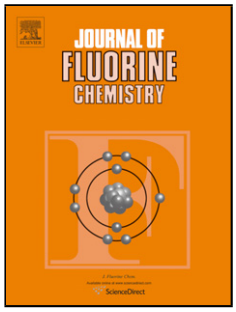

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Regioselective, Nucleophilic Activation of C-F Bonds in *o*-Fluoroanilines

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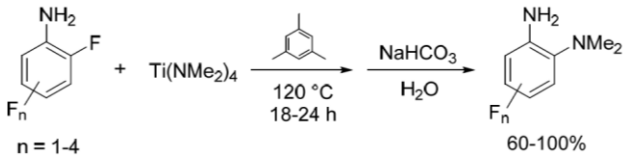
Graphical Abstract



Highlights

- Fluorinated anilines react with $Ti(NMe_2)_4$ to afford products of ortho-defluoroamination.
- Anilines having two *ortho* fluorines can undergo one or two defluoroaminations depending on reaction conditions.
- Reactivity and selectivity patterns are consistent with established ancillary-fluorine substituent effects.

Abstract. Reactions of *ortho*-fluorinated anilines with stoichiometric $Ti(NMe_2)_4$ in mesitylene (typically for 15 h at 120 °C) afforded moderate to high yields of the corresponding *N*,*N*-dimethyl-1,2-phenylenediamine derivatives resulting from defluoroamination of a fluorine atom vicinal to the NH_2 of the starting aniline. Reactivity increases with additional ring fluorination in general accordance with established regiochemical (activating and deactivating) trends.

Introduction

Manipulation of C-F bonds in organic compounds has become increasingly important in areas of organic chemistry where physical properties and bioactivity depend sensitively on the placement of fluorine substituents.[1–4] Fluorination can afford thermal or photolytic stability[5] and help tune local molecular polarities.[2,3,5,6] Much has also been written about the special hydrophobicity and oleophobicity of highly fluorinated aliphatics.[7–9] In

fluorinated arenes, conjugation and local polarity effects play key roles in governing reactivity and properties. Fluorinated aromatic moieties appear in several new drugs and drug candidates ranging from anti-cancer drugs to antipsychotics.[4,10–15] With that background, new research to identify additional reaction sequences for the installation, substitution, or removal of aromatic fluorine substituents seems justified.[16–19]

Aromatic defluorination reactions often involve organometallic species in directing, activating, or stabilizing roles. Processes include oxidative additions, S_NAr-type substitutions, and radical reactions.[2,19–24] Ideally, aromatic defluorinations would be catalytic with respect to the metal.[25–34] However, with early transition metals, M—F bonds tend to be strong, impeding turnover. A common solution employs a co-catalytic main-group compound (for example, an aluminum hydride like DIBAL) to scavenge fluoride by transmetallation and regenerate the active catalytic species.[27,34]

We have particular interest in reactions of the general form shown in Scheme 1, where a Lewis-basic ring substituent coordinates a metal-organic reagent, directing its nucleophilic ligands toward the *ortho* ring position.[35–37] Our interest derives from our serendipitous finding that that pentafluorophenyl-substituted cyclopentadienes and indenes undergo *ortho* C-F bond activation upon treatment with $Ti(NMe_2)_4$ (Scheme 2).[38]

Schrock and co-workers also reported that polydentate ligands containing 2,6-difluorophenyl substituents undergo defluoroaminations when treated with either $Hf(NMe_2)_4$ or $Mo(NMe_2)_4$.[39,40]. In all of these cases, the intended synthetic objective involved the installation of new ligands with removal of dimethylamine, but the reactions were accompanied by exchange of M-NMe_2 bonds and aromatic C-F bonds. We therefore wondered whether this

"side-reaction" could be converted and optimized toward a selective, general, and efficient process in its own right. We now report reactions of *ortho*-fluorinated anilines with $Ti(NMe_2)_4$ to afford products in which an *ortho* fluorine atom is replaced with NMe_2 to form fluorinated 1,2-phenylenediamine derivatives. *N*,*N*-Dimethyl-1,2-phenylenediamines have found application as precursors to multidentate ligands for various transition metal catalysts.[41–43]

Results & Discussion

In Scheme 2, cyclopentadiene played a directing role by coordinating the titanium atom (likely in η^5 fashion) and facilitating an intramolecular substitution process.[38] This proposal neatly rationalized the exclusive *ortho* selectivity. We surmised that the directing role of the cyclopentadiene could be shifted to other acidic ligating groups, such as NH_2 (Scheme 3).

Our experimental approach used ^{19}F NMR to follow reactions and to estimate conversions and yields. We chose substrates having at least two ring fluorine substituents so that we could quantify both the substrate and its defluoroamination product using ^{19}F NMR spectroscopy. The use of mesitylene as the reaction solvent maintained homogeneity of the reaction mixture. (Preliminary studies using *n*-decane led to precipitation of intermediates and very low yields.) Mildly alkaline aqueous workup conditions minimized water-solubility of the aniline products. The crude product mixture still contained the mesitylene solvent and the internal NMR standard, bis(4-fluorophenyl)ether. (We initially chose 3,5-difluoro-1-bromobenzene as the internal standard, but preliminary control experiments showed this compound to be unstable toward the titanium reagent at temperatures above 100 °C.) After ^{19}F NMR spectroscopic analysis to estimate product yields, the mixture was subjected to liquid chromatography to separate the mesitylene solvent and internal NMR standard and to isolate the products.

Product yields are collected in Table 1. Errors of ±5% are conservatively based on the internal reliability of NMR integration method and are reproducible within those limits in multiple trials. Yields are mostly high enough to conclude that the method is general and reasonably efficient. In entries 1, 3, and 4, we still observe some unreacted substrate; likely these reactions could be driven toward higher conversion by increasing the reaction time or temperature. In the case of entries 5, 8, and 9, the substrates are sufficiently reactive to give appreciable yields of products arising from substitution of both *ortho* fluorine atoms.

Mixtures were separated by liquid chromatography, but not particularly efficiently despite our efforts to optimize the eluting solvent. Isolated yields from pure chromatographic fractions were relatively low (ca. 20%) and not particularly reproducible. All new substances were characterized using NMR spectrometry and exact mass determination (HRMS). We found that ^{1}H and ^{19}F NMR spectra were sufficient for unambiguous identification of all major reaction products, therefore we did not collect ^{13}C NMR spectra, which would likely be quite complex due to extensive long-range couplings to ^{19}F. The ^{1}H and ^{19}F spectra show typical chemical shifts and coupling constants for fluoroaromatic compounds. In the spectra of products having an NMe_2 directly adjacent (vicinal) to a fluorine atom, the methyl groups are split into a doublet with $^{5}J_{HF}$ of ca. 2 Hz. This spectral feature was previously documented for *N*,*N*-dimethyl-2-fluoro-aniline and was useful in making signal assignments.[44]

Reactions of Difluoroanilines. As shown in Table 1, difluoroanilines **1a**-**1d** (entries **1**–**4**) reveal an interesting trend in the relative position of the unreactive (ancillary) fluorine atom. Conversion of starting material was lowest when the unreactive and departing fluorine atoms had a *para* relationship (substrate **1c**). Chambers found that fluorines *meta* and *ortho* to the departing fluorine in S_NAr reactions tend to be activating, whereas fluorines *para* to the departing fluorine

tend to be deactivating, although the exact (quantitative) kinetic effects are system-dependent.[45] Likewise, the first substitution in 2,6-difluoroaniline is activated by the presence of another fluorine in a *meta* position, but after that initial substitution, the remaining fluorine atom has no activating substitution and remains inert under the reaction conditions described in Table 1.

Competitive Study of Relative Reaction Rates: All four difluoroanilines were subjected to a tenfold excess of $Ti(NMe_2)_4$ in a competitive experiment at 80 °C. This lower temperature was chosen to slow down all of the reactions so that we could monitor them conveniently by ^{19}F NMR spectroscopic analysis of small aliquots. As shown in Figure 1, 2,6-difluoroaniline had the highest rate of conversion into product, followed closely by 2,4-difluoroaniline. This observation is consistent with Chambers's findings; the fluoroanilines substituted *meta* to the reactive site are highly activated, while 2,5-difluoroaniline, which has a fluorine atom *para* to the reactive site, is highly deactivated in comparison and is the least reactive of the four substrates. Even though these data were obtained at a lower reaction temperature, we believe they will reflect relative reactivity trends at 120 °C, at least qualitatively.

Reactions of Highly Fluorinated Anilines. As shown in Table 1 and Scheme 4, aniline **1e** affords a mixture of three products. The major product (**2e**) arises from substitution of F_2, activated by one *ortho* and one *meta* fluorine substituent (F_3 and F_6, respectively). The minor product (***iso*-2e**) results from substitution of F_6, activated by one *meta* fluorine (F_2) but also deactivated by one *para* fluorine (F_3). Substitution of both F_2 and F_6 also afforded **3e**.

Based on the results with **1e**, we were curious to compare the reactivity of **1f** and **1g** (Scheme 5). While the observed NMR yield of **2f** (104%) is higher than the observed yield of **2g** (83%), we also concede that the estimated error in our NMR yields is probably around ±5%. We wanted a more direct comparison to minimize sources of experimental error. In a competitive reaction with both **1f** and **1g** present in solution at 120 °C for one hour, substrate **1f** underwent 67% conversion to **2f**, whereas substrate **1g** underwent only 33% conversion to **2g**. This result confirms that an ancillary *para* fluorine is deactivating compared to an ancillary *ortho* fluorine.

The reaction of the tetrafluorinated aniline **1h**, shown in Scheme 6, also featured a substrate with two *o*-fluorines in non-equivalent chemical environments. After 23 h at 120 °C, triamine **3h** was the major product, and the remaining product was **2h**; all of the substrate (**1h**) had been consumed. A separate reaction of substrate **1h** at 90 °C for 3 h afforded not only **2h** and **3h**, but also a third product having three signals in the ^{19}F spectrum. Because some unreacted **1h** was also still present, chromatographic separation was difficult, and we were not able to obtain a fraction containing only the third product. Instead we used a fraction containing some **3h**, which was already well characterized, and we used GCMS to provide a nominal assay of the third product present in that fraction. Following this approach we assigned the structure ***iso*-2h** to the third product. Based on these results, we suggest that both isomers (**2h** and ***iso*-2h**) are produced early in the reaction, but of the two isomers, the minor component (***iso*-2h**), whose remaining fluorine has both a *meta* and *ortho* fluorine activating the reaction site, undergoes a more facile defluoroamination, and is thus consumed to form **3h**, compared to **2h**, which has one *meta* fluorine activating and one *para* fluorine deactivating its remaining substitution site.

Pentafluoroaniline (**1i**), as the most activated substrate, afforded exclusively the disubstituted product **3i** in moderate yield at 120 °C. A separate reaction, conducted at 90 °C for 3 h, afforded a product with four signals in the ^{19}F NMR spectrum. We were not able to obtain this product in a pure form, but we assigned the NMR spectrum of the mixture with the aid of simulation software (please see the Supporting Information), and we found the appropriate exact mass upon ESI-MS analysis of the mixture, leading to the assignment of **2i**. Yields are shown in Scheme 7.

Mechanism and Scope. All of the reactions shown in Table 1 involve substitution of fluorine atoms exclusively *ortho* to the NH_2 group. This observation supports a pathway (Scheme 8) in which the dimethylamino group is delivered to the *ortho* position of the aromatic ring by means of prior attachment of the aniline nitrogen to titanium, forming the Meisenheimer intermediate **4** in a process resembling intramolecular S_NAr. We stress, however, that the pathway shown in Scheme 7 is largely speculative. Even though there is strong precedent for such pathways in the published literature,[3,39,40,46] none of the putative intermediates (**4**, **5**, and **6**) were observed spectroscopically. A solution of 2,6-difluoroaniline (**1d**) and $Ti(NMe_2)_4$ prepared in C_6D_6 at 25°C (at which temperature the rate of defluoroamination should be negligible) showed a complex ^{19}F NMR spectrum that we could not assign. At least three prominent intermediates are present. In none of our spectra could we identify any Ti-F species, but we did tentatively assign free dimethylamine in the ^1H NMR spectrum. Spectra are provided in the supporting information.

The overall success of the foregoing synthetic method prompted a preliminary investigation of its scope and generality. As shown in Scheme 9, we subjected *N*-ethyl-2,6-difluoroaniline [47,48] (**8**) to the same reaction conditions as the other compounds in this study (Table 1) and obtained a 42 percent yield of the defluoroamination product (**8**). This result supports the proposal of putative reaction intermediate **4** which arises from metathesis of one aniline N—H bond with one Ti—NMe_2 bond. In particular, the reactivity of **7** argues against the intermediacy of arylimidotitanium species, e.g., $ArN{=}Ti(NMe_2)_2$.

Attempting to cast a wider net, we found that 2,6-dichloroaniline (Scheme 10) is unreactive toward $Ti(NMe_2)_4$ even at 150 °C, and that the reaction of 2,6-difluoroaniline with titanium(IV) isopropoxide under the same conditions returned only the starting aniline. Treatment of 2,6-difluorophenol (**9**) with $Ti(NMe_2)_4$ at 120 °C gave a low conversion to the corresponding monosubstitution product (**10**), and the reaction produced additional byproducts that we were not able to identify.

Conclusions

o-Fluoroanilines undergo defluorodimethylamination when treated with $Ti(NMe_2)_4$. Reactivity increases with added fluorine substituents *ortho* or *meta* to the departing fluorine atom. Trifluoro-, tetra-, and pentafluoroaniline compounds having fluorines in both the 2- and 6-positions undergo substitution at both positions after extended reaction intervals. Preliminary experiments show poor generalization to ortho-fluorinated phenols.

Experimental

Materials and Methods. $Ti(NMe_2)_4$ (Alfa Aesar), bis(4-fluorophenyl)ether (Oakwood), mesitylene (Acros Organics), and fluoroanilines (various suppliers) were used as received. NMR spectrometry was performed using an Agilent U4-DD2 (proton at 400 MHz) or Varian MR4 instrument (proton at 400 MHz). Exact masses of new substances were determined using an Agilent 6220 ESI-TOF instrument.

General Reaction Procedure. In nitrogen glovebox, a flame-dried Schlenk tube was charged with $Ti(NMe_2)_4$ (0.300 g, 1.30 mmol). Under a nitrogen counterstream, 0.15 g of bis(4-fluorophenyl)ether internal standard, 1.15 mmol of the aniline reactant, and 3.0 mL of mesitylene were added. The tube was then sealed (PTFE valve) and heated at 120 °C in an oil bath for 18-24 hours. After cooling, the mixture was diluted with dichloromethane (ca. 50 mL) and quenched with aqueous 10% sodium bicarbonate solution. The layers were separated, and the aqueous portion was extracted with additional dichloromethane (10 mL). The combined organic portions were dried over anhydrous magnesium sulfate, filtered, and evaporated to afford mostly yellow oils. Yields of products (and unreacted starting aniline, if any) were estimated using ^{19}F NMR spectroscopy. A characteristic signal from each fluorinated aniline was integrated against the bis(4-fluorophenyl)ether internal standard, after correcting for concentration and symmetry factors. Products were isolated using liquid chromatography on silica gel, eluting with dichloromethane or ethyl acetate.

N-Ethyl-2,6-difluoroaniline [47,48] was synthesized by *N*-acylation and LAH-reduction of the acyl as follows. First, a mixture of 2,6-difluoroaniline (2.23 g), acetic anhydride (1.9 mL), and 4 mL of glacial acetic acid reacted at 25 °C for 15 h and then diluted with dichloromethane. The solution was washed with 0.75 M aqueous sodium hydroxide solution, dried over anhydrous magnesium sulfate, filtered, and solvent was evaporated to afford a white solid, which was

recrystallized from ethyl acetate/hexanes (3:1) mixture to afford intermediate *N*-acyl-2,6-difluoroaniline as a colorless crystalline solid. This solid was dissolved in dry THF and cooled using a dry ice bath and then lithium aluminum hydride (1.44 g) was added. The reaction was stirred for 20 h while warming to room temperature and then diluted with dichloromethane. The mixture was washed with aqueous sodium bicarbonate, then with water, dried over magnesium sulfate, filtered, and evaporated to form a pale solid, which was found to be impure by NMR spectroscopic analysis. The crude product was purified by silica gel chromatography, eluting with dichloromethane. After evaporation, 0.67 g of a pale oil was obtained. This procedure was not optimized. Analytical data are provided in the Supporting Information.

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References

[1] V. V Grushin, The Organometallic Fluorine Chemistry of Palladium and Rhodium : Studies toward Aromatic Fluorination, Acc. Chem. Res. 43 (2010) 160–171.

[2] J. Weaver, S. Senaweera, C-F activation and functionalization of perfluoro- and polyfluoroarenes, Tetrahedron. 70 (2014) 7413–7428. doi:10.1016/j.tet.2014.06.004.

[3] O. Eisenstein, J. Milani, R.N. Perutz, Selectivity of C-H Activation and Competition between C-H and C-F Bond Activation at Fluorocarbons, Chem. Rev. 117 (2017) 8710–8753. doi:10.1021/acs.chemrev.7b00163.

[4] J. Wang, M. Sánchez-Roselló, J.L. Aceña, C. Del Pozo, A.E. Sorochinsky, S. Fustero, V.A. Soloshonok, H. Liu, Fluorine in pharmaceutical industry: Fluorine-containing drugs introduced to the market in the last decade (2001-2011), Chem. Rev. 114 (2014) 2432–2506. doi:10.1021/cr4002879.

[5] B.Z. Li, Y.Y. Qian, J. Liu, K.S. Chan, Consecutive Aromatic Carbon − Fluorine Bond and Carbon − Hydrogen Bond Activations by Iridium Porphyrins, Organometallics. 3 (2014) 7059–7068. doi:10.1021/om5005594.

[6] V.M. Vlasov, Fluoride ion as a nucleophile and a leaving group in aromatic nucleophilic substitution reactions, J. Fluor. Chem. 61 (1993) 193–216.

[7] D.D. Bume, S.A. Harry, T. Lectka, C.R. Pitts, Catalyzed and Promoted Aliphatic Fluorination, J. Org. Chem. (2018) acs.joc.8b00982. doi:10.1021/acs.joc.8b00982.

[8] B. Lantaño, A. Postigo, Radical fluorination reactions by thermal and photoinduced methods, Org. Biomol. Chem. 15 (2017) 9954–9973. doi:10.1039/c7ob02402a.

[9] D.E. Yerien, S. Bonesi, A. Postigo, Fluorination methods in drug discovery, Org. Biomol. Chem. 14 (2016) 8398–8427. doi:10.1039/C6OB00764C.

[10] A.J. Barker, K.H. Gibson, W. Grundy, A.A. Godfrey, J.J. Barlow, M.P. Healy, J.R. Woodburn, S.E. Ashton, B.J. Curry, L. Scarlett, L. Henthorn, L. Richards, Studies leading to the identification of ZD1839 (IRESSA): An orally active, selective epidermal growth factor receptor tyrosine kinase inhibitor targeted to the treatment of cancer, Bioorg. Med. Chem. Lett. 11 (2001) 1911–1914. doi:S0960894X01003444 [pii].

[11] P. Ballard, R.H. Bradbury, C.S. Harris, L.F.A. Hennequin, M. Hickinson, J.G. Kettle, J. Kendrew, T. Klinowska, D.J. Ogilvie, S.E. Pearson, E.J. Williams, I. Wilson, Inhibitors of epidermal growth factor receptor tyrosine kinase: Optimisation of potency and in vivo pharmacokinetics, Bioorganic Med. Chem. Lett. 16 (2006) 4908–4912. doi:10.1016/j.bmcl.2006.06.054.

[12] E. Faught, Ezogabine: A New Angle on Potassium Gates, Epilepsy Curr. 11 (2011) 75–78. doi:10.5698/1535-7511-11.3.75.

[13] M.Y. Splinter, Ezogabine (Retigabine) and Its Role in the Treatment of Partial-Onset Seizures: A Review, Clin. Ther. 34 (2012) 1845–1856.e1. doi:10.1016/j.clinthera.2012.07.009.

[14] C. Sánchez, K. Bøgesø, B. Ebert, E. Reines, C. Braestrup, Escitalopram versus citalopram: the surprising role of the R-enantiomer, Psychopharmacology (Berl). 174 (2004) 163–176. doi:10.1007/s00213-004-1865-z.

[15] E.S. Istvan, J. Deisenhofer, D. King, K. Office, D. Cox, H. Hughes, E.S. Istvan, J. Deisenhoferl, Structural Mechanism for Statin Inhibition of HMG-CoA Reductase Published by : American Association for the Advancement of Science Stable URL : http://www.jstor.org/stable/3083663 Structural Mechanism for Statin Inhibition of HMG-CoA Reductase, Science (80-.). 292 (2016) 1160–1164.

[16] H. Sun, A.S. Koch, S.G. DiMagno, Rapid preparation of fluorinated aromatic heterocycles, in: ACS Symp. Ser., 2009: pp. 85–104. doi:10.1021/bk-2009-1003.ch002.

[17] T. Fujita, K. Fuchibe, J. Ichikawa, Transition-Metal-Mediated and -Catalyzed C−F Bond Activation by Fluorine Elimination, Angew. Chemie - Int. Ed. 58 (2018) 390–402. doi:10.1002/anie.201805292.

[18] H. Amii, K. Uneyama, C - F Bond Activation in Organic Synthesis, Chem. Rev. 109 (2009) 2119–2183. doi:10.1021/cr800388c.

[19] E. Clot, O. Eisenstein, N. Jasim, S.A. MacGregor, J.E. McGrady, R.N. Perutz, C-F and C-H bond activation of fluorobenzenes and fluoropyridines at transition metal centers: How fluorine tips the scales, Acc. Chem. Res. 44 (2011) 333–348. doi:10.1021/ar100136x.

[20] D.A. Baird, S. Jamal, S.A. Johnson, Influence of the Transmetalating Agent in Difficult Coupling Reactions: Control in the Selectivity of C − F Bond Activation by Ni(0) Complexes in the Presence of $AlMe_3$, Organometallics. 36 (2017) 1436–1446. doi:10.1021/acs.organomet.7b00165.

[21] B.L. Edelbach, W.D. Jones, Mechanism of Carbon - Fluorine Bond Activation by, J . Am. Chem. Soc. 7863 (1997) 7734–7742. doi:10.1021/ja970723r.

[22] E.E. Kwan, Y. Zeng, H.A. Besser, E.N. Jacobsen, Concerted nucleophilic aromatic substitutions, Nat. Chem. 10 (2018) 917–923. doi:10.1038/s41557-018-0079-7.

[23] L. Cronin, C.L. Higgitt, R. Karch, R.N. Perutz, Rapid intermolecular carbon-fluorine bond activation of pentafluoropyridine at nickel(0): Comparative reactivity of fluorinated arene and fluorinated pyridine derivatives, Organometallics. 16 (1997) 4920–4928. doi:10.1021/om9705160.

[24] S. Sabater, J.A. Mata, E. Peris, Hydrodefluorination of Carbon-Fluorine Bonds by the

Synergistic Action of a Ruthenium-Palladium Catalyst, Nat. Commun. 4 (2013) 1–7. doi:10.1038/ncomms3553.

[25] S.M. Senaweera, A. Singh, J.D. Weaver, Photocatalytic Hydrode fl uorination: Facile Access to Partially Fluorinated Aromatics, J . Am. Chem. Soc. 136 (2014) 3002–3006. doi:10.1021/ja500031m.

[26] S. Senaweera, J.D. Weaver, Dual C − F, C − H Functionalization via Photocatalysis: Access to Multi fl uorinated Biaryls, J . Am. Chem. Soc. 138 (2016) 1520–1523. doi:10.1021/jacs.5b13450.

[27] J. Ulrike, M. Klahn, P. Arndt, W. Baumann, A. Spannenberg, V. V Burlakov, U. Rosenthal, Room-temperature catalytic hydrodefluorination of pentafluoro-pyridine by zirconocene fluoro complexes and diisobutylaluminumhydride, J. Mol. Catal. A Chem. 261 (2007) 184–189. doi:10.1016/j.molcata.2006.06.027.

[28] H. Luo, G. Wu, S. Xu, K. Wang, C. Wu, Y. Zhang, J. Wang, Palladium-catalyzed cross-coupling of aryl fluorides with N-tosylhydrazones via C-F bond activation, Chem. Commun. 51 (2015) 13321–13323. doi:10.1039/c5cc05035a.

[29] Z. Luo, H. Zhao, X. Zhang, Highly Selective Pd-Catalyzed Direct C–F Bond Arylation of Polyfluoroarenes, Org. Lett. 20 (2018) 2543–2546. doi:10.1021/acs.orglett.8b00692.

[30] A.D. Sun, J.A. Love, Nickel-Catalyzed Selective Defluorination to Generate Partially Fluorinated Biaryls, Org. Lett. 13 (2011) 2751–2753. doi:10.1021/ol200860t.

[31] J. Vela, J.M. Smith, Y. Yu, N.A. Ketterer, C.J. Flaschenriem, R.J. Lachicotte, P.L. Holland, N. York, Synthesis and Reactivity of Low-Coordinate Iron (II) Fluoride Complexes and Their Use in the Catalytic Hydrodefluorination of Fluorocarbons, J. Am. Chem. Soc. (2005) 7857–7870. doi:10.1021/ja042672l.

[32] J. Hu, J. Zhang, G. Wang, H. Sun, J. Zhang, Constructing a Catalytic Cycle for C − F to C − X (X = O, S, N) Bond Transformation Based on Gold-Mediated Ligand Nucleophilic Attack, Inorg. Chem. 55 (2016) 2271–2283. doi:10.1021/acs.inorgchem.5b02634.

[33] K. Fuchibe, Y. Ohshima, K. Mitomi, T. Akiyama, Hydrodefluorinations by low-valent niobium catalyst, J. Fluor. Chem. 128 (2007) 1158–1167. doi:10.1016/j.jfluchem.2007.06.003.

[34] B. Kim, H. Woo, W. Kim, S. Yun, T. Hwang, Dehalogenation of Monohalopyridines Catalyzed by Group 4 Metallocene Reagent, Bull. Korean Chem. Soc. 21 (2000) 211–214.

[35] A. Nova, R. Mas-Ballesté, A. Lledós, Breaking C-F bonds via nucleophilic attack of coordinated ligands: Transformations from C-F to C-X bonds (X= H, N, O, S), Organometallics. 31 (2012) 1245–1256. doi:10.1021/om2010386.

[36] R.P. Hughes, D.C. Lindner, L.M. Liable-sands, A.L. Rheingold, Conversion of Perfluorobenzyl Complexes of Rhodium to Fluorinated Oxarhodacycles, Organometallics. 3 (2001) 363–366. doi:10.1021/om0008171.

[37] S. Park, M. Pontier-Johnson, D.M. Roundhill, Novel Regioselectivity and C-F Bond Cleavage in the Reactions of Alkylplatinum(II) Complexes with Amide and Alkoxide Anions, J . Am. Chem. Soc. 111 (1989) 3101–3103. doi:10.1021/ja00190a075.

[38] P.A. Deck, M.M. Konaté, B. V. Kelly, C. Slebodnick, C-F activation reactions of (pentafluorophenyl)cyclopentadiene and 3-(pentafluorophenyl)indene with tetrakis(dimethylamido)titanium(IV), Organometallics. 23 (2004) 1089–1097. doi:10.1021/om034385g.

[39] R.R. Schrock, J. Adamchuk, K. Ruhland, L.P.H. Lopez, Zirconium and Hafnium Complexes that Contain the Electron-Withdrawing Diamido/Donor Ligands [(2,6-

$X_2C_6H_3NCH_2)_2C(2\text{-}C_5H_4N)(CH_3)]^{2-}$ (X = Cl or F). An Evaluation of the Role of Ortho Halides in 1-Hexene Polymerization, Organometallics. 22 (2003) 5079–5091. doi:10.1021/om0305364.

[40] F. V. Cochran, P.J. Bonitatebus, R.R. Schrock, Molybdenum, Tungsten, and Rhenium d^2 Complexes That Contain the $[(C_6F_5NCH_2CH_2)_2NMe]^{2-}$ Ligand, Organometallics. 19 (2000) 2414–2416. doi:10.1021/om0001117.

[41] F.C. Sousa, B.J. Bloomer, S.E. Wengryniuk, Reactivity of (NNN) -pincer nickel (II) aryl complex towards oxidative carbon-heteroatom bond formation, Tetrahedron. 74 (2018) 3278–3282. doi:10.1016/j.tet.2018.04.029.

[42] J. Breitenfeld, R. Scopelliti, X. Hu, Synthesis, Reactivity, and Catalytic Application of a Nickel Pincer Hydride Complex, Organometallics. 31 (2012) 2128–2136. doi:10.1021/om201279j.

[43] M. Albrecht, M.M. Lindner, Cleavage of unreactive bonds with pincer metal complexes, Dalt. Trans. 40 (2011) 8733–8744. doi:10.1039/c1dt10339c.

[44] J.P. Bremond, M. Donnier, Y. Limouzin, Entre le noyau phenyle et l'atome de silicium. VI. couplages a longue distance dans les derives aromatiques fluores, J. Organomet. Chem. 90 (1975) 279–284.

[45] R.D. Chambers, P.A. Martin, G. Sandford, D.L.H. Williams, Mechanisms of reactions of halogenated compounds. Part 7. Effects of fluorine and other groups as substituents on nucleophilic aromatic substitution, J. Fluor. Chem. 129 (2008) 998–1002. doi:10.1016/j.jfluchem.2008.04.009.

[46] T. Ahrens, J. Kohlmann, M. Ahrens, T. Braun, Functionalization of fluorinated molecules by transition-metal-mediated C-F bond activation to access fluorinated building blocks,

Chem. Rev. 115 (2015) 931–972. doi:10.1021/cr500257c.

[47] B.R.J. Abraham, D. Macdonald, E.S. Pepper, S. Kline, The Nuclear Magnetic Resonance Spectra of Fluorobenzenes. Part I. The Analysis of the ABB'XX' and ABB'XX'R Spectra of Some 2-Substituted 1,3-Difluorobenzenes, J. Chem. Soc. B Phys. Org. (1967) 835–841.

[48] R.J. Abraham, D.B. Macdonald, E.S. Pepper, Effect of substituents on J(super FF)(sub meta) in fluorobenzenes., Chem. Commun. (1966) 542–543. doi:10.1039/c19660000542.

Figure captions

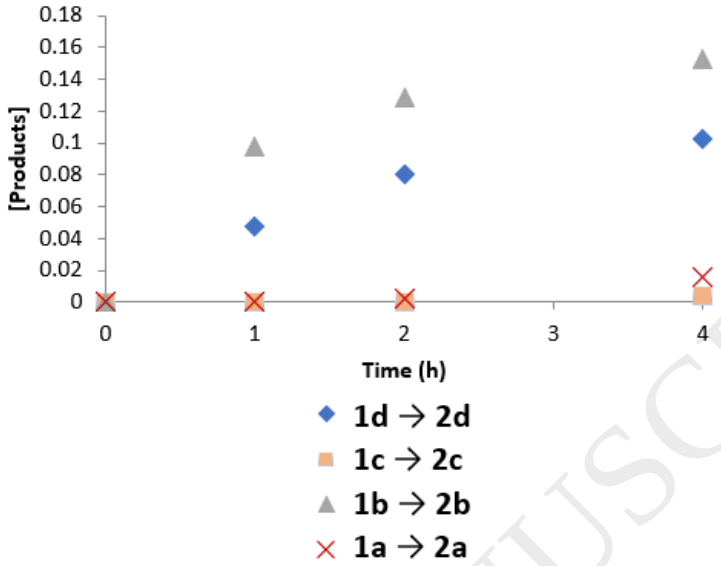
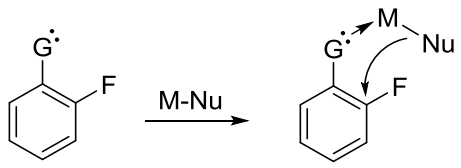


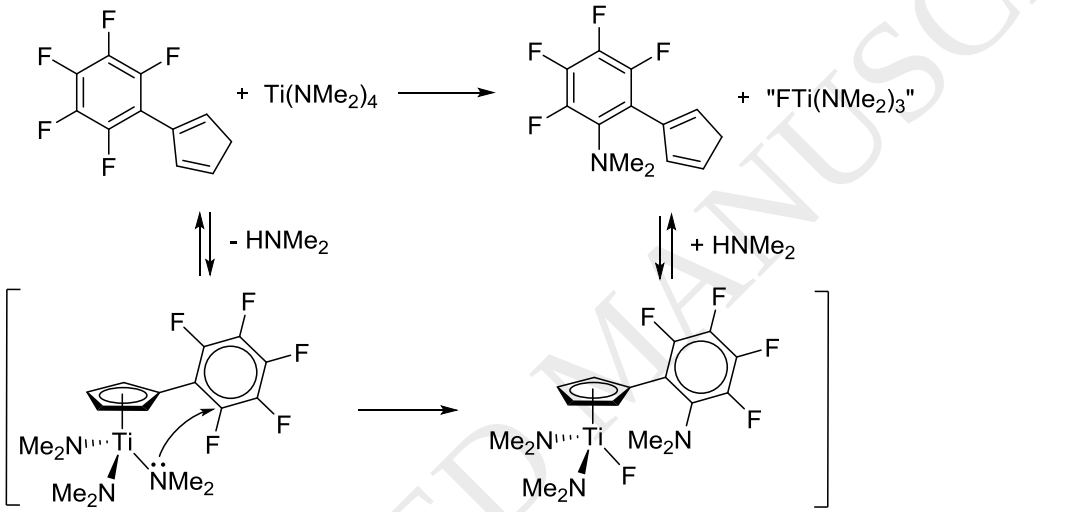
Figure 1: Concentrations of products over time in a competitive reaction of four difluoroanilines with a tenfold excess of $Ti(NMe_2)_4$ in mesitylene at 80 °C.

Scheme captions

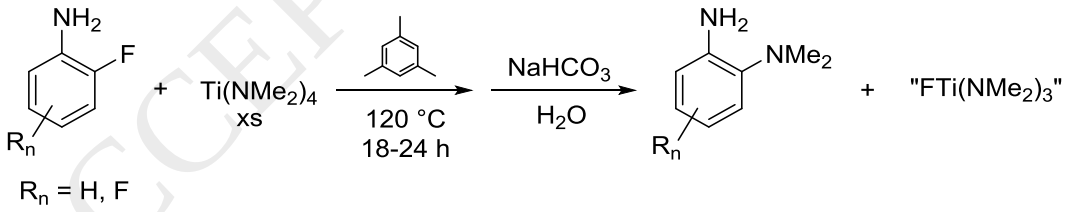
Scheme 1: Aromatic C-F activation using a metal-organic reagent (M−Nu) directed by a ring substituent (G).



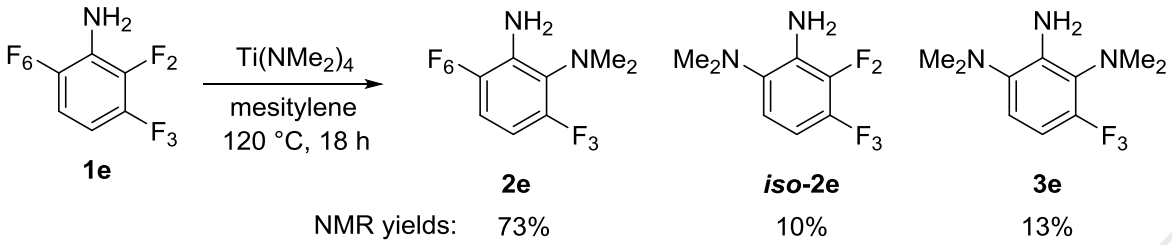
Scheme 2: C-F activation of (pentafluorophenyl)cyclopentadiene with $Ti(NMe_2)_4$.



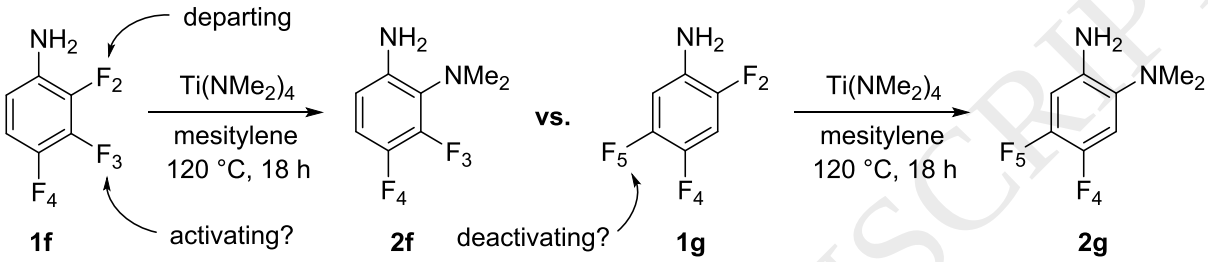
Scheme 3: Defluoroamination of ortho-fluoroanilines using $Ti(NMe_2)_4$.



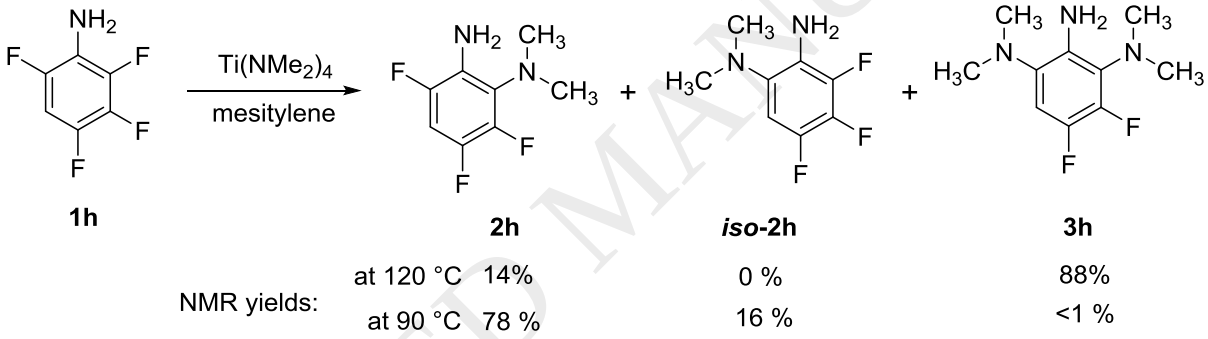
Scheme 4: Reaction of 2,3,6-trifluoroaniline **1e** with $Ti(NMe_2)_4$.



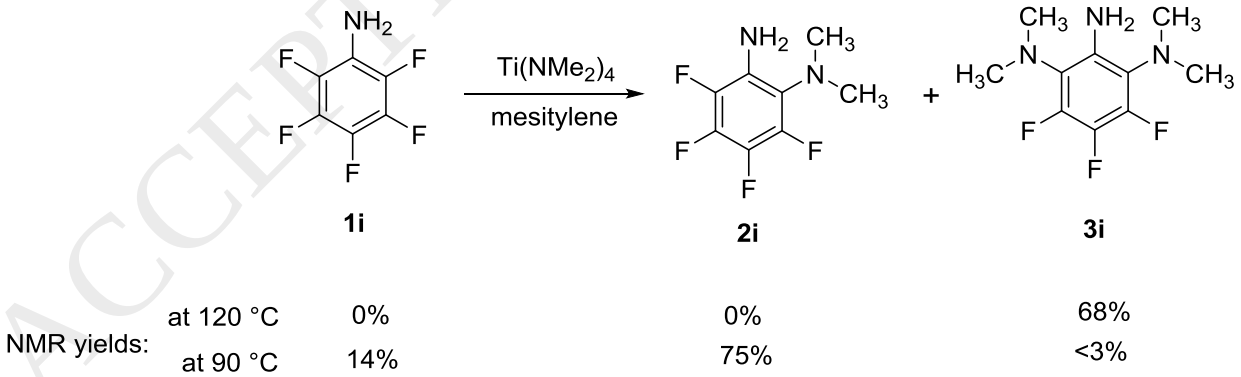
Scheme 5: Reactions of anilines **1f** and **1g** with $Ti(NMe_2)_4$.



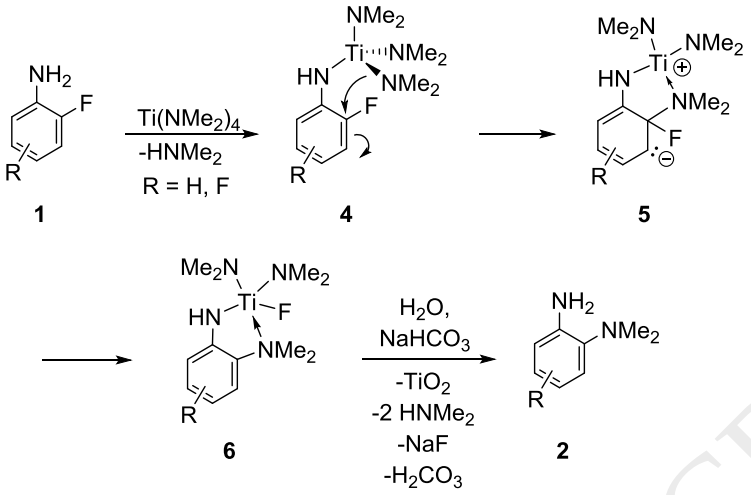
Scheme 6: Temperature-dependent defluoroamination of 2,3,4,6-tetrafluoroaniline.



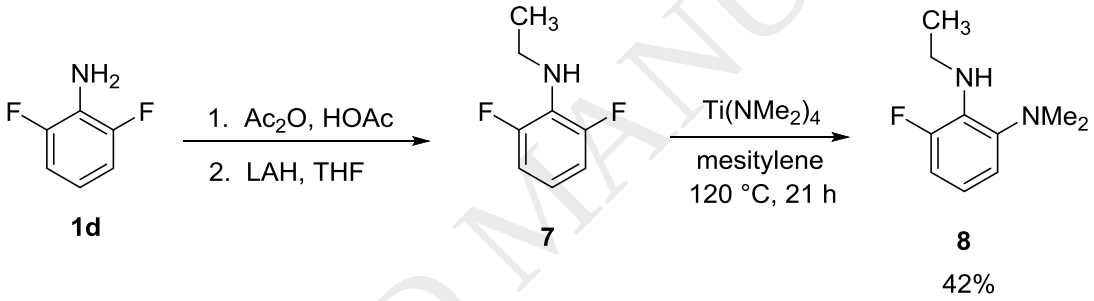
Scheme 7: Temperature-dependent defluoroamination of 2,3,4,5,6-pentafluoroaniline.



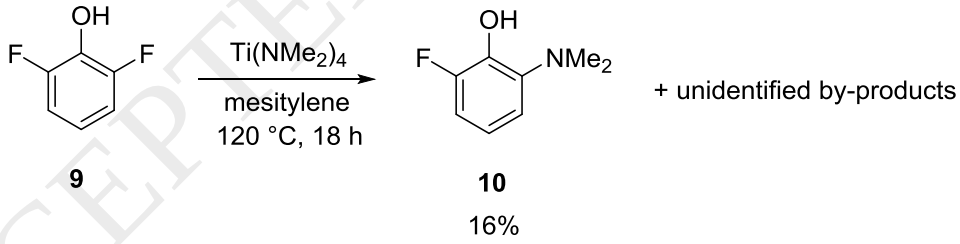
Scheme 8: Possible pathway for reactions of *o*-fluoroanilines with $Ti(NMe_2)_4$.



Scheme 9: Reaction of *N*-ethyl-2,6-difluoroaniline with $Ti(NMe_2)_4$.

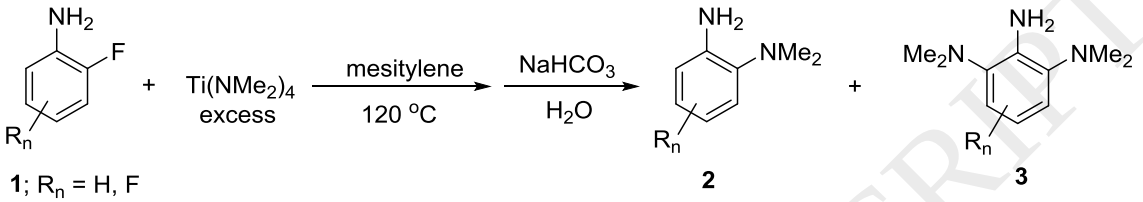


Scheme 10: Reaction of 2,6-difluorophenol with $Ti(NMe_2)_4$.



Table

Table 1. NMR yields of defluoroamination products resulting from the reaction shown. Yields (±5%) were estimated by NMR analysis of crude product mixtures.



1; R_n = H, F **2** **3**

			Yields by ^{19}F NMR, ±5%		
Entry	**Substrate**	**time**	**1**	**2**	**3**
1	2,3-difluoroaniline (**1a**)	20 h	8	86	
2	2,4-difluoroaniline (**1b**)	23 h		92	
3	2,5-difluoroaniline (**1c**)	23 h	31	60	
4	2,6-difluoroaniline (**1d**)	23 h	3	96	
5	2,3,6-trifluoroaniline (**1e**)	23 h		83[a]	13
6	2,3,4- trifluoroaniline (**1f**)	23 h		104	
7	2,4,5- trifluoroaniline (**1g**)	18 h		83	
8	2,3,4,6- tetrafluoroaniline (**1h**)	23 h		14[b]	88
9	2,3,4,5,6-pentafluoroanline (**1i**)	18 h			68

[a] Product **2e** is a 7:1 mixture of 2-dimethylamino-3,6-difluoroaniline (**2e**) and 2,3-difluoro-6-dimethylaminoaniline (***iso*-2e**), respectively. See Scheme 5 below.

[b] Product **2h** is 2-dimethylamino-3,4,6-trifluoroaniline.