Dynamic kinetic resolution of 2-oxo-3-aryl-succinates by organocatalyzed aldolization†

Yajun Wang, Zongxuan Shen, Bin Li, Yong Zhang and Yawen Zhang*

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The dynamic kinetic resolution of 2-oxo-3-arylsuccinates was achieved *via* L-proline-catalyzed addition of acetone in acetonitrile at room temperature, providing the desired adduct in good yield with up to 87 : 13 dr and high ee up to 99%.

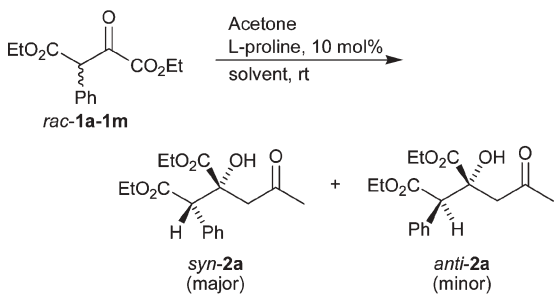
Dynamic kinetic resolution (DKR) is a powerful tool to obtain products with high enantioselectivity from racemic starting materials, which combines the resolution step of kinetic resolution, with an *in situ* equilibration or racemization of the chirally labile substrate.[1] DKR reactions demand racemization of the substrate which can be performed either chemically, biocatalytically or even spontaneously and conditions must be chosen to avoid the racemization of the product. If the asymmetric reaction creates a second stereogenic center, an enantioselective synthesis of a diastereoisomer is also possible.[2] In recent years, increasing attention has been given to the discovery of DKR reactions, which can, theoretically, result in quantitative yield with enantiomeric excess (ee) approaching 100%.[3]

The aldol addition reaction is one of the most widely used synthetic reactions for the construction of stereochemically complex, natural and unnatural products. The enantioselective version of this reaction catalyzed by small organomolecules have drawn much attention in recent years and great advances have been made.[4] Among many advantages of this strategy, the most attractive to us is that the reaction occurs under very mild conditions. Thus, it may be a suitable choice to be employed in DKR of some 1,3-dicarbonyl compounds. However, the substrates as acceptors in intermolecular asymmetric aldol reactions are mostly aldehydes, and our initial research demonstrated that α-formyl ketones, esters, or nitriles did not undergo the desired aldol reaction, probably because they exist almost as the enol form. Recently, we and others have shown that some activated ketones, which has an electron-withdrawing group adjacent to the carbonyl carbon, undergo the asymmetric aldol reaction in the presence of L-proline.[5] Based on these facts, we designed a novel DKR reaction: addition of acetone to 2-oxo-3-phenylsuccinic acid esters. Since these activated ketones have been shown to exist as an equilibrium mixture of keto- and enol-form, and they underwent aldol addition reaction with methyl ketones in the presence of L-proline, we hypothesized that the DKR of this kind of compounds could be achieved in their asymmetric aldol addition reaction.

We first chose the addition of acetone to 2-oxo-3-phenylsuccinic acid diethyl ester **1a**[6] as our research model. While conducted at room temperature for 24 h in acetone in the presence of 10 mol% of L-proline, it gave a combined yield of 90% with 76 : 24 diastereomeric ratio (dr). The enantiomeric excess of the major and the minor diastereomers, determined by HPLC analysis, was 92 and 95%, respectively. The influence of reaction solvent on the DKR was then investigated. The results are shown in Table 1.

The data demonstrated that excellent results could be obtained in many solvents explored, such as acetone, dimethyl sulfoxide, acetonitrile, methylene chloride, toluene, tetrahydrofuran, and 1,4-dioxane. In contrast to the above solvents, which gave >90% ee for both the major and the minor diastereomers, methanol gave a major diastereomer of high ee, but a minor diastereomer of much lower ee. So did chloroform and DMF. In water, no reaction was observed. When acetonitrile was employed as the solvent, the product was obtained in the highest yield and satisfactory ee was observed for both the major and the minor isomers, and the

Table 1 Solvent effects on dynamic kinetic resolution of **1a**



Entry	Solvent	*t*/h	Yield[a] (%)	*syn* : *anti*	ee[b] (%) *syn*	ee[b] (%) *anti*
1	Acetone	24	90	76 : 24	92	95
2	DMSO	12	82	75 : 25	97	94
3	CH_3CN	24	98	79 : 21	97	96
4	CH_2Cl_2	36	86	79 : 21	99	97
5	CH_3OH	72	69[c]	80 : 20	99	53
6	Toluene	72	60[c]	81 : 19	99	92
7	THF	24	80	77 : 23	98	92
8	$CHCl_3$	24	84	81 : 19	99	56
9	DMF	24	47[c]	77 : 23	89	12
10	1,4-Dioxane	24	68	77 : 23	98	95
11	H_2O	240	—	—	—	—

[a] Isolated yields. [b] Determined by HPLC analysis using a Chiralpak AS-H column. [c] Based on the starting material consumed.

Key Laboratory of Organic Synthesis of Province Jiangsu, College of Chemistry and Chemical Engineering, Suzhou University, Suzhou, China. E-mail: zhangyw@suda.edu.cn; Fax: 86 0512 6588 0305; Tel: 86 0512 6588 0339

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Table 2 Influence of reaction temperature on DKR of **1a** in CH_3CN

Entry	*T*/°C	*t*/h	Yield[a] (%)	*syn* : *anti*	ee[b] (%) *syn*	ee[b] (%) *anti*
1	Reflux	12	61[c]	70 : 30	19	25
2	r.t	24	98	79 : 21	97	96
3	0	48	83[c]	89 : 11	97	96
4	−20	96	76[c]	90 : 10	99	97

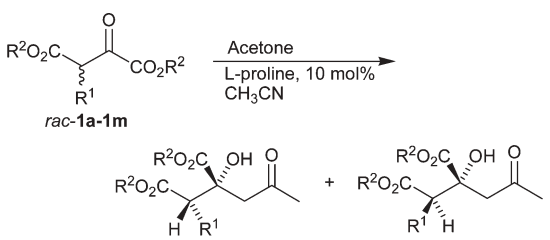
[a] Isolated yields. [b] Determined by HPLC analysis using a Chiralpak AS-H column. [c] Based on the starting material consumed.

reaction completed within 24 h. So we chose acetonitrile as the solvent to investigate the influence of temperature on the DKR of **1a**. The results are listed in Table 2.

The reaction temperature appeared to have strong influence on the diastereoselectivity. A steady improvement in diastereomeric ratio can be observed as the temperature was being lowered.

Long reaction times were required while the reaction was performed at −20 °C. DKR reactions of many other 2-oxo-3-arylsuccinates[7] were then investigated at rt using acetonitrile as the solvent.[8] The results are summarized in Table 3. Data showed that for all ethyl and methyl 2-oxo-3-phenylsuccinates the reaction exhibited high selectivity, both *syn*- and *anti*-products were obtained in almost enantiopure form (entries 1–9). Substituents on 3-phenyl did not significantly affect the reaction, although substrates with *o*- and *p*-chloro- and *p*-methoxy substituent on the 3-phenyl gave enantiopure *syn*- and *anti*-products (entries 3, 4 and

Table 3 Results of DKR of **1a–1m** at 25 °C in CH_3CN



rac-**1a-1m**

syn-**2a-2m** (major) + *anti*-**2a-2m** (minor)

a: R^1 = Ph, R^2 = Et; **b**: R^1 = *o*-FC_6H_4, R^2 = Et; **c**: R^1 = *p*-FC_6H_4, R^2 = Et; **d**: R^1= *o*-ClC_6H_4, R^2 = Et;**e**: R^1 = *p*-ClC_6H_4, R^2 = Et; **f**: R^1 = *p*-BrC_6H_4, R^2 = Et; **g**: R^1 = *o*-$CF_3C_6H_4$, R^2 =Et; **h**: R^1= *p*-$CH_3OC_6H_4$, R^2 = Et; **i**: R^1 = Ph, R^2 = Me; **j**: R^1 = *p*-BrC_6H_4, R^2 = Me; **k**: R^1 = C_6H_5, R^2 = Bn; **l**:R^1 = *o*-ClC_6H_4, R^2 = Bn; **m**: R^1 = *p*-BrC_6H_4, R^2 = Bn

Entry	R^1	R^2	Yield[a] (%)	*syn* : *anti*	% ee[b] *syn*	% ee[b] *anti*
1	*o*-FC_6H_4	Et	44[c]	83 : 17	97	97
2	*p*-FC_6H_4	Et	79	81 : 19	96	96
3	*o*-ClC_6H_4	Et	70	84 : 16	99	99
4	*p*-ClC_6H_4	Et	72	80 : 20	99	99
5	*p*-BrC_6H_4	Et	46[c]	78 : 22	99	95
6	*o*-$CF_3C_6H_4$	Et	55[c]	72 : 28	95	93
7	*p*-$MeOC_6H_4$	Et	88	82 : 18	99	99
8	Ph	Me	86	82 : 18	94	99
9	*p*-BrC_6H_4	Me	79	77 : 23	96	98
10	Ph	Bn	73	82 : 18	88	88
11	*o*-ClC_6H_4	Bn	83	87 : 13	87	91
12	*p*-BrC_6H_4	Bn	75	80 : 20	89	98

[a] Isolated yields. [b] Determined by HPLC analysis using a Chiralpak AS-H column. [c] Based on the starting material consumed.

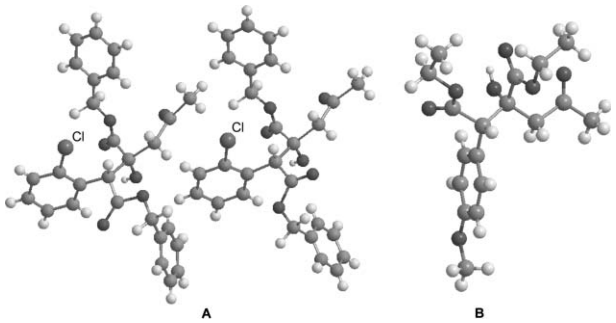


Fig. 1 X-Ray crystal structures of the minor diastereomer of **2l** (A) and the major diastereomer of **2h** (B).

7). In the reaction of benzyl esters, the ee in both *syn*- and *anti*-product was reduced (entries 10–12).

For the absolute configuration assignment, single crystals of the minor diastereomer of **2l** and the major diastereomer of **2h**, were prepared and the structure established by X-ray crystallography. According to the results of the minor diastereomer of **2l**,[9] there are two independent molecules in the asymmetric unit. These have the same absolute configurations of (2*R*,3*R*), but differ in the orientation of a carboxyl group (Fig. 1(A)). From the X-ray analysis of the major diastereomer of **2h**,[9] which consists of all-light-atoms, only the relative configuration of *syn*, could be established. In this molecule, the hydroxyl and the aryl groups are on the same side of the C–C skeleton, as shown in Fig. 1(B). Based on the known mechanism of L-proline-catalyzed asymmetric aldol reaction, these two compounds should have the same configuration at C-2, and hence the absolute configuration of the major diastereomer of **2h** should be (2*R*,3*S*). Considering the mechanistic similarity, in all reactions, the major and the minor diastereomers were considered as of (2*R*,3*S*) and (2*R*,3*R*), respectively.

The observed stereochemistry could be rationalized, using the reaction of **1a** as an example: it was supposed that L-proline catalyzed the addition of acetone to the substrate through the enamine formation[10] There are four possible transition states, that result in the formation of four different stereoisomers **2a-1**, **2a-2**, **2a-3** and **2a-4** (Fig. 2). Transition state **TS1**, resulted from the (*S*)-diethyl 2-oxo-3-phenylsuccinate, was energetically favored and led to the formation of (2*R*,3*S*)-diethyl 2-hydroxy-2-(2-oxopropyl)-3-phenylsuccinate **2a-1**, as the major enantiomer of the *syn*-products; **TS2**, resulted from the (*R*)-diethyl 2-oxo-3-phenylsuccinate, was energetically less favored because of the occurrence of the interaction between the Ar group and the acetone enamine moiety; and therefrom resulted in the formation of (2*R*,3*R*)-diethyl 2-hydroxy-2-(2-oxopropyl)-3-phenylsuccinate **2a-2**, as the main component of the minor diastereomer (*anti*-compound). **TS3** and **TS4** are not favored because of the interaction between the enamine and the ester group, and provide only very small amount of **2a-3** and **2a-4**, respectively. The matched double asymmetric induction of both of the catalyst and the substrate greatly improved the enantioselectivity, resulted in the observed excellent enantioselectivity and good diastereoselectivity.

In summary, we have demonstrated the first highly enantio- and diastereoselective organocatalytic dynamic kinetic resolution (DKR) of 2-oxo-3-arylsuccinates. The reaction proceeds for a number of 2-oxo-3-arylsuccinates and acetone, forming adducts

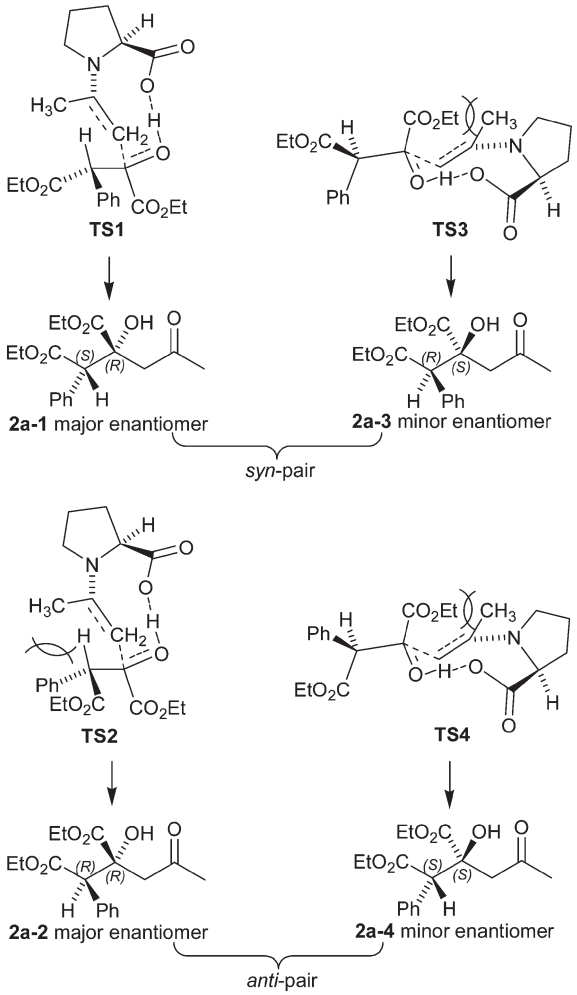


Fig. 2 Proposed transition states and the corresponding adducts.

with two adjacent stereogenic centers. This work represents a rare use of organocatalysts in a dynamic kinetic resolution.

Notes and references

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8 *General procedure* for dynamic kinetic resolutions (DKR) of 2-oxo-3-arylsuccinates: To a stirred solution (or suspension) of L-proline (10 mol%) in a mixture of dry donor ketone (2.0 mL) and the desired solvent (8.0 mL) was added the 2-oxo-3-arylsuccinate (2 mmol). The reaction mixture was stirred at this temperature for the time as specified in Tables 1, 2 and 3 (monitored by TLC) and was then treated with saturated ammonium chloride solution. The mixture was extracted with ethyl acetate (3 × 15 mL), and the combined extracts were washed with brine (5 mL), and dried over anhydrous sodium sulfate. After removal of the solvent, the crude products were purified by column chromatography over silica gel (1 : 8 ethyl acetate–hexane) to furnish the desired diastereomers, which were characterized by elemental analysis, IR, ^{1}H and ^{13}C NMR spectroscopy. Diethyl 2-hydroxy-2-(2-oxopropyl)-3-phenylsuccinate (**2a**): *syn*-isomer: pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$), δ 1.20 (t, J = 7.2 Hz, 3H, OCH_2CH_3), 1.28 (t, J = 7.2 Hz, 3H, OCH_2CH_3), 2.02 (s, 3H, $COCH_3$), 2.64 (d, J = 17.2 Hz, 1H, COCH*H*), 2.80 (d, J = 16.8 Hz, 1H, COC*H*H), 4.07–4.27 (m, 5H, PhC*H*, 2 × OCH_2CH_3), 4.79 (s, 1H, OH), 7.34–7.38 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.92, 13.98, 30.81, 48.99, 56.23, 61.36, 62.02, 76.70, 128.19, 128.54, 129.97, 133.55, 172.19, 173.49, 206.22; IR (film) ν_{max}/cm^{-1} 3409.7, 2982.1, 1731.3, 1605.1, 1384.4, 779.0, 707.8. Anal. Calc. for $C_{17}H_{22}O_6$: C 63.34, H 6.88. Found: C 63.69, H 6.98%. HPLC: Chiralpak AS-H (*i*-PrOH–hexane, 20 : 80, flow rate 1.0 mL min^{-1}, λ = 250 nm): t_{major} = 6.7 min; t_{minor} = 7.9 min; $[\alpha]_D^{25}$ = −71.1 (*c* 1.0, $CHCl_3$), ee > 99%. *anti*-isomer: pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$), δ 1.16 (t, J = 7.4 Hz, 3H, OCH_2CH_3), 1.23 (t, J = 7.0 Hz, 3H, OCH_2CH_3), 2.16 (s, 3H, $COCH_3$), 2.99 (d, J = 16.8 Hz, 1H, COCH*H*), 3.27 (d, J = 16.8 Hz, 1H, COC*H*H), 3.98 (s, 1H, PhCH), 4.06–4.22 (m, 4H, 2 × OCH_2CH_3), 4.33 (s, 1H, OH), 7.31–7.39 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.23, 14.40, 31.44, 49.14, 58.37, 61.59, 62.40, 77.19, 128.47, 128.54, 130.38, 133.59, 171.05, 173.19, 207.63; IR (film) ν_{max}/cm^{-1} 3461.3, 3064.0, 2982.2, 1720.5, 1629.1, 1384.5, 777.1, 703.7; Anal. Calc. for $C_{17}H_{22}O_6$: C 63.34, H 6.88. Found: C 63.29, H 6.79%. HPLC: Chiralpak AS-H (*i*-PrOH–hexane = 20 : 80, flow rate 1.0 mL min^{-1}, λ = 250 nm): t_{major} = 6.3 min, t_{minor} = 6.9 min; $[\alpha]_D^{25}$ = +72.5 (*c* 1.0, $CHCl_3$), ee = 96%.

9 *Crystal data* for **2l**, minor diastereomer: $C_{27}H_{25}ClO_6$, M = 480.92, triclinic, space group $P\bar{1}$, a = 5.7585(11), b = 12.377(2), c = 17.297(3) Å, α = 97.499(19), β = 97.56(2), γ = 103.09(2), V = 1173.8(4) Å^3, Z = 2, D_c = 1.361 Mg m^{-3}, μ = 0.204 mm^{-1}, F(000) = 504, crystal size = 0.65 × 0.37 × 0.05 mm, 3.18 < θ < 25.35°, T = 213(2) K, λ = 0.71070 Å, reflections collected/unique 11389/7036 [R_{int} = 0.0434], goodness-of-fit on F^2 1.116, final R indices [$I > 2\sigma(I)$] R_1 = 0.0685, wR_2 = 0.1378, R indices (all data) R_1 = 0.0939, wR_2 = 0.1555, absolute structure parameter −0.13(9), largest diff. peak and hole 0.229 and −0.260 e Å^{-3}. CCDC 621997. *Crystal data* for **2h**, major diastereomer: $C_{18}H_{24}O_7$, M = 352.37, orthorhombic, space group $P2_12_12_1$, a = 5.5529(6), b = 14.4502(16), c = 22.426(3), V = 1799.5(4) Å^3, Z = 4, D_c = 1.301 Mg m^{-3}, μ = 0.100 mm^{-1}, F(000) = 752, crystal size = 0.58 × 0.42 × 0.30 mm, 3.07 < θ < 25.35°, λ = 0.71070 Å, T = 153(2) K, reflections collected/unique 17443/1929 [R_{int} = 0.0352], refinement method: full-matrix least-squares on F^2, goodness-of-fit on F^2 1.071, final R indices [$I > 2\sigma(I)$] R_1 = 0.0335, wR_2 = 0.0826, R indices (all data) R_1 = 0.0340, wR_2 = 0.0831, largest diff. peak and hole 0.173 and −0.192 e Å^{-3}. CCDC 621996. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b616382c.

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