

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

Min Shi* and Shi-Cong Cui

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China. E-mail: mshi@pub.sioc.ac.cn; Fax: 86-21-64166128

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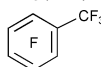
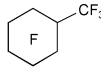

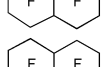
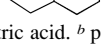
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In this paper, we describe a practical, useful electrophilic aromatic nitration process in fluorous phase by using perfluorodecalin (C₁₀F₁₈, *cis*- and *trans*-mixture) as a fluorous solvent and perfluorinated rare earth metal salt [Yb(OSO₂C₈F₁₇)₃] as a catalyst for the electrophilic aromatic nitration.

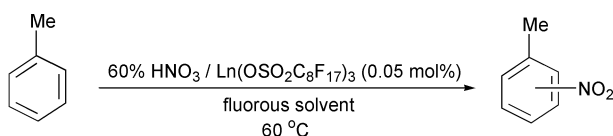
Nitration of organic compounds has long been a very active and rewarding area of research and is the subject of a large body of literature. Extensive and well documented reviews have been published by Ingold,¹ Olah,^{2–4} Schofield,^{5,6} and Ione,⁷ among others. Nitrations in manufacturing process require 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 NO₂⁺, 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(OSO₂C₈F₁₇)₃, Ln = La, Yb, Sc] as the catalysts¹¹ and selected perfluorotoluene (C₇F₈), perfluoro(methylcyclohexane) (C₇F₁₄), perfluorohexane (C₆F₁₄), and perfluorodecalin (C₁₀F₁₈, *cis*- and *trans*-mixture) as the fluorous solvents. The nitration of toluene was first carried out in various fluorous solvents using 60% HNO₃ 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(OSO₂C₈F₁₇)₃ is the most active catalyst in this reaction. The fluorous solvents perfluorohexane (C₆F₁₄) and perfluorotoluene (C₇F₈) 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) (C₇F₁₄) or perfluorodecalin (C₁₀F₁₈, *cis*- and *trans*-mixture) as the fluorous solvent, the fluorous phase is not miscible with aromatic substrates and dissolves only the Ln(OSO₂C₈F₁₇)₃ catalysts. The fluorous layer can be easily isolated from the reaction mixture and reused for the next nitration. Ln(OSO₂C₈F₁₇)₃ catalysts dissolve completely in perfluorocarbon. Based on the ¹⁹F 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) (C₇F₁₄) as the solvent because it is very volatile (bp 76 °C). Perfluorodecalin (C₁₀F₁₈, *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(OSO₂C₈F₁₇)₃, Ln = La, Yb, Sc] by 60% HNO₃. In

Table 1 Nitration of toluene in fluorous phase

Entry	Lewis acid	Fluorous solvent	Time/h	Yield/[%] ^a 1a ^b
1	Yb(OSO ₂ C ₈ F ₁₇) ₃	CF ₃ (CF ₂) ₄ CF ₃	24	56
2	Yb(OSO ₂ C ₈ F ₁₇) ₃		24	56
3	Yb(OSO ₂ C ₈ F ₁₇) ₃		24	52
4	Sc(OSO ₂ C ₈ F ₁₇) ₃		24	60
5	Yb(OSO ₂ C ₈ F ₁₇) ₃		24	57
6	La(OSO ₂ C ₈ F ₁₇) ₃		24	40

^a Isolated yields based on the nitric acid. ^b *p*:*m*:*o* = 76:0:24

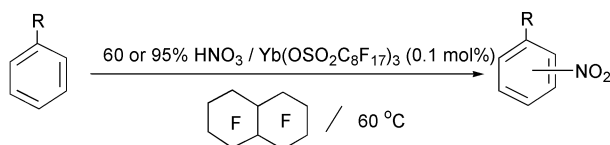


Scheme 1

addition, we found that a catalyst loading of only 0.05–0.10 mol% was required when using fluororous 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(OSO₂C₈F₁₇)₃ as a catalyst and perfluorodecalin (C₁₀F₁₈, *cis*- and *trans*-mixture) as the fluororous 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(OSO₂C₈F₁₇)₃, the (Scheme 2, Table 2) electrophilic aromatic nitration proceeded very well for many substrates at 60 °C. By simple separation of the fluororous phase containing only the perfluorinated rare earth metal catalyst, the nitration can be simply repeated many times without reloading fluororous 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 (SiO₂).] 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 (C₁₀F₁₈, *cis*- and *trans*-mixture) as a fluororous solvent and Yb(OSO₂C₈F₁₇)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 fluororous 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 fluororous phase for the next nitration and the recovery of the employed catalyst from



Scheme 2

Table 2 Isolated yields of nitration of toluene in fluororous 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% HNO₃, *p:m:o* = 76:0:24. ^c 95% HNO₃, *p:m:o* = 76:0:24. ^d 95% HNO₃. ^e 95% HNO₃, *p:m:o* = 60:0:40. ^f 95% HNO₃.

aqueous solution can be avoided; 3) the catalyst loading is only 0.05–0.1 mol% and no loss of catalyst or fluororous solvent occurs.

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- The nitration of some phenols and alkyl aryl ethers with dinitrogen pentoxide (N₂O₅) in perfluorocarbon solvents has been reported by Crampton: M. R. Crampton, L. M. Gibbons and R. Millar, *J. Chem. Soc., Perkin Trans. 2*, 2001, 1662.
- 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 fluororous 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 MgSO₄. 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%).