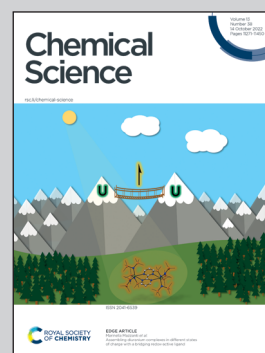


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A photoinduced transient activating strategy for late-stage chemoselective C(sp<sup>3</sup>)-H trifluoromethylation of azines

Nitrogen-containing heterocycles are ubiquitous scaffolds in agrochemicals and bioactive molecules. Although the derivatization of heteroarenes has been well addressed, it is highly challenging to access functionalized heteroaryls at benzylic positions. To address this issue, radical shift can help to overcome the site-selectivity and electronic limitations associated with transmetalation. This work merges Tf-shift of N-heterocycles and radical recombination for the late-stage functionalization of azinyl C(sp<sup>3</sup>)-H bonds. The traceless Tf switch acrobatics offers ample opportunities for site-selective derivatization of heteroaryls, allowing for the rapid increase of molecular complexity.

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# A photoinduced transient activating strategy for late-stage chemoselective C(sp<sup>3</sup>)-H trifluoromethylation of azines†

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The direct functionalization of C(sp<sup>3</sup>)-H bonds is an ultimately ideal synthetic strategy with high atom economy and step efficiency. However, the direct trifluoromethylation of electron-deficient heteroaryl adjacent C(sp<sup>3</sup>)-H bonds remains a formidable challenge. We have described a transient activating strategy involving a Tf-shift process and  $\pi$ - $\pi$  stacking interaction for catalyst-free direct benzylic C(sp<sup>3</sup>)-H trifluoromethylation of azines, such as pyridine, pyrimidine, quinoline, dihydropyridinone, tetrahydroisoquinoline and tetrahydroquinazoline, with an air-stable crystalline imidazolium sulfonate reagent IMDN-Tf. This bench-stable cationic reagent offers a scalable and practical protocol for the late-stage modification of drug molecules with high site selectivity, which avoids the prefunctionalization and the use of stoichiometric metals and strong oxidants. Furthermore, comprehensive mechanistic studies revealed the determining effect of  $\pi$ - $\pi$  stacking for the activation of azinylic C(sp<sup>3</sup>)-H bonds.

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## Introduction

N-Heterocycles as essential fragments exist in many bioactive molecules.<sup>1–4</sup> Azines with six-membered ring systems containing one or several nitrogen atoms demonstrate various activities and applications in medicine and agrochemicals. The selective introduction of functionality at the heterobenzylic site of azines is of significant interest for modification of drugs.<sup>5–9</sup> However, due to the strong basicity of most common azines, namely pyridine, pyrimidine, quinoline, *etc.*, the late-stage functionalization of alkylated azines exhibits inevitable difficulties and often requires harsh conditions. Recent advances in the activation of C(sp<sup>3</sup>)-H bonds using pyridinium salts as precursors have found success in transformations such as fluoroalkylation<sup>7,8</sup> and alkylation<sup>9</sup> (Fig. 1a, left). Considering the significance of fluorine-containing moieties in medicine,<sup>10–17</sup> the introduction of trifluoromethyl groups into organic molecules has attracted considerable attention, and significant progress has been achieved in this field in the past few decades.<sup>18–28</sup> The fluoroalkyl modification of pyridylic C-H bonds to regulate the metabolism is particularly appealing,<sup>29–31</sup> In order to introduce fluoroalkyl groups into heterocyclic

scaffolds, the trifluoromethylation of pyridylic C-H bonds has been achieved using prefunctionalized *N*-oxides<sup>7</sup> and *N*-amido pyridinium salts<sup>8</sup> *via* alkylidene dihydropyridine intermediates followed by nucleophilic or radical addition. However, the formation of the new C(sp<sup>3</sup>)-CF<sub>3</sub> bond through azinylic C(sp<sup>3</sup>)-H fluoroalkylation was limited by tedious substrate preparation and hazardous procedures. In contrast, the direct functionalization of unactivated heterobenzylic C(sp<sup>3</sup>)-H bonds would be strategically appealing and highly desirable. Highly reactive alkylidene dihydropyridine intermediates which were generated from the deprotonation of heterobenzylic C(sp<sup>3</sup>)-H bonds have been effectively exploited in functionalization. Recent advances in Lewis acid or alkali metal base-promoted deprotonation of pyridylic C-H bonds have been reported.<sup>32–35</sup> Transition-metal catalyzed C-H bond addition has also been reported.<sup>36–38</sup> However, these methods usually require harsh conditions, which severely limits the range of functional groups and their practical applications (Fig. 1a, right). Meanwhile, no general protocol for direct azinylic C(sp<sup>3</sup>)-H fluoroalkylation and alkylation is available. In this context, several issues need to be addressed, including inevitable C(sp<sup>2</sup>)-H fluoroalkylation through a radical addition process<sup>39–41</sup> and oxidation of azinylic C-H bonds.<sup>42–44</sup>

We envision that a transient activation strategy to rapidly introduce functional groups into azines could spontaneously generate the alkylidene dihydropyridine intermediate under mild photocatalytic conditions. After the dissociation of the transient activating group, functional groups would shift to the azinylic position to furnish the C(sp<sup>3</sup>)-H alkylation product (Fig. 1b). Recently, we have developed a bench-stable redox-

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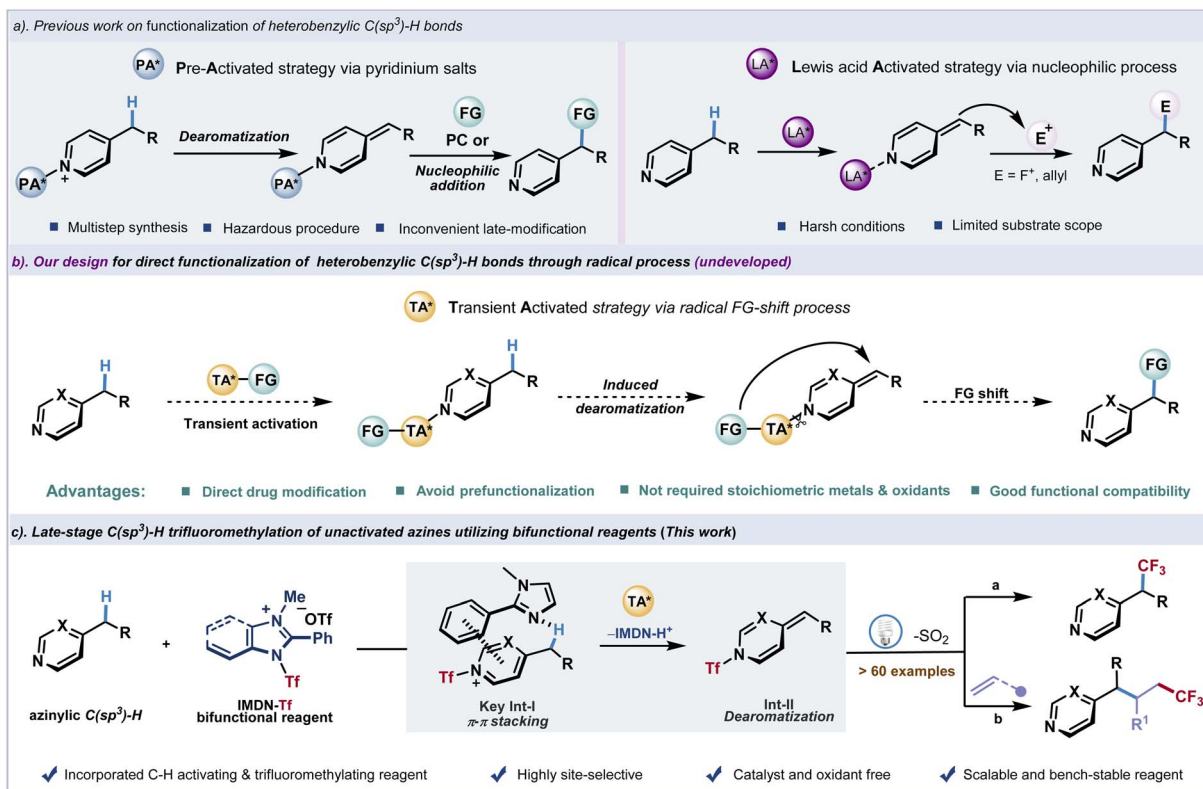


Fig. 1 Synthetic strategies for direct C(sp<sup>3</sup>)-H bond trifluoromethylation.

active imidazolium sulfonate reagent (IMDN-Tf) from inexpensive Tf<sub>2</sub>O and imidazole.<sup>45</sup> Owing to the electron deficiency and strong electrophilicity of this cationic reagent, IMDN-Tf could smoothly undergo an electrophilic Tf transfer process to generate Nu-Tf species through the cleavage of the weak N-S bond (BDE ≈ 70 kcal mol<sup>-1</sup>).<sup>46</sup> Inspired by recent reports on Tf<sub>2</sub>O activation of pyridines,<sup>47</sup> we design a Tf-shift process of IMDN-Tf to generate the azinylium salt *in situ* and imidazole residue, which also activates the azinylic C(sp<sup>3</sup>)-H bond *via* π-π stacking interaction (intermediate **I**) to produce the resonance-stabilized alkylidene dihydropyridine intermediate **II**. Finally, a rapid fragmentation and recombination event of **II** under photoexcitation affords the azinylic trifluoromethylation product and releases SO<sub>2</sub> (Fig. 1c). This reasonable hypothesis could lead to an unprecedented late-stage azinylic C(sp<sup>3</sup>)-H functionalization protocol in a catalyst-free manner. Pre-activation of azine substrates and commonly observed C(sp<sup>2</sup>)-H alkylation could be avoided.

## Results and discussion

Based on our hypothesis, we selected lepidine (**1**) as a pilot substrate to test azinylic trifluoromethylation (Table 1). After extensive screening of conditions, we found that when using 1.8 equiv. of IMDN-Tf **2a** and 1.75 equiv. of 2,6-lutidine in CH<sub>3</sub>CN at room temperature under the irradiation of 26 W CFL, the trifluoromethylation product **3** could be obtained in 73% NMR yield (65% isolated yield). Different IMDN-Tf salts **2b-2f** were

Table 1 Optimization of the reaction conditions<sup>a</sup>

Entry	Variation from the above conditions	Yield <sup>b</sup> /%
1	None	73(65) <sup>c</sup>
2	Tf <sub>2</sub> O instead of <b>2a</b>	0
3	CF <sub>3</sub> SO <sub>2</sub> Cl instead of <b>2a</b>	0
4	Other bases instead of 2,6-lutidine	23–55
5	Other solvents instead of CH <sub>3</sub> CN	5–33
6	60 W blue LED instead of CFL	53
7	Under darkness	18
8	W/o 2,6-lutidine	42
9	1.5 equiv. of <b>2a</b> was used	52

<sup>a</sup> Reaction conditions: **1** (0.2 mmol), **2a** (1.8 equiv.), 2,6-lutidine (1.75 equiv.), MeCN (2 mL), Ar, irradiation with 26 W CFL at r.t. for 2–12 h. <sup>b</sup> Yield determined by <sup>19</sup>F NMR spectroscopy using trifluoromethoxybenzene as an internal standard. <sup>c</sup> Isolated yield.



then examined. The imidazolium reagent **2b** bearing a methoxy group afforded product **3** in a higher yield (76%), while trifluoromethyl-substituted phenyl benzimidazolium salt **2c** furnished product **3** in a very low yield (19%). With imidazolium reagents **2d** and **2e**, the reaction could proceed in lower yields (29% and 59%, respectively). Furthermore, no product **3** was obtained with **2f** and **2g**, in which the methyl substituent or hydrogen was present at the 2-position of imidazole. These results indicated that the  $\pi$ - $\pi$  stacking effect is significant for the activation of azinyl C(sp<sup>3</sup>)-H bonds. When highly corrosive Tf<sub>2</sub>O or CF<sub>3</sub>SO<sub>2</sub>Cl was used as a trifluoromethyl source, no desired product could be obtained, only the decomposition of the reagents was observed (entries 2 and 3). Other organic or inorganic bases could promote the reaction with lower efficiencies (23–52% yields, entry 4). The basicity of the reaction solution has a significant influence on the yield (see ESI Table S1†). A weak base such as pyridine could not promote the dissociation of imidazoles, while a strong base such as Na<sub>2</sub>CO<sub>3</sub> can lead to the decomposition of IMDN-Tf reagents (see Table S1†). When using other solvents such as acetone, THF and ethyl acetate instead of MeCN, the yields of trifluoromethylated product **3** were significantly decreased (entry 5). This may be due to the poor solubility of IMDN-Tf **2a** in those solvents. Basic solvents including DMF and DMSO were also attempted and the decomposition of IMDN-Tf was observed (Table S2†). A blue LED also led to a lower yield compared with that using CFL (entry 6 and Table S4†). In addition, control experiments proved that both light and lutidine were necessary for the reaction (entries 7 and 8). When 1.5 equiv. of **2a** was used, the reaction occurred generating the product in a slightly lower yield with a small amount of unreacted starting material (52%, entry 9). When the amount of IMDN-Tf **2a** was increased to 2.0 equiv., the yield of the product was also decreased with the generation of the bis-trifluoromethylated byproduct (Table S3†).

With the optimized reaction conditions in hand, we next examined the generality of this transformation with different azines (Scheme 1). The primary C(sp<sup>3</sup>)-H substrates including methyl-substituted pyridine, pyrimidine and quinoline could all furnish the corresponding trifluoromethylated products with good yields (3–5). Pyridines and quinolines bearing electron withdrawing or electron-donating groups afforded products **6–14** in moderate to good yields (51–75%). Next, we investigated the direct trifluoromethylation of diversified heteroaromatic secondary C-H bonds. Pyridines and quinolines containing ethyl, propyl, isobutyl, heptyl, cyclohexyl and benzyl substituents afforded products **15–16** and **22–27** in moderate to good yields. Silyl-protected hydroxymethylpyridine reacted with cationic reagent **2a** to afford product **17** in 21% yield. Dihydropyridinone, tetrahydroisoquinoline and tetrahydroquinazoline also furnished trifluoromethylated products in good yields (**19–21**). Pyrimidine and quinoline derivatives bearing ester and amide groups could be well tolerated under standard conditions (**28–35**). Naphthyl-, furanyl- and pyridyl-ester substituted quinolines also readily transformed into the corresponding products **36–38** in moderate yields. The reaction could also be applied to quinoline derivatives involving cycloalkane to produce the desired products in 61–64% yields (**39–40**, **42**).

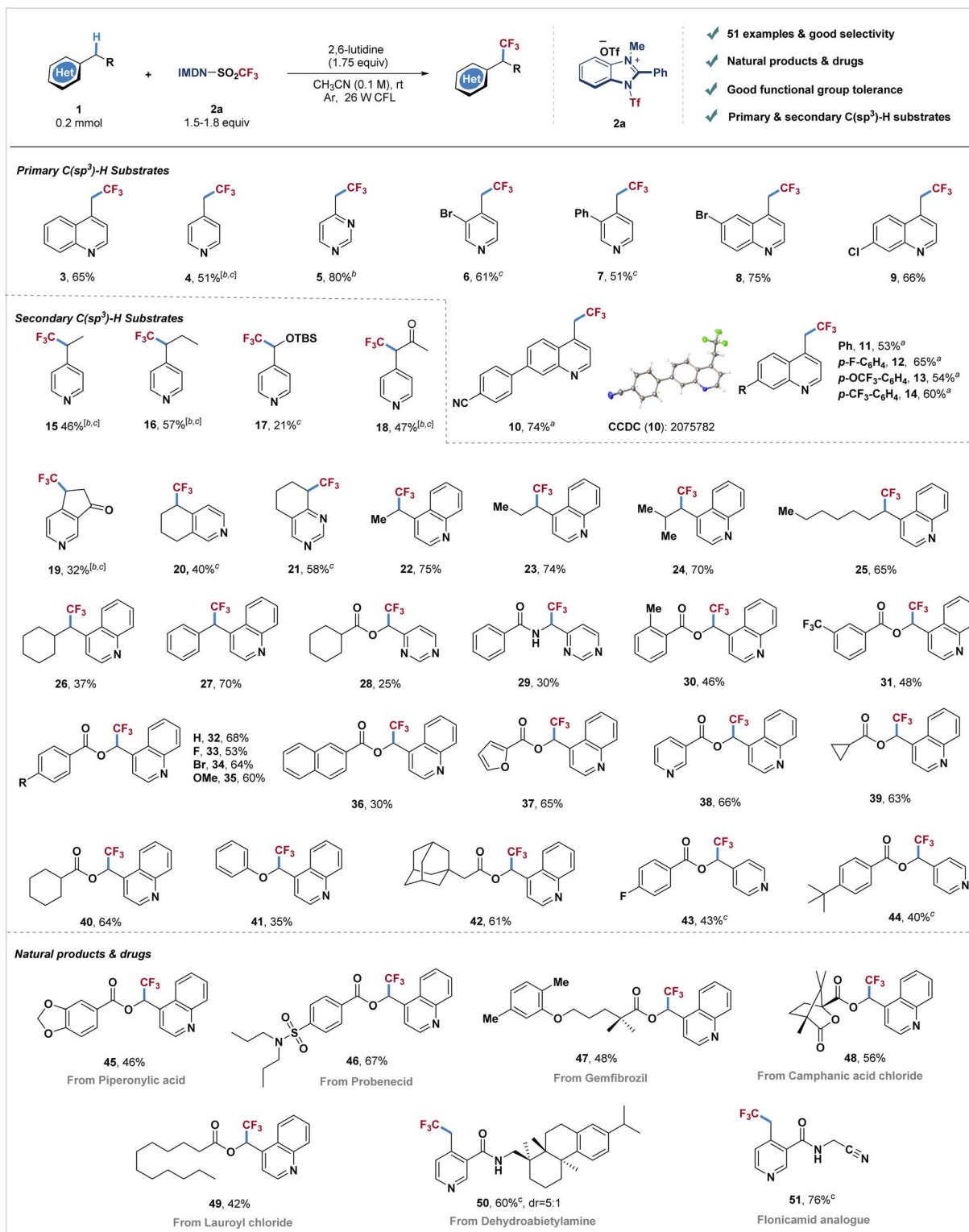
Pyridine derived ester substrates also have good compatibility, and the corresponding products (**43** and **44**) could be obtained in moderate yields. An attempt using more challenging ether substrates resulted in the desired product **41** in moderate yield. To further investigate the reaction scope, this catalyst-free photosynthesis has been applied to late-stage modification of C(sp<sup>3</sup>)-H bonds of azine-containing natural products. Piperonylic acid (**45**), probenecid (**46**), gemfibrozil (**47**), camphanic acid (**48**), lauroyl chloride (**49**) and dehydroabietylamine (**50**) could furnish the corresponding trifluoromethylated products in good yields (42–67%). The insecticide flonicamid analogue (**51**) was also afforded in 76% yield.

Difunctionalization of alkenes to incorporate two functional groups across a double bond has emerged as a powerful transformation to greatly increase molecular complexity in organic synthesis with improved efficiency. However, the Giese reaction involving the activation of electron-deficient heterobenzylic C(sp<sup>3</sup>)-H bonds and fluoroalkyl radical addition remains unexplored.<sup>48</sup> By varying the reaction conditions, this practical strategy has been applied to difunctionalization of  $\alpha,\beta$ -unsaturated olefins with the azinyl C(sp<sup>3</sup>)-H bond (Scheme 2). Several common electron-deficient  $\alpha,\beta$ -unsaturated olefins can participate in the reaction, and three-component coupling products (**52–61**) were obtained in moderate yields (34–60%). Additionally, trifluoromethyl radicals were successfully attached to unactivated olefins to afford fluoroalkylated product **56**. It is noteworthy that biorelevant molecules, such as diacetonefructose, paracetamol, picaridin, benzocaine, diacetone-*D*-glucose and epiandrosterone derived alkenes, afforded three-component coupled trifluoromethylated products in good yields (**63–68**).

To gain further insight into the mechanism of this direct trifluoromethylation of the heteroaryl adjacent C(sp<sup>3</sup>)-H bond, a series of control experiments have been carried out. The formation of the proposed Tf-transfer process and  $\pi$ - $\pi$  stacking effect between quinoline **1** and imidazolium reagent **2a** was monitored by UV/vis absorption spectroscopy. Compared to quinoline **1** and IMDN-Tf **2a**, a strong absorption peak of the mixture [**1** + **2a**] was observed at 280 nm (see ESI†). The treatment of imidazolium **2a** with substrates **1** and **70** furnished the key intermediates **69** and **72**, which were confirmed by GC-MS and X-ray crystallography (Scheme 3a and b). In addition, the optimization of the imidazolium sulfonate reagents **2a–2g** indicates that the activation of the C(sp<sup>3</sup>)-H bond is the key step involving the  $\pi$ - $\pi$  stacking interaction between intermediate **I** and 2-phenylimidazole. When three equivalents of TEMPO were added under standard conditions, the TEMPO adducts **73** and **74** were detected by <sup>19</sup>F NMR and HRMS (Scheme 3c). Furthermore, the treatment of **2a** with 4-benzylpyridine **75** afforded the trifluoromethylated product **76** in 17% yield and the dimerized byproduct **77** could be monitored by HRMS (Scheme 3d). These experimental results indicate that the intermediate **II** may result in a pair of CF<sub>3</sub> and benzyl radicals through the homolytic cleavage of the weak N-S bond.

DFT calculations have been conducted to better understand the mechanism of the overall reaction. The computed potential energy surface is shown in Scheme 4. Initially, the Tf group is

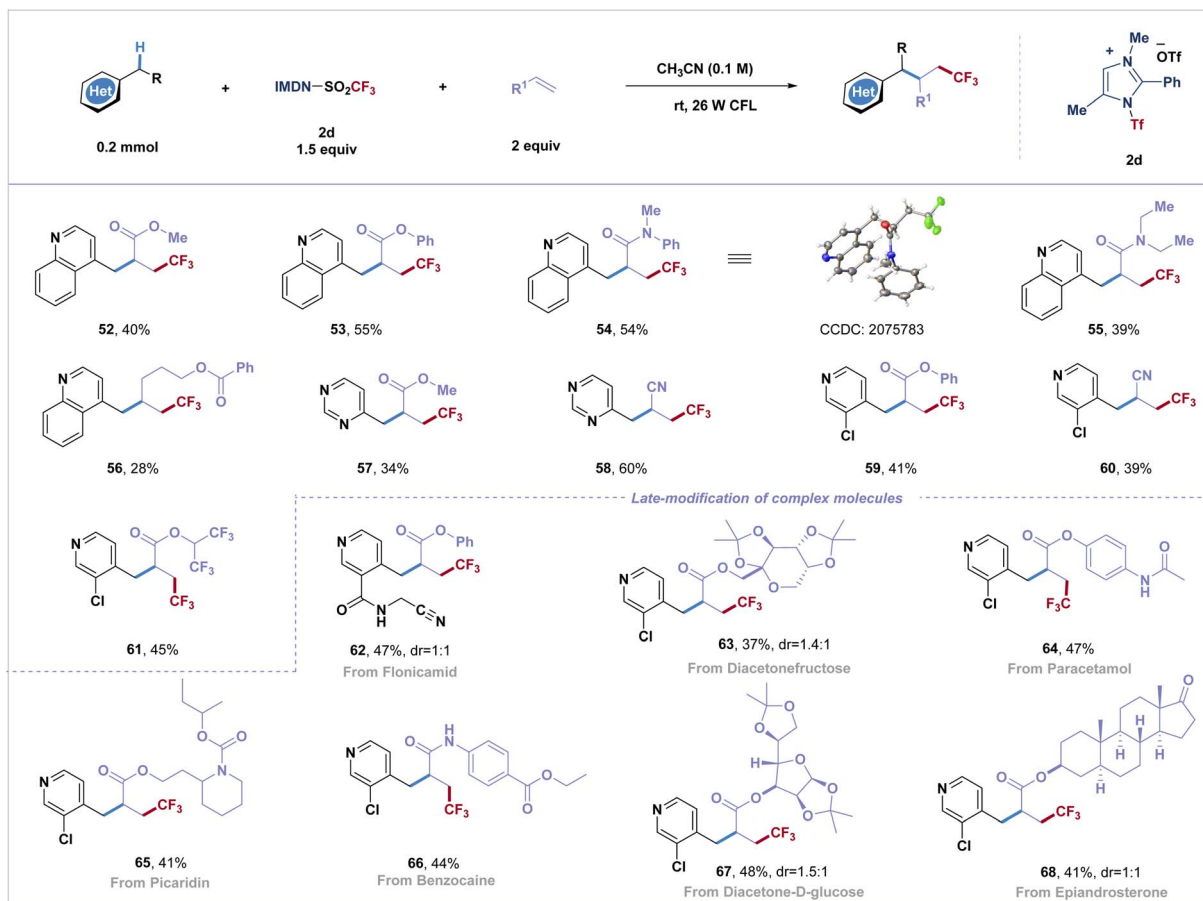




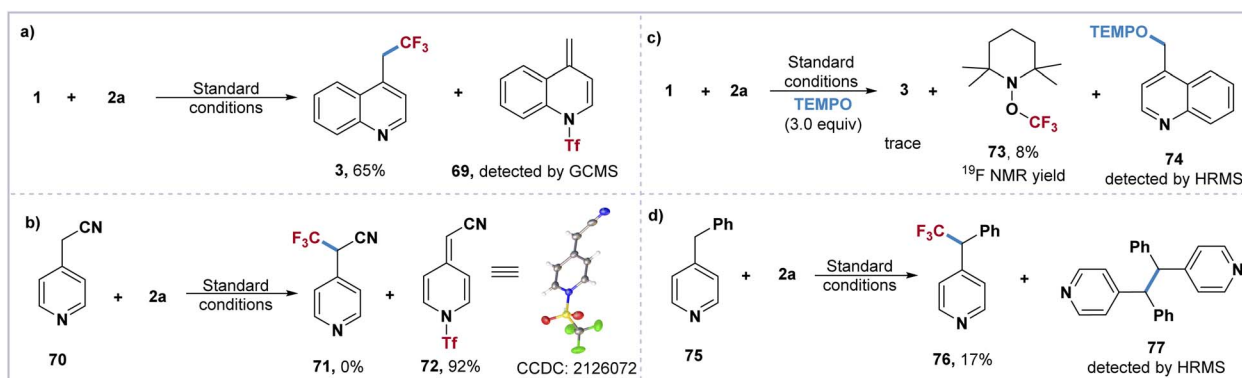
Scheme 1 Substrate scope of azinylic C(sp<sup>3</sup>)-H bond trifluoromethylation. <sup>a</sup>1.5 equiv. of IMDN-Tf 2a was used. <sup>b</sup>Yield determined by <sup>19</sup>F NMR spectroscopy using trifluoromethoxybenzene as the internal standard. <sup>c</sup>50 °C.

readily transferred from 2a to 4-methylquinoline 1 through a S<sub>N</sub>2 process via TS1, forming INT1 and benzimidazole INT2. Then INT1 is deprotonated by INT2 via TS2, with a barrier of 24.1 kcal mol<sup>-1</sup>, leading to protonated benzimidazole INT3 and

the dearomatized intermediate 69. The deprotonation process strongly depends on the imidazolium sulfonate reagent. In TS2, the π-π stacking between the electron-deficient aromatic ring of the substrate and the phenyl on imidazole is clearly observed



Scheme 2 Substrate scope of the three-component direct azinylic C(sp<sup>3</sup>)-H bond functionalization. All reactions were carried out with azines (0.2 mmol), alkenes (0.4 mmol, 2.0 equiv.), IMDN-Tf 2d (0.3 mmol, 1.5 equiv.) in MeCN (2.0 mL) under Ar and 26 W CFL about 12 h.



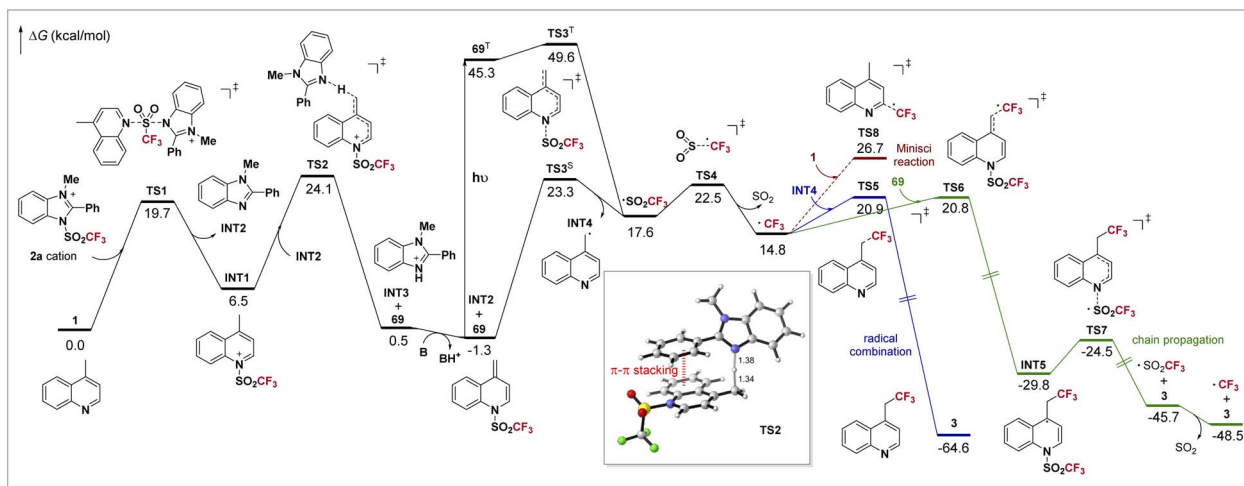
Scheme 3 Mechanistic studies. (a and b) Tf-shift intermediate verification experiment. (c and d) Radical trapping experiment.

(highlighted in red). Combined with our experiments, when the electron-rich 4-methoxyphenyl-containing **2b** gave a comparable yield with that using **2a** but the electron-poor 4-(trifluoromethyl)phenyl-bearing **2c** gave a much lower yield (Table 1), we believe that this non-covalent interaction is crucial to this step. For deprotonation using reagent **2f**, in which such  $\pi$ - $\pi$  stacking does not exist, it is found that an activation free energy as high as 27.3 kcal mol<sup>-1</sup> is required, too high for

a reaction occurring at room temperature (see ESI†), agreeing with the experiment. After the deprotonation, **INT3** further undergoes an acid-base reaction with 2,6-lutidine, which regenerates **INT2** and shifts the chemical equilibrium toward **69**. Now as the formation of **69** is slightly exergonic ( $\Delta G = -1.3$  kcal mol<sup>-1</sup>), it could be detected by GC-MS (Scheme 3a).

For the radical formation step, as the singlet-triplet gap of **69** (46.6 kcal mol<sup>-1</sup>) is well in range of the energy of visible light



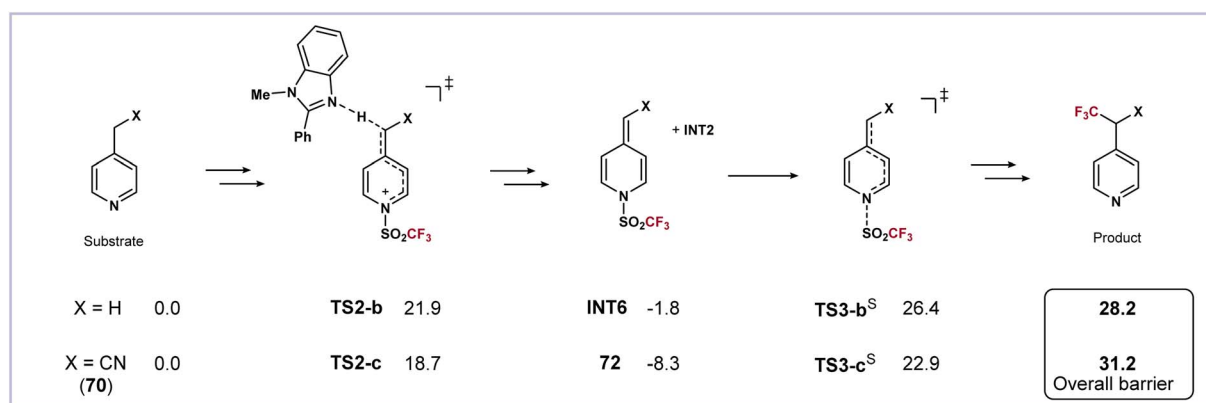


**Scheme 4** DFT study of the reaction mechanism. B = 2,6-lutidine. Relative Gibbs free energies (kcal mol<sup>-1</sup>) were computed with SMD(MeCN)-(U)M06-2X/6-311+G(2d,p)//SMD(MeCN)-(U)M06-2X/6-31G(d,p). S: singlet; T: triplet. All distances are in Å.

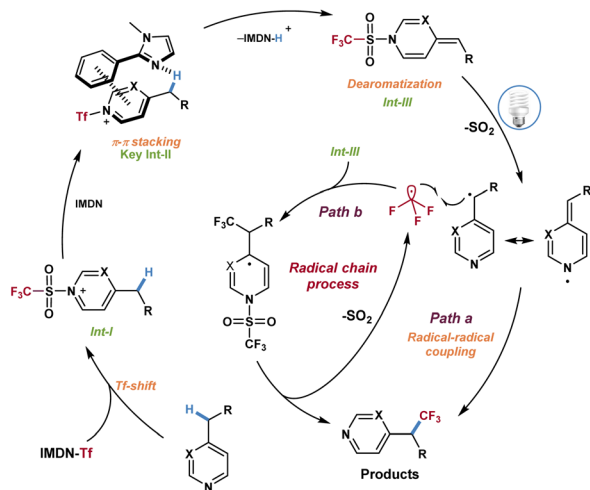
(when  $\lambda = 400$  nm,  $h\nu = 71.5$  kcal mol<sup>-1</sup>), **69** can be excited to its triplet state **69<sup>T</sup>** under irradiation of visible light, and then undergoes a facile homolysis *via* **TS3<sup>T</sup>**, forming **INT4** and Tf radicals. We find that the homolysis is also plausible under thermal conditions *via* **TS3<sup>S</sup>** with a barrier of 24.6 kcal mol<sup>-1</sup>, which is in accordance with a bit lower yield in the dark (entry 7, Table 1). The unstable Tf radical quickly dissociates *via* **TS4** to form the CF<sub>3</sub> radical. The involvement of these radical species agrees with our mechanistic experiments (Scheme 3c and d). The CF<sub>3</sub> radical may undergo a combination with **INT4** *via* **TS5**, yielding product **3** directly (blue line). Otherwise, a chain mechanism is also possible (green line). The CF<sub>3</sub> radical may attack intermediate **69** *via* **TS6** and forms **INT5**, which then undergoes N-S cleavage *via* **TS7** and gives **3** and the Tf radical. Finally, the decomposition of the Tf radical completes the chain propagation. Our calculations indicate that the barriers for both non-chain and chain mechanisms are almost identical. Furthermore, a quantum yield of 0.99 was observed (for details, see ESI<sup>†</sup>). Such results mean that both pathways contribute to

the product formation in our system, as the quantum yield should be far below 1.0 if only the non-chain mechanism is present,<sup>49</sup> and it should be far above 1.0 if the chain mechanism works exclusively.<sup>44,50</sup> In addition, the Minisci reaction resulting in C(sp<sup>2</sup>)-H trifluoromethylation was also documented,<sup>51</sup> which is possibly competitive in our system. However, the reaction between the CF<sub>3</sub> radical and **1** (red line, *via* **TS8**) has a barrier of 28.0 kcal mol<sup>-1</sup>, about 6.0 kcal mol<sup>-1</sup> higher than that of the desired C(sp<sup>3</sup>)-H trifluoromethylation. The exclusion of such side reaction ensures excellent regioselectivity in our reaction.

The computational results can also explain why the reaction of 4-(cyanomethyl)pyridine **70** gives a stable trifluoromethanesulfonyl transfer intermediate **72**. Energy profiles of **70** along with its analog, 4-methylpyridine, were calculated (Scheme 5). Both substrates have a faster deprotonation process than **1**. For 4-methylpyridine, the dearomatized intermediate **INT6** is slightly more stable than the substrate (-1.8 kcal mol<sup>-1</sup>). The subsequent homolysis *via* **TS3-b<sup>S</sup>** requires a slightly higher activation free energy of



**Scheme 5** DFT study on the reactions using 4-methylpyridine and 4-(cyanomethyl)pyridine (**70**) as substrates. Relative Gibbs free energies (kcal mol<sup>-1</sup>) were computed with SMD(MeCN)-(U)M06-2X/6-311+G(2d,p)//SMD(MeCN)-(U)M06-2X/6-31G(d,p). S: singlet.



Scheme 6 Proposed reaction mechanisms.

28.2 kcal mol<sup>-1</sup>, making it less reactive and need an elevated temperature (Scheme 1). On the other hand, owing to the conjugative effect of the cyano group, the intermediate **72** is especially stable (−8.3 kcal mol<sup>-1</sup>). The loss of such a favorable conjugation dramatically increases the difficulty in the next homolysis *via* **TS3-c<sup>s</sup>**. The computed overall barrier is as high as 31.2 kcal mol<sup>-1</sup>, showing that the following radical reactions could not proceed, and thus **72** was eventually isolated (Scheme 3b).

Based on the above investigations and DFT calculations, a plausible mechanism was proposed for this reaction (Scheme 6). First, intermediate **I** was formed in the presence of azines **1** and imidazolium sulfonate reagent **2a** through a Tf-shift process and dissociated out 2-phenylimidazole. Then the azinylic C(sp<sup>3</sup>)-H bond was activated by imidazole *via* π-π stacking interaction to generate the alkylidene dihydropyridine intermediate **III**. Under visible light irradiation, intermediate **III** produced the CF<sub>3</sub> radical and benzyl radical through the homolytic cleavage of the weak N-S bond and released SO<sub>2</sub>. Finally, the CF<sub>3</sub> radical and benzyl radical underwent a radical-radical coupling process to afford trifluoromethylated azines (Scheme 6, path a). Alternatively, the possibility of a chain reaction could not be excluded. The addition of CF<sub>3</sub> radicals to intermediate **III** and fragmentation resulted in the desired product and trifluoromethyl radicals to complete the mechanistic cycle (Scheme 6, path b).

## Experimental

### General procedure for the synthesis of products 3–51

Under argon, corresponding substrates (0.2 mmol) were added to a solution of **2a** (0.36 mmol, 1.8 equiv.) and 2,6-lutidine (0.35 mmol, 1.75 equiv.) in CH<sub>3</sub>CN (2 mL) at room temperature. After that, the tube was exposed to a 26 W compact fluorescent light at room temperature for about 2–12 h until the reaction was complete as monitored by TLC analysis. The reaction mixture was evaporated *in vacuo*. The crude products were

directly purified by flash chromatography on silica gel to give the desired product.

### General procedure for the synthesis of products 52–68

Under argon, corresponding substrates (0.2 mmol) were added to a solution of **2d** (0.3 mmol, 1.5 equiv.) and alkenes (0.4 mmol, 2 equiv.) in CH<sub>3</sub>CN (2 mL) at room temperature. After that, the tube was exposed to a 26 W compact fluorescent light at room temperature for about 12 h until the reaction was complete as monitored by TLC analysis. The reaction mixture was evaporated *in vacuo*. The crude products were directly purified by flash chromatography on silica gel to give the desired product.

## Conclusions

In summary, we have developed a Tf-transfer strategy for photoinduced direct trifluoromethylation of azinylic C(sp<sup>3</sup>)-H bonds with the imidazolium sulfonate cationic reagent IMDN-Tf. The unique electronic character of this bench-stable reagent enables rapid trifluoromethanesulfonyl transfer toward azines. Meanwhile, phenyl-substituted imidazole can also promote the benzylic deprotonation of azines due to the favorable π-π stacking effect. This incorporated C-H activating & trifluoromethylating reagent provides a practical toolbox for site-selective late-stage C(sp<sup>3</sup>)-H functionalization in an unconventional catalyst-free manner. Further investigation of this reagent is underway in the laboratory.

## Data availability

The data that support the findings of this study are available in the ESI† or on request from the corresponding author.

## Author contributions

M. H. conducted all experiments and characterized the novel compounds. Y. W. designed the experiments. Y. L. and J. M. conducted the computational studies. W. Z., Y. L., Y. W. wrote the manuscript. Y. P. was responsible for funding application. Z. Z., H. L., J. L. and L. K. contributed to the analysis and interpretation of the data.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

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## Notes and references

- 1 A. R. Katritzky, *Chem. Rev.*, 2004, **104**, 2125–2126.
- 2 E. Vitaku, D. T. Smith and J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, 10257–10274.
- 3 B. Zhao, B. Prabagar and Z. Shi, *Chem*, 2021, **7**, 2585–2634.
- 4 M. Kaur and J. F. V. Humbeck, *Org. Biomol. Chem.*, 2020, **18**, 606–617.
- 5 K. E. Danahy, J. C. Cooper and J. F. V. Humbeck, *Angew. Chem., Int. Ed.*, 2018, **57**, 5134–5138.
- 6 M. Meanwell, M. B. Nodwell, R. E. Martin and R. Britton, *Angew. Chem., Int. Ed.*, 2016, **55**, 13244–13248.
- 7 Y. Kuninobu, M. Nagase and M. Kanai, *Angew. Chem., Int. Ed.*, 2015, **54**, 10263–10266.
- 8 During the preparation of this manuscript, a report of C(sp<sup>3</sup>)-H functionalization using *N*-amidopyridinium salts and sodium fluoroalkylsulfinate has been published, see: M. Kim, E. You, J. Kim and S. Hong, *Angew. Chem., Int. Ed.*, **61**, e202204217, DOI: [10.1002/anie.202204217](https://doi.org/10.1002/anie.202204217).
- 9 Q. Liu, C. Zhang, H. Sheng, D. Enders, Z. Wang and X. Chen, *Org. Lett.*, 2020, **22**, 5617–5621.
- 10 B. Manteau, S. Pazenok and J.-P. Vors, *J. Fluorine Chem.*, 2014, **131**, 140–158.
- 11 T. Furuya, A. S. Kamlet and T. Ritter, *Nature*, 2011, **473**, 470–477.
- 12 S. M. Ametamey, M. Honer and P. A. Schubiger, *Chem. Rev.*, 2008, **108**, 1501–1516.
- 13 D. O'Hagan, *Chem. Soc. Rev.*, 2008, **37**, 308–319.
- 14 S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320–330.
- 15 P. Jeschke, *ChemBioChem*, 2004, **5**, 571–589.
- 16 K. Müller, C. Faeh and F. Diederich, *Science*, 2007, **317**, 1881–1886.
- 17 H. Yanai, S. Hoshikawa, Y. Moriiwa, A. Shoji, A. Yanagida and T. Matsumoto, *Angew. Chem., Int. Ed.*, 2021, **60**, 5168–5172.
- 18 E. J. McClain, T. M. Monos, M. Mori, J. W. Beatty and C. R. J. Stephenson, *ACS Catal.*, 2020, **10**, 12636–12641.
- 19 B. Yang, D. Yu, X.-H. Xu and F.-L. Qing, *ACS Catal.*, 2018, **8**, 2839–2843.
- 20 L. Li, X. Mu, W. Liu, Y. Wang, Z. Mi and C.-J. Li, *J. Am. Chem. Soc.*, 2016, **138**, 5809–5812.
- 21 D. J. W. Beatty, J. J. Douglas, R. Miller, R. C. McAtee, K. P. Cole and C. R. J. Stephenson, *Chem*, 2016, **1**, 456–472.
- 22 J. W. Beatty, J. J. Douglas, K. P. Cole and C. R. J. Stephenson, *Nat. Commun.*, 2015, **6**, 7919.
- 23 G. Choi, G. S. Lee, B. Park, D. Kim and S. H. Hong, *Angew. Chem., Int. Ed.*, 2021, **60**, 5467–5474.
- 24 J. He, T. N. Nguyen, S. Guo and S. P. Cook, *Org. Lett.*, 2021, **23**, 702–705.
- 25 M. Paeth, W. Carson, J. Luo, D. Tierney, Z. Cao, M. Cheng and W. Liu, *Chem. Eur. J.*, 2018, **24**, 11559–11563.
- 26 S. Guo, D. I. AbuSalim and S. P. Cook, *J. Am. Chem. Soc.*, 2018, **140**, 12378–12382.
- 27 H. Xiao, Z. Liu, H. Shen, B. Zhang, L. Zhu and C. Li, *Chem*, 2019, **5**, 940–949.
- 28 P. J. Sarver, V. Bacauanu, D. M. Schultz, D. A. DiRocco, Y. Lam, E. C. Sherer and D. W. C. MacMillan, *Nat. Chem.*, 2020, **12**, 459–467.
- 29 W. K. Hagmann, *J. Med. Chem.*, 2008, **51**, 4359–4369.
- 30 S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320–330.
- 31 J. Wang, M. Sanchez-Rosello, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok and H. Liu, *Chem. Rev.*, 2014, **114**, 2432–2506.
- 32 H. Komai, T. Yoshino, S. Matsunaga and M. Kanai, *Org. Lett.*, 2011, **13**, 1706–1709.
- 33 M. Rueping and N. Tolstoluzhsky, *Org. Lett.*, 2011, **13**, 1095–1097.
- 34 H. Suzuki, R. Igarashi, Y. Yamashita and S. Kobayashi, *Angew. Chem., Int. Ed.*, 2017, **56**, 4520–4524.
- 35 D. Zhai, X. Zhang, Y. Liu, L. Zheng and B. Guan, *Angew. Chem., Int. Ed.*, 2018, **57**, 1650–1653.
- 36 S. Duez, A. Steib, S. Manolikakes and P. Knochel, *Angew. Chem., Int. Ed.*, 2011, **50**, 7686–7690.
- 37 B. Qian, S. Guo, J. Shao, Q. Zhu, L. Yang, C. Xia and H. Huang, *J. Am. Chem. Soc.*, 2010, **132**, 3650–3651.
- 38 M. Joshi and F. Pigge, *ACS Catal.*, 2016, **6**, 4465–4469.
- 39 V. D. A. Nagib and D. W. C. MacMillan, *Nature*, 2011, **480**, 224–228.
- 40 A. G. O'Brien, A. Maruyama, Y. Inokuma, M. Fujita, P. S. Baran and D. G. Blackmond, *Angew. Chem., Int. Ed.*, 2014, **53**, 11868–11871.
- 41 Z. Zou, W. Zhang, Y. Wang and Y. Pan, *Org. Chem. Front.*, 2021, **8**, 2786–2798.
- 42 R. Vanjari and K. N. Singh, *Chem. Soc. Rev.*, 2015, **44**, 8062–8096.
- 43 E. W. Webb, J. B. Park, E. L. Cole, D. J. Donnelly, S. J. Bonacorsi, W. R. Ewing and A. G. Doyle, *J. Am. Chem. Soc.*, 2020, **142**, 9493–9500.
- 44 L. Yang, D. Tan, W. Fan, X. Liu, J. Wu, Z. Huang, Q. Li and H. Wang, *Angew. Chem., Int. Ed.*, 2021, **60**, 3454–3458.
- 45 W. Zhang, Z. Zou, W. Zhao, S. Lu, Z. Wu, M. Huang, X. Wang, Y. Wang, Y. Liang, Y. Zhu, Y. Zheng and Y. Pan, *Nat. Commun.*, 2020, **11**, 2572.
- 46 E. Kraka, D. Setiawan and D. Cremer, *J. Comput. Chem.*, 2016, **37**, 130–142.
- 47 Y. Ouyang, X.-H. Xu and F.-L. Qing, *Angew. Chem., Int. Ed.*, 2018, **57**, 6926–6929.
- 48 D. M. Kitcatt, S. Nicolle and A.-L. Lee, *Chem. Soc. Rev.*, 2022, **51**, 1415–1453.
- 49 H.-H. Zhang and S. Yu, *Org. Lett.*, 2019, **21**, 3711–3715.
- 50 Y. Zhang, H. Liu, L. Tang, H.-J. Tang, L. Wang, C. Zhu and C. Feng, *J. Am. Chem. Soc.*, 2018, **140**, 10695–10699.
- 51 Y. Fujiwara, J. A. Dixon, F. O'Hara, E. D. Funder, D. D. Dixon, R. A. Rodriguez, R. D. Baxter, B. Herlé, N. Sach, M. R. Collins, Y. Ishihara and P. S. Baran, *Nature*, 2012, **492**, 95–99.

