

Metal-Catalyzed Oxidative Coupling of Ketones and Ketone Enolates

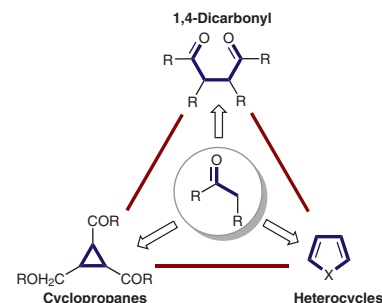
Sandip Murarka^{*a}

Andrey P. Antonchick^{*b,c}

^a Department of Chemistry, Indian Institute of Technology Jodhpur, NH-65, Nagaur Road, Karwar-342037, Jodhpur District, Rajasthan, India sandipmurarka@iitj.ac.in

^b Abteilung für Chemische Biologie, Max-Planck-Institut für Molekulare Physiologie, Otto-Hahn-Straße 11, 44227 Dortmund, Germany andrey.antonchick@mpi-dortmund.mpg.de

^c Fakultät Chemie und Chemische Biologie, Technische Universität Dortmund, Otto-Hahn-Straße 4a, 44227 Dortmund, Germany



Received: 25.02.2018

Accepted after revision: 21.03.2018

Published online: 03.05.2018

DOI: 10.1055/s-0037-1609715; Art ID: ss-2018-z0113-sr

Abstract Recent years have witnessed a significant advancement in the field of radical oxidative coupling of ketones towards the synthesis of highly useful synthetic building blocks, such as 1,4-dicarbonyl compounds, and biologically important heterocyclic and carbocyclic compounds. Besides oxidative homo- and cross-coupling of enolates, other powerful methods involving direct C(sp³)-H functionalizations of ketones have emerged towards the synthesis of 1,4-dicarbonyl compounds. Moreover, direct α -C-H functionalization of ketones has also allowed an efficient access to carbocycles and heterocycles. This review summarizes all these developments made since 2008 in the field of metal-catalyzed/promoted radical-mediated functionalization of ketones at the α -position.

- 1 Introduction
- 2 Synthesis of 1,4-Dicarbonyl Compounds
- 3 Synthesis of Heterocyclic Scaffolds
- 4 Synthesis of Carbocyclic Scaffolds
- 5 Conclusion

Key words ketone, oxidative coupling, C-H functionalization, cross-dehydrogenative coupling, radical

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.¹ 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).^{1,2} 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



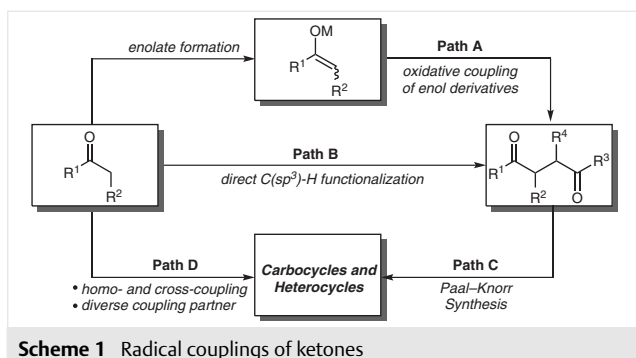
Sandip Murarka received his Ph.D. from WWU Münster, Germany under the supervision of Prof. Armido Studer. Subsequently, he worked as a postdoctoral research fellow in the laboratory of Prof. Herbert Waldmann at Max Planck Institute Dortmund. Since May 2017, he has held the position of an Assistant Professor at Indian Institute of Technology Jodhpur, India. His current research activities revolve around the study of novel activation modes and the development of transition-metal-free and transition-metal-catalyzed chemoselective and sustainable transformations.

Andrey P. Antonchick received his Ph.D. from the Institute of Bioorganic Chemistry of the National Academy of Sciences of Belarus (Minsk, Belarus) and the Max Planck Institute for Chemical Ecology (Jena, Germany) under the guidance of Prof. V. A. Khripach and Dr. B. Schneider. After a postdoctoral appointment with Prof. M. Rueping at Frankfurt University, he joined the group of Prof. H. Waldmann. He was appointed group leader at the Max Planck Institute of Molecular Physiology and TU Dortmund. His research interests lie in the development of new reaction methodologies.

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.³ 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 docu-

mented a Cu(II)-promoted coupling of ester enolates towards the synthesis of succinate esters.⁴ 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.⁵ Subsequent years witnessed the usage of various other oxidants⁶ and non-enolate carbonyl derivatives in oxidative coupling chemistry.^{2a} 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 diastereocontrol.^{2b} 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.⁷ 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.⁸ 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 functionalizations 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.

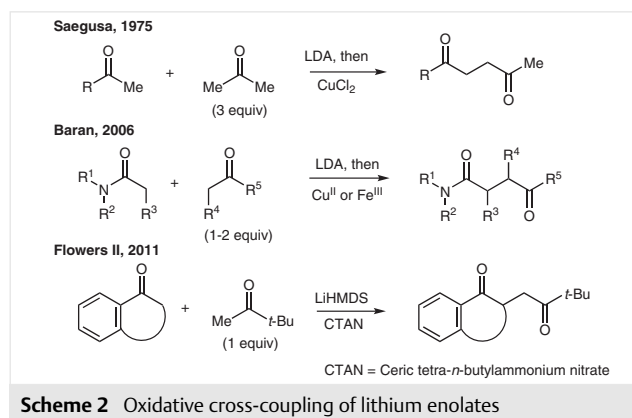


The purpose of this brief review is to summarize all these recent contributions and to provide examples of oxidative coupling involving α -functionalization of ketones for

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 carbonyls 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.^{5,9} 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).⁵ 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.¹⁰ 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).^{10a} 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.^{10b} 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.¹¹ 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.¹² 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.

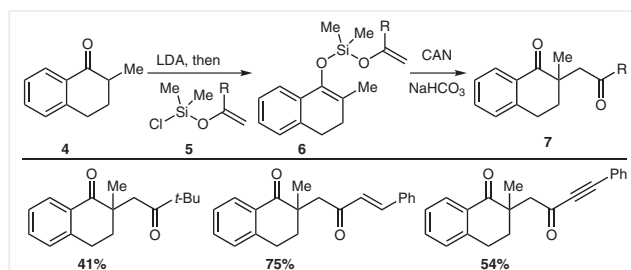
In 2011, Thomson and co-workers developed a method for the synthesis of axially chiral biphenols through the oxidative enolate dimerization of enantioenriched monoketal cyclohex-2-ene-1,4-diones.¹³ To this end, treatment of enone precursors **1** with LDA, followed by oxidative coupling catalyzed by CuCl₂ furnished the dione product **2** while forging the hindered central σ -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

Ar	Yield (%) of 2 (er)	Yield (%) of 3 (er)
4-MeOC ₆ H ₄	50 (99:1)	86 (99:1)
4-FC ₆ H ₄	66 (99:1)	88 (99:1)
2-naphthyl	51 (99:1)	82 (99:1)

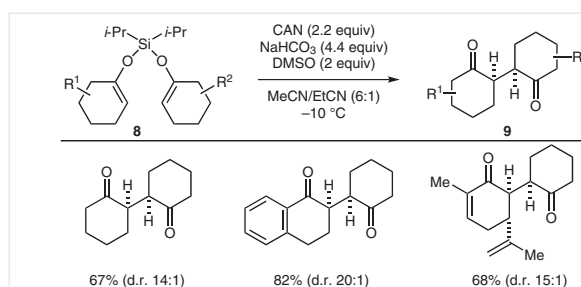
In 1998, Schmittl and co-workers revealed that symmetrical and nonsymmetrical bis-enol ethers in the presence of ceric ammonium nitrate (CAN) undergo intramolecular oxidative coupling to generate 1,4-diketones.¹⁴ In order to further expand the scope of these initial findings, in 2007 Thomson and co-workers documented a general strategy

for the oxidative cross-coupling of tetralone derivatives to afford unsymmetrical 1,4-diketones.¹⁵ 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.



Scheme 3 Oxidative coupling of 2-methyl-1-tetralone-derived unsymmetrical silyl bis-enol ethers

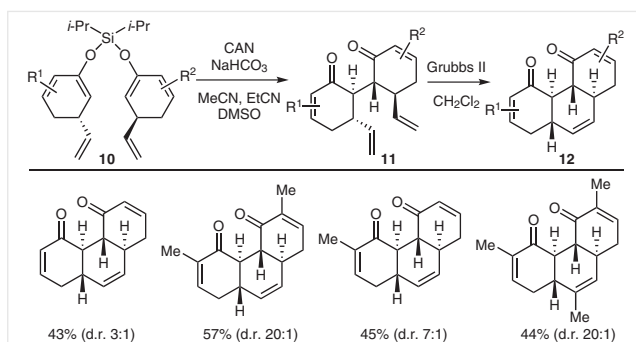
Following this in 2008, Thomson and co-workers investigated the scope of the diastereoselective synthesis of linked complex bicyclic structures through the oxidative coupling of unsymmetrical silyl bis-enol ethers.¹⁶ Through an extensive screening using several silyl bis-enol ethers with varying silicon substituents, it was established that sterically congested diisopropylsilyl 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).



Scheme 4 Diastereoselective oxidative coupling of unsymmetrical silyl bis-enol ethers

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.¹⁷ To this end, optically active silyl bis-

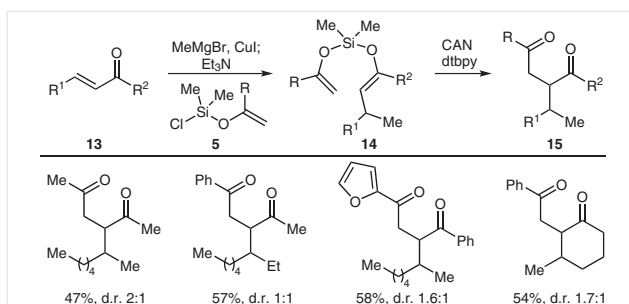
enol ether derivatives **10** bearing a vinyl or allyl group at the 5-position were subjected to their previously documented CAN-promoted oxidative coupling conditions to afford diketo adducts **11**, which upon ring-closing metathesis using Grubbs II catalyst delivered a range of polycyclic compounds **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



Scheme 5 Stereoselective oxidative coupling/ring-closing metathesis sequence towards polycyclic scaffolds

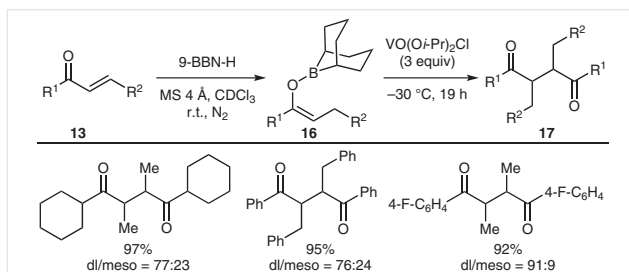
In 2009, Thomson and Clift demonstrated a three-component, two-step merged conjugate addition/oxidative coupling strategy using CAN and 2,6-di-*tert*-butylpyridine (dtbpy) towards the synthesis of a diverse collection of 1,4-diketones **15** in moderate yields (Scheme 6).¹⁹ The desired unsymmetrical silyl bis-enol ethers **14** required for the oxidative coupling were formed in the first step by 1,4-addition of methylmagnesium 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 2,3-disubstituted 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 criti-



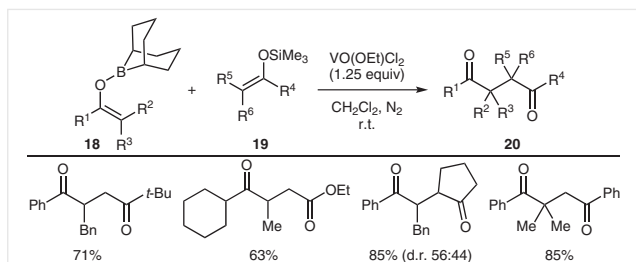
Scheme 6 Merged conjugate addition/oxidative coupling towards 1,4-diketones

cal 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 $\text{VO}(\text{O}i\text{-Pr})_2\text{Cl}$ as the oxidant.



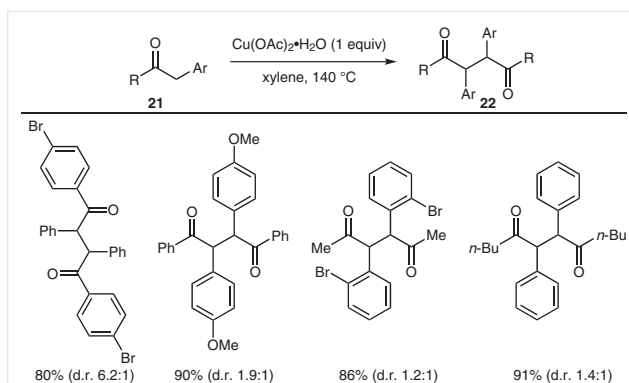
Scheme 7 Oxovanadium(V)-induced oxidative homocoupling of boron enolates

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.



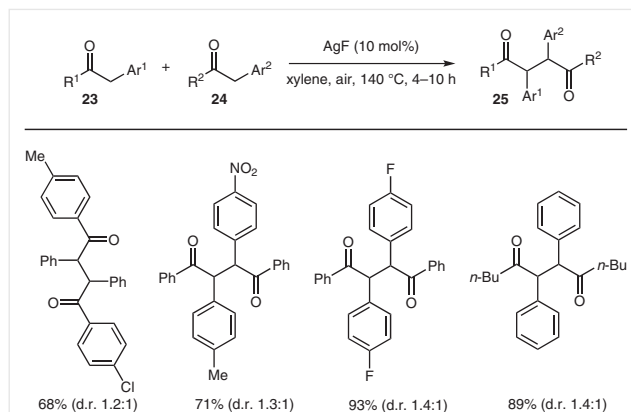
Scheme 8 Oxovanadium(V)-induced oxidative heterocoupling of enolates

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).²³ The method features a broad substrate scope and high functional group tolerance. Mechanistically, it was proposed to proceed through the intermediacy of radicals.

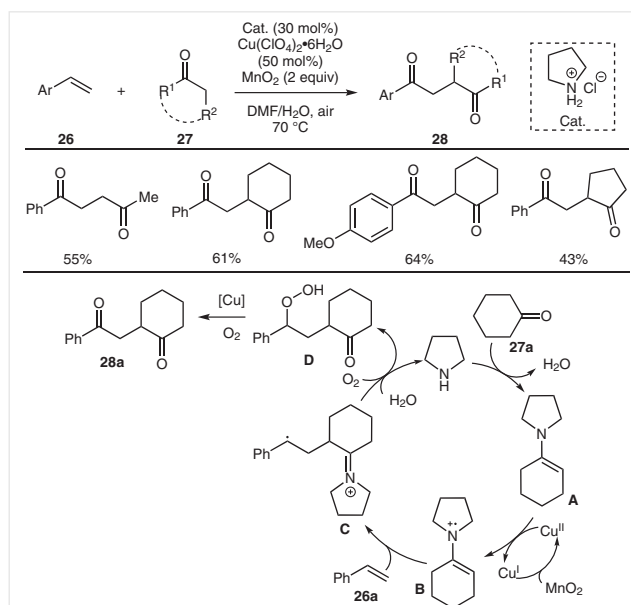
Scheme 9 Cu(II)-promoted oxidative coupling of two C(sp³)-H bonds adjacent to the carbonyl group

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.²⁴ 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 -enolation leading to the formation of γ -ketoaldehydes starting from simple aldehydes and enolsilanes.²⁵ 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).²⁶

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

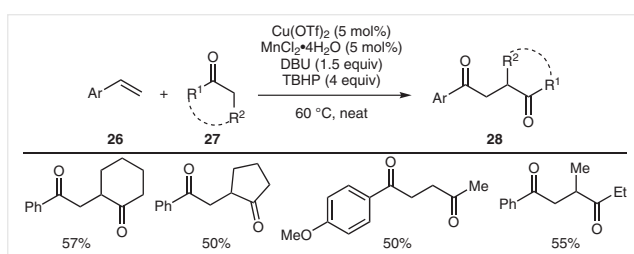
Under the catalysis of pyrrolidine and Cu(ClO₄)₂·6H₂O and in the presence of MnO₂ and air, several dicarbonyl compounds were obtained. According to the proposed mechanism (Scheme 11), pyrrolidine initially reacts with cyclohexanone (**27a**) (a representative carbonyl) to form enamine **A**, which then undergoes single-electron oxidation by Cu(II) to generate the corresponding radical cationic enamine **B**. Then **B** reacts with styrene (**26a**) to form radical intermediate **C**, which upon reaction with oxygen and concomitant hydrolysis delivers peroxide intermediate **D**. Finally, intermediate **D** under copper catalysis affords 1,4-diketo species **28**.



Scheme 11 The cascade carbo-carbonylation of styrenes and ketones

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

oxidant to furnish the corresponding γ -diketones in moderate yields.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 **26** with ketones **27** through C(sp³)-H bond functionalization to afford 1,4-dicarbonyls **28**.²⁸ 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 oxo esters with enol acetates for the synthesis of 1,4-diketones using atmospheric oxygen as the oxidizing agent.²⁹

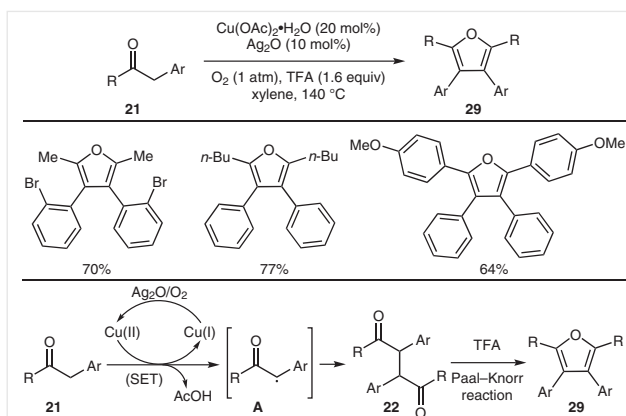


Scheme 12 Cu/Mn-cocatalyzed oxidative coupling of ketones and styrenes

3 Synthesis of Heterocyclic Scaffolds

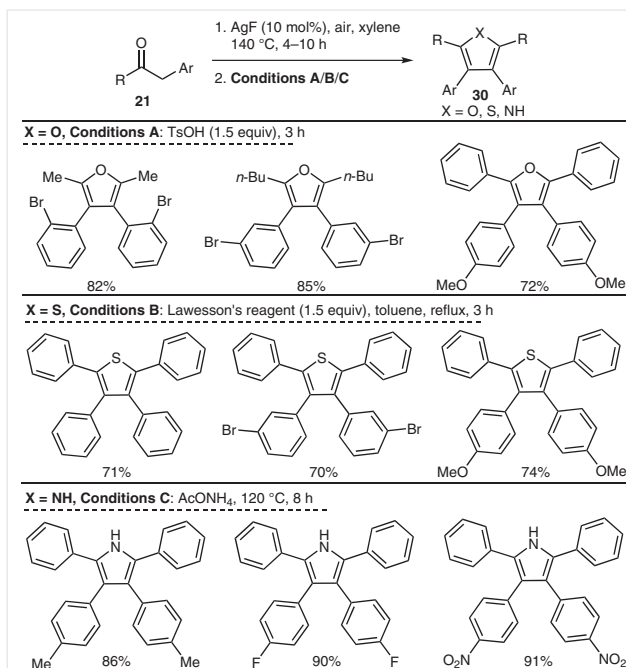
The direct oxidative C-H functionalization of ketones has been successfully applied in the synthesis of several heterocycles, such as furans, dihydrofurans, thiophenes, and pyrroles, that are valuable five-membered heterocycles embedded in multiple natural products, pharmaceuticals and materials.³⁰ In 2015, Wang and co-workers developed a copper and silver cocatalyzed coupling of C(sp³)-H bonds that are adjacent to a carbonyl group to provide a direct and efficient route to a diverse collection of tetrasubstituted furan derivatives **29** using molecular oxygen as the terminal oxidant (Scheme 13).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 **21** by the Cu(II) catalyst to form alkyl radical **A** and Cu(I). Then the resulting alkyl radical **A** undergoes homodimerization to give 1,4-dicarbonyl **22**, which finally, under acidic conditions, produces tetrasubstituted furans **29**. Cu(I) is oxidized by the Ag₂O/O₂ system to regenerate Cu(II) and complete the catalytic cycle.

In a subsequent report,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(sp³)-H bonds generates 1,4-diketones, which subsequently undergo cyclization in a



Scheme 13 Cu/Ag-catalyzed oxidative coupling of ketones for the synthesis of tetrasubstituted furans

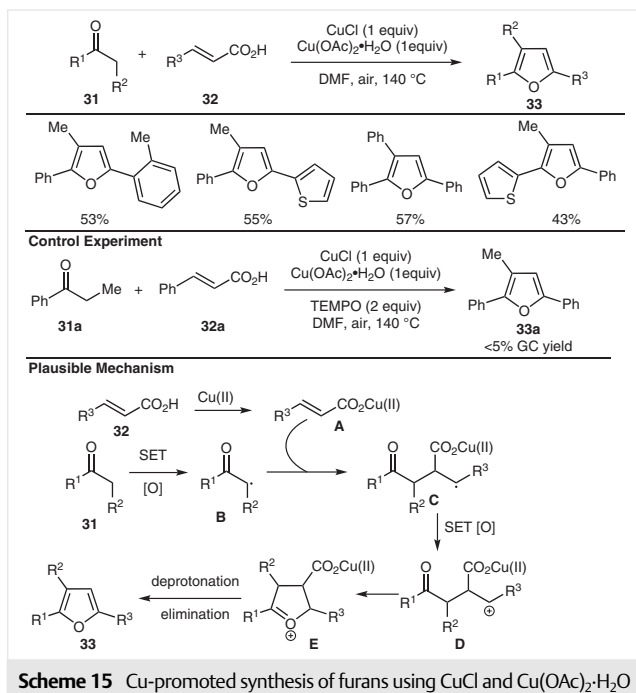
one-pot fashion under different conditions to furnish tetrasubstituted furans (Conditions A), thiophenes (Conditions B), and pyrroles (Conditions C) in good yields (Scheme 14).



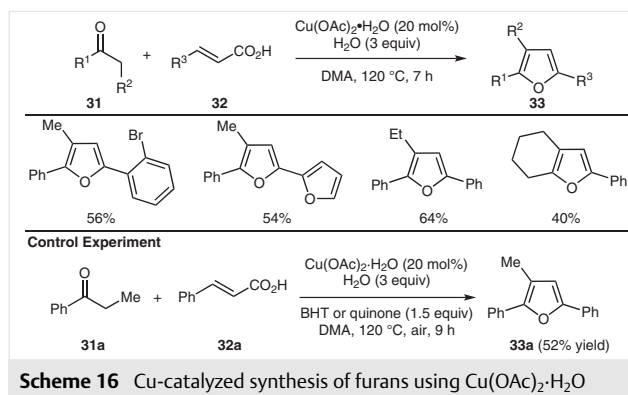
Scheme 14 Ag-catalyzed one-pot synthesis of furans, thiophenes, and pyrroles

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 **31** with acrylic acids **32** for the synthesis of 2,3,5-trisubstituted furans **33** (Scheme 15).³¹ It is important to mention that the reaction was more effective in the presence of both copper salts [CuCl and Cu(OAc)₂·H₂O] and yields decreased in the absence of either of the copper

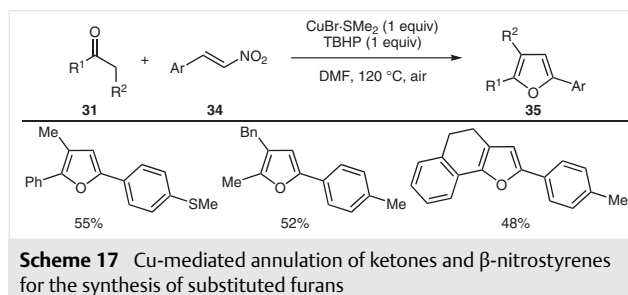
sources. The reaction between ketone **31a** and cinnamic acid (**32a**) was completely suppressed when carried out in the presence of TEMPO as a radical inhibitor, which supports the intermediacy of radicals in this reaction. According to the proposed reaction mechanism, in the first step, upon reaction 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**.



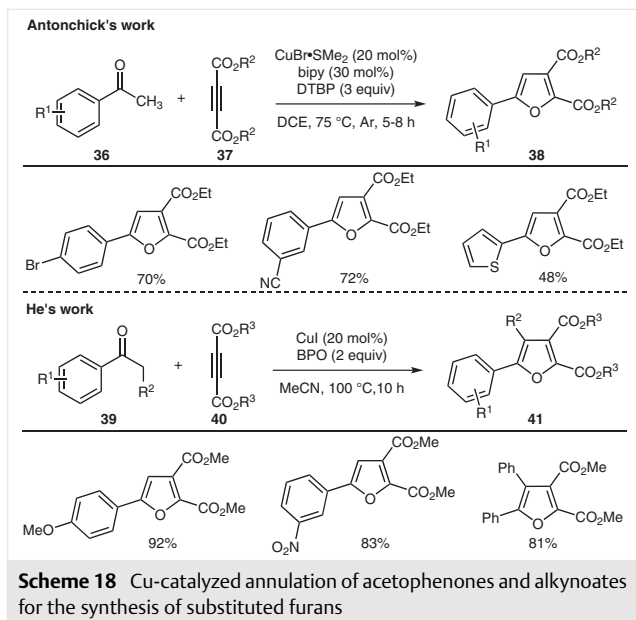
Following this report, in 2015 Hajra and co-workers reported a similar decarboxylative annulation between ketones **31** and acrylic acids **32** towards the regioselective synthesis of trisubstituted furans **33**.³² The method was shown to be quite robust and a library of furan derivatives was prepared. 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.

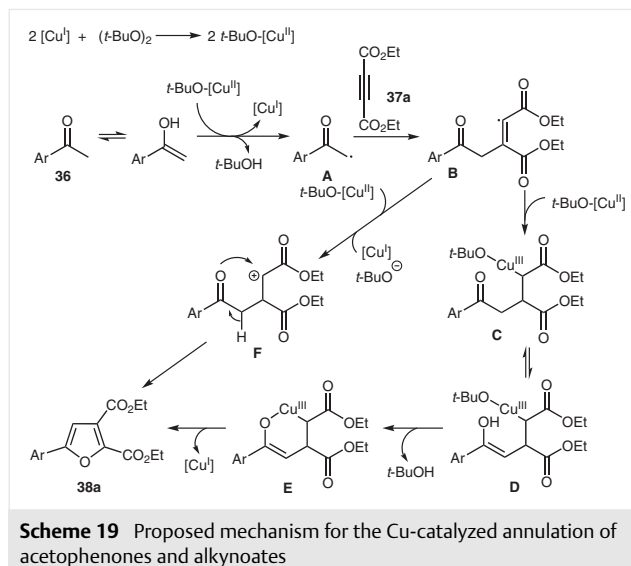


Antonchick and Manna showed that besides activated alkenes, electron-deficient alkynes can also be employed in this type of oxidative cross-coupling reaction. Accordingly, they developed a copper-catalyzed oxidative coupling, using di-*tert*-butyl peroxide (DTBP), between acetophenones **36** and electron-deficient 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.

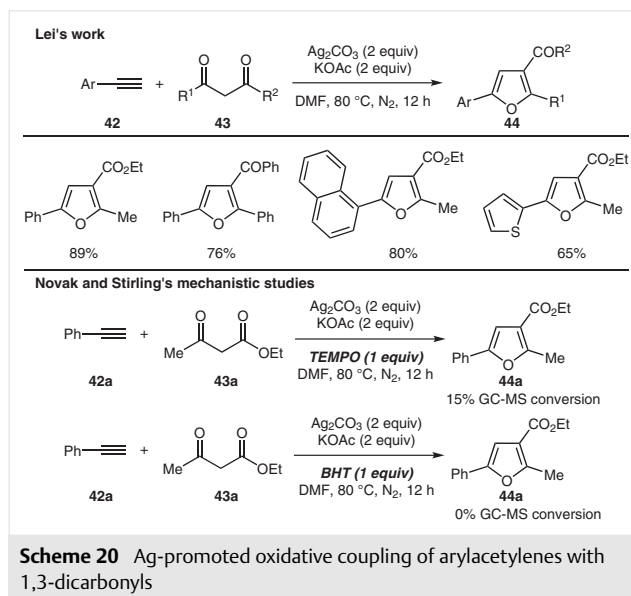


According to the proposed mechanism,³⁴ first the Cu(I) species is oxidized to Cu(II) in the presence of DTBP (Scheme 19). The enol form of the acetophenone derivative is then oxidized to the corresponding alkyl radical **A** by the Cu(II) species. Subsequently, radical **A** undergoes addition to the electron-deficient alkyne **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 metallocycle **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 Novák, Stirling, and co-

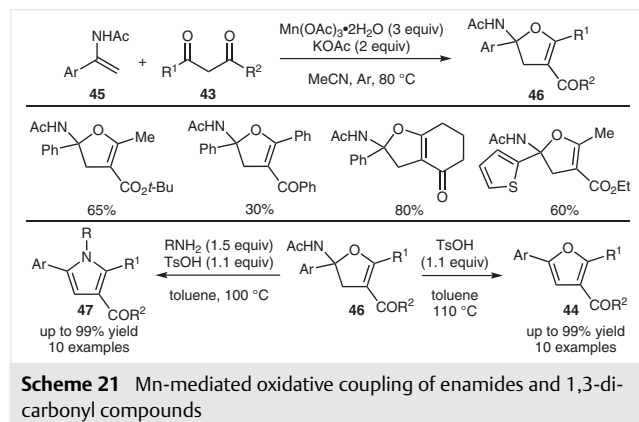


workers and based on their experiments and density functional calculations they unambiguously established that the reaction is indeed going through a radical intermediate.³⁷ The reaction between phenylacetylene (**42a**) and ethyl acetoacetate (**43a**) carried out under the optimized conditions was completely inhibited upon addition of TEMPO or BHT as radical scavengers (Scheme 20).

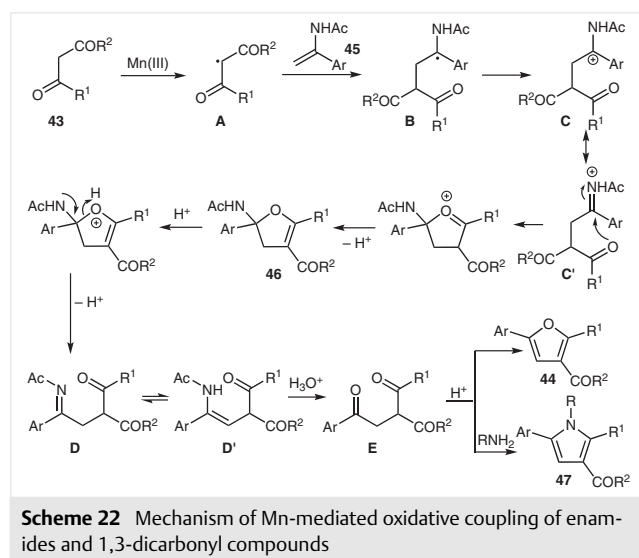


Li and co-workers developed a manganese-mediated efficient synthesis of dihydrofurans **46** through direct oxidative coupling of enamides **45** and 1,3-dicarbonyl compounds **43** (Scheme 21).³⁸ Replacing 1,3-dicarbonyl compounds **43** with 2-substituted 1,3-dicarbonyl compounds in the reaction with enamides under otherwise unchanged conditions, delivered (*Z*)-dicarbonyl enamides. Importantly,

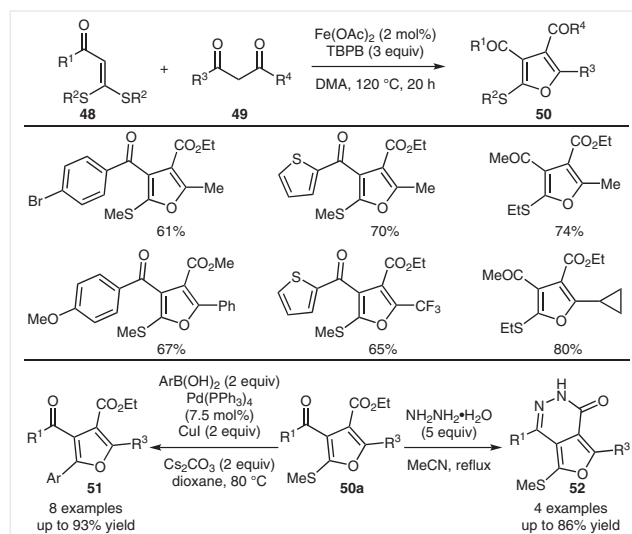
dihydrofurans **46** were conveniently transformed into the corresponding furans **44** and pyrroles **47** in good yields via the classical Paal–Knorr reaction (Scheme 21).



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 $\text{Mn}(\text{OAc})_3$ 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 $\text{Mn}(\text{OAc})_3$ into carbocation **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.

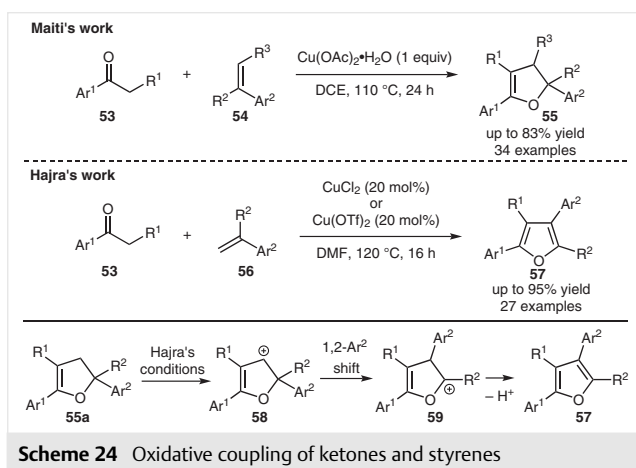


In 2017, Yu and co-workers developed a $\text{Fe}(\text{OAc})_2$ -catalyzed cross-dehydrogenative coupling between 1,3-dicarbonyl compounds **49** and α -oxoketene dithioacetals **48** using *tert*-butyl peroxybenzoate (TBPB) for the synthesis of a library of tetrasubstituted furans **50** in good yields (Scheme 23).³⁹ 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 2-arylfurans **51** or through condensation with hydrazine to yield 2,3-furan-fused pyridazinones **52**.



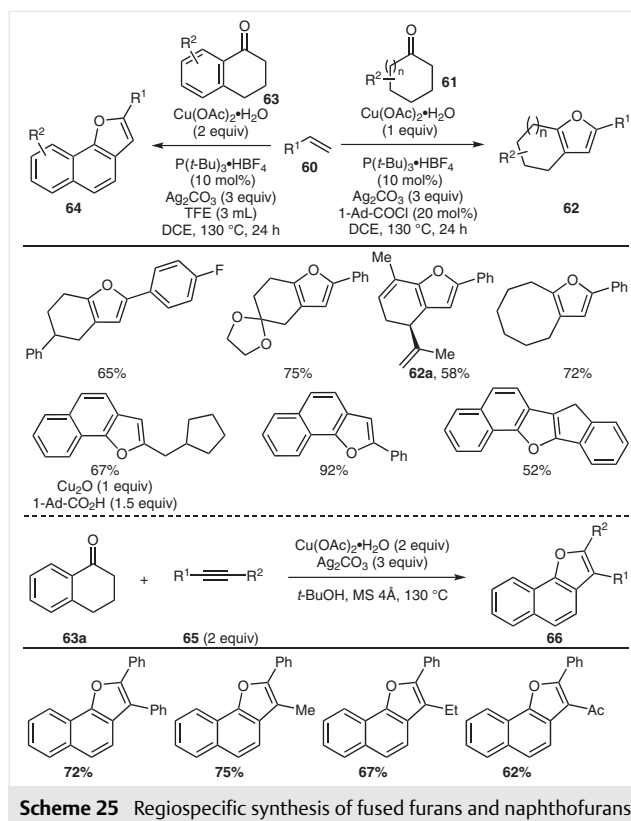
Lei and co-workers reported a copper-catalyzed oxidative coupling between styrenes and 1,3-dicarbonyl compounds in the presence of di-*tert*-butyl peroxide as the external oxidant to provide highly substituted dihydrofurans.⁴⁰ Moreover, they studied the $\text{Cu}(\text{I})/\text{Cu}(\text{II})$ redox process involved in the oxidative cyclization of β -ketocarbonyl derivatives by X-ray absorption and EPR spectroscopy and provided evidence supporting the reduction of $\text{Cu}(\text{II})$ to $\text{Cu}(\text{I})$ 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).⁴¹ 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 $\text{Cu}(\text{II})$ salts to furnish multisubstituted furans **57** (Scheme 24).⁴² Importantly, aliphatic ketones as well as aliphatic alkenes are not viable substrates under both Maiti and Hajra's conditions. Both reactions go through the intermediacy 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 intermediacy of dihy-

drofurans **55**. Based on the proposed mechanism, dihydrofurans **55a**, following further oxidation under Hajra's oxidative conditions, generate carbocationic 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 CuCl_2 -catalyzed oxidative cyclization of aryl ketones and styrenes towards the synthesis of multisubstituted furan derivatives.⁴³ 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).

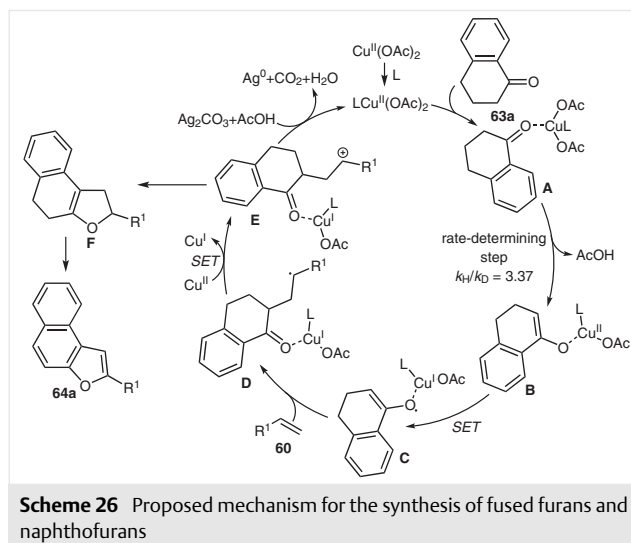


Also in 2017, Maiti and co-workers developed a general and elegant oxidative [3+2] annulation between a variety of cyclic ketones **61** and **63** and diverse alkenes **60** using $\text{Cu}(\text{OAc})_2$ in combination with a tri-*tert*-butylphoshine ligand to furnish a diverse collection of fused furans **62** and naphthofurans **64** under mild conditions (Scheme 25).⁴⁴ 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 fused furans **62**, but it proved to be ineffective in increasing the yield of naphthofurans **64**. Moreover, the generality of the method was further demonstrate by reacting 1-tetralone (**63a**) with several internal alkynes **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**.

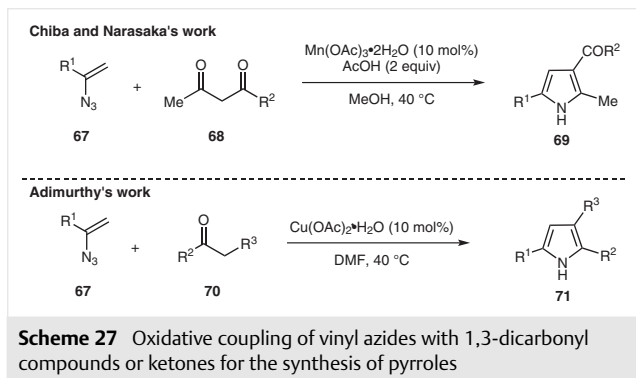


Afterwards, an oxidative cyclization results in dihydrofuran derivative **F**, which finally yields the desired product **64a** through a radical-based dehydrogenation/oxidation sequence.



In 2008, Chiba and Narasaka documented a Cu(II)-catalyzed oxidative annulation between α -(alkoxycarbonyl)-vinyl azides and ethyl acetoacetate towards the synthesis of 1*H*-pyrroles.^{45a} However, the inevitable difficulties in intro-

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 $\text{Mn}(\text{OAc})_3$ -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}

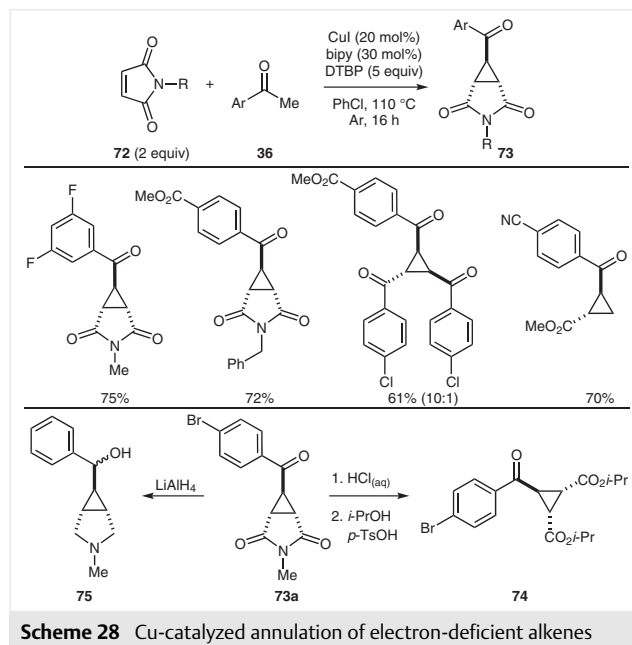


In 2015, Adimurthy and co-workers showed that simple ketones **70**, instead of activated 1,3-dicarbonyl compounds, can also be employed in this kind of transformation. A copper-catalyzed direct $\text{C}(\text{sp}^3)\text{-H}$ functionalization of ketones **70** with vinyl azides **67** was developed 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.

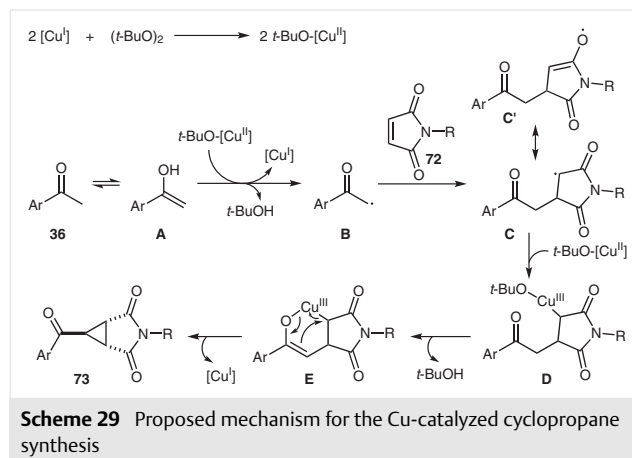
4 Synthesis of Carbocyclic Scaffolds

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 acetophenones **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 acetophenones **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 trans-

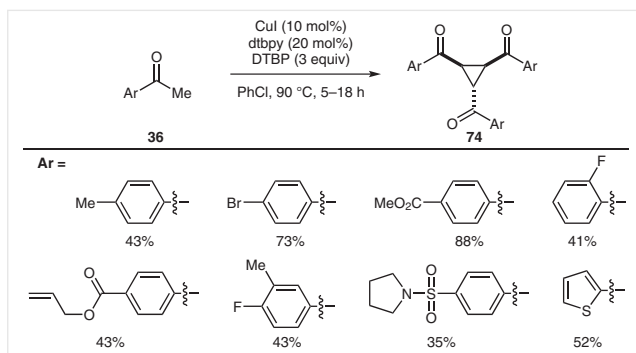
formed into **74** through hydrolysis and subsequent diesterification and into **75** through reduction using lithium aluminum hydride (Scheme 28).



Mechanistically, first Cu(I) is oxidized to a Cu(II) species by DTBP (Scheme 29). In the following step, acetophenone **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.

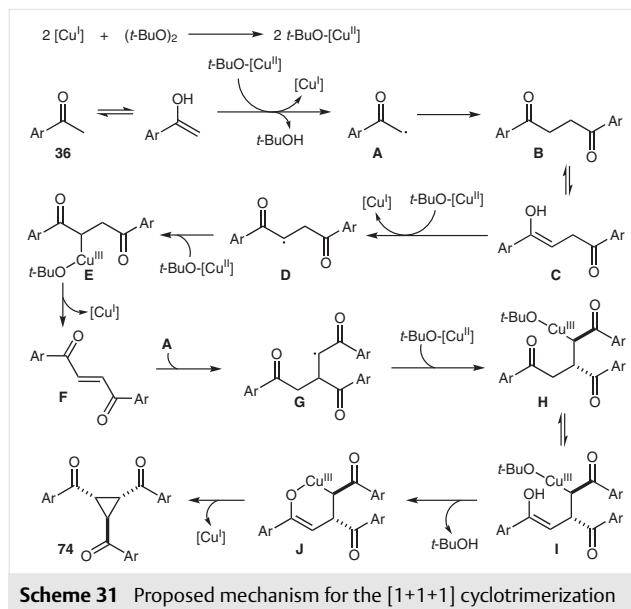


Following this, Antonchick and Manna developed an unprecedented copper-catalyzed [1+1+1] cyclotrimerization cascade of acetophenone derivatives **36** under mild conditions for the stereoselective synthesis of cyclopropanes **74** (Scheme 30).⁴⁹ Various acetophenone derivatives **36** covering an array of functional groups such as halogens, carbonyl, sulfonamide, nitril 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.



Scheme 30 Cu-catalyzed [1+1+1] cyclotrimerization

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) annulation 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(I), which in turn is re-oxidized to Cu(II) by DTBP.



Scheme 31 Proposed mechanism for the [1+1+1] cyclotrimerization

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 has 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.

Funding Information

A.P.A. acknowledges the support of DFG (Heisenberg scholarship AN 1064/4-1) and Boehringer Ingelheim Foundation (Plus 3).

Acknowledgment

Sandip Murarka thanks IIT Jodhpur for funding and infrastructure facilities.

References

- (1) Hodgson, D. M.; Charlton, A. *Tetrahedron* **2014**, *70*, 2207.
- (2) (a) Csaky, A. G.; Plumet, J. *Chem. Soc. Rev.* **2001**, *30*, 313. (b) Guo, F.; Clift, M. D.; Thomson, R. J. *Eur. J. Org. Chem.* **2012**, 4881.
- (3) Ivanoff, D.; Spasoff, A. *Bull. Soc. Chim. Fr.* **1935**, *2*, 76.
- (4) Rathke, M. W.; Lindert, A. *J. Am. Chem. Soc.* **1971**, *93*, 4605.
- (5) Ito, Y.; Konoike, T.; Saegusa, T. *J. Am. Chem. Soc.* **1975**, *97*, 2912.
- (6) (a) Leffingwell, J. C. *Chem. Commun.* **1970**, 357. (b) Fujii, T.; Hirao, T.; Ohshiro, Y. *Tetrahedron Lett.* **1992**, *33*, 5823. (c) Koichi, N.; Tatsuo, O.; Ken, T.; Masaharu, M. *Chem. Lett.* **1992**, *21*, 2099. (d) Yasushi, K.; Koichi, N. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 322.
- (7) (a) Yi, H.; Zhang, G.; Wang, H.; Huang, Z.; Wang, J.; Singh, A. K.; Lei, A. *Chem. Rev.* **2017**, *117*, 9016. (b) Girard, S. A.; Knauber, T.; Li, C.-J. *Angew. Chem. Int. Ed.* **2014**, *53*, 74. (c) Liu, C.; Yuan, J.; Gao, M.; Tang, S.; Li, W.; Shi, R.; Lei, A. *Chem. Rev.* **2015**, *115*, 12138. (d) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335. (e) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Rev.* **2011**, *111*, 1293. (f) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (g) Yoo, W.-J.; Li, C.-J. *Top. Curr. Chem.* **2010**, *292*, 281.
- (8) (a) Kharasch, M. S.; Jensen, E. V.; Urry, W. H. *J. Org. Chem.* **1945**, *10*, 386. (b) Kharasch, M. S.; McBay, H. C.; Urry, W. H. *J. Org. Chem.* **1945**, *10*, 394. (c) Kharasch, M. S.; McBay, H. C.; Urry, W. H. *J. Am. Chem. Soc.* **1948**, *70*, 1269.
- (9) Ito, Y.; Konoike, T.; Harada, T.; Saegusa, T. *J. Am. Chem. Soc.* **1977**, *99*, 1487.
- (10) (a) Baran, P. S.; DeMartino, M. P. *Angew. Chem. Int. Ed.* **2006**, *45*, 7083. (b) DeMartino, M. P.; Chen, K.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 11546.
- (11) Casey, B. M.; Flowers, R. A. II. *J. Am. Chem. Soc.* **2011**, *133*, 11492.
- (12) Do, H.-Q.; Tran-Vu, H.; Daugulis, O. *Organometallics* **2012**, *31*, 7816.
- (13) Guo, F.; Konkol, L. C.; Thomson, R. J. *J. Am. Chem. Soc.* **2011**, *133*, 18.
- (14) Schmittel, M.; Burghart, A.; Malisch, W.; Reising, J.; Söllner, R. *J. Org. Chem.* **1998**, *63*, 396.
- (15) Clift, M. D.; Taylor, C. N.; Thomson, R. J. *Org. Lett.* **2007**, *9*, 4667.
- (16) Avetta, C. T.; Konkol, L. C.; Taylor, C. N.; Dugan, K. C.; Stern, C. L.; Thomson, R. J. *Org. Lett.* **2008**, *10*, 5621.
- (17) Robinson, E. E.; Thomson, R. J. *J. Am. Chem. Soc.* **2018**, *140*, 1956.
- (18) You, L.; Liang, X.-T.; Xu, L.-M.; Wang, Y.-F.; Zhang, J.-J.; Su, Q.; Li, Y.-H.; Zhang, B.; Yang, S.-L.; Chen, J.-H.; Yang, Z. *J. Am. Chem. Soc.* **2015**, *137*, 10120.
- (19) Clift, M. D.; Thomson, R. J. *J. Am. Chem. Soc.* **2009**, *131*, 14579.
- (20) Amaya, T.; Masuda, T.; Maegawa, Y.; Hirao, T. *Chem. Commun.* **2014**, *50*, 2279.
- (21) Amaya, T.; Maegawa, Y.; Masuda, T.; Osafune, Y.; Hirao, T. *J. Am. Chem. Soc.* **2015**, *137*, 10072.
- (22) Amaya, T.; Osafune, Y.; Maegawa, Y.; Hirao, T. *Chem. Asian J.* **2017**, *12*, 1301.
- (23) Mao, S.; Gao, Y.-R.; Zhang, S.-L.; Guo, D.-D.; Wang, Y.-Q. *Eur. J. Org. Chem.* **2015**, 876.
- (24) Mao, S.; Zhu, X.-Q.; Gao, Y.-R.; Guo, D.-D.; Wang, Y.-Q. *Chem. Eur. J.* **2015**, *21*, 11335.
- (25) Jang, H.-Y.; Hong, J.-B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2007**, *129*, 7004.
- (26) Xie, J.; Huang, Z.-Z. *Chem. Commun.* **2010**, *46*, 1947.
- (27) Yasu, Y.; Koike, T.; Akita, M. *Chem. Commun.* **2012**, *48*, 5355.
- (28) Lan, X.-W.; Wang, N.-X.; Zhang, W.; Wen, J.-L.; Bai, C.-B.; Xing, Y.; Li, Y.-H. *Org. Lett.* **2015**, *17*, 4460.
- (29) Geibel, I.; Christoffers, J. *Eur. J. Org. Chem.* **2016**, 918.
- (30) (a) Baumann, M.; Baxendale, I. R.; Ley, S. V.; Nikbin, N. *Beilstein J. Org. Chem.* **2011**, *7*, 442. (b) Wang, C.; Dong, H.; Hu, W.; Liu, Y.; Zhu, D. *Chem. Rev.* **2012**, *112*, 2208.
- (31) Yang, Y.; Yao, J.; Zhang, Y. *Org. Lett.* **2013**, *15*, 3206.
- (32) Ghosh, M.; Mishra, S.; Monir, K.; Hajra, A. *Org. Biomol. Chem.* **2015**, *13*, 309.
- (33) Ghosh, M.; Mishra, S.; Hajra, A. *J. Org. Chem.* **2015**, *80*, 5364.
- (34) Manna, S.; Antonchick, A. P. *Org. Lett.* **2015**, *17*, 4300.
- (35) Luo, Z.; Fang, Y.; Zhao, Y.; Liu, P.; Xu, X.; Feng, C.; Li, Z.; He, J. *RSC Adv.* **2016**, *6*, 5436.
- (36) He, C.; Guo, S.; Ke, J.; Hao, J.; Xu, H.; Chen, H.; Lei, A. *J. Am. Chem. Soc.* **2012**, *134*, 5766.
- (37) Daru, J.; Benda, Z.; Póti, Á.; Novák, Z.; Stirling, A. *Chem. Eur. J.* **2014**, *20*, 15395.
- (38) Li, P.; Zhao, J.; Xia, C.; Li, F. *Org. Lett.* **2014**, *16*, 5992.
- (39) Lou, J.; Wang, Q.; Wu, K.; Wu, P.; Yu, Z. *Org. Lett.* **2017**, *19*, 3287.
- (40) Yi, H.; Liao, Z.; Zhang, G.; Zhang, G.; Fan, C.; Zhang, X.; Bunel, E. E.; Pao, C.-W.; Lee, J.-F.; Lei, A. *Chem. Eur. J.* **2015**, *21*, 18925.
- (41) Naveen, T.; Kancherla, R.; Maiti, D. *Org. Lett.* **2014**, *16*, 5446.
- (42) Dey, A.; Ali, M. A.; Jana, S.; Hajra, A. *J. Org. Chem.* **2017**, *82*, 4812.
- (43) Wu, Y.; Huang, Z.; Luo, Y.; Liu, D.; Deng, Y.; Yi, H.; Lee, J.-F.; Pao, C.-W.; Chen, J.-L.; Lei, A. *Org. Lett.* **2017**, *19*, 2330.
- (44) Naveen, T.; Deb, A.; Maiti, D. *Angew. Chem. Int. Ed.* **2017**, *56*, 1111.
- (45) (a) Chiba, S.; Wang, Y.-F.; Lapointe, G.; Narasaka, K. *Org. Lett.* **2008**, *10*, 313. (b) Wang, Y.-F.; Toh, K. K.; Chiba, S.; Narasaka, K. *Org. Lett.* **2008**, *10*, 5019.
- (46) Donthiri, R. R.; Samanta, S.; Adimurthy, S. *Org. Biomol. Chem.* **2015**, *13*, 10113.
- (47) (a) Chen, D. Y. K.; Pouwer, R. H.; Richard, J.-A. *Chem. Soc. Rev.* **2012**, *41*, 4631. (b) Tang, P.; Qin, Y. *Synthesis* **2012**, *44*, 2969. (c) Bartoli, G.; Bencivenni, G.; Dalpozzo, R. *Synthesis* **2014**, *46*, 979. (d) Schneider, T. F.; Kaschel, J.; Werz, D. B. *Angew. Chem. Int. Ed.* **2014**, *53*, 5504.
- (48) Manna, S.; Antonchick, A. P. *Angew. Chem. Int. Ed.* **2015**, *54*, 14845.
- (49) Manna, S.; Antonchick, A. P. *Angew. Chem. Int. Ed.* **2016**, *55*, 5290.