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A New Example of Organo Click Reactions: TEMPO-Promoted Oxidative Azide-Olefin Cycloaddition for the Synthesis of 1,2,3-Triazoles in Water

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Abstract: An aqueous mediated metal-free TEMPO-promoted oxidative [3+2] cycloaddition of organic azides with electron deficient terminal and internal olefins is reported. A library of 1,4-disubstituted and 1,4,5-trisubstituted-1,2,3-triazoles are synthesised from moderate to excellent yields. This method is compatible not only with open chain olefins but also with cyclic olefins.

Introduction

After the invention of copper catalyzed azide-alkyne cycloaddition (CuAAC),[1] 1,2,3-triazoles emerged as charismatic molecules endowed with a wide spectrum of pharmacological applications[2] such as anticancer, anti-HIV, antituberculosis, antifungal and antibacterial activities. Some of the representative biologically active triazoles are outlined in Figure 1. In addition, they have also achieved new milestones in other fields such as drug discovery,[3] material science,[4] polymers[5] supramolecular chemistry[6] and chemical synthesis.[7]

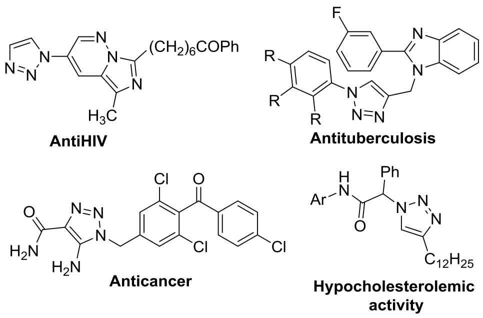
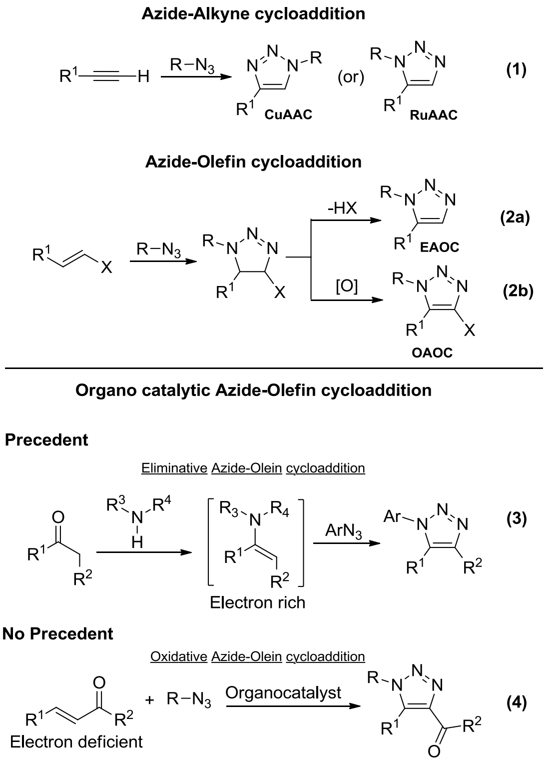


Figure 1. Representative examples of bioactive 1,2,3- triazoles.[2]

In spite of the conventional Huisgen cycloaddition,[8] CuAAC is prominently desired owing to its remarkable selectivity and functional group tolerance.[1] Being selective to 1,4-disubstituted triazoles, CuAAC is restricted to terminal alkynes only. In continuation, ruthenium catalyzed azide-alkyne cycloaddition (RuAAC)[9] was developed which promotes the complementary 1,5-disubstitution on the triazole and it is compatible with internal alkynes as well [Eq. (1), Scheme 1]. However the economic and synthetic viabilities of alkynes pose the need of development of alternative methods to access these privileged molecules. In this regard, olefins were judiciously picked up as the appropriate alternative to the alkynes to achieve the 1,2,3-triazoles. However the product of such azide-olefin cycloaddition is triazoline which is an unstable cyloadduct and it is likely to decompose into various products as dictated by the reaction condition.[10]



Scheme 1. Background of the organo catalytic oxidative azide-olefin cycloaddition.

In order to convert this unstable triazoline into the stable aromatic triazole two ingenious approaches have been adopted in the literature. First one is eliminative azide-olefin cycloaddition (EAOC) where a olefin bearing a leaving group such as nitro,[11] alkoxy,[12] sulphone,[13] acetate[14] etc. would be subjected to cycloaddition with various azides and the resulting triazoline would undergo a concomitant elimination reaction to furnish the required 1,2,3-triazole [Eq. (2a), Scheme 1].

Second approach is oxidative azide-olefin cycloaddition (OAOC) where the triazoline formed by azide-olefin cycloaddition would subsequently be oxidized into the corresponding triazole [Eq. (2b), Scheme 1]. In this area, various metal catalysts such as CuI,[15] Ce(OTf)$_3$,[16] CuO,[17] Cu(OTf)$_2$,[18] Cu(OAC$^{)}_2$,[19] and Fe$_2$O$_3$-nanoparticles[20] were employed to achieve the OAOC of organic azides with electron deficient olefins. Besides that, our research group has also reported the construction of 1,2,3-triazoles by CuO-nanoparticles catalyzed [3+2] cycloaddition of organic azides and electron deficient olefins.[21] However the major drawback of metal catalysts particularly copper is its cytotoxicity and hence it can’t be desirable for the labeling of biomolecules in live cells.[22]

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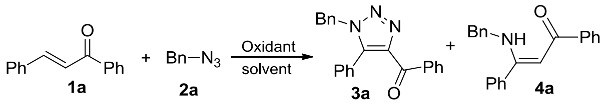
Moreover, problems such as Alzheimer's disease, hepatitis and neurological disorders can also be caused on excessive intake. Hence it is imperative to develop metal-free protocols to accomplish the 1,2,3-triazoles. In response to that overwhelming demand, recently K_2CO_3 promoted OAOC of chalcones and azides have been reported in aqueous solution.[23] In addition to that, 'organo click' reactions [24] were developed where organo catalysts would be employed instead of metal catalysts to accomplish the triazoles. The 'organo click' reactions encapsulate the EAOC of enamines (electron rich olefins) prepared *insitu* from various carbonyl compounds with organic azides (mostly aryl azides) catalyzed by amines [Eq. (3), Scheme 1]. In addition to enamine mediated organo click reactions, enolate mediated organo click reaction has also been reported.[25] However to the best of our knowledge, organo catalysts for the electron deficient olefins such as *α*,*β*-unsaturated enones and quinones have not been reported so far [Eq. (4),Scheme 1]. Here we report the unprecedented oxidative cycloaddition of organic azides with electron deficient olefins promoted by TEMPO.

Results and Discussion

At the outset, we began our optimization with chalcone (**1a**) with benzyl azide (**2a**) as representative substrates using water as the solvent and TEMPO as the oxidant. Despite the formation of meager amount of triazole (**3a**) in the room temperature, the yield gradually increased up to 81% when the temperature was elevated up to 90 ^oC (Table 1, entry 1). While solvent variation was attempted, poor yield of **3a** was obtained in the solvents such as methanol, acetonitrile and 1,4-dioxane (Table 1, entry 2-4). Apparently, solvents like THF, DMSO and $CHCl_3$ have played a hostile role since the yield slumped into trace amount while employing these solvents (Table 1, entry 5-7). On the other hand, substantial increment of triazole formations was observed with toluene and DMF in spite of the trace amount of enaminone **4a** (Table 1, entry 8-9). To our surprise, significant enhancement of yield was observed when the reaction was performed in neat condition (Table 1, entry 10). On the other hand, when the TEMPO was eliminated from the neat reaction, the yield dramatically dropped to 20% witnessing the pivotal role played by TEMPO (Table 1, entry 11). Fixing the water as the best solvent, various oxidants such as $K_2S_2O_8$, oxone, *t*-BuOOH and CAN (Ceric ammonium nitrate) also were investigated in the place of TEMPO and it was unambiguously ascertained that none of them is on par with TEMPO (Table 1, entry 12-15). When TEMPO oxidation was tried with some co-oxidants, oxygen was found to be the best co-oxidant to propel the reaction (Table 1, entry 16-19). At the same time, when this oxidation was attempted under nitrogen atmosphere, the efficacy was retarded to a great extent though stoichiometric amount of TEMPO was utilized (Table 1, entry 20). Fixing the oxygen as the best co-oxidant, when the amount of TEMPO was increased from 0.2 equivalent to 0.5 equivalent, we resolved to fix 0.5 equivalent of TEMPO as the suitable amount to propel this reaction (Table 1, entry 21 - 23). When the reaction was prolonged only with oxygen (in the absence of TEMPO), only 35% yield of triazole was obtained which ascertains the combined role of oxygen and TEMPO in this system (Table 1, entry 24).

Table 1. Optimization of metal-free OAOC.[a]

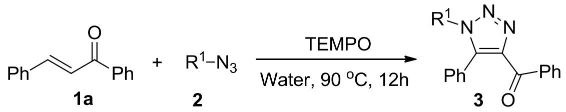


Entry	Oxidant (Equiv)	Additive	Solvent	Yield of 3a(%)[b]	Yield of 4a(%)[b]
1[c]	TEMPO (1.0)	-	H_2O	81	-
2	TEMPO (1.0)	-	MeOH	33	-
3	TEMPO (1.0)	-	CH_3CN	14	-
4	TEMPO (1.0)	-	Dioxane	33	-
5	TEMPO (1.0)	-	THF	Trace	-
6	TEMPO (1.0)	-	DMSO	Trace	-
7	TEMPO (1.0)	-	$CHCl_3$	Trace	
8	TEMPO (1.0)	-	Toluene	58	trace
9	TEMPO (1.0)	-	DMF	66	trace
10[d]	TEMPO (1.0)	-	-	79	
11	-	-	-	20	
12	$K_2S_2O_8$ (1.0)	-	H_2O	Trace	-
13	Oxone (1.0)	-	H_2O	20	-
14	*t*-BuOOH (1.0)	-	H_2O	30	trace
15	CAN (1.0)	-	H_2O	5	-
16	TEMPO (0.2)	$K_2S_2O_8$	H_2O	10	-
17	TEMPO (0.2)	NaOCl	H_2O	44	23
18	TEMPO (0.2)	Oxone	H_2O	32	trace
19	TEMPO (0.2)	Oxygen	H_2O	50	-
20	TEMPO (1.0)	N_2	H_2O	46	-
21	TEMPO (0.4)	O_2	H_2O	80	-
22	**TEMPO (0.5)**	**O_2**	**H_2O**	**83**	**-**
23	TEMPO (0.6)	O_2	H_2O	84	-
24	-	O_2	H_2O	35	-

[a] Reaction conditions: Chalcone (1.0 equiv), Azide (1.5 equiv), oxidant and solvent (4 mL) were heated for 12h. [b] Isolated yields. [c] The yield of **3a** obtained when the reaction was carried out at room temperature, 50 ^oC and 70 ^oC are 10%, 30% and 62% without the formation of **4a**. [d] Reaction was carried out in neat condition with 3.0 equiv of azide.

Having established the optimized condition (Table 1, entry 22) for metal-free OAOC of electron deficient olefin and azide, we extended that condition to various azides with the chalcone (**1a**). While comparing with benzyl azide (**2a**), substitutions such as chloro, methyl and methoxy on the aromatic ring have reduced the yield of the triazoles almost equally (Table 2, entry 1-4). Electron deficient nitro group has considerably suppressed the efficacy of the reaction since yield has dropped into 58 % (Table 2, entry 5). Similarly, unlike benzyl azides, electron deficient phenyl azide also has significantly retarded the yield (Table 2, entry 6). On the contrary, aliphatic azides such as phenethyl and n-octyl azides have enormously enhanced the yield (Table 2, entry 7-8). Ethyl-2-azidoacetate (**2i**) which is an electron poor aliphatic azide has comparatively furnished a moderate yield of triazole (Table 2, entry 9).

Table 2. TEMPO promoted OAOC of **1a** with various azides.[a]

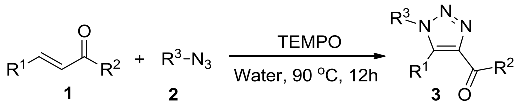


Entry	R^1	Yield (**3**) (%)[b]
1	$PhCH_2$ (**2a**)	83 (**3a**)
2	4-(Cl)$PhCH_2$ (**2b**)	77 (**3b**)
3	4-(CH_3)$PhCH_2$ (**2c**)	76 (**3c**)
4	4-(CH_3O)$PhCH_2$ (**2d**)	74 (**3d**)
5	4-(NO_2)$PhCH_2$ (**2e**)	58(**3e**)
6	Ph (**2f**)	62 (**3f**)
7	$PhCH_2CH_2$ (**2g**)	83 (**3g**)
8	C_6H_{13} (**2h**)	89 (**3h**)
9	$C_2H_5OCOCH_2$ (**2i**)	72 (**3i**)

[a]Reaction conditions: Chalcone (1.0 equiv), Azide (1.5 equiv), TEMPO (0.5 equiv) and water (4 mL) were heated at 90 °C for 12h under oxygen ballon. [b] Isolated yields.

On other part of the reaction, various olefins were screened with benzyl azides to infer the efficacy of this method on olefins (Table 3). Variation of substitutions on both the carbonyl side and the olefin side of the enone was meticulously studied. Chlorophenyl, bromophenyl and methoxyphenyl substitutions on the olefin side invariably furnished excellent yields of triazoles (Table 3, entry 1-5). Electron withdrawing nitro group has substantially retarded the efficacy than the methyl group (Table 3, entry 6-7). On the contrary, very noticeable decline of yield (42%) has been observed with 2-hydroxy phenyl substitution on the olefin side (Table 3, entry 8). Bromophenyl substitution on the carbonyl side also has excessively boosted the reaction to an excellent yield (Table 3, entry 9). Heterocyclic aromatic substitutions such as furanyl and thiophenyl substitutions also have smoothly promoted the reaction with good yields (Table 3, entry 11-13). It is worth mentioning that, as the aliphatic substitution increases in the enone, the yield of the product proportionally decreases (Table 3, entry 14-16). Apart from enones, methyl cinnamate and cinnamaldehyde also react comfortably rendering moderate and good yields of triazoles (Table 3, entry 17-18). As a sign of selectivity, terminal alkene such as methyl vinyl ketone responds feebly to this reaction condition furnishing exceedingly poor yield of triazole than the internal alkenes discussed earlier (Table 3, entry 19).

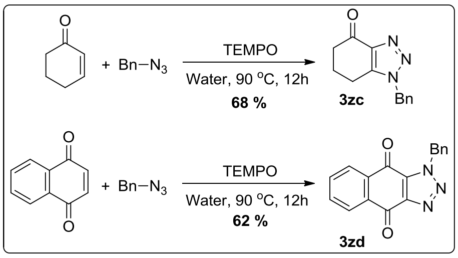
Table 3. Substrate Scope of Olefins and Azides.[a]



Entry	R^1	R^2	R^3	**1**	**3**	Yield (%)[b]
1	4-(Cl)Ph	Ph	Bn	**1b**	**3j**	88
2	4-(Br)Ph	Ph	Bn	**1c**	**3k**	91
3	4-(Br)Ph	Ph	4-(Me)Bn	**1c**	**3l**	99
4	4-(Br)Ph	Ph	4-(MeO)Bn	**1c**	**3m**	95
5	4-(OMe)Ph	Ph	Bn	**1d**	**3n**	91
6	4-(Me)Ph	Ph	Bn	**1e**	**3o**	84
7	4-(NO_2)Ph	Ph	Bn	**1f**	**3p**	79
8	2-(OH)Ph	Ph	Bn	**1g**	**3q**	42
9	Ph	4-(Br)Ph	Bn	**1h**	**3r**	98
10	Ph	3-(Me)Ph	Bn	**1i**	**3s**	90
11	Furanyl	Ph	Bn	**1j**	**3t**	89
12	Thiophenyl	Ph	Bn	**1k**	**3u**	86
13	Furanyl	Me	Bn	**1l**	**3v**	86
14	Ph	Me	Bn	**1m**	**3w**	77
15	Et	Ph	Bn	**1n**	**3x**	60
16	Et	CH_3	Bn	**1o**	**3y**	48
17	Ph	OMe	Bn	**1p**	**3z**	44
18	Ph	H	Bn	**1q**	**3za**	80
19[c]	H	Me	Bn	**1r**	**3zb**	28

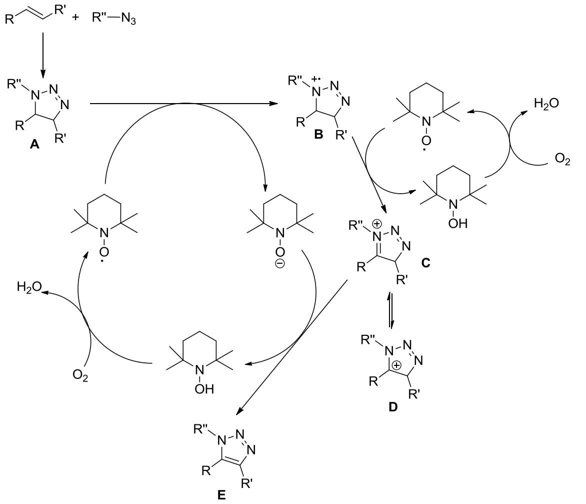
[a] Reaction conditions: Olefin (1.0 equiv), Azide (1.5 equiv), TEMPO (0.5 equiv) and water (4 mL) were heated at 90 °C for 12h under oxygen balloon. [b] Isolated yields. [c] Reaction conditions: Olefin (3.0 equiv), Azide (1.0 equiv), TEMPO (0.5 equiv) under oxygen balloon.

As the most flamboyant part of this work, cyclic enones and dienones such as cyclohexenone and naphthaquinone also were subjected to TEMPO promoted oxidative cycloaddition with benzyl azide. Despite being rarely attempted in the literature,[26] these olefins also could witness the versatile scope of this protocol by furnishing good yields of triazoles (Scheme 2).



Scheme 2. TEMPO promoted OAOC of cyclic enones.

In order to elicit insight on the mechanistic details, the following observations were made. When this reaction was attempted under nitrogen atmosphere, the yield of the triazole was greatly suppressed even though one equivalent of TEMPO was employed (Table 1, entry 20). This indicates the role of oxygen in the reaction. Reaction in the oxygen atmosphere (without TEMPO) also has failed to boost up the reaction to a convincing yield of the product (Table 1, entry 24). This testifies the combined role of TEMPO and oxygen in this transformation. Since 0.5 equivalent of TEMPO was adequate to complete the reaction under oxygen atmosphere, it is evident that TEMPO, after being used up in the reaction process, gets regenerated at some stage by oxygen. ^{1}H NMR of the crude reaction mixture of methyl vinyl ketone (**1r**) and benzyl azide (**2a**) furnished a characteristic peak at chemical shifts at 8.77 ppm (CH from the imine carbon) strongly suggests the involvement of imine-type intermediate. From these observations, we suggest a possible mechanism of the TEMPO promoted OAOC of electron deficient olefins and organic azides as follows. The triazoline **A** generated from azide-alkene cycloaddition is proposed to give the radical cation **B**. Subsequently, the radical cation **B**, by losing hydrogen radical, leads to the formation of iminium ion species **C** which equilibrates with its amino carbenium species **D.** The iminium type intermediate **C** is successfully aromatized into the required triazole **E** by losing a proton. In the meantime TEMPO is converted to its hydroxylamine form which is readily reoxidized by oxygen.



Scheme 3. Proposed mechanism of TEMPO promoted OAOC of enones.

Conclusions

In conclusion we have developed a metal-free, TEMPO promoted and water mediated oxidative cycloaddition of organic azides with various electron deficient olefins to construct a diverse array of disubstituted and trisubstituted 1,2,3-triazoles. This method can be a potential alternative to the existing copper and ruthenium catalysed azide-alkyne cycloaddition because of its metal-free condition and aqueous mediation. Olefins used here are comparatively cheaper than alkynes and they can be easily accessed by synthetic or commercial means. Most importantly this protocol has demonstrated a broad substrate scope of olefins bearing ketones, esters and aldehydes. Rare substrates like cyclohexenone and naphthoquinone also have successfully undergone oxidative cycloaddition. This method is distinct from the previously reported organo click reactions because this method uses electron deficient olefins instead of the electron rich enamines. Organo click reactions are limited to aryl azides [27] while this method is versatile to aryl, aliphatic and benzyl azides. We hope that these salient attributes will merit this method as a highly desirable one among the other existing methods.

Experimental Section

A mixture of olefin (1.0 mmol), azide (1.5 mmol), and TEMPO (0.5 mmol) and water (4 mL) were heated at 90 °C for 12h under oxygen balloon. After completion of the reaction as monitored by TLC, the reaction mixture was extracted with ethyl acetate (2 x 30 mL) and the combined organic solutions were dried with Na_2SO_4. The solvent was evaporated, and the resulting crude product was purified by column chromatography.

Acknowledgements

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Keywords: Metal-Free [3+2] Cycloaddition ● 1,2,3-Triazoles ● Azide-Olefin Cycloaddition ●TEMPO

[1] (a) C. W. Tornøe, C. Christensen, M. Meldal, *J. Org. Chem*. **2002**, *67*, 3057-3064; (b) V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2002**, *41*, 2596-2599.
[2] S. G. Agalave, S. R. Maujan, V. S. Pore, *Chem. Asian J*. **2011**, *6*, 2696-2718.
[3] (a) H. C. Kolb, K. B. Sharpless, *Drug Discovery Today*. **2003**, ***8***, 1128-1137; (b) P. Thirumurugan, D. Matosiuk, K. Jozwiak, *Chem. Rev*. **2013**, *113*, 4905-4979.
[4] (a) W. Xi,T.F. Scott, C.J. Kloxin, C.N. Bowman, *Adv. Funct. Mater*. **2014**, *24*, 2572–2590; (b) W. H. Binder,R. Sachsenhofer, *Macromol. Rapid Commun*. **2008**, *29*, 952-981.
[5] (a) J.-F. Lutz, *Angew. Chem. Int. Ed*. **2007**, *46*, 1018-1025; (b) K. Kempe, A. Krieg, C. R. Becer, U. S. Schubert, *Chem. Soc. Rev*. **2012**, *41*, 176-191; (c) S. Beghdadi, I. A. Miladi, D. Addis, H. B. Romdhane, J. Bernard, E. Drockenmuller, *Polym. Chem*. **2012**, *3*, 1680-1692.

[6] (a) A. C. Fahrenbach, J. F. Stoddart, *Chem. Asian J*. **2011**, *6*, 2660-2669; (b) B. Schulze, U. S.Schubert, *Chem. Soc. Rev*. **2014**, *43*, 2522-2571.

[7] (a) S. Wacharasindhu, S. Bardhan, Z.-K. Wan, K. Tabei, T. S. Mansour, *J. Am. Chem. Soc*. **2009**, *131*, 4174-4175; (b) B. Chattopadhyay, V. Gevorgyan, *Angew. Chem. Int. Ed*. **2012**, *51*, 862-872. (c) B. Seo, W. H. Jeon, J. Kim, S. Kim, P. H. Lee, *J. Org. Chem*. **2015**, *80*, 722-732; (d) C.-E. Kim, Y. Park, S. Park, P. H. Lee, *Adv. Synth. Catal*. **2015**, *357*, 210-220.

[8] (a) R. Huisgen, *Angew.Chem. Int. Ed. Engl*. **1963**, *2*, 565-598; (b) R. Huisgen, *Angew. Chem. Int. Ed. Engl*. **1963**, *2*, 633-645; (c) R. Huisgen, *Angew. Chem*. **1963**, *75*, 604; (d) R. Huisgen, *Angew. Chem*. **1963**, *75*, 742-754.

[9] (a) L. Zhang, X. Chen, P. Xue, H. H. Y. Sun, I. D. Williams, K. B. Sharpless, V. V. Fokin, G. Jia, *J. Am. Chem. Soc*. **2005**, *127*, 15998-15999; (b) L. K. Rasmussen, B. C. Boren, V. V. Fokin, *Org. Lett*. **2007**, *9*, 5337-5339; (c) B. C. Boren, S. Narayan, L. K. Rasmussen, L. Zhang, H. Zhao, Z. Lin, G. Jia, V. V. Fokin, *J. Am. Chem. Soc*. **2008**, *130*, 8923-8930.

[10] (a) S. Husinec, A. E. A. Porter, J. S. Roberts, C. H. Strachan, *J. Chem. Soc. Perkin Trans. 1*, **1984**, 2517-2522; (b) G. T. Anderson, J. R. Henry, S. M. Weinreb, *J. Org. Chem*. **1991**, *56*, 6946-6948; (c) R. H. Prager, P. Razzino, *Aust. J. Chem*. **1994**, *47*, 1375-1385; (d) C.-H. Yang, L.-T. Lee, J.-H. Yang, Y. Wang, G. H.Lee, *Tetrahedron.* **1994**, *50*, 12133-12142; (e) R. S. Dahl, N. S. Finney, *J. Am. Chem. Soc*. **2004**, *126*, 8356-8357; (f) J. M. Mahoney, C. R. Smith, J. N. Johnston, *J. Am. Chem. Soc*. **2005**, *127*, 1354-1355; (g) K. B. Hong, M. G. Donahue, J. N. Johnston, *J. Am.Chem. Soc*. **2008**, *130*, 2323-2328.

[11] (a) D. Amantini, F. Fringuelli, O. Piermatti, F. Pizzo, E. Zunino, L. Vaccaro, *J. Org. Chem.* **2005**, *70*, 6526-6529; (b) S. Sengupta, H. Duan, W. Lu, J. L. Petersen, X. Shi, *Org. Lett*. **2008**, *10*, 1493-1496; (c) Y.-C. Wang, Y.-Y. Xie, H.-E. Qu, H.-S. Wang, Y.-M. Pan F.-P.Huang, *J. Org. Chem*. **2014**, *79*, 4463-4469; (d) Q. Hu, Y. Liu, X. Deng, Y. Li, Y. Chen, *Adv. Synth. Catal*. **2016**, *358*, 1689-1693.

[12] (a) W. Peng, S. Zhu, *Tetrahedron.* **2003**, *59*, 4395-4404; (b) D. R. Roque, J. L. Neill, J. W. Antoon, E. P. Stevens, *Synthesis.* **2005**, 2497-2502.

[13] (a) A. Kayet, T. Pathak, *J. Org. Chem*. **2013**, *78*, 9865–9875; (b) D. Sahu, S. Dey, T. Pathak, B. Ganguly, *Org. Lett*. **2014**, *16*, 2100-2103.

[14] S. G. Hansen, H. H. Jensen, *Synlett*. **2009**, 3275-3276.

[15] D. Janreddy, V. Kavala, C.-W. Kuo, W.-C. Chen, C. Ramesh, T. Kotipalli, T.-S. Kuo, M.-L. Chen, C.-H. He, C.-F. Yao, *Adv. Synth. Catal*. **2013**, *355*, 2918-2927.

[16] Y.-Y. Xie, Y.-C. Wang, H.-E. Qu, X.-C. Tan, H.-S. Wang, Y.-M. Pan, *Adv. Synth. Catal*. **2014**, *356*, 3347–3355.

[17] Y. Zhang, X. Li, J. Li, J. Chen, X. Meng, M. Zhao, B. Chen, *Org. Lett*. **2012**, *14*, 26-29.

[18] Y. Chen, G.Nie, Q. Zhang, S. Ma, H. Li, Q. Hu, *Org. Lett*. **2015**, *17*, 1118-1121.

[19] S. Rohilla, S. S. Patel, N. Jain, *Eur. J. Org. Chem.* **2016**, 847–854.

[20] A. Kamal, P. Swapna, *RSC. Adv*. **2013**, *3*, 7419-7426.

[21] (a) D. Gangaprasad, J. Paul Raj, T. Kiranmye, S. SagubarSadik, J. Elangovan, *RSC Adv*. **2015**, *5*, 63473-63477;; (b) D. Gangaprasad, J. Paul Raj, T. Kiranmye, R. Sasikala, K. Karthikeyan, S. Kutti Rani, J. Elangovan, *Tet. Lett.* **2016**, *57*, 3105-3108.

[22] T. Wang, Z. Guo, *Curr. Med. Chem*. **2006**, *13*, 525–538.

[23] W. Yang, T. Miao, P. Li, L. Wang, *RSC Adv*. **2015**,*5*, 95833-95839.

[24] (a) M. Belkheira, D. E. Abed, J.-M. Pons, C. Bressy, *Chem. Eur. J.* **2011**, *17*, 12917-12921; (b) L. J. T. Danence, Y. Gao, M. Li, Y. Huang, J. Wang, *Chem. Eur. J*. **2011**, *17*, 3584-3587; (c) L. Wang, S. Peng, L. J. T. Danence, Y. Gao, J. Wang, *Chem. Eur. J*. **2012**, *18*, 6088-6093; (d) D. B. Ramachary, A. B. Shashank, *Chem. Eur. J*. **2013**, *19*, 13175-13181; (e) D. K. J. Yeung, T. Gao, J. Huang, S. Sun, H. Guo, J. Wang, *Green Chem*. **2013**, *15*, 2384-2388; (f) W. Li, Q. Jia, Z. Du, J. Wang, *Chem. Commun*. **2013**, *49*, 10187-10189; (g) W. Li, Z. Du, J. Huang, Q. Jia, K. Zhang, J. Wang, *Green Chem*. **2014**, *16*, 3003-3006; (h) M. T. Saraiva, G.P. Costa, N. Seus, R. F. Schumacher, G. Perin, M. W. Paixão, R. Luque,D. Alves, *Org. Lett*. **2015**, *17*, 6206-6209.

[25] (a) D. B. Ramachary, A. B. Shashank, S. Karthik, *Angew. Chem. Int. Ed*. **2014**, *53*, 10420-10424; (b) X. Zhou, X. Xu, K. Liu, H. Gao, W. Wang, W. Li, *Eur. J. Org. Chem*. **2016**, 1886-1890.

[26] (a) T. Shriteh, S. T. Abu-Orabi, R. Madwar, A. Atfeh, M. Abd-Al hakim Badawi, *Jordan. J. Chem*., **2011**, *6*, 257-269; (b) J. Zhang, C-W. Tom Chang*, J. Org. Chem.* **2009**, *74*, 685-695.

[27] For organo click reactions involve non-aromatic azides, please see reference 24g and 25a.

COMMUNICATION

A New Example of Organo Click Reactions: TEMPO-Promoted Oxidative Azide-Olefin Cycloaddition for the Synthesis of 1,2,3-Triazoles in Water

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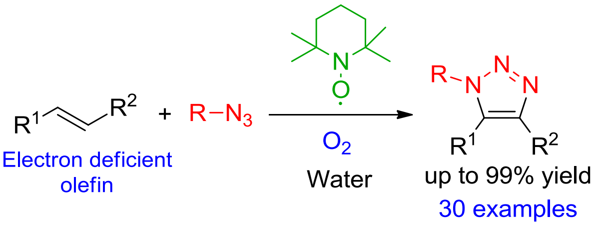

A TEMPO-promoted oxidative [3+2] cycloaddition of organic azides with electron deficient internal, terminal and cyclic olefins is reported under aqueous medium. A diverse array of substituted 1,2,3-triazoles are synthesized from moderate to excellent yields.