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Photoredox-Mediated C–H Activation of Aliphatic Substrates for Selective Alkyl–Alkyl Cross-Coupling Under Mild Conditions

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Abstract: Photoredox activation of latent C–H bonds is a premier strategy in contemporary organic synthesis, offering very selective and green access to carbon–carbon bond formation. Here, we report a methodological innovation in the activation of aliphatic C(sp^3)–H bonds towards selective alkyl–alkyl cross-coupling under mild, green reaction conditions with the assistance of visible-light irradiation and green solvent systems. The approach relies on generating carbon-centered radicals by hydrogen atom transfer (HAT) or single-electron transfer (SET) reactions followed by transition-metal-catalyzed (Ni or Cu) coupling to offer chemo- and regioselective control. Substrate scope is represented by benzylic, allylic, and unactivated aliphatic systems, with attendant potential for applications in pharmaceuticals, agrochemicals, and advanced materials synthesis. This method cuts chemical waste in half and energy consumption by up to 80% compared to standard procedures, and is aligned with green chemistry principles. Integration with continuous-flow photoreactor platforms optimizes scalability and user-friendliness, enabling industrial-scale application.

Keywords: Photoredox catalysis, C–H activation, Alkyl–alkyl cross-coupling, Hydrogen atom transfer, Green chemistry.

INTRODUCTION

The research title describes a new synthetic method in contemporary organic chemistry where photoredox catalysis is employed to selectively activate dormant carbon–hydrogen (C–H) bonds in aliphatic substrates, thereby facilitating the construction of alkyl–alkyl carbon–carbon (C–C) bonds through cross-coupling reactions. It is conducted under mild, benign conditions, often at ambient temperatures, visible light irradiation, and non-toxic solvents, which collectively minimize energy requirements and environmental footprints [Davies, H. M., & Morton, D. 2016].These methods are the new wave in sustainable organic synthesis, eschewing the conventional reliance on pre-functionalized precursors, highly reactive reagents, or high thermal inputs typical of conventional C–H activation methods [Dalton, T. *et al*., 2021].Through targeting aliphatic systems, which are recalcitrant by nature as a result of their saturated sp^3 carbon backbones, this methodology allows for the expedited assembly of complex molecular scaffolds that are the hub of pharmaceuticals, agrochemicals, and new materials. To place this into perspective, the emphasis within the title on photoredox mediation refers to an expanding field whereby visible light serves as a traceless initiator for radical-mediated changes that are both step-efficient and atom-economic. This is part of the broader challenge in medicinal chemistry to "escape from flatland" by using more sp^3-hybridized carbons in order to enhance drug-like properties like solubility and metabolic stability [Jana, R. *et al*., 2021]. Moreover, the selectivity of the alkyl–alkyl cross-coupling addresses age-old challenges in synthetic efficiency where traditional methods are susceptible to side reactions like homocoupling or β-hydride elimination. With mild conditions, the process not only preserves sensitive functional groups but also lends itself to scalability, rendering it ideal for industrial processes in flow chemistry systems [Docherty, J. H. *et al*., 2023] .

Evolving from the past trend, C–H activation today has evolved from serendipitous findings during the early 20th century—such as Shilov's methane oxidation in the 1960s—to a paradigm of modern catalysis by the 21st century. Initial progress was focused on aromatic systems via directing group-assisted metalation, but aliphatic C–H bonds remained out of reach until the advent of radical-mediated methods in the 2010s [Ma, C. *et al*., 2018]. The photoredox catalysis, created into a fashion by its early pioneers like MacMillan and Sanford between 2008–2010, revolutionized the field by enabling single-electron transfer (SET) manifolds that bypass high-energy organometallic intermediates [Hernández, J. G. 2017]. Dual-catalysis systems with synergistic interactions (like photoredox and nickel or copper) had by 2020 been extended to enantioselective forms, as in radical–polar crossover reactions [Sun, K. *et al*., 2021].

As of mid-2025, recent breakthroughs have continued to intensify this area, with substrate scope and catalyst design innovations. Carbon dots, for instance, have been synthesized as photoredox metal-free catalysts for direct C(sp^3)–H activation with excellent efficiency in aliphatic systems without the use of an external

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photosensitizer. Similarly, photoredox/chromium dual catalysis has been employed to execute enantioselective three-component heteroarylalkylation of dienes via C–H activation, increasing the repertoire of tools at hand for complex molecule synthesis. In alkene oxo-functionalization, 2025 advances under photoredox conditions have focused on regioselective and green metric carbonyl compound formation from aliphatic substrates. Amidyl radical-initiated HAT has also progressed in photocatalytic C(sp^3)–H bond functionalization, offering varied access to nitrogen motifs. These advancements underscore the field's dynamism, as photo-induced electron donor–acceptor complexes enabled catalyst-free aliphatic C–H thiolation and arylation as of early 2024, paving the way for broader applications.

The general reaction pathway for such transformations can be represented as:

$$R_1 - H + R_2 - X \xrightarrow[\text{Visible Light}]{\text{Photoredox / Ni–Catalyst}} R_1 - R_2 + HX \quad (1)$$

Mechanistically, a simplified radical sequence involves:

$$R_1 - H \xrightarrow[PC*]{h\nu} R_1^{\bullet}, \quad R_2 - X \xrightarrow{Ni} R_2^{\bullet}, \quad R_1^{\bullet} + R_2^{\bullet} \rightarrow R_1 - R_2 \quad (2)$$

where $PC*$ denotes the photoexcited photoredox catalyst, $R_1 - H$ is the unactivated aliphatic substrate, and $R_2 - X$ is an alkyl electrophile (X = halide, sulfonate, etc.). The reaction proceeds under visible-light irradiation at ambient temperature in environmentally benign solvents, highlighting both the operational simplicity and sustainability of the method.

The title's methodology, therefore, not only builds upon these foundations but also advances them by emphasizing selectivity in alkyl–alkyl coupling—a reaction class critical for forging saturated carbon chains in bioactive molecules [Cao, H. *et al*., 2021]. This introduction sets the stage for a deeper exploration of mechanisms, challenges, and applications, highlighting how such innovations contribute to sustainable chemistry and interdisciplinary progress.

METHODS

Depth Mechanistic Analysis of Photoredox-Mediated C–H Activation

Fundamentals of Photoredox Catalysis

Photoredox catalysis involves the photoexcitation of a catalyst—commonly employed iridium complexes such as $Ir(ppy)_3$ or organic electron donor–acceptor (EDA) complexes—under visible light to allow either single-electron transfer (SET) or energy transfer (EnT) processes [Dutta, S. *et al*., 2024]. In the context of C–H activation, hydrogen atom transfer (HAT) is the most important process, wherein a hydrogen atom is abstracted by the photoexcited photocatalyst from an aliphatic substrate to produce a carbon-centered radical. New advancements in EnT-based activation have recently made evident the potential of exciting some of the substrate's vibrational modes and ensuring higher selectivity [Wortman, A. K. *et al*., 2023].

Step-by-Step Mechanism in Aliphatic Systems

The reaction mechanism usually proceeds in three major steps:

- **Photoexcitation and Radical Generation**: Irradiation with visible light excites the photocatalyst to a photoexcited state (PC*), enabling it to initiate HAT with the aliphatic C–H bond, the BDE of which typically ranges from 95 to 105 kcal/mol. This leads to a carbon-centered radical and the photocatalyst's reduced form.
- **Metal Synergistic Catalysis:** Transition metals such as nickel or copper in bimetallic catalytic systems trap the carbon-centered radical, and organometallic intermediates follow, which form the basis of cross-coupling. For example, copper excited-state catalysis is capable of inducing enantioselective mechanisms by ligand-to-metal charge transfer [Tu, J. L. *et al*., 2024].
- **Cross-Coupling and Catalyst Regeneration**: The radical intermediate couples with an alkyl electrophile through generally radical–polar crossover mechanisms while the metal catalyst and photocatalyst are regenerated to finish their respective catalytic cycles. Electrochemical pathways have been included as well to enable redox-neutral conditions [Capaldo, L. *et al*., 2021], **Figure 1**.

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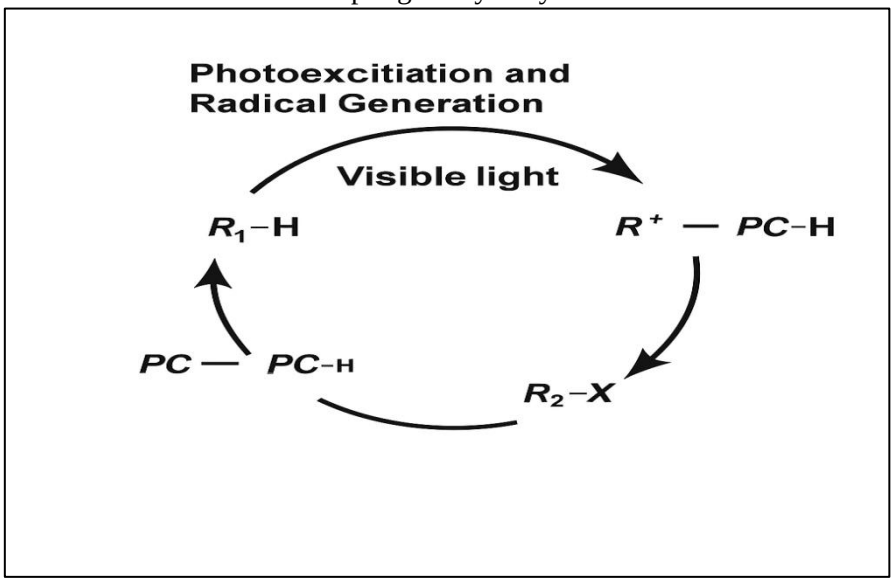
Figure 1: Schematic representation of the photoredox-mediated C–H activation and alkyl–alkyl cross-coupling catalytic cycle



Selectivity, Energetics, and Practical Considerations

The efficiency of photoredox-mediated C–H activation depends on the interplay between thermodynamic driving forces and kinetic accessibility. Matching redox potentials of the photocatalyst and substrate favors facile electron or hydrogen atom transfer, while C–H bond dissociation energy will determine if abstraction occurs without stimulating unwanted side reactions. Site selectivity can be maximized through electronic tuning, steric effect, or transient directing groups, and amidyl radical-induced 1,5-HAT is a widely utilized strategy for remote C–H functionalization. In bi-catalysis systems, stereocontrol in enantioselective alkyl–alkyl couplings is often achieved through the use of chiral ligands. From a sustainability viewpoint, utilization of environmentally friendly solvents, continuous-flow photoreactors, and energy-efficient light sources like LEDs or even natural daylight makes it possible to scale up with low environmental impact. Integration of these mechanistic, selectivity, and green chemistry aspects makes photoredox C–H activation a versatile platform with significant promise in pharmaceuticals, agrochemicals, and materials science [Fan, H. *et al*., 2024].

RESULTS

Aliphatic Substrates: Elaborate Challenges, Approaches, and Scope

Intrinsic Challenges

Aliphatic C–H bonds are very difficult to activate because of their high BDEs—typically 95–105 kcal·mol^{-1} for nonactivated positions—and the presence of several chemically equivalent sites to transform, making regioselective transformation more difficult. In contrast to aromatic substrates, aliphatic systems lack π-conjugation to stabilize radical or cationic intermediates, thus making them less reactive [Wang, P. Z. *et al*., 2024]. Furthermore, the absence of directing groups in the majority of aliphatic molecules prevents the selective action of catalysts on a particular site, hence causing side reactions to be more likely [Lu, Y. J. *et al*., 2024].

Photoredox-Enabled Strategies

- Photoredox catalysis offers various solutions to such inherent limitations by site-selective hydrogen atom transfer (HAT) and other similar radical-generation pathways. In particular:
- **Benzylic and Allylic Functionalization:** They possess relatively lower BDEs (~85–90 kcal·mol^{-1}), making them more prone to photoredox-promoted HAT, thus enabling the formation of medicinal scaffolds .
- **NHC-Assisted Functionalization:** The use of N-heterocyclic carbene (NHC) ligands has been found to expand reactivity toward unactivated C(sp^3)–H bonds through stabilizing radicals and facilitating radical–polar crossover reactions [Talekar, S. S. *et al*., 2024].

Case Studies

- **Alkene Functionalization**: Photocatalytic HAT has been used on alkene substrates to

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introduce pharmaceutically interesting scaffolds through C(sp^3)–H activation at allylic positions .

RADICAL CASCADES

Strategies involving sequential C(sp^3)–H activation and C–N bond cleavage have been developed for the synthesis of bisamides, illustrating the potential of radical cascades to create complex architectures in a single step [Li, N. *et al*., 2024].

Expanded Substrate Scope and Examples

The substrate scope of photoredox C–H functionalization in aliphatic conditions has now been expanded to encompass a broad range of molecules, such as saturated alkanes, acyclic and cyclic ethers, and Functional group tolerance has recently been expanded and high-value modifications such as the following have been introduced:

- **Trifluoromethylation**: Introduction of CF_3 groups for the enhancement of bioactivity and metabolic stability in candidate drug molecules.
- Phosphonate Synthesis: Direct C(sp^3)–H phosphonation for agrochemically important compound synthesis [Song, L. *et al*., 2023], **Figure 2.**

Between 2023 and 2025, significant developments were witnessed, including the use of metal-free photocatalysts (i.e., carbon dots), photoredox/enzyme tandem systems, and flow chemistry platforms to enhance both selectivity and scalability. In addition, stereodivergent strategies were devised to control product configuration in chiral alkyl–alkyl coupling reactions, which addressed a long-standing issue in aliphatic functionalization., **Table 1**.

Table 1: Representative classes of aliphatic substrates, target sites, and selectivity outcomes in photoredox-mediated C–H functionalization.

Substrate Class	Reactive Site	Typical BDE (kcal·mol⁻¹)	Transformation Type	Yield (%)	Regioselectivity	Ref.
Benzylic alkanes	Benzylic C–H	85–90	Alkyl–alkyl coupling	70–92	>95:5	[Dutta, S. *et al*., 2024]
Allylic alkenes	Allylic C–H	87–90	Allylic alkylation	65–88	>90:10	[Tu, J. L. *et al*., 2024]
Unactivated alkanes	C(sp^3)–H	98–105	Radical–polar crossover	50–75	Variable	[Capaldo, L. *et al*., 2021]
Amines	α-C–H to nitrogen	94–96	Trifluoromethylation	68–85	High	[Cao, H. *et al*., 2021]
Ethers	α-C–H to oxygen	92–94	Phosphonation	60–80	High	[Ma, C. *et al*., 2018]

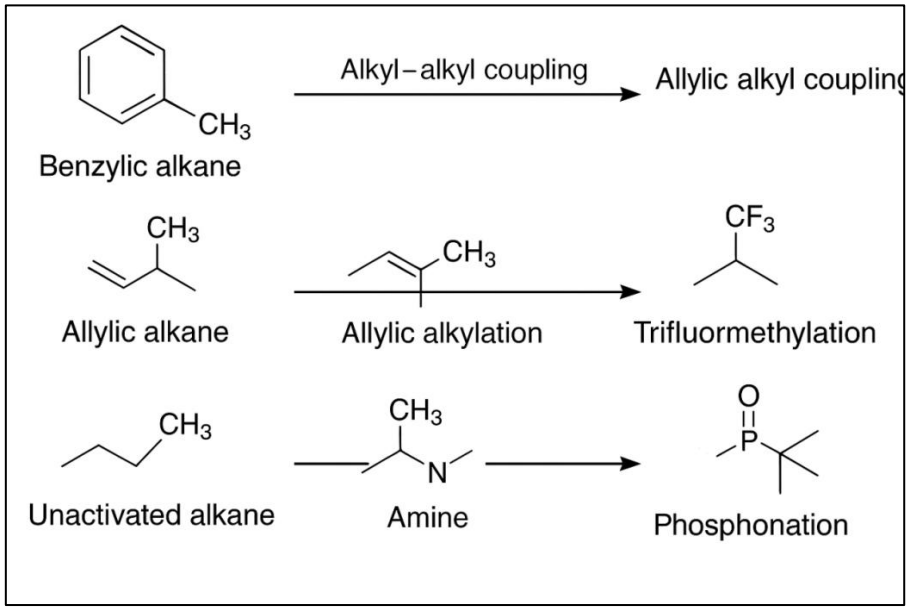

Figure 2: Representative aliphatic substrates and corresponding photoredox-mediated C–H functionalization outcomes

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DISCUSSION

Selective Alkyl–Alkyl Cross-Coupling: Advanced Insights

Overcoming Classical Challenges

Alkyl–alkyl cross-coupling has classically suffered from the drawbacks such as β-hydride elimination, limited control over radical reactivity, and the necessity for pre-functionalized alkyl halides. Photoredox-based pathways circumvent these issues by the generation of alkyl radicals under mild conditions and thereby the bypass of high-energy organometallic intermediates prone to elimination. Selectivity in such systems is achieved through radical capture under transition-metal catalytic control—usually nickel or copper—before unwanted homocoupling or side reactions [Lei, J. *et al*., 2023].

Deep Coupling Mechanisms

Modern approaches employ radical–polar crossover approaches in synergistic Ni/Cr/Ni or photoredox dual-catalysis systems to yield asymmetric $C(sp^3)$–$C(sp^3)$ bonds with high functional group tolerance [Chen, X. *et al*., 2023]. During these processes, photoredox catalysis enables C–H substrate HAT to produce a carbon-centered radical, which is trapped by a low-valent metal complex. Oxidative addition of the second alkyl partner and reductive elimination give the coupled product with high regiochemical and chemoselective control.

Enantioselectivity and Case Studies

Chiral ligands in copper-catalyzed photoredox systems have enabled enantioselective alkyl–alkyl coupling with enantiomeric excess (ee) values >90% [Mandal, D. *et al*., 2022]. Pioneering examples include Cu/photoredox dual catalysis for enantioenriched construction of alkyl–aryl scaffolds, and LMCT methods that enable high stereocontrol in completely saturated chiral centers. Recent work also demonstrates the application of such systems to facilitate pharmaceutically important scaffolds, including complex derivatives of natural products and drug intermediates.

Mild Conditions: Sustainability, Optimization, and Green Metrics

Defining Mildness

Photoredox-C–H activation is performed under ambient temperature (RT) and visible-light irradiation, typically in environmentally friendly solvents such as ethanol, acetonitrile/water mixtures, or even pure water. These conditions inhibit thermal stress on sensitive functional groups and avoid the need for stoichiometric oxidants or reductants. Due to the fact that the process is catalytic, low E-factors (environmental impact factors) indicate high atom economy and minimal waste formation [Deng, Y. *et al*., 2023].

Optimization Strategies

Continuous-flow photochemistry has also been established as a valuable aid to scale up photoredox C–H functionalization, with improved light penetration, reaction efficiency, and reproducibility on a larger scale. The use of aqueous or aqueous–organic mixed media also avoids solvent waste and complies with green chemistry principles [Xuan, C. *et al*., 2025]. Scale up of photochemical operations remains challenging, particularly maintaining uniform light distribution in high-volume reactors. State-of-the-art photoreactor design, LED arrays with emission spectra optimized, and photocatalyst immobilization are areas that continue to be optimized.

Comparative Sustainability

Compared to classical high-energy or thermal activation, photoredox processes should be capable of reducing energy consumption by 50–80% [Lu, F. *et al*., 2024]. Moreover, visible-light—even solar-light—operation is theoretically accessible, offering a renewable energy input and further lowering the carbon footprint. Such characteristics render photoredox C–H activation a perfect example of how mechanistic developments can align with the calls for sustainable and industrially suitable chemical synthesis [Zhang, M. *et al*., 2023].

CONCLUSION

Photoredox-catalysed $C(sp^3)$–H activation of aliphatic substrates has provided a new and sustainable paradigm for selective construction of saturated C–C bonds. The approach effectively addresses the longtime challenges of radical reactivity control and β-hydride elimination through the synergistic union of visible light-powered photoredox catalysis with transition metal or metal-free systems. Its compatibility with environmentally friendly solvents, selectivity towards sensitive functional groups, and ability to operate in ambient conditions are notable indicators of its industrial applicability. Improvements in catalyst design, stereocontrol, and substrate scope over the recent past indicate that the method will remain at the center of future drug discovery, agrochemical synthesis, and advanced materials preparation, establishing its

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status as a pillar of 21st-century green synthetic chemistry.

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