Copper(I)-catalysed site-selective C(sp^3)–H bond chlorination of ketones, (E)-enones and alkylbenzenes by dichloramine-T

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Strategies that enable intermolecular site-selective C–H bond functionalisation of organic molecules provide one of the cornerstones of modern chemical synthesis. In chloroalkane synthesis, such methods for intermolecular site-selective aliphatic C–H bond chlorination have, however, remained conspicuously rare. Here, we present a copper(I)-catalysed synthetic method for the efficient site-selective C(sp^3)–H bond chlorination of ketones, (E)-enones and alkylbenzenes by dichloramine-T at room temperature. A key feature of the broad substrate scope is tolerance to unsaturation, which would normally pose an immense challenge in chemoselective aliphatic C–H bond functionalisation. By unlocking dichloramine-T’s potential as a chlorine radical atom source, the product site-selectivities achieved are among the most selective in alkane functionalisation and should find widespread utility in chemical synthesis. This is exemplified by the late-stage site-selective modification of a number of natural products and bioactive compounds, and gram-scale preparation and formal synthesis of two drug molecules.
**Results and discussion**

**Reaction development.** Our studies began by examining the transition metal-catalysed $\text{C}(sp^3)$–H bond chlorination of 4-methyl-1-phenylpentanone (1a) with dichloramine-T to determine the optimum reaction conditions (Table 1). This revealed that subjecting the ketone and chlorinating agent (1.5 equiv.) to 10 mol% of CuOTf, NaHCO$_3$ (1.5 equiv.) and 4 Å molecular sieves (MS) in acetone at room temperature for 24 h gave the best result (entry 1). Under these reaction conditions, this provided 4-chloro-4-methyl-1-phenylpentanone (2a) in a 78% yield. The structure of the organochloride adduct was determined by comparison with the NMR measurements and X-ray crystallography of a closely related analogue vide infra. A survey of other copper catalysts showed the performance of Cu(OTf)$_2$ or Cu(OAc)$_2$ in place of CuOTf afforded comparable $^1$H NMR yields of 74 and 72% (entries 7 and 8). Lower $^1$H NMR yields of 50–65% were found on the repeating the reaction at a lower catalytic loading of 5 mol% of CuOTf or with CuOAc, Cu(TC), [Cu(MeCN)$_2$][PF$_6$], Cu(HETBA) or Cu as the catalyst (entries 2–6 and 9). Comparable $^1$H NMR yields of 45 and 50% were observed on examining the transition metal complexes Rh$_2$(OAc)$_4$ or [Ir(COD)Cl]$_2$ instead of CuOTf as the catalyst (entries 19 and 21). In contrast, the analogous control reactions mediated by either Pd(OAc)$_2$ or FeCl$_3$ were observed to lead to the recovery of the substrate in near quantitative yield (entries 18 and 20). Similarly, control experiments in the absence of the catalyst, or mediated by CuOTf and with NaOAc or Et$_3$N instead of NaHCO$_3$ as the base, were found to lead to the recovery of the substrate in near quantitative yield (entries 10, 15 and 16). On the other hand, the analogous CuOTf-catalysed experiments at a higher reaction concentration of 0.3 or 0.4 M, or where NaHCO$_3$ was absent or replaced by Na$_2$CO$_3$ or K$_2$PO$_4$ as the base were shown to provide $^1$H NMR yields of 51–80% (entries 11–14 and 17).
In addition to the control experiments described in Table 1, the CuOTf-catalysed chlorination of 1a by dichloramine-T under the various reaction conditions described in Supplementary Table 1 were examined. Along with NaHCO₃ (1.5 equiv.) and 4 Å MS in acetonitrile at room temperature for 24 h, this showed the introduction of 10 mol % of 2,2′-bipyridine, 1,10-phenanthroline, (3aS,8aR)-in-pybox or Xantphos as a ligand to the reaction conditions led to the recovery of only the substrate (entries 1–4). A similar outcome was observed on changing the chlorinating agent from dichloramine-T to chloramine-T, NaOCl, NCS, DCDMH (1,3-dichloro-5,5-dimethylhydantoin) or TCCA (trichloroisocyanuric acid) (entries 5–9). In a final set of control reactions, an evaluation of different reaction solvents showed control experiments with acetonitrile replaced by methanol, tetrahydrofuran, 1,3-dioxane, nitromethane, dichloromethane, or toluene also resulted in no reaction (entries 10–15). The only exceptions were the analogous control experiments with benzonitrile as the solvent, or in acetonitrile in the absence of 4 Å MS, which gave 1H NMR yields of 41 and 48% (entries 16 and 17).

**Substrate scope and utility.** To determine the generality of the present site-selective chlorination procedure, the reactions of a series of ketones containing a secondary or tertiary γ-carbon centre were first evaluated, and the results are summarised in Fig. 2a. Overall, these experiments demonstrated the CuOTf-catalysed reaction conditions to be broad, providing a variety of γ-chloroketone derivatives in 40–83% yield from the corresponding carbonyl compounds 1b–x. Reactions of substrates containing a phenyl motif with electron-donating (1b, 1c, 1f and 1g) or -withdrawing (1d, 1e, 1h and 1i) groups at various positions of the ring or phenanthrenyl (1j) group were found to proceed well. In these experiments, the corresponding γ-chloroketones 2b–j were

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Table 1 Optimisation of the reaction conditions.

| Entry | [M] | Base | Yield (%)a |
|-------|-----|------|------------|
| 1     | CuOTf | NaHCO3 | 81 (78)b |
| 2     | CuOTf | NaHCO3 | 65        |
| 3     | CuOAc | NaHCO3 | 65        |
| 4     | Cu(TC) | NaHCO3 | 50        |
| 5     | Cu(MeCN)2IPF6 | NaHCO3 | 67        |
| 6     | Cu | NaHCO3 | 64        |
| 7     | CuOTf | NaHCO3 | 74        |
| 8     | CuOAc2 | NaHCO3 | 72        |
| 9     | Cu(HETBA) | NaHCO3 | 64        |
| 10   | CuOTf | NaHCO3 | 66        |
| 11   | CuOTf | K2PO4 | 76        |
| 12   | CuOTf | Na2CO3 | 75        |
| 13   | CuOTf | NaHCO3 | 80        |
| 14   | CuOTf | NaHCO3 | 51        |
| 15   | CuOTf | NaOAc | -e        |
| 16   | CuOTf | Et3N | -e        |
| 17   | CuOTf | h | 68        |
| 18   | FeCl3 | NaHCO3 | -e        |
| 19   | Rh2(OAc)4 | NaHCO3 | 45        |
| 20   | Pd(OAc)2 | NaHCO3 | -e        |
| 21   | [Ir(COD)Cl]2 | NaHCO3 | 50        |

All reactions were performed with 1a (35.3 mg, 0.2 mmol) and TcNCl2 (72 mg, 0.3 mmol) in the presence of the metal complex (0.02 mmol), 4 Å MS (50 mg), base (0.3 mmol) in acetonitrile (1 mL, 0.2 M) at room temperature for 24 h.

*aCruel yield of 2a as determined by 1H NMR measurements with dibromomethane as the internal standard.

*bReactions performed at a catalyst loading of 5 mol %.

*cReaction performed in the absence of a catalyst.

*dReactions performed in 0.75 mL (0.3 M) of acetonitrile.

*eReactions performed in the absence of a base.

*fReactions performed in 0.5 mL (0.4 M) of acetonitrile.

-gReactions performed in the absence of a base.

-hReactions performed at a catalyst loading of 5 mol %.

-iReactions performed in the absence of a catalyst.

-jReactions performed in 0.75 mL (0.3 M) of acetonitrile.

-kReactions performed in the absence of a base.

-lReactions performed in 0.5 mL (0.4 M) of acetonitrile.

-mReactions performed in the absence of a base.

-nReactions performed in 0.75 mL (0.3 M) of acetonitrile.

-oReactions performed in the absence of a catalyst.

-pReactions performed in 0.75 mL (0.3 M) of acetonitrile.

-qReactions performed in the absence of a base.

-rReactions performed in 0.75 mL (0.3 M) of acetonitrile.

-sReactions performed in the absence of a base.

-tReactions performed in 0.75 mL (0.3 M) of acetonitrile.

-uReactions performed in the absence of a base.

-vReactions performed in 0.75 mL (0.3 M) of acetonitrile.

-wReactions performed in the absence of a base.

-xReactions performed in 0.75 mL (0.3 M) of acetonitrile.

-yReactions performed in the absence of a base.

-Containing various electron-donating (α- and β-) substituents, the corresponding (-E)-aryl chlorides 4b-f were obtained in yields of 63–83%. Likewise, substrates with a pendant 2-naphthyl ester (3g) or 2-thienyl (3h) group in place of the phenyl moiety were shown to proceed well, delivering the corresponding γ-chlorination products 4g and 4h in 38 and 37% yield, respectively. Reactions of (E)-phenylvinyl ketones containing a gem-dialky1 (3a, 3l and 3j) or cyclohexyl (3k) motif were similarly found to afford (E)-γ-chloroenones 4a and 4i-k in 62–89% yield with the structure of 4k confirmed by X-ray crystallography (Supplementary Fig. 11). We were equally pleased to find that the reaction of toluene (5a) and derivatives of the compound (5b-d) gave the corresponding α-chlorinated adducts (6a-d) in 52–71% yield (Fig. 2c). A similar outcome was found for the transformations of alkylbenzenes containing a p-ketone, -ester or -Weinreb amide moiety, as in 5e-j, as well as α-indanone (5k) and α-tetralone (5l). In our hands, these reactions furnished the corresponding α-aryl chloride products (6e-l) in 60–90% yield. The assembly of 6f is particularly noteworthy as it is a reported key intermediate in the synthesis of a potent MCHR1 antagonist57. Its gram-scale preparation by the present method thus represents a formal synthesis of the bioactive compound. Added to this is the transformation to the non-peptide δ-opioid agonist 7 in 96% yield when treated with N-Boc-piperazone under base-mediated reaction conditions56.

The late-stage modification of natural products and drug molecules represent an efficient strategy for the facile synthesis of compounds with natural-product-like core structures in phenotype-based drug discovery programmes. With this in mind and as part of the study to define the synthetic utility of the present site-selective Cu(I)-catalysed C(sp3)–H bond chlorination procedure, its application to the late-stage modification of a variety of targets illustrated in Fig. 2d were examined. This showed that we were able to deconstruct and site-selectively chlorinate a member of the 4-pyridyl ketone family of tetrameric carbonyl reductase inhibitors, l-leucine, ibuprofen and the retinoic acid receptor morphogen retinoic acid to give the anticipated chlorinated products 8–11 in 50–85% yield. Equally, the analogous reactions with the antimicrobial and antifungal ligand camphamic acid, mixed dyslipidemia suppressant fenofibric acid and musk fragrance celestolide were found to produce the corresponding chloride derivatives 12–14 in 40–97% yield. Considered together, all the above-examined chlorination reactions demonstrated that the C(sp3)–Cl bond-forming process occurs in a highly selective manner. No other regioisomers or di- or trichlorinated adducts of the product resulting from an unselective or successive C(sp3)–Cl bond formation pathway were detected by 1H NMR analysis of the crude reaction mixtures. As highlighted in Fig. 2a, b, this not only included ketones 1b, 1c, 1f, 1g, 1p, 1q, 1w and 1x, and (E)-enones 3b, 3c, 3f and 3h containing either or both a benzyl and electron-rich aryl C–H bond9–23. In the case of experiments involving (E)-enones, the possible formation of compounds due to competitive alken eamination, aziridination, chloroamination or chlorination were likewise not observed by 1H NMR analysis of the crude reaction mixtures.

Mechanistic studies. To gain a better understanding of the possible mechanism of the Cu(I)-catalysed chlorination reaction, the following control experiments were performed (Fig. 3). In the first set of control experiments, subjecting 1a and a stoichiometric amount of TEMPO or BHT to the CuOTf-catalysed reaction conditions depicted in Fig. 3a was found, in both cases, to lead to the formation of a mixture of unidentified decomposition products based on GC and 1H NMR measurements of the crude reaction mixture.
The recovery of the substrate in near quantitative yield. Suggesting the possibility of a radical pathway, this was further corroborated by a CuOTf-catalysed radical clock experiment with the cyclopropyl-substituted (E)-ene 3l, which was found to result in complete substrate consumption (Fig. 3b). While the anticipated 1,3-chlorodiene adduct 15 could not be isolated by flash column chromatography as it was found to be too unstable, its presence in the crude reaction mixture was detected by HRMS measurements. Despite the mechanism for the cyclopropyl ring-opening of 3l currently remaining unclear, one possibility could involve a γ-H⁺ atom abstraction/vinylcyclopropane-type rearrangement/dichlorination/dehydrohalogenation cascade to provide 1,3-chlorodiene 15. The role of the carbonyl functionality in the ketone substrate in facilitating deactivation of the α- and β-positions of the alkyl side-chain was shown by control experiments with the ketone 1y, alkylbenzene 5m and alcohol 17 (Fig. 3c–e). Under the CuOTf-catalysed optimised reaction conditions, this led to either the recovery of the substrate in near

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**Fig. 2 Scope and synthetic applications of the CuOTf-catalysed site-selective C(sp³)-H bond chlorination reaction.**

- **a** γ-Chlorination of ketones
- **b** γ-Chlorination of enones
- **c** α-Chlorination of alkylbenzenes
- **d** Site-selective chlorination of natural products and drug molecules

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**Notes:**
- Reaction performed with 20 mol % of CuOTf and 0.6 mmol of dichloramine-T for 48 h. Under the CuOTf-catalysed optimised reaction conditions, this led to either the recovery of the substrate in near quantitative yield. Suggesting the possibility of a radical pathway, this was further corroborated by a CuOTf-catalysed radical clock experiment with the cyclopropyl-substituted (E)-ene 3l, which was found to result in complete substrate consumption (Fig. 3b). While the anticipated 1,3-chlorodiene adduct 15 could not be isolated by flash column chromatography as it was found to be too unstable, its presence in the crude reaction mixture was detected by HRMS measurements. Despite the mechanism for the cyclopropyl ring-opening of 3l currently remaining unclear, one possibility could involve a γ-H⁺ atom abstraction/vinylcyclopropane-type rearrangement/dichlorination/dehydrohalogenation cascade to provide 1,3-chlorodiene 15. The role of the carbonyl functionality in the ketone substrate in facilitating deactivation of the α- and β-positions of the alkyl side-chain was shown by control experiments with the ketone 1y, alkylbenzene 5m and alcohol 17 (Fig. 3c–e). Under the CuOTf-catalysed optimised reaction conditions, this led to either the recovery of the substrate in near quantitative yield.
Fig. 3 Control experiments. a Influence of the radical scavengers TEMPO and BHT on the reaction of 1a. b Radical clock experiment with 3l.
c-e Determining the role of the carbonyl functionality in the substrate with reactions of 1y, 5m and 17. f Determining the possibility of a \( \alpha \)-HAT reaction/1,3-H* atom shift pathway with the reaction of \( d_2 \). g KIE measurements with 5c and \( d_2 \). h, i Detection of the possible copper species generated from the reaction of CuOTf and dichloramine-T by HRMS measurements and reaction products obtained. *Unless otherwise stated, control reactions were performed with 1.5 equiv. of dichloramine-T, 50 mg of 4 Å MS and 1.5 equiv. of NaHCO3 in acetonitrile (1 mL). In parallel and competitive KIE experiments at room temperature both gave 6c as the only product in 32% yield. 4In parallel KIE experiments at 50 °C afforded 6c and \( d_2 \) in 36 and 6% yield.

quantitative yield or the \( \alpha \)-aryl chloride 6m in 70% yield for the reaction with 5m. These results also hinted that the lower BDE value of a tertiary (96.1 kcal/mol) over that of a secondary (99.1 kcal/mol) Cl(sp^3)–H bond was unlikely to be the sole contributing factor in determining site-selectivity.12 The possibility of the substrate undergoing a \( \alpha \)-HAT reaction/1,3-H* atom shift pathway was next considered but discounted by examining the CuOTf-catalysed chlorination of \( d_2 \) under the optimised reaction conditions for 48 h (Fig. 3f). This test gave the deuterated \( \gamma \)-chloroketone \( d_2 \) in 45% yield and with near-complete retention of D-content at the \( \gamma \)-position of the product based on \(^1\)H NMR measurements. In a final set of control experiments, the in parallel and competitive deuterium kinetic isotope effect (KIE) of the present Cu(I)-catalysed chlorination protocol was examined with 5c and \( d_2 \) as the test substrates (Fig. 3g). In both KIE experiments, analysis by \(^1\)H NMR and HRMS measurements revealed only the formation of 6c in 32% yield along with the recovery of \( d_2 \) in near quantitative yield that implied the possible involvement of quantum mechanical tunnelling. Common in H* atom transfer pathways, this was further suggested by \( k_{H}/k_{D} \) values of 6.0 and 5.8 obtained on repeating the respective in parallel and competitive KIE reactions at 50 °C. The theoretical limit for \( k_{H}/k_{D} \) (at 298 K) of 6.5–7 is estimated for complete C–H bond breaking in H* atom transfer reactions (ref. 58 and references cited therein). A large KIE value, like that measured in our study, is considered an experimental indicator that quantum mechanical tunnelling may be occurring (ref. 59 and references cited therein). This is further supported by our computational findings showing that the KIE value for H* atom abstraction from 5c is 6.4, which is close to the theoretical limit and corresponds with our experimentally observed results. A HRMS measurement of the crude reaction mixture obtained from a control experiment with stoichiometric amounts of CuOTf and dichloramine-T in acetonitrile at room temperature for 1 h was likewise performed (Fig. 3h). This revealed the detection of a molecular ion at \( m/z \) 247.9136 ([IM + H]^+) that could be assigned to [Cu(OTf)Cl], which suggested this Cu(II) species could be formed in situ and be involved in the reaction pathway. Further support for the possible involvement of [Cu(OTf)Cl] was offered by the detection of no reaction and isolation of TsCl in 80% yield on repeating the control experiment in the absence of the catalyst or 10 mol % of CuOTf, respectively (Fig. 3i).

To gain further insight into the mechanism of the present site-selective CuOTf-catalysed chlorination protocol, attention was
**Fig. 4 DFT calculations.**

**a** Energy profiles for the oxidative addition of dichloramine-T to [Cu(CH3CN)2]+ II via the SET mechanistic pathways a and b.

**b** Energy barriers for the HAT reaction of [TsNCl]* at different positions of 1s and relative energies of the ensuing radical species XVIIsα, and XVIIsγ and XVIIsγcy produced from the two most favoured transition states, TS′1s-XVIIsα and TS′1s-XVIIsγ.

**c** Energy profile for the chlorination of XVIIsα, XVIIsγ and XVIIsγcy to 2s. The relative Gibbs free and potential energies (in parentheses) obtained from SMD/B3LYP-D3//SMD/B3LYP-D3/6-31G(d,p), SDD calculations are given in kcal/mol (red), bond lengths in Å (purple) and spin density distribution values in e/Å³ (pink).
next turned to undertaking a series of DFT (density functional theory) calculations (Figs. 4, 5 and Supplementary Figs. 12–23). With the reaction surmised to begin with the oxidative addition of dichloramine-T to the Cu(I) salt, the identity of the reactive metal species involved in this step was first examined (Supplementary Fig. 12). Performed at the SMD/B3LYP-D3/def2-TZVP//SMD/B3LYP-D3/6-31G(d,p), SDD calculations are given in kcal/mol (red) and bond lengths in Å (purple). c Proposed catalytic cycle.

In considering a SET mechanism, our calculations characterised the possibility of two distinct pathways (Fig. 4a). The first involves dichloramine-T approaching the metal centre of II through its N-donor atom to give the T-shaped Cu(I)-encounter complex XI with an energy of 1.5 kcal/mol (Fig. 4a, pathway a). A feature of the organometallic species was found to be a Cu–N bond distance of 2.787 Å due to the weak coordination of the metal salt to two molecules of the solvent, to be the most stable. To this end, the cationic metal complex II was set as the reactive catalytic species for all subsequent calculations directed toward scrutinising whether this crucial oxidative addition step proceeded via a single-electron transfer (SET) or concerted mechanism (Fig. 4a and Supplementary Fig. 13).

Figure 5 DFT calculations and proposed reaction mechanism. Energy profiles for the chlorination of a XXIa to 4a from 3a and [TsNCl]* motif; and b XXVa to 6a from 5a and [TsNCl]* motif. The relative Gibbs free energies and potential energies (in parentheses) obtained from SMD/B3LYP-D3/def2-TZVP//SMD/B3LYP-D3/6-31G(d,p), SDD calculations are given in kcal/mol (red) and bond lengths in Å (purple). c Proposed catalytic cycle.
species MECP1. Providing the triplet excited-state copper(II) species XII, this type of bond rearrangement causes the N1–Cl bond to become weaker and more available to accept an electron from the copper centre. The occupation of the N2–Cl bond of a neutral molecule by an electron is supported by the elongation of the N1–Cl bond in XII and respective spin density distributions of 0.66, 0.56, and 0.55 e/Å² for the Cu, N1, and Cl1 atoms in the complex (noted in pink in Fig. 4a). Once this copper(II) species has formed, the oxidative addition process was found to be completed by transferring the Cl1 atom from the N1 centre to the metal via transition structure TSXII-XIII with an energy barrier of 4.1 kcal/mol. In the ensuing Cu(II) species XIII on the triplet surface, the [TsNCI]* motif weakly coordinates to the metal centre, as evidenced by a long Cu–N1 bond distance of 2.521 Å when compared to that in XII (2.059 Å). The weakening of the Cu–N1 bond thus enables the [TsNCI]* motif to easily dissociate from the metal complex. Calculated to be exergonic by 6.5 kcal/mol with an energy barrier of 4.4 kcal/mol, this generates the three-coordinate copper (II) complex XIV via TSXIII-XIV. The newly formed Cu(II) complex can be further stabilised through its coordination with a triflate anion. This results in the formation of the four-coordinate Cu(II) species I with a relative free energy of 1.3 kcal/mol. Other Cu(II) complexes were also considered but discounted as they were found to be less stable than that of I (Supplementary Fig. 14). The competitive release of the Cl1 atom instead of the [TsNCI]* group from copper(II) species XIII was likewise examined. However, this alternative pathway, which would produce the three-coordinate copper (II) complex XV via TSXIII-XV, was calculated to be endergonic by 20.6 kcal/mol, with an activation barrier of 26.7 kcal/mol. These results, therefore, indicate that it is more favourable for the Cu(II) species XIII to liberate the [TsNCI]* motif than the Cl1 atom.

A second possible SET mechanism that commences with the Cl1-donor atom of dichloramine-T approaching the metal centre of [Cu(MeCN)2]+ II was next explored (Fig. 4a, pathway b). Similar to that observed in Fig. 4a, pathway a, this furnishes the T-shaped Cu(I)-encounter complex XVI with a free energy of 2.2 kcal/mol. Electron transfer in this case proceeded by surmounting the minimum energy crossing point species MECP2, which lies 5.9 kcal/mol higher in energy than MECP1, to give I and the [TsNCI]* motif. Consequently, this suggested dichloramine-T was a more potent oxidant if it interacted with the metal salt through its nitrogen centre.

In a third set of calculations, the possibility of oxidative addition of dichloramine-T to the active copper(II) species II by a concerted mechanism was investigated (Supplementary Fig. 13). This reveals the oxidation of Cu(I) species XI to Cu(III) complex XIII1 via transition structure TSXII-XIII1 was endergonic by 20.6 kcal/mol with an overall activation barrier of 27.9 kcal/mol. The high endergonicity obtained for XIII1 is indicative of the fact that if the [TsNCI]* motif was formed, it would be unlikely to re-interact with a Cu(II) species on the singlet excited-state energy surface to give a stable Cu(III) complex. Taken together, these calculations thus suggest that the oxidative addition of dichloramine-T to [Cu(MeCN)2]+ II is most likely to proceed via the SET mechanism outlined in Fig. 4a, pathway a, as this was the most energetically favoured. It also suggests that the [Cu(MeCN)2OTf]Cl I and [TsNCI]* moieties formed as a result of this step are the two key active species responsible for substrate chlorination. Corroborating this is our findings that showed [CuOTf]Cl to be present in HRMS measurements of the crude reaction mixture and the isolation of TsCl in control experiments with CuOTf and dichloramine-T (Fig. 3b, i). Thus, the Cu(II) complex I and [TsNCI]* motif were set as the reactive chlorination species for all subsequent calculations illustrated in Figs. 4b, c and 5, which focused on revealing the mechanisms of the site-selective C(sp3)–Cl bond formation reactions.

With this in mind and 1-phenylpentanone 1s as a representative example, the free energy barriers for a HAT reaction at the α-, β-, γ-, and δ-positions of the substrate with the [TsNCI]* moiety were initially investigated (Fig. 4b). This predicted the HAT reaction was most likely to proceed at the γ-position of the ketone with the alkyl side-chain occupying a folded conformation. The energy barrier for TS1s-XVIIIγ formation was shown to be 16.0 kcal/mol, some 0.9 kcal/mol lower than that of TS1s-XVIIγ, the next lowest, which is obtained from HAT reaction at the α-position of the substrate. This is consistent with the control experiment described in Fig. 5f, which revealed the chlorination of d1-1s to give d2-2s in 45% yield with complete D-content retention at the α-position of the product. It is also in good agreement with computational calculations that reported polar effects to deactivate the α-position of carboxylic acids to participate in a HAT reaction with a chlorine radical atom despite this being the most thermodynamically favoured.

Our theoretical calculations found that once the γ-carbonyl-centred radical species XVIIIγ forms along with p-TsNHCl, it cyclises to the tetrahydrofuranyl (THFyl) radical adduct XVIIIγp, as it was more stable by 6.3 kcal/mol (Fig. 4b). Additionally, a comparison of the cyclic carbon-centred radical species along with that of XVIIγ and XVIIIγ showed the odd-electron THFyl adduct to exhibit significantly greater reactivity toward chlorination. We rationalise this marked difference in reactivity could offer the reason why only the γ-chloroketone product was observed. As illustrated in Fig. 4c, the reactions of each of these three carbon-centred radical species with the four-coordinate Cu(II) complex I were thus compared. This led to the formation of the corresponding copper(II)-encounter complexes XVIIIγa, XVIIIγp, and XVIIIγd with respective energies of 1.1, 11.0 and 0.9 kcal/mol. For XVIIγ and XVIIIγ, intersystem crossing via the respective minimum energy crossing point species MECPsα and MECPsγ gave the singlet Cu(II) complexes XIXsγ and XIXsγ. In contrast, the Cu(II) complex XVIIIγp was found to be a potent reductant and, as such, reduced the metal centre to give the singlet ground-state Cu(I) species XIXsγ via minimum energy crossing point species MECPsγ. This is followed by the loss of the triflate anion to afford the cationic copper(I) complex XXsγ, which was found to be exergonic by 3.1 kcal/mol. The greater reactivity of XVIIγ and XVIIIγ toward chlorination was thus delineated to be due to MECPsγ (2.6 kcal/mol) lying considerably lower in energy than MECPsα (12.5 kcal/mol) or MECPsδ (16.6 kcal/mol). Once XXsγ formed, its chloride ligand acts as a nucleophile and opens the ring of the THFyl motif via S2 transition state structure TXXXsγ-II with an energy barrier of 17.6 kcal/mol in an exergonic fashion with ΔG = −7.2 kcal/mol. The formation of the ensuing C(sp3)–Cl bond results in the delivery of the product 2s along with the regeneration of [Cu(MeCN)2]+ II.

For the site-selective chlorination of (E)-enones with 3a as a representative example, HAT reaction at the γ-position of the substrate by the [TsNCI]* motif was found to be exergonic by 19.0 kcal/mol with an overall energy barrier of 15.2 kcal/mol (Fig. 5a). Producing the alkyl radical species XXIa and p-TsNHCl, reaction of the former with Cu(II) complex I affords Cu(II) adduct XXIIa on the triplet surface, which lies 4.1 kcal/mol higher in energy. Subsequently, the minimum energy crossing point species MECPS3a connects XXIIa to organometallic complex XXIIIa on the singlet excited-state energy surface in which the copper centre has a formal oxidation state of +1. This change in the oxidation state of the metal centre from +2 to +1 forces the triflate anion to leave to
produce XXIVa where the trigonal planar [Cu(MeCN)₂Cl] complex is stabilised by the in situ generated carbocation motif. However, we were unable to locate any transition state structures for the Cu–Cl bond forming step. As a consequence, this implied that once XXIVa has formed, it immediately undergoes coupling and formation of the C–Cl bond to give the thermodynamically favoured product 4a and [Cu(MeCN)₂]²⁺ II, which was found to be exergonic by 15.3 kcal/mol.

In a final set of calculations, the [TsNCl]⁺ moiety was once again found to serve as a good hydrogen radical atom abstractor in reactions with alkylbenzenes. As depicted in Fig. 5b with 5a as a representative example, removal of the α-H radical atom in the substrate by the [TsNCl]⁺ motif was shown to require an activation energy of 14.3 kcal/mol and was exergonic by ~2.5 kcal/mol. Forming the benzylic radical species XXVa and p-TsNHCl, the former approaches the tetravalent Cu(II) species I with an energy barrier of 2.7 kcal/mol. The thermodynamics of the radical reaction between XVIIa and 5a to give 1s and XXVa was modelled at the SMD/B3LYP-D3/def2-TZVP//SMD/B3LYP-D3/6-31G(d) level of theory to determine if reaction selectivity might be predominantly thermodynamically controlled. The isodesmic reaction was found to be endergonic by 1.6 kcal/mol, Supplementary Fig. 15), indicating XVIIa is intrinsically more stable than that of XXVa. At the same time, our calculations revealed that XVIIa is less reactive toward chlorination with Cu(II) complex 1, as MECPs is 9.4 kcal/mol higher in energy than MEPCa (Figs. 4 and 5). As such, in this case, the intrinsic stability of the radical species is not a determining factor for reactivity. At this juncture, intersystem crossing of the ensuing Cu(I)-encounter complex XXVIa on the triplet excited-state energy surface via the minimum energy crossing point species MEPCa occurs to furnish the singlet ground-state Cu(II) complex XXVIIa. Rapid reductive elimination of the high oxidation state of the metal species leading to C(sp³)–Cl bond formation takes place to give benzyl chloride 6a and [Cu(MeCN)₂]²⁺ II via TSXXVIIa with an exergonicity of 29.6 kcal/mol.

On the basis of the above experimental and computational results, a tentative mechanism for the Cu(I)-catalysed site-selective C(sp³)–Cl bond formation reaction is presented in Fig. 5c. This could involve the initial oxidative addition of chloramine-T to [Cu(MeCN)₂]²⁺ II, formed by solvation of CuOtfs with acetonitrile, via a SET pathway to give the Cu(II) complex XII in which an electron from the metal centre is transferred to the N–Cl bond. As a result, migration of the chlorine atom from the nitrogen centre to that of the metal may occur to give the Cu(II) complex XIII where the [TsNCl]⁺ motif is highly susceptible to dissociation from the metal species. In addition to the formation of the nitrogen-centred radical species, the fragmentation affords the trivalent copper(II) complex XIV, which undergoes triflate anion coordination to give the more stable tetravalent Cu(II) species I. The removal of an α- or γ-H radical atom in the respective alkylbenzene, ketone and (E)-eneone substrate (R–H) by the [TsNCl]⁺ motif via a HAT pathway might then furnish the R⁺ species and p-tosylchloramide. At this juncture, a divergence in the mode of reactivity is thought to occur depending on the nature of the alkyl radical species (R⁺). When the R group is that of the ketone (XVII²⁻) or (E)-eneone (XXXI), its potency as a reductant may lead to the unlikely tendency to furnish a stable Cu(III) complex through the formation of a Cu–R bond. As a consequence, reduction of the tetravalent Cu(II) species by the R⁺ species would deliver the corresponding Cu(I) complexes XXVY and XXIV of the ketone and (E)-eneone via an outer-sphere mechanism (Fig. 5c, pathway a). Subsequent coupling of the alkyl and chloride groups in the respective Cu(I) complexes would result in C(sp³)–Cl bond formation to give γ-chloroketone 2 and (E)-γ-chloroenone 4 along with regenerating [Cu(MeCN)₂]²⁺ II. In the case of R⁺ species derived from an alkylbenzene substrate, the decreased reducing ability of the radical adduct might now make the formation of the Cu(III) complex XVII²⁻ favourable on interacting with Cu(II) species I via an inner-sphere mechanism (Fig. 5c, pathway b). Reductive elimination in this high oxidation state metal complex would result in C(sp³)–Cl bond formation to produce the benzyl chloride 6 and [Cu(MeCN)₂]²⁺ II. An outer-sphere mechanism might be anticipated to be faster than an inner-sphere one because the two reactive species in the former do not need to be in a direct contact with each other. Consequently, if these two pathways are assumed to be in competition, the redox reaction via the outer-sphere mechanism is predicted to be operative, as evidenced by substrates containing both a benzylic and γ-C(sp³)–H bond where the latter is selectively chlorinated.

In summary, we have elucidated a Cu(I)-catalysed synthetic method for the site-selective chlorination of C(sp³)–H bonds of ketones, (E)-enes and alkylbenzenes by dichloramine-T. By realising a rare instance of dichloramine-T as a chlorine radical atom source, it offers a practical and efficient synthetic route to the corresponding chlorinated products with site-selectivities that are among the most selective reported in alkane functionalisation. This site-selectivity was further highlighted by the delivery of only the γ-chlorinated product in reactions involving ketones and (E)-enes containing a benzylic and/or electron-rich aryl C–H bond. The approach was likewise shown to be chemoselective as the chlorination of unsaturated substrates did not suffer from competitive reactions at the more reactive C=C bond or its transposition. This is often the case in allylic chlorination methods that rely on ene-type reactivity. The key to this product selectivity was suggested to be due to a site-selective HAT reaction between the in situ generated [TsNCl]⁺ motif and substrate that was dictated by their electronic interactions. Equally crucial was avoiding the intermediacy of the chlorine free radical atom by the formation of the metal-chloride complex to transfer the halogen radical atom to the substrate radical species to give the product. The ability to access various γ-chloroketones, (E)-γ-chloroenones and α-benzyl chlorides with a single catalytic system will find broad applicability in chemical synthesis and notably impact the way in which many molecules of interest are assembled. In this study, this potential was demonstrated by the late-stage site-selective chlorination of a series of modified bioactive compounds and natural products along with the gram-scale preparation and formal synthesis of two drug molecules. Along with this, we envisage the mechanistic principles provided by our studies will assist future efforts focused on site-selective aliphatic C–H bond functionalisation at other unactivated positions that pervade the compound class.

Methods
To an oven-dried round-bottom flask (10 mL) was added the ketone 1, (E)-eneone 3 or alkylbenzene 5 (0.2 mmol), CuOtfs/0.5PhMe (5.2 mg, 0.02 mmol), NaHCO₃ (25.2 mg, 0.3 mmol) and 4 Å MS (50 mg). The reaction vessel was capped and charged with a nitrogen atmosphere through three cycles of the vacuum-nitrogen-backfill method over 10 min. An anhydrous solution of acetonitrile (1 mL) containing dichloramine-T (72 mg, 0.3 mmol for 1 or 57.6 mg, 0.24 mmol 3 and 5) was then added and the resulting reaction mixture was stirred at room temperature for 24 h. For substrates 1s–x, a further amount of CuOtfs/0.5PhMe (5.2 mg, 0.02 mmol) and dichloramine-T (72 mg, 0.3 mmol) was added at this point and the reaction was stirred for an additional 24 h. Upon completion, the reaction mixture was filtered through a Celite pad with dichloromethane (3 × 1 mL). On removing the organic solvent under reduced pressure, the resulting residue was purified by flash column chromatography on silica gel (petroleum ether/diethyl ether as eluent) to give the desired chlorination product.
Data availability

The data supporting the findings of this study are available in the paper and its Supplementary Information. Further data are available from the corresponding author on request. The X-ray crystallographic coordinates for structures reported in this study have been deposited at the Cambridge Crystallographic Data Centre (CCDC), under deposition numbers CCDC 1562076 (2d) and CCDC 1562075 (4k). These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Received: 1 November 2020; Accepted: 20 May 2021; Published online: 01 July 2021

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Acknowledgements
This work was supported by a Discovery Project Grant (DP210103425) from the Australian Research Council.

Author contributions
P.W.H.C. conceived and directed the project. P.W.H.C., J.J., Y.Z. and S.H.K. designed the experiments and analysed the data. J.J. and Y.Z. performed all of the experiments. A.A. and K.F. performed all of the computational studies. All the authors contributed to the preparation and writing of the manuscript.

Competing interests
The authors declare no competing interests.

Additional information
Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41467-021-23988-y.

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Peer review information Nature Communications thanks Peter Schreiner and the other anonymous reviewer(s) for their contribution to the peer review of this work. Peer reviewer reports are available.

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