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

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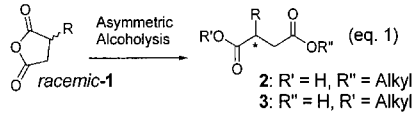
Received July 20, 2001

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 maximize the enantiomeric excess attainable for a product generated via kinetic resolution reactions. However, the development of catalytic parallel kinetic resolutions that affords synthetically useful efficiency with an extensive range of substrates remains highly challenging.[3−6] We report here a broadly effective parallel kinetic resolution mediated by a single organic catalyst that transforms readily accessible racemic monosubstituted succinic anhydrides into synthetically valuable chiral succinate mono esters in high enantiomeric excesses.

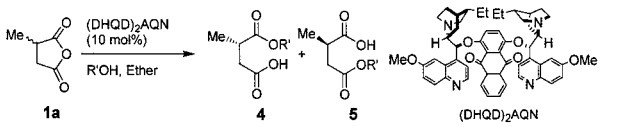
We recently discovered that modified cinchona alkaloids are highly effective chiral Lewis base catalysts for desymmetrization of cyclic anhydrides.[7,8] In view of the synthetic utility of optically active monosubstituted succinate mono esters (**2**, **3**),[9,10] we began to explore their asymmetric synthesis via a modified cinchona alkaloid-catalyzed kinetic resolution of racemic monosubstituted succinic anhydrides (eq 1). Reaction of racemic 2-methylsuccinic



(eq. 1)

anhydride (**1a**, R = Me) with methanol (10 equiv) in ether at room temperature in the presence of $(DHQD)_2AQN$ (10 mol %) was completed in 4 h to afford mono esters **4** and **5** in a ratio of 39:61 (entry 1, Table 1). Furthermore, **4** and **5** were shown by GC analyses to be formed at similar rates throughout the course of the reaction. Surprisingly, we found that **4** and **5** were produced in 74 and 67% ee, respectively. This data indicated that the two enantiomers of anhydride **1a** were converted to optically active hemiesters **4** and **5**, respectively, at similar rates via two parallel enantioselective methanolyses of divergent regioselectivities catalyzed by a common catalyst, $(DHQD)_2AQN$.

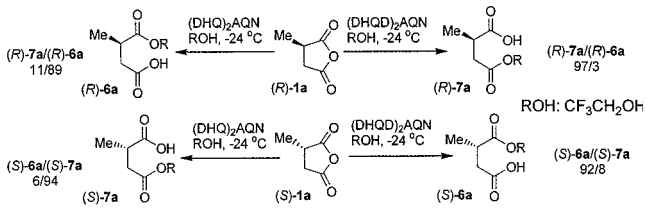
Table 1. $(DHQD)_2AQN$-Catalyzed Parallel Kinetic Resolution of Methylsuccinic Anhydride



entry	R′OH	temp/°C	% conv[a]	**4**/**5**[b]	% ee, **4**[b]	% ee, **5**[b]
1	MeOH	25	100	39/61	74	67
2	EtOH	25	100	49/51	82	67
3	*n*-PrOH	25	100	45/55	81	72
4	*i*-PrOH	25	<2	−	−	−
5	CF_3CH_2OH	25	100	49/51	85[c]	72[c]
6	CF_3CH_2OH	−25	100	44/56	91[c]	80[c]

[a] Determined by GC or NMR analysis. [b] Determined by HPLC analysis as described in Supporting Information. [c] The absolute configuration is determined by comparison with an authentic sample (see Supporting Information).

Scheme 1. Reagent-Controlled Highly Regioselective Alcoholysis of (*R*)- and (*S*)-Methylsuccinic Anhydrides with Modified Cinchona Alkaloids



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 triflouroethanol 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 *R*-**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

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(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.

(2) (a) Vedejs, E.; Rozners, E. *J. Am. Chem. Soc.* **2001**, *123*, 2428. (b) Vedejs, E.; Chen, X. *J. Am. Chem. Soc.* **1997**, *119*, 2584.

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

(4) For examples using chiral metal complexes, see: (a) Bertozzi, F.; Crotti, P.; Macchia, F.; Pineschi, M.; Feringa, B. L. *Angew. Chem., Int. Ed*. **2001**, *40*, 930. (b) Doyle, M. P.; Dyatkin, A. B.; Kalinin, A. V.; Ruppar, D. A.; Martin, S. F.; Spaller, M. R.; Liras, S. *J. Am. Chem. Soc.* **1995**, *117*, 11021. (c) Visser, M. S.; Hoveyda, A. H. *Tetrahedron* **1995**, *51*, 4383. (d) Bolm, C.; Schlingloff, G. *J. Chem. Soc., Chem. Commun*. **1995**, 1247. (e) Martin, S. F.; Spaller, M. R.; Liras, S.; Hartmann, B. *J. Am. Chem. Soc.* **1994**, *116*, 4493.

(5) For examples using enzymes, see: (a) Ozegowski, R.; Kunath, A.; Sehick, H. *Liebigs Ann*. **1995**, 1699. (b) Mischitz, M.; Faber, K. *Tetrahedron Lett*. **1994**, *35*, 81. (c) Petit, F.; Furstoss, R. *Tetrahedron: Asymmetry* **1993**, *4*, 1341. (d) Alphand, V.; Furstoss, R. *J. Org. Chem*. **1992**, *57*, 1306.

(6) For a kinetic resolution involving two different reactions for a complete conversion of starting material to a single optically active product, see: Feng, X.; Shu, L.; Shi, Y. *J. Am. Chem. Soc.* **1999,** *121*, 11002.

(7) Chen, Y.; Tian, S.-K.; Deng, L. *J. Am. Chem. Soc.* **2000**, *122*, 9542.

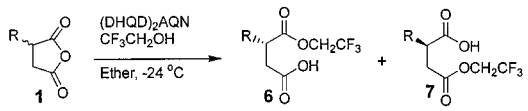
(8) For catalytic desymmetrizations of cyclic anhydrides with natural cinchona alkaloids, see: (a) Hiratake, J.; Yamamoto, Y.; Oda, J. *J. Chem. Soc., Chem. Commun.* **1985,** 1717. (b) Bolm, C.; Schiffers, I.; Dinter, C. L.; Gerlach, A. *J. Org. Chem.* **2000,** *65*, 6984.

(9) For select applications of monosubstituted chiral succinates, see: (a) Sibi, M.; Deshpande, P. K. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1461. (b) Evans, D. A.; Wu, L. D.; Wiener, J. J. M.; Johnson, J. S.; Ripin, D. H. B.; Tedrow, J. S. *J. Org. Chem*. **1999**, *64*, 6411.

(10) For preparations of chiral succinates via catalytic asymmetric hydrogenations, see: Burk, M. J.; Bienewald, F.; Harris, M.; Zanotti-Gerosa, A. *Angew. Chem., Int. Ed*. **1998**, *37*, 1931.

10.1021/ja011766h CCC: $20.00
Published on Web 10/16/2001

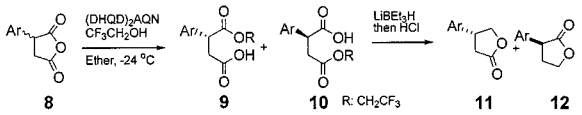
Table 2. $(DHQD)_2AQN$-Catalyzed Parallel Kinetic Resolution of 2-Alkyl Succinic Anhydrides[a,b]



entry	substrate	6/7	% ee[d] 6	% ee[d] 7	% yield[e] 6	% yield[e] 7
1[c]	**1a**: R = −Me	44/55	93	80	36	41
2	**1b**: R = −Et	40/60	91	70	38	50
3	**1c**: R = $-n$-C_8H_{17}	42/56	98	66	38	41
4	**1d**: R = $-CH_2CH{=}CH_2$	46/53	96	82	40	49

[a] Unless noted otherwise, the reaction was performed by treatment of **1** (1.0 mmol) at 0.02 M with CF_3CH_2OH (10 equiv) and $(DHQD)_2AQN$ (15 mol %). [b] Catalyst was recovered in quantitative yield as described in Supporting Information. [c] 20 mol % catalyst was used. [d] See Supporting Information for details of ee analysis. [e] Isolated yield.

Table 3. Asymmetric Synthesis of β-Aryl-γ-Lactones (**11**) via Parallel Kinetic Resolution of 2-Aryl-Succinic Anhydrides (**8**)[a]



entry	substrate	% ee[b,c] 9	% ee[b,c] 10	% ee[b,c] (yield[d]) 11	% ee[b,c] (yield[d]) 12
1[e]	**8a**: Ar = Ph	95	87	95 (44)	82 (32)
2	**8b**: Ar = 3-MeO−C_6H_4	96	83	95 (45)	83 (30)
3	**8c**: Ar = 4-Cl−C_6H_4	96	76	96 (44)	63 (29)

[a] See footnote *a* of Table 2 for reaction conditions. [b] See Supporting Information for ee determination. [c] See Supporting Information for absolute configuration determination. [d] Isolated yield from **8**. [e] With $(DHQ)_2AQN$, 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 succinnates (**6**) in 91−98% enantiomeric excesses and 36−40% isolated yields. The 2-alkyl succinnates (**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 succinic 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 $LiBEt_3H$ and aqueous HCl, 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 succinnate 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.

Acknowledgment. We gratefully acknowledge the financial support of NIH (GM-61591), the Harcourt General Charitable Foundation and Research Corporation (RI-0311).

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

JA011766H

(11) For an enzyme-catalyzed regioselective alcoholysis of cyclic anhydrides, see: Hiratake, J.; Yamamoto, K.; Yamamoto, Y.; Oda, J. *Tetrahedron Lett*. **1989**, *30*, 1555.

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

(13) (a) Takaya, Y.; Senda, T.; Kurushima, H.; Ogasawara, M.; Hayashi, T. *Tetrahedron: Asymmetry* **1999**, *10*, 4047. (b) Bolm, C.; Luong, T. K. K.; Schlingloff, G. *Synlett* **1997**, 115. (c) Dawson, G. J.; Williams, M. J. *Tetrahedron: Asymmetry* **1995**, *6*, 2535. (d) Doyle, M. P.; Oeveren, A. V.; Westrum, L. J.; Protopopova, M. N.; Clayton, T. W., Jr. *J. Am. Chem. Soc.* **1991**, *113*, 8982.

(14) (a) Mazzini, C.; Lebreton, J.; Alphand, V.; Furstoss, R. *Tetrahedron Lett*. **1997**, *38*, 1195. (b) Schoenfelder, A.; Mann, A.; Coz, S. L. *Synlett* **1993**, 63.

(15) Olpe, H. R.; Demiéville, H.; Baltzer, V.; Bencze, E. L.; Koella, W. P.; Wolf, P.; Haas, H. L. *Eur. J. Pharmacol*. **1978**, *52*, 133.

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

(17) For a resolution of racemic 4-methyl-1,2,3,6-tetrahydrophthalic anhydride using a chiral mediator-promoted alcoholysis see: Seebach, D.; Jaeschke, G.; Gottawald, K.; Matsuda, K.; Formisano, R.; Chaplin, D. A.; Breuning, M.; Bringmann, G. *Tetrahedron* **1997**, *53*, 7539.