HHS Public Access

Author manuscript

J Am Chem Soc. Author manuscript; available in PMC 2021 June 03.

Published in final edited form as:

J Am Chem Soc. 2020 June 03; 142(22): 9966–9974. doi:10.1021/jacs.9b13537.

Pd-catalyzed γ-C(sp³)–H Fluorination of Free Amines

Yan-Qiao Chen[†], **Sukriti Singh**[#], **Yongwei Wu**[†], **Zhen Wang**[†], **Pritha Verma**[†], **Jennifer X. Qiao**[§], **Raghavan B. Sunoj**[*,#], **Jin-Quan Yu**[*,†]

[†] Department of Chemistry, The Scripps Research Institute, 10550 N. Torrey Pines Road, La Jolla, California 92037, United States

[#] Department of Chemistry, Indian Institute of Technology Bombay, Powai, Mumbai 400076, India

[§] Discovery Chemistry, Bristol-Myers Squibb, PO Box 4000, Princeton, New Jersey 08543, United States

Abstract

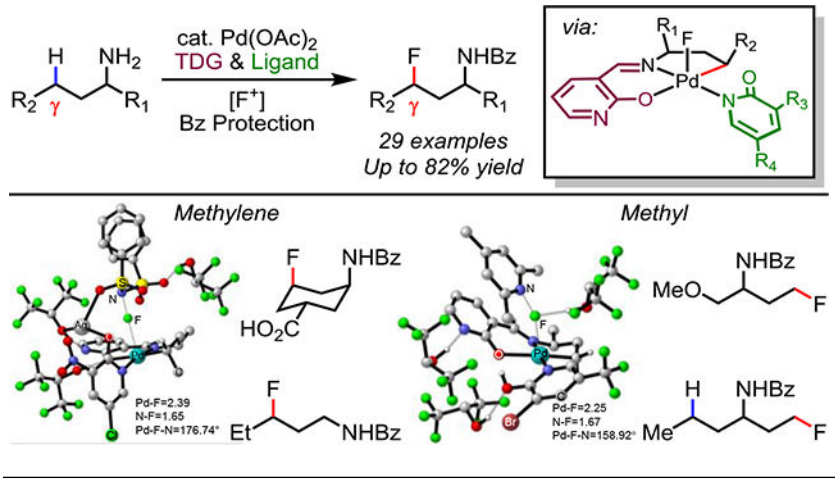
The first example of free amine γ-C(sp^3)–H fluorination is realized using 2-hydroxynicotinaldehyde as the transient directing group. A wide range of cyclohexyl and linear aliphatic amines could be fluorinated selectively at the γ-methyl and methylene positions. Electron withdrawing 3,5-disubstituted pyridone ligands were identified to facilitate this reaction. Computational studies suggest that the oxidative addition step is likely to be the turn-over determining step in both methylene and methyl fluorination reactions. Explicit participation of Ag results in lower energetic span for methylene fluorination and higher energetic span for methyl fluorination, which is consistent with experimental observation that the addition of silver salt is desirable for methylene but not for methyl fluorination. Importantly, energetically preferred pathway has identified an interesting pyridone-assisted bimetallic transition state for the oxidative addition step in methylene fluorination, thus uncovering a potential new role of the pyridone ligand.

Graphical Abstract

[*]**Corresponding authors.** yu200@scripps.edu and sunoj@chem.iitb.ac.in.

Notes. The authors declare no competing financial interest.

Supporting Information Available. Detailed experimental procedures, characterization of new compounds, and computational studies. This material is available free of charge via the internet at http://pubs.acs.org.



1. Introduction

In recent years, the development of transient directing group strategy has emerged as a promising new direction for direct C–H activation of aldehydes, ketones, and free amines.[1] In the context of C(sp^2)–H functionalizations of benzaldehydes, transient directing groups (TDGs) have enabled a wide range of carbon–carbon, carbon–halogen, and carbon–nitrogen bond formation reactions.[1c] On the other hand, C(sp^3)–H functionalizations using TDGs have met with limited success. To date, TDG enabled C(sp^3)–H functionalizations are largely limited to (hetero)arylations.[2–4] While we have recently developed a new chiral TDG enabling enantioselective acetoxylation and fluorination reactions of 2-alkylbenzaldehydes, efforts to extend these reactions to aliphatic aldehydes and ketones remain unsuccessful.[5] Similarly, TDG enabled C(sp^3)–H activation of aliphatic amines have been only limited to (hetero)arylations.[4] Since aliphatic amines are valuable synthetic building blocks and a ubiquitous functional group in drug molecules, we were motivated to develop other C–X bond forming reactions in addition to arylation.

The introduction of fluorine atoms to preclinical drug candidates can significantly enhance their medicinal value by altering their conformation, lipophilicity, and metabolic stability.[6] While a number of C(sp^3)−H fluorination methods using palladium insertion have been reported, these works are largely limited to benzylic or allylic C−H bonds and require the installation and removal of exogenous directing groups.[7–8] Notably, our lab and the Shi lab have developed β-C(sp^3)−H fluorination of α-amino acid derivatives using stoichiometric directing groups.[8c–d] Recently, the Xu group have reported a β-C(sp^3)−H fluorination of aliphatic alcohols using a simple oxime-based auxiliary.[8e] In light of these advancements on directing group design and our previous work on TDG enabled enantioselective fluorination of 2-alkylbenzaldehydes (Scheme 1),[5] we envisioned that aliphatic amines could also be fluorinated using a TDG strategy to provide facile access to fluorine containing amine building blocks and late-stage drug candidates. Nonetheless, C(sp^3)–H fluorination of free amines can potentially pose several challenges: 1) C(sp^3)–H bond cleavage is generally less favored for simple methylene and methyl C–H bonds versus the more reactive benzylic and C(sp^2)–H bonds, 2) the C(sp^3)−F reductive elimination from a high-valent transition metal center is challenging due to a formidable kinetic barrier[7], and 3) free amines might be

reactive with the commonly used electrophilic fluorinating reagents. Recently, we have discovered that electron-deficient 2-pyridones, in addition to enabling both norbornene-mediated *meta*-C(sp^2)−H functionalization and non-directed C(sp^2)−H activation of arenes,[9] could also promote γ-C(sp^3)–H heteroarylation and δ-C(sp^3)–H (hetero)arylation of free amines (Scheme 2).[10] Inspired by this development, we wondered whether 2-pyridone could also promote γ-C(sp^3)–H fluorination of amines. Herein, we report the first example of γ-C(sp^3)–H fluorination of free amines (Scheme 3). A wide range of cyclohexyl and acyclic aliphatic amines could be fluorinated selectively at the unactivated γ positions.

2. Results and Discussion

We began our investigation by conducting γ-fluorination of cyclohexylamine. For ease of isolation and analysis, the crude reaction mixture was treated with methoxyamine to react with the remaining TDG and imine to release the free amine products followed by benzoyl protection.[4b] Under similar reaction conditions as our previous arylation conditions,[10] we were encouraged to find the desired fluorinated products in 17% NMR yield when N-fluoro-2,4,6-trimethylpyridinium salt was used as the fluorinating reagent (Table 1, entry 1). The reaction was shut down when the simple phenol based TDG (**TDG2**) was used instead of our previously identified 2-hydroxynicotinaldehyde TDG (**TDG1**) (entry 2). When we increased the loading of **TDG1** to 50 mol% and 1.0 eq, the yields improved to 34% and 45% respectively (entry 3, 4). Unlike our previously published γ-heteroarylations where only catalytic TDG was used, stoichiometric amounts of **TDG1** is needed for this fluorination reaction. Although at this stage we had already established moderate reactivity, we directed our attention to identify cheaper and more accessible electrophilic fluorinating reagents. Gratifyingly, replacing N-fluoro-2,4,6-trimethylpyridinium salt with NFSI and using 1.2 eq of **TDG1** at 100 °C led to an increased yield of 53% (entry 5). Solvent screening revealed that adding AcOH and using a mixture of HFIP and PhCl could further improve the yield to 58% and 62% respectively (entry 6, 7). Unfortunately, further screening of reaction conditions failed to improve the efficiency of this reaction.

Inspired by our recent observations that electron deficient pyridone ligands can accelerate both γ-C(sp^3)–H and δ-C(sp^3)–H (hetero)arylations of free amines,[10] we wondered whether pyridones would also help in this γ-C(sp^3)–H fluorination reaction (Table 2). To our surprise, 3- and 5- mono-substituted nitro or trifluoromethyl pyridone ligands (**L1-L4**), which were previously found to be superior for γ-C(sp^3)–H and δ-C(sp^3)–H (hetero)arylations, in fact hindered the reactivity of this fluorination reaction, affording only 18–45% of the desired products. Interestingly, when we screened various 3,5-di-disubstituted electron deficient pyridones, reactivity could be restored to 50–60%. Fortuitously, extensive screening of various 3,5-di-substituted pyridone ligands revealed that 5-chloro-3-nitro pyridone (**L6)** provided 71% NMR yield. While our reaction was effective for cyclohexylamine (**2a**), the yield lowered to only 31% when we used the linear substrate 2-aminopentane (**2j**). After extensive screening, we found that simply increasing the loading of **L6** from 50 mol% to 2.0 equivalences in pure HFIP can provide enhanced reactivity to 61% isolated yield.

With the optimal TDG and ligand identified, and the best conditions established, we next investigated the scope of various amines in this reaction (Table 3). Fluorination of *trans*-3-methyl- and *trans*-3-methyl ester-cyclohexylamine (**2b-c**) proceeded smoothly, whereas the *cis* isomer was completely unreactive, presumably due to steric repulsion between the directing group and the methyl group. In contrast, *cis*-4-methyl ester-cyclohexylamine (**2d**) could afford the fluorinated product in 55% yield while the *trans* variant was unreactive. Similarly, *cis*-2-ethyl ester-cyclohexylamine (**2e**) provided the fluorinated product at the 5-position in 46% isolated yield. Free amino acids such as *cis*-4-aminocyclohexane-1-carboxylic acid and *trans*-3-aminocyclohexane-1-carboxylic acid were also reactive (**2f-g**). Notably, the reactivity lowered significantly when only 50 mol% of **L6** was used for **1f-g**.

Other cyclic substrates such as 2-adamantanamine and 2-norboranamine also proceeded smoothly with the former providing 51% of exclusively di-fluorinated product and the latter providing 74% of mono-fluorinated product (**2h-i**), demonstrating this protocol's potential to perform C–H functionalization on structurally more complex substrates. Various acyclic free amines with methyl substitutions at the α-position could also be successfully fluorinated selectively at the γ position with 40–61% yields (**2j-m**). When 3-aminopentane was used, the di-fluorinated product was obtained as the predominant product (**2n**). In the presence of δ-methyl C–H bonds, our protocol is selective towards γ-C–H bonds (**2o**). Furthermore, substrates containing oxygenated functionalities at different positions were tolerated as well (**2p-q**). Lastly, simple aliphatic amines without α-substitutions could also be fluorinated in 32–35% yields (**2r-s**). When only 50 mol% of **L6** was used for pentyl- and hexylamine, the yields diminished to less than 10%, thus demonstrating the importance of the ligand loading effect for this protocol on difficult substrates.

While our protocol worked well with γ-methylene C–H bonds, reactivity was shut down when we tried to fluorinate γ-methyl C–H bonds using *sec*-butylamine as the model substrate (**3a**). Gratifyingly, **3a** could be fluorinated in the absence of silver additives. Further reaction optimization identified 1-fluoro 2,4,6-methylpyridinium tetrafluoroborate and 3-bromo-5-trifluoromethyl-2-pyridone as the best [F^+] reagents and pyridone as the ligand for this reaction. With the best conditions established, we next investigated the amine scope of this methyl fluorination. Simple aliphatic amines with and without α-substituents could be fluorinated in 23–48% yields (**4a-c**). When 3-aminohexane was employed, fluorination proceeded exclusively at the γ-methyl position, leaving the γ−methylene position untouched (**4d**). For 3-aminopentane, di-fluorinated product was isolated as the major product. To our surprise, the minor mono fluorinated product had gone through a second C−H oxidation reaction (presumably from trace H_2O in the solvent), thus providing access to 1-fluoro-5-hydroxy containing amines in a one-pot fashion. Oxygen containing amines could also be fluorinated with moderate yields (**4f-h**). The reaction with *trans*-2-methylcyclohexylamine proceeded with 16% isolated yield, while the *cis* isomer was unreactive.

Since the presence of Ag salts is crucial for methylene fluorination, while the absence of Ag is important for methyl fluorination, the role of silver in both methylene and methyl fluorinations was investigated using computational tools. In our computational studies, we have used 2-aminopentane for methylene fluorination and *sec*-butylamine for methyl

fluorination. Mechanistic investigations of this catalytic transformation were carried out using the density functional theory computations at the SMD(solvent)/B3LYP-D3/6–31G**,SDD(Pd,Ag) level of theory.[11] All key intermediates and transition states involved in the catalytic cycle were optimized in the condensed phase using 2-methyl-1-propanol as the solvent continuum. HFIP was considered as a coordinating solvent throughout the catalytic cycle. The formation of the imine from the corresponding aldehyde (**TDG1**) and alkyl amine was found to be more favored in the presence of one molecule of HFIP.[12] The three major mechanistic steps including (a) C−H activation, (b) oxidative addition to the N−F bond, and (c) reductive elimination leading to the formation of the desired C−F bond, are shown in the following catalytic cycle (Scheme 4).

The catalytic cycle starts with the coordination of imine (formed between the amine substrate and **TDG1** (**1**)) with Pd to generate the catalyst-substrate complex **2**, which facilitates subsequent γ-C(sp^3)−H activation step. Among the various internal bases considered for the C−H cleavage step, computational studies revealed that **TDG1** behaving as a pyridone ligand was most preferred (see Supporting Information for higher energy alternatives).[9c,13] The relative Gibbs free energy of the C−H cleavage transition state **[2–3]‡** was found to be 4.5 kcal/mol (Figure 1). The resulting palladacycle intermediate **3** undergoes ligand displacement with **L6** and coordination with Ag and the fluorination agent (NFSI) to provide the low energy intermediate **4**. Oxidative addition of Pd(II) to the N−F bond via **[4–5]‡** generates the Pd(IV) intermediate **5**.[13] Importantly, computational studies revealed that the oxidative addition step involves a pyridone assisted bimetallic transition state, thus uncovering a potential new role of the pyridone ligand in addition to its ability to behave as an acetate surrogate for the C−H cleavage step. The relative Gibbs free energy of **[4–5]‡** was found to be −15.2 kcal/mol (Figure 1). An axial-equatorial interchange of ligands around the Pd can now help convert intermediate **5** to **6** wherein F moves from axial to the equatorial position, while the Pd-alkyl bond moves from equatorial to the axial position. Such a geometric change sets the stage for the ensuing reductive elimination via **[6–7]‡** to furnish the fluorinated product **7**. The relative Gibbs free energy of **[6–7]‡** was found to be −57.4 kcal/mol.

An analysis of the Gibbs free energy profile for the catalytic cycle (Figure 1) was then undertaken. Application of the *energetic span model* revealed that the most favorable pathway proceeds through a Pd(II)/Pd(IV) redox cycle.[14] Pd-alkyl intermediate **4** was identified as the turn-over determining intermediate (TDI) and the oxidative addition transition state **[4–5]‡** as the turn-over determining transition state (TDTS), with an energetic span (δE) of 8.8 kcal/mol. Interestingly, a δE of 8.7 kcal/mol is also likely, wherein the catalyst-substrate complex **2** serves as the TDI and the C−H activation transition state **[2–3]‡[dummy_similar]** as the TDTS. The alternative pathways, other than that shown in Scheme 4, are found to exhibit higher δE.[15] More importantly, the impact of silver is not uniform across different catalytic steps. In some of the steps, participation of silver salt is beneficial while in others it leads to higher energy (see Section II.4 in the Supporting Information for more details). The major role of silver is found to be in the reductive elimination step as evident from the predicted lowering of the δE from 16.7 kcal/mol (devoid of silver) to 8.8 kcal/mol (with silver in the reductive elimination step). In addition to the lower energy

Pd(II)/Pd(IV) pathway described above, we have also examined a possible alternative involving a Pd(II)/Pd(II) redox couple via a direct F^+ transfer step.[16] However, computational data does not support the likelihood of this scenario (see Supporting Information).

After examining the mechanistic intricacies in methylene fluorination, we next turned our attention to methyl fluorination since the reaction proceeded without Ag salts. It should be noted that the fluorinating agent used here (N-fluoro-2,4,6- trimethylpyridinium tetrafluoroborate) is different from the one for methylene fluorination. To afford a direct comparison, energetics of methyl fluorination was evaluated both in the presence and absence of silver salt additives. The major mechanistic steps remained the same with that of the methylene fluorination. The full Gibbs free energy profile for the most favorable pathway via a Pd(II)/Pd(IV) redox cycle is provided in Figure 2.[17] Intermediate **3** was identified as the TDI and the oxidative addition transition state **[4–5]‡** as the TDTS, with a δE of 15.4 kcal/mol. Explicit inclusion of Ag salts led to a modest increase in δE to 17.2 kcal/mol. In contrast to methylene fluorination where the presence of Ag reduced the δE, Ag participation for methyl fluorination increased the δE. These results are consistent with experimental data and suggest that a pyridone assisted bimetallic oxidative addition is favored for methylene fluorination while a direct oxidative addition is more preferred for methyl fluorination. Akin to the methylene fluorination discussed earlier, the Pd(II)/Pd(II) redox cycle was also found to be unfavorable for methyl fluorination and inconsistent with our experimental data (see Supporting Information).[18]

3. Conclusion

In summary, we have developed the first γ-C(sp^3)–H fluorination of aliphatic free amines using 2-hydroxynicotinaldehyde as the transient directing group. This reaction features a wide amine scope and good functional group tolerance. Through two different reaction conditions (with and without silver additives), free aliphatic amines could be selectively fluorinated at both the γ-methyl and methylene positions. Computational studies revealed that the reaction proceeds via a Pd(II)/(IV) catalytic cycle with the oxidative addition step likely being the TDTS for both methylene and methyl fluorinations. In the case of methylene fluorination, Ag plays a vital role in the reductive elimination step leading to a lowering of the energetic span. In contrast, the explicit participation of Ag increases the energetic span for methyl fluorination, which is consistent with the experimental data Importantly, computational studies have identified a pyridone assisted bimetallic transition state for the oxidative addition step in methylene fluorination, thus uncovering a potential new role of the pyridone ligand in addition to being an acetate surrogate. Efforts to design new pyridone ligands and develop γ-C(sp^3)−H oxidation reactions of alkyl amines are currently underway in light of these findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements.

We gratefully acknowledge The Scripps Research Institute, the NIH (NIGMS 2R01 GM084019), and Bristol-Myers Squibb for financial support. Y-Q. C. thanks the NSF Graduate Research Fellowships for financial support. Dr. Jason Chen and Brittany Sanchez from the Scripps Automated Synthesis Center are acknowledged for guidance on analytical methods and DoE screening. Generous computing facility from IIT Bombay *SpaceTime2* supercomputer is acknowledged.

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12. Inclusion of two HFIP molecules resulted in a higher energy pathway. See Section I in the Supporting Information for additional details on the formation of imine.

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15. See Section II.4 for Gibbs free energy profiles of methylene γ-fluorination in the presence and absence of silver additive.

16. See Section II.5 in the Supporting Information for additional mechanistic possibilities.

17. See Section III.1-III.4 in the Supporting Information for additional details on the possibilities of C −H activation oxidative addition, reductive elimination and Gibbs free energy profile of methyl γ-fluorination in the presence of silver additive.

18. See Section III.5 in the Supporting Information for additional mechanistic possibilities.

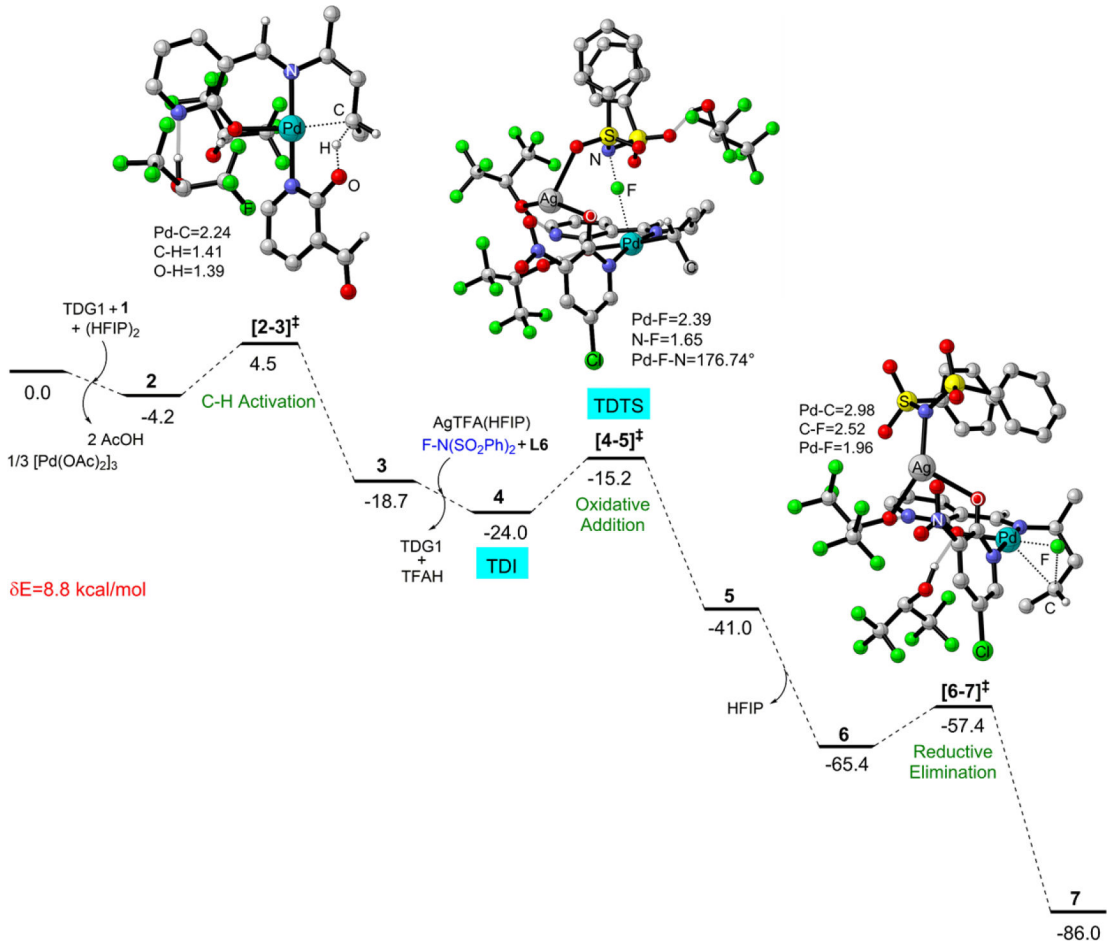


Figure 1.

Gibbs free energy profile (kcal/mol) of methylene γ-fluorination. Optimized geometries of important transition states are shown. Distances are in Å. Only selected hydrogen atoms are shown for improved clarity.

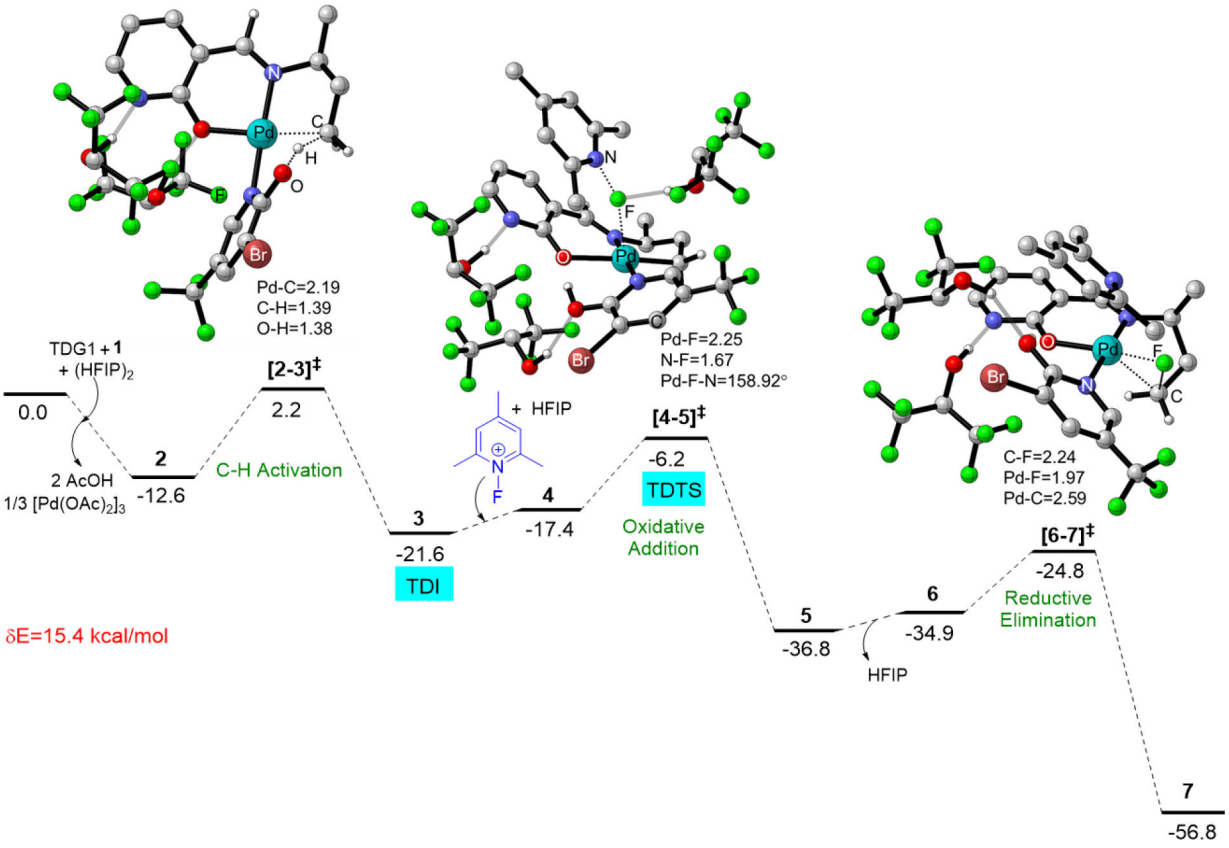
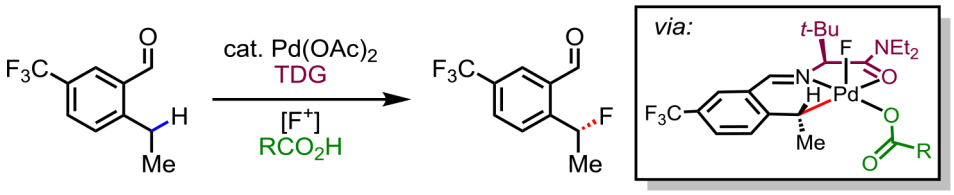
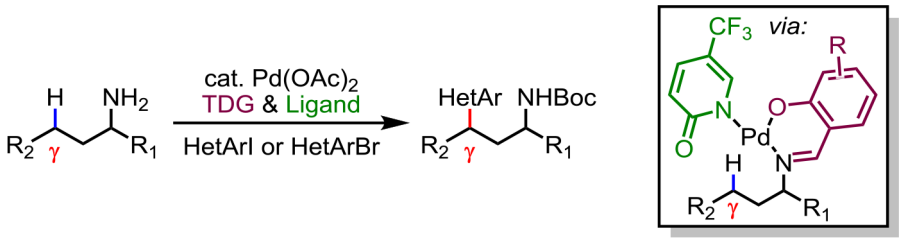


Figure 2.

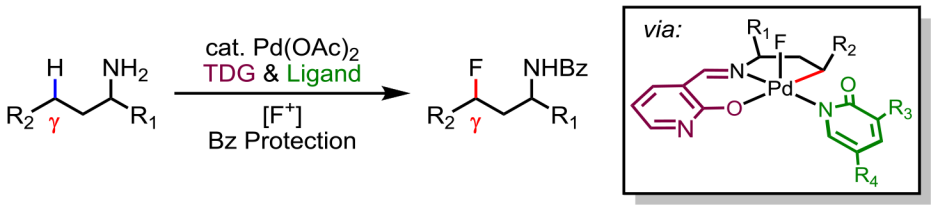
Gibbs free energy profile (kcal/mol) of methyl γ-fluorination. Optimized geometries of important transition states are shown. Distances are in Å. Only selected hydrogen atoms are shown for improved clarity.



Scheme 1:
TDG Enabled Fluorination of 2-Alkylbenzaldehydes

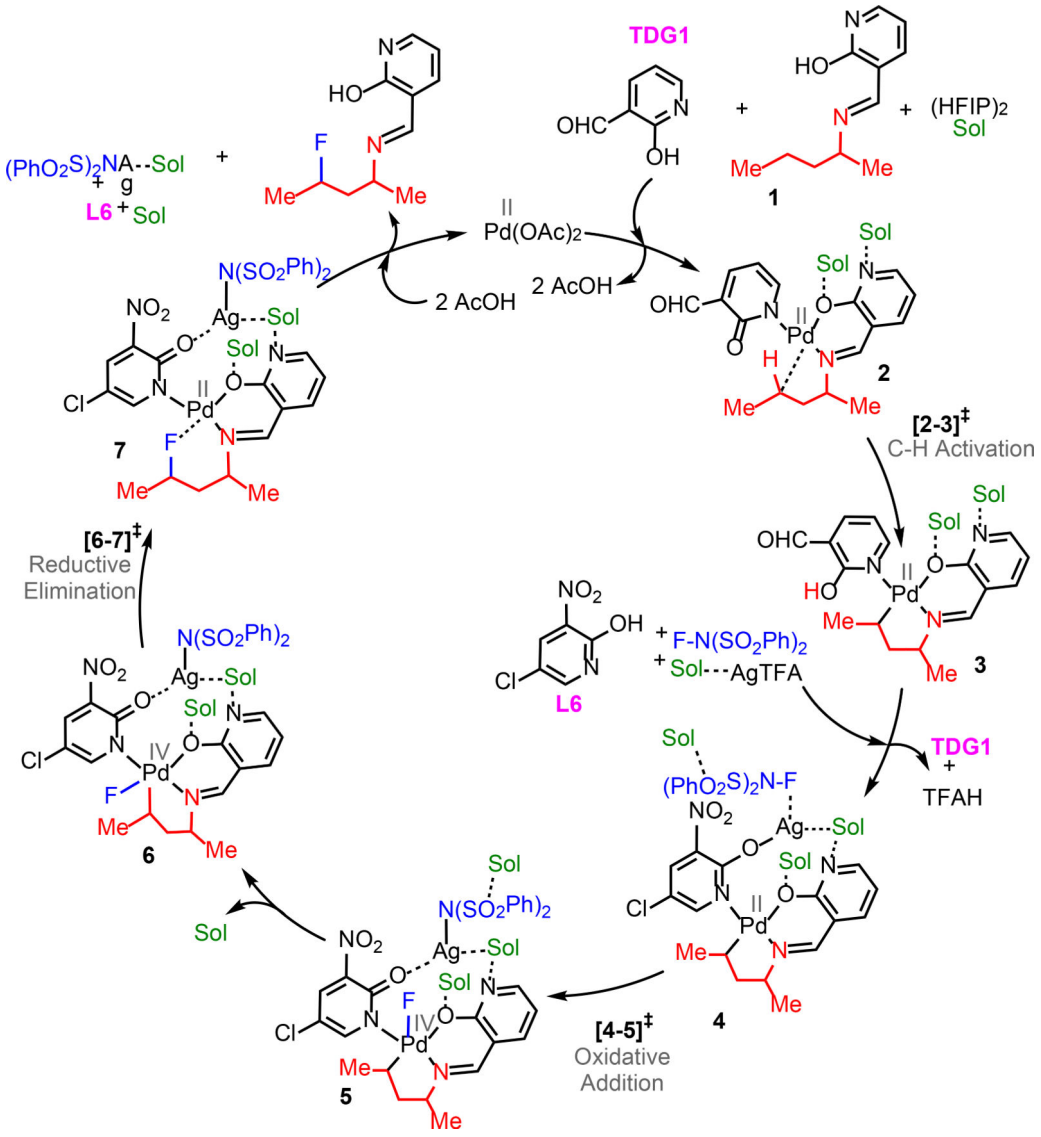


Scheme 2:
Pyridone Enabled γ-C(sp^3)–H Heteroarylation of Free Amines



Scheme 3:

This Work: Pyridone Assisted γ-C(sp^3)–H Fluorination of Free Amines

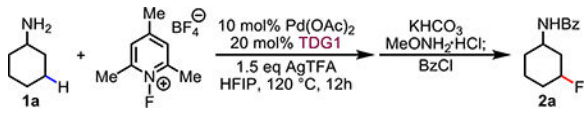


Scheme 4.

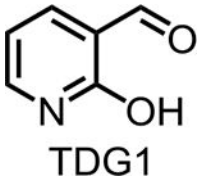
Catalytic Cycle for Pd-catalyzed γ-C(sp^3)−H Fluorination of 2-Aminopentane

Table 1.

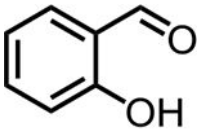
Initial Studies of γ-C(sp^3)–H Fluorination of Amines[a,b]



Entry	Deviations from the above reaction conditions	Yield (%)
1	–	17
2	20 mol% TDG2	trace
3	50 mol% TDG1	34
4	1.0 eq TDG1	45
5	1.2 eq TDG1, 3.0 eq NFSI instead of N-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate, 100 °C	53
6	Entry 5 + 19:1 (HFIP:HOAc)	58
7	Entry 5 + 1:1 (HFIP:PhCl)	**62**



TDG1



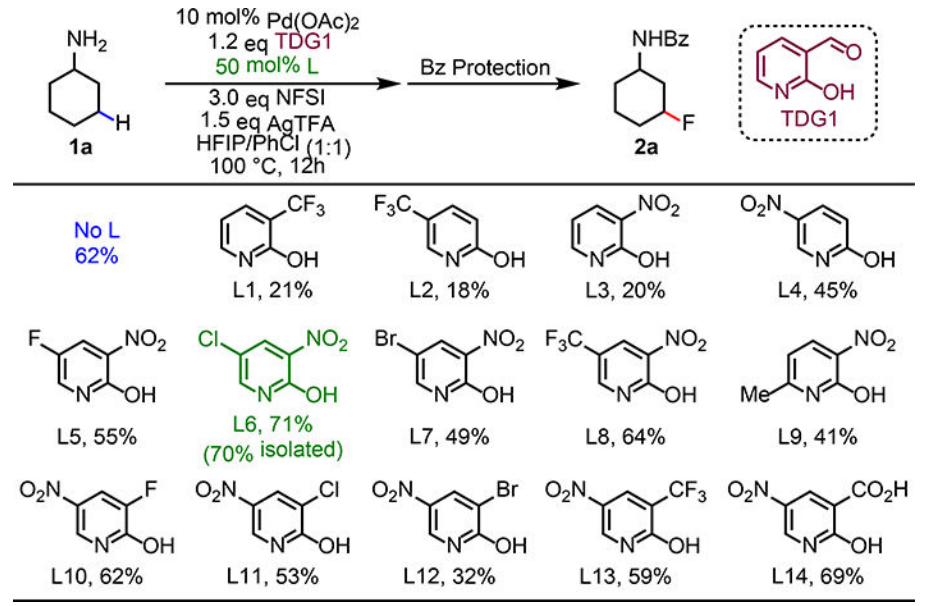
TDG2

[a]Experiments were performed with substrate **1a** (0.10 mmol), $Pd(OAc)_2$ (10 mol%), **TDG1** (0.12 mmol), N-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate (0.15 mmol), AgTFA (0.15 mmol), HFIP (1.0 mL), 120 °C, 12 h.

[b]Yields were determined by ^{1}H NMR analysis of the crude product using CH_2Br_2 as the internal standard.

Table 2.

Ligand Evaluation for γ-Methylene-C(sp^3)–H Fluorination of Alkyl Amines[a,b]

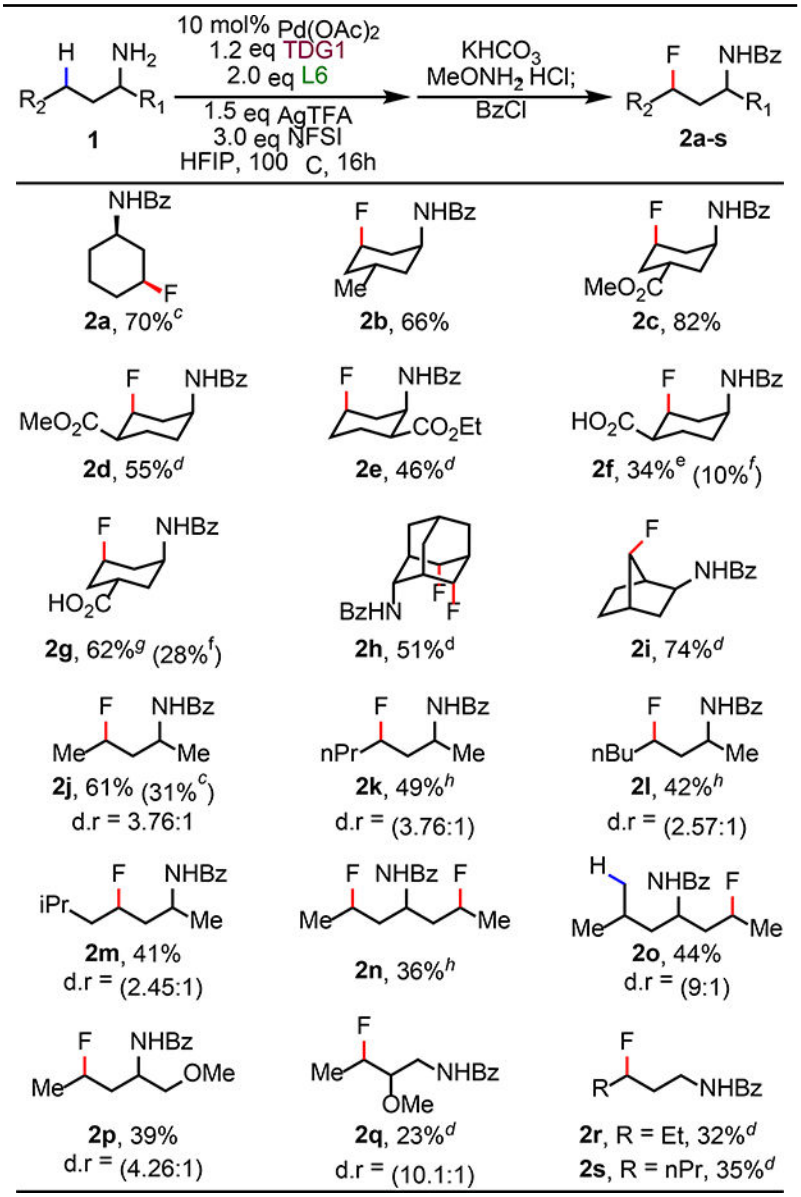


[a]Experiments were performed with substrate **1a** (0.10 mmol), $Pd(OAc)_2$ (10 mol%), **TDG1** (0.12 mmol), NFSI (0.30 mmol), AgTFA (0.15 mmol), HFIP:PhCl (1:1, 1.0 mL), 70 °C, 16 h.

[b]Yields were determined by ^1H NMR analysis of the crude product using CH_2Br_2 as the internal standard.

Table 3.

Scope of Alkyl Amines for γ-Methylene-C(sp^3)–H Fluorination[a,b]



[a]Experiments were performed with substrate **1a** (0.10 mmol), Pd(OAc)$_2$ (0.01 mmol), **TDG1** (0.12 mmol), **L6** (0.20 mmol), NFSI (0.30 mmol), AgTFA (0.15 mmol), HFIP (1.0 mL), 100 °C, 16 h.

[b]Isolated yields.

[c]Reaction performed with 0.5 equiv. of **L6** in a mixture of 1:1 HFIP/PhCl.

[d]Reaction performed at 120 °C.

[e]Reaction ran for 48 h.

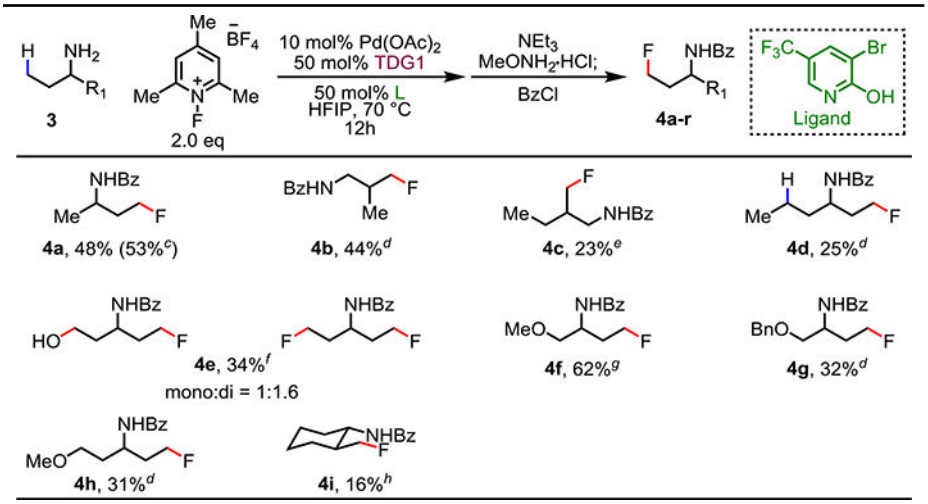
[f]Reaction performed with 0.5 equiv. **L6**.

[g]Reaction performed at 120 °C for 48 h.

[h]Reaction performed at 70 °C.

Table 4.

Scope of Alkyl Amines for Methyl γ-C(sp^3)–H Fluorination[a,b]



[a]Experiments were performed with substrate **1a** (0.10 mmol), $Pd(OAc)_2$ (0.01 mmol), **TDG1** (0.05 mmol), **Ligand** (0.05 mmol), 1-fluoro 2,4,6-methylpyridinium tetrafluoroborate (0.20 mmol), HFIP (1.0 mL), 70 °C, 16 h.

[b]Isolated yields.

[c]Yield determined by ^{1}H NMR analysis of the crude product using 1,1,2,2-tetrachloroethane as an internal standard.

[d]Reaction performed with 75 mol% **TDG1** at 90 °C.

[e]Reaction performed at 90 °C.

[f]Reaction performed with 75 mol% **TDG1**.

[g]Reaction performed with 75 mol% **TDG1** at 100 °C.

[h]Reaction performed at 90 °C.