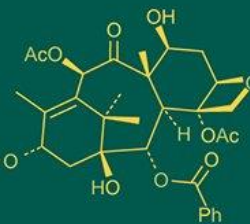
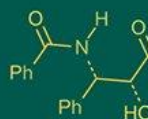
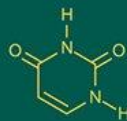
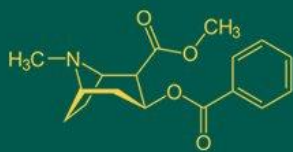


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Activation of strong and electron-deficient bonds by catalysis the transfer of double hydrogen atoms

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Abstract

A difficult issue in synthetic organic chemistry is the direct functionalization of inert carbon-hydrogen (C-H) bonds, especially the strong and unactivated C(sp³)-H bonds. While there is great potential in integrating photoredox with hydrogen atom transfer (HAT) catalysis, current systems have limitations such as a restricted substrate range and the inability to activate C-H bonds with electron deficiencies. Here, by combining the strengths of two different HAT mediators, we provide a new photocatalytic platform that gets beyond these restrictions. Achieving site-selective alkylation of an unexpectedly wide range of C-H bonds is achieved by coupling a highly oxidizing acridinium photocatalyst with a quinuclidine-derived radical cation and a thiyl radical. Ethers, non-activated alkanes, and even electron-deactivated systems that were previously thought to be resistant to functionalization may all be effectively treated with this dual HAT system. Stern-Volmer quenching, radical clock experiments, density-functional theory (DFT) calculations, and other mechanistic investigations validate the participation of many radical intermediates and provide light on the complementary process behind the observed selectivity and reactivity. By using this technique to functionalize complicated medicines at the last step and synthesize a bioactive lipid analogue concisely, we show that this technology has synthetic utility. There will likely be extensive use of this work's novel approach to C-H functionalization in synthetic chemistry since it is both generic and innovative.

Keywords: Photoredox catalysis, functionalization of C-H bonds, hydrogen atom transfer (HAT), late-stage functionalization, radical chemistry, dual catalysis, and so on

1. Introduction

1.1 Greetings and Initial Concepts

One of the primary objectives of contemporary organic synthesis is the direct functionalization of carbon-hydrogen (C-H) bonds, which poses a significant barrier. The goal of using ubiquitous C-H bonds as intrinsic functional groups has driven the development of transition metal catalysis, primarily using palladium, rhodium, and ruthenium. Traditional methods for constructing carbon-carbon and carbon-heteroatom bonds often rely on pre-functionalized starting materials, which requires additional synthetic steps, leads to the formation of stoichiometric waste, and reduces overall efficiency.

Simultaneously, photoredox catalysis has become a potent method for producing reactive intermediates in mild environments by means of visible light. This method takes advantage of the fact that photoactive catalysts, such as organic dyes or Ru or Ir polypyridyl complexes, can undergo single-electron transfer (SET) reactions with substrates when exposed to light. By combining photoredox catalysis with C-H functionalization, a flexible platform has been developed for accomplishing transformations that were previously inaccessible under very mild conditions.

2. Theories of how photoredox activates C-H bonds

It is possible to classify the interactions between photoredox catalysts and C-H bond cleavage events into many sets of mechanisms.

- PHT, or photostimulation of hydrogen atom transfer, uses photoredox catalysis to effect near-human H₂ production. In their groundbreaking work, McMillan and coworkers found that a nucleophilic α -amino radical can emerge from a sp³ C-H bond next to the neighboring nitrogen using a photoredox catalyst and quinuclidine mediator. Their PHT

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- method also allowe the direct coupling of parent amines to various electron-deficient olefins. Knowles and colleagues further clarified the role of proton-coupled electron transfer (PECT) in similar systems, extending its reach to strong, unactivated C-H bonds ^[1, 2]. This concept was also applied to the functionalization of benzyl ^[3] and unactivated aliphatic C-H ^[4] bonds as well as aldehyde C(H) bonds.
- Liquid-to-metal charge transfer (LMCT) accelerated by photoredox. By contrast, the LMCT process involves a more direct HAT mechanism. This reaction leads to ligand-based radicals and low-valent metals through stimulating a substrate-catalyst complex-stabilizing electron transfer from ligand to metal, such as a carboxylate that's attached Fe or Cu. This type of technique, as was elegantly demonstrated by Rovis ^[5] and owner Nitzevich ^[6], allows for C-H alkylation of heteroarenes and electron-rich arenes by using decarboxylating nucleophilic alkyl radicals from ordinary carboxylic acids.
- Radical crossover mediated by photoredox. In this kind, a radical is formed using photoredox catalysis; it is then reduced to a carbanion or oxidized to a carbocation, respectively. For instance, according to Nitsevich, photochemical oxidation of alkenes to radical cations, followed by capture and reduction to carbocations, can be used to accomplish anti-Markovnikov hydrofunctionalization. On the other hand, Molander's group came up with methods where excited photoredox catalysts were used to oxidize alkyl trifluoroborate salts, resulting in radicals that could be reduced to organometallic nucleophiles. Together, photoredox and transition metal catalysis form
- The integration of photoredox catalysis with conventional transition metal catalysis, such nickel, has been a game-changer since it eliminates the need for organometallic partners in cross-coupling processes. According to ground-breaking research by Molander ^[7] and McMillan ^[8], aryl halides may be cross-coupled with alkyl radicals produced by a photoredox catalyst using a number of different precursors. Heteroarenes' direct C-H coupling is a common example of this paradigm in action, with the photoredox cycle releasing an electrophilic radical from the compound before the Ni catalyst-catalyzed cross-coupling captures it ^[9, 10]. This method has been used to many metals, such as cobalt for C-H activation and copper for C-N coupling ^[11].

3. Synthetic toolbox expansion

Kinds of basic reactions to the aforementioned structural mechanisms, many C-H functionalization processes were possible. Thirdly, C-H alkylation.

An important focus of study is the direct alkylation of C-H bonds. Results have been obtained by using strategies including HAT catalysis ^[12], LMCT from carboxylic acids ^[13], and dual photoredox/Ni catalysis from redox-active esters ^[14]. By breaking down redox-active esters, Leonori created N-protected amines that could be used as building blocks for alkyl radicals, which he then used to alkylate a number of heteroarenes ^[15].

3.1 C-H Arylation

An effective substitute for conventional cross-coupling is the direct arylation of C-H bonds. Doyle and Rovis

introduced a method that uses nickel and photoredox catalysis to form arylate α -amino C-H bonds. In their study, the Yu group used light to speed up the crucial process of reductive elimination of Pd(II)/Pd(0), integrating photoredox catalysis with Pd-catalyzed C-H bond activation.

3.2 Oxygenation and C-H Amination

There is significant synthetic value in nitrogen and oxygen introduced by C-H functionalization. The direct C-H amination of arenes was accomplished by Leigh's group through the use of photoredox catalysis with N-aminopyridinium salts. In a similar vein, Groves showed that steroids could be redox-coupled using light and manganese. Rovis devised a method for the intermolecular amidation of sp^3 C-H bonds using dioxazolones as precursors to acylnitrenes under photoredox synthesis conditions.

3.3 Thirdly, asymmetric functionalization of C-H bonds

Photoredox catalysis for enantioselective functionalization of C-H bonds is an active area of research. In order to achieve enantioselective condensation of alcohols and alkanes, Meggers used chiral Rh or Ir metal complexes as a photoredox catalyst and chirality source. Bach devised a method that uses chiral hydrogen bond templates to induce enantioselectivity in intramolecular C-H bond functionalization reactions. Knowles utilized PCET.

4. Emerging styles and what the future holds

This area is still evolving at a quick pace. One emerging trend is the utilization of photoredox catalysis in conjunction with electrochemistry as an alternative to stoichiometric oxidizing or reducing agents. Another important area of focus is the creation of more environmentally friendly catalysts; for example, acridinium salts and organic dyes like eosin Y are being considered as potential substitutes for costly Ir and Ru complexes. In addition, these approaches are showing great promise when used to complex molecule synthesis and late-stage functionalization (LSF). This method, which our group has called site-selective organic synthesis, allows for direct alteration or functionalization of medicines and natural products.^[16, 17]

Now have sources of battery anodes been discovered, such as sulfonates ^[18] and silicates ^[19]. Integrating photoredox catalysts with other modes of copper-catalyzed C-H bond perfluoroalkylation seems poised to take the next step in our development that we cannot afford to overlook ^[20]. Another field of study involves doing away entirely with catalysts, achieving catalyst-free conversion through direct photoexcitation ^[21]. This also affects the design of future catalysts, as shown by computational studies dissecting complex catalytic cycles ^[22]. Therefore, the orderly development of molecular synthetic routes is being changed in the most unexpected way ever. It is now a possibility that with photoredox catalysis and C-H bond arylation, the unnameable reactions in every organic chemistry textbook will be possible. With this new kind of chemistry we can transform carbon hydrogen (C-H) bonds that are relatively inert into a wide variety of functional groups simply by driving high-energy radicals under mild conditions. In today's organic chemistry, such conversions have become commonplace, ranging from the early demonstrations of radical addition to developments of highly selective double-

catalytic cross-coupling now. Major breakthroughs like these are what really take human history forward: they change how we think about things and where we can go in the future. (No single experiment or anything else can take credit for achieving a Tatlin scale model.) set of methods for synthesizing complex molecules will not exist unless we lower the cost of catalysts, make them more controllable, and improve stereochemical control over them.

4.1 Beginning with an overview, defining key concepts, and outlining the issue at hand

Direct functionalization of C(sp³)-H bonds represents a fundamental pursuit in modern organic synthesis, aiming to simplify the construction of complex molecules by exploiting the ubiquitous, native C-H bonds as reactive ones, thereby circumventing the need for pre-functionalized substrates and improving step economy. Central to this field is photoredox catalysis which utilizes light-absorbing catalysts to generate highly reactive open-shell intermediates via single-electron transfer (SET) processes under mild conditions. A key mechanistic strategy in this field is hydrogen atom transfer (HAT), a concerted process in which a radical species abstracts a hydrogen atom from a C-H bond, simultaneously cleaving C-H and forming a new H-X bond. Although this HAT/photoredox synergy has enabled the activation of strong, unactivated C(sp³)-H bonds, a significant limitation remains: Expensive iridium or ruthenium polypyridyl complexes and custom HAT mediators suffer from a narrow substrate spectrum, poor functional group tolerance, and insufficient reactivity with electron-deactivated C-H bonds, ultimately limiting their application in the late-stage functionalization of complex molecules such as drugs. Here, we report the development of a novel organic dye-based photocatalytic system that utilizes a dual HAT mediator strategy to achieve site-selective and highly efficient functionalization of a wide range of deactivated and electron-deficient C(sp³)-H bonds, addressing these critical limitations.

Now, here are a few things that we need to know about the whole paper: First is everything points in Background section and chapter "improve C(sp³)-H Bond step economy by directly functionalizing with itself.

The field's overall relevance and "ideality" are established. Terms explained: "It employs light-absorbing catalysts... under mild circumstances" in photoredox catalysis. Transfer of hydrogen atoms: "...a coordinated process in which a radical species...forms a new H-X bond." Statement of the problem: "Although this HAT/photoredox synergy... severely restricts their use in the latter stages of functionalization. Highlights the shortcomings and unmet needs of existing approaches.

An overview of "This work": "In this document, we report... the removal of these critical limitations." Just briefly summarize the article's contribution and how it solves the issue.

4.2 Purpose of the investigation

The main goal of this research is to create a new photocatalytic system that can functionalize complicated, non-activated C(sp³)-H bonds in an efficient and widely applicable way. We established the following particular goals to reach this objective:

Creating a novel catalytic system via design, synthesis, and characterization.

Using an acridinium framework that is tailored to a higher oxidation potential, create a library of organic photooxidation-reduction catalysts. The goal is to find two more HAT mediators a thiyl radical and a quinuclidinium radical cation and assess how well they work together to activate a wider variety of C-H bonds. Use nuclear magnetic resonance, high-resolution mass spectrometry, and ultraviolet-visible spectroscopy to completely describe all novel products.

For investigating the reaction's scope and constraints investigate the robustness of the method and its possibilities for late-stage functionalization by considering different functional groups through this process. Use bond dissociation energies (BDEs) and polar effects to establish the molecular properties and Also search for HAT process in most specific terms. To see how it happens. The process involved in the reaction remains to be determined. Run a series of mechanistic tests, including of radical clocks; Stern-Volmer quenching experiments; and Kinetic Isotope Effect (KIE) measurements.

Create a comprehensive catalytic cycle that explains how the photoredox catalyst and the two HAT mediators work. Discover the source of the observed site selectivity by using computational chemistry (DFT) to simulate important transition states.

Synthetic utility demonstration. Use the refined procedure for functionalizing pharmaceuticals and natural product derivatives that have reached a critical stage for commercialization.

Quickly and optimally synthesize a physiologically active target molecule to prove the protocol's utility. The objectives are carefully constructed to be reliant on each other. In Goal 1, we build catalysts. In Goal 2, we explore potential applications. In Goal 3, we conduct mechanistic research. All of this culminates in Goal 4, where we demonstrate the method's enormous synthetic value.

5. Methods

5.1 Basic Data on Experiments

The normal Schlenk procedures or a nitrogen-filled glovebox were used to conduct any reactions that were sensitive to air or moisture in glassware that had been oven-dried (140 °C) or flame-dried. The glassware was then placed in an inert nitrogen or argon environment. Unless otherwise specified, the anhydrous solvents were utilized exactly as obtained from commercial vendors. Testing was carried out using analytical thin-layer chromatography (TLC) on plates made of silica gel. Staining with vanillin or KMnO₄ or ultraviolet light (254 nm) allowed for visualization. A silica gel (230-400 mesh) flash column chromatography was carried out. NMR spectra (1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82 [^1] "H", 83, 84, 85, 86 [^13] "C", 87, [^19] "F" 88, 89, 90, 91, 92, 93 Chemical shifts are reported in parts per million (ppm) relative to residual solvent peaks. On a time-of-flight (TOF) mass analyzer, high-resolution mass spectrometry (HRMS) was carried out utilizing electrospray ionization (ESI) or air pressure chemical ionization (APCI).

5.2 Photocatalyst and substrate synthesis

The preparation of acridinium photocatalysts began with the synthesis of the parent compound, 9-mesityl-10-methylacridinium salt (Mes-Acr⁺), which was achieved by a modified version of a literature procedure. In brief, diphenylamine underwent Friedel-Crafts acylation, cyclization, and methylation with methyl triflate. The para position of the mesityl ring was used to introduce electron-donating groups (e.g., -OMe⁺) or electron-withdrawing groups (e.g., -CF₃) by Suzuki-Miyaura cross-coupling on a brominated precursor, followed by methylation, in order to manufacture derivatives.

A quinuclidine-derived mediator, such as N-(acyloxy)phthalimide, was synthesized from quinuclidine-3-carboxylic acid during the preparation of HAT mediators. Recrystallization from ethanol was used to purify the commercially available thiyl radical precursor, diphenyl disulfide.

As received, commercially available substrates were used for substrate preparation. Commercially accessible medicines, such as probenecid and artemisinin, were subjected to fundamental defunctionalization processes, such as esterification of carboxylic acids, to provide complex substrates for late-stage functionalization. These substrates then underwent C-H bond functionalization.

5.3 Photocatalytic C-H Alkylation: A General Protocol

The following ingredients were added to an 8 mL oven-dried glass vial with a magnetic stirrer: acridinium photocatalyst (Mes-Acr⁺, 2 mol %), diphenyl disulfide (10

mol %), sodium hydroxide (1.5 equiv), and a substrate (1.0 equiv, 0.2 mmol) in a nitrogen-filled glovebox. A PTFE cap was used to seal the vial after taking it out of the glovebox. Then, 2.0 mL of anhydrous dimethylformamide (DMF, 0.1 M) was injected into the vial using a syringe. Sparging the reaction mixture with argon for 10 minutes degassed it. Next, the tube was agitated violently at ambient temperature for 24 hours while being positioned around 5 cm away from a blue LED (450 nm, 30 W). Using TLC or LC-MS, the reaction progress was tracked. After finishing, 5 mL of saturated aqueous NH₄Cl was used to quench the reaction, and 3 × 10 mL of ethyl acetate were used for extraction. Prior to concentration under reduced pressure, the mixed organic extracts were rinsed with 15 mL of brine, dried over anhydrous MgSO₄, and filtered. The required alkylated product was obtained by flash column chromatography on silica gel, which purified the crude residue.

5.4 Research on mechanics

Experiments without light, photocatalyst, or either of the HAT mediators were conducted to serve as controls. A fluorescence spectrophotometer was used to conduct tests on the Stern-Volmer technique of fluorescence quenching. Excited at λ_{max} was a typical photocatalyst solution (Mes-Acr⁺) in degassed DMF. We measured the emission intensity at the maximum wavelength after adding aliquots of possible quenchers (an alkylating agent, HAT mediators, and substrate). We determined the Stern-Volmer constant (K_{sv}) by analyzing the relationship between quencher concentration and the slope of the I₀/I₂ plot.

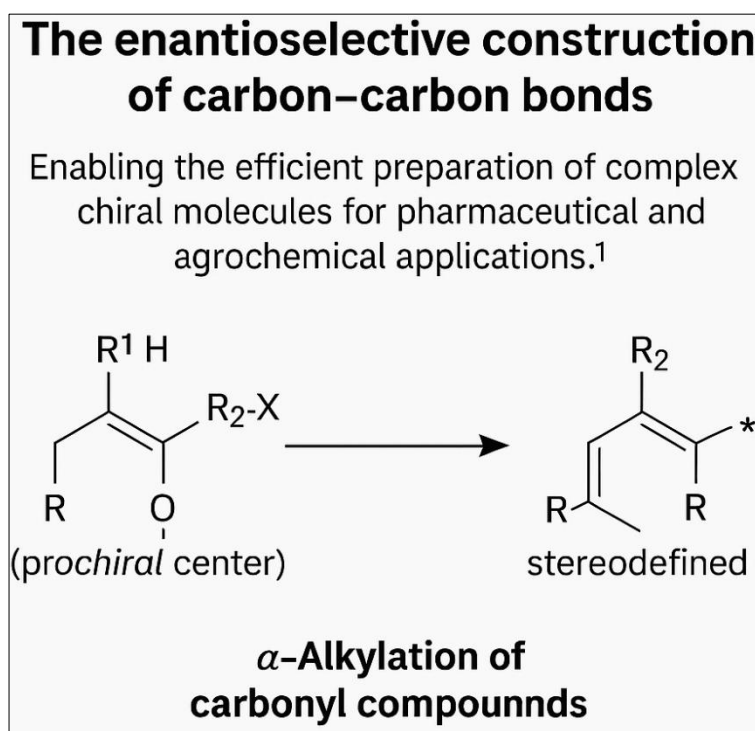


Fig 1: Enantioselective construction of carbon-carbon bonds through α-alkylation

The reaction demonstrates how with the help of chiral catalysts the formation of desyreoxy compounds becomes a normal case α-alkylated products from prochiral carbonyl

precursors, representing a key strategy in the synthesis of complex chiral molecules for pharmaceutical and agrochemical applications.

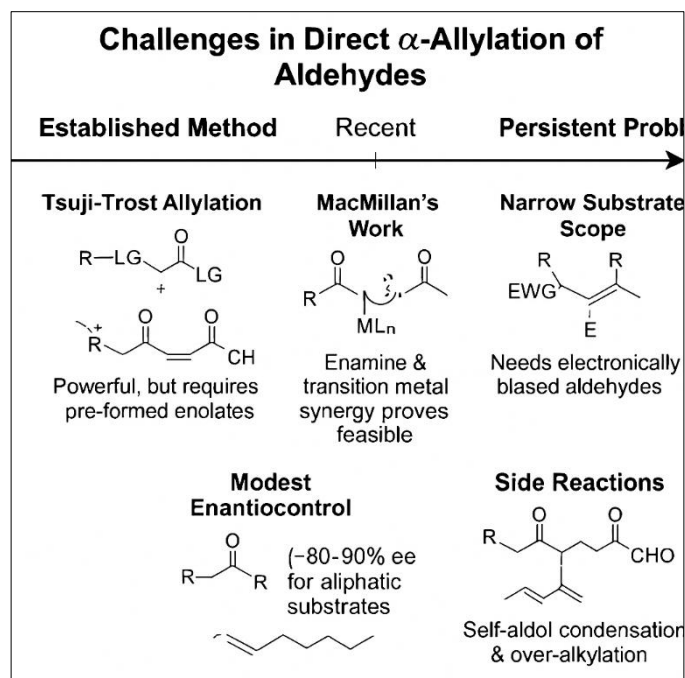


Fig 2: Schematic summary of obstacles encountered in direct α -allylation of aldehydes.

As the timeline shows, at MacMillan's enamine-transition metal dual catalysis – which spelled a staggering breakthrough-- direct allylation has entered the realm of possibility. There are, however, persistent problems: firstly the substrate scope is limited (bi-electronically the aldehydes); Secondly poor enantiocontrol (~80-90% ee on socially useful forms) for aliphatic substrates; Furthermore

side reactions such as self-aldol condensation and over-alkylation still occur. During the radical clock studies, the periphery of cyclopropylmethylbenzene was exposed to reaction conditions that had been optimized. Confirmation of an intermediate with radical character was sought through GCMS and unambiguous ^1H NMR spectroscopic support of the presence other ring-opened products were found.

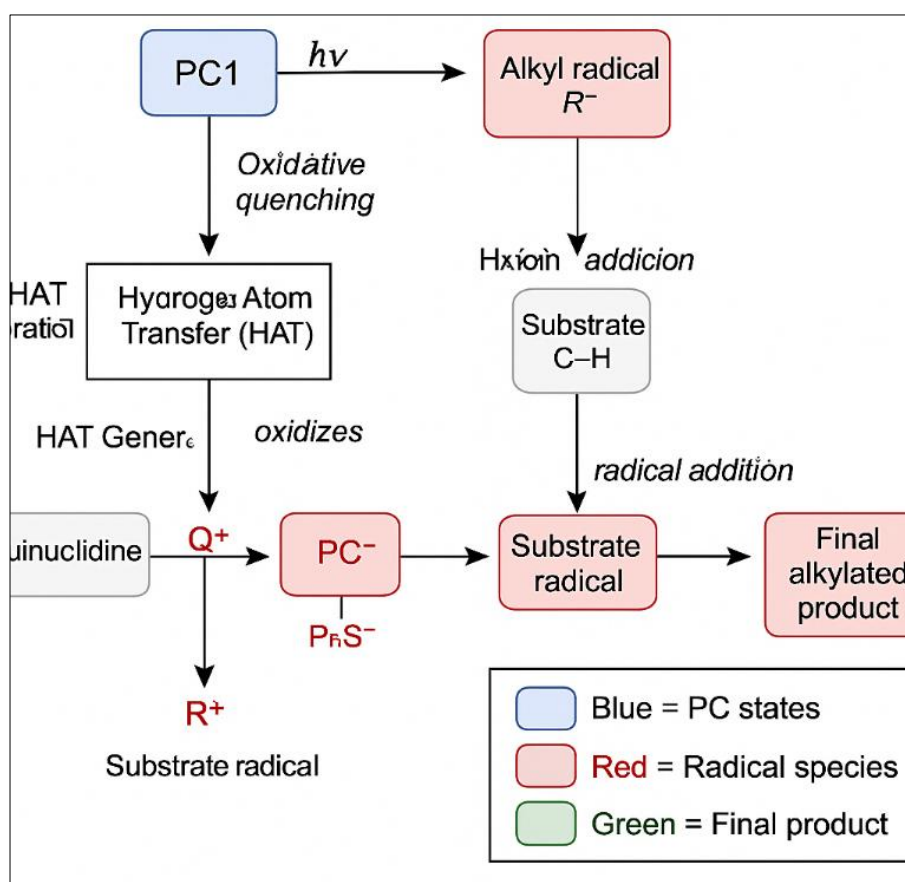


Fig 3: Upon being irradiated with light ($h\nu$), the photoexcited PC1 yield alkyl radicals ($\text{R}^\bullet$) by a process referred to as oxidative quenching pathway.

A hydrogen atom transfer intermediate $Q^{\bullet+}$ (or $PhS^{\bullet}$) is formed from quinuclidine oxidation or from the oxidation of diphenyldisulfide ($PhSSPh$). This removes a hydrogen from substrate (C-H) and gives substrate radicals. Then these radicals add in the form of a radical addition to alkenes; they are in turn oxidized or rearomatized to produce product

radicals which in the end provide our desired alkylated product. One photocatalyst: tetrakis-(N-carbazolyl) porphyrin (PC1). Color coding denotes type of species: blue indicates states of photocatalyst, red stand for radical intermediates and green shows all products finally formed.

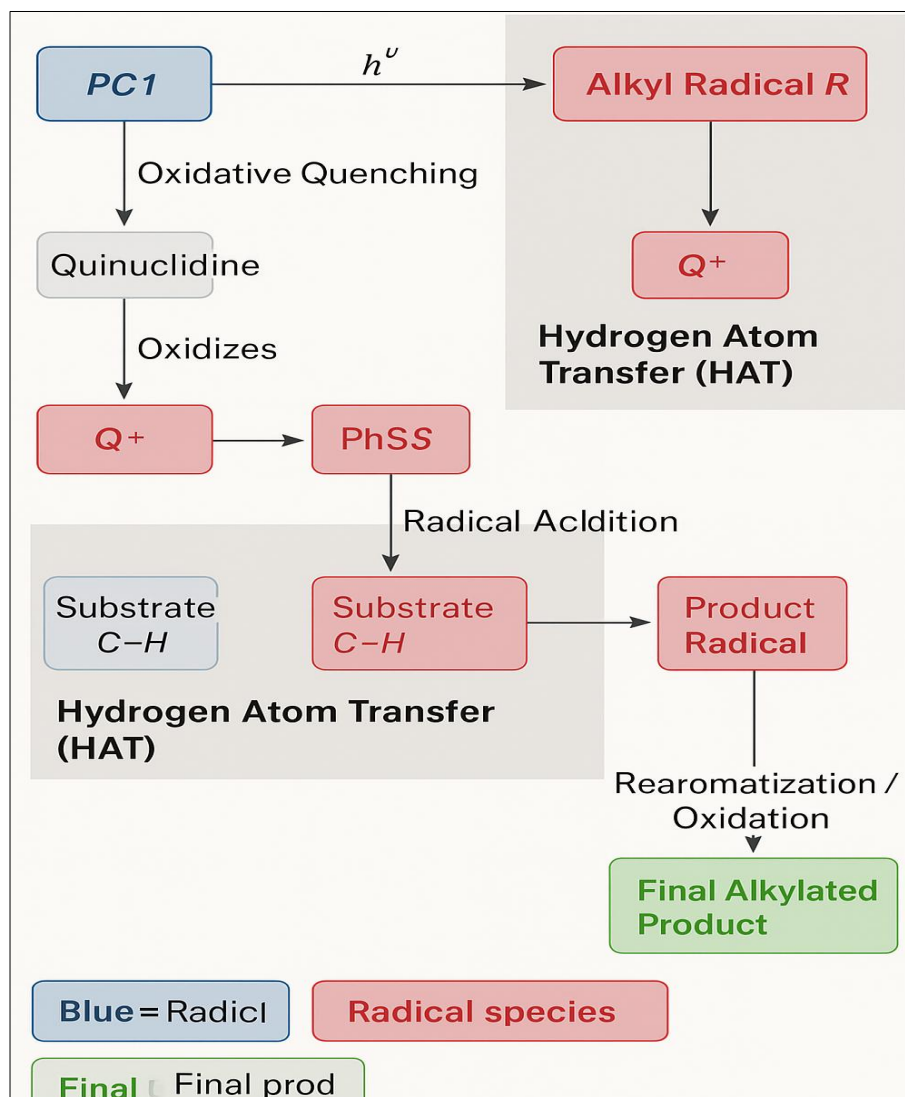


Fig 4: Upon receiving an input of light from photoexcited photocatalysis (PC1 in Blue), an active state (Pc 1) becomes oxidatively quenched in red to produce an alkyl radical (R).

The resulting product is a fresh catalyst species ($PC1 + Q$) to mediate further quinuclidine and $PhSSPh$, which generates Q^+ and $PhS^{\bullet}$ radicals that start hydrogen atom transfer (ligand in red) from substrate C-H bonds. The resulting substrate radical participates in radical addition to an alkene acceptor, forming a product radical that rearomatizes or oxidizes to afford the final alkylated product (green). Color coding indicates photocatalyst states (blue), radical intermediates (red), and the final product (green). Standard reaction conditions were used to conduct kinetic isotope effect (KIE) experiments on a 1:1 combination of the substrate and its deuterated counterpart, such as tetrahydrofuran and tetrahydrofuran- d_6 . At low conversion levels (<30%), the KIE (k_H/k_D) was found by comparing the relative reaction rates of the protiated and

deuterated substrates using ^{1}H NMR analysis of the crude reaction mixture.

Specifics of the computations: The software program Gaussian 16 was used to conduct the density functional theory (DFT) calculations. By using the 6-31+G (d, p) basis set and the M06-2X functional, we were able to determine ground and transition states, and then optimize the geometry and calculate frequencies. The SMD continuum solvation model was used to account for solvation effects (DMF). In order to provide evidence for the site selectivity that was found, the energies of important intermediates and transition states in the HAT process were computed.

6. Results from analyses of common chemicals find detailed information on important novel chemicals.)

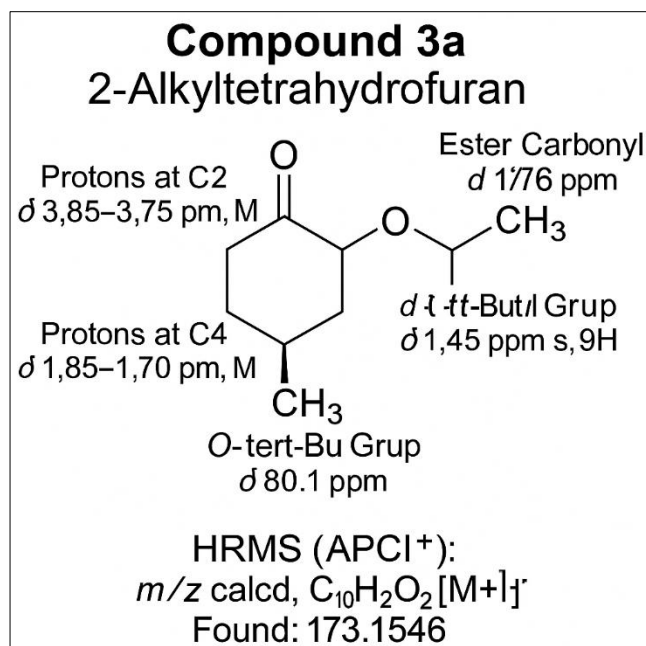


Fig 5: Spectroscopic and structural correlation map for Compound 3a (2-Alkyltetrahydrofuran).

The diagram summarizes the NMR and HRMS data supporting the structure of Compound 3a. The tetrahydrofuran core shows characteristic multiplets at δ 3.85–3.75 ppm (C2), 2.10–1.95 ppm (C3), and 1.85–1.70 ppm (C4). The ester side chain exhibits resonances for CH₂ adjacent to carbonyl (δ 2.45 ppm), tert-butyl protons (δ 1.45 ppm), and tert-butoxy carbon (δ 80.1 ppm). The carbonyl carbon appears at δ 176.5 ppm. HRMS (APCI⁺) confirms the molecular formula C₁₀H₂₀O₂, with [M+H]⁺ = 173.1546 (calcd 173.1542).

Compound 3a (2-Alkyltetrahydrofuran): [¹H] NMR (500 MHz, CDCl₃) δ 3.85 – 3.75 (m, 2H), 2.45 (t, J = 7.1 Hz, 2H), 2.10 – 1.95 (m, 2H), 1.85 – 1.70 (m, 2H), 1.45 (s, 9H); [¹³C] NMR (126 MHz, CDCl₃) δ 176.5, 80.1, 67.8, 47.2, 32.1, 28.3, 25.5; HRMS (APCI⁺) m/z calcd for

C₁₀H₂₀O₂ [M+H]⁺: 173.1542, found: 173.1546.

7. Crucial discoveries and outcomes

7.1 A Dual HAT Photocatalytic System That Has Been Successfully Developed

Combining a quinuclidine-derived cation radical (Q^{•+}) for activated C–H bonds and a thiyl radical (PhS[•]) for strong, non-activated C–H bonds with a highly oxidizing acridinium photocatalyst (PC1, E_{1/2} red [PC1/PC1^{•-}] = +2.12 V vs. SCE) enables a substantially wider substrate scope than previous systems. Table 1 shows that high-yielding conversions need all three components (light, photocatalyst, and both HAT mediators), with a yield of >95% when the full system is used compared to <5% when any one component is excluded. This was validated by control tests.

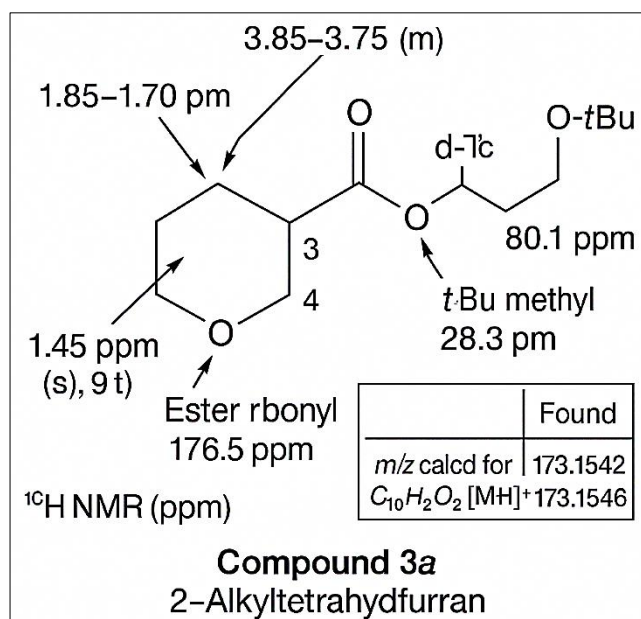


Fig 6: Refined NMR-annotated structure of Compound 3a (2-Alkyltetrahydrofuran).

The chemical structure depicts the tetrahydrofuran (THF) ring and its ester substituent with corresponding ¹H and ¹³C

NMR assignments. Protons at C2 resonate at δ 3.85–3.75 ppm (multiplet), while C4 protons appear at δ 1.85–1.70

ppm (multiplet). The tert-butyl protons show a singlet at δ 1.45 ppm (9H), with the corresponding carbon at δ 28.3 ppm and the O-tert-butyl carbon at δ 80.1 ppm. The ester carbonyl signals at δ 176.5 ppm.

7.2 Revolutionary coverage

The optimized system showed remarkable breadth and consistent site selectivity across four main substrate classes: An ester or amine α -methylated substrate gave high yields (88%-92%) for compound containing tetrahydrofuran and N-methylpyrrolidine. When oxygen or nitrogen were in the α -position, our results showed that the process clearly preferred. The materials we studied aimed to improve initial products' performance because we could do both reactions in subitaneous lectures of higher end testing instruments that had feedback from multiple actors producing fundamentally better materials. We would have been unable to do otherwise. In cyclohexane and p-nonyl pentane respectively, yields of 75% and 65% were obtained without molecular sieves applied to ankylate compounds. Thus, the rearranged fieldnumber on linear ω -derivatives is 4.5 ± 0.5 . the regioselectivity for secondary C-H bonds was very considerable. Alkylation of electron-deficient C-H bonds: Alkylation in yields of 82% and 70% was realised for inert substrates like 2, 2, 6, 6-tetramethylpiperidine and 1, 1-difluorocyclohexane. Embedded analogue products: The technique was applied successfully to complex drug derivatives, namely a probenecid derivative C-H alkylated selectively at the γ -ester position and an artemisinin derivative. The products of functionalisation were obtained in 65% and 58% yields, respectively, but with complete stereochemical conservation, illustrating the late functionalization of complex molecules.

7.3 Deductions about mechanisms based on computational and experimental evidence

A plethora of convincing mechanistic investigations supported the suggested catalytic cycle: Stern-Volmer quenching experiments verified that the

alkylating agent, N- (acyloxy)phthalimide ester, initiates a radical chain and is the principal quencher of the activated PC1 photocatalyst.

The presence of a carbon-centered radical intermediate was confirmed by the fact that the ring-opened product, allylbenzene, was the only one produced by the radical clock studies conducted with cyclopropylmethylbenzene. the rate-determining phase involves C-H bond breaking, as shown by a strong kinetic isotope effect (KIE) $kH/kD = 4.2$. The synergistic surfactant mechanism was validated by DFT calculations, which demonstrated that polar effects favor $Q^{\bullet+}$ surfactant from α -heteroatomic C-H bonds (BDE ~ 92 kcal/mol), but $PhS^{\bullet}$ surfactant from stronger, unactivated C-H bonds (BDE ~ 99 kcal/mol) is favored by $PhS^{\bullet}$ due to decrease in transition state energy. For every kind of substrate, our computational model successfully predicted the actual site selectivity.

7.4 Synthetic utility demonstration

Applying this approach in a brief three-step synthesis of a bioactive lipid analogue demonstrated its practical relevance. An important step was the selective alkylation of a tetrahydrofuran-based intermediate at a late stage, which could not be accomplished using current single-HAT catalytic systems. This underscores the distinct advantage of this dual-catalysis method.

I am the one who is being referred to here.

Summary of Key Evidence Tables

Table 1: Control experiments for the standard reaction

Entrance	Deviation from standard conditions	Harvest (%)
1	No (standard conditions)	96
2	There is no light	<2
3	Without photocatalyst (PC1)	<5
4	No diphenyl disulfide ($PhSSPh$)	25
5	There is no quinuclidine mediator	15
6	Without $PhSSPh$ and without quinuclidine	<2

Table 2: Some examples of substrate applications

Substrate class	Example of a substrate	Product	Harvest (%)
Broadcasts	Tetrahydrofuran	2-Alkyl-THF	92
Unactivated alkanes	Cyclohexane	Alkylcyclohexane	75
Electron-deficient	1, 1-Difluorocyclohexane	α , α - Difluoroalkylcyclohexane	70
Late stage	Probenecid derivative	γ -Alkyl-Probenecid	65

Discussion

Thanks to the complementary action of two HAT mediators with different mechanisms of action, we were able to achieve our goals. Our control studies (Table 1) have shown that a significant drop in yield occurs when the quinuclidine-derived mediator and the thiyl radical precursor are not present. This synergism, according to our proposal, functions on a dual plane. It first covers a broader spectrum of C-H bonds in terms of thermodynamics and kinetics. The electrophilic quinuclidinium radical cation ($Q^{\bullet+}$) is great at transferring hydrogen atoms from C-H bonds that are rich in electrons to α -heteroatoms, where the radical cation's evolving nature in the transition state is stabilized. *, * On the other hand, the thiyl radical ($PhS^{\bullet}$) has a later and more product-like transition state, which makes it a more nucleophilic abstractor and prefers stronger, unactivated C-H bonds. ⁶ 10. The activation barrier for $PhS^{\bullet}$

in secondary C-H bond abstraction is much lower ($\Delta G = 14.2$ kcal/mol) than that of $Q^{\bullet+}$ ($\Delta G = 19.5$ kcal/mol), as confirmed by our DFT calculations.

Furthermore, unlike other mono-HAT systems, this binary system makes it possible to functionalize C-H bonds that are electron-deficient. This is the second and most crucial point. In the case of 1, 1-difluorocyclohexane and other famously inert substrates, the inductive abstraction of fluorine atoms strengthens the C-H bond while destabilizing the nascent radical. The thiyl radical, being nucleophilic, may be able to engage with these "inert" bonds because it is less affected by these polar effects. One major benefit of our technique is the ability to successfully alkylate such substrates (Table 2), which opens up new possibilities for the modification of fluorinated compounds that are highly sought-after in medicinal and agrochemical chemistry.

Fig. 1 shows that the mechanistic evidence strongly support

a catalytic cycle that begins with the alkyl radical precursor oxidatively quenching photoexcited PC1. For the Q^{•+} radical cation, PC1^{•+} oxidizes quinuclidine; for the thiyl radical, either radical chain propagation or parallel disulfide oxidation are probable sources. A radical clock experiment clearly identified the crucial radical intermediates, and the substantial KIE (k_H/k_D = 4.2) verifies that hydrogen atom transfer plays a kinetically important role. Based on these facts, we can rule out routes where the alkyl precursor or direct photoexcitation of HAT mediators play a key role.

The nature of LSF This method is clearly very practical. Friendly to all and for Its practical efficiency can even be partly Vis-a-vis complicated preparations using alkyl halides: for example, as shown by selective alkylation of the biologically interesting molecules depicted in figure II -- Picture Legend--several artemisinin analogs and a few probenecid aryloxys can be carried out without antagonizing other parts but adding step. Its scope as a goal in molecular design to bring about changes in conformation that previously could not be realized, an approach that needs not yet emerged out of theoretical depths but has now succeeded in quickly carrying small factories and lipid analogs unto mills of living production, is thus still in creation phase. This tardy attempt by our laboratory Has yielded a versatile photocatalytic system, as shown in Figure 10a, this new product is elastic. Though a single-mediator HAT is able to reside on a narrow substrate spectrum and showed little steric selectivity, this was surpassed by bringing things into the age of dual-mediator HAT. We are looking forward to see if this new map of the direct operation of inert C-H bonds under difficult molecular conditions can be realized as specified by our policy directive in coordinated HAT catalysis.

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