Organic LETTERS

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Cationic 1,2,3-Triazolium Alkynes: Components To Enhance 1,4-Regioselective Azide–Alkyne Cycloaddition Reactions

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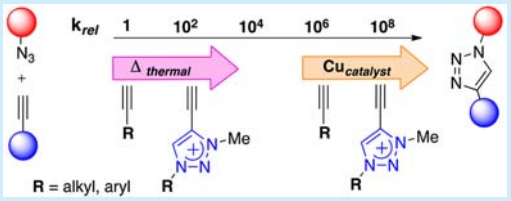
Supporting Information

ABSTRACT: 4-Alkynyl-1,2,3-triazolium cations undergo thermal [3 + 2] cycloaddition reactions with azides roughly 50- to 100-fold faster than comparable noncharged alkynes. Further, the reaction is highly 1,4-regioselective (dr up to 99:1) owing to the selective stabilization of 1,4-TS transition states via conjugative π-acceptor assistance of the alkyne triazolium ring. The novel cationic triazolium alkynes also accelerate the CuAAC reaction to provide bis(1,2,3-triazoles) in an "ultrafast" way (<5 min).



Enhancing the clickability[1] of the intrinsically sluggish and nonselective Huisgen[2] azide–alkyne [3 + 2] cycloaddition reaction (Figure 1, top) has resulted in some of the most

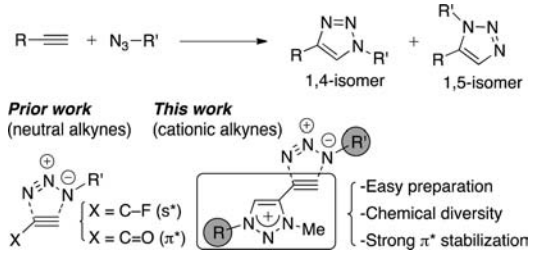


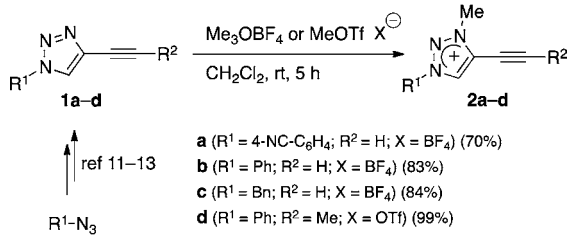
Figure 1. Azide–alkyne [3 + 2] cycloaddition reaction activation via transition states stabilized with electron-deficient alkynes.

versatile methods to connect molecules covalently through 1,2,3-triazole units. The Sharpless/Meldal copper(I)-accelerated version of the reaction (CuAAC)[3] and Bertozzi's strain-promoted cycloalkyne variation (SPAAC)[4] are excellent examples of the transformation of such a reaction into a "click" process.

In order to avoid the biotoxicity of copper salts and the inherent instability and cumbersome synthesis of highly strained alkynes,[5] several authors have proposed the use of electron-deficient *o*-nitrophenylalkynes[6] or propiolates[7] to carry out copper-free Huisgen reactions. Recently, Alabugin has developed this approach to activate nonstrained alkynes by stabilizing the reaction transition state via hyperconjugative assistance with propargylic electron-withdrawing groups (Figure 1, bottom left).[8] Although satisfactory reaction rate increases were attained in some instances, these cycloadditions displayed no or, at best, modest regioselectivity[9] and were very limited in their substitution scope.

We surmised that robust cationic alkynes containing the 3-methyl-1,2,3-triazolium moiety[10] could act as strong π-accepting dipolarophiles toward donor azides providing highly activated cycloadditions suitable to overcome the aforementioned drawbacks (Figure 1, bottom right). To test our hypothesis, we first synthesized a variety of 4-ethynyl-1,2,3-triazoles **1** from azides following a standard CuAAC approach[11,12] (Scheme 1) and achieved their *N*-methylation with the Meerwein salt Me_3OBF_4 or methyl triflate to obtain the desired triazolium alkynes **2** in good to excellent yields.[13]

Scheme 1. Synthesis of 4-Ethynyl-1,2,3-triazoles 1 and 4-Alkynyl-3-methyltriazolium Salts 2



With the triazolium alkynes in hand, we conducted a kinetic study to determine the reaction rates of the second-order cycloaddition of benzyl azide **3a** with the neutral alkyne **1a** and cationic analogue **2a** (Table 1, top). The reactions were conducted in MeCN-d_3 at 80 °C, and the formation of each 1,4- and 1,5-isomer of the resulting bis-triazoles **4** and **5** was monitored by ^{1}H NMR (see SI, Figure S2). In agreement with our hypothesis, the cationic alkyne **2a** reacted with benzyl azide to afford the regioisomer $\mathbf{5}_{1,4}$ about 2 orders of magnitude

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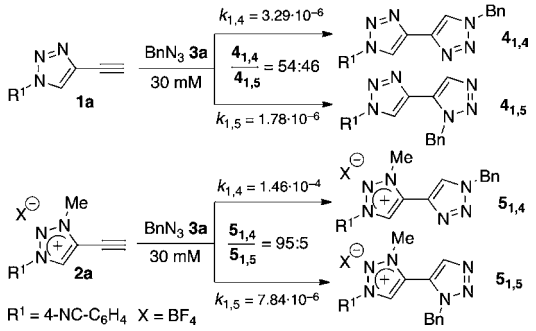
Table 1. Reaction Rate Constants (MeCN-3*d*, 80 °C) and Activation Parameters for Alkynes 1a and 2a



entry[a]	product	$\Delta E^{\ddagger}_{exp}$	$\Delta H^{\ddagger}_{exp}$	$\Delta S^{\ddagger}_{exp}$[b]	$\Delta G^{\ddagger}_{exp}$[c]	$\Delta\Delta G^{\ddagger}_{exp}$[c]
1	$\mathbf{4}_{1,4}$	14.9	14.2	−43	29.4	0.3
2	$\mathbf{4}_{1,5}$	15.5	14.9	−42	29.7	
3	$\mathbf{5}_{1,4}$	8.4	7.7	−55	27.0	2.1
4	$\mathbf{5}_{1,5}$	9.4	8.7	−58	29.0	

[a]Determined from experiments conducted at 60, 80, and 100 °C. Values in kcal·mol^{-1}. [b]In cal·mol^{-1}·K^{-1}. [c]Values adjusted to 80 °C.

faster than the neutral alkyne **1a** to give $\mathbf{4}_{1,4}$. Surprisingly, regioisomer $\mathbf{5}_{1,5}$ was formed only 4-fold faster than $\mathbf{4}_{1,5}$ under identical conditions. As a result, cationic adducts **5** were obtained in an excellent 95:5 isomer ratio, whereas the neutral analogues **4** gave a roughly equimolar mixture. The Arrhenius activation energies (Table 1, $\Delta E^{\ddagger}_{exp}$) of the cycloadditions confirmed that *N*-methylation of **1a** to **2a** caused a lowering of 6 kcal·mol^{-1}, which was in good agreement with the reaction rate increase observed experimentally. More significantly, the Eyring–Polanyi plots for each regioisomer showed a free energy difference ($\Delta\Delta G^{\ddagger}_{exp}$) of only 0.3 kcal·mol^{-1} between the activation barriers of triazoles $\mathbf{4}_{1,5}$ and $\mathbf{4}_{1,5}$, whereas such value increased to 2.1 kcal·mol^{-1} for $\mathbf{5}_{1,5}$ and $\mathbf{5}_{1,4}$. When the activation energies were measured in DMSO-d_6, a destabilizing solvent effect of 3.2–2.8 kcal·mol^{-1} relative to acetonitrile was recorded for the catonic alkyne **2a** but not for the less polar **1a** (SI, Table S3).

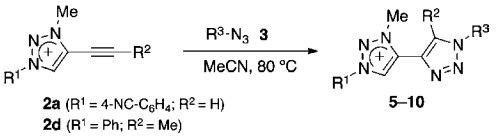
Next, we studied the cycloaddition reaction of cationic triazolium alkynes **2a** and **2d** with several azides **3** of variable electron density in acetonitrile at 80 °C (Table 2). In all instances, high yields and excellent 1,4-regioselectivities were attained irrespective of the azide used. Reaction rate constants $k_{1,4}$ were strongly dependent on the electron-donating ability of the azide. For instance, aromatic azides (entries 2–4), typically reacted 1 order of magnitude slower than aliphatic azides (entry 1), and the very electron-rich bis(trimethylsilyl)methyl azide **3e** (entry 5) reacted 100-fold faster than phenyl azide **3c**. In contrast, reaction rate constants $k_{1,5}$ remained almost unaffected by the electronic nature of the azide in values close to 10^{-6} M^{-1}·s^{-1} (SI, Figures S5 and S6). Finally, the cationic internal alkyne **2d** also reacted with benzyl azide at 130 °C in toluene to afford the triazole **10** in a 90:10 regioisomer ratio, a much higher regioselectivity than attained in related cycloadditions.[6]

In parallel with the kinetic determinations, we computationally explored the origin of the high regioselectivity observed for cationic alkynes **2**. Ab initio calculations at the B3LYP/6-31++G** level of theory (MeCN solvent) using the Gaussian09 suite of programs yielded the four transition states shown in Figure 2 (top). Their activation Gibbs energies corrected to 80 °C were in good agreement with the experimental values (Table 1) and accounted for the activation free energy difference $\Delta\Delta G^{\ddagger}$ of about 2–3 kcal·mol^{-1} between cationic TS-$\mathbf{5}_{1,4}$ and TS-$\mathbf{5}_{1,5}$ as well as the absence of such a gap for neutral TS-$\mathbf{4}_{1,4}$ and TS-$\mathbf{4}_{1,5}$ (SI, Figure S8). Reaction activation energies were also divided in terms of distortion (ΔE_{dis}) and interaction (ΔE_{int}) energies, following Houk's model.[14] We found that the total distortion energy difference between 1,5- and 1,4-transition states was only 1.4 kcal·mol^{-1} for neutral alkyne **1a** and 4.2 kcal·mol^{-1} for the cationic analogue **2a**. Such an energy difference emerged mostly from the azide component. On the other hand, interaction energies released in electrostatic and frontier orbital interactions were very similar for each 1,4-/1,5-transition-state pair, but their values were 6–8 kcal·mol^{-1} more negative for TS-$\mathbf{5}_{1,4}$ and TS-$\mathbf{5}_{1,5}$, in line with their charged electronic nature.

Finally, the structural and stereoelectronic characteristics of the transition states depicted in Figure 2 were examined. Although the formation of C–N bonds was appreciably more asynchronous for the transition states arising from the cationic alkyne **2a**, the forming bond length differences could not be correlated with the observed 1,4-/1,5-regioselectivities. Much more meaningful was the comparison of the dihedral angles θ encompassing the N–C–C–N atoms between the two triazole rings in the transition states. Actually, all of them were essentially coplanar with the exception of TS-$\mathbf{5}_{1,5}$, which was orthogonal (θ = −90°).

A fragment analysis of frontier molecular orbitals of TS-$\mathbf{5}_{1,4}$ and TS-$\mathbf{5}_{1,5}$ using the ADF software[15] at an HF/DZ level of theory allowed the identification of the bonding orbital approaches A and B for TS-$\mathbf{5}_{1,4}$ and C for TS-$\mathbf{5}_{1,5}$ (SI, Figures

Table 2. Cycloaddition of Cationic Triazolium Alkynes with Azides



entry	reag[a]	R^2	R^3	prod[b]	1,4-/1,5-	$k_{1,4}$[c]	$k_{1,5}$[c]
1	**2a**/**3a**	H	Bn	**5** (73)	95:5	1.46×10^{-4}	7.84×10^{-6}
2	**2a**/**3b**	H	4-MeOC$_6$H$_4$	**6** (72)	95:5	7.84×10^{-5}	4.45×10^{-6}
3	**2a**/**3c**	H	Ph	**7** (70)	96:4	2.33×10^{-5}	1.90×10^{-6}
4	**2a**/**3d**	H	4-FC$_6$H$_4$	**8** (70)	94:6	3.56×10^{-5}	2.09×10^{-6}
5	**2a**/**3e**	H	$(Me_3Si)_2CH$	**9** (88)	99:1	1.17×10^{-3}	8.15×10^{-5}
6[d]	**2d**/**3a**	Me	Bn	**10** (62)	90:10	*e*	*e*

[a]Alkyne/azide. [b]Isolated yield of 1,4-isomer. [c]Rate constants in M^{-1} s^{-1}. [d]Reaction conducted in toluene at 130 °C. [e]Not determined.

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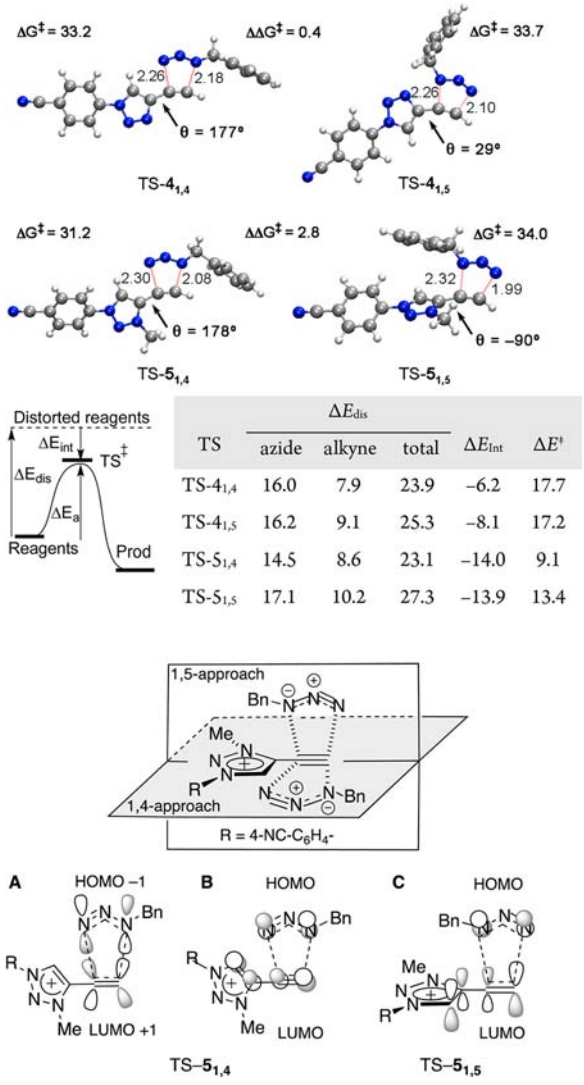

TS	ΔE$_{dis}$ azide	ΔE$_{dis}$ alkyne	ΔE$_{dis}$ total	ΔE$_{Int}$	ΔE‡
TS-4$_{1,4}$	16.0	7.9	23.9	−6.2	17.7
TS-4$_{1,5}$	16.2	9.1	25.3	−8.1	17.2
TS-5$_{1,4}$	14.5	8.6	23.1	−14.0	9.1
TS-5$_{1,5}$	17.1	10.2	27.3	−13.9	13.4

Figure 2. Transition states of the reaction of benzyl azide **3a** with alkynes **1a** and **2a**. (Top) B3LYP/6-31++G** structures and activation free energy barriers (kcal·mol^{-1}) calculated at 80 °C in MeCN. Interatomic distances in Å. (Middle) Distortion, interaction, and activation energies (kcal·mol^{-1}). (Bottom) Approaching geometries and frontier molecular orbital interactions for transition states TS-**5**$_{1,4}$ and TS-**5**$_{1,5}$.

S9 and S10). The quantitative Kohn−Sham electronic structure analysis for the formation of the 1,2,3-triazole ring in TS-**5**$_{1,4}$ yielded an expected coplanar approach of the azide (Figure 2, bottom, interaction A), stabilized through a conjugative π-acceptor assistance (B). However, in the case of TS-**5**$_{1,5}$, such stabilization was canceled by the orthogonal disposition of HOMO$_{azide}$ and LUMO$_{alkyne}$ (approach C), and the alternative HOMO−1$_{azide}$ and LUMO+1$_{alkyne}$ approach was precluded by the steric hindrance between the azide substituent and the alkyne triazolium *N*-methyl group. The absence of this obstacle in the uncharged TS-**4**$_{1,5}$ accounted for the low regioselectivity observed during the cycloaddition of alkyne **1a**.

Encouraged by the successful activation of thermal [3 + 2] cycloadditions achieved with cationic alkynes **2**, we explored their use as components of copper-catalyzed reactions. We anticipated that the strongly electron-deficient triazolium moiety would stabilize the transition state D (Figure 3, top), which is the rate-limiting step of the CuAAC catalytic cycle.[16]

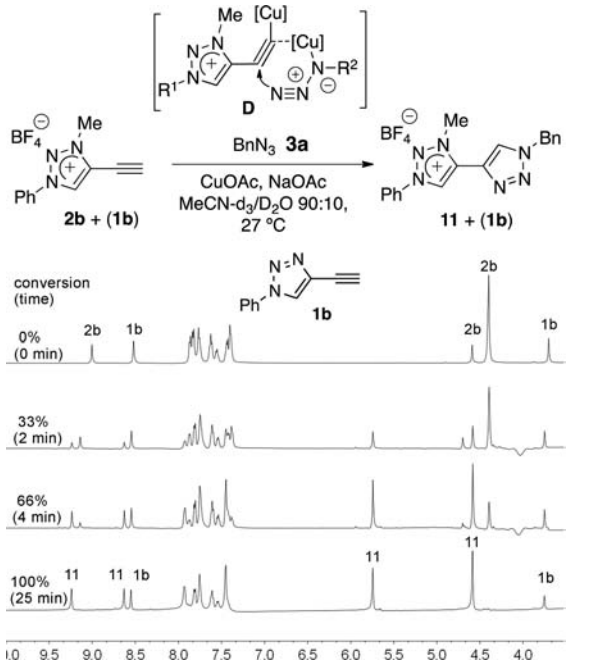

Figure 3. ^{1}H NMR (500 MHz, MeCN-d_3/D$_2$O 10:1, 27 °C) spectra for the competition reaction of benzyl azide **3a** with the cationic alkyne **2b** in the presence of the noncharged alkyne **1b**.

Indeed, when the reaction of an equimolar mixture of alkynes **2b** and **1b** and benzyl azide **3a** was catalyzed by 20 mol % of CuOAc/NaOAc, a totally chemoselective transformation occurred to give exclusively the adduct **11**, leaving the alkyne **1b** unchanged.[11] When the transformation was monitored by ^{1}H NMR from initial 35 mM solutions of the reagents at 27 °C, the conversion was complete in few minutes (SI, Figure S7).

Finally, the preparative scope of the methodology was checked for different azides. As shown in Table 3, "ultrafast" click reactions of triazolium alkynes were very efficient under the standard Sharpless conditions using 20 mol % CuSO$_4$/sodium ascorbate catalyst (entry 1). In addition, the metal load could be further reduced to 1 mol % without compromising the reaction performance using CuOAc as catalysts in the presence of 2 equiv of NaOAc.[16b] The scope of the reaction included standard aliphatic azides (entry 1) and also poorly reactive aromatic azides with electron-withdrawing groups (see entries 4 and 6). The reaction also worked efficiently for strongly hindered aromatic azides (see entries 7 and 8) and was tolerant with functionalized aliphatic azides (entries 9 and 10). Overall, this alkyne-activated reaction proved highly efficient and suitable to complement alternative "ultrafast" CuAAC approaches based on copper-chelating pyridyl azides.[17]

In conclusion, we have described a novel family of *N*-methyl-1,2,3-triazolium cationic alkynes **2** displaying a very particular combination of electronic activation and punctual steric hindrance, both provided by the *N*-methylation of 4-alkynyl-1,2,3-triazoles. We have also studied their [3 + 2] cycloaddition reaction with azides unveiling the mechanistic details underlying the simultaneous torquoselective-like[18] 1,4-activation and 1,5-deactivation through the corresponding transition states. This has permitted the development of a general, mild, and very 1,4-regioselective version of the Huisgen reaction. Cationic alkynes **2** have also been found to strongly accelerate the copper-catalyzed reaction with azides providing unprecedented "ultrafast" CuAAC reactions that complete in very short

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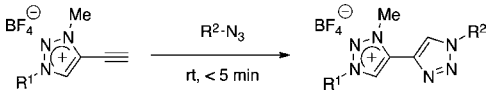
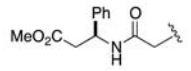
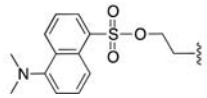
Table 3. "Ultrafast" CuAAC Reaction of Cationic Triazolium Alkynes with Azides Promoted by Cu(I) Sources



entry	R^1	azide	R^2	cat.[a]	prod[b]
1	4-NC-C_4H_6	**3a**	Bn	A	**5** (73)
2	Ph	**3a**	Bn	B	**11** (89)
3	Bn	**3c**	Ph	A	**12** (83)
4	Ph	**3f**	4-NO_2-C_6H_4	B	**13** (78)
5	Ph	**3b**	4-MeO-C_6H_4	B	**14** (84)
6	Ph	**3d**	4-F-C_6H_4	A	**15** (63)
7	Ph	**3g**	2,6(*i*-Pr)$_2$$C_6H_3$	A	**16** (66)
8	Ph	**3h**	2,4,6(Me)$_3$$C_6H_2$	A	**17** (64)
9	Ph	**3i**		A	**18** (70)
10	Ph	**3j**		B	**19** (82)

[a]Key: (A) $CuSO_4$ (20 mol %)/sodium ascorbate in THF/*t*-BuOH/H_2O; (B) CuOAc (1 mol %)/NaOAc (200 mol %) in MeCN/H_2O. [b]Yield of isolated pure product.

reaction times (<5 min) and proceed with complete chemoselectivity in the presence of ordinary noncharged alkynes. Further studies are being conducted in our laboratory to extend the reactivity of cationic triazolium alkynes to other 1,3-dipoles and nucleophiles.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00055.

Preparation procedures; NMR spectra of compounds **1d**, **2b,d**, and **4**−**19**; determination of reaction rate constants and activation parameters, computational geometries, energies and fragment analysis for transition states TS-$\mathbf{4}_{1,4}$, TS-$\mathbf{4}_{1,5}$, TS-$\mathbf{5}_{1,4}$ and TS-$\mathbf{5}_{1,5}$ (PDF)

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Notes

The authors declare no competing financial interest.

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