

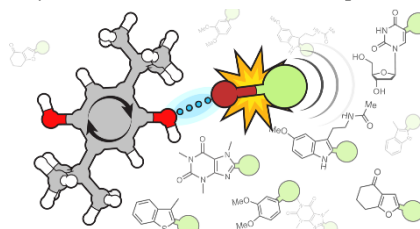
Radical Perfluoroalkylation Enabled by a Catalytically Generated Halogen Bonding Complex and Visible Light Irradiation

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Supporting Information Placeholder

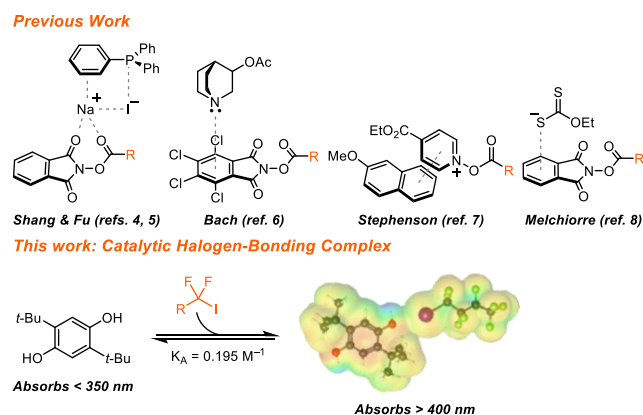
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ABSTRACT: Despite the many recent advances in exploiting stoichiometric charge-transfer complexes in visible light promoted single-electron redox reactions, catalytic approaches to charge-transfer complex formation remain limited. This report describes the radical perfluoroalkylation of electron-rich (hetero)arenes and iodoperfluoroalkylation of alkenes and alkynes promoted by a substituted hydroquinone catalyst. Mechanistic and computational studies indicate that the reaction is initiated by the formation of a visible light absorbing halogen bonding complex between the hydroquinone catalyst and the perfluoroalkyl iodide radical precursor.

In recent years, the synthetic community has begun to exploit an alternate photochemical approach involving the association of an electron-rich substrate (donor) and an electron-poor substrate (acceptor) in the ground state, forming an electron donor-acceptor or charge-transfer complex (CTC).^{1,2} While the individual substrates do not absorb in the visible region (400-700 nm), the CTC often does, providing practitioners with alternative strategies for single-electron redox reactions initiated by visible light irradiation.³ However, a drawback to this approach is that it generally requires the stoichiometric use of specifically tailored substrates, limiting the overall scope of these transformations. One solution that remains underexplored is a catalytic approach to CTC formation. This strategy alleviates the requirement of using two substrates in stoichiometric quantities to form a CTC and has the potential to greatly expand the scope of suitable acceptors (radical precursors). Examples of such systems are extremely limited, likely owing to the difficulty of implementing a suitable catalyst turn-over step¹, or because of issues arising from catalyst deactivation that result from radical addition to the catalyst. Scheme 1 highlights the seminal contributions from Shang and Fu^{4,5}, Bach⁶, Stephenson⁷ and Melchiorre⁸ for catalytic CTC systems that use a donor catalyst which serves to engage acceptors, generating radicals under visible light irradiation. While these examples represent important advancements in the field, they are limited in the scope of the acceptor; namely *N*-(acyloxy)phthalimide esters, *N*-alkylpyridinium salts, Togni's reagent and pyridine *N*-oxides generated from acid chlorides and anhydrides. Furthermore, only Stephenson's method is suitable to access readily available materials⁷, while the others require further derivatization for reactivity.

Scheme 1. Examples of catalytic charge-transfer complexes.



In order to broaden the scope of acceptors (radical precursors), we envisioned that hydroquinones (HQs) could serve to catalytically engage alkyl halides through CTC formation. The quinone/hydroquinone redox couple has been widely exploited for catalytic oxidation reactions in organic synthesis.⁹ We hypothesized that by starting with appropriately substituted HQs that would not be prone to radical addition, the lone pairs on the hydroxyls could serve to engage with alkyl halides via a halogen bonding interaction¹⁰, leading to a selective CTC that could be activated by visible-light irradiation.^{11,12} Successful implementation of a halogen bonding photocatalytic system would greatly expand the chemical space of acceptors for CTC photocatalysis, owing to the prevalence and ease of synthesis of alkyl halides.

In this report, we present the radical perfluoroalkylation of electron-rich (hetero)arenes and the iodoperfluoroalkylation of

alkenes and alkynes promoted by the visible light irradiation of a catalytically generated CTC between a HQ catalyst and the perfluoroalkyl halide precursor (Scheme 1). Insights into the underlying mechanism of these transformations is also disclosed.

We chose to begin our examination of HQs as halogen bonding photocatalysts with the radical perfluoroalkylation of caffeine (Table 1). Perfluoroalkyl iodides have been shown to participate in halogen bonding interactions¹²⁻¹⁸ owing to their large σ -holes^{19,20}, providing a suitable reaction to investigate the reactivity of HQ as catalysts. Furthermore, while there are examples utilizing sub-stoichiometric donors for the activation of perfluoroalkyl halides^{11,21-23}, many of these reactions all proceed via a chain-propagating atom-transfer radical addition (ATRA) mechanism. Therefore, these sub-stoichiometric donors likely only serve as initiators in these systems, limiting the scope of suitable substrates to alkenes and alkynes. After a preliminary set of experiments (see SI), we identified 2,5-di-*t*Bu-HQ (DTHQ) as a suitable catalyst for our perfluoroalkylation reactions. After further optimization, the desired perfluoroalkylated caffeine product **1** could be generated in 65% yield using 3 equiv. of perfluorobutyl iodide ($\text{C}_4\text{F}_9\text{I}$), 10 mol% DTHQ, 50 mol% sodium triacetoxyborohydride (STAB) as a sacrificial reductant to aid with catalytic turnover, 2 equiv. NaHCO_3 , an 11:1 mixture of MeCN:MeOH as the solvent and irradiation from two white LEDs for 24 h (Table 1, entry 1).²⁴ Control reactions demonstrated that degassed conditions, NaHCO_3 , DTHQ, and light were all integral for reactivity (entries 2-5). Pleasingly, the reaction could be conducted in the absence of STAB without any loss in reactivity (entry 6), and the yield of **1** could be increased to 70% by increasing the reaction time to 30 h (entry 7). Addition of TEMPO to the reaction mixture suppressed the production of **1** (entry 8) while also yielding 14% of the TEMPO- C_4F_9 adduct (see SI), supporting the formation of radical intermediates derived from the perfluoroalkyl iodides.

Table 1. Optimization and control reactions for the perfluoroalkylation of caffeine.

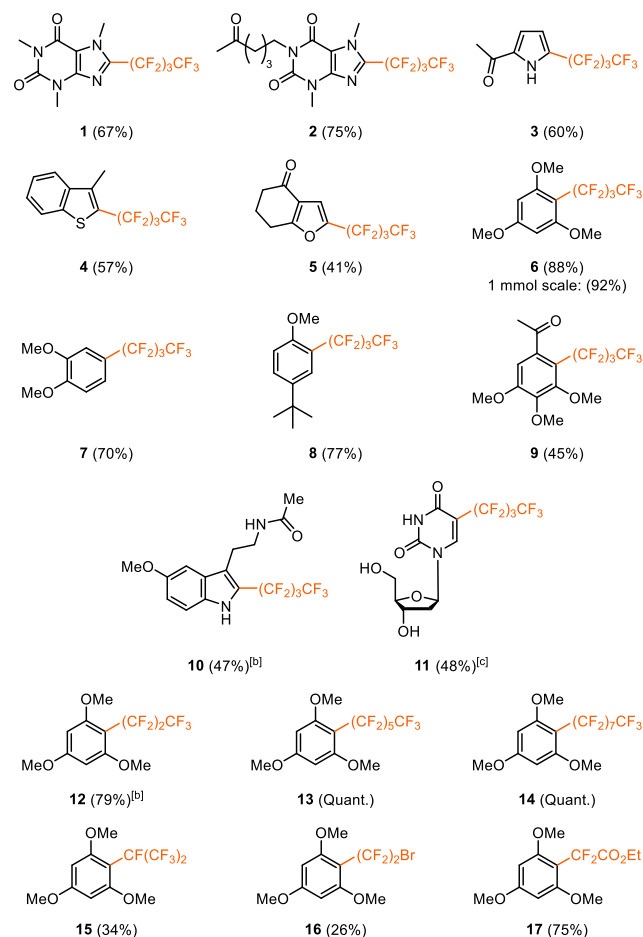
entry	deviations from standard conditions	yield (%) ^[a]
1	None	65
2	reaction conducted under air	8
3	no NaHCO_3	22
4	no DTHQ	Trace
5	reaction conducted in the dark	Trace
6	no STAB	61
7	no STAB, reaction time: 30 h	70
8	no STAB, TEMPO (1 equiv)	Trace

[a] Yields determined by ^{19}F NMR using 4-fluorobenzoic acid as an external standard. STAB: sodium triacetoxyborohydride.

With optimized conditions identified, we examined the scope of the DTHQ-catalyzed perfluoroalkylation of (hetero)arenes (Scheme 2). Five-membered nitrogen-, sulfur- and oxygen-based heteroarenes (**1-5**) were all well tolerated. Electron-rich arenes also reacted well under our reaction conditions (**6-9**). Moreover, the reaction with 1,3,5-trimethoxybenzene (**6**) could be performed at 1 mmol scale without any loss in reactivity. Biologically active heteroarenes melatonin and 2'-deoxyuridine

gave perfluoroalkylated products **10** and **11** in 47% and 48% yield, respectively. For examples in which more than one regioisomer is possible, complete selectivity for addition to the most nucleophilic position of the (hetero)arene was observed (see **3**, **5**, **7**, **8**, and **11**). Using 1,3,5-trimethoxybenzene as the radical acceptor, the scope of the perfluoroalkyl iodide was also evaluated. Perfluoropropyl, perfluorohexyl, and perfluorooctyl iodide all reacted in high yields under our optimized conditions (**12-14**). The more sterically hindered perfluoroisopropyl iodide was less efficient, giving **15** in 34% yield. Notably, 1-bromo-2-iodotetrafluoroethane formed the radical exclusively through activation of the C-I bond over the C-Br bond, albeit giving product **16** in a modest 26% isolated yield. A difluorinated alkyl iodide bearing an electron-withdrawing ester was also tolerated, giving **17** in 75% isolated yield.

Scheme 2. Reaction scope for the radical perfluoroalkylation of (hetero)arenes.^[a]

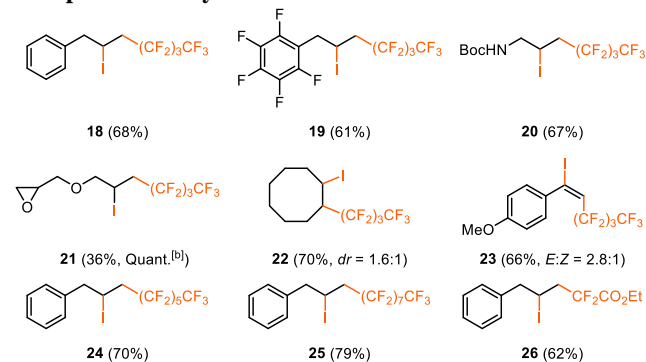


[a] Yields of isolated, purified products after 30 h of irradiation using the optimized conditions (see General Procedure in the Supporting Information). [b] Reaction conducted with 1 equiv. of $\text{R}_\text{f}\text{I}$. [c] Reaction conducted in DMSO.

Next, we examined whether our catalytic CTC formation strategy was also suitable for the ATRA reaction of alkenes and perfluoroalkyl iodides (Scheme 3). Pleasingly, the ATRA reaction proceeded in good yields (61-79%) for a range of alkenes (**18-22**), alkynes (**23**) and perfluoroalkyl iodide precursors (**24-26**). The reaction was also found to tolerate epoxides (**21**), which have previously been shown to be susceptible to redox reactions under photoredox conditions.²⁵⁻²⁸ This highlights the potential synthetic utility of our catalytic halogen bonding activation

strategy, as C–I bonds can be selectively cleaved even in the presence of other redox-sensitive functional groups.

Scheme 3. Reaction scope for the ATRA reaction of alkenes with perfluoroalkyl iodides.^[a]



[a] Yields of isolated, purified products after 30 h of irradiation using the optimized conditions (see General Procedure in the Supporting Information). [b] Yield determined by ¹⁹F NMR using 4-fluorobenzoic acid as an external standard.

To determine whether a CTC between the DTHQ catalyst and the perfluoroalkyl iodide was responsible for the observed reactivity under visible light irradiation, we turned to UV-Vis studies (Figure 1). While DTHQ does not absorb in the visible region on its own, addition of C₄F₉I resulted in large redshift in the absorbance, which is indicative of the formation of a CTC.³ It is important to note that the CTC complex occurs with the protonated form of DTHQ and not the phenolate anion, as no change was observed in the absorption spectrum of DTHQ upon the addition of NaHCO₃ (see SI for a spectrum of the corresponding phenolate). Benesi–Hildebrand analysis²⁹ of the C₄F₉I–DTHQ complex indicated that the stoichiometry of the complex is 1:1 with an association constant (K_A) of 0.195 M⁻¹ (see SI).

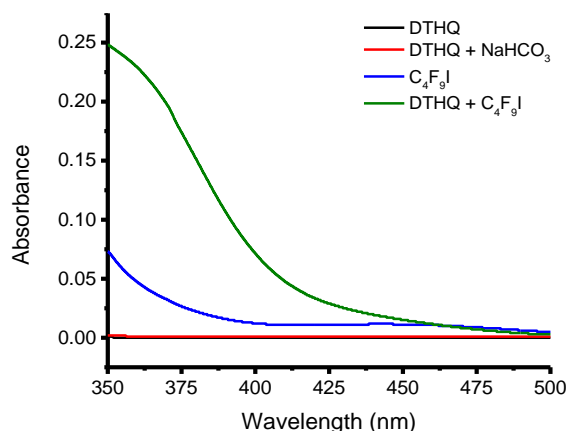
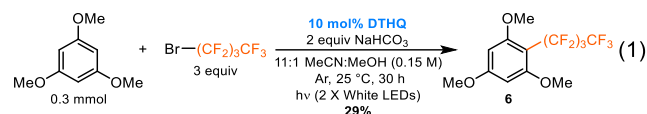


FIGURE 1. Absorption spectra of DTHQ, DTHQ + NaHCO₃, C₄F₉I, and DTHQ + C₄F₉I. [DTHQ] = 15 mM, [NaHCO₃] = 0.3 M, [C₄F₉I] = 0.45 M in 11:1 MeCN:MeOH.

To investigate whether or not the DTHQ–C₄F₉I occurs through a halogen bonding interaction, we employed a series of computational studies to assess the nature and relative strength of possible noncovalent interactions (see SI for complete details of all calculations performed). DFT configurational scans were performed using a minimal 3-21G basis set with the Gaussian03 package and the B3LYP functional,^{30–33} and they identified the dominant contacts to be between the iodine of C₄F₉I and electron-rich hydroxyl and aromatic ring regions of DTHQ. The enthalpies were found to favor halogen bonding to the hydroxyl

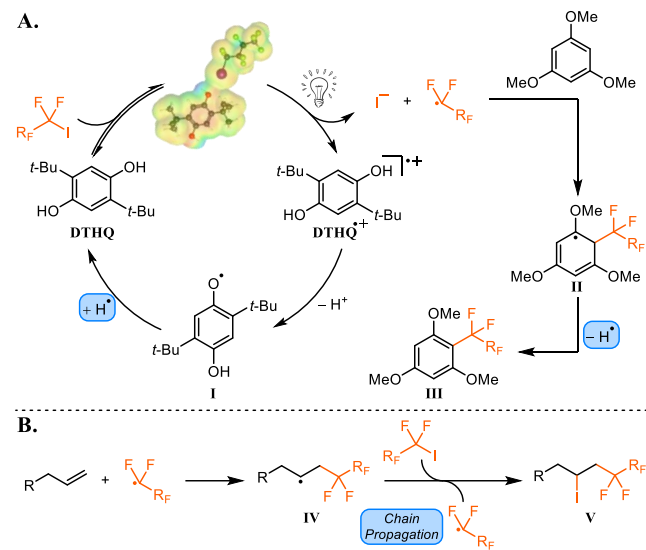
group by 3.9 kJ/mol. The relative halogen bond strengths for a series of simplified HQs and substrate structures were screened to identify an accurate functional and basis set combination, B3LYP/Def2-TZVPP with DFT-D3 dispersion correction.^{30,32–35} These calculations indicated strong halogen bonding enthalpies for both the DTHQ–C₄F₉I (–12.2 kJ/mol) and DTHQ–C₄F₉Br (–7.7 kJ/mol) complexes, and these interactions have the potential to be further strengthened through HQ modification that reduces steric occlusion near the hydroxyl groups observed with DTHQ. While the bulky *t*Bu groups were found to interfere with halogen bonding, in practice they serve the important purpose of eliminating catalyst deactivation by blocking perfluoroalkyl radical addition to the catalyst, an issue we observed with unsubstituted HQ in our preliminary studies.

As the calculations indicate significant halogen bonding interaction strength for the C₄F₉Br, we tested the reactivity of this substrate in functionalization of 1,3,5-trimethoxybenzene, a system where we observed near quantitative yields with C₄F₉I (see Scheme 2). The reaction was successful, though with reduced yield (eq 1), likely owing to both the stronger C–Br bond and weaker halogen bond strength between DTHQ and the bromine.



The proposed mechanism for the radical perfluoroalkylation of (hetero)arenes is outlined in Scheme 4A. A CTC complex is initially formed between DTHQ and the perfluoroalkyl iodide, which occurs through a halogen bonding interaction between the hydroxyl lone pair and the σ* orbital of the C–I bond. The CTC is then excited with white LED irradiation leading to single-electron transfer, generating a perfluoroalkyl radical and a DTHQ^{•+}, which is subsequently deprotonated to form phenoxy radical **I**. The perfluoroalkyl radical adds to the electron-rich (hetero)arene to give intermediate **II**, which undergoes a HAT reaction with **I** to yield the perfluoroalkylated (hetero)arene (**III**) and DTHQ, completing the crucial catalyst turnover step, often noted as the primary challenge in CTC catalysis. For the ATRA reaction of alkenes (Scheme 4B), the perfluoroalkyl radical adds to the alkene to give radical intermediate **IV**, which can abstract an iodine atom from another perfluoroalkyl iodide in a chain propagating event to yield the ATRA product **V**.

Scheme 4. Proposed mechanism for the DTHQ-catalyzed radical perfluoroalkylation of electron-rich (hetero)arenes (A) and alkenes via an ATRA reaction (B).



In summary, a method for visible light mediated radical perfluoroalkylation reactions with (hetero)arenes and alkenes utilizing a substituted hydroquinone as a donor catalyst for CTC formation has been developed. The formation of the CTC is believed to proceed via a halogen bonding interaction between the lone pair of the hydroxyl group of DTHQ and the σ^* orbital of the C–I bond. The reaction is tolerant of several (hetero)arene substrates and can also be expanded to include functionalization of olefins through an ATRA mechanism, demonstrating that catalytic CTC formation can be an efficient and general strategy for radical perfluoroalkylation reactions.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, reaction optimization, compound characterization, computational studies and NMR spectra (PDF)

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Notes

The authors declare no competing financial interests

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