Tetrahedron 71 (2015) 5932–5938

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

# Rhodium-catalyzed benzylic fluorination of trichloroacetimidates

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ARTICLE INFO

*Article history:*
Received 25 March 2015
Received in revised form 19 April 2015
Accepted 20 April 2015
Available online 30 April 2015

This manuscript is dedicated to Professor Barry Trost on the occasion of his receiving the 2015 Tetrahedron Award

*Keywords:*
Fluorination
Trichloroacetimidate
Rhodium
Benzylic Fluorides
Catalysis

ABSTRACT

Benzylic fluorides were synthesized via rhodium-catalyzed nucleophilic fluorination of benzylic trichloroacetimidates. A variety of naphthyl, phenyl, and pyridinyl trichloroacetimidates were fluorinated with $Et_3N{\cdot}3HF$ reagent to provide fluorine-containing compounds in moderate to high yields under mild and operationally simple conditions. Preliminary mechanistic studies suggest that benzylic fluorination of trichloroacetimidate substrates are more likely to proceed through a discrete benzylic cation, generated by rhodium catalyst.

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## 1. Introduction

Organic compounds containing carbon-fluoride bonds are common building blocks for the synthesis of pharmaceutical drug candidates and can be used as radiotracers for medical imaging.[1] The introduction of such C–F bonds can lead to the improved bioavailability, and in turn the efficacy, of a substrate over its non-fluorinated parent compound by affecting a wide variety of properties including p$K_a$, lipophilicity, and binding affinity.[1,2] In particular, benzylic fluorides have been the targets of much research due to their presence in a number of biologically active pharmaceuticals and radiotracers (Fig. 1).[3–5] For example, benzylic fluorides are motifs present in important pharmaceutical targets such as cholesteryl ester transfer protein (CETP) inhibitor **1**,[3] *N*-methyl-D-aspartate receptor antagonist **2**,[4] and [$^{18}$F]benzylic fluoride-containing COX inhibitor **3**.[5a]

Traditionally, benzylic fluorides are prepared by the exchange of halides with tetrabutylammonium fluoride and displacement of benzylic hydroxyl groups with (diethylamino)sulfur trifluoride.[2a] Recent reported efforts toward benzylic fluorination have also included metal catalysis involving palladium,[6] platinum,[7] iron,[8] and manganese.[9] Transition-metal-free benzylic fluorination has been reported through the utilization of Lewis-acid-catalyzed epoxide opening[10] photochemical C–H activation,[11] and several other methods.[12] Synthetic transformations that utilize rapid, late-stage benzylic fluorination procedures may be suitable for the synthesis of radiotracers by introducing radioactive fluorine-18 into the benzylic position of bioactive target molecules. Benzylic $^{18}$F-fluorination[13] utilizing Mn-salen catalysts has been recently reported by Groves[5] and Carroll.[14]

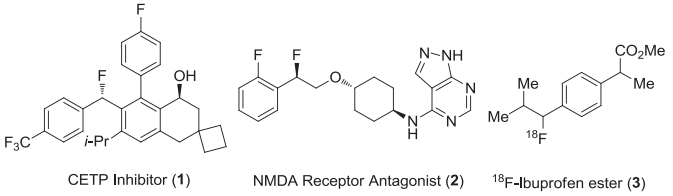


**Fig. 1.** Biologically relevant compounds and PET radiotracers containing benzylic fluoride functionality.

Recently, our group has reported an iridium-catalyzed allylic substitution of trichloroacetimidates and a rhodium-catalyzed selective opening of vinyl epoxides with $Et_3N{\cdot}3HF$ to produce the desired allylic fluorides and fluorohydrins, respectively, in good yields and with excellent branched selectivity.[15,16] The efficient and rapid fluorination of that work inspired us to hypothesize that the

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http://dx.doi.org/10.1016/j.tet.2015.04.066
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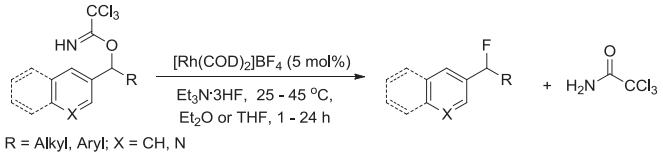
combination of trichloroacetimidates with $Et_3N{\cdot}3HF$ reagent, mediated by transition-metal catalysis, could potentially allow rapid and efficient incorporation of fluorine ion into the benzylic position of organic compounds. Herein, we report an effective methodology for the synthesis of benzylic fluorides via rhodium-catalyzed nucleophilic fluorination of trichloroacetimidates. A wide variety of naphthyl, phenyl, and pyridinyl substrates were fluorinated with $Et_3N{\cdot}3HF$ to provide the corresponding fluorine-containing compounds in moderate to high yields under mild and operationally simple conditions (Scheme 1).



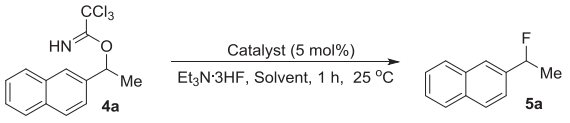

**Scheme 1.** Rhodium-catalyzed benzylic fluorination reaction.

## 2. Results and discussion

### 2.1. Optimization studies

We hypothesized that benzylic trichloroacetimidates would be suitable electrophiles for fluorination reactions because C–O bonds are likely to undergo heterolytic cleavage and generate $\eta^3$-benzyl-metal complexes.[17] The well-documented literature of metal-catalyzed nucleophilic substitution reactions of benzylic electrophiles is consistent with this hypothesis.[17] We first tested our hypothesis with naphthylic trichloroacetimidate **4a** (Table 1) because the extended aromaticity of the naphthyl ring is likely to stabilize an $\eta^3$-benzyl-metal intermediate.[18] At the outset of our studies, we investigated the reaction of **4a** with $Et_3N{\cdot}3HF$ under both iridium- and rhodium-catalyzed conditions.[15] We observed low conversion to benzylic fluoride **5a** (Table 1, entry 1). The by-product trichloroacetamide was also observed in the reaction by $^1H$ NMR analysis. Switching to the rhodium dimer catalyst $[RhCl(COD)]_2$ (entry 2) further improved conversion (33%→55%). We hypothesized that utilization of a more reactive cationic rhodium catalyst could further accelerate the rate of fluorination.[16] As expected, reaction of imidate **4a** with 5 mol % of $[Rh(COD)_2]BF_4$ (entry 3) reached 100% conversion in 1 h.

**Table 1**
Optimization of fluorination of benzylic trichloroacetimidates[a]




| Entry | Catalyst | Solvent | NMR yield[b] (%) |
|---|---|---|---|
| 1 | $[IrCl(COD)]_2$ | $Et_2O$ | 33 |
| 2 | $[RhCl(COD)]_2$ | $Et_2O$ | 55 |
| *3* | *$[Rh(COD)_2]BF_4$* | *$Et_2O$* | *100* |
| 4 | $[Rh(NBD)_2]BF_4$ | $Et_2O$ | 68 |
| 5 | $[Rh(COD)(dppb)]BF_4$ | $Et_2O$ | 61 |
| 6 | $[Rh(COD)_2]OTf$ | $Et_2O$ | 62 |
| 7 | $[Rh(COD)_2]BF_4$ | THF | 61 |
| 8 | $[Rh(COD)_2]BF_4$ | MTBE | 43 |
| 9 | $[Rh(COD)_2]BF_4$ | Dioxane | 92 |
| 10 | $[Rh(COD)_2]BF_4$ | Toluene | 50 |
| 11 | None | $Et_2O$ | 23 |
| 12 | $BF_3{\cdot}OEt_2$ | $Et_2O$ | 67 |
| 13 | CSA | $Et_2O$ | 74 |

[a] All benzylic fluorination reactions were conducted at 0.3 M with 3 equiv of $Et_3N{\cdot}3HF$.
[b] Determined by $^{19}F$ NMR analysis using $PhCF_3$ as an internal standard.

We continued our optimization studies by varying the nature of the ligands (Table 1, entries 4 and 5) on rhodium catalysts and found that these rhodium catalysts are not as effective as was $[Rh(COD)_2]BF_4$ (entry 3) to activate trichloroacetimidate **4a**. We hypothesized that this is likely due to the effect of the ligand bite angle that imparts both steric and electronic influence on metal catalysts.[19] We also examined the fluorination of **4a** with 5 mol % of $[Rh(COD)_2]OTf$ (entry 6), and only 62% NMR conversion of naphthylic fluoride **5a** was observed in the reaction. This experiment illustrated the effect of counterions on the reactivity of the fluorination reaction (entry 3 vs entry 6). Rhodium with a more strongly coordinating counterion ($^-OTf$, entry 6) gave the fluorine-containing product with lower conversion than rhodium with a weaker coordinating counterion ($BF_4^-$, entry 3).[20]

Next, we turned our attention to investigating the effects of solvent (Table 1, entries 7–10). While dioxane (entry 9) was also an effective solvent for the synthesis of benzylic fluoride **5a** with slightly lower NMR yield (92%) than $Et_2O$, other solvents were not suitable. We have previously examined the reaction of allylic trichloroacetimidates and vinyl epoxides with a series of fluoride reagents (CsF, AgF, TBAT, KF, and pyridine·HF)[15,16] and found that these fluoride sources proved ineffective in comparison to $Et_3N{\cdot}3HF$ under both iridium- and rhodium-catalyzed conditions. As a result, we did not attempt to investigate these fluoride ions with naphthylic substrate **4a**.

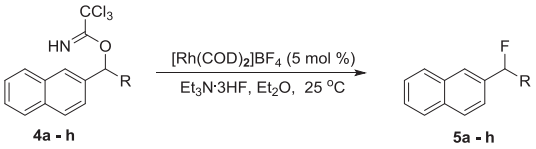
A control experiment was then conducted in the absence of the rhodium catalyst (Table 1, entry 11), and the fluorination reaction was stopped at 1 h in order to compare to the optimized rhodium-catalyzed conditions (entry 3); only 23% NMR conversion was observed under the identical conditions absent the catalyst (entry 11). In a separate reaction, the catalyst-free reaction only reached completion after 24 h. To determine if Lewis acid or Brønsted acid behavior alone was responsible for the reactivity of the rhodium species, other control experiments were performed with $BF_3{\cdot}OEt_2$ (entry 12) and camphorsulfonic acid (CSA, entry 13), commonly used reagents to activate trichloroacetimidates. The desired naphthylic fluoride **5a** was observed with moderate conversion (67–74%). While both Lewis and Brønsted acids did not provide superior results to $[Rh(COD)_2]BF_4$, these data offered mechanistic insight into the reaction (vide infra).

### 2.2. Substrate scope

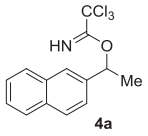
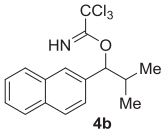
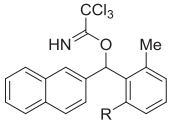
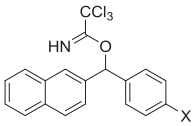
With the optimized catalytic protocol in hand, we next sought to examine the scope of the fluorination (Table 2). We designed a number of naphthyl substituted trichloroacetimidate substrates **4a–g** bearing varying electronic properties and degrees of steric congestion. All naphthlyic fluorides were monitored by $^{19}F$ NMR spectroscopy for conversion and subsequently isolated for full characterization and yield determination. For example, although quantitative conversion was seen via $^{19}F$ NMR analysis (entry 1), the isolated yield of the desired fluoride product **5a** was only 84% (entry 1) due to its volatility.[24] The fluorination was slightly slower with bulky substrate **4b** (entry 2), yet the isolated yield of benzylic fluoride **5b** (entry 2) was not significantly affected (88%). In addition, steric bulk at the *ortho*-position of aryl groups was feasible under rhodium conditions (entries 3 and 4), and the fluorination proceeded smoothly to produce benzylic fluorides **5c** and **5d** in 68–73% yield.

To further highlight the synthetic advantage of our method, we next focused on the synthesis of 1,1-diaryl fluorides **5e–h** (Table 2, entries 5–8), where the arenes have similar steric properties and are only differentiated by the *para*-substituents. Although the fluorination reactions reached completion after 4–8 h, electron-withdrawing groups on the aryl rings of imidates

**Table 2**
Fluorination of naphthylic trichloroacetimidates[a]




4a - h 5a - h

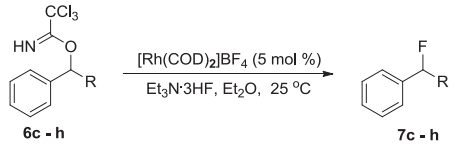
| Entry | Imidate | Time (h) | NMR yield[b] (%) | Isolated yield[c] (%) |
|---|---|---|---|---|
| 1 |  4a | 1 | **5a** (100) | **5a** (84) |
| 2 |  4b | 4 | **5b** (85) | **5b** (88) |
| |  | | | |
| 3 | **4c** (R=H) | 1 | **5c** (95) | **5c** (68) |
| 4 | **4d** (R=Me) | 1 | **5d** (95) | **5d** (73) |
| |  | | | |
| 5 | **4e** (X=H) | 4 | **5e** (76) | **5e** (78) |
| 6 | **4f** (X=F) | 8 | **5f** (87) | **5f** (76) |
| 7 | **4g** (X=Cl) | 4 | **5g** (95) | **5g** (89) |
| 8 | **4h** (X=OMe) | 4 | **5h** (98) | **5h** ND[d] |

[a] All reactions were conducted at 0.3 M with 3 equiv of $Et_3N{\cdot}3HF$.
[b] Determined by $^{19}F$ NMR using $PhCF_3$ as an internal standard.
[c] Isolated yield determined after column chromatography.
[d] ND=not determined due to its rapid decomposition after isolation.

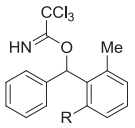
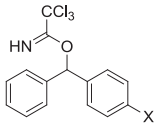
were well-tolerated (76–89%, entries 6 and 7). The aryl chloride moiety of the fluoride product **5g** (entry 7) provides functionality for further chemical modification. In contrast, a strong electron-donating *para*-OMe group demonstrated high transformation by $^{19}F$ NMR analysis yet decomposed upon purification (entry 8). This was most likely caused by elimination of fluoride due to the electron-donating properties of the aromatic ring. The leaving group ability of fluoride has been recently demonstrated by Gouverneur and co-workers in palladium-catalyzed substitution and cross-coupling of benzylic fluorides with a wide variety of nucleophiles.[21] Nevertheless, the crude product **5h** possessing an electronic-rich *para*-OMe group was confirmed by $^1H$ and $^{19}F$ NMR analyses.

After successfully fluorinating a range of naphthyl-substituted compounds, we tested our method on the less extended aromatic substrates to determine the generality of the fluorination (Table 3). Due to attenuation of aromaticity upon π-benzyl-metal or cationic formation, mono-cyclic benzylic trichloroacetimidates **6c**–**h** (Table 3) are expected to be challenging substrates. Gratifyingly, the desired benzyl fluoride products showed similar yields to their naphthyl counterparts except for the biphenyl-substituted fluoride **7e** (entry 3); its isolated yield was only 36%. As observed with the naphthyl fluoride **5h** (Table 2, entry 8), the desired phenyl product **7h** (Table 3, entry 6) was not isolated due to decomposition.

**Table 3**
Reactivity of mono-cyclic benzylic trichloroacetimidates[a]



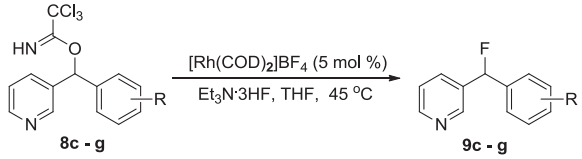

6c - h 7c - h

| Entry | Imidate | Time (h) | NMR yield[b] (%) | Isolated yield[c] (%) |
|---|---|---|---|---|
| |  | | | |
| 1 | **6c** (R=H) | 4 | **7c** (85) | **7c** (74) |
| 2 | **6d** (R=Me) | 4 | **7d** (100) | **7d** (83) |
| |  | | | |
| 3 | **6e** (X=H) | 2 | **7e** (84) | **7e** (36) |
| 4 | **6f** (X=F) | 8 | **7f** (95) | **7f** (73) |
| 5 | **6g** (X=Cl) | 8 | **7g** (97) | **7g** (50) |
| 6 | **6h** (X=OMe) | 4 | **7h** (98) | **7h** ND[d] |

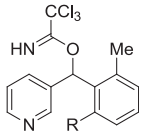
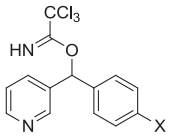
[a] All reactions were conducted at 0.3 M with 3 equiv of $Et_3N{\cdot}3HF$.
[b] Determined by $^{19}F$ NMR using $PhCF_3$ as an internal standard.
[c] Isolated yield determined after column chromatography.
[d] ND=not determined due to its rapid decomposition after isolation.

*N*-Heterocyclic trichloroacetimidates (Table 4) are another challenging class of substrates that we envisioned could undergo fluorination reactions. *N*-Heterocyclic motifs are often found in a variety of bioactive molecules and thus represent important targets.[22] Our original fluorination conditions were not suitable for these *N*-heterocyclic substrates. We also investigated the fluorination of pyridinyl substrates with $BF_3{\cdot}OEt_2$ and CSA, but only poor

**Table 4**
Reactivity of *N*-heterocyclic trichloroacetimidates[a]




8c - g 9c - g

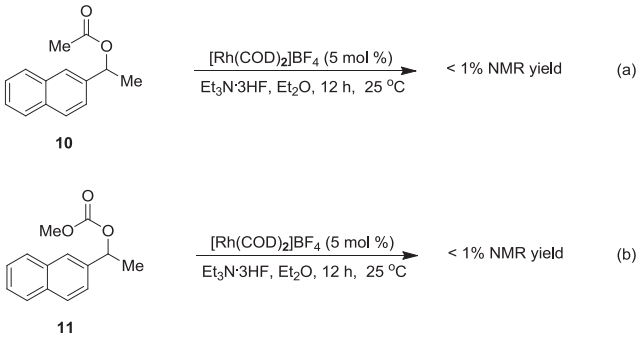
| Entry | Imidate | Time (h) | NMR yield[b] (%) | Isolated yield[c] (%) |
|---|---|---|---|---|
| |  | | | |
| 1 | **8c** (R=H) | 24 | **9c** (83) | **9c** (78) |
| 2 | **8d** (R=Me) | 24 | **9d** (74) | **9d** (69) |
| |  | | | |
| 3 | **8e** (R=H) | 24 | **9e** (77) | **9e** (71) |
| 4 | **8f** (R=F) | 24 | **9f** (70) | **9f** (48) |
| 5 | **8g** (R=Cl) | 24 | **9g** (39) | **9g** (39) |

[a] All reactions were conducted at 0.3 M with 3 equiv of $Et_3N{\cdot}3HF$.
[b] Determined by $^{19}F$ NMR using $PhCF_3$ as an internal standard.
[c] Isolated yield determined after column chromatography.

conversion was observed in the reaction. Ultimately, it was found that the pyridinyl imidates **8c**–**g** could be fluorinated under rhodium-catalyzed conditions, but required longer reaction times (24 h) and higher temperatures (45 °C). Nevertheless, the desired fluoride products **9c**–**g** (Table 4) were isolated with comparable yields to the phenyl and naphthyl counterparts.[24] We hypothesize that coordination of rhodium to the pyridine nitrogen slows down the rate of fluorination.

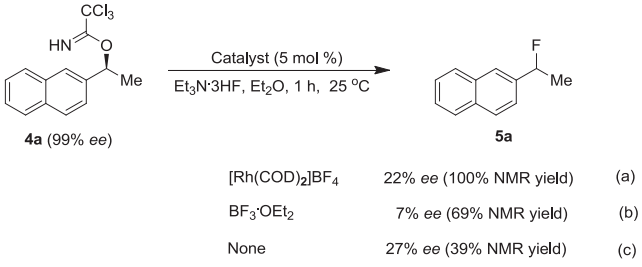
### 2.3. Preliminary mechanistic study

To evaluate the unique reactivity and efficiency of benzylic trichloroacetimidate, both naphthylic acetate **10** and carbonate **11** (Scheme 2) were subjected to our fluorination conditions. Less than 1% conversion was observed for both substrates after 12 h, suggesting that the trichloroacetimidate group is much more reactive than both the acetate and carbonate groups.



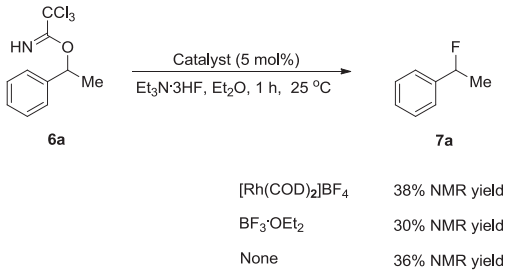

**Scheme 2.** Fluorination of naphthylic acetate and carbonate.

To elucidate the mechanism of the benzylic fluorination reactions, enantiopure trichloroacetimidate **4a** (99% ee Scheme 3) was synthesized from commercially available enantiopure alcohol. When enantioenriched substrate **4a** was exposed to our catalytic conditions, the fluorinated product **5a** was isolated with significant loss of enantiomeric excess (Scheme 3a). This result suggests that the reaction does not go through a concerted $S_N2$ mechanism, but may involve a discrete benzylic cation through, which complete racemization would be observed. However, an alternative reaction pathway that proceeds through an $\eta^3$-benzyl-rhodium intermediate,[17,18,23] could also be likely to take place. To distinguish between the two reaction pathways, fluorination studies conducted with $BF_3 \cdot OEt_2$ (Scheme 3b), and the fluoride product **5a** was observed in 69% NMR yield with a complete racemization (7% ee). This result suggests that the fluorination is likely to involve a discrete benzylic cation intermediate. Under the catalyst-free conditions, the reaction of trichloroacetimidate **4a** with $Et_3N \cdot 3HF$ resulted in 39% NMR conversion of **5a** with 27% ee (Scheme 3c), indicating that the fluorinating reagent itself could be acidic enough to promote the formation of a benzylic cation.




**Scheme 3.** Fluorination of enantiopure naphthylic trichloroacetimidate.

To further support the cationic intermediate notion, another series of control experiments were performed with mono-cyclic benzylic trichloroacetimidate substrate **6a** (Scheme 4). If the fluorination does go through a benzylic cation intermediate, one would expect to observe similar conversions under both Lewis acid and rhodium conditions. As illustrated in Scheme 4, both $[Rh(COD)_2]BF_4$ and $BF_3 \cdot OEt_2$ provided benzylic fluoride **7a** with almost identical conversion.




**Scheme 4.** Fluorination of mono-cyclic benzylic trichloroacetimidate.

Overall, the above experiments allow us to gain insight into the possible mechanism of the rhodium-catalyzed fluorination of benzylic trichloroacetimdiates. It appears that the fluorination of both naphthyl and phenyl trichloroacetimidate starting materials is more likely to proceed through a benzylic intermediate as the operative reaction pathway. The differences in naphthyl and phenyl substrate conversions suggest that the formation of the benzylic intermediate would completely break the aromaticity of the phenyl ring but not the naphthyl ring due to the extended conjugation of the naphthyl system.

## 3. Conclusion

In summary, we have developed a new methodology for the efficient synthesis of benzylic fluorides possessing a wide variety of mono-cyclic aromatic, naphthlyic, and *N*-heterocyclic rings in moderate to good yields under mild and operationally simple conditions. This fluorination methodology relies on the ability of the trichloroacetimidate to act as the efficient leaving group in the presence of trimethylamine trihydrofluoride and 5 mol % of $[Rh(COD)_2]BF_4$ catalyst. The use of the rhodium catalyst allows to distinguish between the two possible mechanisms (the discrete cationic intermediate vs the $\eta^3$-benzyl-rhodium complex) of the benzylic fluorination of trichloroacetimidates. Initial mechanistic studies suggest that the fluorination is more likely to proceed through a discrete benzylic cation intermediate, generated by rhodium acting as a Lewis acid. Overall, this mild, rapid, and operationally simple fluorination methodology provides the foundation for further investigations of the utility of benzylic trichloroacetimidate substrates in radiofluorination.[5,14] The use of the rhodium catalyst and/or Brønsted acid[25] to promote the incorporation of radioactive fluorine-18 into benzylic systems of radiotracers for use in PET imaging studies will be reported in due course.

## 4. Experimental

### 4.1. General information

All reactions were performed in oven-dried Schlenk flasks fitted with glass stoppers under positive nitrogen/argon pressure. Organic solutions were concentrated by rotary evaporation below 40 °C at 25 Torr. Analytical thin-layer chromatography (TLC) or $^{19}F$ NMR analysis was routinely used to monitor the progress of the

reactions. TLC was performed using pre-coated glass plates with 230–400 mesh silica gel impregnated with a fluorescent indicator (250 nm). Visualization was accomplished using UV light, potassium permanganate, and/or phosphomolybdic acid. Dry organic solvents were obtained from an SG Waters solvent system utilizing activated alumina columns under argon pressure or purchased from Sigma–Aldrich in Sure/Seal™ bottles. The rhodium and iridium catalysts were handled and transferred to Schlenk flasks within a glovebox under a nitrogen atmosphere. Lewis acid $BF_3{\cdot}OEt_2$ and all chemicals and reagents were obtained from commercial vendors and used without further purification. Flash chromatography was performed on a Teledyne Isco Combi-Flash $R_f$ system utilizing normal phase pre-column cartridges and gold high performance columns. The ees were determined on an Agilent 1200 series HPLC using a Diacel Chiralcel OJ-3 4.6×150 mm column fitted with guard columns with flow rates and mobile phases as indicated. All proton ($^1$H) nuclear magnetic resonance spectra were recorded on a 400 MHz or 500 MHz spectrometer. All carbon ($^{13}$C) nuclear magnetic resonance spectra were recorded on a 101 MHz or 126 MHz NMR spectrometer with proton decoupling. All fluorine ($^{19}$F) nuclear magnetic resonance spectra were recorded on a 282 MHz, 376 MHz or 471 MHz spectrometer with proton decoupling. All deuterated solvents were used as received from Cambridge Isotope Laboratories. $^1$H NMR, $^{13}$C NMR, and $^{19}$F NMR chemical shifts are expressed in parts per million ($\delta$ scale) relative to the chemical shift of residual solvent. Reference peaks for $CDCl_3$ in $^1$H NMR and $^{13}$C NMR spectra were set at 7.26 ppm and 77.16 ppm, respectively. The $^{19}$F NMR reference peak was set at −63 ppm for α,α,α-trifluorotoluene in $CDCl_3$ as an internal standard. Data are presented as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, and br s=broad singlet), integration, and coupling constant in hertz (Hz). High-resolution TOF mass spectrometry utilizing electrospray ionization in positive mode was performed to confirm the identity of the compounds.

### 4.2. General procedure of trichloroacetimidate formation

Trichloroacetonitrile (1.1 mL, 10.8 mmol, 3.0 equiv) was added to a solution of α-methyl-2-naphthalenemethanol (0.62 g, 3.6 mmol, 1.0 equiv) in $CH_2Cl_2$ (7.2 mL) at 0 °C in an oven-dried Schlenk flask. After the solution had been stirring for 5 min, DBU (0.27 mL, 0.25 mmol, 0.5 equiv) was then added dropwise. The resulting mixture was allowed to warm slowly to room temperature overnight. Upon completion, the reaction mixture was concentrated in vacuo and loaded directly onto a RediSep load cartridge containing pre-equilibrated and dried silica. Purification by silica gel flash column chromatography (pre-equilibrated 10 g RediSep column, 10% ethyl acetate/hexane+3% triethylamine) resulted in **4a** (0.93 g, 82%) as a white solid.

### 4.3. General procedure for fluorination of both naphthyl and phenyl substrates

An oven-dried 10 mL Schlenk flask was charged with $[Rh(COD)_2]BF_4$ (4.1 mg, 0.01 mmol, 5 mol %) within glovebox and then $Et_2O$ (0.40 mL) at room temperature. A solution of trichloroacetimidate (**4a**) (63 mg, 0.20 mmol, 1 equiv) and α,α,α-trifluorotoluene (8.2 μL, 0.067 mmol, 0.33 equiv) in $Et_2O$ (0.35 mL) was then added under $N_2$. After the resulting mixture had been stirred for 5 min, $Et_3N{\cdot}3HF$ (0.1 mL, 0.60 mmol, 3 equiv) was added dropwise. The reaction mixture was monitored by $^{19}$F NMR analysis at 30-min intervals. Upon completion, the biphasic reaction mixture was diluted with $Et_2O$ (1 mL). The two layers were separated, and the aqueous layer was back extracted with $Et_2O$ (3×1 mL). The combined organic extracts were concentrated in vacuo, and the residue was loaded directly onto a RediSep load cartridge. Purification by silica gel flash column chromatography resulted in **5a** (29 mg, 84%) as a white solid.

### 4.4. General procedure for fluorination of pyridinyl substrates

An oven-dried 10 mL Schlenk flask was charged with $[Rh(COD)_2]BF_4$ (4.1 mg, 0.01 mmol, 5 mol %) within glovebox and then THF (1.0 mL) at room temperature. A solution of trichloroacetimidate (**8c**) (69 mg, 0.20 mmol, 1 equiv) and α,α,α-trifluorotoluene (8.2 μL, 0.067 mmol, 0.33 equiv) in THF (1.00 mL) was then added. After the mixture had been stirred for 5 min, $Et_3N{\cdot}3HF$ (0.1 mL, 0.60 mmol, 3.0 equiv) was added dropwise. The resulting mixture was then heated to 45 °C and stirred for 24 h. Upon completion, the reaction mixture was concentrated in vacuo and loaded directly onto a RediSep load cartridge. Purification by silica gel flash column resulted in **9c** (31 mg, 78%) as a light yellow solid.

### 4.5. Structural data

*4.5.1. 2-(1-Fluoroethyl)naphthalene (**5a**).* Yield 84%, 29.20 mg. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$=7.94–7.84 (m, 3H), 7.83 (s, 1H), 7.55–7.48 (m, 3H), 5.82 (dq, $J$=47.6, 6.4 Hz, 1H), 1.76 (dd, $J$=23.9, 6.5 Hz, 3H); $^{13}$C NMR (126 MHz, $CDCl_3$): $\delta$=139.0 (d, $J$=19.5 Hz), 133.3, 133.2, 128.5, 128.2, 127.9, 126.4 (d, $J$=15.0 Hz), 124.3, 124.3, 123.3 (d, $J$=5.8 Hz), 91.2 (d, $J$=167.8 Hz), 23.1 (d, $J$=25.2 Hz); $^{19}$F NMR (471 MHz, $CDCl_3$): $\delta$=−167.0; HRMS (TOF EI$^+$): calculated for $C_{12}H_{11}F$ $(M)^+$: 174.0845; found: 174.0858.

*4.5.2. 2-(1-Fluoro-2-methylpropyl)naphthalene (**5b**).* Yield 88%, 35.80 mg. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$=7.91–7.83 (m, 3H), 7.77 (s, 1H), 7.56–7.48 (m, 2H), 7.45 (dd, $J$=8.6, 1.7 Hz, 1H), 5.29 (dd, $J$=47.0, 6.8 Hz, 1H), 2.36–2.04 (m, 1H), 1.09 (dd, $J$=6.6, 1.0 Hz, 3H), 0.91 (d, $J$=6.9 Hz, 3H); $^{13}$C NMR (126 MHz, $CDCl_3$): $\delta$=137.0 (d, $J$=20.3 Hz), 133.3, 133.1, 128.2, 128.2, 127.8, 126.4, 126.2, 125.6 (d, $J$=8.4 Hz), 123.9 (d, $J$=6.2 Hz), 99.6 (d, $J$=174.0 Hz), 34.5 (d, $J$=22.8 Hz), 18.2 (dd, $J$=103.4, 5.4 Hz); $^{19}$F NMR (471 MHz, $CDCl_3$): $\delta$=−179.7. HRMS (TOF EI$^+$): calculated for $C_{14}H_{15}F$ $(M)^+$: 202.1158; found: 202.1168.

*4.5.3. 2-(Fluoro(o-tolyl)methyl)naphthalene (**5c**).* Yield 68%, 31.40 mg. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=7.86–7.77 (m, 4H), 7.76 (s, 1H), 7.52–7.45 (m, 2H), 7.45–7.37 (m, 2H), 7.31–7.21 (m, 2H), 7.21–7.15 (m, 1H), 6.78 (d, $J$=47.1 Hz, 1H), 2.27 (s, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta$=137.6 (d, $J$=20.2 Hz), 136.5 (d, $J$=21.7 Hz), 135.9 (d, $J$=4.4 Hz), 133.4 (d, $J$=1.6 Hz), 133.2, 130.8, 128.7 (d, $J$=2.1 Hz), 128.5, 128.4, 127.8, 127.05 (d, $J$=8.6 Hz), 126.53 (d, $J$=11.5 Hz), 126.41 (d, $J$=7.3 Hz), 126.2, 124.9, 124.8, 92.7 (d, $J$=171.6 Hz), 19.5; $^{19}$F NMR (376 MHz, $CDCl_3$): $\delta$=−166.8. HRMS (TOF EI$^+$): calculated for $C_{18}H_{15}F$ $(M)^+$: 250.1158; found: 250.1167.

*4.5.4. 2-((2,6-Dimethylphenyl)fluoromethyl)naphthalene (**5d**).* Yield 73%, 37.20 mg. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=7.85 (d, $J$=8.5 Hz, 2H), 7.83–7.75 (m, 1H), 7.63 (s, 1H), 7.50 (dd, $J$=6.4, 2.9 Hz, 2H), 7.43 (d, $J$=8.6 Hz, 1H), 7.29–7.20 (m, 1H), 7.13 (d, $J$=47.8 Hz, 1H), 7.12 (d, $J$=7.6 Hz, 2H), 2.32 (s, 6H).

$^{13}$C NMR (101 MHz, $CDCl_3$): $\delta$=137.6 (d, $J$=3.6 Hz), 137.0 (d, $J$=22.0 Hz), 135.0 (d, $J$=16.6 Hz), 133.2, 133.0, 129.3, 128.8 (d, $J$=1.9 Hz), 128.4 (d, $J$=7.6 Hz), 127.8, 126.4 (d, $J$=6.8 Hz), 124.6 (d, $J$=6.4 Hz), 123.9 (d, $J$=5.5 Hz), 91.4 (d, $J$=170.8 Hz), 20.6 (d, $J$=2.6 Hz). $^{19}$F NMR (376 MHz, $CDCl_3$): $\delta$=−175.5. HRMS (TOF EI$^+$): calculated for $C_{19}H_{17}F$ $(M)^+$: 264.1314; found: 264.1310.

*4.5.5. 2-(Fluoro(phenyl)methyl)naphthalene (**5e**).* Yield 78%, 35.40 mg. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$=7.92–7.82 (m, 4H), 7.57–7.50 (m, 2H), 7.49–7.34 (m, 6H), 6.67 (d, $J$=47.4 Hz, 1H); $^{13}$C

NMR (126 MHz, $CDCl_3$): $\delta$=139.9 (d, $J$=21.7 Hz), 137.3 (d, $J$=21.6 Hz), 133.4, 133.1, 128.7, 128.6 (d, $J$=2.2 Hz), 128.6, 128.4, 127.9, 126.9 (d, $J$=6.2 Hz), 126.6, 126.5, 125.81 (d, $J$=7.7 Hz), 124.3 (d, $J$=5.2 Hz), 94.8 (d, $J$=173.1 Hz); $^{19}$F NMR (376 MHz, $CDCl_3$): $\delta$=−167.0. HRMS (TOF EI$^+$): calculated for $C_{17}H_{13}F$ $(M)^+$: 236.1001; found: 236.0990.

*4.5.6. 2-(Fluoro(4-fluorophenyl)methyl)naphthalene (**5f**).* Yield 76%, 40.40 mg. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$=7.87 (d, $J$=8.8 Hz, 4H), 7.59–7.50 (m, 2H), 7.47–7.34 (m, 3H), 7.13–7.03 (m, 2H), 6.64 (d, $J$=47.3 Hz, 1H); $^{13}$C NMR (126 MHz, $CDCl_3$): $\delta$=162.8 (d, $J$=247.4 Hz), 136.9 (d, $J$=21.7 Hz), 135.7 (dd, $J$=22.2, 3.1 Hz), 133.3 (d, $J$=1.4 Hz), 133.0, 129.2 (d, $J$=8.2 Hz), 128.8 (dd, $J$=8.3, 6.0 Hz), 128.5, 128.2, 127.8, 126.5 (d, $J$=4.6 Hz), 125.6 (d, $J$=7.7 Hz), 124.0 (d, $J$=5.2 Hz), 115.5 (d, $J$=21.7 Hz), 94.0 (d, $J$=173.4 Hz); $^{19}$F NMR (471 MHz, $CDCl_3$): $\delta$=−113.2, −164.9. HRMS (TOF EI$^+$): calculated $C_{17}H_{12}F_2$ $(M)^+$: 254.0907; found: 254.0914.

*4.5.7. 2-((4-Chlorophenyl)fluoromethyl)naphthalene (**5g**).* Yield 89%, 49.90 mg. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$=7.91–7.79 (m, 4H), 7.57–7.48 (m, 2H), 7.43–7.30 (m, 5H), 6.62 (d, $J$=47.3 Hz, 1H); $^{13}$C NMR (126 MHz, $CDCl_3$): $\delta$=138.3 (d, $J$=22.2 Hz), 136.6, 134.5 (d, $J$=2.6 Hz), 133.3 (d, $J$=1.6 Hz), 133.0, 128.8, 128.6, 128.2, 128.1 (d, $J$=6.2 Hz), 127.8, 126.7, 126.6, 125.8 (d, $J$=7.6 Hz), 124.1 (d, $J$=5.0 Hz), 94.0 (d, $J$=173.9 Hz); $^{19}$F NMR (471 MHz, $CDCl_3$): $\delta$=−166.5. HRMS (TOF EI$^+$): calculated for $C_{17}H_{12}ClF$ $(M)^+$: 270.0612; found: 270.0600.

*4.5.8. 2-(Fluoro(4-methoxyphenyl)methyl)naphthalene (**5h**).* Yield: not isolated due to instability; crude $^1$H NMR and $^{19}$F NMR data are provided in the spectrum file. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$=6.45 (d, $J$=47.6 Hz, 1H, HC–F); $^{19}$F NMR (471 MHz, $CDCl_3$): $\delta$=−163.6.

*4.5.9. 1-(Fluoro(phenyl)methyl)-2-methylbenzene (**7c**).* Yield 74%, 28.70 mg. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=7.47–7.23 (m, 8H), 7.21–7.14 (m, 1H), 6.63 (d, $J$=47.2 Hz, 1H), 2.25 (s, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta$=139.1 (d, $J$=21.5 Hz), 137.7 (d, $J$=20.4 Hz), 135.7 (d, $J$=4.6 Hz), 130.8, 128.6, 128.6, 127.3, 127.2, 126.8 (d, $J$=9.0 Hz), 126.2, 92.6 (d, $J$=171.4 Hz), 19.4; $^{19}$F NMR (376 MHz, $CDCl_3$): $\delta$=−166.9. HRMS (TOF EI$^+$): calculated for $C_{14}H_{13}F$ $(M)^+$: 200.1001; found: 200.1007.

*4.5.10. 2-(Fluoro(phenyl)methyl)-1,3-dimethylbenzene (**7d**).* Yield 83%, 38.30 mg. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=7.36–7.25 (m, 3H), 7.24–7.13 (m, 3H), 7.05 (d, $J$=7.6 Hz, 2H), 6.95 (d, $J$=48.0 Hz, 1H), 2.25 (d, $J$=2.5 Hz, 6H); $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta$=139.6 (d, $J$=22.1 Hz), 137.4 (d, $J$=3.6 Hz), 135.1 (d, $J$=16.7 Hz), 129.4–129.0 (m), 128.73 (d, $J$=1.9 Hz), 128.5, 127.9 (d, $J$=1.6 Hz), 125.7 (d, $J$=6.0 Hz), 91.2 (d, $J$=170.4 Hz), 20.6 (d, $J$=2.4 Hz); $^{19}$F NMR (376 MHz, $CDCl_3$): $\delta$=−176.1. HRMS (TOF EI$^+$): calculated for $C_{15}H_{15}F$ $(M)^+$: 214.1158; found: 214.1163.

*4.5.11. (Fluoromethylene)dibenzene (**7e**).* Yield 36%, 13.60 mg. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$=7.47–7.27 (m, 10H), 6.49 (d, $J$=47.3 Hz, 1H); $^{19}$F NMR (282 MHz, $CDCl_3$): $\delta$=−166.9.

*4.5.12. 1-Fluoro-4-(fluoro(phenyl)methyl)benzene (**7f**).* Yield 73%, 30.20 mg. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=7.54–7.29 (m, 7H), 7.15–6.95 (m, 2H), 6.47 (d, $J$=47.4 Hz, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta$=162.9 (d, $J$=247.3 Hz), 139.7 (d, $J$=21.8 Hz), 135.9 (dd, $J$=22.2, 3.4 Hz), 129.5–128.1 (m), 126.6 (d, $J$=6.2 Hz), 115.6 (d, $J$=21.6 Hz), 94.0 (d, $J$=173.0 Hz); $^{19}$F NMR (376 MHz, $CDCl_3$): $\delta$=−113.5, −165.0. HRMS (TOF EI$^+$): calculated for $C_{13}H_{10}F_2$ $(M-F)^+$: 185.0761; found: 185.0777.

*4.5.13. 1-Chloro-4-(fluoro(phenyl)methyl)benzene (**7g**).* Yield 50%, 20.30 mg. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=7.43–7.25 (m, 9H), 6.45 (d, $J$=47.4 Hz, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta$=139.5 (d, $J$=21.8 Hz), 138.5 (d, $J$=22.4 Hz), 134.5 (d, $J$=2.3 Hz), 128.8, 128.8 (d, $J$=2.3 Hz), 128.7, 128.1 (d, $J$=6.3 Hz), 126.7 (d, $J$=6.2 Hz), 93.9 (d, $J$=173.7 Hz); $^{19}$F NMR (376 MHz, $CDCl_3$): $\delta$=−166.7. HRMS (TOF EI$^+$): calculated $C_{13}H_{10}ClF$ $(M)^+$: 220.0455; found: 220.0465.

*4.5.14. 1-(Fluoro(phenyl)methyl)-4-methoxybenzene (**7h**).* Yield: not isolated due to instability; crude $^1$H NMR and $^{19}$F NMR data are provided in spectrum file. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$=6.33 (d, $J$=47.8 Hz, 1H, HC–F); $^{19}$F NMR (471 MHz, $CDCl_3$): $\delta$=−163.6.

*4.5.15. 2-(Fluoro(o-tolyl)methyl)pyridine (**9c**).* Yield 78%, 39.30 mg. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=8.62–8.55 (m, 2H), 7.60 (dd, $J$=8.0, 1.8 Hz, 1H), 7.37 (dd, $J$=6.7, 2.4 Hz, 1H), 7.33–7.23 (m, 3H), 7.20 (dd, $J$=6.3, 2.2 Hz, 1H), 6.67 (d, $J$=46.9 Hz, 1H), 2.24 (s, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta$=149.8, 148.7, 136.4 (d, $J$=19.9 Hz), 135.5 (d, $J$=4.4 Hz), 134.8 (d, $J$=22.4 Hz), 134.8 (d, $J$=5.2 Hz), 131.0, 129.0, 126.7 (d, $J$=8.8 Hz), 126.4, 123.6, 90.7 (d, $J$=172.4 Hz), 19.3; $^{19}$F NMR (471 MHz, $CDCl_3$): $\delta$=−169.6. HRMS (TOF EI$^+$): calculated for $C_{13}H_{12}FN$ $(M)^+$: 201.0954; found: 201.0960.

*4.5.16. 2-((2,6-Dimethylphenyl)fluoromethyl)pyridine (**9d**).* Yield 69%, 29.70 mg. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=8.60–8.44 (m, 2H), 7.57–7.50 (m, 1H), 7.34–7.23 (m, 1H), 7.23–7.14 (m, 1H), 7.06 (t, $J$=7.8 Hz, 2H), 6.98 (d, $J$=47.6 Hz, 1H), 2.38 (s, 3H), 2.25 (s, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta$=149.0 (d, $J$=48.4 Hz), 147.5, 138.2, 137.2 (d, $J$=5.0 Hz), 133.5 (d, $J$=2.6 Hz), 129.4, 129.3, 129.1 (d, $J$=18.7 Hz), 123.3, 89.5 (d, $J$=165.1 Hz), 20.5 (d, $J$=2.3 Hz); $^{19}$F NMR (471 MHz, $CDCl_3$): $\delta$=−178.2. HRMS (TOF EI$^+$): calculated for $C_{14}H_{14}FN$ $(M)^+$: 215.1110; found: 215.1126.

*4.5.17. 2-(Fluoro(phenyl)methyl)pyridine (**9e**).* Yield 71%, 26.50 mg. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$=8.65–8.54 (m, 2H), 7.68–7.61 (m, 1H), 7.47–7.28 (m, 6H), 6.51 (d, $J$=47.0 Hz, 1H); $^{13}$C NMR (126 MHz, $CDCl_3$): $\delta$=149.8, 148.2 (d, $J$=6.8 Hz), 138.7 (d, $J$=21.4 Hz), 135.6 (d, $J$=22.4 Hz), 134.4 (d, $J$=5.9 Hz), 129.0, 128.9, 126.6 (d, $J$=6.2 Hz), 123.6, 92.6 (d, $J$=173.8 Hz); $^{19}$F NMR (471 MHz, $CDCl_3$): $\delta$=−169.2. HRMS (TOF EI$^+$): calculated for $C_{12}H_{10}FN$ $(M)^+$: 187.0797; found: 187.0812.

*4.5.18. 2-(Fluoro(4-fluorophenyl)methyl)pyridine (**9f**).* Yield 48%, 22.30 mg. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$=8.64–8.52 (m, 2H), 7.65–7.62 (m, 1H), 7.41–7.28 (m, 3H), 7.15–7.00 (m, 2H), 6.49 (d, $J$=47.0 Hz, 1H); $^{13}$C NMR (126 MHz, $CDCl_3$): $\delta$=163.0 (d, $J$=239.2 Hz), 149.9, 148.0 (d, $J$=6.7 Hz), 135.4 (d, $J$=22.5 Hz), 134.6 (dd, $J$=21.8, 3.2 Hz), 134.3 (d, $J$=5.9 Hz), 128.7 (dd, $J$=8.4, 6.0 Hz), 123.6, 115.9 (d, $J$=21.8 Hz), 92.0 (d, $J$=174.1 Hz); $^{19}$F NMR (471 MHz, $CDCl_3$): $\delta$=−112.4, −167.5. HRMS (TOF EI$^+$): calculated for $C_{12}H_9NF_2$ $(M)^+$: 205.0703; found: 205.0718.

*4.5.19. 2-((4-Chlorophenyl)fluoromethyl)pyridine (**9g**).* Yield 39%, 19.10 mg. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$=8.65–8.49 (m, 2H), 7.65–7.49 (m, 1H), 7.42–7.02 (m, 7H), 6.44 (d, $J$=46.9 Hz, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta$=150.2 (d, $J$=2.1 Hz), 148.3 (d, $J$=6.6 Hz), 137.3 (d, $J$=22.0 Hz), 135.0 (d, $J$=2.7 Hz), 134.3 (d, $J$=5.6 Hz), 129.1, 128.5, 128.0 (d, $J$=6.1 Hz), 123.6, 92.0 (d, $J$=174.6 Hz); $^{19}$F NMR (471 MHz, $CDCl_3$): $\delta$=−169.3. HRMS (TOF EI$^+$): calculated for $C_{12}H_9ClFN$ $(M)^+$: 221.0408; found: 221.0405.

## Acknowledgements

We would like to thank the University of Iowa for financial support. Q.Z. and G.J.R. thank the Graduate College for the Summer Research Fellowship. J.C.M. thanks the University of Iowa for the ICRU fellowship.

## Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2015.04.066.

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23. Recent studies demonstrate that the $\eta^3$-benzyl-rhodium complex is configurationally stable, see: Bleuel, E.; Schwab, P.; Laubender, M.; Werner, H. *J. Chem. Soc., Dalton Trans.* **2000**, 266–273 Thus, if the $\eta^3$-benzyl-rhodium complex is the operative reaction pathway, it is anticipated that fluorination of enantiopure substrate **4a** would proceed with the conservation of stereochemistry in the product **5a**. However, fluorination of enantiopure **4a** proceeded with almost complete racemization under rhodium conditions, suggesting that the reaction is more likely to proceed via the discreet benzylic cation intermediate.
24. A significant lower yield (<50%) of **5a** was isolated under both $BF_3{\cdot}OEt_2$ and CSA conditions. We also investigated these Lewis and Brønsted acids conditions with other naphthylic substrates, and the fluorination proceeded with much lower conversions in compared to the rhodium catalyst.
25. Preliminary studies showed that Brønsted acid, such as CSA (Table 1, entry 13), is capable of promoting the fluorination of naphthylic trichloroacetimidate **4a** in good NMR conversion, but moderate isolated yield.