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Organocatalytic Asymmetric Decarboxylative Amination of β-Keto Acids: Access to Optically Active α-Amino Ketones and 1,2-Amino Alcohols

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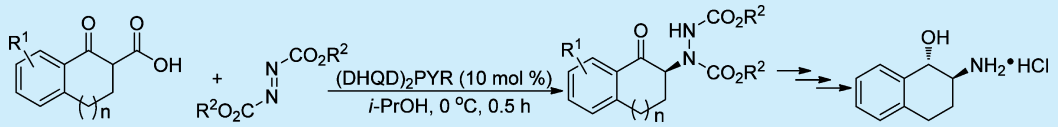
Supporting Information



ABSTRACT: An organocatalytic asymmetric decarboxylative amination reaction of β-keto acids is described. Under mild reaction conditions, a series of chiral α-amino ketones were obtained in good to high yields (up to 99%) and enantioselectivities (up to 95% ee). A chiral 1,2-amino alcohol was synthesized from the corresponding decarboxylative amination product in several steps without loss of enantioselectivity.

Optically active α-amino ketones are a very important class of compounds in synthetic chemistry, which can be readily converted into other useful building blocks, such as amines, 1,2-amino alcohols, and α-amino acid derivatives (Figure 1a).[1] Furthermore, a very large number of natural products and active pharmaceutical molecules contain the α-amino ketones and its derivatives (Figure 1b).[2] The catalytic asymmetric α-amination of various carbonyl substrates

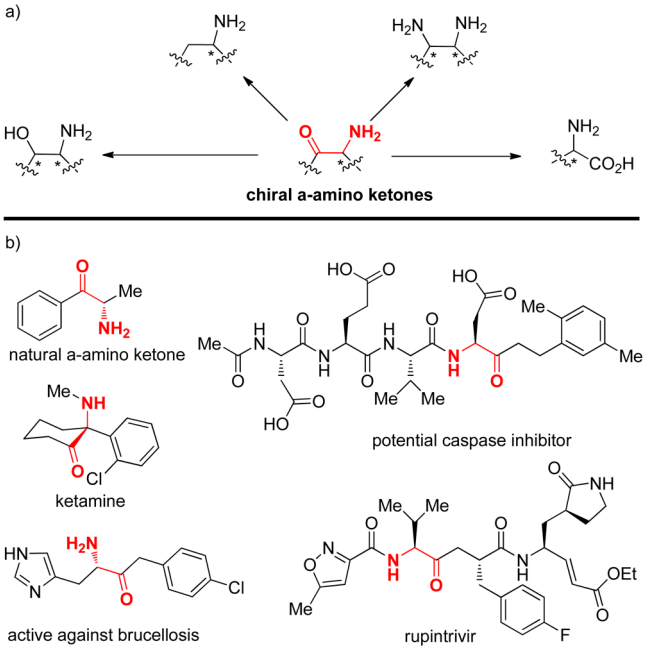
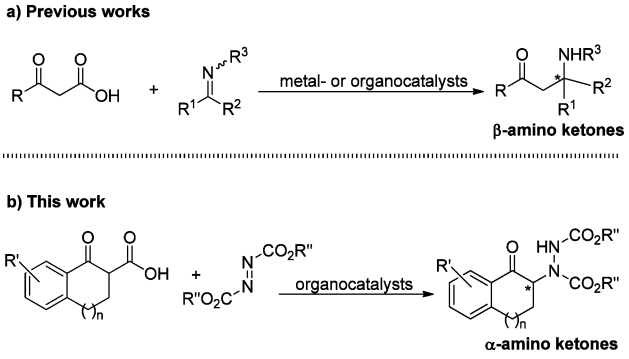


Figure 1. Synthetic transformation and selected bioactive compounds of α-amino ketones.

Scheme 1. Catalytic Asymmetric Synthesis of β-Amino Ketones and α-Amino Ketones



represents a most attractive route to this important class of products, and many practical enantioselective methods have been enabled by the identification of various chiral metal and organic catalysts.[3] Despite the impressive advances made in this subarea, it is still highly desirable to develop new catalytic enantioselective amination reactions of carbonyl compounds and to broaden the diversity of α-amino ketones.

The utility of β-keto acids to generate highly reactive ketone enolate equivalents has emerged as a very useful platform in asymmetric catalysis.[4,5] In this context, three groups of Tian,[6] Lu,[7] and Ma[8] described the asymmetric decarboxylative Mannich reactions of β-keto acids with imines under the catalysis of chiral metal complexes or small organic molecules for the synthesis of optically active β-amino ketones (Scheme 1a). On the basis of this behavior, we considered whether

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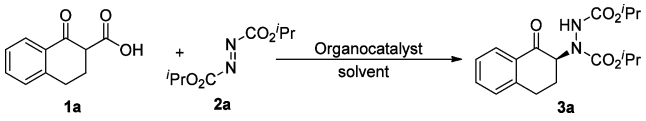
Table 1. Optimization of Conditions for the Asymmetric Decarboxylative Amination Reaction[a]



1a 2a 3a

entry	catalyst (mol %)	solvent/temp (°C)/time (h)	yield (%)[b]	ee (%)[c]
1	**I** (10)	THF/25/24	99	30
2	**II** (10)	THF/25/24	86	57
3	**III** (10)	THF/25/12	89	43
4	**IV** (10)	THF/25/12	89	66
5	**V** (10)	THF/25/12	92	25
6	**VI** (10)	THF/25/12	97	47
7	**VII** (10)	THF/25/12	99	32
8	**IV** (10)	CH_2Cl_2/25/12	99	65
9	**IV** (10)	Et_2O/25/12	99	44
10	**IV** (10)	toluene/25/12	99	4
11	**IV** (10)	CH_3CN/25/24	75	80
12	**IV** (10)	CH_3OH/25/24	88	70
13	**IV** (10)	EtOH/25/12	90	90
14	**IV** (10)	*n*-PrOH/25/12	88	90
15	**IV** (10)	*i*-PrOH/25/12	92	92
16	**IV** (10)	*t*-BuOH/25/12	90	92
17	**IV** (10)	*i*-PrOH/0/12	90	94
18	**IV** (10)	*i*-PrOH/−20/12	90	93
19	**IV** (10)	*i*-PrOH/0/1	92	94
20	**IV** (10)	*i*-PrOH/0/0.5	92	95
21	**IV** (10)	*i*-PrOH/0/0.25	85	92
22	**IV** (5)	*i*-PrOH/0/0.5	90	88

[a]The reaction was carried out with β-keto acid **1a** (0.2 mmol), diisopropyl azodicarboxylate **2a** (0.4 mmol), and organocatalyst **I**−**VII** (5−10 mol %) in solvent. [b]Yields of isolated product averaged over two runs. [c]Enantiomeric excess (ee) was determined by chiral HPLC analysis.

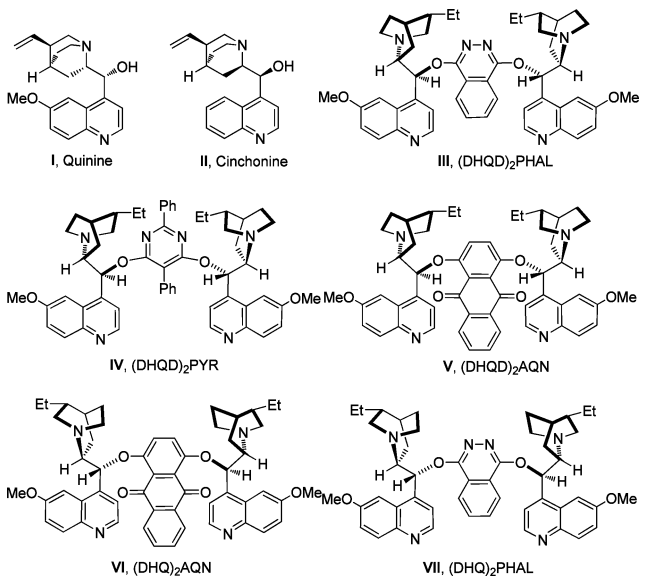
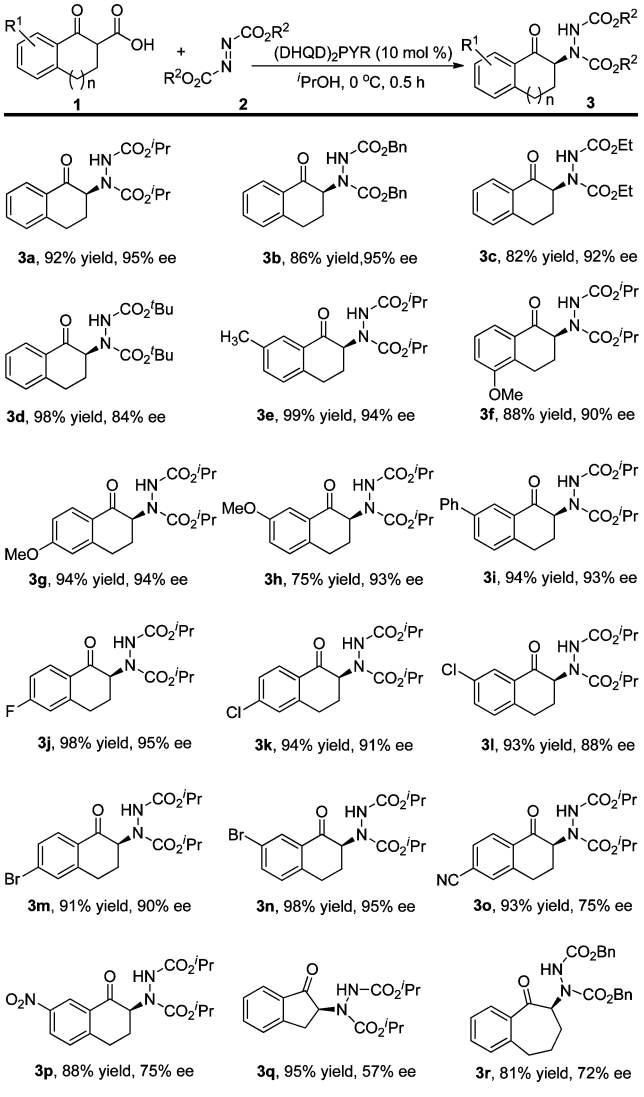


Figure 2. Structures of cinchona alkaloids tested.

azodicarboxylates could be engaged in the catalytic asymmetric amination reaction with β-keto acids (Scheme 1b). In this scenario, the use of chiral amine organocatalysts may generate and position an enolate species for nucleophilic addition to give

Scheme 2. Scope for the Organocatalytic Asymmetric Decarboxylative Amination of β-Keto Acids



the desired enantioenriched α-amino ketones. Herein, we describe the successful implementation of this process to provide α-amino ketone derivatives and significant opportunities for structural diversification.

In the initial studies, we conducted the asymmetric decarboxylative amination reaction of 1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid **1a** with diisopropyl azodicarboxylate **2a** by employing a series of commercially available cinchona alkaloids **I**−**VII** (Figure 2) as chiral organocatalysts in tetrahydrofuran (THF) at room temperature. We discovered that the amination product **3a** could be obtained in high yield and variable enantioselectivity (Table 1, entries 1−7), with the catalyst $(DHQD)_2PYR$ (**IV**) giving the best performance (entry 4). Subsequently, the solvent was found to have an important effect on the reactivity (entries 8−16). Among the solvents tested, isopropanol (*i*-PrOH) was found to be the best with respect to the asymmetric induction. The reaction temperature and time were also found to exert profound effects on enantioselectivity (entries 17−21). Optimal results were obtained in *i*-PrOH at 0 °C within 0.5 h (entry 20). In addition, the reduction of the catalyst loading had a deleterious effect on both yield and ee (entry 22).

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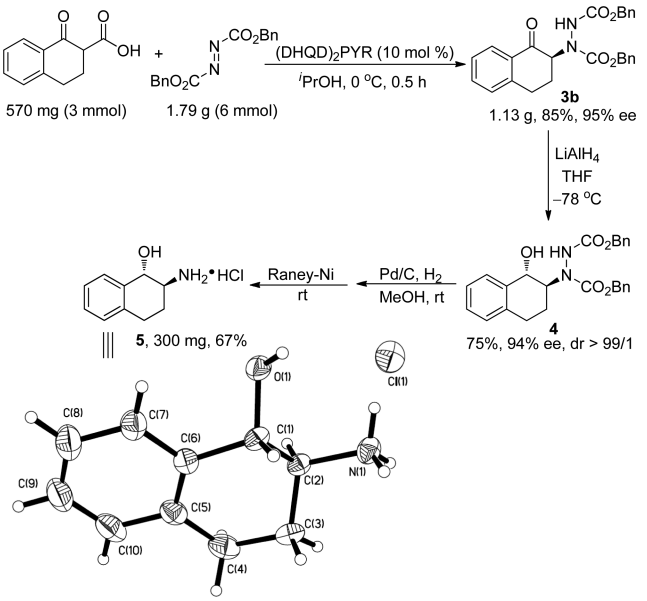
Scheme 3. Scaled-up Decarboxylative Amination, Further Synthetic Transformation, and X-ray Crystallographic Structure of the Product 5 (Thermal Ellipsoids Shown at 50% Probability)



With the optimized conditions in hand, the scope of this organocatalytic asymmetric decarboxylative amination reaction was probed by varying both azodicarboxylates and β-keto acids. The results are summarized in Scheme 2. A series of azodicarboxylates were found to participate in enantioselective amination reactions with β-keto acid **1a** catalyzed by $(DHQD)_2PYR$ (**IV**), and the desired products **3a–d** were obtained in good to high yields and enantioselectivities. Subsequently, a variety of 1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylic acids were tested. Most of the α-amino ketones (**3e–n**) could be produced in 75–99% yields with high enantioselectivities (88–95% ee). However, the strong electron-withdrawing substituent at the phenyl ring has little effect on the enantioselectivity. These reactants gave the amination products **3o** and **3p** with 75% ee. Indanone- and 1-benzosuberanone-derived β-keto acids are also viable substrates, affording the desired product **3q** and **3r** with 57% ee and 72% ee, respectively. In addition, we investigated the amination reactions of diisopropyl azodicarboxylate **2a** with 2-oxocyclopentanecarboxylic acid, 2-oxocyclohexanecarboxylic acid, and 2-oxocycloheptanecarboxylic acid. These β-keto acids were found to be unsuitable for this asymmetric transformation, and no expected products were observed. Acyclic 2-benzoylbutanoic acid gave the corresponding amination product in 56% yield with poor enantioselectivity (15% ee).[9]

To evaluate this organocatalytic asymmetric system on a large scale, 3 mmol of β-keto acid **1a** were used to perform the amination reaction and the product **3b** was obtained in 85% yield and 95% ee (Scheme 3). Furthermore, the organocatalyst $(DHQD)_2PYR$ (**IV**) was recovered in almost quantitative yield and reused without any loss of reactivity and enantioselectivity.[10] A direct reduction process using $LiAlH_4$ gave rise to the intermediate alcohol **4** in good yield and excellent diastereoselectivity without racemization. Subsequent deprotection and hydrogenolytic *N*, *N*-bond cleavage furnished the corresponding α-amino alcohol **5** in 67% yield.[11] Simple recrystallization in MeOH/ethyl acetate provided the single stereoisomer **5** with excellent optical purity, and its absolute configuration was determined to be (*S*,*S*) from the X-ray structural analysis.[12]

In summary, we have developed an efficient organocatalytic asymmetric decarboxylative amination reaction of β-keto acids by using dialkyl azodicarboxylates as amination reagents. In the presence of biscinchona alkaloids, a series of chiral α-amino ketone derivatives were obtained in good to high yields (up to 99%) and enantioselectivities (up to 95% ee) under mild reaction conditions. Moreover, the synthetic potential of this methodology was also demonstrated to access an optically active 1,2-amino alcohol. Further application of α-amino ketones and related products is currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00797.

Experimental details, ^1H and ^{13}C NMR spectra, and HPLC analytic results for **3a–r** and **4** (PDF)

Crystallographic data for compound **5** (CIF)

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Notes

The authors declare no competing financial interest.

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(12) CCDC 1537877 contains the supplementary crystallographic data for the compound **5**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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