

Lanthanide Formamidinates as Improved Catalysts for the Tishchenko Reaction

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The tris(formamidinato)lanthanum(III) complexes [La(*o*-TolForm)₃(thf)₂] **1**; *o*-TolForm = *N,N'*-bis(*o*-tolyl)formamidinate], [La(XylForm)₃(thf)] **2**; XylForm = *N,N'*-bis(2,6-dimethylphenyl)formamidinate], and [La(EtForm)₃] **3**, EtForm = *N,N'*-bis(2,6-diethylphenyl)formamidinate] are a new class of precatalysts for the Tishchenko reaction. Their catalytic activity is a result of their high Lewis acidity and the ease with which the ligand spheres can be interchanged. For the dimerization of benzaldehyde to give benzyl benzoate,

which is a benchmark reaction, compound **1** is, to the best of our knowledge, the most active catalyst ever reported. On a preparative scale, the reaction can be performed in the absence of solvent. A range of aromatic, heteroaromatic, and aliphatic aldehydes was rapidly converted into the corresponding esters by using catalysts **1–3**.

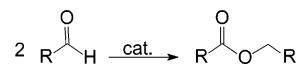
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Introduction

Lanthanide organometallic and coordination compounds have undergone significant development in organic synthesis in recent years. Lanthanide compounds have been utilized in a great number of synthetic reactions, in both stoichiometric and catalytic quantities.^[1] Lanthanide cations are considered hard Lewis acids, according to the hard–soft acid–base (HSAB) classification of Pearson. They are electrophilic, oxophilic, and redox stable. These properties, which can be finetuned by variation of the ionic radius of the lanthanide cation, are the driving force for various catalytic processes.^[2] Thus, lanthanide triflates [Ln(OTf)₃] turned out to be very active catalysts for aldol,^[3] Michael,^[4] allylation,^[5] Diels–Alder,^[6] and glycosylation reactions^[7], as well as for Friedel–Crafts acylations.^[8,9] Lanthanide alkoxides [Ln(OR)₃] have proven to be useful catalysts for the Meerwein–Ponndorf–Verley reduction^[10] and for hydrocyanation,^[11] whereas lanthanide shift reagents such as Eu(fod)₃ (fod = 6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionate) can be used as catalysts for Diels–Alder^[12] and hetero-Diels–Alder reactions.^[13]

One of the catalytic transformations that we are interested in is the so-called Tishchenko reaction (or Claisen–Tishchenko reaction).^[14–16] The Tishchenko reaction, which has been known for about a century,^[17] is the dimerization of an aldehyde to form the corresponding carboxylic ester (Scheme 1).^[18] Its industrial importance is mirrored in the

great number of patents derived from it. The Tishchenko ester of 3-cyclohexenecarbaldehyde is the precursor for the formation of epoxy resin, which is durable against environmental influences, whereas benzyl benzoate is used as a dye carrier; other uses of this reaction include the production of solvents for cellulose derivatives, and it has been used in the formation of plasticizers and in the food industry.^[19] Traditionally, aluminum alkoxides^[20–22] have been used as homogeneous catalysts for the Tishchenko reaction. More recently, other catalysts such as boric acid^[23] and a few transition-metal complexes have been used.^[24–26] However, these alternative catalysts are either only reactive under extreme reaction conditions (e.g. boric acid) or they are slow (e.g. [(C₅H₅)₂ZrH₂]),^[24] expensive (e.g. [H₂Ru(PPh₃)₂]),^[25] or give low yields (e.g. K₂[Fe(CO)₄]).^[26]



Scheme 1.

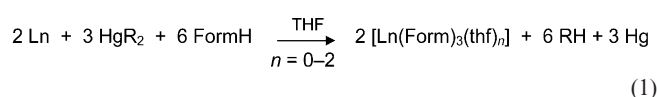
Recently, it was shown that the lanthanide complexes [(C₅Me₅)₂LaCH(SiMe₃)₂]^[27] and [Ln{N(SiMe₃)₂}₃]^[14,16] are the most active catalysts for the Tishchenko reaction because of their high Lewis acidity and easily interchangeable ligand spheres. Further advantages of these compounds as catalysts include the environmentally benign nature of the metals, their high activity, and their high durability. [La{N(SiMe₃)₂}₃] is more accessible than [(η⁵-C₅Me₅)₂La-CH(SiMe₃)₂]. Although somewhat less active, [La₂(*t*Bu₂pz)₆] (*t*Bu₂pz = 3,5-di-*tert*-butylpyrazolate) can be readily prepared from La metal and the appropriate pyr-

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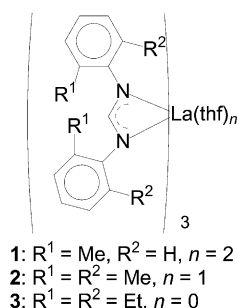
azole.^[15] Furthermore, very recently the homoleptic bis-(trimethylsilyl)amides of the alkaline earth metals $[M\{N(SiMe_3)_2\}_2]$ ($M = Ca, Sr, Ba$) were reported as precatalysts for the Tishchenko reaction, and they are almost as active as the lanthanide compounds.^[28]

Here, we report a series of tris(formamidinato)lanthanum(III) complexes as precatalysts for the Tishchenko reaction. These compounds are, for most of the conversions described, more active than any other system reported. The tris(formamidinato)lanthanide(III) complexes were recently reported to be accessible from the reaction of N,N' -bis(aryl)formamidines (FormH) with lanthanide metals and bis(pentafluorophenyl)mercury $[Hg(C_6F_5)_2]$ in THF [Equation (1), ($R = C_6F_5$)].^[29]



Results and Discussion

It was shown in our previous studies that the rate of the catalytic conversion of aldehydes to carboxylic esters depends on the ionic radius of the lanthanide atom involved. In these studies, derivatives whose central metal possessed the largest ionic radius were the most active.^[14] Therefore, we focused our studies on the tris(formamidinato)lanthanum(III) complexes $[La(o-TolForm)_3(thf)_2]$ **1**; $o-TolForm = N,N'$ -bis(o -tolyl)formamidinate], $[La(XylForm)_3(thf)]$ **2**; $XylForm = N,N'$ -bis(2,6-dimethylphenyl)formamidinate], and $[La(EtForm)_3]$ **3**, $EtForm = N,N'$ -bis(2,6-diethylphenyl)formamidinate] (Scheme 2). These compounds differ in their substitution pattern on the aromatic ring and, more importantly, in the number of thf molecules coordinated to the central metal.



Scheme 2.

To compare the reaction rates of catalysts **1–3** with those of other catalysts, the standard reaction of benzaldehyde to form benzyl benzoate was chosen. The yields were determined by 1H NMR spectroscopy in C_6D_6 with approximately 1 mol-% catalyst at room temperature (Table 1). The turnover frequencies (TOFs) were determined from complete conversion.^[30] The increase in the intensity of the benzyl group proton signal, concomitant with a decrease in the

characteristic aldehyde proton signal in the 1H NMR spectrum, provided evidence for the production of benzyl benzoate. Upon reaction of compound **1** with benzaldehyde in a 1:5 stoichiometry, the formamidinate ligand was partially cleaved off during the catalytic conversion. A comparison of compounds **1**, **2**, and **3** (Table 1, Entries 1–3) shows that, for quantitative turnover, complex **1** exhibited the highest activity. To rationalize this difference in rate, we suggest that the sterically less hindered complex **1** with two labile thf ligands and the smallest Form ligands is most easily attacked by the aldehyde and thus the initial conversion of the precatalyst is the fastest. The reaction of complex **2** was repeated on a preparative scale (2.2 g of reactant), in the absence of solvent, to determine the isolated yield and to characterize the product fully. The workup of the reaction was very simple because the product could easily be transferred by vacuum. The reaction went to completion immediately and thus was faster than the same reaction on an NMR scale. The fast conversion results from internal heating of the very exothermic reaction. In contrast to experiments in solution, there is no solvent to dissipate the heat.

Table 1. Tishchenko reaction of benzaldehyde giving benzyl benzoate.

Entry	Catalyst	mol-%	Conditions [°C, h] ^[a]	Yield [%] ^[b]	TOF [h ⁻¹]	Ref.
1	$[La(o-TolForm)_3(thf)_2]$ (1)	1	r.t., 0.5	99	200	
2	$[La(XylForm)_3(thf)]$ (2)	1	r.t., 0.75	99	133	
				93 ^[c]		
3	$[La(EtForm)_3]$ (3)	1	r.t., 1	99	100	
4	$[La\{N(SiMe_3)_2\}_3]$ (4)	1	r.t., –	98	87	[16]
5	$[(\eta^5-C_5Me_5)_2LaCH(SiMe_3)_2]$ (5)	1	r.t., 72	94	1.3	[27]
6	$[La(OiPr)_3]$	1	r.t., –	–	–	[16]
7	SmI_2	1	r.t., –	–	–	[16]
8	$[Sm\{O-2,6-(tBu)_2C_6H_3\}_3]$	1	r.t., –	70	1.9	[16]
9	$[Ca\{N(SiMe_3)_2\}_2(thf)_2]$ (6)	1	r.t., –	97	>100	[28]
10	$Al(OiPr)_3$	1	r.t., –	51	8	[16]
11		1	r.t., 5	67		[33]
12		1	r.t., 5	76		[33]
13		2	r.t., 5	68		[34]
14	$[(C_5H_5)_2ZrH_2]$	5	17, –	7		[24]
15	$[(C_5H_5)_2HfH_2]$	5	17, –	9		[24]
16	$[H_3Ru(PPh_3)_2]$		20, –	23		[25]
17	$K_2[Fe(CO)_4]$	20	46, –	46	<<1	[26]
18	$B(OH)_3$	13.4	250, 6	34		[23]
19		1	r.t., 12	86		[35]

[a] Reaction conditions (this work): Catalyst in C_6D_6 . [b] Determined by 1H NMR spectroscopy. [c] Isolated yield.

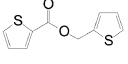
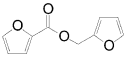
Comparison with other lanthanum catalysts such as $[La\{N(SiMe_3)_2\}_3]$ (**4**) and $[(\eta^5-C_5Me_5)_2LaCH(SiMe_3)_2]$ (**5**) shows that compounds **1–3** are significantly more active for the conversion of benzaldehyde to benzyl benzoate

(Table 1). Moreover, the commercially available lanthanide compounds SmI_2 ^[31] and $\text{La}(\text{O}i\text{Pr})_3$ ^[27] (Table 1, Entries 6 and 7), which are known Tishchenko catalysts, proved to be inactive for the coupling of benzaldehyde. In contrast, the homoleptic aryloxide $[\text{Sm}\{\text{O}-2,6-(t\text{Bu})_2-\text{C}_6\text{H}_3\}_3]$, which was recently introduced as a catalyst, showed some degree of activity (Table 1, Entry 8).^[32] However, the TOFs and the yields obtained with the use of the aforementioned catalysts were significantly lower than those observed for **1–3**. In addition, the recently introduced alkaline earth metal amides, such as $[\text{Ca}\{\text{N}(\text{SiMe}_3)_2\}_2(\text{thf})_2]$ (**6**) (Table 1, Entry 9), cannot compete with the lanthanum catalysts. The use of the standard aluminum catalyst $\text{Al}(\text{O}i\text{Pr})_3$ ^[21,22] under the reaction conditions described above led to a low yield of product (Table 1, Entry 10). Even the so-called high-speed Tishchenko catalysts (2,7-dimethyl-1,8-biphenyldioxy)-bis[diisopropoxyaluminum(III)] (Table 1, Entry 11) and (2,7-dimethyl-1,8-biphenyldioxy)bis[dibenzoyloxyaluminum(III)] (Table 1, Entry 12)^[33] or other aluminum-based catalysts (Table 1, Entry 13)^[34] did not reach the level of activity of the lanthanum compounds. All classical transition-metal catalysts,^[23–25] as well as boric acid^[22] (Table 1, Entries 14–18), failed to catalyze the reaction to complete conversion. Some more recent examples from transition-metal chemistry show high yields, but are still slower than the lanthanide systems (Table 1, Entry 19).^[35] In summary, compound **1** is, to the best of our knowledge, the most active catalyst for the benchmark Tishchenko reaction of benzaldehyde to give benzyl benzoate.

To study the scope and limitations of compounds **1–3** with respect to the Tishchenko reaction, the reactions of aromatic, heteroaromatic (Table 2), and aliphatic aldehydes (Table 3) in the presence of 0.5–1.0 mol-% of the catalysts were investigated. The reactions were initially performed on small scale. Unsurprisingly, the intramolecular Tishchenko reaction of *o*-phthalaldehyde to form the corresponding lactone gave high yields and was very fast (TOF > 1500 h^{−1}; Table 2, Entry 1). Furthermore, the suitability of **1** and **3** for the dimerization of heteroatom-functionalized substrates was investigated by using two substrates that are known to be difficult to dimerize (Table 2, Entries 2 and 3). Evidently, the heteroatom of the substrate can form a hemilabile Lewis acid–Lewis base adduct with the catalyst, which thus hampers the Tishchenko process, as the required aldehyde–catalyst interaction is impeded. Indeed, the poor reactivity of furfural is well known. Thus, by using an aluminum alkoxide or $\text{K}_2[\text{Fe}(\text{CO})_4]$ /crown ether catalysts, very low yields are observed.^[21,26,36] For example, only a 3.4% yield was obtained by using the $\text{K}_2[\text{Fe}(\text{CO})_4]$ /crown ether catalysts. In contrast, lanthanum formamidinate is much more reactive (Table 2, Entry 3).

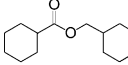
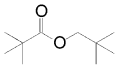
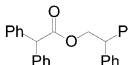
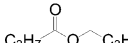
Both cyclic and noncyclic aliphatic aldehydes were also investigated as potential substrates for the Tishchenko reaction (Table 3). On an NMR scale, quantitative yields were observed for most substrates. As seen for other lanthanum catalysts, the dimerization of cyclohexanecarboxaldehyde proceeded extremely fast (Table 3, Entry 1) so that the reactants could not be detected immediately after mixing. This

Table 2. Results for the catalyzed dimerization of aromatic aldehydes.^[a]

Entry	Substrate	Product	Catalyst	mol-% ^[a]	<i>T</i> [°C]	<i>t</i> [h]	Yield [%] ^[b]	TOF [h ^{−1}]
1			1	1.0	r.t.	0.066	quant.	>1500
			4 ^[c]	1.0	r.t.		85	>1500
			5 ^[d]	1.0	60	24	95	95
			6 ^[e]	1.0	r.t.		95	>500
2			1	0.5	r.t.	120	88	1.47
			3	0.5	r.t.	120	77	1.3
			3	0.5	60	16	88	
3			1	0.5	r.t.	120	45	0.75
			1	0.5	60	16	79	
			4 ^[c]	1.0	r.t.		40	2
			$\text{K}_2[\text{Fe}(\text{CO})_4]$ ^[f]	33	60	24	3.4	<<1

[a] Reaction conditions: 0.5–1 mol-% catalyst in C_6D_6 . [b] Determined by ¹H NMR spectroscopy. [c] Ref.^[16] [d] Ref.^[27] [e] Ref.^[28] [f] Ref.^[26]

Table 3. Results for the catalyzed dimerization of aliphatic aldehydes.^[a]

Entry	Substrate	Product	Catalyst	mol-%	<i>T</i> [°C]	<i>t</i> [h]	Yield [%] ^[b]	TOF [h ^{−1}]
1			1	1	r.t.	0.066	quant.	>1500
			2	1	r.t.	0.066	quant.	>1500
			3	1	r.t.	0.066	quant.	>1500
			4 ^[d]	1	r.t.		quant.	>1500
			6 ^[e]	5	r.t.		>95	>100
2			1	0.5	r.t.	4	91	45
			2	0.5	r.t.	10	90	18
			3	0.5	r.t.	10	86	17.2
			4 ^[c]	1	r.t.		quant.	>1500
			6 ^[d]	2	r.t.		98	>100
3			1	1	60	20	80	5
4			1	0.5	r.t.	0.02	16 ^[f]	

[a] Reaction conditions: 0.5–1 mol-% catalyst in C_6D_6 . [b] Determined by ¹H NMR spectroscopy. [c] Isolated yield. [d] Ref.^[16] [e] Ref.^[28] [f] Trimers and tetramers were produced as a byproducts, as determined by GC–MS.

reaction was also repeated on a preparative scale (2.2 g of reactant), in the absence of solvent, and gave a high isolated yield.

Surprisingly, the dimerization of pivalaldehyde is slower than expected by using catalysts **1–3**, possibly owing to the steric bulk of the substrate (Table 3, Entry 2). In all other cases, catalysts **1–3** were superior to compounds **4** and **5**. Although complex **1** catalyzed the dimerization of aldehydes, with or without an α -H atom, quickly and in high yields, the reaction of butanal at 21 °C gave mostly higher coupling products (Table 3, Entry 4).^[22,37,38] Identification of the products, butyl butyrate and the trimeric and tetrameric coupling products, which were formed by a tandem aldol–Tishchenko reaction,^[39–41] was established by GC–MS.

Summary

Tris(formamidinato)lanthanum(III) complexes **1–3** represent a new and improved class of Tishchenko catalysts. Their catalytic activity is a result of their Lewis acidity and the ease with which the ligand spheres can be interchanged. For the Tishchenko dimerization of benzaldehyde to benzyl benzoate, these complexes are, to the best of our knowledge, the most active catalysts ever reported and their effectiveness is in the order **1** > **2** > **3**.

Experimental Section

General Considerations: Deuterated solvents were obtained from Chemotrade Chemiehandelsgesellschaft mbH (all ≥ 99 atom-% D) and they were degassed, dried, and stored in vacuo in resealable flasks over Na/K alloy. NMR spectra were recorded with a Jeol JNM-LA 400 FTNMR spectrometer. Chemical shifts were referenced to internal solvent resonances and are reported relative to tetramethylsilane. Elemental analyses were carried out with an Elementar vario EL III. All aldehydes were obtained from Sigma-Aldrich and were degassed, dried with CaH_2 , and stored under an atmosphere of nitrogen in resealable flasks. Catalysts **1–3** were prepared following a literature procedure.^[29]

General Procedure for the Tishchenko Reaction (NMR-Scale Reaction): Lanthanide complex **1**, **2**, or **3** was weighed, under a nitrogen atmosphere, into an NMR tube. C_6D_6 (≈ 0.7 mL) was condensed into the NMR tube, and the mixture was frozen to -196°C . The reactant was injected onto the solid mixture, and the whole sample was melted and mixed immediately prior to insertion into the core of the NMR instrument (t_0). For the kinetic measurement the ratio of reactant to product was calculated by a comparison of the integration of the CHO with the CH_2O signals.

General Procedure for the Tishchenko Reaction (Preparative-Scale Reaction): Under an atmosphere of nitrogen the catalyst was stirred in a tempered reaction flask. The reactant (2.2 g) was added directly to the catalyst and an exothermic reaction was observed. After 1 d the product was isolated by distillation. [The products with high TOFs were worked up immediately (see Tables 1 and 2).]

Benzyl Benzoate:^[24] ^1H NMR (400 MHz, C_6D_6 , 25°C): δ = 5.12 (s, 2 H), 6.95–7.17 (m, 8 H, Ph) 8.05–8.07 (m, 2 H, Ph) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, C_6D_6 , 25°C): δ = 66.7, 128.2, 128.4, 128.5, 128.7, 129.9, 132.9, 136.6, 166.1 ppm. $\text{C}_{14}\text{H}_{12}\text{O}_2$ (212.09): calcd. C 79.22, H 5.70; found C 79.23, H 5.26.

Phthalide:^[42] ^1H NMR (400 MHz, C_6D_6 , 25°C): δ = 4.46 (s, 2 H, CH_2O), 6.70 [d, $^3J(^1\text{H},^1\text{H})$ = 6.70 Hz, 1 H, Ph], 6.95 [t, $^3J(^1\text{H},^1\text{H})$ = 7.44 Hz, 1 H, Ph], 7.08 [t, $^3J(^1\text{H},^1\text{H})$ = 7.44 Hz, 1 H, Ph], 7.66 [d, $^3J(^1\text{H},^1\text{H})$ = 6.70 Hz, 1 H, Ph] ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, C_6D_6 , 25°C): δ = 69.0, 122.1, 125.4, 126.2, 128.7, 133.4, 146.8, 171.0 ppm.

2-Thienylmethyl 2-Thiophenecarboxylate:^[27] ^1H NMR (400 MHz, C_6D_6 , 25°C): δ = 5.11 (s, 2 H, CH_2O), 6.44–6.48 (m, 2 H, aromatic), 6.54–6.57 (m, 1 H, aromatic), 6.76–6.80 (m, 2 H, aromatic), 7.56–7.57 (m, 1 H, aromatic) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, C_6D_6 , 25°C): δ = 60.9, 126.9, 127.0, 127.8, 128.6, 132.5, 133.8, 133.9, 138.2, 161.6 ppm.

2-Furylmethyl 2-Furancarboxylate:^[43] ^1H NMR (400 MHz, C_6D_6 , 25°C): δ = 4.99 (s, 2 H, CH_2O), 5.79–5.81 (m, 2 H, aromatic), 5.92–5.94 (m, 1 H, aromatic) 6.11–6.12 (m, 1 H, aromatic), 6.81–6.82 (m, 2 H, aromatic) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, C_6D_6 ,

25°C): δ = 58.0, 110.8, 111.2, 111.8, 118.3, 143.4, 144.8, 146.4, 149.8, 158.0 ppm.

Cyclohexylmethyl Cyclohexanecarboxylate:^[24] ^1H NMR (400 MHz, C_6D_6 , 25°C): δ = 0.80–0.86 (m, 2 H), 0.98–1.09 (m, 6 H), 1.35–1.67 (m, 11 H), 1.85–1.87 (m, 2 H), 2.16–2.28 (m, 1 H), 3.86 [d, $J(^1\text{H},^1\text{H})$ = 2.80 Hz, 2 H, CH_2O] ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, C_6D_6 , 25°C): δ = 25.7, 26.0, 26.1, 26.6, 29.4, 29.9, 37.5, 43.4, 69.1, 175.4 ppm. $\text{C}_{14}\text{H}_{24}\text{O}_2$ (224.18): calcd. C 74.95, H 10.78; found C 74.33, H 10.62.

Neopentyl Neopentanoate:^[24] ^1H NMR (400 MHz, C_6D_6 , 25°C): δ = 0.79 [s, 9 H, $(\text{CH}_3)_3\text{C}$], 1.45 [s, 9 H, $(\text{CH}_3)_3\text{C}$], 3.71 (s, 2 H, CH_2O) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, C_6D_6 , 25°C): δ = 26.4, 27.4, 31.4, 38.9, 73.4, 177.4 ppm.

2,2-Diphenylethyl Diphenylacetate:^[44] ^1H NMR (400 MHz, C_6D_6 , 25°C): δ = 4.15 [t, $J(^1\text{H},^1\text{H})$ = 7.6 Hz, 1 H, CHPh_2], 4.56 [d, $J(^1\text{H},^1\text{H})$ = 7.6 Hz, 2 H, CH_2O], 4.90 (s, 1 H), 6.90–7.20 (m, 20 H, Ph) ppm. $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, C_6D_6 , 25°C): δ = 50.0, 57.5, 67.4, 126.8, 127.3, 128.5, 128.6, 128.7, 129.0, 139.1, 141.3, 172.0 ppm.

Acknowledgments

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