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From carboxylic acids or their derivatives to amines and ethers: modern decarboxylative approaches for sustainable C–N and C–O bond formation

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Amines and ethers represent essential structural motifs in pharmaceuticals, natural products, organic materials, and catalytic systems. The development of novel, environmentally friendly, and cost-effective strategies for constructing C–N and C–O bonds is therefore of significant importance for the synthesis of these compounds. In recent years, carboxylic acids and their derivatives have emerged as attractive, inexpensive, non-toxic, and readily available synthetic building blocks, serving as promising alternatives to aryl halides. Growing evidence has demonstrated that decarboxylative amination and etherification of carboxylic acid derivatives offer a powerful approach for the synthesis of amines and ethers. These transformations proceed *via* three principal mechanistic pathways, each offering high atom economy. Specifically, carbanions (or organometallic species) generated through heterolytic decarboxylation can react with suitable electrophiles to form C–heteroatom bonds. In contrast, carbon-centred radicals produced through homolytic decarboxylation can couple with heteroatom-based reagents *via* radical recombination or oxidative trapping. Additionally, carbocations are typically formed *via* electrochemical oxidation of carboxylic acids: oxidative decarboxylation first yields a carbon radical, which is then further oxidized at the anode to generate a carbocation. This highly electrophilic intermediate can subsequently be intercepted by heteroatom nucleophiles to construct C–N or C–O bonds. This review highlights recent advances in the field, with a focus on transition metal catalysis, photoredox catalysis, and electrochemical methods for decarboxylative amination and etherification.

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1. Introduction

The formation of C–N and C–O bonds lies at the heart of constructing amines and ethers, which are integral to a broad spectrum of fields, including pharmaceutical sciences, natural product synthesis, organic functional materials, and catalysis.[1] These structural motifs often constitute key reactive centres or biologically active sites, underpinning the widespread utility of aromatic amines and ethers in both academic and industrial applications.[2] As a result, the development of efficient and versatile methods for the synthesis of amines and ethers continues to be a central and rapidly evolving area of research.

Over the past decade, a variety of synthetic strategies have been established for the efficient construction of amines and ethers through the incorporation of nitrogen and oxygen atoms into organic frameworks. Notable examples include the Buchwald–Hartwig amination,[3] Ullmann coupling,[4] and Chan–Lam coupling reactions.[5] These seminal developments have significantly enriched the field, offering valuable insights and guiding principles for the formation of C–N and C–O bonds. However, several intrinsic limitations persist, such as the reliance on stoichiometric copper reagents, elevated reaction temperatures, complex phosphine ligands, and limited substrate scope. Consequently, considerable research attention has shifted toward the development of milder, more economical catalytic systems that promote C–N and C–O bond formation with improved atom and step economy.

Carboxylic acids and their derivatives are widely recognized as valuable starting materials in organic synthesis owing to their stability, broad availability, and low cost.[6] A diverse array of structurally complex carboxylic acids can be readily synthesized through well-established methodologies.[7] Consequently, these compounds have emerged as attractive alternatives to aryl halides for the construction of C–X (X = C, N, O, S, and P) bonds in a more cost-effective manner.[8] Reflecting these advantages, several research groups have

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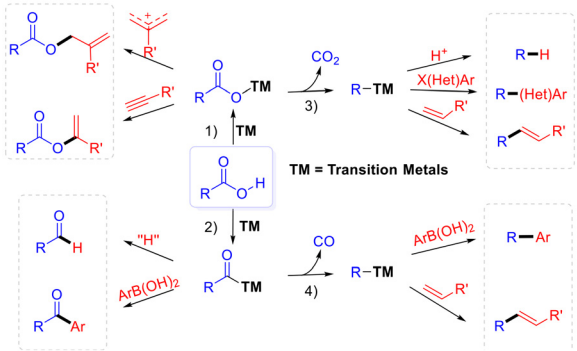
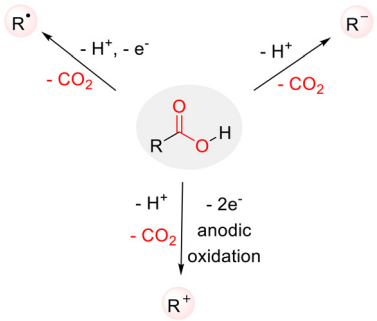
explored the use of carboxylic acids in the synthesis of heteroatom-containing molecules.[9] From a mechanistic perspective, the reactivity of carboxylic acids is largely governed by the two oxygen atoms in the carboxyl group—the carbonyl and hydroxyl functionalities. Under basic conditions, deprotonation of the carboxylic acid yields the corresponding carboxylate anion, whereas acidic conditions facilitate substitution at the hydroxy position.[10]

Building upon the intrinsic reactivity of carboxylic acids, their use has been extended to transition-metal-catalyzed transformations, enabling selective bond activation and functional manipulation. Four key types of reactions have emerged based on the polarity and reactive sites of the carboxylic acid moiety (Scheme 1): (1) cleavage of the O–H bond, leading to carboxylate formation;[11] (2) transition-metal insertion into the C–O bond to form acyl–metal complexes;[12] (3) decarboxylative transformations involving the release of CO_2;[13] and (4) decarbonylative transformations involving the extrusion of CO.[14] These transformations demonstrate how the functional diversity of carboxylic acids can be expanded *via* transition metal catalysis, providing access to selective bond activations and new synthetic pathways, particularly in the context of decarboxylative transformations.[15]

Among these, the decarboxylation of carboxylic acids is particularly versatile and mechanistically intriguing, as it can proceed through three primary pathways (Scheme 2).[16] First, deprotonation of the C–COOH group, followed by decarboxylation, can generate carbanions (or organometallic intermediates). Second, homolytic cleavage of the carboxyl group can produce carbon-centred radicals. Third, oxidative decarboxylation under electrochemical conditions, followed by anodic oxidation, can generate carbocations. In recent decades, decarboxylation of carboxylic acids has significantly contributed to organic synthesis by enabling the incorporation of various heteroatoms, particularly nitrogen and oxygen, into organic frameworks.[17]



Scheme 1 Four common reaction types of carboxylic acids.



Scheme 2 Three possible mechanisms for the decarboxylative process of carboxylic acids.

This review primarily focuses on recent methodologies for the construction of C–N and C–O bonds *via* decarboxylation, which can be broadly categorized into four main approaches: (1) transition-metal-catalyzed decarboxylative amination and alkoxylation; (2) photoredox-catalyzed or -induced decarboxylative amination and alkoxylation, which harness light to drive

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these transformations; (3) electrochemically induced decarboxylative amination and alkoxylation, which employ electrolysis as a green and sustainable tool to promote carboxylate umpolung and subsequent bond formation; and (4) transition-metal-free decarboxylative amination and alkoxylation, which often rely on azide compounds or other structurally unique nucleophiles that undergo rearrangement to furnish amines and ethers under mild and environmentally benign conditions. Each of these approaches offers distinct advantages in terms of reactivity, selectivity, and sustainability, making them valuable strategies for the next generation of C–N and C–O bond-forming reactions.

2. Decarboxylative amination

Amines are indispensable building blocks in chemistry due to their broad bioactivity and widespread applications in pharmaceuticals, materials science, and agrochemicals.[18] Despite their importance, the formation of C–N bonds has posed long-standing challenges, largely due to the difficulty of reductive elimination from carbon–metal species and the competing β-hydride elimination. In the early 20th century, ground-breaking contributions by Ullmann,[19] Goldberg,[20] Buchwald,[21] and Hartwig[22] revolutionized the synthesis of aryl amines. These researchers developed methodologies that employed aryl halides and nucleophilic amines as substrates, with copper or palladium catalysts facilitating C–N bond formation. These transformations enabled the selective and efficient synthesis of aromatic amines, marking a significant advancement in synthetic organic chemistry.[23]

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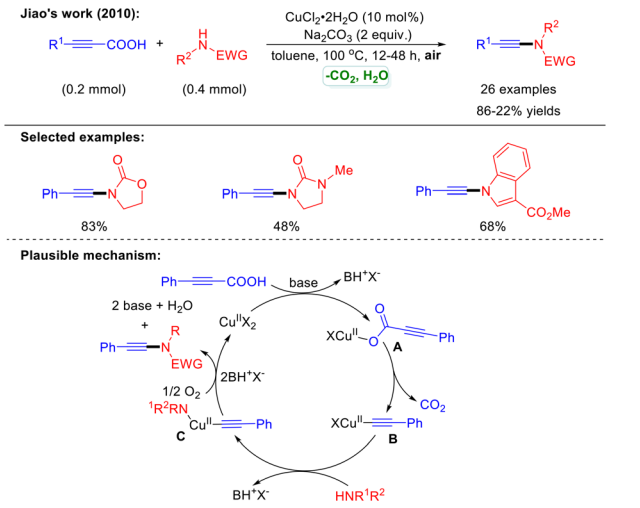
Yasushi Nishihara received his B.S. degree from Hiroshima University in 1992. From 1993 to 1994, he conducted research as a research associate at the University of Notre Dame, USA. He earned his Ph.D. in 1997 from the Graduate University for Advanced Studies (SOKENDAI) under the supervision of Prof. Dr Tamotsu Takahashi. In 1996, he was appointed as an assistant professor at the Tokyo Institute of Technology, and in 2004, he joined Okayama University as an associate professor. He was promoted to full professor in 2010 and has been serving as a professor at the Research Institute for Interdisciplinary Science, Okayama University since 2016. His current research interests include the development of nickel- and palladium-catalyzed decarbonylative transformations of acyl fluorides, as well as the efficient and selective synthesis of π-conjugated organic molecules for use in functional materials such as organic field-effect transistors and organic photovoltaics.

However, these classical methods are not without limitations. The Ullmann–Goldberg reaction typically requires stoichiometric amounts of copper compounds, posing challenges for cost and scalability.[24] Similarly, Buchwald–Hartwig coupling often depends on bulky and expensive phosphine ligands, which may reduce atom economy and complicate large-scale applications.[25] These drawbacks underscore the need for more sustainable, cost-effective, and environmentally friendly strategies for the synthesis of aryl amines.[26] As a result, ongoing research efforts continue to focus on lowering catalyst loadings, reducing waste generation, and developing alternative catalytic systems that promote greener and more scalable processes.

2.1 Transition-metal-catalyzed decarboxylative amination

2.1.1 Cu-catalyzed decarboxylative amination. The first example of copper-catalyzed decarboxylative amination of carboxylic acids was reported by Jiao and co-workers, who employed a variety of substituted propiolic acids under aerobic conditions to synthesize a series of alkynylamines, thereby efficiently constructing C(sp)–N bonds (Scheme 3, top).[27] This pioneering strategy laid the groundwork for the development of decarboxylative amination and has since served as a valuable inspiration for the synthesis of other C–N bond-containing compounds. The authors proposed a plausible reaction mechanism (Scheme 3, bottom), beginning with the formation of a Cu(II) species **A** through deprotonation in the presence of a base. This is followed by decarboxylation to afford intermediate **B**, which subsequently undergoes nucleophilic attack by the amine to generate Cu(II) species **C**. Finally, reductive elimination, facilitated by an external oxidant, furnishes the desired alkynylamine products. Despite the innovation of this approach, a notable limitation is the requirement for strong electron-withdrawing groups on the amine substrates to promote the reaction. While this method represents a breakthrough, it also highlights the need for further optimization to



Scheme 3 Decarboxylative amination of substituted propiolic acid.

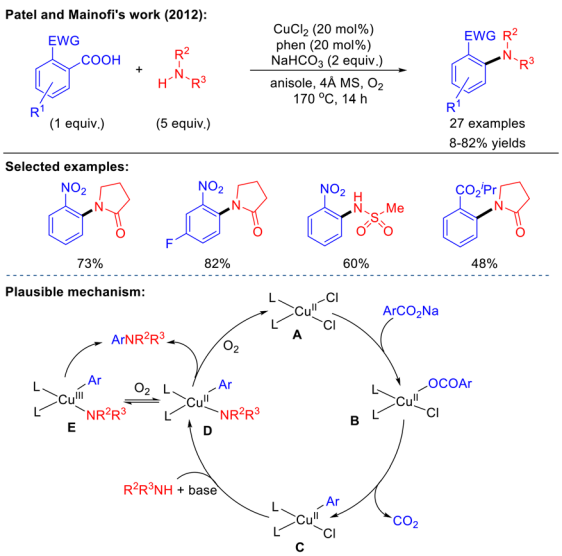
broaden the substrate scope and improve functional-group tolerance.

In 2012, Mainolfi, Patel, and their co-workers reported a notable example of decarboxylative C(sp^2)–N cross-coupling (Scheme 4, top).[28] They investigated the model reaction between 2-nitrobenzoic acid and 2-pyrrolidinone, optimizing a variety of copper catalysts, ligands, solvents, and oxidants. Their findings revealed that polar solvents, such as NMP and DMSO, can hinder the amination step, potentially affecting the interaction with the aryl metal centre. The reaction demonstrated good tolerance for both electron-donating and electron-withdrawing groups on the substrates. Furthermore, *N*-nucleophiles, including cyclic amides, acyclic amides, cyclic ureas, and sulfonamides, were successfully incorporated, yielding moderate results. The authors also proposed a plausible mechanism for this transformation (Scheme 4, bottom): following a decarboxylation and amination sequence, intermediate **D** is formed, and the presence of oxygen may facilitate the generation of Cu(III) species **E**. This species, in turn, promotes the reductive elimination of the C–N bond to yield the desired product.

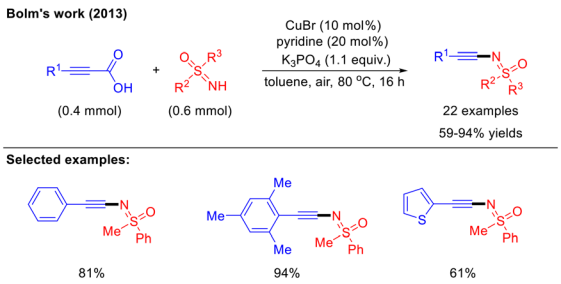
Encouraged by Jiao's work, Bolm and his co-workers developed the Cu-catalyzed oxidative decarboxylative coupling to synthesize a range of sulfoximidoyl alkynes using sulfoximines and aryl propiolic acids, achieving good to excellent yields (Scheme 5).[29] Their study demonstrated that the CuBr/pyridine catalytic system effectively suppresses side reactions, such as the Glaser–Hay reaction. Furthermore, this reaction employed an inexpensive catalytic system and utilized air as a convenient oxidant, providing a practical and sustainable protocol with water and carbon dioxide as the only by-products. This approach significantly expands the potential of decarboxylative C–N bond construction.

Although the aforementioned studies made significant progress in C–N bond formation, the scope of *N*-nucleophiles was largely restricted to specific amides, such as lactams, sulfoximines, and oxazolidin-2-ones. In 2015, Jia *et al.* reported a decarboxylative C(sp^2)–N cross-coupling of potassium 2-nitrobenzenoates with NH-containing fragments, mediated by the inexpensive $CuSO_4$ (Scheme 6).[30] Their study successfully extended decarboxylative amination to both electron-deficient and electron-donating substituents on NH-containing linkages, affording the products in moderate to high yields. Notably, anilines were also found to be compatible with the coupling of potassium 2-nitrobenzenoates, providing a cost-effective route for the synthesis of aromatic amines. This approach offered a complementary method for the efficient construction of aromatic secondary amines using readily available aniline derivatives as coupling partners.

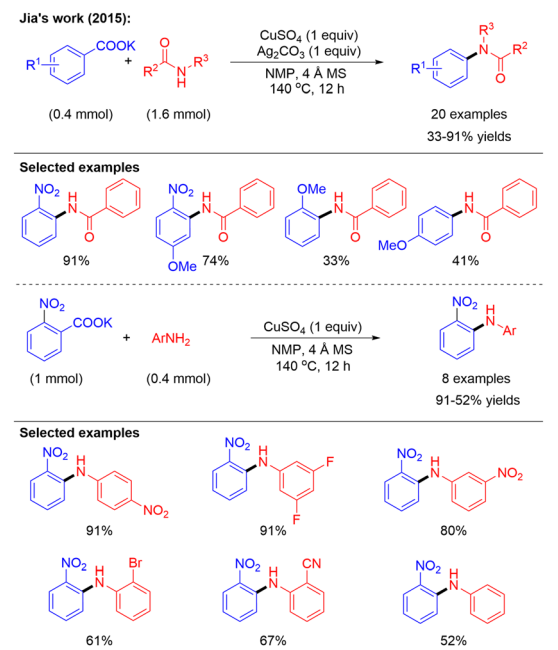
There is no doubt that the research progress outlined above provides valuable insights and a solid foundation for further breakthroughs in decarboxylative amination. However, side reactions resulting from the oxidation of amines remain a sig-



Scheme 4 Cu-catalyzed decarboxylation of aromatic carboxylic acids.



Scheme 5 Decarboxylative oxidative coupling of sulfoximines with aryl propiolic acids.

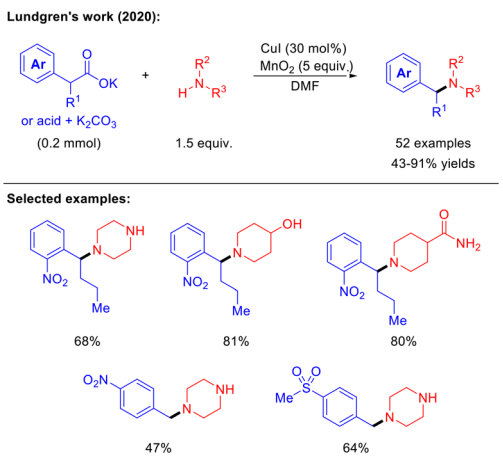


Scheme 6 Decarboxylative C–N cross-coupling of potassium benzoate with NH-containing fragments.

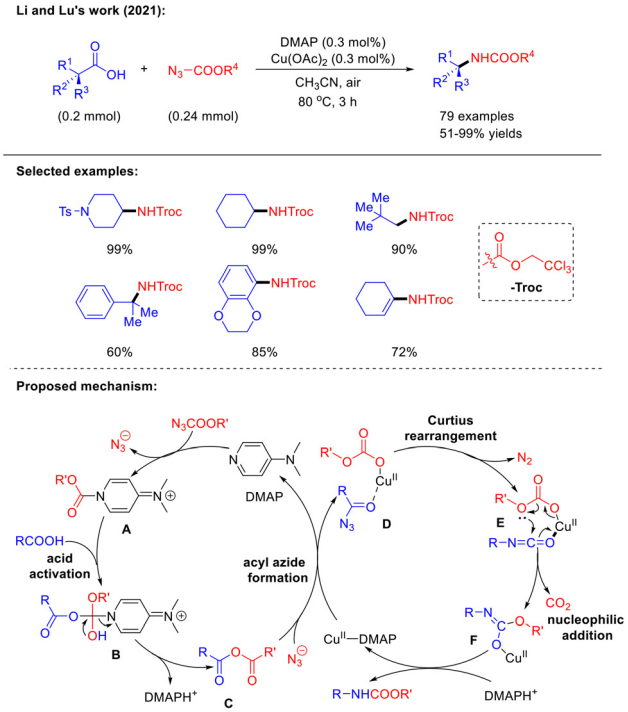
nificant concern for chemists, especially with the addition of exogenous oxidants. Notably, oxidative dimerization of anilines and oxidative decomposition of aliphatic amines are common issues. Furthermore, decarboxylative amination often requires weakly nucleophilic nitrogen partners, such as carbamates, lactams, indoles, and sulfoximines, to react with carbanions generated from decarboxylation of carboxylic acids. This requirement imposes a substantial limitation on the substrate scope of decarboxylative amination reactions.

In 2020, Lundgren and co-workers disclosed a range of primary and secondary potassium aryl acetates as effective *N*-benzylation reagents for the construction of various benzylic amines using an oxidative Cu-catalytic system (Scheme 7).[31] Notably, the native acids with the base also proved compatible with this system, although they provided the target product in relatively lower yields compared to carboxylates. Additionally, base-sensitive functional groups, such as hydroxyl and formyl groups, were tolerated, giving the products in moderate to good yields. The reaction proceeds under mild conditions, with the transformation occurring at room temperature. Mechanistic studies suggest that the process follows elementary steps similar to the Chan–Evans–Lam reaction:[26b] after the formation of a benzyl anion *via* ionic decarboxylation, the Cu catalyst captures the anion, forming a Cu(II) complex, which is then converted to a Cu(III) species through disproportionation, and the target benzylic amines are generated *via* reductive elimination.

Recently, Li, Lu, and co-workers developed a copper-catalyzed decarboxylative amination of azidoformates with a broad range of carboxylic acids, affording alkyl, alkenyl, and aryl amines in excellent yields (Scheme 8, top).[32] In this protocol, *N*,*N*-dimethylaminopyridine (DMAP) acts as a co-catalyst and nucleophilically attacks the electron-deficient azidoformates to generate an azido anion and intermediate **A**. Intermediate **A** then reacts with a carboxylic acid to form intermediate **B**, which releases $DMAPH^+$ to afford a mixed anhydride **C**. Subsequent nucleophilic attack of the azido anion on **C** furnishes the acyl azide **D**, which undergoes a Curtius rearrangement to give isocyanate intermediate **E**. Finally, decarboxylation of **E** produces intermediate **F**, which upon protonation provides the desired amine products (Scheme 8, bottom).

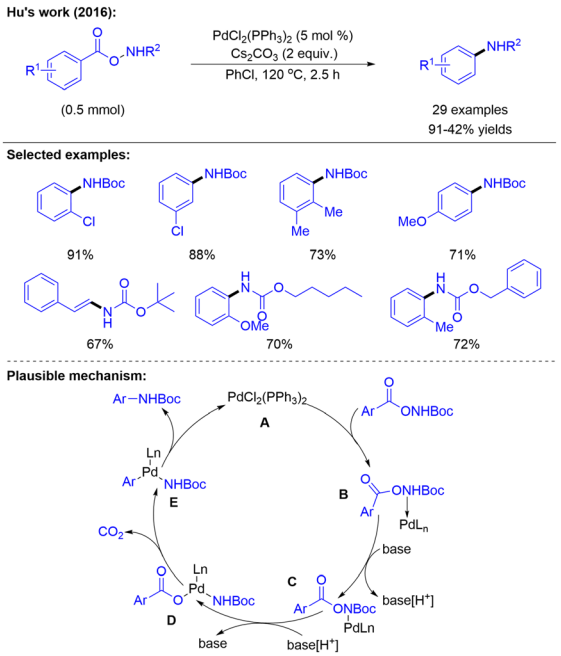


Scheme 7 Cu-catalyzed decarboxylative amination for the synthesis of various benzylic amines.



Scheme 8 Cu/DMAP-catalyzed decarboxylative amination.

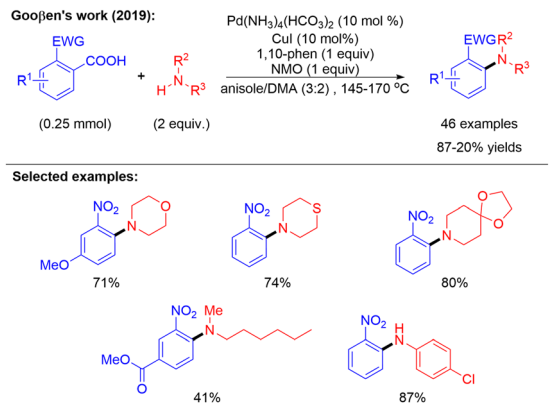
2.1.2 Pd-catalyzed decarboxylative amination. While Cu catalysis has garnered significant attention in the field of decarboxylative amination of carboxylic acids, palladium-catalyzed transformations have also been developed by researchers. However, one major challenge in these processes is the thermodynamically unfavourable reductive elimination of the C–N bond, which can be mitigated by the addition of exogenous oxidants. These oxidants facilitate the formation of high-valent transition metal intermediates, thereby significantly lowering the energy barrier of the reaction.[33] In 2016, Hu and co-workers reported a palladium-catalyzed intramolecular decarboxylative amination that successfully synthesized a series of anilines within a relatively short reaction time, eliminating the need for stoichiometric amounts of copper compounds (Scheme 9, top).[34] Moreover, their study demonstrated a broad substrate scope for intramolecular decarboxylative coupling of carboxylic acids, which was no longer limited to *ortho*-electron-withdrawing groups as directing groups, providing good regioselectivity under mild conditions. The proposed mechanism, as shown in Scheme 9, bottom, begins with the interaction between Pd species **A** and hydroxycarbamates to generate intermediate **B**. The intermediate then undergoes deprotonation and N–O bond cleavage to form the acyl carboxylate–Pd intermediate **D**. Finally, sequential decarboxylation and reductive elimination generate the desired product.



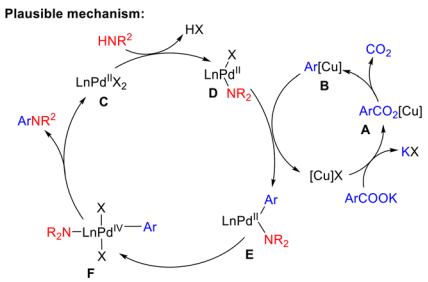
Scheme 9 Pd-catalyzed intramolecular decarboxylative amination.

2.1.3 Pd/Cu co-catalyzed decarboxylative amination. In 2019, Gooßen and colleagues developed a Pd/Cu bimetallic catalytic system for decarboxylative amination, which enabled the use of stronger *N*-nucleophiles, such as aliphatic amines, morpholine, and other simple heterocyclic amines (Scheme 10).[35] Notably, secondary cyclic amines only required an air atmosphere to achieve optimal results without the need for any additives. In contrast, the use of over-stoichiometric amounts of *N*-methylmorpholine *N*-oxide (NMO) as an oxidant was necessary for achieving the best results with primary and acyclic secondary amines.

Based on the experimental results, the authors proposed a plausible mechanism, as shown in Scheme 11. Initially, upon reaction between CuX and potassium aryl carboxylate, copper



Scheme 10 Pd/Cu co-catalyzed decarboxylative amination of aromatic carboxylic acids.



Scheme 11 Mechanism of Pd/Cu co-catalyzed decarboxylative amination.

species **A** is generated, which undergoes a decarboxylative process to form arylcopper intermediate **B**. Meanwhile, amines coordinate with the Pd catalyst **C** to form species **D**, which then undergoes transmetalation with the formed arylcopper complex **B** to generate the Pd(II) intermediate **E**. Intermediate **E** is subsequently oxidized to the Pd(IV) species **F**, followed by reductive elimination to release the desired product and regenerate the Pd catalyst **C**. This study presents a novel and efficient strategy that broadens the scope of amine substrates to encompass both aliphatic and aromatic amines, thereby enabling the formation of diverse C(sp^2)–N bonds. Electron-rich anilines are also demonstrated to be effective coupling partners.

The decarboxylative amination of carboxylic acids, as demonstrated by Jiao, Mainolfi, Jia, and Gooßen, has significantly advanced and expanded the methodologies for C–N bond construction. Despite these advancements, several challenges remain, such as the use of toxic and impractical catalytic systems, limited substrate scope, and harsh reaction conditions. Therefore, addressing these limitations and developing more cost-effective and efficient methods to synthesize a broader range of both aromatic and aliphatic amines are crucial for further progress in this field.

2.2 Photoredox-induced decarboxylative amination

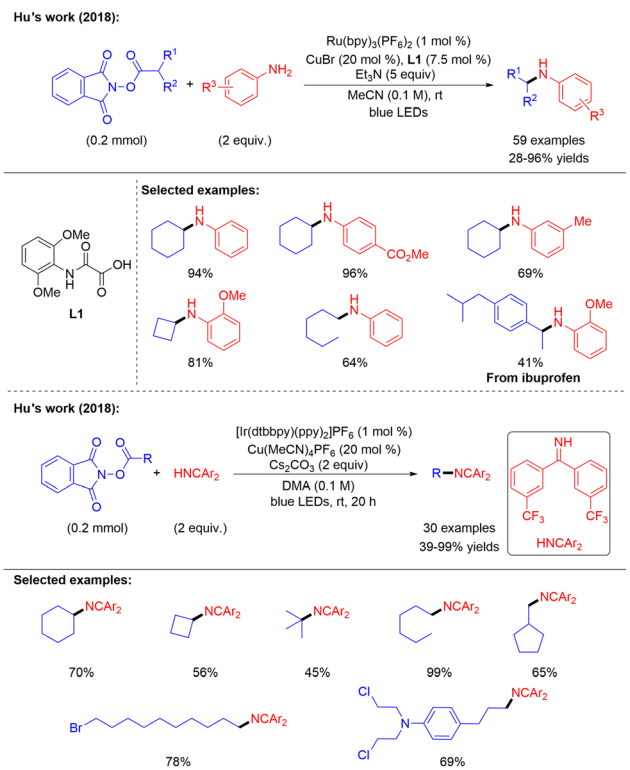
Aliphatic (hetero)carbocyclic amines are highly valued as building blocks in medicinal chemistry, materials science, and catalysis. While several decarboxylative amination methods have been developed for the construction of C(sp)–N and C(sp^2)–N bonds, the incorporation of amine functionalities into aliphatic compounds remains relatively rare.[36] This scarcity is primarily attributed to challenges such as β-H elimination, decomposition of alkyl metal complexes, and the high energy barrier associated with the reductive elimination of C(sp^3)–N bonds.[37] Consequently, the development of efficient strategies for C(sp^3)–N bond formation continues to present a significant challenge. Notably, light-induced, synergistic transition-metal-catalyzed approaches represent a promising exception for achieving this transformation.[38]

Carboxylic acids are a versatile class of compounds renowned for their commercial availability, stability, and non-toxic nature, making them highly suitable for photoredox dec-

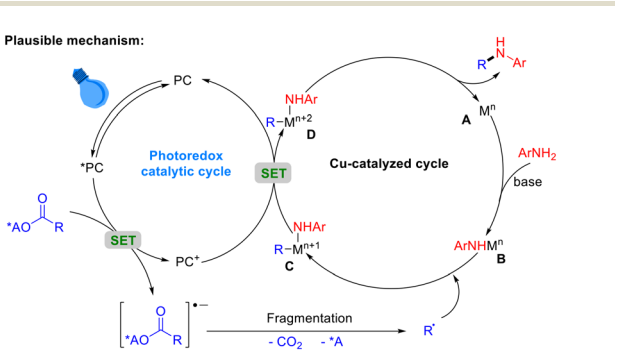
arboxylative amination, either directly or indirectly.[39] *N*-Hydroxyphthalimides (NHPIs), which can be readily synthesized from carboxylic acids, are a prototypical class of redox-active esters widely used for efficient C–N bond formation. However, the application of tertiary alkyl NHPI esters is limited due to steric hindrance and challenges associated with reductive elimination. To address these issues, benzophenone-derived imine nucleophiles have been employed, as they offer greater steric accessibility and facilitate reductive elimination more readily.[40] Building on these findings, Hu's group developed two photoredox/Cu-cocatalyzed decarboxylative couplings using either anilines or imines as nucleophiles, thereby enabling the construction of diverse C–N bonds. Notably, the method showed compatibility with primary, secondary, and even tertiary electrophilic esters. As a result, a series of substituted anilines (Scheme 12, top)[41] and benzophenone imines (Scheme 12, bottom)[42] were synthesized with high efficiency through a synergistic photoredox and Cu-catalyzed strategy. Furthermore, the authors reported a similar strategy for synthesizing amines with long alkyl chains and heterocycles, utilizing the aforementioned coupling partners, catalyzed solely by the novel photocatalyst 4CzIPN (1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene). This approach enabled a decarboxylative reaction without any ligands, significantly broadening the substrate scope to include bulky primary and secondary alkyl carboxylic acids.[43] This cost-effective and straightforward methodology has been successfully applied to the synthesis of natural products and pharmaceuticals.

The authors proposed a plausible mechanism for the photoredox/Cu cocatalyzed decarboxylative amination (Scheme 13). Initially, the photocatalyst (PC) is excited upon visible light irradiation, reducing the redox-active ester *via* a single-electron transfer (SET) process. This reduction induces the decarboxylation of the ester, generating an alkyl radical *via* fragmentation. The formed alkyl radical is then captured by a low-valent metal amido complex **B**, forming intermediate **C**, which undergoes a single-electron oxidation, regenerating the photocatalyst and yielding intermediate **D**. Finally, the desired amine product is formed through reductive elimination of intermediate **D**, which also regenerates the low-valent metal catalyst **A**. Furthermore, the proposed mechanism was studied and supplemented by Zhang's group using a density functional theory (DFT) computational study, providing additional details to clarify some ambiguous aspects of the mechanism. According to the calculations, Et_3N serves not only as the proton acceptor to generate the active copper catalyst but also as the quencher of Ru(III) species, regenerating the Ru(II) photocatalyst. Additionally, the Cu(I) catalysis is initiated by a Cu(I)-oxidation-first pathway, rather than an aniline-deprotonation-first pathway.[44]

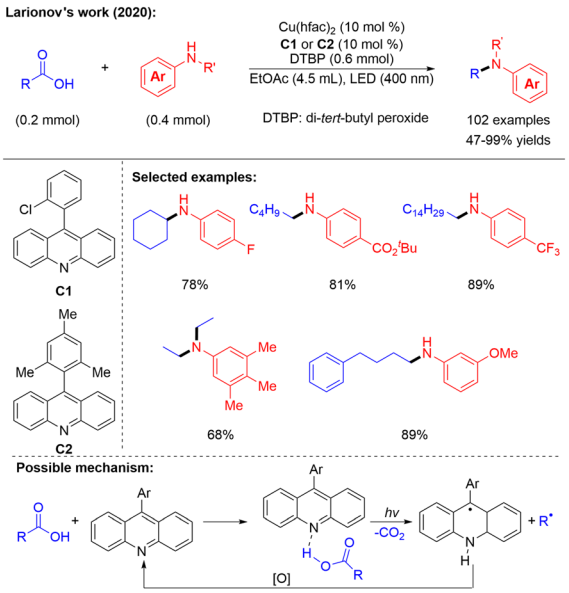
Activated carboxylic acids are commonly employed in photocatalytic systems, such as the NHPI esters reported by Hu *et al.* However, the preparation and isolation of these active carboxylic acids often require additional steps. To enable the step-economical and highly efficient construction of C(sp^3)–N bonds, Larionov and co-workers developed a direct photoinduced Cu-catalyzed decarboxylative alkylation of anilines in 2019, utilizing a distinct photoinduced proton-coupled electron transfer (PCET) mechanism (Scheme 14).[45] The authors introduced novel photocatalysts, **C1** and **C2**, capable of facilitating the decarboxylation of carboxylic acids to generate alkyl radicals *via* the PCET process upon excitation with blue LEDs. Remarkably, this reaction tolerates a variety of alkyl carboxylic acids, enabling the synthesis of *N*-alkylated secondary and tertiary anilines, N-heterocycles, and deuterated methyl aniline derivatives.



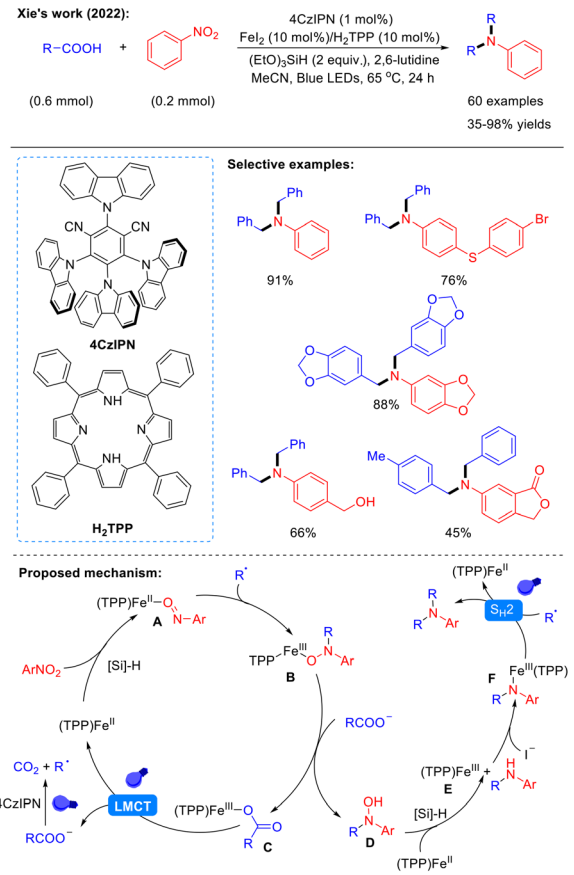
Scheme 12 Synergetic photoredox and Cu-catalyzed C(sp^3)–N decarboxylative amination.



Scheme 13 The mechanism of photoredox and transition metal-synergetic-catalyzed decarboxylative amination.



Scheme 14 Direct decarboxylative amination of aliphatic carboxylic acids.



Scheme 15 Synergetic photoredox and FeI_2-catalyzed C–N decarboxylative amination.

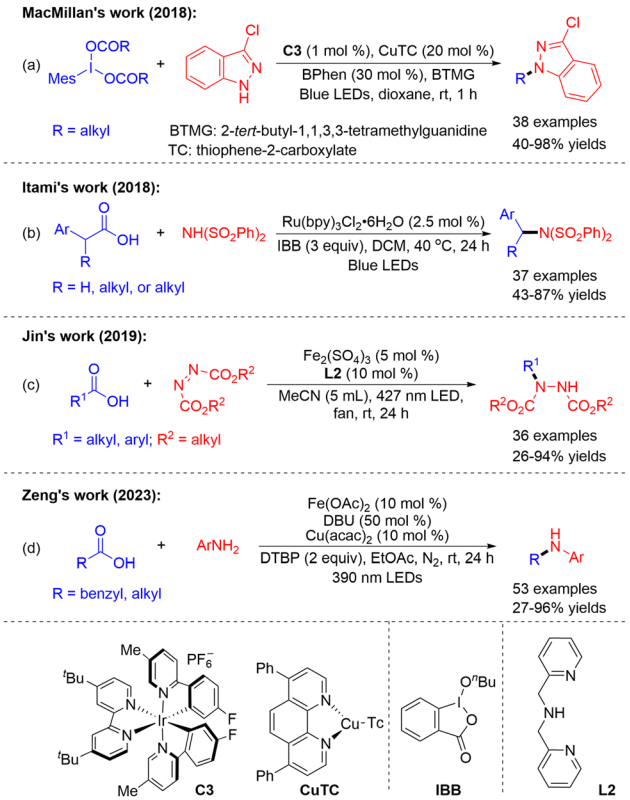
Benzylic tertiary amines are highly valuable in organic and pharmaceutical chemistry. However, transforming primary amines into tertiary amines through traditional methods is challenging due to the potential for side reactions, such as consecutive overalkylation.[46] In 2022, Xie's group reported a novel visible-light-induced Fe-catalyzed methodology to achieve this transformation, using phenylacetic acid and nitrobenzene as coupling partners (Scheme 15, top).[47] The success of this reaction represents a significant advancement in simplifying the synthesis of tertiary amines, using inexpensive nitrobenzene and achieving a wide range of tertiary amines in excellent yields. Notably, two different carboxylic acids can be introduced to efficiently produce unsymmetrical tertiary amines in acceptable yields.

Accordingly, the authors proposed a possible mechanism, as shown in Scheme 15, bottom. Initially, nitrobenzene is reduced by the (TPP)Fe(II) catalyst in the presence of $(EtO)_3SiH$, forming Fe(II) complexes **A**. Subsequently, either the visible-light-induced single-electron oxidation of the carboxylate anion or a photo-induced ligand-to-metal charge transfer (LMCT) process of the Fe-carboxylate generates an alkyl radical, which then attacks the Fe(II) complex **A** to form the Fe(III) species **B**. This intermediate **B** undergoes an anion exchange process with the carboxylate anion, leading to the formation of hydroxylamine compound **D** and Fe(III) complex **C**. Meanwhile, hydroxylamine **D** reacts with (TPP)Fe(II) to produce (TPP)Fe(III) **E** and secondary amines. In the presence of an iodide anion, Fe(III) complex **F** is generated. Finally, under blue LED irradiation, the desired product is obtained *via* a bimolecular homolytic process (S_H2). Mechanistic experiments indicate that while the photocatalyst is not crucial, it helps enhance the reaction yield. Additionally, the iodide anion of FeI_2 and the ligand play essential roles in the subsequent reduction of *N*-based intermediates.

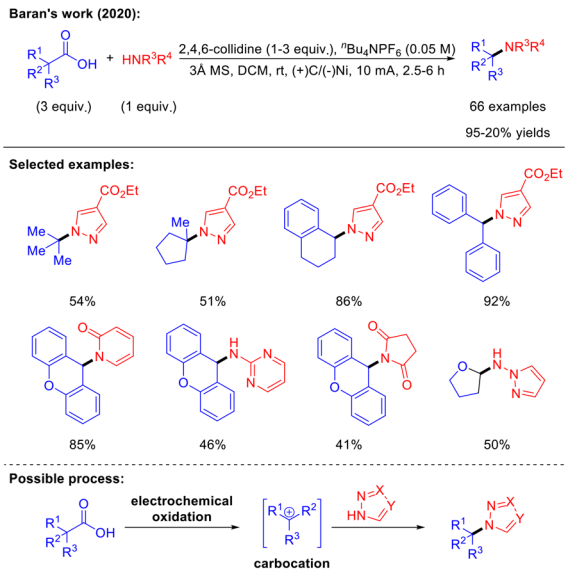
Photoredox decarboxylative coupling for constructing $C(sp^3)$–N bonds has emerged as a valuable complement to classical C–N bond-forming strategies. Several research groups, including MacMillan,[48] Itami,[49] Fu,[50] Liu,[51] Zeng,[52] and Jin,[53] have successfully employed this approach to synthesize a broad spectrum of primary, secondary, and tertiary amines (Scheme 16). However, these transformations typically rely on pre-activated carboxylic acid derivatives, such as NHPI esters or iodine(III) carboxylates, which require additional synthetic steps to prepare the requisite starting materials. Furthermore, direct decarboxylative coupling often depends on the use of oxidants to regenerate the active copper catalyst. Therefore, the development of atom- and step-economical strategies is still highly desirable for the efficient synthesis of diverse and valuable amines.

2.3 Electrochemical method for decarboxylative amination

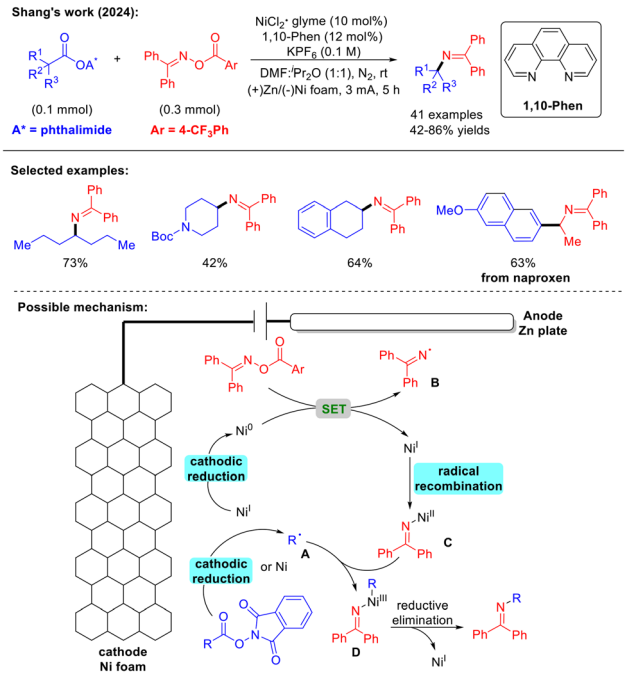
Electrochemistry has emerged as a powerful tool in organic synthesis, offering several inherent advantages such as operational simplicity, scalability, the elimination of hazardous chemical oxidants or reductants, and precise control over reaction conditions.[54] In the context of decarboxylative amination,



Scheme 16 Other studies of photoredox decarboxylative amination.



Scheme 17 Direct electrochemical decarboxylative amination.



Scheme 18 Electrochemical Ni-catalyzed decarboxylative amination of NHPI esters.

electrochemical methods facilitate the generation of carbocations or alkyl radicals from carboxylic acids, which are key intermediates for C(sp^3)–N bond formation.

Building on the classical Kolbe electrolysis approach,[55] Baran and co-workers reported an electrochemical decarboxylation method that generates carbocation intermediates through anodic oxidation of carboxylate anions derived from carboxylic acids (Scheme 17).[56] These intermediates can be intercepted by alcohols to form sterically hindered ethers. Subsequently, Wang,[57] Shi,[58] and Baran[59] extended this strategy to enable electrochemical decarboxylative amination, demonstrating its applicability to a variety of nitrogen nucleophiles, including azoles and lactams.

Recently, Shang and co-workers developed a reductive electrochemical strategy utilizing redox-active *N*-hydroxyphthalimide (NHPI) esters, which were generated *in situ* from carboxylic acids and benzophenone-based oxime esters as substrates (Scheme 18, top).[60] The authors proposed that the oxime ester is reduced by a low-valent Ni species to form an iminyl radical **B**, which then recombines with the Ni catalyst to yield intermediate **C**. Simultaneously, an alkyl radical **A** is generated either directly on the cathode surface or, to a lesser extent, *via* Ni-mediated reduction of the NHPI ester. The alkyl radical **A** is subsequently intercepted by intermediate **C**, forming intermediate **D**, which undergoes reductive elimination to afford the desired amination product (Scheme 18, bottom).

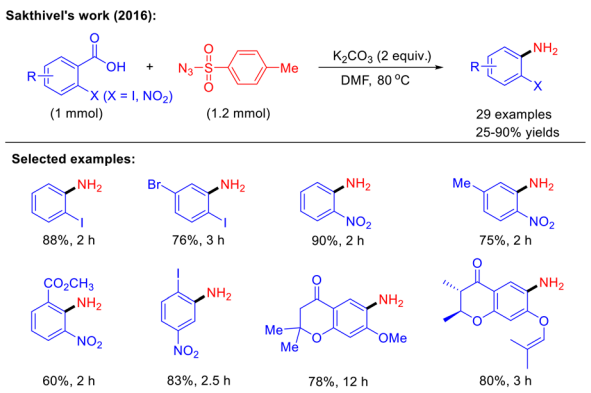
2.4 Transition-metal-free decarboxylative amination

Catalytic decarboxylation has long been recognized as a practical and versatile method for transforming carboxylic acids into valuable and structurally complex molecules.[61] However, current strategies for C–N bond formation still encounter notable challenges, including the requirement for elevated temperatures, *ortho*-substituted benzoic acids as directing groups, and high catalyst loadings (in transition-metal-cata-

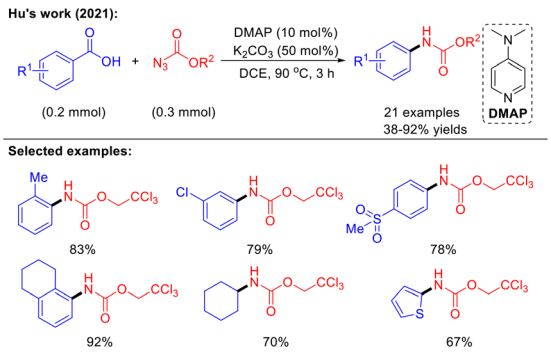
lyzed processes), the use of pre-activated acids, and the reliance on oxidants in photoredox-mediated transformations. To overcome these limitations and develop a more cost-effective and sustainable approach, transition-metal-free decarboxylation methods offer a green and economical strategy for efficient C–N bond formation. For instance, Xu's group reported a decarboxylative amidation using inexpensive α–keto acids as acyl anion equivalents to construct amides, with the reaction promoted by singlet oxygen.[62] In addition, certain nitrogen-containing reagents can engage in decarboxylative amination *via* rearrangement pathways, further expanding the synthetic utility of this approach. Sakthivel and co-workers reported a transition-metal-free decarboxylative amination for the synthesis of anilines, employing benzoic acid derivatives and tosyl azides as substrates (Scheme 19).[63] In this method, tosyl azide acts as a source of the tosyl nitrene intermediate, which undergoes nucleophilic substitution to afford the desired aniline products. Mechanistic studies revealed that both electron-withdrawing substituents and steric hindrance significantly influence the decarboxylative amination efficiency. Although the authors successfully synthesized a variety of aniline derivatives, the substrate scope remains limited, as only 2-iodo- or 2-nitro-substituted benzoic acids proved to be effective, with tosyl azides serving as the sole nitrogen source.

Subsequently, Hu's group reported a metal-free decarboxylative amination strategy featuring a mechanism distinct from previously described approaches (Scheme 20).[64] In this reaction, the target amine product is formed *via* the *in situ* generation of a reactive isocyanate intermediate through a Curtius rearrangement, followed by nucleophilic attack. Notably, this method broadens the substrate scope to include a diverse array of benzoic acid derivatives, as well as several heterocyclic moieties tethered to the benzoic acid framework.

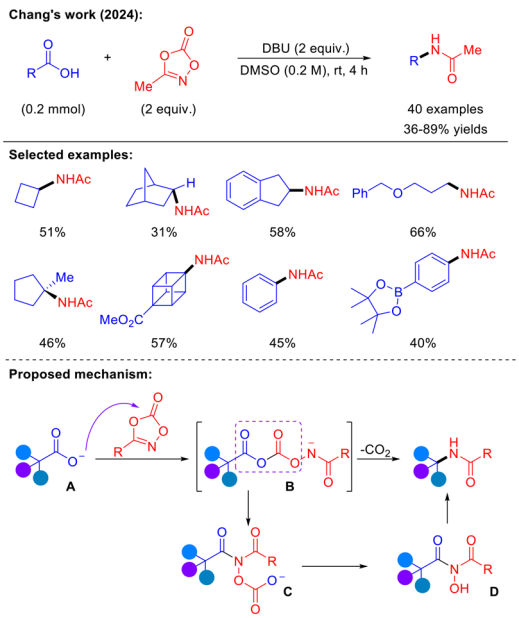
In 2024, Chang's group developed a novel, transition-metal-free strategy for the stereoretentive conversion of chiral carboxylic acids into alkyl amines, employing 1,4,2-dioxazol-5-ones as key reaction partners under mild conditions (Scheme 21, top).[65] Based on experimental and computational



Scheme 19 Transition-metal-free decarboxylative amination with tosyl azides.



Scheme 20 Transition-metal-free decarboxylative amination *via* Curtius rearrangement of an isocyanate intermediate.



Scheme 21 Transition-metal-free decarboxylative amination of carboxylic acids with 1,4,2-dioxazol-5-ones.

studies, the authors proposed a reaction mechanism involving the nucleophilic addition of the carboxylate **A** to the dioxazolone, generating a dicarbonyl *N*-hydroxy intermediate **D** (Scheme 21, bottom). This intermediate then undergoes a Lossen-type rearrangement to produce an isocyanate, which subsequently reacts *in situ* with the carboxylate to form the desired C–N bond with retention of stereochemistry. Notably, this method exhibits excellent functional-group tolerance and applies to a wide range of primary, secondary, and tertiary carboxylic acids under basic conditions.

3. Decarboxylative alkoxylation

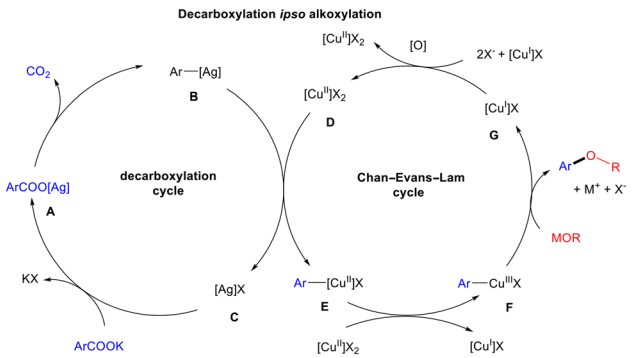
3.1 Transition-metal-catalyzed decarboxylative alkoxylation

Ethers are also ubiquitous structural motifs in medicinal, agricultural, and materials chemistry.[66] Among the most well-

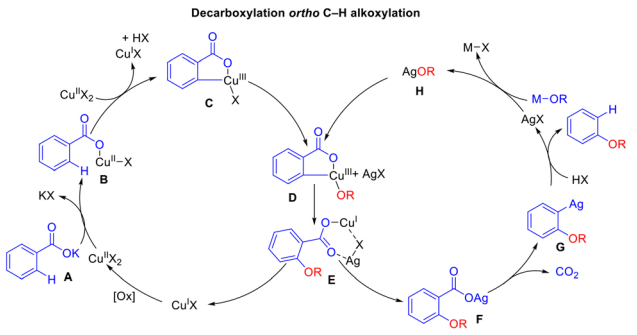
established methods for introducing ether functionalities onto aromatic compounds are the Ullmann coupling[67] and Buchwald–Hartwig coupling.[3] While these strategies have been widely adopted, they present several limitations, including the requirement for stoichiometric amounts of copper compounds, the reliance on sterically demanding and often complex phosphine ligands, and a relatively narrow substrate scope.

In 2012, Gooßen and co-workers introduced two distinct strategies for forming C(sp^2)–O bonds *via* decarboxylative alkoxylation: (1) *ipso*-alkoxylation, where the C(sp^2)–O bond is formed at the original carboxylate position of benzoates, and (2) *ortho*-alkoxylation, where the C(sp^2)–O bond is formed at the *ortho*-position relative to the eliminated carboxyl group.[68,69] These transformations proceed *via* different mechanisms. The *ipso*-alkoxylation operates through a combination of a Chan–Evans–Lam-type copper-catalyzed alkoxylation cycle and a silver-mediated decarboxylation process (Scheme 22). In contrast, the *ortho*-alkoxylation involves *ortho*-C–H activation and CO_2 extrusion, co-catalyzed by silver and copper salts (Scheme 23).

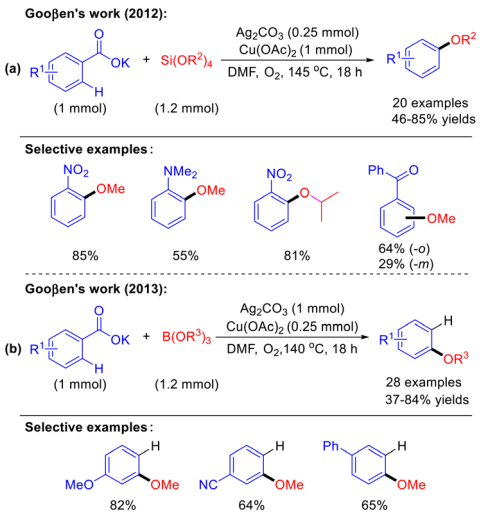
They first examined the decarboxylative *ipso*-alkoxylation using reactive potassium 2-nitrobenzoates and alkyl orthosilicates (Scheme 24a).[68] After optimizing the reaction conditions, a diverse substrate scope was evaluated. The



Scheme 22 Mechanism of decarboxylative *ipso*-alkoxylation.



Scheme 23 Mechanism of decarboxylative *ortho*-C–H alkoxylation.



Scheme 24 (a) *ipso*- and (b) *ortho*-C–H decarboxylative alkoxylation.

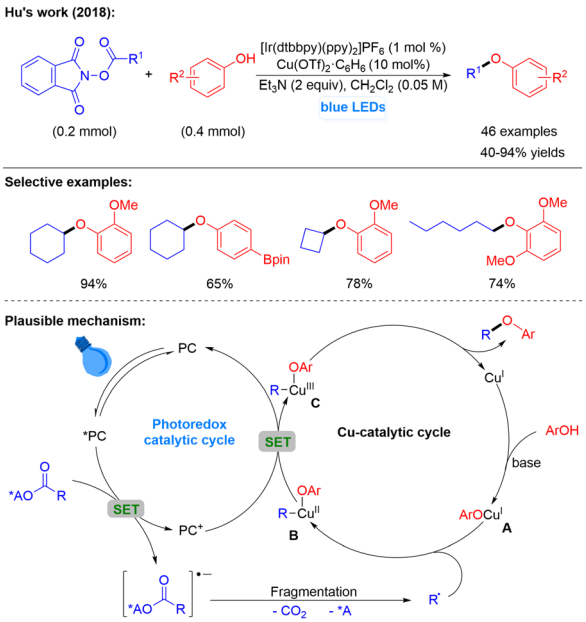
results revealed that electron-deficient substituents on the benzoate ring favoured *ipso*-alkoxylation, whereas electron-donating groups tended to promote by-product formation *via* *ortho*-alkoxylation. For instance, potassium 2-benzoylbenzoate yielded 64% of the *ipso*-product, along with 29% of the *ortho*-substituted product. To complement this study, the authors also investigated decarboxylative *ortho*-alkoxylation using potassium benzoates and trialkoxyborates (Scheme 24b).[69] In this protocol, competing *ipso*-alkoxylation was minimal, and only *ortho*-alkoxylation occurred with benzoates, confirming a distinct mechanistic divergence between the two pathways.

3.2 Photoredox-induced decarboxylative alkoxylation

Transition-metal-catalyzed C–O bond formation is traditionally achieved through nucleophilic substitution reactions,[70,71] which typically require elevated temperatures. The previously discussed examples relied on electron-withdrawing substituents as directing groups on benzoates. However, these strategies face limitations, such as the difficulty of removing directing groups and a restricted substrate scope confined to aromatic carboxylic acids.

In 2018, Hu's group addressed these issues by reporting a photoredox/Cu co-catalyzed decarboxylative alkoxylation using NHPI esters and phenol derivatives as coupling partners (Scheme 25, top).[72] This protocol enabled the synthesis of a wide range of aryl alkyl ethers, including both cyclic and acyclic alkyl groups, in moderate to excellent yields.

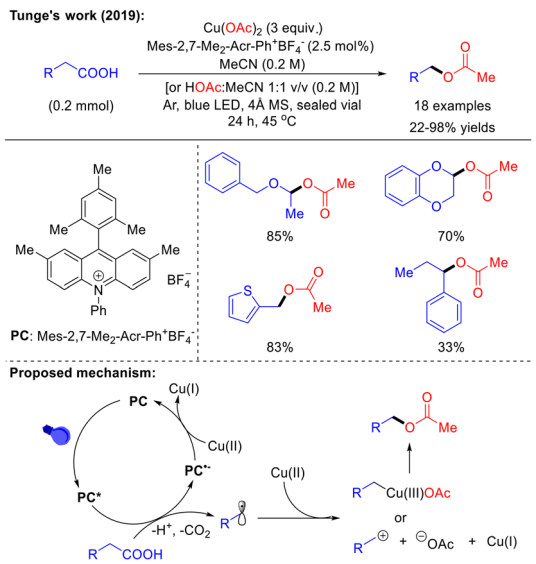
Based on experimental evidence, the authors proposed a plausible mechanism (Scheme 25, bottom). Initially, the phenol coordinates with a Cu(I) species to form a Cu(I) alkoxide intermediate **A**, which subsequently captures an alkyl radical generated *via* the photoredox cycle from NHPI esters, forming the Cu(II) intermediate **B**. Then, PC^+ oxidizes inter-



Scheme 25 Synergetic photoredox-induced and copper-catalyzed decarboxylative alkoxylation.

mediate **B** to form alkyl(alkoxo)copper(III) intermediate **C**, regenerating the photocatalyst. Finally, reductive elimination of intermediate **C** delivers the desired aryl alkyl ethers as the products.

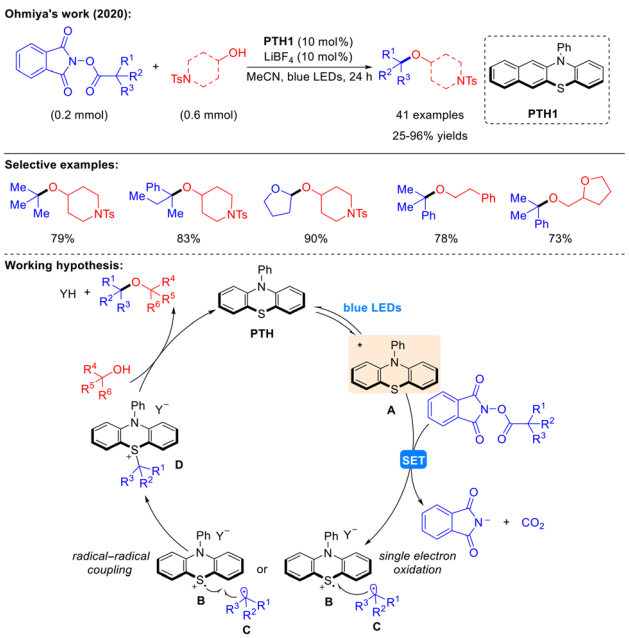
In 2019, Tunge and co-workers described a copper-mediated photocatalytic decarboxylative carbon–acetoxylation reaction that enables the synthesis of diverse C(sp^3)–OAc bonds found in natural products, pharmaceuticals, and agrochemicals (Scheme 26, top).[73] In this system, copper acetate



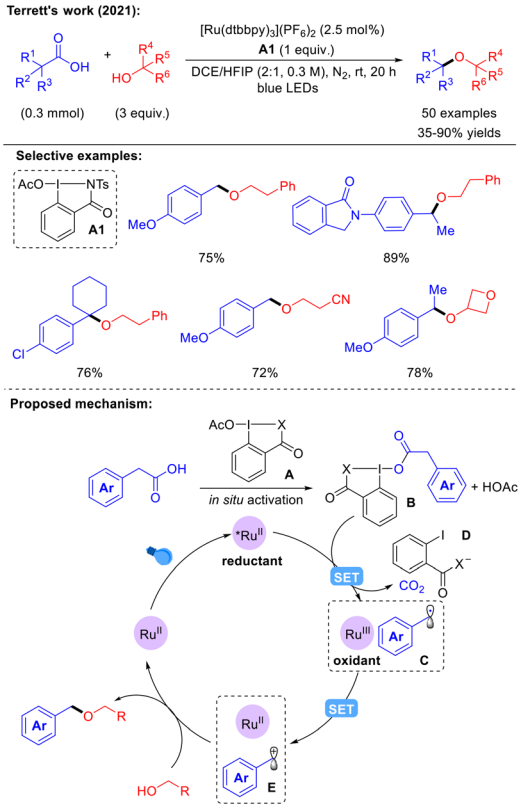
Scheme 26 Photoredox-induced decarboxylative acetoxylation.

serves multiple roles: as an oxidant, a base, and an acetate source. The reaction initiates with photoinduced decarboxylation to generate a carbon-centred radical, which can be captured by $Cu(OAc)_2$ to form a metastable alkylcopper(III) intermediate. Subsequent reductive elimination affords the C–OAc product. Alternatively, the carbon-centered radical can be oxidized by $Cu(OAc)_2$ to a carbocation, which is subsequently trapped by acetate to afford the final product (Scheme 26, bottom).

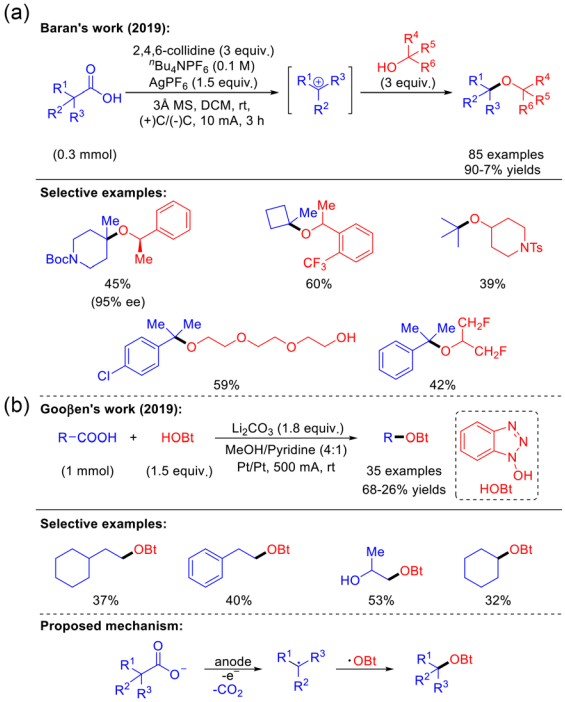
In 2020, Ohmiya's group introduced a new strategy for synthesizing a range of alkyl ethers *via* a radical-polar crossover (RPC) process.[74] In this method, the authors employed *N*-Ar-phenothiazine as the photocatalyst, taking advantage of its high reduction potential and the persistent properties of its corresponding radical cation (Scheme 27). This methodology is highly versatile, accommodating a wide range of primary, secondary, and tertiary redox-active esters, as well as alkyl alcohols, including heterocyclic alcohols and active esters. The catalytic cycle begins with the excitation of phenothiazine upon irradiation with a light-emitting diode (LED), generating a highly reducing excited state **A**. This excited state undergoes a single-electron transfer to the active ester, resulting in the formation of the radical cation of the catalyst **B** and an alkyl radical **C**. Subsequently, the alkyl radical and the radical cation can either couple to form an alkylsulfonium intermediate **D** or undergo a single-electron oxidation of **C** by **B**. The resulting carbocation from intermediate **D** then reacts with alcohol in a deprotonation process, regenerating the ground state of the organosulfide photocatalyst to complete the catalytic cycle.



Scheme 27 Photoredox-induced decarboxylative C(sp^3)–O bond formation.



Scheme 28 Photoredox-induced decarboxylation alkoxylation *via* a radical-polar crossover reaction.



Scheme 29 Electrochemical decarboxylative C(sp^3)–O coupling reactions.

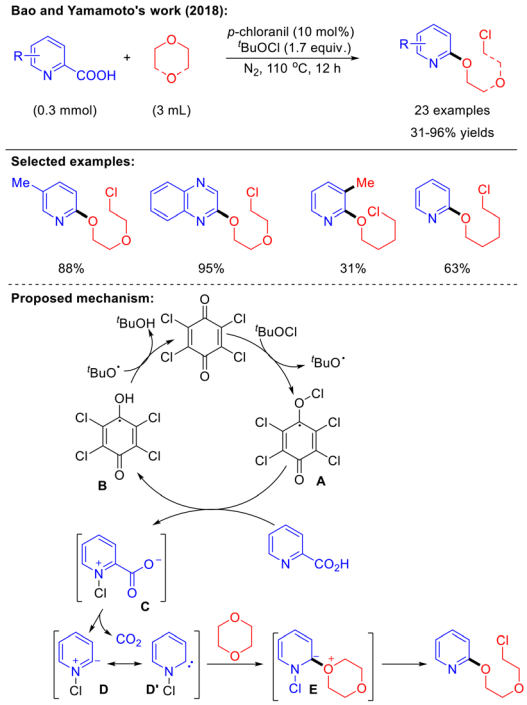
In 2021, Terrett *et al.* introduced a photoredox-catalyzed and iodine(III)-mediated decarboxylative etherification method to synthesize a series of ethers from natural carboxylic acids and alcohols, applicable to primary, secondary, and tertiary carboxylic acid substrates (Scheme 28, top).[75] Remarkably, the method also enabled the use of alcohols to achieve a direct decarboxylative alkoxylation reaction. The authors proposed that this transformation proceeds through a radical-polar crossover reaction, generating a discrete benzylic carbocation intermediate, which is then intercepted by nucleophilic alcohol to yield the desired product (Scheme 28, bottom). This mechanism avoids the inherent issues associated with electron mismatch.

3.3 Electrochemical decarboxylative alkoxylation

Inspired by the Hofer–Moest reaction,[76] Baran's group developed a straightforward method for synthesizing hindered alkyl aryl ethers *via* electrochemical oxidation, which liberates key high-energy carbocations from alkyl carboxylic acids. These carbocations can then be trapped by nucleophilic alcohols (Scheme 29, top).[56] In the same year, Gooßen and co-workers reported a similar transformation involving carboxylic acids and 1-hydroxybenzotriazole, using an electrochemical decarboxylative C–O coupling strategy (Scheme 29, bottom).[77] They proposed that under the reaction conditions, carboxylic acids and alcohols are deprotonated to form nucleophilic anions, which are attracted to the anode. These oxygen nucleophiles are oxidized to yield oxygen radicals, while, simultaneously, alkyl radicals are generated *via* Kolbe decarboxylation under high current densities. The C–O bond formation then proceeds through the combination of alkyl and oxygen radicals.

Decarboxylative alkoxylation is a low-cost, green, and efficient method for preparing aromatic ethers, incorporating strategies such as transition-metal-catalyzed reactions, photoredox-induced decarboxylative etherification, and electrochemical approaches. In 2018, Bao's group reported a three-component reaction to construct new C–N and C–Cl bonds in good to excellent yields. In this reaction, 2-picolinic acid or its derivatives were used as a carbon source to react with cyclic ethers, with *p*-chloranil serving as the oxidant and ^{t}BuOCl as the chlorine source (Scheme 30, top).[78]

In addition, the authors proposed a plausible mechanism based on experimental results (Scheme 30, bottom). Initially, *p*-chloranil reacts with ^{t}BuOCl to form a ^{t}BuO$^\bullet$ radical and a semiquinone radical **A**. Then, the semiquinone radical **B** and a zwitterionic intermediate **C** are generated by the reaction of radical **A** with picolinic acid. Following this, a decarboxylative process occurs, leading to the formation of an ylide, *N*-chloropyridinium **D**, which also exists as a reasonable resonance form, carbene **D′**. After the construction of the C–O and C–Cl bonds, the desired product is formed. This mechanism paves the way for the development of a broader variety of *O*-nucleophiles, facilitating more efficient, simple, and atom-economical syntheses of aryl ethers.



Scheme 30 Electrochemical decarboxylative three-component coupling.

4. Conclusions and outlook

In summary, this review focuses on decarbonylative amination and alkoxylation as synthetic protocols. It systematically organizes and outlines various approaches, providing a detailed description of the diverse solutions for constructing C–N and C–O bonds through methods such as transition metal catalysis, photoredox catalysis, electrochemical induction, and other pathways. These strategies facilitate the coupling of two nucleophiles through mechanisms like the addition of oxidants, activation of carboxylic acids to form activated esters, and umpolung of carboxylic acids induced by electrochemical oxidation. As a result, a series of anilines or ethers are formed with good atom utilization efficiency. Crucially, the common by-products in these catalytic systems are water and carbon dioxide, underscoring the potential and value of these protocols.

However, several challenges remain that need to be addressed: (1) transition-metal-catalyzed decarboxylation reactions often require activation of carboxylic acids and amines with electron-withdrawing groups to facilitate the reaction, and elevated temperatures (>100 °C) are necessary to extrude CO_2. Additionally, the use of stoichiometric oxidants can lead to waste production, and (2) photoredox or electrochemical-induced radical coupling requires the pre-formation of active carboxylates, such as iodine(III) carboxylates or NHPI esters, necessitating an extra step to prepare starting materials.

Despite these challenges, it is believed that the ongoing development of decarboxylative amination and etherification will become one of the most promising research directions in modern organic chemistry. In particular, the advancement of more universal transition-metal catalytic systems and photoredox catalytic systems holds great potential. The development of these reaction systems has the potential to greatly enhance the stability of synthetic intermediates such as transition metal complexes and free radicals, thereby increasing the generality and expanding the potential of related research.

Conflicts of interest

There are no conflicts to declare.

Data availability

This is a review article; hence, no primary research results, software, or code have been included, and no new data were generated or analysed as part of this review.

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