CJC Chinese Journal of Chemistry 中国化学 - An International Journal

Review–Cornerstones in Chemistry

Cite this paper: *Chin. J. Chem.* **2026**, *44*, 2593—2605. **DOI: 10.1002/cjoc.70623**

DMSO: A Magic Chemical for Bromination and Chlorination

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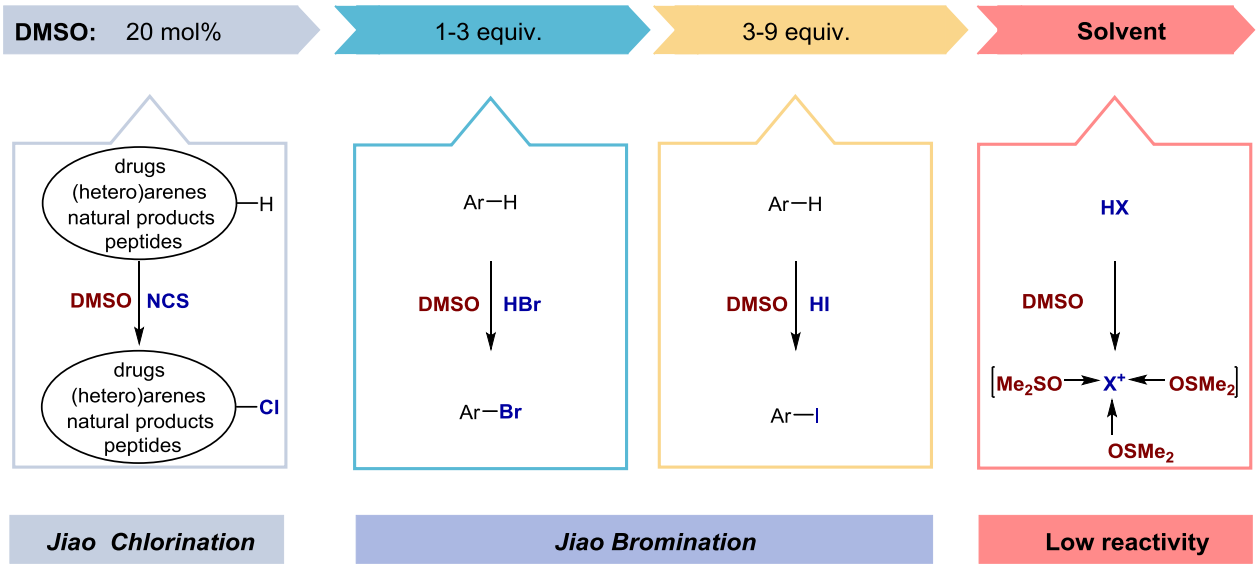
Keywords

Dimethyl sulfoxide | Halogenation | Bromination | Hydrobromic acid | Chlorination | *N*-Chlorosuccinimide | Lewis base catalysis | Late-stage modification

Comprehensive Summary



Halogenation plays a crucial role in organic synthesis. Over the past century, numerous reaction systems have been developed for the synthesis of halogen-containing molecules. However, traditional halogenation reactions rely on highly reactive halogenating reagents, suffer from poor regioselectivity and limited functional group tolerance. In 2015, Jiao *et al.* from Peking University achieved the efficient oxidative bromination of (hetero)arenes and alkenes using a mild reaction system consisting of stoichiometric amounts of dimethyl sulfoxide (DMSO) and aqueous hydrobromic acid (Jiao Bromination). Following in-depth research on Lewis base activation systems, Jiao and coworkers further developed a DMSO-catalyzed chlorination of (hetero)arenes using *N*-chlorosuccinimide (NCS), which enables the late-stage modification of complex molecules (Jiao Chlorination). Their works clarify that DMSO plays distinct roles at different loadings: stoichiometric DMSO acts as a mild oxidant to drive oxidative bromination with hydrobromic acid, catalytic DMSO serves as a Lewis base catalyst to activate NCS for selective chlorination, and excess DMSO forms an inert $(DMSO)_n \bullet X^+$ adduct to inhibit reaction activity. The theoretical framework promotes the innovation of halogenation strategies. Jiao halogenation has been widely applied to various fields of organic synthesis, including late-stage modification of bioactive compounds, total synthesis of natural products, and preparation of material molecules.

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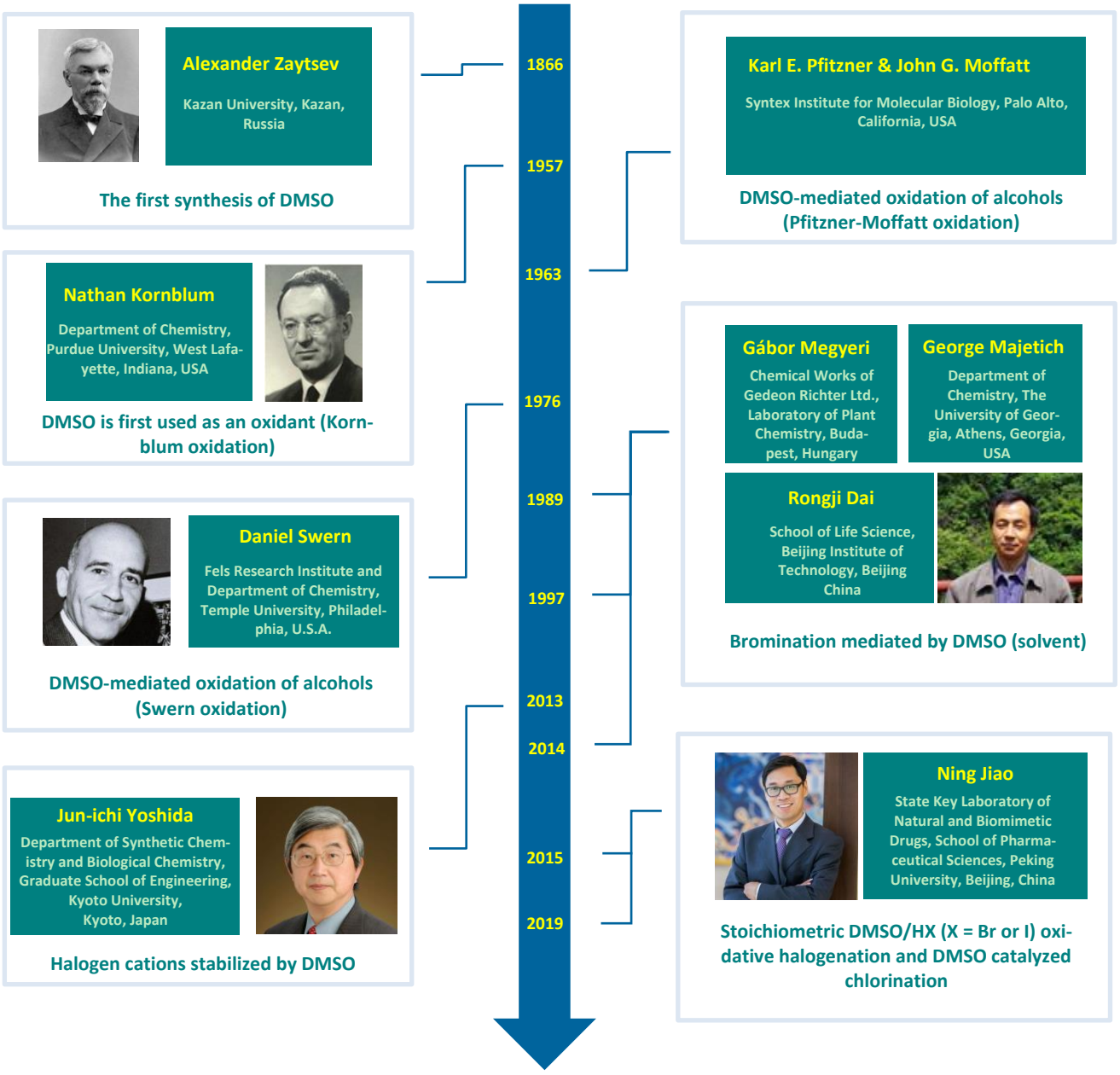
Key Scientists

In 1866, Alexander Zaytsev first synthesized dimethyl sulfoxide (DMSO).[1] In 1957, Kornblum's group discovered that alkyl halides could be efficiently oxidized by simply dissolving the substrates in DMSO.[2] Later, in 1963, Moffatt and his student Pfitzner observed that primary and secondary alcohols could be oxidized to aldehydes and ketones, respectively, when DMSO was activated by dicyclohexyl carbodiimide (DCC) in the presence of catalytic anhydrous phosphoric acid.[3] In 1976, Swern and colleagues showed that activation of DMSO with trifluoroacetic anhydride (TFAA) also enabled the rapid oxidation of primary and secondary alcohols.[4] Subsequently, Megyeri,[5] Majetich,[6] and Dai,[7] independently reported the oxidative bromination of arenes using DMSO as the oxidant in 1989, 1997, and 2014, respectively. In 2013, Yoshida and co-workers demonstrated through experiments and density functional theory calculations that DMSO could stabilize halogen cations (Br^+, I^+) via coordination.[8] In 2015, Jiao's group achieved an efficient halogenation of arenes using stoichiometric combination of DMSO/HX (rather than as a solvent).[9] This approach avoided the significant reduction in reactivity of X^+ species caused by excess DMSO, enabling highly efficient oxidative halogenation of arenes. The system was subsequently extended to the halogenation of various substrates, including alkenes, alkynes, ketones, benzyl bromides, and benzylic alcohols.[10-13] In 2019, the same group further showed that DMSO could also act as a catalyst to activate electrophilic halogenating reagents, enabling late-stage chlorination of various bioactive molecules and pharmaceuticals.[14]



Contents

1. Introduction

Organic halides are important synthons, and a wide variety of compounds can be obtained through functional group transformations or coupling reactions.[15-16] Meanwhile, halogenation represents a critical strategy in drug discovery, as halogen atoms directly modulate key compound properties such as biological activity, metabolic stability, and physicochemical profiles.[17] Among the 352 drugs approved by the FDA between 2018 and 2024, over 30% contain halogenated structures.[18] Hence, developing efficient and practical halogenation methods, especially for the synthesis of aryl halides, remains a high priority in the field of organic synthesis.[19]

Numerous electrophilic halogenating reagents (Figure 1) have been developed for aromatic halogenation reactions, including *N*-halosuccinimides (NXS), dibromohydantoin (DBDMH), and *tert*-butyl hypochlorite (*t*-BuOCl). Entering the 21st century, halogenating reagents, such as Barluenga's reagent (IPy_2BF_4),[20-21] iododiethylsulfonium bromopentachloroantimonate (IDSI),[22] *N*-chloro-*N*-fluorobenzenesulfonimide (CFBSA),[23] Palau'chlor,[24] and *N*–X (X = Cl, Br) anomeric amides,[25] have also been successively developed for the halogenation of alkenes or arenes. Although these advancements have significantly improved the efficiency of halogenation reactions and led to their widespread application in organic synthesis, they still suffer from limitations such as low reactivity, poor selectivity, or low atom economy when targeting complex molecules.

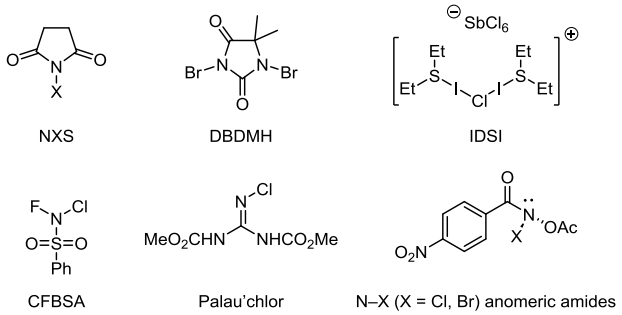


Figure 1 Representative halogenating reagents.

In addition, enzyme-catalyzed halogenation process in biological systems is based on the enzymatic oxidative of halide ions,[26-27] in which mild conditions enable compatibility with complex molecules. However, such catalysts are not readily available. Meanwhile, the oxidative halogenation reactions have also been developed using chemical oxidants or electro-chemistry.[28-33] However, these methods suffer from a major limitation: most oxidants employed exhibit excessively strong oxidizing ability, making them hardly applicable to complex molecules.

Late-stage functionalization of bioactive molecules is a critical strategy for generating diverse compound libraries in drug discovery and development process, which avoids the *de novo* synthesis. However, the presence of multiple unprotected functional groups in bioactive molecules tends to interfere with electrophilic halogenating reagents, and challenges in controlling the chemo-, regio-, and stereoselectivity of the reaction render late-stage halogenation of complex molecules highly demanding, and direct halogenation modification methods remain underdeveloped (Figure 2).

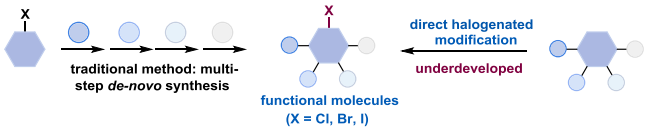


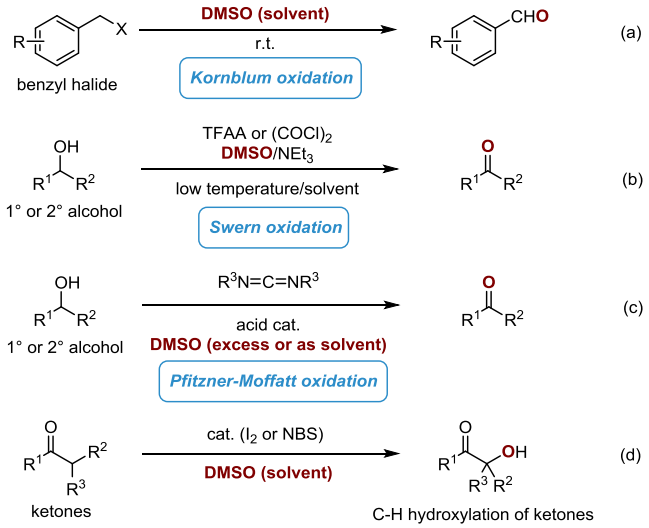
Figure 2 The importance of direct halogenation modification methods.

2. DMSO: A Magic Chemical

Since its discovery in the 19th century, dimethyl sulfoxide (DMSO) has evolved into a versatile and commonly used reagent, with its core applications spanning multiple fields such as chemistry, biology, and medicine.[34-36] Owing to its unique physical properties, it can serve as an S_N2 solvent to accelerate reactions; it is also a highly adaptable NMR solvent, particularly suitable for high polarity compounds such as polypeptides and carbohydrates. Additionally, DMSO is widely applied in cell experiments and animal studies.

Meanwhile, typical chemical properties of DMSO include oxidizability and Lewis basicity, which enable it to participate in various classic oxidation reactions. For instance, the Kornblum oxidation (Scheme 1a) enables the direct conversion of primary alkyl halides to aldehydes,[2] while the mild-condition Swern oxidation (Scheme 1b) and Pfitzner-Moffatt oxidation (Scheme 1c) can efficiently convert hydroxyl groups to carbonyl groups,[37-38] avoiding the use of strong oxidants or transition metals, and thus have been widely applied in organic synthesis. Building on these efforts, Jiao and coworkers from Peking University (PKU) developed a novel *N*-bromosuccinimide (NBS) or I_2 catalyzed C–H hydroxylation of ketones using DMSO as solvent oxygen source and oxidant to regenerate the halonium catalyst (Scheme 1d).[39]

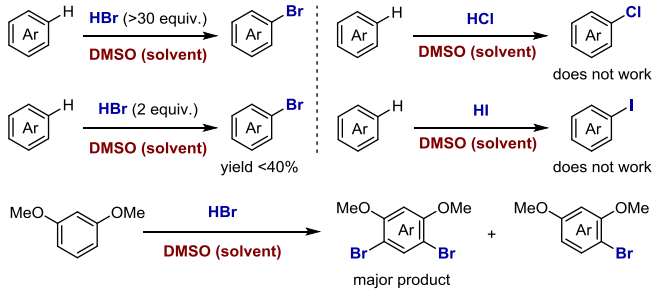
Scheme 1 Oxidation and oxygenation reactions using DMSO as oxidant and oxygen source



Oxidative halogenation is one of the sustainable methods for

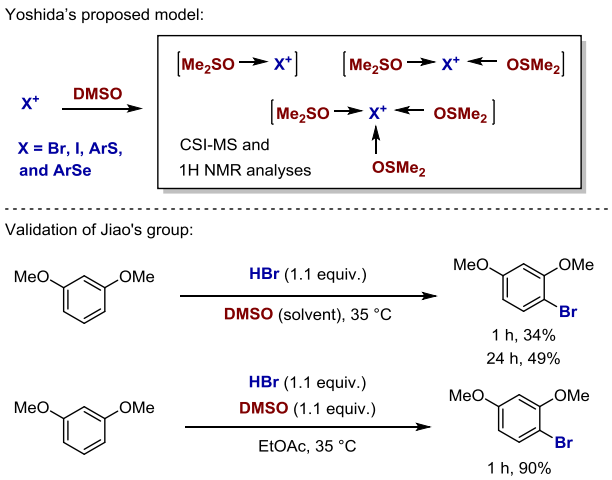
the synthesis of organic halides. Given its low-oxidizability, DMSO is utilized as both a solvent and a mild oxidant in oxidative halogenation reactions.[40] Early reports in the 1990s demonstrated that DMSO oxidized halide anions when used as a solvent under acidic conditions,[5,7,41] which revealed that bromodimethylsulfonium bromide ($DMSBr^+Br^-$), generated *in situ* by treating dimethyl sulfoxide with aqueous hydrobromic acid, was the key reagent for electrophilic aromatic bromination. However, the reported reactions suffered from several limitations: (1) The bromination of heteroarenes with DMSO/HBr had not been reported except for pyrrole derivatives; (2) the iodination of arenes cannot be achieved by their strategies; (3) the dibromination was uncontrollable due to the use of >9 equiv. of HBr (thus, the bromination of electron-rich arenes such as *m*-dimethoxybenzene mainly afforded the dibrominated product); (4) a less than 40% yield was obtained when 2 equiv. of HBr were employed. In addition, the heating of HBr in DMSO may induce explosive hazards.[42] Overall, poor reactivity, selectivity and potential explosion risk have hampered the applications of these methods (Scheme 2).

Scheme 2 Early research on the halogenation of arenes using DMSO/HX



In 2013, Yoshida's group discovered that halogen and chalcogen cations (X^+ = Br^+, I^+, ArS^+, and $ArSe^+$) could be generated via low-temperature electrochemical oxidation in the presence of DMSO (Scheme 3). Density functional theory (DFT) calculations indicated that DMSO stabilizes these cations through coordination.[8] Based on the this research and their NBS catalyzed oxygenation reaction with DMSO as the oxidant to regenerate halonium catalyst (Scheme 1d),[39] Jiao and co-workers hypothesized that the excessive DMSO in Majetich's report had significantly reduced the reactivity of X^+ species generated from the DMSO/HX system.[41] They further postulated that efficient halogenation of arenes using stoichiometric combination of DMSO/HX could be achieved (rather than as a solvent) (Scheme 3).[9]

Scheme 3 Proposed model and validation of halogen and chalcogen cations stabilized by DMSO



To further verify the hypothesis and explore the activating model of DMSO in depth, they carried out high-resolution mass spectrometry (HRMS) capture experiments.[14] When DMSO/*N*-chlorosuccinimide (NCS) (1 : 1) was dissolved in $CHCl_3$, $DMSO{\cdot}Cl^+$ was detected. When NCS was dissolved in DMSO (>50 equiv.), the $DMSO{\cdot}Cl^+$ peak disappeared (Figure 3). These results meant that excessive DMSO would coordinate to $DMSO{\cdot}Cl^+$ forming $(DMSO)_2{\cdot}Cl^+$, which was inert in the aromatic chlorination.

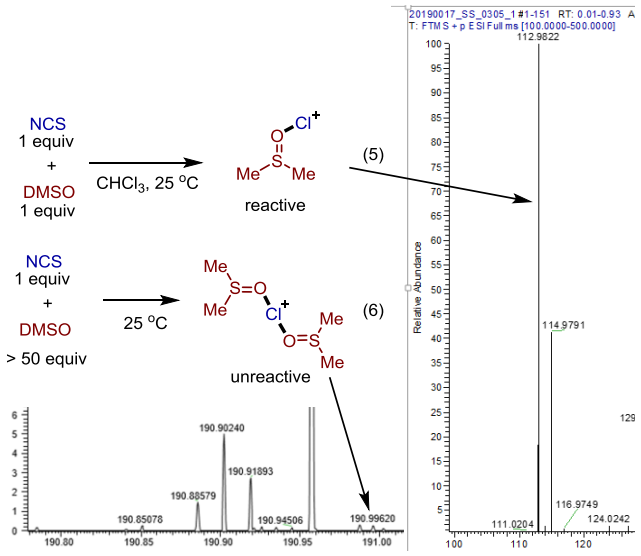
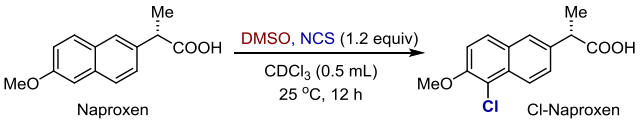


Figure 3 The detection of intermediates by HRMS under different DMSO loading.

Interestingly, investigations showed that the chlorination of naproxen proceeded smoothly to afford product Cl-naproxen in high yield when 0.2–1.0 equivalents of DMSO were employed; however, the yield decreased considerably with the increase in DMSO loading. This indicated that DMSO could serve as a catalyst to activate electrophilic halogenating reagents, rather than functioning as an oxidant. Corresponding intermediate concentrations were determined via HRMS, which revealed that the concentration of the $DMSO{\cdot}Cl^+$ species decreased significantly as the DMSO loading increased. This observation thereby further confirmed that $DMSO{\cdot}Cl^+$ is the active species responsible for the chlorination reaction (Figure 4).



Entry	DMSO	Yield of Cl-Naproxen	NL value in HRMS	relative concertration of $DMSO{\cdot}Cl^+$ in HRMS
1	0	trace		
2	0.2 equiv	97%		
3	0.5 equiv	96%		
4	1 equiv	94%	5.05E6	1
5	2.0 equiv	76%	1.32E6	0.26
6	5.0 equiv	35%	2.12E5	0.042
7	10.0 equiv	17%	6.02E4	0.012
8	50.0 equiv	trace	2.49E3	0.00049

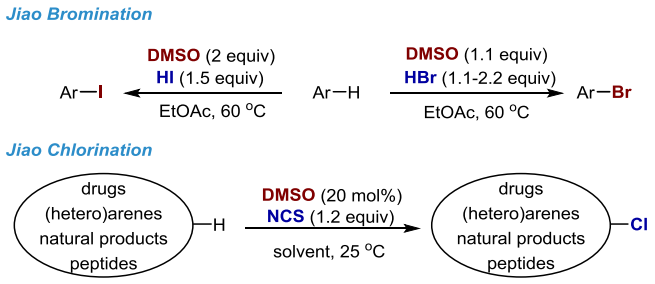
Figure 4 The influence of DMSO loading on the yield.

DFT calculations also confirmed that the $DMSO{\cdot}Cl^+$ species exhibits significantly higher reactivity than NCS. Specifically, it underwent reaction with the π-electrons of (hetero)arenes; however, excess DMSO coordinates to $DMSO{\cdot}Cl^+$ to form $(DMSO)_2{\cdot}Cl^+$—a kinetically inert adduct that was unreactive

toward (hetero)arenes, thereby inhibiting the aromatic chlorination reaction. Interestingly, the DFT calculation studies conducted by the Grimme group also supported their hypothesis.[43]

Based on these results and evidence above, Jiao and co-workers developed two types of halogenation reactions using DMSO as oxidant or catalyst: DMSO/HX (X = Br or I) oxidative halogenation and the DMSO catalyzed chlorination.[9,14] Owing to their simplicity, high efficiency, and excellent practicality, these methods were respectively recognized as "Jiao Bromination" (DMSO/HBr) and "Jiao Chlorination" (DMSO/NCS), and have been widely used in organic synthesis (Scheme 4).

Scheme 4 Jiao halogenation (including Jiao bromination and Jiao chlorination)

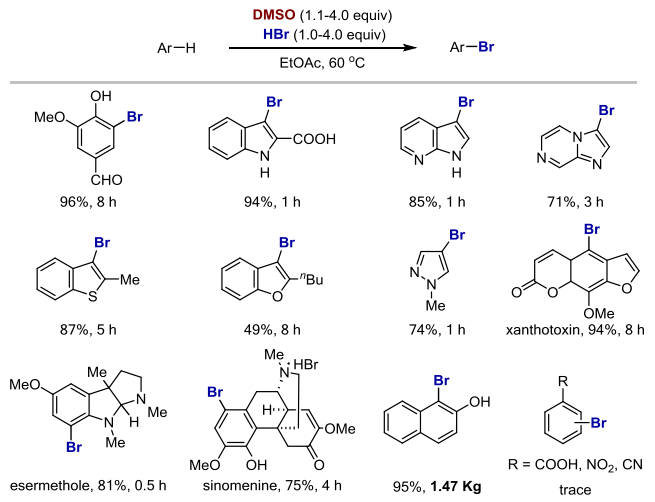


3. Jiao Bromination (DMSO/HBr)

3.1. Bromination and iodination of arenes and heteroarenes

In 2015, the Jiao group developed a highly efficient oxidative halogenation system for the halogenation of (hetero)arenes using DMSO/HX (X = Br, I).[9] Specifically, this system employed stoichiometric DMSO (acting as an oxidant rather than a solvent) in ethyl acetate under open air. Notably, this method exhibits excellent tolerance towards a variety of functional groups, including hydroxyl groups, carboxylic acids, amines, and *N*-heteroarenes. Critically, this system shows limited applicability to strongly electron-deficient arenes. Nevertheless, the reaction system is highly scalable—evidenced by the successfully conducted a kilogram-scale bromination—demonstrating its potential for large-scale industrial applications (Scheme 5). Subsequently, they extended this system to the halogenation of various substrates, including alkenes, alkynes, ketones, benzyl bromides, and benzylic alcohols.

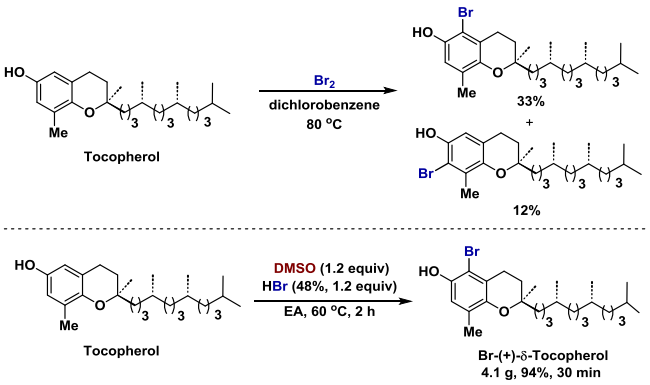
Scheme 5 Scope of Jiao bromination (DMSO/HBr) for arenes



It has been praised by the academic community as "an elegant procedure",[44] "easier to handle",[45] "excellent yield",[46] "has significant industrial potential",[47] "practical and mild",[48] "the most effective",[49] and "environmentally acceptable".[50] For these reasons, the DMSO/HBr system has become known as "Jiao bromination",[51-52] and has been widely applied in organic synthesis.[49,51,53-76]

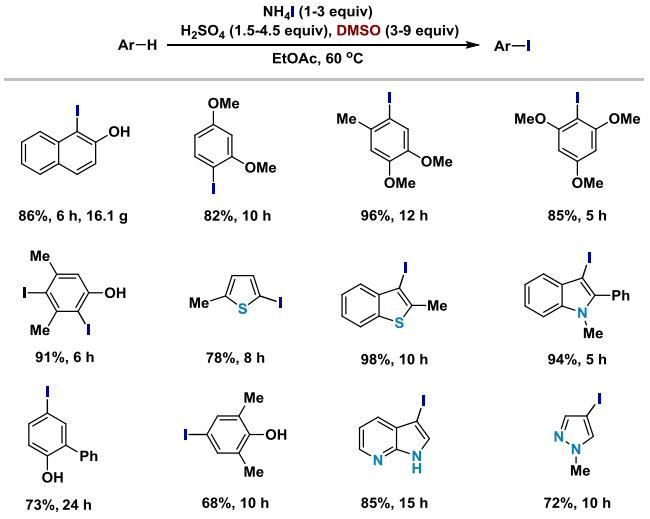
The bromination of tocopherol exemplifies the robustness of this method. While the use of Br_2 results in low yield and a mixture of regioisomers,[77] the Jiao bromination enables the large-scale preparation of Br-(+)-δ-tocopherol with a high yield of 94% (Scheme 6). The highly regioselective halogenation of arenes results from the slow *in situ* generation of Br_2. According to previous discussion, the HBr is oxidized by DMSO to Br_2 or DMS·Br_2. The reaction of Br_2 or DMS·Br_2 with arene affords the aryl halides with the formation of HBr which is oxidized by DMSO for the next oxidative cycle. Consequently, the highly reactive Br_2 or DMS·Br_2 remains at a low concentration during the reaction, effectively suppressing the occurrence of side reactions.

Scheme 6 Bromination of tocopherol



This system is also applicable to the efficient iodination of arenes (Scheme 7). Of note, in the study by Majetich and co-workers, the use of HI with DMSO as the solvent failed to achieve this transformation.

Scheme 7 Iodination of arenes using Jiao bromination

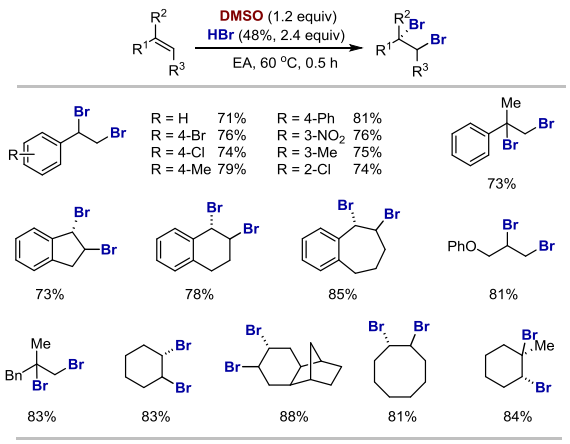


3.2. Bromination of olefins, alkynes and ketones

Subsequently, the Jiao bromination (DMSO/HX) has been extended to the dibromination of alkenes and alkynes, as well as the bromination of ketones.[12] For alkene substrates, the reaction exhibits excellent diastereoselectivity, yielding only *trans* or *ortho* products. Notably, this system demonstrates excellent compatibil-

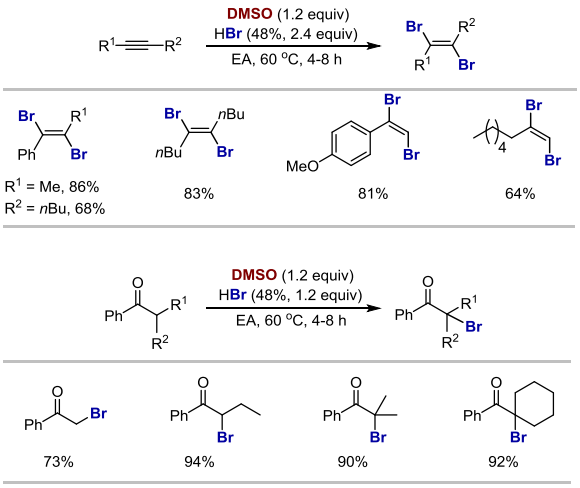
ity with both activated and unactivated alkenes. Specifically, monosubstituted, disubstituted, and trisubstituted alkenes are enabled to undergo transformation to the corresponding brominated products in excellent yields (Scheme 8).

Scheme 8 Scope of Jiao bromination for alkenes



In the case of alkyne substrates, both terminal and internal alkynes can be efficiently and selectively converted into (*E*)-dibromoalkenes. Additionally, all of the primary, secondary, and tertiary α-bromoketones are efficiently prepared from ketone feedstocks under Jiao bromination conditions (Scheme 9).

Scheme 9 Scope of Jiao bromination for alkynes and ketones



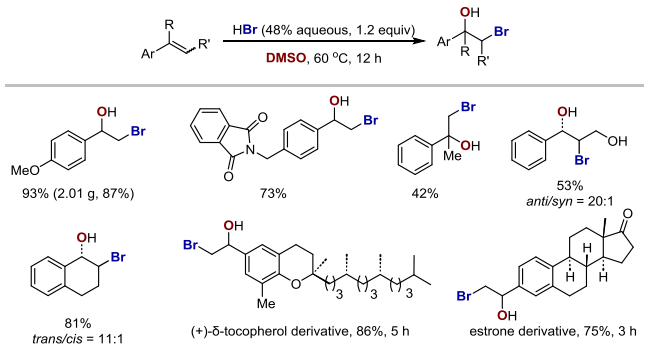
3.3. Bromohydrin synthesis with DMSO

Beyond (hetero)arene halogenation, the non-trivial condition of Jiao bromination (DMSO/HX system) facilitates the practical hydrobromination of styrenes with high efficiency.[11] Notably, the scale-up synthesis, as well as the late-stage functionalization of δ-tocopherol derivatives and estrone derivatives has been achieved by this method. These transformations demonstrate that the DMSO/HBr system is well-suited for the functionalization and modification of complex alkenes with natural product skeletons, and possesses considerable potential for applications in biological evaluation (Scheme 10).

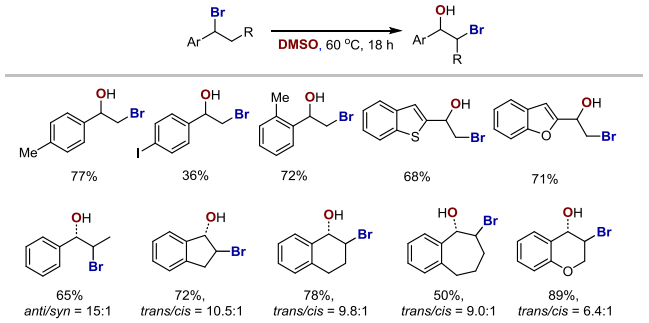
Surprisingly, the DMSO/HBr system also enables the synthesis of bromohydrins from secondary benzyl bromides, realizing the formal halogen atom translocation (Scheme 11).[11]

A possible reaction mechanism has been proposed in Scheme 12: benzyl bromide first undergoes elimination to generate an alkene intermediate, which then undergoes electrophilic halogenation to form a bromonium ion. This bromonium ion is subjected

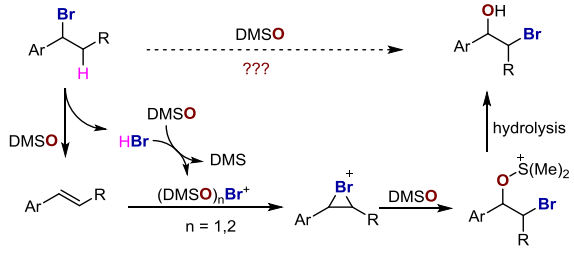
Scheme 10 Scope of Jiao bromination for hydrobromination of styrenes



Scheme 11 Scope of Jiao bromination for hydrobromination of secondary benzyl bromides



Scheme 12 Proposed mechanism for hydrobromination of secondary benzyl bromides

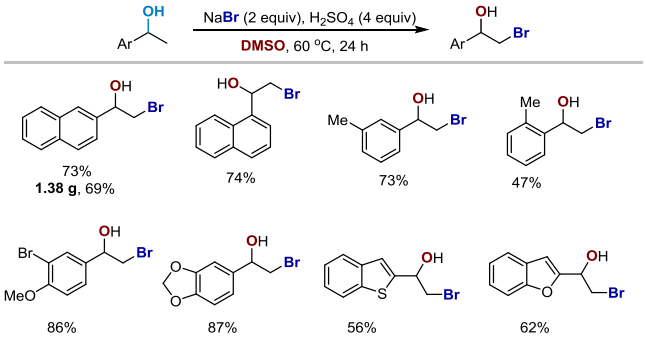


to nucleophilic attack by DMSO followed by hydrolysis, ultimately affording the hydrobromination product.[78] Notably, DMSO serves as both an oxidant and an activating reagent for the generation of the key intermediate $[(DMSO)_nBr^+]Br^-$ (n = 1 or 2).[8,79] In 2017, the group of Jiao further extended this system, furnishing the iodohydroxylation of alkenes under the conditions of DMSO/NaI/H_2SO_4.[10]

Furthermore, under DMSO/HX conditions, the group also achieved the β-halogenation of benzylic alcohols, with halenium reagents generated *in situ* from sodium halides and DMSO (Scheme 13).[13] The reaction proceeds via an initial dehydration step to form an alkene intermediate, which then undergoes a halohydroxylation process analogous to that described above, yielding halohydrin compounds. This provides a novel route for the preparation of halohydrins.

Overall, Jiao bromination is characterized by high reaction efficiency, facile operation, and readily available low-cost reagents, which endows it with great potential for scalable application. Nevertheless, there are still some limiting factors that need to be resolved to realize its large-scale application, including the corrosion of reaction equipment caused by strong acids and the environmental pollution induced by the malodorous gas dimethyl sulfide. Resolving these constraints will further advance the practical utilization of Jiao bromination.

Scheme 13 Scope of Jiao bromination for β-halogenation of benzylic alcohols

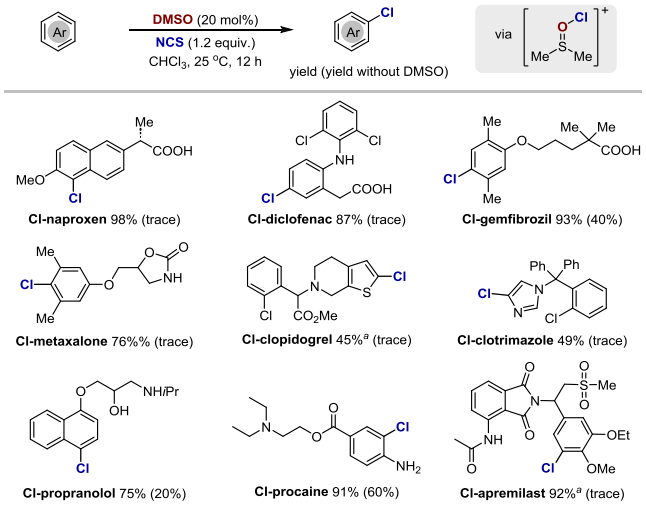


4. Jiao Chlorination (DMSO/NCS)

During their research on DMSO-mediated oxidative halogenation reactions where DMSO acts as a mild oxidant, Jiao and colleagues recognized that the nucleophilic oxygen in DMSO can serve as a Lewis base catalyst to activate halonium ions. Based on this insight, in 2020, Jiao and coworkers reported a highly efficient, simple, and practical DMSO-catalyzed chlorination system (DMSO/NCS), which enables the C–H bond chlorination modification of a series of (hetero)arenes.[14]

Notably, this method has tackled several persistent challenges in the field, including the requirement for high-cost chlorinating reagents, harsh reaction conditions, and poor functional group tolerance. It demonstrates excellent compatibility with a variety of functional groups, encompassing acid-sensitive groups (OH, NH_2, alkenes), base-sensitive groups (ketones, esters), and oxidant-sensitive groups (NH_2, *N*-heterocycles, aldehydes). The catalytic system shows remarkable versatility in the late-stage chlorination of bioactive molecules and pharmaceuticals. Nucleophilic groups like amines or hydroxyl groups can readily interact with chloronium ions, which might hinder chlorination; however, these experiments highlight the catalytic activity of DMSO, as evidenced by the improved yields compared to those obtained without DMSO catalysis (yields in parentheses) (Scheme 14).

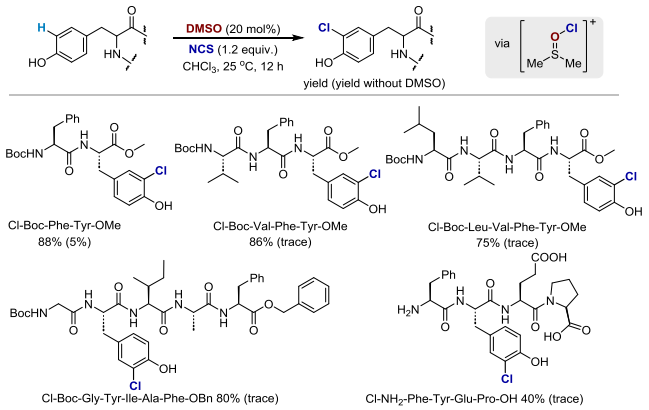
Scheme 14 Scope of Jiao chlorination for late-stage modification of pharmaceuticals



Consequently, this method has become known as "Jiao chlorination"[53,80] and hailed as "a useful tool in the fields of organic chemistry and medicinal chemistry",[81] "high efficiency and selectivity",[82] "efficient",[83] and "practical",[84] which has been widely applied in organic synthesis.[53,59-60,74,85-92]

Chemical modification of amino acid residues in peptides has become a valuable tool in biochemistry. Prior to the report of this method, however, halogen-mediated chemical modification of peptides or proteins had not been achieved. Encouragingly, the selective chlorination of tyrosine residues in various peptides proceeds with high yields and excellent selectivity (Scheme 15). It is noteworthy that the chlorination of unprotected tetrapeptide (NH_2-Phe-Tyr-Glu-Pro-OH) also proceeds smoothly with 40 mol% DMSO loading. This method was hailed by Maji as "the only reported method for the late-stage chlorination of peptides".

Scheme 15 Scope of Jiao chlorination for late-stage modification of peptides



5. Representative Applications

Compared with some of the electrophilic halogenating reagent systems mentioned earlier, Jiao halogenation has obvious advantages in experimental operation, scope of application, scalability, and late-stage functionalization (Table 1). For example, IPy_2BF_4 and IDSI can only be applied to the halogenation of alkenes;[20-22] CFBSA can be used for the halogenation of arenes and ketones, but it lacks the verification of scale-up experiments and the application of late-stage functionalization.[23] Palau'chlor and N–X anomeric amides have a wide scope of application, can be implemented on a gram scale, and can be used for late-stage functionalization, but they require pre-synthesis.[24-25] In contrast, Jiao bromination only requires easily accessible reagents and experimental operations, and can be applied to a variety of reaction systems, including the bromination (iodination) of electron-rich aromatics, the bromination of ketones, the dibromination of alkenes and alkynes, and the bromohydroxylation of alkenes. It can not only be scaled up to the kilogram scale but also applied to the

Table 1 Comparison of Jiao halogenation with selected halogenation methods using electrophilic halogenating reagents

Halogenation method	Substrate scope	Scale	Last-stage functionalization
IPy_2BF_4	Alkene	mg	Not applied
IDSI	Alkene	mg	Not applied
CFBSA	Electron-rich arene, ketone	mg	Not applied
Palau'chlor	Electron-rich arene, alkene, ketone	g	Applied
N–X anomeric amides	Electron-rich arene, alkene, ketone	g	Applied
DMSO/HX (Jiao bromination)	Electron-rich arene, alkene, alkyne, ketone	kg	Applied
DMSO/NCS (Jiao chlorination)	Electron-rich arene	g	Applied

late-stage functionalization of complex substrates. Jiao chlorination has a strong advantage in late-stage halogenation.

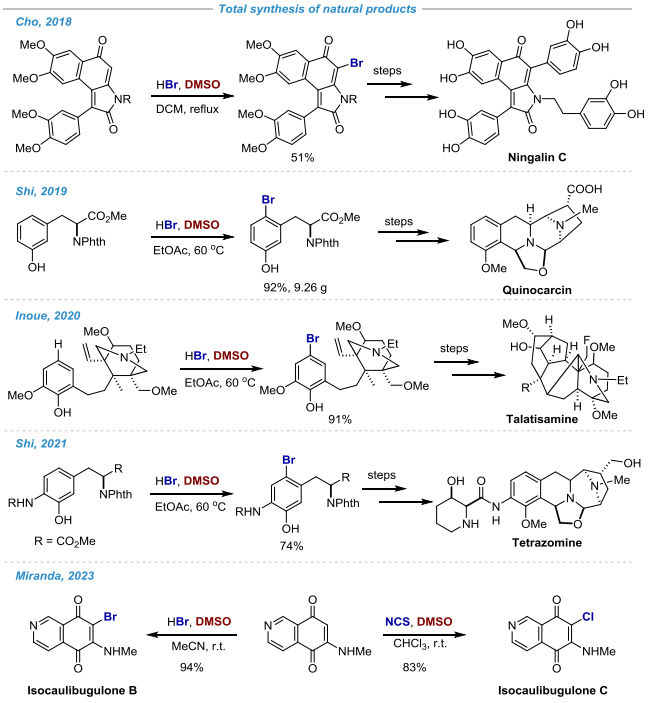
Owing to the above advantages, Jiao bromination and Jiao chlorination found widespread application and have been cited 445 and 188 times, respectively. Among them, some representative applications were reported by over fifty research teams.

5.1. Electrophilic halogenation for the synthesis of valuable organohalides

In the Jiao halogenation reaction, the highly active electrophilic X^+ (X = Cl, Br, I) species generated *in situ* from DMSO guarantees the efficient progression of halogenation. The *in-situ* formation or catalytic activation of electrophilic X^+ maintains a low concentration of this species during the reaction, which significantly improves the selectivity of the halogenation reaction. Coupled with low-cost, easily accessible starting materials and simple, scalable experimental operations, the Jiao halogenation strategy has been widely employed for the synthesis of natural products, bioactive compounds and material molecules.

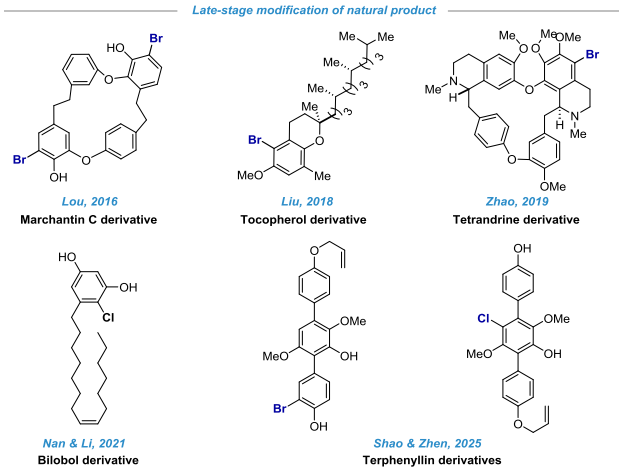
For total synthesis of natural products (Scheme 16), the Cho group accomplished the synthesis of ningalin C via Jiao bromination.[49] In 2019 and 2021, respectively, the Shi group applied this bromination for the total synthesis of two natural products, quinocarcin and tetrazomine. In addition, the group of Inoue applied Jiao bromination in the total syntheses of the natural product talatisamine, affording the brominated products in excellent yields.[58] Notably, Miranda's group from Brazil successfully synthesized isocaulibugulones B and C via Jiao chlorination and bromination late-stage modification approaches, respectively.[59]

Scheme 16 Jiao halogenation for total synthesis of natural products



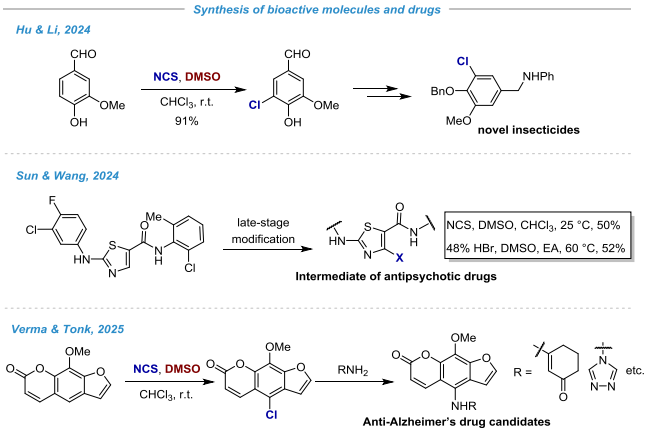
Late-stage modification of natural products is an effective strategy for rapidly accessing diverse natural product derivatives and modulating their biological activities (Scheme 17). Lou and coworkers have achieved the modification of marine natural products and discovered anti-tumor lead compounds, with their activity enhanced tenfold compared to the unmodified counterparts.[55,70] The groups of Liu and the Zhao have respectively constructed tocopherol derivative and tetrandrine derivative.[56,61] Nan and coworkers reported that chlorination of bilobol via Jiao chlorination enhanced its inhibitory activity against death associated apoptotic protein kinase 2.[85] Additionally, the Shao and Zhen groups modified terphenyllin derivatives using Jiao bromination and chlorination reactions, which significantly improved the antifouling activity of these marine-derived terphenyllin derivatives.[88]

Scheme 17 Jiao halogenation for late-stage modification



The development of halogenation methods has promoted new paradigms for the construction of libraries of bioactive molecules. Taking this halogenation methodology as the key step (Scheme 18), Hu, Li and coworkers have successfully synthesized insecticide candidate molecules.[89] The antipsychotic drugs were prepared by Sun and Wang, and corresponding medicinal chemistry studies were also carried out.[60] Additionally, Verma, Tonk *et al.* derivatized 8-methoxypsoralen into anti-Alzheimer's disease drug candidates.[87]

Scheme 18 Jiao halogenation for synthesis of bioactive molecules and drugs

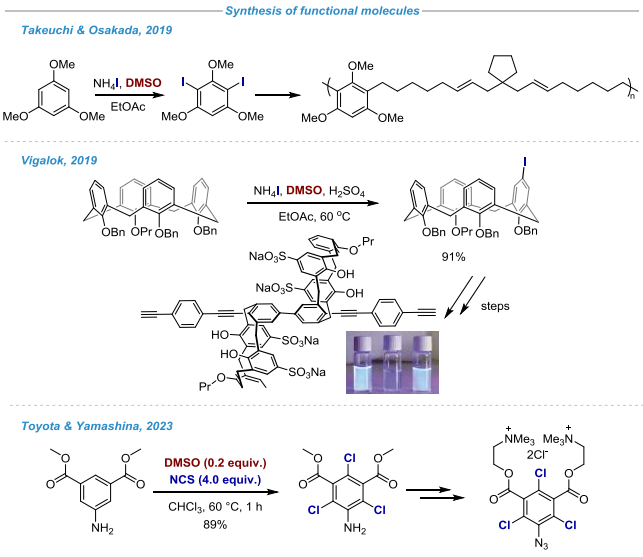


Jiao halogenation has been found wide applications in the synthesis of functional molecules (Scheme 19). In parallel, Takeuchi, Osakada and coworkers have utilized diiodinated arenes as monomers for polymer synthesis,[66] while the Vigalok group from Israel focused on synthesizing optoelectronic material molecules.[57] Toyota has efficiently obtained surfactant molecular precursors via chlorination reactions.[86]

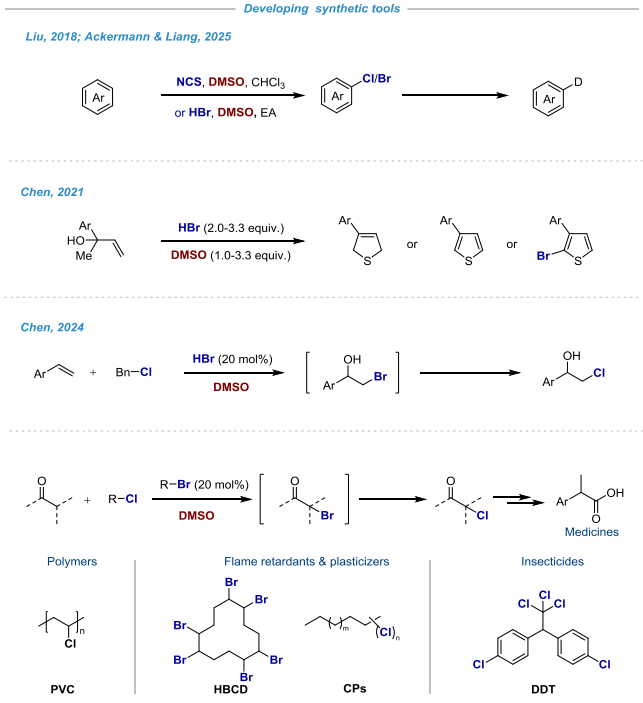
5.2. Tandem Jiao halogenation and halide transformation

Combined with halide transformation, the Jiao halogenation reactions have also been exploited as versatile platforms for developing advanced chemical synthetic tools (Scheme 20). Liu,

Scheme 19 Jiao halogenation for synthesis of functional molecules



Scheme 20 Jiao halogenation for developing synthetic tools

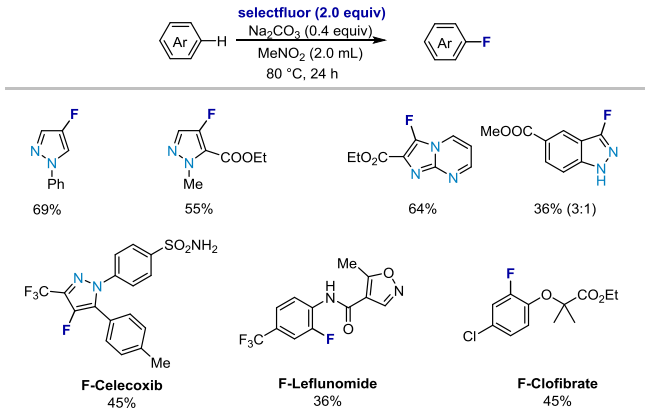


Ackermann, Liang *et al*. achieved the deuteration of various aromatic compounds by leveraging Jiao halogenation.[53,61] In 2021, Chen group demonstrated the valorization of dimethyl sulfide, a byproduct of DMSO in the Jiao bromination reaction, for the redox-divergent construction of dihydrothiophenes, thiophenes, and bromothiophenes.[76] In addition, inspired by the Jiao bromination-based synthesis of bromohydrins, Chen group extended this strategy to realize the chlorohydroxylation of olefins, with bromohydrins serving as key reaction intermediates.[93] Taking a step further, they utilized *α*-bromoketones generated via the Jiao bromination reaction as pivotal intermediates, and combined them with halogen exchange processes to develop an alkyl bromide-catalyzed chlorine transfer reaction. Notably, this protocol enables the reuse of a broad range of halogenated organic pollutants, including poly(vinyl chloride) (PVC), hexabromocyclododecane (HBCD), chlorinated paraffins (CPs), and dichlorodiphenyltrichloroethane (DDT), into *α*-chloroketones, which are valuable synthons for pharmaceutical synthesis. Furthermore, the Chen group has also exploited the oxidizing properties of DMSO to achieve the efficient synthesis of bicyclo[3.2.1]octanes.[94]

5.3. Other halogenation reactions inspired by Jiao halogenation

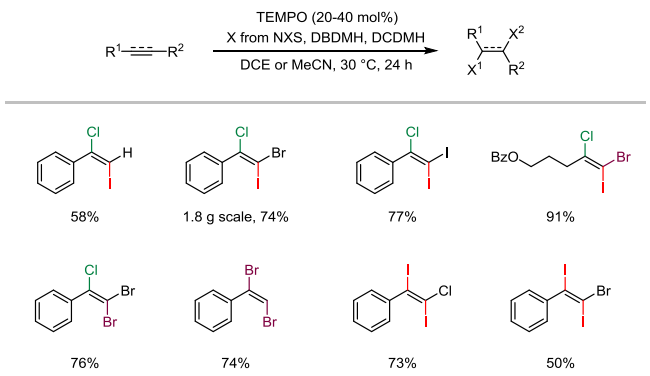
Given that DMSO could act as a Lewis base to activate electrophilic halogenating reagents, Jiao and colleagues hypothesized that nitromethane, a commonly used solvent, could act as an oxygen-centered Lewis base to activate electrophilic fluorinating reagents. Furthermore, due to its high dielectric constant (ε = 36.16),[95] nitromethane can also serve as a carbocation stabilizer to suppress potential side reactions of intermediates. Building on their previous research on oxygen-centered Lewis bases and nitromethane ($MeNO_2$),[14,96-97] they developed a general electrophilic fluorination methodology, which enables a variety of electrophilic fluorination reactions through the activation of electrophilic fluorinating reagents by nitromethane (Scheme 21).[98] The mild reaction conditions, readily available reagents, and high regioselectivity render this reaction highly attractive. This method expands the new application of nitromethane in organic synthesis and provides a novel approach for the synthesis of various organofluorides.

Scheme 21 Fluorination promoted by $MeNO_2$



Inspired by Jiao chlorination, Zhu and coworkers established a TEMPO catalyzed cross-dihalogenation reaction via redox-regulation of the otherwise complex system of dual electrophilic X^+ reagents (Scheme 22). Formally, the ICl, BrCl, I_2 and Br_2 were generated *in situ*, which enabled highly regio- or stereoselective access to a myriad of iodochlorination, bromochlorination and homo-dihalogenation products with a wide spectrum of functionalities.[99]

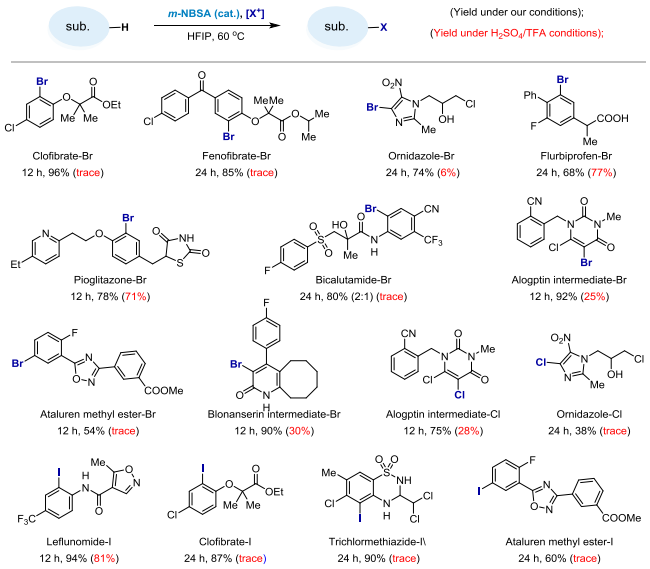
Scheme 22 TEMPO-catalyzed cross-dihalogenation



While Jiao halogenation offers exceptional mildness and func-

tional group compatibility, it still faces an unresolved challenge: the electrophilic halogenation of electron-deficient arenes. Building on their studies on the activation of electrophilic halogenating reagents, Jiao and colleagues achieved a catalytic electrophilic halogenation method for electron-deficient arenes using sulfonic acid-based catalysts in HFIP (Scheme 23).[100] This catalytic system was applied to the late-stage halogenation modification of various pharmaceutical molecules and provided an efficient route for the late-stage halogenation modification of electron-deficient arenes. Further studies revealed that hexafluoroisopropanol (HFIP) could be substituted with catalytic amounts of TfOH (trifluoromethanesulfonic acid) in $MeNO_2$.

Scheme 23 Electrophilic halogenation of electron-deficient arenes



6. Conclusions and Perspectives

In summary, the Jiao group has developed a series of green, mild, and efficient halogenation reactions, including oxidative halogenation systems, Lewis base-activated halogenating reagent systems, and halogenation of inert electron-deficient arenes.[101] Among these, the bromination (DMSO/HBr) and chlorination (DMSO/NCS) protocols, renowned for their exceptional practicality, have been termed "Jiao bromination" and "Jiao chlorination". These methods have been successfully applied in the synthesis of pharmaceuticals, material molecules and natural products, significantly expanding the scope of halogenation reactions and paving the way for new advances in pharmaceuticals and other related fields.

Looking ahead, the field of halogenation still faces formidable challenges. First and foremost, site-selective halogenation of *N*-heteroarenes such as pyridine and pyrimidine remains particularly challenging, as existing methods often lack the necessary efficiency and selectivity—especially during the late-stage halogenation process. Secondly, enantioselective halogenation of bioactive molecules represents a promising area for advancing the synthesis of chiral pharmaceuticals. Finally, developing green, safe, efficient, and scalable halogenation reactions is the key to realizing practical application. DMSO-based halogenation provides some insights into addressing these issues; for instance, Lewis base-activated halogenating reagents based on chiral sulfoxides may be a potential approach to achieving enantioselective halogenation, and the combination of Jiao halogenation with continuous flow chemistry may enable the development of more efficient and practical halogenation procedures. Halogenation reactions require further exploration to meet the synthetic demand for valuable bioactive compounds.

Acknowledgement

Financial support from the National Natural Science Foundation of China (22402191) and the Dalian Science and Technology Talent Innovation Support Policy Project (2024RQ088) is acknowledged.

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Manuscript received: January 12, 2026
Manuscript revised: April 14, 2026
Manuscript accepted: April 24, 2026
Version of record online: XXXX, 2026

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