ACS OMEGA

Open Access

http://pubs.acs.org/journal/acsodf

Review

Organic Peroxides in Transition-Metal-Free Cyclization and Coupling Reactions (C−C) via Oxidative Transformation

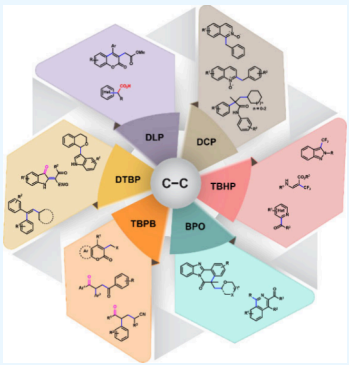
Amin Rezaeifard, Fatemeh Doraghi, Fatemeh Akbari, Bahareh Bari, Ebrahim Kianmehr, Ali Ramazani, Mehdi Khoobi,* and Alireza Foroumadi*

Cite This: *ACS Omega* 2025, 10, 15852−15907

Read Online

ACCESS | Metrics & More | Article Recommendations

ABSTRACT: Transition-metal-free transformations are recognized as green and sustainable methods for constructing carbon−carbon bonds in organic synthesis. This review describes the application of six organic peroxides, including *tert*-butyl hydroperoxide (TBHP), di-*tert*-butyl peroxide (DTBP), *tert*-butyl peroxybenzoate (TBPB), benzoyl peroxide (BPO), dialauroyl peroxide (DLP), and diguyl peroxide (DCP), in C−C bond construction, highlighting selected examples and mechanisms of challenging transformations. Each section concludes with a detailed overview of suitable reagents for various coupling reactions and strengths and weaknesses of the reported works. This work aims to inspire further innovations in transition-metal-free oxidative transformations, promoting sustainable and eco-friendly chemical processes and paving the way for new peroxide-based organic synthesis methods.

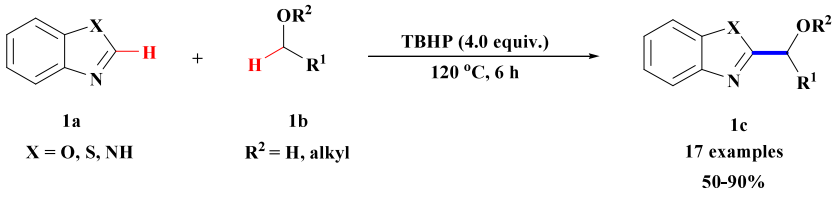


1. INTRODUCTION

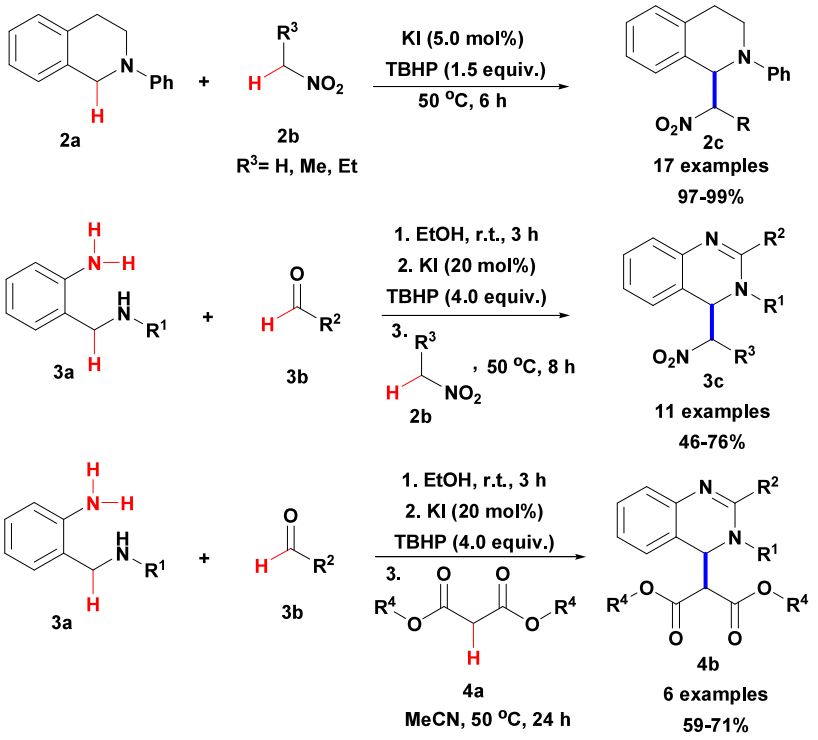
Since Wöhler's first synthesis of an organic compound, synthesis paradigms have evolved significantly. The development of straightforward and practical methods for creating heterocycles has garnered considerable interest due to their extensive applications in various fields.[1] Heterocyclic compounds are crucial and impactful in synthesizing biological and pharmaceutical compounds.[2] The formation of carbon−carbon (C−C) bonds from two different carbon−hydrogen (C−H) bonds, without using transition metals, has intrigued synthetic chemists during the last years, generating evolutionary progress in the synthesis of valuable organic compounds. The use of transition metal catalysts in oxidative reactions is limited by their high cost, sensitivity to oxygen and moisture, and potential toxicity.[3−6] Researchers have thus explored metal-free radical reactions, where radical species are typically generated by an oxidant under mild reaction conditions. These reactions exhibit high activity and excellent tolerance toward various functional groups.[7,8] In direct oxidative transformations, terminal oxidants play an incisive role in promoting the reaction.[9] Over the years, a diverse array of organic and inorganic oxidants have been employed in oxidative processes, each contributing uniquely to the advancement of synthetic methodologies.[10] Oxidants have been utilized in hundreds of published studies for the oxidation of various organic compounds.[11−14] Among them, organic peroxides have emerged as an significant option, gaining widespread popularity due to their versatility and efficacy in both metal-catalyzed and metal-free oxidative transformations.[15] Peroxides exhibit versatile reactivity, enabling reactions to occur at elevated temperatures as well as serving as effective primary oxidants under room temperature when subjected to UV or visible light irradiation.[16] Both heat and photoirradiation can readily break the O−O bonds in peroxides due to steric repulsion between the two oxygen atoms. The resulting reactive species have a short lifetime and readily oxidize other organic compounds in the reaction medium. These reactions typically proceed through radical pathways, which can be investigated using radical trappers like (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) and butylated hydroxytoluene (BHT), which trap free radicals in the medium and inhibit the progression of the reaction.[17] In the past decade, significant strides have been made in transition-metal-free oxidative transformations using peroxides as compatible oxidants.[18,19] Despite their extensive application and notable progress achieved in this domain, a conspicuous gap remains in the literature, and there has not been a comprehensive published review paper covering the full scope of organic peroxide-assisted oxidative transformations, including the latest advancements in this area. To fill this gap, this review aims to provide a detailed and systematic exploration of the role of organic peroxides in facilitating a

Received: December 30, 2024
Revised: March 29, 2025
Accepted: April 4, 2025
Published: April 14, 2025

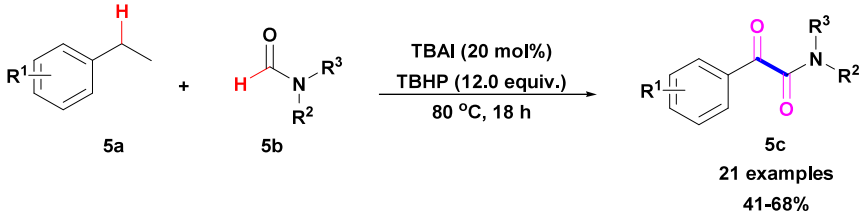
Scheme 1. Cross-Coupling Reaction of Azoles with Alcohols and Ethers



Scheme 2. CDC Coupling between Amines and Nitroalkanes/Dialkylmalonates Catalyzed by Potassium Iodide



Scheme 3. TBHP/TBAI Oxidative System for the Synthesis of α-Ketoamides



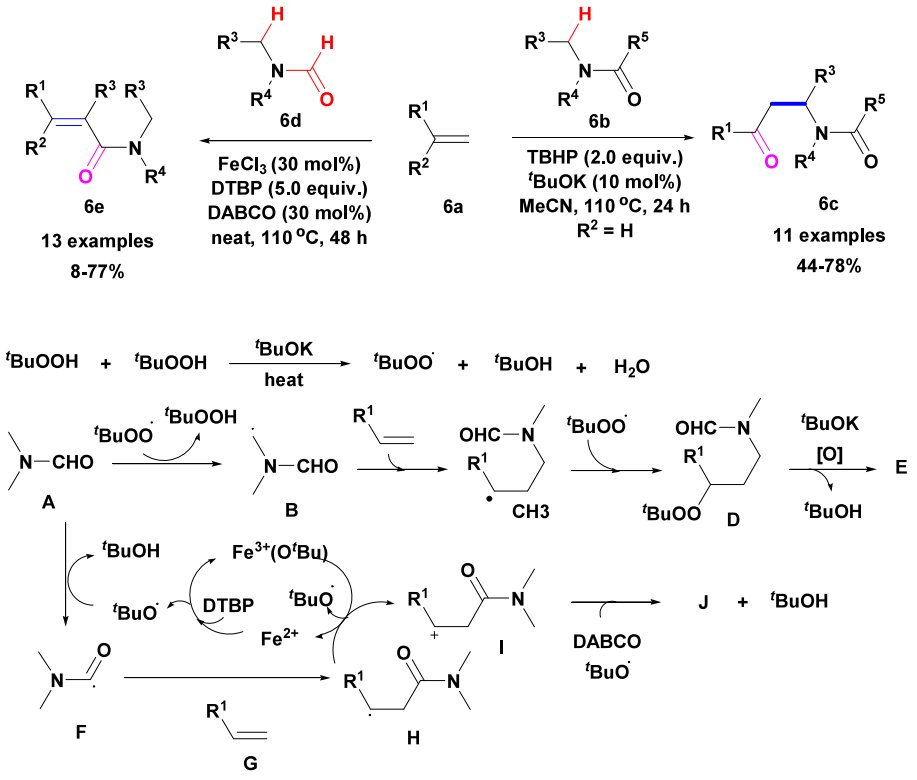
wide range of oxidative transformations, thereby underscoring their pivotal role in the evolution of green and sustainable chemistry. Our primary focus is on the application of organic peroxides, including di-*tert*-butyl peroxide (DTBP), *tert*-butyl peroxybenzoate (TBPB), *tert*-butyl hydroperoxide (TBHP), benzoyl peroxide (BPO), dialauroyl peroxide (DLP), and dicumyl peroxide (DCP), in transition-metal-free cyclization and coupling reactions. These peroxides have been successfully employed in the synthesis of various pharmacologically active compounds such as indoles, azoles, coumarins, quinazolines, and quinolones. We have focused herein on the application of the eight peroxides used in carbon−carbon (C−C) bond reactions. The content is organized based on the types of peroxides used in the reactions. Due to the extensive volume of literature, only selected examples are highlighted. The features of these reactions are discussed, and the mechanisms of particularly challenging reactions are emphasized. Each section concludes with a detailed overview of suitable reagents for various coupling reactions. This review tries to inspire organic chemists to further investigate and innovate the realm of transition-metal-free oxidative transformations. By embracing these green methodologies, the scientific community can contribute to the development of more sustainable and eco-friendly chemical processes, ultimately benefiting both industry and the environment. It is hoped that this review will pave the way for the design of new transformations using peroxides in organic synthesis, especially for metal-free oxidative reactions.

2. OXIDATIVE TRANSFORMATION BY PEROXIDES

2.1. Coupling Reactions with TBHP. Direct C−H functionalization reactions utilize metal catalysts and have notable advantages, but they are also accompanied by

https://doi.org/10.1021/acsomega.4c11574
ACS Omega 2025, 10, 15852−15907

Scheme 4. Oxidation-Induced Coupling of Unactivated Terminal Alkenes Together with Amides by TBHP/^{t}BuOK Oxidation and Suggested Mechanisms



drawbacks,[20] including the employment of expensive and hazardous transition-metal catalysts such as Pd, Ru, Pt, Rh, Cu, Co, Fe, or Ni complexes, as well as the requirement for strong bases in most cases. Consequently, there is a strong desire to develop simple, cost-effective, and environmentally friendly metal-free methods for these transformations. In this regard, researchers have extensively explored application of photocatalysts, nonmetal catalysts, and organic or inorganic oxidants.[21] C−C bond formation will positively influence the next generation of chemical syntheses, both economically and ecologically. One notable oxidant among them is *tert*-butyl hydroperoxide (TBHP), which is a colorless liquid when dissolved in a 70% aqueous solution.[15] It exhibits a half-life of 1 h at 193 °C and 10 h at 169 °C, making it a commonly used reagent in organic synthesis. Furthermore, the combination of TBHP with tetrabutyl ammonium iodide (TBAI), potassium iodide (KI), molecular iodine (I_2), or potassium *tert*-butoxide (^{t}BuOK) has shown compatibility and effectiveness as an oxidative system for various cross-coupling transformations. In 2011, the Wang group reported an efficient metal-free approach for the direct C2-alkylation of azoles **1a** using alcohols and ethers **1b** through oxidative C−H activation. This process, referred to as cross-dehydrogenative coupling (CDC), involves the activation of C(sp^3)−H bonds in alcohols and ethers, with C(sp^2)−H bonds in azoles in the presence of TBHP under solvent-free conditions (Scheme 1).[22] The reaction yielded moderate product yields when other oxidants, such as TBPB, DCP, and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), were used. However, when DTBP, dibenzoyl peroxide, and cyclohexanone peroxide were employed, the product yields were significantly lower.

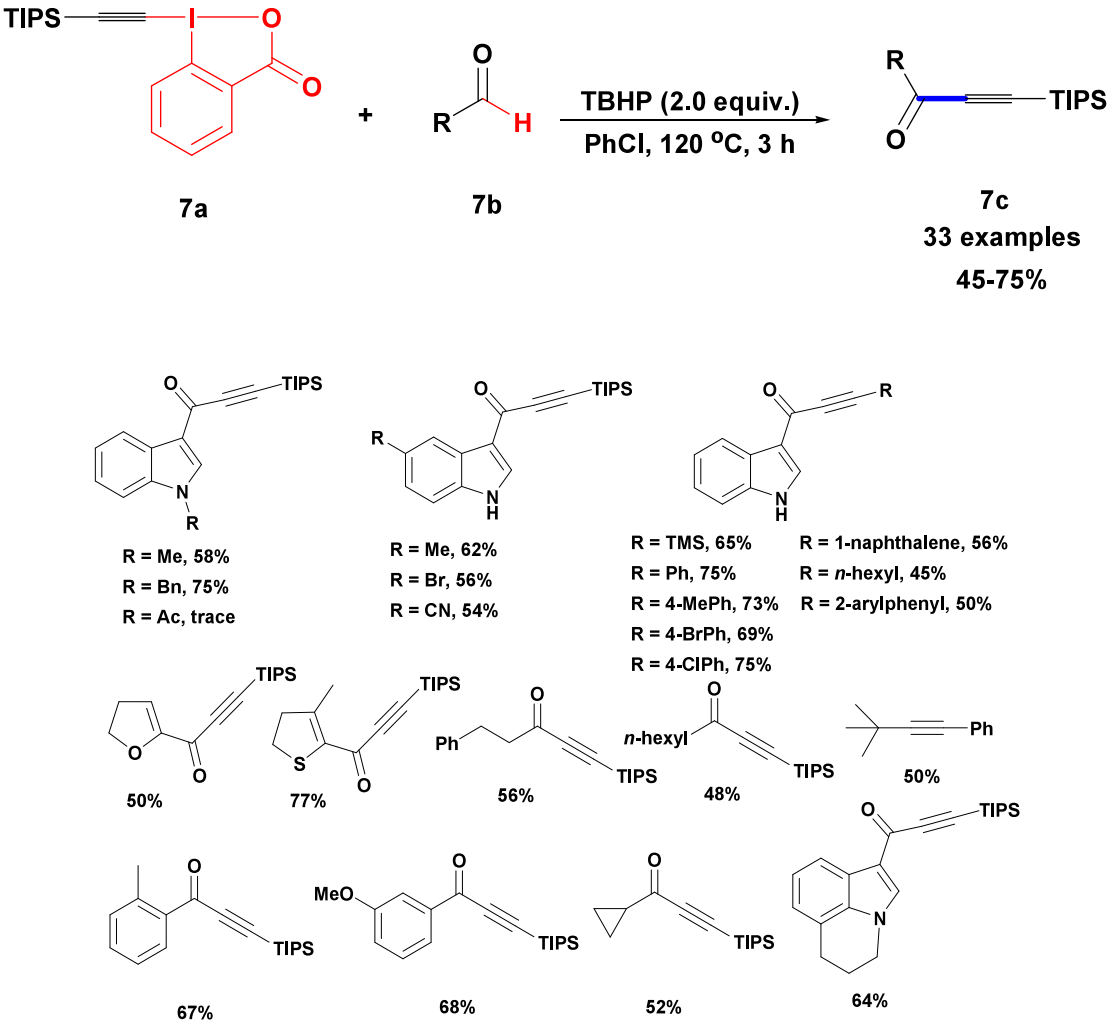
Reddy and colleagues reported the utilization of KI and TBHP in the C−C coupling of amines **2a** and **3a** together with nitroalkanes **2b** (Scheme 2).[23] This reaction enabled the synthesis of various biologically significant *N*-heterocycles, including tetrahydroisoquinolines **2c** and 3,4-dihydroquinazoline **3c**. Excellent yields were obtained for all isolated products. The same methodology was also applied to the synthesis of dialkyl 2-(2,3-diphenyl-3,4-dihydroquinazolin-4-yl) malonate derivatives **4b**, using dialkylmalonates **4a** as nucleophiles instead of nitroalkanes.

Sun et al. utilized the TBAI/TBHP oxidative system to synthesize α-ketoamides **5c** by activating multiple inert C(sp^3)−H bonds in ethylarenes **5a** and their subsequent reaction with *N*,*N*-dialkylformamide **5b**, as shown in Scheme 3.[24] This transformation involved the cleavage of the C−N bond in *N*,*N*-dialkylformamide by this oxidative system, which was confirmed by a ^{13}C-isotope labeling experiment. Moreover, the product's two oxygen atoms were produced through the oxidation of the compound by TBHP.

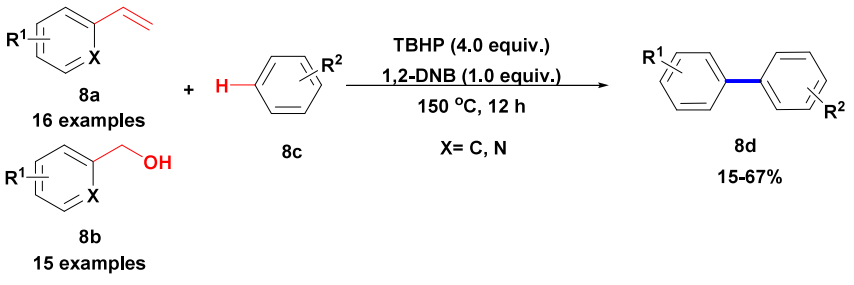
The Li group recently introduced a novel method for the oxidation-induced coupling of inactivated terminal alkenes (**6a**) with amides (**6b** and **6d**) as shown in Scheme 4.[25] This process involves the selective modification of C(sp^3)−H bonds next to the nitrogen atom using the TBHP/^{t}BuOK system, resulting in the formation of β-amino ketones (**6c**). However, when $FeCl_3$ is incorporated in the presence of DTBP and DABCO, the chemoselectivity changes, leading to the production of α,β-unsaturated amides (**6e**). It is suggested that $FeCl_3$ reduces the reactivity of alkenes (**6a**) toward the C(sp^3)−H bonds of amines by consuming OH radicals and the formation of Fe^{n+}(OH) species. Two proposed radical pathways are illustrated in Scheme 4. In the first pathway, alkyl radical **B** is generated by abstracting the α-H atom of **A** with ^{t}BuOO·, derived from TBHP upon heating with ^{t}BuOK. Alkyl radical **C** is then formed by adding **B** to alkene **G**. The

https://doi.org/10.1021/acsomega.4c11574
ACS Omega 2025, 10, 15852−15907

Scheme 5. Cross-Coupling of Aldehydes with Ethynyl Benziodoxolones



Scheme 6. TBHP-Promoted Cross-Coupling Reaction of Styrenes and Benzyl Alcohols with Arenes



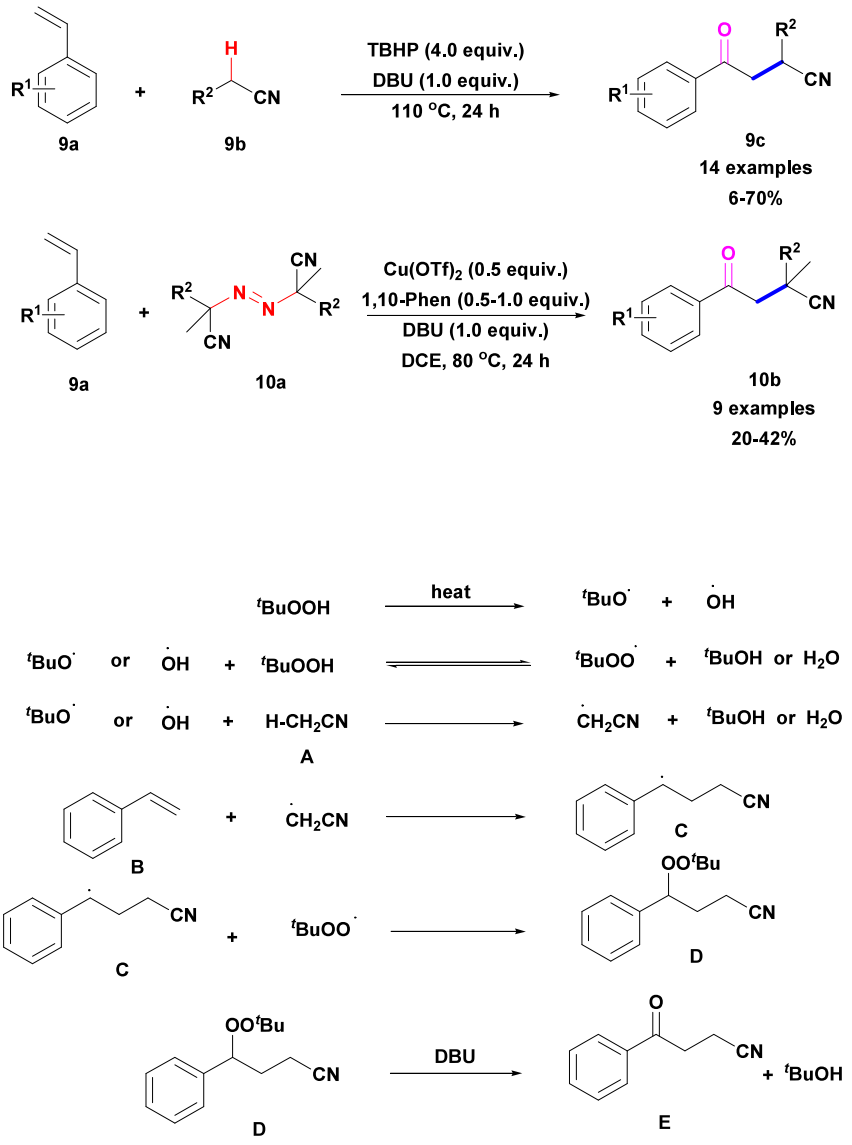
reaction of **C** with ^{t}BuOO· produces intermediate **D**, whose O−O bond is cleaved by ^{t}BuOK, followed by oxidation with TBHP to yield compound **E**. In the second pathway, Fe^{2+} ions convert DTBP to $Fe^{3+}(O^{t}Bu)$, generating ^{t}BuO radicals. These radicals detach a hydrogen atom from **A**, forming radical carbonyl **F**. Subsequent addition across alkene **G** produces alkyl radical **H**. A single electron transfer (SET) between **H** and $Fe^{3+}(O^{t}Bu)$ generates alkyl cation **I**, Fe^{2+} species, and $^{t}BuO^{-}$. Finally, **I** undergoes β-H elimination with $^{t}BuO^{-}$ in the presence of DABCO, yielding the desired product **J**.

Li and colleagues have devised a metal-free approach for TBHP-mediated oxidative alkynylation of carbonyl C(sp^2)−H bonds in aldehydes (**7b**) using (triisopropylsilyl)ethynyl benziodoxolones (TIPS-EBX) (**7a**), leading to the synthesis of ynones (**7c**) as illustrated in Scheme 5.[26] This protocol utilizes an oxidative radical coupling process for carbonyl C(sp^2)−H bonds, providing a versatile approach to construct ynone derivatives flexible to a diverse range of substrates and boasting excellent functional group compatibility.

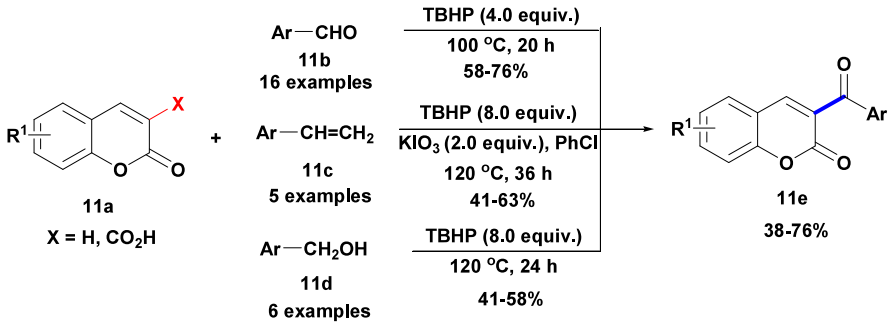
Shah and Kumar developed a method for the oxidative coupling of styrenes **8a** or benzyl alcohols **8b** with arenes **8c**, leading to the formation of biaryls **8d** (Scheme 6).[27] The reaction process involves the formation of an aldehyde intermediate through the oxidative C−C bond cleavage of styrene and the oxidation of benzyl alcohols. This intermediate then undergoes decarbonylation and arylation steps to produce

https://doi.org/10.1021/acsomega.4c11574
ACS Omega 2025, 10, 15852−15907

Scheme 7. Functionalization of Alkyl Nitriles and AIBN Analogues with Terminal Vinyl Arenes and the Associated Mechanistic Pathway



Scheme 8. Synthesis of 3-Acyl Coumarins with Various Acylating Reagents

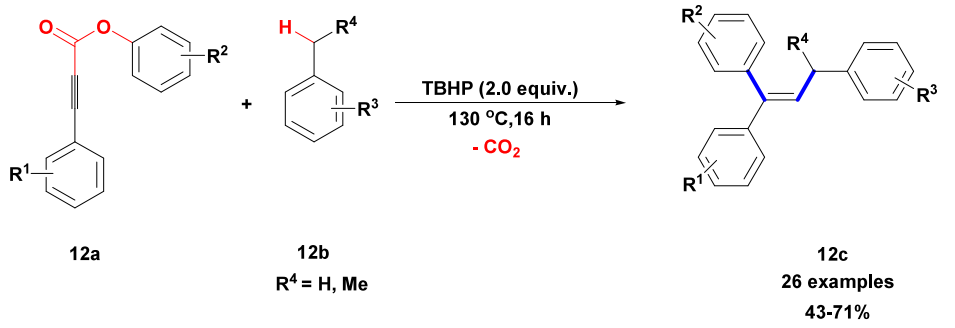


the desired biaryl compounds. The reaction efficiently works across a broad spectrum of substrates and shows supreme tolerance for diverse functional groups. However, using 2-vinylpyridine as a styrene derivative reduced the yield.

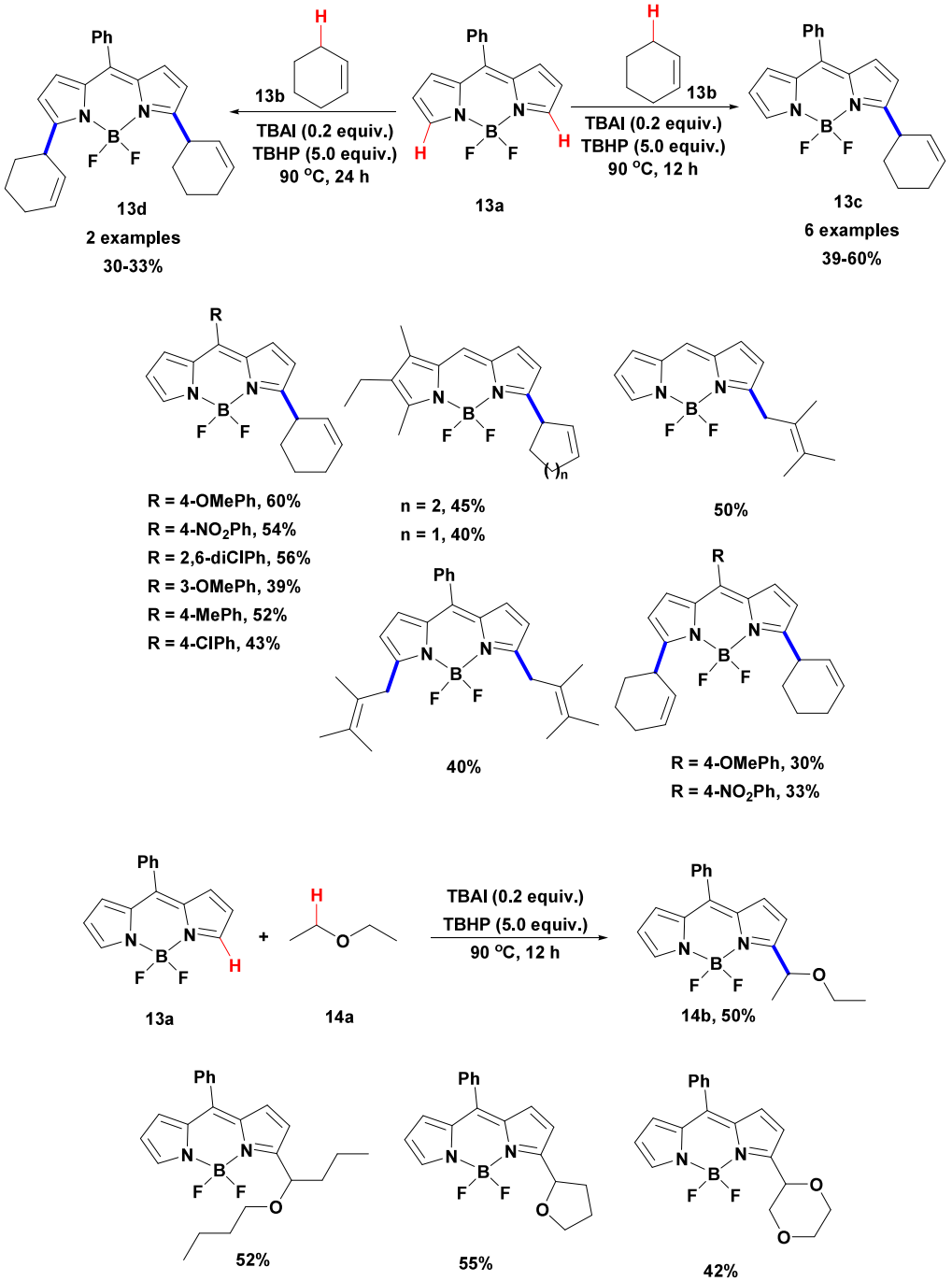
Wang and colleagues introduced a metal-free approach for the functionalization of inactivated C(sp^3)−H bonds in alkyl nitriles **9b** with terminal vinyl arenes **9a** (Scheme 7).[28] The reaction is advantageous due to its simplicity, broad substrate range, and atom economy. In the presence of $Cu(OTf)_2$/1,10-phenanthroline/DBU, azodiisobutyronitrile (AIBN) **10a** and its analogs react with terminal vinyl arenes **9a** to produce γ-ketonitriles **10b** through a radical process. The involvement of a free-radical pathway was certified by catching an alkyl radical with a radical scavenger and through density functional theory

https://doi.org/10.1021/acsomega.4c11574
ACS Omega 2025, 10, 15852−15907

Scheme 9. Synthesis of Three-Substituent Alkenes from Aryl Alkynoates and Toluene Derivatives

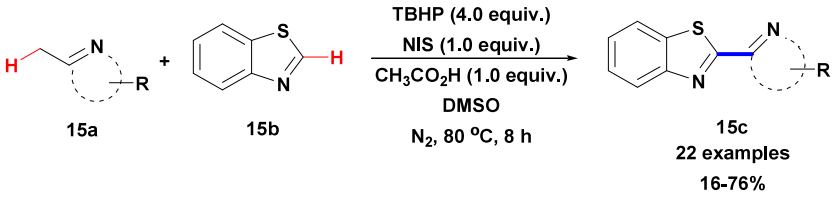


Scheme 10. Synthesis of α-Functionalized BODIPYs Using Allylic Alkenes and Ethers

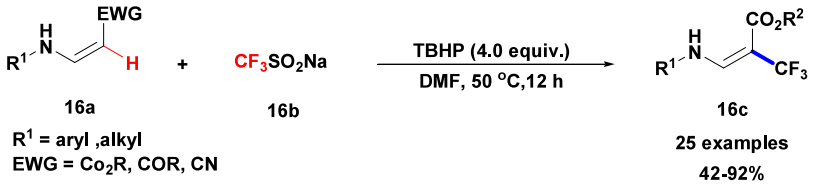


https://doi.org/10.1021/acsomega.4c11574
ACS Omega 2025, 10, 15852−15907

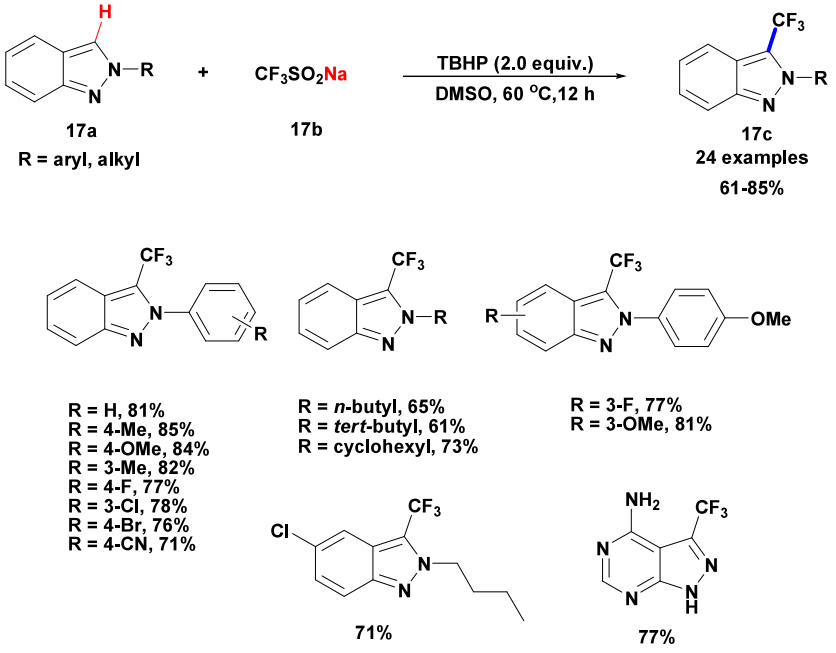
Scheme 11. Synthesis of 2-Heteroarylbenzothiazoles Using NIS and TBHP



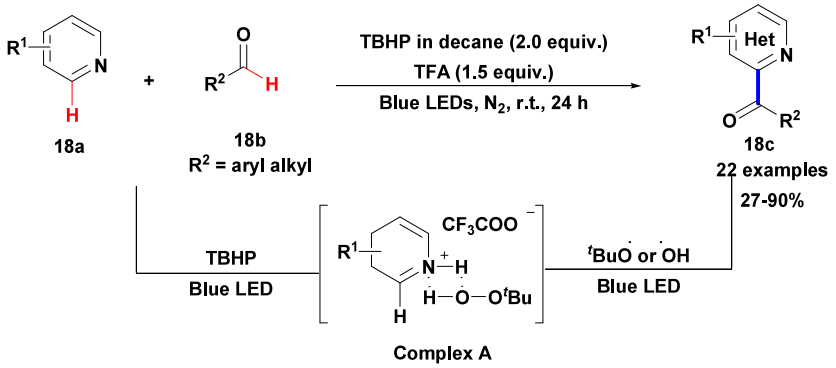
Scheme 12. TBHP-Mediated Trifluoromethylation of Enamines with Trifluoromethanesulfinate



Scheme 13. Direct Trifluoromethylation of Indazoles with Sodium Trifluoromethanesulfinate



Scheme 14. Acylation of *N*-Heterocycles with Aldehydes

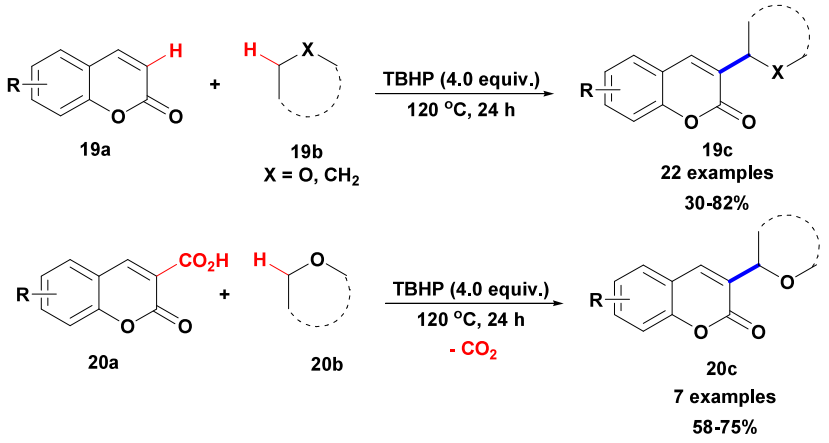


(DFT) calculations. Initially, ^{t}BuO· and HO· radicals, generated from the decomposition of TBHP under the reaction conditions, abstracted the α-H atom of acetonitrile **A**, forming a primary alkyl radical ·CH_2CN. This ·CH_2CN radical then adds to the double bond of vinyl arene **B**, creating a radical intermediate **C**, which reacts with ^{t}BuOO· to form intermediate **D**. Finally, peroxide intermediate **D** is converted to final product **E** in the presence of DBU.

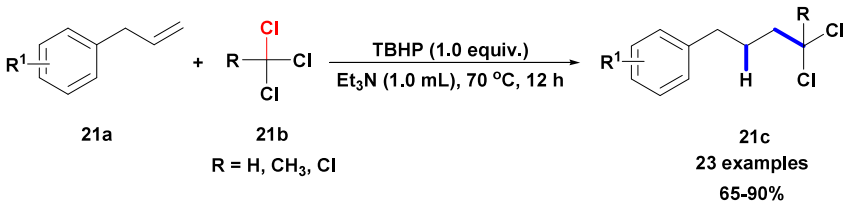
3-Aroyl coumarins have demonstrated diverse biological activities, including α-glucosidase inhibitory, DPPH scaveng-

https://doi.org/10.1021/acsomega.4c11574
ACS Omega 2025, 10, 15852−15907

Scheme 15. TBHP-Mediated C3-Alkylation of Coumarins and Coumarin-3-carboxylic Acids



Scheme 16. Oxidative Radical Addition−Chlorination of Alkenes



ing, antibacterial, and antioxidant activities, and have also been used as fluorescent chemosensors.[29−32] Jafarpour and Abbasnia devised a metal-free TBHP-mediated technique for the regioselective C−H functionalization of coumarins **11a**, resulting in the synthesis of 3-acyl coumarins **11e** (Scheme 8).[33] This approach involves reacting coumarins or coumarin-3-carboxylic acids with aromatic aldehydes **11b**. Additionally, styrenes **11c** and benzyl alcohols **11d** were used as acylating agents and demonstrated good reactivity. This protocol enables the efficient regioselective carbonylation of coumarins with aromatic aldehydes through metal-free coupling, effectively utilizing benzyl alcohol and styrene derivatives. *In situ* decarboxylation extends its applicability to coumarin-3-carboxylic acids, showing good functional group tolerance and efficiency.

Wang and their team described a technique for the oxidative difunctionalization of aryl alkynoate **12a**, which includes intramolecular 1,4-aryl migration followed by a decarboxylation tandem process. The reaction utilized TBHP as the sole oxidant (Scheme 9).[34] Comparable yields were achieved using cumene hydroperoxide (CHP) instead of TBHP, whereas other peroxides such as DTBP, TBPB, DCP, and BPO led to reduced yields. Oxidants such as H_2O_2, O_2, m-CPBA, and $PhI(OAc)_2$ and inorganic oxidants like $K_2S_2O_8$ and Ag_2O failed to produce the desired product. This technique provides a straightforward and selective route for synthesizing three-substituent alkenes **12c** from basic toluene derivatives **12b** and aryl alkynoates **12a**.

Jiao and colleagues described a highly regioselective CDC reaction of boron dipyrromethene (BODIPY) dyes **13a** with allylic alkenes **13b** and ethers **14a** utilizing TBHP as the oxidant (Scheme 10).[35] Alternative oxidants, including O_2, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), $K_2S_2O_8$, and DTBP, were determined to be unsuccessful in facilitating this reaction. The reaction followed a radical route and provided a convenient method to synthesize diverse α-functionalized BODIPYs **13c** and **13d**, which were challenging to access using previous methods.

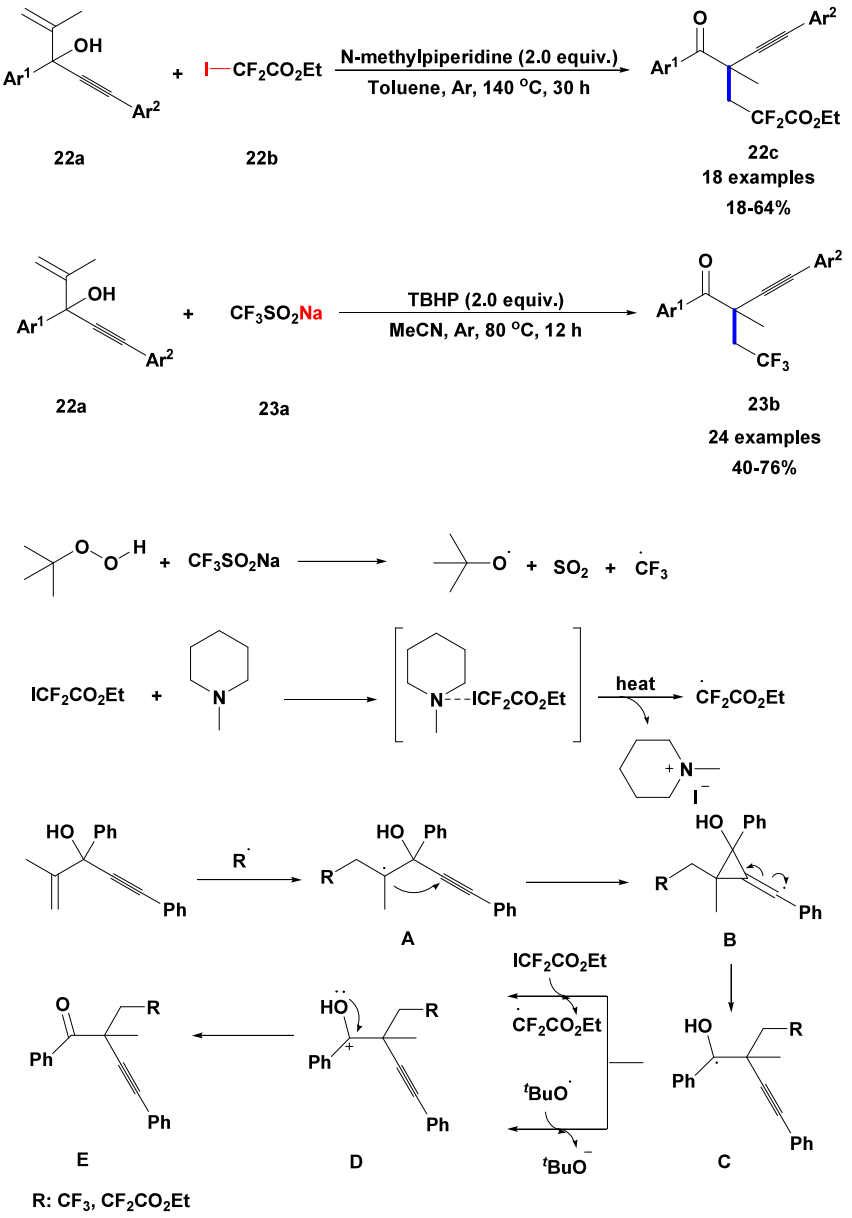
Traditionally, the synthesis of 2-substituted benzothiazole derivatives involves the condensation of 2-aminothiophenol with aldehydes, esters, and carboxylic acids[36] or utilizes transition metals as catalysts in the cross-coupling reactions between aryl halides and benzothiazole.[37−40] However, in 2017, Ma and his team introduced a one-pot metal-free method for synthesizing 2-heteroaryl benzothiazoles **15c** using *N*-iodosuccinimide (NIS) and TBHP as an efficient oxidative system (Scheme 11).[41] This method enables the oxidative condensation of benzothiazoles **15b** with quinoline derivatives **15a**, leading to the creation of the desired coupling products.

In the same year, Jiang and colleagues introduced a cost-effective, transition-metal-free method for the trifluoromethylation of enamines **16a**, utilizing trifluoromethanesulfinate **16b** (commonly known as Langlois' reagent) as the CF_3 group source (Scheme 12).[42] A diverse array of β-trifluoromethyl-substituted enamines **16c** with *E*-configurations were synthesized by selectively attacking the electron-deficient CF_3 radical to the electronegative β-carbon. Screening other peroxides, such as DTBP, H_2O_2, and benzoquinone (BQ), was unsuccessful; however, $K_2S_2O_8$ worked with moderate efficacy. The method could be employed for efficient preparation of (*E*)-β-CF_3 enamines via direct C−H trifluoromethylation using Langlois' reagent and TBHP. The reaction benefits are mild to excellent yield, air- and water-tolerant conditions, and available β-amino acid precursors.

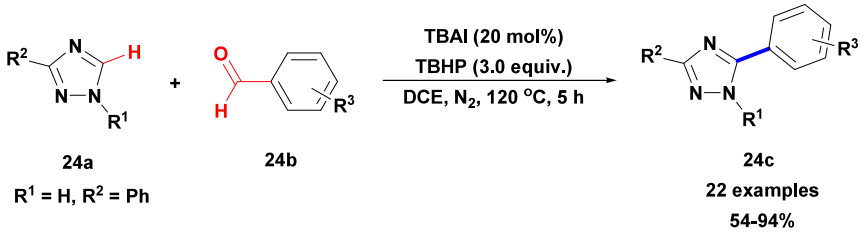
Hajra developed a method for the trifluoromethylation of indazoles **17a** using CF_3 radicals generated from Langlois' reagent **17b** under the same reaction conditions. This approach achieved the trifluoromethylation of a series of substituted 2*H*-indazoles, resulting in products **17c** using the inexpensive Langlois' reagent as the CF_3 source (Scheme 13).[43] This method provides a straightforward regioselective trifluoromethylation of 2*H*-indazoles under mild, metal-free

https://doi.org/10.1021/acsomega.4c11574
ACS Omega 2025, 10, 15852−15907

Scheme 17. Radical Difluoroalkylation/Trifluoromethylation and Alkynylation of Unactivated Alkenes, Along with the Proposed Mechanism



Scheme 18. TBAI/TBHP-Mediated Synthesis of 1,3,5-Trisubstituted/3,5-Disubstituted 1*H*-1,2,4-Triazoles

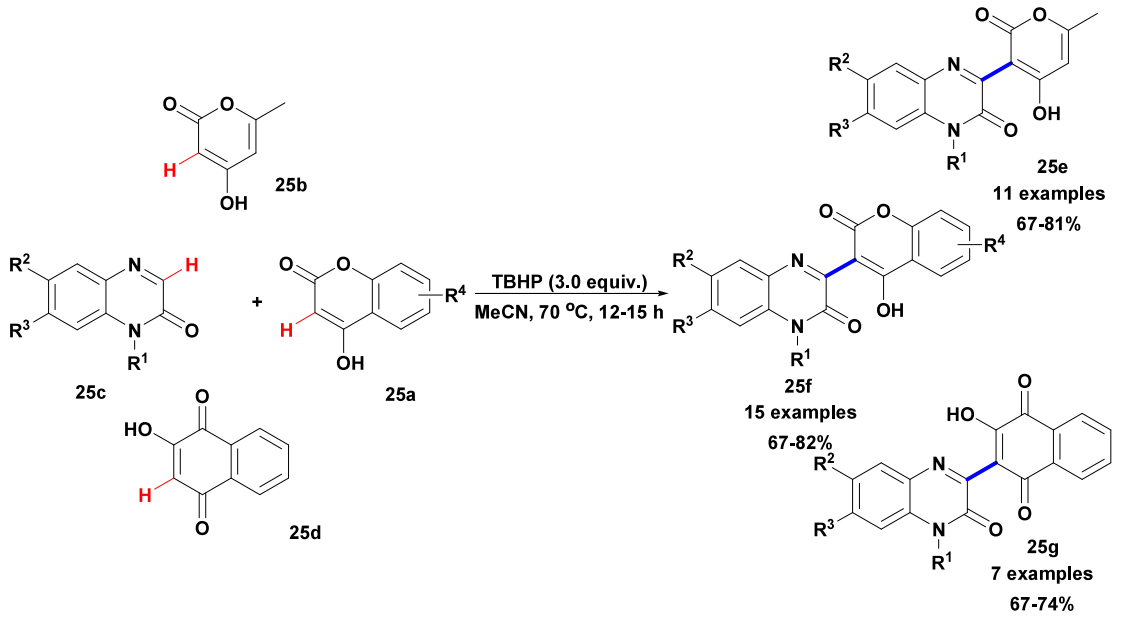


conditions. It demonstrated high functional group tolerance, regioselectivity, and scalability. This approach shows potential in the fields of organic synthesis, medicinal chemistry, and material sciences.

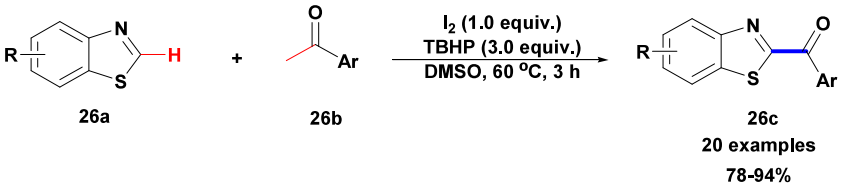
Lei et al. developed a visible-light-mediated direct cross-coupling reaction involving *N*-heterocycles **18a** and aldehydes **18b** (Scheme 14).[44] They successfully synthesized acylated *N*-heterocycles **18c** using either aliphatic or aromatic aldehydes, achieving moderate to high yields. The reaction proceeded with the formation of complex **A** in the presence of blue LED and TBHP. Then, through a HAT process, acyl radical formation, and subsequent SET process, the target product was formed. This method could efficiently and mildly acylate

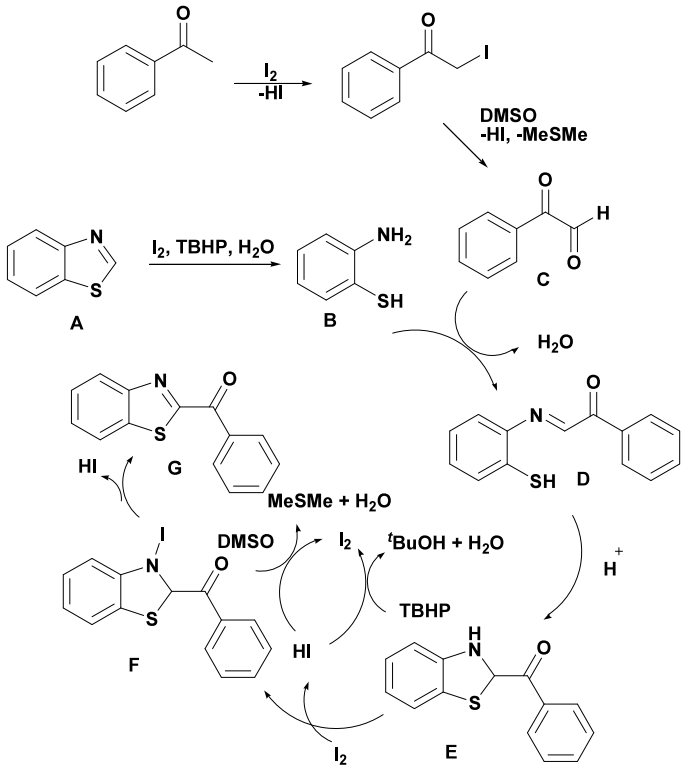
https://doi.org/10.1021/acsomega.4c11574
ACS Omega 2025, 10, 15852−15907

Scheme 19. CDC Reaction between Quinoxalin-2(1*H*)-ones and 4-Hydroxycoumarins, 4-Hydroxy-6-methyl-2-pyrone, or 2-Hydroxy-1,4-naphthoquinone



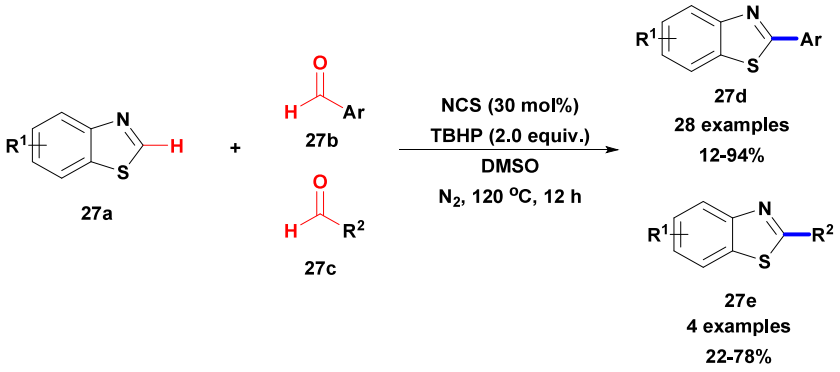
Scheme 20. I_2/TBHP as an Oxidative System for Acylation of the Benzothiazoles Using Aryl Ketones and Plausible Mechanism



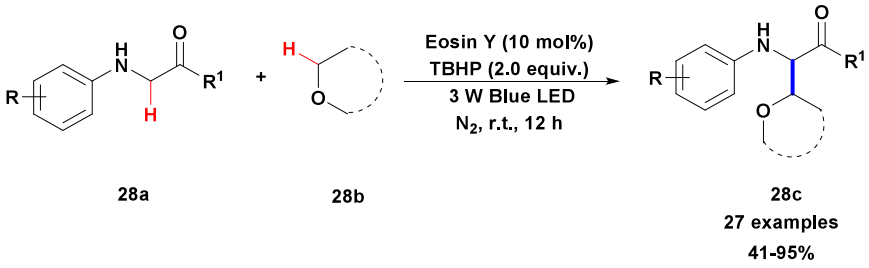


https://doi.org/10.1021/acsomega.4c11574
ACS Omega 2025, 10, 15852−15907

Scheme 21. NCS/TBHP-Promoted Arylation of the Benzothiazoles Using Aryl Aldehydes



Scheme 22. α-Alkylation of Glycine Derivatives via Ether Compounds



various *N*-heterocycles with diverse aldehydes, showing high functional group tolerance and scalability.

Regioselective C3-alkylation of coumarins **19a** and coumarin-3-carboxylic acids **20a** with inactive ethers and alkanes **19b** and **20b** was achieved by TBHP as a commercially available oxidant (Scheme 15).[45] The cross-coupling reaction was successfully performed under conditions free of metals, bases, and solvents, demonstrating efficacy across a wide range of coumarins. This practical and innovative approach, with its wide substrate scope, presents a valuable substitute for traditional transition-metal-catalyzed cross-coupling methods. It offers significant potential for expanding the library of coumarins, which are particularly prominent in the pharmaceutical industry.

Liu and colleagues have devised a metal-free method using TBHP to synthesize a series of dichloroaryl compounds **21c** from terminal alkenes **21a** (Scheme 16).[46] The reaction involves oxidative radical addition/chlorination with simple chloro reagents, eliminating the need for inert gas protection. This efficient, regioselective one-pot method is compatible with a wide range of functional groups. Preliminary mechanistic studies suggest that an oxidative radical process is involved, with triethylamine functioning as a base to suppress ATRA and facilitate proton transfer. This transformation showcases considerable potential for novel organic reactions. This strategy demonstrates high efficiency across a wide range of substrates and exhibits excellent tolerance for various functional groups, offering a new metal-free approach for the synthesis of biaryls. The advantages include metal-free conditions, avoiding metal catalysts, and being greener and more sustainable. It also offers excellent functional group tolerance, allowing a wide range of substrates to achieve appropriate yields of the products. However, the disadvantage is a reduction in yield with certain derivatives, such as using 2-vinylpyridine, which decreases the reaction yield.

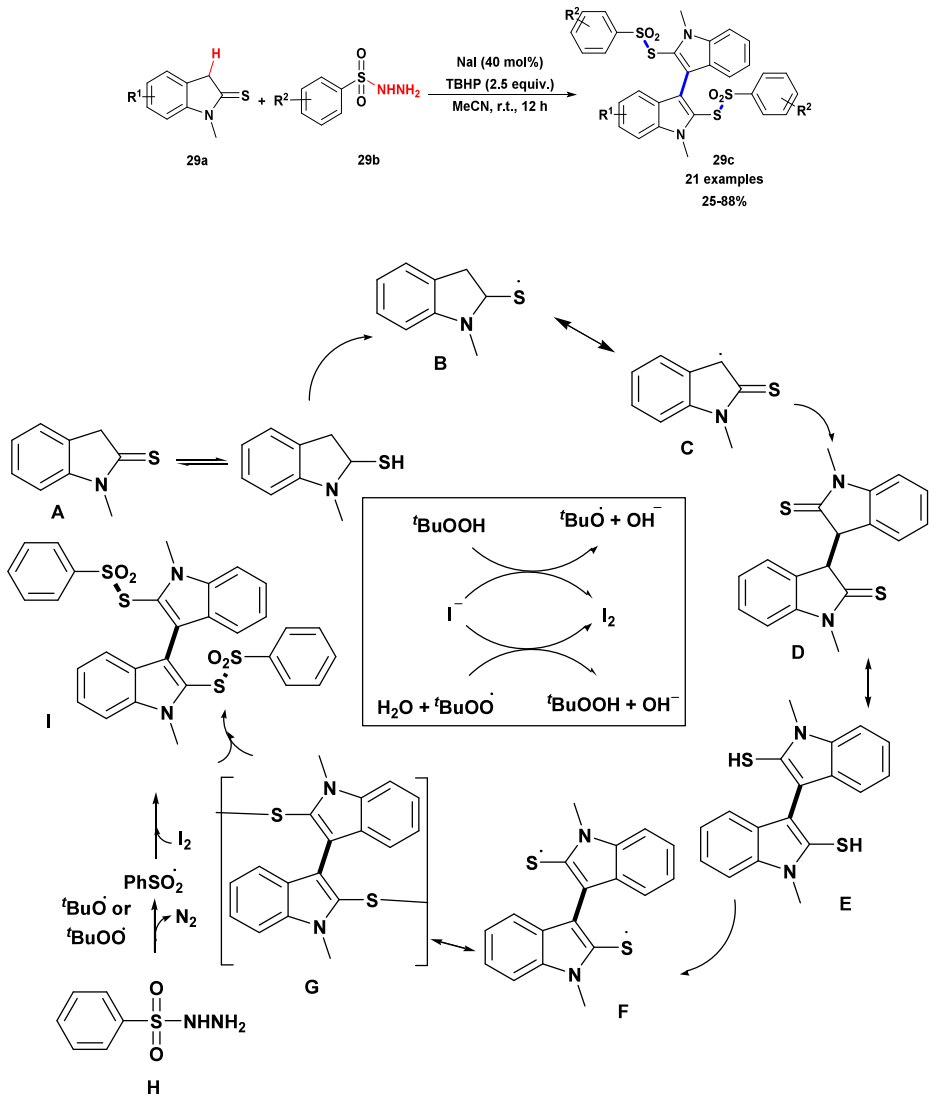
In 2019, the Liang research team expanded the radical difluoroalkylation/trifluoromethylation and alkynylation of unactivated alkenes **22a** under mild conditions (Scheme 17).[47] This method involved synthesizing CF_2/CF_3-substituted linear alkynyl ketones **22c** via 1,2-alkynyl radical migration. The authors suggested a radical pathway for this transformation, where CF_2CO_2Et and $\cdot CF_3$ radical species were generated from ICF_2CO_2Et **22b** and CF_3SO_2Na **23a** in the presence of *N*-methylpiperidine and TBHP. The addition of $\cdot CF_2CO_2Et$ or $\cdot CF_3$ radicals to the inactivated double bond of the 1,4-enyne formed the radical intermediate **A**, which then underwent 3-exo-dig cyclization subsequently to 1,2-alkynyl migration to produce the hydroxyalkyl radical **C**. Intermediate **C** was oxidized by $\cdot CF_2CO_2Et$ or $^tBuO\cdot$ radicals to yield intermediate **D**, which was later transformed into target product **E** via deprotonation (Scheme 17).

Triazoles, identifiable by their five-membered unsaturated ring with three nitrogen atoms, have been recognized as biologically and pharmaceutically active molecules (Scheme 18).[35,48−53] In 2020, a general procedure for synthesizing 1,3,5-trisubstituted 1,2,4-triazoles **24c** from 1,3-disubstituted 1,2,4-triazoles **24a** in the presence of TBAI/TBHP via decarbonylation of aromatic aldehydes **24b** was reported. Abebe Agisho and colleagues developed a straightforward, efficient, and environmentally friendly method for synthesizing 3,5-disubstituted 1,2,4-triazoles and 1,3,5-trisubstituted 1,2,4-triazoles from 3-monosubstituted 1,2,4-triazoles and 1,3-disubstituted 1,2,4-triazoles, to utilize potassium iodide as a catalyst and TBHP as an oxidizing agent under gentle reaction conditions. This approach provided structurally varied diverse 3,5-disubstituted and 1,3,5-trisubstituted 1,2,4-triazole compounds in good to outstanding yields.

Oxidative coupling of quinoxalin-2(1*H*)-ones **25c** with coumarin derivatives **25a**, 4-hydroxy-6-methyl-2-pyrone **25b**, or 2-hydroxy-1,4-naphthoquinone **25d** can be efficiently promoted by TBHP (Scheme 19).[54] Various 3-substituted

https://doi.org/10.1021/acsomega.4c11574
ACS Omega 2025, 10, 15852−15907

Scheme 23. Cross-Coupling Rection between Indole-2-thiones and Arylsulfonyl Hydrazides and Proposed Mechanism Reported



quinoxalin-2(1*H*)-one derivatives of **25c** were compatible with this method. The reaction also successfully proceeded using $K_2S_2O_8$, resulting in the coupling products with good yields. Under the reaction conditions, other oxidants such as $Na_2S_2O_8$, $(NH_4)_2S_2O_8$, Mn $(OAc)_3$, CAN, TBPB, and DTBP were ineffective for this transformation. Simple operation and using no toxic reagents were the advantages of this protocol.

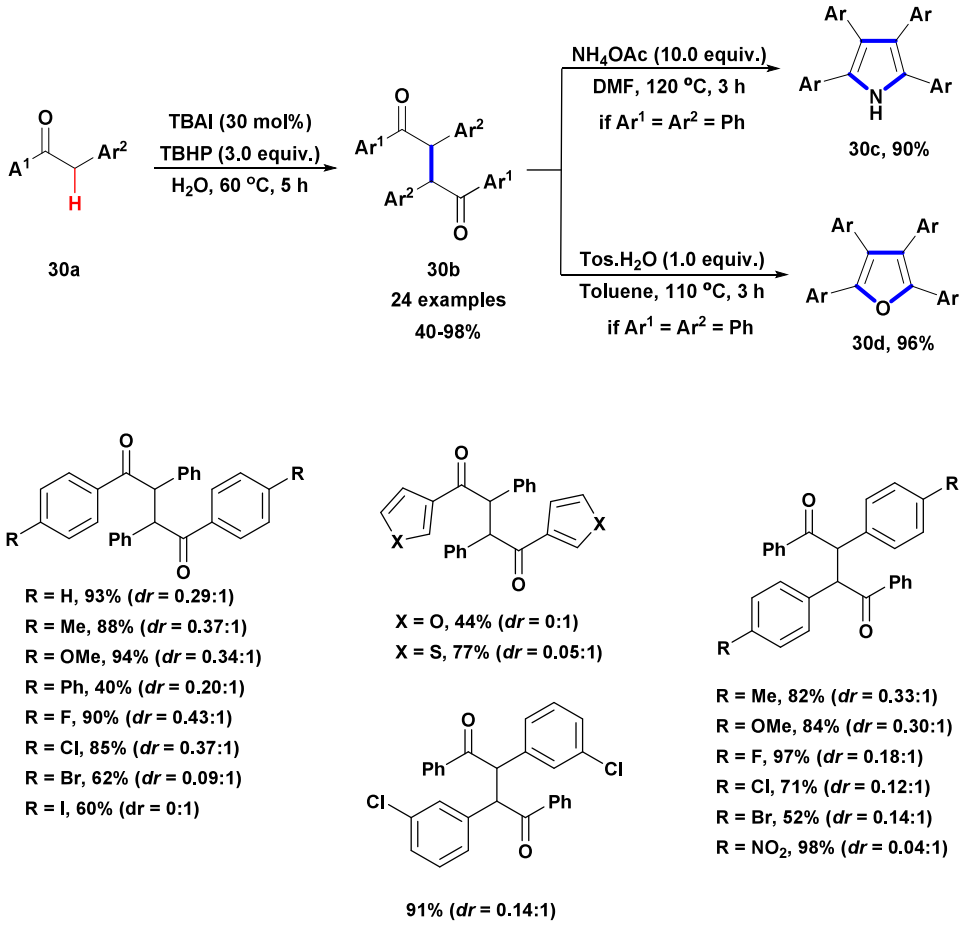
Acylation of the benzothiazoles **26a** using aryl ketones **26b** as an acylating agent can be achieved by I_2 and TBHP as ring-opening reagents with a short reaction time and at low temperature (Scheme 20).[55] According to the reported mechanism for the reaction, aryl ketone is transformed into arylglyoxal **A** during exposure to I_2 in DMSO with Kornblum oxidation. HI is oxidized by DMSO or TBHP to reproduce I_2 during exposure to I_2, TBHP, and H_2O, and the thiazole ring undergoes a ring-opening reaction to form 2-aminobenzenethiol. The reaction of intermediate **B** with intermediate **C** produces imine intermediate **D**, which is then converted to intermediate **E** through an intramolecular addition reaction. Next, the substitution reaction between intermediate **E** and I_2 produces intermediate **F**, which ends with the final product **G** via the elimination of HI (Scheme 20).

Arylation of benzothiazoles **27a** can be carried out by using aryl aldehydes **27b** with TBHP and *N*-chlorosuccinimide (NCS) (Scheme 21).[56] Acylated products **27e** were obtained amid the reaction conditions when 5-acetalbenzothiazole and aliphatic aldehydes **27c** were used as the substrates. Also, it has been found that DMSO can act as a strong Lewis base, facilitating the cleavage of C−H acidic bonds. The inexpensive organic catalyst NCS serves as a radical initiator with TBHP as the oxidant. This reaction accommodates a broad substrate scope, yielding arylated products in 12−94% yield for 28 examples. Additionally, the method produces acylated benzothiazoles from aryl aldehydes and aliphatic aldehydes with four examples. Nevertheless, the reaction's disadvantages consist of requiring high temperatures and extended reaction durations as well as low isolate yield for some of the products.

Amides constitute vital structural elements in biologically relevant molecules, such as proteins, natural products, pharmaceuticals, and synthetic intermediates.[57−59] In 2021, Yao et al. synthesized a series of α-etherized glycine derivatives **28c**, consisting of α-amino esters, α-amino ketones, or α-amino amides, through α-alkylation of glycines **28a** with open-chain and cyclic ethers **28b** (Scheme 22).[60] This visible-light-

https://doi.org/10.1021/acsomega.4c11574
ACS Omega 2025, 10, 15852−15907

Scheme 24. TBAI-Catalyzed Homocoupling of Benzyl Ketones



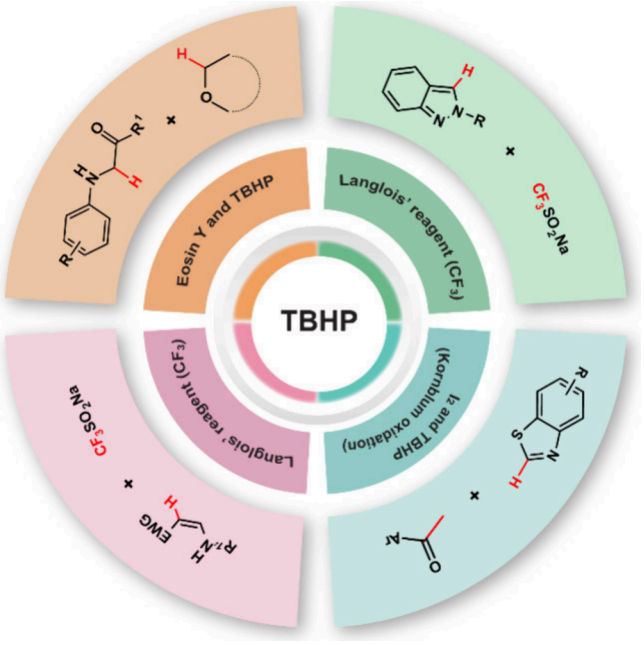


Figure 1. Suitable reagents for various types of coupling reactions with TBHP.

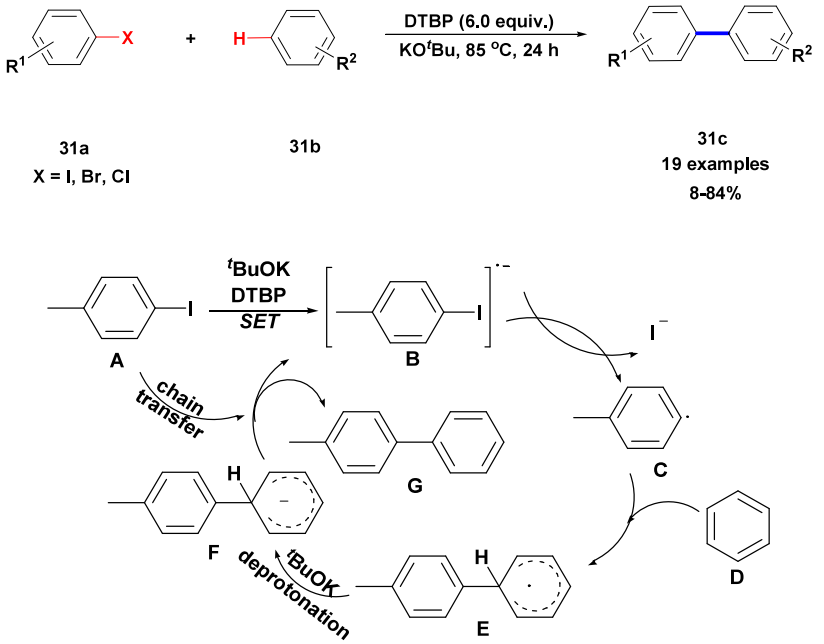
induced oxidative α-alkylation of glycine derivatives uses catalytic eosin Y and a 3 W blue LED, attaining good to supreme yields and functional group tolerance using TBHP at room temperature. It delivers a budget-friendly, metal-free, and mild synthesis solution.

In one study, one-pot metal-free cross-coupling reaction between indole-2-thiones **29a** and arylsulfonyl hydrazides **29b** afforded achiral axial 3,3′-biindole-2,2′-dibenzenesulfonothioate derivatives **29c** (Scheme 23).[61] The reaction was performed in the presence of a NaI/TBHP catalytic system. Applying TBPB and DTBP was not useful in this oxidative reaction. The product was also produced in the presence of I_2, TBAI, NIS, or KI as catalysts, but in lower yields. The radical pathway mechanism reported by the authors is seen in the scheme. In the proposed mechanism, the reaction of TBHP with I^- generates ^{t}BuOO· and ^{t}BuO· radicals. Next, these radicals react with indole-2-thione **A** to obtain radical **B**, which gives compound **C** via a homocoupling process. Oxidation of the thiol enol tautomer of intermediate **C** affords radical **D**. The homocoupling of radical **D** leads to disulfide **E**. On the other hand, under oxidative conditions, sulfonyl radicals are formed from sulfonyl hydrazides, which then produce arenesulfonyl iodides by I_2. Finally, arenesulfonyl iodides react with disulfide **E** to create product **I** through the radical propagation (Scheme 23).

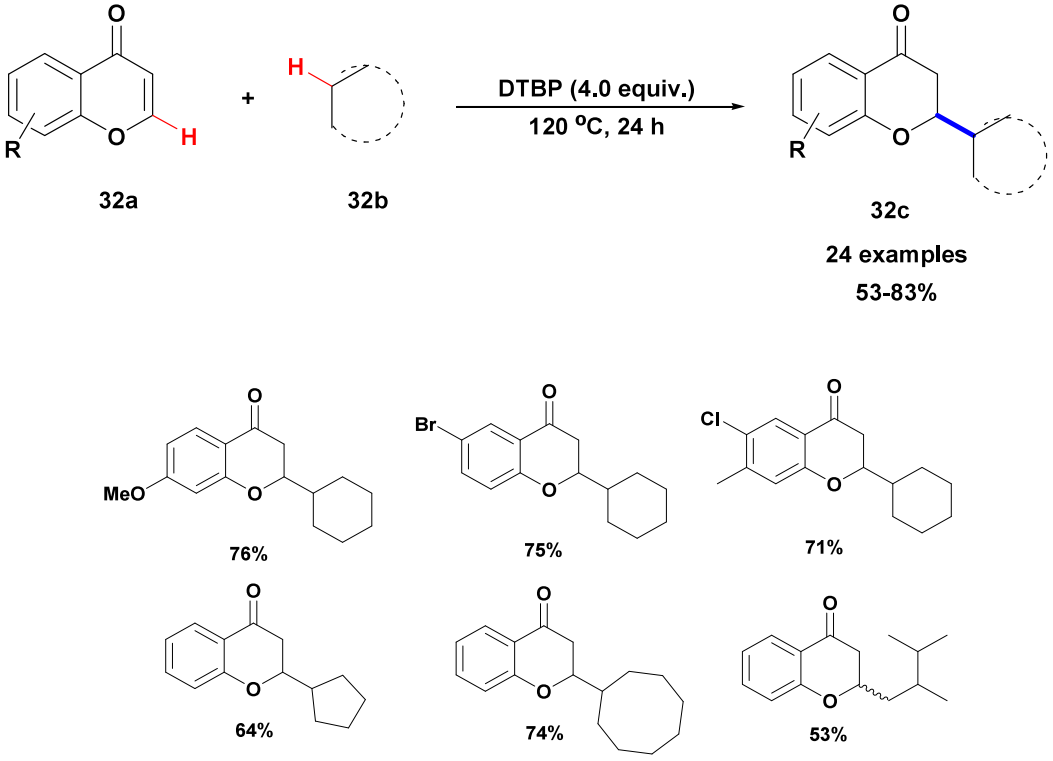
Just recently, in 2022, Bai and associates described an environmentally benign approach to produce diaryldiketone derivatives **30b** applying TBAI and TBHP in an aqueous medium (Scheme 24).[62] Both electron-donating groups ($-CH_3$ and $-OCH_3$) and electron-withdrawing groups (−F, −Cl, −Br, and $-NO_2$) on the aromatic rings were compatible in the present reaction. Heteroaromatic substrates, including

https://doi.org/10.1021/acsomega.4c11574
ACS Omega 2025, 10, 15852−15907

Scheme 25. Carbon−Hydrogen Arylation of Inactivated Benzene Derivatives via Aryl Halides and the Proposed Mechanism Reported



Scheme 26. DTBP-Mediated Oxidative Activation of sp^3 C−H Bonds of Nonreactive Alkanes and Addition Reaction to Chromones

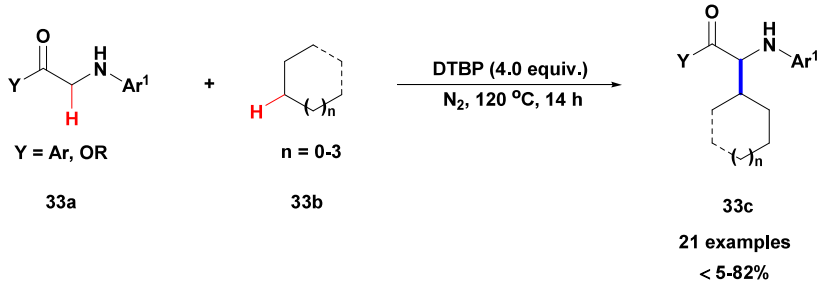


furan, thiophene, and naphthalene, also successfully generated the desired compounds in achieving yields between 44% and 85%. In the next step, a series of tetrasubstituted pyrroles **30c** and furans **30d** were smoothly prepared from α-methylene ketones.

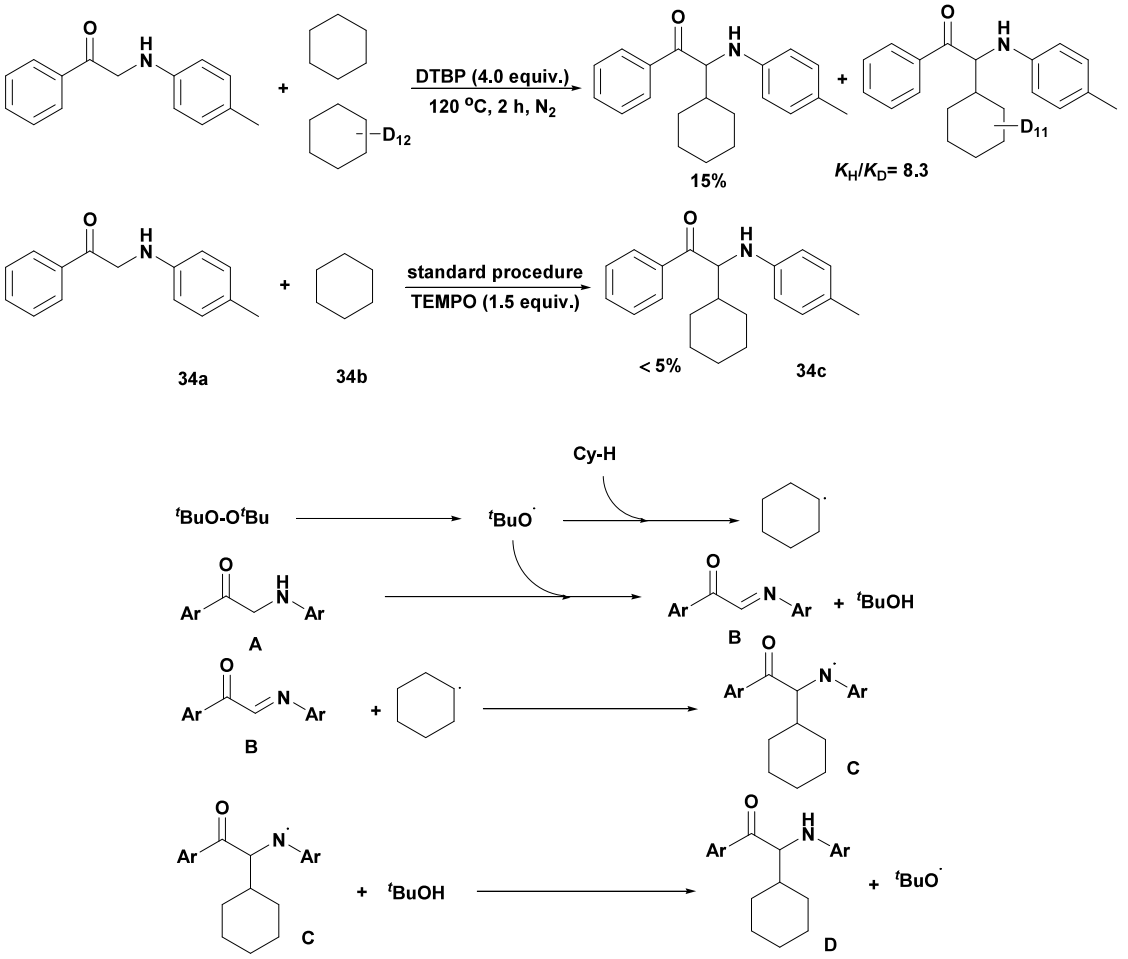
2.1.1. Innovative Approaches to Organic Synthesis Using TBHP. The methodologies presented in this study demonstrate innovative approaches to organic synthesis (Figure 1). The use of substrates containing an active α carbon, such as glycines, for carbon−carbon coupling with open-chain and cyclic ethers showcases a robust process enhanced by eosin Y and TBHP. This method improves product yield, making it a valuable addition to synthetic chemistry.[60] The use of light in photochemistry is energy-efficient and eco-friendly. Eosin Y, a nontoxic, cost-effective dye, effectively promotes chemical transformations and competes with metal-based processes. It

https://doi.org/10.1021/acsomega.4c11574
ACS Omega 2025, 10, 15852−15907

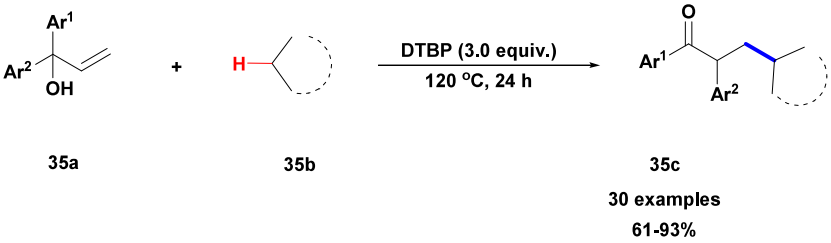
Scheme 27. DTBP-Mediated α-Alkylation of α-Amino Carbonyl Derivatives by Basic Alkanes



Scheme 28. Control Experiments for α-Alkylation of Amino Compounds and the Proposed Mechanism Reported



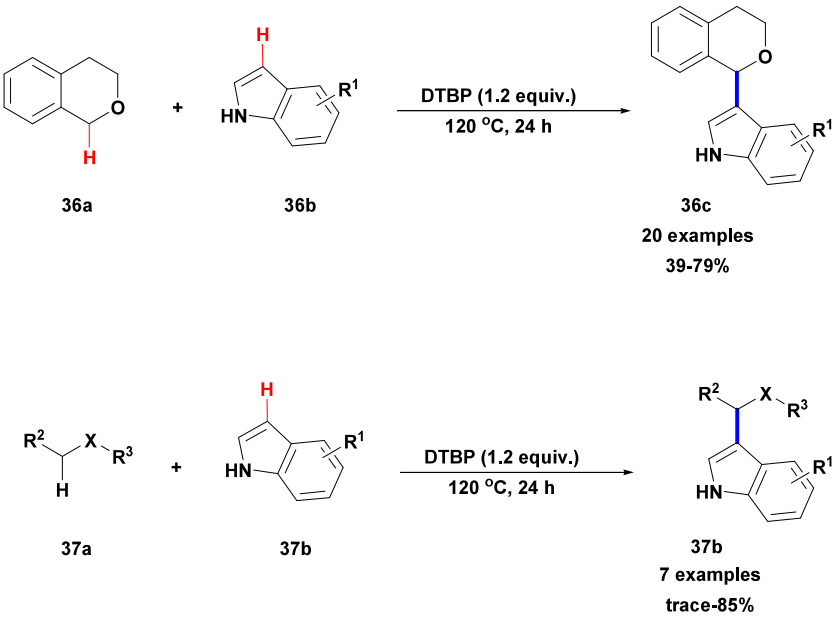
Scheme 29. Direct Preparation of an α-Aryl-β-alkylated Carbonyl Ketone through a Radical 1,2-Aryl Shift in α,α-Diaryl Allylic Alcohol



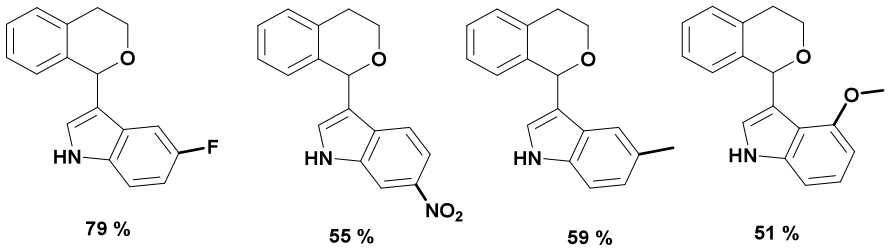
remains a promising green photocatalyst, especially for stereoselective photoredox transformations.[63] Furthermore, the reaction between thiazole derivatives and ketones using iodine (I_2) and TBHP highlights a significant improvement in the carbon−carbon bond formation through Kornblum oxidation and subsequent intramolecular reactions. The

https://doi.org/10.1021/acsomega.4c11574
ACS Omega 2025, 10, 15852−15907

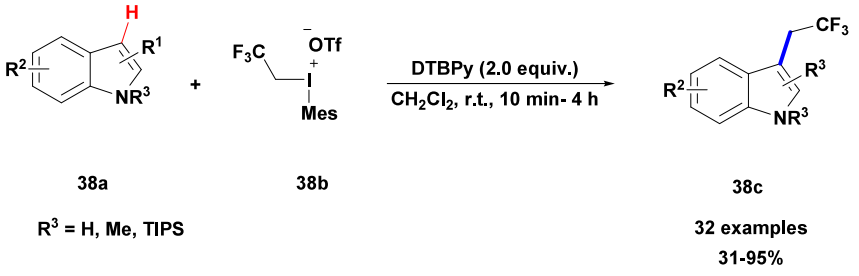
Scheme 30. DTBP-Promoted Direct Coupling of Isochroman and indole



Scheme 31. Scope of Some Indoles with Different Electronic Groups



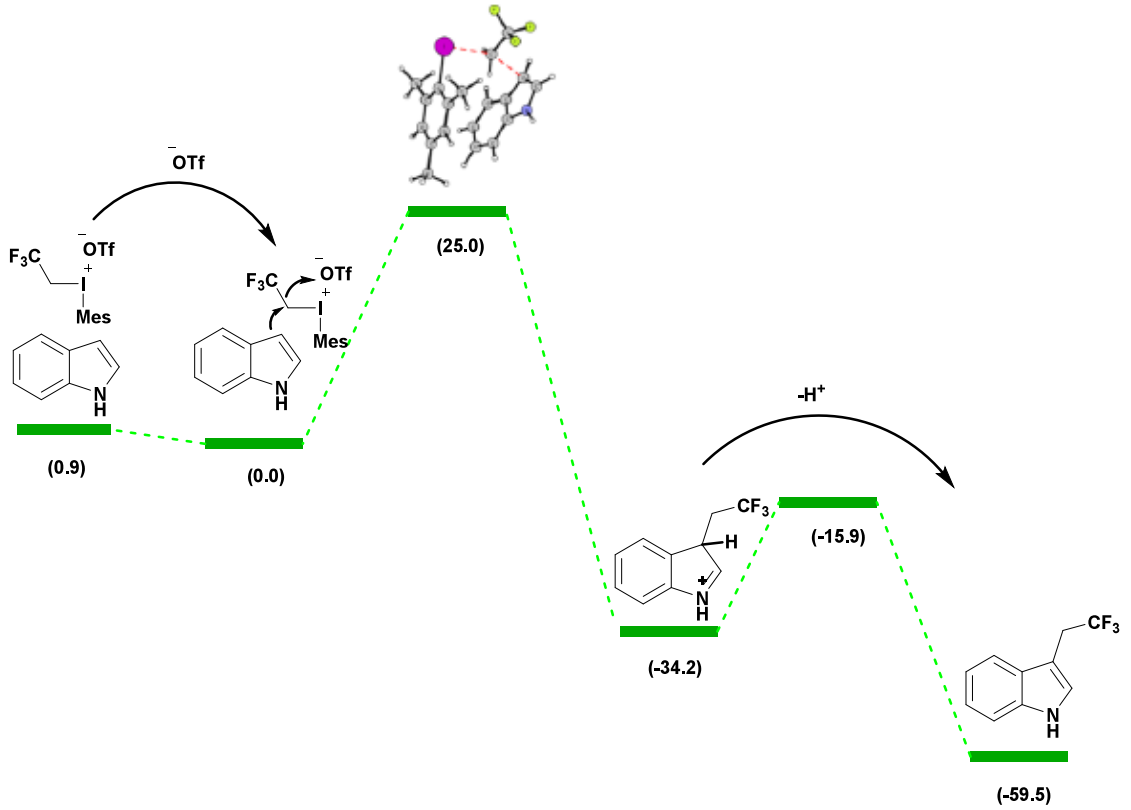
Scheme 32. Trifluoroethylation of Indoles Promoted bt DTBPy



efficiency of this method underscores the importance of I_2 and TBHP in facilitating complex transformations.[55] The I_2/TBHP system has significantly advanced synthetic conversions for industrial and pharmacological products. It offers easy access to various starting materials and enables efficient, eco-friendly carbon−carbon, carbon−nitrogen, and carbon−sulfur linkage formation and ring-closure reactions. This system is also effective in developing ring-fused systems, including incorporating bioactive fused heterocycles, using accessible materials, making it a vital tool in organic synthesis.[64,65] The addition of CF_3 groups of enamine derivatives with sodium trifluoromethanesulfinate (Langlois reagent) exemplifies a highly selective and effective approach, outperforming other peroxide-based methods. The reagent's ability to target the electronegative β-carbon of enamines illustrates its potential as a specialized and economical tool in synthetic processes.[43] The Langlois reagent is an efficient trifluoromethylating and fluoroalkylating agent with diverse functionality, a broad substrate scope, and easy handling. It is widely used in CF_3-incorporated compounds with various applications. However, its preparation involves fluoroalkyl halides, posing an environmental threat and necessitating an alternative route.[66,67] Finally, the trifluoromethylation of indazole derivatives using the Langlois reagent and TBHP further demonstrates the reagent's utility and effectiveness in synthesizing valuable trifluoromethylated compounds.[42] Langlois' reagent is widely used for trifluoromethylation, serving as an excellent CF_3 source for difunctionalizing carbon−carbon double and triple bonds. It enables the formation of various functionalities, such as alkenyl, alkyl, carbonyl, and cyano groups, due to its versatile electrophilic, nucleophilic, and radical character.[68] These methodologies collectively highlight significant advancements

https://doi.org/10.1021/acsomega.4c11574
ACS Omega 2025, 10, 15852−15907

Scheme 33. Energy Diagram in kcal·mol^{-1} of the Transformation Based on Density Functional Theory Calculation



in organic synthesis, offering efficient, economical, and specialized solutions for various synthetic challenges (Figure 1).

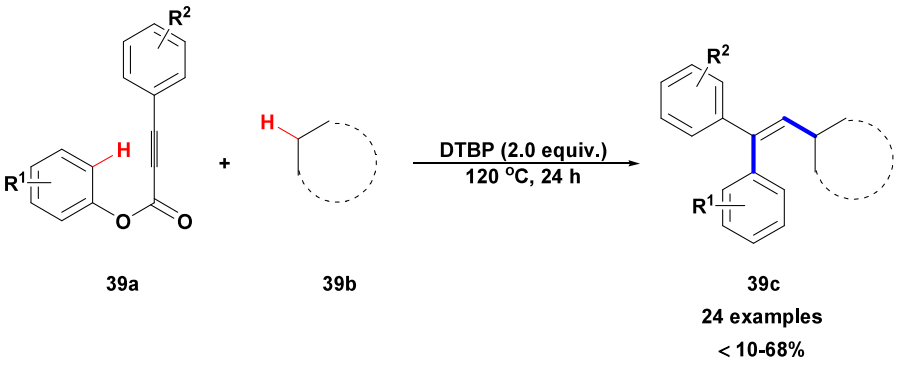
2.2. Coupling Reactions with DTBP. In recent years, efforts to replace transition metals in cross-coupling reactions have led scientists to choose organic peroxides as potential promoters in these syntheses.[69] DTBP, owing to the bulky *tert*-butyl groups, is one of the most stable peroxides commonly used as a radical initiator in a variety of reactions such as intramolecular addition reactions, fragmentation reactions, and homolytic substitution reactions.[70] DTBP is a colorless liquid with a half-life of approximately 3 h at 140 °C and 24 h at 120 °C. Heating, as well as UV irradiation, can dissociate DTBP to *tert*-butoxy radicals that can abstract the H atom of the molecules or attack the molecules.[71] In 2014, Yi published a direct attachment of aryl groups of an unreactive aromatic C−H bond **31b** by applying DTBP as an oxidant and ^{t}BuOK as a base under mild reaction conditions (Scheme 25).[72] The transformation occurred through radical anion intermediates, and no coupling outcome was achieved without adding oxidants. In this reaction condition, bromobenzene afforded a slightly lower yield, and chlorobenzene yielded no product. The reason seems to be that the homolysis of the aryl carbon−chlorine bond is more challenging than that of the aryl carbon−iodine bond. A possible mechanism described by the authors involves an SET pathway. Initially, radical anion **B** is generated from aryl halide **A** through a single electron transfer process assisted by DTBP and ^{t}BuOK. Then, **B** is converted into radical **C** and attached to benzene to afford cyclohexadienyl radical **E**. Subsequently, ^{t}BuOK abstracts a proton from **E** to generate the radical anion **F**. Then, product **G** is achieved via a radical chain transfer between **F** and **A** and also the regeneration of the radical anion **B**.

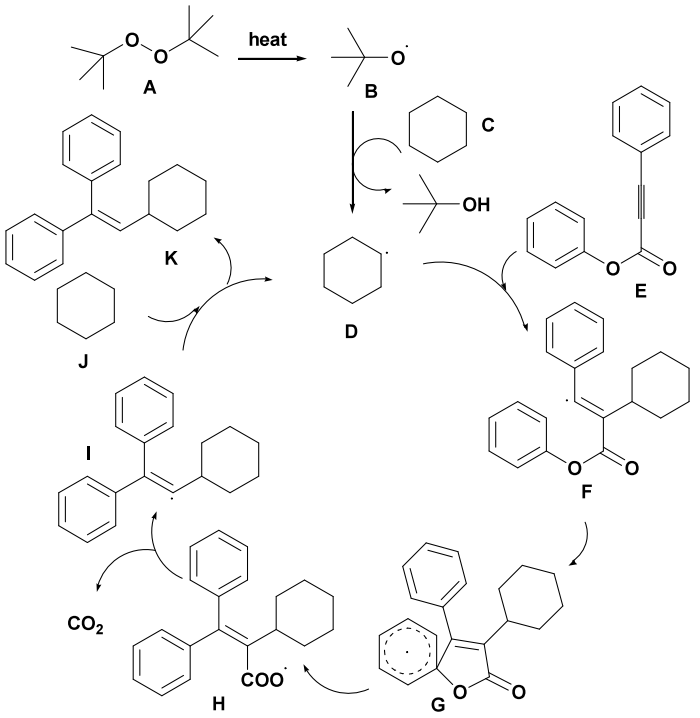
The chromanone framework is found in various bioactive natural substances and medicinal compounds, which exhibit a diverse array of biological actions, featuring antitumor, anticancer, antioxidant, antimicrobial, and antibacterial attributes.[73−76] Transition-metal-catalyzed alkylation of chromanone derivatives through conjugate addition reactions has been published by various research teams.[73,77−79] The Han group described oxidative C(sp^3)−H bond activation mediated by DTBP of nonreactive alkanes **32b** and conjugate addition involving chromone derivatives **32a** (Scheme 26).[80] The product **32c** was obtained in 51% yield when 2.0 equiv of DTBP was used. The effectiveness increased by raising the loading of DTBP to 4.0 equiv (72% yield). Other peroxides like H_2O_2, TBHP, TBPB, BPO, and DCP were less effective, and there was no product when oxidants such as $K_2S_2O_8$, BQ, DDQ, NaClO, and O_2 (1 atm) were used. In their procedure, 2-alkylchromanones were provided in satisfactory to high yields.

Cheng's team developed a cross-dehydrogenative coupling reaction of α-amino carbonyl derivatives **33a** with basic alkanes **33b** followed by α-alkylation of amino compounds **33c** (Scheme 27).[81] Cyclohexane, cyclopentane, cycloheptane, cyclooctane, adamantine, and glycine esters demonstrated good reactivity in the reaction. The authors conducted some validation experiments to understand the reaction pathway. During the kinetic isotope effect investigation, the ratio of k_H/k_D for cyclohexane **34b** was found to be 8.3, and the incorporation of TEMPO notably diminished the yield of the product. These results indicated the bond cleavage of the C(sp^3)−H was the rate-limiting step, and a radical pathway

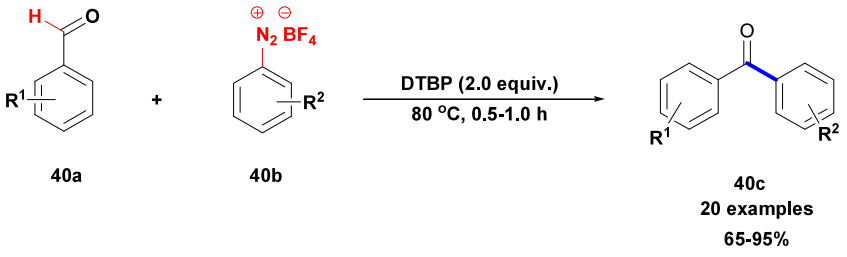
https://doi.org/10.1021/acsomega.4c11574
ACS Omega 2025, 10, 15852−15907

Scheme 34. Reaction of Aryl Alkynoates with Cycloalkanes Using DTBP and the Proposed Mechanism Reported





Scheme 35. Preparation of Diaryl Ketone Compounds

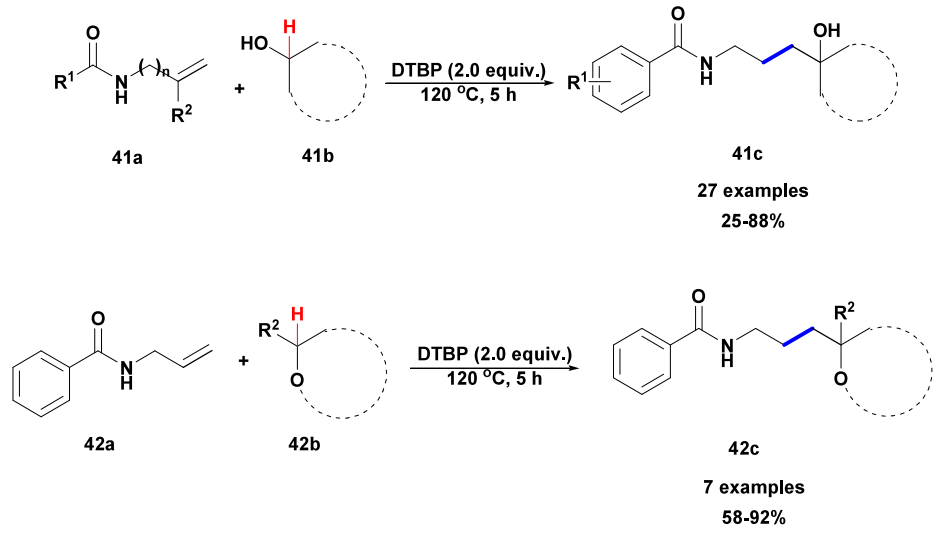


was implicated in the reaction. Hence, the scientists put forward a radical mechanism in which the dissociation of DTBP under heating resulted in the formation of *tert*-butoxy radicals. Then, hydrogen atom abstraction by a *tert*-butoxy radical resulted in a cyclohexyl radical, which was identified as the rate-determining step. On the other hand, α-amino carbonyl produced imine intermediate **B**. Subsequently, a cyclohexyl radical was attached to **B** to create radical intermediate **C**. Finally, the capture of a hydrogen atom by intermediate **C** led to the creation of the final product **D** (Scheme 28).

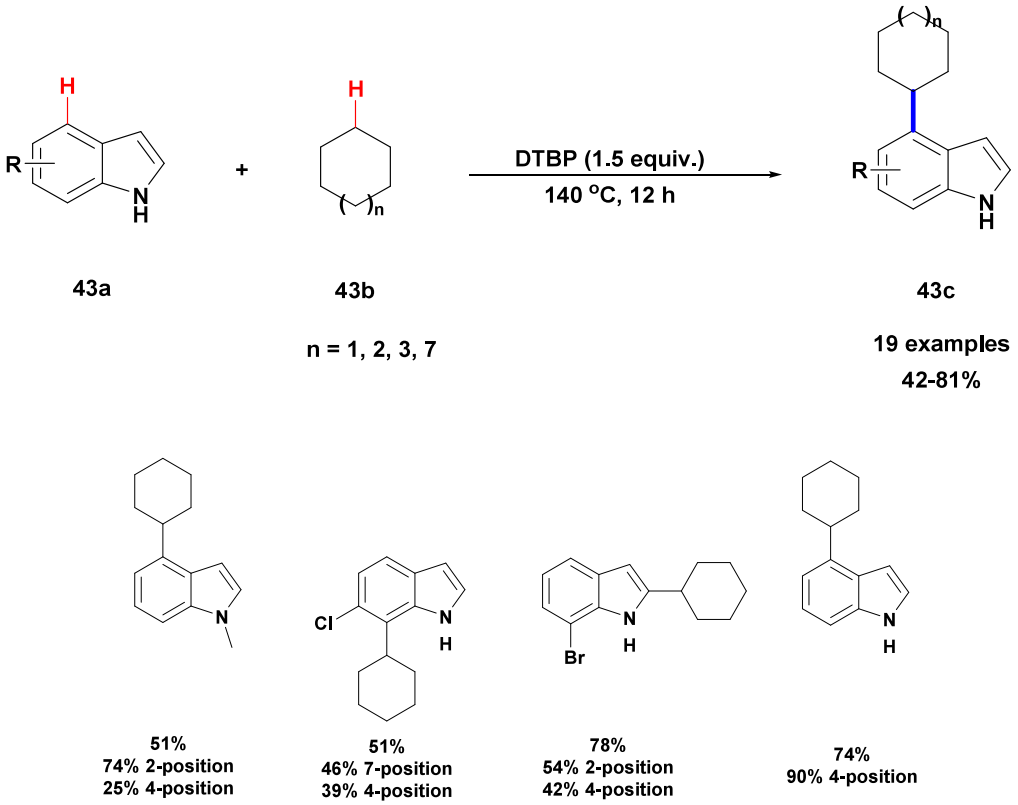
Han and colleagues reported the direct synthesis of α-aryl-β-alkylated carbonyl ketones **35c** through radical alkylation of symmetrical and unsymmetrical α,α-diaryl allylic alcohols **35a** with basic alkanes **35b** (Scheme 29).[82] Direct C(sp^3)−H activation and 1,2-aryl shift in α,α-diaryl allylic alcohol derivatives resulted in the creation of C(Ar)−C(sp^3) and C(sp^3)−C(sp^3) in a single step. It is noteworthy that selective transfer of the two distinct aryl groups occurred in this

https://doi.org/10.1021/acsomega.4c11574
ACS Omega 2025, 10, 15852−15907

Scheme 36. Direct Synthesis of α,ω-Amino Alcohols Promoted by DTBP



Scheme 37. DTBP-Mediated Coupling Reaction of Indole Compounds with Cyclic Alkanes



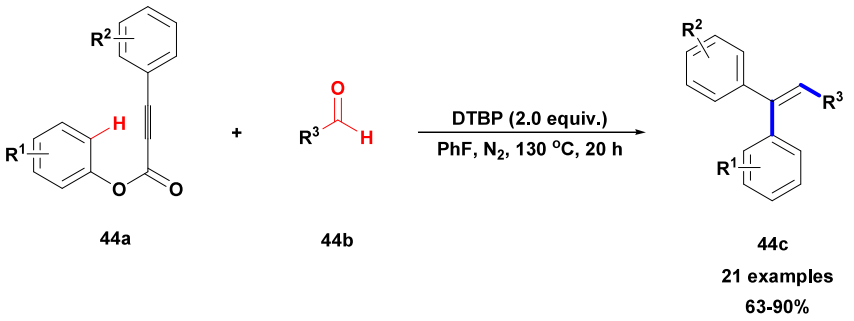
transformation. They developed a DTBP-promoted radical addition reaction of olefins with alcohols and ether compounds, forming new C(sp^3)−C(sp^3) bonds without metal catalysts or light. This process, which functionalizes C(sp^3)−H bonds, produces α,ω-amino alcohols directly from olefins and exhibits a wide range of substrates and high yields, enriching metal-free radical addition reactions.

Cai and colleagues documented the formation of C(sp^3)−C(sp^2) bonds between isochroman compound **36a** and indole derivatives **36b**. Several cyclic ethers were achieved in reasonable yields, utilizing DTBP as the only oxidant in the absence of solvents (Scheme 30). Indoles with electron-withdrawing and electron-neutral groups exhibited good yields. However, electron-donor groups showed somewhat reduced yields relative to the electron-poor indoles. Under the conditions, no substituents on the 1- and 2-positions of indoles had a remarkable effect on the reaction. By contrast, the electronic properties of substituents situated at the 6- and 7-positions played a minor role in yields (Scheme 31).[83]

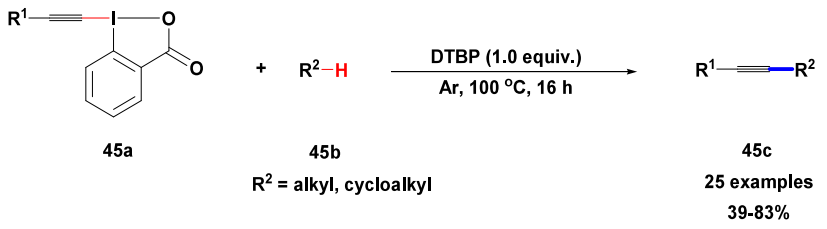
Novák and co-workers reported specific trifluoroethylation at the C3 position of unprotected indoles **38c** using 2,2,2-trifluoroethyl(mesityl)-iodonium triflate **38b** in the presence of 2,6-di-*tert*-butylpyridine or DTBPy at room temperature (Scheme 32).[84] Electron-rich alkyl and alkoxy indoles **38a**

https://doi.org/10.1021/acsomega.4c11574
ACS Omega 2025, 10, 15852−15907

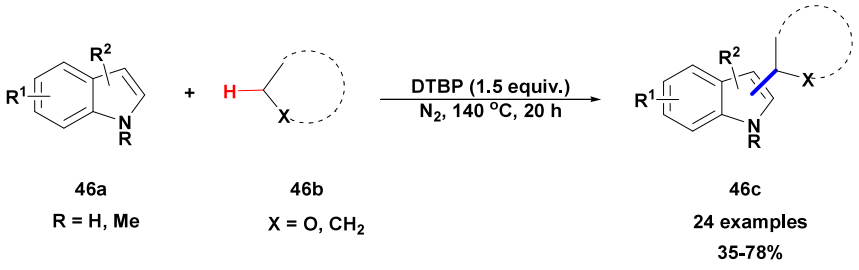
Scheme 38. DTBP-Mediated Decarbonylative Alkylation/Arylation of Alkyne Esters with Aldehyde Compounds



Scheme 39. DTBP-Mediated Alkynylation of Alkanes with Ethynylbenziodoxolones



Scheme 40. Oxidative Cross-Coupling of Indole Compounds with Ether Compounds or Cycloalkanes



exhibited good to excellent yields, while electron-deficient ones afforded a lower efficiency. The authors used DFT calculations to study the mechanism and selectivity. The separation of the triflate ion was demonstrated to be energy-releasing (−0.9 kcal·mol^{-1}). Hence, the slowest step was the attachment of a trifluoromethyl group to the indole nucleus. In the subsequent step, deprotonation of the σ-complex by the base occurred with a barrier of 18.3 kcal·mol^{-1}. Both steps were highly energy-releasing, indicating one-way changes. Activation energy levels for all of the reactants were computed. The reaction pathway was excluded based on the prohibitively high barrier (52 kcal·mol^{-1}) for constructing the key intermediate from 1 and 2 (Scheme 33).

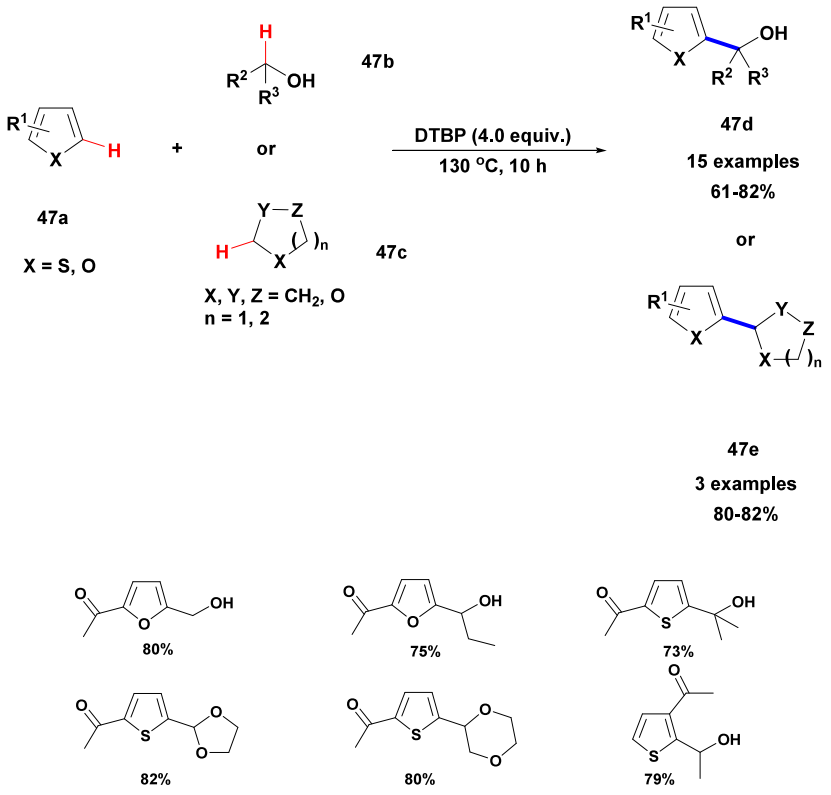
The same research group described another type of alkylation and migration in the decarboxylative arylation reaction on alkynoates (Scheme 34).[85] A radical cascade difunctionalization reaction of aromatic alkynoates **39a** proceeded through a consecutive reaction comprising breaking of the C(sp^3)−H bond of cyclic alkanes **39b**, alkylation of the C−C triple bond in **39a**, 1,4-shift of the aryl group, and removal of a carboxyl group. According to the proposed mechanism by the authors, *tert*-butoxy radical intermediate **B** is formed through homolysis of DTBP under heating. H atom removal of cyclohexane compound **C** by a *tert*-butoxy radical forms cyclohexane radical species **D**, which reacts with the C−C triple bond of alkyne esters to afford species **F**. Then, **F** undergoes ipso ring closure to form spiro compound **G**. The following shift of the aryl group on the ester moiety forms carboxyl radical species **H**, which undergoes the decarboxylation reaction with the release of the CO_2 to furnish species **I**. Finally, H atom removal of **J** by **I** creates the desired products **K** and **D**.

Yadav et al. reported DTBP-promoted cross-coupling of aromatic aldehyde compounds **40a** with aryldiazonium tetrafluoroborates **40b** to access diaryl ketones **40c** under metal-free conditions (Scheme 35).[86] They developed an efficient one-pot method for synthesizing diaryl ketone compounds via a metal-free coupling reaction of aromatic aldehyde compounds and aryldiazonium tetrafluoroborates, using DTBP as a radical starter. This represents the first example of creating diaryl ketone compounds from aromatic aldehyde compounds through a radical−radical coupling reaction, offering new applications for DTBP in metal-free reactions and offering a substitute to the Friedel−Crafts acylation.

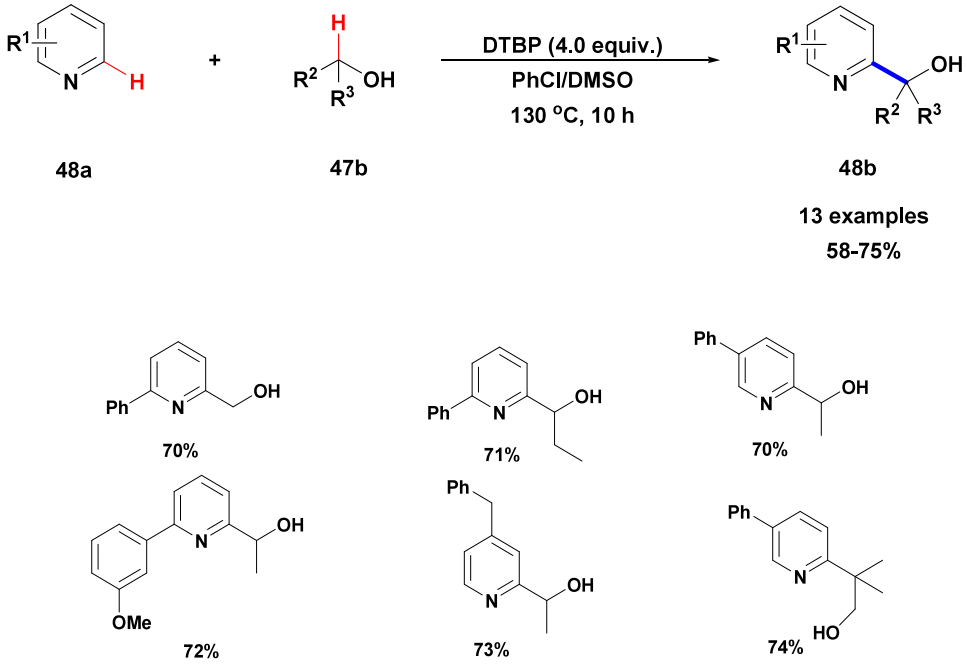
The Han group described metal-free radical addition of primary and secondary hydroxyl compounds **41b** or ethers **42b** with *N*-allylbenzamides **41a**/**42a** employing DTBP as the sole oxidant in the reaction (Scheme 36).[82] Creation of a new carbon−carbon bond from functionalization of a C(sp^3)−H bond using a radical addition cascade process resulted in straightforward synthesis of α,ω-amino alcohols **41c**/**42c** from easily available olefins. It provides a wide range of substrates

https://doi.org/10.1021/acsomega.4c11574
ACS Omega 2025, 10, 15852−15907

Scheme 41. DTBP-Promoted Hydroxyalkylation of Heterocycle Compounds with Alcohols and Cyclic Ether Compounds



Scheme 42. DTBP-Promoted Hydroxyalkylation of Pyridines with Alcohols



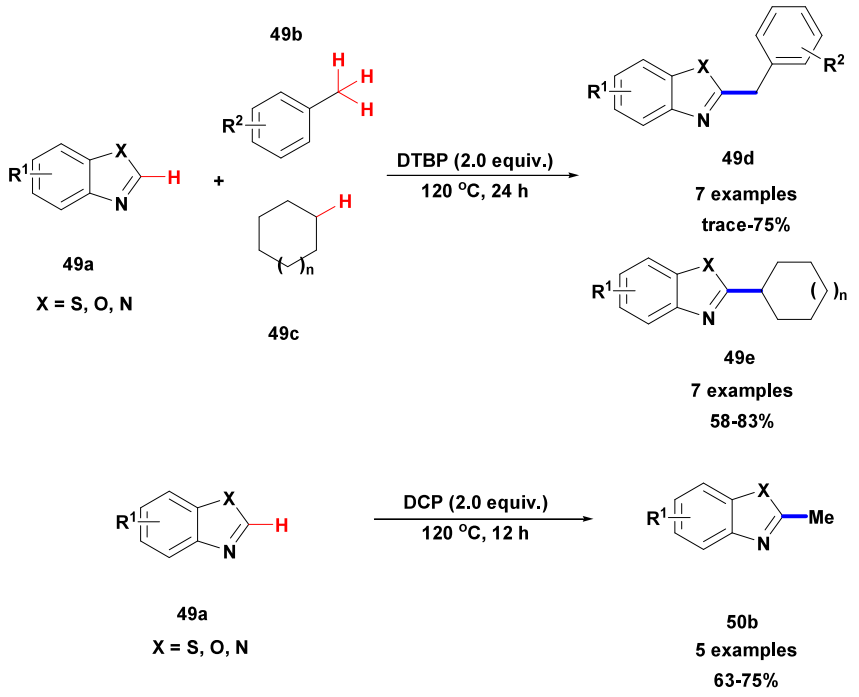
and favorable yields, enhancing the scope of radical addition under metal-free conditions.

Direct functionalization of indoles often occurs at the 2- or 3-position.[87−89] In 2016, Yi reported C4-regioselective oxidative alkylation of unprotected indoles **43a** with cycloalkanes **43b** using DTBP as the sole oxidant in the reaction for the first time.[90] Various indoles bearing substituents at different positions underwent this functionalization at 2-, 4-, and 7-positions with moderate to high regioselectivity (Scheme 37).

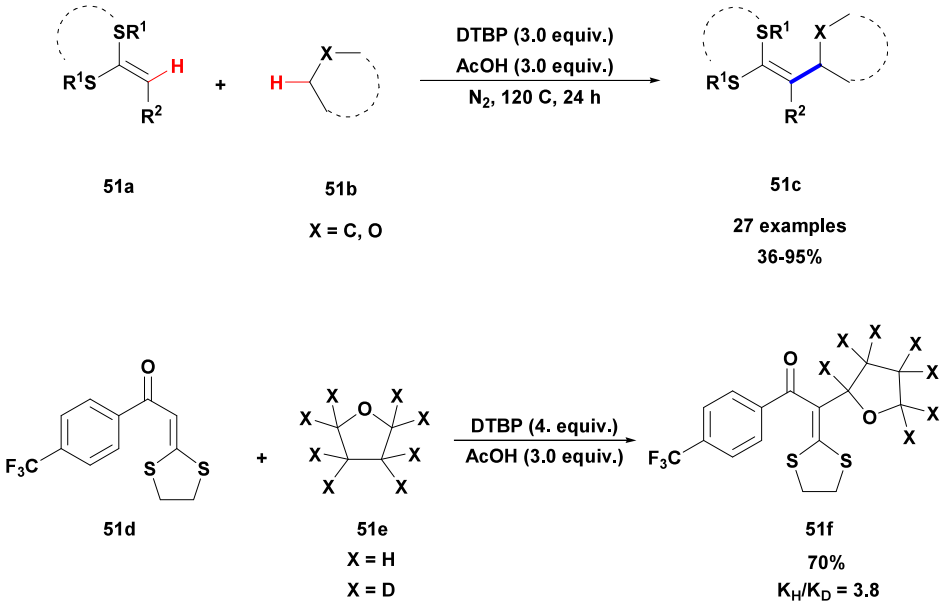
In 2016, Pan and Yu reported decarbonylative alkylation via 1,4-shift of the aryl group and removal of a carboxyl group of diaryl alkyne esters **44a** with aliphatic aldehydes **44b** as an inexpensive and plentiful alkyl radical source in the presence of DTBP (Scheme 38).[91] A large number of trisubstituted alkenes **44c** in reasonable to good yields were produced. They

https://doi.org/10.1021/acsomega.4c11574
ACS Omega 2025, 10, 15852−15907

Scheme 43. C−H Alkylation of Azoles Using DTBP and DCP



Scheme 44. Metal-Free C−H Alkylation of Ketene Dithioacetals and KIE Experiment



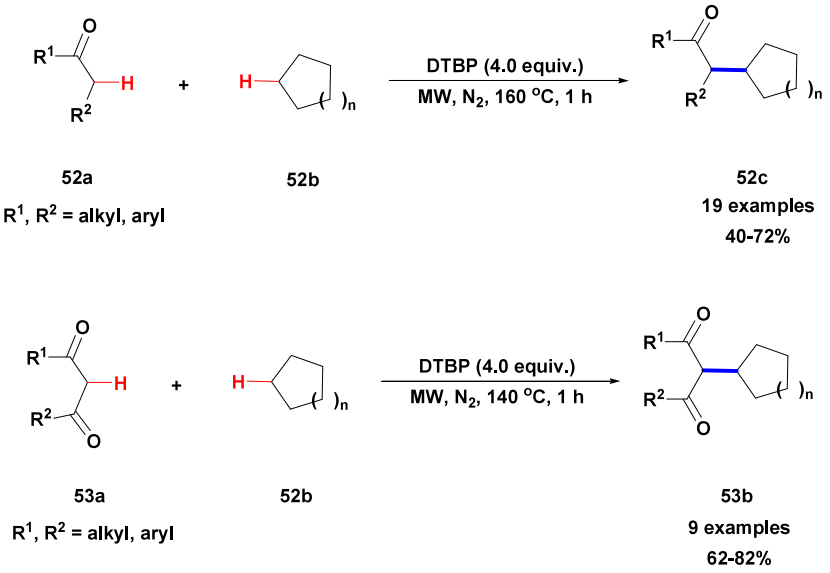
designed a metal-free approach for the oxidative decarbonylative alkylation of diaryl alkyne esters with aliphatic aldehydes, producing trisubstituted olefins in good to moderate yields. The process includes the removal of a carbonyl group, radical addition, 1,4-shift of the aryl group, and removal of a carboxyl group, all performed in a single pot. This approach efficiently and economically synthesizes 1,1-diaryl-2-alkyl ethylene compounds using aliphatic aldehyde compounds.

Xu and co-workers described direct radical formation of a C(sp^3)−C(sp) bond between inactivated saturated alkanes **45b** and hypervalent iodine alkynyl reagents like ethynylbenziodoxolones **45a** using DTBP (Scheme 39).[92] In a large-scale experiment using cyclohexane as the alkyl reagent, coupling product **45c** was achieved with a good yield of 73%. This process was effective with various saturated hydrocarbons and hypervalent iodine alkynyl reagents, offering an efficient way to synthesize alkyl-substituted alkynes under gentle, metal-free conditions .

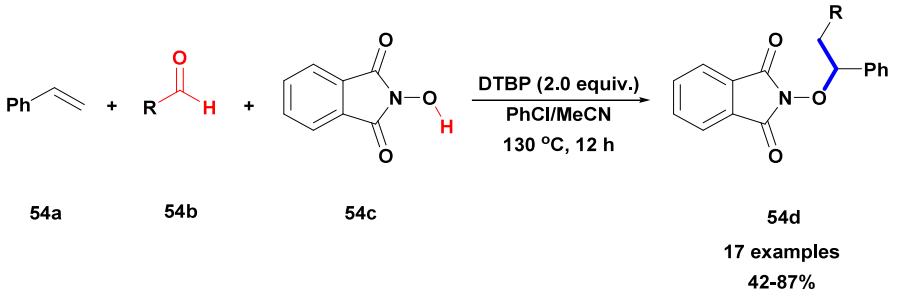
Kwong's research team developed a transition-metal-free cross-dehydrogenative bond (CDC) formation. Using di-*tert*-butyl peroxide, they effectively coupled indoles with cyclic ethers and cycloalkanes, resulting in satisfactory yields. C2 and C3 functionalization of indoles has received significant attention from chemists in the organic synthesis field. Direct cross-coupling of unprotected indoles **46a** with cyclic ether

https://doi.org/10.1021/acsomega.4c11574
ACS Omega 2025, 10, 15852−15907

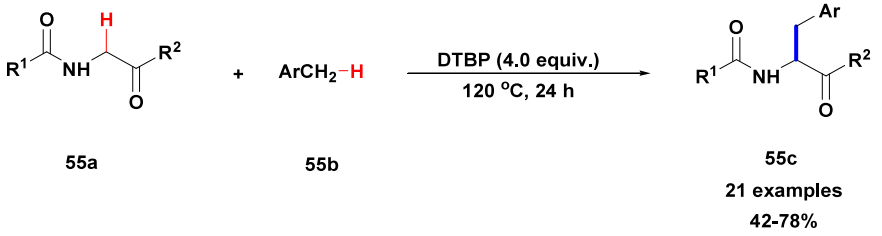
Scheme 45. α-Alkylation of Ketones and 1,3-Diketones Using CDC Reaction



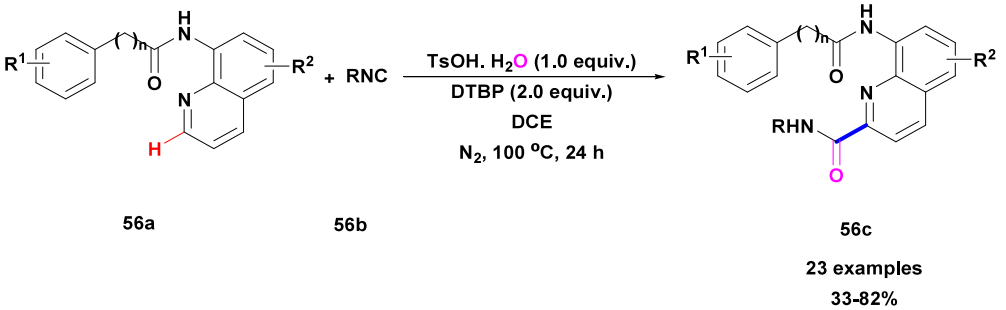
Scheme 46. Oxidative Decarbonylative Alkylation−Aminoxidation



Scheme 47. Selective Direct Benzylation of *N*-Acyl-2-aminoacetophenone Compounds with Toluene-Based Compounds



Scheme 48. selective metal-free C2−H amidation of 8-amidoquinoline compounds

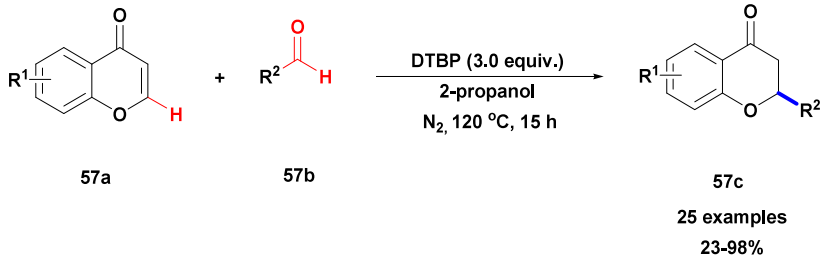


compounds **46b** or cyclic alkanes using only DTBP as an oxidant in the reaction was performed (Scheme 40).[93] The product **46c** in the presence of 1.5 equiv of TBPB was also obtained in satisfactory yield (45%).

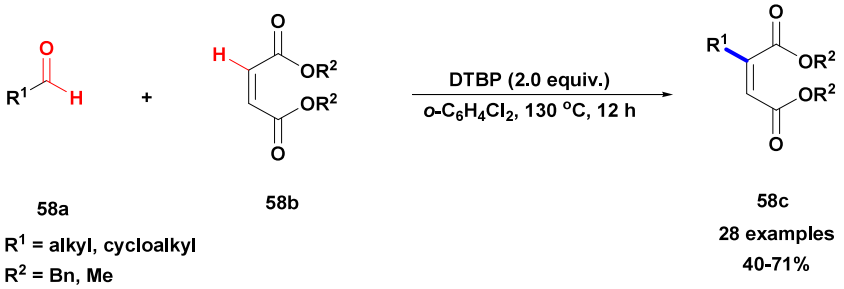
Kianmehr's research team described a straightforward metal-free CDC reaction between neutral heterocycles **47a** with alcohols and cyclic ether compounds **47b**/**47c** (Scheme 41).[94] In their protocol, heterocycles such as thiophene, furan, and

https://doi.org/10.1021/acsomega.4c11574
ACS Omega 2025, 10, 15852−15907

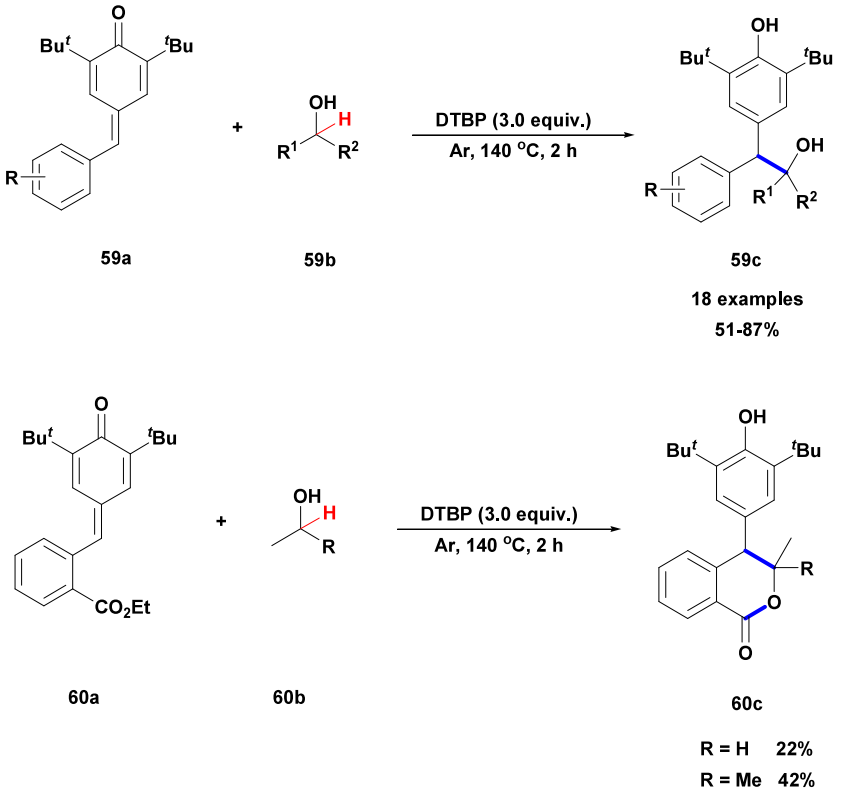
Scheme 49. DTBP-Promoted Alkylation of Chromone Compounds Employing Aliphatic Aldehyde Compounds



Scheme 50. DTBP-Mediated Alkylation of Electron-Deficient Alkenes Using Aliphatic Aldehydes



Scheme 51. DTBP-Mediated α-Alkylation of Alcohols with Paraquinone Methide Compounds

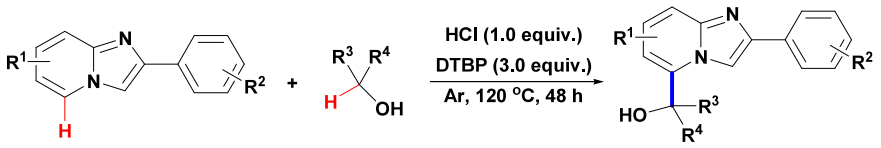


pyridine **48a** with first and secondary alcohol **47b** and also cyclic ethers reacted with satisfactory efficiency (Scheme 42). They developed a simple and effective approach for the straightforward C-2 alkylation of nonbasic nitrogen-free and basic nitrogen-containing heterocycles employing different alcohols and cyclic ether compounds. This metal- and acid-free process, using DTBP, yields the desired products in moderate to high yields.

Cai's research team described C−H alkylation and benzylation of azoles, like benzothiazoles, benzoxazoles, and benzimidazoles **49a**, with cycloalkanes **49c** or methylarenes **49b** using DTBP as the oxidant and also methylation of these heteroarenes with dicumyl peroxide (DCP) as the methylation agent (Scheme 43).[95] They developed an efficient, metal-free method for synthesizing 2-substituted azoles via C−H activation. The process involves reacting benzothiazole, benzoxazole, and benzimidazole compounds with dicumyl

https://doi.org/10.1021/acsomega.4c11574
ACS Omega 2025, 10, 15852−15907

Scheme 52. C-5 Hydroxylkylation of Imidazopyridines with Alcohols

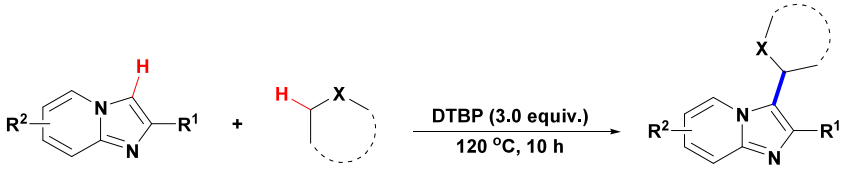


61a 61b 61c

30 examples

26-83%

Scheme 53. Oxidative Cross-Coupling of Imidazopyridines and 1-Naphthylamines with Cycloalkanes and Cyclic Ethers

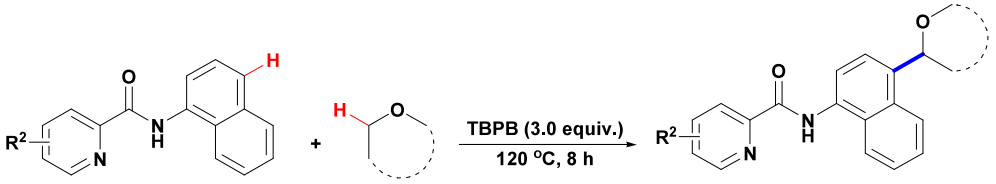


62a 62b 62c

X = O, C

12 examples

38-62%



63a 63b 63c

9 examples

39-63%

Scheme 54. Oxidative Cross-Coupling of Imidazopyridines and 1-Naphthylamines with Cycloalkanes and Cyclic Ethers

64a 64b 64c

16 examples

38-66%

65a 65b 65c

4 examples

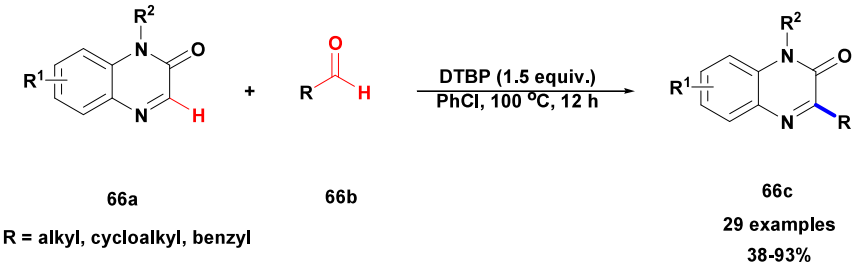
40-50%

peroxide, methyl-substituted arenes, and cyclic alkanes using DTBP or DCP at 120 °C, resulting in good yields.

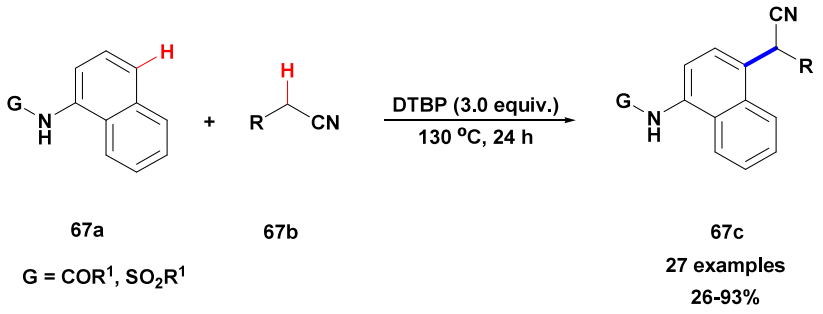
After a while, another C−H alkylation was reported by the Lei group. Their new protocol involved cross-dehydrogenative

https://doi.org/10.1021/acsomega.4c11574
ACS Omega 2025, 10, 15852−15907

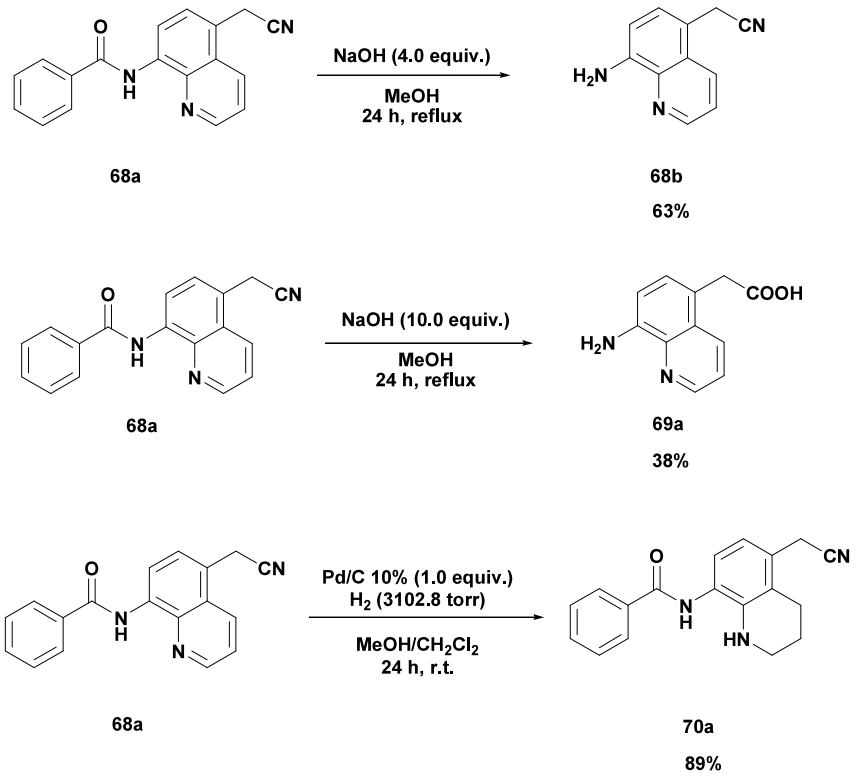
Scheme 55. DTBP-Promoted Direct Alkylation of Quinoxaline-2(1*H*)-ones



Scheme 56. DTBP-Promoted C-5 Cyanoalkylation of 8-Aminoquinolineamides/Sulfonamides with Alkyl Nitriles



Scheme 57. Conversion of Cyanoalkylated Aminoquinolineamides into Other Products



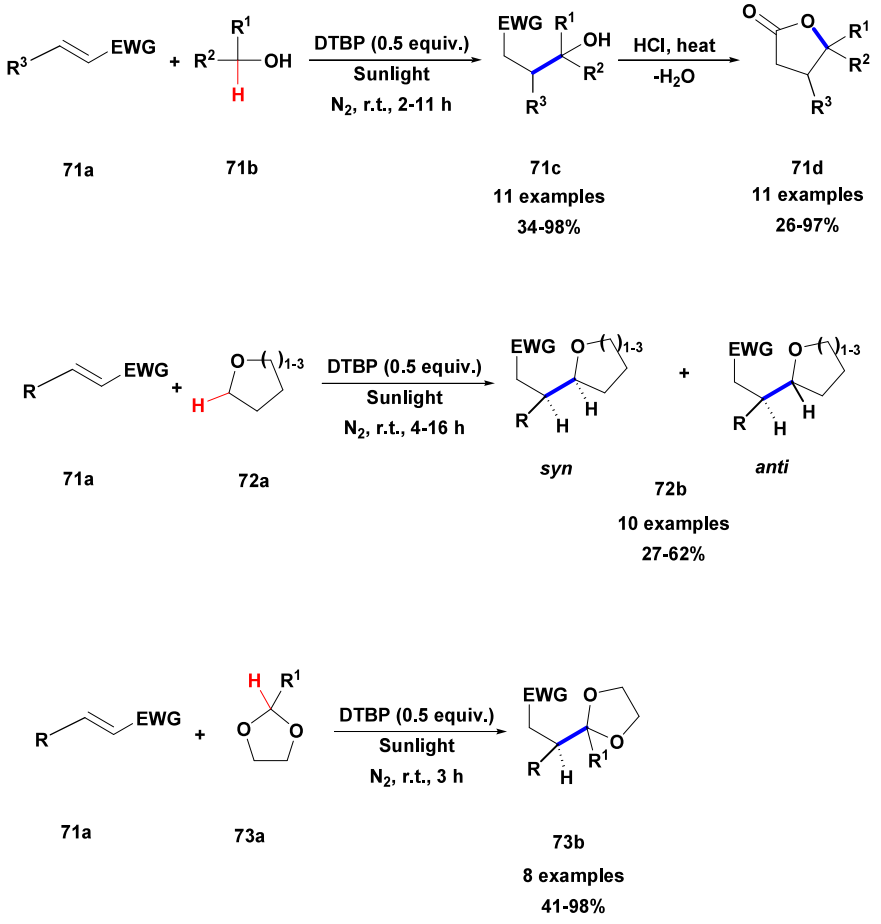
coupling between ketene dithioacetals **51a** with simple alkanes, cycloalkanes, or cyclic ethers **51b** under metal-free conditions with DTBP serving as the oxidant in acetic acid as the solvent (Scheme 44).[96] Kinetic investigation of one of the derivatives showed k_H/k_D = 3.8, which demonstrated that the C−H bond breaking occurred in the rate-limiting step.

Zhang and Fan introduced metal-free α-alkylation of ketone derivatives **52a** with cycloalkanes **52b** *via* CDC reaction using DTBP under microwave irradiation for 1 h (Scheme 45).[97] Under microwave heating, DTBP-initiated formation of α-ketone carbon **53a** and cycloalkyl radical **52b** results in the formation of coupling product **53b**. However, the homocoupling products were also observed in lower yields.

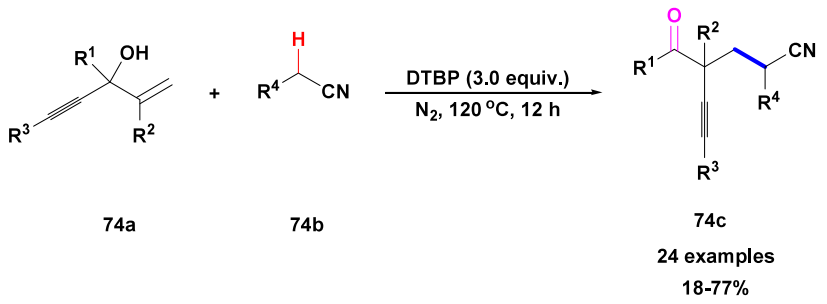
Yang's team introduced an unprecedented cascade three-component decarbonylative alkylation/aminoxidation of styrene **54a** with different aliphatic aldehyde compounds **54b** and *N*-hydroxyphthalimide (NHPI) **54c** in the absence of metals (Scheme 46).[98] The process advanced via the conversion of α-

https://doi.org/10.1021/acsomega.4c11574
ACS Omega 2025, 10, 15852−15907

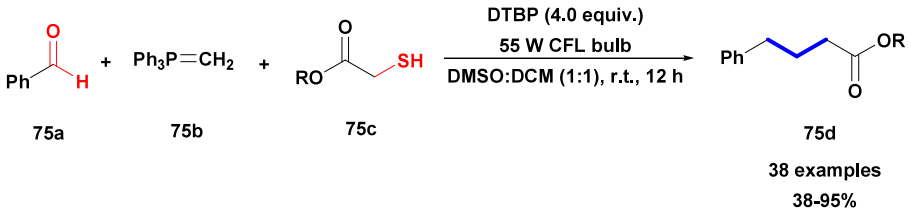
Scheme 58. Sunlight-Induced C−C Bond Formation between Alcohols, Ethers, Acetals, and Olefins



Scheme 59. Cyanoalkylation/Alkynylation of Allylic Alcohol



Scheme 60. Visible-Light-Induced Nonmetal Sequential Wittig/Hydroalkylation Process

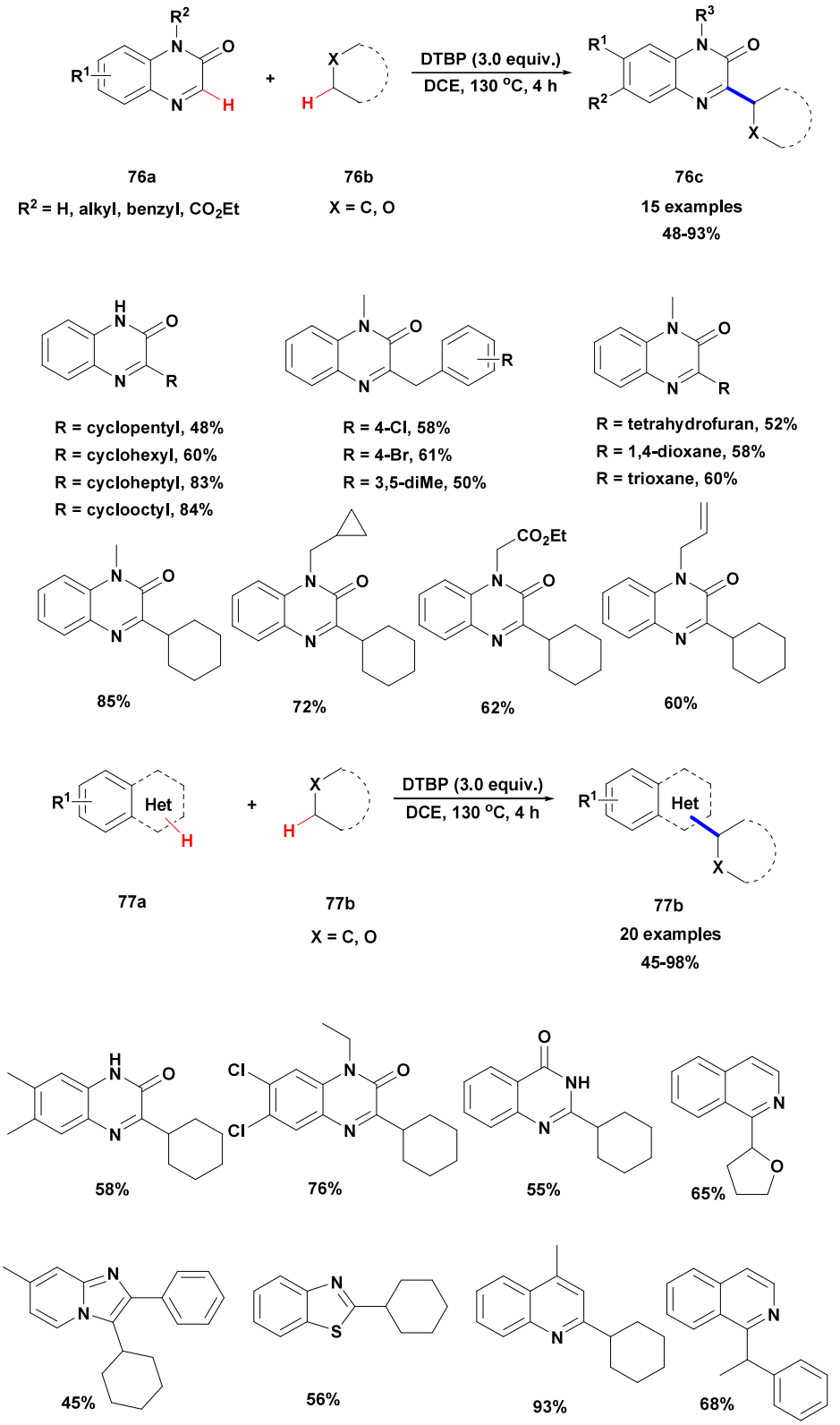


monosubstituted and α-disubstituted aliphatic aldehyde compounds into secondary and tertiary alkyl radicals for the sequential formation of C(sp^3)−C(sp^3) and C(sp^3)−O bonds.

Straightforward functionalization of the carbon−hydrogen bond adjacent to the nitrogen atom in an amide has garnered notable attention in recent times.[99] Yu's research team introduced a method for selective direct benzylation of *N*-acyl-2-aminoacetophenones **55a** with toluene derivatives **55b** employing DTBP as the sole oxidant (Scheme 47).[100] Different toluene derivatives with electron-donating and -withdrawing groups were effectively tolerated in this oxidative system. Amides with a methyl group on different positions of the benzoyl group did not show any steric hindrance with the benzylating agents.

https://doi.org/10.1021/acsomega.4c11574
ACS Omega 2025, 10, 15852−15907

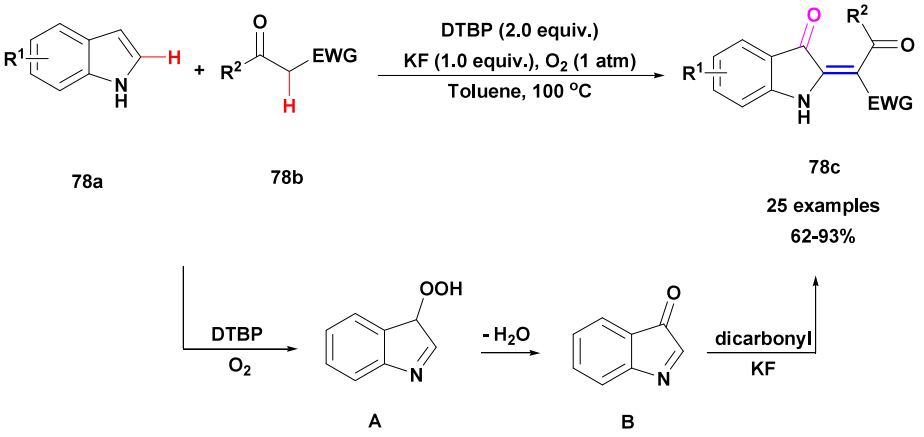
Scheme 61. Direct Functionalization of Heterocycles with Unactivated Alkanes and Direct Functionalization of Quinoxalin-2(1*H*)-one Compounds with Nonactivated Alkanes



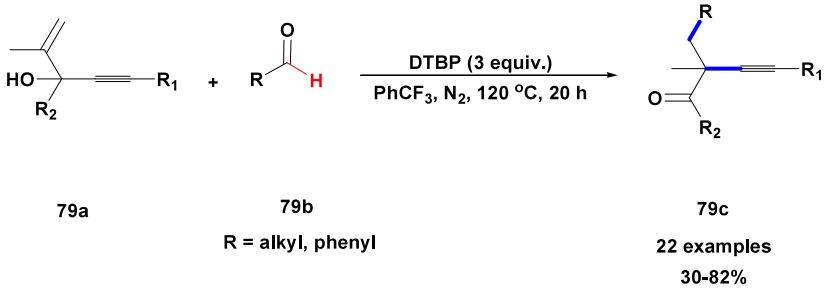
The Liu group created a metal-free regioselective C2−H amidation of 8-amidoquinolines **56a** to produce a series of C2-amidated 8-amidoquinoline derivatives **56c** (Scheme 48).[101] In their work, isocyanides **56b** were employed as the amide source. The ^{18}O labeling experiment proved that H_2O served as an oxygen atom source for amide. This method offers a simple and straightforward method to C2-amidated 8-amidoquinoline compounds through selective metal-free C2−H amidation of 8-amidoquinoline compounds, employing isocyanides as the amide provider. This one-pot oxidation

https://doi.org/10.1021/acsomega.4c11574
ACS Omega 2025, 10, 15852−15907

Scheme 62. Oxidative Ketonization/Olefination of Indoles by Cross-Coupling Reactions with 1,3-Dicarbonyl Compounds



Scheme 63. Oxidative Alkylation/Alkynylation of Terminal Alkenes through Aliphatic Aldehyde Decarbonylation and 1,2-Alkynyl Shift



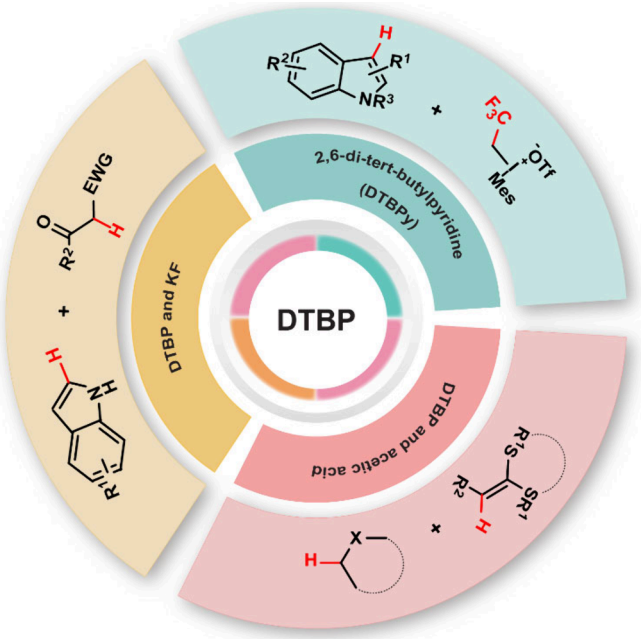


Figure 2. Suitable reagents for various types of coupling reactions with DTBP.

protocol yields a range of 8-quinoline-2-carboxamide compounds in fair to good yields, highlighting its practical utility.

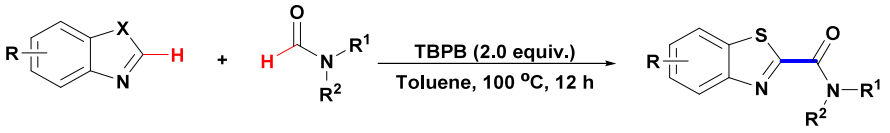
Upon heating, DTBP can generate an acyl radical from aliphatic aldehydes **57b**. Subsequently, through the removal of CO, the resulting alkyl radical attacks the C-2 position of chromones **57a**, leading to the formation of alkylated products **57c** (Scheme 49).[102] In summary, this method represents an oxidative decarbonylation and alkylation of chromone compounds using aliphatic aldehyde compounds as alkylation agents through radical-based conjugate addition without metals. Tertiary, secondary, and primary alkyl aldehyde compounds have been shown to be effective alkyl radical donors, producing the respective 2-alkylated chromanones in fair to excellent yields. Additionally, preparation of the racemate of the natural product flindersiachromanone was effectively accomplished under the standard conditions. This approach serves as an efficient tool for the alkylation and late-stage modification of chromone-related bioactive compounds.

At the same time, another approach was developed for C−H alkylation employing aliphatic aldehyde **58a** as the alkylation agents. This alkylation was performed on the electron-poor alkene compounds **58b** utilizing DTBP as an oxidant and radical starter (Scheme 50).[103] The conversion of easily accessible α-unsubstituted, α-monosubstituted, and α-disubstituted aliphatic aldehydes **58a** into primary, secondary, and tertiary alkyl radicals for the radical conjugate addition was observed in the transformation.

The Cui team described a CDC reaction between the α-carbon of alcohols and C−H olefin of *para*-quinone methides using DTBP as a radical starter (Scheme 51).[104] In the presence of DTBP, the alcohols were converted to α-oxy radicals, which then attached to *para*-quinone methide compounds to form phenol-containing alcohols and dihydroisocoumarins. Synthesis of two dihydroisocoumarin compounds **60c** in optimized reaction conditions was also successful. This metal-free α-alkylation of alcohols with *para*-quinone methide compounds to obtain phenol-containing alcohols and dihydroisocoumarin compounds represents a

https://doi.org/10.1021/acsomega.4c11574
ACS Omega 2025, 10, 15852−15907

Scheme 64. Direct Amidation of Azoles Facilitated by TBPB in the Presence of Formamides

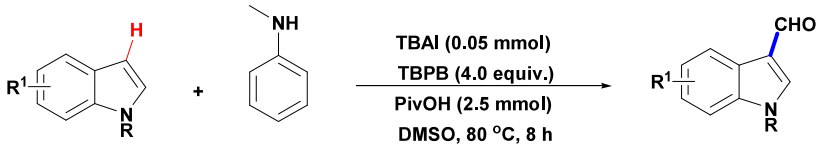


80a
X = O, S

80b

80c
17 examples
53-75%

Scheme 65. $^{n}Bu_4NI$-Catalyzed C3-Formylation of Indoles Using *N*-Methylaniline

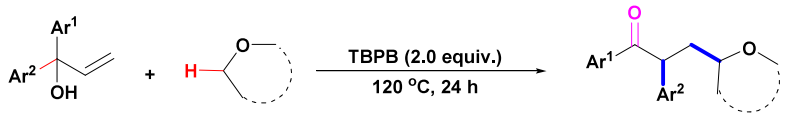


81a
R = H, Me, Ph, Bn

81b

81c
17 examples
7-82%

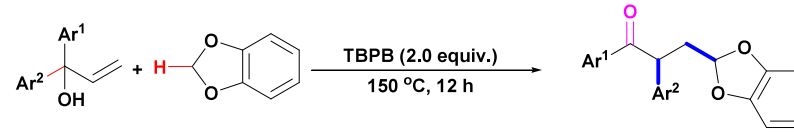
Scheme 66. TBPB-Facilitated Alkylation of α,α-Diaryl Allylic Alcohols with Basic Ethers, Along with the Proposed Mechanism



82a

82b

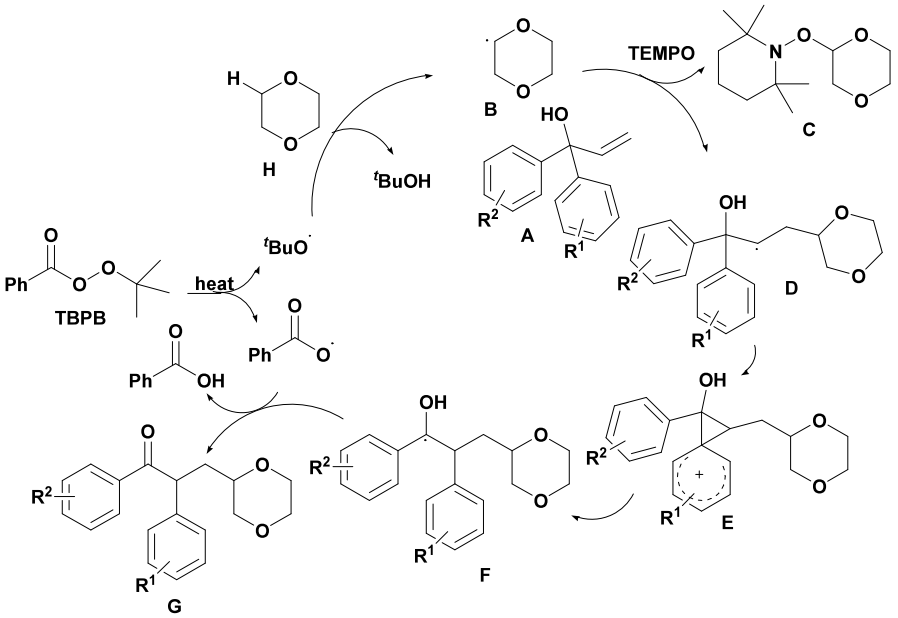
82c
15 examples
38-95%



82a

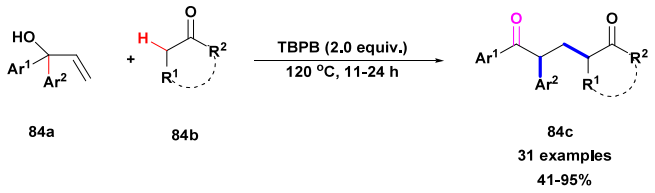
83a

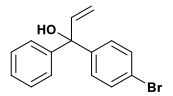
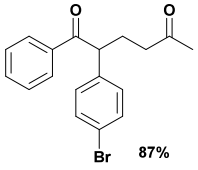
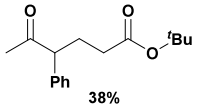
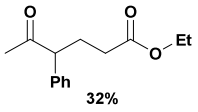
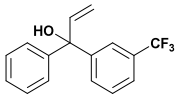
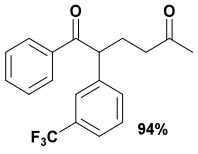
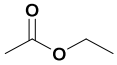
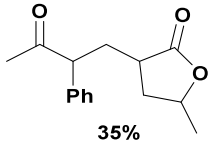
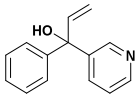
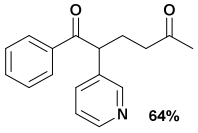
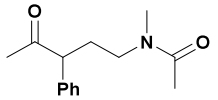
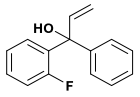
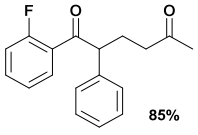
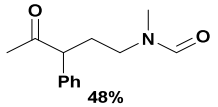
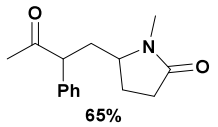
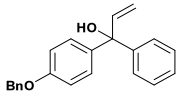
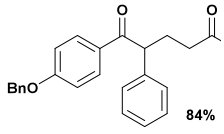
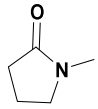
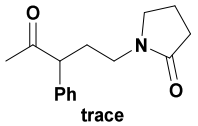
83b
6 examples
43-60%



https://doi.org/10.1021/acsomega.4c11574
ACS Omega 2025, 10, 15852−15907

Scheme 67. Alkylation of α,α-Diaryl Allylic Alcohols with Carbonyl Compounds Facilitated by TBPB



Scope of α,α-diaryl allylic alcohols	Corresponding product	Scope of carbonyl compounds	Corresponding product
	 87%		 38%  32%
	 94%		 35%
	 64%		 75%
	 85%		 48%  65%
	 84%		 trace

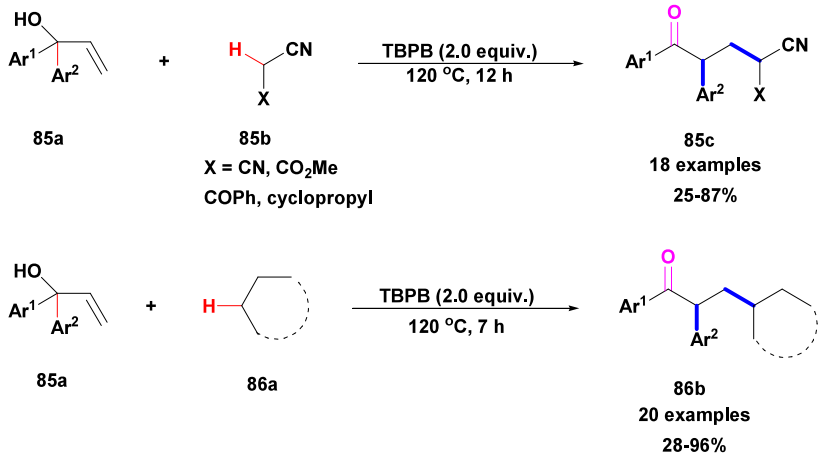
straightforward C(sp^3)−C(sp^3) bond formation and extends the scope of radical addition reactions involving *para*-quinone methides.

Various studies have investigated the coupling reactions of imidazo[1,2-*a*]pyridines **61a** having a substituent on the C-3 position of the heterocycle ring. In 2019, Lin and Yan et al. introduced a new approach to C-5 regioselective hydroxyalkylation of imidazo[1,2-*a*]pyridines **61a** with simple alcohols **61b** using DTBP (Scheme 52).[105] The procedure had good compatibility with electron-attracting and -releasing groups on the aromatic ring of the 2-phenylimidazo[1,2-*a*]pyridines.

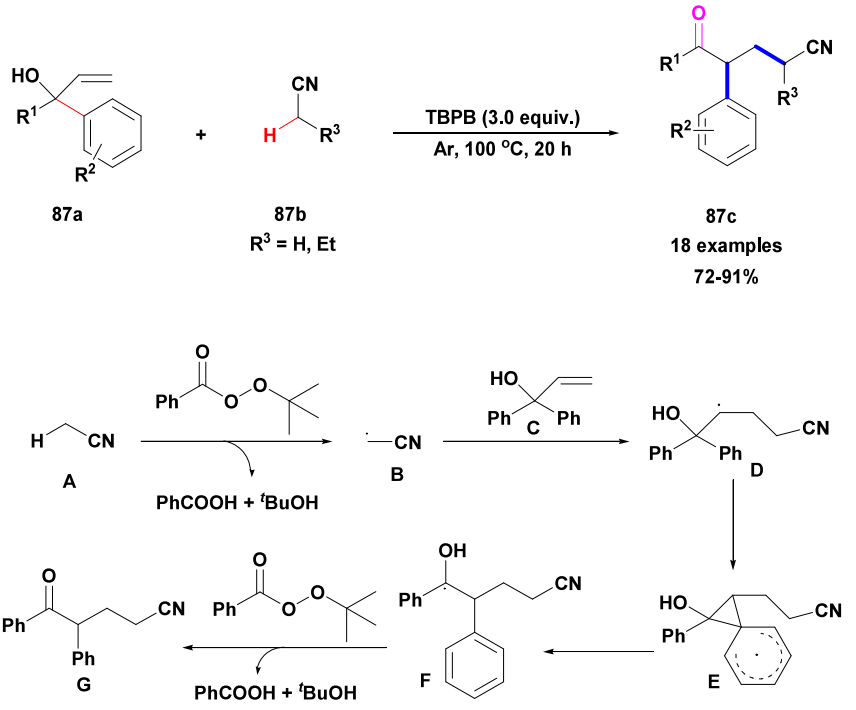
In 2020, Guo et al. described a metal-free oxidative cross-coupling of imidazopyridines **62a** or 1-naphthylamines **63a** with cycloalkanes **62b** or cyclic ethers **63b** using peroxides (Scheme 53).[106] In their protocol, 3-alkyl-imidazopyridine **62c** and 4-alkyl-1-naphthylamine derivatives **63c** were isolated in moderate to good yields. This innovative, catalyst- and additive-free approach enables the synthesis of derivatives of 3-alkyl-imidazopyridine and 4-alkyl-1-naphthylamine under gentle conditions. The process demonstrates excellent func-

https://doi.org/10.1021/acsomega.4c11574
ACS Omega 2025, 10, 15852−15907

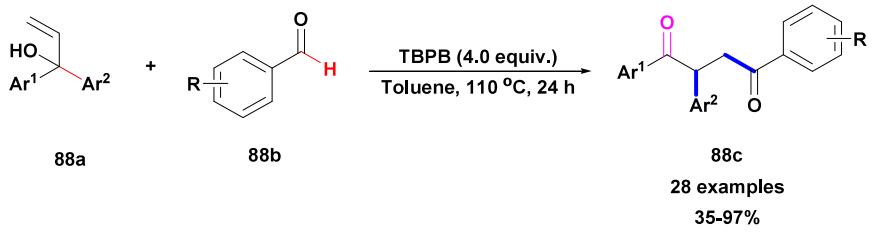
Scheme 68. TBPB-Mediated Cyanomethylation and Alkylation of α,α-Diaryl Allylic Alcohols



Scheme 69. 1,2-Alkylarylation of Alkenes with α-C(sp³)−H Bonds from Acetonitriles and the Proposed Mechanism



Scheme 70. Cross-Coupling of α,α-Diarylallylic Alcohols and Aromatic Aldehydes Facilitated by TBPB

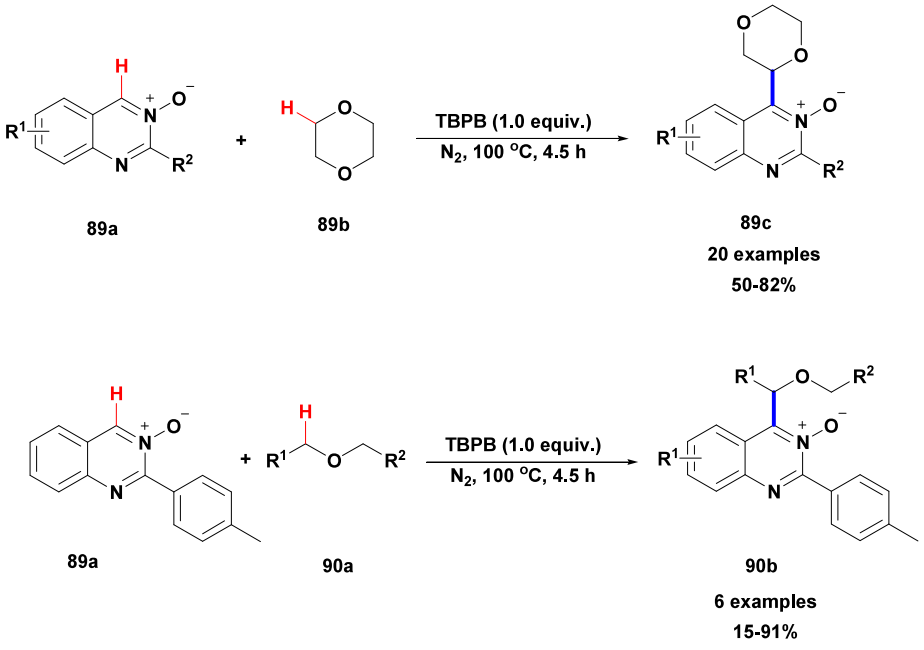


tional group compatibility, offering an efficient method for synthesizing imidazopyridine and 1-naphthylamine compounds with significant usefulness in medicinal compounds and functional materials.

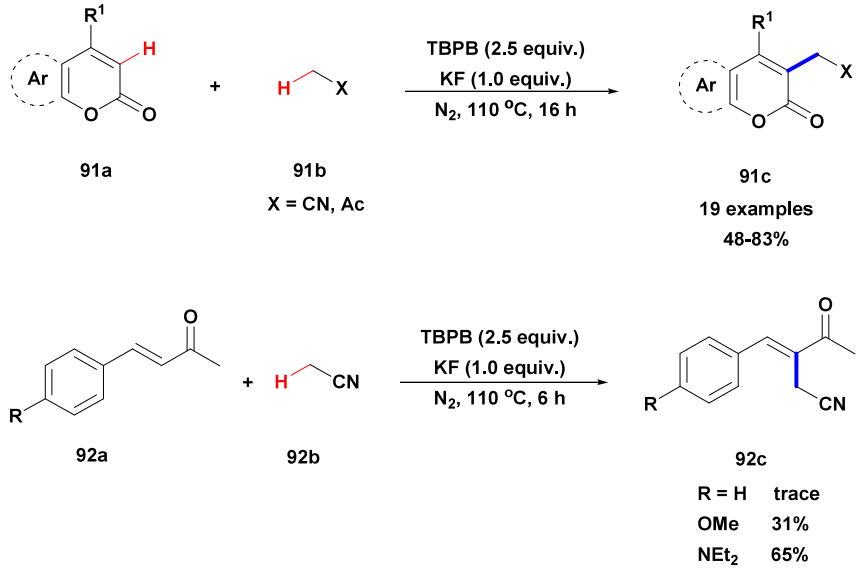
Han and et al. described an additional example of an oxidative coupling process between biologically active quinolinone compounds **64a** with ethers **64b** or cycloalkanes **65b** in the presence of peroxides (Scheme 54).[107] 3-Alkylquinolinones **64c**/**65c** were prepared in this transformation. They developed an innovative DTBP-assisted radical CDC reaction of quinoline derivatives with ether compounds, enabling the preparation of various 3-alkylquinolinones under gentle conditions, without requiring transition metals. The approach demonstrates a diverse substrate range and great effectiveness, offering an appealing pathway for synthesizing quinolinone structures with significant utility in

https://doi.org/10.1021/acsomega.4c11574
ACS Omega 2025, 10, 15852−15907

Scheme 71. TBPB-Initiated Cross-Dehydrogenative Coupling of Quinazoline-3-oxides with 1,4-Dioxane



Scheme 72. Oxidative Cross-Coupling of Coumarins and α,β-Unsaturated Ketones with Acetonitrile and Acetone



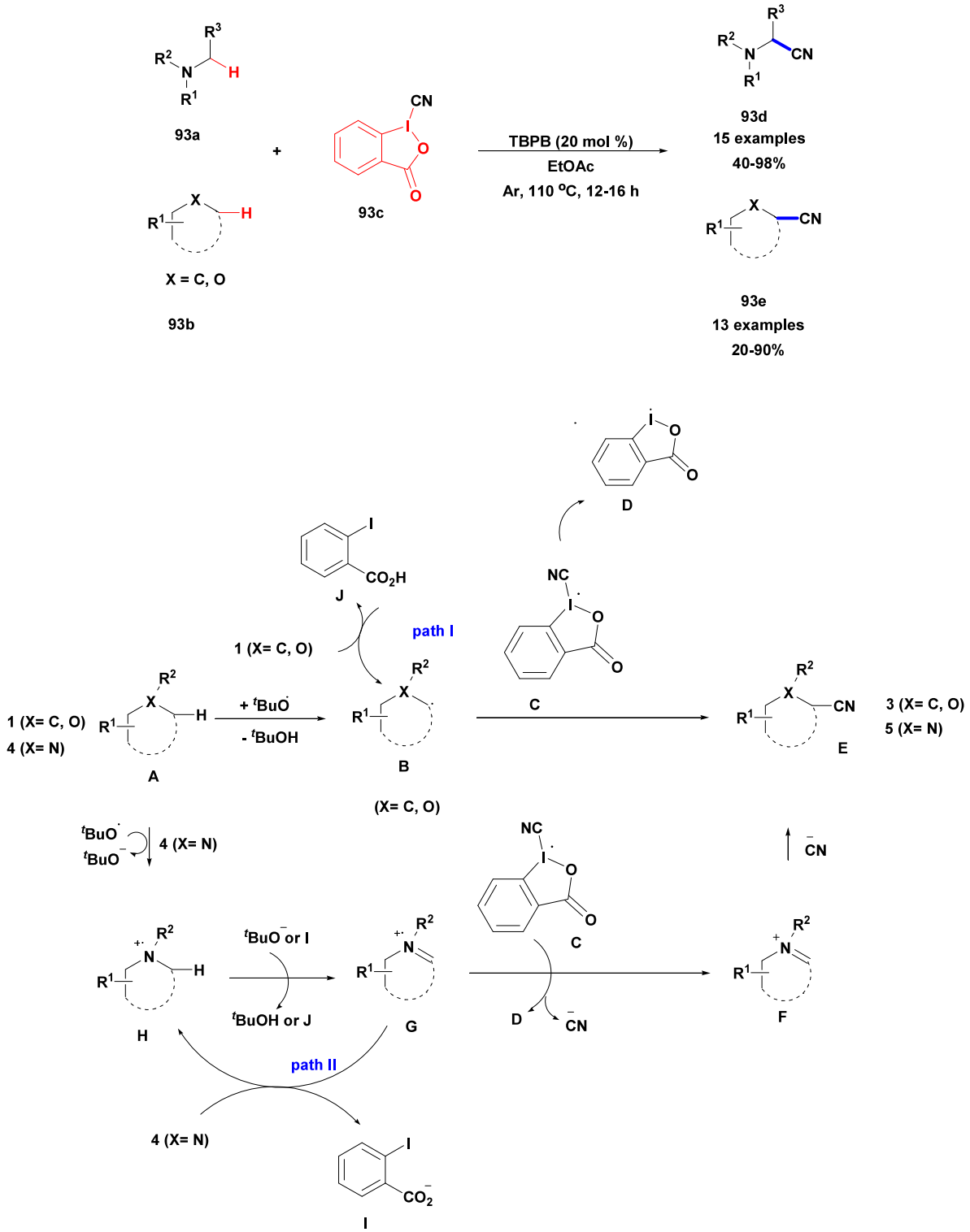
drugs and functional materials. Overall, the direct CDC method offers step-saving, atom-economical, and eco-friendly benefits.

The Yao and Lin group created a method for the metal-free carbon removal and alkylation of quinoxaline-2(1*H*)-one compounds **66a** with aliphatic aldehyde compounds **66b**, utilizing di-*tert*-butyl peroxide (DTBP) as a promoter (Scheme 55).[108] Other peroxides, including TBHP, *tert*-butyl hydroperoxide; H_2O_2, hydrogen peroxide; DCP, dicumyl peroxide; and CHP, cumene hydroperoxide, were less effective in the coupling process. The use of metal catalysts, such as $Ni(CH_3COO)_2{\cdot}4H_2O$, $Mn(OAc)_3{\cdot}2H_2O$, $Mn(OAc)_2{\cdot}4H_2O$, and $Mn(OAc)_2$ resulted in lower yields. Compared with previous methods, this system demonstrates excellent compatibility with quinoxaline-2(1*H*)-one compounds, irrespective of whether the substituents on the nitrogen-containing ring and benzene ring are electron-accepting or electron-releasing groups. This procedure is expected to serve as a valuable approach for quinoxaline-2(1*H*)-one derivatization.

Kianmehr and his team described C5-cyanoalkylation of 8-aminoquinolineamides/sulfonamides **67a** with alkyl nitriles **67b** using DTBP exclusively (Scheme 56).[109] Various aryl, heteroaryl, and alkyl amides and sulfonamides as well as simple alkyl nitriles, especially acetonitrile as the simplest cyanomethylated reagent, were tolerated well in this kind of cross-coupling reaction. Transformation also resulted in the expected products with good efficiency in the presence of other H-active reagents such as acetone and nitromethane. Kinetic isotope effect experiments conducted on solvent revealed that the C(sp^3)−H bond breaking of CH_3CN was the slowest step. In the next step, the conversion of cyanoalkylated aminoquinolineamides **67c** into other products was investigated.

https://doi.org/10.1021/acsomega.4c11574
ACS Omega 2025, 10, 15852−15907

Scheme 73. Cyanation of Tertiary Amines, Alkanes, and Ethers and the Tentative Mechanism

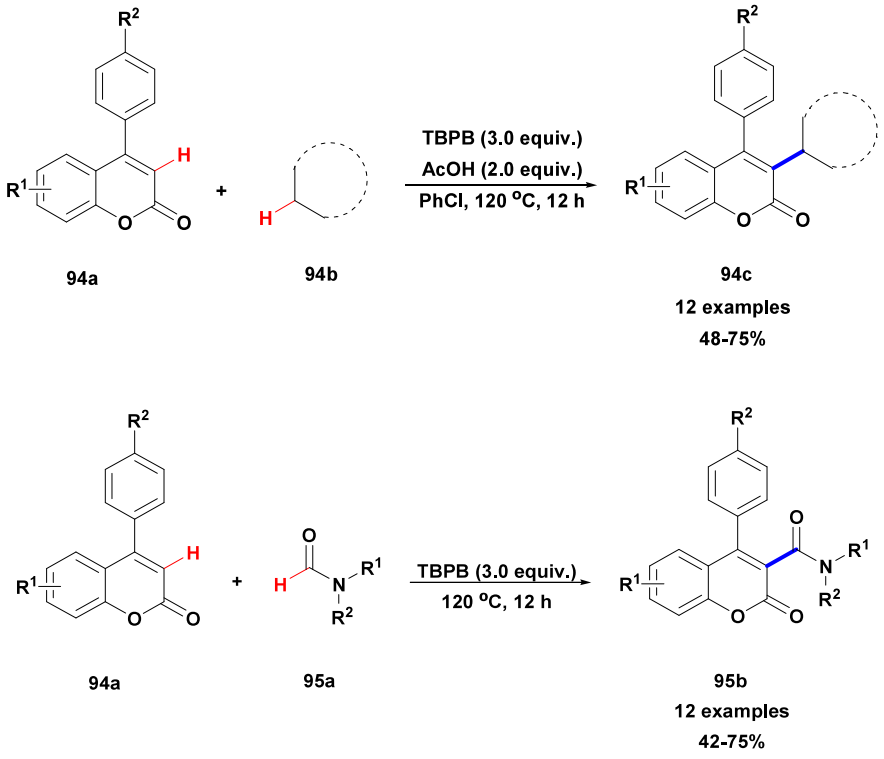


The aroyl moiety was easily removed through hydrolysis to produce 2-(8-aminoquinolin-5-yl) acetonitrile **68b** (63% yield). Further basic hydrolysis converted the cyano group to a carboxylic acid group **69a** (38% yield). Also, the 1,2,3,4-tetrahydroquinoline **70a** scaffold was prepared from the reduction reaction of the pyridine ring in the presence of 10% Pd/C under H_2 gas (89% yield) (Scheme 57).

Ouchi and his team showed a sunlight-induced, DTBP-mediated C−C bond formation between alcohols, ethers, or acetals (**71b**, **72a**, **73a**) and olefins **71a** (Scheme 58).[110] The reaction was efficiently completed within 3−4 h of sunlight irradiation at room temperature. The study also explored the addition of cyclic ethers or cyclic acetals to olefins under sunlight photolysis. The authors noted that yields of the products (**71c**, **71d**, **72b**, **73b**) exceeded those achieved using

https://doi.org/10.1021/acsomega.4c11574
ACS Omega 2025, 10, 15852−15907

Scheme 74. TBPB-Facilitated C-3 Functionalization of Coumarins



a Xe lamp, which could be attributed to the intensity of sunlight. The reactions proceeded more rapidly and with comparable or better yields than those of many previously reported methods using sunlight and conventional lamp photolysis. Furthermore, gram-quantity experiments were conducted to test the practicality of this reaction in organic synthesis, demonstrating the method's efficiency and scalability.

In the difunctionalization of α-aryl α-alkynyl allylic alcohol compounds **74a** with alkyl nitrile compounds **74b** mediated by DTBP as the sole oxidant, two key transformations, including C(sp^3)−H bond breaking of alkyl nitrile compounds and radical 3-exo-dig cyclization followed by 1,2-alkynyl radical migration occurred. These transformations allowed for the synthesis of numerous α-alkynyl γ-cyano functionalized ketones **74c** (Scheme 59).[111] When peroxides like TBHP, TBPB, DCP, and BPO were utilized instead of DTBP, the respective products were achieved in reduced yields

Sun and his team described an approach for a cascade Wittig/hydroalkylation procedure using aldehydes **75a**, ylides **75b**, and ethyl 2-mercaptoesters **75c** (Scheme 60).[112] The saturated C3-homologation products **75d** were obtained in the presence of DTBP as the alkoxyl radical mediator for hydrogen atom transfer (HAT) under visible-light irradiation. This innovative cascade Wittig/hydroalkylation process is initiated by visible light exposure, representing an eco-friendly and metal-free radical method that operates under gentle conditions and is suitable for different functional groups. This method provides direct access to saturated C3 homologation products from aldehydes or ketones via radical hydroalkylation to olefins.

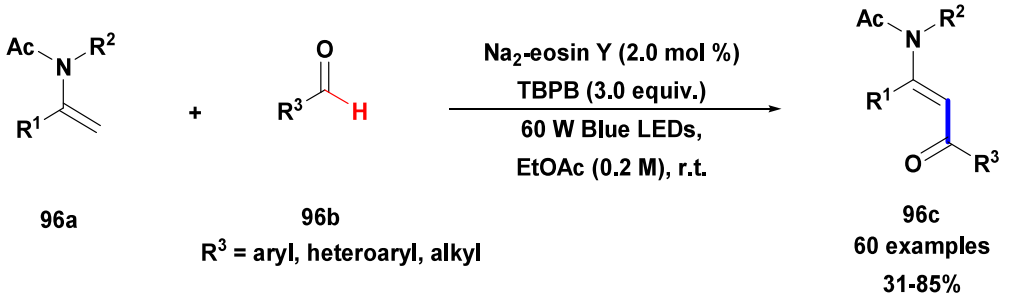
Quinoxalins make up a significant group of *N*-heterocycles that act as c-met kinase inhibitors, histamine-4 receptor antagonists, angiotensin-II receptor antagonists, antitumors, and antidiabetic agents. Roy et al. developed transition nonmetal functionalization of quinoxalin-2(1*H*)-one derivatives **76a** with cycloalkanes, cyclic ethers, or alkyl arenes **76b**/**77b** as coupling partners (Scheme 61).[113] Many substrates like quinolines, isoquinolines, quinazoline, benzothiazole, and phenylimidazo[1,2-*a*]pyridine **76c** afforded coupling products in good yield. This protocol shows excellent compatibility and selectivity for various functional groups and allows selective functionalization of strong C−H bonds in adamantane. Its practical applications include accessing bioactive pharmaceuticals.

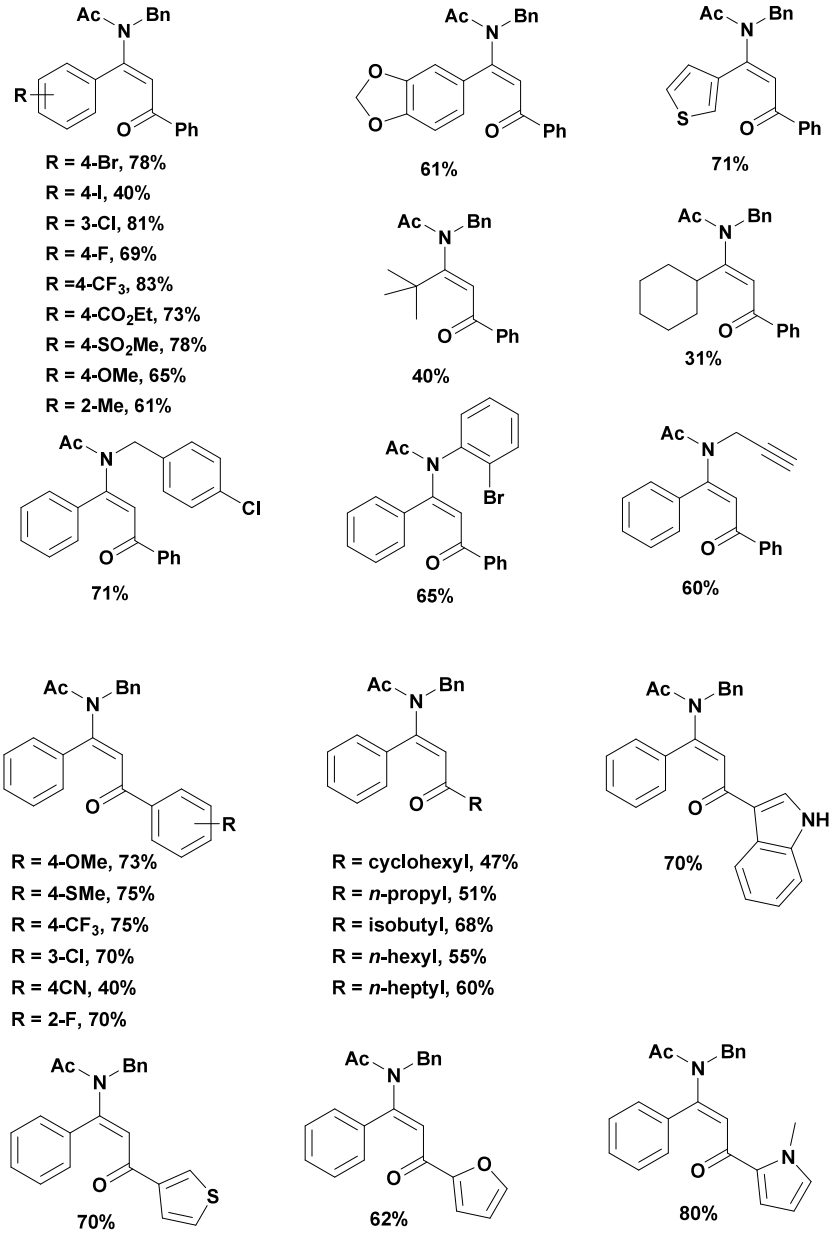
The Jin group synthesized 3-carbonyl-2-ene-indole compounds **78c** from ketonization and olefin formation of indoles **78a** by coupling reactions with 1,3-dicarbonyls **78b** where DTBP worked as an oxidant and KF as a base (Scheme 62).[114] The reaction proceeded through the creation of intermediate indol-3-one **B** with DTBP and O_2, which had a significant role in this transformation. This innovative, metal-free oxidative ketonization/olefination method facilitates the creation of 3-carbonyl-2-ene-indole compounds. The reaction advances effectively without requiring metal catalysts or additives, providing quick access to a range of 3-carbonyl-2-ene-indole derivatives in medium to high yields.

Xiang et al. described oxidative alkene alkylation and alkynylation of 1,4-enyn-3-ols **79a** with tertiary, secondary, and primary alkylaldehydes **79b** through decarbonylation and 1,2-alkynyl migration using DTBP as an oxidant (Scheme 63).[115] The reaction operated successfully by utilizing other peroxides such as TBPB and DCP, while H_2O_2 resulted in trace products. Various α-alkynyl ketones **79c** were prepared through the construction of C(sp^3)−C(sp^3) and C(sp^3)−C(sp) bonds via a radical pathway. This method is compatible with tertiary, secondary, and primary alkylaldehydes, demonstrating significant functional group tolerance and a wide range

https://doi.org/10.1021/acsomega.4c11574
ACS Omega 2025, 10, 15852−15907

Scheme 75. Na_2-eosin Y Catalyzed Acylation of Enamides with Aldehydes in the Presence of TBPB



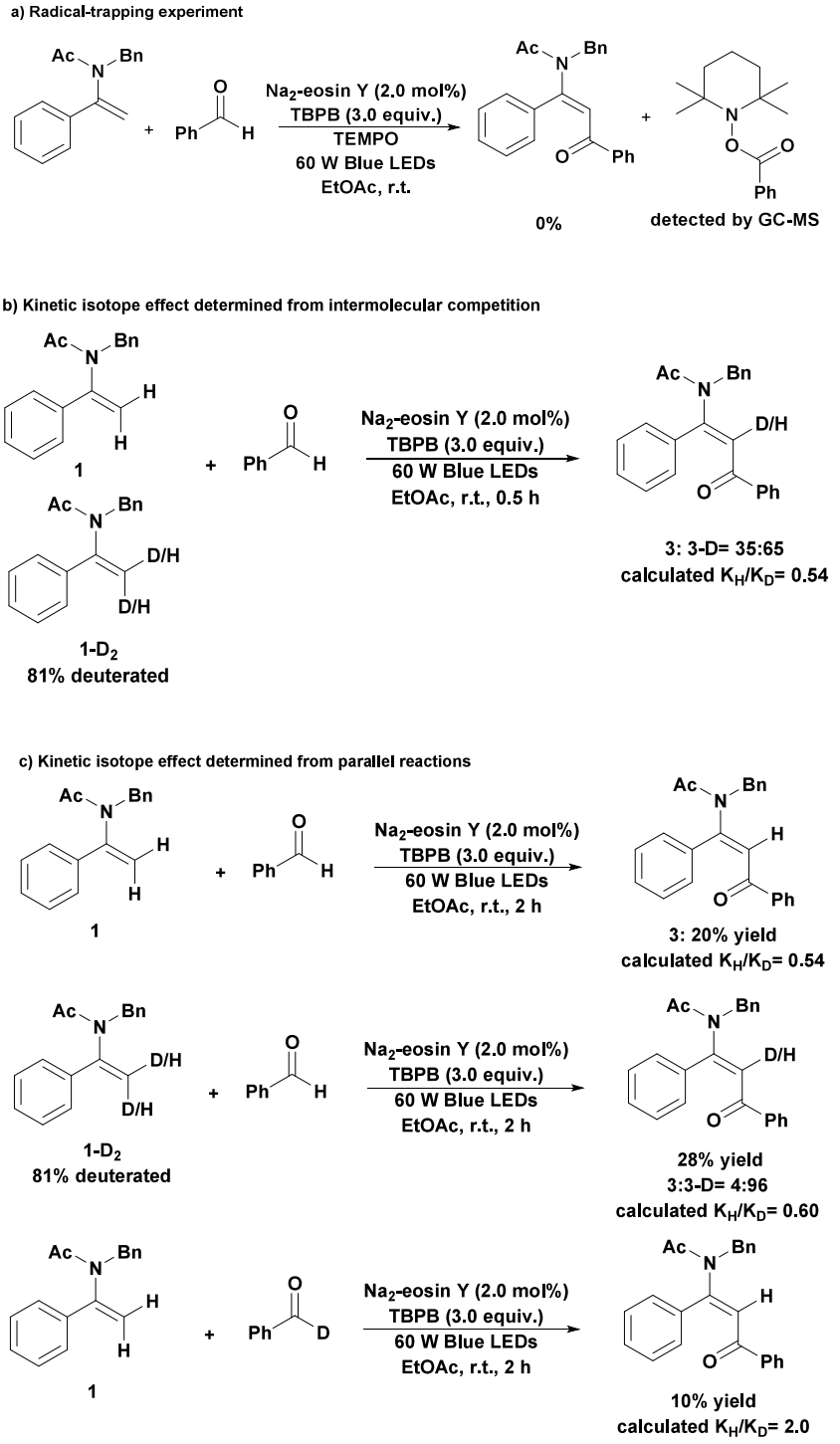


of substrates. It is particularly effective for synthesizing quaternary carbon-based but-3-yn-1-ones.

2.2.1. DTBP for Selective Functionalization and Coupling Reactions in Organic Synthesis. This section of the study identifies suitable reagents for various types of reactions, including C3-selective trifluoromethylation of indoles, C−H alkylation by oxidative coupling, and the preparation of 3-carbonyl-2-ene-indole derivatives. The C3-selective trifluoromethylation of indole derivatives in the presence of 2,2,2-trifluoroethyl(mesityl)iodonium triflate in the presence of 2,6-di-*tert*-butylpyridine (DTBPy) as a specific reagent demonstrates exceptional efficiency. The high achieved yields and

https://doi.org/10.1021/acsomega.4c11574
ACS Omega 2025, 10, 15852−15907

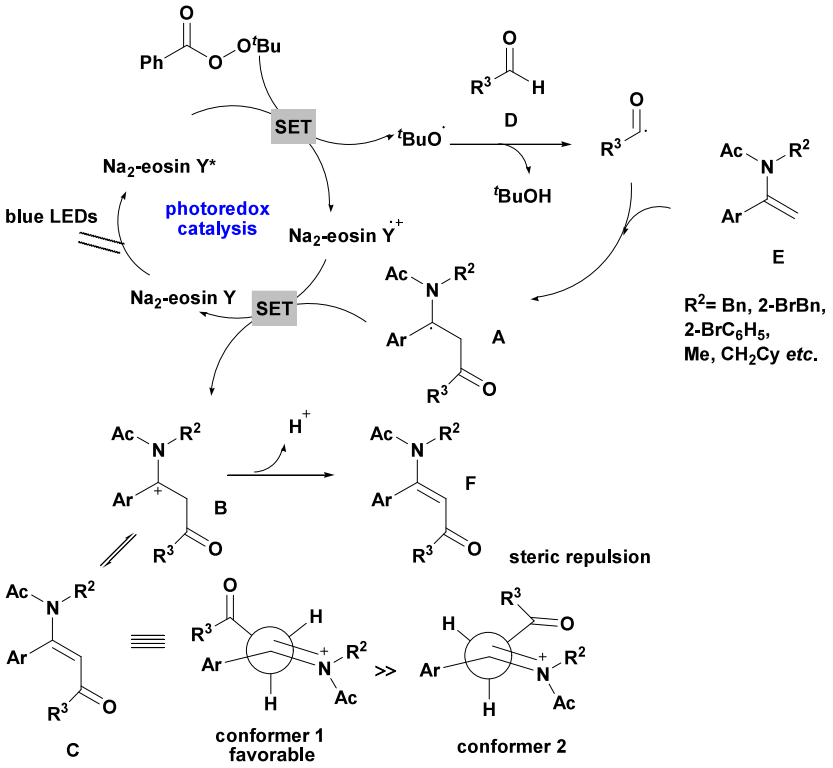
Scheme 76. Control Experiments and KIE Studies



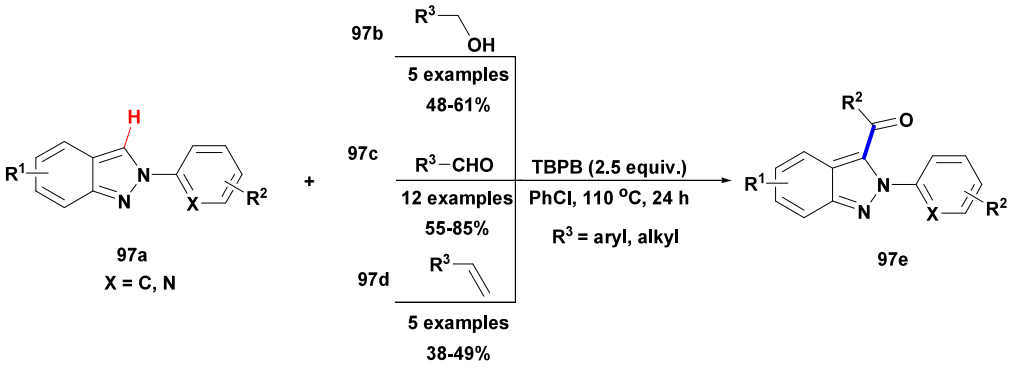
selectivity make this reagent a highly suitable option for the selective trifluoromethylation of indole-based compounds, establishing it as a valuable tool in organic synthesis.[84] Selective trifluoromethylation could also be evaluated by similar substrates and heterocycles having similar reactivity profiles like indole, using DTBPy. This reaction can be performed under similar conditions to achieve high selectivity and yield.[116] C−H alkylation of heteroaromatic compounds and cross-dehydrogenative coupling (CDC) reactions could also be examined on heteroaromatic compounds such as pyridines and pyrazoles using DTBPy as a catalyst. This method allows for the direct functionalization of C−H bonds, providing a straightforward approach to synthesizing alkylated heteroaromatic derivatives. These reactions highlight the versatility of DTBPy in various organic synthesis applications, making it a valuable tool for chemists working with indole-based and other heteroaromatic compounds.[117] Additionally, the dehydrogenative cross-coupling of ketene dithioacetals with simple alkanes, cycloalkanes, or cyclic ethers is achieved effectively under metal-free conditions using diethyl peroxide (DTBP) as an oxidant in acetic acid. Acetic acid plays a crucial role by stabilizing reaction intermediates and creating a

https://doi.org/10.1021/acsomega.4c11574
ACS Omega 2025, 10, 15852−15907

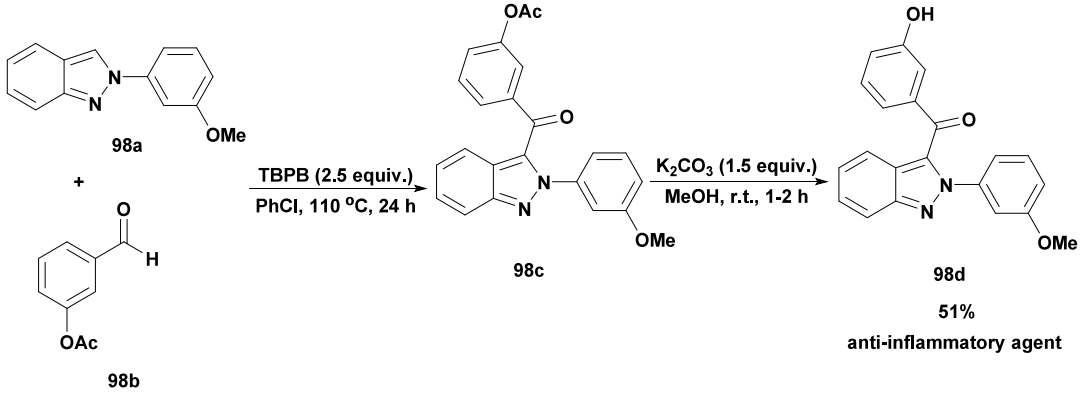
Scheme 77. Plausible Mechanism for Acylation of Enamides with Aldehydes



Scheme 78. C-3 Acylation and Benzoylation of 2*H*-Indazoles Using TBPB



Scheme 79. Synthesis of Anti-inflammatory Agent 98d



conducive environment, leading to a high efficiency and selectivity. The type of the employed solvent and oxidant has a great role in DTBP-assisted carbon−carbon bond formation.[96] It could also be applied for other heterocyclic compounds with similar reactivity profiles. For instance, DTBP has been used for the cross-dehydrogenative coupling of 3-aryl benzofuran-

https://doi.org/10.1021/acsomega.4c11574
ACS Omega 2025, 10, 15852−15907

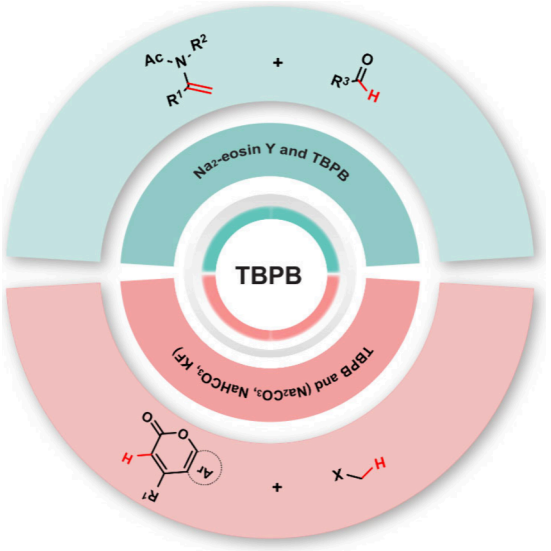


Figure 3. Suitable reagents for various types of coupling reactions with TBPB.

2(3*H*)-ones and toluenes/phenols, generating all-carbon quaternary centers.[118] Furthermore, for the synthesis of 3-carbonyl-2-ene-indole derivatives and other structurally related compounds, DTBP can be used as an oxidant in combination with KF as a base.[114] This approach is especially effective for substrates with activated methylene groups and 1,3-dicarbonyl compounds. The metal-free oxidative ketonization/olefination method could also be extended to other indole derivatives or heterocyclic compounds with similar reactivity profiles, showcasing its versatility and effectiveness in organic synthesis[119−121] (Figure 2).

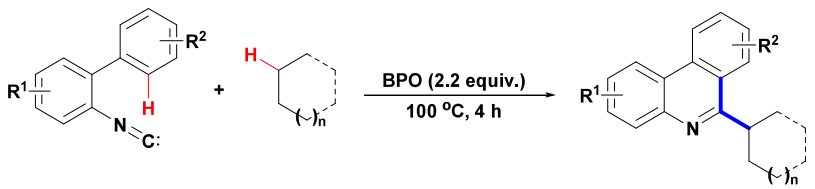
2.3. Coupling Reactions with TBPB. *tert*-Butyl peroxybenzoate (TBPB) is a light yellow liquid ester peroxide with a half-life of 10 h at 104 °C, 1 h at 124 °C, and 1 min at 165 °C.[122] TBPB, due to the *tert*-butyl and benzoyl groups, has good solubility in organic solvents. Therefore, it has been used in various coupling reactions with transition metals or in the absence of metals as an efficient radical initiator.[123] In 2011, Wang and co-workers reported a metal-free and without base method for C2-amidation of azole **80a** derivatives in the use of TBPB as the sole oxidant in the reaction (Scheme 64).[124] Screening of other organic oxidants such as $(t\text{-}C_4H_9O)_2$, $(C_6H_5COO)_2$, TBHP, and DCP showed that none of them yielded better results. When inorganic oxidants $K_2S_2O_8$ and $(NH_4)_2S_2O_8$ were utilized, product **80c** was achieved in a lower yield. Moreover, no product was isolated in the presence of cyclohexanone peroxide, I_2, $PhI(OAc)_2$, Ag_2CO_3, and Ag_2O. The authors also investigated the reaction under transition metal conditions ($FeCl_3$: 57% yield, $FeCl_2$: 26% yield, $Fe(OAc)_2$: 65% yield, $Cu(OAc)_2$: 23% yield, $CuBr_2$: 14% yield, $CoCl_2$: 32% yield, $Pd(OAc)_2$: 0% yield). The reaction exhibited a lower efficiency under such conditions. The findings showed that metals did not enhance the reaction speed but hindered it. The target product was achieved with a 75% yield when TBPB was used under metal-free conditions.

In 2012, Wang et al. documented the C3-formylation of both N−H and *N*-substituted indoles **81a** with *N*-methylaniline **81b**. This reaction was catalyzed by $^nBu_4NI$ and employed TBPB as the oxidant (Scheme 65).[125] Notably, exploration of various amines, including Et_3N, DMF, Et_2NMe, Me_2NH, Cy_2NMe, Ph_2NMe, and BnNHPh, as potential carbonyl sources for the formylation of indoles **81c** did not yield any formylation products. However, $PhNMe_2$ and $BnNMe_2$ produced the corresponding formylation products with yields of 39% and 5%, respectively. This approach is especially beneficial because it can be used for both N−H and *N*-substituted indoles without requiring harmful phosphorus oxychloride or transition metals.

The Ji group introduced an innovative method for the functionalization of C(sp^3)−H bonds in both cyclic and open-chain ethers **82b** using *α*,*α*-diaryl allylic alcohols **82a**, facilitated by TBPB, and notably without the use of any transition metals (Scheme 66).[126] In the protocol, a variety of *α*-aryl-*β*-alkylated carbonyl ketones were produced through cascade oxidative addition and migration, achieving yields ranging from moderate to excellent. With the introduction of a radical scavenger (TEMPO) by the authors, the reaction was entirely halted. This finding indicated that the reaction followed a radical mechanism, with the decomposition of TBPB leading to the formation of ^{t}BuO· and benzoate radicals. Then, hydrogen abstraction of 1,4-dioxane with the ^{t}BuO· radical resulted in the formation of the alkyl radical **B**, which attached to allylic alcohol **A**, providing intermediate **D**. Subsequently, intramolecular 5-ipso cyclization produced spiro[2,5]octadienyl **E**. Simultaneously, 1,2-aryl migration formed the radical species **F**. Finally, the expected product **G** was isolated by further oxidation and deprotonation.

Following a similar strategy, Ji and colleagues outlined a technique for the alkylation of *α*,*α*-diaryl allylic alcohols **84a** with carbonyl compounds **84b**, including ketones, esters, and amides, utilizing TBPB (Scheme 67).[127] They synthesized 1,5-diketones **84c** from simple ketones, 1,5-diketones and *γ*-acyloxy ketones from esters, and *γ*-amido ketones from amide substrates. This method showcases efficient C(sp^3)−H functionalization alongside radical addition and 1,2-aryl migration using simple carbonyl derivatives. It demonstrates excellent functional group compatibility and selectivity,

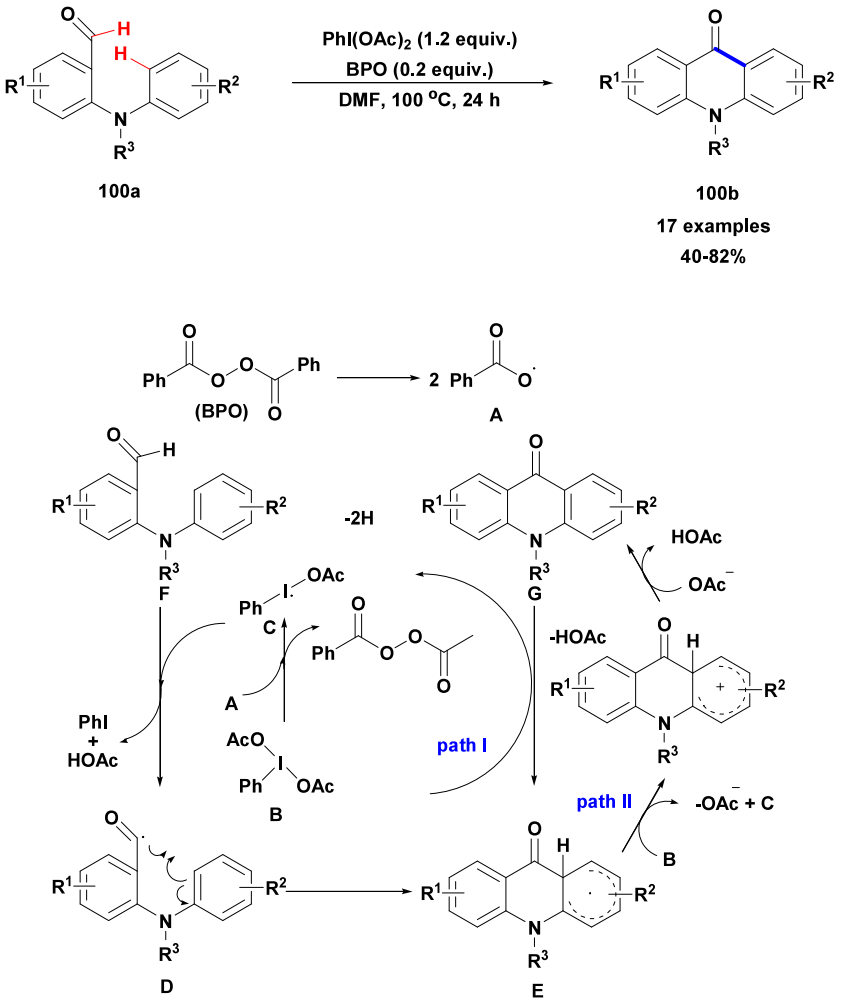
Scheme 80. BPO-Promoted Phenanthridinylation of Simple Alkanes with 2-Aryl Phenyl Isonitrile



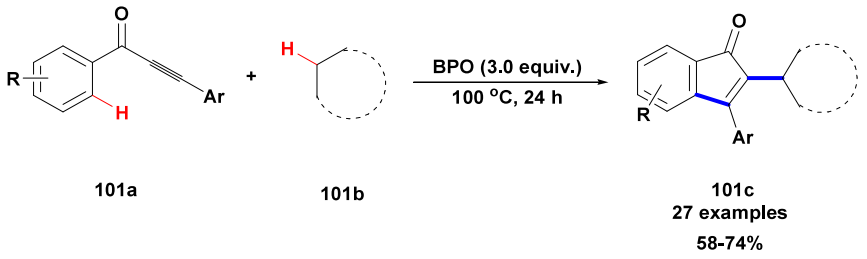
99a 99b 99c
17 examples
30-81%

https://doi.org/10.1021/acsomega.4c11574
ACS Omega 2025, 10, 15852−15907

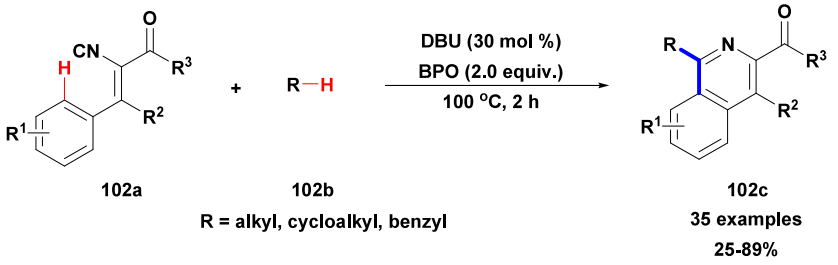
Scheme 81. Proposed Mechanism and Intramolecular Oxidative Aryl-aldehyde C(sp^2)−C(sp^2) Bond Formation Facilitated by $PhI(OAc)_2$



Scheme 82. BPO-Mediated Construction of 3-Aryl-2-cycloalkyl Indenones



Scheme 83. BPO-Promoted Preparation of 1-Alkylisoquinolines



producing various diketones and ketones. Future work should be performed to delve into the reaction mechanism.

Nitriles serve as versatile intermediates for the preparation of amides, amidines, esters, primary amines, ketones, aldehydes,

https://doi.org/10.1021/acsomega.4c11574
ACS Omega 2025, 10, 15852−15907

Scheme 84. Direct Oxidative C(sp^3)−H Functionalization of Unactivated Alkanes Facilitated by BPO

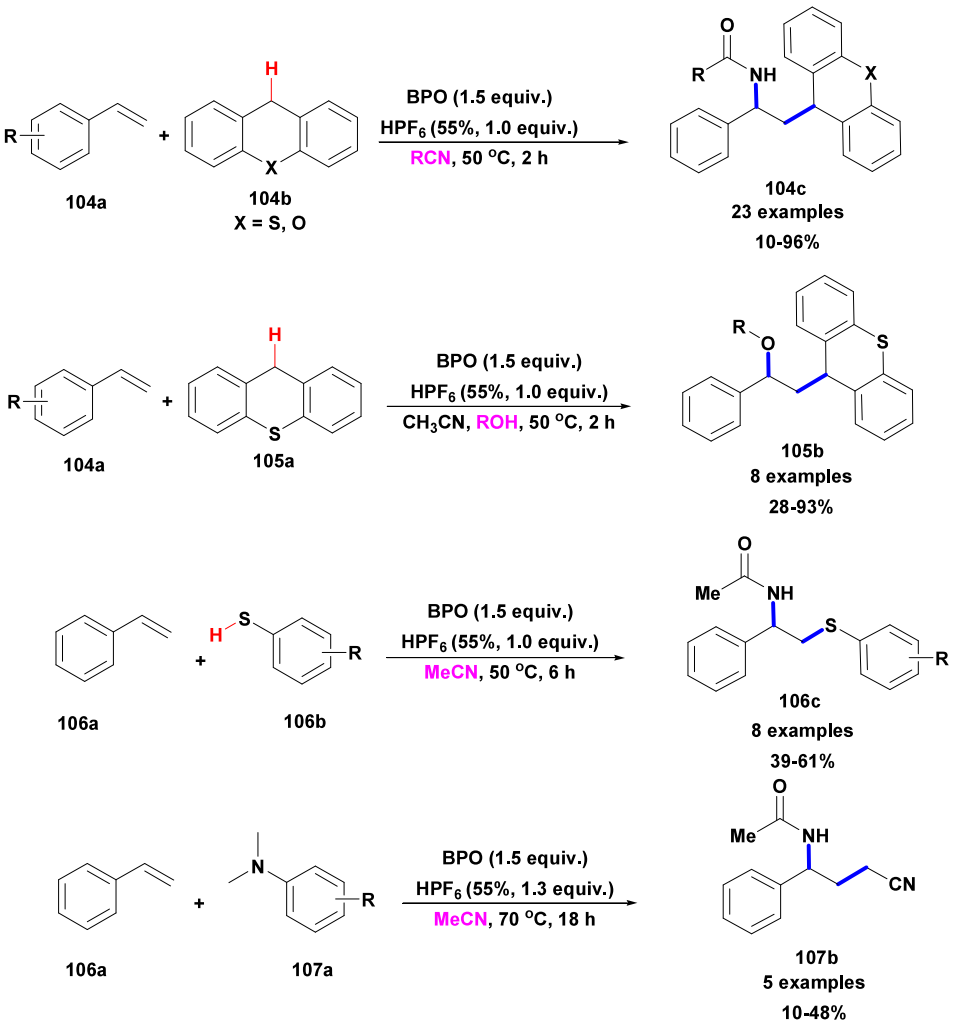
and carboxylic acids.[128,129] Hence, the synthesis of these compounds *via* cross-coupling has been highly regarded as being useful by scientists in this field. In 2015, the same group investigated the same conditions in α,α-diaryl allylic alcohols with acetonitrile and simple alkanes (Scheme 68). Echoing their earlier research, this procedure also entailed cascade oxidative addition and migration in α,α-diaryl allylic alcohols, culminating in the production of satisfactory results.[130]

Li and colleagues outlined a technique for synthesizing 5-oxo-pentanenitriles **87c** through the oxidative radical 1,2-alkylarylation. This process involves the reaction between the C−C double bonds of inactive alkenes, such as α-aryl allylic alcohols **87a**, and the α-C(sp^3)−H bonds of acetonitriles **87b** (Scheme 69).[131] As outlined by the authors, the proposed mechanism suggests that the decomposition of TBPB leads to the generation of ^{t}BuO· and PhCOO· radicals. Subsequently, alkyl radical **B** was generated via SET and then added to the C−C double bond of substrate **C**, resulting in the formation of alkyl radical **D**. At the same time, alkyl radical intermediate **D** underwent a 1,2-migration of the aryl group through spiro[2,5]octadienyl radical **E**, leading to the formation of intermediate **F**. The further oxidation of intermediate **F** led to the formation of the final product **G** with the help of TBPB (Scheme 70).

Wu's group detailed the oxidative acylation of α,α-diarylallylic alcohol compounds **88a** with aromatic aldehyde compounds **88b**, utilizing TBPB without the use of heavy metals (Scheme 70).[132] 3.0 equiv of TBPB resulted in a 76% yield of the product, while 4.0 equiv of TBPB resulted in a yield of 94%. Utilization of other oxidants, including TBHP, DTBP, $K_2S_2O_8$, H_2O_2, and O_2, was partially effective in this reaction. They introduced an innovative acylation technique for α,α-diarylallylic alcohols, which utilizes aryl aldehydes and involves aryl rearrangement. This process results in the formation of new C(Ar)−C(sp^3) and C(sp^3)−C(CO) bonds, yielding various 1,2,4-triphenylbutane-1,4-diones with moderate to excellent efficiency. The reaction also demonstrated the chemoselective migration of diverse aryl groups.

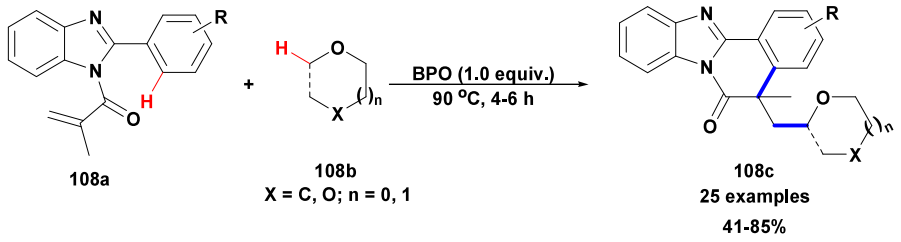
Peng and Ding conducted an extensive study of the direct C-4 alkylation of quinazoline *N*-oxides with ethers through an

Scheme 85. Difunctionalization of Styrenes with Stabilized Radicals and (N,O)-Nucleophiles Facilitated by HPF_6/BPO

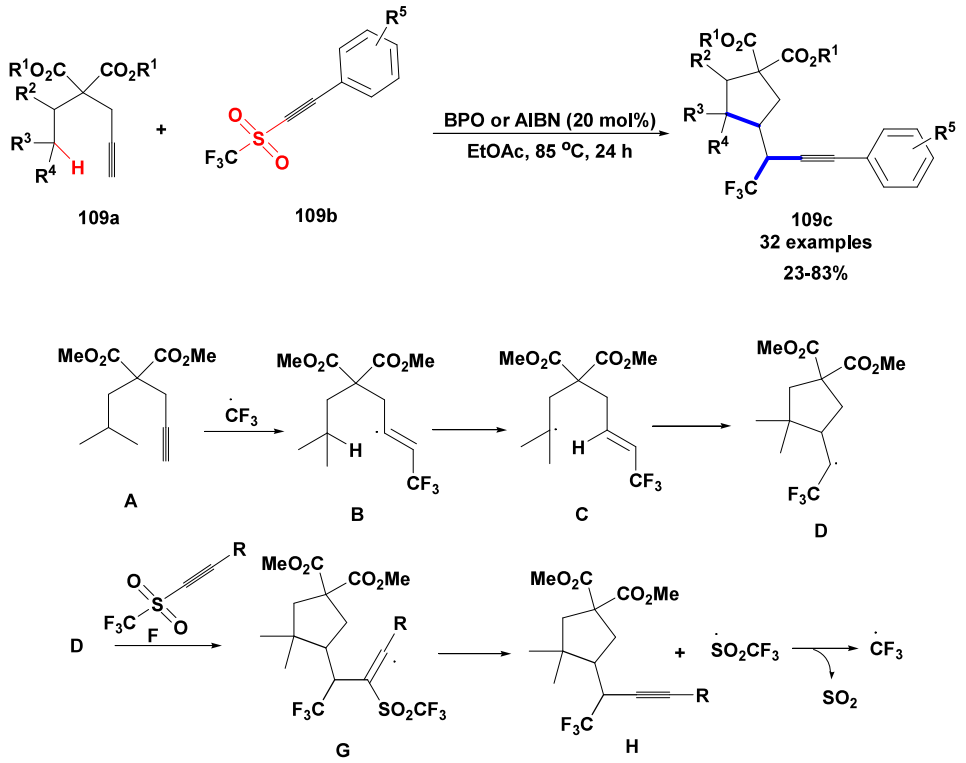


https://doi.org/10.1021/acsomega.4c11574
ACS Omega 2025, 10, 15852−15907

Scheme 86. Metal-Free Preparation of Benzimidazo[2,1-*a*]isoquinolin-6(5*H*)-ones



Scheme 87. BPO/AIBN-Promoted 1,1,2-Trifunctionalization of Terminal Alkynes and the Suggested Mechanism Reported



oxidative cross-coupling reaction in the absence of metals. Their research emphasized cross-dehydrogenative coupling between quinazoline-3-oxide derivatives and ethers, utilizing TBPB as the oxidizing agent (Scheme 71).[133] The direct alkylation of quinazoline *N*-oxides specifically targeted the C4-position of the substrates. Utilizing cyclic and open-chain ethers, including 1,4-dioxane, 1,3-dioxolane, 1,3-benzodioxole, 1,2-dimethoxyethane, diethoxymethane, and diethyl ether, resulted in moderate to good yields.

Yan et al. successfully developed a radical C3-functionalization method for coumarin derivatives using acetonitrile and acetone (**91b** and **92b**) using *tert*-butyl peroxybenzoate (TBPB) as the oxidant, thereby eliminating the necessity for a metal catalyst (Scheme 72).[134] Their study also explored the 3-cyanomethylation of *α,β*-unsaturated ketones under these conditions. In their experiments, inorganic bases such as Na_2CO_3 (61%), $NaHCO_3$ (43%), and KF (67%) proved to be more effective than organic bases like NEt_3 (23%) or DBU (trace) for synthesizing C3-cyanomethylated coumarin **91c** derivatives. They reported an innovative dehydrogenation coupling reaction involving coumarins and acetonitrile through direct C(sp^3)−H activation of acetonitrile, resulting in the production of 3-cyanomethyl-coumarins with commendable functional group tolerance and moderate to good yields. When acetonitrile was replaced by acetone, this led to the production of 3-acetomethyl coumarins in moderate yields. This approach offers a highly effective and novel method for synthesizing cyanomethyl- (or acetomethyl)-substituted coumarins. The proposed mechanism involves a radical pathway to explain the oxidative C−H activation of acetonitrile.

Zhang's team devised a method for the direct C(sp^3)−H cyanation of hydrocarbons, utilizing cyanobenziodoxolones **93c** as both cyanating reagents and oxidants (Scheme 73).[135] Tertiary amines **93a** or simple alkanes/ethers **93b** underwent this transformation, and a series of corresponding nitriles **93d**/**93e** were obtained. The mechanistic investigations revealed that, based on the substrates used, alkanes and ethers followed a free radical pathway, while tertiary amines underwent an oxidative pathway. The mechanism suggested by the authors involved two types of peptides (**I** and **II**). A free radical mechanism was proposed for the cyanation of alkanes and ethers, while an oxidative cyanation pathway (pathway **II**) was suggested for tertiary amines. Both mechanisms initiated with the generation of the ^{t}BuO· radical from TBPB. In the radical pathway **I**, hydrogen atom abstraction from an R−H bond in the substrate by the tBuO· radical led to the formation of

https://doi.org/10.1021/acsomega.4c11574
ACS Omega 2025, 10, 15852−15907

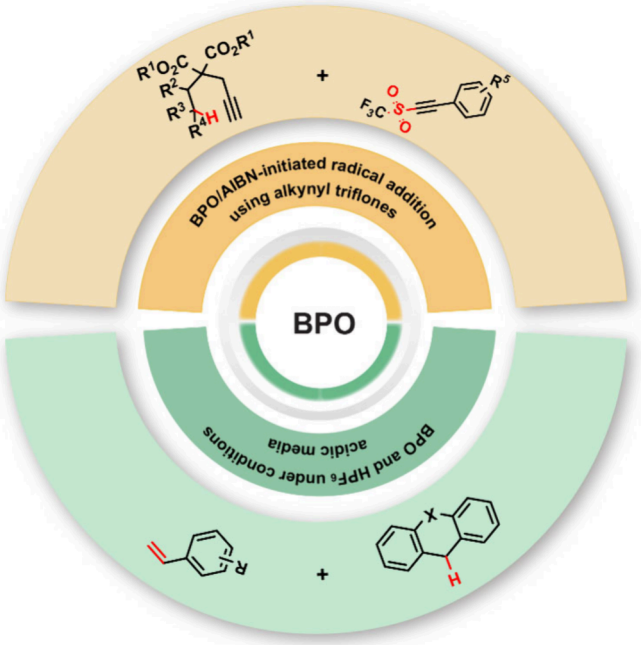


Figure 4. Suitable reagents for coupling reactions with BPO.

carbon radical **B**. The interaction between **C** and **B** resulted in the capture of **B** by **C**, producing nitrile **3**(**E**) and an iodine-centered radical **D**. Subsequently, **D** underwent hydrogen atom abstraction from the substrate via a metal-free catalytic process. Concurrently, **B** was regenerated, leading to the formation of 2-iodobenzoic acid **J**. In tertiary amines, a single-electron transfer (SET) process occurred from nitrogen to the *tert*-butoxy radical, forming nitrogen-centered cation radical **H** and a *tert*-butoxy anion. The α-C(sp^3) radical **G** was generated from **H** via deprotonation by a base, which then underwent SET oxidation by **C** to produce iminium cations **F** and released **D** alongside a cyanide anion. The nucleophilic addition of a cyanide anion to **F** formed cyanated product **5**(**E**), while **H** was regenerated through SET oxidation of substrate **4** with **D** (Scheme 73).

Patel described a method for C3-functionalization of 4-arylcoumarins **94a** using cycloalkanes **94b** as the cycloalkylation reagents, formamides **95a** as the amidation sources, and TBPB as the reaction oxidant (Scheme 74).[136] They introduced a technique for C-3 cycloalkylation and amidation of 4-arylcoumarins. This method demonstrates excellent tolerance for a variety of substituted 4-arylcoumarins, cycloalkanes, and formamides, resulting in C-3 functionalized products. This streamlined protocol significantly enhances the efficiency of the C−H bond functionalization process, particularly for internal alkenes.

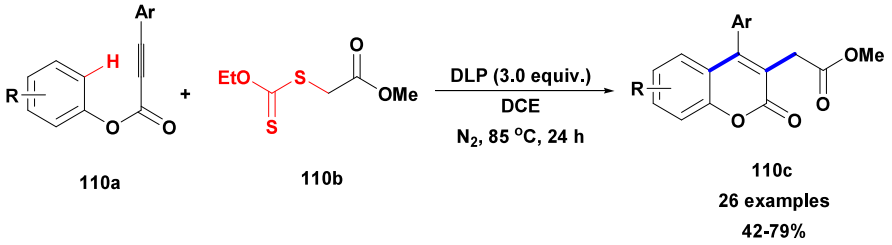
Zhao and his team developed an elegant method for the β-selective C(sp^2)−H acylation of enamides **96a** with aldehydes **96b**. The reaction utilizes Na_2-eosin Y as a photocatalyst and TBPB as the oxidant, under the irradiation of a 60 W blue LED at room temperature (Scheme 75).[137] The yields of the products **96c** were lower in the absence of irradiation, Na_2-eosin Y, or TBPB. After screening some photocatalysts such as fac-Ir$(ppy)_3$ (37%), Ru$(bpy)_3Cl_2$ (trace), and eosin Y (37%), various oxidants such as H_2O_2 (12%), PhI$(OAc)_2$ (13%), $K_2S_2O_8$ (15%), BPO (34%), and O_2 (trace) and also a series of solvents including 1,2-dichloroethane (39%), dioxane (33%), toluene (43%), and acetonitrile (61%), optimal results were achieved using Na_2-eosin Y and TBPB in ethyl acetate, yielding 69%. Various enamides bearing different para-, ortho-, or meta-substituents as well as sensitive ester and sulfone substituents with different aliphatic and aromatic aldehydes were investigated under reaction conditions. Some control experiments and KIE studies were conducted by the authors.

In a radical-trapping experiment, the use of TEMPO prevented the formation of the product, suggesting that the reaction proceeded through a radical pathway. During intermolecular competition between enamide and enamide-d_2, a K_H/K_D value of 0.54 was observed, indicating that cleavage of the olefinic C−H bond was unlikely to be the rate-determining step. In parallel experiments, when enamide-d_2 was used, the kinetic isotope effect (KIE) displayed a K_H/K_D value of 0.60, while a K_H/K_D value of 2.0 was obtained when aldehyde-*d* was used. This suggests that the rate-limiting step in the reaction may involve generation of the acyl radical via cleavage of the C−H bond in aldehydes (Scheme 76).

Consequently, the authors suggested a mechanism in which Na_2-eosin Y transitions into its excited state, Na_2-eosin Y*, upon absorbing a photon. This is followed by a single-electron transfer (SET) between the excited Na_2-eosin Y* and TBPB, generating a radical cation Na_2-eosin Y^+ and a ^{t}BuO· radical. Afterward, the ^{t}BuO· radical interacted with aldehyde **D**, forming an acyl radical species, which was then intercepted by enamide **E** to create the radical intermediate **A**. Subsequently, the single-electron oxidation of A by Na_2-eosin Y^+ produced carbon cationic species **B**, which could be transformed into iminium ion **C**. Finally, the desired product **F** was obtained through the deprotonation of intermediate **C** or **D**. The analysis of iminium ion **D** to clarify stereospecificity in the reaction demonstrated that conformer **1** was sterically more favorable compared to conformer **2** due to reduced allylic strain between the newly introduced acyl group and the bulky group on the nitrogen atom, leading to the preferential formation of the E-acylated enamides following deprotonation (Scheme 77).

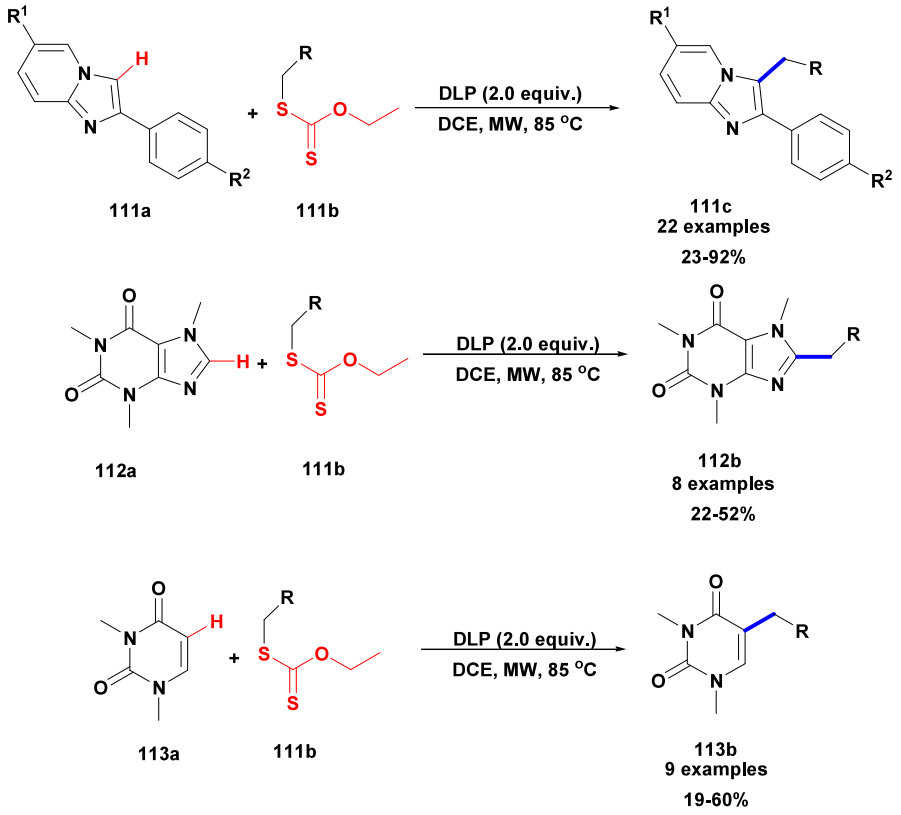
Chaudhary and colleagues introduced a method for regioselective straightforward C-3 acylation and benzoylation

Scheme 88. DLP-Promoted Radical Addition/Cyclization of Alkynoates with Xanthates

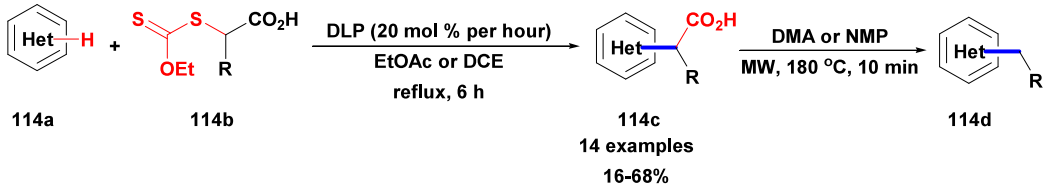


https://doi.org/10.1021/acsomega.4c11574
ACS Omega 2025, 10, 15852−15907

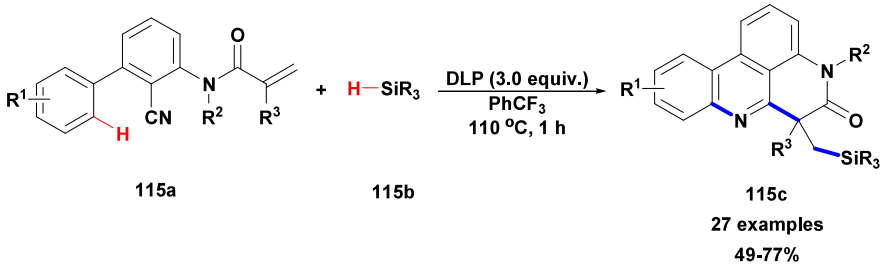
Scheme 89. Oxidative Radical Alkylation of Imidazo[1,2-*a*]pyridines, Caffeine, and 1,3-Dimethyluracil



Scheme 90. DLP-Mediated Methylation and Related Alkylations of Heteroarenes and Decarboxylation by MW Irradiation



Scheme 91. DLP-Mediated Synthesis of Silyl-Functionalized Pyrido[4,3,2-gh]phenanthridin-5(6*H*)-one Derivatives



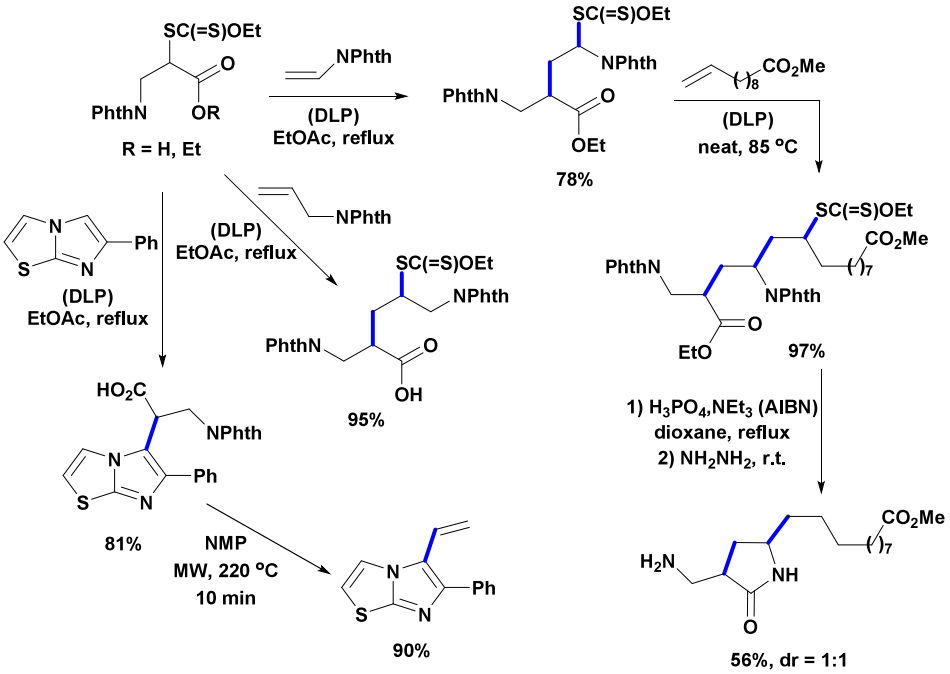
of substituted 2*H*-indazoles **97a** using a diverse variety of aldehydes **97c**, benzyl alcohols **97b**, and styrenes **97d** to generate substituted 3-(acyl/benzoyl)-2*H*-indazoles **97e** (Scheme 78).[123] Aryl and heteroaryl 2*H*-indazoles **98a** reacted well with 4-methylbenzaldehyde **98b**, producing the corresponding products **98c** with moderate to good yields, while 2-cyclohexyl-2*H*-indazole and 1*H*-indazole were unreactive under this reaction system.

The gram-scale synthesis and introduction of a simple metal-free method for the synthesis of anti-inflammatory agent **98d** were other advantages of this work (Scheme 79).

2.3.1. Versatility and Efficiency of TBPB in Organic Synthesis. This section of the study categorizes suitable reagents for various types of reactions, highlighting the versatility and effectiveness of TBPB in facilitating diverse coupling reactions. TBPB could be employed as an oxidant in the C3 radical functionalization of coumarin derivatives with acetonitrile and acetone under metal-free conditions. Inorganic bases such as Na_2CO_3, $NaHCO_3$, and KF exhibited higher efficiency compared to organic bases like NEt_3 and DBU. To broaden the applicability of this reaction, it is promising to explore decarboxylative coupling reactions with aliphatic carboxylic acids to synthesize 3-alkyl coumarins under metal-

https://doi.org/10.1021/acsomega.4c11574
ACS Omega 2025, 10, 15852−15907

Scheme 92. Flexible Route to β^2-Amino Acids and β-Heteroarylethylamines in the Presence of DLP



free conditions.[134] The reaction proceeds via the decarboxylation of aliphatic carboxylic acids, forming a carbon−carbon bond.[138−140] Additionally, investigating the 3-cyanomethylation of other α,β-unsaturated ketones or similar substrates can further broaden the applicability of this method.[13,141] Furthermore, similar metal-free conditions could be applied to functionalize other heterocyclic compounds, to create diverse bioactive molecules.[142] These proposals leverage the efficiency of TBPB and metal-free conditions to develop innovative synthetic methodologies for a wide range of substrates. For β-selective C(sp^2)−H acylation of enamides, Na_2-eosin Y could serve as a photocatalyst and TBPB as an oxidant. Future proposals for C(sp^2)−H acylation include exploring the acylation of different enamides with aldehydes or various ketones to broaden the reaction scope.[137] Additionally, radical addition reactions involving other alkenes and benzaldehydes can be investigated for the synthesis of new carbonyl-containing compounds.[123] Moreover, C(sp^2)−H functionalization of other substrates, such as aromatic compounds, could be explored to create new derivatives with diverse functional groups[143,144] (Figure 3).

2.4. Coupling Reactions with BPO. Dibenzoyl peroxide (BPO) is a white granular solid peroxide with a half-life of 1 h at 91 °C and 10 h at 72 °C, which is mainly used in polymerization and also the medical industry.[145] In 2014, Cheng and co-workers described phenanthridinylation of simple alkanes **99b** with 2-aryl phenyl isonitrile **99a** using BPO as the sole oxidant in a radical aromatic cyclization reaction (Scheme 80).[146] Notably, the utilization of $FeCl_2$, $CuCl_2$, and CuI in the reaction did not improve the efficiency. Both alkanes and cycloalkanes, especially cyclohexane, were tolerated well in the transformation. Mechanistic investigations (K_H/K_D = 6.1−8.1) indicated that the rate-determining step involved the cleavage of the C(sp^3)−H bond in alkanes.

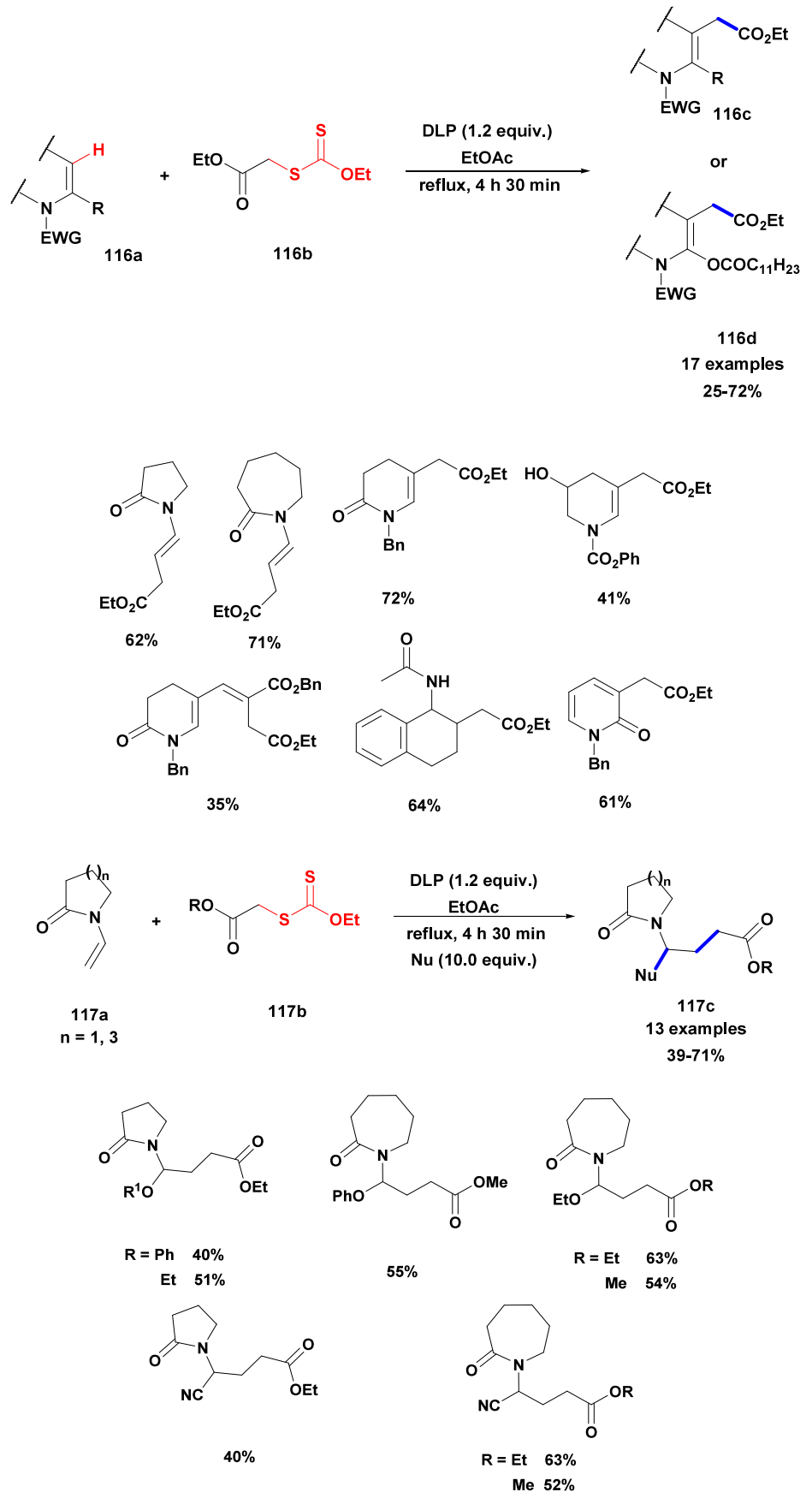
Zhao and his team introduced a procedure for intramolecular aryl-aldehyde **100a** C(sp^2)−C(sp^2) bond formation through CDC, mediated by $PhI(OAc)_2$ to generate acridones **100b** (Scheme 81).[147] In previous studies, the construction of acridones was performed by using metals, whereas iodine(III) was used as a reagent in this process. A plausible radical mechanism for this transformation begins with the decomposition of BPO upon heating, producing benzoyloxy radical **A**. This radical then reacts with iodobenzene diacetate **B**, forming radical **C**. Radical **C** abstracts a hydrogen atom from the CHO group of aldehyde **F**, leading to the generation of the acyl radical **D**. Subsequently, the splitting of a π-bond results in the formation of cyclohexadienyl radical **E**. The second hydrogen atom abstraction by radical **B** from the C(sp^3) position restores aromaticity, thereby forming desired product **G**. Alternatively, single-electron oxidation of radical **E** by either **B** or radical **C** produces cation **F**, which is then deprotonated by the acetate anion to yield final product **G** (Scheme 81).

Carbocycle frameworks such as indinones are widely abundant in natural compounds.[148−151] The construction of an indenone skeleton is conventionally achieved in the presence of transition metals such as Pd, Co, Rh, and Mn or MeOTf.[152−160] Pan and Yu reported a protocol for preparation of 2-alkyl-3-aryl indenones **101c** through a radically oxidative carboannulation of ynones **101a** with simple alkanes **101b** smoothly promoted by benzoyl peroxide (BPO) under metal- and solvent-free conditions (Scheme 82).[161] This BPO-promoted method tolerates various functional groups, producing indenone **101c** efficiently.

Isoquinolines are important building blocks of natural products, serving as excellent scaffolds in drug discovery.[162−165] Traditionally, isoquinoline scaffolds are synthesized via Pomeranz−Fritsch, Bischler−Napieralski, and Pictet−Spengler reactions.[166−169] Due to the harsh conditions often associated with such reactions, the functionalization of the C−H bond to form the C−C bond through oxidative cross-coupling has gained much interest in recent years. In 2018, Shao and his team reported the synthesis of 1-alkylisoquinolines **102c** via a radical cyclization of vinyl isocyanides **102a** with simple alkanes **102b** (Scheme 83).[170] Different aliphatic

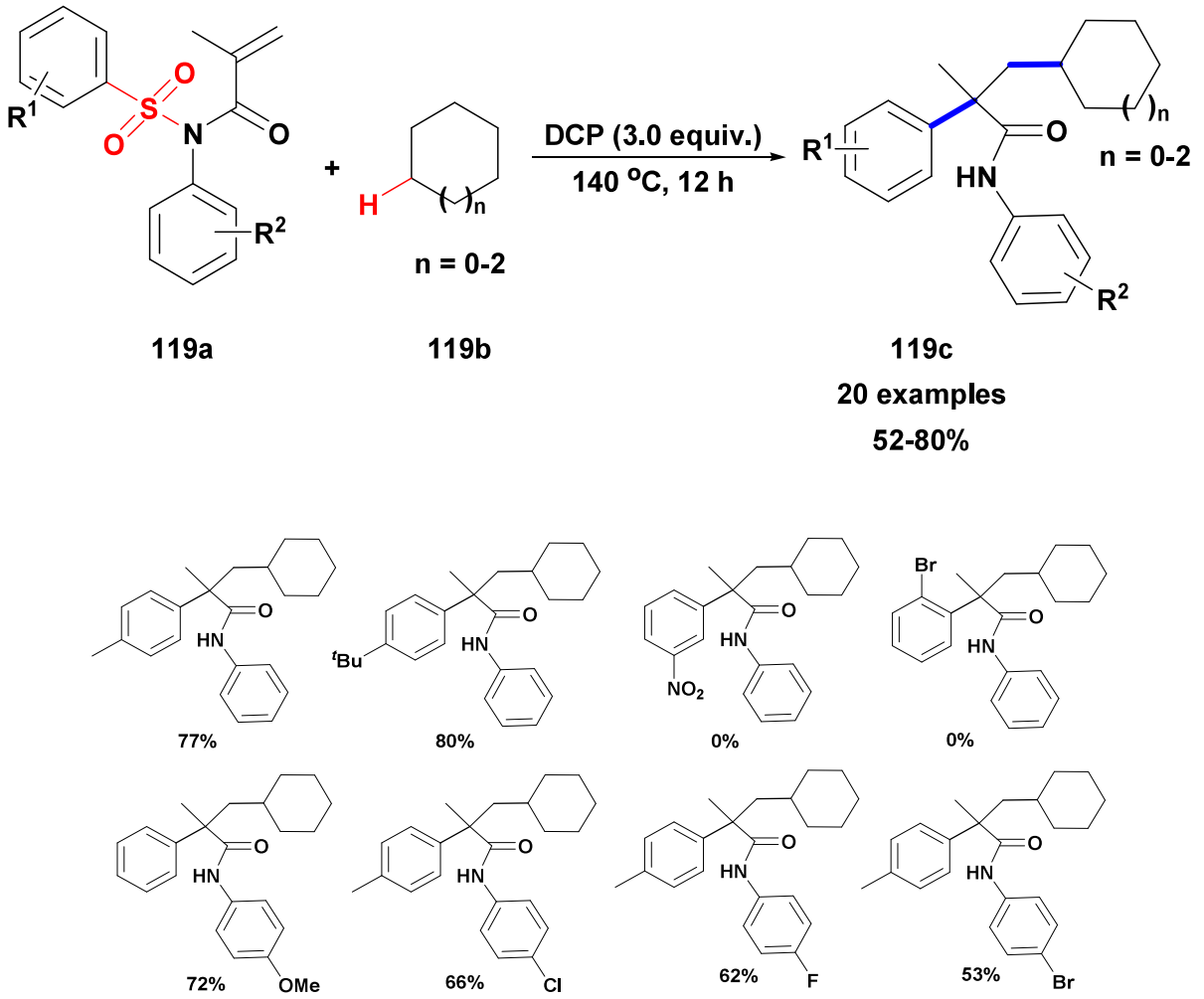
https://doi.org/10.1021/acsomega.4c11574
ACS Omega 2025, 10, 15852−15907

Scheme 93. DLP-Promoted β-C(sp^2)−H Alkylation of Enamides and DLP-Promoted Difunctionalization of Enamides



https://doi.org/10.1021/acsomega.4c11574
ACS Omega 2025, 10, 15852−15907

Scheme 94. Cascade Reaction between *N*-Phenyl-*N*-(phenylsulfonyl)-methacrylamides and Cyclohexane



alkanes, cycloalkanes, toluene, 2-ethylpyridine, 4-ethylpyridine, 3-ethylpyridine, and phenylethane exhibited moderate to good yields in this cyclization reaction.

In 2019, Sun and Liu devised a method for synthesizing a range of 6-alkyl 6*H*-benzo[c]chromene derivatives **103c**. This was achieved through a cascade reaction involving biaryl vinyl ethers **103a** and inactivated alkanes **103b**, mediated by BPO in a transition-metal-free environment (Scheme 84).[171] Benzoyloxy radicals abstract an H atom from alkanes, which results in the formation of alkane radicals. The addition of these alkane radicals to the C═C double bond of biaryl vinyl ethers leads to the cyclization products. This method efficiently accesses 6-alkyl-6*H*-benzo[c]chromenes, avoiding costly catalysts and bases. It also enables the synthesis of 6-alkyl-6*H*-benzo[c]-thiochromenes and holds promise for medicinal chemists in constructing oxygen- or sulfur-containing heterocyclic compounds.

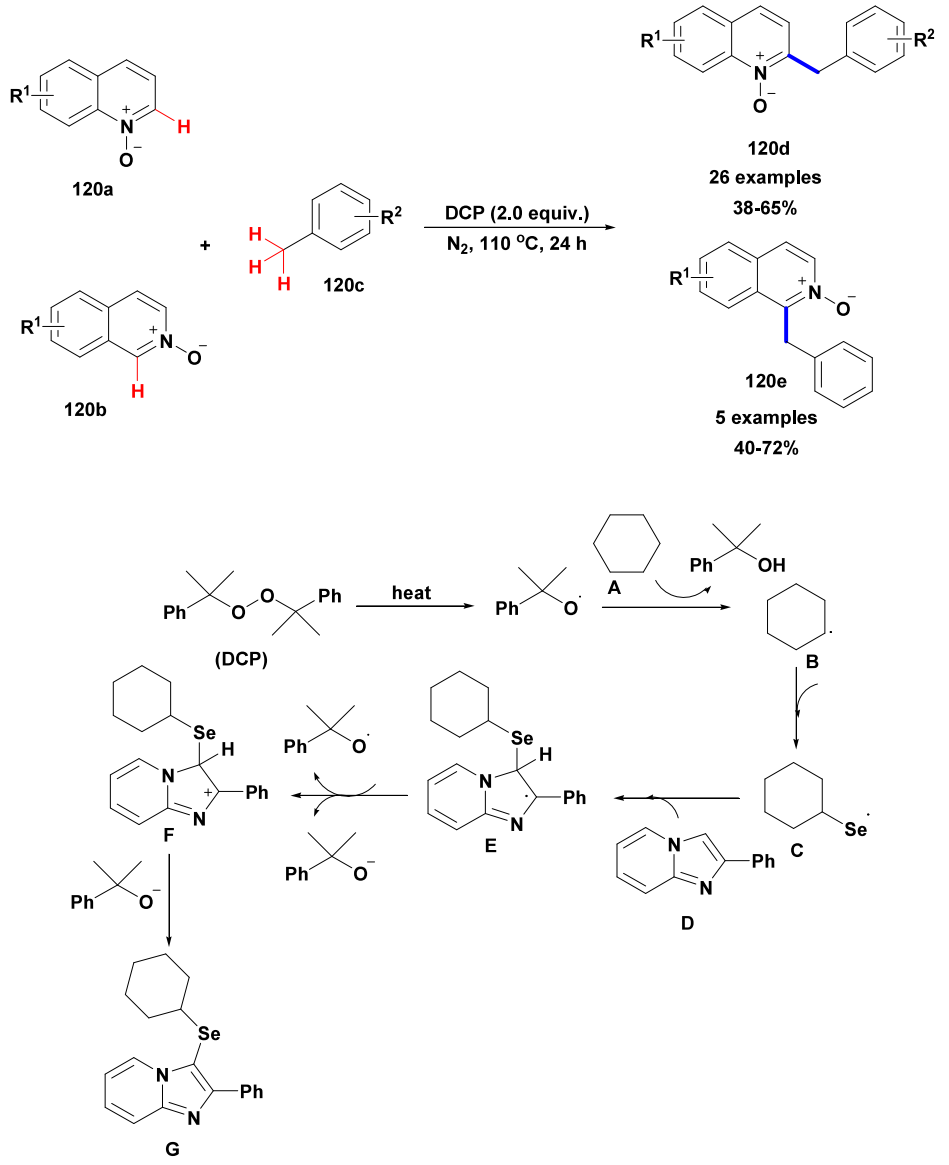
Klussmann and Liu devised a technique for the difunctionalization of styrenes **104a** through the sequential addition of a radical and a nucleophile (Scheme 85).[172] The combination of BPO with HPF_6 as a strong Brønsted acid facilitated the radical initiation to transfer both the radical and nucleophile to thioxanthene **105b** and xanthene **104c**. The study demonstrated that BPO remained unchanged, even in the acidic environment created by HPF_6. However, when thioxanthene was present, benzoic acid was formed, highlighting thioxanthene's significant role in peroxide decomposition and HPF_6's influence on the reduction potential of BPO. In the reaction, nitriles, alcohols, and thiophenols **106b** also served as nucleophiles. The product was not formed without BPO or in the presence of other peroxides. In the presence of *N*,*N*-dimethylaniline derivatives **107a**, two molecules of CH_3CN were added to styrene, creating the target product **107b**.

Sun and colleagues presented a metal-free approach for synthesizing structurally diverse benzimidazo[2,1-*a*]-isoquinolin-6(5*H*)-ones **108c**. This was achieved through a radical carbocyclization reaction involving 2-arylbenzoimidazoles **108a** and cyclic ethers **108b**, with BPO acting as the sole oxidant in the process (Scheme 86).[173] Peroxides, including TBPB (75%), TBHP (58%), DTBP (33%), and DCP (41%), resulted in the formation of the desired products in lower yields compared with BPO (76%). During the process, the only byproducts of the reaction were nontoxic benzoic acids.

There are different methods for functionalization of terminal alkynes such as radical vicinal difunctionalization,[174−176] radical−addition−translocation−cyclization,[177−184] nonradical geminal difunctionalization,[185−188] nonradical reductive geminal difunctionalization,[189−192] and 1,1,2-trifunctionalization.[193] Studer and his team unveiled a radical addition−translocation−cyclization−trapping process initiated by BPO/AIBN, utilizing readily accessible alkynyl triflones as trifluoromethyl radical precursors and trapping agents (Scheme

https://doi.org/10.1021/acsomega.4c11574
ACS Omega 2025, 10, 15852−15907

Scheme 95. Possible Mechanism for Selenation of Imidazoheterocycles with Alkanes or Ethers



87).[194] A series of (1-trifluoromethyl)propargyl cyclopentane diastereoisomers **109c** was successfully synthesized through the addition of the trifluoromethyl **109b** radical to a terminal alkyne **109a**, followed by 1,5-hydrogen atom transfer and 5-exocyclization. DLP, TBHP, DTBP, TBPB, and ACBN also served as initiators in the reaction. Among them, DLP showed better efficiency, while the others provided lower yields. A mixture of two diastereoisomers was isolated in the transformation. The authors suggested a radical mechanism involving the formation of a $\cdot CF_3$ radical by thermal decomposition of BPO or AIBN and its reaction with triflone via an addition, β-elimination, SO_2-fragmentation sequence. Then, the chemoselective addition of the trifluoromethyl radical at the terminal position of the alkyne resulted in the formation of the vinyl radical **B**. Radical **B** then underwent 1,5-HAT to form radical **C**. Subsequently, 5-exocyclization resulted in radical **D**, which was trapped by the triflone reagent **F** to produce vinyl radical **G**. β-Fragmentation furnished target product **H** along with further fragmentation of the trifluoromethylsulfonyl radical to produce SO_2 and the CF_3 radical (Scheme 87).

2.4.1. Versatility and Effectiveness of BPO in Coupling Reactions. The studies highlight the versatility and effectiveness of BPO in facilitating diverse coupling reactions. In the difunctionalization of styrenes, benzoyl peroxide (BPO) and hexafluorophosphoric acid (HPF_6) play crucial roles. BPO, as an oxidant, generates benzoyloxyl radicals that abstract hydrogen atoms from thioxanthene, forming new radicals that add to styrenes to produce benzylic cations. These cations are then oxidized to yield the final products. HPF_6, acting as a strong Brønsted acid, facilitates the radical initiation by protonating BPO, enhancing its reduction potential and promoting overall reaction efficiency.[172] Given the significant role of thioxanthene in peroxide decomposition, other derivatives of thioxanthene and similar substrates could also be explored for similar reactions. Additionally, nitriles, alcohols, thiophenols, and other nucleophiles used in the reaction can be tested with different substrates to expand the reaction scope. BPO and HPF_6 could be employed to develop innovative synthetic methodologies for a wide range of substrates, potentially leading to the synthesis of new compounds with diverse functional groups.[195,196] In the

https://doi.org/10.1021/acsomega.4c11574
ACS Omega 2025, 10, 15852−15907

functionalization of terminal alkynes, BPO and AIBN act as initiators, generating radicals. These radicals undergo a series of reactions, including addition, displacement, cyclization, and trapping, to form final products. The crucial steps include generating a trifluoromethyl radical, which reacts with the terminal alkyne. This is followed by hydrogen atom transfer and cyclization, resulting in the formation of the target cyclopentane derivatives.[194] Suggestions for similar substrates include using alkynes with electron-withdrawing groups such as cyano, nitro, or ester groups, which can undergo comparable radical reactions. Additionally, alkenes with halogen substituents such as bromine or iodine are suitable for similar radical addition processes. Furthermore, unsaturated carbonyl compounds such as halogen-containing malonic acid/esters can be employed to generate radicals under visible light irradiation[197−199] (Figure 4).

2.5. Coupling Reactions with DLP. Lauroyl peroxide or dilauroyl peroxide (DLP) is a white solid diacylperoxide with a fast half-life of 1 h at 79 °C and 10 h at 61 °C. DLP is a readily biodegradable peroxide commonly used for polymerization processes. However, there are some reports of the use of this peroxide as a radical initiator in cross-coupling reactions. Construction of the coumarin framework has attracted significant attention because of its valuable pharmacological activities.[200−204] Pan and Yu described a radical addition/cyclization method to access 3-(*β*-carbonyl)coumarins **110c** via a DLP-promoted cascade reaction using aryl alkynoates **110a** and xanthates **110b** (Scheme 88).[205] Yield of the products was low in the presence of other organic oxidants such as BPO, DTBP, and TBHP. The utilization of $K_2S_2O_8$, $PhI(OAc)_2$, and H_2O_2 was not effective in this reaction.

Miranda and colleagues devised a method employing xanthate-based radical chemistry for the regioselective direct alkylation of caffeine, uracil, and imidazo[1,2-*a*]pyridine systems. This technique utilizes dilauroyl peroxide (DLP) as both the initiator and the oxidant under microwave irradiation. It enables the formation of Csp^2-Csp^3 bonds via C−H functionalization, starting from readily available materials. Electrophilic radicals (positioned alpha to a carbonyl function, like ketones, amides, esters, malonates, and cyano groups) can be regioselectively added to imidazo[1,2-*a*]pyridines, caffeine, and 1,3-dimethyluracil in the presence of DLP as a radical initiator under microwave irradiation (Scheme 89).[206] Cross-coupling reaction results in low products under convectional heating; however, the yield increases under microwave heating.

In general, due to the widespread presence of heteroarenes in many biologically active molecules and functional organic compounds, the synthesis and functionalization of these structures have garnered significant importance.[207] In 2018, Zard introduced a strategy for the synthesis of methylated and alkylated heteroarenes **114c** using an excess amount of xanthates **114b** in the presence of stoichiometric DLP, added to the reaction in an amount of 20 mol % per 1 h (Scheme 90).[208] Then, decarboxylation of the carboxymethyl adduct was carried out using MW irradiation at 180 °C for 10 min, resulting in the formation of alkylated product **114d**. In this transformation, prevalent heteroarenes in the pharmaceutical field, such as caffeine, pyrazine, quinoxaline, purine, and also imidazopyridine, imidazopyrimidine, and imidazopyridazine exhibited a satisfactory reactivity.

Sun and colleagues detailed a radical cascade addition/cyclization reaction between *N*-arylacrylamides **115a** and trialkylsilanes **115b** using DLP under metal-free conditions (Scheme 91).[209] Mechanistic studies indicated that the reaction commenced with the addition of a silyl radical to the electron-deficient C═C bond in *N*-arylacrylamides, followed by intramolecular cyclization involving the CN group. This sequence culminated in the formation of the desired product via hydrogen abstraction. They devised a rapid cascade cyclization method to synthesize silyl-functionalized pyrido[4,3,2-gh]phenanthridin derivatives, using easily accessible hydrosilanes as sources of silyl radicals, all under metal-free conditions. This reaction is both efficient and atom-economical, exhibiting good tolerance for functional groups, thus proving valuable for organic synthesis and pharmaceutical research.

Zard and Chen reported a surprising vinylation reaction in which the radical addition of *β*-phthalimido-*α*-xanthyl propionic acid, whether as the free carboxylic acid or its ethyl ester, resulted in the formation of various protected β^2-amino acids and *β*-heteroarylethylamines (Scheme 92).[210] The reaction was effectively performed in stoichiometric quantities of peroxide. Key practical advantages of this method include the low cost and ready availability of the reagents, the mildness of the experimental conditions, and the compatibility with various functionalities, particularly polar groups.

DLP-promoted regioselective *β*-C(sp^2)−H alkylation of cyclic and acyclic enamides **116a** by xanthates **116b** leads to the formation of *γ*-amino-*β*,*γ*-unsaturated acyl scaffold **116c**/**116d** (Scheme 93).[211] MeOH, EtOH, and PhOH are used as the related nucleophiles. The process involves a radical and polar reaction. This innovative regioselective reaction offers a wide substrate scope and exceptional functional group tolerance, demonstrating considerable potential for synthesizing a diverse range of *N*-containing building blocks. The extensive availability of xanthates further enhances the reaction's versatility, effectively merging a radical process with a polar reaction.

2.6. Coupling Reactions with DCP. Dicumyl peroxide (DCP) is a white solid organic peroxide with a half-life of 1 h at 135 °C and 10 h at 114 °C. It recently showed good potential as a radical initiator and also a methylating reagent in cross-coupling reactions.[212] Zhu and colleagues outlined a protocol for a cascade reaction involving *N*-phenyl-*N*-(phenyl sulfonyl)-methacrylamides **119a**, which includes C(sp^3)−H activation, SO_2 elimination, and C−C bond formation. This process is conducted with simple alkanes **119b** using DCP as the only oxidant (Scheme 94).[213] In this metal-free process, amides with an electron-donating group on the aromatic ring afforded high yields of products **119c**. Moreover, *N*-phenyl-*N*-(phenylsulfonyl)-methacrylamide provided a good yield. When an aromatic ring with an electron-withdrawing group was employed, the yields of the products were moderate. Additionally, no expected product was observed when using amides with groups such as NO_2 or Br on the *N*-phenyl (SO_2).

Guo's team described the formation of benzylated quinoline *N*-oxides **120d**, isoquinoline *N*-oxides **120e**, and pyridine *N*-oxides **120a**, and **120b** with toluene derivatives **120c** was mediated by DCP as the sole oxidant (Scheme 95).[214] A significant decrease in the yield was observed when the reaction was performed at a higher temperature (120−130 °C) or in the presence of 3.0 equiv of the oxidant. Benzoylated products emerged under these conditions. The substitutes on the phenyl ring or pyridyl ring of the *N*-oxide compounds had no obvious effects in this cross-coupling reaction, whereas electron-rich toluenes showed higher reactivity compared to

https://doi.org/10.1021/acsomega.4c11574
ACS Omega 2025, 10, 15852−15907

electron-poor ones due to the higher nucleophilicity of the generated benzylic carbon radical.

3. CONCLUSION AND PERSPECTIVE

In summary, the use of organic peroxides in transition-metal-free cyclization and coupling reactions marks a significant advancement in green and sustainable chemistry. This comprehensive review underscores the versatility and effectiveness of organic peroxides, such as TBHP, DTBP, TBPB, BPO, DLP, and DCP, in facilitating a wide range of oxidative transformations. These methodologies present a promising alternative to traditional transition-metal-catalyzed processes, thereby reducing the environmental impact and potential toxicity associated with heavy metals. The ability to achieve multibond cleavage and formation in a single step, driven by free radical mechanisms, highlights the efficiency of these processes. Despite the progress made, challenges remain in fully elucidating the mechanistic pathways of peroxide-mediated reactions, particularly when combined with nonmetal catalysts. Further research is needed to explore the exact roles of nonmetal catalysts and additives in these transformations. Additionally, developing novel, low-cost, and environmentally friendly methods for drug synthesis and other applications under metal-free conditions is crucial to the continued advancement of this field. The future of organic synthesis lies in the development and implementation of green and sustainable methodologies. The use of organic peroxides in transition-metal-free cyclization and coupling reactions represents a pivotal step toward achieving this goal. Moving forward, several avenues of research can be pursued to further enhance the application of organic peroxides in transition-metal-free reactions. First, a deeper understanding of the mechanistic pathways involved in peroxide-mediated transformations is essential. Advanced spectroscopic and computational techniques can be employed to elucidate the roles of free radicals, nonmetal catalysts, and additives in these reactions. Such insights will enable the rational design of more efficient and selective synthetic protocols. Second, the exploration of novel organic peroxides with tailored reactivity profiles can expand the scope of transition-metal-free oxidative transformations. By designing peroxides with specific functional groups or steric properties, chemists can achieve greater control over reaction outcomes, thereby broadening the range of accessible chemical structures with excellent regioselectivity and stereoselectivity. Third, the integration of organic peroxides with other green chemistry principles, such as solvent-free conditions, microwave-assisted synthesis, and flow chemistry, holds promise for the development of more sustainable and scalable synthetic processes. These approaches can reduce the environmental footprint of chemical manufacturing and enhance the overall efficiency of synthetic routes. Furthermore, the application of organic peroxide-mediated reactions in the synthesis of complex natural products, pharmaceuticals, and advanced materials presents a significant opportunity for innovation. By leveraging the unique reactivity of organic peroxides, chemists can develop new strategies for the construction of intricate molecular architectures, thereby addressing the current challenges in drug discovery and materials science. In conclusion, the continued exploration and optimization of organic peroxide-mediated transition-metal-free reactions will play a crucial role in advancing the field of green chemistry. By embracing these methodologies, the scientific community can contribute to the development of more sustainable and eco-friendly chemical processes, ultimately benefiting both industry and the environment. The insights and perspectives provided in this Review are expected to inspire further research and innovation in this exciting and rapidly evolving area of organic synthesis.

AUTHOR INFORMATION

Corresponding Authors

Mehdi Khoobi − *Drug Design and Development Research Center, The Institute of Pharmaceutical Sciences, Tehran University of Medical Sciences, Tehran 14176-14411, Iran; Department of Radiopharmacy, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran 11141-33314, Iran*; Email: mehdi.khoobi@gmail.com

Alireza Foroumadi − *Drug Design and Development Research Center, The Institute of Pharmaceutical Sciences, Tehran University of Medical Sciences, Tehran 14176-14411, Iran; Department of Medicinal Chemistry, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran 11141-33314, Iran*; orcid.org/0000-0003-2416-5611; Email: aforoumadi@yahoo.com

Authors

Amin Rezaeifard − *Drug Design and Development Research Center, The Institute of Pharmaceutical Sciences, Tehran University of Medical Sciences, Tehran 14176-14411, Iran*

Fatemeh Doraghi − *School of Chemistry, College of Science, University of Tehran, Tehran 14174-66191, Iran*

Fatemeh Akbari − *Department of Chemistry, Uppsala University, Uppsala 751-05, Sweden*

Bahareh Bari − *School of Chemistry, College of Science, University of Tehran, Tehran 14174-66191, Iran*

Ebrahim Kianmehr − *School of Chemistry, College of Science, University of Tehran, Tehran 14174-66191, Iran*; orcid.org/0000-0003-2973-924X

Ali Ramazani − *Department of Chemistry, Faculty of Science, University of Zanjan, Zanjan 45371-38791, Iran*; orcid.org/0000-0003-3072-7924

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.4c11574

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We gratefully acknowledge the financial support of Tehran University of Medical Sciences.

ABBREVIATIONS

CDC	Cross-dehydrogenative coupling
DPPH	1,1-Diphenyl-2-picrylhydrazyl
NCS	*N*-Chlorosuccinimide
NIS	*N*-Iodosuccinimide
KIE	Kinetic isotope effect
DABCO	1,4-Diazabicyclo[2.2.2]octane
TEMPO	2,2,6,6-Tetramethylpiperidinyloxy

REFERENCES

(1) Sheikh, A. R.; Arif, A.; Khan, M. M. Aryl glyoxal: a prime synthetic equivalent for multicomponent reactions in the designing of oxygen heterocycles. *RSC adv.* **2023**, *13*, 11652−11684.

(2) Mohammadi Ziarani, G.; Moradi, R.; Ahmadi, T.; Gholamzadeh, P. The molecular diversity scope of 4-hydroxycoumarin in the

https://doi.org/10.1021/acsomega.4c11574
ACS Omega 2025, 10, 15852−15907

synthesis of heterocyclic compounds via multicomponent reactions. *Mol. Divers.* **2019**, *23*, 1029−1064.
(3) Liu, Q.; Hong, J.; Sun, B.; Bai, G.; Li, F.; Liu, G.; Yang, Y.; Mo, F. Transition-metal-free borylation of alkyl iodides via a radical mechanism. *Org. Lett.* **2019**, *21*, 6597−6602.
(4) Yu, Y.; Wang, T.; Zhang, Y.; You, J.; Hu, F.; Zhang, H. Recent progress of transition metal compounds as electrocatalysts for electrocatalytic water splitting. *Chem. Rec.* **2023**, *23*, No. e202300109.
(5) Lu, L.; Cheng, D.; Zhan, Y.; Shi, R.; Chiang, C.-W.; Lei, A. Metal-free radical oxidative alkoxycarbonylation and imidation of alkanes. *Chem. Commun.* **2017**, *53*, 6852−6855.
(6) Sun, K.; Chen, X.-L.; Zhang, Y.-L.; Li, K.; Huang, X.-Q.; Peng, Y.-Y.; Qu, L.-B.; Yu, B. Metal-free sulfonyl radical-initiated cascade cyclization to access sulfonated indolo [1, 2-a] quinolines. *ChemComm.* **2019**, *55*, 12615−12618.
(7) Chen, J.-R.; Hu, X.-Q.; Lu, L.-Q.; Xiao, W.-J. Visible light photoredox-controlled reactions of N-radicals and radical ions. *Chem. Soc. Rev.* **2016**, *45*, 2044−2056.
(8) Yi, H.; Zhang, G.; Wang, H.; Huang, Z.; Wang, J.; Singh, A. K.; Lei, A. Recent advances in radical C−H activation/radical cross-coupling. *Chem. Rev.* **2017**, *117*, 9016−9085.
(9) Mandal, S.; Bera, T.; Dubey, G.; Saha, J.; Laha, J. K. Uses of K2S2O8 in metal-catalyzed and metal-free oxidative transformations. *ACS Catal.* **2018**, *8*, 5085−5144.
(10) Miller, J. L.; Lawrence, J.-M. I.; Del Rey, F. O. R.; Floreancig, P. E. Synthetic applications of hydride abstraction reactions by organic oxidants. *Chem. Soc. Rev.* **2022**, *51*, 5660−5690.
(11) Qiu, L.; Cooks, R. G. Spontaneous oxidation in aqueous microdroplets: water radical cation as primary oxidizing agent. *Angew. Chem., Int. Ed.* **2024**, *136*, No. e202400118.
(12) Wu, T.; Müller, T.; Wang, N.; Byron, J.; Langer, S.; Williams, J.; Licina, D. Indoor Emission, Oxidation, and New Particle Formation of Personal Care Product Related Volatile Organic Compounds. *Environ. Sci. Technol. Lett.* **2024**, *11*, 1053−1061.
(13) Jyoti; Devi, S.; Manisha; Wadhwa, D.; Sindhu, J.; Kumar, V. TBHP: A Sustainable Alternative For Carbon-Oxygen Bond Formation. *Eur. J. Org. Chem.* **2024**, *27*, No. e202301030.
(14) Dixit, V.; Kumar, G.; Kumar, P.; Soni, A.; Nemiwal, M. Emerging Strategies for Synthesis of Heterocyclic Compounds Enabled by Titanium Oxide Nanoparticles as Heterogeneous Catalyst. *Tetrahedron* **2024**, *160*, No. 134039.
(15) Loch-Caruso, R.; Korte, C. S.; Hogan, K. A.; Liao, S.; Harris, C. Tert-butyl hydroperoxide stimulated apoptosis independent of prostaglandin E2 and IL-6 in the HTR-8/SVneo human placental cell line. *Reprod. Sci.* **2020**, *27*, 2104−2114.
(16) Kawamura, S.; Mukherjee, S.; Sodeoka, M. Recent advances in reactions using diacyl peroxides as sources of O-and C-functional groups. *Org. Biomol. Chem.* **2021**, *19*, 2096−2109.
(17) Ono, T. Electrochemical Analysis Using Organic Nitroxyl Radicals. *Yakugaku Zasshi: J. Pharm. Soc. Jpn.* **2023**, *143*, 95−100.
(18) Shi, L.; Li, T.; Mei, G.-J. Recent advances in transition-metal-free C−H functionalization of imidazo [1, 2-a] pyridines. *Green Synth. Catal. Lett.* **2022**, *3*, 227−242.
(19) Kumar, S.; Padala, K. The recent advances in K2S2O8-mediated cyclization/coupling reactions via an oxidative trans-formation. *Chem. Commun.* **2020**, *56*, 15101−15117.
(20) Das, A.; Patil, N. T. Enantioselective C- H functionalization reactions under gold catalysis. *Chem. Eur. J.* **2022**, *28*, No. e202104371.
(21) Tsiotsias, A. I.; Charisiou, N. D.; Yentekakis, I. V.; Goula, M. A. Bimetallic Ni-based catalysts for CO2 methanation: a review. *Nanomaterials* **2021**, *11*, 28.
(22) He, T.; Yu, L.; Zhang, L.; Wang, L.; Wang, M. Direct C2-alkylation of azoles with alcohols and ethers through dehydrogenative cross-coupling under metal-free conditions. *Org. Lett.* **2011**, *13*, 5016−5019.
(23) Kumar, R. A.; Saidulu, G.; Prasad, K. R.; Kumar, G. S.; Sridhar, B.; Reddy, K. R. Transition Metal-Free α-C (sp3)-H Bond Functionalization of Amines by Oxidative Cross Dehydrogenative Coupling Reaction: Simple and Direct Access to C-4-Alkylated 3, 4-Dihydroquinazoline Derivatives. *Adv. Synth. Catal.* **2012**, *354*, 2985−2991.
(24) Du, B.; Jin, B.; Sun, P. The syntheses of α-ketoamides via nBu4NI-catalyzed multiple sp 3 C−H bond oxidation of ethylarenes and sequential coupling with dialkylformamides. *Org. Biomol. Chem.* **2014**, *12*, 4586−4589.
(25) Yang, X.-H.; Wei, W.-T.; Li, H.-B.; Song, R.-J.; Li, J.-H. Oxidative coupling of alkenes with amides using peroxides: selective amide C (sp3)−H versus C (sp2)−H functionalization. *Chem. Commun. Lett.* **2014**, *50*, 12867−12869.
(26) Ouyang, X.-H.; Song, R.-J.; Wang, C.-Y.; Yang, Y.; Li, J.-H. Metal-free carbonyl C (sp2)−H oxidative alkynylation of aldehydes using hypervalent iodine reagents leading to ynones. *Chem. Commun.* **2015**, *51*, 14497−14500.
(27) Kumar, A.; Shah, B. A. Synthesis of biaryls via benzylic C−C bond cleavage of styrenes and benzyl alcohols. *Organic lett.* **2015**, *17*, 5232−5235.
(28) Lan, X.-W.; Wang, N.-X.; Bai, C.-B.; Lan, C.-L.; Zhang, T.; Chen, S.-L.; Xing, Y. Unactivated C (sp^3)−H Bond Functionalization of Alkyl Nitriles with Vinylarenes and Mechanistic Studies. *Organic lett.* **2016**, *18*, 5986−5989.
(29) Chen, P.; Niu, Z.; Wang, E. 3-Aroylbenzocoumarin-Based Luminogens: Bright Solid-State Emission, AIE Properties and Cell Imaging Application. *J. Fluoresc.* **2024**, 1−8.
(30) Raju, B. C.; Tiwari, A. K.; Kumar, J. A.; Ali, A. Z.; Agawane, S. B.; Saidachary, G.; Madhusudana, K. α-Glucosidase inhibitory antihyperglycemic activity of substituted chromenone derivatives. *Bioorg. Med. Chem.* **2010**, *18*, 358−365.
(31) Vazquez-Rodriguez, S.; Figueroa-Guinez, R.; Matos, M. J.; Santana, L.; Uriarte, E.; Lapier, M.; Maya, J. D.; Olea-Azar, C. Synthesis of coumarin−chalcone hybrids and evaluation of their antioxidant and trypanocidal properties. *MedChemComm.* **2013**, *4*, 993−1000.
(32) Vazquez-Rodriguez, S.; Lama Lopez, R.; Matos, M. J.; Armesto-Quintas, G.; Serra, S.; Uriarte, E.; Santana, L.; Borges, F.; Munoz Crego, A.; Santos, Y. Design, synthesis and antibacterial study of new potent and selective coumarin−chalcone derivatives for the treatment of tenacibaculosis. *Bioorg. Med. Chem.* **2015**, *23*, 7045−7052.
(33) Jafarpour, F.; Abbasnia, M. A regioselective metal-free construction of 3-aroyl coumarins by Csp2-H functionalization. *J. Org. Chem.* **2016**, *81*, 11982−11986.
(34) Miao, T.; Xia, D.; Li, Y.; Li, P.; Wang, L. Direct difunctionalization of activated alkynes via domino oxidative benzylation/1, 4-aryl migration/decarboxylation reactions under metal-free conditions. *Chem. Commun.* **2016**, *52*, 3175−3178.
(35) Yu, Y.; Jiao, L.; Wang, J.; Wang, H.; Yu, C.; Hao, E.; Boens, N. Bu4 NI/tBuOOH catalyzed, α-regioselective cross-dehydrogenative coupling of BODIPY with allylic alkenes and ethers. *Chem.Comm.* **2017**, *53*, 581−584.
(36) Teli, S.; Sethiya, A.; Agarwal, S. Pioneering Synthetic Strategies of 2-Substituted Benzothiazoles Using 2-Aminothiophenol. *Chemistry* **2024**, *6*, 165−206.
(37) Yokooji, A.; Okazawa, T.; Satoh, T.; Miura, M.; Nomura, M. Palladium-catalyzed direct arylation of thiazoles with aryl bromides. *Tetrahedron* **2003**, *59*, 5685−5689.
(38) Huang, J.; Chan, J.; Chen, Y.; Borths, C. J.; Baucom, K. D.; Larsen, R. D.; Faul, M. M. A highly efficient palladium/copper cocatalytic system for direct arylation of heteroarenes: an unexpected effect of Cu (Xantphos) I. *JACS.* **2010**, *132*, 3674−3675.
(39) Xie, K.; Yang, Z.; Zhou, X.; Li, X.; Wang, S.; Tan, Z.; An, X.; Guo, C.-C. Pd-catalyzed decarboxylative arylation of thiazole, benzoxazole, and polyfluorobenzene with substituted benzoic acids. *Org. Lett.* **2010**, *12*, 1564−1567.
(40) Yu, X.; Tian, R.; Shi, C.; Song, R.; Wei, Z. Commercial Nickel-catalyzed Cross-coupling of Organolithium Reagents with 2-arylbenzothiazoles. *Catal. Lett.* **2024**, *154*, 5069−5074.
(41) Chu, X.; Duan, T.; Liu, X.; Feng, L.; Jia, J.; Ma, C. N-Iodosuccinimide involved one-pot metal-free synthesis of 2-

https://doi.org/10.1021/acsomega.4c11574
ACS Omega 2025, 10, 15852−15907

heteroaromatic benzothiazole compounds. *Org. Biomol. Chem.* **2017**, *15*, 1606−1611.
(42) Jiang, H.; Huang, W.; Yu, Y.; Yi, S.; Li, J.; Wu, W. Transition-metal-free synthesis of ß-trifluoromethylated enamines with trifluoromethanesulfinate. *Chem. Commun.* **2017**, *53*, 7473−7476.
(43) Ghosh, P.; Mondal, S.; Hajra, A. Metal-free trifluoromethylation of indazoles. *JOC* **2018**, *83*, 13618−13623.
(44) Zhang, L.; Zhang, G.; Li, Y.; Wang, S.; Lei, A. The synergistic effect of self-assembly and visible-light induced the oxidative C−H acylation of N-heterocyclic aromatic compounds with aldehydes. *Chem. Commun.* **2018**, *54*, 5744−5747.
(45) Jafarpour, F.; Darvishmolla, M. Peroxy mediated Csp2−Csp3 dehydrogenative coupling: regioselective functionalization of coumarins and coumarin-3-carboxylic acids. *Org. Biomol. Chem.* **2018**, *16*, 3396−3401.
(46) Chen, C.; Li, Y.; Pan, Y.; Duan, L.; Liu, W. Oxidative radical addition−chlorination of alkenes to access 1, 1-dichloroalkanes from simple reagents. *Org. Chem. Front.* **2019**, *6*, 2032−2036.
(47) Li, M.; Zhu, X. Y.; Qiu, Y. F.; Han, Y. P.; Xia, Y.; Wang, C. T.; Li, X. S.; Wei, W. X.; Liang, Y. M. Metal-Free Promoted CF2/CF3-Difunctionalization of Unactivated Alkenes. *Adv. Synth. Catal.* **2019**, *361*, 2945−2950.
(48) Naim, M.; Gestetner, B.; Zilkah, S.; Birk, Y.; Bondi, A. Soybean isoflavones. Characterization, determination, and antifungal activity. *JAFC* **1974**, *22*, 806−810.
(49) Parmar, N. S.; Tariq, M.; Ageel, A. M. Effect of thromboxane A2 and leukotriene C4 inhibitors on the experimentally induced gastric lesions in the rat. *Research communications in chemical pathology and pharmacology* **1987**, *58*, 15−25.
(50) Marder, M.; Viola, H.; Bacigaluppo, J. A.; Colombo, M. a. I.; Wasowski, C.; Wolfman, C.; Medina, J. H.; Rúveda, E. A.; Paladini, A. C. Detection of benzodiazepine receptor ligands in small libraries of flavone derivatives synthesized by solution phase combinatorial chemistry. *Biochem. Biophys. Res. Commun.* **1998**, *249*, 481−485.
(51) Chohan, Z. H.; Shaikh, A. U.; Rauf, A.; Supuran, C. T. Antibacterial, antifungal and cytotoxic properties of novel N-substituted sulfonamides from 4-hydroxycoumarin. *J. Enzyme Inhib. Med. Chem.* **2006**, *21*, 741−748.
(52) Zhou, T.; Shi, Q.; Lee, K. H. Anti-AIDS agents 83. Efficient microwave-assisted one-pot preparation of angular 2, 2-dimethyl-2H-chromone containing compounds. *Tetrahedron lett.* **2010**, *51*, 4382−4386.
(53) Agisho, H. A.; Esatu, H.; Hairat, S.; Zaki, M. TBHP/TBAI−Mediated simple and efficient synthesis of 3, 5-disubstituted and 1, 3, 5-trisubstituted 1H-1, 2, 4-triazoles via oxidative decarbonylation of aromatic aldehydes and testing for antibacterial activities. *Tetrahedron Lett.* **2020**, *61*, No. 151989.
(54) Sharma, S.; Dutta, N. B.; Bhuyan, M.; Das, B.; Baishya, G. tert-Butylhydroperoxide (TBHP) mediated oxidative cross-dehydrogenative coupling of quinoxalin-2 (1H)-ones with 4-hydroxycoumarins, 4-hydroxy-6-methyl-2-pyrone and 2-hydroxy-1, 4-naphthoquinone under metal-free conditions. *Org. Biomol. Chem.* **2020**, *18*, 6537−6548.
(55) Wang, B.; Zhang, Q.; Guo, Z.; Ablajan, K. Iodine-and TBHP-promoted acylation of benzothiazoles under metal-free conditions. *Synthesis* **2020**, *52*, 3058−3064.
(56) Xu, W.-X.; Ye, F.-X.; Liu, X.-H.; Weng, J.-Q. NCS/TBHP promoted C2 arylation of benzothiazoles with aldehydes in DMSO. *Tetrahedron Lett.* **2020**, *61*, No. 151807.
(57) Yuan, Y.; Li, M.; Apostolopoulos, V.; Matsoukas, J.; Wolf, W. M.; Blaskovich, M. A.; Bojarska, J.; Ziora, Z. M. Tetrazoles: A multi-potent motif in drug design. *Eur. J. Med. Chem.* **2024**, *279*, No. 116870.
(58) Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. Analysis of the reactions used for the preparation of drug candidate molecules. *Org. Biomol. Chem.* **2006**, *4*, 2337−2347.
(59) Allen, C. L.; Williams, J. M. Metal-catalysed approaches to amide bond formation. *Chem. Soc. Rev.* **2011**, *40*, 3405−3415.
(60) Song, Y.; Zhang, H.; Guo, J.; Shao, Y.; Ding, Y.; Zhu, L.; Yao, X. Visible-Light-Induced Oxidative [a]-Alkylation of Glycine Derivatives with Ethers under Metal-Free Conditions. *Eur. J. Org. Chem.* **2021**, *2021*, 5914−5921.
(61) Xu, L.; Xu, P.; Zhu, Y.-M.; Rao, W.; Wang, S.-Y. NaI/TBHP-promoted reaction of indole-2-thiones with arylsulfonyl hydrazides: construction of achiral axial 3, 3′-biindole-2, 2′-dibenzenesulfonothioate derivatives. *Org. Chem. Front.* **2021**, *8*, 5383−5388.
(62) Kong, L.; Hu, X.; Bai, L.-P. TBAI-catalyzed oxidative coupling of benzyl ketones to synthesize 2, 3-diaryl-1, 4-diketones in Water. *ACS omega* **2022**, *7*, 2337−2343.
(63) Herbrik, F.; Camarero González, P.; Krstic, M.; Puglisi, A.; Benaglia, M.; Sanz, M. A.; Rossi, S. Eosin Y: Homogeneous photocatalytic in-flow reactions and solid-supported catalysts for in-batch synthetic transformations. *Appl. Sci.* **2020**, *10*, 5596.
(64) Slathia, N.; Gupta, A.; Kapoor, K. K. I2/TBHP Reagent System: A Modern Paradigm for Organic Transformations. *Eur. J. Org. Chem.* **2022**, *2022*, No. e202200460.
(65) Gao, X.; Yang, H.; Cheng, C.; Jia, Q.; Gao, F.; Chen, H.; Cai, Q.; Wang, C. Iodide reagent controlled reaction pathway of iodoperoxidation of alkenes: a high regioselectivity synthesis of α- and β-iodoperoxidates under solvent-free conditions. *Green Chem.* **2018**, *20*, 2225−2230.
(66) Anusha, K.; Mahesh, M.; Shikha, S.; Rangarajan, T. M.; Pasricha, S. Langlois Reagent: An Efficient Trifluoromethylation Reagent. *SynOpen* **2023**, *7*, 65−68.
(67) Uozumi, Y.; Niimi, R. Graphene Oxide-Catalyzed Trifluoromethylation of Alkynes with Quinoxalinones. *Synfacts* **2022**, *18*, 0413.
(68) Aradi, K.; Kiss, L. Carbotrifluoromethylations of C- C Multiple Bonds (Excluding Aryl-and Alkynyltrifluoromethylations). *Chem. Eur. J.* **2023**, *29*, No. e202203499.
(69) Zhu, N.; Yao, H.; Zhang, X.; Bao, H. Metal-catalyzed asymmetric reactions enabled by organic peroxides. *Chem. Soc. Rev.* **2024**, *53*, 2326.
(70) Li, J.-Z.; Mei, L.; Yu, X.-C.; Wang, L.-T.; Cai, X.-E.; Li, T.; Wei, W.-T. C-centered radical-initiated cyclization by directed C (sp3)−H oxidative functionalization. *Org. Chem. Front.* **2022**, *9*, 5726−5757.
(71) Ryckaert, B.; Demeyere, E.; Degroote, F.; Janssens, H.; Winne, J. M. 1, 4-Dithianes: attractive C2-building blocks for the synthesis of complex molecular architectures. *Beilstein J. Org. Chem.* **2023**, *19*, 115−132.
(72) Zhu, Y. W.; Yi, W. B.; Qian, J. L.; Cai, C. Di-tert-butyl Peroxide Promoted Direct C-H Arylation of Unactivated Arenes with Aryl Halides. *ChemCatChem.* **2014**, *6*, 733−735.
(73) Kamboj, S.; Singh, R. Chromanone-A prerogative therapeutic scaffold: an overview. *Arab. J. Sci. Eng.* **2022**, *47*, 75−111.
(74) Gorbulenko, N.; Shokol, T.; Khilya, V. Chromones Modified with 7-Membered Heterocycles: Synthesis and Biological Activity. *Fr.-Ukr. J. Chem.* **2023**, *11*, 95−116.
(75) Chakraborty, K.; Francis, P. Apoptotic effect of chromanone derivative, hyrtiosone A from marine demosponge Hyrtios erectus in hepatocellular carcinoma HepG2 cells. *Bioorg. Chem.* **2021**, *114*, No. 105119.
(76) Bakherad, M.; Keivanloo, A.; Bajestani, M. A.; Rezaeifard, A. Green synthesis of chromeno [2, 3-c] pyrazoles and 4, 4′-(arylmethylene) bis (1H-pyrazole-5-ols) via catalyst-free multi-component reaction in magnetized distilled water. *S. Afr. J. Chem.* **2023**, *77*, 171−177.
(77) Wang, X.-H.; Liu, X.; Xue, Y.-W.; Wei, X.-H.; Wang, Y.-B.; Su, Q. Acid-Promoted Multicomponent Reaction To Synthesize 4-Phosphorylated 4 H-Chromenes. *J. Org. Chem.* **2024**, *89*, 8531−8536.
(78) Narayan, R.; Antonchick, A. P. Hypervalent Iodine-Mediated Selective Oxidative Functionalization of (Thio) chromones with Alkanes. *Chem. Eur. J.* **2014**, *20*, 4568−4572.
(79) Zimmerman, J. R.; Manpadi, M.; Spatney, R. Tin-free radical reactions under minimal solvent conditions for the synthesis of substituted chromones and coumarins. *Green Chem.* **2011**, *13*, 3103−3106.

https://doi.org/10.1021/acsomega.4c11574
ACS Omega 2025, 10, 15852−15907

(80) Zhao, J.; Fang, H.; Qian, P.; Han, J.; Pan, Y. Metal-free oxidative C (sp3)−H bond functionalization of alkanes and conjugate addition to chromones. *Organic lett.* **2014**, *16*, 5342−5345.
(81) Peng, H.; Yu, J.-T.; Jiang, Y.; Yang, H.; Cheng, J. Di-tert-butyl peroxide-promoted α-alkylation of α-amino carbonyl compounds by simple alkanes. *J. Org. Chem.* **2014**, *79*, 9847−9853.
(82) Zhou, W.; Qian, P.; Zhao, J.; Fang, H.; Han, J.; Pan, Y. Metal-free oxidative functionalization of C (sp3)−H bond adjacent to oxygen and radical addition to olefins. *Org. lett.* **2015**, *17*, 1160−1163.
(83) Jin, L.; Feng, J.; Lu, G.; Cai, C. Di-tert-butyl Peroxide (DTBP)-Mediated Oxidative Cross-Coupling of Isochroman and Indole Derivatives. *Adv. Synth. Catal.* **2015**, *357*, 2105−2110.
(84) Tolnai, G. L.; Székely, A.; Makó, Z.; Gáti, T.; Daru, J.; Bihari, T.; Stirling, A.; Novák, Z. Efficient direct 2, 2, 2-trifluoroethylation of indoles via C−H functionalization. *Chem. Commun.* **2015**, *51*, 4488−4491.
(85) Ni, S.; Zhang, Y.; Xie, C.; Mei, H.; Han, J.; Pan, Y. Oxidative difunctionalization of alkynoates through alkylation and migration decarboxylative arylation. *Org. lett.* **2015**, *17*, 5524−5527.
(86) Tripathi, S.; Singh, S. N.; Yadav, L. D. S. Metal-free efficient cross coupling of aromatic aldehydes with aryldiazonium tetrafluoroborates using DTBP as a radical initiator. *Tetrahedron lett.* **2015**, *56*, 4211−4214.
(87) Cano, R.; Yus, M.; Ramon, D. J. Environmentally friendly and regioselective C3-alkylation of indoles with alcohols through a hydrogen autotransfer strategy. *Tetrahedron Lett.* **2013**, *54*, 3394−3397.
(88) Cao, L.-L.; Wang, D.-S.; Jiang, G.-F.; Zhou, Y.-G. An efficient route to 2, 3-disubstituted indoles via reductive alkylation using H2 as reductant. *Tetrahedron lett.* **2011**, *52*, 2837−2839.
(89) Fukuda, T.; Mine, Y.; Iwao, M. Selective C-3 and C-2 lithiation of 1-(2, 2-diethylbutanoyl) indole. *Tetrahedron* **2001**, *57*, 975−979.
(90) Xiu, J.; Yi, W. Radical-based regioselective cross-coupling of indoles and cycloalkanes. *Catal. Sci. Technol.* **2016**, *6*, 998−1002.
(91) Pan, C.; Chen, Y.; Song, S.; Li, L.; Yu, J.-T. Metal-Free Cascade Oxidative Decarbonylative Alkylation/Arylation of Alkynoates with Alphatic Aldehydes. *J. Org. Chem.* **2016**, *81*, 12065−12069.
(92) Cheng, Z.-F.; Feng, Y.-S.; Rong, C.; Xu, T.; Wang, P.-F.; Xu, J.; Dai, J.-J.; Xu, H.-J. Directed alkynylation of unactivated C (sp3)−H bonds with ethynylbenziodoxolones mediated by DTBP. *Green Chem.* **2016**, *18*, 4185−4188.
(93) Yang, Q.; Choy, P. Y.; Wu, Y.; Fan, B.; Kwong, F. Y. Oxidative coupling between C (sp2)−H and C (sp3)−H bonds of indoles and cyclic ethers/cycloalkanes. *Org. Biomol. Chem.* **2016**, *14*, 2608−2612.
(94) Kianmehr, E.; Fardpour, M.; Khan, K. M. Direct Regioselective Alkylation of Non-Basic Heterocycles with Alcohols and Cyclic Ethers through a Dehydrogenative Cross-Coupling Reaction under Metal-Free Conditions. *Eur. J. Org. Chem.* **2017**, *2017*, 2661−2668.
(95) Li, Z.-l.; Jin, L.-k.; Cai, C. Efficient synthesis of 2-substituted azoles: radical C−H alkylation of azoles with dicumyl peroxide, methylarenes and cycloalkanes under metal-free condition. *Org. Chem. Front.* **2017**, *4*, 2039−2043.
(96) Wen, J.; Zhang, F.; Shi, W.; Lei, A. Metal-Free Direct Alkylation of Ketene Dithioacetals by Oxidative C (sp2)- H/C (sp3)- H Cross-Coupling. *Chem. Eur. J.* **2017**, *23*, 8814−8817.
(97) Wang, Q. Q.; Wang, Z. X.; Zhang, X. Y.; Fan, X. S. Microwave-promoted metal-free α-alkylation of ketones with cycloalkanes through cross-coupling of C (sp3)- H bonds. *Asian J. Org. Chem.* **2017**, *6*, 1445−1450.
(98) Li, Y.-X.; Wang, Q.-Q.; Yang, L. Metal-free decarbonylative alkylation−aminoxidation of styrene derivatives with aliphatic aldehydes and N-hydroxyphthalimide. *Org. Biomol. Chem.* **2017**, *15*, 1338−1342.
(99) Mou, Q.; Zhao, R.; Sun, B. Recent Advances in Transition-Metal-Catalyzed C- H Functionalization of Ferrocene Amides. *Chem. Asian J.* **2022**, *17*, No. e202200818.
(100) Yu, H.; Xu, Y.; Dong, R.; Fang, Y. Direct Oxidative Cross-Coupling of Toluene Derivatives and N-Acyl-2-aminoacetophenones. *Adv. Synth. Catal.* **2017**, *359*, 39−43.
(101) Hao, W.; Wang, Y.; Miao, J.; Liu, Y. Metal-Free Selective C2-H Amidation of 8-Amidoquinolines by Using Isocyanide as the Source of Amide. *ChemistrySelect* **2018**, *3*, 5194−5197.
(102) Chen, R.; Yu, J.-T.; Cheng, J. Metal-free oxidative decarbonylative alkylation of chromones using aliphatic aldehydes. *Org. Biomol. Chem.* **2018**, *16*, 3568−3571.
(103) Li, Y.-X.; Li, W.-Y.; Jiang, Y.-Y.; Yang, L. Decarbonylative radical conjugate addition of aliphatic aldehydes for alkylation of electron-deficient alkenes. *Tetrahedron Lett.* **2018**, *59*, 2934−2937.
(104) Qi, J.; Deng, Z.; Huang, B.; Cui, S. Metal-free α-alkylation of alcohols with para-quinone methides. *Org. Biomol. Chem.* **2018**, *16*, 2762−2767.
(105) Jin, S.; Xie, B.; Lin, S.; Min, C.; Deng, R.; Yan, Z. Metal-free site-specific hydroxyalkylation of imidazo [1, 2-a] pyridines with alcohols through radical reaction. *Org. lett.* **2019**, *21*, 3436−3440.
(106) Dong, Z.; Liu, Y.; Zhou, C.-W.; Huang, J.-J.; Guo, T.; Wang, Y. Direct cross-dehydrogenative coupling reactions of imidazopyridines and 1-naphthylamines with ethers under metal-free conditions. *Synth. Commun.* **2020**, *50*, 1972−1981.
(107) Wang, G.; Wang, J.-T.; Zhao, B.; Chen, H.; Zhang, P.-K.; Han, S.-L. Transition-metal-free direct cross-dehydrogenative coupling reactions of quinolinones with ethers. *Tetrahedron Lett.* **2020**, *61*, No. 151426.
(108) Wang, B.; Yao, H.; Zhong, X.; Yan, Z.; Lin, S. DTBP-promoted decarbonylative alkylation of quinoxaline-2 (1H)-ones with aldehydes. *Tetrahedron Lett.* **2021**, *64*, No. 152720.
(109) Doraghi, F.; Kianmehr, E.; Foroumadi, A. Metal-free regioselective C5-cyanoalkylation of the 8-aminoquinolineamides/sulfonamides via oxidative cross-dehydrogenative coupling with alkylnitriles. *Org. Chem. Front.* **2021**, *8*, 5424−5431.
(110) Hayakawa, M.; Shirota, H.; Hirayama, S.; Yamada, R.; Aoyama, T.; Ouchi, A. Sunlight-induced CC bond formation reaction: Radical addition of alcohols/ethers/acetals to olefins. *J. Photochem. Photobiol., A* **2021**, *413*, No. 113263.
(111) Jin, S.; Chen, F.; Qian, P.; Cheng, J. Cyanoalkylation/alkynylation of allylic alcohol through intramolecular radical 1, 2-alkynyl migration. *Org. Biomol. Chem.* **2021**, *19*, 2416−2419.
(112) Miao, P.; Li, R.; Lin, X.; Rao, L.; Sun, Z. Visible-light induced metal-free cascade Wittig/hydroalkylation reactions. *Green Chem.* **2021**, *23*, 1638−1641.
(113) Singh, S.; Dagar, N.; Raha Roy, S. Direct functionalization of quinoxalin-2 (1 H)-one with alkanes: C(sp2)−H/C(sp3)−H cross coupling in transition metal-free mode. *Org. Biomol. Chem.* **2021**, *19*, 5383−5394.
(114) Tan, X.; Zhang, J.; Liu, X.; Jin, Y. Metal-free oxidative ketonization−olefination of indoles by cross-coupling with 1, 3-dicarbonyl substrate. *Tetrahedron Lett.* **2021**, *80*, No. 153322.
(115) Zhang, J.-J.; Chen, D.; Qin, Y.-Q.; Deng, W.; Luo, Y.-Y.; Xiang, J.-N. Oxidative alkylation/alkynylation of terminal alkenes via alkylaldehyde decarbonylation and 1, 2-alkynyl migration. *Org. Biomol. Chem.* **2021**, *19*, 3154−3158.
(116) Kuninobu, Y.; Torigoe, T. Regioselective CH trifluoromethylation of heteroaromatic compounds. *Bull. Chem. Soc. Jpn.* **2021**, *94*, 532−541.
(117) Budhwan, R.; Yadav, S.; Murarka, S. Late stage functionalization of heterocycles using hypervalent iodine (III) reagents. *Org. Biomol. Chem.* **2019**, *17*, 6326−6341.
(118) Tong, Z.; Peng, X.; Tang, Z.; Yang, W.; Deng, W.; Yin, S.-F.; Kambe, N.; Qiu, R. DTBP-mediated cross-dehydrogenative coupling of 3-aryl benzofuran-2 (3H)-ones with toluenes/phenols for all-carbon quaternary centers. *RSC adv.* **2022**, *12*, 35215−35220.
(119) Gangai, S.; Fernandes, R.; Mhaske, K.; Narayan, R. Cu (ii)-catalyzed aerobic oxidative coupling of furans with indoles enables expeditious synthesis of indolyl−furans with blue fluorescence. *RSC adv.* **2024**, *14*, 1239−1249.
(120) Zhang, L. Y.; Wang, N. X.; Lucan, D.; Cheung, W.; Xing, Y. Recent Advances in Aerobic Oxidative of C- H Bond by Molecular Oxygen Focus on Heterocycles. *Chem. Eur. J.* **2023**, *29*, No. e202301700.

https://doi.org/10.1021/acsomega.4c11574
ACS Omega 2025, 10, 15852−15907

(121) Duh, Y.-S.; Kao, C.-S.; Lee, W.-L. W. Chemical kinetics on thermal decompositions of di-tert-butyl peroxide studied by calorimetry: An overview. *J. Therm. Anal. Calorim.* **2017**, *127*, 1071−1087.
(122) Dahiya, A.; Patel, B. K. The Rich Legacy and Bright Future of Transition-Metal Catalyzed Peroxide Based Radical Reactions. *Chem. Rec.* **2021**, *21*, 3589−3612.
(123) Sharma, R.; Yadav, L.; Yadav, R. K.; Chaudhary, S. Oxidative cross-dehydrogenative coupling (CDC) via C(sp2)−H bond functionalization: tert-butyl peroxybenzoate (TBPB)-promoted regioselective direct C-3 acylation/benzoylation of 2H-indazoles with aldehydes/benzyl alcohols/styrenes. *RSC adv.* **2021**, *11*, 14178−14192.
(124) He, T.; Li, H.; Li, P.; Wang, L. Direct amidation of azoles with formamides via metal-free C−H activation in the presence of tert-butyl perbenzoate. *Chem. Commun.* **2011**, *47*, 8946−8948.
(125) Li, L.-T.; Huang, J.; Li, H.-Y.; Wen, L.-J.; Wang, P.; Wang, B. nBu4NI-catalyzed C3-formylation of indoles with N-methylaniline. *Chem. Commun.* **2012**, *48*, 5187−5189.
(126) Chu, X.-Q.; Meng, H.; Zi, Y.; Xu, X.-P.; Ji, S.-J. Metal-free oxidative direct C(sp3)−H bond functionalization of ethers with α,α-diaryl allylic alcohols. *Chem. Commun.* **2014**, *50*, 9718−9721.
(127) Chu, X. Q.; Meng, H.; Zi, Y.; Xu, X. P.; Ji, S. J. Metal-Free Oxidative Radical Addition of Carbonyl Compounds to α,α-Diaryl Allylic Alcohols: Synthesis of Highly Functionalized Ketones. *Chem. Eur. J.* **2014**, *20*, 17198−17206.
(128) Cai, X.; Wei, X.; Huang, M. Recent Developments of Transition-Metal-Catalyzed Cross-Coupling of Nitriles and Alcohols. *ChemistrySelect* **2024**, *9*, No. e202402955.
(129) Song, P.; Cui, Z.; Meng, T.; Rong, H.; Mao, M.; Yang, C. A Simple Conversion of Aldoximes to Nitriles Using Thiourea Dioxide. *Asian J. Org. Chem.* **2024**, *13*, No. e202400291.
(130) Chu, X.-Q.; Meng, H.; Zi, Y.; Xu, X.-P.; Ji, S.-J. Oxidative C(sp3)−H functionalization of acetonitrile and alkanes with allylic alcohols under metal-free conditions. *Org. Chem. Front.* **2015**, *2*, 216−220.
(131) Li, Y.; Liu, B.; Li, H.-B.; Wang, Q.; Li, J.-H. Oxidative radical 1, 2-alkylarylation of alkenes with α-C(sp3)−H bonds of acetonitriles involving 1, 2-aryl migration. *Chem. Commun.* **2015**, *51*, 1024−1026.
(132) Li, Y.; Leng, Y.; Wang, S.; Gao, Y.; Lv, H.; Chang, J.; Wu, Y.; Wu, Y. Oxidative acylation of α,α-diarylallylic alcohols: Synthesis of 1, 2, 4-triarylbutane-1, 4-diones. *Appl. Organomet. Chem.* **2018**, *32*, No. e4407.
(133) Yang, Q.; Lou, M.; Yin, Z.; Deng, Z.; Ding, Q.; Peng, Y. Direct C-4 alkylation of quinazoline N-oxides with ethers via an oxidative cross-coupling reaction under metal-free conditions. *Org. Biomol. Chem.* **2018**, *16*, 8724−8731.
(134) Zhang, R.; Jin, S.; Liu, Q.; Lin, S.; Yan, Z. Transition metal-free cross-dehydrogenative coupling reaction of coumarins with acetonitrile or acetone. *J. Org. Chem.* **2018**, *83*, 13030−13035.
(135) Sun, M.-X.; Wang, Y.-F.; Xu, B.-H.; Ma, X.-Q.; Zhang, S.-J. A metal-free direct C(sp3)−H cyanation reaction with cyanobenziodoxolones. *Org. Biomol. Chem.* **2018**, *16*, 1971−1975.
(136) Joychandra Singh, S.; Ahmad Mir, B.; Patel, B. K. A TBPB-Mediated C-3 Cycloalkylation and Formamidation of 4-Arylcoumarin. *Eur. J. Org. Chem.* **2018**, *2018*, 1026−1033.
(137) Zhao, K.; Zhang, X.-C.; Tao, J.-Y.; Wu, X.-D.; Wu, J.-X.; Li, W.-M.; Zhu, T.-H.; Loh, T.-P. Regio-and stereoselective C(sp2)−H acylation of enamides with aldehydes via transition-metal-free photoredox catalysis. *Green Chem.* **2020**, *22*, 5497−5503.
(138) Hooshmand, S. E.; Alavioon, S. I.; Saeb, M.; Brahmachari, G.; Shiri, M. Decarboxylation and cross-coupling reactions of coumarin-3-carboxylic acid: a comprehensive review. *Tetrahedron* **2024**, *167*, No. 134238.
(139) Rahaman, A.; Chauhan, S. S.; Bhadra, S. Recent advances in catalytic decarboxylative transformations of carboxylic acid groups attached to a non-aromatic sp2 or sp carbon. *Org. Biomol. Chem.* **2023**, *21*, 5691−5724.
(140) Patel, D. J.; Patel, P. P.; Chikhalia, K. H. Recent Advances in the Decarboxylative Strategy of Coumarin-3-carboxylic Acid. *ChemistrySelect* **2023**, *8*, No. e202301755.
(141) Yu, Y.; Zhuang, S.; Liu, P.; Sun, P. Cyanomethylation and cyclization of aryl alkynoates with acetonitrile under transition-metal-free conditions: Synthesis of 3-cyanomethylated coumarins. *J. Org. Chem.* **2016**, *81*, 11489−11495.
(142) Batra, A.; Singh, K. N. Recent Developments in Transition Metal-Free Cross-Dehydrogenative Coupling Reactions for C−C Bond Formation. *Eur. J. Org. Chem.* **2020**, *2020*, 6676−6703.
(143) Fang, H.; Zhao, J.; Ni, S.; Mei, H.; Han, J.; Pan, Y. Metal-free oxidative functionalization of a C(sp3)−H bond adjacent to nitrogen and intramolecular aromatic cyclization for the preparation of 6-amidophenanthridines. *J. Org. Chem.* **2015**, *80*, 3151−3158.
(144) Wang, K.; Meng, L.-G.; Wang, L. Visible-light-initiated Na2-Eosin Y catalyzed highly regio-and stereoselective difunctionalization of alkynes with alkyl bromides. *J. Org. Chem.* **2016**, *81*, 7080−7087.
(145) Reyes, P.; D'hooge, D. R.; Cardon, L.; Cornillie, P. From identifying polymeric resins to corrosion casting applications. *J. Appl. Polym. Sci.* **2022**, *139*, No. 52284.
(146) Sha, W.; Yu, J.-T.; Jiang, Y.; Yang, H.; Cheng, J. The benzoyl peroxide-promoted functionalization of simple alkanes with 2-aryl phenyl isonitrile. *Chem. Commun.* **2014**, *50*, 9179−9181.
(147) Zheng, Z.; Dian, L.; Yuan, Y.; Zhang-Negrerie, D.; Du, Y.; Zhao, K. PhI (OAc)2-Mediated Intramolecular Oxidative Aryl-Aldehyde C Sp2−C Sp2 Bond Formation: Metal-Free Synthesis of Acridone Derivatives. *J. Org. Chem.* **2014**, *79*, 7451−7458.
(148) Han, C.; Dang, Y.; Mo, L.; Zhao, R.; Wang, Z.; Zhao, J. Approach to Seven-Membered Carbocycles via a Lewis Acid Catalyzed Intramolecular Michael Addition of Allenone. *Org. Lett.* **2023**, *25*, 4923−4927.
(149) Ahn, J. H.; Shin, M. S.; Jung, S. H.; Kang, S. K.; Kim, K. R.; Rhee, S. D.; Jung, W. H.; Yang, S. D.; Kim, S. J.; Woo, J. R.; et al. Indenone derivatives: a novel template for peroxisome proliferator-activated receptor γ (PPARγ) agonists. *J. Med. Chem.* **2006**, *49*, 4781−4784.
(150) Anstead, G. M.; Wilson, S. R.; Katzenellenbogen, J. A. 2-Arylindenes and 2-arylindenones: molecular structures and considerations in the binding orientation of unsymmetrical nonsteroidal ligands to the estrogen receptor. *J. Med. Chem.* **1989**, *32*, 2163−2171.
(151) Morrell, A.; Placzek, M.; Parmley, S.; Grella, B.; Antony, S.; Pommier, Y.; Cushman, M. Optimization of the indenone ring of indenoisoquinoline topoisomerase I inhibitors. *J. Med. Chem.* **2007**, *50*, 4388−4404.
(152) Jafarpour, F.; Azizzade, M.; Golpazir-Sorkheh, Y.; Navid, H.; Rajai-Daryasarei, S. Divergent synthesis of α-aroyloxy ketones and indenones: a controlled domino radical reaction for di-and trifunctionalization of alkynes. *J. Org. Chem.* **2020**, *85*, 8287−8294.
(153) Chen, S.; Yu, J.; Jiang, Y.; Chen, F.; Cheng, J. Rhodium-catalyzed direct annulation of aldehydes with alkynes leading to indenones: proceeding through in situ directing group formation and removal. *Org. lett.* **2013**, *15*, 4754−4757.
(154) Fatma, S.; Ahmad, F.; Pankhade, Y. A.; Ranga, P. K.; Vijaya Anand, R. A HMPA−H2O mediated oxygenative carbocyclization of 2-alkynylphenyl-substituted p-quinone methides to indenones. *Org. Biomol. Chem.* **2024**, *22*, 5891−5896.
(155) Li, B. J.; Wang, H. Y.; Zhu, Q. L.; Shi, Z. J. Rhodium/copper-catalyzed annulation of benzimides with internal alkynes: indenone synthesis through sequential CH and CN cleavage. *Angew. Chem. (International ed. in English)* **2012**, *51*, 3948−3952.
(156) Liu, C. C.; Korivi, R. P.; Cheng, C. H. Cobalt-Catalyzed Regioselective Synthesis of Indenamine from o-Iodobenzaldimine and Alkyne: Intriguing Difference to the Nickel-Catalyzed Reaction. *Chem. Eur. J.* **2008**, *14*, 9503−9506.
(157) Miura, T.; Murakami, M. Rhodium-catalyzed annulation reactions of 2-cyanophenylboronic acid with alkynes and strained alkenes. *Org. Lett.* **2005**, *7*, 3339−3341.
(158) Pletnev, A. A.; Tian, Q.; Larock, R. C. Carbopalladation of nitriles: synthesis of 2, 3-diarylindenones and polycyclic aromatic

https://doi.org/10.1021/acsomega.4c11574
ACS Omega 2025, 10, 15852−15907

ketones by the Pd-catalyzed annulation of alkynes and bicyclic alkenes by 2-iodoarenenitriles. *J. Org. Chem.* **2002**, *67*, 9276−9287.
(159) Qi, Z.; Wang, M.; Li, X. Access to indenones by rhodium (III)-catalyzed C−H annulation of arylnitrones with internal alkynes. *Org. lett.* **2013**, *15*, 5440−5443.
(160) Tsukamoto, H.; Kondo, Y. Palladium (II)-catalyzed annulation of alkynes with ortho-ester-containing phenylboronic acids. *Org. lett.* **2007**, *9*, 4227−4230.
(161) Pan, C.; Huang, B.; Hu, W.; Feng, X.; Yu, J.-T. Metal-free radical oxidative annulation of ynones with alkanes to access indenones. *J. Org. Chem.* **2016**, *81*, 2087−2093.
(162) Peterson, K. E.; Cinelli, M. A.; Morrell, A. E.; Mehta, A.; Dexheimer, T. S.; Agama, K.; Antony, S.; Pommier, Y.; Cushman, M. Alcohol-, diol-, and carbohydrate-substituted indenoisoquinolines as topoisomerase I inhibitors: investigating the relationships involving stereochemistry, hydrogen bonding, and biological activity. *J. Med. Chem.* **2011**, *54*, 4937−4953.
(163) Trotter, B. W.; Nanda, K. K.; Kett, N. R.; Regan, C. P.; Lynch, J. J.; Stump, G. L.; Kiss, L.; Wang, J.; Spencer, R. H.; Kane, S. A.; et al. Design and synthesis of novel isoquinoline-3-nitriles as orally bioavailable Kv1. 5 antagonists for the treatment of atrial fibrillation. *J. Med. Chem.* **2006**, *49*, 6954−6957.
(164) Ukita, T.; Nakamura, Y.; Kubo, A.; Yamamoto, Y.; Moritani, Y.; Saruta, K.; Higashijima, T.; Kotera, J.; Takagi, M.; Kikkawa, K.; et al. Novel, potent, and selective phosphodiesterase 5 inhibitors: synthesis and biological activities of a series of 4-aryl-1-isoquinolinone derivatives. *J. Med. Chem.* **2001**, *44*, 2204−2218.
(165) Garcia Maza, L. J.; Salgado, A. M.; Kouznetsov, V. V.; Melendez, C. M. Pyrrolo [2, 1-a] isoquinoline scaffolds for developing anti-cancer agents. *RSC Adv.* **2024**, *14* (3), 1710−1728.
(166) Fu, R.; Xu, X.; Dang, Q.; Bai, X. Synthesis of Novel Tricyclic Pyrimido [4, 5-b][1, 4] benzothiazepines via Bischler- Napieralski-Type Reactions. *J. Org. Chem.* **2005**, *70*, 10810−10816.
(167) Kotha, S.; Deodhar, D.; Khedkar, P. Diversity-oriented synthesis of medicinally important 1, 2, 3, 4-tetrahydroisoquinoline-3-carboxylic acid (Tic) derivatives and higher analogs. *Org. Biomol. Chem.* **2014**, *12*, 9054−9091.
(168) Zein, A. L.; Valluru, G.; Georghiou, P. E. Recent asymmetric syntheses of tetrahydroisoquinolines using "named" and some other newer methods. *Stud. Nat. Prod. Chem.* **2012**, *38*, 53−80.
(169) Yang, X.; Miao, X.; Dai, L.; Guo, X.; Jenis, J.; Zhang, J.; Shang, X. Isolation, biological activity, and synthesis of isoquinoline alkaloids. *Nat. Prod. Rep.* **2024**, *41*, 1652−1722.
(170) Xue, D.; Xue, Y.; Yu, H.; Shao, L. Metal-Free Radical Cyclization of Vinyl Isocyanides with Alkanes: Synthesis of 1-Alkylisoquinolines. *Synthesis* **2019**, *51*, 874−884.
(171) Ji, L.; Deng, Q.; Liu, P.; Sun, P. BPO-promoted direct oxidative C−H functionalization of unactivated alkanes into 6-alkyl-6H-benzo [c] chromenes under transition-metal-free conditions. *Org. Biomol. Chem.* **2019**, *17*, 7715−7722.
(172) Liu, S.; Klussmann, M. Acid promoted radical-chain difunctionalization of styrenes with stabilized radicals and (N, O)-nucleophiles. *Chem. Commun.* **2020**, *56*, 1557−1560.
(173) Sun, K.; Li, G.; Li, Y.; Yu, J.; Zhao, Q.; Zhang, Z.; Zhang, G. Oxidative Radical Relay Functionalization for the Synthesis of Benzimidazo [2, 1-a] iso-quinolin-6 (5H)-ones. *Adv. Synth. Catal.* **2020**, *362*, 1947−1954.
(174) Wang, J.; Wu, X.; Cao, Z.; Zhang, X.; Wang, X.; Li, J.; Zhu, C. E-Selective Radical Difunctionalization of Unactivated Alkynes: Preparation of Functionalized Allyl Alcohols from Aliphatic Alkynes. *Adv. Sci.* **2024**, *11*, No. 2309022.
(175) Huang, M.-H.; Hao, W.-J.; Li, G.; Tu, S.-J.; Jiang, B. Recent advances in radical transformations of internal alkynes. *Chem. Commun.* **2018**, *54*, 10791−10811.
(176) Xuan, J.; Studer, A. Radical cascade cyclization of 1, n-enynes and diynes for the synthesis of carbocycles and heterocycles. *Chem. Soc. Rev.* **2017**, *46*, 4329−4346.
(177) Beaufils, F.; Dénès, F.; Becattini, B.; Renaud, P.; Schenk, K. Thiophenol-Mediated 1, 5-Hydrogen Atom Abstraction: Easy Access to Mono-and Bicyclic Compounds. *Adv. Synth. Catal.* **2005**, *347*, 1587−1594.
(178) Beaufils, F.; Dénès, F.; Renaud, P. Thiophenol-mediated hydrogen atom abstraction: an efficient tin-free procedure for the preparation of cyclopentane derivatives. *Org. lett.* **2004**, *6*, 2563−2566.
(179) Denes, F.; Beaufils, F.; Renaud, P. Preparation of five-membered rings via the translocation-cyclization of vinyl radicals. *Synlett.* **2008**, *2008*, 2389−2399.
(180) Dénès, F.; Beaufils, F.; Renaud, P. Thiophenol-mediated 1, 5-hydrogen transfer for the preparation of pyrrolizidines, indolizidines, and related compounds. *Org. lett.* **2007**, *9*, 4375−4378.
(181) Gloor, C. S.; Dénès, F.; Renaud, P. Hydrosulfonylation reaction with arenesulfonyl chlorides and tetrahydrofuran: conversion of terminal alkynes into cyclopentylmethyl sulfones. *Angew. Chem., Int. Ed.* **2017**, *129*, 13514−13517.
(182) Huang, L.; Ye, L.; Li, X.-H.; Li, Z.-L.; Lin, J.-S.; Liu, X.-Y. Stereoselective radical cyclization cascades triggered by addition of diverse radicals to alkynes to construct 6 (5)−6−5 fused rings. *Org. lett.* **2016**, *18*, 5284−5287.
(183) Lachia, M.; Dénès, F.; Beaufils, F.; Renaud, P. Highly Diastereoselective Formation of Spirocyclic Compounds via 1, 5-Hydrogen Transfer: A Total Synthesis of (−)-Erythrodiene. *Org. lett.* **2005**, *7*, 4103−4106.
(184) Renaud, P.; Beaufils, F.; Feray, L.; Schenk, K. Diastereoselective radical mediated hydrogen atom abstraction. *Recent Developments in Radical-Mediated Hydrogen Atom Transfer Reaction* **2003**, *43*.
(185) Kehr, G.; Erker, G. 1, 1-Carboboration. *Chem. Commun.* **2012**, *48*, 1839−1850.
(186) Krautwald, S.; Bezdek, M. J.; Chirik, P. J. Cobalt-catalyzed 1, 1-diboration of terminal alkynes: scope, mechanism, and synthetic applications. *J. Am. Chem. Soc.* **2017**, *139*, 3868−3875.
(187) Morinaga, A.; Nagao, K.; Ohmiya, H.; Sawamura, M. Synthesis of 1, 1-Diborylalkenes through a Brønsted Base Catalyzed Reaction between Terminal Alkynes and Bis (pinacolato) diboron. *Angew. Chem., Int. Ed.* **2015**, *127*, 16085−16088.
(188) Sun, Q.; Li, L.; Liu, L.; Yang, Y.; Zha, Z.; Wang, Z. Copper-catalyzed 1, 1-difunctionalization of terminal alkynes: a three-component reaction for the construction of vinyl sulfones. *Sci. China Chem.* **2019**, *62*, 904−908.
(189) Armstrong, M. K.; Lalic, G. Differential dihydrofunctionalization of terminal alkynes: synthesis of benzylic alkyl boronates through reductive three-component coupling. *JACS.* **2019**, *141*, 6173−6179.
(190) Gao, D.-W.; Gao, Y.; Shao, H.; Qiao, T.-Z.; Wang, X.; Sanchez, B. B.; Chen, J. S.; Liu, P.; Engle, K. M. Cascade CuH-catalysed conversion of alkynes into enantioenriched 1, 1-disubstituted products. *Nat. Catal.* **2020**, *3*, 23−29.
(191) Guo, J.; Wang, H.; Xing, S.; Hong, X.; Lu, Z. Cobalt-catalyzed asymmetric synthesis of gem-bis (silyl) alkanes by double hydrosilylation of aliphatic terminal alkynes. *Chem.* **2019**, *5*, 881−895.
(192) Nishino, S.; Hirano, K.; Miura, M. Cu-Catalyzed Reductive gem-Difunctionalization of Terminal Alkynes via Hydrosilylation/Hydroamination Cascade: Concise Synthesis of α-Aminosilanes. *Chem. Eur. J.* **2020**, *26*, 8725−8728.
(193) Liu, Z.; Chen, J.; Lu, H. X.; Li, X.; Gao, Y.; Coombs, J. R.; Goldfogel, M. J.; Engle, K. M. Palladium (0)-Catalyzed Directed syn-1, 2-Carboboration and-Silylation: Alkene Scope, Applications in Dearomatization, and Stereocontrol by a Chiral Auxiliary. *Angew. Chem. Int. Ed* **2019**, *58*, 17068−17073.
(194) Yang, Y.; Daniliuc, C. G.; Studer, A. 1, 1, 2-Trifunctionalization of terminal alkynes by radical addition−translocation−cyclization−trapping for the construction of highly substituted cyclopentanes. *Angew. Chem.* **2021**, *133*, 2173−2176.
(195) Yao, H.; Hu, W.; Zhang, W. Difunctionalization of alkenes and alkynes via intermolecular radical and nucleophilic additions. *Molecules* **2021**, *26*, 105.
(196) Liu, S. *Difunctionalization of Olefins by Radicals and Nucleophiles*; Universität zu Köln, 2021.

https://doi.org/10.1021/acsomega.4c11574
ACS Omega 2025, 10, 15852−15907

(197) Yu, X.-Y.; Chen, J.-R.; Xiao, W.-J. Visible light-driven radical-mediated C−C bond cleavage/functionalization in organic synthesis. *Chem. Rev.* **2021**, *121*, 506−561.
(198) Varala, R.; Seema, V.; Hussein, M.; Alam, M. M.; Beda, D. P. tert-Butyl Hydroperoxide (TBHP): Recent Progress in C-H Functionalization and Heteroatom-Heteroatom Bond Formations. *ChemistrySelect* **2024**, *9*, No. e202401937.
(199) Ramani, A.; Desai, B.; Patel, M.; Naveen, T. Recent advances in the functionalization of terminal and internal alkynes. *Asian J. Org. Chem.* **2022**, *11*, No. e202200047.
(200) Chimenti, F.; Bizzarri, B.; Bolasco, A.; Secci, D.; Chimenti, P.; Granese, A.; Carradori, S.; Rivanera, D.; Zicari, A.; Scaltrito, M. M.; et al. Synthesis, selective anti-Helicobacter pylori activity, and cytotoxicity of novel N-substituted-2-oxo-2H-1-benzopyran-3-carboxamides. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 4922−4926.
(201) Lyu, H.-W.; Liang, H.-M.; Zhu, M.; Wang, H.; Li, X. Research progress in biosynthesis-related enzymes of coumarin compounds and their bioactivities. *China Journal of Chinese Materia Medica* **2024**, *49*, 3693−3705.
(202) Medina, F. G.; Marrero, J. G.; Macias-Alonso, M.; Gonzalez, M. C.; Cordova-Guerrero, I.; Teissier Garcia, A. G.; Osegueda-Robles, S. Coumarin heterocyclic derivatives: chemical synthesis and biological activity. *Nat. Prod. Rep.* **2015**, *32*, 1472−1507.
(203) Srikrishna, D.; Godugu, C.; Dubey, P. K. A review on pharmacological properties of coumarins. *Mini reviews in Med. Chem.* **2018**, *18*, 113−141.
(204) Kostova, I.; Bhatia, S.; Grigorov, P.; Balkansky, S.; Parmar, V.; Prasad, A.; Saso, L. Coumarins as antioxidants. *Curr. Med. Chem.* **2011**, *18*, 3929−3951.
(205) Pan, C.; Chen, R.; Shao, W.; Yu, J.-T. Metal-free radical addition/cyclization of alkynoates with xanthates towards 3-(ß-carbonyl) coumarins. *Org. Biomol. Chem.* **2016**, *14*, 9033−9039.
(206) Pérez, V. M.; Fregoso-López, D.; Miranda, L. D. Xanthate-based microwave-assisted CH radical functionalization of caffeine, 1, 3-dimethyluracil, and imidazo [1, 2-a] pyridines. *Tetrahedron Lett.* **2017**, *58*, 1326−1329.
(207) Bromer, W.; Egge, H.; Eiter, K.; Eyjólfsson, R.; Gross, D.; Hikino, H.; Hikino, Y.; Jackson, B.; Morin, R.; Pike, J. *Fortschritte der Chemie organischer Naturstoffe/Progress in the Chemistry of Organic Natural Products*; Springer Science & Business Media: 2012; Vol. *28*.
(208) Huang, Q.; Zard, S. Z. Inexpensive radical methylation and related alkylations of heteroarenes. *Org. lett.* **2018**, *20*, 1413−1416.
(209) Zhang, C.; Pi, J.; Wang, L.; Liu, P.; Sun, P. Silyl radical initiated radical cascade addition/cyclization: synthesis of silyl functionalized 4 H-pyrido [4, 3, 2-gh] phenanthridin-5 (6H)-ones. *Org. Biomol. Chem.* **2018**, *16*, 9223−9229.
(210) Chen, X.; Zard, S. Z. Convergent Route to ß-Amino Acids and to ß-Heteroarylethylamines: An Unexpected Vinylation Reaction. *Org. let.* **2020**, *22*, 3628−3632.
(211) Bertho, S.; Dondasse, I.; Retailleau, P.; Nicolas, C.; Gillaizeau, I. ß-C (sp2)−H alkylation of enamides using xanthate chemistry. *New J. Chem.* **2020**, *44*, 7129−7141.
(212) Kubo, T.; Chatani, N. Dicumyl peroxide as a methylating reagent in the Ni-catalyzed methylation of ortho C−H bonds in aromatic amides. *Org. lett.* **2016**, *18*, 1698−1701.
(213) Zhang, H.; Pan, C.; Jin, N.; Gu, Z.; Hu, H.; Zhu, C. Metal-free cascade construction of C−C bonds by activation of inert C(sp3)−H bonds. *Chem. Commun.* **2015**, *51*, 1320−1322.
(214) Wan, L.; Qiao, K.; Sun, X.; Di, Z.; Fang, Z.; Li, Z.; Guo, K. Benzylation of heterocyclic N-oxides via direct oxidative cross-dehydrogenative coupling with toluene derivatives. *New J. Chem.* **2016**, *40*, 10227−10232.

https://doi.org/10.1021/acsomega.4c11574
ACS Omega 2025, 10, 15852−15907