Synthetic Methods

DOI: 10.1002/ange.201306104

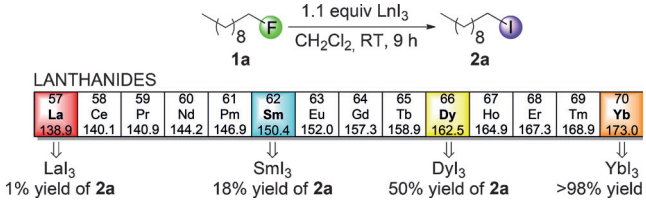
Selective C–F Bond Activation: Substitution of Unactivated Alkyl Fluorides using YbI_3**

*Annika M. Träff, Mario Janjetovic, Linda Ta, and Göran Hilmersson**

Fluorine is an important functionality which nowadays is widely used in modern pharmaceuticals, agrochemicals, and pesticides because of its ability to favorably influence chemical and physical properties of organic molecules.[1] These valuable properties, conferred by C–F functionalities, have led to the generation of numerous methods for the introduction of fluorine, for example, by electrophilic or nucleophilic fluorinating reagents, or by radical procedures.[2] The increasing popularity and ability to introduce fluorine into organic compounds now provides the opportunity for selective C–F bond activation, and the development of novel methods to synthetically alter these compounds further. Aryl C–F bond activation has been comprehensively elucidated.[3] Additionally, several procedures for substitution of activated C–F bonds, for example, at the benzylic or allylic position or α to a carbonyl group, have been developed.[4] However, a synthetically valuable method for C–F bond activation of unactivated aliphatic fluorocarbons still remains a challenge. A few attempts to manipulate such C–F bonds have been addressed utilizing strong Lewis acids, which in general are highly oxophilic, thus making their use impractical in the presence of other functional groups.[5] Consequently, all of these Lewis acids only allow substitution of simple, unsubstituted alkyl fluorides, thus greatly limiting their synthetic usefulness.

Trivalent lanthanides are known not only to be excellent Lewis acids, but also to form strong bonds to fluorides.[6] As such, it stands to reason that they could potentially be utilized to activate C–F bonds. The Lewis acidity of lanthanides increases from left to right in the periodic table, with simultaneous decrease in oxophilicity.[7] This conclusive pattern makes ytterbium an interesting candidate for activation of the aliphatic C–F bond. Herein we report our exploration of YbI_3 as a novel, very powerful, iodination reagent. Selective substitution of alkyl fluorides in the presence of other common functionalities is expected to open up new synthetic strategies in organic chemistry. Hence, it would not only enable the substitution of a highly inert group (C–F) with a highly reactive group (C–I), but also implement activation of that specific carbon atom towards general synthetic diversification.

During recent studies of reductive cleavage of C–F bonds with $Sm(HMDS)_2$ (HMDS = hexamethyldisilazide), we discovered that traces of alkyl iodides could be detected in the reaction mixtures.[8] Encouraged by this finding we turned our attention to trivalent lanthanides. 1-Fluorodecane (**1a**) was exposed to SmI_3 in THF at room temperature. Surprisingly, GC analysis revealed a small amount of 1-iododecane within 24 hours (10% yield), thus indicating a novel F/I substitution. A solvent screen highlighted CH_2Cl_2 as the most efficient medium yielding 98% of 1-iododecane within the same time frame. A correlation between the yield of substitution and the Lewis acidity of the respective lanthanide triiodide was examined (Scheme 1).



Scheme 1. Investigating the reactivity of different lanthanide triiodide reagents. Reaction conditions: LnI_3 (0.0484 mmol, 24.2 mM), CH_2Cl_2 (2.0 mL), **1a** (0.0440 mmol, 22.0 mM). *n*-Dodecane (0.044 mmol, 22 mM) was used as an internal standard. Analyzed by GC-FID.

The use of LaI_3 resulted in only 1% F/I substitution, while SmI_3, DyI_3, and YbI_3 provided 18%, 50%, and greater than 98% yields, respectively, within 9 hours. Gratifyingly, the reaction was compatible with standard laboratory quality (>99.5%) solvent and could be conducted open to the atmosphere. However, a small amount of deliberately added water (1% V/V) was deleterious for the reaction. Thus, the reaction as well as the reagent (YbI_3) is insensitive towards moisture and air, thereby indicating that these iodides are stable towards hydrolysis. With a substoichiometric amount of YbI_3 relative to 1-fluorodecane, the reaction rate decreased significantly without reaching full conversion, thus implying that only one iodide is readily transferred. Full conversion was achieved with 1.1 equivalents of YbI_3. Employing MgI_2 gave a considerably lower yield of 1-iododecane along with several byproducts according to GC analysis. No formation of 1-iododecane was observed when employing simple iodides such as KI, LiI, AlI_3, or CuI. The reaction was successfully performed in the dark, thus excluding light induction. The reaction of YbI_3 with 1-fluorodecane was also studied in

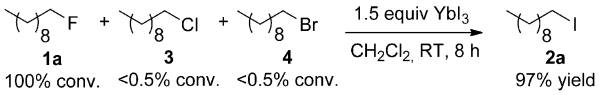
[*] Dr. A. M. Träff, M. Janjetovic, L. Ta, Prof. Dr. G. Hilmersson
Department of Chemistry and Molecular Biology
University of Gothenburg
Kemivägen 10, SE-412 96 Gothenburg (Sweden)
E-mail: Hilmers@chem.gu.se

[**] The authors gratefully acknowledge the Swedish Research Council and the University of Gotheburg for financial support. Prof. Per-Ola Norrby is gratefully acknowledged by his contribution of mechanistic insight.

Supporting information for this article (experimental details) is available on the WWW under http://dx.doi.org/10.1002/anie.201306104.

a variety of solvents (see Table S1 in the Supporting Information). The trend observed was that in nonpolar solvents such as *i*-hexane, in which YbI_3 was not soluble, less than 10% yield was obtained within 9 hours. In polar, coordinating solvents such as THF, EtOH, acetone, Et_3N, and DMF, less than 10% conversion was observed, whereas in Et_2O and MeCN approximately 30% yield of 1-iododecane was achieved. Almost full conversion and yield was achieved in polar, noncoordinating solvents such as $CHCl_3$ or CH_2Cl_2 (>90% yield). The results above indicate that the reaction is facilitated by an activation of the fluoride–carbon bond by ytterbium. A competing interaction of the solvent with ytterbium can prevent the C–F bond activation to occur.

Upon addition of an excess of YbI_3 (1.5 equiv) to a 1:1:1 mixture of 1-fluoro-, 1-chloro-, and 1-bromodecane, 100% conversion of 1-fluorodecane into 1-iododecane was observed within 8 hours, whereas less than 0.5% of 1-chlorodecane and 1-bromodecane were consumed (Scheme 2). No further substitution of **3** and **4** was observed after leaving the reaction to run for a longer period of time (24 h), thus demonstrating exclusive selectivity of the reagent for alkyl fluorides.

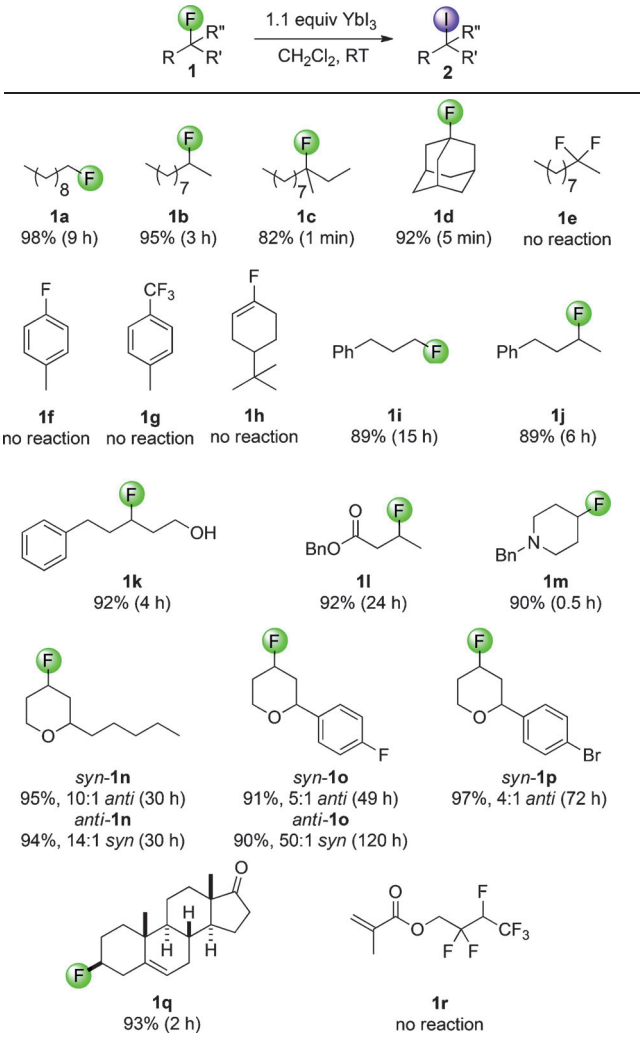


Scheme 2. Selectivity study of YbI_3 towards different aliphatic carbon–halogen bonds. Reaction conditions: YbI_3 (0.066 mmol, 33 mM), CH_2Cl_2 (2.0 mL), **1a** (0.044 mmol, 22 mM), **3** (0.044 mmol, 22 mM), **4** (0.044 mmol, 22 mM). *n*-Dodecane (0.044 mmol, 22 mM) was used as an internal standard. Analyzed by GC-FID.

The proficiency of any synthetic method depends on several aspects, one of the most important being high tolerance towards diverse functional groups. Performing the substitution of 1-fluorodecane in the presence of various organic compounds, each containing a common functional group, gave us some comprehension of the scope of the method (see Table S2 of the Supporting Information). Functionalities such as ketone, alcohol, cyanide, trialkylamine, or ether did not interfere with the F/I substitution reaction. Benzamide and adamantyl carboxylic acid reduced the rate of the reaction but not the yield, possibly by coordinating strongly to YbI_3. It should be underlined that the above substrates were recovered in quantitative yield after the reaction. Thiophenol was not compatible with the reaction conditions because of oxidative formation of diphenyl disulfide (PhS–SPh).[9] Trivalent lanthanides are also known to mediate transesterification reactions.[10] Nevertheless, when YbI_3 was added to a mixture of ethyl acetate and 4-phenyl-1-propanol in the presence of 1-fluorodecane, only substitution of the fluoride with iodide was observed. The rate of the reaction was somewhat lower, thus indicating a competing coordination of YbI_3 with the ester or the alcohol.

The scope of the reaction was further elaborated by its application on primary, secondary, and tertiary alkyl fluorides (**1a–d**; Table 1), in which all the substrates were converted

Table 1: Substrate scope of the F/I substitution.



Yields of the isolated iodinated compounds are reported. Note: for **1o** only the alkyl fluoride reacted and not the aryl fluoride. Reaction conditions: YbI_3 (0.484 mmol, 24.2 mM), CH_2Cl_2 (20 mL), substrate (0.440 mmol, 22.0 mM).

into the corresponding iodides in excellent yields. The straight forward isolation of the iodo-substituted compounds involved a simple filtration and subsequent concentration under vacuum, thus yielding the product in very high (>96%) purity as determined by ^1H NMR spectroscopy. The tertiary iodide resulting from **1c** is rather unstable and readily undergoes elimination to a mixture of alkenes, thus explaining the moderate yield (82%) upon isolation. No substitution was observed for substrates having two or three fluorides on the same carbon atom (**1e**, **1g**), or on sp^2-hybridized carbon atoms (**1f**, **1h**). These outcomes are consistent with the higher bond strengths for CF_2 and CF_3 groups as well as for sp^2-carbon atoms, as compared to monofluorinated sp^3-carbon atoms.[1b] The substitution proceeded in high yield but at a significantly lower rate with a phenyl group present in the substrate (**1i**, **1j**). This lower rate is attributed to the likely interaction of the aromatic ring with YbI_3.[7] Substrates containing an alcohol (**1k**), ester (**1l**), and benzyl-protected

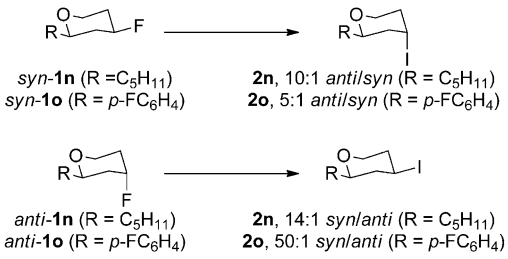
amine (**1m**) were all compatible with the reaction conditions, thus providing iodo-substituted products in excellent yields in all cases. Notably the tetrahydropuran derivatives (**1n**, **1o**, and **1p**) underwent clean and selective substitution of their aliphatic fluoride with iodide. The substitution occurs only on the sp^3 C–F, without affecting the sp^2 C–F/Br (**1o**, **1p**), once again demonstrating the extraordinary selectivity of the reaction. Considering that ketones are prone to undergoing aldol condensation in the presence of trivalent lanthanides, we were very satisfied to achieve full conversion of the bulky steroid **1q**, which contains both an alkene and a ketone functionality, within 2 hours.[11] The corresponding iodo compound **2q** was isolated in 93% yield. The polyfluorinated alkyl **1r** did not react, possibly because of chelation of Yb^{3+} with two, or several fluorines. The presence of adjacent fluorines weakens the activation of the C–F bond with Yb^{3+}, while simultaneously increasing the bond strength to the carbon center.

Based on simple competition experiments with primary, secondary, and tertiary alkyl fluorides, valuable mechanistic insights were gained. Hence, comparing the reaction rates of **1a**, **1b**, **1c**, and **1d** revealed a reactivity order of tertiary > secondary > primary. The same trend was observed when YbI_3 was added to a mixture of **1a**, **1b**, and **1d**. This order of reactivity may be indicative of an S_N1 mechanism. It should however be emphasized that for 1-fluoroadamantane (**1d**), formation of a carbocation is highly unfavorable at the bridgehead atom.[12] Instead an internal nucleophilic substitution (S_Ni) mechanism could explain the behavior of **1d**.

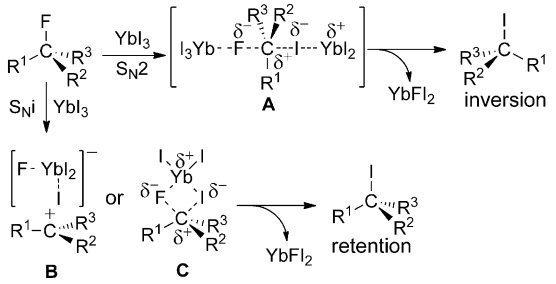
Further insights into the mechanism were gained through stereochemical analysis of *syn*-**1n** and *syn*-**1o** (Scheme 3). Analysis of the iodo-substituted ether products showed that *anti*-iodo ether had been formed in a 10:1 ratio (*anti*-**2n**) and a 5:1 ratio (*anti*-**2o**). Likewise, starting from the corresponding *anti*-alkyl fluorides (*anti*-**1n** and *anti*-**1o**) resulted in the respective *syn*-iodo ether products (14:1 *syn*-**2n** and 50:1 *syn*-**2o**). Thus, the reaction displays a high degree of stereospecificity, with inversion at the stereogenic center, and points to an S_N2 reaction pathway.[5c,13,14]

Initial rate studies were performed to obtain basic kinetic information. An approximate rate order of 1.0 with respect to [1-fluorodecane], and 1.5 with respect to [YbI_3] for the substitution was observed.

Based on the stereochemical outcome and the kinetic experiments, as well as the competition reaction and rate order, a mechanistic proposal is outlined in Scheme 4. The



Scheme 3. Stereochemical analysis of tetrahydropyran derivatives **1n** and **1o**. Reaction conditions: YbI_3 (0.0484 mmol, 2.42 mM), CH_2Cl_2 (2 mL), substrate (0.044 mmol, 2.2 mM).



Scheme 4. Mechanistic proposal for the F/I substitution.

S_N2 mechanism is believed to proceed via a transition state involving two equivalents of YbI_3 (**A**). The S_Ni mechanism is proposed to go through an intimate ion pair (**B**). Alternatively, simultaneous C–F bond activation and F/I substitution could occur (**C**). Both intermediates **B** and **C** result in retention of configuration.

In conclusion an efficient protocol for substitution of alkyl fluorides with iodide by means of YbI_3 under mild reaction conditions has been developed. To the best of our knowledge, this is the first report of synthetically useful unactivated aliphatic C–F bond substitution. The procedure is exceptionally selective towards alkyl fluorides, and it is compatible with a large range of common functional groups. The substitution is proposed to proceed by an S_N2 mechanism with a competing S_Ni pathway, with the ratio of products from either pathway being dependent on the substrate. The YbI_3-mediated selective substitution of the exceptionally strong carbon–fluorine bond is expected to have considerable impact in modern organic chemistry as it may initiate novel synthetic routes. This strategy paves the way for the use of fluorine as a small, sterically unhindered protecting group which now is easy to remove. In addition, it is a direct and powerful route for late-stage incorporation of iodine into complex target molecules. The F/I substitution with YbI_3 leads to a highly reactive C–I group, which easily can be converted into practically any other functional group. Supplementary mechanistic studies are envisioned to provide a deeper understanding of the reaction and its selectivity.

Received: July 13, 2013
Published online: September 24, 2013

Keywords: chemoselectivity · fluorine · iodine · synthetic methods · ytterbium

[1] a) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320; b) D. O'Hagan, *Chem. Soc. Rev.* **2008**, *37*, 308.
[2] a) N. Al-Maharik, D. O'Hagan, *Aldrichimica Acta* **2011**, *44*, 65; b) M. Rueda-Becerril, C. C. Sazepin, J. C. T. Leung, T. Okbinoglu, P. Kennepohl, J.-F. Paquin, G. M. Sammis, *J. Am. Chem. Soc.* **2012**, *134*, 4026; c) F. Yin, Z. Wang, Z. Li, C. Li, *J. Am. Chem. Soc.* **2012**, *134*, 10401; d) M. P. Sibi, Y. Landais, *Angew. Chem.* **2013**, *125*, 3654; *Angew. Chem. Int. Ed.* **2013**, *52*, 3570.
[3] H. Amii, K. Uneyama, *Chem. Rev.* **2009**, *109*, 2119.
[4] a) L. Zhang, W. Zhang, J. Liu, J. Hu, *J. Org. Chem.* **2009**, *74*, 2850; b) G. Blessley, P. Holden, M. Walker, J. M. Brown, V.

Gouverneur, *Org. Lett.* **2012**, *14*, 2754; c) E. Benedetto, M. Keita, M. Tredwell, C. Hollingworth, J. M. Brown, V. Gouverneur, *Organometallics* **2012**, *31*, 1408; d) A. Hazari, V. Gouverneur, J. M. Brown, *Angew. Chem.* **2009**, *121*, 1322; *Angew. Chem. Int. Ed.* **2009**, *48*, 1296; e) K. Mikami, Y. Tomita, Y. Itoh, *Angew. Chem.* **2010**, *122*, 3907; *Angew. Chem. Int. Ed.* **2010**, *49*, 3819; f) T. Iida, R. Hashimoto, K. Aikawa, S. Ito, K. Mikami, *Angew. Chem.* **2012**, *124*, 9673; *Angew. Chem. Int. Ed.* **2012**, *51*, 9535.

[5] a) K. Hirano, H. Yorimitsu, K. Oshima, *Org. Lett.* **2004**, *6*, 4873; b) T. Hatakeyama, S. Ito, M. Nakamura, E. Nakamura, *J. Am. Chem. Soc.* **2005**, *127*, 14192; c) J. Terao, S. A. Begum, Y. Shinohara, M. Tomita, Y. Naitoh, N. Kambe, *Chem. Commun.* **2007**, 855; d) C. Douvris, O. V. Ozerov, *Science* **2008**, *321*, 1188; e) W. Gu, M. R. Haneline, C. Douvris, O. V. Ozerov, *J. Am. Chem. Soc.* **2009**, *131*, 11203; f) J. Choi, D. Y. Wang, S. Kundu, Y. Choliy, T. J. Emge, K. Krogh-Jespersen, A. S. Goldman, *Science* **2011**, *332*, 1545; g) K. Matsubara, T. Ishibashi, Y. Koga, *Org. Lett.* **2009**, *11*, 1765; S. A. Begum, J. Terao, N. Kombe, *Chem. Lett.* **2007**, *36*, 196.

[6] a) G. B. Deacon, C. M. Forsyth, P. C. Junk, J. Wang, *Chem. Eur. J.* **2009**, *15*, 3082; b) M. Klahn, U. Rosenthal, *Organometallics* **2012**, *31*, 1235.

[7] R. Anwander, *Lanthanides: Chemistry And Use In Organic Synthesis* (Ed.: S. Kobayashi), Springer, Berlin, **1999**, pp. 1 – 61.

[8] M. Janjetovic, A. M. Träff, T. Ankner, J. Wettergren, G. Hilmersson, *Chem. Commun.* **2013**, *49*, 1826.

[9] D. Witt, *Synthesis* **2008**, 2491.

[10] S.-I. Fukuzawa, Y. Hongo, *Tetrahedron Lett.* **1998**, *39*, 3521.

[11] J. Collin, N. Giuseppone, P. Van de Weghe, *Coord. Chem. Rev.* **1998**, *178 – 180*, 117.

[12] M. B. Smith, J. March, *March's Advanced Organic Chemistry: Reactions, Mechanism, and Structure*, 6th ed., Wiley, Hoboken, **2007**, p. 245.

[13] IUPAC definition of stereospecific. A. D. McNaught, A. Wilkinson, *Compendium of Chemical Terminology*, 2nd ed., Blackwell Scientific Publications, Oxford, **1997**; XML on-line corrected version: http://goldbook.iupac.org (2006-) created by M. Nic, J. Jirat, B. Kosata; Updates compiled by A. Jenkins.

[14] a) A. Nova, R. Mas-Ballesté, G. Ujaque, P. González-Duarte, *Chem. Commun.* **2008**, 3130; b) A. Nova, R. Mas-Ballesté, A. Lledós, *Organometallics* **2012**, *31*, 1245.