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## S<sub>8</sub>-Catalyzed triple cleavage of bromodifluoro compounds for the assembly of N-containing heterocycles†

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An unprecedented S<sub>8</sub>-catalyzed selective triple-cleavage of bromodifluoroacetamides is disclosed for the first time. Valuable 2-amido substituted benzimidazoles, benzoxazoles and benzothiazoles were obtained in good to excellent yields in a cascade protocol in this strategy. Mechanistic studies suggested that a C<sub>2</sub> source was generated *in situ* by selective cleavage of three C–X bonds, including two inert C(sp<sup>3</sup>)–F bonds on bromodifluoroacetamides, while leaving C–C bonds intact. This strategy will undoubtedly further consummate the role of halo difluoro compounds and enrich both fluorine chemistry and pharmaceutical sciences.

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The activation of C–F bonds concomitant with further transformations has emerged as a significant and ongoing theme in synthetic organic chemistry, which opens up new platforms for molecular construction.<sup>1</sup> For the activation of C–F bonds, the strategies predominantly rely on metal catalysts and the formation of a B–F, Al–F, Si–F or Ge–F bond to surmount the high C–F bond dissociation energy.<sup>2</sup> Although metal-mediated and -catalyzed C–F activation has attracted intensive attention, publications on metal-free activation of C–F bonds are rare.<sup>3</sup> In the past few decades, halogenated difluoro compounds (XCF<sub>2</sub>R) have proven to be promising difluoroalkylation reagents by one C–X cleavage, enabling the rapid preparation of innumerable difluoroalkylated compounds<sup>4</sup> (Scheme 1A). Aside from the single cleavage, halogenated difluoro compounds could also undergo the double cleavage of C–X and C–R bonds to be used as difluorocarbene precursors, which enable the introduction of difluorinated units into targeted molecules by difluoromethylation<sup>5</sup> (Scheme 1A). Based on the bond strength, the above two cleavages are not a surprise, since the bond dissociation energy (BDE) of C–F is 485 kJ mol<sup>−1</sup>, which is much

higher than that of the C–X bond (C–Cl: 328 kJ mol<sup>−1</sup>; C–Br: 276 kJ mol<sup>−1</sup>) and C–R bond (C–C: 332 kJ mol<sup>−1</sup>; C–H: 414 kJ mol<sup>−1</sup>). Very recently, our group developed an unprecedented strategy for the synthesis of N-containing compounds by using BrCF<sub>2</sub>COOEt (or ClCF<sub>2</sub>COONa) as a new C<sub>1</sub> source, which represents the first example for quadruple cleavage of BrCF<sub>2</sub>COOEt (or ClCF<sub>2</sub>COONa)<sup>6</sup> by breaking all four bonds attached to the fluorinated carbon (Scheme 1A). In light of our recent quadruple cleavage study of halo difluoro compounds, we envisage whether it is possible to achieve a transition-metal free triple cleavage of halo difluoro compounds by selectively breaking three C–X bonds, including two very stable C(sp<sup>3</sup>)–F bonds while keeping the C–C bond intact. If successful, we can willingly selectively cleave each of the four bonds on the fluorinated carbon in halo difluoro compounds based on the necessity of the transformation. It will undoubtedly further consummate the role of halo difluoro compounds and enrich fluorine chemistry.

However, in this scenario, several challenges need to be addressed in this transformation: (1) how to overcome the energy barrier under transition metal-free and strong base-free conditions because the C–F bond, based on fundamental knowledge, is too strong and too inert to be broken without transition-metal assistance or strong bases; (2) given the bond dissociation energy, how to selectively cleave three C–X bonds, including two very stable aliphatic C–F bonds (485.6 kJ mol<sup>−1</sup>) on the same carbon atom while keeping the weak C–C bond (332 kJ mol<sup>−1</sup>) untouched; and (3) how to harness the *in situ* generated C<sub>2</sub> source and convert it into valuable products. In our previous work, the saponification of halo difluoro compounds was the initial step to achieve quadruple cleavage. We postulate that if the cleavage of the C–F bond preferentially

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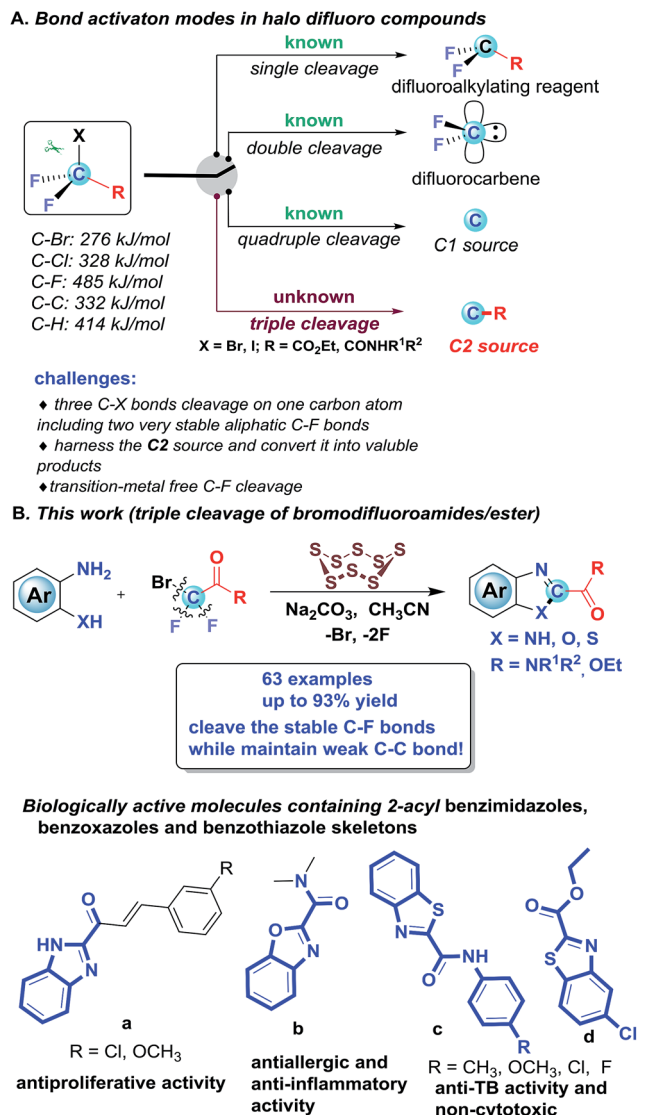
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Scheme 1 Various activation patterns for halo difluoroalkyl compounds: single cleavage, double cleavage, quadruple cleavage and the newly disclosed triple cleavage.

takes place prior to the saponification under the set conditions, in other words, if the saponification of difluoroalkylating compounds is suppressed, the triple cleavage of halo difluoro compounds might be acquired at this point.

To test our assumption, the difluorobromoamides were selected as benchmark materials, since their saponification is more difficult than that of their ester counterparts. Recently we have been interested in sulfur chemistry and found elemental sulfur as a polyvalent synthon could bring forth unexpected reactivity and has been widely utilized to mediate/catalyze a wide array of reactions.<sup>7</sup> Inspired by the peculiarity of elemental sulfur, when a catalytic amount of S<sub>8</sub> was added to our system, the triple cleavage of halo difluoro compounds was indeed achieved, in which various 2-amido/ester substituted benzimidazoles, benzoxazoles and benzothiazoles were obtained. Although various tactics have been developed to

assemble 2-aryl and 2-alkyl substituted benzimidazoles, benzoxazoles and benzothiazoles,<sup>8</sup> effective methods for the construction of 2-amido/ester substituted benzimidazoles, benzoxazoles and benzothiazoles were sparsely documented and the only known synthetic method is tedious (four steps are required to access 2-amidobenzothiazoles),<sup>9</sup> notwithstanding their prevailing structural motifs in bioactive molecules as shown in Scheme 1B.<sup>10</sup> Herein, we would like to report our new discovery on efficient S<sub>8</sub>-catalyzed triple cleavage of halogenated difluoro compounds for the assembly of 2-amido/ester benzimidazoles, benzoxazoles and benzothiazoles, which represents the first example for triple cleavage of halogenated difluoro compounds under transition metal-free conditions (Scheme 1B); meanwhile it also provides pragmatic synthetic methods for high value N-containing heterocycles which are prevalent skeletons in drugs and pharmaceuticals.

Initially, we employed benzene-1,2-diamine (**1a**) and 2-bromo-2,2-difluoro-N-isopropylacetamide (**2a**) as benchmark substrates to explore the optimal reaction conditions (Table 1). Gratifyingly, the desired product N-isopropyl-1H-benzo[d]imidazole-2-carboxamide (**3a**) was obtained in 89% yield when the reaction was performed by using S<sub>8</sub> (20 mol%) and Na<sub>2</sub>CO<sub>3</sub> (3 equiv.) in MeCN (1 mL) at 130 °C for 16 h, which was proven to be the optimum conditions (Table 1, entry 1). A sequence of alterations was also conducted to test the influence on the optimal results. No desired product was observed when the model reaction proceeded in the absence of S<sub>8</sub> (entry 2), and replacing S<sub>8</sub> with I<sub>2</sub> just resulted in a sluggish reaction (entry 3), which indicated that S<sub>8</sub> was a prerequisite for this transformation. When we reduced the reaction temperature from 130 °C to 120 °C or 100 °C, lower reactivities were achieved (entries 4 and 5); this may be necessary to reach a high enough

Table 1 Development of optimized conditions<sup>a</sup>

Entry	Variation from the standard conditions	Yield <sup>b</sup> (%)
1	None	89
2	Without S <sub>8</sub>	n.r.
3	I <sub>2</sub> instead of S <sub>8</sub>	n.r.
4	At 120 °C	17
5	At 100 °C	Trace
6	Under air	29
7	6 h instead of 16 h	16
8	NaHCO <sub>3</sub> instead of Na <sub>2</sub> CO <sub>3</sub>	72
9	CsF instead of Na <sub>2</sub> CO <sub>3</sub>	61
10	K <sub>2</sub> HPO <sub>4</sub> instead of Na <sub>2</sub> CO <sub>3</sub>	Trace
11	Acetone instead of MeCN	42
12	DMF instead of MeCN	82
13	EtOH instead of MeCN	84

<sup>a</sup> Reaction conditions: **1a** (0.3 mmol), **2a** (1.2 equiv.), S<sub>8</sub> (20% mmol), Na<sub>2</sub>CO<sub>3</sub> (3 equiv.), and MeCN (1 mL) under N<sub>2</sub> for 16 h under 130 °C.  
<sup>b</sup> Yield of isolated product. n.r. = no reaction.



temperature to overcome the energy barrier. The yield of **3a** sharply decreased to 29% when the reaction was carried out under an air atmosphere (entry 6). The attempt to shorten the reaction time led to inferior results (entry 7). No improvements were acquired when other bases such as NaHCO<sub>3</sub>, CsF and K<sub>2</sub>HPO<sub>4</sub> were utilized instead of K<sub>2</sub>CO<sub>3</sub> (entries 8–10). Further solvent screening failed to deliver superior results, which showed that CH<sub>3</sub>CN was still the best reaction medium for this transformation (entries 11–13).

Having the optimal reaction conditions in hand, we then evaluated the generality of this S<sub>8</sub>-promoted triple cleavage of bromodifluoro compounds for the synthesis of benzimidazoles, which is summarized in Scheme 2. First, we examined a range of difluorobromoacetamides to react with *o*-phenylenediamine. In addition to 2-bromo-2,2-difluoro-*N*-isopropylacetamide (**2a**), *tert*-butyl, benzyl, allyl, phenyl and cyclopropyl substituted bromodifluoroamides were also good donors in this S<sub>8</sub>-promoted triple cleavage, rendering the expected products (**3a–3e**) in 55–93% yields. Cyclopropyl is widely used in medicinal chemistry because of its unique properties, which may enhance the drug's efficacy, change lipophilicity and PK properties it is gratifying that 2-bromo-*N*-cyclopropyl-2,2-difluoroacetamide also gives the corresponding product (**3f**) in 32% yields.<sup>11</sup> We then also investigated a number of *N*-disubstituted difluorobromoacetamide compounds. For instance, 2-bromo-2,2-difluoro-1-(pyrrolidin-1-yl)ethan-1-one (**2g**) was a good partner in this transformation, enabling the generation of **3g** in 74% yield. *N*-Diethyl and *N*-dibenzyl bromodifluoroamides **2h** and **2i** could be engaged in this reaction as well, producing the benzimidazoles **3h** and **3i** in 45% and 91% yield, respectively. Subsequently, we focused on the substrate scope with regard to *o*-phenylenediamines. A series of *o*-phenylenediamines with different electronic properties were

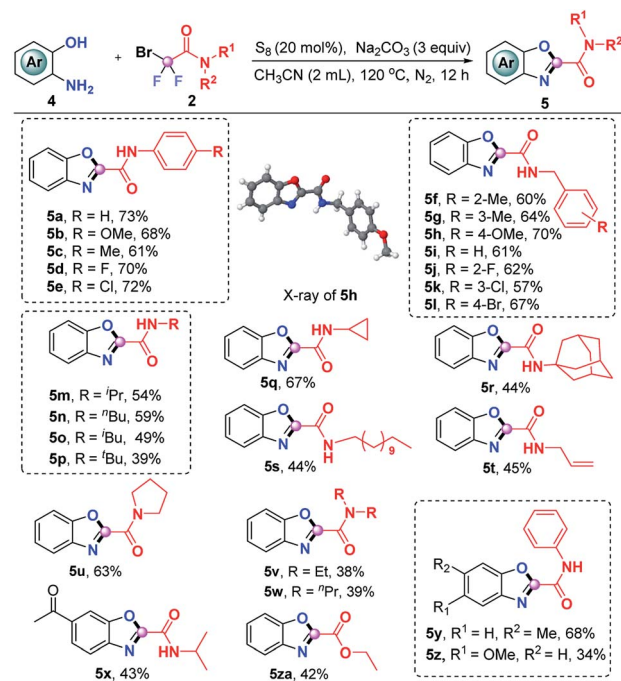
proven to be suitable substrates, delivering the targeted benzimidazoles (**3j–3n**) in 30–77% yields. The treatment of ethyl difluorobromoacetate with *o*-phenylenediamine was also successful and the desired ethyl 1*H*-benzo[*d*]imidazole-2-carboxylate (**3o**) could be obtained in modest yield, which highlights the generality of the current procedure. In order to verify the scalability of this protocol, we also carried out a gram-scale reaction of *o*-phenylenediamine (**1a**) and 2-bromo-2,2-difluoro-*N*-isopropylacetamide (**2a**) and **3a** was readily obtained in 80% yield without loss of the efficiency.

The current S<sub>8</sub>-promoted triple cleavage of bromodifluoro compounds can also be extended to 2-aminophenols for the construction of 2-amido/ester benzoxazoles. As showcased in Scheme 3, a series of *N*-phenyl substituted difluorobromoamides having different substituents on the aromatic ring exhibited good reactivity in this transformation, affording the benzoxazoles (**5a–5e**) in 61–73% yields. Aside from *N*-phenyl substituted difluorobromoamides, various *N*-benzyl substituted difluorobromoamides were also good candidates, furnishing **5f–5l** in decent yields. The structure of **5h** was explicitly confirmed by X-ray crystallographic analysis. *N*-Alkylmonosubstituted difluorobromoamides could work smoothly in this transformation as well, producing the benzoxazoles **5m–5t** in moderate yields. To our delight, more sterically hindered *N*-disubstituted difluorobromoamides were also compatible under identical conditions, furnishing the expected products **5u–5w** in 38–63% yields. The optimal reaction conditions were also proven to be suitable with a number of 2-aminophenols which could be readily converted into the corresponding benzoxazoles (**5x–5z**). It was also pleasingly found that the reaction



<sup>a</sup>Reaction conditions: **1** (0.3 mmol), **2** (1.2 equiv), S<sub>8</sub> (20% mmol), Na<sub>2</sub>CO<sub>3</sub> (3 equiv), MeCN (1 mL) at N<sub>2</sub> for 16 h under 130 °C. <sup>b</sup>Yield of scale up reaction. <sup>c</sup>Mixture ratio.

Scheme 2 The scope of the synthesis of 2-amidobenzimidazoles.<sup>a</sup>



<sup>a</sup>Reaction conditions: **4** (0.3 mmol), **2** (1.2 equiv), S<sub>8</sub> (20% mmol), Na<sub>2</sub>CO<sub>3</sub> (3 equiv), MeCN (2 mL) at N<sub>2</sub> for 12 h under 120 °C. Isolated yields.

Scheme 3 The scope of the synthesis of 2-amidobenzoxazoles.<sup>a</sup>



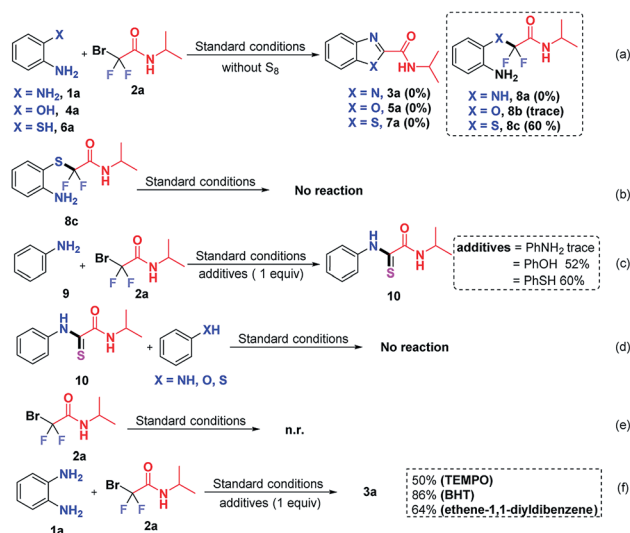


of ethyl bromodifluoroacetate and 2-aminophenol could produce **5za** in moderate yield, which could either be hydrolyzed into carboxylic acid or converted into other derivatives.

To further broaden the substrate scope and limitations of this system, we subsequently investigated the reactions of 2-aminothiophenols with a variety of halogenated difluoro reagents.

We were glad to find that this  $S_8$ -promoted triple cleavage of bromodifluoro compounds could also be employed to 2-aminothiophenols which reacted with numerous difluoro reagents to readily assemble various benzothiazoles in good yields (Scheme 4). A range of *N*-aryl and *N*-alkyl derived difluoro-bromoamides were amenable to this metal-free triple cleavage transformation, enabling the production of *N*-benzo[*d*]thiazole-2-carboxamides (**7a–7m**) in 54–90% yields. The structure of **7h** was determined by single crystal X-ray diffraction analysis. In addition, *N,N'*-dialkyl substituted difluorobromoamides were also tolerated under the identified conditions, rendering the targeted products **7n–7s** in moderate to good yields. Of note, the product **7q** is a significant category of benzothiazoles which have anti-TB activity.<sup>10g</sup> Similar to *o*-phenylenediamine and 2-aminophenol, the reaction of ethyl difluorobromoacetate with 2-aminothiophenol was also successful, which gave rise to **7t** and **7u** in 75% and 46% yields, respectively.

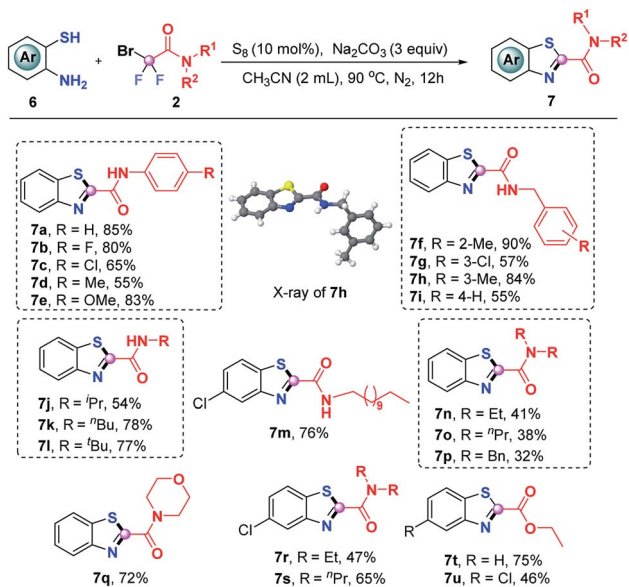
To clarify the reaction mechanism, a string of control experiments was carried out. Not surprisingly, no desired heterocycles were detected when the reactions were conducted without  $S_8$  since  $S_8$  plays a prerequisite role in these transformations. Interestingly, 60% yield of 2-((2-aminophenyl)thio)-2,2-difluoro-*N*-isopropylacetamide (**8c**) was obtained when 2-aminothiophenol was used as the starting material (Scheme 5a). In order to figure out whether **8c** is the intermediate, subsequently, the obtained **8c** was subjected to the standard



Scheme 5 Control experiments for mechanistic studies.

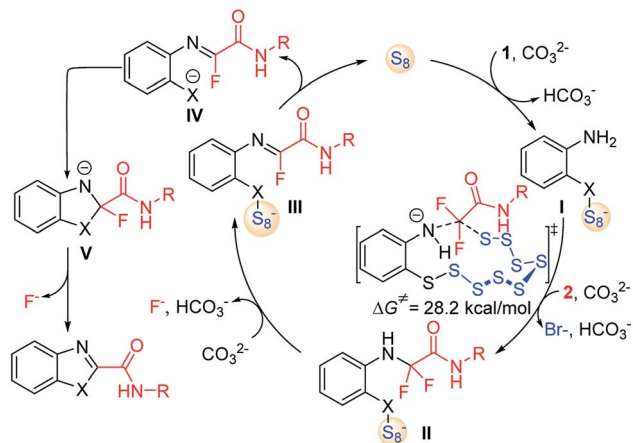
conditions; however, no reaction was observed (Scheme 5b), which indicated that **8c** was not an intermediate in this transformation. In light of this result, we postulated that the free  $NH_2$  group should react with **2** preferentially. To test our hypothesis, aniline (**9**) was treated with **2a**, using stoichiometric aniline, phenol and benzenethiol as additives (Scheme 5c). To our surprise and delight, the thioamide **10** was detected when phenol or benzenethiol was added to the reaction, which suggested that compound **10** might be the possible intermediate in this  $S_8$ -catalyzed triple cleavage. Subsequently, thioamide **10** was subjected to aniline (**9**), phenol or benzenethiol under the standard conditions (Scheme 5d) and no further transformation was observed at this point, probably due to the difficulty of the intermolecular reaction pattern (in our cases, three transformations are intramolecular patterns) or it suggested that thioamide **10** was not the key intermediate in the transformations in this study. In order to verify whether the reaction was initiated from bromodifluoro compounds with  $S_8$ , the reaction of 2-bromo-2,2-difluoro-*N*-isopropylacetamide (**2a**) and  $S_8$  was also conducted (Scheme 5e). However, no transformation was detected by the analysis of the reaction mixture and  $^{18}F$ -NMR. Therefore it excludes the possibility that  $S_8$  reacted with the difluoroalkylating reagent first, which further gave us a hint that  $S_8$  should be involved in the intermediate formation steps. To further gain insights into whether these are radical involved transformations, we also carried out radical trapping experiments and it was found that these reactions were not inhibited by the radical scavengers, indicating that this transformation was not a radical involved reaction regime (Scheme 5f).

Combined with the above experimental observations and previous reports,<sup>12</sup> the mechanism of  $S_8$ -catalyzed triple cleavage of halogenated difluoro compounds is proposed in Scheme 6. Deprotonation of sulfhydryl of reactant **1** followed by nucleophilic attack on  $S_8$  affords the ring-opened sulfanyl anion **I**. Then intermolecular nucleophilic substitution of



Scheme 4 The scope of the synthesis of 2-amidobenzothiazoles.<sup>a</sup>





Scheme 6 Proposed reaction mechanism.

intermediate **I** with  $\alpha$ -trihalogeno amide reactant **2** leads to the generation of a new C–N bond in amino amide **II**. The calculated free energy of this step is  $28.2 \text{ kcal mol}^{-1}$ , which is considered to be the rate-determining step for the whole transformation. Subsequently, hydrogen fluoride elimination of intermediate **II** could afford monofluoride substituted imine **III**. The cleavage of the X–S bond can release S<sub>8</sub> to finish the catalytic cycle by the release of anionic species **IV**. Then an outer sphere intramolecular nucleophilic addition of X to the imine moiety achieves the annulation in intermediate **V**, which can undergo further defluorination to provide the desired products. Further computational and experimental studies of the detailed mechanism are underway.

In summary, we have successfully developed an effective and direct S<sub>8</sub>-promoted synthesis of 2-amide/ester benzimidazoles, benzoxazoles and benzothiazoles from simple and readily available *o*-phenylenediamine, *o*-aminophenol and *o*-aminothiophenol *via* triple cleavage of halogenated difluoro compounds. The three halogen–carbon bonds of the halogenated difluoro compounds were simultaneously cleaved in this transformation in the absence of transition metal catalysts, ligands and external oxidants, which assembles the targeted N-containing heterocycles in good to excellent yields with a wide substrate scope. Further mechanistic studies of this S<sub>8</sub> promoted triple cleavage of halogenated difluoro compounds and synthetic applications of this metal free protocol are in progress in our laboratory.

## Conflicts of interest

The authors declare no competing financial interest.

## Acknowledgements

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## Notes and references

- (a) H. Amii and K. Uneyama, *Chem. Rev.*, 2009, **109**, 2119–2183; (b) M. Hu, Z. He, B. Gao, L. Li, C. Ni and J. Hu, *J. Am. Chem. Soc.*, 2013, **135**, 17302–17305.
- G. Meißner, K. Kretschmar, T. Braun and E. Kemnitz, *Angew. Chem., Int. Ed.*, 2017, **56**, 16338–16341.
- (a) T. Ahrens, J. Kohlmann, M. Ahrens and T. Braun, *Chem. Rev.*, 2017, **115**, 931–972; (b) M. Y. Wang, X. Pu, Y. Zhao, P. Wang, Z. Li, C. Zhu and Z. Shi, *J. Am. Chem. Soc.*, 2018, **140**, 9061–9065.
- (a) Z. Feng, Q.-Q. Min, Y.-L. Xiao, B. Zhang and X. Zhang, *Angew. Chem., Int. Ed.*, 2014, **53**, 1669–1673; (b) Y.-L. Xiao, W.-H. Guo, G.-Z. He, Q. Pan and X. Zhang, *Angew. Chem., Int. Ed.*, 2014, **53**, 9909–9913; (c) J. Wu, Q. Zhao, T. C. Wilson, S. Verhoog, L. Lu, V. Gouverneur and Q. Shen, *Angew. Chem., Int. Ed.*, 2019, **58**, 2413–2417; (d) J.-W. Gu, Q.-Q. Min, L.-C. Yu and X. Zhang, *Angew. Chem., Int. Ed.*, 2016, **55**, 12270–12274; (e) J. Xie, T. Zhang, F. Chen, N. Mehrkens, F. Rominger, M. Rudolph and A. S. K. Hashmi, *Angew. Chem., Int. Ed.*, 2016, **55**, 2934–2938; (f) M. Ke, Q. Feng, K. Yang and Q. Song, *Org. Chem. Front.*, 2016, **3**, 150–155; (g) M. Ke and Q. Song, *J. Org. Chem.*, 2016, **81**, 3654–3664; (h) M. Ke and Q. Song, *Chem. Commun.*, 2016, **53**, 2222–2225; (i) M. Ke and Q. Song, *Adv. Synth. Catal.*, 2017, **359**, 384–389; (j) W. Fu and Q. Song, *Org. Lett.*, 2018, **20**, 393–396; (k) L. An, C. Xu and X. Zhang, *Nat. Commun.*, 2017, **8**, 1460–1468; (l) J. Xu, Z. Kuang and Q. Song, *Chin. Chem. Lett.*, 2017, **29**, 963–966; (m) C. Xu, W.-H. Guo, X. He, Y.-L. Guo, X.-Y. Zhang and X. Zhang, *Nat. Commun.*, 2018, **9**, 1170–1179.
- (a) M. Hu, C. Hu, L. Li, Y. Han and J. Hu, *J. Am. Chem. Soc.*, 2015, **137**, 14496–14501; (b) L. Li, F. Wang, C. Ni and J. Hu, *Angew. Chem., Int. Ed.*, 2013, **125**, 12616–12620; (c) Z. Feng, Q.-Q. Min, X.-P. Fu, L. An and X. Zhang, *Nat. Chem.*, 2017, **9**, 918–923; (d) C. Yu, J. Su, X. Ma, Y. Zhou and Q. Song, *Asian J. Org. Chem.*, 2019, **8**, 694–697; (e) X. Ma, Q. Xuan and Q. Song, *Acta Chim. Sin.*, 2018, **76**, 972–976.
- (a) X. Ma, Y. Zhou and Q. Song, *Org. Lett.*, 2018, **20**, 4777–4781; (b) X. Ma, S. Mai, Y. Zhou, G.-J. Cheng and Q. Song, *Chem. Commun.*, 2018, **54**, 8960–8963; (c) X. Ma, S. Deng and Q. Song, *Org. Chem. Front.*, 2018, **5**, 3505–3509.
- (a) J. Yu, J.-H. Lin and J.-C. Xiao, *Angew. Chem., Int. Ed.*, 2017, **56**, 16669–16673; (b) Y. Xie, X. Chen, Z. Wang, H. Huang, B. Yi and G.-J. Deng, *Green Chem.*, 2017, **19**, 4294–4298; (c) J. Derendorf, C. Jenne and M. Keßler, *Angew. Chem., Int. Ed.*, 2017, **56**, 8281–8284; (d) Z. Wang, X. Chen, H. Xie, D. Wang, H. Huang and G.-J. Deng, *Org. Lett.*, 2018, **20**, 5470–5473; (e) T. B. Nguyen, L. Ermolenko and A. Al-Mourabit, *J. Am. Chem. Soc.*, 2018, **135**, 118–121.
- (a) T. B. Nguyen, L. Ermolenko, P. Retailleau and A. Al-Mourabit, *Angew. Chem., Int. Ed.*, 2014, **53**, 13808–13812; (b) X. Zhu, Y. Yang, G. Xiao, J. Song, Y. Liang and G. Deng, *Chem. Commun.*, 2017, **53**, 11917–11920; (c) G. Li, H. Xie,



- J. Chen, Y. Guo and G.-J. Deng, *Green Chem.*, 2017, **19**, 4043–4047; (d) Y. Huang, D. Yan, X. Wang, P. Zhou, W. Wu and H. Jiang, *Chem. Commun.*, 2018, **54**, 1742–1745; (e) Q. Song, Q. Feng and M. Zhou, *Org. Lett.*, 2013, **15**, 5990–5993; (f) S.-Q. Zhu, Y.-L. Liu, H. Li, X.-H. Xu and F.-L. Qing, *J. Am. Chem. Soc.*, 2018, **140**, 11613–11617.
- 9 (a) Y.-P. Zhu, M. Lian, F.-C. Jia, M.-C. Liu, J.-J. Yuan, Q.-H. Gao and A.-X. Wu, *Chem. Commun.*, 2012, **48**, 9086–9088; (b) Q. Feng and Q. Song, *Adv. Synth. Catal.*, 2014, **356**, 2445–2452.
- 10 (a) P. Shah, T. M. Dhameliya, R. Bansal, M. Nautiyal, D. N. Kommi, P. S. Jadhavar, J. P. Sridevi, P. Yogeeshwari and D. Sriramb, *Med. Chem. Commun.*, 2014, **5**, 1489–1495; (b) X.-L. Chen, X. Li, L.-B. Qu, Y.-C. Tang, W.-P. Mai, D.-H. Wei, W.-Z. Bi, L.-K. Duan, K. Sun, J.-Y. Chen, D.-D. Ke and Y.-F. Zhao, *J. Org. Chem.*, 2014, **79**, 8407–8416; (c) S. N. Mistry, J. Shonberg, C. J. Draper-Joyce, C. K. Herenbrink, M. Michino, L. Shi, A. Christopoulos, B. Capuano, P. J. Scammells and J. R. Lane, *J. Med. Chem.*, 2015, **58**, 6819–6843; (d) Y. Nagasawa, Y. Tachikawa, E. Yamaguchi, N. Tada, T. Miura and A. Itoh, *Adv. Synth. Catal.*, 2016, **358**, 178–182; (e) S. Pancholia, T. M. Dhameliya, P. Shah, P. S. Jadhavar, J. P. Sridevi, P. Yogeeshwari, D. Sriram and A. K. Chakraborti, *Eur. J. Med. Chem.*, 2016, **116**, 187–199; (f) L.-T. Wu, Z. Jiang, J.-J. Shen, H. Yi, Y.-C. Zhan, M.-Q. Sha, Z. Wang, S.-T. Xue and Z.-R. Li, *Eur. J. Med. Chem.*, 2016, **114**, 328–336; (g) T. M. Dhameliya, R. Tiwari, A. Banerjee, S. Pancholia, D. Sriram, D. Panda and A. Chakraborti, *Eur. J. Med. Chem.*, 2018, **155**, 364–380.
- 11 (a) Y. Kazuta, K. Hirano, K. Natsume, S. Yamada, R. Kimura, S. Matsumoto, K. Furuichi, A. Matsuda and S. Shuto, *J. Med. Chem.*, 2013, **46**, 1980–1988; (b) A. R. Renslo, P. Jaishankar, R. Venkatachalam, C. Hackbarth, S. Lopez, D. V. Patel and M. F. Gordeev, *J. Med. Chem.*, 2005, **48**, 5009–5024; (c) T. T. Talele, *J. Med. Chem.*, 2016, **59**, 8712–8756.
- 12 (a) X. Chen, Z. Wang, H. Huang and G.-J. Deng, *Adv. Synth. Catal.*, 2018, **360**, 4017–4022; (b) J. Zheng, R. Cheng, J.-H. Lin, D.-H. Yu, L. Ma, L. Jia, L. Zhang, L. Wang, J.-C. Xiao and S. H. Liang, *Angew. Chem., Int. Ed.*, 2017, **56**, 3196–3200.

