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Highly Enantioselective γ-Amination of α,β-Unsaturated Acyl Chlorides with Azodicarboxylates: Efficient Synthesis of Chiral γ-Amino Acid Derivatives

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Supporting Information

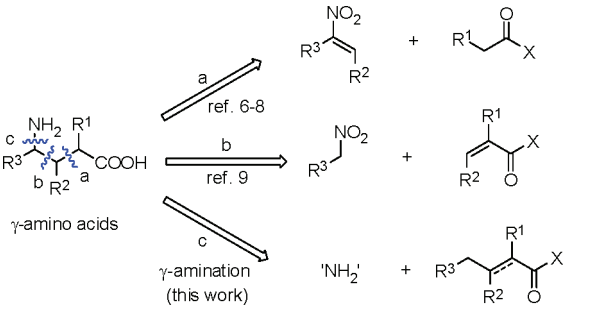
ABSTRACT: The cinchona alkaloid-catalyzed γ-amination of α,β-unsaturated acyl chlorides with azodicarboxylates to give the corresponding dihydropyridazinones in good yields with high enantioselectivities has been developed. Reductive ring opening of the dihydropyridazinones afforded series of cyclic and acyclic γ-amino acid derivatives in good yields with high enantiopurity.

γ-Amino acids have attracted great attention because of their biological activities in the central nervous system of mammals[1] and applications in hybrid peptides.[2] Thus, significant efforts have been devoted to the stereoselective synthesis of γ-amino acids.[3,4] However, most approaches to enantiopure γ-amino acids employ chiral auxiliaries. There are very few examples that afford chiral γ-amino acid by a catalytic enantioselective approach.[5] One typical approach relies on the Michael addition of carbonyl compounds to nitroethylene (Scheme 1, route a), which has been successfully established via H-bonding catalysis,[6] Lewis acid catalysis,[7] and enamine catalysis.[8] Another approach involving the Michael addition of nitroalkanes via phase-transfer catalysis (Scheme 1, route b) has also been reported.[9] Amination reactions play an important role in the synthesis of N-containing compounds.[10] In this communication, we report an enantioselective γ-amination approach to γ-amino acid derivatives (Scheme 1, route c). In comparison with the well-developed catalytic α-amination of carbonyl compounds,[11] the catalytic γ-amination of carbonyl compounds is far less explored but highly desirable.[12]

In 2007, Tiseni and Peters[13] reported the pioneering cinchona alkaloid-catalyzed cyclization of α,β-unsaturated acyl chlorides with aldehydes. Very recently, we demonstrated that N-heterocyclic carbenes (NHCs)[14] are efficient catalysts for the cyclization reaction of α,β-unsaturated acyl chlorides with activated ketones.[15] Thus, we proposed a catalytic cyclization of α,β-unsaturated acyl chlorides with azodicarboxylate to give γ-amino acid derivatives.[16]

The reaction of α,β-unsaturated acyl chloride **1a** and ethyl azodicarboxylate (**2**) was investigated under various reaction conditions (Table 1). In the presence of a 10 mol % loading of NHC precursor **A**[17] derived from L-pyroglutamic acid, the reaction gave the desired cyclization product **3a** in 85% yield but without enantioselectivity (entry 1). When NHC precursor **B**[17b] derived from aminoindanol was employed, the reaction proceeded well, but the enantioselectivity (18% ee) was not satisfactory (entry 2). Cinchona alkaloids were then utilized as catalysts. We were happy to find that the reaction catalyzed by 10 mol % *O*-benzoylquinidine (**C**) gave the desired cycloadduct **3a** in 75% yield with 52% ee (entry 3). Better enantioselectivity (67% ee) resulted when *O*-trimethylsilylquinidine (**D**)[18] was used (entry 4). Solvent screening revealed that the reaction worked in tetrahydrofuran (THF), ether, dichloromethane (DCM), and toluene, with toluene being the best choice (entries 4−7). Satisfactory enantioselectivity (99% ee) was obtained when the reaction temperature was lowered to −40 °C (entry 8), and the yield was improved to 92% when 1.5 equiv of acyl chloride was employed (entry 9). Decreasing the catalyst loading to 5 mol % had no apparent effect on the yield and enantioselectivity, while using 1 mol % catalyst resulted in low yield but still gave 99% ee (entries 10 and 11).

Scheme 1. Typical Catalytic Approaches to γ-Amino Acid Derivatives



With the optimized reaction conditions in hand, we briefly investigated the reaction scope (Chart 1). Di-*tert*-butyl azodicarboxylate (**2′**) worked as well as diethyl azodicarboxylate (**2**), giving the corresponding adduct **3a′** in 90% yield with 99% ee. α,β-Unsaturated acyl chlorides **1b**−**d** with six-, seven-, and eight-membered carbocycles, respectively, all worked well, and good yields and enantioselectivities of the corresponding products **3b**−**d** were generally achieved. Acyl chloride **1e** derived from tetrahydrothiophene also worked well, giving cycloadduct **3e′** in 88% yield with 99% ee.[19] It is noteworthy that although a mixture of two diastereoisomers of **1e** (4:3 dr) was employed, only one isomer of **3e′** was obtained (88% yield), in which the γ-carbon connected with sulfur was aminated; this is due to the enhanced

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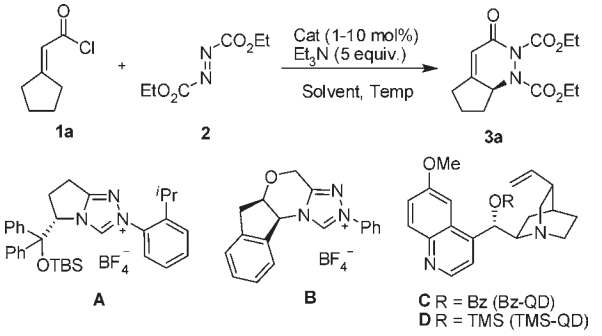
Table 1. Optimization of Reaction Conditions



entry	cat (mol %)	solvent	T (°C)	yield (%)[a]	ee (%)[b]
1	**A**[c] (10)	THF	−20	85	0
2	**B**[c] (10)	THF	−20	85	−18
3	**C** (10)	THF	−20	75	52
4	**D** (10)	THF	−20	78	67
5	**D** (10)	ether	−20	75	71
6	**D** (10)	DCM	−20	56	45
7	**D** (10)	toluene	−20	83	75
8	**D** (10)	toluene	−40	85	99
9[d]	**D** (10)	toluene	−40	92	99
10[d]	**D** (5)	toluene	−40	92	99
11[d]	**D** (1)	toluene	−40	54	99

[a] Isolated yields. [b] Determined by HPLC on a chiral column. [c] NHCs were freshly generated from the precatalysts **A** and **B** (10 mol %) in the presence of Cs_2CO_3 (20 mol %) at room temperature for 30 min and used immediately. [d] 1.5 equiv of acyl chloride **1a** was used.

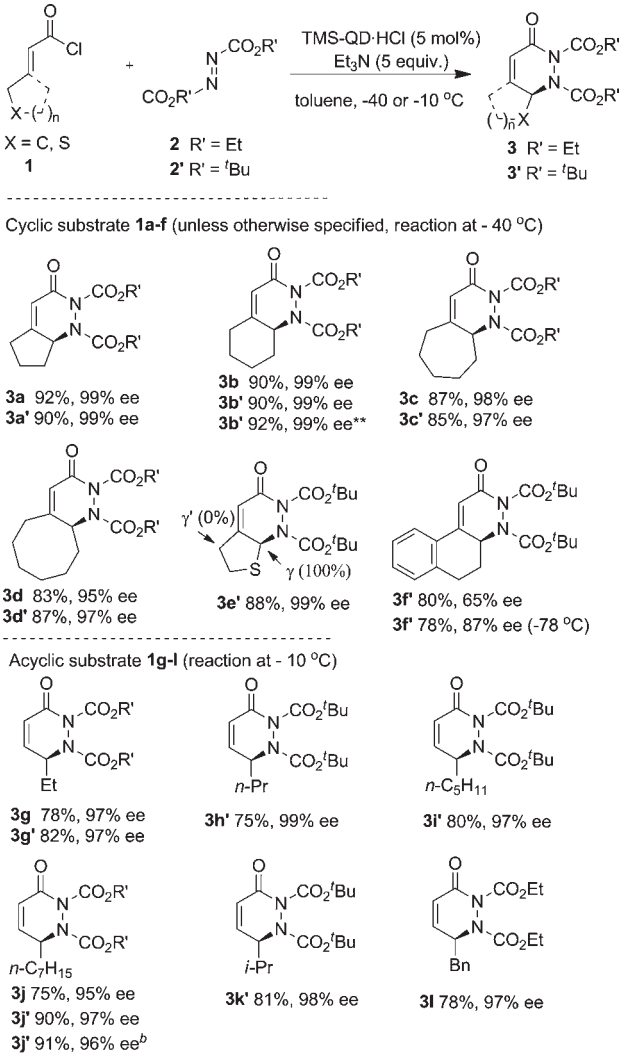
acidity of the proton adjacent to sulfur. Acyl chloride **1f** with tetrahydronaphthalene gave the desired cycloadduct **3f′** in 78% yield with 87% ee when the reaction was carried out at −78 °C.

Acyclic substrates were then tested for the reaction.[20] It was found that the reaction of acyclic substrates worked better at −10 °C than at −40 °C. Substrates **1g**−**j** with various linear alkyl chains gave the corresponding cycloadducts **3g′**−**j′** in good yields with high enantioselectivity. A substrate with a branched alkyl chain (**1k**) also worked well, giving cycloadduct **3k′** in 81% yield with 98% ee. In addition, a substrate with a benzyl group, 5-phenylpent-2-enoyl chloride (**1l**), afforded the product in 78% yield with 97% ee.

Quinine, the pseudoenantiomer of quinidine, was then employed for the catalytic reaction (Chart 2). It was found that TMS-quinine (TMS-QN) worked essentially as well as TMS-quinidine (TMS-QD), offering the opposite enantiomers in good yields with high enantioselectivities. As expected, both cyclic substrates (**1a**, **1b**, and **1e**) and acyclic substrates (**1g**, **1j**, and **1l**) worked well for the reaction catalyzed by TMS-QN. Although high enantioselectivities were generally maintained, a small decrease in enantioselectivity was observed in some cases (91% ee for *ent*-**3j′**; 92% ee for *ent*-**3b′**) relative to the reaction catalyzed by TMS-QN.

As expected, the resulting dihydropyridazinones **3′** could be easily transformed to γ-amino amides **5** via deprotection and reductive ring opening (Chart 3). γ-Amino amides **5b**, **5e**, **5j**, and **5k**, with cyclic, heterocyclic, linear alkyl, and branched alkyl substituents, respectively, were obtained in good yields without erosion of the enantioselectivity. It is noteworthy that only one

Chart 1. Reaction Catalyzed by TMS-Quinidine[a]

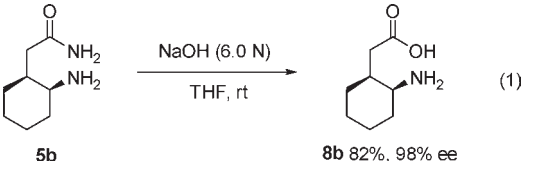


[a] Unless otherwise specified, **1** (0.375 mmol) and **2** or **2′** (0.25 mmol) were used. [b] **1** (6 mmol) and **2′** (4 mmol) were used.

diastereomer was observed for the reductive reaction of **4b** and **4e** catalyzed by Raney Ni.

A series of chiral amino acids could be synthesized from the cycloadducts **3′** in good yields without loss of enantiopurity using a process of hydrogenation, hydrolysis, deprotection, and N−N bond cleavage (Chart 4). It is also noteworthy that only one diastereomer **6b** was obtained exclusively in quantitative yield when cycloadduct **3b′** was hydrogenated with Pd/C.

In addition, hydrolysis of γ-amino amide **5b** also afforded the corresponding γ-amino acid **8b**[21] in good yield with 98% ee (eq 1)



A plausible catalytic cycle is depicted in Figure 1. In the presence of base, the addition of the cinchona alkaloid to the α,β-unsaturated chloride gives vinyl enolate A, which reacts with the

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Chart 2. Reaction Catalyzed by TMS-Quinine

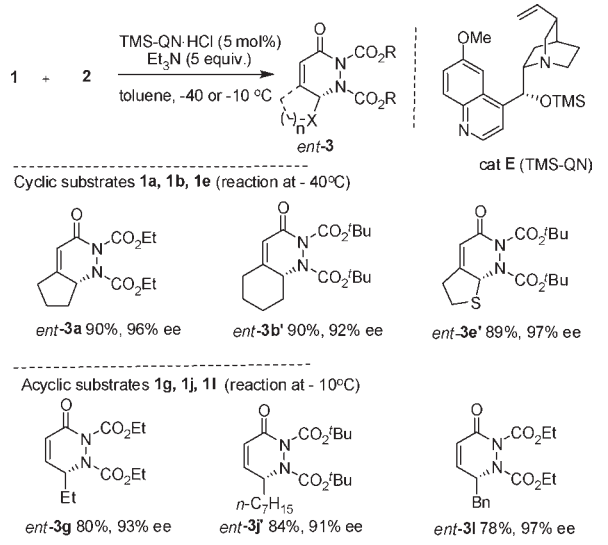
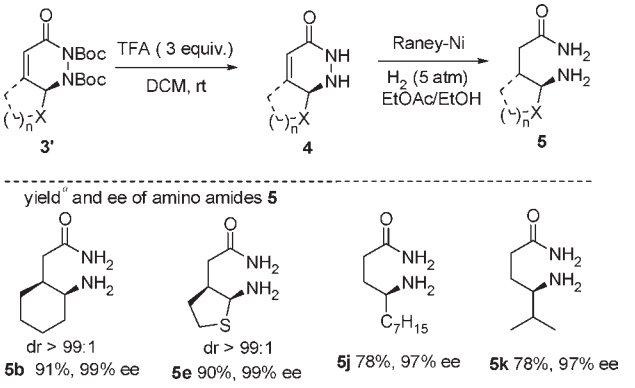
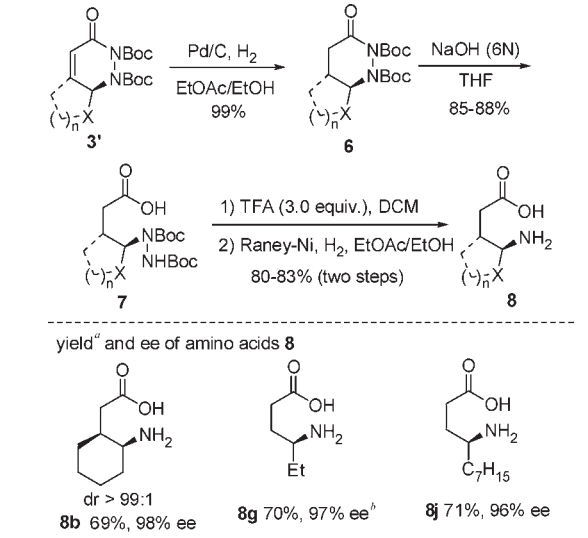


Chart 3. Synthesis of γ-Amino Amides



[a]Overall yields for two steps.

Chart 4. Synthesis of γ-Amino Acids



[a]Overall yield from 3′. [b]Determined via its precursor 7g.

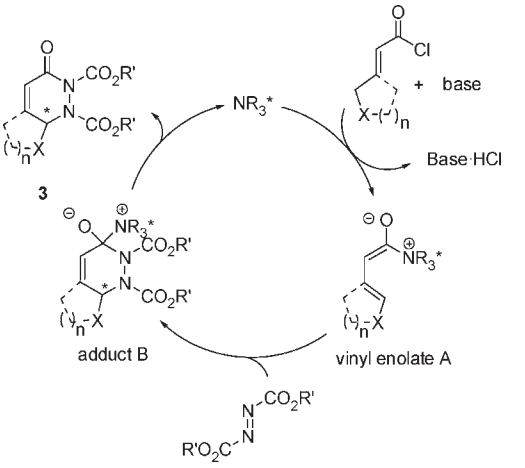


Figure 1. Plausible catalytic cycle.

azodicarboxylate to afford cycloadduct B. Fragmentation of B furnishes dihydropyridazinone **3** and regenerates the cinchona alkaloid.

In conclusion, a cinchona alkaloid-catalyzed γ-amination of α,β-unsaturated acyl chlorides with azodicarboxylates to give the corresponding dihydropyridazinones in good yields with high enantioselectivities has been developed. A series of enantiopure cyclic and acyclic γ-amino acid derivatives could then be easily prepared by reductive ring opening of the dihydropyridazinones.

■ ASSOCIATED CONTENT

Supporting Information. Experimental and spectroscopic details and a CIF file for **3e′**. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENT

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(18) The hydrochloride salt of the cinchona alkaloid derivative was used for its easy manipulation. Control experiments showed no difference in the results of reactions catalyzed by the salt or the alkaloid derivative itself.

(19) The absolute configuration of cycloadduct **3e′** was unambiguously established by X-ray analysis of its crystal.

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