Sequential C–F Bond Functionalizations of Trifluoroacetamides and Acetates via Spin-Center Shifts

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Monofluoro- and difluoro-substituted organic molecules have properties that make them valuable in many applications. New methods to synthesize these molecules attract wide interest. Among various methods reported for accessing fluorinated compounds, introduction of trifluoromethyl groups has been an effective and economical pathway, since many trifluoromethyl sources are inexpensive and readily available. Thus, a large number of defluorination approaches have been developed to produce mono and difluoro compounds. However, selectively producing either difluoro or monofluoro compounds from trifluoro is exceedingly challenging, because when the first C–F bond is broken, the remaining two get weaker, thus often resulting in exhaustive defluorination. Therefore, "strategies that selectively snip off one or two C–F bonds would be very valuable in synthetic and medicinal chemistry," said Professor Yi-Feng Wang, from the University of Science and Technology of China (Hefei, P. R. of China), whose research program is focused on discovery of new chemical reactivity and synthetic applications of Lewis base–boryl radicals. "During our studies, we had developed a Lewis base–boryl radical enabled desulfurizative reduction of thioamides to organic amines (*Org. Lett.* **2018**, *20*, 24–27)," continued Professor Wang, who added: "Encouraged by these findings, we next conceived an analogous radical reduction reaction of amides. Surprisingly, when a trifluoroacetamide was treated with 4-dimethylaminopyridine (DMAP)-BH_2·, hydrodefluorination reactions occurred instead, giving a mixture of di- and monofluoromethyl products, albeit with moderate chemoselectivity. After optimization of reaction conditions, we successfully improved both the chemoselectivity and yields, leading to selective formation of mono- and dihydrodefluorination products." Preliminary mechanistic studies suggested that α-fluorocarbonyl radical intermediates were generated during the defluorination process. The group was intrigued by this finding, because C–F bonds are supposed to be inert, with a very high bond dissociation energy that constrains homolytic cleavage. The authors thought that clarification of this defluorinative radical generation mechanism would be of great interest. "After checking literature precedents and especially discussing with Prof. S. Z. Zard (École Polytechnique, Paris, France), when he visited us in November 2018, we were drawn to consider a spin-center shift (SCS) mechanism that involves 1,2-radical delocalization and leaving-group elimination," explained Professor Wang. He continued: "We surmised that the defluorination reaction would likely proceed through the attack of DMAP-BH_2· to the carbonyl oxygen atom, followed by an SCS process to eliminate a fluoride ion. More importantly, the repeat of this process to the resulting product would enable the second C–F bond cleavage. On this basis, we hypothesized a two-stage process with each stage involving an SCS for the C–F bond cleavage of trifluoroacetic acid derivatives (Scheme 1A)." According to Professor Wang, in **stage A**, the first SCS of the transient **Int-II** – generated through the attack of the carbonyl oxygen atom by DMAP-BH_2· – takes place, triggering the cleavage of a single β-C–F bond. "The resulting α,α-difluorocarbonyl radical, **Int-III**, can be subsequently captured by a radical trap to provide an α,α-difluoroacetyl product and complete the monodefluorinative transformation," continued Professor Wang. "In **stage B**, if the DMAP-BH_2· is continuously present, the **stage A** product participates in a second SCS to generate the radical **Int-V**, which is then trapped by a second component to furnish monofluorinated products. The use of different traps in **stages A** and **B** should enable rapid and efficient synthesis of densely functionalized monofluoro products."

To the group's delight, this two-stage process showed broad substrate scope and good chemoselectivity (Scheme 1B). "For example, reduction of intermediates in **stages A** and **B**, wherein RSH was used as the polarity reversal catalyst, could afford di- and mono-fluoromethyl products selectively, and only minor over-reduction products were observed in the formation of difluoro products," remarked Professor Wang, continuing: "Notably, no trihydrodefluorination product was detected in either case. Alkenes could be used as the radical trap in both **stages A** and **B**, leading to diverse defluorinative coupling products. Interestingly, when two different alkenes were employed in **stages A** and **B**, products containing a monofluorinated tertiary stereogenic center were constructed."

To gain deeper insight into the SCS process, as well as to figure out the effect responsible for controlling the chemoselectivity, the group carried out detailed computational studies in collaboration with Prof. K. N. Houk (University of California, Los Angeles, USA). "This collaboration started when we met at a lecture that Prof. Houk gave at Nankai University," explained Professor Wang. He continued: "We then worked on it together for around one and a half years. The results showed

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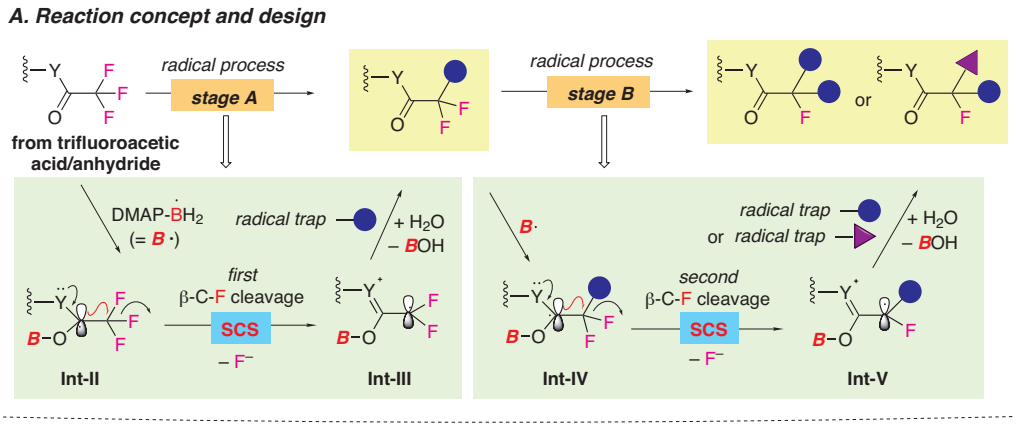
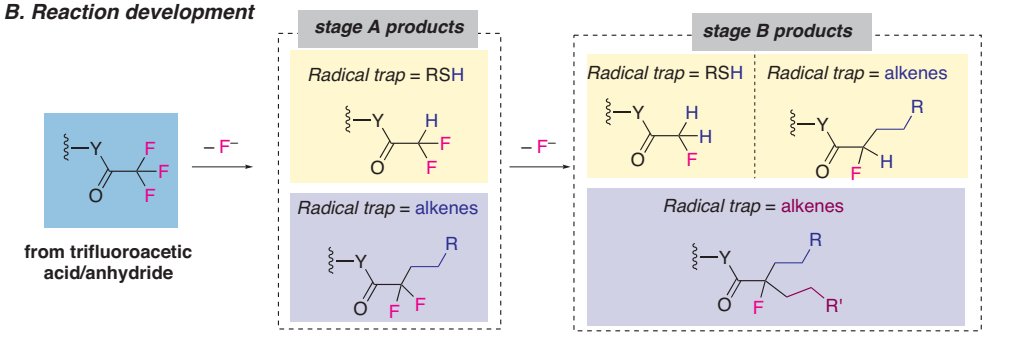
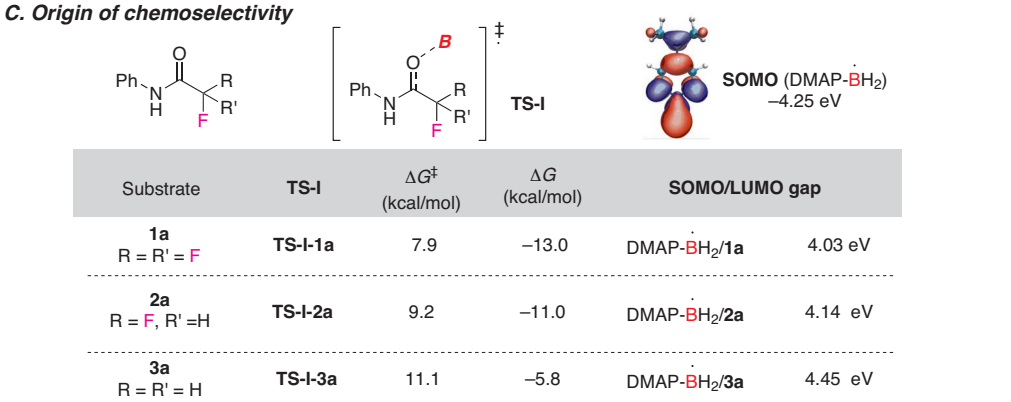






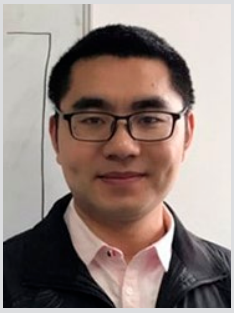
Substrate	TS-I	ΔG‡ (kcal/mol)	ΔG (kcal/mol)	SOMO/LUMO gap	
1a R = R' = F	**TS-I-1a**	7.9	–13.0	DMAP-BH_2/**1a**	4.03 eV
2a R = F, R' =H	**TS-I-2a**	9.2	–11.0	DMAP-BH_2/**2a**	4.14 eV
3a R = R' = H	**TS-I-3a**	11.1	–5.8	DMAP-BH_2/**3a**	4.45 eV

Scheme 1 Sequential C–F bond functionalizations of trifluoroacetamides and trifluoroacetates via spin-center shifts (SCSs)

that the SCS process proceeded with a surmountable energy barrier for N–H amide, while a Na salt is essential to assist the cleavage of a C–F bond in tertiary amides and esters. These theoretical results are consistent with experimental ones. Further DFT calculations revealed that the chemoselectivity is determined by the declining reactivity of DMAP-BH_2• towards the addition to defluorinated products (Scheme 1C). This trend is attributed to the increasing singly occupied molecular orbital (SOMO)/lowest unoccupied molecular orbital (LUMO) gaps between DMAP-BH_2· and the substrates. Therefore, once the first C–F is removed, the resulting carbonyl group is less attractive to the DMAP-BH_2·, thus ensuring exquisite chemoselectivity during defluorination."

Professor Wang concluded: "We believe that the SCS strategy reported in this work will be applicable to other carbon–heteroatom bonds (i.e., C–O, C–N, and C–Cl, among others) and we are now exploring these transformations."

About the authors



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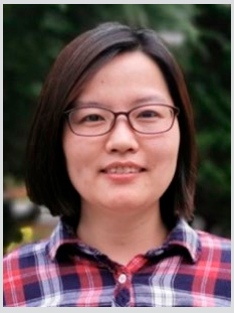

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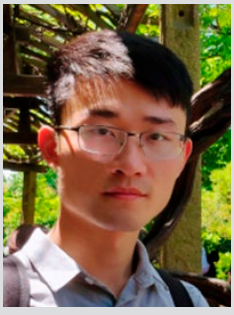

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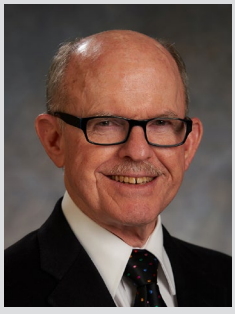
C. Chen

Chen Chen received her B.S. (2018) in organic chemistry at USTC. She learned skills of synthesis in the Wang lab and did her undergraduate thesis under the supervision of Prof. Y.-F. Wang. She is now a Ph.D. candidate at Department of Materials Science and Engineering at the University of Illinois, Urbana-Champaign (USA).



Prof. K. N. Houk

K. N. Houk received his Ph.D. at Harvard (USA), working with R. B. Woodward on experimental tests of orbital symmetry selection rules. He has taught at Louisiana State University (USA), the University of Pittsburgh (USA), and UCLA (USA) since 1986. He is the Saul Winstein Research Chair in Organic Chemistry. His research group develops rules to understand reactivity and builds computational models of complex organic reactions. He collaborates prodigiously with chemists all over the world, publishing over 1320 articles in refereed journals to date.

Prof. Y.-F. Wang

Yi-Feng Wang received his Ph.D. in 2011 at the Nanyang Technological University, Singapore under the supervision of Profs. Koichi Narasaka and Shunsuke Chiba. He continued to work with Prof. Chiba as a research fellow (2011–2015) and was appointed as a Lee Kuan Yew Postdoctoral Fellow during 2012–2014. In 2015, he started his independent research work at USTC as a full professor. His research interests include radical chemistry, organoboron chemistry, and the synthesis of bioactive molecules.

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