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Insertion Reactions

$Ln[N(SiMe_3)_2]_3$-Catalyzed Cross-Diinsertion of C≡N/C≡C into an N–H Bond: Facile Synthesis of 1,2,4-Trisubstituted Imidazoles from Propargylamines and Nitriles

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Abstract: A lanthanide-catalyzed sequential insertion of C≡N and C≡C into an N–H bond is presented. The convenient reaction, which proceeds under mild conditions, is an efficient method for preparing 1,2,4-trisubstituted imidazoles directly from readily available propargylamines and nitriles.

N–H bonds are common in natural and synthetic organic compounds. The addition of N–H bonds across unsaturated C–C and carbon–heteroatom functional groups represents an efficient, atom-economical, and desirable route to nitrogen-containing organic compounds, which are important for a variety of applications.[1] Lanthanide catalysis has played an important role in the development of many of these processes owing to the high levels of activity that are observed in the absence of base or accelerating ligand and their ability to generate unprecedented types of reactivity.[1b,2,3] In addition to the development of efficient and selective catalysts for this highly valuable but challenging transformation, considerable recent interest has focused on the design of related tandem or sequential reactions for the efficient construction of complex molecules. The elegant work of the research groups of Marks and Molander involving lanthanide-catalyzed intramolecular multiple insertion of alkenes or alkynes into an N–H bond allows facile access to bi- and tricyclic azacycles.[4] Furthermore, lanthanide-catalyzed intra- and intermolecular cross-diinsertion reactions of an alkene and an alkyne into an N–H bond has also been studied.[5]

Apart from the above investigations, the lanthanide-catalyzed sequential insertion of alkenes (alkynes) and other polar unsaturated functional groups into N–H bonds has remained unexplored to date, despite such tandem reactions being expected to have synthetic potential. The major reason for this paucity can be attributed to the difficulties encountered in controlling required selectivity and to the incompatibility of cross insertion of polar functional groups with non-polar groups.[6] Heteroatoms often coordinate more strongly to rare earth metals than alkenes (alkynes), thus inhibiting catalytic turnover.

Substituted imidazoles are important structural components of a vast array of naturally occurring and pharmacologically active molecules.[7] They can also serve as intermediates for the synthesis of many important drugs,[8] heterocyclic ligands,[9] or precursors for materials with interesting properties.[10] In this connection, the limitations of traditional synthetic methodology for preparing heterocycles have stimulated considerable interest in developing new, efficient homogeneous catalytic methods for the synthesis of such compounds.[11] Among many synthetic strategies developed, the preparation of imidazoles directly from alkynes and nitriles is especially attractive because a large number of these starting materials are commercially available or readily prepared. Recently, Xie and Shen found that titanacarborane amide can catalyze the cycloaddition of nitriles with propargylamines to form imidazoles.[12] However, for terminal alkynes and secondary amines, the procedure generally suffers from low yields and poor reactivity, probably owing to competing alkynylation and steric effects, respectively. Given the fact that larger rare earth metals often coordinate more strongly to the amido ligand than titanium, but bind more weakly to alkyl/alkynyl groups than titanium, we were interested in establishing whether the replacement of titanium with rare earth metals would inhibit the terminal alkyne from quenching the M–C/N bond and be compatible with sterically demanding disubstituted amines. Herein, we describe a new catalytic system with wide reactant scope for the tandem amidination/hydroamination/cyclization reaction of propargylamines and nitriles.

Considering that $Ln[N(SiMe_3)_2]_3$ could serve as readily available, inexpensive, and highly versatile reagents for catalytic N–H and C–H bond functionalizations,[3g–i,13,14] we initiated our research on the model reaction of benzonitrile **1a** with propargylamine **2a** by using $Ln[N(SiMe_3)_2]_3$ as the precatalyst (Table 1). By screening reaction conditions, it was found that the sequential amidination/cyclization reaction of propargylamines with nitriles can be catalyzed by $Sm[N(SiMe_3)_2]_3$ at 60 °C (**1a**/**2a** = 1:1.2) to give **3aa** in 93% yield (Table 1, entry 15). Elevating or decreasing the reaction temperature resulted in lower yields of product (Table 1, entries 6–9). THF was found to

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Table 1. Optimization of reactions conditions for the preparation of imidazoles.[a]

1a 2a 3aa

Entry	Ln	Solvent	*T* [°C]	*t* [h]	Yield [%][b]
1	La	toluene	RT	24	9
2	Sm	toluene	RT	24	51
3	Nd	toluene	RT	24	22
4	Gd	toluene	RT	24	4
5	Y	toluene	RT	24	29
6	Sm	toluene	40	24	68
7	Sm	toluene	60	24	70
8	Sm	toluene	80	24	53
9	Sm	toluene	100	24	43
10	Sm	toluene	60	36	79
11	Sm	THF	60	24	84
12	Sm	hexane	60	24	–
13	Sm	DCE	60	24	–
14	Sm	DMF	60	24	–
15[c]	Sm	THF	60	24	93
16	$SmCl_3$	THF	60	24	–
17	$Sm(OTf)_3$	THF	60	24	–

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), catalyst (0.01 mmol), solvent (1 mL), under N_2. [b] Yield of isolated product. [c] 1.2 equiv of **2a** was used.

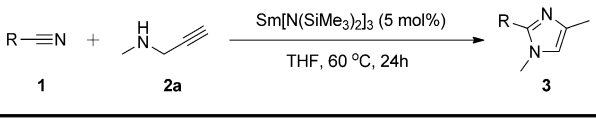
be the solvent of choice (Table 1, entries 10–14). The use of other rare earth metal sources such as $SmCl_3$ or $Sm(OTf)_3$ was ineffective (Table 1, entries 16 and 17). In addition, the reaction proceeds in a 5-*exo*-dig fashion; no product derived from a 6-*endo*-dig cyclization was observed, indicating excellent regioselectivity.

With optimized conditions established for the cyclization of **1a** with **2a**, we proceeded to explore different substrate combinations, as shown in Table 2. In general, the presence of strong coordinating atoms on nitriles led to lower yields because the Lewis basic sites of such starting materials can coordinate preferentially to the highly Lewis acidic lanthanide ions, thus precluding η^2-coordination of alkynes and the migratory insertion processes necessary for cyclization. For example, reaction of **1a** with aromatic nitrile **1e**, which contains a methoxy group on the aromatic ring, gave **3ea** in moderate yield, while the use of 4-nitrobenzonitrile (**1f**) was ineffective. Similarly, 2-cyanothiophene (**1i**) gave an inferior result for the preparation of **3ia**. The trend is quite a contrast to that previously observation.[6] Notably, the position of a methyl group on the aromatic ring has an effect. For example, a benzylnitrile with a methyl at the *ortho* position (**1n**) gave expected product **3na** in a lower yield than the conversion of substrate **1k**, which bears a *tert*-butyl at the *para*-position, to give **3ka**, probably owing to a steric effect. Nevertheless, this method is applicable to most aliphatic nitriles.

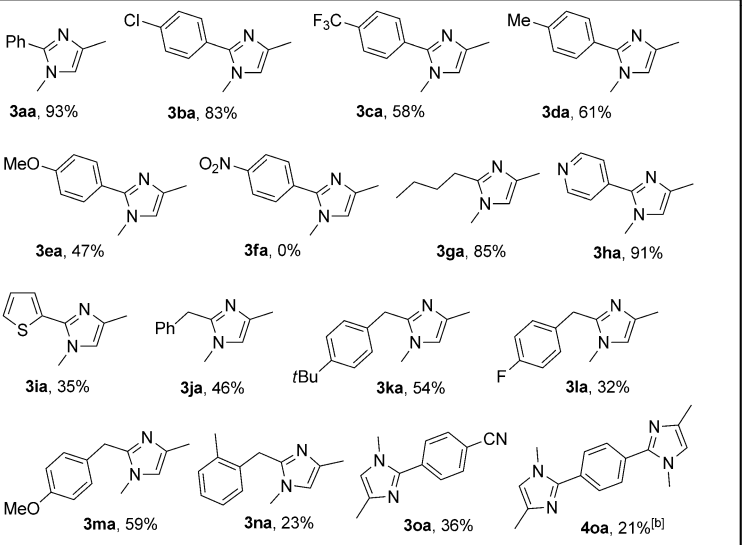
To our delight, the catalytic system is effective for the transformation of a number of terminal alkynes. For example, reaction of **2a** with **1a** and **1b** provided the desired products **3aa** and **3ba** in 93% and 83% yields, respectively. In contrast, these transformations in the Ti-based catalytic system provided the products in only 20–21% yield, even with a longer reaction time and a higher reaction temperature.[12] This difference may be attributed to the stronger Lewis acidity of Sm compared to Ti, thus preventing the terminal alkyne from quenching the metal–carbon/nitrogen bond.

The use of various propargylamines was also examined (Table 3). Propargylamines with an internal/terminal C≡C bond are all compatible with this reaction. Arylalkynes are more reactive than alkylalkynes, presumably because aryl substituents facilitate the coordination of the alkyne moiety to the catalyst through their weak interaction with the metal center,[15] thus offering higher yields of products (**3ak** versus **3ah**–**aj**). Surprisingly, when the optimized conditions were applied to the cyclization of *N*-phenyl propargylamine (**2d**) in an attempt to prepare *N*-phenyl imidazole (**3ad**), the reaction did not go to completion. When $Yb[N(SiMe_3)_2]_3$ was used as catalyst and the reaction temperature raised to 140 °C, with xylene as the solvent, **3ad** was obtained together with significant amounts of amidine intermediates (Scheme 1). The sluggishness of this reaction likely results from steric hindrance of the aryl group and the increasing acidity of *N*-aryl propargylamines compared with *N*-alkyl propargylamines, thus leading to a preference for amidinate abstraction over alkyne insertion. Simply switching the catalyst to $Y[N(SiMe_3)_2]_3$ provided desired compounds **3** in decent yields (Table 3, **3ad**–**af**). In addition, this catalytic proto-

Table 2. Nitrile scope.[a]

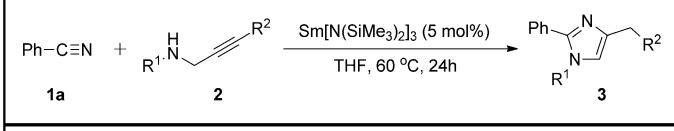


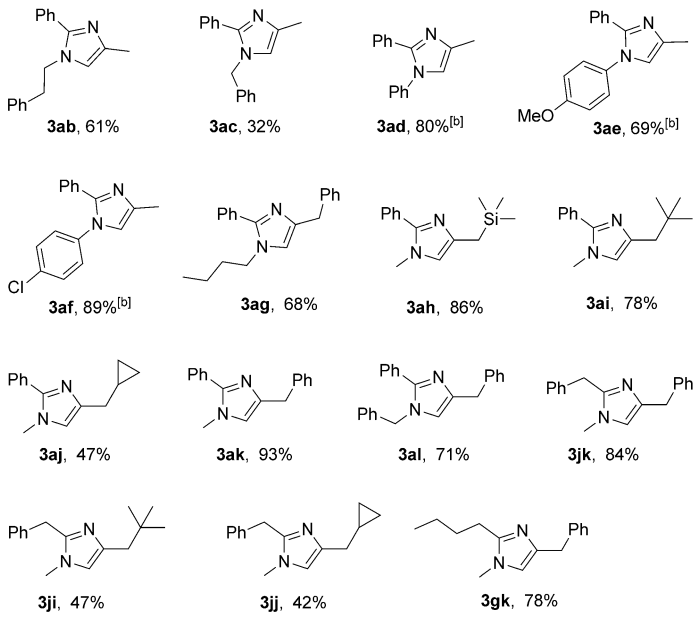
1 2a 3



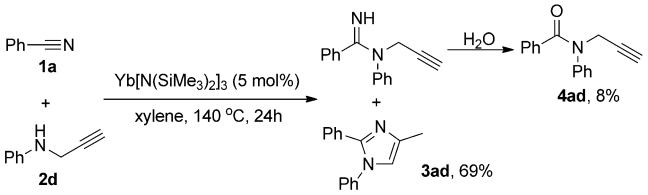
[a] Reaction conditions: **1** (0.4 mmol), **2a** (0.48 mmol), $Sm[N(SiMe_3)_2]_3$ (0.02 mmol), THF (2 mL) under N_2, yield of isolated product. [b] 3 equiv of **2a** was used.

Table 3. Propargylamine scope.[a]





[a] Reaction conditions: **1** (0.4 mmol), **2** (0.48 mmol), $Sm[N(SiMe_3)_2]_3$ (0.02 mmol), THF (2 mL), under N_2, isolated yield. [b] Reaction was carried out at 140 °C under N_2, using xylene as the solvent, $Y[N(SiMe_3)_2]_3$ as catalyst, and 1.5 equiv of propargylamine was used.



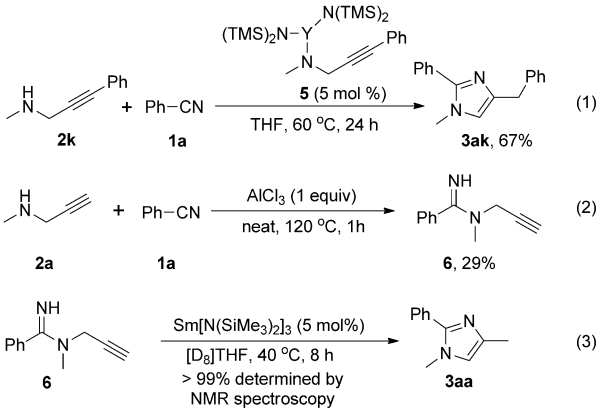
Scheme 1. Tandem cyclization of *N*-phenyl propargylamine.

col also allow the efficient cyclization of substrates bearing a silyl and cyclopropyl groups at another alkyne terminus. Compound **3ak** was further confirmed by single-crystal X-ray analyses as shown in Figure 1.

To shed light on the mechanism of the reaction, the following experiments were conducted. Firstly, propargylamido yttrium complex **5**, generated in situ from $[(TMS)_2N]_2YCl$ and propargyl sodium, was used to catalyze the cyclization of **1a** with **2k**; the yield of **3ak** was 67%, as determined using GC [Eq. (1)]. This result suggests that initial protonation of the catalyst with **2k** to form a propargylamido-yttrium intermediate might be involved. In another experiment, *N*-methyl-*N*-(propargyl)benzimidamide (**6**) was synthesized by the literature method (equation 2).[16] Subsequent cyclization was performed under the aforementioned conditions, giving the desired product in almost quantitative yield (determined by using NMR spectroscopy; equation 3). Moreover, the amidine intermediate was also observed in the reaction of **1a** with **2d** (Scheme 1). These results are in accordance with an amidinate complex being a reactive intermediate.

In order to draw more support for a mechanism, we carried out the reaction with the *N*-deuterated propargylamine [D]-**2k**. Under the aforementioned conditions, reaction of **1a** with [D]-**2k** gave the deuterated product [D]-**3ak**, enriched at the benzylic position with >92% D, in 78% yield (Scheme 2). This result clearly indicates that the C–C double bond isomerization takes place after protonation (Scheme 3, route A) rather than before protonation (route B).

Based on the results described above, a reasonable pathway for the cyclization of propargylamines with nitriles described herein is shown in Scheme 4. Activation of the N–H bond leads to the formation of a lanthanide-amido complex (**A**) together with the liberation of $HN(SiMe_3)_2$. Coordination and sequential insertion of one nitrile into the Ln–N bond of **A** gives a key lanthanide-amidinate intermediate (**B**). Subsequently, the intramolecular addition of C≡C bond to the Ln–N bond of **B** leads to cyclization, affording vinyl complex **C**. Then, predominant protonation of **C** with another propargylamine affords cyclization intermediate **D** and regenerates active intermediate **A**. Finally, double-bond migration of **D** results in the formation of the imidazole product **3**. Examples of insertions of unsaturated functional groups into the lanthanide–amidinate linkage are rare.[17] To our knowledge, the present work represents the first example of alkyne insertion into a lanthanide-amidinate linkage.



In summary, we have demonstrated a $Ln[N(SiMe_3)_2]_3$-catalyzed cyclization of a range of nitriles with propargylamines, thus significantly expanding the scope of such transformations. The reactions proceeded smoothly with excellent regioselectivity, providing convenient access to 1,2,4-trisubstituted imidazoles, which are difficult to synthesize by other means. This lanthanide-mediated tandem insertion of C≡N and C≡C bonds

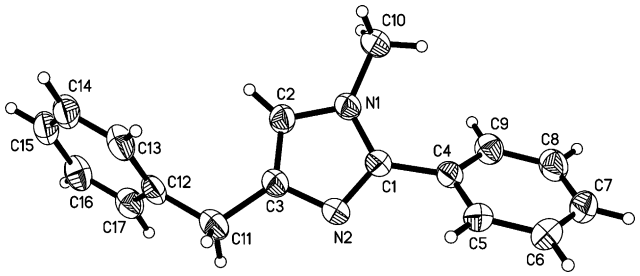
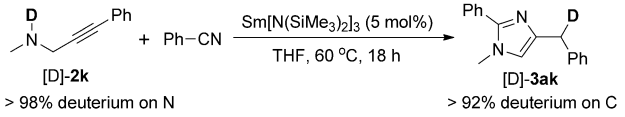
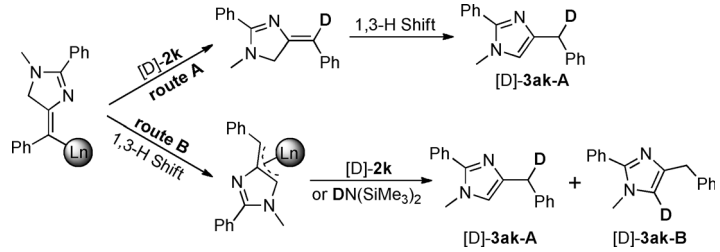


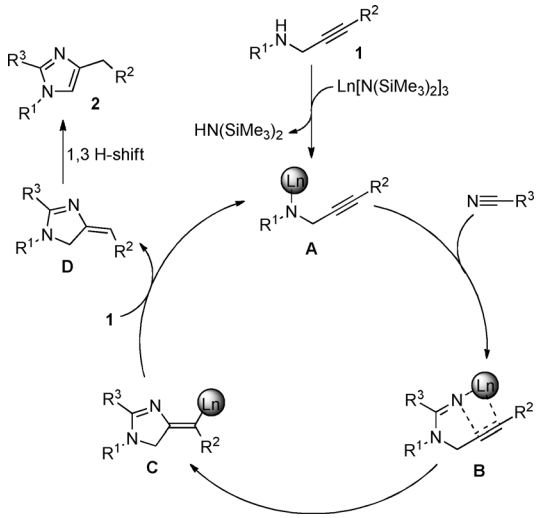
Figure 1. ORTEP drawing of **3ak**. Selected bond length [Å]: C1–N1 1.354(3), C1–N2 1.323(3), C2–N1 1.377(3), C2–C3 1.347(4), C3–C11 1.506(4), C3–N2 1.374(3).



Scheme 2. Deuterium-labeling experiment.



Scheme 3. Hypothetical routes for aromatization.



Scheme 4. Possible mechanism for lanthanide-catalyzed tandem addition/cyclization of propargylamines and nitriles.

into an N–H bond should lead to the development of new applications of lanthanides in organic synthesis. Further development of this methodology is currently under way in our laboratory.

Experimental Section

General procedure

In a glovebox, $Sm[N(SiMe_3)_2]_3$ (12.6 mg, 0.02 mmol) and THF (2 mL) were added to a Schlenk tube equipped with a magnetic stirring bar and a Teflon cap. The sealed reaction tube was taken out of the glovebox, and the progargylamine (0.48 mmol) and nitrile (0.4 mmol) were added under a N_2 atmosphere. Then, the reaction mixture within the sealed Schlenk tube was stirred in an oil bath at 60 °C. After completion of the reaction, as indicated by GC-MS analysis, the mixture was quenched with water (2 mL) and the resulting solution was extracted with ethyl acetate (3×5 mL). The organic layers were combined and dried over sodium sulfate. The pure 1,2,4-trisubstituted imidazole product was obtained by flash column chromatography on silica gel with ethyl acetate/hexane (1:1 to 3:1).

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Keywords: C–C coupling · imidazoles · nitriles · lanthanides · propargylamines

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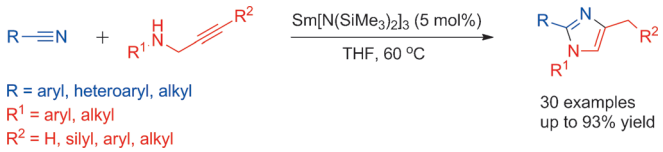
$Ln[N(SiMe_3)_2]_3$-Catalyzed Cross-Diinsertion of C≡N/C≡C into an N–H Bond: Facile Synthesis of 1,2,4-Trisubstituted Imidazoles from Propargylamines and Nitriles



Cross-diinsertion: Sequential insertion of C≡N and C≡C bonds into an N–H bond can be effected using a lanthanide catalyst (see scheme). The method efficient gives direct access to 1,2,4-trisubstituted imidazoles from readily available nitriles and propargylamines.