C–F Bond Activation

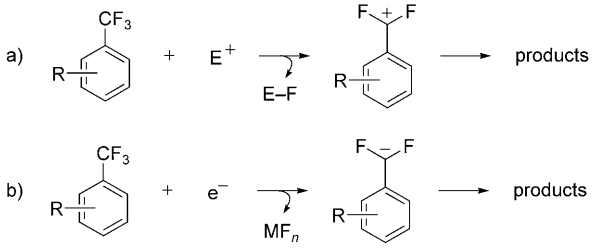
DOI: 10.1002/anie.200904344

Niobium-Catalyzed Activation of Aryl Trifluoromethyl Groups and Functionalization of C–H Bonds: An Efficient and Convergent Approach to the Synthesis of N-Heterocycles

*Tom G. Driver**

carbenoids · C–F activation · CF_3 group · C–H insertion · niobium

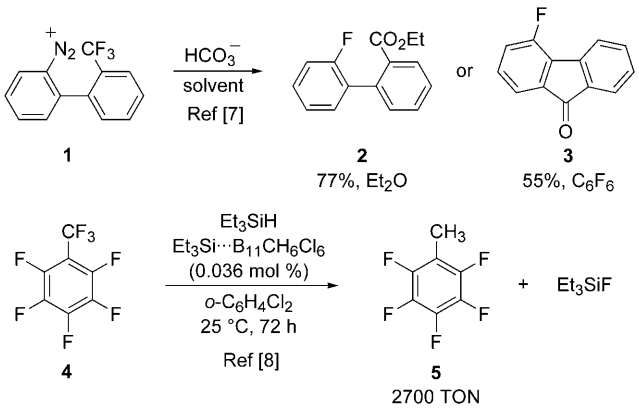
The functionalization of carbon–fluorine bonds is an area of current interest because of the toxic and persistent nature of perfluorinated compounds and because the C–F bond represents one of the most inert functionalities in chemistry. While substantial strides have been made in the transition-metal-catalyzed activation of aryl C–F bonds as well as the hydro-defluorination of alkyl C–F bonds,[1] methods to synthesize complex, functionalized molecules by the manipulation of a C–F bond are relatively underdeveloped. In comparison to other organofluorine functionalities, the aryl trifluoromethyl group is particularly difficult to activate. Its inertness originates from both thermodynamic and kinetic considerations. The strength of the benzylic C–F bond increases with additional fluorination and its length decreases to result in increased steric shielding at the carbon center.[2] Recently though, two promising strategies have emerged to activate this group. One approach uses a cation to abstract a fluoride anion to produce defluorinated products (Scheme 1 a). Orthogonally, α,α,α-trifluorotoluene derivatives can be reduced electrochemically or with a low-valent metal to directly access functionalized products (Scheme 1 b).



Scheme 1. General strategies for the activation of the aryl trifluoromethyl group.

[*] T. G. Driver
Department of Chemistry
University of Illinois at Chicago
845 W Taylor St, Chicago, IL 60607 (USA)
Fax: (+1) 312-996-0431
E-mail: tgd@uic.edu
Homepage: http://www.chem.uic.edu/driver

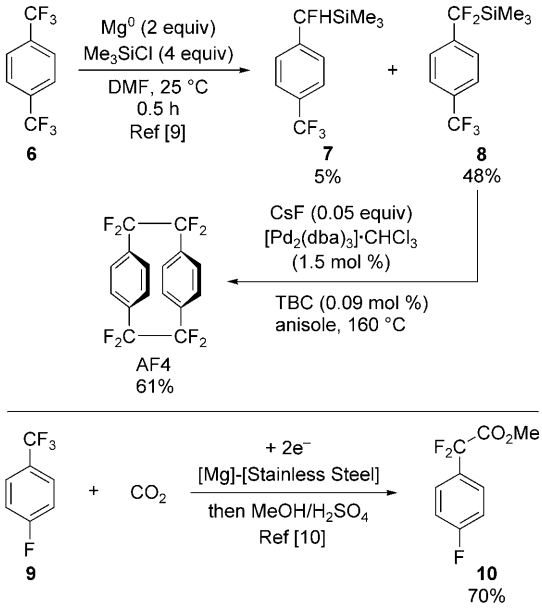
Significant progress has been made in the abstraction of a benzylic fluorine atom by a cation (Scheme 2). In 1997, Lectka and co-workers reported that aryl carbocations successfully abstract a neighboring fluoride ion to produce biaryl **2** in Et_2O or fluorenone **3** if C_6F_6 was used as the



Scheme 2. Cation-mediated abstraction of the benzylic fluorine atom.

reaction solvent.[3] Subsequently in 2008, Douvris and Ozerov reported that silylium–carborane catalysts exhibited high turnover numbers (TON) for hydro-defluorination of either alkyl- or aryl trifluoromethyl groups.[4] The high selectivity of their method for $C(sp^3)$–F bond activation was demonstrated by the dehydrofluorination of **4**.

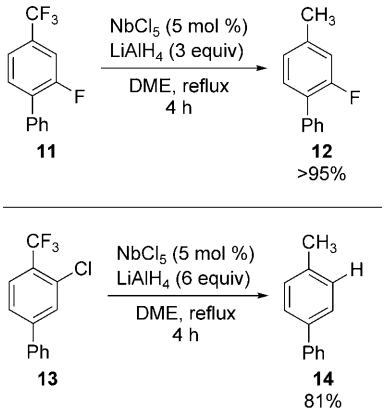
Reduction of the aryl trifluoromethyl group is possible using magnesium or electrochemistry (Scheme 3). In 2001, Uneyama and co-workers reported that magnesium promoted the defluorinative silylation of bis(trifluoromethyl)benzene **6** to produce mixtures of **7** and **8**.[5] A subsequent CsF-catalyzed C–F bond functionalization of **8** produced cyclophane AF4. In 1989, the electroreductive couplings of trifluoromethylarenes with electrophiles was reported by Troupel and co-workers.[6] Electrolysis of **9** and CO_2 in an undivided cell fitted with a sacrificial magnesium anode produced methylester **10**.



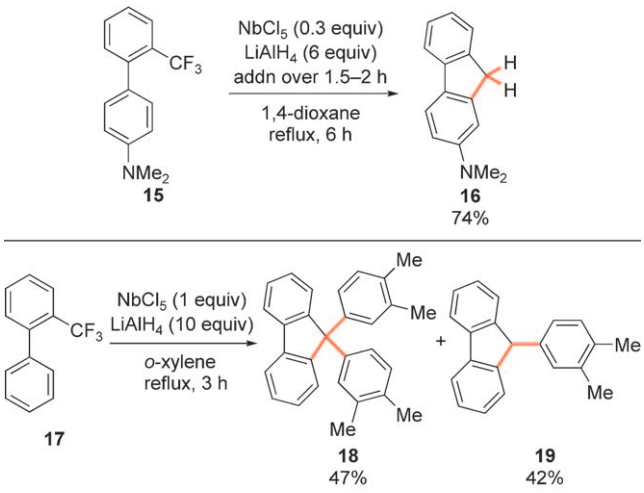
Scheme 3. Single electron reduction of aryl trifluoromethyl groups. dba = dibenzylideneacetone, DMF = *N*,*N*-dimethylformamide, TBC = 4-*tert*-butylcatechol.

Akiyama and co-workers discovered that CF_3 groups could be reduced by zero-valent niobium complexes.[7–9] The required niobium catalyst was generated through exposure of $NbCl_5$ to an excess of lithium aluminum hydride. While hydro-defluorination of α,α,α-trifluorotoluene derivatives was efficient, the functional group tolerance of the method appeared limited to nonreducible substituents (Scheme 4). Substrates, such as **13**, could be defluorinated, but reduction of the aryl C–Cl bond also occurred.

In addition to hydro-defluorination, Akiyama and co-workers demonstrated that C–C bonds could be formed from the reduction of *ortho*-arylated α,α,α-trifluorotoluene derivatives (Scheme 5).[7,9,10] The slow addition of $LiAlH_4$ was necessary to achieve high yields of fluorenes such as **16**. When the reaction was performed in an aromatic solvent, intermolecular C–C bond formation occurred to produce mixtures of



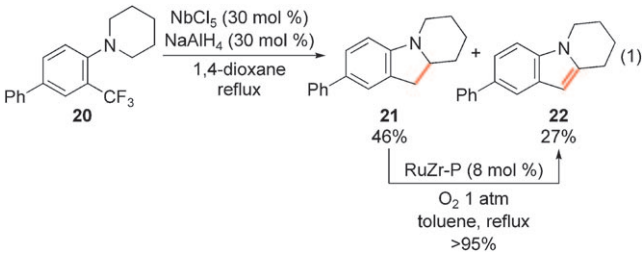
Scheme 4. Hydro-defluorination of CF_3 groups by low-valent niobium complexes. DME = 1,2-dimethoxyethane.



Scheme 5. Fluorene synthesis from *ortho*-arylated α,α,α-trifluorotoluene derivatives by low-valent niobium complexes.

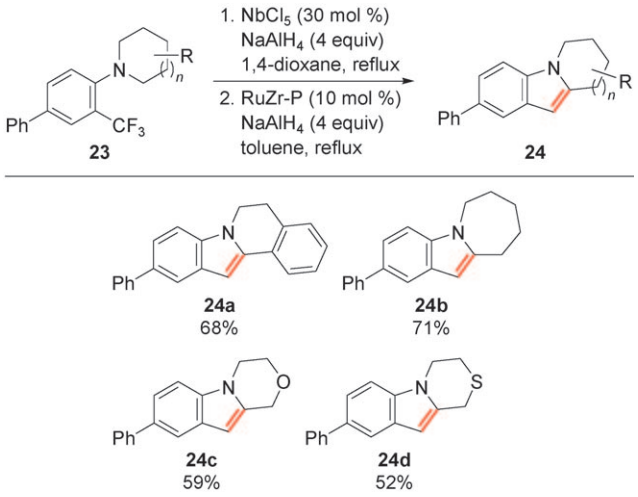
mono- and diarylated fluorenes **18** and **19**. Meanwhile low-valent niobium was demonstrated to efficiently reduce trifluoromethyl groups to produce fluorenes or indenes: the methodology appeared limited to the functionalization of $C(sp^2)$–H bonds.

The achievement of $C(sp^3)$–H bond functionalization by Akiyama and co-workers represents a significant development in the activation of trifluoromethyl groups.[11] In their report, aryl amines such as **20** were reduced by low-valent niobium to produce mixtures of indoline **21** and indole **22** [Eq. (1)]. Subsequent ruthenium-catalyzed dehydrogenation quantitatively transformed this mixture into indole **22** exclusively.[12] The N-fused structural motif is prevalent in a large number of biologically active small molecules.[13] As the aryl amines are available in one step from commercially available material,[14,15] Akiyama's methodology is a highly efficient and convergent synthesis of these important N-heterocycles.



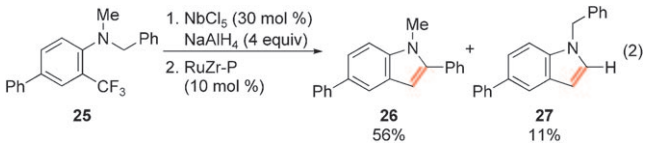
The similarity between the optimal reaction conditions for the formation of N-fused indoles and earlier reports by Akiyama and co-workers illustrates the generality of their niobium-catalyzed defluorination method. As before, the best yields were produced using 30 mol% of $NbCl_5$ and 1,4-dioxane as solvent. The identity of the reducing agent influenced the rate of the reaction: significantly higher conversions were obtained when $NaAlH_4$ was used in place of $LiAlH_4$. No reduction was observed when alkoxy-substi-

tuted aluminum hydride reagents were used. These conditions enabled the synthesis of a range of N-fused indoles—a few leading examples are shown in Scheme 6.



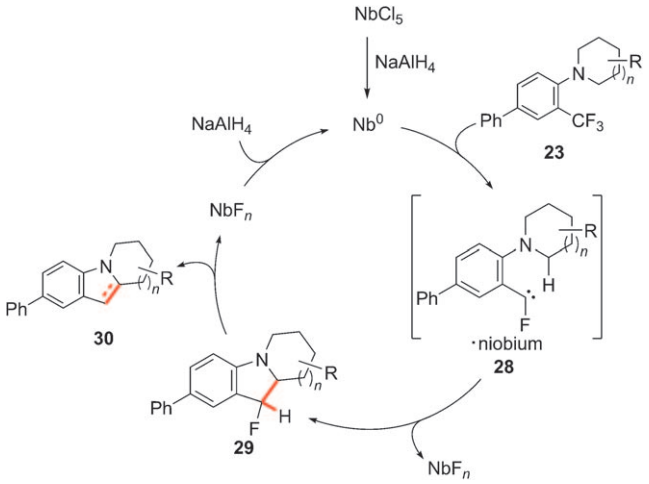
Scheme 6. Selected examples for the synthesis of N-fused indoles.

The selectivity of niobium-catalyzed formation of N-heterocycles appears to be under electronic control [Eq. (2)]. Preferential functionalization of the benzylic C–H bond afforded indole **26**. The selectivity exhibited by niobium contrasts with $[Rh_2((S)\text{-dosp})_4]$ (dosp = (*N*-dodecylbenzenesulfonyl)prolinate) where insertion into the sterically more accessible methyl C–H bond occurs.[16]



The mechanism for this transformation was proposed to occur through a carbenoid reactive intermediate (Scheme 7).[9,11] The niobium catalyst is generated by reduction using sodium aluminum hydride. This species defluorinates the aryl trifluoromethyl group to afford fluorine-substituted carbenoid **28**, which reacts with the proximal C–H bond to afford indoline **29**. Dehydrofluorination of **29** would provide indole, whereas hydro-defluorination would produce indoline. If the rate of dehydrofluorination versus hydro-defluorination could be controlled, the selective formation of either indole or indoline product could be achieved.

The recent report by Akiyama and co-workers offers exciting opportunities and exposes new challenges for the development of methodology that exploits niobium-catalyzed aryl carbon–fluorine bond activation. A few of these challenges include the functionalization of non-activated, aliphatic C–H bonds to form carbocycles, as well as the development of intermolecular variants that transform simple molecules



Scheme 7. Potential catalytic cycle.

into value-added commodities. Future methods to access complex, functionalized molecules through the niobium-catalyzed reduction of trifluoromethyl groups are eagerly anticipated.

Received: August 4, 2009
Published online: September 24, 2009

[1] For a recent review, see: H. Amii, K. Uneyama, *Chem. Rev.* **2009**, *109*, 2119.
[2] J. Burdeniuc, B. Jedicka, R. H. Crabtree, *Chem. Ber.* **1997**, *130*, 145.
[3] D. Ferraris, C. Cox, R. Anand, T. Lectka, *J. Am. Chem. Soc.* **1997**, *119*, 4319.
[4] C. Douvris, O. V. Ozerov, *Science* **2008**, *321*, 1188.
[5] H. Amii, Y. Hatamoto, M. Seo, K. Uneyama, *J. Org. Chem.* **2001**, *66*, 7216.
[6] C. Saboureau, M. Troupel, S. Sibille, J. Périchon, *J. Chem. Soc. Chem. Commun.* **1989**, 1138.
[7] K. Fuchibe, T. Akiyama, *J. Am. Chem. Soc.* **2006**, *128*, 1434.
[8] K. Fuchibe, Y. Ohshima, K. Mitomi, T. Akiyama, *Org. Lett.* **2007**, *9*, 1497.
[9] K. Fuchibe, K. Mitomi, R. Suzuki, T. Akiyama, *Chem. Asian J.* **2008**, *3*, 261.
[10] K. Fuchibe, K. Mitomi, T. Akiyama, *Chem. Lett.* **2007**, *36*, 24.
[11] K. Fuchibe, T. Kaneko, K. Mori, T. Akiyama, *Angew. Chem.* **2009**, *121*, 8214; *Angew. Chem. Int. Ed.* **2009**, *43*, 8070.
[12] Ruthenium is supported on zirconium phosphate.
[13] G. W. Gribble, M. G. Saulnier, E. T. Pelkey, T. L. S. Kishbaugh, Y. Liu, J. Jiang, H. A. Trujillo, D. J. Keavy, D. A. Davis, S. C. Conway, F. L. Switzer, S. Roy, R. A. Silva, J. A. Obaza-Nutaitis, M. P. Sibi, N. V. Moskalev, T. C. Barden, L. Chang, W. M. Habeski (née Simon), B. Pelcman, W. R. Sponholtz III, R. W. Chau, B. D. Allison, S. D. Garaas, M. S. Sinha, M. A. McGowan, M. R. Reese, K. S. Harpp, *Curr. Org. Chem.* **2005**, *9*, 1493.
[14] J. P. Wolfe, S. Wagaw, J. F. Marcoux, S. L. Buchwald, *Acc. Chem. Res.* **1998**, *31*, 805.
[15] J. F. Hartwig, *Nature* **2008**, *455*, 314.
[16] H. M. L. Davies, C. Venkataramani, *Angew. Chem.* **2002**, *114*, 2301; *Angew. Chem. Int. Ed.* **2002**, *41*, 2197; *Angew. Chem.* **2002**, *114*, 2301.

