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Rh(III)-Catalyzed α-fluoroalkenylation of *N*-nitrosoanilines with 2,2-difluorovinyl tosylates *via* C–H bond activation†

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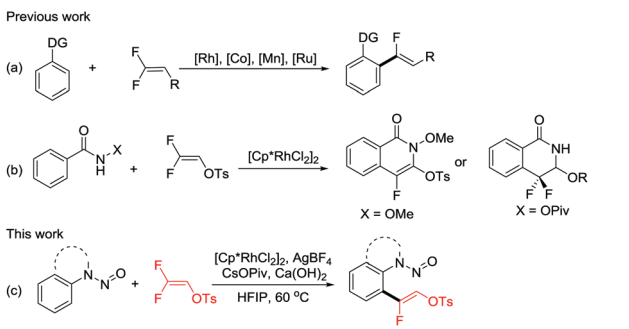
Rh(III)-Catalyzed α-fluoroalkenylation of *N*-nitrosoanilines with 2,2-difluorovinyl tosylates has been realized. This reaction proceeded *via* chelation-assisted C–H activation, olefin insertion and β-F elimination, leading to the synthesis of monofluoroalkenes with high *Z*-selectivity with respect to the olefin. This catalytic system is highly efficient over a broad range of substrates under mild and redox-neutral conditions.

Organic fluorine chemistry has flourished owing to its significant applications in pharmaceutical, agrochemical, and materials sciences in the past few decades.[1] Introduction of fluorine atoms to organics often enhances their pharmacological and biological activities with enhanced lipophilicity and polarity.[1f] Among the fluorine-containing organics, monofluoroalkenes play a vital role in medicinal chemistry, organic synthesis, and peptide chemistry.[2] Monofluoroalkenes have also been used extensively as amide isosteres, which have emerged as useful peptide mimics.[3] The fluorine atoms in these olefin moieties preserve the dipolar nature of the peptide linkage and may participate in hydrogen bonding between the backbone and the peptide bond surrogate.[4] Thus, great efforts have been devoted to developing efficient methods for their synthesis. Recently, α-fluoroalkenylation reactions have been realized by Loh,[5] our group,[6] Ackermann,[7] and others *via* C–H bond activation of arenes and coupling with difluorostyrenes (Scheme 1a). Despite these achievements, transition metal-catalyzed α-fluoroalkenylation reactions have been mostly limited to the employment of *gem*-difluorostyrenes or perfluoroalkylated olefins, and it is relatively more challenging to apply functionalized *gem*-difluoroalkenes as substrates[8] Wang and Li[8a] applied 2,2-difluorovinyl tosylate as a coupling reagent in Rh(III)-catalyzed C–H activation of *N*-OMe benzamides, which delivered a monofluorinated alkene with the retention of the tosylate functionality. Of note, subsequent one-pot acid treatment allowed the efficient synthesis of 4-fluoroisoquinolin-1(2*H*)-ones (Scheme 1b). Despite progress, the efficiency and selectivity of these systems leave large room for improvement, especially for the coupling of functionalized *gem*-difluoroalkenes.

Among the C–H activation reactions, directing groups (DGs) have been commonly employed to enhance the effective concentration of the catalyst, leading to reactive metallacyclic intermediates for subsequent functionalization.[9] The easily obtainable *N*-nitrosoanilines have attracted intensive interest in transition metal-catalyzed C–H bond activation[10] because the nitroso group can serve as an efficient directing group for various C–H activation systems.[11] We now report Rh(III)-catalyzed α-fluoroalkenylation of *N*-nitrosoanilines with 2,2-difluorovinyl tosylates *via* C–H bond activation and β-F elimination. The reaction proceeded with good regio- and stereoselectivity (Scheme 1c).

We initiated our investigation by examining the reaction parameters of the coupling of *N*-nitrosoanilines (**1a**) with 2,2-difluorovinyl 4-methylbenzenesulfonate (**2a**, 1.2 equiv.) in the



Scheme 1 α-Fluoroalkenylation using difluoroalkenes.

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†Electronic supplementary information (ESI) available: Detailed experimental procedures, analytical data and NMR spectra. See DOI: 10.1039/c8qo00947c

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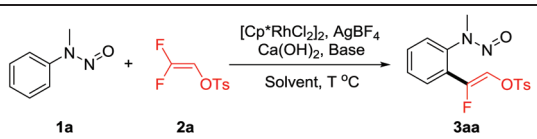
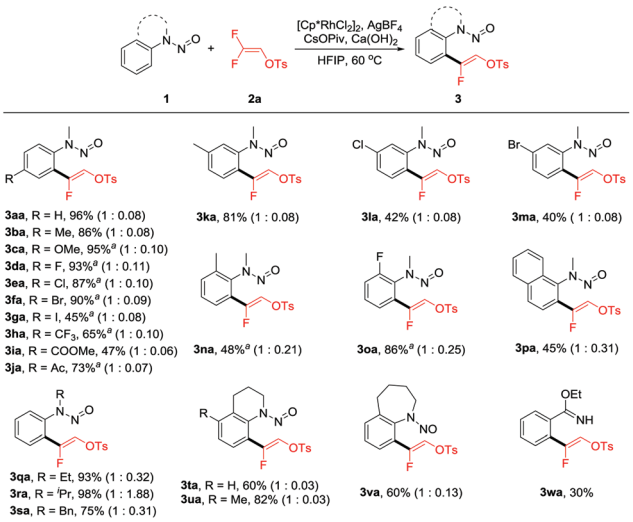
Table 1 Optimization of the reaction conditions[a]



Entry	Base (equiv.)	Solvent	Temp. (°C)	Yield[b] (%) (*syn : anti*)
1	**CsOPiv (1.0)**	**HFIP**	**60**	**96 (1 : 0.08)**
2[c]	CsOPiv (1.0)	HFIP	60	76 (1 : 0.08)
3[d]	CsOPiv (1.0)	HFIP	60	72 (1 : 0.08)
4	CsOAc (1.0)	HFIP	60	89 (1 : 0.08)
5	CsOPiv (1.0)	MeOH	60	0
6	CsOPiv (1.0)	Acetone	60	0
7	CsOPiv (1.0)	TFE	60	6 (1 : 0.08)
8	CsOPiv (1.0)	HFIP	40	91 (1 : 0.08)
9	CsOPiv (1.0)	HFIP	80	66 (1 : 0.08)
10[e]	CsOPiv (1.0)	HFIP	60	55 (1 : 0.08)

[a] Reaction conditions: $[Cp^*RhCl_2]_2$ (4%), $AgBF_4$ (16%), base (1.0 equiv.), $Ca(OH)_2$ (1.0 equiv.), solvent (2 mL), 40–80 °C. [b] Isolated yield (*syn : anti* ratio of the nitroso group in parentheses). [c] $[Cp^*RhCl_2]_2$ (2%) and $AgBF_4$ (8%) were used. [d] No $AgBF_4$ was used. [e] No $Ca(OH)_2$ was used.



Scheme 2 Substrate scope of *N*-nitrosoanilines. Reaction conditions A: **1** (0.2 mmol), **2a** (0.24 mmol), $[Cp^*RhCl_2]_2$ (4.0 mmol%), $AgBF_4$ (16 mmol%), CsOPiv (1.0 equiv.), $Ca(OH)_2$ (1.0 equiv.), HFIP (2 mL), 60 °C for 6 h. Isolated yield (*syn : anti* ratio in parentheses). [a] Reaction conditions B: **1** (0.2 mmol), **2a** (0.24 mmol), $[Cp^*RhCl_2]_2$ (4.0 mmol%), $AgBF_4$ (16 mmol%), CsOAc (1.0 equiv.), $Ca(OH)_2$ (1.0 equiv.), HFIP (2 mL), 60 °C for 6 h. Isolated yield (*syn : anti* ratio in parentheses).

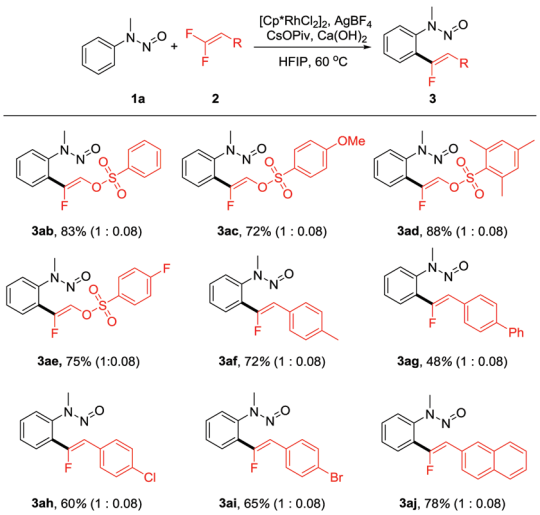
presence of $[Cp^*RhCl_2]_2$ (4 mol%), $AgBF_4$ (16%), CsOPiv, and $Ca(OH)_2$. To our delight, the desired monofluoroalkene product (**3aa**) was obtained in 96% yield in HFIP as a single *Z*-isomer with respect to the olefin unit and with high stereoselectivity with respect to the nitroso group (*syn : anti* = 1 : 0.08, Table 1, entry 1). A lower yield was obtained when the catalyst loading was reduced to 2 mol% (entry 2). A yield of 72% was achieved when $AgBF_4$ was omitted (entry 3). When CsOPiv was switched to CsOAc, **3aa** was obtained in 89% yield (entry 4). Lowering the temperature to 40 °C afforded the product in a slightly lower yield (entry 8), while the yield diminished when the temperature was increased to 80 °C (entry 9). The yield of **3aa** was lowered to 55% when $Ca(OH)_2$ was omitted (Table 1, entry 10).

With the optimized reaction conditions in hand, we next investigated the scope of this coupling reaction using a series of *N*-nitrosoanilines (**1**) with 2,2-difluorovinyl 4-methylbenzenesulfonate (**2a**) as the coupling partner (Scheme 2). It was found that *N*-nitrosoanilines bearing electron-donating and -withdrawing groups at the *para* position all reacted smoothly to provide the corresponding monofluoroalkenes in moderate to excellent yields (**3ba–3ja**). The electronic nature of the substrate affected the yield of the products, and substrates bearing electron-donating groups were more efficient than those with electron-withdrawing ones (**3ba–3ca** *vs.* **3ha–3ja**). Halogen groups (**3da–3ga**) were tolerated in this reaction under slightly modified conditions (conditions B). Furthermore, the reaction showed good regioselectivity and occurred at the less hindered *ortho* site when *N*-nitrosoanilines bearing a *meta* Me, Cl and Br group (**3ka–3ma**) were used. *Ortho*-F substituted nitrosoaniline was also viable for this transformation, affording **3oa** in a yield of 86% under the modified standard conditions. However, the steric resistance effect had a great influence, as in the synthesis of **3na** (48%). *N*-Methyl-*N*-(naphthalen-1-yl)nitrous amide also reacted smoothly to produce **3pa** in moderate yield. By varying the *N*-alkyl group, the corresponding products **3qa–3va** were obtained in good to excellent yields with lower *syn*/*anti* ratios, as a result of the lower *syn*/*anti* ratio of the corresponding arene starting materials. Thus, the ratio of *syn*/*anti* is closely related to the steric resistance of the substituent on nitrogen.[10a] Product **3wa** was obtained in 30% yield when the arene was switched to ethyl benzimidate.

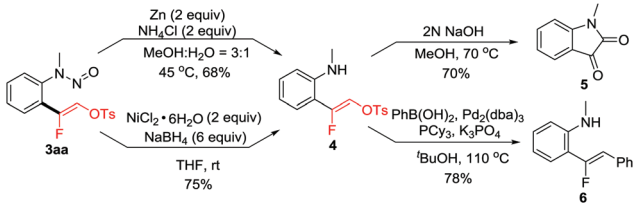
We further investigated the scope of the 2,2-difluorovinyl arenesulfonate in this coupling reaction (Scheme 3). It was found that the reaction efficiency was only marginally influenced by the nature of the substituent in the phenyl ring (**3ab–3ae**). The difluoroalkene substrate was not limited to a 2,2-difluorovinyl arenesulfonate, and *gem*-difluorostyrenes were also applicable, as have been briefly demonstrated in the synthesis of products **3af–3aj** in moderate to good yields.

The synthetic applications of a coupled product (**3aa**) have been briefly explored (Scheme 4). The *N*-nitroso group was reductively cleaved under either Zn/NH_4Cl in a mixed solvent of MeOH and H_2O or $NiCl_2{\cdot}6H_2O/NaBH_4$ in THF, affording aniline **4** as a single stereoisomer. Further treatment of **4** with NaOH in MeOH afforded isatin **5** in good yield. Besides, the OTs group of aniline **4** could be converted to an aryl through palladium-catalyzed Suzuki–Miyaura coupling reaction, affording **6** in 78% yield.

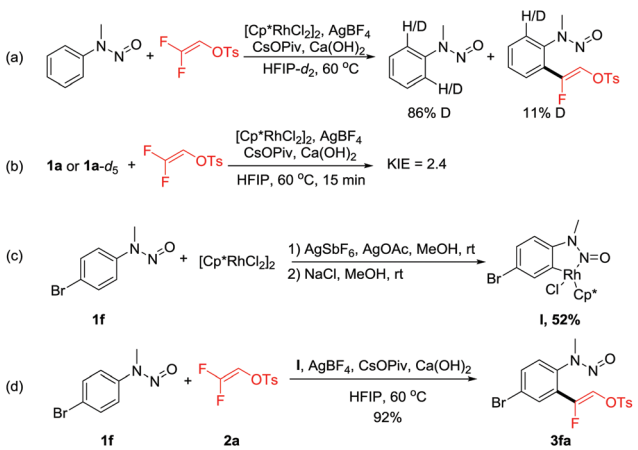
Several experiments have been performed to briefly explore the reaction mechanism (Scheme 5). H/D exchange has been carried out for the reaction of **1a** and **2a** in the presence of deuterated HFIP. The recovered *N*-nitrosoaniline was significantly deuterated at both *ortho* positions (86% D), and product



Scheme 3 Substrate scope of difluoroalkenes. Reaction conditions A: **1a** (0.2 mmol), **2** (0.24 mmol), $[Cp^*RhCl_2]_2$ (4.0 mmol%), $AgBF_4$ (16 mmol%), CsOPiv (1.0 equiv.), $Ca(OH)_2$ (1.0 equiv.), HFIP (2 mL), 60 °C for 6 h. Isolated yield (*syn : anti* ratio in parentheses).

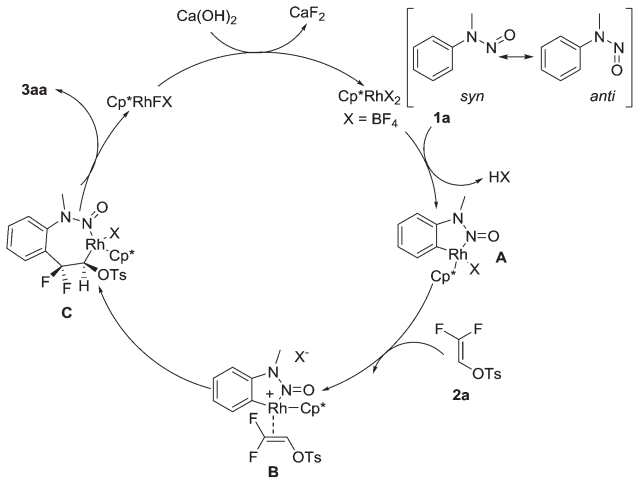


Scheme 4 Synthetic applications.



Scheme 5 Mechanistic studies.

3aa was also deuterated (11% D) at the *ortho* position (Scheme 5a), indicating reversibility of the C–H activation process. The kinetic isotope effect of this coupling was then determined from two parallel experiments (Scheme 5b), and a value of k_H/k_D = 2.4 suggests that the C–H bond cleavage may



Scheme 6 Proposed catalytic cycle.

be involved in the turnover-limiting step. To further probe this C–H activation process, rhodacyclic complex **I**[10j] was prepared (Scheme 5c). Application of **1** as a catalyst precursor to the coupling of **1f** and **2a** afforded product **3af** in comparably good yield (Scheme 5d), further confirming the relevance of C–H activation.

On the basis of these results and previous reports,[5–8] a plausible mechanism for the formation of monofluoroalkenes **3aa** is proposed in Scheme 6. An active $RhCp^*X_2$ species is generated from the anion exchange between $[RhCp^*Cl_2]_2$ and $AgBF_4$. Cyclometalation of *N*-nitrosoaniline **1a** delivers a five-membered rhodacyclic intermediate **A**. Coordination of a *gem*-difluoroalkene then gives an olefin intermediate **B**, which is followed by regioselective migratory insertion of the aryl group into the olefin to give intermediate **C**. On this basis, intermediate **C** undergoes selective β-F elimination *via* a *syn*-coplanar transition state to deliver the olefinated product **3aa**, together with a Rh(III) fluoride.[5a,8a] HF was released by protonolysis of the Rh–F bond, and $Ca(OH)_2$ could abstract the fluoride anion and facilitate β-F elimination with the regeneration of the active Rh(III) catalyst for the next catalytic cycle.

Conclusions

We have realized Rh(III)-catalyzed C–C coupling of *N*-nitrosoanilines and 2,2-difluorovinyl tosylates *via* C–H bond activation and C–F bond cleavage, leading to the efficient synthesis of a series of monofluoro *Z*-olefins under mild conditions. This protocol has been applied to a wide range of substrates with high efficiency and stereoselectivity with respect to the olefin unit. This method may find application in the synthesis of related fluoroalkenes.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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