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An Enolate-Mediated Organocatalytic Azide–Ketone [3+2]-Cycloaddition Reaction: Regioselective High-Yielding Synthesis of Fully Decorated 1,2,3-Triazoles

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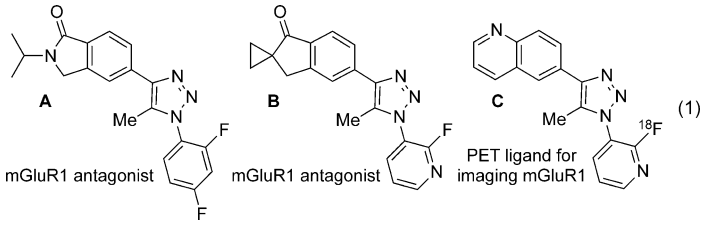
Abstract: An enolate-mediated organocatalytic azide–ketone [3+2]-cycloaddition (OrgAKC) reaction of a variety of enolizable arylacetones and deoxybenzoins with aryl azides was developed for the synthesis of fully decorated 1,4-diaryl-5-methyl(alkyl)-1,2,3-triazoles in excellent yields with high regioselectivity at 25 °C for 0.5–6 h. This reaction has an excellent outcome with reference to reaction rate, yield, regioselectivity, operation simplicity, and availability of substrates and catalyst. This reaction has advantages over the previously known metal-mediated reactions.

Even though the thermally-induced Huisgen [3+2]-cycloaddition of alkynes with azides has been known for over one century to make 1,2,3-triazoles, these compounds came to the limelight only in the last two decades due to their excellent copper-catalyzed regioselective synthesis developed by the Meldal and Sharpless groups.[1] Recently 1,2,3-triazoles have become important compounds with unique chemical and physical properties and are widely used as pharmaceuticals.[2] Many of the 1,2,3-triazoles have found wide range applications in medicinal, organic, bioorganic, polymer, and materials chemistry.[2] Design and utilization of 1,2,3-triazoles has mainly depended on their 1,4-disubstitutions or 1,4,5-trisubstitutions and for to this reason, the development of more general catalytic methods for their selective fully decorated synthesis is of significant interest.[3]



(1)

For example, 1,4-diaryl-5-methyl(alkyl)-1,2,3-triazoles have a significant role in pharmaceutical chemistry (**A**–**C**) and herein, we have shown interest in developing a single-step general protocol for their high-yielding regioselective synthesis. Very little is known about the regioselective synthesis of 1,4-diaryl-5-methyl(alkyl)-1,2,3-triazoles. When we analyzed the previous approaches, we found that metal-catalyzed or thermally-induced coupling reactions of internal alkynes with aryl azides lack regioselectivity and also generality.[4] An alternative approach to such 1,4-diaryl-5-methyl(alkyl) 1,2,3-triazoles is the use of in situ generated metalated triazoles, in which metal acetylides (metal = Li, Mg, Zn and Te) were treated with organic azides followed by further in situ reaction with various electrophiles.[5] However, this approach is limited because of the reverse selectivity and high reactivity of the metalated triazoles. Other routes include palladium- or copper-catalyzed arylation of 1,4-disubtituted 1,2,3-triazoles with aryl halides (Scheme 1a)[6] and/or the copper-catalyzed cycloaddition of organic azides with 1-iodoalkynes or 1-*n*-butyltelluro alkynes followed by palladium-catalyzed arylation of the corresponding 5-iodo-1,2,3-triazoles or 5-telluro-1,2,3-triazoles with arylboronic acid or potassium aryltrifluoroborates, respectively (Scheme 1b).[7] Alternative routes include bulky ruthenium-catalyzed azide-internal alkyne cycloaddition reactions,[8] condensation of *N*-tosylhydrazones and anilines under stoichiometric amounts of copper salts and excess additives at higher temperatures,[9] and amine/acid-catalyzed three-component condensation of aldehydes, nitroalkanes/malononitrile, and organic azides at higher temperatures for longer reaction times.[10] A strain-promoted [3+2]-cycloaddition reaction of aryl azides with functionalized cyclooctynes[11] and amino acid catalyzed enamine-mediated azide–carbonyl [3+2]-cycloaddition reaction of active methylenes or symmetrical ketones with aryl azides furnished the 1,4,5-trisubstituted 1,2,3-triazoles at higher temperatures (Scheme 1c).[12]

In many of the above methods, either they used costly and less reactive alkynes or noncommercial substrates other than the simple arylacetones as starting materials. Also the requirement of toxic transition-metal catalysts, heavy ligands and reagents, higher temperatures, longer reaction times, and loading stoichiometric amounts of catalysts made the above reaction conditions inferior. These drawbacks inspired us to develop a general metal-free protocol for the high-yielding regioselective synthesis of 1,4-diaryl-5-methyl-(alkyl)-1,2,3-triazoles by using a recently discovered enolate-

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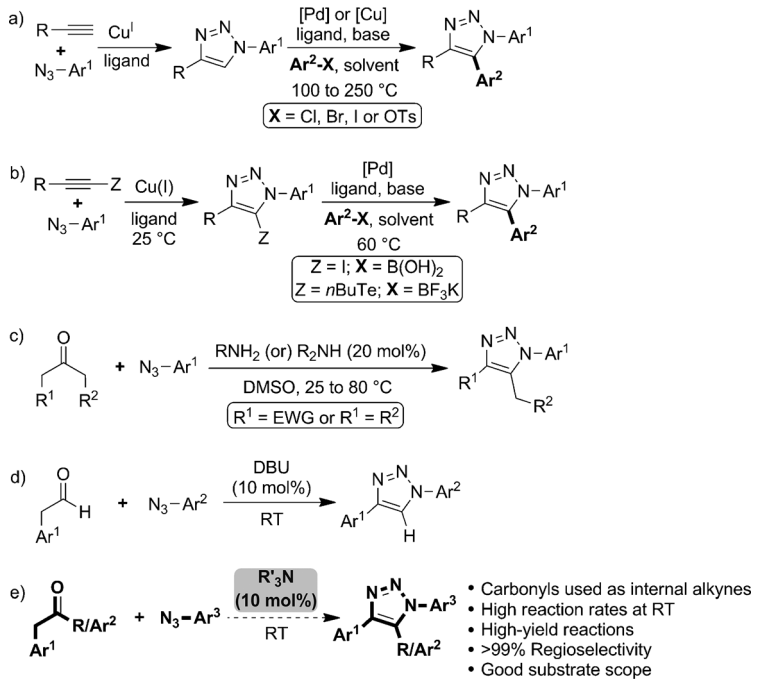


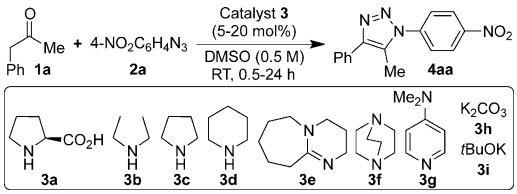
Scheme 1. Reaction design for the enolate-mediated OrgAKC reaction. a) Direct Pd- or Cu-catalyzed arylation of 1,2,3-triazoles: Gevorgyan, Oshima, and Ackerman; b) direct Cu- or Pd-catalyzed synthesis of functionalized 1,2,3-triazoles: Fokin and Stefani; c) amine-catalyzed enamine-mediated click reaction: Ramachary, Pons-Bressy, and Wang; d) amine-catalyzed enolate-mediated click reaction: Ramachary; e) amine-catalyzed enolate-mediated click synthesis of trisubstituted 1,2,3-triazoles: this work.

mediated organocatalytic click reaction (Scheme 1d).[13] Herein, we disclosed general, rapid, and operationally simple either enamine- or enolate-mediated organocatalytic azide–ketone [3+2]-cycloaddition (OrgAKC) reactions for the chemo- and regioselective synthesis of fully decorated 1,2,3-triazoles from the easily available arylacetones/deoxybenzoins, aryl azides, and catalytic amounts of *sec*-amine or *tert*-amine (Scheme 1e).

We commenced the prior optimization of the OrgAKC reaction by screening simple catalysts for the organo-click reaction of phenylacetone **1a** with 1.5 equivalents of 4-$NO_2C_6H_4N_3$ **2a** (Table 1). Reaction of **1a** with **2a** in DMSO under 20 mol% of proline **3a** catalysis at RT for 11 h furnished the expected product **4aa** as a single regioisomer in only 23% yield (Table 1, entry 1). The same reaction at RT for 2 h under the 20 mol% of diethylamine **3b**, pyrrolidine **3c**, or piperidine **3d** catalysis furnished the fully substituted 1,2,3-triazole **4aa** in 85, 90, and 90% yields, respectively (entries 2–4). But on decreasing the catalyst **3c** loading from 20 mol% to 10 or 5 mol%, the reaction became inferior with respect to rate and yield (entries 5 and 6). After obtaining moderate results with catalysts **3a**–**d** through enamine-formation, we thought of exploring the same reaction through in situ enolate formation, for which we tested some *tert*-amines **3e**–**g** and nonamine bases **3h**–**i** as the catalysts for the OrgAKC reaction (Table 1).[13] Intriguingly, the reaction of **1a** with **2a** in DMSO under 20 mol% of **3e** (DBU) catalysis at 25 °C for 0.5 h furnished **4aa** in 97% yield (entry 7). Surprisingly, the same reaction with 10 mol% of **3e** catalysis also furnished **4aa** in 95% yield within 0.5 h (entry 8). But the same OrgAKC reaction under the catalysis of relatively less basic *tert*-amines, **3f** (DABCO) or **3g** (DMAP) furnished **4aa** in poor yields (entries 9 and 10). Interestingly, the same reaction under 10 mol% of nonamine bases, **3h** (K_2CO_3) and **3i** (*t*BuOK) catalysis also furnished the 1,2,3-triazole **4aa** in moderate to good yields (entries 11–12). There was no reaction observed under the self- or autocatalytic conditions in DMSO for 24 h at 25 °C (entries 13 and 14). Finally we envisioned the optimized conditions to be 25 °C in DMSO under 10 mol% of **3e** catalysis to furnish the single isomer of fully decorated 1,2,3-traizole **4aa** in 95% yield from **1a** and **2a** (entry 8).

With the best conditions in hand, the generality of the enolate-mediated OrgAKC reaction was investigated. First, various aryl and alkyl azides **2b**–**s** were reacted with phenylacetone **1a** catalyzed by 10 mol% of DBU (**3e**) at 25 °C in DMSO for 0.5–2 h (Table 2). Fascinatingly, the aryl azides containing different functional groups (H, alkyl, halogen, electron-withdrawing (EWG) and -donating (EDG) groups) **2b**–**o** furnished the expected fully substituted 1,2,3-triazoles **4ab**–**ao** in excellent yields within 0.5–2 h (Table 2). Yields of the 1,2,3-triazoles **4ab**–**ao** were obtained in a similar manner for different aryl azides **2**, but the reaction rate slightly decreased with *ortho*-substitution and also for EDG substitution. Interestingly, DBU-catalyzed OrgAKC reaction of **1a** with benzyl/acyl/tosyl/mesyl azides **2p**–**s** did not furnish the expected products **4**, but the same reaction under *t*BuOK **3i** catalysis furnished the triazole **4ap** in 90% yield, decarboxylated triazole **4aq**′ along with ester triazole **4aq** in 90% and

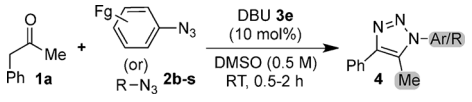
Table 1. Reaction optimization.[a]



Entry	Catalyst **3**	*t* [h]	Yield **4aa** [%][b]
1	**3a** (20 mol%)	11	23
2	**3b** (20 mol%)	2	85
3	**3c** (20 mol%)	2	90
4	**3d** (20 mol%)	2	90
5	**3c** (10 mol%)	8	50
6	**3c** (5 mol%)	9	25
7	**3e** (20 mol%)	0.5	97
8	**3e (10 mol%)**	**0.5**	**95**
9	**3f** (20 mol%)	24	40
10	**3g** (20 mol%)	24	30
11	**3h** (10 mol%)	0.5	60
12	**3i (10 mol%)**	**0.5**	**90**
13	**4aa** (20 mol%)	24	–
14	–	24	–

[a] Reactions were carried out in solvent (0.5 M) with 1.5 equiv of **2a** relative to **1a** (0.5 mmol) in the presence of 5–20 mol% of catalyst **3**. [b] Yield refers to the column-purified product.

Table 2. Azide scope with phenylacetone **1a**.[a]



Entry	Ar-N_3 (or) R-N_3 **2**	Yield **4** [%][b]
1	**2b** (Fg = H)	90 (**4ab**)
2	**2c** (Fg = 2-NO_2)	90 (**4ac**)
3	**2d** (Fg = 4-CO_2Et)	95 (**4ad**)
4	**2e** (Fg = 4-CN)	92 (**4ae**)
5	**2f** (Fg = 4-CF_3)	92 (**4af**)
6	**2g** (Fg = 3-CHO)	80 (**4ag**)
7	**2h** (Fg = 4-F)	90 (**4ah**)
8	**2i** (Fg = 4-Cl)	92 (**4ai**)
9	**2j** (Fg = 3-Cl)	93 (**4aj**)
10	**2k** (Fg = 4-Br)	90 (**4ak**)
11	**2l** (Fg = 2-Br)	70 (**4al**)
12	**2m** (Fg = 4-Me)	89 (**4am**)
13	**2n** (Ar = 1-naphthyl)	90 (**4an**)
14	**2o** (Fg = 4-OMe)	90 (**4ao**)
15[c]	**2p** (R = $PhCH_2$)	90 (**4ap**)
16[c,d]	**2q** (R = $EtCO_2$)	90 (**4aq**)
17	**2r** (R = Ts)	– (**4ar**)
18	**2s** (R = Ms)	– (**4as**)

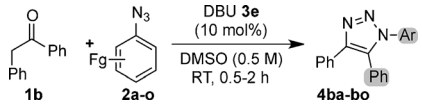
[a] Reactions were carried out in DMSO (0.5 M) with 1.5 equiv of **2b**–**s** relative to **1a** (0.5 mmol) in the presence of 10 mol% of **3e**. [b] Yield refers to the column-purified product. [c] *t*BuOK-catalysis at RT for 1 h. [d] A 1.5:1 ratio of decarboxylated triazole **4aq′** and ester triazole **4aq** was obtained, respectively.

4ar/4as was not formed at all (Table 2, entries 15–18). The structure and the regiochemistry of the OrgAKC products **4ab**–**aq** were confirmed by NMR spectroscopic analysis and also finally confirmed by the X-ray structure analysis on **4ao** as shown in Figure S1 (see the Supporting Information).[14]

After comprehending the OrgAKC reaction by probing the electronic factors of alkyl or aryl azides **2a**–**s** with **1a**, we further showed interest to investigate the electronic factors of aryl azides **2a**–**o** with deoxybenzoin **1b** in the OrgAKC reaction (Table 3). Stimulatingly, the reaction of aryl azides **2a**–**o** containing different functional groups of alkyl, halogen, EWG's, and EDG's with deoxybenzoin **1b** under 10 mol% of **3e** catalysis furnished the single isomer of 1,4,5-trisubstituted-1,2,3-triazoles **4ba**–**bo** in excellent yields within 0.5–2 h at 25 °C similar to phenylacetone **1a** (Table 3). The results in Table 3 demonstrate the broad scope of this protocol covering a structurally diverse group of aryl azides **2a**–**o** and simple ketone **1b**.

To develop a diverse library of fully decorated triazoles **4** and also to further understand the electronic factors of substituted phenylacetones/deoxybenzoins **1** in the OrgAKC reaction, we have chosen different ketones **1c**–**r**, which contain less or more acidic α-methylene groups compared to **1a**–**b** (Table 4). The OrgAKC reaction of 4-nitrophenylacetone **1c** with less reactive $C_6H_5N_3$ (**2b**) under **3e** catalysis at 25 °C for 0.5 h furnished the expected 1,2,3-triazole **4cb** in 90% yield (Table 4, entry 1). In a similar manner, we have also tested five more examples of halogen-, methoxy-, methyl-, and acetylene-substituted phenylacetones **1d**–**h** for the OrgAKC reaction with **2b**, which furnished the 1,2,3-triazoles **4db**–**hb** in excellent yields (entries 2–6). The OrgAKC reaction of nitro-, bromo-, chloro-, methyl-, and methoxy-substituted deoxybenzoins **1i**–**n** with **2a** under **3e** catalysis at 25 °C for 1.0 h furnished the fully decorated 1,2,3-triazoles **4ia**–**na** in 88–92% yields without

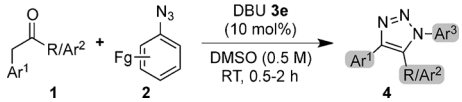
Table 3. Azide scope with deoxybenzoin **1b**.[a]



Entry	Ar-N_3 **2**	Yield **4ba**–**bo** [%][b]
1	**2a** (Fg = 4-NO_2)	96 (**4ba**)
2	**2b** (Fg = H)	90 (**4bb**)
3	**2c** (Fg = 2-NO_2)	95 (**4bc**)
4	**2d** (Fg = 4-CO_2Et)	94 (**4bd**)
5	**2e** (Fg = 4-CN)	93 (**4be**)
6	**2f** (Fg = 4-CF_3)	95 (**4bf**)
7	**2g** (Fg = 3-CHO)	95 (**4bg**)
8	**2h** (Fg = 4-F)	92 (**4bh**)
9	**2i** (Fg = 4-Cl)	95 (**4bi**)
10	**2j** (Fg = 3-Cl)	93 (**4bj**)
11	**2k** (Fg = 4-Br)	95 (**4bk**)
12	**2l** (Fg = 2-Br)	72 (**4bl**)
13	**2m** (Fg = 4-Me)	90 (**4bm**)
14	**2n** (Ar = 1-naphthyl)	85 (**4bn**)
15	**2o** (Fg = 4-OMe)	90 (**4bo**)

[a] Reactions were carried out in DMSO (0.5 M) with 1.5 equiv of **2a**–**o** relative to **1b** (0.5 mmol) in the presence of 10 mol% of **3e**. [b] Yield refers to the column-purified product.

Table 4. OrgAKC reaction scope with different azides and ketones.[a]

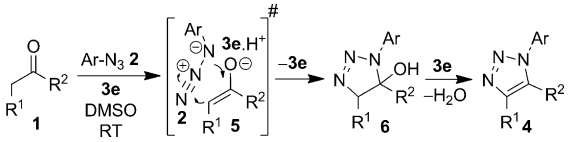


Entry	Ar^1 and R/Ar^2 **1**	Ar^3-N_3 **2**	Yield **4** [%][b]
1	**1c** (Ar^1 = 4-$NO_2C_6H_4$; R = Me)	**2b**	90 (**4cb**)
2	**1d** (Ar^1 = 4-BrC_6H_4; R = Me)	**2b**	93 (**4db**)
3	**1e** (Ar^1 = 4-ClC_6H_4; R = Me)	**2b**	95 (**4eb**)
4	**1f** (Ar^1 = 4-$OMeC_6H_4$; R = Me)	**2b**	74 (**4fb**)
5	**1g** (Ar^1 = 4-MeC_6H_4; R = Me)	**2b**	92 (**4gb**)
6	**1h** (Ar^1 = 4-$HCCC_6H_4$; R = Me)	**2b**	95 (**4hb**)
7	**1i** (Ar^1 = 4-$NO_2C_6H_4$; Ar^2 = Ph)	**2a**	92 (**4ia**)
8	**1j** (Ar^1 = 4-BrC_6H_4; Ar^2 = Ph)	**2a**	90 (**4ja**)
9	**1k** (Ar^1 = 4-BrC_6H_4; Ar^2 = 4-MeC_6H_4)	**2a**	90 (**4ka**)
10	**1l** (Ar^1 = Ph; Ar^2 = 4-ClC_6H_4)	**2a**	90 (**4la**)
11	**1m** (Ar^1 = Ph; Ar^2 = 4-MeC_6H_4)	**2a**	90 (**4ma**)
12	**1n** (Ar^1 = Ph; Ar^2 = 4-$OMeC_6H_4$)	**2a**	88 (**4na**)
13	**1o** (β-tetralone)	**2b**	85 (**4ob**)
14	**1o** (β-tetralone)	**2o**	60 (**4oo**)
15	**1p** (Ar^1 = 2-naphthyl; R = Me)	**2b**	92 (**4pb**)
16[c]	**1p** (Ar^1 = 2-naphthyl; R = Me)	**2t**	90 (**4pt**)
17[c]	**1p** (Ar^1 = 2-naphthyl; R = Me)	**2u**	92 (**4pu**)
18[c]	**1p** (Ar^1 = 2-naphthyl; R = Me)	**2v**	93 (**4pv**)
19	**1q** (Ar^1 = $PhCH_2$; R = Me)	**2a**	– (**4qa**)
20	**1r** (Ar^1 = Ph; R = Et)	**2a**	80 (**4ra**)
21	**1r** (Ar^1 = Ph; R = Et)	**2b**	80 (**4rb**)

[a] Reactions were carried out in DMSO (0.5 M) with 1.5 equiv of **2** relative to **1** (0.5 mmol) in the presence of 10 mol% of **3e**. [b] Yield refers to the column-purified product. [c] **2t**: 2,3-$F_2C_6H_3N_3$; **2u**: 2,4-$F_2C_6H_3N_3$; **2v**: 3-azido-2-bromopyridine.

showing much of electronic factors (entries 7–12). To understand the in situ enolate formation and their reactivity from cyclic arylacetones with DBU, we have chosen β-tetralone **1o** as the substrate in the OrgAKC reaction. The OrgAKC reaction of **1o** with aryl azides **2b** and **2o** under **3e** catalysis at 25 °C for 0.5 h furnished the single isomer of triazoles **4ob** and **4oo** in 85 and 60% yields, respectively (entries 13–14). With applications in mind, we have prepared a few more 1,4,5-trisubstituted-1,2,3-triazoles **4pb** and **4pt**–**pv** from the treatment of 2-naphthylacetone **1p** with aryl azides $C_6H_5N_3$ (**2b**), 2,3-$F_2C_6H_3N_3$ (**2t**), 2,4-$F_2C_6H_3N_3$ (**2u**), and 3-azido-2-bromopyridine (**2v**) at 25 °C for 0.5 h under **3e** catalysis (entries 15–18). The compounds **4pb** and **4pt**–**pv** are analogues of PET ligands for imaging mGluR1 **C**.[2c–e] Surprisingly, there is no triazole formation from the reaction of benzylacetone **1q** with **2a** under **3e** or **3i** catalysis (entry 19). Interestingly, the OrgAKC reaction of 1-phenylbutan-2-one **1r** with aryl azides **2a** and **2b** under **3e** catalysis at 25 °C for 0.5 h furnished the single isomer of 1,2,3-triazoles **4ra**–**rb** in 80% yield each (entries 20–21). Many of the products **4** yields/selectivity obtained were excellent compared to the previous methods and out of fifty-six compounds synthesized here only seventeen are known (Table S1, see the Supporting Information).

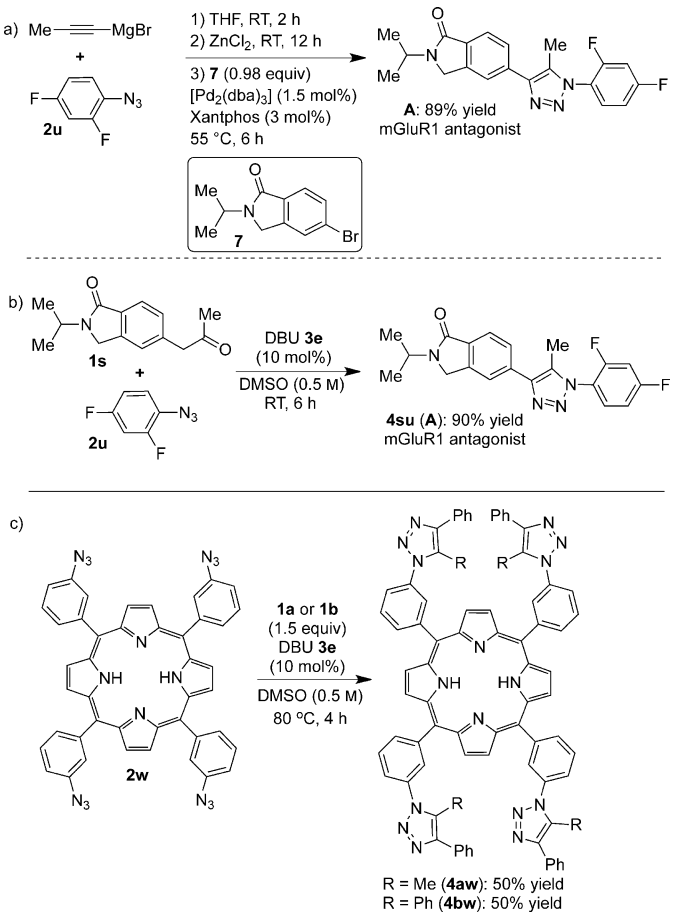
The provisional mechanism for the OrgAKC reaction is illustrated in Scheme 2. Reaction of phenylacetones/deoxybenzoins **1** with catalyst **3e** generates the enolate **5**, which on quick in



Scheme 2. Reaction mechanism of OrgAKC.

situ treatment with Ar-N_3 **2** furnishes selectively the adduct 1,2,3-triazolines **6** by concerted or stepwise [3+2]-cycloaddition,[13] which further transforms into the fully decorated triazole **4** through rapid elimination of water at ambient conditions.

The versatility of the OrgAKC reaction was further exemplified by synthesizing medicinally and materially useful compounds **4su**, **4aw**, and **4bw** (Scheme 3).[2c–e] As shown in Scheme 3B, mGluR1 antagonist triazole **4su** (**A**) was synthesized in very good yield with a single isomer from the arylacetone **1s** and 2,4-$F_2C_6H_3N_3$ **2u** under the metal-free **3e**-catalysis at ambient conditions. By contrast, the literature synthesis of this antagonist triazole **4su** starting from 1-propynylmagnesiumbromide and **2u** requires metal (Mg, Zn, Pd)-mediated three reactions (Scheme 3A).[2e] Further, we synthesized the compounds **4aw/4bw** through the OrgAKC reaction of metal-free fully substituted tetraarylporphyrin azide **2w** with **1a/1b** in DMSO at 80 °C for 4 h. Compound **4aw/4bw** was isolated as a single regioisomer in moderate yield (Scheme 3C).[2f] These results clearly demonstrate the exceptional advantages of the OrgAKC protocol, which enables a high-yielding metal-free synthesis of medicinally important triazoles.



Scheme 3. Application of the OrgAKC reaction. a) Literature metal-mediated approach to mGluR1 antagonist; b) our organocatalytic approach to mGluR1 antagonist; c) OrgAKC approach to triazole-linked porphyrins.

In conclusion, we have developed a versatile enolate-mediated organocatalytic azide-ketone [3+2]-cycloaddition reaction that generates 1,4-diaryl-5-methyl(alkyl) 1,2,3-triazoles decorated with useful functional groups. Our OrgAKC protocol highlights the metal-free conditions with high reaction rate and regioselectivity, and it provides an easy access to a library of functionalized 1,2,3-triazoles that are inaccessible by other methods. This OrgAKC reaction was well tolerated by many functional groups (such as nitro, nitrile, aldehydes, ketones, esters, halides, amides, and alkynes) under these mild reaction conditions. Moreover, many of the reported syntheses have the disadvantage of requiring heavy metals and less available unsymmetric internal alkynes; therefore, this protocol is very convenient. Further work is in progress to utilize the enolate-mediated OrgAKC reactions in medicinal and material chemistry.

Acknowledgements

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Keywords: azides · click reaction · ketones · organocatalysis · triazoles

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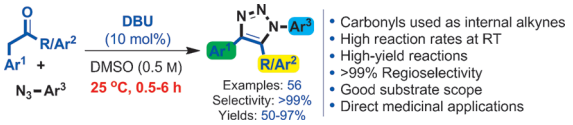
An Enolate-Mediated Organocatalytic Azide–Ketone [3+2]-Cycloaddition Reaction: Regioselective High-Yielding Synthesis of Fully Decorated 1,2,3-Triazoles



Fully functionalized 1,2,3-triazoles were synthesized by a metal-free clicking through an enolate-mediated organocatalytic azide–ketone [3+2]-cycloaddition (OrgAKC) reaction. Very simple and readily available aryl azides and enolizable arylacetones/deoxybenzoins were employed in this organocatalytic transformation (see scheme).