Copper(I)-catalyzed asymmetric decarboxylative Mannich reaction enabled by acidic activation of 2H-azirines

Hai-Jun Zhang¹, Yan-Cheng Xie¹ & Liang Yin¹

Chiral aziridines are structure units found in many biologically active compounds and are important building blocks in organic synthesis. Herein, by merging nucleophilic generation through copper(I)-catalyzed decarboxylation and activation of poorly electrophilic 2H-azirines through protonation with carboxylic acids, an asymmetric decarboxylative Mannich reaction between α,α-disubstituted cyanoacetic acids and 2H-azirines is uncovered, which leads to generation of chiral aziridines containing vicinal tetrasubstituted and acyclic quaternary stereogenic carbon centers in good to excellent diastereo- and enantioselectivities. At last, transformations of the produced chiral aziridine are successfully carried out to deliver synthetically useful compounds.

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Nature uses a mild but powerful strategy to generate a nucleophile through decarboxylation of a malonic acid half thioester in the presence of an enzyme, which is typically employed in the biosynthesis of fatty acids and polyketides. Inspired by this fantastic method in nature, Shair and colleagues developed a Cu(II)-catalyzed asymmetric thioester aldol reaction, which was compatible with a broad range of protic functional groups and enolizable aldehydes due to the mild acidic reaction conditions. Unfortunately, their following research uncovered that their reaction occurred by a different mechanism from the nature’s reaction (the nucleophile was actually not generated through decarboxylation). In 2009, Shibasaki and Kanai group mimicked the method in nature by using α-methyl-α-phenyl cyanoacetic acid as a pronucleophile and accomplished a decarboxylative Mannich-type reaction of N-diphenyl-phosphinoyl aldines and a decarboxylative aldol reaction of aldehydes under copper(I) catalysis, which generated contiguous trisubstituted and acyclic quaternary stereocenters in moderate to high diastereo- and enantioselectivities.

However, in the above two catalytic asymmetric decarboxylative reactions, cyanoacetic acid was only employed as the precursor for decarboxylative nucleophile generation by anion exchange with CuOAc–bisphosphine complex (decarboxylative protonation was a side reaction). However, the acidic nature of cyanoacetic acid was not fully utilized. Considering the basicity and the poor electrophilicity of 2H-azirines, we propose a strategy that basic 2H-azirines might be activated by a cyanoacetic acid through protonation to afford more electrophilic iminium species (Fig. 1). Meanwhile, the anion exchange leads to the formation of copper(I) cyanoacetate, which affords the nucleophilic copper(I) ketenimide through extrusion of CO₂. Then, asymmetric addition of the nucleophilic copper(I) ketenimide to the electrophilic iminium species would allow the easy formation of a series of chiral aziridines in good yields, which contain chiral adjacent tetrasubstituted and acyclic quaternary stereocenters. These chiral aziridines would serve as intermediates to furnish synthetically useful compounds through the transformations of the aziridine functional group.

It is well known that chiral aziridines are important intermediates in organic synthesis, as they can react with nucleophiles to generate chiral amines through ring-opening reactions. Moreover, chiral aziridines are structure units found in many natural products and man-made molecules, which exhibit a broad range of biological properties, such as antitumor and antibacterial activities. Therefore, the asymmetric synthesis of chiral aziridines has received significant attention from the chemical community. One of the straightforward methods is the catalytic asymmetric addition of nucleophiles to 2H-azirines. However, the lower reactivity of 2H-azirines has led to much less developments in this area.

Here, by activation of the poorly electrophilic 2H-azirines with carboxylic acids, we disclose a copper(I)-catalyzed decarboxylative Mannich reaction of 2H-azirines, which affords a series of chiral aziridines in good to high yields, diastereoselectivity, and enantioselectivity. More importantly, adjacent chiral tetrasubstituted and acyclic quaternary stereocenters are generated efficiently.

**Results**

**Optimization of reaction conditions.** The reaction between α-methyl-α-phenyl cyanoacetic acid (1a) and 2H-azirine 2a was studied for the optimization of reaction conditions as shown in Table 1. The decarboxylative Mannich reaction proceeded smoothly in the presence of 5 mol % of CuOAc and 5 mol % of (R)-BINAP at 0 °C in tetrahydrofuran (THF), which delivered product 3a in 81% yield with 2.0/1 dr and 8% ee for the major diastereoisomer (Table 1, entry 1). Screening of the commercially available bisphosphine ligands, including (R)-TOL-BINAP, (R)-SEGPHOS, (R)-DIPFFORPHOS, (R,R)-QUINOXP*, (R,R)-Ph-BPE, (R,R)-TANIAPHOS, (R)-DTBM-SEGPHOS, and (R)-DIPA-MeO-BIPHEP, identified (R)-DTBM-SEGPHOS and (R)-DIPA-MeO-BIPHEP as the suitable ligands (Table 1, entries 2–9). With (R)-DTBM-SEGPHOS as the ligand, product 3a was generated in 88% yield with 4.0/1 dr and 93% ee for the major diastereoisomer (Table 1, entry 8). In the case of (R)-DIPA-MeO-BIPHEP, product 3a was obtained in 62% yield with 5.7/1 dr and 91% ee for the major diastereoisomer (Table 1, entry 9).

![Fig. 1 Initial design. Our working hypothesis for the catalytic asymmetric decarboxylative Mannich reaction of 2H-azirines](https://example.com/fig1.png)
With (R)-DTBM-SEGPHOS as the ligand, the studies of copper(I) source, reaction solvent, and temperature effect were not fruitful (see Supplementary Table 1-3 for details). Fortunately, decreasing the reaction temperature to \(-20^\circ\text{C}\) resulted in improved yield, diastereo-, and enantioselectivities in the case of (R)-DIPA-MeO-BIPHEP (Table 1, entry 10). By further lowering the reaction temperature to \(-60^\circ\text{C}\), product 3a was generated in 98% yield with >20/1 dr and 98% ee (Table 1, entry 11). Moreover, the loading of CuOAc-(R)-DIPA-MeO-BIPHEP complex was successfully reduced to 3 mol % by prolonging the reaction time from 24 h to 36 h (Table 1, entry 12). It was verified that both CuOAc and ligand ((R)-DIPA-MeO-BIPHEP) were indispensable, as no product 3a was observed in the absence of either (Table 1, entries 13, 14). The catalyst loading was further reduced to 2 mol % with the success of a gram-scale reaction as shown in Fig. 2. Remarkably, 1.358 g of aziridine 3a was isolated in 91% yield with >20/1 dr and 97% ee.

### Substrate scope

The study of the substrate scope of aromatic 2H-azirines (2) with 3 mol % of CuOAc-(R)-DIPA-MeO-BIPHEP complex was described in Table 2. Both electron-donating groups and electron-withdrawing groups were accepted at the para-position of the phenyl group (3a–3j). Although the diastereoselectivity was moderate in some cases, both the yield and the

### Table 1 Optimization of the reaction conditions

| Entry | Ligand | T | yield (%) | dr | ee (%) |
|-------|--------|---|-----------|----|--------|
| 1     | (R)-BINAP | 0 | 81        | 2.0/1 | 8/61   |
| 2     | (R)-TOL-BINAP | 0 | 76        | 1.8/1 | 12/46  |
| 3     | (R)-SEPHOS  | 0 | 87        | 1.8/1 | 15/70  |
| 4     | (R)-DIFLUORPHOS | 0 | 88        | 1.7/1 | 17/69  |
| 5     | (R,R)-QUINOXP* | 0 | 39        | 2.4/1 | 41/33  |
| 6     | (R,R)-Ph-BPE | 0 | 62        | 2.0/1 | -19/-47|
| 7     | (R,R)-TANIAPHOS | 0 | 28        | 7.3/1 | 26/-52 |
| 8     | (R)-DTBM-SEGPHOS | 0 | 88        | 4.0/1 | 93/43  |
| 9     | (R)-DIPA-MeO-BIPHEP | 0 | 62        | 5.7/1 | 91/55  |
| 10    | (R)-DIPA-MeO-BIPHEP | -20 | 88        | 9.1/1 | 93/70  |
| 11    | (R)-DIPA-MeO-BIPHEP | -60 | 98        | >20/1 | 98/70  |
| 12*   | (R)-DIPA-MeO-BIPHEP | -60 | 99        | >20/1 | 98/68  |
| 13*   | (R)-DIPA-MeO-BIPHEP | -60 | 0         | -    | -      |
| 14*   | -      | -60 | 0         | -    | -      |

*1a: 0.3 mmol, 2a: 0.2 mmol. *2Determined by $^1$H NMR analysis of reaction crude mixture using CH$_3$NO$_2$ as an internal standard. *3Determined by chiral-stationary-phase HPLC analysis. *43 mol % of CuOAc and 3 mol % of (R)-DIPA-MeO-BIPHEP were employed. 36 h. *5Performed without CuOAc. *6Performed without (R)-DIPA-MeO-BIPHEP.
enantioselectivity were high to excellent. Several aromatic 2H-azirines with a substituent at the meta-position served as appropriate substrates to afford the aziridines in good to excellent stereoselectivities (3k–3n). Unfortunately, a substituent was not well tolerated at the ortho-position largely due to the increased steric hindrance. 2H-Azirine with a 2-naphthyl group was also a suitable substrate as excellent results were obtained (3o). Moreover, both 3-thienyl and benzothiophen-2-yl groups did not have a negative effect on the reaction results (3p and 3q).

Then, complex molecules containing an aromatic 2H-azirine moiety were investigated. 2,4-Dichlorophenoxyacetic acid, a systemic herbicide, was successfully attached to the 2H-azirine group through an ester linker (2r). 2r underwent the copper(I)-catalyzed decarboxylative Mannich reaction smoothly to afford product 3r in excellent both yield and stereoselectivity. By using the same linker, isoxepac acid (an advanced intermediate toward the synthesis of olopataidine, which is sold as a prescription eye drop), probenecid (a medication that is primarily toward the synthesis of olopatadine, which is sold as a systemic herbicide, was successfully attached to the 2H-azirine 2a under basic conditions. The same diastereo- and enantioselectivities were observed both in the decarboxylative version and in the proton-transfer version, indicating that the same copper(I) intermediate was generated. It is reasonable that the proton-transfer version led to very low yield as 2H-azirine 2a is a poor electrophile as described in literature. As 2H-azirine 2a is an imine base, it is also reasonable that the protonation of 2a by 1a might occur smoothly to give an iminium cation, which is a highly electrophilic species. Moreover, it was observed that the copper(I)-catalyzed decarboxylation protonation of 1a proceeded very slowly in the absence of 2a at −60 °C, which indicated the interaction between 1a and 2a (the activation of 2a by 1a through a hydrogen-bonding effect can not be excluded completely at present). The difference of the electrophiles in the Mannich reaction resulted in different yields. The same tendency was also observed in the Mannich reaction of aliphatic 2H-azirine 4a with (R)-DTBM-SEGPHOS as the ligand (Fig. 3c, d). It is obvious that the present acidic reaction conditions are superior to the classical basic proton-transfer reaction conditions in the construction of contiguous tetrasubstituted and quaternary stereocenters.

**Demonstration of the strategy.** The present decarboxylative Mannich reaction exhibited an impressive advantage over the classical proton-transfer version. As shown in Fig. 3, the proton-transfer Mannich reaction of 1a′ and 2a proceeded in <5% yield in the presence of 5 mol % of CuOAc-(R)-DIPA-MeO-BIPHEP complex (Fig. 3b), while the decarboxylative version occurred in 98% yield (Fig. 3a). Moreover, the retro-Mannich reaction of 3a in the presence of 5 mol % of CuOAc and 5 mol % of (R)-DIPA-MeO-BIPHEP at −60 °C did not proceed at all, indicating that the very low yield of the proton-transfer Mannich reaction between 1a′ and 2a was not attributed to the retro-Mannich reaction of 3a under basic conditions. The same diastereo- and enantioselectivities were observed both in the decarboxylative version and in the proton-transfer version, indicating that the same copper(I) intermediate was generated. It is reasonable that the proton-transfer version led to very low yield as 2H-azirine 2a is a poor electrophile as described in literature. As 2H-azirine 2a is an imine base, it is also reasonable that the protonation of 2a by 1a might occur smoothly to give an iminium cation, which is a highly electrophilic species. Moreover, it was observed that the copper(I)-catalyzed decarboxylation protonation of 1a proceeded very slowly in the absence of 2a at −60 °C, which indicated the interaction between 1a and 2a (the activation of 2a by 1a through a hydrogen-bonding effect can not be excluded completely at present). The difference of the electrophiles in the Mannich reaction resulted in different yields. The same tendency was also observed in the Mannich reaction of aliphatic 2H-azirine 4a with (R)-DTBM-SEGPHOS as the ligand (Fig. 3c, d). It is obvious that the present acidic reaction conditions are superior to the classical basic proton-transfer reaction conditions in the construction of contiguous tetrasubstituted and quaternary stereocenters.

**Transformations.** Transformations of 3a were shown in Fig. 4. After protection of 3a with an acid chloride, the rearrangement of the aziridine moiety in 3a to an oxazoline group produced 6 in 63% yield with maintained enantioselectivity. The reduction of cyano group by DIBAL-H afforded carbamate 7 in 60% yield after protection of the free amine with Boc₂O. Moreover, the acidic opening of the aziridine group in 3a with HCl proceeded smoothly to furnish amine 8 in 80% yield. Obviously, the primary alkyl chloride moiety in 8 allows further structure elaboration. At last, the absolute configurations of the stereocenters in 8 were determined by the X-ray analysis of its single crystals as depicted in Fig. 4, which led to the determination of the exact stereochemistry of 3a. Then, the absolute configurations in 3 and 5 were assigned tentatively by analogy (see Supplementary Fig. 40 and Supplementary Table 4 for details).
Table 2 Substrate scope of aromatic 2H-azirines

| R      | Product | Yield | Diastereoselectivity | Enantiomeric Excess |
|--------|---------|-------|-----------------------|---------------------|
| H      | 3a      | 92%   | >20/1 dr, 98% ee      |
| Me     | 3b      | 98%   | >20/1 dr, 97% ee      |
| Bu     | 3c      | 97%   | >20/1 dr, 98% ee      |
| Me     | 3d      | 96%   | >20/1 dr, 97% ee      |
| F      | 3e      | 93%   | 12/1 dr, 93% ee       |
| Cl     | 3f      | 97%   | 9/1 dr, 95% ee        |
| Br     | 3g      | 91%   | 8/1 dr, 96% ee        |
| Ph     | 3h      | 98%   | >20/1 dr, 98% ee      |
| OCF₃   | 3i      | 89%   | 5/1 dr, 97% ee        |
| BPin   | 3j      | 83%   | >20/1 dr, 96% ee      |
| Me     | 3k      | 99%   | >20/1 dr, 97% ee      |
| OMe    | 3l      | 97%   | 12/1 dr, 96% ee       |
| Cl     | 3m      | 97%   | 9/1 dr, 95% ee        |
| Br     | 3n      | 98%   | 8/1 dr, 96% ee        |
| Ph     | 3o      | 97%   | 12/1 dr, 97% ee       |
| OCF₃   | 3p      | 98%   | 12/1 dr, 96% ee       |
| BPin   | 3q      | 99%   | >20/1 dr, 93% ee      |
| Me     | 3r      | 97%   | 12/1 dr, 97% ee       |
| OMe    | 3s      | 99%   | 11/1 dr, 98% ee       |
| Cl     | 3t      | 98%   | 11/1 dr, 98% ee       |
| Br     | 3u      | 99%   | 12/1 dr, 98% ee       |
| Me     | 3v      | 98%   | >20/1 dr, 98% ee      |

*1a: 0.3 mmol, 2: 0.2 mmol. Isolated yield was reported. Diastereoselectivity was determined by 1H NMR analysis of reaction crude mixture. Enantiomeric excess was determined by chiral-stationary-phase HPLC analysis. **8 h. ***24 h. ****48 h. *****72 h. ******90 h. 1e: 0.6 mmol, 2: 0.2 mmol, 6 mol% of CuOAc and 6 mol% of (R)-DIPA-MeO-BIPHEP were employed. 80 h. 1Diastereoselectivities (dr and de) were determined by chiral-stationary-phase HPLC analysis.

CuOAc (3 mol %) + (R)-DIPA-MeO-BIPHEP (3 mol %) THF (0.1 M), –60 °C, 36 h
Discussion

In conclusion, a copper(I)-catalyzed decarboxylative Mannich reaction between α,α-disubstituted cyanoacetic acids and various 2H-azirines was disclosed, which efficiently constructed chiral aziridines bearing vicinal tetrasubstituted and acyclic quaternary stereogenic carbon centers. The present reaction enjoyed the advantages of mild reaction conditions, easy reaction protocol, broad substrate scope, and high to excellent stereoselectivity. The activation of basic 2H-azirines by cyanoacetic acids, which might generate highly electrophilic iminium species, was proposed to be the key for the success of the present challenging reaction. At last, several transformations of the product were successfully carried out by means of the synthetically versatile cyano and aziridine groups. Expansion of both the present activation strategy and the mild nucleophile generation strategy through copper (I)-catalyzed decarboxylation in asymmetric catalysis is currently in progress in our laboratory.

Methods

General procedure for the synthesis of 3a. A dried 25 mL Schlenk tube equipped with a magnetic stirring bar was charged with CuOAc (2.94 mg, 0.024 mmol) and (R)-DIPA-MeO-BIPHEP (26.2 mg, 0.024 mmol) in a glove box under Ar atmosphere. Anhydrous THF (4 mL) was added via a syringe pump. Isolated yield was reported.

Table 3 Substrate scope of aliphatic 2H-azirines

| Alkyl | Ar | NC | COOH | Alkyl | NH | Alkyl | Ar | CN | CuOAc (3 mol %) (R)-DTBM-SEGPHOS (3 mol %) THF (0.67 M), −20 °C, 12 h |
|-------|----|----|------|-------|----|-------|----|----|---------------------------------------------------------------|
|       |    |    |      |       |    |       |    |    | 5i, 81%, 10/1 dr, 96% ee                                       |
|       |    |    |      |       |    |       |    |    | R = Et, 5g, 62%, 2.4/1 dr, 96% ee                             |
|       |    |    |      |       |    |       |    |    | R = Allyl, 5h, 73%, 2.9/1 dr, 96% ee                         |
|       |    |    |      |       |    |       |    |    |                                                                 |
|       |    |    |      |       |    |       |    |    | 5j, 92%, 14.5/1 dr, 96% de                                  |
|       |    |    |      |       |    |       |    |    |                                                                 |

a: 0.5 mmol, b: 0.2 mmol. 1 was added in 12 h with a syringe pump. Isolated yield was reported.

diastereoselectivity was determined by 1H NMR analysis of reaction crude mixture. Enantioselectivity was determined by chiral-stationary-phase HPLC analysis. bDiastereoselectivities (dr and de) were determined by chiral-stationary-phase HPLC analysis.

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mixture was then cooled to −60 °C and cyanooctacetic acid 1a (0.3 M in THF, 1.0 mL, 0.3 mmol, 1.5 equiv, 52.6 mg) was added dropwise over 2 min. The resulting reaction mixture was stirred at −60 °C for 36 h. The diastereomeric ratio of the crude reaction mixture was determined by 1H NMR spectroscopy. Then, the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 5/1) to give 3a in 92% yield as pale yellow solid.

Fig. 3 Demonstration of the strategy—one substrate activation by the other. a Decarboxylative Mannich reaction of aromatic 2H-azirine. b Proton-transfer Mannich reaction of aromatic 2H-azirine. c Decarboxylative Mannich reaction of aliphatic 2H-azirine. d Proton-transfer Mannich reaction of aliphatic 2H-azirine.

Fig. 4 Transformations of the product 3a. Boc, tert-butoxycarbonyl; Dibal-H, disobutylaluminium hydride.

Data availability
The X-ray crystallographic coordinates for structures reported in this study have been deposited at the Cambridge Crystallographic Data Centre (CCDC), under deposition number CCDC 1891666 (8). These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif. The data supporting the findings of this study are available within the article and its
Supplementary Information file. Any further relevant data are available from the authors on request.

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Author contributions

L.Y. guided the research and wrote the manuscript. H.-J.Z. and Y.-C.X. performed the experiments.

Additional information

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