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$Ln[N(SiMe_3)_2]_3$-catalyzed cycloaddition of terminal alkynes to azides leading to 1,5-disubstituted 1,2,3-triazoles: new mechanistic features†‡

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The first example of rare earth metal-catalyzed cycloaddition of terminal alkynes to azides resulting in the formation of 1,5-disubstituted 1,2,3-triazoles is described. Preliminary studies revealed that the present cycloaddition shows unprecedented mechanistic features involving a tandem anionic cascade cyclization and *anti*-addition across the C≡C triple bond.

The development of synthetic methods for the construction of substituted 1,2,3-triazoles has been of longstanding importance in organic chemistry[1,2] because of the frequent existence of such structures in biologically active molecules,[3] natural products[4] and designed materials[1d,5] as well as their role as synthetic intermediates[6] and ligands.[7] Among them the cycloaddition of alkynes with azides is an exceedingly attractive method for the construction of 1,2,3-triazole derivatives in a highly atom economical manner.[1] Furthermore, the reaction also provides a simple method for labeling oligonucleotides with fluorescent dyes, sugars, peptides and other reporter groups, probing the binding landscapes of biological molecules, and modifying DNA.[8] Much attention has been paid to the development of the catalytic systems for such cycloadditions in the last decade. The pioneering studies show that copper[6a,9] and silver[10] can effect the catalytic cycloaddition of terminal alkynes to azides in the presence of a base or acid, forming 1,4-disubstituted 1,2,3-triazoles regioselectively. In contrast, there are as yet few satisfactory catalytic systems for the regioselective formation of 1,5-disubstituted 1,2,3-triazoles. Typical synthetic routes to the corresponding 1,5-disubstituted regioisomers employ the reaction of azides with the *in situ* generated sodium, lithium, or magnesium acetylides.[1e,11] However, these synthetic approaches suffer some disadvantages, such as the required use of stoichiometric or even large excess amounts of strong bases and the problem of generating waste. Although a few reports of the metal-catalyzed version that forms regioselectively 1,5-disubstituted 1,2,3-triazoles have appeared recently, all the reactions require the use of expensive ruthenium complexes as catalysts.[2a,12] Very recently, Fokin *et al.* reported the first base-catalyzed cycloaddition of terminal alkynes and azides, which provides access to 1,5-diaryl-substituted triazoles.[13] Nevertheless, the reaction is limited to aryl acetylenes and aryl azides. Therefore, there still exists a need for the development of new and mild methods for obtaining 1,5-disubstituted 1,2,3-triazoles under conditions tolerated by sensitive functional groups.

Despite significant advances in activation of C–H bonds,[14] there has been no precedent for the formation of heterocycles by organolanthanide-catalyzed tandem insertion of unsaturated C–C and heteroatom-containing functional groups into the C–H bond. Heteroatoms often coordinate more strongly to rare earth metals than alkenes (alkynes) and inhibit such catalytic turnover. On the other hand, an important challenge during organolanthanide-catalyzed intramolecular addition–cyclization reaction of unsaturated substrates remains the versatile control of the regioselectivity, in which exocyclic products resulting from *syn*-addition are generally obtained.[15] Our continuous interest in organolanthanide-catalyzed transformations of alkynes[16] prompted us to explore the possibility of using a combination of tandem inter- and intramolecular insertion into the lanthanide–ligand bond and the C–H bond activation as key steps for the catalytic cycloaddition of alkynes with azides. Herein, we report the results.

We initiated our research on the model reaction of benzyl azide with phenylacetylene under different reaction conditions (Table 1). 1,5-Disubstituted 1,2,3-triazole (**3aa**) was obtained in 75% isolated yield upon treatment of a 1 : 1 mixture of **1a** and **2a** with 5 mol% $Sm[N(SiMe_3)_2]_3$ in toluene at 50 °C (entry 2). The structure of **3aa** was confirmed by X-ray diffraction analysis.[12a] Screening of the solvents gave toluene as the solvent of choice (entries 2 and 5–10). Examination of different rare earth metal catalysts revealed $Sm[N(SiMe_3)_2]_3$ as the best catalyst (entries 2 and 11–13). As observed in the previous reports,[16b,17] the presence of 10 mol% $^nBuNH_2$ could improve the yield (entry 14).

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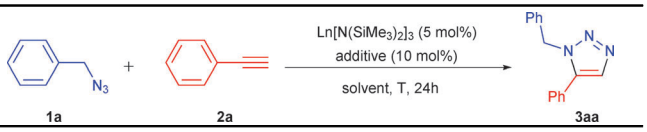
Table 1 Optimization of the reaction conditions[a]



Entry	Ln	Solvent	T/°C	Additive	Yield[b] (%)
1	Sm	Toluene	25		64 (59)
2	Sm	Toluene	50		80 (75)[c]
3	Sm	Toluene	75		74 (66)
4	Sm	Toluene	Reflux		63
5	Sm	THF	50		54
6	Sm	DMF	50		34
7	Sm	DMSO	50		35
8	Sm	CH_3CN	50		35
9	Sm	DCE	50		37
10	Sm	Hexane	50		42
11	Nd	Toluene	50		73 (65)
12	Y	Toluene	50		67 (61)
13	Gd	Toluene	50		68 (60)
14	Sm	Toluene	50	^{n}BuNH$_2$	88 (82)[c]
15	Sm	Toluene	50	PhNH$_2$	47 (40)
16	Sm	Toluene	50	^{i}Pr$_2$NH	73 (65)
17	Sm	Toluene	50	Et$_3$N	48 (40)
18[d]	Sm	Toluene	50	^{n}BuNH$_2$	91 (85)

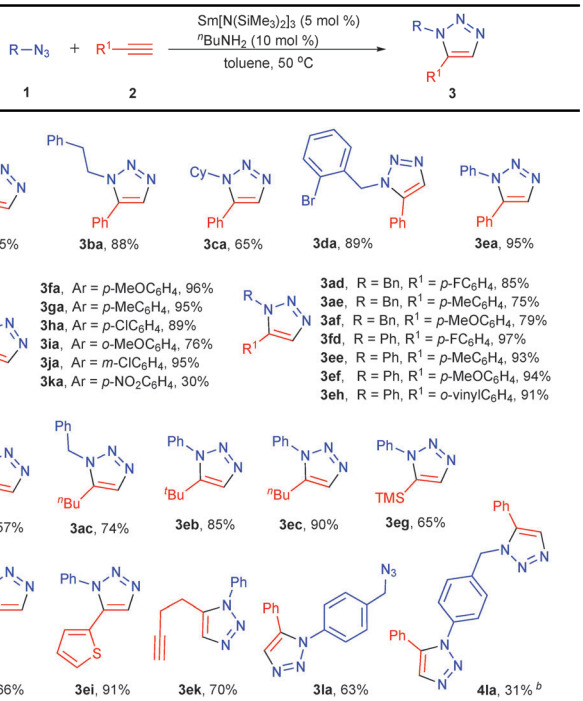
[a] **1a** (0.2 mmol), **2a** (0.2 mmol), catalyst (0.01 mmol), additive (10 mol%), solvent (1 mL) for 24 h under N_2. [b] Yield determined using GC-MS with isopropylbenzene as an internal standard, and isolated yields in parentheses. [c] Average of three runs. [d] 0.24 mmol of **2a** was used.

Different azides and alkynes were then applied to evaluate the reaction substrate scope. As shown in Table 2, the protocol is effective for the transformation of a number of different substrate combinations. Aryl azides (**1e–1j**) are more reactive than alkyl azides (**1a–1d**), which might be attributed to the fact that the aryl ring is favorable to the delocalization of negative charge to its neighboring N atom by conjugation, leading to the strengthening nucleophilicity of the N atom in the cyclization process. The reaction was hardly affected by non-coordinated substituents at the *para* position of aromatic azides (**1f–1h**). However, *o*-methoxyphenyl azide (**1i**) produced **3ia** in moderate yield, which might be a consequence of the chelating coordination capable of increasing the kinetic inertness and thermodynamical stability of the Ln–N bond. In addition, the competing coordination of nitro to the metal led to the decrease in yield (**3ka**) too. Similarly, the strong chelating coordination of the pyridyl group reduces the reactivity of alkyne (**2j**).

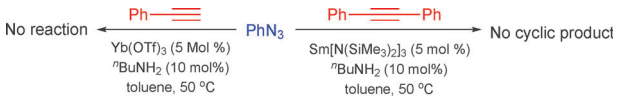
In contrast to the observation in the base-catalytic system,[13] aliphatic azides (**1a–1d**) and aliphatic alkynes (**2b**, **2c**, **2g**, **2k**) worked well under the current conditions, affording the corresponding triazoles (**3aa–3af**, **3ba–3da**, **3eb**, **3ec**, **3eg** and **3ek**) in moderate to excellent yields. 1-Azido-4-(azidomethyl)benzene gave the mono- and dicyclization products **3la** and **4la**, respectively, depending on the stoichiometric ratio. However, reaction of hexa-1,5-diyne (**2k**) with **1e** afforded only the monocyclization product **3ek** as the main product.

All the previously reported metal-catalyzed cycloadditions of azides with alkynes proceeded through a sequential oxidative-coupling–reductive-cyclization pathway.[9,12] Obviously, the present cycloaddition is likely to operate through another mechanistic pathway. To gain a better understanding of how the cyclization occurs under these conditions, we examined the reaction of PhC≡CPh with PhN_3 in the presence of Sm[N(SiMe$_3$)$_2$]$_3$, indicating that no cycloaddition product was formed. In addition,

Table 2 Sm[N(SiMe$_3$)$_2$]$_3$-catalyzed cycloaddition of terminal alkynes with azides[a]



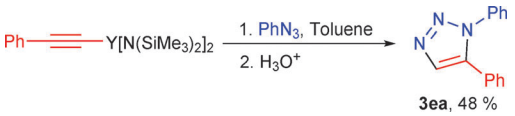
[a] **1** (0.4 mmol), **2** (0.48 mmol), Sm[N(SiMe$_3$)$_2$]$_3$ (0.02 mmol), ^{n}BuNH$_2$ (10 mol%), toluene (2 mL) for 24 h at 50 °C under N_2, isolated yield of **3**. [b] 2.4 equiv. of **2a** was used.



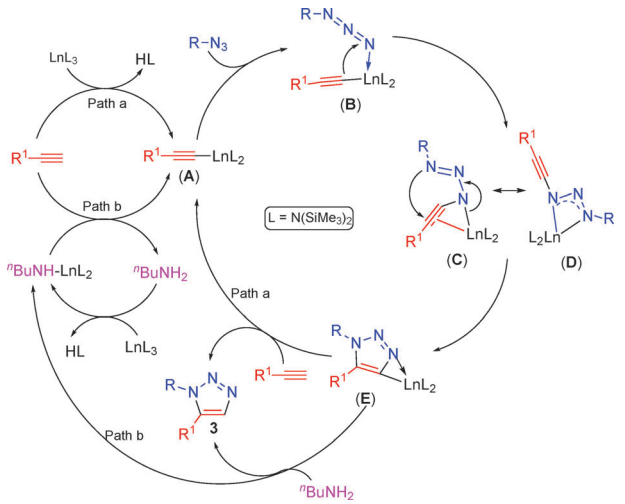
Scheme 1 The role of lanthanide acetylides as a reaction trigger.

attempts to catalyze cycloaddition of **1e** to **2a** using Yb(OTf)$_3$ were unsuccessful (Scheme 1). However, (PhC≡C)Y[N(SiMe$_3$)$_2$]$_2$ could undergo the cyclization with **1e**, giving the hydrolysis product **3ea** in 48% yield (Scheme 2). These results suggest that the formation of the acetylide complex intermediate should be involved in the reaction and play an important role in both determining the reactivity trend of alkynes and controlling selectivity.

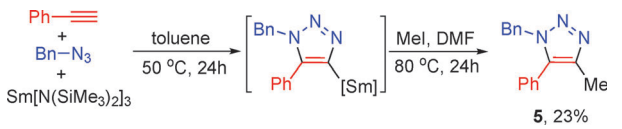
Based on the results described above, a plausible reaction pathway for Ln[N(SiMe$_3$)$_2$]$_3$-catalyzed cycloaddition of terminal alkynes to azides is shown in Scheme 3. Terminal alkyne C–H bond activation leads to the formation of lanthanide acetylide (**A**) together with liberation of HN(SiMe$_3$)$_2$. Coordination and subsequent 1,1-insertion of azide into the Ln–C bond of **A** gives the key intermediates (**C** and **D**).[18] Subsequently, the intramolecular anti-nucleophilic attack of the far N atom to the π-coordinated alkyne moiety would lead to the formation of triazolate complex (**E**). Finally, protonation of **E** with another alkyne affords **3** and regenerates **A** (Path a). Alternatively, the catalytic cycle might be carried out *via* Path b.



Scheme 2 Cyclization of yttrium acetylide with phenyl azide.



Scheme 3 Proposed mechanism.



Scheme 4 Trapping of the triazolate samarium intermediate by MeI.

Since amines can act as proton sources to abstract the resulting triazolate ligand and as suitable ligands to activate the catalyst in the catalytic cycle,[16b,17] the presence of amine additives would be favorable to the cycloaddition.

Consistent with this, the treatment of a 1 : 1 mixture of **1a** and **2a** with one equivalent of $Sm[N(SiMe_3)_2]_3$ followed by reacting with MeI gave the expected product **5** in 23% yield (Scheme 4).

In conclusion, the $Ln[N(SiMe_3)_2]_3$-catalyzed cycloaddition of terminal alkynes with azides is an ideal addition to the family of click reactions. The process exhibits broad scope, readily available catalyst and mild conditions, and provides 1,5-disubstituted 1,2,3-triazoles in moderate to excellent yields. Furthermore, the present catalytic system not only differentiates between internal and terminal alkynes but also shows unprecedented mechanistic features involving a tandem anionic cascade cyclization reaction and *anti*-addition across the C≡C triple bond. Quite generally, organolanthanide-catalyzed intramolecular hydroelementation reactions produce exclusively the exocyclic hydroamination products resulting from *syn*-addition.[15] We believe that the present 5-*endo* cyclization pattern seems to indicate the untapped potential of organolanthanide catalysis, and would have a great impact on the regioselectivity control of lanthanide-mediated intramolecular additions. Further investigations regarding the mechanism and synthetic applications are in progress.

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