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Article

Difluoromethylation of Unactivated Alkenes Using Freon-22 through Tertiary Amine-Borane-Triggered Halogen Atom Transfer

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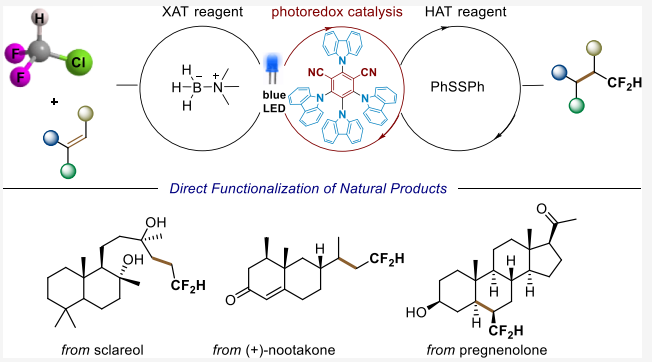
ABSTRACT: The application of abundant and inexpensive fluorine feedstock sources to synthesize fluorinated compounds is an appealing yet underexplored strategy. Here, we report a photocatalytic radical hydrodifluoromethylation of unactivated alkenes with an inexpensive industrial chemical, chlorodifluoromethane ($ClCF_2H$, Freon-22). This protocol is realized by merging tertiary amine-ligated boryl radical-induced halogen atom transfer (XAT) with organophotoredox catalysis under blue light irradiation. A broad scope of readily accessible alkenes featuring a variety of functional groups and drug and natural product moieties could be selectively difluoromethylated with good efficiency in a metal-free manner. Combined experimental and computational studies suggest that the key XAT process of $ClCF_2H$ is both thermodynamically and kinetically favored over the hydrogen atom transfer pathway owing to the formation of a strong boron−chlorine (B−Cl) bond and the low-lying antibonding orbital of the carbon−chlorine (C−Cl) bond.



INTRODUCTION

The difluoromethyl group (CF_2H) linked to the C(sp^3) atom has attracted enormous interest in pharmaceutical and agrochemical science owing to its unique properties and can be found in numerous bioactive compounds (Figure 1A).[1] It can serve as a competent lipophilic hydrogen bond donor and as a bioisostere of hydroxyl, thiol, and amine groups.[2] Therefore, difluoromethylation has become a powerful strategy to modify the biological activity and solubility of a lead compound, especially through late-stage functionalization (LSF).[3] Even though C(sp^3)−CF_2H bond formation has been achieved through nucleophilic, electrophilic, and free-radical difluoromethylation, most of the methods rely on expensive reagents or building blocks that require multiple steps to prepare.[4] Difluoromethylation using abundant and inexpensive feedstock as the reagents under operationally simple and sustainable conditions is still challenging and highly desirable.

Chlorodifluoromethane ($ClCF_2H$, also known as Freon-22) represents an excellent fluorine source and is an abundant industrial raw material for the production of a variety of fluorinated polymers, such as Teflon and polyvinylidene fluoride.[5] Even though $ClCF_2H$ is a potent greenhouse gas, developing a synthetic protocol to consume this inexpensive industrial chemical as a fluoroalkylation reagent is of great interest. However, organic transformations of $ClCF_2H$ are rather limited due to its low reactivity, which mostly involves difluorocarbene intermediates.[6] Notably, Zhang et al. recently reported excellent studies on the difluoromethylation of (hetero)arylboronic acids and esters or terminal alkynes with $ClCF_2H$ through a palladium difluorocarbene pathway.[7] The same group also achieved the nickel-catalyzed difluoromethylation of (hetero)aryl chlorides and bromides with $ClCF_2H$ through a radical mechanism.[8]

Emerging and rapidly expanding photocatalysis has offered enormous opportunities to access fluorinated carbon radicals to realize previously inaccessible chemical spaces in a green and sustainable manner.[9] Among them, a variety of transformations have been developed for the difluoromethylation of alkenes.[10] Normally, HCF_2SO_2Cl and its derivatives such as difluoromethylsulfinate salts are used as CF_2H radical precursors, which are prepared from $ClCF_2H$ through several steps.[11] Therefore, it would be cost-efficient and step-economic to directly utilize $ClCF_2H$ under photocatalysis conditions, which remains challenging and has not been successfully realized.

As an inert gas, the activation of $ClCF_2H$ through hydrogen atom transfer (HAT) or halogen atom transfer (XAT) is challenging due to the high bond dissociation energies (BDEs)

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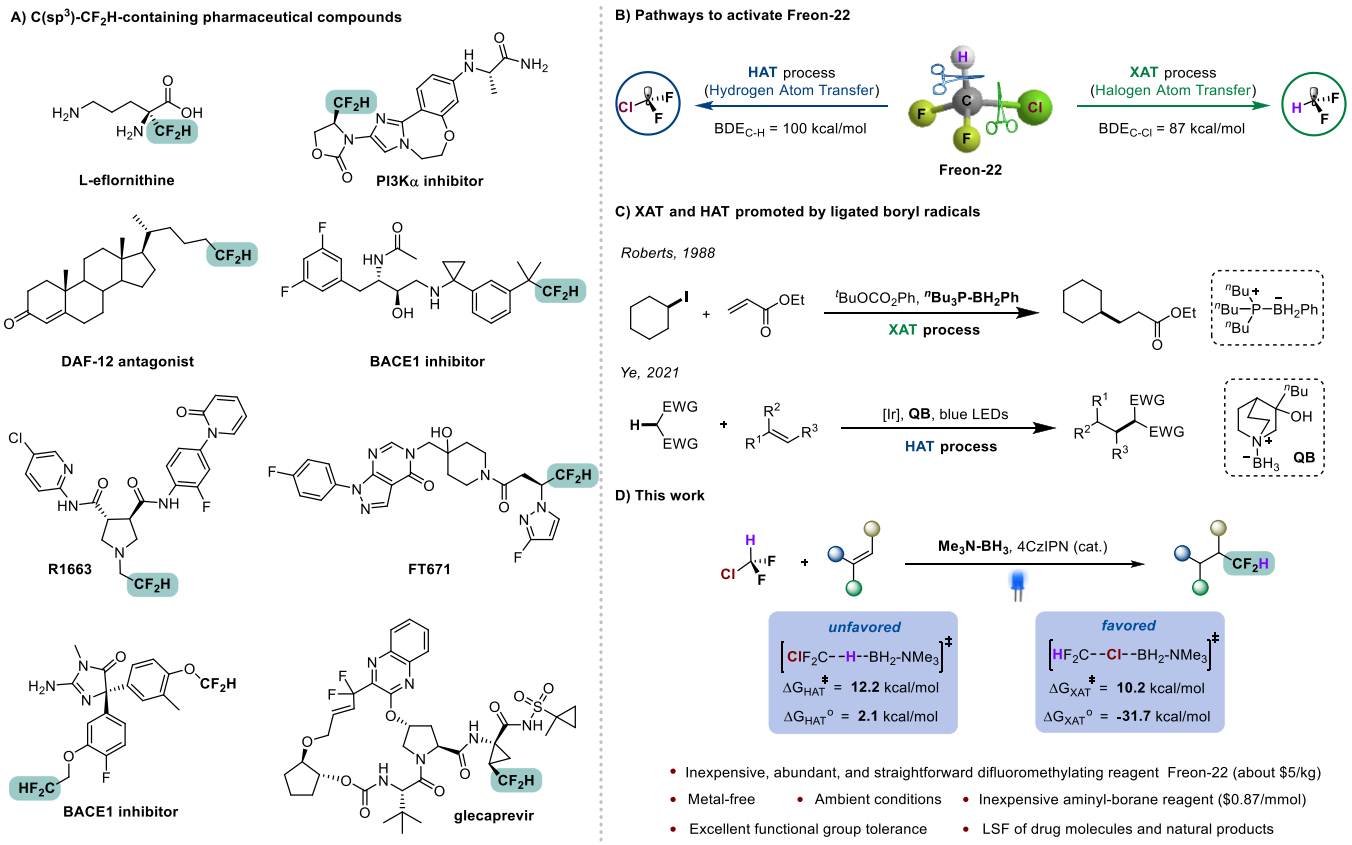

Figure 1. Difluoromethylation of unactivated alkenes using Freon-22 through a photoredox-promoted XAT process. (A) Selected examples of $C(sp^3)-CF_2H$ motifs in pharmaceutical compounds. (B) Activation of Freon-22 through HAT or XAT processes. (C) Utilization of ligated boryl radicals in XAT and HAT processes. (D) This work: development of the difluoromethylation of unactivated alkenes using inexpensive reagents in a metal-free manner. The price of Freon-22 is based on Vemac Services Pte Ltd in Singapore; the price of the trimethyl amine-borane reagent is based on Sigma-Aldrich in Singapore.

of both the C−H (~100 kcal/mol) and C−Cl (~87 kcal/mol) bonds[12] (Figure 1B). In this context, ligated boryl radicals (general formula: L_B^+-$R_2B^{\bullet-}$), pioneered by Roberts et al., have shown great potential for both XAT and HAT processes (Figure 1C)[13] owing to the accessible wide range of $BDEs_{(B-H)}$ modulated by ligands[14] and the nucleophilic character of boryl radicals. The XAT reactivity was further demonstrated by Curran and Ryu using NHC-boranes for deiodination[15] and hydroxymethylation reactions.[16] However, the synthetic application of XAT by ligated boryl radicals was limited to the activation of alkyl iodides and bromides. Very recently, the Ye group realized a HAT process for hydroalkylation of unactivated olefins using amine-boranes under photoredox catalysis.[17] In line with our ongoing interest in visible light-induced transformations using gaseous reagents as feedstocks[18] and fluoroalkylation reactions,[19] we hypothesized that a photoredox-induced ligated boryl radical may trigger either XAT or HAT with $ClCF_2H$ to produce the corresponding active radical, which can participate in subsequent transformations. We herein report the successful execution of a XAT process with $ClCF_2H$ instead of a HAT process using amine-boryl radicals for difluoromethylation of unactivated alkenes in a metal-free fashion, which can be applied for LSF of pharmaceutical compounds and natural products (Figure 1D).

RESULTS AND DISCUSSION

Reaction Optimization. Our study was initiated by evaluating the activation of Freon-22 by using ligated boranes under photoredox conditions. After extensive investigation of various ligated boranes, photocatalysts, hydrogen donors, and solvents, we found that the combination of the organic photocatalyst 4CzIPN (6 mol %), Me_3N-BH_3 (**B1**, 1.5 equiv), and PhSSPh (10 mol %) in ^{t}BuCN (0.1 M) at room temperature under 1 atm Freon-22 and 456 nm blue LED light irradiation afforded difluoromethylation product **2** in 94% yield with excellent anti-Markovnikov regioselectivity (Table 1, entry 1). Notably, no chlorodifluoromethylation product was detected, indicating that the amine-boryl radical-promoted HAT process was unfavorable compared with the XAT process (Figure 1D). Replacing Me_3N-BH_3 **B1** with other amine-boranes **B2** or **B3** resulted in decreased product yields (27 and 84%, respectively, Table 1, entry 2). No difluoromethylation product was generated when employing pyridine-borane **B4**, phosphine-borane **B5**, or NHC-borane **B6** (entry 3), probably due to the decreasing BDE values of the formed corresponding B−Cl bonds. Therefore, Me_3N-BH_3 was the most economical and effective XAT reagent to activate $ClCF_2H$ and was used throughout the rest of the study. In addition, $(TMS)_3SiH$, which has shown good halogen-atom abstraction ability under photoredox conditions,[20] was not tolerated in this transformation, generating an almost equivalent hydrosilylation byproduct (entry 4). Switching the photocatalyst from 4CzIPN to $Ir(dFCF_3ppy)_2(dtbbpy)PF_6$ or *fac*-$Ir(ppy)_3$ gave product **2** in much lower yields (entries 5 and 6). Hydromethylcyanadation became a competing pathway when MeCN instead of ^{t}BuCN was used as the solvent (entry 7). This

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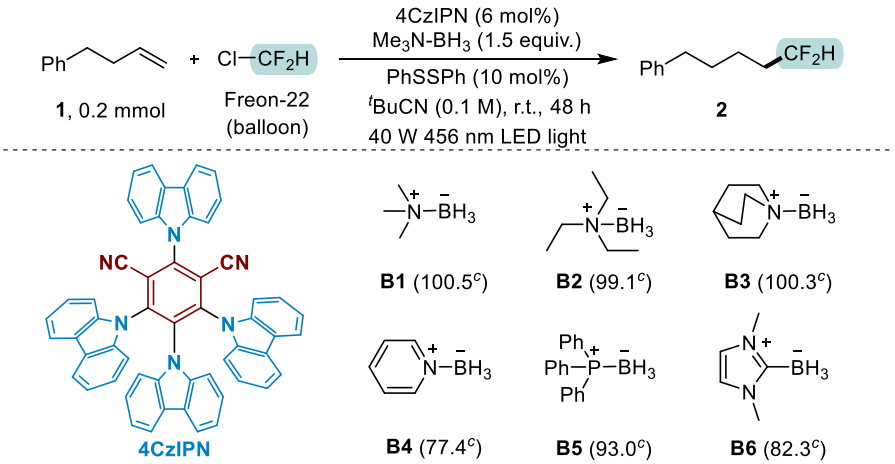
Table 1. Evaluation of Reaction Conditions for the Difluoromethylation of Unactivated Alkenes Using Freon-22



entry	deviation	yield (%)[a]
1	**none**	**94** (**90**[b])
2	**B2** or **B3** instead of **B1**	27/84
3	**B4** or **B5** or **B6** instead of **B1**	0
4	$(TMS)_3SiH$ instead of **B1**	0[d]
5	$Ir(dFCF_3ppy)_2(dtbbpy)PF_6$ instead of 4CzIPN	40
6	*fac*-$Ir(ppy)_3$ instead of 4CzIPN	0
7	MeCN instead of ^{t}BuCN	37[e]
8	without 4CzIPN or light or $Me_3N{-}BH_3$	0
9	without PhSSPh	26
10[f]	10 mmol scale	76 (1.4 g)

[a]Yields were determined by analysis of the crude ^{1}H NMR spectra using CH_2Br_2 as an external standard. [b]Isolated yield. [c]Calculated BDE of the B−H bond (kcal/mol). [d]Obtained hydrosilylation byproduct. [e]Obtained hydromethylcyanadation byproduct. [f]Reaction conducted at the 10 mmol scale using 2 equiv of $Me_3N{-}BH_3$ under 200 W 456 nm LED light irradiation for 4 days. The isolated mass of the product in parentheses. See the Supporting Information for details.

observation indicated that amine-boryl radicals induced hydrogen-atom abstraction with MeCN (a BDE_{C-H} of MeCN: ∼93 kcal/mol)[12a] to deliver cyanomethyl radicals, which underwent subsequent radical addition with alkenes. No product was detected in the absence of 4CzIPN, $Me_3N{-}BH_3$, or light, demonstrating the essential role of all these components (entry 8). PhSSPh was found to be necessary to achieve an efficient difluoromethylation of unactivated alkenes (entry 9). Finally, the reaction could be easily scaled up to gram quantities (entry 10), illustrating the practical synthetic usage of this protocol.

Substrate Scope. To our delight, the reaction protocol proves to be widely applicable to an extremely broad set of unactivated alkenes (Figure 2). Simple mono-substituted alkenes bearing various functional groups, including free hydroxyl, tosylate, chloride, carboxylic ester, carboxylic acid, and amide groups, were all well tolerated, giving the corresponding difluoromethylated alkanes **3**−**8** in 72−96% yields. Nitrogen, boron, silicon, and phosphorus atom-tethered alkenes were also competent reaction partners (**9**−**12**). Intriguingly, this light-promoted difluoromethylation reaction tolerated strained rings such as oxetane (**13**) and cyclopropane (**14**). Alkenes possessing different aromatic scaffolds, including substituted phenyl (**15**−**17**), carbazole (**18**), furan (**19**), and thiophene (**20**) moieties, could smoothly participate in hydrodifluoromethylation. Furthermore, di-substituted terminal alkenes with different aliphatic chains were well accommodated and led to the corresponding products **21**−**26** in moderate to good yields with excellent anti-Markovnikov regioselectivity. The presence of cyclic structures, including cyclobutane, piperidine, adamantane, and cyclododecane rings, was found to be amenable to deliver the desired products **27**−**30**, among which cyclobutane derivative **27** was obtained as a mixture of diastereoisomers. Both cyclic and acyclic di-substituted internal alkenes could also effectively participate in this reaction and afforded CF_2H-functionalized cyclononane **31** and α-CF_2H boronic ester **32** (1.5:1 regioselectivity) in good yields. Importantly, constant anti-Markovnikov regioselectivity was obtained with tri-substituted alkenes, and the difluoromethylation products **33**−**35** were obtained in moderate to good yields. However, sterically encumbered tetra-substituted alkene was unreactive under the current conditions (**36**). Moreover, a substrate bearing two olefin motifs could be fully difluoromethylated at both sites, affording compound **37** in 92% yield. However, styrenes and electron-deficient alkenes were not tolerated under our reaction conditions, where a significant amount of hydrogenation byproducts was generated owing to the strong reducing ability of the amino-borane reagent.

The broad scope of hydrodifluoromethylation inspired us to explore the feasibility of its application to the LSF of complex pharmaceutical molecules and natural products. To our delight, the protocol was effective for an extremely wide range of complex alkenes directly from or derived from natural products, drug molecules, and functional material molecules (Figure 3). Mono-substituted alkenes derived from menthol (**38**), borneol (**39**), sultam (**40**), ibuprofen (**41**), dichlorophenoxyacetic acid (**42**), carprofen (**43**), sclareol (**44**), vinclozolin (**45**), and bioallethrin (**46**) were all suitable substrates. Di-substituted terminal alkenes featured in the core structures of camphene

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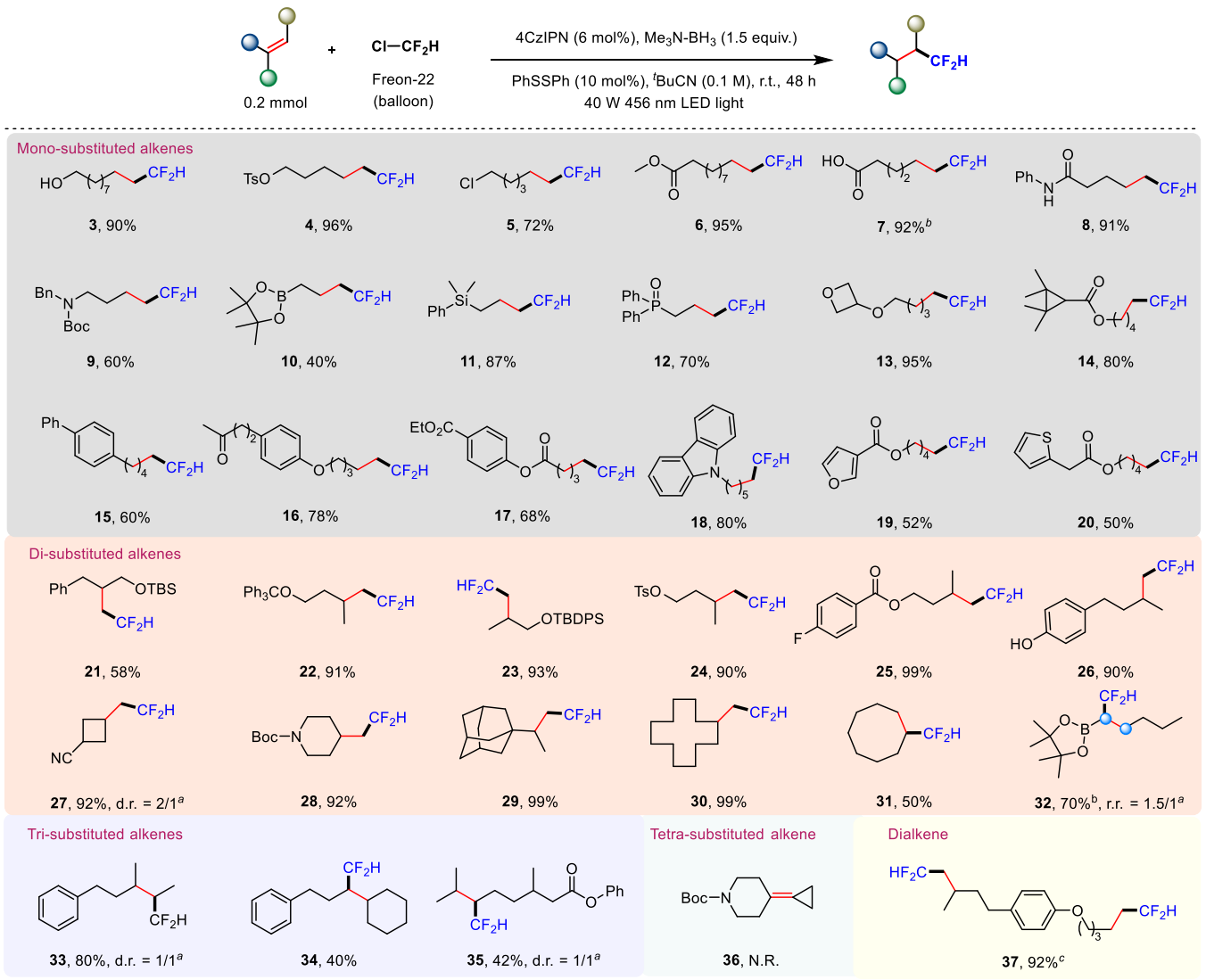

Figure 2. Hydrodifluoromethylation of unactivated olefins using Freon-22. (a) Diastereomeric ratio (d.r.) or regioisomeric ratio (r.r.) values were determined by ^{1}H or ^{19}F NMR analysis of the crude reaction mixture. (b) 2.0 equiv of Me_3N-BH_3 was used. (c) 10 mol % of 4CzIPN and 4.0 equiv of Me_3N-BH_3 were used.

(**47**), isopulegol (**48**), dihydrocarvone (**49**), liquid crystal building blocks (**50**), longifolene (**51**), nootakone (**52**), and roteone (**53**) could also smoothly undergo difluoromethylation. A di-substituted internal alkene located in an open aliphatic chain derived from petroselinic acid gave the difluoromethylation product **54** in a 1:1 regioselectivity. It is worth noting that tri-substituted acyclic and cyclic alkene-containing natural products including citronellol, pregnenolone, and cholesterol participated in this transformation to deliver the difluoromethylation products **55** to **57** in an anti-Markovnikov fashion with excellent regioselectivity. Good diastereoselectivity was observed in products **56** and **57**, and the absolute configuration of the major isomer of **56** was ambiguously assigned by single-crystal X-ray analysis of its derivative. These preliminary results highlight the promising potential of this protocol for practical usage in drug discovery.

Mechanistic Studies. A series of experimental and computational studies were conducted to explore the mechanism of this reaction (Figure 4). First, examining the mass balance of the model reaction confirmed the generation of Me_3N-BH_2Cl (**58**) and Me_3N-$BHCl_2$ (**59**) as the corresponding byproducts (Figure 4A), in line with the initially proposed XAT process. The radical trapping experiment with the radical scavenger 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) completely inhibited the formation of difluoromethylated product **2**, and the adduct TEMPO-CF_2H was detected (Figure 4B). A radical clock experiment with bicyclic terpene β-pinene under standard conditions afforded the ring-opened product **60** in 50% yield (Figure 4C). These two observations clearly supported the radical nature of this transformation. Importantly, the reaction could be extended to other electron-deficient alkyl halides effectively (**61** and **63**), while alkyl halides without electron-withdrawing substituents gave no products (**62** and **64**, Figure 4D), mainly due to the stabilized partial negative charge in the XAT transition state (TS) in the presence of electron-withdrawing substituents.[20e] Furthermore, two parallel reactions using Me_3N-BH_3 and Me_3N-BD_3 were conducted, and a small amount of deuterium atoms was incorporated into product **2** (16% D) in the latter case. The kinetic isotope effect (KIE) value was measured to be 1.2, implying that boryl radical generation might not be involved in the rate-determining step (Figure 4E). Control experiments with the addition of deuterium oxide led to

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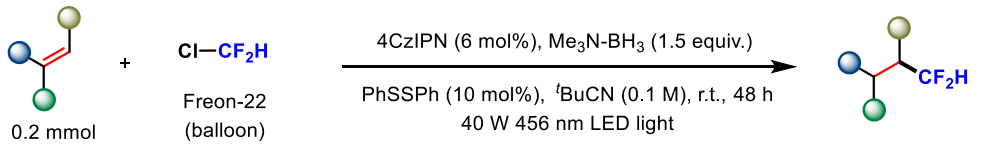

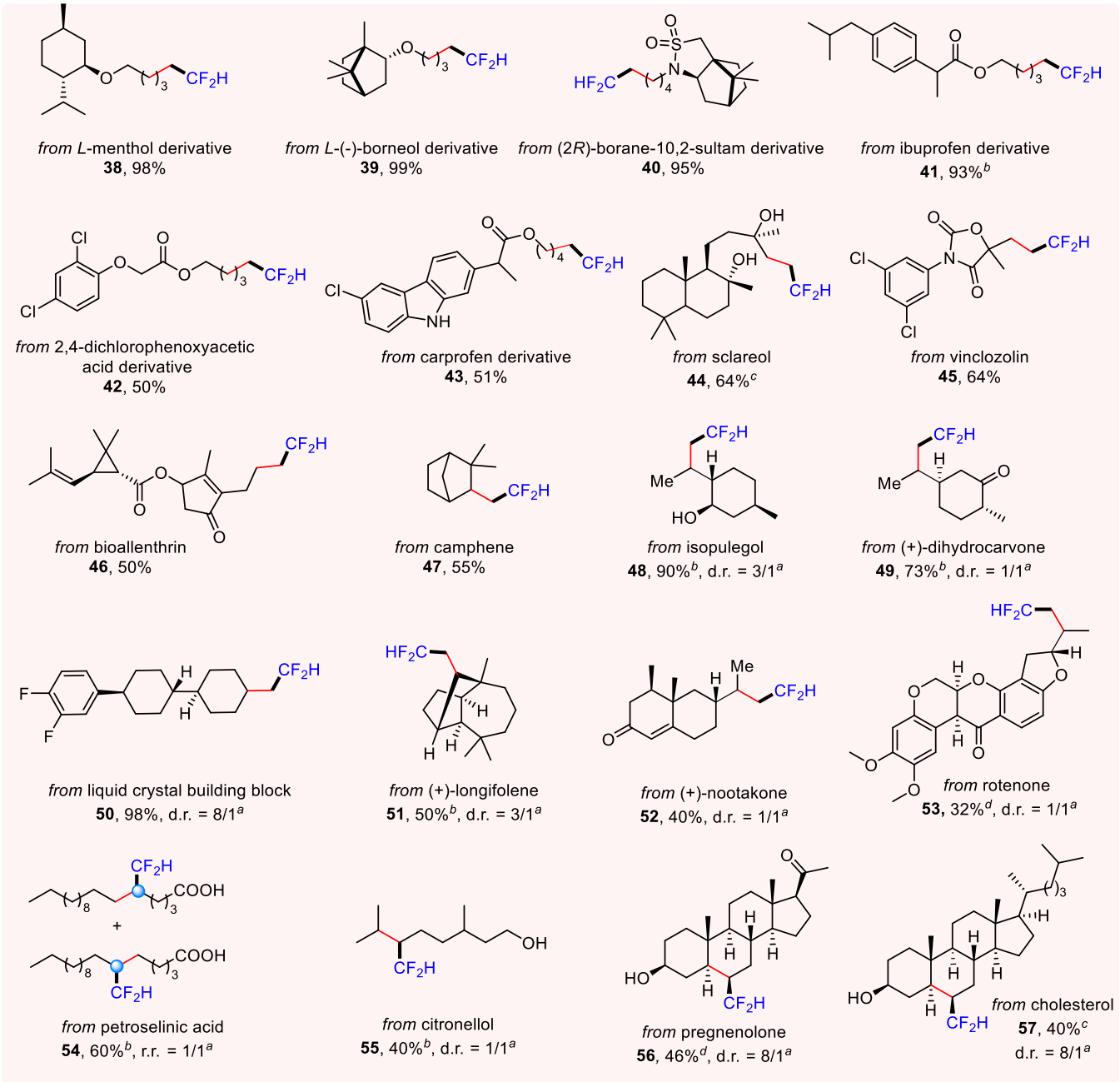

Figure 3. LSF through hydrodifluoromethylation of pharmaceutical compounds, natural products, and derivatives. (a) Diastereomeric ratio (d.r.) or regioisomeric ratio (r.r.) values were determined by ^{1}H or ^{19}F NMR analysis of the crude reaction mixture; (b) 2.0 equiv of Me_3N-BH_3 was used; (c) 3.0 equiv of Me_3N-BH_3 was used; and (d) DMSO/^{t}BuCN = 1/1, 10 mol % 4CzIPN, and 3.0 equiv of Me_3N—BH_3 were used.

the formation of product **2** with 80% deuterium incorporation, suggesting that proton exchange is possible during the reaction process. Stern—Volmer quenching experiments with Me_3N-BH_3 and PhSSPh indicated that the excited photocatalyst could be quenched more effectively by PhSSPh than by Me_3N-BH_3 (Figure 4F).

Moreover, density functional theory (DFT) calculations (Figure 5A, see the Supporting Information for details) demonstrated a facile and irreversible XAT process, which possesses an activation barrier of 10.2 kcal/mol and is exergonic by 31.7 kcal/mol (Figure 5A-1). For comparison, the HAT process is slightly endergonic and disfavored due to a barrier higher than that of XAT by 2.0 kcal/mol. This energy difference could be ascribed to the molecular orbitals of $ClCF_2H$ where the antibonding orbital of the C—Cl bond (σ*C—Cl, LUMO) lies below that of the C—H bond (σ^{*}_{C-H}, LUMO + 1) (Figure 5A-2).

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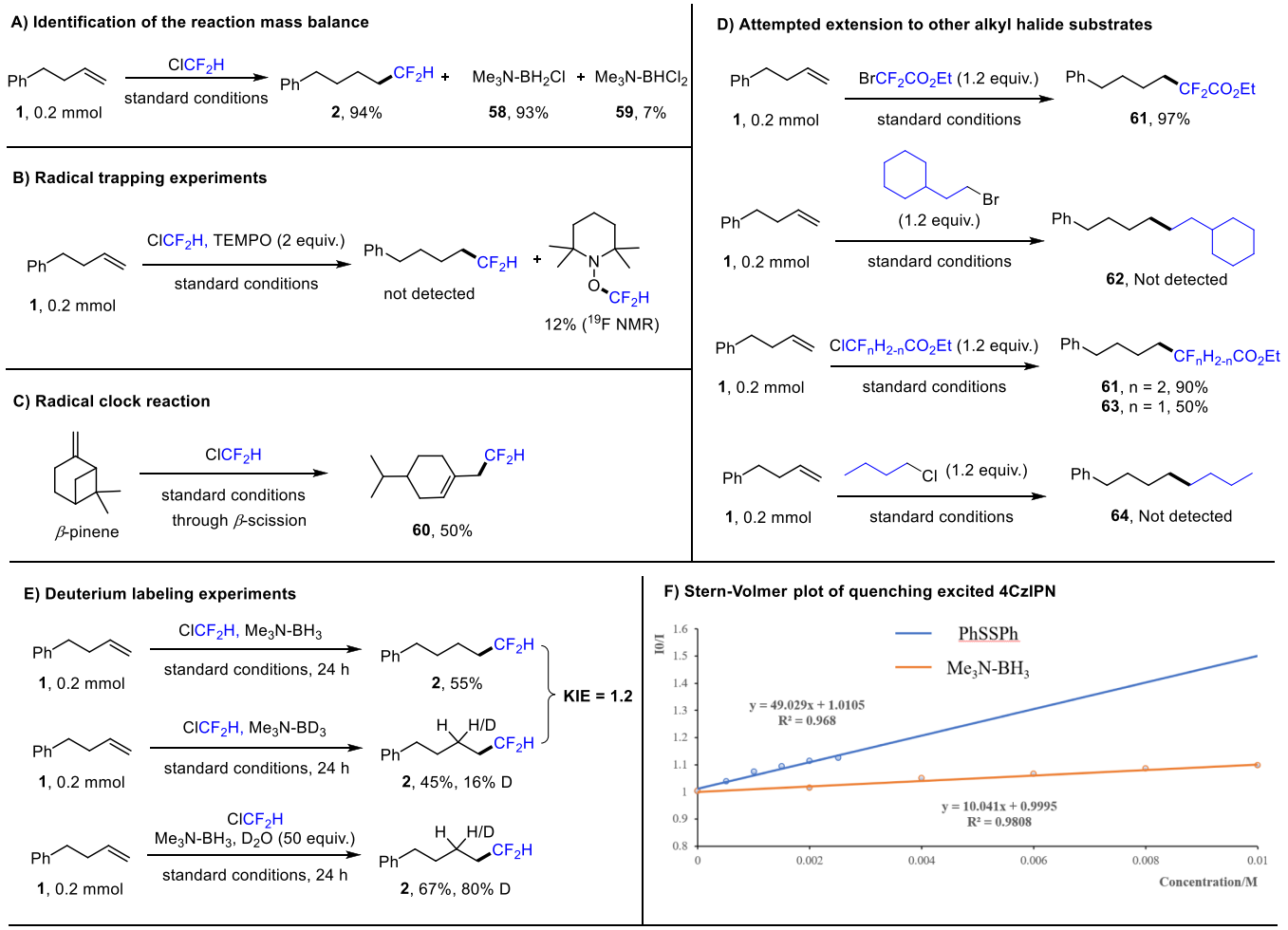

Figure 4. Control experiments for mechanistic studies.

Therefore, the former orbital preferentially interacts with the singly occupied molecular orbital of the ligated boryl radical. Clearly, the thermodynamic driving force for the XAT reaction is the formation of a more stable B−Cl bond (calc. BDE = 117 kcal/mol) compared to the original C−Cl bond (calc. BDE = 86 kcal/mol). The nucleophilic character of the amine-boryl radical allows the accumulation of a partial positive charge on the boron atom, thus decreasing the XAT barrier through a polar effect (Figure 5A-3). As a consequence, mono- and dichloroboryl radicals are not nucleophilic enough to accelerate the reaction. The XAT process has an early-stage TS where the C−Cl bond is slightly elongated by 0.16 Å (change from 1.78 to 1.94). The reaction coordinate derived from this TS shows that partial spin transfer precedes C−Cl bond cleavage as the spin density of the amine-boryl radical decreased to 0.621 (TS) from 1.000 (separated radicals).

Based on all the experimental and calculation results and previous literature studies,[17,21] a tentative mechanism is proposed as shown in Figure 5B. Aryl thiyl radicals are generated from disulfide homolysis under blue light irradiation and can be reduced [$E(PhS^{\bullet}/PhS^{-}) = 0.16$ V vs SCE] by the excited state of 4CzIPN* [$E_{1/2}$ ($PC^{\bullet+}/PC^{*}$) = −1.18 V vs SCE in MeCN] to give thiol anion species and the oxidized form $PC^{\bullet+}$ of the photocatalyst. The amine-boryl radical may be produced with the aid of $4CzIPN^{\bullet+}$ either through a single electron transfer (SET)/deprotonation sequence or via a concerted proton-coupled electron transfer (PCET) process. Subsequently, the nucleophilic boryl radical undergoes a facile XAT process with $ClCF_2H$ to generate the transient CF_2H radical. An intermolecular radical addition occurs with the alkene substrate followed by a HAT event of the radical adduct with thiophenol, which leads to the final hydrodifluoromethylation product and regenerates the thiyl radical.

CONCLUSIONS

In summary, hydrodifluoromethylation of unactivated alkenes by using cheap and abundant HCF_2Cl as the fluorine source has been successfully established under mild and metal-free conditions. This method features a remarkably wide substrate scope and versatile LSF of complex bioactive molecules. The combination of photoredox catalysis with ligated tertiary amine boranes proves to be a powerful strategy for the selective XAT process to activate $ClCF_2H$, thus opening a new direction for the utilization of Freon chemical feedstock in practical synthetic chemistry.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.2c05356.

General procedures, reaction optimizations, analytical data, calculation details, and characterization data for all the products (PDF)

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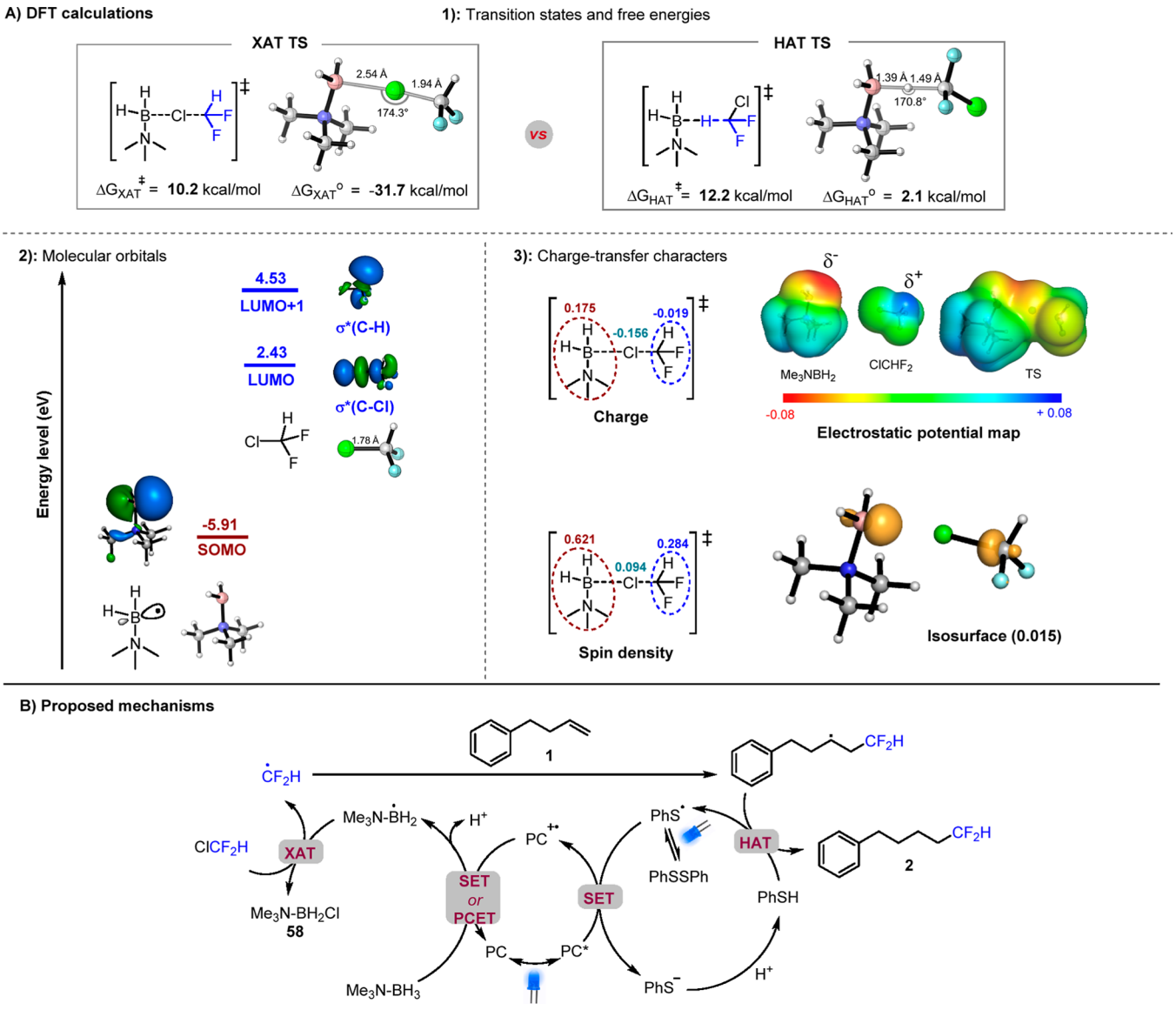

Figure 5. Computational mechanistic studies and proposed mechanisms.

Accession Codes

CCDC 2173428 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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