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Amine-Catalyzed [3+2] Huisgen Cycloaddition Strategy for the Efficient Assembly of Highly Substituted 1,2,3-Triazoles

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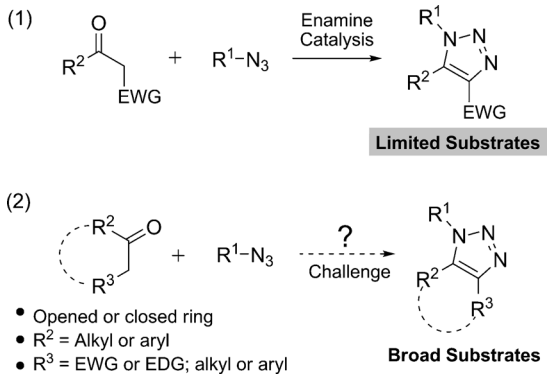
Abstract: An enamine-catalyzed strategy has been utilized to fully promote the Huisgen [3+2] cycloaddition with a broad spectrum of carbonyl compounds and azides, thereby permitting the efficient assembly of a vast pool of highly substituted 1,2,3-triazoles. In particular, the employment of commonly used and commercially available carbonyl compounds has resulted in the introduction of a diverse set of functional groups, such as alkyl, aryl, nitrile, ester, and ketone groups, at the 1-, 4-, or 5-positions of the 1,2,3-triazole scaffold. This approach might be manipulated to access more useful and sophisticated heterocyclic compounds. Most significantly, the reaction process exhibits complete regioselectivity, with the formation of only one regioisomer.

Keywords: cycloaddition · enamines · organocatalysis · regiospecificity · triazoles

Introduction

Organocatalytic activation of readily available substrates has led to the rapid development of many reactions in the last decade.[1] Enamine catalysis, as one of the most powerful tools, has been extensively investigated, and has been reported to facilitate a diverse set of transformations based on the enamine intermediates generated in situ.[2] Although many transformations have been reported, the enamine–azide [3+2] Huisgen cycloaddition still remains a challenging topic. Recently, we discovered the first examples of organocatalytic regiospecific enamide–azide [3+2] cycloadditions of α-functionalized ketones to azides [Eq. (1)].[3] However, we recognized that the substituents at the 4-position on the 1,2,3-triazole skeleton were essentially limited to electron-withdrawing groups. This limitation may potentially restrict the wider application of this synthetic methodology. Herein, we wish to report our further endeavors in examples of amine-catalyzed [3+2] cycloadditions of a broad spectrum of carbonyl compounds and azides with a view to achieving the efficient assembly of a vast pool of highly substituted 1,2,3-triazoles [Eq. (2)].[4]



The 1,2,3-triazole core is a prominent scaffold that is featured in a large number of bioactive molecules.[5] Additionally, 1,2,3-triazole moieties are attractive connections in biological systems because they are stable to metabolic degradation and capable of hydrogen bonding to biomolecular targets, which can also improve solubility.[6] Although the 1,2,3-triazole unit does not occur in Nature, it has biological activity.[7] Thereby, the significance of triazole compounds in medicinal chemistry is indubitable. In view of their occurrence in a broad spectrum of important pharmaceutically active compounds, such as those examples outlined in Figure 1,[5u–w] highly substituted 1,2,3-triazoles continue to attract ever increasing attention in the synthetic chemistry community. Although elegant preparative methods for such motifs have been reported, synthetic methodologies allowing the rapid and regiospecific construction of 1,4,5-trisubstituted 1,2,3-triazoles tend to be extremely demanding.[8]

While some direct protocols leading to 1,2,3-triazoles have been described, including tradition thermal[9] or metal-free[8c,d,f] [3+2] cycloadditions of linear alkynes or highly strained alkynes with azides, these reactions are often slow because of high activation energies (ca. 16–24 kcal mol^{-1}),[10] and also produce a mixture of regioisomers (Scheme 1). The Cu^{I}-catalyzed azide–alkyne cycloaddition (CuAAC) has been developed as a powerful tool to access 1,2,3-triazole molecules, but is usually restricted to terminal alkynes and

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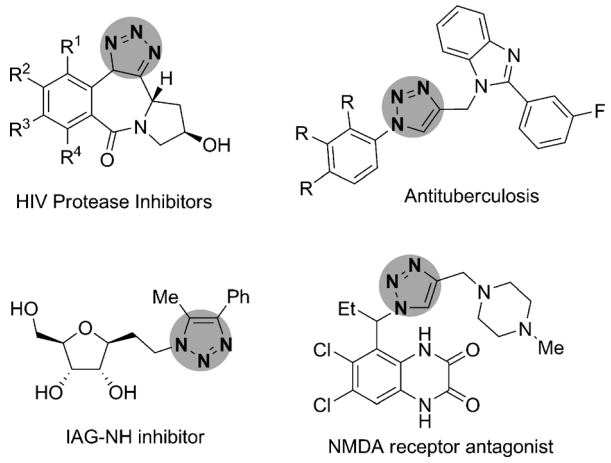


Figure 1. Representative examples of bioactive 1,2,3-triazoles.

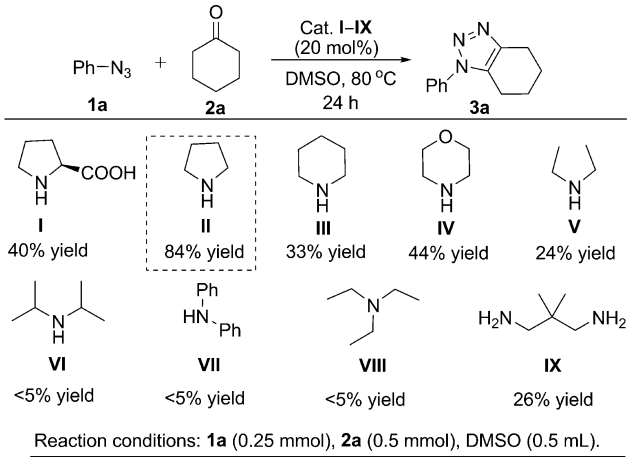
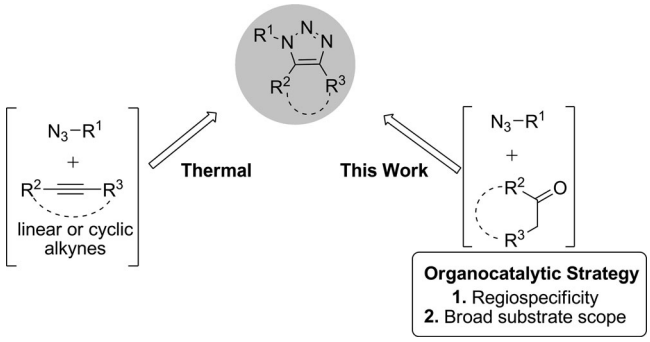


Figure 2. Evaluation of organocatalysts.



Scheme 1. Methods for the synthesis of highly substituted 1,2,3-triazoles.

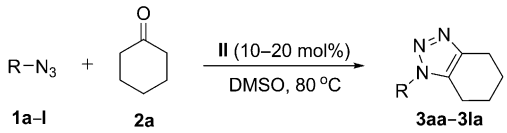
only facilitates 1,4-disubstituted 1,2,3-triazole formation (Scheme 1).[11] In addition, in spite of its vast success in industry, this strategy is not ideal for biological applications. Recent studies have indicated that Cu^{I} can cause oxidative DNA degradation,[12] although careful selection of Cu^{I}-stabilizing ligands can avoid DNA degradation and even facilitate this cycloaddition process in living organisms.[13] However, Cu is intrinsically cytotoxic and this may remain an issue when pharmaceutical therapeutics are desired. Therefore, in the search for an ideal strategy to replace known methods, we believe that a metal-free, enamine-catalyzed, and broad substrate-tolerant method may offer a preferred solution.

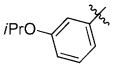
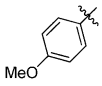
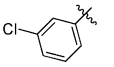
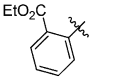
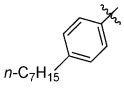
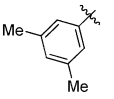
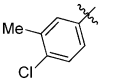
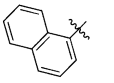
Results and Discussion

Optimization studies of organocatalytic enamine–azide [3+2] cycloaddition were initiated by an investigation of phenyl azide **1a** and cyclohexanone **2a** in the presence of a catalytic amount of the secondary α-amino acid L-proline (**I**; Figure 2). The initial experimental result showed that only 40% yield was obtained in 24 h. With a view to improving the catalytic activity, we then examined six-membered-ring-based secondary amine catalysts **III** and **IV**. It became apparent that the ring size is not crucial for reaction yield and rate (Figure 2, 33% and 44% yield, respectively). Moreover, a diverse set of acyclic secondary amines was tested (**V**, **VI**, **VII**), but these exhibited inferior catalytic performances (24%, <5%, and <5%, respectively). Besides secondary amines, primary amine **IX** and tertiary amine **VIII** were also evaluated in this model reaction system. As shown in Figure 2, tertiary amine **VIII** displayed no catalytic activity in the process (<5% yield). Primary amine **IX** afforded only a 26% yield in 24 h. Finally, an unsubstituted, less bulky secondary amine, pyrrolidine **II**, displayed a higher activity (84%, 24 h). After identifying the suitable catalyst **II**, we attempted to optimize the reaction by systematically varying several other parameters. Initially, various solvents including *N*-methylpyrrolidine> (NMP), DMF, dimethylacetamide (DMA), MeOH, 1,4-dioxane, 1,2-dichloroethane (DCE), toluene, and CH_3CN were screened (see the Supporting Information), and we eventually concluded that higher yields in polar solvents were most likely due to strengthened polar interactions between substrate and catalyst. Screening showed that no obvious improvement in reaction rate or yield could be achieved in other solvents. We also investigated the effects of temperature and catalyst loading (see the Supporting Information). As expected, a lower temperature (50°C) or lower catalyst loading (5 mol%) incurred a significant decrease in yield. Consequently, the use of pyrrolidine **II** in DMSO was found to lead to satisfactory results in the organocatalytic enamine–azide [3+2] cycloaddition process.

Once the optimized conditions had been identified (Figure 2), various substrates were examined. The scope of the amine-catalyzed [3+2] Huisgen cycloaddition of azides is indicated by the examples listed in Table 1. It was found that the pyrrolidine **II**-catalyzed cycloaddition was applicable to a variety of azides **1a–l** to afford 1,2,3-triazoles in moderate to high yields (Table 1, 45–88%). The reactions proceeded smoothly and were little affected by the electronic nature of the substituents on the aromatic ring. Electron-withdrawing (Table 1, entries 5, 6, and 8), electron-donating

Table 1. Substrate scope of azides.[a]



Entry	R	Product[b]	Entry	R	Product[b]
1		**3aa**; 84% 24 h	7		**3ga**; 75% 12 h
2		**3ba**; 88%; 16 h (78%; 30 h)[c]	8		**3ha**; 62% 24 h
3		**3ca**; 85% 14 h	9		**3ia**; 45% 18 h
4		**3da**; 72% 12 h	10		**3ja**; 80% 20 h
5		**3ea**; 72% 16 h	11		**3ka**; 67% 10 h
6		**3fa**; 68% 18 h	12		**3la**; 60% 16 h

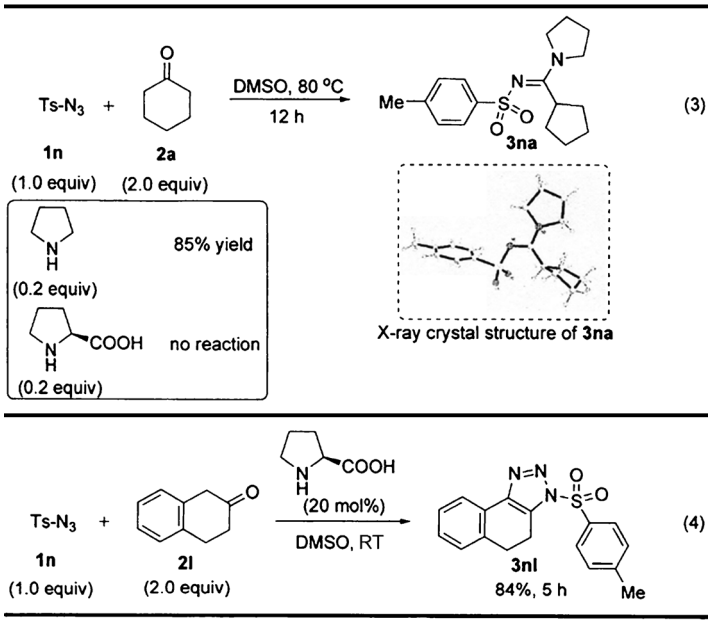
[a] Reaction conditions: **1a–i** (0.25 mmol, 1.0 equiv), **2a** (0.5 mmol, 2.0 equiv), DMSO (0.5 mL), 20 mol% catalyst **II** at 80°C. [b] Yield of isolated product. [c] 10 mol% of catalyst.

(Table 1, entries 2–4 and 10), or electron-neutral (Table 1, entry 1) groups on the phenyl ring of the azide did not affect the reaction. In some cases, a steric interaction appeared to have a negative effect on the reaction yield. For example, the presence of an ester group at the *o*-position of the phenyl ring led to a lower yield (Table 1, entry 9, 45%). Notably, a naphthalene ring was also tolerated in this reactem (Table 1, entry 12, 60%). If a lower catalyst loading (10 mol%) was employed, the reaction still afforded a good yield in a reasonable time (Table 1, 78%, 30 h). However, the reaction dramatically slowed down (<5% yield, 24 h) when an alkyl (ethyl group) azide was applied to replace the phenyl azide. Slow conversion of starting material was detected by ^{1}H NMR analysis.

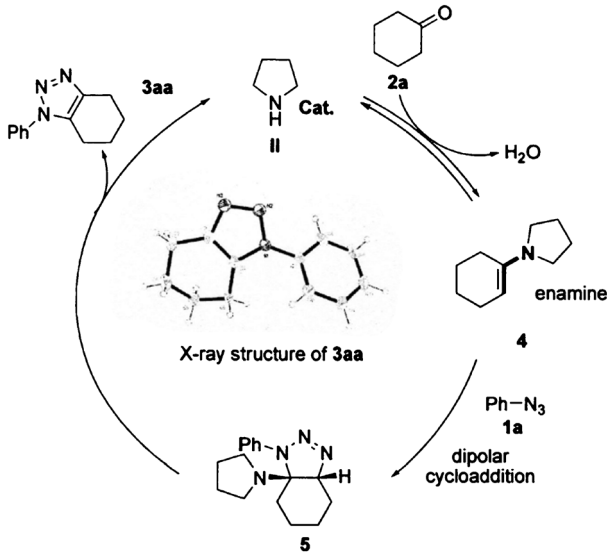
Having investigated the reactivity of azides, we then evaluated carbonyls (Table 2). To our delight, this method can tolerate a broad range of unmodified, commercially available carbonyl compounds. Cyclic six-member ring based ketones gave good to high yields (Table 2, entries 1–6). This six-member ring can bear alkyl, ester, dialkyl, or ketal groups at the β- or γ-positions with respect to the ketone function (Table 2, entries 1–5). Furthermore, the six-membered ring can also incorporate a heteroatom (Table 2, entry 6). Interestingly, seven- or eight-membered-ring cyclic ketones also efficiently provided high yields under the standard conditions, thus demonstrating that the ring size of the ketone had little effect on this cycloaddition (Table 2, entries 7 and 8, 94% and 85%, respectively). To verify the high reaction efficiency seen with seven- or eight-membered-ring ketones, we reduced the catalyst loading from 20 mol% to 10 mol%. The reaction still afforded an 89% yield in 30 h (Table 2, entry 7). It is noteworthy that acyclic ketones also gave appreciable reaction yields (Table 2, entries 9 and 10). For example, the asymmetric acyclic ketone 2-butanone **2j** gave a 75% yield of **3aj** in 24 h (Table 2, entry 9), and no other regioisomers were observed. We deduce that the thermodynamically controlled enamine formation of 2-butanone **2j** affects the regioselectivity of this reaction. The symmetric acyclic ketone 3-pentanone **2k** gave a 65% yield of **3ak** in 20 h. Additionally, a phenyl-ring-fused cyclohexanone **2l** also reacted at room temperature (Table 2, entry 11) to afford **3al**, albeit in a slightly lower yield (57%, 10 h) due to some decomposition of this product under the reaction conditions. Besides the above types of ketones **2a–l**, we also examined some α-functionalized ketones (Table 2, entries 12–16). Gratifyingly, β-ketonitrile **2m**, 1,3-diketone **2n**, and α-ester ketone **2o** reacted efficiently, giving high product yields (Table 2, entries 12–14, 90–95%). Moreover, alkyl azide **1m** could be reacted with active β-ketonitrile **2m** to afford an appreciable synthetic yield of **3mm** (Table 2, entry 16, 80%, 24 h). In contrast to our previously reported results for reactions catalyzed by an acyclic secondary amine catalyst (diethylamine **V**),[3] we found that the cyclic secondary amine (pyrrolidine **II**) could also efficiently catalyze such transformations under the optimized reaction conditions. The regioselectivities of products **3aa**[14] and **3ac**[15] were determined by single-crystal X-ray diffraction analysis.

To further extend the scope in terms of azides, we proceeded to examine tosyl azide **1n**. As shown in Equation (3), the reaction with this substrate was completely different. In this case, pyrrolidine **II** served as a starting material, providing easy access to the biologically interesting *N*-tosyl amidine **3na**[16] in 85% yield. We deduce that when the triazoline ring bears an electron-withdrawing group at the N1-position, it is very labile. Thus, the initially formed triazoline intermediate decomposes immediately to produce amidine **3na** through rearrangement with the loss of N_2. Surprisingly, L-proline showed no activity in this reaction. However, β-tetralone **2l** reacted with tosyl azide **1n** in the presence of L-proline to efficiently produce the desired triazole compound **3nl** (Equation (4), 85%, 5 h, RT). In this case, no amidine product was formed. This may possibly be attributed to the steric hindrance of the carboxylic group, which would inhibit the potential rearrangement and prohibit the formation of the crowded amidine. Subsequent attempts to subject two linear aldehydes (propionaldehyde **2r** and 2-phenylacetaldehyde **2s**) to the reaction were unsuccessful. The failure to obtain the desired triazoles might be attributed to a competitive self-aldol reaction.

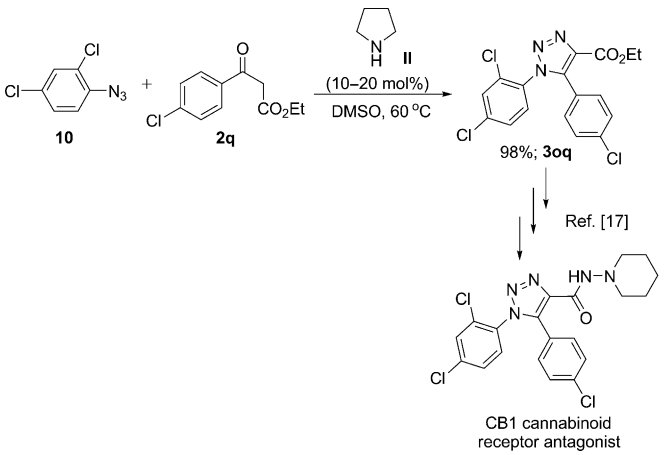
To demonstrate the synthetic utility of this methodology, we applied it to the synthesis of a CB1 cannabinoid receptor antagonist (Scheme 2). The pyrrolidine **II**-catalyzed Huisgen [3+2] cycloaddition between azide **1o** and β-keto ester **2q** under optimized conditions (see Figure 2 and the Supporting Information) furnished the intermediate **3oq** in 98% yield



Scheme 2. Synthesis of CB1 cannabinoid receptor antagonist.[17]



Scheme 3. Plausible reaction mechanism.



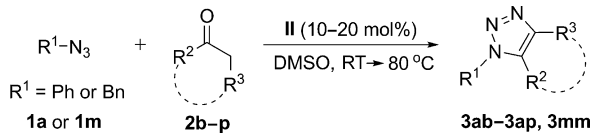
in 0.5 h. Compound **3oq** is a key intermediate that can be converted into the target CB1 cannabinoid receptor antagonist by a known method.

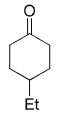
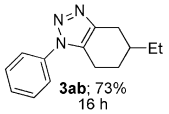
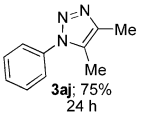
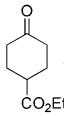
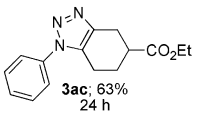
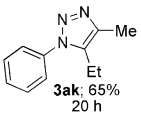
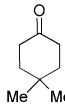
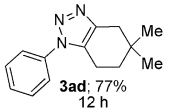
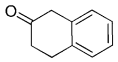
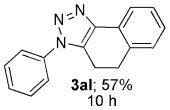
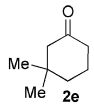
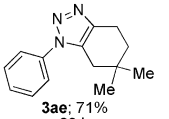
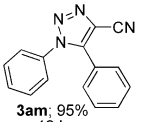
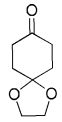
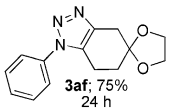
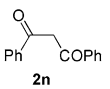
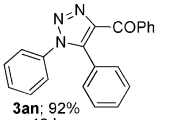
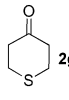
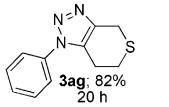
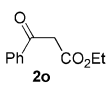
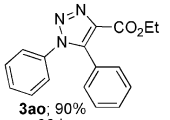
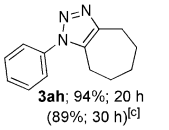
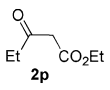
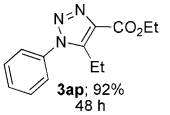
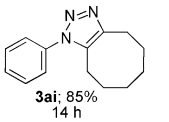
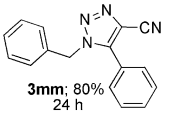
As shown in Scheme 3, we propose a plausible catalytic cycle to explain the reaction pathway. While the reaction mechanism is still unclear at this stage, it is believed that the sequence is triggered by the generation of enamine **4** by the condensation of ketone **2a** and pyrrolidine catalyst **II**. Enamine **4** acts as the electron-rich olefinic partner, and reacts with phenyl azide **1a** in a Huisgen 1,3-dipolar cycloaddition process to afford the intermediate, triazoline **5**. Most importantly, this process demonstrates a complete and unique regiospecificity, which allowed us to readily introduce a diverse set of functional substituents at the desired 1-, 4-, and 5-positions. In fact, besides an enamine-triggered cycloaddition process, an enolate-triggered cycloaddition process catalyzed by an organic base may also potentially afford the desired intermediate **5**. The results of the catalyst screening suggested that the process catalyzed by an organic base, such as tertiary amine **VIII** (Figure 2, $<5\%$ yield), will not be the main contribution for 1,2,3-triazole synthesis. Thereafter, a plausible 1,3-hydride shift might assist the formation of a zwitterion. Finally, an elimination step regioselectively generated the final product, 1,2,3-triazole **3aa**. Meanwhile, the catalyst **II** was released and could partake in the next catalytic cycle. According to our experimental evidence, we predict that the rate-determining step is probably the 1,3-dipolar cycloaddition process. The observation of enamine formation by LC-MS suggests that the catalytic cycle accumulates at this stage. In addition, no further evidence indicates the presence of the triazoline intermediate **5**. Finally, we are aware that the identification of an active catalytic enamine species will provide a more reliable validation of this reaction mechanism.

Conclusion

Driven by the lack of an efficient synthesis of highly substituted 1,2,3-triazoles, we have developed an enamine-catalyzed strategy, using a small organic molecule as organocatalyst, to fully promote Huisgen [3+2] cycloaddition reactions. This strategy has been applied to a broad spectrum of carbonyl compounds and azides, thereby providing efficient access to a vast pool of highly substituted 1,2,3-triazoles. In particular, the employment of commonly used and commercially available carbonyl compounds has allowed the introduction of a diverse set of functional groups, such as alkyl, aryl, nitrile, ester, and ketone groups, at the 1-, 4-, or 5-positions of the 1,2,3-triazole scaffold. This approach might be further manipulated to access more useful and sophisticated heterocyclic compounds. Most significantly, the reaction process exhibits complete regioselectivity, with no regioisomer

Table 2. Substrate scope of carbonyl compounds.[a]



Entry	2b–i	Product[b]	Entry	2j–p	Product[b]
1		 3ab; 73% 16 h	9		 3aj; 75% 24 h
2		 3ac; 63% 24 h	10		 3ak; 65% 20 h
3		 3ad; 77% 12 h	11[d]		 3al; 57% 10 h
4		 3ae; 71% 20 h	12		 3am; 95% 12 h
5		 3af; 75% 24 h	13[e]		 3an; 92% 12 h
6		 3ag; 82% 20 h	14[e]		 3ao; 90% 36 h
7		 3ah; 94%; 20 h (89%; 30 h)[c]	15[e]		 3ap; 92% 48 h
8		 3ai; 85% 14 h	16[e]		 3mm; 80% 24 h

[a] Reaction conditions: **1a–i** (0.25 mmol, 1.0 equiv), **2a** (0.5 mmol, 2.0 equiv), DMSO (0.5 mL), 20 mol% **II** at 80 °C. [b] Yield of isolated product. [c] 10 mol% of **II**. [d] Room temperature. [e] 70 °C.

formation. The versatility of amine-catalyzed Huisgen cycloaddition seems endless, yet we are still in the early development stages of this concept-driven research. In addition, we believe that the presented methodology will open access to more interesting compounds for potential biological evaluation. Further extension of this synthetic strategy to other types of reactions is under way in our laboratory and our results will be presented in due course.

Experimental Section

General procedure for amine-catalyzed Huisgen [3+2] cycloaddition: The catalyst pyrrolidine **II** (4.1 μL, 0.05 mmol, 0.2 equiv) was added to a solution of phenyl azide **1a** (0.25 mmol, 1 equiv) and cyclohexanone **2a** (0.5 mmol, 2.0 equiv) in DMSO (0.5 mL), and the reaction mixture was stirred at 80 °C for 24 h. The crude product was purified by column chromatography on silica gel, eluting with hexane/EtOAc (10:1 → 4:1), to afford the desired product **3aa** (42 mg, 84% yield) as a pale-yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.57–7.50 (m, 4H), 7.47–7.43 (m, 1H), 2.85 (t, J = 4.9 Hz, 2H), 2.75 (t, J = 5.0 Hz, 2H), 1.93–1.84 ppm (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 144.43, 137.37, 132.47, 129.89, 129.02, 123.56, 23.20, 22.92, 22.39, 22.27 ppm; HRMS (ESI): calcd for $C_{12}H_{14}N_3$ $[M+H]^+$ 200.1182, found 200.1186.

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