

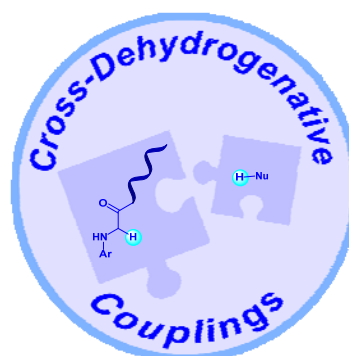
# Cross-Dehydrogenative Coupling Reactions for the Functionalization of $\alpha$ -Amino Acid Derivatives and Peptides

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**Abstract.** The functionalization of typically unreactive C(sp<sup>3</sup>)-H bonds holds great promise for reducing the reliance on existing functional groups while improving atom-economy and energy efficiency. As a result, this topic is a matter of genuine concern for scientists in order to achieve greener chemical processes. The site-specific modification of  $\alpha$ -amino acid and peptides based upon C(sp<sup>3</sup>)-H functionalization still represents a great challenge of utmost synthetic importance. This short review summarizes the most recent advances in “Cross-Dehydrogenative Couplings” of  $\alpha$ -amino carbonyl compounds and peptide derivatives with a variety of nucleophilic coupling partners.

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**Key words** cross-dehydrogenative coupling, peptide,  $\alpha$ -amino acid, oxidative, C-H functionalization

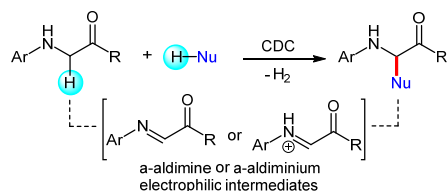
## 1 Introduction

$\alpha$ -Amino acids form the core backbone of proteins and are among the most versatile, yet widespread, building-blocks for the assembly of biologically relevant compounds at the frontiers of organic synthesis and drug discovery.<sup>1</sup> Owing to the limited availability of natural  $\alpha$ -amino acid derivatives, the development of efficient synthetic methods for the preparation of non-natural  $\alpha$ -amino carbonyl compounds represents a challenging task of paramount importance in biomedicine and chemical sciences.<sup>2</sup> Accordingly, site-specific chemical modification of peptides and proteins has recently emerged as a unique and intriguing platform for the construction of a large library of novel peptide-based structures, which can often display enhanced biological

activities.<sup>3</sup> However, the regio- and stereoselective modification of a given peptide is far from being trivial due to the presence of multiple reactive functional groups. In this respect, metal-catalyzed C-H functionalization unlocks new exciting opportunities and expands our synthetic toolbox for improving the efficiency of peptide syntheses.

Transition-metal chemistry is continually delivering new modes of chemical activation involving distinct bond-forming or bond-breaking pathways, which are often unprecedented within the realm of organic chemistry. As a result, metal catalysis stands out as a constantly evolving platform for the construction of organic molecules upon innovative bond disconnections. The recent years have witnessed a revolution in the field of C-H functionalization,<sup>4</sup> thus becoming a significant discipline within the cross-coupling arena. Based on their high atom-economy and environmentally friendly character, direct C-H functionalization reactions have undoubtedly changed the landscape of organic synthesis, thus allowing for the design of new tactics for the assembly of a wide variety of C-C and C-heteroatom linkages. The oxidative coupling between two unreactive C-H bonds is referred to as “Cross-Dehydrogenative Coupling” (CDC)<sup>5</sup> and formally implies the release of H<sub>2</sub> along the process; however, it typically does not occur and the two hydrogen atoms are often removed by the oxidant. Of particular importance are the direct C(sp<sup>3</sup>)-H functionalization methods which enable the modification of  $\alpha$ -C(sp<sup>3</sup>)-H bonds adjacent to an heteroatom upon radical oxidative coupling processes.<sup>6</sup> In this regard, CDCs allow for the straightforward construction of  $\alpha$ -substituted amino carbonyl derivatives that are beyond the reach of traditional methods based on carbanion chemistry and solid phase techniques. Given the importance of  $\alpha$ -amino carbonyl compounds in both industrial and academic environments, and with the aim to complement recent reviews on the topic,<sup>6a,b</sup> we will primarily focus herein on the key recent advances in the field of C(sp<sup>3</sup>)-H functionalization of  $\alpha$ -amino carbonyl compounds with a variety of nucleophilic entities through CDC reactions. The

main achievements in this area of expertise have been categorized according to both the nature of the nucleophilic counterpart and the bond formed within the oxidative process. Despite the fact that most of the processes share a general mechanistic scenario based on the formation of an electrophilic  $\alpha$ -aldimine or  $\alpha$ -aldiminium intermediate, through oxidation of the starting  $\alpha$ -amino carbonyl compound and further reaction with the corresponding nucleophile (Scheme 1), a detailed underlying mechanism will be commented when appropriate.



**Scheme 1** CDCs of  $\alpha$ -amino carbonyl compounds

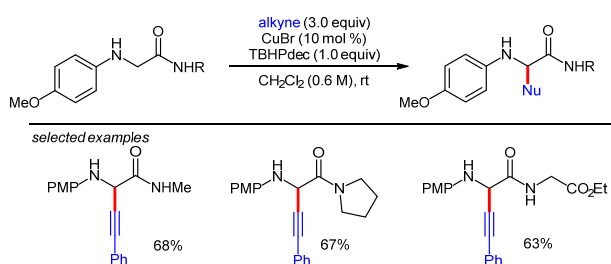
Metal-catalyzed borylations, acetoxylation, halogenations and arylation reactions,<sup>7</sup> which occurred at the side chains of the  $\alpha$ -amino acid precursors, as well as oxidative couplings with organometallic species<sup>8</sup> are beyond the scope of this review.

## 2 C–C Bond-Forming Oxidative Couplings

In this category, reactions where a carbon-nucleophile is introduced  $\alpha$  to the nitrogen atom of the amino carbonyl compound through oxidative coupling reactions will be disclosed.

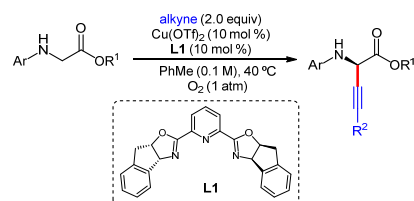
### 2.1 Reaction with Alkynes

On the basis of the groundbreaking investigations on Cu-catalyzed CDCs of tertiary amines,<sup>9</sup> in 2008 Li and co-workers reported the first cross-dehydrogenative alkylation of glycine derivatives with aromatic alkynes.<sup>10</sup> In the presence of catalytic amounts of CuBr and a decane solution of *tert*-butylhydroperoxide (TBHP) as oxidant, a variety of *N*-(*p*-methoxyphenyl)glycine amides underwent the corresponding coupling at room temperature (Scheme 2). Conversely, glycine esters or ketones were found unsuitable substrates, which was tentatively attributed to their higher oxidation potential and comparatively lower stability of the *in situ* formed imine intermediates. Importantly, the performance of the process at 70 °C in 1,2-dichloroethane (DCE) as solvent allowed the selective functionalization of the *N*-terminal Gly unit within the short peptides PMP-Gly-Gly-OEt and PMP-Gly-Gly-Gly-OEt.<sup>11</sup> Concerning the proposed mechanism, the terminal alkyne would first form a copper acetylide, which would eventually undergo a nucleophilic addition to the *in situ* formed imine intermediate.



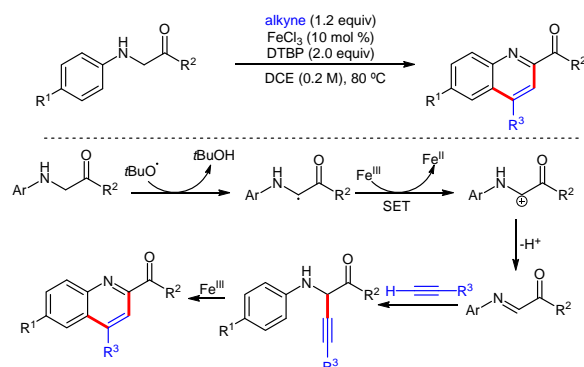
**Scheme 2** Cu-catalyzed alkylation of glycine amides

Recently, a Cu-catalyzed aerobic enantioselective approach has been described by the Liu group.<sup>12</sup> The method allowed for the alkylation of a wide variety of *N*-aryl glycine esters with both aryl and alkyl alkynes in an enantioselective fashion, featuring the convenient use of oxygen as the terminal oxidant (Scheme 3). Screening experiments revealed the high efficiency of pybox-type ligand **L1** to provide the corresponding alkylation of glycine compounds in high yields and good enantioselectivities (up to 86% *ee*). The *N*-aryl group was crucial for success and *N*-alkyl and *N*-acyl glycine derivatives remained unreactive. The authors found that the addition sequence of reaction components was determinant to the enantioselectivity and that the process likely occurred via the formation of an imine intermediate.



**Scheme 3** Cu-catalyzed enantioselective alkylation of *N*-aryl glycine esters

Despite the extended use of copper salts in CDC reactions, iron catalysis<sup>13</sup> represents a cost-efficient, yet sustainable, alternative which often offers new modes of reactivity. In fact, the use of FeCl<sub>3</sub> along with di-*tert*-butyl peroxide (DTBP) resulted in the unprecedented assembly of quinolones through a tandem alkylation/oxidative cyclization.<sup>14</sup> Importantly, numerous *N*-aryl glycine amides and esters smoothly underwent the oxidative coupling with aromatic alkynes. The practicality and robustness of the method were demonstrated by scaling up the process to 0.1 mol. Based on control experiments with an imine-type substrate, the authors proposed the mechanism depicted on scheme 4. The glycine derivative could be oxidized to the corresponding imine intermediate through a hydrogen atom abstraction step and subsequent Single Electron Transfer (SET) assisted by *tert*-butoxy radical and Fe(III), respectively. Further nucleophilic attack of the alkyne followed by an intramolecular Friedel-Crafts oxidative reaction would furnish the target quinolone product.

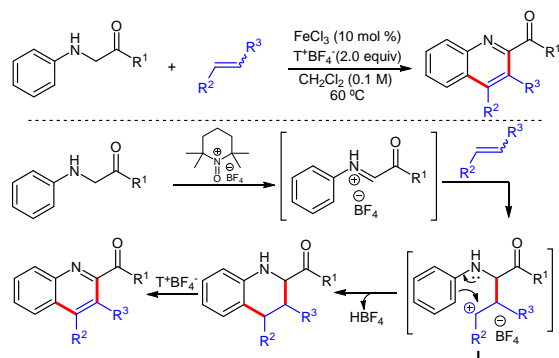


**Scheme 4** Fe-catalyzed enantioselective alkylation of *N*-aryl glycine esters

### 2.2. Reaction with Alkenes

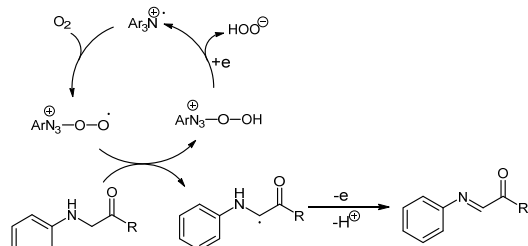
Aside from alkynes, numerous alkenes have proven to be excellent coupling partners to perform related [4+2] cycloaddition processes. In 2011, Mancheño and co-workers reported a CDC reaction of *N*-aryl glycine esters with a variety of

olefins toward the construction of quinolone derivatives upon a tandem dehydrogenative Povarov/oxidation process.<sup>15</sup> This method featured the use of inexpensive  $\text{FeCl}_3$  as the Lewis acid catalyst and a TEMPO oxonium salt as the mild oxidant. A variety of  $\alpha$ -amino carbonyl compounds, including ketones, could be efficiently coupled with styrenes, aliphatic olefins and 1,2-disubstituted alkenes. The proposed mechanism involved the first oxidation of the glycine derivative by the TEMPO salt followed by a nucleophilic attack of the olefin. The resulting carbocationic species **I** next underwent an intramolecular electrophilic aromatic substitution and further dehydrogenation afforded the corresponding heterocyclic compound (Scheme 5). In a follow-up study, the use of such oxidant in combination with catalytic amounts of  $\text{Fe}(\text{OTf})_2$  provided dihydroquinazolines upon homocondensation of glycine esters.<sup>16</sup>



**Scheme 5** Fe-catalyzed dehydrogenative Povarov/oxidation

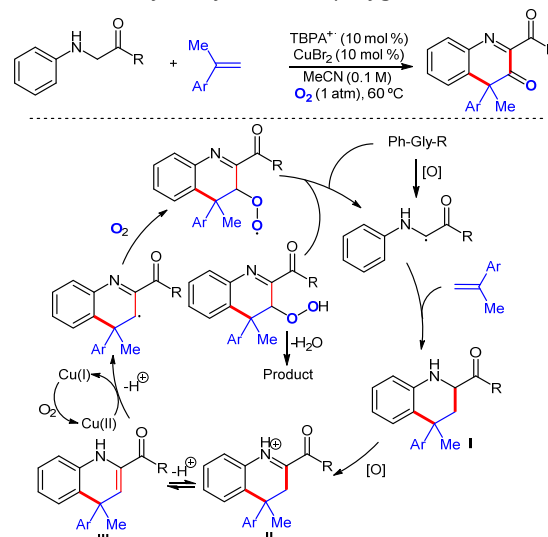
Economic and environmental concerns have recently prompted to search for more attractive and greener oxidation systems based on oxygen, which would ultimately produce water as the only chemical waste. In this light, Jia and co-workers introduced the commercially available tris(4-bromophenyl)ammonium hexafluoroantimonate salt, which under an oxygen atmosphere could decompose to furnish a peroxy radical cation responsible for the hydrogen abstraction from the corresponding glycine esters (Scheme 6).<sup>17</sup>



**Scheme 6** Aerobic C-H oxidation induced by TBPA<sup>+</sup>

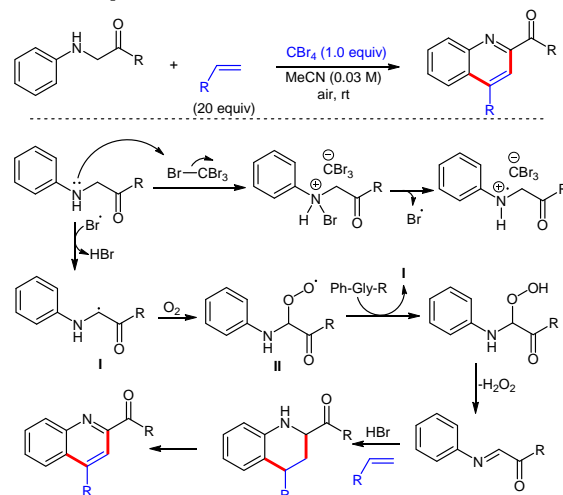
The reaction was shown to be accelerated by catalytic amounts of  $\text{InCl}_3$ , which was proposed to enhance the imino Diels-Alder reaction between the *in situ* formed imines and olefins. The method was further extended to the use of glycine amides<sup>18</sup> and short PMP-*N*-substituted peptides as well as *N*-aryl glycine cinammyl esters and amides,<sup>19</sup> which underwent the tandem oxidative functionalization in an intramolecular fashion in the absence of  $\text{InCl}_3$ . Owing to the high price of the required radical cation salts, they next developed an improved methodology where the latter were *in situ* generated in a catalytic manner by oxidation of triaryl amines with CAN<sup>20</sup> and upon completion of the process, the corresponding tertiary amines could be easily recovered by column chromatography purification. Interestingly,

$\alpha$ -methylstyrenes could block the terminal aromatization pathway and the oxidation of the C3-position could be achieved instead (Scheme 7).<sup>21</sup> There, the tetrahydroquinoline **I** resulted from the Povarov reaction was further oxidized to the iminium ion **II**, which after tautomerization to the corresponding enamine **III** was oxidized by the system  $\text{CuBr}_2/\text{oxygen}$ .



**Scheme 7** Consecutive C-H oxidations

In 2014, the Huo laboratory designed an auto-oxidative Povarov/aromatization tandem reaction using air as the sole oxidant in the absence of a redox-active catalyst.<sup>22</sup> However, the substrate scope was restricted to the use of electron-rich styrenes and only moderate yields (28-53%) could be obtained, mainly due to the undesired formation of self-oxidation products. Shortly after, the same group implemented the use of stoichiometric amounts of cheap  $\text{CBr}_4$  to promote the coupling of glycine esters and amides with a variety of styrenes under an air atmosphere.<sup>23</sup> The practicality of the method was verified by the performance of a 20 mmol scale process and the application to the use of dipeptide PMP-Gly-Gly-OEt. The proposed mechanism involved an initial reaction of  $\text{CBr}_4$  with the corresponding secondary amine to produce a bromine radical capable of the first H-abstraction (Scheme 8). The so-formed radical intermediate **I** could react with  $\text{O}_2$  producing peroxide radical **II**, which would eventually afford the required imine compound for the [4+2] cycloaddition process.

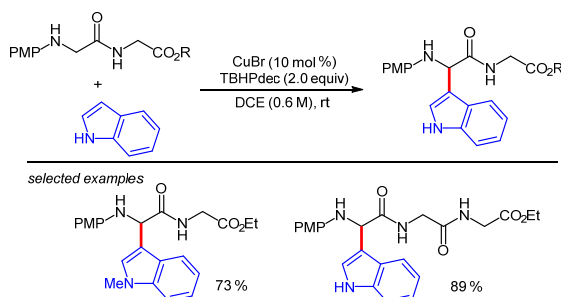


**Scheme 8**  $\text{CBr}_4$ -mediated oxidation

Very recently, numerous related aerobic approaches have been devised utilizing copper catalysis in combination with stoichiometric amounts of inexpensive  $K_2S_2O_8$ <sup>24</sup> or  $NHPI$ <sup>25</sup> as co-catalyst, a gold-oxazoline<sup>26</sup> based-catalyst, visible-light induced photoredox catalysis<sup>27</sup> or even *tert*-butyl nitrite<sup>28</sup> as a metal-free reagent. They all represent more sustainable and economic alternatives to assist the formation of the required imine derivative via oxidation of the  $\alpha$ -C(sp<sup>3</sup>)-H bond of the  $\alpha$ -amino carbonyl compound.

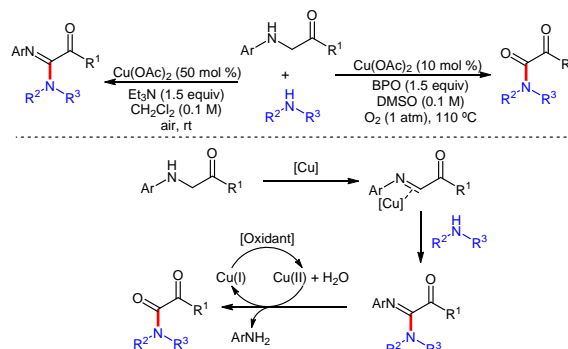
### 2.3 Reaction with (Hetero)arenes

Traditional methods for the  $\alpha$ -arylation of  $\alpha$ -amino carbonyl compounds require the use of expensive aryl sources and strong bases to generate the corresponding enolate intermediates.<sup>29</sup> Such reaction conditions are not applicable to peptide modifications because they are not site-specific and often induce racemization of existing chiral centers. In this respect, CDC reactions with (hetero)arenes overcome the former drawbacks and stand out as convenient protocols for the assembly of  $\alpha$ -arylated  $\alpha$ -amino carbonyl derivatives. In line with this notion, in 2009 the Li group introduced a  $CuBr/TBHP$  system for the selective arylation of short peptides (PMP-Gly-Gly-OEt and PMP-Gly-Gly-Gly-OEt) with indoles at the *N*-terminal Gly unit (Scheme 9).<sup>11</sup> This pioneering work, where boronic acids and terminal alkynes could also be used as nucleophilic components, set the basis for future advances in the field and a vast array of methodologies have been devised in the last years for the  $\alpha$ -arylation of amino acid derivatives with (hetero)arenes.



**Scheme 9** Cu-catalyzed heteroarylation of short peptides

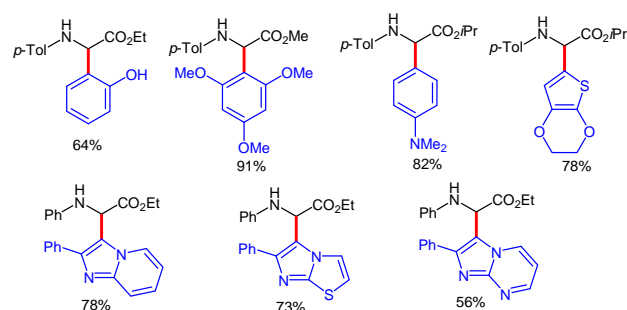
A significant step forward was the Cu-catalyzed aerobic oxidative coupling of glycine esters and amides with a variety of indoles reported by Huo, which featured the convenient use of oxygen as the terminal oxidant.<sup>30</sup> Interestingly, the *p*-Tol-Gly-Gly-OEt peptide could be selectively arylated in high yields and the utility of the method was verified by the performance of the process on a high scale (>10 g). Following up Li's<sup>11</sup> and Huo's work,<sup>30</sup> slight modifications in the reaction conditions led to the unprecedented conversion of *N*-aryl glycine esters and ketones into structurally related 2-imino and 2-oxo-carbonyl derivatives<sup>31</sup> (Scheme 10). The use of the  $CuCl/TBHP$  system under an argon atmosphere provided the former through a Friedel-Crafts alkylation with indoles and conducting the process under stronger oxidizing conditions ( $CuCl_2/TBHP$ , air) favored a subsequent hydrolysis reaction to yield the corresponding 1,2-diones or 2-keto esters. Interestingly, <sup>18</sup>O-labelling experiments verified that the newly formed carbonyl group upon hydrolysis was derived from water. Later on, the former were prepared under palladium-<sup>32</sup> and iron-catalyzed<sup>33</sup> oxidative couplings.



**Scheme 10** Cu-catalyzed heteroarylation of glycine derivatives

Alternatively, the use of catalytic amounts of the radical cation triarylammonium salt<sup>34</sup> resulted in the formation of a distinct product through an aerobic double Friedel-Crafts alkylation reaction, where the *N*-aryl unit was eliminated from the starting *N*-aryl glycine esters or amides.

Other than indoles, a number of (hetero)arenes have been explored as powerful nucleophiles in these oxidative couplings. Huang and co-workers implemented the use of phenols and 1,3,5-trimethoxybenzene<sup>35</sup> as coupling partners in the presence of catalytic amounts of  $Cu(OAc)_2$  and DTBP as oxidant. The Bao group utilized *m*-CPBA for the CDC of 2-naphthols with 2-aminoacetate derivatives for the assembly of related  $\alpha$ -arylated glycine esters.<sup>36</sup> Similar Cu(I)-catalyzed aerobic reaction conditions have been recently applied for the successful coupling of *N*-aryl glycine esters with imidazopyridines,<sup>37</sup> imidazothiazoles,<sup>37</sup> 3,4-ethylenedioxythiophene<sup>38</sup> and *N,N*-dimethylanilines<sup>38</sup> as the nucleophiles (Scheme 11).

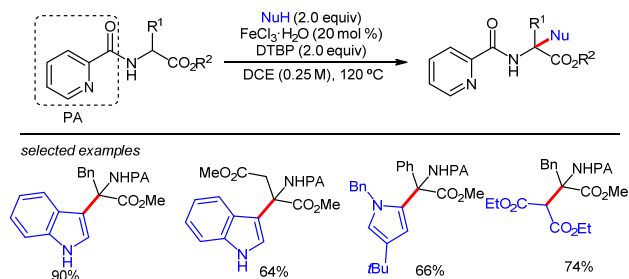


**Scheme 11** Selected examples of Cu-catalyzed heteroarylations

A major breakthrough in the field came with the first assembly of  $\alpha,\alpha$ -disubstituted  $\alpha$ -amino acid derivatives upon iron-catalyzed CDC reactions reported by the Yu group.<sup>39</sup> Inspired by the concept of chelation-assisted C(sp<sup>3</sup>)-H functionalization, they envisioned that the use of a directing group at the *N*-terminus of the amino acid derivative could facilitate the challenging formation of a ketimine intermediate prone to react with other nucleophiles. Accordingly, they found that the 2-pyridinecarbonyl group (PA) assisted the oxidative coupling of a wide variety of natural tertiary amino esters such as Phe, Ala, Trp and Asp-OMe as well as other non-natural  $\alpha$ -amino acid substrates with indoles and other electron-rich heterocycles such as indolizines, azaindoles, thiophenes or *N*-alkylpyrroles (Scheme 12). The inexpensive  $FeCl_3 \cdot 6H_2O$  along with DTBP under air at 120 °C provided an efficient system for forging  $\alpha$ -quaternary amino acid derivatives. Notably, malonates were also found suitable nucleophilic counterparts. Iron catalysis in

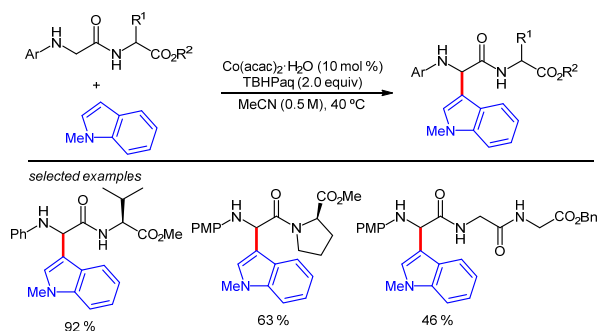


combination with TBHP as oxidant have been also applied to the direct  $\alpha$ -arylation of  $\alpha$ -amino ketones and esters with indoles.<sup>40</sup> Furthermore, benzoxazin-2-ones have been employed as reaction partners and their arylation reaction was successfully applied to the gram-scale synthesis of natural product Cephalandole A.<sup>41</sup>



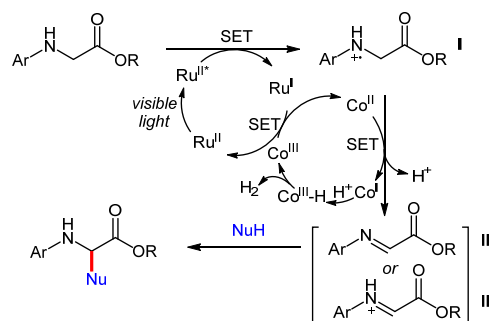
**Scheme 12** Fe-catalyzed CDCs of  $\alpha$ -tertiary  $\alpha$ -amino esters

Correa and co-workers have recently introduced the alternative use of cobalt salts in combination with an aqueous solution of TBHP for the selective arylation of glycine esters and short peptides.<sup>42</sup> Remarkably, HPLC analysis verified the integrity of the existing stereocenter in peptides containing valine and proline units (Scheme 13).



**Scheme 13** Co-catalyzed  $C(sp^3)$ -H arylation of short peptides

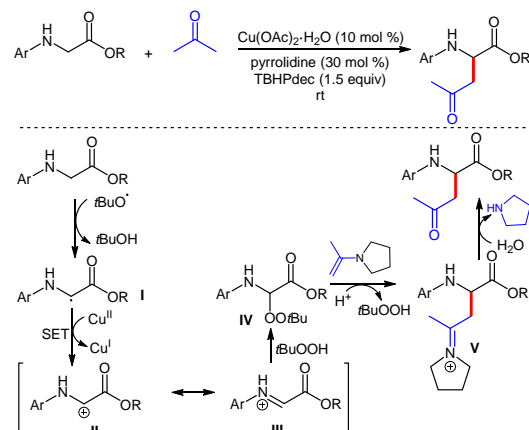
The oxidation of the  $\alpha$ - $C(sp^3)$ -H bonds to the nitrogen atom toward the formation of the required electrophilic imine intermediate have been also achieved upon visible light photoredox catalysis using both Ru<sup>43</sup>- and Ir-based<sup>44</sup> catalyst systems under aerobic conditions. Interestingly, Wu and co-workers have recently described an alternative oxidant-free cross-coupling hydrogen evolution reaction<sup>45</sup> between indoles and PMP-Gly-OEt which occurred with Ru(bpy)<sub>3</sub>(PF<sub>6</sub>)<sub>2</sub> and Co(dmgH)<sub>2</sub>pyCl (dmgH = dimethylglyoximate) as photosensitizer and catalyst, respectively. This method was found also suitable for the use of  $\beta$ -ketoesters. Mechanistically, upon visible light irradiation of the Ru-catalyst to its excited state an electron was transferred from the substrate to provide an amine radical cation **I** (Scheme 14). Such species was further oxidized to the corresponding iminium **II** or imine intermediate **III** by the Co(II)-catalyst, and the so-formed Co(I) was protonated thus delivering Co(III)-H. The release of H<sub>2</sub> was proposed to occur either upon protonation of Co(III)-H, H<sub>2</sub> elimination and ultimate reduction of Co(III) to Co(II) or alternatively by reduction of Co(III)-H hydride to Co(II)-H followed by protonation to give H<sub>2</sub> and Co(II). Liu and co-workers have utilized indoles as powerful nucleophiles in a distinct type of C5-site specific Cu(II)-catalyzed oxidative couplings under proline-based peptide derivatives.<sup>46</sup>



**Scheme 14** Cross-coupling hydrogen evolution reaction

## 2.4 Reaction with Alkyl Reagents

CDCs involving two distinct  $C(sp^3)$ -H bonds are very challenging and a dual activation is always required to transform both the  $\alpha$ -amino carbonyl compound and the  $C(sp^3)$ -H containing pronucleophilic coupling partner into the corresponding active electrophile and nucleophile, respectively. Following this strategy, various  $C(sp^3)$ -H acid bonds have been successfully used in the oxidative alkylation of glycine derivatives. The group of Li was pioneer in the field and in 2008 reported the first  $C(sp^3)$ - $C(sp^3)$  bond forming CDC reaction from *N*-acetyl glycine esters and malonates.<sup>47</sup> The use of stoichiometric amounts of Cu(OAc)<sub>2</sub> and di(2-pyridyl)ketone as supporting ligand were crucial for the process to occur. In the presence of a base, the stabilized carbanion generated from the malonate ester reacted in a Mannich-type fashion with the *in situ* generated imine derivative. Later on, Huang and Xie introduced a cooperative metal/organocatalytic approach for the CDC reaction of *N*-aryl glycine esters with ketones.<sup>48</sup> This dual catalytic effect resulted from the *in situ* formation of the electrophilic intermediate **III** upon Cu-catalyzed C-H oxidation of the amino ester, which further reacted with the nucleophilic enamine derived from pyrrolidine and the corresponding ketone. The proposed mechanism involved the formation of a key peroxide intermediate **IV** by reaction of *t*BuOOH with the iminium ion **III**, which was identified by <sup>1</sup>H NMR and MS analysis (Scheme 15). Eventually, nucleophilic attack of the enamine derived from acetone and pyrrolidine would generate iminium ion **V**, which upon hydrolysis would deliver the target product. Interestingly, the replacement of TBHP by DDQ allowed the use of cyclohexanone derivatives.

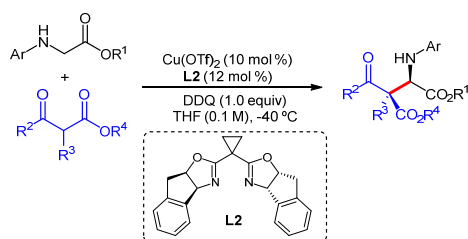


**Scheme 15** Cooperative dual Cu/aminocatalysis

In 2012, Hu implemented the alternative, yet practical, use of FeCl<sub>3</sub> as the catalyst of choice for performing the latter oxidative processes.<sup>14a</sup> Shortly thereafter, Wu and co-workers introduced a

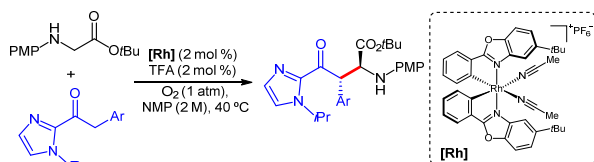
rather sustainable protocol based on the use of a visible light photocatalyst along with a Cu-catalyst for the aerobic oxidative coupling of *N*-aryl glycine esters with  $\beta$ -keto esters.<sup>49</sup> There, the oxidation of the glycine ester to the corresponding iminium intermediate was proposed to proceed upon visible light catalysis in the presence of O<sub>2</sub> as terminal oxidant, and the copper source was postulated to generate a more active nucleophilic species by coordination with the corresponding  $\beta$ -keto ester.

The use of chiral ligands in the oxidative Mannich-type reaction resulted in the formation of racemic products but, conversely, chiral organocatalysts produced the coupling products in up to 15% ee. Although poor enantioselectivity was achieved,<sup>48</sup> these preliminary results set the stage for further discoveries. In 2011, Wang and co-workers reported an asymmetric CDC reaction between *N*-aryl glycine esters and  $\alpha$ -substituted  $\beta$ -ketoesters featuring the use of a Cu(II)-chiral bisoxazoline (BOX) catalyst system (Scheme 16).<sup>50</sup> The use of DDQ as oxidant and low temperatures afforded the coupling products in moderate diastereoselectivities (up to 6:1) and high enantioselectivities (up to 92% ee). The mechanism proposal involved a nucleophilic attack of the chiral Lewis acid-bonded nucleophile, derived from the chelation of the  $\beta$ -ketoester and the Cu/BOX complex, to the *in situ* generated imine upon  $\alpha$ -C(sp<sup>3</sup>)-H oxidation with DDQ.



**Scheme 16** Cu-catalyzed asymmetric alkylation

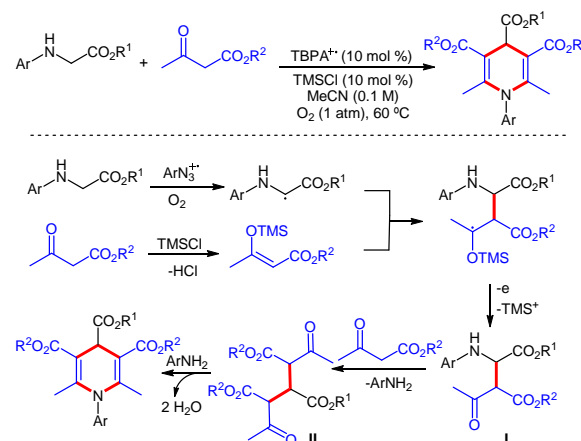
More recently, Gong and Meggers have developed an asymmetric sustainable CDC reaction between PMP-*N*-Gly-*O**t*Bu and 2-acylimidazoles in the presence of a chiral Rh(III) catalyst and oxygen as the terminal oxidant (Scheme 17).<sup>51</sup> The method provided the corresponding Mannich-type products with high diastereoselectivities (up to 10:1) and excellent enantioselectivities (96–97% ee). The authors proposed a mechanism based on the formation of a chiral enolate through coordination/deprotonation of the acyl imidazole with the Rh catalyst, and subsequent reaction in a stereocontrolled fashion with the imine intermediate derived from the self-oxidation of the corresponding glycine ester.



**Scheme 17** Rh-catalyzed asymmetric CDC

Interestingly, the performance of the oxidative coupling of *N*-aryl glycine esters and  $\beta$ -ketoesters in the presence of TBPA<sup>+</sup> and oxygen resulted in the unprecedented formation of 1,4-dihydropyridines.<sup>52</sup> The authors proposed a mechanism where the glycine ester was oxidized by the radical cation salt in the presence of O<sub>2</sub> and further reacted with the TMSCl-activated 1,3-dicarbonyl compound. Subsequent oxidation and loss of TMS<sup>+</sup> furnished intermediate **I**, which next underwent a C–N bond

cleavage, in which the aniline group served as the leaving group. The so-formed aniline derivative eventually reacted with the 1,5-dicarbonyl intermediate **II** to yield 1,4-dihydropyridine compounds. Later on, Le and Zhu performed the former aerobic cascade cyclization reactions in the presence of catalytic amounts of Cu(OTf)<sub>2</sub>.<sup>53</sup>



**Scheme 18** Assembly of 1,4-dihydropyridines

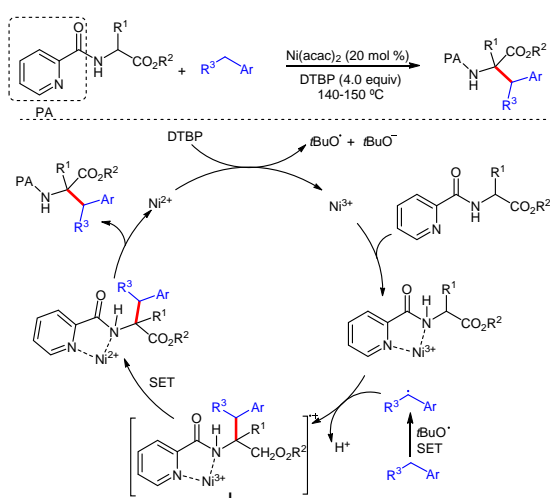
Aside from carbonyl compounds, other C(sp<sup>3</sup>)-H coupling partners have been employed in oxidative alkylations. In this respect, activated alkyl compounds such as nitroalkanes<sup>54</sup> have been successfully coupled with *N*-aryl glycine esters to yield the corresponding  $\beta$ -nitro  $\alpha$ -amino acid derivatives. The method was based on the use of catalytic amounts of CuI and oxygen as the terminal oxidant. The addition of Et<sub>3</sub>N was crucial for the process to occur, which was attributed to the activation of the corresponding nitroalkane as the more nucleophilic nitronate species.

Simple alkanes, which are the major components of petroleum and natural gas, have also been introduced in  $\alpha$ -amino carbonyl compounds upon oxidative C(sp<sup>3</sup>)-H functionalization reactions. In particular,  $\alpha$ -amino ketones and esters were coupled with cyclic alkanes<sup>55</sup> in the presence of high excess of DTBP as oxidant at 120 °C. Of particular significance is the use of acyclic hexane, which exhibited a high reactivity, albeit providing mixtures of isomers. The proposed mechanism relied on the formation of alkyl radicals assisted by *t*BuO radical species, which then reacted with the *in situ* formed imine derivatives.

2-Methylquinolines<sup>56</sup> can react with *N*-aryl glycine esters through a cooperative metal and Brønsted acid catalysis. In this regard, Huang and co-workers found that a combination of catalytic amounts of both Cu(OAc)<sub>2</sub> and pivalic acid under an oxygen atmosphere allowed for the assembly of  $\beta$ -quinolinyl  $\alpha$ -amino acid esters. The use of a protic acid favored the formation of a nucleophilic enamine intermediate prone to react with the imine compound derived from the Cu-catalyzed oxidation of the starting glycine derivative.

In connection with their previous findings in the synthesis of  $\alpha$ -quaternary amino acid compounds,<sup>39</sup> You and co-workers applied the coordinating activation strategy to the unprecedented construction of  $\beta$ -aromatic  $\alpha$ -amino ester derivatives from benzylic C(sp<sup>3</sup>)-H substrates.<sup>57</sup> The method relied on the generation of benzyl free radicals upon the use of nickel catalysis and high excess of DTBP as oxidant at high temperatures. A variety of protecting groups were evaluated and,

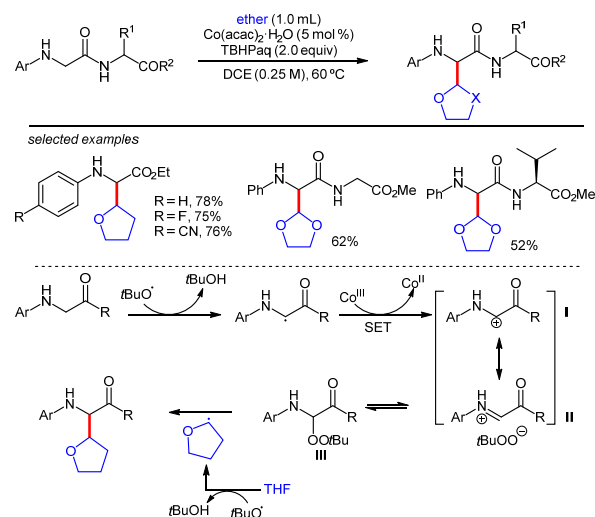
once again, picolinamido group provided the best results. The protocol exhibited a wide group tolerance and numerous (hetero)arylmethanes could be oxidatively couple with a vast range of  $\alpha$ -amino esters (Gly, Ala, Val, Leu, Ile, Asp, Tyr, Trp, Met, Lys and Ser, among others). Based on control experiments, the authors ruled out the intermediacy of an electrophilic ketimine compound and the addition of the *in situ* formed benzyl radicals to the  $\alpha$ -carbon of amino ester was proposed instead. The resulting radical cation intermediate **I** would then undergo an intramolecular SET by the high-valent Ni<sup>3+</sup> species, to finally release the target products and the active Ni(II) catalyst. Accordingly, the PA group was assumed to facilitate the attack of the benzyl radical, stabilize the radical cation and assist the intramolecular SET event. More recently, they have demonstrated that the replacement of Ni(acac)<sub>2</sub> by Co(OAc)<sub>2</sub>·4H<sub>2</sub>O allowed for the efficient benzylation of  $\alpha$ -aminoketones.<sup>58</sup>



**Scheme 19** Assembly of  $\beta$ -aromatic  $\alpha$ -amino esters

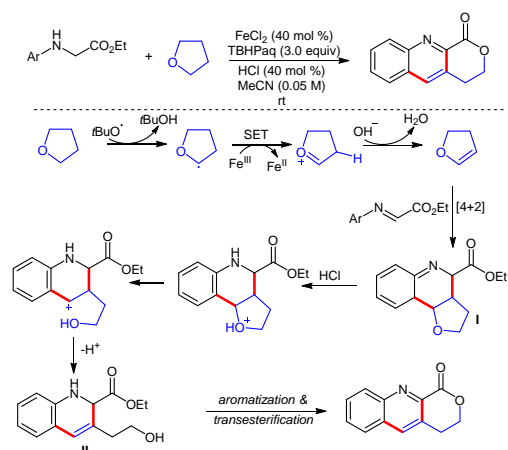
The last years have witnessed the emergence of simple cyclic ethers as useful chemical feedstocks in oxidative radical reactions.<sup>6a,b</sup> As a result, distinct alkylation reactions involving dual C(sp<sup>3</sup>)-H functionalization processes have been devised. In 2014, the Li group reported the first  $\alpha$ -alkylation of a wide variety of  $\alpha$ -amino ketones, esters and amides with cyclic ethers such as THF and tetrahydropyran and acyclic ones, such as diethyl ether and 1,2-dimethoxyethane,<sup>59</sup> which are common solvents in a plethora of organic transformations. The optimal system was formed by catalytic amounts of CuCl<sub>2</sub> and TBHP as oxidant. The proposed mechanism consisted of a *tert*-butoxy radical-assisted H-atom abstraction to produce an alkyl radical species, which was triggered by the glycine derivative. The resulting radical cation intermediate would then undergo a Cu(II)-catalyzed H-atom abstraction to deliver the target product and the active Cu(I) catalyst. More recently, the Correa group implemented the use of cobalt catalysis in combination with an inexpensive aqueous solution of TBHP as a practical alternative for performing the alkylation of a wide variety of *N*-aryl glycine esters and amides with cyclic ethers, including the versatile 1,3-dioxolane,<sup>39</sup> which could lead to the corresponding aldehyde derivatives upon hydrolysis. Notably, the latter method was successfully applied to the site-selective alkylation of short peptides at the terminal *N*-aryl glycine unit. Unlike previous methods restricted to the use of *N*-PMP substituted peptides, the

oxidative coupling could occur even in substrates bearing an *N*-Ph or *N*-(3-ClPh)-glycine units. Interestingly, control experiments evidenced that peroxide derivative **III** could be a competent intermediate within the reaction pathway. The mechanism proposal involved the initial formation of the iminium ion **II** with the aid of Co(II)/TBHP system. The latter was proposed to be further activated by direct reaction with *t*BuOOH to yield intermediate **III**, and the final coupling with the *in situ* generated  $\alpha$ -oxy radical species from the cyclic ether afforded the target products.



**Scheme 20** Co-catalyzed alkylation with cyclic ethers

Iron catalysts sometimes adopt distinct modes of reactivity, thus offering new opportunities in organic synthesis. In this regard, Huo and co-workers demonstrated that *N*-aryl glycine esters could undergo a dehydrogenative annulation with THF in the presence of FeCl<sub>2</sub> (40 mol %) and HCl (40 mol %).<sup>60</sup> Control experiments indicated that 2,3-dihydrofuran was a competent intermediate within the process, and its formation was proposed to occur upon a H-abstraction/SET/deprotonation sequence from THF. Such dehydrogenated THF could undergo a [4+2] cycloaddition with the *in situ* formed imine derivative to deliver the corresponding tetrahydroquinazoline compound **I**. Eventually, the latter was converted to 2,3-disubstituted quinolone intermediate **II** under acidic conditions, and final aromatization and ester exchange ring closure furnished the corresponding product. Later on, the same group described a similar process based on a combination of CuCl<sub>2</sub>/H<sub>2</sub>SO<sub>4</sub> to produce the latter compounds under aerobic conditions featuring the use of 2,3-hydrofurans and 2,3-dihydropyrroles as alternative coupling partners.<sup>61</sup> More recently, they have demonstrated that CBr<sub>4</sub> can be an efficient radical initiator to perform an aerobic double dehydrogenative cyclization between *N*-aryl glycine amides and 1,4-dioxane.<sup>62</sup>



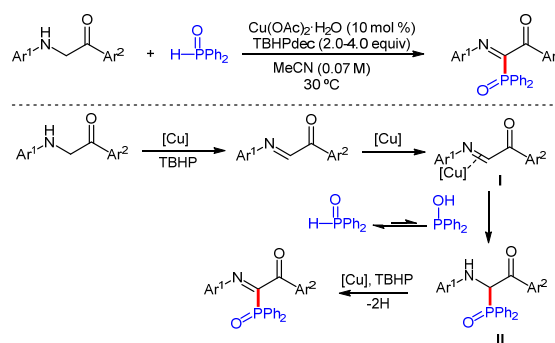
Scheme 21 Dual oxidative dehydrogenative couplings

### 3 C-heteroatom Bond-Forming Oxidative Couplings

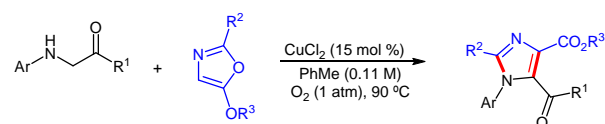
The cleavage of  $\alpha$ -C(sp<sup>3</sup>)-H bonds in  $\alpha$ -amino carbonyl compounds in the presence of carbon-nucleophiles has been intensively explored; however, the parent processes toward the forging of challenging C(sp<sup>3</sup>)-heteroatom linkages are rare in the literature and just a few examples have been reported. In this section, C-heteroatom bond-forming oxidative couplings will be disclosed and they have been classified according to the nature of the nucleophilic component of the process.

#### 3.1 C-P Bond Formation

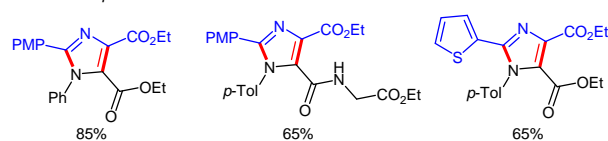
Owing to prevalence and important applications of organophosphorus compounds in organic chemistry and material science, the development of novel, yet efficient, C-P bond-forming oxidative processes has gained a great deal of attention in the last years. Inspired by the seminal work by Li on the Cu-catalyzed CDCs between tertiary amines and dialkyl phosphonates,<sup>63</sup> in 2013 the Yang group reported the first C-P bond-forming oxidative coupling involving the use of  $\alpha$ -amino carbonyl compounds.<sup>64</sup> In particular, they described a novel Cu-catalyzed phosphonation of  $\alpha$ -amino ketones with diphenylphosphine oxide toward the selective assembly of imidoylphosphonate derivatives (Scheme 22). Based on several control experiments, they proposed a plausible mechanism starting by the generally accepted oxidation of the glycine derivative to the corresponding imine. Further coordination with the copper catalyst of the latter provided the activated species **I**, which underwent a nucleophilic addition of the phosphorus compound to afford the phosphonated derivative **II**. Eventually, oxidative deprotonation delivered the corresponding imidoyl derivative. Interestingly, whereas initial attempts resulted in the formation of mixtures of the latter phosphorus-containing compounds, the judicious choice of the reaction conditions led to the selective formation of the fully oxidized product.

Scheme 22 Oxidative phosphorylation of  $\alpha$ -amino ketones

In 2016, Li and co-workers described the oxidative coupling of *N*-(methoxyphenyl)glycine amides with different alkyl and aryl phosphites to produce the corresponding phosphorylated glycine compounds (Scheme 23).<sup>65</sup> The method featured a mixture of catalytic amounts of a copper salt along with an organic solution of TBHP (in nonane) as the best oxidizing system. Despite the utility of the process, tertiary amides and esters were found unsuitable substrates and the success of the reaction was limited to the use of activated *N*-(methoxyphenyl) substrates.



selected examples

Scheme 23 Oxidative phosphorylation of  $\alpha$ -amino amides

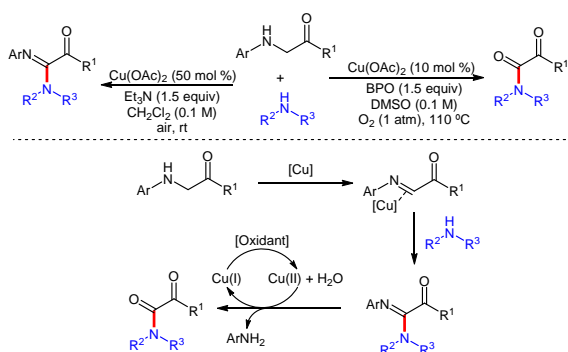
In connection with previous studies on the development of alternative radical cation salt-induced aerobic CDC reactions,<sup>17</sup> the Jia group has recently reported the efficient phosphorylation of *N*-aryl glycine amides with trialkyl phosphites as the nucleophilic coupling partners.<sup>66</sup> This method complemented the synthetic scope of existing protocols, as tertiary amides and even glycine esters were perfectly accommodated. Remarkably, a wide range of *N*-aryl substituents were shown compatible, hence overcoming the method by Li,<sup>65</sup> which was restricted to the use of *N*-PMP-glycine compounds. Conversely, secondary amides provided much lower yields and undesired *N*-alkylation was observed as side-reaction in those cases.

#### 3.2 C-N Bond Formation

In 2016, the Huang laboratory reported an unprecedented oxidative coupling of  $\alpha$ -amino ketones with secondary amines.<sup>67</sup> As previously observed by Li in heteroarylation reactions,<sup>31</sup> the judicious choice of the reaction conditions enabled the selective formation of either 2-imino or 2-oxocarbonyl compounds (Scheme 24). A variety of secondary amines such as morpholine, dimethylamine or piperidine underwent the oxidative amination in moderate to good yields. Unfortunately, primary amines and  $\alpha$ -amino ester derivatives were found unreactive under the optimized reaction conditions. Based on control experiments and literature precedents, the proposed mechanism involved the formation of an imine intermediate, which upon copper

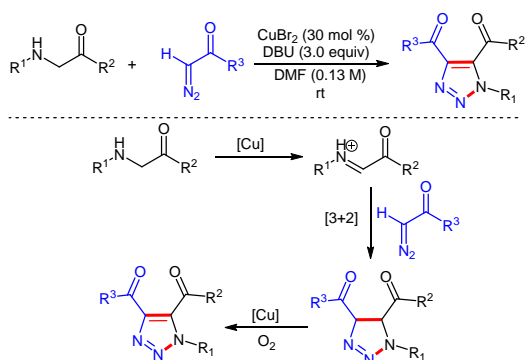


coordination could undergo a nucleophilic attack of the corresponding amine. Under stronger oxidizing reaction conditions the latter could be hydrolyzed to the corresponding 1,2-dicarbonyl compounds. Despite the novelty of the method to introduce nitrogen moieties into the  $\alpha$ -amino ketone backbone, the major drawback relied on the use of substoichiometric amounts of a copper salt and high temperatures.



**Scheme 24** Oxidative coupling with amines

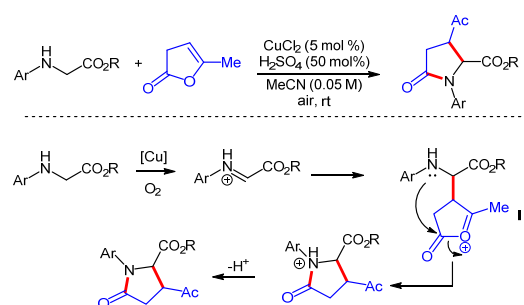
Prompted by the pioneering work on dehydrogenative [4+2] cycloadditions by Mancheño,<sup>15</sup> a number of *N*-containing heterocycles have been recently synthesized upon novel dehydrogenative cycloadditions of glycine derivatives through the formation of challenging C–N bonds. In this respect, the Liu group applied the oxidative [3+2] cycloaddition of  $\alpha$ -amino esters and amides with  $\alpha$ -diazo compounds for the assembly of biologically relevant 1,2,3-triazoles<sup>68</sup> (Scheme 25). Notably, the protocol involved the convenient use of O<sub>2</sub> as the terminal oxidant and was successfully applied to a wide range of glycine derivatives, including often unreactive *N*-alkyl substituted compounds, and a number of  $\alpha$ -diazocarbonyl compounds. On the basis of control experiments, they proposed a mechanism featuring the key formation of an iminium ion through a Cu-catalyzed oxidation, which would then undergo a [3+2] cycloaddition. Finally, a Cu-catalyzed aerobic oxidation delivered the target 1,2,3-triazole product.



**Scheme 25** Oxidative [3+2] toward the assembly of 1,2,3-triazoles

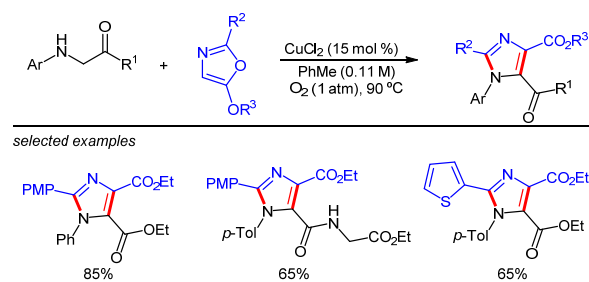
In 2015, Huo and co-workers introduced the use of  $\alpha$ -angelicalactone for the construction of pyrrolidinones upon Cu-catalyzed aerobic oxidative formal [2+3] cyclizations with glycine esters<sup>69</sup> (Scheme 26). The mechanism proposal started by the accepted formation of an electrophilic iminium intermediate under Cu-catalyzed aerobic conditions. Subsequent nucleophilic addition provided intermediate **I**, which would ultimately undergo an intramolecular nucleophilic substitution and

deprotonation to provide the corresponding pyrrolidone derivative.



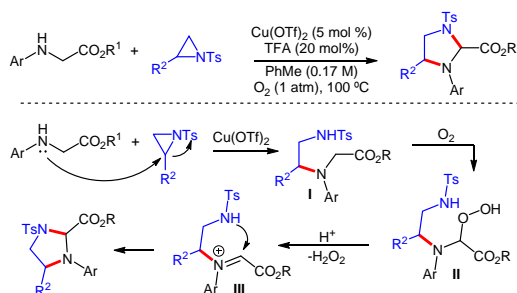
**Scheme 26** Oxidative cycloaddition for the synthesis of pyrrolidones

A similar strategy was followed by Wang and co-workers to access tetrasubstituted 4,5-biscarbonyl imidazoles from 5-alkoxyoxazoles<sup>70</sup> (Scheme 27). There, various *N*-aryl glycine esters and amides underwent a Cu-catalyzed aerobic [2+3] cycloaddition/aromatization cascade reaction. The proposed mechanism involved the formation of electrophilic imine species, which upon activation with the copper salt could be attacked by the nucleophilic carbon of the corresponding oxazole. Subsequent cyclization, ring opening and aromatization would furnish the desired heterocyclic compounds.



**Scheme 27** Oxidative cycloaddition for the synthesis of 4,5-biscarbonyl imidazoles

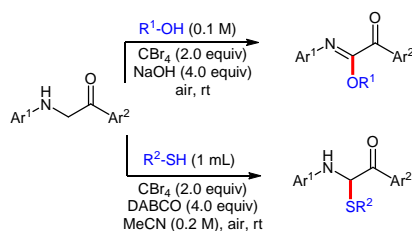
Very recently, the Huo group has utilized aziridines as novel nitrogen sources in oxidative cycloaddition processes with glycine derivatives.<sup>71</sup> The latter cyclic amines constitute masked 1,3-dipoles prone to undergo formal [3+2] cyclizations with dipolarophiles. Accordingly, they described the synthesis of imidazolidine compounds through a novel oxidative dehydrogenative reaction of *N*-aryl glycine esters and *N*-sulfonylaziridines. Control experiments ruled out the formation of the commonly accepted imine intermediate, and the intermediacy of the hydroperoxide derivative **II** detected by GC-MS analysis was proposed instead. Based on experimental evidences, they assumed a first attack of the *N*-aryl glycine compound to the aziridine, thus generating the ring-opened species **I**. The auto-oxidation of the latter would deliver the hydroperoxide intermediate **II**, which upon an acid-catalyzed S<sub>N</sub><sup>1</sup>-type procedure would provide the iminium species **III**. Eventually, the intramolecular C–N bond forming cyclization would produce the corresponding heterocyclic compound. Interestingly, diastereomerically enriched products were achieved and the major formation of the corresponding 2,4-*cis* isomers was attributed to the easier attack of the iminium species **III** from its sterically most accessible back side.



**Scheme 28** Synthesis of imidazolidines

### 3.3 C–O and C–S Bond Formation

In 2018, the group of Huang reported a new method to incorporate both alcohols and thiols into  $\alpha$ -amino ketones through a metal-free oxidative coupling reaction.<sup>72</sup> The use of  $\text{CBr}_4$  under air and basic conditions allowed the efficient coupling of a wide range of aromatic ketones and numerous alkyl alcohols and thiols. However, glycine esters and phenols or thiophenol derivatives were found unreactive under the optimized conditions. Based on the different acidity as well as distinct nature of the final coupling product when using alcohols or thiols, two different mechanisms were proposed. The formation of an electrophilic imine compound was proposed when employing alcohols as nucleophiles. Conversely, more acidic thiols were proposed to initially react with  $\text{CBr}_4$  in the presence of an excess of base, thus providing a sulfur-centered electrophilic species which would be ultimately trapped by the  $\alpha$ -amino carbonyl compound.



**Scheme 29** CDCs with alcohols and thiols

## 4 Conclusions

The direct oxidative  $\alpha$ -C(sp<sup>3</sup>)-H coupling of  $\alpha$ -amino carbonyl compounds with various nucleophiles has lately become a powerful and practical means for the assembly of structurally diverse  $\alpha$ -amino acid and peptide derivatives. Indeed, expanding the landscape of nucleophilic coupling partners has garnered considerable attention and the procedures available have reached a significant level of versatility, selectivity, efficiency and sustainability. As a result, CDCs rank as robust and promising coupling reactions for the access of peptide-based structures, which sometimes outcompete well-established methods based on pre-functionalized starting materials, carbanion chemistry or solid-phase techniques. The key aspect of the CDCs described along this review relies on the *in situ* generation of catalytically competent electrophilic imine or iminium species that rapidly react with a variety of nucleophilic counterparts. Despite the advances realized, several challenges need to be addressed to render CDCs the method choice for the construction of those compounds in industrial environments. Firstly, limited knowledge has been gathered regarding the mechanism of some of the metal-catalyzed events disclosed herein, which sometimes are merely speculative and based on indirect experimental

evidences. In this respect, mechanistic understanding of the underlying key elemental steps upon isolation of putative reaction intermediates will certainly fuel wider applications in the years to come at the forefront of organometallic chemistry and peptide synthesis. Secondly, efficient CDCs for the late-stage functionalization of peptides are still rare in the literature. Such methodologies would be of crucial importance in proteomics and peptide-based drug discovery, given the rapid derivatization of a lead peptide into a myriad of peptidomimetics and the high-value of the resulting biological targets. Thirdly, few advances have been made in the development of asymmetric CDC reactions. Accordingly, the pursuit of novel C(sp<sup>3</sup>)-H coupling processes which occur in an enantioselective fashion still remains an elusive goal, and it would clearly open up new synthetic opportunities of paramount chemical significance in the synthesis of complex peptides and proteins. Therefore, we anticipate that efforts along these lines would have a significant impact on this field of expertise and we hope this review could serve as a practical guide, yet scientific inspiration, for practitioners in the field.

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## Biosketches

	<p><b>Marcos San Segundo</b> (right) was born in Zarautz in 1990. He received his B.Sc. degree from the University of the Basque Country (UPV/EHU) in 2015. Then, he got his M.Sc. in September 2016 guided by Prof. Rosa López and Claudio Palomo working in the field of organocatalysis. He is currently doing his Ph.D. under the supervision of Dr. A. Correa at UPV/EHU. He is working on the development of catalytic methods for the assembly of <math>\alpha</math>-amino carbonyl compounds and peptide derivatives.</p> <p><b>Arkaitz Correa</b> (left) was born in Bilbao in 1979. He studied chemistry at the University of the Basque Country (UPV/EHU), where he completed his PhD studies in 2006 under the guidance of Prof. Esther Domínguez. Along that time, he did a short stay with Prof. Ben L. Feringa at the University of Groningen. In 2007, he undertook his first postdoctoral studies with Prof. Carsten Bolm at RWTH Aachen University (2007–2008). Subsequently, he joined the group of Prof. Ruben Martin at ICIQ (Tarragona) as a postdoctoral fellow (2008–2010). In 2010, he joined a collaborative project with Bayer CropScience at the CSIC under the supervision of Prof. J. M. Lassaletta. From april 2011 to march 2014, he went back to the group of Prof. Ruben Martin at ICIQ as a Juan de la Cierva associate researcher. In April 2014, he started his independent career at UPV/EHU as a Ramón y Cajal fellow. His current research interests include sustainable catalysis within the field of C–H functionalization as well as peptide and heterocyclic chemistry.</p>
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