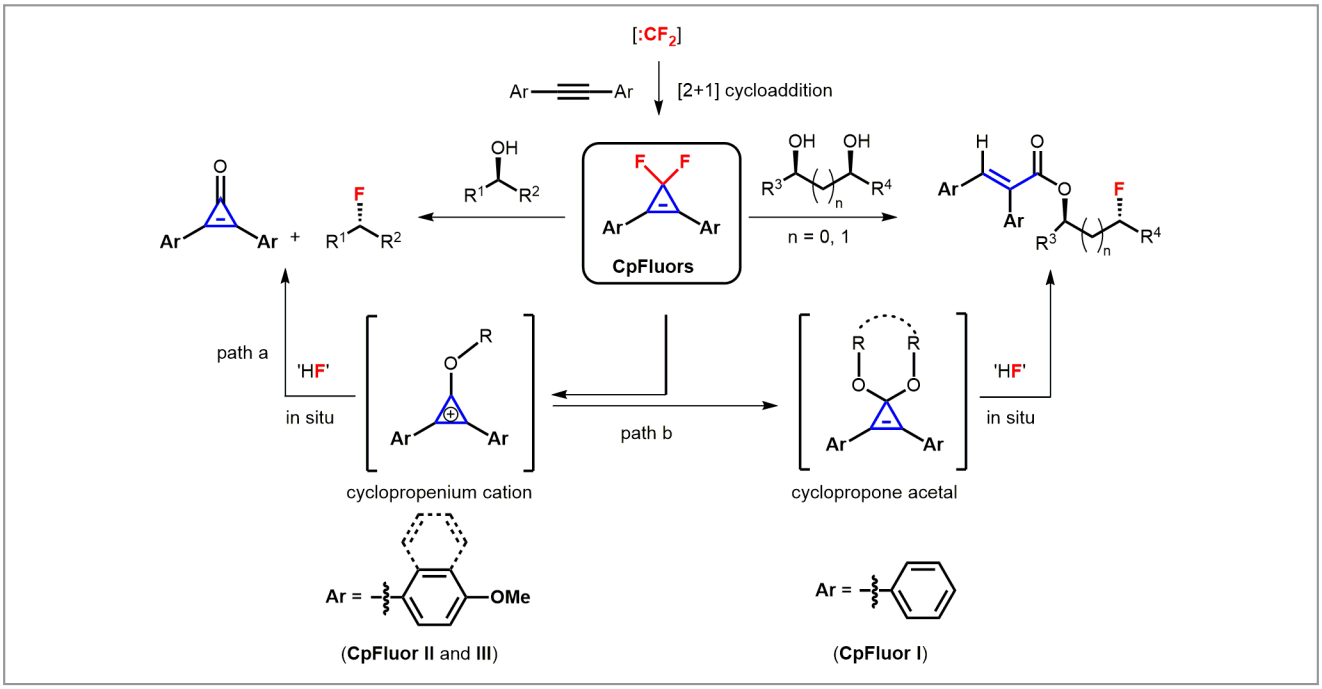
Deoxyfluorination of Alcohols with 3,3-Difluoro-1,2-diaryl-cyclopropenes

Nat. Commun. **2016**, *7*, 13320

The unique characteristics of fluorine-containing substituents and their effects on molecular properties have led to numerous applications of organofluorine compounds in medicinal chemistry, chemical biology and drug discovery. Alkyl fluorides constitute a valuable class of organofluorine compounds for pK_a modulation, lipophilicity tuning, and selective blocking of oxidative metabolism.[1] Consequently, a myriad of fluorination methods have been developed for their synthesis. Among them, the deoxyfluorination of alcohols via in situ activation is a leading approach due to the ready availability of both natural and synthetic alcohols.[2]

Known deoxyfluorination reactions mainly rely on 'S-F' reagents (such as DAST, Deoxo-Fluor, XtalFluor, Fluolead, and PyFluor) and 'N-C-F' reagents {such as Ishikawa reagent, *N*-[difluoro(*m*-tolyl)methyl]-*N*-ethylethanamine, PhenoFluor, and recently developed AlkylFluor}, which facilitate the replacement of an OH group with fluorine by means of heteroatom-promoted activation of alcohols followed by the nucleophilic attack of self-released or external fluoride ion.[2] While these reagents possess features such as high reactivity, good chemoselectivity, enhanced shelf stability, ready availability or low cost, their selective reaction with multiple alcohols is usually paid little attention, except in the case of PhenoFluor, with apparently sterically controlled selectivity. Moreover, there is still a lack of a deoxyfluorination method that is capable of fluorinating multiple alcohols selectively at the relatively electron-rich position rather than the less sterically hindered position.

To tackle the existing chemoselectivity problem, the group of Professor Jinbo Hu from the Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences (P. R. of China) developed a novel strategy for the deoxyfluorination of alcohols based on cyclopropenium cation activation by use of 3,3-difluoro-1,2-diarylcyclopropenes (CpFluors) as easily accessible and reactivity-tunable reagents (Scheme 1). The synthetic potential of this strategy is demonstrated by the fluorination of



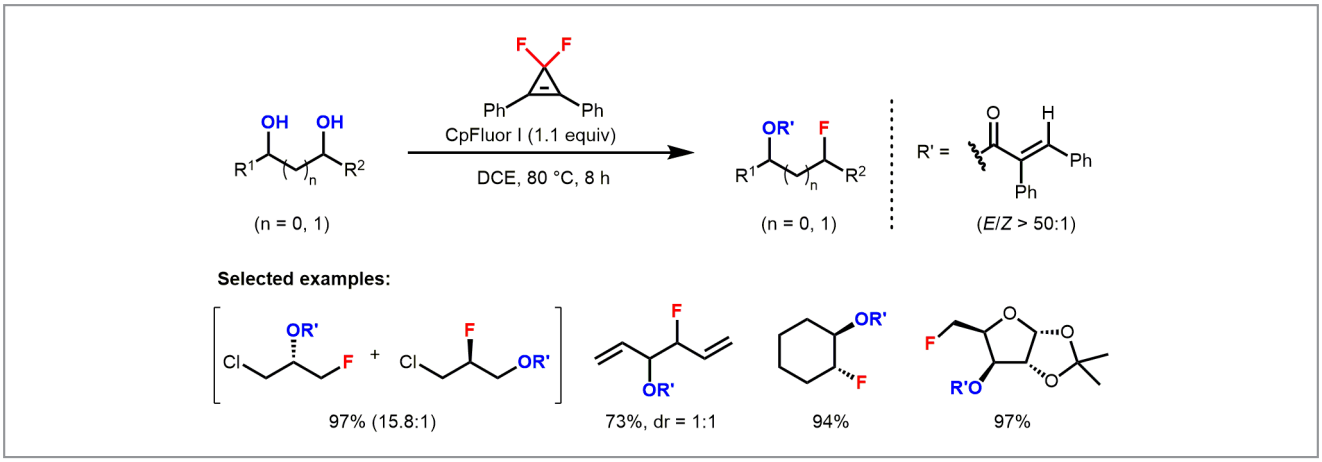
Scheme 1 Pathways for deoxyfluorination of alcohols with CpFluors

monoalcohols, fluorinative acylation of 1,2- and 1,3-diols, and selective fluorination of electron-rich alcohols.

Professor Hu explained: "Cyclopropenium cations have considerable thermodynamic stability owing to the Hückel aromaticity, and the stability and reactivity of this class of molecules can be tuned by changing the electronic property of the substituents. As unique molecules with the binary properties of aromatic stability and ionic charge, they have been used for deoxyfunctionalization and in organic catalysis. However, their use for deoxyfluorination is a great challenge due to the low nucleophilicity of the fluoride ion and the corrosive nature of HF towards glass." Professor Hu continued: "Actually, we had started the project more than six years ago, when Professor Tristan H. Lambert and his co-worker from Columbia University (USA) just published a paper on the chlorination of alcohols with *gem*-dichlorocyclopropenes.[3] It happened that at the time we were working on the synthesis of *gem*-difluorocyclopropenes with difluorocarbene.[4] Inspired by our interest on difluorocarbene chemistry and Professor Lambert's work on cyclopropenium cation activation, we decided to use the readily available difluorocarbene reagents as the source of fluoride for deoxyfluorination by virtue of the thermally stable *gem*-difluorocyclopropenes, hoping that we could develop a practical method for the fluorination of alcohols."

Professor Hu revealed that initially numerous experiments evaluating the deoxyfluorination ability of 3,3-difluoro-1,2-diphenylcyclopropene (CpFluor I) were performed in glassware by Dr. Fei Wang, a senior graduate student at that time. "Interestingly, Dr. Wang found that this fluorination had only a limited scope of substrates including carboxylic acids and benzylic alcohols,[5] which is different from Lambert's chlorination chemistry," recalled Professor Hu, adding: "Fortunately, we did not give up this project. After the graduation of Dr. Wang, Dr. Lingchun Li joined our group as a graduate student and he took up Dr. Wang's project. Dr. Li is scrupulous, and he found that the fluorination of non-activated monoalcohols with CpFluor I could be achieved by performing the reaction in non-glass ware to avoid corrosion by HF, although the highest yield was only moderate. With the help of Dr. Chuanfa Ni, an associate professor, also my first graduate student, Dr. Li eventually established that there was one more difference between the fluorination and chlorination after months of experimental investigations." Professor Hu explained: "Because the fluoride ion is less nucleophilic than the chloride ion, the charged reactive intermediate, an alkoxycyclopropenium cation, prefers to form a neutral intermediate, a cyclopropenone acetal, rather than undergoing nucleophilic substitution by fluoride ion. The cyclopropenone acetal is also reactive but contributes less to the desired fluorination of monoalcohols. As a matter of fact," continued Professor Hu: "by taking advantage of this feature, we easily achieved the fluorination of 1,2- and 1,3-diols with CpFluor I (Scheme 2), in which the cyclic acetal intermediates, 1,3-dioxolanes and 1,3-dioxanes, readily formed regardless of the electronic nature of 3,3-difluoro-1,2-diarylcyclopropenes, thus always furnishing the fluorinative acylation products in high yields through thermally induced ring opening of the electron-rich cyclopropenes followed by fluorination."

Eventually, the group was delighted to find that the pathway for fluorination of monoalcohols could be switched by changing the electronic properties of CpFluors (Scheme 3). "Electron-rich aryl substituents are beneficial for the formation and stabilization of the alkoxycyclopropenium

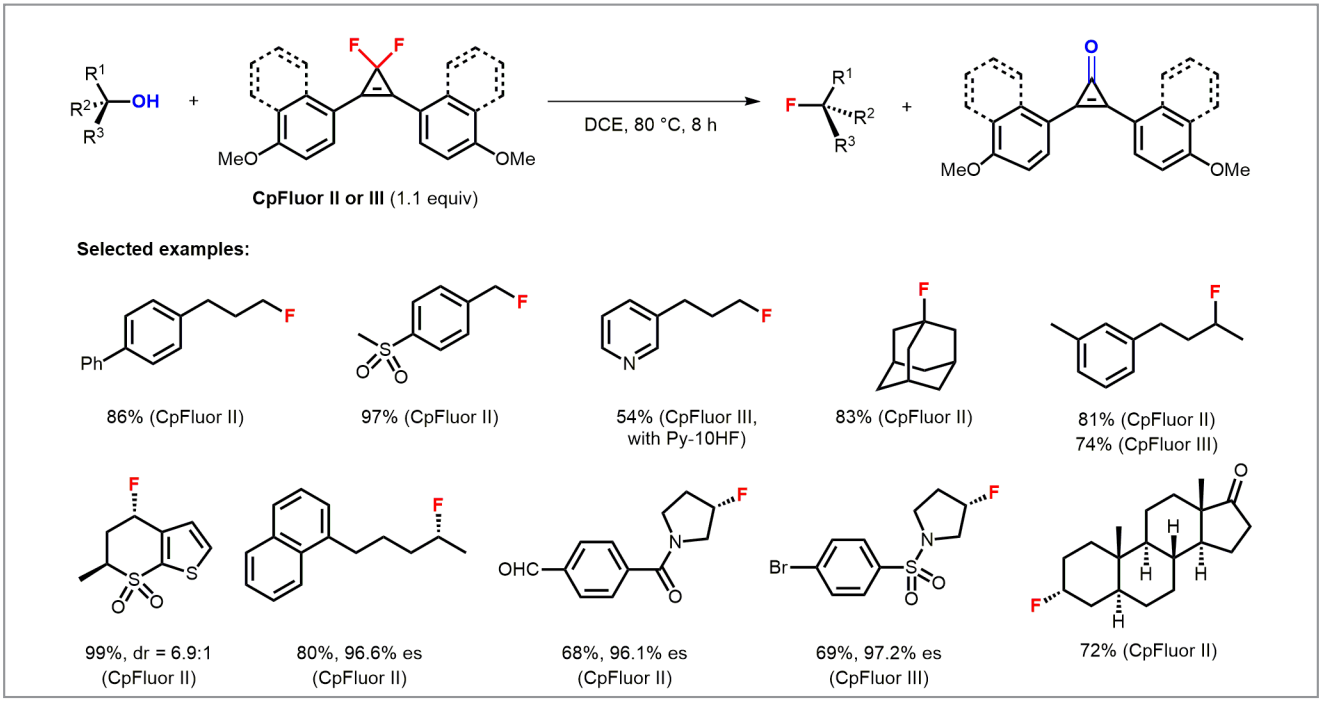


Scheme 2 Deoxyfluorination of 1,2- and 1,3-diols with CpFluor I

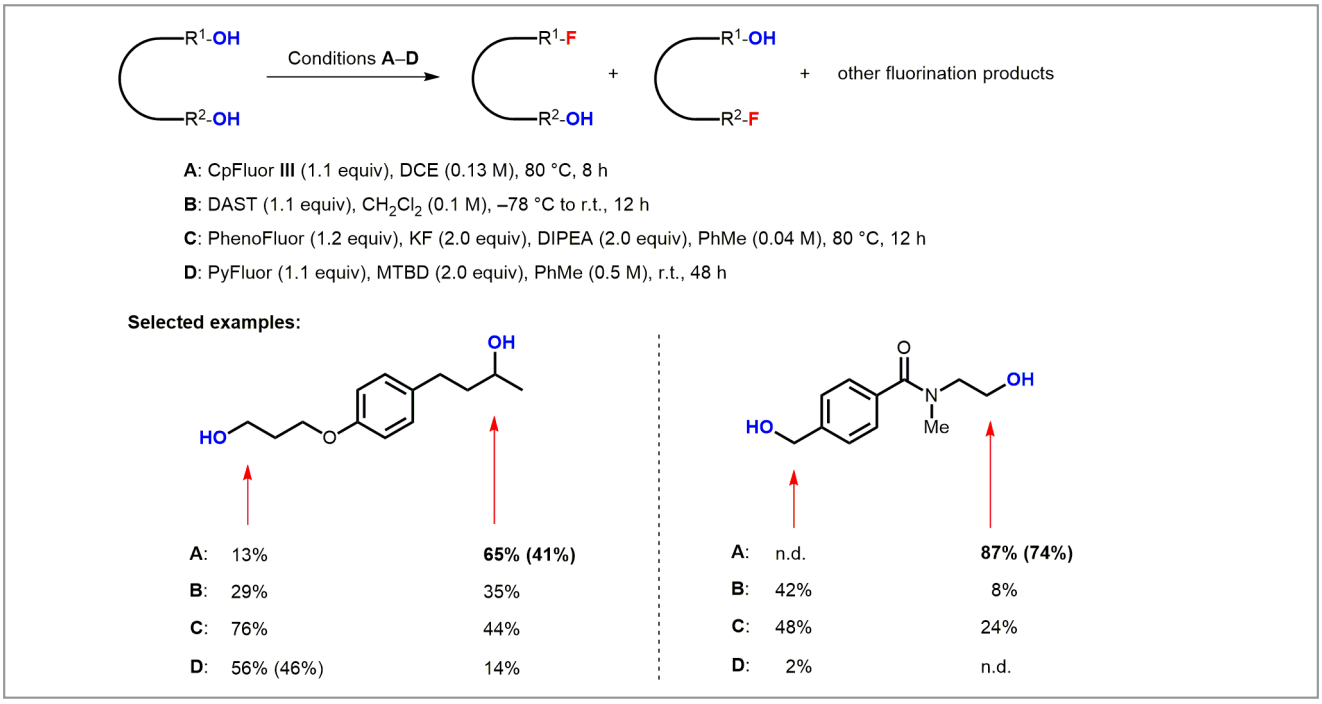
cations, thus facilitating the fluorination of monoalcohols with high efficiency. Employing 3,3-difluoro-1,2-bis(4′-methoxynaphthalen-1′-yl)cyclopropene (CpFluor II) or 3,3-difluoro-1,2-bis(4′-methoxyphenyl)cyclopropene (CpFluor III) as the reagent, a series of primary and secondary monoalcohols smoothly underwent the deoxyfluorination to give alkyl fluorides in moderate to excellent yields," explained Professor Hu. "Chiral secondary alcohols were normally deoxyfluorinated with inversion of configuration."

The invention of CpFluors as efficient deoxyfluorination reagents provided the group an opportunity to exploit the aforementioned challenging task, that is, selective fluorination of electron-rich alcohols (Scheme 4). Professor Hu explained: "The observation that the fluorination pathway of a given alcohol was sensitive to the electronic nature of CpFluors indicates that the chemical outcome of this fluorination method should also be sensitive to the electronic nature of alcohols, because both the alkoxy substituent and the aryl substituents can influence the stabilization of the cyclopropenium cation intermediate." At first, Dr. Li and Dr. Ni conducted the competitive deoxyfluorination of two monoalcohols by the use of CpFluor III as the reagent and found that electron-rich alcohols did react faster than the relatively electron-poor ones. Having developed a proof-of-concept, the authors applied it in the transformation of diols with hydroxyl groups separated by several carbon centers. "Compared with other reagents such as DAST, PhenoFluor and PyFluor, CpFluor reagents are the most sensitive towards the electronic nature of the alcohols, which represents a breakthrough in deoxyfluorination of alcohols," said Professor Hu.

"In conclusion, an alcohol fluorination protocol using CpFluors as a novel class of deoxyfluorination reagents has been developed after a long-standing pursuit," said Professor Hu. "The finding that the electronic properties of the aryl substituents on the scaffold of CpFluors can dramatically influence the transformation of alcohols is instructive, which shows the way for achieving selective fluorination of electron-rich alcohols." He concluded: "This research also sheds light on the divergent reactivity of cyclopropenium cations in the transformation of alcohols. We hope that this concept will find application in other selective deoxyfunctionalizations of alcohols."



Scheme 3 Deoxyfluorination of monoalcohols with CpFluor II and III; es refers to enantiospecificity: es = (ee of starting material)/(ee of product) x 100%.



Scheme 4 Selective deoxyfluorination of electron-rich alcohols with CpFluor III (yields are total fluorination yields at the given position determined by ^{19}F NMR spectroscopy, yields in parentheses refer to isolated yields of monofluorination products with retention of the other hydroxyl group)

REFERENCES

(1) Q. A. Huchet, B. Kuhn, B. Wagner, N. A. Kratochwil, H. Fischer, M. Kansy, D. Zimmerli, E. M. Carreira, K. Müller *J. Med. Chem.* **2015**, *58*, 9041.
(2) For a review: (a) P. A. Champagne, J. Desroches, J.-D. Hamel, M. Vandamme, J.-F. Paquin *Chem. Rev.* **2015**, *115*, 9073; For recent examples: (b) M. K. Nielsen, C. R. Ugaz, W. Li, A. G. Doyle *J. Am. Chem. Soc.* **2015**, *137*, 9571; (c) N. W. Goldberg, X. Shen, J. Li, T. Ritter *Org. Lett.* **2016**, *18*, 6102.
(3) B. D. Kelly, T. H. Lambert *J. Am. Chem. Soc.* **2009**, *131*, 13930.
(4) (a) F. Wang, W. Zhang, J. Zhu, H. Li, K.-W. Huang, J. Hu *Chem. Commun.* **2011**, *47*, 2411; For a review: (b) C. Ni, J. Hu *Synthesis* **2014**, *46*, 842.
(5) (a) F. Wang, Ph.D. dissertation, Shanghai Institute of Organic Chemistry, CAS, **2011**; (b) J. Hu, F. Wang, M. Hu, X. Shen, T. Luo *Chinese Patent* CN 102285849 A, **2011**.

About the authors

Dr. L. Li

Lingchun Li was born in Jiangsu (P. R. of China) in 1988. He obtained his BSc degree from Tongji University (P. R. of China) in 2010 and his Ph.D. in organic chemistry from Shanghai Institute of Organic Chemistry (SIOC), Chinese Academy of Sciences in 2015 under the supervision of Professor Jinbo Hu. Then he joined a SIOC and Merck Sharp & Dohme (MSD) joint postdoctoral program under the supervision of Prof. Jinbo Hu (SIOC) and Dr. Yongxin Han (MSD) (2015–2016). His research involved fluoroalkylation and fluorination based on difluorocarbene chemistry. Currently he is studying ATRP with Professor Krzysztof Matyjaszewski at Carnegie Mellon University as a visiting scholar with an SIOC fellowship.

Dr. C. Ni

Chuanfa Ni obtained his BSc degree in chemistry from Shandong Normal University in 2003. After graduate work (2003–2009) at the Shanghai Institute of Organic Chemistry (SIOC) under the supervision of Professor Jinbo Hu and postdoctoral work (2009–2012) at the University of Southern California under the supervision of Professor G. K. Surya Prakash, he has worked as an associate professor at Professor Jinbo Hu's group since 2012.

Dr. F. Wang

Fei Wang was born in Zhengjiang, China, in 1983. He received his B.S degree in chemistry from Ocean University of China in 2006, then he began his graduate studies at Shanghai Institute of Organic Chemistry (SIOC) with a focus on the development of novel difluorocarbene and fluorinating reagents under the supervision of Professor Jinbo Hu, and he was awarded his Ph.D. from SIOC in 2011. He carried out postdoctoral work from 2011 to 2015 at the University of Florida. He is currently a Sr. Organic Chemist at Walter Reed Army Institute of Research.

Prof. J. Hu

Jinbo Hu was born in Zhejiang, China, in 1973. After he completed his BS (Hangzhou University) and MS (Chinese Academy of Sciences) degrees, he carried out his PhD work from 1997 to 2002 at the University of Southern California with Professors G. K. Surya Prakash and G. A. Olah. After his postdoctoral work at USC, he accepted a Research Professorship at the Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences (SIOC, CAS) in early 2005, where he is currently the Head of the CAS Key Laboratory of Organofluorine Chemistry. He is the recipient of the RSC Fluorine Prize 2009 and the Novartis Chemistry Lectureship 2015–2016. His current research interests include selective fluorination, defluorination, fluoroalkylation methods, and fluorinated materials.

© Georg Thieme Verlag Stuttgart • New York – Synform **2017/02**, A30–A34 • Published online: January 18, 2017 • DOI: 10.1055/s-0036-1589816