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Oxidation

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Direct Access to β-Fluorinated Aldehydes by Nitrite-Modified Wacker Oxidation

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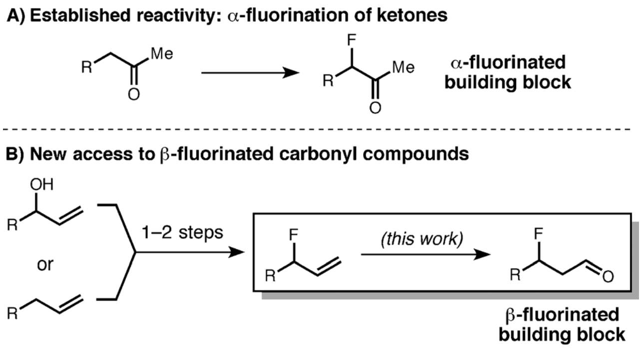
Abstract: *An aldehyde-selective Wacker-type oxidation of allylic fluorides proceeds with a nitrite catalyst. The method represents a direct route to prepare β-fluorinated aldehydes. Allylic fluorides bearing a variety of functional groups are transformed in high yield and very high regioselectivity. Additionally, the unpurified aldehyde products serve as versatile intermediates, thus enabling access to a diverse array of fluorinated building blocks. Preliminary mechanistic investigations suggest that inductive effects have a strong influence on the rate and regioselectivity of the oxidation.*

The demand for organofluorine compounds is rapidly growing as a result of their prevalence in the pharmaceutical,[1] agrochemical,[2] and materials[3] industries. Because of a low abundance of fluorinated chemical feedstocks,[4] the development of efficient routes toward organofluorine building blocks has been recognized as an important challenge in the synthetic community.[5] Traditional fluorination protocols typically employ harsh reagents such as diethylaminosulfur trifluoride (DAST), thus restricting their tolerance of functional groups. Consequently, careful selection of an appropriate fluorinating agent must often be performed on a case-by-case basis.[6]

Significant progress has been made toward mild, catalytic alkyl fluorination, with much of this work dedicated to installing fluorine atoms adjacent to π systems (Scheme 1 A).[7] α-Fluorination of carbonyl compounds is achieved efficiently by organocatalysis and transition-metal catalysis.[8] Allylic fluorides can also be readily prepared by regio- and enantioselective methods.[7a–d,f,h] For example, iridium-catalyzed allylic substitution[7d,h] and palladium-catalyzed C−H fluorination[7f] methods can serve as convenient approaches to allylic fluorides.

Despite the depth of research dedicated to α-fluorination of activated π systems, catalytic installation of fluorine β to functional groups remains a major challenge.[9] One promising strategy enables the syntheses of β- and γ- fluorinated ketones by catalytic ring opening of strained cyclopropanols and cyclobutanols, respectively.[10] Alternative methods amenable to producing β-fluorinated carbonyl compounds have been reported,[11] but a general solution employing simple starting materials has yet to be developed. Herein, we report



Scheme 1. Strategies toward alkylfluorine compounds.

a catalytic approach to directly access β-fluorinated aldehydes from readily accessible allylic fluorides (Scheme 1 B).

The Wacker reaction is a powerful method[12] for the oxidation of olefins and typically favors Markovnikov selectivity.[13] However, in the presence of proximal functional groups, regioselectivity of oxidation can be difficult to rationally predict.[14] In our recent study of a dicationic palladium-catalyzed Wacker-type oxidation of internal olefins,[15] inductively withdrawing trifluoromethyl groups were found to substantially enhance selectivity for distal oxidation.[16] In fact, even the oxidation of a terminal olefin, 4,4,4-trifluoro-1-butene, occurred with modest *anti*-Markovnikov selectivity (3:1 aldehyde/ketone). We therefore reasoned that modified Wacker conditions, combined with the inductive influence of allylic fluorides, could be employed as a general strategy for the synthesis of β-fluorinated aldehydes under mild reaction conditions.

The model allylic fluoride **A** (Figure 1) was initially subjected to a range of Wacker-type oxidation conditions toward optimization of aldehyde selectivity.[17] Traditional Tsuji–Wacker conditions proved poorly suited for oxidation of the electron-deficient allylic fluoride, thus resulting in defluorination and no aldehyde selectivity (Figure 1 a). When subjected to our previously reported dicationic palladium system, this substrate was oxidized in moderate yield with preference for the aldehyde (3:1 aldehyde/ketone; Figure 1 b), thus revealing some innate aldehyde selectivity of the substrate.

To emphasize this effect, we next explored nitrite ligands[18] and exogenous nitrite cocatalysts, utilized by the group of Feringa and our own group, respectively, for the catalyst-controlled oxidation of terminal olefins to aldehydes. When **A** was subjected to Feringa's conditions, catalyzed by $[PdNO_2Cl(MeCN)_2]$,[19] high aldehyde selectivity was observed (18:1 aldehyde/ketone), albeit in poor yield (Fig-

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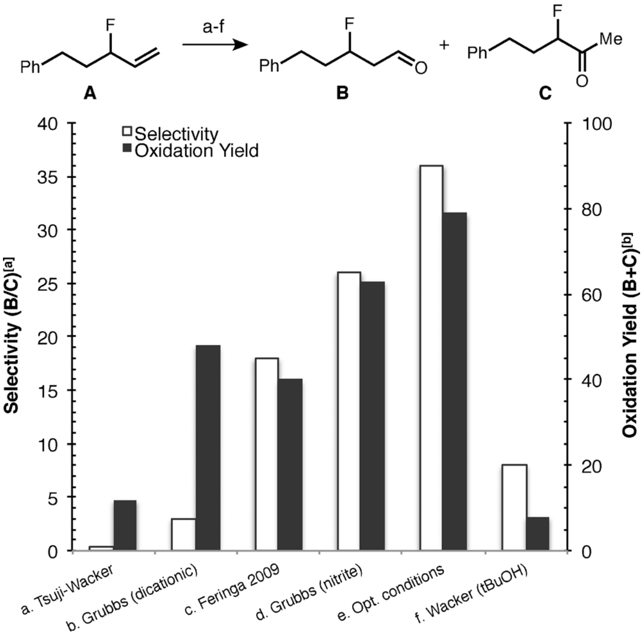
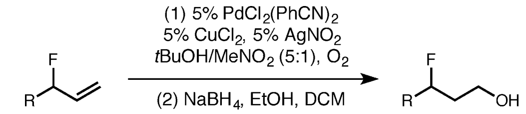
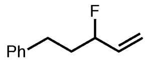
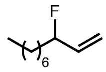
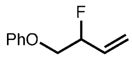
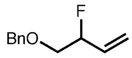
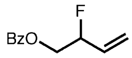
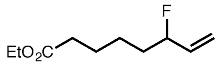
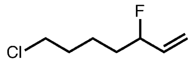
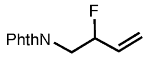


Figure 1. Comparison of oxidation conditions with a model substrate. [a] Selectivity (aldehyde/ketone) determined by ^{1}H NMR analysis. [b] Oxidation yield (aldehyde + ketone) determined by ^{1}H NMR analysis versus an internal standard. Only fluorinated products included (see Table 1 for optimized reaction conditions).

Table 1: Nitrite-modified Wacker oxidations of allylic fluorides: Substrate scope.



Entry	Substrate	Yield [%][a]	Selectivity[b]
1		82	≥20:1
2		87	≥20:1
3		94	≥20:1
4		93	≥20:1
5		93	≥20:1
6		72	≥20:1
7		81[c]	≥20:1
8		77	≥20:1

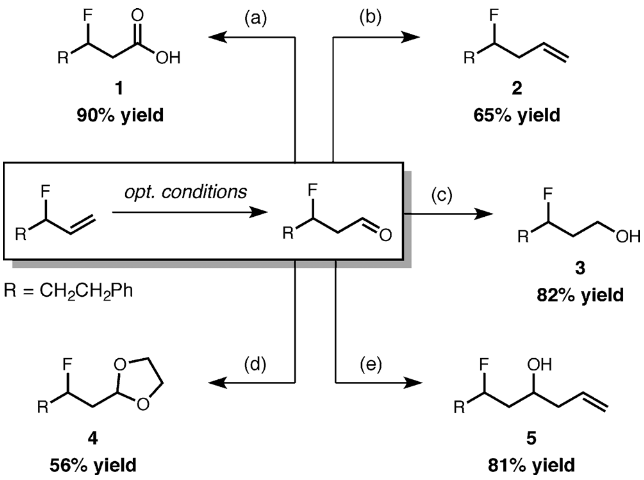
[a] Yield is of the purified product obtained after $NaBH_4$ reduction. [b] Selectivity (aldehyde/ketone) determined by ^{1}H NMR analysis of crude reaction mixture prior to reduction. [c] Yield of aldehyde determined by ^{1}H NMR analysis versus an internal standard. DCM = dichloromethane.

ure 1 c). Our group recently developed a Wacker system that employs an exogenous nitrite catalyst in a *t*BuOH/$MeNO_2$ solvent system, which oxidizes unbiased terminal olefins with *anti*-Markovnikov selectivity.[20] This nitrite-cocatalyzed system oxidized the allylic fluoride **A** in moderate yield and high selectivity (26:1 aldehyde/ketone; Figure 1 d). Further optimization, involving exclusion of water from the reaction system, increased nitromethane concentration, and even a reduction in catalyst loading, resulted in very high selectivity for aldehyde formation (36:1 aldehyde/ketone) in high yield (77 %; Figure 1 e). Since the use of *t*BuOH has been established as a strategy to enhance aldehyde selectivity in Wacker-type oxidations,[21,22] the importance of the nitrite catalyst and nitromethane as a cosolvent was assessed. Elimination of these components from the optimized reaction conditions led to diminished aldehyde selectivity (8:1 aldehyde/ketone) and formation of defluorination products (Figure 1 f).[23]

With optimized reaction conditions in hand, we next explored the reaction scope, and found the method to be well suited for regioselective oxidation of allylic fluorides bearing a variety of functional groups.[24] Branched allylic fluorides without added bias were oxidized to the corresponding β-fluorinated aldehydes in high yield and greater than 20:1 selectivity, with an ester and alkyl chloride being well tolerated (Table 1, entries 1, 2, 6, and 7). High aldehyde selectivities were maintained for allylic fluorides bearing an additional directing group. Olefins with phenyl and benzyl ethers, benzoate, and phthalimide branches were oxidized to the corresponding aldehydes with only trace levels of ketone detected (entries 3, 4, 5, and 8). When comparing previous nitrite-modified Wacker oxidations of functionalized olefins, fluoride was shown to be an exceptionally potent directing group.

Despite the relative instability of β-fluorinated aldehydes, the high purity of the crude reaction mixture allows direct transformation into a variety of organofluorine compounds. Reaction with Oxone furnished the β-fluorinated carboxylic acid **1** in excellent yield (Scheme 2 a). Wittig olefination and protection of the carbonyl were achieved in synthetically useful yields in spite of potential base or acid lability of the fluoride (Scheme 2 b,d). The aldehyde was reduced nearly quantitatively to the γ-fluorinated alcohol **3** (Scheme 2 c). Furthermore, nucleophilic addition to aldehydes provides access to a range of new fluorinated building blocks, as demonstrated by the addition of allylB(pin) to produce the homoallylic alcohol **5** (Scheme 2 e). Overall, the efficient preparation of β-fluorinated aldehydes by Wacker-type oxidation serves as a unique synthetic handle to produce diverse fluorinated molecules.

To investigate how our method may be used to generate stereodefined organofluorines, we were interested in the aldehyde-selective oxidation of enantioenriched allylic fluoride **6** [Eq. (1)].[7h] Under the optimal reaction conditions, oxidation occurred without erosion of enantiopurity,[25] thus allowing the isolation of enantioenriched fluorinated product **7** in good yield and enantiomeric excess. This result suggests that palladium-catalyzed olefin isomerization does not occur on the time scale of oxidation to the aldehyde product.



Scheme 2. Derivatization of a β-fluorinated aldehyde crude product. All derivatizations performed using crude Wacker oxidation product. Yields reported over 2 steps. a) Oxone, DMF. b) $MePPh_3Br$, *n*BuLi, THF. c) $NaBH_4$, DCM/EtOH (7:5). d) *p*TsOH, ethylene glycol, molecular sieves. e) AllylB(pin), DCM. DMF = *N*,*N*-dimethylformamide, THF = tetrahydrofuran, Ts = 4-toluenesulfonyl.

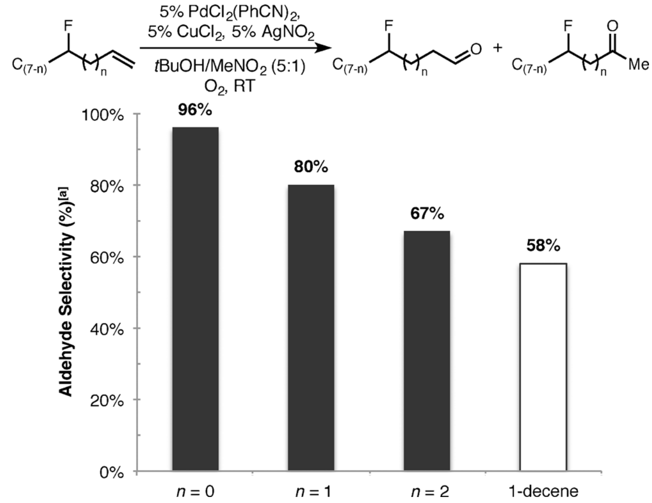
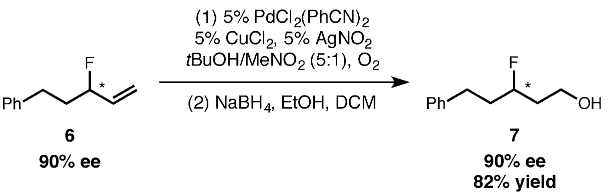


Figure 2. Influence of fluoride proximity on regioselectivity of oxidation. [a] Selectivity (aldehyde/total oxidation yield) determined by ^{1}H NMR analysis.

 (1)

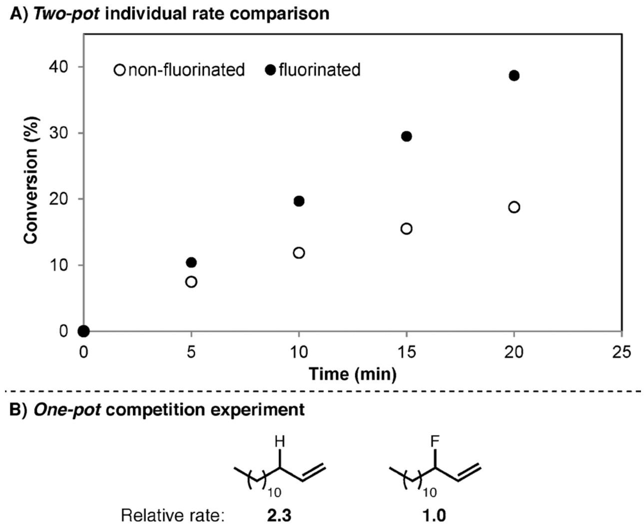


Figure 3. Individual rate and competition experiments performed to measure relative rates of conversion.

Having demonstrated the synthetic utility of the transformation, we sought to gain insight into the role of the fluoride in influencing regioselectivity and reactivity. To this end, a study of the distance-dependence of regioselectivity on fluoride proximity was conducted. Three alkyl fluoride isomers were synthesized with systematic variation of the distance between fluoride and olefin. The oxidations of these compounds under our standard reaction conditions were then compared along with that of 1-decene (Figure 2). The high aldehyde selectivity (96 %) in the case of the allylic fluoride ($n=0$) depreciates as n increases. A strong preference for oxidation to the aldehyde is maintained in the reaction of a homoallylic fluoride ($n=1$), thus suggesting that this method can provide a convenient route to γ-fluorinated aldehydes. However, aldehyde selectivity diminishes for the analogue fluorinated in a more distal position ($n=2$), and poor regioselectivity is observed in the oxidation of the unbiased olefin 1-decene (58 %).[26] The gradual loss in selectivity as fluoride substitution is placed further from the olefin is consistent with a key inductive effect which enhances regioselectivity under these nitrite-modified Wacker conditions.

The relative rates of conversion of a fluorinated and non-fluorinated olefin were studied to further elucidate the effect of fluoride substitution (Figure 3). Individual rate comparisons of the two compounds show that the more electron-deficient fluorinated olefin reacts at an accelerated rate relative to the unfunctionalized olefin (Figure 3 A). However, when the two olefins were oxidized in competition in a 1:1 ratio, the non-fluorinated olefin was consumed 2.3 times faster than the allylic fluoride, potentially because of saturation of the catalyst with the non-fluorinated olefin (Figure 3 B). This inversion of relative reactivity, which results from a decrease in the rate of conversion of the fluorinated olefin rather than an increase in the rate of conversion of the non-fluorinated olefin, suggests that stronger olefin coordination does not inherently lead to accelerated rate of oxidation.

In summary, we have developed a practical synthesis of β-fluorinated aldehydes from readily accessible allylic fluorides. This method represents a rare example of catalysis to produce β-fluorinated carbonyl compounds under procedurally simple conditions. Direct transformation of crude aldehyde products demonstrates the versatility of β-fluorinated aldehyde building blocks. Preliminary mechanistic studies are consistent with inductive effects having a significant influence on both the regioselectivity and rate of oxidation and will facilitate further study of this new catalytic system.

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Keywords: aldehydes · fluorine · oxidation · palladium · regioselectivity

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5561 – 5565; *Angew. Chem.* **2013**, *125*, 5671 – 5675; f) S. L. Bourne, S. V. Ley, *Adv. Synth. Catal.* **2013**, *355*, 1905 – 1910.
[23] In addition to 9% unsaturated aldehyde detected by ^{1}H NMR spectroscopy, a linear allylic alcohol (S_N2') was formed in 28% yield, confirmed by GC-MS.
[24] Although β-fluorinated aldehydes are not stable to column chromatography, the crude products could be directly reduced to stable alcohol derivatives by treatment with $NaBH_4$.
[25] Studies by Feringa have shown retention of enantiopurity in allylic amides (Ref. [21]) and racemization in the case of allylic esters (Ref. [22e]).
[26] Under related reaction conditions optimized for the oxidation of unbiased olefins, 1-dodecene was oxidized with 79% aldehyde selectivity (Ref. [20a]).

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Communications

Oxidation

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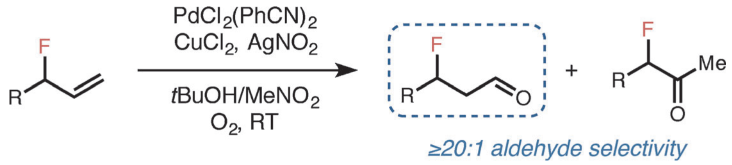
Direct Access to β-Fluorinated Aldehydes by Nitrite-Modified Wacker Oxidation



Out of Wack(er): The aldehyde-selective Wacker-type oxidation of allylic fluorides was accomplished using catalytic nitrite, thus providing a direct route to β-fluorinated aldehydes. Allylic fluorides bearing a variety of functional groups are transformed in high yield and regioselectivity. Preliminary mechanistic investigations suggest that inductive effects have a strong influence on the rate and regioselectivity of the oxidation.

