Metal-Catalyzed Oxidative Coupling of Ketones and Ketone Enolates

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1 Introduction

An enolizable ketone typically reacts with a range of electrophiles through the enol form to furnish conventional nucleophile–electrophile coupling products and this, thereby, ultimately leads to the α-functionalization of the ketone moiety. An alternative way to perform the α-functionalization of ketones would be through the oxidative coupling of the enolate thus providing a direct and convergent method to synthetically useful 1,4-dicarbonyl motifs (Scheme 1, Path A). One advantage of such an oxidative coupling strategy is that it obviates the need for functional group umpolung and thereby streamlines the synthetic sequence. The first example of such an oxidative enolate coupling was reported in 1935, when Ivanoff and Spasoff showed that the enolate of phenylacetic acid undergoes oxidative homocoupling in the presence of molecular oxygen or molecular iodine. This exciting transformation turned out to be less synthetically useful due to low yields and multiple unwanted side products. This field remained unexplored until the 1970s, when the interest towards the development of preparatively and synthetically useful oxidative enolate coupling was reinvigorated. In 1971, Rathke and Lindert...
mented a Cu(II)-promoted coupling of ester enolates towards the synthesis of succinate esters. The first oxidative enolate coupling involving ketones dates back to 1975; when Saegusa and co-workers documented the use of CuCl₂ as an effective oxidant for the dimerization of ketone enolates. Subsequent years witnessed the usage of various other oxidants and non-enolate carbonyl derivatives in oxidative coupling chemistry. In several of these cases more challenging oxidative cross-coupling could be achieved, but typically they required stoichiometric advantage of one coupling partner. Recent years have witnessed significant advances in these areas in terms of efficient methodology development, cross-coupling with equal stoichiometry of reacting partners, and attainment of high levels of diastereorecontrol. Strategically, cross-dehydrogenative coupling (CDC) between two simple C–H bonds leading to the formation of a C–C bond is of great interest due to its atom and step economy. In 1948, in one of the earliest examples of CDC, Kharasch and co-workers showed that upon treatment with diacetyl peroxide, aliphatic ketones undergo dimerization through direct C–H functionalization to give the corresponding 1,4-dicarbonyl compounds. Interestingly, since this initial report, noteworthy development has been made and powerful methods have emerged regarding the application of CDC approach towards the synthesis of 1,4-dicarbonyl compounds through direct C(sp³)–H functionalization of ketones (Scheme 1, Path B).

Importantly, 1,4-dicarbonyl compounds synthesized through these powerful oxidative coupling methods serve as highly useful synthetic precursors for various carbocyclic and heterocyclic compounds (Scheme 1, Path C). Moreover, in recent years, several other direct oxidative homocouplings of ketones and also cross-couplings between ketones and diverse other coupling partners have been developed that lead to the formation of carbocycles and biologically important heterocycles. These cross-couplings may (Scheme 1, Path C) or may not (Scheme 1, Path D) go through the intermediacy of a 1,4-dicarbonyl motif.

The purpose of this brief review is to summarize all these recent contributions and to provide examples of oxidative coupling involving α-functionalization of ketones for the synthesis of 1,4-dicarbonyl compounds and diverse heterocycles and carbocycles. This review specifically covers the advancements made since 2008 in the field of the metal-catalyzed couplings of ketones which occur through radical pathway and lead to the α-functionalization of ketones. This review does not cover oxidative coupling involving carboxyls other than ketones (such as esters and amides) and metal-free couplings involving ketones.

## 2 Synthesis of 1,4-Dicarbonyl Compounds

Oxidative coupling of enolates through single-electron oxidation represents a direct and straightforward approach for the construction of 1,4-diketones. Oxidative dimerization of ketone-derived lithium enolates was first studied by Saegusa and co-workers in the 1970s. Formally, this transformation utilizes the direct coupling of two identical sp³-hybridized carbon atoms with no substrate pre-functionalization. A comprehensive list of an analogous process using two different types of enolates allowing selective and controlled heterocoupling is quite brief. The first intermolecular oxidative cross-coupling was reported by Saegusa and co-workers using at least a threefold excess of one of the ketone coupling partners and gave the desired products in synthetically useful yields (Scheme 2). Although the power of this approach towards the synthesis of unsymmetrical 1,4-diketones is unquestionable, the necessity of using one coupling partner in manifold excess has restricted its use in more complex settings.

Selective cross-coupling received no further attention and the field remained unexplored until 2006 when Baran and co-workers reported the intermolecular oxidative heterocoupling of enolates. They showed that a selective heterocoupling between two different enolates can be achieved by exploiting the natural electronic or steric differences in both coupling partners. Accordingly, for the first time a cross-coupling between a ketone and an amide with equal stoichiometry of the reacting partners was demonstrated by Baran and DeMartino taking advantage of the
difference in oxidation potential of ketone and amide lithium enolates (Scheme 2). A subsequent report in 2008 detailing the full scope of the reaction revealed that good yields were obtained across a range of substrates when appropriate lithium enolates were cross-coupled in the presence of Fe(III)- or Cu(II)-based oxidants. Furthermore, it was also shown that best results were obtained in THF solvent. While these studies by Baran and co-workers provided important and much needed insight into oxidative heterocoupling of lithium enolates, subsequent work by Casey and Flowers, supported by spectroscopic and mechanistic data, showcased that selective formation of cross-coupled products for the ketones they investigated was due to the heteroaggregation of the corresponding lithium enolates. In an interesting finding, Daugulis and co-workers showed that oxidative dimerization of ketone enolates can be carried out using a copper catalyst and molecular oxygen as the terminal oxidant. The lithium enolates of diverse ketones underwent facile dimerization in the presence of Cu(acac)₂ catalyst, zinc chloride additive, and molecular oxygen to afford the desired symmetrical 1,4-diketones in moderate to good yields. This is a significant improvement, as the existing oxidative homocouplings required metal oxidant in stoichiometric amounts.

In 2011, Thomson and co-workers developed a method for the synthesis of axially chiral biphenols through the oxidative enolate dimerization of enantioenriched monoketal cyclohex-2-ene-1,4-diones. To this end, treatment of enone precursors 1 with LDA, followed by oxidative coupling catalyzed by CuCl₂, furnished the dione product 2 while forging the hindered central α-bond linkage. Finally, a Lewis acid promoted loss of methanol with a concomitant double aromatization event furnished a range of desired biphenols 3 with traceless central-to-axial chirality exchange (Table 1).

Table 1 Synthesis of Biphenols from 1,4-Diketones by Traceless Central-to-Axial Chirality Exchange

<table>
<thead>
<tr>
<th>Ar</th>
<th>Yield (%) of 2 (dr)</th>
<th>Yield (%) of 3 (dr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-MeOC₆H₄</td>
<td>50 (99:1)</td>
<td>86 (99:1)</td>
</tr>
<tr>
<td>4-FC₆H₄</td>
<td>66 (99:1)</td>
<td>88 (99:1)</td>
</tr>
<tr>
<td>2-naphthyl</td>
<td>51 (99:1)</td>
<td>82 (99:1)</td>
</tr>
</tbody>
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In 1998, Schmittel and co-workers revealed that symmetrical and nonsymmetrical bis-enol ethers in the presence of ceric ammonium nitrate (CAN) undergo intramolecular oxidative coupling to generate 1,4-diketones. In order to further expand the scope of these initial findings, in 2007 Thomson and co-workers documented a general strategy for the oxidative cross-coupling of tetralone derivatives to afford unsymmetrical 1,4-diketones. Treatment of 2-methyl-1-tetralone (4) with LDA followed by addition of chlorosilane 5 resulted in the clean formation of the desired unsymmetrical silyl bis-enol ethers 6, which were then subjected to oxidative coupling conditions in the presence of CAN to afford the desired diketones 7 with simultaneous generation of a quaternary stereocenter (Scheme 3). Several methyl ketone derivatives 5 reacted with the tetralone component 4 to furnish the final products in moderate to good yields.

Following this in 2008, Thomson and co-workers investigated the scope of the diastereoselective synthesis of linked complex bicyclic structures through the oxidative coupling of unsymmetrical silyl bis-enol ethers. Through an extensive screening using several silyl bis-enol ethers with varying silicon substituents, it was established that sterically congested disopropylsilyl bis-enol ether 8 was the optimal substrate giving the highest levels of yield and diastereoselectivity. The robustness of the protocol was demonstrated through the preparation of several linked bicyclic diketones 9 with high diastereoselectivity (Scheme 4).

Taking this a step further in 2018, Thomson and Robinson developed a modular approach based on the stereoselective coupling of symmetrical or unsymmetrical silyl bis-enol ethers, followed by a ring-closing metathesis sequence towards the synthesis of stereochemically rich polycyclic compounds that are embedded in numerous bioactive natural product families. To this end, optically active silyl bis-
enol ether derivatives 10 bearing a vinyl or allyl group at the 5-position were subjected to their previously documented CAN-promoted oxidative coupling conditions to afford diketo adducts 11, which upon ring-closing metathesis using Grubbs II catalyst delivered a range of polycyclic compounds 12 in moderate yield and good diastereoselectivity (Scheme 5). Interestingly, several prepared compounds exhibited potent cytotoxic activity against a panel of tumor cell lines. Importantly, enones were employed as starting materials for the regioselective formation of the silyl bis-enol ethers and also to ensure that subsequent oxidative coupling takes place in the desired fashion. In addition, using an enantiomerically pure starting material was indispensable to this powerful reaction sequence, as the union of racemic precursors gave the undesired formation of diastereomeric mixtures. It is important to mention that the CAN-promoted oxidative heterocoupling of enol silanes has been successfully applied as a key step in the total synthesis of the natural product propindilactone G.18

In 2009, Thomson and Clift demonstrated a three-component, two-step merged conjugate addition/oxidative coupling strategy using CAN and 2,6-di-tert-butylpyridine (dtbpy) towards the synthesis of a diverse collection of 1,4-diketones 15 in moderate yields (Scheme 6). The desired unsymmetrical silyl bis-enol ethers 14 required for the oxidative coupling were formed in the first step by 1,4-addition of magnesium bromide with subsequent trapping of the thus-generated enolate by chlorosilyl enol ether 5.

In 2014, Hirao and co-workers developed an oxidative homocoupling of boron enolates 16 using oxovanadium(V) compounds to give the corresponding 1,4-diketones 17 in good yields (Scheme 7).20 The required boron enolates 16 were prepared via the 1,4-hydroboration of enones 13; the geometric configuration of the resulting enolate 16 was established using 1H NMR spectroscopy. Interestingly, the choice of oxovanadium(V) oxidant was critical to attaining high stereoselectivity. Accordingly, high selectivity (up to 94:6) was obtained when the oxidative coupling was carried out at –30 °C and in the presence of VO(Oi-Pr)Cl as the oxidant.

Subsequently in 2015, Hirao and co-workers reported a oxovanadium(V)-induced selective oxidative cross-coupling between boron 18 and ketone-derived silyl enolates 19 as an efficient and straightforward strategy for the synthesis of unsymmetrical 1,4-dicarbonyl compounds 20 (Scheme 8).21 The reactivity difference between boron and silicon in the enolates 18 and 19 proved to be crucial as it allowed selective one-electron oxidation of the more reactive boron enolate 18 leaving the silyl enolate 19 intact. Strategically, selective one-electron oxidation of the boron enolate 18 generates an electrophilic α-radical species, which is immediately trapped by the silyl enolate 19. A broad substrate scope with regard to both enolates was demonstrated and the resulting 1,4-dicarbonyls 20 were obtained in good yields. In 2017, they also showed that the same oxovanadium(V)-induced cross-coupling strategy can be extrapolated to the cross-coupling of various combinations of boron and silyl enolates in a ketone–ester, ester–ester, amide–ester, and amide–ketone enolate coupling.22 These findings unequivocally established the versatility of this oxovanadium(V)-induced oxidative cross-coupling strategy.
In 2015, Wang and co-workers developed an efficient Cu(II)-promoted direct oxidative coupling between two C(sp³)–H bonds in the α-position to a carbonyl group as a more attractive way to build the 2,3-disubstituted 1,4-diketone motif 22 (Scheme 9). The method features a broad substrate scope and high functional group tolerance. Mechanistically, it was proposed to proceed through the intermediacy of radicals.

Contemporaneously, they developed a more sustainable silver-catalyzed protocol to achieve a similar cross-dehydrogenative coupling of two C(sp³)–H bonds for the synthesis of 1,4-diketones with air as the terminal oxidant. This catalytic CDC protocol is highly attractive, as besides homocoupling it also allows the cross-coupling of two different ketones 23 and 24 under similar conditions to afford the corresponding products 25 in good yields (Scheme 10).

In their pioneering studies in 2007, MacMillan and co-workers exploited their novel organocatalytic singly occupied molecular orbital (SOMO) activation strategy to report the first asymmetric aldehyde α-eneolation leading to the formation of γ-ketoaldehydes starting from simple aldehydes and enol silanes. In 2010, Huang and Xie developed a merging organocatalyst and transition-metal-catalyzed carbo-carbonylation of styrenes 26 with ketones 27 by cascade SOMO catalysis and oxidation to furnish 1,4-dicarbonyl compounds 28 in moderate to good yields (Scheme 11).

Along these lines, Koike, Akita, and Yasu developed a visible-light photoredox-catalyzed oxidative cross-coupling of enamines and silyl enol ethers in the presence of quinone.

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**Scheme 8** Oxovanadium(V)-induced oxidative heterocoupling of enolates

**Scheme 9** Cu(II)-promoted oxidative coupling of two C(sp³)–H bonds adjacent to the carbonyl group

**Scheme 10** Ag(I)-catalyzed oxidative coupling of two C(sp³)–H bonds adjacent to a carbonyl group

**Scheme 11** The cascade carbo-carbonylation of styrenes and ketones
oxidant to furnish the corresponding γ-diketones in moderate yields.\textsuperscript{27} In a conceptually novel approach, Xing and co-workers documented a copper/manganese-cocatalyzed and tert-butyl hydroperoxide (TBHP) promoted direct oxidative coupling of styrene derivatives\textsuperscript{26} with ketones\textsuperscript{27} through C(sp\textsuperscript{3})–H bond functionalization to afford 1,4-dicarboxyls\textsuperscript{28,29}. Various ketones underwent a smooth free-radical addition to styrenes to furnish a range of 1,4-diketone compounds with excellent regioselectivity (Scheme 12). Similarly, Christoffers and Geibel reported a cerium-catalyzed coupling of o xo esters with enol acetates for the synthesis of 1,4-dicarbonyls using atmospheric oxygen as the oxidizing agent.\textsuperscript{29}

3 Synthesis of Heterocyclic Scaffolds

The direct oxidative C–H functionalization of ketones has been successfully applied in the synthesis of several heterocycles, such as furans, dihydrofurans, thiophenes, and pyrroles, that are valuable five-membered heterocycles embedded in multiple natural products, pharmaceuticals and materials.\textsuperscript{30} In 2015, Wang and co-workers developed a copper and silver cocatalyzed coupling of C(sp\textsuperscript{3})–H bonds that are adjacent to a carbonyl group to provide a direct and efficient route to a diverse collection of tetrasubstituted furan derivatives\textsuperscript{29} using molecular oxygen as the terminal oxidant (Scheme 13).\textsuperscript{23} Importantly, the oxidative coupling did not occur when carried out in the presence of the radical inhibitor TEMPO. Based on this radical trapping experiment, they proposed that the reaction begins by deprotonation and single-electron-transfer oxidation of ketone\textsuperscript{21} by the Cu(II) catalyst to form alkyl radical\textsuperscript{A} and Cu(I). Then the resulting alkyl radical\textsuperscript{A} undergoes homodimerization to give 1,4-dicarboxyl\textsuperscript{22}, which finally, under acidic conditions, produces tetrasubstituted furans\textsuperscript{29}. Cu(I) is oxidized by the Ag\textsubscript{2}O/O\textsubscript{2} system to regenerate Cu(II) and complete the catalytic cycle.

In a subsequent report,\textsuperscript{24} they demonstrated a silver-catalyzed general oxidative coupling approach for the synthesis of polysubstituted furans, thiophenes, and pyrroles (Scheme 14, see also Scheme 10). Initially, silver-catalyzed oxidative coupling of two C(sp\textsuperscript{3})–H bonds generates 1,4-diketones, which subsequently undergo cyclization in a one-pot fashion under different conditions to furnish tetrasubstituted furans (Conditions A), thiophenes (Conditions B), and pyrroles (Conditions C) in good yields (Scheme 14).

Furans have also been synthesized through intermolecular oxidative coupling between ketones and electron-deficient alkenes. To this end, in 2013 Zhang and co-workers reported a novel copper-mediated intermolecular annulation of alkyl ketones\textsuperscript{31} with acrylic acids\textsuperscript{32} for the synthesis of 2,3,5-trisubstituted furans\textsuperscript{33} (Scheme 15).\textsuperscript{31} It is important to mention that the reaction was more effective in the presence of both copper salts [CuCl and Cu(OAc)]\textsubscript{2}·H\textsubscript{2}O] and yields decreased in the absence of either of the copper
sources. The reaction between ketone 31a and cinnamic acid (32a) was completely suppressed when carried out in the presence of TEMPO as a radical inhibitor, which supports the intermediacy of radicals in this reaction. According to the proposed reaction mechanism, in the first step, upon reaction with copper salts, the cinnamic acid 32 generates Cu(II) cinnamate A and the alkyl ketone 31 produces the corresponding alkyl radical B (Scheme 15). Addition of the generated alkyl radical B to the α-position of the double bond in Cu(II) cinnamate A, followed by single-electron-transfer oxidation delivers the carbocationic intermediate D. Subsequently, D undergoes intramolecular cyclization to give intermediate E, which upon deprotonation and elimination delivers the corresponding furan product 33.

Following this report, in 2015 Hajra and co-workers reported a similar decarboxylative annulation between ketones 31 and acrylic acids 32 towards the regioselective synthesis of trisubstituted furans 33,32 The method was shown to be quite robust and a library of furan derivatives was prepared. Interestingly, whereas the method of Zhang and co-workers required two different copper salts in stoichiometric amounts, the protocol of Hajra and co-workers utilized a single copper salt in catalytic amounts and a stoichiometric amount of water as an important additive. Furthermore, Hajra and co-workers ruled out the possibility of a radical pathway, as radical scavengers like quinone and 2,6-di-tert-butyl-4-methylphenol (BHT) did not inhibit the reaction between 31a and 32a and the corresponding furan 33a was obtained in 52% yield (Scheme 16).

Also in 2015, Hajra and co-workers demonstrated a copper-mediated annulation of alkyl ketones 31 and β-nitrostyrenes 34 for the synthesis of 2,3,5-trisubstituted furans 35 using tert-butyl hydroperoxide as an oxidant (Scheme 17).33 In contrast to their previous report, they showed, based on radical trapping experiments, that this reaction proceeds through a radical pathway.

Antonchick and Manna showed that besides activated alkenes, electron-deficient alkynes can also be employed in this type of oxidative cross-coupling reaction. Accordingly, they developed a copper-catalyzed oxidative coupling, using di-tert-butyl peroxide (DTBP), between acetophenones 36 and electron-deficient alkynes 37 for the synthesis of trisubstituted furans 38 (Scheme 18).34 Subsequent to this report, Luo, He, and co-workers demonstrated a similar Cu(I)-catalyzed oxidative annulation between substituted acetophenones 39 and alkynoates 40 using benzoyl peroxide (BPO) as an external oxidant (Scheme 18).35 Both protocols are mechanistically similar and work quite efficiently giving multisubstituted furans in good yields. In contrast to the protocol of Antonchick and Manna, which exclusively worked for electron-poor acetophenones 36, the method of Luo, He, and co-workers was shown to be applicable to electron-rich acetophenones 39 as well.
According to the proposed mechanism, first the Cu(I) species is oxidized to Cu(II) in the presence of DTBP (Scheme 19). The enol form of the acetoephone derivative is then oxidized to the corresponding alkyl radical A by the Cu(II) species. Subsequently, radical A undergoes addition to the electron-deficient alkylene 37a to give intermediate B, which after oxidative addition of Cu(II) generates intermediate C. Intermediate C is in equilibrium with intermediate D through keto–enol tautomerization. A ligand exchange in intermediate D forms metalloxycenter E, which finally undergoes reductive elimination to afford product 38a. The Cu(II) catalyst is regenerated by oxidation of Cu(I) with DTBP. In an alternative pathway, radical B can be oxidized to the corresponding cation F by Cu(II), which concomitantly undergoes intramolecular cyclization to the desired final product 38a. However, this pathway was considered to be less likely, as in control experiments the authors were not able to trap the cationic intermediate using various nucleophiles.

In 2012, Lei and co-workers demonstrated that simple unactivated terminal alkynes 42 can also be employed in direct oxidative cross-coupling by using 1,3-dicarbonyl compounds 43 possessing an active methylene group instead of simple alkyl ketones as the other coupling partner. They developed a silver-mediated CDC between 1,3-dicarbonyl compounds 43 and arylacetylenes 42 furnishing a range of polysubstituted furans 44 in good yields (Scheme 20).36 The reaction worked only with terminal alkynes and trace product formation was observed in cases using internal alkynes. It was speculated that this transformation might not proceed through an oxidative radical cyclization. In 2014, the mechanism of this silver-mediated oxidative coupling reaction was studied by Nováčk, Stirling, and co-workers and based on their experiments and density functional calculations they unambiguously established that the reaction is indeed going through a radical intermediate.37 The reaction between phenylacetylene (42a) and ethyl acetoacetate (43a) carried out under the optimized conditions was completely inhibited upon addition of TEMPO or BHT as radical scavengers (Scheme 20).

Li and co-workers developed a manganese-mediated efficient synthesis of dihydrofurans 46 through direct oxidative coupling of enamides 45 and 1,3-dicarbonyl compounds 43 (Scheme 21).38 Replacing 1,3-dicarbonyl compounds 43 with 2-substituted 1,3-dicarbonyl compounds in the reaction with enamides under otherwise unchanged conditions, delivered (2)-dicarbonyl enamides. Importantly,
dihydrofurans 46 were conveniently transformed into the corresponding furans 44 and pyrroles 47 in good yields via the classical Paal–Knorr reaction (Scheme 21).

Based on radical trapping experiments, a radical mechanism was proposed for this transformation (Scheme 22). The reaction begins with the oxidation of 1,3-dicarbonyl compounds 43 by Mn(OAc)₃ to generate an electron-deficient radical A, which subsequently adds to the electron-rich enamide 45 to generate radical B. Radical B gets further oxidized by Mn(OAc)₃ into carboxylation C or iminium ion C', which readily undergoes cyclization/deprotonation to afford desired dihydrofuran 46. Under the influence of acid 46 undergoes ring cleavage to give imine D or enamide D', which further hydrolyzes to the corresponding 1,4-dicarbonyl intermediate E. The intermediate E then delivers the corresponding furans 44 and pyrroles 47 under Paal–Knorr conditions.

In 2017, Yu and co-workers developed a Fe(OAc)_2-catalyzed cross-dehydrogenative coupling between 1,3-dicarbonyl compounds 49 and α-oxoketene dithioacetals 48 using tert-butyl peroxybenzoate (TBPB) for the synthesis of a library of tetrasubstituted furans 50 in good yields (Scheme 23). Importantly, the highly functionalized furan derivatives are amenable to further synthetic manipulation through palladium-catalyzed selective C–S bond cleavage and concomitant arylation to yield α-arylfurans 51 or through condensation with hydrazine to yield 2,3-furan-fused pyridazinones 52.

Lei and co-workers reported a copper-catalyzed oxidative coupling between styrenes and 1,3-dicarbonyl compounds in the presence of di-tert-butyl peroxide as the external oxidant to provide highly substituted dihydrofurans. Moreover, they studied the Cu(I)/Cu(II) redox process involved in the oxidative cyclization of β-ketocarbonyl derivatives by X-ray absorption and EPR spectroscopy and provided evidence supporting the reduction of Cu(II) to Cu(I) by 1,3-diketones. In an interesting report, Maiti and co-workers demonstrated a copper-mediated annulation of aryl ketones 53 and styrenes 54 allowing efficient access to a diverse range of dihydrofurans 55 in good synthetic yields (Scheme 24). Meanwhile, along the same lines, Hajra and co-workers showed that aryl ketones 53 and styrenes 56 can also be oxidatively cross-coupled in the presence of catalytic amounts of Cu(II) salts to furnish multisubstituted furans 57 (Scheme 24). Importantly, aliphatic ketones as well as aliphatic alkenes are not viable substrates under both Maiti and Hajra’s conditions. Both reactions go through the intermediary of radicals as demonstrated by the use of radical scavenger experiments. Interestingly, as per the proposed mechanism of Hajra and co-workers, formation of furans 57 goes through the intermediary of dihy-
drofurans 55. Based on the proposed mechanism, dihydrofurans 55a, following further oxidation under Hajra’s oxidative conditions, generate carboxcaticon intermediate 58, which finally undergoes 1,2-aryl shift and elimination to furnish desired furan derivative 57 (Scheme 24). Similarly in 2017, Lei and co-workers reported a facile CuCl2-catalyzed oxidative cyclization of aryl ketones and styrenes towards the synthesis of multisubstituted furan derivatives. Interestingly, through X-ray absorption and electron paramagnetic studies they revealed that DMSO, besides serving as a solvent, plays the crucial role of an oxidant to promote the oxidation of Cu(I) to Cu(II).

Also in 2017, Maiti and co-workers developed a general and elegant oxidative [3+2] annulation between a variety of cyclic ketones 61 and 63 and diverse alkenes 60 using Cu(OAc)2 in combination with a tri-tert-butylphoshine ligand to furnish a diverse collection of fused furans 62 and naphthofurans 64 under mild conditions (Scheme 25). Importantly, naturally occurring chiral substrates, such as (R)-(−)-carvone underwent smooth reaction with styrene to provide fused furan 62a in 58% yield. Using adamantane-1-carbonyl chloride as an additive was essential to the synthesis of naphthofurans 64. Moreover, the generality of the method was further demonstrate by reacting 1-tetralone (63a) with several internal alkenes 65 furnishing 2,3-disubstituted naphthofurans 66 in good yields (Scheme 25). Use of molecular sieves as a drying agent and tert-butyl alcohol as the solvent was critical in obtaining good yields in this transformation.

Based on several control experiments, a radical-based mechanism was proposed as shown in Scheme 26. The reaction begins by the coordination of a copper complex with 1-tetralone (63a) to generate intermediate A, which upon elimination of acetic acid leads to B. Subsequently, single-electron transfer from B, followed by radical addition of C onto the β-position of alkene 60 provides intermediate D.

Afterwards, an oxidative cyclization results in dihydrofuran derivative F, which finally yields the desired product 64a through a radical-based dehydrogenation/oxidation sequence.
ducing an alkoxy carbonyl moiety at the α-position of the vinyl azide and the inability of 1,3-diketones other than ethyl acetoacetate to participate in this copper-catalyzed protocol, prompted the further development of a more general method. Accordingly, they developed a Mn(OAc)₃-catalyzed coupling between diverse vinyl azides 67 and a variety of 1,3-dicarbonyl compounds 68, including the corresponding diketone analogues, to afford a versatile collection of 1H-pyrroles 69 (Scheme 27).45b

**Scheme 27** Oxidative coupling of vinyl azides with 1,3-dicarbonyl compounds or ketones for the synthesis of pyrroles

In 2015, Adimurthy and co-workers showed that simple ketones 70, instead of activated 1,3-dicarbonyl compounds, can also be employed in this kind of transformation. A copper-catalyzed direct C(sp³)–H functionalization of ketones 70 with vinyl azides 67 was developed for the straightforward and efficient synthesis of 2,3,5-trisubstituted 1H-pyrroles 71 (Scheme 27).46 Several electronically and structurally diverse vinyl azides reacted with both aliphatic and aromatic ketones to furnish the desired products in moderate to good yields.

### 4 Synthesis of Carbocyclic Scaffolds

Strained carbocycles, such as cyclopropanes, impart unique reactivity in organic synthesis and are embedded in many natural products and medicinally important compounds.47 Antonchick and Manna have developed a copper-catalyzed cross-dehydrogenative annulation of electron-deficient alkenes 72 and acetoephones 36 involving direct double C–H functionalization at the α-position of the ketone using di-tert-butyl peroxide as the terminal oxidant towards the stereoselective synthesis of fused cyclopropanes 73 (Scheme 28).48 A broad substrate scope with regard to electronically diverse acetoephones 36 and N-alkyl-substituted maleimides 72 gave versatile fused cyclopropane scaffolds 73 in good yields. Moreover, besides N-substituted maleimides, other electron-deficient alkenes, such as acrylic acid derivatives, were shown to be tolerated under the reaction conditions. Importantly, the highly functionalized final products were amenable to further synthetic transformations. Accordingly, product 73a was transformed into 74 through hydrolysis and subsequent diesterification and into 75 through reduction using lithium aluminum hydride (Scheme 28).

**Scheme 28** Cu-catalyzed annulation of electron-deficient alkenes

Mechanistically, first Cu(I) is oxidized to a Cu(II) species by DTBP (Scheme 29). In the following step, acetoephone 36 through its enol form A gets oxidized by the Cu(II) species to alkyl radical B. The resulting radical B then adds to the maleimide derivative 72 to produce C, which is stabilized through the resonance form C'. Subsequent addition of C on the Cu(II) species generates intermediate D, which upon enolization at the keto functionality and ligand exchange delivers E. Importantly, formation of E is the stereo-determining step of this annulation process. Finally, reductive elimination of Cu(I) from E generates the final product 73 and the Cu(II) catalyst is regenerated by oxidation of Cu(I) by DTBP.
Following this, Antonchick and Manna developed an unprecedented copper-catalyzed [1+1+1] cyclotrimerization cascade of acetophenone derivatives 36 under mild conditions for the stereoselective synthesis of cyclopropanes 74 (Scheme 30). Various acetophenone derivatives 36 covering an array of functional groups such as halogens, carbonyl, sulfonamide, nitryl etc. participated in this oxidative annulation affording the corresponding cyclopropanes 74 in modest to good yields. Importantly, heterocycle derivatives such as 2-acetylthiophene delivered the desired product in 52% yield.

On the basis of several control experiments carried out with possible intermediates, it was established that this intriguing cyclotrimerization proceeds through the following steps: (i) initial dimerization of ketones to 1,4-diketones (formation of B in Scheme 31), (ii) oxidation of 1,4-diketones to but-2-ene-1,4-diones (formation of F), and (iii) annihilation of but-2-ene-1,4-diones with the third equivalent of acetophenone (formation of G). According to the proposed mechanism, the reaction begins with the oxidation of Cu(I) to a Cu(II) complex by DTBP (Scheme 31). Next, acetophenone 36 is oxidized by the Cu(II) species to radical A through its enol form. Following this, dimerization of A leads to 1,4-ketone B, which through its enol form C is further oxidized by a Cu(II) species to radical D. Radical D then adds on the Cu(II) species to form organocuprate E that subsequently undergoes β-hydride elimination to yield unsaturated diketone F with complete trans selectivity. Addition of radical A to F, followed by trapping with a Cu(II) species affords organocuprate[III] intermediate H. Subsequently, H is converted into the metallacycle J through ligand exchange of copper in the enol form I. Finally, the desired cyclopropane products 74 are obtained by the reductive elimination of Cu(II), which in turn is re-oxidized to Cu(II) by DTBP.

5 Conclusion

In this review we have attempted to cover the tremendous advancement made since 2008 in the field of metal-catalyzed radical coupling reactions leading to the α-functionalization of ketones. The oxidative enolate coupling focusing on the synthesis of 1,4-dicarbonyl compounds has witnessed the development of novel and efficient synthetic methods, cross-couplings with equal stoichiometry of reacting partners, and highly diastereoselective transformations. Besides elegant homo- and heterocoupling of enolates, powerful methods involving direct C(sp3)–H functionalization of ketones towards the synthesis of 1,4-dicarbonyl compounds have emerged.

Importantly, 1,4-dicarbonyl compounds synthesized through these powerful oxidative coupling methods served as highly useful synthetic precursors for various heterocyclic and carbocyclic compounds. An efficient and direct access to these important molecular scaffolds via oxidative homocoupling of ketones or by cross-coupling between ketones and diverse other coupling partners have recently evolved.

These methodological advances in the field of radical oxidative coupling have enriched the repertoire of synthetic tools available to synthetic chemists and should pave the way for future advancement in this important field of research. Despite these achievements, more challenges remain to be addressed. Future studies should see further development of direct oxidative cross-coupling reactions that are more predictable and highly chemoselective. Further applications of radical C–H functionalization in the context of synthesis of complex molecular scaffolds would broaden the horizon in this field. There is a broad scope with regard to the development of asymmetric transformations involving CDC reactions of ketones. We are convinced that this ex-
citing field of radical coupling reactions will continue to flourish and more general and useful methodologies involving such couplings will be developed.

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