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Mild Amidation of Aldehydes with Amines Mediated by Lanthanide Catalysts

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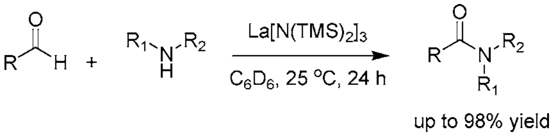
ABSTRACT



Catalytic amidation of aldehydes with amines is efficiently mediated by homoleptic lanthanide amido complexes, Ln[N(SiMe$_3$)$_2$]$_3$ (Ln = La, Sm, and Y). Amidation reactivity follows the trend: La > Sm ≈ Y. These reactions proceed in high yield without added oxidants, bases, and/or heat or light, which are usually required in other catalytic amidation processes. The reaction is demonstrated with a variety of amines, with yields as high as 98% based on amine.

Aromatic and aliphatic amides are functional groups of great importance in polymers, natural products, and pharmaceuticals.[1] Generally, amide groups are introduced by reacting carboxylic acids or their corresponding derivatives with amines.[1,2] Alternative methods such as late transition metal-catalyzed aminocarbonylation of halides with CO and amines,[3] modified Staudinger reactions,[4] and mercury-catalyzed rearrangements of ketoximes[5] have been utilized due to the lability of activated carboxylic acid derivatives under appropriate reaction conditions. Another attractive approach, reflecting the economical and abundant nature of the starting materials, is direct aldehyde amidation with amines. To date, only a few examples of this type of transformation have been reported.[6−11] Davidson's and Marko's groups described radical-mediated oxidative amidation using radical initiators[6a] and light,[6b] while Wang's and Ishihara's groups recently reported amidation via Cannizzaro reactions using LDA[7] or lanthanide reagents,[8] respectively. Very recently, Rovis's and Bode's groups also reported amidation using N-heterocyclic carbene (NHC) catalysts.[9] However, most catalytic amidation processes have utilized

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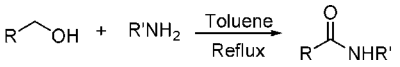
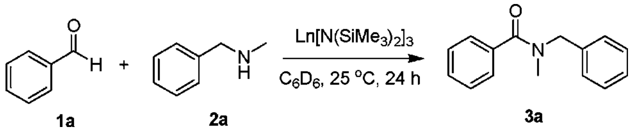
transition metal complexes (e.g., Cu,[10a] Rh,[10b] Ru,[10c] Pd,[10d] Ni[10e]) with an added oxidant.[11] Very recently, Milstein et al. reported direct, endothermic[12] amidation from alcohols and amines via aldehyde intermediates, using Ru PNN pincer catalysts, and driven by H_2 removal (eq 1).[13] Note that all of these catalytic systems require relatively harsh reaction conditions, such as oxidants, strong bases, and/or heat or light.



(1)

Homoleptic $Ln[N(SiMe_3)_2]_3$ lanthanide amido complexes[14] are versatile catalysts for hydroelementation processes, such as hydroamination,[15,20a] hydrosilylation,[16] hydroboration,[17] hydrophosphination,[18] and hydroalkoxylation.[19] Recently, Roesky et al. reported homoleptic lanthanide amido catalyst-mediated Tishchenko aldehyde dimerizations to yield the corresponding carboxylic esters.[20] Inspired by this successful esterification process, the challenging amidation of simple aldehydes and amines is explored in the present contribution. Homoleptic $Ln[N(SiMe_3)_2]_3$ complexes are found by in situ ^1H NMR spectroscopy to undergo instantaneous protonlysis with primary or secondary amines at room temperature to yield the corresponding lanthanide amido complexes and free $HN(SiMe_3)_2$. Addition of aldehydes affords the corresponding amidation products as discussed below. Preliminary studies with benzaldehyde and *N*-methylbenzylamine revealed that the *N*-benzyl-*N*-methylbenzamide amidation product is produced in a moderate yield (37%) after 24 h at 25 °C (entry 1, Table 1).

Table 1. Optimization of the $Ln[N(SiMe_3)_2]_3$-Catalyzed Amidation of Aldehydes with Amines[a]



1a **2a** **3a**

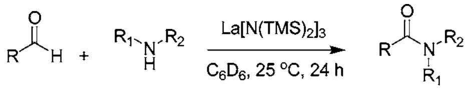
entry	molar ratio (**1**:**2**)	metal	mol % of catalyst	yield (%)[b]
1	1:1	La	5	37
2	3:2	La	5	61
3	2:1	La	5	71
4	3:1	La	5	78
5	1:2	La	5	48
6	1:1	La	10	47
7	2:1	La	10	72
8	3:1	Sm	5	54
9	3:1	Y	5	47

[a] Starting amine, aldehyde, and catalyst concentrations are identical in each experiment. See Supporting Information for reaction details. [b] Isolated yields based on *N*-methylbenzylamine except entry 5.

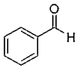
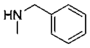
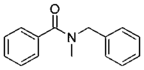
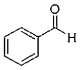
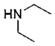
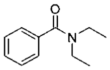
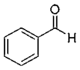
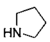
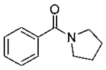
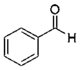
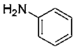
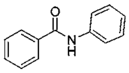
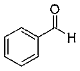
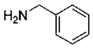
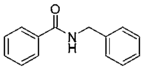
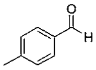
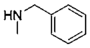
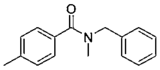
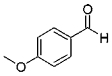
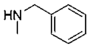
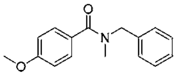
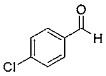
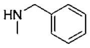
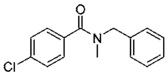
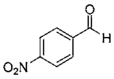
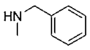
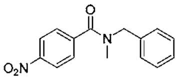
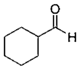
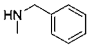
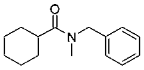
Optimization studies reveal that increasing the aldehyde equivalents enhances the yield significantly, up to 78% (entries 2−4, Table 1). The yield is, however, improved only marginally with increased amine (entry 1 vs 5, Table 1) or catalyst stoichiometries (entries 1, 3 vs 6, 7, Table 1). Several homoleptic amido complexes were used to assess the effect of Ln^{3+} ionic radius on activity (entries 8 and 9, Table 1), and the trend follows the order La > Sm ≈ Y.

With reaction conditions optimized (entry 4, Table 1), we then examined the scope of this lanthanide-catalyzed amidation with selected aldehydes and amines (Table 2).

Table 2. Lanthanide-Mediated Amidation of Aldehydes with Amines[a]



1 **2** **3**

entry	aldehyde	amine	amide	yield (%)[b]
1	 1a	 2a	 3a	78
2	 1a	 2b	 3b	27
3	 1a	 2c	 3c	38
4	 1a	 2d	 3d	80
5	 1a	 2e	 3e	23
6	 1b	 2a	 3f	76
7	 1c	 2a	 3g	80
8	 1d	 2a	 3h	98
9	 1e	 2a	 3i	92
10	 1f	 2a	 3j	37

[a] Starting amine, aldehyde, and catalyst concentrations are identical in each experiment. [b] Isolated yields based on amine.

In general, amidation proceeds efficiently at room temperature to provide the desired products in high yields. Aldehyde

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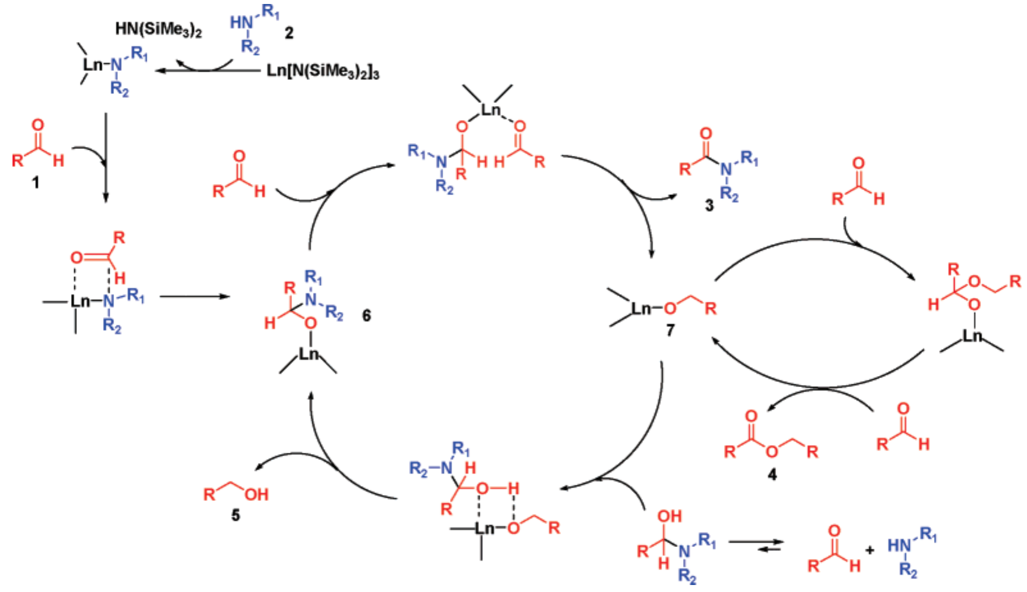
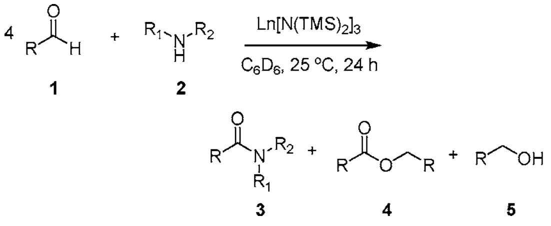
(19) Yu, X.; Seo, S.; Marks, T. J. *J. Am. Chem. Soc.* **2007**, *129*, 7244−7245.

Scheme 1. Proposed Catalytic Cycle for Lanthanide Amido-Mediated Aldehyde + Amine Amidation



electrophilicity likely plays a significant role as shown by the higher yields for electron-poor (entries 8 and 9, Table 2) versus electron-rich aryl aldehydes (entries 1, 6, 7, and 10, Table 2). Amine nucleophilicity[21] also likely plays a role as suggested by the moderate yields in the case of secondary alkyl amines (entries 2 and 3, Table 2). Surprisingly, this amidation also proceeds in the case of primary amines (entries 4 and 5, Table 2). The low yield with benzyl amine (entry 5, Table 2) is found to result from catalyst deactivation due to water production via imine formation and the inherent water sensitivity of the catalyst. Taken together, these results indicate that electronic effects play an important role in the rates of the present amidation processes.

In the present catalytic amidations, two side products are identified as ester **4** and alcohol **5**, produced in the stoichiometry of eq 2.



(2)

In essence, aldehyde **1** serves as the H_2 acceptor. Detailed kinetic/mechanistic analysis will be required to fully elucidate the catalytic pathway operative here, and the multiplicity of possible cycles and side reactions place this beyond the scope of a communication. In the tentative catalytic cycle of Scheme 1, catalyst **6** is active for amidation and **7** for Tishchenko coupling.[20] To probe for the presence of species **6** and **7**, a series of NMR-scale experiments were performed: (i) The addition order was varied; that is, aldehyde was added first to the catalytic solution, then amine. (ii) A mixture of aldehyde and amine was added to the active catalyst solution. Both procedures resulted in amide formation at a similar rate to the original conditions. (iii) Proposed catalyst **7** was generated in situ from $La[N(SiMe_3)_2]_3$ + benzyl alcohol and used to mediate the amidation reaction. After addition of aldehyde and amine to **7**, amide and ester formation was verified by ^1H NMR spectroscopy. (iv) To investigate the possibility of direct ester to amide conversion, $La[N(SiMe_3)_2]_3$was combined with ester + amine. Here, no amide formation is observed, consistent with Scheme 1.

In summary, we have developed a mild, room temperature homoleptic lanthanide amido-catalyzed aldehyde + amine amidation process that does not involve strong added oxidants, bases, and/or heat or light and provides yields as high as 98%. Further investigations regarding mechanism and synthetic applications are in progress.

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Supporting Information Available: Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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