Addition of Terminal Alkynes to Aromatic Nitriles Catalyzed by Divalent Lanthanide Amides Supported by Amidates: Synthesis of Ynones

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Abstract: An efficient protocol has been established for the synthesis of conjugated ynones via addition of terminal alkynes to aromatic nitriles, which is catalyzed by novel divalent lanthanide amide complexes. All the reactions gave the products in good to excellent yields at room temperature under solvent-free conditions without any additives. The novel lanthanide amide catalysts were also synthesized and structurally characterized for the first time.

Key words: terminal alkyne, aromatic nitrile, divalent lanthanide complex, amidate, ynone

Conjugated ynones are versatile building blocks in organic synthesis[1] and widely present in natural products and synthetic materials.[2] Recently, some researchers have paid much attention to prepare ynones through metal-catalyzed cross-coupling reactions. Beller and co-workers have reported the Pd-catalyzed carbonylative Sonogashira coupling of aryl derivatives, such as aryl bromides, aryl amines, and aryl triflates,[3] while several groups have also reported the similar reactions by using aryl iodides as the substrates.[4] In 2011, Lee and co-workers found the palladium-catalyzed carbonylative reactions of aryl iodides and alkynyl carboxylic acids via decarboxylative coupling.[5] In addition, some researchers synthesized ynones by palladium-catalyzed coupling of terminal alkynes with acid chlorides.[6] Among the published methods, corrosive acyl chlorides or strictly prepared carbon monoxide, as well as indispensable stoichiometric amounts of bases are usually required. In 2012, Cheng and co-workers found that the iron-catalyzed synthesis of ynones from silylated alkynes with acid chlorides could smoothly undergo without any bases.[7] But this reaction should be carried out in toxic $MeNO_2$ at low temperature (–15 °C). To the best of our knowledge, there is only one paper available reporting the direct addition of aromatic nitriles to terminal alkynes to afford conjugated ynones catalyzed by $Ln[N(TMS)_2]_3$.[8] However, in Zhou's method, an appropriate acidity of primary amines is still required, and the yields are moderate to good. Thus, the search for new catalysts for a more efficient and convenient strategy for the preparation of conjugated ynones is of great interest and importance.

As steric and electronic properties of the amidate ligand can be easily tunable, the trivalent rare-earth-metal complexes bearing amidate ligands have been reported to show broaden applications in catalytic transformations, such as hydroamination,[9] amidation,[10] and polymerization.[11] Meanwhile, the divalent lanthanide chemistry has received considerable attention in recent years, as they are found to have wide applications in various homogeneous reactions.[12] However, the amidate ligand system has not been introduced in divalent lanthanide chemistry to date.

Herein, we successfully synthesized and characterized the divalent ytterbium and europium amide complexes stabilized by amidate ligands for the first time. As expected, these divalent lanthanide amides were found to be efficient single-component catalysts for the preparation of ynones by the addition reaction of terminal alkynes with aromatic nitriles, and the europium complexes showed higher catalytic activity, which represents the rare example that divalent europium complex exhibited high catalytic activity in catalytic organic reactions.[12i]

The protonolysis reaction of the appropriate amide proligands with $Ln[N(TMS)_2]_2$ (Ln = Eu, Yb) gave the four divalent amidate lanthanide amides, $\{LLn[N(TMS)_2](THF)\}_2$ [L^1 = 2,6-*i*-$Pr_2C_6H_3NC(O)Ph$, Ln = Eu (**1**), Yb (**2**); L^2 = 2,6-$Me_2C_6H_3NC(O)Ph$, Ln = Yb (**3**)], and $\{L^2{}_2Eu_2[N(TMS)_2]_2(THF)_3\}$ (**4**) in good yields (Scheme 1), and crystals suitable for X-ray diffraction were obtained from mixed hexane–THF solvent at room temperature.

The crystal structure of complex **1** is given in Figure 1 (a). Complex **1** has a dinuclear centrosymmetric structure. The Eu center in complex **1** is five-coordinated by one oxygen atom and one nitrogen atom from an amidate ligand (L^1), one nitrogen atom from the $N(TMS)_2$ group, and two oxygen atoms from another amidate ligand and the solvated THF molecule, respectively. The coordination geometry around each central metal can be described as a tetrahedron, when the chelating amidate ligand is considered to occupy a single coordination vertex. Complexes **2** and **3** are isostructural with complex **1**. Complex **4** has also a dinuclear structure (Figure 1, b), but the coordination environment around the two europium atoms is inequivalent. The Eu^1 is six-coordinated by two oxygen atoms and two nitrogen atoms from two amidate ligands (L^2), one nitrogen atom from a $N(TMS)_2$ group, and one oxygen atom from a THF molecule. The coordination geometry around the Eu^1 center can also be described as a tetrahedron in view of single vertex for each amidate. However, the Eu^2 center is five-coordinated by two oxygen atoms from two amidate ligands, one nitrogen atom

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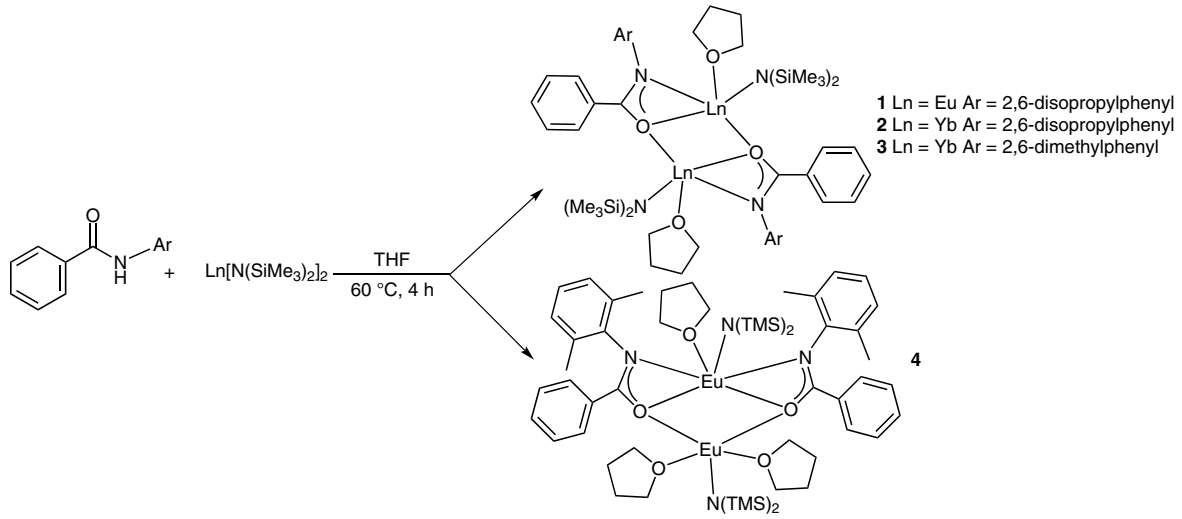


Scheme 1 Preparation of divalent lanthanide amides supported by amidates

from a $N(TMS)_2$ group, and two oxygen atoms from two coordinated THF molecules. The coordination geometry around the Eu^2 center can be described as a distorted quadrangular pyramid, where the four oxygen atoms are almost coplanar, with the sum of the bond angles nearly 360°, and the nitrogen atom N4 locates at the axial vertex.

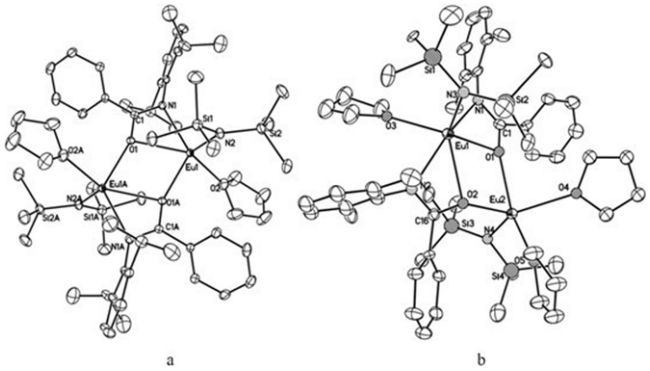
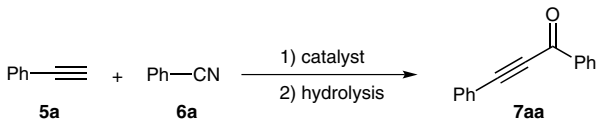


Figure 1 ORTEP diagrams of complexes **1** and **4** with the probability ellipsoids drawn at the 20% level, and hydrogen atoms are omitted for clarity, respectively.

With the easily prepared complexes in hand, the catalytic behaviors of the divalent amidate lanthanide amides were explored. The addition reaction of phenylacetylene **5a** with cyanophenyl **6a** was first examined as a model reaction catalyzed by these divalent lanthanide amides, and the preliminary results are summarized in Table 1. It can be seen that all of these complexes can successfully catalyze this addition reaction to give conjugated ynones at room temperature and the optimum choice of the catalyst loading can be reduced to 2.5 mol%. The activity greatly depends on the central metals, with the activity trend of Yb < Eu (Table 1, entries 11 and 15–17). The bulkiness of the substituents on the aryl ring of the amidate ligand also affects the activity. The complex stabilized by the ligand with 2,6-diisopropylphenyl is more efficient (Table 1, entry 11 vs. entry 17). The effects of the reaction conditions on the yield were further examined using complex **1**, since it showed the highest activity for this reaction. As expected, the reaction was sensitive to temperature, where room temperature proved to be the optimum choice (Table 1, entries 1 and 4–6). The yield increased with the increase of the molar ratio of alkyne to nitrile, and the maximum yield was obtained at the ratio of 3:1 (Table 1, entries 1, 7, and 8). The excess amount of acetylene used was recovered almost quantitatively. Moreover, the yield can reach up to 95% under solvent-free conditions for 12 hours (Table 1, entry 11).

The substrate scope and limitation of this methodology were subsequently investigated, and the results are summarized in Table 2. It can be seen that most of the alkynes and nitriles proceeded smoothly to produce conjugated ynones in good to excellent isolated yields, varied from 82–96%. However, the location of the substituent on the phenyl ring of nitrile had significant effect on this reaction. For example, the reaction of phenylacetylene with *o*-tolunitrile proceeded sluggishly, only trace of product was isolated (Table 2, entry 5), whereas the reactions underwent smoothly for other aromatic nitriles, including heteroaromatic nitrile (Table 2, entry 9). However, efforts toward realization of the addition of phenylacetylene to aliphatic nitriles failed (Table 2, entry 10). As for the steric or electronic properties of aromatic alkynes, there were scarcely any effects on the yields of ynones (Table 2, entries 11–20). Aliphatic alkynes underwent the addition reaction to produce the desired products, but the yields decreased apparently (Table 2, entries 21 and 22). It may be attributed to the slower activation speed in comparison with that of aromatic alkynes, which can be considered as one of the key steps included in the catalytic cycle.[13] It was unexpected that heteroaromatic alkyne hardly gave the target product under the given conditions (Table 2, entry 23).

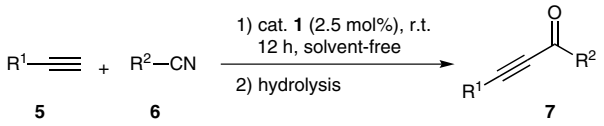
Table 1 Optimization of the Reaction Conditions



Entry	Catalyst	Catalyst loading (mol%)	Time (h)	Temp	**5a**/**6a**	Solvent	Yield (%)[a]
1	**1**	2.5	24	r.t.	1:1		78
2	**1**	1	24	r.t.	1:1		50
3	**1**	5	24	r.t.	1:1		66
4	**1**	2.5	24	40 °C	1:1		65
5	**1**	2.5	24	60 °C	1:1		26
6	**1**	2.5	24	0 °C	1:1		31
7	**1**	2.5	24	r.t.	2:1		87
8	**1**	2.5	24	r.t.	3:1		96
9	**1**	2.5	3	r.t.	3:1		74
10	**1**	2.5	6	r.t.	3:1		88
11	**1**	2.5	12	r.t.	3:1		95
12	**1**	2.5	12	r.t.	3:1	THF	57
13	**1**	2.5	12	r.t.	3:1	toluene	70
14	**1**	2.5	12	r.t.	3:1	hexane	78
15	**2**	2.5	12	r.t.	3:1		29
16	**3**	2.5	12	r.t.	3:1		18
17	**4**	2.5	12	r.t.	3:1		53

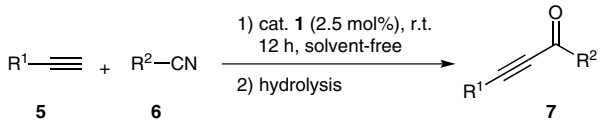
[a] Isolated yield based on nitrile.

Table 2 The Addition of Terminal Alkynes with Aromatic Nitriles Catalyzed by Complex **1**[a]



Entry	Alkyne	R^1	Nitrile	R^2	Ynone	Yield (%)[b]
1	**5a**	Ph	**6a**	Ph	**7aa**	95
2	**5a**	Ph	**6b**	4-MeC_6H_4	**7ab**	96
3	**5a**	Ph	**6c**	3-MeC_6H_4	**7ac**	91
4	**5a**	Ph	**6d**	4-$F_3CC_6H_4$	**7ad**	92
5	**5a**	Ph	**6e**	2-MeC_6H_4	**7ae**	trace
6	**5a**	Ph	**6f**	4-$MeOC_6H_4$	**7af**	72
7	**5a**	Ph	**6g**	4-ClC_6H_4	**7ag**	82
8	**5a**	Ph	**6h**	4-BrC_6H_4	**7ah**	77
9	**5a**	Ph	**6i**	2-thienyl	**7ai**	47
10	**5a**	Ph	**6j**	Me	**7aj**	messy

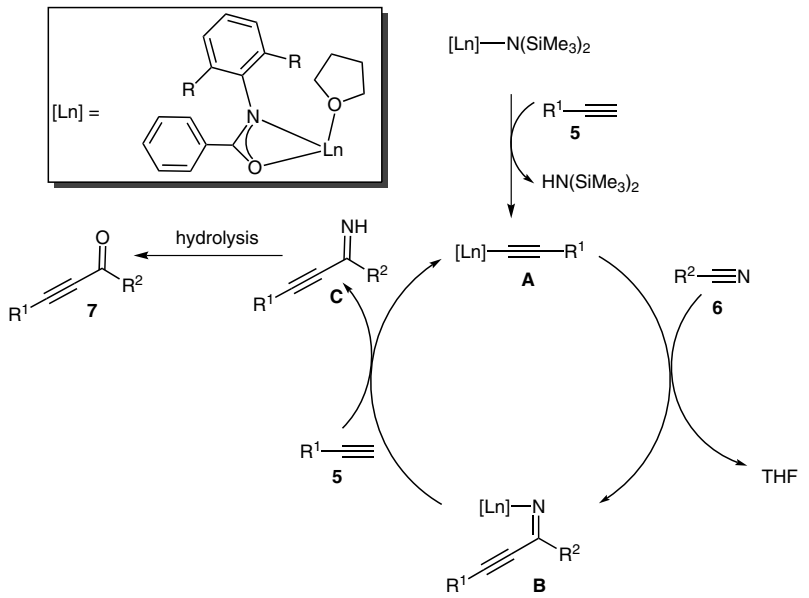
Table 2 The Addition of Terminal Alkynes with Aromatic Nitriles Catalyzed by Complex **1**[a] (continued)



Entry	Alkyne	R^1	Nitrile	R^2	Ynone	Yield (%)[b]
11	**5b**	4-FC_6H_4	**6a**	Ph	**7ba**	93
12	**5b**	4-FC_6H_4	**6b**	4-MeC_6H_4	**7bb**	92
13	**5b**	4-FC_6H_4	**6c**	3-MeC_6H_4	**7bc**	91
14	**5b**	4-FC_6H_4	**6d**	4-$F_3CC_6H_4$	**7bd**	93
15	**5c**	4-MeC_6H_4	**6a**	Ph	**7ca**	90
16	**5c**	4-MeC_6H_4	**6b**	4-MeC_6H_4	**7cb**	94
17	**5c**	4-MeC_6H_4	**6c**	3-MeC_6H_4	**7cc**	92
18	**5c**	4-MeC_6H_4	**6d**	4-$F_3CC_6H_4$	**7cd**	91
19	**5d**	3-MeC_6H_4	**6a**	Ph	**7da**	90
20	**5e**	2-FC_6H_4	**6a**	Ph	**7ea**	85
21	**5f**	*n*-Bu	**6a**	Ph	**7fa**	61
22	**5g**	TMS	**6a**	Ph	**7ga**	28
23	**5h**	2-thienyl	**6a**	Ph	**7fa**	trace

[a] All reactions were conducted with 2.5 mol% of complex **1** at r.t. for 12 h without solvent. And the molar ratio of terminal alkynes to aromatic nitriles is 3:1.
[b] Isolated yield based on nitrile.

Based on the mechanism raised by Z. Hou,[13e] a possible catalytic cycle for the present monoaddition reaction is proposed in Scheme 2. The acid–base reaction of divalent lanthanide amide with a terminal alkyne should yield an alkynide species **A**, which is the key intermediate of the catalytic cycle. Coordination and subsequent insertion of a nitrile to **A** could afford an imino lanthanide intermediate **B**. Then, **B** regenerates **A** by receiving a proton from another molecule of the alkyne, while the addition product **C** is taken off. Hydrolysis of **C** gives the corresponding ynone.



Scheme 2 A possible mechanism for the catalytic addition of terminal alkynes to nitriles

In summary, we have developed an efficient protocol to construct conjugated ynone frameworks via the economical reactions of terminal alkynes with aromatic nitriles catalyzed by divalent amidate lanthanide amides under solvent-free conditions in good to excellent yields. The structures of the novel catalysts are well characterized by the X-ray diffraction analyses. The reactivity depends apparently on both the central metals of the catalysts, and the properties of the amidate ligands. It is noteworthy that the divalent europium complex **1** showed the highest activity on the reaction, which represents the rare example that divalent europium complex exhibited high catalytic activity in homogeneous catalysis. However, the reaction with aliphatic nitriles or heteroaromatic alkyne has not been successful yet. Efforts in this direction are ongoing in our laboratory.

General Procedure for the Preparation of Divalent Amidate Lanthanide Amide Complexes

Synthesis of $\{L^1Eu[N(TMS)_2](THF)\}_2$ (1)
To a stirred THF solution of $Eu[N(TMS)_2]_2(THF)_2$ (10 mL, 1.23 g, 2.00 mmol), a THF solution of L^1 (20 mL, 0.56 g, 2.00 mmol) was added dropwise. The mixture was stirred for 4 h at 60 °C and then concentrated under reduced pressure to give a pale yellow solid. The product was recrystallized by dissolving in a minimum amount of hexanes, with a few drops of THF. Yellow crystals were obtained at r.t. in several days (1.04 g, 78%). Anal. Calcd for $(C_{29}H_{48}N_2O_2Si_2Eu)_2$: C, 52.39; H, 7.28; N, 4.21. Found: C, 52.45; H, 7.61; N, 4.13.

Synthesis of $\{L^1Yb[N(SiMe_3)_2](THF)\}_2$ (2)
The synthesis of complex **2** was carried out in the same way as that described for complex **1**, but $Yb[N(TMS)_2]_2(THF)_2$ (1.27 g, 2.00 mmol) was used instead of $Eu[N(TMS)_2]_2(THF)_2$. Black crystals were obtained at r.t. in several days (1.12 g, 82%). Anal. Calcd for $(C_{29}H_{48}N_2O_2Si_2Yb)_2$: C, 50.78; H, 7.05; N, 4.08. Found: C, 50.85; H, 7.21; N, 3.95.

Synthesis of $\{L^2Yb[N(TMS)_2](THF)\}_2$ (3)
The synthesis of complex **3** was carried out in the same way as that described for complex **2**, but L^2 (0.45 g, 2.00 mmol) was used instead of L^1. Black crystals were obtained at r.t. in several days (0.88 g, 70%). Anal. Calcd for $(C_{25}H_{40}N_2O_2Si_2Yb)_2$: C, 47.67; H, 6.40; N, 4.45. Found: C, 47.70; H, 6.55; N, 4.23.

Synthesis of $\{L^2{}_2Eu_2[N(TMS)_2]_2(THF)_3\}$ (4)
The synthesis of complex **4** was carried out in the same way as that described for complex **1**, but L^2 (0.45 g, 2.00 mmol) was used instead of L^1. Yellow crystals were obtained at r.t. in several days (0.71 g, 55%). Anal. Calcd for $C_{54}H_{88}N_4O_5Si_4Eu_2$: C, 50.29; H, 6.88; N, 4.34. Found: C, 50.31; H, 6.95; N, 4.27.

General Experimental Procedure for the Direct Synthesis of Conjugated Ynones Catalyzed by Complex 1
A 10 mL Schlenk tube under dried argon was charged with the complex **1** (33 mg, 0.025 mmol). Alkyne (3 mmol) was added, after stirring for 3 min, nitrile (1 mmol) was then added. The mixture was stirred at r.t. for 12 h and then was quenched with 0.5 M H_2SO_4. The mixture was extracted with Et_2O. The organic layer was separated, dried over anhyd $MgSO_4$, concentrated under reduced pressure, and purified by flash column chromatography to afford desired product. Flash column chromatography was performed over silica gel (300–400 mesh) using the mixture of PE and EtOAc (50:1 or 25:1) as eluent.

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