Direct mono-insertion of isocyanides into terminal alkynes catalyzed by rare-earth silylamides†

Kimihiro Komeyama,* Daisuke Sasayama, Tomonori Kawabata, Katsuomi Takehira and Ken Takaki

Received (in Cambridge, UK) 17th September 2004, Accepted 26th October 2004
First published as an Advance Article on the web 13th December 2004
DOI: 10.1039/b414302g

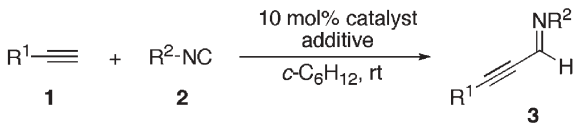
Rare-earth silylamide complexes, Ln[N(SiMe$_3$)$_2$]$_3$ (Ln = Y, La, Sm, Yb), effectively catalyzed the coupling reaction of isocyanides with both aliphatic and aromatic terminal alkynes under mild conditions.

The insertion reaction of carbon–carbon unsaturated compounds into various transition metal–carbon bonds is one of the most powerful methods for carbon chain construction, and it has been widely utilized as a key step in organic synthesis. This process was also used in the lanthanide-catalyzed transformation of alkynes and alkenes: for example, cyclization/hydrosilylation and oligomerization.[1] In addition, one-carbon elongation using carbon monoxide and isocyanides has been recognized as an important tool in the formation of carbonyl and iminoyl functions, which lead to multi-functionalized alcohols and amines.[2] The reaction is mainly promoted by late transition metals.[3,4] However, there has been no precedent for the catalytic direct mono-insertion of isocyanides into terminal alkynes. Very recently, Eisen *et al.* reported the insertion of *tert*-butyl isocyanide into terminal alkynes catalyzed by actinides.[5] With respect to rare-earth complexes, their unique reactions with carbon monoxide and useful synthetic reaction, though stoichiometric, *via* isocyanide insertion into Ln-carbon bond have been reported.[6,7]

In our previous work, rare-earth silylamide, Ln(btsa)$_3$ [btsa = N(SiMe$_3$)$_2$], was found to catalyze the dimerization of aliphatic and aromatic terminal alkynes, leading to 1,3-enynes with high regio- and stereoselectivities.[8,9] During the investigation, we also found that a coupling reaction of terminal alkynes and isocyanides took place effectively in the presence of the silylamide catalysts and amine additives (Scheme 1). In this Communication, we would like to disclose these results.

When oct-1-yne (**1a**) was treated with equimolar amounts of 2-mesityl isocyanide (**2d**) in the presence of Sm(btsa)$_3$ (10 mol%) for 24 h at room temperature in cyclohexane, the coupling product, 1-(2-mesitylimino)non-2-yne (**3ad**), was obtained in only 10% yield as a mixture of *syn* and *anti* isomers. The alkyne was recovered in 48%, but most of the isocyanide **2d** was consumed to provide oligomeric products. We therefore focused our attention on inhibiting the oligomerization of isocyanide by amine additives that altered the catalyst activities and served as a proton source in the dimerization of terminal alkynes.[8] These results are summarized in Table 1. Addition of aniline caused a low conversion of **1a** and **2d** (entry 2), whereas yield of the product **3ad** drastically increased to 76% with amylamine (entry 3). Tertiary amines like triethylamine showed no obvious effect (entry 4). By screening the catalyst, it became apparent that the lager metals, Sm and La, gave the better yield of **3ad** (entries 3, and 5–7).

A selection of various terminal alkynes **1a–h** and isocyanides **2a–e** was investigated using Sm(btsa)$_3$ (10 mol%) and amylamine (20 mol%) in cyclohexane at room temperature (Table 2). The reaction of oct-1-yne (**1a**) with *tert*-butyl isocyanide (**2a**) did not commenced under the present conditions (entry 1). At elevated temperature (65 °C), the isocyanide **2a** was completely changed to oligomers, though the alkyne **1a** was mostly remained. Phenyl isocyanide (**2b**) gave similar results (entry 2). These results implied that the insertion of isocyanide **2** into the metal–carbon bond of the iminoyl intermediate took place faster than its competitive protonation. In fact, it is clear that with the aromatic isocyanides having bulkier substituents at *o*-position, the selectivity of **3** was



R^1 = C_6H_{13} (**1a**), ^{t}Bu (**1b**), Bn_2NCH_2 (**1c**), $TBSOCH_2$ (**1d**), Ph (**1e**), *p*-$MeOC_6H_4$ (**1f**), *p*-BrC_6H_4 (**1g**), *p*-$(CH_2O)_2CHC_6H_4$ (**1h**)

R^2 = ^{t}Bu (**2a**), Ph (**2b**), 2,6-$Me_2C_6H_3$ (**2c**), 2,4,6-$Me_3C_6H_2$ (**2d**), 2,6-$^i Pr_2C_6H_3$ (**2e**)

Scheme 1 Catalytic coupling of terminal alkynes and isocyanides. TBS = *tert*-butyl dimethyl silyl.

Table 1 Effect of amines and catalysts for the coupling reaction of **1a** with **2d**

			Yield (%)[a]	Recovery (%)[a]	
Entry	Catalyst	Additive (mol%)	**3ad**	**1a**	**2d**
1	Sm(btsa)$_3$	None	10	48	11
2	Sm(btsa)$_3$	$PhNH_2$ (25)	7	66	67
3	Sm(btsa)$_3$	$C_5H_{11}NH_2$ (20)	76	16	0
4	Sm(btsa)$_3$	Et_3N (25)	9	52	32
5	Yb(btsa)$_3$	$C_5H_{11}NH_2$ (20)	38	59	28
6	Y(btsa)$_3$	$C_5H_{11}NH_2$ (20)	35	36	17
7	La(btsa)$_3$	$C_5H_{11}NH_2$ (20)	62	15	tr

[a] Determined by GC.

† Electronic supplementary information (ESI) available: Details of the procedure and spectral data for the products in Table 2. See http://www.rsc.org/suppdata/cc/b4/b414302g/

*kkome@hiroshima-u.ac.jp

Table 2 Examples for the coupling of alkynes (**1**) and isocyanides (**2**) catalyzed by $Sm(btsa)_3$ in the presence of amylamine

Entry	Alkyne	Isocyanide	Time/h	Product	Yield (%)[a]
1	**1a**	**2a**	20	**3aa**	0
2	**1a**	**2b**	5	**3ab**	0
3	**1a**	**2c**	9	**3ac**	53
4	**1a**	**2d**	9	**3ad**	76
5	**1a**	**2e**	9	**3ae**	88
6	**1b**	**2e**	9	**3be**	86
7	**1c**	**2e**	6	**3ce**	94
8	**1d**	**2e**	24	**3de**	88
9	**1e**	**2e**	6	**3ee**	95
10	**1f**	**2e**	6	**3fe**	95
11	**1g**	**2e**	9	**3ge**	85
12	**1h**	**2e**	6	**3he**	93

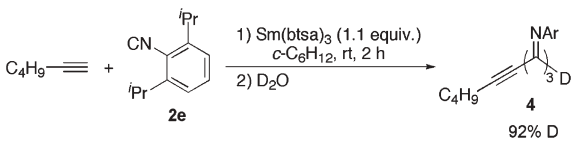
[a] Determined by GC and ^{1}H NMR.

higher due to the inhibition of the oligomerization (entries 2–5). Thus, the product **3ae** was obtained in 88% yield, using 2,6-diisopropylphenyl isocyanide (**2e**).

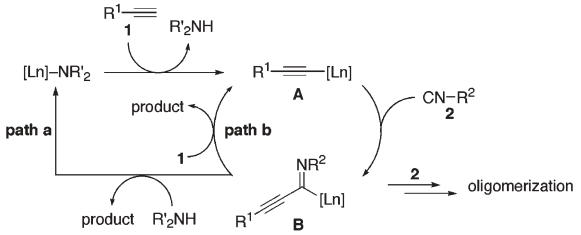
Compatibility of the present reaction was tested in the screening of various terminal alkynes for the coupling reaction with **2e** (Table 2, entries 6–12). 3,3-Dimethylbut-1-yne (**1b**) provided the corresponding aldimine **3be** in high yield (entry 6). Interestingly, the presence of tertiary amino group did not appear to alter the yield and product selectivity (entry 7), whereas TBS-protected propargyl alcohol **1d** required a longer period to complete the reaction (entry 8). However, the corresponding alkynes containing primary amino group and TMS-protected alcohol moiety could not be used, because no reaction took place under the similar conditions. Aromatic alkynes were more reactive than aliphatic ones in general (entries 5 *vs.* 9). Electron-donating substituents such as *p*-methoxyphenylacetylene (**1f**) led to slightly increase yield (95%), as compared to electron-withdrawing substituents of **1g** (85%) in the same position (entries 10 *vs.* 11). Although acetalated formyl groups have been known to usually disturb the rare-earth-catalyzed reaction because of its strong acidity,[1b] the present silylamide catalyst could notably perform the coupling reaction of **1h** to give **3he** in 93% yield (entry 12).

The reaction of hex-1-yne with **2e** was carried out using stoichiometric amounts of $Sm(btsa)_3$ without the amine additives in order to get information about the reaction mechanism (Scheme 2). Quenching of the reaction mixture with D_2O gave a mixture of oligomers, from which the compound **4**, derived from the alkyne and three molecules of **2e**, was isolated in 10% yield as the least molecular weight fraction. The iminoyl proton of **4** was found to be deuterated in 92%.

Based on the results described above, a reaction process would be explained as depicted in Scheme 3. 1,1-Insertion of the isocyanide **2** to rare-earth alkynide **A**, generated from alkyne **1** and the amide species,[8] would yield a key iminoyl intermediate **B**. Then, predominant protonation of **B** with the amine additive could afford the product **3** and rare-earth amide (path a). In the



Scheme 2 Labelling of the stoichiometric reaction of hex-1-yne with **2e**.



Scheme 3 Plausible reaction mechanism of mono-insertion of isocyanide into terminal alkynes.

absence of the amine additive, multiple insertion of **2** to **B** in preference to its protonation with **1** (path b) would result in oligomerization.

In summary, we have demonstrated that readily available rare-earth silylamide complexes are able to catalyze mono-insertion of isocyanides into terminal alkynes. This reaction proceeds in high yield and compatibility with various aromatic and aliphatic terminal alkynes in the presence of amine additives.‡

Kimihiro Komeyama,* Daisuke Sasayama, Tomonori Kawabata, Katsuomi Takehira and Ken Takaki
Department of Chemistry and Chemical Engineering, Graduate School of Engineering, Hiroshima University, Kagamiyama, Higashi-Hiroshima, 739-8527, Japan.
E-mail: kkome@hiroshima-u.ac.jp; Fax: +81 82 424 5494; Tel: +81 82 424 7738

Notes and references

‡ *Representative experimental procedure*: All reactions were carried out under Ar atmosphere. A solution of **1a** (99 μL, 0.67 mmol), **2e** (125 mg, 0.67 mmol), and amylamine (15.4 μL, 0.134 mmol) in cyclohexane (0.7 mL) was added into $Sm(btsa)_3$ (42 mg, 0.067 mmol). After 9 h of stirring at room temperature, the reaction mixture was quenched with distilled water and ether. Yield of **3ae** was measured by gas chromatography with dimethyl terephthalate as an internal standard. After extraction with ether, the combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. Kugelrohr distillation of the mixture (250 °C/10^{-2} mmHg) gave 1-(2,6-diisopropylphenylimino)non-2-yne (**3ae**) (117 mg, 59%) as a yellow oil mixture of the *syn* and *anti*-isomers (65/35). MS *m/z* (70 eV) 297 (M^+, 36), 282 (100), 212 (35). ^{1}H NMR ($CDCl_3$) *anti isomer*: δ 0.91 (3H, t, J = 7.0 Hz), 1.01–1.49 (18 H, m), 1.61–1.69 (2H, m), 2.46 (2H, dt, J = 1.5, 7.2 Hz), 2.92 (2H, sept, J = 6.9 Hz), 7.03–7.14 (3H, m), 7.40 (1H, t, J = 1.5 Hz); *syn isomer* (assignable peaks only): δ 0.84 (3H, t, J = 7.2 Hz), 1.01–1.49 (18 H, m), 2.14 (2H, dt, J = 1.4, 6.9 Hz), 2.82 (2H, sept, J = 6.9 Hz), 7.03–7.14 (3H, m), 7.84 (1H, t, J = 1.4 Hz). ^{13}C NMR ($CDCl_3$) *anti isomer*: δ 14.01, 19.5, 22.5, 23.5, 27.71, 27.86, 28.0, 31.3, 78.9, 97.0, 123.0, 124.6, 137.5, 147.1, 148.6. *syn isomer*: δ 14.05, 19.0, 22.4, 23.3, 27.67, 27.84, 28.7, 31.2, 76.5, 100.3, 122.7, 124.1, 136.3, 145.2, 147.3. Anal. Calcd for $C_{21}H_{31}N$: C, 84.79; H, 10.50; N, 4.71. Found: C, 84.89; H, 10.62; N, 4.49.

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