

Chem Soc Rev

Chemical Society Reviews

www.rsc.org/chemsocrev



ISSN 0306-0012



TUTORIAL REVIEW

Chuanfa Ni and Jinbo Hu

The unique fluorine effects in organic reactions: recent facts and insights into fluoroalkylations

175
YEARS



Cite this: *Chem. Soc. Rev.*, 2016, 45, 5441

The unique fluorine effects in organic reactions: recent facts and insights into fluoroalkylations

Chuanfa Ni and Jinbo Hu*

Fluoroalkylation reaction, featuring the transfer of a fluoroalkyl group to a substrate, is a straightforward and efficient method for the synthesis of organofluorine compounds. In fluoroalkylation reactions, fluorine substitution can dramatically influence the chemical outcome. On the one hand, the chemistry of alkylation with non-fluorinated reagents may not be applicable to fluoroalkylations, so it is necessary to tackle the fluorine effects to achieve efficient fluoroalkylation reactions. On the other hand, fluorine substitution may bring about new reactivities and transformations that cannot be realized in alkylation with non-fluorinated reagents; thus, fluorine substitution can be used to explore new synthetic methods. This tutorial review provides a brief overview of the unique fluorine effects in recently developed nucleophilic, electrophilic, radical, and transition metal-mediated fluoroalkylation reactions by comparing with either their non-fluorinated counterparts or fluorinated counterparts with different numbers of fluorine substituents.

Received 30th April 2016

DOI: 10.1039/c6cs00351f

www.rsc.org/chemsocrev

Key learning points

- (1) Fluorine substitution can dramatically influence the chemical outcome of fluoroalkylation reactions.
- (2) The chemistry of alkylation with non-fluorinated reagents may not be applicable to fluoroalkylation chemistry.
- (3) Fluorine substitution may bring about new reactivities and transformations that cannot be achieved in alkylation with non-fluorinated reagents.
- (4) Understanding the unique fluorine effects can help to predict, design, and further develop fluoroalkylation chemistry.

1. Introduction

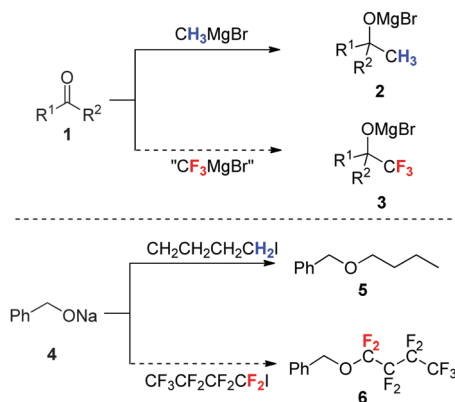
Nowadays, one of the major efforts of chemists in both academia and industry is the search for “special effect” chemicals with new structures and functions.^{1,2} In this context, fluorine is undoubtedly one of the elements that has attracted the highest recent research interest in several aspects of chemistry, since the judicious incorporation of the fluorine atom or the fluorinated moiety into organic compounds or polymers has become a powerful tool to discover new chemical entities possessing unique physical, chemical and/or biological properties.^{2–4} For instance, fluorinated materials have been widely used in liquid crystal displays of smart phones and in photovoltaic solar cells.^{5,6} ¹⁸F-labeled molecules are essential radiotracers for positron emission tomography (PET), which serves as a privileged diagnostic tool for cancers and other diseases.⁷ Polyfluorinated (fluorous) molecules are used in ¹⁹F magnetic resonance imaging (MRI) thanks to the high sensitivity of ¹⁹F nuclei in nuclear

magnetic resonance (NMR) measurements.⁸ The highest impact of fluorine in life sciences is associated with the development of agrochemicals and pharmaceuticals. Recently, it has been estimated that about 30% of new approved drugs (excluding biopharmaceutical products) contained fluorine atoms or fluoroalkyl groups.^{9–11} The fact that fluorinated organic compounds and materials often show unusual physical, chemical, and/or biological properties and behaviour (in comparison with their nonfluorinated counterparts) is often called “fluorine effects” or “fluorine magic”.^{4,12,13}

The profound effect of fluorine substitution on the chemical reactivity of organic compounds is an interesting research topic in organic chemistry.^{2–4} In this context, many fluoroalkylation reactions have been extensively studied over the past decade. Fluoroalkylation reactions, such as tri-, di-, and mono-fluoromethylations and other perfluoroalkylations and polyfluoroalkylations, represent one of the most straightforward and efficient methods for the incorporation of a fluoroalkyl group (such as CF₃, CF₂H, or CH₂F group) into organic molecules.¹⁴ Traditionally, fluoroalkylation reactions can be divided into four categories: nucleophilic fluoroalkylation, electrophilic fluoroalkylation, radical fluoroalkylation, and transition metal-mediated fluoroalkylation.^{2–4} However, fluoroalkylation reactions are often

Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Ling-Ling Road, Shanghai 200032, China. E-mail: jinbohu@sioc.ac.cn





Scheme 1 Unique features of fluoroalkylations compared to general alkylation reactions.

surprisingly different from general alkylation reactions in organic chemistry, and the known knowledge of general alkylation chemistry cannot be simply used to predict the fluoroalkylation chemistry. Two typical examples are shown in Scheme 1. Firstly, Grignard reagent CH_3MgBr can readily undergo nucleophilic addition to an aldehyde or ketone **1** to give product **2**; however, a similar addition with CF_3MgBr is very difficult, because CF_3MgBr is highly unstable and readily decomposes to difluorocarbene ($:\text{CF}_2$) and magnesium bromofluoride.^{2–4} Secondly, Williamson ether synthesis between sodium alkoxide **4** and *n*-butyl iodide gives ether product **5** through an $\text{S}_{\text{N}}2$ reaction pathway; however, a similar $\text{S}_{\text{N}}2$ reaction between **4** and perfluorobutyl iodide cannot proceed to give ether product **6**. This is because the perfluorobutyl group in *n*- $\text{C}_4\text{F}_9\text{I}$ is more electronegative than iodine, and the polarisation is thus reversed and nucleophile **4** attacks iodine rather than the carbon atom of the perfluorobutyl group.^{2–4}

Therefore, the understanding of the unique fluorine effects in fluoroalkylation reactions not only facilitates the prediction,

design, and further development of fluoroalkylation chemistry, but also provides deeper insights into the unique features of fluorine and its related science. In this tutorial review, we wish to highlight some fluoroalkylation reactions that have been developed recently, and discuss the unique fluorine effects involved in these “surprising” reactions. The examples selected here merely help to interpret the concept of this review; for recent developments in fluoroalkylation reactions, one can refer to some comprehensive reviews.^{9,14–18}

2. The unique fluorine effects in nucleophilic fluoroalkylation reactions

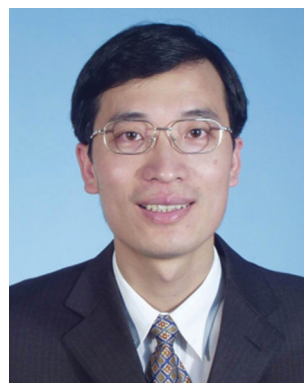
Nucleophilic fluoroalkylation features the transfer of a fluoroalkyl group to an electrophile, in which either a free fluorocarbanion, an equivalent of a fluorocarbanion (*i.e.*, a species that has a similar reactivity character to a fluorocarbanion, such as penta-coordinate silicon species), or a fluoroalkyl metal species (R_fM , M = main group metals in most cases) is involved. Fluorine substitution can influence the generation, the thermodynamic stability, and the kinetic reactivity (including the desired nucleophilic fluoroalkylation, competitive decomposition and protonation) of a fluorinated carbanion, thus distinguishing nucleophilic fluoroalkylations from non-fluorinated transformations and their counterparts with different number of fluorine substituents.^{19,20} In terms of the kinetic reactivity of fluorocarbanion, the competitive decomposition, which tends to occur more easily as the number of fluorine substituents increases, always has a negative (unfavourable) influence on the desired nucleophilic fluoroalkylation reaction.^{19,20} Nevertheless, in some cases, the fluorine substitution can play a positive (favourable) role in nucleophilic fluoroalkylations by facilitating the generation and stabilizing the reaction intermediates. In this section, we mainly



Chuanfa Ni

research professor in 2012. His research interests lie in the development of new methodologies for the synthesis of fluorinated molecules.

Chuanfa Ni was born in Shandong, China, in 1982 and 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 joined the Hu group at SIOC as an associate



Jinbo Hu

2005, where he is currently the Head of the CAS Key Laboratory of Organofluorine Chemistry. He is the recipient of RSC Fluorine Prize 2009 and Novartis Chemistry Lectureship 2015–2016. His current research interests include selective fluorination, defluorination, fluoroalkylation methodologies, and fluorinated materials.

Jinbo Hu was born in Zhejiang, China, in 1973. After he completed his BS (Hangzhou University) and MS (Chinese Academy of Sciences) degrees, he did his PhD work from 1997 to 2002 at the University of Southern California with Professors G. K. S. Prakash and G. A. Olah. After his postdoctoral work at USC, he accepted the Research Professorship at the Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences (SIOC, CAS) in early

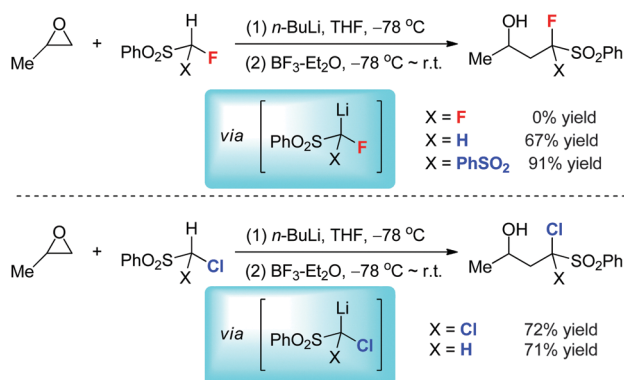


explain the influence of fluorine substitution on the reactivity of α/β -fluorocarbanions and the methods for tuning their nucleophilic fluoroalkylation reactivity by changing the counterions, the neighbouring substituents, the catalysts, the solvents, and so on.

2.1 Fluoroalkylation of epoxides with fluoroalkyl sulfones: exploring new fluoroalkylations by tackling the negative fluorine effect

In 2006, a study of nucleophilic ring-opening fluoroalkylation of epoxides conducted by us summarized the influence of α -fluorine substitution on the chemical reactivities of various carbanions.²¹ Reactions with di- and monofluoro(phenylsulfonyl)methyl lithium showed that α -fluorine substitution on the carbanion dramatically decreases the carbanion's reactivity towards epoxides (Scheme 2). From the product yields, the reactivity of fluorinated carbanions (Nu^-) toward propylene oxide decreases in the following orders: (1) for different fluorinated anions: $(\text{PhSO}_2)_2\text{CF}^- > \text{PhSO}_2\text{CHF}^- > \text{PhSO}_2\text{CF}_2^-$; (2) for different halogen-substituted anions: $\text{PhSO}_2\text{CCl}_2^- > \text{PhSO}_2\text{CF}_2^-$. This unfavourable (negative) influence of fluorine substitution on the reaction of the carbanions was described as the "negative fluorine effect (NFE)".²¹

The NFE in many nucleophilic fluoroalkylations, including but not restricted to the above mentioned fluoroalkylation of epoxides, can be attributed to the following two aspects: (1) the low thermal stability of the fluorine-substituted carbanion caused by its high tendency to undergo α -elimination of a fluoride ion (or another leaving group such as PhSO_2^-); (2) its intrinsic low nucleophilicity towards a certain electrophile such as the epoxide caused by factors such as the unmatched hard/soft nature.^{19,20} Although the NFE could not be used to summarize all reactivity aspects of α -fluorocarbanions in nucleophilic fluoroalkylation reactions, it is at least helpful to better understand many nucleophilic fluoroalkylation reactions. The knowledge of the NFE can be used to tune and improve a nucleophilic fluoroalkylation reaction in the following manners: (1) slightly changing the neighboring groups; (2) changing the metal counterions; (3) enhancing the reactivity of the electrophiles. For a detailed discussion on the nucleophilic fluoroalkylation



Scheme 2 Nucleophilic ring-opening fluoro- and chloromethylation of propylene oxide.

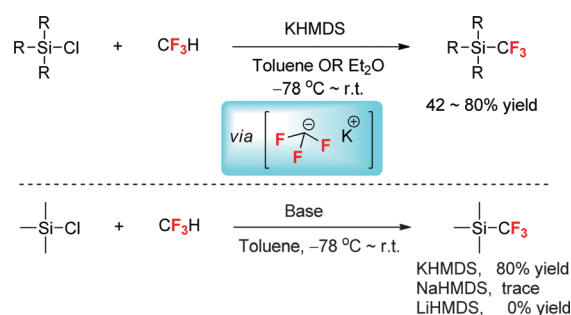
of various organic compounds by tackling the NFE, the readers are recommended to refer to our previous reviews.^{19,20}

2.2 Direct trifluoromethylation with CF_3H : enhancing the reactivity by changing the metal-fluorine interaction

The metal-fluorine interaction can significantly influence the outcome of nucleophilic trifluoromethylation. Previously, fluoroform (CF_3H) was used for the trifluoromethylation of carbonyl compounds with a strong base in aprotic polar solvents. The *in situ* trapping of CF_3^- by a solvent such as DMF to form an adduct is deemed to be important for stabilizing the labile trifluoromethyl anion, thus facilitating the nucleophilic trifluoromethylation.²² In 2012, Prakash *et al.*²² disclosed that the direct nucleophilic trifluoromethylation of silicon-, boron-, sulfur-, and carbon-centers with CF_3H can be best performed in THF, ether, and toluene when potassium hexamethyldisilazide (KHMDS) was used as a base (Scheme 3). In this case, CF_3^- generated from the deprotonation of CF_3H undergoes nucleophilic trifluoromethylation rather than decomposition to the fluoride ion and singlet difluorocarbene. Indeed, CF_3^- with K^+ /18-crown-6 as a counterion has been observed in a recent study.²³ Control experiments demonstrated the importance of the counterion effect.²² Taking the reaction between CF_3H and Me_3SiCl in toluene for an example, the use of KHMDS gives Me_3SiCF_3 as a major product; in sharp contrast, sodium hexamethyldisilazide (NaHMDS) gives Me_3SiCF_3 as a minor product, whereas lithium hexamethyldisilazide (LiHMDS) cannot give the desired product. These observations show that the counterion K^+ is important in stabilizing CF_3^- due to a weakened metal-fluorine interaction.

2.3 Trifluoro- vs. trichloromethylation of MBH-fluorides with Me_3SiCF_3 : electron-withdrawing and electron-donating effects of fluorine on the reactivity of CF_3^-

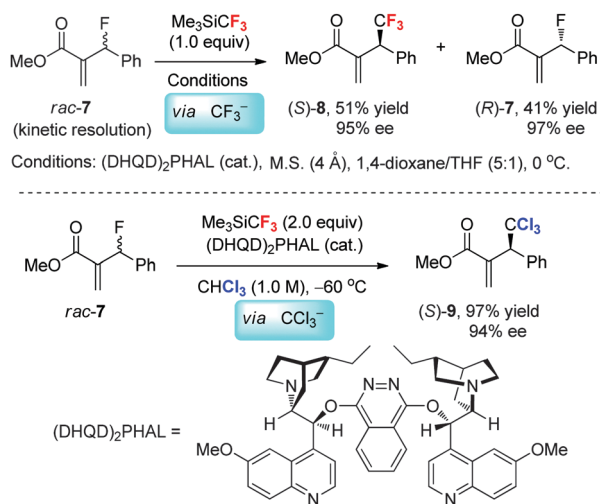
Although fluorine is more electronegative than the chlorine atom, the α -fluorine atom is less effective for stabilizing the α -fluorocarbanion due to the repulsion between the lone-pair electrons of the carbanion and the electron-rich fluorine atom.⁴ As a result, the methine proton of CHCl_3 ($\text{pK}_a = 21$, in H_2O) is more acidic than CF_3H ($\text{pK}_a = 30.5$, in H_2O). Therefore, the *in situ* generated CF_3^- from Me_3SiCF_3 can be used as an effective base for the deprotonation of carbon acids such as CH_3CN and CHCl_3 . Shibata *et al.*²⁴ reported that Morita-Baylis-Hillman (MBH)-type allyl fluoride 7 can undergo enantioselective



Scheme 3 Nucleophilic trifluoromethylation with CF_3H .



Tutorial Review



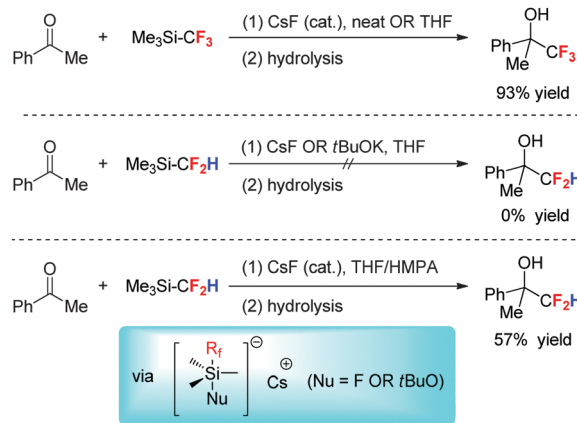
Scheme 4 Trifluoromethylation and trichloromethylation of MBH-fluorides with Me₃SiCF₃.

nucleophilic trifluoromethylation, proceeding through the cleavage of the C–F bond of MBH-fluoride by a cooperative system that consisted of the bis(cinchona alkaloid) and Me₃SiCF₃ (Scheme 4). When conducting the reaction in ether solvents, the trifluoromethylation product **8** is formed *via* two subsequent S_N2' reactions: (1) the addition of the chiral tertiary amine catalyst at the terminal alkenyl position of one enantiomer of MBH-fluoride, which leads to the formation of a chiral allylic ammonium intermediate and the subsequent activation of Me₃SiCF₃; (2) the stereoselective addition of CF₃[−] released from Me₃SiCF₃ to the chiral allylic ammonium gives the product. However, when CHCl₃ is used instead of the ether solvents, the *in situ* generated CF₃[−] readily deprotonates CHCl₃ rather than undergoing nucleophilic trifluoromethylation, thus giving rise to trichloromethylation product **9**.²⁵ By taking advantage of the *in situ* generated CF₃[−] as a base, the allylation of carbon acids that are more acidic than CF₃H has also been achieved enantioselectively.

2.4 Direct fluoromethylations with Me₃SiCF₂H vs. Me₃SiCF₃: the important inductive effect of fluorine on the reactivity of Me₃SiR_f

Me₃SiCF₂H, as an analogue of Me₃SiCF₃, is a potentially useful difluoromethyl anion (HCF₂[−]) source for direct nucleophilic difluoromethylation. However, due to the weaker electron-withdrawing ability of a CF₂H group than a CF₃ group, the reactivity of Me₃SiCF₂H is distinct from the well-documented trifluoromethylation with Me₃SiCF₃ (Scheme 5). The trifluoromethylation with Me₃SiCF₃ can be readily initiated by a wide range of nucleophiles under mild conditions,^{9,26} whereas the initiation of a similar difluoromethylation is quite demanding. Calculations showed that the bond order of the Si–CF₂H bond (0.436) is significantly higher than that of the Si–CF₃ bond (0.220), which is in accordance with the observation that the cleavage of the Si–CF₂H bond is more difficult than that of the Si–CF₃ bond.²⁷

In 2011, we performed an exhaustive investigation on the reaction conditions and revealed that cesium fluoride (CsF)/DMF



Scheme 5 Nucleophilic tri- and difluoromethylation of acetophenone with Me₃SiR_f.

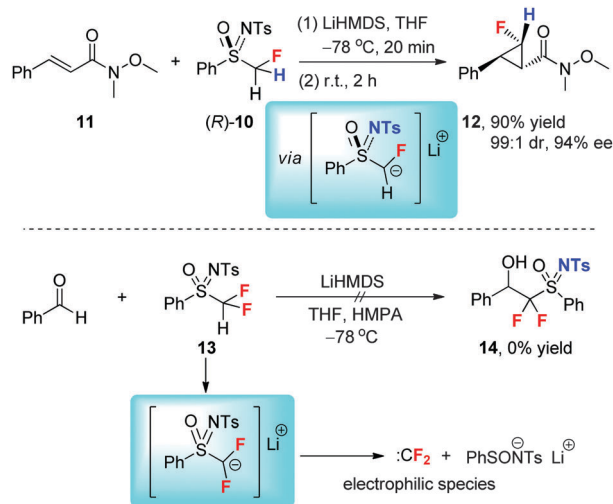
and potassium *tert*-butoxide (*t*BuOK)/THF could allow efficient difluoromethylation of various aldehydes, diaryl ketones, and imines with Me₃SiCF₂H at room temperature or even at −78 °C.²⁷ However, this protocol could not efficiently difluoromethylate enolizable ketones due to either the competitive difluoromethylation of the solvent (when conducted in DMF) or the strong basicity of HCF₂[−] (when conducted in THF). The latter can lead to enolization and subsequent condensation reaction of the ketones. Very recently, Radchenko *et al.*²⁸ showed that the difluoromethylation of enolizable ketones can be achieved by performing the reaction in THF in the presence of an unreactive polar additive such as HMPA, albeit in only moderate yields. It is obvious that the additive HMPA plays an important role in inhibiting the enolization of ketones, thus improving the nucleophilic difluoromethyl anion.

2.5 Mono- vs. difluoromethylation with sulfoximines: a balance between the inductive effect of fluorine and the leaving ability of the neighbouring substitution

Fluorinated sulfoximines have been used as versatile fluoro-alkylation reagents. In 2012, we reported the first highly diastereo- and enantioselective monofluorocyclopropanation reaction with enantiopure monofluoromethyl sulfoximine (*R*)-**10** (Scheme 6).²⁹ This novel reaction was carried out through the Michael-addition of a chiral α-fluorocarbanion generated from sulfoximine (*R*)-**10** to α,β-unsaturated Weinreb amides (such as **11**) followed by γ-elimination of the sulfoximidoyl group, giving optically enriched cyclopropanes (such as **12**). The good leaving ability of the *N*-tosylated sulfoximine moiety and the moderate stability of this monofluorocarbanion are responsible for such a cyclization reaction. However, the nucleophilic difluoromethylation or *gem*-difluoromethylation with the difluorinated analogue **13** was proved to be unsuccessful due to the ready decomposition of the difluorinated carbanion to form difluorocarbene (Scheme 6).²⁹

The reactivity of the difluoromethyl sulfoximine can be tuned from electrophilic to nucleophilic by changing the *N*-substituent from the electron-withdrawing tosyl (Ts) group to the electron-donating *tert*-butyldimethylsilyl (TBS) group (Scheme 7).²⁹



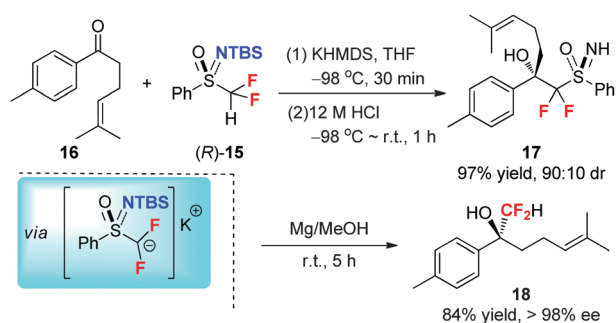


Scheme 6 Nucleophilic monofluoromethylation and difluoromethylation with *N*-tosyl sulfoximines.

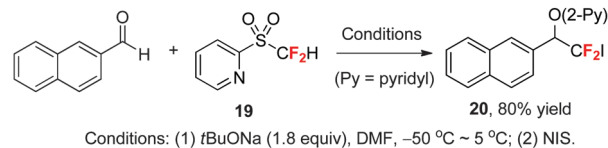
A proper balance between the induction effect of the two fluorine atoms and the weak leaving ability of the *N*-silylated sulfoximine moiety enables the nucleophilic difluoromethylation reaction. The addition of sulfoximine (*R*)-15 to a variety of aryl alkyl ketones (such as 16) followed by reductive desulfoximidoylation furnishes optically enriched difluoromethyl tertiary alcohols (such as 18).

2.6 Iodo- and bromodifluoromethylation vs. (aminosulfonyl)methylation with 2-pyridyl sulfones: fluorine substitution facilitates SO₂ extrusion

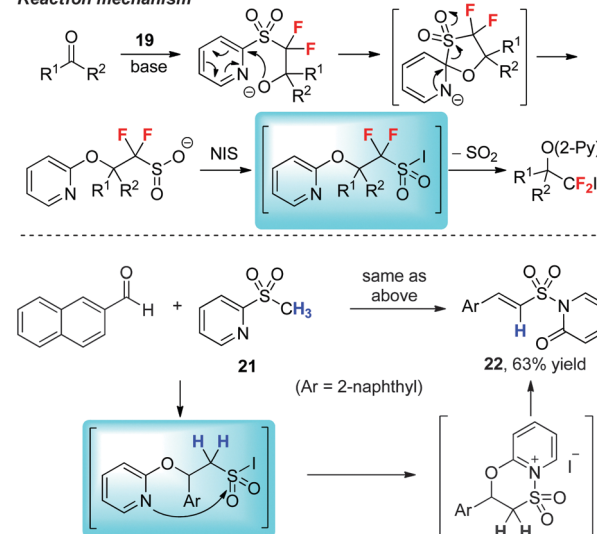
The synthesis of iodo- and bromodifluoromethylated tertiary alcohols through direct nucleophilic fluoroalkylation of ketones is particularly challenging, because of the high tendency of the decomposition of CF₂Br⁻ and CF₂I⁻ to difluorocarbene. To overcome this synthetic problem, we developed formal nucleophilic iodo- and bromodifluoromethylation by using the combination of a nucleophilic difluoroolefination reagent and an electrophilic halogenation reagent.³⁰ In the previously disclosed Julia-Kocienski-type *gem*-difluoroolefination of carbonyl compounds with difluoromethyl 2-pyridyl sulfone (19),³⁰ we found that 2-pyridyl sulfone, which is rarely used in Julia-Kocienski reaction



Scheme 7 Nucleophilic difluoromethylation of ketones with *N*-silyl sulfoximine.



Reaction mechanism



Scheme 8 Iododifluoromethylation and (aminosulfonyl)-methylation with 2-pyridyl sulfones.

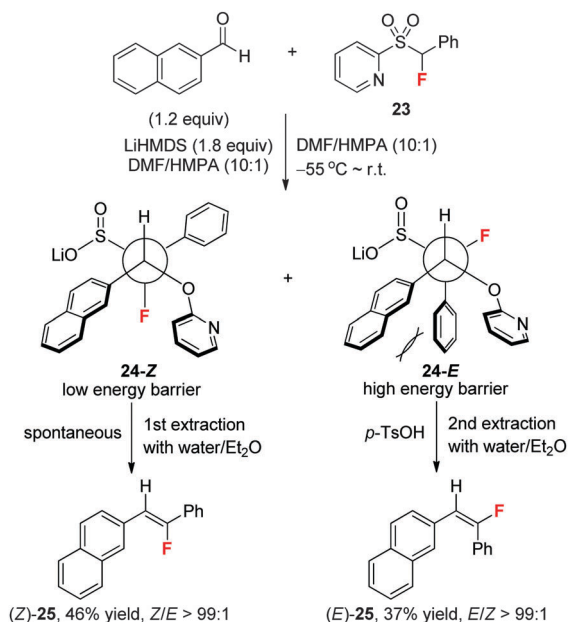
due to its relatively weak electron-withdrawing ability, is an optimal scaffold for *gem*-difluoroolefination due to the fluorine effect. We noticed that the sulfinate intermediates generated *in situ* are relatively stable. Thus, halogenation of the sulfinate intermediates can provide halodifluoromethylation products (such as 20), which change the reaction pathway from the traditional olefination to alkylation (Scheme 8).

In the case of methyl 2-pyridyl sulfone 21, a non-fluorinated sulfone, the halogenation of the sulfinate intermediate proceeds in a different manner, affording aminosulfonylated alkene (*E*)-22 as the main product.³⁰ The change in the reaction pathway may result from the difference in the stabilities of the non- and difluorinated sulfonyl iodide intermediates, with the latter readily extruding SO₂.

2.7 Stereoselective synthesis of monofluoroolefins via Julia-Kocienski reaction: the stereoelectronic effect of fluorine facilitates the kinetic resolution of the sulfinate intermediates

During our pursuit of carbonyl fluoroolefination with heteroaryl sulfones, we developed a spontaneous kinetic resolution of water-soluble Julia-Kocienski intermediates that facilitates liquid-liquid extractive separation of (*Z*)- and (*E*)-monofluoroolefins (Scheme 9).³¹ Although the carbonyl addition with the fluorinated sulfones (such as 23) is non-stereoselective, the decomposition rates of the two diastereomeric sulfinate intermediates (such as 24) from a ready Smiles rearrangement are significantly different. Intermediate 24-*Z* spontaneously and rapidly decomposed to monofluoroalkene (*Z*)-25 at room temperature, whereas its diastereomeric isomer 24-*E* only broke down upon addition of an acid. Thus, after



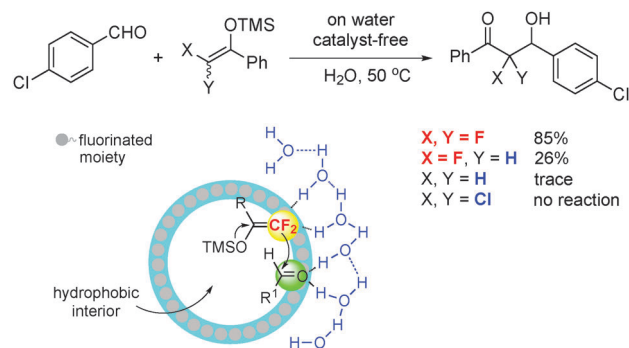


Scheme 9 Stereoselective synthesis of monofluoroolefins *via* kinetic resolution of Julia–Kocienski reaction intermediates.

separating (*Z*)-25 *via* extraction of the mixture with water/ether, acidification of the aqueous phase (*24-E*) followed by a second water/ether extraction can afford another stereoisomer (*E*)-25. This kinetic resolution probably arises from the distinct energy barriers for the decomposition of the fluorinated sulfinate intermediates, which is partially influenced by the stereo-electronic effect of fluorine.³¹

2.8 Difluoroalkylation with silyl difluoroenol ethers “on-water”: the remarkable accelerating effect of F–H interaction

Similar to their non-fluorinated counterparts, the Mukaiyama addition reactions of silyl difluoroenol ethers normally require either a Lewis acid or a Brønsted acid to activate the carbonyl compounds or imine substrate. In 2014, Zhou *et al.*³² reported a highly efficient “on water”, catalyst-free nucleophilic addition reaction of silyl difluoroenol ethers (Scheme 10). The experiments are performed using water as the only solvent without adding any additives. A wide range of substrates, including aromatic aldehydes, activated ketones, and isatylidene malonitriles (Michael acceptors), worked well to give the corresponding difluoroalkylation products in high yields. Control experiments with nonfluorinated, monofluorinated, and dichlorinated enol ethers showed that the fluorine effect on the reaction is remarkable. The reaction of the nonfluorinated silyl enol ether and the aldehyde gave only trace amounts of the product, whereas the monofluorinated silyl enol ether reacted sluggishly to give the product in only 26% yield under the same reaction conditions. Moreover, the dichlorinated analogue failed to undergo the reaction. An explanation is that the C–F...H–O interactions between difluorinated enol ethers and the hydrogen bond network of water at the phase boundary of the reactants promote the formation of a unique microstructure, thus facilitating the “on-water” catalyst-free addition reaction.³²

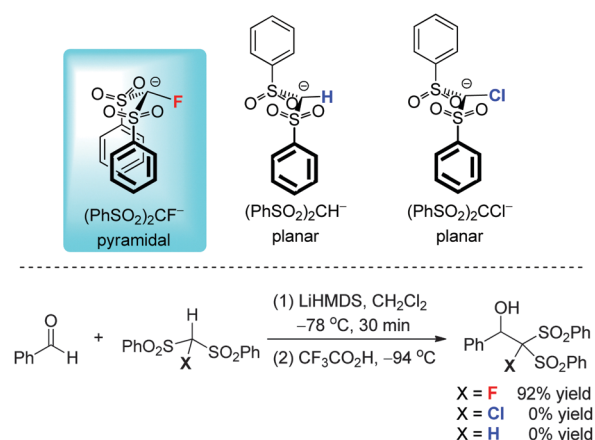


Scheme 10 “On-water” difluoroalkylation with silyl difluoroenol ethers.

2.9 Monofluoromethylation of aldehydes with (PhSO₂)₂CHF: the electronic effect of fluorine facilitates the addition reaction

Fluorobis(phenylsulfonyl)methane [(PhSO₂)₂CHF] is a synthetically useful nucleophilic monofluoromethylation reagent. X-ray crystallographic studies have shown that its anion (PhSO₂)₂CF[−] has a pyramidal structure, whereas its nonfluorinated counterpart (PhSO₂)₂CH[−] and a brominated anion (C₄F₉SO₂)₂CBr[−] adopt planar structures. NMR and computational studies confirm that the highly electronegative fluorine substituent plays an important role in pyramidalization of the carbon center of (PhSO₂)₂CF[−] (Scheme 11).³³

Compared with the non-fluorinated sulfones (PhSO₂)₂CH₂, fluorine substitution can improve the reactivity of the bis(phenylsulfonyl)methyl anion. An example is the nucleophilic addition reaction between (PhSO₂)₂CHF and an aldehyde reported by us (Scheme 11).³⁴ This reaction was previously considered to be unattainable because of the steric hindrance of the (PhSO₂)₂CF group. We accomplished the reaction by using lithium hexamethyldisilazide (LiHMDS) as the base to promote the formation of the alcoholate. Control experiments with lithium, sodium, and potassium hexamethyldisilazides showed that LiHMDS serves as the best base for the addition reaction, indicating that the strong Li–O coordination in the alcoholate intermediate plays an important role in its stabilization. Furthermore, under the same reaction conditions, similar nucleophilic addition



Scheme 11 Monofluoromethylation of aldehydes with (PhSO₂)₂CHF.



reactions between $(\text{PhSO}_2)_2\text{CH}_2$ or $(\text{PhSO}_2)_2\text{CHCl}$ and an aldehyde are unsuccessful. This suggests that the fluorine substitution, which helps to strengthen the newly formed C–C bond, is also of great importance for the nucleophilic fluoromethylation reaction. Taking together, the Li–O interaction and the fluorine substitution simultaneously promote this aldehyde addition reaction.³⁴

2.10 Asymmetric Mannich-type reaction of $\alpha\text{-CF}_3$ amide through bidentate coordination: stabilization effect of CF_3 vs. $\beta\text{-fluoride}$ elimination

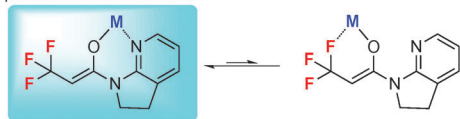
Although the strong electron-withdrawing $\alpha\text{-trifluoromethyl}$ group is more effective than $\alpha\text{-fluorine}$ atom for the stabilization of a carbanion electronically, $\alpha\text{-CF}_3$ carbanions with “hard” metal counterions usually readily eliminate a $\beta\text{-fluoride}$ to form *gem*-difluoroolefins due to the strong metal–fluorine interaction (Scheme 12).³⁵ This undesired $\beta\text{-fluoride}$ elimination reaction is a main obstacle for effective synthetic application of $\alpha\text{-CF}_3$ carbanions.

$\alpha\text{-Trifluoromethyl}$ enolates are active nucleophiles for synthesizing CF_3 -bearing functionalized organic molecules. However, methods for tuning their nucleophilic reactivity are very limited. Very recently, Kumagai, Shibasaki *et al.*³⁵ developed a catalytic method for the generation of $\alpha\text{-CF}_3$ enolate through bidentate coordination of a soft Lewis acidic metal counterion with the enolate oxygen and an amide auxiliary group (Scheme 12). The inhibition of the metal–fluorine interaction enables the catalytic generation of $\alpha\text{-trifluoromethyl}$ enolate without competitive fluoride elimination. Thus, the catalytic asymmetric Mannich-type reaction using an $\alpha\text{-CF}_3$ amide **26** via soft Lewis acid/hard Brønsted base cooperative catalysis affords the Mannich products (such as **27**) in excellent yields with high diastereo- and enantioselectivity.

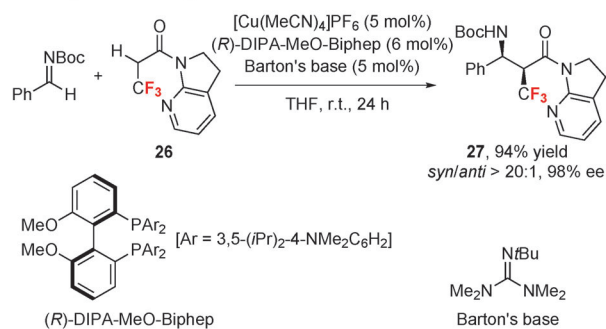
Lewis acidic metal-promoted $\beta\text{-fluoride}$ elimination



Inhibit $\beta\text{-fluoride}$ elimination via bidentate coordination



Cu-catalyzed Mannich-type reaction



Scheme 12 Asymmetric Mannich-type reaction of $\alpha\text{-CF}_3$ amide through bidentate coordination.

3. The unique fluorine effects in electrophilic fluoroalkylation reactions

Despite the strong electron-withdrawing ability of fluorine atoms, the $\alpha\text{-fluorine}$ atom can stabilize carbocations through the interaction between the lone-pair electron of fluorine and the unoccupied p-orbital of the cationic carbon center. Studies have indicated that the stability of fluorinated carbocations decreases as follows: $\text{HCF}_2^+ > \text{CH}_2\text{F}^+ > \text{CF}_3^+ > \text{CH}_3^+$. Although the fluorine effect is complex for CF_3^+ , this trend at least shows that $\alpha\text{-fluorine}$ substitution is effective for stabilizing carbocations.⁴

However, in real electrophilic fluoroalkylation reactions, the fluoroalkylating agents are usually equivalents of fluorinated carbocations, rather than free fluorocarocations. Thus, the electrophilic fluoroalkylations commence with the reaction of a nucleophilic centre (usually negatively charged) with an electrophilic fluorinated carbon centre, and conclude with the formation of a fluorinated sp^3 -carbon centre. In this section, we will give a brief summary on the influence of fluorine substitution on the chemoselectivity and reaction mechanism of electrophilic fluoroalkylations.

3.1 *O*-Trifluoromethylation with a hypervalent iodine reagent: flipping the reactivity of trifluoromethyl from nucleophilic to electrophilic

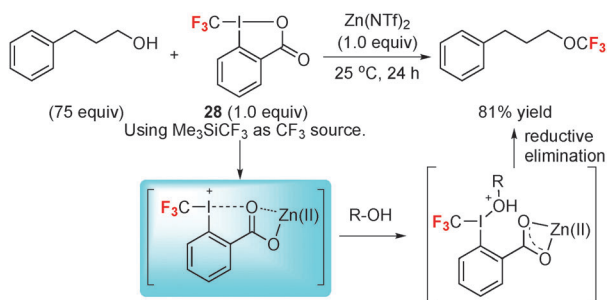
As mentioned in the Introduction part, the direct perfluoroalkylation of a hard nucleophile with $\text{R}_f\text{-I}$ is difficult to achieve due to the reversed polarisation of R_f by the fluorine substitution. Since 2006, Togni *et al.*^{18,36} have introduced (per)fluoroalkylated hypervalent iodine compounds for electrophilic introduction of the trifluoromethyl group and longer (per)fluorinated alkyl chains. Enhancing the valence of the iodine atom is an elegant method to change the reaction pathway to the desired electrophilic perfluoroalkylation.

Trifluoromethyl ethers are useful in materials, agricultural, and pharmaceutical sciences; however, their traditional synthesis relies on multi-step transformations. In 2009, Togni *et al.*¹⁸ reported a practical *O*-trifluoromethylation of aliphatic alcohols under the activation of $\text{CF}_3\text{-I(III)}$ reagent **28** by Lewis acid $\text{Zn}(\text{NTf}_2)_2$ (Scheme 13). The reaction probably proceeds *via* Zn(II) -promoted ligand exchange with alcohol followed by reductive elimination of the product.

3.2 *C*- vs. *O*-fluoroalkylation of ketoesters with a fluorinated sulfoximinium salt: the influence of fluorine on the chemoselectivity

Sulfoximinium salt is also a useful scaffold for electrophilic fluoroalkylations (Scheme 14).³⁷ *S*-Trifluoromethyl sulfoximinium salt **29** is an electrophilic trifluoromethylation reagent. Its reaction with $\beta\text{-ketoester}$ **30** affords *C*-trifluoromethylation product **31**. The control experiment showed that adding nitrobenzene does not decrease the yield, thus suggesting a normal electrophilic trifluoromethylation pathway. However, the reaction of **32** and $\beta\text{-ketoester}$ **30** gives a mixture of *C*- and *O*-difluoromethylation products **33** and **34**. More interestingly, the monofluorinated





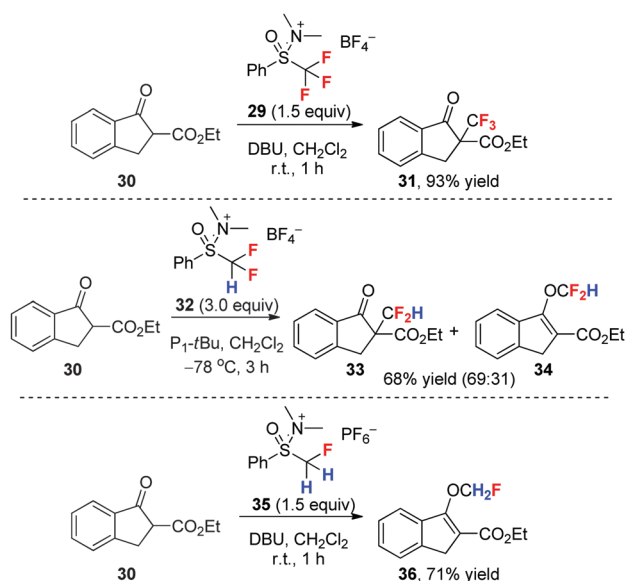
Scheme 13 O-Trifluoromethylation with a hypervalent iodine reagent.

analogue **35** is an efficient electrophilic monofluoromethylation reagent with inherent *O*-selectivity. Its reaction with β -ketoester **30** gives *O*-monofluoromethyl compound **36** in high yield.

Computational studies provided some insights into the different chemoselectivity of the tri-, di and monofluoromethylation of β -ketoester.³⁷ The *C*-/*O*-selectivity should be attributed to the electronic character of tri-, di- and monofluoromethyl cations or radicals. Trifluoromethylation with *C*-selectivity possibly involves the formation of a more cationic species like CF_3^+ . For difluoromethylation, it may involve both radical and cationic species, thus providing a mixture of *C*- and *O*-difluoromethylation products. Monofluoromethylation probably proceeds involving a more radical-like species.³⁷

3.3 *O*-Difluoromethylation of phenols with Me_3SiCF_3 vs. $\text{Me}_3\text{SiCF}_2\text{Br}$: the inhibition effect of a third fluorine substitution on the generation of difluorocarbene in an aqueous system

Difluorocarbene ($:\text{CF}_2$, with a singlet ground state) is the most stable dihalocarbene owing to the interaction of the lone pairs of its fluorine substituents with the carbene center. The combined destabilization effect by the negative inductive effect of fluorine



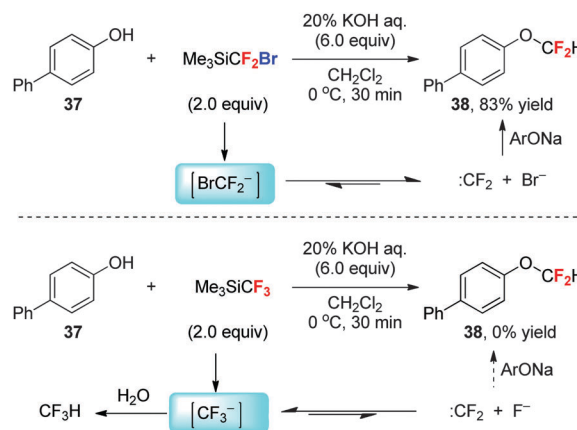
Scheme 14 Fluoroalkylation of ketoester with fluorinated sulfoximines.

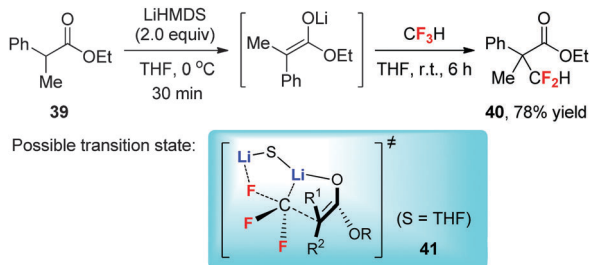
and stabilization effect by π -donation from the fluorine to the vacant p-orbital of carbon render $:\text{CF}_2$ a moderately reactive electrophilic species.³⁸ In the past few years, we and Prakash *et al.* developed Me_3SiCF_3 , $\text{Me}_3\text{SiCF}_2\text{Cl}$ and $\text{Me}_3\text{SiCF}_2\text{Br}$ as novel difluorocarbene reagents. These three fluoromethylsilanes can generate $:\text{CF}_2$ effectively and have been used for the *gem*-difluorocyclization of alkynes and alkenes *via* [2+1] cycloaddition in organic solvents.³⁸

However, the heteroatom-difluoromethylation usually needs an alkaline base (such as KOH) to activate the pronucleophiles (such as phenols) by deprotonation. Hence, an aqueous solution of base is preferred for the activation of both the substrates and the difluorocarbene reagents. $\text{Me}_3\text{SiCF}_2\text{Br}$ and $\text{Me}_3\text{SiCF}_2\text{Cl}$ are suitable reagents for difluoromethylation of phenol **37** in a mixed solvent system consisting of CH_2Cl_2 and water, but Me_3SiCF_3 fails to react with **37** under the same conditions, being hydrolysed to CF_3H completely (Scheme 15).³⁹ The electronic nature of α -halo substituents determines the feasibility of the difluorocarbene pathway. In the reaction using Me_3SiCF_3 and aqueous KOH, the strong electron-withdrawing ability of fluorine stabilizes the CF_3 anion, rendering α -fluoro elimination much difficult; therefore, the protonation of CF_3 anion prevails.

3.4 *C*-Difluoromethylation of ester with CF_3H : an electrophilic lithiodifluoromethylation pathway facilitated by intermolecular lithium–fluorine interaction

In contrast to the negative role of F–Li interaction in nucleophilic trifluoromethylation with CF_3Li , this interaction can promote electrophilic difluoromethylation with CF_3Li . Mikami *et al.* reported the direct α -difluoromethylation of carbonyl compounds such as ester **39** with CF_3H under the promotion of lithium hexamethyldisilazide (LiHMDS) (Scheme 16).⁴⁰ Among various alkali metals (Li, Na, K, Cs) used for both deprotonations, only LiHMDS , which contains the most Lewis acidic metal counteranion, works for this difluoromethylation. Moreover, the amount of the base used is found to be crucial for the reaction; two equivalents (relative to the substrate) give the highest yields. Computational studies⁴⁰ showed that the

Scheme 15 *O*-Difluoromethylation of phenol with $\text{Me}_3\text{SiCF}_2\text{Br}$ and Me_3SiCF_3 .

Scheme 16 C-Difluoromethylation of ester with CF_3H .

reaction proceeds through transition state **41** involving a bimetallic difluoromethylene carbenoid species $[\text{Li}-\text{F}-\text{CF}_2-\text{Li}]^\ddagger$. Nucleophilic attack of the enolate carbon on the electrophilic difluoromethylene carbenoid through an $\text{S}_{\text{N}}2$ -like mechanism followed by protonation furnishes this difluoromethylation.

4. The unique fluorine effects in radical fluoroalkylation reactions

Fluoroalkyl radicals, as very important reactive intermediates in organofluorine chemistry, not only participate in fluoroalkyl addition to unsaturated systems, but also play roles in fluoroalkylation of nucleophiles (*via* single electron-transfer mechanism).

α -Fluorination has a special effect on the structure and stabilization of methyl radicals. The trifluoromethyl radical is essentially tetrahedral, and difluoromethyl and monofluoromethyl radicals are pyramidal, while the methyl radical is planar.⁴ The kinetic analysis on the C–C bond homolytic cleavage of various fluorinated *tert*-butoxy radicals by Jiang *et al.* showed that the relative rate for the formation of methyl and fluoromethyl radicals decreases as follows: HCF_2^\bullet (10.2) > $\text{CH}_2\text{F}^\bullet$ (9.0) > CH_3^\bullet (1.0) > CF_3^\bullet (0.08).^{2,4} C–H bond dissociation energy calculations for fluorinated methanes also suggest that the thermodynamic stability of fluoromethyl radicals decreases in a similar order: $\text{CH}_2\text{F}^\bullet > \text{HCF}_2^\bullet > \text{CH}_3^\bullet > \text{CF}_3^\bullet$.^{2,4} These data indicate that both mono- and difluorination stabilize the methyl radical, whereas trifluorination destabilizes the radical.⁴ Calculations suggest that fluorine substitution destabilized the α -radicals inductively, but slightly stabilizes α -radicals through resonance; overall, the tetrahedral trifluoromethyl radical becomes the most unstable one among fluoro-methyl radicals due to the diminished resonance stabilization.⁴

The reactivity of a fluoroalkyl radical can be divided into nucleophilicity and electrophilicity. On the one hand, due to the electron-donating resonance effect of lone-pair electrons on the α -fluoro substituent, all fluoromethyl radicals have lower ionization potential than CH_3^\bullet , with HCF_2^\bullet being more nucleophilic than CH_3^\bullet ; on the other hand, due to the strong inductive effect of the α -fluorine, CF_3^\bullet is more electrophilic than CH_3^\bullet .^{4,41}

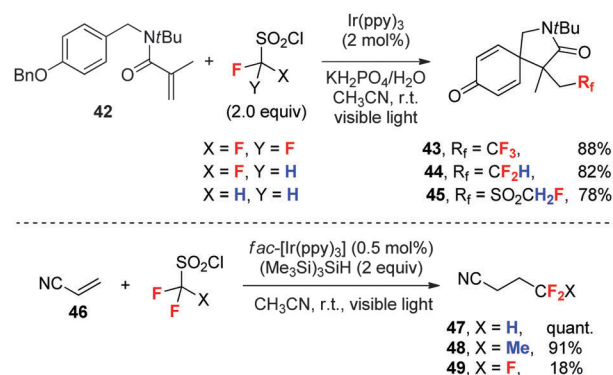
In radical fluoroalkylation with reagents of various forms, not only the stability and reactivity of the fluoroalkyl radicals, but also other factors such as the reduction potential and the stability of the fluoroalkyl radical precursors can influence the whole chemical outcome.

4.1 Fluoroalkylation of alkenes with sulfonyl chlorides: the influence of fluorine substitution on the generation and reactivity of fluoroalkyl radicals

Fluoroalkanesulfonyl chlorides are excellent fluoroalkyl radical precursors, which can be reduced more readily through single electron transfer (SET) than fluoroalkyl iodides owing to the stronger electron-withdrawing ability of the fluoroalkanesulfonyl group than a simple fluoroalkyl group. Fluoroalkanesulfonyl chlorides have been used for radical fluoroalkylation of arenes and alkenes.¹⁴ In spite of their relatively high reactivity, the influence of fluorine substitution on the generation and reactivity of fluoroalkyl radicals is still significant.

In a photoredox-catalyzed dearomative radical cyclization of *N*-benzylacrylamides such as **42** (Scheme 17), Dolbier *et al.*⁴² showed that the reaction with $\text{CF}_3\text{SO}_2\text{Cl}$ or $\text{HCF}_2\text{SO}_2\text{Cl}$ at room temperature provides tri- or difluoromethylation products **43** and **44**, respectively, with the loss of SO_2 . However, the reaction with $\text{CH}_2\text{FSO}_2\text{Cl}$ under the same conditions gives monofluoromethanesulfonylation product **45** with the retaining of SO_2 . Obviously, the weak electron-withdrawing ability of the CH_2F group makes the loss of SO_2 at a low temperature difficult.

A study on hydrodifluoroalkylations of electron-deficient alkenes such as acrylonitrile (**46**) under photoredox catalysis showed that difluoroalkylations (including difluoromethylation) readily take place, while trifluoromethylation is sluggish (Scheme 17).⁴¹ Computational studies using acrylonitrile and propene as model substrates showed that the nucleophilic/electrophilic nature of various fluoroalkyl groups is consistent with their electron-donating/-withdrawing ability.⁴¹ The reactions of RCF_2^\bullet with acrylonitrile, an electron-deficient alkene, prefer the charge-transfer (CT) transition state $\text{RCF}_2^\bullet/[\text{CH}_2=\text{CHCN}]^-$, which significantly lowers the activation barrier. In the reactions of CF_3^\bullet with propene, an electron-rich alkene, the preferential formation of the CT state $\text{CF}_3^\bullet/[\text{CH}_2=\text{CHCH}_3]^+$ is expected, thus lowering its barrier to a value smaller than that for acrylonitrile. For the reaction of CF_3^\bullet with acrylonitrile, although the activation barrier is similar to that for RCF_2^\bullet due to its large enthalpy, the observed low yield probably arises from the competitive hydrogen abstraction reaction of CF_3^\bullet .⁴¹



Scheme 17 Fluoroalkylation of alkenes with sulfonyl chlorides.



4.2 Tri- vs. difluoromethylation of arenes with sulfinate salts: the influence of fluorine substitution on site-selectivity

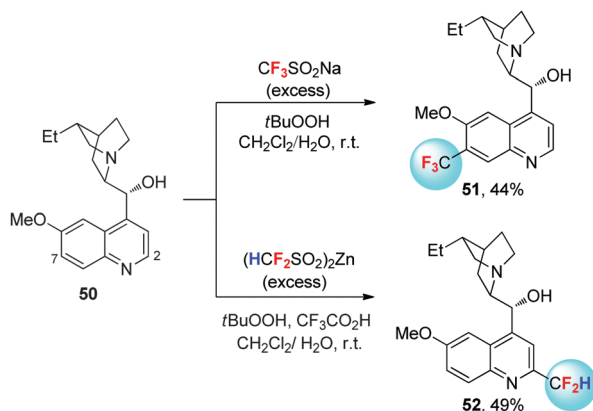
The site-selectivity in the fluoroalkylation of hetero(aromatic) compounds is another case for interpreting the influence of fluorosubstitution on the nucleophilicity/electrophilicity of alkyl radicals. Baran *et al.* reported the oxidative tri- and difluoromethylation of hetero(arenes) with sulfinate salts $\text{CF}_3\text{SO}_2\text{Na}$ and $(\text{HCF}_2\text{SO}_2)_2\text{Zn}$ as the radical sources (Scheme 18).⁴³ Dihydroquinine (**50**) reacts with $\text{CF}_3\text{SO}_2\text{Na}$ in the presence of TBHP, to give product **51**, with site-selectivity toward the *o*-position of the methoxy group (C-7 site), demonstrating the electrophilic nature of CF_3^\bullet . In contrast, difluoromethylation of dihydroquinine with $(\text{HCF}_2\text{SO}_2)_2\text{Zn}$ under similar conditions takes place at the electron-deficient C-2 site to give **52**, coinciding with the nucleophilic nature of HCF_2^\bullet .

4.3 Fluoroalkylation of isocyanides with sulfones: fluorine effects on the generation of fluoroalkyl radicals

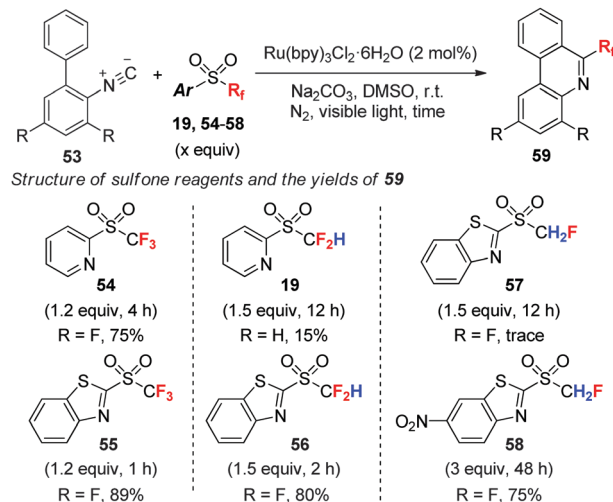
Fluorinated sulfones have been used as versatile radical precursors. We showed that under visible-light photoredox catalysis, a wide range of readily available mono-, di-, and trifluoromethyl heteroaryl sulfones readily fluoroalkylate isocyanides (such as **53**) (Scheme 19).⁴⁴ The electronic nature the heteroaryl group is pivotal for the generation of fluoroalkyl radicals. Trifluoromethyl sulfones with both 2-pyridyl (**54**) and 2-benzo[*d*]thiazolyl (BT) (**55**) groups readily undergo trifluoromethylation due to the strong electron-withdrawing ability of the CF_3 group. For difluoromethylation, only the more electron-deficient 2-BT group (**56**) works well. Nevertheless, in the case of monofluoromethylation, increasing the reduction potential of monofluoromethyl sulfone by introducing a nitro group (**58**) on the 2-BT moiety is required to promote the monofluoromethylation reaction.⁴⁴

4.4 Monofluoromethylation of phenols with fluorinated sulfoximine: the influence of fluorine substitution on the reactivity

We reported the monofluoromethylation of phenols with *N*-tosyl-*S*-monofluoromethyl sulfoximine **10** (Scheme 20),²⁹ which is also a nucleophilic fluoroalkylation reagent as mentioned previously



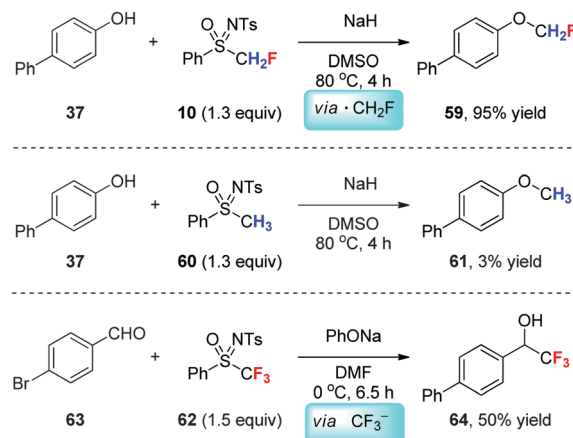
Scheme 18 Tri- and difluoromethylation of arenes with sulfinate salts.



Scheme 19 Fluoroalkylation of isocyanides with sulfones.

(see Scheme 6). Compared with its non-fluorinated counterpart **60**, reagent **10** reacts with phenol **37** at a much faster reaction rate. This phenomenon is inconsistent with a typical $\text{S}_{\text{N}}2$ reaction pathway, in which α -fluorine substitution should decrease the reactivity of an electrophile. Therefore, a single-electron transfer (SET) mechanism involving $\text{CH}_2\text{F}^\bullet$ is proposed, which is supported by radical inhibition experiments.²⁹ In contrast, the reaction between PhONa and trifluoromethyl sulfoximine **62**, gives CF_3H instead of an *O*-trifluoromethylation product. The addition of aldehyde **63** to the reaction system affords the nucleophilic trifluoromethylation product **64**, supporting the generation of CF_3^- during the reaction (Scheme 14).²⁹

It is obvious that the degree of fluorine substitution significantly affects the reactivity of mono-, di- and trifluoromethyl sulfoximines. In comparison with radical monofluoromethylation with $\text{PhSO}(\text{NTs})\text{CH}_2\text{F}$ (**10**) *via* $\text{CH}_2\text{F}^\bullet$ and electrophilic difluoromethylation with $\text{PhSO}(\text{NTs})\text{CF}_2\text{H}$ (**13**) *via* $:\text{CF}_2$ (see Scheme 6), $\text{PhSO}(\text{NTs})\text{CF}_3$ (**62**) is a nucleophilic trifluoromethylation reagent *via* CF_3^- .



Scheme 20 Reaction of *N*-tosyl mono- and trifluoromethyl sulfoximines with phenol.



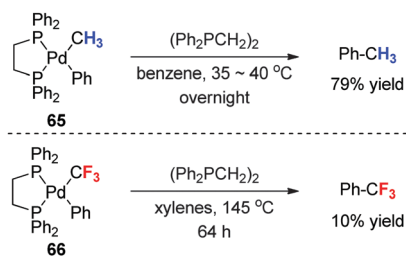
5. Unique fluorine effects in transition metal-mediated fluoroalkylation reactions

Transition metals, which may be considered as the counterions of fluoroalkyl anions, can significantly influence the fluoroalkylation reactions due to their varying hard/soft nature, oxidation state and ligand effect. The stability and reactivity problems associated with fluoroalkyl metal species are major hurdles in developing transition metal mediated fluoroalkylation reactions. For example, unlike perfluoroalkyl copper reagents such as CuCF_3 , the CuCF_2H reagent prepared by a metathesis reaction between $\text{Cd}(\text{CF}_2\text{H})_2$ and CuBr undergoes a rapid decomposition to give 1,1,2,2-tetrafluoroethane and (*Z*)-1,2-difluoroethene at temperatures above -30°C .⁴⁵ As another example (Scheme 21), Ph-Pd(II)-CF_3 complex **65** with a bidentate phosphine ligand $(\text{Ph}_2\text{PCH}_2)_2$ is reluctant to undergo reductive elimination to form Ph-CF_3 even at an elevated temperature (145°C), while its nonfluorinated analogue **66** readily releases Ph-CH_3 at relatively low temperatures ($15\text{--}40^\circ\text{C}$).¹⁷ In recent years, great progress has been achieved in transition-metal mediated fluoroalkylations by changing the metal species and the ligands. In this section, we only introduce some typical examples that are related to the fluorine effect, including trifluoromethylation, difluoroalkylation, monofluoroalkylation, and β -fluoroalkylation reactions.

5.1 Palladium-catalyzed trifluoromethylation of aryl chlorides: tackling the fluorine effect by changing the ligand

As mentioned above, it is usually difficult for the Ph-Pd(II)-CF_3 complex to undergo reductive elimination due to the electronic effect of the CF_3 group.¹⁷ The strong electron-withdrawing CF_3 group renders the palladium more Lewis acidic, which significantly improves the activation barrier for Ph-CF_3 elimination and impedes the development of a Pd-catalyzed nucleophilic trifluoromethylation of aryl halides with normal phosphine ligands.

In 2010, Buchwald *et al.*⁴⁶ developed the first Pd-catalyzed trifluoromethylation of aryl chlorides (such as **67**) by using the steric hindered electron-rich phosphine ligand BrettPhos (Scheme 22). Stoichiometric reaction showed that the Ar-Pd-CF_3 complex **69**, which is ligated with only one BrettPhos ligand, can easily undergo reductive elimination at 80°C . Computational studies showed that in comparison to the ground states, the Pd-CF_3 distance in the transition states is substantially elongated,



Scheme 21 Reductive elimination of methyl- and trifluoromethyl palladium complexes.

whereas the distance between the Pd atom and the aryl ring remains essentially unchanged, suggesting that the main contribution of BrettPhos to the activation energy is the breaking of the strong Pd-CF_3 bond.⁴⁶

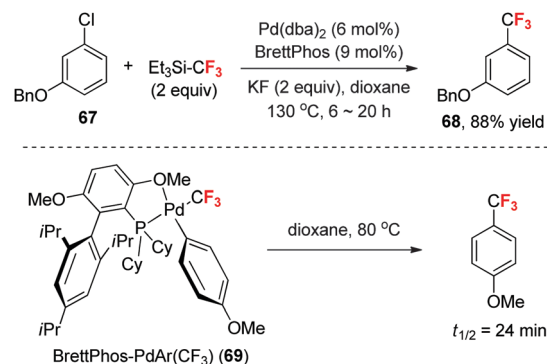
5.2 Nucleophilic mono- vs. trifluoromethylation of arynes: tackling the fluorine effect by changing the metal counteraction

Arynes, with their low-lying lowest unoccupied molecular orbital (LUMO), can be considered as soft electrophiles. During our investigation of the hard/soft nature of α -fluoro carbanions, we developed the nucleophilic monofluoromethylation of arynes (*in situ* generated from precursors such as **70**) by using a soft monofluoromethide anion equivalent, $(\text{PhSO}_2)_2\text{CF}^-$ (Scheme 23).⁴⁷

However, arynes failed to react with the trifluoromethyl anion generated from TMSCF_3 and a fluoride salt such as CsF , presumably because of the low stability of CF_3^- and the mismatch between the soft aryne and the hard CF_3^- species (due to the fluorine substitution) under the provided conditions. This synthetic problem was finally solved by using AgCF_3 , a trifluoromethylmetallic species possessing increased stability and softness in comparison with the “naked” CF_3^- .⁴⁷ Thus, *in situ*-generated aryne species reacts with AgCF_3 to form an *o*-(trifluoromethyl)arylsilver complex, which further reacts with the alkynyl iodide (an iodination reagent) to give vicinally iodotrifluoromethylated aromatics such as **73**.

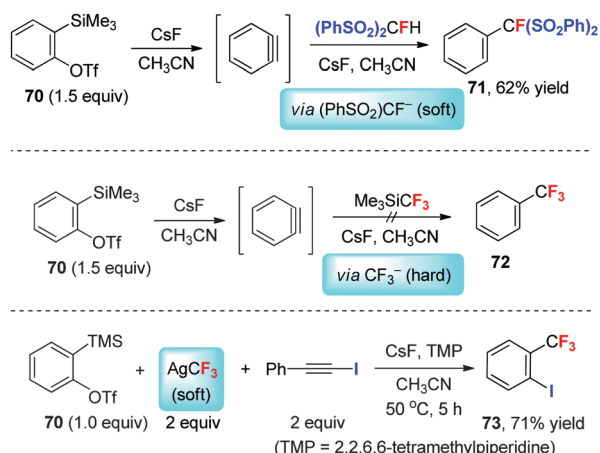
5.3 Palladium-catalyzed regiodivergent allylic fluoroalkylation: the electronic effect of fluorine on the yield and regioselectivity

In 2015, Altman *et al.*⁴⁸ reported a palladium-catalyzed regiodivergent allylic fluoroalkylation with difluorinated β -ketoesters **74** as the substrates (Scheme 24). By changing the ligand structure, either linear or branched α -allyl- α,α -difluoroketone is obtained in good yield and regioselectivity. Interestingly, the ligand-controlled regioselective reaction only works for the difluorinated ketoesters, and the analogous mono- and non-fluorinated substrates cannot provide branched products with a similar chemical outcome. It is obvious that the fluorine substitution on the substrate facilitates the generation of the branched product.



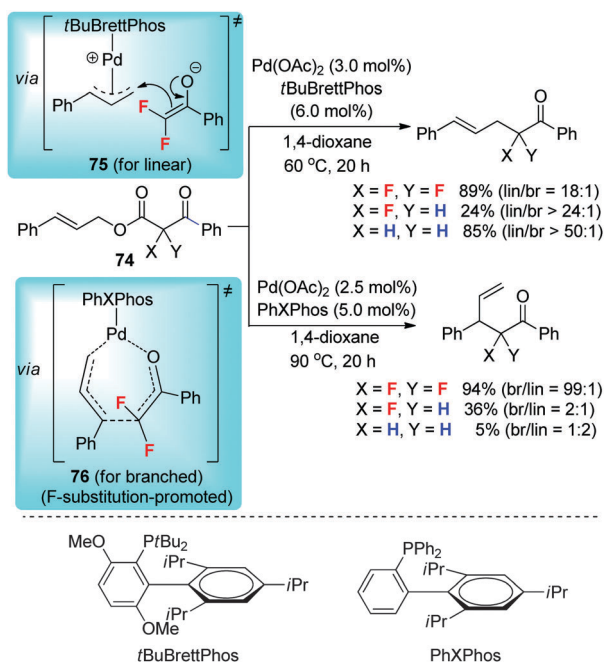
Scheme 22 Palladium-catalyzed trifluoromethylation of aryl chlorides.





Scheme 23 Nucleophilic mono- and trifluoromethylation of arynes.

An analysis of the relationship between the electronic properties of the difluorinated substrates and the regioselectivities of the catalytic reactions implies two distinct pathways accounting for the linear and branched products.⁴⁸ On the one hand, under the catalytic conditions with *t*BuBrettPhos as the ligand, electron-rich cinnamyl esters provides linear products with lower selectivity than electron-deficient cinnamyl esters, which is in accordance with a normal outer-sphere mechanism involving transition state 75. On the other hand, under the catalytic conditions with PhXPhos as the ligand, the electronic properties of cinnamyl esters do not influence the regioselectivity significantly. Moreover, this reaction is consistent with the accelerating effect of fluorine in non-metal-catalyzed 3,3-sigmatropic rearrangements of allyl α,α -difluoroenol ethers. Therefore, the combined unique



Scheme 24 Palladium-catalyzed regiodivergent allylic fluoroalkylation reaction.

electronic effect of the fluorine atom and the ligand effect of PhXPhos may facilitate an analogues rearrangement, in which an η^1 -allyl palladium(enolate) intermediate undergoes the sigmatropic rearrangement *via* palladacyclic transition state 76 to afford the branched product.⁴⁸

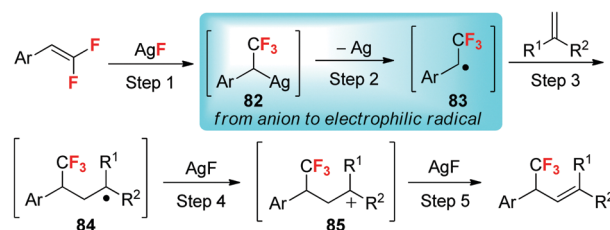
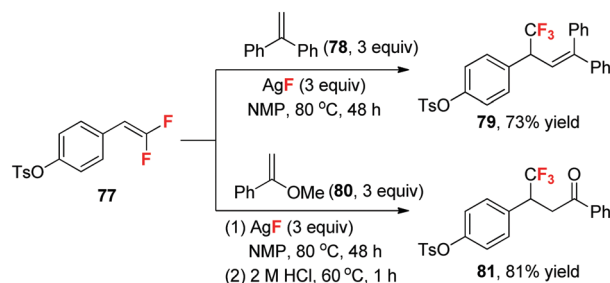
5.4 AgF-mediated fluorinative cross-coupling of two olefins: the electronic effect of fluorine on the reactivity of olefins

As mentioned previously (see Section 2.10), the β -fluoride elimination of the α -CF₃ carbanion is a competitive reaction that influences the synthetic application of such an anion. Because the electron-withdrawing inductive effect of the fluorine atoms together with electron repulsion between the double bond and the fluorine atoms render the difluorinated carbon atom of *gem*-difluoroolefin very electrophilic, we conceived that the reverse fluoride addition to difluoroolefin may be a possible solution to the β -fluoride elimination problem. However, one challenge associated with this method is the spontaneous protonation of the α -CF₃ carbanion when an alkali metal salt is used as the fluoride source.

We found that AgF can be used to react with *gem*-difluorostyrene derivatives (such as 77) and to stabilize the intermediates (Scheme 25).⁴⁹ The ready homocoupling reaction indicates that the intermediates are α -CF₃-benzylsilver species 82 with radical reactivity.⁴⁹ Thus, the use of electron-rich terminal olefins (such as 78 and 80) as the α -CF₃-benzyl radical acceptor leads to a AgF-mediated fluorinative cross-coupling reaction between *gem*-difluoroolefins and non-fluorinated olefins, providing a facile access to both α -CF₃ alkenes (such as 79) and β -CF₃ ketones (such as 81) that otherwise remain challenging to be directly prepared.⁴⁹

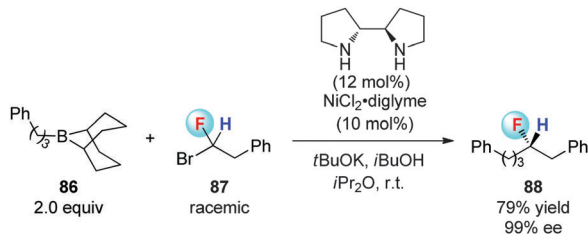
5.5 Nickel-mediated enantioselective Suzuki cross-coupling of unactivated 1-halo-1-fluoroalkanes: the steric effect of fluorine substituents on the enantioselectivity

Although the van der Waal radii of fluorine (1.47 Å) is only a little larger than that of hydrogen (1.20 Å) and is usually



Scheme 25 AgF-mediated fluorinative cross-coupling of two olefins.





Scheme 26 Nickel-mediated enantioselective Suzuki cross-coupling of unactivated 1-halo-1-fluoroalkanes.

recognized as a mimic of hydrogen, the steric effect of fluorine is remarkable in many transformations.⁴

Very recently, Gandelman *et al.*⁵⁰ reported a Ni-mediated Suzuki-cross coupling of unactivated 1-halo-1-fluoroalkanes with alkylboranes for the synthesis of secondary alkyl fluorides (Scheme 26). Racemic 1-halo-1-fluoroalkanes (such as **87**) bearing directing groups such as phenyl, keto, and sulfonamide substituents at various distant positions efficiently participate in stereoconvergent enantioselective Suzuki reactions with good enantioselectivity. The enantioselectivity of the product and the absence of kinetic resolution for 1-halo-1-fluoroalkane **87**⁵⁰ indicate that the coupling reaction may proceed through a single electron-transfer process involving α -fluoroalkyl radicals.

6. Conclusions

Incorporating fluorine atom(s) *via* fluoroalkylation has become a useful strategy in drug design and new functional material development. In fluoroalkylation reactions, the fluorine substitutions can dramatically influence the chemical outcome. As a result, the chemistry of alkylation with their non-fluorinated counterparts may not be applicable to fluoroalkylations. Therefore, tackling the unique fluorine effects is necessary to achieve desired fluoroalkylation reactions. On the other hand, the fluorine substitution can bring about new reactivities and transformations that cannot be achieved in alkylation with non-fluorinated reagents, thus fluorine substitution is also a tool to explore new synthetic methods.

Fluorine effects are ubiquitous in fluoroalkylations, which are either negative or positive for the reactions. Understanding the unique fluorine effects in fluoroalkylation reactions not only facilitates the prediction, design, and further development of fluoroalkylation chemistry, but also provides deeper insights into unique features of fluorine and its related science. It is worthwhile to note that Cahard and Bizet¹² also published a tutorial review on fluorine effects, concentrating on asymmetric synthesis using fluorinated substrates and fluorinated catalysts. Our Tutorial Review mainly discusses fluoroalkylation reactions, that is, the organic synthesis using fluorinated reagents. These two reviews complement each other, providing readers an opportunity to deeply understand the unique fluorine effects in organic chemistry.

Acknowledgements

We thank the National Basic Research Program of China (2015CB931900 and 2012CB821600), the National Natural

Science Foundation of China (21421002, 21372246, and 21472221), the Chinese Academy of Sciences, Shanghai Academic Research Leader Program (15XD1504400), Shanghai Rising-Star Program (16QA1404600), and the Youth Innovation Promotion Association CAS (2014231) for financial support.

Notes and references

- P. Vollhardt and N. Schore, *Organic Chemistry: Structure and Function*, Freeman, New York, 7th edn, 2014.
- R. D. Chambers, *Fluorine in Organic Chemistry*, Blackwell, Oxford, 2004, and reference therein.
- P. Kirsch, *Modern Fluoroorganic Chemistry. Synthesis, Reactivity, Applications*, Wiley-VCH, Weinheim, 2nd edn, 2013.
- K. Uneyama, *Organofluorine Chemistry*, Blackwell, Oxford, 2006, and references therein.
- P. Kirsch, *J. Fluorine Chem.*, 2015, **177**, 29–36.
- A. C. Stuart, J. R. Tumbleston, H. Zhou, W. Li, S. Liu, H. Ade and W. You, *J. Am. Chem. Soc.*, 2013, **135**, 1806–1815.
- S. Preshlock, M. Tredwell and V. Gouverneur, *Chem. Rev.*, 2016, **116**, 719–766.
- I. Tirotta, V. Dichiarante, C. Pigliacelli, G. Cavallo, G. Terraneo, F. B. Bombelli, P. Metrangolo and G. Resnati, *Chem. Rev.*, 2015, **115**, 1106–1129.
- Y. Zhou, J. Wang, G. Zhanni, S. Wang, W. Zhu, J. L. Acena, V. A. Soloshonok, K. Izawa and H. Liu, *Chem. Rev.*, 2016, **116**, 422–518.
- E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly and N. A. Meanwell, *J. Med. Chem.*, 2015, **58**, 8315–8359.
- S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320–330.
- D. Cahard and V. Bizet, *Chem. Soc. Rev.*, 2014, **43**, 135–147.
- D. O'Hagan, *Chem. Soc. Rev.*, 2008, **37**, 308–309.
- C. Ni, M. Hu and J. Hu, *Chem. Rev.*, 2015, **115**, 765–825, and references therein.
- M.-C. Belhomme, T. Besset, T. Poisson and X. Pannecoucke, *Chem. – Eur. J.*, 2015, **21**, 12836–12865.
- C. Alonso, E. M. de Marigorta, G. Rubiales and F. Palacios, *Chem. Rev.*, 2015, **115**, 1847–1935.
- O. A. Tomashenko and V. V. Grushin, *Chem. Rev.*, 2011, **111**, 4475–4521, and references therein.
- J. Charpentier, N. Früh and A. Togni, *Chem. Rev.*, 2015, **115**, 650–682, and references therein.
- C. Ni and J. Hu, *Synlett*, 2011, 770–782, and references therein.
- C. Ni, W. Zhang and J. Hu, *Top. Curr. Chem.*, 2012, **308**, 25–44, and references therein.
- C. Ni, Y. Li and J. Hu, *J. Org. Chem.*, 2006, **71**, 6829–6833.
- G. K. S. Prakash, P. V. Jog, P. T. D. Batamack and G. A. Olah, *Science*, 2012, **338**, 1324–1327, and references therein.
- G. K. S. Prakash, F. Wang, Z. Zhang, R. Haiges, M. Rahm, K. O. Christe, T. Mathew and G. A. Olah, *Angew. Chem., Int. Ed.*, 2014, **53**, 11575–11578.
- T. Nishimine, K. Fukushi, N. Shibata, H. Taira, E. Tokunaga, A. Yamano, M. Shiro and N. Shibata, *Angew. Chem., Int. Ed.*, 2014, **53**, 517–520.



- 25 T. Nishimine, H. Taira, E. Tokunaga, M. Shiro and N. Shibata, *Angew. Chem., Int. Ed.*, 2016, **55**, 359–363.
- 26 R. P. Singh, G. Cao, R. L. Kirchmeier and J. M. Shreeve, *J. Org. Chem.*, 1999, **64**, 2873–2876.
- 27 Y. Zhao, W. Huang, J. Zheng and J. Hu, *Org. Lett.*, 2011, **13**, 5342–5345, and references therein.
- 28 O. M. Michurin, D. S. Radchenko and I. V. Komarov, *Tetrahedron*, 2016, **72**, 1351–1356, and references therein.
- 29 X. Shen and J. Hu, *Eur. J. Org. Chem.*, 2014, 4437–4451, and references therein.
- 30 Y. Zhao, B. Gao and J. Hu, *J. Am. Chem. Soc.*, 2012, **134**, 5790–5793, and references therein.
- 31 Y. Zhao, F. Jiang and J. Hu, *J. Am. Chem. Soc.*, 2015, **137**, 5199–5203. In this paper, the authors found that the ground state structure of **24-E** adopts a conformation in which the C(1)–H bond is anti-periplanar to the C(2)–F bond.
- 32 J.-S. Yu, Y.-L. Liu, J. Tang, X. Wang and J. Zhou, *Angew. Chem., Int. Ed.*, 2014, **53**, 9512–9516, and references therein.
- 33 G. K. S. Prakash, F. Wang, N. Shao, T. Mathew, G. Rasul, R. Haiges, T. Stewart and G. A. Olah, *Angew. Chem., Int. Ed.*, 2009, **48**, 5358–5362.
- 34 X. Shen, L. Zhang, Y. Zhao, L. Zhu, G. Li and J. Hu, *Angew. Chem., Int. Ed.*, 2011, **50**, 2588–2592.
- 35 L. Yin, L. Brewitz, N. Kumagai and M. Shibasaki, *J. Am. Chem. Soc.*, 2014, **136**, 17958–17961, and references therein.
- 36 V. Matoušek, J. Václavík, P. Hájek, J. Charpentier, Z. E. Blastik, E. Pietrasiak, A. Budinská, A. Togni and P. Beier, *Chem. – Eur. J.*, 2016, **22**, 417–424.
- 37 Y.-D. Yang, X. Lu, G. Liu, E. Tokunaga, S. Tsuzuki and N. Shibata, *ChemistryOpen*, 2012, **1**, 221–226, and references therein.
- 38 C. Ni and J. Hu, *Synthesis*, 2014, 842–863, and references therein.
- 39 L. Li, F. Wang, C. Ni and J. Hu, *Angew. Chem., Int. Ed.*, 2013, **52**, 12390–12394.
- 40 K. Honda, T. V. Harris, M. Hatanaka, K. Morokuma and K. Mikami, *Chem. – Eur. J.*, 2016, **22**, 8796–8800, and references therein.
- 41 X.-J. Tang, Z. Zhang and W. R. Dolbier, Jr., *Chem. – Eur. J.*, 2015, **21**, 18961–18965, and references therein.
- 42 Z. Zhang, X.-J. Tang and W. R. Dolbier, Jr., *Org. Lett.*, 2016, **18**, 1048–1051.
- 43 Y. Fujiwara, J. A. Dixon, R. A. Rodriguez, R. D. Baxter, D. D. Dixon, M. R. Collins, D. G. Blackmond and P. S. Baran, *J. Am. Chem. Soc.*, 2012, **134**, 1494–1497, and references therein.
- 44 J. Rong, L. Deng, P. Tan, C. Ni, Y. Gu and J. Hu, *Angew. Chem., Int. Ed.*, 2016, **55**, 2743–2747.
- 45 J. Hu, W. Zhang and F. Wang, *Chem. Commun.*, 2009, 7465–7478, and references therein.
- 46 E. J. Cho, T. D. Senecal, T. Kinzel, Y. Zhang, D. A. Watson and S. L. Buchwald, *Science*, 2010, **328**, 1679–1681.
- 47 Y. Zeng, L. Zhang, Y. Zhao, C. Ni, J. Zhao and J. Hu, *J. Am. Chem. Soc.*, 2013, **135**, 2955–2958, and references therein.
- 48 M.-H. Yang, D. L. Orsi and R. A. Altman, *Angew. Chem., Int. Ed.*, 2015, **54**, 2361–2365.
- 49 B. Gao, Y. Zhao and J. Hu, *Angew. Chem., Int. Ed.*, 2015, **54**, 638–642, and references therein.
- 50 X. Jiang and M. Gandelman, *J. Am. Chem. Soc.*, 2015, **137**, 2542–2547.

