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Gold-catalyzed O-transfer involving alkynes and nitriles as a straightforward diazo-free route to oxazoles

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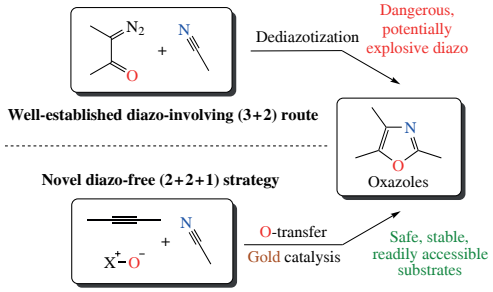
In the recent years, the synthesis of oxazoles *via* (2+2+1) gold-catalyzed oxygen-transfer reactions involving alkynes and nitriles has become a dynamic field of study. The practical utility of this straightforward diazo-free method has been illustrated through a number of publications, among which are findings from our research group. This focus article aims to present a comprehensive critical analysis of the current progress made in the area, including advantages, limitations, and future prospects for the practical application.



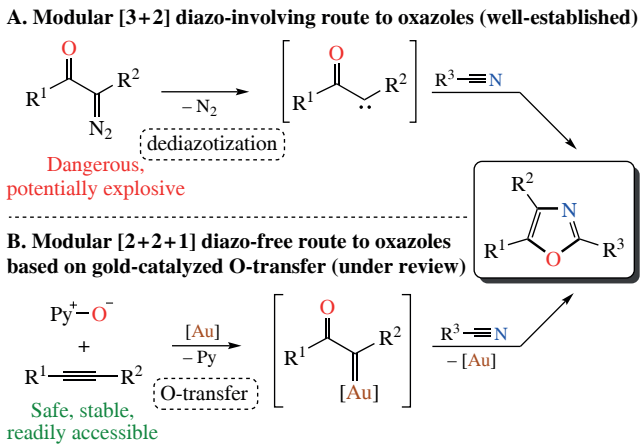
Keywords: gold catalysis, homogeneous catalysis, alkynes, nitriles, oxazoles, heterocycles, oxidation.

Introduction

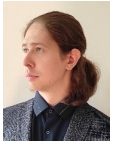
The realm of 1,3-oxazoles is identified as one of the most fascinating area of modern heterocyclic chemistry.[1] The oxazole core serves as an important structural element in pharmaceuticals,[2,3] functional materials,[4,5] agrochemicals,[6] and catalysts.[7,8] Oxazoles can be prepared from either α-amino acids or proteins, thus establishing these heterocycles as genetically related to natural products.[9–11] The role of oxazoles as synthetic intermediates facilitates a wide range of practical transformations in target-oriented synthesis.[12] Notably, significant variability in substituents at the positions 2, 4 and 5 is essential for the diverse applications of oxazoles. Consequently, there is high demand for methods that streamline the synthesis of functionalized oxazoles or enable access to previously unexplored substitution patterns.

While numerous methodologies for the assembly of multisubstituted oxazoles have been documented, the further development of rapid, flexible, and efficient synthetic approaches to oxazoles continues to be a vital area of modern research.[13,14] In this context, the synthesis of oxazoles *via* a modular (3+2) assembly involving α-diazo carbonyl compounds[15–18] and nitriles appears particularly advantageous [Scheme 1(A)]. These dediazotization reactions driven by metal complexes[19,20] (predominantly rhodium),[21] Lewis[22]/Brønsted[23] acids, and visible light,[24] have been the subject of active investigation in recent years. The primary strong point of this methodology based on the generation of α-oxo carbene and carbenoid intermediates is the ability to produce oxazole cores in a single step using readily available building blocks.[25] However, the instability and potentially explosive nature of diazo compounds, along with their hazardous azide precursors, severely restrict the practical applications of this synthetic approach.[26–28]

At the beginning of the new millennium, it became apparent that cationic gold, characterized by its outstanding π-philic properties, can effectively activate chemically inert alkyne triple bonds.[29] The discovery of numerous gold-catalyzed reactions



Scheme 1



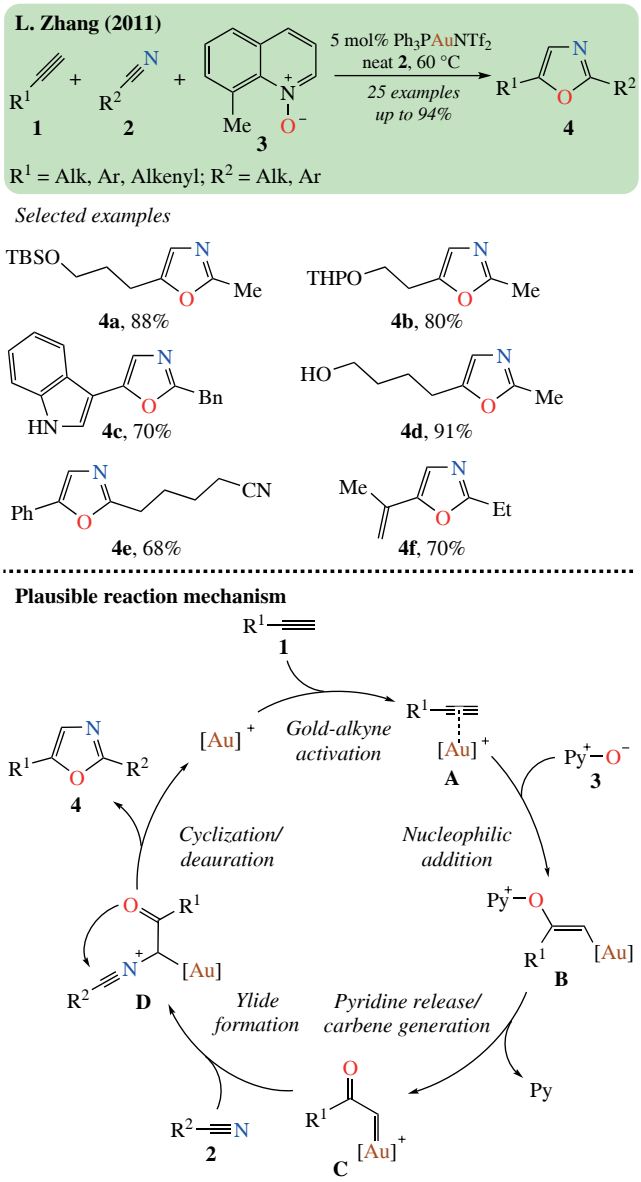
Alexey Yu. Dubovtsev, born in 1992 in Yurla, (Perm Krai, Russia), earned his degree from Perm State University in 2014. He pursued research on the chemistry of pyrroles at the same institution, culminating in a PhD degree in chemistry in 2017. The same year, he joined Professor V. Yu. Kukushkin's research group at Saint Petersburg State University as a postdoctoral researcher and currently leads a research team focused on metal-promoted transformations and their synthetic applications.

involving alkynes marked a new 'golden era' in the domain of metal complex catalysis.[30–42] In particular, gold-catalyzed oxygen transfer to alkynes has emerged as a robust methodology for the construction of oxygen-containing products.[43–45] This redox transformation, utilizing safe starting materials (alkynes as substrates and various nucleophilic O-transfer reagents) for the facile generation of highly reactive gold α-oxo carbenes, is considered a convenient alternative for syntheses using diazo compounds.[46]

Zhang reported the first diazo-free oxazole synthesis based on the reaction of nitriles and gold α-oxo carbenes generated *via* the gold-catalyzed O-transfer methodology.[47] Since then, the (2+2+1) gold-catalyzed annulation of alkynes, pyridine *N*-oxides (as O-transfer reagents), and nitriles (as C=N synthons) has been recognized as an effective approach for the modular construction of the oxazole scaffold [Scheme 1(B)]. The efficacy of this novel diazo-free synthetic strategy has been corroborated by many recent works utilizing various classes of alkyne substrates for the one-step assembly of polysubstituted oxazoles; a number of studies in this rapidly evolving research field have been published by our research group.

The presented focus article aims to systematically analyze the existing literature concerning the diazo-free synthesis of oxazoles through the gold-catalyzed O-transfer (2+2+1) reactions involving alkynes and nitriles. The impetus for publishing of this review stems from the absence of a comprehensive exploration of the selected topic. While one of the most relevant reviews published in 2025[48] examines various reactions catalyzed by gold that yield oxazole products, the pertinent processes based on gold-catalyzed O-transfer have only been partially addressed therein. Moreover, the last extensive review on gold-catalyzed O-transfers was published in 2021,[43] and it does not account for the new findings presented in this review.

The focus article is structured chronologically, highlighting the chemical characteristics of the alkynyl substrates used. The first part of the review considers reactions of terminal alkyne substrates, which consequently lead to 2,5-disubstituted oxazoles. The second part is devoted to reactions of internal alkynes used for the synthesis of fully substituted oxazoles.



Scheme 2 Synthesis of oxazoles **4** from terminal alkynes and nitriles according to Zhang.[47]

Oxazole syntheses based on gold-catalyzed O-transfers involving terminal alkynes

The pioneering research presented by Zhang and coworkers describes an efficient synthetic methodology providing 2,5-disubstituted oxazoles *via* gold-catalyzed intermolecular alkyne oxidation (Scheme 2).[47] This reaction represents the first successful intermolecular reaction of gold α-oxo carbene intermediates generated through gold-catalyzed O-transfer to alkynes. The reaction works well with terminal alkyne substrates **1** in combination with nitriles **2** as both reaction partners and solvents. Various pyridine *N*-oxides were tested as O-transfer reagents, and the best results were achieved using 8-methylquinoline *N*-oxide **3** at 60 °C for 3 h. Among the examined gold catalysts, $Ph_3PAuNTf_2$ and $BrettPhosAuNTf_2$ exhibited exceptional catalytic performance at low loadings (1–5 mol%).

The method demonstrated good scope, producing over 25 different 2,5-disubstituted oxazoles **4** with yields mostly above 80%. A standout feature of this methodology is its exceptional compatibility with diverse functional groups under mild gold-catalyzed reaction conditions. The reactions tolerated unprotected hydroxy groups, free carboxylic acids, acid-labile protective groups (TBSO, THP, Boc), oxidizable functionalities (PhS), alkyl halides, and various aryl groups with different electronic and steric properties. This wide functional group tolerance is particularly valuable in complex molecule synthesis, where protecting group strategies often complicate synthetic routes. A weakness of the methodology is the need to use nitriles as solvents; nonetheless, for expensive or commercially unavailable nitriles, the researchers demonstrated that only three equivalents could be sufficient without solvent.

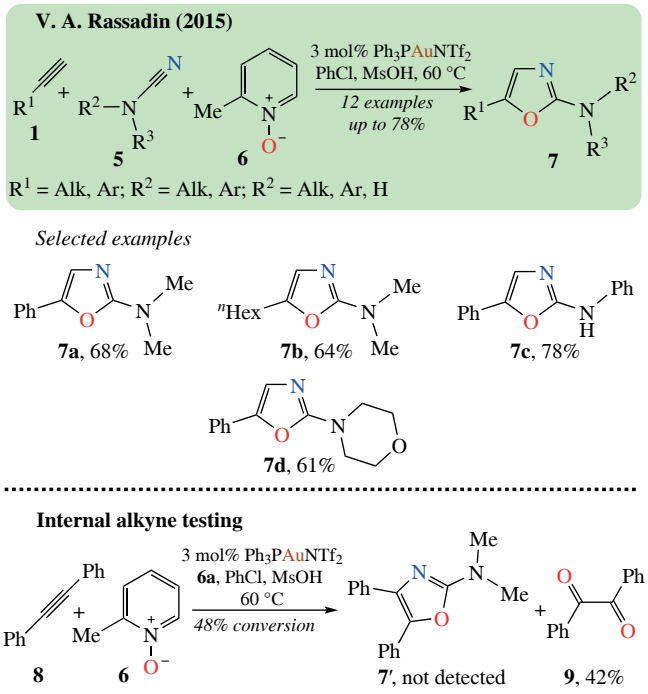
Control experiments confirmed the specific catalytic role of gold, as neither $AgNTf_2$ nor $HNTf_2$ could catalyze the reaction. This underscores gold's distinctive ability to activate alkynes and to facilitate carbene formation *via* oxidation. Several side reactions were identified, primarily with specific alkyne substrates. With propargylic alcohols and their derivatives, intramolecular trapping of the α-oxo gold carbene intermediates became competitive resulting in lower yields of the desired oxazoles.[49] Similarly, homopropargylic alcohols performed poorly unless protected. Propargyl and homopropargyl bromides were also unsuitable substrates.

Mechanistically, the synthesis of 2,5-disubstituted oxazoles initiates with the coordination of alkyne **1** to cationic gold, thereby producing complex **A**. Following this, a nucleophilic addition of pyridine *N*-oxide **3** occurs at the activated C≡C bond, resulting in gold vinyl intermediate **B**. The release of pyridine then triggers the generation of a highly electrophilic gold α-oxo carbene **C**, which is subsequently subjected to a

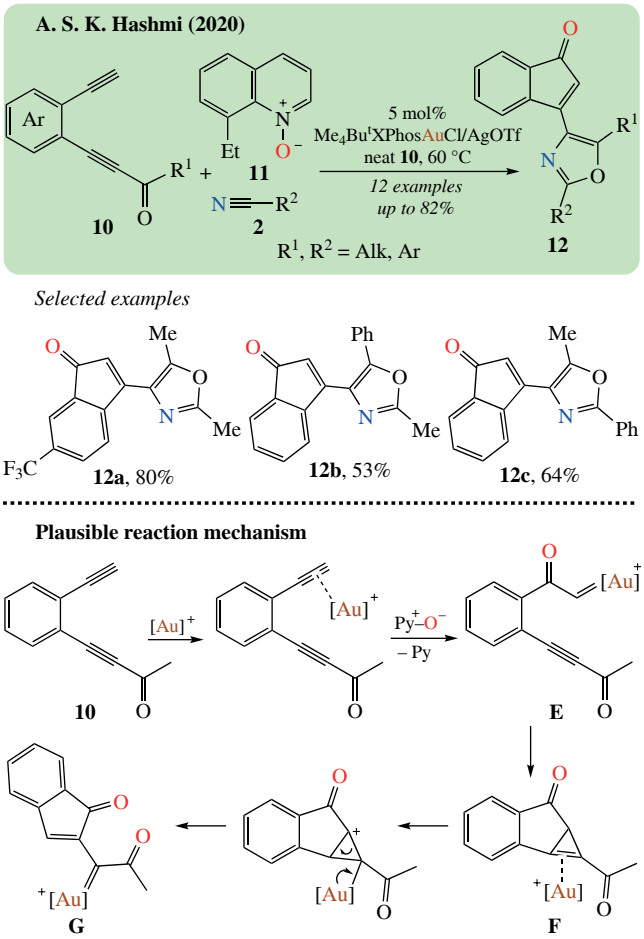
nucleophilic attack by nitrile **2**. The resulting gold ylide **D** is then undergoes cyclization to form an aromatic oxazole ring, accompanied by the deauration and the regeneration of the gold catalyst. The high concentration of nitriles (when used as solvents) ensured that the carbene intermediates reacted preferentially with nitriles rather than with oxidants or their reduced forms, which would lead to unwanted side reactions. This mechanism can be applied to rationalize all the gold-catalyzed O-transfer reactions of alkynes and nitriles leading to oxazoles described below.

The scope of this methodology discovered by Zhang was further extended by other researchers who synthesized nine new 2,5-disubstituted oxazoles under very similar gold-catalyzed conditions; the antiproliferative activity of the resulting oxazoles was also studied.[50] Another innovation proposed by Cai was to replace homogeneous gold catalysts with heterogeneous ones: this allowed the catalyst to be regenerated after the reaction and used up to 8 times without significant loss of activity.[51] The (2+2+1)-assembly of the oxazole framework has also found application for the late-stage functionalization of complex molecules.[52,53]

The research by Rassadin *et al.* presents a novel gold-catalyzed heterocyclization reaction between terminal alkynes **1** and cyanamides **5** to produce 5-substituted 2-aminooxazoles **7** (Scheme 3).[54] The reaction employs $Ph_3PAuNTf_2$ (3 mol%) as the catalyst, MsOH as a co-catalyst, and 2-picoline *N*-oxide **6** as an oxidant at 60 °C for 2 h. This methodology effectively transforms readily available starting materials including phenylacetylene derivatives, terminal aliphatic alkynes, and mono/disubstituted cyanamides into 2-aminooxazoles with good to moderate yields (56–78%). The 2-aminooxazole products obtained through this methodology are functionalized at both the nitrogen atom and the position 5 of the heterocyclic ring, offering structural diversity. Previous methods for synthesizing 2-aminooxazoles were rather limited, and this work expands the synthetic toolbox for accessing these biologically relevant heterocycles.[55,56] The gold-catalyzed reaction proceeds better when cyanamides are used as solvents, but their excess can be reduced to three equivalents. The role of methanesulfonic acid as a co-catalyst is to prevent poisoning[57] of the gold catalyst by 2-picoline, which is formed during oxygen transfer. Additionally, when using the internal diphenylacetylene **8** instead of terminal alkynes, the reaction primarily yielded 1,2-diphenylethane-1,2-dione **9** (42%) rather than the expected oxazole **7′**.



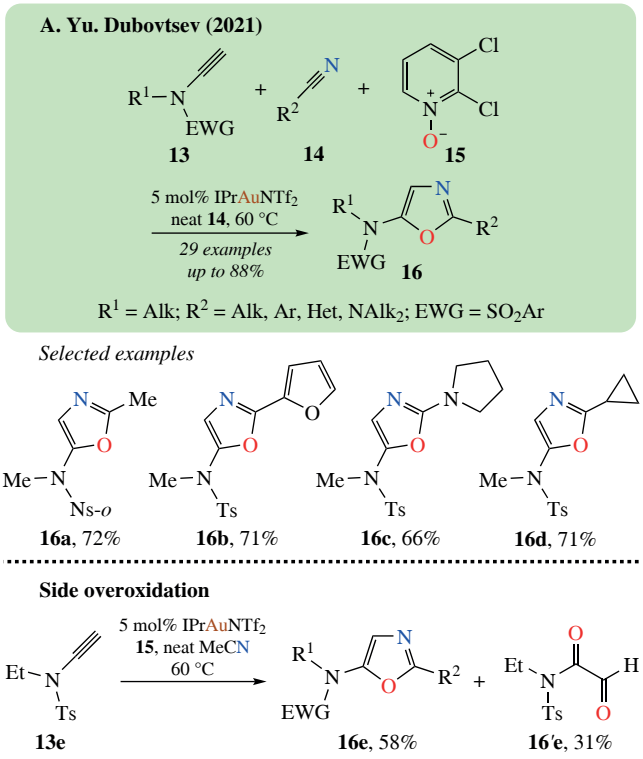
Scheme 3 Synthesis of 2-aminooxazoles **7** from terminal alkynes and cyanamides according to Rassadin.[54]



Scheme 4 Synthesis of 3-oxazol-4-yl-1*H*-inden-1-ones **12** from diynes and nitriles according to Hashmi.[58]

The research by Hashmi describes an innovative gold-catalyzed intermolecular oxidative diyne cyclization that proceeds through a 1,6-carbene transfer mechanism.[58] This reaction employs diyne substrates **10** containing one terminal alkyne and one alkyne conjugated to a carbonyl group, which undergo oxidative cyclization in the presence of gold catalysts, *N*-oxides as oxidants, and nitriles **2** as reaction partners (Scheme 4). The optimized conditions utilize 5 mol% $Me_4Bu^tXPhosAuCl/AgOTf$ as a catalyst, 8-ethylquinoline *N*-oxide **11** as an oxidizer in neat nitriles at 60 °C, producing 3-oxazol-4-yl-1*H*-inden-1-ones **12** in good-to-moderate yields (12 examples up to 82%). The limitation observed was the inability to use aldehyde-bearing diyne substrates instead of ketone ones, which the authors attribute to the decreased nucleophilicity of the aldehyde oxygen atom. Additionally, reduced concentrations of nitriles resulted in lower yields.

This study represents a significant advancement in gold-catalyzed transformations by demonstrating that gold carbenes generated through a 1,6-carbene shift can be trapped by intermolecularly offered reagents. Mechanistically, the reaction proceeds through initial π-activation of the terminal alkyne by the gold catalyst, followed by oxygen transfer from the *N*-oxide to generate α-oxo gold carbene **E**. This carbene undergoes intramolecular cyclopropenation with the second alkyne, forming a strained intermediate **F** that experiences ring opening to generate a new α-oxo carbene **G**. This species is then captured



Scheme 5 Synthesis of 5-aminooxazoles **16** from terminal ynamides and nitriles according to Dubovtsev.[59]

by the nitrile, forming an ylide intermediate that undergoes intramolecular cyclization to deliver the final oxazole product **12**, in accordance with the general mechanism (see Scheme 2). This cascade process showcases the unique ability of gold catalysts to mediate complex transformations through the generation and controlled reactivity of carbene intermediates.

Dubovtsev *et al*. presented a gold(I)-catalyzed oxidative annulation involving terminal ynamides **13** (Scheme 5).[59] This reaction efficiently produces 5-aminooxazoles **16** with remarkable regioselectivity compared to that of previously reported methods. The synthetic protocol employs $IPrAuNTf_2$ serving as the optimal gold catalyst, and 2,3-dichloropyridine *N*-oxide **15** as the O-transfer reagent. The scientific novelty of this work lies in the reversed regioselectivity achieved through O-transfer. Previous gold-catalyzed syntheses of aminooxazoles relied on nitrene transfer from *N*-ylides to ynamides, resulting exclusively in 4-aminooxazoles.[60] By contrast, this novel approach generates 5-aminooxazoles through an initial oxygen attack on gold-activated ynamides[61] followed by nitrile trapping. This mechanistic divergence represents a fundamental advancement in synthetic methodology as it enables access to previously challenging substitution patterns in oxazole chemistry.

The reported method demonstrates excellent functional group tolerance, accommodating a diverse range of *N*-sulfonyl protecting groups on ynamides, including electron-donating, electron-withdrawing, and sterically demanding substituents. Similarly, various nitriles **14** (aliphatic, aromatic, and heteroaromatic) and cyanamides participate effectively in the reaction. The researchers synthesized 29 examples of 5-amino- and 2,5-diaminooxazoles with yields ranging from 49 to 88%, demonstrating both synthetic scope and practicality. The methodology was successfully scaled up to gram quantities, further confirming its synthetic utility.

A competing side reaction was observed with internal ynamides, which underwent gold-catalyzed overoxidation to form α-keto amides instead of the oxazole formation. Even terminal ynamides experienced partial overoxidation, as demonstrated in the case of ynamide **13e**, which produced a mixture of oxazole **16e** (58%) and glyoxamide **16′e** (31%). The researchers attributed this to the higher rate of overoxidation compared to that of the desired annulation pathway under the reaction conditions.

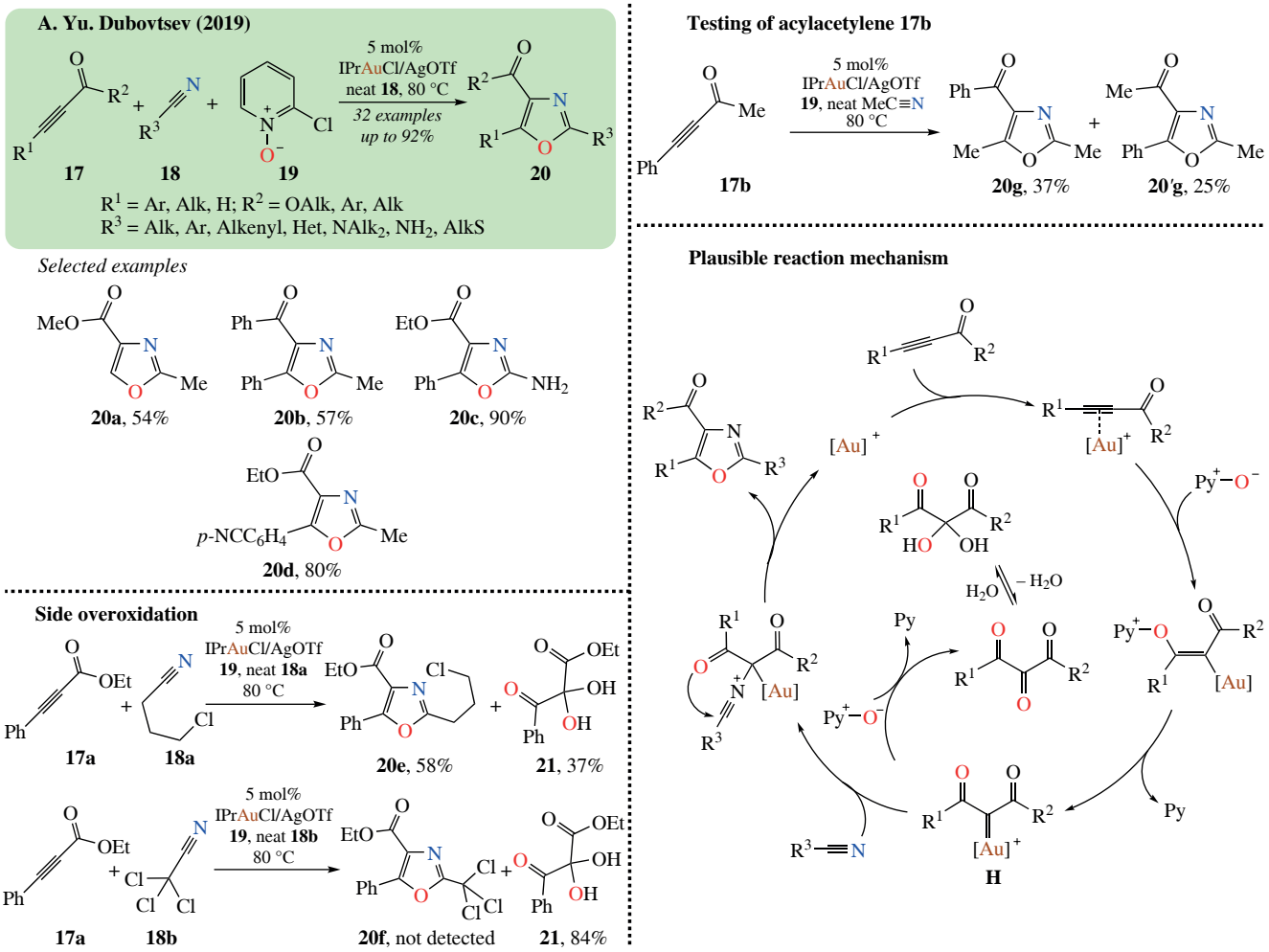
Oxazole syntheses based on gold-catalyzed O-transfers involving internal alkynes

The use of internal alkynes in organic synthesis presents a major challenge. While reactions of terminal alkynes often proceed smoothly, the transition to substrates with an internal triple bond is difficult resulting in both decreased selectivity and reactivity.[62] Dubovtsev *et al*. described a gold(I)-catalyzed (2 + 2 + 1) reaction for the synthesis of fully substituted oxazoles (Scheme 6).[63] The scientific novelty of this research lies in the successful application of internal alkynes. Previous studies observed in this focus article were largely limited to terminal alkynes, and attempts to employ internal alkynes failed. The authors overcame these limitations by using alkyne esters and ketones whose electron-withdrawing groups directed the O-transfer to the β-alkyne position and also stabilized the gold α-oxo carbene intermediate. The reaction conditions combine IPrAuCl/AgOTf (5 mol%) as a catalyst and 2-chloropyridine *N*-oxide as an oxygen donor in neat nitriles at 80 °C. The optimized conditions showed compatibility with various functional groups, achieving good to excellent yields (up to 92%) across 32 examples. The reaction also accommodates push–pull nitriles such as cyanamides and thiocyanates allowing for the synthesis of 2-amino- and 2-thiooxazoles, which are challenging to obtain by other methods. An important feature of the methodology is the ability to incorporate an unprotected NH_2 group at the position 2 of the oxazole ring, which provides opportunities for further derivatization. The presence of an ester or ketone substituent at the position 4 opens additional possibilities for structural modifications *via* reduction or hydrolysis–decarboxylation followed by C–H functionalization.

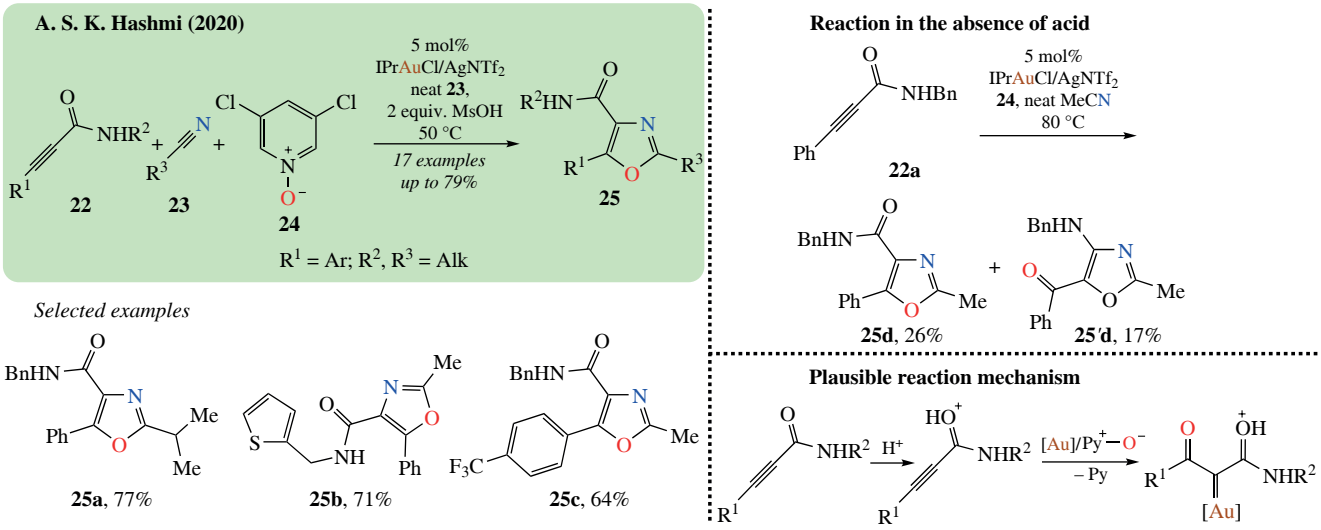
An interesting aspect of the study is the observation of a competing overoxidation pathway.[64] In some cases, especially with less reactive electron-deficient nitriles, the formation of tricarbonyl compounds as by-products became prevalent. For instance, the use of γ-chlorobutyronitrile led to a mixture of oxazole **20e** and tricarbonyl compound **21** in a 3 : 2 ratio; when trichloroacetonitrile was used, **21** was the only reaction product. This overoxidation occurs through the interaction of the gold α-oxo carbene intermediate with another molecule of *N*-oxide. For the case of acylacetylene **17b**, the formation of two isomeric oxazoles **20g** and **20′g** was observed. This can be rationalized by the competition between the two carbonyl groups presented in the α,α′-dioxo carbene intermediate, as well as the potential occurrence of the Cornforth rearrangement.

The proposed mechanism involves initial coordination of the cationic gold fragment to the internal triple bond followed by highly selective nucleophilic β-oxygenation by the pyridine *N*-oxide *via* an addition–elimination process. The resulting gold α,α′-dioxo carbene intermediate **H** undergoes nucleophilic attack by the nitrile to form an ylide that cyclizes to the oxazole product with regeneration of the catalyst. In cases of insufficient nitrile activity, **H** reacts with a second molecule of oxidant to yield a tricarbonyl byproduct.

A year later, Hashmi and coworkers demonstrated that propiolic amides could also be used as internal alkynes in the synthesis of fully substituted 4-amidooxazoles (Scheme 7).[65] This methodology employs 5 mol% $IPrAuCl/AgNTf_2$ and 2 equiv. MsOH as the optimal catalyst system, with 3,5-dichloropyridine *N*-oxide serving as the most effective oxidant for the transformation; the reaction operates under



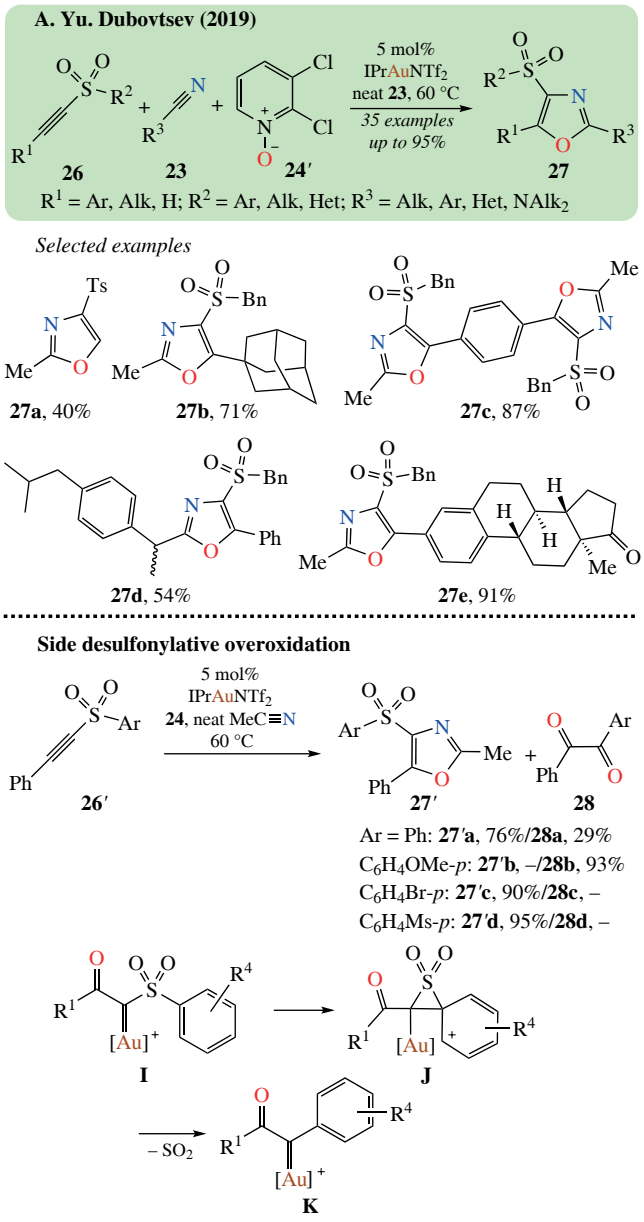
Scheme 6 Synthesis of 4-acyloxazoles **20** from acylacetylenes and nitriles according to Dubovtsev.[63]



Scheme 7 Synthesis of 4-amido-substituted oxazoles **25** from propiolic amides and nitriles according to Hashmi.[65]

relatively mild conditions (50–80 °C) in neat nitriles. One of the key challenges addressed in this work was the suppression of the side reaction: without acidic additives, a mixture of isomeric products (**25d** and **25′d**) was observed when using alkynamide substrate **22a**. The addition of MsOH was crucial for achieving perfect selectivity toward product **25d**, effectively preventing the formation of isomer **25′d**. This is attributed to the acid's ability to decrease the nucleophilicity of the amide group, promoting selective cyclization *via* the ketone functionality. Furthermore, the authors demonstrated that the addition of an acid is not necessary for the relevant synthesis of oxazoles from propiolic esters.

Dubovtsev and colleagues developed an efficient gold-catalyzed annulation of internal alkynylsulfones[66,67] **26** to produce valuable 4-sulfonyloxazoles **27** (Scheme 8).[68] The reaction operates under relatively mild conditions (5 mol% $IPrAuNTf_2$, 2,3-dichloropyridine *N*-oxide, neat nitrile, room temperature or 60 °C), providing a safer alternative to conventional methods that rely on hazardous diazo compounds. The method was successfully applied for the preparation of



Scheme 8 Synthesis of 4-sulfonyloxazoles **27**/**27′** from alkynylsulfones and nitriles according to Dubovtsev.[68]

4-sulfonyl-1,3-oxazoles with 14–95% yields (35 examples). The reaction was also amenable to scale-up, as demonstrated by the gram-scale synthesis of one of the products. Researchers employed their methodology to modify some bioactive molecules, including the steroid estrone and the nonsteroidal anti-inflammatory drug ibuprofen.

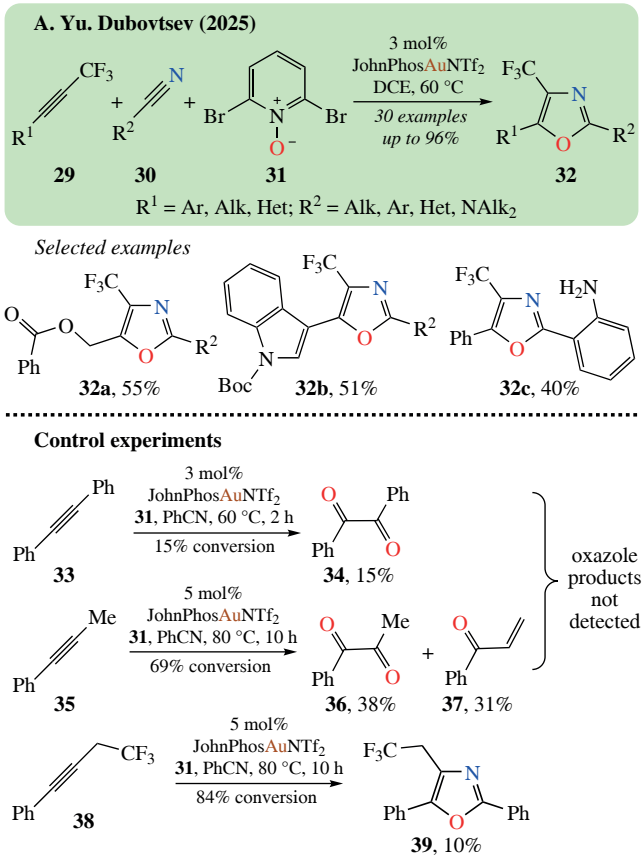
Interestingly, alkynyl sulfone substrates **26′** bearing electron-rich arylsulfonyl substituents were prone to desulfonylation side reactions, resulting in 1,2-diketones as major byproducts. This limitation was overcome by employing substrates containing electron-withdrawing substituents (Br, Ms) on the aryl fragment, which suppressed undesirable desulfonylation.

Based on control experiments, a reaction mechanism rationalizing the formation of 4-sulfonyloxazoles and desulfonylated diketones was proposed. The gold α-oxo carbene **I**, formed according to the standard scheme, can not only react with the nitrile but also undergo cyclization to form thiirane **J**. Species **J**, in turn, is stabilized through the extrusion of SO_2 resulting in carbene intermediate **K**, which yields the corresponding desulfonylated products.

The first example of the use of trifluoromethylated alkynes in gold-catalyzed O-transfer reactions was described very recently (Scheme 9).[69] This approach was extended by Dubovtsev and coworkers to the synthesis of 4-trifluoromethylated oxazoles based on the gold-catalyzed reaction of internal trifluoromethylated alkynes **29**, pyridine *N*-oxides and nitriles. This three-component transformation occurs under relatively mild conditions (3 mol% of JohnPhosAuNTf$_2$, 2,6-dibromopyridine *N*-oxide, in 1,2-dichloroethane at 60 °C; yields up to 96%; 30 examples). The scientific novelty of this work lies in utilizing the inductive mechanism of the CF_3-group to direct O-nucleophilic attack specifically to the β-alkyne position. In contrast, previous gold-catalyzed O-transfer processes with internal alkynes typically employed directing groups operating through mesomeric mechanisms. Unlike the previous reactions described in this section, the synthesis of oxazoles from trifluoromethylated alkynes can be conducted in an inert solvent (1,2-dichloroethane, CH_2Cl_2, PhCl), and the loading of the nitrile can be reduced to fivefold.

The synthesized 4-(trifluoromethyl)oxazoles represent an important family of heterocyclic compounds with significant therapeutic potential, particularly as anticancer agents.[70,71] The fluorinated moiety enhances the bioavailability and metabolic stability of these compounds, making them attractive targets for medicinal chemistry.[72–74] The developed methodology demonstrates excellent functional group tolerance, accommodating various substituents including cyano, nitro, ether, and even oxidation-sensitive sulfide moieties. Importantly, protective groups such as Boc and Bz survive the reaction conditions.

A significant challenge addressed in this work was suppressing the competing double O-transfer pathway, which would lead to the formation of CF_3-containing 1,2-diketones as byproducts. The researchers found that using sterically hindered 2,6-dibromopyridine *N*-oxide **31** as the oxygen source significantly reduced this side reaction by preventing a second oxygen transfer, thus promoting the desired single O-transfer process.



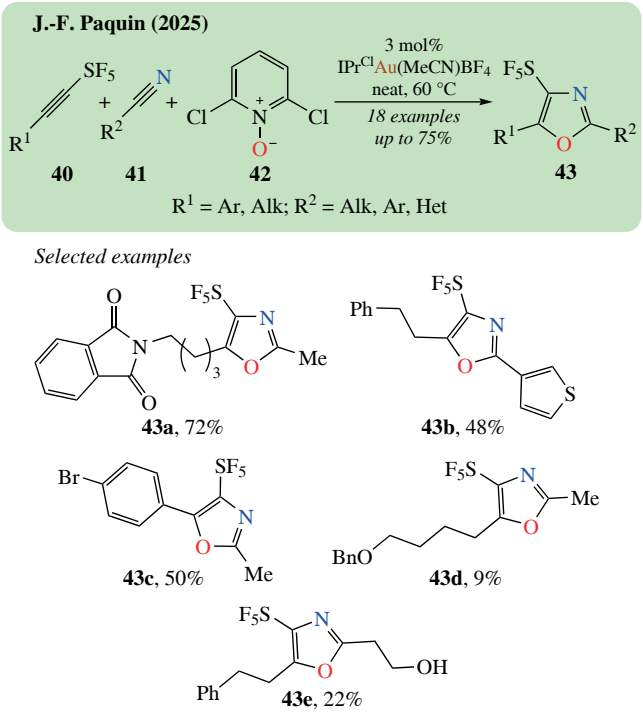
Scheme 9 Synthesis of 4-trifluoromethylated oxazoles **32** from trifluoromethylated alkynes and nitriles according to Dubovtsev.[69]

Control experiments indicate the crucial role of the directing CF_3-substituent. While other internal alkynes **33** and **35** do not yield oxazole products under the optimized conditions, moving the CF_3-substituent from the triple bond leads to the desired product **39**, albeit with a reduced yield. The latter experiment highlights the essential impact of the inductive effect of the directing CF_3-group.

The research by Paquin *et al.* presents a gold(I)-catalyzed formal (2+2+1) cycloaddition between SF_5-alkynes **40**, nitriles, and pyridine *N*-oxides to afford 4-pentafluoro-λ^6-sulfanyl-1,3-oxazoles **43** (Scheme 10).[75] This work establishes the first method for accessing pentafluoro-λ^6-sulfanyl-substituted oxazoles, providing 18 examples with varying structural complexity. The unique properties of the SF_5-group, including its high electronegativity and *tert*-butyl-like steric demand, make these fluorinated oxazoles valuable additions to the toolkit of medicinal and agricultural chemists seeking novel bioactive compounds.

The optimization studies revealed that $IPr^{Cl}Au(CMeCN)BF_4$ emerged as the most effective catalyst providing 75% NMR yield under optimal conditions (3 mol% catalyst loading, 60 °C, 18 h, neat nitrile). The choice of pyridine *N*-oxide proved crucial, with 2,6-dichloropyridine *N*-oxide (**42**) demonstrating superior performance compared to its dibromo analogue or differently substituted variants. Despite the promising NMR yields, the isolation of pure products presented significant challenges due to the chromatographic properties of the desired oxazoles: reverse-phase flash chromatography was employed to address these purification difficulties, though isolated yields remained modest (up to 52%).

The proposed mechanistic pathway involves initial complexation of SF_5-alkyne to the gold catalyst followed by nucleophilic attack from pyridine *N*-oxide at the distal carbon atom of the alkyne. The observed β-O-transfer regioselectivity stems from the electronic properties of the SF_5-group, which creates a pronounced electronic gradient along the alkyne. The reaction further proceeds through either a gold α-oxo carbene intermediate or *via* direct S_N2' attack of the nitrile, ultimately leading to cyclization and regeneration of the catalyst.



Scheme 10 Synthesis of 4-pentafluorosulfanylated oxazoles **43** from SF_5-alkynes and nitriles according to Paquin.[75]

Conclusion

Gold-catalyzed O-transfer represents an innovative method for the synthesis of oxazoles without using potentially hazardous diazo compounds. This approach is based on the ability of gold cations to activate alkynes for nucleophilic addition and to facilitate the formation of highly reactive gold α-oxo carbenes. Since the pioneering work of Zhang, this methodology has significantly expanded and now encompasses various classes of alkynes and nitriles for constructing a wide spectrum of polysubstituted oxazoles in the single-step.

The general mechanism of these transformations begins with π-activation of the alkyne by the cationic gold catalyst, followed by nucleophilic attack by the *N*-oxide. This leads to the formation of a gold α-oxo carbene intermediate, which undergoes nucleophilic attack by the nitrile to form an ylide intermediate. Finally, cyclization occurs to form the oxazole ring with regeneration of the catalyst.

Various classes of alkynes have been successfully employed in this transformation. Terminal alkynes, including arylacetylenes and aliphatic terminal alkynes, generally provide 2,5-disubstituted oxazoles in good to excellent yields. Internal alkynes, which traditionally present challenges in organic synthesis due to decreased selectivity and reactivity, have also been effectively utilized through careful substrate design. These include alkyne esters and ketones, alkynylamides, alkynyl sulfones, and CF_3/SF_5-containing alkynes. Specialized substrates such as diynes and terminal ynamides have further expanded the scope of this methodology. The nitrile component demonstrates similar versatility, with aliphatic, aromatic, and heteroaromatic nitriles all participating effectively in the reaction. Push–pull nitriles such as cyanamides and thiocyanates enable the synthesis of 2-amino- and 2-thiooxazoles, which are challenging to obtain by other methods. This diversity in both alkyne and nitrile partners allows for the construction of oxazoles with customizable substitution patterns.

Typical reaction conditions for these transformations involve gold(I) catalysts at relatively low loadings (1–5 mol%). Various pyridine *N*-oxides serve as effective oxygen donors in these reactions. Nitriles are often used in excess or as solvents, though in some cases, their amount can be reduced to three equivalents. Additional additives, *e.g.*, Brønsted acids, can be employed to prevent catalyst poisoning or suppress side reactions. The reactions typically proceed under mild conditions (from room temperature to 80 °C).

Despite its many advantages, the methodology exhibits some limitations. An inherent feature of the oxazole synthesis based on the O-transfer strategy is the requirement for the use of costly gold catalysts. However, an alternative diazo-free pathway typically involves rhodium catalysis. Considering that rhodium is rarer and considerably more expensive than gold, the gold-catalyzed O-transfer synthesis of nitriles is perceived as a more economically rational choice. Other significant shortcomings of the reviewed diazo-free strategy include: (*i*) the requirement to use nitriles in excess (often as solvents), which can be problematic for expensive or commercially unavailable nitriles; (*ii*) the onset of side reactions, predominantly, the overoxidation. Nevertheless, the aforementioned issues can often be addressed through the optimization of reaction parameters and the selection of suitable O-transfer reagents and gold catalysts.

In the future, several promising research avenues may be explored, including the extension of the methodology to additional classes of alkynes and nitriles, the search for new O-transfer reagents, the design of more effective gold catalysts, further investigation into synergistic catalytic systems, the exploration of relevant cascade processes, and application for total synthesis. The fundamental insights obtained from these

studies have substantially advanced the fields of gold catalysis and heterocyclic chemistry. The demonstrated capability to efficiently construct valuable oxazoles under mild conditions, along with the high tolerance for various functional groups, positions this synthetic strategy as a powerful tool for pharmaceutical chemistry and materials science.

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