Parallel Kinetic Resolutions of Monosubstituted Succinic Anhydrides Catalyzed by a Modified Cinchona Alkaloid

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Efficient kinetic resolution processes continue to play a critical role in asymmetric synthesis.1 Using two chiral reagents to effect two parallel running enantioselective resolution reactions, Vedejs and co-workers demonstrated that, through minimizing a build-up of the less reactive enantiomer by simultaneously consuming both enantiomers of the racemic starting material, the two resolution reactions work synergistically to render the efficiency of the parallel kinetic resolution dramatically higher than that of each of the individual enantioselective resolution reactions.2 Parallel kinetic resolution thus represents an especially attractive strategy to explore their asymmetric synthesis via a modified cinchona alkaloids, see: (a) Hiratake, J.; Yamamoto, Y.; Oda, J. Angew. Chem., Int. Ed. 2001, 40, 930. (b) Doyle, M. P.; Dyatkin, A. B.; Kalinin, A. V.; Ruppar, D. A.; Ad (1) For reviews see: (a) Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. Adv. Synth. Catal. 2001, 343, 5. (b) Kagan, H. B.; Fiaud, J. C. Top. Stereochem. 1988, 18, 249.


(3) For a review, see: Eames, J. Angew. Chem., Int. Ed. 2000, 39, 885.


Further evaluations of a variety of reaction parameters revealed that the enantioselectivity of the parallel kinetic resolution is influenced considerably by the structure of the alcohol (Table 1). Increasing the size of the alcohol from methanol to n-propanol significantly enhances the enantioselectivity of the reaction (entries 1–3, Table 1). On the other hand, the use of 2-propanol almost completely halted the reaction. Importantly, the (DHQD)2AQN-catalyzed parallel kinetic resolution of 1a with trifluoroethanol at −24 °C afforded succinates 4 and 5 in synthetically useful enantiomeric excesses (entry 6, Table 1).

The divergent regioselectivity of the (DHQD)2AQN-catalyzed alcoholysis for (R)- and (S)-2-methyl succinic anhydrides (R- and S-1a), respectively, is demonstrated experimentally (Scheme 1). Commercially available optically pure R- and S-2-methyl succinic acids were converted respectively to the corresponding optically pure 2-methyl succinic anhydrides (R- and S-1a), which were next individually subjected to (DHQD)2AQN-catalyzed trifluoroethanolysis. While R-1a was converted to succinates 7a and 6a in a ratio of 97:3, the alcoholysis of S-1a under the identical condition affords S-6a and -7a in a ratio of 92:8. We also demonstrated that, with a given enantiomer of 1a (R- or S-1a), the regioselectivity of ring-opening alcoholysis can be controlled by choosing either (DHQD)2AQN or (DHQ)2AQN as the catalyst.
The mixture of succinates 9 and 10 was converted to β- and α-aryl-γ-butyrolactones (11 and 12), which are chromatographically readily separable. The highly enantioselective generation of β-aryl-γ-butyrolactones (11) in excellent overall yields from racemic anhydrides 8 represents a general and new route toward this versatile and pharmaceutically important class of chiral intermediates. Compared to other catalytic enantioselective approaches,13 the route described here is particularly attractive for employing simple and mild experimental protocols involving easily accessible starting material, cheap reagents, and a readily available and fully recyclable catalyst. Given that lactone 11c has previously been converted in excellent yield to baclofen,14 its highly enantioselective generation via the parallel kinetic resolution of racemic anhydride 8c could serve as a key step for the efficient synthesis of this effective GABA receptor agonist which is a therapeutic reagent for muscle spasticity.15 The crucial role played by the parallel kinetic resolution process in this route can be appreciated, considering that a conventional kinetic resolution of a selectivity factor of at least 112 would be required to obtain lactone 11c from racemic anhydrides 8 with the same ee and yield afforded by the parallel kinetic resolution process.16 Such an extraordinary enantioselectivity is beyond the reach of most known chemical kinetic resolution processes.

In summary, we have developed a new catalytic method for the synthesis of optically active succinate mono esters via a highly efficient parallel kinetic resolution process, which involves two simultaneous enantioselective and divergently regioselective alcoholyses of two enantiomers of the monosubstituted succinic anhydrides promoted by a common bis-cinchona alkaloid derivative.17 To our knowledge, this is the first case of an efficient catalytic parallel kinetic resolution of racemic bifunctional substrates mediated by a single organic catalyst. In our studies of modified cinchona alkaloid-catalyzed asymmetric alcoholysis of cyclic anhydrides, we have demonstrated that a catalyst that promotes desymmetrizations of meso or prochiral bifunctional substrates may also catalyze the parallel kinetic resolution of related racemic bifunctional substrates. This trend could, in principle, occur with other catalytic transformations of bifunctional substrates.

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**Supporting Information Available:** Experimental details (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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**Table 2.** (DHQD)$_2$AQN-Catalyzed Parallel Kinetic Resolution of 2-Alkyl Succinic Anhydrides$a,b$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>% ee$^c$</th>
<th>% Yield$^d$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1c</td>
<td>1a: R = −Me</td>
<td>44/55</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td>1b: R = −Et</td>
<td>40/60</td>
<td>91</td>
</tr>
<tr>
<td>3</td>
<td>1c: R = −n-C$_4$H$_9$</td>
<td>42/56</td>
<td>98</td>
</tr>
<tr>
<td>4d</td>
<td>1d: R = −CH$_2$CH=CH$_2$</td>
<td>46/53</td>
<td>96</td>
</tr>
</tbody>
</table>

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$a$ Unless noted otherwise, the reaction was performed by treatment of 1 (1.0 mmol) at 0.02 M with CH$_3$CO$_2$H (10 equiv) and (DHQD)$_2$AQN (15 mol %). $^b$ Catalyst was recovered in quantitative yield as described in Supporting Information. $^c$ See Supporting Information for details of ee analysis. $^d$ Isolated yield.

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**Table 3.** Asymmetric Synthesis of β-Aryl-γ-Lactones (11) via Parallel Kinetic Resolution of 2-Aryl-Succinic Anhydrides (8)$^e$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>% ee$^e$</th>
<th>% ee$^f$ (yield$^d$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1c</td>
<td>8a: Ar = Ph</td>
<td>95</td>
<td>87 (95 (44))</td>
</tr>
<tr>
<td>2</td>
<td>8b: Ar = 3-MeO- C$_6$H$_4$</td>
<td>96</td>
<td>83 (95 (45))</td>
</tr>
<tr>
<td>3</td>
<td>8c: Ar = 4-Cl-C$_6$H$_4$</td>
<td>96</td>
<td>76 (96 (44))</td>
</tr>
</tbody>
</table>

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$^e$ See footnote a of Table 2 for reaction conditions. $^f$ See Supporting Information for ee determination. $^d$ See Supporting Information for absolute configuration determination. $^c$ Isolated yield from 8. $^d$ With (DHQD)$_2$AQN, ent-11a was obtained in 44% yield and 88% ee.

(Scheme 1). The sequence outlined in Scheme 1 thus constitutes the first example of a reagent-controlled, highly regioselective catalytic functionalization of optically active monosubstituted succinic acids and succinic anhydrides.11

The scope of the parallel kinetic resolution was first investigated with a series of racemic 2-alkyl succinic anhydrides (Table 2). Racemic succinic anhydrides bearing alkyl groups with a range of steric properties are effectively resolved to afford the corresponding 3-alkyl succinates (6) in 91–98% enantiomeric excesses and 36–40% isolated yields. The 2-alkyl succinates (7) are obtained in 66–82% ee and 41–50% isolated yields. It is important to note that mixtures of hemiesters 6 and 7 can be separated via normal chromatographic purifications.

We were particularly pleased to find that the efficiency of the parallel kinetic resolution remains high with 2-aryl succinyl anhydrides with either an electron-rich or -poor aromatic ring (Table 3). Optically active 3- and 2-aryl succinate mono esters (9 and 10), previously inaccessible from catalytic enantioselective approaches,10,12 are generated in 95–96 and 76–87% ee, respectively. When treated sequentially with LiBr$_2$H and aqueous HCl,


(12) For an efficient chiral auxiliary-based approach, see ref 9b.


(16) The minimum value of the required stereoselectivity factor ($s = k_{fast}$/$k_{slow}$) was calculated using the equation $s = \ln[1 - (1 + ee)]/\ln[1 - (1 - ee)]$, where the isolated yield of 11c from 8c (44%) is used as the value for C (conversion of the reaction).