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Scandium Trifluoromethanesulfonate as Catalyst in the Hydrogen/Deuterium Exchange of 1,3,5-Trimethoxybenzene: Evidence for a Direct Interaction of Scandium with the Aromatic Ring

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Abstract—Scandium trifluoromethanesulfonate in CD_3OD is a very active catalyst for hydrogen/deuterium exchange at the aromatic nucleus of 1,3,5-trimethoxybenzene. The very low proticity of the system, spectrophotometric evidence, and easy iodination of the substrate point to the formation of a transient unprecedented arylscandium species as a plausible intermediate of the reaction. © 2000 Elsevier Science Ltd. All rights reserved.

Introduction

The use of scandium trifluoromethanesulfonate (triflate) in homogeneous organic catalysis has expanded in the last decade.[1,2] Although it is generally accepted that Sc^{3+} exerts catalytic activity thanks to the strong oxophilicity and Lewis acid character, most papers simply deal with the preparative aspects of the described reactions and rarely investigate the mechanism in detail. However, a better knowledge of the role exerted by scandium triflate should be very helpful for extending the use of this active catalyst in organic synthesis.

Among several electrophilic aromatic substitution rections, only Friedel–Crafts acylation and deformylation of aromatic aldehydes have been reported to be catalyzed by $Sc(OTf)_3$ so far. During our previous studies on the anhydrous $Sc(OTf)_3$ catalyzed protiodeformylation of aromatic aldehydes in MeOD,[3] we observed that the fast deformylation of 1,3,5-trimethoxybenzaldehyde under very mild conditions was accompanied by a rapid and complete hydrogen/deuterium exchange of both the substrate and the deformylation product, i.e. 1,3,5-trimethoxybenzene (**1**), at all the positions of the aromatic nucleus. By contrast, the exchange did not exceed 15% in the absence of the Lewis acid. $Sc(OTf)_3$ assisted deuteriation reactions have never been described before in the literature.

Hydrogen exchange is one of the most useful reactions for the study of the mechanism of electrophilic aromatic substitutions; moreover, 1,3,5-trimethoxybenzene is a particularly suitable substrate due to the activating effect of the methoxy groups. Therefore, it seemed worthy to investigate this reaction in detail. Our results point out to the intermediate formation of an unprecedented arylscandium species which may be involved in a number of Sc^{III}-catalyzed reactions of arenes.

Results and Discussion

^1H NMR measurements indicated that the deuteriation of **1** in the presence of anhydrous $Sc(OTf)_3$ (substrate 1.3 M in CD_3OD; molar ratio substrate–catalyst=6:1; 20°C) followed a pseudo first-order path, with $K_{Sc}=1.5\times10^{-3}\ s^{-1}$. Under the same experimental conditions, anhydrous lanthanum and yttrium triflates also promoted the proton–deuterium exchange, albeit much less efficiently, the rate constants being $K_{La}=9\times10^{-7}\ s^{-1}$, and $K_Y=3\times10^{-5}\ s^{-1}$, respectively.[†]

The catalytic properties of $Sc(OTf)_3$ were then extended to the deuteriation of other aromatic compounds such as 1,3-dimethoxybenzene and 1,3,5-trimethylbenzene under the reaction conditions indicated above. The former compound, which did not give rise to any H/D exchange in the absence

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Keywords: scandium and compounds; exchange reactions; substitution; metalation.

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[†] Since unavoidable traces of water affected the measurements to some extent, the reported values are merely indicative of the relative catalytic effect.

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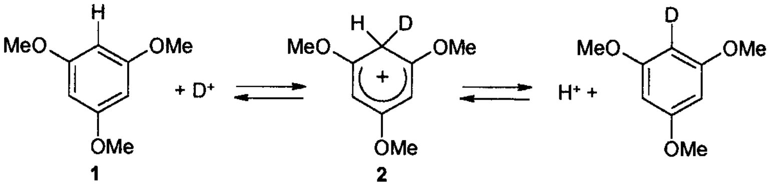


Scheme 1. Accepted mechanism for the acid catalyzed H/D exchange of aromatic compounds.

of $Sc(OTf)_3$, gave the corresponding 2,4,6-trideuterated derivative in 77% yield after 15 days, along with minor amounts of 4,6-dideuterated-1,3-dimethoxybenzene. By contrast, 1,3,5-trimethylbenzene was not deuterated after the same period.

Consistent with our previous results, these data showed an increase of the catalytic activity of rare earth(III) ions upon decreasing the cation size and increasing the electron density on the aromatic ring.[3,4]

Acidic catalysts generally promote the aromatic hydrogen–deuterium exchange quite efficiently and, notwithstanding the wide variety of reagents employed, it is generally accepted that the reactions take place via a general A-S_E2 mechanism.[5] In particular, this mechanism was ascertained for the deuteriation of compound **1** when it is catalyzed by protic acids.[6] The intermediate trimethoxybenzenonium ion was characterized by means of electronic and NMR spectroscopy.[7]

When transition or non-transition metal ions are used as Lewis acid catalysts, aromatic radical-ions may be formed;[8] however, in our case, a mechanism involving an aryl radical was immediately excluded since the system was ESR silent.

With this background, the following mechanisms were considered for explaining the accelerating activity of $Sc(OTf)_3$.

(i) coordination to Sc^{III} increased the proticity of MeOD and the H/D exchange then followed the usual arenium ion mechanism of protic acids (Scheme 1);
(ii) Sc^{III} directly activated the aromatic substrate, and the exchange occurred through the intermediate metalation of the arene ring by Sc^{III}, according to the mechanism outlined in Scheme 2.

The two mechanisms were investigated as follows.

Mechanism of Scheme 1

A thorough understanding of the catalytic behaviour of $Sc(OTf)_3$ in CD_3OD would require knowledge of the composition and the structure of the first coordination sphere. It is known that alcohols are good ligands to RE^{III} ions and such coordinated hydroxy groups behave as relatively strong acids,[4,9] but no information concerns specifically $Sc(OTf)_3$. It is reported that $RE(OTf)_3$ in anhydrous organic solvents display a significant innersphere interaction between the RE^{III} cation and the counter anion; whether they behave as 1:2 or 1:1 electrolytes depends on the solvent and on the presence of traces of H_2O. For instance, $La(OTf)_3$ behaves as a 1:2 electrolyte in anhydrous MeOH, while the species $[La(OTf)_2]^+$ prevails in MeCN. Moreover, the amount of complexation with more than one anion per cation seems to be higher for lighter lanthanides and the presence of traces of water has a crucial effect on the dissociation.[10]

Therefore, being impossible to have an accurate account of the composition of the species occurring in our solution, we assumed the simultaneous presence of solvated species such as $[Sc(MeOD)_n]^{3+}$, $[Sc(OTf)(MeOD)_{n-1}]^{2+}$, and $[Sc(OTf)_2(MeOD)_{n-2}]^+$, which all should exhibit a significant proticity. Indeed, in the $-\mathrm{Log}[H^+]$ range 4–9, potentiometric titrations of $Sc(OTf)_3$ with NaOMe in methanol (see Experimental) could be interpreted in terms of the presence of two deprotonation steps (Fig. 1), according to the following equilibria [Eq. (1) and (2)]

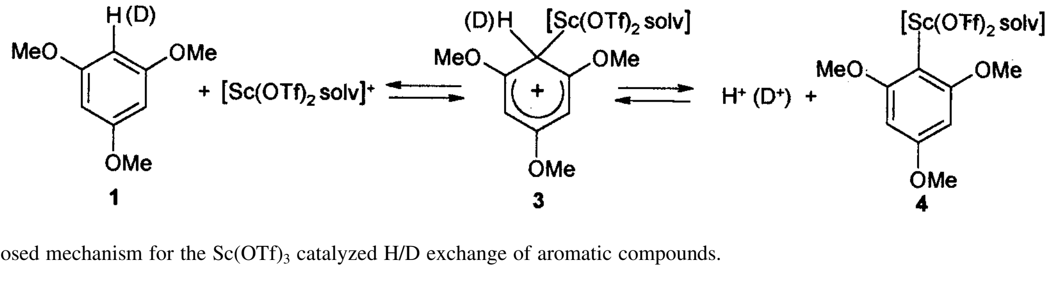
$$Sc[(MeOH)_n]^{3+} \rightleftarrows Sc[(MeOH)_{n-1}(OMe)]^{2+} + H^+ \qquad (1)$$

$$Sc[(MeOH)_{n-1}(OMe)]^{2+} \rightleftarrows Sc[(MeOH)_{n-2}(OMe)_2]^+ + H^+ \qquad (2)$$

having $pK_1=5.35$ and $pK_2=6.12$, respectively.

Considering a negligible isotopic effect, the above constants allowed us to calculate the $[D^+]$ of our system to be 2.5×10^{-4} M.

Therefore, assuming that [DOTf] matched $[D^+]$ in a very diluted methanolic solution, we established a value of $K_{DOTf}=2.68\times10^{-5}\ s^{-1}$ for the deuteriation rate of compound **1** in the presence of 2.5×10^{-4} M DOTf. The same



Scheme 2. Proposed mechanism for the $Sc(OTf)_3$ catalyzed H/D exchange of aromatic compounds.

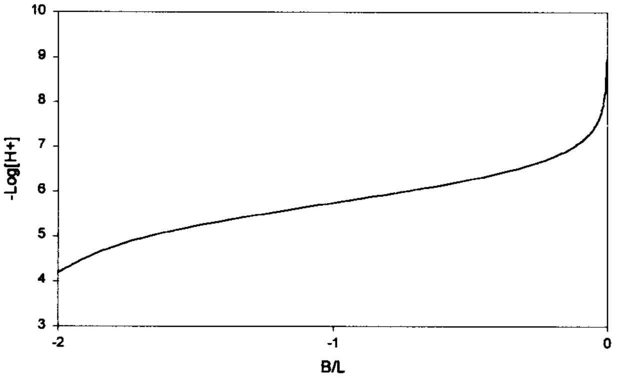


Figure 1. Titration curve of Sc(OTf)$_3$ with NaOMe in MeOH. B/L is the ratio of the moles of standard base added to the moles of Sc(OTf)$_3$. Negative values indicate excess of acid.

experiment was then repeated in the presence of 2.5×10^{-4} M DCl (the value of pK_a=1,23 for HCl in MeOH[11] indicated a complete dissociation at the employed molarity) in order to exclude that methanolic DOTf behaved as a weak acid. The value determined for K_{DCl} was 3.5×10^{-5} s^{-1}, which matched nicely K_{DOTf}. These rate constants, being more than two orders of magnitude lower than K_{Sc}, clearly excluded that the increased proticity of MeOD could entirely account for the accelerating effect of Sc(OTf)$_3$ on the deuteriation of compound **1**. The mechanism of Scheme 1 was therefore discarded.

Mechanism of Scheme 2

As mentioned before, the protonated species **2**, which is considered an intermediate of the acid-catalyzed deuteriation of aromatic compounds (Scheme 1), could be identified by means of electronic and NMR spectroscopy.[7]

If an arenium–scandium species **3**, analogous to **2**, were formed in the Sc(OTf)$_3$-catalyzed deuteriation of compound **1**, analogous spectral evidence would be expected. Actually, these clearly emerged from the comparative spectrophotometric study of the systems **1**-protic acids and **1**-Sc(OTf)$_3$ in anhydrous acetonitrile. This aprotic solvent was used instead of MeOD in order to prevent the very rapid exchange reaction which precluded the detection of species **3** in methanol (vide infra).

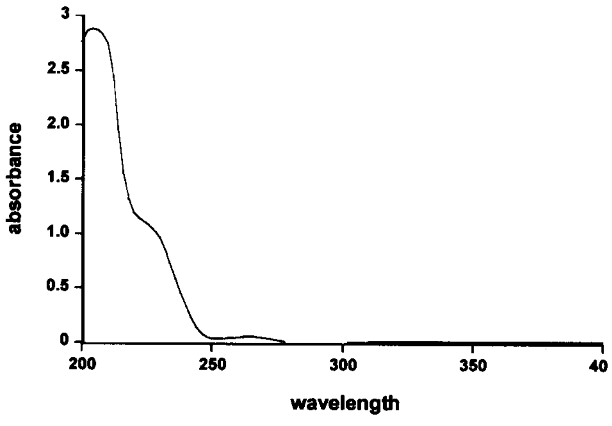


Figure 2. UV spectrum of 1,3,5-trimethoxybenzene (**1**), 1.0×10^{-3} M in MeCN.

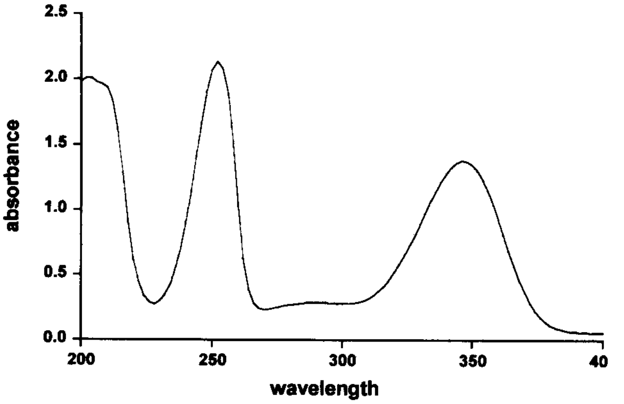


Figure 3. UV spectrum of 1,3,5-trimethoxybenzene (**1**), 1.0×10^{-3} M in anhydrous HOTf.

The electronic spectrum of **1** in neutral organic solvents (Fig. 2) shows a very strong band below 230 nm (ϵ 8.7×10^{3}) and a weak absorption band at about 260 nm (ϵ 530), which is characteristic of hydroxy- and alkoxybenzenes; in aqueous HClO$_4$, the 260 nm band is shifted to 250 nm (ϵ 2×10^{4}) and a new band appears at 347 nm (ϵ 1.23×10^{4}) which is assigned to the arenium species **2** (D=H).[‡] Protonation is almost complete in 65% HClO$_4$.[7a] As expected, we observed identical spectral modifications in anhydrous trifluoroacetic acid, anhydrous HOTf (Fig. 3),[§] 5 M aqueous HOTf, 9 M trifluoroacetic acid in MeCN and 1 M HOTf in MeCN.[‖]

When excess Sc(OTf)$_3$ was added to a concentrated solution of **1** in MeCN (substrate concentration>0.1 M; substrate–Sc^{3+}, about 1:5 molar ratio) or, conversely, increasing amounts of compound **1** were added to a concentrated solution of Sc(OTf)$_3$ in MeCN, the UV spectrum was immediately perturbed in a similar way (Fig. 4), except that the absorption band at 350 nm was much less intense than that at 260 nm. This feature precluded the study of the 260 nm band since at concentrations suitable to the study of this region, no band was detectable at 350 nm.

Anyhow, in our opinion, the band at 350 nm could be attributed to a direct interaction of Sc$^{\mathrm{III}}$ with the aromatic ring, leading to chromophore **3** which is quite similar to the protonated species **1**. Indeed, detection of the weak band at 350 nm required very high concentration of the reagents, indicating that the molar ratio arylscandium species **3**:substrate **1** was very low.

For this reason, all our attempts to determine the constant of formation of intermediate **3** failed, as well as our efforts to detect this species in CD$_3$CN by means of NMR spectroscopy.

[‡] Slight shifts, due to experimental conditions, occur to this band. Therefore, it will be reported as 350 nm band.

[§] Anhydrous HOTf and 60% HClO$_4$ have about the same molarity.

[‖] 1 M HOTf does not interfere with MeCN.

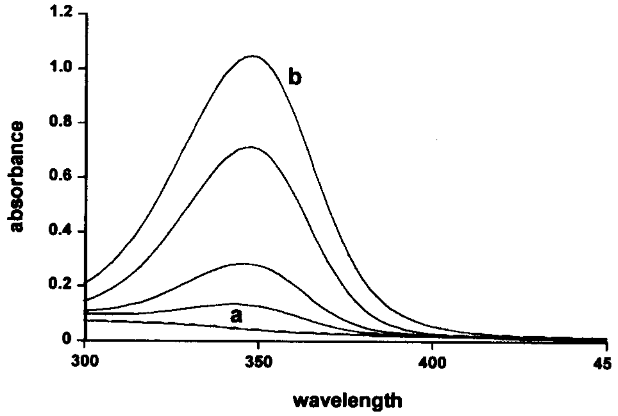


Figure 4. UV spectra of the system $Sc(OTf)_3$ – 1,3,5-trimethoxybenzene (**1**) in anhydrous MeCN. Only the significant region (300–450 nm) is shown. Spectrum **a**, 0.354 M $Sc(OTf)_3$; spectrum **b**, molar ratio $Sc(OTf)_3$:1,3,5-trimethoxybenzene (**1**)=1:10; intermediate spectra, molar ratios 1:1; 1:2; 1:5.

In order to exclude that the weak 350 nm band could be due to interference of traces of HOTf produced by minor hydrolysis of $Sc(OTf)_3$, the spectrophotometric investigation was repeated in the presence of 2,6-di-tert-butylpyridine (base–Sc^{III}=1:1 molar ratio). As expected, the spectra were superimposable with those recorded in the absence of the base. Moreover, if the 350 nm band was caused by moisture, addition of H_2O should increase the intensity. By contrast, successive additions of H_2O to the system gradually decreased the intensity of the band at 350 nm which eventually disappeared.

Altogether, in our opinion, the above results strongly support a mechanism of the type outlined in Scheme 2. According to this, an electrophilic scandium species, of the type $[Sc(OTf)_2(solv)]^+$ (solv=CD_3OD), would form the metalated arenium ion **3** which can then restore the aromatic sextet either reverting to the starting compound **1** or leading to the arylscandium species **4**.

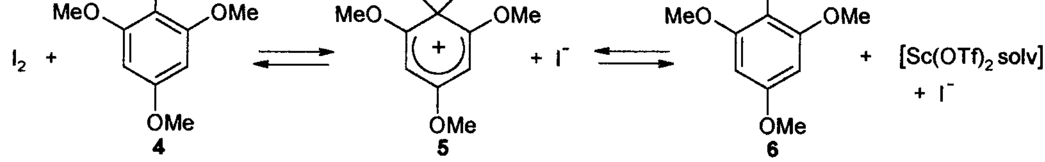
The solvated $Sc(OTf)_2^+$ cation is thus supposed to be the active species in the same way as $Tl(OTf)_2^+$ and $Tl(O_2CCF_3)_2^+$ have been recognized to be the active electron acceptors in the thalliation of arenes promoted by $Tl(OTf)_3$ and $Tl(O_2CCF_3)_3$ respectively.[12] The analogy of the catalytic behaviour of these ions can be ascribed to the analogous closed shells configurations of Sc^{III} and Tl^{III}. It is worthy to underline that $Tl(OTf)_3$ is a more effective thalliating agent than $Tl(O_2CCF_3)_3$ due to a greater ionization of the former salt and/or to a greater electrophilicity of $Tl(OTf)_2^+$ compared to $Tl(O_2CCF_3)_2^+$; moreover, having Sc^{III} a higher ionic potential than Tl^{III}, the species $Sc(OTf)_2^+$ should be more electrophilic than $Tl(OTf)_2^+$.

Species **4** has a structure similar to known isolable arylmetal derivatives in which the aryl-metal bond is readily cleaved by protonation, according to a mechanism involving an intermediate metalated arenium ion of the type **3**. Moreover, a proton transfer from medium to substrate was proved to be involved in the rate determining step of these reactions.[13]

In conclusion, comparing the mechanism shown in Scheme 2 with the acid catalyzed deuteriation of 1,3,5-trimethoxybenzene (**1**) (Scheme 1), one can explain the accelerating effect of $Sc(OTf)_3$ by assuming that equilibrium Scheme 2 largely favours compound **1** and that the readily formed arylscandium species **4** is more reactive than substrate **1** towards D^+ attack. This difference in reactivity is likely due to an increased stabilization of intermediate **3** compared to **2** as it has been reported for other metalated arenium ions.[13] In addition, coordination of CD_3OD to scandium, besides increasing the proticity of the hydroxy group, might facilitate the exchange reaction through a template effect.

Since the H/D exchange occurs rapidly, concentration of **3** in MeOD must remain extremely low, thus precluding the detection by spectrophotometric investigation. Much for the same reasons, it was impossible to obtain direct evidence of the intermediate formation of species **4**. Therefore, in order to give support to our hypothesis, we compared the reactivity of **1** towards iodine in the absence and in the presence of $Sc(OTf)_3$; in fact, it is known that arenes undergo easy iodination with I_2 in the presence of efficient metalating salts such as trifluoroacetates of Tl^{III}, Hg^{II}, and Ag^{I}.[14] In particular, the mechanism of benzene iodination in the presence of thallium(III)trifluoroacetate has been investigated in detail.[15] The reaction proceeds through the initial thalliation of the arene ring, followed by the electrophilic substitution of thallium by iodine; the so formed I^- is oxidized to I_2 by Tl^{III} which is recovered as Tl^{I}. Thus, one molar equivalent of iodine produces two equivalents of monoiodobenzene. Instead, one molar equivalent of iodine produces one molar equivalent of monoiodobenzene, if Ag^{I} or Hg^{II} trifluoroacetates are used, since they are not capable to oxidize the I^- species.

We examined the iodination of **1** in the presence of $Sc(OTf)_3$, both by ^1H NMR spectroscopy and by conventional methods (see experimental section). The ^1H NMR spectra showed that the reaction at room temperature reached the equilibrium after about 15 min, giving the monoiodinated product in 15% yield, while in the absence



Scheme 3. Proposed mechanism for the $Sc(OTf)_3$ catalyzed iodination of 1,3,5-trimethoxybenzene (**1**).

of the catalyst, the same product was obtained in 5% yield. These results were qualitatively confirmed monitoring the reaction by TLC.

The iodination of **1** was then carried out in MeCN on a preparative scale in the presence of $Pb(NO_3)_2$ as scavenger of I^-. A preliminary test done by ^1H NMR spectroscopy ascertained the inactivity of $Pb(NO_3)_2$ towards iodination. The reaction appeared to be clean (TLC) and crystals of the monoiodinated product **5** were eventually isolated. These experiments, which parallel the reported iodination of arenes in the presence of Ag^I, Hg^{II} or Tl^{III} species, support the hypothesis that a labile scandiated derivative of the type **4** is also involved in the iodination of **1** (Scheme 3).

The instability of the scandiated species **4** can be easily understood considering that Sc^{III}, contrary to Tl^{III}, Hg^{II}, and Ag^I lacks the d-electrons necessary for the d–π back donation.

Conclusions

This paper describes a new kind of electrophilic aromatic substitution reaction catalyzed by $Sc(OTf)_3$. The proposed mechanism involves an arylscandium species as a likely intermediate. The activation of chemically inert C–H bonds through a transient metalation might be involved in other organic reactions catalyzed by scandium triflate.

Experimental

All reagents and solvents are commercially available (Aldrich). Anhydrous $Sc(OTf)_3$ was prepared as reported,[4] as well as 2-iodo-1,3,5-trimethoxybenzene.[16] UV spectra were recorded in the 200–400 nm range with a HP 8452A diode array spectrophotometer. ^1H NMR spectra were recorded at 20°C. on a Bruker ACE 300 (300 MHz) spectrometer in MeCN-d_3 or MeOH-d_4 with TMS as an internal standard.

Potentiometric studies of $Sc(OTf)_3$ in methanol. The experiments were carried out using the fully automatic system described previously.[17] Methanolic solutions (0,05 dm^3) of $Sc(OTf)_3$ about 10^{-3} M, made 0.1 M in ionic strength with $LiClO_4$, were titrated with 0.2N NaOMe in MeOH. The standard electrode potential was determined for each experiment with the Grahn's method using 0.2N $HClO_4$ in MeOH. Nernst's equation was obeyed by the electrode in this medium. The titration curves were fitted and the equilibrium constants were calculated using the non-linear least squares program HYPERQUAD.[18]

Iodination of 1,3,5-trimethoxybenzene (**1**) in the presence of $Sc(OTf)_3$. A 0.5 M solution of 1,3,5-trimethoxybenzene (**1**) in MeCN added with one molar equivalent of $Sc(OTf)_3$ and 0.5 molar equivalents of $Pb(NO_3)_2$ (Solution A), was poured in a two-necks flask equipped with a short Dufton column and a $CaCl_2$ tube and kept in a thermostatic bath set at 20°C. A 0.25 M solution of I_2 in MeCN was added portionwise (10 μl) under magnetic stirring. The iodine color immediately disappeared after the initial additions, while yellow PbI_2 readily precipitated making it difficult to appreciate the end-point. This roughly occurred after the addition of 0.25 molar equivalents of I_2. A parallel experiment was carried out in the absence of $Sc(OTf)_3$ (Solution B). Under these conditions, iodine was consumed very slowly since the very beginning of the experiment, the reacting solution assuming a dark orange color after few additions. Both reaction mixtures were then warmed to 60°C for 20 min. While solution A remained unaltered, solution B turned to dark brown and then to blue-green. 2-Iodo-1,3,5-trimethoxybenzene was isolated from solution A, following a procedure similar to that reported in the literature.[16,19] The reaction mixture was cooled, filtered, and added with an aqueous solutions of $NaHCO_3$ and $Na_2S_2O_3$. MeCN was removed by evaporation under reduced pressure and the aqueous phase was extracted with $CHCl_3$. The organic solution was dried over $MgSO_4$ and evaporated to dryness under reduced pressure. The crude product was crystallized from CH_2Cl_2 to give crystals of 2-iodo-1,3,5-trimethoxybenzene, mp 122–123°C, identical with an authentic sample.

Acknowledgements

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