HETEROCYCLIC SYNTHESIS BY \(\pi\)-ACIDIC METAL CATALYZED REACTIONS VIA N-O BOND CLEAVAGE

Itaru Nakamura\(^1\,*\) and Masahiro Terada\(^1,2\)

\(^1\)Research and Analytical Center for Giant Molecules, Graduate School of Science, Tohoku University, Sendai 980-8578, Japan. \(^2\)Department of Chemistry, Graduate School of Science, Tohoku University, Sendai 980-8578, Japan

Abstract – This review contains recent progress in heterocyclic synthesis by \(\pi\)-acidic metal catalyzed reactions via N-O bond cleavage. The reaction involving a terminal N-O bond (R\(_3\)N\(^+\)-O\(^-\)) predominantly proceeds via nucleophilic attack of the O atom and subsequent formation of an \(\alpha\)-oxo carbenoid intermediate through N-O bond cleavage. In contrast, the reaction of oximes and hydroxylamine derivatives having an internal N-O bond (R\(_2\)N-OR\(^-\)) is initiated by the nucleophilic attack of either N or O atom. In addition, hydroxylamine derivatives have been utilized as an external reagent in the cyclization reaction. The methodology produces a wide variety of highly functionalized nitrogen and oxygen heterocycles in an efficient manner under mild reaction conditions.

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1. INTRODUCTION

\(\pi\)-Acidic metal catalysis is a powerful tool to transform readily accessible organic molecules into highly elaborate ones under mild reaction conditions having high functional group tolerance. Because of its features, the catalysis has been frequently utilized in heterocyclic synthesis.\(^1\) The transformation often involves the cleavage of various \(\sigma\) bonds, such as carbon-hydrogen, heteroatom-hydrogen, carbon-carbon, and carbon-heteroatom bonds.\(^2-5\) Recently, \(\pi\)-acidic metal catalyzed reactions via cleavage of a nitrogen-oxygen (N-O) \(\sigma\) bond have received much attention as an efficient method for heterocyclic synthesis (Scheme 1). Not only terminal N-O bonds (R\(_3\)N\(^+\)-O\(^-\)), such as nitro compounds, nitrones, pyridine N-oxides, and amine N-oxides, but also internal N-O bonds (R\(_2\)N-OR\(^-'\)), such as hydroxylamines and oximes, have been employed as the substrate. Substrates having an N-O bond are generally accessible by various synthetic methods, such as the condensation with commercially available hydroxylamine hydrochlorides, the Mitsunobu reaction with N-hydroxyphthalimides, the oxidation of amines and imines, and the reduction of a nitro group.\(^6\) It is also advantageous that the starting material is stable and storable for a long time despite the low dissociation energy of the N-O bond. Apparently, an atom-efficient transformation via N-O bond cleavage yields organic molecules bearing both nitrogen and oxygen functional groups. Typically, one atom of the cleaved N-O bond becomes a part of the constructed heterocyclic structure and the other atom becomes a functional group of the heterocycle. In this review, we comprehensively summarize recent progress in \(\pi\)-acidic metal catalyzed heterocyclic synthesis via N-O bond cleavage.

![Scheme 1. \(\pi\)-Acidic metal catalyzed heterocyclic synthesis via N-O bond cleavage](image-url)
2. REACTIONS VIA CLEAVAGE OF TERMINAL N-O BOND

The reaction of alkynes having a terminal N-O bond is generally initiated by nucleophilic attack of the anionic oxygen atom on the carbon-carbon triple bond, which is electrophilically activated by a \( \pi \)-coordinated metal catalyst (Scheme 2, 1). Resulting vinylmetal intermediate 2 typically undergoes N-O bond cleavage driven by the donation of electrons from the metal center, leading to \( \alpha \)-oxo carbenoid species 3. The intramolecular version of the oxygen transfer process from 1 to 3 is the so-called internal redox reaction, whereas the oxygen transfer proceeds even in an intermolecular manner. The electrophilic carbon of \( \alpha \)-oxo carbenoid species 3 is often subjected to intramolecular nucleophilic attack by a heteroatom to form a heterocyclic framework. Metal carbenoid intermediates 3 are conventionally generated from corresponding diazo compounds 4, which are potentially explosive and limited to large-scale synthesis. Therefore, the reaction of stable alkynes and \( N \)-oxides is a viable alternative to generate carbenoid intermediates 3. Several alkynes bearing a terminal N-O bond are known to undergo thermal transformations, such as the [3+2] dipolar cycloaddition–Baldwin rearrangement cascade, in the absence of a metal catalyst. However, \( \pi \)-acidic metal catalysts have been proven to promote a wider variety of transformations under extremely mild reaction conditions. Whereas Xiao and Li have published an excellent review on the chemistry of gold \( \alpha \)-oxo carbenoids in catalysis, in this review we introduce heterocyclic synthesis by \( \pi \)-acidic metal catalyzed reactions initiated by the nucleophilic attack of a terminal N-O bond.

![Scheme 2. Oxygen transfer process in \( \pi \)-acidic metal-catalyzed reaction of alkynes via N-O bond cleavage](image)

2.1 Reactions of nitroalkynes

In 2003, Yamamoto, Asao, and co-worker developed the gold-catalyzed cyclization of ortho-alkynylnitrobenzenes 5 to produce isatogens 6 and anthranils 7 involving cleavage of a nitro N-O bond (eq 1). The reaction of 5a in the presence of a catalytic amount of AuBr\(_3\) afforded isatogen 6a as the major product along with a small amount of anthranil 7a. Nitroalkyne 5b bearing a bulky tert-butyl group at the alkyne terminus was selectively converted into anthranil 7b. The groups of Söderberg and Ramara independently reported that the cycloisomerization of nitroalkyne to isatogen 6 was also...
efficiently promoted by a palladium catalyst, such as PdCl₂(PPh₃)₂ and PdCl₂(MeCN)₂.¹⁰,¹¹ The palladium-catalyzed reaction was utilized as the key transformation for the synthesis of (−)-isatisine A (eq 2).¹² In addition, 2-iodoisatogen 6c was prepared from trimethylsilylalkyne 5c by using N-iodosuccinimide (NIS) and silver catalysts (eq 3).¹⁰ The cycloisomerization of nitroalkynes 5 to isatogens 6 is known to proceed under thermal or photochemical conditions¹³ and π-acidic metal catalysts enable use of a wider range of substrates with higher efficiencies under much milder reaction conditions. For example, the reaction of 5a in the absence of metal catalysts required an elevated temperature (120 °C) and a prolonged reaction time (five days) to afford products 6a and 7a with low selectivities.⁹

Liu and co-workers demonstrated that the gold-catalyzed redox-cascade reaction of terminal alkyne 5d with electron-rich alkenes 8 gave azacyclic compounds 9 (eq 4).¹⁴ For example, the reaction of nitroalkyne 5d and benzyl vinyl ether 8a, phenyl vinyl sulfide 8b, and p-methoxystyrene 8c in the presence of 5 mol% Gagosz catalyst (PPh₃AuNTf₂)¹⁵ and dichloroethane (DCE) at 25 °C gave corresponding products 9a, 9b, and 9c in 86, 92, and 73% yields, respectively. The gold-catalyzed reaction of 5d in the presence of an excess amount of styrene afforded cyclopropylated product 10, suggesting the intermediacy of the carbenoid species (eq 5).
The reaction mechanism of the catalytic cycloisomerization of nitroalkyne 5 based on the internal redox reaction is illustrated in Scheme 3. Initially, the electrophilically activated triple bond is subjected to intramolecular nucleophilic attack by the oxygen atom in the nitro group in either a 6-endo or 5-exo manner, and subsequent N-O bond cleavage leads to the formation of metal α-oxo carbenoid complex 12 or 13. The carbenoid carbon of 12 is nucleophilically attacked by the nitroso oxygen atom and subsequent elimination of the catalyst gives anthranil 7. On the other hand, carbenoid 13 is subjected to nucleophilic attack by either the nitrogen or oxygen atom of the nitroso group to furnish ylide 14 or 15. Elimination of the metal catalyst from 14 gives isatogen 6, whereas [3+2] cycloaddition with an external olefin produces bicyclic nitrogen heterocycle 9.
2.2 Reactions of nitrones

Shin and co-workers reported that the gold-catalyzed reaction of ortho-alkynylbenzaldonitrones 16 having a pendant carbon-carbon multiple bond afforded azobicyclo[3.2.1]octane 17 in good to excellent yields (eq 6).\(^1\) The reaction was initiated by an internal redox reaction followed by a nucleophilic attack by the imine nitrogen on the carbenoid carbon of \(\alpha\)-oxo carbenoid intermediate 18. Then, intramolecular \([3+2]\) cycloaddition of resulting azomethine ylide 19 having a pendant carbon-carbon multiple bond furnished bicyclic product 17. They also developed a method for the synthesis of 5,6-fused azacycles 21, which involved the gold-catalyzed cascade reaction of alkynylnitrones 20 having an allylic alcohol moiety (eq 7).\(^2\) Gold carbenoid intermediate 22, which was generated from the internal redox reaction, underwent a 1,2-alkyl shift followed by the Mannich cyclization from metal enolate 23 and a spontaneous Michael reaction of \(\alpha,\beta\)-unsaturated carbonyl 24 to afford product 21.
The iridium-catalyzed synthesis of azomethine ylides 26 from \textit{ortho}-ethynlnitrone 25 was reported by Jia, Li, and co-workers (eq 8).\textsuperscript{19} The one-pot reaction that consisted of the formation of azomethine ylide 26 followed by the intermolecular \([3+2]\) cycloaddition reaction with added electron-deficient olefins, such as \(N\)-methylmaleimide, produced bicyclic compound 27 (eq 9). They also observed that the gold-catalyzed reaction of \(N\)-\textit{tert}-butyl-substituted nitrone 25\textsubscript{a} produced iminoester 28 (eq 10), in contrast to the iridium catalysis.\textsuperscript{20} The bulky \textit{tert}-butyl group interferes with the nucleophilic attack of the imine nitrogen atom. Instead, the hydrogen shift from the imine to the carbenoid carbon takes place and subsequent \(O\)-attack of the enolate moiety on the nitrilium carbon in resulting intermediate 30 gives iminoester 28. Moreover, Shin and co-workers efficiently obtained isoindole derivatives 32 by the cationic gold-catalyzed reaction of nitrone 31 (eq 11).\textsuperscript{21} Initially, the internal redox reaction proceeds through 7-\textit{endo} cyclized intermediate 33. The subsequent nucleophilic attack of the imine nitrogen atom leads to isoindole 32.
Liu and co-workers reported that the platinum-catalyzed intermolecular reaction of nitrone 35 with ynamide 34 gave formal oxoarylation product 36 (eq 12).\textsuperscript{22} Cleavage of the N-O bond takes place in the [3,3]-sigmatropic shift of β-oxyalkenylnplatinum intermediate 37. The cascade sequence consisting of platinum-catalyzed oxoarylation, reduction by NaBH\textsubscript{3}CN, and heating with silica gel produced indolin-2-ones 38 in good yields (eq 13).
Recently, Anderson and co-worker reported the rearrangement of \( N \)-arylnitrones 39 to epoxyketimines 40 in the presence of catalytic amounts of CuCl and 1,10-phenanthroline (phen) (eq 14). The reaction proceeds via nucleophilic attack of the nitrone oxygen atom on the electrophilically activated carbon-carbon double bond of \( \pi \)-complex 41. Subsequent N-O bond cleavage of resulting cyclized intermediate 42 takes place as an “N-O switched type” of the Baldwin rearrangement, leading to epoxyketimine 40. Treatment of epoxyketimine 40 with BF\(_3 \cdot \)OEt\(_2\) followed by reduction with NaBH\(_4\) efficiently afforded tetrahydroquinolines 43 as a single diastereomer (eq 15).

2.3 Reactions of pyridine \( N \)-oxides

Zhang and co-workers developed gold-catalyzed cascade reactions of homopropargylic alcohols 45 in the presence of pyridine \( N \)-oxide 46 to afford dihydrofuran-3-ones 47 in good to high yields (eq 16). The cascade process involves the intermolecular oxidation and the intramolecular O-H insertion of gold \( \alpha \)-oxo carbenoid intermediate 48. Of significance was the fact that they improved the methodology to enable synthesis of a wide variety of heterocycles, such as oxetan-3-ones, chroman-3-ones, and azetidin-3-ones, which involved the insertion of a heteroatom-hydrogen or carbon-hydrogen bond. In particular, a synthetic protocol utilizing (\( R \)-)tert-butylsulfinamide as the chiral auxiliary efficiently produced chiral azepinones 50 with excellent enantioselectivities (eq 17). They also demonstrated an efficient synthesis of 2,5-disubstituted oxazoles 52 by the gold-catalyzed [2+2+1] annulation reaction of alkyne 51 and acetonitrile using as solvent in the presence of quinoline \( N \)-oxide 46d, which proceeded via
the intermolecular addition of acetonitrile to α-oxo carbenoid intermediate 53 (eq 18).

Not only aliphatic nitriles but also benzonitriles were efficiently employed as the substrate for the [2+2+1] annulation. It should be noted that the use of bulky pyridine or quinoline N-oxides, such as 46c and 46d, enabled dispensing with the acid additive, whereas initially employed pyridine N-oxides, such as 46a and 46b, required stoichiometric amounts of methanesulfonic acid as the additive. The methodology using pyridine N-oxides has been extended to a variety of gold- and rhodium-catalyzed heterocyclic synthesis. Moreover, it should be emphasized that the methodology has benefited the total synthesis of natural products, such as citrinadin A and B, because the alkyne functional group was efficiently converted into the carbonyl group under mild reaction conditions having high functional group tolerance.
Ohe and co-workers demonstrated that the gold-catalyzed cycloisomerization of 2-(2-propynyl)pyridine N-oxides 55 generated indolizinones 56 in good to high yields (eq 19). The reaction proceeds via intramolecular oxygen transfer to form gold carbene complex 57. Subsequent migration of the benzoyl group gives β-pyridylenone species 58. Finally, cycloisomerization of the enone via intramolecular nucleophilic attack of the pyridine nitrogen atom on the σ-activated carbonyl furnishes indolizinone 56.

\[
\begin{align*}
55 & \quad 2 \text{ mol} \% \text{AuCl(P}^3\text{Bu}_3)/\text{AgSbF}_6 \quad \text{DCE, 80 } ^\circ \text{C} \\
55a (R = \text{Ph}) & \quad 55b (R = \text{nBu}) \\
55 & \quad 56 \\
56a (R = \text{Ph}) & \quad 86\% \\
56b (R = \text{nBu}) & \quad 64\%
\end{align*}
\]

2.4 Reaction of alkynylamine N-oxides

Zhang and co-workers reported that the one-pot reaction of N-(1-butynyl)anilines 59 via oxidation by \(m\)-CPBA followed by the gold-catalyzed cyclization gave tetrahydrobenzoxepinones 61 in good to high yields (eq 20). The oxygen atom is relayed from \(m\)-CPBA to the carbonyl carbon of product 61 through amine N-oxide 60. This expedient methodology was applied to the total synthesis of (±)-cermizine C from 2,4-dimethylpiperidine (Scheme 4). Computational and experimental studies conducted by Zhang, Houk, and co-workers suggest that the gold-catalyzed reaction of 62 to form 63 proceeds in an unusual manner, as illustrated in Scheme 5. First, the coordination of the cationic gold complex, \(\text{H}_3\text{PAu}^+\), to the oxygen anion of 62 takes place instead of the \(\pi\)-coordination to the alkyne. Intramolecular \textit{syn} addition to the alkyne moiety (64 \(\rightarrow\) 65) and subsequent hetero-retroene reaction involving the concerted migration of a hydrogen atom at the less hindered methyl group occur without the formation of gold carbenoid species. Finally, cyclization of iminium intermediate 66 gives azacycle 63. Their computational studies imply that the hetero-retroene reaction could be operative in other metal-catalyzed N-O cleavage reactions.
Scheme 4. Total synthesis of (±)-cermizine by gold-catalyzed reaction

Scheme 5. Reaction mechanism of gold-catalyzed rearrangement of acetylenic amine-N-oxides proposed by Zhang and Houk

3. REACTIONS VIA CLEAVAGE OF AN INTERNAL N-O BOND

Functional groups having an internal N-O bond, such as oximes and hydroxylamines, have been also utilized in π-acidic metal catalyzed reactions. In contrast to the terminal N-O bond, nucleophilic attack of the internal N-O bond takes place either at N or O atom, as illustrated in Scheme 6. In addition, N-O bond cleavage of reactive intermediates, such as N-alkoxyenamines and O-aminoenols, which are formed through a π-acidic metal catalyzed reaction, often takes place in cascade reactions. Furthermore, hydroxylamine derivatives, such as N-hydroxsuccinimide and O-benzoylhydroxylamines, have been utilized as an oxidant or amine electrophile in π-acidic metal catalyzed intermolecular reactions.
3.1 Intermolecular reactions with hydroxylamine derivatives

In 2002, Trost and co-worker reported that the ruthenium-catalyzed oxidative cyclization of homopropargylic alcohols 67 with \( N \)-hydroxysuccinimide 68 produced \( \delta \)-lactone 69 (eq 21).\(^{37} \) The reaction is initiated by \( \pi \)-coordination of the ruthenium catalyst followed by hydrogen migration, leading to ruthenium vinylidene complex 70. The addition of the hydroxyl group to the vinylidene group furnishes ruthenium carbenoid intermediate 71. Subsequent attack of the oxygen atom of 68 on the carbenoid carbon and elimination of the ruthenium catalyst and succinimide give lactone 69.

The copper-catalyzed annulative amination of \( ortho \)-alkynylphenols 72 with \( O \)-acylated hydroxylamines 73 to produce 3-aminobenzofurans 74 was developed by Hirano, Miura, and co-worker (eq 22).\(^{38} \) The reaction proceeds via nucleophilic attack of phenol oxygen on the \( \pi \)-activated carbon-carbon triple bond, followed by electrophilic amination of resulting organocopper intermediate 75. The methodology is readily extended to the synthesis of 3-aminoindoles 77 by using \( ortho \)-alkynyl-\( N \)-mesylanilines 76 (eq 23).\(^{39} \)
Zhang and co-workers developed a synthetic method for indoles 80, which involved the annihilation reaction of alkynes 78 and N-arylhydroxamic acids 79 with cooperative gold and zinc catalysis (eq 24).\(^4\) Initially, nucleophilically activated zinc hydroxamate 81 attacks π-complex 82 and the following protodeauration produces intermediate 83. Subsequent 3,3-sigmatropic rearrangement involving N-O bond cleavage and intramolecular condensation give indole 80.
3.2 Reaction of ortho-alkynylaryl oximes
Shin and co-workers reported in 2009 that the Z isomer of ortho-alkynylaryl ketoximes (Z)-84 was converted into isoindoles 85 in good yields in the presence of cationic gold catalysts (eq 25). The reaction proceeds via nucleophilic attack of the oxime oxygen atom to form cyclized intermediate 86 via 7-endo-dig cyclization and N-O bond cleavage driven by back-donation from the gold atom to furnish gold carbenoid intermediate 87. Subsequent nucleophilic attack of the nitrogen atom on the electrophilic carbenoid carbon gives isoindoles 85. In contrast, the reaction of corresponding E isomer (E)-84 in the presence of a catalytic amount of a cationic gold complex and TfOH afforded isoquinoline N-oxide 88 via nucleophilic attack of the oxime nitrogen atom (eq 26). Wu and co-workers reported that the reaction between ortho-alkynylbenzaldoxime 89 and aryne 93, which was generated from ortho-(trimethylsilyl)phenyl triflates 90, produced 2-oxa-6-azabicyclo[3.2.2]nona-6,8-diene derivatives 91 in the presence of silver catalysts (eq 27). The bicyclic framework is constructed through the [3+2] cycloaddition reaction of isoquinoline N-oxide 92, which is formed via the silver-catalyzed cyclization reaction, with aryne 93 followed by the migration of the oxygen atom from nitrogen to carbon. The cascade reaction of 89 with alkylidencyclopropanes.
afforded bicyclic products through silver-catalyzed cyclization, [3+2] cyclization, and N-O bond cleavage involving ring opening of the cyclopropyl group (eq 28).42

The groups of Zhang and Shin independently developed the silver-catalyzed reaction of O-alkyl ortho-alkynylaryl oximes to produce isoquinoline derivatives (eq 29).43,44 N-O bond cleavage takes place via E2 type elimination of the aldehyde from cyclized vinylsilver intermediate.
Zhang and co-worker also demonstrated that the silver-catalyzed reaction of \textit{O}-acyl 
\textit{ortho}-alkynylarylaldoximes \textit{99} afforded isoquinolin-1(2\textit{H})-ones \textit{100} (eq 30). The reaction proceeds
via \textit{2,3}-rearrangement of the acetyl group in cyclized intermediate \textit{101} followed by hydrolysis.

\begin{equation*}
\begin{array}{c}
\text{N} \quad \text{R} \\
\text{OAc} \\
\end{array}
\begin{array}{c}
\text{cat. AgOTf, DMF, rt} \text{ then H}_2\text{O} \\
\end{array}
\begin{array}{c}
\text{O} \\
\text{NH} \\
\end{array}
\begin{array}{c}
\text{cat. AgOTf, DMF, rt} \text{ then H}_2\text{O} \\
\end{array}
\begin{array}{c}
\text{O} \\
\text{Me} \\
\end{array}
\begin{array}{c}
\text{cat. AgOTf, DMF, rt} \text{ then H}_2\text{O} \\
\end{array}
\begin{array}{c}
\text{O} \\
\text{N} \\
\end{array}
\begin{array}{c}
\text{cat. AgOTf, DMF, rt} \text{ then H}_2\text{O} \\
\end{array}
\begin{array}{c}
\text{O} \\
\text{N} \\
\end{array}
\begin{array}{c}
\text{cat. AgOTf, DMF, rt} \text{ then H}_2\text{O} \\
\end{array}
\begin{array}{c}
\text{O} \\
\text{N} \\
\end{array}
\begin{array}{c}
\text{cat. AgOTf, DMF, rt} \text{ then H}_2\text{O} \\
\end{array}
\begin{array}{c}
\text{O} \\
\text{N} \\
\end{array}
\begin{array}{c}
\text{cat. AgOTf, DMF, rt} \text{ then H}_2\text{O} \\
\end{array}
\begin{array}{c}
\text{O} \\
\text{N} \\
\end{array}
\begin{array}{c}
\text{cat. AgOTf, DMF, rt} \text{ then H}_2\text{O} \\
\end{array}
\begin{array}{c}
\text{O} \\
\text{N} \\
\end{array}
\begin{array}{c}
\text{cat. AgOTf, DMF, rt} \text{ then H}_2\text{O} \\
\end{array}
\begin{array}{c}
\text{O} \\
\text{N} \\
\end{array}
\begin{array}{c}
\text{cat. AgOTf, DMF, rt} \text{ then H}_2\text{O} \\
\end{array}
\begin{array}{c}
\text{O} \\
\text{N} \\
\end{array}
\begin{array}{c}
\text{cat. AgOTf, DMF, rt} \text{ then H}_2\text{O} \\
\end{array}
\begin{array}{c}
\text{O} \\
\text{N} \\
\end{array}
\begin{array}{c}
\text{cat. AgOTf, DMF, rt} \text{ then H}_2\text{O} \\
\end{array}
\begin{array}{c}
\text{O} \\
\text{N} \\
\end{array}\\
\end{array}
\end{equation*}

\textit{99a} (R = Ph) \\
\textit{99b} (R = nBu) \\
\textit{100a} (R = Ph) 93% \\
\textit{100b} (R = nBu) 78% \\
\textit{102} \text{ gave 1-acetoxymethylisoquinolines \textit{103} in good yields (eq 31). The reaction proceeds} \\
via [3,3]-sigmatropic rearrangement of the acyl group in cyclized intermediate \textit{104} to result in N-O bond 
\textit{cleavage}. The reaction of \textit{102} in the presence of enoates \textit{105} gives olefinated products \textit{106} through 
tandem cyclization/olefination (eq 32).

\begin{equation*}
\begin{array}{c}
\text{O} \\
\text{N} \\
\end{array}
\begin{array}{c}
\text{cat. AgOTf, DMF, rt} \text{ then H}_2\text{O} \\
\end{array}
\begin{array}{c}
\text{O} \\
\text{N} \\
\end{array}
\begin{array}{c}
\text{cat. AgOTf, DMF, rt} \text{ then H}_2\text{O} \\
\end{array}
\begin{array}{c}
\text{O} \\
\text{N} \\
\end{array}
\begin{array}{c}
\text{cat. AgOTf, DMF, rt} \text{ then H}_2\text{O} \\
\end{array}
\begin{array}{c}
\text{O} \\
\text{N} \\
\end{array}
\begin{array}{c}
\text{cat. AgOTf, DMF, rt} \text{ then H}_2\text{O} \\
\end{array}
\begin{array}{c}
\text{O} \\
\text{N} \\
\end{array}
\begin{array}{c}
\text{cat. AgOTf, DMF, rt} \text{ then H}_2\text{O} \\
\end{array}
\begin{array}{c}
\text{O} \\
\text{N} \\
\end{array}
\begin{array}{c}
\text{cat. AgOTf, DMF, rt} \text{ then H}_2\text{O} \\
\end{array}
\begin{array}{c}
\text{O} \\
\text{N} \\
\end{array}
\begin{array}{c}
\text{cat. AgOTf, DMF, rt} \text{ then H}_2\text{O} \\
\end{array}
\begin{array}{c}
\text{O} \\
\text{N} \\
\end{array}
\begin{array}{c}
\text{cat. AgOTf, DMF, rt} \text{ then H}_2\text{O} \\
\end{array}
\begin{array}{c}
\text{O} \\
\text{N} \\
\end{array}
\begin{array}{c}
\text{cat. AgOTf, DMF, rt} \text{ then H}_2\text{O} \\
\end{array}
\begin{array}{c}
\text{O} \\
\text{N} \\
\end{array}
\begin{array}{c}
\text{cat. AgOTf, DMF, rt} \text{ then H}_2\text{O} \\
\end{array}
\begin{array}{c}
\text{O} \\
\text{N} \\
\end{array}\\
\end{array}
\end{equation*}

\textit{102a} (R = Ph) \\
\textit{102b} (R = nBu) \\
\textit{103a} (R = Ph) 65% \\
\textit{103b} (R = nBu) 68% \\
\textit{102} \\
\textit{103}
3.3 Reactions of O-propargylic oximes

We reported that the copper-catalyzed reaction of O-propargylic phenylacetaldoximes 107 afforded N-styrenyl epoxyketimines 108 in good to excellent yields (eq 33).\(^{46}\) The use of a bulky base, such as dicyclohexylmethylamine, is crucial to enhance the catalytic activity. We proposed the following mechanism: internal redox reaction via nucleophilic attack of the oxime nitrogen atom, elimination of a proton at the $\alpha$ position of iminium group, and N-O bond cleavage. According to Anderson’s report (eq 14),\(^{23}\) however, it is also possible that N-O bond cleavage takes place through cyclized intermediate 109 to directly form the oxirane ring without formation of carbenoid intermediate 110. Further mechanistic studies are underway in our laboratory.

We recently found that the copper-catalyzed three-step cascade reaction between O-propargylic oximes 111 and electron-deficient olefins 112, such as maleimides and fumarates, afforded oxazepine derivatives 113 (eq 34).\(^{47}\) Initially, copper-catalyzed 2,3-rearrangement of O-propargylic oxime 111 to
N-allenyl nitrone intermediate 115 occurs through cyclized vinylcopper intermediate 114. Then, \textit{exo}-[3+2] cycloaddition with dipolarophile 112 followed by 1,3-oxygen migration from the nitrogen atom to the allene center carbon in resulting \textit{N}-allenyl oxazolidine species 116 leads to oxazepine 113. Mechanistic studies suggested that the copper catalyst efficiently promoted not only the 2,3-rearrangement but also the 1,3-oxygen migration process from 116 to 113. It is noteworthy that \textit{O}-propargylic oximes are unique substrates for catalytic skeletal rearrangement to synthesize various ring-sized heterocycles, such as pyridine oxides, azete oxides (four-membered cyclic nitrones), and azepine oxides.

\begin{align*}
\text{R}_1 & \quad \text{R}_2 \\
\text{R}_3 & \quad \text{R}_4 \\
\text{R}_5 & \quad \text{R}_6 \\
\text{N} & \quad \text{O}
\end{align*}

\begin{align*}
\text{N} & \quad \text{O} \\
\text{R}_1 & \quad \text{R}_2 \\
\text{R}_3 & \quad \text{R}_4 \\
\text{R}_5 & \quad \text{R}_6
\end{align*}

\text{Cu}

3.4 Reactions of alkynyl hydroxylamine derivatives

We reported that the platinum-catalyzed dehydroalkoxylation–cyclization cascade of \textit{N-ortho}-alkynylphenyl-\textit{N}-aryl ureas 117 having an alkoxy group on the nitrogen atom afforded tetracyclic compounds 118 in good to excellent yields (eq 35). Only PtI$_4$ exhibited excellent catalytic activity for the reaction. Various functional groups, such as alkyl, aryl, and ethoxycarbonyl groups, were tolerated as the substituent at the alkyne terminus. At the initial stage, nucleophilic attack by the nitrogen atom on the electrophilically activated triple bond proceeds in a 6-\textit{exo}-dig manner to furnish vinylplatinum species 119. Subsequent N-O bond cleavage leads to elimination of the methoxy anion. Thereafter, intramolecular C-H insertion into iminium-bound platinum carbenoid 120 followed by deprotonation gives product 118.
Ukaji, Inomata, and co-workers reported the transformation of $N$-propargylhydroxylamines 121 into $cis$-acylaziridines 122 by using silver and copper catalysts (eq 36). The reaction proceeds via hydroalkoxylation and the concerted 1,3-sigmatropic migration of resulting 4-isoxazoline 123 promoted by copper salts. Indeed, they demonstrated that isolated 4-isoxazoline 123 was isomerized to the acylaziridines by the action of the copper salt.

Shin and co-workers developed the gold-catalyzed reaction of homopropargylhydroxylamine 124 to afford 3-pyrrolidinones 125 (eq 37). The internal redox reaction proceeds in a 5-\textit{exo} O-attack manner to form gold carbenoid intermediate 126. Then, the attack of the sulfonamide anion and the elimination of the gold catalyst give 3-pyrrolidinones 125. In sharp contrast, the gold-catalyzed reaction of corresponding internal alkynes 127 gives cyclic nitrones 128 via 5-\textit{endo} $N$-attack and subsequent 1,3-sulfonyl migration (eq 38).
4. PERSPECTIVES

As described in this review, the efficient syntheses of nitrogen and oxygen heterocycles have been achieved by methodology based on $\pi$-acidic metal catalyzed N-O bond cleavage. Recent studies featuring this approach have yielded new and general transformations leading to densely functionalized heterocycles under mild reaction conditions. It is noteworthy that various metals, such as Au, Pd, Ir, Pt, Ru, Rh, Ag, and Cu, have been chosen as the appropriate catalyst for each transformation. N-O bond cleaves through various elemental processes, although further mechanistic investigations are required at the present stage. Nevertheless, the appropriate design of substrates incorporating N-O bond cleavage is expected to provide highly functional heterocyclic compounds in an efficient manner, which would be beneficial for such research fields as drug discovery and material science.

REFERENCES AND NOTES


16. Asao, Yamamoto, and co-workers have proposed a different mechanism in Ref. 9.


**Professor Itaru Nakamura** was born in Sapporo, Japan in 1973. He received his PhD in 2001 from Tohoku University under the supervision of Professor Yoshinori Yamamoto. He was appointed to the position of assistant professor in Professor Yamamoto’s group. He joined Professor Armin de Meijere’s group at Goettingen University, Germany in 2003 for four months as a visiting research fellow. He was promoted to lecturer in 2008 and associate professor in 2009 in Professor Masahiro Terada’s group at Tohoku University. He is a recipient of the Banyu Chemist Award (2010) and the Incentive Award in Synthetic Organic Chemistry, Japan (2010). His research interest includes the development of new transition metal catalyzed reactions and the efficient organic synthesis of heterocyclic compounds.

**Professor Masahiro Terada** was born in Tokyo, Japan in 1964. He graduated from Tokyo Institute of Technology in 1986 and received his PhD from the same institution in 1993. He was appointed to the position of assistant professor in Professor Mikami’s Laboratory at Tokyo Institute of Technology in 1989. He worked as a postdoctoral fellow with Professor M. D. Shair at Harvard University in 1999-2000 and joined Tohoku University as an associate professor in 2001. He has been a professor of chemistry at the Graduate School of Science, Tohoku University (Japan) since 2006. He is a recipient of the Incentive Award in Synthetic Organic Chemistry, Japan (2003), The Chemical Society of Japan Award for Creative Work (2008), the Mukaiyama Award (2010), and Nagoya Silver Medal (2012). His current research interests are the development of new and useful synthetic methodologies based on the design of novel chiral Brønsted-acid and -base catalysts as well as the utilization of transition-metal catalysts.