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# Asymmetric synthesis of β,γ-unsaturated α-amino acids via efficient kinetic resolution with cinchona alkaloids

Jianfeng Hang, Li Deng *

*Department of Chemistry, Brandeis University, 415 South St., Waltham, MA 02454-9110, United States*

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ABSTRACT

The β,γ-unsaturated amino acids are versatile chiral building blocks and biologically interesting compounds. The asymmetric synthesis of β,γ-unsaturated amino acids presents a challenging task as these compounds are labile toward racemization as well as the undesirable double bond isomerization. An efficient, general and mild kinetic resolution with readily accessible and fully recyclable cinchona alkaloid catalysts has been developed to provide a reliably useful approach toward optically active β,γ-unsaturated amino acids.



The β,γ-unsaturated α-amino acids are versatile chiral building blocks.[1] In addition they have displayed antibiotic effects[2] and exhibited significant biological activity as suicide inhibitors for pyridoxal phosphate dependent enzymes.[3] Many synthetic routes toward optically active β,γ-unsaturated α-amino acids that make use of chiral synthons[4–7] and chiral auxiliaries[8] have been developed. Catalytic enantioselective approaches to these amino acids have been explored with the use of asymmetric Strecker reaction,[9] and more recently an enantioselective α-sulfenylation of aldehydes followed by a stereospecific [2,3] sigmatropic rearrangement.[10] The presence of the olefinic functionality renders β,γ-unsaturated α-amino acids labile toward base-[7c,8b] and acid-catalyzed[9a,11] racemization as well as isomerization of the double bond to α,β-position[6], thereby making the asymmetric syntheses of these delicate amino acids highly challenging. Therefore, the development of efficient, mild and general catalytic enantioselective methods for the preparations of β,γ-unsaturated α-amino acids remains a synthetically important task.[12]

Numerous methods for the synthesis of a wide variety of racemic β,γ-unsaturated α-amino acids have been established.[13–20] Thus, it is attractive to develop a general and efficient kinetic resolution of racemic β,γ-unsaturated α-amino acids as a means to produce optically active β,γ-unsaturated α-amino acids. However, to our knowledge, this possibility has only been explored with enzymes, which has met with limited success.[21] We reported an efficient kinetic resolution of urethane-protected α-amino acid *N*-carboxyanhydrides (UNCAs) via modified cinchona alkaloid-catalyzed alcoholysis. This kinetic resolution is applicable for the asymmetric synthesis of a broad range of optically active α-amino acids bearing aryl and alkyl side chains.[22] In addition to its generality, the reactions were carried out under very mild conditions utilizing readily accessible and fully recyclable chiral organic catalysts. The high enantioselectivity and the mild conditions prompted us to explore the possibility of applying this kinetic resolution to the asymmetric synthesis of β,γ-unsaturated α-amino acids. We report herein our progress in achieving this goal.

We prepared a variety of α-amino acid UNCAs bearing cyclic and acyclic β,γ-unsaturated side chains.[23] Specifically, these α-amino acids presented trisubstituted double bond of various substitution patterns (**1a**, **1b**, **1c**, **1d**); 1,2-disubstituted (**1e**, **1f**), double bond in both *Z* (**1e**) and *E* configurations (**1f**). With $(DHQD)_2AQN$ (10 mol %) as the catalyst and ethanol (1.5 equiv) as the nucleophile, α-alkenyl UNCAs **1a–f** were resolved cleanly and efficiently at −78 to −40 °C to afford a mixture of amino ester **2** and unreacted **1**. The selectivity factors measured for the resolution of **1a–f** were uniformly high, ranging from 26 to 149. A reliable protocol was also developed for the conversion of the unreacted enantiomerically enriched UNCA **1** into the corresponding α-amino acids **3** without compromising the optical purity. Once the alcoholysis reached a desirable conversion, the reaction mixture was poured into a precooled aqueous HCl solution where UNCA **1** was rapidly and cleanly hydrolyzed into amino acid **3**.[24] Overall, optically active amino esters **2** and amino acids **3** were obtained in 88–97%

* Corresponding author.
*E-mail address:* deng@brandeis.edu (L. Deng).

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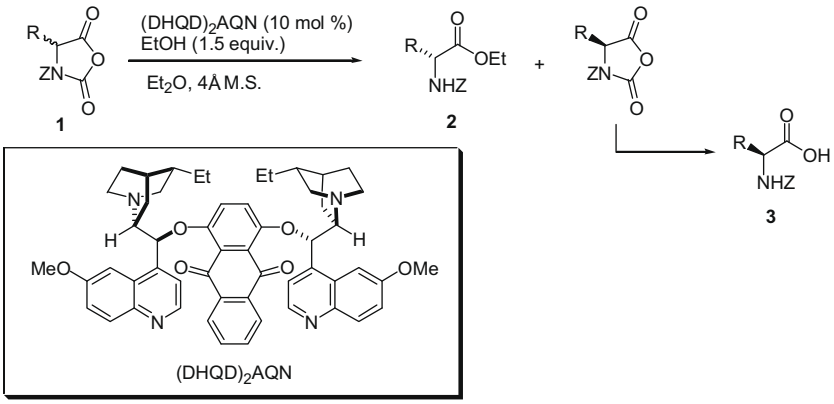
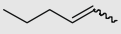
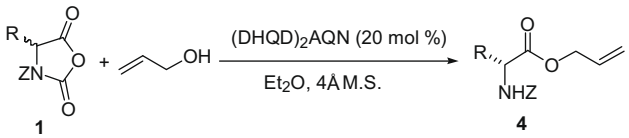
**Table 1**
Kinetic resolution of UNCA via modified cinchona alkaloids-catalyzed alcoholysis[a]

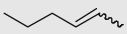



| Entry | R | | Temperature (°C) | Time (h) | conv[b] (%) | ee[c] yield[d] (%) | | S[e] |
|---|---|---|---|---|---|---|---|---|
| | | | | | | (*S*)-**3** | (*R*)-**2** | |
| **1** |  | **a** | −78 | 14 | 51 | 95 (42) | 93 (49) | 114 |
| **2** |  | **b** | −40 | 7.5 | 57 | 96 (42) | 75 (55) | 39 |
| **3** |  | **c** | −52 | 19 | 52 | 99 (44) | 93 (50) | 149 |
| **4** |  | **d** | −52 | 18 | 52 | 95[f] (44) | 85 (50) | 40 |
| **5** |  | **e** | −40 | 13 | 57[g] | 96 (38) | 74 (57) | 26 |
| **6** |  | **f** | −73 | 42 | 49[g] | 91 (40) | 95 (48) | 125 |

[a] The reaction was performed by treatment of **1** (0.1 mmol) with $(DHQD)_2AQN$ (10 mol %) and ethanol (1.5 equiv) in ether (7.0 mL).
[b] Unless otherwise noted, the conversion was determined by GC analysis.
[c] For ee analysis, see Supplementary data.
[d] Isolated yield.
[e] Selectivity factor, $s = k_f/k_s = \ln[1 - C(1 + ee)]/\ln[1 - C(1 - ee)]$, where ee is the percent enantiomeric excess of **2** and C is the conversion.
[f] Absolute configuration of **3d** was determined by comparing the optical rotation value of amino acid derived from **3d** with literature value, see Supplementary data. Other absolute configurations were assigned by analogy.
[g] The conversion was determined by $^1H$ NMR.

**Table 2**
Dynamic kinetic resolution of UNCA via modified cinchona alkaloids-catalyzed alcoholysis[a]




| Entry | R | | Temperature (°C) | Addition time (h) | Reaction time (h) | Conv[b] (%) | Yield[c] (%) | ee[d] |
|---|---|---|---|---|---|---|---|---|
| 1 |  | **c** | 23 | 1.3 | 4.5 | >97 | 80 | 75 |
| 2 | | **c** | 34 | 1.3 | 3.0 | >99 | 88 | 79 |
| 3 | | **c** | 34 | 2.0 | 3.0 | >99 | 94 | 81 |
| 4 |  | **f** | 34 | 2.0 | 2.0 | >99 | 76 | 87 |
| 5 |  | **a** | 34 | 2.0 | 2.0 | >99 | 89 | 88 |

[a] DKR procedure: A 1.0 or 1.2% (v/v) solution of allyl alcohol (0.12 mmol, 1.2 equiv) in ether was added over 1.3–2.0 h to a mixture of substrate **1** (0.10 mmol), $(DHQD)_2AQN$ (20 mol %) and 4 Å MS (10 mg) in ether (7.0 mL) at the indicated temperature; see Supplementary data for details.
[b] The conversion was determined by GC analysis.
[c] Isolated yield.
[d] For ee analysis, see Supplementary data.

combined isolated yields (Table 1). This is the first general and non-enzymatic kinetic resolution method for the asymmetric synthesis of β,γ-unsaturated α-amino acids. It should be noted that optically active amino acids **3a–c** had not been reported previously.

We found that enantioenriched UNCA **1** underwent racemization in the presence of $(DHQD)_2AQN$ at room temperature. This raised the possibility of realizing a dynamic kinetic resolution (DKR) with $(DHQD)_2AQN$ as a dual-function catalyst, promoting both the racemization and the enantioselective alcoholysis of UNCA **1**.[22b,c,25] It is noteworthy that, to our knowledge, the only literature precedent of DKR of a racemic β,γ-unsaturated α-amino acid involved an amidase-catalyzed but incomplete hydrolysis of 3,4-dehydro-D,L-prolinamide, from which L-3,4-dehydroproline was generated in 75% yield and 80% ee.[26]

Our initial attempts to develop an efficient DKR of α-aryl UNCAs[22b] revealed that, during a slow addition of a solution of allyl alcohol in $Et_2O$ to a mixture of UNCA **1c**, $(DHQD)_2AQN$ and 4 Å molecular sieves in $Et_2O$, amino ester **4c** was formed in 86% ee at 13% conversion, and the ee of **4c** decreased to 75% ee when the alcoholysis proceeded to 97% conversion. This slight ee deterioration over the course of the reaction indicated that the rate of the $(DHQD)_2AQN$-catalyzed racemization was still slower than the rate of alcoholysis of UNCA **1c** ($k_{rac}/k_{slow} < 1$). Subsequently, we found that the overall efficiency of the DKR could be improved by increasing the reaction temperature (34 °C in $Et_2O$) while extending the addition time of the alcohol (Table 2, entry 3 vs 1). Under the optimized conditions, amino esters **4c**, **4f** and **4a** were obtained in 81–88% ee and 76–94% isolated yields from their respective racemic counterparts. Importantly, we also established that the allyl amino ester **4c** (81% ee) could be converted into the corresponding amino acid **3c** in 93 % yield without migration of the double bond and deterioration of the optical purity (81% ee).[27]

In summary, we have established a general catalytic method for the asymmetric synthesis of β,γ-unsaturated α-amino acids via a cinchona alkaloids-catalyzed kinetic resolution. This mild method effectively circumvented the problematic racemization and double bond isomerization associated with the optically active β,γ-unsaturated α-amino acids, thereby providing a useful access to these sensitive but important amino acids.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2009.03.152.

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27. For this conversion, see **Supplementary data** for details.