# Rare Earth Perfluorooctanoate [RE(PFO)$_3$]-Catalyzed Condensations of Indole with Carbonyl Compounds

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Dedicated to Professor Qian Changtao on the occasion of his 70th birthday.

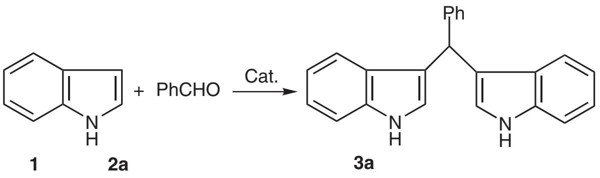
**Abstract:** New rare earth perfluorooctanoates [RE(PFO)$_3$] were developed and applied to the condensation reactions of indole with carbonyl compounds at ambient temperature. It was found that these catalysts could be completely recovered and reused without loss of catalytic activities.

**Key words:** rare earth perfluorooctanoate [RE(PFO)$_3$], indole, bis-indolylmethanes, aldehyde, ketones

Indole derivatives are well known to possess various biological activities, which are generally used in pharmaceuticals, antioxidatives and so on,[1] so the synthesis of different indole compounds has received considerable attention and interest. The condensations of indole with carbonyl compounds have been known to form bis-indolylmethanes catalyzed by different acids. The acids utilized in this type of reaction are protic acids[2] (e.g. HCl) and Lewis acids[3] (e.g. $BF_3$ and $AlCl_3$), usually in excess under homogeneous conditions, and are required to stand for many hours. Generally, these traditional Lewis acid catalysts are moisture-sensitive and are easily decomposed or deactivated in the presence of even a small amount of water, and are thus difficult to handle; furthermore, the disposal of these excess acids is apt to lead to environmental pollution.

At present, with the rapid development in the fields of synthetic and catalytic chemistry, researchers have started to pay more attention to the detrimental effects of non-green processes to the environment, and in the past few years, they have developed some environmentally benign catalysts to avoid or minimize these harmful effects. Particularly, the condensation of indoles and carbonyl compounds has been carried out successfully using $NaHSO_4 \cdot SiO_2$,[4a] ionic liquids,[4b] $Fe^{3+}$,[4c] $I_2$,[4d] Montmorillonite K10 clay,[4e] NBS,[4f] and rare earth catalysts[5] such as $LnCl_3$ and $Ln(OTf)_3$.

Recently, rare earth catalysts have gained recognition as possible environmentally friendly replacements of conventional Lewis acid catalysts in various synthetic processes because of their unique advantages,[6] and they have attracted the attention of chemists in the pursuit of a new rare earth catalyst possessing high catalytic activity. We all know that perfluorooctanoic acid (PFOA) is an excellent dispersant which has favorable surfactivity, and in recent years the micellar dispersion and aggregate characteristics of its metallic salts, such as sodium or cesium perfluorooctanoate, in different solutions have been deeply researched in the fields of interfacial chemistry.[7] In continuation of our studies focused on rare earth salts catalysts, bearing the Lewis acid–surfactants combined catalyst (LASC) concepts[8] in mind, we have developed the new catalyst RE(PFO)$_3$ for the first time, which show high catalytic activities and are easy to prepare, stable and storable in air for a long time without any changes, easily recycled, and reused without obvious loss of activity. RE(PFO)$_3$ are regarded as a new type of Lewis acid and will be employed in many organic reactions. Herein, we wish to report novel lanthanide perfluorooctanoate-catalyzed condensation reactions of indole with carbonyl compounds, applied to the synthesis of bis-indolylmethanes under mild conditions in EtOH.



**Equation 1**

First, we examined the rare earth salt Lewis acid [La(PFO)$_3$] in the model reaction of indole with benzaldehyde (Equation 1) in different reaction media to investigate the solvent effect. The results are summarized in Table 1 and show that polar solvents such as EtOH are better than non-polar ones. Remarkably, the condensation proceeded smoothly both in water and under solvent-free conditions to afford desired product in good yields, suggesting that La(PFO)$_3$ is a water-stable Lewis acid and shows high catalytic activity even in water; this performance is among the most useful and promising because water is safe, benign, and cheap compared with organic solvents. However, for this reaction, considering the laboratory not industry, the best results were achieved by carrying out the reaction at room temperature in EtOH for two hours using La(PFO)$_3$ as a catalyst.

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**Table 1** Effect of Solvents in the Reaction of Indole with Benzaldehyde Catalyzed by $La(PFO)_3$

| Solvents | EtOH | $CH_2Cl_2$ | $H_2O$ | Toluene | Benzene | $CH_3OCH_3$ | None |
|---|---|---|---|---|---|---|---|
| Yield (%)[a] | 96 | 87 | 93 | 90 | 92 | 86% | 95 |

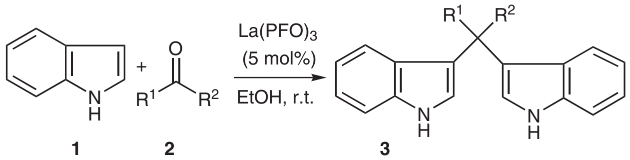
[a] Isolated yields.

Next, the catalytic activities of different rare earth metal salt catalysts were also tested, and are shown in Table 2. The catalytic activity of $RE(PFO)_3$ was higher than other ones, and $RE(PFO)_3$ were better than or equal to the corresponding rare earth triflates,[5] chlorides, or short perfluoroalkyl chains such as perfluorobutyrate and trifluoroacetate. This is likely due to the surface activity of their long chains; in other words, these rare earth perfluorooctanoates can efficiently disperse the catalysts into the substrates to promote the desired reaction. With respect to the amount of catalyst, the yield depended on the catalyst loading, and in the presence of 5 mol% of $La(PFO)_3$ the reaction afforded the corresponding product in 96% yield (Table 1). Further studies showed that increasing the amounts of catalyst does not produce obviously better yields. Another advantage of the use of $La(PFO)_3$ was that it could be easily recovered and recycled in subsequent reactions without significantly decreasing the activity of the catalyst, which was easily separated by simple extraction and filtration. The catalyst could be recycled three times without obvious loss of activity (entry 8: 96%, 1st run; 85%, 2nd run; 80%, 3rd run).

**Table 2** Effect of Different Rare Earth Metal Salt Lewis Acids in the Reaction of Indole with Benzaldehyde[a]

| Entry | Catalyst | Amount of catalyst (mol%) | Time (h) | Yield (%)[b] |
|---|---|---|---|---|
| 1 | $Yb(CF_3COO)_3$ | 5 | 2 | 50 |
| 2 | $Yb[CF_3(CF_2)_2CO_2]_3$ | 5 | 2 | 58 |
| 3 | $LaCl_3$ | 10 | 1.5 | 80 |
| 4 | $Yb(OTf)_3$ | 5 | 1.5 | 80 |
| 5 | $La(OTf)_3$ | 5 | 1.5 | 82 |
| 6 | $Sm(PFO)_3$ | 5 | 1.5 | 70 |
| 7 | $Yb(PFO)_3$ | 5 | 1.5 | 89 |
| 8 | $La(PFO)_3$[c] | 5 | 1.5 | 96, 85, 80 |

[a] The reaction was carried out in EtOH at r.t.
[b] Isolated yields.
[c] The catalyst was recycled three times.



**Equation 2**

A variety of carbonyl compounds reacted smoothly with indole to produce bis-indolylmethanes in the presence of 5 mol% $La(PFO)_3$ as a catalyst at room temperature in EtOH (Equation 2). The results are listed in Table 3.

**Table 3** Synthesis of Bis-indolylmethanes Catalyzed by $La(PFO)_3$[a]

| Entry | $R^1$ | $R^2$ | Product (**3**) | Time (min) | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 | $C_6H_4$ | H | **3a** | 30 | 90 |
| 2 | $4-(MeO)C_6H_4$ | H | **3b** | 30 | 95 |
| 3 | $2-(HO)C_6H_4$ | H | **3c** | 30 | 85 |
| 4 | $4-(O_2N)C_6H_4$ | H | **3d** | 60 | 80 |
| 5 | $4-(H_3C)C_6H_4$ | H | **3e** | 30 | 92 |
| 6 | $4-(F)\ C_6H_4$ | H | **3f** | 30 | 90 |
| 7 | $R^1 = R^2 = -(CH_2)_5-$ |  | **3g** | 90 | 85 |
| 8 | $R^1 = R^2 = -(CH_2)_4-$ |  | **3h** | 90 | 60 |
| 9 | $4-CH_3$-2-thienyl | H | **3i** | 30 | 95 |
| 10 | 2-thienyl | H | **3j** | 30 | 90 |
| 11 | $C_6H_5CH=CH$ | H | **3k** | 30 | 94 |
| 12 | $CH_3(CH_2)_2$ | H | **3l** | 60 | 90 |
| 13 | $CH_3$ | $CH_3$ | **3m** | 90 | 50 |

[a] All reactions were carried out in EtOH at r.t.
[b] Isolated yields.

In all cases, aldehydes reacted more rapidly, and gave higher yields than ketones. Most of the reactions of aromatic aldehydes proceeded nearly quantitatively, and the nature of substituents on the aromatic ring showed some effects on this conversion. On the one hand, the electron-rich substitutes (OH, $OCH_3$) required shorter reaction time than the electron-deficient counterparts such as $NO_2$. On the other hand, hydrobenzaldehyde and methoxybenzaldehyde gave better yields than nitro-subsitituted arylaldehyde. In addition, the aliphatic aldehydes such as *n*-butanal also afforded 90% yield in 60 minutes. The reaction of cyclohexanone with indole gave a better yield than cyclopentanone, perhaps due to the six-membered ring, which is more stable than a five-membered ring. From Table 3, we can see that the scope and generality of the present method have been shown with respect to various carbonyl compounds. All products were characterized by $^1H$ NMR and mass spectral analysis, and comparison with authentic samples.[4]

In summary, we have demonstrated the lanthanide perfluorooctanoates [Ln(PFO)$_3$] to be mild and effective catalysts for the condensation of indole with aldehydes and ketones in EtOH at room temperature to afford bis-indolylmethanes in high yields. RE(PFO)$_3$ show high catalytic activity as a new type of rare earth catalysts. They are easy to prepare, stable and storable in air for a long time without any changes, easily recycled, and reused without obvious loss of activity. With the additional water-repellent and oil-repellent character of the perfluorooctyl chains, the catalysts could form the middle layer between a supernatant liquid such as hexane or dichloromethane and the lower water layer when extracting. Therefore, the procedure is expected to become a useful method for the synthesis of bis-indolylmethanes.

### Typical Experimental Procedure

#### Catalyst Preparation

To a stirring solution of perfluorooctanoic acid (PFOA, 2.5 g, 0.6 mmol) in $H_2O$ (5 mL), $La_2O_3$ (0.32 g, 0.1 mmol) was added, and the mixture was stirred for 12 h under reflux. The aqueous layer was decanted and washed with $H_2O$ to give a gelatin-like solid. The solid was dried in vacuum at r.t. for 2 h to give a white sheet solid.

**La(PFO)$_3$**: mp:138–140 °C. IR (KBr): 3400–3500 (m), 1650 (m), 1620 (vs), 1200 (vs), 1150 (vs) cm$^{-1}$. ICP: found: La = 11%, calcd for La(PFO)$_3$: La = 10.08%. $^{19}$F NMR (500 MHz, DMSO): $\delta$ = –81.17 (t, 9 F, $J$ = 0.02 Hz), –115.94 (t, 6 F, $J$ = 0.02 Hz), –112.3 (s, 6 F), –122.74 (s, 12 F, $J$ = 0.13 Hz), –123.51 (s, 6 F), –126.73 (s, 6 F). Compared to PFOA, a 1 ppm shift showed in –115.94 Hz, which can illustrate coordination of the La ion. EDS (%): C, 7.12; O, 7.77; F, 68.88; La, 16.23.

#### General Procedure for Preparation of Bis-indolylmethanes

To a mixture of indole (2 mmol 0.234 g), aldehydes or ketones (1 mmol, 0.1 mL), EtOH (2 mL), lanthanum perfluorooctanoate [La(PFO)$_3$] (0.01 mmol, 5%mol) was added and stirred at r.t. for the appropriate time. When the reaction was complete, the solvent was removed under reduced pressure. $CH_2Cl_2$ (10 mL) and sat. aq NaCl solution (10 mL) was added to stand for several minutes, the filtrate was separated and the water layer was extracted with $CH_2Cl_2$ (3 × 10 mL), the combined organic layer were dried using anhyd $Na_2SO_4$ and filtered, and the solvent was evaporated. The crude products were purified by column chromatography and eluted with EtOAc–petroleum ether mixture to afford the products.

After adding the $CH_2Cl_2$ and sat. aq NaCl solution, the catalyst was deposited in the middle of two phases. Since the catalyst is not soluble in either $CH_2Cl_2$ or $H_2O$, catalyst recovery was accomplished simply by filtration and drying in air or under vacuum.

**Product 3a**:[4c] solid, mp 125–126 °C. $^1$H NMR ($CDCl_3$): $\delta$ = 5.89 (s, 1 H,), 6.66 (d, 2 H, $J$ = 1.8 Hz), 7.01 (t, 2 H, $J$ = 7.4 Hz), 7.17 (t, 3 H, $J$ = 7.8 Hz), 7.28 (s, 2 H, $J$ = 7.3 Hz), 7.37 (m, 6 H), 7.91 (br s, 2 H, NH). MS (EI): $m/z$ (%) = 322 (100) [M$^+$], 245 (50), 204 (25). IR (KBr): 3450, 3020, 1600, 1490, 1220, 1070, 750 cm$^{-1}$.

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