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Catalytic Iodination of the Aliphatic C–F Bond by $YbI_3(THF)_3$: Mechanistic Insight and Synthetic Utility

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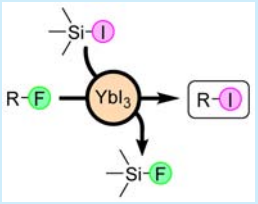
Supporting Information

ABSTRACT: A facile iodination protocol of unactivated alkyl fluorides using catalytic amounts of $YbI_3(THF)_3$ in the presence of iodotrimethylsilane as a stoichiometric fluoride trapping agent is presented. ^{1}H NMR spectroscopy demonstrates a two-step catalytic cycle where TMSI regenerates active $YbI_3(THF)_3$. Finally, the catalytic reaction is extended into a one-pot procedure to demonstrate a potential application of the method. Overall, the findings present a distinct strategy for C–F bond transformations in the presence of catalytic $YbI_3(THF)_3$.



The C–F bond is the strongest single bond that can be formed between carbon and another element.[1] The characteristic inertness of the C_{sp3}–F functional group has resulted in widespread applications, e.g., within pharmaceutical, agricultural, and material sciences.[2] This demand for fluorinated compounds has led to the development of numerous fluorinating protocols.[3] The fact that fluorinated compounds are extensively used, extremely long-lived, and potentially toxic inspires the development of vital and novel methods for C–F bond activation and transformation.[4−6] Our group has recently communicated that lanthanide(III) reagents facilitate mild and selective activation of aliphatic fluorides.[6] It was proposed therein that the strong lanthanide–fluoride interaction is responsible for the C–F bond cleavage. Having established $YbI_3(THF)_3$ as a stoichiometric reagent for selective halogen exchange transformation (F to I), we envisioned that treatment of the lanthanide(III) reagent with a fluoride trapping agent would allow the usage of $YbI_3(THF)_3$ in a catalytic amount. The majority of synthetically valuable methods for substitution of unactivated alkyl fluorides still apply stoichiometric amounts of Lewis acids (Scheme 1a).[4] Catalytic main-group Lewis acid hydrodefluorinations of alkyl fluorides have been developed (Scheme 1b).[5] However, catalytic halogen exchange reactions of unactivated alkyl fluorides are scarce.[4a] Herein we describe the first example of $YbI_3(THF)_3$ catalyzed iodination of alkyl fluorides in the presence of iodotrimethylsilane (TMSI) as a stoichiometric fluoride trapping agent (Scheme 1). In addition, the mechanism has been extensively studied to expand the understanding of $YbI_3(THF)_3$ and its application in C–F bond transformations.

Olah et al. have shown that substitution of alkyl fluorides to alkyl iodides is feasible using 1.1 equiv of TMSI in dichloromethane (CH_2Cl_2).[7] However, they reported that displacement of primary fluorides is sluggish and incomplete even during heating and at extended reaction times. Indeed, when such a reaction was attempted in our laboratory, using 1-fluorodecane as a model substrate with 3 equiv of TMSI, only a 2% yield was achieved after 13 h (Table 1, entry 1).

To test the notion that $YbI_3(THF)_3$ could be used in catalytic amounts, 1-fluorodecane was subjected to a mixture of 3 equiv of TMSI and 1, 5, and 10 mol % of $YbI_3(THF)_3$ (Table 1, entries 2–4). A GC yield of 95% of 1-iododecane was

Scheme 1. Lewis Acid Promoted C–F Bond Substitution

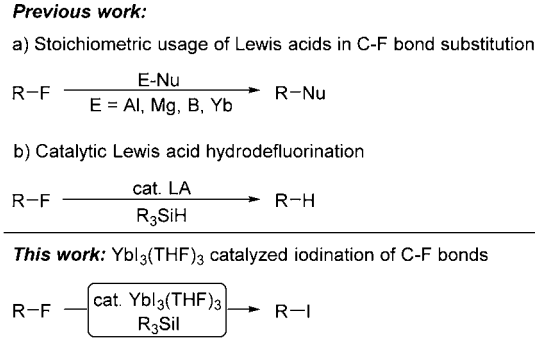
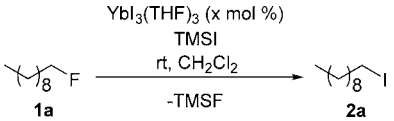


Table 1. Optimization of $YbI_3(THF)_3$ Catalyzed C–F Bond Substitution of 1-Fluorodecane in the Presence of TMSI[a]



1a 2a

entry	$YbI_3(THF)_3$ (mol %)	TMSI (equiv)	t (h)	yield (%)[b]
1	0	3	13	2
2	1	3	13	21
3	5	3	13	60
4	10	3	13	95
5	10	1.5	13	77
6	10	6	8	95

[a]Reaction conditions: **1a** (0.04 mmol), CH_2Cl_2 (0.4 mL). Dodecane was used as internal standard. [b]Analyzed by GC-FID.

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successfully obtained utilizing 10 mol % of $YbI_3(THF)_3$ within 13 h at room temperature without any rearrangements (entry 4). Using only 1.5 equiv of TMSI gave a somewhat lower yield of 77% within 13 h (entry 5), while increasing TMSI to 6 equiv afforded 1-iododecane in 95% yield within 8 h (entry 6). Optimized reaction conditions were found to be 10 mol % of $YbI_3(THF)_3$ and 3 equiv of TMSI in CH_2Cl_2 at room temperature.

With ^1H and ^{19}F NMR spectroscopy we could confirm the regeneration of active $YbI_3(THF)_3$ by TMSI. 1-Fluoroadamantane (**1b**) was chosen as a model substrate, and all reagents were added in stoichiometric amounts. NMR spectra acquired directly after adding 1 equiv of $YbI_3(THF)_3$ to 1 equiv of 1-fluoroadamantane in CD_2Cl_2 showed full conversion of starting material to 1-iodoadamantane (**2b**) (Figure 1A to B; no

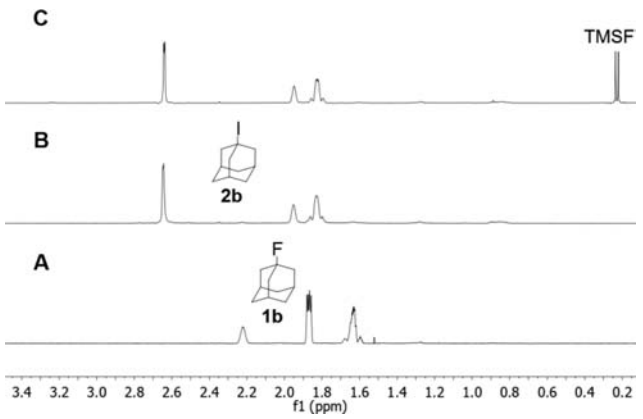


Figure 1. ^1H NMR spectra of (A) 1-fluoroadamantane (**1b**) in CD_2Cl_2; (B) instantaneous and quantitative conversion of **1b** to 1-iodoadamantane (**2b**) upon addition of $YbI_3(THF)_3$ to A; and (C) further addition of TMSI revealing instantaneous formation of TMSF.

fluorine signal present in ^{19}F NMR) and most likely forming the paramagnetic "$YbI_2F(THF)_3$" in situ. Based on previous results, it is known that "$YbI_2F(THF)_3$" is inactive and cannot participate in C−F bond substitution.[6c] When adding 1 equiv of TMSI to this unreactive reagent, a new set of signals appeared instantaneously, corresponding to TMSF, as determined by ^1H and ^{19}F NMR spectroscopy (Figure 1C). These findings confirm that TMSF, formed upon addition of TMSI, is a direct result of the subtraction of fluorine from the "$YbI_2F(THF)_3$" complex.[8] Thus, TMSI acts as a trapping agent which facilitates the regeneration of $YbI_3(THF)_3$ in this case. Again, with full conversion of TMSI to TMSF, the only iodination source present is $YbI_3(THF)_3$. So when **1b** was added a second time, full conversion of starting material to **2b** occurred (see Supporting Information (SI)).

To gain insight into the catalytic reagent system and how TMSI influences the surroundings of the catalyst, we exchanged the paramagnetic $YbI_3(THF)_3$ for the closely related but diamagnetic $LaI_3(THF)_4$ and were thereby able to study the process by ^1H NMR spectroscopy (Figure 2). Analysis of the ^1H NMR spectrum acquired after mixing 8 equiv of TMSI and 1 equiv of $LaI_3(THF)_4$ in CD_2Cl_2 showed a new set of signals corresponding to (4-iodobutoxy)trimethylsilane (Figure 2B). Thus, we have confirmed that the $LaI_3(THF)_4$ complex readily undergoes ring opening of the THF ligands, most likely resulting in a THF free oligomeric complex of LaI_3.[9] Interestingly, when the reaction mixture was left for an

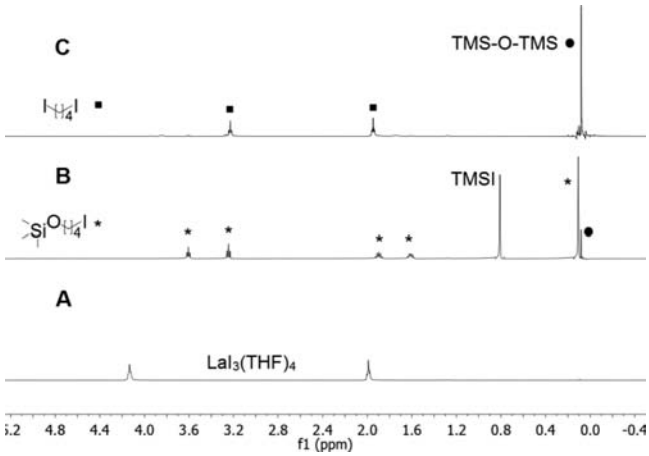


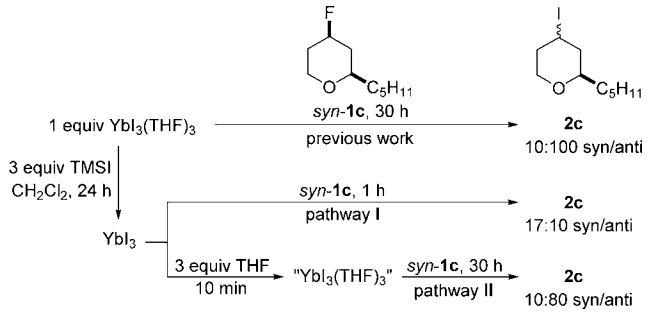
Figure 2. ^1H NMR spectra of (A) THF signals from $LaI_3(THF)_4$ in CD_2Cl_2. (B) Spectra obtained 5 min after addition of TMSI showing quantitative ring opening of THF to yield (4-iodobutoxy)-trimethylsilane. (C) Spectra showing after an additional 18 h only 1,4-diiodobutane and hexamethyldisiloxane are detected.

extended time, the (4-iodobutoxy)trimethylsilane (confirmed by GC-MS) was further substituted to 1,4-diiodobutane and hexamethyldisiloxane (Figure 2C). These NMR results show that it is possible to form a catalytic reagent which is free of THF.

To further understand the effect THF ligands have on the catalytic reagent system, the stereochemical outcome of the iodo substitution of *syn*-fluoropyran **1c** was studied. As previously reported by us, the reaction between *syn*-**1c** and $YbI_3(THF)_3$ in stoichiometric amounts favors the formation of *anti*-iodopyran (syn/anti 10:100), indicative of an S_N2-type mechanism.[6c]

A striking difference in selectivity was observed when reacting THF-free YbI_3, generated in situ through extended premixing of $YbI_3(THF)_3$ and TMSI, with *syn*-**1c** (Scheme 2,

Scheme 2. Study of the THF Effect on the $YbI_3(THF)_3$ Substitution of *syn*-1c



pathway I). The ratio between the two stereoisomers now slightly favored the *syn*-configuration, possibly indicating an S_N1-type mechanism with a short-lived carbocation. The influence of THF was further validated by deliberate addition of THF to YbI_3, regenerating "$YbI_3(THF)_3$", followed by *syn*-**1c** (pathway II). This process reverted the stereoisomeric selectivity to the original ratio. Thus, the reactivity of the catalyst is clearly affected by THF and its cleavage product in the presence of TMSI.

The difference in stereochemical outcome of *syn*-**1c**, when subjected to $YbI_3(THF)_3$-TMSI, is seemingly influenced by the

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presence of coordinated THF. This became even more evident when investigating the importance of premixing time between $YbI_3(THF)_3$ and TMSI. *syn*-**1c** was added to eight separate experiments with premix times ranging from 1 to 180 min. Each reaction was quenched after 30 s and analyzed. Various syn/anti ratios were obtained (Figure 3). In addition, subjecting

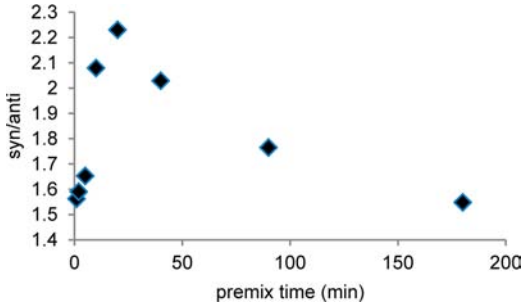
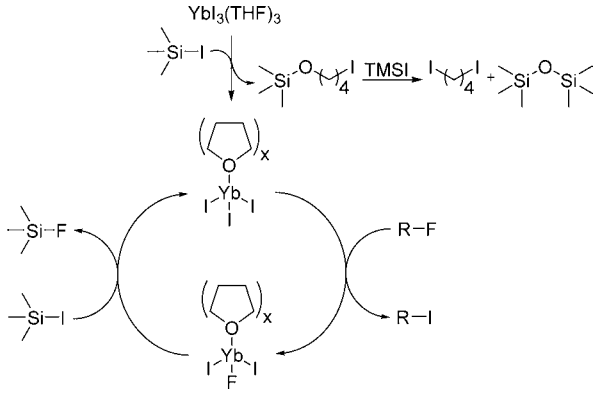


Figure 3. Analysis of syn/anti ratio from the stereochemical outcome of *syn*-**1c** by varying the premix time of $YbI_3(THF)_3$ and TMSI.

syn-**1c** to $YbI_3(THF)_3$–TMSI with a premix time of 180 min led to a constant syn/anti ratio (16:10) over the course of the reaction (see SI). A premix time of 30 min resulted in a variation of syn/anti ratio (from 22:10 to 16:10) when analyzing **2c** over time. Consequently, different reactive catalytic species are generated over the course of the reaction as a result of the ring opening of THF.

Overall, the mechanistic investigation supports the proposed catalytic cycle presented in Scheme 3. The ring opening of

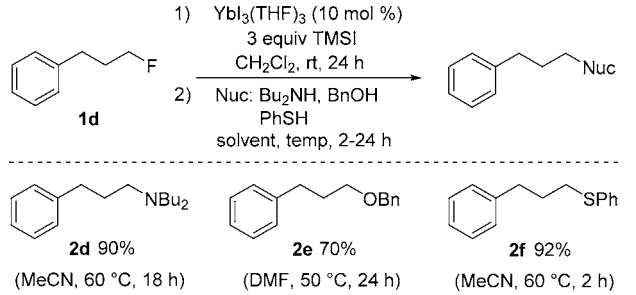
Scheme 3. Proposed Mechanism of $YbI_3(THF)_x$ Catalyzed C–F Bond Substitution in the Presence of TMSI (x = 0–3 THF Molecules Coordinated)



THF, upon addition of TMSI, generates ligand-free YbI_3. Such ring opening was detected by ^1H NMR of the closely related lanthanide $LaI_3(THF)_4$ (Figure 2). The desolvation of $YbI_3(THF)_3$ promoted by TMSI results in the altered stereochemical outcome of *syn*-**1c** (Scheme 2). When subjected to $YbI_3(THF)_3$ the reaction proceeds via an S_N2-type mechanism, while the THF-free YbI_3 reagent predominantly proceeds via an S_N1-type mechanism. Notably, both $YbI_3(THF)_3$ and ligand-free YbI_3 reagents are catalytically active species. It is also important to note that the cleavage of coordinated THF is rapid, since 1 min of premixing time is sufficient to significantly change the stereochemical outcome of *syn*-**1c** (Figure 3). However, a premix time of 180 min is necessary to generate a THF-free catalytic complex with a well-defined reactivity. Furthermore, TMSF formed upon regeneration of $YbI_3(THF)_3$ from a "$YbI_2F(THF)_3$" complex demonstrates that TMSI acts as a stoichiometric fluoride trapping agent as hypothesized (Figure 1).

To show the applicability of the reagent system, a one-pot, two-step reaction system was designed by using 3-fluoropropyl benzene (**1d**) as a model substrate (Scheme 4). Various

Scheme 4. One-Pot Two-Step Substitution Reaction of 3-Fluoropropyl Benzene to Various Substituted Propyl Benzene Derivatives Using Cat. $YbI_3(THF)_3$ and TMSI As a Key Step



nucleophiles could be introduced, and the corresponding products were isolated in high to excellent yield by substitution of the corresponding 3-iodopropyl benzene, formed in situ by reacting **1d** with $YbI_3(THF)_3$–TMSI for 24 h at room temperature. Our method now allows us to incorporate various common functional groups from an inert alkyl fluoride via a highly reactive iodo-intermediate.

Finally, a selectivity test between fluoro-, chloro-, and bromoalkane was conducted. The substitution promoted by catalytic $YbI_3(THF)_3$ showed excellent selectivity toward the alkyl fluoride, with 95% conversion of 1-fluorodecane within 16 h, and less than 2% conversion of 1-chloro- and 1-bromodecane, respectively (see SI).

In conclusion, we have developed a novel $YbI_3(THF)_3$ catalyzed C–F bond activation method in the presence of stoichiometric TMSI. The reaction proceeds under mild conditions and expands the usage of $YbI_3(THF)_3$ as a versatile and powerful reagent for C–F bond activation. The methodology allows the usage of fluorine as a small, sterically unhindered surrogate protecting group. In comparison to hydrodefluorination processes, our approach enables a direct and powerful route for late-stage incorporation of iodine, in which the highly reactive iodo-compound can be converted into other functional groups. Mechanistic investigations have presented results supporting a two-step catalytic cycle, where TMSI regenerates the active catalyst. In addition, $YbI_3(THF)_3$ undergoes ring-opening of THF in the presence of TMSI over time, which is a process that clearly affects the stereochemical outcome of a reaction. It still needs to be determined whether the catalytic reaction has a broad substrate scope. For this purpose, we are currently exploring this reagent system with other classes of alkyl fluorides.

■ ASSOCIATED CONTENT

Supporting Information

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Preparation of catalyst, general experimental procedure, and mechanistic data (PDF)

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Notes

The authors declare no competing financial interest.

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