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Electrophilic aromatic nitration using perfluorinated rare earth metal salts in fluorous phase

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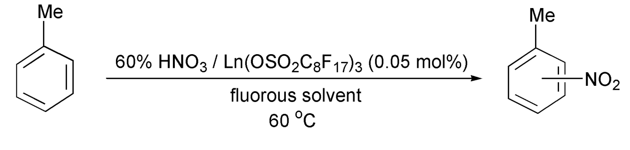
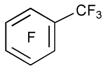
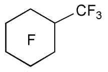
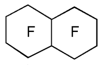
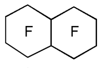
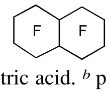
In this paper, we describe a practical, useful electrophilic aromatic nitration process in fluorous phase by using perfluorodecalin ($C_{10}F_{18}$, *cis*- and *trans*-mixture) as a fluorous solvent and perfluorinated rare earth metal salt [$Yb(OSO_2C_8F_{17})_3$] as a catalyst for the electrophilic aromatic nitration.

Nitration of organic compounds has long been a very active and rewarding area of research and is the subject of a large body of literature. Extensive and well documented reviews have been published by Ingold,[1] Olah,[2–4] Schofield,[5,6] and Ione,[7] among others. Nitrations in manufacturing process require the use of potent mixtures of concentrated or fuming nitric acid with sulfuric acid leading to excessive acid waste streams and added expense. The obvious disadvantages of the commercial manufacturing process currently used has led to a substantial effort to develop viable alternatives, such as using solid-acid catalysts, other sources of NO_2^+, organic nitrating agents, other acids replacing sulfuric acid *etc*. Recently, it was found that lanthanide(III) triflates (1–10 mol%) [$Ln(OTf)_3$] can catalyze the nitration of a range of simple aromatic compounds in good to excellent yield using stoichiometric quantities of 69% nitric acid, the only by-product being water and the catalyst being readily recycled by simple evaporation.[8] However, this nitration was carried out in refluxing 1,2-dichloroethane, an environmentally hazardous solvent. In addition, the recovery of the catalyst from aqueous solution is not an economic process. On the other hand, perfluorocarbon fluids, especially perfluoro-alkanes have some unique properties which make them attractive alternatives for conventional organic solvents.[9] They have limited miscibility with conventional organic solvents. Compounds functionalized with perfluorinated groups often dissolve preferentially in fluorous solvents and this property can be used to extract fluorous components from reaction mixtures.[10] Thus, we attempted to apply fluorous phase separation techniques in perfluorinated rare earth metal salt catalyzed nitration. With this method, a practical electrophilic aromatic nitration process can be established: using 1,2-dichloroethane as a solvent the recovery of perfluorinated rare earth metal catalysts from aqueous solution can be avoided. In order to achieve nitration in the fluorous phase, we prepared perfluorinated rare earth metal salts [$Ln(OSO_2C_8F_{17})_3$, Ln = La, Yb, Sc] as the catalysts[11] and selected perfluorotoluene (C_7F_8), perfluoro(methylcyclohexane) (C_7F_{14}), perfluorohexane (C_6F_{14}), and perfluorodecalin ($C_{10}F_{18}$, *cis*- and *trans*-mixture) as the fluorous solvents. The nitration of toluene was first carried out in various fluorous solvents using 60% HNO_3 as the nitration reagent in the absence of halogenated organic solvent and with a catalyst loading of only 0.05 mol% (Scheme 1). We found that, in general, the nitrated toluene was isolated in 51–60% at 60 °C. The yields were obtained based on the nitric acid. Results are summarized in Table 1. $Sc(OSO_2C_8F_{17})_3$ is the most active catalyst in this reaction. The fluorous solvents perfluorohexane (C_6F_{14}) and perfluorotoluene (C_7F_8) are in fact miscible with aromatic substrate such as toluene. Thus, it is impossible to separate the fluorous layer containing catalyst from the reaction mixture. Using perfluoro(methylcyclohexane) (C_7F_{14}) or perfluorodecalin ($C_{10}F_{18}$, *cis*- and *trans*-mixture) as the fluorous solvent, the fluorous phase is not miscible with aromatic substrates and dissolves only the $Ln(OSO_2C_8F_{17})_3$ catalysts. The fluorous layer can be easily isolated from the reaction mixture and reused for the next nitration. $Ln(OSO_2C_8F_{17})_3$ catalysts dissolve completely in perfluorocarbon. Based on the ^{19}F NMR spectroscopic data and GC-MS, no loss of catalyst or perfluorodecalin to the organic and water phases can be detected. But we found that, during repeated nitration reactions, the loss of fluorous solvent is very serious when using perfluoro(methylcyclohexane) (C_7F_{14}) as the solvent because it is very volatile (bp 76 °C). Perfluorodecalin ($C_{10}F_{18}$, *cis*- and *trans*-mixture) is the best fluorous solvent for nitration (Table 1, entry 4–6).[12] This electrophilic aromatic nitration is a triphasic reaction [top layer is the aromatic compound (organic phase); middle layer is the nitric acid (water phase); bottom layer is the perfluorocarbon (fluorous phase)]. Based on the general concept of fluorous phase chemistry, we also used hexane as a co-solvent for the nitration of toluene. We found that, upon heating at 60 °C, the organic phase is miscible with fluorous phase and the nitration became a biphasic reaction [top layer is the nitric acid (water phase); bottom layer is the perfluorocarbon with aromatic compound (organic phase)]. However, the yield of nitrated toluene is very similar to that found with triphasic nitration. It should be emphasized here the *ortho*, *meta* and *para* distribution is almost same in the cases shown in Table 1 with the ratio $p:m:o = 76:0:24$. The control experiment elucidates that only 10% of nitrated product could be obtained in the absence of perfluorinated rare earth metal salts [$Ln(OSO_2C_8F_{17})_3$, Ln = La, Yb, Sc] by 60% HNO_3. In



Scheme 1

Table 1 Nitration of toluene in fluorous phase

Entry	Lewis acid	Fluorous solvent	Time/h	Yield/[%][a] **1a**[b]
1	$Yb(OSO_2C_8F_{17})_3$	$CF_3(CF_2)_4CF_3$	24	56
2	$Yb(OSO_2C_8F_{17})_3$		24	56
3	$Yb(OSO_2C_8F_{17})_3$		24	52
4	$Sc(OSO_2C_8F_{17})_3$		24	60
5	$Yb(OSO_2C_8F_{17})_3$		24	57
6	$La(OSO_2C_8F_{17})_3$		24	40

[a] Isolated yields based on the nitric acid. [b] $p:m:o = 76:0:24$

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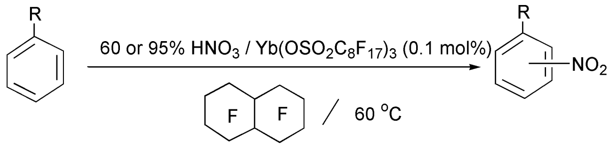
addition, we found that a catalyst loading of only 0.05–0.10 mol% was required when using fluorous phase technology, which is more effective than the 10 mol% of lanthanide(III) triflates [Ln(OTf)$_3$] required to catalyze the nitration in a halogenated solvent such as 1,2-dichloroethane.

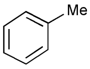
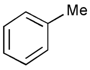
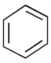
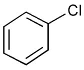
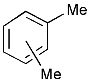
Thus, in order to seek out a practical, useful electrophilic aromatic nitration process, we decided to use the relatively cheap and similarly active Yb(OSO$_2$C$_8$F$_{17}$)$_3$ as a catalyst and perfluorodecalin (C$_{10}$F$_{18}$, *cis*- and *trans*-mixture) as the fluorous solvent in a triphasic system for electrophilic aromatic nitration (Scheme 2).[13] The results are shown in Table 2. We found that, using 60 or 95% nitric acid in the presence of 0.1 mol% of Yb(OSO$_2$C$_8$F$_{17}$)$_3$, the (Scheme 2, Table 2) electrophilic aromatic nitration proceeded very well for many substrates at 60 °C. By simple separation of the fluorous phase containing only the perfluorinated rare earth metal catalyst, the nitration can be simply repeated many times without reloading fluorous solvent and the catalyst. In Table 2, we show that the yields of nitrated products do not decrease over 5 cycles for many substrates (Table 2). [The yields shown in Tables 1 and 2 are isolated yields after column chromatography (SiO$_2$).] Higher product yields are obtained using 95% nitric acid as the nitrating reagent. The unaccounted for yield is due to the unconverted substrate.

In conclusion, we have explored a practical, useful electrophilic aromatic nitration process. By using perfluorodecalin (C$_{10}$F$_{18}$, *cis*- and *trans*-mixture) as a fluorous solvent and Yb(OSO$_2$C$_8$F$_{17}$)$_3$ as a catalyst, the nitration can be repeated many times without loss of catalyst. There are three major environmental benefits from using perfluorinated rare earth metal salts in the fluorous phase in this electrophilic aromatic nitration: 1) the nitration process does not require sulfuric acid and halogenated solvent; 2) the nitration can be repeated many times simply by separation of the fluorous phase for the next nitration and the recovery of the employed catalyst from aqueous solution can be avoided; 3) the catalyst loading is only 0.05–0.1 mol% and no loss of catalyst or fluorous solvent occurs.



Scheme 2

Table 2 Isolated yields of nitration of toluene in fluorous phase for 48 h[a]

Run	1	2	3	4	5
	57[b]	60	56	54	53
	70[c]	65	70	66	71
	63[d]	60	60	64	54
	63[e]	60	60	64	54
	88[f]	83	83	80	68

[a] Isolated yields (%) based on the nitric acid. [b] 60% HNO$_3$, *p*:*m*:*o* = 76:0:24. [c] 95% HNO$_3$, *p*:*m*:*o* = 76:0:24. [d] 95% HNO$_3$. [e] 95% HNO$_3$, *p*:*m*:*o* = 60:0:40. [f] 95% HNO$_3$.

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13 Typical reaction procedure: 95% nitric acid (0.5 ml, 12 mmol) was slowly added into a mixture of Yb(OPf)$_3$ (20 mg, 0.012 mmol), toluene (2.1 ml, 20 mmol) and perfluorodecalin (*cis*- and *trans*-mixture, 1.5 ml). The mixture was stirred at 60 °C for 24 h. Then, the fluorous layer was separated for the next nitration. The reaction mixture (organic layer and water phase) was washed with water (5 ml) and extracted with dichloromethane (2 × 15 ml). The combined organic layers were dried over MgSO$_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (EtOAc:hexane = 1:20) to give the product as a yellowish liquid (1.18 g, 70%).