

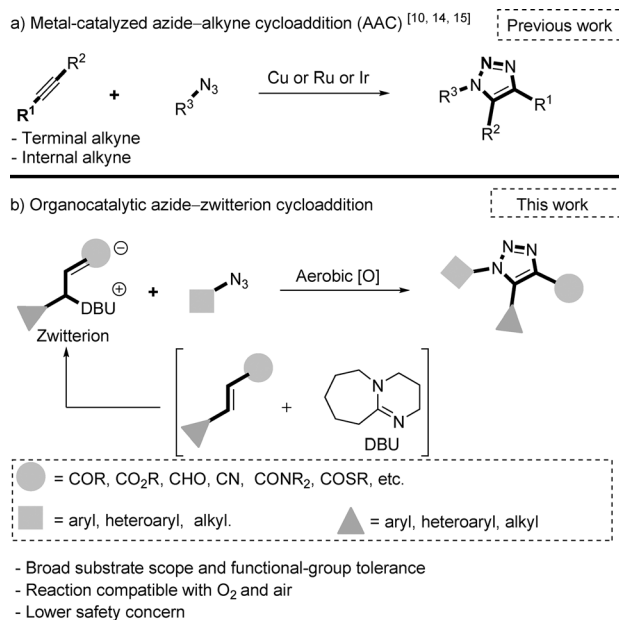
Lewis Base Catalyzed Aerobic Oxidative Intermolecular Azide–Zwitterion Cycloaddition**

Wenjun Li and Jian Wang*

Abstract: The discovery of a novel aerobic oxidative intermolecular azide–zwitterion reaction catalyzed by an organocatalyst is presented. It is demonstrated that the merger of the Lewis base 1,8-diazabicyclo[5.4.0]undec-7-ene and electron-deficient olefins generates reactive zwitterion intermediates, which readily participate in cycloaddition reactions with an array of azides, thus providing facile entry to fully or highly substituted 1,2,3-triazole frameworks. The reaction features an excellent substrate scope, and the products are obtained with high yields and excellent regioselectivities. It is demonstrated that some of these products can be transformed into pharmaceutically important agents. In addition to the experimental results, a detailed mechanistic survey is also provided, including MS studies rationalizing the origin of regioselective control.

The 1,2,3-triazole core is a privileged scaffold which is featured in a vast number of bioactive molecules.^[1] They have exhibited considerable biological and pharmaceutical activities.^[1–2] Notably, they have been disclosed as attractive connections in biological systems because they are stable to metabolic degradation and capable of hydrogen bonding to biomolecular targets.^[3] Moreover, the application of triazole chemistry is not only limited to drug discovery but also largely extended to numerous other scientific fields,^[4] such as bioconjugation,^[5] material science,^[6] and polymer chemistry.^[7]

Although the ubiquitous 1,2,3-triazoles have been known for over several decades, they have not been utilized as widely as other members of the azole family.^[8] The conspicuous lack of the literature reports is likely due to the limited repertoire of synthetic methods leading to these heterocycles. Huisgen 1,3-dipolar azide–alkyne cycloaddition (AAC) is the most straightforward and atom-economical synthetic method for the construction of these heterocycles.^[9] However, the traditional thermal AAC conditions typically require high temperatures and proceed with limited regioselectivity. In 2002, the groups of Sharpless^[10a] and Meldal^[10b] independently reported their copper-catalyzed azide–terminal alkyne cycloaddition (Scheme 1 a), thus providing a mild and efficient synthesis of 1,4-disubstituted 1,2,3-triazoles.^[11] In contrast to the widely successful use of terminal alkynes (including metal acetylides) in catalyzed AACs,^[12] the corresponding reactions of internal



Scheme 1. a) Metal-catalyzed azide–alkyne cycloaddition. b) Organocatalytic azide–zwitterion cycloaddition.

alkynes for the synthesis of fully substituted 1,2,3-triazoles remain a challenge^[13] owing to the increased energy barrier and difficulty in regiocontrol, particularly for intermolecular reactions. While the advent of ruthenium-based catalytic systems (RuAAC)^[14] and iridium-based catalytic systems (IrAAC)^[15] has addressed the challenge to some extent (Scheme 1 a), additional efficient catalytic systems complementary to CuAAC, RuAAC, and IrAAC remain in high demand. More recently, organocatalytic triazole formation has been used as a powerful, albeit less developed, alternative to metal-catalyzed AAC reactions. The groups of Ramachary^[16a,b] and Bressy^[16c] as well as our group,^[16b,d,f,g,j] independently reported the organocatalytic regioselective synthesis of substituted 1,2,3-triazoles through enamine intermediates formed in situ. This method attracted much attention because of the common green features of organocatalysis.^[17] However, these approaches are restricted to ketone or cyclic enone substrates, which have largely limited its applications. In continuation of our studies in searching for new methods for the formation of densely functionalized 1,2,3-triazoles,^[18] we report herein the first metal-free catalytic aerobic oxidative intermolecular azide–zwitterion cycloaddition (AZC) reaction (Scheme 1 b). Specifically, a facile intermolecular AZC reaction of an in situ generated zwitterion has been realized for the first time, and also could be utilized to assemble highly substituted 1,2,3-triazoles.

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Zwitterions represent a basic class of important organic intermediates and have received renewed attention in synthetic organic transformations.^[19] The Morita–Baylis–Hillman (MBH) reaction has become one of the most useful and popular carbon–carbon bond-forming reactions with enormous synthetic utility, promise, and potential.^[20] According to currently accepted reaction mechanism,^[21] the first step of a MBH reaction is commonly referred to as the in situ zwitterion formation by addition of catalytic amount of amine or phosphine to electron-deficient olefins. Building on these pioneering scientific discoveries, we started to verify our hypothesis. Upon exposure of the α,β -unsaturated ester **1a** and phenyl azide (**2a**) to the catalyst **I** (20 mol %) in DMSO at 80 °C, we observed low conversion into **3aa** after 48 hours (Table 1, entry 1). After extensive screening of commonly

Table 1: Optimization of the reaction conditions.^[a,f]

Reaction scheme showing the synthesis of **3aa** from **1a** and **2a** using catalysts **I-VII** (20 mol%), solvent, air, and 80 °C.

Chemical structures of catalysts **I-VII**: **I** (DBU), **II** (DBU), **III** (DBU), **IV** (DBU), **V** (PPh_3), **VI** (Me_2PPh), **VII** (PCy_3).

Entry	Cat.	Solvent	<i>t</i> [h]	Yield [%] ^[b]
1	I	DMSO	36	16
2	II	DMSO	36	25
3	III	DMSO	36	72
4	IV	DMSO	36	19
5	V	DMSO	36	< 5
6	VI	DMSO	36	< 5
7	VII	DMSO	36	23
8	III	DMF	36	59
9	III	DMA	36	53
10	III	MeOH	36	46
11	III	toluene	36	61
12	III	THF	36	75
13	III	CH_3CN	36	42
14	III	CHCl_3	36	87
15 ^[c]	III	CHCl_3	72	41
16 ^[d,g]	III	CHCl_3	48	85
17 ^[e]	III	CHCl_3	72	76

[a] Reaction conditions: A mixture of **1a** (0.10 mmol), **2a** (0.20 mmol), and the catalyst (20 mol %) in solvent (0.3 mL) was stirred at 80 °C under air for 36 h. [b] Yield of isolated product. [c] The reaction was conducted at 50 °C for 72 h. [d] 10 mol % catalyst used. [e] 5 mol % catalyst used. [f] No reaction takes place without catalyst or oxygen in the atmosphere. [g] If O₂ balloon used, t = 36 h. [h] **2a** (0.12 mmol, 1.2 equiv), 67% yield. DMA = dimethylacetamide, DMSO = dimethylsulfoxide.

used amine or phosphine catalysts, we found that the addition of 0.2 equivalents of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) played a pivotal role for the high efficiency of the desired reaction (entry 3). Notably, if phosphine catalysts were used, **2a** was partially decomposed because of the plausible Staudinger reaction. This kind of beneficial effect of DBU as a superb nucleophile in catalytic MBH reactions has

recently been demonstrated by the group of Aggarwal.^[22] After surveying a variety of solvents, the best result was obtained using CHCl₃ (entry 14). Further screening of the reaction temperature indicated that a decreased temperature led to a slow conversion (entry 15). It is worth noting that lowering the catalyst loading to 10 mol % caused no significant change in the chemical yield (entry 16). Finally, optimization of the reaction parameters led us to identify DBU as a catalyst and CHCl₃ as an ideal medium for the desired transformation, thus furnishing **3aa** not only in essentially high yield but also with absolute regioselectivity.

With the standard reaction conditions established, the scope and limitations of our DBU-catalyzed AZC reactions were explored. As shown in Table 2, a wide range of aryl and

Table 2: Scope with respect to the azides.^[a]

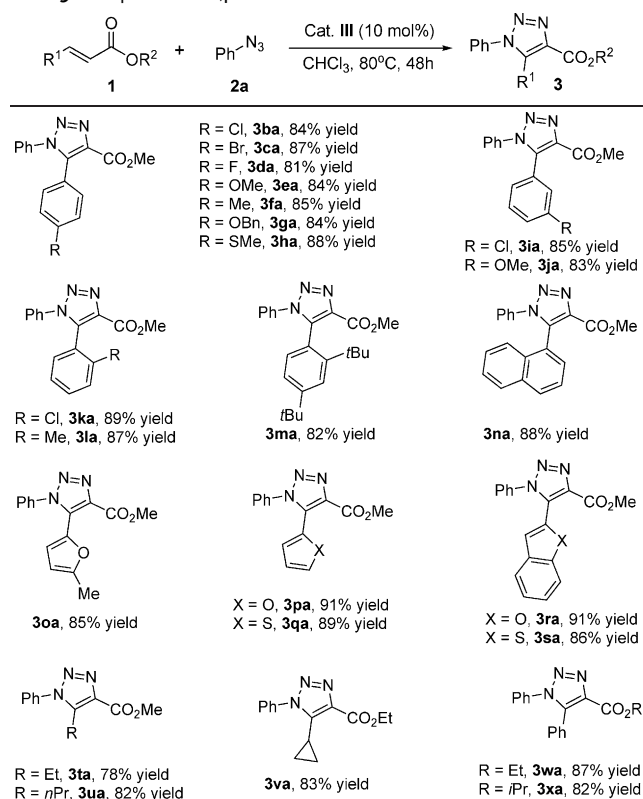
3aa , 85% yield	3ab , 81% yield	3ac , 84% yield
3ad , 89% yield	3ae , 85% yield	3af , 91% yield
3ag , 86% yield	3ah , 84% yield	3ai , 82% yield
3aj , 85% yield	3ak , 88% yield	3al , 84% yield
3am , 87% yield	3an , 68% yield	3ao , 83% yield
3ap , 81% yield	3aq , 85% yield	3ar , 82% yield

[a] Reaction conditions: A mixture of **1a** (0.10 mmol), **2** (0.20 mmol), and **III** (10 mol %) in CHCl₃ (0.3 mL) was stirred at 80 °C under air for 48 h.

alkyl azides participated in the cycloaddition to give the fully substituted 1,2,3-triazoles in high to excellent yields. Substrates bearing different substitution patterns on the benzene ring undergoing AZC reactions all led to the expected products **3aa–al** and **3ao–ap** (81–91%). Alkyl azides also afforded the expected adducts in high chemical yields (**3ao–ar**; 81–85%). Naphthyl and heteroaryl azides were smoothly converted into the desired products **3am** and **3an**, respectively, under the same reaction conditions.

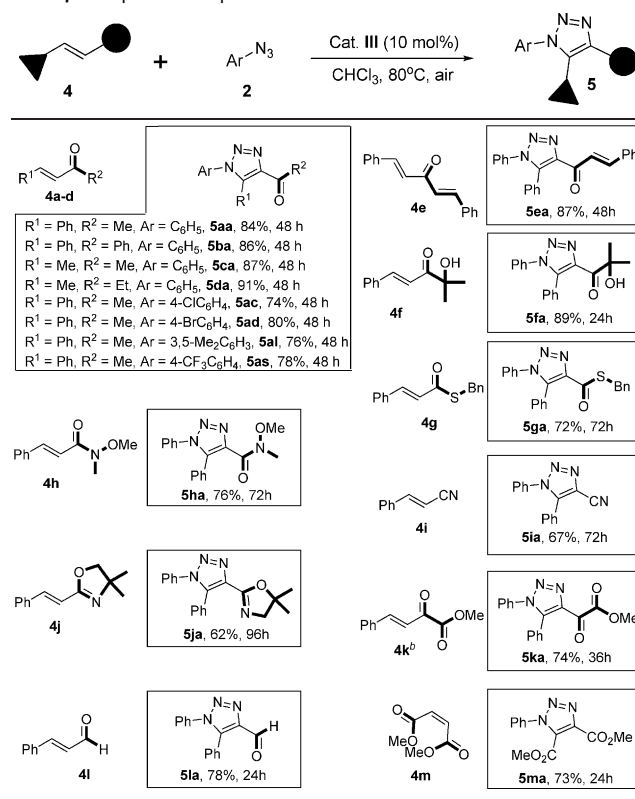
Next, we turned our attention to α,β -unsaturated esters (Table 3). A diverse array of α,β -unsaturated methyl esters (**1**) with aryl and alkyl substituents on alkenes engaged in the

Table 3: Scope of the α,β -unsaturated esters.^[a]



[a] Reaction conditions: A mixture of **1** (0.10 mmol), **2a** (0.20 mmol), and **III** (10 mol%) in CHCl_3 (0.3 mL) was stirred at 80°C under air for 48 h.

Table 4: Scope with respect to the electron-deficient olefins.^[a]

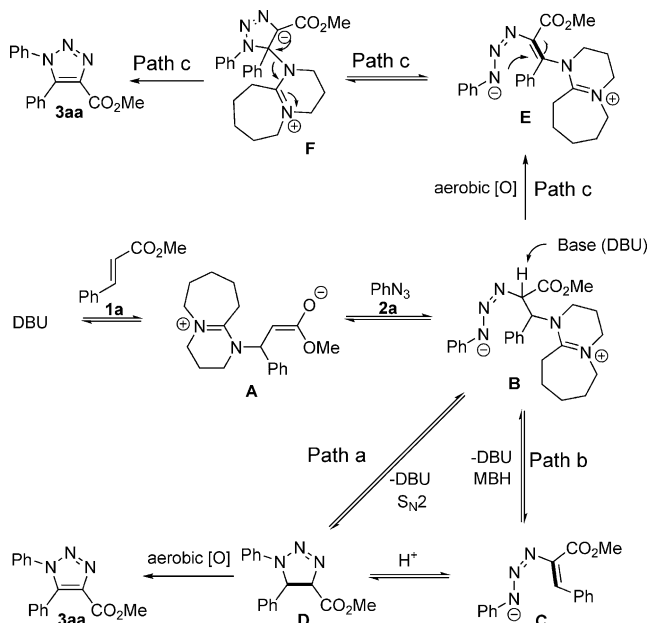


[a] Reaction conditions: A mixture of **4** (0.10 mmol), **2a** (0.20 mmol), and **III** (10 mol%) in CHCl_3 (0.3 mL) was stirred under air at 80°C .
[b] Triethylamine (TEA) as the catalyst.

cycloaddition reaction to give the corresponding densely functionalized 1,2,3-triazoles in high to excellent yields with complete regioselectivities (**3ba–va**; 78–91%).^[23] We also examined ethyl and isopropyl cinnamates and both gave expected adducts **3wa** (87%) and **3xa** (82%) high chemical yields.

To further demonstrate the generality of the DBU-catalyzed AZC reactions, it is shown that other types of activated olefins are equally capable in participating in the developed reaction (Table 4). It was discovered that the reaction tolerated a variety of functionalized electron-deficient olefins, such as α,β -unsaturated ketones (**4a–f**), an α,β -unsaturated thioester (**4g**), α,β -unsaturated amide (**4h**), nitrile olefin (**4i**), α,β -unsaturated dihydrooxazole (**4j**), α,β -unsaturated ketoester (**4k**),^[24] α,β -unsaturated aldehyde (**4l**), and maleate (**4m**). It should be noted that, a few of the electron-deficient olefin systems (such as nitroolefins and quinones) commonly used in Diels–Alder reactions gave no desired adducts under the standard reaction conditions.

The mechanistic proposal is depicted in Scheme 2. DBU reacts to some extent with the starting α,β -unsaturated ester **1a** to form the zwitterion intermediate **A**. Subsequent addition of **A** to **2a** forms the intermediate **B**. Building on the active intermediate **B**, three plausible reaction pathways were postulated. For path a: an $\text{S}_{\text{N}}2$ reaction of **B** generates the cyclic intermediate 1,2-dihydro triazole **D**, which is subsequently oxidized into desired product **3aa**. For path b:



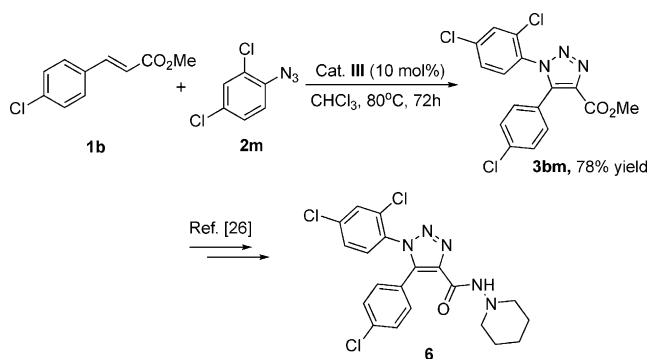
Scheme 2. Postulated mechanism.

elimination of DBU produces the olefin intermediate **C**, which can proceed to the desired product **3aa** through a 6 π electrocyclic and oxidative aromatization sequence.

For path c: aerobic oxidation of **B** generates the key olefin intermediate **E**, which undergoes a 6π electrocycloaddition and subsequent liberation of DBU from the intermediate **F** to eventually form the cycloaddition product **3aa**. The high regioselectivity of this reaction is clearly due to the presence of various electron-withdrawing groups on the dipolarophiles **1** and **4**, groups which lower the energy of the lowest unoccupied molecular orbital (LUMO) and causes the β -carbon atom to be most electrophilic. Thus, DBU is expected to attack the partially positively charged β position of the olefins in a AZC reaction to form a zwitterion intermediate, which would react with the azide and then eliminate DBU to regioselectively yield a triazole with the carboxy and the phenyl group at the C4 and the C5 positions, respectively.

To corroborate our hypothesis outlined in Scheme 2, we carried out a mass spectrometric (MS) study.^[25] Several experiments began with the ESI-MS monitoring of the reaction of **1a** and **2a** catalyzed by DBU in CHCl_3 (see the Supporting Information). After 2 hours, a zwitterion species directly related to the proposed Morita-Baylis–Hillman catalytic cycle was detected as a major ion: $[\mathbf{A} + \text{H}_2\text{O} + \text{H}]^+$ of m/z 333 and $[\mathbf{A} + 2\text{H}_2\text{O} + \text{H}]^+$ of m/z 351. The ESI-MS spectrum for the reaction of **1a** and **2a** catalyzed by DBU shows two major ions, m/z 153 and m/z 432 ($[\mathbf{E} + \text{H}]^+$ or $[\mathbf{F} + \text{H}]^+$), thus indicating the preference to probably form the key intermediates **E** and **F** (Scheme 2). Taken together, these experimental observations convincingly demonstrated that path c is more favorable than others.

To further demonstrate the utility of this methodology, we embarked on the synthesis of CB1 cannabinoid receptor antagonist **6** (Scheme 3). DBU-catalyzed AZC reaction of



Scheme 3. Synthesis of CB1 cannabinoid receptor antagonist (**6**).

2m and the α,β -unsaturated ester **1b** enabled led to **3bm** in 78% yield. Finally, **3bm** was converted into the desired product **6** by using a known procedure.^[26] In contrast to the known strategy for constructing **3bm** (61%, 3 steps),^[26] our method is much more efficient (78%, 1 step).

In summary, the first organocatalytic aerobic oxidative intermolecular azide–zwitterion cycloaddition (AZC) reaction is presented. With the proper choice of catalyst, various azides and in situ generated zwitterions, from a variety of electron-deficient alkenes, can participate in this efficient

cycloaddition to furnish a wide range of fully or highly substituted 1,2,3-triazoles. Additional detailed investigations on the organocatalytic AZC are underway.

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