ORGANIC LETTERS

2002
Vol. 4, No. 19
3321−3324

Development of a Rapid, Room-Temperature Dynamic Kinetic Resolution for Efficient Asymmetric Synthesis of α-Aryl Amino Acids

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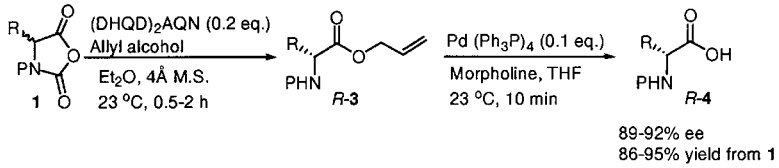
Received August 2, 2002

ABSTRACT



A rapid, highly efficient and general dynamic kinetic resolution (DKR) of racemic α-aryl UNCAs with the dual-function catalysis of modified cinchona alkaloid was accomplished at room temperature. This DKR led to the development of a highly enantioselective catalytic method for the practical synthesis of a wide range of α-aryl and α-heteroaryl amino acids in 89−92% ee and 86−95% yield from racemic UNCAs.

α-Aryl amino acids are particularly important nonproteinogenic amino acids because they are precursors for many biologically important compounds.[1] However, they are not accessible via some of the more established enantioselective catalytic methods for amino acid synthesis such as asymmetric hydrogenation[2] and asymmetric alkylation by phase transfer catalysis.[3] Although the asymmetric Strecker reaction,[4] aminohydroxylation of styrene derivatives,[5] and arylation of imines[6] have emerged recently as promising approaches, efficient catalytic asymmetric synthesis of α-aryl amino acids remains a challenging task. We recently reported that modified cinchona alkaloids promote highly enantioselective kinetic resolutions of urethane-protected α-amino acid *N*-carboxyanhydrides (UNCA).[7] We have also established that the cinchona alkaloids are able to serve dual catalytic roles, catalyzing both the racemization and the enantioselective alcoholytic ring opening, to facilitate efficient dynamic kinetic resolutions of 5-aryl dioxolanediones.[8] We are interested in expanding the scope of the dual-function catalysis of cinchona alkaloids in the context of developing new dynamic kinetic resolutions of synthetic utility.[9−11] In this paper, we describe a highly efficient dynamic kinetic resolution of α-aryl UNCAs for the asymmetric synthesis of a broad range of α-aryl amino acids.

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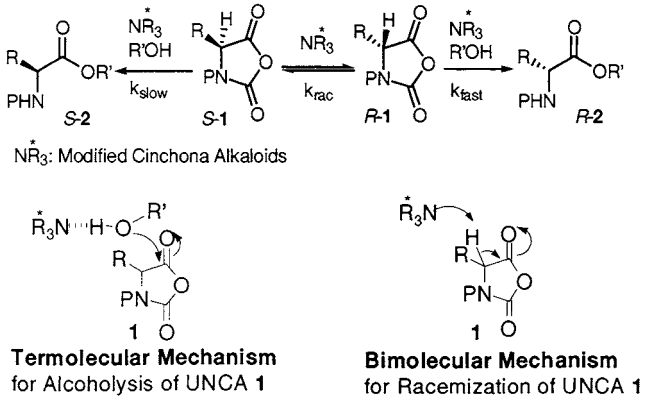
10.1021/ol026660l CCC: $22.00
Published on Web 08/17/2002

An efficient dynamic kinetic resolution requires that racemization be faster than highly enantioselective transformation of the racemic starting material.[12] The $(DHQD)_2$AQN-catalyzed racemization and alcoholysis of 5-phenyl dioxolanedione meets this requirement, thus allowing an efficient dynamic kinetic resolution of the racemic dioxolanedione at −78 °C. In contrast, alcoholysis of α-phenyl UNCA **1a** with $(DHQD)_2$AQN was found to be a highly enantioselective, but normal, kinetic resolution at −78 °C, indicating that the rate of racemization is negligible compared to the rate of alcoholysis of **1a** ($k_{rac} \ll k_{fast}$, k_{slow}).[7] The challenge for realizing a cinchona alkaloid-catalyzed dynamic kinetic resolution of UNCA (Scheme 1) is to accelerate the racemization relative to the alcoholysis while maintaining the large difference between k_{fast} and k_{slow}.

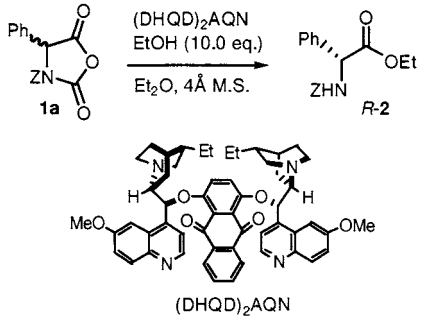
Scheme 1



Our kinetic studies indicate a general base catalysis mechanism for the $(DHQD)_2$AQN-catalyzed alcoholysis of UNCA **1**,[7] which involves the catalyst, UNCA **1**, and the alcohol in a termolecular transition state (Scheme 1). On the other hand, the racemization involving **1** and $(DHQD)_2$AQN is a bimolecular reaction (Scheme 1). The entropy of activation for the termolecular alcoholysis is expected to be more negative than that for the bimolecular racemization ($\Delta S^{\ddagger}$alcoholysis < $\Delta S^{\ddagger}$racemization). We reasoned that reinforcing this difference in the respective entropy of activation for the racemization and the alcoholysis by raising the reaction temperature could lead to a significantly accelerated racemization relative to the alcoholysis.

Our hypothesis was confirmed by results from ethanolysis of **1a** with $(DHQD)_2$AQN at various temperatures. As the temperature was raised from −78 to 34 °C, the rate of racemization increased relative to that of alcoholysis, as shown by the increasing enantiomeric ratio (er) of amino ester **2** at complete conversion of racemic **1a** (entries 2−7, Table 1). At 34 °C and with the addition of ethanol (1.2 equiv) over 1 h, the ee values of **1a** and **2** were found to be nearly constant throughout the course of the reaction at 0−5 and 86% ee, respectively, indicating that the racemization became faster than the alcoholysis under this condition (entry 8, Table 1). Further optimization by substituting ethanol with allyl alcohol resulted in a highly efficient dynamic kinetic resolution at room temperature, converting racemic **1a** to allyl amino ester **3a** in 91% ee and essentially quantitative yield (entry 1, Table 2).

Table 1. Acceleration of Racemization Relative to Alcoholysis of UNCA **1a** by Increasing Reaction Temperature[a]



entry	temp (°C)	time (h)	conv (%)	er of **2**[b]
1	−78	2.0	48	97:3
2	−78	336	100	56:44
3	−40	22	100	61:39
4	−20	3.0	100	66:34
5	0	1.0	100	72:28
6	23	0.3	100	78:22
7	34	0.2	100	79:21
8[c]	34	2.0	100	93:7

[a] Unless otherwise noted, the reaction was performed by treatment of **1a** (0.05 mmol) with $(DHQD)_2$AQN (20 mol %) and ethanol (10.0 equiv) in ether (3.5 mL) at the indicated temperature; see Supporting Information for details. [b] Determined by HPLC analysis; see Supporting Information. [c] Ethanol (1.2 equiv) was added as a solution in ether (1.0%, v/v) over 1.0 h; see Supporting Information for details.

The scope of the dynamic kinetic resolution was found to be general. Transformations of various racemic α-aryl UNCAs **1** into the corresponding optically active amino esters (*R*)-**3** with $(DHQD)_2$AQN were conveniently and rapidly achieved at room temperature in excellent enantioselectivity and 93−98% yields (Table 2). Complete conversion of racemic **1i** to (*S*)-**3i** was achieved with $(DHQ)_2$AQN but in only 74% ee at room temperature. The ee of (*S*)-**3i** was, however, found to be 85% at 20% conversion of **1i**, indicating that the unsatisfactory dynamic kinetic resolution was caused by the relatively slow racemization of **1i** with $(DHQ)_2$AQN. The dependence of the relative rates of

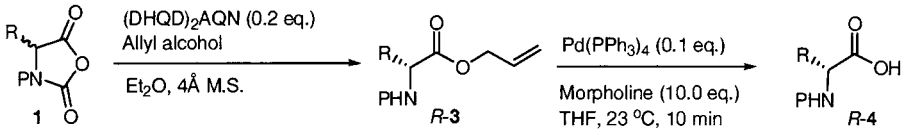
(9) Reviews on dynamic kinetic resolutions: (a) Huerta, F. F.; Minidis, A. B. E.; Bäckvall, J.-E. *Chem. Soc. Rev.* **2001**, *30*, 321. (b) Faber, K. *Chem. Eur. J.* **2001**, *7*, 5005. (c) Caddick, S.; Jenkins, K. *Chem. Soc. Rev.* **1996**, *25*, 447. (d) Ward, R. S. *Tetrahedron*: *Asymmetry* **1995**, *6*, 1475. (e) Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36.

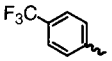
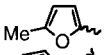
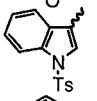
(10) For metal-catalyzed efficient dynamic kinetic resolutions see: (a) Jurkauskas, V.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 2892. (b) Noyori, R.; Ikeda, T.; Ohkuma, T.; Widhalm, M.; Kitamura, M.; Takaya, H.; Akutagawa, S.; Sayo, N.; Saito, T.; Taketomi, T.; Kumobayashi, H. *J. Am. Chem. Soc.* **1989**, *111*, 9134. (c) Schaus, S. E.; Jacobsen, E. N. *Tetrahedron Lett.* **1996**, *37*, 7937.

(11) For a study of dynamic kinetic resolutions of azlactones, see: Liang, J.; Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 3154.

(12) Kitamura, M.; Tokunaga, M.; Noyori, R. *J. Am. Chem. Soc.* **1993**, *115*, 144.

Table 2. Dynamic Kinetic Resolution of UNCA **1** with Alcoholysis by $(DHQD)_2AQN$ and $(DHQ)_2AQN$[a,b]



entry	R		P	temp (°C)	Time (h)	3 %ee[c]	3 %yield[d]	4 %ee[c]	4 %yield[e]
1		**a**	Cbz	23 (34)	1 (1)	91 (83)	97 (96)	90	91
2		**b**	Cbz	23	1	90	96	90	93
3		**c**	Cbz	23	1	92	97	92	92
4		**d**	Cbz	23	1	90	95	90	88
5		**e**	Cbz	-30	2	92	93	92	93
6		**f**	Cbz	23 (23)	1 (2)	91 (84)	95 (95)	91	94
7		**g**	Cbz	23 (-30)	0.5 (1)	91 (92)	98 (91)	89	86
8		**h**	Cbz	23 (0)	0.5 (0.5)	93 (92)	97 (93)	91	92
9		**i**	Cbz	0 (34)	1.5 (0.5)	90 (82)	95 (93)	89	95[f]
10		**j**	Fmoc	23	1	90	98	90	92[f,g]

[a]DKR procedure: A 1.0% (v/v) solution of allyl alcohol (0.24 mmol, 1.2 equiv) in ether was added over 0.15−1.0 h to a mixture of substrate **1** (0.20 mmol), $(DHQD)_2AQN$ (0.04 mmol, 0.2 equiv), and 4 Å MS (20 mg) in ether (14.0 mL) at the indicated temperature; see Supporting Information for details. [b] Results in parentheses were obtained from reactions with $(DHQ)_2AQN$, which afforded (*S*)-**3**. [c] For determinations of ee (**3** and **4**) and absolute configurations (**4a**,**c**,**e**,**f**,**j**), see Supporting Information. [d] Isolated yield. [e] Unless otherwise noted, the yield is overall isolated yield from **1** using an extractive procedure; see Supporting Information. [f]Purified by flash chromatography as described in Supporting Information. [g] Morpholine (1.5 equiv) was used in transformation of **3j** to **4j**.

racemization and alcoholysis of UNCAs on temperature provided us with a handle for fine-tuning the dynamic kinetic resolution. As expected, the efficiency of the dynamic kinetic resolution of **1i** was improved at 34 °C, affording (*S*)-**3i** in 82% ee and 93% yield (entry 9, Table 2). As shown in Table 2 (entries 1 and 6−9), dynamic kinetic resolutions with either $(DHQD)_2AQN$ or $(DHQ)_2AQN$ at or near room temperature provide high yield and highly enantioselective access to either enantiomer of amino esters **3**.

Ring opening of UNCAs **1** with allyl alcohol offers an important benefit, generating optically active allyl amino esters (**3**) that can be transformed into the corresponding amino acids (**4**) under mild conditions. The clean dynamic kinetic resolution permits us to use an extractive procedure to fully recover the catalyst and to isolate crude **3** of already high purity (no detectable impurity by NMR and HPLC analysis) in quantitative fashion. Amino esters **3** thus obtained were converted at room temperature in excellent yields to amino acids **4** without deterioration in ee following Kunz's procedure.[13] Consequently, suitably protected α-aryl amino acids (**4**) of high optical purity, including those bearing indole, furan, and thiophene rings, were obtained from corresponding racemic UNCAs (**1**) in 86−95% overall yields, in most cases, involving no chromatographic separation (Table 2). On a preparative scale (4.0 mmol), amino acid **4h** of 91% ee was obtained from (±)-**1h** in 94% yield. To our knowledge, no efficient nonenzymatic catalytic asymmetric synthesis of amino acids bearing α-heterocycles, such as **4e**−**i**, was previously reported.[14]

In summary, highly efficient dynamic kinetic resolutions of α-aryl UNCAs at room temperature were realized via the

(13) Kunz, H.; Waldmann, H. *Angew. Chem., Int. Ed.* **1984**, *23*, 71.
(14) For a catalytic asymmetric synthesis of 3-pyridylglycine, see ref 5.
(15) Review of recent approaches of using transition-metal−enzyme combinations to effect fast racemization required for efficient kinetic resolutions: El Gihani, M. T.; Williams, J. M. J. *Curr. Opin. Chem. Biol.* **1999**, *3*, 11.
(16) (a) Um, P.-J.; Drueckhammer, D. G. *J. Am. Chem. Soc.* **1998**, *120*, 5605. (b) Tan, D. S.; Gunter, M. M.; Drueckhammer, D. G. *J. Am. Chem. Soc.* **1995**, *117*, 9093.
(17) Buchwald and co-workers observed that the efficiency of the dynamic kinetic resolution of 3,5-dialkyl cyclopentenones can be improved by increasing the reaction temperature, presumably via acceleration of the racemization relative to the enantioselective transformation of 3,5-dialkyl cyclopentenones; see ref 10(a).

dual-function catalysis of modified cinchona alkaloids. This allowed us to develop a mild and high-yielding catalytic asymmetric synthesis of α-aryl and heteroaryl amino acids. It is noteworthy that mechanistic insight into the dual-function catalysis of cinchona alkaloids enabled us to accelerate the racemization relative to the alcoholysis of the UNCA via temperature adjustment. This experimentally simple approach may become useful in the development and optimization of new dynamic kinetic resolutions.[15−17]

Acknowledgment. We are grateful for financial support from NIH (GM-61591) and the Harcourt General Charitable Foundation and a gift from Daiso. The authors also thank Professor Barry B. Snider for helpful discussions.

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

OL026660L