



# The merger of decatungstate and copper catalysis to enable aliphatic C(sp<sup>3</sup>)-H trifluoromethylation

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**The introduction of a trifluoromethyl (CF<sub>3</sub>) group can dramatically improve a compound's biological properties. Despite the well-established importance of trifluoromethylated compounds, general methods for the trifluoromethylation of alkyl C-H bonds remain elusive. Here we report the development of a dual-catalytic C(sp<sup>3</sup>)-H trifluoromethylation through the merger of light-driven, decatungstate-catalysed hydrogen atom transfer and copper catalysis. This metallaphotoredox methodology enables the direct conversion of both strong aliphatic and benzylic C-H bonds into the corresponding C(sp<sup>3</sup>)-CF<sub>3</sub> products in a single step using a bench-stable, commercially available trifluoromethylation reagent. The reaction requires only a single equivalent of substrate and proceeds with excellent selectivity for positions distal to unprotected amines. To demonstrate the utility of this new methodology for late-stage functionalization, we have directly derivatized a broad range of approved drugs and natural products to generate valuable trifluoromethylated analogues. Preliminary mechanistic experiments reveal that a 'Cu-CF<sub>3</sub>' species is formed during this process and the critical C(sp<sup>3</sup>)-CF<sub>3</sub> bond-forming step involves the copper catalyst.**

It has long been established that the incorporation of the trifluoromethyl (CF<sub>3</sub>) group into drug molecules can often improve their pharmacokinetic properties, including permeability, metabolic stability and protein binding affinities (Fig. 1a)<sup>1,2</sup>. As such, the development of general technologies that enable aryl and alkyl trifluoromethylation has become a major area of both industrial and academic research in recent years<sup>3,4</sup>. Significant efforts have focused on the direct conversion of C-H bonds to C-CF<sub>3</sub> bonds, which removes the need for prefunctionalization of drug intermediates and allows derivatization at carbon sites that lack traditional functional handles. To this end, aromatic C(sp<sup>2</sup>)-H trifluoromethylations via Minisci-type pathways have become widely utilized in a variety of contexts<sup>5,6</sup>; however, such methods are not amenable to aliphatic C(sp<sup>3</sup>)-H bond functionalization (Fig. 1b). Although C(sp<sup>3</sup>)-H trifluoromethylation protocols have been developed for allylic<sup>7,8</sup> and benzylic systems<sup>9–11</sup>, as well as substrates that incorporate Lewis basic directing groups<sup>12</sup>, there have been no reports so far of general methods for the non-directed C(sp<sup>3</sup>)-H trifluoromethylation of strong aliphatic C-H bonds. With this in mind, we recently sought to design a new, direct trifluoromethylation technology that allows the rapid synthesis of CF<sub>3</sub>-bearing fragments from simple feedstocks, as well as provides single-step access to trifluoromethyl analogues of pharmaceutically important molecules via late-stage functionalization.

Over the last five years, metallaphotoredox has emerged as a valuable catalysis platform that enables native functional groups, such as carboxylic acids and alcohols, to be employed as C(sp<sup>3</sup>)-coupling partners via the intermediacy of open-shell species<sup>13</sup>. Within this paradigm, a range of highly modular C-H functionalizations have also been developed by combining photoredox-mediated hydrogen atom transfer (HAT) with nickel-catalysed radical cross-coupling to deliver a series of aliphatic-arylation protocols<sup>14–17</sup>. Beyond nickel, a number of metallaphotoredox mechanisms have successfully employed copper as the coupling catalyst<sup>18</sup>, which, given its remarkable capacity for both radical capture<sup>19–21</sup> and traditionally difficult reductive elimination

steps<sup>22</sup>, has allowed the invention of robust methods for the synthesis of formerly elusive C(sp<sup>3</sup>)-N (ref. 23) and C(sp<sup>3</sup>)-CF<sub>3</sub> bonds<sup>24,25</sup>.

Inspired by these collective studies, we recently sought to combine copper catalysis with a strong C(sp<sup>3</sup>)-H bond-cleaving HAT catalyst in the presence of a suitable CF<sub>3</sub> radical source. Given the remarkable efficiency with which photoexcited decatungstate (\*[W<sub>10</sub>O<sub>32</sub>]<sup>4-</sup>) can cleave strong C-H bonds<sup>26,27</sup>, it is no surprise that this polyoxometallate has found broad application in a number of synthetically useful C(sp<sup>3</sup>)-H functionalizations<sup>28</sup>, including oxidations<sup>29,30</sup>, dehydrogenations<sup>31</sup>, fluorinations<sup>32</sup>, azidations<sup>33</sup> and conjugate additions<sup>34</sup>. Moreover, the highly electrophilic ligand-to-metal charge transfer excited state of decatungstate is known to engage aliphatic substrates with predictable selectivity for abstraction of the most sterically accessible, electron-rich C(sp<sup>3</sup>)-H bond<sup>35</sup>. Recently, our laboratory utilized this oxometallate HAT agent in the development of a nickel/decatungstate dual-catalytic C(sp<sup>3</sup>)-H arylation methodology, which demonstrates the potential to combine decatungstate photocatalysis with transition metal-catalysed cross-coupling<sup>36</sup>. Herein, we describe the first merger of decatungstate anion photochemistry with copper catalysis and introduce a new protocol for the direct trifluoromethylation of C(sp<sup>3</sup>)-H aliphatic substrates (Fig. 1c). To ensure utility in a medicinal chemistry setting, we sought to identify a dual catalysis platform that would tolerate a range of polar functional groups, such as unprotected amines and carboxylic acids<sup>37</sup>, while implementing a commercially available, bench-stable trifluoromethylation reagent. Perhaps as important, this methodology employs only a single equivalent of the C(sp<sup>3</sup>)-H-bearing substrate, an unusual and especially attractive feature for late-stage C-H functionalization of complex or medicinally relevant molecules.

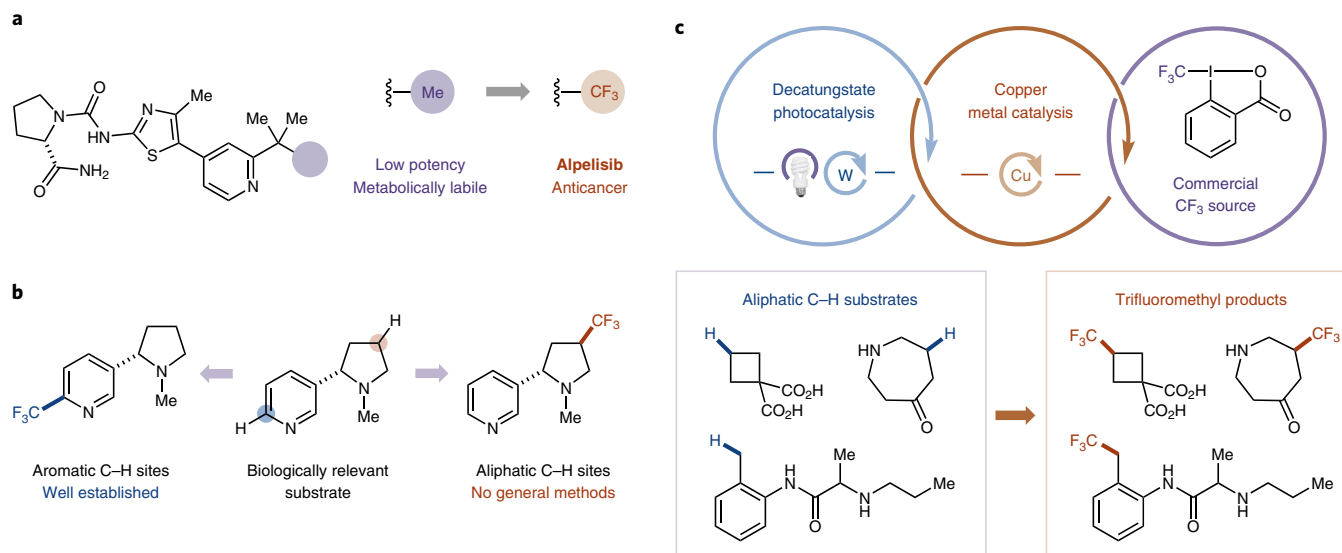
## Results and discussion

A detailed description of our reaction design is provided in Fig. 2. Photoexcitation of [W<sub>10</sub>O<sub>32</sub>]<sup>4-</sup> (**1**) was expected to afford the oxometallate excited state **2**. In the case of amine substrates such as

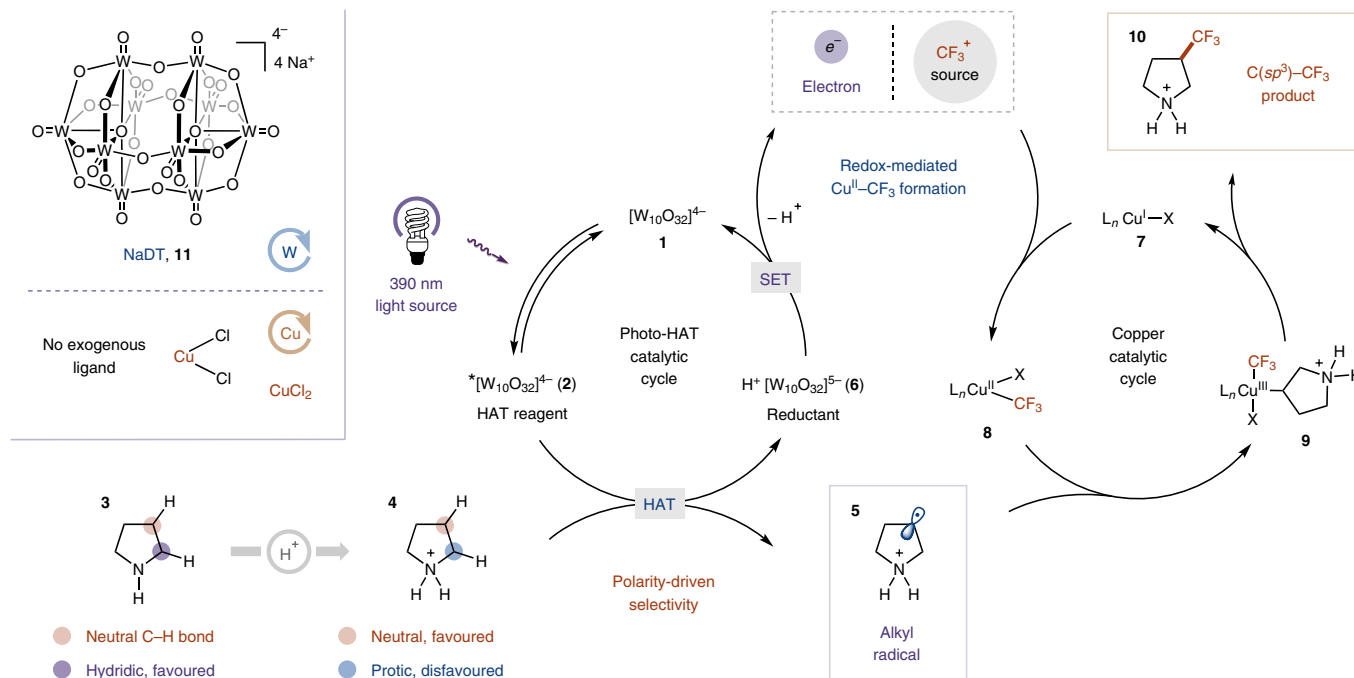
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**Fig. 1 | Dual decatungstate/copper metallaphotoredox catalysis enables direct C(sp<sup>3</sup>)-H trifluoromethylation.** Despite the broadly appreciated importance of trifluoromethylated compounds in the pharmaceutical industry, general catalytic methods for C(sp<sup>3</sup>)-H trifluoromethylation remain elusive. This transformation has now been achieved through the merger of decatungstate and copper metallaphotoredox catalysis. **a**, The synthesis of trifluoromethylated compounds has become an invaluable tool for the development of potent, metabolically stable pharmaceuticals, as demonstrated by the approved pharmaceutical alpelisib<sup>2</sup>. **b**, To enable more efficient syntheses of these valuable compounds, recent efforts have focused on the development of broadly applicable C–H trifluoromethylations. Despite significant progress in aryl C–H trifluoromethylation, no general catalytic methods for alkyl C–H trifluoromethylation have been developed. **c**, By combining decatungstate-catalysed HAT with copper catalysis, we have developed a broadly applicable C(sp<sup>3</sup>)-H trifluoromethylation of strong aliphatic and benzylic C–H bonds.



**Fig. 2 | Mechanistic design for direct C(sp<sup>3</sup>)-H trifluoromethylation via decatungstate and copper catalysis.** Excitation of decatungstate (**1**) with near-ultraviolet light affords highly reactive excited state **2**. Pyrrolidine (**3**), which is protonated under acidic reaction conditions to afford pyrrolidinium **4**, undergoes a subsequent HAT by **2** at the more electron-rich β-position to afford a reactive alkyl radical (**5**) and reduced decatungstate (**6**). Formal reduction of an electrophilic trifluoromethylation reagent by **6** in the presence of a copper(I) catalyst (**7**) generates a Cu(II)-CF<sub>3</sub> species (**8**), which can rapidly trap alkyl radical **5** to produce key alkyl-Cu(III)-CF<sub>3</sub> species **9**, which undergoes facile reductive elimination to regenerate the Cu(I) catalyst **7** and form C(sp<sup>3</sup>)-CF<sub>3</sub> product **10**.

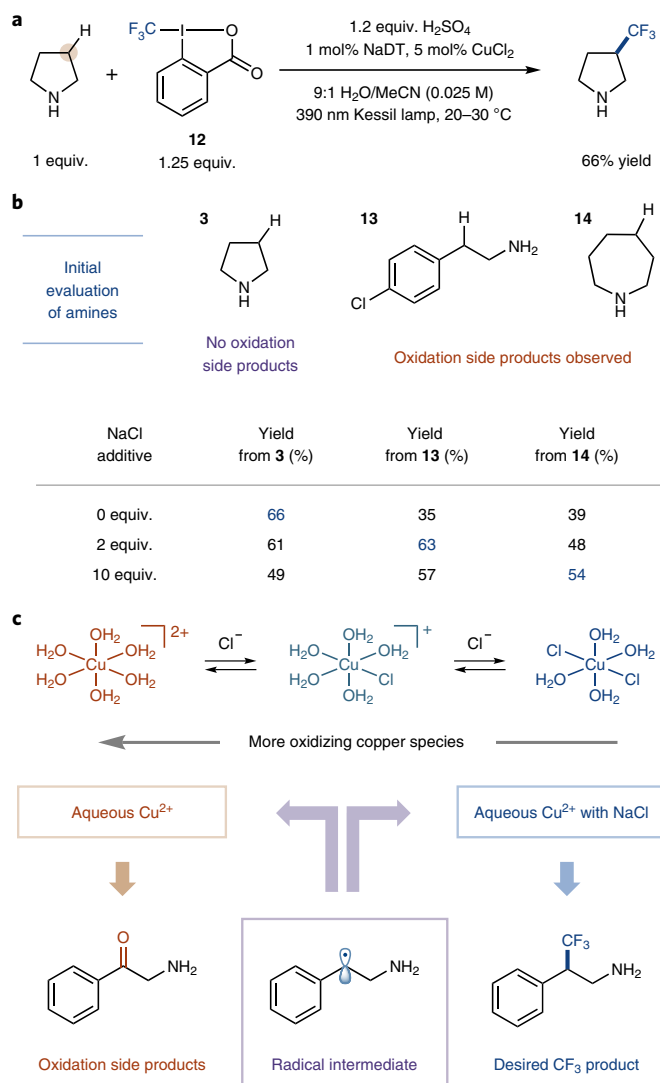
pyrrolidine (**3**), protonation of the basic nitrogen atom renders the adjacent hydrogen atoms both stronger and less hydric<sup>38</sup>, enabling reactivity at the traditionally less reactive distal position<sup>39–41</sup>.

This polarity modulation strategy has previously been implemented in the direct, distal oxidation of aliphatic amines to generate ketones in lieu of amide moieties<sup>29</sup>. Thus, subsequent HAT from the more

polarity-matched  $\beta$ -C( $sp^3$ )-H bond of pyrrolidinium **4** by electrophilic excited state decatungstate **2** would produce the alkyl radical **5** and the reduced decatungstate **6**. Formal reduction of an electrophilic CF<sub>3</sub> source by the ground-state polyoxometallate **6** in the presence of a Cu(I) catalyst (**7**) should then afford a Cu(II)-CF<sub>3</sub> intermediate (**8**) and regenerate the decatungstate anion (**1**) (Supplementary Fig. 25). At this stage, we assumed the copper(II)-CF<sub>3</sub> species **8** would capture the carbon-centred radical **5**<sup>42,43</sup> at near-diffusion rates to produce the critical alkyl-Cu(III)-CF<sub>3</sub> complex (**9**)<sup>20</sup>, which, upon reductive elimination, would afford the desired C( $sp^3$ )-CF<sub>3</sub> product **10** while regenerating the Cu(I) catalyst<sup>11,44</sup>. Computational studies support the feasibility of the radical capture and reductive elimination steps (Supplementary Section 10), although alternative mechanisms have not been ruled out at this time.

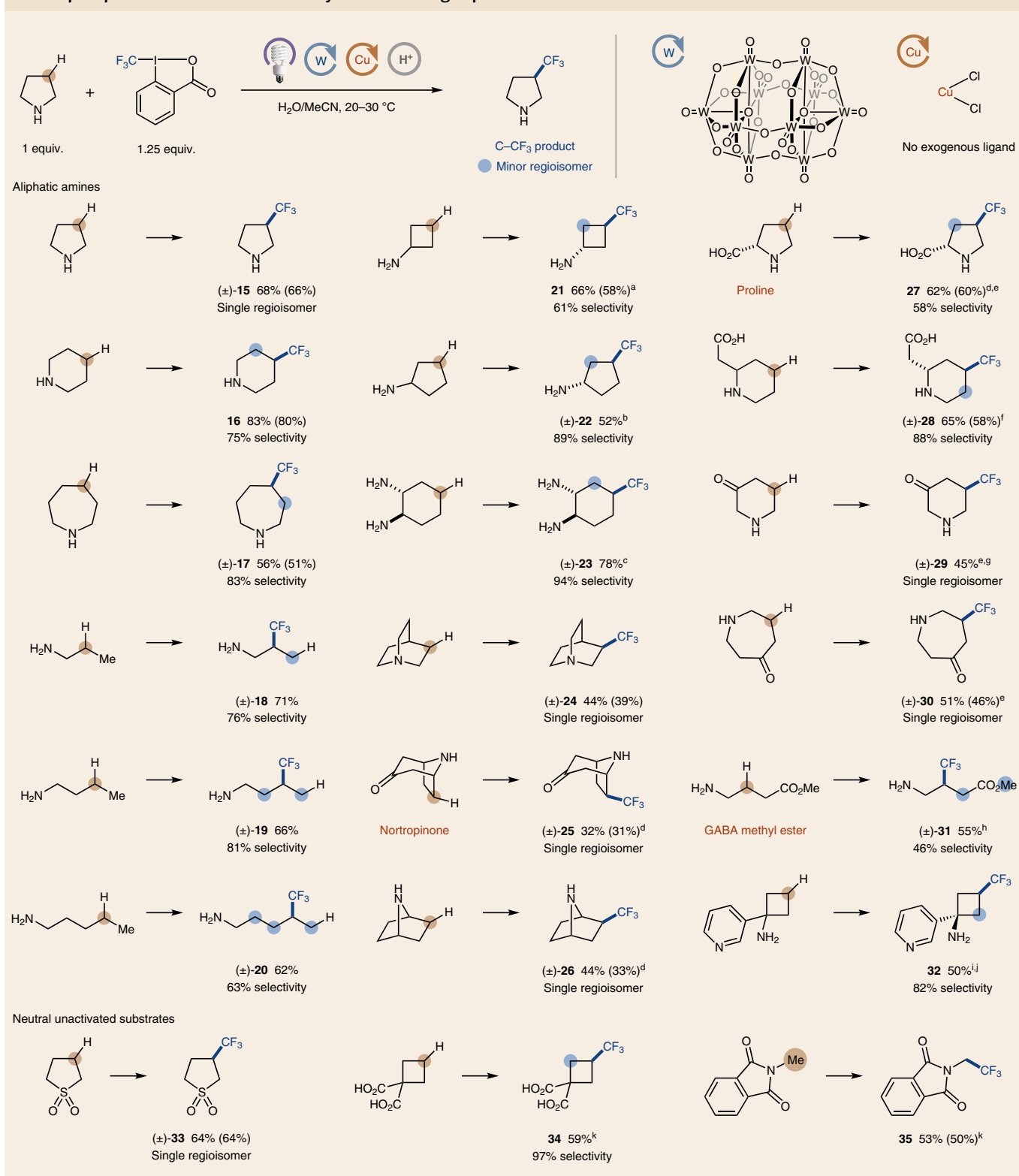
Preliminary studies into this new C-H trifluoromethylation reaction were performed with pyrrolidine, Togni reagent II (1.25 equiv., **12**)<sup>4</sup>, sodium decatungstate (1 mol%, **11**), a copper(II) chloride precatalyst (5 mol%), an acidic medium (1.2 equiv. H<sub>2</sub>SO<sub>4</sub>) of water/acetonitrile (90:10) and a Kessil 40 W 390 nm lamp to provide the desired  $\beta$ -CF<sub>3</sub> product in 66% yield as a single regioisomer (Fig. 3). Further investigations revealed a surprising finding for decatungstate chemistry: specifically that the presence of chloride anion (1–10 equiv.) can substantially improve the yield of this transformation for a number of substrate classes (vide infra). Control experiments highlighted that this trend is general for a broad range chloride sources, but specific to the chloride anion in lieu of other metal counterions (Supplementary Tables 13 and 14). Notably, this effect is not observed uniformly, as the presence of chloride was not found to be beneficial for pyrrolidine functionalization (possibly due to unproductive quenching of excited decatungstate<sup>45</sup>), and the reaction is competent with numerous other copper precatalysts (Supplementary Table 6). Although the precise origin of this effect remains under investigation, preliminary studies suggest that chloride anion alters the ligand sphere of copper under these reaction conditions. This proposal is supported by changes observed in the ultraviolet–vis spectrum of aqueous copper(II) chloride at reaction concentrations upon addition of sodium chloride (from predominantly Cu<sup>2+</sup> to CuCl<sup>+</sup> based on literature spectra in water<sup>46</sup>; Supplementary Figs. 14–17) and effects on diastereoselectivity that trend with chloride concentration (Supplementary Table 15). We presume that the presence of chloride should make the resulting copper ensemble less cationic, and therefore less oxidizing, a characteristic that would disfavor the formation of alkene or solvolysis products associated with the well-established oxidation of alkyl radicals by Cu(II) salts<sup>47,48</sup>. Our hypothesis finds further support in that the addition of sodium chloride (1–10 equiv.) substantially improves reaction efficiencies for substrates that can readily render oxidative byproducts such as ketones, alcohols and alkenes. An alternative hypothesis for the beneficial role of chloride ion is that the HAT step is mediated by chlorine radicals generated via oxidation by excited decatungstate. Although certainly plausible based on observed quenching rate constants<sup>45</sup>, efforts to mediate the reaction with chlorine radicals by replacing decatungstate with other oxidizing photocatalysts have thus far proven unsuccessful (Supplementary Table 16).

Given the importance of the amine moiety in biomedically relevant molecules and the unique HAT selectivity enabled by protonation at nitrogen, we first examined our reaction scope on a diverse set of alkyl amines (Table 1). Despite the wide range of C-H bond dissociation energies and bond polarities, our conditions proved general for a broad array of cyclic and linear amines, with good to excellent selectivities for trifluoromethylation at positions distal to the protonated nitrogen (**15**–**23**, 52–83% yield, 61 to >95% selectivity, defined as the percentage of the major regioisomer over all regioisomers). In the case of *n*-pentylamine (**20**, 62% yield), a 2.5:1 ratio of  $\delta$  to  $\gamma$  functionalization was observed, illustrating the decatungstate



**Fig. 3 | Effect of chloride anion on reaction efficiency.** During the course of optimization, the presence of chloride was found to dramatically affect reaction efficiency. See Supplementary Sections 4, 6 and 7 for experimental details and further discussion. **a**, Irradiating a solution of pyrrolidine and Togni reagent II (**12**) in acidic water/acetonitrile with near-ultraviolet light in the presence of catalytic sodium decatungstate and copper(II) chloride affords the desired 3-trifluoromethylpyrrolidine product in 66% analytical yield. **b**, Subsequent investigation of the reaction scope revealed a substrate-dependent effect of chloride anion concentration on the yield of this transformation. **c**, A potential mechanistic basis for this trend is the effect of chloride on the ligand sphere of copper. In the presence of chloride, a less oxidizing copper chloride species appears to produce fewer oxidative side products, resulting in improved reaction efficiency.

anion's ability to discriminate between hydrogen atoms three and four bonds away from an electron-withdrawing group. Moreover, *trans*-1,2-diaminocyclohexane, a common ligand scaffold<sup>49</sup>, was directly converted to the 4-trifluoromethylated product (**23**) in good yield (78%) and excellent selectivity (94%). This C-H trifluoromethylation methodology was further found to be applicable to a range of medically relevant bicyclic amines (**24**–**26**, 32–44% yield, single regioisomer in all cases). For example, nortropinone, a common scaffold in bioactive molecules<sup>50</sup>, was successfully functionalized to generate a single CF<sub>3</sub>-addition product (**25**, 32% yield). Notably, in cases for which the synthesis of the trifluoromethyl analogue was previously

**Table 1 | Scope of the direct trifluoromethylation of strong aliphatic C–H bonds**

All yields and selectivities were determined by <sup>19</sup>F NMR versus 2,2,2-trifluoroethanol (average of two trials). Isolated yields appear in parentheses. Selectivity is reported as the percentage of the major regioisomer over all regioisomers. 'Single regioisomer' refers to substrates for which >95% selectivity was observed. Volatile amines were isolated as the corresponding trifluoroacetate or chloride salt. Standard conditions: substrate (0.5 mmol, 1 equiv.), Togni reagent II (**12**, 1.25 equiv.), NaDT (1–3 mol%), CuCl<sub>2</sub> (5–10 mol%), H<sub>2</sub>SO<sub>4</sub> (0–2.5 equiv.), NaCl (0–10 equiv.), H<sub>2</sub>O/MeCN (9:1 to 1:1, 0.025 M), 8–12 h of irradiation with a Kessil 40 W 390 nm lamp at 20–30 °C. See Supplementary Section 15 for full experimental details. <sup>a</sup>1.5:1 d.r. (major), >20:1 d.r. (minor). <sup>b</sup>1.7:1 d.r. (major), >20:1 d.r. (minor). <sup>c</sup>1.2:1 d.r. (major), >20:1 d.r. (minor). <sup>d</sup>>20:1 d.r. (all regioisomers). <sup>e</sup>two additions of Togni reagent and NaDT. <sup>f</sup>1.3:1 d.r. (major), >20:1 d.r. (minor). <sup>g</sup>isolated and characterized following reduction with NaBH<sub>4</sub>. <sup>h</sup>3:1 substrate:Togni reagent (0.5 mmol). <sup>i</sup>2.5:1 d.r. (major), 1.7:1 d.r. (minor). <sup>j</sup>0.1 mmol scale. <sup>k</sup>20–25% CD<sub>3</sub>CN in H<sub>2</sub>O as solvent.

reported, the capacity to selectively engage the C–H bonds of simple, unprotected amines greatly improves the step efficiency relative to traditional functional group conversion protocols<sup>51,52</sup>.

Our subsequent studies focused on the direct trifluoromethylation of aliphatic amines that incorporate a wide array of functional groups that are often challenging in metal-mediated couplings.



For example, proline was directly engaged at positions distal to the protonated amine, generating CF<sub>3</sub>-bearing analogues in a single step and with excellent diastereoselectivity (**27**, 62% yield, 58% selectivity, >20:1 d.r.). The reaction's tolerance for carboxylic acids proved general, with **28** formed in good efficiency (65% yield) and excellent C–H abstraction selectivity (88%). The presence of other electron-withdrawing groups, including ketones and esters, further improved the regiocontrol of this transformation, enabling the synthesis of the corresponding trifluoromethyl adducts (**29–31**) in good yields (45–55%) and good to excellent selectivities (46 to >95%). For example, the methyl ester of  $\gamma$ -aminobutyric acid (GABA), an important neurotransmitter, was successfully engaged to afford **31** (55% yield, 46% selectivity), a notable result given the prevalence of lipophilic GABA analogues among approved drugs<sup>53</sup>. Additionally, a pyridine-bearing cyclobutylamine was successfully subjected to trifluoromethylation with excellent regioselectivity for the most electron-rich position (**32**, 50% yield, 82% selectivity), underscoring both the selectivity of our transformation and the broad tolerance for coordinating functional groups provided by the mildly acidic reaction medium.

A number of non-amine-bearing compounds were also competent substrates for this new CF<sub>3</sub>-installation technology (**33–35**, 53–64% yield, >95% selectivity), demonstrating that this protocol is also applicable to organic substrates, broadly defined. For example, both sulfolane and cyclobutane-1,1-dicarboxylic acid afforded the corresponding C(sp<sup>3</sup>)-CF<sub>3</sub> products with excellent regioselectivity, favouring the positions furthest from the electron-withdrawing groups (**33** and **34**, 64 and 59% yield, respectively). Implementation of *N*-methylphthalimide yielded the corresponding C–H trifluoromethylation product (**35**, 53% yield), indicating that our transformation can effectively functionalize electron-poor  $\alpha$ -heteroatom C–H bonds. It should be noted that more electron-rich  $\alpha$ -heteroatom positions are not successful using this protocol (Supplementary Fig. 45), presumably due to facile copper-mediated oxidation of the intermediate  $\alpha$ -amino or  $\alpha$ -oxy radical.

We next sought to evaluate the scope of this transformation with respect to substrates bearing benzylic C–H bonds, a common motif found among pharmaceutical agents. Given the metabolic lability of benzylic C–H bonds to cytochrome P450-mediated oxidation<sup>54</sup>, we envisioned that an operationally simple trifluoromethylation of such compounds would provide a useful tool for medicinal chemists. Furthermore, the lower bond dissociation energy of benzylic C–H bonds compared to alkyl C–H bonds should enable robust, predictable selectivity in late-stage functionalization. Fortunately, our methodology proved effective for a broad range of benzylic and heterobenzylic substrates, affording primary and secondary trifluoromethylation adducts with complete selectivity observed for the benzylic position (>20:1 regioisomeric ratio in all cases; Fig. 4a,b). Phenethylamines, an important class of neuroactive molecules<sup>55</sup>, provided the corresponding benzylic C–CF<sub>3</sub> products in good to high efficiency (**36–38**, 47–72% yield) and with complete preservation of enantiopurity in the case of (*S*)-1-aminoindane (**38**, >99% e.e.). Similarly, aliphatic systems bearing ester, chloride or acetoxy substituents were selectively converted to the benzylic trifluoromethyl analogues (**39–41**, 52–59% yield). A broad range of functional groups were also tolerated on the aryl ring, including ketones, esters, sulfonamides and tetrazoles (**42–45**, 65–77% yield). Notably, selectivity for the benzylic position was still observed when strongly electron-withdrawing groups were incorporated at the aryl *para* positions, suggesting that the polarity preference for electron-rich sites can be overridden by the bond dissociation energy differential between benzylic and primary C–H bonds. Moreover, an unsubstituted aniline, which would typically quench the excited state of a photocatalyst under basic or neutral conditions<sup>45</sup>, was efficiently functionalized at the benzylic position when an acidic medium was employed (**46**, 71% yield). Benzylic

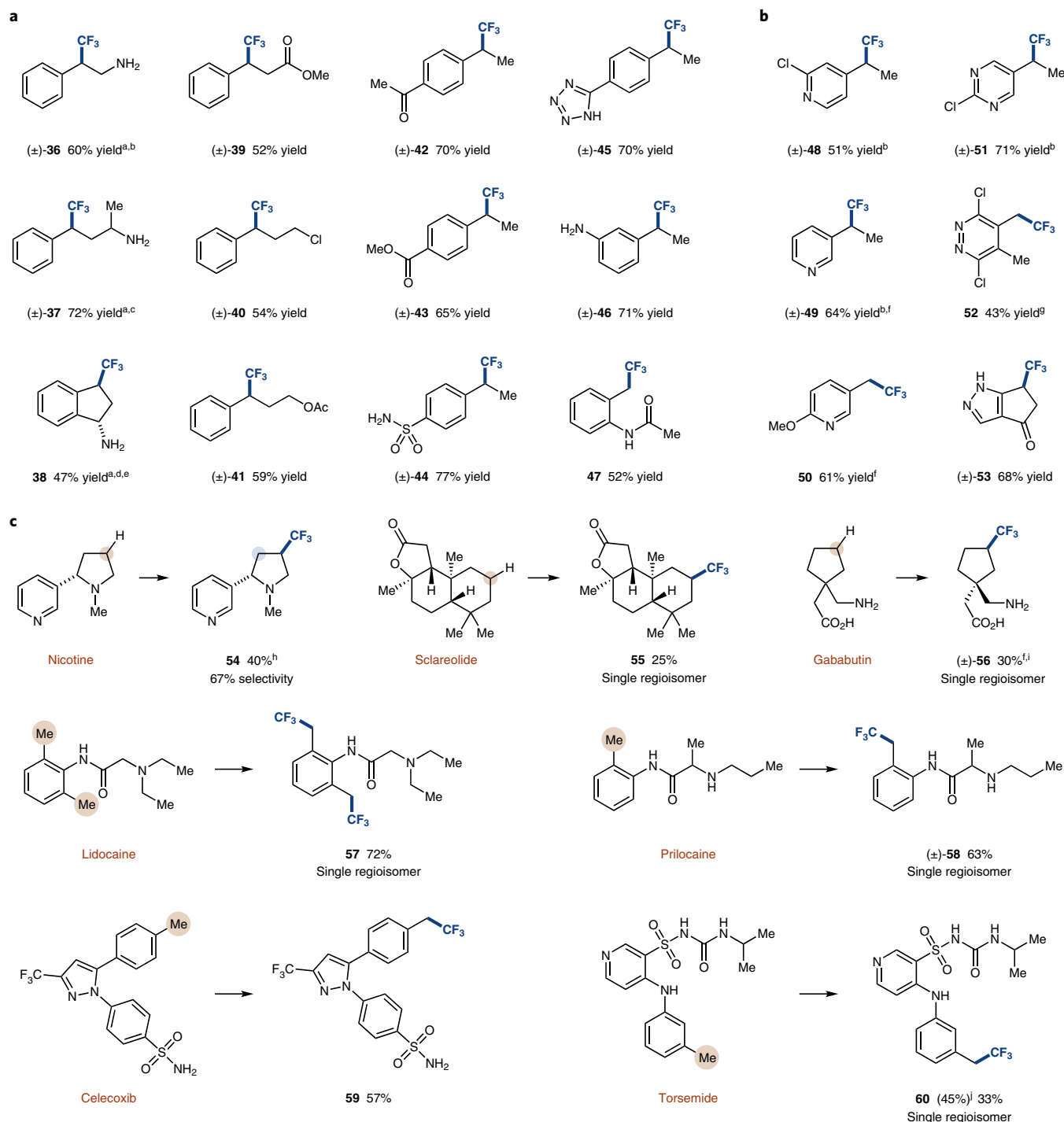
functionalization with *ortho*-substituted aryl systems was also possible to efficiently generate the CF<sub>3</sub>-adduct **47** from the corresponding toluene derivative (52% yield).

Next, investigations into medicinally relevant heterocyclic scaffolds demonstrated that a range of pyridines (**48–50**, 51–64% yield) can be employed to generate the corresponding C(sp<sup>3</sup>)-CF<sub>3</sub> adducts in good yields. Remarkably, electron-poor heteroarenes such as pyrimidines (**51**, 71% yield) and pyridazines (**52**, 43% yield) were also efficiently functionalized, highlighting the potency of decatungstate as a HAT catalyst, even in cases of electronically mismatched C–H abstraction. Five-membered heteroarenes were also competent under our protocol, as demonstrated by the trifluoromethylation of a bicyclic pyrazole (**53**, 68% yield).

Furthermore, we set out to demonstrate the applicability of this transformation to the late-stage functionalization of pharmaceuticals and natural products (Fig. 4c). For example, nicotine readily underwent trifluoromethylation at positions distal to the protonated amine and pyridine moieties to afford previously unreported analogues in a single step (**54**, 40% yield, 67% selectivity). In this case, selectivity was observed for the strong, electron-neutral C–H bonds over the  $\alpha$ -ammonium heterobenzylic position due to the high degree of polarity mismatch<sup>56</sup>. Sclareolide, a well-studied sesquiterpenoid, reacted to afford a single regio- and diastereoisomer (**55**, 25% yield). The gabapentin analogue gababutin<sup>53</sup> was directly trifluoromethylated with comprehensive regiocontrol to afford two diastereomeric derivatives, albeit in modest yield (**56**, 30% yield). For pharmaceuticals bearing benzylic C–H bonds less polarity-mismatched than those in nicotine, excellent selectivity was observed for benzylic functionalization (**57–60**, 33–72% yield). Moreover, lidocaine was successfully engaged at both benzylic positions to afford the *bis*-CF<sub>3</sub> analogue **57** (72% yield). Perhaps most notably, torsemide afforded the corresponding benzylic trifluoromethylation adduct (**60**, 33% yield), further highlighting the remarkable functional group tolerance and predictable selectivity of this new C(sp<sup>3</sup>)-CF<sub>3</sub> installation protocol.

Given the broad range of copper-catalysed reactions employing Togni reagent II but surprisingly limited mechanistic understanding of such transformations<sup>4</sup>, we concluded our studies by investigating the mechanism of this dual-catalytic system. Consistent with our mechanistic design (Fig. 2), these studies provide substantial evidence for a mechanism in which 'Cu–CF<sub>3</sub> complexes' are generated via the interaction of copper(I) with Togni reagent II, and that the copper catalyst is involved in the critical C(sp<sup>3</sup>)-CF<sub>3</sub> bond-forming step. Key components of this evidence include (1) the privileged nature of copper as a catalyst for this transformation; (2) the generation of Cu–CF<sub>3</sub> species via the reaction of copper(I) with Togni reagent II, the competency of these species in our transformation, and the observation of such species under reaction conditions; (3) the observation of enantioinduction and improvements to diastereoselectivity in the presence of a chiral ligand.

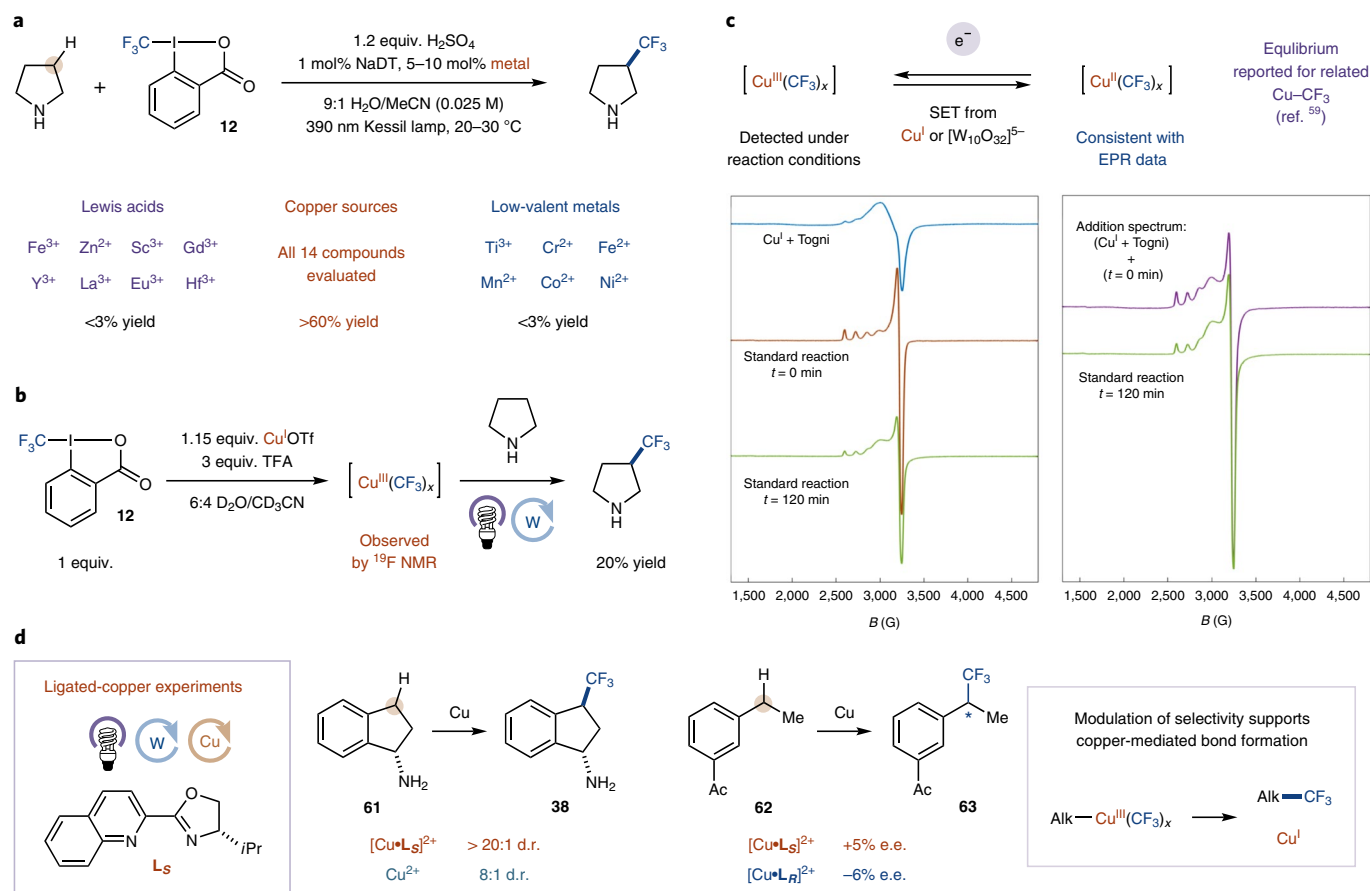
To elaborate, control experiments indicated that copper is unique in its effectiveness for this C(sp<sup>3</sup>)-H trifluoromethylation when compared to water-stable Lewis acids<sup>57</sup> or other metals known to reduce Togni reagent II (Fig. 5a and Supplementary Tables 9 and 10)<sup>4</sup>. These data suggest that copper probably plays a more significant role than merely single-electron reduction of Togni reagent II<sup>58</sup>, consistent with our mechanistic design invoking the generation of Cu(II)–CF<sub>3</sub>. In support of this hypothesis, the mixing of copper(I) triflate with Togni reagent II under reaction-relevant conditions was shown to generate a <sup>19</sup>F NMR-active Cu(III)–CF<sub>3</sub> species and a new electron paramagnetic resonance (EPR)-active copper(II) species (Fig. 5b,c). Based on the previously reported equilibrium between relevant Cu<sup>III</sup>- and Cu<sup>II</sup>-CF<sub>3</sub> complexes in the presence of copper(I)<sup>59</sup>, we attribute this new EPR signal to a species of the form Cu<sup>II</sup>(CF<sub>3</sub>)<sub>2</sub>; further studies into the exact structure of this copper complex are ongoing. Subsequent experiments conclusively demonstrate that



**Fig. 4 | Extension to benzylic C–H trifluoromethylation and application to natural products and pharmaceuticals.** This methodology was found to be applicable to a broad range of benzylic substrates, pharmaceuticals and natural products. Standard conditions: substrate (0.5 mmol, 1 equiv.), Togni reagent II (**12**, 1.25 equiv.), NaDT (1 mol%), CuCl<sub>2</sub> (5–10 mol%), H<sub>2</sub>SO<sub>4</sub> (0–1.5 equiv.), H<sub>2</sub>O/MeCN (9:1 to 1:1, 0.025 M), 12 h of irradiation with a Kessil 40 W 390 nm lamp at 20–30 °C. All yields are isolated unless otherwise noted. <sup>a</sup>Isolated as the chloride salt. <sup>b</sup>Performed with NaCl (1–10 equiv.). <sup>c</sup>1:1 d.r. <sup>d</sup>16:1 d.r. <sup>e</sup>Performed with Cu(OTf)<sub>2</sub> (Supplementary Table 15). <sup>f</sup>The <sup>19</sup>F NMR yield versus 2,2,2-trifluoroethanol. <sup>g</sup>20% CD<sub>3</sub>CN in H<sub>2</sub>O as solvent. <sup>h</sup>1.5:1 d.r. (major). <sup>i</sup>2.3:1 d.r. <sup>j</sup>2:1 substrate:Togni reagent. See Supplementary Section 15 for full experimental details. **a**, Compounds bearing benzylic C–H bonds are directly trifluoromethylated with excellent selectivity for the benzylic position in all cases. A diverse range of functionality on the aryl ring and alkyl chain is tolerated. **b**, Heterobenzylic substrates, including electron-poor pyridines and pyrimidines, were directly functionalized at the benzylic position. **c**, A diverse array of approved pharmaceuticals, bioactive compounds and natural products are directly trifluoromethylated to afford valuable C(sp<sup>3</sup>)–CF<sub>3</sub> analogues. Selectivity is reported as the percentage of the major regioisomer over all regioisomers. Blue circles denote sites where minor regioisomers are observed.

this ensemble of ‘Cu–CF<sub>3</sub>’ species is a competent replacement for the copper(II) chloride and trifluoromethyl source employed under the optimized conditions (Fig. 5b), indicating that such Cu–CF<sub>3</sub>

complexes are potentially catalytic intermediates. Subsequent spectroscopic investigations revealed that the aforementioned Cu<sup>III</sup>(CF<sub>3</sub>)<sub>x</sub> complex is also observed at partial conversion under the



**Fig. 5 | Mechanistic investigations into the role of copper.** Studies were conducted into the role of copper in this dual-catalytic transformation. **a**, Control experiments indicated that copper is unique in its effectiveness when compared with water-stable Lewis acids or other metals known to reduce Togni reagent II. **b**, Competent  $\text{Cu}-\text{CF}_3$  species are formed in stoichiometric experiments. The combination of Togni reagent II with copper(I) triflate under reaction-relevant conditions affords a mixture containing a  $\text{Cu}(\text{III})-\text{CF}_3$  complex observable by  $^{19}\text{F}$  NMR. This mixture was shown to be a competent replacement for the copper(II) chloride and trifluoromethyl source employed under our optimized reaction conditions. **c**, The same  $\text{Cu}(\text{III})(\text{CF}_3)_x$  species is also observed under standard reaction conditions and exists in equilibrium with an EPR-active copper(II) compound, provisionally assigned as  $\text{Cu}^{\text{I}}(\text{CF}_3)_x$  based on a reported equilibrium for a related  $\text{Cu}(\text{III})-\text{CF}_3$  species<sup>59</sup>. A simple linear combination of the EPR signal for solvated  $\text{Cu}^{2+}$  (standard reaction before irradiation) and the ‘ $\text{Cu}(\text{II})-\text{CF}_3$ ’ complex derived from the reaction of copper(I) with Togni reagent II shows excellent agreement with the spectrum for the standard reaction at partial conversion. **d**, Significant improvement in diastereoselectivity, as well as moderate but reproducible enantioinduction, is observed when employing an *i*Pr-QuinOx ligand ( $\text{L}_\text{S}$  or  $\text{L}_\text{R}$ , absolute stereochemistry indicated in subscript). The modulation of selectivity as a function of copper ligand environment supports a mechanism in which the bond-forming event is mediated by copper. Asterisk indicates the stereocentre at which enantioenrichment is observed.

standard  $\text{C}(\text{sp}^3)-\text{H}$  trifluoromethylation conditions (Supplementary Figs. 22 and 29), clearly indicating that  $\text{Cu}-\text{CF}_3$  complexes are present throughout the course of the reaction. Furthermore, the EPR signal previously assigned to  $\text{Cu}^{\text{III}}(\text{CF}_3)_x$  was shown to develop rapidly (<2 min; Supplementary Fig. 32) and remain constant during irradiation (Supplementary Fig. 33), as evidenced by the excellent fit of the partial conversion EPR spectrum provided by a simple linear combination of the spectrum prior to irradiation and the spectrum of the reaction of  $\text{Cu}(\text{OTf})$  with Togni reagent II (Fig. 5c). The loss of this signal upon reaction completion is again consistent with a mechanism involving a  $\text{Cu}-\text{CF}_3$  intermediate. Finally, and perhaps most compelling, a significant improvement in diastereoselectivity (from 8:1 to >20:1 d.r.) and reproducible enantioinduction (5–6% e.e.) were observed when employing a chiral QuinOx ligand<sup>60</sup> (Fig. 5d). These results reveal that copper is involved in the critical  $\text{C}(\text{sp}^3)-\text{CF}_3$  bond-forming process, consistent with the radical capture/reductive elimination sequence proposed in Fig. 2. In summary, these studies provide significant insight into the nature of the interaction between copper and Togni reagent II, definitive proof

of the existence of a reactive  $\text{Cu}-\text{CF}_3$  species under our standard conditions, and salient evidence that copper is involved in the key bond-forming step.

In summary, the merger of decatungstate photocatalysis with copper catalysis has enabled the development of a general  $\text{C}(\text{sp}^3)-\text{H}$  trifluoromethylation using a widely available  $\text{CF}_3$  source and requiring only a single equivalent of the  $\text{C}(\text{sp}^3)-\text{H}$ -bearing substrate. This method provides a valuable approach to biorelevant, synthetically challenging aliphatic trifluoromethyl compounds, as evidenced by its effective application to the direct  $\text{C}-\text{H}$  trifluoromethylation of natural products and medicinal agents. Mechanistic studies have provided evidence that  $\text{C}(\text{sp}^3)-\text{CF}_3$  bond formation is mediated by copper, a finding with significant implications for the broad field of copper-catalysed trifluoromethylations employing hypervalent iodine-based reagents. Furthermore, the successful development of a decatungstate/copper dual-catalytic transformation illustrates the generality of decatungstate metallaphotoredox catalysis, suggesting that this platform could enable a number of other elusive  $\text{C}(\text{sp}^3)-\text{H}$  engagement protocols.

## Online content

Any Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at <https://doi.org/10.1038/s41557-020-0436-1>.

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### Data availability

The data supporting the findings of this study are available within the article and its Supplementary Information.

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### Author contributions

P.J.S. and V.B. performed and analysed the experiments. P.J.S., V.B., D.M.S., D.A.D. and D.W.C.M. designed the experiments. Y.-h.L. and E.C.S. performed the computational analysis. P.J.S., V.B. and D.W.C.M. prepared the manuscript.

### Competing interests

The authors declare no competing interests.

### Additional information

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