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Lanthanide Amides $[(Me_3Si)_2N]_3Ln(\mu\text{-}Cl)Li(THF)_3$ Catalyzed Hydrophosphonylation of Aryl Aldehydes

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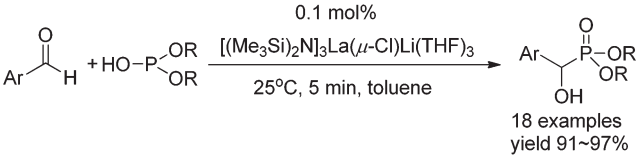

A highly efficient method for the synthesis of α-hydroxy phosphonates via lanthanide amides $[(Me_3Si)_2N]_3Ln(\mu\text{-}Cl)Li(THF)_3$ catalyzed hydrophosphonylation of aromatic aldehydes was developed. The reactions produced the products in excellent yields in the presence of 0.1 mol % $[(Me_3Si)_2N]_3La(\mu\text{-}Cl)Li(THF)_3$ at room temperature within 5 min. The existence of LiCl in the catalyst was a key factor affecting the catalytic activity. The mechanism for the process of high efficiency was proposed.

α-Hydroxy phosphonate exists as an important structural unit in many biologically active compounds which have been widely used as pesticides, antibiotics, anticancer drugs, antiviral agents, enzyme inhibitors, and so on.[1] Alternative methods such as reduction of keto phosphonates,[2] α-hydroxylation of alkyl phosphonates,[3] and addition of trialkyl phosphites to aldehydes[4] have been utilized for the synthesis of α-hydroxy phosphonates. Besides these pathways, the addition of dialkyl phosphites to aldehydes, known as the Pudovik reaction,[5] is undoubtedly the most straightforward and atom-economical one to α-hydroxy phosphonates. However, the Pudovik reaction cannot proceed spontaneously without heating in the absence of catalyst. Many research groups dedicated their efforts to develop highly active catalysts for this reaction in recent years. As a consequence, some catalysts or promoters, including metal oxides (such as MgO[6] and Al_2O_3[7]), Lewis bases[8] (such as Et_3N,[9] pyridine,[10] and TMG[11]), Bronsted bases (such as EtONa[12] and $Ti(O^iPr)_4$[13,7b]), and some others (such as KF[14] and MoO_2Cl_2[15]), were found to be effective for this transformation. In addition, several examples of the reaction under thermal noncatalyzed conditions[16] were also reported. It came to our notice that most of these systems require relatively harsh reaction conditions, such as high temperature (above 100 °C), long time (over 1 h), and/or high catalyst loading (more than 10 mol %). Moreover, the yields were not always good and in some instances the target products may cleave and regenerate the starting raw materials.[12,16b,17] More recently, to meet the growing demand for enantiomerically pure materials, the asymmetric synthesis of α-hydroxy phosphonates has been greatly developed[18] while the methods reported for the

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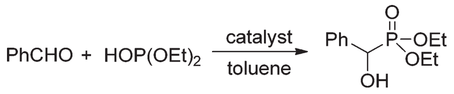
stereoselective hydrophosphonylation of aldehydes usually involve high catalyst loading. Therefore, the further development of novel catalysts and relevant processes of high efficiency for the synthesis of α-hydroxy phosphonate as valuable small molecule still remains of great interest.

Homoleptic bis(trimethylsilyl)amides of lanthanides $Ln[N(SiMe_3)_2]_3$[19] have been found to be efficient catalysts for a series of intermolecular or intramolecular reactions, including the Tishchenko reaction,[20] amidation,[21] monoaddition of terminal alkynes to nitriles,[22] coupling reaction of isocyanides with terminal alkynes,[23] and dimerization of terminal alkynes.[24] They also show high activity as catalysts for versatile hydroelementation processes such as hydrosilylation,[25] hydroboration,[26] hydroamination,[20b,27] hydrophosphination,[28] and hydroalkoxylation.[29] The tetracoordinate lanthanide amides $[(Me_3Si)_2N]_3Ln(\mu\text{-}Cl)Li(THF)_3$,[30] a chloride-bridged "ate" complex derived from $Ln[N(SiMe_3)_2]_3$, also work well as catalysts for aldol condensation,[31] MMA polymerization,[30c,d] aza-Henry reaction,[32] and guanylation of amines.[33] Although $[(Me_3Si)_2N]_3Ln(\mu\text{-}Cl)Li(THF)_3$ is more readily available than $Ln[N(SiMe_3)_2]_3$ from the viewpoint of the synthetic method, the application of the former as an efficient catalyst is comparatively limited. In some instances reported, the catalytic activities of the tricoordinate $Ln[N(SiMe_3)_2]_3$ and tetracoordinate $[(Me_3Si)_2N]_3Ln(\mu\text{-}Cl)Li(THF)_3$ were compared with each other. The results indicated that the existence of LiCl in $[(Me_3Si)_2N]_3Ln(\mu\text{-}Cl)Li(THF)_3$ may sometimes[31,32] improve the activity of $Ln[N(SiMe_3)_2]_3$ while at other times[33] produce the opposite effect.

TABLE 1. Catalysts Screening for the Reaction of Benzaldehyde with Diethyl Phosphite[a]



entry	catalyst	loading (mol %)	time	yield (%)
1	$LaCl_3$	2.0	12 h	0
2	$LaBr_3$	2.0	12 h	0
3	LaI_3	2.0	12 h	0
4	$Yb(OTf)_3$	2.0	6 h	0
5	$La[N(SiMe_3)_2]_3$	0.5	5 min	63
6	$La[N(SiMe_3)_2]_3$	0.1	5 min	0
7	$[(Me_3Si)_2N]_3La(\mu\text{-}Cl)Li(THF)_3$	0.5	5 min	96
8	$[(Me_3Si)_2N]_3La(\mu\text{-}Cl)Li(THF)_3$	0.1	5 min	92
9	$[(Me_3Si)_2N]_3La(\mu\text{-}Cl)Li(THF)_3$	0.05	5 min	43
10	LiCl	1.0	48 h	0

[a] Reactions were performed with 1 mmol of PhCHO and 1.2 mmol of $HOP(OEt)_2$ in 1 mL of toluene at 25 °C.

In continuation of our previous studies on lanthanide-catalyzed carbon−nitrogen bond-forming reactions,[34] we investigated the effectiveness of lanthanide amides as catalysts for the carbon−phosphorus bond-forming reactions. Herein, the paper presents a highly efficient process affording α-hydroxy phosphonates by the lanthanide amides-catalyzed Pudovik reaction.

The addition of diethyl phosphite to benzaldehyde to afford diethyl [hydroxy(phenyl)methyl]phosphonate was used as the model reaction in our initial screening of potential lanthanide catalysts. As shown in Table 1, typical Lewis acid-type compounds such as lanthanum trihalides (LaX_3, X = Cl, Br, I) and ytterbium triflate [$Yb(OTf)_3$] cannot initiate the reaction with the catalyst loading of 20 mol % (entries 1−4), indicating that the Lewis acidity of the lanthanide compounds was not decisive in catalyzing this reaction. In strong contrast, homoleptic lanthanum amide $La[N(SiMe_3)_2]_3$ catalyzed the reaction with high efficiency. The product was obtained in 63% yield with 0.5 mol % $La[N(SiMe_3)_2]_3$ at 25 °C for 5 min (entry 5). However, no desired product was observed when the catalyst loading was decreased to 0.1 mol % (entry 6). To our delight, the tetracoordinate lanthanum amide $[(Me_3Si)_2N]_3La(\mu\text{-}Cl)Li(THF)_3$ exhibited the catalytic activity that was still superior to that of tricoordinate lanthanum amide $La[N(SiMe_3)_2]_3$. The utility of 0.5 mol % of $[(Me_3Si)_2N]_3La(\mu\text{-}Cl)Li(THF)_3$ gave the product in an excellent 96% yield within 5 min (entry 7). Optimization studies revealed that decreasing the catalyst loading to 0.1 mol % kept the yield at 92% (entry 8). Further decreased catalyst loading of 0.05 mol % led to a dramatically lowered yield of 43% (entry 9). Because $[(Me_3Si)_2N]_3La(\mu\text{-}Cl)Li(THF)_3$ can be regarded as a solvated adduct of $La[N(SiMe_3)_2]_3$ and LiCl, anhydrous LiCl was tried alone to verify whether it can act as a catalyst independently. No product was detected after 48 h (entry 10). Besides, the use of the mixture of $La[N(SiMe_3)_2]_3$ and

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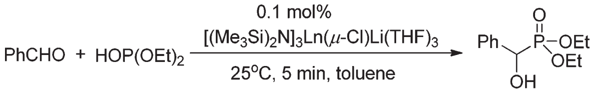
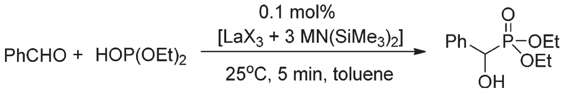
TABLE 2. The Influence of Lanthanide Metal on the Reaction[a]



	Ln =					
	Y	La	Nd	Sm	Er	Yb
yield (%)	93	93	94	92	90	82

[a] Reactions were performed with 1 mmol of PhCHO and 1.2 mmol of $HOP(OEt)_2$ in 1 mL of toluene at 25 °C for 5 min.

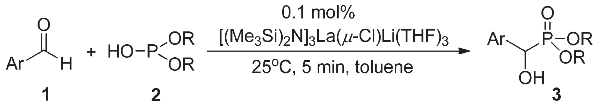
TABLE 3. The Influence of Alkali Metals and Halogens on the Reaction[a]



entry	M	X	yield (%)
1	Li	Cl	94
2	Li	Br	91
3	Li	I	14
4	Na	Cl	18
5	Na	I	0

[a] Reactions were performed with 1 mmol of PhCHO and 1.2 mmol of $HOP(OEt)_2$ in 1 mL of toluene at 25 °C for 5 min.

TABLE 4. $[(Me_3Si)_2N]_3La(\mu\text{-Cl})Li(THF)_3$-Catalyzed Reaction of Aromatic Aldehydes with Dialkyl Phosphites[a]



entry	Ar	R	product	yield (%)
1	Ph	Et	**3a**	92
2	1-naphthyl	Et	**3b**	97
3	2-furyl	Et	**3c**	94
4	$2\text{-}Me_2N\text{-}C_6H_4$	Et	**3d**	92
5	$4\text{-}Me_2N\text{-}C_6H_4$	Et	**3e**	91
6	$2\text{-}CH_3O\text{-}C_6H_4$	Et	**3f**	92
7	$3\text{-}CH_3O\text{-}C_6H_4$	Et	**3g**	94
8	$4\text{-}CH_3O\text{-}C_6H_4$	Et	**3h**	96
9	$2\text{-}CH_3\text{-}C_6H_4$	Et	**3i**	92
10	$4\text{-}CH_3\text{-}C_6H_4$	Et	**3j**	93
11	$2\text{-}Cl\text{-}C_6H_4$	Et	**3k**	96
12	$4\text{-}Cl\text{-}C_6H_4$	Et	**3*l***	94
13	$4\text{-}Br\text{-}C_6H_4$	Et	**3m**	94
14	$4\text{-}F\text{-}C_6H_4$	Et	**3n**	94
15	$3\text{-}NO_2\text{-}C_6H_4$	Et	**3o**	94
16	$4\text{-}NO_2\text{-}C_6H_4$	Et	**3p**	95
17	Ph	*i*-Pr	**3q**	94
18	Ph	Ph	**3r**	91

[a] Reactions were performed with 1 mmol of aldehyde and 1.2 mmol of dialkyl phosphite in 1 mL of toluene at 25 °C for 5 min.

anhydrous LiCl in 1:1 ratio in THF as catalyst failed to produce the same effect with $[(Me_3Si)_2N]_3La(\mu\text{-Cl})Li(THF)_3$. The result indicated that the combination manner of $La[N(SiMe_3)_2]_3$ with LiCl in crystalline $[(Me_3Si)_2N]_3La(\mu\text{-Cl})Li(THF)_3$ may be a key factor affecting its catalytic ability. Then, the reaction conditions were selected as 0.1 mol % of $[(Me_3Si)_2N]_3Ln(\mu\text{-Cl})Li(THF)_3$ at 25 °C for 5 min for the following studies.

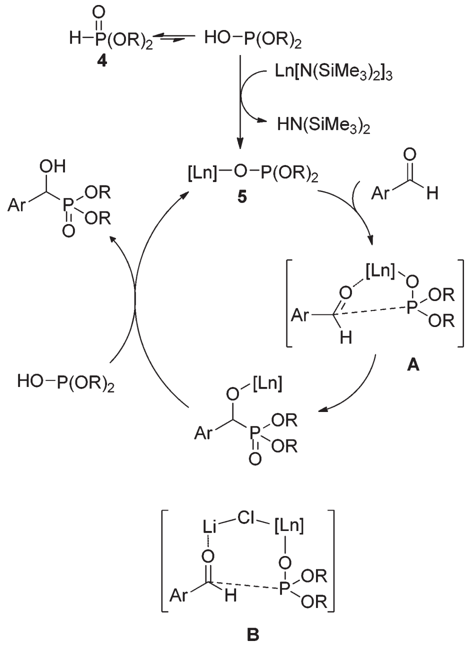
Next, a series of lanthanide amides were used to assess the influence of central metal on the activity and the results are shown in Table 2. It was found that the decrease in the Ln(III) ionic radii from the light rare earth La to heavy rare earth Er and Y has little influence on the reaction and the high yields above 90% were obtained. When $[(Me_3Si)_2N]_3Yb(\mu\text{-Cl})Li(THF)_3$ was used, a slightly decreased yield of 82% was observed. So, the amide complex of La, the largest metal among those tested, was chosen as a representative lanthanide source for carrying out the following studies.

Considering the obvious difference in the activity presented between $La[N(SiMe_3)_2]_3$ and $[(Me_3Si)_2N]_3La(\mu\text{-Cl})Li(THF)_3$, a new question arose if LiCl is the best partner of $La[N(SiMe_3)_2]_3$ in improving the activity. It was known that $[(Me_3Si)_2N]_3Ln(\mu\text{-Cl})Li(THF)_3$ can be formed in situ by the metathesis reaction of $LnCl_3$ with 3 equiv of $LiN(SiMe_3)_2$ in THF.[30c−e] To learn more about the influence of alkali metal ion and halide ion on the reaction, the model reaction with in situ formed tetracoordinate lanthanum amides, generated by the reaction of lanthanum trihalides with silylamides of sodium or lithium, as catalysts was performed. The results are presented in Table 3. As we expected, the in situ formed $[(Me_3Si)_2N]_3La(\mu\text{-Cl})Li(THF)_3$ showed the same activity as that of prepared $[(Me_3Si)_2N]_3La(\mu\text{-Cl})Li(THF)_3$ under the standard reaction conditions. However, either changing Cl to Br and I or changing Li to Na led to a decrease of the yield. For example, the utility of LaI_3 instead of $LaCl_3$ gave a yield of 14% (entry 3) while using $NaN(SiMe_3)_2$ instead of $LiN(SiMe_3)_2$ provided an 18% yield (entry 4). The catalyst generated from $NaN(SiMe_3)_2$ and LaI_3 failed to give the desired product (entry 5).

With the optimum reaction conditions in hand, the scope of the reaction was explored to various aromatic aldehydes and dialkyl phosphites. As shown in Table 4, all the reactions proceeded smoothly and quickly affording the corresponding α-hydroxy phosphonates in excellent yields (91−97%) at room temperature within 5 min. The reaction was general for aromatic aldehydes bearing substitutions at ortho-, meta-, and para-positions and tolerates both electron-deficient aldehydes and those that are electron rich. Heteroatoms either in the functional groups of the benzene ring or in heteroaromatics such as furan had no influence on the reaction. Dialkyl phosphites with different steric hindrances underwent the reaction giving the yields with little difference. The results suggest that $[(Me_3Si)_2N]_3La(\mu\text{-Cl})Li(THF)_3$ is highly active in catalyzing the hydrophosphonylation of aromatic aldehydes, regardless of electronic effects or steric effects of the substrates.

According to the distinctive properties of lanthanide amides, the proposed mechanism (Scheme 1) for the Pudovik reaction may involve rapid deprotonation of the dialkyl phosphite, which may exist in its tautomeric form as the phosphonate, releasing amine and forming the intermediate **5**, which is most probably the catalytically active species. **5** then reacts as a nucleophile toward the carbonyl carbon atoms of the aldehyde to generate the target α-hydroxy phosphonate. The superiority in the catalytic ability of $[(Me_3Si)_2N]_3Ln(\mu\text{-Cl})Li(THF)_3$ over $Ln[N(SiMe_3)_2]_3$ may be accounted for by two possibilities. First, it has been found that the Ln−N bond lengths in $[(Me_3Si)_2N]_3Ln(\mu\text{-Cl})Li(THF)_3$ are longer than those found in $Ln[N(SiMe_3)_2]_3$. For example, the average Nd−N bond distance of 2.336 Å[30b] in $[(Me_3Si)_2N]_3Nd(\mu\text{-Cl})Li(THF)_3$ is longer than the Nd−N bond length of 2.29 Å[19d] found in $Nd[N(SiMe_3)_2]_3$, and the average Sm−N

SCHEME 1. Proposed Mechanism for the Lanthanide Amide-Catalyzed Pudovik Reaction



bond distance of 2.319 Å[30c] in $[(Me_3Si)_2N]_3Sm(\mu\text{-}Cl)Li(THF)_3$ is longer than the Sm−N bond length of 2.284 Å[19e] found in $Sm[N(SiMe_3)_2]_3$. These deviations of bond lengths may be ascribed to the different steric hindrance around the lanthanide metal center. The sterically more crowded $[(Me_3Si)_2N]_3Ln(\mu\text{-}Cl)Li(THF)_3$ may undergo the metathesis reaction with $HOP(OR)_2$ more rapidly to form species **5**. Besides, the extraordinary activity that $[(Me_3Si)_2N]_3Ln(\mu\text{-}Cl)Li(THF)_3$ displayed may be rationalized by the cooperation of lanthanide and lithium. In the case of using $Ln[N(SiMe_3)_2]_3$ as catalyst, the lanthanide center in species **5** may coordinate to the aldehyde and lead to a close contact between the aldehyde and the nucleophilic phosphorus atom via a transition state **A**, wherein the lanthanide acts as a Bronsted base to deprotonate $HOP(OR)_2$ as well as a Lewis acid to activate the aldehyde. However, the formation of the transition state **A** may be suppressed to a certain extent by the steric repulsive interactions of the two substrates. When the sterically more flexible $[(Me_3Si)_2N]_3Ln(\mu\text{-}Cl)Li(THF)_3$[35] is used, the aldehyde may coordinate to the lithium to form the sterically less crowded transition state **B**, wherein the Li moiety in the catalyst functions as a Lewis acid instead of lanthanide. The stability of the transition state **B** caused by the cooperation of lanthanide and lithium may be an important factor resulting in the high efficiency of $[(Me_3Si)_2N]_3Ln(\mu\text{-}Cl)Li(THF)_3$.

In conclusion, we demonstrated here a highly efficient method for the synthesis of α-hydroxy phosphonates via hydrophosphonylation of aromatic aldehydes catalyzed by the tetracoordinate lanthanide amides $[(Me_3Si)_2N]_3Ln(\mu\text{-}Cl)Li(THF)_3$. The target products could be obtained in excellent yields in the presence of 0.1 mol % of $[(Me_3Si)_2N]_3La(\mu\text{-}Cl)Li(THF)_3$ at room temperature within 5 min. The existence of LiCl in the catalyst was a key factor affecting the catalytic activity. The further applications of this reaction for the stereoselective synthesis of α-hydroxy phosphonates are currently under investigation.

Experimental Section

Representative Procedure for Hydrophosphonylation of Aromatic Aldehydes. A mixture of $[(Me_3Si)_2N]_3La(\mu\text{-}Cl)Li(THF)_3$ (8.8 mg, 0.01 mmol) and diethyl phosphite (1.66 g, 12 mmol) in toluene (10 mL) was stirred for 10 min. Benzaldehyde (1.06 g, 10 mmol) was then added and the resulting mixture was allowed to stir at 25 °C for 5 min. Water was added, and the mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated in vacuo, and purified by chromatography on silica gel [eluent: acetone/petroleum ether (60−90 °C) 1:5] to afford **3a** (2.24 g, 92%) as white crystals.

Diethyl (hydroxy(phenyl)methyl)phosphonate (3a): mp 82−83 °C (white crystals, lit.[36] mp 83 °C); ^1H NMR (400 MHz, $CDCl_3$) δ 7.50−7.48 (m, 2H), 7.39−7.30 (m, 3H), 5.03 (d, J = 10.8 Hz, 1H), 4.11−3.93 (m, 4H), 3.62 (br s, 1H), 1.27 (t, J = 7.2 Hz, 3H), 1.22 (t, J = 7.2 Hz, 3H).

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Supporting Information Available: General experimental procedure, characterization data, and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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