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# Activation of perfluoroalkyl iodides by anions: extending the scope of halogen bond activation to C(sp<sup>3</sup>)-H amidation, C(sp<sup>2</sup>)-H iodination, and perfluoroalkylation reactions†

Yaxin Wang,<sup>‡\*ab</sup> Zehui Cao,<sup>‡a</sup> Qin He,<sup>‡a</sup> Xin Huang,<sup>c</sup> Jiayi Liu,<sup>a</sup> Helfried Neumann,<sup>ID\*ab</sup> Gong Chen<sup>ID\*c</sup> and Matthias Beller<sup>ID\*ab</sup>

A simple, efficient, and convenient activation of perfluoroalkyl iodides by *t*BuONa or KOH, without expensive photo- or transition metal catalysts, allows the promotion of versatile  $\alpha$ -sp<sup>3</sup> C-H amidation reactions of alkyl ethers and benzylic hydrocarbons, C-H iodination of heteroaryl compounds, and perfluoroalkylations of electron-rich  $\pi$  bonds. Mechanistic studies show that these novel protocols are based on the halogen bond interaction between perfluoroalkyl iodides and *t*BuONa or KOH, which promote homolysis of perfluoroalkyl iodides under mild conditions.

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## Introduction

Developing new activation modes for carbon-halogen bonds of fluoroalkyl halides offers interesting possibilities for the synthesis of pharmaceuticals, agrochemicals, and new materials.<sup>1,2</sup> Unlike typical alkyl halides, halogen atoms linked to strongly electron-withdrawing groups possess an electrophilic character, the so-called  $\sigma$  hole, which is opposite to that for R-X bonds. This type of organic halide (donor) can form an additional halogen bond (HX) with a Lewis base (acceptor) through an  $n \rightarrow \sigma^*$  charge-transfer interaction.<sup>3</sup> Despite its importance in crystal engineering<sup>4</sup> and supramolecular chemistry,<sup>5</sup> utilization of HX interactions is still in its infancy for the development of new synthetic methodologies. In their pioneering studies, Bolm,<sup>6</sup> Huber<sup>7</sup> and others<sup>8</sup> demonstrated that the  $\sigma^*$  acidity of HX donors can be used to activate several types of HX acceptors, including N-heteroarenes, carbonyl groups, and halides. Recently, Chen,<sup>9</sup> Melchiorre,<sup>10</sup> Yu, and other groups<sup>11</sup> showed that perfluoroalkyl iodides (R<sub>f</sub>-I) represent valuable H-X donors, which can be activated by amines (HX acceptor) under light irradiation. Thereby perfluoroalkyl radicals are generated, which subsequently can be added to various electron-rich  $\pi$  bonds to give perfluoroalkylated products (Scheme 1A). Most

recently, Niu and co-workers also discovered that allyl glycosyl sulfones can form halogen bond complexes with perfluoroalkyl iodides, which, by means of visible light irradiation, fragment *via* radical intermediates to give synthetically valuable glycosyl iodides.<sup>12</sup> Despite these interesting results, activation of fluoroalkyl halides by different anions has been largely ignored in organic synthesis.<sup>13</sup>

Herein, we report a general method for activation of perfluoroalkyl iodides *via* halogen bond interaction with *t*BuONa or KOH at ambient temperature. This novel activation mode enables several interesting synthetic applications to be carried out, including C(sp<sup>3</sup>)-H amidation of ethers and benzylic hydrocarbons, C-H iodination of heteroarenes, and perfluoroalkylation of electron-rich  $\pi$  bonds under very mild conditions (Scheme 1B).

## Results and discussion

### Discovery of selective amidation reactions of ethers and benzylic compounds

Recently, some of us discovered that perfluoroalkyl iodides could be efficiently activated by light irradiation in the presence of amine (such as *N,N,N',N'*-tetraethylethylenediamine (TEEDA)) to generate the corresponding R<sub>f</sub> radicals.<sup>9</sup> Based on this work, we had the idea of directed Pd-catalyzed, selective C(sp<sup>2</sup>)-H perfluoroalkylation of substrate **1** (Scheme 2). Here, the palladacycle intermediate **In 1'**, which is generated by Pd-catalyzed C-H activation, would react with perfluoroalkyl radicals produced *via* photochemical activation of the halogen bond complex (R<sub>f</sub>·TEEDA) to form the Pd<sup>III</sup> intermediate **In 2'**, which can undergo reductive elimination to form selective C(sp<sup>2</sup>)-H perfluoroalkylation products.

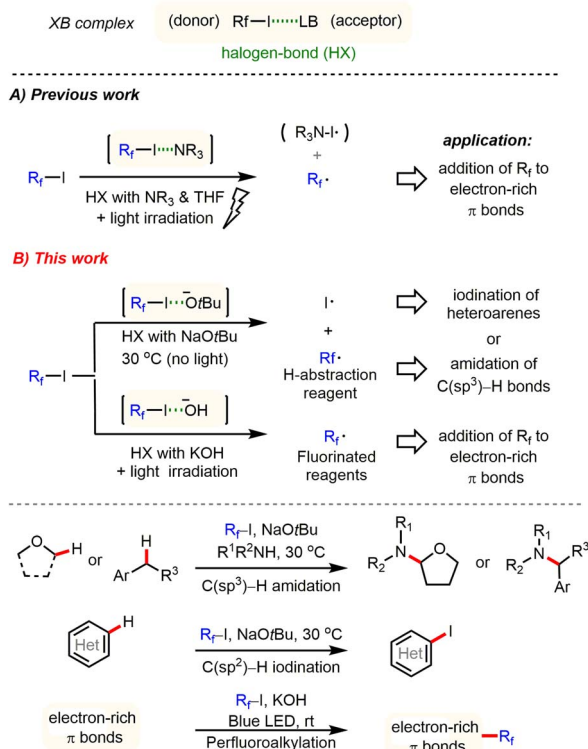
<sup>a</sup>College of Pharmacy, Nanjing University of Chinese Medicine, Nanjing 210023, China. E-mail: 300500@njucm.edu.cn; Yaxin.Wang@catalysis.de

<sup>b</sup>Leibniz-Institute for Catalysis, Albert-Einstein-Str. 29a, Rostock 18059, Germany. E-mail: Matthias.Beller@catalysis.de

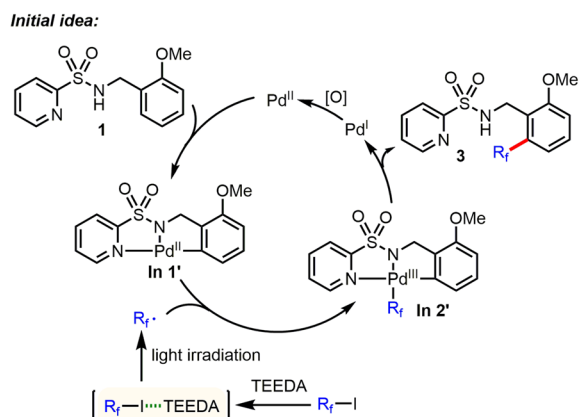
<sup>c</sup>State Key Laboratory and Institute of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, China

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‡ Equal contribution from Y. W. and Z. C. and Q. H.



Scheme 1 General principles of halogen bond-promoted activation of perfluoroalkyl iodides: selected known examples and this work.



Scheme 2 Initial idea of Pd-catalyzed, selective C(sp<sup>2</sup>)-H perfluoroalkylation. \*TEEDA: *N,N,N',N'*-tetraethylethylenediamine.

We began to evaluate this hypothesis by using *N*-benzyl pyridylsulfonamide **1** as substrate. However, performing the model reaction of *N*-benzyl pyridylsulfonamide **1** with C<sub>4</sub>F<sub>9</sub>-I, in the presence of TEEDA and palladium acetate, did not give the desired product **3**. Instead, unexpectedly, a small amount of the C-H amidated product of tetrahydrofuran (THF) solvent was generated (Table 1, entry 1). Surprisingly, using the inorganic base Cs<sub>2</sub>CO<sub>3</sub> gave **2** in 62% yield (Table 1, entry 2). Even more astonishing, the reaction in the absence of Pd also gave **2** in 65% yield (Table 1, entry 3). While the activation of

**Table 1** Optimization of conditions for C(sp<sup>3</sup>)-H amidation of THF using *N*-benzyl pyridylsulfonamide (**1**) and nonafluoro iodobutane (C<sub>4</sub>F<sub>9</sub>I)<sup>a</sup>

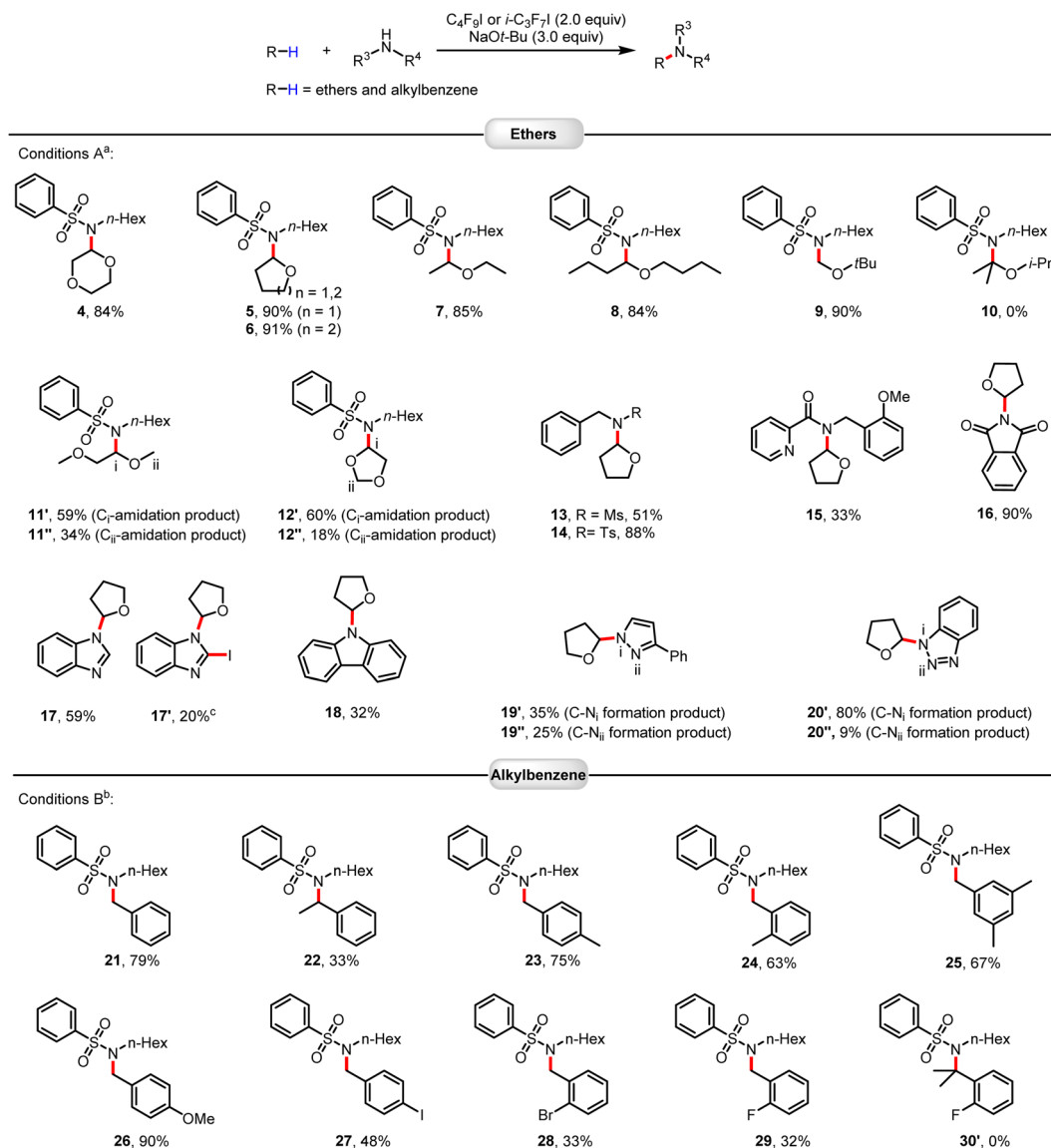
Entry	Reagents (equiv.)/temperature	Solvent	Yield <sup>a</sup> (%), 2
1 <sup>b</sup>	Pd(OAc) <sub>2</sub> (0.1), TEEDA (3), 60 °C	THF	23
2	Pd(OAc) <sub>2</sub> (0.1), Cs <sub>2</sub> CO <sub>3</sub> (3), 60 °C	THF	62
3	Cs <sub>2</sub> CO <sub>3</sub> (3), 60 °C	THF	65 (56 <sup>c</sup> )
4	Cs <sub>2</sub> CO <sub>3</sub> (3), 30 °C	THF	<2
5	K <sub>2</sub> CO <sub>3</sub> (3), 60 °C	THF	10
6	Na <sub>2</sub> CO <sub>3</sub> (3), 60 °C	THF	<2
7	NaOCH <sub>3</sub> (3), 60 °C	THF	33
8	KOtBu (3), 60 °C	THF	<2
9	NaOtBu (3), 60 °C	THF	>99 (90 <sup>c</sup> )
10	KOtBu (3), 30 °C	THF	<2
11	<b>NaOtBu (3), 30 °C</b>	<b>THF</b>	<b>&gt;99 (90<sup>c</sup>)</b>
12	NaOtBu (2), 30 °C	THF	81
13	NaOtBu (1), 30 °C	THF	58
14 <sup>d</sup>	NaOtBu (3), 30 °C	THF	>99 (90 <sup>c</sup> )
15	NaH (3), 30 °C	THF	<2
16	NaOtBu (3), 30 °C, air	THF	28
17	NaOtBu (3), THF (10), 30 °C	CCl <sub>4</sub>	71
18	NaOtBu (3), THF (10), 30 °C	PhCF <sub>3</sub>	67
19 <sup>b</sup>	TEEDA (3), 30 °C	THF	21
20 <sup>b</sup>	Et <sub>3</sub> N (3), 30 °C	THF	18
21 <sup>d</sup>	Et <sub>3</sub> N (3), 30 °C	THF	<2
22	Bu <sub>4</sub> NCl or Bu <sub>4</sub> NBr or Bu <sub>4</sub> NI (3), 30 °C	THF	<2
23	Bu <sub>4</sub> NCl (3), NaH (1), 30 °C	THF	65
24	Bu <sub>4</sub> NBr (3), NaH (1), 30 °C	THF	63
25	Bu <sub>4</sub> NI (3), NaH (1), 30 °C	THF	64

<sup>a</sup> Yields are based on <sup>1</sup>H NMR analysis on a 0.2 mmol scale in 4 mL glass vial. <sup>b</sup> CFL light (25 W) irradiation. <sup>c</sup> Isolated yield. <sup>d</sup> In darkness.

perfluoroalkyl iodides (R<sub>f</sub>-I) by Cs<sub>2</sub>CO<sub>3</sub> has been reported,<sup>14</sup> the underlying mechanism is still unknown. We suspected that the carbonate ligand of Cs<sub>2</sub>CO<sub>3</sub> might activate R<sub>f</sub>-I *via* the halogen bond under the specific conditions applied. Thus, we examined the effect of different bases. Interestingly, NaOtBu facilitated the reaction at 30 °C in near quantitative yield (Table 1, entry 11). In contrast, the use of KOtBu gave little product (Table 1, entry 10). Next, we studied the influence of different reaction parameters. Notably, the amidation reaction proceeded well with and without light (Table 1, entry 11 *vs.* entry 14); however, the reaction yield diminished to 28% when the reaction was carried out under an atmosphere of air (Table 1, entry 16). In addition, the activation of R<sub>f</sub>-I is also feasible by halide anions (Cl<sup>-</sup>, Br<sup>-</sup>, I<sup>-</sup>) (Table 1, entries 23–25).

With optimized conditions in hand, we explored the scope of this amidation of ethers.<sup>15</sup> As shown in Fig. 1, a variety of cyclic and linear ethers worked well (**4–12**). The regioselectivity of these transformations was very high, with C-H activation





**Fig. 1** Scope of C(sp<sup>3</sup>)-H amidation of ethers and alkylbenzenes. Reactions were performed on a 0.2 mmol scale. Isolated yields are given. <sup>a</sup>Conditions A: C<sub>4</sub>F<sub>9</sub>I (2.0 equiv.), NaOtBu (3.0 equiv.), T = 30 °C. <sup>b</sup>Conditions B: *i*-C<sub>3</sub>F<sub>7</sub>I (2.0 equiv.), NaOtBu (3.0 equiv.), Ar-H (10.0 equiv.), T = 60 °C, solvent PhCF<sub>3</sub> (1 mL). <sup>c</sup>Iodination product **17'** of compound **17** was obtained (see ESI†).

occurring at a specific C-H bond in the *ortho*-position to the oxygen atom. This can be explained by the relatively lower bond dissociation energy of this C-H bond compared to the other bonds and the stability of the resulting carbon radicals. It should be noted that the electron density of the substrate ethers influences the reaction (**12'** vs. **12''**). However, this reaction system was not applicable to sterically hindered substituted ethers, such as 2-isopropoxypropane (**10**). Substrates containing functional groups, including sulfonamides, Ms, Ts, amide, imide, and nitrogen-containing heteroarenes, can be well applied in this protocol. Apart from ethers, selective sp<sup>3</sup> C-H amidation of benzylic hydrocarbons could also be achieved smoothly using the same strategy. Here, activation of the halogen bond of heptafluoroisopropyl iodide with NaOtBu allowed for smooth functionalization with high efficiency and

good functional group tolerance. Again, the steric hindrance had a strong impact on the outcome of the amidation reactions (**21** vs. **22**). In general, benzylic hydrocarbons with electron-donating groups performed better than benzylic hydrocarbons containing electron-withdrawing groups (**24** vs. **29**).

### Discovery and substrate scope of selective C-H iodination reactions

Much to our surprise, the amination of THF with benzimidazole under standard reaction conditions not only gave the desired aminated product **17** in 59% isolated yield but also led to the iodinated product of compound **17** (Fig. 1, **17'**). Apparently, in addition to the perfluoroalkyl radical, an iodine radical could be produced in our reaction system. This should allow selective iodination of heteroarenes with perfluoroalkyl iodides



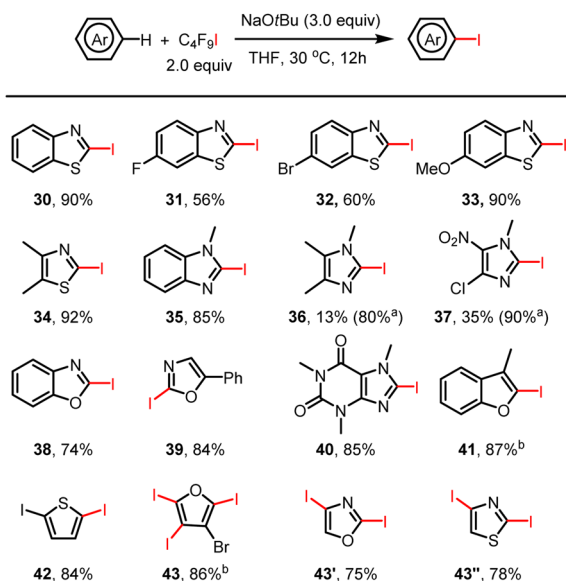


Fig. 2 Selective heteroaryl C(sp<sup>2</sup>)-H iodination by halogen bond-promoted activation. Reactions were performed on a 0.2 mmol scale. Isolated yields are given. <sup>a</sup>Crude <sup>1</sup>H NMR yield. <sup>b</sup>4.0 equiv. of C<sub>4</sub>F<sub>9</sub>I and NaOtBu were used.

under similarly mild conditions to be achieved. Indeed, as shown in Fig. 2, a wide variety of heteroarenes could be successfully reacted with C<sub>4</sub>F<sub>9</sub>-I in the presence of NaOtBu with

good to excellent yields and regioselectivity. More specifically, thiazole, oxazole, imidazole, benzothiazole, benzoxazole, and benzimidazole derivatives were all efficiently iodinated with high selectivity in the 2-position (30–39). Moreover, when 4- and 5-unprotected oxazole and thiazole were examined for the iodination system, di-iodinated products were obtained in high isolated yield (43' and 43''). The observed regioselectivity in these reactions agrees with iodination reactions of heterocycles using other iodination reagents.<sup>16</sup> As an example of a bioactive compound, caffeine offered the iodinated product in an excellent yield of 85% (40). In all cases, good to excellent isolated product yields were achieved; however, in the case of 4-chloro-1-methyl-5-nitro-imidazole and 1,4,5-trimethylimidazole isolation of the products was more difficult, leading to a lower isolated yield. Finally, it should be mentioned that it is possible to obtain multiple iodinated products, as shown in the case of triple iodination of 3-bromofuran.

### Discovery of perfluoroalkylation reactions: synthesis of perfluoroalkylated phenanthridines and isoquinolines

Clearly, the interaction of perfluoroalkyl iodides with the halide bond acceptor leads to activation of the iodide and the perfluoroalkyl residue. Hence, following this concept, it should be possible to perform perfluoroalkylation reactions as well. Indeed, when using other substrate classes, such as isocyanides, olefins, alkynes, and electron-rich arenes or heteroarenes, under previously developed standard conditions, we

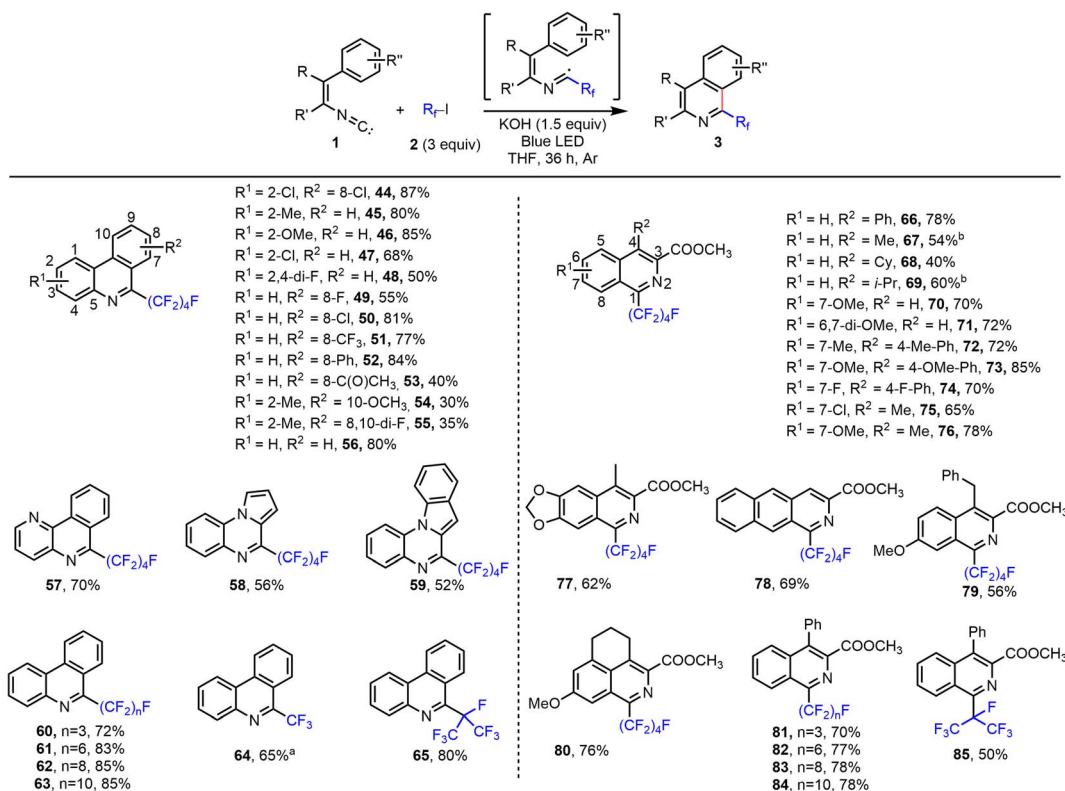


Fig. 3 Halogen bond-promoted reaction system for perfluoroalkylated phenanthridine and isoquinoline synthesis. Reactions were performed on a 0.2 mmol scale. Isolated yields are given. <sup>a</sup>Excess of CF<sub>3</sub>I was used (sparging THF solution with CF<sub>3</sub>I gas; see the ESI†). <sup>b</sup>6 equiv. C<sub>4</sub>F<sub>9</sub>I and 3 equiv. KOH were used.



observed perfluoroalkylation reactions. As shown in Scheme S7 (see ESI†), the synthesis of 6-perfluoroalkylated phenanthridine **44** was achieved from 4',5-dichloro-2-isocyano-1,1'-biphenyl and  $C_4F_9-I$  in the presence of  $tBuONa$ . While **44** was obtained in 23% yield when the reaction was performed in the dark, the product yield increased in the presence of light. More specifically, under irradiation with a blue light-emitting diode (LED), and utilizing 1.5 equiv. of  $tBuONa$ , provided **44** in 72% yield in THF. Notably, using irradiation with blue LED without  $tBuONa$  present, the reaction gave only a poor yield (see ESI† for details). Interestingly, under LED irradiation a variety of other anions act as halide bond acceptors and could promote this reaction (see

ESI, Scheme S7†). To our surprise, even simple potassium hydroxide was an effective additive and gave excellent results, providing **44** in 87% isolated yield. With KOH as additive, the reaction also gave high yields of the product under irradiation from a low-intensity Hg UV lamp (254 nm, 25 W) or sunlight. For halide anion additives, the lighter, more charge dense halides were more effective in this reaction ( $F^- > Cl^- > Br^- > I^-$ ), which is in line with the trend of reported values for the association constant ( $K_a$ ) for interactions of anions with  $C_4F_9I$ .<sup>13</sup>

Next, the scope of the phenanthridine and isoquinoline synthesis was explored under the optimized conditions with KOH additive and blue LED light irradiation (Fig. 3). 2-

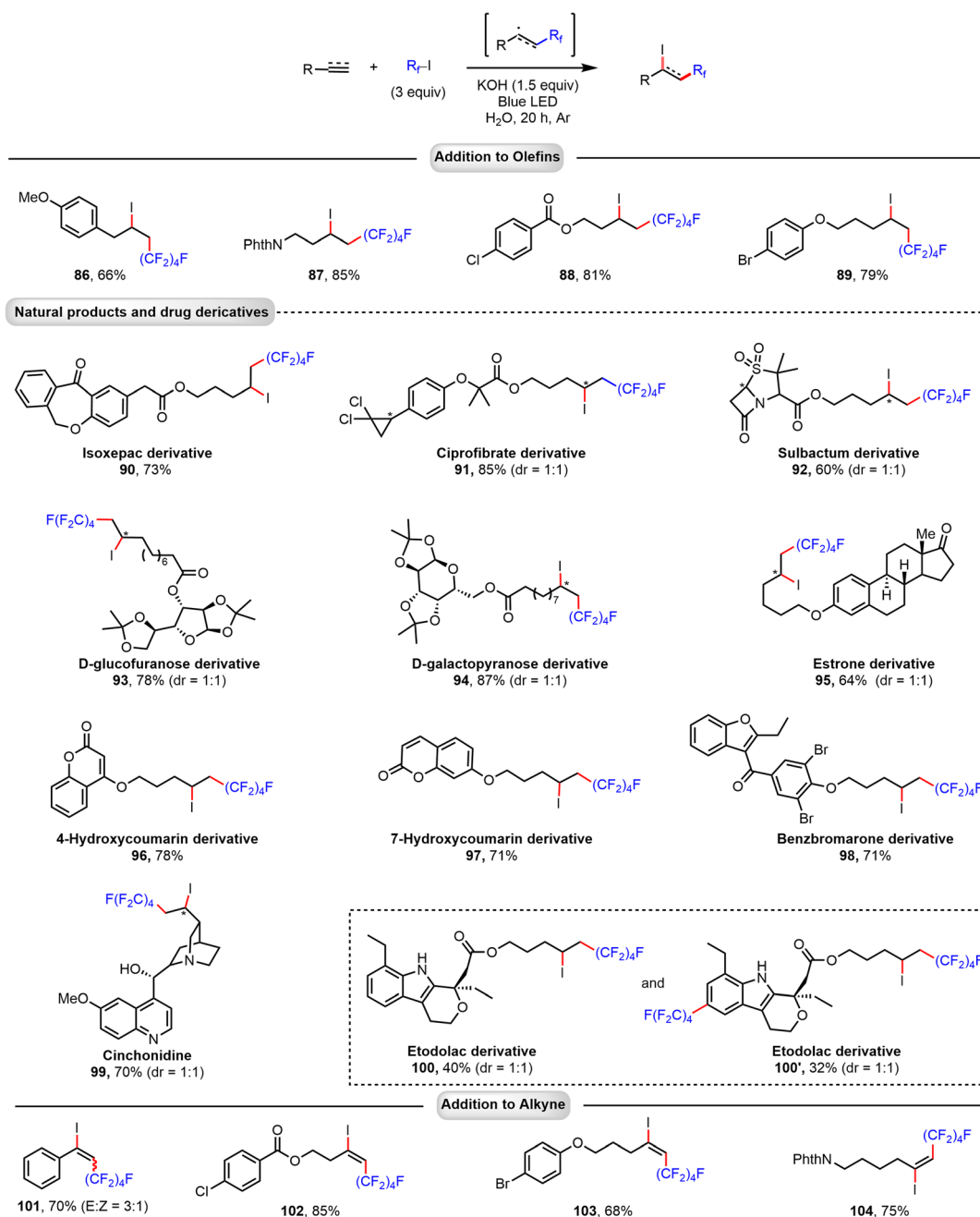


Fig. 4 Addition of perfluoroalkyl iodide to alkenes and alkynes. Reactions were performed on a 0.2 mmol scale. Isolated yields are given.





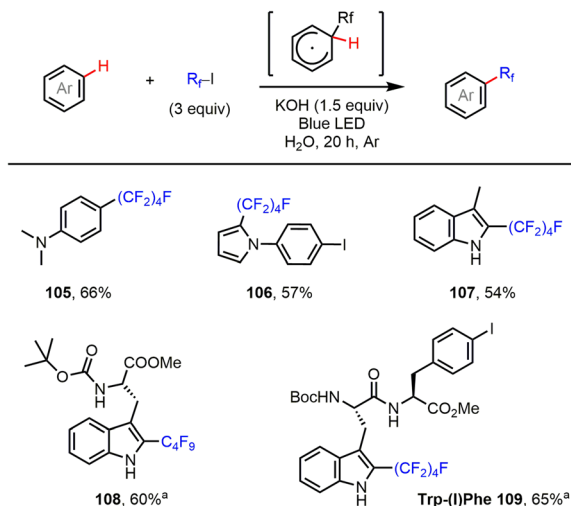


Fig. 5 C–H perfluoroalkylation of aniline and electron-rich heteroarenes. Reactions were performed on a 0.2 mmol scale. Isolated yields are given. <sup>a</sup>CH<sub>2</sub>Cl<sub>2</sub> was used as solvent.

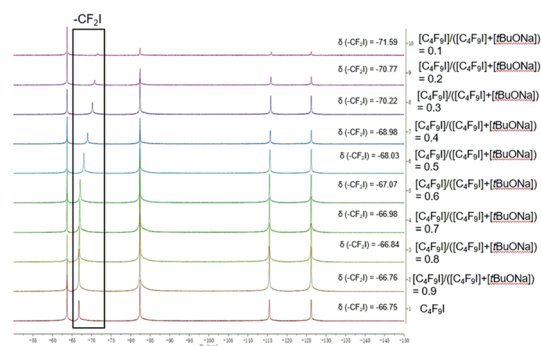
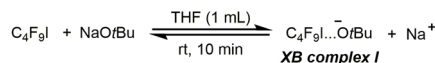
Isocyanobiphenyls (**44–56**) and vinyl isocyanide (**66–76**) bearing various substitution patterns reacted smoothly with C<sub>4</sub>F<sub>9</sub>–I with good to excellent yield and regioselectivity. Isocyanide substrates containing a pyridine, pyrrole, indole, dioxolane, or naphthalene ring were tolerated (see **57–59**, **77**, and **78**). Furthermore, reactions of both linear and branched perfluoroalkyl iodides of various lengths provided excellent results, to give products **60–65** and **81–85**.

### Addition reactions of perfluoroalkyl iodides to alkenes and alkynes

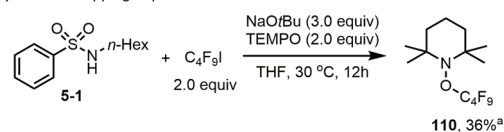
Applying the same conditions as above (KOH as additive and blue LED light irradiation) for the reaction of C<sub>4</sub>F<sub>9</sub>–I with terminal alkenes, a 1,2-addition process to give iodoperfluoroalkylated products is observed. Notably, using water as solvent, excellent regioselectivity is achieved (Fig. 4). Functional groups, such as phthalimide (PhthN), benzoate ester, phenyl ether, and ketone, were tolerated. Various alkene substrates derived from natural products and drugs were also surveyed. For example, terminal alkenes bearing isoxepac (**90**), ciprofibrate (**91**), sulbactam (**92**), D-glucofuranose (**93**), D-galactopyranose (**94**), estrone (**95**), coumarin (**96**, **97**), benzobromarone (**98**), and etodolac (**100**) can be conveniently applied to give the corresponding products in good yields (60–87%). Notably, subjecting quinine, which contains hydroxyl and pyridine moieties, to the reaction provided **99** in good yield and selectivity. Perfluoroalkyl iodides also reacted, under similar conditions, with terminal alkynes to give iodoperfluoroalkylation products in good yield and excellent regioselectivity, and halogen (Cl, Br), benzoate ester, phenyl ether, and PhthN substituents were well tolerated. In all these reactions, we assume that perfluoroalkyl radicals generated *via* photochemical activation of the halogen bond complex (C<sub>4</sub>F<sub>9</sub>I...<sup>–</sup>OH) add directly to the alkene or alkyne substrate to form a secondary alkyl or vinyl radical intermediate. The resulting radical could then abstract an iodine atom

#### A) Titration experiment of C<sub>4</sub>F<sub>9</sub>I with <sup>t</sup>BuONa

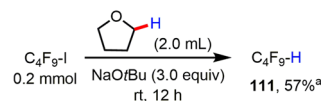
XB complex (donor) Rf–I...LB (acceptor)



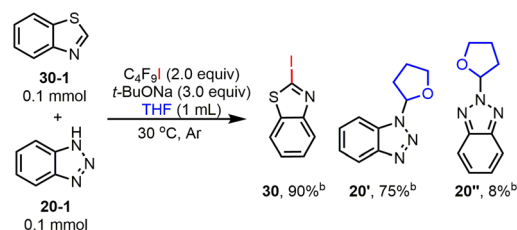
#### B) TEMPO trapping experiment



#### C) Reaction of C<sub>4</sub>F<sub>9</sub>–I with THF



#### D) Reaction of C<sub>4</sub>F<sub>9</sub>–I with benzothiazole and benzotriazole



Scheme 3 Mechanistic experiments. <sup>a</sup>Crude <sup>19</sup>F NMR yield. <sup>b</sup>Isolated yield.

from a perfluoroalkyl iodide molecule to give the difunctionalized product and propagate the radical chain.

### C–H perfluoroalkylation of electron-rich arenes and heteroarenes

Finally, the C–H perfluoroalkylation of electron-rich arenes and heteroarenes with perfluoroalkyl iodides was investigated. Such transformations have been achieved using several different radical initiation systems.<sup>9,17</sup> As shown in Fig. 5, reactions of aniline and pyrrole, as well as indole, using our halogen bond-promoted method (C<sub>4</sub>F<sub>9</sub>I...<sup>–</sup>OH) provided perfluoroalkylated products (**105–107**) in moderate to good yields. Furthermore, we were delighted to find that tryptophan (Trp)-containing short peptides could be perfluoroalkylated at the C2 position of the Trp residue, in good yield and with excellent selectivity, under the standard reaction conditions. This reaction might offer



a valuable orthogonal strategy for peptide labeling based on under-explored Trp chemistry.

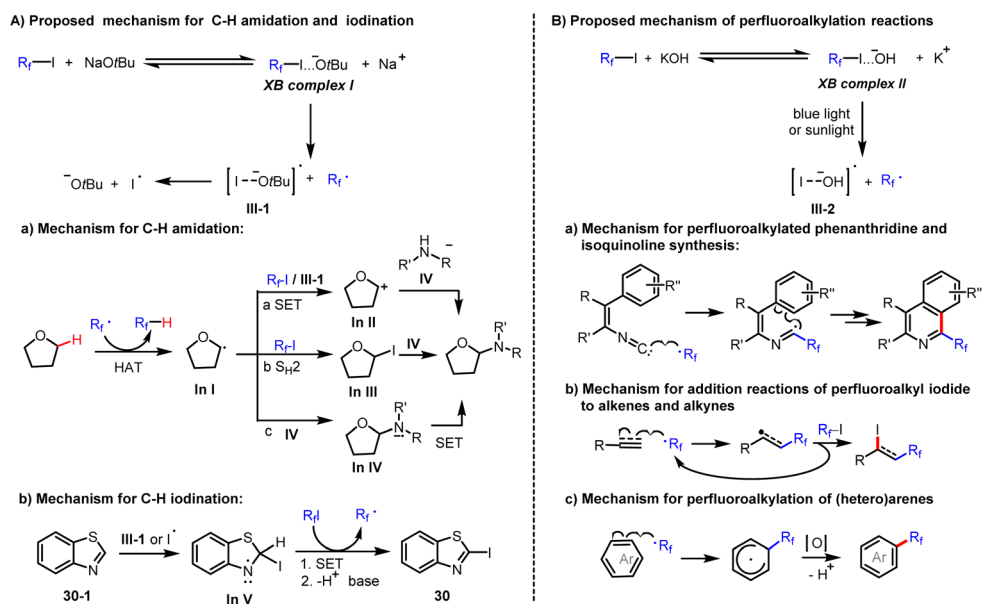
### Mechanistic investigations and studies

Having explored the synthetic utility of this novel activation mode for perfluoroalkyl iodide, we turned our attention to the mechanism, to explain the different outcomes of the amidation, iodination, and perfluoroalkylation reactions. In 2013, the interactions of iodoperfluoroarenes and iodoperfluoroalkanes with anions in organic solvent were studied by Taylor and co-workers, and their data indicated that favorable halogen bonding interactions exist between halide anions and iodoperfluoroalkanes.<sup>13b,c,e</sup> Based on this and our previous work,<sup>9</sup> we speculated that, in the present reaction system, oxoanions ( $t\text{BuO}^-$  and  $\text{OH}^-$ ) should have a halogen bonding interaction with perfluoroalkyl iodides under mild conditions. To verify the existence of the proposed halogen bonding interaction between  $t\text{BuO}^-$  and  $\text{R}_f\text{I}$ , a series of NMR experiments were performed using a solution of  $\text{NaOtBu}$  and  $\text{C}_4\text{F}_9\text{I}$  in the reaction solvent THF. The formation of a halogen bonding complex between  $\text{NaOtBu}$  and  $\text{C}_4\text{F}_9\text{I}$  is supported by the  $^{19}\text{F}$  NMR titration experiments. The resonance corresponding to the F of the  $\text{CF}_2\text{I}$  group was shifted to the upfield region when  $\text{NaOtBu}$  was added to the THF solution of  $\text{C}_4\text{F}_9\text{I}$  (Scheme 3A).<sup>18–20</sup> It is worth mentioning that the molar ratio (donor vs. acceptor) and the binding constant of the halogen bond complex ( $\text{R}_f\text{I} \cdots \text{OtBu}^-$ ) could not be accurately measured because  $\text{NaOtBu}$  was not completely soluble in the solvent, and the substrate  $\text{R}_f\text{I}$  is converted to perfluorobutane over time. For  $\text{C}_4\text{F}_9\text{I}$  and  $\text{KOH}$ , a similar halogen bonding interaction was observed, which is also supported by the  $^{19}\text{F}$  NMR titration experiments (see ESI†). Moreover, from  $^{19}\text{F}$  NMR titration experiments of  $\text{C}_4\text{F}_9\text{I}$  with  $t\text{BuONa}$  and  $\text{C}_4\text{F}_9\text{I}$  with  $\text{KOH}$ , it was found that  $t\text{BuONa}$  has a stronger

interaction with perfluoroalkyl iodides than does  $\text{KOH}$  (Table S2 vs. S3†).

Moreover, when a radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was present in a reaction mixture containing  $\text{C}_4\text{F}_9\text{I}$  and  $\text{NaOtBu}$ , formation of **5** was completely inhibited; instead, the corresponding product of radical trapping **110** (ref. 21 and 22) was obtained in 36% yield (Scheme 3B). Furthermore, perfluorobutyl iodide and  $t\text{BuONa}$  were dispersed in THF and the reaction mixture was stirred at 30 °C for 12 h. After adding  $\text{PhCF}_3$  as an internal standard for  $^{19}\text{F}$  NMR analysis, the formation of  $\text{C}_4\text{F}_9\text{H}$  was confirmed in 57% yield (Scheme 3C). These studies confirmed that: (1)  $\text{C}_4\text{F}_9\text{I}$  and  $\text{NaOtBu}$  have halogen bonding interactions in the present reaction system; (2) the halogen bonding complex between  $\text{C}_4\text{F}_9\text{I}$  and  $\text{NaOtBu}$  could produce perfluorobutyl radicals; and (3) the perfluorobutyl radical could serve as an H abstractor to activate a specific  $\text{C}(\text{sp}^3)\text{--H}$  bond of THF. Finally, amidation and iodination reactions could proceed simultaneously under the standard reaction conditions (Scheme 3D), suggesting that perfluorobutyl and iodine radicals are produced. For the iodination reaction of benzothiazole, we noted that when 3 equivalents of TEMPO were added to the reaction mixture, product formation was suppressed (see ESI, Scheme S17†).

Based on the above results, we propose the following mechanism (Scheme 4). Reaction of perfluoroalkyl iodides with  $t\text{BuONa}$  leads to the formation of the corresponding halogen bonding complexes (**XB complex I**). Due to this activation, the weak C–I bond of **XB complexes I** presumably undergo homolytic cleavage to form both a perfluoroalkyl radical and an iodine radical under mild conditions (Scheme 4). In the observed amidation reactions, the generated perfluoroalkyl radical acts as a hydrogen abstractor to convert the C–H substrate to a carbon-centered radical, **In I**. For the



Scheme 4 Proposed mechanism.



transformation of **In I** to the observed product, different reaction paths are feasible. In path (a), **In I** is further oxidised by single electron transfer (SET) to obtain the carbocation **In II**, which reacts with amide anion to produce the amidation product. In path (b), **In I** reacts with  $R_f-I$  by  $S_H2$  (homolytic bimolecular substitution) to give **In III**, which again reacts with amide anion by  $S_N2$  (bimolecular nucleophilic substitution) to produce the amidation product. Finally, in path (c), the carbon-centered radical **In I** reacts with amide anion to form the corresponding radical anion (**In IV**), which is easily oxidized by perfluoroalkyl iodides to obtain the amidation product and generates perfluoroalkyl radical as well as iodide anion during the process (Scheme 4). In contrast, in the observed iodination reactions, an iodine radical attacks the 2-position of heterocycles to form iodinated **In V**. Then, the iodinated **In V** undergoes a SET and deprotonation to generate the observed iodination product (Scheme 4). Similarly, perfluoroalkyl iodides form halogen bonding complexes (**XB complex II**) with KOH (Scheme 4). Under irradiation with blue light or sunlight, the C–I bond of **XB complexes II** undergoes homolytic cleavage to form both a perfluoroalkyl radical and an iodine radical (**III-2**). The former radical reacts with isonitriles or electron-rich  $\pi$  bonds of alkenes, alkynes, and (hetero)arenes to accomplish perfluoroalkylation addition reactions.

## Conclusions

In conclusion, we have developed versatile reaction systems for the amidation of alkyl ethers and benzylic hydrocarbons, for  $\alpha$ -C(sp<sup>3</sup>)–H bond amidation, (hetero)arenes C–H iodination, and addition of perfluoroalkyl iodides to electron-rich  $\pi$  bonds. All these different synthetic protocols rely on activation of perfluoroalkyl iodides by simple inorganic bases, such as sodium butoxide or potassium hydroxide. Mechanistic studies suggest that halogen bond interactions between perfluoroalkyl iodides and the inorganic base promote the homolysis of perfluoroalkyl iodides. Notably, there is no requirement for expensive photoredox catalysts or transition metals, and the generated perfluoroalkyl radicals act as a hydrogen abstractor, iodine source, or perfluoroalkyl source for the synthesis of hemiaminal ethers, *N*-benzyl-arenesulfonamides, heteroaryl iodides, and perfluoroalkyl-substituted, and potentially bioactive, molecules. In addition, the practicality, easy scale up, and mild reaction conditions make these synthetic transformations attractive and valuable for organic synthesis.

## Author contributions

Yaxin Wang formulated the initial ideas of this work, supervised the project, carried out most of the reaction optimization, C(sp<sup>3</sup>)–H amidation reaction study, C(sp<sup>3</sup>)–H iodination reaction study, structural determination of products, and prepared manuscript and the ESI. Zehui Cao and Qin He developed perfluoroalkylation reactions and take part in the mechanism study. Xin Huang prepared some amide substrates and take part in the C(sp<sup>3</sup>)–H amidation reaction study and Jiaxi Liu prepared some isonitrile substrates and take part in

perfluoroalkylation reactions study. Helfried Neumann provide fund for the project and revised the manuscript and the ESI. Gong Chen provide fund for the project and gave suggestion for the project and manuscript. Matthias Beller provide fund, gave suggestion for the project and prepared most of the manuscript.

## Conflicts of interest

There are no conflicts to declare.

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## Notes and references

- Activation of carbon-halogen bond of alkyl halides: (a) D. A. Nagib, M. E. Scott and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2009, **131**, 10875–10877; (b) P. V. Pham, D. A. Nagib and D. W. C. MacMillan, *Angew. Chem., Int. Ed.*, 2011, **50**, 6119–6122; (c) C.-J. Wallentin, J. D. Nguyen, P. Finkbeiner and C. R. J. Stephenson, *J. Am. Chem. Soc.*, 2012, **134**, 8875–8884; (d) N. Iqbal, S. Choi, E. Ko and E. J. Cho, *Tetrahedron Lett.*, 2012, **53**, 2005–2008; (e) H. Jiang, Y. Z. Cheng, R. Z. Wang, M. M. Zheng, Y. Zhang and S. Y. Yu, *Angew. Chem., Int. Ed.*, 2013, **52**, 13289–13292; (f) E. Kim, S. Choi, H. Kim and E. J. Cho, *Chem.–Eur. J.*, 2013, **19**, 6209–6212; (g) N. Iqbal, J. Jung, S. Park and E. J. Cho, *Angew. Chem., Int. Ed.*, 2014, **53**, 539–542; (h) N. J. W. Straathof, H. P. L. Gemoets, X. Wang, J. C. Schouten, V. Hessel and T. Noël, *ChemSusChem*, 2014, **7**, 1612–1617; (i) S. Tang, Y. L. Deng, J. Li, W. X. Wang, G. L. Ding, M. W. Wang, Z. P. Xiao, Y. C. Wang and R. L. Sheng, *J. Org. Chem.*, 2015, **80**, 12599–12605; (j) C. Bottecchia, X. J. Wei, K. P. L. Kuijpers, V. Hessel and T. Noël, *J. Org. Chem.*, 2016, **81**, 7301–7307; (k) A. Postigo, *Eur. J. Org. Chem.*, 2018, 6391–6404; (l) S. Zhang, N. Rottaloria, F. Weniger, J. Rabeah, H. Neumann, C. Taeschler and M. Beller, *Chem. Commun.*, 2019, **55**, 6723–6726; (m) Y. Li, H. Neumann and M. Beller, *Chem.–Eur. J.*, 2020, **26**, 6784; (n) K. P. S. Cheung, D. Kurandina, T. Yata and V. Gevorgyan, *J. Am. Chem. Soc.*, 2020, **142**, 9932–9937; (o) D. E. Yerien, S. Barata-Vallejo, E. W. M. Flores and A. Postigo, *Catal. Sci. Technol.*, 2020, **10**, 5113–5128; (p) M. Lubbesmeyer, E. G. Mackay, M. A. R. Raycroft, J. Elfert, D. A. Pratt and A. Studer, *J. Am. Chem. Soc.*, 2020, **142**, 2609–2616.
- Activation of carbon-halogen bond of aryl halides: (a) E. Shirakawa, K. I. Itoh, T. Higashino and A. Hayashi, *J. Am. Chem. Soc.*, 2010, **132**, 15537–15539; (b) L. Zhang, H. Yang and L. Jiao, *J. Am. Chem. Soc.*, 2016, **138**, 7151–7160; (c) L. Zhang and L. Jiao, *J. Am. Chem. Soc.*, 2017, **139**, 607–610; (d) S. Zhou, E. Doni, G. M. Anderson, R. G. Kane,





- S. W. MacDougall, V. M. Ironmonger, T. Tuttle and J. A. Murphy, *J. Am. Chem. Soc.*, 2014, **136**, 17818–17826; (e) J. P. Barham, G. Coulthard, K. J. Emery, E. Doni, F. Cumine, G. Nocera, M. P. John, L. E. A. Berlouis, T. McGuire, T. Tuttle and J. A. Murphy, *J. Am. Chem. Soc.*, 2016, **138**, 7402–7410; (f) S. Yanagisawa, K. Ueda, T. Taniguchi and K. Itami, *Org. Lett.*, 2008, **10**, 4673–4676; (g) W. Liu, H. Cao, H. Zhang, H. Zhang, K. H. Chung, C. He, H. Wang, F. Y. Kwong and A. W. Lei, *J. Am. Chem. Soc.*, 2010, **132**, 16737–16740; (h) Y. Qiu, Y. Liu, K. Yang, W. K. Hong, Z. Li, Z. Y. Wang, Z. Y. Yao and S. Jiang, *Org. Lett.*, 2011, **13**, 3556–3559; (i) B. S. Bhakuni, A. Kumar, S. J. Balkrishna, J. A. Sheikh, S. Konar and S. Kumar, *Org. Lett.*, 2012, **14**, 2838–2841; (j) B. S. Bhakuni, A. Yadav, S. Kumar, S. Patel, S. Sharma and S. Kumar, *J. Org. Chem.*, 2014, **79**, 2944–2954; (k) C. L. Sun, Y. F. Gu, W. P. Huang and Z. J. Shi, *Chem. Commun.*, 2011, **47**, 9813–9815; (l) C. L. Sun, H. Li, D. G. Yu, M. Yu, X. Zhou, X. Y. Lu, K. Huang, S. F. Zheng, B. J. Li and Z. J. Shi, *Nat. Chem.*, 2010, **2**, 1044–1049; (m) J. Chen and J. Wu, *Angew. Chem., Int. Ed.*, 2017, **56**, 3951–3955; (n) H. Q. Zhao, J. Shen, C. L. Ren, W. Zeng and H. Q. Zeng, *Org. Lett.*, 2017, **19**, 2190–2193.
- 3 (a) R. S. Mulliken, *J. Am. Chem. Soc.*, 1950, **72**, 600–608; (b) O. Hassel, *Science*, 1970, **170**, 497–502; (c) P. Metrangolo, H. Neukirch, T. Pilati and G. Resnati, *Acc. Chem. Res.*, 2005, **38**, 386–395; (d) M. Erdélyi, *Chem. Soc. Rev.*, 2012, **41**, 3547–3557; (e) S. M. Huber, E. Jimenez-Izal, J. M. Ugalde and I. Infante, *Chem. Commun.*, 2012, **48**, 7708–7710; (f) M. P. Mitoraj and A. Michalak, *J. Mol. Model.*, 2013, **19**, 4681–4688; (g) L. P. Wolters, P. Schyman, M. J. Pavan, W. L. Jorgensen, F. M. Bickelhaupt and S. Kozuch, *Wiley Interdiscip. Rev.: Comput. Mol. Sci.*, 2014, **4**, 523–540; (h) G. Cavallo, P. Metrangolo, R. Milani, T. Pilati, A. Priimagi, G. Resnati and G. Terraneo, *Chem. Rev.*, 2016, **116**, 2478–2601.
- 4 (a) S. C. Blackstock, J. P. Lorand and J. K. Kochi, *J. Org. Chem.*, 1987, **52**, 1451–1460; (b) P. Metrangolo, F. Meyer, T. Pilati, G. Resnati and G. Terraneo, *Angew. Chem., Int. Ed.*, 2008, **47**, 6114–6127; (c) A. C. Legon, *Phys. Chem. Chem. Phys.*, 2010, **12**, 7736–7747; (d) G. Cavallo, P. Metrangolo, T. Pilati, G. Resnati, M. Sansotera and G. Terraneo, *Chem. Soc. Rev.*, 2010, **39**, 3772–3783; (e) T. M. Beale, M. G. Chudzinski, M. G. Sarwar and M. S. Taylor, *Chem. Soc. Rev.*, 2013, **42**, 1667–1680; (f) G. R. Desiraju, P. S. Ho, L. Kloo, A. C. Legon, R. Marquardt, P. Metrangolo, P. Politzer, G. Resnati and K. Rissanen, *Pure Appl. Chem.*, 2013, **85**, 1711–1713; (g) A. Mukherjee, S. Tothadi and G. R. Desiraju, *Acc. Chem. Res.*, 2014, **47**, 2514–2524.
- 5 (a) A. C. Legon, *Angew. Chem., Int. Ed.*, 1999, **38**, 2686–2714; (b) E. Corradi, S. V. Meille, M. T. Messina, P. Metrangolo and G. Resnati, *Tetrahedron Lett.*, 1999, 7519–7523; (c) P. Metrangolo, W. Panzeri, F. Recupero and G. Resnati, *J. Fluorine Chem.*, 2002, **114**, 27–33; (d) P. Metrangolo, T. Pilati, G. Resnati and A. Stevenazzi, *Chem. Commun.*, 2004, 1492–1493; (e) T. Caronna, R. Liantonio, T. A. Logothetis, P. Metrangolo, T. Pilati and G. Resnati, *J. Am. Chem. Soc.*, 2004, **126**, 4500–4501; (f) A. Casnati, R. Liantonio, P. Metrangolo, G. Resnati, R. Ungaro and F. Ugozzoli, *Angew. Chem., Int. Ed.*, 2006, **45**, 1915–1918; (g) P. Metrangolo, T. Pilati, G. Terraneo, S. Biella and G. Resnati, *CrystEngComm*, 2009, **11**, 1187–1196; (h) F. Meyer and P. Dubois, *CrystEngComm*, 2013, **15**, 3058–3071; (i) A. Priimagi, G. Cavallo, P. Metrangolo and G. Resnati, *Acc. Chem. Res.*, 2013, **46**, 2686–2695; (j) L. C. Gilday, S. W. Robinson, T. A. Barendt, M. J. Langton, B. R. Mullaney and P. D. Beer, *Chem. Rev.*, 2015, **115**, 7118–7195; (k) B. Li, S. Q. Zanga, L. Y. Wang and T. C. W. Mak, *Coord. Chem. Rev.*, 2016, **308**, 1–21; (l) A. Abate, R. Dehmel, A. Sepe, N. Linh Nguyen, B. Roose, N. Marzari, J. K. Hong, J. M. Hook, U. Steiner and C. Neto, *J. Mater. Chem. A*, 2019, **7**, 24445–24453.
- 6 A. Bruckmann, M. A. Pena and C. Bolm, *Synlett*, 2008, **6**, 900–902.
- 7 (a) S. M. Walter, F. Kniep, E. Herdtweck and S. M. Huber, *Angew. Chem., Int. Ed.*, 2011, **50**, 7187–7191; (b) S. M. Huber, E. Jimenez-Izal, J. M. Ugalde and I. Infante, *Chem. Commun.*, 2012, **48**, 7708–7710; (c) F. Kniep, S. H. Jungbauer, Q. Zhang, S. M. Walter, S. Schindler, I. Schnapperelle, E. Herdtweck and S. M. Huber, *Angew. Chem., Int. Ed.*, 2013, **52**, 7028–7032; (d) S. H. Jungbauer, S. M. Walter, S. Schindler, L. Rout, F. Kniep and S. M. Huber, *Chem. Commun.*, 2014, **50**, 6281–6284; (e) S. H. Jungbauer and S. M. Huber, *J. Am. Chem. Soc.*, 2015, **137**, 12110–12120; (f) R. L. Sutar and S. M. Huber, *ACS Catal.*, 2019, **9**, 9622–9639.
- 8 (a) S. Dordonne, B. Crousse, D. Bonnet-Delpon and J. Legros, *Chem. Commun.*, 2011, **47**, 5855–5857; (b) W. He, Y. C. Ge and C. H. Tan, *Org. Lett.*, 2014, **16**, 3244–3247; (c) Y. Takeda, D. Hisakuni, C. H. Lin and S. Minakata, *Org. Lett.*, 2015, **17**, 318–321; (d) F. Sladojevich, E. McNeill, J. Bçrgel, S. L. Zheng and T. Ritter, *Angew. Chem., Int. Ed.*, 2015, **54**, 3712–3716; (e) M. Saito, N. Tsuji, Y. Kobayashi and Y. Takemoto, *Org. Lett.*, 2015, **17**, 3000–3003.
- 9 Y. X. Wang, J. H. Wang, G.-X. Li, G. He and G. Chen, *Org. Lett.*, 2017, **19**, 1442–1445.
- 10 (a) M. Nappi, G. Bergonzini and P. Melchiorre, *Angew. Chem., Int. Ed.*, 2014, **53**, 4921–4925; (b) G. E. M. Crisenza, D. Mazzarella and P. Melchiorre, *J. Am. Chem. Soc.*, 2020, **142**, 5461–5476.
- 11 (a) Y. Z. Cheng, X. A. Yuan, J. Ma and S. Y. Yu, *Chem.–Eur. J.*, 2015, **21**, 8355–8359; (b) Y. Z. Cheng and S. Y. Yu, *Org. Lett.*, 2016, **18**, 2962–2965; (c) X. Y. Sun, Y. Y. He and S. Y. Yu, *J. Photochem. Photobiol., C*, 2018, **355**, 326–331; (d) X. Tang and A. Studer, *Angew. Chem., Int. Ed.*, 2018, **57**, 814–817; (e) J. Cao, G. Wang, L. Gao, H. Chen, X. Liu, X. Cheng and S. Li, *Chem. Sci.*, 2019, **10**, 2767–2772.
- 12 C. Zhang, H. Zuo, G. Y. Lee, Y. Zou, Q. Dang, K. N. Houk and D. Niu, *Nat. Chem.*, 2022, **14**, 686–694.
- 13 (a) A. E. Feiring, *J. Org. Chem.*, 1985, **50**, 3269–3274; (b) E. Dimitrijevic, O. Kvak and M. S. Taylor, *Chem. Commun.*, 2010, **46**, 9025–9027; (c) M. S. Taylor, *Top. Curr. Chem.*, 2014, 27–48, Halogen Bonding II; (d) L. K. Morka, V. Tata,



- D. J. Ulnessa, B. G. Ericksonb and M. W. Gealy, *J. Mol. Liq.*, 2018, **271**, 647–654; (e) M. G. Sarwar, B. Dragisić, E. Dimitrijević and M. S. Taylor, *Chem.–Eur. J.*, 2013, **19**, 2050–2058.
- 14 (a) Y. Aihara, M. Tobisu, Y. Fukumoto and N. Chatani, *J. Am. Chem. Soc.*, 2014, **136**, 15509–15512; (b) B. Zhang and A. Studer, *Org. Lett.*, 2014, **16**, 3990–3993; (c) S. Zhang, N. R. Loria, F. Weniger, J. Rabeah, H. Neumann, C. Taeschlerc and M. Beller, *Chem. Commun.*, 2019, **55**, 6723–6726; (d) Y. Li, H. Neumann and M. Beller, *Chem.–Eur. J.*, 2020, **26**, 6784–6788.
- 15 (a) H. M. L. Davies and J. R. Manning, *Nature*, 2008, **451**, 417–424; (b) M. Daz-Requejo and P. Prez, *Chem. Rev.*, 2008, **108**, 3379–3394; (c) W. B. Parker, *Chem. Rev.*, 2009, **109**, 2880–2893; (d) P. Merino, T. Tejero and I. Delso, *Curr. Med. Chem.*, 2008, **15**, 954–967; (e) R. Garg, S. P. Gupta, H. Gao, M. S. Babu, A. K. Debnath and C. Hansch, *Chem. Rev.*, 1999, **99**, 3525–3602.
- 16 (a) L. Tanwar, J. Börgel, J. Lehmann and T. Ritter, *Org. Lett.*, 2021, **23**, 5024–5027; (b) Q. Shi, S. Zhang, J. Zhang, V. F. Oswald, A. Amassian, S. R. Marder and S. B. Blakey, *J. Am. Chem. Soc.*, 2016, **138**, 3946–3949; (c) H. Do and O. Daugulis, *Org. Lett.*, 2009, **11**, 421–423.
- 17 (a) S. Barata-Vallejo, M. M. Flesia, B. Lantano, J. E. Arguello, A. B. Penenory and A. Postigo, *Eur. J. Org. Chem.*, 2013, **2013**, 998–1008; (b) N. Iqbal, S. Choi, E. Ko and E. J. Cho, *Tetrahedron Lett.*, 2012, **53**, 2005–2008; (c) N. J. W. Straathof, H. P. L. Gemoets, X. Wang, J. C. V. Schouten, V. Hessel and T. Noel, *ChemSusChem*, 2014, **7**, 1612–1617.
- 18 For details of the  $^{19}\text{F}$  NMR titration experiments, see the ESI.†
- 19 For  $^{19}\text{F}$  NMR analysis of XB complexes of  $\text{R}_\text{f}\text{–I}$ , see: (a) P. Job, *Justus Liebigs Ann. Chem.*, 1928, **9**, 113–118; (b) M. T. Messina, P. Metrangolo, W. Panzeri, E. Ragg and G. Resnati, *Tetrahedron Lett.*, 1998, **39**, 9069–9072; (c) D. V. G. Tiers, *J. Fluorine Chem.*, 2000, **102**, 175–184; (d) D. D. Burton, F. Fontana, P. Metrangolo, T. Pilati and G. Resnati, *Tetrahedron Lett.*, 2003, **44**, 645–648.
- 20 M. G. Sarwar, B. Dragisic, L. J. Salsberg, C. Gouliaras and M. S. Taylor, *J. Am. Chem. Soc.*, 2010, **132**, 1646–1653.
- 21 (a) A. Foris, *Magn. Reson. Chem.*, 2004, **42**, 534–555; (b) M. Hanack and J. Ullmann, *J. Org. Chem.*, 1989, **54**, 1432–1435; (c) X. Wang, H. Song, S. Wang, J. Yang, H. Qin, X. Jiang and C. Zhang, *Tetrahedron*, 2016, **72**, 7606–7612.
- 22 D. Jiang, C. Liu, Y. Guo, J. Xiao and Q. Chen, *Eur. J. Org. Chem.*, 2014, **2014**, 6303–6309.

