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REVIEW

Recent Advances in the Use of Dimethyl Sulfoxide as a Synthon in Organic Chemistry

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Abstract

Dimethyl sulfoxide (DMSO), as extremely important aprotic polar solvent and reaction medium, has attracted widespread attention from chemists in recent years due to its wide range of uses and the multiple functions it displays in various chemical processes. Especially in the past decade, dimethyl sulfoxide has become increasingly favored as a synthon in organic chemistry, resulting in great progress in this research field. In this context, this review provides a comprehensive summary of the literature on the recent progress in organic synthesis using dimethyl sulfoxide as a synthon, covering all the reports from 1 January 2016 to 11 May 2022. This type of reaction is mainly performed by transferring one or more units of dimethyl sulfoxide, such as oxygen (–O–, =O), methyl ($–CH_3$), methylene ($–CH_2–$), methylidene ($=CH_2$), methine (=CH–), donor of formylation (–CHO), sulfur (–S–), methylthio (–SMe), methyl sulfoxide (–SOMe), donor of methyl thiomethylation ($–CH_2SMe$), or donor of methyl sulfoxide methylation ($–CH_2SOMe$), to the target molecules. At the same time, we hope that this review will stimulate future studies and promote developments in this area.

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Graphical Abstract

Keywords Dimethyl sulfoxide (DMSO) · Aprotic polar solvent · Reaction medium · Synthon · Progress

Abbreviations

DMSO	Dimethyl sulfoxide
DMS	Dimethyl sulfide
CuI	Cuprous iodide
$CuBr_2$	Copper(II) bromide
TEMPO	2,2,6,6-Tetramethylpiperidine-1-oxyl
AgTFA	Silver trifluoroacetate
$(COCl)_2$	Carbonyl chloride
CH_3CN	Acetonitrile
$CHCl_3$	Trichloromethane
CH_2Cl_2	Dichloromethane
$FeCl_2$	Ferrous chloride
H_2O_2	Hydrogen peroxide
$TMSN_3$	Trimethylsilyl azide
$FeSO_4$	Ferrous sulfate
$K_2S_2O_8$	Potassium persulfate
DABCO	1,4-Diazabicyclo[2.2.2]octane
^{t}BuONa	Sodium *tert*-butoxide
TDMSOI	Trideuteromethyl sulfoxonium iodide
TMSOI	Trimethyl sulfoxonium iodide
DMSO-d_6	(Methyl sulfoxide)-d_6
^{t}BuOK	Potassium *tert*-butoxide
H_3PO_4	Phosphoric acid
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
Tf_2O	Trifluoromethanesulfonic anhydride

AcCl	Acetyl chloride
$Pd(OAc)_2$	Palladium acetate
$KHSO_5$	Potassium monopersulfate triple salt
$Pd(dba)_2$	Bis(dibenzylideneacetone)palladium
DABSO	Bis(sulfur dioxide)-1,4-diazabicyclo[2.2.2]octane adduct
THIQ	1,2,3,4-Tetrahydroisoquinoline
TMEDA	Trimethylethylenediamine
TsOH	4-Methylbenzenesulfonic acid
TFA	Trifluoroacetic acid
TBHP	*tert*-Butyl hydroperoxide
$Zn(OTf)_2$	Zinc trifluoromethanesulfonate
BHT	Butylated hydroxytoluene
$PhI(OAc)_2$	(Diacetoxyiodo)benzene
NH_4OAc	Ammonium acetate
NBS	*N*-Bromosuccinimide

1 Introduction

Dimethyl sulfoxide (DMSO) has been widely used as an important high-polarity reaction medium in organic synthetic chemistry due to its good thermal stability, high boiling point, low price, and low toxicity [1–6]. In terms of molecular structure, it is composed of two hydrophobic methyl groups and one strongly polar sulfoxide group, which gives DMSO excellent properties [7, 8]. In addition to be widely used as a solvent and reaction reagent, DMSO is also valuable in pharmaceuticals [9, 10], pesticides [11, 12], materials [13], analysis [14], etc. In the pharmaceutical industry, DMSO is used as a raw material for drugs and their carriers, and is often added to drugs as the active ingredient in painkillers [15]. At the same time, DMSO can be used as an additive for pesticides by taking advantage of its carrier properties. The addition of small amounts of DMSO to certain pesticides helps the pesticide penetrate into the plant to improve its efficacy [16]. DMSO was one of the first transdermal penetration enhancers used for its ability to denature proteins within skin keratinocytes, thereby removing keratin-layer lipids and lipoproteins [17]. In addition, DMSO exhibits good solubility for various resins, and can be used as a solubilizer in some lacquers [18]. More importantly, DMSO is used as a paint remover. By adding alkali to DMSO, various kinds of varnishes including epoxy resins can be removed effectively [19]. These results indicate that DMSO is an efficient and highly versatile aprotic polar solvent with various current applications in everyday life.

DMSO plays the dual role of reaction solvent and reaction reagent in chemical reactions, and some unrealizable reactions can be carried out smoothly in DMSO. It is also used as a general reagent for many well-known reactions, such as nucleophilic substitution [20, 21], elimination [22–24], electrophilic [25], and substitution reactions [26]. In conclusion, DMSO has opened up a new pathway in chemical preparation by which many new substances have been prepared, and is of great significance in theory and practice as a new means of synthesizing substrates via

chemical reactions. To date, a few reports have systematically summarized the synthetic transformations using fragments of dimethyl sulfoxide as building blocks [27–30]. We focus instead on a more comprehensive and updated review of DMSO as a synthon, based on a review published by Magolan in 2016 and summarizing the latest reports in the field from 1 January 2016 to 11 May 2022.

The current review presents the latest research progress on the use of dimethyl sulfoxide as a synthon by transferring one or more of its units after binding to target molecules. The notable uses described in this review are: (i) as an oxygen source (–O–, =O); (ii) as carbon sources, involving methyl (–CH_3), methylene (–CH_2–), methylidene (=CH_2), methine (=CH–), and donor of formylation (–CHO); (iii) as a sulfur source (–S–); (iv) as a methylthio source (–SMe), methyl sulfoxide source (–SOMe), methyl thiomethylation donor (–CH_2SMe), and methyl sulfoxide methylation donor (–CH_2SOMe) (Fig. 1). Moreover, typical reactions, selected examples, reaction mechanisms, and potential applications in synthesis are discussed. It is worth noting that this review covers various synthetic methods that have been recently reviewed elsewhere and which will thus not be discussed in detail.

2 As Oxygen Source (–O– and =O)

In 2016, Jiao's group reported an efficient strategy for preparation of substituted catechols via I_2-catalyzed oxidation of cheap and readily available cyclohexanones [31]. In that work, the protocol was made greener and more practical by using DMSO as oxygen source, oxidant, and solvent. 3,3′,4,4′-Tetrahydroxybiphenyl **2** is a very useful drug molecule and is widely used as a transition-metal ligand. The conventional method to obtain it is based on Pd-catalyzed Suzuki coupling followed by addition of boron tribromide for cleavage of methyl ether. In contrast, it can be easily obtained in higher yields from the readily marketed 4,4′-bicyclohexanone **1** and DMSO (Scheme 1a). Also, cholesterol derivative **3** as well as norethindrone **5** can convert smoothly to catechol product **4** (Scheme 1b) and α-carbonylation product **6** (Scheme 1c) under standard conditions. Interesting mechanistic studies, kinetic profile, and density functional theory (DFT) calculations provided valuable information

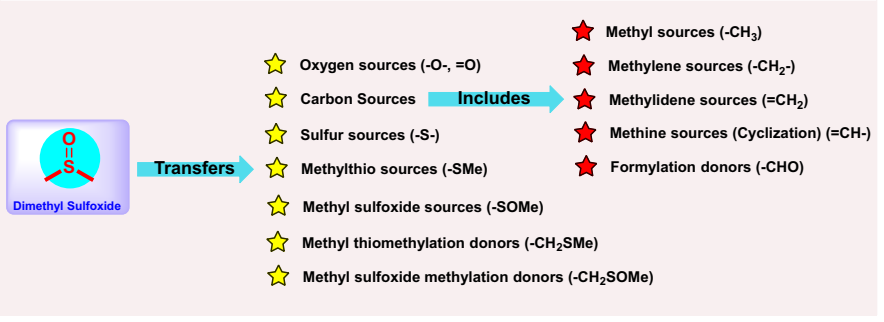
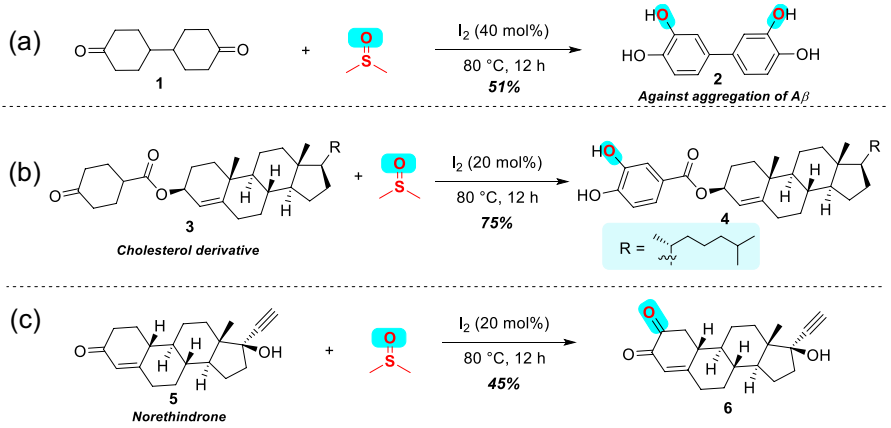


Fig. 1 Transfers of DMSO in organic synthesis

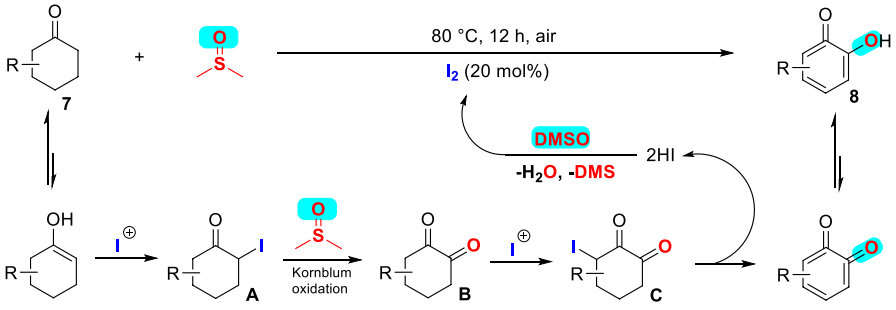


Scheme 1 Synthesis using DMSO as oxygen source, oxidant, and solvent [31]

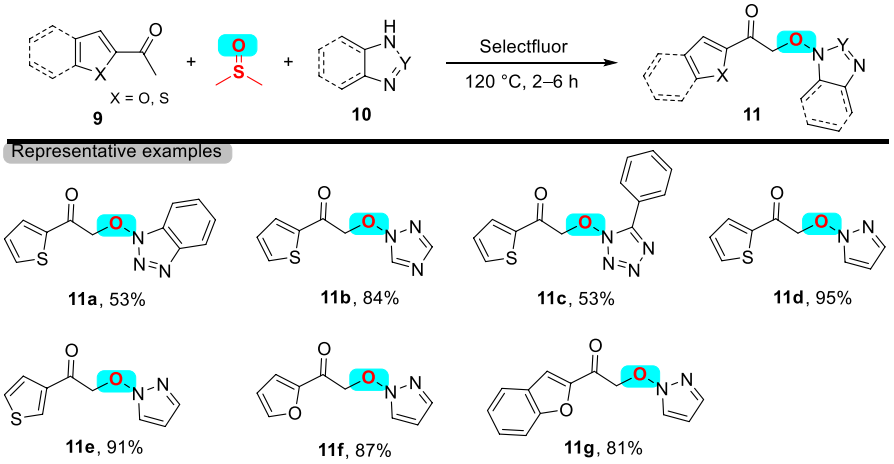
on the reaction mechanism. Cyclohexanones were subjected to electrophilic iodination, Kornblum oxidation, HI elimination, and isomerization to give the final catechol products (Scheme 2). The success of this protocol provides a viable pathway for the modification of bioactive compounds.

The same year, Wang and colleagues disclosed a procedure for synthesis of β-amino ketones **11** from acetyl-containing five-membered heterocycles **9** with azoles **10** under selective fluorine promotion using dimethyl sulfoxide as oxygen source and solvent (Scheme 2) [32]. Meanwhile, the strategy exhibited excellent substrate adaptability and functional group tolerance, thus providing an attractive addition to the traditional Mannich-type reaction (Scheme 3).

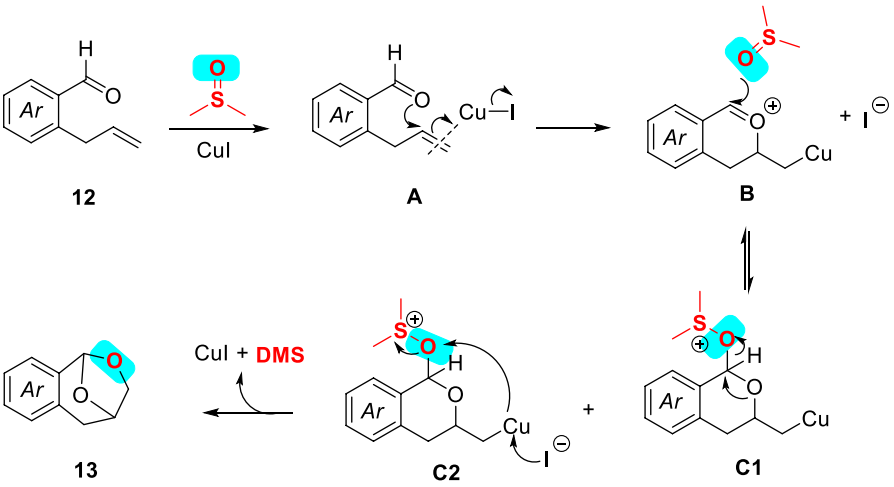
A CuI/DMSO-promoted method for synthesis of benzobicyclo[3.2.1]octanes **13** using *o*-carbonyl allylbenzenes **12** as starting materials was developed by Chang's group in 2017 (Scheme 4) [33]. Among them, the structures of some compounds **13** were confirmed by X-ray crystallographic analysis, confirming that these critical products have the core framework structure of benzofused dioxabicyclo[3.2.1] octane.



Scheme 2 The proposed mechanism [31]

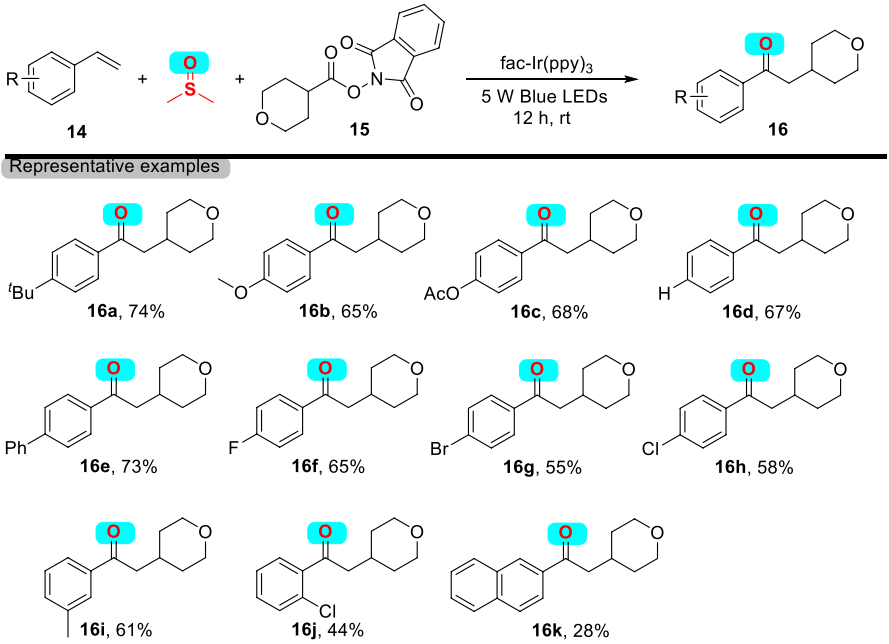


Scheme 3 Synthesis of β-amino ketones **11** using 2′-heterocyclic ketones and azoles [32]



Scheme 4 Plausible mechanism for synthesis of benzobicyclo[3.2.1]octanes **13** by using *o*-carbonyl allylbenzenes [33]

In 2018, Glorius et al. described a visible-light-mediated synthesis of α-alkyl acetophenones **16** through reaction of styrenes **14** and *N*-(acyloxy)phthalimides **15** in good yields (Scheme 5) [34]. The protocol has the remarkable features of simple operation, mild conditions, high efficiency, and low photocatalyst loading. It is worth mentioning that the *para*-position of styrenes tolerates various electron-donating and electron-withdrawing functional groups very well. This synthetic method is also applicable for some biologically active compounds such as deoxycholic acid, gemfibrozil, and Boc-protected γ-aminobutyric acid.

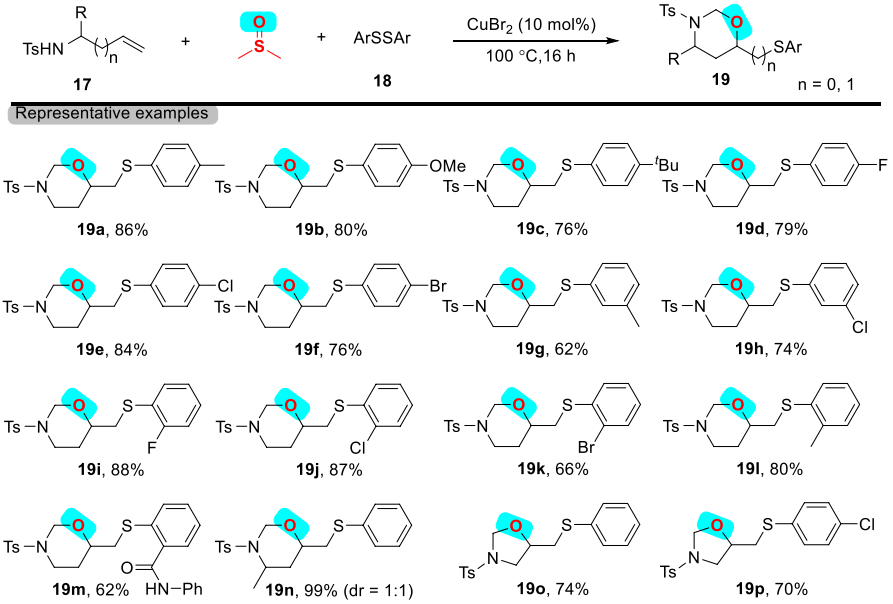


Scheme 5 Synthesis of α-alkyl-acetophenones **16** by oxidative alkylation reaction [34]

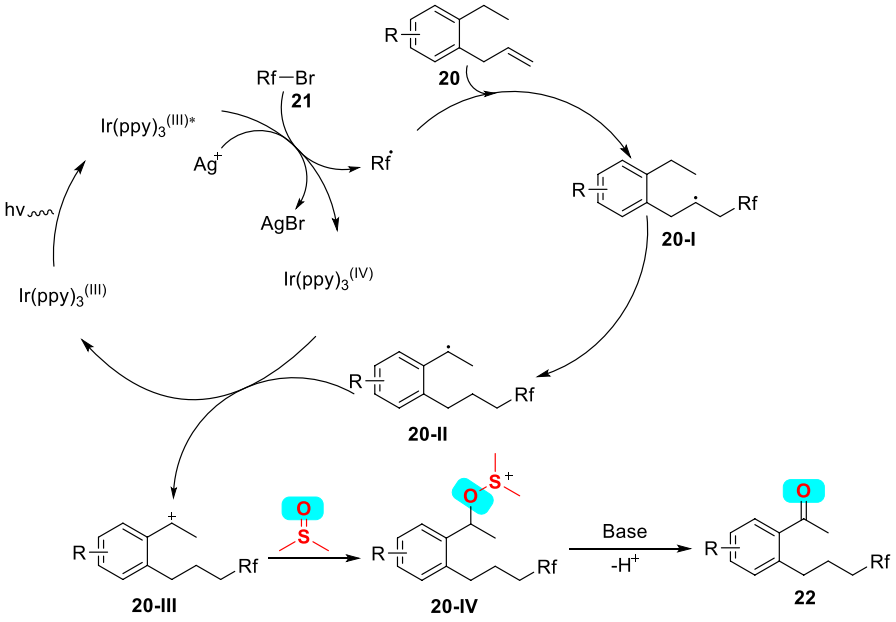
After that, Zhong's group developed a novel route for synthesis of sulfonated 1,3-oxazolidines and oxazolidines **19** with high selectivity for the first time (Scheme 6) [35]. The protocol is a thia-aza-Prins cyclization of alkenylamines **17** and disulfides **18** with DMSO as reaction medium via formaldehyde substitution. Using this efficient and inexpensive catalytic system, various useful oxazolidines can be readily prepared under air. Also, disulfides have many advantages as a source of sulfited reagents, such as adjustable stability, remarkable biocompatibility, and ready availability.

In 2019, Ma et al. described a procedure for obtaining 1,6-fluoroalkyl ketones **22** by visible-light-mediated highly selective activation of alkenes **20** at room temperature for the first time (Scheme 7) [36]. The attractive feature of this protocol is the Kornblum reaction of remote-benzyl C–H bond activation by 1,5-H transfer of highly controlled olefin fluorination **21** sites using DMSO as a green oxygen source and solvent. In addition, no target product was detected when adding 4 equiv. of TEMPO to the reaction system. Also, free radical adducts were detected by high-resolution mass spectrometry (HRMS) when using this strategy, indicating that the process is a free radical reaction.

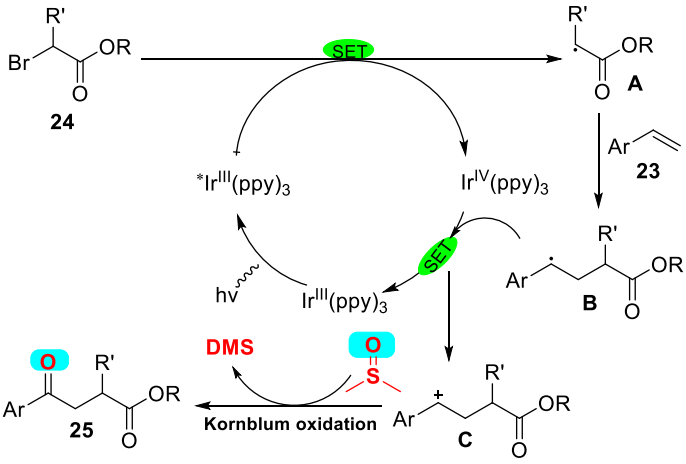
On the other hand, Liu et al. revealed a similar process by using a photocatalytic strategy (Scheme 8). Various γ-ketoesters **25** were obtained in excellent yields by oxidative coupling reactions of styrenes **23** with bromocarboxylates **24** when using DMSO as terminal oxidant and solvent [37]. Considering the practicality of the protocol, scale-up to tenfold gram level also proceeded smoothly under standard conditions, with γ-ketoester **25a** being obtained in 71% isolation yield.



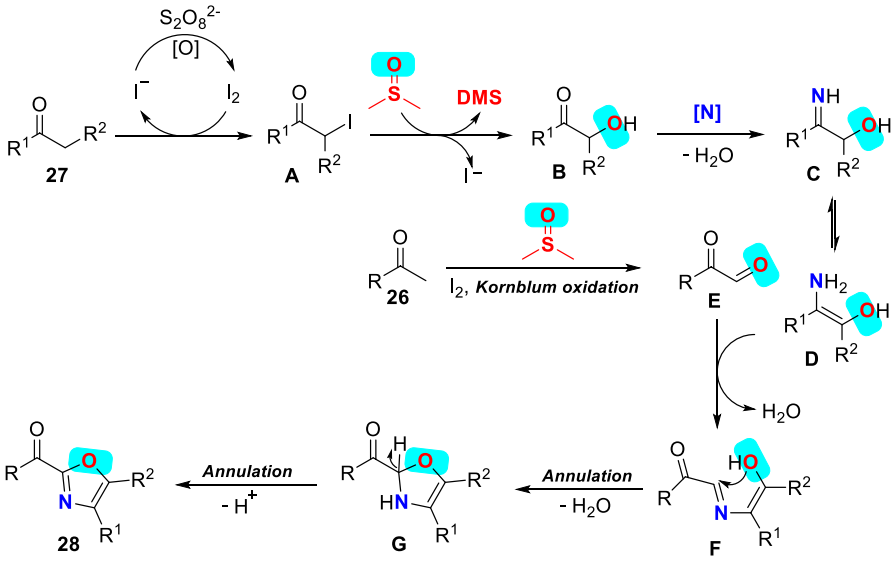
Scheme 6 Copper-catalyzed thia-aza-Prins cyclization for synthesis of 1,3-oxazinanes **19** [35]



Scheme 7 Plausible mechanism for synthesis of 1,6-fluoroalkyl ketones **22** [36]



Scheme 8 Plausible mechanism for synthesis of γ-ketoesters **25** [37]



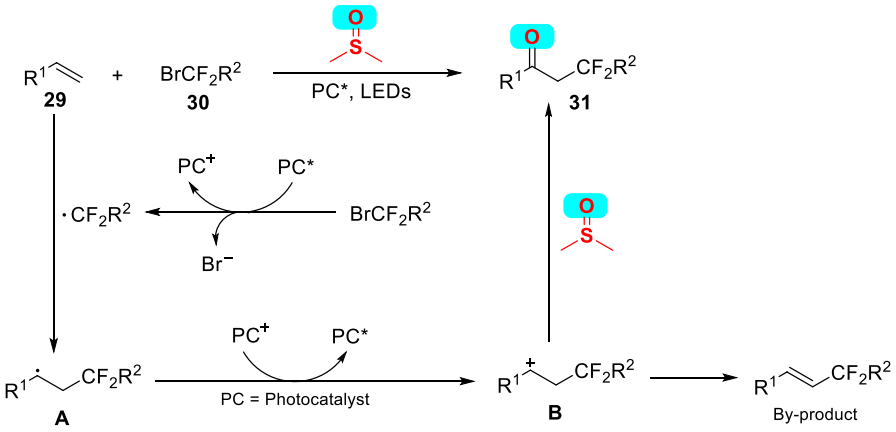
Scheme 9 Plausible mechanism for synthesis of substituted oxazoles **28** [38]

Additionally, Guo and coworkers reported four-component cyclization of ketones **26**–**27**, ammonium, and DMSO for synthesis of substituted oxazoles **28** (Scheme 9) [38]. This protocol provided 22 examples of 2,4-disubstituted oxazoles in excellent yields when using DMSO as cyclization oxygen source. 2,4,5-Trisubstituted oxazoles can also be obtained by this method via cross-condensation reaction of methyl and nonmethyl ketones. The successful implementation of the protocol on gram scale confirms its potential utility in organic synthesis.

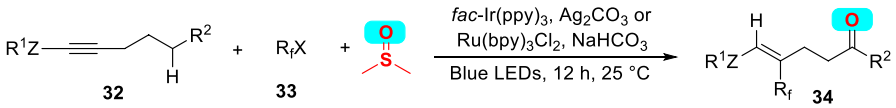
Similarly, Tang et al. revealed a photoredox-catalyzed cascade reaction of styrenes **29** and bromodifluoro compounds **30** to synthesize difluorinated ketones **31** (Scheme 10) [39]. AgTFA as an additive gave significantly higher yields compared with other additives for this reaction. Meanwhile, the protocol offers many advantages such as mild conditions, simple operation, and efficient regioselectivity.

In 2020, Li et al. revealed a novel visible-light-induced fluoroalkylation **33** of remote alkynes **32** in high yields to obtain various ε-oxygenated fluoroalkylated (*Z*)-alkenes **34** (Scheme 11) [40]. The protocol enables remote oxygen alkylation of heterocyclic hydrocarbons using DMSO as green oxygen source. Replacement of DMSO with H_2O as oxygen source also enabled remote hydroxytrifluoromethylation. Additionally, the experimental results of the mechanism studies indicated that DMSO can act as an oxygen donor for the formation of carbonyl groups.

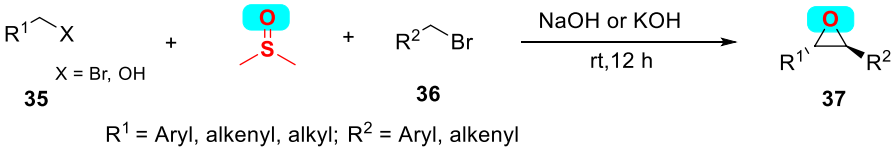
In the same year, Liu's group developed an interesting procedure for preparation of 1,2-disubstituted epoxides **37** from alcohols or alkyl bromides **35** and benzyl bromides **36** at room temperature (Scheme 12) [41]. In this reaction, dimethyl sulfide



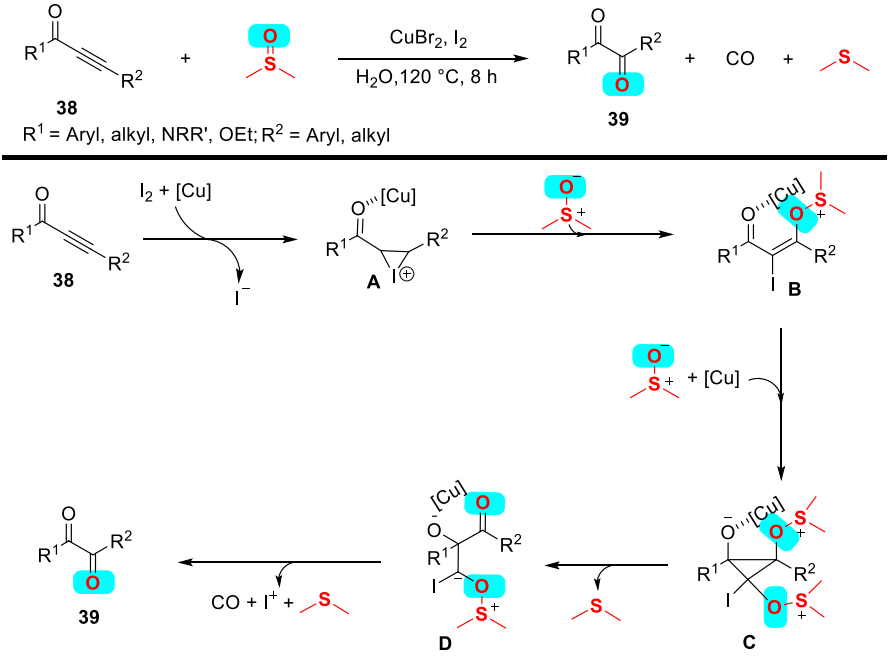
Scheme 10 Alkene oxydifluoroalkylation [39]



Scheme 11 Synthesis of complex fluoroalkylated (*Z*)-alkenes **34** [40]



Scheme 12 Synthesis of 1,2-disubstituted epoxides **37** by Kornblum oxidation reaction [41]



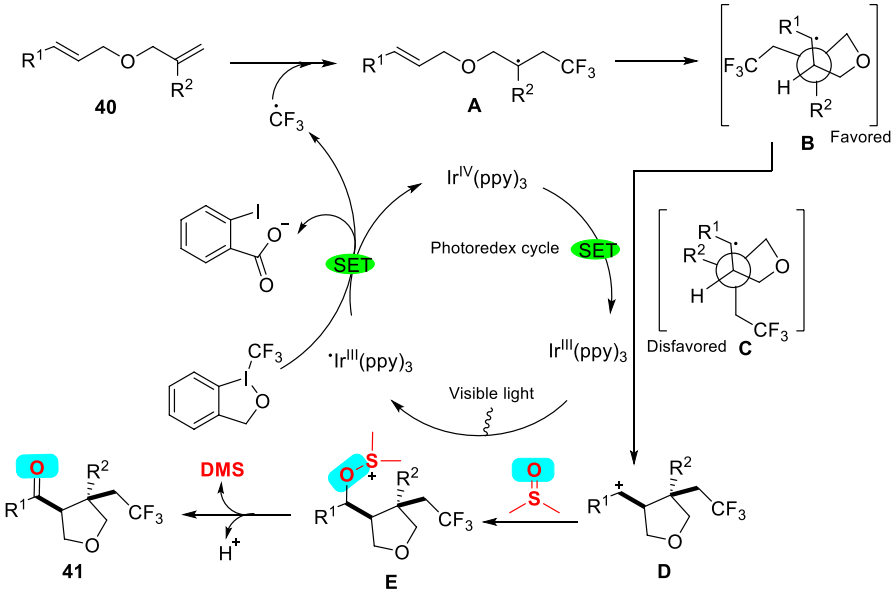
Scheme 13 Possible mechanisms for synthesis of various 1,2-dicarbonyl compounds **39** [42]

produced by oxidation of DMSO formed substituted dimethyl sulfides in situ, which involved the Corey–Chaykovsky epoxidation reaction. The results of four sets of control experiments further indicated that Kornblum oxidation was the decisive step in the domino reaction, and the formation of sulfonium salt is likely to be reversible. The successful preparation of a series of useful epoxides will provide an efficient pathway in this field.

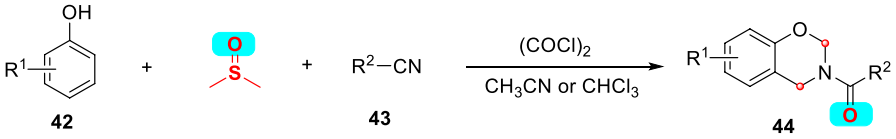
Subsequently, Li's group developed a novel reaction to prepare various 1,2-dicarbonyl compounds **39** by oxidative tandem reaction using 2-alkynyl carbonyl compounds **38** and dimethyl sulfoxide (Scheme 13) [42]. The significant advantages of this protocol are high chemoselectivity, wide range of substrate adaptability, and good tolerance of functional groups. This would provide an alternative activation mode for 1,2-dicarbonyl unit coupling reaction.

Immediately thereafter, an interesting visible-light-catalyzed oxidation of 1,6-dienes for synthesis of CF_3-containing five-membered heterocycles was reported by Zhu et al. (Scheme 14) [43]. This mild protocol produced various tetrahydropyrrole and tetrahydrofuran compounds containing trifluoromethyl in good yields with excellent diastereoselectivity. Two gram-scale syntheses were successfully achieved at the same time, further demonstrating the practicality of this synthesis protocol.

In 2021, Liang et al. reported a synthetic method to obtain 34 *N*-acylbenzoxazoles **44** in moderate to good yields by three-component tandem cyclization reaction of phenols **42** with nitriles **43** and dimethyl sulfoxide using catalytic equivalents of $(COCl)_2$ (Scheme 15) [44]. The 6 equiv. of DMSO in this cyclization system not



Scheme 14 Remote oxidative cyclization of 1,6-dienes [43]



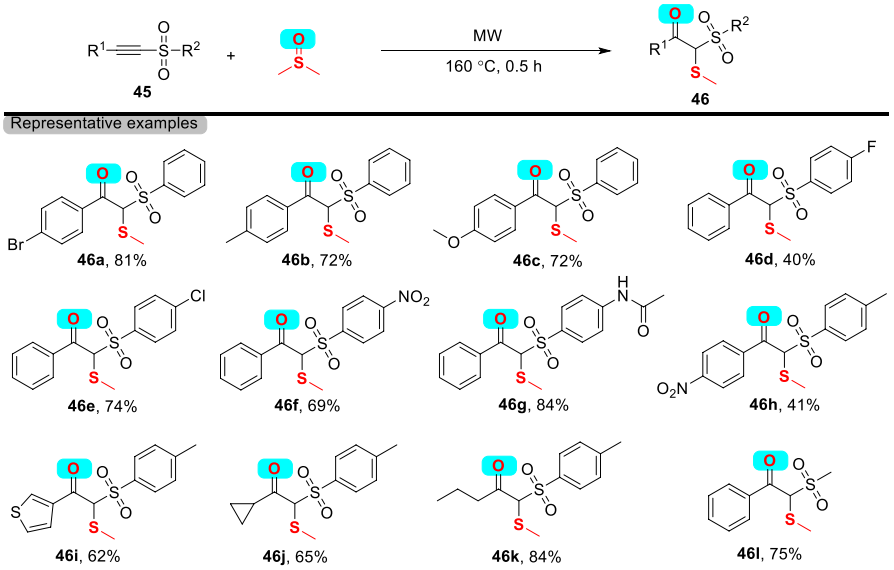
Scheme 15 Preparation of *N*-acylbenzoxazines **44** [44]

only replace formaldehyde as an oxygen source, but also provide two methylene sources.

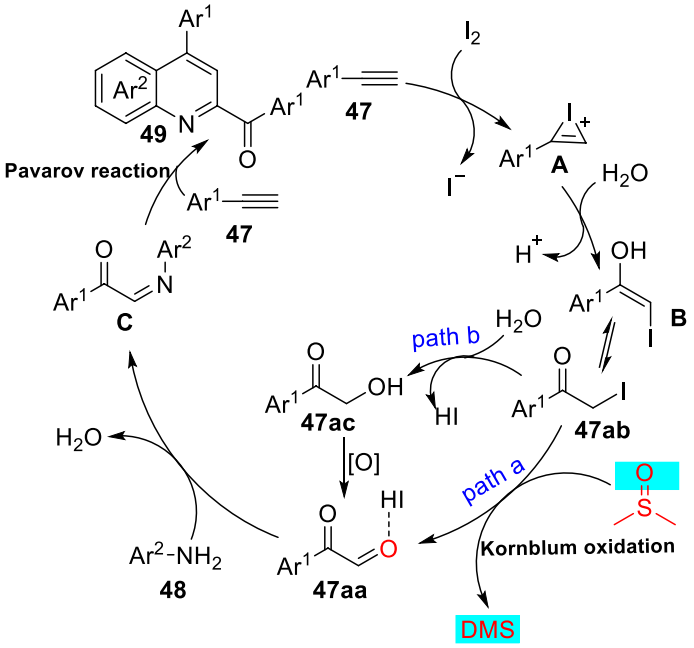
After that, Xu's group reported efficient synthesis of β-keto thiosulfones **46** using easily available ethylsulfonyl raw materials **45** and DMSO (Scheme 16) [45]. This bifunctionalization method is characterized by simple operation, readily available raw materials, and the absence of other additives. Nine sets of control experiments allowed better verification of the reaction mechanism.

Then, Wu's group reported an interesting I_2-mediated Povarov reaction for synthesis of various 2,4-substituted quinolines **49** (Scheme 17) [46]. In this work, oxidative carbonylation of C(*sp*)–H of arylacetylenes followed by [4+2] cycloaddition was achieved by using common arylacetylenes **47** and anilines **48** as starting materials. This discovery significantly broadens the novel diene precursors in the Povarov reaction for the construction of more nitrogen-containing heterocycles.

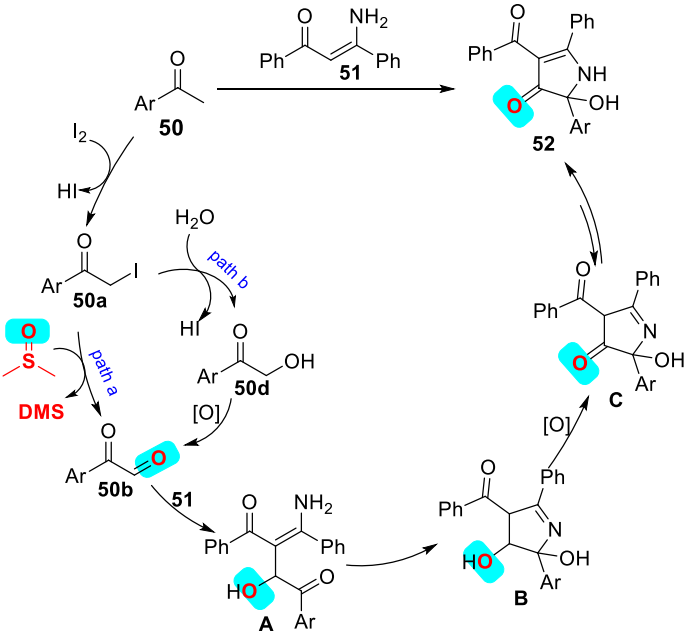
Immediately after, Wu's group went on to develop a new cyclization reaction of aryl methyl ketones **50** with enaminone **51** using the I_2/DMSO system as a simple method for synthesis of various 2-hydroxy-pyrrol-3(2*H*)-ones **52** (Scheme 18) [47].



Scheme 16 Preparation of β-keto thiosulfones [45]



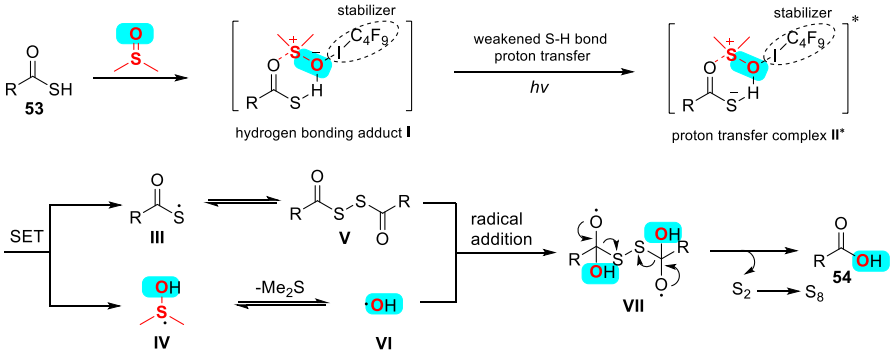
Scheme 17 Synthesis of 2,4-substituted quinolones **49** [46]



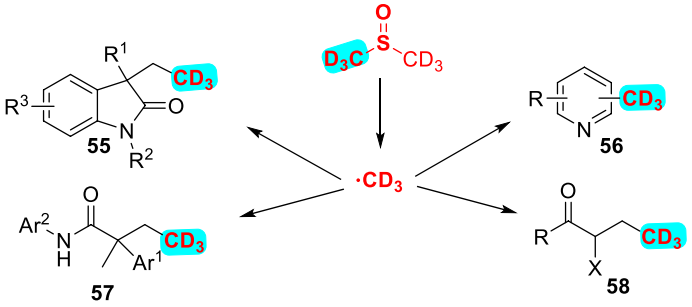
Scheme 18 Proposed mechanism for synthesis of 2-hydroxy-pyrrol-3(2*H*)-ones **52** [47]

The purification of products **52** was achieved simply by washing with CH_2Cl_2 solvent, which saves more time as well as avoiding traditional chromatographic methods. The drawback of this protocol is that the range of substrates for enaminones is too narrow, and it is unknown whether other substituents can be adapted to this reaction.

In 2022, Liang et al. revealed a visible-light-promoted conversion of thioacids **53** to carboxylic acids **54** via substitution protocols, obtaining various carboxylic acids **54** in yields exceeding 90% and up to 99% (Scheme 19) [48]. DMSO plays the role



Scheme 19 Proposed mechanism for synthesis of carboxylic acids **54** [48]



Scheme 20 Deuterated methylation reactions [51]

of solvent, initiator, and oxygen source in this efficient transformation. It is worth mentioning that a wide variety of alkyl thioacids can also be converted smoothly to corresponding alkyl carboxylic acids in excellent yields. In addition, this plausible reaction mechanism demonstrates the good potential of hydrogen-bonding adducts in atomic substitution reactions.

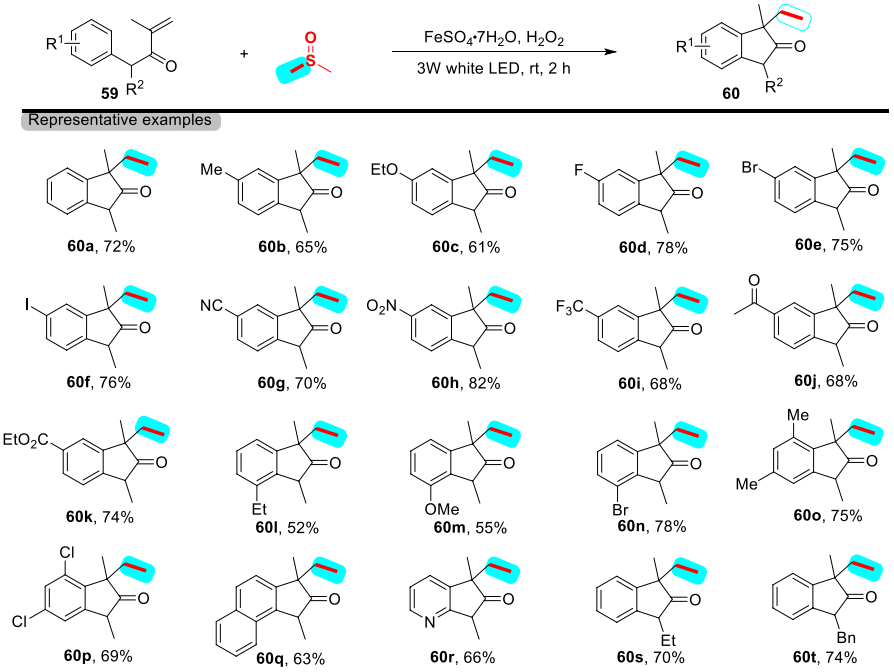
3 As Carbon Source (–CH_3, –CH_2–, =CH_2, =CH–, and –CHO)

3.1 Methyl Donor (–CH_3)

Methyl group is one of the more prevalent functional groups in many biologically active molecules. Whereas methylation is particularly important in the synthesis of some drugs, often the pharmacological properties of some drugs can be positively influenced depending on the introduction of methyl groups [49, 50]. The usage of dimethyl sulfoxide as the methyl source is characterized by low toxicity, low cost, and simple operation. The following is a summary of the use of dimethyl sulfoxide as a methylation reagent from 2016 to 2021.

In 2016, Antonchick and coworkers reported a method for synthesis of labeled heterocycles and trideuterated compounds **55**–**58** by using deuterated dimethyl sulfoxide as deuterated methyl reagent at room temperature (Scheme 20) [51]. The reaction conditions were screened accordingly, and $FeCl_2$ was found to significantly increase the reaction yield compared with other iron salts. The successful conversion of this strategy under free radical reaction conditions can be applied to many biomolecules that require selective deuteration.

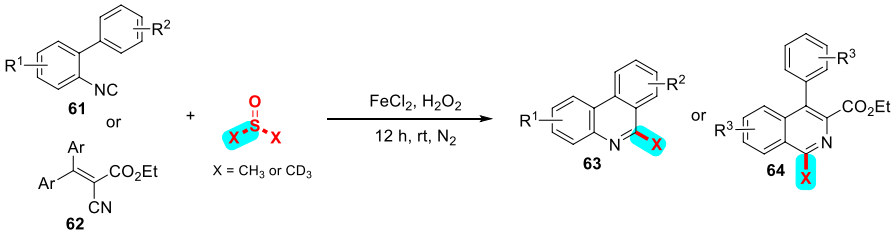
In 2017, Wang's group reported a visible-light-promoted reaction route for synthesis of 3-ethyl-3-methyl oxindoles **60** (Scheme 21) [52]. Various *N*-arylacrylamides **59** were successfully used in the cascade reaction with dimethyl sulfoxide catalyzed by iron salts to obtain corresponding methyl oxindoles derivatives in favorable yields. A variety of *N*-arylacrylamides with different electronic groups and substitution patterns were investigated, showing good results. At the same time, the method offers many advantages such as the simplicity of the reaction process, the versatility of the products, and the mildness of the reaction conditions.



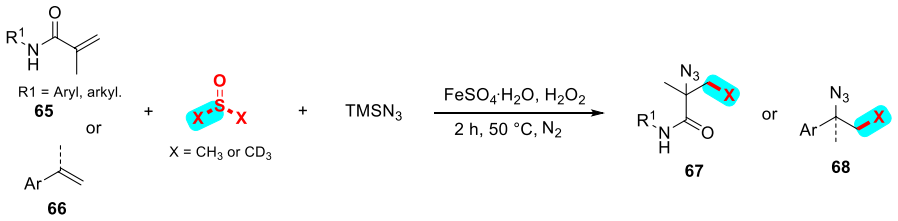
Scheme 21 Synthesis by methylation of *N*-arylacrylamides [52]

In the same year, Zhang et al. developed radical methylation or trideuterium methylation reaction procedures for selective access to phenanthridines **63** and isoquinolines **64** via cyclization of various 2-isocyano-1,1′-biphenyls **61** or ethyl 2-cyano-3,3-diphenylacrylates **62** with dimethyl sulfoxide (Scheme 22) [53]. This protocol is similar to previously described reaction conditions, which also require catalysis by iron salts and promotion of H_2O_2 to proceed smoothly at room temperature. The methylation and trideuteromethylation can be achieved by using dimethyl sulfoxide, thus providing an option for labeling experiments.

Then, in 2018, Zhang et al. further reported a similar free radical methylation reaction (Scheme 23) [54]. Different from the previous reaction, this reaction is based on the three-component cascade of radically active alkenes **65**–**66**



Scheme 22 Preparation of phenanthridines or isoquinolines [53]



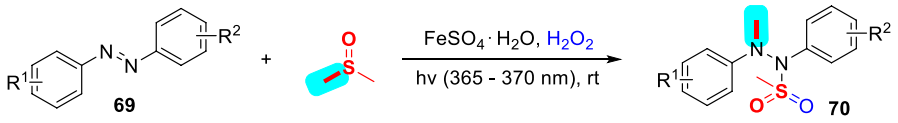
Scheme 23 Preparation of azide-methylated and azide-trideuterated methylated derivatives [54]

with $TMSN_3$ and dimethyl sulfoxide, achieving radical azide methylation of various alkenes. The introduction of azido and methyl groups can lead to conversion to related amine derivatives and heterocyclic compounds **67**–**68**. This three-component method offers an attractive option for preparation of valuable organic azides owing to its advantages of low cost, mildness, and simple operation. At the same time, the protocol can be scaled up, and the resulting products can undergo other useful transformations.

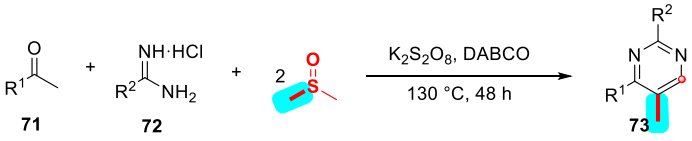
In 2018, Wang et al. described a procedure for *N*-methylation and *N*-sulfonylation of azobenzenes **69** under $FeSO_4{\cdot}7H_2O/H_2O_2$ and photocatalytic conditions, obtaining various symmetrical and asymmetrical *N*′-methyl-*N*,*N*′-diphenylmethanesulfono hydrazides **70** in moderate to good yields (Scheme 24) [55]. It is worth mentioning that the reaction obtained the target products **70** via light-induced bifunctionalization by radical addition to N=N of the azo compound.

Wu et al. developed a four-component tandem cyclization reaction of 5-methyl pyrimidine derivatives **73** via $K_2S_2O_8$-mediated methyl ketones **71**, amidine hydrochlorides **72**, and dimethyl sulfoxide (Scheme 25) [56]. Methyl ketones and amidine hydrochlorides are cheap and readily available as starting materials, while dimethyl sulfoxide acts as a dual synthesis substrate, i.e., as a methyl source and a methyl precursor. The advantages of this protocol are simplicity of operation, good functional group tolerance, and wide substrate range.

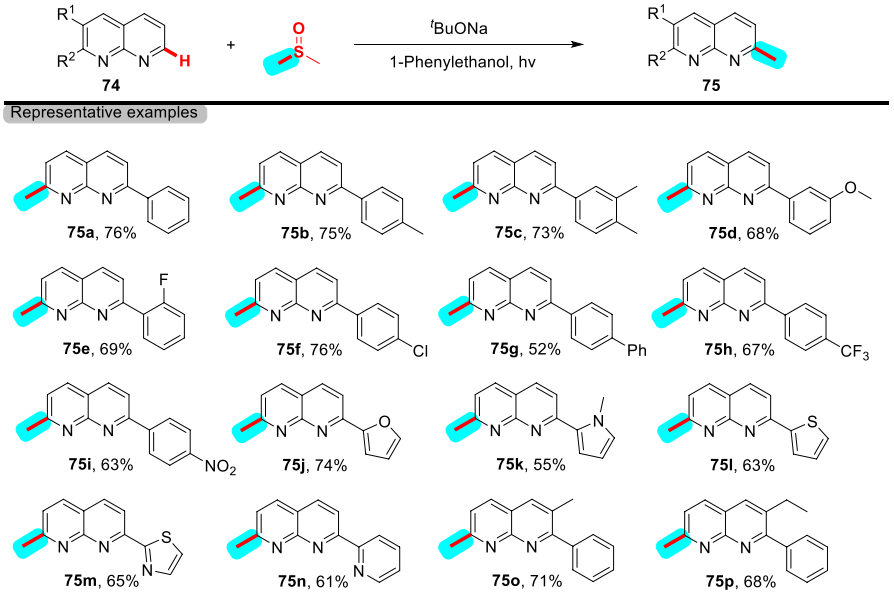
In 2019, Chen's group revealed a practical pathway for straightforward α-methylation of 1,8-naphthyridines **74** under base promotion to obtain various important 2-methyl-1,8-naphthyridine compounds **75** in good yields (Scheme 26)



Scheme 24 Preparation of *N*′-methyl-*N*,*N*′-diphenylmethanesulfonohydrazides [55]



Scheme 25 Preparation of 5-methyl pyrimidines [56]

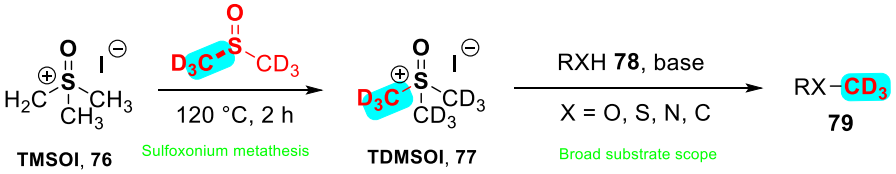


Scheme 26 Preparation of 2-methyl-1,8-naphthyridines [57]

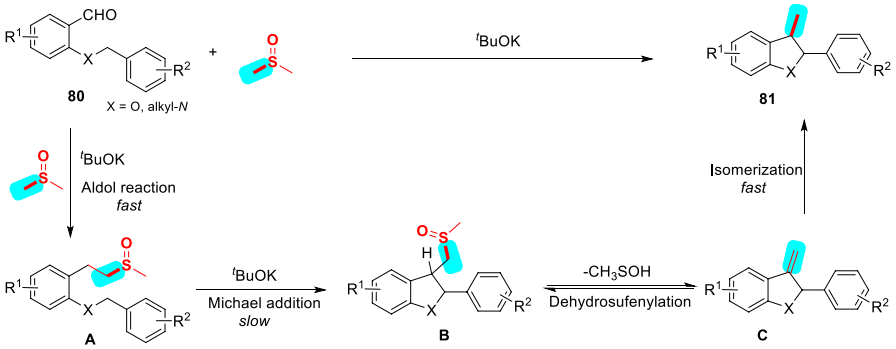
[57]. This methylation method shows good chemoselectivity as well as good functional group tolerance. Meanwhile, the 2-methyl of the *N*-heterocycles as a single-carbon bridge is a good reactive site to obtain various (*E*)-2-alkenylazepines and imidazole-fused *N*-heterocyclic compounds in moderate to good yields.

In the same year, Wang et al. reported one-pot synthesis of the trideuterated reagent TDMSOI **77** by heating a mixture of TMSOI **76** and DMSO-d_6 for thiosubstitution (Scheme 27) [58]. The obtained new reagent TDMSOI can then participate in trideuterated methylation reactions with phenols, thiophenols, acidic amines, and enolizable methylene units **78** to synthesize trideuterated methylation products **79** with higher yields and high deuteration rates. This new protocol can remove the need for the expensive CD_3I and $(CD_3)_2SO_4$ reagents involved in some tridemethylation reactions.

Subsequently, Wang's group described synthesis of disubstituted 2-arylindoles and benzofurans **81** by *N*- or *O*-benzylbenzaldehydes **80** with dimethyl sulfoxide in good yields on the basis of promotion of *t*BuOK (Scheme 28) [59]. The suggested



Scheme 27 Synthesis of tridemethylation reagents [58]

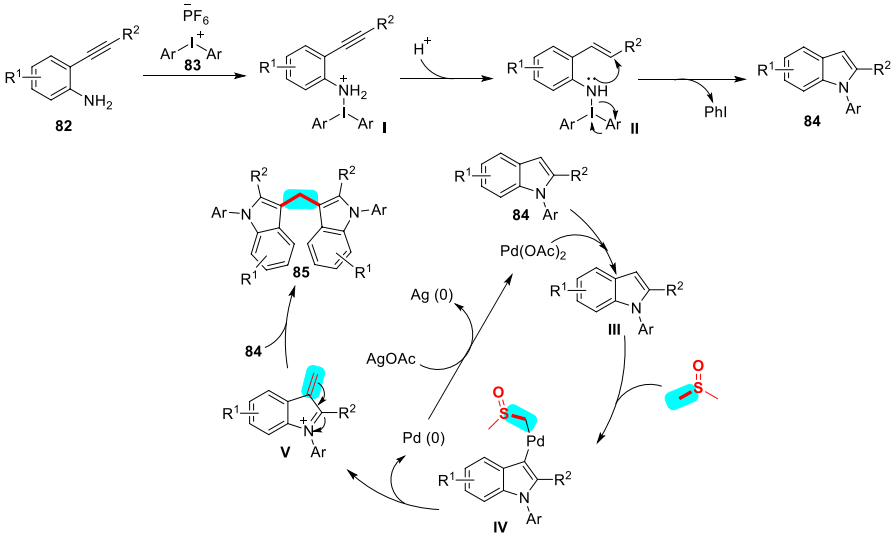


Scheme 28 Preparation of disubstituted 2-arylindoles and benzofurans [59]

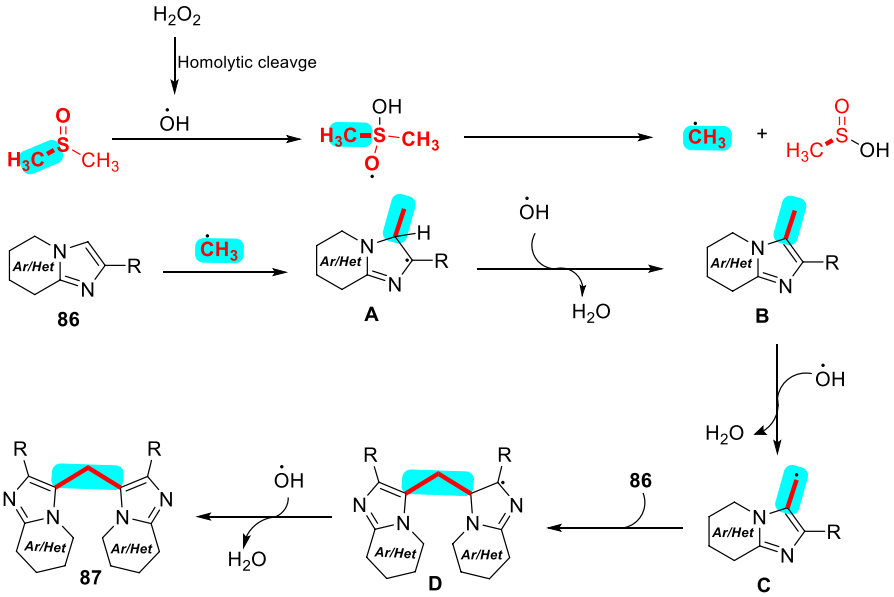
reaction mechanism relies on a four-step sequence including aldol condensation, Michael addition, dehydrosulfenation reaction, and isomerization reaction. This protocol allowed short-time access to various 2-aryl-3-methylindoles and benzofurans under mild conditions.

3.2 Methylene (–CH_2–)

In 2016, Cui's group reported a convenient route to synthesize 1,2-disubstituted indoles **84** from readily available 2-alkylanilines **82** and diaryliodonium salts **83** [60]. Meanwhile, **84** can be further converted to bis(1,2-diphenyl-1*H*-indol-3-yl) methanes **85** under palladium catalyst synergistic with dimethyl sulfoxide conditions (Scheme 29). The simple protocol provided 28 indole derivatives in up to



Scheme 29 Plausible mechanisms for preparation of indole derivatives [60]



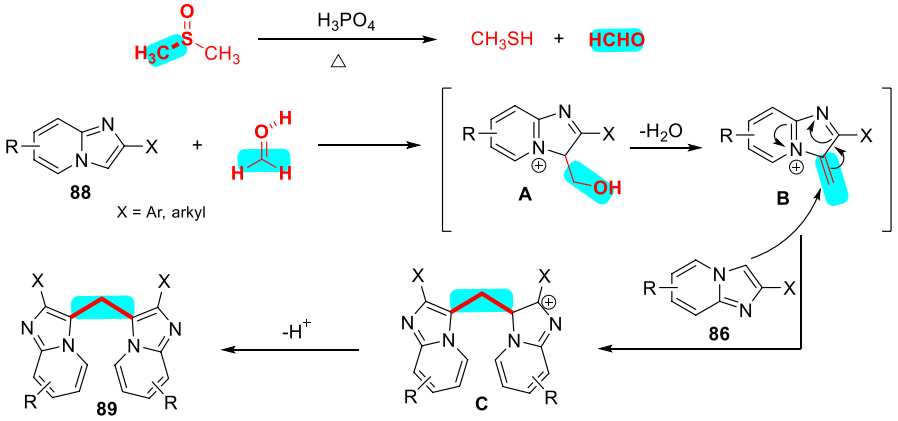
Scheme 30 Plausible mechanisms for preparation of 3,3′-bisimidazopyridinylmethanes [61]

90% yield under efficient conditions. The results of isotopic labeling experiments indicated that the methylene in 3,3′-diindolylmethane was sourced from dimethyl sulfoxide.

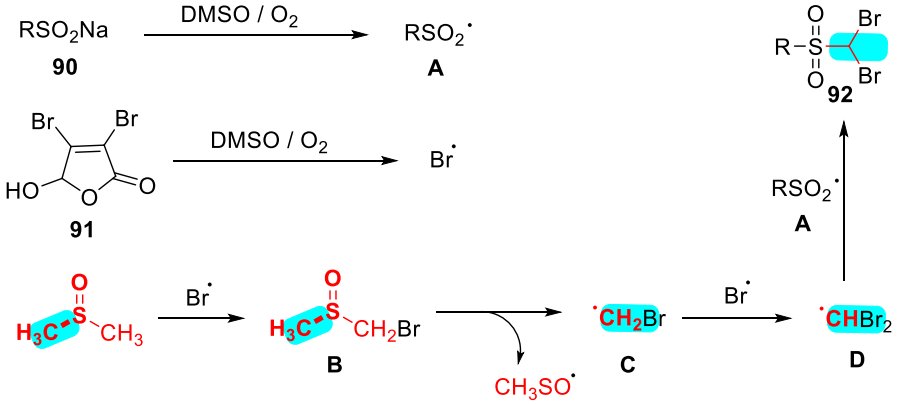
In the same year, Yadav's group revealed a new route for efficient synthesis of various 3,3′-bisimidazolopyridylmethanes **87** by functionalizing imidazo[1,2-*a*] pyridines **86** with dimethyl sulfoxide using H_2O_2 as oxidant (Scheme 30) [61]. The protocol identified a reliable possible radical mechanism through radical capture experiments, labeling experiments, and electrospray ionization mass spectrometry (ESI–MS) analysis experiments. The mechanistic results showed that H_2O_2 underwent C(sp^2)–H/C(sp^3)-H activation in a cascade mode to provide symmetrical and asymmetrical target products in good yields.

Interestingly, in the same year, Sun's group reported a procedure to obtain symmetric methylene-bridged imidazole heterocycles **89** similar to the type of Yadav's group [62]. The method used H_3PO_4 as promoter for efficient regioselective methylenation of imidazole heterocycles **88**, and effectively provided various **89** in good yields (Scheme 31). Mechanistic studies have shown that, firstly, H_3PO_4 is involved in the decomposition of dimethyl sulfoxide to produce formaldehyde, followed by addition of formaldehyde as a methylene bridge to imidazo[1,2-*a*]pyridines. Therefore, the synergistic effect of H_3PO_4/DMSO in this reaction is crucial.

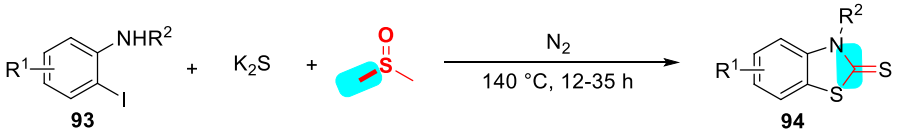
A new route to obtain arylsulfonyl dibromomethanes **92** by free radical coupling reaction of sodium arylsulfates **90–91** and dimethyl sulfoxide under air atmosphere was reported by Wang et al. (Scheme 32) [63]. This protocol provides a novel method of bridging bridges using DMSO as C_1 source. The mechanistic results indicated that the reaction is a radical coupling reaction.



Scheme 31 Plausible mechanisms for methylenation of imidazo-[1,2-*a*]pyridines [62]

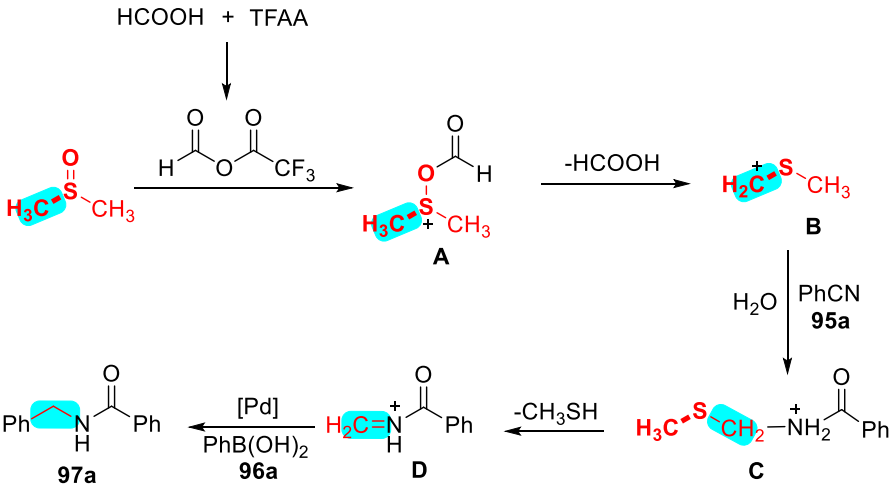


Scheme 32 Plausible mechanisms for preparation of arylsulfonyl dibromomethanes [63]

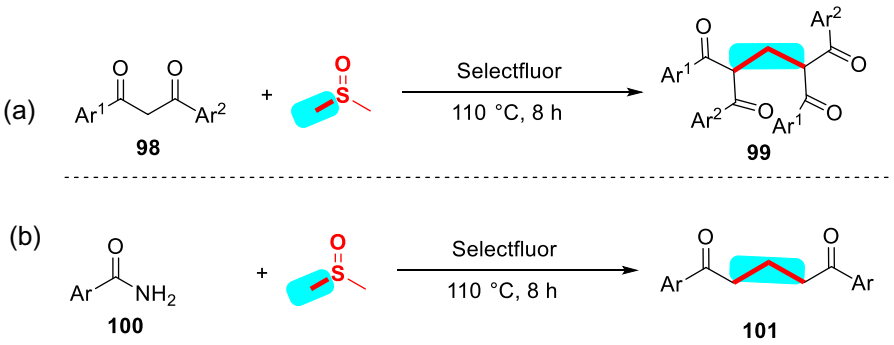


Scheme 33 Preparation of benzothiazolethiones [64]

In 2018, Liu et al. revealed a three-component cyclization reaction of *o*-iodoanilines **93**, potassium sulfide, with dimethyl sulfoxide to obtain various benzothiazoles **94** in moderate to good yields (Scheme 33) [64]. The protocol was carried out without addition of catalysts or additives, reflecting its characteristics of ecofriendliness, simplicity of operation, and novelty. Also, thioureas can be prepared from primary diamines by this method.



Scheme 34 Preparation of benzothiazolethiones [65]

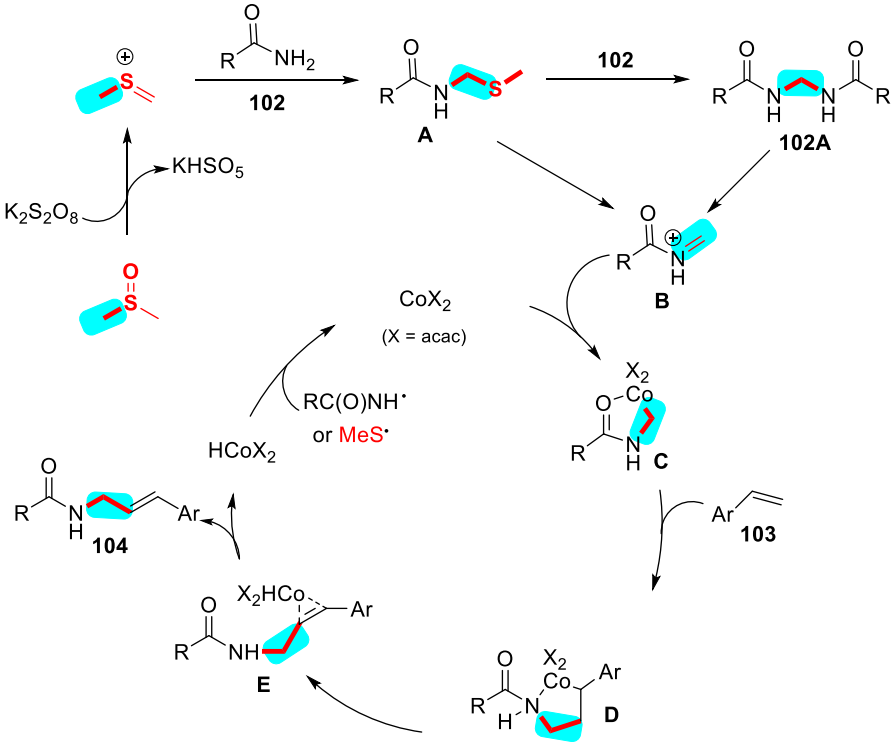


Scheme 35 Preparation of methylene-bridged compounds **99** and **101** [66, 67]

In the same year, Wu et al. reported a palladium-catalyzed three-component cross-coupling strategy using benzonitriles **95**, arylboronic acids **96**, and dimethyl sulfoxide with high selectivity to obtain various *N*-benzylbenzamides **97** (Scheme 34) [65]. In addition, this is a valuable approach for using dimethyl sulfoxide as a source of bridging carbon (–CH_2–) articulation.

Interestingly, Ma's group reported a strategy for methylation of 1,3-diketones **98** using dimethyl sulfoxide with promotion by Selectfluor. Various bis-1,3-dicarbonyl derivatives **99** bridged with methylene were obtained in moderate to high yields (Scheme 35a) [66]. Also, addition of ammonium salts to 1,3-diketones can enable efficient conversion to Hantzsch-type pyridines by three-component cyclization reaction. Selectfluor was selected as a thermally stable and ecofriendly oxidant, making the protocol efficient and easy to operate.

In the same year, Ma's group further used the Selectfluor/DMSO system to achieve direct methylenation of amides **100** and thereby obtain 18



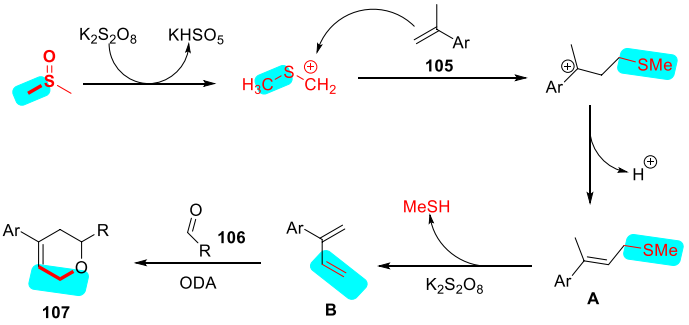
Scheme 36 Preparation of privileged allylic amines **104** [68]

methylene-bridged bis-amide derivatives **101** (Scheme 35b) [67]. The successful implementation of this method proved the practicality and universality of the Selectfluor/DMSO system.

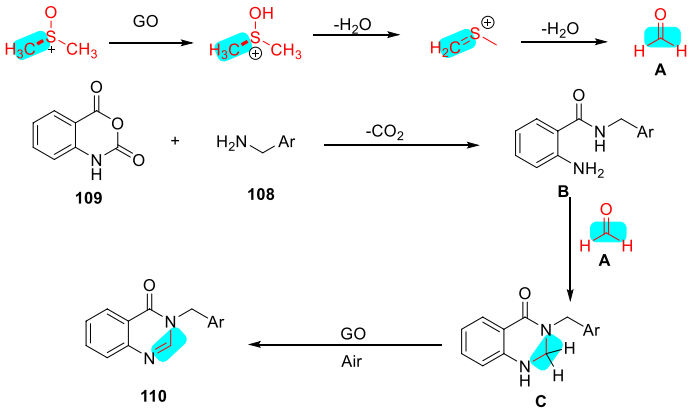
In 2019, Yi et al. reported cobalt-catalyzed allylation of amides **102** with styrenes **103** for highly selective synthesis of various privileged allylamines **104** (Scheme 36) [68]. DMSO was used as bridging carbon source with $K_2S_2O_8$-mediated sequential oxidation in this transformation. Also, this reaction offered high yields as well as high selectivity of (*E*)-isomers.

Guo et al. reported efficient synthesis of various 3,6-dihydro-2*H*-pyrans **107** by a strategy based on three-component [3+2+1] cyclization of 2-substituted propylenes **105**, aldehydes **106**, and dimethyl sulfoxide promoted by $K_2S_2O_8$ (Scheme 37) [69]. DMSO plays a dual role as solvent and bridging carbon in the reaction. At the same time, the strategy was equally applicable to direct C–H activation of propylene units and DMSO for synthesis of 2,4-disubstituted 3,6-dihydro-2*H*-pyrans via [4+2] cyclization, reflecting the generality and versatility of the process.

In the same year, Kumari et al. reported graphene oxide (GO)-promoted three-component cascade cyclization reaction of benzylamines **108**, isovaleric anhydride **109**, and DMSO to prepare 3-substituted quinazolinones **110** in good yields (Scheme 38) [70]. Among them, graphene oxide was used as a recyclable accelerator. The obtained graphene oxide was characterized by scanning electron microscopy



Scheme 37 Preparation of 3,6-dihydro-2*H*-pyrans **107** [69]

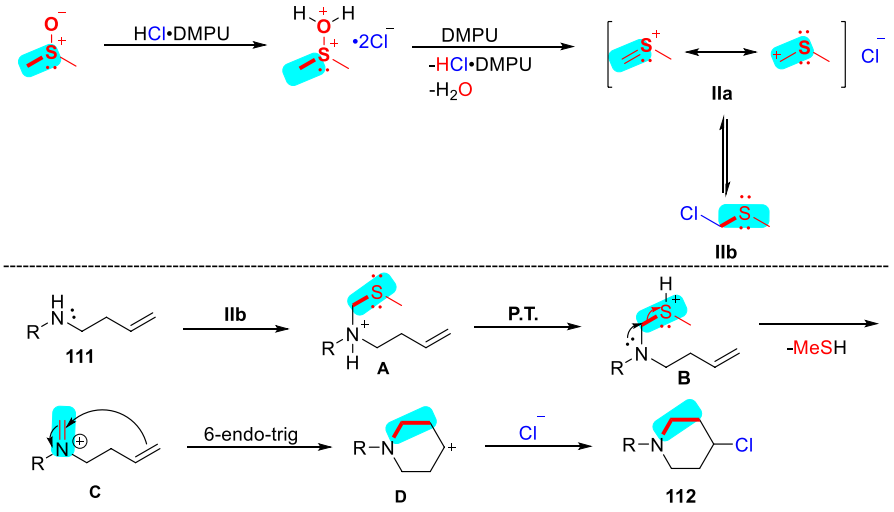


Scheme 38 Preparation of 3-substituted quinazolinones [70]

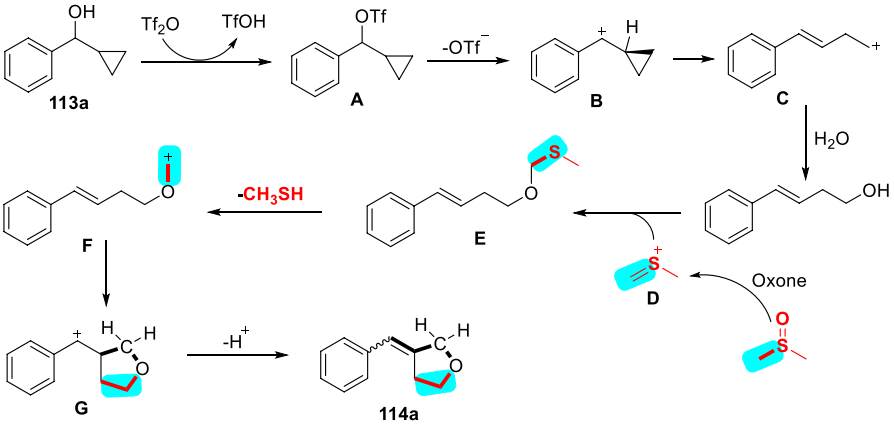
(SEM), X-ray diffraction (XRD), and energy-dispersive x-ray (EDX) analyses, while its thermal stability was confirmed by thermogravimetric analysis (TGA).

Interestingly, Xu et al. reported a strategy to induce formation of electrophile unit (thiomethyl)methylammonium carbons from dimethyl sulfoxide via the HCl-DMPU system followed by cyclization with allylamines **110**, giving a variety of 4-chloropiperidines **112** in good yields (Scheme 39) [71]. The reaction demonstrates a very broad range of substrates, and allyl amines can be applied to a variety of aromatic and aliphatic amines. The reaction produces an imine ion intermediate followed by cyclization to form 4-chloropiperidines **110** by means of the za-Pummerer reaction.

In 2020, Yan et al. reported a one-pot cyclization pathway using cyclopropanemethanols **113** and dimethyl sulfoxide to prepare 3-benzylidene-tetrahydrofurans **114** (Scheme 40) [72]. The reaction proceeded smoothly with various common substituent groups on cyclopropanemethanols, obtaining **114** in moderate to good yields. The reaction mechanism shows that, in the presence of Tf_2O, the cyclopropane moiety undergoes a ring-opening reaction with water to form homoenol units, which then react with DMSO to form 3-benzylidene-tetrahydrofuran.



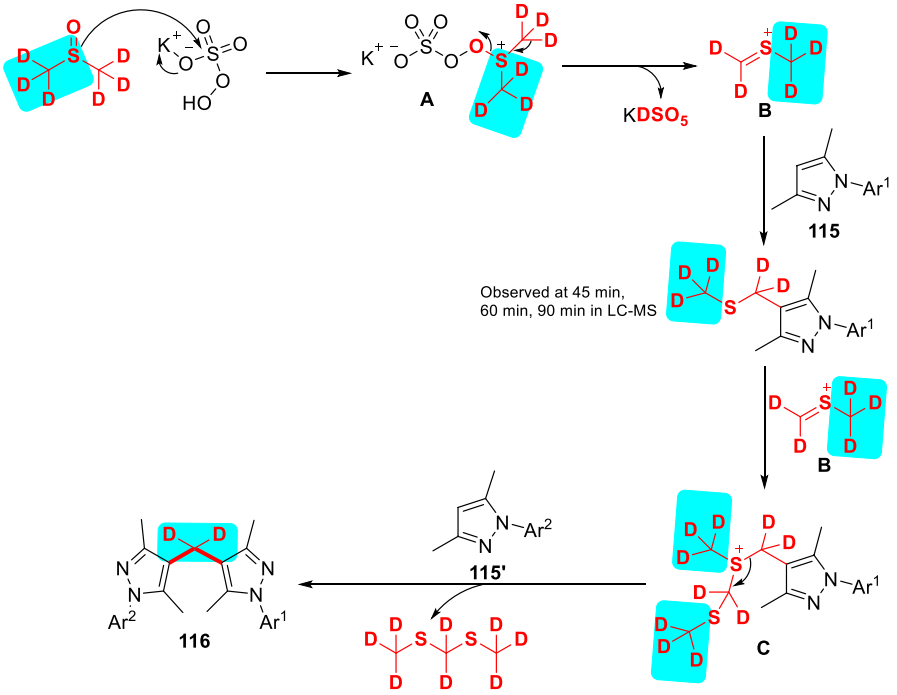
Scheme 39 Preparation of 4-chloropiperidines **112** [71]



Scheme 40 Preparation of 3-benzylidene-tetrahydrofurans **114** [72]

In the same year, Sawant's group revealed a novel method for synthesis of double heterocyclic scaffolds (Scheme 41) [73]. The formation of new C–C bonds activates DMSO to insert smoothly into pyridines **115** in the methylene form, and various symmetric, asymmetric bispyrazoles, and pyrazole-based bisheterocyclic molecules **116** can be obtained in moderate to high yields. DFT calculations reconfirmed the possible mechanism. Also, a chiral center was generated by further modification of the bridging methylene in the asymmetric pyrazole, expanding the application of the method.

In 2021, Ma's group reported a selective fluorine-promoted cascade cyclization reaction of amidines **117** and dimethyl sulfoxide to obtain various

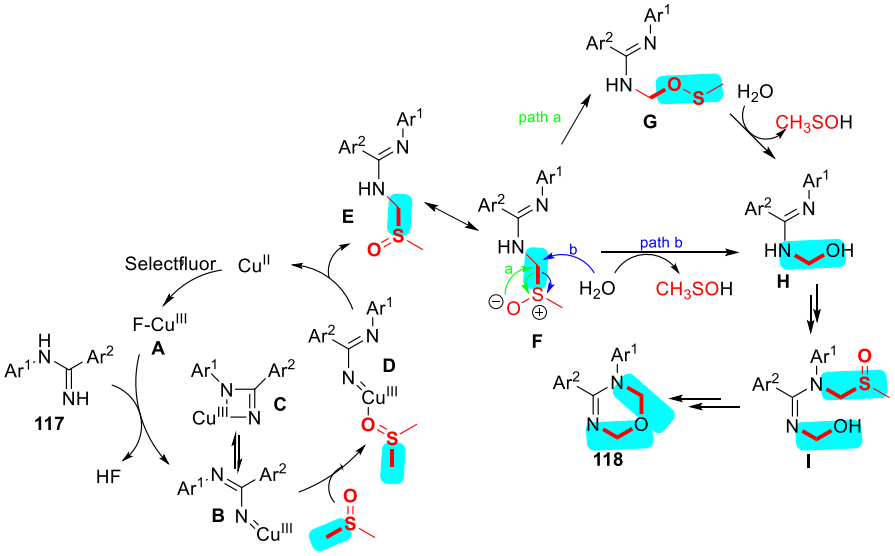


Scheme 41 Preparation of bispyrazoles and pyrazole-based bisheterocyclic molecules [73]

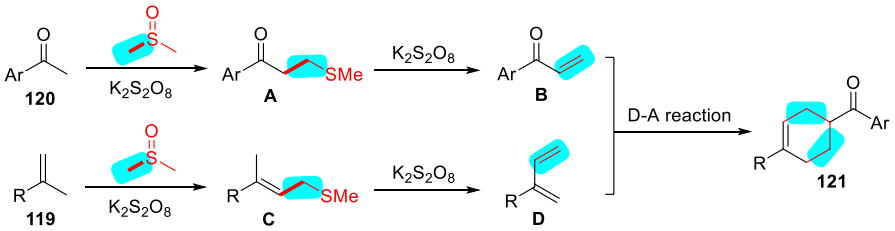
1,3,5-oxadiazines **118** with high selectivity (Scheme 42) [74]. In this case, DMSO is used as a two-carbon synthesis source and water is used as an oxygen source to construct the oxadiazine ring. Meanwhile the oxygen in the structure of the oxadiazine ring was confirmed by controlled experiments. The reacting substrates are widely applicable, and 1,3,5-oxadiazines **118** can be synthesized in good yields with various electron-donating and electron-withdrawing groups on the amidine **117** moiety.

Interestingly, Guo et al. reported for the first time a [3+1+1+1] cascade cyclization reaction of propylenes **119**, ketones **120**, and DMSO with promotion by $K_2S_2O_8$, resulting in highly selective synthesis of 39 examples of spirocyclohexene backbones **121** (Scheme 43) [75]. The reaction involved the formation of four new C–C bonds and the use of dimethyl sulfoxide as a bridging carbon skeleton to provide two carbons for the six-membered carbon ring. Based on multiple sets of detailed control experiments, a plausible mechanism was proposed.

A new strategy for highly selective synthesis of cyclopentenes **124** (Scheme 44X) and cyclohexenes **125** (Scheme 44Y) by cobalt(II)-catalyzed three-component coupling of β-1,3-dione **122**, alkenes **123**, and dimethyl sulfoxide was reported by Zhang's group [76]. This convenient strategy uses DMSO as a solvent and bridging carbon source, demonstrating a wide range of substrates, simplicity, and readily available starting materials. Informative mechanistic research experiments further validated the plausible mechanism.



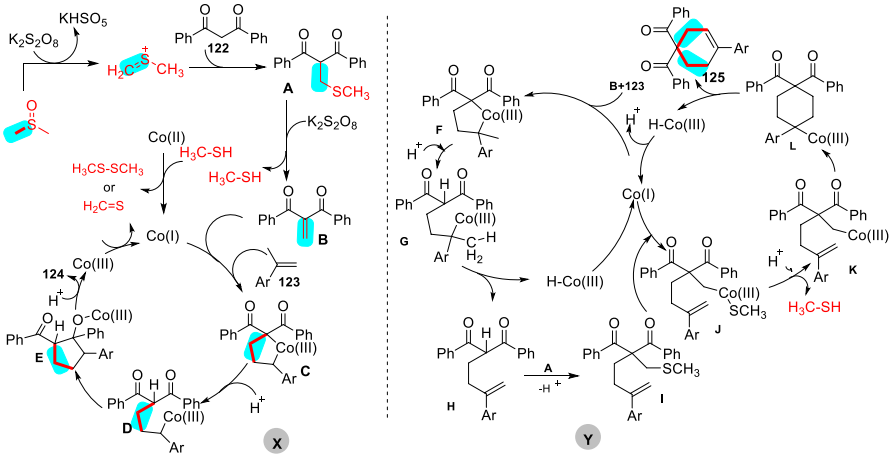
Scheme 42 Plausible mechanism for synthesis 1,3,5-oxadiazines [74]



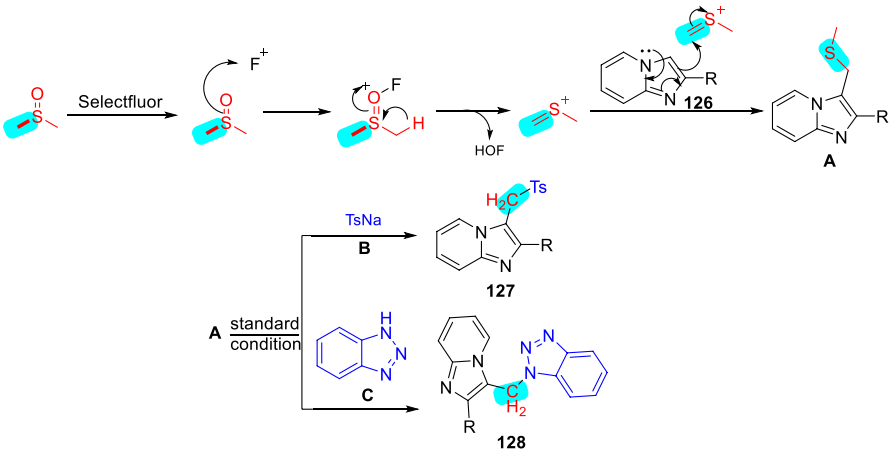
Scheme 43 Plausible mechanism for synthesis of spirocyclohexene backbones [75]

Recently, Rode et al. reported Selectfluor-mediated three-component synthesis of methylene-tethered aryl sulfonates **127** and benzotriazoles **128** from imidazoles **126**, aryl sulfonates, or benzotriazoles with DMSO, in which DMSO is activated by Selectfluor as a solvent and bridge carbon source (Scheme 45) [77]. Benzotriazolylation of β-naphthol and methylene-tethered aromatic sulfonation can be achieved by this protocol, as well, showing that the reaction has wide applicability.

In 2022, Zhang, Liu et al. revealed a protocol for hydroxymethylation of carbonyl compounds **129** under $AcCl/Na_2CO_3$ promotion to obtain various α-hydroxymethylated carbonyl compounds **130** with full quaternary carbon centers in excellent yields under mild conditions (Scheme 46) [78]. In this efficient conversion, H_2O is used as a green oxygen source and DMSO as a methylene ($–CH_2–$) source as well as solvent. In addition, the reaction conditions are mild, and it can be carried out at room temperature. Detailed mechanistic studies further demonstrated the effectiveness of the conversion.



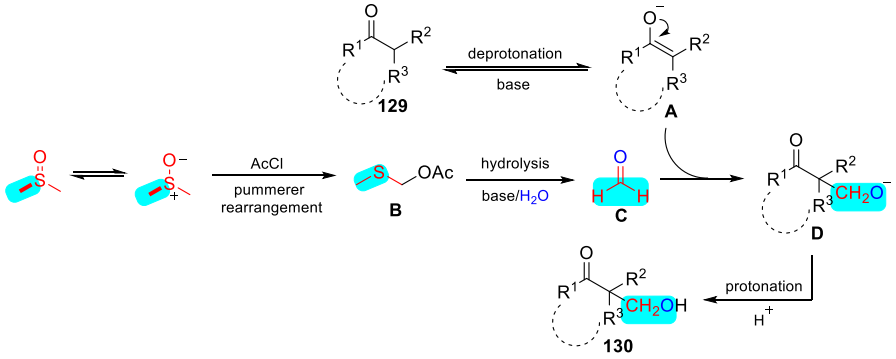
Scheme 44 Plausible mechanism for synthesis of cyclopentenes and cyclohexenes [76]



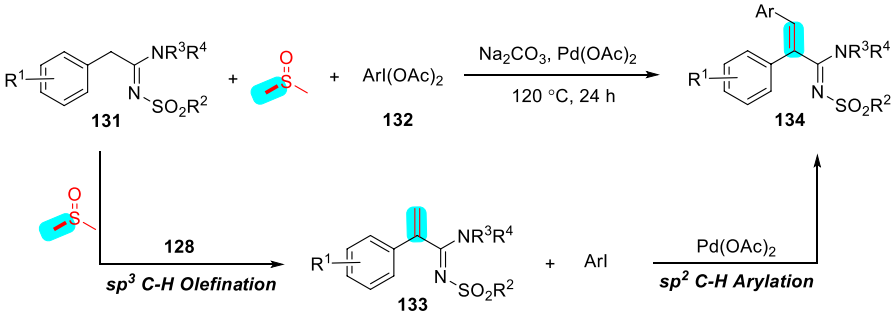
Scheme 45 Plausible mechanism for synthesis of methylene-tethered arylsulfonation and benzotriazolation of imidazopyridines [77]

3.3 Methylidene Donor (=CH_2)

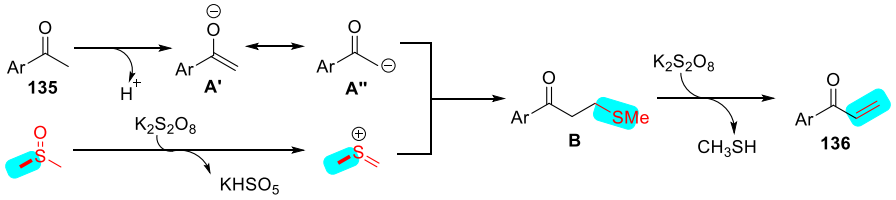
In 2017, Namitharan et al. developed an efficient three-component (amidines **131**, hypervalent aromatic reagents **132**, and dimethyl sulfoxide) transition-metal-free C–H functionalization reaction to synthesize various 1,2-diaryl acrylamides **133** in good yields with a wide range of applications (Scheme 47) [79]. Dimethyl sulfoxide as C_1 source was confirmed by deuterated labeling experiments. The method is universal in its ability to sequentially combine olefin aromatizations for C–H functionalization under palladium catalysis, and various 2,3-diaryl acrylamides **134** were obtained in good yields.



Scheme 46 Plausible mechanism for synthesis of α-hydroxymethylated carbonyl compounds **130** [78]



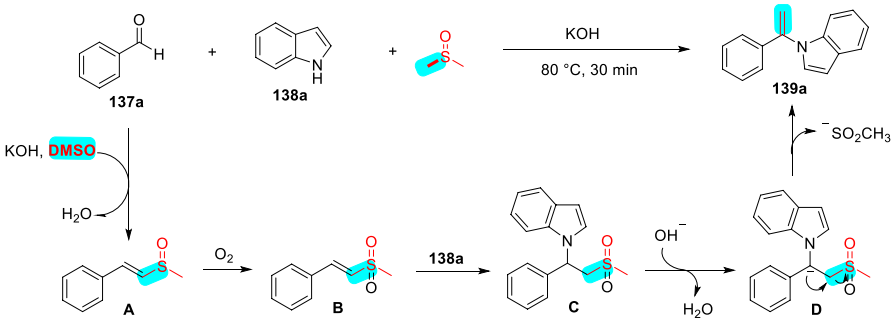
Scheme 47 Methods for preparation of acrylamides [79]



Scheme 48 Preparation of α,β-unsaturated carbonyl compounds **136** [80]

In the same year, Guo et al. reported a direct α-Csp^3-H methylation strategy of dimethyl sulfoxide with aryl ketones **135** to obtain a variety of α,β-unsaturated carbonyl compounds **136** in 42–90% yields (Scheme 48) [80]. The protocol is characterized by a wide range of substrates, no addition of transition metals, as well as simple and readily available raw materials.

Immediately afterwards, Guo et al. reported a three-component cascade assembly strategy of aromatic aldehydes **137**, azoles **138**, and dimethyl sulfoxide for efficient preparation of multiple substituted *N*-vinylazoles **139** (Scheme 49) [81]. DMSO was used as terminal carbon source and formed a new C=C bond. Simultaneous



Scheme 49 Preparation of *N*-vinylazoles **139** [81]

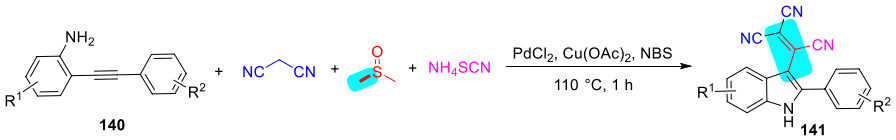
10 mmol amplification gram-scale experiments demonstrated the utility and effectiveness of the protocol.

In 2021, Patel et al. presented a one-pot, four-component cascade reaction of *o*-alkynyl anilines **140**, propanedial, dimethyl sulfoxide, and ammonium thiocyanate under Pd(II)/Cu(II) to synthesize various tricyanovinylidoles **141** in moderate to good yields (Scheme 50) [82]. This strategy utilizes dimethyl sulfoxide as a bridge carbon substitute to efficiently construct new C=C, C–C, and C–N bonds. Meanwhile, further modification of tricyanovinylidoles **141** demonstrated the utility of this four-component cascade reaction to obtain interesting 4-cyano-3-indolylmaleimides.

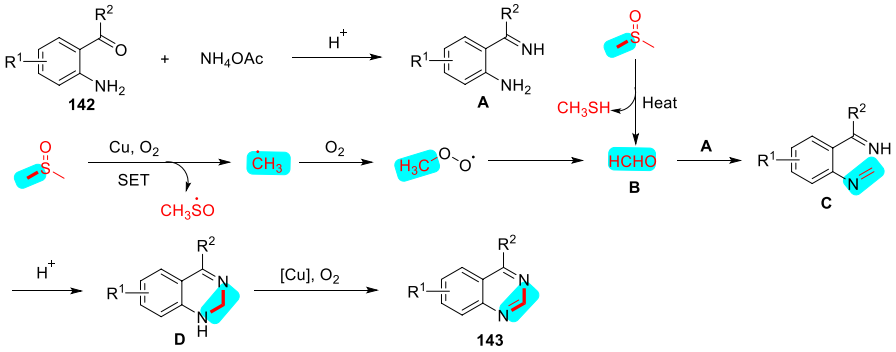
3.4 Methine Donor (=CH–, Used for Cyclization or Aromatization)

In 2016, Ma et al. reported a copper-catalyzed three-component reaction of 2-aminobenzophenones **142**, aqueous ammonia, and dimethyl sulfoxide to synthesize a series of quinazoline derivatives **143** in moderate to good yields (Scheme 51) [83]. The protocol was environmentally friendly, using clean oxygen as oxidant and avoiding the use of peroxides and iodides. Also, ammonium acetate as an *N* source involves direct inorganic to organic conversion through [4+1+1] cycloaddition reaction.

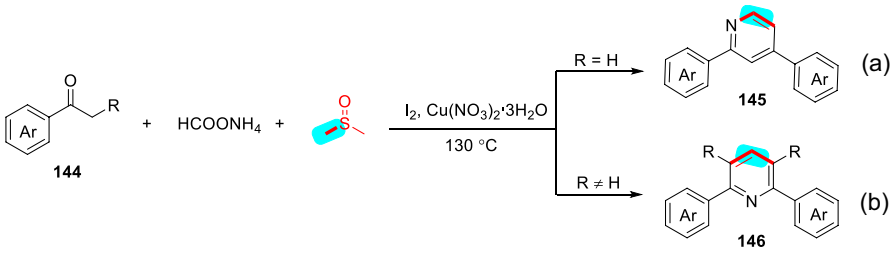
Next, Wu et al. reported an efficient method for synthesis of substituted pyridines **145** by three-component cyclization of aryl methyl ketones **144**, ammonium formate, and DMSO (Scheme 52a) [84]. The transformation is carried out by cleaving the C–S bond of DMSO to provide a methylene intermediate to participate in the subsequent cyclization. Interestingly, the protocol demonstrated a broad range of



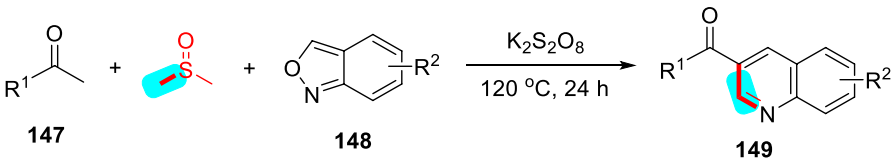
Scheme 50 Preparation of tricyanoindoles **141** [82]



Scheme 51 Preparation of quinazoline derivatives **143** [83]



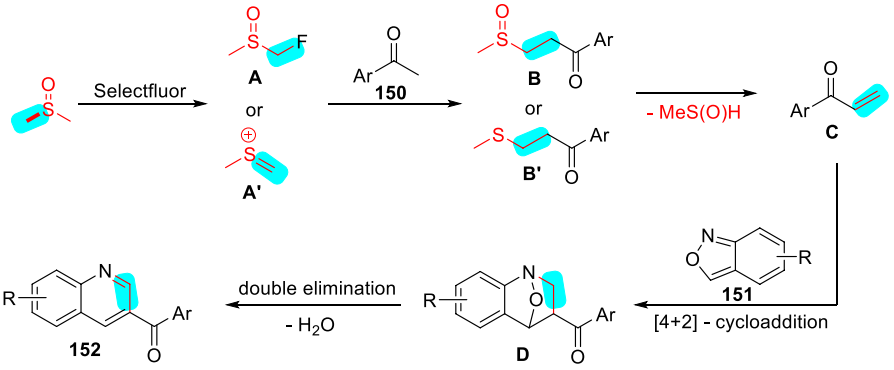
Scheme 52 Synthesis of substituted pyridines [84]



Scheme 53 Synthesis of 3-substituted quinolines [85]

substrates, and α-substituted ketones could also produce a variety of corresponding substituted pyridines **146** in good yields (Scheme 52b). In addition, seven sets of control experiments further showed the feasibility of the mechanism.

In 2017, Tiwari et al. revealed a one-pot metal-free cascade reaction of acetophenones **147**, dimethyl sulfoxide, and anthranils **148** to prepare 26 functionalized 3-substituted quinoline compounds **149** in good yields (Scheme 53) [85]. As described above, DMSO acts as both solvent and methylene unit in this reaction. The successful conversion of 1,4-benzodiazepine heterocycle and 3-phenylquinoline via **149** demonstrated the effective applicability of the method. In 2019, Ma et al. also reported the efficient transformation of Selectfluor-promoted acetophenones **150** with dimethyl sulfoxide and anthranils **151** for three-component synthesis of 3-functionalized quinolines **152** (Scheme 54) [86]. Both cascade cyclizations benefit from a wide range of substrates and simple reaction conditions.

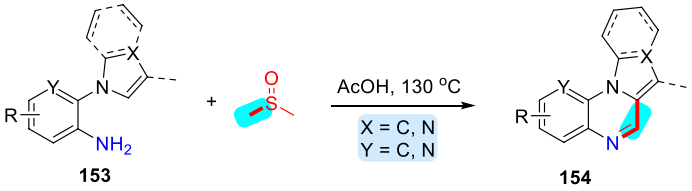


Scheme 54 Mechanism for synthesis of 3-substituted quinolines [86]

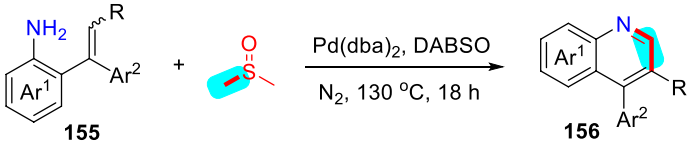
Interestingly, an efficient method for synthesis of novel *N*-heterocycle-fused quinoxalines **154** was reported by Ma's group (Scheme 55) [87]. 2-(1*H*-pyrrol-1-yl)anilines **153** with dimethyl sulfoxide were successfully constructed as interesting starting materials for 34 useful products **154**. This protocol with simple conditions and ease of operation provides a pathway for organic and medicinal chemistry synthesis.

In the same year, Cheng et al. revealed a $Pd(dba)_2$/DABSO-activated cyclization reaction of *o*-vinylanilines **155** with DMSO to synthesize various 4-aryl quinolines **156** in moderate to good yields (Scheme 56) [88]. Interestingly, both DMSO and DABSO played dual roles in the reaction, where DMSO acted as solvent and cyclized the methylene unit while DABSO acted as oxidant in addition to activating DMSO.

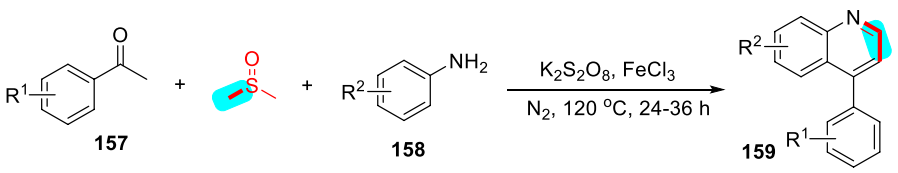
Singh and Jadhav reported an efficient strategy for one-pot synthesis of 4-arylquinolines **159** (Scheme 57) from readily available methyl ketones **157**, anilines **158**, and dimethyl sulfoxide promoted by $K_2S_2O_8$ [89]. Under standard conditions of substitution of anilines for formamide without addition of $FeCl_3$, 4-aryl pyrimidines



Scheme 55 Synthesis of *N*-heterocycle-fused quinoxalines [87]



Scheme 56 Preparation of 4-arylquinolines **156** [88]



Scheme 57 Preparation of 4-arylquinolines **159** [89, 90]

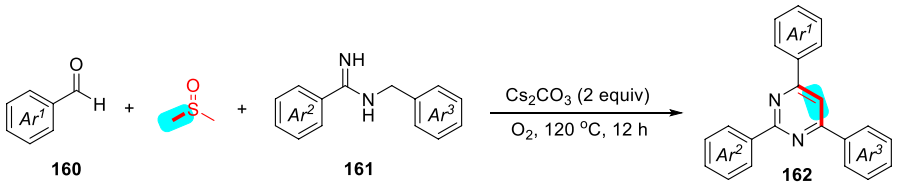
can also be obtained by this protocol. The successful implementation of this strategy effectively avoids the use of expensive transition metals and also provides an efficient route for synthesis of 4-substituted quinolines. Interestingly in 2018, Jiang et al. reported the same method for synthesis of 4-arylquinolines [90] using anilines with aryl methyl ketones and dimethyl sulfoxide. The difference is that Jiang used CH_3SO_3H as the oxidant for 36 h.

Interestingly, Cheng et al. reported Cs_2CO_3-promoted three-component [4+1+1] oxidative cyclization of aldehydes **160**, dimethyl sulfoxide, and *N*-benzylamidines **161** to obtain 2,4,6-triaryl pyrimidines **162** in moderate to good yields (Scheme 58) [91]. DMSO as carbon source was susceptible to methylation when promoted by a base, allowing for better subsequent cyclization reactions. At the same time, the substitution of O_2 for other oxidants in this conversion makes the protocol environmentally friendly.

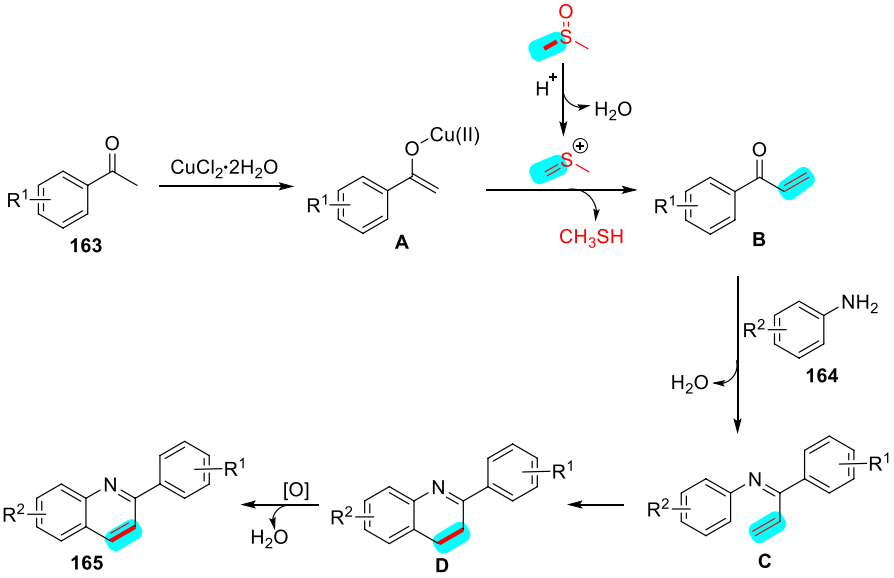
In 2018, Guo et al. reported a Cu(II)-catalyzed three-component oxidative cyclization reaction from readily available aryl methyl ketones **163**, anilines **164**, and dimethyl sulfoxide to obtain various 2-arylquinolines **165** in moderate to good yields (Scheme 59) [92]. Five sets of control experiments further demonstrated the effectiveness of the method. The protocol conditions were simple and used oxygen as the oxygen source. Five sets of control experiments provided strong evidence for a possible mechanism.

Encouragingly, Liu et al. reported an interesting method for construction of benzothiazolethiones **167** by three-component cyclization of *o*-iodoanilines **166** with dimethyl sulfoxide and potassium sulfide (Scheme 60) [64]. The reaction conditions were simple and effective without additional catalysts or additives, giving a novel and environmentally friendly protocol. In addition, DMSO acts as a bridging carbon and oxidant in the reaction.

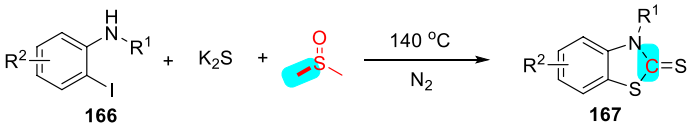
Then, Tiwari's group reported three-component oxidative cyclization of anilines **168** with terminal alkynes **169** and dimethyl sulfoxide under promotion by $K_2S_2O_8$



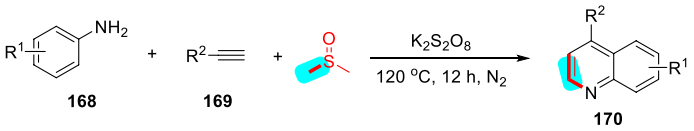
Scheme 58 Preparation of 2,4,6-triaryl pyrimidines **162** [91]



Scheme 59 Preparation of various 2-arylquinolines **165** [92]



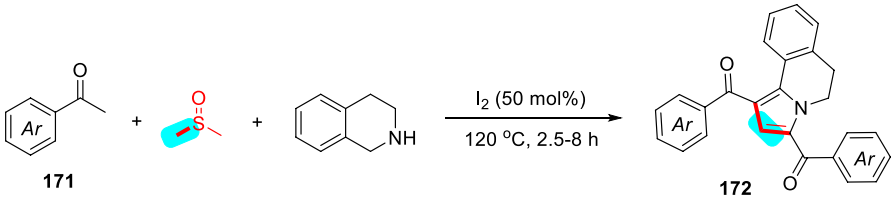
Scheme 60 Preparation of various benzothiazolethiones **167** [64]



Scheme 61 Preparation of various 4-arylquinolines **170** [93]

to synthesize various 4-arylquinolines **170** in moderate to good yields (Scheme 61) [93]. The synthetic utility of the protocol reflected the practicality of the reaction, while five sets of control experiments provided very important evidence for the possible mechanism.

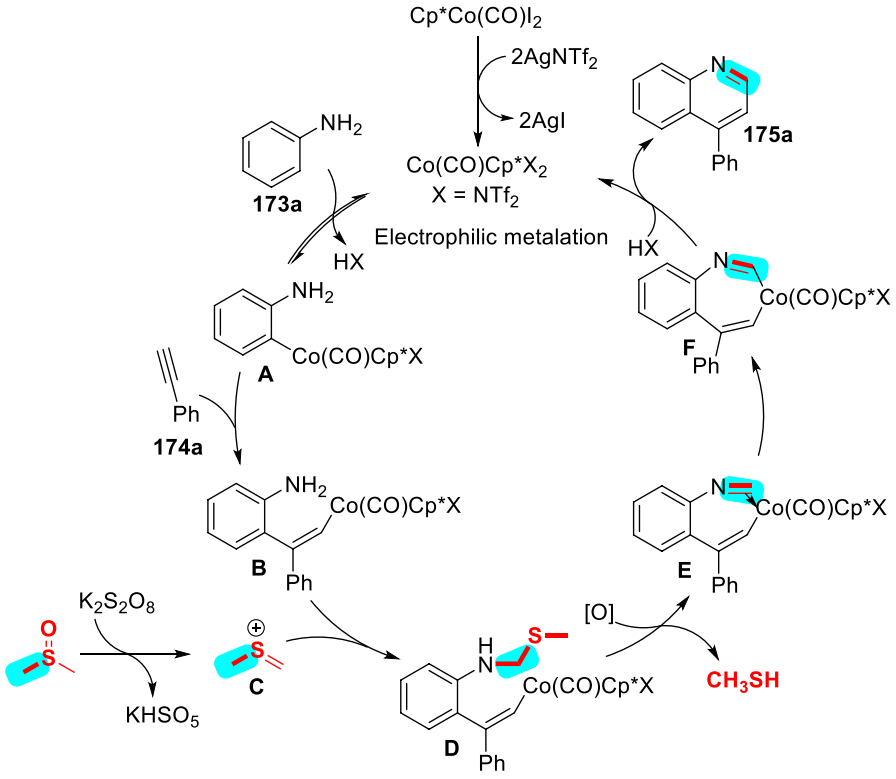
Interestingly, Wu's group reported I_2-mediated three-component [2+1+1+1] cascade oxidative cyclization of aryl methyl ketones **171** with dimethyl sulfoxide and 1,2,3,4-tetrahydroisoquinoline (THIQ) to obtain a series of pyrrolo[2,1-*a*]isoquinolines **172** in moderate to excellent yields (Scheme 62) [94]. Adequate mechanistic validation indicated that dimethyl sulfoxide as methylene source led to the formation of three C–C bonds and one C–N bond. The protocol was characterized by



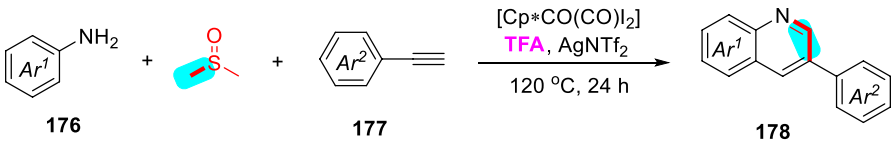
Scheme 62 Preparation of various pyrrolo[2,1-*a*]isoquinolines **172** [94]

readily available starting materials, simple reaction conditions, and a wide range of substrates.

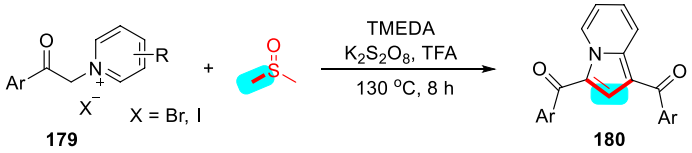
Yi et al. first reported a Co(III)-catalyzed three-component [3+2+1] oxidative cyclization strategy based on anilines **173** with alkynes **174** and dimethyl sulfoxide to obtain various 4-arylquinolines **175** in good to excellent yields (Scheme 63) [95]. The starting materials used for this transformation are readily available and inexpensive. The experimental results of the mechanistic study further indicate that DMSO is not only used as a solvent but also acts as a bridge carbon (C_1) in the protocol. Interestingly, Yi's group reported a TFA-controlled three-component [3+2+1]



Scheme 63 Plausible mechanism for synthesis of 4-arylquinolines **175** [95]



Scheme 64 Synthesis of 3-arylquinolines **178** [96]



Scheme 65 Synthesis of indolizine derivatives **180** [97]

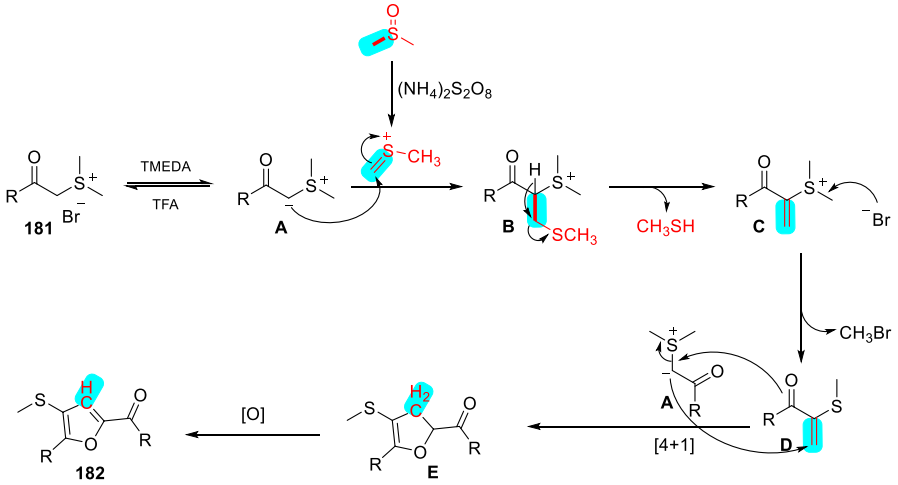
cyclization of anilines **176** with terminal alkynes **177** and dimethyl sulfoxide for one-pot highly regioselective synthesis of various 3-arylquinolines **178** in 2019 (Scheme 64) [96]. This method provides a viable option for quinoline intercalation aromatization.

In 2019, Wu et al. revealed a cascade oxidative cyclization reaction of pyridinium salts **179** with DMSO under $K_2S_2O_8$ oxidation to synthesize a series of indolizine derivatives **180** in moderate to excellent yields (Scheme 65) [97]. DMSO plays a very important role in this cyclization strategy as a solvent and bridge single carbon source. Also, the presence of trimethylethylenediamine (TMEDA) plays a crucial role for I^- and Br^- dissociation.

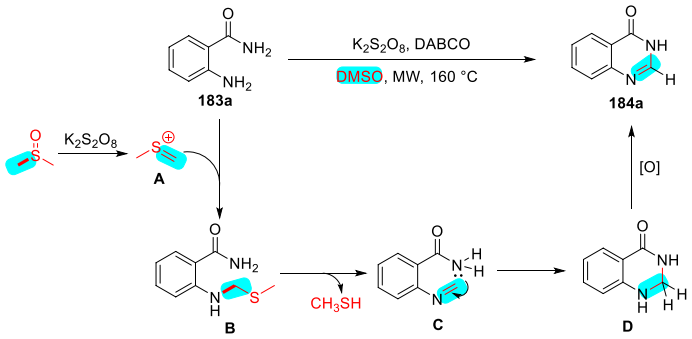
In the same year, Wu's group further reported a cascade oxidative cyclization strategy using dimethyl sulfoxide as C_1 source with stabilized sulfonium salts **181**, successfully preparing polyfunctional furan compounds **182** in good yields (Scheme 66) [98]. Mechanistic validation results showed that the one-pot conversion by activation of dimethyl sulfoxide of the α-methylsulfonium salts generated in situ further underwent [4+1] oxidative cyclization with the sulfurylimines.

Remarkably, Jung et al. revealed a strategy of [5+1] cascade oxidative cyclization of 2-aminobenzamides **183** and dimethyl sulfoxide promoted by $K_2S_2O_8$ to obtain a series of biologically significant quinazolinones **184** in moderate to good yields (Scheme 67) [99]. The advantages of this protocol are the reaction time of only 2 h, the wide range of substrates, and the absence of transition metals. Interestingly, the central nervous system depressant drug methaqualone could able be prepared by this method.

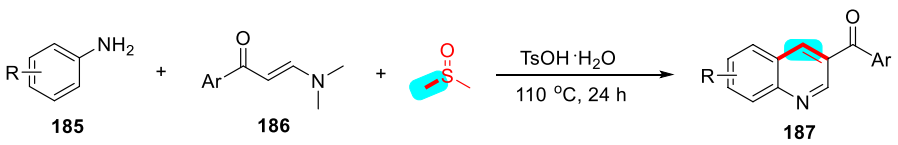
In the same year, *p*-toluenesulfonic acid-mediated three-component cascade cyclization of anilines **185** with dimethyl sulfoxide and enaminones **186** for preparation of 3-ketoquinolines **187** was reported by Jiang et al. (Scheme 68) [100]. In this protocol, DMSO is activated by $TsOH{\cdot}H_2O$ to provide the bridge carbon, enabling the reaction to proceed smoothly. The mechanistic results suggest that DMSO may undergo Pummerer rearrangement under acidic conditions. Interestingly, Tiwari et al. also reported $K_2S_2O_8$-promoted three-component synthesis of a series of 3-ketoquinolines **190** (Scheme 69) with good yields and high selectivity by [3+2+1]



Scheme 66 Synthesis of polyfunctional furan compounds **182** [98]



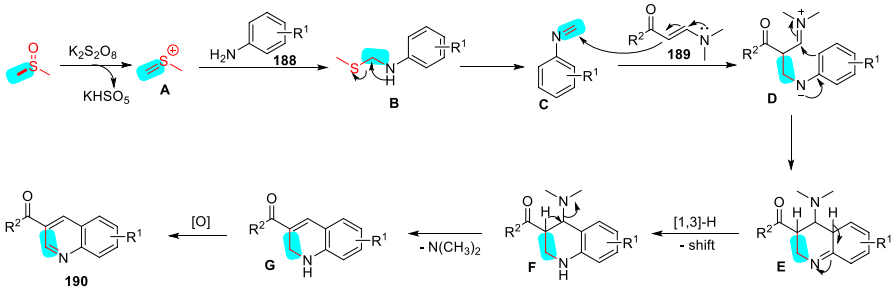
Scheme 67 Mechanisms for preparation of quinazolinones **184** [99]



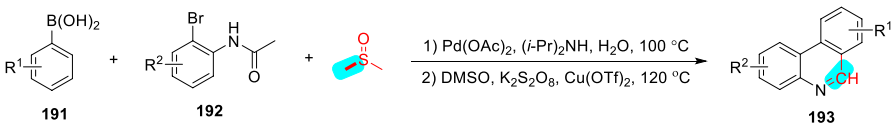
Scheme 68 Preparation of 3-ketoquinolines **187** [100]

oxidative cyclization of anilines **188** with enaminones **189** and dimethyl sulfoxide [101]. The method mainly consists of oxidation of $K_2S_2O_8$ to activate DMSO, which leads to in situ generation of intermediate **A** by DMSO before the reaction.

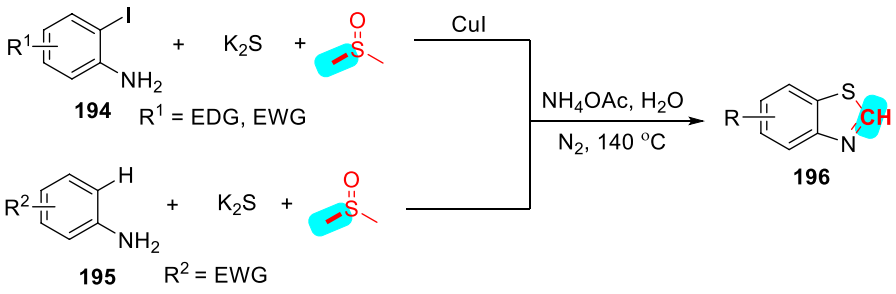
In 2020, Ma's group described a one-pot, two-step oxidative cascade cyclization strategy based on arylboronic acids **191** with dimethyl sulfoxide and *o*-bromoaryl amides **192** to prepare various phenanthridines **193** in moderate to good yields (Scheme 70) [102]. Fifty phenanthridines were obtained by a two-step pathway of



Scheme 69 Mechanisms for preparation of 3-ketoquinolines **190** [101]



Scheme 70 Synthesis of phenanthridines **193** [102]

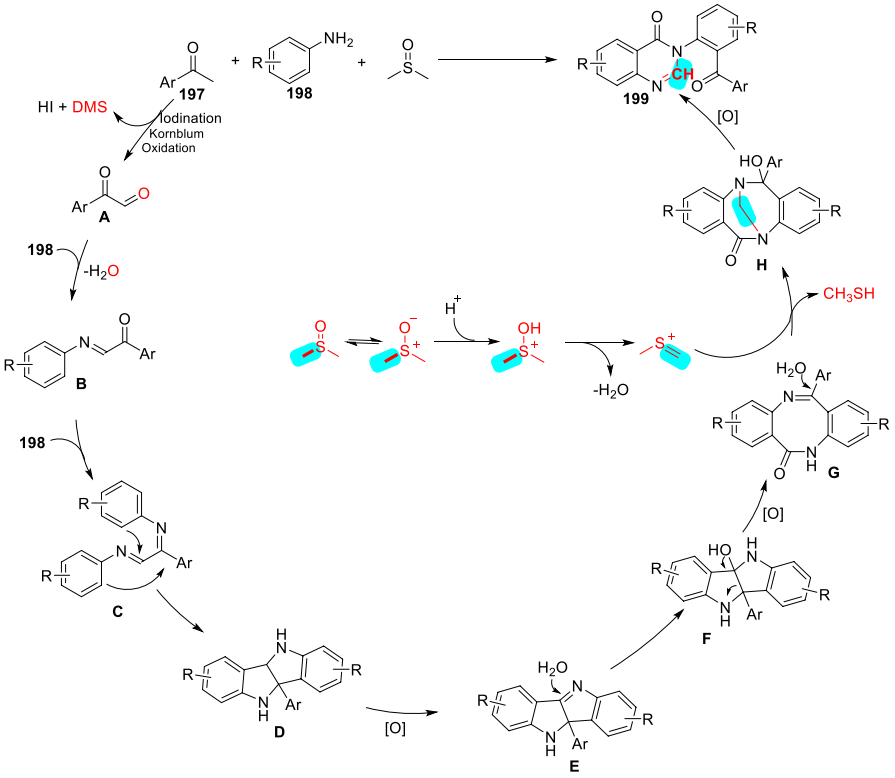


Scheme 71 Synthesis of 2-unsubstituted benzothiazoles **196** [103]

Pd-catalyzed and $K_2S_2O_8$ oxidation. Simultaneous mechanistic verification showed that DMSO acts as both a solvent and a bridging single carbon donor.

Interestingly, Zhu et al. reported a three-component oxidative cyclization strategy based on *o*-iodoanilines **194** with dimethyl sulfoxide and K_2S to obtain 2-unsubstituted benzothiazoles **196** in moderate to good yields (Scheme 71) [103]. The substitution of **194** by aromatic amines **195** enabled successful preparation of **196** under standard conditions without addition of copper catalyst. The results of control experiments indicated that dimethyl sulfoxide acts as a single carbon donor in addition to an oxidant and solvent in this reaction.

In the same year, Wu et al. reported a one-pot three-component sequential oxidative cyclization reaction of aryl methyl ketones **197** with anilines **198** and dimethyl sulfoxide to obtain a series of aryl quinazolinones **199** in moderate yields (Scheme 72) [104]. The transformation is characterized by cleavage of



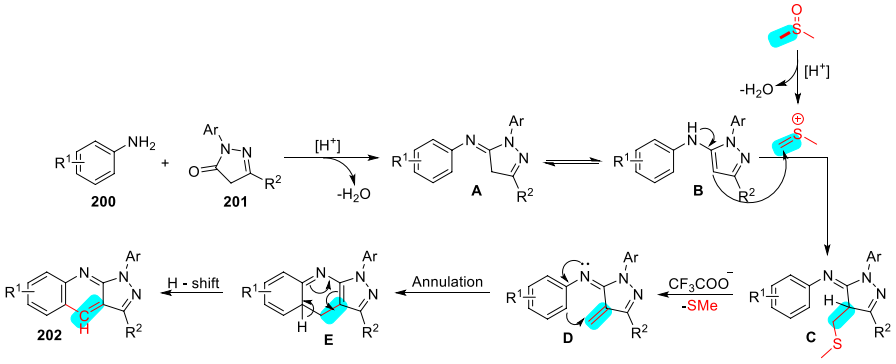
Scheme 72 Synthesis of aryl quinazolinones **199** [104]

dimethyl sulfoxide as a methylene donor to achieve sequential cyclization. Multi-component control experiments provided valid evidence for potential mechanistic studies.

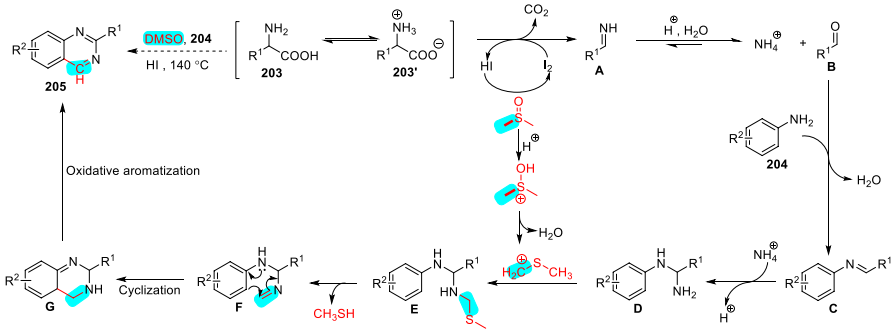
In 2021, Tiwari's group further reported a TFA-promoted three-component tandem cyclization reaction of anilines **200** with dimethyl sulfoxide and pyrazolones **201** to obtain a series of pyrazolo[3,4-*b*]quinolones **202** in good to excellent yields (Scheme 73) [105]. Also DMSO plays a dual role in the reaction, not only as a reaction solvent but also as a donor of cyclization bridge carbon. Furthermore, the application of the method further demonstrated the practicality of the reaction.

Then, Wu's group revealed for the first time a three-component cyclization strategy of amino acids **203** with anilines **204** and dimethyl sulfoxide to synthesize 2-arylquinazolines **205** in moderate to good yields (Scheme 74) [106]. The mechanistic results indicated a sequential HI-mediated decomposition of amino acids to aldehydes followed by reconstitution with anilines. The validity of this result was further verified by controlled experiments.

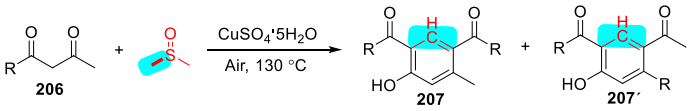
Interestingly, Wang et al. reported a $CuSO_4 \cdot 5H_2O$-catalyzed cyclization strategy based on 1,3-dicarbonyl compounds **206** and dimethyl sulfoxide to synthesize



Scheme 73 Synthesis of pyrazolo[3,4-*b*]quinolones **202** [105]



Scheme 74 Synthesis of 2-arylquinazolines **205** [106]

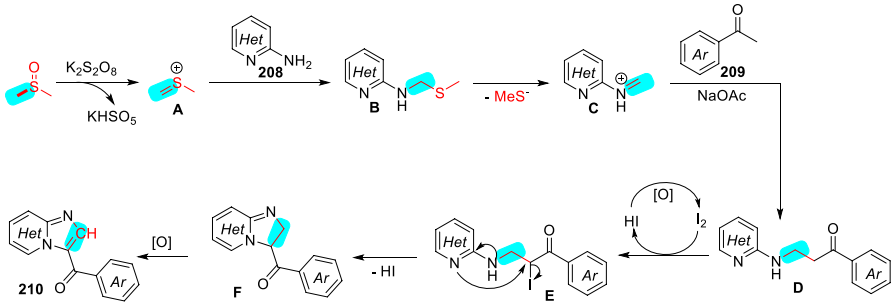


Scheme 75 Synthesis of phenolic derivatives **207** [107]

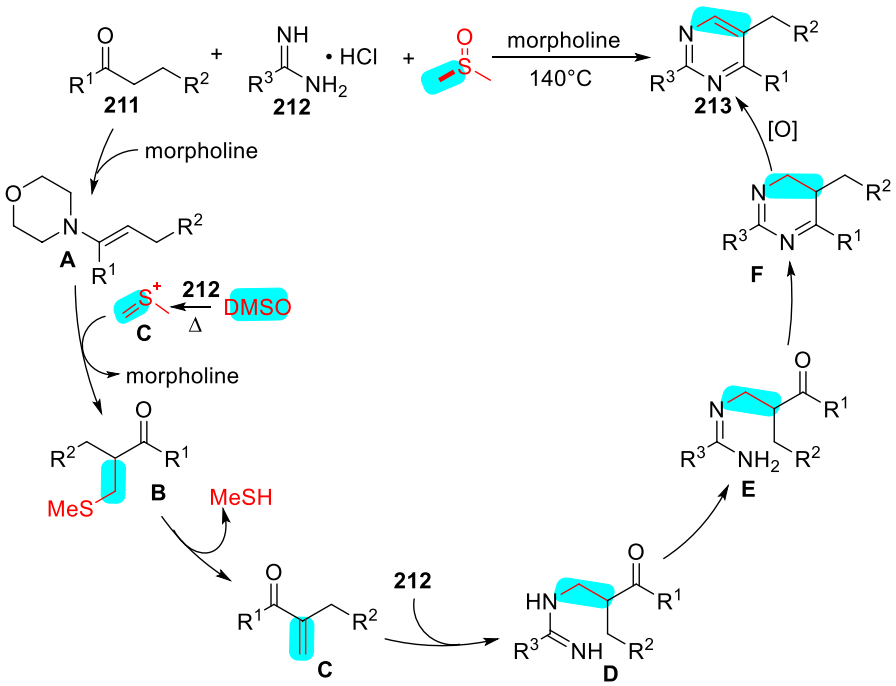
phenolic derivatives **207** with isomers in up to 93% isolated yields (Scheme 75) [107]. Deuterium labeling experiments indicated that the C_2 of phenol derivatives was derived from dimethyl sulfoxide.

Recently, Ma et al. reported a three-component cascade cyclization strategy based on 2-amino-*N*-heterocycles **208** with aryl methyl ketones **209** and dimethyl sulfoxide under synergistic promotion by $K_2S_2O_8/I_2$ to synthesize 3-aroylimidazo[1,2-*a*]-*N*-heterocycles **210** in moderate to good yields (Scheme 76) [108]. This one-pot protocol also involved dimethyl sulfoxide as the solvent and methylene source for the cyclization procedure.

Also recently, Jiang's group revealed a metal-free three-component cascade cyclization reaction of ketones **211** with amidine hydrochlorides **212** and dimethyl



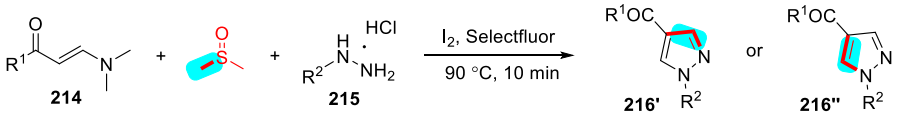
Scheme 76 Synthesis of 3-aroylimidazo[1,2-*a*]-*N*-heterocycles **210** [108]



Scheme 77 Synthesis of a series of pyrimidines **213** [109]

sulfoxide for highly selective synthesis of a series of pyrimidines **213** (Scheme 77) [109]. Interestingly, amidine hydrochlorides not only acted as a reactant in this transformation, but also activated DMSO to participate smoothly in the subsequent cyclization procedure.

In 2022, Wan et al. revealed an I_2-catalyzed one-pot three-component cascade cyclization procedure based on enaminones **214**, dimethyl sulfoxide, and hydrazines **215** to obtain various 1,4-disubstituted pyrazoles **216** in moderate to good yields (Scheme 78) [110]. The results of control experiments demonstrated that dimethyl sulfoxide acted as a donor of C_1 at two sites of the pyrazole ring, while dimethyl



Scheme 78 Synthesis of various 1,4-disubstituted pyrazoles **216** [110]

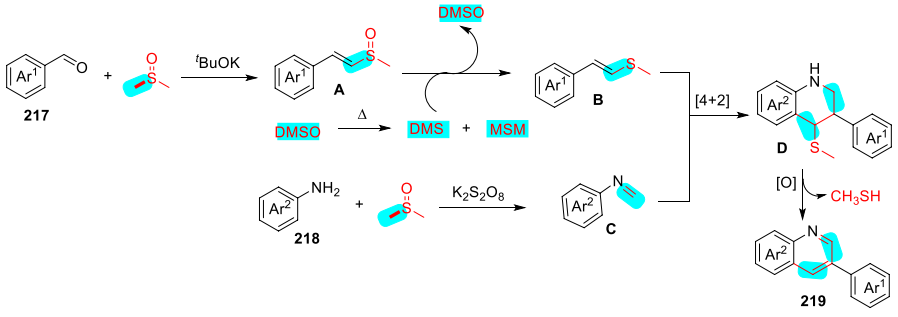
sulfoxide served as an effective solvent. This transformation is characterized by easy availability of starting materials, a wide range of substrates, and a short reaction time of 10 min. In addition, the ability of pyrazole **216a** to proceed smoothly in the reaction with styrene and diphenylacetylene demonstrated the practical application of pyrazole.

Just recently, Guo et al. developed *t*BuOK-promoted one-pot [3+1+1+1] cascade cyclization of aromatic aldehydes **217**, dimethyl sulfoxide, and arylamines **218** to synthesize various 3-arylquinolines **219** in good yields (Scheme 79) [111]. Interestingly, DMSO provided two nonadjacent C_1 donors for the pyridine ring in the 3-substituted quinoline molecules, in addition to acting as a solvent. Deuterium labeling experiments demonstrated that the two nonadjacent carbons were derived from dimethyl sulfoxide. It is worth mentioning that, when the reaction was carried out using phenyl methyl sulfoxide instead of dimethyl sulfoxide, the product **219a** was also obtained, but in a lower yield of 19%.

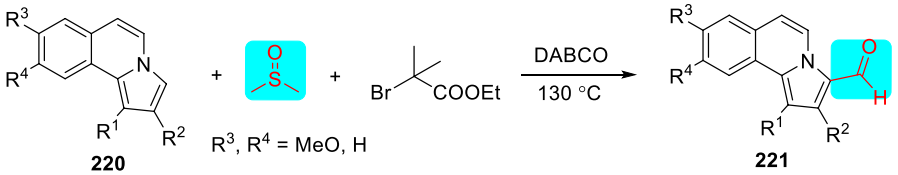
3.5 Donors of Formylation (–CHO)

In 2021, a three-component synthesis based on dihydropyrrole isoquinolines **220** with dimethyl sulfoxide and bromobutyric acid, giving a series of formylated pyrrole isoquinolines **221** in up to 94% isolated yield, was reported by Cui et al. (Scheme 80) [112]. The protocol is an efficient method to achieve formylation by using dimethyl sulfoxide as a carbonyl source. Meanwhile, the gram-scale experiment and transformation experiment of **221a** further demonstrated the practicality of the reaction.

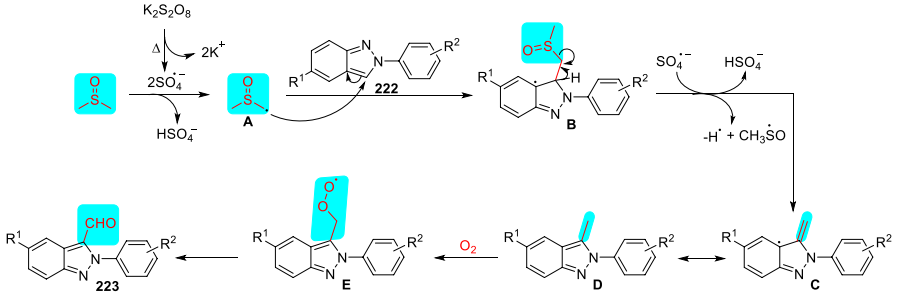
Recently, Hajra et al. revealed a method for functionalization of 2*H*-indazoles **222** at the C_3 position using dimethyl sulfoxide as a formylation donor (Scheme 81) [113]. This facile and efficient method synthesized a series of formylated indazole



Scheme 79 Synthesis of various 3-arylquinolines **219** [111]



Scheme 80 Synthesis of formylated pyrrole isoquinolines **221** [112]



Scheme 81 Synthesis of formylated indazole derivatives **223** [113]

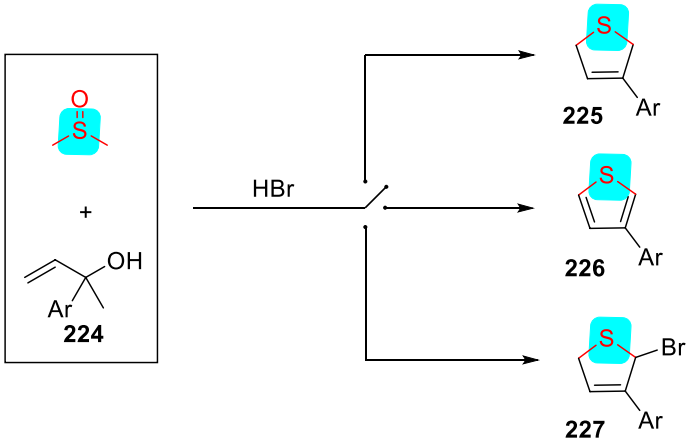
derivatives **223** in moderate to good yields under the condition of $K_2S_2O_8$ as oxidant. The results of controlled experiments and mechanistic studies indicated that the protocol proceeded via the radical pathway. At the same time, this transformation was characterized by easy access to substrates, simple operation, and a wide range of substrates.

4 As Sulfur Source (–S–)

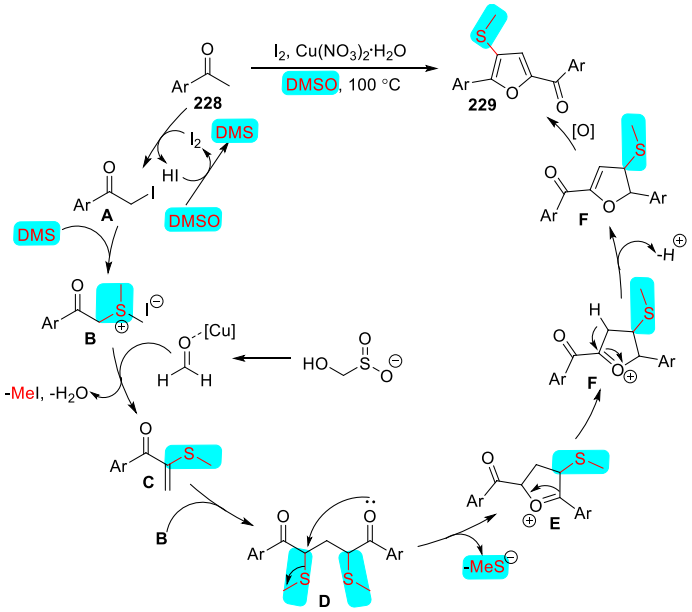
Thiophene rings are found widely in natural products as one of the most common sulfur-containing heterocycles [114–116]. Just recently, Chen's group reported a one-pot redox strategy for synthesis of dihydrothiophenes **225**, thiophenes **226**, and bromothiophenes **227** from readily available allylic alcohols **224** with DMSO and HBr with high regioselectivity (Scheme 82) [117]. This high selectivity was mainly achieved by modulating the dosage regulation of DMSO and HBr. In addition, mechanistic findings further indicated that dimethyl sulfoxide acts as both oxidant and sulfur donor. Various biologically active molecules could be successfully transformed by this protocol, demonstrating its practicality.

5 As Methylthio Source (–SMe)

In 2016, Wu et al. reported a protocol for I_2/Cu(II)-mediated C(sp^3)–H functionalization of aryl methyl ketones **228** to obtain a series of 2,4,5-trisubstituted furans **229** in good to excellent isolated yields (Scheme 83) [118]. The ability of the gram-scale



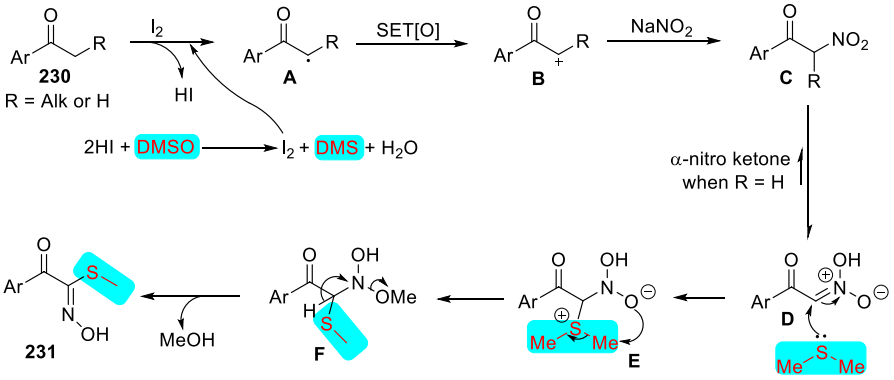
Scheme 82 Redox strategy for DMSO and HBr [117]



Scheme 83 I_2/Cu(II)-mediated protocol for C(sp^3)–H functionalization of aryl methyl ketones **228** [118]

reactions to proceed smoothly further demonstrated the practicality of the protocol. In addition, the results of the mechanistic study showed that dimethyl sulfoxide plays a pivotal role in this transformation and provides a sulfur methyl source for the 3-position of furan.

In the same year, Batra et al. revealed an I_2-promoted three-component α-C–H functionalization strategy for propiophenones **230** with $NaNO_2$ and dimethyl sulfoxide to obtain various thiohydroximic acids **231** in moderate to excellent isolation

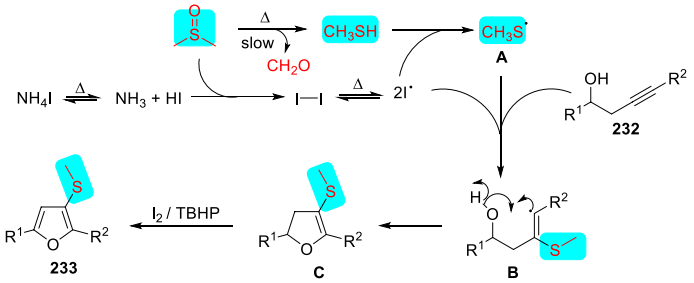


Scheme 84 Synthesis of thiohydroximic acids **231** [119]

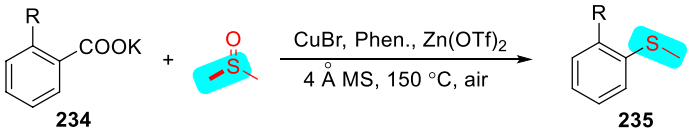
yields (Scheme 84) [119]. The protocol is characterized by simplicity of operation, the absence of transition-metal catalysis, a wide range of substrates, and the availability of commercially available starting materials.

Interestingly, I_2/TBHP-promoted tandem cyclization synthesis of 3-methylthiofurans **233** from homopropargylic alcohols **232** and dimethyl sulfoxide protocol was reported by Yan et al. (Scheme 85) [120]. The results of the mechanism study showed that DMSO was used as a solvent in addition to acting as a methylthio donor. In addition, the reaction proceeded smoothly with homopropargylic alcohols containing various substituent groups, with moderate to good yields.

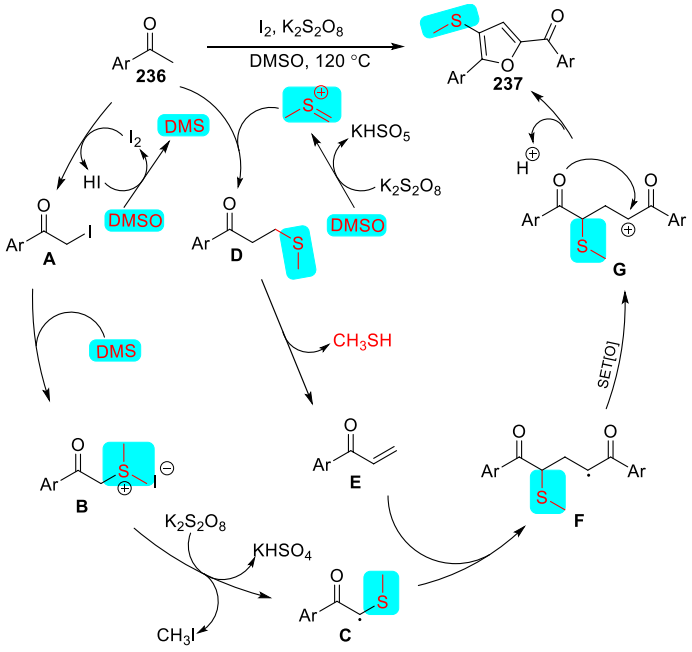
In 2017, Tan et al. revealed a copper-catalyzed one-pot protocol using potassium aryl carboxylates **234** and dimethyl sulfoxide to obtain various aryl methyl sulfides **235** in moderate to good yields (Scheme 86) [121]. The transformation successfully used dimethyl sulfoxide as a methylthio source. Optimization of the conditions showed that the use of 2 equiv. of $Zn(OTf)_2$ as an additive greatly



Scheme 85 I_2/TBHP-promoted tandem cyclization protocol [120]



Scheme 86 Synthesis of aryl methyl sulfides **235** [121]



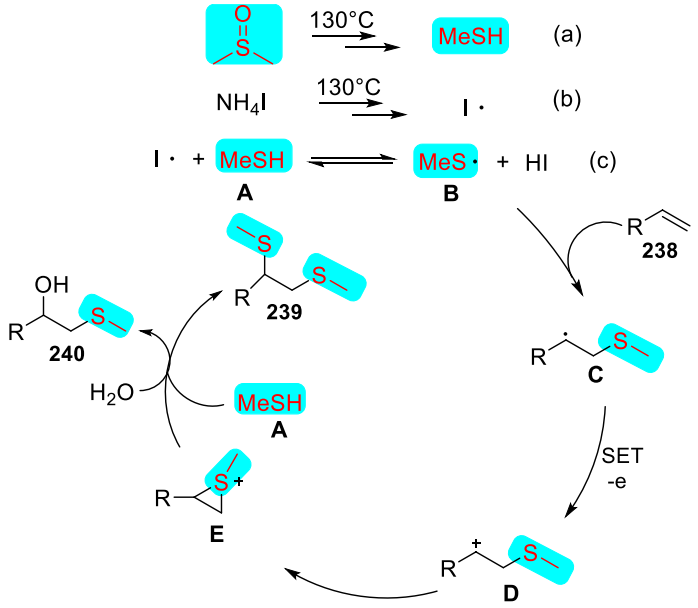
Scheme 87 Synthesis of multisubstituted furans **237** [122]

improved the yields of the target products, while the reaction needed to be carried out directly in air.

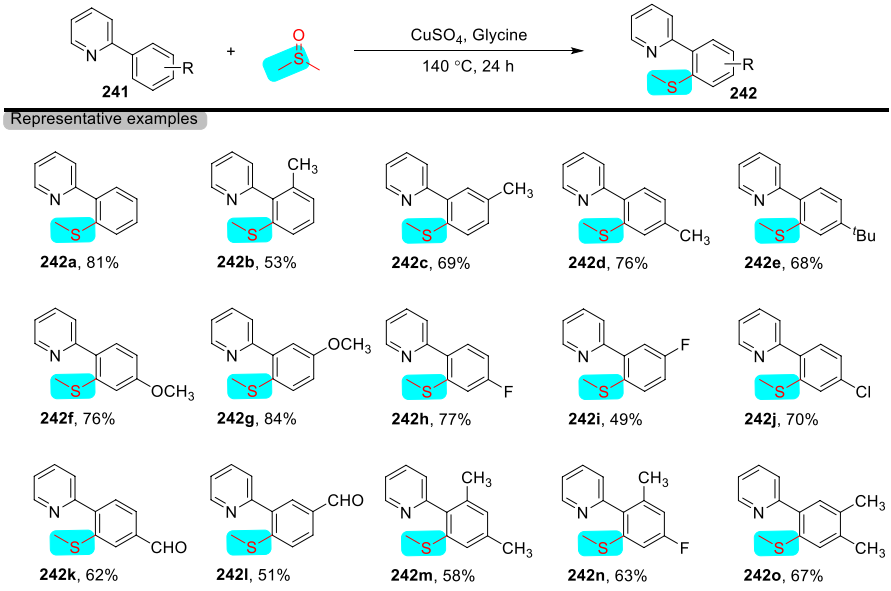
In 2019, Guo's group further reported an I_2-mediated one-pot C(sp^3)–H functionalization protocol for aryl methyl ketones **236** with DMSO to give a series of multisubstituted furans **237** in moderate to good yields (Scheme 87) [122]. DMSO acted as a solvent in this transformation, but also as a methylthio donor and a methylene single carbon source. The results for the optimization of the conditions indicated that $K_2S_2O_8$ was critical as a promoter for this reaction. Furthermore, the reaction with **236w** proceeded smoothly on gram scale under standard conditions, clearly demonstrating the potential utility of this transformation in organic synthesis.

In the same year, He et al. revealed a strategy based on intermolecular bifunctionalization of alkenes **238** under NH_4I promotion for highly selective synthesis of various bis-dimethyl sulfanes **239** and β-hydroxysulfides **240** (Scheme 88) [123]. Interestingly, water played a key role in this transformation, and the amount of water used could modulate the transformation of different products. Mechanistic studies indicated that dimethyl sulfoxide was first decomposed to CH_3SH at 130 °C, followed by the involvement of CH_3SH with I^- in the subsequent conversion.

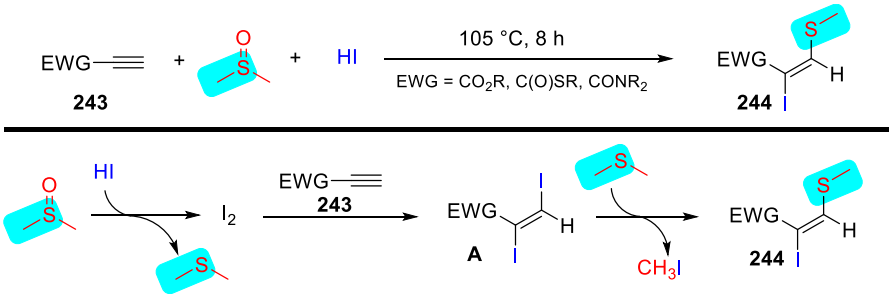
Next, Xu et al. reported an amino acid ligand-promoted one-pot protocol using 2-phenylpyridines **241** and dimethyl sulfoxide to synthesize a series of aryl methyl sulfides **242** in moderate to good yields (Scheme 89) [124]. This highly regioselective protocol did not require additional solvents, while being compatible with a wide range of functional groups.



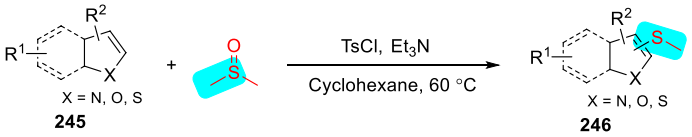
Scheme 88 Synthesis of bis-dimethyl sulfanes **239** and β-hydroxysulfides **240** [123]



Scheme 89 Synthesis of aryl methyl sulfides **242** [124]



Scheme 90 Preparation of various (*E*)-2-iodo-3(methylthio)acrylates **244** [125]



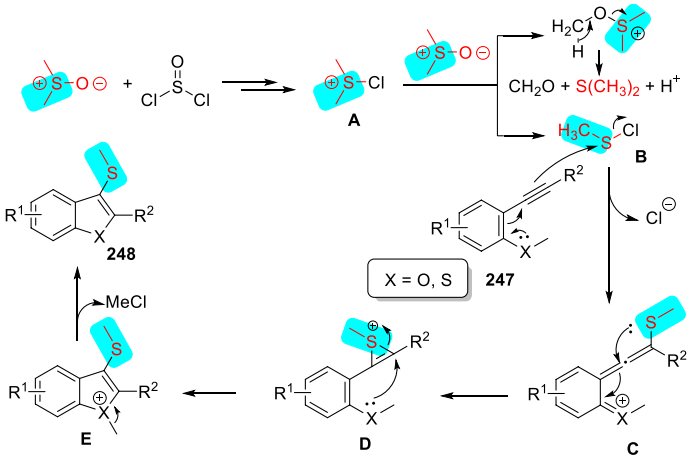
Scheme 91 Direct methanethiolation of electron-rich heterocyclic compounds [126]

In 2021, Wu's group developed a strategy for one-pot iodomethylation of alkynes **243** with aqueous HI solution and dimethyl sulfoxide to prepare various (*E*)-2-iodo-3(methylthio)acrylates **244** in good to excellent yields (Scheme 90) [125]. This transformation was characterized by simple reaction conditions, very good functional group tolerance, a wide range of substrates, and no need for additional catalysts or additives.

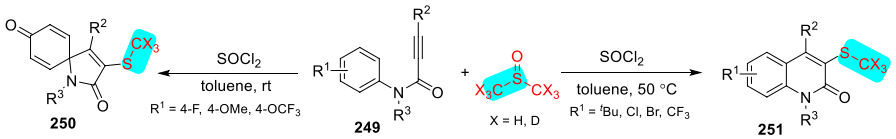
In the same year, Xing et al. revealed a one-pot methanethiolation protocol using electron-rich heterocyclic compounds **245** with dimethyl sulfoxide for synthesis of various pyrrole, furan, and thiophene derivatives **246** with high regioselectivity in yields up to 96% (Scheme 91) [126]. The success of four combined application experiments and 10 mmol scale-up experiments further demonstrated the potential utility of this transformation in organic synthesis.

Interestingly, Du's group reported the use of $SOCl_2$-interacting 2-alkynyl anisoles/sulfides **247** to synthesize biologically conceptual 3-(methylthio)-benzo[*b*] furans/thiophenes **248** in good to excellent yields by an intramolecular cyclization strategy under dimethyl sulfoxide as a methylthio source (Scheme 92) [127]. This intramolecular cyclization transformation protocol proceeded smoothly when using DMSO-d_6 instead of DMSO.

Just recently, Du et al. went on to report a protocol for intramolecular electrophilic cyclization of *N*-aryl propynamides **249** using dimethyl sulfoxide as methylthio donor to obtain spiro[4,5]trienones **250** and quinolin-2-ones **251** in good to excellent yields (Scheme 93) [128]. This intramolecular electrophilic cyclization protocol was characterized by mild reaction conditions, no need for additional metals, and a wide range of substrates. At the same time, the quantum chemical approach provided an effective demonstration of the possible mechanism.



Scheme 92 Intramolecular cyclization strategy with DMSO as methylthio donor [127]



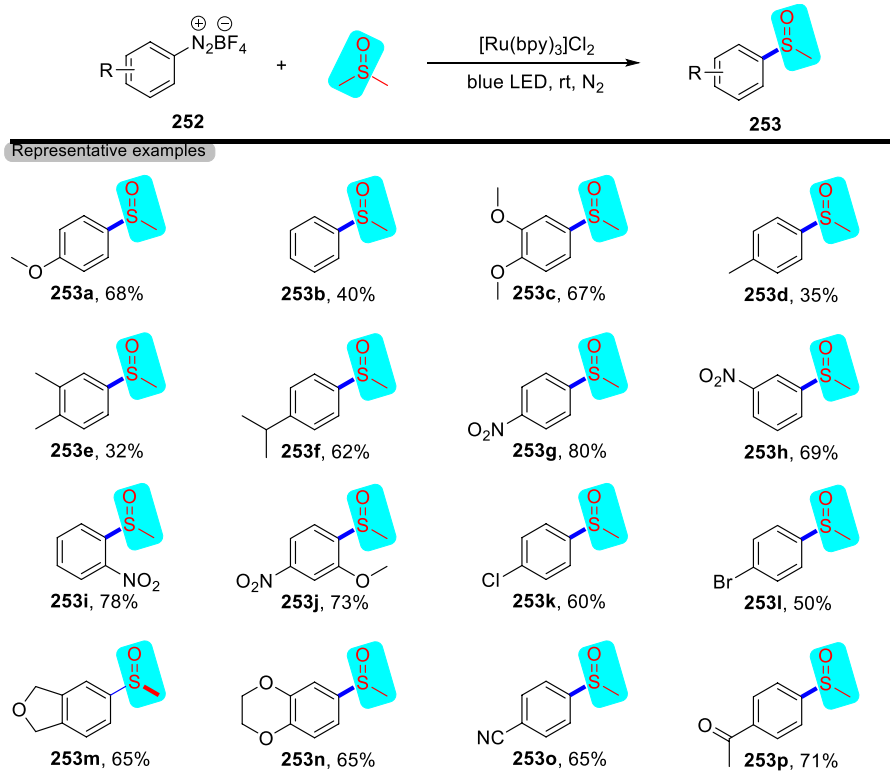
Scheme 93 Intramolecular electrophilic cyclization protocol based on *N*-aryl propynamides [128]

6 As Methyl Sulfoxide Source (–SOMe)

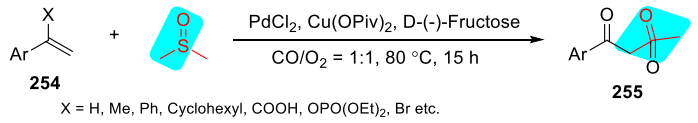
In 2016, Pramanik and Rastogi reported for the first time a visible-light-induced protocol for methyl oxysulfide of aryl diazonium salts **252** using dimethyl sulfoxide as methyl sulfoxide donor, obtaining various aryl methanesulfonates **253** in moderate to good yields at room temperature (Scheme 94) [129]. Various functional groups are widely tolerated in this transformation, which is compatible with various functional groups on diazonium salt aryl and heteroaryl groups, including –OMe, $–NO_2$, –CN, –SCN, etc. This transformation proceeds smoothly when using DMSO-d_6 instead of DMSO.

In 2017, Lei's group reported a Cu/Pd-catalyzed one-pot oxysulfonation protocol of olefins **254** with dimethyl sulfoxide to synthesize a series of biologically valuable oxosulfonates **255** in moderate to good yields (Scheme 95) [130]. This conversion was able to proceed smoothly with cleavage of carbon–carbon and carbon–heteroatom bonds under the assistance of CO/O_2. The advantages of this protocol are mild reaction conditions, a wide range of substrates, and easy availability of starting materials.

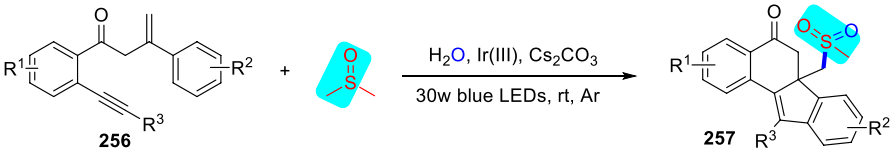
In 2018, Jiang et al. reported a protocol for visible-light-induced bicyclization of C(sp^3)-based 1,7-olefins **256** using DMSO in concert with H_2O as methanesulfonation source to synthesize various benzo[*a*]fluoren-5-ones **257** with



Scheme 94 Synthesis of aryl methanesulfonates **253** [129]

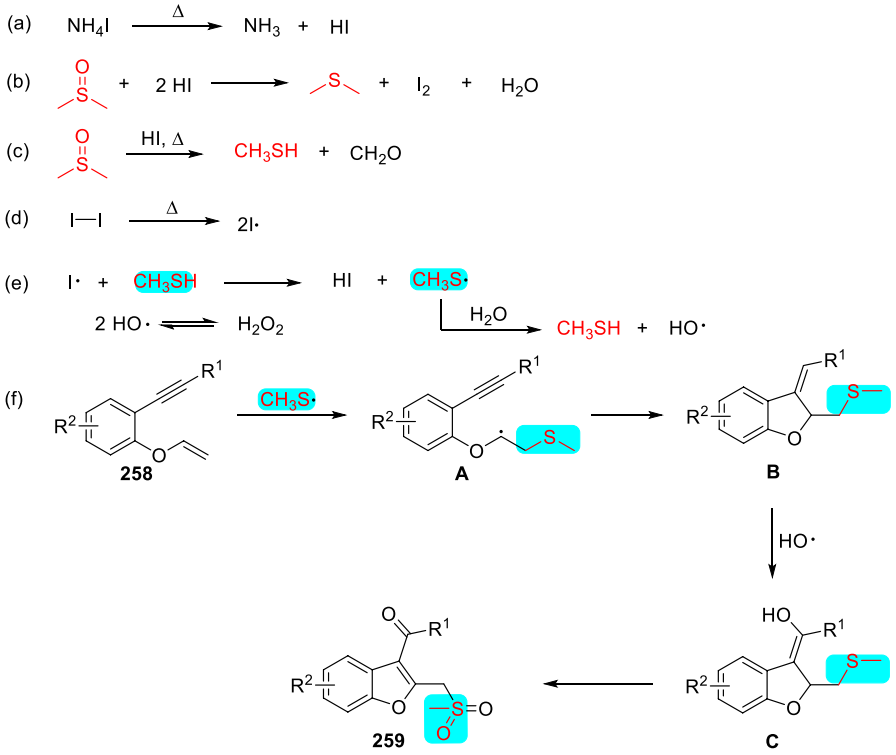


Scheme 95 Synthesis of biologically valuable oxosulfonates **255** [130]



Scheme 96 Synthesis of various benzo[*a*]fluoren-5-ones **257** [131]

functionalization in moderate to good yields (Scheme 96) [131]. The advantages of this dual cyclization strategy are mild reaction conditions, a wide range of substrates, and the use of H_2O as an oxygen source. No production of **257a**



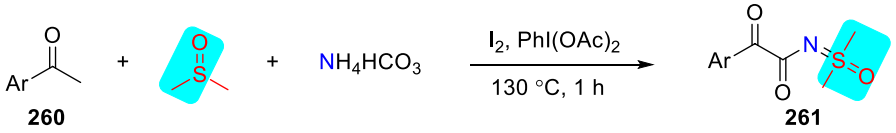
Scheme 97 Synthesis of various dual-functional benzofurans **259** [132]

was observed when TEMPO and BHT were used as free radical scavengers under standard conditions, suggesting that this protocol may be a free radical process.

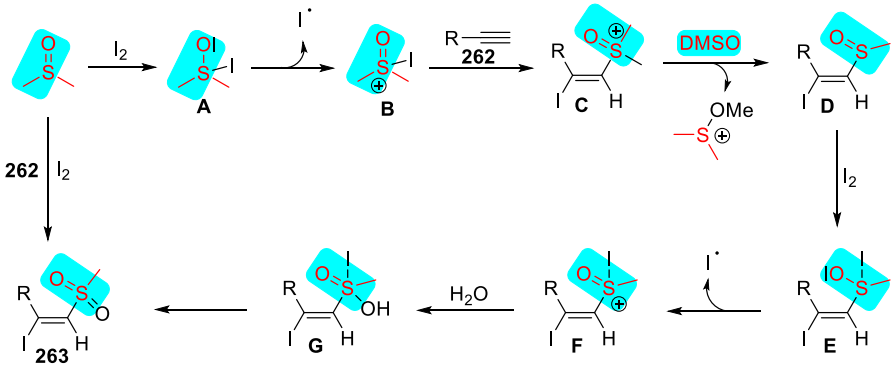
In the same year, Sun et al. revealed an NH_4I-promoted one-pot cascade cyclization procedure for oxygen-linked 1,6-enynes **258** with dimethyl sulfoxide to obtain dual-functional benzofurans **259** in good yields (Scheme 97) [132]. This protocol had utility in organic synthesis and could synthesize benzothiophene from sulfur-linked 1,6-enyne. In addition, the transformation was able to tolerate various functional groups, such as –OMe, $–CF_3$, –CN, –COMe, etc.

In 2019, Wu's group developed a three-component protocol based on I_2/$PhI(OAc)_2$ co-promotion of aryl methyl ketones **260** with DMSO and ammonium bicarbonate to obtain α-dicarbonyl sulfoximines **261** in moderate to good yields (Scheme 98) [133]. Interestingly, tetramethylene sulfoxide as a substitute for DMSO was also able to perform this ammonification strategy under standard conditions. In addition, the aryl methyl ketones offered a broad range of substrates that could be applied to various functional groups and different sites.

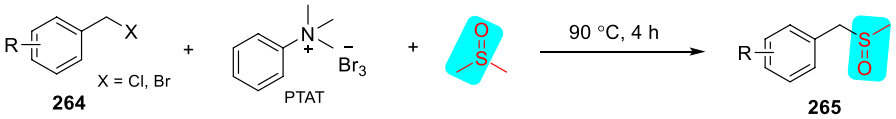
In the same year, Liu et al. reported for the first time an iodination–methylsulfoxidation strategy using I_2 with DMSO and alkynes **262** to synthesize a series of (*E*)-α-iodo-β-methylsulfonyl alkenes **263** in good yields (Scheme 99) [134].



Scheme 98 Synthesis of various α-dicarbonyl sulfoximines **261** [133]



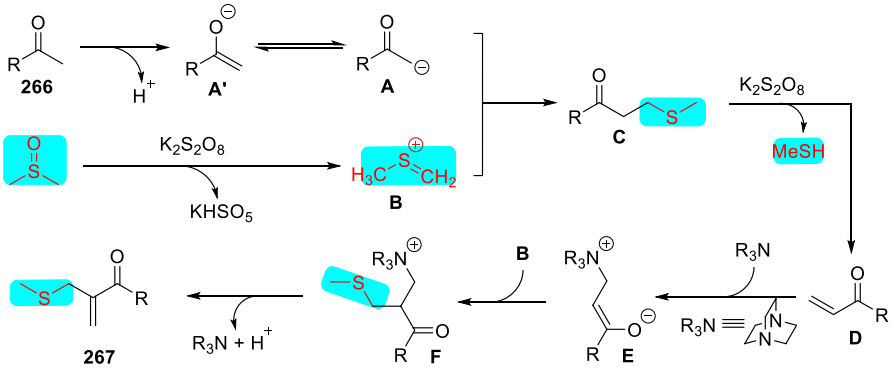
Scheme 99 Proposed mechanism for synthesis of **263** [134]



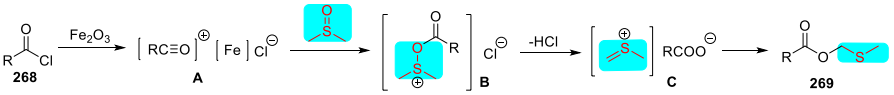
Scheme 100 Synthesis of various benzyl methyl sulfides **265** [135]

This four-component transformation is characterized by water as oxygen source, a wide range of substrates, and high chemoselectivity. In addition, labeling experiments with ^{18}O further demonstrated that one oxygen atom in the $–SO_2Me$ group is derived from water.

In 2020, Xu et al. reported a one-pot nucleophilic substitution protocol using benzyl halides **264** and dimethyl sulfoxide to obtain various benzyl methyl sulfides **265** in moderate to good yields (Scheme 100) [135]. This protocol has a wide range of substrates and can be applied with a variety of functional groups such as benzo, halo, CN, CF_3, MeO, CHO, etc. Furthermore, when the reaction time was shortened to 2 h under standard conditions, 2% of the by-product benzyl (methyl) sulfide was obtained, suggesting that benzyl (methyl) sulfide may be produced from benzyl chloride.



Scheme 101 Synthesis of β-methylthio isopropenylketones **267** [136]



Scheme 102 Proposed mechanism for synthesis of alkyl thiomethyl esters **269** [137]

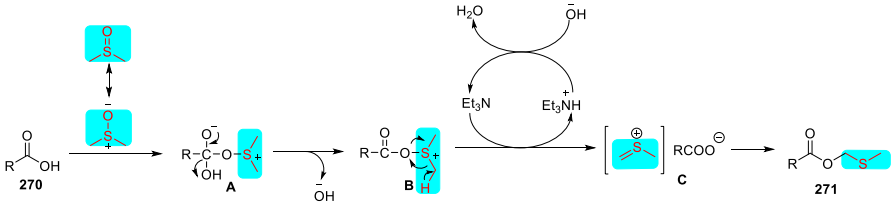
7 As Methyl Thiomethylation Source (–CH_2SMe)

In 2017, Guo et al. reported a one-pot cross-coupling strategy for methyl ketones **266** with DMSO to obtain β-methylthio isopropenylketones **267** with various substituted functional groups in moderate to good yields (Scheme 101) [136]. Seven sets of detailed control experiments confirmed the rationality of the reaction mechanism. In addition, gram-scale experiments further demonstrated the potential utility of this cross-coupling of C(sp^3)–H bonds.

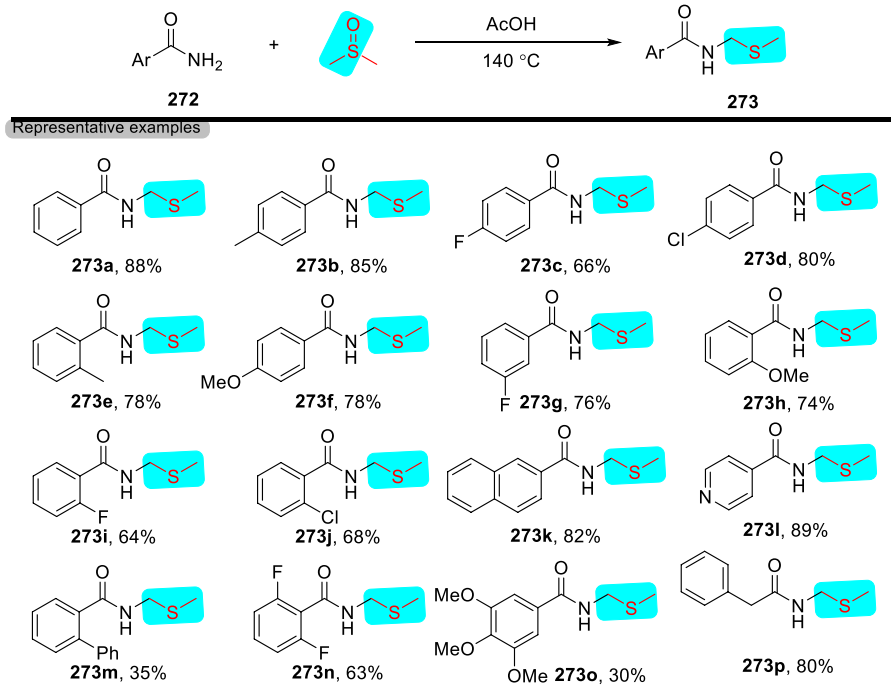
In the same year, Yang et al. developed an Fe(III)-catalyzed one-pot Pummerer rearrangement procedure for acyl chlorides **268** with dimethyl sulfoxide to obtain various alkyl thiomethyl esters **269** in good to excellent yields (Scheme 102) [137]. This procedure is characterized by inexpensive starting materials, mild reaction conditions, simplicity of operation, a wide range of substrates, and high product yields.

Then, in 2019, Cai et al. went on to report a method for synthesis of alkyl thiomethyl esters **271** using readily available carboxylic acids **270** and dimethyl sulfoxide via a Pummerer-type rearrangement protocol (Scheme 103) [138]. This transformation is characterized by a wide range of substrates and inexpensive starting materials. Moreover, this transformation was achieved using Et_3N as promoter for 20 h. On the downside, the reaction time is long and the temperature is high.

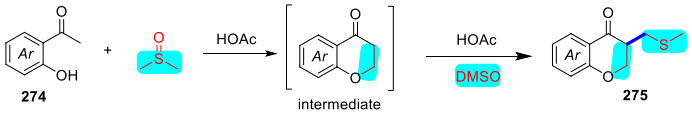
In 2020, Ma et al. revealed an efficient one-pot AcOH-promoted procedure for benzamides **272** with dimethyl sulfoxide to obtain *N*-[(methylthio)methyl]benzamides **273** in good yields (Scheme 104) [139]. In this conversion, dimethyl sulfoxide plays a pivotal dual role as solvent and donor for methyl sulfide. Interestingly, **272** and **273** could be further converted to asymmetric methylene-bridged bisamides in



Scheme 103 Proposed mechanism for synthesis of alkyl thiomethyl esters **271** [138]



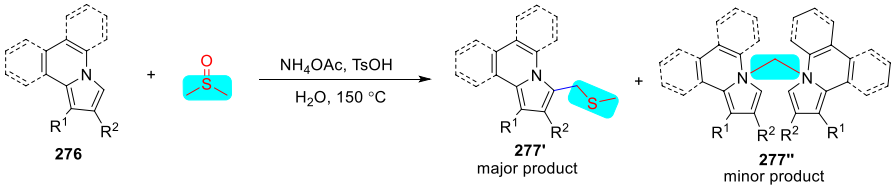
Scheme 104 Synthesis of *N*-[(methylthio)methyl]benzamides **273** [139]



Scheme 105 Synthesis of chroman-4-ones **275** [140]

the presence of dimethyl sulfoxide as a bridging carbon donor. This reaction provides a new approach for efficient synthesis of asymmetric bisamides.

In 2022, Jiang et al. revealed an HOAc-promoted protocol for cascade cyclization of *o*-hydroxyacetophenones **274** with dimethyl sulfoxide to obtain a series of 3-(methylthiomethyl)chromanones **275** in moderate to good yields (Scheme 105)



Scheme 106 Methylthiomethylation and methylenation transformations [141]

[140]. The protocol involved the activation of two molecules of dimethyl sulfoxide by HOAc followed by cascade cyclization as two molecules of synthons and *o*-hydroxyacetophenones **174**. The advantages of this transformation are high selectivity and the absence of any additives.

Just recently, Cui et al. reported a methylthio strategy for pyrroloquinolines and pyrroloisoquinolines **276** in the presence of TsOH/NH_4OAc, obtaining various thioethers **277′** in moderate to good yields (Scheme 106) [141]. It is worth mentioning that DMSO can be used as a methylene-bridging carbon source **277″** in addition to solvent and methyl thiomethylation source in this transformation. The method is characterized by simple reaction conditions, scalability to gram scale, and conversion to sulfone and sulfoxide by simple oxidation.

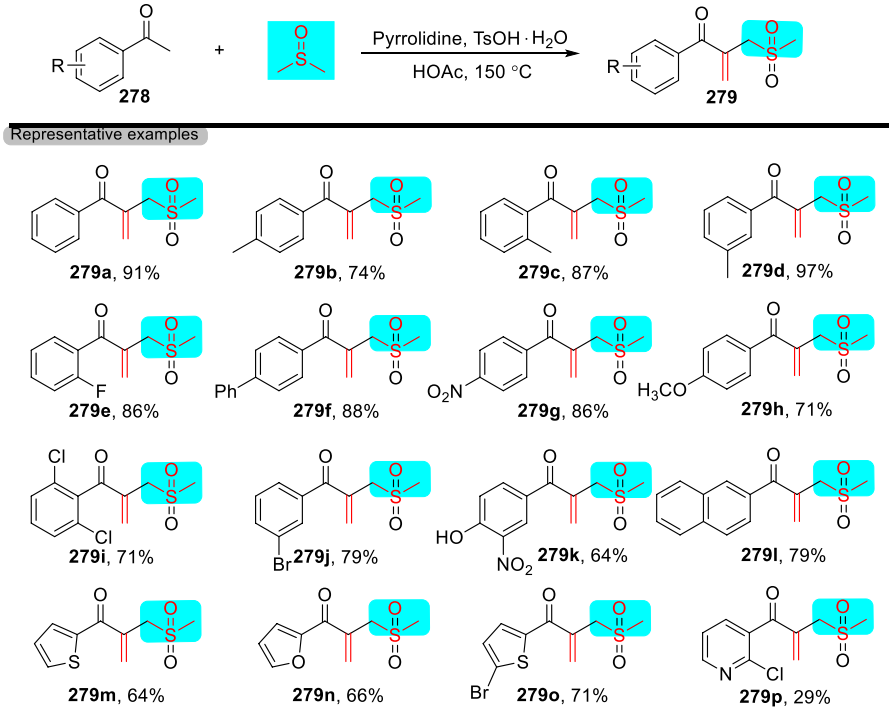
8 As Methyl Sulfoxide Methylation Donor (–CH_2SOMe)

In 2017, Wen et al. reported a one-pot direct cross-coupling strategy for aryl methyl ketones **278** with dimethyl sulfoxide to obtain various β-acyl allylic methylsulfones **279** in moderate to good yields (Scheme 107) [142]. The protocol could provide β-acyl allylic methylsulfides under similar reaction conditions. Seven sets of control experiments further validated the rationality of the reaction mechanism.

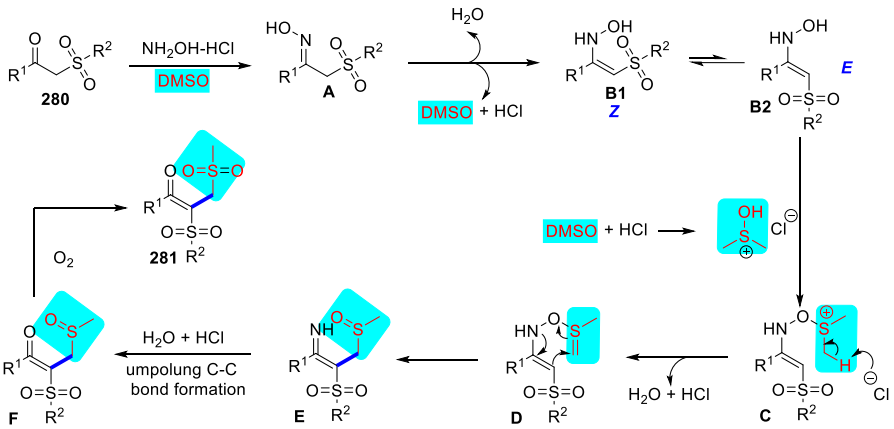
In 2019, Chang et al. revealed an NH_2OH·HCl-mediated intermolecular umpolung α-methanesulfonation protocol for α-sulfonyl ketones **280** with dimethyl sulfoxide to obtain a variety of α,β-bissulfonyl arylketones **281** in good to excellent yields (Scheme 108) [143]. This novel and efficient route is characterized by simple reaction conditions, a wide range of substrates, and easy preparation of starting materials. The practicality of the method was further illustrated by synthetic transformation experiments of α,β-bis(sulfonyl)aryl ketones.

In 2020, Tang et al. revealed for the first time an NBS-promoted cross-dehydroesterification procedure for carboxylic acids **282** with DMSO to obtain various (methylsulfinyl)methyl esters **283** via Pummerer-type rearrangement (Scheme 109) [144]. This transformation is characterized by mild reaction conditions, easy availability of starting materials, a wide range of substrates, and simplicity of operation. In addition, the preparation of deuterated **283** by using deuterated labeled DMSO as a reagent is of potential practical value.

In the same year, Zhang's group reported an HCl-promoted one-pot dehydrogenation coupling protocol for β-keto sulfones **284** with dimethyl sulfoxide to obtain

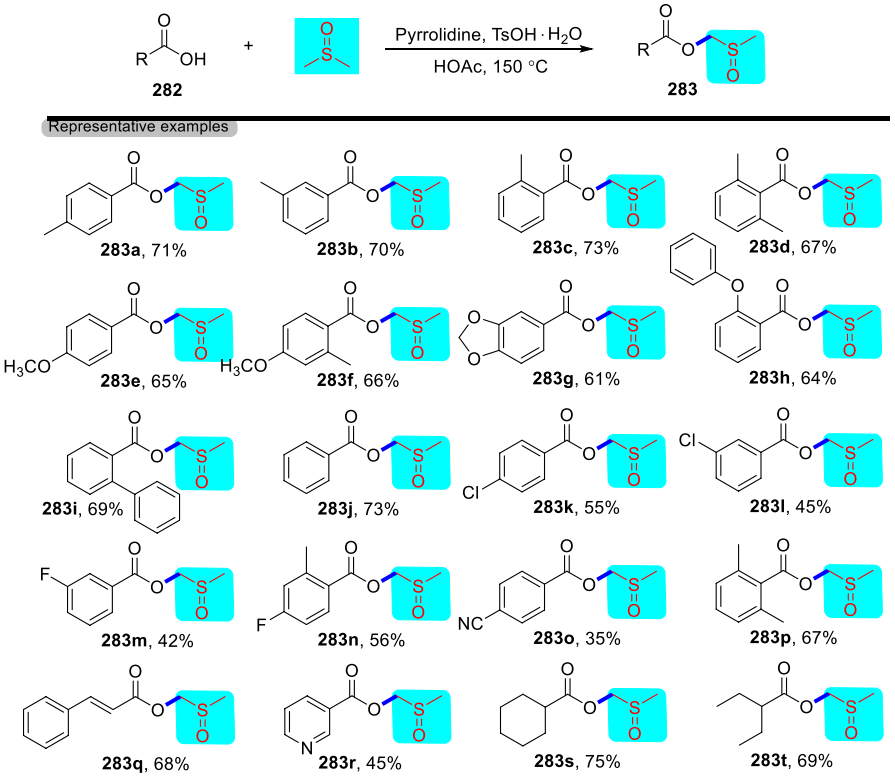


Scheme 107 Synthesis of β-acyl allylic methylsulfones **279** [142]

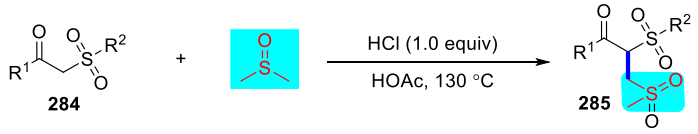


Scheme 108 Plausible mechanism for synthesis of α,β-bis(sulfonyl)aryl ketones **281** [143]

various α,β-disulfonyl ketones **285** in good to excellent yields (Scheme 110) [145]. Interestingly, the reaction conditions afforded smooth access to β-sulfinyl ketones without addition of HCl. The potential of the mechanism was further verified by eight sets of control experiments.

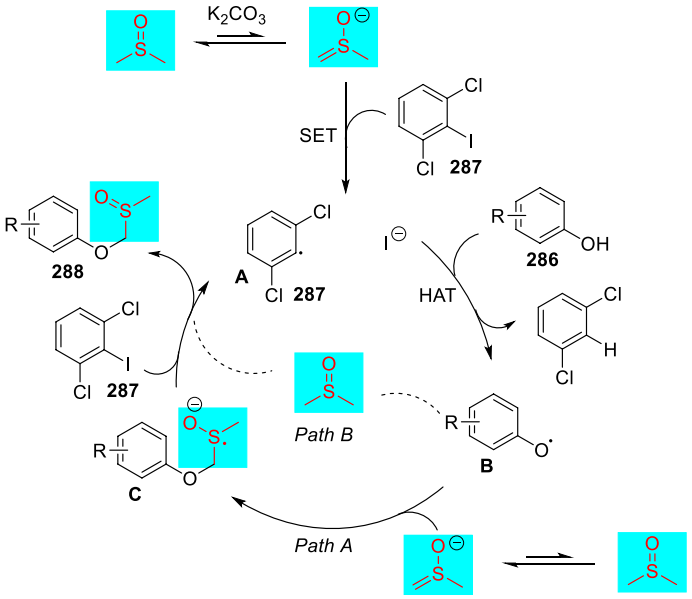


Scheme 109 Synthesis of (methylsulfinyl)methyl esters **283** [144]



Scheme 110 Synthesis of α,β-disulfonyl ketones **285** [145]

Interestingly, Barriault et al. reported a one-pot base-promoted single-electron-transfer protocol for phenols **286** and 2,6-dichloroiodobenzene **287** with DMSO to obtain methylthiomethyl ethers **288** in moderate yields (Scheme 111) [146]. Mechanistic studies showed that dimethyl sulfoxide acts as a single-electron reductant in the presence of base, in addition to its role as a solvent. Meanwhile, four sets of control experiments further validated the mechanistic possibility.



Scheme 111 Plausible mechanism for synthesis of methylthiomethyl ethers **288** [146]

9 Summary and Outlook

This review focuses on recent advances in the use of dimethyl sulfoxide as a synthon in organic chemistry and covers all the reports from 1 January 2016 to 11 May 2022, providing more than 110 reactions using dimethyl sulfoxide as an organic synthon. The reactions are summarized based on the use of dimethyl sulfoxide as oxygen (–O–, =O), methyl ($–CH_3$), methylene ($–CH_2–$), methylidene ($=CH_2$), methine (=CH–), donor of formylation (–CHO), sulfur (–S–), methylthio (–SMe), methyl sulfoxide (–SOMe), donor of methyl thiomethylation ($–CH_2SMe$), donor of methyl sulfoxide methylation ($–CH_2SOMe$), highlighting various synthetic pathways.

Despite the excellent progress that has been made in this area with dimethyl sulfoxide, a number of challenges remain. First, there are few examples of the use of dimethyl sulfoxide as a sulfur-derived precursor for construction of thiophene and new C–S bonds. Secondly, the use of dimethyl sulfoxide as a donor in the synthesis of some useful natural products as well as the transformation of important drug molecules remains less successful. Finally, some reaction conditions may need to be further optimized to accommodate more functional groups and milder reaction conditions. This review covers almost all the literature from 1 January 2016 to 11 May 2022 using dimethyl sulfoxide as a donor, providing scientists with easy access to the literature. The success stories achieved so far lead us to boldly predict that new types of reactions, more interesting reaction mechanisms, and milder reaction conditions will be discovered and reported in the near future. We also anticipate that dimethyl sulfoxide will be used more widely in organic synthesis, bioengineering, and drug discovery procedures.

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Declarations

Conflict of interest The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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