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Dynamic Kinetic Resolution via Dual-Function Catalysis of Modified Cinchona Alkaloids: Asymmetric Synthesis of α-Hydroxy Carboxylic Acids

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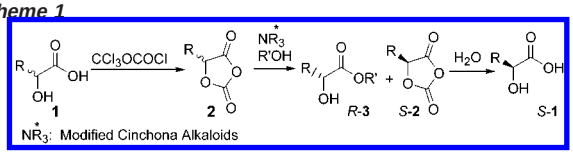
Optically active α-hydroxy acids are ubiquitous structural motifs in numerous biologically interesting natural and unnatural compounds.[1] Accordingly, considerable effort has been devoted to the asymmetric synthesis of α-hydroxy acids.[2−5] Catalytic methods based on chiral transition metal complexes have emerged as promising nonenzymatic approaches.[4,5] We recently reported that modified cinchona alkaloids catalyzed highly enantioselective ring-opening alcoholyses of cyclic anhydrides and *N*-carboxyanhydrides.[6] We envisaged that an efficient cinchona alkaloid-catalyzed kinetic resolution of 1,3-dioxolane-2,4-diones **2** could provide a new, straightforward and metal-free catalytic approach toward optically active α-hydroxy acids from their readily accessible racemic counterparts (Scheme 1). Furthermore, the acidic nature of the α-proton of dioxolanediones **2** presented us with an attractive opportunity to develop an efficient dynamic kinetic resolution.[7] Ideally the cinchona alkaloids could serve dual catalytic roles to mediate both the enantioselective alcoholytic ring opening and the in situ racemization of **2** (Scheme 2). We report here progress toward achieving these goals.

Condensations of α-hydroxy acids with phosgene or one of its equivalents represent a direct route for the preparation of dioxolanediones **2**. However, very few such condensations were reported.[8] In the best procedure, reported by Toyooka, reaction of α-hydroxy acids with trichloromethyl chloroformate (diphosgene) in refluxing THF produced **2** in 46−78% yield.[8a] Using this procedure, we found that α-hydroxy acids **1** reacted with diphosgene cleanly. However, a significant amount of 4-chlorobutyl chloroformate was produced. A yield-compromising recrystalization or distillation was required for the purification of **2**. We performed the condensation at room temperature with activated charcoal[9] and found that **2** was formed cleanly, while the amount of 4-chlorobutyl chloroformate in the reaction mixture was reduced nearly 10-fold. Filtration of the reaction mixture followed by solvent evaporation afforded dioxolanediones **2a**−**n** in high yield and greater than 95% purity (Table 1).

We next focused on the kinetic resolution of 5-phenyl-1,3-dioxolane-2,4-dione (**2a**). Reaction of racemic **2a** with ethanol in ether in the presence of $(DHQD)_2AQN$ (10 mol %) proceeded to completion within 24 h at −78 °C. The enantiomeric excesses of the product (**3a**) and the starting material (**2a**) were determined at various conversions and were found to remain constant at 95% and nearly 0%, respectively. In control experiments, we found that treatment of optically pure **2a** with $(DHQD)_2AQN$ generated the corresponding racemic mixture within minutes. Also the $(DHQD)_2AQN$-catalyzed alcoholysis of either (*R*)- or (*S*)-**2a** gave the same product, (*R*)-**3a**, in 95% ee. Neither racemization nor alcoholysis occurred without the amine catalyst. These results establish that $(DHQD)_2AQN$ serves a dual role, mediating both the in situ racemization of **2a** and the enantioselective alcoholysis of

Scheme 1



Scheme 2

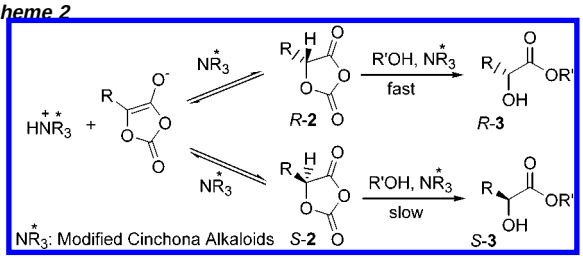
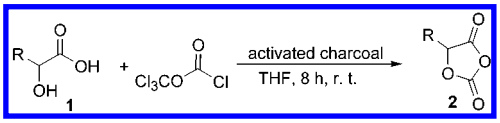


Table 1. Preparations of 5-Substituted 1,3-Dioxolane-2,4-diones[a]



entry		R	yield/%	entry		R	yield/%
1	**a**	C_6H_5	100	8	**h**	1-naphthyl	100
2	**b**	4-Cl−C_6H_4	100	9	**i**	2-Cl−C_6H_4	100
3	**c**	4-Br−C_6H_4	100	10	**j**	2-Me-C_6H_4	95
4	**d**	4-F−C_6H_4	100	11	**k**	$C_6H_5CH_2$	95
5	**e**	4-CF_3-C_6H_4	100	12	**l**	$C_6H_5CH_2CH_2$	97
6	**f**	4-^{i}Pr-C_6H_4	100	13	**m**	$CH_3(CH_2)_3$	92
7	**g**	3,4-F_2-C_6H_3	100	14	**n**	$(CH_3)_2CH$	90

[a] See Supporting Information for experimental details.

(*R*)-**2a**. The racemization is much faster than the alcoholysis. Consequently, both enantiomers of racemic **2a** are converted to a single optically active product (**3a**) via an efficient dynamic kinetic resolution mediated by a single catalyst, $(DHQD)_2AQN$.

Efficient dynamic kinetic resolutions by synthetic catalysts are scarce.[10−12] We were pleased to observe that efficient dynamic kinetic resolutions were achieved for a variety of 5-aryl-1,3-dioxolane-2,4-diones (**2a**−**h**, Table 2), affording esters **3a**−**h** in 90−96% ee and isolated yields (65−85%) far exceeding the maximum (50%) for a conventional kinetic resolution.[13] The use of $(DHQD)_2AQN$ consistently afforded (*R*)-**3** as the only detectable product by both GC and HPLC analysis. However, a NMR analysis of the crude reaction mixture revealed the formation of minor side products which are possibly $H(OCHRCO)_nOEt$.[8b] The efficiency of the dynamic kinetic resolution was reduced with dioxolanediones (**2i**−**j**) bearing an *o*-substituted benzene ring (entry 9−10, Table 2). The ee of esters **3i**−**j** was found to decrease gradually as the reaction proceeded to completion (90 to 62% for **3i** and 85 to 60% for **3j**). The initially high ee indicates that the alcoholyses of **2i**−**j** are still highly enantioselective. The reduced efficiency of the

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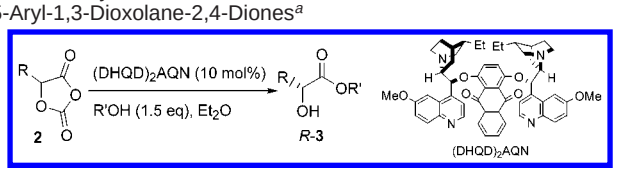
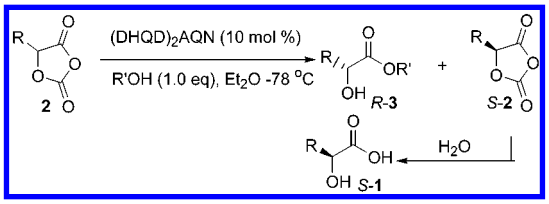
Table 2. Dynamic Kinetic Resolution of 5-Aryl-1,3-Dioxolane-2,4-Diones[a]



entry		R	R′OH	T/°C	time/h	yield/%[d]	ee/%
1	**a**	C_6H_5[b]	EtOH	−78	24	71	95
2	**b**	4-Cl−C_6H_4	EtOH	−78	24	70	96
3	**c**	4-Br−C_6H_4	EtOH	−78	24	80	96
4	**d**	4-F−C_6H_4	EtOH	−78	24	65	95
5	**e**	4-CF_3-C_6H_4	EtOH	−78	24	85	93
6	**f**	4-^{i}Pr−C_6H_4	EtOH	−20	8	68	91
7	**g**	3,4-F_2-C_6H_3	EtOH	−78	24	65	94
8	**h**	1-naphthyl[c]	^{n}PrOH	−40	14	74	91
9	**i**	2-Cl−C_6H_4	EtOH	−60	10	66	62
10	**j**	2-Me-C_6H_4	EtOH	−20	4	61	60

[a] Unless noted, the reaction was performed with **2** (1.0 mmol) in ether (50 mL) and went to completion, see Supporting Information for experimental details. [b] When the reaction was performed with $(DHQ)_2AQN$ (20 mol %), S-**3a** was obtained in 73% yield and 88% ee. [c] This reaction was perfomed in THF. *R*-**3h** was obtained in 88% ee with EtOH. [d] Isolated yield.

Table 3. Kinetic Resolution of 5-Alkyl 1,3-Dioxolane-2,4-diones[a]



					ee (yield)[b]/%		
entry		R	R′	time/h	*S*-**1**	*R*-**3**	s[c]
1	**k**	$PhCH_2$	Et	12	95 (39)	96 (47)	133
2	**l**	$PhCH_2CH_2$	Et	24	85 (40)	93 (46)	67
3	**m**	$CH_3(CH_2)_3$	Et	36	95 (36)	92 (46)	57
4	**n**	$(CH_3)_2CH$	Allyl	6	93 (32)	90 (48)	49

[a] The reaction was perfromed with **2** (1.0 mmol) in ether (50 mL), see Supporting Information for experimental details. [b] Isolated yield. [c] The lower limit of the selectivity factor *s* was estimated using the equation $s = k_f/k_s = \ln[1 - C(1 + ee)]/\ln[1 - C(1 - ee)]$, where ee is the percent enantiomeric excess of the product **3** and the isolated yield of **3** was used as the value for *C* (conversion of the reaction).

dynamic kinetic resolution is therefore caused by the slow racemizations of **2i**−**j** relative to their alcoholyses.[14] The enantioselectivity of the reaction remains high when the aryl groups in **2** are replaced by alkyl groups of various length and bulk (Table 3). Although the reduced acidity of the α-proton renders **2k**−**n** unepimerizable with $(DHQD)_2AQN$, the highly enantioselective ring opening of **2** afforded both *S*-**2** and *R*-**3** in high optical purity. The crude mixture containing **2** and **3** was subjected to hydrolysis to give a mixture of acid **1** and ester **3**. Both **1** and **3** were obtained in excellent ee and good yields following an extractive purification (Table 3).

In summary, we have developed a new catalytic approach toward optically active α-hydroxy acid derivatives via a highly enantioselective kinetic resolution of dioxolanediones **2**. The reaction employs accessible substrates, reagents, catalysts, and a simple protocol with mild conditions. The realization of an efficient dynamic kinetic resolution of 5-aryl-1,3-dioxolane-2,4-diones with a chiral amine-catalyzed acyl-transfer reaction is conceptually interesting. It adds a new dimension to the scope of asymmetric acyl-transfer catalysis by synthetic catalysts.[3c−d,11,15] The demonstration of a chiral organic Lewis base as a dual-function catalyst provides experimental proof for a new approach for the development of efficient catalytic dynamic kinetic resolutions, which remain among the most challenging, yet desirable, goals in catalytic asymmetric synthesis.[11]

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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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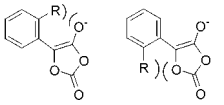
(14) The repulsion shown below between the ortho substituent and the dioxolanedione ring renders enolates derived from **2i**−**j** less stable than those derived from **2a**−**g**. This in turn slows down the racemizations of **2i**−**j**.



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