JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

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Iridium-Catalyzed Allylic Fluorination of Trichloroacetimidates

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Supporting Information

ABSTRACT: A rapid allylic fluorination method utilizing trichloroacetimidates in conjunction with an iridium catalyst has been developed. The reaction is conducted at room temperature under ambient air and relies on $Et_3N \cdot 3HF$ reagent to provide branched allylic fluorides with complete regioselectivity. This high-yielding reaction can be conducted on a multigram scale and shows considerable functional group tolerance. The use of [^{18}F]KF·Kryptofix allowed $^{18}F^-$ incorporation in 10 min.

The past decade has seen an explosion in the use of selectively fluorinated molecules for applications in pharmaceuticals and medical imaging.[1,2] The fluorine atom has unique properties that make it an ideal bioisostere for hydrogen or oxygen. This substitution imparts fluorinated products with improved potency, metabolic stability, and pharmacokinetics.[1] In addition, ^{18}F atom appears to be an ideal isotope for use in positron emission tomography (PET) imaging because of its low-energy emission, ease of preparation from [^{18}O]water, and 110 min half-life.[2] These characteristics, although advantageous to the product, make incorporation of fluorine challenging.[1e,3,4] As a result, fluorination methods have not been adequately developed in comparison to other protocols that form carbon−heteroatom bonds.[1e,3,4] This warrants the discovery of general and rapid strategies for fluorine incorporation into bioactive molecules.[1,2]

Many elegant approaches have been developed for the formation of aryl fluorides[5] and α-fluorocarbonyl compounds.[6] Despite their potential applications as valuable building blocks in a variety of pharmaceutical compounds, only a few methods for the preparation of allylic fluorides are available.[7] Allylic fluorides are traditionally prepared by displacement of allylic alcohols with (diethylamino)sulfur trifluoride. This transformation is not regioselective or enantioselective.[7] Other strategies for the synthesis of allylic fluorides have been developed, including electrophilic desilylation.[8] Transition-metal-catalyzed fluorination of allylic electrophiles would be a conceptually novel approach for the regio- and enantioselective preparation of branched allylic fluorides. This approach has not been fully explored because of a number of anticipated challenges. First, the nucleophilicity of the fluoride ion is significantly decreased in its solvated form, reducing the efficacy of fluorine incorporation into the target molecule.[1,2c,7] Second, competitive elimination is often observed, as the desolvated fluoride ion can act as a strong base.[9b] Third, because palladium and platinum are known to form π-allyl complexes with allylic fluorides,[9] employing transition metals in these reactions was not thought to be possible.[9a] Despite these challenges, the recent work of Doyle has shown that Pd-catalyzed fluorination of allylic halides is possible.[10] The 24−48 h fluorination time precludes the use of this method for [^{18}F] labeling. Another report by Gouverneur has also shown the feasibility of Pd-catalyzed fluorination reactions of allylic *p*-nitrobenzoates,[11] in which primary allylic fluorides are formed in moderate to good yields. Herein we report a complementary iridium-catalyzed fluorination leading to secondary and tertiary allylic fluorides.

We recently reported the novel use of trichloroacetimidate as the leaving group in rhodium-catalyzed allylic substitution with unactivated anilines.[12,13] The amination proceeded with excellent regioselectivity. We postulated that this reaction manifold and the unique properties of the trichloroacetimidate leaving group might lead to an efficient fluorination reaction. To test our hypothesis, allylic trichloroacetimidate **1** (Table 1) was chosen as a

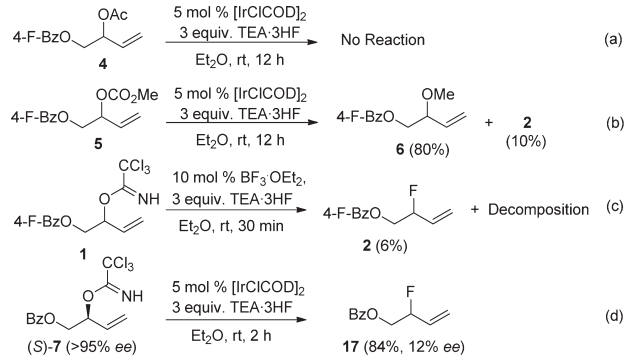
Table 1. Screening of Catalysts and Fluoride Sources[a]

Entry	Catalyst	F Source	Solvent	Time (h)	Conv. (%)	Yield **2** (%)[c]	Yield **3** (%)[c]
1	$RhCl(P(OPh)_3)_3$	CsF	THF	20	<10	0	0
2	$RhCl(P(OPh)_3)_3$	TBAT	THF	20	<10	0	0
3	$RhCl(P(OPh)_3)_3$	TEA·3HF	THF	20	<10	1	0
4	$RhCl(PPh_3)_3$	TEA·3HF	THF	20	<10	0	0
5	$[RhClCOD]_2$[b]	TEA·3HF	THF	2	20	7	0
6	$RhCOD_2OTf$	TEA·3HF	THF	0.5	100	45	31
7	$RhCOD_2BF_4$	TEA·3HF	THF	0.5	100	48	30
8	$RhCOD_2BF_4$	TEA·3HF	Acetone	0.5	100	56	35
9	$RhCOD_2BF_4$	TEA·3HF	*t*-BuOH	0.5	100	48	15
10	$RhCOD_2BF_4$	TEA·3HF	$PhCH_3$	0.5	100	70	12
11	$RhCOD_2BF_4$	TEA·3HF	MTBE	0.5	89	62	11
12	$RhCOD_2BF_4$	TEA·3HF	Et_2O	0.5	100	75(69)[d]	7
13	$[IrClCOD]_2$[b]	TEA·3HF	Et_2O	2	100	95(93)[d]	1
14	None	TEA·3HF	Et_2O	18	0	0	0
15	$[IrClCOD]_2$[e]	TEA·3HF	Et_2O	2	100	88[d]	1

[a] All reactions were conducted at 0.3 M. [b] 5 mol % catalyst was used in the reaction. [c] Yields were determined by ^{19}F NMR analysis using $PhCF_3$ as an internal standard. [d] Isolated yields. [e] 4 g scale, 2.5 mol % Ir catalyst.

Received: September 15, 2011
Published: November 07, 2011

Scheme 1. Control Studies

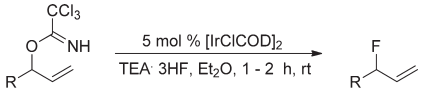


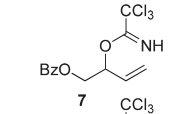
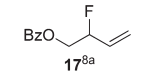
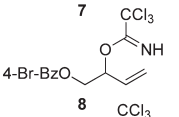
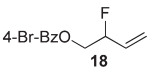
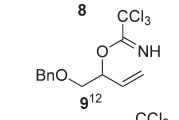
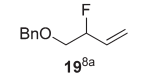
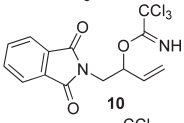
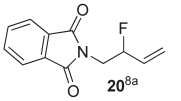
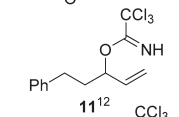
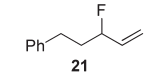
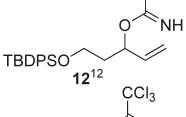
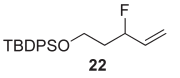
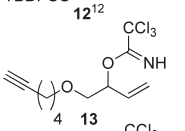
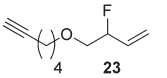
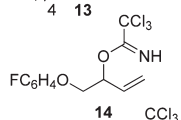
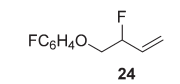
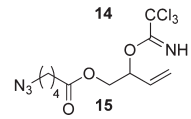
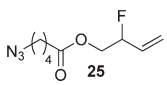
model substrate because the 4-fluorobenzoate group would provide a means of monitoring the reaction by ^{19}F NMR analysis of the crude reaction mixture.[14] Initial efforts utilizing RhCl(P(OPh)$_3$)$_3$[12,15] and a variety of fluoride sources (CsF, TBAT, and TEA·3HF) did not afford allylic fluoride **2** (entries 1−3). A number of Rh(I) catalysts were screened. Both RhCOD$_2$OTf and RhCOD$_2$BF$_4$ (entries 6 and 7) provided **2** in moderate yields along with elimination product **3**. In all cases, the linear allylic fluoride was not detected by crude ^{19}F NMR analysis. Subsequent efforts to suppress the competing elimination reaction were met with success when the solvent was varied. Use of nonpolar solvents (Et$_2$O, MTBE, and PhCH$_3$) resulted in a biphasic mixture. This phase separation not only simplified the purification of allylic fluoride **2**, eliminating the need for an aqueous workup, but also provided **2** in the highest yield (entries 10−12). Additional studies showed that [IrClCOD]$_2$ was a better catalyst than RhCOD$_2$BF$_4$, and product **2** was isolated in 93% yield (entry 13). A control experiment (entry 14) without iridium catalyst was performed, and no reaction was apparent after 18 h. The application to a large scale was explored utilizing 4 g of imidate **1** (entry 15), and allylic fluoride **2** was obtained in 88% yield.

To evaluate the unique nature of the trichloroacetimidate potentially to act as both the leaving group and the directing group, allylic acetate **4** (Scheme 1a) was subjected to our reaction conditions, and no reaction was observed after 12 h. Methyl ether **6** (Scheme 1b) was the major product when allylic carbonate **5** was used in the fluorination. To determine whether iridium acts as a Lewis acid, we explored the reaction of imidate **1** with 10 mol % BF$_3$·OEt$_2$ (Scheme 1c). Less than 6% yield of allylic fluoride **2** was detected along with decomposition. No reaction was observed with the milder Lewis acids Zn(OTf)$_2$ and Cu(OTf)$_2$. Use of the palladium catalysts Pd(PPh$_3$)$_4$ and Pd-[COP-OAc][13a] led to decomposition of the starting material. To elucidate the stereochemical outcome of the fluorination, enantiopure allylic imidate **7** was investigated (Scheme 1d). Fluoride **17** was isolated with nearly complete racemization (12% ee).[16]

To establish the scope of the fluorination, secondary allylic imidates **7**−**15** (Table 2) were studied. A variety of functional groups were tolerated, affording branched allylic fluorides **17**−**25** in good yields as single regioisomers. For instance, fluorination of imidate **10** (entry 4) provided fluoride **20**[8a] in 89% yield. The silyl ether group in imidate **12**[12] (entry 6) proved to be stable under iridium conditions, and fluoride **22** was obtained in 78% yield. Imidate **13** containing the terminal alkyne group (entry 7) was also compatible, and allylic fluoride **23** was obtained in 68% yield. This alkyne is capable of conjugating to bioorthogonal

Table 2. Survey of Secondary Allylic Imidates[a]



Entry	Trichloroacetimidates	Products	Time (h)[b]	Isolated Yield
1	 **7**	 **17**[8a]	2	91%
2	 **8**	 **18**	2	83%
3	 **9**[12]	 **19**[8a]	1.5	85%
4	 **10**	 **20**[8a]	1.5	89%
5	 **11**[12]	 **21**	1	68%
6	 **12**[12]	 **22**	1	78%[c]
7	 **13**	 **23**	1.5	68%
8	 **14**	 **24**	1.5	90%
9	 **15**	 **25**	1	64%

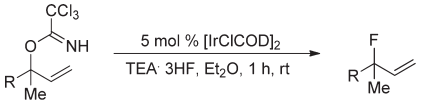
[a] All reactions were conducted at 0.3 M in Et$_2$O for 1−2 h. [b] Fluorination with RhCOD$_2$BF$_4$ proceeded to completion in 30 min, and the isolated yields were 50−65% for imidates **7**−**15**. [c] Quenched with 3 equiv of TEA.

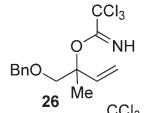
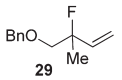
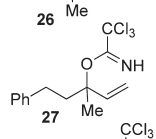
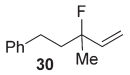
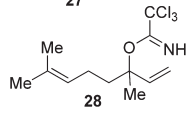
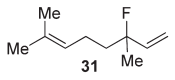
azide, which can be incorporated into a variety of biomolecules.[17] Allylic fluoride **24** (entry 8), a functionality that has been introduced into prostaglandin analogues,[18] was isolated in 90% yield. The azide group in imidate **15** (entry 9) was stable under the fluorination conditions, and fluoride **25** (entry 9) was isolated in 64% yield. This azide can undergo "Cu-free" cycloaddition with strained cyclooctynes.[19,20] These secondary allylic fluorides can be stored at ambient temperature for weeks without decomposition.

The application of the fluorination process was further investigated with tertiary allylic imidates **26**−**28** (Table 3).[12b] In contrast to secondary substrates, tertiary allylic fluorides **29**−**31** were unstable toward isolation, and polymerization/decomposition was observed.[22] Nevertheless, the reaction was fast and proceeded with excellent regioselectivity. Use of imidate **26** (entry 1) provided tertiary fluoride **29** in 67% yield [branched (b)/linear (l) = 25:1]. Reaction of imidate **28** (entry 3) afforded a 73% yield (b/l = 10:1) of fluoromonoterpenoid **31**, a potential

dx.doi.org/10.1021/ja2087213 |J. Am. Chem. Soc. 2011, 133, 19318–19321

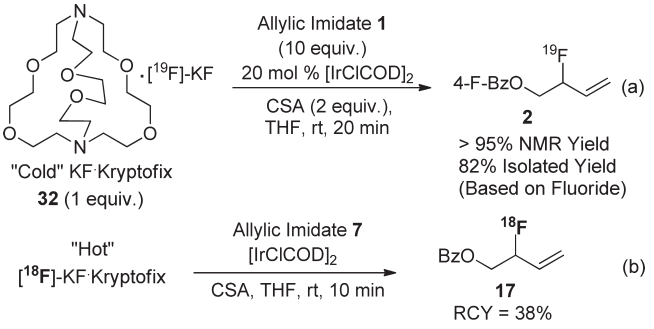
Table 3. Survey of Tertiary Allylic Imidates[a]



Entry	TrichloroacetImidates	Products	Time (h)	NMR Yield[b]
1	 **26**	 **29**	1	67% (b/l = 25:1)
2	 **27**	 **30**	1	71% (b/l = 20:1)
3	 **28**	 **31**	1	73% (b/l = 10:1)

[a] All reactions were conducted at 0.3 M in Et_2O under ambient air for 1 h. [b] Yields were determined by ^{19}F NMR analysis using $PhCF_3$ as an internal standard; "b/l" is the ratio of branched and linear regioisomers.

Scheme 2. Fluorination with KF·Kryptofix



lead for the synthesis of insecticide analogues.[21] To illustrate the utility of tertiary allylic fluorides, crude product **30** (entry 2) was derivatized via hydrogenation over Pd/C, and the corresponding tertiary alkyl fluoride was isolated in 50% yield over two steps.

Overall, the rapid fluorination conditions and broad functional group tolerance indicate the potential application of this method for use in labeling of allylic compounds with $^{18}F^-$. Accordingly, the reaction of allylic imidate **1** (Scheme 2a) with "cold" [^{19}F]KF·Kryptofix [2.2.2] complex **32**[2a] was explored. This KF·Kryptofix complex was selected because it is the most commonly used source of $^{18}F^-$ for radiolabeling studies.[2a] Typically, under [^{18}F]-labeling conditions, the target substrate is used in 100−1000 fold excess relative to $^{18}F^-$.[2a] Therefore, 10 equiv of imidate **1** was used with 1 equiv of "cold" [^{19}F]KF·Kryptofix in the presence of $[IrClCOD]_2$ and camphorsulfonic acid (CSA) (Scheme 2a). Fluoride incorporation was observed in 20 min, and compound **2** was obtained in 82% yield.[23] Encouraged by this result, initial trials with "hot" [^{18}F]KF·Kryptofix complex were conducted on allylic trichloroacetimidate **7** (Scheme 2b). The decay-corrected radiochemical yield (RCY) of allylic fluoride **17** was determined to be 38%, which is competitive with those obtained using other methods.[11]

In summary, we have developed a novel method for the synthesis of secondary and tertiary allylic fluorides. The reaction is simple in operation and provides allylic fluorides in high yields with excellent regioselectivities. Efforts to render the fluorination enantioselective, further application to the preparation of [^{18}F]-labeled allylic fluoride radiotracers, and mechanistic studies will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information. Full experimental details and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENT

This work is dedicated to Professor Barry Trost on the occasion of his 70th birthday. We thank Professor Geert-Jan Boon at the University of Georgia for providing 4-dibenzocyclooctynol, the ACS Division of Medicinal Chemistry for the graduate fellowship to J.J.T, and the University of Iowa for financial support.

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