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Tandem enantioselective organo- and biocatalysis: a direct entry for the synthesis of enantiomerically pure aldols

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Abstract—Direct proline-catalyzed aldol reactions were linked in sequence with lipase-catalyzed kinetic resolutions to afford enantiomerically pure (>99% ee) aldol adducts in higher conversion than a standard resolution of racemic materials. The combination of organocatalytic aldol reactions and enzymatic kinetic resolutions provided exclusively either the (*R*)- or (*S*)-enantiomer of the aldol adducts even though an (*R*)-selective lipase catalyzed the kinetic resolutions. Furthermore, the one-pot tandem reactions are inexpensive, are operationally simple, circumvents the use of organic solvent and are environmentally benign.

One of the ultimate goals and challenges in chemistry is to develop stereoselective transformations for the creation of optically active functional molecules from simple readily available starting materials. There are several methods for the preparation of enantiomerically pure compounds and among these asymmetric catalysis is a highly active research field.[1,2]

Enantiomerically pure β-hydroxy ketones (aldols) are important synthetic building blocks.[3–6] The β-hydroxy ketone structural motif is often encountered in several biologically active compounds, such as macrolide antibiotics and cancer drugs, and aldols have therefore been used on numerous occasions in the total synthesis of natural products.[3]

There is a plethora of methods for the stereoselective synthesis of β-hydroxy ketones. Among these, catalytic indirect and direct asymmetric aldol reactions are very important.[7,8] In addition, biocatalysis can be employed to furnish β-hydroxy ketones with high stereoselectivity. Examples are the use of aldolase enzymes,[9] aldolase antibodies,[10] and baker's yeast-mediated reduction of 1,3-diketones.[11] However, there are only a few reports on the use of lipase-catalyzed kinetic resolutions of racemic aldols.[12] For instance, Nair and co-workers have reported the use of *Candida cylindracea* lipase (CCL) as the catalyst for kinetic resolutions of racemic β-hydroxy ketone adducts.[12a,b]

Organocatalysis has recently experienced a revitalization in catalytic asymmetric synthesis.[13] Asymmetric transformations mediated by amino acids have been particularly successful in enantioselective Robinson annulations.[14] Furthermore, List et al. have developed the first direct organocatalytic asymmetric intermolecular organocatalytic aldol reaction, which furnished β-hydroxy ketones.[15] After this initial study several direct organocatalytic aldol and cross-aldol reactions have been reported.[16] For example, the simple and inexpensive (*S*)-proline affords aryl β-hydroxy ketones with 60–76% ee.[15,16]

Sih and co-workers have demonstrated that by performing sequential enzymatic hydrolysis reactions of nonracemic substrates, less selective enzymes can be used and result in higher conversion and selectivity when compared to a similar kinetic resolution of racemic material.[17] Even though there are reports of coupling two asymmetric reactions or an asymmetric reaction and a kinetic resolution to furnish compounds with high ee, this combination of techniques have not often been applied.[18] Based on these studies and our previous research on asymmetric reactions catalyzed by amino acid derivatives and combination of transition-metal catalysis and enzyme catalysis,[19,20] we envisioned the possibility of combining nontoxic organocatalysis with

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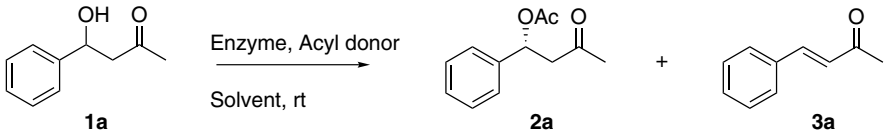
Table 1. Enzyme screen for the kinetic resolution of **1**[a]



Entry	Enzyme	Acyl donor	Solvent	[*S*] (M)	Time (h)	**2a**[b] (%)	**3a**[b] (%)	ee[c] (%)
1	Amano II		$CHCl_3$	0.2	46	0	0	—
2	Amano II		PhMe	0.2	41	0	0	—
3	CALB		PhMe	0.1	72	0	0	—
3	CCL[d,e]		—	0.2	16	<10	n.d	n.d
4	Amano II[d,e]		—	0.2	16	20	28	>99
5	Amano II[d,e]		—	0.2	16	30	9	>99
6	Amano I[d]		—	0.2[f]	24[f]	51[f]	0	97[f]

[a] To 0.2 mmol of **1a** and 4.0 mmol of isopropenyl acetate in 1 mL of organic solvent was added 12 mg of enzyme and the reaction was stirred for the time indicated.
[b] The yield was estimated by NMR and GC.
[c] The ee was determined by chiral-phase HPLC analyses.
[d] 245 mg enzyme/mmol substrate.
[e] Temp = 30 °C.
[f] Molecular sieves were added.

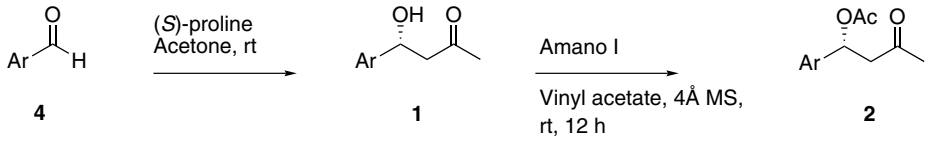
lipase-catalyzed kinetic resolutions for the preparation of β-hydroxy ketones. Moreover, the potential of performing these tandem reactions in one pot would not only bring the advantages of decreasing waste generation but also obviate the tedious separation and purification of intermediate products. Herein, we report a novel route for the synthesis of enantiomerically pure β-hydroxy ketones via one-pot combinations of proline-catalyzed aldol reactions and *Pseudomonas cepacia* lipase (Amano I)-catalyzed kinetic resolutions.

We initially performed a screen of the ability of commercially available lipases to mediate the kinetic resolution of 4-hydroxy-4-phenyl-butan-2-one **1a** under different reaction conditions (Table 1). The screen revealed that *P. cepacia* lipases Amano I and II were able to acetylate efficiently the (*R*)-enantiomer of **1a** with >99% ee in neat vinyl acetate. The enantioselectivity (*E*) of the lipases was in each case high ($E > 200$). We also found that addition of molecular sieves to the reaction mixture suppressed the formation of the dehydrated compound **3**, which significantly increased the yield of (*R*)-**2**. For example, Amano I was able to acylate 51% of racemic **1** to acetate **2** with 97% ee. The lipase from *C. cylindracea* (CCL) furnished acetate **2** in low conversion <10%, which is in contrast to the report of Nair and co-workers,[12a,b] and was therefore not further investigated. In addition, the lipases from *P. cepacia* exhibited much higher selectivity and efficiency then CCL.

Next, we performed sequential aldol reactions and kinetic resolutions (Table 2).[21] The proline-catalyzed aldol reactions were investigated in neat acetone to reduce the amount of organic solvent. In addition, the solvents commonly used in the direct organocatalytic aldol reactions such as DMSO and DMF are toxic and inhibit the activity of *P. cepacia* lipase. To our delight the reactions proceeded smoothly affording the corresponding aldols **1a**–**c** in comparable or slightly higher yield and enantioselectivity as compared to the reactions in DMSO. The aldol adducts **1** were next efficiently acetylated by Amano I in neat vinyl acetate to give the corresponding acetylated adducts **2a**–**c** in good to high yield with >99% ee. The sequential resolution of scalemic product mixtures significantly increased the yield of the enantiomerically pure aryl aldol adducts as compared to a standard resolution of racemic material.

The sequential reactions were also investigated as a novel route for the synthesis (*S*)-β-hydroxy aldol adducts. In this case, the (*R*)-selective lipase needs to exhibit a high *E* value for the substrate and consequently exclusively react with the minor enantiomer of the scalemic mixture. As demonstrated earlier both *P.*

Table 2. Sequential direct catalytic aldol reactions and lipase-catalyzed kinetic resolutions[a]



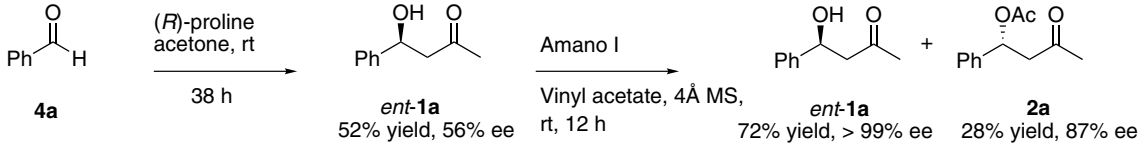
Entry	Ar	Prod. **1**	Time (aldol) (h)	Yield **1**[b] (%)	ee **1**[d] (%)	Prod. **2**	Yield **2**[c] (%)	ee **2**[d] (%)
1	C_6H_5	**1a**	33	50	64	**2a**	81	>99
2	*p*-ClC_6H_4	**1b**	25	71	68	**2b**	65	>99
3	*p*-$NO_2C_6H_4$	**1c**	8	79	77	**2c**	76	>99

[a] In a typical experiment, (*S*)-proline (26 mg, 0.22 mmol) was added to a stirred solution of aldehyde **4** (0.75 mmol) in acetone (7.5 mL) under argon in a dry flask. The reaction was stirred at rt and quenched by the addition of satd aq NH_4Cl (3 mL). The mixture was extracted with EtOAc and the organic phases were washed with brine and dried ($MgSO_4$). Flash chromatography furnished the scalemic mixtures of aldol adduct **1**. Next, to a stirred mixture of the isolated **1** and 4 Å molecular sieves in vinyl acetate (1 mL) was added PS-C Amano I (245 mg/mmol). The flask was evacuated and filled with argon three times before it was closed and the reaction was left stirred at rt to give the enantiomerically pure acetates **2**. No traces of elimination product were seen.

[b] Isolated yield after silica-gel column chromatography.

[c] NMR yield.

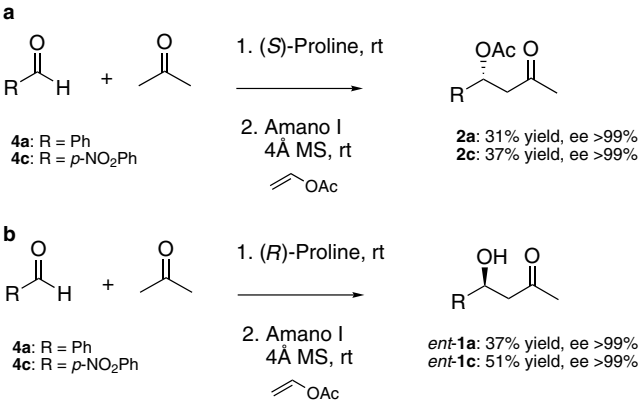
[d] Determined by chiral-phase HPLC and GC analyses.



Scheme 1. Sequential asymmetric synthesis of *ent*-**1a**.

cepacia lipases Amano I and II exhibited high *E*-values for aldol adducts **1a**. Hence, we were able to obtain *ent*-**1a** in 72% NMR yield with >99% ee from an (*R*)-proline-derived scalemic *ent*-**1a** mixture with 56% ee (Scheme 1). Thus, the combination of organocatalytic aldol reactions and enzymatic kinetic resolutions provided exclusively either the (*R*)- or (*S*)-enantiomer of the aldol adducts even though the enzyme only exists in one enantiomeric form.

Next, we performed the tandem reactions in one pot. Consequently, direct (*S*)- or (*R*)-proline-catalyzed intermolecular aldol reactions between aldehydes **4** and acetone were linked in one pot with Amano I-catalyzed kinetic resolution. To improve the efficiency of the lipase-catalyzed kinetic resolutions the acetone was removed under reduced pressure prior to the addition of neat vinyl acetate.[22] The one-pot tandem reactions proceeded smoothly providing enantiomerically pure acetates **2a** and **2c** or *ent*-**1a** and *ent*-**1c** via the (*S*)-proline-catalyzed entry and the (*R*)-proline-catalyzed entry, respectively (Scheme 2).[23] The overall yields from the one-pot operations were slightly decreased as compared with the sequential reactions performed with isolated aldol intermediates (see Table 1). For example, the overall yield of **2a** decreased from 40% to 31%. Importantly, the enantiomeric excesses of the products were not affected by the one-pot procedure. Furthermore, the one-pot operations reduced the amount of waste generation and circumvented isolation of the intermediate scalemic **1** mixture.



Scheme 2. (a) One-pot tandem (*S*)-proline-catalyzed aldol and lipase-catalyzed kinetic resolution; (b) one-pot tandem (*R*)-proline-catalyzed aldol and lipase-catalyzed kinetic resolution.

In summary, we have developed a novel combination of organocatalytic aldol reactions and enzyme-catalyzed kinetic resolutions that furnish enantiomerically pure β-hydroxy ketones. The direct proline-catalyzed catalytic asymmetric aldol reactions were performed neat, which made the reaction compatible with enzyme catalysis, without inflicting upon the efficacy and enantioselectivity of the transformations. The lipases Amano I and II from *P. cepacia* were excellent catalysts for the kinetic resolution of β-hydroxy ketone adducts **1** demonstrating *E*-values of >200. The two systems were

efficiently combined in sequence to afford enantiomerically pure aldol adducts in higher conversion than a standard resolution of racemic materials. In addition, the tandem reactions were performed in one-pot circumventing isolation of the intermediate scalemic aldol adducts. All reactions were performed with nontoxic catalysts under environmentally benign reaction conditions.

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21. (*S*)-Proline (26 mg, 0.22 mmol) was added to a stirred solution of *p*-nitrobenzaldehyde (0.113 mg, 0.748 mmol) in

acetone (7.5 mL) under argon in a dry flask. The reaction was stirred at rt for 8 h before it was quenched by the addition of satd aq NH_4Cl (3 mL). The mixture was extracted with EtOAc and the organic phases were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue furnished hydroxy ketone **1c** (0.124 g, 79%) with 77% ee as determined by chiral-phase HPLC analysis. Next, to a stirred mixture of hydroxy ketone **1c** (38 mg, 0.182 mmol) and 4 Å molecular sieves in vinyl acetate (1 mL) was added PS-C Amano I (45 mg). The flask was evacuated and filled with argon three times before it was closed and the reaction left to stir at rt for 12 h to furnish acetate **2c** in 76% yield with ee >99% as determined by chiral-phase HPLC analysis. No trace of the elimination product was detected by NMR or HPLC analyses.

22. The direct addition of vinyl acetate to the reaction mixture containing acetone significantly decreased the lipase-catalyzed kinetic resolution step.

23. (*R*)-Proline (35 mg, 0.30 mmol) was added to a stirred solution of *p*-nitrobenzaldehyde (0.151 mg, 1.00 mmol) in acetone (10 mL) under argon in a dry 50 mL Schlenk tube. The tube was closed and the reaction was stirred at rt for 8 h. Upon cooling the reaction mixture in an ice bath, acetone was evaporated under vacuum via a glass tube to an acetone/dry ice cold trap. To the residue, vinyl acetate (2.7 mL), 4 Å molecular sieves and PS-C Amano I (0.123 g) were added sequentially. The flask was evacuated and filled with argon three times before it was sealed, and the reaction was stirred at rt. After 20 h the mixture was filtered and the solids were washed with EtOAc. The filtrate was washed with brine and the aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4) and evaporated and the residue purified by silica-gel column chromatography to provide hydroxy ketone *ent*-**1c** in 51% yield (0.11 g) with >99% ee.