JOC*Note*

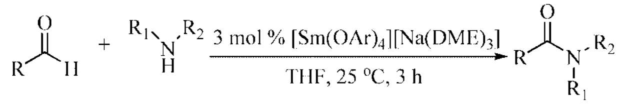
Heterobimetallic Lanthanide/Sodium Phenoxides: Efficient Catalysts for Amidation of Aldehydes with Amines

Junmei Li,[†] Fan Xu,[†] Yong Zhang,[†] and Qi Shen*[,†,‡]

Key Laboratory of Organic Synthesis of Jiangsu Province, Department of Chemistry and Chemical Engineering, Dushu Lake Campus, Suzhou University, Suzhou 215123, People's Republic of China, and State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China

qshen@suda.edu.cn

Received November 26, 2008



Heterobimetallic lanthanide/sodium phenoxides were found to be efficient catalysts for amidation of aldehydes with amines under mild conditions. The reactivity follows the order Nd < Y < Sm for metals and 2,6-(Me)$_2$C$_6$H$_3$O < 2,6-(^{i}Pr)$_2$C$_6$H$_3$O < 2,6-(^{t}Bu)$_2$C$_6$H$_3$O for phenoxide groups. In comparison with the corresponding monometallic complexes, heterobimetallic complexes show higher activity and a wider range of scope of amines. A cooperation of lanthanide and sodium in this process is proposed to contribute to the high activity of the present catalyst.

The formation of a C−N bond is one of the most important reactions in organic syntheses, in which amide bond formation is a particularly interesting topic, as the amide group is an essential motif in biological systems as well as in important molecules in the areas of polymers, natural products, and pharmaceuticals.[1] The direct amidation of aldehydes with amines is the most desired approach to amides as economical and available starting materials. Various efficient catalysts have been explored for this process,[2−7] and some of these systems need to use peroxide,[2] heating, or equivalent alkali metal amides.[4] Very recently, homoleptic lanthanide amides Ln[N(SiMe$_3$)$_2$]$_3$ have been reported to be efficient catalysts for amidation of aldehydes with amines under mild conditions without the use of peroxide and base.[8] But this kind of catalyst is not suitable for the amidation of aldehydes with secondary cyclic amines.[8] Thus, the search of a new class of lanthanide catalysts with a wider scope of substrates is certanly required in the synthesis of amides.

Homoleptic lanthanide phenoxides, a class of robust catalysts, have been extensively used in organic systheses[9] as well as ring-opening polymerization of lactones.[10] Heterobimetallic lanthanide phenoxides have recently been found to be more active catalysts for ring-opening polymerization of ε-caprolactone and copolymerization of ε-caprolactone and cyclocarbonate than the corresponding monometallic ones.[11] Heterobimetallic lanthanum/lithium phenoxide/pybox has been reported to be an efficient catalyst for the direct asymmetric Mannich-type reactions of α-keto anilides reaction.[12] These results encouraged us to test the activity of heterobimetallic lanthanide phenoxides for amidation of aldehydes with amines. It was found that heterobimetallic lanthanide phenoxides can serve as efficient catalysts for amides formation and the catalysts have the advantages of wide substrate scope including secondary cyclic amines such as pyrrolidine, piperidine, and morphorline. Here we reporte the results.

Heterobimetallic yttrium/sodium complexes with various phenoxides [Y(OAr)$_4$][Na(DME)$_3$] were synthesized by the metathesis reaction of lanthanide trichloride with sodium salt, respectively. [Ln(OAr)$_4$][Na(DME)$_3$] (Ln = Nd and Sm)[11] and the corresponding monometallic complexes[13] were also synthesized according to the literature method. The molecular structure of complex **III** was determined by X-ray crystal structure analysis to be the ion pair complex composed of an anion [Y(OAr)$_4$]$^-$ and a cation [Na(DME)$_3$]$^+$, which was isostructural to those for the analogues of Nd and Sm.[11] But the exact bond angles and bond lengths cannot be calculated because of the poor data. All the complexes used here are listed in Scheme 1.

With the complexes in hand, the reaction of benzaldehyde **1a** with pyrrolidine **2d** by using various complexes was first

---

[†] Suzhou University.

[‡] Chinese Academy of Sciences.

(1) Humphrey, J. M.; Chamberlin, A. R. *Chem. Rev.* **1997**, *97*, 2243–2266.

(2) (a) Davidson, R. S.; Edwards, J.; Warburton, S. K. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1511–1514. (b) Marko, I. E.; Mekhalfia, A. *Tetrahedron Lett.* **1990**, *31*, 7237–7240.

(3) Ishihara, K.; Yano, T. *Org. Lett.* **2004**, *6*, 1983–1986.

(4) Zhang, L.; Wang, S.; Zhou, S.; Yang, G.; Sheng, E. *J. Org. Chem.* **2006**, *71*, 3149–3153.

(5) (a) Nakagawa, K.; Onoue, H.; Minami, K. *Chem. Commun.* **1966**, 17–18. (b) Tamaru, Y.; Yamada, Y.; Yoshida, Z. *Synthesis* **1983**, 474–476. (c) Naota, T.; Murahashi, S. *Synlett* **1991**, 693–694. (d) Tillack, A.; Rudloff, I.; Beller, M. *Eur. J. Org. Chem.* **2001**, 523–528. (e) Yoo, W.; Li, C. *J. Am. Chem. Soc.* **2006**, *128*, 13064–13065. (f) Reddy, K. R.; Maheswari, C. U.; Venkateshwar, M.; Kantam, M. L. *Eur. J. Org. Chem.* **2008**, 3619–3622. (g) Chang, J. W. W.; Chan, P. W. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 1138–1140.

(6) (a) Vora, H. U.; Rovis, T. *J. Am. Chem. Soc.* **2007**, *129*, 13796–13797. (b) Bode, J. W.; Sohn, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 13798–13799. (c) Ekoue-Kovi, K.; Wolf, C. *Org. Lett.* **2007**, *9*, 3429–3432.

(7) Gunanathan, C.; Ben-David, Y.; Milstein, D. *Science* **2007**, 790.

(8) Seo, S.; Marks, T. J. *Org. Lett.* **2008**, *10*, 317–319.

(9) (a) Shibasaki, M.; Yoshikawa, N. *Chem. Rev.* **2002**, *102*, 2187–2209. (b) Kobayashi, S.; Sugiura, M.; Kitagawa, H.; Lam, W. W. L. *Chem. Rev.* **2002**, *102*, 2227–2302.

(10) (a) Yasuda, H.; Aludin, M. S.; Kitamura, N.; Tanabe, M.; Sirahama, H. *Macromolecules* **1999**, *32*, 6047. (b) Ling, J.; Shen, Z. Q.; Huang, Q. H. *Macromolecules* **2001**, *34*, 7613. (c) Yu, C. P.; Zhang, L. F.; Shen, Z. Q. *J. Mol. Catal. A* **2004**, *212*, 365. (d) Ling, J.; Shen, Z. Q. *Macromol. Chem. Phys.* **2002**, *203*, 735. (e) Stevels, W. M.; Ankone, M. J. K.; Dijkstra, P. J.; Feijen, J. *Macromolecules* **1996**, *29*, 3332. (f) Martin, E.; Dubois, P.; Robert, J. *Macromolecules* **2000**, *33*, 1530. (g) Ling, J.; Chen, W.; Shen, Z. Q. *J. Polym. Sci., Part A: Polym. Chem.* **2005**, *43*, 1787.

(11) Sheng, H.; Zhou, L.; Zhang, Y.; Yao, Y.; Shen, Q. *J. Polym Sci., Part A: Polym. Chem.* **2007**, *45*, 1210–1218.

(12) (a) Lu, G.; Morimoto, H.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 6847–6850. (b) Morimoto, H.; Lu, G.; Aoyama, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.,* **2007**, *129*, 9588–9589.

(13) Hitchcock, P. B.; Lappert, M. F.; Singh, A. *J. Chem. Soc., Chem. Commun.* **1983**, 1499.

10.1021/jo802617d CCC: $40.75

SCHEME 1

$[Ln(OAr)_4][Na(DME)_3]$ Ln = Nd **I**, Sm **II**, Y **III** (ArO = 2,6-di-tert-butyl-phenoxide)

$[Y(OAr')_4][Na(DME)_3]$ **IV** (Ar'O = 2,6-diisopropylphenoxide)

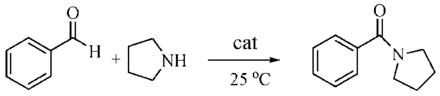
$[Y(OAr'')_4][Na(DME)_3]$ **V** (Ar''O = 2,6-dimethylphenoxide)

$[Ln(OAr)_3][THF]_2$ Ln = Nd **VI**, Sm **VII**, Y **VIII** (ArO = 2,6-di-tert-butyl-phenoxide)

$[Y(OAr')_3][THF]_2$ **IX** (Ar'O = 2,6-diisopropylphenoxide)

$[Y(OAr'')_3][THF]_2$ **X** (Ar''O = 2,6-dimethylphenoxide)

TABLE 1. Amidation of 1a with 2d Catalyzed by Various Complexes[a]

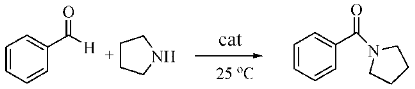


1a **2d** **3ad**

entry	molar ratio (**1a**:**2d**)	catalyst	mol % of catalyst[b]	time (h)	yield (%)[c]
1	3:1	**I**	3	3	83
2	3:1	**II**	3	3	96
3	3:1	**III**	3	3	93
4	3:1	**IV**	3	3	53
5	3:1	**V**	3	3	24
6	3:1	**VI**	3	3	30
7	3:1	**VII**	3	3	32
8	3:1	**VIII**	3	3	27
9	3:1	**IX**	3	3	10
10	3:1	**X**	3	3	
11	3:1	NaOAr	3	3	20
12[d]	3:1	**VII** + NaOAr	3 + 3	3	70
13[e]	3:1	**VII** + NaOAr	3 + 3	3	98
14[f]	3:1	$La[N(SiMe_3)_2]_3$	5	24	38

[a] Amine was first added to the catalyst solution, after 30 min, aldehyde was added, the solvent was THF. [b] On the basis of lanthanide metal. [c] Isolated yield based on pyrrolidine. [d] Amine was first added to the catalyst solution, after 30 min, aldehyde was added. [e] The catalyst solution was mixed 12 h, then amine was first added, after 30 min, aldehyde was added. [f] Reference 8.

TABLE 2. Optimization Amidation of 1a with 2d Catalyzed by Complex II[a]



1a **2d** **3ad**

entry	molar ratio (**1a**:**2d**)	catalyst	mol % of catalyst[b]	time (h)	yield (%)[c]
1	1:1	**II**	3	3	43
2	2:1	**II**	3	3	72
3	3:1	**II**	3	3	96
4	3:1	**II**	3	2	83
5	3:1	**II**	2	3	84
6[d]	3:1	**II**	3	3	80
7[e]	3:1	**II**	3	3	88
8[f]	3:1	**II**	3	3	90
9[g]	3:1	**II**	3	3	70

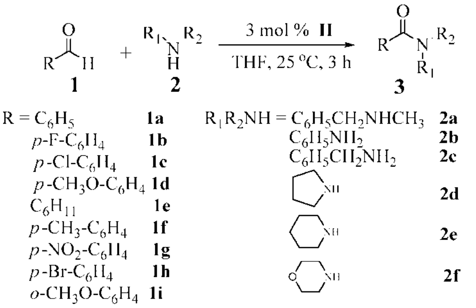
[a] Amine was first added to the catalyst solution, after 30 min, aldehyde was added, the solvent was THF. [b] On the basis of lanthanide metal. [c] Isolated yield based on pyrrolidine. [d] Aldehyde was first added to the catalyst solution, after 30 min, then amine was added. [e] Amine was first added to the catalyst solution, then aldehyde was added. [f] The solvent was toluene. [g] Solvent free.

examined at 25 °C with 3 mol % catalyst loading. We are pleased to find that all the heterobimetallic complexes except **V** can serve as catalysts for this transformation yielding the amide **3ad** in good to excellent yields (Table 1 entries 1−5). The yields are much higher than that obtained by homoleptic lanthanide amides (Table 1, entry 14). In contrast, the monometallic complexes showed much lower activity (Table 1, entries 6−10). The sodium phenoxide complex NaOAr (Ar = 2,6-di-*tert*-butylphenoxide) was not efficient under the same conditions providing **3ad** in only 20% yield (Table 1, entry 11). A mixted system of NaOAr and **VII** afforded **3ad** in 70% yield. When the mixture of NaOAr and **VII** was stirred for 12 h at room temperature, then the amine was added and at last the aldehyde was introduced; the product **3ad** was prepared in 98% yield, which is almost equal to the yield obtained by heterobimetallic catalyst **II** (Table 1, entries 3, 12, and 13). These experiments clearly demonstrated that the differences in activity between heterobimetallic and monometallic complexes may be attributed to a cooperation effect resulting from lanthanide and sodium metal in the amidation reaction. The influence of both central metals and the phenoxide groups on the activity is observed. The active sequences are Nd < Y < Sm for metals and 2,6-$(Me)_2C_6H_3O$ < 2,6-$(^iPr)_2C_6H_3O$ < 2,6-$(^tBu)_2C_6H_3O$ for phenoxide groups (Table 1, entries 1−10). The highest activity for the most bulky phenoxide may be attributed to the most active Ln−phenoxide bond caused from the crowd coordination sphere around the metal with four bulky phenoxide groups. Optimization experiments were then conducted with **II**. The results indicate that an excess of aldehyde (3 equiv) is required for obtaining a product in high yield (Table 2, entries 1−3), as aldehyde acts as not only a reactant but also an oxidant. Besides, a side reaction possibly occurred in this process, namely the Tishchenko reaction, also needed to consume aldehyde. High yield can be obtained with the feeding sequence of adding aldehyde into the mixture of amine and catalyst in comparison with the feeding sequence of adding amine into the mixture of aldehyde and catalyst (Table 2, entries 3 and 6) because the Tishchenko reaction is a competitive reaction against the amidation. A decrease of catalyst loading resulted in a decrease in yields (Table 2, entry 5). THF is a better solvent than toluene (Table 2, entries 3 and 8). The reaction proceeded in solvent free condition affording **3ad** in the lowest yield (Table 2, entry 9) compared to the reaction in THF and toluene.

With the optimizing conditions (Table 2, entry 3), we then screened various aldehydes and amines to explore the generality and scope of the reaction (Table 3).

All the reactions proceeded efficiently to afford the corresponding amides in good to excellent yields after 3 h. The aromatic aldehydes with an electron-withdrawing group at the para-position on the ring give higher yield relative to the aldehydes with an electron-donating group (Table 3, entries 1−4 and 9−20). The reaction with primary aromatic amine (aniline) proceeded smoothly to give the amide in good yield, while the same reaction with aliphatic aldehyde (cyclohexane carboxaldehyde) afforded the product in moderate yield (Table 3, entry 7). However, the reaction with benzylamine afforded the product **3ac** in only 60% yield, which may be attributed to catalyst deactivation by water produced via imine formation. Indeed, the yield can be improved to 75% when the reaction proceeded in the presence of molecular sieves 4Å (Table 3, entry 8). It was noticed that the reactions of **2d** with other aromatic aldehydes also occurred smoothly and yielded the corresponding amides in good to excellent yields and was completed within 3 h at 25 °C with 3 mol % of **II**. For example, *p*-chlorobenzaldehyde (**1c**) and *p*-flourobenzaldehyde (**1b**) were almost quantitatively converted to *N*-(*p*-chlorobenzoyl)pyrrolidine (**3cd**)

TABLE 3. Complex II Catalyzed Amidation of Aldehydes with Amines[a]



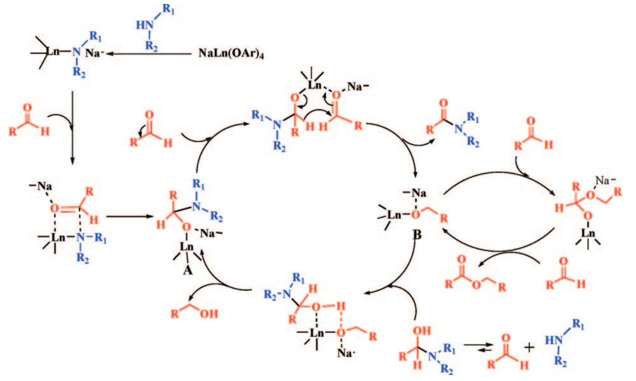
entry	aldehyde	amine	amide	yield (%)[b]
1	**1a**	**2a**	**3aa**	90
2	**1b**	**2a**	**3ba**	94
3	**1c**	**2a**	**3ca**	93
4	**1d**	**2a**	**3da**	73
5	**1a**	**2b**	**3ab**	80
6	**1b**	**2b**	**3bb**	82
7	**1e**	**2b**	**3eb**	45
8	**1a**	**2c**	**3ac**	60 (75,[c] 83[d])
9	**1a**	**2d**	**3ad**	96
10	**1b**	**2d**	**3bd**	97
11	**1c**	**2d**	**3cd**	98
12	**1d**	**2d**	**3dd**	72
13	**1f**	**2d**	**3fd**	71
14	**1g**	**2d**	**3gd**	94
15	**1h**	**2d**	**3hd**	92
16	**1a**	**2e**	**3ae**	91
17	**1b**	**2e**	**3be**	94
18	**1c**	**2e**	**3ce**	97
19	**1d**	**2e**	**3de**	68
20	**1f**	**2e**	**3fe**	72
21	**1a**	**2f**	**3af**	92
22	**1b**	**2f**	**3bf**	97
23	**1c**	**2f**	**3cf**	96
24	**1d**	**2f**	**3df**	90
25	**1f**	**2f**	**3ff**	88
26	**1h**	**2f**	**3hf**	99
27	**1i**	**2f**	**3if**	88

[a] Starting amine, aldehyde, and **II** concentrations are identical in each experiment. [b] Isolated yield based on amine. [c] Molecular sieves 4Å was added. [d] 5 mol % of **II** without molecular sieves 4Å.

and *N*-(*p*-flourobenzoyl)pyrrolidine (**3bd**) (Table 3, entries 10 and 11), although electron-rich aromatic aldehydes are less active and afford the corresponding amides in about 72% yields (Table 3, entries 12 and 13). We were pleased to find that the present catalysts can also afford benzoylpiperidines **3ae**−**3ce**, in 91−97% yields (Table 3, entries 16−18), and benzoylmorpholines **3af**−**3if**, in 88−99% yields (Table 3, entries 21−27). A possible mechanism is proposed according to the mechanism proposed by Marks' group[8] and the results on the influence of feeding sequence on the yields of amide. The heterobimetallic complex reacts first with amine to afford the heterobimetallic complex [Ln(OAr)$_3$(NHAr)][Na(DME)$_3$], which reacts with aldehyde affording the active species **A** (Scheme 2). The active species **A** reacts with aldehyde to generate **B** (Scheme 2), which might be the active species for the Tishchenko reaction.

In summary, we have developed heterobimetallic lanthanide/sodium phenoxides as a new class of bimetallic catalysts for amidation of aldehydes with amines. The new catalysts show high activity and a wide range of scope to produce amides in good to excellent yields under mild conditions. A cooperation effect between lanthanide and alkali metals for high activity is proposed.

SCHEME 2. Proposed Catalytic Cycle for Amidation



Experimental Section

General Procedure. All manipulations and reactions were performed under a purified argon atmosphere with standard Schlenk techniques. Solvents were degassed and distilled from sodium benzophenone ketyl prior to use. [Ln(OAr)$_4$][Na(DME)$_3$] (Ln = Nd (**I**), Sm (**II**); ArO = 2,6-di-*tert*-butylphenoxide) were prepared according to the literature.[11] [Ln(OAr)$_3$][THF]$_2$ (Ln = Nd (**VI**), Sm (**VII**), Y (**VIII**); ArO = 2,6-di-*tert*-butylphenoxide), [Y(OAr′)$_3$][THF]$_2$ (**IX**) (Ar′O = 2,6-diisopropylphenoxide), and [Y(OAr″)$_3$][THF]$_2$ (**X**) (Ar″O = 2,6-dimethylphenoxide) were prepared according to the literature.[13] All aldehydes and amines were predried, sublimed, recrystallized, or distilled before use. Melting points were determined in a sealed Ar-filled capillary tube, and uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Unity Inova-400 spectrometer. Chemical shifts (δ) were reported in ppm. HRMS were recorded on a GCT-TOF instrument.

General Procedure for the Synthesis of III−V Complexes ([Y(OAr)$_4$][Na(DME)$_3$], III, as an example). A stirred suspension of YCl_3 (0.59 g, 3 mmol) in THF (20 mL) was treated with NaOAr (2.74 g, 12 mmol) in THF (15 mL). The reaction mixture was stirred at room temperature for 24 h, and the solvent was removed in vacuo. The residue was extracted with toluene (40 mL) and the volume of the extract was reduced to 10 mL followed by an addition of DME (1 mL). Cooling to 0 °C afforded **III** as yellow crystals. Yield 2.53 g (70%), melting point 120−123 °C. Anal. Calcd for $C_{68}H_{114}NaYO_{10}$ (MW 1203.52): C, 67.86; H, 9.55; Y, 7.39. Found: C, 67.12; H, 9.35; Y, 7.01. IR (KBr pellet, cm^{-1}) 3430 (s), 3066 (w), 2934 (s), 2897 (w), 2855 (w), 1595 (s), 1472 (m), 1423 (s), 1346 (m), 1236 (m), 1132 (m), 1106 (m), 1032 (w), 879 (m), 758 (m), 510 (w). ^{1}H NMR (400 MHz, C_6D_6, 25 °C) δ 7.22−7.24 (br, 12H, Ph), 3.38 (m, 12H, OCH_2CH_2O), 3.17 (s, 18H, OCH_3), 1.40 [s, 72H, $C(CH_3)_3$] ppm.

General Procedure for the Synthesis of Amides from Reaction of Amines with Aldehydes Catalyzed by Complex II (product *N*-benzyl-*N*-methylbenzamide, 3aa, as an example). A 30 mL Schlenk flask was charged with a solution of complex **II** (3.00 mL, 0.03 mmol). *N*-Methylbenzylamine was added (0.13 mL, 1.00 mmol), then after 0.5 h of stirring, benzaldehyde was added (0.30 mL, 3.00 mmol). The resulting mixture was stirred at 25 °C for 3 h then filtered through a small plug of silica gel to remove the catalyst. The crude product was purified by column chromatography: (ethyl acetate:petroleum ether = 1: 5) yielding 203 mg (90%).

Acknowledgment. We are grateful to the National Natural Science Foundation of China (Grant no. 20632040) for financial support.

Supporting Information Available: Experimental details and characterization data for all amides. This material is available free of charge via the Internet at http://pubs.acs.org.

JO802617D