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Rhodium-Catalyzed Cyclopropanation of Fluorinated Olefins: A Straightforward Route to Highly Functionalized Fluorocyclopropanes

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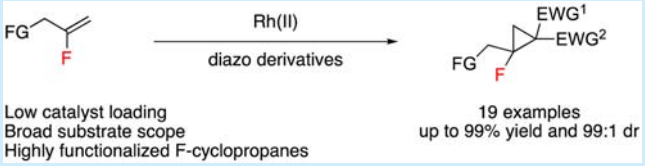
Supporting Information

ABSTRACT: An efficient access to highly functionalized monofluorocyclopropanes is described. The developed methodology allowed straightforward access to a large panel of polysubstituted fluorinated cyclopropanes in good to excellent yields and good diastereoselectivities. The Rh-catalyzed cyclopropanation proved to be efficient on several fluorinated olefins and several diazo compounds. This method represents the first general route to complex fluorinated cyclopropanes.



Over the past decade, new transformations to introduce fluorine into organic molecules have blossomed. Unique properties of the fluorine atom including its electronegativity, its size, and the high energy of the C−F provide fluorinated molecules with unique physical and biological properties.[1] On the other hand, fluorine is well recognized as a hydrogen isostere capable of confering higher metabolic stability with minimal structural alterations. Consequently, more than 20% of pharmaceuticals and 35% of agrochemicals contain at least one fluorine atom.[2] Thus, it is not surprising that organic chemists have devoted great effort toward developing new and efficient methods for the introduction of fluorine and fluorinated building blocks onto key scaffolds.[3] Further, the cyclopropane ring is a very popular subunit encountered in several natural and non-natural bioactive compounds. As the smallest cycloalkane, the cyclopropane ring is able to bring constraint and a higher stability to a particular molecule, thus affording new biological features.[4]

Hence, monofluorinated cyclopropane represents an interesting building block combining the impressive features of the fluorine atom and the cyclopropane ring.[5] This prolific combination is highlighted in several bioactive compounds with highly promising biological activities, as depicted in Figure 1.[6]

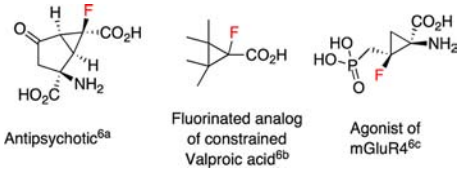


Figure 1. Relevant bioactive fluorinated cyclopropanes.

These target molecules are usually obtained by (1) the addition of a fluorocarbene to alkene,[7] (2) the direct fluorination of cyclopropane,[8] (3) Michael initiated ring closure,[9] and (4) the addition of carbenes to fluoroalkenes. This last approach pioneered by Haszeldine[10] in 1969 mainly focused on the addition of a zinc carbenoid to monofluorinated alkene according to a Simmons−Smith process.[11] Later the transition-metal-catalyzed carbene addition to fluorinated alkenes was explored. In 2000, Haufe and co-workers[12] described an elegant Cu-catalyzed addition of diazoacetate to alkyl- and aryl-substituted fluorinated alkenes, while the Rh-catalyzed addition of diazo compounds to fluoroalkenes showed a narrow substrate scope and remains restricted to α-fluoro styrenes,[13] fluorodienes,[6a] intramolecular processes,[14] or fluorinated alkenes substituted with an electron-withdrawing group (e.g., 1-fluoro-1-(phenylsulfonyl)ethylene) (Scheme 1).[15] It is worthy to note that in the case of the Cu-catalyzed addition of diazoacetate to fluorinated alkenes only restricted functionalities are obtained on the expected fluorinated cyclopropane, whereas the Rh-catalyzed cyclopropanation gave moderate yields even in the intramolecular version.[14]

To circumvent these limitations and as part of our ongoing research program devoted to the design of new routes to monofluorinated cyclopropanes,[16] we report herein a straightforward method to access polyfunctionalized monofluorinated cyclopropanes by means of a Rh-catalyzed addition of various diazo compounds to functionalized fluorinated alkenes.

At the outset of the project, we explored the addition of **1a** to fluorinated alkenes **2a** in order to determine the optimized reaction conditions.

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Scheme 1. Common Methods To Access Fluorocyclopropanes

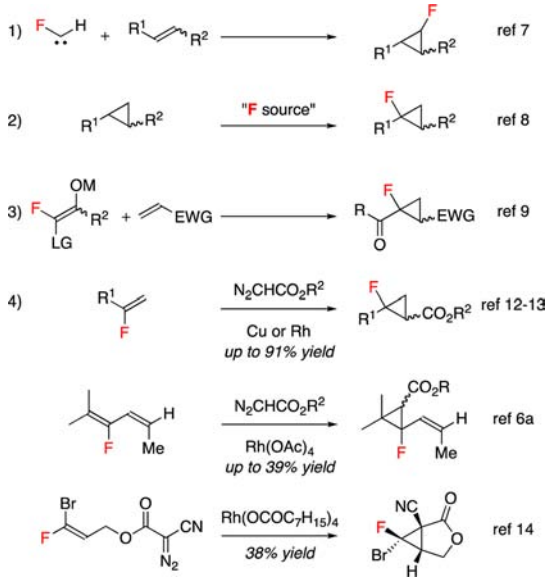
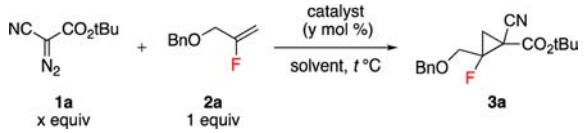


Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	solvent	x	y	temp (°C)	dr[b]	yield[c] (%)
1	$Cu(OTf)_2$	DCM	1	2	rt		NR
2	CuI	DCM	1	2	rt		NR
3	$Pd(OAc)_2$	DCM	1	2	rt		NR
4	$AgBF_4$	DCM	1	2	rt		NR
5	$Rh_2(OAc)_4$	DCM	1	2	rt	32:68	3
6	$Rh_2(OPiv)_4$	DCM	1	2	rt	23:77	48
7	$Rh_2(OPiv)_4$	Et_2O	1	2	rt	19:81	28
8	$Rh_2(OPiv)_4$	toluene	1	2	rt	44:56	23
9	$Rh_2(OPiv)_4$	MeCN	1	2	rt	37:63	11
10	$Rh_2(OPiv)_4$	DCM	1	2	0	21:79	94
11	$Rh_2(OPiv)_4$	DCM	1	2	−20	24:76	91
12	$Rh_2(OPiv)_4$	DCM	1.5	2	0	23:77	97
13	$Rh_2(OPiv)_4$	DCM	2	2	0	21:79	90
14	$Rh_2(OPiv)_4$	DCM	1.5	0.5	0	24:76	99[d]

[a]Conditions: **2a** (0.25 mmol), solvent (2 mL) under an Ar atmosphere. [b]Diastereomeric ratio was determined by ^{19}F NMR on the crude reaction mixture (*trans*/*cis*). [c]Yield determined by ^{19}F NMR using *α*,*α*,*α*-trifluorotoluene as an internal standard. [d]Isolated yield.

Initial attempts using Cu, Pd, or Ag catalyst did not give any trace of the desired monofluorinated cyclopropane **3a** (entries 1−4), while $Rh_2(OAc)_4$ afforded the desired target albeit in very low yield (entry 5). Pleasingly, the replacement of $Rh_2(OAc)_4$ by the more soluble $Rh_2(OPiv)_4$ gave the desired fluorocyclopropane in 48% yield with a decent 23:77 diastereomeric ratio (entry 6). Then, a solvent survey revealed that dichloromethane (DCM) was the best solvent for this transformation (entries 7−9). Further optimizations of the reaction conditions showed that lowering the reaction temperature to 0 °C enhanced the reaction yield to 94% (entry 10), while the reaction performed at −20 °C gave **3a** in a slightly lower yield without improvement of the diastereoselectivity of the reaction (entry 11). An examination of the stoichiometry of **1a** showed that 1.5 equiv afforded the best conditions, giving the fluorinated cyclopropane **3a** in 97% yield and 23:77 dr (entries 12−13). Finally a decrease of the catalyst loading to 0.5 mol % gave the monofluorinated cyclopropane **3a** in 99% isolated yield as an inseparable 24:76 *trans*/*cis* mixture of diastereomers (entry 14).

With these optimized conditions in hand and in order to highlight the versatility of our developed methodology, the scope of the reaction was extended to several diazo compounds **1a**−**e** and fluorinated olefins **2a**−**e** (Scheme 2).

First, we decided to assess the efficiency of the process by conducting the reaction on a gram scale. To our delight, starting from 4 mmol of **2a**, cyclopropane **3a** was isolated with 85% yield and an improved diastereoisomeric ratio (17:83). We then moved on the extension of the reaction scope with the *O*-benzylated fluoroallylic alcohol **2a** and several diazo derivatives **1a**−**e**. Pleasingly, the addition of the ethyl cyanodiazoacetate **1b** proceeded well, giving the desired fluorocyclopropane **3b** in 74% yield with a somewhat lower selectivity (64:36 dr). It is worth noting that the relative configuration of the major isomer (*cis*-isomer) has been confirmed by X-ray crystallographic analysis.[17] The addition of diethyl diazomalonate **1c** furnished the expected fluorocyclopropane **3c**, which appeared to be quite unstable on silica gel since it was isolated with only 43% yield despite an 80% NMR yield measured on the crude reaction mixture. The addition of ethyl diazonitroacetate **1d** on **2a** was more delicate; 3 equiv of diazo compound **1d** was required to ensure a decent conversion, and fluorinated cyclopropane **3d** was isolated with 54% yield and 76:24 dr. Finally, by replacing $Rh_2(OPiv)_4$ by $Rh_2(esp)_2$ (1 mol %),[18] nitrodiazo(*p*-methoxyacetophenone) **1e** was successfully reacted with fluoroolefin **2a** giving the polyfunctionalized fluorocyclopropane **3e** in 65% isolated yield and 56:44 dr. The replacement of the benzyl protecting group on the fluorinated olefin by a PMB protecting group did not affect the reaction outcome, and the corresponding fluorocyclopropanes **3f**, **3g**, and **3h** were obtained with similar yields and selectivities. We then applied our methodology to 3-chloro-2-fluoropropene **2c**. *α*-Cyano diazoacetates **1a** and **1b** as well as diethyl diazomalonate **1c** reacted successfully with **2a** under our optimized conditions and gave the corresponding fluorocyclopropanes **3i**, **3j**, and **3k** with 67%, 85%, and 80% yield, respectively. The addition of nitro-containing diazo compounds was more challenging; 3 equiv of diazo derivatives was required as well as the replacement of $Rh_2(OPiv)_4$ by $Rh_2(esp)_2$ (1 or 2 mol %) to obtain cyclopropane **3l** and **3m** in 95% and 33% isolated yield with good to excellent diastereoisomeric ratios (99:1 and 79:21). We then turned our attention to the cyclopropanation of the valuable phosphonate derivative **2d**. As with olefin **2c**, diazo compounds **1a**−**c** gave the expected cyclopropanes **3n**−**p** under our standard reaction conditions, whereas diazo compounds bearing a nitro group were once again less efficient and amounts of **1d** and **1e** had to be increased from 1.5 to 3 equiv to ensure a good conversion into the desired fluorocyclopropane **3q** and **3r** (78% and 87% yield, respectively). Interestingly, a complete diastereoselectivity was observed in the case of **3q**. Finally, the more sterically hindered trisubstituted fluoroolefins **2e** was tested and to our delight afforded the corresponding pentasubstituted fluorocyclopropane **3s** in 47% yield and 90:10 dr.

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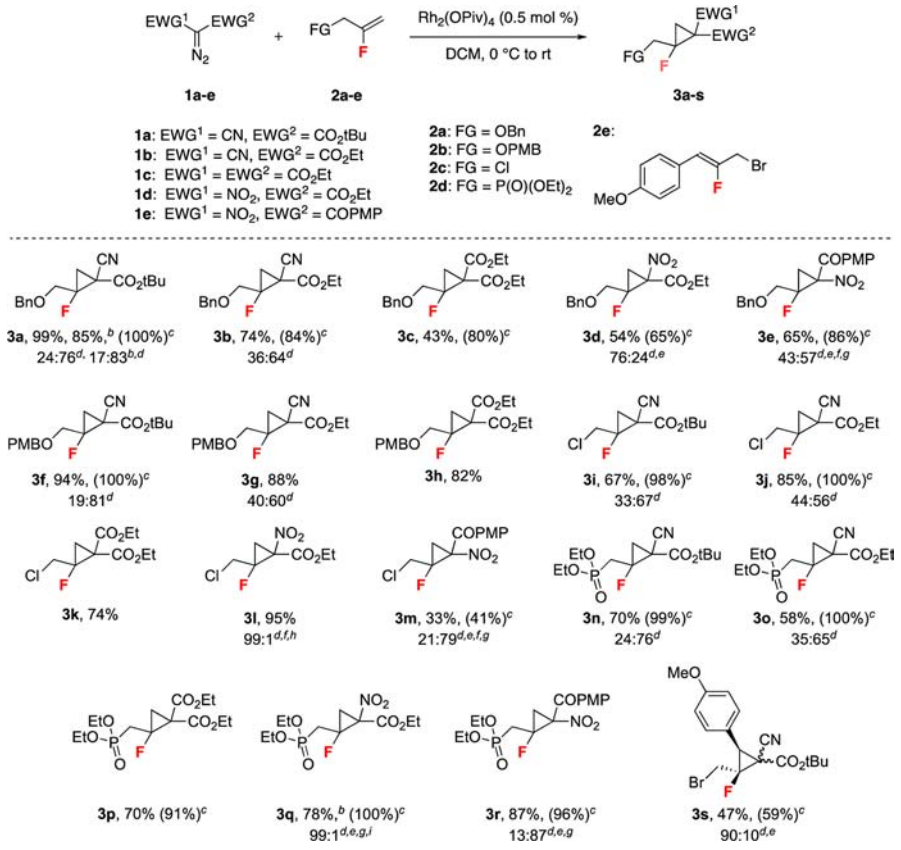
Scheme 2. Scope of the Reaction[a]

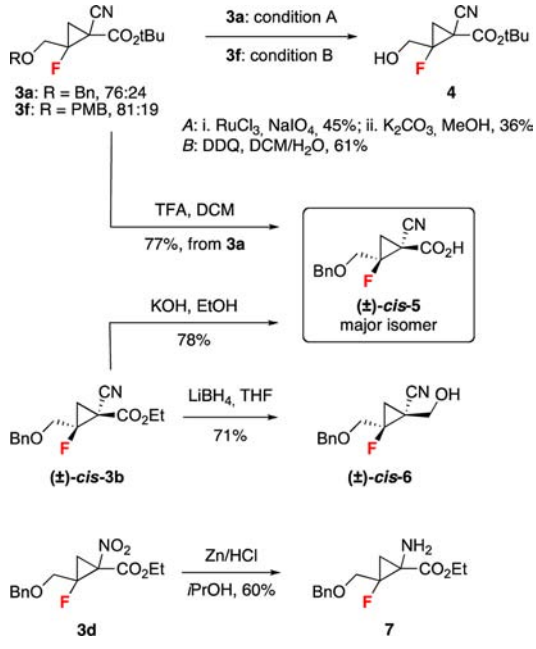


[a]Conditions: **1a–e** (0.75 mmol), **2a–d** (0.5 mmol), $Rh_2(OPiv)_4$ (2.5 mol %), DCM (2 mL), 0 °C. [b]Reaction was performed on 4 mmol scale of **2a**. [c]NMR yield determined by ^{19}F NMR using α,α,α-trifluorotoluene as an internal standard. [d]Diastereomeric ratio (*trans*/*cis*) determined by ^{19}F NMR on the crude reaction mixture; for the determination of the major isomer see the Supporting Information. [e]3 equiv of diazo was used. [f]$Rh_2(esp)_2$ was used instead of $Rh_2(OPiv)_4$. [g]1 mol % of catalyst was used. [h]2 mol % of catalyst and 2 equiv of **1d** were used. [i]Reaction was performed on 4.3 mmol scale.

Having established the scope of our methodology we then turned our attention to the functional group manipulation of the fluorocyclopropanes thus obtained (Scheme 3).

All our attempts to remove the benzyl protecting group by using a standard procedure such as Pt- or Pd-catalyzed hydrogenation were unsuccessful. However, we were able to cleave this protecting group through a two-step sequence: oxidation followed by a selective debenzoylation to obtain **4**, albeit in moderate yields. This drawback could be easily circumvented by replacing the benzyl group by a PMP protecting group, which was smoothly removed by oxidative cleavage with DDQ in 61% yield to access to the corresponding primary alcohol **4**. The *tert*-butyl ester group was readily converted into the corresponding carboxylic acid **5** in 77% isolated yield. The saponification of the pure *trans*-isomer of **3b** furnished the corresponding acid (±)-***trans*-5b** in 78% yield and unequivocally established the trans configuration of the major diastereoisomer of **3a**. The reduction of the ethyl ester (±)-***trans*-3b** was performed in good yield to access to the corresponding primary alcohol (±)-***trans*-6** in 71% yield. Finally, the selective reduction of the nitro group of **3d** was achieved by using Zn/HCl and **7** was obtained in 60% isolated yield. All these postfunctionalizations clearly illustrate the versatility of the newly synthesized fluorinated cyclopropanes and showcase their use as key fluorinated building blocks, particularly in the quest of new bioactive compounds.

Scheme 3. Synthetically Useful Transformations of the Products



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In summary, we report herein a mild and general approach to highly functionalized fluorocyclopropanes. The Rh-catalyzed cyclopropanation of di- and trisubstituted fluorinated olefins gave the corresponding fluorocyclopropanes in good to excellent yields and good diastereoselectivities. The depicted methodology was applied to a broad range of diazo compounds and fluorinated olefins, thus highlighting the efficiency of the process and representing the first general method to access highly functionalized monofluorocyclopropanes. Finally, functional group manipulations of these highly functionalized fluorinated building blocks was performed to prove their broad synthetic utility. Applications and extension of this methodology are currently underway in our laboratory.[19]

■ ASSOCIATED CONTENT

Supporting Information

^{1}H ^{13}C, and ^{19}F NMR spectra and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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