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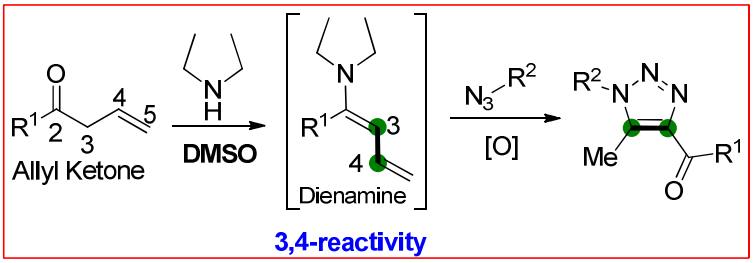

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ARTICLE TYPE

Direct Access to 1,2,3-Triazoles through Organocatalytic 1,3-Dipolar Cycloaddition Reaction of Allyl Ketones with Azides

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In the past few years, 1,2,3-triazole-containing molecules have proven to be potential targets for drug discovery.[1,2] A large number of 1,2,3-triazoles exhibit biologically important activities, e.g. antiviral, antibacterial, antifungal and anticancer activities.[3,4] As shown in Figure 1, tetracyclic 1,2,3-triazoles **1** exhibited good serine protease inhibition activity;[5] *tert*-butyldimethylsilylspiroaminooxathioledioxide **2** (known as TSAO) was identified as the potent nucleoside derivative non-nucloside reverse transcriptase inhibitor;[6] 4-alkoxycarbonyl-1,5-diaryl-1,2,3-triazoles **3** were marked as potent CB1 cannabinoid receptors.[7] The recent successful discovery of 1,2,3-triazole pharmacophore based highly functionalized antiviral cyclic amino acid oseltamivir and zanamivir have amplified the importance of triazoles to even a greater extent.[8] In addition, the 1,2,3-triazole moiety is found to be a constituent part of many modified nucleosides or carbanucleosides with antiviral, anti-HIV or cytostatic activities.[9] Moreover, the application of triazole chemistry is not only limited to drug discovery but also largely extended to numerous other scientific fields, such as bioconjugation,[10] macromolecule chemistry,[11] and polymer sciences.[12]

Scheme 1. Organocatalytic strategies in preparation of triazoles.

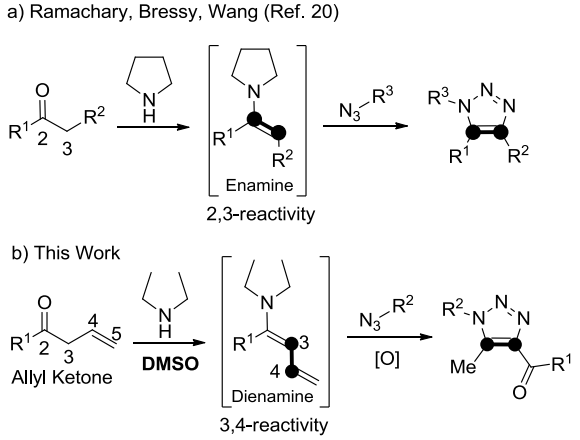
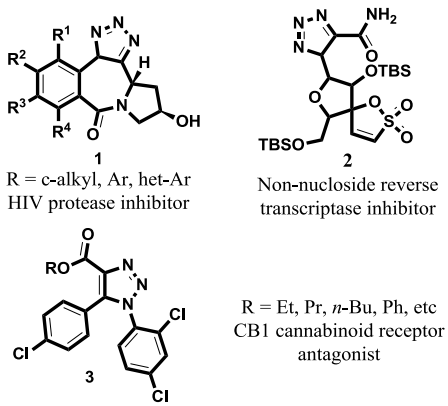
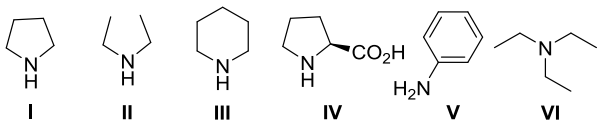


Fig 1: Examples of important 1,2,3-triazoles.



The most powerful protocol for the synthesis of 1,2,3-triazoles is the Huisgen 1,3-dipolar cycloaddition of organic azides with acetylenes.[13] The classical Huisgen reaction, thermally induced, gives an approximate 1:1 mixture of 1,4- and 1,5-disubstituted 1,2,3-triazole isomers.[14] However, when Cu(I) catalysis is applied, the reaction becomes regioselective, exclusively yielding the 1,4-regioisomer within a relatively short reaction time.[15] Recently, Cu(I)-catalyzed azide–alkyne cycloaddition (CuAAC) has become the basis of the so-called click chemistry concept due to its wide applicability and efficiency. This discovery has clearly advanced the research of 1,2,3-triazoles and related chemistry to be one of the "hottest" research fields during the last decade.[16] This robust method has been widely applied to various areas as an efficient strategy for combining different functionalities under mild conditions. Driven by the great success of the synthesis of 1,2,3-triazoles, more attentions have been put into investigating the fundamental reactivity of this interesting heterocycle.[17] Various attractive applications have been reported that are associated with the unique 1,2,3-triazole core structure, including the formation of

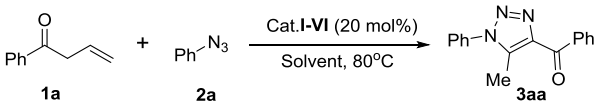
Fig 2: Screened catalysts.



carbene intermediates[18] and adjusting the transition metal reactivity with triazole ligands.[19] These studies further extended the versatility of 1,2,3-triazole building blocks. Fast-growing research in this area has led to the urgent need for effective syntheses of different triazole analogous, especially those that provide good regio and stereo-selectivity. More recently, Ramachary, Bressy and our group independently reported the organocatalytic regioselective synthesis of highly substituted 1,2,3-triazoles through the *in situ* formed enamine intermediate (Scheme 1a).[20] This method attracted much attention due to the common green features of organocatalysis. However, these methods are restricted to ketone or cyclic enone substrates, which have largely limited its applications.[20a-d] As part of our continued interest in extending substrate scope and diversity of 1,2,3-triazoles,[20e-g] herein, we report our new discovery regarding an organocatalytic cycloaddition of allyl ketones to azides in the presence of a catalytic amount of simple and commercial available secondary amine (Scheme 1b). Notably, the desired products was formed by utilizing a unusual 3,4-reactivity of dienamine intermediate.[21]

Initial experiments were conducted on allyl ketone **1a** and phenyl azide **2a** in the presence of 10 mol% of amines (**I–VI**). As indicated in Table 1, diethyl amine **II** is identified as the most active catalyst for this transformation (entries 1-6). Further optimization of other reaction parameters revealed that the solvent is one of crucial factors. When the reaction was carried out in DMSO, reactivity was positively influenced, leading to the desired product **3aa** in 67% yield. Other solvents, such as toluene, THF, 1,4-dioxane, MeOH, DMA, and DMF, significantly diminished the chemical yields (Table 1, <5-47%). Changing the ratio of **1a/2a** from 1:1 to 1:2 indicated a beneficial effect on the efficacy of the reaction (entry 14, yield increased to 85%). Further increasing the equivalent of **2a** didn't improve the chemical yield (entry 15, **1a/2a** = 1:3, 86%). Lowering the catalyst loading to 10 mol% afforded product **3aa** in 83% yield in a reasonable time (entry 16, 24 h). Further lowering the catalyst loading to 5 mol% still afforded a good chemical yield but requested a long reaction time (entry 17, 74%, 72 h). However, decreasing the temperature to 50°C caused a rapid loss in chemical yield (entry 13, 32%, 24 h). Finally, the best compromise was achieved when performing the reaction in DMSO at 80°C, using 10 mol% of cat. **II** and **1a/2a** = 1:2.

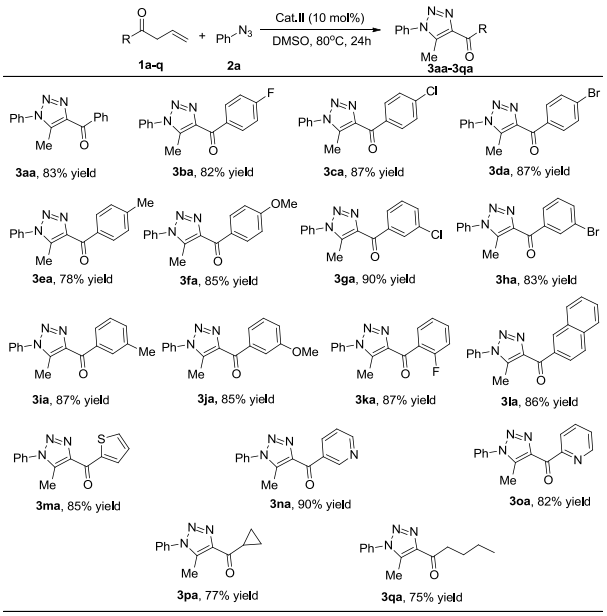
Table 1: Optimization of reaction conditions.[a]



entry	cat.	solvent	t (h)	yield (%)[b]
1	**I**	DMSO	12	43
2	**II**	DMSO	12	67
3	**III**	DMSO	12	54
4	**IV**	DMSO	12	25
5	**V**	DMSO	12	37
6	**VI**	DMSO	12	21
7	**II**	DMF	12	47
8	**II**	DMA	12	45
9	**II**	Toluene	12	34
10	**II**	MeOH	12	28
11	**II**	THF	12	24
12	**II**	1,4-Dioxane	12	<5
13[c]	**II**	DMSO	24	32
14[d]	**II**	DMSO	12	85
15[e]	**II**	DMSO	12	86
16[d,f]	**II**	DMSO	24	83
17[d,g]	**II**	DMSO	72	74

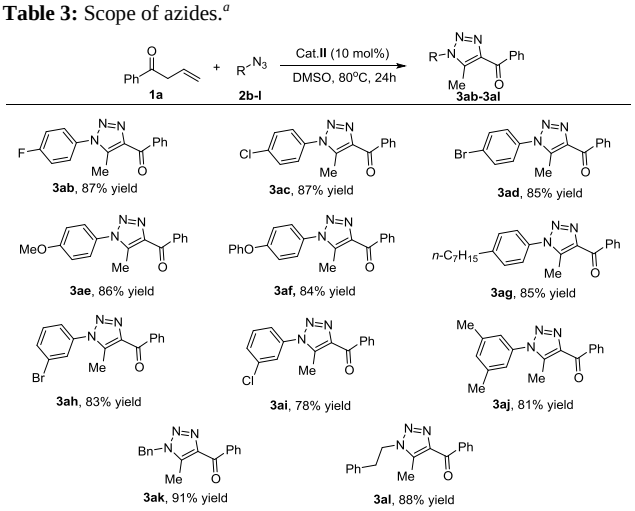
[a]Reaction conditions: A mixture of **1a** (0.10 mmol), **2a** (0.10 mmol) and catalyst (20 mol%) in the solvent (0.3 mL) was stirred at 80°C for 12h.[b]Isolated yield. [c]The reaction was conducted at 50°C for 24h. [d]**1a**:**2a** = 1.0:2.0. [e]**1a**:**2a** = 1.0:3.0. [f]10 mol% catalyst used. [g]5 mol% catalyst used.

Table 2. Scope of allyl ketones.[a]



[a]Reaction conditions: A mixture of **1a-q** (0.10 mmol), **2a** (0.20 mmol) and cat. **II** (10 mol%) in DMSO (0.3 mL) was stirred at 80°C for 24h.

Table 3: Scope of azides.[a]

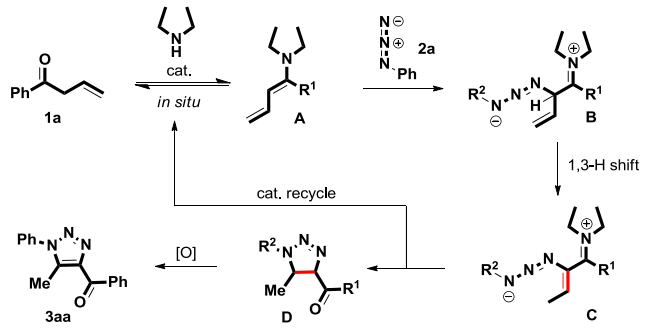


[a]Reaction conditions: A mixture of **1a** (0.10 mmol), **2** (0.20 mmol) and **II** (10 mol%) in DMSO (0.3 mL) was stirred at 80°C for 24h.

The scope of allyl ketones was then evaluated. As summarized in Table 2, the reaction is general for allyl ketones no matter what R is alkyl or aryl group. The substitution pattern of allyl aryl ketones (R = aryl group) could be varied successfully: electron-withdrawing, neutral and electron-donating substituents were tolerated and demonstrated remarkably high yields in all cases (**3aa–3la**, 87–90%). Notably, allyl heteroaryl ketones exhibited high degrees of reactivities and generated the desired products in high yields (**3ma–3oa**, 82–90%). In addition, allyl alkyl ketone **1p** and **1q** was also engaged in reaction and gave the corresponding product **3pa and 3qa** in 77% yield and 75% yield, respectively.

With this promising result in hand, we then investigated the generality of azides. As shown in Table 3, various substitutents of phenyl azides, including electron-donating groups (e.g. alkoxy, aryloxy and alkyl groups), electron-withdrawing groups (halogens), were all compatible under the optimal reaction conditions (**3ab–3aj**, 78–87%). Additionally, alkyl azides were also involved in the reaction to afford good yields (**3ak** and **3al**, 91% and 88%, respectively). The configuration of the products was assigned based on single-crystal X-ray analysis of **3ea**.[22]

Scheme 2: Postulated mechanism.



As shown in Scheme 2, we suggested a plausible mechanism to explain the reaction. First, **1a** reacts with catalyst **I** to form dienamine **A**. Dienamine **A**, an electron-rich olefinic partner, reacts with phenyl azide **2a** to furnish intermediate **B**. Subsequently, 1,3-H shift allows intermediate **B** transfer to intermediate **C**. Intermediate **C** then undergoes an intramolecular addition to afford intermediate **D**, which then starts an aerobic oxidation step to eventually generate the final product **3aa**.

Conclusions

In summary, a general organocatalytic 1,3-dipolar cycloaddition reaction between allyl ketones and various azides has been developed. The reaction is catalyzed by a secondary amine to generate substituted 1,2,3-triazoles with high levels of regioselectivity. It is noteworthy that this cycloaddition proceeds efficiently by a simple and inexpensive catalyst. Considering the ready availability of the azides and the operational simplicity, a convenient, practical and highly modular highly substituted 1,2,3-triazole synthesis has been achieved. We believe that this work will arouse more research interest in green synthesis of other important heterocycles. Such studies are under way in our laboratory, and more results will be reported in due course.

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

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22 CCDC 983786 (**3ea**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/ data_request/cif.