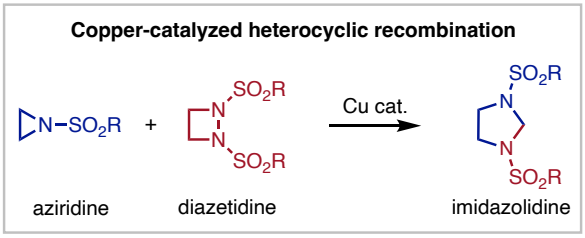
Copper-catalyzed heterocyclic recombination of aziridine and diazetidine for the synthesis of imidazolidine

Daiki Higuchi,[a] Satoshi Matsubara,[a] Hiroki Kadowaki,[a] Daisuke Tanaka,[a] Kei Murakami*[a,b]

[a] Department of Chemistry, School of Science, Kwansei Gakuin University, Gakuen Uegahara 1, Sanda, Hyogo 669-1330, Japan.
[b] JST-PRESTO, 7 Gobancho, Chiyoda, Tokyo, 102-0076 Japan.



Copper catalyst, diazetidine, aziridine, imidazolidine

ABSTRACT: The discovery of new catalytic applications for metals remains an important goal in organic synthesis. If a catalyst has multiple functions, such as inducing bond cleavage and formation, it can streamline multi-step transformations. Herein, we report the Cu-catalyzed synthesis of imidazolidine through heterocyclic recombination between aziridine and diazetidine. Mechanistically, Cu catalyzes the conversion of diazetidine into the corresponding imine, which then reacts with aziridine to form imidazolidine. The scope is sufficiently wide to form various imidazolidines, as many functional groups are compatible with the reaction conditions.

Copper catalysis has been extensively utilized in the organic synthesis of nitrogen-containing heterocycles through the formation of new carbon–nitrogen (C–N) bonds,[1] which are ubiquitous in pharmaceuticals, agrochemicals, and natural products. However, Cu-catalyzed bond dissociation chemistry has not been widely studied.[2] Novel catalytic bond dissociation activities may be investigated to explore the potential of Cu catalysis. Shi *et al.* reported pioneering examples of the Cu-catalyzed nitrogen–nitrogen (N–N) bond cleavage of diaziridinone, which was applied to the synthesis of imidazolidinone (Figure 1a).[2] They proposed that diaziridinone reacts with a Cu catalyst to afford the corresponding copper–nitrogen complex. Inspired by Shi's work, we focused on diazetidine as a precursor of the copper–nitrogen complex. Serendipitously, we found that the reaction of diazetidine with a Cu catalyst afforded triazinane and diaminomethane (Figure 1b). These products were generated from the corresponding imine, which can be formed through the Cu-catalyzed ring cleavage of diazetidine.[3] Based on this finding, we investigated whether two heterocycles recombine with a "single" Cu catalyst (Figure 1c). Considering that Cu can catalyze both, the cleavage of diazetidine and the reaction between the resulting imine and other heterocycles, such as aziridine, imidazolidine is formed through recombination. The Cu catalyst should act as a dual-function catalyst, that is, it should generate the imine from diazetidine, and form imidazolidine from aziridine with the resulting imine.

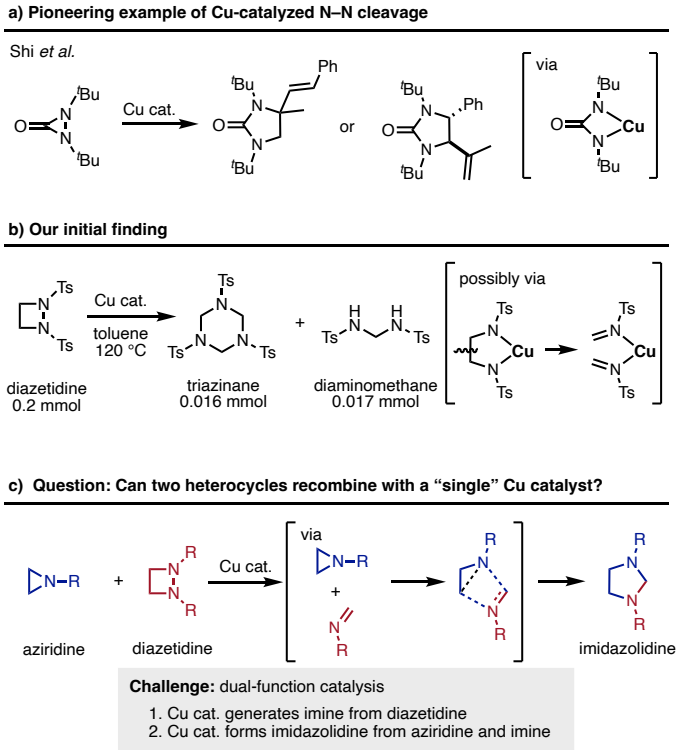


Figure 1. Summary of previous studies and this work.

Although there have been many examples of imidazolidine formation from aziridine[4–9], Cu-catalyzed reactions of imines and aziridines have rarely been reported. Fortunately, we discovered that the CuBr/bipyridine catalyst was efficient for the envisioned reaction. Herein, we report the Cu-catalyzed heterocyclic recombination reaction of aziridine and diazetidine, which forms imidazolidine through C–C and N–N bond cleavage.

The treatment of tosylaziridine **1a** with diazetidine **2a** in the presence of CuBr and 5,5'-dimethyl-2,2'-bipyridine **L1** as the catalyst in toluene at 120 °C for 20 h afforded **3a** in 78% isolated yield (Figure 2a). In this reaction, the addition of a Cu catalyst was essential, and no product was obtained in the absence of CuBr and **L1**. Moreover, the ligand effect was critical, and only 16% **3a** was obtained without **L1**. Because the addition of the ligand improved the yield, we investigated its effect further (Figure 2b). The use of the considerably bulkier 6,6'-dimethyl-2,2'-bipyridine **L2** resulted in a lower yield (47% ^{1}H NMR yield). A series of 4,4'-disubstituted bipyridines were similarly effective, and moderate yields of **3a** were obtained when **L3**–**L5** were utilized as the ligand (67–70% ^{1}H NMR yields). Simple bipyridine **L6** was less effective than substituted bipyridines, affording **3a** in 62% yield. Other ligands, such as **L7** and **L8**, were not effective in this reaction (40% and 17% ^{1}H NMR yields, respectively). The scope of diazetidine was investigated, and the results are summarized in Figure 2c. Diazetidine, when substituted with electron-donating groups (CH_3 and OCH_3) or electron-withdrawing groups (CF_3), reacted to afford the corresponding products (**3b**–**3d**) in moderate to good yields. Both, aryl- and alkyl-substituted diazetidines, afforded **3e** in 65% yield.

We then investigated the scope of aziridine (Figure 3a). Various sulfonylaziridines were converted to their corresponding products. Naphthylsulfonyl aziridine was reacted with diazetidine **2b** to furnish **4a** in 54% yield. Note that the same compound can be derived from aziridine **1a** and diazetidine **2a** (Figure 2a). For substituents on the arylsulfonyl group, electron-donating methoxy or acetylamino groups were compatible with the reaction conditions to provide **4b** and **4c** in 69% and 45% yields, respectively. The electron-withdrawing trifluoromethyl-substituted aziridine gave **4d** in 64% yield. Other alkyl-substituted aziridines were converted to **4e** in 68% yield. Methyl-, cyclohexylmethyl-, tetradecanyl-, and benzyl-substituted aziridines were converted into the corresponding products **4f**–**4i** in moderate to good yields. Aryl, vinyl, ester, or amide-substituted aziridines afforded products **4j**–**4n** without the loss of these functional groups. We performed a gram-scale synthesis that allowed us to obtain **4o** in 1.1 g at a 4.0 mmol scale. To investigate the stereoselectivity of the reaction, (***S***)-**1b** was subjected to the same reaction conditions to provide (***S***)-**4i** in 57% yield with retention of stereochemistry (for the detailed reaction mechanism, *vide infra*). This reaction can be applied to pharmaceuticals, such as celecoxib (Figure 3c). The amide moiety in celecoxib was converted to the corresponding aziridine **1p**.[10] Aziridine **1p** was treated with diazetidine to afford product **5** in 57% yield, which highlights the utility of the reaction.

The proposed mechanism is illustrated in Figure 4a. The reaction involves two catalytic cycles: 1. The formation of imines from diazetidines 2. The reaction of aziridine with the resulting imine. In Cycle 1, Cu catalyst **A** reacts with diazetidine **2** to provide intermediate **B**. Reductive C–C bond cleavage provides the Cu intermediate **C**, which releases imine **D**.[11] In Cycle 2, Cu catalyst **A** activates imine **D** through coordination to give **E**. It is also possible that the O atom of sulfonylimine **D** coordinates to the Cu catalyst, which activates imine **D**. Aziridine **1** then attacks **E** to produce intermediate **F**. Finally, ring-closing cyclization affords product **3**. As it is unclear whether Cu activates imine **D** or aziridine **1**, the aziridine activation mechanism is also shown in the SI (Figure S4).

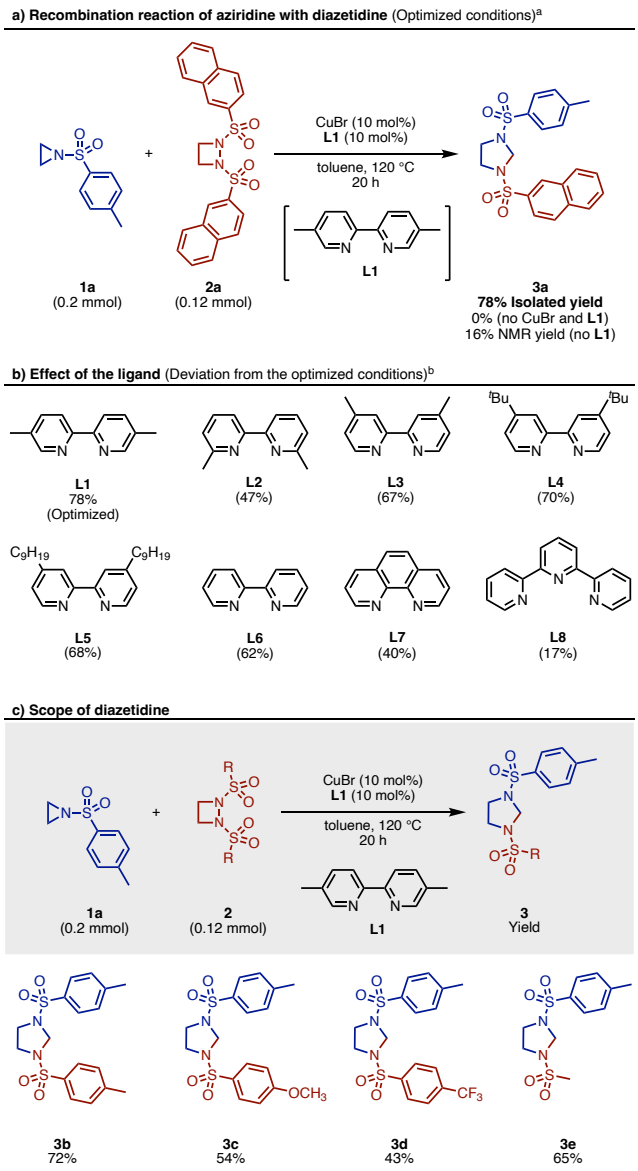


Figure 2. (a) Recombination reaction of aziridine with diazetidine. (b) Effect of the ligand. (c) Scope of diazetidine. [a]The yields were calculated based on **1a** as the limiting reagent. [b] ^{1}H NMR yields are shown in the parenthesis using 1,1,2,2-tetrachloroethane as the internal standard.

To examine the regioselectivity of the cyclization step, we investigated the reaction of chiral aziridine (***S***)-**1b** with **2a** (Figure 4b). The reaction afforded diastereomixtures **6** and **6'** (**6**/**6'** = 16:1) in 60% yield. Although **6** and **6'** were not separable by silica-gel column chromatography, recrystallization afforded analytically pure **6**. The structure was confirmed using X-ray crystallography. This experiment revealed that the imine reacted with the less-hindered unsubstituted carbon to give the product. We then performed competitive experiments to investigate the substituent effects of aziridine and diazetidine, which are summarized in Figure 4c (for the details of each

experiment, see SI, Figure S4). When a mixture of unsubstituted aziridine **1a** and benzyl-substituted aziridine **1j** was reacted with diazetidine **2b** for 1 h, **1a** was preferentially converted (Figure S4, eq 1.). Bulkier benzyl-substituted **1j** was less reactive than unsubstituted **1a**. When we examined the electronic effect on the arylsulfonyl group of diazetidine, methyl-substituted **2b** reacted as fast as methoxy-substituted **2c** (Figure S4, eq. 5). As diazetidine reacts in cycles 1 and 2, the electronic effect is minimal in both, diazetidine fragmentation and imidazolidine formation.

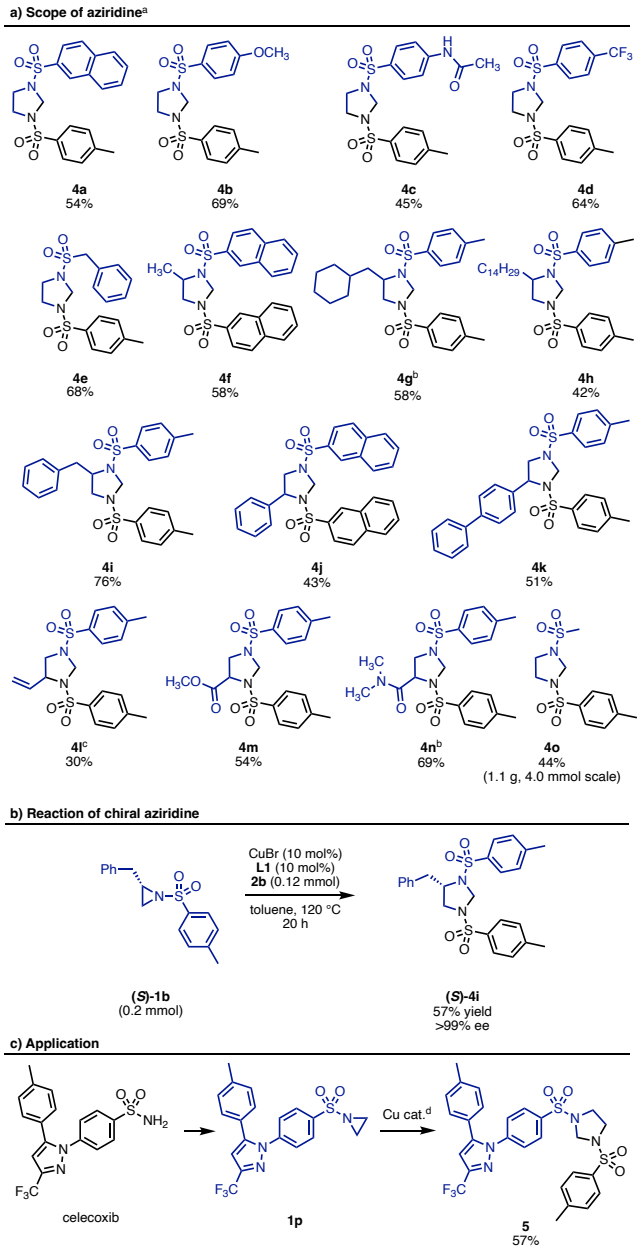


Figure 3. Scope of aziridine [a]**1** (0.20 mmol), **2** (0.12 mmol), CuBr (10 mol%), **L1** (10 mol%), toluene (0.5 mL), 120 °C, 20 h. [b]**1** (0.22 mmol), **2** (0.10 mmol). [c]**1** (0.20 mmol), **2** (0.10 mmol). [d]**1p** (0.17 mmol), **2b** (0.2 mmol) CuBr (10 mol%), **L1** (10 mol%), toluene (0.5 mL), 120 °C, 20 h.

In summary, we developed a Cu-catalyzed reaction that recombines two heterocycles of aziridine and diazetidine. This reaction provided various imidazolidines with excellent functional group compatibility. A new catalytic activity for Cu was revealed. Further investigations of the reaction mechanism are ongoing in our laboratory.

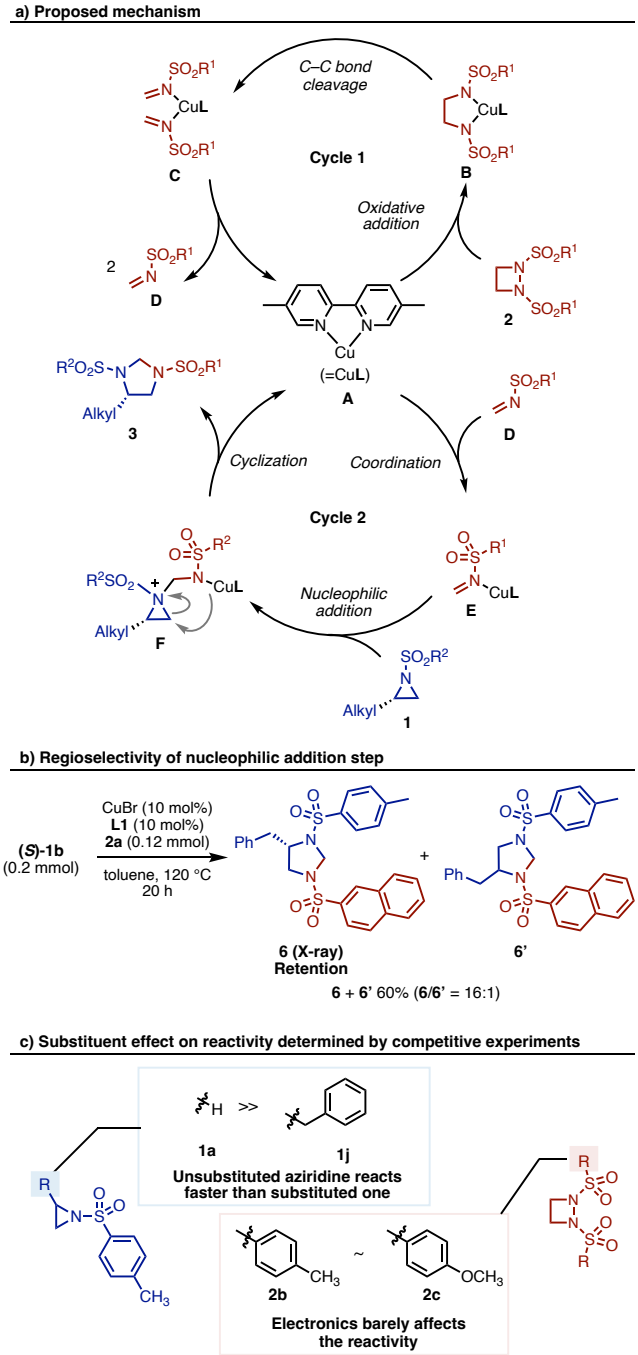


Figure 4. Proposed mechanism and mechanistic investigation.

ASSOCIATED CONTENT

Supporting Information

General experimental details, experimental procedure, characterization data, and NMR spectral data (PDF).

AUTHOR INFORMATION

Corresponding Author

* E-mail: kei.murakami@kwansei.ac.jp.

Author Contributions

The manuscript was written through the contributions of all authors. All the authors approved the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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