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Highly Efficient Organocatalytic Kinetic Resolution of Activated Nitroallylic Acetates with Aldehydes via Conjugate Addition−Elimination

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A novel, efficient, and unprecedented organocatalytic kinetic resolution has been developed. For the first time, a variety of nitroallylic acetates 1a−i have been resolved with aldehydes in the presence of 2 (2.5 mol %) via conjugate addition−elimination. The densely functionalized products 3a−o were obtained with excellent enantioselectivities (up to >99% ee), and unreacted substrates 1a−i were recovered with good to excellent optical purity (up to 98% ee).

Kinetic resolution (KR) is an important and attractive method for the production of enantiomerically enriched substances from racemic mixtures.[1] The process of kinetic resolution involves a chiral agent that promotes the selective reaction of one enantiomer over the other. In the best scenario, both the product and the less reactive enantiomeric substrate are obtained with high enantiomeric purity. Many metal-catalyzed kinetic resolution procedures have been realized.[2] Nonenzymatic KR has been predominately developed to resolve various alcohols and amines via organic molecule-mediated *O*/*N*-acylation[3] and *O*-silylation.[4] One of the advantages and challenges of the KR process is the creation of new chiral centers in the more reactive enantiomer with high asymmetric induction.[5] Although small

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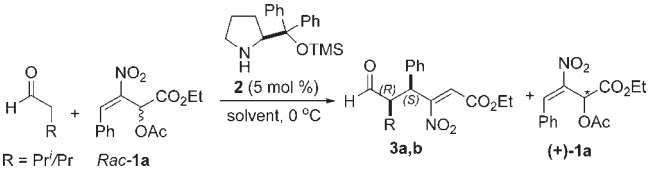
Table 1. Optimization of the Organocatalytic Kinetic Resolution[a]



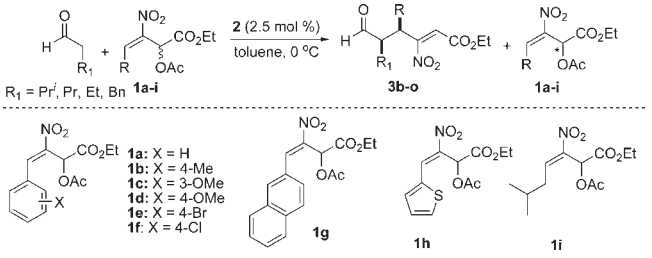
entry	R	solvent	time (h)	conv (%)[b]	**3a,b** % ee[c,d]	(+)-**1a** % ee[d]
1	Pr^i	toluene	3	52	**3a**/>99	52
2	Pr^i	CH_2Cl_2	5	30	**3a**/>95	38
3	Pr^i	Et_2O	5	43	**3a**/>99	26
4	Pr^i	THF	5	20	**3a**/>96	11
5	Pr^i	xylenes	2	48	**3a**/>99	26
6	Pr^i	hexanes	2	47	**3a**/>99	20
7[e]	Pr^i	toluene	15	48	**3a**/>99	63
8[e]	**Pr**	**toluene**	**10**	**65**	**3b/>95**	**94**

[a] Unless otherwise noted, all reactions were carried out with **1a** (0.2 mmol) and isovaleraldehyde (0.6 mmol) with **2** (5 mol %) in the indicated solvent (0.4 mL) at 0 °C. [b] Determined by ^{1}H NMR analysis of the crude mixture. [c] The *syn*-diastereoselectivity (>99:1) was determined by crude ^{1}H NMR analysis. [d] Determined by chiral HPLC analyses. [e] 1.5 equiv of aldehyde and 2.5 mol % of **2** were used.

organic molecule catalysis has been reported,[3g,h,6] the creation of new stereogenic centers via the organocatalytic KR process has not yet been explored.[7] In this communication, we wish to describe our preliminary results on the unprecedented organocatalytic kinetic resolution of a functionalized racemic nitroallylic acetates (derived from nitroallylic alcohols[8]) with aldehydes *via* conjugate addition−elimination reactions (S_N2' reaction).

Diphenylprolinol trimethylsilyl ether (**2**)[9] is now recognized as one of most useful catalysts in asymmetric organocatalysis.[10] Thus, we began our study of the aforementioned kinetic resolution process by using *rac*-**1a** and

Table 2. Substrate Scope of the Organocatalytic Kinetic Resolution[a]



Entry	**1**	R_1	time (h)	conv (%)[b]	yield **3** (%)[c,d]	yield **1** (%)[c]	ee (%)[e] **3/1**
1	**1a**	Pr	10	65	**3b**/50	**1a**/26	>95/94
2	**1a**	Et	10	68	**3c**/52	**1a**/28	>99/97
3[f]	**1a**	Bn	12	52	**3d**/38	**1a**/40	>90/80
4	**1b**	Pr	12	57	**3e**/42	**1b**/32	>99/90
5	**1b**	Et	12	58	**3f**/42	**1b**/32	>99/91
6	**1c**	Pr	12	66	**3g**/50	**1c**/30	>99/90
7	**1c**	Et	12	65	**3h**/49	**1c**/34	>98/90
8	**1d**	Et	12	55	**3i**/40	**1d**/38	>95/91
9	**1e**	Pr	10	66	**3j**/51	**1e**/30	>99/96
10	**1f**	Pr	15	61	**3k**/48	**1f**/36	>99/82
11	**1g**	Pr^i	15	53	**3l**/42	**1g**/40	>99/84
12	**1g**	Pr	12	68	**3m**/54	**1g**/28	>99/98
13[f]	**1h**	Pr^i	20	28	**3n**/20	**1h**/56	>99/32
14[g]	**1i**	Pr^i	48	40	**3o**/22	**1i**/35	>89/39

[a] All reactions performed on a 0.2 mmol scale. [b] Determined by ^{1}H NMR analyses of crude reaction mixtures. [c] Isolated yield. [d] Diastereoselectivities of products **3a**−**o** by crude ^{1}H NMR analyses (see Supporting Information). [e] Determined by chiral HPLC analyses. [f] 5 mol % of **2** was used. [g] With 10 mol % of **2**.

isovaleraldehyde as model substrates in the presence of **2** (Table 1). After extensive optimization, catalyst **2** was shown to be highly active for this process with the desired product **3a** being obtained with excellent enantioselectivity (>99% ee) (Table 1, entry 1). However, the unreacted acetate **1a** was also obtained with unsatisfactory enantioselectivity. While various solvents afforded the product with excellent enantioselectivity, they failed to improve the enantioselectivity of the recovered substrate (Table 1, entries 2−6). Further optimization of the reaction conditions was carried out by varying the catalyst loadings, concentration, temperature, and additive effects in toluene (see Supporting Information). The resolution proceeded smoothly with **2** (2.5 mol %) and isovaleraldehyde (1.5 equiv), and the recovery of acetate **1a** was obtained with a reasonably good enantioselectivity (63% ee) at 48% conversion (Table 2, entry 7). Surprisingly, the KR process with valeraldehyde proceeded smoothly with a high level of conversion (Table 1, entry 8). Gratifyingly, both the product **3b** and the unreacted

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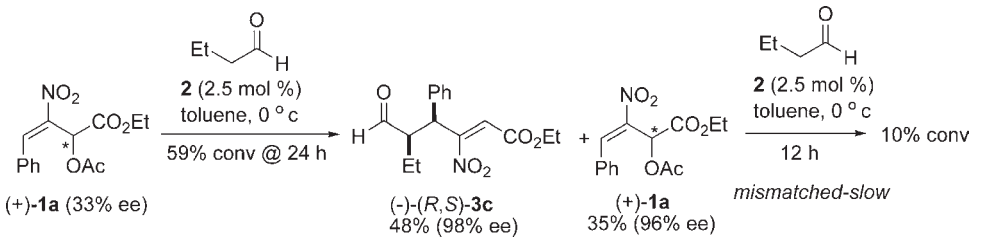
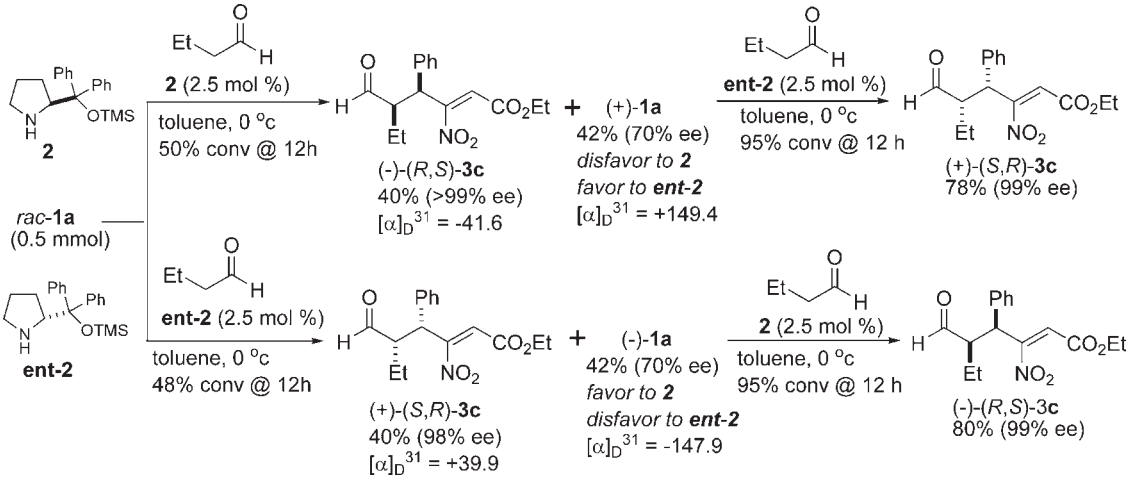
Scheme 1. Reactivity and Resolution Effect of **1a**



Scheme 2. Synthesis of both enantiomers of **3c**



substrate **1a** were obtained with excellent enantioselectivity at 65% conversion when 1.5 equiv of valeraldehyde was used in the presence of 2.5 mol % of **2** in toluene at 0 °C.

Encouraged by these results, we next examined the scope of different nitroallylic acetates (**1a**−**i**) with aldehydes to establish the general utility of our organocatalytic KR process (Table 2). Various aldehydes reacted comfortably with nitroallylic acetates **1** to give highly functionalized products **3a**−**o** with high chemical yields and excellent enantioselectivities under the optimal reaction conditions. With 2.5 mol % of catalyst **2**, the reactions with linear aldehydes (valeraldehyde and butyraldehyde) proceeded in comparable smooth conversions. High chemical yields and excellent enantioselectivities were obtained for desired products **3b** and **3c** as well as the recovery substrate **1a** (Table 2, entries 1 and 2). The use of 3-phenyl propionaldehyde with **1a** in the presence of 5 mol % of **2** afforded a high level of enantioselectivity (80% ee) of recovered **1a** with minimal sacrifice of the enantioselectivity of **3d** (Table 2, entry 3). The resolution of nitroallylic acetates (**1b**−**f**) with electron-withdrawing and electron-donating groups on the aromatic ring also proceeded with high levels of conversion (Table 2, entries 4−10). The 2-naphthyl substituent **1g** was an excellent substrate for this kinetic resolution, which proceeded remarkably well with isovaleraldehyde and valeraldehyde (Table 2, entries 11 and 12). On the other hand, the heteroaromatic acetate **1h** and aliphatic substrate **1i** were found to be poor substrates with isovaleraldehye under the optimal reaction conditions. The reaction required the use of 5 and 10 mol % of **2**, respectively, for reasonable conversions. However, to our satisfaction, the desired products **3n** and **3o** were obtained with high enantioselectivity (Table 2, entries 13 and 14). These data demonstrate that the organocatalytic KR protocol has broad applicability to resolve the multifunctional acetates (**1a**−**i**) with high chemical yields and enantioselectivities. Notably, the densely functionalized products (**3a**−**o**) were obtained in a nearly optically pure form with high stereospecificity in most cases examined. The absolute configuration of product **3a** was determined to be as an (*R*, *S*) configuration by single crystal X-ray data analysis of camphanyl ester derived from **3a**.[11]

The excellent enantioselectivities of **3** and the recovery of optically active nitroallylic acetate **1** are impressive. In order to understand this, the reactivity and resolution process were studied using enantiomerically enriched nitroallylic acetate **1a**. Interestingly, the acetate **1a** (33% ee) reacted slower with butyraldehyde under similar reaction conditions (Scheme 1 vs Table 2, entry 2). Additionally, only 10% conversion was observed when the same reaction

(11) Detailed X-ray crystallographic data are available from the CCDC, 12 Union Road, Cambridge CB2, 1EZ, UK (www.ccdc.cam.ac.uk/data_request/cif) for camphanyl derived ester of **3a** (CCDC No. 785442; see Supporting information).

was carried out with 96% ee of the recovery acetate **1a**. This clearly demonstrates that the more reactive enantiomer of the acetate **1a** was swept away. Thus, the present recovered enantiomer (**1a** at 96% ee) was not configurationally favored in allowing product formation.

The capability to produce both enantiomers with high degrees of optical purity is important in organic synthesis. We assumed that the *in situ* formation of a nucleophilic enamine intermediate was occurring which preferentially reacted with one enantiomer of a racemate with a high level of stereospecificity. For practical significance, we studied the kinetic resolution of racemic **1a** and butyraldehyde catalyzed by enantiomeric catalysts **2** and **ent-2** under the optimal reaction conditions, respectively. From Scheme 2, the kinetic resolution procedure enabled the synthesis of both enantiomers of product (−)-(*R*, *S*)-**3c** (> 99% ee) and (+)-(*S*, *R*)-**3c** (> 98% ee) with the recovery of nitroallylic acetates (+)- and (−)-**1a** (70% ee) at ∼50% conversion, respectively. The recovered nitroallylic acetate (+)-**1a** (obtained from the reaction with **2**) was further treated with butyraldehyde in the presence of catalyst **ent-2**. The enantiomeric (+)-(*S*, *R*)-**3c** was obtained with excellent enantioselectivity and near complete conversion in 12 h. This indicates that the recovered acetate (+)-**1a** was configurationally favorable for reacting with the **ent-2-**derived enamine. Similarly, the recovered acetate (−)-**1a** (70% ee, obtained from **ent-2** catalyst) was complimented with catalyst **2** to allow a near complete conversion. Overall, these studies have revealed matched and mismatched sets of acetate **1a** with organocatalysts **2** and **ent-2**. This was also evident from the differing rates of reaction for the enantiomeric nitroallylic acetates.

In conclusion, we have successfully developed a novel and practical organocatalytic KR procedure for the synthesis of highly functionalized nitroalkenes. To the best of our knowledge, nitroallylic acetates have been resolved for the first time by the use of the popular and prominent diphenylprolinol ether **2**. The KR method proceeds with the generation of new stereogenic centers via an unusual S_N2' mechanism. Several other features are worth noting: (a) the KR process proceeds smoothly with low catalyst loading (2.5 mol %); (b) the kinetic resolution process affords excellent enantioselectivities of **3a**−**o**, with the unreactive substrate **1a**−**i** being recovered with good to excellent optical purity; and (c) the reaction proceeds in a highly stereospecific fashion, where both enantiomerically enriched products are obtained when either enantiomeric catalyst is used. The scope of this novel resolution process and its mechanistic aspects are currently under investigation.

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Supporting Information Available. Experimental procedures, characterization data for new compounds, and X-ray crystallographic data (CIF) of camphanyl ester derived from **3a**. This material is available free of charge via the Internet at http://pubs.acs.org