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Research Article

The neighboring group effect of fluorine in the tritium labeling of organic substrates with $[Cp^*(PMe_3)IrMe(CH_2Cl_2)]^+[BAr_f]^-$, a cationic iridium(III) complex

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Summary

The cationic Ir(III) complex, $[Cp^*(PMe_3)IrMe(CH_2Cl_2)][BAr_f]$ (**1**, $Cp^* = \eta^5$-C_5Me_5, $BAr_f = MeB(C_6F_5)_3$), has been shown to be a useful reagent in the tritium and deuterium labeling of organic substrates. During a recent reaction of **1** with a fluorinated molecule, we observed an unusually high incorporation of tritium *ortho* to the aromatic fluorines. To probe whether this was an isolated incident or a more general phenomenon, we have investigated the application of **1** towards the tritiation of simple fluorinated organic substrates. Our results indicate that aromatic fluorine indeed does exhibit a neighboring group effect in terms of directing *ortho* H/T exchange. The directing influence appears to be at least as strong as the hydroxyl moiety reported in previous works. Copyright © 2006 John Wiley & Sons, Ltd.

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Key Words: iridium; fluorine; tritium; exchange; Bergman; neighboring group effect

Introduction

The C–H bond activation of organic substrates with highly active Ir(III) complexes, such as $[Cp^*(PMe_3)IrMe(CH_2Cl_2)][BAr_f]$ (**1**, Figure 1, $Cp^* = \eta^5$-C_5Me_5, $BAr_f = B[3,5\text{-}(CF_3)_2C_6H_3]_4$, has been extensively studied,[1–12] and the application to tritium and deuterium labeling of both simple organic

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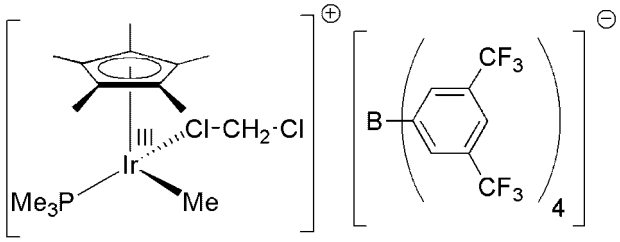

1

Figure 1.

molecules and more complex pharmaceutical templates has been recently demonstrated by our groups.[13,14] We found that **1** exchanges tritium most easily with the protons of aromatic rings. Exchange was also observed in simple alkyl groups that are activated by electron-withdrawing heteroatoms, such as nitrogen or oxygen, though to a lesser degree. In general, **1** is a sterically sensitive complex, with labeling occurring *meta* or *para* to a substituent on an aromatic ring. Thus far, the lone exception appeared to be phenyl groups containing hydroxyl or methoxy groups, where significant labeling occurred *ortho* to the substituent. It was reasoned that this might be due to coordination of the oxygen to the Ir metal, which in turn directs the activation *ortho* analogous to previously reported methods using Ir(I) catalysts.

In a recent study designed to examine the mechanism of methyl/arene exchange in C–H activating Ir cations, Tellers and coworkers conducted kinetic experiments using Cp*(PMe_3)IrMeOTf and 1,2-difluorobenzene as the substrate.[3] They observed the 1,2,3- and 1,3,4-trisubstituted arene in a 1:2 ratio, respectively (Scheme 1). This regioselectivity is in line for what one would expect if purely steric factors guided the substitution process. We now report that H/T exchange reactions carried out on simple fluorinated benzenes with **1** show dramatically different regioselectivity.

Results and discussion

The reactive Ir complex **1** was prepared by stirring the precursor, Cp*(PMe_3)IrMeCl (**2**), with $NaBAr_f$ in an inert atmosphere as reported previously.[13] Complex **1** was then mixed in a 1.1:1 ratio with the appropriate fluorinated substrate from Table 1. All substrates were commercially available except *N*-(2-fluoro-6-hydroxyphenyl)acetamide, which was prepared from 2,6-difluoronitrobenzene in a four-step reaction sequence adapted from Erikkson *et al.* (Scheme 2).[15] After 20 min of stirring, the Ir–substrate complex was exposed to a mixture of T_2 and H_2 gas, then worked up by removing base-exchangeable tritiums and purifying by solid-phase extraction.

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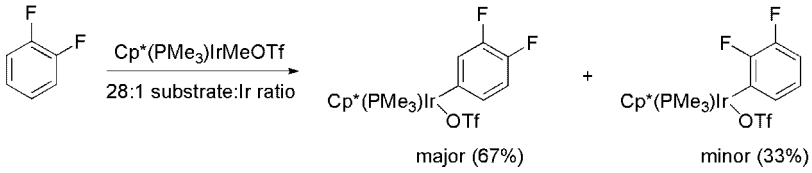

Scheme 1.

Results of the tritiation experiments are shown in Table 1. Entries 1–5 describe the outcome of the reaction of **1** with simple fluorinated acetanilides (entries 1 and 2), acetophenone (entry 3), or difluorobenzene (in comparison to the Tellers experiment, entries 4 and 5), while entries 6–8 display the results from molecules designed to probe how fluorine influences tritiation ('internal competition') in the presence of free phenyl groups (entry 6) or hydroxyl moieties (entries 7 and 8). For 3-fluoroacetanilide (entry 1), there is no labeling *ortho* to the acetamide substituent, which is consistent with the pattern seen previously for acetanilide substrates.[13] The remaining two positions sets up a competition between a relatively unhindered positon *meta* to the acetamide and fluorine moieties and a position *ortho* to the fluorine. The results clearly show the preference of the position *ortho* to the fluorine (57%) relative to the unhindered *meta* position (43%). Once again, one would expect to see a substitution pattern heavily skewed towards the *meta* position if purely steric factors dominated, as Tellers observed. Entry 2 (2,6-difluoroacetamide) corroborates these findings by once again showing an inclination towards substitution *ortho* to the fluorines (77% – a random distribution would be 66%) vs the relatively unhindered position *meta* to the fluorines (23%). Entries 4 and 5 attempt to recreate the Tellers experiment using 1,2-difluorobenzene as the substrate. In this case, we observed an almost equal distribution of tritium label *ortho* and *meta* to the fluorines. Using a T_2/H_2 mixture or no carrier-added T_2 produces a statistically equivalent distribution of tritium. This is in contrast to the Tellers experiment, where distribution of the Ir isomers was heavily skewed towards the *meta*-substituted Ir complex. For entry 6, a direct competition is arranged in a benzophenone template between a phenyl ring with no fluorines and one with two fluorines. In this case, the sterically benevolent positions on the free phenyl ring are favored (accounting for 79% of the tritium) and the label is equally distributed amongst the *meta* and *para* positions. However, even in the difluorinated ring it can be seen that there is a clear preference for the label to be incorporated *ortho* to the fluorine – absolutely none occurs *meta* to the fluorines.

As mentioned before, hydroxyl (and to a lesser extent methoxy) moieties appear to be exceptions to the steric model for tritium substitutions involving **1** in terms of their ability to direct *ortho* exchange. Entries 7 and 8 pit fluorine against hydroxyl in a disubstituted acetanilide and benzophenone,

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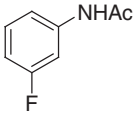
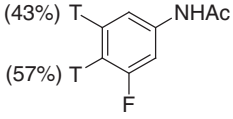
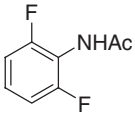
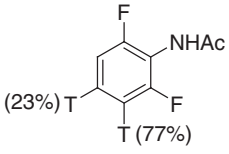
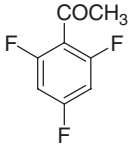
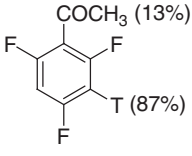
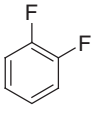
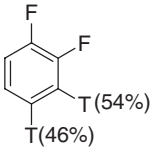
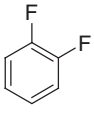
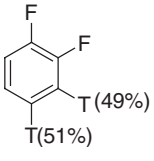
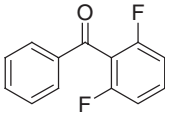
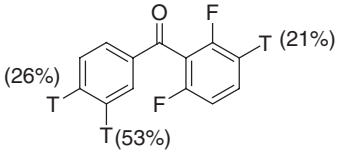
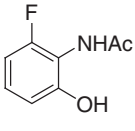
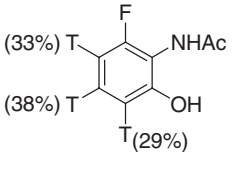
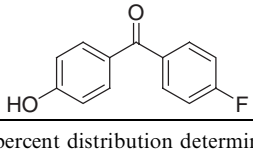
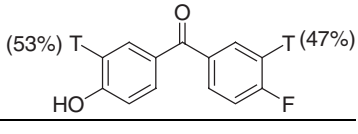
Table 1. Tritiation of fluorinated phenyl substrates

Entry	Substrate	T Position[a]
1		
2		
3		
4		
5[b]		
6		
7		
8		

[a]Tritium location and percent distribution determined by ^{3}H NMR.
[b]Carrier-free T_2 used.

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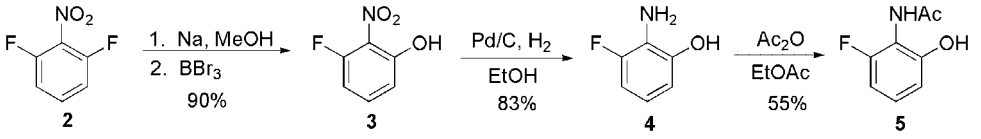

Scheme 2.

respectively. The results show that fluorine is almost equal to hydroxyl in terms of its 'directing power'. In entry 7, 33% of the label is *ortho* to fluorine, while 29% is *ortho* to the hydroxyl moiety. For the benzophenone substrate (entry 8), the results are similar – 53% of the label is *ortho* to the hydroxyl vs 47% for fluorine.

Several conclusions can be drawn from these data. First, there is a clear neighboring group effect of fluorine on H/T exchange. Tritiations *ortho* to fluorine occur at a relative rate more rapid than that which would be expected from steric factors, or even a random distribution of tritium. Substitution *ortho* to the fluorine is often favored, not just tolerated. Second, when there exists both unhindered protons on a free phenyl ring and protons *ortho* to fluorines on a different ring, exchange at the free phenyl ring is favored (entry 4). The obvious warning is that this is based on a singular example in which the fluorines are located in a 2,6-disubstitution pattern in benzophenone. Third, fluorine has about the same 'directing power' or neighboring group effect as hydroxyl (entries 5 and 6).[†]

The exact mechanism of this fluorine-based directing influence on H/T exchange is not clear. It is unlikely that a simple electronic effect can be invoked (i.e. fluorine's high electronegativity and subsequent decrease of electron density at the *ortho* position increase the reactivity of the *ortho* C–H bond), since at least one study suggests that more electron-deficient arenes react more slowly with **1** than more electron-rich arenes.[3] A more likely set of scenarios using 1,2-difluorobenzene as an example substrate is illustrated in Scheme 3.

In the first scenario (A), the *meta*-substituted Ir complex undergoes decomposition faster than the *ortho*-substituted congener ($k_{D'} > k_D$). This would have the net effect of preferential accumulation of the *ortho* Ir complex and subsequently a higher proportion of *ortho*-tritiated product. In the second scenario (B), differing tritiation/hydrogenation rates lead to the disparate distribution of products (since the majority of these experiments were carried out using tracer quantities of T_2 gas). In other words, if $k_T/k_H >> k_{T'}/k_{H'}$, one would expect a preferential accumulation of the *ortho*-tritiated product. However, the fact that the tritium distribution for

[†]In making these conclusions, it should be noted that no attempts were made to monitor the extent of tritiation over time; therefore, the authors cannot verify that the exchange process has come to equilibrium.

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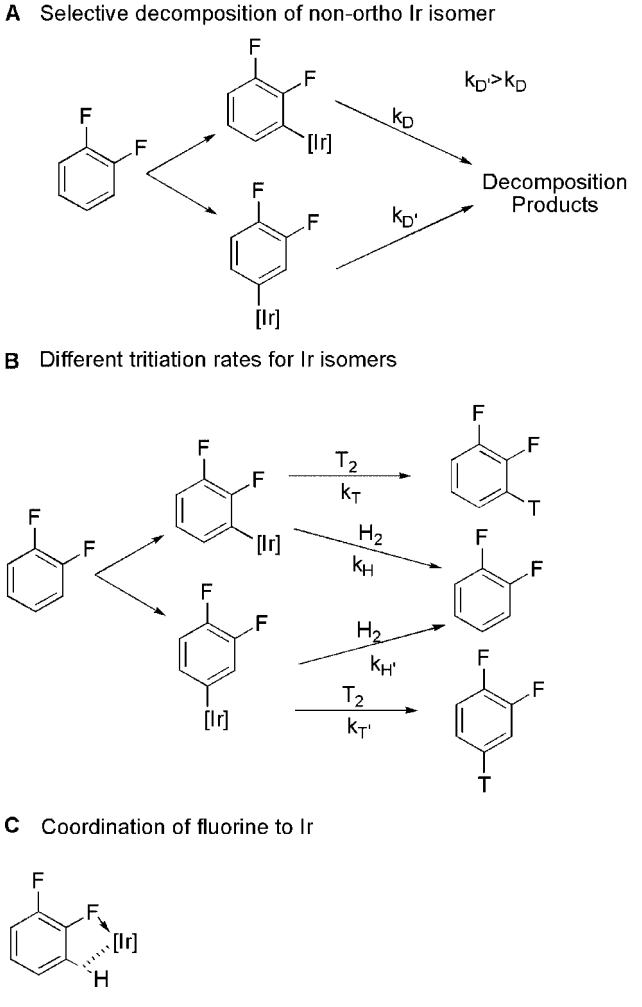

Scheme 3.

1,2-difluorobenzene is statistically indistinguishable whether tracer or no carrier-added T_2 was used (Table 1, entries 4 and 5) strongly suggests that this scenario is unlikely.

A more probable situation (C) is that fluorine is weakly coordinating via its *p*-type lone pairs ('secondary bonding') to the Ir metal. The reversible coordination directs the Ir to activate the C–H bond *ortho* to the C–F bond in the arene. Cotton *et al.* have reported bromocarbon and fluorocarbon binding to various transition metal cations, including Ir(III).[16,17] Crabtree and coworkers have also shown that cationic Ir(I) and – (III) complexes can bind the halogens of halocarbons, including fluorine.[18–20] Interestingly, they found that the iodo-, bromo-, and chlorocarbon Ir–X distance is equal to the sum of the covalent radii, while the Ir–F distance in the 8-fluoroquinoline complex

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lies between the sum of the covalent radii and the sum of the van der Waals radii. This intermediate distance suggests that the interaction is weaker than that of a full covalent bond.[18] The fact that we have not observed the same effect with other halogens could mean that there is a delicate interplay between the relatively small size of fluorine and its more reversible mode of coordination to Ir, which in turn allows it to direct *ortho* H/T exchange in a more facile nature.

Conclusions

We have treated a series of fluorinated organic substrates with **1** and T_2 gas to investigate the fluorine-directing potential of H/T exchange. Our results indicate that fluorine exerts a clear neighboring group influence on the C–H bond *ortho* to the fluorines in these substrates, with incorporation exceeding that predicted by random exchange or that predicted intuitively from previous studies on Ir(III)-mediated C–H activation *ortho* to arene substituents, including halogens. Fluorine's 'directing influence' seems to be at least as strong as the hydroxyl moiety. Mechanistic understanding of why this occurs is at this point lacking. An experiment comparing tritiated product ratios using tracer and no carrier-added T_2 suggest that the effect is not due to differing tritiation vs hydrogenation rates of the substituted Ir complex intermediates. Alternatively, the literature suggests that Ir–F coordination is a more plausible explanation. These results not only further our understanding of this labeling system, but also its application to drug substrates in light of the ubiquitous presence of fluorine in many pharmaceutical libraries.

Experimental

The CH_2Cl_2 used for the stoichiometric tritiations was purchased from J. T. Baker (BakerDRY^{TM}, catalog No. 9295-10) without further purification. 2′,6′-Difluorobenzophenone, 2,6-difluoronitrobenzene, 1,2-difluorobenzene and 3-fluoroacetanilide were purchased from Aldrich, 4-fluoro-4′-hydroxybenzophenone from TCI America, 2,4,6-trifluoroacetophenone from Matrix Scientific, and 2,6-difluoroacetanilide from SynQuest. All reagents were used without further purification. Mass spectrometric data were collected on a Waters Micromass ZQ (ESI). Thin-layer chromatography (Analtech scored glass 10 cm × 20 cm hard TLC plates) was used to assess the Sep-Pak® eluent profile and to determine final radiochemical purity. ^{1}H, ^{3}H, and ^{13}C NMR spectra were obtained on a Bruker 300 or 400 MHz Ultrashield spectrometer. Resonances are reported in parts per million relative to the incomplete deuteration signal from the NMR solvent. For the tritiated compounds, percentages in the ^{3}H NMR data correspond to the fraction of the total integrated signal. Tritium NMR integration error limits are on the order of $\pm$ 1%, as determined by three consecutive 4096 scan experiments on 5 mCi

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of [^{3}H]1,2-difluorobenzene (1.11 Ci no carrier-added T_2 run, *vide infra*). Radioactivity measurements were made on a Packard Tricarb 1900CA liquid scintillation analyzer. Radio-TLC analysis was performed on a Bioscan AR-2000 Imager using WinScan 2.2 software.

General procedure for stoichiometric H/T exchanges

All manipulations prior to Trisorber use were performed in a N_2 dry box. Cp*Ir(PMe_3)MeCl[6] (5.20–5.42 μmol, 1.10 equiv.) was added to an oven-dried 2.5 ml round-bottom flask with stir bar, then $NaBAr_f$ (5.20–5.42 μmol, 1.10 equiv.) was added. The dry mixture was solubilized in CH_2Cl_2 (150 μl), creating a dark orange solution. The flask was capped and stirred vigorously for 10 min. A solution of the substrate (4.73–4.93 μmol, 1.00 equiv.) in CH_2Cl_2 (150 μl) was added to the Ir solution. The flask was fitted with an oven-dried 2-way stopcock valve (stopcock in closed position), and the reaction mixture was stirred for 20 min at 25°C. The assembly was removed from the dry box and attached to an IN/US Trisorber TS-1000 manifold (IN/US Systems Inc., Tampa, FL). The solution was degassed by freeze-pump-thaw (1 cycle). The sensitive volume (the volume of gas to be opened to the reaction flask = V_e, 3.08 ml) was loaded with 5 torr T_2 (48.4 mCi), and the manifold volume (V_a, 9.99 ml) was loaded with 152 torr H_2 (tracer chemistry was used to minimize waste and maximize safety). The two chambers were quickly mixed, resulting in 119 torr H_2/T_2 (19.7 μmol, 7.99–8.33 equiv.) in the sensitive volume, V_e. The sensitive volume was opened to the flask and the reaction was stirred vigorously for 2 h. The reaction mixture was frozen and the excess gas transferred to a uranium oxide waste bed. The manifold and flask were backfilled with He and the flask/stopcock assembly removed from the Trisorber manifold.

For substrates in table entries 1, 2, 7 and 8, exchangeable tritium was removed by adding 0.3 ml ethanol and distilling the solvents under vacuum. The crude material was redissolved in 250 μl of the mobile phase, and loaded onto 2 tandem SiO_2 Sep-Paks (Waters, WAT051910). The eluent was collected in 1.5–3 ml fractions and the activity and purity of the fractions was monitored by LSC and TLC, respectively. The appropriate fractions were then evaporated under nitrogen and a final purity assessed by TLC (reported values are final purities).

For [^{3}H]2,4,6-trifluoroacetophenone and 1,2-difluorobenzene (Table entries 4 and 5), the crude reaction was vacuum distilled bulb-to-bulb without the addition of ethanol. For the experiment involving no carrier-added T_2, 1.11 Ci was used. ^{3}H NMR experiments were performed by diluting a 2–5 mCi sample of the distillate with 600 μl CD_2Cl_2.

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[^{3}H]3-Fluoroacetanilide (Table Entry 1)

Addition of the substrate to the Ir/$NaBAr_f$ solution produced an orange solution. The color changed to yellow upon exposure to H_2/T_2 gas. SPE solvent system: Et_2O. Radio-TLC purity = 99%. Activity in crude, post-distillation: 3.87 mCi. Activity in distillate: 11.1 mCi. Activity of pure tritiated substrate recovered from crude: 1.64 mCi. ^{3}H NMR (CD_2Cl_2, 320 MHz) δ 6.93 (d, J_{T-F} = 8.8 Hz, 57%), 7.39 (d, J_{T-F} = 6.8 Hz, 43%).

[^{3}H] 2,6-Difluoroacetanilide (Table Entry 2)

Addition of the substrate to the Ir/$NaBAr_f$ solution produced an orange solution. The color changed to yellow upon exposure to H_2/T_2 gas. SPE solvent system: Et_2O. Radio-TLC purity = 97%. Activity in crude, post-distillation: 1.41 mCi. Activity in distillate: 15.8 mCi. Activity of pure tritiated substrate recovered from crude: 0.554 mCi. ^{3}H NMR ($CDCl_3$, 320 MHz) δ 7.08 (d, J_{T-F} = 9.2 Hz, 77%), 7.32 (m, 23%).

[^{3}H]2,4,6-Trifluoroacetophenone (Table Entry 3)

Note: due to the volatility of this compound, exchangeable tritiums were not removed prior to SPE purification. Evaporations under N_2 were done with the vial containing the compound in an ice bath to prevent excess evaporation of tritrated compound. Addition of the substrate to the Ir/$NaBAr_f$ solution produced an orange solution. The color remained orange upon exposure to H_2/T_2 gas. SPE solvent system: 10% Et_2O/Pentane. Radio-TLC purity = 82% (difficult to assess due to volatility). Activity in crude: 17.4 mCi. Activity of pure tritiated substrate recovered from crude: 1.40 mCi. ^{3}H NMR (CD_3OD, 320 MHz) δ 2.62 (s, 13%), 7.08 (t, J_{T-F} = 10.1 Hz, 87%).

[^{3}H]1,2-Difluorobenzene (Table Entries 4 and 5)

Addition of the substrate to the Ir/$NaBAr_f$ solution produced an orange solution. The color changed to yellow upon exposure to H_2/T_2 gas, and was unchanged for the no carrier-added T_2 experiment. *Tracer Run Data*: Activity in crude, prior to distillation: 29.2 mCi. Activity in crude, post-distillation: 8.98 mCi. Activity in distillate: 16.7 mCi. ^{3}H NMR ($CDCl_3$, 320 MHz) δ 7.24 (s, 46%), 7.31 (app. dd, J_{T-F} = 11.0, 9.0 Hz, 54%). *N.C.A. T_2 Run Data*: Activity in crude, prior to distillation: 102.3 mCi. Activity in crude, post-distillation: 55.8 mCi. Activity in distillate: 44.0 mCi. ^{3}H NMR ($CDCl_3$, 320 MHz, average of three successive acquisitions at 4096 scans each) δ 7.24 (app. s, 51%), 7.31 (dd, J_{T-F} = 11.0, 8.9 Hz, 49%).

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[^{3}H] 2′,6′-Difluorobenzophenone (Table Entry 6)

Addition of the substrate to the Ir/$NaBAr_f$ solution produced an orange solution. The color changed to a lighter orange upon exposure to H_2/T_2 gas. SPE solvent system: 10% Et_2O/Pentane. Radio-TLC purity = 100%. Activity in crude, post-distillation: 6.30 mCi. Activity in distillate: 14.9 mCi. Activity of pure tritiated substrate recovered from crude: 4.23 mCi. ^{3}H NMR ([$^2H_6$]acetone, 320 MHz) δ 7.33 (d, J_{T-F} = 9.2 Hz, 21%), 7.71 (s, 53%), 7.85 (s, 26%).

[^{3}H]2-Fluoro-6-hydroxyacetanilide (Table Entry 7)

Addition of the substrate to the Ir/$NaBAr_f$ solution produced an orange solution. The color changed to yellow upon exposure to H_2/T_2 gas. SPE solvent system: Et_2O. Radio-TLC purity = 94%. Activity in crude, post-distillation: 4.62 mCi. Activity in distillate: 27.3 mCi. Activity of pure tritiated substrate recovered from crude: 0.98 mCi. ^{3}H NMR ($CDCl_3$, 320 MHz) δ 6.78 (d, J_{T-F} = 11.0 Hz, 33%), 6.93 (s, 29%), 7.17 (d, J_{T-F} = 7.1 Hz, 38%).

[^{3}H]4-Fluoro-4′-hydroxybenzophenone (Table Entry 8)

Addition of the substrate to the Ir/$NaBAr_f$ solution produced a very dark orange solution. The color changed to yellow upon exposure to H_2/T_2 gas. SPE solvent system: 50% Et_2O/Pentane. Radio-TLC purity = 98%. Activity in crude, post-distillation: 6.42 mCi. Activity in distillate: 22.4 mCi. Activity of pure tritiated substrate recovered from crude: 4.05 mCi. ^{3}H NMR ([$^2H_6$]acetone, 320 MHz) δ 7.08 (s, 53%), 7.41 (d, J_{T-F} = 9.0 Hz, 47%).

*3-Fluoro-2-nitrophenol (**3**)*

Following a procedure adapted from Eriksson,[15] sodium metal (81.9 mg, 2.56 mmol) was added to a 15 ml round bottom flask containing 3.6 ml anhydrous methanol at 0°C. The solution was stirred until the sodium had completely dissolved. This NaOMe solution was added dropwise to a solution of 2,6-difluoronitrobenzene (**2**, 501 mg, 3.15 mmol) in 9 ml anhydrous MeOH. The reaction turned a yellow-orange color and was stirred overnight at RT. TLC showed conversion of most of the starting material to a more polar spot. The MeOH was evaporated *in vacuo* and the residue was partitioned between water (5 ml) and diethyl ether (10 ml). The layers were separated and the aqueous layer was extracted two more times with ether (10 ml each). The organics were combined, dried with Na_2SO_4, and evaporated *in vacuo* to give the crude 1-fluoro-3-methoxy-2-nitrobenzene as a pinkish yellow solid (540 mg). This was used in the deprotection without further purification.

For the deprotection, the crude 1-fluoro-3-methoxy-2-nitrobenzene was dissolved in anhydrous CH_2Cl_2 (6.2 ml) and cooled to 0°C. To this was added a 1M solution of BBr_3 in CH_2Cl_2 (8.00 ml, 8.00 mmol) dropwise. The reaction

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was warmed to RT and the dark red solution was allowed to stir overnight. LC-MS showed complete conversion of the starting material to the product. The reaction was cooled to 0°C and was quenched slowly with 6 ml water and stirred for 1 h, during which time a chunky, red suspension formed. The suspension was filtered through a course fritted funnel, and the biphasic filtrate was separated. The aqueous layer was extracted with ether (3×5 ml), and the organics were combined and evaporated *in vacuo* to a brown residue. The residue was dissolved in 10 ml ether and extracted with 2M NaOH (3×1.7 ml) and water (1 ml). The combined basic extracts were neutralized with 6M HCl, then extracted with ether (3×8 ml). The combined ether extracts were dried with Na_2SO_4 and evaporated *in vacuo* to an orange solid (481 mg). The crude material was purified by flash chromatography (SiO_2, 30% EtOAc/Hex) to give **3** (446 mg, 90%). MS (ESI neg) *m/z* 156 (M-H, 100).

*2-Amino-3-fluorophenol (**4**)*

To a solution of **3** (446 mg, 2.84 mmol) in EtOH (20 ml) was added Pd/C (90 mg). The flask was evacuated of air and filled/purged with H_2 gas three times. The reaction was stirred vigorously under H_2 balloon pressure overnight. The suspension was then filtered through a short pad of Celite to remove the Pd/C, and the orange filtrate was evaporated *in vacuo* to a solid (426 mg). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.20 (s, 1H), 6.57–6.71 (m, 3H); MS (ESI neg) *m/z* 126 (M-H, 100).

*N-(2-fluoro-6-hydroxyphenyl)acetamide (**5**)*

To a solution of **4** (300 mg, 2.36 mmol) in EtOAc (2.4 ml) at 0°C was added acetic anhydride (560 µl, 5.9 mmol) dropwise. The reaction was warmed to RT and stirred overnight, then poured into a separatory funnel containing 5 ml saturated $NaHCO_3$. The layers were separated and the organic layer was washed two more times with saturated $NaHCO_3$ (2×5 ml), then dried with Na_2SO_4 and evaporated *in vacuo* to a solid. The crude solid was purified by flash chromatography (SiO_2, 30–60% EtOAc/Hex) to give the title compound as a slightly yellow solid (220 mg, 55%), as well as the N,O-diacetylated product (148 mg, 30%). ^{1}H NMR (CD_3OD, 400 MHz) δ 2.07 (s, 3H), 6.51–6.60 (m, 2H), 6.95–7.02 (m, 1H); ^{13}C NMR (CD_3OD, 100 MHz) δ 22.6 (107.3, 107.5; $J_{C-F} = 21.1$ Hz), (113.38, 113.41; $J_{C-F} = 3.0$ Hz), 114.4, 128.9, 155.2 (158.3, 160.7; $J_{C-F} = 247$ Hz), 173.1; MS (ESI neg) *m/z* 168 (M-H, 100).

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