Recent developments in decarboxylative cross-coupling reactions between carboxylic acids and N–H compounds

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Carboxylic acids and their derivatives are ubiquitous compounds in organic chemistry, and are widely commercially available in a large structural variety. Recently, carboxylic acids have been frequently used as non-toxic and environmentally benign alternatives to traditional organohalide coupling partners in various carbon–carbon and carbon–heteroatom cross-coupling reactions. Along this line, several methods have been reported for the synthesis of nitrogen-containing organic compounds through decarboxylative cross-coupling reactions between carboxylic acids and N–H compounds. This review focuses on recent advances and discoveries on these reactions with special attention on the mechanistic aspects of the reactions.

1. Introduction

Carbon–nitrogen bond formation is the key strategy in the synthesis of nitrogen-containing organic molecules that have widespread application in many fields such as medicinal chemistry, agrochemistry, and organic synthesis. Over the past decades, several protocols have been developed to construct various C–N bonds. General synthetic methods toward the construction of C(sp^3)–N bonds involve the nucleophilic substitution reactions between nitrogen nucleophiles and alkyl halides, N-alkylation of nitrogen nucleophiles with alcohols under Mitsunobu conditions, and hydroamination reactions of alkenes with nitrogen nucleophiles. The most popular methods for the formation of C(sp^2)–N bonds include the S_NAr reaction of electron-poor aryl halides with nitrogen nucleophiles, Buchwald–Hartwig reaction, Ullmann reaction, and organocatalysis.
coupling," and Chan–Lam amination.26 The construction of C(sp)–N bonds mainly relies on the coupling of haloalkynes with N-nucleophiles.44 However, most of these methods, if not all, suffer from use of high cost, toxic or hazardous starting materials, limited substrate scope, prolonged reaction times and harsh reaction conditions. Thus, the development of a general, convenient, and truly efficient protocol for the formation of all the three kinds of C–N bonds (Calkyl−N, Caryl−N, Calkynyl−N) remains a challenge.

In recent years, decarboxylative cross-coupling reactions has emerged as a novel, selective, and powerful strategy to carbon–carbon12–15 and carbon–heteroatom16–18 bonds formations. This synthetic strategy utilizes readily available, high stable, very soluble, and low toxic carboxylic acids as alternative to traditional coupling partners containing unfavorable (pseudo) halide-leaving groups and extrudes carbon dioxide as an innocuous by-product. Thus, these reactions meet the criteria of green chemistry. Since a number of discoveries and developments in the decarboxylative C–N cross-coupling reactions have occurred during the current decade, a comprehensive review in this interesting and novel research field seems to be timely. As a part of our continuing reviews on cross-coupling reactions29 and new methodologies in organic synthesis,26 in this focus-review we will highlight recent progress in the decarboxylative cross-coupling reactions between carboxylic acids and N–H compounds (Fig. 1), with special emphasis on the mechanistic aspects of the reactions. It is noted that the reactions were classified based on the type of starting carboxylic acids (e.g. alkyl, aryl, and alkylnyl carboxylic acids).

2. Cross-coupling reactions between Calkyl−CO_2H and N−H bonds

Decarboxylative cross-coupling reactions between aliphatic carboxylic acids and N–H compounds has scarcely been studied. In fact, only four examples of such reactions were reported in literature thus far. In 2011, Yan and Wang reported a promising metal-free protocol for the synthesis of biologically important quinazoline derivatives 3 through the hitherto unknown intramolecular oxidative decarboxylative coupling reaction between primary α-amino acids 1 and 2-aminobenzoketones 2 using molecular iodine as catalyst and TBHP ( tert-butyl hydroperoxide) as the terminal oxidant.21 The reaction was carried out in an atmosphere of air at 80 °C, tolerated various electron-rich and electron-poor substrates, and provided functionalized quinazolines 3 in good to quantitative yields (Scheme 1a). However, the steric hindrance of the substrates greatly affected the efficiency of the transformation. For example, trimethyl substituted 2-aminobenzaldehyde failed to undergo the cyclization and 2-aminobenzaldehyde bearing 2,5-dimethyl substituents led to poor yield of the desired product. As shown in Scheme 2, this reaction is believed to proceed through a condensation/oxidization/CO_2 elimination/ H+ elimination/1,6-H transfer/cyclization/aromatization sequential process. In a related investigation, the same

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authors showed that 2-arylquinazolines 6 were formed from oxidative deacryboxylative amination of carboxylic acids 4 with 2-aminobenzoketones 5 and ammonium acetate in a similar process employing Cu(OAc)₂ as a catalyst and molecular oxygen as the sole oxidant in NMP at 120 °C (Scheme 1b).²²

In 2016, primary aliphatic carboxylic acids 7 were found by Xiao-Fu research team to undergo intramolecular deacryboxylative C–N coupling reaction in the presence of 10 mol% of Cu(OTf)₂ as a low-cost commercially available catalyst, 30 mol% of DMAP as additive and 2 equiv. of PhIO as an oxidant, using dichloromethane as solvent at 100 °C, to afford the corresponding 5- and 6-membered cyclic amines 8 in moderate to high yields (Scheme 3).²³ The reaction was also tolerated secondary aliphatic carboxylic acids and provided the expected products with yield range from 42 to 48%. However, tertiary carboxylic acids failed to participate in this transformation. The results revealed that the cyclization of chiral primary carboxylic acids under the standard condition gave the products with retention of configuration but in the cases of secondary carboxylic acids diastereoccontrol of this reaction was not good and mixture of diastereoisomers were obtained. Interestingly, this reaction also showed outstanding site-selectivity in the C–N bond formation process. The selectivity was found to be dictated by the N-protecting groups on the substrates. An

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**Scheme 1** (a) I₂-catalyzed deacryboxylative C–N coupling reactions of primary α-amino acids 1 and 2-aminobenzoketones 2 developed by Wang; (b) synthesis of 2-arylquinazolines 6 through deacryboxylative amination of ary lacetic acids 4 with 2-aminobenzoketones 5 and NH₄OAc.
example of a site-selective reaction is shown in Scheme 4, where the substrates having both the Bz- and PA-protected amino groups, the products cyclized at the PANH side were obtained as the sole products. Noteworthy, the size of newly forming rings would not affect the site-selectivity. Based on literature reports, a possible mechanism was proposed by the authors (Scheme 5), whereby the reaction is initiated by reaction of starting carboxylic acid 7a with PhIO in the presence of Cu$^{II}$–L to give hypervalent iodine(III) intermediate A, which undergoes a homolytic cleavage of one I–O bond affording two radical
intermediates B and C. The intermediate B is then converted to an alkyl radical intermediate D through a decarboxylation process. Then, oxidative addition of the alkyl radical to the CuII which is chelated by the directing group affords the intermediate E, which after reductive elimination delivers the final product 8a and the intermediate CuI–L. Finally, the whole catalytic cycle is accomplished with the oxidation of CuI–L to CuII–L in the presence of intermediate C or decomposition products thereof. Shortly thereafter, Yang, Jiang, and Shi theoretically investigated the detailed mechanism of this reaction using density functional theory (DFT) calculations. Some important information of this study is listed below: (i) the reaction proceeds through a IIII–O bond heterolysis/single electron transfer/hydrogen atom transfer/decarboxylation/proton transfer/reductive elimination sequential process; (ii) The heterolytic cleavage of the IIII–O bond is much easier with the help of +HDMAP, whereas the homolytic pathways need to overcome higher enthalpy barriers and thus show less feasibility; and (iii) the chelation of the PA directing group to the Cu(III) center significantly facilitates the proton transfer process, which is the rate-determining step.

Very recently, MacMillan and colleagues reported an elegant intermolecular version of this reaction using a synergistic combination of copper(i) and photoredox catalysis. With the mesl(OAc)2/CuTC/Ir(F-Meppy)2(dtbbpy)PF6/BPhen/BTMG system, direct C–N coupling of a variety of primary, secondary and tertiary alkyl carboxylic acids 11 with a range of nitrogen nucleophiles (N-heterocycles, amides, sulfonamides and anilines) 12 proceeded efficiently to produce N-alkyl products 13 in moderate to almost quantitative yields. Some reported examples are shown in Scheme 6. It is noted that the reaction took place in dioxane at room temperature under irradiation of blue LED light (34 W) and tolerated a library of important functional groups, including fluoro, chloro, bromo, iodo, amide, ether, and ester functionalities. Thus this procedure offers scope for further elaboration of products. The authors
assume that the mechanistic pathway of this transformation involves the initial formation of triplet-excited-state \( ^{3}\text{Ir}^{III} \) complex \( B \) via the excitation of photocatalyst \( A \) under light irradiation. Meanwhile, coordination of the nitrogen nucleophile \( 12 \) with a copper(I) precatalyst followed by deprotonation forms the copper(I)-amido species \( C \), which after oxidation by complex \( B \) gives the copper(II)-amido system \( D \) and the iridium(II) complex \( E \). Next, reduction of idomesitylene dicarboxylate \( F \) (which is generated from carboxylic acid \( 11 \) and idomesitylene diacetate) by \( ^{3}\text{Ir}^{III} \) species \( E \) leads to the desired alkyl radical \( G \), while reconstituting the ground-state photocatalyst \( A \). Finally, the capture of alkyl radical \( G \) by copper(I)-amido complex \( D \) yields copper(II) complex \( H \), which upon reductive elimination affords \( C(\text{sp}^3)-N \) bearing adduct \( 13 \) and regenerate copper(I) catalyst \( C \) (Scheme 7).

### 3. Cross-coupling reactions between C\(_{\text{aryl}}\)-\( \text{CO}_2\text{H} \) and \( \text{N-H} \) bonds

In 2012, Zhang, Patel, and Mainolli demonstrated a simple and highly efficient method for the construction \( C(\text{aryl})-N \) bonds from aromatic benzoic acids and amide derivatives via Cu-catalyzed decarboxylative cross-coupling reaction using molecular oxygen as the sole oxidant. As studying a number of catalysts, such as CuI, CuCl, CuCl\(_2\), Cu(OAc)\(_2\), and Cu(OTf)\(_2\), ligands, such as bpy and phen, and solvents, such as diglyme, tAmyOH, toluene, and anisole, a combination of CuCl\(_2\)/phen/anisole with 2.0 equiv. of sodium bicarbonate as an inexpensive base at 170 °C was found to be optimum with respect to the yield of product isolated. Under the optimized conditions, several ortho-substituted benzoic acid derivatives \( 14 \) underwent coupling with various \( N \)-nucleophiles \( 15 \) and gave the expected \( N \)-arylated products \( 16 \) in modestly to high yields (Scheme 8a).

The plausible mechanism for this decarboxylative C–N coupling transformation is shown in Scheme 8b and starts with the generation of a copper(u) carboxylate intermediate \( B \) from the reaction of benzoic acid \( 14 \) with copper catalyst \( A \) through a deprotonation process, which is followed by its decarboxylation to furnish intermediate \( C \). Subsequently, the reaction of this intermediate with \( N \)-nucleophile \( 15 \) in the presence of a base gives complex \( D \) that is in equilibrium with the complex \( E \). Finally, reductive elimination of these complexes affords the final product \( 16 \).
Not long after this report, Jia and co-workers extended the above cross-coupling to anilines. They showed that the reaction of potassium 2-nitrobenzoate with primary anilines in the presence of 1.0 equiv. of CuSO$_4$ as mediator in NMP afforded the corresponding diarylamines in moderate to excellent yields (Scheme 9). Satisfactorily, a series of important functional groups such as F, Cl, Br, NO$_2$, and CN were well tolerated by the reaction conditions employed, thus providing a useful approach to functionalized diarylamines. Noteworthy, the reaction works also for amides if the Ag$_2$CO$_3$ additive is used. However, just like previous work, this protocol requires harsh reaction conditions (140 °C). In 2017, Sarkate and colleagues improved the efficiency of this reaction in the terms of reaction time, temperature, and yield by performing the process under microwave irradiation.

Very recently, Goossen and co-workers extended the substrate scope of this reaction system and reported the decarboxylative ipso-amination of potassium salt of electron-deficient benzoic acids with aliphatic amines. A variety of N-arylated amines were obtained in up to 81% yields in a solvent mixture of anisole and dimethylacetamide (DMAc) employing Pd(NH$_3$)$_4$(HCO$_3$)$_2$/CuI/1,10-phen combination as a catalytic system at 145 °C. Some reported examples are shown in Scheme 10. It should be mentioned that, in the cases of cyclic secondary amines, the best results were obtained under an air atmosphere without any additional oxidant, while for primary and acyclic secondary amines, the use of over-stoichiometric amounts of N-methylmorpholine N-oxide (NMO) as an oxidant gave the best results. Beside aliphatic amines, electron-rich anilines have also been successfully applied in this methodology.
4. Cross-coupling reactions between C$_{\text{carbonyl}}$–CO$_2$H and N–H bonds

The first example of decarboxylative amidation of $\alpha$-keto acids withamines was reported by Lan–Lei's research team in 2014; a broad range of 2-oxo-2-arylacetic acids 23 were reacted with various aliphatic and aromatic primary amines 24 in the presence of [Ru(phen)$_3$]Cl$_2$ as a photocatalyst under irradiation by visible light in the presence of molecular oxygen and afforded the corresponding secondary amides 25 in moderate to high yields (Scheme 11).

2-Oxo-2-methylacetic acid did not work well in the reaction and therefore no other 2-oxo-2-alkylacetic acids were examined in the protocol. Furthermore, the reaction did not give satisfactory yield with N-propargylamine. Interestingly, when 2-phenylenediamine or analogously oxygen- or mercapto-substituted anilines are used, the corresponding 2-substituted benzazoles can be prepared through a tandem cross-coupling and condensation reaction. The authors proposed mechanism of this visible-light-mediated decarboxylative amidation reaction is depicted in Scheme 12. Similar amidation work was also reported by Xu and co-workers. They showed that the reaction of similar substrates in a mixed solvent of dioxane and water (5:1) under the irradiation of a 23 W fluorescent light bulb and catalyst-free conditions afforded the expected amides in 48 hours.

In 2016, Liu, Wang, and co-workers demonstrated an interesting amidation of $\alpha$-keto acids 26 with N-benzylpicolinamide derivatives 27 through a palladium-catalyzed decarboxylative process. This new methodology provides a concise and efficient synthesis of various substituted imides 28 in fair to excellent yields. The results proved that the reaction was not dependent on the electronic and steric effects of substituents in the phenyl ring of N-benzylpicolinamides. Thus, the system tolerated both electron-withdrawing and electron-donating substituents on the para, ortho, and meta positions of the phenyl ring.
aromatic ring of amides according to Scheme 13. However, the outcome of reaction was strongly dependent on the electronic character of the substituents on the phenyl ring periphery of 2-oxo-2-arylacetic acids. Generally, electron-rich carboxylic acids afforded better yields compared to electron-poor ones. It is noted that the strongly electron-poor 2-oxo-2-(p-NO2-phenyl) acetic acid failed to afford the product. To probe the mechanistic pathway of this reaction, a free-radical trap test was investigated. The reaction was completely inhibited in the presence of 2,2,6,6-tetramethylpiperidine N-oxide (TEMPO), a radical scavenger, which suggested that a radical process is probably involved in this reaction. The authors mentioned that the reaction mechanism involves three steps (Scheme 14): (i) chelation of picolinamide 27 with Pd(OAc)2 to generate the five-membered intermediate A; (ii) reaction of A with the acyl radical B (generated by decarboxylation of α-keto acid 26 in the presence of K2S2O8) to form the Pd(IV)-intermediate C; and (iii) reductive elimination of intermediate C to afford the final product 28 along with the release of Pd(II) species.

In a related investigation, He and Xu along with their co-workers reported an Ag-catalyzed synthesis of secondary amides 31 from α-keto acids 29 and anilines 30 under an air atmosphere and mild conditions. In this study, various silver catalysts (e.g., AgF, AgOTf, AgBF4, AgNO3, Ag2CO3, Ag2O), and binary solvents (e.g., MeCN/H2O, DMSO/H2O, DMF/H2O, NMP/H2O, DCE/H2O) were examined and 2 equiv. of AgOTf in MeCN/H2O (2:1) was found to be optimal for this transformation. This reaction tolerates a wide range of functional groups such as fluoro, chloro, iodo, methoxy, hydroxyl and ester functionalities and could be applied to both aromatic and aliphatic α-keto acids (Scheme 15). Recently, the methodology was extended to a series of NH-free sulfoximines, using CuBr/K2S2O8 combination as an effective catalytic system, and the N-aroylsulfoximines were obtained with yield range from 14 to 91%.

5. Cross-coupling reactions between Calkynyl–CO2H and N–H bonds

Although direct decarboxylative cross-coupling of alkylnyl carboxylic acids with C–H bonds has been well known, the decarboxylative hetero-coupling reactions between C(sp)–CO2H

![Scheme 12](image)

Scheme 12: Mechanism proposed to explain the secondary amides 25 synthesis.

![Scheme 13](image)

Scheme 13: Synthesis of imides 28 via Pd-catalyzed decarboxylative amidation of α-keto acids 26 with N-benzylpicolinamides 27.
and heteroatom–H (especially N–H) bonds were less developed. One of the earliest reports of the C–N bond forming reactions through decarboxylative cross-coupling of alkynyl carboxylic acids with N-nucleophiles has been reported by Jia and Jiao in 2010, when a range of aryl-, heteroaryl-, alkenyl-, and alkyl-substituted propiolic acids 32 underwent coupling reaction with N-nucleophiles 33 in the presence of 10 mol% of CuCl₂ + 2H₂O as a catalyst and 2.0 equiv. of Na₂CO₃ as a base in toluene to form the corresponding C(sp)–N bearing adducts 34 within 12–60 h (Scheme 16). The results showed that the reactivity order for the carboxylic acids under these reaction conditions was aryl-substituted propiolic acids > alkyl-substituted propiolic acids > alkenyl-substituted propiolic acids > heteroaryl-substituted propiolic acids. It is noteworthy that other commercially available Cu catalysts such as CuBr₂, Cu₂O, Cu(OAc)₂ + H₂O and CuSO₄ + 5H₂O were also found to promote this coupling reaction; albeit

Scheme 14  Plausible mechanism for Liu–Wang’s synthesis of imides 28.

Scheme 15  Ag-catalyzed synthesis of secondary amides 31 from α-keto acids 29 and anilines 30 via a decarboxylative process.

Scheme 16  Cu(II)-catalyzed amidation of propiolic acids 32 with nitrogen nucleophiles 33.
with reduced efficiencies. A proposed mechanistic possibility is depicted in Scheme 17. This transformation start with the formation of copper(II) intermediate A by reaction between the Cu(II) catalyst and carboxylic acid 32 in the presence of a base. Its decarboxylation leads to the alkynyl copper(II) intermediate B, which after nucleophilic attack by N-nucleophile 33 affords the CuII(alkynyl)(amidate) intermediate C. Finally, reductive elimination of this intermediate provides the expected product 34 and the copper catalyst is recycled.

Inspired by this work, in 2013, the group of Bolm developed an interesting N-alkynylated sulfoximines synthetic strategy via Cu(i)-catalyzed decarboxylative coupling of aryl propiolic acids with sulfoximines under air atmosphere. Different variables affecting the reaction (e.g., such as catalyst, base, additive, solvent, and temperature) were carefully studied and optimized. It was found that using CuBr/K3PO4/pyridine combination as a catalytic system resulted in the best yields. Among the various solvents like DMF, DMSO, DCM, toluene, and 1,4-dioxane, toluene was the most efficient for this reaction. It should be mentioned that the presence of pyridine was crucial for the success of the reaction since it minimize the occurrence of the Glaser–Hay homocoupling. Various aryl propiolic acids 35 reacted well with N–H sulfoximines 36 under the standard conditions to produce the corresponding sulfoximidoyl-functionalized alkynes 37 in good to excellent yields (Scheme 18). It is observed that several functional groups, such as F, Cl, Br, OMe, and NO2 groups, on the aromatic ring of both substrates were well-tolerated. This transformation provides many opportunities for applications to organic synthesis. For example, the synthesized N-alkynylated sulfoximines could be used to prepare alkenylated sulfoximines by reduction of their alkyne moieties, and cyclobutenone sulfoximines by reaction with isobutyl chloride.
6. Conclusion

In summary, this focus-review highlights the recent discoveries and developments in decarboxylative cross-coupling reactions between carboxylic acids and N–H compounds. This strategy enables the facile construction of carbon–nitrogen bonds by avoiding the use of environmentally hazardous organohalide or organometallic reagents, thereby providing an efficient and green approach to various biologically and synthetically important nitrogen-containing organic molecules. As illustrated, all the three kinds of C–N bonds [C(sp^3)–N, C(sp^2)–N, C(sp)–N] could be effectively formed by this methodology demonstrating the general applicability of the procedure. Despite stellar achievements during the past nine years in this research arena, many challenges still remain to be overcome: (i) the number of reported examples are narrow and there is further need to study the scope and limitations of these reactions; (ii) most of the reactions covered in this review are limited to the use of bulk metal catalysts. Therefore, exploration of organocatalysts and nano-sized metal catalysts are highly desirable from the view point of green chemistry; and (iii) other reactions such as coupling of alkenyl carboxylic acids with N–H compounds should be explored. We conclude this review by hoping that it will stimulate researchers to further thinking and research in this domain.

Conflicts of interest

There are no conflicts to declare.

References
