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TRANSITION METAL-MEDIATED SYNTHESIS OF OXAZOLES

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Abstract – Among the synthetic methods for the formation of the oxazole ring, transition metal-mediated protocols are the most attractive in terms of selectivity, efficiency and mildness of reaction conditions. In this review we discuss methods for the preparation of oxazoles using transition metal complexes highlighting the key bonds being formed. This reveals critical gaps in the existing literature for the construction of this biologically significant ring system highlighting exciting opportunities for further research.

INTRODUCTION

Oxazoles represent an important class of heterocyclic compound, which are found in numerous natural and synthetic bioactive molecules as well as in a number of organic building blocks. While many methods for assembly of the oxazole ring have been reported to date, the development of efficient, selective and mild synthetic methods for the construction of this important aromatic ring system remains an important contemporary research topic. This is especially the case for multicomponent methods where the potential for array synthesis exists. Protocols employing transition metals play a major role in this context, since the transformations involved in these methods frequently proceed through catalytic domino and/or multicomponent cascades with key bond construction processes being mediated by unique properties of the metal.

This review describes synthetic protocols in which transition metal complexes mediate formation of the oxazole ring. The majority of these transformations, driven by the transition metal complexes, involve nucleophilic additions to activated C—C multiple bonds, cycloaddition reactions and N—H insertion reactions of carbenoids, C—H activation processes, cross-coupling reactions and ring enlargement processes are also operative in a number of protocols. The transition metal can be involved in the synthesis of a key intermediate and/or in the cyclisation of such a species, which leads to assembly of the oxazole core. These protocols employ both catalytic and stoichiometric amounts of either a single or a combination
of transition metals with salts of zinc and mercury being included for completeness. The sections in this review are organised based on the specific bond(s) being formed and transition metal employed. A brief mechanistic discussion, if provided in the original manuscript, is also included. Transition metal-mediated protocols for the synthesis of benzoazoles and for the functionalisation of oxazoles are not described.

Oxazole (Figure 1) is a weakly basic aromatic compound with three potential points of substitution, C2, C4 and C5. Throughout this review key bonds for the disconnection of this molecule are used within the division of sections. The order of presentation reflects the number of publications describing each specific strategy.

![Figure 1. The oxazole unit](image)

**O1–C2 AND N3–C4 BOND DISCONNECTIONS**

**RHODIUM(II)**

By far the most explored method for the preparation of oxazoles using transition metal catalysis involves the reaction of a diazo compound and a nitrile substrate in the presence of a Rh(II) species. In 1986, Helquist described the preparation of trisubstituted oxazoles 3 through the Rh(II)-catalysed decomposition of dimethyl diazomalonate 1 in the presence of a nitrile 2 (Scheme 1).\(^2\)–4 The majority of nitriles 2 reacted with 1 to deliver 3 in good to excellent yields apart from nitriles containing C=C double bonds or free hydroxyl groups which resulted in competitive insertion products lowering the yield of oxazole. Despite these limitations this overall strategy has evolved to provide a robust and efficient method to construct oxazoles.

![Scheme 1. Rh(II)-catalysed synthesis of oxazoles 3](image)

R\(^1\) = Ph, 4-ClC\(_6\)H\(_4\), 4-MeC\(_6\)H\(_4\), 4-MeOC\(_6\)H\(_4\), 4-NO\(_2\)C\(_6\)H\(_4\), 3-ClC\(_6\)H\(_4\), PhCH\(_2\), PhCH=CH, Me, n-Pr, Me(CH\(_2\))\(_2\)CH\(_2\), i-Pr, t-Bu, MeCH=CH, CH\(_2\)=CHCH\(_2\), HOCH\(_2\)CH\(_2\), EtOCH=CH

i) 1 (1.0-2.0 eq), 2 (3.6-8.0 eq), Rh\(_2\)(OAc)\(_4\) (0.5-1.0 mol%), CHCl\(_3\) or C\(_2\)H\(_4\)Cl\(_2\) or neat, rt then reflux, 8-29 h.

The applicability of this transformation was extended by Helquist, who described the regioselective preparation of 2,4-disubstituted oxazoles 5 through the Rh(II)-catalysed decomposition of ethyl...
formyl diazomalonate 4 in the presence of nitrile 2 as the solvent (Scheme 2). The reaction proceeds via the 1,3-dipolar cycloaddition of a metal carbenoid 7 and a nitrile 2 to give 5 (Scheme 2, Pathway A) or more plausibly, via the formation of a carbene complex 8, which reacts with 2 to generate a nitrile ylide 9 followed by cyclisation to give 5 (Scheme 2, Pathway B). This protocol provides a convenient method for the rapid synthesis of a range of 2,4-disubstituted oxazoles in good yield. A limitation of this work was the competing dimerization of 4 leading to 6.

Scheme 2. Rh(II)-catalysed synthesis of oxazoles 5

To introduce functionality at the 4-position of the oxazole ring, Moody reported the synthesis of trisubstituted oxazoles 11 through the Rh(II)-catalysed reaction of diazo compounds 10 with a nitrile 2 (Scheme 3). In some cases, Rh(II) trifluoroacetamide proved to be a more efficient catalyst than Rh(II) acetate. Application of this method to the synthesis of bisoxazoles 15 through two consecutive Rh(II)-catalysed cycloaddition reactions provided an important extension to this methodology with application in natural product synthesis (Scheme 4).
Yuan further extended the scope of the 4-substituent by the preparation of oxazole-4-phosphonates 17 through the Rh(II)-catalysed reaction of diazophosphonates 16 and a nitrile 2 (Scheme 5). The substrate scope reported was limited to aromatic nitriles.

Exploitation of this strategy in the preparation of poly-oxazole systems was reported by Yoo, who demonstrated the synthesis of tris-oxazole 22 through sequential Rh(II)-catalysed reactions of dimethyl diazomalonate 1 with nitrile 18 (Scheme 6). The presence of poly-oxazole motifs in marine metabolites makes this an attractive protocol in natural product synthesis.
An interesting mechanistic investigation on the Rh(II)-catalysed decomposition of α-diazocarbonyl compounds in the presence of nitriles was presented by Ibata, who described a Rh(II)-catalysed reaction of diazoacetophenones 23 with benzonitrile 13 in the presence of dimethyl acetylenedicarboxylate 27 (Scheme 7). The reaction course can be explained through the formation of a nitrile ylide 24, which undergoes intramolecular 1,5-cyclisation to yield oxazole 25 or intermolecular 1,3-dipolar cycloaddition with 27 to give pyrrole 26. Each of these products provides strong support for the intermediate 24.

The synthesis of 2,5-disubstituted oxazoles 29 through the Rh(II)-catalysed decomposition of diazoacetyl indole 28 in the presence of nitriles 2 (Scheme 8) provides an important extension to this methodology. The knowledge that indole containing diazo compounds were suitable substrates for this rhodium catalysed method to access 2,5-disubstituted oxazoles was applied to the synthesis of more complex targets such as the core of diazonamide A.
As suggested through the work of Moody, the Rh(II)-catalysed reaction of diazo compounds with nitriles has found a number of applications in complex natural product synthesis highlighting the importance of this reaction in synthesis. Targets include phorboxazoles A and B, siphonazole, leucascandrolide A, telomestatin, nocardimicin B and discokiolide B.

Xu described the preparation of fluorinated oxazoles using the reaction of ethyl 3-trifluoro-2-diazo-propionate and nitriles (Scheme 9). Interestingly, there was no formation of oxazole observed from picolinonitrile (R\(^1\) = pyridin-2-yl) under the reaction conditions.

Ibata further extended this work using cyanamides as substrates to furnish 2-aminooxazoles (Scheme 10). The substrate scope of this reaction was quite broad, however unsubstituted and monoalkyl cyanamides generated the corresponding oxazole in low yield.
More recently Zhu showed fluorination of the 5-substituent was also possible using this diazonium technology (Scheme 11). The reaction proceeds regioselectively, providing trisubstituted oxazoles 36 in modest to excellent yields. Nitriles 2 bearing conjugated alkenyl or aryl groups led to high yields of 36 while substrates 35 containing perfluoroalkylated motifs were less effective.

![Scheme 11. Rh(II)-catalysed synthesis of oxazoles 36](image)

Marsden prepared 4-silylated oxazoles 38 by performing a Rh(II)-catalysed reaction of (triethylsilyl)diazoacetates 37 and nitriles 2 (Scheme 12). A range of nitriles 2 successfully underwent cycloaddition with 37. Nitriles bearing pyridyl or hydroxyl groups failed to give any oxazole product, due to catalyst deactivation or OH insertion reactions, respectively. Treatment of the product 38 with fluoride led to the corresponding 3,5-disubstituted oxazole, whereas treatment with \(N\)-halosuccinimides allowed introduction of halogens at the 4-position providing the opportunity for further elaboration.

![Scheme 12. Rh(II)-catalysed synthesis of oxazoles 38](image)

As an alternative to diazocarbonyl compounds, the Rh(II)-catalysed reaction of iodonium ylide 39 and nitriles 2 to give oxazoles 40 was disclosed by Hadjiarapoglou (Scheme 13). Notably, the rhodium catalysed transformation proceeded with higher yields than the analogous Cu(II)-catalysed process.
Lee extended the scope of this transformation to the reaction of iodonium ylides and nitriles to generate oxazoles (Scheme 14). The reaction proceeded via formation of the carbene, which reacts with to generate a nitrile ylide followed by cyclisation to give. Along with formation of oxazoles, an undesired transformation leading to a dihydrofuran nucleus also takes place.

The scope of this approach was extended by Hadjiarapoglou to the synthesis of trisubstituted oxazoles through the reaction of carbomethoxy iodonium ylides and nitriles (Scheme 15). This transformation proceeds efficiently with a number of substrates and provides the oxazole products in moderate to good yields. In the case of chloroacetonitrile and iodonium ylide (R = Me), a mixture of oxazoles with a low level of regio control was observed.
In 2007, Ganem reported that using acyl cyanide 47 as a substrate led to the formation of an inseparable mixture of the oxazole 48 and the diazoester derived dimer 49 (Scheme 16).\(^{26}\)

More recently, Doyle disclosed an efficient synthesis of trisubstituted oxazoles 52 through the Rh(II)-catalysed reaction of styryl diazoacetate 50 with aryl oxime 51 (Scheme 17).\(^ {27}\) The reaction proceeds via the formation of a metal carbene 53, which reacts with the oxime 51 to give a rhodium enolate 55. Cyclisation of 55 generates 56, which upon dehydration furnishes the observed oxazole 52. Notably, aryl oximes proved more effective than the corresponding nitrile analogues as substrates. Furthermore, the nature of the \( R^1 \) substituent appears to have little effect on the reaction outcome.
Overall the Rh(II) catalysed reaction has proven to be a versatile method for the preparation of functionalised oxazoles, with a high functional group tolerance and broad substrate applicability. The scope and limitations of this method has been thoroughly explored such that the likely success of a proposed transformation can be readily evaluated based upon the significant literature precedent.

**COPPER(I) AND COPPER(II)**

Despite the success achieved with rhodium in preparing the oxazole framework, a considerable amount of research effort has been dedicated to establishing alternative transition metals to bring about the same overall reaction. The preparation of oxazoles through the reaction of diazocarbonyl compounds with nitriles was first introduced by Huisgen in 1961. Only trace amounts of oxazole were detected when this reaction was carried out thermally. Notably, the yields of the desired oxazole product were significantly increased by addition of a Cu(I) or Cu(II) catalyst. This transformation was further investigated by Alonso, who described the synthesis of oxazoles through the Cu(II)-catalysed reaction of ethyl diazopyruvate and nitriles (Scheme 18). This protocol provided moderate yields of the oxazole product.

![Scheme 18. Cu(II)-catalysed synthesis of oxazole](image)

Iodonium ylides were also shown to be feasible substrates within a Cu(II)-catalysed reaction of acetonitrile via a diketocarbene intermediate (Scheme 19). Although the substrate scope was not explored, this protocol shows the potential of Cu(II) as an alternative catalyst in the preparation of oxazoles.

![Scheme 19. Cu(II)-catalysed synthesis of oxazoles](image)
Sato described an interesting one-pot regioselective synthesis of trisubstituted oxazoles 62 through the Cu(II)-mediated oxidation of ketones 61 in the presence of acetonitrile 59 (Scheme 20). The reaction was proposed to proceed via two consecutive single-electron oxidations of 61 by Cu(OTf)_2. Although the functional group tolerance was not explored, this early work provides an outstanding foundation with which to develop this transformation.

More recently, Wang described the synthesis of trisubstituted oxazoles 68 through the Cu(II)-catalysed tandem oxidative cyclisation of 1,3-dicarbonyl compounds 66 and benzylamines 67 (Scheme 21). The reaction proceeds via formation of 69, which undergoes oxidation to give 70. Cu(II)-catalysed cyclisation
Scheme 21. Cu(II)-catalysed tandem oxidative cyclisation of 1,3-dicarbonyl compounds 66 and benzylamines 67 of 70 generates an oxazoline 71, which upon oxidation furnishes the observed oxazole 68. This reaction displays a good scope. Cyclisation of substrates 67 possessing electron-withdrawing groups gave higher yields of 68 than those bearing electron-donating groups. Overall it has been shown that copper can be used to mirror the reactivity of rhodium, although the reactions tend to be less efficient. One distinct advantage offered through the use of copper is the potential to use ketones as substrates rather than the reaction with potentially hazardous diazo compounds.

PALLADIUM(II)

In an early example Teyssié reported the synthesis of 2,5-disubstituted oxazoles 73 through the Pd(II)-catalysed reaction of ethyl diazoacetate 72 with nitriles 2 (Scheme 22). The reaction proceeds via the Pd(II)-catalysed decomposition of 72 generating a metal carbene species which undergoes 1,3-dipolar cycloaddition with 2 to furnish oxazole 73. Subsequently, Teyssié found that higher yields of 73 were achieved using Cu(OTf)2 as the catalyst (15–80%) and a butyldiazoacetate substrate.

Scheme 22. Pd(II)-catalysed synthesis of oxazoles 73

TUNGSTEN(VI)

Use of tungsten in the decomposition of diazo compounds was shown to be possible by Kitatani who
described a synthesis of trisubstituted oxazoles 75 (Scheme 23).\textsuperscript{35,36} Notably, due to a highly Lewis acidic character and a good affinity for carbenes, WCl\textsubscript{6} proved more effective than copper(II) salts.\textsuperscript{37}

**RUTHENIUM(II)**

Lacour described the synthesis of trisubstituted oxazoles 79 through the Ru(II)-catalysed cyclisation of diazoacetoacetate 78 and nitriles 2 in the presence of 1,10-phenanthroline 81 as a ligand (Scheme 24).\textsuperscript{38} The reactions proceed regioselectively, delivering trisubstituted oxazoles in up to 75\% yield. Further development could make ruthenium complexes an attractive alternative to the more commonly employed rhodium and copper salts in this class of transformation.
**TIN(II)**

An interesting alternative approach to the preparation of oxazoles was reported by Russowsky who described the Sn(II) catalysed reaction of benzils $82$ in the presence of NH$_4$OAc (Scheme 25).$^{39}$ The use of SnCl$_2$ as a mild and inexpensive Lewis acid catalyst makes this a simple protocol for the preparation of triaryloxazoles, with the specific limitation that each aryl group is identical.

![Scheme 25. Sn(II)-catalysed synthesis of oxazoles $83$](image)

**IRON(III), ZIRCONIUM(IV), MOLYBDENUM(V), TIN(IV), TITANIUM(IV), TANTALUM(V) AND TUNGSTEN(VI)**

In 1980, Doyle described a synthesis of disubstituted oxazoles $84$ through the Lewis acid (LA) promoted cycloaddition reaction of diazocarbonyl compounds $23$ in the presence of acetonitrile $59$ as the solvent (Scheme 26).$^{40}$ The reaction proceeded via the cycloaddition of a Lewis acid activated diazocarbonyl compound $85$ with $59$ leading to $86$ (Scheme 26, Pathway A), or more plausibly via $87$ which upon reaction with $23$ generates $88$ (Scheme 26, Pathway B). A range of Lewis acids such as FeCl$_3$, ZrCl$_4$, MoCl$_5$, SnCl$_4$, TiF$_4$, TaCl$_5$ and WCl$_6$ were also successfully employed for this transformation providing oxazoles $84$ in moderate to excellent yields. Interestingly, CuF$_2$, NiBr$_2$ and ZnCl$_2$ failed to produce the corresponding oxazole product. A limitation of this protocol is the α-chlorination of $23$, which was observed predominantly when using ZrCl$_4$, MoCl$_5$, SnCl$_4$ or TiF$_4$ as the Lewis acid. Notably, no products generated by Wolff rearrangement were observed under the reaction conditions.
Preparation of oxazoles through an O1–C2 and N3–C4 bond disconnection has been thoroughly investigated and represents a versatile method for the preparation of di- and trisubstituted variants. The assortment of catalysts which are effective for this transformation provide significant alternatives for those adopting this disconnective strategy. The major challenge within this work is preparation of the diazonium (or equivalent) substrate. Recent advances using oxidative cyclisations with ketone substrates provide a useful alternative and further development of this reaction class would be particularly helpful.

**O1–C5 AND N3–C4 BOND DISCONNECTION**

**RHODIUM(II)**

In 1996, Moody demonstrated an alternative approach to access oxazoles based on the Rh(II)-catalysed reaction of diazocarbonyl compounds 74 and amides 89 (Scheme 27). The reaction proceeds through the regioselective insertion of a Rh-carbenoid into the NH bond of 89 to give 90, which can subsequently undergo cyclodehydration as described by Wipf. A range of diazomalonates 74 and amides 89 were
successfully used for this transformation, providing 75 in moderate to good yield. Notably, in the case of \(\alpha\)-chiral amides, the reaction generated products without erosion of optical purity, greatly adding to the applicability of this work. The method was applied to the synthesis of trisubstituted oxazoles 93 which proceeds in high yields when compared to the analogous rhodium carbene transformation employing nitriles as substrates (Scheme 28). \(^{42}\)

![Proposed reaction mechanism](image)

R\(^1\) = (EtO)\(_2\)CH(CH\(_2\))\(_2\), CBzNHCH\(_2\), (S)-CBzNHCHMe, (S)-CBzNHCH\(_2\)Pr, (S)-N-CBz-pyrrolidin-2-yl, (S)-N-BocNHCH\(_2\)Pr; R\(^2\) = MeO\(_2\)C, t-BuO\(_2\)C, EtO\(_2\)C; R\(^3\) = MeO, t-BuO, Me, Et, Ph, ClCH\(_2\)

**Scheme 27.** Rh(II)-catalysed reaction of diazocarbonyl compounds 74 and amides 89 followed by cyclodehydration

![Scheme 27](image)

**Scheme 28.** Rh(II)-catalysed reaction of diazocarbonyl compounds 91 and amides 92 followed by cyclodehydration

Giacomelli demonstrated this methodology could be applied to the preparation of a range of novel optically active oxazole-containing amino acids. \(^{44}\) Thus, the Rh(II)-catalysed reaction of 94 and 95 followed by cyclodehydration afforded oxazoles 96 in modest to good yields (Scheme 29).
Scheme 29. Rh(II)-catalysed reaction of diazocarbonyl compounds 94 and amides 95 followed by cyclodehydration

Expansion of the substrate scope to encompass aliphatic and aromatic amides 89 as well as diazocarbonyl substrates 74 also met with success (Scheme 30). Janda adapted this chemistry for solid-phase synthesis using a polymer-bound α-diazo-β-ketoester.

Scheme 30. Rh(II)-catalysed reaction of α-diazo-β-keto-carboxylate 74 with amides 89 followed by cyclodehydration

With 3-indolyl α-diazo-β-ketoester 97 substrates a competing N—H insertion and Wolff rearrangement during the Rh(II)-catalysed reaction has been reported (Scheme 31). Ketoamides 99 were subsequently transformed into the corresponding oxazoles 101 upon cyclodehydration (Scheme 32). Notably, the presence of strong electron-withdrawing groups on the indole moiety favoured the N—H insertion process over Wolff rearrangement which was exploited to prepare a potential precursor to the natural product martefragin A.
In 2009, Moody described a robust regioselective synthesis of oxazole-4-carboxylates and oxazole-4-phosphonates. For example, Rh(II)-catalysed reaction of α-diazo-β-keto-carboxylate 102 with carboxamide 89 afforded oxazole-4-carboxylate 103 (Scheme 33) whilst the same transformation applied to α-diazo-β-keto-phosphonate 104 and benzamide 105 provides oxazole-4-phosphonate 106 (Scheme 34).\textsuperscript{48,49} Surprisingly, α-diazo-β-keto-sulfones failed to deliver the 4-sulfonyloxazoles analogue under similar reaction conditions and presents opportunities for further research.

$$\text{MeO}_2\text{C} \equiv \text{N}_2 + \text{NH}_2\text{CO} \rightarrow \text{MeO}_2\text{C} \equiv \text{N}_2 \text{CO} \text{R}^1$$

\(\text{R}^1 = \text{Ph}, 4-\text{MeOC}_6\text{H}_4, 4-\text{BrC}_6\text{H}_4\)

i) 102 (1.1 eq), 89 (1.0 eq), Rh\(_2\)(OAc)\(_4\) (2 mol%), C\(_2\)H\(_4\)Cl\(_2\), reflux, on;  
ii) PPh\(_3\) (2.0 eq), I\(_2\) (2.0 eq), Et\(_3\)N (4.1 eq), CH\(_2\)Cl\(_2\), n, on.

Scheme 33. Rh(II)-catalysed reaction of α-diazo-β-keto-carboxylate 102 with amides 89 followed by cyclodehydration
Remarkably, when the above transformation was performed using dirhodium tetrakis(heptafluorobutyramide) as a catalyst, regioisomeric oxazole-5-carboxylates 107 were obtained as the only products (Scheme 35). In the same fashion, oxazole-5-phosphonates 109 (Scheme 36) and oxazole-5-sulfones 111 (Scheme 37) were also prepared.\textsuperscript{48,49} Of particular note is the ready availability of carboxamides 89 which renders this protocol a convenient, selective and attractive method to access both 4- and 5-functionalised oxazoles based upon judicious choice of catalyst.

\begin{align*}
\text{MeO}_2\text{C} & + \text{NH}_2 + \text{O} \xrightarrow{\text{i), ii)} \text{C}_4\text{H}_2\text{Cl}_2, \text{reflux, on;}} \text{MeO}_2\text{C} \\
102 & + 89 & 107 (18\text{–}38\%) \\
R^1 & = \text{Ph, 4-MeOC}_6\text{H}_4, 4-\text{BrC}_6\text{H}_4 \\
\text{i) } 102 & (1.1 \text{ eq}), 89 (1.0 \text{ eq}), \text{Rh}_2(\text{NHCOC}_3\text{F}_7)_4 (2 \text{ mol\%}), \text{MW irr, C}_2\text{H}_4\text{Cl}_2, 105 \text{ °C, 30 min.} \\
\end{align*}

Scheme 35. Rh(II)-catalysed synthesis of oxazole-5-carboxylates 107

\begin{align*}
\text{(R}_3\text{O})_2\text{OP} & + \text{NH}_2 + \text{O} \xrightarrow{\text{i)} \text{MeO}_2\text{C}} \\
108 & + 89 & 109 (26\text{–}73\%) \\
R^1 & = \text{Ph, 2-BrC}_6\text{H}_4, 2-\text{BnOC}_6\text{H}_4, 4-\text{BrC}_6\text{H}_4, 4-\text{MeOC}_6\text{H}_4, 4-\text{NO}_2\text{C}_6\text{H}_4, 4-\text{CbzNHCC}_6\text{H}_4, \text{3,5-}2\text{y}_{2}\text{C}_6\text{H}_3, \text{thiophen}-2\text{-yl, benzothiophen}-2\text{-yl, PhCH=CH;}} \\
R^2 & = \text{Me, Ph;} \\
R^3 & = \text{Me, Et} \\
\text{i) } 108 & (1.1 \text{ eq}), 89 (1.0 \text{ eq}), \text{Rh}_2(\text{NHCOC}_3\text{F}_7)_4 (2 \text{ mol\%}), \text{PhMe, refl, 16 h or} \\
108 & (1.1 \text{ eq}), 89 (1.0 \text{ eq}), \text{Rh}_2(\text{NHCOC}_3\text{F}_7)_4 (2 \text{ mol\%}), \text{MW irr, PhMe, 135 °C, 30 min.} \\
\end{align*}

Scheme 36. Rh(II)-catalysed synthesis of oxazole-5-phosphonates 109
This overall method can also be applied to the synthesis of trifluoromethyloxazoles e.g. 113 and 114. Rh(II)-catalysed reaction of trifluoroacetyl diazoketoester 112 with amide 89 generated a mixture of regioisomeric 5-trifluoromethyloxazoles 113 and 4-trifluoromethyloxazoles 114 (Scheme 38). The lack of regioselectivity in formation of 5-trifluoromethyloxazoles 113 is due to a competing \( \text{O}—\text{H} \) insertion process of the carbenoid species generated from 112, suggesting the trifluoromethyl group influences the electrophilicity of the carbenoid.

The power of this Rh(II)-catalysed synthesis of oxazoles can be seen in its applications in natural product synthesis with the preparation of diazonamide \( A \),\(^{51-54}\) (+)-nostocyclamide,\(^{55}\) promothiocin \( A \),\(^{56}\) telomestatin,\(^{16}\) siphonazole\(^{14}\) and martefragin \( A \).\(^{47}\)

**COPPER(I), COPPER(II)**

Along with rhodium, copper has also been shown to be an efficient catalyst for this strategy of preparing oxazoles. Glorious described an interesting single-step synthesis of 116 through the Cu(I)-catalysed domino reaction of 1,2-dihaloalkenes 115 and primary amides 89 (Scheme 39).\(^{57}\) This transformation proceeds via a sequential Cu(I)-catalysed C—N and C—O bond forming process. Initial non-regioselective
formation of an enamide intermediate followed by cyclisation gives a mixture of 2,4- and 2,5-disubstituted oxazoles 116. The use of 1,2-dibromo olefins favours the formation of 2,5-disubstituted oxazoles over the 2,4-disubstituted isomers. Use of the more reactive 1,2-diiodo olefins tended to generate 1:1 mixtures or to favour the formation of 2,4-disubstituted oxazoles suggesting complementary strategies for oxazole synthesis may be possible.

Scheme 39. Cu(I)-catalysed synthesis of oxazoles 116

Buchwald reported an alternative C—N and C—O bond forming process to access the oxazole core. Cu(I)-catalysed reaction of aliphatic or aromatic amides 89 with vinyl bromides 118 generates enamides 119. Iodine-promoted cyclisation of 119 furnishes oxazolines 120, which lead to the oxazole product 75 upon reaction with base (Scheme 40). This method allowed for an efficient synthesis of a range of trisubstituted oxazoles from readily available starting materials in good yield. To overcome the issue of regioselectivity described by Glorious, Buchwald applied this strategy to a one-pot regioselective synthesis of disubstituted oxazoles 122 through the Cu(I)-catalysed reaction of 1,2-iodobromoalkene 121 and amide 89 (Scheme 41). Notably, the initial C—N bond formation occurred solely at the vinyl iodide moiety. The need of a general method for the synthesis of 121 represents a drawback of this protocol.
More recently, Pérez described a catalytic and regioselective synthesis of 2,5-disubstituted oxazoles through the cycloaddition of terminal alkynes and acyl azides using a copper(I) catalyst precursor (Scheme 42). The reaction proceeds via the [3+2] cycloaddition of the copper acetylide of with generating a copper triazolyl intermediate. Conversion of to a copper ketenimide proceeds via the formation of or . Protonation of promotes cyclisation to or , followed by a 1,2-hydrogen shift to give and release of the catalyst. Trisubstituted oxazoles can also be generated through the aromatisation of and coupling with a copper acetylide. Although substrate scope was limited with alkyl acetylenes and internal alkynes being ineffective substrates, development of more reactive catalysts will make this an attractive and readily accessible methodology for oxazole construction.
GOLD(I), GOLD(III)

Davies described an interesting synthesis of fully substituted oxazoles 138 through the Au(III)-catalysed [3+2] cycloaddition of ynamides 136 and aminides 137 (Scheme 43), providing the first example of a gold-catalysed intermolecular cycloaddition across a C—C π-system. The reactions proceeded regioselectively and chemoselectively, delivering highly substituted and functionalised oxazole products in good yield. The reaction proceeds by nucleophilic attack of an amide 137 to a gold activated ynamide 140/140' giving 141. Adduct 141 cyclises to 143/143' after extrusion of pyridine either through a 4π
electrocyclisation via 144/144', or more plausibly via 142. Elimination of the gold-catalyst from 143 then yields oxazole 138. Of particular note with this work is the high functional group tolerance which makes this methodology particularly attractive.

Scheme 43. Au(III)-catalysed [3+2] intermolecular cycloaddition of ynamides 136 and aminides 137

The scope for this class of transformation was expanded by Davies, who described the preparation of trisubstituted oxazoles 75 through the Au(I)-catalysed [3+2] cycloaddition of unsymmetrical alkynes 145 and aminides 137 (Scheme 44). Remarkably, the reactions proceeded with excellent regioselectivity, due to the π-electron-donating ability of the remote nitrogen in R². A broad range of 3-indolyl and benzenoid alkynes 145, including substrates bearing sterically hindered groups, successfully delivered oxazoles 75 in good yield. Importantly, 3-indolyl alkynes 145 bearing alkyl substituents, unlike the ynamide counterparts previously employed, were generally less effective substrates.
An efficient modular synthesis of 2,4-disubstituted oxazoles 125 through a [3+2] annulation strategy between a terminal alkyne 123 and a carboxamide 89 using a gold catalysed oxidation strategy has also been described (Scheme 45). Careful choice of supporting ligand for gold provided the key to success in this work. It is established that terminal α-oxo gold carbenes are highly electrophilic species and thus can only be trapped efficiently intramolecularly or using solvent as the nucleophile. Within this work it was shown that terminal α-oxo gold carbenes (e.g. 147) could be stabilised with the bidentate ligand Mor-DalPhos through a tricoordinated Au(I) complex. This stabilisation allows trapping of the Au(I) intermediate by stoichiometric external nucleophiles greatly increasing the efficiency of the procedure. It is possible this observation will open up further exciting opportunities in homogeneous gold catalysis.

\[
\begin{align*}
\text{R}^1 &= \text{Ph}, 2-\text{BrC}_6\text{H}_4, 4-\text{MeOC}_6\text{H}_4, 4-\text{FC}_6\text{H}_4, \text{furan-2-yl, thiophen-2-yl;} \\
\text{R}^2 &= \text{indol-3-yl, 1-Me-indol-3-yl, 1-Bn-indol-3-yl, 1-allyl-indol-3-yl, 5-Br-1-Me-indol-3-yl, 6-MeO}_2\text{C-indol-3-yl,} \\
& \quad 4-\text{Me}_2\text{NC}_6\text{H}_4, 4(\text{morpholin-4-yl})\text{C}_6\text{H}_4, 4(\text{pyrrolidin-1-yl})\text{C}_6\text{H}_4, 3(\text{pyrrolidin-1-yl})\text{C}_6\text{H}_4, 4-\text{MeOC}_6\text{H}_4; \\
\text{R}^3 &= \text{Ph, thiophen-2-yl, furan-2-yl, 4-MeOC}_6\text{H}_4, 4-\text{FC}_6\text{H}_4, \text{cyclopropyl, 2-BrC}_6\text{H}_4 \\
i) \quad 137 (1.5 \text{ eq}), 145 (1.0 \text{ eq}), 146 (5 \text{ mol\%}), \text{m-xylene, 120 \text{ °C}, 24 or 48 h.}
\end{align*}
\]

Scheme 44. Au(I)-catalysed synthesis of oxazoles 75

\[
\text{R}^1 = 4-\text{MeC}_6\text{H}_4, \text{Ph, 4-ClC}_6\text{H}_4, 4-\text{BrC}_6\text{H}_4, 4-\text{FC}_6\text{H}_4, \text{furan-2-yl, thiophen-2-yl, PhCH=CH,} \\
& \quad \text{MeCH=CH, (Me)}_2\text{C=CH, 4-MeOC}_6\text{H}_4; \\
\text{R}^2 &= \text{n-decyl, cyclohexyl, cyclopropyl, PhthN(CH}_2)_4, \text{TIPSO(CH}_2)_4, \text{Cl(CH}_2)_4, \text{AcO(CH}_2)_4, \\
& \quad \text{Ph(CH}_2)_2, \text{Ph, 4-MeC}_6\text{H}_4, 4-\text{MeOC}_6\text{H}_4
\]

\[
i) \quad 123 (1.5 \text{ or 2.0 eq}), 89 (1.0 \text{ eq}), \text{Mor-DalPhosAuCl (5 mol\%), NaBARF}_4 (10 \text{ mol\%}), 8\text{-methylquinoline-N-oxide} \\
& \quad 151 (2.2 \text{ or 3.0 eq}), \text{chlorobenzene, 60 or 100 \text{ °C, 16 h.}
\]

Scheme 45. Au(I)-catalysed [3+2] annulation of terminal alkynes 123 and carboxamides 89
Mechanistically, it was proposed the reaction proceeded via nucleophilic attack of 89 on 147 to give imidate 148. Protodeauration, cyclisation and dehydration then leads to the 2,4-substituted oxazole 125. The efficient trapping of 147 by 89 is ascribed to the formation of a tricoordinated gold carbene species through coordination of the nitrogen atom of Mor-DalPhos to the gold atom of 147 which reduces the electrophilicity of the carbenoid carbon. Functional group tolerance was not extensively explored within this work, however, some useful functionality was introduced.

**SILVER(I)**

Moses developed a Ag(I)-mediated synthesis of 2,4-disubstituted- and 2,4,5-trisubstituted oxazoles 75 through the microwave promoted reaction of α-bromo-ketones 152 and primary amides 89 in the presence of a stoichiometric silver salt (Scheme 46). The reaction proceeds via the nucleophilic attack of an amide 89 on 152 followed by intramolecular cyclisation to give the oxazoline 155. Dehydration of 155 leads to the corresponding oxazole 75. Although this method represents an improvement of the Blümlein-Lewy oxazole synthesis, the scope in amides 89 is primarily limited to aromatic substrates. In an extension of the work a symmetrical bis-oxazole was also prepared using this method.

In a useful study, Moses explored alternative α-haloketone substrates 156 (Scheme 47). α-Bromo and α-iodoketones were better substrates in comparison with their α-chloroketone analogues. No formation of oxazole was observed using a methanesulfonyloxy substrate under the reaction conditions. This suggests the reaction occurs via pathway A (Scheme 47), supported by the known halophilicity of silver(I) salts.
Scheme 47. Ag(I)-mediated synthesis of oxazoles 157

Scheme 48. Ag(II)-catalysed cyclisation of \( N \)-sulfonylpropargylamides 163
The synthesis of trisubstituted oxazoles $164$ through the Ag(I)-catalysed cyclisation of $N$-sulfonyl-propargylamides $163$ (Scheme 48) was reported by Wan.\(^{68}\) It was proposed that Ag(I) complexes both the alkyne and the acyloxy groups of $163$ to generate $165$, which upon 6-endo-dig cyclisation produces $166$. Intermediate $166$ collapses to the allene species $167$. Cyclisation of $167$ furnishes $168$, which undergoes a sulfonyl shift resulting in the observed oxazole $164$. The reaction scope was limited to aryl-substituted $N$-sulfonylpropargylamides $163$.

**IRON(III)**

Iron represents a cheap and abundant transition metal and therefore has received significant interest from the synthetic community as an alternative to precious metal catalysts. In 2009, Lin described a one-pot method for the preparation of trisubstituted oxazoles $170$ through the Fe(III)-catalysed tandem propargylation/cycloisomerisation reaction of propargyl acetates $169$ and amides $89$ under microwave irradiation (Scheme 49).\(^{69}\) Reactions employing electron rich amides provided better yields of the oxazole products $170$.

![Scheme 49. Fe(III)-catalysed synthesis of oxazoles 170](image)

More recently, a complimentary one-pot regioselective Fe(III)-mediated synthesis of 2,5-di- and 2,4,5-trisubstituted oxazoles $174$ through the reaction of propargylamines $172$ and acid chlorides $173$ was reported (Scheme 50).\(^{70}\) The reaction proceeds via the formation of the propargylamide $175$ followed by 5-exo-dig cyclisation leading to $174$. A range of propargylamines $172$ bearing a variety of functional groups was prepared and reacted to afford $174$ in good to excellent yields. The operational simplicity as well as the efficiency of this inexpensive protocol is particularly noteworthy.
Ruthenium(III) and Gold(III)

In 2004, Uemura described a one-pot synthesis of 2,4,5-trisubstituted oxazoles 174 through the sequential

\[ R^1 = \text{n-nonyl, 3,4,5-(MeO)3C6H2CH} = \text{CH, PhCH} = \text{CH, n-Bu, 2-Cl-4-NO2C6H4, 3-MeO-4-HOC6H4, 2-MeNHCH2CH3, furan-2-y1, benzo-furan-2-y1, benzothiophen-2-y1, indol-2-y1, 5-nitrofuran-2-y1, f-Bu, Me, 3,4-(MeO)3C6H3, Ph, 4-MeC6H4, 3-MeOC6H4, 3,4,5-(MeO)3C6H4, 2-BrC6H4, 4-F3CC6H4, 3-NO2C6H4, 4-NO2C6H4;}
\[ R^2 = \text{H, Ph}
\]

Scheme 50. Fe(III)-mediated synthesis of oxazoles 174

\[ \text{Ruthenium(III) and Gold(III)} \]

In 2004, Uemura described a one-pot synthesis of 2,4,5-trisubstituted oxazoles 174 through the sequential

\[ R^1 = \text{i-Pr, Me, vinyl, CH2=CH-Me, 4-MeC6H4, 4-ClC6H4;}
\[ R^2 = \text{Ph, 4-MeC6H4, 4-ClC6H4, naphthalen-2-y1, Ph2C=CH}
\]

Scheme 51. One-pot Ru(III)- and Au(III)-catalysed cyclisation of terminal propargylic alcohols 179 with amides 89
Ru(III)- and Au(III)-catalysed cyclisation of terminal propargylic alcohols 179 and amides 89 (Scheme 51). This transformation occurs with complete regioselectivity and delivered oxazoles 174 in up to 88% yield. The reaction proceeds via the formation of propargylic amide 175, isomerisation to the allenamide 181 followed by intramolecular cyclisation to give the oxazole 174 (Scheme 51). The reaction is effective for both alkyl- and aryl-substituted amides but no reaction is observed in the case of alkyl-substituted propargylic alcohols.

**ZINC(II) AND RUTHENIUM(II)**

Liu reported the Zn(II)- and Ru(II)-catalysed synthesis of trisubstituted oxazoles 182 through the reaction of terminal propargylic alcohols 179 with amides 89 (Scheme 52). Mechanistic studies suggested that Zn(OTf)_2 was involved in the C–(2)-amination of 179, which generates an α-carbonyl amide intermediate 183. Although the Zn(OTf)_2 could also bring about subsequent cyclisation to give 182, the co-catalyst TpRuPPh_3(MeCN)_2PF_6 proved more effective for this process leading to the oxazole products in high yield.

![Scheme 52. Zn(II)- and Ru(II)-catalysed reaction of propargylic alcohols 179 with amides 89](image)

R^1 = Ph, n-pentyl, MeC=CH_2; R^2 = 4-FC_6H_4, 4-MeC_6H_4, 4-MeOC_6H_4, benzo[d][1,3]dioxolyl-5-yl

i) 179 (1.0 eq), 89 (1.2 eq), Zn(OTf)_2 (10 mol%), TpRuPPh_3(MeCN)_2PF_6 (10 mol%), PhMe, 100 °C, 5 h.

**RUTHENIUM(II) AND COPPER(II)**

He and co-workers described an intriguing synthesis of disubstituted oxazoles 186 through the tandem Ru(II)/Cu(II)-catalysed reaction of aryl acetylenes 184 and 3-aryl-1,4,2-dioxazol-5-ones 185 in the presence of iodine (Scheme 53). It was proposed the reaction proceeded via the thermal decomposition of 185 in the presence of iodine and Ru(TTP)CO generating a ruthenium imido complex 188, which reacts with 187 to give an acylaziridine 190. Isomerisation of 190 to 191 in the presence of CuCl_2 and subsequent rearrangement gives 192. Cyclisation of 192 generates 186 and releases the CuCl_2. Easy access to the starting materials 184 and 185 and the use of mild reaction conditions make this transformation a convenient method for delivering 2,5-diaryloxazoles.
Hashmi reported the synthesis of 2,5-disubstituted oxazoles 195 through a Au(III)-catalysed 5-exo-dig cyclisation of terminal $N$-propargylamides 194 (Scheme 54). The reaction proceeds via a stereospecific anti-addition across the gold-activated triple bond, which generates 198. Proto-demetallation of 198 furnishes an alkylidene oxazoline 199, which isomerises to give the oxazole 195. Functional group diversity at the 2-position was good but substituted $N$-propargylamides and some electron-deficient substrates gave no product.
The substrate scope of this approach was subsequently expanded to include aliphatic and aromatic terminal N-propargylamides 195 (Scheme 55).

Interestingly, substrates containing multiple propargylic moieties (e.g. 200 and 202) also underwent cyclisation to furnish the corresponding di- and tri-oxazoles 201 and 203. Some representative results are summarized in Scheme 56. In general, N-propargylamides bearing electron-withdrawing substituents were less effective substrates, presumably due to a decreased nucleophilicity of the oxygen atom.
Remarkably, 204, which failed to provide the corresponding oxazole under Au(III) catalysis, successfully delivered oxazole 205 in good yield using a Au(I) precatalyst (Scheme 57). In the majority of cases under these reaction conditions the proposed intermediate methyleneoxazolines were obtained selectively using Au(III) catalysis, without further prototopic isomerisation to the corresponding oxazole. Methyleneoxazolines can also serve as reactive partners for electrophilic reagents such as NBS or NCS, which generate halomethyloxazoles 205, albeit in poor yield (Scheme 58).

\[
\begin{align*}
\text{204} \quad \text{CO}_2\text{Et} & \quad \text{N} \quad \text{CO}_2\text{Et} \quad \text{205} (81\%) \\
\end{align*}
\]

i) [PPh₃Au]OTs (5 mol%), CH₂Cl₂, rt, 48 h.

Scheme 57. Au(I)-catalysed synthesis of oxazole 205

\[
\begin{align*}
\text{206} \quad \text{N} \quad \text{(CH₂)₆Me} \quad \text{X} \quad \text{207 (7–29\%)} \\
\end{align*}
\]

i) NCS or NBS (1.2-5.0 eq), [PPh₃Au]NTf₂ (3.0 mol%) or AuCl₃ (3.0 mol%), CH₂Cl₂, 20 or 40 °C, 48 h.

Scheme 58. Au(I)- and Au(III)-catalysed syntheses of halomethyloxazoles 207
The scope of this chemistry was expanded by De Brabander, who reported the preparation of 5-bromomethyl oxazoles 208 through a one-pot Au(III)-catalysed cyclisation-bromination of N-propargylamides 194 (Scheme 59). Under the optimised conditions, various 2,5-disubstituted oxazoles including amino acid-derived oxazoles were prepared in good yield. No epimerization of an α-stereogenic centre was observed under these reaction conditions increasing the power of this transformation. The substrate scope for the Au(III)-catalysed cyclisation of terminal N-propargylamides was further investigated by Padwa who showed that the transformation was tolerant of the indole nucleus within the substrate.

Scheme 59. One-pot Au(III)-catalysed synthesis of 5-bromomethyl oxazoles 208

It has also been shown that the Au(I)-catalysed cyclisation of the internal N-propargylamide 209 delivered six-membered oxazines 210 via a 6-endo-dig cyclisation pathway (Scheme 60). Under the same reaction conditions, no product was formed using a Au(III) catalyst. The scope of the Au(I)-catalysed cyclisation of 209 was subsequently expanded to give functionalised alkyl- and aryl-N-propargylamides 211, which result in the formation of 2,5-disubstituted oxazoles 212, oxazolines 213 and oxazines 214 (Scheme 61). A combination of two catalysts (IPr)AuCl and AgOTs was required for this transformation. Although the method is not general for the synthesis of oxazoles, it shows product distribution from this reaction can be significantly influenced through both substrate and catalyst architecture.

Scheme 60. Au(I)-catalysed cyclisation of internal N-propargylamides 209
The preparation of oxazoles 195 through the Au(III)-catalysed cycloisomerisation of N-propargyl amides 194 using a range of gold catalysts was reported by Urriolabeitia and Contel (Scheme 62).\(^8\) Yields of oxazoles 195 obtained using the gold iminophosphorane complexes 215 and 216 were comparable to those using \(\text{AuCl}_3\), albeit with longer reaction times being required.

\[
\text{R}^1 = \text{Me, Et, } n\text{-Pr, } n\text{-Bu, ClCH}_2\text{, CH}_3\text{OCH}_2\text{, HC=C(CH}_2)_3\text{, HC=CCH}_2\text{OCH}_2\text{HC=C(CH}_2)_4\text{, CH}_2\text{=CH(CH}_2)_3\text{, 4-NO}_2\text{C}_6\text{H}_4\text{, pyridin-2-yl, naphthalen-1-yl, 4-MeOCH}_2\text{H}_4\text{, 4-CNC}_6\text{H}_4\text{, 4-CHOC}_6\text{H}_4, thiophen-2-yl, 5-formyl-furan-2-yl, Ph;}
\]
\[
\text{R}^2 = \text{Ph, furan-2-yl, Bn, } t\text{-Bu, 4-BrC}_6\text{H}_4\text{, PhCH=CH}_2\text{, 2,5-dimethylfuran-3-yl, adamantan-1-yl}
\]

\(i)\) \((\text{IPr})\text{AuCl (5 mol%), AgOTs (5 mol%), THF, rt or } 40 \, ^\circ\text{C, 12 h-6 d.}\)

Scheme 61. Au(I)-catalysed cyclisation of internal \(N\)-propargylamides 211

This technology was applied to the preparation of a fluorescent chemical sensor for the detection of Au(III) ions. The protocol is based on the cyclisation of the rhodamine-alkyne derivative 217, which generates the oxazole 218 in the presence of Au(III) ions (Scheme 63),\(^8\) providing a fluorescent and colourimetric chemical probe for the selective detection of gold(III) species.

Another interesting application of the gold catalysed cyclisation of propargylamides was reported by Ahn who described the development of a selective Au(I)/(III) sensor (Scheme 64).\(^8\) Treatment of the rhodamine derived alkyne 217 with either a Au(I) or Au(III) species led to 218 and 219 which provides a fluorescent and colourimetric method for the detection of these gold species.
Scheme 63. Au(III)-mediated synthesis of oxazole 218

i) AuCl₃, 1:1 EtOH/PBS buffer (pH = 7.4), λₑₓ = 558 nm.

Scheme 64. Au(I) and Au(III)-mediated synthesis of oxazole 218 and 219

i) AuCl or AuCl₃, 1:1 MeCN/PBS buffer (pH = 7.2), λₑₓ = 530 nm.
Ahn reported the preparation of 2-phenyloxazole-5-carboxaldehyde 225 through the Au(I)/(III)-mediated cyclisation of N-(propargyl)benzamide 224 in aqueous media (Scheme 65). The formyloxazole 225 was only formed as the major product either using a stoichiometric amount of a Au(III) or Au(I) species or an excess of a Au(I) species. The reaction proceeds via the gold-mediated 5-exo-dig cyclisation of 224 generating a vinylgold intermediate 226 followed by oxidation generating the carbenoid intermediate 227 which leads to 225 in the presence of water. This alternative fate for a vinyl gold species reveals interesting opportunities for alternative functionalisations in this class of transformation.

Scheme 65. Au(I)- or Au(III)-mediated preparation of formyloxazole 225

In 2012, Hashmi described a one-pot synthesis of disubstituted oxazoles 229/231 through the Au(I)-catalysed cycloisomerisation of N-propargylamides 194 in the presence of enophiles 228/230

![Scheme 66. Au(I)-catalysed synthesis of oxazoles 229 and 231](image-url)
The reaction proceeds via the formation of an oxazoline 232, which undergoes Alder-Ene reaction with enophiles 228 or 230 to yield oxazoles 229 or 231, respectively. Reaction of 194 with enophile 228 provided good to high yields of the corresponding oxazole while 230 was less effective. Higher yields of the oxazole products could be obtained in some cases by employing Au(I) catalysts containing ligands from the KIT-PHOS family.

In search for alternative Au(III) catalysts, Blanc and Frémont discovered that the cycloisomerisation of \( N \)-propargylamide 224 catalysed by \( N \)-heterocyclic carbene complexes 235 and 236 in the presence of \( \text{AgSbF}_6 \) yielded a mixture of oxazole 233 and oxazoline 234 (Scheme 67).

Tran-Dubé showed that formation of the amide substrate and subsequent cyclisation could be carried out in one-pot through the preparation of trisubstituted oxazoles 174 (Scheme 68). The transformation proceeds via the reaction of propargyl amines 172 and acid chlorides 173 to give a propargylamide 175, which
undergoes Au(III)-catalysed cyclisation to yield oxazoles 174. Although the scope of the reaction is broad with tolerance for a wide array of functional groups, reactants 172 bearing heterocyclic substituents were less effective substrates and required a higher catalyst loading and longer reaction times to provide reasonable quantities of the product. Nevertheless, this protocol provides a quick access to trisubstituted oxazoles from readily available starting materials.

The scope and limitations of the gold catalysed preparation of oxazoles through the construction of the O1—C5 bond has been thoroughly investigated. Subtleties associated with the nature of the gold catalyst, supporting ligand and substitution pattern of the starting materials allows for appropriate reaction conditions to be selected after careful consideration of literature precedent. Of particular note are the mild reaction conditions, convenient access to starting materials and the high functional group tolerance which make this methodology particularly attractive.

**SILVER(I)**

During a study of the multicomponent reaction of α-isocyanamide 237, acetone 238 and benzylamine 239 leading to 2H-2-imidazoline 241 (Scheme 69), Orru discovered conditions where the disubstituted oxazole 240 was obtained as the major product. Oxazole 240 is generated via the formation of the activated α-isocyanamide 242 followed by a 5-endo cyclisation leading to 243, which upon proto-demettallation generates oxazole 240. Selective functionalisation at the C4 and C5 positions is uncommon, therefore this procedure provides access to alternative oxazole substitution patterns.

![Scheme 69. Ag(I)-catalysed synthesis of oxazoles 240](image)

i) 237 (1.0 eq), 238 (2.0 eq), 239 (1.5 eq), MgSO₄ (0.8 eq), AgOAc (2 mol%), MeOH, rt, 21 h.
A versatile method for the preparation of fully substituted oxazoles 245 involves the Ag(I)-mediated 5-endo cyclisation of β-bis(methylthio)enamides 244 (Scheme 70). Enamides 244 can be prepared in 2-steps from readily available starting materials and give the corresponding oxazoles 245 in excellent yield (74-98%). Although the substitution pattern of the product is specific, the ability to readily manipulate functionality in the 5-position of the oxazole makes this a useful procedure. Reducing the amount of silver required for this transformation would significantly increase the applicability of this process.

\[ \text{O} = \text{R}^1 \quad \text{MeS} \quad \text{NH} \quad \text{Ph} \quad \text{i)} \quad \text{O} \quad \text{MeS} \quad \text{O} \quad \text{Ph} \quad \text{245 (74-98\%)} \]

\[ R^1 = \text{EtO, MeO, t-BuO, PhO, Et, n-Bu, Ph, 4-MeOC}_6\text{H}_4, 2-\text{NH}_2\text{C}_6\text{H}_4\text{NH, PhNH}, 4-\text{MeOC}_6\text{H}_4\text{NH, 4-FC}_6\text{H}_4\text{NH, 4-Me-2-BrC}_6\text{H}_3\text{NH, EtNH}} \]

\[ \text{indol-3-yl-(CH}_2)_2\text{NH}, \text{PhCH}_2\text{NMMe, piperidin-1-yl, 4-benzylpiperazin-1-yl, 4-ETO}_2\text{C-piperazin-1-yl, MeSCH}_2\text{CH}_2\text{(CH)}\text{CO}_2\text{EtNH, i-Pr-(CH)}\text{CO}_2\text{EtNH, PhCH}_2\text{(CH)CO}_2\text{EtNH} \]

\[ \text{i) 306 (1.0 eq), Ag}_2\text{CO}_3 (4.0 eq), \text{MeCN, reflux, 3-4 h.} \]

Scheme 70. Ag(I)-mediated synthesis of oxazoles 245

The synthesis of vinyloxazoles 247 through the Ag(I)-catalysed cyclisation of allenylamides 246 was reported by Wan (Scheme 71). The reaction proceeds through intramolecular cyclisation of 248 to give

\[ \text{O} \quad \text{CO} \quad \text{N} \quad \text{Ts} \quad \text{R}^2 \quad \text{R}^1 \quad \text{i)} \quad \text{R}^1 \quad \text{O} \quad \text{N} \quad \text{R}^2 \quad \text{247 (58-85\%)} \]

\[ R^1 = \text{Ph, Me, 3-BrC}_6\text{H}_4, 3-\text{MeOC}_6\text{H}_4, 4-\text{MeC}_6\text{H}_4, 4-\text{FC}_6\text{H}_4, \text{furan-2-yl, cyclopentyl; R}^2 = \text{Ph, 2-FC}_6\text{H}_4, 3-\text{FC}_6\text{H}_4, 4-\text{BrC}_6\text{H}_4, \text{furan-2-yl, naphthalen-2-yl} \]

Proposed reaction mechanism

\[ \text{246} \quad \text{AgBF}_4 \quad \text{[Ag]} \quad \text{248} \quad \text{R}^2 \quad \text{N} \quad \text{Ts} \quad \text{R}^1 \quad \text{R}^1 \quad \text{CO}_2\text{Ts} \quad \text{249} \quad \text{R}^2 \quad \text{CO}_2\text{Ts} \]

\[ \text{i) AgBF}_4 (10 \text{ mol\%), PhMe, 80 °C, 16-20 h.} \]

Scheme 71. Ag(II)-catalysed cyclisation of allenylamides 246
followed by elimination of the sulfonyl and acyloxy groups. Substrates bearing a range of aryl and alkyl \( R^1 \) substituents and aryl \( R^2 \) groups successfully generated the corresponding oxazoles 247 in moderate to high yields.

More recently, Sueda reported the synthesis of 2,5-disubstituted oxazoles 252 (and 254) through the Ag(I)-catalysed cyclisation of ynimides 250 (and 253) in the presence of alcohols 251 (Scheme 72).\(^9\) The reaction proceeds via activation of the carbonyl group of the ynimide 250 by the silver catalyst, followed by addition of the alcohol 251 generating the N-alkynyl amide 258. Cyclisation of 258 gives the oxazole 252 and regenerates the catalyst. Ynimides bearing sterically demanding and aromatic substituents (\( R^1 \)) required harsh reaction conditions to bring about the transformation.

\[
\begin{align*}
\text{R}^1= & \text{n-Bu, cyclopropyl, t-Bu, Ph;} \\
\text{R}^2= & \text{Me, Et, CF}_3\text{CH}_2, \text{i-Pr, t-Bu, Ph}
\end{align*}
\]

Proposed reaction mechanism

\[
\begin{align*}
\text{i) 250 or 253 (1.0 eq), 251 (2.5 eq), Ag}_2\text{O (30 mol%), CH}_3\text{Cl}_2, \text{rt, 24 h; ii) 250 or 253 (1.0 eq), 251 (50.0 eq), Ag}_2\text{O (30 mol%), CH}_3\text{Cl}_2, 80^\circ\text{C, 1-24 h; iii) 250 or 253 (1.0 eq), 251 (solvent), Ag}_2\text{O (30 mol%), CH}_3\text{Cl}_2, 80^\circ\text{C, 1-24 h.}}
\end{align*}
\]

Scheme 72. Ag(I)-catalysed cyclisation of ynimides 250 (and 253) in the presence of alcohols 251
Each of these silver(I) catalysed processes represent effective methods for the preparation of oxazoles. The requirement to prepare highly specific substrates to bring about the transformation provides significant opportunities for developing this area of research further.

**COPPER(I), COPPER(II)**

In 1992, Das described a synthesis of trisubstituted oxazole 262 through the Cu(II)-mediated cyclisation of vinyl bromide 260 (and vinyl dibromide 261) in the presence of a base (Scheme 73).\(^9^2\) The proposed reaction mechanism involves the formation of a common intermediate followed by cyclisation to generate the oxazole 262 in good yield.

![Proposed reaction mechanism for Cu(II)-mediated synthesis of oxazoles](image)

Stahl described a synthesis of 2,5-disubstituted oxazoles 125 through a Cu(II)-mediated oxidative cyclisation of enamides 267 (Scheme 74).\(^9^3\) It was proposed the reaction proceeded via a radical pathway involving the single-electron oxidation of 267 by CuCl\(_2\), generating a radical-cation intermediate 268, followed by cyclisation to give 270. A second single-electron oxidation of 270 gives the observed oxazole 125. Oxygen re-oxidises the resulting Cu(I) species to Cu(II) completing the catalytic cycle. The best yields
were obtained with enamides 267 bearing electron-rich aromatic substituents, whereas their alkyl-substituted counterparts provided 125 in poor yield.

\[
\begin{align*}
\text{R}^1 & = \text{Ph, 4-MeOC}_6\text{H}_4, 4-\text{NO}_2\text{C}_6\text{H}_4, \ t\text{-Bu, PhCH}=\text{CH}; \\
\text{R}^2 & = \text{Ph, 4-MeOC}_6\text{H}_4, 3-4-\text{(MeO)}_2\text{C}_6\text{H}_3, 4-\text{ClC}_6\text{H}_4, 4-\text{MeC}_6\text{H}_4, 4-\text{t-BuC}_6\text{H}_4, \ n\text{-Bu}
\end{align*}
\]

Proposed reaction mechanism

\[
\begin{align*}
\text{R}^1 & = \text{Ph, 4-MeOC}_6\text{H}_4, 4-\text{MeC}_6\text{H}_4, 4-\text{ClC}_6\text{H}_4, 4-\text{FC}_6\text{H}_4, 4-\text{F}_3\text{CC}_6\text{H}_4, 4-\text{NO}_2\text{C}_6\text{H}_4, 3-\text{NO}_2\text{C}_6\text{H}_4, \\
& 4-\text{BrC}_6\text{H}_4, 4-\text{t-BuC}_6\text{H}_4, \ t\text{-Bu, 3,4,5-} (\\text{MeO})_3\text{C}_6\text{H}_2, \ 1\text{-cyclohexenyl, thiophen-2-yl,}
\text{thiophen-3-yl, furan-2-yl, 3,4-(MeO)}_2\text{C}_6\text{H}_3\text{CH}=\text{CH, 2-MeC}_6\text{H}_4, \ n\text{aphthalen-2-yl, PhCH}=\text{CH;}
\text{R}^2 & = \text{Ph, 4-MeOC}_6\text{H}_4, 4-\text{MeOCOC}_6\text{H}_4, 4-\text{MeC}_6\text{H}_4, 4-\text{ClC}_6\text{H}_4, 4-\text{BrC}_6\text{H}_4, 4-\text{FC}_6\text{H}_4, \\
& 3,4-\text{F}_2\text{C}_6\text{H}_3, 2-\text{MeC}_6\text{H}_4, \ n\text{-octyl, thiophen-3-yl, } N\text{-benzoyl-5-indolyl}
\end{align*}
\]

Proposed reaction mechanism

\[
\begin{align*}
\text{i} & \text{ CuCl}_2 (2.0 \text{ eq), } N\text{-methylimidazole (2.0 eq), air, 1,4-dioxane, 140 ^\circ\text{C}, 20 h.}
\end{align*}
\]

Scheme 74. Cu(II)-mediated oxidative cyclisation of enamides 267

\[
\begin{align*}
\text{R}^1 & = \text{Ph, 4-MeOC}_6\text{H}_4, 4-\text{MeC}_6\text{H}_4, 4-\text{ClC}_6\text{H}_4, 4-\text{FC}_6\text{H}_4, 4-\text{F}_3\text{CC}_6\text{H}_4, 4-\text{NO}_2\text{C}_6\text{H}_4, 3-\text{NO}_2\text{C}_6\text{H}_4, \\
& 4-\text{BrC}_6\text{H}_4, 4-\text{t-BuC}_6\text{H}_4, \ t\text{-Bu, 3,4,5-} (\\text{MeO})_3\text{C}_6\text{H}_2, \ 1\text{-cyclohexenyl, thiophen-2-yl,}
\text{thiophen-3-yl, furan-2-yl, 3,4-(MeO)}_2\text{C}_6\text{H}_3\text{CH}=\text{CH, 2-MeC}_6\text{H}_4, \ n\text{aphthalen-2-yl, PhCH}=\text{CH;}
\text{R}^2 & = \text{Ph, 4-MeOC}_6\text{H}_4, 4-\text{MeOCOC}_6\text{H}_4, 4-\text{MeC}_6\text{H}_4, 4-\text{ClC}_6\text{H}_4, 4-\text{BrC}_6\text{H}_4, 4-\text{FC}_6\text{H}_4, \\
& 3,4-\text{F}_2\text{C}_6\text{H}_3, 2-\text{MeC}_6\text{H}_4, \ n\text{-octyl, thiophen-3-yl, } N\text{-benzoyl-5-indolyl}
\end{align*}
\]

Proposed reaction mechanism

\[
\begin{align*}
\text{i} & \text{ CuBr}_2 (7.5-15 \text{ mol%), ethyl nicotinate (15-30 \text{ mol%), TBAB (1.2 eq), K}_2\text{S}_2\text{O}_8 (1.3 eq), MeCN, rt, 24 h.}
\end{align*}
\]

Scheme 75. Cu(II)-catalysed oxidative cyclisation of enamides 272
The substrate scope for this class of transformation was expanded by Buchwald, who described the preparation of 2,5-disubstituted oxazoles 125 through the Cu(II)-catalysed oxidative cyclisation of enamides 272 (Scheme 75). In a similar manner to the vinylic C—H functionalization developed by Stahl, the reaction involves the single-electron oxidation of 272 by CuCl₂, generating a radical-cation 273, which undergoes cyclisation. A second single-electron oxidation of 271 leads to 125. The reduced Cu(I) species generated is re-oxidised to Cu(II) by potassium persulfate completing the catalytic cycle. A wide variety of enamides 272 underwent oxidative cyclisation to yield 2,5-disubstituted oxazoles 125 in moderate to excellent yields under exceptionally mild reaction conditions.

The synthetic application of this class of transformation was expanded to include the preparation of 2,4,5-trisubstituted oxazoles 275 through the Cu(I)-catalysed 5-endo-trig cyclisation of β-(methylthio)enamides 274 (Scheme 76). This protocol provides considerable advantages over the previous Ag(I)-mediated cyclisation described above (Scheme 70), including the use of catalytic amounts of copper and the ability to introduce carbon based substituents at the 5-position.

![Scheme 76](image.png)

Scheme 76. Cu(I)-catalysed synthesis of oxazoles 275

Overall the copper catalysed processes described deliver high functional group tolerance and good structural diversity in the oxazole products. Although commercial availability of substrates is limited, challenges to prepare these compound are less significant than with alternative approaches.

**PALLADIUM(0) AND PALLADIUM(II)**

Cacchi described the synthesis of 2,5-disubstituted oxazoles 277 through the Pd(0)-catalysed reaction of N-propargylamides 194 and aryl iodides 276 (Scheme 77). The reaction appears to proceed through a palladium catalysed coupling followed by intramolecular cyclisation to give the observed oxazoles 277. Although little mechanistic evidence was provided in this study a competing base-mediated cyclisation to...
generate 195 was also noted. A more detailed understanding of this protocol will render this simple methodology very attractive.

![Chemical Reaction](image_url)

\[ R^1 = \text{Ph, 4-MeOC}_8\text{H}_4, \text{3-CF}_3\text{C}_8\text{H}_4, \text{CF}_3, \text{4-MeC}_8\text{H}_4; \]
\[ R^2 = \text{2-MeC}_6\text{H}_4, \text{3-MeC}_6\text{H}_4, \text{4-MeC}_6\text{H}_4, \text{3,5-Me}_2\text{C}_6\text{H}_3, \text{3-MeOC}_6\text{H}_4, \text{4-MeOC}_6\text{H}_4. \]

\[ \text{Ph, 4-ClC}_6\text{H}_4, \text{3-CF}_3\text{C}_6\text{H}_4, \text{3-FC}_6\text{H}_4, \text{4-FC}_6\text{H}_4, \text{4-MeCOC}_6\text{H}_4 \]

i) 194 (1.0 eq), 276 (1.2 eq), NaOt-Bu (2.0 eq), Pd\(_2\)(dba)\(_3\) (2.5 mol%), P(2-furyl)\(_3\) (10 mol%), MeCN, 40 °C, 4-20 h.

Scheme 77. Pd(0)-catalysed/base-mediated synthesis of oxazoles 277

Saito and Hanzawa expanded the substrate scope of this class of transformation to encompass the coupling of terminal and internal \(N\)-propargylamides 278 with allyl ethyl carbonate 279 (Scheme 78).97 Although a number of allyl carbonate derivatives were successfully employed for this transformation, competing reaction pathways detract from this method.96

![Chemical Reaction](image_url)

\[ R^1 = \text{Ph, H, 4-MeOC}_8\text{H}_4, \text{4-MeC}_8\text{H}_4, \text{4-ClC}_8\text{H}_4, \text{4-NO}_2\text{C}_8\text{H}_4, 2\text{-thienyl, 2-furyl, CH=CH}_2\text{Ph, CH}_2\text{CH}_2\text{Ph}; \]
\[ R^2 = \text{H, Et, t-Bu, Ph, 4-MeOC}_8\text{H}_4, \text{4-NO}_2\text{C}_8\text{H}_4 \]

i) 278 (1.0 eq), 279 (3.0 or 6.0 eq), Pd\(_2\)(dba)\(_3\) (2.5 or 5 mol%), P(2-furyl)\(_3\) (10 or 20 mol%), C\(_9\)H\(_8\) (3.0 or 6.0 eq), MeCN, 90 °C, 21 h.

Scheme 78. Pd(0)-catalysed cycloisomerisation-allylation reaction of \(N\)-propargylamides 278 and allyl ethyl carbonate 279

The synthesis of 2,5-disubstituted oxazoles 282 through the Pd(II)-catalysed oxidative cyclisation of \(N\)-propargylamides 194 in the presence of an oxidant 317 was reported by Broggini (Scheme 79).98 The reaction proceeds via the intramolecular nucleophilic attack of the carbonyl oxygen at the Pd(II)-activated triple bond to give 284. Reaction of 284 with water generates 285, which undergoes reductive elimination to form 286 and a Pd(0) species. Tautomerisation of 256 furnishes oxazoline 287. Subsequent oxidation of 287 and the Pd(0) species gives the desired oxazoles 282 and regenerates the catalyst. A variety of \(N\)-propargylamides 194 bearing aliphatic and aromatic substituents were successfully employed in this transformation, affording 5-oxazolecarboxaldehydes 282 in moderate to good yields.
The accessibility of \(N\)-propargyl amides makes the palladium catalysed synthetic strategy to prepare oxazoles very attractive. Focus on rendering the subsequent functionalisation of the Pd(II) intermediate selective will undoubtedly increase the uptake of this work.

**MERCURY(II)**

The first example of Hg(II)-mediated cycloisomerisation of \(N\)-propargylamides 194 to oxazoles was reported by Deryckere in 1973 (Scheme 80).\(^9\) Reaction of 194 with Hg(OAc)\(_2\) in the presence of acetic acid provided moderate to good yields of oxazole 195 (50–74\%). This protocol has found a number of applications in the synthesis of bioactive oxazole-containing compounds.\(^1\)

\[
\begin{align*}
\text{Scheme 80. Hg(II)-mediated cycloisomerisation of } \text{N-propargylamides } 194 \\
\end{align*}
\]

Kim used this protocol to develop a ratiometric chemodosimeter for the selective detection of mercuric ions based on the cyclisation of 288 in aqueous ethanol (Scheme 81).\(^1\) Hg(II)-promoted intramolecular cyclisation of 288 generates 292, which reacts with water and a second Hg(II) ion to form the dimercurate.
intermediate 293. Loss of mercury leads to oxazole 289.

Scheme 81. Hg(II)-mediated synthesis of oxazole 289

**TUNGSTEN(0)**

Kim has also shown that the W(0)-catalysed cyclisation of terminal N-propargylamides 175 in the presence of trimethylamine N-oxide as an oxidant leads to a mixture of oxazoline 294 and oxazole 174 with low levels of selectivity (Scheme 82).

![Scheme 82. W(0)-catalysed cyclisation of N-propargylamides 175](image)

The O1–C5 bond disconnection represents a simple and versatile method for the preparation of mono-, di- and tri-substituted oxazole products using a broad range of transition metal catalysts. Improving access to the appropriate starting materials for many of these transformations would enhance the applicability of this strategy.
Ganem reported the synthesis of 2,5-disubstituted oxazoles 298 through the Zn(II)-promoted three-component condensation of ethyl isocyanatoacetate 295, carbonyl compounds 296 and trimethylsilyl chloride 297 in the presence of a base (Scheme 83). The reaction proceeds via the nucleophilic attack of 295 on 296 to give a nitrilium ion 299. Intramolecular cyclisation of 299 generates 300, which upon deprotonation leads to 298. A range of aliphatic and aromatic carbonyl compounds 296 could efficiently be employed in this transformation. This metal-promoted variant of the Passerini reaction provides a mild protocol for the synthesis of a range of 2-substituted-5-alkoxyoxazoles in moderate yield.

Scheme 83. Zn(II)-promoted synthesis of oxazoles 298

The substrate scope of this transformation was expanded to the condensation of isocyanatoacetamides 301 and carbonyl compounds 302 in the presence of silyl chlorides 303 (Scheme 84). A number of
2-substituted 5-aminooxazoles could be obtained in good yields via this method. 2,4,5-Trisubstituted oxazoles can also be accessed through the Zn(II)-promoted four-component condensation of isocyanooacetamides, carbonyl compounds and silyl chlorides.\textsuperscript{107}
Scheme 85. Zn(II)-mediated synthesis of oxazoles 307

Trisubstituted oxazoles 307 have also been prepared through the Zn(II)-mediated reaction of \( \alpha \)-isocyanooacetimidates 305 and propargylamines 306 (Scheme 85). The reaction proceeds via the formation of an alkyne-ZnBr\(_2\) \( \pi \)-complex 308, which undergoes 1,5-hydride shift to generate iminium ion.
310. Interaction of 305 and 310 leads to 311, which undergoes cyclisation to form 312. Aromatisation of 312 generates 313, which upon 1,6-elimination of an allylamine and subsequent isomerisation gives 307. A range of isocyanooacetamidates 305 bearing benzyl, alkyl and aryl substituents and a series of alkyl-substituted propargylamines 306 were successfully employed in this transformation.

**TIN(II)**

Oxazoles 316 can be prepared through the Sn(II)-catalysed condensation of α-isocyanooacetamides 305 and aldehydes 315 under very mild reaction conditions (Scheme 86). This transformation works well with a range of aliphatic linear and α-branched aldehydes 315, whereas aromatic aldehydes were generally less effective substrates and required extended reaction times. Use of a chiral supporting ligand gave the product with up to 80% ee.

![Scheme 86. Sn(II)-catalysed synthesis of oxazoles 316](image)

The O1–C2 bond disconnection for the preparation of oxazoles is substantially less explored than alternative disconnections due to the challenges associated with preparation of the required isonitriles. However, functional group tolerance and mild conditions provide significant opportunities for the preparation of richly functionalised oxazole products.

**O1–C2, O1–C5 AND N3–C4 BOND DISCONNECTION**

**COPPER(II)**

Jiang described an intriguing Cu(II)-catalysed [2+2+1] cycloaddition of internal alkynes 145, nitriles 2 and water (Scheme 87). The transformation proceeds via the regioselective nucleophilic addition of a nitrile 2 to a Lewis acid activated alkyne 145 leading to 317. Addition of water followed by isomerisation and reductive elimination gives 75. Dioxygen oxidises the reduced copper species completing the catalytic cycle. Importantly, the reaction of unsymmetrical alkynes proceeds with predictable regioselectivity based
upon electronic effects. The transformation showed good compatibility with a range of functional groups, providing a rapid and convenient access to the trisubstituted oxazole core.

![Scheme 87](image)

**Proposed reaction mechanism**

i) 2 (2.5 or 3.0 eq), 145 (1.0 eq), Cu(OAc)$_2$ (5 or 10 mol%), BF$_3$·OEt$_2$ (1.0 eq), H$_2$O (5.0 eq), O$_2$ (1 atm), MeNO$_2$ (solvent), 80 or 100 °C, 12 h.

Scheme 87. Cu(II)-catalysed [2+2+1] annulation for the synthesis of oxazoles 75

Jiao described a highly efficient synthesis of disubstituted oxazoles 125 through the Cu(II)-mediated aerobic oxidative dehydrogenative annulation of aldehydes 320 and amines 321 (Scheme 88). The proposed mechanism involves the oxidation of an imine 322 to give a radical 323, which undergoes 1,5-hydrogen atom abstraction and subsequent intramolecular radical coupling leading to an oxazoline 325. Oxidation of 325 with molecular oxygen provides the oxazole 125. A broad variety of readily available aryl and aliphatic amines 321 could efficiently be converted to the corresponding oxazoles 125 using this method. The ability to form the oxazole core with specific substitution from such simple starting materials renders this a powerful piece of methodology.
Au(I)-catalysed [2+2+1] annulation of alkynes 123, nitriles 2 and an N-oxide also leads to the corresponding oxazole (Scheme 89). The reaction proceeds via the Au(I)-catalysed oxidation of alkyne 123, to give the gold carbene intermediate 326. In situ reaction of 326 with a nitrile 2 leads to the oxazole product 125. A broad variety of functional groups are tolerated using this method giving the oxazole in good to excellent isolated yields (59–93%). The method provides an attractive alternative to the use of hazardous \( \alpha \)-diazoketones, generating an \( \alpha \)-oxo gold carbene in situ. Due to the high reactivity of gold carbenes it was necessary to use the nitrile as the solvent to bring about an efficient transformation. This drawback can be circumvented by the use of the more expensive catalyst BrettPhosAuNTf₂ which allows the use of three equivalents of the nitrile substrate to achieve acceptable yields. The mild reaction conditions and functional group tolerance make this a particularly attractive convergent method for the preparation of 2,5-substituted oxazoles.
Lee reported a rapid microwave-assisted synthesis of 2,4- and 2,4,5-substituted oxazoles through the Hg(II)-mediated reaction of aromatic ketones 61 and benzonitrile 13 (Scheme 90). The reaction proceeds as follows:

**Scheme 90. Hg(II)-mediated synthesis of oxazoles 328**

\[
\begin{align*}
\text{R}^1 &= \text{Ph, 4-ClC}_6\text{H}_4, 4-\text{MeC}_6\text{H}_4, 4-\text{FC}_6\text{H}_4, \text{CO}_2\text{Et;} \\
\text{R}^2 &= \text{H, Me, CH}_2\text{Me}
\end{align*}
\]

i) 61 (1.0 eq), 13 (5.0 eq), Hg(OTs)\(_2\) (1.0 eq), MW irradi, 2-4 min.
via the enolisation of 61 to generate 329, reaction of 329 with the nitrile to give 333, which upon aromatisation gives the observed oxazole 328. Ketones bearing a more acidic methylene group α- to the carbonyl functionality proved to be more effective substrates for this transformation, potentially due to a higher enol content.

The ability to construct three bonds in one-pot provides an attractive, versatile and diversity oriented method for the preparation of oxazoles. Of particular note is the combination of alkynes and nitriles or ketones and nitriles. Construction of oxazoles from each of these combinations of monomers provides excellent opportunity for significant structural diversity in the heterocyclic products.

O1–C5 AND C2–N3 BOND DISCONNECTION

PALLADIUM(II) AND COPPER(I)

An interesting one-pot three-component synthesis of oxazoles 336 using both Cu(I)- and Pd(II)-catalysis was reported by Müller (Scheme 91). The reaction proceeds via a proposed amidation-coupling-cycloisomerisation sequence (ACCI). Reaction of 335 with 173 generates amide 194, which undergoes coupling with 334 under modified Sonogashira conditions to give 337. Brønsted acid-mediated cycloisomerization of 337 yields oxazoles 336. A range of acid chlorides 334 and 173 were employed in this protocol, providing the corresponding oxazoles 336 in moderate to good yields. Müller also exploited this transformation in a four-component procedure.

Scheme 91. One-pot three-component synthesis of oxazoles 336
ZINC(II)

Trisubstituted oxazoles 340 can also be prepared through the Zn(II)-mediated coupling of isonitriles 338 with carboxylic acids 339 (Scheme 92). Addition of the carboxylic acid 339 to a Lewis acid activated isonitrile followed by migratory insertion leads to 343. Coordination of 343 with a second isonitrile leads to 344, which undergoes a second migratory insertion leading to 346. The resulting ketenimine 346 undergoes rearrangement to give 347. Intramolecular cyclisation of 347 followed by dealkylation provides the observed oxazole 340. A stoichiometric amount of ZnBr₂ is required for this protocol, due to the oxazole’s ability to chelate Zn²⁺ ions, however, a broad scope of isonitriles 338 as well as a wide range of carboxylic acids 339 bearing aromatic, heteroaromatic, aliphatic and α,β-unsaturated substituents could effectively be used in this process.

Scheme 92. Zn(II)-mediated synthesis of oxazoles 340
There has been significant progress in developing multi-component methods using simple starting materials in recent years providing accessible and versatile methods for the preparation of the core oxazole structure which should find good applicability in the field of medicinal chemistry.

**O1–C5 AND C4–C5 BOND DISCONNECTION**

**TIN(IV)**

Bisoxazoles 350 are available through the Sn(IV)-mediated reaction of diamides 349 and acetic anhydride (Scheme 93).\(^{117}\) Although this protocol furnished bisoxazoles 350 in good to excellent yields, the substrate scope reported was limited to 4,4'-pyridyl and 5,5'-methyl substituents. Further exploration and understanding of this scope would be useful.

**Scheme 93. Sn(IV)-mediated synthesis of bis-oxazoles 350**

**ZINC(II)**

Ciufolini described an automated parallel synthesis of 2,4,5-trisubstituted oxazoles 352 through the Zn(II)-mediated cyclisation of isonitriles 338 and α-chloroglycinates 351 (Scheme 94).\(^{118}\) Although Me₂AlCl proved to be a superior Lewis acid promoter for this transformation, automated parallel reactions were conducted using ZnCl₂ due to the convenience of handling this reagent.

**Scheme 94. Zn(II)-mediated synthesis of oxazoles 352**
GOLD(III)
The Au(III)-catalysed synthesis of oxazoles 354 through the cycloisomerisation of propargyl trichloroacetimidates 353 was disclosed by Hashmi (Scheme 95).\textsuperscript{119,120} Only two substrates (353; R = H or Me) were reported to be successful under these conditions, which provides significant opportunity to expand the functional group tolerance and substrate scope of this promising procedure. Interestingly, when using Au(I) catalysts the intermediate 355 could be isolated in good yield (81%, R\textsuperscript{1} = H).

\begin{center}
\begin{tikzpicture}
\node (A) at (0,0) {353 \quad \text{R}^1 = H (82\%), Me (29\%)};
\node (B) at (2,0) {354 \quad 355}
\draw[->,thick] (A) -- (B) node[midway, above] {i) AuCl\textsubscript{3} (3 mol\%, 10 w/w\% in CD\textsubscript{3}CN), CDCl\textsubscript{3}, rt., 3 d.}
\end{tikzpicture}
\end{center}

Scheme 95. Au(III)-catalysed cycloisomerisation of propargyl trichloroacetimidates 353

It is interesting that the corresponding intermolecular reaction of propargylic alcohols with nitriles has yet to be described to access the oxazole core suggesting this procedure is challenging to bring about.

O1–C2 AND C4–C5 BOND DISCONNECTION

COPPER(I)
Ila reported a novel synthesis of bis-oxazole 358 through the Cu(I)-catalysed reaction of oxazolone 356 and isocyanides 357 (Scheme 96).\textsuperscript{121} The reaction proceeds via the nucleophilic ring opening of 356 by the organo copper species 365 generating the copper enolate 360, which undergoes cyclisation to intermediate 361. Protonation of 361 gives oxazole 362 and regenerates the active catalyst. The resulting oxazole 362 undergoes formation of the copper chelated intermediate 363, which leads to bis-oxazole 358 via a 5-endo cyclisation. This protocol provides additional flexibility for access to a trisubstituted oxazole core when compared to the related methods developed by the same group.\textsuperscript{89,95}
O1–C5, C2–N3 AND C4–C5 BOND DISCONNECTION

GOLD(III)

A one-pot three-component Au(III)-catalysed synthesis of trisubstituted oxazoles 368 from N-benzylimines 366, acid chlorides 367 and alkynes 123 was recently described by Strand (Scheme 97). The reaction proceeds via coupling of a copper acetylide 370 with an iminium species 369 to give a propargylamide 371. Cyclisation of 371 by acid catalysis followed by debenzylation generates 373. Isomerisation of 373 forms...
Substrate scope encompassed aliphatic, aryl and heteroaryl substituents. The method allows for preparation of a range of trisubstituted oxazoles 368 in moderate to excellent yields. The same transformation was performed in a seven-component fashion, which provided a tris-oxazole product in modest yield.\textsuperscript{122}

\[
\begin{align*}
R^1 &= \text{adamantan-1-yl, } t-\text{Bu, } \text{MeO}_{2}\text{CC(Me)}_2, \text{H, Ph, } \text{BnOCH}_2\text{C(Me)}_2, \text{CH}_2=\text{CHCH}_2\text{C(Me)}_2; \\
R^2 &= 4-\text{FC}_6\text{H}_4, t-\text{BuSiMe}_2, \text{ClCH}_2\text{CH}_2\text{Cl}; \\
R^3 &= 4-\text{FC}_6\text{H}_4, \text{thiophen-2-yl, } i-\text{Bu, 4-} \text{MeOC}_6\text{H}_4, t-\text{Bu, Ph}
\end{align*}
\]

Scheme 97. Three-component Au(III)-catalysed domino reaction

\begin{align*}
\text{O1–C5, C2–N3, N3–C4 AND C4–C5 BOND DISCONNECTION}
\end{align*}

\textbf{COPPER(I)}

A one-pot four-component Cu(I)-catalysed synthesis of oxazoles 368 from an alkyne 123, aldehyde 377, acid chlorides 367 and silylamide 378 has been described (Scheme 98).\textsuperscript{123} The reaction proceeds via imine formation followed by acylation to generate an iminium species 380. Coupling of 380 with a copper acetylide 382 generates a secondary propargylamide 381, which undergoes cycloisomerisation in the presence of a base to provide oxazole 368. This transformation can also be performed using Zn(II)-catalysis.\textsuperscript{123} The protocol allows for the rapid assembly of trisubstituted oxazoles from simple building blocks.
This ambitious process proceeds in remarkably high yields and provides an exceptionally effective way of preparing densely functionalised tri-substituted oxazole products. Although the strongly basic reaction conditions limit functional group tolerance, the ability to combine four components in a controlled and reliable manner is testament to understanding and knowledge of mechanism and reactivity applied in the development of this transformation.

**CONCLUSIONS**

The repertoire of chemical transformations developed for assembly of the oxazole ring is extensive. This is particularly the case for transition metal catalysed processes. In recent years significant progress has been made in developing simple and effective methods for the preparation of this important heterocycle. Of note is the emerging trend to develop protocols which have applicability to medicinal chemistry through the use of starting materials for which diverse monomer sets exist. Efforts to combine multi-step sequences into one-pot procedures have proved successful in this field circumventing the challenges associated with preparation of complex or unstable starting materials. This review has highlighted this progress and revealed further opportunities to develop additional oxazole-ring forming protocols. Notwithstanding the
considerable advances achieved in this field, synthetic applications of transition metals have not yet been fully exploited. A more detailed understanding of reactivity and selectivity will be essential to create a platform for further development.

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REFERENCES

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Stefano Bresciani was born in Viadana, Italy, in 1979. He received his M.Sc. in Chemistry and Pharmaceutical Technologies (2004) from the University of Parma. After around two years in industry, he moved to the University of St Andrews in 2007, where he received his PhD (2010) in organofluorine chemistry under the supervision of Professor David O’Hagan. In 2011 he joined the research group of Professor Nicholas Tomkinson for a postdoctoral position in synthetic organic and medicinal chemistry. This included an initial period at the University of Strathclyde, Glasgow, UK. He is currently completing his postdoctoral contract (2011–present) at GlaxoSmithKline, Stevenage, UK.

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