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Cite this: *Chem. Commun.*, 2022, **58**, 7593

Oxamic acids: useful precursors of carbamoyl radicals

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Received 5th April 2022,
Accepted 16th June 2022

DOI: 10.1039/d2cc01953a

rsc.li/chemcomm

This review article describes the recent development in the chemistry of carbamoyl radicals generated from oxamic acids. This mild and efficient method compares well with previous methods of generation of these nucleophilic radicals. The oxidative decarboxylation of oxamic acids can be mediated through thermal, photochemical, electrochemical or photoelectrochemical means, generating carbamoyl radicals, which may further add to unsaturated systems to provide a broad range of important amides. Oxidative decarboxylation of oxamic acids also offers a straightforward entry for the preparation of urethanes, ureas, and thioureas.

1. Introduction

Oxamic acids **I** also known to as oxalic acid monoamides have emerged as potent precursors for the generation of the carbamoyl radical **II** (Fig. 1). Oxamic acids can easily undergo decarboxylation through a single electron oxidation resulting in the generation of the reactive carbamoyl radical, which can then engage in diverse radical reactions or undergo a second single electron oxidation as originally unveiled by Minisci.[1] Oxamic acids are thus versatile intermediates for the synthesis of nitrogen-containing organic molecules.

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Ekad and Rokach first demonstrated that carbamoyl radical **II**, generated through photolysis of formamides ($R_2NC(=O)H$) was able to add to terminal and non-terminal olefins.[2] **II** is nucleophilic in nature and therefore readily adds to electron deficient systems, but also to alkynes, arenes, and heteroarenes, providing a reliable tool for the construction of nitrogen-containing substrates.[3] Carbamoyl radicals may be observed by Electron-Spin-Resonance (ESR) depending on the nature of the substitution on the nitrogen.[4] For instance, *N*-alkyl and *N*-alkyl-*N*-aryl carbamoyl radicals are both stable enough to be observed through ESR,[5] while the *N*-arylcarbamoyl analogue **IIa** is transient and tends to decarbonylate to generate the more stable persistent arylaminyl radical **IV**. Sutcliffe and Ingold[6] showed through ESR and NMR experiments that the relative proportion of the s-*cis* and s-*trans* conformations of the carbamoyl radical **II**, resulting from the abstraction of formamides CHO hydrogen paralleled that of the parent formamide conformations in every respect. Radical **II** is a σ-type radical, which displays a reactivity similar to that of

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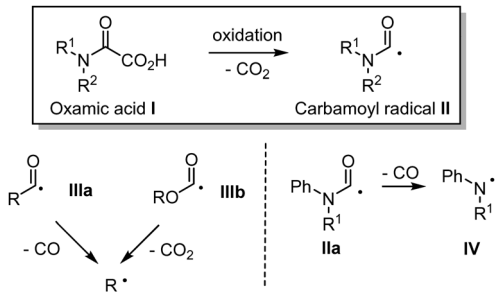
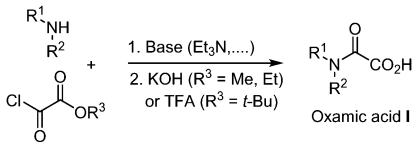


Fig. 1 Carbamoyl radicals from oxamic acids. Related acyl radicals.

closely related α-type acyl **IIIa** and alkoxycarbonyl **IIIb** radicals (Fig. 1).[7] However and in contrast, radical **II** lifetime is relatively long as compared to that of **IIIa** and **IIIb**, which are prone to decarbonylation and decarboxylation respectively, resulting in the generation of the more stable alkyl radicals.[8] Decarbonylation of carbamoyl radical **II** is less favoured (except in arylaminyl cases **IIa**, *vide supra*), as it would lead to a higher energetic aminyl radical. Although less attention was paid to carbamoyl radical as compared to its acyl radical analogues, recent years have witnessed an increasing interest in the use of **II** in synthetic organic chemistry, which may be attributed among other factors, to the renaissance of oxamic acid as its potent precursor. Carbamoyl radical is traditionally generated by the homolytic cleavage of $R_2NC(=O)$–X precursors using a radical initiator, heat, or UV light, where X can be H,[9,10] SPh,[11] xanthate,[12] Co(salophen),[7] cyclohexadienyl,[13] TePh,[14] SePh[15] or Cl.[16] Other methods to access carbamoyl radicals include photocatalyzed cleavage of weak S–C bond in dithiocarbamate,[17a] or carbamoyl-Hantzsch esters,[17b–e] reductive decarboxylation of *N*-hydroxyphthalimido oxamides,[18] and oxidation of phenylhydrazinecarboxamide.[19] These strategies have their own merits but often rely on the synthesis of precursors, which require several steps and the use of complex reagents, leading to poor atom economy. Regioselectivity problems were also observed, for instance during the generation of the carbamoyl radical through formamides C–H abstraction, which can provide a mixture of products, resulting from the competitive abstraction at CHO and α to nitrogen.[9,20] In contrast, the generation of carbamoyl radicals through decarboxylation of oxamic acids has been shown to be very efficient and circumvent the regioselectivity issues associated with classical routes. Unlike the well-studied decarboxylative coupling of carboxylic acids and ketoacids, decarboxylation of oxamic acids proceeds under mild reaction conditions. Oxamic acids are bench stable and non-toxic compounds that can be easily prepared by direct coupling of amines with commercially available oxalic acid monoester derivatives (Scheme 1).[21] The oxamate ester intermediate may be hydrolysed under basic conditions when methyl and ethyl esters are present, while acidic conditions were found very convenient with *t*-Bu esters directly leading to the oxamic acid. This simple two-step procedure gives access to oxamic acids of wide structural diversity using various amines and does not require tedious purification processes. We describe in this review article recent efforts to exploit the versatile reactivity of the simple, yet attractive, carbamoyl radical in addition, coupling and oxidative processes.



Scheme 1 Oxamic acid preparation from oxalic acid chloride monoester.

2. Decarboxylative coupling reactions using oxamic acids

As mentioned earlier, Minisci and co-workers[1,9a,b] originally showed that oxidative decarboxylation of oxamic acids **1** using a stoichiometric amount of ammonium persulfate as oxidant and

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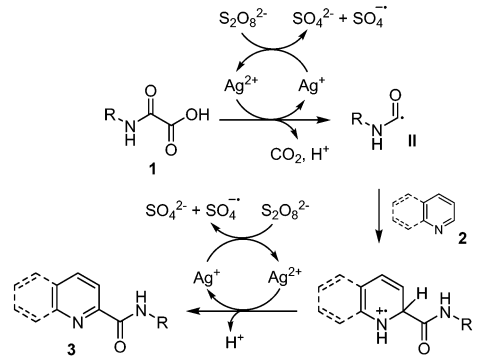


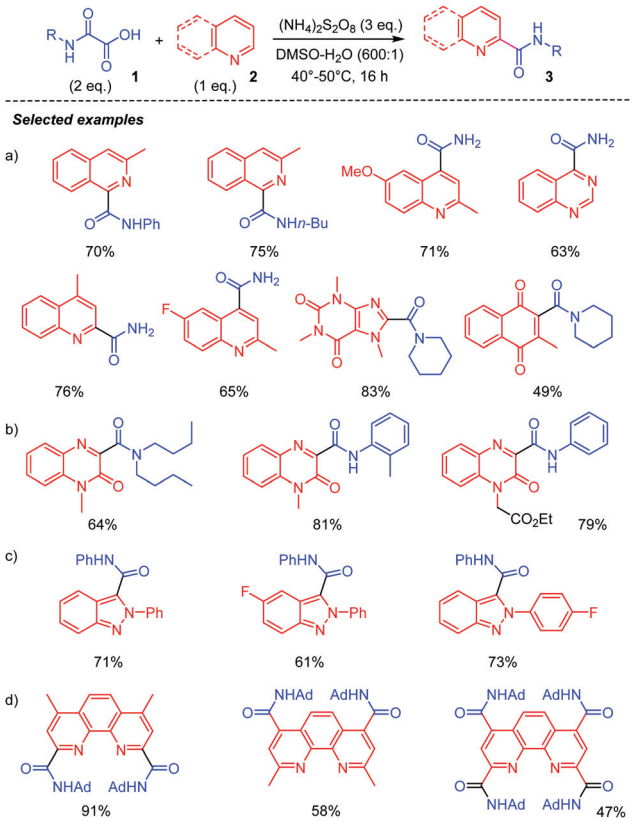
Scheme 2 Ag(I)/persulfate-mediated generation of carbamoyl radical **II** and addition to heteroarenes.

a silver salt as a catalyst generates the carbamoyl radical **II**, which could then be trapped by a protonated heteroaromatic base **2**,[22] to furnish the corresponding amide **3** in excellent yield (Scheme 2). According to their mechanism, the Ag(II) species, generated through the oxidation of Ag(I) by the persulfate, triggered the oxidation of oxamic acid into carbamoyl radical **II**. This seminal work has continued to attract increasing attention in organic synthesis and has led to many different simple procedures for the preparation of amides of biological interests using oxamic acids.[23]

A silver-free version of the above Minisci reaction was recently reported by different laboratories and demonstrated to be efficient for carbamoylation of a variety of heteroarenes, including quinoxalin-2(1*H*)-ones,[24] phenanthrolines[25] and 2*H*-indazoles (Scheme 3).[26] This procedure relies on the use of $(NH_4)_2S_2O_8$ as an oxidant, DMSO/H_2O as solvents, and a temperature between 40–60 °C to furnish the corresponding amides **3** in moderate to high yield, without the need for a silver salt catalyst or acidification. The choice of solvent proved to be crucial, the reaction being greatly accelerated in a DMSO : H_2O (600 : 1) mixture. DMSO or water alone gave inferior product yield, while other organic solvents such as DCE, CH_3CN, MeOH, and 1,4-dioxane were not suitable for the reaction. The procedure led to high yield of amidation of quinolines (Scheme 3, (a))[25a] quinoxalin-2(1*H*)-ones, (b)[24] and 2*H*-indazoles, (c).[26] A direct C–H functionalization of phenanthrolines, useful ligands in Cu- or Fe-catalyzed processes, has also been carried out using this strategy, (d).[25b] Polyamides were thus at hand through a simple treatment of phenanthroline precursors with excess oxamic acid.

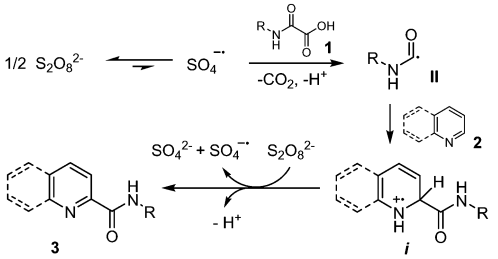
A plausible mechanism proposed by Yuan and co-workers[24] (Scheme 4) suggests that the reaction proceeds first by homolytic cleavage of $S_2O_8^{2-}$ in DMSO to give $SO_4^{\bullet-}$, the latter then mediating the oxidative decarboxylation of oxamic acid **1** into carbamoyl radical **II**. A regioselective addition of the carbamoyl radical onto the heteroarene **2** would then follow, leading to intermediate ***i***. A single electron transfer (SET) from ***i*** mediated by $S_2O_8^{2-}$ would then give a cationic species, which undergoes deprotonation and rearomatization to afford the final product **3**.

Our group recently developed a visible light-mediated carbamoyl radical addition to heteroarenes using oxamic acids (Scheme 5).[27] This metal-free and efficient process operates at

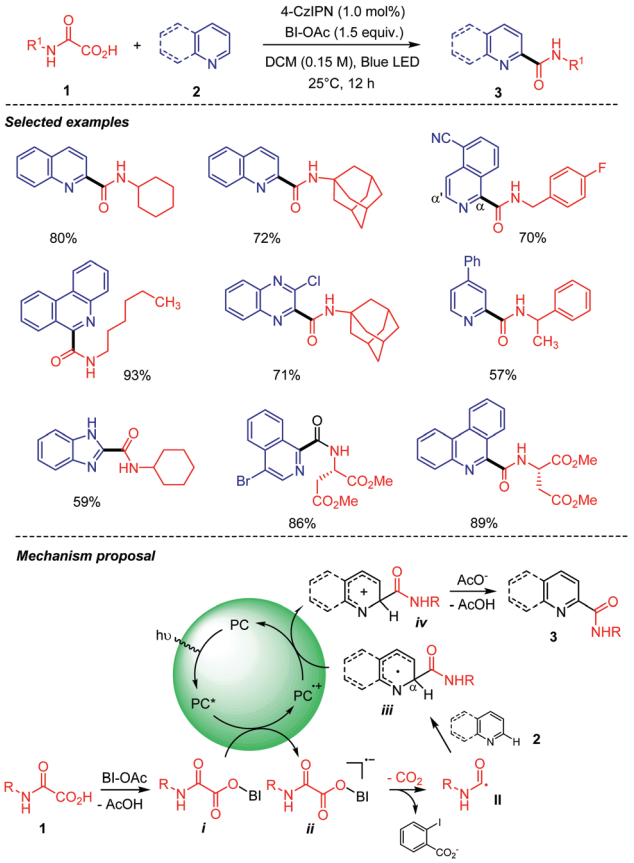


Scheme 3 Persulfate-mediated generation of carbamoyl radical **II** and addition to heteroarenes.

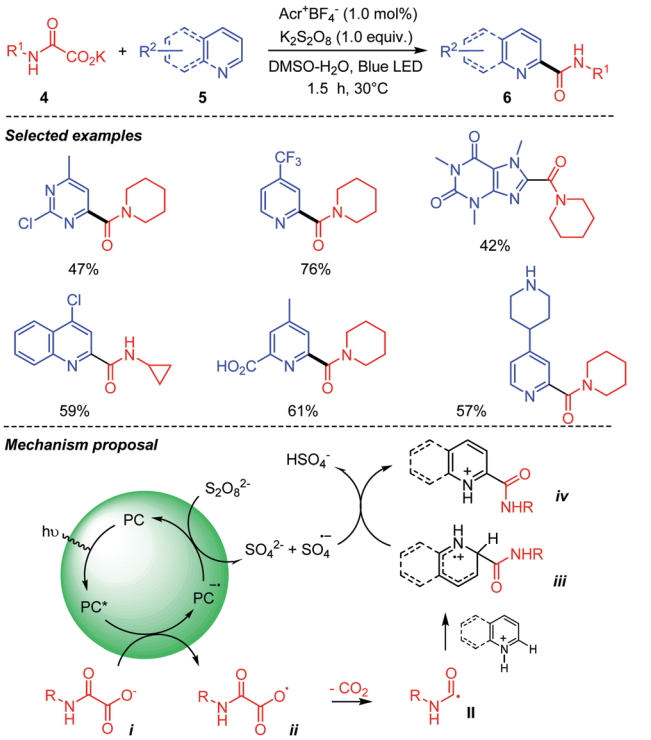
room temperature, using a hypervalent iodine reagent, *i.e.* acetoxybenziodoxolone (BI-OAc) as an oxidant, and an organic dye, *i.e.* 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4-CzIPN) to mediate the oxidative decarboxylation of oxamic acid **1** into the carbamoyl radical **II**, which in the presence of heteroaromatic base **2** delivered the corresponding amide **3** in good to high yields. The procedure is compatible with a wide range of oxamic acids **1**, including chiral ones to furnish the desired chiral amides without racemization. The involvement of the carbamoyl radical **II** was unambiguously demonstrated through its trapping with (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO), an alkynylsulfone, or an allylsilane, leading respectively to a TEMPO-**II** adduct, an alkynylamide, or an unsaturated amide. A plausible mechanism for the transformation suggests that the photoexcited catalyst (4-CzIPN*) is



Scheme 4 Mechanism of the metal-free persulfate decarboxylation of oxamic acids and addition to heteroarenes.



Scheme 5 Photocatalyzed decarboxylation of oxamic acids in the presence of heteroarenes. Heteroarenes scope and mechanistic proposal.



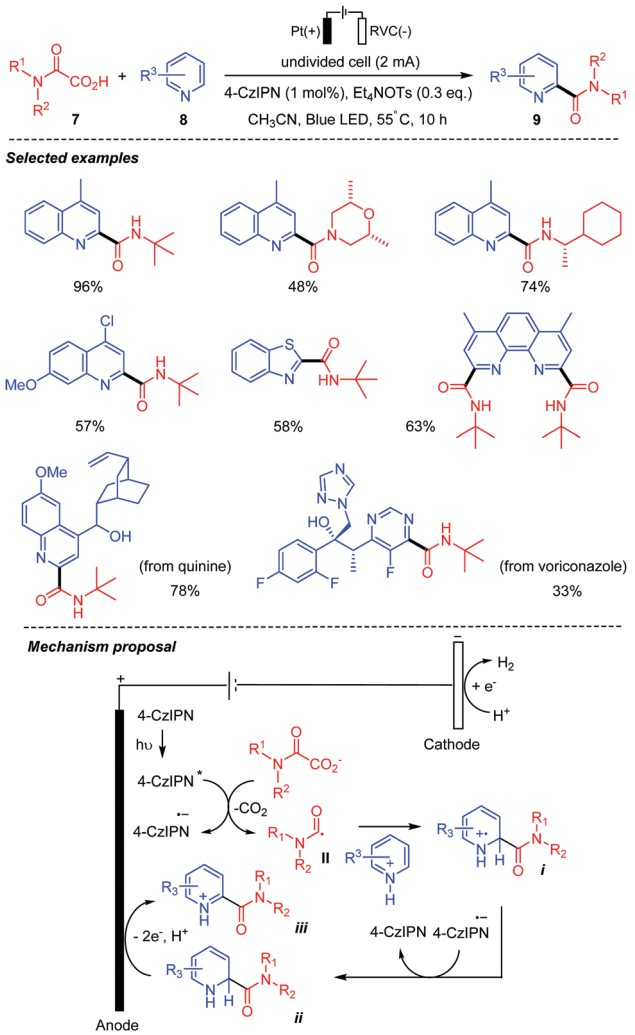
Scheme 6 Acridinium-mediated photocatalyzed decarboxylation of oxamic acids in the presence of heteroarenes.

quenched by a hypoiodite species ***i*** formed by a ligand exchange between oxamic acid **1** and BI-OAc (Scheme 5). The generated unstable radical anion ***ii*** collapses to give the carbamoyl radical **II**. The latter then undergoes radical addition to the heteroaromatic base **2** to give a radical intermediate ***iii***, which is oxidized by the photocatalyst in its semi-oxidized form (4-CzIPN^{+}) to give cationic species ***iv***. Deprotonation and rearomatization of ***iv*** then furnish the product **3**. As proposed by Minisci,[1] the carbamoyl radical addition likely occurs onto the protonated heteroaromatic base **2** under these conditions where acetic acid is produced in the first step. Very recently, Chen, Yu, and co-workers[28] repeated the above experiments using a heterogeneous conjugated polymeric photocatalyst (CPP3) based on 4-CzIPN and were able to catalyze the addition of a cyclohexyloxamic acid to quinoline albeit with a lower yield than with the simple 4-CzIPN (60% *vs.* 80% with 4-CzIPN, Scheme 5).

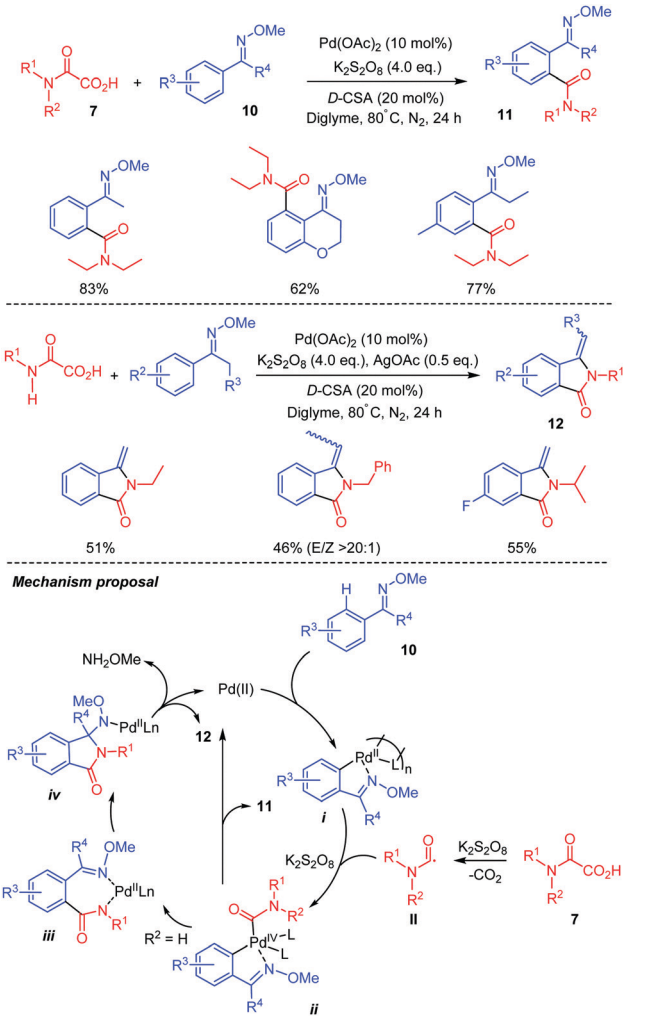
Jouffroy and Kong,[29] in the meantime, reported a similar visible light mediated decarboxylative carbamoylation of heteroaromatic bases **5** using oxamic acids and their potassium oxamate **4** (Scheme 6). Their method employs potassium persulfate as an oxidant in aqueous DMSO to achieve the decarboxylative carbamoylation under visible light irradiation using an acridinium-based photocatalyst. The desired amides **6** were obtained in moderate to good yields using aliphatic potassium oxamates. Interestingly, from a mechanistic point of view, the photocatalyst in its excited state is reduced by the oxamate salt and the oxidant is used here to reoxidize the photocatalyst back to its ground state. The reaction led to good results whatever the primary or secondary nature of the oxamic acid.

In 2020, Song and co-workers[30] unveiled an electrophotocatalytic decarboxylative Minisci reaction between oxamic acids **7** and heteroarenes **8** (Scheme 7). This strategy, that combined organic electrochemistry, and photocatalysis with the anodic oxidation replacing the chemical oxidant, was shown to be efficient for the preparation of various amides **9**. The authors demonstrated that both the light and electricity were essential for the transformation as only 3 to 18% of the desired product was observed in the absence of either of them. The procedure was compatible with a wide range of oxamic acids and heteroarenes with good functional group tolerance. A plausible mechanism for the transformation involves a single electron oxidative decarboxylation of the oxamate ion ($E_{p/2ox}$ = +1.17 V *vs.* SCE) by the photoexcited catalyst 4-CzIPN* ($E_{p/2red}$ = +1.35 V *vs.* SCE), followed by the addition of the generated carbamoyl radical **II** to the protonated heteroarene, to give a radical-cation intermediate ***i***. The latter accepts an electron from the highly reducing photocatalyst radical anion (4-CzIPN$^{\cdot-}$) leading to intermediate ***ii***, along with the regenerated photocatalyst. Finally, anodic oxidation of ***ii*** furnished the final product ***iii***.

Besides heteroarenes as coupling partners, several other compounds can serve as competent coupling partners with oxamic acids, providing useful and efficient synthetic methods for the synthesis of amides. Wang and co-workers thus presented a palladium-catalyzed decarboxylative amidation using



Scheme 7 Electrophotocatalytic decarboxylative Minisci reaction between oxamic acids and heteroarenes.

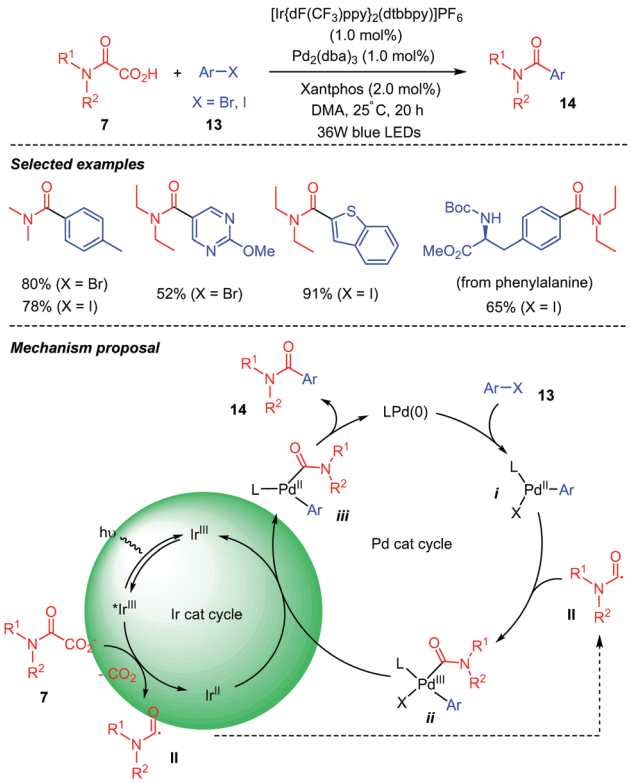


Scheme 8 Pd(II)-catalyzed C–H amidation by oxamic acids, of arenes having a ketoxime directing group.

oxamic acids and arenes with ketoxime group **10** as a coupling partner (Scheme 8).[31] The reaction works well with a wide range of *N*,*N*-disubstituted oxamic acids including cyclic ones to give the corresponding *ortho*-amidated ketoximes **11** in good yields and regioselectivity. With *N*-monosubstituted oxamic acids (**7**, R^2 = H), isoindolinones **12** were obtained instead through an intramolecular cyclization of the *ortho*-amidated ketoximes formed. The authors proposed that the reaction proceeds through the formation of a five-membered palladacycle ***i*** (Scheme 8). This is followed by the oxidative addition of the carbamoyl radical **II**, issued from oxamic acid decarboxylation, to the complex, to form a Pd(IV) intermediate ***ii***. The reductive elimination of ***ii*** would furnish product **11** and regenerates the Pd(II). When monosubstituted oxamic acid is used, the *ortho*-amidated ketoxime formed can further complex with Pd(II) to give a new complex ***iii***, which undergoes intramolecular insertion to give intermediate ***iv***. Then, removal of methoxyamine *via* β-H elimination affords the 3-methyleneisoindolinone **12**.

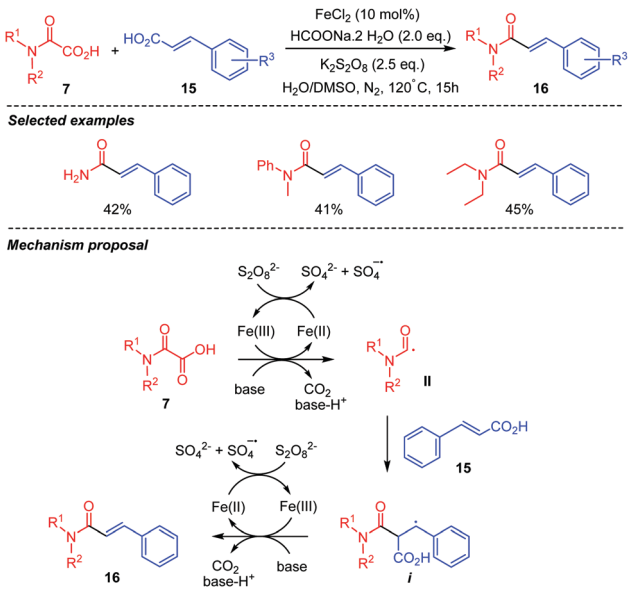
Fu and co-workers[32] reported a decarboxylative coupling of oxamic acids **7** and aryl halides **13** using a dual iridium and palladium photoredox catalytic system (Scheme 9). The authors showed that both catalytic partners were necessary for the reaction, as the desired product was not observed in the absence of either one of them. Although different possible mechanistic pathways were proposed for this transformation, in all, the photoexcited iridium (Ir(III)*) is implicated in the decarboxylation of the oxamic acid into carbamoyl radical **II**. Amongst three calculated pathways, one emerges and is depicted in Scheme 9 below, in which oxidative addition of Ar–X **13** onto Pd(0) provides a Pd(II) intermediate ***i***, which is able to capture the carbamoyl radical **II** to generate a Pd(III) species ***ii***. Reduction of the latter by Ir(II) restores Ir(III) in its ground state and a Pd(II) intermediate ***iv***, the reductive elimination of which affords product **14** and Pd(0).

Coupling of oxamic acids **7** with C(sp^2) centers in cinnamic acids **15** has also been reported (Scheme 10).[33] Fe(II) mediated oxidative decarboxylative cross-coupling of oxamic acids and acrylic acids was thus shown to afford α,β-unsaturated amides **16** (Scheme 10), albeit in moderate yields over a small number of examples. The mechanism is thought to proceed through the addition of the carbamoyl radical **II** onto the C(sp^2) center

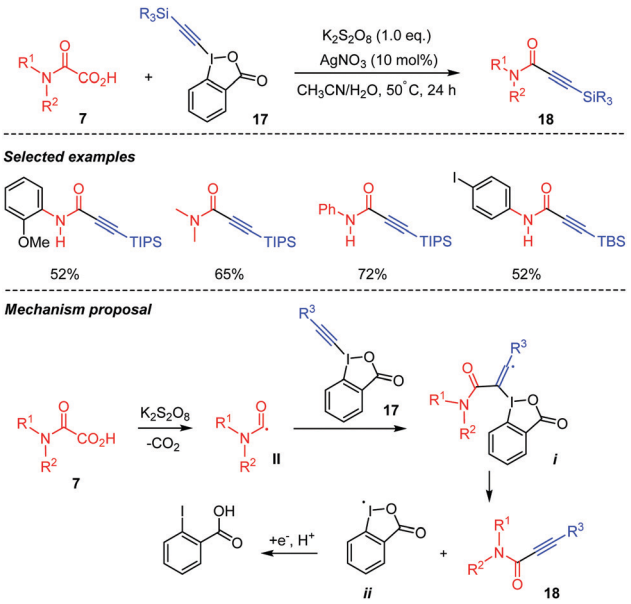


Scheme 9 Dual Ir–Pd photoredox catalyzed decarboxylative cross-coupling of oxamic acids and aryl halides.

bearing the CO_2H group to generate a benzylic radical intermediate ***i***. β-Elimination and release of CO_2 from ***i*** afford the cinnamoyl amide **16**. The persulfate oxidizes Fe(II) into Fe(III), the latter mediating the oxidative decarboxylation of the oxamic acid and the generation of the carbamoyl radical **II**.



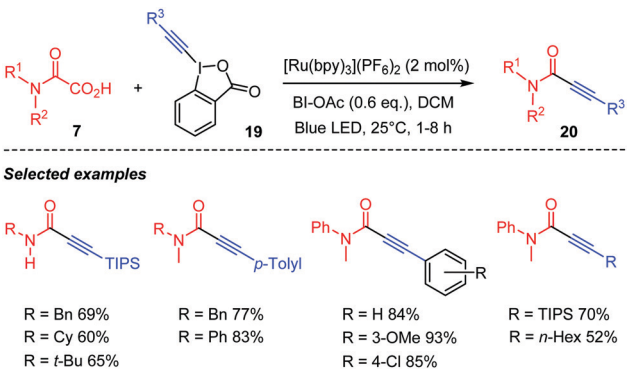
Scheme 10 Fe(II)-mediated oxidative decarboxylative cross-coupling between oxamic acids and cinnamic acids.



Scheme 11 Decarboxylative alkynylation of oxamic acids.

Oxamic acids can also be used for the formation of Csp^2–Csp bonds through decarboxylative coupling with alkynyl compounds. In 2015, Duan's group presented a decarboxylative alkynylation of oxamic acids **7** using hypervalent alkynyl iodide reagent **17** as the alkynylating agent (Scheme 11).[34] This strategy gave access to a wide range of propiolamides **18** in moderate yields using different oxamic acids and alkynyl coupling partners. Propiolamides are important synthons for organic synthesis and interesting building blocks for natural product synthesis.[34] The authors proposed that the reaction proceeds through the $K_2S_2O_8$ mediated decarboxylation of the oxamic acid **7** to generate carbamoyl radical **II**, which adds to the triple bond of the hypervalent iodine species **17**, leading to radical intermediate ***i*** capable of undergoing a β-elimination to deliver the desired product **18** and the benziodoxolonyl radical ***ii***. The latter is converted into benzoic acid through a reduction/protonation process.

Chen's group proposed in the meantime a visible light mediated version of this decarboxylative coupling of oxamic



Scheme 12 Photocatalyzed decarboxylative alkynylation of oxamic acids for the preparation of ynamides.

acids with hypervalent alkynyl iodine species **19** for the preparation of ynamides **20** (Scheme 12).[35] They demonstrated that the reaction was compatible with a wide range of oxamic acids, furnishing the corresponding ynamides in high yields.

3. Decarboxylative cyclization of oxamic acids for heterocycles synthesis

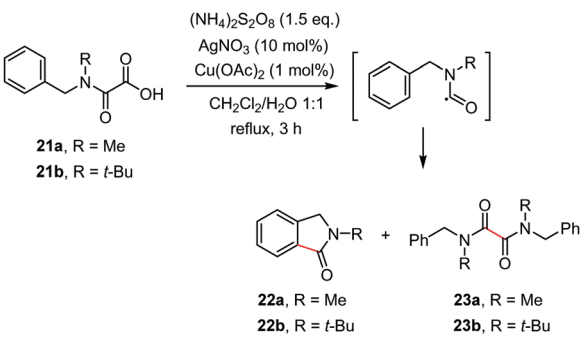
Recent years have witnessed the development of several useful synthetic procedures based on decarboxylative cyclization of oxamic acids for accessing heterocycles through C–C and C–X bonds formation. The progress in this area is summarized in this section.

The first decarboxylative cyclization of oxamic acids resulting in the formation of heterocyclic compounds was reported by Minisci and co-workers in 1995.[1b] They showed that the Ag-catalyzed radical decarboxylation of *N*-methyl (or *tert*-butyl)-*N*-benzyl-oxamic acids **21a–b** led to the cyclized products **22a–b** alongside with homocoupling products **23a–b**, though the details for the yields of the product were not available (Scheme 13). As the oxidation of the carbamoyl radical of secondary alkylamines is slow relative to that of primary ones, cyclization and dimerization of the radical was observed to afford a mixture of **22** and **23.**

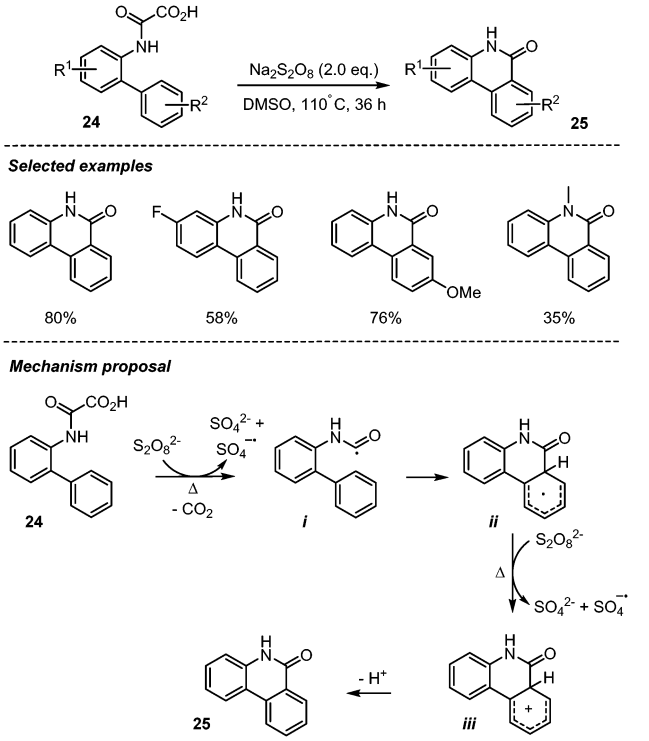
Zhang group in 2015 developed an efficient transition-metal-free procedure for accessing phenanthridinones **25** *via* $Na_2S_2O_8$-mediated decarboxylative cyclization of biphenyl-2-oxamic acids **24** (Scheme 14).[36] This simple procedure was shown to be efficient with different biphenyl-2-oxamic acids having both electron-withdrawing and electron-donating groups, furnishing the target compounds in moderate to high yields without precautions to exclude air from the reaction mixture. The authors proposed that the reaction possibly progressed through a homolytic aromatic substitution,[37] involving the addition of a carbamoyl radical ***i*** onto the proximal arene, followed by the oxidation of the resulting cyclohexadienyl radical ***ii*** into cation ***iii***, by $S_2O_8^{2-}$ and rearomatization and loss of a proton.

The procedure was also applied for the synthesis of isoindolinone **26a** as well as isoquinolinone **26b** (Scheme 15).[36]

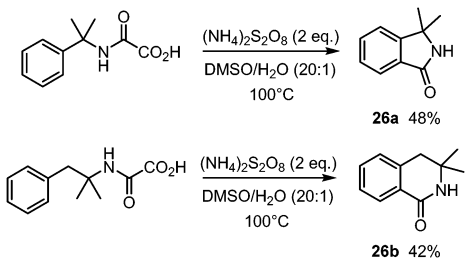
In 2018, Wang *et al.*, reported a hypervalent iodine(III)-mediated decarboxylative intramolecular Heck-type reaction



Scheme 13 Ag/Cu-mediated decarboxylative cyclization of oxamic acids.

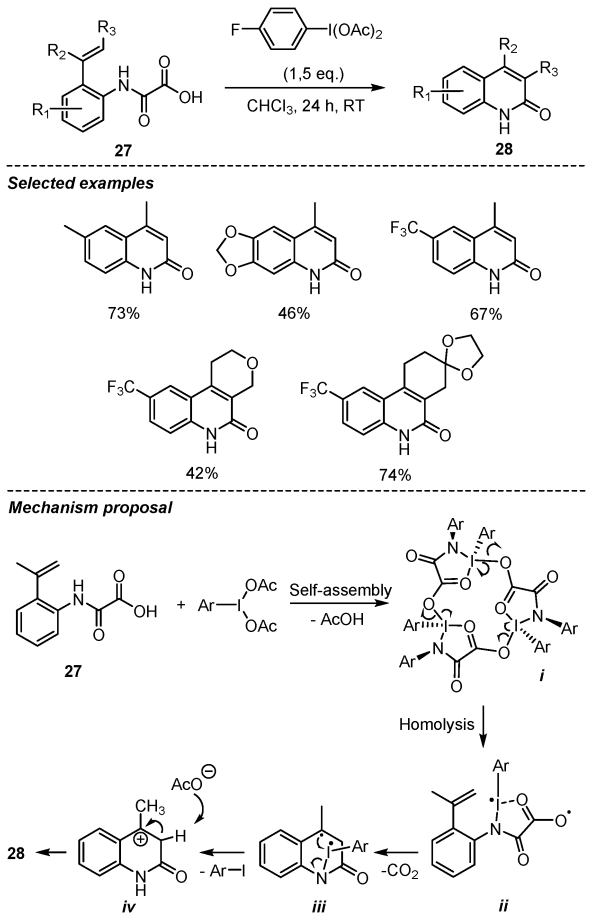


Scheme 14 Decarboxylative cyclization of oxamic acids for phenanthridinones synthesis.



Scheme 15 Decarboxylative cyclization of oxamic acids. An access to isoindolinones and isoquinolinones.

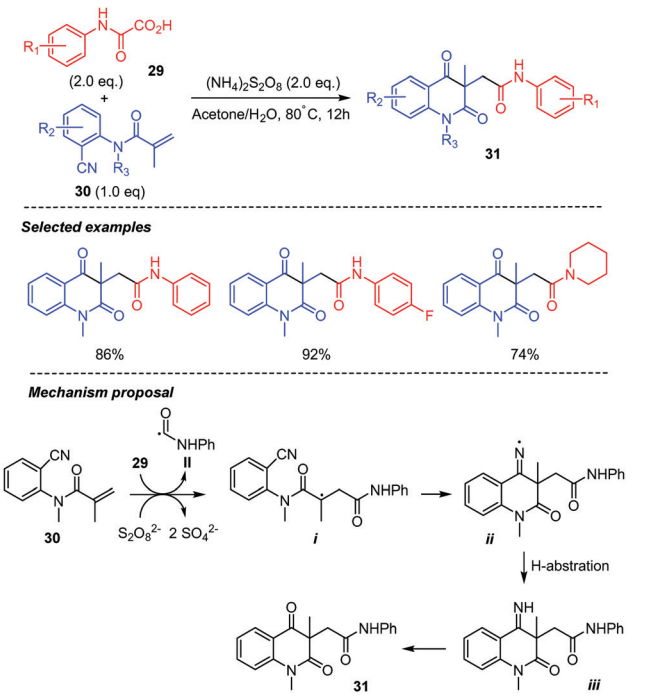
of oxamic acids for the synthesis of 2-quinolinones, a well-known structural motif in many natural products and pharmaceutical agents (Scheme 16).[38] This mild and metal-free procedure delivered a wide range of 2-quinolinones **28** in good yields from the corresponding 2-vinyl-phenyl oxamic acid **27**. Usual phenyliodine(III) diacetate (PIDA) and phenyliodine(III) bis-trifluoroacetate (PIFA) reagents were found to be less efficient than the *p*-fluoro analogue. The authors showed that the presence of TEMPO in the reaction mixture significantly suppressed the formation of 2-quinolinones, suggesting the involvement of a radical pathway. Based on this and literature precedent, they proposed a ring-strain-enabled radical decarboxylation mechanism, in which the hypervalent iodine reagent first forms a macrocyclic iodine(III) trimer ***i*** through self-assembly. A similar macrocycle generated from amino-acids and PIDA was reported by Zhdankin *et al.* and its structure unambiguously assigned through X-ray diffraction studies.[39] A significant high



Scheme 16 Intramolecular decarboxylative Heck-type reactions of oxamic acids.

ring strain in this macrocyclic species is believed to facilitate the homolysis of the iodine-oxygen bond to generate diradical intermediate ***ii***. This is followed by decarboxylative radical addition onto the olefin and cyclization. Subsequent intramolecular electron transfer in ***iii*** leads to a benzylic cation intermediate ***iv***. The formation of the latter is supported by the observation that when the benzylic CH_3 was replaced by $-CF_3$, the reaction was completely shutdown. The presence of the NH group in the oxamic acid also proved very important, as the desired product was not observed when *N*-methyl substituted oxamic acid was used.

Intermolecular addition-cyclization cascade reactions using oxamic acids have also been described. These reactions are summarized below. A new and efficient procedure for the synthesis of carbamoyl quinoline-2,4-diones **31** based on persulfate mediated tandem radical cyclization of *ortho*-cyanoarylacrylamides **30** with oxamic acids **29** was reported (Scheme 17).[40] A wide range of oxamic acids with different substituents on the phenyl ring and *N*-(2-cyanoaryl)acrylamides were compatible with the reaction conditions, providing the desired product in moderate to high yields. However, acrylamides with a free N–H bond were not suitable. As described above, the reaction proceeds through the $(NH_4)_2S_2O_8$-mediated decarboxylation of oxamic acid **29** generating the carbamoyl radical **II**, which adds to the *ortho*-cyanoarylacrylamides **30** to give an alkyl radical intermediate ***i***. The latter then undergoes a

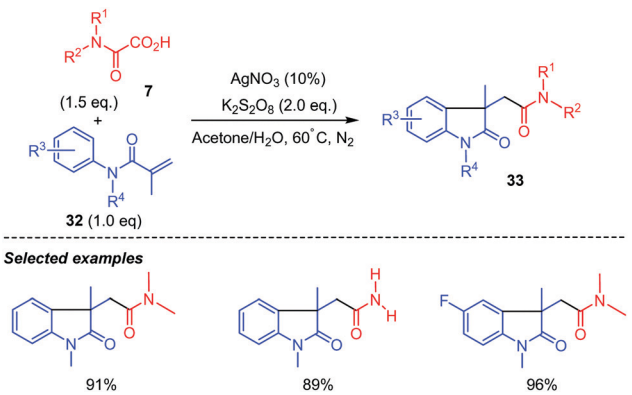


Scheme 17 Persulfate mediated tandem addition-cyclization of carbamoyl radicals to *ortho*-cyanoarylacrylamides.

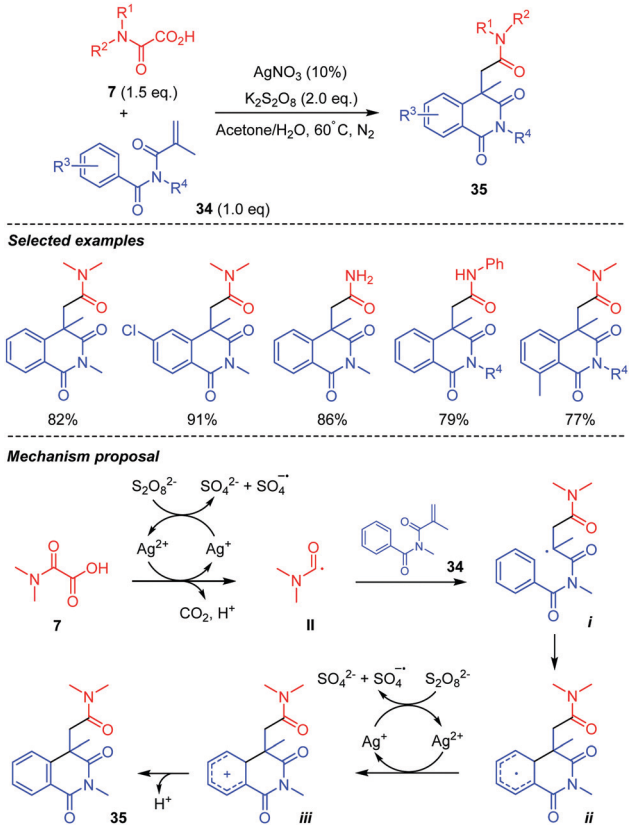
6-*exo*-dig cyclization on the nitrile group to give an iminyl radical ***ii***, followed by H-abstraction (from the solvent) to give imine ***iii***. The latter would finally undergo hydrolysis to deliver the final product **31**.

Interestingly, when acrylamide **30** does not bear an *ortho* CN substituent as in **32**, radical intermediate **i** was shown by Ma and co-workers[41] to directly cyclize onto the aromatic ring providing the 5-membered ring lactam **33** in generally high yields whatever the substitution on the aromatic ring (Scheme 18). *N*-Protected acrylamide **32** was however compulsory as the reaction with the N–H analogue did not afford the desired lactam.

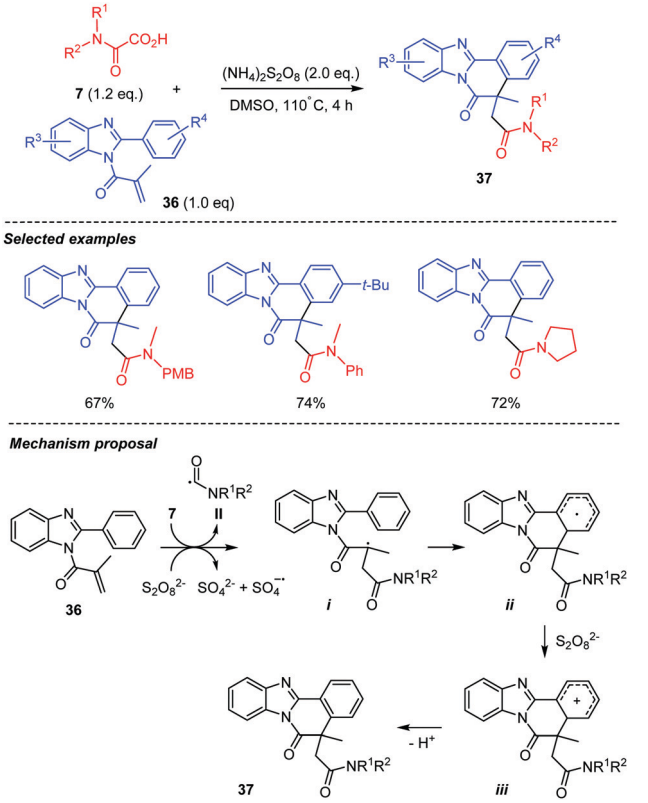
The same authors generalized the approach to the addition of carbamoyl radical **II** to acrylimides **34** (Scheme 19).[41] In this



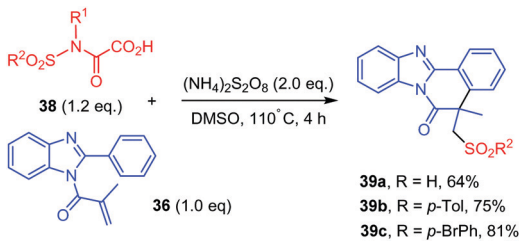
Scheme 18 Persulfate mediated tandem addition-cyclization of carbamoyl radicals to arylacrylamides.



Scheme 19 Persulfate mediated tandem addition-cyclization of carbamoyl radicals to arylacrylimides.



Scheme 20 Persulfate mediated tandem addition-cyclization of carbamoyl radicals to benzimidazoylacrylamides.



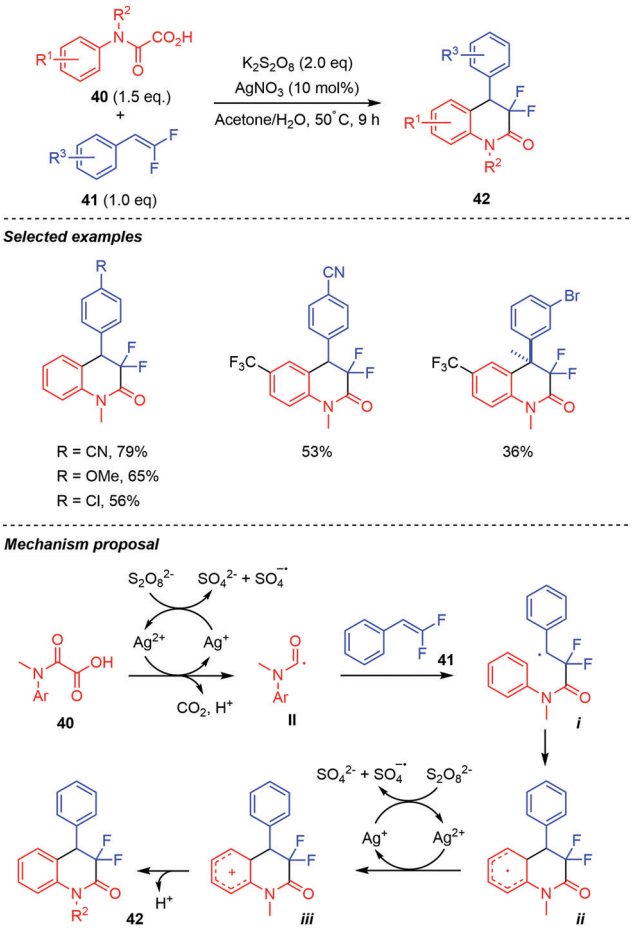
Scheme 21 Persulfate mediated tandem addition-cyclization of sulfonyl radicals to *ortho*-cyanoarylacrylamides.

case, the addition was followed by a 6-*exo* cyclization of the radical ***i***, onto the aromatic ring, affording the corresponding cyclohexadienyl radical ***ii***. Oxidation of the latter led to the corresponding cation ***iii***, giving to the 6-membered ring imide **35** after rearomatization. The scope of the reaction was shown to be rather broad, reaction conditions being compatible with electron-poor and rich substituents on the arene, the process also working with mono- and unsubstituted oxamic acids **7**.

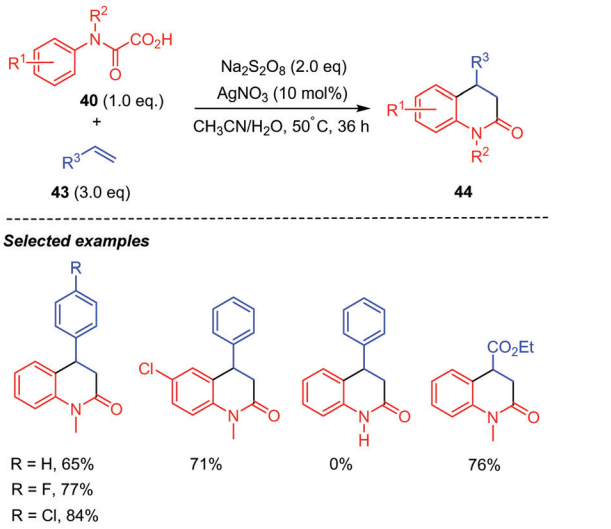
A closely related studies was recently reported, which included the intermolecular addition of a carbamoyl radical onto an unsaturated amide attached to a benzimidazole skeleton **36** (Scheme 20).[42] The carbamoyl radical **II** was generated as above from **7** through thermal decomposition of a persulfate in DMSO. The addition of the carbamoyl radical **II** onto **36** is followed by a cyclization of the resulting radical ***i*** onto the neighbouring arene to generate ***ii***, further oxidized into the cation ***iii***, which finally rearomatizes to afford **37**.

Interestingly, in the same study,[42] *N*-sulfonyloxamic acids **38** were submitted to the similar reaction conditions, which led to the addition of the sulfonyl group resulting from a homolytic cleavage of the N–S bond, leading to **39** (Scheme 21).

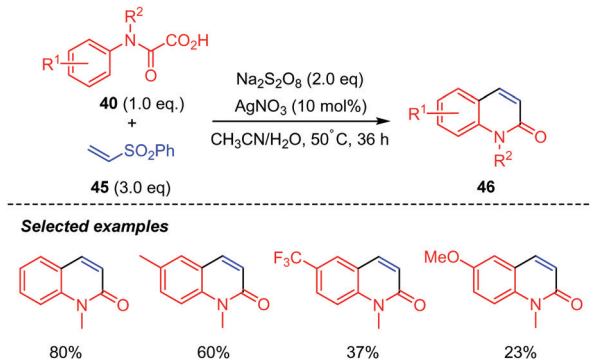
Liu and co-workers reported a closely related Ag-promoted decarboxylative radical addition/annulation of oxamic acids **40** with *gem*-difluoro-olefins **41**, leading to CF_2-containing 3,4-dihydroquinolin-2-ones **42** (Scheme 22).[43] Various *N*-substituted aniline-derived oxamic acids and *gem*-difluoroalkenes **41** bearing electron-withdrawing and electron-donating groups on the benzene ring were compatible with the reaction, furnishing the desired products in moderate to good yields. Aliphatic *gem*-difluoroalkenes were however not compatible with the reaction conditions. Control experiments showed that Ag(I) catalyst was essential for the reaction, as the product was not observed in its absence. Furthermore, the reaction was inhibited by radical scavengers including TEMPO and 3,5-di-*tert*-butyl-4-hydroxytoluene (BHT), indicating the involvement of a radical in the transformation. Based on these and pioneering work by Minisci, the authors proposed that the reaction proceeds by the generation of the carbamoyl radical-mediated by Ag(II),[1] followed by an intermolecular radical addition onto the *gem*-difluoroalkene. This leads to a benzyl radical intermediate ***i***, which undergoes intramolecular cyclization



Scheme 22 Persulfate mediated tandem addition-cyclization of carbamoyl radicals to difluorostyrenes.



Scheme 23 Persulfate mediated tandem addition-cyclization of carbamoyl radicals to styrenes and electron-deficient alkenes.



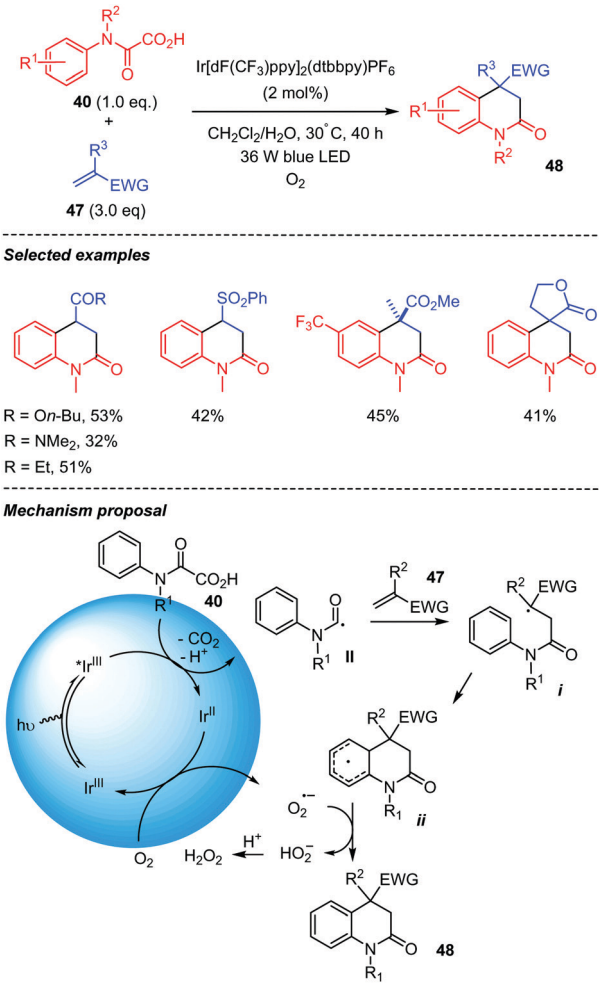
Scheme 24 Persulfate mediated tandem addition-cyclization of carbamoyl radicals to vinylsulfones.

(to generate ***ii***), then dehydroaromatization by the highly oxidizing $SO_4^{\bullet -}$ to furnish the final product.

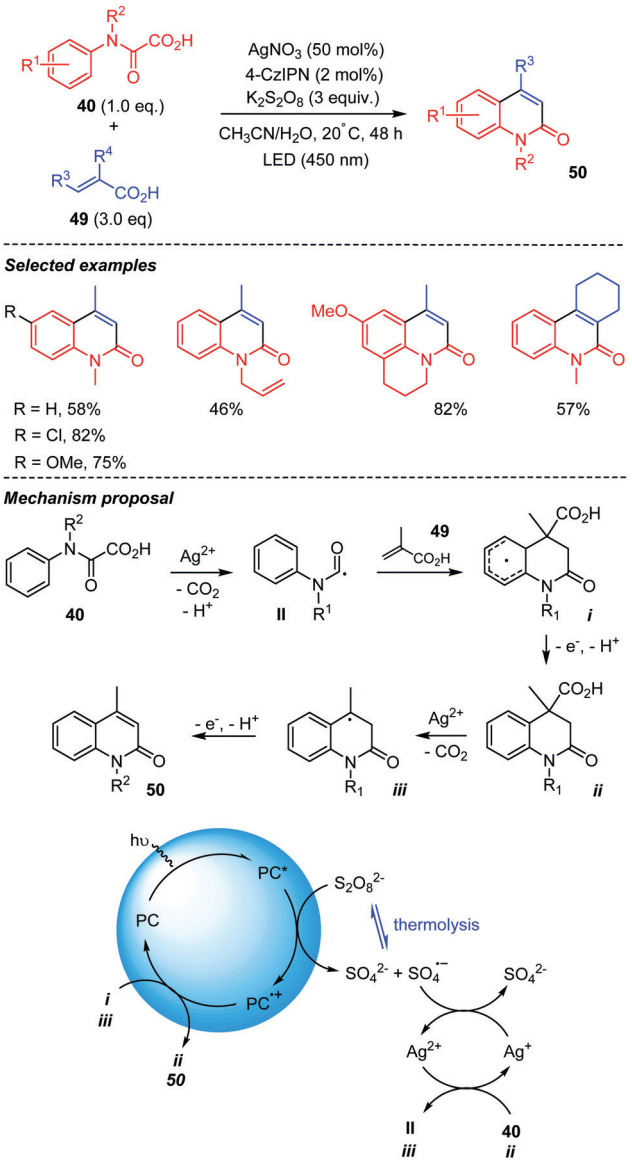
A similar silver-catalyzed tandem decarboxylative radical addition/cyclization of oxamic acids with simple alkenes for the synthesis of substituted 3,4-dihydroquinolin-2(1*H*)-ones **44** was also reported by the Feng group (Scheme 23).[44] Their method demonstrated a wide substrates scope, including not only styrenes (**43**, R^3 = Ar), but also various electron-deficient alkenes such as ethyl vinyl ketone, ethyl acrylate (**43**, $R^3 = CO_2Et$), and α-methylene-γ-butyrolactone, which were competent partners for the reaction, furnishing the expected dihydroquinolin-2-ones in moderate yields. In contrast, monosubstituted oxamic acids were not competent substrates for this reaction.

Phenyl vinyl sulfones **45** were also good candidates for the reaction but delivered quinolin-2(1*H*)-ones **37** instead (Scheme 24).[44] The authors proposed that the generated 4-(phenylsulfonyl)-3,4-dihydroquinolin-2(1*H*)-ones possibly underwent Julia–Lythgoe elimination at high temperature to give the corresponding quinolin-2(1*H*)-ones **46**. Furthermore, control experiment indicated that $AgNO_3$ was necessary for the reaction, as the product was not observed in its absence. In addition, methyl- and phenyl-*N*-protected oxamic acids displayed interesting chemoselectivity, while the benzyl counterpart gave a mixture of two products including a radical rearrangement product.

A visible light mediated decarboxylation addition/cyclization of oxamic acids for the synthesis of 3,4-dihydroquinolin-2(1*H*)-ones was reported by Feng and co-workers in 2018 (Scheme 25).[45] Various aniline derived oxamic acids with different substituents and electron-deficient alkenes **47**, including acrylonitrile, phenyl vinyl sulfone, butyl acrylate, ethyl vinyl ketone and *N*,*N*-dimethylacrylamide, were suitable for the reaction, leading to diverse 3,4-dihydroquinolin-2(1*H*)-ones **48** in moderate yields. The authors proposed that the transformation proceeds by oxamic acid decarboxylation mediated by the Ir(III)* catalyst in its excited state. The carbamoyl radical **II** thus generated would undergo intermolecular addition to the electron deficient alkene **47** to give radical intermediate ***i***, which would cyclize leading to the cyclohexadienyl radical ***ii***. Oxygen present in the medium would play the role of an external oxidant by regenerating the reduced catalyst Ir(II) in its ground state Ir(III). The oxygen radical anion generated would then abstract a proton from ***ii*** to afford the product **48** and H_2O_2. Interestingly, the photochemical conditions described here provide a different outcome for the reaction involving a



Scheme 25 Visible-light-mediated tandem addition-cyclization of carbamoyl radicals onto electron-deficient alkenes.



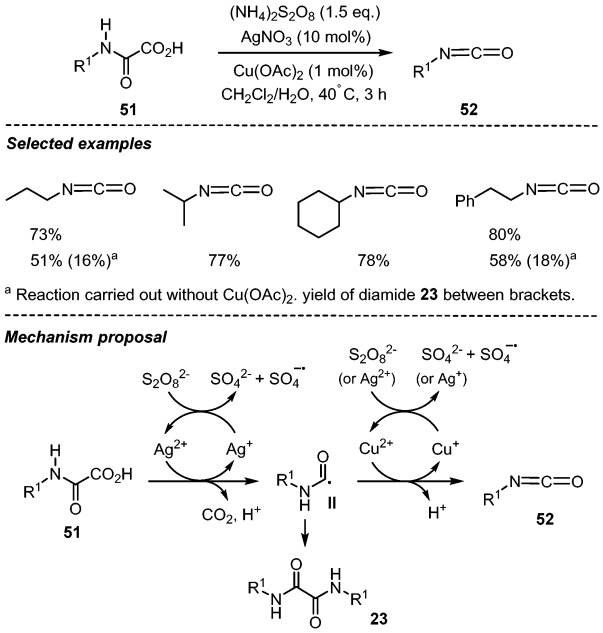
Scheme 26 Photocatalyzed-Persulfate mediated tandem addition-cyclization of carbamoyl radicals to acrylic acids.

vinylsulfone such as **45** (Scheme 24), leading to the 4-(phenylsulfonyl)-3,4-dihydroquinolin-2(1*H*)-ones instead of the elimination as mentioned above using persulfate conditions.

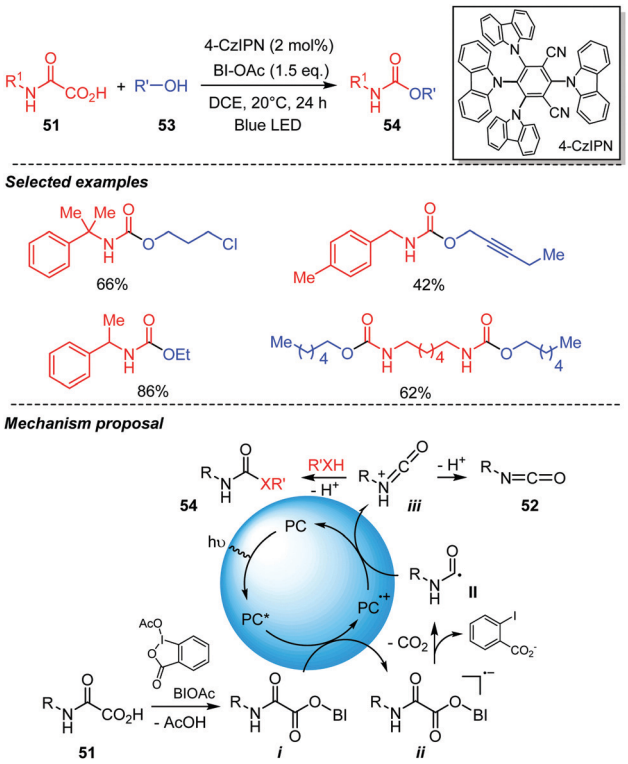
Pedersen *et al.* recently reported on a double decarboxylative addition of oxamic acids onto acrylic acids (Scheme 26).[46] This addition-cyclization cascade provided a series of quinoline-2-ones in good yields. The process is reminiscent to the one described in Scheme 24, where a sulfone moiety was eliminated in the last stage of the process. The reaction may be performed under thermal or photocatalytic conditions as summarized in Scheme 26. The organophotocatalyst (4-CzIPN) in its excited state (PC*) reduces the persulfate into the sulfate radical anion $SO_4^{\bullet -}$, which then oxidizes Ag(I) in to Ag(II). The latter generates the carbamoyl radical **II** from oxamic acid **40**, which adds to the acrylic acid **49**. The addition-cyclization process then affords intermediate ***i***, the oxidation of which with $PC^{+\bullet}$ and loss of a proton give dihydroquinolin-2-one ***ii***, returning the photocatalyst in its ground state. A similar decarboxylation-elimination pathway finally converts ***ii*** into **50** through ***iii***. Under thermal conditions, the authors propose that H-abstraction by $SO_4^{\bullet -}$, issued from thermolysis of $S_2O_8^{2-}$, replaces SET and loss of proton.

4. Oxamic acids as precursors of isocyanates, urethanes, and ureas

Decarboxylation of oxamic acids and further oxidation of the carbamoyl radical were originally shown by Minisci *et al.* to afford a straightforward entry towards isocyanates.[1] Therefore, oxamic acids have recently been designated as potent green precursors for the synthesis of urethanes and ureas through *in situ* generation of isocyanates using a non-phosgene route.[21] This strategy is particularly relevant as it avoids the manipulation of carcinogenic isocyanates and highly toxic gaseous phosgene. Minisci and co-workers originally showed that oxamic acids can be oxidized into isocyanates using $S_2O_8^{2-}$ as an oxidant, $AgNO_3$ and $Cu(OAc)_2$ as catalysts, and a biphasic medium involving water and an organic solvent (Scheme 27).[1] Various isocyanates **52** could be accessed with their method in



Scheme 27 Persulfate mediated generation of isocyanate from oxamic acids.



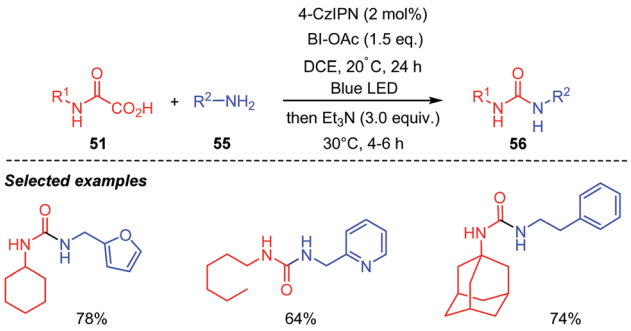
Scheme 28 Urethane synthesis through visible-light mediated decarboxylation of oxamic acids.

moderate to good yields using different monooxamic acids **51**. Interestingly, oxidation of secondary oxamic acid into isocyanate was not feasible, pointing toward the importance of the –NHCO– group in the second oxidation process. The silver salt was vital for the reaction as no isocyanates were observed in its absence, while $Cu(OAc)_2$ was required to favor the slow oxidation of the carbamoyl radical **II** into isocyanate, thereby minimizing the homocoupling and the formation of the corresponding diamide (*i.e.* **23a–b**, Scheme 13).

Although this method gave access to isocyanates, yields were generally moderate due to partial hydrolysis of the generated isocyanate into amine in the aqueous medium. Moreover, direct access to urethane using this method was not feasible, leaving the option of isolating and purifying the generated carcinogenic isocyanate.

Recently our group developed a metal-free photocatalyzed procedure for direct access to urethanes and ureas from oxamic acids (Scheme 28).[21] This mild and efficient method uses an organic dye as photocatalyst, hypervalent iodine reagent as oxidant and visible-light irradiation to trigger the free-radical oxidation of oxamic acids **51** into *in situ* generated isocyanates in an organic solvent. In the presence of alcohols **53**, the reaction furnished urethanes **54** in a one-pot process, thereby avoiding the isolation and purification of the generated isocyanate. 4-CzIPN was shown to be the most efficient organic photocatalyst for the reaction though $Ru(bpy)_3Cl_2$ and $AcrMes^+ClO_4^-$ could also serve as competent photocatalysts for the reaction. On the other hand, Eosin-Y and rose-Bengal gave only trace amount of the desired product. Furthermore, BI-OAc demonstrated superior performance as an oxidant for the reaction compared to other hypervalent iodine reagents tested including hydroxybenziodoxolone (BI-OH), PIDA and PIFA. The reaction worked efficiently with DCE or DCM as solvent while THF, CH_3CN or DMF resulted in low product yield and DMSO failed to provide the product. This new photocatalyzed procedure exhibited a wide substrate scope. A broad variety of oxamic acids and alcohols were compatible with the system furnishing the desired urethanes in good to excellent yields with high functional group tolerance. Based on experimental evidences, a mechanism was proposed suggesting that the photoexcited catalyst (PC*) was quenched by intermediate ***i***, formed through ligand exchange between oxamic acid **51** and BI-OAc. This led to an unstable radical-anion ***ii***, which collapsed into carbamoyl radical **II** and *o*-iodobenzoic acid anion (Scheme 28). Further oxidation of **II** by the photocatalyst radical cation $PC^{\bullet+}$ then afforded the corresponding protonated isocyanate ***iii***, while the photocatalyst was regenerated. The protonated isocyanate can either reacts *in situ* with the alcohol **53** to furnish the desired urethane **54** or loses a proton to give isocyanate **52**, which is effectively isolated in good yield when the reaction is performed in the absence of alcohols, further supporting the mechanism below.

Extension of the process to the preparation of unsymmetrical ureas **56** was also performed successfully (Scheme 29). However, in this case, a two-step one pot protocol was adopted, in which isocyanate **52** was first generated *in situ* under photocatalytic conditions, and then the amine **55** added to furnish the corresponding urea **56** without isolation and purification of the generated isocyanate. A recent report by Li and co-workers described a similar work using BI-OAc as an oxidant and a (polyaniline)-*g*-C_3N_4–TiO_2 composite as a photocatalyst.[47] Addition

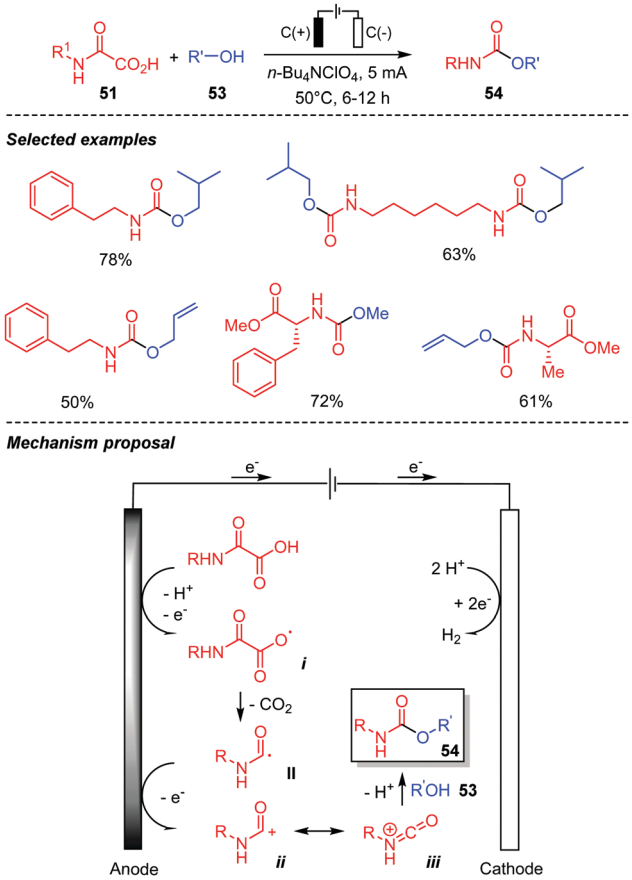


Scheme 29 Urea synthesis through visible-light mediated decarboxylation of oxamic acids.

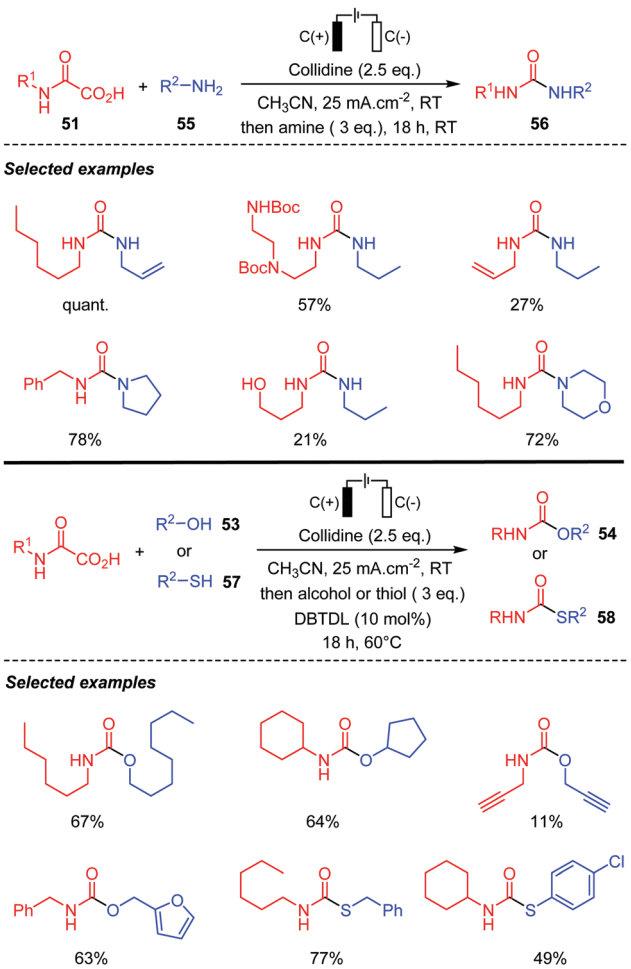
of the amine as above, after the photocatalytic process led to various unsymmetrical ureas in satisfying yields.

Pursuing in this direction, our laboratory also developed an electrochemical version of the above reaction, in order to replace the hypervalent iodine oxidant by an anodic oxidation. This metal-, photocatalyst-, light and chemical oxidant-free procedure thus led to a broad range of urethanes, including some prepared from chiral oxamic acids (Scheme 30).[48] The latter were accessible without racemization. Simple inexpensive graphite anodes and cathodes in an undivided cell were used in this context. Alcohols were generally present as solvents, but the excess could be recovered by simple distillation at the end of the process. With MeOH as a solvent the reaction did not require any electrolyte, while *n*-Bu_4NCl and a gentle heating were necessary with other less conducting alcohols. This Hofer–Moest process proceeds through the oxidation at the anode of the oxamic acid into the carboxyl radical ***i***, which upon decarboxylation provides the carbamoyl radical **II**. Further oxidation of the latter at the anode finally generates the cationic species ***ii***, which reacts with alcohols affording the desired urethanes. Evidences for this mechanism was supported by the isolation of a bis-amide (such as **23a–b**, Scheme 13) resulting from the dimerization of the carbamoyl radical **II**, when the reaction was carried out with a minimum amount of alcohol. The occurrence of cation ***iii*** was supported by the isolation of a diethylurea resulting from the reaction of ***iii*** with diethylamine issued for the anodic oxidation of NEt_3 used as a base. As observed by Minisci, the carbamoyl radical oxidation is slow, explaining the formation of the bis-amide in some cases.

Lam and co-workers[49] recently reported a modified version of this electrochemical process, by adding collidine as an anodically stable base. The reaction led to the isocyanate, which



Scheme 30 Electrochemical decarboxylation of oxamic acids in the presence of alcohols.



Scheme 31 Electrochemical decarboxylation of oxamic acids in the presence of amines, alcohols and thiols using collidine as a base.

was directly trapped by a nucleophile after the electrolysis. Various amines **55** were thus added leading to the corresponding ureas **56** in high yields (Scheme 31). The process was compatible with protected amines and also afforded unsaturated ureas, albeit with lower yields. When the nucleophile is an alcohol **53**, the addition onto the isocyanate required heating and the presence of a tin catalyst (DBTDL: dibutyltin dilaurate). Chiral oxamic acids, free hydroxy groups, and alkyne substituents were compatible with the reaction conditions. The reaction was also extended to the preparation of thiocarbamates **58** by the addition of thiols **57**. Finally, the authors were able to translate successfully their process to continuous flow technology.

5. Conclusions

In summary, oxamic acids chemistry has recently experienced a renaissance after the pioneering work of Minisci on silver-catalyzed decarboxylation.[1] These readily available amido-acids proved to be environmentally benign precursors of carbamoyl radicals, capable of replacing most of the precursors previously used, which often required several synthetic steps. The few examples described above demonstrate that these nucleophilic radicals may be generated under mild conditions, in the presence of an oxidant. The latter is generally a persulfate, although hypervalent iodine reagents have demonstrated their usefulness in this context. Anodic oxidation also allows the presence of an oxidant in a stoichiometric quantity to be dispensed with. The activation of oxamic acid in the presence of the oxidant can either be thermal or photochemical. It is worth noticing that the use of silver salts to decompose persulfate is now unnecessary and has been superseded by the simple heating of the persulfate with DMSO.[24–26] The radicals thus produced add efficiently to a broad range of unsaturated systems, including alkenes, both electron-rich and electron-poor and aromatic heterocycles (Minisci reaction) giving access to diversely functionalized amides. Finally, oxidation of oxamic acids in the presence of alcohols, amines, or thiols gives access to the corresponding urethanes, ureas and thioureas.[21,47–49] With these new conditions in hand, the chemistry of oxamic acids and carbamoyl radicals should find new directions and original applications in the not too distant a future, including addition reactions to various unsaturated systems not investigated until now. The use of the CO_2, released during the decarboxylation process, as a C1 synthon in a radical process would be worth looking at, offering an access to new structures limiting the carbon waste. Finally, metal-catalyzed coupling involving carbamoyl radicals has been overlooked so far and would certainly open new directions in the synthesis of functionalized amides.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

IMO and GK respectively thank the Alex-Ekwueme Federal University Ndufu-Alike Ikwo (AE-FUNAI) and the TUBITAK BIDEB-2219 (grant no. 1059B191900553) for PhD and post-doctoral funding. We gratefully acknowledge the ANR (NCO-INNOV, No. 20-CE07-0015-01), the University of Bordeaux and the CNRS for financial support.

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