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ARTICLE TYPE

Organocatalytic 1,3-dipolar cycloaddition reactions of ketones and azides with water as a solvent

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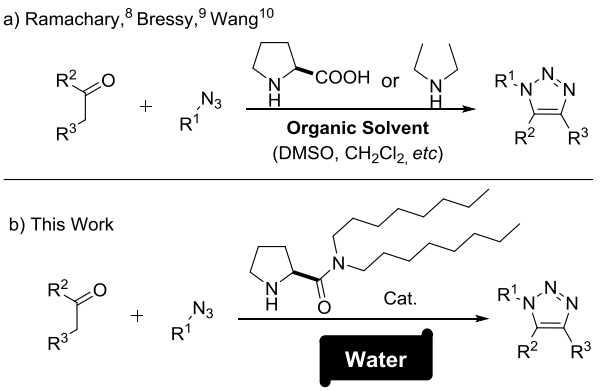
We reported an enamine catalyzed strategy to fully promote a 1,3-dipolar cycloaddition to access a vast pool of substituted 1,2,3-triazoles with water as the only solvent.

In active pharmaceutical ingredient synthesis, the choice of reaction media is a major consideration because solvents make up more than 80% of the material usage, consume about 60% of the overall energy used, and account for 50% of the post treatment green-house gas emissions.[1] Despite some limitations, water holds the potential to be an ideal solvent due to economic and environmental benign features. Consequently, considerable attention has been drawn to the development of catalytic reactions that can operate with water as the medium. A large number of metal-catalyzed reactions can now be carried out in aqueous environments.[2,3]

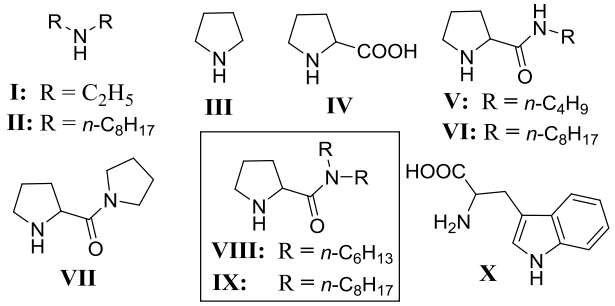
Scheme 1 Organocatalytic strategies in preparation of triazoles.



In recent years, organocatalytic reactions have emerged as an alternative synthetic approach that can eventually reach large-scale applications for the synthesis of pharmaceuticals.[4] Since organocatalysts are typically stable in the presence of water, the development of organocatalytic reactions in water is particularly promising. For example, multiple amine-catalyzed reactions have been found to work well in aqueous environments.[5,6]

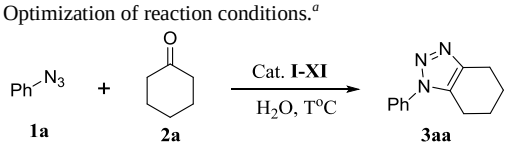
As one of the most important privileged scaffolds, the 1,2,3-triazole core has been featured in a large number of bioactive molecules.[7] Consequently, it has attracted much attention from both academy and industry. Recently, organocatalytic synthesis

Fig. 1 Organocatalyst screened.



of 1,2,3-triazole molecules through an inverse-electron-demand Huisgen 1,3-dipolar cycloaddition strategy have been successfully reported by Ramachary,[8] Bressy[9], our group[10] and others[11]. However, these reported organocatalytic methods are

Table 1 Optimization of reaction conditions.[a]



Entry	Cat.	T (°C)	*t* (h)	Yield (%)[g]
1	**I**	80	48	12
2	**II**	80	48	22
3	**III**	80	48	18
4	**IV**	80	48	<5
5	**V**	80	48	35
6	**VI**	80	48	42
7	**VII**	80	48	<5
8	**VIII**	80	48	75
9	**IX**	**80**	**48**	**81**
10	**IX**	RT	120	30
11	**IX**	50	72	53
12	**IX**	100	48	85
13[b]	**IX**	80	72	62
14[c]	**IX**	80	48	60
15[d]	**IX**	80	48	70
16[e]	**IX**	80	48	76
17[f]	**IX**	80	48	66
18	**X**	80	48	<5

[a] Unless otherwise stated, reaction conditions are: **1a** (0.25 mmol, 1.0 equiv.), **2a** (0.50 mmol, 2.0 equiv), Cat. (0.05 mmol, 0.2 equiv.), 0.5 mL of H_2O. [b] Cat **IX** (0.025 mmol, 0.1 equiv.). [c] **1a/2a** (1:1). [d] **1a/2a** (1:1.5). [e] 1.0 mL of H_2O. [f] 0.25 mL of H_2O. [g] Isolated yield after column chromatography.

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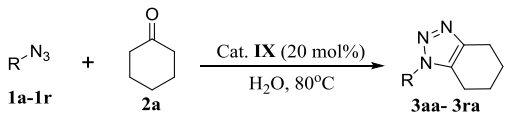
Table 2 Scope of azides.[a]



Entry	R	Product[b]	Entry	R	Product[b]
1	1a	**3aa**; 81% 48 h	2	1b	**3ba**; 92% 36 h
3	1c	**3ca**; 90% 36 h	4	1d	**3da**; 83% 48 h
5	1e	**3ea**; 80% 36 h	6	1f	**3fa**; 79% 48 h
7	1g	**3ga**; 72% 48 h	8	1h	**3ha**; 68% 24 h
9	1i	**3ia**; 81%, 24 h	10	1j	**3ja**; 75% 24 h
11	1k	**3ka**; 69%, 48 h	12	1l	**3la**; 76% 48 h
13	1m	**3ma**; 73% 36 h	14	1n	**3na**; 86% 36 h
15	1o	**3oa**; 77% 36 h	16	1p	**3pa**; 83% 48 h
17	1q	**3qa**; 74% 24 h	18	1r	**3ra**; 72%, 48 h

[a] Unless otherwise stated, the reaction conditions are: **1a-r** (0.25 mmol, 1.0 equiv.), **2a** (0.5 mmol, 2 equiv.), H_2O (0.5 mL), 20 mol% catalyst **IX** at 80°C. [b] Yield of isolated product.

highly restricted to use organic solvents (*e.g.* DMSO, CH_2Cl_2) (Scheme **1a**), which limiting its further practical application. As part of our continued interest in developing more practicable and green process, herein, we report our new results regarding an organocatalytic cycloaddition of ketones and azides with water as a solvent (Scheme **1b**).

In fact, natural aldolase enzymes and aldolase catalytic antibodies have successfully promoted aldol reactions in water.[12] These examples implied that diminishing contacts between water and the reaction transition states may be critical for reactivity. Thus, we hypothesized that a small organic catalyst with appropriate hydrophobic groups should assemble with hydrophobic reactants in water and sequester the reaction transition state from water. As a result, the outcome of the reaction should be similar to that performed in organic solvents.

To test the possibility of this hypothesis in 1,3-dipolar cycloaddition reaction, initial experiments were conducted in water by using phenyl azide **1a** and cyclohexanone **2a** in the presence of amine catalyst (Figure 1). A rapid screening of amine catalysts exhibited different levels of reaction activities. Acyclic amines (e.g. diethyl amine **I** and long aliphatic chain based dialkyl amine **II**) showed poor activities in aqueous medium (Table 1, entry 1 and 2, 12% and 22%, respectively). Then we turned our attention to screen cyclic amines.

Prolinamide (2° amide) catalyst **V** and **VI** both catalyzed the reaction, but low chemical yield were observed (entries 5 and 6). Surprisingly, cyclic prolinamide (3° amide) catalyst **VII** indicated almost no reaction (entry 7). Pleasingly, the reaction with prolinamide (3° amide) catalyst **VIII** or **IX** bearing long alkyl groups afforded good chemical yields (entries 8 and 9, 75% and 81%, respectively). However, no reaction progress was detected after 48 h in water by using amino acid as catalyst (entry 4 and 18, cat. **IV** and **X**). After identifying the suitable catalyst **IX**, we attempted to optimize the reaction by varying other parameters systemically. As expected, a lower temperature (50 °C and room temperature) or lower catalyst loading (10 mol%) incurred a significant decrease in chemical yield and prolonged reaction time (entries 10-11 and 13). If reaction temperature increased to 100 °C, there was no major improvement on reaction rate (entry 12). Changing the ratio of **1a**/**2a** from 1:2 to 1:1.5 or 1:1 had a harmful effect on the efficacy of the reaction (entries 14−15). In addition, the appropriate amount of water was also found to be a critical factor (entries 16−17).

With the optimized conditions in hand, we then investigated a variety of azides with cyclohexanone **2a** in the reaction catalyzed by a long alkyl-chain based second amine **IX** (20 mol%) at 80 °C. The results are summarized in Table 2. It was found that the prolinamide **IX** catalyzed cycloaddition was applicable to a variety of azides **1a-r** to afford 1,2,3-triazoles in moderate to high yields (Table 2, 68–92%). The reactions were performed smoothly and rarely affected by the electronic nature of the substituents on the aromic rings. Electron-withdrawing (Table 2, entries 2–11), electron-donating (Table 2, entries 12–16), or electron-neutral (Table 2, entry 1) groups on the phenyl ring of azides did not affect the reaction. Notably, naphthalene ring was also suitable for this system to afford the desired product **3ra** (Table 2, entry 18, 72%).

To further indicate the generality and potential of our approach, we then investigated a variety of ketones. The results are summarized in Table 3. Interestingly, among the various examined ketones, cyclic ketones, from six to eight member ring, all gave good to excellent yields under standard conditions (Table 3, entries 1−10, **3ab-3ak**, 69-86%, 36−48 h). The best yield was obtained with cycloheptanone, which afforded the corresponding 1,2,3-triazole in 93% isolated yield (Table 3, **3aj**). It is worth noting that dissymmetrical cyclic ketone afforded a high level of regioselectivity. For example, 3,3-dimethylcyclohexanone led to

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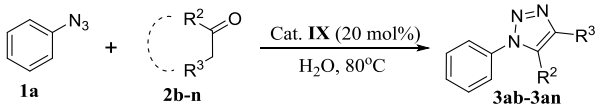
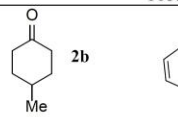
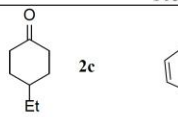
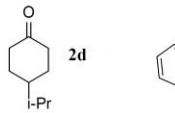
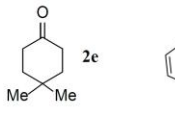
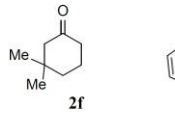
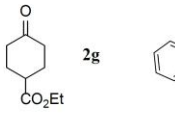
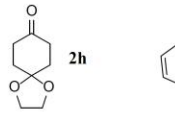
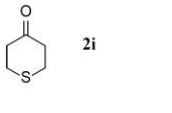
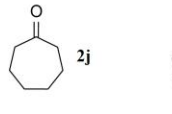
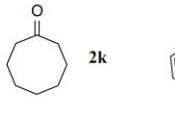
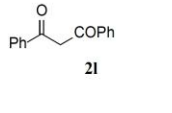
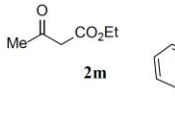
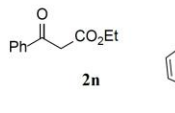
Table 3 Scope of carbonyl compounds.[a]



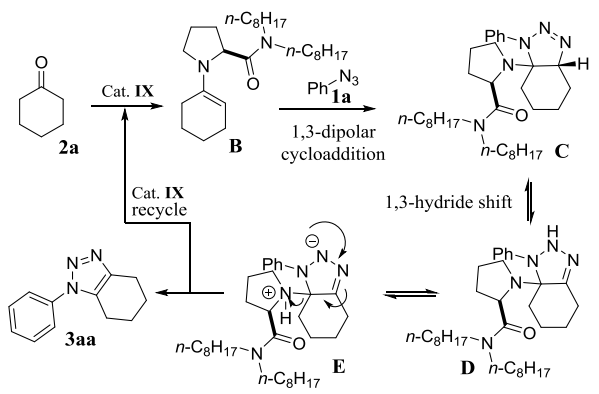
Entry	Product[b]	Entry	Product[b]
1	 **3ab**; 81% 36 h	2	 **3ac**; 82% 36 h
3	 **3ad**; 71% 48 h	4	 **3ae**; 74% 48 h
5	 **3af**; 71% 48 h	6[c]	 **3ag**; 69% 48 h
7	 **3ah**; 73% 48 h	8	 **3ai**; 77% 36 h
9	 **3aj**; 93% 36 h	10	 **3ak**; 86% 48 h
11[c]	 **3al**; 88% 48 h	12[c]	 **3am**; 85% 48 h
13[c]	 **3an**; 85% 36h		

[a] Unless otherwise stated, the reaction conditions are: **1a-q** (0.25 mmol, 1.0 equiv.), **2a** (0.5 mmol, 2 equiv.), H_2O (0.5 mL), 20 mol% catalyst **IX** at 80°C. [b] Yield of isolated product.

a single regioisomer **3af** (Table 3, entry 5), in which the heterocycle is furthest from the *gem*-dimethyl group for steric reasons. On the other hand, 4,4-dimethylcyclohexanone furnished 1,2,3-triazole **3ae** (Table 3, entry 4), which is an isomer of **3af**. The regioselectivity can be explained by the cycloaddition occurring with most stabilized enamine. Moreover, regioselective cycloadditions of phenyl azide **1a** with *in situ* formed enaminoester or enaminone (β-ketoesters or β-diketones reacted with cat. **IX**) was investigated. Both reactions successfully conducted and achieved results similar to those obtained for the general ketone counterparts ((Table 3, entries 11−13, **3al−3an**).

The plausible reaction mechanism for the green synthesis of 1,2,3-triazoles is illustrated in Scheme 2. The catalytic cycle is started from the generation of iminium **B** via the condensation of cyclohexaone **1a** and amino-catalyst **IX**. Subsequently, iminium **B** acts as the electron-rich olefinic partner to react with phenyl azide **1a** via an inverse-electron-demand 1,3-dipolar cycloaddition process to access the intermediate **C** in water. Then, a sequential hydride shift to eventually allow intermediate **C** to convert to a stabilized zwitterionic intermediate **E**. Lastly, a *syn*-elimination step induces **E** to form final product **3aa** and recycles catalyst **IX**. The aromatization of triazole product **3aa** will be the potential driving force of the reaction.

Scheme 2 Plausible mechanism.



Conclusions

In summary, driven by the lack of green synthesis of important 1,2,3-triazole molecules, herein, we reported an enamine catalyzed strategy by using a long aliphatic chain tolerated prolinamide as an efficient organocatalyst to fully promote the Huisgen 1,3-dipolar cycloaddition to access a vast pool of substituted 1,2,3-triazoles with water as the only solvent. Further extension of this green synthetic strategy to other types of reactions is under way in our laboratory and will be presented in due course.

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Notes and references

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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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