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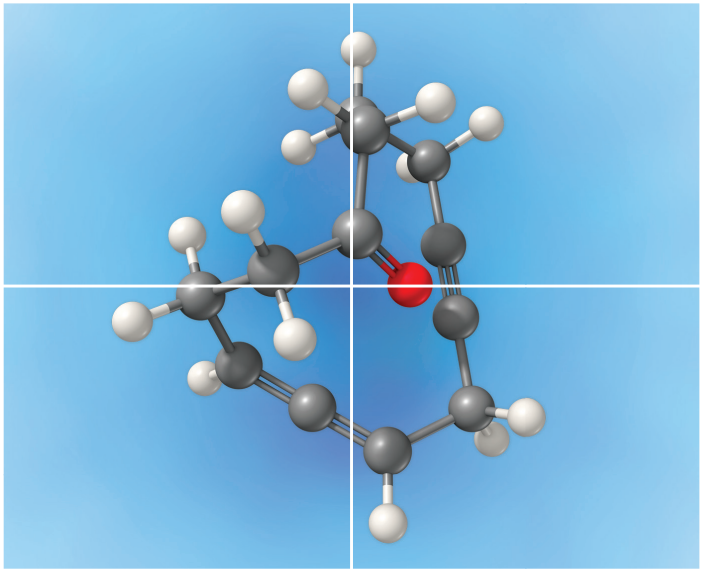

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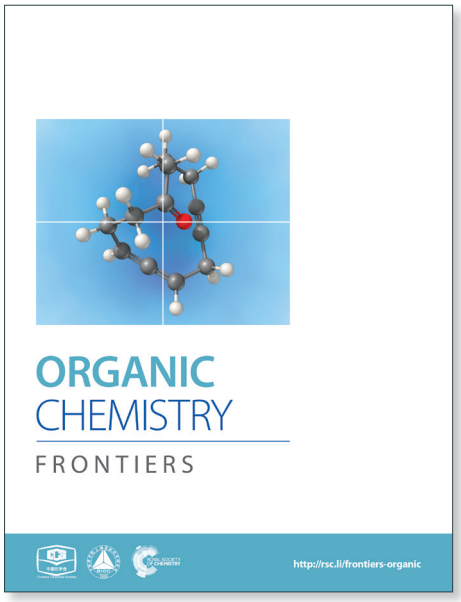

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TUTORIAL ACCOUNT

Difluoromethyl 2-Pyridyl Sulfone: A Versatile Carbonyl *gem*-Difluoroolefination Reagent

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This tutorial account describes a robust carbonyl *gem*-difluoroolefination reagent, difluoromethyl 2-pyridyl sulfone (2-PySO_2CF_2H), developed in our group recently. Guidelines for its laboratory preparation and applications are presented in detail for potential users.

Introduction

Fluoroalkenes attract extensive research interest from synthetic community for decades owing to their unique properties and important applications.[1,2] Recently, exploring reagents and methods for the synthesis of *gem*-difluoroolefins with high reliability and broad scope is particularly active.[3,4] Taking into account the cost and availability of the starting materials, the deoxygenative *gem*-difluoroolefination of carbonyl compounds is particularly attractive.[4] We have recently developed a new reagent, difluoromethyl 2-pyridyl sulfone (2-PySO_2CF_2H), which is capable of converting various aldehydes, ketones, even some lactones to corresponding *gem*-difluoroolefins efficiently.[5] Preliminary mechanistic studies disclosed that this reaction is a typical Julia-Kocienski olefination.[5,6] Further modification and innovation of reaction conditions on the basis of mechanistic insights have rendered this reagent even wider applications.[7-13] In this tutorial account, we aim to provide a detailed introduction on the preparation and application of 2-PySO_2CF_2H as a difluoroolefination reagent, which we hope could serve as useful guidelines for potential users.

Results and discussion

The Julia-Kocienski olefination has been widely employed as a powerful tool to synthesize alkenes from carbonyl compounds.[6] Generally, a carbonyl substrate firstly undergoes a nucleophilic addition with a heteroaryl sulfone-stabilized carbanion, and the resulting adduct rearranges spontaneously to afford a sulfinate salt, which fragmentizes to give the alkene product. A series of heteroaryl sulfones have been successively developed and investigated since the pioneering discovery by Julia, among which the 1-*tert*-Butyl-1H-tetrazol-5-yl (TBT), 1,3-benzothiazol-2-yl (BT), 1-phenyl-1H-tetrazol-5-yl (PT) sulfones have been found to be most effective. Nevertheless, the 2-pyridyl (2-Py) sulfone derivatives have been less studied and rarely used in conventional Julia-Kocienski reactions. We recently succeeded in the synthesis of monofluorinated alkenes from aldehydes and ketones with TBTSO_2CH_2F.[14] However, its difluoromethyl analogue (TBTSO_2CF_2H) could not afford the *gem*-difluoroolefination product under similar conditions, indicating an unusual reactivity as a result of the increased fluorine-substitution. Meanwhile, the BT- and PT-sulfones also provide unsatisfactory results.[5b] We tried to make minimal modulation on difluoromethyl phenyl sulfone ($PhSO_2CF_2H$) that is known as an efficient nucleophilic difluoromethylation reagent.[15] The optimization of the aryl group finally leaded to the new compound 2-PySO_2CF_2H, which was later found to be a powerful *gem*-difluoroolefination reagent.

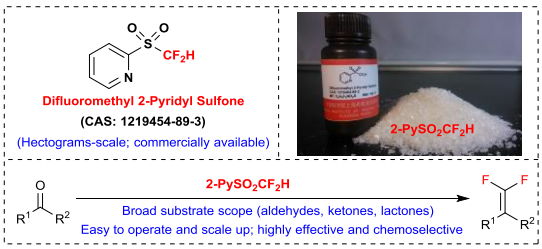

Fig. 1 Difluoromethyl 2-Pyridyl Sulfone and its carbonyl *gem*-difluoroolefination reaction.

Difluoromethyl 2-pyridyl sulfone was prepared according to the following procedure: 1) the difluoromethylation of 2-mercaptopyridine (2-PySH) with difluorochloromethane (HCF_2Cl) or diethyl bromodifluoromethanephosphonate [$BrCF_2P(O)(OEt)_2$];[5,10] 2) the oxidation of 2-PySCF$_2$H under either the $NaIO_4/RuCl_3{\cdot}xH_2O$(cat.)/$CH_3CN/CCl_4/H_2O$ conditions or the $H_2O_2/Na_2WO_4{\cdot}2H_2O$(cat.)/MeOH conditions (the later one is preferred; however, caution should be exercised to avoid H_2O_2 residual in the work-up step).[8,9] The raw materials are inexpensive and the reaction can be scaled up to hectogram scale in laboratory without the requirement of

chromatography purification (distillation for the first step and crystallization for the second step). Obtained as colourless crystalline, this reagent is fairly stable when exposed to air, moisture, and visible light for more than two years (Fig. 1). It is now commercially available and is also called the "Hu reagnt".[10]

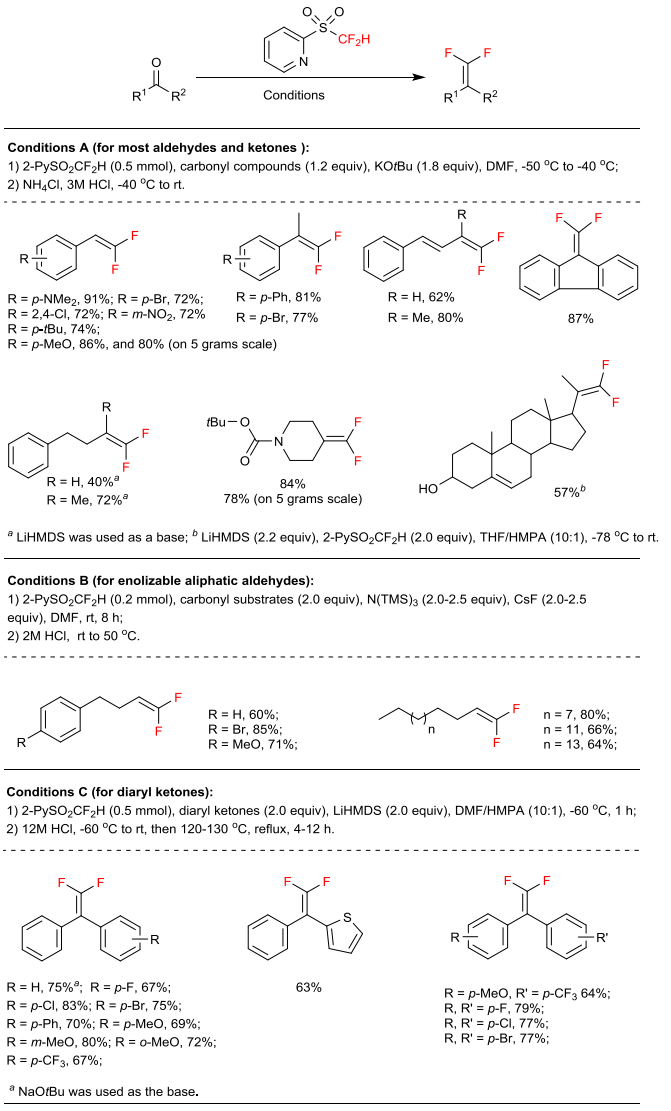

Fig. 2 The *gem*-difluoroolefination of different types of carbonyl compounds with difluoromethyl 2-pyridyl sulfone.

In a typical carbonyl *gem*-difluoroolefination procedure (Fig. 2, Conditions A), an excess amount of base (KO*t*Bu solved in 1.0 mL DMF, 1.8 equiv) was slowly injected into a DMF solution of substrate (1.2 equiv) and 2-PySO_2CF_2H (0.5 mmol) at -50 °C under N_2 atmosphere, the reaction mixture was subsequently warmed to -40 °C over 15 min and then quenched with 3M HCl (Tips: the temperature during the HCl-quenching step should be maintained at a relatively low level, -40 °C in most cases, so as to avoid side-reactions). Normally, most of aldehydes and ketones were readily converted to *gem*-difluoroolefins in high yields. The reaction is reliable, easy-to-operate, and reproducible even on large scales. For instance, both anisic aldehyde (Fig. 2, 80%) and the precursor of thrombin inhibitor SSR182289A (Fig. 2, 78%) could be effectively converted to corresponding olefins on a 5-gram scale.[16]

The fluorinated sulfinate salt, a key intermediate after the Smiles rearrangement step in Julia-Kocienski olefination,[17] was found relatively stable under basic conditions and could be captured by CH_3I (monitored by the ^{19}F NMR). These findings clearly suggest a Julia-Kocienski mechanism (Fig. 3, Path A). At the onset, the 2-Py$SO_2CF_2^-$ anion undergoes nucleophilic addition to the carbonyl group, and then a spontaneous Smiles rearrangement takes place giving the sulfinate intermediate. The latter species undergoes rapid protonolysis to afford the corresponding *gem*-difluoroolefin when treated with an acid. The understanding of the reaction mechanism allows chemists to find more variations of this important reaction. For instance, a formal nucleophilic iodo- and bromodifluoromethylation of carbonyl compounds has been achieved by changing the reaction pathway from olefination to alkylation.[9]

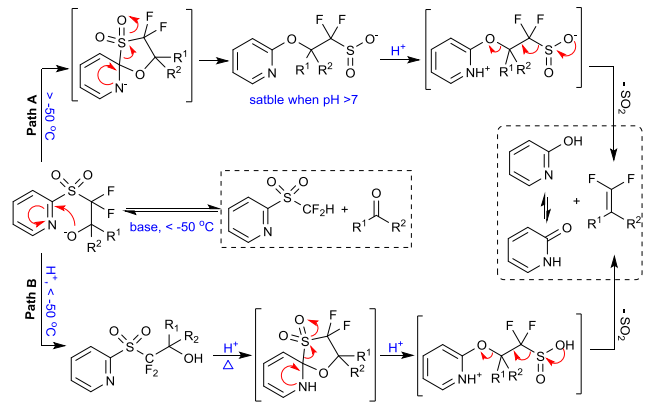

Fig. 3 Optional reaction pathways on the basis of mechanistic insights.

In conventional Julia-Kocienski reactions, the nonfluorinated heteroaryl sulfone was firstly deprotonated by strong base before its reaction with carbonyl substrates. This pre-generation (of the carbanion) strategy can be used to extend the reaction scope to base-sensitive substrates. However, the Barbier-type in-situ generation protocol is essential in our reaction due to the poor stability of the 2-Py$SO_2CF_2^-$ anion.[18] As a consequence, enolizable aldehydes are not well tolerated under the present highly basic conditions (Fig. 2, Conditions A). Intriguingly, by using cesium fluoride (CsF) as an initiator and excess tris(trimethylsilyl)amine [$N(TMS)_3$] as the base precursor,[19] the *gem*-difluoroolefination of enolizable aldehydes was successfully achieved at room temperature in high yields (Fig. 2, Conditions B). This modified reaction conditions avoid the exposure of aldehydes to the excess amount of strong base, and therefore suppressed the side reactions.

On the other hand, the *gem*-difluoolefination of diaryl ketones had been a long-standing challenge. It was found, on the basis of controlled experiments, that the retro-nucleophilic

addition reaction would outstrip the Smile rearrangement at elevated temperature under basic conditions. This was tentatively ascribed to the steric hindrance of the aryl groups. To solve the problem, we speculated that an acid-promoted rearrangement could minimize the decomposition of the key nucleophilic addition intermediate (Fig. 3, Path B). This hypothesis was finally realized via a one-pot procedure. Namely, the nucleophilic addition adduct between diaryl ketone and 2-PySO_2CF_2H was quenched by acid at -60 °C in DMF after 1 h of reaction under basic conditions; the resulting alcohol was further subjected to solvent reflux temperature under acidic conditions for hours until its full conversion to corresponding *gem*-difluoroolefin (Fig. 2, Condition C). This method gave satisfactory results for various diarylketones and represented the first example of acid-promoted Julia-Kocienski olefination.

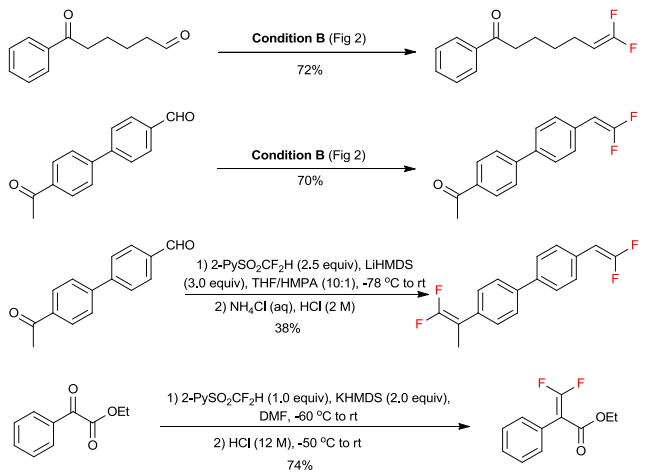

Fig. 4 The chemoselective *gem*-difluoroolefination of carbonyl compounds.

Functionalities under different chemical circumstances usually exhibit different reactivity. Therefore, one could realize selective transformations via adjusting the reactivity of the regents or the reaction conditions.[20] The 2-PySO_2CF_2H reagent is capable of chemoselectively *gem*-difluoroolefinating different carbonyl functionalities under specific conditions (Fig. 4). For instance, the aldehyde group could be efficiently converted to *gem*-difluorovinyl group under the N(TMS)$_3$/CsF/DMF conditions while the ketone was left untouched. This is probably due to the fact that the terminal carbonyl group (aldehyde) was more reactive toward 2-Py$SO_2CF_2^-$ anion than the internal one (ketone). Alternatively, both aldehyde and ketone could be converted to olefins when treated with excess 2-PySO_2CF_2H under the LiHMDS/DMF conditions at low temperature. A similar selectivity was also observed for ketoesters under the KHMDS/DMF conditions. Recently, the nucleophilic addition product of 2-PySO_2CF_2H and sugar lactone was also successfully converted to *gem*-difluoroolefin under reflux in the TBME solvent of $NaHCO_3$.[13] It should be noted that we also attempted the *gem*-difluoroolefination of the carbonyl groups in carboxylic esters and amides with 2-PySO_2CF_2H reagent, but with no success.

Conclusions

In summary, a new Julia-Kocienski type *gem*-difluoroolefination reagent, difluoromethyl 2-pyridyl sulfone (2-PySO_2CF_2H), was recently developed in our group. This reagent can convert diverse carbonyl functionalities to *gem*-difluorovinyl motifs with high efficacy and good functional group tolerance. For more demanding substrates (such as enolizable aldehydes and diarylketones), modified reaction conditions have been developed to successfully tackle these problems. The chemoselective transformations of aldehydes in the presence of ketones (or ketones in the presence of esters) can also be realized under specified reaction conditions. On the other hand, this reagent is currently inapplicable to carboxylic esters and amide, some base-sensitive or highly functionalized compounds may also not be well tolerated. Nevertheless, with ready availability, easy operation and excellent performance, the 2-PySO_2CF_2H reagent promises to find more applications in synthetic fluorine chemistry.

Experimental

Preparation of difluoromethyl 2-pyridyl sulfone.

***Step one* (from HCF_2Cl):** To the DMF (400 mL) solution of NaH [60%(wt.), 19.8 g, 0.495 mol, 1.1 equiv), was slowly added pyridine-2-thiol (50 g, 0.45 mol, 1.0 equiv) at 0 °C under N_2 atmosphere. The reaction mixture was allowed to warm up to room temperature and stirred for another 1 h until the release of hydrogen stopped. The HCF_2Cl gas was then bubbled into the stirring mixture from a cylinder for 1 h. A noticeable exothermic process was observed in the first few minutes. After the mixture was stirred overnight (10 h), the reaction was quenched by adding excess amount of H_2O carefully, followed by full extraction with Et_2O (150 mL x 4). The organic phase was washed with brine, and then dried over anhydrous $MgSO_4$. After filtration, the solvent was removed under vacuum and the residue was subjected to distillation. The 2-PySCF_2H was obtained as pale yellow oil (56.8 g, 78%, 65 °C under 8 torr).

***Step two* (with H_2O_2):** To a round-bottom flask with a magnetic stir bar, were added 2-PySCF_2H (56.8 g, 0.353 mol, 1.0 equiv), MeOH (300 mL), $Na_2WO_4{\cdot}2H_2O$ (13.2 g, 0.1 equiv), and then H_2O_2 (30%$_{aq}$, 100 mL, 2.5 equiv). Being equipped with reflux condensing tube, the resulting mixture was slowly heated with a blow drier (1100W, 50 Hz) to induce the reaction. Once the reaction was initiated, it became violently exothermic and heating was ceased (Tips: The oxidation is exothermic and can take place at room temperature, heating will shorten the inducing period of the oxidation, otherwise long inducing time was needed). After completion, excess aqueous Na_2SO_3 solvent was added to remove residual H_2O_2. Another 100 mL of H_2O was added, and then most of products participated as white solids and were collected via filtration. The resulting solvent was evacuated to remove MeOH and further extracted with ether (100 mL x 3). The combined organic phase was washed successively with saturated $NaHCO_3$ and NaCl solutions, and then dried over anhydrous $MgSO_4$. After filtration the solvent

was evaporated under vacuum and the combined residue was crystallized in the mixture of ethyl acetate and petroleum ether to give 2-PySO_2CF_2H as colorless solid (59 g, 86%, MP, 45-47 ^oC).

Reaction condition A for the *gem*-difluoolefination of aromatic aldehydes.

Under the N_2 atmosphere, KO*t*Bu (101 mg, 0.90 mmol) dissolved in DMF (1mL) was added to a solution of carbonyl substrate (0.6 mmol) and 2-PySO_2CF_2H (96.6 mg, 0.5 mmol) in 2 mL DMF at -50 ^oC. The reaction mixture was allowed to warm up to -40 ^oC within about 15 min (or to room temperature within hours). Then, the reaction is quenched with aqueous saturated NH_4Cl (1mL) at -40 ^oC followed by 3N HCl (1mL). The resulting mixture was then allowed to warm up to room temperature (for electron-deficient aromatic aldehydes, the mixture was heated to 60 ^oC for 30 min). After completion (monitored by ^{19}F NMR), the reaction mixture was extracted with Et_2O (20 mL x 3), the organic phase was then successively washed with saturated aqueous $NaHCO_3$ and brine, and dried over anhydrous $MgSO_4$. After filtration the solvent was evaporated under vacuum and the residue was subjected to flash chromatography purification to give pure product.

Reaction condition B for the *gem*-difluoolefination of aliphatic aldehyde.

Under the N_2 atmosphere, to an oven-dried Schlenk tube were successively added 2-PySO_2CF_2H (38.6 mg, 0.2 mmol), $N(TMS)_3$ (93.4 mg, 0.4 mmol), CsF (75.6 mg, 0.4 mmol), DMF (2.0 mL) and aldehyde (0.3 mmol). The reaction mixture was stirred at room temperature until the full consumption of 2-PySO_2CF_2H (monitored by ^{19}F NMR). After being cooled to 0 ^oC, saturated aqueous NH_4Cl (1.0 mL) and aqueous HCl (2 M, 1.5 mL, 3.0 mmol) was successively added, and the resulting mixture was stirred for another 30 min at 50 ^oC until the full consumption of the sulfinate salt as determined by ^{19}F NMR. Thereafter, the mixture was poured into ice water (50 mL), and extracted with ether (20 mL x 3). The combined organic layer was washed with brine, dried with anhydrous $MgSO_4$, and concentrated under vacuum. The target product was obtained after the flash chromatography purification with ethyl acetate and petroleum ether.

Reaction condition C for the *gem*-difluoolefination of diaryl ketones.

Under the N_2 atmosphere, DMF (4.0 mL) and HMPA (0.4 mL) were added to an oven-dried 20-mL Schlenk tube containing 2-PySO_2CF_2H (96.6 mg, 0.5 mmol) and diaryl ketone (1.0 mmol). The reaction mixture was then cooled to –60 ^oC in the dry ice-acetone bath. A THF solution of $(TMS)_2NLi$ (LiHMDS, 1.0 M, 1.0 mmol) was slowly added within 5 minutes, and then the reaction mixture was stirred at the same temperature for 1 h. Thereafter an aqueous solution of HCl (2.0 M, 1.0 mL) was injected to quench the reaction at –60 ^oC. After being warmed to room temperature, another portion of HCl (12 M, 1.5 mL) was added, and the reaction mixture was heated to reflux for 4 to 10 hours with an oil bath between 120 and 130 ^oC. When the reaction was completed as monitored by ^{19}F NMR, the mixture was poured into ice-water (50 mL) and extracted with ether (20 mL x 3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under vacuum. The target product was obtained after the flash chromatography purification with ethyl acetate and petroleum ether.

The preparation of *gem*-difluoolefins in 5-grams scale (e.g. anisic aldehyde).

Under the N_2 atmosphere, anisic aldehyde (4.23g, 31.1 mmol) and 2-PySO_2CF_2H (5g, 25.9 mmol) was added to an oven-dried three-necked bottle equipped with magnetic stir bar. 30 mL DMF was injected and the solvent was cooled to -50 ^oC (dry ice-acetone bath), thereafter 20 mL DMF solvent of KO*t*Bu (5.23 g, 46.6 mmol) was slowly added to the reaction mixture within 10 mins. The reaction system was stirred at -50 ^oC for 15 mins and then gradually warmed up to -40 ^oC. Once the starting material was completely converted to sulfinate salt (monitored by ^{19}F NMR), it was quenched with aqueous saturated NH_4Cl (20 mL) at -40 ^oC followed by 3N HCl (20 mL). The resulting mixture was then allowed to warm up to room temperature. After the sulfinate was completely consumed (monitored by ^{19}F NMR), the reaction mixture was diluted with 60 mL water and extracted with Et_2O (30 mL x 3), the organic phase was then successively washed with saturated aqueous $NaHCO_3$ and brine, and dried over anhydrous $MgSO_4$. After filtration the solvent was evaporated under vacuum and the residue was subjected to flash chromatography purification to give colourless oil 3.51g (80% yield).

Acknowledgements

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Notes and references

1 (*a*) P. Kirsch, *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*, 2nd Ed., Wiley-VCH, Weinheim, 2013; (*b*) K. Uneyama, *Organofluorine Chemistry*, Blackwell, Oxford, 2006; (*c*) R. D. Chambers, *Organofluorine Chemistry: Fluorinated Alkenes and Reactive Intermediates*, Springer, New York, 1997.

2 For recent applications of *gem*-difluoroolefins, see: (*a*) J. Ichikawa, M. Yokota, T. Kudo and S. Umezaki, *Angew. Chem., Int. Ed.*, 2008, **47**, 4870; (b) M. Takachi, Y. Kita, M. Tobisu, Y. Fukumoto and N. Chatani, *Angew. Chem., Int. Ed.*, 2010, **49**, 8717; (c) P. J. Riss and F. I. Aigbirhio, *Chem. Commun.*, 2011, **47**, 11873; (d) M. Ohashi, H. Saijo, M. Shibata and S. Ogoshi, *Eur. J. Org. Chem.*, 2013, 443; (e) K. Fuchibe, Y. Mayumi, N. Zhao, S. Watanabe, M. Yokota and J. Ichikawa, *Angew. Chem., Int. Ed.*, 2013, **52**, 7825; (f) Y. Xiong, X. Zhang, T. Huang and S. Cao, *J. Org. Chem.*, 2014, **79**, 6395; (g) B. Gao, Y. Zhao, C. Ni and J. Hu, *Org. Lett.*, 2014, **16**, 102; (h) B. Gao,

Y. Zhao and J. Hu, *Angew. Chem., Int. Ed.*, 2014, DOI: 10.1002/anie.201409705.

3 (*a*) M. Hu, Z. He, B. Gao, L. Li, C. Ni and J. Hu, *J. Am. Chem. Soc.*, 2013, **135**, 17302; (*b*) M.-O. Turcotte-Savard and J.-F. Paquin, *Org. Biomol. Chem.*, 2013, **11**, 1367; (*c*) S. Y. Han and I. H. Jeong, *Org. Lett.*, 2010, **12**, 5518; (*d*) G. K. S. Prakash, J. Hu, Y. Wang and G. A. Olah, *Angew. Chem., Int. Ed.*, 2004, **43**, 5203; (*e*) J. Ichikawa, H. Fukui and Y. Ishibashi, *J. Org. Chem.*, 2003, **68**, 7800.

4 (*a*) F. Wang, L, Li, C. Ni and J, Hu, *Beilstein J. Org. Chem.*, 2014, **10**, 344; (*b*) J. Zheng, J. Cai, J.-H. Lin, Y. Guo and J.-C. Xiao, *Chem. Commun.*, 2013, **49**, 7513; (*c*) C. S. Thomoson, H. Martinez and W. R. Dolbier, *J. Fluorine Chem.*, 2013, **150**, 53; (*d*) D. J. Burton, Z.-Y. Yang and W. Qiu, *Chem. Rev.*, 1996, **96**, 1641, and reference therein; (*e*) I. Nowak and M. J. Robins, *Org. Lett.*, 2005, 7, 721; (*f*) S. A. Fuqua, W. G. Duncan and R. M. Silverstein, *J. Org. Chem.*, 1965, **30**, 2543.

5 (*a*) B. Gao, Y. Zhao, M. Hu, C. Ni and J. Hu, *Chem. Eur. J.* 2014, **20**, 7803; (*b*) Y. Zhao, W. Huang, L. Zhu and J. Hu, *Org. Lett.* 2010, **12**, 1444.

6 (*a*) J. B. Baudin, G. Hareau, S. A. Julia and O. Ruel, *Tetrahedron Lett.*, 1991, **32**, 1175; (*b*) J. B. Baudin, G. Hareau, S. A. Julia and O. Ruel, *Bull. Soc. Chim. Fr.* 1993, **130**, 856; (*c*) P. R. Blakemore, W. J. Cole, P. J. Kocieński and A. Morley, *Synlett*, 1998, 26; (*d*) P. J. Kocienski, A. Bell and P. R. Blakemore, *Synlett*, 2000, 365; (*e*) B. Zajc, R. Kumar, *Synthesis*, 2010, 1822.

7 Y. Zhao, L. Zhang, G. Xu, J. Zheng, J. Hu, *Sci. Sin.: Chim.* 2011, **41**, 1833.

8 G. K. S. Prakash, C. Ni, F. Wang, J. Hu and G. A. Olah, *Angew. Chem., Int. Ed.*, 2011, **50**, 2559.

9 Y. Zhao, B. Gao and J. Hu, *J. Am. Chem. Soc.*, 2012, **134**, 5790.

10 Q. Zhou, A. Ruffoni, R. Gianatassio, Y. Fujiwara, E. Sella, D. Shabat and P. S. Baran, *Angew. Chem., Int. Ed.*, 2013, **52**, 3949.

11. G. K. S. Prakash, C. Ni, F. Wang, Z. Zhang, R. Haiges, G. A. Olah, *Angew. Chem., Int. Ed.*, 2013, **52**, 10835.

12 W. Miao, C. Ni, Y. Zhao and J. Hu, *J. Fluorine Chem.*, 2014, **167**, 231.

13 X. Liu, Q. Yin, J. Yin, G. Chen, X. Wang, Q.-D. You, Y.-L. Chen, B. Xiong and J. Shen, *Eur. J. Org. Chem.*, 2014, 6150.

14 L. Zhu, C. Ni, Y. Zhao and J. Hu, *Tetrahedron*, 2010, **66**, 5089.

15 (*a*) C. Ni and J. Hu, *Synlett*, 2011, 770; (*b*) J. Hu, W. Zhang and F. Wang, *Chem. Commun.*, 2009, 7465; (*c*) G. K. S. Prakash and J. Hu, *Acc. Chem. Res.*, 2007, **40**, 921; *(d)* C. Ni, M. Hu and J. Hu, *Chem. Rev.* **2015**, DOI: 10.1021/cr5002386.

16 J.-M. Altenburger, G. Y. Lassalle, M. Matrougui, D. Galtier, J.-C. Jetha, Z. Bocskei, C. N. Berry, C. Lunven, J. Lorrain, J.-P. Herault, P. Schaeffer, S. E. O'Connor and J.-M. Herbert, *Bioorg. Med. Chem.*, 2004, **12**, 1713.

17 (*a*) L. A. Warren and S. Smiles, *J. Chem. Soc.*, 1930, 1327; (*b*) J. F. Burnett and R. E. Zahler, *Chem. Rev.*, 1951, **49**, 273.

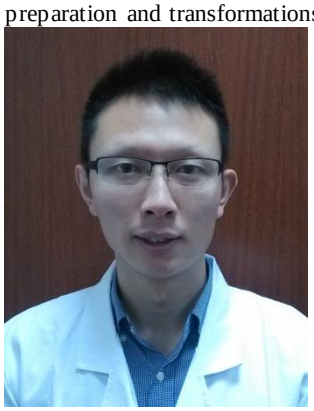
18 C. Blomberg, *The Barbier Reaction and Related One-Step Processes*, Springler-Verlag, Berlin, 1993.

19 (*a*) T. Billard, S. Bruns and B. R. Langlois, *Org. Lett.*, 2000, **2**, 2101; (*b*) S. Large, N. Roques and B. R. Langlois, *J. Org. Chem.*, 2000, **65**, 8848; (*c*) M. Hu, B. Gao, C. Ni, L. Zhang and J. Hu, *J. Fluorine Chem.*, 2013, **155**, 52.

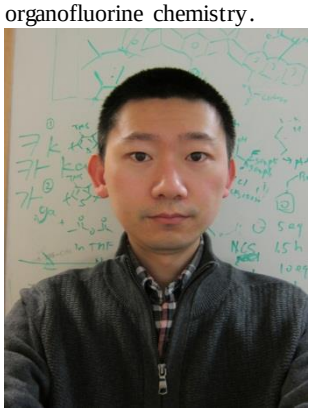
20 (*a*) R. A. Shenvi, D. P. O'Malley and P. S. Baran, *Acc. Chem. Res.*, 2009, **42**, 530; (*b*) N. A. Afagh and A. K. Yudin, *Angew. Chem., Int. Ed.*, 2010, **49**, 262.

Biography

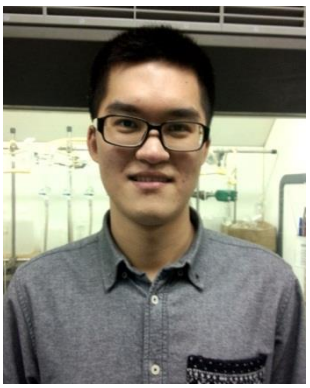
Bing Gao was born in Sichuan, China in 1986. He received his B.S. degree in chemistry from Jilin University in 2009, and got his Ph.D. degree in 2014 from the Shanghai Institute of Organic Chemistry, Chinese Academy of Science (SIOC, CAS) under the supervision of Professor Jinbo Hu. He is currently a research assistant at the CAS Key Laboratory of Organofluorine Chemistry, SIOC. His doctoral research focused on the preparation and transformations of fluoroalkenes.



Yanchuan Zhao was born in Jilin, China, in 1983. He received his Ph.D. degree in 2012 from the Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences (SIOC, CAS) under the guidance of Professor Jinbo Hu, working in the field of organofluorine chemistry and focusing on development of novel fluoroalkylation and fluoroolefination reagents. He is currently a postdoctoral research associate with Professor Timothy M. Swager at Massachusetts Institute of Technology, where he uses ^{19}F NMR to fingerprint various organic molecules. His scientific interests include chemical sensors, molecular recognition, mechanochemistry, and organofluorine chemistry.



Jingyu Hu was born in Shandong, China in 1992. After he completed his B.S. (East China University of Science and Technology) degrees in 2013, he is now doing his M.S. work at the Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences (SIOC, CAS) under the supervision of Professor Jinbo Hu. His current research interests focus on fluoroalkylation methodologies.



Jinbo Hu was born in Zhejiang, China in 1973. After he completed his B.S. (Hangzhou University) and M.S. (Chinese Academy of Sciences) degrees, he did his Ph.D. work during 1997 to 2002 at the University of Southern California with Professors G. K. S. Prakash and G. A. Olah. After his postdotoral work at USC, he joined the Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences (SIOC, CAS) as a Research Professor in early 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 Tan Kah-Kee Young Scientist Award 2012. His current research interests include selective fluorination, defluorination, fluoroalkylation methodologies, and fluorinated materials.