Homogeneous Catalysis

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Synthesis of (*Z*)-1-Aza-1,3-enynes by the Cross-Coupling of Terminal Alkynes with Isocyanides Catalyzed by Rare-Earth Metal Complexes**

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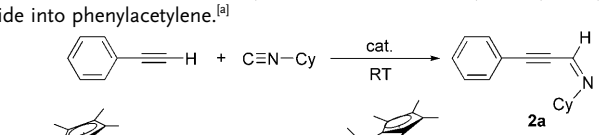
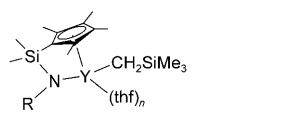
The 1,1-insertion of isocyanides into the C–H bond of terminal alkynes is a straightforward, atom economical route to conjugated 1-aza-1,3-enynes (RC≡C-CH=NR′), which are compounds that are bifunctional (a basic nitrogen center found in the C=N bond and a C≡C bond) and are useful synthons in organic synthesis.[1–3] However, very few catalysts are known to promote the catalytic coupling reaction of isocyanides with terminal alkynes,[1] whereas stoichiometric insertion of isocyanides into a metal–acetylide bond is well documented.[2] In 2004, Eisen and co-workers reported the first catalytic coupling of isocyanides with terminal alkynes catalyzed by actinide metallocene complexes, which afforded the corresponding (*E*)-1-aza-1,3-enynes as a major product together with alkyne oligomerization products and double-insertion products.[1a,d] Takaki and co-workers found that rare-earth silylamides, such as $[Ln\{N(SiMe_3)_2\}_3]$ (Ln = Y, La, Sm, Yb), could also catalyze the cross-coupling of isocyanides with terminal alkynes in the presence of amine additives to yield a mixture of *E* and *Z* isomers of 1-aza-1,3-enynes.[1b,c] As far as we are aware, selective formation of (*Z*)-1-aza-1,3-enynes in the reaction of terminal alkynes with isocyanides has not been reported previously. The search for new catalysts for the efficient and selective cross-coupling reaction of terminal alkynes and isocyanides is therefore of interest and importance.

We recently found that half-sandwich rare-earth metal alkyl complexes bearing a silylene-linked cyclopentadienylamido ligand[4] served as efficient catalysts for the catalytic dimerization of terminal alkynes to give the corresponding *Z* enynes.[4c,5] They also worked for the catalytic addition of terminal alkyne C–H, amine N–H, and phosphine P–H bonds to carbodiimides to give the corresponding propiolamidines,[4a,6a] guanidines,[4a,6b,c] and phosphaguanidines,[4a,6d,e] respectively. We report herein that such half-sandwich rare-earth metal complexes can also serve as excellent catalysts for the cross-coupling of isocyanides with terminal alkynes to give an unprecedented selective formation of (*Z*)-1-aza-1,3-enynes. Mechanistic aspects of this catalytic process are also described.

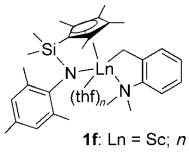
As a control experiment, a 1:1 mixture of cyclohexyl isocyanide and phenylacetylene in $[D_6]$benzene was stirred at room temperature or 90 °C for 12 hours, but no coupling product was observed.[7] In contrast, in the presence of a small amount of a half-sandwich rare-earth metal alkyl complex, a rapid cross-coupling reaction took place at room temperature to give the corresponding (*Z*)-1-aza-1,3-enyne product **2a** (Table 1). Benzene or toluene seemed to be better as solvents relative to THF (Table 1, entries 2–4). Among the rare-earth

Table 1: Rare-earth-metal-catalyzed monoinsertion of cyclohexyl isocyanide into phenylacetylene.[a]





1a: Ln = Y; R = Ph; *n* = 2
1b: Ln = Y; R = $C_6H_2Me_3$-2,4,6; *n* = 1
1c: Ln = Y; R = *t*Bu; *n* = 1
1d: Ln = Yb; R = Ph; *n* = 2
1e: Ln = Lu; R = Ph; *n* = 2



1f: Ln = Sc; *n* = 0
1g: Ln = Y; *n* = 1
1h: Ln = Sm; *n* = 1
1i: Ln = Nd; *n* = 1
1j: Ln = La; *n* = 1

Entry	Cat. (Ln, mol%)	Solvent	*t* [h]	Yield of **2a** [%][b]
1	0	$[D_6]$benzene	12	0
2	**1a** (Y, 2)	$[D_6]$benzene	0.5	80
3	**1a** (Y, 2)	$[D_8]$THF	4	41
4	**1a** (Y, 2)	$[D_8]$toluene	0.5	79
5	**1a** (Y, 1)	$[D_6]$benzene	2	>99
6	**1a** (Y, 0.5)	$[D_6]$benzene	5	98
7	**1b** (Y, 2)	$[D_6]$benzene	0.5	80
8	**1c** (Y, 2)	$[D_6]$benzene	0.5	79
9	**1d** (Yb, 2)	$[D_6]$benzene	0.5	48
10	**1e** (Lu, 2)	$[D_6]$benzene	0.5	42
11	**1f** (Sc, 2)	$[D_6]$benzene	2	0
12	**1g** (Y, 2)	$[D_6]$benzene	0.5	80
13	**1h** (Sm, 2)	$[D_6]$benzene	0.5	66
14	**1i** (Nd, 2)	$[D_6]$benzene	0.5	64
15	**1j** (La, 2)	$[D_6]$benzene	0.5	50

[a] Conditions: phenylacetylene (0.50 mmol), cyclohexyl isocyanide (0.50 mmol). [b] Conversion determined by ^{1}H NMR analysis. Cy = cyclohexyl.

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Supporting information for this article is available (experimental details, X-ray crystallographic data, and scanned NMR spectra of all new products) on the WWW under http://dx.doi.org/10.1002/anie.200804306. CCDC 699801 and CCDC 699802 contain the supplementary crystallographic data for **2q** and **3**, respectively. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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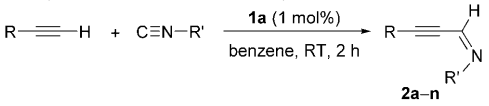
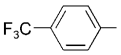
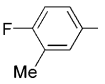
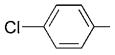
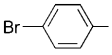
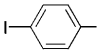
complexes surveyed, the yttrium complexes (e.g., **1a**,**g**) showed the highest activity for this reaction (Table 1, entries 2 and 9–15), whereas the scandium complex (**1f**) was not effective under the same conditions (Table 1, entry 11). The yttrium trimethylsilylmethyl complex **1a** showed the same activity as that of the aminobenzyl analogue **1g** (Table 1, entries 2 and 12), suggesting that the activity of the present catalyst system is not significantly affected by the initial alkyl group. Thus, in the presence of 1 mol% of **1a** in [D_6]benzene at room temperature, the reaction of phenylacetylene with cyclohexyl isocyanide quantitatively yielded cross-coupling product **2a** within 2 hours (Table 1, entry 5). Formation of a phenylacetylene homodimerization product[5] or double-insertion products[1a,d] was not observed.

Table 2 summarizes some representative results of the reactions between various terminal alkynes and isocyanides catalyzed by yttrium complex **1a**. A wide range of aromatic

Table 2: Catalytic monoinsertion of isocyanides into terminal alkynes.[a]



2a–n

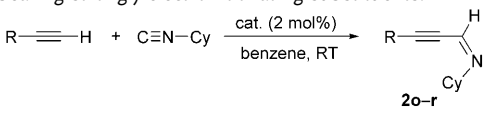
Entry	R	R′	Product (Yield [%])[b]
1		Cy	**2a** (98)
2		*t*Bu	**2b** (95)
3		Cy	**2c** (95)
4		Cy	**2d** (96)
5		Cy	**2e** (95)
6		Cy	**2f** (95)
7		Cy	**2g** (94)
8		Cy	**2h** (93)
9		Cy	**2i** (98)
10		Cy	**2j** (95)
11		Cy	**2k** (94)
12	$CH_3(CH_2)_4$–	Cy	**2l** (95)
13	*t*Bu–	Cy	**2m** (96)
14	$Cl(CH_2)_3$–	Cy	**2n** (93)

[a] Conditions: terminal alkynes (2.02 mmol), isocyanides (2.00 mmol), **1a** (0.02 mmol), benzene (5 mL). [b] Yield of isolated product.

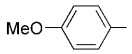
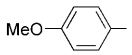
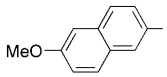
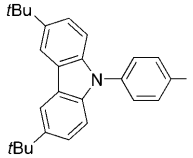
terminal alkynes could be used as the nucleophiles and aromatic C–F, C–Cl, C–Br, and C–I bonds survived the catalytic conditions to selectively yield the corresponding halogen-substituted 1-aza-1,3-enynes **2d–h** (Table 2, entries 4–8). Thiophenyl-, cyclohexenyl-, and alkyl-substituted alkynes were also used (Table 2, entries 10–13). An aliphatic C–Cl bond also survived the reaction conditions (Table 2, entry 14).

In the case of cyclohexyl isocyanide reacting with terminal alkynes with a strongly electron-donating substituent, such as 4-methoxyphenylacetylene, yttrium complex **1a** was less efficient and afforded the coupling product **2o** in only 22% yield after 24 hours (Table 3, entry 1). The larger lanthanum

Table 3: Catalytic monoinsertion of isocyanides into aromatic terminal alkynes bearing strongly electron-donating substituents.[a]



2o–r

Entry	R	Cat.	*t* [h]	Product (Yield [%])[b]
1		**1a**	24	**2o** (22)
2		**1j**	12	**2o** (97)
3		**1j**	12	**2p** (98)
4		**1j**	12	**2q** (95)
5		**1a**	24	**2r** (50)
6		**1j**	12	**2r** (95)

[a] Conditions: terminal alkynes (2.02 mmol), cyclohexyl isocyanide (2.00 mmol), cat. (0.04 mmol), benzene (5 mL). [b] Yield of isolated product.

complex **1j**, however, showed much higher activity for this reaction, and **2o** was isolated in 97% yield after 12 hours by using the same reaction conditions (Table 3, entry 2). These results are in sharp contrast with what was observed for the reaction of phenylacetylene with cyclohexyl isocyanide (see Table 1, entries 2, 12, and 15), indicating that the effect of the size of the metal ion on the catalytic activity could depend on the substrates. Carbazolyl-substituted phenylacetylene[5b] and pyridylacetylene were also added to cyclohexyl isocyanide using lanthanum complex **1j** to give the corresponding 1-aza-1,3-enyne products **2q** and **2r**, respectively, in high yields (Table 3, entries 4 and 6).

The ^{1}H and ^{13}C NMR spectra of the 1-aza-1,3-enyne products **2a–r** showed one set of signals, which was assigned to the *Z* isomer. In the case of **2q**, single crystals suitable for X-ray crystallographic analysis were obtained, and an X-ray diffraction study revealed that the solid structure of **2q** adopts a *Z* configuration in which the Cy group is placed *cis* to the acetylenic moiety around the C=N bond (Figure 1). The *Z* products obtained were stable at room temperature, but

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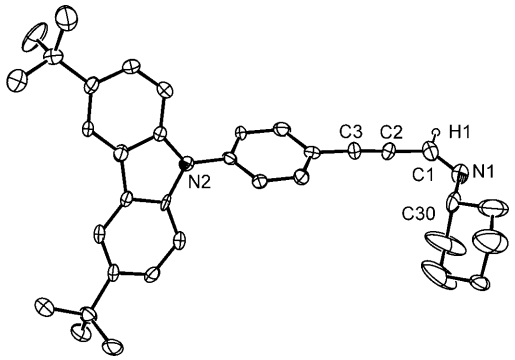


Figure 1. ORTEP drawing of **2q** with 30% probability thermal ellipsoids. Hydrogen atoms, except that on the C1 atom, have been omitted for clarity. Selected bond length [Å] and angles [°]: C1–N1 1.273(8), C2–C3 1.173(9), C1–C2 1.457(10), C1-N1-C30 116.4(9), C2-C1-N1 127.8(9).

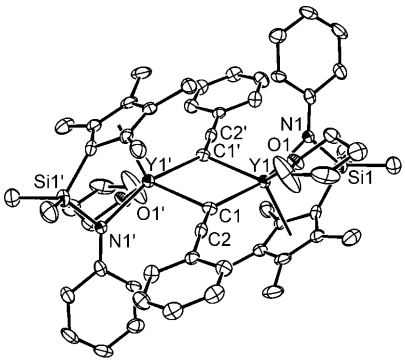
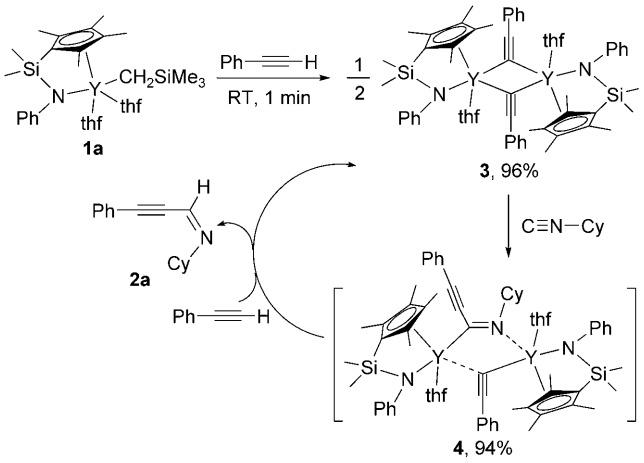


Figure 2. ORTEP drawing of **3** with 30% probability thermal ellipsoids. Hydrogen atoms have been omitted for clarity. Selected bond lengths [Å] and angles [°]: Y1–C1 2.558(4), Y1–C1′ 2.488(4), C1–C2 1.219(5), C1-Y1-C1′ 78.99(14), Y1-C1-Y1′ 101.01(14). Symmetry operation denoted ′ = $-x+1$, $-y$, $-z+1$.

could isomerize at high temperatures to give a mixture of the *Z*/*E* isomers. Upon heating **2a** at 100 °C for 12 hours in [D_6]benzene in a closed NMR tube, the formation of a 5:13 mixture of the *Z*/*E* isomers was observed.[1d,8] The selective formation of (*Z*)-1-aza-1,3-enynes in the present reaction is in contrast with what was previously observed for other catalyst systems, in which the *E* isomers were the main product[1a,d] or a mixture of the *E*/*Z* isomers were obtained.[1b,c] To the best of our knowledge, this is the first example of regio- and stereoselective 1:1 cross-coupling between a terminal alkyne and isocyanide to exclusively give the (*Z*)-1-aza-1,3-enyne.

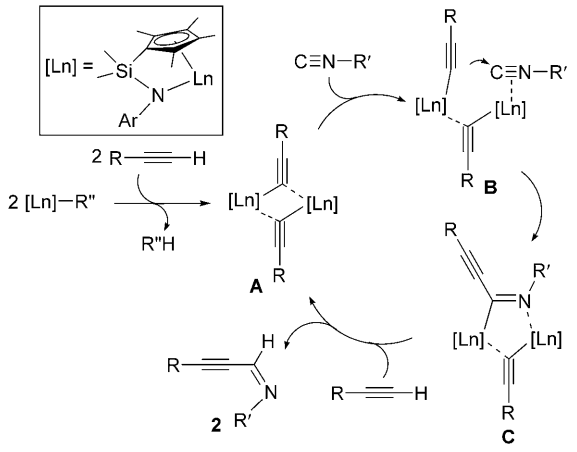
To gain information on the mechanistic aspects of the present catalytic process, a stoichiometric reaction of **1a** with 1 equivalent of phenylacetylene was carried out in benzene at room temperature, and after a reaction time of 1 minnute the corresponding phenylacetylide complex **3** was isolated in 96% yield (Scheme 1). An X-ray crystallographic analysis



Scheme 1. Stoichiometric reactions of **1a**.

showed that **3** adopts a dimeric structure, in which the two yttrium centers are bridged by two phenylacetylides (Figure 2). There is a crystallographic inversion center at the center of the whole molecule. The ^{13}C NMR spectrum of **3** in [D_6]benzene displayed a triplet at $\delta = 138.7$ ppm with $J_{Y,C} = 22.5$ Hz for the acetylide carbon atoms, suggesting that the acetylide bridges remain intact in solution. This structure is in contrast to the bis(cyclopentadienyl)-ligated rare-earth or actinide alkynide complexes which tend to form monomeric structures.[1a,d,9] The addition of 1 equivalent of cyclohexyl isocyanide to **3** in [D_6]benzene at room temperature rapidly gave monoinsertion product **4** (Scheme 1). Although a single crystal of **4** suitable for X-ray crystallographic analysis was not obtained, its ^{1}H and ^{13}C NMR spectra were rather informative for the elucidation of the structure. The imine carbon atom in **4** showed a doublet at $\delta = 181.8$ ppm with $J_{Y,C} = 6.5$ Hz, and the phenylacetylide carbon atom gave a triplet at $\delta = 137.6$ ppm with $J_{Y,C} = 23.9$ Hz in the ^{13}C NMR spectrum in [D_6]benzene, suggesting that **4** still possesses a dimeric structure. The addition of 1 equivalent of phenylacetylene to **4** in [D_6]benzene yielded (*Z*)-1-aza-1,3-enyne **2a** and regenerated phenylacetylide **3** quantitatively (Scheme 1).

On the basis of the above experimental results, a possible catalytic cycle for the present cross-coupling reaction is proposed in Scheme 2. The acid-base reaction between a half-



Scheme 2. A possible mechanism of catalytic cross-coupling of terminal alkynes with isocyanides.

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sandwich rare-earth alkyl and a terminal alkyne should yield a dimeric alkynide species such as **A**. Coordination of an isocynide to one of the metal centers of the dimeric alkynide species could afford **B** by breaking one of the two alkynide bridges. Attack of the terminal alkynide to the coordinated isocynide on another metal center in binuclear species **B** in an intermolecular fashion should give **C**, which upon abstraction of a proton from another molecule of the alkyne would yield the corresponding (*Z*)-1-aza-1,3-enyne **2** and regenerate alkynide **A**. Apparently, having the coupling reaction take place at the two metal centers in a binuclear species such as **B** is the key to the selective formation of the *Z*-isomer product in the present catalyst system.[1,5]

In summary, we have demonstrated that half-sandwich rare-earth metal alkyl complexes can act as excellent catalyst precursors for the cross-coupling of various terminal alkynes with isocyanides, selectively affording the (*Z*)-1-aza-1,3-enyne products. The unprecedented *Z* selectivity could arise from formation of an alkynide-bridged binuclear catalyst species, in which the cross-coupling reaction takes place at the two metal centers in an intermolecular fashion.

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Keywords: cross-coupling · enynes · isocyanides · rare-earth metals · sandwich complexes

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