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Rhodium-catalyzed benzylic fluorination of trichloroacetimidates

Qi Zhang [†], Jason C. Mixdorf [†], Gilbert J. Reynders, III, Hien M. Nguyen [*]

Department of Chemistry, University of Iowa, Iowa City, IA 52246, USA

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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.

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 pK_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]

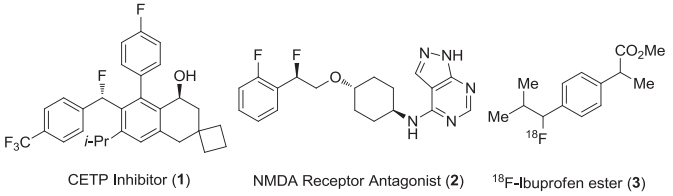

Fig. 1. Biologically relevant compounds and PET radiotracers containing benzylic fluoride functionality.

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

* Corresponding author. Tel.: +1 319 384 1887; fax: +1 319 335 1270; e-mail address: hien-nguyen@uiowa.edu (H.M. Nguyen).
† The authors contributed equally to the present work.

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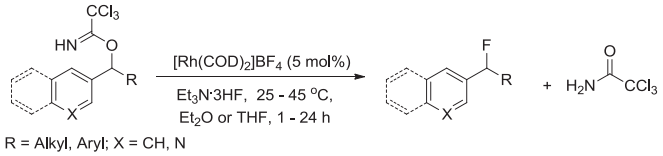
combination of trichloroacetimidates with $Et_3N{\cdot}3HF$ reagent, mediated by transition-metal catalysis, could potentially allow rapid and efficient incorporation of fluorine ion into the benzylic position of organic compounds. Herein, we report an effective methodology for the synthesis of benzylic 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).



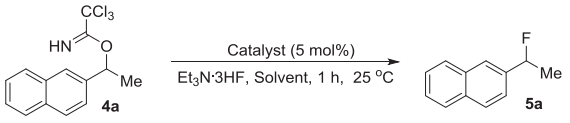
Scheme 1. Rhodium-catalyzed benzylic fluorination reaction.

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 η^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 η^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