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[3 + 3]-Cycloaddition of α-Diazocarbonyl Compounds and *N*-Tosylaziridines: Synthesis of Polysubstituted 2*H*-1,4-Oxazines through Synergetic Catalysis of AgOTf/Cu(OAc)$_2$

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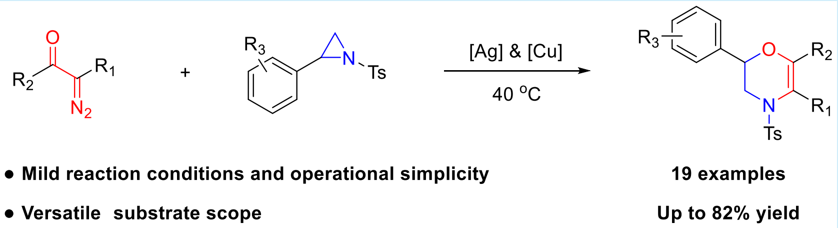
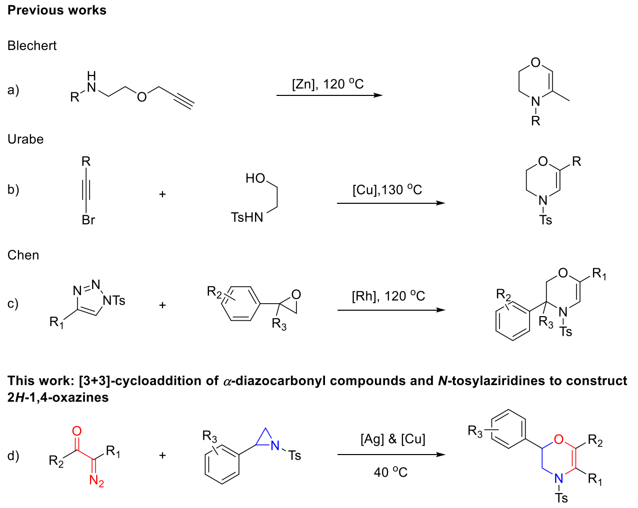
Supporting Information



ABSTRACT: An impressive and new [3 + 3]-cycloaddition of α-diazocarbonyl compounds with *N*-tosylaziridines via synergetic catalysis of AgOTf and Cu(OAc)$_2$ has been well described, which offers efficient access to highly substituted 2*H*-1,4-oxazine derivatives. A variety of α-diazocarbonyl compounds and *N*-tosylaziridines were compatible substrates with convenient operations under mild reaction conditions.

2*H*-1,4-oxazines are six-membered heterocycles that are present in a myriad of pharmaceutical, agrochemical, biological, and material molecules with significant activities.[1] Several approaches to 2*H*-1,4-oxazines have been reported for the past few years. For example, Blechert and colleagues showed the Zn-catalyzed intramolecular hydroamination of functionalized alkenes and alkynes to construct 2*H*-1,4-oxazines (Scheme 1a).[2] In 2008, Urabe et al. developed the facile preparation of 2*H*-1,4-oxazines through copper-catalyzed [2 + 4]-cycloaddition of 1-halo-1-alkynes and hydroxyl *N*-tosylethanolamines (Scheme 1b).[3] Recently, [3 + 3]-cycloaddition of triazoles and epoxides to 2*H*-1,4-oxazines was well developed by Chen's group (Scheme 1c).[4] Despite significant progress in this field, most systems reported so far suffered from high temperature and tedious side reactions. Thus, the development of mild and efficient methods for the construction of 2*H*-1,4-oxazine derivatives has been both a challenge and a focus of synthetic chemistry.

Scheme 1. Synthesis of 2*H*-1,4-Oxazines



In past decades, α-diazocarbonyl compounds have received widespread attention[5] because they can convert into metal−carbene complexes and then react with alkenes, alkynes, or nitriles to deliver cycloaddition products. Doyle and co-workers have made great achievements in this field;[6] they realized a series of cyclization reaction using enoldiazo compounds and proper dipoles. Aziridine,[7] which bears a nucleophilic nitrogen and an electrophilic carbon atom, has been widely applied in the synthesis of heterocyclic scaffolds. As a continuation of our research in diazo chemistry,[8] we envisioned that the [3 + 3]-cycloaddition between α-diazocarbonyl compounds and aziridines would afford a novel approach to the synthesis of highly substituted 2*H*-1,4-oxazine derivatives (Scheme 1d). Compared with traditional methods, this methodology was distinguished by mild conditions and wide substrate scope.

Initially, we chose ethyl 2-diazo-3-oxobutanoate **1a** and *N*-tosylaziridine **2a** as model substrates to test our hypothesis. It has been widely reported that *N*-tosylaziridines can undergo nucleophilic ring opening aided by Lewis acid.[9] AgOTf, one of

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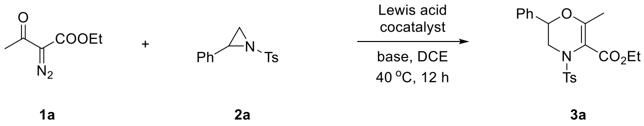
the most commonly used Lewis acid catalysts,[10] was used for this 2*H*-1,4-oxazine formation reaction. By analyzing the reaction mixture, the desired product **3a** was detected in an isolated yield of 43% (Table 1, entry 1). To optimize this cycloaddition reaction, a variety of Lewis acids were tested, but no better results were obtained (for details, see Table S1 in the Supporting Information). Because the matching of ring opening rate and metal−carbene formation rate will be critical to the formation of products,[11] we next screened an appropriate cocatalyst to control the rate of α-diazocarbonyl compound dediazoniation (Table 1, entries 2−9). After extensive screenings, $Cu(OAc)_2$ was found to be the best cocatalyst and afforded the desired product **3a** in high 80% yield (Table 1, entry 7). Notably, no product **3a** was detected in the absence of AgOTf (Table 1, entry 10), indicating that it was indispensable for the generation of 2*H*-1,4-oxazines. Other Lewis acid catalysts were tested under $Cu(OAc)_2$ conditions, but no better results were obtained for this transformation (Table 1, entries 11−16). Based on these results, it was reasonable to believe that AgOTf induced this transformation and $Cu(OAc)_2$ made this process more efficient. For the base, Na_2CO_3, KOH, DBU, and DMAP all led to dramatically decreased yields, compared to that with $NaHCO_3$ (Table 1, entries 16−19). Based on these screening results, the optimal reaction conditions were established as follows: using AgOTf (15 mol %) as the catalyst, $Cu(OAc)_2$ (10 mol %) as the cocatalyst, and $NaHCO_3$ (0.4 mmol) as base for reaction of **1a** (0.2 mmol) and **2a** (0.6 mmol) in 0.4 mL of DCE at 40 °C for 12 h.

Table 1. Optimization of Reaction Conditions[a]

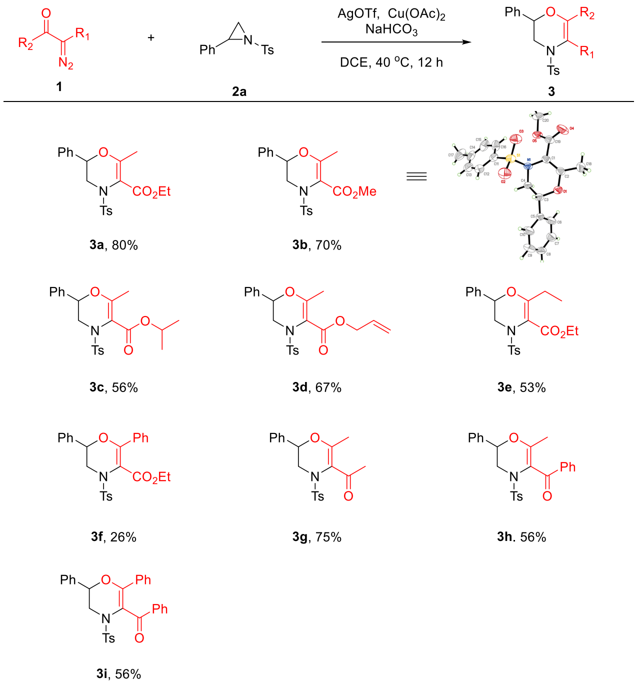


entry	catalyst	cocatalyst	base	yield (%)[b]
1	AgOTf		$NaHCO_3$	43
2	AgOTf	$FeSO_4·7H_2O$	$NaHCO_3$	45
3	AgOTf	$Co(acac)_2$	$NaHCO_3$	<5
4	AgOTf	$Ni(OTf)_2$	$NaHCO_3$	45
5	AgOTf	$Cu(OTf)_2$	$NaHCO_3$	75
6	AgOTf	$CuSO_4$	$NaHCO_3$	69
7	**AgOTf**	**$Cu(OAc)_2$**	**$NaHCO_3$**	**80**
8	AgOTf	$Cu(acac)_2$	$NaHCO_3$	<5
9	AgOTf	CuCl	$NaHCO_3$	75
10		$Cu(OAc)_2$	$NaHCO_3$	<5
11	$BF_3·Et_2O$	$Cu(OAc)_2$	$NaHCO_3$	<5
12	$In(OTf)_3$	$Cu(OAc)_2$	$NaHCO_3$	69
13	$Sn(OTf)_2$	$Cu(OAc)_2$	$NaHCO_3$	<5
14	$Pd(OAc)_2$	$Cu(OAc)_2$	$NaHCO_3$	<5
15	AgOAc	$Cu(OAc)_2$	$NaHCO_3$	<5
16	$AgBF_4$	$Cu(OAc)_2$	Na_2CO_3	<5
17	AgOTf	$Cu(OAc)_2$	KOH	<5
18	AgOTf	$Cu(OAc)_2$	DBU	<5
19	AgOTf	$Cu(OAc)_2$	DMAP	<5
20	AgOTf	$Cu(OAc)_2$		75

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.6 mmol), Lewis acid (0.03 mmol, 15 mol %), cocatalyst (0.02 mmol, 10 mol %), and base (0.4 mmol) in DCE (0.4 mL) at 40 °C for 12 h. [b]Isolated yield.

Having established the optimal reaction conditions, we next examined a variety of α-diazocarbonyl compounds for 2*H*-1,4-oxazine formation, and the results are summarized in Scheme 2.

Scheme 2. Scope of α-Diazocarbonyl Compounds[a]

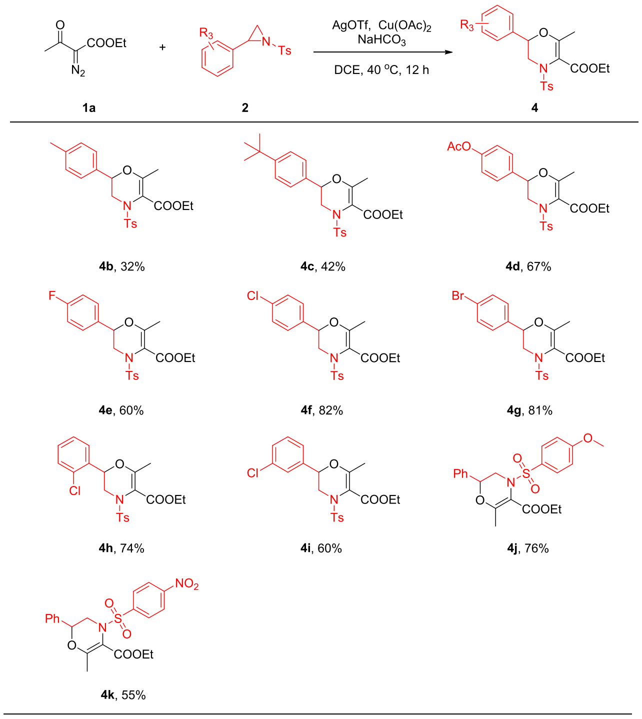


[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.6 mmol), AgOTf (0.03 mmol, 15 mol %), $Cu(OAc)_2$ (0.02 mmol, 10 mol %), and $NaHCO_3$ (0.4 mmol) in DCE (0.4 mL) at 40 °C for 12 h. Isolated yield.

Acyl α-diazoesters bearing different ester groups and acyl substituents were investigated, affording the corresponding products **3a**−**3f** in moderate to good yields. The benzoyl-substituted diazo compound worked well and delivered the desired product **3f** in 26% yield, most probably owing to the electronic effects. Notably, acyl α-diazoketones were suitable substrates for this reaction, providing the corresponding products in moderate to good yields (**3g**−**3i**), and the steric effects were not obvious. The exact configuration of **3b** was further determined by single X-ray crystallography (for more details, see the Supporting Information).

Next, we tested various substituted 2-aryl-*N*-tosylaziridines for 2*H*-1,4-oxazine formation. As shown in Scheme 3, the substrates bearing electron-donating groups or electron-withdrawing groups could take part in this transformation smoothly, affording the corresponding products (**4b**−**4k**) in moderate to high yields. Additionally, the alkyl-substituted 2-aryl-*N*-tosylaziridines (**4b** and **4c**) were less efficient than others, presumably due to the electronic effects. It was noteworthy that this transformation showed favorable compatibility of halogen atoms (**4e**−**4i**), such as fluoro, chloro, and bromo, and the desired products were afforded in good yields. Based on these results (**4f**, **4h**, and **4i**), it was noteworthy that the steric effect of substituents on the aromatic ring did not conspicuously influence the reaction efficiency. The variations of the benzenesulfonyl group were also tested for this transformation in which the 2-aryl-*N*-(*para*-methoxylsulfonyl)aziridine and 2-aryl-*N*-(*para*-nitrosulfonyl)aziridine afforded the corresponding products **4j** and **4k** in 76 and 55% yields, respectively. To further prove the practical utility of this methodology, the reaction was carried out on 7.0 mmol scale, and the desired product **3a** (2.06 g) was obtained in good 73% yield (Scheme 4).

Scheme 3. Scope of Aziridines[a]

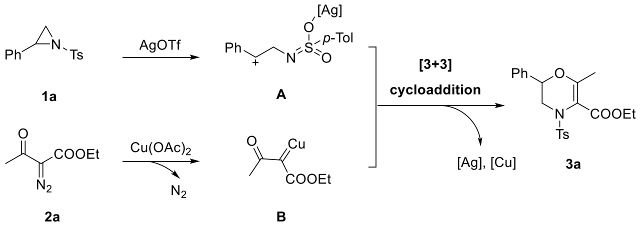


[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.6 mmol), AgOTf (0.03 mmol, 15 mol %), $Cu(OAc)_2$ (0.02 mmol, 10 mol %), and $NaHCO_3$ (0.4 mmol) in DCE (0.4 mL) at 40 °C for 12 h. Isolated yield. **4c** proceeded on 0.5 mmol scale. **4i** proceeded on 1.0 mmol scale.

Scheme 4. Gram-Scale Synthesis of 2*H*-1,4-Oxazines

Based on the previous literature report,[12] a plausible mechanism was depicted in Scheme 5. The aziridine **1a** reacts with AgOTf to afford stabilized zwitterionic intermediate **A**. At the same time, diazo compound **2a** delivers the copper−carbene intermediate **B** and releases nitrogen in the presence of $Cu(OAc)_2$ catalyst. Subsequent [3 + 3]-cycloaddition generates the desired 2*H*-1,4-oxazines **3a** and Ag/Cu catalyst for the next circulation. At present, we do not rule out a nucleophilic attack that takes place between metal−carbene and aziridine to afford the ylide intermediate, which leads to the desired product after further [3 + 3] cyclization.[13]

Scheme 5. Proposed Mechanism



In summary, we have disclosed a mild and general [3 + 3]-cycloaddition reaction between *α*-diazocarbonyl compounds and *N*-tosylaziridines, leading to polysubstituted 2*H*-1,4-oxazines through synergetic catalysis of AgOTf/$Cu(OAc)_2$. This methodology also successfully expands the scope of *α*-diazocarbonyl compounds in the [3 + 3]-cycloaddition reaction. Further investigations on the detailed mechanism and potential application are ongoing 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.9b00632.

Experimental procedure, characterization data, copies of ^1H, ^{13}C, and ^{19}F NMR spectra (PDF)

Accession Codes

CCDC 1879327 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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