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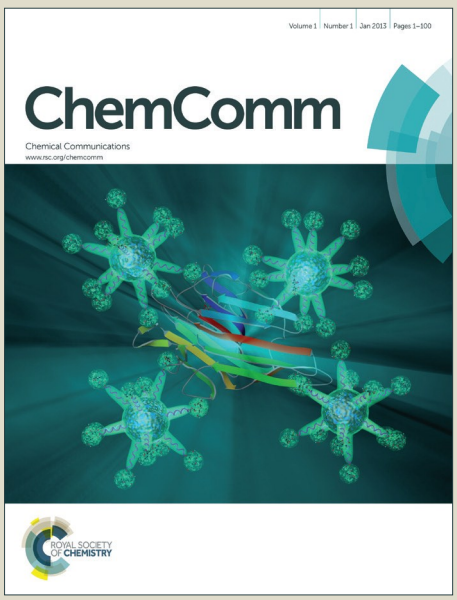

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Direct Fluorination of Styrenes

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We have developed a practical method to synthesize fluorostyrene compounds. A mild and regioselective mono-fluorination reaction occurred smoothly for various di- and trisubstituted styrenes in the presence of $RuCl_3$ and *N*-Fluorobenzenesulfonimide (NFSI). A tandem alkyne hydroarylation/olefin fluorination was also developed using Au catalysis.

Fluorine atom plays a very unique role in modulating the property of functional molecules such as pharmaceuticals, peptides, polymers and agrochemicals.[1] Its enhanced lipophilicity and metabolic stability has made fluorination a exceptional tool to modify a molecule's overall physicochemical properties. Among fluorinated compounds, fluoroalkenes found wide application in peptidomimics[2] and fluoropolymers.[3] For example; vinyl fluoride has a size and dipole moment similar to an amide bond (Figure 1), therefore has been used as an amide isostere to alter the conformation of peptides.

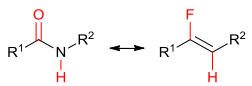


Figure 1. Fluoroalkenes as amide isostere

Considering the importance of fluoroalkenes in medicinal chemistry and material science, they have become an important target for synthetic method development. The classical Wittig olefination using phosphonium monofluoromethylides is a robust method for converting aldehydes and ketones to their corresponding fluoroolefin derivatives.[4] Fluoromethylenation of ketones can be accomplished via Julia-Kocienski olefination.[5] Alkyl halides can be converted to terminal fluoroalkenes using fluorobis-(phenylsulfonyl)methane in a substitution-elimination sequence.[6] In addition, nucleophilic SN2′ additions of nucleophiles (cuprates, organolithium and amines) to 3,3-difluoropropenes were also reported.[7] More recently, efforts have been focused on transition metals catalyzed processes that accommodated wide functional group tolerance and mild reaction condition (Figure 2). Gold-catalysed hydrofluorination reaction of alkyne using various F^- reagents was reported independently by Sadighi, Miller, Nolan, Hammond and Xu.[8] Gouverneur and Nevado groups reported synthesis of fluoroalkenes using propargyl esters under gold catalysis.[9] Related hydrofluorination of alkenes using F^+ reagents were independently accomplished by Gouverneur, Boger, Shigehisa and Hiroya (Figure 2).[10] Aminofluorination of alkenes using palladium catalysis was reported by Liu.[11] Despite these advances, direct conversion of industrial olefinic hydrocarbon feedstock to fluoroalkenes remains a significant challenge. Herein, we report our progress on converting styrenes to fluorostyrenes using Ru catalysis.

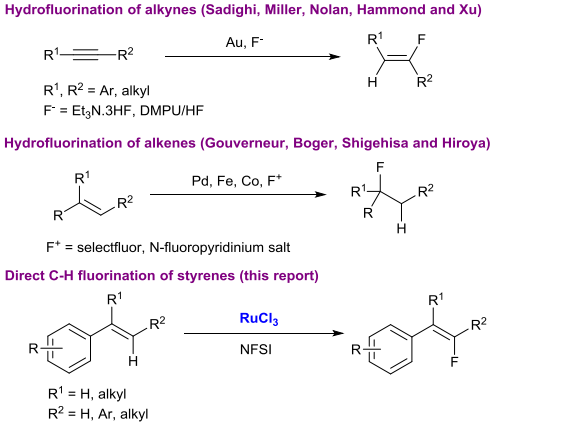
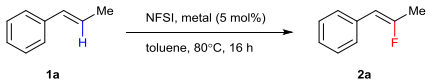


Figure 2. Fluorination of alkynes and alkenes using transition metal catalysis

We initiated our investigation by affecting *trans*-β-methylstyrene with various electrophilic fluorinating agents using transition metals. Most F^+ reagents generated complex mixtures, with only NFSI led to a small amount of the desired fluoroolefin product. A number of transition metals were found to promote this direct C-H fluorination

Considering the importance of fluoroalkenes in medicinal chemistry When the reaction was performed using 5 mol% $RuCl_3$ and 1.2 eq. NFSI in toluene at 80°C for 16 hours, product **2a** was observed in 70% GC yield. The catalyst loading could be lowered to 2 mol% without compromising yield. The use of 4Å molecular sieves further improved conversion and the product was isolated in 78% yield (Table 1, entry 14). The reaction occurred exclusively at the β position of the styrene, with the (*Z*) product being the sole olefinic isomer. No α- or allylic fluorination product was observed.

Table 1. Catalyst survey for the fluorination of *trans*-β-methylstyrene[a]



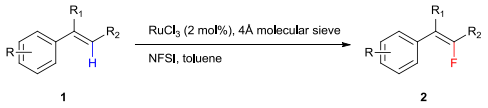
1a 2a

entry	catalyst	yield (%)[b]
1	$Pd(OAc)_2$	--
2	$Cu(OAc)_2$	--
3	$Cu(OPiv)_2$	38
4	$FeCl_2$	--
5	AgOAc	39
6	$[RhCp^*(OAc)_2]_2$	42
7	$Yb(OTf)_3.H_2O$	--
8	$Sc(OTf)_3$	--
9	$In(OTf)_3$	6
10	$Zn(OTf)_2$	31
11	$NiCl_2$	48
12	Ph_3PAuCl	54
13	$RuCl_3$	70
14[c]	$RuCl_3$	78

[a] Unless noted otherwise, the reaction was conducted using **1a** (0.5 mmol), NFSI (0.6 mmol), and a metal catalyst (0.025 mmol, 5 mol%) in toluene (2.5 mL) at 80°C for 16 hr. [b] Yields were determined by GC-MS using biphenyl as the internal standard. [c] The catalyst loading was 2 mol%; Molecular sieves (4Å, 100 mg) was used; isolated yield.

With the optimized reaction condition in hand, we next turned our attention to examine the scope of styrene (Table 2). For styrenes bearing a β substituent, the monofluorination occurred at the β-carbon only. Both alkyl and aryl groups were tolerated. The reaction of β-isopropyl *p*-methoxystyrene proceeded smoothly at 80°C, affording the desired fluorostyrene product **2f** in 91% yield. Terminal styrenes also underwent smooth monofluorination. (*Z*)-2-fluoro-*p*-methoxystyrene **2b** was prepared in 75% yield from *p*-methoxy styrene. It is noteworthy that this exclusive site-selectivity is unprecedented, considering the fluorination occurred at the most crowded cis β-C–H bond. Neither aryl C–H fluorination or oxidation of the aryl were observed for electron-rich substrates. Both *p*- and *o*-methoxystyrene analogues were fluorinated in high yield. Heterocyclic vinyl C–H worked equally well. Stilbenes and cinnamyl substrates were less reactive and further elevated temperature was required. For 2-acyl indole, the fluorination occurred at the C2 position.

Table 2. Substrate scope of terminal and substituted styrenes[a]



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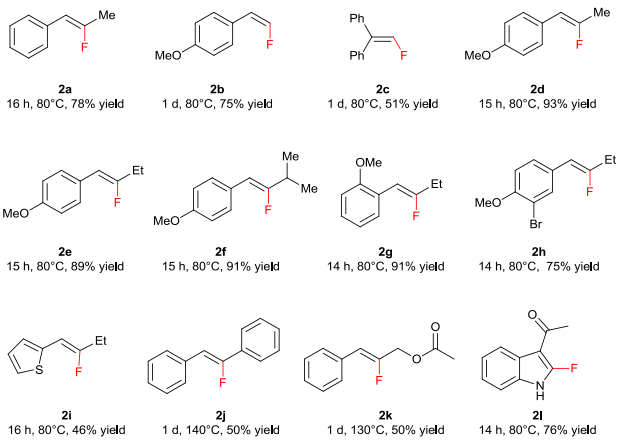


2a 16 h, 80°C, 78% yield; **2b** 1 d, 80°C, 75% yield; **2c** 1 d, 80°C, 51% yield; **2d** 15 h, 80°C, 93% yield

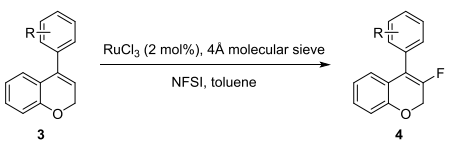
2e 15 h, 80°C, 89% yield; **2f** 15 h, 80°C, 91% yield; **2g** 14 h, 80°C, 91% yield; **2h** 14 h, 80°C, 75% yield

2i 16 h, 80°C, 46% yield; **2j** 1 d, 140°C, 50% yield; **2k** 1 d, 130°C, 50% yield; **2l** 14 h, 80°C, 76% yield

[a] The reactions were performed on a 0.5 mmol scale; isolated yield.

The selectivity for the cis β-C–H was intriguing. We next examined substrates with the cis β position blocked. A number of chromenes were tested (Table 3). To our delight, chromenes bearing either electron-rich or electron-poor substituents underwent facile trans β-C–H fluorination at lower temperature. The reaction was noticeably faster for electron-rich olefins. For substrate containing a strong electron-withdrawing NO_2 group, the reaction required 80°C to proceed. Again, no aryl and allylic fluorination was observed.

Table 3. The Substrate Scope of Chromenes[a]



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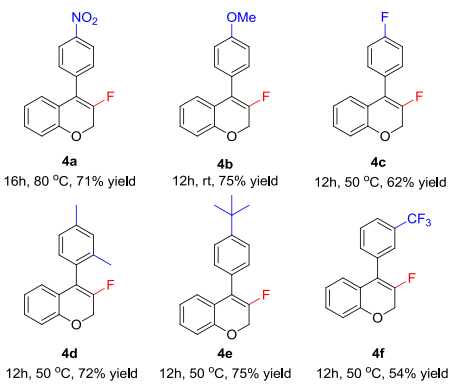

4a 16h, 80 °C, 71% yield; **4b** 12h, rt, 75% yield; **4c** 12h, 50 °C, 62% yield

4d 12h, 50 °C, 72% yield; **4e** 12h, 50 °C, 75% yield; **4f** 12h, 50 °C, 54% yield

[a] The reactions were performed on a 0.5 mmol scale; isolated yield.

Based on this result, we were encouraged to develop a hydroarylation/fluorination cascade reaction to synthesize fluorochromenes using more readily available aryl propargyl ethers.

Ru failed to promote the first hydroarylation step. Gold, on the other hand, was found to catalyse both C C and C F bond formation sequentially (Figure 3). For this cascade, the fluorination was believed to occur via a vinyl gold intermediate.[12]

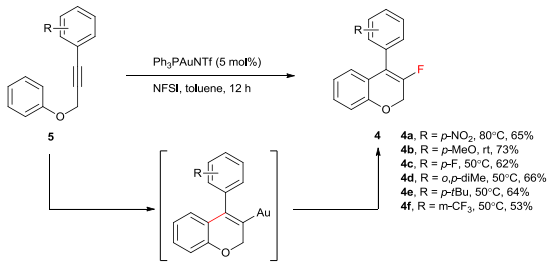

Figure 3. Tandem hydroarylation/fluorination of aryl propargyl ethers

Isotope experiments were performed and the rate difference between H and D substrates was not significant enough for direct involvement of a C H bond cleavage as the rate limiting step. Liu and co workers developed a palladium catalyzed aminofluorination reaction of styrenes using NSFI. In their work, small quantity of the corresponding styrenyl fluoride was observed as a 1:2 E/Z isomeric mixture (6%).[11] The exclusive cis β selectivity observed using our method suggests a different reaction mechanism using Ru. In addition, the Liu's product was subjected to our standard condition, and no desired styrenyl fluoride was obtained. Therefore, the aminofluorinated intermediate is not the intermediate for our reaction. The exact reaction mechanism remained unclear. Likely, an electrophilic fluorination pathway is operable. The exclusive cis β-selectivity might be a result of intramolecular hydrogen bonding between fluorine and the ortho aryl C H bond. In depth mechanistic investigation is currently ongoing.

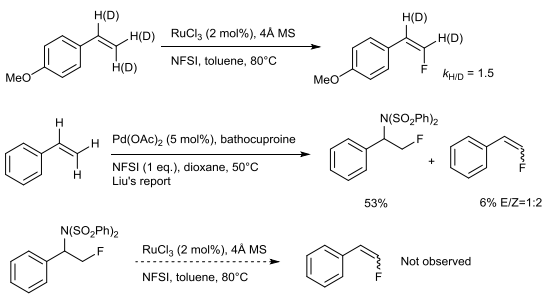

Figure 4. Mechanistic experiments

Conclusions

In summary, we report a high selective olefin fluorination reaction using aryl olefins. A wide range of styrenyl and chromenyl fluorides were synthesized in good yields using $RuCl_3$ as catalyst. A gold catalysed hydroarylation/fluorination cascade has also been developed to access substituted fluorochromene analogues using propargyl ethers.

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Notes and references

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† Electronic Supplementary Information (ESI) available: experimental procedures, product characterizations and copies of NMR spectra. See DOI: 10.1039/c000000x/

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