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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.

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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,¹ agrochemistry,² and organic synthesis.³ Over the past decades, several protocols have been developed to construct various C–N bonds. General synthetic methods toward the construction of C(sp³)–N bonds involve the nucleophilic substitution reactions between nitrogen nucleophiles and alkyl halides,⁴ N-alkylation of nitrogen nucleophiles with alcohols under Mitsunobu conditions,⁵ and hydroamination reactions of alkenes with nitrogen nucleophiles.⁶ The most popular methods for the formation of C(sp²)–N bonds include the S_NAr reaction of electron-poor aryl halides with nitrogen nucleophiles,⁷ Buchwald–Hartwig reaction,⁸ Ullmann

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coupling,⁹ and Chan–Lam amination.¹⁰ The construction of C(sp)–N bonds mainly relies on the coupling of haloalkynes with N-nucleophiles.¹¹ 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 (C_{alkyl}–N, C_{aryl}–N, C_{alkynyl}–N) remains a challenge.

In recent years, decarboxylative cross-coupling reactions has emerged as a novel, selective, and powerful strategy to carbon–carbon^{12–15} and carbon–heteroatom^{16–18} 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 reactions¹⁹ and new methodologies in organic synthesis,²⁰ 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 alkynyl carboxylic acids).

2. Cross-coupling reactions between C_{alkyl}–CO₂H 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/CO₂ elimination/H⁺ elimination/1,6-H transfer/cyclization/aromatization sequential process. In a related investigation, the same



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Noor University as full Professor of Organic Chemistry. His research interests include theoretical organic chemistry, new methodologies in organic synthesis and spectral studies of organic compounds.



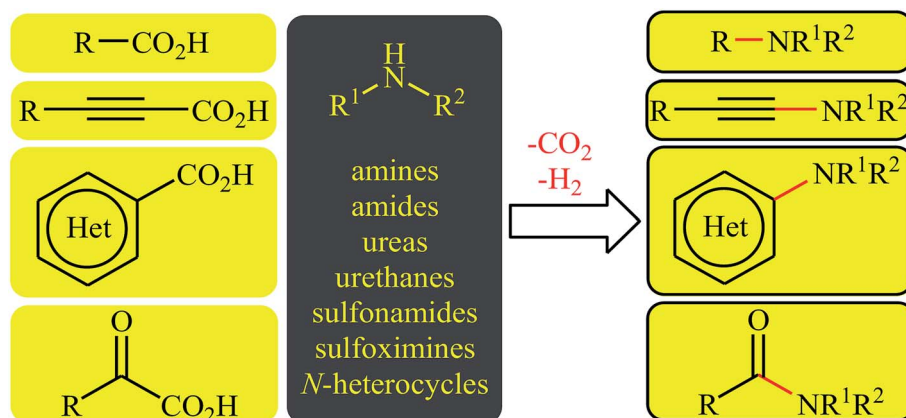
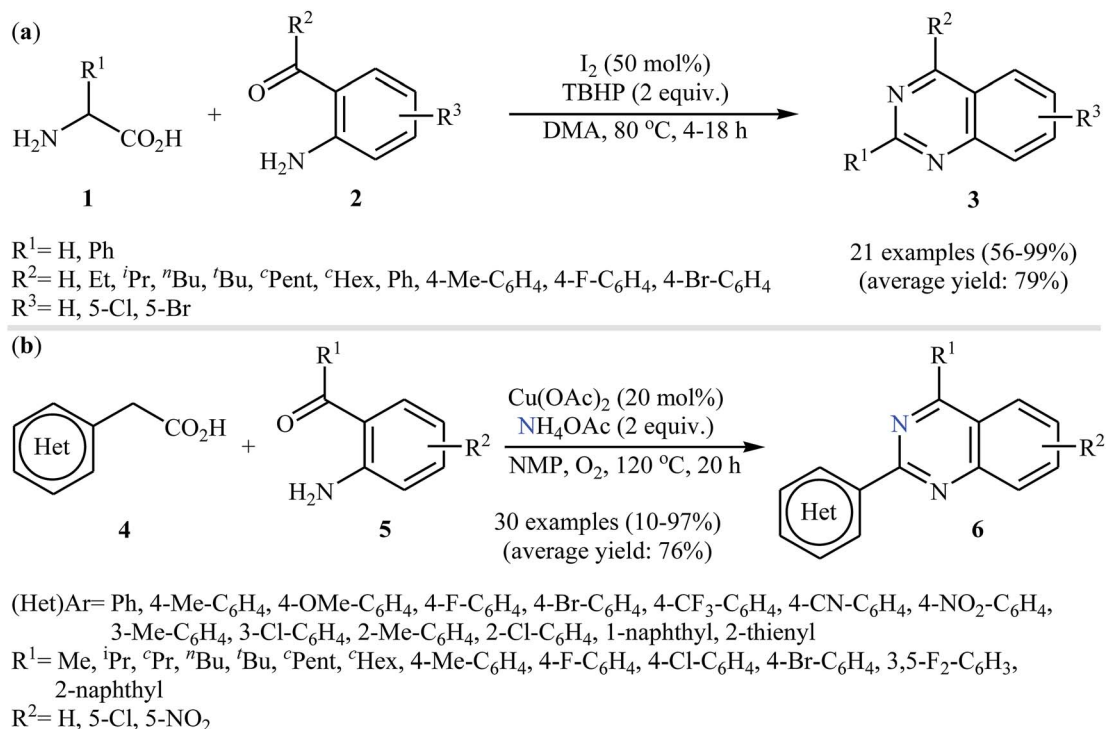


Fig. 1 Decarboxylative C–N cross-coupling reactions.

authors showed that 2-arylquinazolines **6** were formed from oxidative decarboxylative amination of carboxylic acids **4** with 2-aminobenzoketones **5** and ammonium acetate in a similar process employing $\text{Cu}(\text{OAc})_2$ as a catalyst and molecular oxygen as the sole oxidant in NMP at 120 °C (Scheme 1b).²²

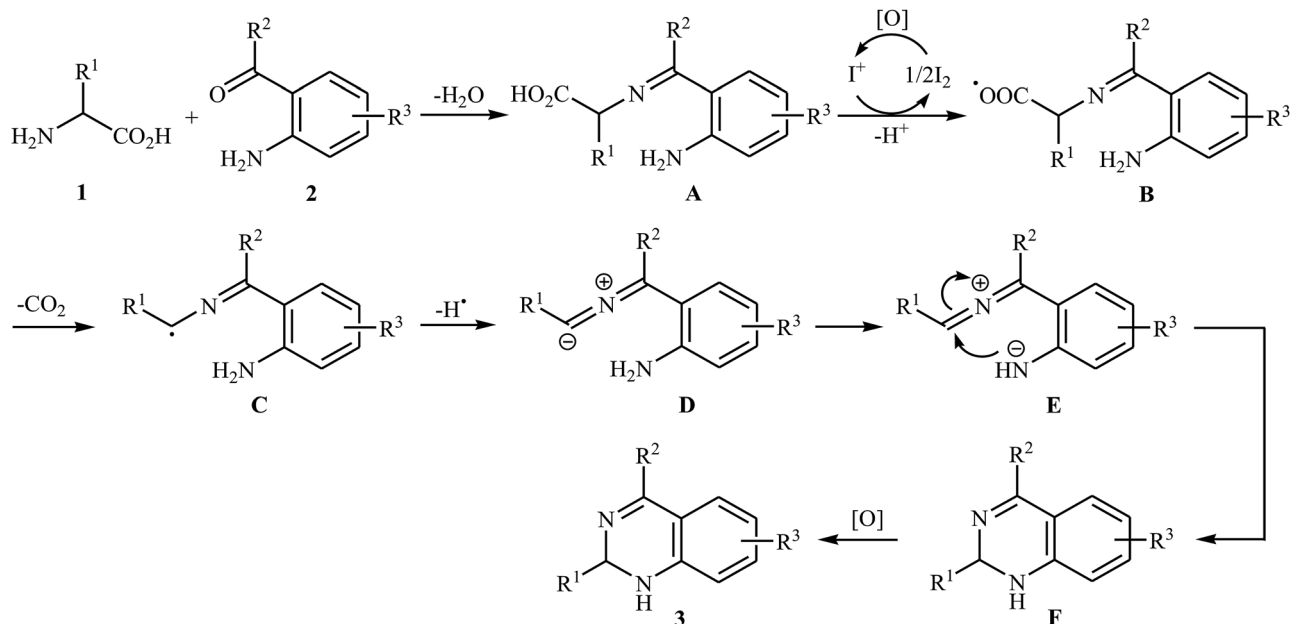
In 2016, primary aliphatic carboxylic acids **7** were found by Xiao-Fu research team to undergo intramolecular decarboxylative C–N coupling reaction in the presence of 10 mol% of $\text{Cu}(\text{OTf})_2$ as a low-cost commercially available catalyst, 30 mol% of DMAP as additive and 2 equiv. of PhIO 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 diastereocontrol 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



Scheme 1 (a) I_2 -catalyzed decarboxylative C–N coupling reactions of primary α -amino acids **1** and 2-aminobenzoketones **2** developed by Wang; (b) synthesis of 2-arylquinazolines **6** through decarboxylative amination of arylacetic acids **4** with 2-aminobenzoketones **5** and NH_4OAc .

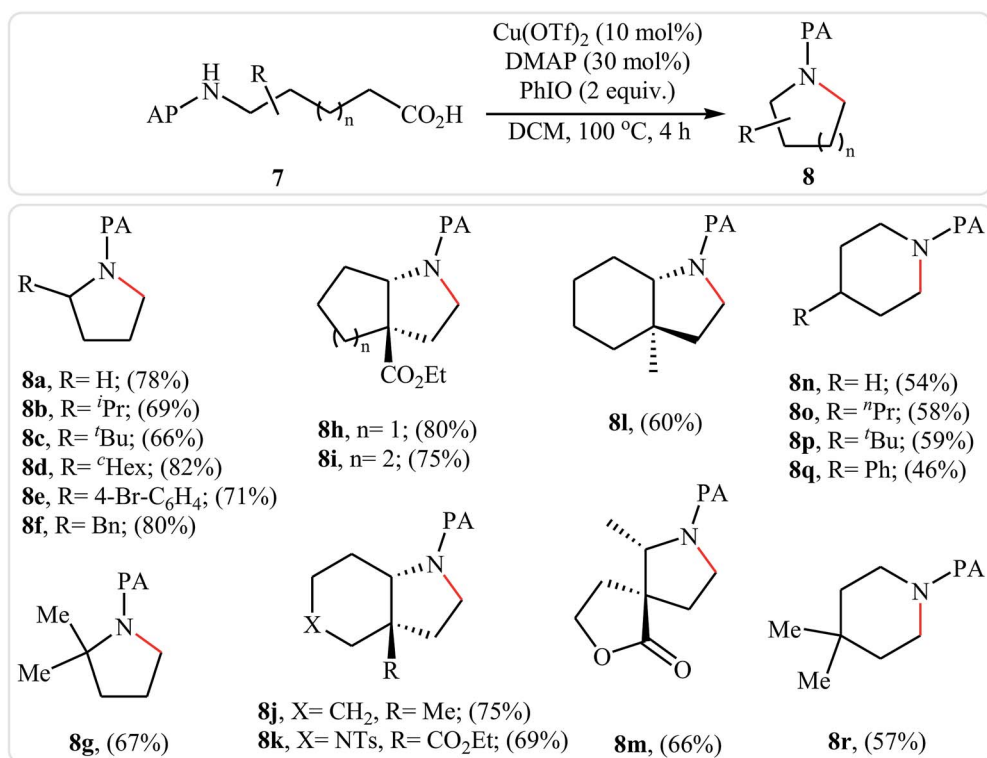




Scheme 2 Mechanistic proposal for the formation of quinazoline derivatives 3.

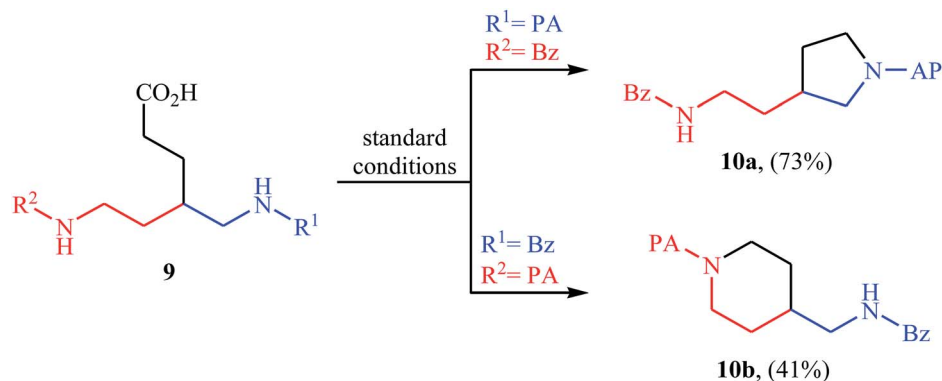
example of a site-selective reaction is shown in Scheme 4, where the substrates having both the Bz- and PA-protected amino groups, the products cyclized at the PANH side were obtained as the sole products. Noteworthy, the size of newly forming rings would not affect the site-selectivity. Based on literature 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 $\text{Cu}^{\text{II}}\text{-L}$ to give hypervalent iodine(III) intermediate A, which undergoes a homolytic cleavage of one I-O bond affording two radical



Scheme 3 Cu^{II} -catalyzed intramolecular decarboxylative C-N coupling reaction of primary aliphatic carboxylic acids 7.



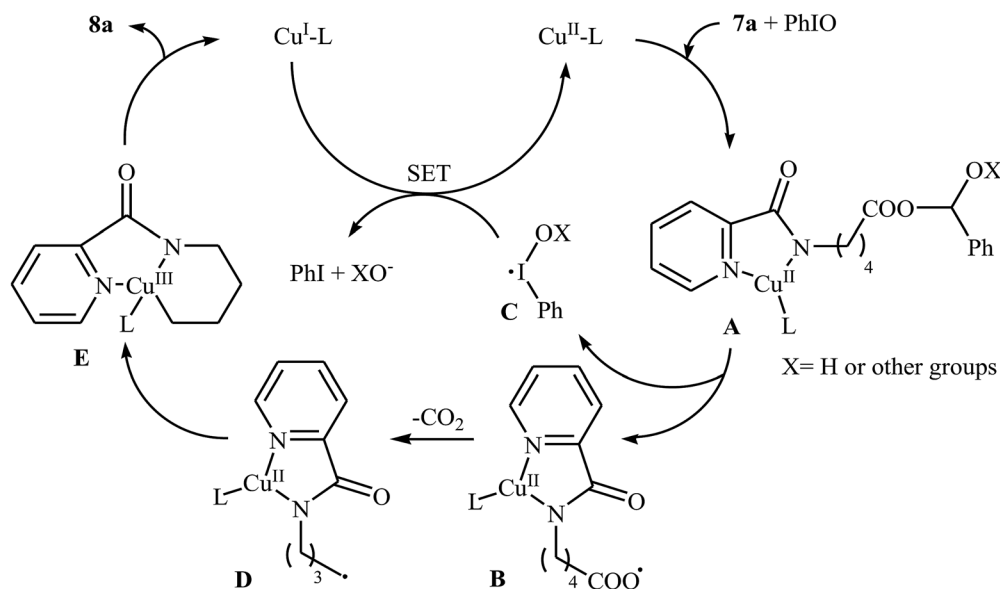


Scheme 4 Site-selectivity controlled by a directing group in the intramolecular decarboxylative C–N coupling process.

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 Cu^{II} which is chelated by the directing group affords the intermediate **E**, which after reductive elimination delivers the final product **8a** and the intermediate $\text{Cu}^{\text{I}}\text{-L}$. Finally, the whole catalytic cycle is accomplished with the oxidation of $\text{Cu}^{\text{I}}\text{-L}$ to $\text{Cu}^{\text{II}}\text{-L}$ 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.²⁴ Some important information of this study is listed below: (i) the reaction proceeds through a $\text{I}^{\text{III}}\text{-O}$ bond heterolysis/single electron transfer/hydrogen atom transfer/decarboxylation/proton transfer/reductive elimination sequential process; (ii) The heterolytic cleavage of the $\text{I}^{\text{III}}\text{-O}$ bond is much easier with the help of $^+\text{HDMAP}$, whereas the homolytic pathways need to overcome higher enthalpy barriers and thus show less feasibility; and (iii)

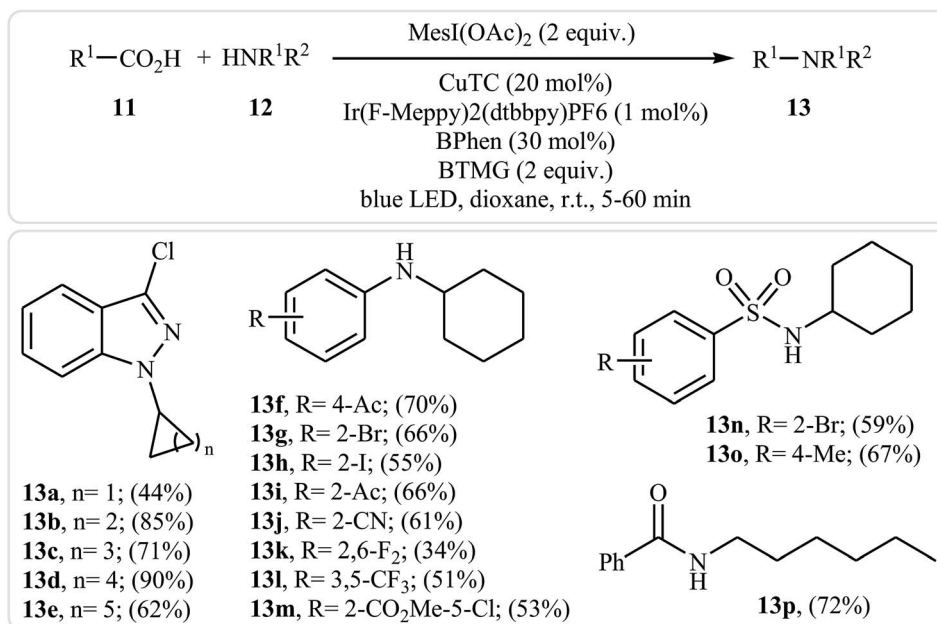
the chelation of the PA directing group to the $\text{Cu}(\text{III})$ center significantly facilitates the proton transfer process, which is the rate-determining step.

Very recently, MacMillan and colleagues reported an elegant intermolecular version of this reaction using a synergistic combination of copper(i) and photoredox catalysis.²⁵ With the $\text{mes}(\text{OAc})_2/\text{CuTC}/\text{Ir}(\text{F-Meppy})_2(\text{dtbbpy})\text{PF}_6/\text{BPhen}/\text{BTMG}$ 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



Scheme 5 Mechanism proposed to explain the formation of cyclic amines **8**.





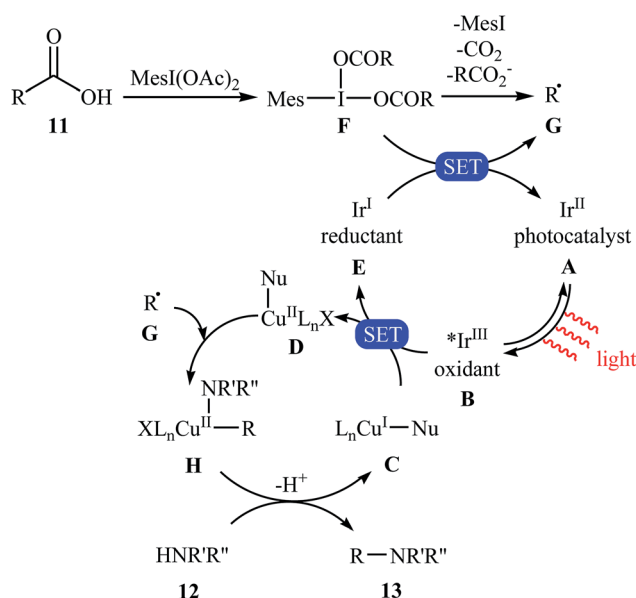
Scheme 6 Decarboxylative cross-coupling of alkyl carboxylic acids **11** with nitrogen nucleophiles **12** developed by MacMillan research team.

assume that the mechanistic pathway of this transformation involves the initial formation of triplet-excited-state $^*\text{Ir}^{\text{III}}$ 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 iodomesitylene dicarboxylate **F** (which is generated from carboxylic acid **11** and iodomesitylene diacetate) by Ir^{II} 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(II)-amido complex **D** yields copper(III) complex **H**, which upon reductive elimination affords $\text{C}(\text{sp}^3)\text{-N}$ bearing adduct **13** and regenerate copper(i) catalyst **C** (Scheme 7).

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

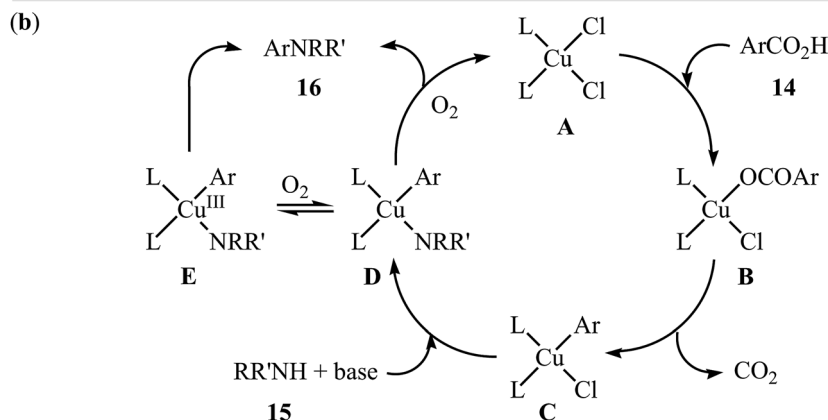
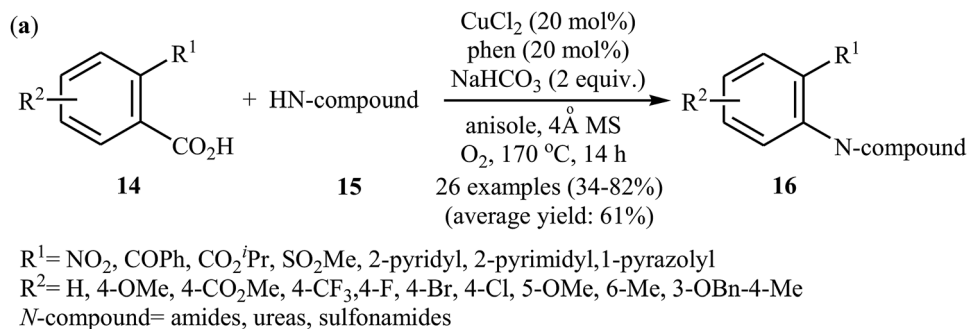
In 2012, Zhang, Patel, and Mainolfi demonstrated a simple and highly efficient method for the construction $\text{C}(\text{aryl})\text{-N}$ bonds from aromatic benzoic acids and amide derivatives via Cu-catalyzed decarboxylative cross-coupling reaction using molecular oxygen as the sole oxidant.²⁶ After 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, *t*AmyOH, toluene, and anisole, a combination of $\text{CuCl}_2/\text{phen}/\text{anisole}$ 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(II) 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**.



Scheme 7 Plausible mechanism for reaction in Scheme 6.

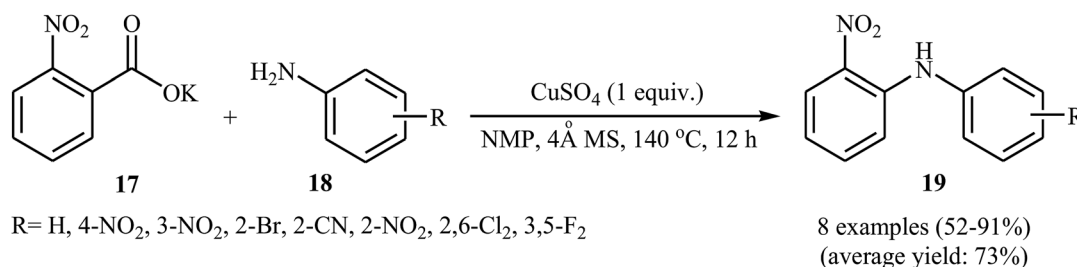




Scheme 8 (a) Cu(II)-catalyzed decarboxylative C–N coupling reaction between *ortho*-substituted benzoic acid derivatives **14** and nitrogen nucleophiles **15**; (b) mechanism proposed to explain the *N*-arylated products **16** synthesis.

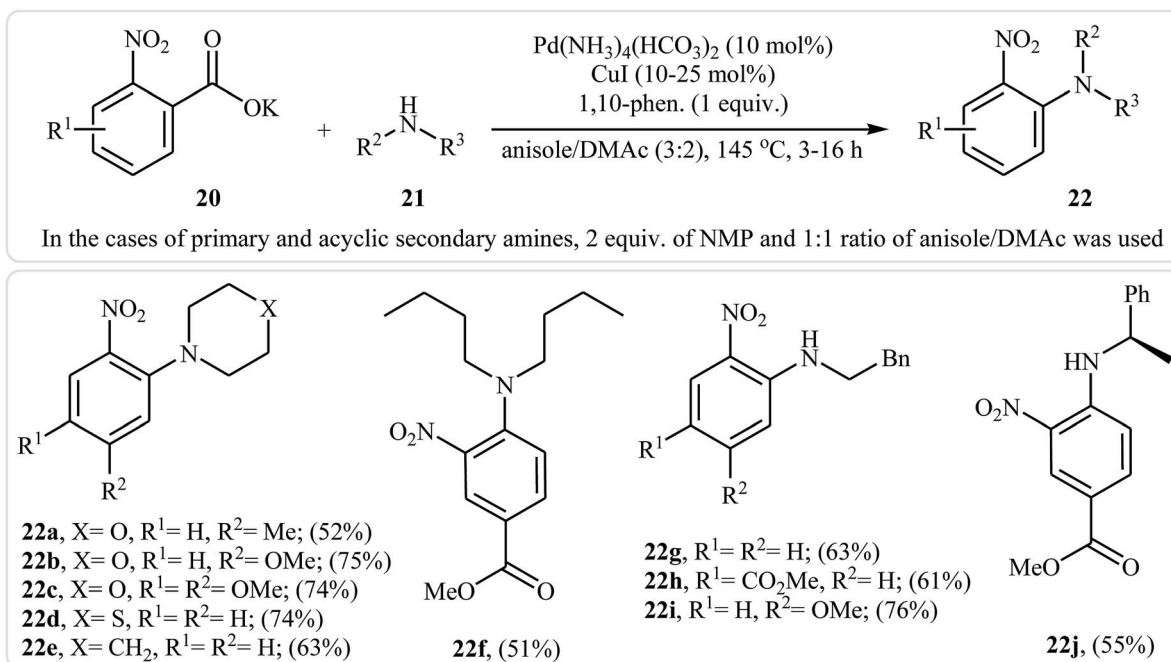
Not long after this report, Jia and co-workers extended the above cross-coupling to anilines.²⁷ They showed that the reaction of potassium 2-nitrobenzoate **17** with primary anilines **18** in the presence of 1.0 equiv. of CuSO_4 as mediator in NMP afforded the corresponding diarylamines **19** in moderate 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_2CO_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.²⁸

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 **20** with aliphatic amines **21**.²⁹ A variety of *N*-arylated amines **22** were obtained in up to 81% yields in a solvent mixture of anisole and dimethylacetamide (DMAc) employing $\text{Pd}(\text{NH}_3)_4(\text{HCO}_3)_2/\text{CuI}/1,10\text{-phen}$ 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.



Scheme 9 Jia's synthesis of diarylamines **19**.





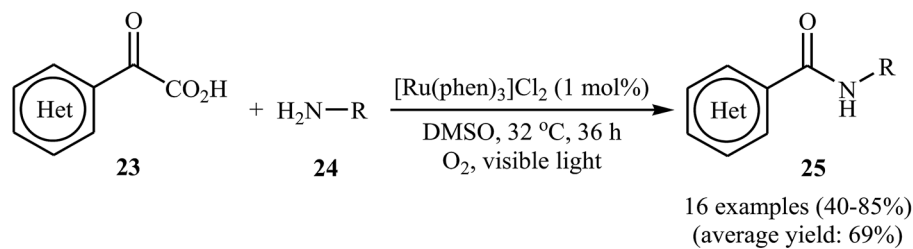
Scheme 10 Decarboxylative *ipso*-amination of benzoic acids **20** with aliphatic amines **21** reported by Gooßen.

4. Cross-coupling reactions between C_{carbonyl}-CO₂H and N-H bonds

The first example of decarboxylative amidation of α -keto acids with amines 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]Cl₂ 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).³⁰ 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.³¹ 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.

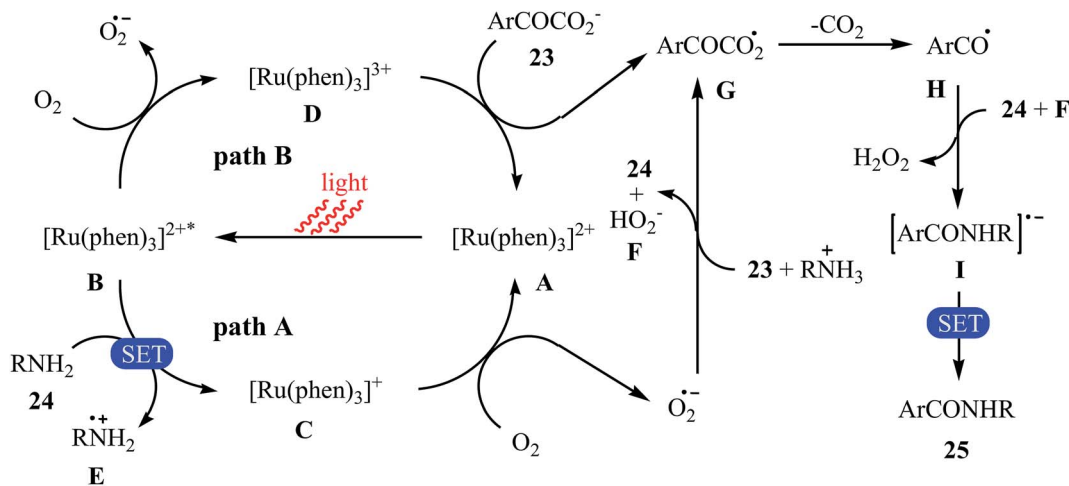
In 2016, Liu, Wang, and co-workers demonstrated an interesting amidation of α -keto acids **26** with *N*-benzylpicolinamide derivatives **27** through a palladium-catalyzed decarboxylative process.³² This new methodology provides a concise and efficient synthesis of various substituted imides **28** 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



(Het)Ar= Ph, 4-Me-C₆H₄, 4-OMe-C₆H₄, 4-CF₃-C₆H₄, 4-Cl-C₆H₄, 4-Br-C₆H₄, 2-naphthyl, 2-thienyl
 R= ⁿBu, ^cHex, Ph, 4-Me-C₆H₄, 4-^tBu-C₆H₄, 4-SMe-C₆H₄, 4-NMe₂-C₆H₄, 2-OMe-C₆H₄

Scheme 11 Ru-catalyzed decarboxylative amidation of α -keto acids **23** with amines **24** reported by Lei.





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

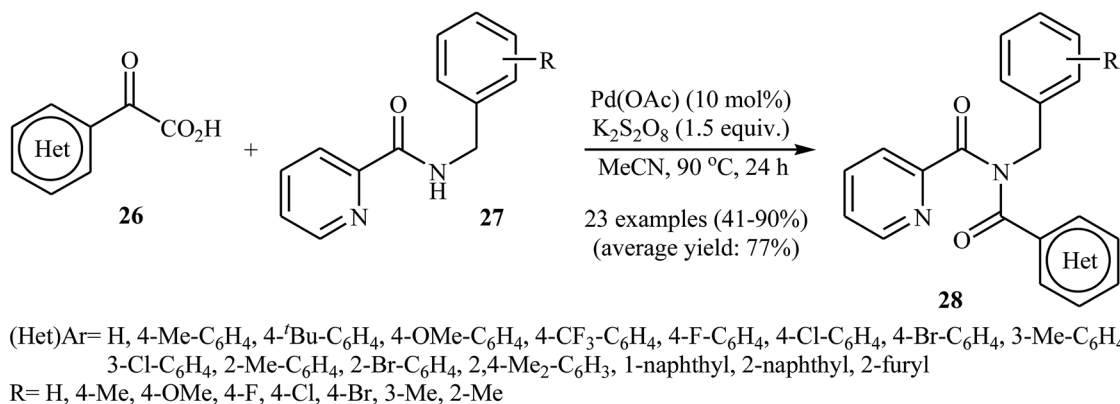
aromatic ring of amides according to Scheme 13. However, the outcome of reaction was strongly dependent on the electronic character of the substituents on the phenyl ring periphery of 2-oxo-2-arylacetic acids. Generally, electron-rich carboxylic acids afforded better yields compared to electron-poor 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.³³ 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%.³⁴

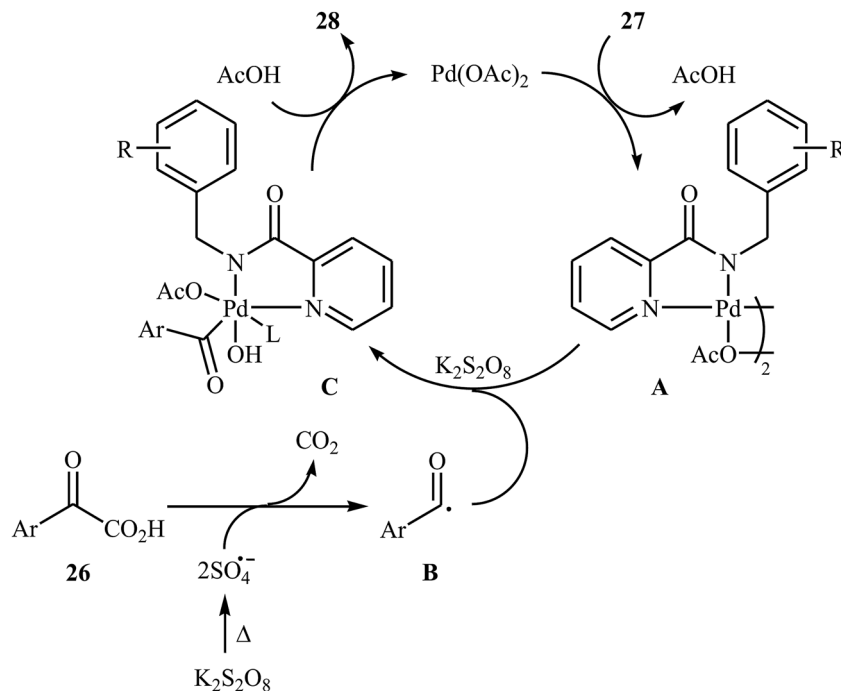
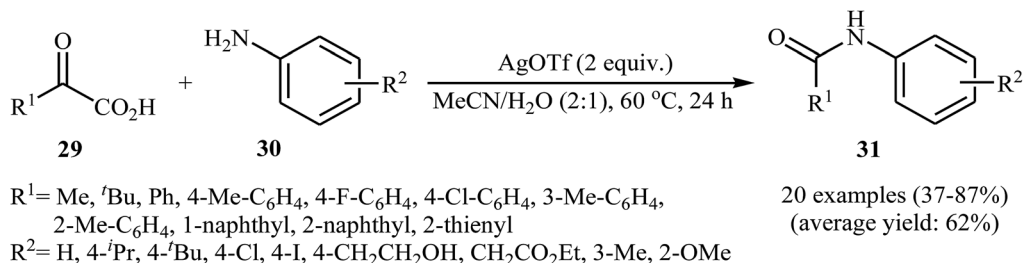
5. Cross-coupling reactions between C_{alkynyl}-CO₂H and N-H bonds

Although direct decarboxylative cross-coupling of alkynyl carboxylic acids with C-H bonds has been well known,³⁵ the decarboxylative hetero-coupling reactions between C(sp)-CO₂H



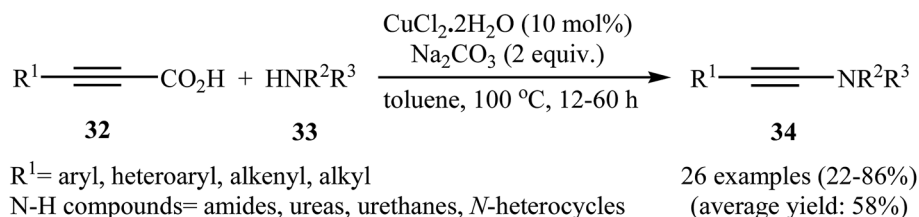
Scheme 13 Synthesis of imides **28** via Pd-catalyzed decarboxylative amidation of α -keto acids **26** with *N*-benzylpicolinamides **27**.

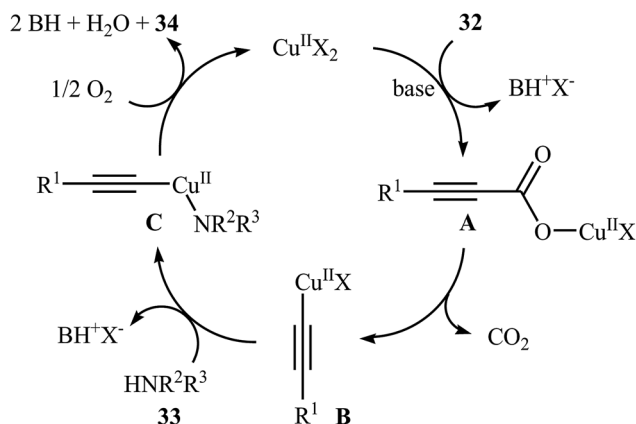


Scheme 14 Plausible mechanism for Liu-Wang's synthesis of imides **28**.Scheme 15 Ag-catalyzed synthesis of secondary amides **31** from α -keto acids **29** and anilines **30** via a decarboxylative process.

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 $\text{CuCl}_2 + 2\text{H}_2\text{O}$ as a catalyst and 2.0 equiv. of Na_2CO_3 as a base in toluene to

form the corresponding C(sp)-N bearing adducts **34** within 12–60 h (Scheme 16).³⁶ 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 CuBr_2 , Cu_2O , $\text{Cu}(\text{OAc})_2 + \text{H}_2\text{O}$ and $\text{CuSO}_4 + 5\text{H}_2\text{O}$ were also found to promote this coupling reaction; albeit

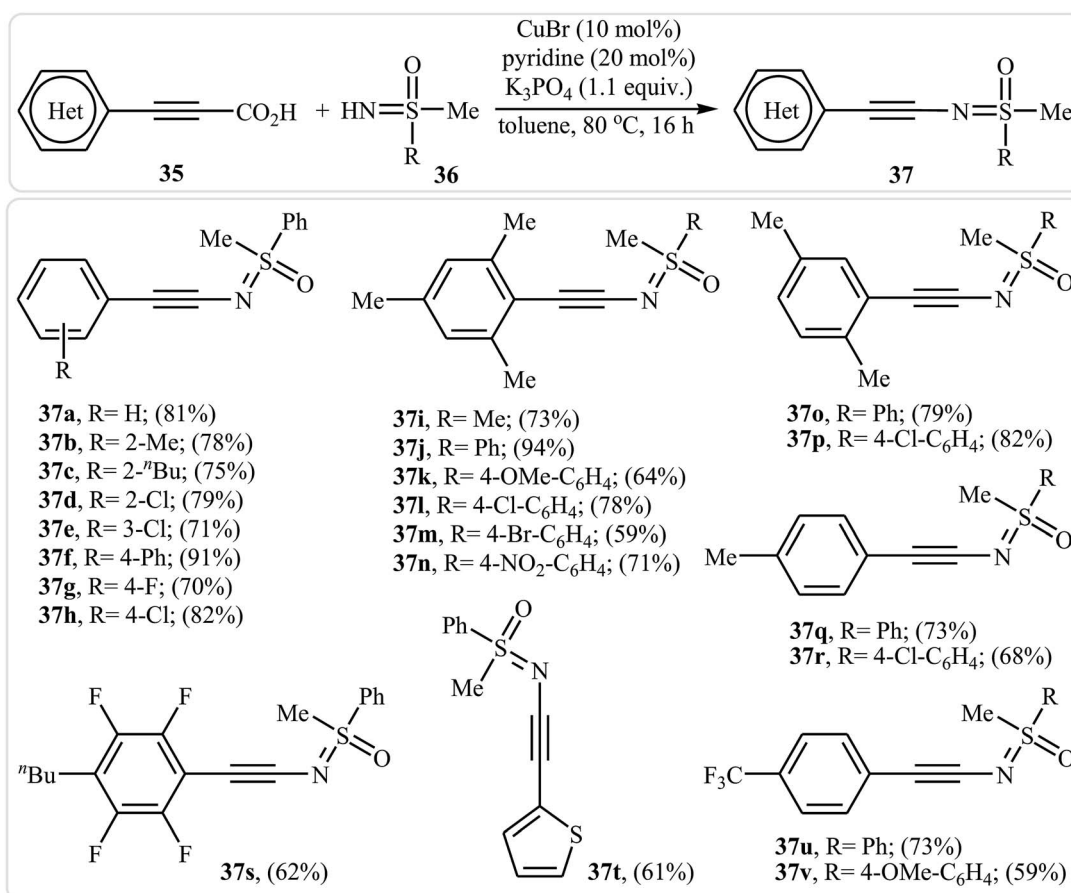
Scheme 16 Cu(II)-catalyzed amidation of propiolic acids **32** with nitrogen nucleophiles **33**.



Scheme 17 Plausible mechanism for the reaction in Scheme 16.

with reduced efficiencies. A proposed mechanistic possibility is depicted in Scheme 17. This transformation starts 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 Cu(II)(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.³⁷ 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 minimizes 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 isobutyryl chloride.

Scheme 18 Bolm's synthesis of sulfoximidoyl-functionalized alkynes **37**.

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(sp³)–N, C(sp²)–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.

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