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Synthesis of monofluoroalkenes through selective hydrodefluorination of *gem*-difluoroalkenes with Red-Al®

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A novel and practical approach for the selective hydrodefluorination of *gem*-difluoroalkenes using Red-Al® as reductant at room temperature in CH_2Cl_2 without any additional base and metal catalyst was reported. Various monofluoroalkenes were obtained in moderate to high yields with good *E*-selectivity.

The monofluoroalkenes are an important class of fluorinated compounds and have potential applications in medicinal chemistry and material sciences.[1] Meanwhile, they can be used as fluorinated building blocks for further transformation in organic syntheses.[2] Nowadays, various methods for the preparation of monofluoroalkenes have therefore been developed,[3] including reductive defluorination of allylic *gem*-difluorides with Pd catalyst,[4a] gold-catalyzed hydrofluorination of alkynes in the presence of $Et_3N{\cdot}3HF$,[4b] fluorination of alkenylboronic acid [4c] and Julia-Kocienski fluoroolefination reaction with various ketones and aldehydes.[4d]

Hydrodefluorination (HDF) is the simplest transformation of C–F bond.[5] Selective hydrodefluorination of polyfluorinated compounds has become a useful approach to access partially fluorinated compounds which are difficult to obtain otherwise.[6] However, most research focused on the catalytic selective hydrodefluorination of fluoroarenes, the selective hydrodefluorination of fluoroalkenes have remained rare.[7] In particular, only few examples referring to the transformation of difluoroalkene derivatives to the corresponding monofluoroalkenes have been observed.[8] Xiao and Hong have reported the preparation of 2-fluorovinyl tosylate by treating 2,2-difluorovinyl tosylate with $LiAlH_4$ in ether.[8a] Shi has described that the reductive reaction of 2-[(trimethylsilyl)methyl]-substituted 3,3-difluoropropenoate with $LiAlH_4$ led exclusively to the formation of the *Z*-configurated monofluorinated allylic (only one example),[8b] whereas the reaction of $LiAlH_4$ with a simple 2-alkyl-substituted 3,3-difluoropropenoate reported by Watanabe gave monofluoroallylic alcohols with little stereoselectivity.[8c]

Recently, Paquin and coworkers developed two novel methods for the synthesis of β-fluorostyrene and 1,1-diaryl-2-fluoroethenes respectively. [9] In both pathways, a common intermediate (*Z*)-1-aryl-2-fluoro-1-(trimethylsilyl)ethene was generated via an addition/elimination reaction of lithium triethylhydridoborate ($LiEt_3BH$) to silylated β,β-difluorostyrene derivative. Furthermore, Red-Al® ($NaAlH_2(OCH_2CH_2OCH_3)_2$) was also used as a reducing agent for the conversion of difluoroalkenes to monofluoroalkenes.[10] However, these methods suffer from several drawbacks, such as narrow substrate scope, low stereoselectivity, lack generality, over reduction and the use of environmentally unfriendly solvent such as benzene and toluene. Consequently, the development of the synthesis of monofluoroalkenes via the selective reduction of common difluoroalkenes under mild reaction conditions is highly desirable. Herein, we report an efficient and practical approach for the monofluoroalkenes via the hydrodefluorination of difluoroalkenes using Red-Al® as reductant at room temperature in CH_2Cl_2 without any added base and metal catalyst (Scheme 1).

Scheme 1 Selective hydrodefluorination of *gem*-difluoroalkenes with Red-Al®

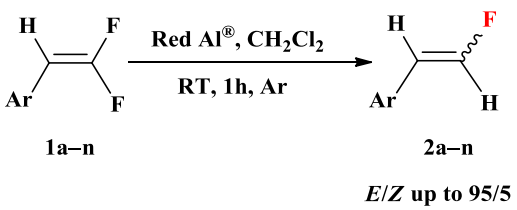
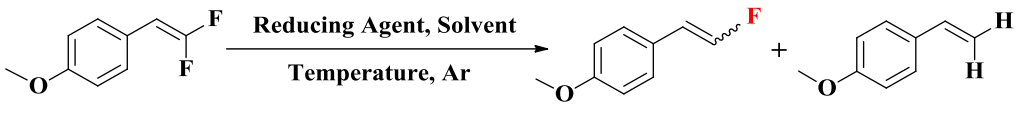


Table 1 Selective hydrodefluorination of 2,2-difluoroalkenes under different conditions [a]



1a **2a** **3a**

Entry	Reducing agent (equiv)	Solvent	Temp (℃)	Time (h)	Yield (%) (**2a/3a**)[b]
1	NaH (4.0)	THF	60	4	N.R.
2	$NaBH_4$ (4.0)	THF	60	4	N.R.
3	Bu_3SnH (4.0)	THF	60	4	N.R.
4	$LiAl(O\text{-}t\text{-}C_4H_9)_3$ (4.0)	THF	60	4	N.R.
5	DIBAL-H (4.0)	THF	60	4	12/0
6	$LiEt_3BH$ (4.0)	THF	60	4	58/42
7	$LiAlH_4$ (2.0)	THF	60	4	81/5
8	Red Al® (2.8)	THF	60	4	87/13
9	Red Al® (4.0)	THF	60	4	68/32
10	Red Al® (8.0)	THF	60	4	35/65
11	Red Al® (2.8)	THF	R.T	1	95/5
12	Red Al® (2.8)	Et_2O	R.T.	1	97/3
13	Red Al® (2.8)	toluene	R.T.	1	95/5
14	Red Al® (2.8)	benzene	R.T.	1	97/3
15	Red Al® (2.8)	CH_2Cl_2	R.T.	1	99/1
16	Red Al® (2.0)	CH_2Cl_2	R.T.	1	94/0
17	Red Al® (1.4)	CH_2Cl_2	R.T.	1	89/0

[a] Reaction condition: **1a** (1.0 mmol), solvent (8 mL). [b] Yields determined by GC analysis.

As part of our continued interest in the C–F bond of organofluorine compounds,[11] in this communication, we focused on the selective reductive cleavage of sp^2 C–F bonds of *gem*-difluoroalkenes. Initially, we used 1-(2,2-difluorovinyl)-4-methoxy-benzene **1a** as the model substrate to examine the reduction activities of various reducing agents (Table 1, entries 1–8). Among the reducing agents tested, $LiAlH_4$, $LiEt_3BH$ and Red-Al® promoted the reaction much more efficiently and gave a mixture of monofluoro product **2a** and over-reduction product **3a** in high yields but with poor selectivity (entries 6–8). It is reported that Red-Al® is a safer substitute for $LiAlH_4$ and $LiEt_3BH$,[12] therefore, we chose Red-Al® as the reductant for further optimization of reaction conditions.

The reaction results were significantly affected by the amount of Red-Al®. The use of 2.8 equiv of Red-Al® could provide monofluoroalkene **2a** as major product along with small amount of 1-methoxy-4-vinylbenzene **3a** (entry 8). However, when the amount of Red-Al® was increased to 4.0 or 8.0 equiv, the yields of **2a** decreased dramatically (entries 9 and 10). Interestingly, attempts to further improve the yield of **3a** by using large amount of Red-Al® were unsuccessful.

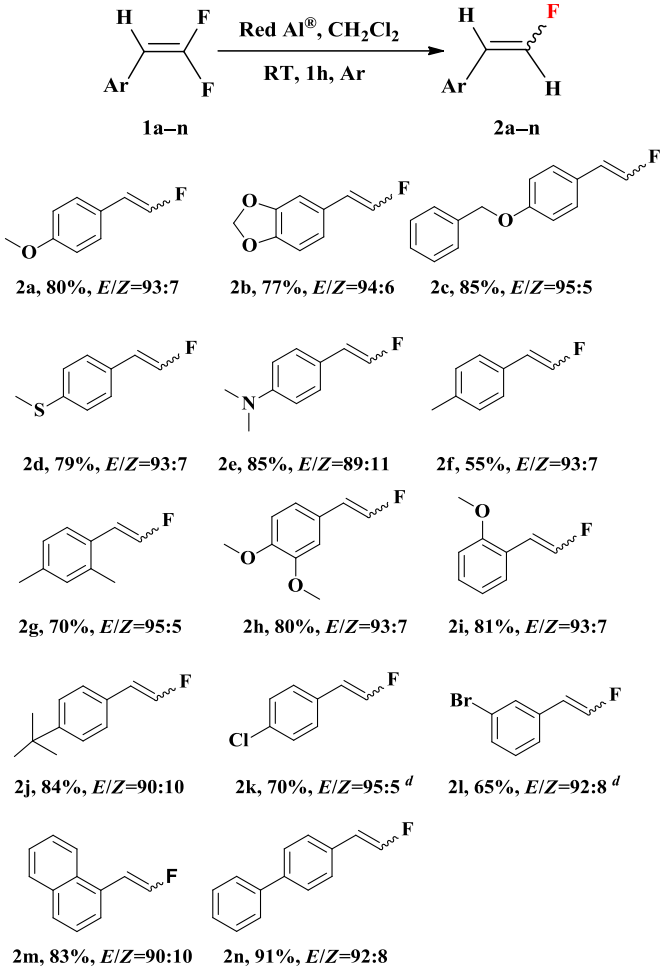
To our delight, when the reaction was performed at room temperature within 1 hour, the desired product **2a** was obtained in higher yield and the amount of over-reduction product **3a** decreased obviously (entry 8 vs. entry 11). Further screening of the solvent showed that Et_2O, toluene, benzene and CH_2Cl_2 were also suitable for this transformation (entries 12–15). However, when THF, Et_2O, toluene and benzene were used as solvents, the yield of byproduct **3a** would increase after a prolonged reaction time, whereas CH_2Cl_2 still afforded the monofluoro product **2a** in excellent yield with high *E*-selectivity (entry 15). Considering the generality, toxicity and volatility of solvent, CH_2Cl_2 was the most suitable solvent for this reaction.

In addition, the reaction proceeded less efficiently when the amount of Red-Al® was decreased to 2.0 or 1.4 equiv (entries 16 and 17).

Having established the optimized method (Table 1, entry 15), we next probe the generality and scope of this hydrodefluorination reaction of different *gem*-difluoroalkenes with Red-Al® (Table 2). All the *gem*-difluoroalkenes (**1a**–**n**) were prepared according to the reported procedure.[13] It was found that difluoroethenes with strong electron-donating substituents on the aromatic ring afforded the corresponding *E*-monofluoro products **2a**–**j** in good to high yields (more than 96%, GC/MS) and good stereoselectivity. 1-(2,2-Difluorovinyl) naphthalene (**1m**) and 4-(2,2-difluorovinyl)-1,1'-biphenyl (**1n**) were also good substrates for this reduction reaction. When difluoroethenes with weak electron-withdrawing substituent on the aromatic ring such as 1-chloro-4-(2,2-difluorovinyl)benzene (**1k**) and 1-bromo-3-(2,2-difluorovinyl)benzene (**1l**) were used as substrates, the reaction also proceeded smoothly. Unfortunately, (*E*)-isomers could not be separated from the corresponding (*Z*)-isomers due to their similarity in affinity to chromatographic silica gel.

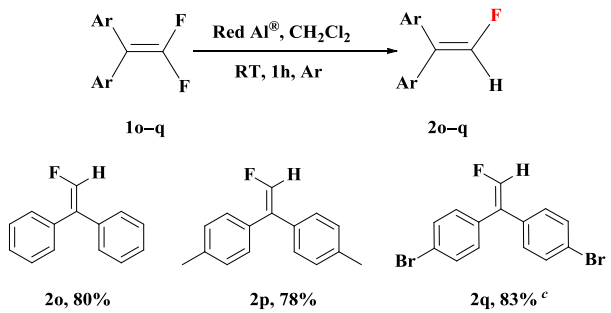
Finally, symmetrical *gem*-difluoroalkenes **1o–q** were also compatible with the reaction conditions and gave the monofluoro products **2o–q** in good yields (Table 3). The symmetrical *gem*-difluoroalkenes (**1o–q**) were prepared according to the reported procedure.[14]

Table 2 Selective hydrodefluorination of various *gem*-difluoroalkenes [a,b,c]



[a] Reaction condition: *gem*-difluoroalkenes (1.0 mmol), Red-Al® (2.8 mmol), CH_2Cl_2 (8 mL), 25 ℃. [b] Isolated yield. [c] The *E*/*Z* selectivity were determined by ^{19}F NMR. [d] The reaction was completed within 15–20 minutes.

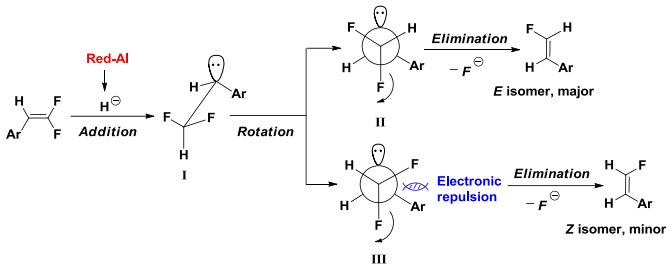
Table 3 Selective hydrodefluorination of symmetrical *gem*-difluoroalkenes [a,b]



[a] Reaction condition: symmetrical *gem*-difluoroalkenes (1.0 mmol), Red-Al® (2.8 mmol), CH_2Cl_2 (8 mL), 25 ℃. [b] Isolated yield. [c] The reaction was completed within 5 minutes.

On the basis of the above results and literatures[15], we tentatively suggest a plausible mechanism (Scheme 2). In the first step, addition of negative hydrogen ion (H^-) originated from Red-Al® to *gem*-difluoroalkene would result in the formation of the key carbanion intermediate **I**. Subsequently, rotation of the intermediate **I** by ±60 degrees would generate two conformations, **II** and **III**. The conformation **III** is unstable due to electronic repulsion between the aryl group and fluorine atom. Finally, the elimination of a fluoride ion from the preferred conformation **II** affords (*E*)-isomer as the major product.

Scheme 2 A plausible mechanism



In summary, we have developed a novel and highly efficient method for the selective reduction of difluoroalkenes with Red-Al® in CH_2Cl_2 under mild conditions. The monofluoro products were obtained in moderate to high yields with high *E*-selectivity. Compared with the previously reported method[10], the protocol developed in this communication has some obvious synthetic advantages such as the use of relative green solvent (CH_2Cl_2 versus benzene), performing the reaction under mild condition (room temperature versus reflux), the high stereoselectivity (9:1 versus 3:1) and the broad substrate scope. Furthermore, no over-reduction products were observed even after a prolonged reaction time. The protocol reported herein provided a practical access to a variety of different monofluoroalkenes.

Acknowledgements

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Notes and references

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† Electronic Supplementary Information (ESI) available: [Experimental details and characterization data for all compounds]. See DOI: 10.1039/c000000x/

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