# Catalytic Access to α-Oxo Gold Carbenes by N–O Bond Oxidants

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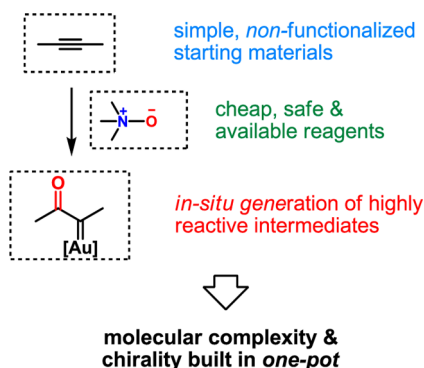
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## CONSPECTUS

**M**etal carbenes are highly versatile species that mediate various transformations. Recent advances in gold catalysis have allowed catalytic access to α-oxo metal carbenes from the alkyne functionality. Compared with traditional methods that rely upon metal-catalyzed decomposition of diazo precursors, the generation of this synthon occurs in an environmentally more appealing fashion by gold-catalyzed alkyne oxygenation.

Hydroxylamine derivatives are typically prepared from hydroxylamine salts that are cheap and can be handled without special precaution. In reactions with an alkyne activated by gold, relatively stable nitrones and related reagents undergo efficient O-atom transfer to form putative α-oxo gold carbenes. The highly reactive nature of these species could be utilized in a variety of cascade transformations. Herein, recent synthetic methods based on this reactivity as well as the currently available mechanistic and structural studies through computational and experimental methods have been discussed.

A variety of tandem reactions performed by our laboratory and others have demonstrated the synthetic utility of catalytically generated α-oxo gold carbenes and enabled access to various heterocycles. For example, a reaction between nitrones and alkynes led to azomethine ylides for the [3 + 2] dipolar cycloaddition. Alternatively, α-oxo gold carbenes can be transformed into enolate equivalents through a 1,2-pinacol shift. The addition of hydroxylamine derivatives across triple bonds led to oxoamination, providing α-aminocarbonyl compounds or regioselective Fisher indole-type synthesis. N–O bond cleaving redox chemistry paved the way for intermolecular redox processes, most notably by use of pyridine-*N*-oxide derivatives with expanding synthetic applications.

In closing, other metal-based oxygenations using N–O bond oxidants will be highlighted. One particularly interesting aspect is the process leading to metal vinylidene complexes. Trapping of this intermediate resulted in opposite regioselectivity from gold catalysis in alkyne oxygenation and led to ketene intermediates for use in subsequent cascade transformations.

simple, *non*-functionalized starting materials

cheap, safe & available reagents

*in-situ* generation of highly reactive intermediates

**molecular complexity & chirality built in *one-pot***

## 1. Introduction

Efforts in streamlining chemical synthesis have led to several conceptual guides in the reaction design, such as atom, step, and redox economy. The latter of these refers to a minimum use of oxidations and reductions and to avoid generating noxious byproducts. In this respect, one approach to increase synthetic efficiency is to develop redox-neutral processes in which the oxidation states are exchanged between two reacting partners to fulfill the requisite redox processes.[1] During these processes, reactive intermediates can be generated in a catalytic fashion from readily available starting materials. For example, an oxygen-exchange process between reagents having an N–O bond and alkynes may generate highly useful α-oxo

metal carbenes and R₃N for various tandem transformations (Scheme 1).

In gold catalysis, a number of functional groups, including oximes, nitrones, amine-*N*-oxides, nitro groups, and pyridine-*N*-oxides, have been demonstrated to participate in this formal redox chemistry with alkynes.[2] The addition of an O-atom of these compounds onto gold-activated alkynes generates vinyl gold intermediates, **A**. Concomitant with a N–O cleavage, **A** breaks down into what are functionally equivalent to α-oxo gold carbenes, **B** (Scheme 1). Pioneering studies based on the decomposition of diazo compounds have established rich synthetic applications of these intermediates.[3] Considering the safety concerns in the use (especially of compounds without electron-withdrawing

substituents)[4] and preparation of diazo precursors,[5] alternative methods of generating these metal carbenes will be certainly desirable. The N−O bond redox chemistry that has been developed in various tandem cyclizations, cycloadditions, and intermolecular redox processes, most notably by use of pyridine-*N*-oxide derivatives, has significantly expanded the utility of this protocol.

This Account highlights various synthetic applications mediated by these *in situ* generated gold carbenes. Chemoselectivity control unique to each functional group introduced in the N−O bond redox process has been the key for the development in this area. In this respect, currently available information on the structure and reactivity of the *in situ* generated α-oxo gold carbenes will be discussed.

## 2. Historic Perspective

The utilization of a N−O bond cleavage (generally less than 55 kcal/mol of bond enthalpy) has a long history in organic synthesis. This process promotes diverse reactions such as Beckmann rearrangement, Neber rearrangement, the conversion of oximes into nitriles and various [1,3]- and [3,3]-sigmatropic rearrangements.[6] Even before the advent of electrophilic metal catalysis, several conspicuous tandem reactions involving N−O bond cleavage were reported, including synthesis of indole derivatives **2** (Scheme 2A)[7] and Baldwin rearrangement for synthesis of acyl aziridines and 2,3-dihydrooxazoles **5** (Scheme 2B).[6d] These transformations involve thermal rearrangement of N−O bond adducts concomitant with N−O bond cleavage. These processes generally require higher temperatures than the metal-catalyzed processes discussed below.[8]

In contrast to the metal-free reactions, transition metal-catalyzed routes are much milder alternatives. The N−O cleaving rearrangement catalyzed by group 11 metals was first demonstrated by Kinugasa et al. in 1972 for the synthesis of β-lactams (Scheme 3A).[9] This process was proposed to involve the [3 + 2] cycloaddition of copper acetylides from **6** with nitrones **7**, followed by protonation and fragmentation of Cu-bound 3,4-dihydroisoxazoles.

In 1993, Gasparrini et al. demonstrated that the AuCl₃-catalyzed reaction between nitrate ions and alkynes in biphasic media formed nitrile oxides for a dipolar [3 + 2] cycloaddition (Scheme 3B).[10] One mechanistic scenario for this transformation involves the formation of oxime **C** and its oxidation by a nitrate into a nitrile oxide. A nitrite ion generated during this process then participates in nucleophilic addition onto a gold-activated alkyne. The mechanism of the key N−O cleaving step has not been supported by

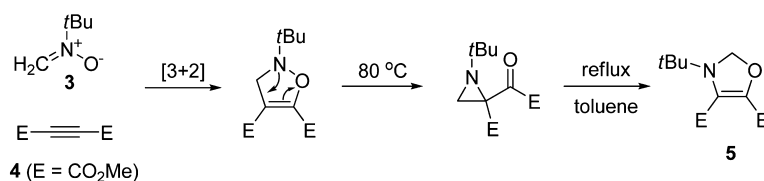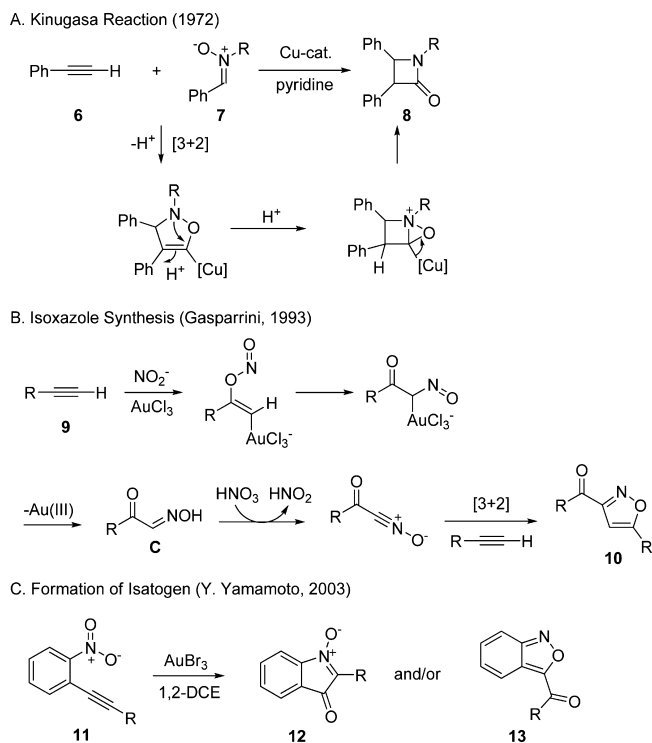**SCHEME 1.** Formal Metal Carbene Synthons
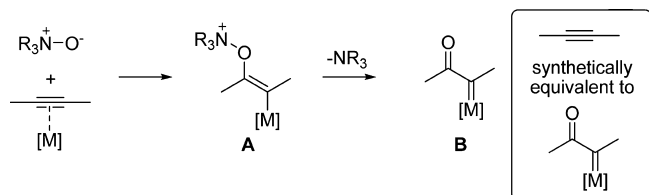


**SCHEME 2.** Metal-Free N−O Cleaving Redox Reactions

A. Coates, R. M. (1979)



B. Baldwin, J. E. (1968)



**4** (E = CO₂Me)
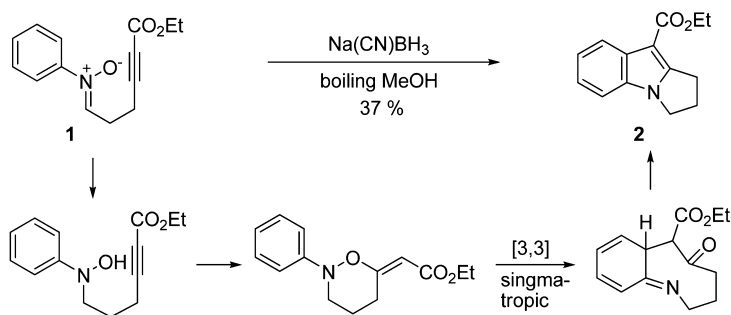
**SCHEME 3.** Earlier Examples of Catalytic Cleavage of N—O Bond by Group 11 Metals

A. Kinugasa Reaction (1972)



B. Isoxazole Synthesis (Gasparrini, 1993)



C. Formation of Isatogen (Y. Yamamoto, 2003)



experimental evidence, although the existence of the nitrile oxide has been confirmed.

In 2003, the Asao and Yamamoto group disclosed a rearrangement of *o*-alkynylnitrobenzenes into isatogens or anthranils in the presence of AuBr$_3$ (Scheme 3C).[11] Although not stated in their original paper, the formation of isatogens can be rationalized by a 5-*exo* O-attack of NO$_2$ on the alkynes followed by N—O redox. Similarly, anthranils form by the corresponding 6-*endo* attack and subsequent N—O redox.

## 3. Mechanism of N—O Cleaving Redox Reaction: Reactions of Oximes

Oximes are readily available from the condensation of aldehydes with hydroxylamine because of their resonance stabilization. Due to this stability, however, an alkyne should be strongly activated by highly electrophilic metal catalysts for the O-atom of an oxime to participate as a nucleophile onto the alkyne. In studying the Ag(I) catalyzed 6-*endo* cyclization of *o*-alkynyl benzaldoxime derivatives into isoquinoline-*N*-oxides,[12] an interesting N—O cleaving redox reaction product **15** was observed (Scheme 4A). To further probe the mechanism of its formation, the effect of oxime geometry was investigated.[13] Ketoximes **16**, in which (Z)-geometry is more available than in aldoximes,

**SCHEME 4.** Gold-Catalyzed N—O Redox Reactions of Oximes
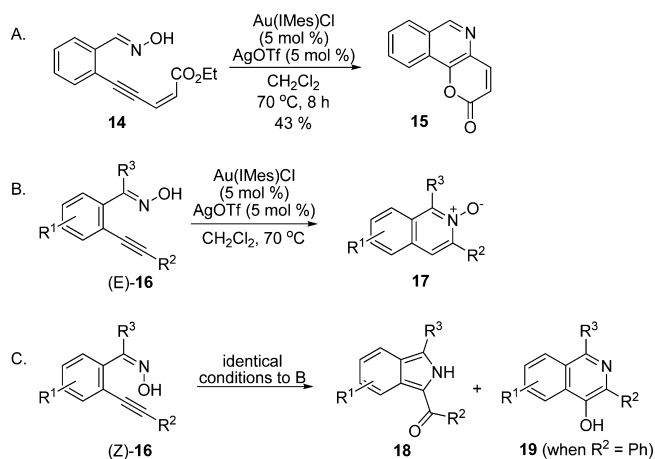


were chosen as model substrates, and a (Z)/(E) mixture was carefully separated by chromatography. The reaction of (E)-**16** invariably gave isoquinoline-*N*-oxides **17** in an exclusive fashion in the presence of Au(IMes)Cl and AgOTf (5 mol % each), similar to the Ag(I) catalyst (Scheme 4B). In sharp contrast, the corresponding (Z)-**16** only gave 1-acylisoindoles **18** under identical conditions (Scheme 4C). In this case, the presence of an aryl group at the alkyne (R$^2$) favored the formation of 4-hydroxyisoquinolines **19** slightly over **18**. It is notable that oxime isomerization did not occur during these processes, indicating a higher barrier of *E/Z* inversion than that of respective cyclizations either into **17** or **18/19**.

The geometry-dependent divergence into isoquinoline-*N*-oxides and isoindoles in Au(I)-catalyzed cyclization of oximes can be rationalized by the mechanism shown in Scheme 5. (E)-Oximes kinetically favor 6-*endo* N-attack, and the following protonolysis leads to isoquinoline-*N*-oxides. In contrast, the reaction of (Z)-oximes, which have O-atoms in close proximity to the alkyne, is initiated by 6-*exo* or 7-*endo*-dig O-attack depending on the alkyne substitution. The subsequent 1,2-proton shift presumably facilitates N—O cleavage. The presence of a Ph substituent at the alkyne slightly favors 6-*exo* product **19** over 7-*endo* product **18**, which is explained by α-cation stabilization of the intermediate **D** by the Ph group.

## 4. Gold-Catalyzed N—O Cleavage of Nitrones

Based on the proposed mechanism of N—O bond cleaving redox reactions of oximes, we projected that reactions between nitrones and alkynes would lead to α-oxo gold carbenes and imines that could form azomethine ylides. 1,3-Dipolar cycloaddition of azomethine ylides with π-bonds is a powerful tool for the construction of *N*-heterocyclic

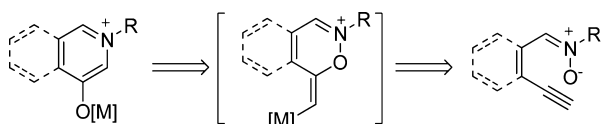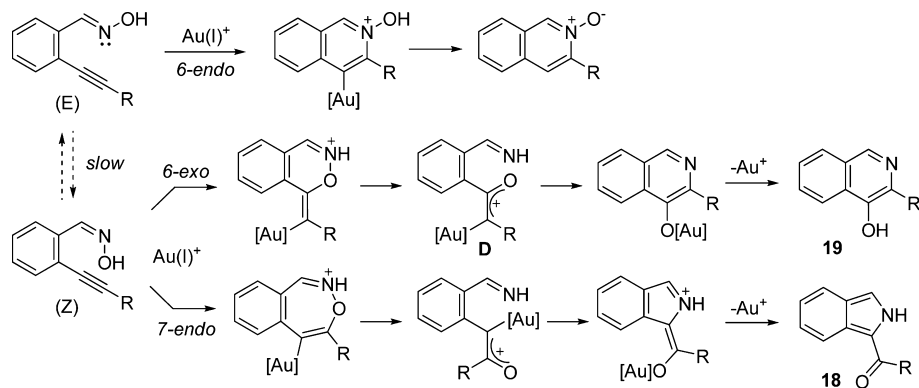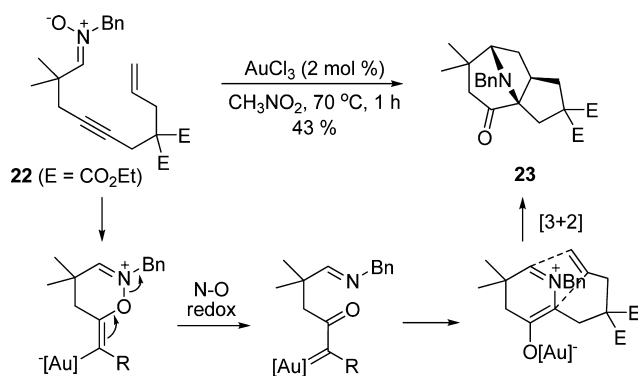**SCHEME 5.** Mechanism of the Geometry-Dependent Divergence





**FIGURE 1.** Gold-catalyzed generation of 3-oxidopyridinium and 4-oxidoisoquinolinium as 1,3-dipoles.

compounds. For example, 3-oxidopyridinium or 4-oxidoisoquinolinium salts have been utilized to construct complex, cage-shaped azacyclic natural products.[14] In this method, gold-catalyzed internal redox chemistry sets up synthetic equivalency between these dipolar species and readily available alkynyl nitrone precursors (Figure 1). The unique features of this approach are such that oxygen-exchange redox occurs in an atom-economical fashion while reactive intermediates (imines, carbenes, and azomethine ylides) are generated *in situ* from stable and readily available precursors.

Due to the resonance stabilization of nitrones, they are readily available but inert as oxidants of alkynes.[15] This stands in sharp contrast to their structural isomers, oxaziridines, which mediate diverse oxidative transformations.[16] Various metal salts and complexes such as $PtCl_2$, $PtBr_2$, $Rh(PPh_3)_3Cl$, $AuCl_3$, $AgSbF_6$, and *in situ* formed $Au(IMes)OTf$ turned out to catalyze the transformation of **20** with varying efficiency (Scheme 6).[17] Among these, $AuCl_3$ in $CH_3NO_2$ returned the best result, providing 88% of tandem internal redox–[3 + 2] cycloaddition adduct **21** with 2 mol % catalyst loading at 70 °C. The use of cationic Au(I) catalysts was less selective, producing isoindoles (Scheme 4C) along with the desired cycloadduct. Notably, this internal redox–cycloaddition cascade occurred chemoselectively. None of the intraor intermolecular [3 + 2] dipolar cycloadditions between the nitrone and the alkyne competed with the desired transformation. The substrate scope was quite general, and various

substituents in the olefins (dipolarophile), N-substituents of nitrones, and the tethers connecting 1,6-enynes or nitrones and alkynes were generally well-accommodated. Substrate **22**, which has an aliphatic tether between the alkyne and nitrone underwent a smooth reaction. This clearly shows that electrocyclic pathways are not viable mechanisms and that the N–O bond cleavage occurred through Au–C=C–O–N bonds similar to what was proposed for (Z)-ketoximes (Scheme 7). Control experiments for nitrone reactions shown in Scheme 6 indicated that the rate and product yield were unaffected by irradiation with UV light (254 nm). Moreover, reactions progressed smoothly in the presence of a radical inhibitor (BHT), indicating that photochemical or radical pathways are less likely.

Isolation of the proposed azomethine ylide intermediates will not only provide a sound basis for the above mechanism but also help determine whether metal mediation is involved in the subsequent [3 + 2] cycloaddition step. Furthermore, structural characterization of a metal-bound azomethine ylide would provide information for the development of asymmetric [3 + 2] cycloaddition. Unfortunately, isolation of this key intermediate was not possible using various stoichiometric Au(I) and Au(III) salts. For example, treatment of substrate **20** with a stoichiometric amount of $AuCl_3$ led to immediate (<5 min) decomposition. In 2009, Li et al. reported that the $[Cp^*IrCl_2]_2$ complex could also catalyze redox cyclization of alkynyl nitrone substrates **23** to give azomethine ylides that were isolated and characterized.[18] The chromatographically isolated metal-free azomethine ylide or its Ir-complex **24** underwent efficient intermolecular [3 + 2] cycloadditions with various alkenes and alkynes (2 equiv) at room temperature. The Ir(III)-complex of azomethine **24** was isolated in a stoichiometric reaction and characterized by X-ray crystallography. Interestingly, its solid-state structure was

**SCHEME 6.** Formation of Azomethine Ylides for [3 + 2] Cycloaddition



**20** (E = CO₂Et)  →  [3+2]  →  **21** (81 %)

83 %     (R = CH₂OBn) 89 %     58 %     43 %
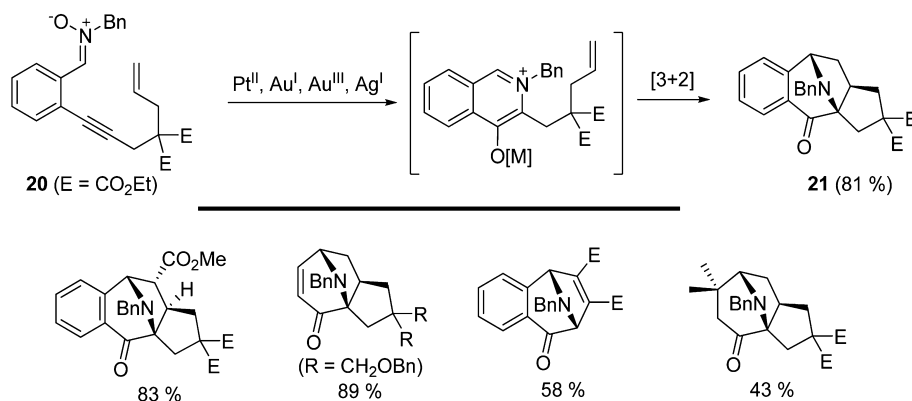
**SCHEME 7.** Mechanism of N–O Bond Redox in Nitronyl Alkynes



AuCl₃ (2 mol %)
CH₃NO₂, 70 °C, 1 h
43 %

**22** (E = CO₂Et)     **23**

N–O redox     [3+2]

obtained exclusively as an O-bound Ir-enolate of azomethines (Scheme 8).

Under such circumstances, the development of asymmetric [3 + 2] cycloaddition using a chiral catalyst was difficult because it required enantiofacial differentiation of the azomethine plane through the C–O–M bond having a large degree of freedom. Not surprisingly, all our attempts using chiral [Au(L*)]X or Au(III)/L* complexes led to racemic products. However, auxiliary-controlled asymmetric [3 + 2] cycloaddition was achieved in a highly stereoselective fashion using electronically tuned *N*-(1-phenylethyl)hydroxylamine derivatives (Scheme 9).[19] Diastereofacial selection on the azomethine plane was strongly affected by the C–Ar bond dipole in the azomethine **E**. A DFT calculation indicated that the C–Ar (Ar = *p*-nitrophenyl) bond had a strong tendency to lie perpendicular to the azomethine plane, directing the approach of a dipolarophile from the opposite side. Removal of the auxiliary under hydrogenolysis conditions from **26** proceeded smoothly to provide enantiomerically pure 8-aza[3.2.1]-bicyclooctanes.

Based on the success with the O-exchange reaction of nitrones, transformation of a postulated electrophilic gold-carbene intermediate into a nucleophilic gold-enolate was next considered. To this end, placing a tertiary alcohol at the alkynyl terminus in **27** as a carbene trap will convert **G** into the enolate **H** through a 1,2-pinacol shift. Stereoselective intramolecular addition to the *in situ* generated imine would then deliver a Mannich adduct **28** (Scheme 10).[20] In the presence of AuCl₃ or cationic Au(JohnPhos)NTf₂ (2 mol %, JohnPhos = P(*o*-biphenyl)*t*Bu₂), the alkynyl nitrones **27** with tertiary-alcohol substituents underwent an efficient tandem redox–pinacol–Mannich reaction at room temperature to provide **28**. A notable feature in this cascade is the ability to selectively introduce various groups at the quaternary α-center in **28**. Smaller alkyl groups migrated in preference to larger alkyl groups in the 1,2-pinacol shift (Me > Et > *i*Pr), likely indicating a compact transition state. In addition, π-functional groups, such as phenyl, alkynyl, and vinyl, that can interact with the cationic carbenic center in the transition state migrated in preference to the alkyl group to give **28b–d**. For cyclic tertiary carbinol substrates, reversed selectivity was observed due to a subtle conformational effect, as in the formation of **28f**. These cascade reactions allowed concise routes to achieve the core scaffolds of a variety of pharmaceutical agents and natural products.
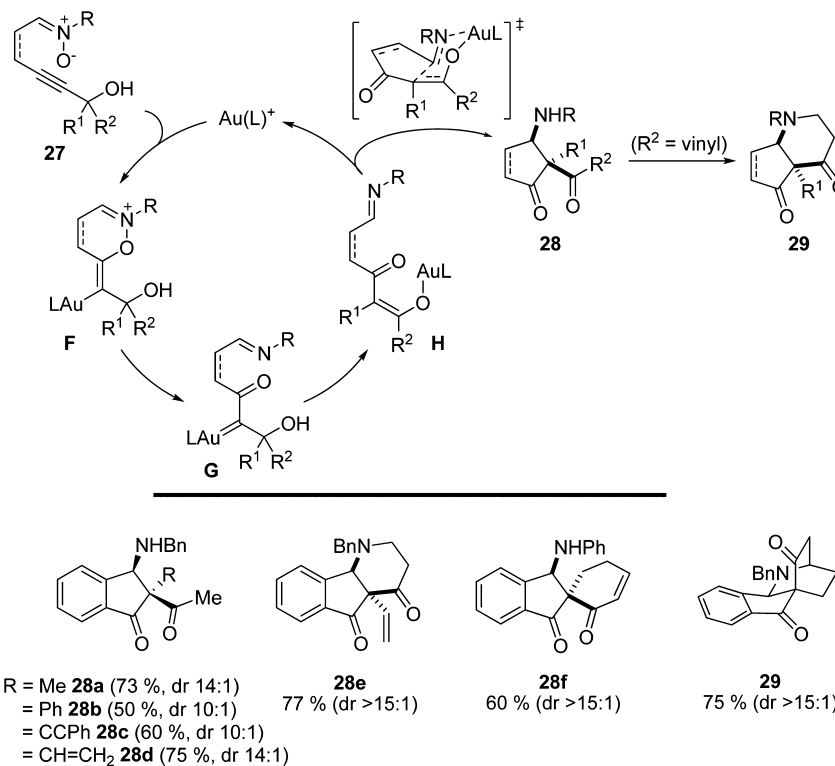
Intermolecular redox reactions using nitrones as external oxidants were first reported by Liu et al. in 2011 (Scheme 11).[21] To achieve intermolecular oxygenation of alkynes, some complicating issues must be overcome: (1) the desired transformation must be faster than a [3 + 2] dipolar cycloaddition between nitrones and alkynes; (2) the reduced form of R₃N⁺–O⁻, that is, R₃N (in this case, imine), may coordinate to Au⁺, resulting in an inactive complex; (3) the liberated imines may be a competitive nucleophile

**SCHEME 8.** Isolation of an Azomethine–Ir(III) Complex[18]
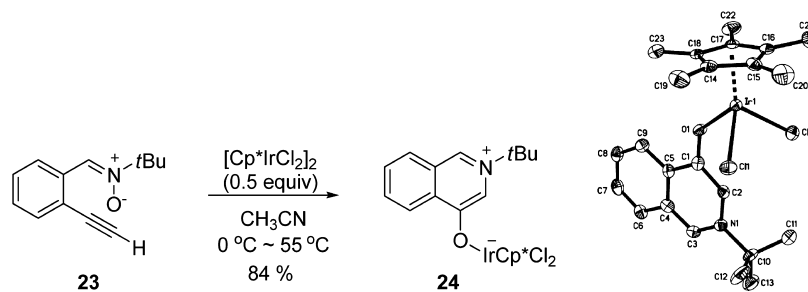


**SCHEME 9.** Auxiliary-Based Asymmetric [3 + 2] Cycloaddition
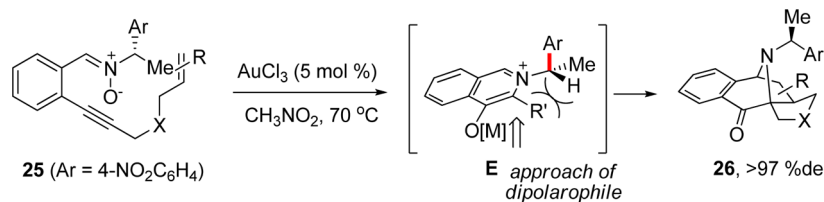


**SCHEME 10.** Cascade Redox–Pinacol–Mannich–(Michael) Sequence: Conversion of Metal Carbenes into Enolate



R = Me **28a** (73 %, dr 14:1)
= Ph **28b** (50 %, dr 10:1)
= CCPh **28c** (60 %, dr 10:1)
= CH=CH₂ **28d** (75 %, dr 14:1)

**28e**
77 % (dr >15:1)

**28f**
60 % (dr >15:1)

**29**
75 % (dr >15:1)

toward the alkyne, producing side-products; and (4) over-oxidation may lead to 1,2-diketo compounds.[22] By using the ynamide **30** as an alkyne component and N-aryl nitrone **31** as an external oxidant for the alkyne, a regioselective alkyne oxygenation occurred, leading to α-amino carbonyl compound **32**. The nitrones played the dual role of nucleophilic

oxidant and source of N-nucleophile (liberated imine) trapping the highly electrophilic gold carbene, thus increasing overall atom economy.

The authors proposed generation of gold carbene **J** for the mechanism of this transformation, based on the observation of a 1,2-H shift (**33**) and *ortho* sp² C–H activation of

the *N*-phenyl group (**34**). In addition, no crossover was observed in the presence of the added imine with a different *N*-Ar substituent. If the hypothesized gold carbene route is involved, the process should occur through a tight ion-dipole pair. However, ambiguity remains regarding the sequence of N−O bond breaking (Scheme 12). For example, in the formation of **33**, N−O bond cleavage may be coupled to a 1,2-H shift or elimination of a $\gamma$-proton from **L** in a concerted manner. In addition, the *N*-aryl C−H activation leading to **34** might proceed through [3,3]-rearrangement of intermediate **M**.[23] The nature of N−O bond cleavage will be further discussed in section 7.

## 5. Gold-Catalyzed N−O Bond Cleavage of Hydroxylamines

Oxoamination of alkynes represents one of the most atom-economical approaches for synthesizing α-amino carbonyl compounds (Scheme 13A), an important building block in

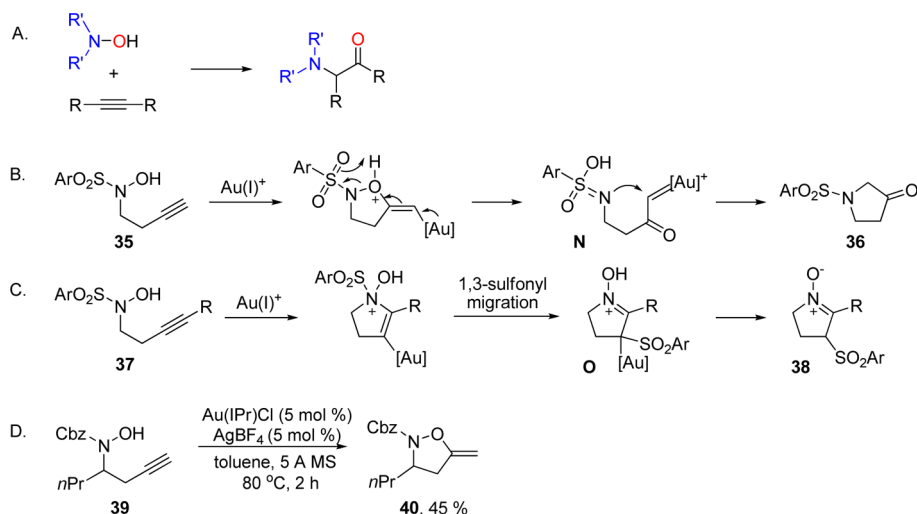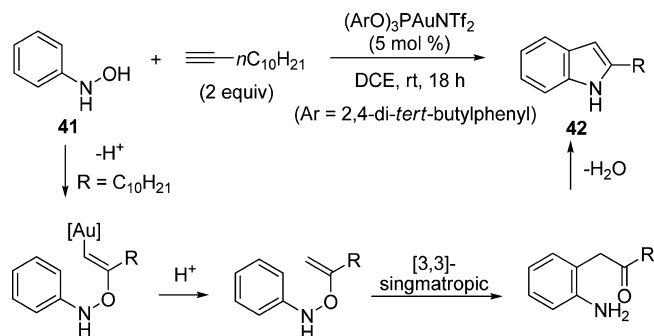**SCHEME 11.** Oxoamination of Alkynes by Intermolecular Redox by Alkynes
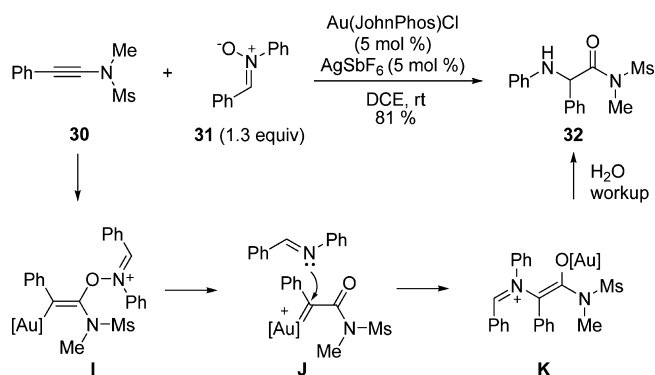


**SCHEME 12.** Alternative Pathways for the Oxoamination of Alkynes
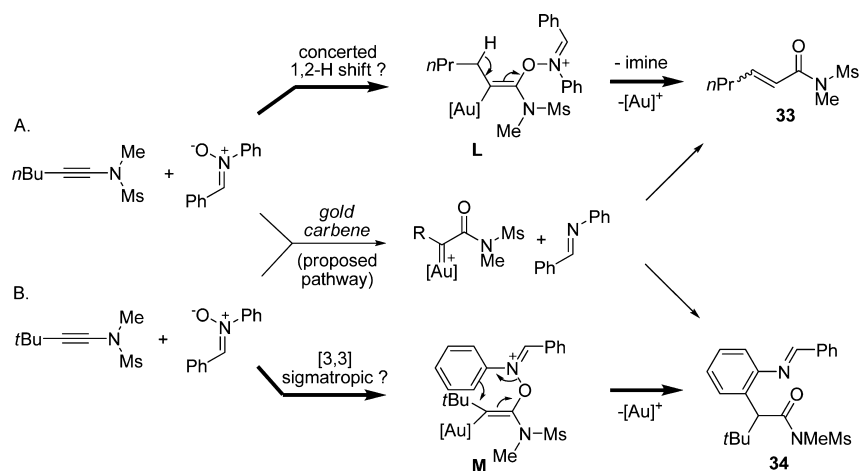


**SCHEME 13.** Oxoamination of Alkynes by Intramolecular Redox by Alkynes

**SCHEME 14.** Gold-Catalyzed Regioselective Fischer Indole-Type Synthesis



organic chemistry and biology. Gold catalysis enabled the addition of tethered hydroxylamines on alkynes.[24] Hydroxylamine such as **35** or **37** is a bifunctional (N or O) nucleophile, and the addition of hydroxylamines onto alkynes occurs through either N-attack or O-attack, depending on the alkynyl substituents. Intramolecular 5-*exo* O-attack of terminal alkyne substrate **35** was followed by N−O cleavage, which presumably led to an electrophilic α-oxo gold-carbene **N** that subsequently underwent formal N−H insertion to provide **36** (Scheme 13B). In contrast, internal alkyne substrates **37** underwent an alternative 5-*endo* N-attack on the alkyne. The subsequent 1,3-sulfonyl migration from **O** ultimately led to nitrones **38** after proton transfer (Scheme 13C). For the key N−O bond cleavage, a strong electron acceptor (ArSO$_2$) must be present at the N-atom. Otherwise, the reaction stops at the simple O-addition to give **40**, supporting the ionic character in the N−O cleavage step (Scheme 13D).[25]

The intermolecular redox chemistry of hydroxylamine was examined by Zhang et al. in the context of Fischer indole synthesis (Scheme 14).[26] In Fischer indole synthesis, controlling the regioselectivity of hydrazine condensation with nonsymmetrical ketones presents a significant challenge. This issue was successfully addressed by the Au-catalyzed Markovnikov O-addition of hydroxylamines **41** onto terminal alkynes. The subsequent [3,3]-sigmatropic rearrangement led to various 2-alkylindoles **42**.

## 6. Intermolecular Alkyne Oxygenation

Most of the reactions discussed thus far have involved the intramolecular oxygenation of alkynes, in which substrates with an N−O oxidant were tethered to the alkynes (internal oxidant). Outside the scope of this Account, versions of intermolecular alkyne oxygenation that use pyridine-*N*-oxide derivatives deserve some comment. By having an external oxidant, product diversity is not limited to the

residual atoms of the oxidant, and there is no need to preassemble appropriate substrates. Zhang et al. first developed external alkyne oxidation in 2010 using pyridine-*N*-oxides.[27] Unlike nitrones, these pyridine-*N*-oxides are reluctant to undergo [3 + 2] dipolar cycloadditions with alkynes and can participate as outer-sphere oxidants on a Au-coordinated alkyne. This external oxygenation strategy was widely successful in O−H/N−H insertion,[28] 1,2-H shift for the synthesis of α,β-unsaturated carbonyls,[29] C−H insertion,[30] cyclopropanation,[31] and halide abstraction from solvents.[32]

## 7. Involvement of the Gold Carbenes in the Cleavage of N−O Bond?

In the preceding reactions of oximes, nitrones, or hydroxylamines, N−O bond cleavage has been rationalized by a postulated gold-carbene species with a double bond between Au and the carbenic carbon.[33] The true nature of bonding in these reactive intermediates has been a topic of intense theoretical and experimental study.[34] Bonds in Au(I)−carbene complexes fall into a continuum between Au(I)-stabilized singlet carbene (with a bond order less than or equal to one) and Au(I)-coordinated carbocation. The nature of bonds strongly depends on the carbene substituents and ancillary ligands on gold. Although Fischer-type gold-carbene complexes with π-donor carbene substituents (such as OR and NR$_2$) have been structurally characterized by X-ray diffraction analysis,[35] crystallographic data of complexes without such π-donor substituents are not available. The closest example is a benzylidene complex [IMesAu=CHPh]$^+$ that has been generated from the ylide precursor by electrospray ionization, which was characterized by tandem mass spectroscopy.[36]

Experimental evidence supporting the involvement of α-oxo gold carbenes is still lacking, and their involvement has been refuted in a number of studies.[30,37] It is likely that the key N−O cleavage step may be concerted with a 1,2-H (or alkyl) shift (Schemes 10 and 12A) or a S$_N$2′ attack.[38] In addition, a [3,3]-sigmatropic shift[23,37b] is possible in many cases (Scheme 12B), and the *antarafacial* [1,3]-sigmatropic shift for N−O cleavage has not been completely ruled out.[39]

Facile 1,2-H (or alkyl) shifts or C−H insertions have frequently been cited as supporting evidence for the existence of gold-carbenes. However, an increasing number of reports show that N−O cleavage may not necessarily be accompanied by gold-carbene intermediates.[37,40] The oxygen exchange reaction from tertiary amine-*N*-oxides to alkynes (**41** into **42**) is one such example (Scheme 15) that has been examined by DFT computational study

**SCHEME 15.** Mechanism Proposed for the Rearrangement of Alkynyl Amine-*N*-Oxides[a]
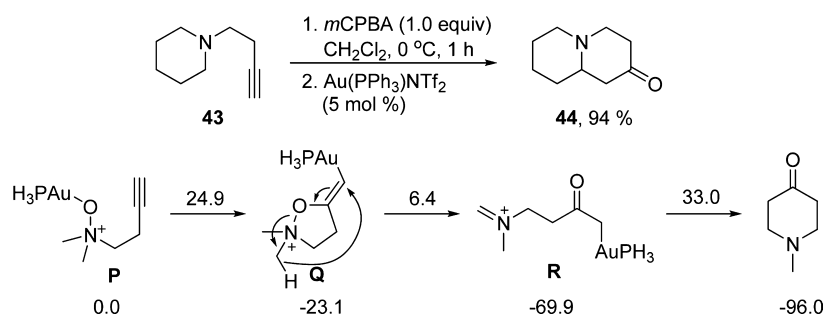


[a]Relative free energies and activation energies (in kcal/mol) are shown below the structure and above the reaction arrows, respectively, as determined by B3LYP-D3.
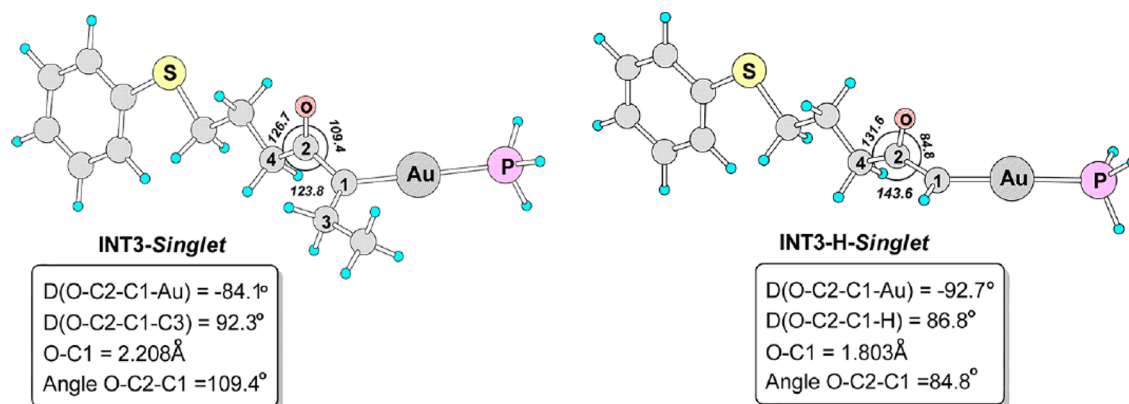


**INT3-*Singlet***

D(O-C2-C1-Au) = -84.1°
D(O-C2-C1-C3) = 92.3°
O-C1 = 2.208Å
Angle O-C2-C1 =109.4°

**INT3-H-*Singlet***

D(O-C2-C1-Au) = -92.7°
D(O-C2-C1-H) = 86.8°
O-C1 = 1.803Å
Angle O-C2-C1 =84.8°

**FIGURE 2.** Optimized DFT-structure of α-oxo gold singlet carbene.

(B3LYP-D3/LANL2DZ level).[37a] Notable conclusions of this computational study include the following: (1) preferential coordination of Au^{+} onto the O-atom of amine-*N*-oxides rather than alkynes; (2) *cis*-addition (inner-sphere mechanism due to strong coordination of $R_3N^+-O^-$ to Au) onto alkynes rather than *trans*-addition (**P** into **Q**); and most importantly, (3) a concerted hetero retro-ene pathway (1,5-hydride shift, **Q** into **R**) favored over a gold carbene route for cleavage of the N−O bond. While the former process has an activation barrier of 6.4 kcal/mol, the alternative α-oxo carbene pathway was determined to have a much higher barrier (25.6 kcal/mol). The gold-catalyzed retro-ene pathway has much lower activation energy (by ∼10 kcal/mol) than the uncatalyzed reaction, highlighting the important role of gold in this transformation.[40] In some cases, metal-free C(sp[3])-H functionalization of *o*-alkynyl aniline derivatives was also reported using pyridine-*N*-oxides as external oxidants.[41]

The structure of α-oxo gold carbene has been computationally studied (Figure 2).[37b] The minimized conformation of the α-oxo gold carbene structure shows that the dihedral angle between C=O and $C_\alpha-C_\beta$ bonds is nearly perpendicular and that the carbonyl oxygen is tilted toward

the gold-bound $C_\alpha$ carbon, especially for structures without substituents at the α-carbon. This indicates donation of electron density from the carbonyl oxygen into the empty p-orbital of Au−C. For sulfoxide redox reactions with terminal alkynes, the [3,3]-sigmatropic pathway is favored over the carbene pathway by 3.2 kcal/mol in accordance with Ujaque, Asensio, and co-workers.[23] With internal alkynes, the gold-carbene intermediate occurs at a relatively shallow local minimum with a barrier of 2.3 kcal/mol en route to a 1,2-H shift.

These alternative mechanisms should be considered in future experimental and computational studies, because these mechanistic possibilities will have implications in reaction design. For example, the mechanisms will impact the design of asymmetric reactions and diverse intermolecular reactions based on N−O bond redox chemistry.

## 8. Alkyne Oxygenation by Other Metals Using N−O Bond Oxidants: Metal Alkylidene Intermediates

Before closing this Account, other metal-mediated catalytic oxygenations of alkynes that employ N−O bond-based oxidants will be highlighted. One intriguing aspect in this

regard is the possibility of obtaining opposite regioselectivity in alkyne oxygenation (path B, Scheme 16). The most notable examples involve metal (Ru and Rh) vinylidene intermediates that subsequently undergo oxygenation by N—O bond-based reagents.

In 1999, Trost and co-workers reported that the cyclization of homopropargyl alcohols **45** by Ru(I) complexes led to cyclic oxacarbene Ru-complex **T** via a Ru-vinylidene complex **S**. Subsequent nucleophilic oxidation by *N*-hydroxysuccinimide led to lactone products **46** (Scheme 17A).[42] Liu and co-workers reported that Ru-catalyzed oxygenative cyclization of alkynyl nitrones **47** led to regioisomeric isoquinolinone **48** rather than an azomethine ylide, which was rationalized by the oxygenation of Ru-vinylidene **U** to ketene **V** (Scheme 17B).[43] Recently, Lee and co-workers showed that Rh-vinylidenes can be oxygenated to give

ketenes **W** that undergo intermolecular addition of various nucleophiles, such as alcohols and amines (Scheme 17C).[44] Tang and co-workers demonstrated that Rh-carbene **X** underwent metathesis with pendant alkynes to give a new carbene **Y** that could be trapped to provide carbonyl functionality in **51**.[45]

## 9. Concluding Remarks

Catalytic oxygenation of alkynes leads to an α-oxo gold carbene synthon with diverse synthetic ramifications. Such a reactive intermediate is readily formed by reacting oxidants with N—O bonds and gold-activated alkynes. α-Oxo gold carbenes have been postulated in intramolecular reactions, prompting diverse synthetic applications. Complex cascade transformations have been realized, including dipolar cycloaddition, N—H insertion and 1,2-alkyl (or H) shift. With the advent of intermolecular oxygenation based on pyridine-*N*-oxides, this alkyne oxygenation strategy has significantly expanded its scope. The mechanistic pathways involved in the reaction of N—O bond oxidants with alkynes can be explained by the *in situ* formation of gold carbenes. However, at least in some cases, concerted mechanisms bypassing a discrete gold carbene can also explain the reaction outcomes. This aspect should be addressed in future reaction design and mechanistic studies. Given the

**SCHEME 16.** Switch of Regioselectivity in Alkyne Oxygenation
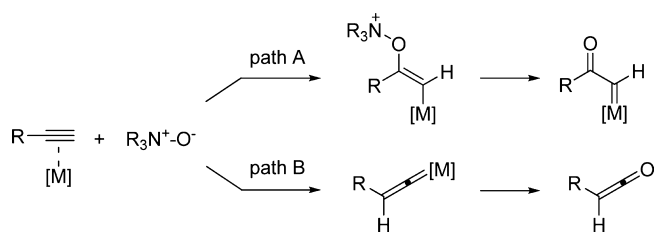


**SCHEME 17.** Oxidation of Terminal Alkynes into Metal-Alkylidenes via N—O Oxidants
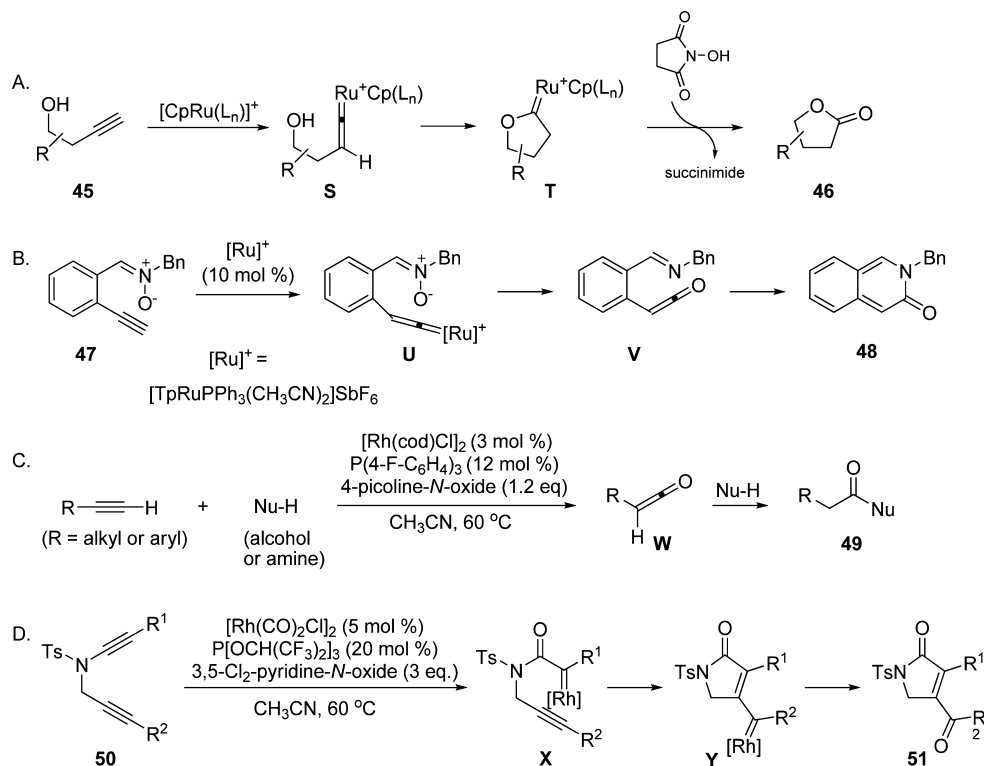
lack of a general rule in terms of the choice of catalysts and oxidants, introduction of new types of ligands and oxidants (possibly other than pyridine-*N*-oxides) is certainly warranted.[46] Finally, asymmetric variants based on alkyne oxidation by N−O bond oxidants will be a challenging but intriguing subject.

## BIOGRAPHICAL INFORMATION

**Hyun-Suk Yeom** received his Ph.D. in 2012 under the guidance of Prof. Shin at Hanyang University. He then began his postdoctoral study at the University of Wisconsin under the guidance of Prof. Richard Hsung. He then returned to Korea as a senior researcher at Korean Research Institute of Chemical Technology (KRICT). His present research interest involves development of ecofriendly agrochemicals.

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