

Lanthanide bis(trifluoromethylsulfonyl)amides vs. trifluoromethylsulfonates as catalysts for Friedel–Crafts acylations

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Abstract

The use of catalytic amounts: 1 mol% or less of perfluoroalkyl lanthanide salts as homogeneous catalysts for Friedel–Crafts acylations in non-hazardous solvents is thereafter investigated. Lanthanide bis(trifluoromethylsulfonyl)amides are better catalysts than the triflate analogues towards the acetylation of activated aromatic rings.

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1. Introduction

A wide variety of Lewis acid complexes has been developed to catalyse organic reactions, but cheap, reusable catalysts for industrial uses often remain to be discovered. Among all these organic reactions, the Friedel–Crafts acylation which is one of the most important carbon–carbon bond formation processes in organic synthesis has been the object of particular attention. To replace the ubiquitous stoichiometric aluminium chloride, a great number of metal salts, especially hard Lewis acids, non-hydrolysable f metal derivatives, have been tested.

The lanthanide halides or uranyl salts have been described as both very efficient and reusable catalysts for the alkylation or benzylation of activated aromatic compounds [1–4] but are ineffective for

acetylation. More efficient and also reusable trifluoromethylsulfonates (triflates) [5–9] and bis(trifluoromethylsulfonyl)amides (triflimidates) [10,11] or tris(perfluoroalkylsulfonyl)methide complexes [12] give good results in acetylation reactions, especially in fluoruous biphasic media [13–15]. However, the reported good results are obtained from very large amounts of lanthanide “catalyst”: generally 20 mol%, and in nitromethane, a very hazardous solvent not advisable for industrial use. In many cases, the “catalysts” are scandium derivatives but the very high cost of these compounds makes these complexes economically unusable and restrains them for laboratory uses only.¹

¹ Scandium is quite common, its abundance being comparable to that of arsenic and twice than boron, but it is not readily available owing to a lack of rich sources and difficulty of separation. Thus, the total world production of this element is only a few hundred kilograms per year.

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To establish whether it was really possible to consider a possible future industrial use of lanthanide perfluoroalkyl derivatives as homogeneous catalysts, we have investigated the activity of low amounts (0.01 equiv. or less) of these salts in non-hazardous solvents towards acylation reactions.

2. Results and discussion

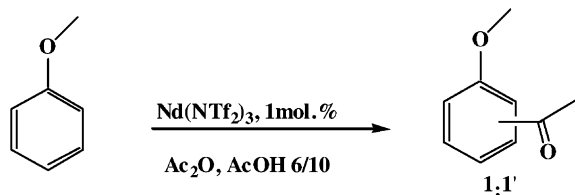
2.1. The catalysts

The lanthanide trifluoromethylsulfonates named triflates: $\text{Ln}(\text{OTf})_3$ ($\text{Tf} = \text{SO}_2\text{CF}_3$) are commercially available samples or are synthesised in water from lanthanide carbonates and trifluoromethanesulfonic acid. The monohydrated bis(trifluoromethylsulfonyl)amides named triflimidates: $\text{Ln}(\text{NTf}_2)_3(\text{H}_2\text{O})$ are synthesised in water from carbonates and bis(trifluoromethylsulfonyl)imide: HNTf_2 according to a method developed in the laboratory.

2.2. Acetylation experiments

To compare with previous experiments, acetylation reactions are performed with anisole as a substrate. The experiments have been carried out in a mixture of acetic acid and acetic anhydride acting simultaneously as a solvent and as acetylation reagent using 1% of neodymium triflimidate as a catalyst (Scheme 1).

The reaction is monitored by gas chromatography. In Fig. 1, the yields of acetylation products (4- and 2-methoxyacetophenone: **1** and **1'**) are plotted as a function of time for reactions performed at different temperatures. At room temperature or at 50 °C, yields are low, even after 3 h, whereas at 120 °C the reaction is fast and highly selective affording after 30 min of refluxing, a mixture of **1** and **1'** in a 97/3 ratio in 85%



Scheme 1. Acetylation of anisole.

Table 1

Yield of the acetylation of anisole with different reagents, $\text{Nd}(\text{NTf}_2)_3$ 1 mol%, 120 °C, 3.5 h

Reagent (equiv.)	Anisole (equiv.)	TR (%)	Yield (%)
$\text{Ac}_2\text{O}/\text{AcOH}$ (6/10)	1	100	>95
Ac_2O (20)	1	100	85
Ac_2O (1)	5	100	>95
AcOH (20)	1	0	0

yield. The consumption of the anisole is complete after 2.5 h and the acetylation products are obtained in 95% yield.

Of course at higher temperature, the reaction might be more faster, but requires the use of a pressure resistant apparatus. All the following experiments will be performed at atmospheric pressure.

To optimise the experimental conditions, some experiments are carried out in order to establish the influence of the reagents, of the element and of the amount of the catalyst. All the experiments are monitored: samples are taken and analysed by GC. The role of the acylation reagents has been studied first, the results are reported in Table 1.

The best results are obtained with the acetic acid/acetic anhydride mixture used in excess or with acetic anhydride in the presence of an excess of anisole whereas with acetic acid alone, the acetylation reaction does not occur.

The most important question is the nature of the catalyst, Table 2 reports the experiments performed with different rare earth triflimidates as catalyst. The yields are high and very similar for neodymium and ytterbium whereas, as previously reported for halides or triflates, lanthanum salts are less efficient [3,16].

Table 2

Yield of the acetylation of anisole with different f metal triflimidates: 1 mol% catalyst, 120 °C, $\text{Ac}_2\text{O}/\text{AcOH} = 6/10$

Element	Yield (%) after		
	20 min	80 min	210 min
Nd	85 (88) ^a	89 (97) ^a	>95 (100) ^a
Yb	80	82	>95 (100) ^a
La	40	55	80 (88) ^a
U ^b	80	88	>95 (100) ^a

^a Transformation rate (TR, %).

^b Uranyl salt $\text{UO}_2(\text{NTf}_2)_2$.

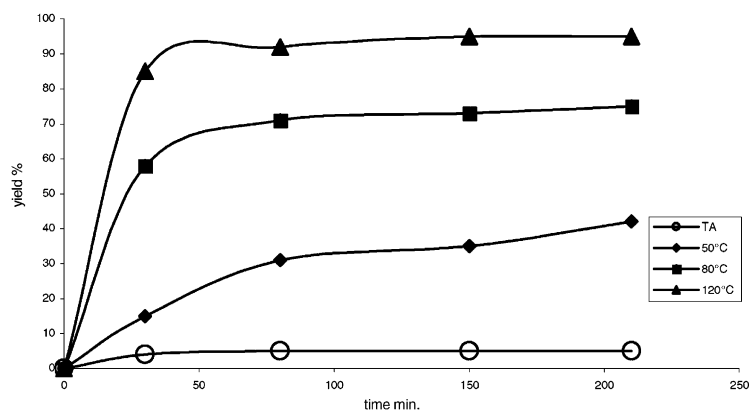


Fig. 1. Yield of anisole acetylation reaction at different temperatures.

It had been established that uranyl halides were much more efficient catalysts for benzoylation reactions than their lanthanide analogues [4]. To verify if uranyl triflimidate (synthesised from uranyl acetate) is also a more efficient catalyst than lanthanide triflimidates towards acetylation, a reaction was performed with this salt. In the same conditions, the yields are very similar for uranyl or neodymium derivatives (Table 2).

An important point is to establish the minimal amount of catalyst which allows a satisfactory yield in a reasonable time. In Fig. 2, the yield of the acetylation of anisole is plotted as a function of time in the refluxing mixture $\text{Ac}_2\text{O}/\text{AcOH}$ (6/10)

with, respectively, 1, 0.5 and 0.1% of neodymium triflimidate.

It can be seen that after 30 min, an 88% yield is obtained with 1 mol% of catalyst and 85% with only 0.5 mol%, whereas the yield is substantially lower (68%) when 0.1 mol% is used. Moreover, with this amount of catalyst, the reaction is not complete even after 3.5 h. Thus, 0.5 mol% of neodymium triflimidate is enough to obtain a high yield after only 30 min refluxing.

The comparison of the catalytic activity of triflates vs. triflimidates was performed for neodymium and lanthanum derivatives. It was also interesting to compare the activity of perfluoroalkylsul-

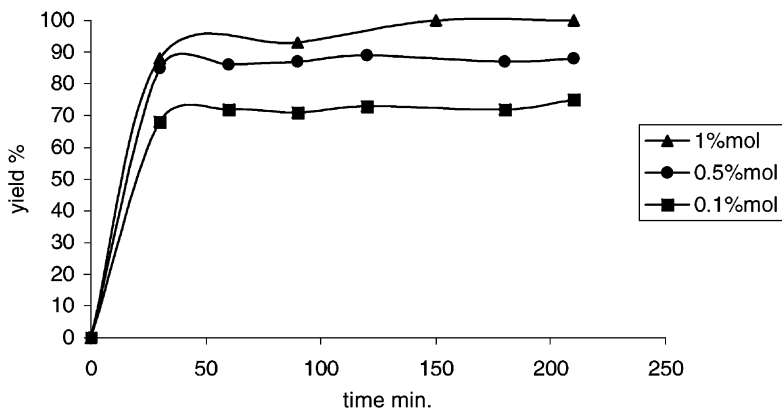


Fig. 2. Yield of anisole acetylation reaction with 1, 0.5 and 0.1 mol% of $\text{Nd}(\text{NTf}_2)_3$ as catalyst ($\text{Ac}_2\text{O}/\text{AcOH} = 6/10$, 120°C).

Table 3

Comparison of the yield of the acetylation reaction with neodymium and lanthanum triflates, triflimidates and halides as catalysts (1 mol% catalyst, 120 °C, Ac₂O/AcOH = 6/10)

Catalyst	Yield (%) after		
	20 min	80 min	210 min
Nd(NTf ₂) ₃	84	89	>95
Nd(OTf) ₃	17	42	55
La(NTf ₂) ₃	40	55	80
La(OTf) ₃	5	18	40
NdCl ₃ , 3THF	0	0	0

fonyl lanthanide salts towards much cheaper halides (Table 3).

Incontestably, in the same conditions, the triflimidates are more efficient catalysts than triflates and neodymium derivatives are better than the analogous lanthanum complexes. It is noteworthy that neodymium trichloride (THF adduct) does not act as a catalyst in this reaction.

Until now, with lanthanide halides or triflates as catalysts, the acetylation or benzylation reactions were only possible on activated substrates such as anisole, phenetole, methoxynaphthalene, etc. All attempts at acylating weakly activated aromatic compounds (toluene, xylene, etc.) give only poor yields, even in nitromethane, except for mesitylene, but with 20 mol% of scandium triflate [5], and have failed with other solvents. On the opposite, such acylations were performed in high yield using bismuth triflate as a catalyst [17].

The first experiment was carried out on toluene used as a solvent (5 equiv.) with acetic anhydride (1 equiv.) as acylating agent and 1 mol% neodymium triflimidate. After 5 h of refluxing, only 4% of **2** is obtained and two other compounds are formed in

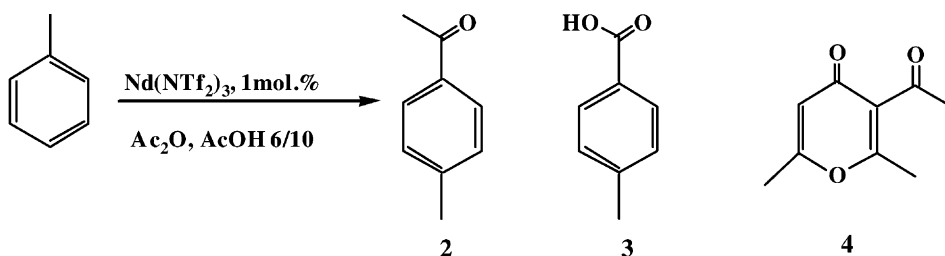
significant amount: 4-methylbenzoic acid (**3**) (3%) and 3-acetyl-2,6-dimethylpyrone (**4**) (6%) identified by comparison of mass and ¹H NMR spectra with an authentic sample (Scheme 2).

Some attempts at improving the acetylation yield were made. The reactions are performed under nitrogen to avoid the formation of **3**. The better, but low yield (14%) is obtained with 5% ytterbium triflimidate and acetyl chloride after 24 h. In the same conditions, with ytterbium triflate, the formation of **2** cannot be detected. From fluorobenzene, 4-fluoroacetophenone is not formed, even after 24 h of refluxing.

The formation of **4** was unexpected. This compound has first been obtained by acetylation of 2,6-dimethylpyrone [18,19], but has been also obtained by heating the diacetylacetic ethyl ester in acidic medium [20]. Some experiments were carried out to understand this formation. Acetic acid or acetyl chloride do not lead to this compound. Compound **4** is obtained in ca. 10% yield with ytterbium triflimidate or triflate and only when acetic anhydride is used as acylating agent. Its formation seems to be the result of a self-condensation of acetic anhydride in the presence of H⁺ and the lanthanide cation. All attempts at increasing the yield were unsuccessful.

The formation of **3** occurs only under air, it has been shown that this compound comes from the oxidation of **2** and this oxidation only occurs when the lanthanide salt is present. So, the oxidation of **2** in the presence of lanthanide salts has been investigated.

In all cases, nearby large amounts of aldolisation product, the reaction affords low yields of acid (**3**), exclusively when acetic anhydride or acetyl chloride are present. The same reaction, carried under pressurised oxygen, affords 20% of **3** under 3 bar and 28% under 6 bar. 2-Methylacetophenone



Scheme 2. Products formed in toluene acetylation.

Table 4
Benzoylation of activated aromatic rings with 1 equiv. of PhCOCl

Substrate	Catalyst (mol%)	Solvent	T (°C)	Time (h)	Yield (%)	Reference
Anisole	Sc(OTf) ₃ (20%)	MeNO ₂	50	18	79	[6]
Anisole	Cu(OTf) ₂ (5%)	Anisole	80	8	83	[21]
Anisole	NdCl ₃ (5%)	Anisole	154	5	91	[3]
Phenetole	NdCl ₃ (5%)	Phenetole	170	5	34	[3]
Anisole	UO ₂ Cl ₂ (1%)	Anisole	154	1	90	[4]
Phenetole	UO ₂ Cl ₂ (1%)	Phenetole	170	1	73	[4]
Phenetole	Nd(NTf ₂) ₃	Phenetole	170	4	86	This work

affords *o*-toluic acid in very similar yields. In the same conditions, in Ac₂O, only 3% of **3** is formed with Yb(OTf)₃ and it has not been detected when bis(trifluoromethylsulfonyl)imide: H(NTf₂) is used instead of the lanthanide salt.

2.3. Benzoylation experiments

Benzoylation experiments using metal triflates or metal salts have been reported. Table 4 summarises some significant results from the literature.

In all cases, 4-methoxybenzophenone was obtained in high yield from anisole, whereas the benzoylation of phenetole afforded the expected mixture of 3- and 4-ethoxybenzophenone (**5**) in moderate yield and a large amount (20–40%) of secondary products, essentially phenyl benzoate (**6**). The formation of these secondary products implied the de-ethylation of phenetole (Scheme 3).

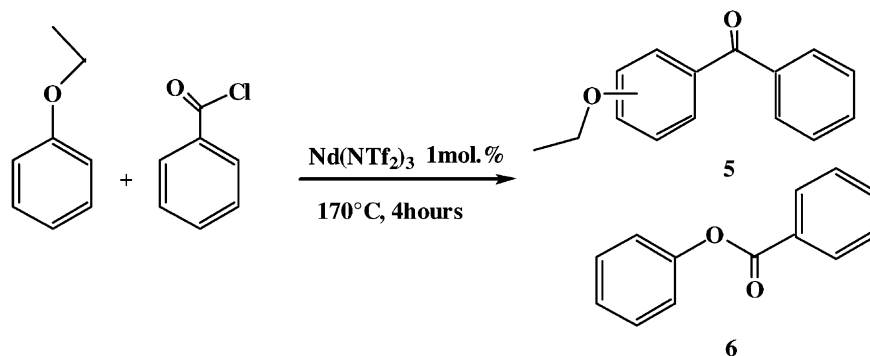
This reaction has been reinvestigated using 1 mol% Nd(NTf₂)₃ as a catalyst. A mixture of 4- and 2-ethoxy-

benzophenone (**5**) (in a 80/20 ratio) is isolated in 86% yield with only ca. 3% of the de-ethylation product.

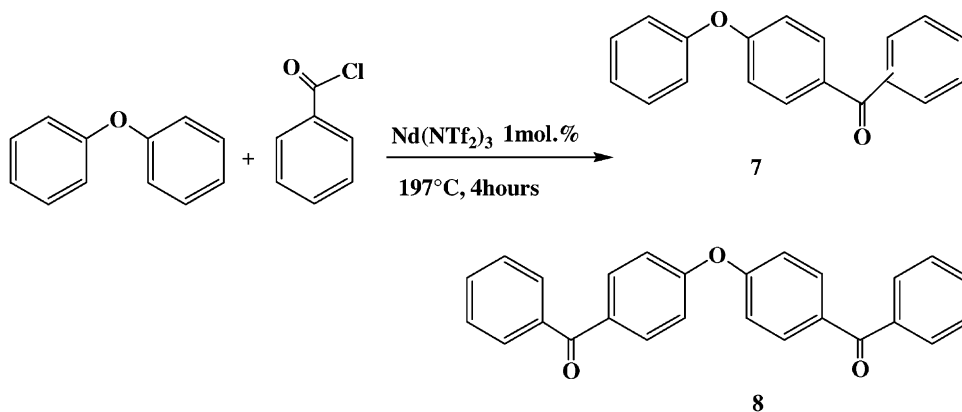
The catalytic activity of Nd(NTf₂)₃ has been also tested in the benzoylation of diphenyl ether to synthesise precursors of polyetherketones. An excess of benzoyl chloride reacts with diphenyl oxide to give a mixture of mono (**7**) and disubstituted (**8**) products in the ratio 7/8 = 20/80 (Scheme 4). Compound **8** is obtained as a pure white crystalline powder after removal of **7** with diethyl ether and recrystallisation in chloroform.

In the same manner, terephthaloyl chloride reacts with diphenyl oxide used in a fivefold excess to avoid polycondensation. After extraction with diethyl ether to remove the excess of diphenyl oxide, the expected diketodiether (**9**) is obtained in high yield (Scheme 5).

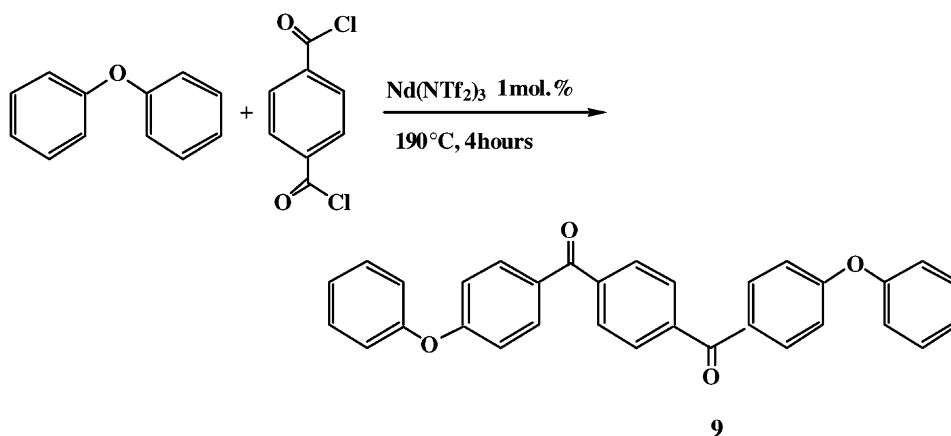
A second step would be the condensation of these precursors with terephthaloyl chloride to obtain polymeric chains of polyetherketones.



Scheme 3. Benzoylation of phenetole.



Scheme 4. Benzoylation of diphenyl oxide.



Scheme 5. Condensation of diphenyl oxide and terephthaloyl chloride.

3. Conclusion

Lanthanide triflimidates are more efficient acylation catalysts than the analogous triflates. Catalytic amounts of these salts: 0.5–1 mol%, in non-hazardous solvents lead to the rapid and high yield of acylation of activated aromatic cycles.

4. Experimental

4.1. Analytical techniques

The composition and yield of the organic reaction products were determined by gas chromatography

with a GC 8000 Series equipped with a flame ionisation detector, and a 25 m × 0.32 mm OV1 capillary column.

¹H NMR spectra were recorded on a Bruker AC 200 apparatus in CDCl₃. Mass spectra were recorded on a Hewlett Packard G 1800 A GCD apparatus equipped with a 30 m × 0.25 mm HPS capillary column. Elemental analyses were carried out on a Fisons Instrument EA 1108 CHNS-O.

4.2. Materials

All the reagents and solvents are commercially available samples used without further purification.

The trifluoromethylsulfonic acid (triflic acid), bis-(trifluoromethylsulfonyl)amine (triflimic acid) and lanthanide carbonates were purchased by Rhodia Chimie.

Lanthanide bis(trifluoromethylsulfonyl)imides are synthesised from lanthanide carbonates in water. In a typical experiment, 1 g of lanthanide carbonate was stirred in 10 ml of water and a slight excess of a 0.4 M aqueous solution of triflimic acid was added. The solution was stirred for 30 min after complete dissolution of the carbonate, then water was removed under reduced pressure. The viscous liquid was pumped off during 24 h at 100 °C to remove water and the excess of triflimic acid (which sublimates at 50 °C under 1 mbar). The exceedingly hygroscopic white powders of general formula $\text{Ln}(\text{NTf}_2)_3(\text{H}_2\text{O})$ were stored in the glove box.

Uranyl bis(trifluoromethylsulfonyl)amide was synthesised in the same manner from uranyl acetate (Pro-labo).

4.3. Acetylation of anisole

In the glove box, 50.6 mg (0.051 mmol) of $\text{Nd}(\text{NTf}_2)_3$ were weighed in a 50 ml vessel. The vessel was connected to a nitrogen inlet, anisole: 0.54 (5 mmol), acetic anhydride: 2.83 g (30 mmol) and acetic acid: 2.77 g (46.2 mmol) were added with a syringe and the mixture was stirred magnetically for 3.5 h at 120 °C. After cooling, 20 ml of diethyl ether were added and the solution was washed with a saturated solution of sodium hydrogen carbonate is added until neutral. The organic layer was dried over magnesium sulfate and the solvent was removed. A sample was taken and analysed by GC and NMR; yield ca. 95%.

4.4. Attempted acetylation of toluene

In the glove box, 547 mg (0.54 mmol) of $\text{Yb}(\text{NTf}_2)_3$ were weighed in a 50 ml vessel. The vessel was connected to a nitrogen inlet or kept under air or under oxygen pressure. Toluene: 1 g (10.8 mmol) and acetyl chloride: 2.83 g (30 mmol) were added with a syringe. The mixture was stirred for 5 h at 70 °C. Aliquots (0.1 ml) were taken after a given time, 1 ml of decane in diethyl ether was added, the solution was stirred with 1 ml saturated solution of sodium hydrogen car-

bonate and the ether layer was analysed by GC and GC/MS.

4.5. Formation of 3-acetyl-2,6-dimethylpyrone (4)

In the glove box, 737.2 mg (0.075 mmol) of $\text{Nd}(\text{NTf}_2)_3$ were weighed in a 50 ml vessel. The vessel was connected to a nitrogen inlet, 7.67 g (0.075 mol) of acetic anhydride were added with a syringe and the mixture was stirred magnetically for 2 h at 110 °C. After cooling, acetic anhydride was removed. The 20 ml of methylene chloride were added and the solution was washed with a saturated solution of sodium hydrogen carbonate until neutral. The organic layer was dried over magnesium sulfate and the solvent was removed. The yellow powder was extracted with 20 ml of boiling ethanol. After filtration and removal of the solvent, 332 mg of pale yellow compound **4** were obtained, 10% yield.

^1H NMR: 2.24 (s, 3H); 2.34 (s, 3H); 2.5; 10.93 (s, 3H); 6.15 ppm (s, 1H). Mass spectrum, m/e : 166 ($[\text{M}]^+$, 56); 151 ($[\text{M} - 15]^+$, 22); 109 ($[\text{C}_6\text{H}_5\text{O}_2]^+$, 38); 67 ($[\text{C}_4\text{H}_5\text{O}]^+$, 100).

4.6. Benzoylation of phenetole

Two grams (16.4 mmol) of phenetole, 2.1 g (15 mmol) of benzoyl chloride and 148 mg (0.15 mmol) of $\text{Nd}(\text{NTf}_2)_3$ were refluxed until complete consumption of phenetole (4 h). The red solution was cooled at room temperature; 15 ml diethyl ether and 10 ml water were added, after 10 min stirring and decantation, the aqueous phase was washed twice with 10 ml diethyl ether. The ether solution was dried on magnesium sulfate. After removal of the solvent, 3.05 g of a viscous oil was obtained and analysed by GC: 4-ethoxybenzophenone 77%, 2-ethoxybenzophenone 20%, phenyl benzoate 3%; 2+4-ethoxybenzophenone: 86% yield.

4.7. Benzoylation of diphenyl oxide

One gram (5.9 mmol) of diphenyl oxide, 4.14 g (29.5 mmol) of benzoyl chloride and 58 mg (0.059 mmol) of $\text{Nd}(\text{NTf}_2)_3$ were refluxed for 4 h (197 °C). After cooling the red solution, a reddish solid was obtained. The 20 ml toluene was added, the toluene solution was stirred for 12 h with 10 ml of 20% aqueous

sodium hydroxide to remove the excess of benzoyl chloride. After drying and removal of the solvent, 1.98 g of a yellow powder was obtained and analysed by GC. It contained ca. 20% of monosubstituted product (**7**) and 80% of disubstituted product (**8**).

The yellow solid was washed with 3×10 ml of diethyl ether. Removal of ether afforded pure **7**. The insoluble brown solid was quite pure (**8**). The 1.23 g (55% yield) of analytically pure white crystals were obtained after crystallisation in chloroform. Elemental analysis: Calc. for $C_{26}H_{18}O_3$: C, 82.53%; H, 4.76%. Found: C, 81.29%; H, 4.71%.

4.8. Terephthaloyl chloride and diphenyl oxide

The 1.08 g (5.4 mmol) of terephthaloyl chloride, 9.1 g (54 mmol) of diphenyl oxide and 53 mg (0.054 mmol) of $Nd(NTf_2)_3$ were heated for 4 h at 190 °C. The mixture turned purple and a crystalline red brown solid was formed. After cooling at 30 °C, the solution was filtered, the solid was washed with 3×20 ml of diethyl ether and dried at 100 °C. The 2.05 g of a pale pink microcrystalline product was obtained (82% yield). Crystallisation in toluene afforded analytically pure white crystals of **9**. Elemental analysis: Calc. for $C_{32}H_{22}O_4$: C, 81.70%; H, 4.68%. Found: C, 81.51%; H, 4.68%.

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