Green Chemistry

TUTORIAL REVIEW

View Article Online
View Journal | View Issue

Cite this: *Green Chem.*, 2023, **25**, 8313

Research progress in electrochemical/photochemical utilization of methanol as a C1 source

Hai-Tao Tang, Yong-Zhou Pan and Ying-Ming Pan *

Received 14th June 2023,
Accepted 25th September 2023

DOI: 10.1039/d3gc02106h

rsc.li/greenchem

Methanol is an important C1 source in organic synthesis because of its low cost, abundance, and biodegradability. Therefore, using methanol as a C1 source to synthesize high-value-added compounds is crucial. This review highlights the recent advances in various electrochemical and photochemical reactions using methanol as a sustainable source. This study mainly introduces the reaction of methylation, methoxylation, hydroxymethylation, and cyclization under the conditions of light and electricity. The reaction mechanisms of these reactions are also discussed. This study provides a reference for the future application of this kind of reaction in organic synthesis.

1. Introduction

In recent decades, C1 chemistry has developed rapidly. Common C1 sources are iodomethane, diazomethane, CO_2, CO, isonitrile, and carbon tetrabromide.[1] Although good progress has been made in the applications of these C1 sources, some defects remain, such as low activity, thermodynamic instability, toxicity, corrosion, and harsh reaction conditions. These defects seriously limit the further conversion and applications of C1 sources. The search for convenient and green C1 reagents is urgently needed to avoid the problems mentioned. Methanol has the advantages of abundant reserves, low cost, ease of obtaining, slight harm, and biodegradability.[2] Therefore, methanol has become a good source of organic C1.

In line with today's sustainable and environmental strategies worldwide, electrochemistry and photochemistry have developed rapidly as powerful tools for organic conversion over the past decades. Electro-organic synthesis uses electrons as redox reagents to replace the traditional oxidation/reduction catalysts successfully; thus, the cost of reaction is greatly reduced, the occurrence of side reactions is inhibited well, and the utilization rate of atoms is improved.[3] Visible light catalysis is an efficient and gentle catalytic strategy that achieves redox reactions through single-electron transfer (SET) or energy transfer (ET), developing previously unattainable organic

State Key Laboratory for Chemistry and Molecular Engineering of Medicinal Resources, School of Chemistry and Pharmaceutical Sciences of Guangxi Normal University, Guilin 541004, People's Republic of China.
E-mail: panym@mailbox.gxnu.edu.cn

Hai-Tao Tang

Hai-Tao Tang is an Associate Professor in the Guangxi Normal University. He was born in 1988, in Guangxi, China. He obtained his BSc degree from Central South University and PhD degree in 2017 from Xiamen University (China). He entered Guangxi Normal University as a lecturer in 2017. His current research interests focus on electrochemical synthesis and heterogeneous catalysis. Now, he wants to modify some heterogeneous catalysts onto electrodes, hoping to develop some new organic synthesis.

Yong-Zhou Pan

Yong-Zhou Pan was born in Jiangxi, China in 1996. He obtained his BSc degree from Gannan Normal University. His current research interests focus on electrochemical synthesis and heterogeneous catalysis.

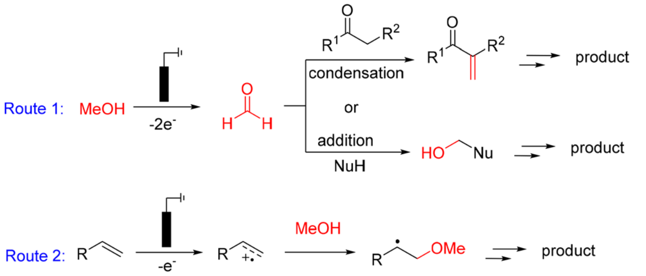


Fig. 1 General mechanism of electrochemical reactions using methanol as C1 source.

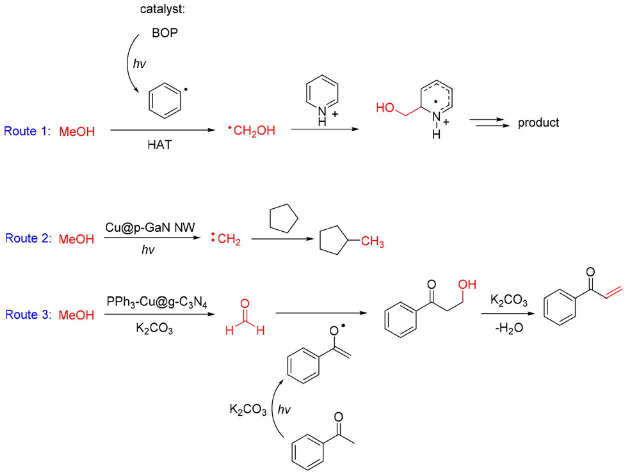


Fig. 2 General mechanism of photochemical reactions using methanol as C1 source.

conversion.[4] Therefore, using electrochemical and photochemical methods with methanol as the C1 source to achieve organic conversion has continually attracted the attention of chemists.

Under electrochemical conditions, the general mechanism using methanol as the C1 source could be subdivided into the following two possible routes: (1) methanol first loses two electrons during anodic oxidation to generate formaldehyde, and then undergoes a condensation reaction with ketone or an addition reaction with nucleophilic reagent to obtain the corresponding product. (2) Olefins and other substrates undergo SET process at the anode to obtain corresponding radical cation intermediates, and methanol reacts with them as a nucleophilic reagent to obtain corresponding products (Fig. 1).

Under photochemical conditions, the general mechanism using methanol as the C1 source could be subdivided into the following three possible routes: (1) for example, catalysts such as BOP first split into benzene radicals under light, which can undergo a HAT process with methanol to obtain subsequent products. (2) Methanol is photocatalytic activated on the surface of gallium nitride nanowires (GaN NW) to form methyl carbene, which can react with other substrates such as cyclopentane. (3) Similarly, methanol can also be oxidized to formaldehyde under the catalysis of PPh_3–Cu@g-C_3N_4, and then react with other radicals generated by light to obtain the final product (Fig. 2).

Ying-Ming Pan

Ying-Ming Pan is a Professor in the Guangxi Normal University. He was born in Jiangxi, China. He received his BSc degree from Gannan Normal University and Msc degree from Guangxi University (China). He obtained his PhD degree at the Xianmen University in 2010. He was awarded Mingde Teacher Award in 2018. His present research interests focus on electrochemical synthesis and heterogeneous catalysis.

Although MeOH is an excellent C1 source under photoelectric conditions, their reaction mechanisms are significantly different. For example, under electrochemical conditions, methanol is usually anodized to formaldehyde, followed by subsequent reactions. Under photochemical conditions, photosensitizers or catalysts are first excited by light to obtain highly active intermediates, which then undergo HAT and other processes with MeOH to obtain the final product.

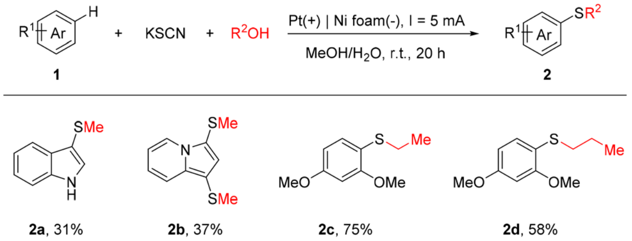
In the present study, we classify different reaction types and summarize the research progress of various electrochemical and photochemical reactions based on the use of methanol as a sustainable source.

2. Electrochemical utilization of methanol as C1 source

Electrochemical synthesis is a powerful, environmentally benign, and green protocol that has been proved to be one of the most attractive and promising strategies for forging various chemical bonds. It drives the conversion of the starting material by precisely regulating the current or electrode potential. Thus, the use of toxic or dangerous oxidants or reducing agents is avoided. Therefore, using an electrochemical method and methanol as the C1 source is essential in the functional modification of the starting material.

2.1 Electrochemical methylation reaction

Zhao and co-workers[5] reported the realization of C–H methylthiolation of aromatic hydrocarbons *via* a three-component cross-coupling strategy under electrochemical conditions (Scheme 1). The prominent advantage of this method is that it avoids the use of methyl mercaptan (with high biological toxicity) and metal catalysts, and the reaction conditions are

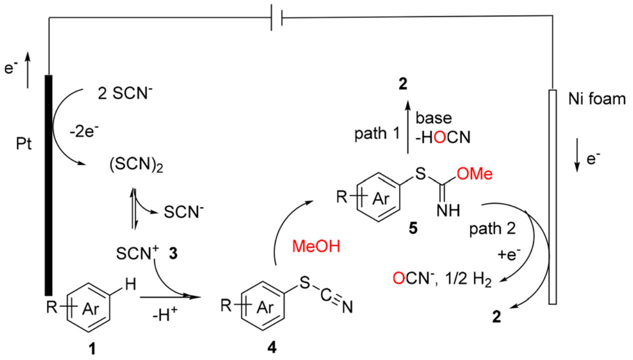


Scheme 1 Electrochemical C–H methylthiolation of aromatics.

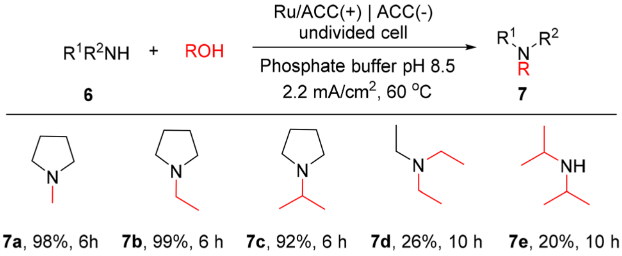
mild. In this strategy, Pt is used as the anode, Ni foam is used as the cathode, potassium thiocyanate is used as the supporting electrolyte and sulfur source, and methanol is used as the methylation reagent in an undivided cell. The method suits various electron-rich aromatics with mild reaction conditions and good reaction efficiency. Electrochemical methyl vulcanization occurs at the *para* or *ortho* position of anilines and aryl ether. Methyl vulcanization occurs selectively at the C-3 position when indole is used as a substrate (**1a**). The corresponding bismethylthiolated products are provided when indolizine is used as substrate (**1b**). When the researchers changed methanol to ethanol or *n*-propyl alcohol (**1c**, **1d**), they also obtained the corresponding products, ethyl sulfide or propyl sulfides, in moderate to good yields.

Based on deuterium labeling studies and previous reports, the researchers also proposed the following reasonable mechanism (Scheme 2). SCN^- initially forms an SCN radical during anodic oxidation. $(SCN)_2$ can be formed through radical coupling, which can further generate the electrophile SCN^+ **3**. Subsequently, the substrate undergoes electrophilic substitution with SCN to form aryl-thiocyanate **4**. Then, aryl-thiocyanate **4** reacts with methanol to form the intermediate **5**. The intermediate **5** can undergo intramolecular rearrangement under electrochemical deprotonation to obtain the desired product **2** and remove the cyanic acid (HOCN).

Jackson and co-workers[6] developed the *N*-alkylation of amines (**6**) with alcohols in the aqueous solution (Scheme 3). They optimized the reaction conditions to obtain the best values: current of 2.2 mA cm^{-2}, temperature of 60 °C, and optimal methanol concentration of 5% v/v in 0.01 M phosphate buffer at pH 8.5. Under the catalysis of Ru in the (Ru/ACC) electrode, the strategy performs well with methanol, primary alcohol, and secondary alcohol. It can also be applied to primary amine and secondary amine.



Scheme 2 Mechanism of electrochemical C–H methylthiolation of aromatics.

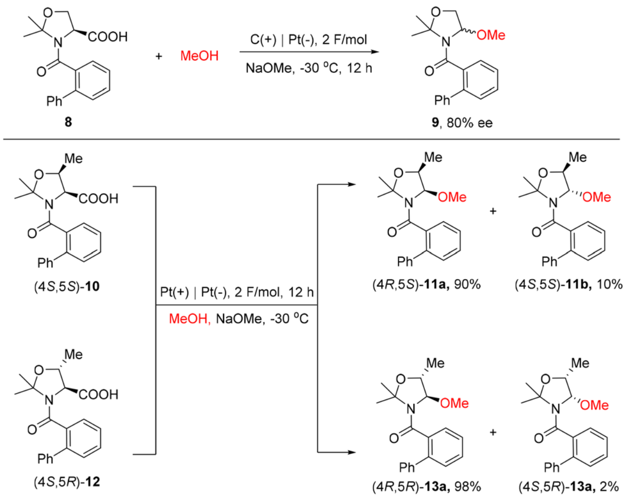


Scheme 3 Electroactivated alkylation of amines with alcohols.

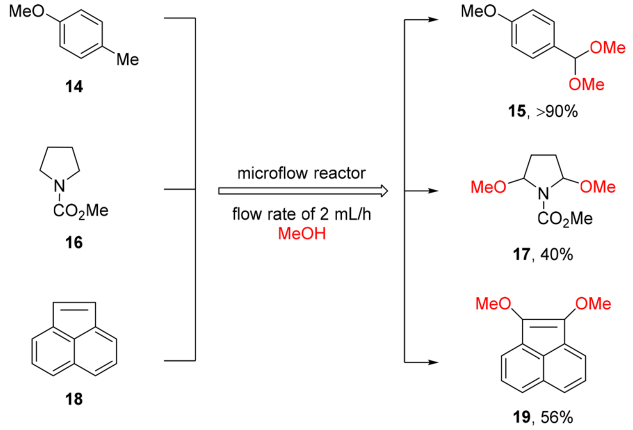
2.2 Electrochemical methoxylation reaction

Matsumura and co-workers[7] chemically oxidized *N*-acylated serine derivatives using methanol as the C1 source to obtain optically active methoxylation compounds (Scheme 4). The key to the success of the reaction is that the substrate contains a bulky *o*-phenyl benzoyl *N*-protecting group. The method was performed with platinum as the anode and cathode and the excess of base (NaOMe) and methanol as the solvents at −30 °C. The optically active α-methoxylate derivatives of *N*-acylated serine were obtained with 80% ee, and the α-methoxylate derivatives and threonine derivatives were obtained with 80% and 96% de, respectively (**11**, **13**).

Electrochemical microflow reactor (ECR) have been widely applied by chemists.[8] In 2005, Yoshida and co-workers[9] developed using ECRs for the methoxylation of *p*-methoxytoluene without a supporting electrolyte (Scheme 5). In this system, the entire electrochemical chamber is filled with carbon felt electrodes; as a result, the electrodes obtain large surface areas. The researchers found that protons are likely to be charge carriers of electricity. Therefore, they pretreated the



Scheme 4 Electrochemical oxidation of amino acid derivatives.

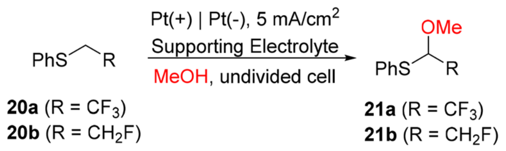


Scheme 5 Microflow electroorganic synthesis.

reactor with TfOH solution (0.125 M methanol, 0.5 mL) before electrolysis, significantly improving the conductivity. They also studied the flow rate, the spacer's thickness, and the membrane's pore size. They concluded that the optimal reaction condition is a flow rate of 2 mL h^{-1} using a PTFE membrane (75 mm thickness and 3 mm pore size). They also achieved the methoxylation of *N*-methoxycarbonyl pyrrolidine (**16**) and acenaphthylene (**18**) under standard conditions.

Site separation refers to the attachment of opposing reagents (*e.g.*, acid/base and oxidizing/reducing reagents) to the respective insoluble polymers to suppress their mutual destruction.[10] Tajima and co-workers[11] applied the concept of site isolation to electrochemical reactions. They successfully demonstrated the acceleration of the deprotonation step in the anodic methoxylation of fluoroethyl phenyl sulfides using silica-gel-supported 1,5,7-triazabicyclo[4.4.0]dec-5-ene (Si-TBD). They also measured the cyclic voltammograms of 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD) and Si-TBD in MeCN. The results showed that compared with saturated calomel electrode (SCE), MTBD oxidizes easily at *ca.* 1.0 V. However, Si-TBD is not oxidized at all in the same potential range. The supported reagent should be used as a site-isolated heterogeneous reagent in the electrochemical reaction and should not be destroyed by oxidation and reduction on the electrode (Table 1).

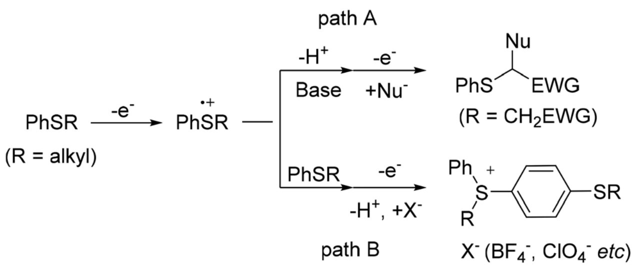
Table 1 Anodized methoxylation of fluoroethyl phenyl sulfide by heterogeneous base



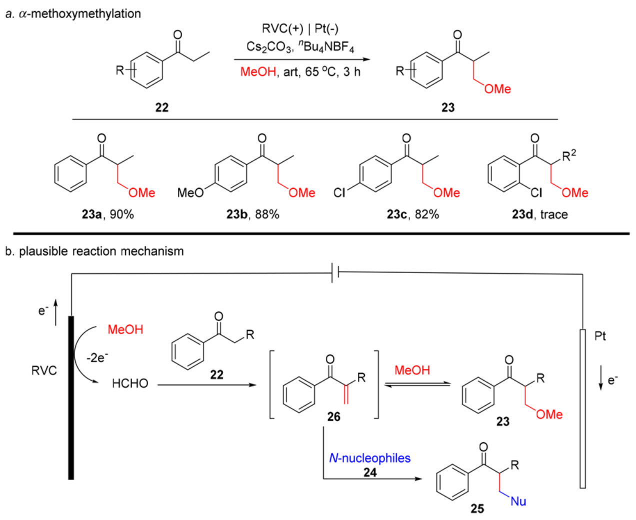
R	Supporting electrolyte	Electricity/Faraday (mol^{-1})	Yied (%)
CF_3	0.1 M $NaClO_4$	3	31
CF_3	0.2 M Si-TBD	7	76
CH_2F	0.1 M $NaClO_4$	3	Trace
CH_2F	0.2 M Si-TBD	3	16

Alkyl phenyl sulfide has electron-withdrawing groups at the α-position of the sulfur atoms and is prone to substitution reactions with nucleophiles under the action of base (Scheme 6, path A).[12] Anodizing alkyl phenyl sulfide usually causes sulfonamide ions to form sulfonamide salts with anions derived from supporting electrolytes (Scheme 6, path B).[13] The researchers used cyclic voltammograms to demonstrate that Si-TBD accelerates the deprotonation of radical cationic intermediates and inhibits the occurrence of path B.

In 2020, Pan and co-workers[14] developed a strategy for the α-methoxymethylation of propiophenones using methanol as the C1 source under electrochemical conditions (Scheme 7a). The reaction was performed at 65 °C for 3 h at a constant current of 10 mA in an undivided cell with a mesh glass carbon (RVC) anode and platinum cathode, Cs_2CO_3 as the base, $^{n}Bu_4NBF_4$ as the electrolyte, and methanol as the solvent. The substrate phenyl ring can be converted to the corresponding α-methoxymethylation products when it has electron-donating or electron-withdrawing groups. This strategy is greatly affected by steric hindrance, and only trace products can be observed when substituents are located in the *ortho*-position (**23d**). This strategy is incompatible with aliphatic ketones and has certain limitations.



Scheme 6 Anodizing of alkyl phenyl sulfide by anhydrous organic solvent.



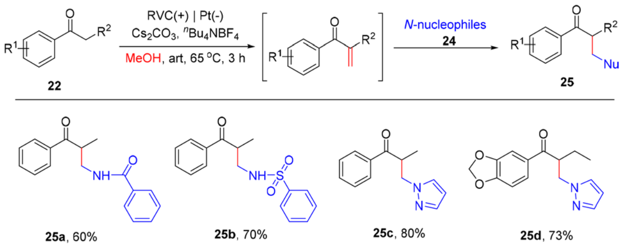
Scheme 7 Electrochemical α-methoxymethylation of propiophenones.

In this strategy, methanol plays two key roles. Firstly, methanol undergoes anodic oxidation to generate formaldehyde, which then reacts with the substrate to obtain the intermediate enone **26**. Secondly, the nucleophilic addition of methanol and enone **26** ultimately yields product **23** (Scheme 7b).

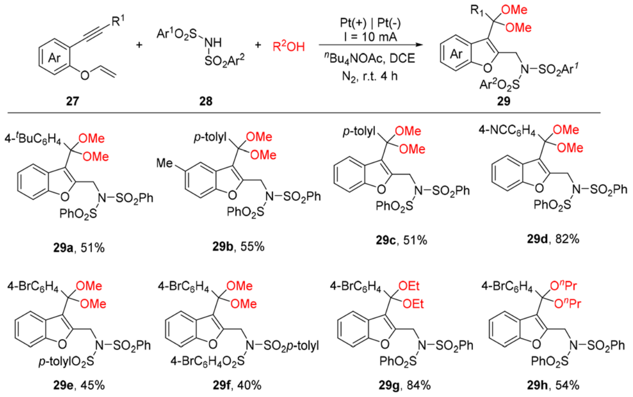
The researchers also found that **22** and methanol react under standard conditions without separation. Then, aminomethylation product (**25**) can be obtained by adding *N*-nucleophile (**24**) into the system and refluxing for 2 h in the absence of current (Scheme 8).

Jiang and co-workers[15] reported a new electrochemical method for synthesizing benzofurans using 1,6-enynes (**27**) and disulfonimides (**28**) as reaction substrates and methanol as a nucleophile to produce a series of functionalized benzofurans. In this strategy, the undivided cell was used for electrolysis, with Pt as the anode and cathode, ^{n}Bu$_4$NOAc as the electrolyte, a constant current of 10 mA in a nitrogen atmosphere, and MeCN and MeOH (V/V = 3.5/1.5) as mixed solvents (Scheme 9). The 1,6-enynes with different electronic properties and the dibenzenesulfonimide with substituents at various positions of the benzene ring can participate successfully in electrocatalytic cyclization. This strategy can also produce the corresponding benzofuran by substituting methanol for other alkyl alcohols, such as ethanol and *n*-propanol (**29g**, **29h**).

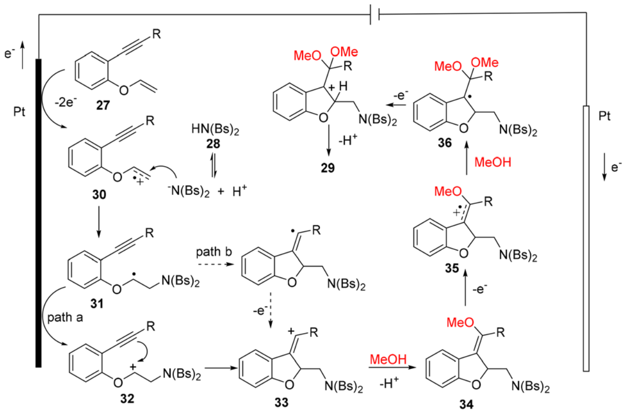
Based on the experimental results and previous reports,[16] the following reasonable mechanism was proposed (Scheme 10). First, 1,6-enynes **27** are anodized to provide free radical cation **30**, which is then nucleophilically added with disulfonimides **28** to provide free radical **31**. Then, the radical **31** goes through two possible paths. In path a, free radical **31** is anodized to form intermediate **32**, which is cyclized to obtain intermediate **33**. In path b, the free radical induces five-membered cyclization, followed by a one-electron oxidation reaction, to form intermediates **33**. The nucleophilic addition of methanol to **33** gives benzofuran **34**, which is oxidized to form a radical cation **35**. Then, **35** is nucleophilically added with methanol to obtain intermediate **36**. Finally, **36** is converted to the final product **29** *via* single electron oxidation and deprotonation.



Scheme 8 Electrochemical aminomethylation of propiophenones.



Scheme 9 Electrochemical amino-ketonation and amino-oxidation of 1,6-enyness.

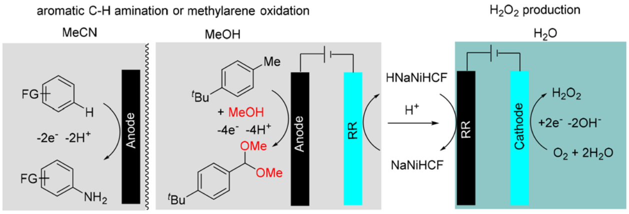


Scheme 10 Mechanism of electrochemical amino-ketonation and amino-oxidation of 1,6-enyness.

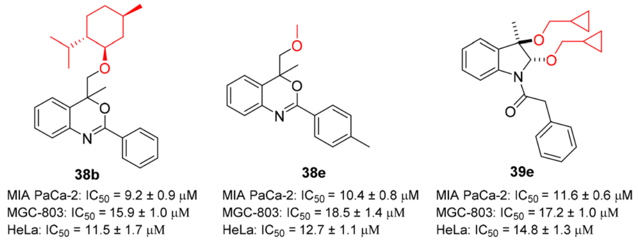
Paired electrolysis can improve the efficiency, sustainability, and economy of large-scale applications because the method produces valuable products at both electrodes.[17] However, the optimal conditions and rates of different reactions are rarely the same. Thus, the development and widespread application of electrochemical reactions remains a challenge. The modular electrochemical synthesis (ModES) approach supported by redox repositories (RRs) alleviates the challenges of achieving paired electrolysis.[18] RRS are solid-state battery materials that temporarily store/release ions and electrons to balance the ion/electron transfer steps occurring at the working electrode.

Jin and co-workers[19] used the ModES method supported by NiHCF RR to realize the electrosynthesis reaction between two solvents: methylene oxidation in methanol or naphthalene C–H amination in acetonitrile and oxygen to hydrogen peroxide in water (Scheme 11). The traditional chemical anthraquinone process requires high energy consumption, expensive catalysts, and multiple steps to produce H_2O_2.[20] The production cost of H_2O_2 can be greatly reduced by using this electrochemical method.

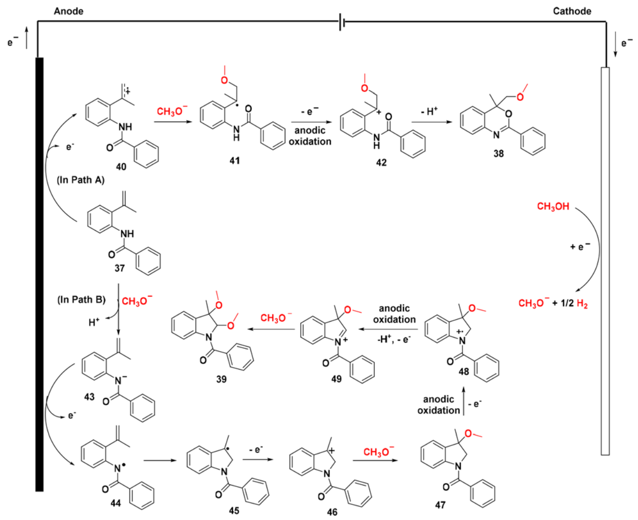
Mo and co-workers[21] developed a novel electrochemical cyclization strategy. This method uses olefinic amides (**37**) as substrates and methanol as the C1 source. By simply adjusting the reaction conditions, two different skeletons can be constructed: alkoxylated 4*H*-3,1-benzoxazines (**38**) and indomo-



Scheme 11 Paired electrolysis in different solvents.



Scheme 13 IC_{50} (μM) values for compounds **38b**, **38e** and **39e**.

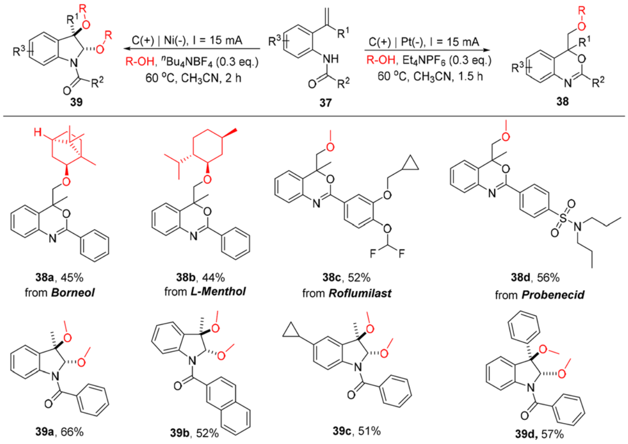


Scheme 14 Mechanism of electrochemical oxidative cyclization of olefin amides and alcohols.

lines (**39**). The optimal reaction conditions for benzoxazine generation involve electrolysis, with Et_4NPF_6 as the electrolyte in the MeCN in an undivided cell, a graphite rod as the anode, and a Pt plate as the cathode at a constant current of 15 mA at 60 °C for 1.5 h (Scheme 12). When the cathode changes to a Ni plate, the electrolyte changes from Et_4NPF_6 to $^nBu_4NBF_4$, and the reaction time is extended to 2 h. The electrolytic product is indomolines. The natural products borneol (**38a**) and L-menthol (**38b**) can be modified using this strategy. In addition, small-molecule drugs, such as roflumilast and probenecid, can also generate the corresponding benzoxazine products (**38c**) and (**38d**).

The cytotoxic activity of benzoxazines and indolines against four tumor cell lines (MGC-803, MIA Pa Ca-2, MDA-MB-231, and HeLa) was screened *in vitro* by MTT assay to study their antitumor activities. The results indicated that the compounds **38b**, **38e**, and **39e** show high anticancer activity *in vitro* in MGC-803, MIA Pa Ca-2, and HeLa cell lines (Scheme 13).

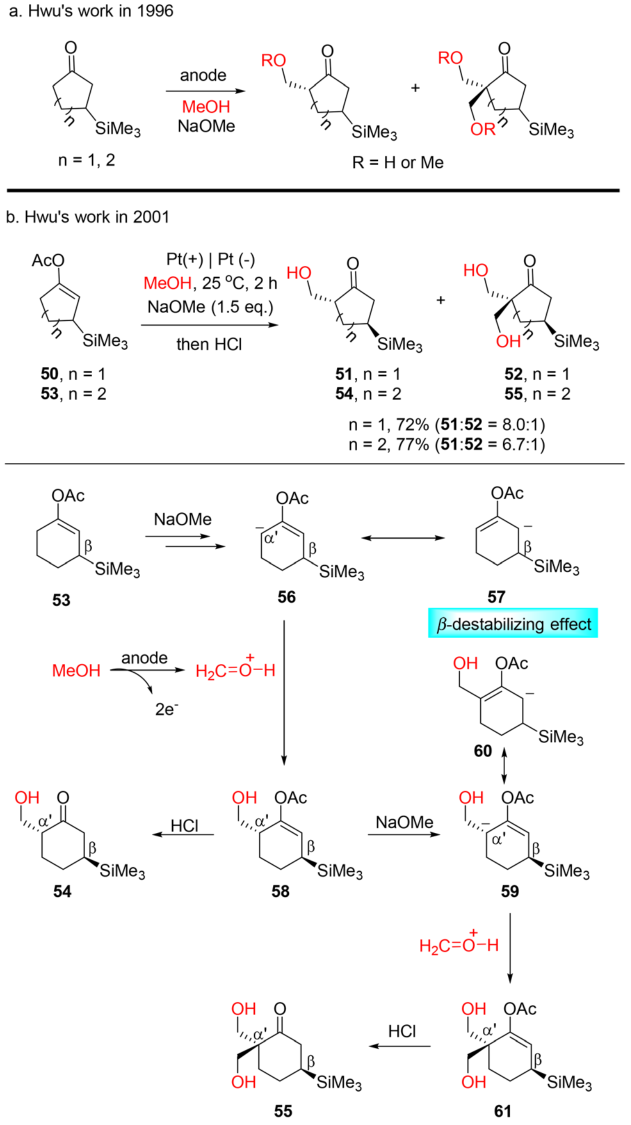
Based on controlled experiments and cyclic voltammetry studies, two reasonable mechanisms were proposed (Scheme 14). In path A, **37** is oxidized at the anode to form free radical cation **40**. Then, intermediate a is nucleophilically added to methanol to form intermediate **41**. The free radical intermediate **41** is further anodized to obtain carbocation **42**. Finally, **38** is obtained after nucleophilic attack and deprotonation. Anion **43**, which is then oxidized to nitrogen radical intermediate **44** at the anode. The intermediate **44** cyclization forms the carbon radical **45**. Then, **45** oxidizes to produce carbocation **46**, which is captured by methanol to form an intermediate **47**. Then, intermediate **47** loses an electron to form a cationic radical **48**. The imide ion intermediate **49** is produced by anodizing. It is captured by another molecule of methanol to form the final product **39**.



Scheme 12 Electrochemical oxidative cyclization of olefin amides and alcohols.

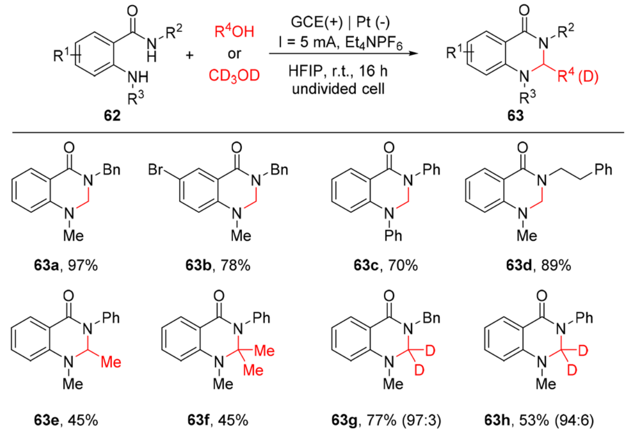
2.3 Other electrochemical reactions

In 1996, Hwu *et al.*[22] reported the development of silicon-directed aldol condensation reactions under electrochemical conditions (Scheme 15a). The reaction has good regioselectivity, but it usually provides a mixture of products containing mono- and bishydroxymethyl groups. It also has the potential to produce complex mixtures of hydroxymethylated and methoxymethylated ketones. In 2001, Hwu *et al.*[23] developed a regionally selective hydroxymethylation of β-(trimethylsilyl)-cycloalkanone enol acetates with methanol catalyzed *via* electrochemical catalysis under basic conditions (Scheme 15b). Given the strong destabilizing effect of the dissociated β-allyl anions **57** and **60**, hydroxymethylation is selectively performed at the α′ sites **56** and **59**. In addition, the desired mono- and bis-α′-hydroxymethylated cycloalkanone main products can be obtained in moderate yields by controlling the amount of the added base NaOMe.

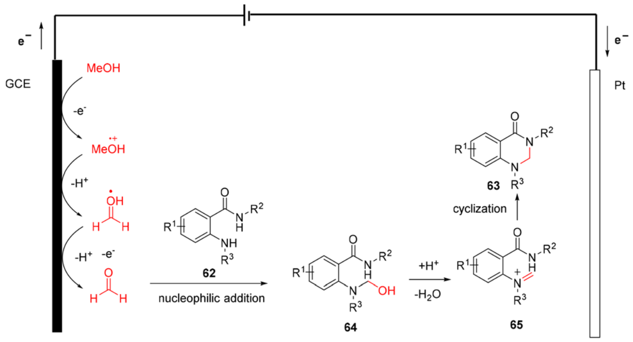


Scheme 15 Electrochemical hydroxymethylation of β-silylcycloalkanone enols.

Wei *et al.*[24] developed a method for the electrocatalytic synthesis of 2,3-dihydroquinazolin-4(1*H*)-one (**63**) using methanol as the C1 source (Scheme 16). The reaction was carried out in an undivided cell equipped with a glassy carbon electrode anode, a platinum cathode, ^{n}Et$_4$NPF$_6$ as the electrolyte, MeOH/HFIP (1 : 1) as the solvent, and electrolysis at a constant current of 5 mA for 16 h at room temperature. Both electron-withdrawing and electron-donating 5-substituted anthranilamides can obtain the corresponding dihydroquinazolinone compounds in excellent yields. When methanol is replaced by other alcohols (ethanol or 2-propanol), the corresponding product can still be obtained, even though the yield is reduced because of steric hindrance (**63e**, **63f**). Deuterium components can be used for mechanism, spectrum, and tracer studies in drug discovery and development. Therefore, methanol-d_4 was used as the C1 source, and a deuterated methylene motif was successfully introduced into the N-heterocycles to obtain the 2,2-deuterated dihydroquinazolin-4(1*H*)-ones (**63g**, **63h**).



Scheme 16 The cyclization of electrooxidized methanol with 2-aminobenzamide.



Scheme 17 The cyclization reaction mechanism of electrooxidized methanol and 2-aminobenzamide.

Based on controlled experiments, the following reasonable mechanism was proposed (Scheme 17). First, methanol is continuously oxidized to formaldehyde at the anode. Substrate **62** reacts with formaldehyde to form intermediate **64**. Then, intermediate **64** was dehydrated to generate iminium ion **65**. Finally, the target product **63** was obtained by cyclization of the iminium ion **65**.

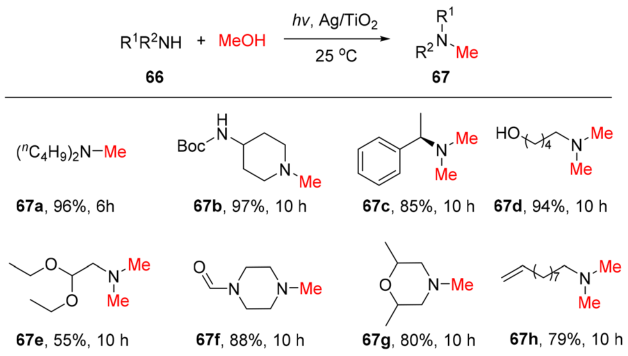
3. Photochemical utilization of methanol as C1 source

Visible-light photoredox catalysis has become a powerful tool in modern organic synthesis techniques. The chemical conversion of organic substrates is achieved *via* a SET process or ET. Thus, using external stoichiometric activation reagents or toxic initiators is avoided. Visible-light photoredox catalysis is a good strategy for inducing methanol *via* visible light and achieving various chemical transformations of the initial substance.

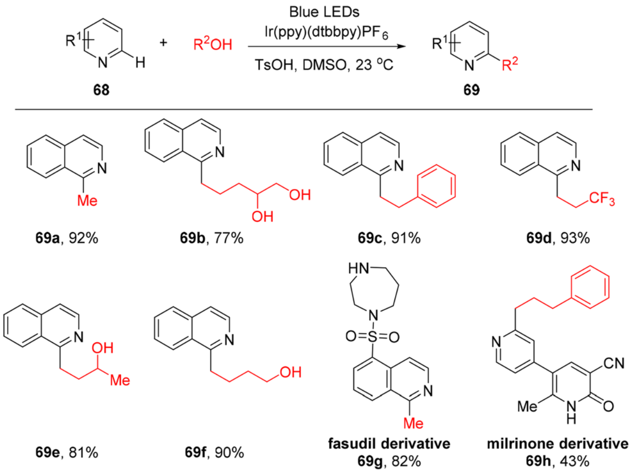
3.1 Photochemical methylation reaction

In 1986, Kagiya's group reported that in the presence of platinized titanium dioxide (TiO_2/Pt), *N*,*N*-dimethylbenzylamine is successfully synthesized by *N*-methylation of benzylamine as the substrate and methanol as the C1 source.[25] However, this *N*-methylation strategy has a low yield (28%). In 2015, Saito and co-workers[26] developed a photocatalytic *N*-methylation reaction between amine (**66**) and methanol in the presence of a silver-supported titanium dioxide (Ag/TiO_2) photocatalyst (Scheme 18). This strategy is suitable for both anhydrous/watery and acidic/neutral/alkaline conditions. It also has a wide range of functional group tolerance and achieves *N*-methylation of various functional groups. Including *N*-allyl, *N*-Boc, *N*-benzyl, hydroxyl, ether, acetal, formamide, carboxamide and olefin.

In 2015, inspired by the use of an enzyme process in DNA biosynthesis for effectively breaking the C–O bond to generate instantaneous freedom, MacMillan's group[27] realized the alkylation reaction of iso-aromatics and methanol under photocatalysis (Scheme 19). Isoquinolines with electron-donating or electron-withdrawing substituents have excellent functionalization efficiency. They can obtain methylated products with excellent yields. Steric bulk proximal to thealcohol functionality is tolerated, such as β-tetrahydropyran (**69b**), β-aryl (**69c**), and β-trifluoromethyl (**69d**). Diols (**69e**) and tetrahydrofuran (**69f**) are also suitable for this strategy. In addition, the group used the strategy to synthesize two drugs: fasudil (**69g**) and milrinone (**69h**).



Scheme 18 Photocatalytic *N*-methylation of amines and methanol.

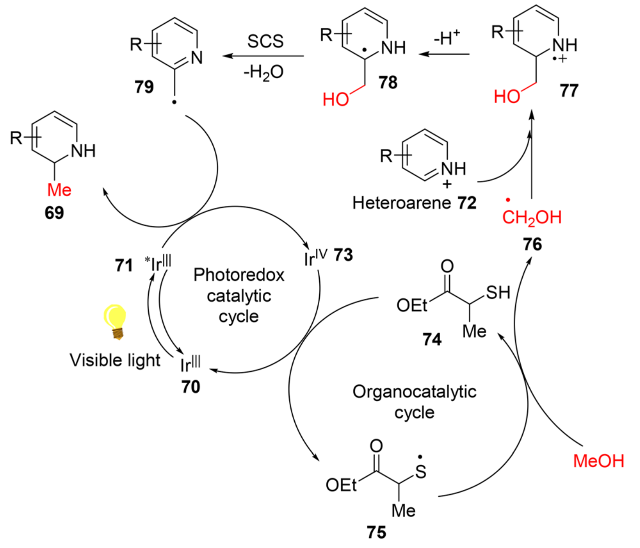


Scheme 19 Photocatalytic alkylation of heteraromatics.

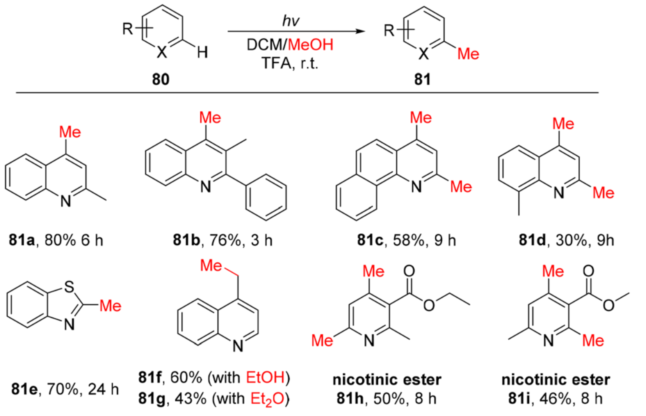
The group also proposed a dual catalytic mechanism for the alkylation of heteroarenes with alcohols (Scheme 20). Ir $(ppy)_2(dtbbpy)^+$ **70** (in which ppy = 2-phenylpyridine; dtbbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine) generates $^*Ir(ppy)_2(dtbbpy)^+$ **71** excited states (τ = 557 ns) by irradiation. Then, **71** undergoes event that sacrifices the quantity of protomized heteroarene **72** and provides the oxidizing $Ir(ppy)_2(dtbbpy)^{2+}$ **73**. The mercaptan catalyst and **73** undergo SET to form Ir $(ppy)_2(dtbbpy)^+$ **71** and **75**.

Methanol and **75** undergo hydrogen transfer to form **74** and **76**. Then, nucleophilic α-oxy **76** combines with protonated electron-deficient heteroarene **72** in a Minisci-type pathway toform aminyl radical cation **77**. Then, **77** undergoes deprotonation to form **78**, which undergoes a spin-center shift to eliminate H_2O and generate benzylic radical **79**. Then, **79** undergoes protonation followed by a second SET event with the excited photocatalyst **71** to regenerate **73** while providing the desired alkylation product **69**.

Aromatic methylation usually requires the use of transition metals, directional groups, and stoichiometric oxidants; this approach increases the reaction cost and may cause metal residues.[28] Thus, Li and co-workers[29] developed a strategy to induce the methylation of heteroarenes (**80**) using methanol as the methylating reagent under photocatalysis (Scheme 21). The reaction conditions are mild and simple to operate without any external catalyst. Experiments have shown that adding dichloromethane (DCM) as a co-solvent can significantly increase the yield of methylation products. Under the



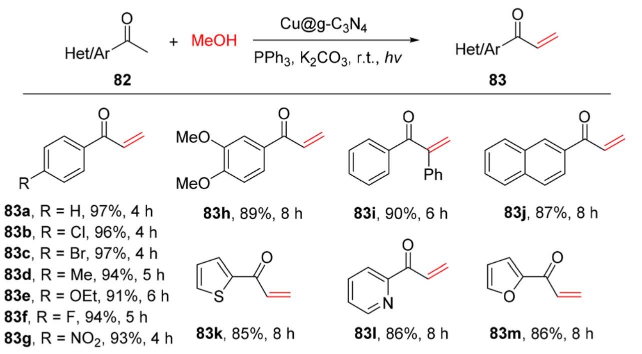
Scheme 20 The mechanism of photocatalytic alkylation of heteraromatics.



Scheme 21 Photo-induced methylation of heteroarenes with methanol.

optimal condition, different substituted 2-phenylquinolines are compatible with this strategy. Substrates with two reaction sites are dimethylated with prolonged reaction time. Five-membered heterocyclic benzothiazoles can also be methylated by this strategy (**81e**). Alkylation can also be performed using ethanol, ether, and deuterated methanol instead of methanol (**81f** and **81g**). Nicotinic ester can be synthesized successfully using this strategy (**81h**, **81i**).

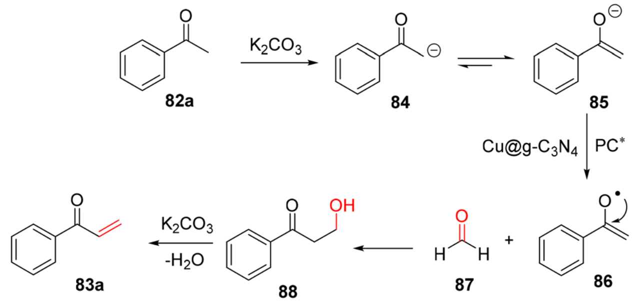
Various α,β-unsaturated carbonyl compounds are synthesized by the reaction of terminal alkenes with aldehydes and ketones, usually using formaldehyde or polyformaldehyde.[30] However, formaldehyde is toxic, limiting the development of this kind of reaction. Thus, chemists use DMA, DMF, and DMSO instead of formaldehyde, but these substitutes are less reactive than the latter.[31] Rai and co-workers[32] reported for the first time the construction of a C=C bond by α-methylenation of aryl ketones (**82**) using methanol as the C1 source (Scheme 22). The reaction was carried out under visible light conditions with Cu graphitic C_3N_4 (Cu@g-C_3N_4) as the catalyst without using any oxidant. The operation is simple and performed under mild reaction conditions. The Cu@g-C_3N_4 catalyst can be reused five times without significant loss of activity. This reaction has a wide range of substrates and has no special effect on phenyl/heterocyclic groups, whether electron-withdrawing or electron-donating substituents. However, this strategy does not apply to aliphatic ketones, possibly because aliphatic ketones are volatile, and the reaction is not carried out in a closed container.



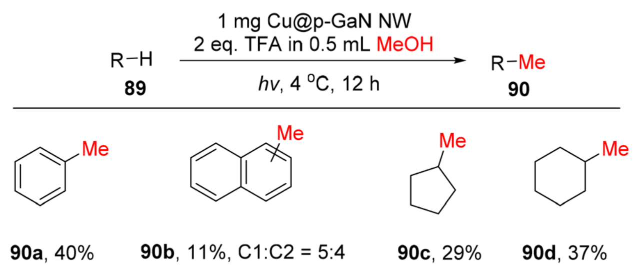
Scheme 22 Photocatalytic methylation of ketone.

Based on the experimental results and previous reports,[33] the following reasonable mechanism was proposed (Scheme 23). First, **82a** deprotonates to form **84** in the presence of K_2CO_3. Then, the corresponding free radical **85** is generated under photochemical excitation. Free radical **85** reacts with formaldehyde **87** to form alcohol **88.** The remaining radicals are dehydrated by K_2CO_3 to obtain product **83a.**

In 2020, Li and co-workers[34] developed the direct methylation of unactivated sp[3] and sp[2] C–H bonds with methanol as the C1 source under photocatalysis. Gallium nitride was used as the photocatalyst (Scheme 24). The existing use of methanol for photocatalytic C–H methylation of heteroaromatic hydrocarbons requires the use of electrophilic starting materials, as methanol produces nucleophilic hydroxymethyl radicals, thereby limiting the substrate range.[29] The key to the success of this strategy is that under photocatalysis, methanol can overcome the high bond strength of the C–O bond on the surface of gallium nitride nanowires (GaN NW) and remove nucleophilic oxygen, generating methyl carbene (:CH_2), thereby achieving the methylation of the inactive C–H bond. This strategy uses photochemical methods and avoids the use of stoichiometric oxidants. Moreover, the reaction conditions are relatively mild. Benzene, naphthalene, cyclohexane, and *n*-hexane are applicable to this strategy (**90a–90d**). GaN catalyst is reusable and shows no significant degradation after nine consecutive catalytic cycles.

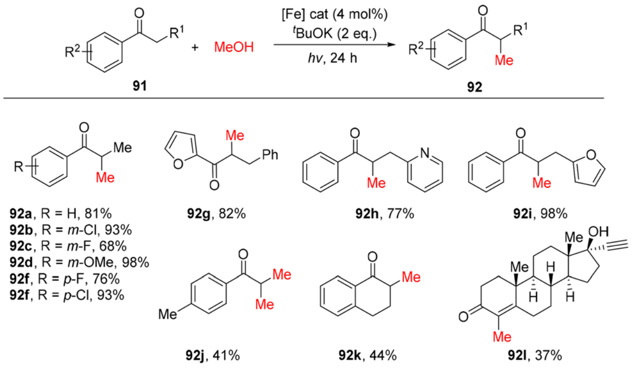


Scheme 23 The mechanism of photocatalytic methylation of ketone.



Scheme 24 Photocatalytic methylation of nonactivated C–H on GaN.

In 2022, Sundararaju group[35] developed a strategy for the synthesizing the α-methylenation of ketones using methanol as C1 source under visible light. This strategy replaces traditional ketone methylation reagents (methyl halides, diazomethane, or methyl sulfate) with methanol, and does not require the use of expensive metal ligands, and the reaction conditions are mild. Various aromatic methyl ketones can be obtained in moderate to good yields after 24 h of visible light irradiation by using Knölker as the catalyst and potassium *tert*-butoxide as the base (Scheme 25). Heterocyclic rings can also be obtained by this strategy (**92g–92i**). However, the α,α-dimethylated ketone product is obtained in 41% yield when acetophenone is methylated (**92j**). The cyclic substrates with aliphatic backbones, such as α-tetralone and ethisterone (**92k**, **92l**), can also obtain the corresponding methylation products.

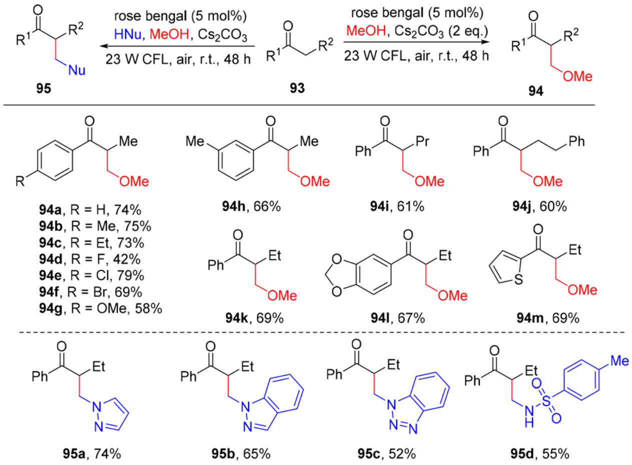


Scheme 25 Iron-catalyzed α-methylation of ketones under photoirradiation.

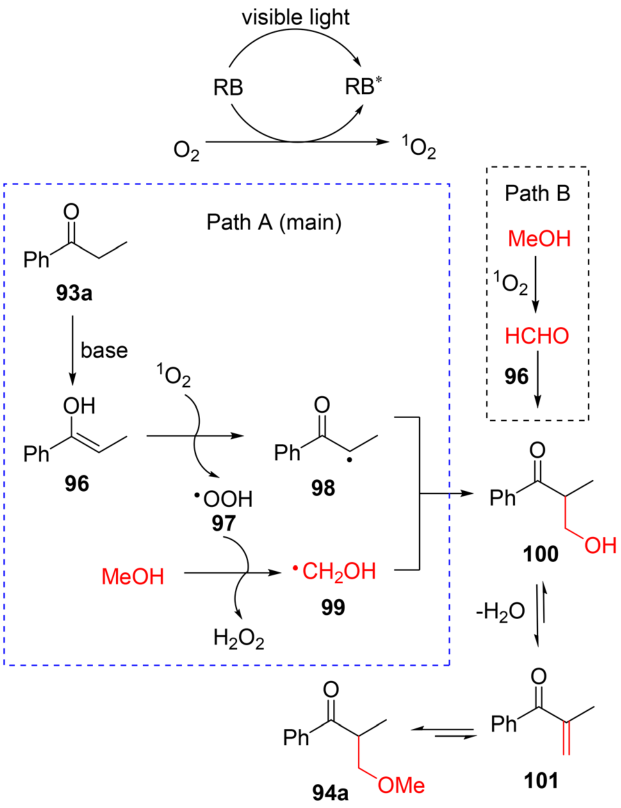
3.2 Photochemical methoxymethylation reaction

Li's group[36] developed a photochemical method for α-methoxy methylation of ketones as the source of green C1. With rose bengal (RB) as the photosensitizer and air as the oxidant, the α-methoxymethylation products are obtained with medium to good yields of ketones under visible light irradiation (Scheme 26). Under optimal conditions, both electron-withdrawing and electron-donating mono-substituted phenylpropanone compounds can smoothly undergo α-methoxymethylation. In addition, ketones with long alkyl chains and those that contain heterocycles can obtain the target products in moderate yields (**94l** and **94m**). The group found that the aminomethylation ofketones with methanol and *N*-nucleophiles can be achieved by the two-step, one-pot method (**95a–95d**).

Based on the experimental results and previous reports,[37] the following reasonable mechanism was proposed (Scheme 27). RB is initially excited by the excited state RB* under visible light irradiation. Then, RB* interacts with O_2 *via* ET to provide $^1O_2$. The subsequent conversion of ketone **93a** to the intermediate α-hydroxymethylated ketone **100** may occur through two pathways. In path A, **93a** is treated with a base to form enolate **96** and quickly reacts with $^1O_2$ to form free radical **98** and hydroperoxide radical **97**. Then, **97** abstracts a hydrogen atom from methanol to form free radical **98**. Then, **98** reacts with **99** to form **100**. In path B, methanol is oxidized by $^1O_2$ to form formaldehyde, which reacts with **96** to form **100**. Finally, **100** is dehydrated to produce enone **101**, which is then reacted with methanol or *N*-nucleophile by the oxa-Michael reaction to give methoxymethylation product **94a.**

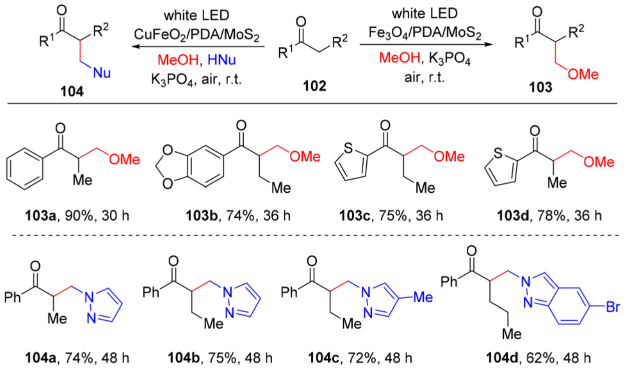


Scheme 26 Visible-light-promotes α-methoxymethylation and aminomethylation of ketones.



Scheme 27 The mechanism of visible-light-promotes α-methoxymethylation and aminomethylation of ketones.

Zhang' group[38] reported the α-methoxymethylation of aromatic ketones under visible light irradiation using $CuFeO_2$/



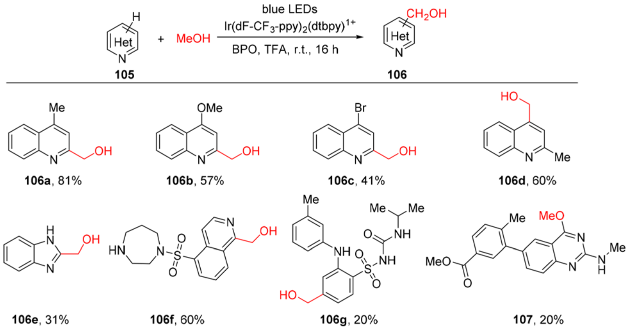
Scheme 28 Magnetic MoS$_2$ catalyzed α-methoxymethylation and aminomethylation of ketones under photoirradiation.

PDA/MoS$_2$ nanocomposites as photocatalysts and methanol as the C1 source (Scheme 28). The introduction of magnetic CuFeO$_2$ not only enhances the catalytic activity of the catalyst but also enables the magnetic separation and recovery of the catalyst. CuFeO$_2$/PDA/MoS$_2$ still exhibits good catalytic activity after five times of repeated use. The structure and morphology of the catalyst were characterized by X-ray diffraction, Fourier transform infrared spectroscopy, scanning electron microscopy, transmission electron microscopy, X-ray photoelectron spectroscopy, and energy dispersive X-ray. The α-methoxymethylation of aromatic ketones and heteroaryl thiophene propanone can be achieved successfully with this strategy (**103a–103d**). However, aliphatic ketones are not compatible with this strategy. The aminomethylation of aromatic ketones, methanol, and pyrazole derivatives was achieved through a two-step, one-pot process (**104a–104d**).

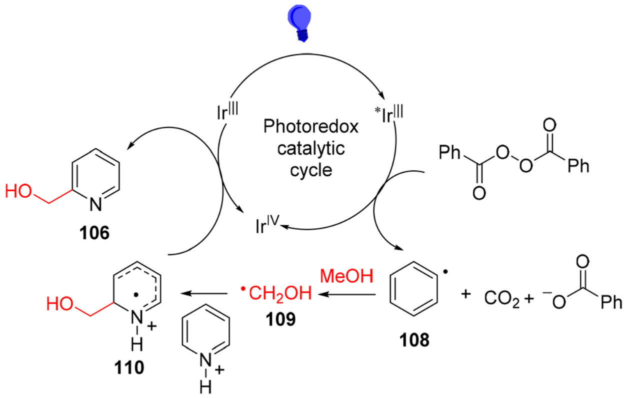
3.3 Photochemical hydroxymethylation reaction

Introducing hydroxymethyl functional groups (–CH$_2$OH) into a compound can change its physical properties, such as log *P* and solubility, and a hydroxymethyl group can be used as a point of diversification to obtain other target compounds.[39] Krska's group[40] reported a method of hydroxyl methylation of heteroaromatic hydrocarbons at room temperature. The method uses BPO as the oxidant and methanol as the solvent (Scheme 29). Under visible light irradiation, it is suitable for various heterocyclic rings and has a tolerance for functional groups that are easily oxidized (**106a–106e**). Using this method, the group successfully achieved the late functionalization of various drug molecules, such as isoquinoline-containing drug (**106f**) and pyridine-containing diuretic torsemide (**106g**). Instead of hydroxymethylation, the methoxylation of containing quinazoline (**107**) was achieved by this strategy.

A plausible mechanism for the hydroxymethylation reaction is proposed in Scheme 30. Ir^{III} is irradiated by the blue light to form an excited complex Ir^{III}*, which is then oxidized by BPO to form Ir^{IV} and phenyl radical **108**. The phenyl radical **108** extracts a hydrogen atom from MeOH to produce the hydroxymethyl radical **109**. Then, **109** is added to the activated position of a protonated heterocycle generating the intermediate **110**. Finally, **110** is oxidized by Ir^{IV} to obtain the target product **106**.



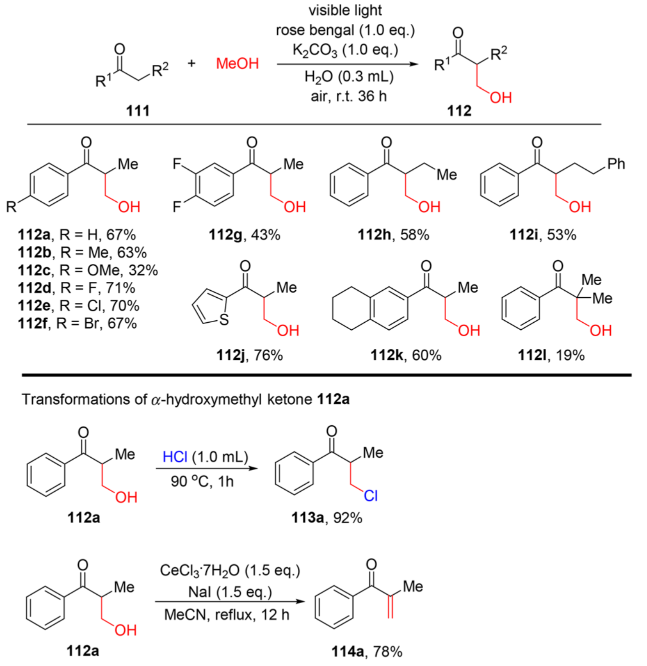
Scheme 29 Photoredox-catalyzed hydroxymethylation of heteroaromatic bases.



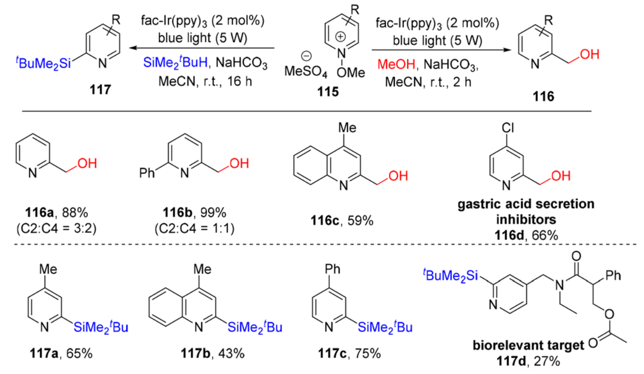
Scheme 30 The mechanism of photoredox-catalyzed hydroxymethylation of heteroaromatic bases.

In 2018, Yang and co-workers[41] reported for the first time the visible light catalytic method of α-C(sp^3)–H hydroxymethylation of ketones using methanol as the hydroxymethylating reagent (Scheme 31). The strategy was carried out at room temperature with RB as the photosensitizer, MeOH/H$_2$O (1 mL/0.3 mL) as the solvent, and air as the oxidant. A series of α-hydroxymethylation reactions of phenylacetone was successfully achieved by using this strategy (**112a–112l**). The preparation of a gram of phenylacetone (**111**) was achieved under standard conditions. At the same time, the derivatization experiment of product (**112a**) was conducted, proving the practicability of the product.

Lakhdar and co-workers[42] developed an effective method for the C–H hydroxymethylation of pyridine and related heterocyclic rings (**115**) under blue light irradiation with *N*-methoxypyridinium ions as the substrate and methanol as the C1 source under the low catalyst load (2 mol%) condition (Scheme 32). When unsubstituted and 2-substituted pyridine salts are used, two regional isomers are obtained in an almost 1 : 1 ratio (**116a**, **116b**). The reaction effect is good (**116c**) when 4-methylquinoline is used as the substrate. The method successfully synthesizes gastric acid secretion inhibitors (**116d**). In addition, C–H silanization of pyridine and related heterocyclic rings can be achieved when silane is used instead of methanol (**117a–117d**).



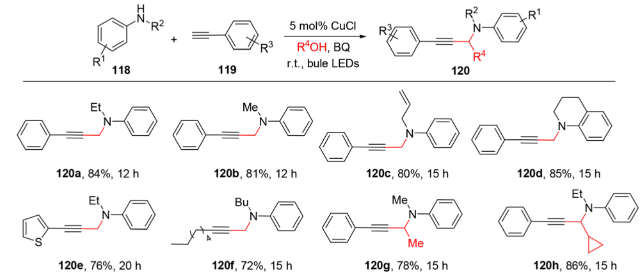
Scheme 31 Visible light mediated hydroxymethylation of ketones with methanol.



Scheme 32 Photochemical hydroxymethylation and silylation of pyridines.

3.4 Other photochemical reactions

In the field of photochemistry, copper complexes as catalysts have been rapidly developed and successfully used in many cross-coupling reactions.[43] Thus, Hwang and co-workers[44] reported the first visible light-mediated copper-catalyzed three-component coupling of *N*-alkylanilines (**118**), terminal alkyne (**119**), and methanol to produce propyleneylamine. The reaction uses CuCl as the catalyst and benzoquinone as the oxidant. It occurs at room temperature without the addition of other ligands and bases (Scheme 33). A wide range of *N*-alkyl/benzylaniline is suitable for this strategy to obtain the corresponding propylpargyne in good yield (**120a–120d**). In addition to aryl alkynes, thiophene alkynes and *n*-octyl alkynes are suitable for this strategy (**120e, 120f**). A series of aliphatic alcohols is also compatible with this strategy (**120g, 120h**).

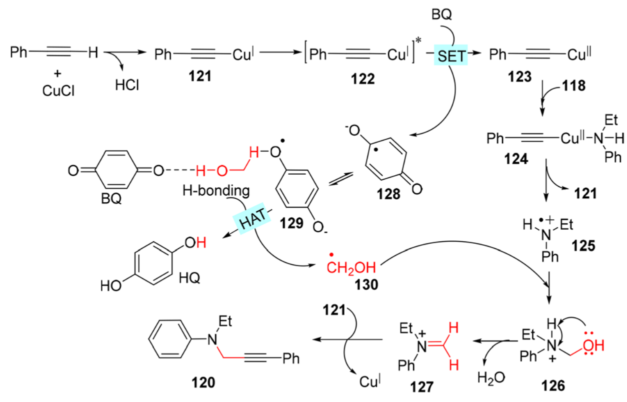


Scheme 33 Copper photoredox catalyzed A3′ coupling of arylamines, terminal alkynes, and alcohols.

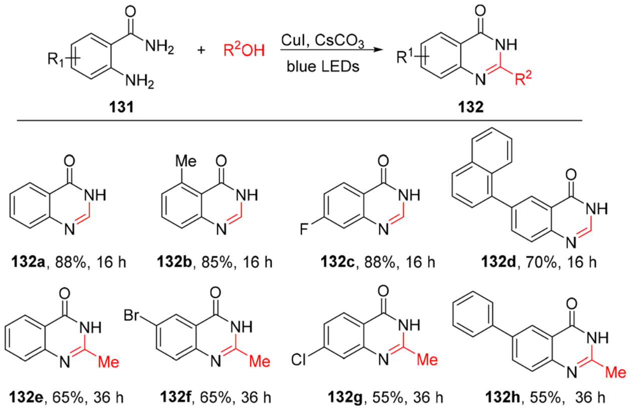
Based on the experimental results, the following reasonable mechanism was proposed (Scheme 34). First, **121** generates **122** excited states (τ = 15.95 ms) under visible light irradiation. The **122** electrons transfer to BQ, resulting in BQ radical anion **128** and an intermediate **123**. Then, the BQ radical anion **128** or **129** undergoes HAT from methanol to form the α-oxy radical **130** and hydroquinone. Then, **123** reacts with **118** to form **124**, which occurs *via* photoexcitation. Ligand-to-metal charge transfer occurs to form the amino radical cation **125** and **121**. Then, α-oxy radical **130** is cross-coupled with **125** radical to obtain the complex **126**. Then, **126** undergoes the elimination of H_2O, furnishing the iminium species **127**. Adding **121** leads to **120** with concomitant regeneration of CuCl.

Anandhan and co-workers[45] developed a method for synthesizing quinazolinones **131** *via* oxidative cyclization of *o*-aminobenzamide **132** and methanol catalyzed by CuI under visible light irradiation (Scheme 35). In this method, many *o*-phenylformamide derivatives successfully react with methanol to form the corresponding quinazolinones (**132a–132d**). In addition, *o*-aminobenzamide can be reacted with ethanol through this method (**132e–132h**). However, the method takes a long time because of the lower reactivity of ethanol, and its yield is slightly lower than that of methanol.

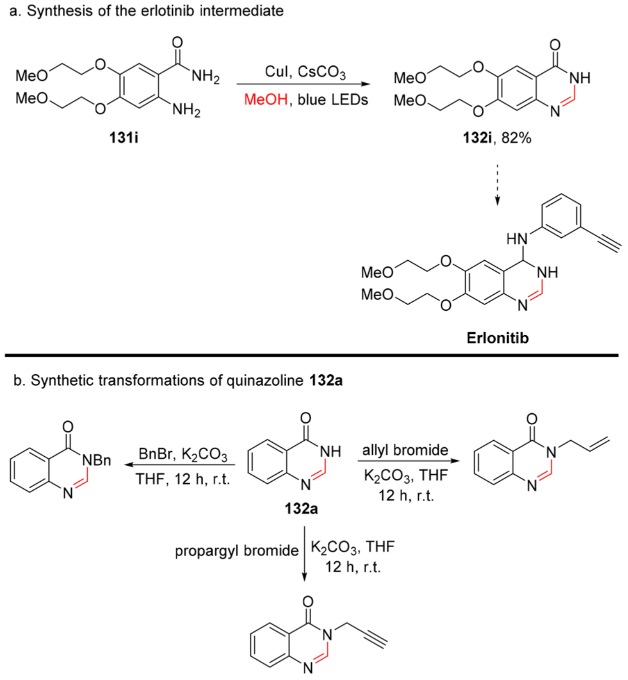
The synthesis of the intermediate **132i** of the anticancer drug quinazolone erlotinib and some functionalizations ofquinazolone **132a** was implemented to demonstrate the practicability of the method (Scheme 36).



Scheme 34 The mechanism of copper photoredox catalyzed A3′ coupling of arylamines, terminal alkynes, and alcohols.



Scheme 35 Visible-light induced cyclization of *o*-aminobenzamides with methanol and ethanol.



Scheme 36 Synthetic **132i** and transformations of quinazoline **132a**.

4. Conclusions and outlook

This study mainly summarizes the methylation, methoxylation, hydroxymethylation, and cyclization of ketones, alkenes, amines, aromatics, and other compounds with methanol as the green C1 source under electric or photocatalytic conditions. In many active drugs, the presence of methyl or hydroxymethyl groups can greatly increase the biological activity of drug molecules. Thus, the realization of drug functional modification through methylation or hydroxymethylation reaction is an important means of drug production. Unlike other C1 sources with low activity and toxic properties (for example, CO_2, CO, formaldehyde, and isonitrile), methanol is abundant and easy to obtain. It also has high chemical activity, and its by-product is water. Using electricity and photocatalysis of methanol can avoid the use of stoichiometric oxidants. Thus, this approach is friendly to the environment.

Although significant progress has been made in using methanol as a C1 source in electrochemistry/photochemistry, there are still shortcomings. (1) There are few reports on the use of electrooxidation of methanol for methylation or hydroxymethylation, and specific substrates are needed to remove the oxygen atoms of methanol. (2) MeOH participates in more homogeneous photo-reactions and less heterogeneous ones. The reason may be that heterogeneous photocatalysts are more difficult to excite. (3) The bonding type is single, and the current application of methods mainly focuses on the construction of C–C or C–O, while the construction of C–X bonds needs to be strengthened. Heteroatomic substrates are more prone to self redox reactions, which makes it difficult to react with MeOH according to the envisioned pathway. (4) Further research is needed on the application of enantioselective methylation. Ligands are unstable under photochemical or electrochemical conditions. Therefore, it is necessary to develop more ligands that are compatible under both photochemical and electrochemical conditions.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank the Guangxi Science and Technology Base and Talent Project (High level Innovative Talents and Team Training) (Guike AD23026094), Guangxi Natural Science Foundation of China (2021GXNSFFA220005) and National Natural Science Foundation of China (No. 22061003, 22161008) for financial support.

References

1 (*a*) M. Tobisu, M. Oshita, S. Yoshioka, A. Kitajima and N. Chatani, *Pure Appl. Chem.*, 2006, **78**, 275–280; (*b*) N. Barsu, S. K. Bolli and B. Sundaraju, *Chem. Sci.*, 2017, **8**, 2431–2435; (*c*) M. D. Anker, C. E. Kefalidis, Y. Yang, J. Fang, M. S. Hill, M. F. Mahon and L. Maron, *J. Am. Chem. Soc.*, 2017, **139**, 10036–10054; (*d*) D. Kalsi, N. Barsu, P. Dahiya and B. Sundaraju, *Synthesis*, 2017, 3937–3944; (*e*) H. L. Barlow, C. J. Teskey and M. F. Greaney, *Org. Lett.*, 2017, **19**, 6662–6665; (*f*) Y.-Z. Pan, Q. Xia, J.-X. Zhu, Y.-C. Wang, Y. Liang, H. Wang, H.-T. Tang and Y.-M. Pan, *Org. Lett.*, 2022, **24**, 8239–8243.

2 (*a*) J. Jin and D. W. C. MacMillan, *Nature*, 2015, **525**, 87–90; (*b*) M. Mastalir, E. Pittenauer, G. Allmaier and K. Kirchner,

J. Am. Chem. Soc., 2017, **139**, 8812–8815; (*c*) M. Holmes, K. D. Nguyen, L. A. Schwartz, T. Luong and M. J. Krische, *J. Am. Chem. Soc.*, 2017, **139**, 8114–8117; (*d*) W. Liu, X. Yang, Z.-Z. Zhou and C.-J. Li, *Chem*, 2017, **2**, 688–702; (*e*) G. Choi and S. H. Hong, *Angew. Chem., Int. Ed.*, 2018, **57**, 6166–6170; (*f*) L. Wang, H. Neumann and M. Beller, *Angew. Chem., Int. Ed.*, 2019, **58**, 5417–5421; (*g*) A. Kaithal, P. Bonn, M. Hölscher and W. Leitner, *Angew. Chem., Int. Ed.*, 2020, **59**, 215–220; (*h*) M. Schlagbauer, F. Kallmeier, T. Irrgang and R. Kempe, *Angew. Chem., Int. Ed.*, 2020, **59**, 1485–1490.

3 (*a*) L. F. T. Novaes, J. Liu, Y. Shen, L. Lu, J. M. Meinhardt and S. Lin, *Chem. Soc. Rev.*, 2021, **50**, 7941–8002; (*b*) H. Wang, M. Yu, P. Zhang, H. Wan, H. Cong and A. Lei, *Sci. Bull.*, 2022, **67**, 79–84; (*c*) C.-Y. Cai, Y.-T. Zheng, J.-F. Li and H.-C. Xu, *J. Am. Chem. Soc.*, 2022, **144**(27), 11980–11985; (*d*) Z.-H. Wang, P.-S. Gao, X. Wang, J.-Q. Gao, X.-T. Xu, Z. He, C. Ma and T.-S. Mei, *J. Am. Chem. Soc.*, 2021, **143**, 15599–15605; (*e*) Z. Tan, F. Xiang, K. Xu and C. Zeng, *Org. Lett.*, 2022, **24**, 5345–5350; (*f*) Z.-M. Fu, J.-S. Ye and J.-M. Huang, *Org. Lett.*, 2022, **24**, 5874–5878; (*g*) Z. Xu, Y. Li, G. Mo, Y. Zheng, S. Zeng, P.-H. Sun and Z. Ruan, *Org. Lett.*, 2020, **22**, 4016–4020; (*h*) X.-Y. Wang, S.-H. Wu, Y.-J. Zhong, Y.-C. Wang, Y.-M. Pan and H.-T. Tang, *Chin. Chem. Lett.*, 2023, **34**, 107537; (*i*) Z. Shi, W.-Z. Wang, N. Li, Y. Yuan and K.-Y. Ye, *Org. Lett.*, 2022, **24**, 6321–6325; (*j*) W. Zhang, L. Lu, W. Zhang, Y. Wang, S. Ware, J. Mondragon, J. Rein, N. Strotman, D. Lehnherr, K. See and S. Lin, *Nature*, 2022, **604**, 292–297; (*k*) H.-Y. Zhou, H.-T. Tang and W.-M. He, *Chin. J. Catal.*, 2023, **46**, 4–10.

4 (*a*) B. Dam, B. Das and B. K. Patel, *Green Chem.*, 2023, **25**, 3374–3397; (*b*) L. Song, L. Cai, L. Gong and E. V. V. Eycken, *Chem. Soc. Rev.*, 2023, **52**, 2358–2376; (*c*) M. Wang, H. Zhou and F. Wang, *Acc. Chem. Res.*, 2023, **56**, 1057–1069; (*d*) J. Xu, C. Liang, J. Shen, Q. Chen, W. Li and P. Zhang, *Green Chem.*, 2023, **25**, 1975–1981; (*e*) X. Liu, R. Qi, S. Li, W. Liu, Y. Yu, J. Wang, S. Wu, K. Ding and Y. Yu, *J. Am. Chem. Soc.*, 2022, **144**(51), 23396–23404; (*f*) M. K. Ghosh, K. S. Sharma and G. Pandey, *Org. Biomol. Chem.*, 2023, **21**, 538–550; (*g*) J. Sakizadeh, J. P. Cline, E. Wolfe, R. Thorpe, M. A. Snyder, C. J. Kiely and S. McIntosh, *Green Chem.*, 2023, **25**, 566–578.

5 Y. Wu, H. Ding, M. Zhao, Z.-H. Ni and J.-P. Cao, *Green Chem.*, 2020, **22**, 4906–4911.

6 B. Appiagyei, S. Bhatia, G. L. Keeney, T. Dolmetsch and J. E. Jackson, *Green Chem.*, 2020, **22**, 860–869.

7 G. N. Wanyoike, O. Onomura, T. Maki and Y. Matsumura, *Org. Lett.*, 2002, **4**, 1875–1877.

8 (*a*) J. Heo, K. J. Thomas, G. H. Seong and R. M. Crooks, *Anal. Chem.*, 2003, **75**, 22–26; (*b*) W. Zhan, J. Alvarez and R. M. Crooks, *Anal. Chem.*, 2003, **75**, 313–318; (*c*) W. Zhan, J. Alvarez, L. Sun and R. M. Crooks, *Anal. Chem.*, 2003, **75**, 1233–1238.

9 R. Horcajada, M. Okajima, S. Suga and J. Yoshida, *Chem. Commun.*, 2005, 1303–1305.

10 (*a*) B. J. Cohen, M. A. Kraus and A. Patchornik, *J. Am. Chem. Soc.*, 1977, **99**, 4165–4167; (*b*) B. J. Cohen, M. A. Kraus and A. Patchornik, *J. Am. Chem. Soc.*, 1981, **103**, 7620–7629.

11 T. Tajima and H. Kurihara, *Chem. Commun.*, 2008, 5167–5169.

12 (*a*) T. Fuchigami, Y. Nakagawa and T. Nonaka, *Tetrahedron Lett.*, 1986, **27**, 3869–3872; (*b*) T. Fuchigami, K. Yamamoto and A. Konno, *Tetrahedron*, 1991, **47**, 625–634; (*c*) T. Fuchigami, K. Yamamoto and Y. Nakagawa, *J. Org. Chem.*, 1991, **56**, 137–142.

13 M. N. Elinson, J. Simonet and L. Toupet, *J. Electroanal. Chem.*, 1993, **350**, 117–132.

14 X.-J. Meng, Y.-Z. Pan, S.-K. Mo, H.-S. Wang, H.-T. Tang and Y.-M. Pan, *Org. Chem. Front.*, 2020, **7**, 2399–2404.

15 X.-S. Ji, H.-D. Zuo, Y.-T. Shen, W.-J. Hao, S.-J. Tu and B. Jiang, *Chem. Commun.*, 2022, **58**, 10420–10423.

16 (*a*) A. Wiebe, T. Gieshoff, S. Moehle, E. Rodrigo, M. Zirbes and S. R. Waldvogel, *Angew. Chem., Int. Ed.*, 2018, **57**, 5594–5619; (*b*) S. R. Waldvogel, S. Lips, M. Selt, B. Riehl and J. C. Kampf, *Chem. Rev.*, 2018, **118**, 6706–6765; (*c*) K.-J. Jiao, Y.-K. Xing, Q.-L. Yang, H. Qiu and T.-S. Mei, *Acc. Chem. Res.*, 2020, **53**, 300–310; (*d*) J. C. Siu, N. Fu and S. Lin, *Acc. Chem. Res.*, 2020, **53**, 547–560; (*e*) J. Li, S. Zhang and K. Xu, *Chin. Chem. Lett.*, 2021, **32**, 2729–2735; (*f*) C. A. Malapit, M. B. Prater, J. R. Cabrera-Pardo, M. Li, T. D. Pham, T. P. McFadden, S. Blank and S. D. Minteer, *Chem. Rev.*, 2022, **122**, 3180–3218.

17 (*a*) G. Hilt, *ChemElectroChem*, 2020, **7**, 395–405; (*b*) N. Sbei, T. Hardwick and N. Ahmed, *ACS Sustainable Chem. Eng.*, 2021, **9**, 6148–6169; (*c*) H. Sheng, A. N. Janes, R. D. Ross, H. Hofstetter, K. Lee, J. R. Schmidt and S. Jin, *Nat. Catal.*, 2022, **5**, 716–725.

18 F. Wang, W. Li, R. Wang, T. Guo, H. Sheng, H.-C. Fu, S. S. Stahl and S. Jin, *Joule*, 2021, **5**, 149–165.

19 K. H. Michael, Z.-M. Su, R. Wang, H. Sheng, W. Li, F. Wang, S. S. Stahl and S. Jin, *J. Am. Chem. Soc.*, 2022, **144**, 22641–22650.

20 J. C. Vantourout, *Org. Process Res. Dev.*, 2021, **25**, 2581–2586.

21 W.-J. Wei, L. Zhan, C.-N. Jiang, H.-T. Tang, Y.-M. Pan, X.-L. Ma and Z.-Y. Mo, *Green Chem.*, 2023, **25**, 928–933.

22 L. C. Lin, Y. C. Li, C. C. Lin and J. R. Hwu, *Chem. Commun.*, 1996, 509–510.

23 J. R. Hwu, S.-C. Tsay, L. C. Lin and L. L. Chueh, *J. Am. Chem. Soc.*, 2001, **123**, 5104–5105.

24 M. Liu, L. Xu and Y. Wei, *Chin. Chem. Lett.*, 2022, **33**, 1559–1562.

25 B. Ohtani, H. Osaki, S.-i. Nishimoto and T. Kagiya, *J. Am. Chem. Soc.*, 1986, **108**, 308–310.

26 V. N. Tsarev, Y. Morioka, J. Caner, Q. Wang, R. Ushimaru, A. Kudo, H. Naka and S. Saito, *Org. Lett.*, 2015, **17**, 2530–2533.

27 L. Neubert, D. Michalik, S. Bahn, S. Imm, H. Neumann, J. Atzrodt, V. Derdau, W. Holla and M. Beller, *J. Am. Chem. Soc.*, 2012, **134**, 12239–12244.

28 J. Jin and D. W. C. MacMillan, *Nature*, 2015, **525**, 87–90.

29 W. Liu, X. Yang, Z.-Z. Zhou and C.-J. Li, *Chem*, 2017, **2**, 688–702.

30 (*a*) A. Erkkila and P. M. Pihko, *J. Org. Chem.*, 2006, **71**, 2538–2541; (*b*) A. Bugarin, K. D. Jones and B. T. Connell, *Chem. Commun.*, 2010, **46**, 1715–1717.

31 (*a*) J. Liu, H. Yi, X. Zhang, C. Liu, R. Liu, G. Zhang and A. Lei, *Chem. Commun.*, 2014, **50**, 7636–7638; (*b*) Y.-F. Liu, P.-Y. Ji, J.-W. Xu, Y.-Q. Hu, Q. Liu, W.-P. Luo and C.-C. Guo, *J. Org. Chem.*, 2017, **82**, 7159–7164.

32 F. Verma, P. Shukla, S. R. Bhardiya, M. Singh, A. Rai and V. K. Rai, *Adv. Synth. Catal.*, 2019, **361**, 1247–1252.

33 (*a*) L. K. M. Chan, D. L. Poole, D. Shen, M. P. Healy and T. J. Donohoe, *Angew. Chem., Int. Ed.*, 2014, **53**, 761–765; (*b*) X. Quan, S. Kerdphon and P. G. Andersson, *Chem. – Eur. J.*, 2015, **21**, 3576–3579; (*c*) Z. Liu, Z. Yang, X. Yu, H. Zhang, B. Yu, Y. Zhao and Z. Liu, *Org. Lett.*, 2017, **19**, 5228–5231.

34 M. Liu, Z. Qiu, L. Tan, R. T. Rashid, S. Chu, Y. Cen, Z. Luo, R. Z. Khaliullin, Z. Mi and C.-J. Li, *ACS Catal.*, 2020, **10**, 6248–6253.

35 B. Emayavaramban, P. Chakraborty, P. Dahiya and B. Sundararaju, *Org. Lett.*, 2022, **24**, 6219–6223.

36 J. Yang, C. Liu, H. Zhou, R. Fan, B. Ma and Z. Li, *Org. Biomol. Chem.*, 2021, **19**, 5572.

37 (*a*) J. Yang, D. Xie, H. Zhou, S. Chen, J. Duan, C. Huo and Z. Li, *Adv. Synth. Catal.*, 2018, **360**, 3471–3476; (*b*) J. Yang, S. Chen, H. Zhou, C. Wu, B. Ma and J. Xiao, *Org. Lett.*, 2018, **20**, 6774–6779.

38 Y.-M. Wang, W.-J. Li, M.-M. Wang, M. Zhang and Z.-H. Zhang, *Catal. Sci. Technol.*, 2023, **13**, 665–674.

39 K. B. Sloan and N. Bodor, *Int. J. Pharm.*, 1982, **12**, 299–313.

40 C. A. Huff, R. D. Cohen, K. D. Dykstra, E. Streckfuss, D. A. DiRocco and S. W. Krska, *J. Org. Chem.*, 2016, **81**, 6980–6987.

41 J. Yang, D. Xie, H. Zhou, S. Chen, J. Duan, C. Huo and Z. Lia, *Adv. Synth. Catal.*, 2018, **360**, 3471–3476.

42 F. Rammal, D. Gao, S. Boujnah, A. A. Hussein, J. Lalevee, A.-C. Gaumont, M.-S. Fabrice and S. Lakhdar, *ACS Catal.*, 2020, **10**, 13710–13717.

43 (*a*) O. Reiser, *Acc. Chem. Res.*, 2016, **49**, 1990–1996; (*b*) J. M. Ahn, T. S. Ratani, K. I. Hannoun, G. C. Fu and J. C. Peters, *J. Am. Chem. Soc.*, 2017, **139**, 12716–12723; (*c*) A. Hazra, M. T. Lee, J. F. Chiu and G. Lalic, *Angew. Chem., Int. Ed.*, 2018, **57**, 5492–5496.

44 A. Sagadevan, V. K. K. Pampana and K. C. Hwang, *Angew. Chem., Int. Ed.*, 2019, **58**, 3838–3842.

45 M. B. Reddy, K. Prasanth and R. Anandhan, *Org. Biomol. Chem.*, 2020, **18**, 9601–9605.