Asymmetric Synthesis of α-Amino Acids via Cinchona Alkaloid-Catalyzed Kinetic Resolution of Urethane-Protected α-Amino Acid *N*-Carboxyanhydrides

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Acyl-transfer reactions use cheap reagents to transform readily available starting materials into useful and easily purified products. These characteristics, in combination with high enantioselectivity, enable acyl-transfer reactions catalyzed by enzymes such as lipases and esterases to become highly valuable methods for asymmetric synthesis.[1] The development of synthetic catalysts to mimic lipases/esterases with the goal of further expanding the scope of asymmetric acyl transfer catalysis is of both conceptual and practical significance for asymmetric catalysis.[2] Although effective phosphorus and nitrogen synthetic catalysts for the kinetic resolution of racemic alcohols have emerged,[3,4] efforts to develop small molecule-catalyzed kinetic resolutions of racemic carbonyl derivatives have met with limited success despite their great potential in asymmetric synthesis.[5] We report here an exceedingly general and highly enantioselective kinetic resolution of urethane-protected α-amino acid *N*-carboxyanhydrides (UNCA) that generates optically active α-amino acid derivatives suitable for further synthetic elaboration such as peptide synthesis.

Encouraged by our discovery of modified cinchona alkaloids as efficient catalysts for asymmetric alcoholysis of meso and racemic cyclic anhydrides,[6−8] we became interested in the kinetic resolution of urethane-protected α-amino acid *N*-carboxyanhydrides (UNCA, **2**) via cinchona alkaloid-catalyzed alcoholysis (Scheme 1). UNCAs (**2**) can be easily prepared from the readily available racemic amino acids (**1**).[9] Their alcoholysis generates the carbamate-protected amino ester **3** and CO_2. When suitably protected, amino ester **3** will not interfere with the cinchona alkaloid-catalyzed alcoholysis. Furthermore, the unreacted enantiomerically enriched UNCA (**2**) can be hydrolyzed to protected amino acid (**4**) (Scheme 1). The resulting mixture of the basic amine catalyst, the acidic amino acid (**4**) and the neutral amino ester (**3**), can be separated using simple extractive procedures to give **3**, **4**, and the recovered amine catalyst in desired chemical and optical purity.

Scheme 1

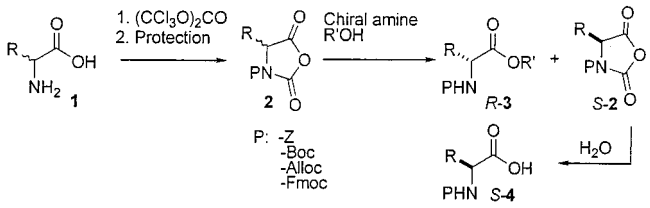
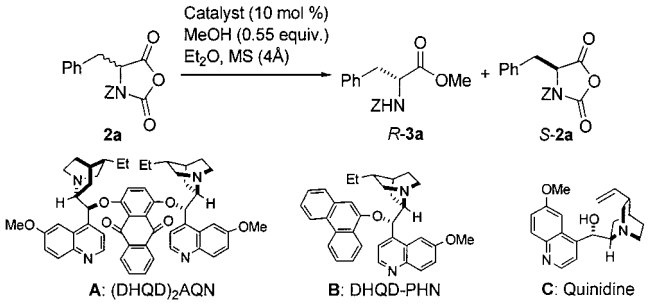


Table 1. Kinetic Resolution of UNCA **2a** with Cinchona Alkaloids[a,b]



entry	catalyst	T/°C	conv/%	ee of **3a**/%	s [c]
1	A	25	42	80	16
2	A	-60	50	92	79
3	B	-60	45	91	47
4	C[d]	-60	44	86	27

[a] The reaction was performed with **2a** (0.1 mmol) in ether (7.0 mL). [b] See Supporting Information for experimental details. [c] Selectivity factor, $s = k_f/k_s = \ln[1 - C(1 + \text{ee})]/\ln[1 - C(1 - \text{ee})]$, where ee is the percent enantiomeric excess of **3a** and C is the conversion. [d] 20 mol % catalyst was used.

We initially utilized racemic *N*-Cbz-phenylalanine NCA (**2a**) as a model substrate. Reaction of **2a** with methanol (0.55 equiv) in ether at room temperature with $(DHQD)_2AQN$ (10 mol %) and molecular sieves (4 Å) afforded ester **3a** in 80% ee at 42% conversion, corresponding to a selectivity factor (*s*) of 16 for the kinetic resolution (entry 1, Table 1). Importantly, the enantioselectivity of the kinetic resolution could be dramatically improved at low temperature and, at −60 °C, reached a level ($s = 79$, entry 2, Table 1) comparable to that of an enzyme-catalyzed resolution. Further catalyst screening studies revealed that $(DHQD)_2AQN$ is the most effective catalyst. Notably, high enantioselectivity is also achieved with the monocinchona alkaloids, DHQD-PHN, and quinidine (entries 3, 4, Table 1). Interestingly, under the same conditions, other related amines such as $(DHQD)_2PYR$, $(DHQD)_2$-PHAL, DHQD-MEQ, DHQD-CLB, and quinuclidine afforded only minuscule conversions (1−4%). Subsequently, a preparative scale kinetic resolution of **2a** (4.0 mmol) is found to proceed cleanly to allow the isolation of ester **3a** and acid **4a** in nearly quantitative yields and high ee and the full recovery of the catalyst (Table 2) using an extractive procedure.[10] The recovered catalyst was reused for another reaction cycle, showing no deterioration in catalytic activity and selectivity (Table 2).

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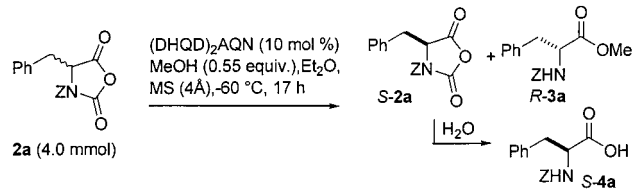
Table 2. Preparative Scale Resolution of **2a** with Recycled $(DHQD)_2AQN$



cycle	conv[a]	ee (yield[b]) /% 3a	4a	*s*
1	51	93 (48)	97 (48)	114
2[c]	52	91 (49)	98 (47)	104

[a] The conversion, calculated using the equation: $C = 100 \times ee_{2a}/(ee_{3a} + ee_{2a})$, is consistent with that determined experimentally, see Supporting Information. [b] Isolated yield. [c] Reaction is performed with recycled $(DHQD)_2AQN$.

Table 3. Kinetic Resolution of UNCA (**2**) via Modified Cinchona Alkaloid-Catalyzed Alcoholysis[a]

entry	UNCA **2**			temp (°C)	time (h)	conv[b] (%)	ee[c] (yield)/%[d] (*S*)-**4**	(*R*)-**3**	*s*[e]
		R	P						
1	**a**	$PhCH_2$[f]	Cbz	−60	17	51	98 (48)	93 (48)	114
2	**b**	4-F−$C_6H_4CH_2$	Cbz	−78	31	50	93 (42)	92 (48)	79
3	**c**	4-Cl−$C_6H_4CH_2$	Cbz	−60	18	52	97[i] (43)	88 (52)	59
4	**d**	4-Br−$C_6H_4CH_2$	Cbz	−78	45	51	92[i] (39)	87 (51)	45
5	**e**	2-thienylmethyl	Cbz	−78	25	50	95 (47)	94 (49)	115
6	**f**	$CH_3(CH_2)_5$	Cbz	−60	37	51	94[i] (42)	91 (49)	78[j]
7	**g**	$BnOCH_2$	Cbz	−78	72	52	96 (44)	89 (49)	69
8	**h**	$(CH_3)_2CH$[g]	Cbz	0	22	59	96 (40)	67 (58)	19
9	**i**	Ph[h]	Cbz	−78	16	46	84 (46)	97 (45)	170
10	**j**	4-MeO−C_6H_4[h]	Cbz	−78	85	56	95 (43)	74 (56)	23
11	**k**	$PhCH_2$	Fmoc	−78	46	51	96 (47)	92 (50)	93
12	**l**	$PhCH_2$	Boc	−40	15	59	98 (41)	67 (56)	19
13	**m**	$PhCH_2$	Alloc	−60	15	50	91 (45)	91 (45)	67
14	**n**	$PhCH_2CH_2$	Alloc	−60	36	54	96[i] (41)	81 (53)	35

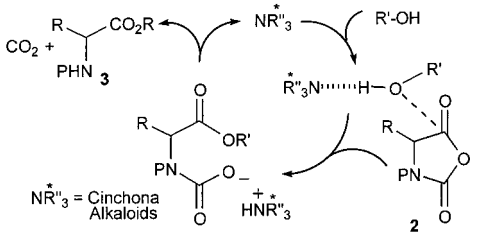
[a] Unless noted, the reaction was performed by treatment of **2** (0.1 mmol) with $(DHQD)_2AQN$ (10 mol %) and methanol (0.52−1.0 equiv) in ether (7.0 mL). [b] The calculated conversion, $C = 100 \times ee_2/(ee_3 + ee_2)$, is consistent with experimental value, see Supporting Information. The ee's of **4** and unreacted **2** are assumed to be equal. [c] For ee analysis and absolute configuration determination, see Supporting Information. [d] Isoluated yield. [e] See footnote *c* of Table 1. [f] The reaction employed 4.0 mmol of **2a**. [g] The reaction employed DHQD-PHN (20 mol %). [h] Ethanol was used as the nucleophile. [i] Absolute configurations are assigned by analogy. [j] *s* was determined to be 33 for kinetic resolution of **2f** with $(DHQ)_2AQN$.

The scope of the reaction was found to be extremely general. Clean kinetic resolutions of extraordinarily high enantioselectivities were attainable with a wide range of UNCAs bearing various substituents and protecting groups (Table 3). Using the same extractive procedure for the isolation of **3a** and **4a**, optically active α-amino esters **3** and amino acids **4** were routinely obtained in a combined yield of greater than 90%. Furthermore, (*R*)-**3** and (*S*)-**4** were obtained consistently from the $(DHQD)_2AQN$-catalyzed kinetic resolution of racemic-**2** (**a**−**b**, **e**, **g**−**m**).

Preliminary kinetic studies were carried out on the $(DHQD)_2$-AQN-catalyzed methanolysis of (*R*)-**2a** at −60 °C in toluene. In this solvent, the reaction mixture appeared homogeneous, and kinetic resolutions of racemic **2a** were found to proceed at similar rate and in high enantioselectivity with $(DHQD)_2AQN$ ($s = 41$) and DHQD-PHN ($s = 50$), respectively.[11] The reaction followed a first-order dependence on methanol, the substrate (**2a**) and either

(10) See Supporting Information for a detailed description of the extractive workup of the preparative-scale kinetic resolution of **2a**.

Scheme 2. General Base Catalysis for Cinchona Alkaloid-Catalyzed Alcoholysis of UNCA **2**



$(DHQD)_2AQN$ or DHQD-PHN. Moreover, a reproducible kinetic isotope effect ($k_{MeOH}/k_{MeOD} = 1.3$) was detected under pseudo-first-order reaction conditions. These results are most consistent with a general base catalysis mechanism (Scheme 2),[12] in which the ring opening of UNCA **2** by alcoholysis is the rate-determining step and is mediated by a single dihydroquinidinyl group.

In summary, we have developed the first efficient and general nonenzymatic catalytic method for the asymmetric synthesis of α-amino acids via a kinetic resolution strategy.[5a,13−15] With its extraordinary enantioselectivity and generality, the kinetic resolution of UNCA (**2**) via asymmetric alcoholysis catalyzed by cinchona alkaloids provides a useful and reliable catalytic entry into optically active amino acid derivatives that are suitably protected for further synthetic elaboration. These results constitute a significant progress toward achieving a small molecule-catalyzed kinetic resolution of racemic carbonyl derivatives with a broad substrate scope yet an enzyme-like efficiency. Results from our kinetic studies indicate that the cinchona alkaloids facilitate this remarkable catalytic kinetic resolution with one dihydroquinidinyl group and through weak interactions with the reacting 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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(11) For experimental details of kinetic studies, see: Supporting Information.

(12) For discussions and mechanistic studies of cinchona alkaloids-catalyzed alcoholysis of cyclic anhydrides, see: refs 7b and 8.

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