%)[d]
1	1.2	70	70	>95:5	>99
2	1.2	80	67	>95:5	>99
3	1.2	90	72	>95:5	>99
4	2.5	90	89	>95:5	>99
5[e]	2.5	90	79	>95:5	>99
6[f]	3.5	90	99 (92)	98:2[g]	>99

[a] The reactions were run on a 0.25 mmol scale under hydrogen for 20 h followed by argon for 24 h. Unless otherwise noted, 10 mg of immobilized CALB was employed. [b] PCPA = *p*-chlorophenyl acetate. [c] Determined by ^{1}H NMR spectroscopy. The isolated yield of pure acetate is given in parentheses. [d] Determined by HPLC. [e] Reaction was run under hydrogen for 48 h. [f] Using 20 mg of CALB. [g] Determined by HPLC on pure acetate.

The first parameter to be investigated was the temperature (Table 1, entries 1−3). Neither the conversion, dr, nor *ee* changed with increasing temperature. However, the syn/anti ratio of the intermediate alcohol **4a** proved to be highly temperature-dependent and first showed a 1:1 ratio at 90 °C. This indicates that a temperature of 90 °C is required for an efficient epimerization. The next parameters to be changed were the amounts of the acyl donor and the catalysts. Increasing the amount of the acyl donor PCPA to 2.5

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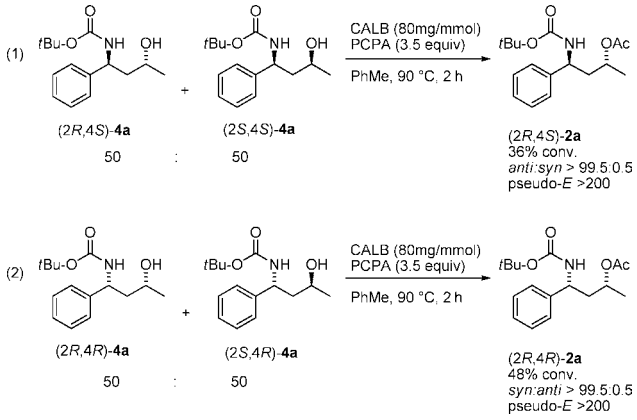
equiv gave a higher conversion (Table 1, entry 4), while increasing the loading of the Shvo catalyst **3** from 2 to 4 mol % did not lead to any notable improvement. However, when the amount of CALB was doubled and the amount of PCPA was further increased to 3.5 equiv, the reaction reached full conversion after 48 h, and (2*R*,4*S*)-**2a** was isolated in 92% yield with a dr of 98:2 and an *ee* of >99% (entry 6).

Hydrogen gas was required in the first step of the process for the reduction of the ketone. However, it was not necessary in the epimerization of the alcohol and not even desirable. In fact, the epimerization rate decreased when hydrogen gas was present during the whole reaction (Table 1, entry 5). The atmosphere was therefore changed from hydrogen to argon after 20 h, and this procedure gave the best results for the coupled reduction/DKR process.[13]

The results using the optimized reduction/DKR conditions indicate that CALB has a very high selectivity for the *R* configuration of the alcohol in the diastereomeric alcohols. To measure the pseudo-*E* value, a kinetic asymmetric transformation (KAT) of a 50:50 mixture of (2*R*,4*S*)-**4a** and (2*S*,4*S*)-**4a** as well as of a 50:50 mixture of (2*R*,4*R*)-**4a** and (2*S*,4*R*)-**4a** were carried out (Scheme 2).

Scheme 2. Determination of the Pseudo-*E* Value



Enzymatic resolution (KAT) of a 50:50 mixture of (2*R*,4*S*)-**4a** and (2*S*,4*S*)-**4a** led to the formation of (2*R*,4*S*)-**2a** with an anti/syn ratio of >99.5:0.5 at 36% conversion. At this conversion, the anti/syn ratio of the starting material **4a** had changed from 50:50 to 20:80. This gave a pseudo-*E* value of >200 (350) for this kinetic asymmetric transformation (eq 1 in Scheme 2). CALB also showed a high selectivity for the other pair of diastereomers. At 48% conversion, the aminoacetate (2*R*,4*R*)-**2a** had been formed in a syn/anti ratio of >99.5:0.5, and the syn/anti ratio of the starting material changed from 50:50 to 3:97 (eq 2 in Scheme 2). Thus, the pseudo-*E* value was >200 (700).

To investigate the scope of the process, a wide range of imines were subjected to the proline-catalyzed Mannich reaction, and the aminoketones obtained were then subjected to the optimized DYKAT conditions. The 1,3-aminoacetates were obtained in dr's up to >98:2 and *ee*'s of >99%, and both (*S*)- and (*R*)-aminoketones were tolerated, providing access to both (2*R*,4*S*)- and (2*R*,4*R*)-aminoacetates (Figure 1). It is interesting to note that the high selectivity of the DYKAT reaction completely overrides the inherent diastereoselectivity to give either the *syn*- or *anti*-1,3-aminoacetate in good to high yield and high *ee*. The phenyl derivative as well as electron-rich *p*-methoxy and electron-deficient *p*-chloro derivatives were transformed to enantiomerically pure aminoacetates **2a**, **2b**, and **2c**, respectively, of either syn or anti form. Also, *p*- and *m*-tolyl derivatives were converted to (2*R*,4*S*)-**2d** and (2*R*,4*S*)-**2e**, respectively, in high yields and high *ee*, and the more bulky naphthyl derivative afforded (2*R*,4*S*)-**2e** in high yield and 99% *ee* with a dr of >97:3.[14] Finally, to our delight, the 2-furyl derivative was obtained in good yield with high enantio- and diastereoselectivity.

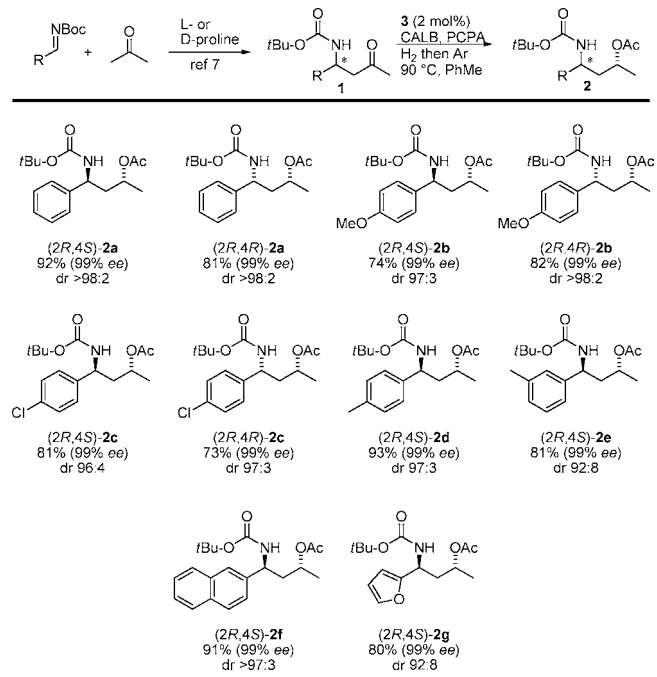
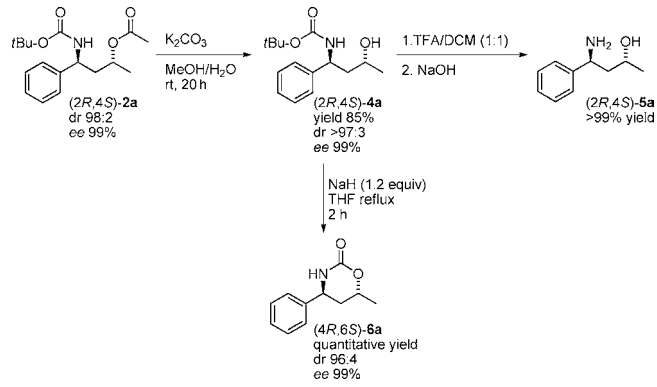


Figure 1. Reaction scope of γ-aminaoalcohol synthesis.

Scheme 3. Deprotection of *N*-Boc-aminoacetate



The *N*-Boc-protected aminoacetate was easily deprotected in two steps with retained enantiomeric and diastereomeric excess (Scheme 3). Hydrolysis of the acetate in the presence of K_2CO_3 in MeOH/water yielded (2*R*,4*S*)-**4a** in 85% yield with a >97:3 anti/syn ratio and >99% *ee*. The Boc group was cleaved off in the presence of trifluoroacetic acid in dichloromethane, yielding the free aminoalcohol (2*R*,4*S*)-**5a** in quantitative yield. The stereochemical assignment of the aminoalcohol was confirmed by transformation into its cyclic carbamate (4*R*,6*S*)-**6a**.

In conclusion, we have developed an efficient procedure for enantio- and diastereoselective synthesis of *N*-Boc-protected 1,3-aminoacetates via an organocatalytic Mannich reaction and a subsequent highly enantioselective tandem reduction/DYKAT. The procedure illustrates the combination of organo-, organometallic, and enzymatic catalysis. The two diastereomers (2*R*,4*S*) and (2*R*,4*R*) were obtained in high *ee* and high diastereoselectivity. Hydrolysis of the acetate as well as of the *tert*-butylcarbamate was carried out without any loss of enantio- or diastereoselectivity.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) After 20 h under a H_2 atmosphere, the (2*R*,4*S*)-**2a**/(2*S*,4*R*)-**4a**/(*S*)-**1a** ratio was 70:30:0, and (2*R*,4*S*)-**4a** could not be detected.

(14) The *ee* of **2f** could not be determined with precision because of peak overlap in the HPLC analysis, as the peak of the minor enantiomer overlapped with the peak of the minor diastereoisomer. Since the major part of the small peak was attributed to the minor diastereoisomer, we indirectly concluded that the *ee* was >99%.

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