# Halogen-atom and group transfer reactivity enabled by hydrogen tunnelling

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**Abstract:** The generation of carbon radicals by halogen-atom and group transfer reactions is generally achieved using tin and silicon reagents that maximize the interplay of enthalpic (thermodynamic) and polar (kinetic) effects. Herein, we demonstrate a distinct reactivity mode enabled by quantum mechanical tunnelling that uses the cyclohexadiene derivative γ-terpinene as the abstractor under mild photochemical conditions. This protocol activates alkyl and aryl halides as well as several alcohol and thiol derivatives. Experimental and computational studies unveiled a non-canonical pathway whereby a cyclohexadienyl radical undergoes concerted aromatization and halogen-atom/group abstraction through the reactivity of an effective H-atom. This activation mechanism is seemingly thermodynamically and kinetically unfavorable, but is rendered feasible through quantum tunnelling.

**One Sentence Summary:** Quantum mechanical tunnelling control enables halogen-atom and group transfer reactions through direct H-atom reactivity.

**Main Text:** Carbon radicals are integral reactive species for the synthesis of numerous organic compounds.(*1-4*) Among the methods for their generation, strategies based on halogen-atom and group transfer chemistry are advantageous for their use of halides and alcohol/thiol derivatives that are commercially available or otherwise easy to access.(*5-9*)

Halogen-atom transfer processes follow three general reactivity principles (Fig. 1A): (i) they rely on a collinear arrangement among the three atoms involved in the process (i.e. C, X and Y) to achieve maximum orbital overlap between the abstracting radical (Y•) SOMO (singly occupied molecular orbital) and the carbon–halogen antibonding orbital (σ*); (ii) the Y–halogen bond needs to be stronger than the original carbon–halogen bond in the reactant so that the process is thermodynamically favorable (exergonic, $\Delta G^o < 0$, "enthalpic effect"); (iii) rapid kinetics ensue from the interplay of "polar effects" at the transition state that lower the barriers by charge transfer. Considering the natural polarization of carbon–halogen bonds,(*10*) nucleophilic radicals are ideally suited to stabilize emerging positive character and therefore accelerate the abstraction. Species like tin and silicon radicals maximize both enthalpic and polar effects and are therefore routinely used for radical generation despite their toxicity, cost and waste management issues.(*9, 11-13*)

Herein, we report a distinct approach for halogen-atom transfer that does not adhere to any of these three features. This non-canonical process exploits the reactivity of cyclohexadienyl radicals that enable, through concerted aromatization–abstraction event, the use of formal hydrogen atoms (H•) as the abstracting species. This process relies on a collinear arrangement of four atoms in the transition state and its feasibility is enabled by quantum mechanical tunnelling rather than thermodynamic (enthalpic) or kinetic (polar) considerations. The mechanistic blueprint is not limited to the activation of organic halides but likewise enables the generation of carbon radicals from alcohol and thiol derivatives, which suggests quantum tunnelling is operating also in group transfer chemistry.

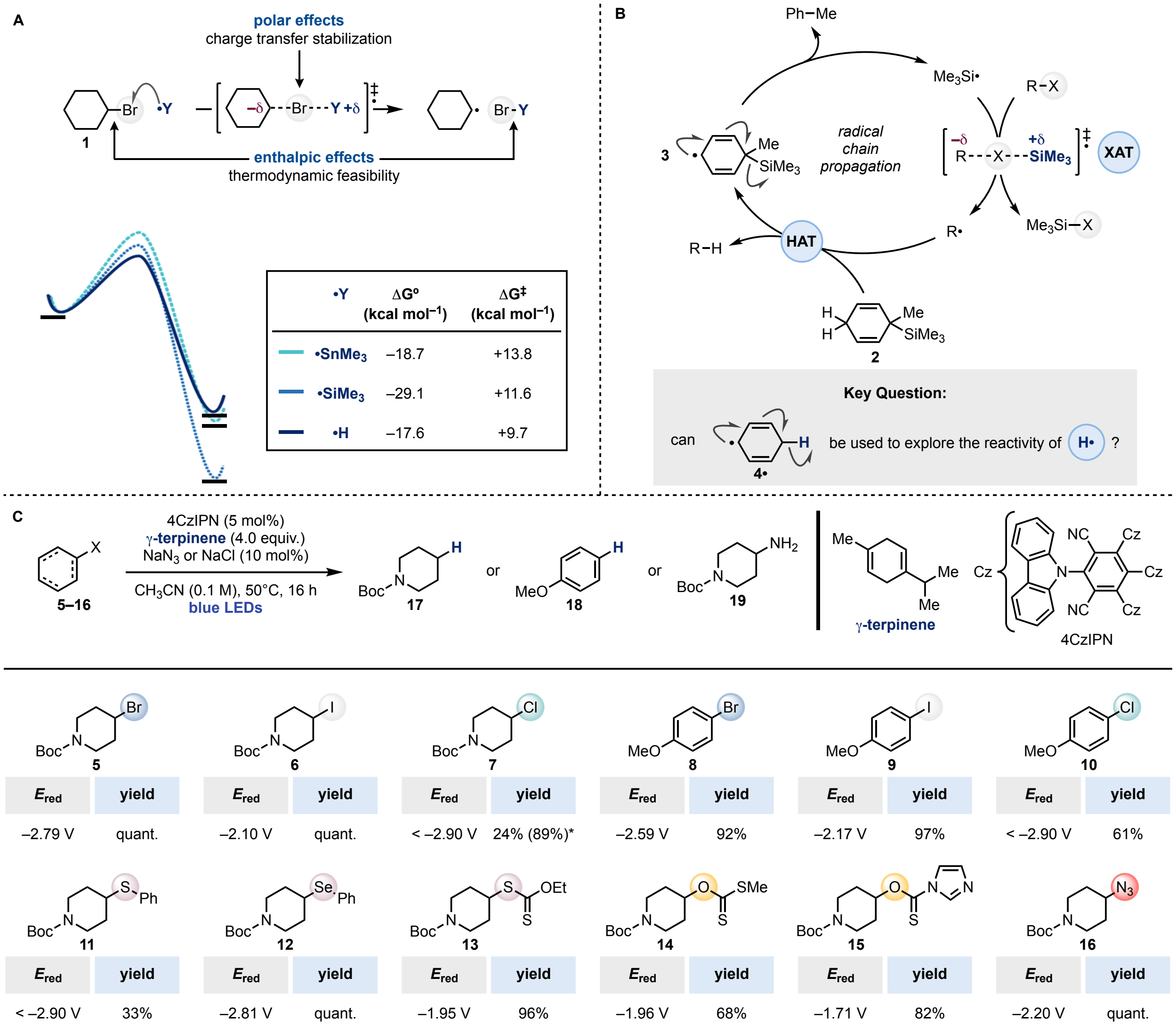
The development of this alternative strategy for carbon radical generation started with the analysis of the key thermodynamic and polar features controlling halogen-atom transfer. This led us to speculate that a hydrogen-atom, H•, might be a suitable reagent to perform these reactions. This mechanistic hypothesis was based on the evidence that H–halogen bonds are stronger than standard C–halogen bonds and they immediately dissociate in weakly basic media.(*14*) This combination should make the overall radical abstraction exothermic. Furthermore, the H-atom should polarize the transition state through the emergence of proton-like character, thus aiding charge transfer stabilization. Indeed, a computational comparison of halogen-atom transfer reactions on Cy–Br **1** mediated by $Me_3Sn•$, $Me_3Si•$ and H• demonstrated that all three abstractions are highly exothermic but the one mediated by H• faces the smallest kinetic barrier (Fig. 1A).(*15*) Although these results would support this mode for halogen abstraction, its implementation is clearly hampered by the lack of methods for generating naked H• in synthetic settings.

In approaching this challenge, we turned our attention to the concept of pro-aromaticity that has been extensively applied to the generation of silicon radicals (Fig. 1B).(*16-20*) This strategy requires the preparation of bespoke $Me_3Si$-containing cyclohexadiene derivatives (e.g. **2**) that are activated by HAT (H-atom transfer) at the bis-allylic methylenic position. This event generates the cyclohexadienyl radical **3**, that, through a thermodynamically favorable aromatization process, ejects $Me_3Si•$. This species can then be used in many types of radical chain propagations based on halogen-atom as well as group transfer chemistry. Our initial mechanistic plan sought synthetic conditions to translate this reactivity blueprint to simple cyclohexadiene radical **4•** as a gateway to generate and implement H• reactivity in synthetic radical chemistry.

To experimentally validate this hypothesis, we looked at dehalogenation reactions, which are heavily exploited by the pharmaceutical sector but still require large excess of difficult-to-handle tin and silicon reagents with AIBN (azobisisobutyronitrile) at often high temperatures (> 100 ºC).

Pleasingly, we demonstrated that the cyclohexadiene derivative γ-terpinene, a feedstock derived from the essential oil of *Melaleuca alternifolia*, led to the quantitative debromination of **5** (to give **17**) under mild photoredox conditions using the organic dye 4CzIPN as the photocatalyst (5 mol%), NaCl or $NaN_3$ as an additive (10 mol%) in acetonitrile solvent under blue LED irradiation. The supplementary material discusses the identification of other reaction conditions of similar efficiency based on the use of diarylketones photocatalysts, which demonstrates that this γ-terpinene-mediated debromination can be adapted to manifolds outside the realm of photoredox catalysis (Fig. S19 and Table S8). In addition, the replacement of γ-terpinene by other pro-aromatic agents such as simple 1,4-cyclohexadiene provided similar experimental results, in line with our working hypothesis (Fig. S3 and Table S2). In terms of substrate scope, this reactivity was extended to the activation and dehalogenation of the corresponding C-4 iodide (**6**) and, importantly, chloride (**7**). Deactivated and electron-rich aryl halides were also competent substrates as demonstrated by the high-yielding dehalogenation of **8**–**10** (to give **18**), which presumably proceeds via the formation of an aryl radical. Compounds **7** and **10** exemplify a class of highly sought-after precursors for application in radical chemistry that are still difficult to engage in methods based on both single-electron transfer (SET) as well as halogen-atom transfer reactivity.(*21-26*)

This γ-terpinene-based strategy is not limited to the activation of organic halides and we successfully translated it into group transfer settings. This enabled the defunctionalisation of C-4 sulphide (**11**), selenide (**12**), xanthate (**13**) and alcohol derivatives (**14** and **15**) in moderate to excellent yields (to give **17**). Alkyl azide **16** was also readily engaged providing access to the corresponding primary amine **19**, thus offering a transition metal-free option to standard hydrogenation conditions.



| •Y | ΔG° (kcal mol$^{-1}$) | ΔG‡ (kcal mol$^{-1}$) |
|---|---|---|
| $•SnMe_3$ | –18.7 | +13.8 |
| $•SiMe_3$ | –29.1 | +11.6 |
| •H | –17.6 | +9.7 |

| | $E_{red}$ | yield |
|---|---|---|
| 5 | –2.79 V | quant. |
| 6 | –2.10 V | quant. |
| 7 | < –2.90 V | 24% (89%)* |
| 8 | –2.59 V | 92% |
| 9 | –2.17 V | 97% |
| 10 | < –2.90 V | 61% |
| 11 | < –2.90 V | 33% |
| 12 | –2.81 V | quant. |
| 13 | –1.95 V | 96% |
| 14 | –1.96 V | 68% |
| 15 | –1.71 V | 82% |
| 16 | –2.20 V | quant. |

**Figure 1. A γ-terpinene-mediated radical generation by halogen-atom and group transfer.** (A) General mechanism for halogen-atom transfer reactions and computational studies on three model bromine-atom abstractions [DFT method: (u)M06-2X/def2-TZVP-SMD(MeCN) in kcal mol$^{-1}$, where Gibbs free energies are based on the individual reactants and products]. (B) Si-containing pro-aromatic cyclohexadienyl radicals that generate silicon radicals by fragmentation. (C) Development of a general strategy for halogen-atom and group transfer chemistry using γ-terpinene as the formal H• donor. Yields are isolated. $^*$Yield obtained using $Ir(ppy)_3$ as the photocatalyst.

Taken together these results demonstrate that this mild γ-terpinene-mediated reactivity engages the whole spectrum of substrates classically activated by tin and silicon radical chemistry while bypassing single-electron transfer (SET) activation, and therefore the requirement for strong reductants. These features should make it a useful tool for carbon radical generation, so we conducted an extensive scope investigation with the aim of benchmarking its utility in synthetic settings. Numerous functionalized alkyl and aryl halides **20–59** were susceptible to this reaction, leading to generally high yields of the corresponding reduced products (Fig. 2A-C). The reactivity spanned a broad class of unactivated alkyl derivatives (primary, secondary and tertiary) and was compatible with commonly encountered organic functionalities including free and protected alcohols and amines, acetal, ester, lactone, lactam, aldehyde and ketone as well as HAT-labile benzylic, allylic and α-heteroatom centers. Although most of the scope exploration was conducted on 0.1 mmol scale, these reactions can be translated to larger scale in similar yields and efficiencies through the use of photochemical flow reactors (Fig.s S15 and S16).(*15*) In exploring the aryl halide scope, we mostly focused on substrates containing strongly electron donating substituents that challenge the implementation of SET-based approaches; several privileged N-heterocycles; as well as groups that can act as a handle for cross coupling reactivity, such as pinacol boronic ester. Pleasingly, all these derivatives worked well, giving the desired products in high yields. Synthetic applications in group transfer and reduction chemistry were demonstrated on alcohol/thiol derivatives (**60** and **61**) as well as several alkyl azides giving the corresponding primary amines (**62**–**65**) (Fig. 2D).

As mentioned above, radical defunctionalization processes are often encountered in the pharmaceutical literature for the preparation of high-value bioactive compounds. Substrates **66**–**70** exemplify some of these processes which are generally performed through the use of toxic tin/silicon reagents at high temperature (Fig. 2E).(*27-29*) Our γ-terpinene-based protocol proved applicable to these targets, thus offering, in similar chemical yields, milder and more sustainable conditions with a volatile aromatic by-product in place of tin/silicon waste.

As a further demonstration of the general utility of this method, we explored the use of alkyl and aryl halides in other modes (Fig. 2F) such as reductive *5-exo-trig* cyclizations (**71**–**73** to give **77**–**79** and **74**–**76** to give **80**) and Giese additions (**81**–**83**).

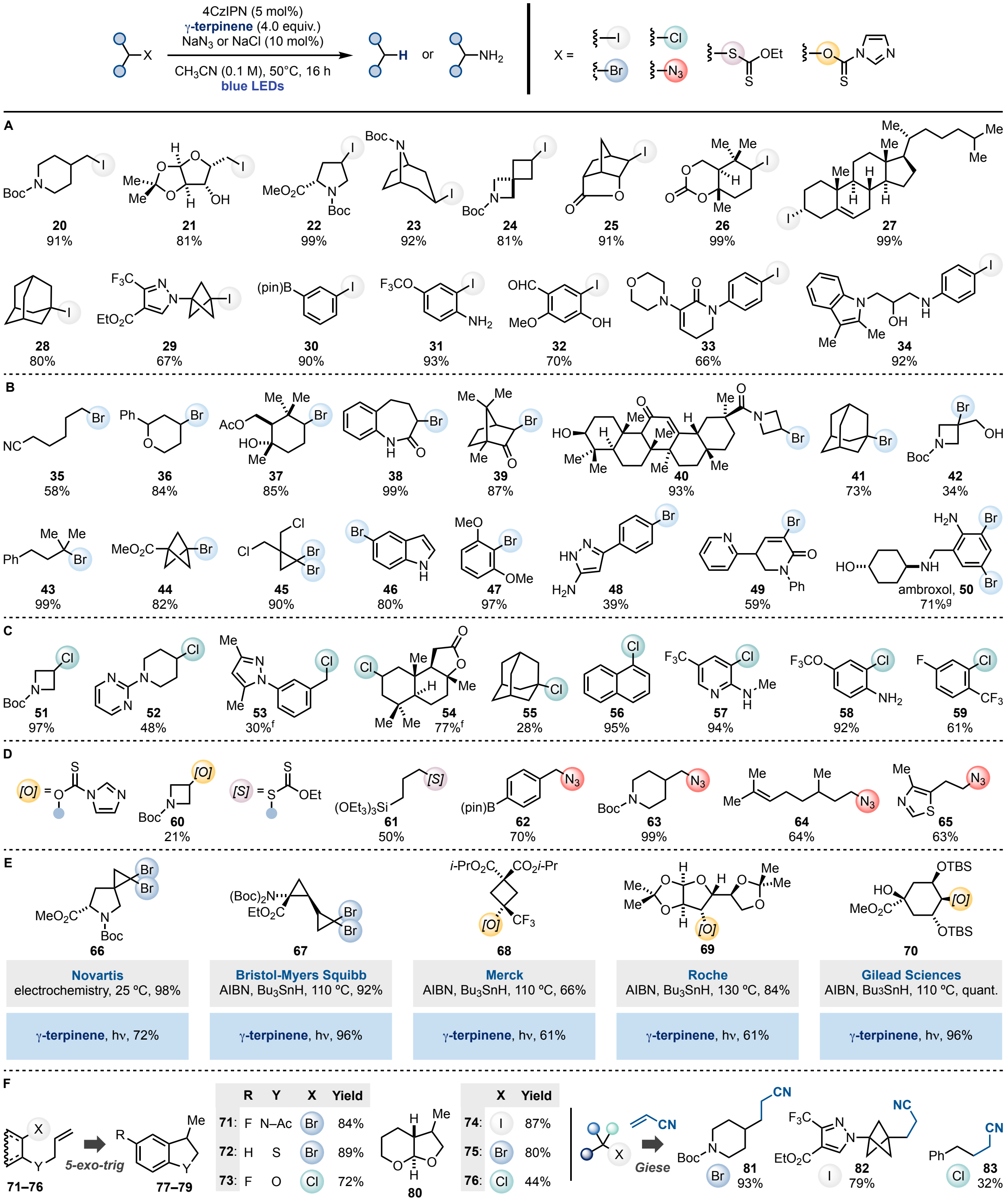


**Figure 2. Extended substrate scope.** (A) alkyl and aryl iodides; (B) alkyl and aryl bromides; (C) alkyl and aryl chlorides; (D) alcohol and thiol derivatives and alkyl azides. (E) Application of the reactivity to industrially relevant defunctionalizations (*27-29*). (F) Application to other modes of radical reactivity. Yields are isolated.

We next turned our attention to the underlying reaction mechanism. First, we performed control experiments to verify that γ-terpinene and light are essential to observe reactivity, while different bases, initiators and photocatalysts can all be used (Tables S1, S3, S5–7).(*15*) We then monitored the generation and reactivity of the cyclohexadienyl radical **4•** ($\lambda_{max}$ = 315 nm) by laser-flash photolysis measurements,(*30-33*) irradiating cyclohexadiene at hν = 355 nm in the presence of ($t$-BuO)$_2$ and several alkyl and aryl halides (Fig. 3A). Interestingly, all these experiments resulted in the decay of **4•** with similar bimolecular rate constants ($k_2$, $M^{-1}$ $s^{-1}$), all clustered around $10^5$ $M^{-1}$ $s^{-1}$.(*15*) This kinetic outcome contrasts with the large difference in rates measured for the decays of silicon radicals in the presence of similar quenchers, which are generally faster and highly dependent on the BDE of the carbon–halogen bond, thus spanning over three orders of magnitude.(*34, 35*) We initially attributed this non-canonical outcome on the basis of a rate-limiting aromatization, followed by a faster halogen abstraction from H•. However, computational analysis of this reaction profile demonstrated the generation of naked H• to be energetically uphill of >15 kcal mol$^{-1}$ with a high kinetic barrier that would not be compatible with the fast reactivity observed under our synthetic experiments (Fig. 3B-i).(*15*)

These findings pointed to a distinct mechanistic pathway operating under these reaction conditions. We ruled out bromine-atom transfer (and also group transfer) taking place from **4•** as this process is highly endergonic ($\Delta G^o$ = 23.1 kcal mol$^{-1}$) and kinetically unfavorable ($\Delta G^‡$ = 38.8 kcal mol$^{-1}$) (Fig. 3B-ii)(*15*): the halogen abstraction would generate a bis-allylic carbon–bromine bond which is weaker than the bond in the starting material while offering minimal charge transfer stabilization. A deprotonation of **4•** to the corresponding phenyl radical anion **4**$^{•-}$ followed by SET(*36, 37*) activation of the substrates was also excluded on the basis of calculated high p$K_a$ = 28 (DMSO) for the methylenic proton in **4•** (predicted to increase in the experimentally relevant solvent $CH_3CN$) (Fig. 3B-iii).(*15*) Furthermore, attempts to translate the γ-terpinene reactivity to substrates that are easy to reduce but that cannot undergo atom/group transfer chemistry led to no reactivity thus ruling out the involvement of SET (Table S13 and Fig. S30).(*15*)

We then revisited our initial hypothesis and considered a hybrid mechanism where the aromatization and the H•-mediated halogen abstraction are linked and occur simultaneously (Fig. 3B-iv). Such a mechanistic option represents a non-canonical avenue in halogen-atom and group transfer chemistry as it would feature the collinear arrangement of four atoms instead of three in the transition state. Our calculations demonstrated that by linking the aromatization to the halogen transfer, the bromine abstraction between **4•** and **1** is typically close to thermoneutral ($\Delta G^o$ = –2.0 kcal mol$^{-1}$) but still characterized by a significantly high kinetic barrier ($\Delta G^‡$ = 37.3 kcal mol$^{-1}$) which should thwart reactivity. However, the very large imaginary frequency observed (ν = –1780 cm$^{-1}$) implied a barrier with a very narrow width.(*15, 38-40*) Under these circumstances a light particle, like an H-atom, is not strictly required to have enough kinetic energy to overcome the transition state height but can penetrate the potential energy barrier through quantum mechanical tunnelling.(*41-45*) To validate this mechanistic scenario, we measured the kinetic isotope effect (KIE) as unusually large values are strong indicators for the involvement of quantum tunnelling in chemical reactions. Our calculations of fully deuterated cyclohexadienyl radical **4**-$d_8$ in the model bromine abstraction process predicted a KIE = 6 based on standard transition state theory. Crucially, when corrected with the incorporation of small curvature tunnelling (SCT),(*46*) a KIE = 27 was obtained. We therefore prepared the fully deuterated cyclohexadiene and repeated the flash-laser photolysis kinetic studies with **1**, which resulted in a large measured KIE = 23, which agrees with our calculations. Furthermore, we repeated the kinetic measurements for the photolysis of cyclohexadiene in the presence **1** at a lower temperature (T = –15 ºC) and observed an almost identical bimolecular decay rate ($k_2 = 4.14\ 10^5\ M^{-1}\ s^{-1}$ at T = 20 ºC vs $2.92\ 10^5\ M^{-1}\ s^{-1}$ at T = –15 ºC) (Table S16).(*15*) As quantum mechanical tunnelling does not follow the traditional rules of chemical kinetics,(*47*) the insensitivity of reaction rates to the temperature is an additional evidence for its involvement. Overall, we propose this γ-terpinene-based process to be based on a photoredox-initiated radical chain propagation (Fig. 3C). The SET oxidation of NaCl/$NaN_3$ additives is used to access the corresponding Cl•/$N_3$•. These species would initiate the radical propagation by generating of the cyclohexadienyl radical **4•** via fast and favorable H-atom abstraction with cyclohexadiene (or γ-terpinene(*48*)). Quantum mechanical tunnelling-enabled aromatization–halogen-atom transfer would convert, through the reactivity of a formal H-atom, the various starting materials into the corresponding alkyl and aryl radicals. These species can re-initiate the chain by HAT on **4**(*49*) (or γ-terpinene) or engage first in other types of reactivity (i.e. cyclization or Giese addition). Computational analysis for the reaction profile of the various halogen-atom and group transfer processes realized in Fig. 1C on other types of alkyl and aryl derivatives resulted in similar reaction parameters and barrier features (Table S10). Collectively, these results support quantum mechanical tunnelling as an important component for the whole class of radical generations.

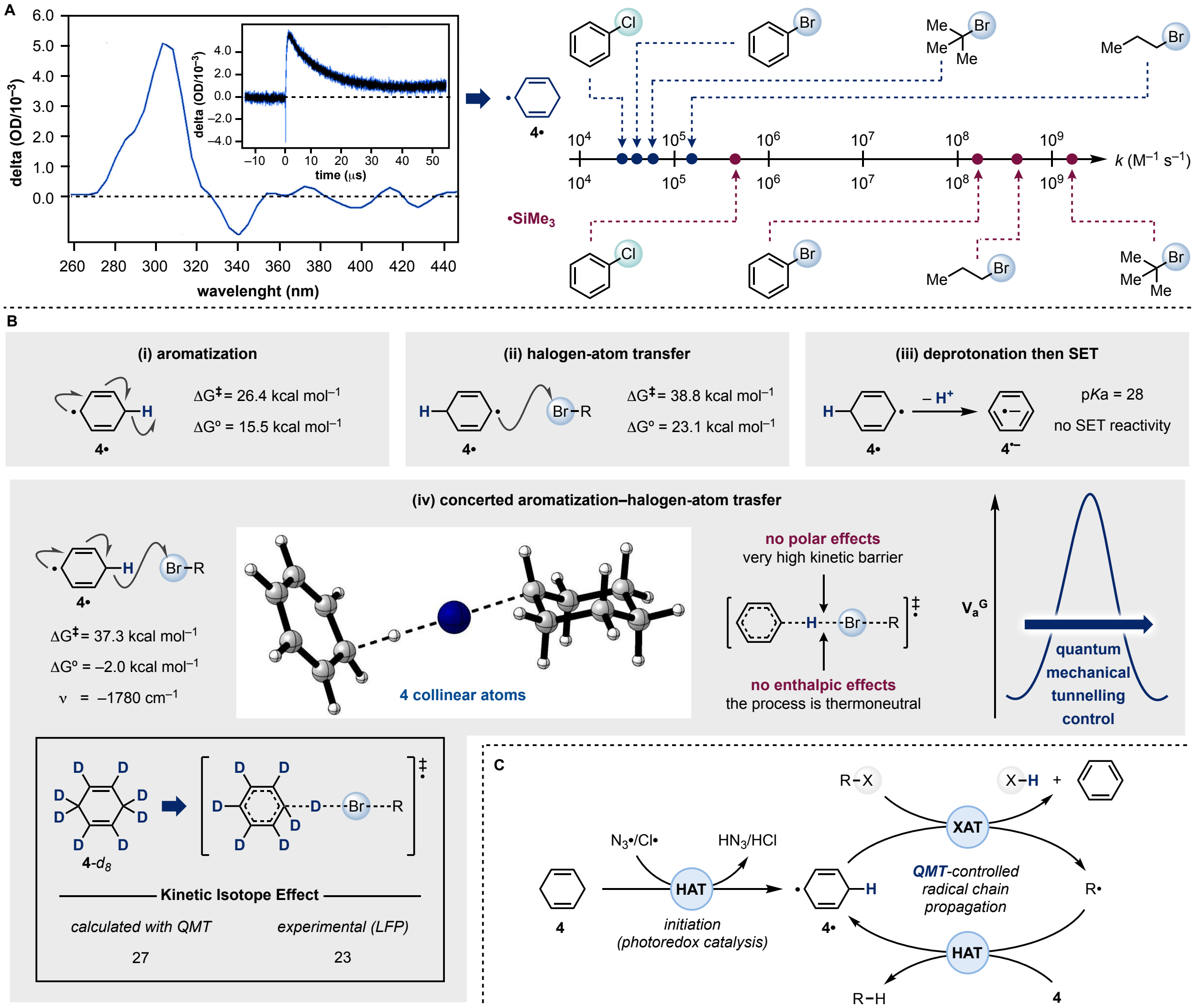


**Figure 3. Mechanistic studies.** (A) Laser flash photolysis studies monitoring the decay of the cyclohexadienyl radical. (B) Outline of possible mechanistic scenarios leading to quantum tunnelling-controlled concerted aromatization–halogen-atom transfer [DFT method: (u)M06-2X/def2-TZVP-SMD(MeCN) in kcal mol$^{-1}$, where Gibbs free energies are based on the individual reactants and products]. (C) Proposed quantum tunnelling-enabled radical chain propagations.

Our current understanding of halogen-atom and group transfer chemistry is based around the consideration of enthalpic and polar effects. The results presented here demonstrate that transition state theory is not the only framework to approach these reactions and that quantum tunnelling can be leveraged to enable otherwise elusive types of reactivity. We hope that this blueprint for carbon radical generation might stimulate the development of further alternative strategies that challenge thermodynamic and kinetic control.

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## Supplementary Materials

Materials and Methods
Figures S1 to S35
Tables S1 to S34
NMR Spectra
References (*50-177*)

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