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HETEROCYCLIC SYNTHESIS BY π-ACIDIC METAL CATALYZED REACTIONS VIA N-O BOND CLEAVAGE

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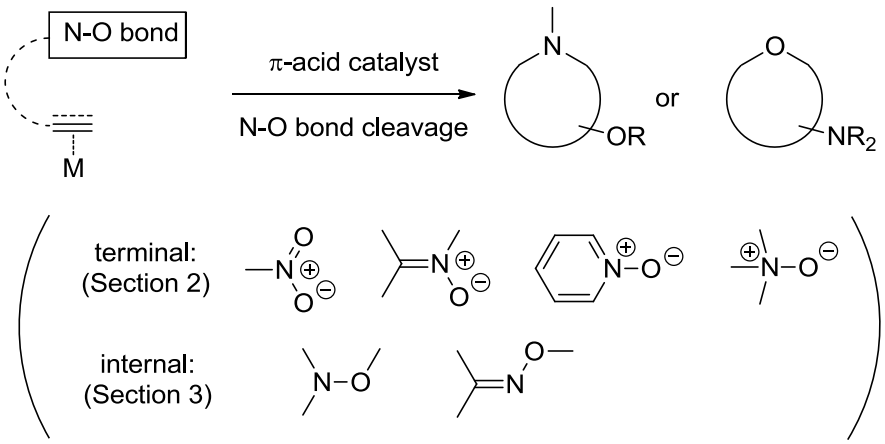
Abstract – This review contains recent progress in heterocyclic synthesis by π-acidic metal catalyzed reactions via N-O bond cleavage. The reaction involving a terminal N-O bond (R_3N^+-O^-) predominantly proceeds via nucleophilic attack of the O atom and subsequent formation of an α-oxo carbenoid intermediate through N-O bond cleavage. In contrast, the reaction of oximes and hydroxylamine derivatives having an internal N-O bond (R_2N-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.

CONTENTS

4. Perspectives

1. INTRODUCTION

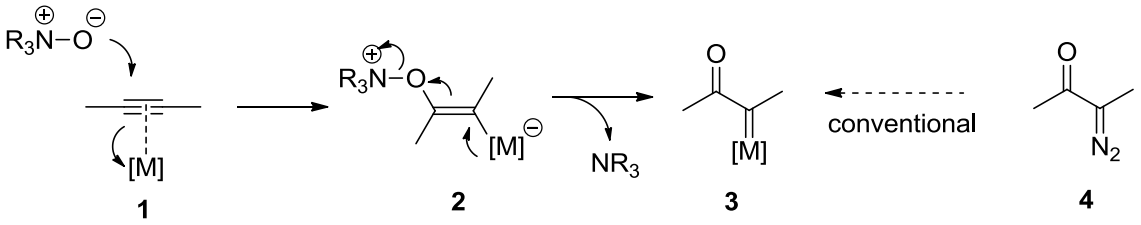
π-Acidic metal catalysis is a powerful tool to transform readily accessible organic molecules into highly elaborate ones under mild reaction conditions having high functional group tolerance. Because of its features, the catalysis has been frequently utilized in heterocyclic synthesis.[1] The transformation often involves the cleavage of various σ bonds, such as carbon-hydrogen, heteroatom-hydrogen, carbon-carbon, and carbon-heteroatom bonds.[2-5] Recently, π-acidic metal catalyzed reactions via cleavage of a nitrogen-oxygen (N-O) σ bond have received much attention as an efficient method for heterocyclic synthesis (Scheme 1). Not only terminal N-O bonds ($R_3N^+–O^-$), such as nitro compounds, nitrones, pyridine *N*-oxides, and amine *N*-oxides, but also internal N-O bonds ($R_2N–OR'$), 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 π-acidic metal catalyzed heterocyclic synthesis via N-O bond cleavage.



Scheme 1. π-Acidic metal catalyzed heterocyclic synthesis via N-O bond cleavage

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 π-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 α-oxo carbenoid species **3**.[7] 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 α-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.[8] However, π-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 α-oxo carbenoids in catalysis,[7] in this review we introduce heterocyclic synthesis by π-acidic metal catalyzed reactions initiated by the nucleophilic attack of a terminal N-O bond.

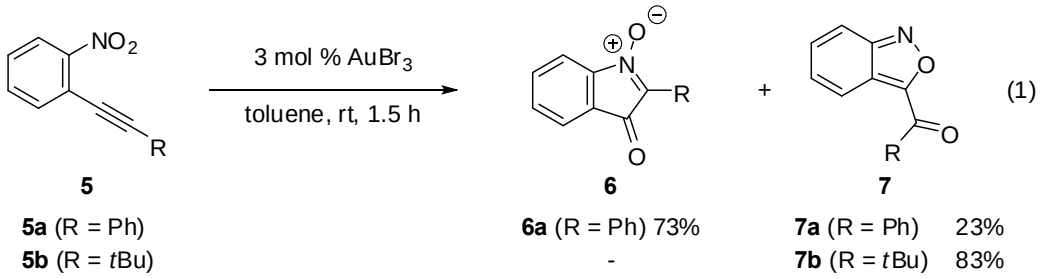


Scheme 2. Oxygen transfer process in π-acidic metal-catalyzed reaction of alkynes via N-O bond cleavage

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).[9] 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 $PdCl_2(PPh_3)_2$ and $PdCl_2(MeCN)_2$.[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*-iodosuccimide (NIS) and silver catalysts (eq 3).[10] The cycloisomerization of nitroalkynes **5** to isatogens **6** is known to proceed under thermal or photochemical conditions[13] 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]



5

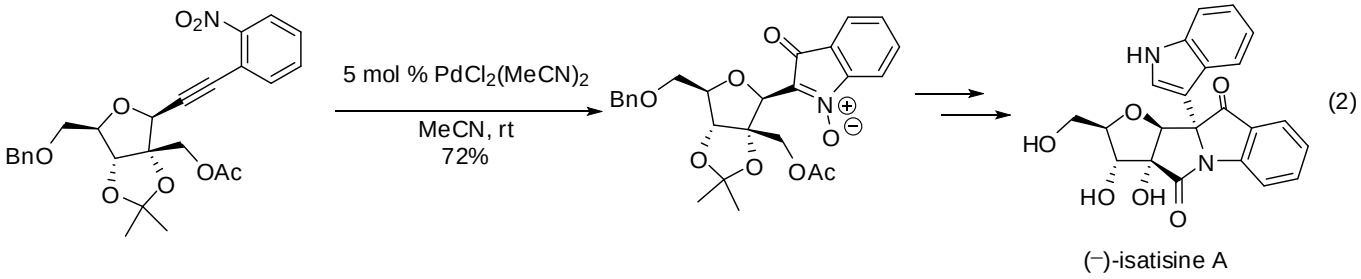
5a (R = Ph)
5b (R = *t*Bu)

6

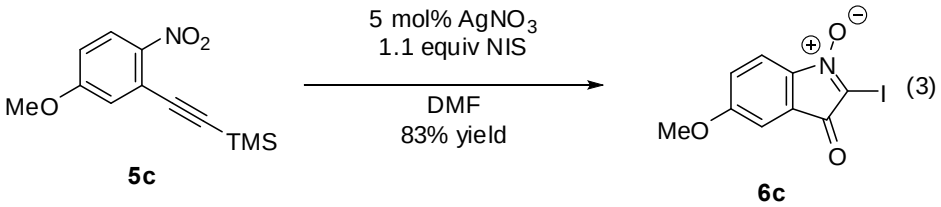
6a (R = Ph) 73%
-

7

7a (R = Ph) 23%
7b (R = *t*Bu) 83%



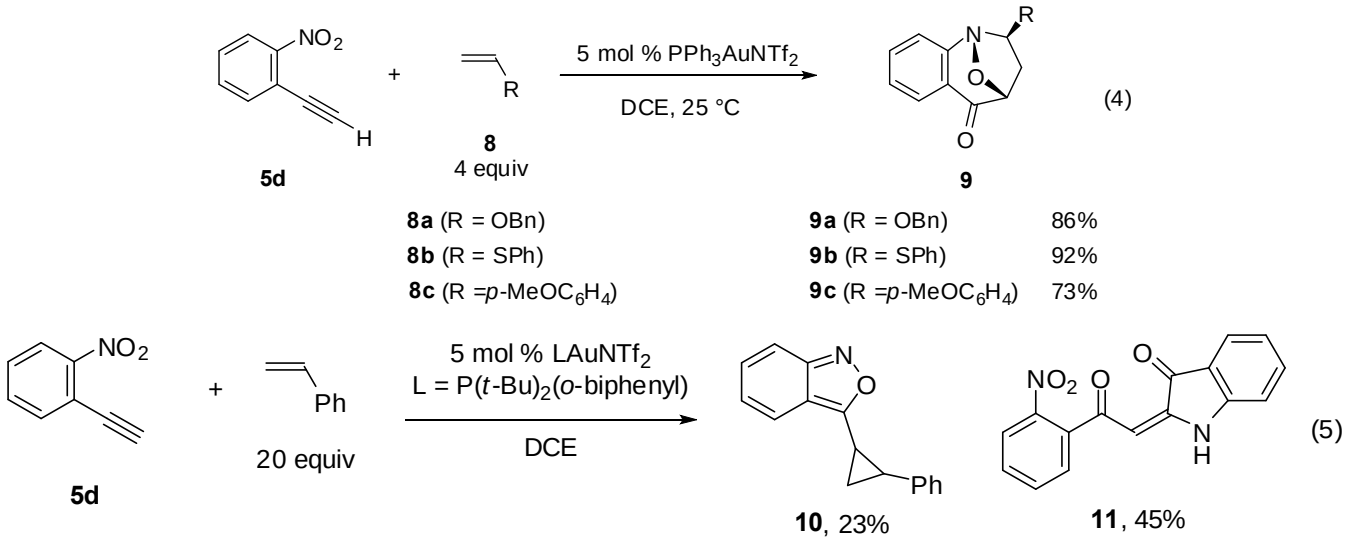
(–)-isatisine A



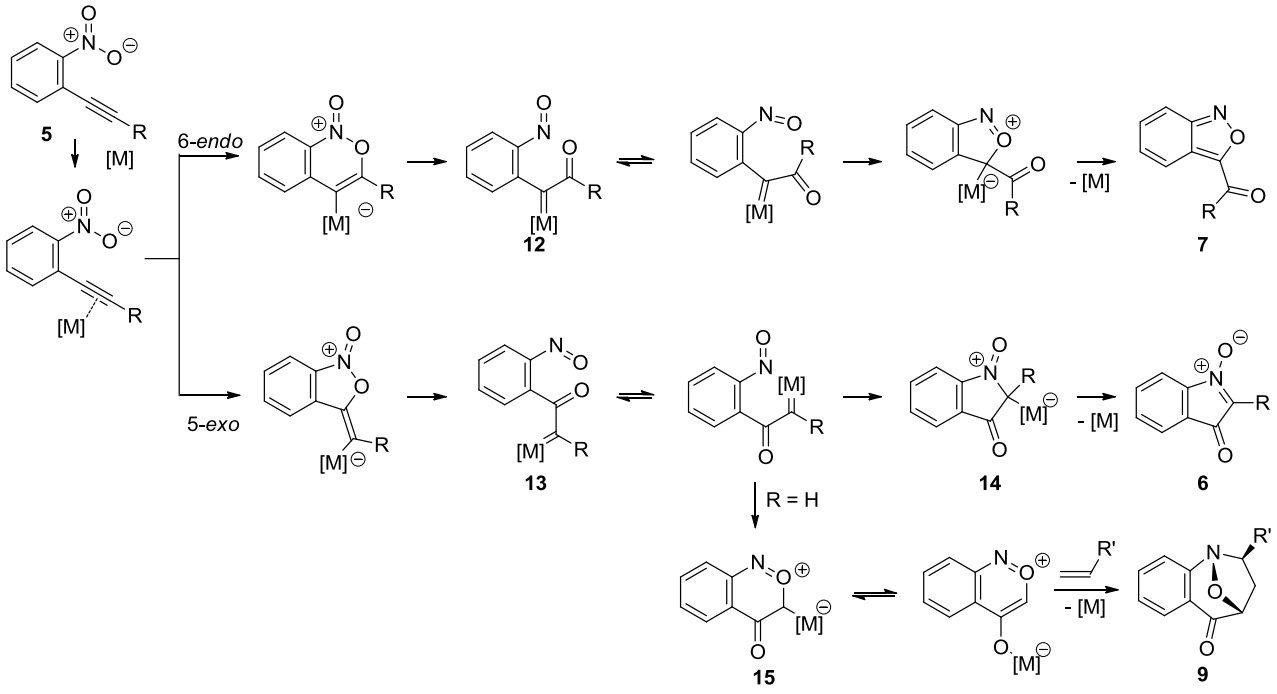
5c

6c

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 (PPh_3AuNTf_2)[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).



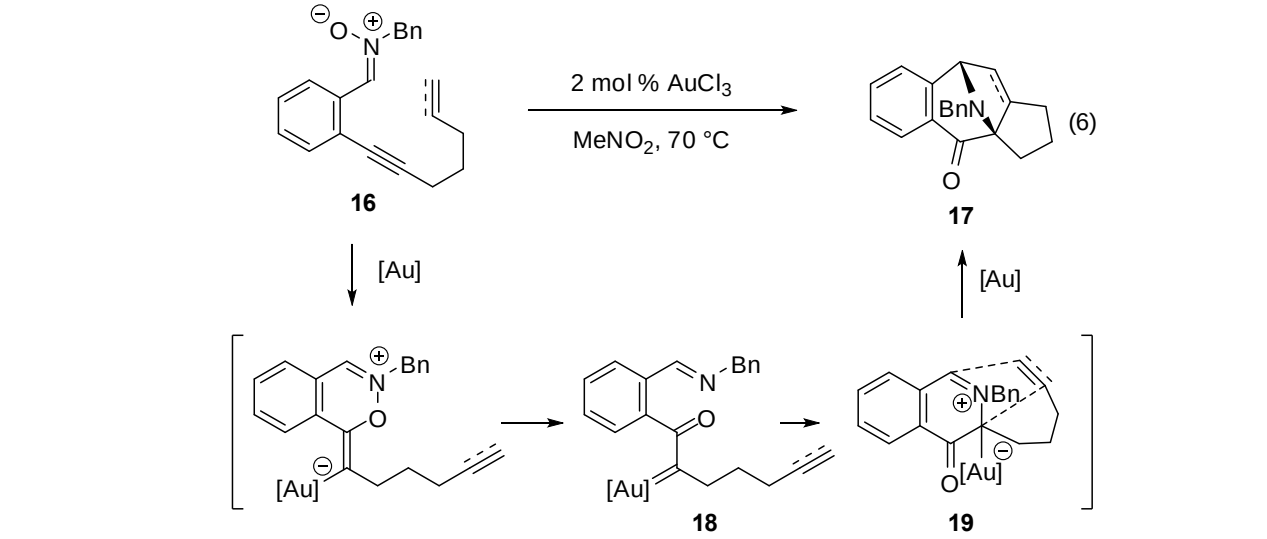
The reaction mechanism of the catalytic cycloisomerization of nitroalkyne **5** based on the internal redox reaction is illustrated in Scheme 3.[7,14,16] Initially, the electrophilically activated triple bond is subjected to intramolecular nucleophilic attack by the oxygen atom in the nitro group in 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**.

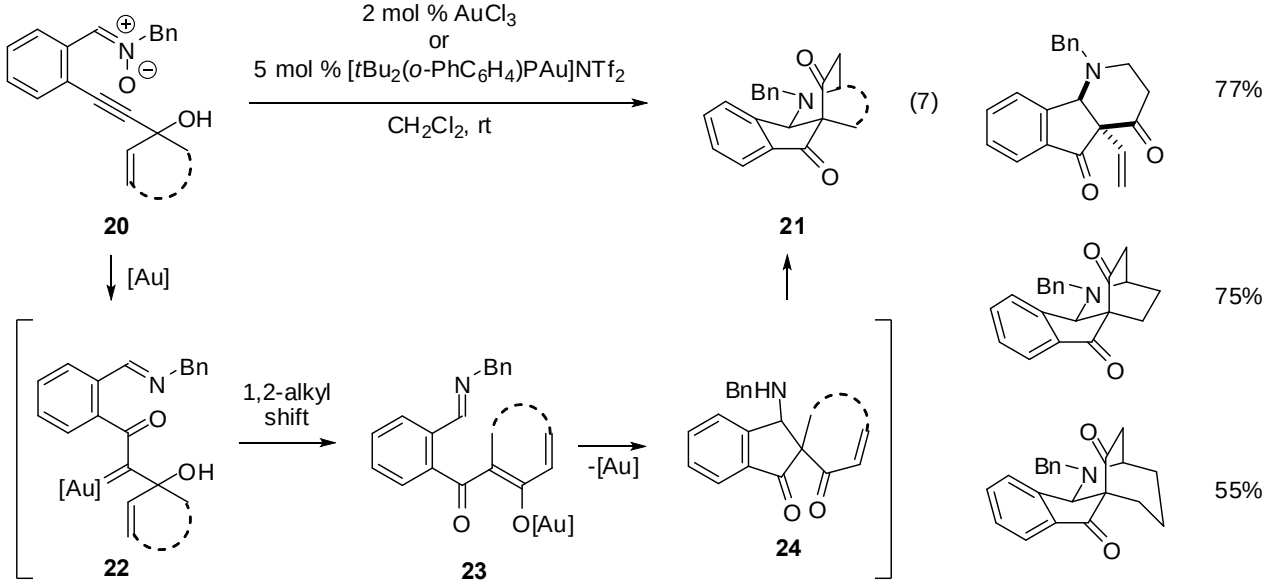


Scheme 3. Proposed mechanism of catalytic cycloisomerization of nitroalkyne **5**

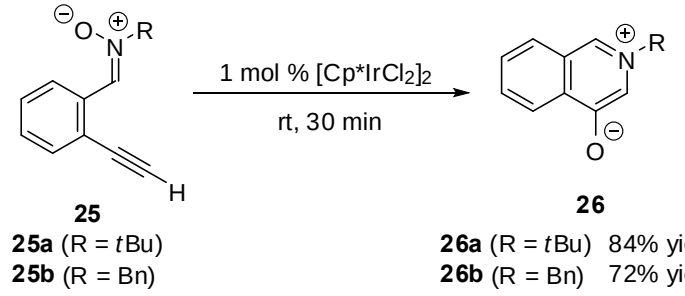
2.2 Reactions of nitrones

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).[17] The reaction was initiated by an internal redox reaction followed by a nucleophilic attack by the imine nitrogen on the carbenoid carbon of α-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).[18] 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 α,β-unsaturated carbonyl **24** to afford product **21**.





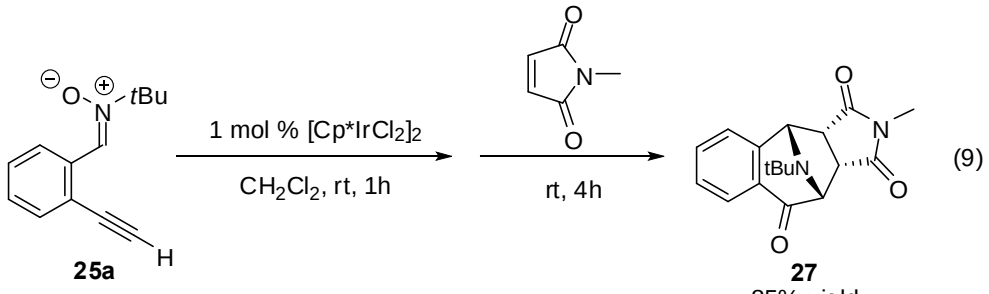
The iridium-catalyzed synthesis of azomethine ylides **26** from *ortho*-ethynylnitrones **25** was reported by Jia, Li, and co-workers (eq 8).[19] The one-pot reaction that consisted of the formation of azomethine ylide **26** followed by the intermolecular [3+2] cycloaddition reaction with added electron-deficient olefins, such as *N*-methylmaleimide, produced bicyclic compound **27** (eq 9). They also observed that the gold-catalyzed reaction of *N*-*tert*-butyl-substituted nitrone **25a** produced iminoester **28** (eq 10), in contrast to the iridium catalysis.[20] The bulky *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).[21] Initially, the internal redox reaction proceeds through 7-*endo* cyclized intermediate **33.** The subsequent nucleophilic attack of the imine nitrogen atom leads to isoindole **32**.



25
25a (R = *t*Bu)
25b (R = Bn)

26
26a (R = *t*Bu) 84% yield
26b (R = Bn) 72% yield

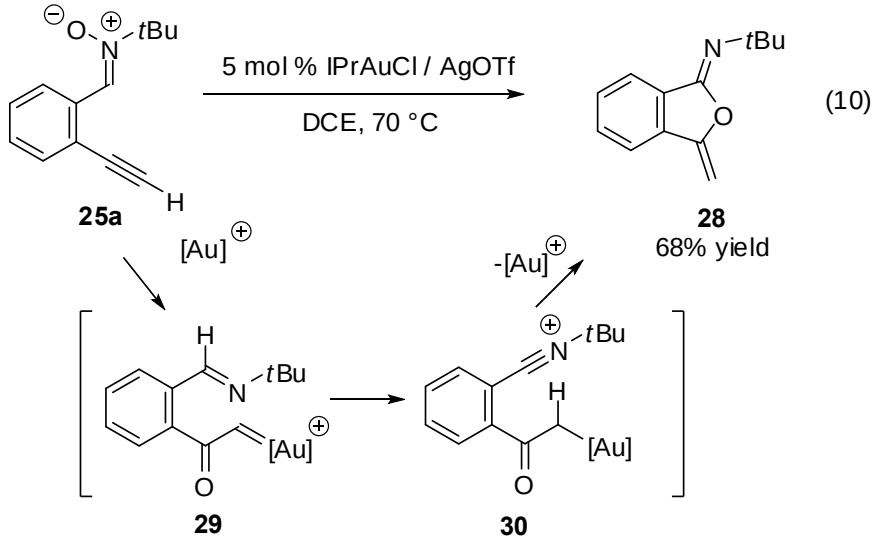
(8)



25a

27
85% yield

(9)

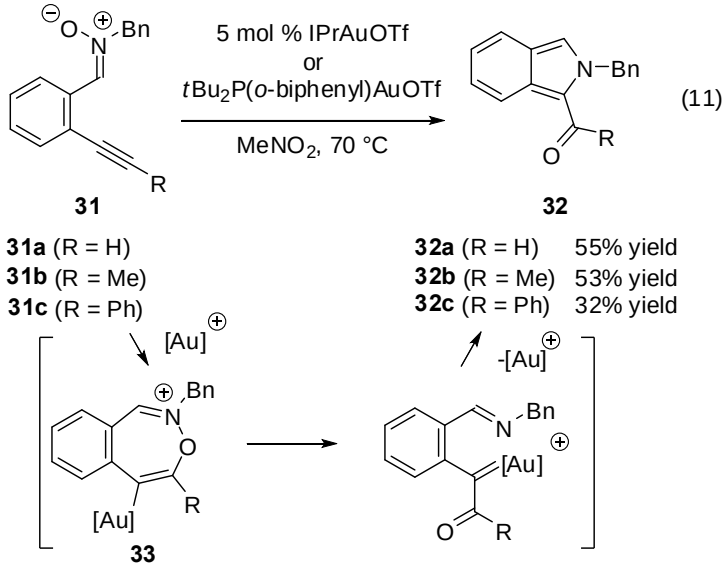


25a

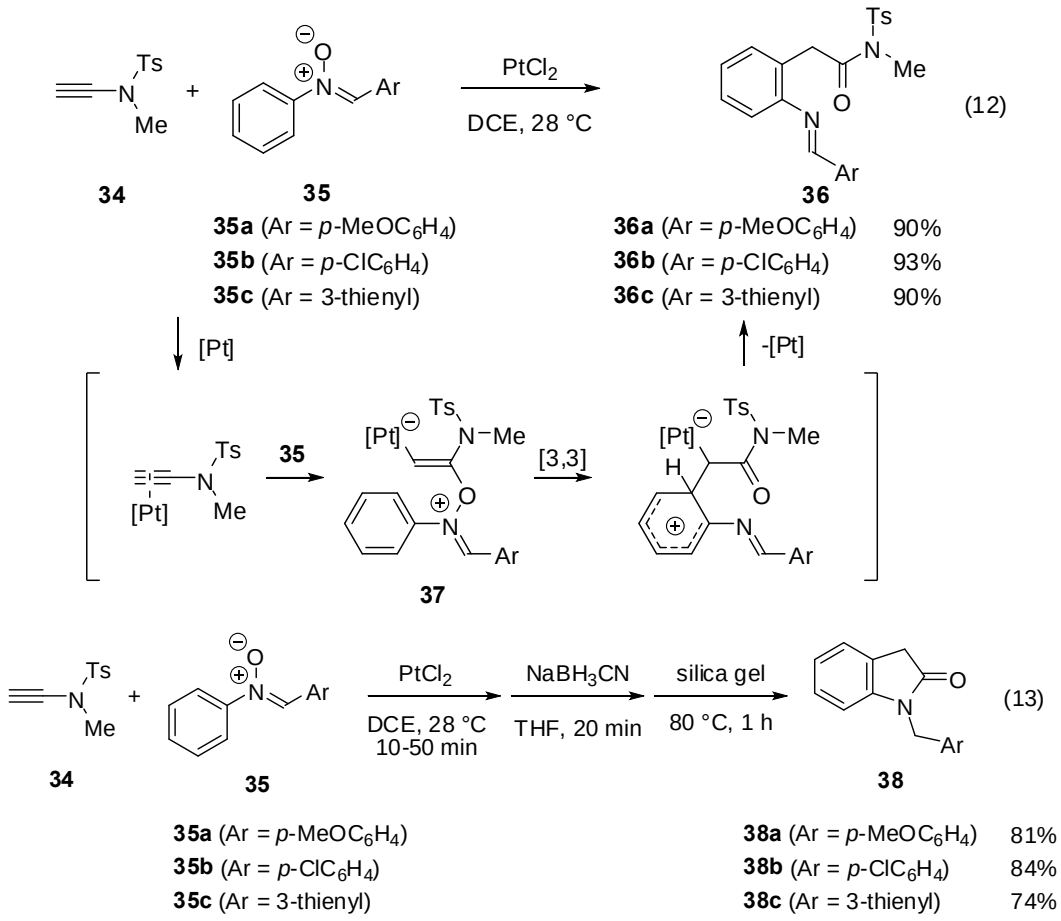
28
68% yield

(10)

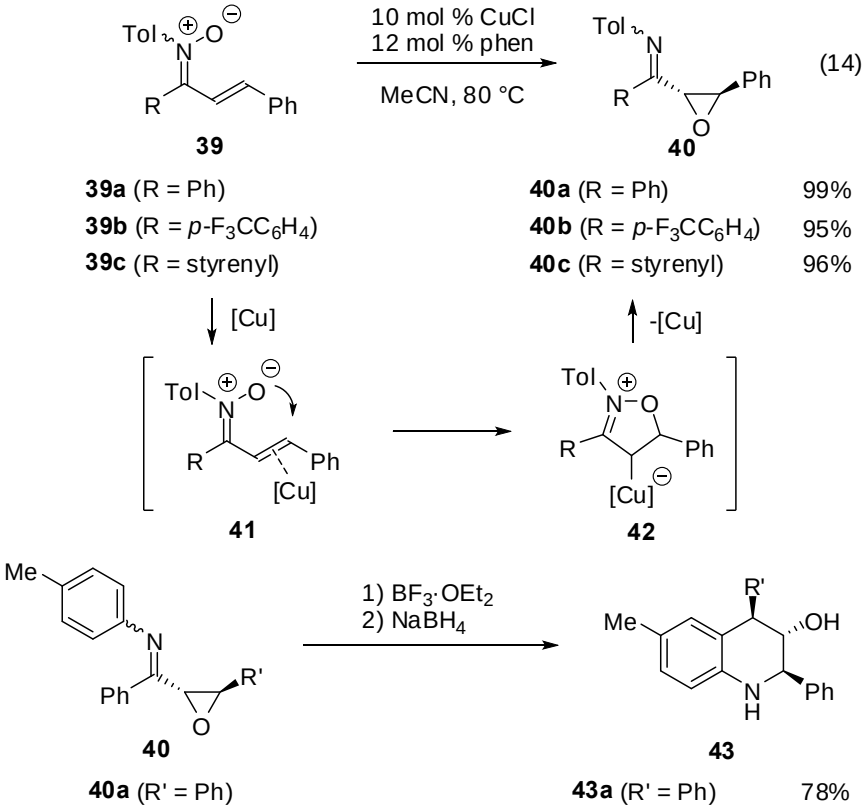
29 **30**



Liu and co-workers reported that the platinum-catalyzed intermolecular reaction of nitrone **35** with ynamide **34** gave formal oxoarylation product **36** (eq 12).[22] Cleavage of the N-O bond takes place in the [3,3]-sigmatropic shift of β-oxyalkenylplatinum intermediate **37**. The cascade sequence consisting of platinum-catalyzed oxoarylation, reduction by $NaBH_3CN$, and heating with silica gel produced indolin-2-ones **38** in good yields (eq 13).



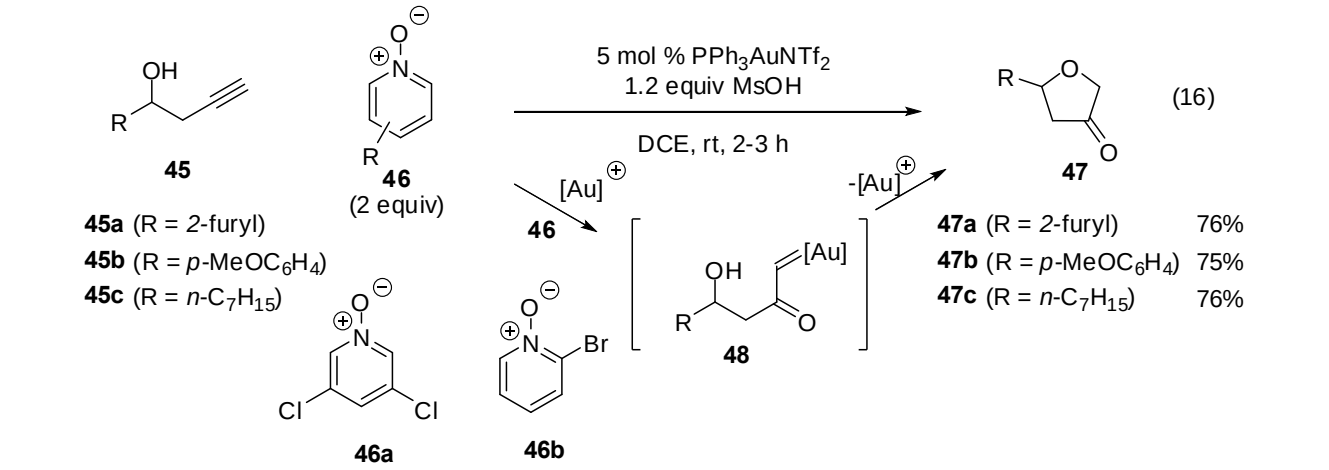
Recently, Anderson and co-worker reported the rearrangement of *N*-arylnitrones **39** to epoxyketimines **40** in the presence of catalytic amounts of CuCl and 1,10-phenanthroline (phen) (eq 14).[23] The reaction proceeds via nucleophilic attack of the nitrone oxygen atom on the electrophilically activated carbon-carbon double bond of π-complex **41**. Subsequent N-O bond cleavage of resulting cyclized intermediate **42** takes place as an "N-O switched type" of the Baldwin rearrangement,[24] 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).

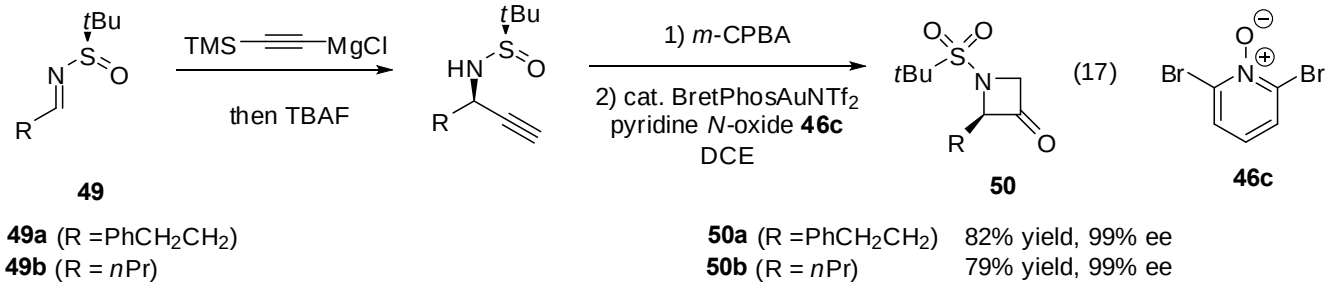


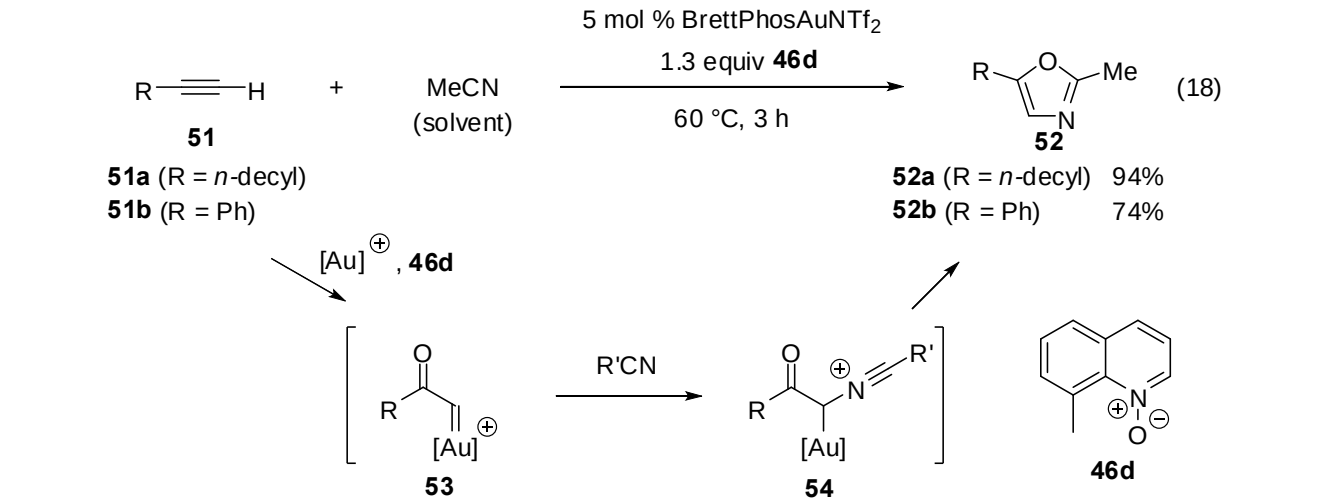
2.3 Reactions of pyridine *N*-oxides

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).[25] The cascade process involves the intermolecular oxidation and the intramolecular O-H insertion of gold α-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,[26] chroman-3-ones,[27] and azetidin-3-ones,[28] 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).[28] 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

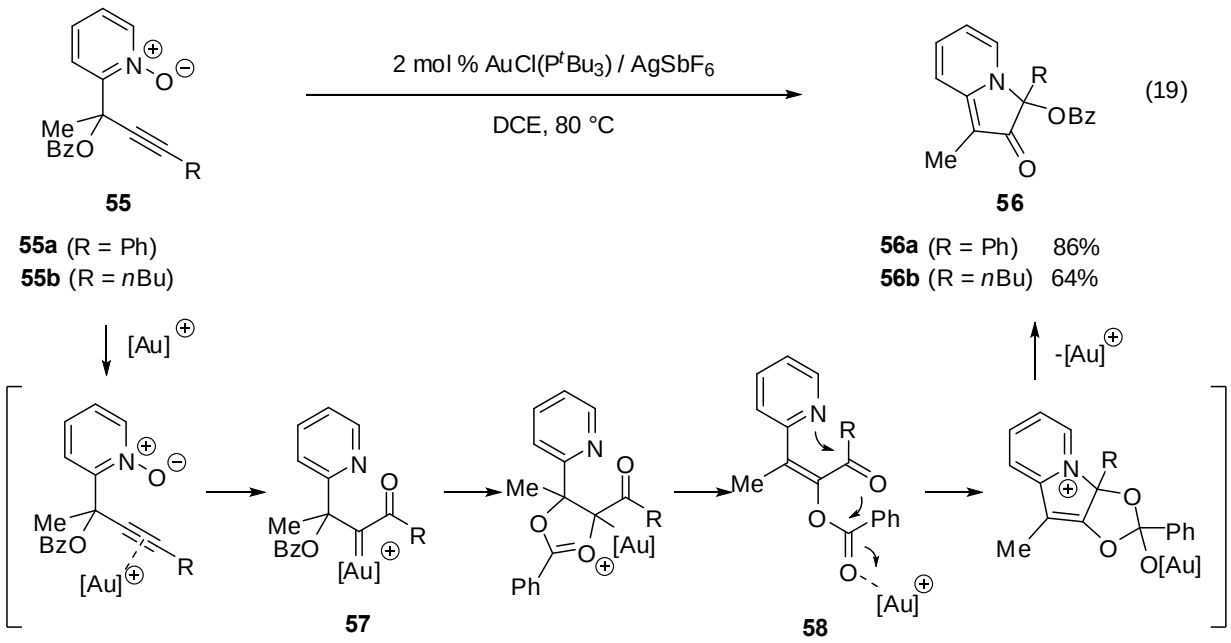
the intermolecular addition of acetonitrile to α-oxo carbenoid intermediate **53** (eq 18).[29] Not only aliphatic nitriles but also benzonitriles were efficiently employed as the substrate for the [2+2+1] annulation. It should be noted that the use of bulky pyridine or quinoline *N*-oxides, such as **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.[30] The methodology using pyridine *N*-oxides has been extended to a variety of gold- and rhodium-catalyzed heterocyclic synthesis.[31,32] 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.[33]





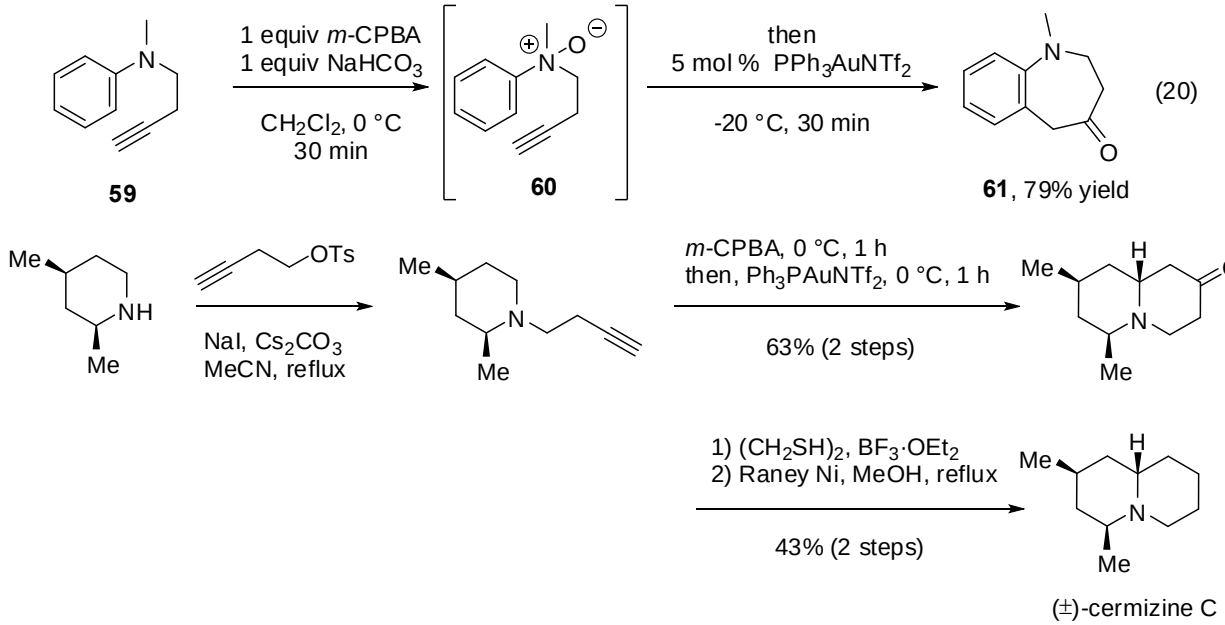


Ohe and co-workers demonstrated that the gold-catalyzed cycloisomerization of 2-(2-propynyl)pyridine *N*-oxides **55** generated indolizinones **56** in good to high yields (eq 19).[34] The reaction proceeds via intramolecular oxygen transfer to form gold carbene complex **57**. Subsequent migration 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**.

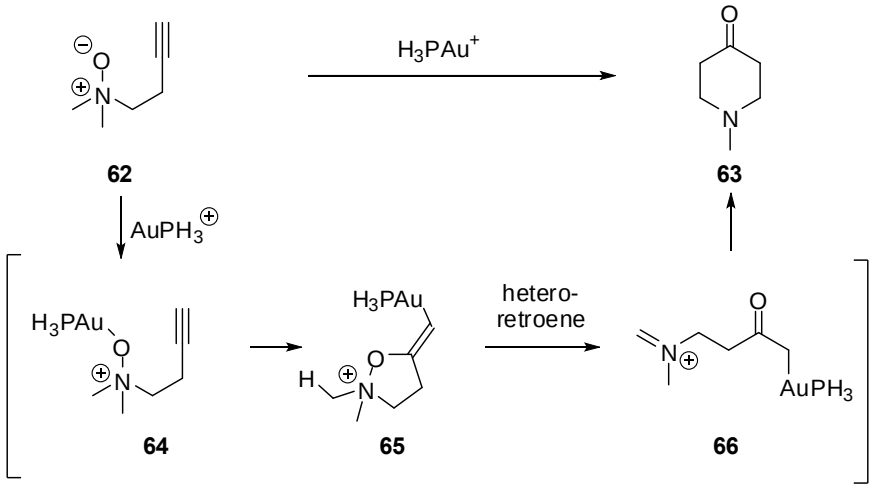


2.4 Reaction of alkynylamine *N*-oxides

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 tetrahydrobenzoazepinones **61** in good to high yields (eq 20).[35] 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.[36] First, the coordination of the cationic gold complex, H_3PAu^+, to the oxygen anion of **62** takes place instead of the π-coordination to the alkyne. Intramolecular s*yn* addition to the alkyne moiety (**64** → **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.



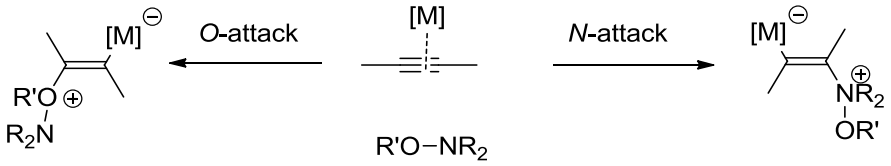
Scheme 4. Total synthesis of (±)-cermizine by gold-catalyzed reaction



Scheme 5. Reaction mechanism of gold-catalyzed rearrangement of acetylenic amine-*N*-oxides proposed by Zhang and Houk[36]

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

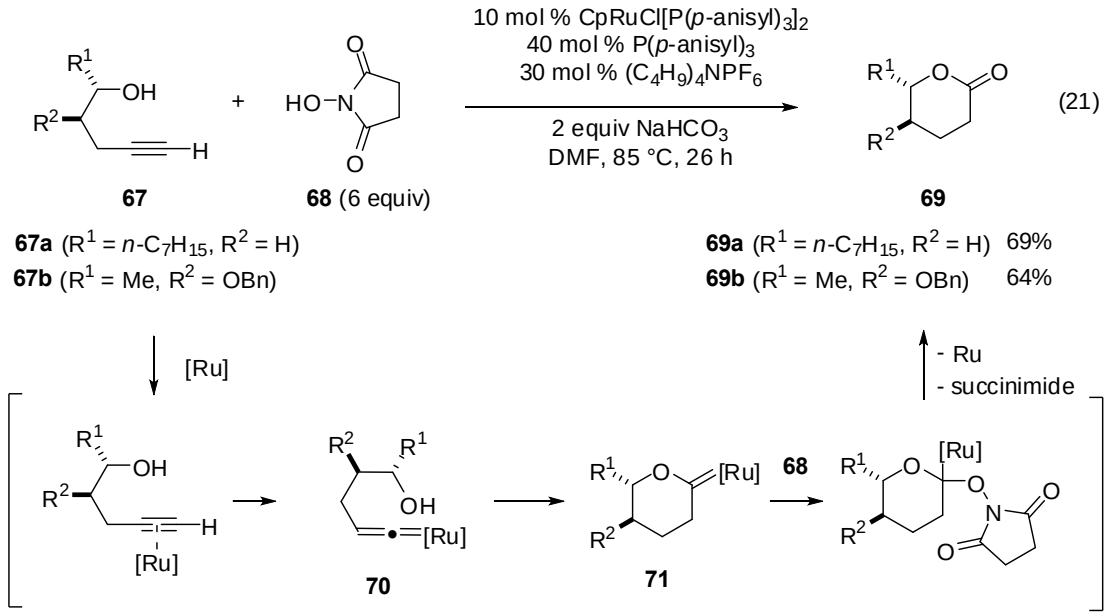
Functional groups having an internal N-O bond, such as oximes and hydroxylamines, have been also utilized in π-acidic metal catalyzed reactions. In contrast to the terminal N-O bond, nucleophilic attack of the internal N-O bond takes place either at N or O atom, as illustrated in Scheme 6. In addition, 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*-hydroxysuccinimide and *O*-benzoylhydroxylamines, have been utilized as an oxidant or amine electrophile in π-acidic metal catalyzed intermolecular reactions.



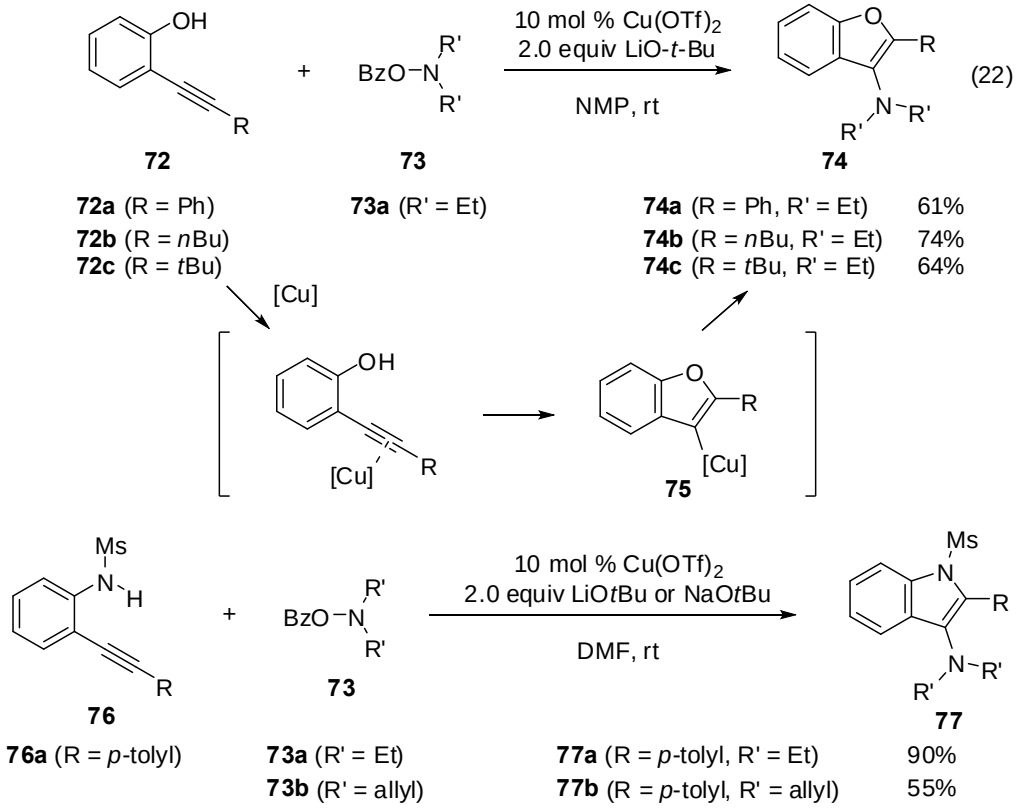
Scheme 6. Nucleophilic attack of internal N-O bond on π-activated alkyne

3.1 Intermolecular reactions with hydroxylamine derivatives

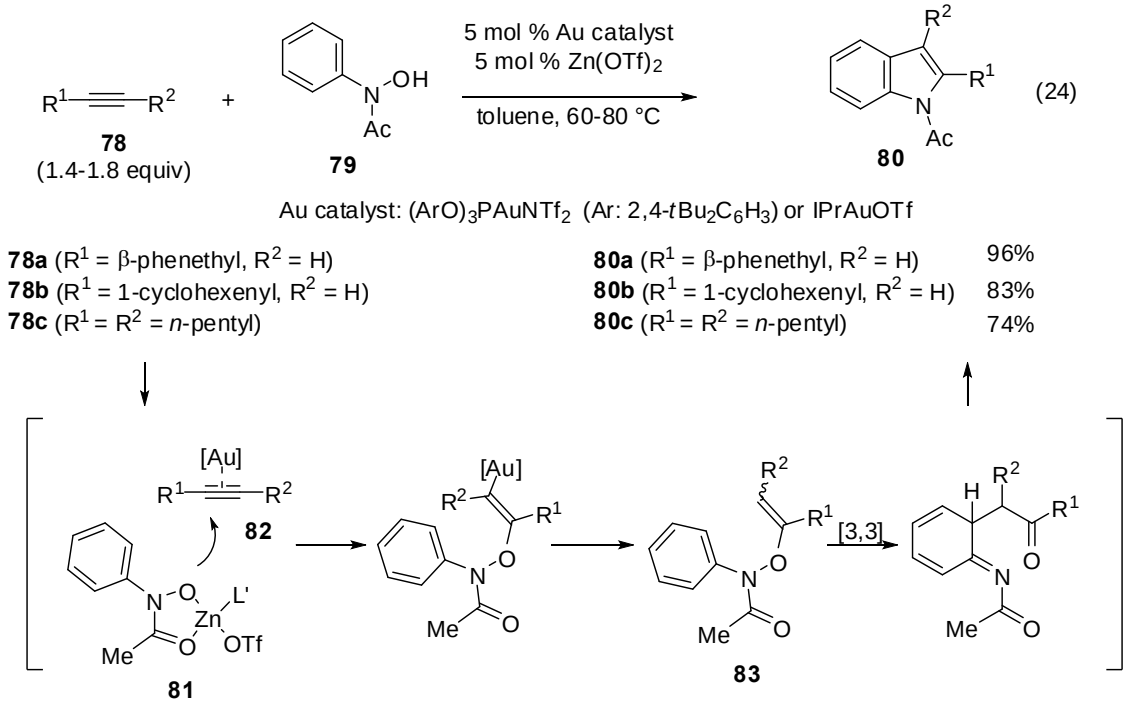
In 2002, Trost and co-worker reported that the ruthenium-catalyzed oxidative cyclization of homopropargylic alcohols **67** with *N*-hydroxysuccinimide **68** produced δ-lactone **69** (eq 21).[37] The reaction is initiated by π-coordination of the ruthenium catalyst followed by hydrogen migration, leading 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 π-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]

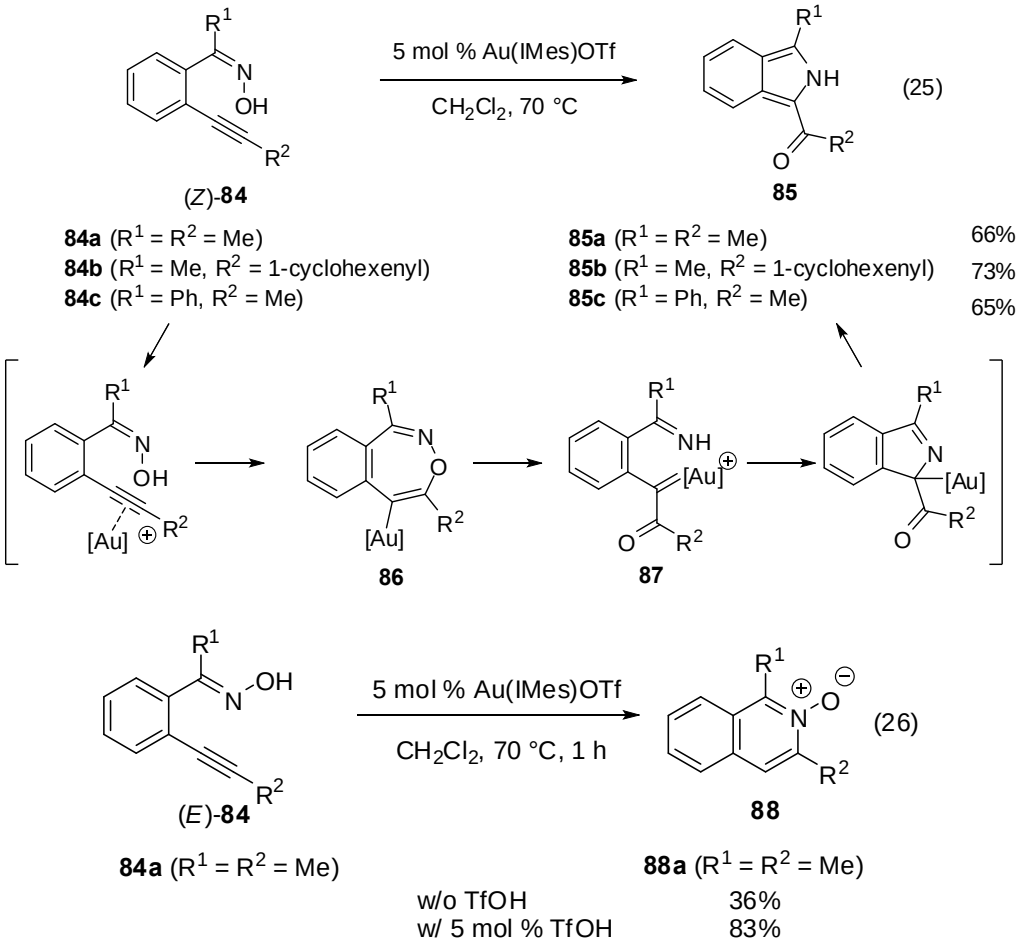


Zhang and co-workers developed a synthetic method for indoles **80**, which involved the annulation reaction of alkynes **78** and *N*-arylhydroxamic acids **79** with cooperative gold and zinc catalysis (eq 24).[40] Initially, nucleophilically activated zinc hydroxamate **81** attacks π-complex **82** and the following protodeauration produces intermediate **83**. Subsequent 3,3-sigmatropic rearrangement involving N-O bond cleavage and intramolecular condensation give indole **80**.



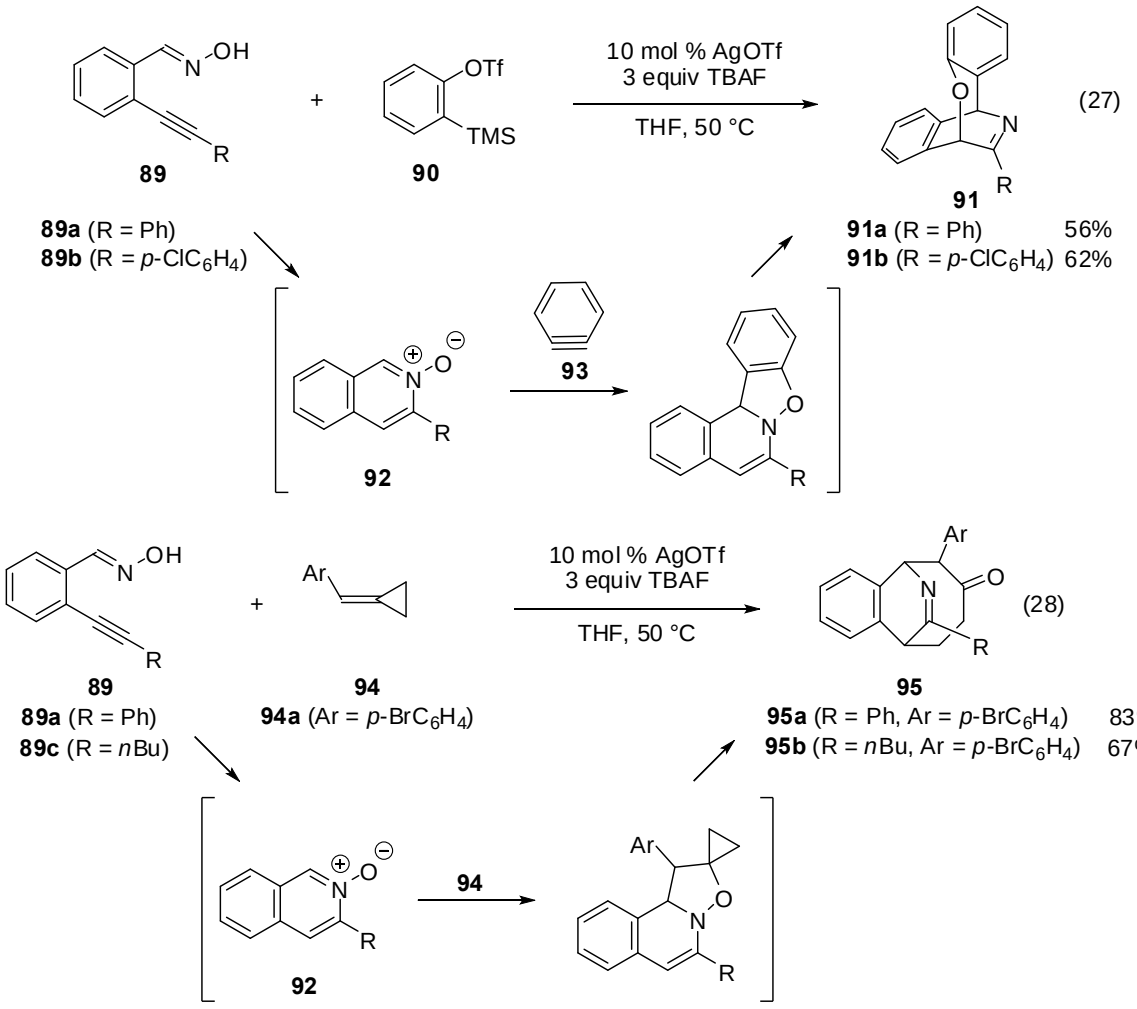
3.2 Reaction of *ortho*-alkynylaryl oximes

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).[21] 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).[21]

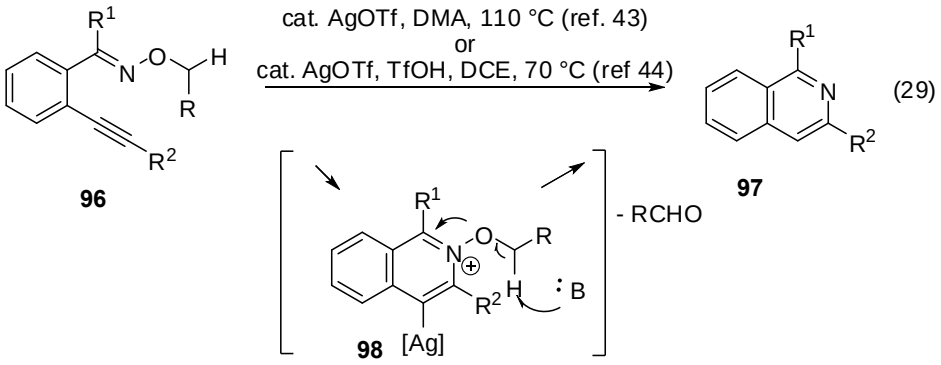


Wu and co-workers reported that the reaction between *ortho*-alkynylbenzaldoxime **89** and aryne **93**, which was generated from *ortho*-(trimethylsilyl)phenyl triflates **90**, produced 2-oxa-6-azabicyclo[3.2.2]nona-6,8-diene derivatives **91** in the presence of silver catalysts (eq 27).[41] The 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 alkylidenecyclopropanes **94** afforded bicyclic

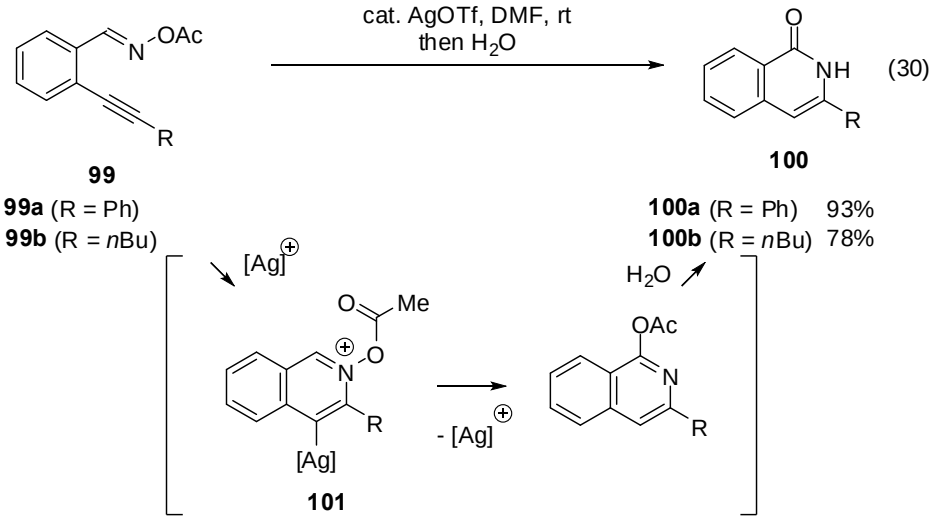
products **95** through silver-catalyzed cyclization, [3+2] cyclization, and N-O bond cleavage involving ring opening of the cyclopropyl group (eq 28).[42]



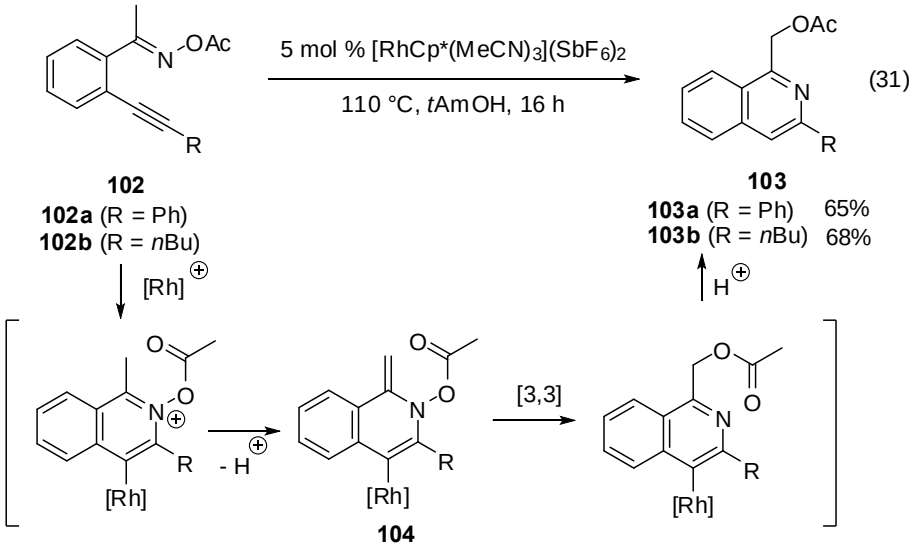
The groups of Zhang and Shin independently developed the silver-catalyzed reaction of *O*-alkyl *ortho*-alkynylaryl oximes **96** to produce isoquinoline derivatives **97** (eq 29).[43,44] N-O bond cleavage takes place via E2 type elimination of the aldehyde from cyclized vinylsilver intermediate **98**.

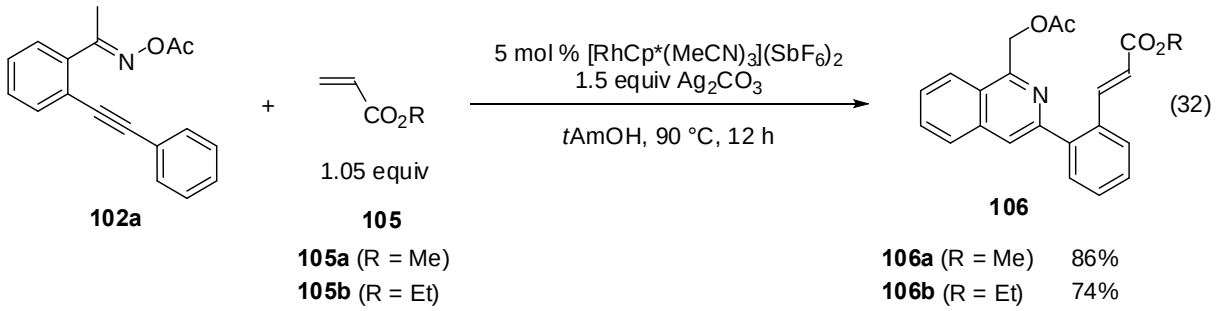


Zhang and co-worker also demonstrated that the silver-catalyzed reaction of *O*-acyl *ortho*-alkynylarylaldoximes **99** afforded isoquinolin-1(2*H*)-ones **100** (eq 30).[43] The reaction proceeds via 2,3-rearrangement of the acetyl group in cyclized intermediate **101** followed by hydrolysis.



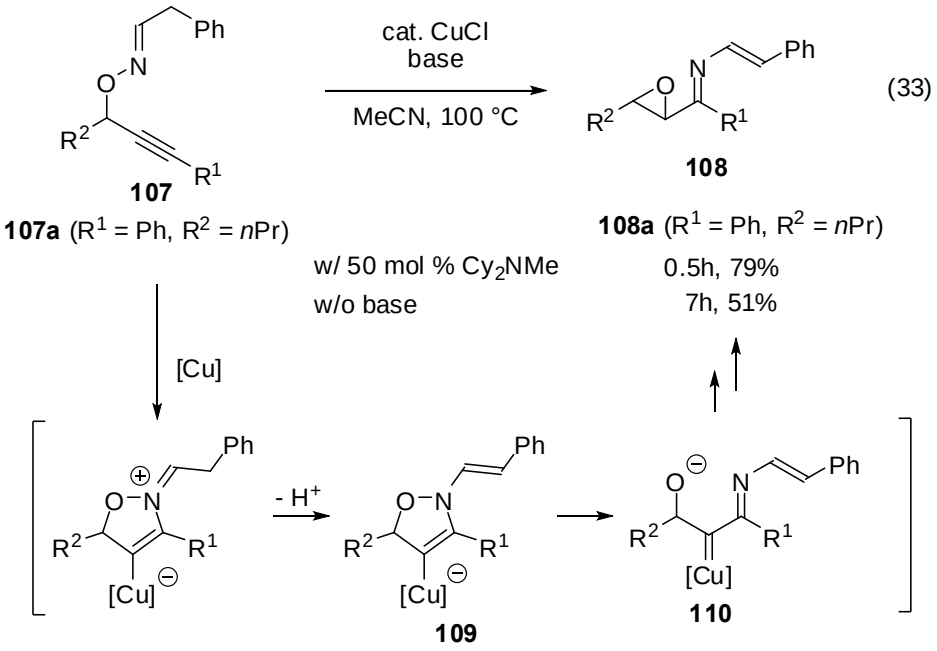
Li and co-workers reported that the rhodium-catalyzed cyclization of *O*-acyl *ortho*-alkynylaryl methyl ketoximes **102** gave 1-acetoxymethylisoquinolines **103** in good yields (eq 31).[45] The reaction proceeds via [3,3]-sigmatropic rearrangement of the acyl group in cyclized intermediate **104** to result in N-O bond cleavage. The reaction of **102** in the presence of enoates **105** gives olefinated products **106** through tandem cyclization/olefination (eq 32).





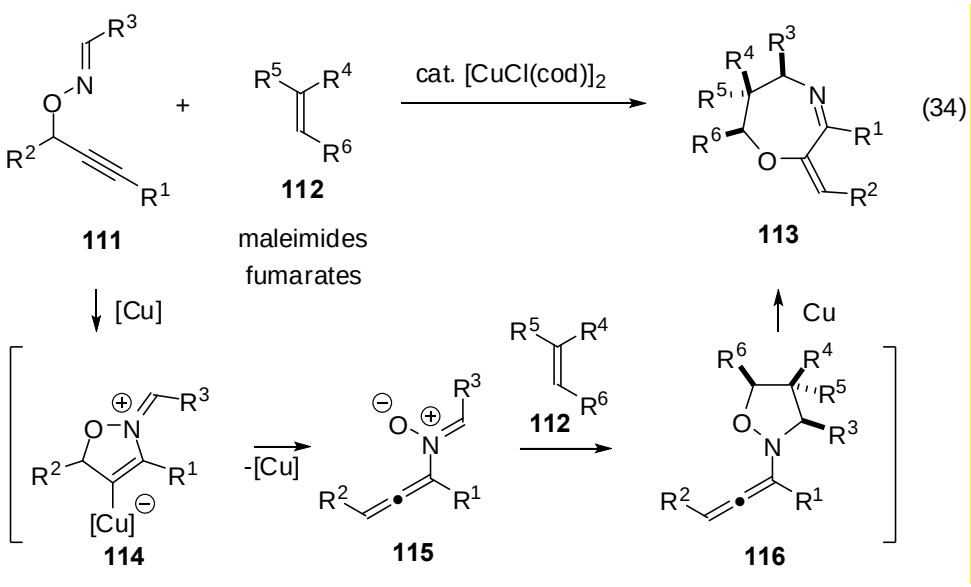
3.3 Reactions of *O*-propargylic oximes

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 α 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.



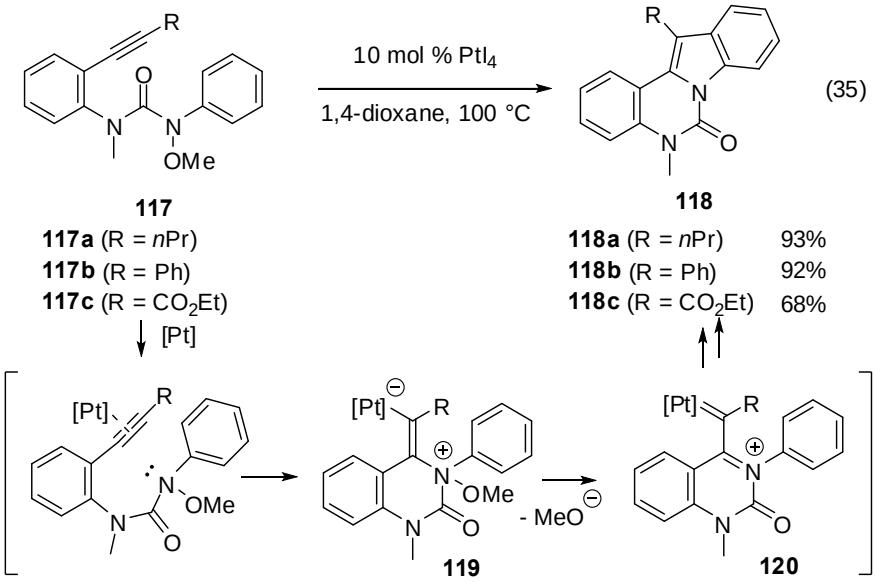
We recently found that the copper-catalyzed three-step cascade reaction between *O*-propargylic oximes **111** and electron-deficient olefins **112**, such as maleimides and fumarates, afforded oxazepine derivatives **113** (eq 34).[47] Initially, copper-catalyzed 2,3-rearrangement of *O*-propargylic oxime **111** to *N*-allenylnitrone

intermediate **115** occurs through cyclized vinylcopper intermediate **114**. Then, *exo*-[3+2] cycloaddition with dipolarophile **112** followed by 1,3-oxygen migration from the nitrogen atom to the allene center carbon in resulting *N*-allenyloxazolidine 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 *O*-propargylic oximes are unique substrates for catalytic skeletal rearrangement to synthesize various ring-sized heterocycles, such as pyridine oxides,[48] azete oxides (four-membered cyclic nitrones),[49] and azepine oxides.[50]

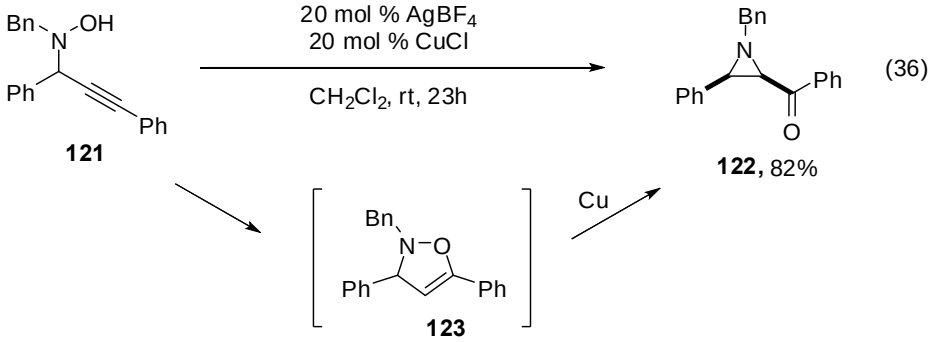


3.4 Reactions of alkynyl hydroxylamine derivatives

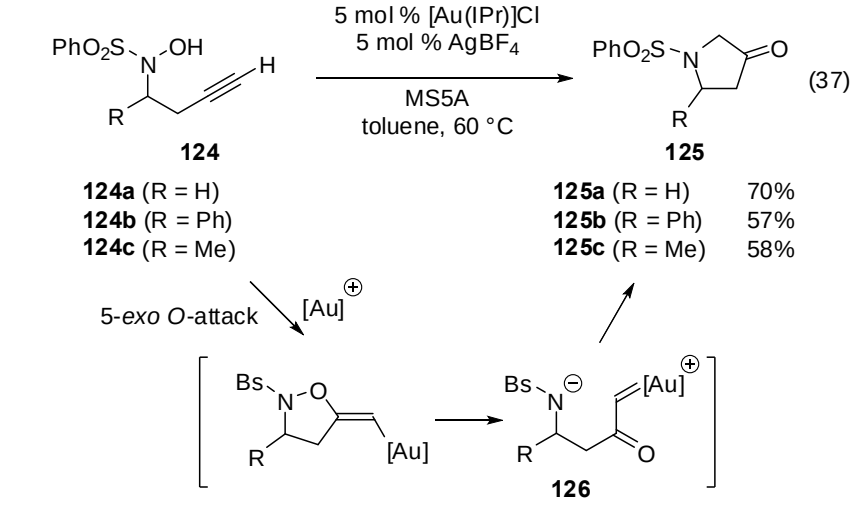
We reported that the platinum-catalyzed dehydroalkoxylation–cyclization cascade of *N*-*ortho*-alkynylphenyl-*N*-aryl ureas **117** having an alkoxy group on the nitrogen atom afforded tetracyclic compounds **118** in good to excellent yields (eq 35).[51] Only PtI_4 exhibited excellent catalytic activity 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-*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**.

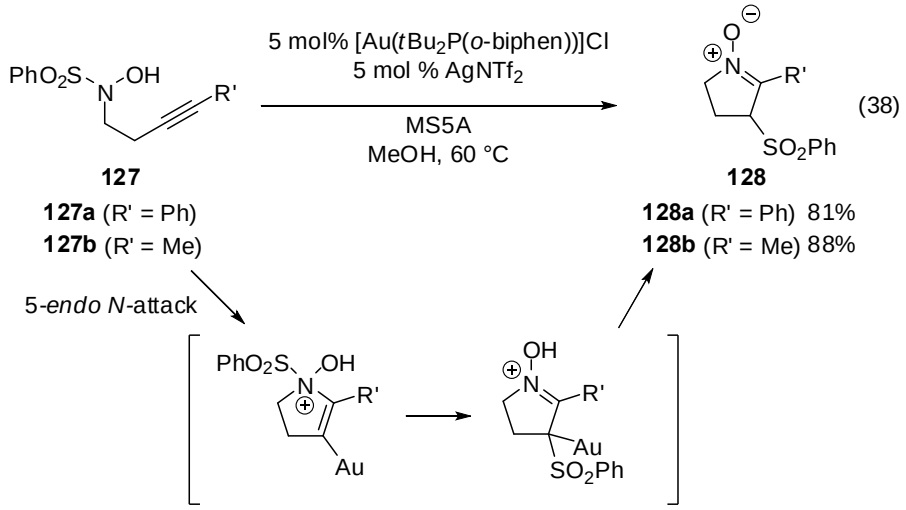


Ukaji, Inomata, and co-workers reported the transformation of *N*-propargylhydroxylamines **121** into *cis*-acylaziridines **122** by using silver and copper catalysts (eq 36).[52] The reaction proceeds via hydroalkoxylation and the concerted 1,3-sigmatropic migration of resulting 4-isoxazoline **123** 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).[53] The internal redox reaction proceeds in a 5-*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-*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 π-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.

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