

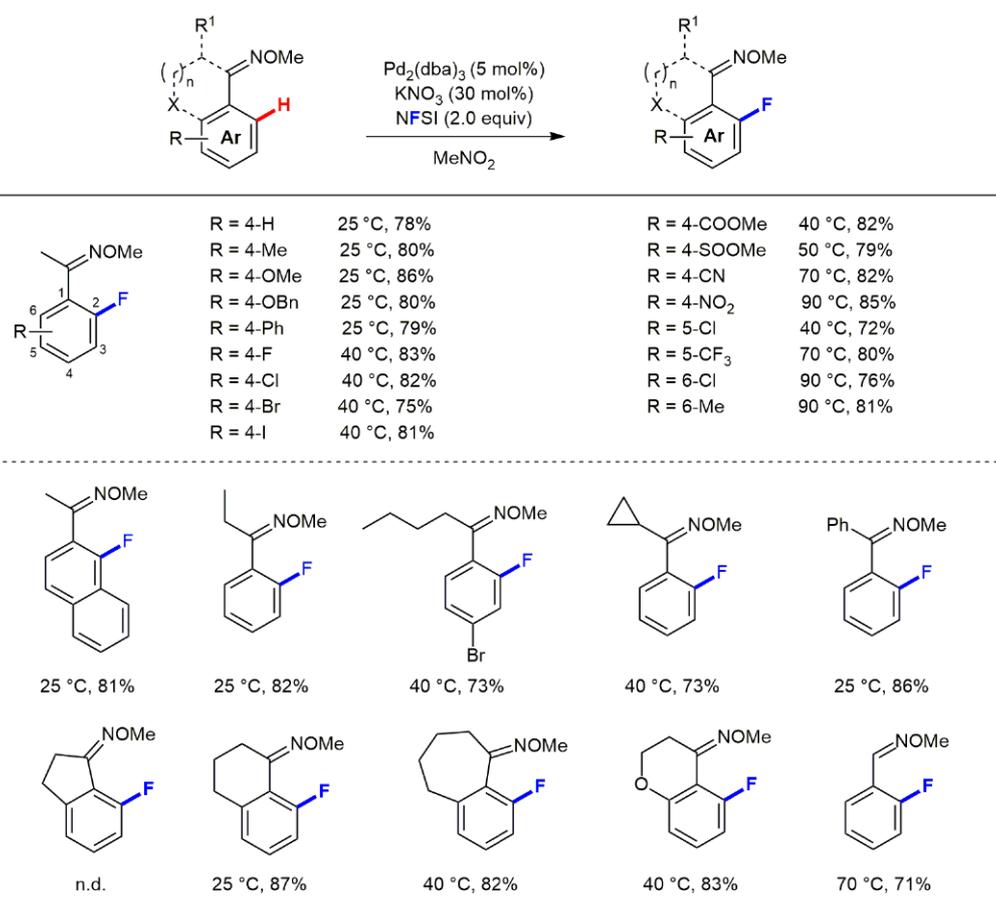
Mild and Versatile Nitrate-Promoted C–H Bond Fluorination

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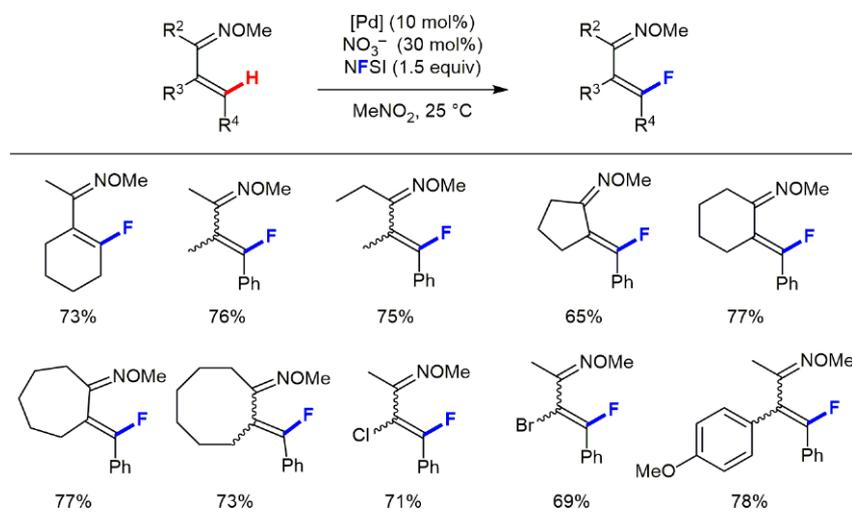
Carbon–fluorine bond construction has consistently been of great interest to chemists due to the unique characteristics of fluorinated molecules and the synthetic challenges connected with the introduction of fluorine into organic molecules. Apart from the *ipso*-fluorination of pre-functionalized substrates, C–H bond fluorination is a prospective alternative and has received a great deal of attention in recent years. However, several challenges, for example, relatively harsh conditions, excess amounts of fluorinating agents (oxidants), narrow substrate scopes and poor selectivity still need to be addressed for this emerging area. Given the broad application of fluorinated

compounds in pharmaceuticals, agrochemicals and materials, a mild and versatile C–H bond fluorination protocol is highly desirable. Very recently, a novel and facile nitrate-promoted regioselective fluorination of aromatic and olefinic sp^2 -C–H bonds under mild conditions was described by Professors Dan-Qian Xu and Zhen-Yuan Xu, and Dr. Shao-Jie Lou from Zhejiang University of Technology (P. R. of China).

Generally, the fluorination reactions took place under very mild conditions (close to room temperature in most cases). Professor D.-Q. Xu said: “Conventionally, C–H bond fluorination requires harsh conditions with respect to the great



Scheme 1 Aromatic C–H bond fluorination



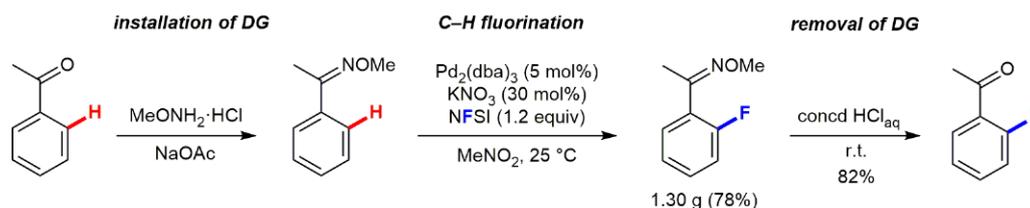
Scheme 2 Olefinic C–H bond fluorination

strength of both C–H and C–F bonds, so we were delighted to find that the current palladium-nitrate catalytic system enabled the process in a much milder manner.”

“A catalytic amount of simple, non-toxic and cheap potassium nitrate served as a highly efficient promoter,” said Professor D.-Q. Xu. “Actually, silver nitrate was found to be an efficient additive for this transformation at the outset of this program,” she explained. Since silver salts were demonstrated to be incorporated in several C–F bond formation reactions, various silver salts were then screened. However, only silver nitrate and silver nitrite could successfully promote the reaction, whereas other silver salts were ineffective. Professor Z.-Y. Xu said: “The unique counter-anion effect led us to hypothesize that the nitrate anion might be the pivotal promoter. To our delight, nitrates were finally found to exhibit a unique ligand effect in this catalytic fluorination protocol.” He continued: “Though the actual role of the nitrate is still not clear at this stage, we proposed that a highly active cationic $\text{Pd}(\text{NO}_3)^+$

was generated in situ and initialized the C–H activation under mild conditions. Meanwhile, the poorly nucleophilic nitrate additives might also be responsible for the selective reductive elimination of the C–F bond from the Ar–Pd(IV)–F intermediate (*Angew. Chem. Int. Ed.* **2011**, *50*, 1478).”

The process shows a remarkably broad substrate scope for both aromatic and olefinic sp^2 -C–H bonds. In general, both electron-donating and electron-withdrawing functional groups were well tolerated by cautiously adjusting the reaction temperature of the aromatic C–H bond fluorination. Moreover, good mono-/di-fluorination selectivity could also be achieved by controlling the reaction temperature. Professor D.-Q. Xu said: “Notably, the first example of chelation-assisted olefinic sp^2 -C–H bond fluorination was also reported in this paper. Various functionalities, for example, alkyl-, halo-, and aryl-substituted α,β -unsaturated oximes were well tolerated and furnished the β -fluorinated products in good yields at room temperature.



Scheme 3 C–H fluorination of ketones

In addition, the oximyl directing group can be efficiently installed or removed, which would provide opportunities for further derivatization of the fluorinated ketone products. Gram-scale C–H bond fluorination proceeded smoothly with a reduced loading of fluorinating agent.

Professor Z.-Y. Xu said: “Given the mild conditions and universality of this method, the present fluorination protocol may enable the late-stage fluorination of more complex sub-

strates without touching the other functional groups. Attempts to apply this system to more substrates are ongoing in our lab.

In conclusion, we have developed a novel nitrate-promoted fluorination system, which features broad substrate scope, good functional group tolerance and simple operations,” said Professor D.-Q. Xu. “It should pave the way for mild and versatile C–H bond fluorination in synthetic and pharmaceutical chemistry.” ■

Matteo Zanda

About the authors



Dr. S.-J. Lou

Shao-Jie Lou was born in Zhejiang (P. R. of China) in 1985. He received his BSc in 2008 and PhD in 2013 under the guidance of Professor Dan-Qian Xu at Zhejiang University of Technology (P. R. of China). Then he continued to work in the Catalytic Hydrogenation Research Center at Zhejiang University of Technology as a postdoctoral fellow with Professor Dan-Qian Xu in 2013. His research interest concerns transition-metal-catalyzed C–H bond functionalization.



Prof. D.-Q. Xu

Dan-Qian Xu was born in Zhejiang (P. R. of China) in 1963. She obtained her BSc in chemistry from East China Normal University (P. R. of China) in 1986 and her PhD in industrial catalysis under the guidance of Professor Yin-Chu Shen at Zhejiang University of Technology (P. R. of China) in 2005. In 2001, she was promoted to Professor. Her research interests include organocatalysis, transition-metal catalysis and fine chemicals. She has received several honors and awards, including the ‘Million Talents Projects’ (2007) sponsored by the Ministry of Personnel and two awards for National Progress in Science and Technology (2001 and 2005).



Prof. Z.-Y. Xu

After receiving his Bachelor’s degree at Beijing Agricultural University (P. R. of China) in 1963, **Zhen-Yuan Xu** directly joined the Faculty of the Beijing Agricultural University (P. R. of China). In 1976, he joined the faculty at Northwestern University (P. R. of China). Since 1985, he has been a member of the faculty of Zhejiang University of Technology (P. R. of China) where he was promoted to Professor of Chemistry in 1988. Professor Xu has received numerous awards, including one award for National Invention (1989), four awards for National Progress in Science and Technology (1991, 1997, 2001, and 2005), and one award for Chinese Outstanding Patented Invention (2009).