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THE UTILITY OF OXOAMMONIUM SPECIES IN ORGANIC SYNTHESIS: BEYOND ALCOHOL OXIDATION

Shota Nagasawa, Yusuke Sasano, and Yoshiharu Iwabuchi*

Graduate School of Pharmaceutical Sciences, Tohoku University, 6-3, Aoba, Aramaki, Aoba-ku, Sendai, 980-8578, Japan

Abstract – Oxoammonium species are electrophilic chemical species generated via single electron oxidation of nitroxyl radicals. Although this species and its salts are known as useful oxidants and active species for (catalytic) oxidation of alcohols into carbonyl compounds in organic synthesis, the benefits of oxoammonium species for the oxidative transformations of numerous types of substrates apart from alcohols has been reported. This review summarizes the synthetic utility of oxoammonium species under both stoichiometric and catalytic conditions with the exception of alcohol oxidation.

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This paper is dedicated to Prof. Somsak Ruchirawat on the occasion of his 80th birthday.

1. INTRODUCTION

Oxidation is one of the most fundamental and crucial synthetic processes used in organic chemistry because it activates the substrate by generating its corresponding electron-deficient species to enable the installation of various functional groups. Numerous methods and reagents (that is, oxidants) have been developed to achieve selective and efficient oxidation of organic molecule.^{1,2} Historically, transition metal derivatives in their high-oxidation state, such as chromium and manganese oxides, play major roles in the oxidation of organic molecules. Synthetic organic chemists have employed these oxidants for a several decades because of their inherent reactivity and excellent chemoselectivity. To address several issues regarding synthetic organic transformations, a variety of non-transition metal-based organic/inorganic oxidants such as peracid, peroxide, and halogenation reagents have also been developed. Although the benefits of these oxidants have been recognized, recent trends of modern organic synthesis on more complex synthetic targets such as natural products as well as safety and environmental concerns to avoid harmful and wasteful reagent are growing. This have led to the need for milder, highly selective, and more environmentally friendly oxidation methods than these "traditional" methodologies.³

Oxoammonium species and their salts are organic molecule-based oxidants. Since Golubev disclosed its reactivity towards alcohols,^{4,5} these species have been frequently employed for the oxidation of alcohols into their corresponding carbonyl compounds such as aldehydes, ketones and carboxylic acids. Currently, oxoammonium-mediated or catalyzed oxidation of alcohols has been established as one of the most reliable transformations in organic chemistry,⁶⁻¹⁰ with numerous applications toward the synthesis of complex molecules such as pharmaceuticals and natural products.¹¹ Oxoammonium species has a unique modular nature, the stereoelectronic properties of which are tuned by their properties such as skeletal structures, substituents, counter ions, and additives. This plays a significant role in the discovery and development of various useful oxidative transformations beyond alcohol oxidation, showcasing cutting-edge research in organic chemistry.¹²⁻¹⁹

This review highlights the various oxidative transformations reported in the literature, which are mediated or catalyzed by oxoammonium species with the exception of alcohol oxidation. Non-oxoammonium species-mediated oxidative transformations employing nitroxyl radicals such as metal/nitroxyl radical co-catalytic systems are not included in this review. We have classified the reported conditions in terms of the substrate (functional groups) and types of products formed to explain the advantages and diverse reactivity of oxoammonium species. This is the first comprehensive review summarizing the application of various structural types of oxoammonium species, including the recent progress in this field of research.

2. OXOAMMONIUM SPECIES

Nitroxyl radicals are known to exhibit a wide range of reactivity due to the stereoelectronic effects of the substituents on the N atom. In organic chemistry, this reversible electron transfer process has been utilized in a wide range of fields, from material science to life science, for various techniques such as forming functional materials, secondary batteries, electron spin resonance (ESR) spin-trapping methods, and bio-imaging.²⁰ In the field of synthetic organic chemistry, nitroxyl radicals have been proven to be useful as living radical polymerization initiators^{17,21,22} and oxidation catalysts (or precursors). Based on the structure of their substituents, nitroxyl radicals can be classified into two types: (i) imidoxy (*N,N*-diacyl substituted) nitroxyl radicals (imidoxy radicals) such as phthalimide *N*-oxyl (PINO)^{23,24} and (ii) aminoxy (*N,N*-dialkyl substituted) nitroxyl radicals (aminoxy radicals) such as 2,2,6,6-tetramethylpiperidine *N*-oxyl (TEMPO)²⁵ (**Figure 1a**). Nitroxyl radicals themselves potentially undergo one-electron oxidation to yield their corresponding oxoammonium species and H⁺-coupled-one-electron reduction to yield their hydroxylamines (**Figure 1b**).^{4,26} However, most oxoammonium species with reasonable stability and lifetime that are useful in synthetic chemistry are derived from nitroxyl radicals formed from the easily oxidized aminoxy (*N,N*-dialkyl substituted)-type precursor. Because these processes are substantially reversible, nitroxyl radicals have been used as redox catalysts in the presence of stoichiometric oxidants such as NaClO, PhI(OAc)₂, and even molecular oxygen with the combination of appropriate mediator (NO_x, laccase), for many oxidative transformations, and the resulting oxoammonium salts are recoverable as their corresponding hydroxylamines. Oxoammonium species derived from *N,N*-dialkyl substituted nitroxyl radicals are isolable as a salt with an appropriate counter anion such as tetrafluoroborate (BF₄⁻). 4-Acetamido-2,2,6,6-tetramethylpiperidine *N*-oxoammonium tetrafluoroborate (4-NHAc-TEMPO⁺BF₄⁻) is widely referred to as “Bobbitt’s salt”, which is a frequently used oxidant in organic chemistry.²⁷ Most of the currently available oxoammonium salts are based on the structure of TEMPO or its derivatives. Recently, the discovery of the markedly enhanced catalytic efficiency of sterically less-hindered nitroxyl radicals such as 9-azabicyclo[3.3.1]nonane *N*-oxyl (ABNO)²⁸ and 2-azaadamantane *N*-oxyl (AZADO),^{9,29,30} has prompted chemists to investigate the reactivity of oxoammonium species (**Figure 1c**).

As mentioned in Section 1, Golubev discovered that oxoammonium species react with alcohols to yield their corresponding carbonyl compounds and hydroxylamines.^{4,5} The generally accepted mechanism of the oxoammonium species-mediated oxidation of alcohols is shown in **Figure 2**. Under basic conditions, the oxygen atom of the hydroxyl group attacks the nitrogen atom of the oxoammonium species. The resulting intermediate undergoes Cope-type elimination to furnish the corresponding carbonyl compound and hydroxylamine.³¹ In contrast, under neutral and acidic conditions, the oxoammonium species

abstracts a hydride (H^-) from the alcohol to yield its corresponding carbonyl compound and protonated hydroxylamine.³²

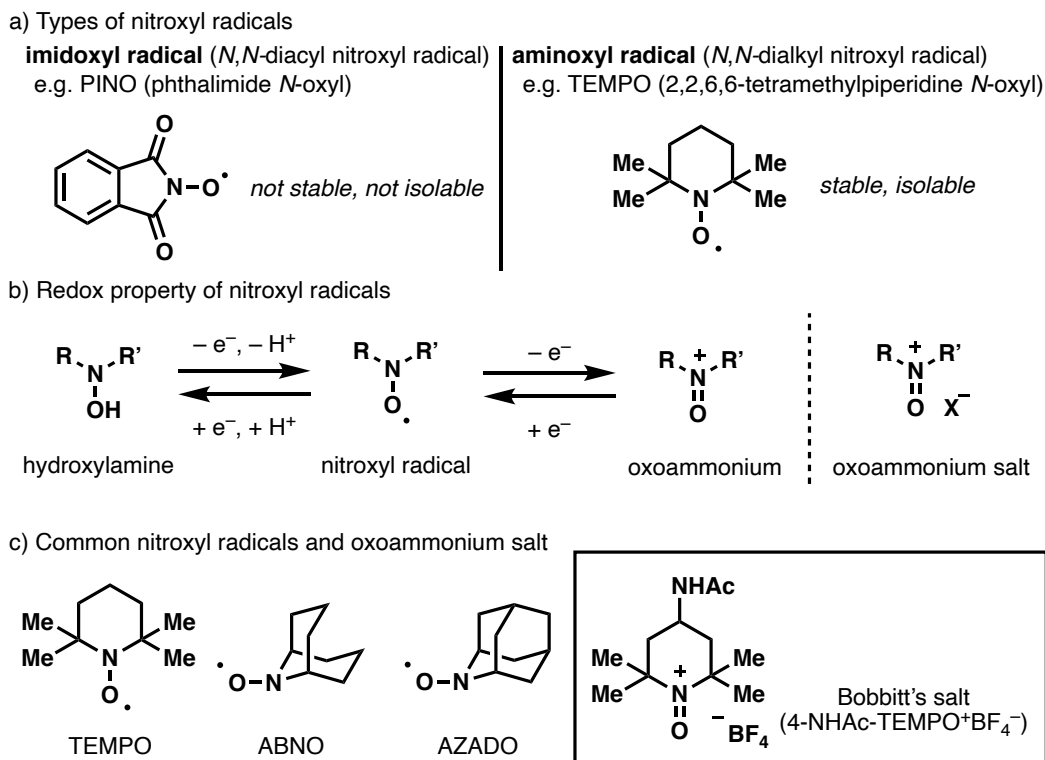


Figure 1. Nitroxyl radical and oxoammonium species

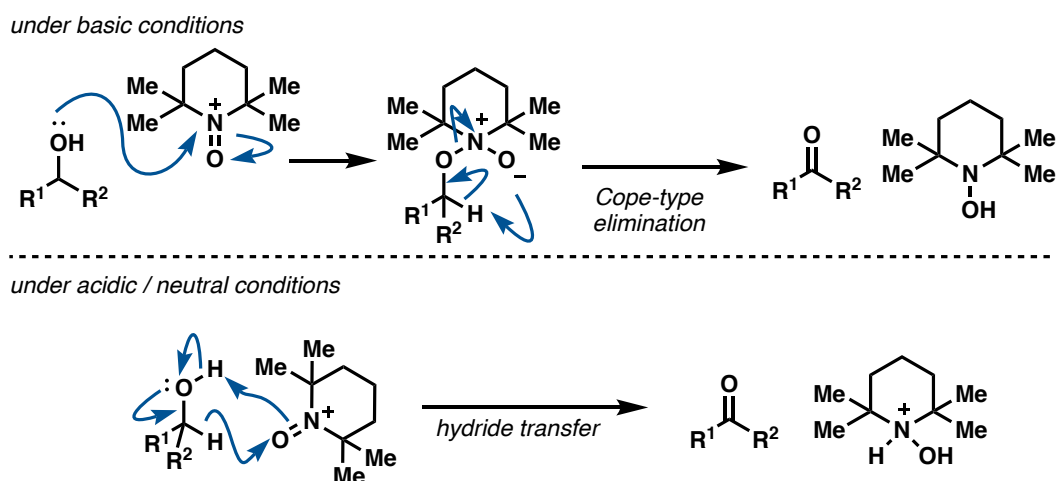


Figure 2. Mechanism of the oxidation of alcohols mediated by oxoammonium species

3. OXOAMMONIUM SPECIES(SALT)-MEDIATED OXIDATIVE TRANSFORMATION

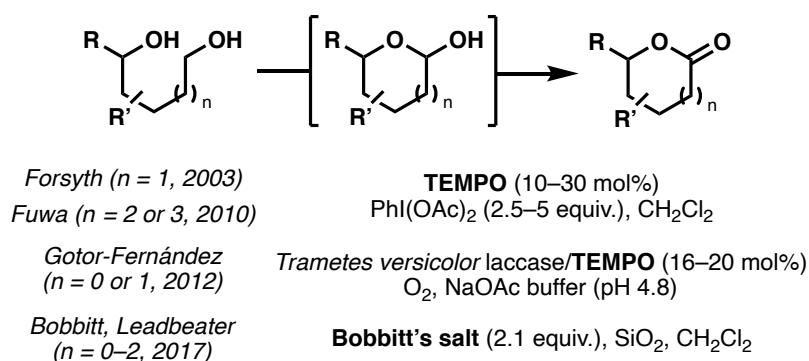
In this section, oxidative molecular transformations involving oxoammonium species are presented and categorized by the substrate or the functional groups.

3-1. Oxidative esterification/amidation

It may appear to be almost identical to the oxidation of alcohols, but oxidative esterification/amidation is one of the most useful transformations mediated by oxoammonium species. In these reactions, both the facile formation of a hemiacetal or hemiaminal intermediate and its smooth oxidation into the corresponding carbonyl compounds are required. Therefore, the design of the substrates and reactions are crucial for the success.

3-1-1. Oxidative lactonization of 1,m-diols (**Scheme 1**)

The oxidative lactonization of 1,m-diols is recognized as an efficient method to obtain lactones, which appear in numerous natural products and pharmaceuticals and are useful synthetic building blocks. The reaction requires the chemo-/regioselective oxidation of one primary alcohol and the subsequently formation of a lactol without oxidation of another alcohol. Early studies have indicated that TEMPO-catalyzed oxidation is suitable for this purpose^{33–35}; however, further investigations have not been performed until recently. In 2003, Forsyth et al. reported a TEMPO/PhI(OAc)₂ system used for the oxidative lactonization of highly functionalized 1,5-diols to provide δ -lactones in good yield.³⁶ Later, Fuwa et al. expanded the substrate applicability into 1,6- and 1,7-diols to yield seven- and eight-membered lactones.³⁷ In 2012, Gotor-Fernández et al. reported an aerobic conditions using *Trametes versicolor* laccase/TEMPO catalytic system.^{38,39} Miller, Bobbitt, and Leadbeater reported that Bobbitt's salt oxidizes terminal diols to provide γ , δ , ϵ -lactones in moderate to good yields in 2017.⁴⁰

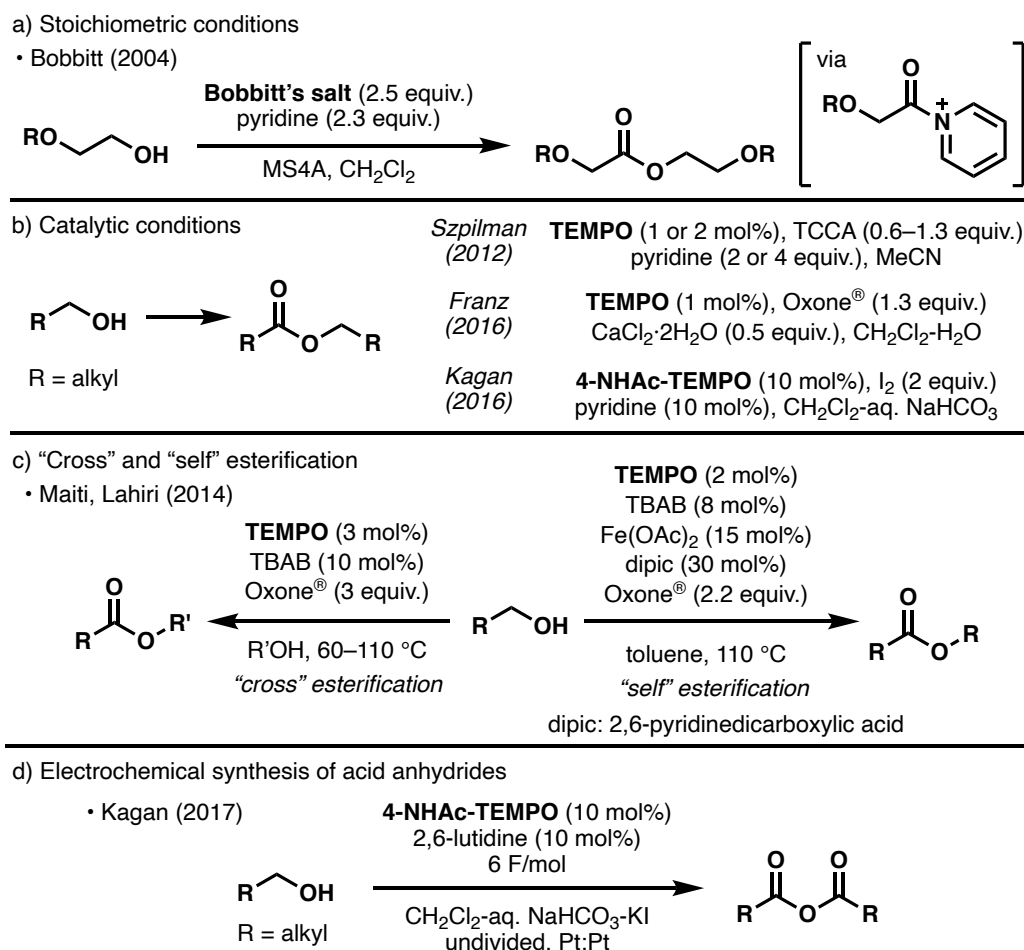


Scheme 1. Oxidative lactonization of 1,m-diols

3-1-2. Oxidative esterification of alcohols

In 2004, Bobbitt et al. reported the oxidative dimerization of β -oxygenated primary alcohols mediated by Bobbitt's salt to yield esters as the sole product of the reaction (**Scheme 2a**).⁴¹ Notably, pyridine played an essential role in promoting the desired reaction. A later study in 2014 revealed that the corresponding aldehyde was obtained as a major product when 2,6-lutidine was employed instead of pyridine.⁴² They proposed that the in-situ formation of an *N*-acylpyridinium species, which would not be generated if a

sterically hindered base (that is 2,6-lutidine) was employed, may explain the crucial effect of pyridine. In 2012, Szpilman et al. reported the catalytic oxidative dimerization of primary alcohols to yield their corresponding ester products using a TEMPO/trichloroisocyanuric acid (TCCA)/pyridine system.⁴³ Later, Franz and Hackbusch⁴⁴ and Kagan et al.⁴⁵ each reported the catalytic oxidative esterification of primary alcohols employing Oxone[®] and I₂ as oxidants, respectively (**Scheme 2b**). Notably, Maiti and Lahiri et al. reported both “cross” and “self” oxidative esterification of primary alcohols catalyzed by TEMPO in 2014 (**Scheme 2c**).⁴⁶ The “cross” conditions employed the TEMPO/tetrabutylammonium bromide (TBAB)/Oxone[®] system, and, in contrast, the “self” conditions employed Fe(OAc)₂/2,6-pyridinedicarboxylic acid (dipic) catalysis in addition to the “cross” conditions. Furthermore, Kagan et al. reported the electrochemical formation of acid anhydrides from alcohols in 2017 (**Scheme 2d**).⁴⁷



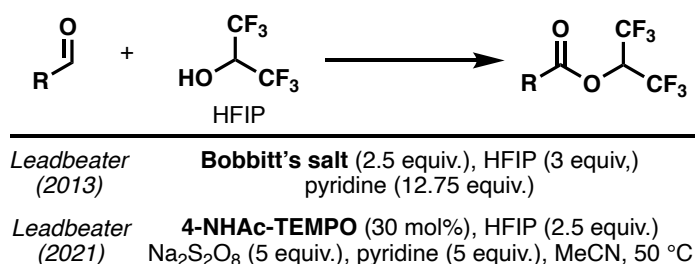
Scheme 2. Oxidative esterification of alcohols

3-1-3. Oxidative esterification/amidation of aldehydes

Recent studies have focused on more complex oxidative esterification/amidation reactions employing aldehydes as the substrate. In 2013, Leadbeater et al. reported the Bobbitt’s salt-mediated oxidative

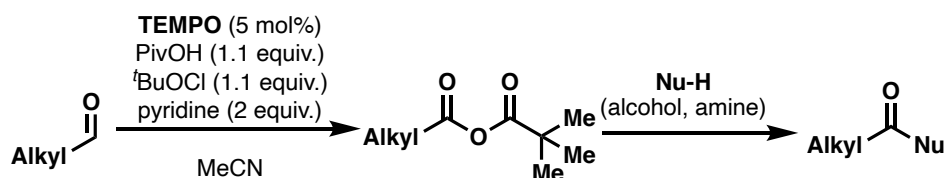
esterification of aldehydes using 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) to yield their corresponding HFIP esters (**Scheme 3a**).⁴⁸ By using HFIP, the authors avoided the undesired oxidation of the alcohol coupling partner. They later reported a catalytic conditions using $\text{Na}_2\text{S}_2\text{O}_8$ as an oxidant.⁴⁹ In 2013, Szpilman et al. reported the TEMPO-catalyzed oxidative formation of mixed anhydrides in the presence of a carboxylic acid as the coupling partner (**Scheme 3b**).⁵⁰ The resulting mixed anhydrides can be used for further coupling reactions with nucleophiles to yield various carbonyl compounds. In 2017, Leadbeater et al. reported a Bobbitt's salt-mediated synthesis of *N*-acyl azoles from aldehydes utilizing an oxidative amidation reaction (**Scheme 3c**).⁵¹ Notably, alcohols could be used as the starting material in this reaction. In the same year, they reported a similar transformation to yield *N*-acyl pyrazoles by employing a photoredox catalyst/TEMPO catalytic system.⁵²

a) Preparation of HFIP esters

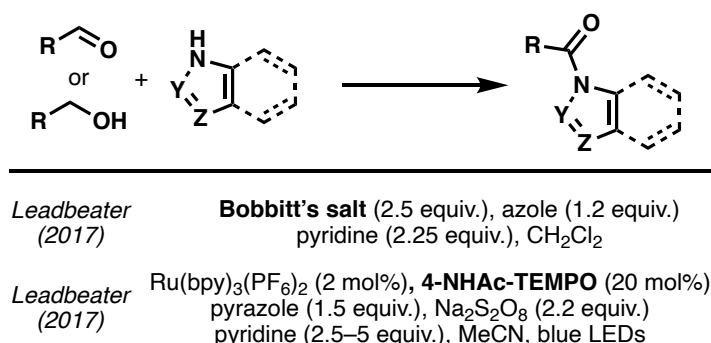


b) Preparation of mixed anhydride followed by addition of nucleophile

• Szpilman (2013)



c) Preparation of *N*-acyl azoles

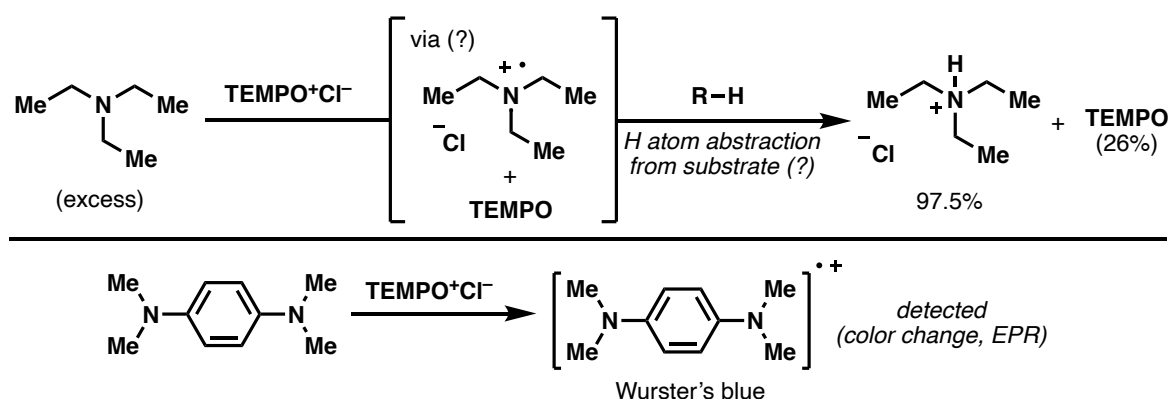


Scheme 3. Oxidative esterification/amidation of aldehydes

3-2. Oxidation of amines (imines)

Amines (imines) can be used as substrates in oxoammonium species-mediated oxidative transformations. Early trials in 1965 by Golubev et al. revealed that triethylamine and

N,N,N',N'-tetramethyl-*p*-phenylenediamine can react with an oxoammonium salt to yield their corresponding cation radicals (**Scheme 4**).⁴ This observation showed that amines act as substrates in the oxoammonium species (salt)-mediated oxidation reaction; however, this was not investigated further at that time. Recent efforts by researchers have opened up their utility and efficiency in organic synthesis. The reported transformations can be divided into several categories based on the substrate used or product formed.



Scheme 4. Oxidation of amines using TEMPO^+ conducted by Golubev in 1965

3-2-1. Nitrile synthesis

The first example of nitrile formation using the oxoammonium species-mediated oxidation of primary amines was reported by Semmelhack and Schmid in 1983 (**Table 1**).⁵³ They employed TEMPO as a mediator under anhydrous electrochemical oxidation conditions. In contrast, their corresponding carbonyl compounds were obtained under aqueous conditions, which will be highlighted in Section 3-2-2. Following this report, some researchers have developed the same molecular transformation using polymer- or electrode-supported TEMPO.^{54,55} In 2003, Chen et al. reported the catalytic synthesis of nitriles from primary amines using 1 mol% of TEMPO and trichloroisocyanuric acid (TCCA).⁵⁶ In 2014, Wiberg and Bailey et al. reported that Bobbitt's salt is an effective stoichiometric oxidant for the conversion of various primary amines into nitriles.⁵⁷ Although this protocol was the first example of oxoammonium salt-mediated oxidative nitrile synthesis, four equivalents of Bobbitt's salt, extremely anhydrous conditions to prevent hydrolysis of the intermediate imine, and slow addition of the primary amine substrate to avoid the rapid formation of the homo-coupled imines were required. In 2016, they developed an improved catalytic protocol which employed the 4-NHAc-TEMPO/pyridinium bromide/Oxone[®]/pyridine system.⁵⁸

Researchers have noticed that, generally, the direct oxidation of amines into nitriles using oxoammonium species is not an efficient transformation. Therefore, the recent research trend in nitrile synthesis using oxoammonium species has shifted towards methodology that employ an ammonia source and aldehyde as

Table 1. Direct oxidation of amines into nitriles
$$\text{R}-\text{NH}_2 \longrightarrow \text{R}-\text{CN}$$

<i>Semmelhack</i> (1983)	TEMPO (20 or 40 mol%), 2,6-lutidine (8 equiv.) 0.33 V vs. Ag/Ag ⁺ , 0.5 M LiClO ₄ in MeCN, divided, Pt:Pt
<i>Kashiwagi</i> (1998)	2,6-lutidine (8 equiv.), 0.6 V vs. Ag/Ag ⁺ , 0.2 M LiClO ₄ in MeCN divided, TEMPO -modified Graphite:Pt
<i>Chen</i> (2003)	TEMPO (1 mol%), TCCA (1.3 equiv.), CH ₂ Cl ₂ , 10 °C
<i>Wiberg, Bailey</i> (2014)	Bobbitt's salt (4 equiv.), pyridine (8 equiv.), CH ₂ Cl ₂
<i>Bailey</i> (2016)	4-NHAc-TEMPO (5 mol%), pyridinium bromide (4.5 mol%) Oxone [®] (4.4 equiv.), pyridine (6 equiv.), CH ₂ Cl ₂

the starting materials (**Table 2**). For example, Bailey, Leadbeater et al. reported that mixing an aldehyde, 1,1,1,3,3,3-hexamethyldisilazane (HMDS), and Bobbitt's salt provided the nitrile product in excellent yield in 2015.^{59,60} In the same year, Kim and Noh reported the 4-NHAc-TEMPO-catalyzed aerobic synthesis of nitriles from aromatic aldehydes using ammonium acetate as an ammonia source.⁶¹ In 2016, Shen et al. reported another aerobic catalytic synthesis of nitriles from aldehydes using HMDS as an ammonia source.⁶² They later reported an improved TEMPO-mediated electrochemical synthesis of nitriles from aldehydes using HMDS in 2016⁶³ and ammonium acetate in 2017,^{64,65} respectively. In 2017, Kim (M.-J.), Mun, and Kim (J.) reported stoichiometric Bobbitt's salt-mediated conditions using ammonium acetate as an ammonia source.⁶⁶ When compared with their previous catalytic conditions,⁶¹ the scope of the protocol was expanded to aliphatic aldehydes. Recently, Leadbeater et al. introduced photoredox catalysis in 4-NHAc-TEMPO-catalyzed nitrile synthesis from aldehydes. The first-generation catalytic system, which employed ammonium persulfate as the sole ammonia source and oxidant, had a limited substrate scope and required elevated temperature and moisture-free conditions.⁶⁷ These limitations were successfully overcome by the development of a second-generation catalytic system, which employs ammonium carbamate as the ammonia source.⁶⁸

Table 2. Nitrile synthesis from aldehydes and an ammonia source
$$\text{R}-\text{CHO} + \text{ammonia source} \longrightarrow \text{R}-\text{CN}$$

<i>Bailey, Leadbeater</i> (2015)	Bobbitt's salt (2.5 equiv.), <i>HMDS</i> (2.5 equiv.) pyridine (1.1 equiv.), CH ₂ Cl ₂
<i>Kim</i> (2015)	4-NHAc-TEMPO (5 mol%), NaNO ₂ (10 mol%), HNO ₃ (20 mol%) <i>NH₄OAc</i> (2.4 equiv.), AcOH, 50 °C, O ₂ , R = Ar
<i>Shen</i> (2016)	TEMPO (10 mol%), KPF ₆ (10 mol%), NaNO ₂ or <i>t</i> BuONO (10 mol%) <i>HMDS</i> (2.5 equiv.), (AcOH), MeCN, O ₂

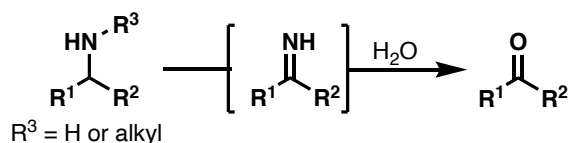
Shen, Li (2016)	TEMPO (10 mol%), <i>HMDS</i> (2.5 equiv.), AcOH (2.5 equiv.) 1.5 V vs. Ag/Ag ⁺ , 0.1 M NaClO ₄ in MeCN, undivided, Pt:Pt
Shen, Li (2017)	4-NHAc-TEMPO (10 mol%), <i>NH₄OAc</i> (2.5 equiv.) 1.5 V vs. Ag/Ag ⁺ , 0.1 M NaClO ₄ in MeCN, undivided, Pt:Pt, R = Ar
Shen, Li (2017)	TEMPO (15 mol%), <i>NH₄OAc</i> (3 equiv.), 1.5 V vs. Ag/Ag ⁺ 0.1 M NaClO ₄ in MeCN, undivided, Pt:Pt, R = Ar (Alcohol as a substrate)
Kim (2017)	Bobbitt's salt (2 equiv.), <i>NH₄OAc</i> (4 equiv.), AcOH, 70 °C
Leadbeater (2018)	Ru(bpy) ₃ (PF ₆) ₂ (2 mol%), 4-NHAc-TEMPO (20 mol%), (<i>NH₄</i>) ₂ S ₂ O ₈ (2.2 equiv.) pyridine (6 equiv.), MS3A, MeCN, -50 °C, blue LEDs, R = Ar
Leadbeater (2019)	Ru(bpy) ₃ (PF ₆) ₂ (2 mol%) 4-NHAc-TEMPO (20 mol%), (<i>NH₄</i>) ₂ S ₂ O ₈ (2.2 equiv.) pyridine (2.5 or 5 equiv.), <i>NH₄CO₂NH₂</i> (4 equiv.), MeCN:H ₂ O (95:5), blue LEDs, R = Ar

3-2-2. Imine (iminium) formation followed by capture by an nitrogen/oxygen nucleophile

3-2-2-1. Primary and secondary amines

The oxidation of primary amines into their corresponding imines (iminiums) using oxoammonium species was first described by Semmelhack and Schmid in 1983 (**Scheme 5a**), as mentioned in the beginning of Section 3-2-1.⁵³ They employed TEMPO as a mediator under aqueous electrochemical oxidation conditions, and the resulting imine products were subsequently hydrolyzed to yield their corresponding carbonyl compounds. In 2015, Galletti and Giacomni et al. reported an aerobic conditions using *Trametes versicolor* laccase/TEMPO catalytic system.⁶⁹ In 2018, they reported a selective oxidation of amines into their corresponding carbonyl compounds using a TEMPO/NaIO₄ catalytic system in an organic-aqueous medium.⁷⁰ Bansode and Suryavanshi also reported a similar transformation employing the TEMPO/PhI(OAc)₂ system.⁷¹ A pioneering application of this methodology was reported by Kashiwagi et al. in 1999. They reported an enantioselective oxidation (that is oxidative kinetic resolution) of racemic benzylamines using a chiral nitroxide as a mediator (**Scheme 5b**).⁷² The resulting imine was captured by H₂O to yield its corresponding ketone and the remaining amine was resolved in moderate enantiomeric excess. In 2015, Gotor-Fernández and Lavandera et al. reported an oxoammonium species-mediated deprotection of *N*-Bn group using *Trametes versicolor* laccase/TEMPO catalytic system (**Scheme 5c**).⁷³ In 2020, Ostaszewski et al. reported a chemoenzymatic synthesis of Passerini adducts using primary amines as a aldehyde precursor (**Scheme 5d**).⁷⁴ In 2020, Leadbeater et al. developed an oxidative amidation of amines using the combination of 4-NHAc-TEMPO and photoredox catalysis (**Scheme 5e**).⁷⁵ The resulting imines were hydrolyzed, captured with pyrazole, and oxidized into their corresponding *N*-acyl pyrazole products. Finally, the obtained *N*-acyl pyrazoles were treated with amines to yield their corresponding amides.

a) Catalytic oxidation of amines into carbonyl compounds



Semmelhack (1983) **TEMPO** (20 or 40 mol%), 2,6-lutidine (8 equiv.), 0.33 V vs. Ag/Ag⁺ 0.5 M LiClO₄ in MeCN/H₂O, divided, Pt:Pt

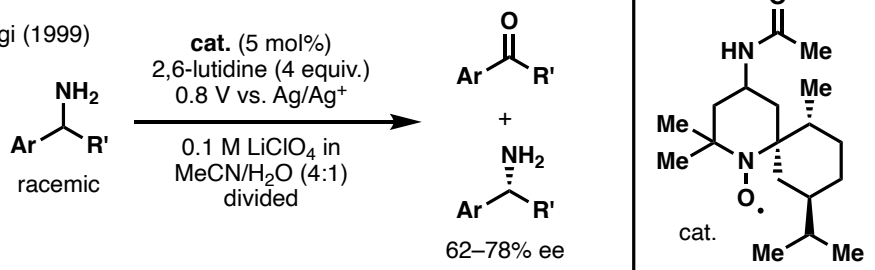
Galletti, Giacomini (2015) *Trametes versicolor* laccase/**TEMPO** (20 mol%) O₂, acetate buffer (pH 4.5) (R¹ = Ar, R² = H or alkyl)

Galletti, Giacomini (2018) **TEMPO** (10 mol%), NaIO₄ (1 equiv.), AcOH, H₂O/MeCN (R¹ = Ar, R² = H or alkyl)

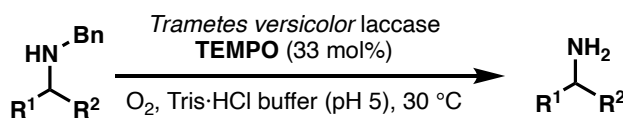
Suryavanshi (2018) **TEMPO** (10 mol%), PhI(OAc)₂ (1 equiv.), CH₂Cl₂, 0 °C to rt

b) Application to oxidative kinetic resolution of secondary amines

• Kashiwagi (1999)


 c) Application to selective deprotection of *N*-benzyl group

• Gotor-Fernández, Lavandera (2015)



d) Application to Passerini reaction

• Ostaszewski (2020) *Trametes versicolor* laccase **TEMPO** (20 mol%) AcOH (1 equiv.) O₂ phosphate buffer (pH 5.2) 30 °C

$$\begin{array}{c}
 \text{Ar}-\text{CH}_2-\text{NH}_2
 \end{array}
 \xrightarrow{\text{O}_2, \text{phosphate buffer (pH 5.2), 30 }^\circ\text{C}}
 \left[\begin{array}{c} \text{O} \\ || \\ \text{Ar}-\text{C} \end{array} \right]
 \xrightarrow[\text{DODAB: dimethyldioctadecyl-ammonium bromide}]{\begin{array}{c} \text{DODAB (20 mol\%)} \\ \text{R}^1\text{-CO}_2\text{H (1 equiv.)} \\ \text{R}^2\text{-NC (1 equiv.)} \end{array}}
 \begin{array}{c}
 \text{O} \\
 || \\
 \text{Ar}-\text{C}-\text{O}-\text{C}-\text{R}^1 \\
 | \\
 \text{HN}-\text{R}^2
 \end{array}$$

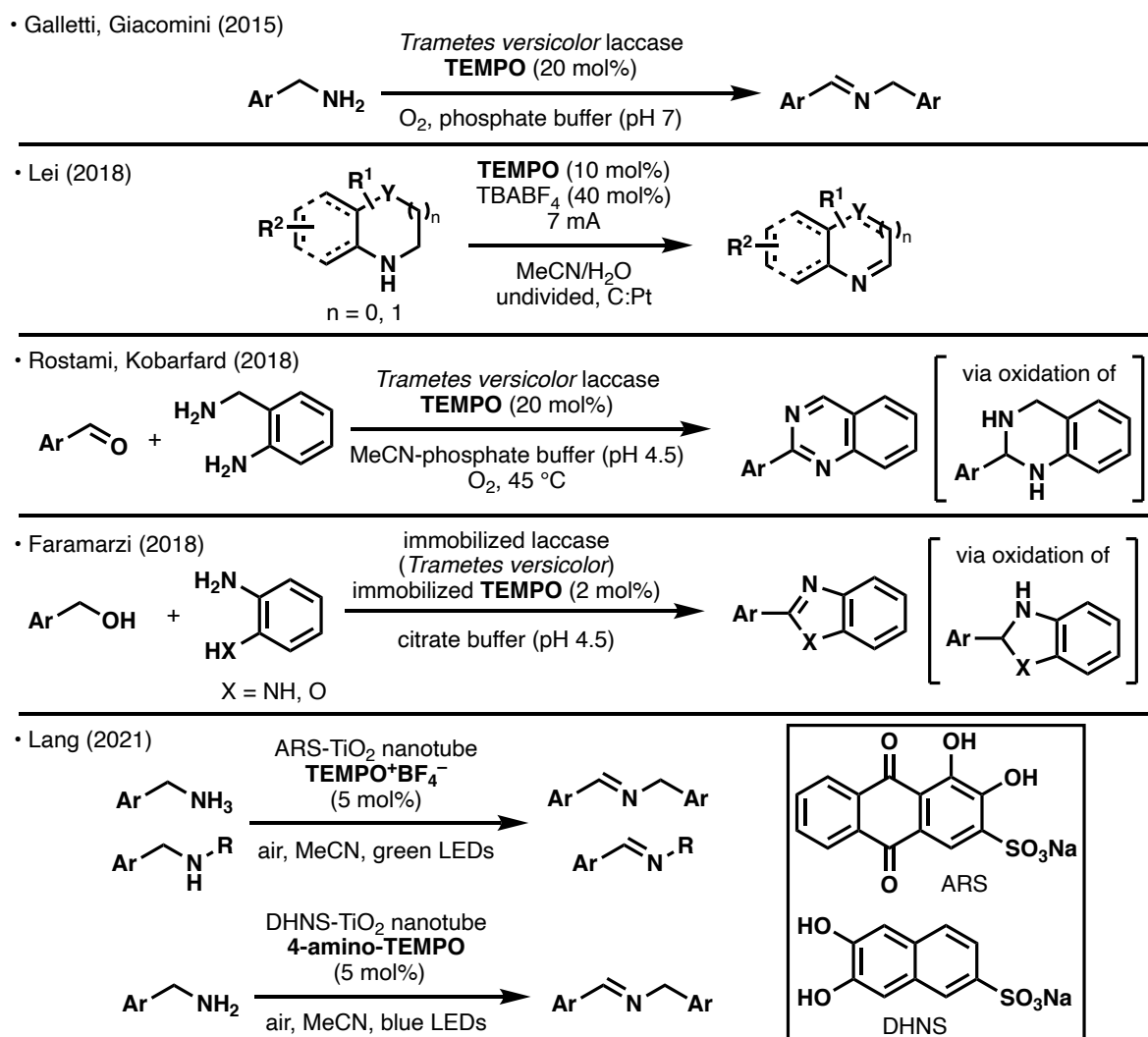
e) Application to oxidative amidation of amines

• Leadbeater (2020) Ru(bpy)₃(PF₆)₂ (2 mol%) **4-NHAc-TEMPO** (20 mol%) LiBF₄ (30 mol%) pyrazole (1.5 equiv.) Na₂S₂O₈ (5 equiv.) pyridine (5 equiv.) MeCN, blue LEDs then filtration

$$\begin{array}{c}
 \text{Ar}-\text{CH}_2-\text{NH}_2
 \end{array}
 \xrightarrow[\text{MeCN, blue LEDs then filtration}]{\begin{array}{c} \text{Ru(bpy)}_3\text{(PF}_6\text{)}_2 \text{ (2 mol\%)} \\ \text{4-NHAc-TEMPO (20 mol\%)} \\ \text{LiBF}_4 \text{ (30 mol\%)} \\ \text{pyrazole (1.5 equiv.)} \\ \text{Na}_2\text{S}_2\text{O}_8 \text{ (5 equiv.)} \\ \text{pyridine (5 equiv.)} \end{array}}
 \left[\begin{array}{c} \text{O} \\ || \\ \text{Ar}-\text{C} \\ | \\ \text{N} \end{array} \right]
 \xrightarrow[\text{R-NH}_2 \text{ (3 equiv.)}]{\text{R-NH}_2 \text{ (3 equiv.)}}
 \begin{array}{c}
 \text{O} \\
 || \\
 \text{Ar}-\text{C}-\text{N}-\text{R} \\
 | \\
 \text{H}
 \end{array}$$
Scheme 5. Oxidation of amines into carbonyl compounds and its applications

Other types of reactions utilizing the formation of imines from primary and secondary amines have been reported (**Scheme 6**). In 2015, Galletti, Giacomini et al. reported an aerobic dimerization of primary amines into their corresponding imines using *Trametes versicolor* laccase/TEMPO catalytic system.⁶⁹ In

2018, Lei et al. reported the TEMPO-mediated electrochemical dehydrogenation of nitrogen heterocycles to yield nitrogen-containing aromatic heterocycles, although this does not include the nucleophilic capture of their resulting imines.⁷⁶ In the same year, Rostami and Kobarfard et al. reported an aerobic aromatization of in-situ generated tetrahydroquinazolines and related nitrogen heterocycles using laccase-TEMPO catalysis.⁷⁷ Faramarzi et al. also reported an aerobic synthesis of benzimidazole and benzoxazole products including dehydrogenation of the corresponding cyclized intermediates using immobilized laccase and immobilized TEMPO.⁷⁸ In 2021, Lang et al. reported a unique cooperative photocatalytic system for the aerobic oxidation of amines to imines, including the release of ammonia releasing using dye-TiO₂ nanotubes with TEMPO⁺BF₄⁻ or 4-NH₂-TEMPO as the catalyst.^{79,80}

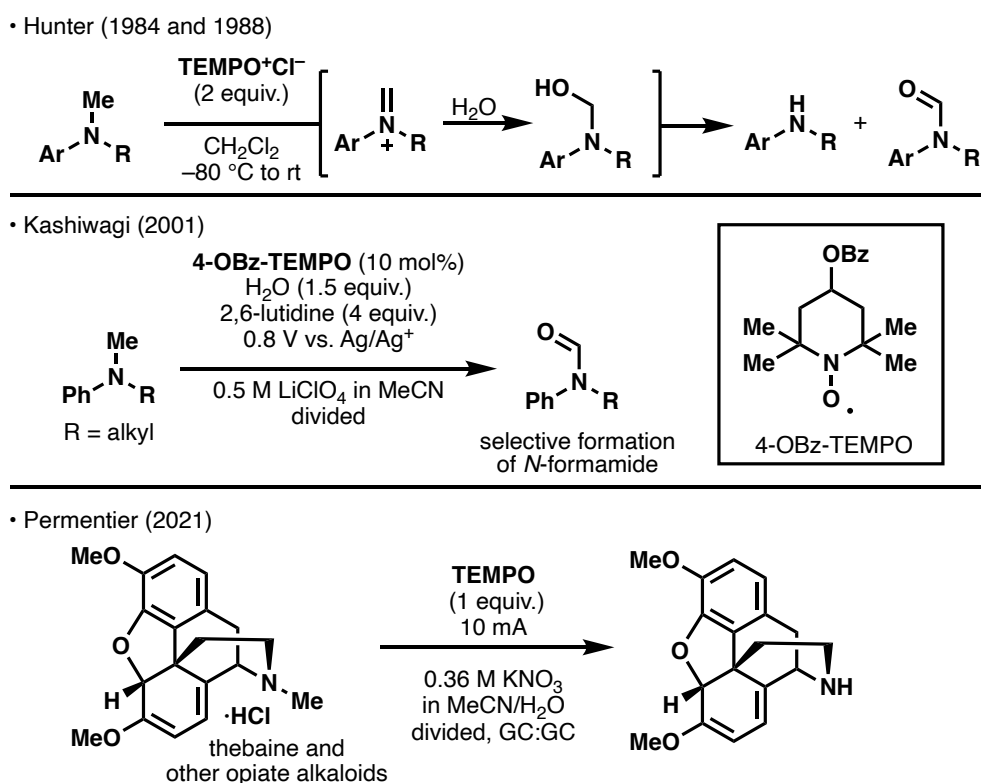


Scheme 6. Oxidation of primary and secondary amines to form imines

3-2-2-2. Tertiary amines

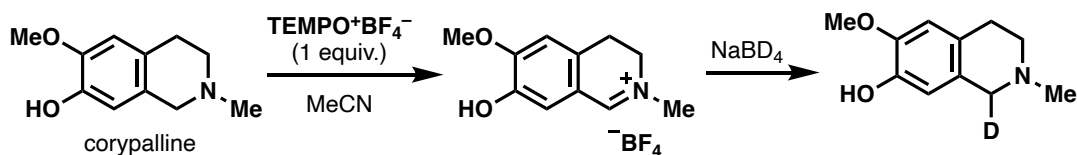
N-Methyl tertiary amines have been investigated as a substrate in oxoammonium species-mediated oxidation (**Scheme 7**). In 1984, Hunter et al. reported that *N,N*-dimethylaniline reacted with 2 equivalents

of TEMPO⁺Cl⁻ to give *N*-methylaniline and *N*-methylformanilide.⁸¹ This result strongly indicated the formation of an iminium species during the reaction, which was captured by H₂O to give the hemiaminal. In 1988, they evaluated the applicability of this demethylation reaction using a variety of *N*-alkyl-*N*-methylanilines.⁸² Later, Kashiwagi and Anzai reported a selective TEMPO-mediated electrochemical conversion of *N*-alkyl-*N*-methylanilines into *N*-alkyl-*N*-formylanilides.⁸³ In contrast, Permentier et al. applied the amine oxidation system to an electrochemical *N*-demethylation of opiate alkaloids in 2021.⁸⁴



Scheme 7. Iminium formation from *N*-Me tertiary amines: formation of formamides and demethylation

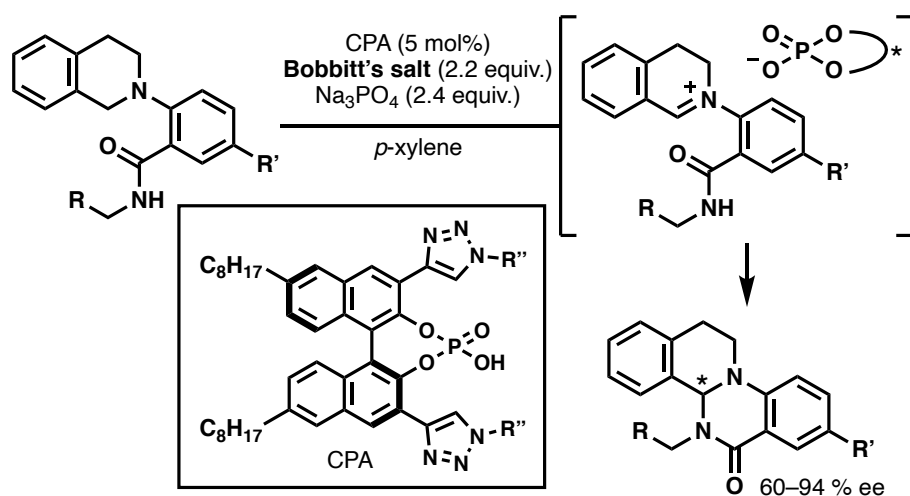
Not only *N*-methylamines, but various tertiary amines can also be applied in this oxidative functionalization reaction. Among them, cyclic amines such as piperidine, pyrrolidine, and tetrahydroisoquinoline have been frequently employed as a substrate to yield their corresponding cyclic iminium species, which can be captured by some nucleophiles. Preliminary results were reported by Bobbitt and Ma in 1992 (**Scheme 8**).⁸⁵ They found that corypalline was converted into its iminium salt by



Scheme 8. Iminium formation from corypalline and its nucleophilic capture (Bobbitt, 1992)

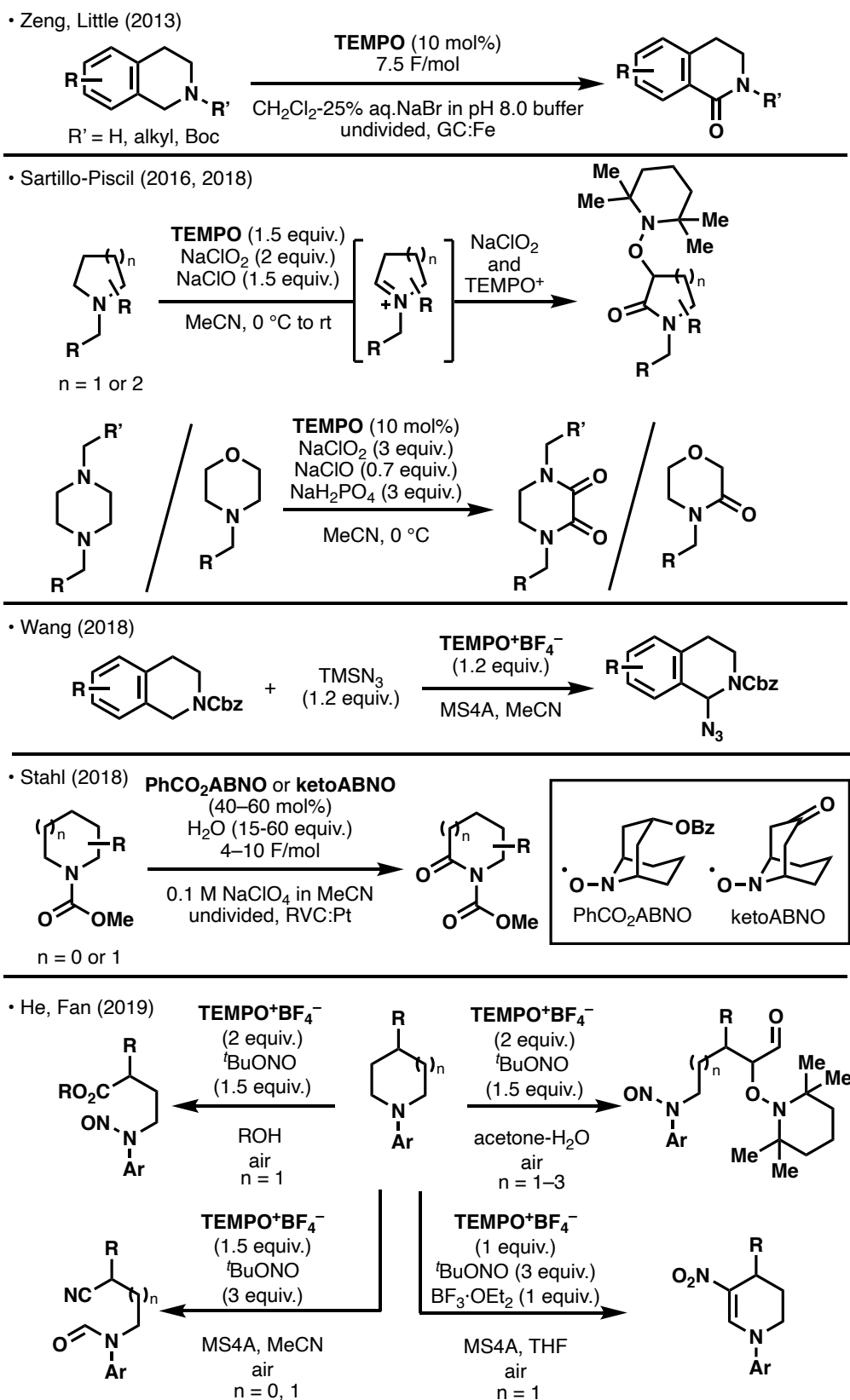
TEMPO⁺BF₄⁻ under neutral conditions. Although they tried to reduce the iminium species with NaBD₄, further studies for the functionalization of the iminium salt have not been explored at that time.

In 2013, Toste et al. reported an enantioselective intramolecular oxidative amination of tetrahydroisoquinolines using a triazole-containing chiral phosphoric acid catalyst and Bobbitt's salt as the oxidant (**Scheme 9**).⁸⁶ Later, Sigman et al. obtained a considerably simplified mathematical correlation between the substrate and catalyst structure and enantioselectivity of the reaction using multidimensional correlation analysis.⁸⁷ In addition, Mancheño et al. showed the importance of having an appropriate regioisomeric triazole group in the BINOL backbone for high enantioselectivity.⁸⁸



Scheme 9. Enantioselective intramolecular oxidative amination (Toste, 2013)

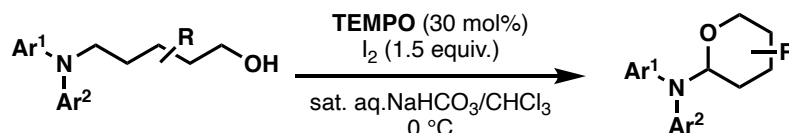
The intermolecular nucleophilic capture of iminium species has been investigated (**Scheme 10**). In 2013, Zeng, Little et al. developed a TEMPO-mediated electrochemical oxidation of tetrahydroisoquinolines to yield their corresponding lactams.⁸⁹ In 2016, Sartillo-Piscil et al. reported a dual oxidation of cyclic amines to yield 3-alkoxyamine lactams using a TEMPO/NaClO/NaClO₂ system.^{90,91} Later, in 2018, they expanded this methodology to piperazines and morpholines.⁹² Zhang et al. reported a TEMPO-mediated electrochemical oxidation of glycine to yield glyoxylate (not shown).⁹³ In 2018, Wang et al. reported the C–H azidation of tetrahydroisoquinolines and tetrahydro-β-carbolines using TMSN₃ and TEMPO⁺BF₄⁻.⁹⁴ Stahl et al. developed a Shono-type oxidation of cyclic carbamate with bicyclic *N*-oxyl mediators, such as PhCO₂ABNO and ketoABNO.⁹⁵ In 2019, He, Fan et al. reported the selective cleavage of cyclic amines and tunable functionalization of C–C/C–N bonds in *N*-arylpiperidines using tBuONO and TEMPO⁺BF₄⁻.⁹⁶ Following this paper, they reported a synthesis of β-nitrated *N*-heterocycles and *N*-nitroso-2-alkoxyamine aldehydes from *N*-aryl cyclic amines using a similar reagent system.⁹⁷



Scheme 10. Iminium formation from tertiary amines: conversion of cyclic amines

Acyclic tertiary amines are rarely employed as a substrate for oxidative transformation by oxoammonium species. In 2016, Kim et al. reported an oxidative cyclization of *N,N*-diaryl-1,5-amino alcohols under

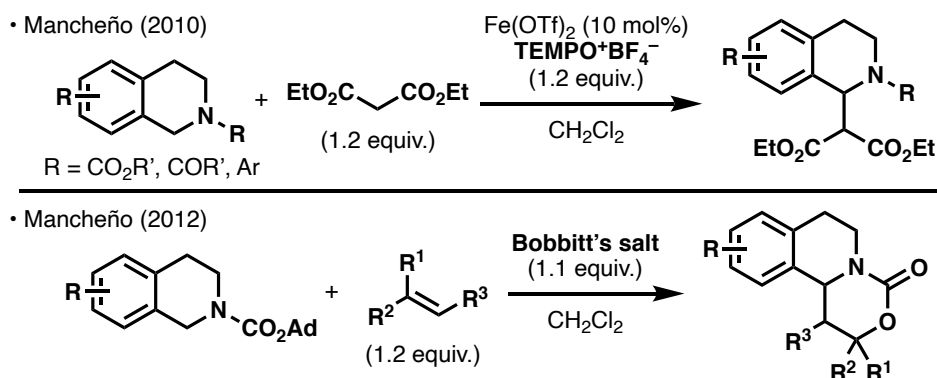
TEMPO/I₂ catalysis.⁹⁸ Later, in 2017, they investigated the reaction mechanism using computational methods and revealed that an ionic pathway (oxoammonium species-mediated path) was plausible.⁹⁹



Scheme 11. Iminium formation from acyclic tertiary amines (Kim, 2015)

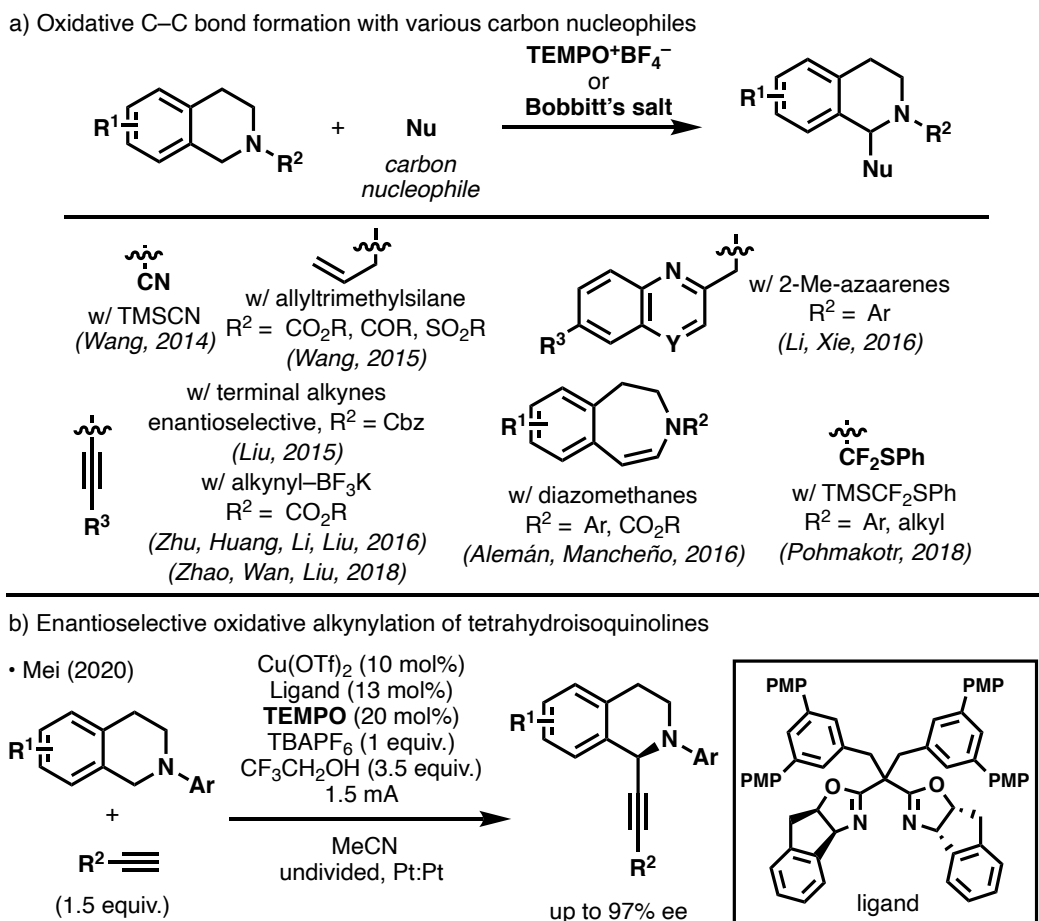
3-2-3. Oxidative C-C bond formation

Direct C–C bond formation at the α -position of a nitrogen atom has been investigated by several chemists using various methodologies. Among them, the oxidative C–C coupling reaction is one of the most frequently employed strategies used to achieve such this transformation, and recent studies have revealed that oxoammonium species (oxoammonium salt) are suitable oxidants for this purpose. The first successful example of this type of reaction was reported by Mancheño and Richter in 2010 (**Scheme 12**). They reported a Fe(OTf)₂-catalyzed cross dehydrogenative cross-coupling at the benzylic position adjacent to an oxygen or nitrogen atom with 1,3-dicarbonyl compounds.¹⁰⁰ Furthermore, they reported a metal-free tandem α -alkylation/cyclization of *N*-benzylcarbamates with various olefins in 2012.¹⁰¹ In these reports, they demonstrated that tetrahydroisoquinolines can be used as a good substrate for this type of transformation. Some researchers have reported various oxidative C-C bond forming reactions of tetrahydroisoquinolines or related substrates (such as tetrahydro- β -carbolines) with various nucleophiles (such as cyanide (Wang, 2014),¹⁰² acetylenes (enantioselective, Liu, 2015),¹⁰³ allyltrimethylsilane (Wang, 2015),¹⁰⁴ 2-methylazaarenes (Li and Xie, 2016),¹⁰⁵ diazomethanes (Alemán and Mancheño, 2016),¹⁰⁶ alkynyl potassium trifluoroborate (Zhu, Huang, Li, and Liu, 2016 and Zhao, Wan, and Liu, 2018),^{107,108} TMSCF₂SPh (Pohmakotr, 2018)¹⁰⁹ after the Mancheño's work (**Scheme 13a**). In 2020, Mei et al. reported



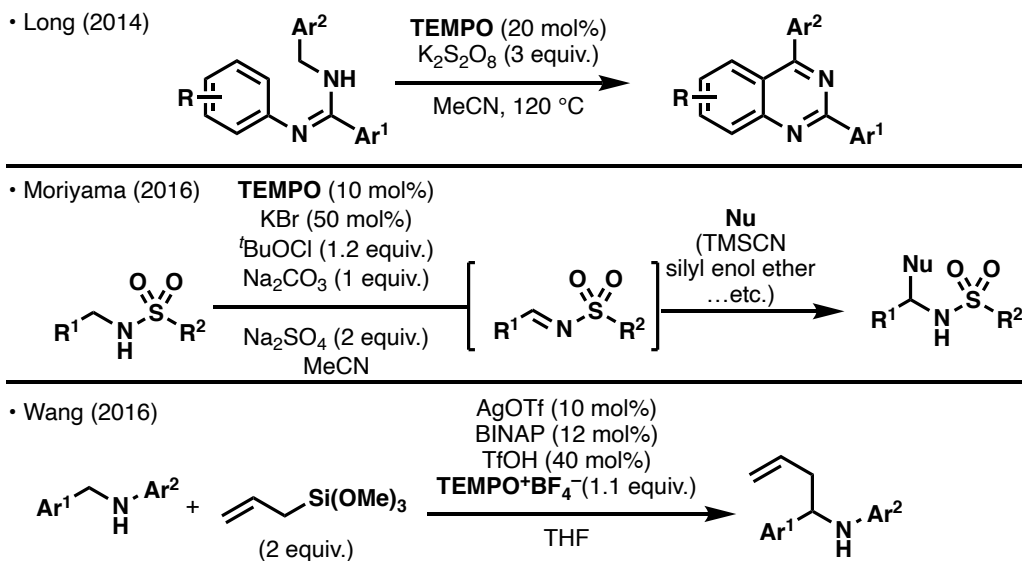
Scheme 12. Mancheño's work: oxidative C–C bond formation of tetrahydroisoquinolines

an electrochemical catalytic enantioselective C–H alkynylation of tetrahydroisoquinolines using a chiral Cu-box complex and TEMPO as a mediator (**Scheme 13b**).¹¹⁰



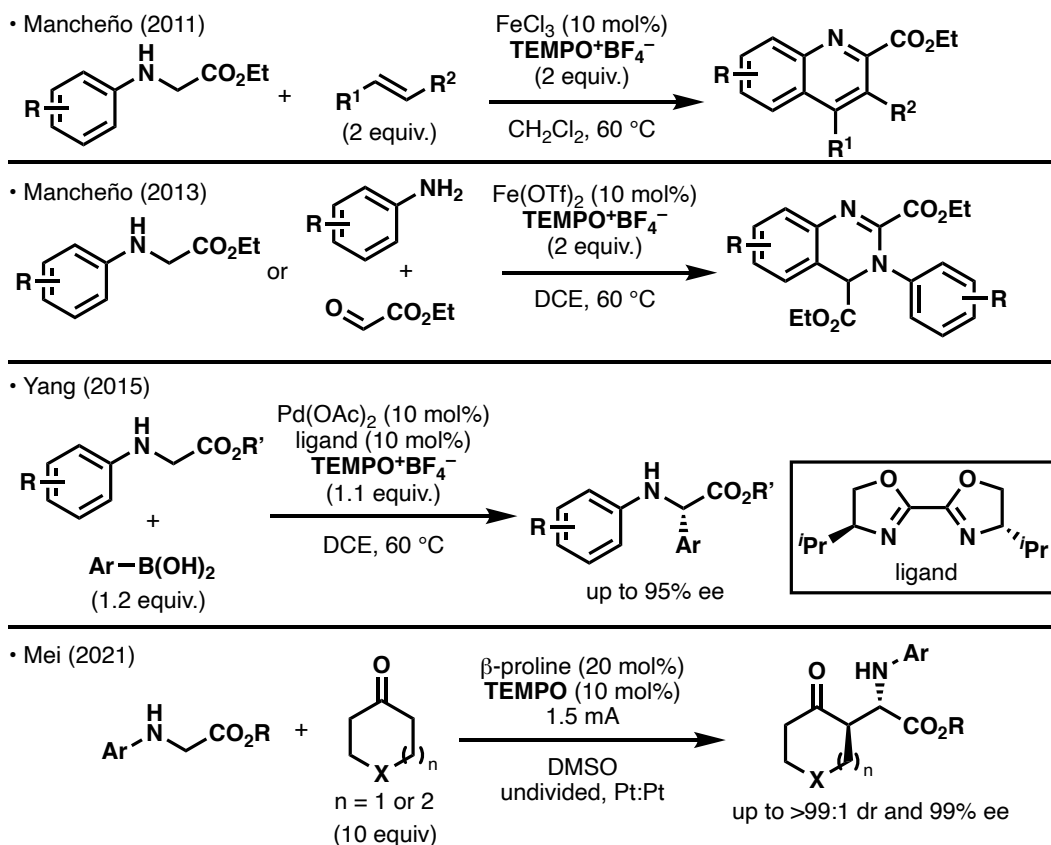
Scheme 13. Oxidative C–C bond formation of tetrahydroisoquinolines

Not only tetrahydroisoquinolines, but other amines can also be used as a substrate for oxidative C–C bond formation (**Scheme 14**). Benzylic amines, which are structurally similar to tetrahydroisoquinolines, are frequently used substrates. In 2014, Long et al. reported the TEMPO-catalyzed oxidative annulation of arylamidines to form quinazolines via an intramolecular Friedel-Crafts reaction of the in-situ generated iminium species, followed by aromatization.¹¹¹ In 2016, Moriyama et al. reported the TEMPO-catalyzed oxidative C–C bond formation of sulfonamides via *N*-halogenation.¹¹² Various silylated carbon nucleophiles such as trimethylsilyl cyanide (TMSCN), allyltrimethylsilane, and silyl enol ethers were applicable in this reaction. Wang and Yang reported an oxidative allylation of arylbenzylamines using a Ag-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) catalytic system with TEMPO⁺BF₄⁻ as the oxidant.¹¹³



Scheme 14. Oxidative C–C bond formation of benzylic amines

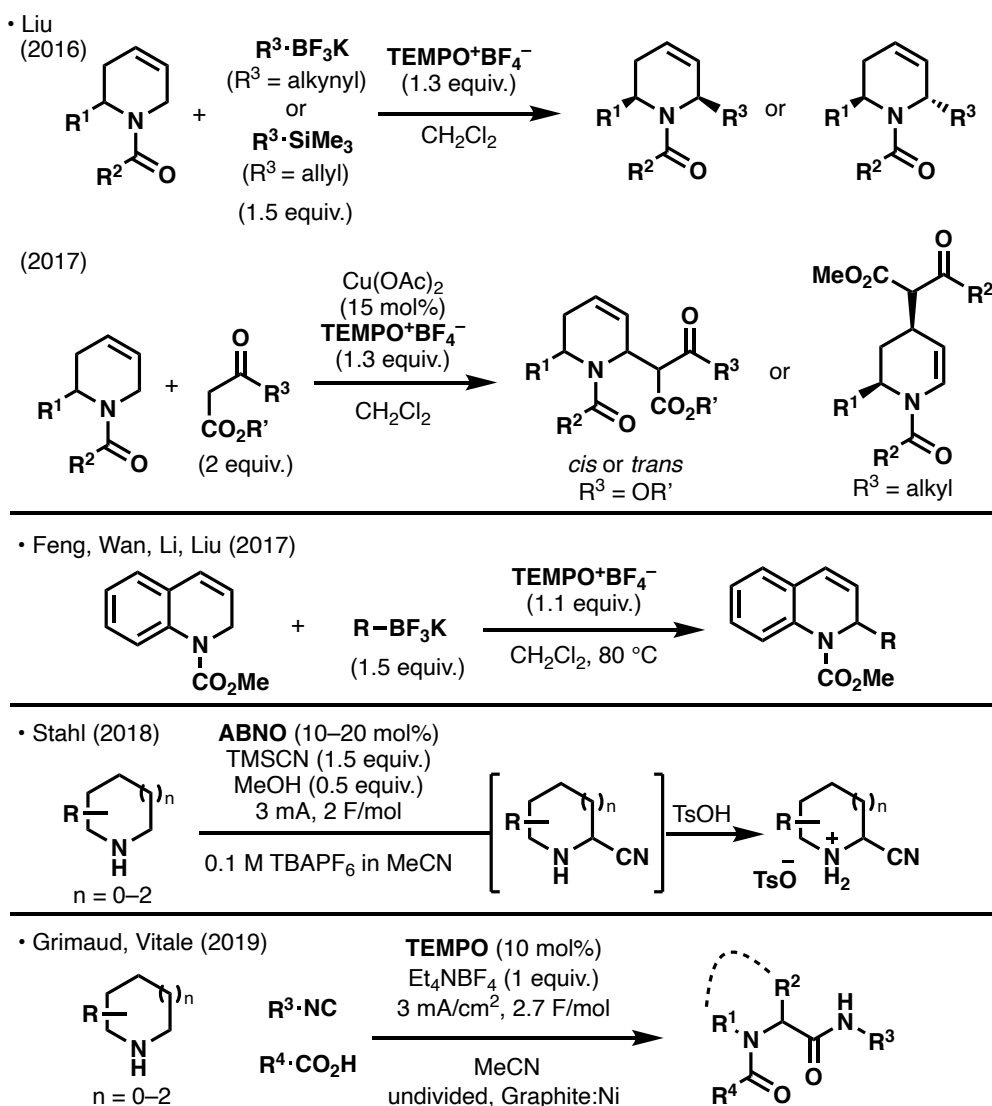
N-Arylglycines have also been used for oxidative C–C bond formation (**Scheme 15**). Mancheño and Richter developed a FeCl₃-catalyzed dehydrogenative Povarov/oxidation tandem reaction of *N*-arylglycines to yield substituted quinolines using TEMPO⁺BF₄[−] as an oxidant in 2011.¹¹⁴ In this reaction, TEMPO⁺BF₄[−] promoted the formation of the iminium species and the aromatization step. They



Scheme 15. Oxidative C–C bond formation of *N*-arylglycines

expanded this methodology to the synthesis of dihydroquinazolines in 2013.¹¹⁵ In 2015, Yang et al. reported the enantioselective synthesis of arylglycine derivatives via the oxidative cross coupling of *N*-aryl glycines and arylboronic acids using palladium catalysis and TEMPO⁺BF₄⁻.¹¹⁶ In 2021, Mei reported an electrochemical enantioselective Shono-type oxidative coupling of *N*-aryl glycines with ketones using TEMPO as a mediator and β-proline as an organocatalyst.¹¹⁷

Some cyclic amines can also be employed as the substrate (**Scheme 16**). Liu et al. reported the diastereoselective oxidative alkynylation/allylation of 2-substituted tetrahydropyridines to give 2,6-disubstituted tetrahydropyridines.¹¹⁸ In the following year (2017) they reported the Cu-catalyzed coupling of 2-substituted tetrahydropyridines and 1,3-dicarbonyl compounds.¹¹⁹ Feng, Wan, Li, and Liu et al. reported the C–H alkynylation of 1,2-dihydroquinolines using alkynyl potassium trifluoroborates as a nucleophiles.¹²⁰ Stahl et al. reported an electrochemical α-cyanation of unprotected secondary piperidines and other nitrogen heterocycles using ABNO as a mediator.¹²¹ Notably, the obtained cyanated



Scheme 16. Oxidative C–C bond formation of cyclic amines

compounds could be converted into various pipercolic acid derivatives. Grimaud and Vitale et al. reported the TEMPO-mediated electrochemical multicomponent α -carbamylation of unprotected secondary cyclic amines.¹²²

3-3. Oxidation of ethers

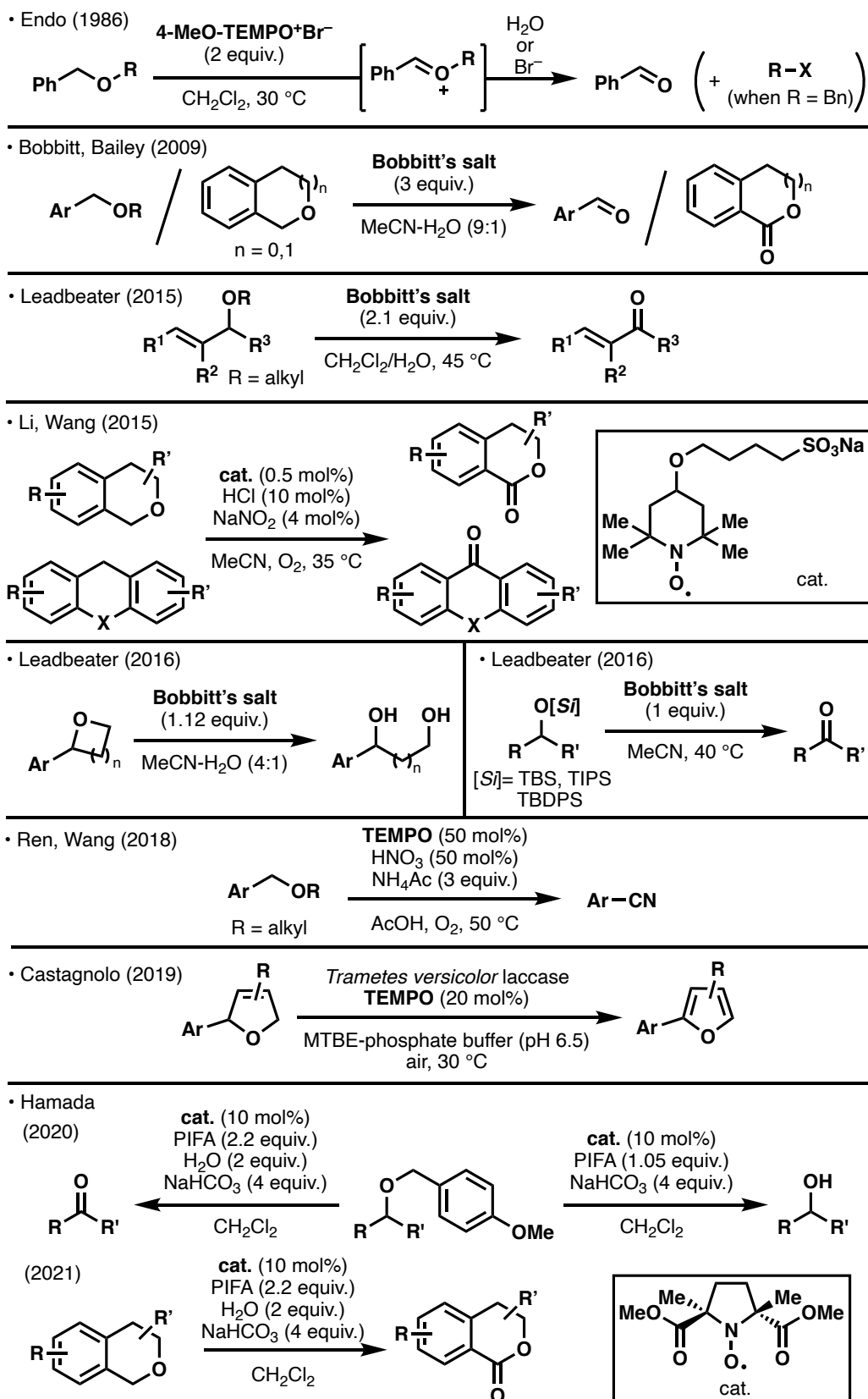
It is known that oxoammonium species can be used as a mild oxidant at the α -position of an oxygen atom. This reactivity has been applied to the oxidative cleavage of ethereal protecting groups and oxidative C–C bond formation.

3-3-1. C–H Oxidation and C–O cleavage of ethers (**Scheme 17**)

The oxoammonium species-mediated C–O cleavage of ethers was firstly reported by Endo and Miyazawa in 1986.¹²³ They found that TEMPO⁺X⁻ (X = Cl or Br) cleaved a series of benzylic ethers to give benzaldehyde. Galli and Gentili et al. attempted to apply the laccase-catalyzed aerobic C–H oxidation and C–C cleavage of benzylic ethers with TEMPO in 2002–03; however, their efficiency was low (not shown).^{124,125} Pradhan, Bobbitt, and Bailey reported the first practical and widely-applicable reactions for the oxidative cleavage of benzylic and other ethers using Bobbitt's salt in 2009.¹²⁶ Notably, isochroman and phthalan were converted into their corresponding lactones under the reaction conditions. Leadbeater et al. reported the oxidative cleavage of alkyl allyl ethers by Bobbitt's salt to yield unsaturated aldehydes/ketones.¹²⁷ Li and Wang et al. have reported the aerobic benzylic C–H oxidation of isochromans using recyclable TEMPO as a catalyst in 2015.¹²⁸ They also demonstrated that this catalytic system could be applicable of benzylic C–H oxygenation of alkylarenes. Leadbeater et al. reported an oxidative ring-opening of cyclic ethers using Bobbitt's salt to give hydroxyketones in 2016.¹²⁹ They also reported the oxidative cleavage of silyl ethers using Bobbitt's salt to give aldehydes or ketones in the same year.¹³⁰ In 2018, Ren and Wang et al. reported the direct conversion of benzyl ethers into aryl nitriles under aerobic conditions (1 MPa O₂) using a TEMPO/HNO₃ oxidation system with ammonium acetate used as an ammonia source.¹³¹ In 2019, Castagnolo et al. reported the aerobic chemoenzymatic aromatization of 2,5-dihydrofurans, which was synthesized by ring-closing metathesis of diallyl ether, using laccase-TEMPO catalytic system.¹³² In 2020, Hamada et al. reported the catalytic chemoselective cleavage of *p*-methoxybenzyl ethers using their electronically tuned nitroxyl radical.¹³³ They expanded the utility of the electronically tuned nitroxyl radical to the catalytic oxidation of cyclic ethers.¹³⁴

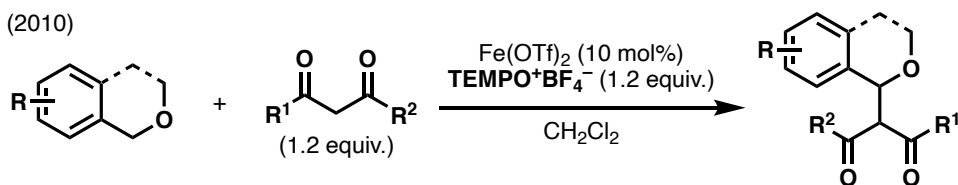
3-3-2. Oxidative C–C (C–X) bond formation (**Scheme 18**)

Not only amines, but (cyclic) ethers are also applicable as substrates for oxidative C–C bond formation, and oxoammonium species can act as a suitable oxidant for this purpose. As mentioned in the beginning

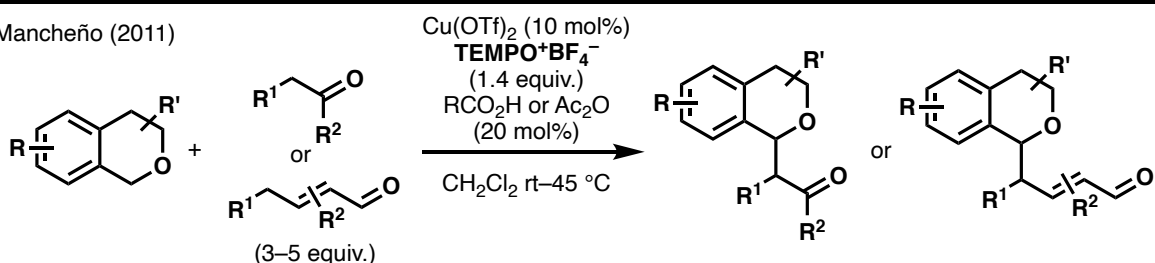


Scheme 17. C–H Oxidation and C–O cleavage of ethers

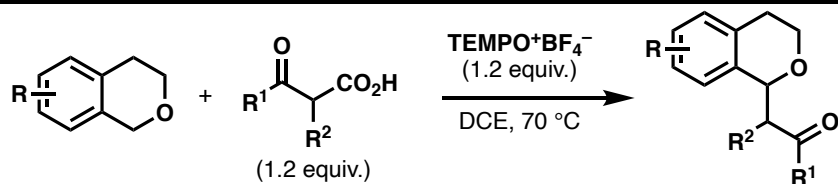
• Mancheño (2010)



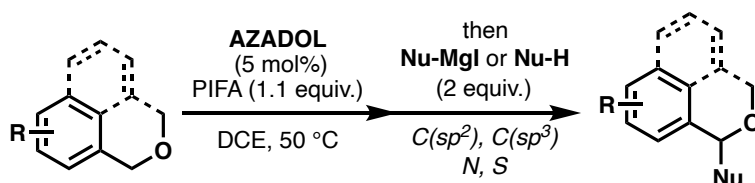
• Mancheño (2011)



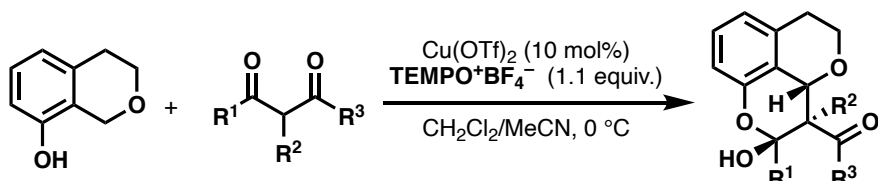
• Tian (2013)



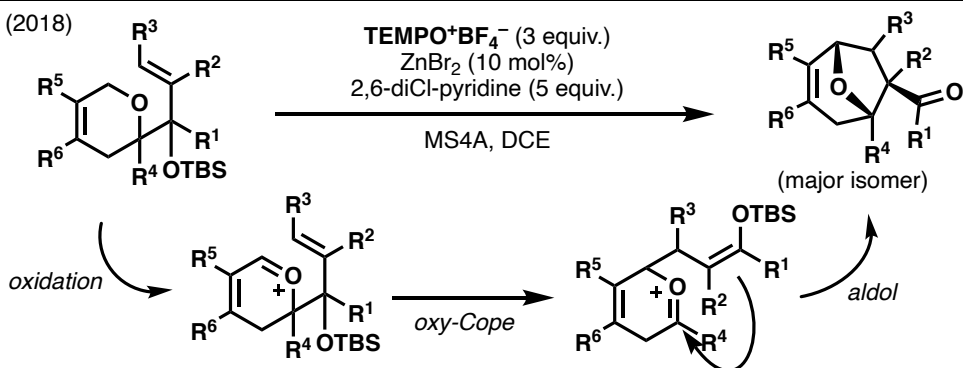
• Muramatsu (2015)



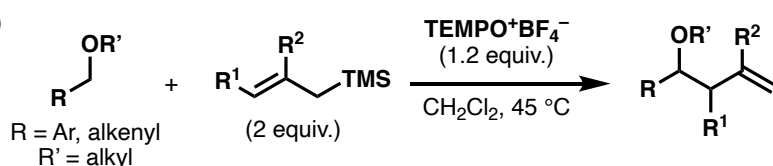
• Tu (2019)



• Tu, Wang (2018)



• Pradal, Poli (2021)

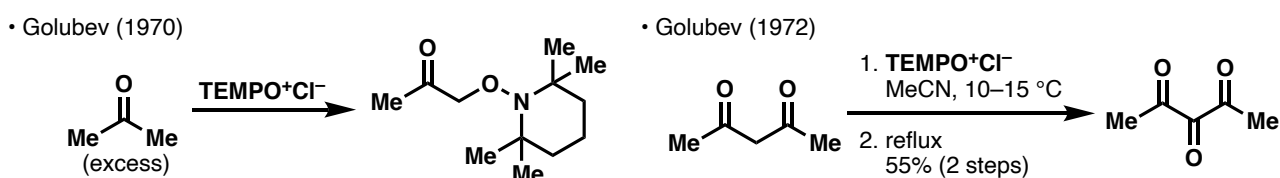


Scheme 18. Oxidative C-C bond formation

of Section 3-2-4, Mancheño and Richter reported the $\text{Fe}(\text{OTf})_2$ -catalyzed cross dehydrogenative coupling of the benzylic position adjacent to an oxygen or nitrogen atom with 1,3-dicarbonyl compounds.¹⁰⁰ In the following year, Mancheño reported the Cu-catalyzed oxidative C–C coupling of isochroman and enolizable aldehydes using $\text{TEMPO}^+\text{BF}_4^-$ as an oxidant.¹³⁵ In 2013, Tian and Chen reported a decarboxylative oxidative C–C coupling of isochroman and β -keto acids using $\text{TEMPO}^+\text{PF}_6^-$ as an oxidant.¹³⁶ Muramatsu and Nakano reported an AZADOL-catalyzed oxidative C–C coupling of isochroman and various nucleophiles in 2015.¹³⁷ Grignard reagents, sulfonamides, azide, imidazole, malonate, and thiophenols were applicable in the reaction. Wang's report on the C–H azidation of tetrahydroisoquinolines and tetrahydro- β -carbolines using TMSN_3 and $\text{TEMPO}^+\text{BF}_4^-$ (as shown in **Scheme 10**) is also applicable to chromans and related cyclic benzyl ethers (not shown).⁹⁴ In 2019, Tu reported the copper-catalyzed diastereoselective coupling of 1,3-dicarbonyl compounds and 8-hydroxychromanes using $\text{TEMPO}^+\text{BF}_4^-$ as an oxidant to give tricyclic chromane products.¹³⁸ Few examples of other types of ether substrate have been reported. Tu and Wang et al. reported the synthesis of 8-oxabicyclo[3.2.1]octanes via a tandem $\text{TEMPO}^+\text{BF}_4^-$ -mediated C–H oxidation/oxa-Cope rearrangement/aldol reaction.¹³⁹ Pradal and Poli have reported the $\text{TEMPO}^+\text{BF}_4^-$ -mediated coupling reaction of allylsilanes and allyl and benzyl methyl ethers.¹⁴⁰

3-4. Oxidation of enols: α -Aminooxygenation of carbonyl compounds and further applications

Oxoammonium salts are also known as useful reagents for the α -aminooxygenation of various carbonyl compounds via nucleophilic attack of enolates (enols) at its oxygen atom. Early reports by Golubev et al. revealed that the enolizable ketones easily react with oxoammonium salt to yield alkoxyamine, which can be efficiently converted into 1,2-dicarbonyl or 1,2,3-tricarbonyl compounds (**Scheme 19**).^{141,142} Similar observations have been reported by other researchers.^{81,143,144}



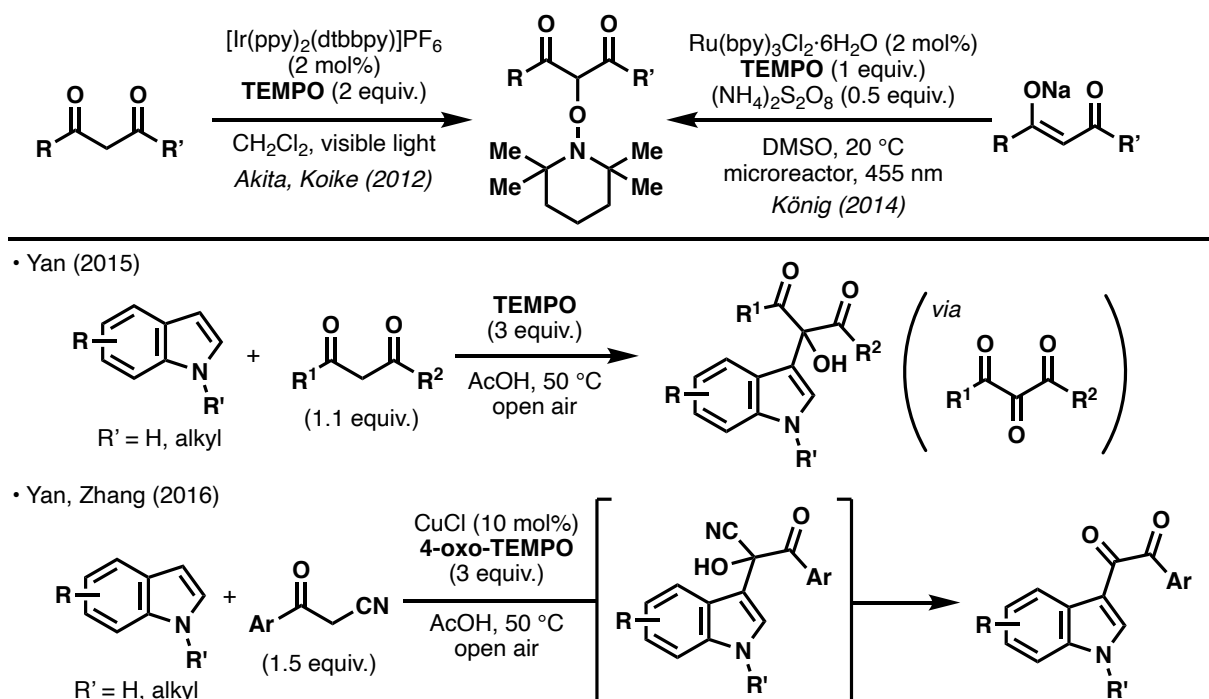
Scheme 19. Reactivity of oxoammonium species with enols: Early discoveries

3-4-1. Aminoalkoxylation of enols

3-4-1-1. Aminoalkoxylation of 1,3-dicarbonyl compounds (**Scheme 20**)

Koike, Yasu, and Akita reported the visible light-driven aminoxygenation of 1,3-dicarbonyl compounds using TEMPO in combination with a photoredox catalyst.¹⁴⁵ König and Schroll also reported a similar catalytic system utilizing a microreactor in 2014.¹⁴⁶ In 2015, Yan et al. reported the Friedel-Crafts

reaction of indoles with vicinal tricarbonyl compounds, which were generated in situ via the aminoxygenation of a 1,3-dicarbonyl compound using the oxoammonium of TEMPO, followed by N–O bond cleavage.¹⁴⁷ They expanded this methodology to β -ketonitriles to generate 1,2-dicarbonyl indoles via a retro-cyanohydration reaction.¹⁴⁸ In 2019, Tang and Ren et al. reported the Selectfluor[®]-mediated aminoxygenation of 1,3-dicarbonyl compounds (not shown).¹⁴⁹

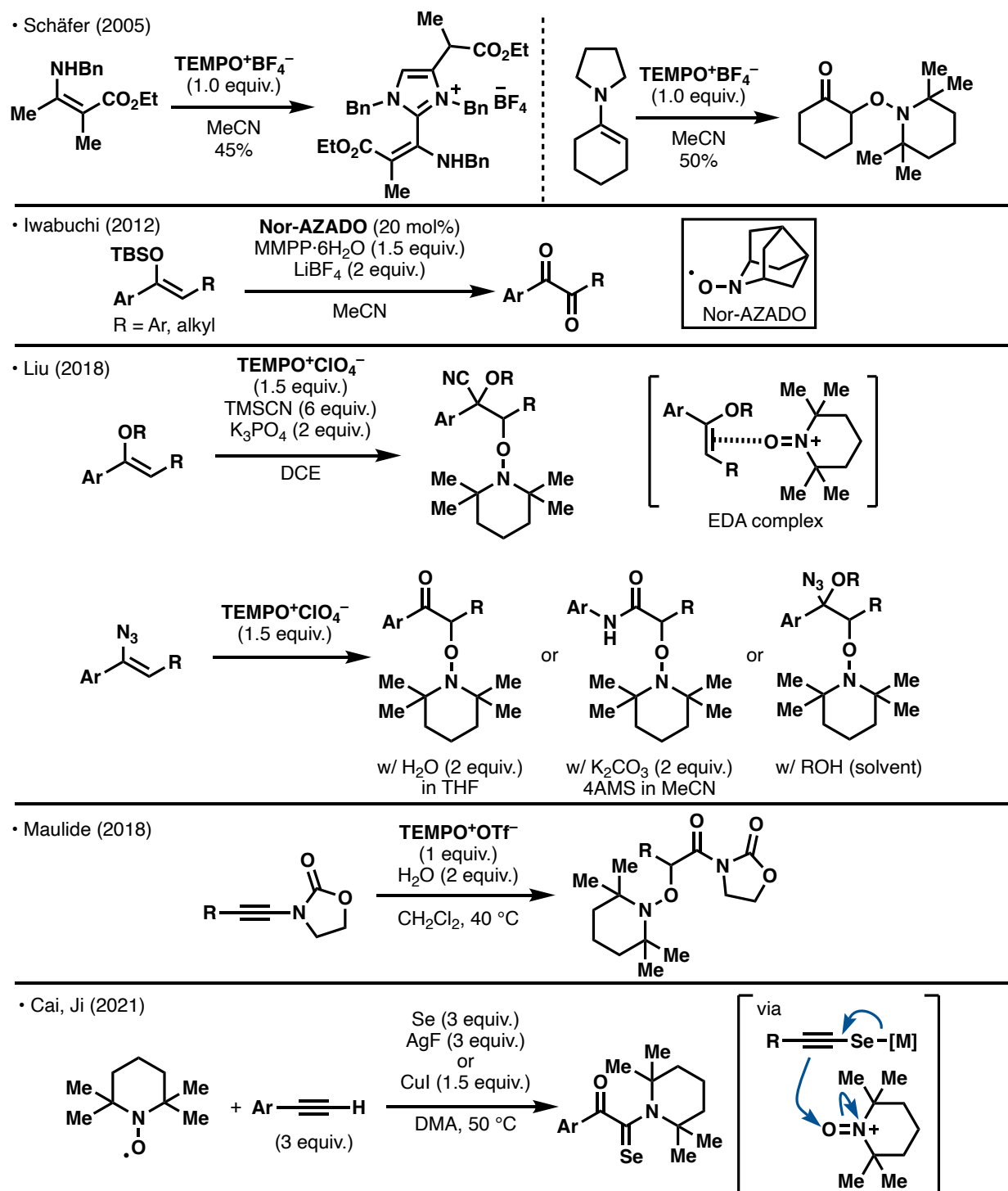


Scheme 20. Recent examples of the aminoalkoxylation of 1,3-dicarbonyls and its application

3-4-1-2. Aminoalkoxylation of enols/enamines and these variants and its applications (Scheme 21)

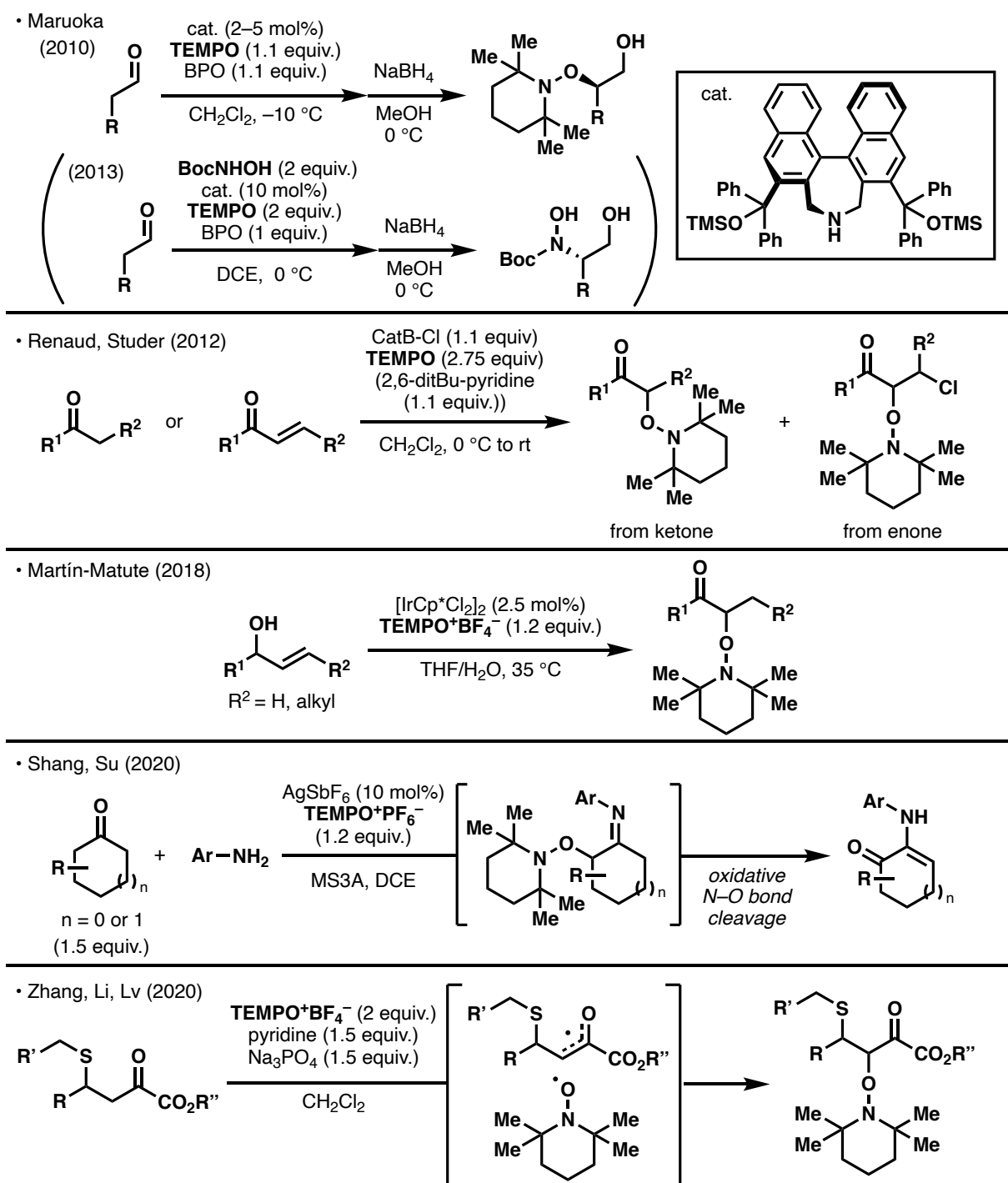
In 2005, Schäfer and Schämamm reported the novel reactivity of oxoammonium species with enamines.¹⁵⁰ They reported the synthesis of imidazolium species via an oxoammonium species-mediated trimerization of an enaminoester and α -aminoxygenation of enamines to yield α -aminooxygenated ketones. Iwabuchi et al. reported the catalytic conversion of silyl enol ethers into 1,2-diketones using a 9-azanoradamantane *N*-oxyl (Nor-AZADO)/magnesium monoperoxyphthalate hexahydrate (MMPP·6H₂O) system.¹⁵¹ The in-situ generation of alkoxyamines and their oxidative cleavage by MMPP proceed catalytically in the reaction. Liu et al. reported the oxycyanation of enol ethers using TEMPO⁺ClO₄⁻ and TMSCN.¹⁵² Using mechanistic studies, they proposed the formation of an electron-donor-acceptor complex and that subsequent single-electron-transfer could be involved in the reaction. A similar transformation and mechanism were observed when vinyl azide was used as a substrate instead of an enol ether.¹⁵³ Maulide et al. reported the hydrative aminoxygenation of ynamides using TEMPO⁺OTf⁻ in 2017.¹⁵⁴ In 2021, Cai and Ji et al. reported the copper- or silver-catalyzed synthesis of α -oxo-selenoamides from terminal

alkynes and elemental selenium using TEMPO.¹⁵⁵ They proposed that the terminal alkyne undergoes a sequential amidation-ketonization-selenation process via a selenoketenyl-metal complex.



Scheme 21. Reaction with enol ethers, enamines, and other related substrates

Carbonyl compounds (aldehydes and ketones) can be directly employed in the reaction with oxoammonium species in combination with a reagent to promote enolization (Scheme 22). In 2010, Maruoka et al. showed that TEMPO⁺ acts as a good reagent for the asymmetric aminoxylation of aldehydes with a chiral secondary amine catalyst.¹⁵⁶ Notably, the asymmetric hydroxyamination reaction occurs in the presence of *N*-Boc-hydroxylamines under the same reaction conditions.¹⁵⁷ In 2012, Renaud and Studer et al. reported the α -aminoxylation of ketones and β -chloro- α -aminoxylation of enones using

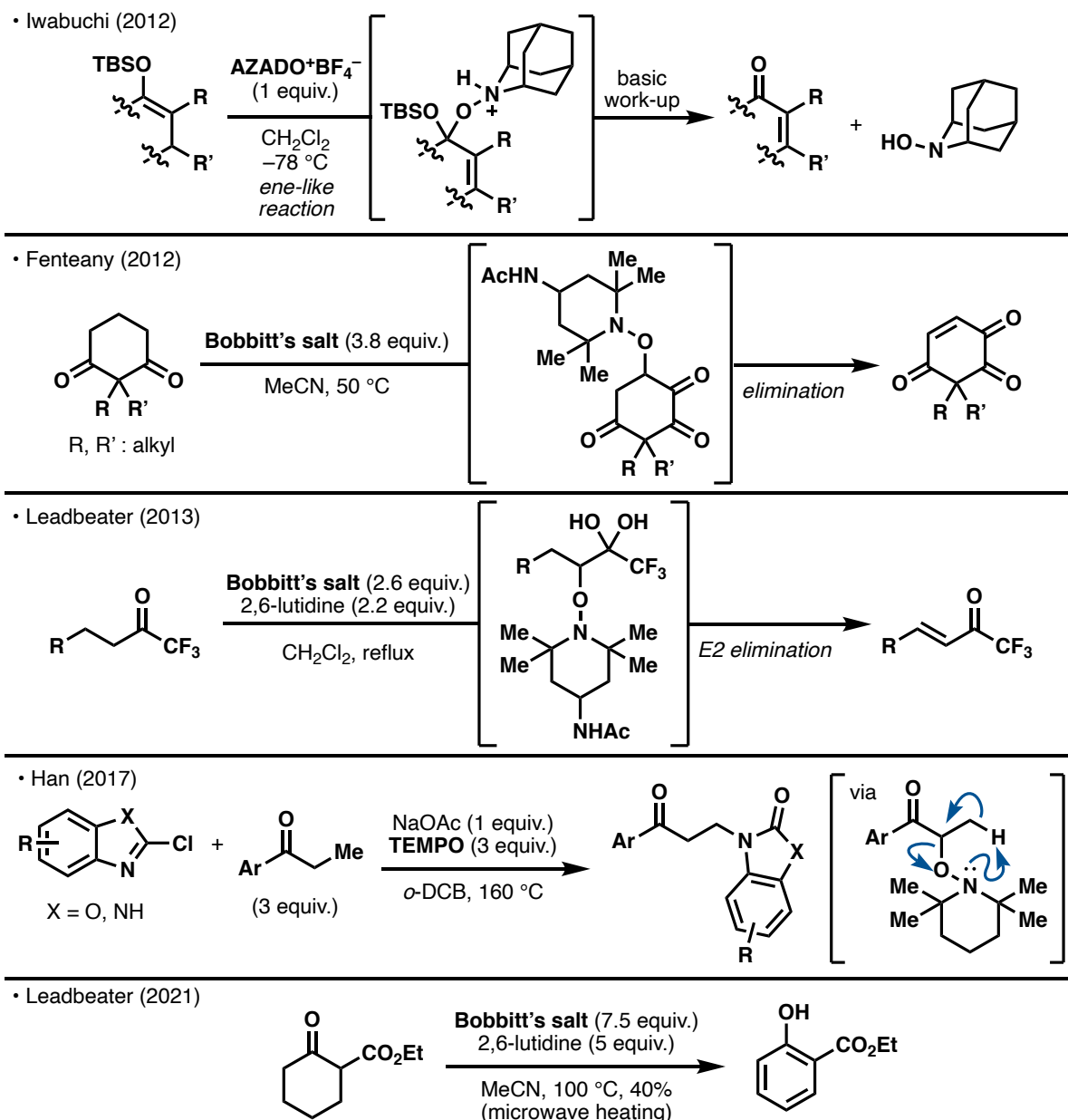


Scheme 22. Reaction of carbonyl compounds with oxoammonium species

TEMPO and chlorocatecholborane.¹⁵⁸ $\text{TEMPO}^+\text{Cl}^-$ generated in situ from TEMPO and chlorocatecholborane act as an aminoxylation reagent for borone enolates. As mentioned beforehand (**Scheme 10**), Sartillo-Piscil et al. reported the dual oxidation of cyclic amines to give 3-alkoxyamine lactams using a TEMPO/NaClO/NaClO₂ system (not shown).⁹⁰ This reaction involves α -aminoxygenation of the resulting enamines. Martín-Matute et al. reported the selective synthesis of unsymmetrical aliphatic acylolins from allylic alcohols via aminoxylation of in-situ formed iridium enolates using TEMPO⁺.¹⁵⁹ In 2020, Shang and Su et al. reported the conversion of cyclic ketones into α -enaminones mediated by catalytic AgSbF₆ and stoichiometric TEMPO⁺PF₆⁻.¹⁶⁰ Zhang, Li, and Lv et al. reported the α -aminoxygenation of pyruvate via a concerted proton-electron transfer mechanism using TEMPO⁺BF₄⁻.¹⁶¹

3-4-2. Dehydrogenation of carbonyl compounds via enols (**Scheme 23**)

Although there are few examples, oxoammonium species have been used as a dehydrogenation reagents for carbonyl compounds and their equivalents. Iwabuchi et al. reported the conversion of silyl enol ethers into α,β -unsaturated ketones using AZADO⁺BF₄⁻ in 2012.¹⁶² They proposed that the sterically less-hindered azaadamantane-type oxoammonium salt reacts with silyl enol ethers in an ene-like manner to yield a mixed acetal that collapses into α,β -unsaturated ketones under acidic conditions. In the same year, Fenteany et al. demonstrated that 1,3-cyclohexanediones can be oxidized into their corresponding ene-triketones using 3.8 equivalents of Bobbitt's salt.¹⁶³ They proposed that this transformation involves not only the α -aminoxygenation of the starting 1,3-cyclohexanediones, followed by N–O cleavage, but also dehydrogenation of the resulting 1,4-diketone moiety into an ene-dione via the elimination of hydroxylamine. In 2013, Leadbeater et al. reported a Bobbitt's salt-mediated dehydrogenation of perfluoroalkyl ketones via the α -aminoxygenation of perfluoroalkyl ketones.¹⁶⁴ In 2017, Han et al. reported the β -C–H amination of saturated ketones with heteroaryl halides using TEMPO.¹⁶⁵ They proposed that the formation of the α -aminoxyated ketone followed by Cope-type elimination yielded α,β -unsaturated ketones that react with the nitrogen nucleophiles generated from the heteroaryl halides. In 2021, Leadbeater et al. reported the deoxygenation of ethyl 2-oxocyclohexanecarboxylate to yield ethyl salicylate using Bobbitt's salt, although 7.5 equivalents of Bobbitt's salt and elevated temperature (microwave heating) were required.¹⁶⁶



Scheme 23. Oxoammonium species-mediated dehydrogenation of carbonyl compounds

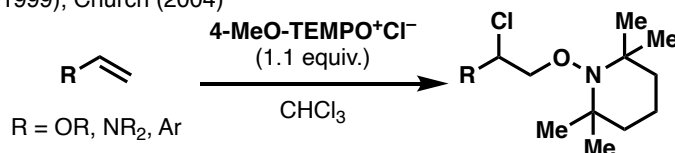
3-5. Oxidation of alkenes

It is reasonable that electrophilic oxoammonium species react with nucleophilic alkenes such as styrene (**Scheme 24a**). This phenomenon was first reported by Endo et al. in 1999. They found that 4-MeO-TEMPO⁺Cl⁻ reacted with various electron-rich olefins (such as enol ethers, enamines, and styrenes) to yield their corresponding alkoxyamines regioselectively.¹⁶⁷ A similar transformation was reported by Church et al. in 2004.¹⁶⁸ In 2016, Donohoe et al. reported an orthogonal dioxygenation of alkenes using TEMPO in HFIP or TFE/AcOH.¹⁶⁹ Chisholm et al. reported the amino-oxidation of electron-rich alkenes using Bobbitt's salt and anilines in 2020.¹⁷⁰ They also reported the tandem elimination–oxidation of tertiary benzylic alcohols to give allylic alkoxyamines using Bobbitt's salt.¹⁷¹ Other alkenes can also be used for the alkoxyamine synthesis. Pradhan, Bobbitt, and Bailey reported the

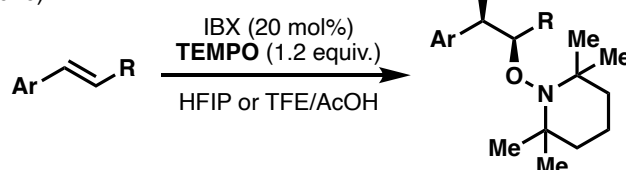
ene-like addition of Bobbitt's salt to trisubstituted alkenes to yield allylic alkoxyamines in 2006 (**Scheme 24b**).¹⁷²

a) Reaction with styrene-type substrates

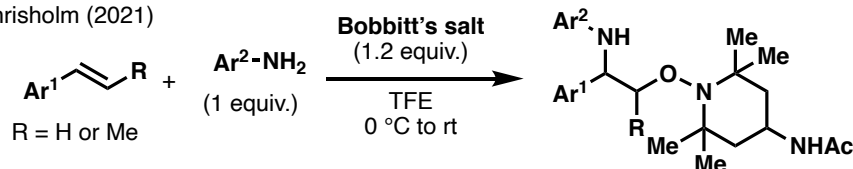
• Endo (1999), Church (2004)



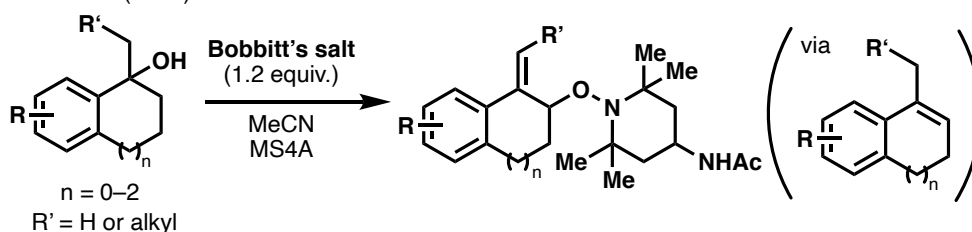
• Donohoe (2016)



• Chrisholm (2021)

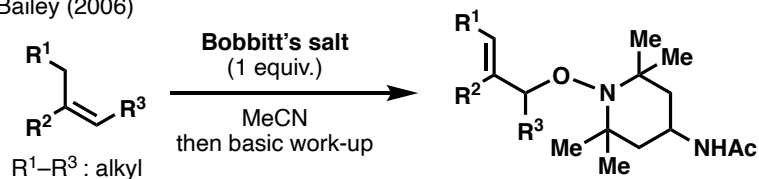


• Chrisholm (2021)



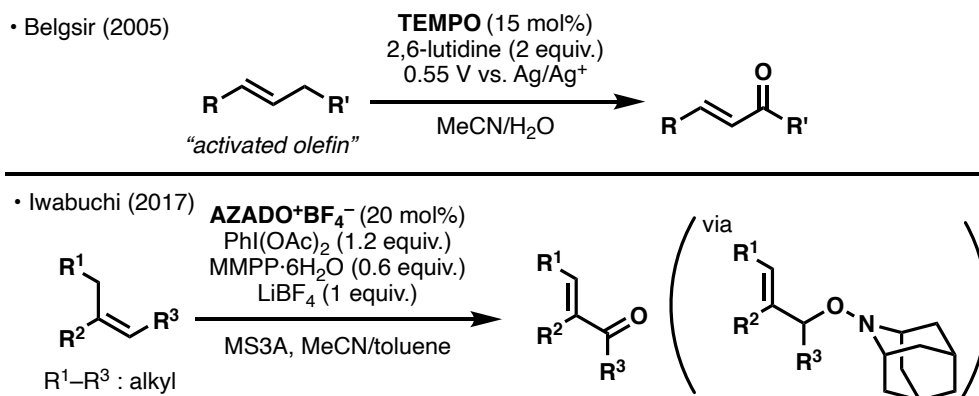
b) Reaction with trisubstituted alkenes

• Bobbitt, Bailey (2006)



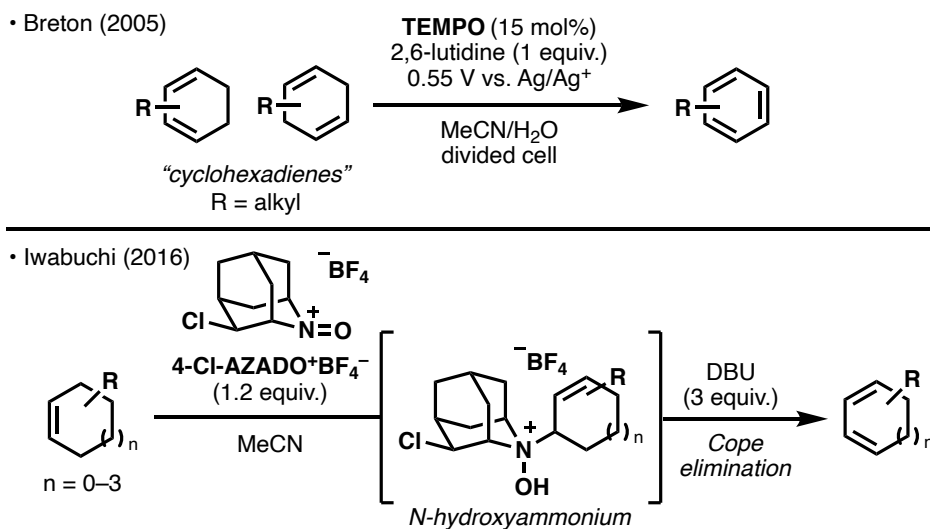
Scheme 24. Reactivity of oxoammonium species with alkenes: Alkoxyamine formation

Based on these reactivities, some researchers have developed the catalytic oxygenation reaction of alkenes (**Scheme 25**). In 2005, Belgsir et al. reported the electrochemical oxygenation of “activated” alkenes, such as styrenes and skipped polyenes, using TEMPO as a mediator.¹⁷³ In 2017, Iwabuchi et al. developed the catalytic oxygenative allylic transposition of alkenes into enones using AZADO⁺BF₄⁻ as a catalyst.¹⁷⁴ This reaction involved the oxidative N–O bond cleavage of the resulting alkoxyamine, followed by regeneration of the hydroxylamine.¹⁷⁵



Scheme 25. Reactivity of oxoammonium species with alkenes: Catalytic oxygenation

Not only oxygenation, but dehydrogenation is also a plausible transformation for alkenes using oxoammonium species (**Scheme 26**). In 2005, Breton et al. reported an electrochemical dehydrogenation of cyclohexadienes using TEMPO as a mediator.¹⁷⁶ In 2016, Iwabuchi et al. reported the dehydrogenation of cycloalkenes to yield 1,3-cycloalkadienes using 4-Cl-AZADO⁺BF₄⁻, an azaadamantane-type oxoammonium salt.¹⁷⁷ Mechanistically, it is important to note that an *N*-hydroxyammonium species was generated via an ene-like addition to preferentially form the C–N bond in this reaction. This was in contrast to all of the previous reports on the reaction of oxoammonium species with alkenes (that is alkoxyamine formation).



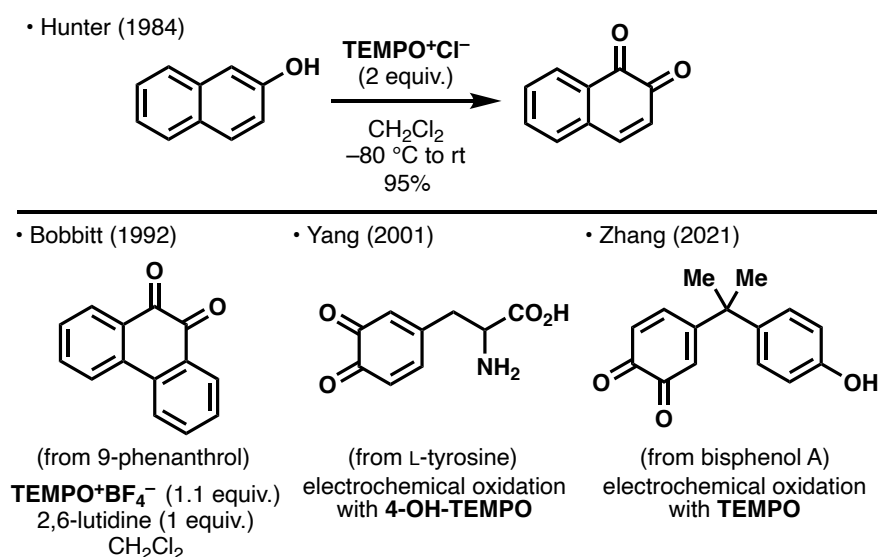
Scheme 26. Reactivity of oxoammonium species with alkenes: Dehydrogenation

3-6. Oxidation of aromatic compounds

A few examples of the reactivity of oxoammonium species toward electron-rich aromatics have been reported. Phenols and indoles are commonly used substrates for this purpose.

3-6-1. Oxidation of phenols

Hunter et al. first reported that 1-naphthol and 2-naphthol were oxidized into 1,2- and/or 1,4-naphthoquinones using 2 equivalents of TEMPO⁺Cl⁻ (**Scheme 27**).⁸¹ Although 1-naphthol was converted into a mixture of 1,2-naphthoquinone (15% yield) and 1,4-naphthoquinone (20% yield), 2-naphthol is cleanly converted into 1,2-naphthoquinone in 95% yield. After this report, this type of oxidation (that is oxygenation of phenol) has been reported by several researchers.^{85,178,179}

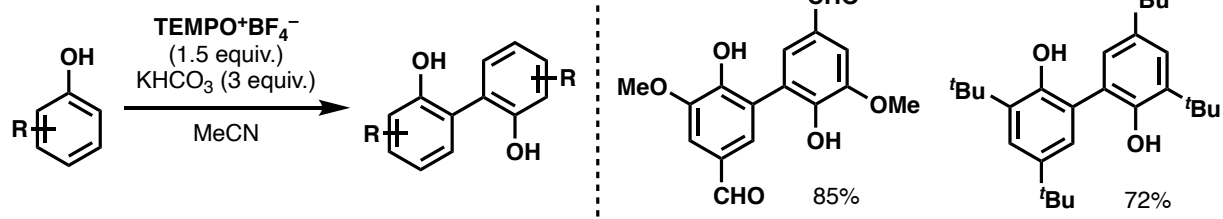


Scheme 27. Formation of *o*-quinone from phenols using oxoammonium species

Another important transformation of phenols mediated by oxoammonium species is the oxidative phenol coupling reaction. Bobbitt and Ma reported the oxidative dimerization of various phenolic substrates using TEMPO⁺BF₄⁻ in 1992 (**Scheme 28a**).⁸⁵ In the following year, some researchers reported similar transformations; however, there are limited examples. (1992 Guo,¹⁸⁰ 1993 Osa,¹⁸¹ 1994 Liu¹⁸²). Recently, Saladino et al. reported the intramolecular dearomative coupling of tethered phenol using laccase-TEMPO catalysis; however, its applicability was not fully evaluated (**Scheme 28b**).¹⁸³ These facts indicate that the reactivity of oxoammonium species with phenol has not been fully investigated and that further studies must be conducted.

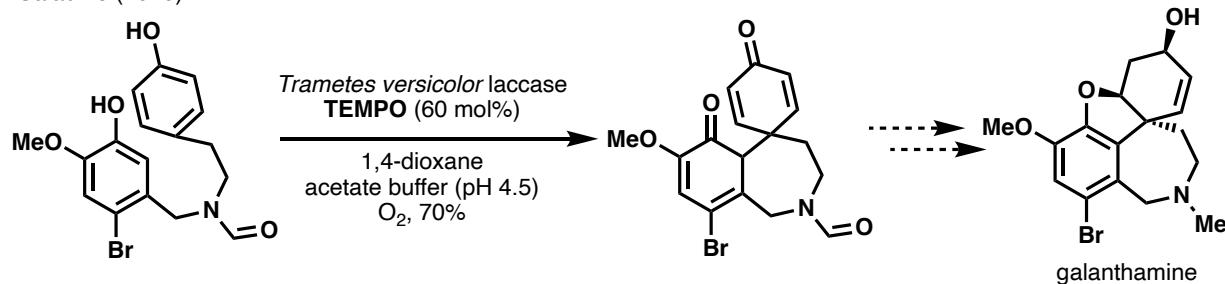
a) Oxidative dimerization of phenols

• Bobbitt (1992)

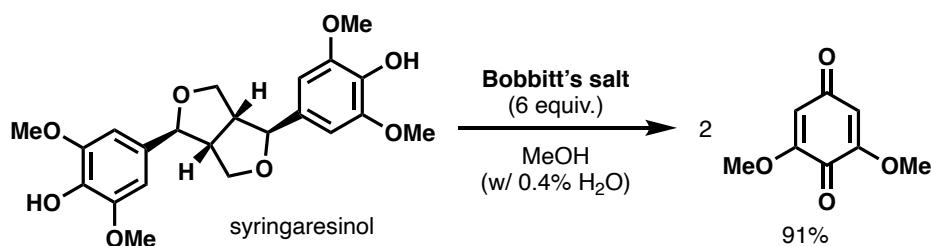


b) Intramolecular dearomative coupling of tethered phenol

• Saladino (2020)

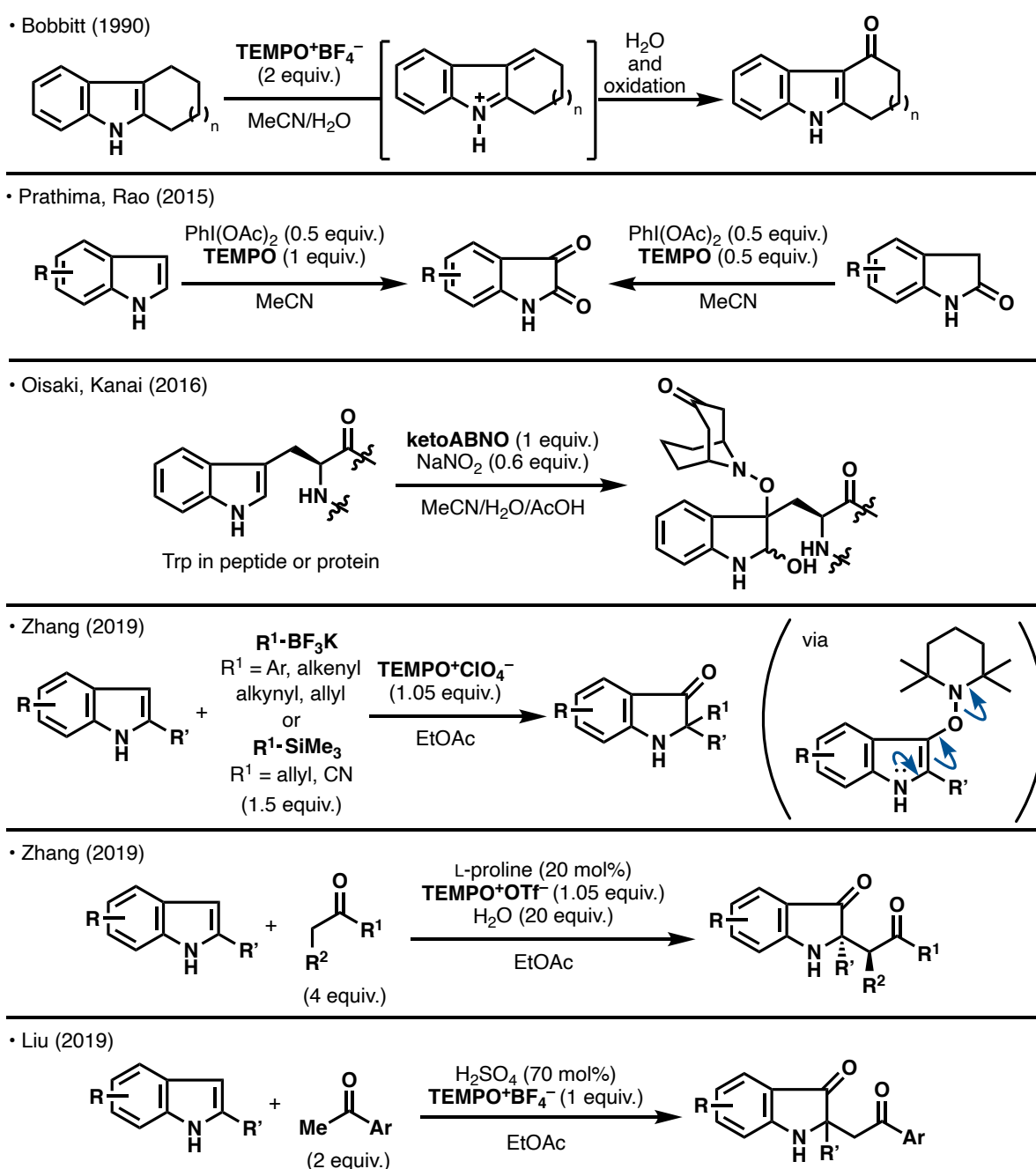
**Scheme 28.** Oxidative phenol coupling by oxoammonium species

Recently, a new application of oxoammonium species for the oxidation of phenolic substrates has been reported. Samec et al. found that Bobbitt's salt can be used for the depolymerization of lignin, an aromatic polymer obtained from woody biomass (**Scheme 29**).¹⁸⁴ For example, a lignin model compound (syringaresinol) was degraded into 2,6-dimethoxybenzoquinone via cleavage of the C–C bond. They claimed that this method is an alternative to conventional methods used for the depolymerization of lignin, which relies on C–O bond cleavage in the polymer.

**Scheme 29.** Oxidative cleavage of lignin model compounds using Bobbitt's salt (Samec, 2021)3-6-2. Oxidation of indoles (**Scheme 30**)

The initial report on the oxoammonium salt-mediated oxidation of indoles was reported by Bobbitt et al. in 1990.¹⁸⁵ They reported that cycloalkylindoles can be converted into their corresponding keto compounds using $\text{TEMPO}^+\text{BF}_4^-$ in the presence of water. In contrast, tetrahydrocarbazole dimerized to yield a mixture of products via Diels-Alder reaction under anhydrous conditions (not shown). After this report, however, indoles were not investigated as a substrate in oxoammonium species-mediated

oxidative transformation for over 20 years. In 2015, Bikshapathi, Prathima, and Rao reported the conversion of indoles into isatins using a TEMPO/PhI(OAc)₂ catalytic system.¹⁸⁶ Oxindoles were also converted into isatins under these conditions. In 2016, Oisaki and Kanai et al. discovered the new reactivity of oxoammonium species with tryptophan, an indole-containing amino acid, to yield a C3-aminoxygenated product, and they expanded this observation to the bioconjugation of peptides and proteins.¹⁸⁷ In 2017, Liu et al. reported various transformations including the C3 oxygenation of indole, followed by nucleophilic addition at the C2 position of indole mediated by TEMPO-metal system (not shown).¹⁸⁸ Although the detailed mechanism is unknown, they proposed an oxoammonium

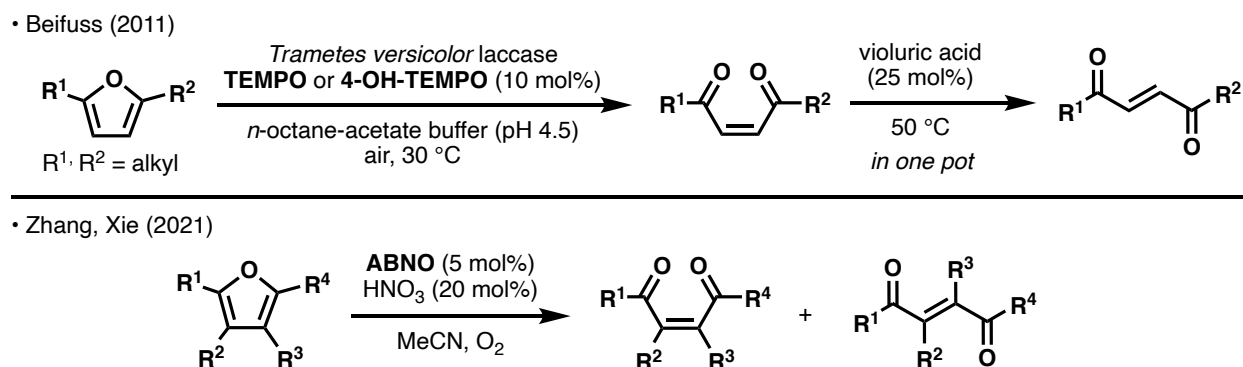


Scheme 30. Oxidative transformation of indoles using oxoammonium species

species-mediated oxidation of the C3 position of indole. In 2019, Zhang et al. reported the oxoammonium salt-mediated dearomative oxyalkynylation/oxyalkenylation of indoles using alkynyl potassium trifluoroborates as nucleophiles.¹⁸⁹ They expanded this methodology to the asymmetric dearomative oxyalkylation of indoles using L-proline as an organocatalyst.¹⁹⁰ Later, Zhu, and Liu et al. reported a similar Brønsted acid-mediated similar racemic transformation.¹⁹¹

3-6-3. Oxidation of furan (Scheme 31)

In 2011, Beifuss et al. reported the chemoenzymatic transformation of furans into *cis*- and *trans*-2-ene-1,4-diones using laccase-TEMPO catalytic system with or without violuric acid.¹⁹² In the following year, they expanded this methodology to the chemoenzymatic Achmatowicz reaction (not shown).¹⁹³ Recently, Zhang and Xie et al. reported the aerobic oxidation of substituted furans into corresponding *cis*-2-ene-1,4-diones using an ABNO/HNO₃ catalytic system.¹⁹⁴ They proposed that this transformation involves the nucleophilic addition of furans at the C2 position to form ABNO oxoammonium species.



Scheme 31. Oxidative transformation of furans

3-7. Oxidation of other substrates

Oxoammonium species can also be used as an oxidant for various oxidative transformations other than those mentioned in the previous sections.

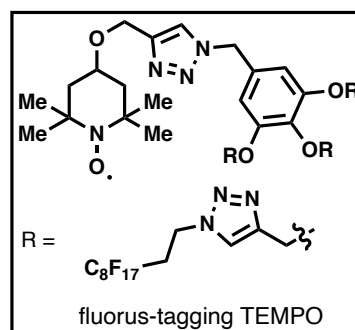
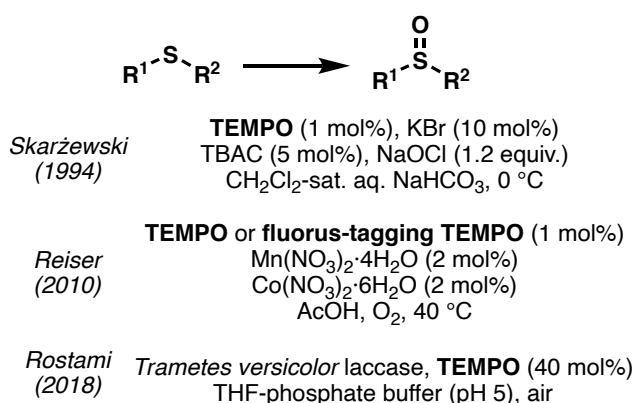
3-7-1. Oxidation of organosulfur compounds

The oxidation of sulfides into sulfoxides using oxoammonium species as a catalyst has been reported (Scheme 32a). In 1994, Skarzewski and Siedlecka reported the TEMPO-catalyzed oxidation of sulfides into sulfoxides with NaOCl used as a co-oxidant.¹⁹⁵ The authors claimed that this two-phase conditions enabled the selective formation of sulfoxides and the diastereoselective oxidation of bissulfides. Chinnusamy and Reiser reported the aerobic oxidation of sulfides into sulfoxides using a recyclable

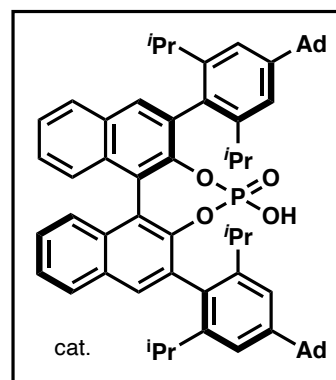
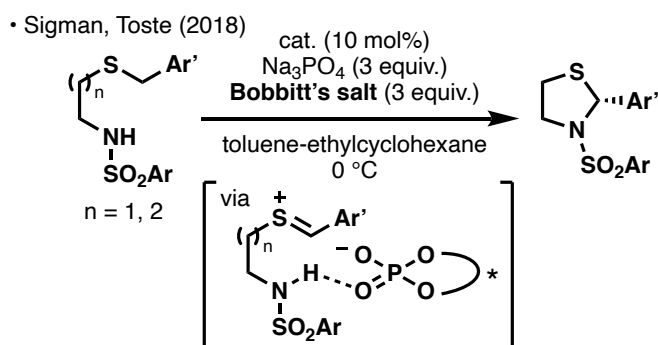
fluorous-tagging TEMPO catalyst in 2010.¹⁹⁶ In 2018, Rostami et al. reported the chemoenzymatic conditions using laccase-TEMPO system.¹⁹⁷

In 2018, Sigman and Toste et al. reported an enantioselective oxidative Pummerer-type transformation to yield cyclic *N,S*-acetal compounds using chiral phase-transfer catalysis with TEMPO⁺BF₄⁻ as an oxidant (**Scheme 32b**).¹⁹⁸ TEMPO⁺BF₄⁻ caused the direct oxidation of the sulfide into a thionium cation. In 2021, Sen' et al. reported an oxygen atom transfer reaction from oxoammonium species to dimethyl sulfoxide (**Scheme 32c**).¹⁹⁹

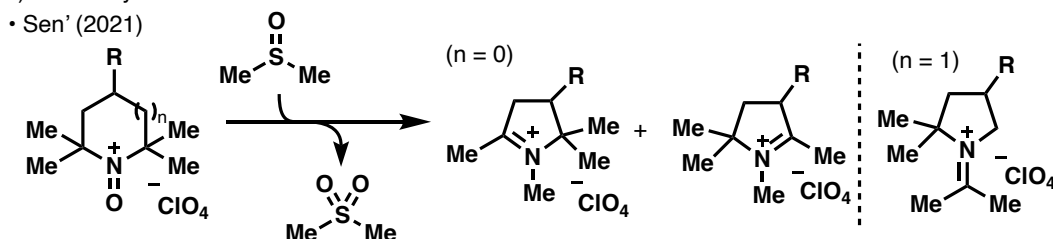
a) Selective oxidation of sulfides to sulfoxides



b) Enantioselective oxidative construction of *N,S*-acetals



c) Reactivity of oxoammonium salt with DMSO

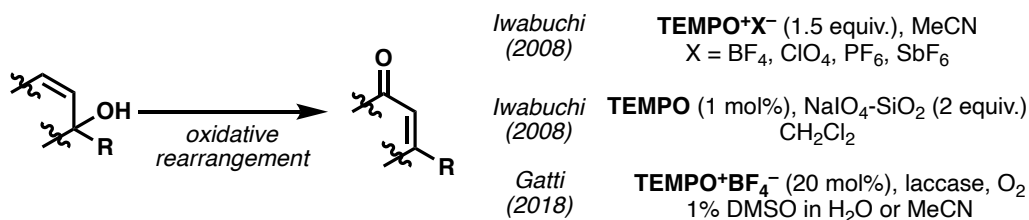


Scheme 32. Oxidative transformation of organosulfur compounds using oxoammonium species

3-7-2. Oxidative rearrangement of tertiary allylic alcohols (**Scheme 33**)

Specific alcoholic substrates undergo a special reaction using oxoammonium species. In 2008, Iwabuchi et al. reported the oxidative rearrangement of tertiary allylic alcohols using TEMPO⁺X⁻.²⁰⁰ This

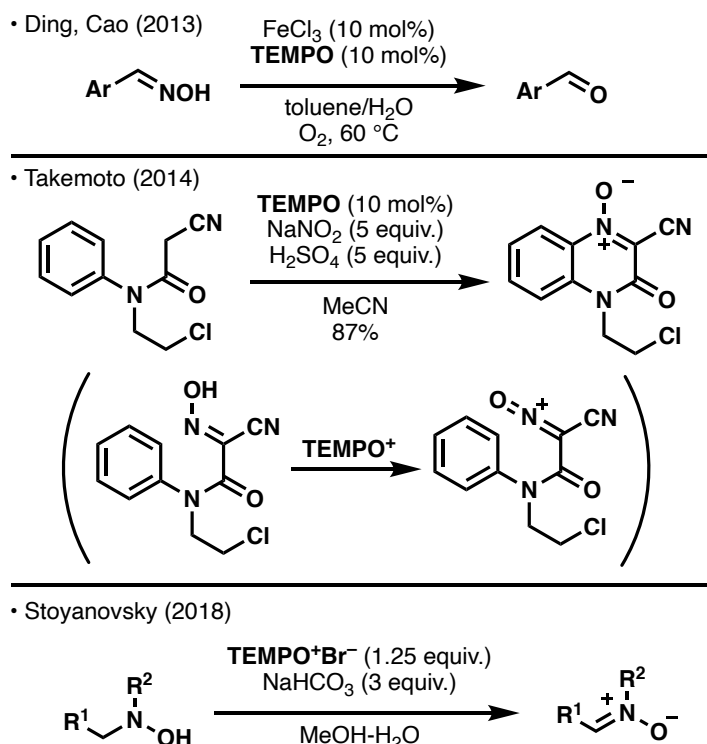
transformation is usually promoted by Cr(VI)- or I(V)-based reagents. They also revealed that weakly coordinating X^- (counter anion of TEMPO^+) such as tetrafluoroborate (BF_4^-) and perchlorate (ClO_4^-), are crucial for the reactivity of this reaction. In the same year, they reported a catalytic version of the reaction employing $\text{NaIO}_4\text{-SiO}_2$ as an oxidant.²⁰¹ In 2018, Gatti et al. developed a chemoenzymatic reaction system employing $\text{TEMPO}^+\text{BF}_4^-$ -laccase catalysis.²⁰²



Scheme 33. Oxidative rearrangement of tertiary allylic alcohols using oxoammonium species

3-7-3. Oxidation of the oxime N-OH bond (Scheme 34)

In 2013, Ding and Cao et al. reported an aerobic oxidative deoxygenation of aldoximes to yield aldehydes using a $\text{FeCl}_3/\text{TEMPO}$ catalytic system.²⁰³ They claimed that the in-situ generated oxoammonium species will facilitate the generation of the nitrogen monoxide (NO) from the aldoxime, which is involved in the catalytic cycle. In 2014, Kimachi and Takemoto et al. reported the diversity-oriented synthesis of caroverine derivatives using a TEMPO-promoted aerobic oxidative C–N bond forming reaction.²⁰⁴ This

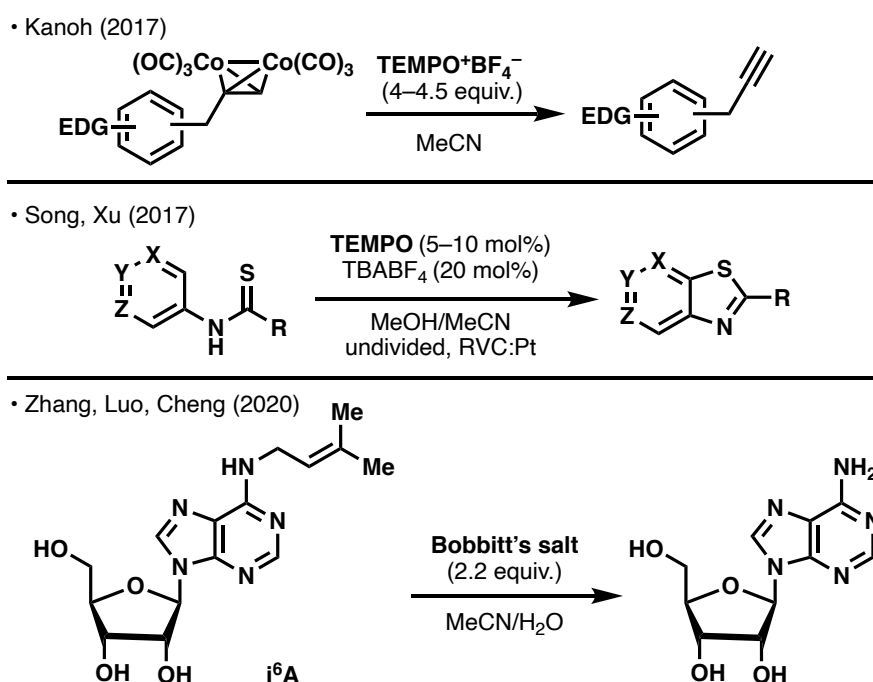


Scheme 34. Oxidation of oxime N-OH bonds using oxoammonium species

reaction involved the formation of an *N*-oxonitrenium intermediate via the oxidation of an in-situ generated oxime by TEMPO⁺. In 2018, Stoyanovski (A.D.) and Stoyanovski (D.A.) reported the conversion of α -H *N,N*-dialkylhydroxylamines to nitrones by TEMPO⁺Br⁻ via a two-electron oxidation mechanism.²⁰⁵

3-7-4 Miscellaneous (Scheme 35)

In 2017, Kanoh et al. reported that TEMPO⁺BF₄⁻ was a superior reagent for the decomplexation of an alkyne-dicobalt hexacarbonyl (Co₂(CO)₆) complex.²⁰⁶ In the case of oxidatively-labile substrates, TEMPO⁺BF₄⁻ provided better yields than the conventional oxidants frequently used for decomplexation, such as NMO and CAN. In 2017, Song and Xu reported a TEMPO-catalyzed electrochemical C–H thiolation reaction, which gave benzothiazoles and thiazolopyridines from thioamides.²⁰⁷ The formation of the S–O bond between TEMPO⁺ and the thioamide, followed by cleavage gave a thioamidyl radical, which attacks the pendant aromatic ring. In 2020, Zhang, Luo, and Cheng et al. reported that Bobbitt's salt promoted the chemical deprenylation of *N*⁶-isopentenyladenosine (i⁶A) RNA.²⁰⁸ Surprisingly, Bobbitt's salt was effective in both living cells and plants.



Scheme 35. Miscellaneous reactions mediated by oxoammonium species

3-8. Oxoammonium species for single electron oxidation

Oxoammonium species can act as a single electron oxidant in some cases. Although this fact has been known from the beginning of the study of nitroxyl radical (oxoammonium species) chemistry (Golubev, 1965 (Scheme 4);⁴ Endo 1994 (not shown)²⁰⁹), its application to synthetic organic chemistry has not been

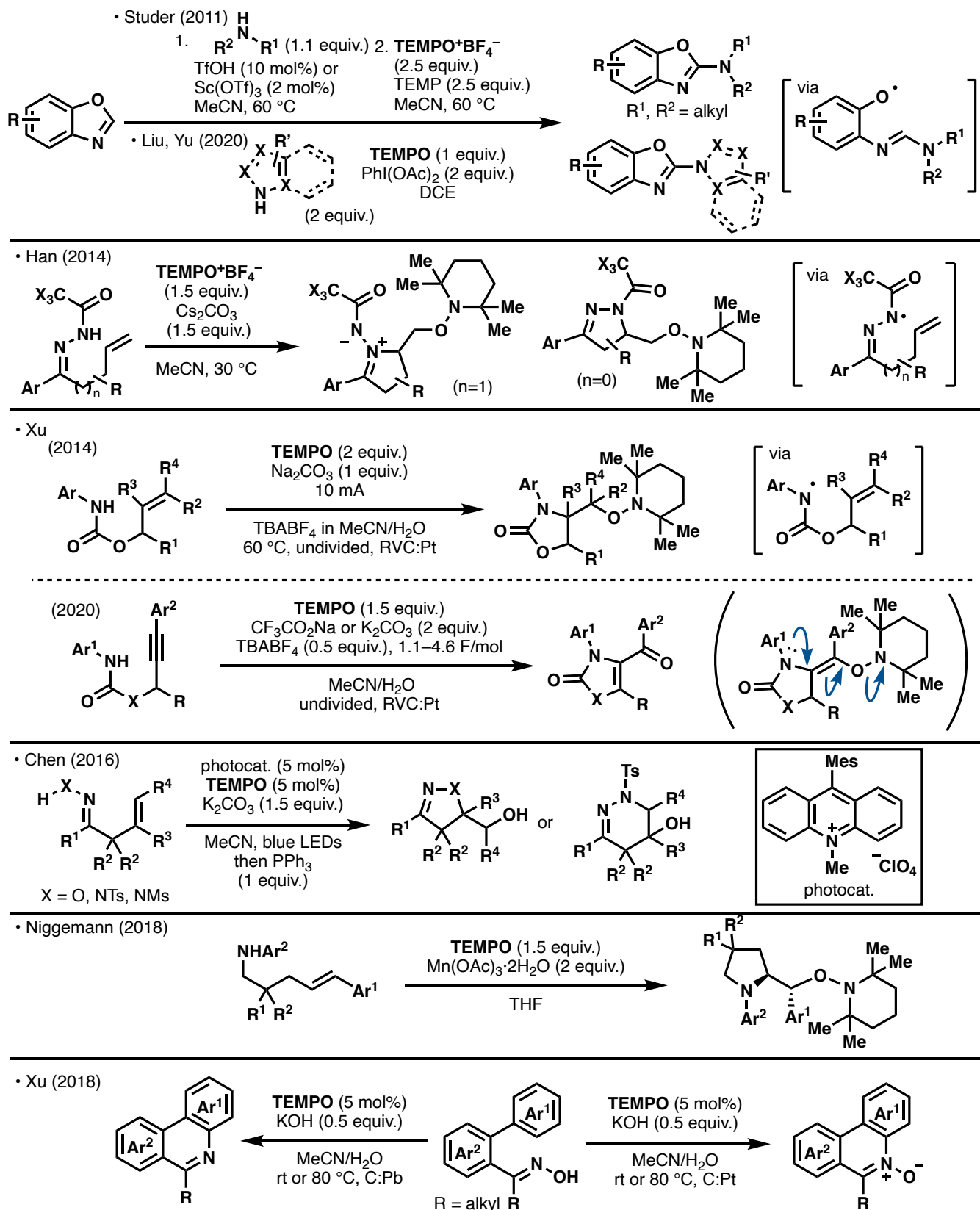
investigated so much for several decades. Over the past few years, its uniqueness and usefulness have been recognized among organic chemists.

3-8-1. Intramolecular reaction of heteroatom-centered radical species (Scheme 36)

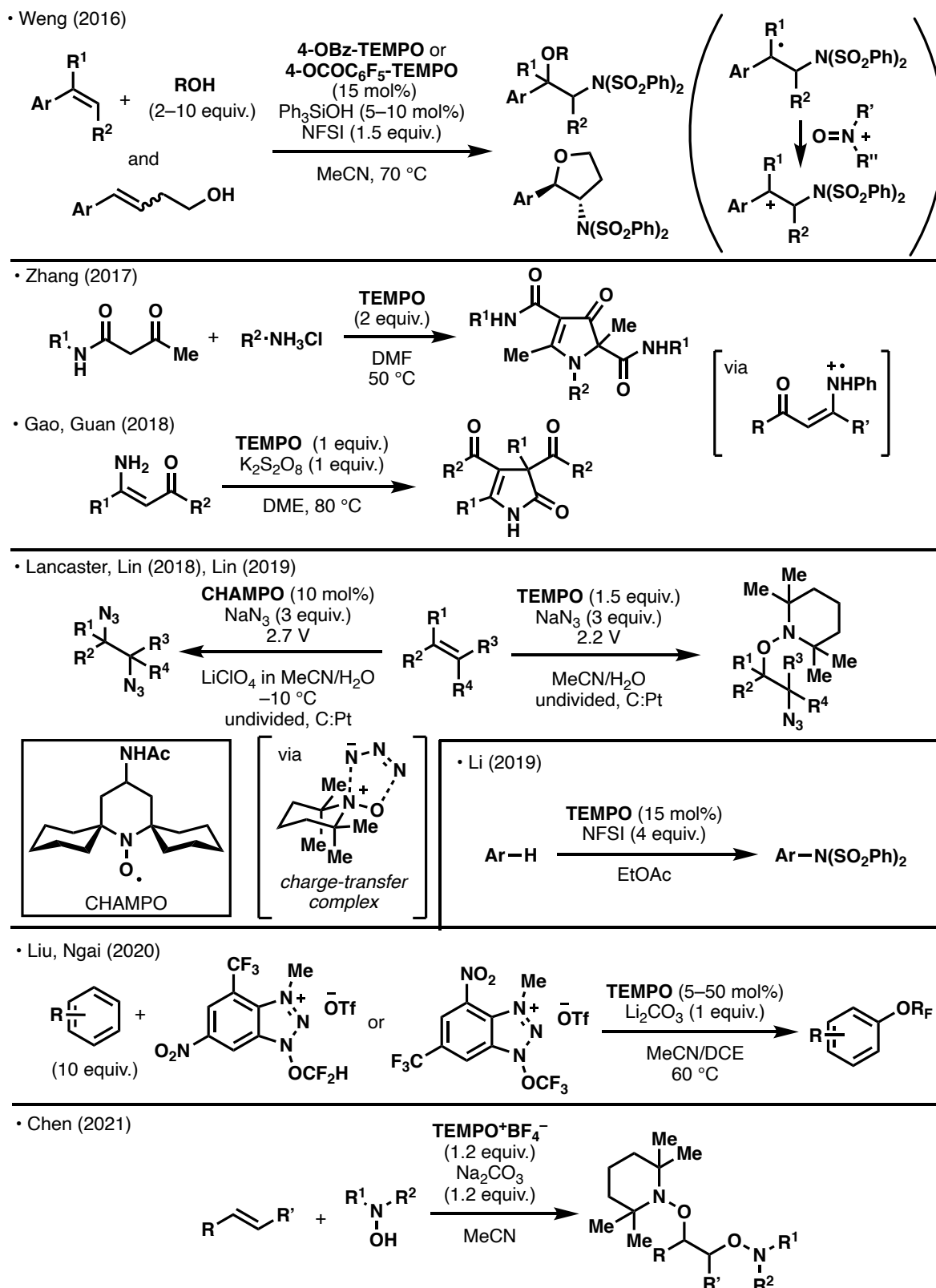
In 2011, Studer et al. reported the amination reaction of benzoxazole and 1,3,4-oxadiazole by using $\text{TEMPO}^+\text{BF}_4^-$ as an oxidant.²¹⁰ They proposed that a single electron oxidation of the intermediate phenol by $\text{TEMPO}^+\text{BF}_4^-$ will generate an *O*-centered radical, which closes the five-membered ring. A similar reaction system employing *N*-heteroaromatics as an aminating reagent was developed by Liu and Yu et al. in 2020.²¹¹ In 2014, Han et al. found that hydrazonyl radicals can be conveniently generated by $\text{TEMPO}^+\text{BF}_4^-$ via a single electron oxidation of their corresponding hydrazones.²¹² The generated radicals undergo an intramolecular 5-*exo-tet* cyclization, followed by trapping of the resulting *C*-centered radicals with TEMPO. In 2014, Xu et al. reported an electrochemical intramolecular aminooxygenation of unactivated alkenes mediated by oxoammonium species.²¹³ The authors proposed that TEMPO^+ oxidized the carbamate in a one-electron manner to generate an *N*-centered radical, which attacks the alkene, followed by trapping of the resulting radical by TEMPO. Later they expanded the applicability of the reaction to alkynes to afford a carbonyl compounds in 2020.²¹⁴ In 2016, Chen et al. reported the organophotocatalytic intramolecular oxyamination and dioxygenation of β,γ -unsaturated hydrazones and oximes.²¹⁵ In 2018, Niggemann and Gao reported the intramolecular oxyamination of alkenes mediated by a TEMPO/ $\text{Mn}(\text{OAc})_3$ system.²¹⁶ The authors proposed that Mn(III) oxidized TEMPO to form TEMPO^+ , which generates an *N*-centered radical via a single electron oxidation. In 2018, Xu et al. reported the electrochemical C–H functionalization of biaryl ketoximes to yield *N*-heteroaromatic or *N*-oxides mediated by TEMPO.²¹⁷ Switching the cathode under the electrochemical conditions changed the resulting product.

3-8-2. Intermolecular reaction of heteroatom-centered radical species (Scheme 37)

In 2016, Weng and Zhang reported a 4-substituted TEMPO-catalyzed intermolecular aminooxygenation of styrenes and inter/intramolecular aminoalkoxylation of homoallylic alcohols using *N*-fluorobenzenesulfonimide (NFSI) as an oxidant and aminating reagent.²¹⁸ This reaction is based on a similar stoichiometric reaction using TEMPO-Na reported by Studer et al.^{219,220} The authors accomplished the catalytic transformation using an external nucleophile (H_2O and pendant alcohol). In 2017, Zhang et al. reported a TEMPO^+ -mediated tandem cyclization of β -oxoamides with amine hydrochlorides to yield pyrrolin-4-ones.²²¹ The authors claimed that in-situ generated TEMPO^+ acts as a single electron oxidant and mediates several oxidation events in the mechanism, such as the dimerization of in-situ generated enaminoamides. A similar cyclization of enaminoesters and enaminoes was reported



Scheme 36. Intramolecular reactions of heteroatom-centered radical species generated by an oxoammonium species-mediated single electron oxidation process



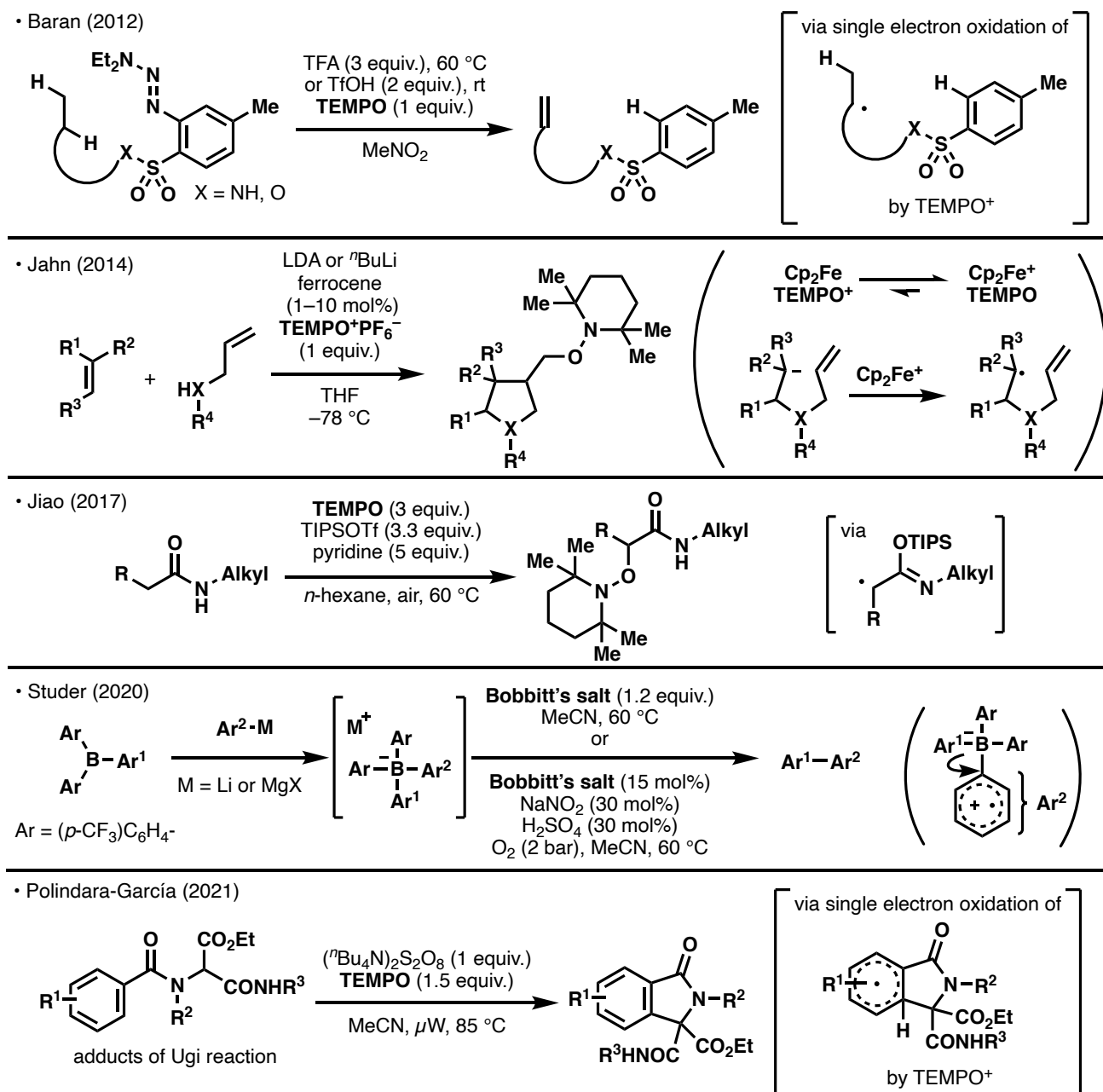
Scheme 37. Intermolecular reaction mediated by heteroatom-centered radicals generated by oxoammonium species

by Gao and Guan et al. in 2018.²²² In 2018, Lancaster and Lin et al. reported the electrochemical azidooxygenation of alkenes mediated by a TEMPO–N₃ charge-transfer complex.²²³ The authors proposed the electrochemically generated TEMPO⁺ forms a charge-transfer complex with azide (TEMPO–N₃), which facilitates the generation of an azidyl radical (•N₃) after extensive mechanistic studies. The author expanded this methodology to the diazidation of alkenes using cyclohexane-substituted (4-acetamidopiperidin-1-yl)oxyl (CHAMPO) in 2019.²²⁴ In 2019, Li et al. reported a TEMPO-catalyzed C–H amination of arenes using NFSI as an oxidant and aminating reagent.²²⁵ TEMPO⁺ acts as an oxidizing reagent used to generate aryl radicals. Zheng et al. reported a similar azidooxygenation using a stoichiometric amount of TEMPO⁺BF₄[–] (not shown).²²⁶ In 2020, Liu and Ngai et al. reported the TEMPO-catalyzed redox-neutral C–H di- and trifluoromethoxylation of (hetero)arenes.²²⁷ The principle of the reaction was similar to the NFSI-mediated C–H amination reaction. The generation of radical species from the reagent for di- and trifluoromethoxylation by TEMPO and single electron oxidation of the resulting radical intermediate are crucial for this transformation. In 2021, Chen et al. reported the regioselective vicinal di-aminoxygenation of alkenes using combination of *N*-hydroxyphthalimide (NHPI) or its variant and TEMPO⁺BF₄[–].²²⁸ PINO generated via the oxidation of NHPI using TEMPO⁺BF₄[–] via single electron transfer is added to the alkene to generate a C-centered radical. This radical is trapped via in-situ generated TEMPO to give diaminoxygenated compounds.

3-8-3. Other oxidative transformations (Scheme 38)

In 2012, Baran et al. reported the guided desaturation of unactivated aliphatic C–H bonds using “portable desaturase”, which is a triazene-based reagent.²²⁹ TEMPO is oxidized by in-situ generated diazonium to yield its corresponding oxoammonium species, which captures an electron from a C-centered radical to provide the carbocations that undergo an E1 elimination to yield an alkene. In 2014, Jahn et al. reported an oxidative single electron transfer-induced tandem anion-radical cyclization.²³⁰ In this reaction, TEMPO⁺PF₆[–] oxidized ferrocene to ferrocenium, which oxidized an enolate to provide its corresponding radical. This radical undergoes cyclization and forms another C-centered radical, which is captured by the in-situ generated TEMPO. In 2017, Jiao et al. reported the α -aminoxygenation and hydroxylation of aliphatic secondary amides using TEMPO.²³¹ They proposed that TEMPO⁺OTf[–], which was generated in-situ via disproportionation with TIPSOTf, oxidized an in-situ generated imidate, and the resulting radical immediately bound to TEMPO to yield an α -aminoxygenated compound. In 2020, Gerleve and Studer reported the oxidative coupling of tetraarylborate to biaryls using a stoichiometric amount of Bobbitt’s salt or catalytic 4-NHAc-TEMPO/NO_x/O₂ system.²³² Bobbitt’s salt oxidized the tetraarylborate via single electron transfer to provide a radical cation intermediate, which undergoes 1,2-aryl shift and further oxidation, followed by C–B bond cleavage to yield the biaryl product. In 2021, Polindara-García

et al. reported the synthesis of isoindolines via an intramolecular radical cyclization of 1,3-dicarbonyl compounds, which was derived from the Ugi reaction.²³³ TEMPO⁺ oxidizes the in-situ generated cyclohexadienyl radical intermediate and their subsequent aromatization yielded the desired product.



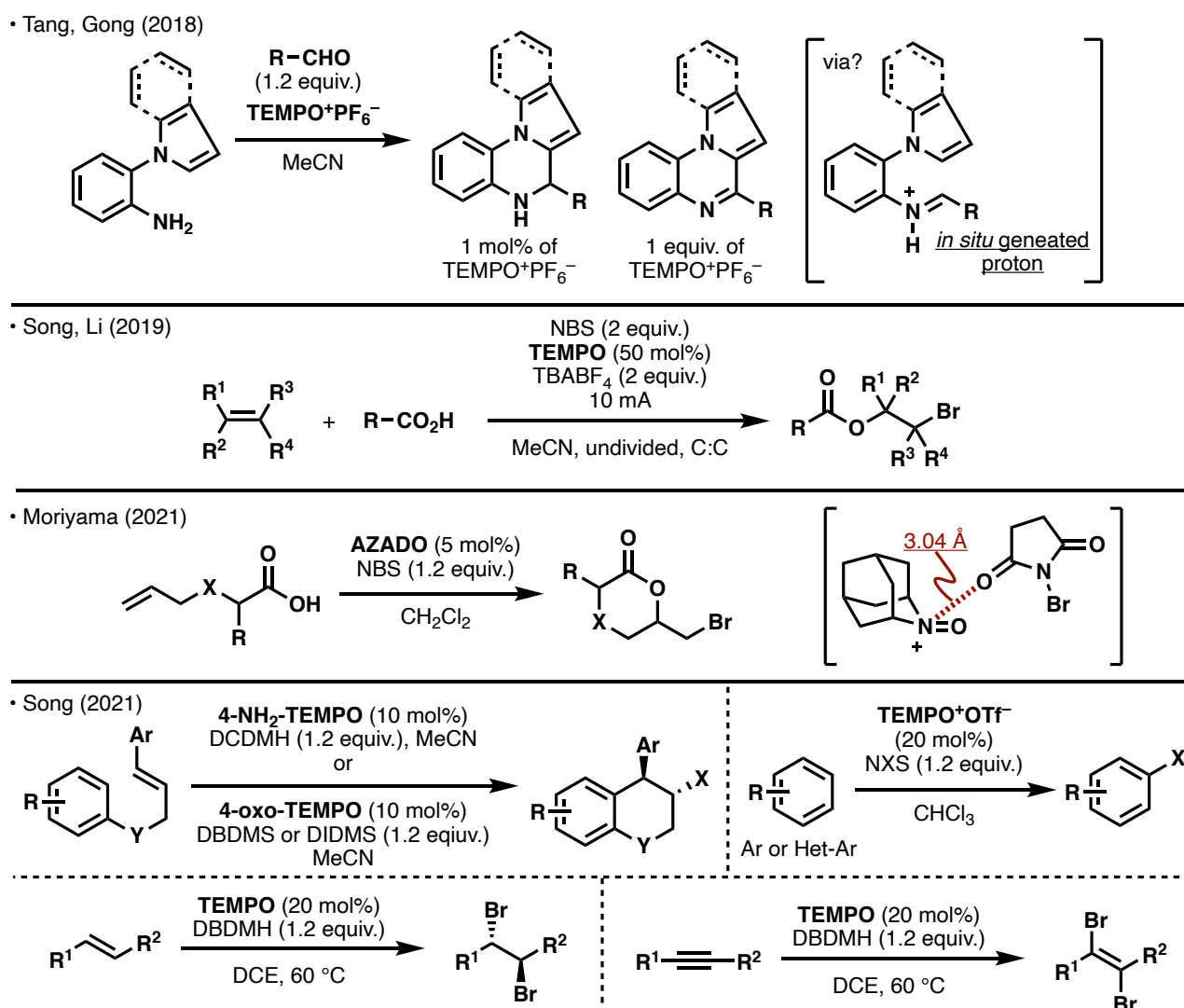
Scheme 38. Oxidative transformations mediated by single electron oxidation using oxoammonium species

3-9. Oxoammonium species as a Lewis acids (Scheme 39)

Recently, a new activity of oxoammonium species has been discovered, which was reported by some researchers but not fully investigated until 2021. In 2018, Gong, Tang, and Huo reported an oxoammonium salt-catalyzed synthesis of (dihydro)quinoxalines via a Pictet-Spengler reaction, followed

by oxidation.²³⁴ The authors proposed the possibility of the activation of the intermediate imine to facilitate the Pictet-Spengler process by the oxoammonium salt, although they finally concluded that an in-situ generated catalytic amount of acid may be the true activator of the imine. Furthermore, Wan, Song (R.-J.), and Li reported an electrooxidative intermolecular bromoesterification of alkenes using TEMPO as an initiator in 2019.²³⁵ They proposed that NBS adds to the alkene to form a bromonium cation intermediate with the aid of TEMPO⁺. However, they did not suggest any evidence how TEMPO⁺ facilitated the formation of the bromonium cation.

In 2021, Moriyama et al. first revealed the Lewis acidity of oxoammonium species using computational evidence.²³⁶ They reported that AZADO catalyzes the bromolactonization of alkenes with NBS. They computationally proposed that an in-situ generated oxoammonium species activated NBS upon coordination to the carbonyl group on the nitrogen center. This phenomenon strongly suggests that oxoammonium species acts as a Lewis acid. Furthermore, Song (S.) et al. also reported that TEMPO



Scheme 39. Oxoammonium species used as a Lewis acids

catalyzes the intramolecular haloarylation of alkenes, dibromination of alkenes/alkynes, and halogenation of (hetero)arenes using halogenating reagents such as *N*-halosuccinimides (NXS) and *N,N*-dihalodimethylhydantoins (DXDMH).²³⁷

4. CONCLUSIONS AND OUTLOOK

In this review, we have summarized the use of oxoammonium species in synthetic organic chemistry for oxidative transformations with the exception of the oxidation of alcohols. As readers may recognize, a diverse range of oxidative transformations have been prompted by oxoammonium species. We believe that this fascinating species will be widely used for the development of reactions as well as complex molecule synthesis in the future of organic synthesis. During these studies, chemists have discovered unexpected reactivities or novel transformations mediated by oxoammonium species. Such studies will continue to expand the utility of oxoammonium species in organic chemistry.

Furthermore, this mild and recoverable oxidant is beneficial in the view of the recent global momentum toward “green chemistry”. In addition to using a stoichiometric amount of oxoammonium salt, catalytic oxidation conditions have also been developed. In particular, the use of molecular oxygen as a terminal oxidant is ideal because water is the only by-product; however, the number of such examples is insufficient. Green catalytic processes prompted by catalytic amounts of oxoammonium species will be demanded by the organic synthesis community in the future.

To expand the utility of this fascinating chemical species, researchers will need to discover new reactivities of oxoammonium species and develop a “designed” oxoammonium species to achieve highly-difficult chemical transformations. For example, electronically tuning the redox properties of the oxoammonium species upon the introduction of appropriate substituents and the development of oxoammonium species with novel scaffolds (with the exception of tetramethylpiperidine/pyrrolidine, 9-azabicyclo[3.3.1]nonane, and 2-azaadamantane) will be plausible strategies. Not only the direct modification of oxoammonium species, but also the utilization of “designed” counter anions may be another plausible strategy because oxoammonium species are cationic. Another way to discover novel transformations using oxoammonium species will be the combination of other catalytic systems (that is, the construction of cooperative catalytic systems) such as organocatalysis, photoredox catalysis, and enzymatic catalysis. Although, as mentioned in this review, some exploratory research studies have been reported, such attempts are currently under development. Contributions from organic chemists as well as chemists in various fields, such as theoretical and computational chemistry, will continue to find new aspects of the chemistry of oxoammonium species.

ACKNOWLEDGEMENTS

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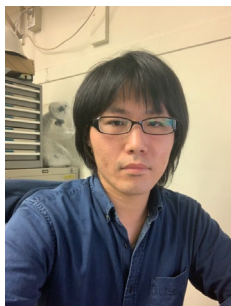
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Dr. Shota Nagasawa was born in Yamagata, Japan, in 1989. He studied at the Department of Pharmaceutical Sciences, Tohoku University, where he obtained his B.S. degree in 2012 and his Ph.D. degree in 2017 under the supervision of Prof. Yoshiharu Iwabuchi. He then carried out postdoctoral research at the University of California, Berkeley with Professor Richmond Sarpong (2017–2019). In 2019, he returned to Tohoku University as an Assistant Professor and joined the research group of Professor Yoshiharu Iwabuchi. His research interests include the oxidative molecular transformation, natural product chemistry, and caged-hydrocarbon chemistry.



Dr. Yusuke Sasano was born in Sagami-hara, Kanagawa, Japan, in 1986. He studied at the Department of Pharmaceutical Sciences, Tohoku University, where he obtained his B.S. degree in 2008 and his Ph.D. degree in 2014 under the supervision of Prof. Yoshiharu Iwabuchi. He was appointed a Research Instructor in Professor Iwabuchi's laboratory at Tohoku University in 2012 and an Assistant Professor in the same laboratory in 2014. He worked as a Research Associate in Professor Ryan Shenvi's laboratory at The Scripps Research Institute in 2014–2015. He was promoted to a Lecturer in Professor Iwabuchi's laboratory at Tohoku University in 2020. His current research interest is the development of selective oxidation using his original catalysts as a synthetic methodology.



Dr. Yoshiharu Iwabuchi was born in Yamagata, Japan, in 1963. He studied at the Department of Pharmaceutical Sciences, Tohoku University, where he obtained his B.S. in 1986, and his Ph.D. under the supervision of Profs. Seiichi Takano and Kunio Ogasawara in 1991. After a year of postdoctoral work with Prof. K. C. Nicolaou in The Scripps Research Institute, he joined the group of Dr. Ikuo Fujii at the Protein Engineering Research Institute. In 1997 he was appointed Associate Professor in Prof. Susumi Hatakeyama's group at Nagasaki University. In 2002 he returned to Tohoku University as a Full Professor. His research interest includes the development of organocatalysts, synthetic methodology, and natural product synthesis.