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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.[1] 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 benzoxazoles 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.

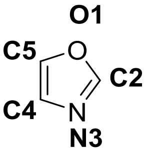
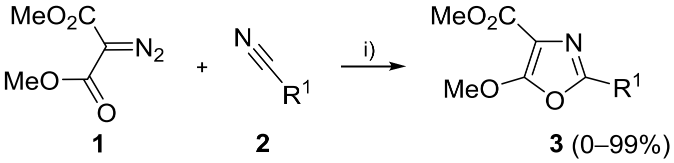


Figure 1. The oxazole unit

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.

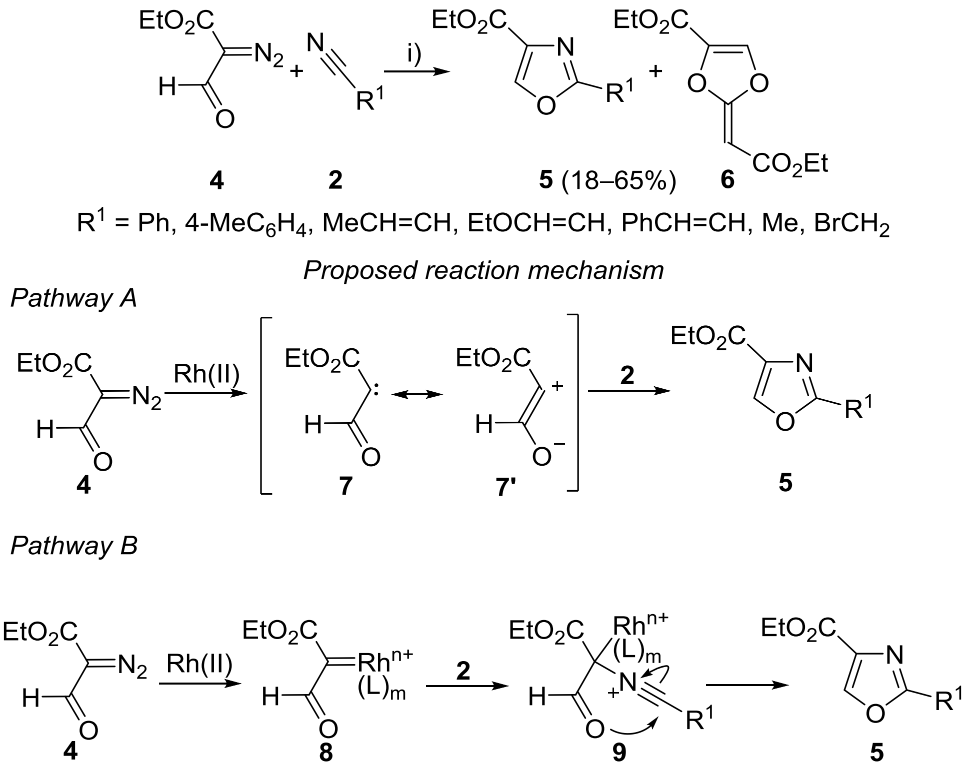


R^1 = Ph, 4-ClC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-NO$_2$C$_6$H$_4$, 3-ClC$_6$H$_4$, PhCH$_2$, PhCH=CH, Me, *n*-Pr, Me(CH$_2$)$_7$CH$_2$, *i*-Pr, *t*-Bu, MeCH=CH, CH$_2$=CHCH$_2$, HOCH$_2$CH$_2$, EtOCH=CH

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.

Scheme 1. Rh(II)-catalysed synthesis of oxazoles **3**

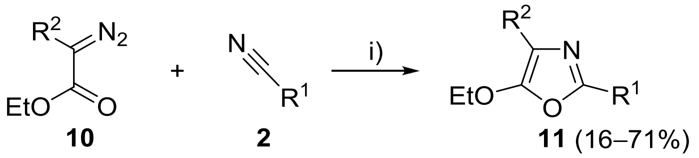
The applicability of this transformation was extended by Helquist, who described the regioselective preparation of 2,4-disubstituted oxazoles **5** through the Rh(II)-catalysed decomposition of ethyl formyldiazomalonate **4** in the presence of nitrile **2** as the solvent (Scheme 2).[3,5] The reaction 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**.



i) **4** (1.0 eq), **2** (solvent), $Rh_2(OAc)_4$ (1.5 mol%), 65-95 °C, 10 h.

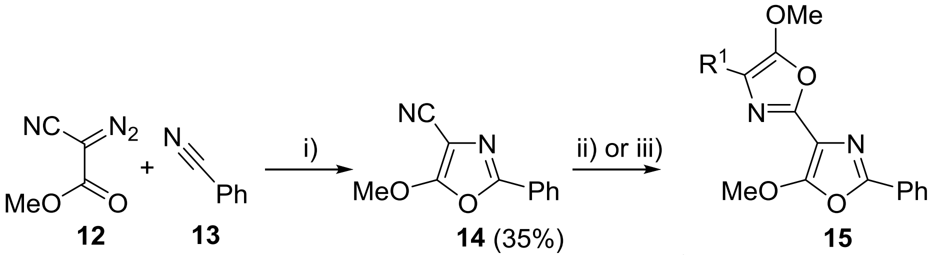
Scheme 2. Rh(II)-catalysed synthesis of oxazoles **5**

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).[6,7] In some cases, Rh(II) trifluoroacetamide proved to be a more efficient catalysts 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).[6,7]



R^1 = Et, Ph, 2-ClC_6H_4, 4-ClC_6H_4, 3-$MeOC_6H_4$, 4-$MeOC_6H_4$, thiophen-2-yl;
R^2 = SO_2Ph, $PO(OEt)_2$, CN
i) **10** (1.0 eq), **2** (1.5-5.0 eq), $Rh_2(OAc)_4$ (1 mol%), $CHCl_3$, rt, 6-10 h then reflux 1 h.

Scheme 3. Rh(II)-catalysed syntheses of oxazoles **11**

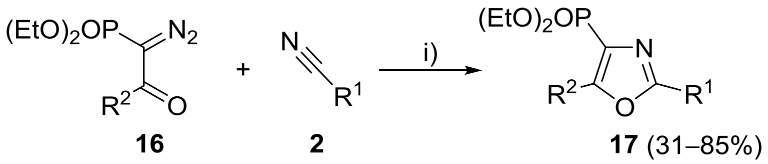


R^1 = CN (62%), CO_2Me (53%)

i) **12** (1.0 eq), **13** (2.0 eq), $Rh_2(OAc)_4$ (1 mol%), $CHCl_3$, rt, 20 h, then reflux, 2 h;
ii) $(MeO_2C)_2C=N_2$ (1.2 eq), $Rh_2(NHCOCF_3)_4$ (2 mol%), $CHCl_3$, rt, 10 h, then reflux, 2 h;
iii) **12** (2.0 eq), $Rh_2(OAc)_4$ (5 mol%), $CHCl_3$, rt, 10 h, then reflux, 4 h.

Scheme 4. Rh(II)-catalysed synthesis of bisoxazoles **15**

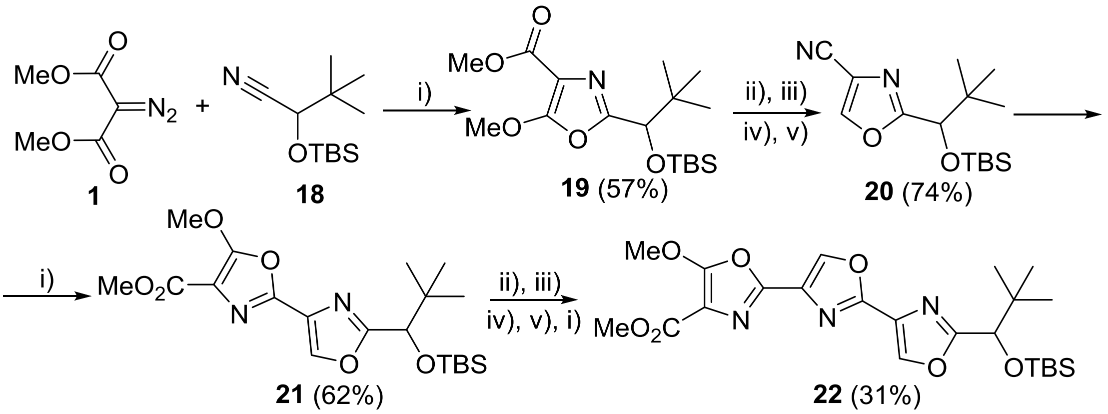
Yuan further extended the scope of the 4-substituent by the preparation of oxazole-4-phosphonates **17** through the Rh(II)-catalysed reaction of diazophosphonates **16** and a nitrile **2** (Scheme 5).[8] The substrate scope reported was limited to aromatic nitriles.



R^1 = Ph, 2-MeC_6H_4, 3-MeC_6H_4;
R^2 = Me, Ph, MeO, EtO
i) **16** (1.0 eq), **2** (solvent), $Rh_2(OAc)_4$ (1 mol%), 85 ºC.

Scheme 5. Rh(II)-catalysed synthesis of oxazoles **17**

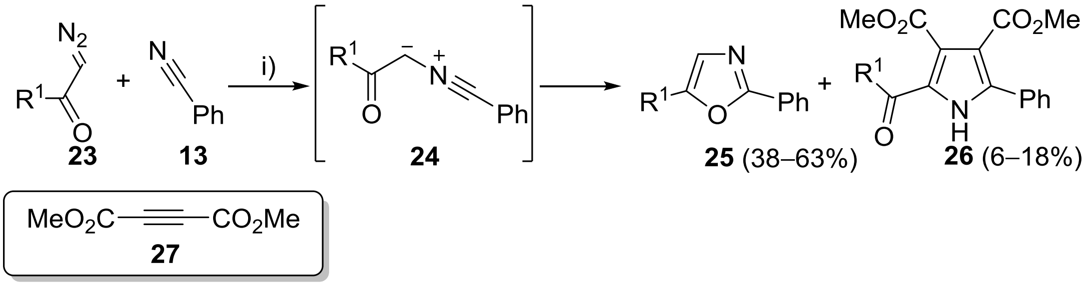
Exploitation of this strategy in the preparation of poly-oxazole systems was reported by Yoo, who demonstrated the synthesis of tris-oxazole **22** through sequential Rh(II)-catalysed reactions of dimethyl diazomalonate **1** with nitrile **18** (Scheme 6).[9] The presence of poly-oxazole motifs in marine metabolites makes this an attractive protocol in natural product synthesis.



i) **1** (1.5 eq), **18** (1.0 eq), $Rh_2(OAc)_4$ (2.0 mol%), $CHCl_3$, reflux; ii) $LiAlH_4$ (0.8 eq), THF, -78 °C for 3 h then rt; iii) oxalyl chloride, DMSO, NEt_3, CH_2Cl_2; iv) $NH_2OH{\cdot}HCl$, K_2CO_3, EtOH; v) triflic anhydride, Et_3N, CH_2Cl_2, -78 °C to 0 °C.

Scheme 6. Rh(II)-catalysed synthesis of tris-oxazole **22**

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).[10] 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**.

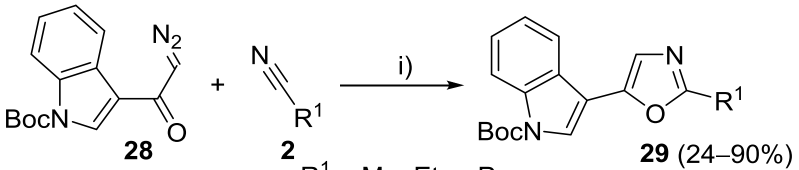


R^1 = 4-$MeOC_6H_4$, Ph, 4-ClC_6H_4, 3-ClC_6H_4, 4-CNC_6H_4, 4-$NO_2C_6H_4$, 3-$NO_2C_6H_4$

i) **25** (1.0 eq), **27** (20.0 eq), **13** (solvent), $Rh_2(OAc)_4$ (5 mol%), 60 °C.

Scheme 7. Rh(II)-catalysed reaction of **23** and **13** in the presence of **27**

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.[11,12] 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.[12]



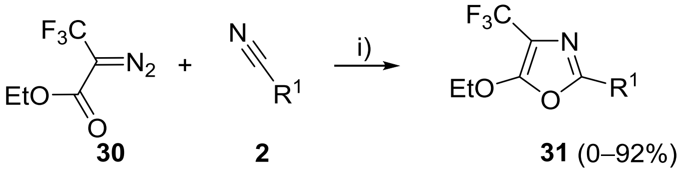
R^1 = Me, Et, *n*-Pr

i) **28** (1.0 eq), **2** (solvent), $Rh_2(NHCOCF_3)_4$ (1 mol%), $CHCl_3$, rt, 3-14 h.

Scheme 8. Rh(II)-catalysed synthesis of oxazolylindolyl alkaloids **29**

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,[13] siphonazole,[14] leucascandrolide A,[15] telomestatin,[16] nocardimicin B[17] and discokiolide B.[18]

Xu described the preparation of fluorinated oxazoles **31** using the reaction of ethyl 3-trifluoro-2-diazo-propionate **30** and nitriles **2** (Scheme 9).[19] Interestingly, there was no formation of oxazole observed from picolinonitrile (R^1 = pyridin-2-yl) under the reaction conditions.

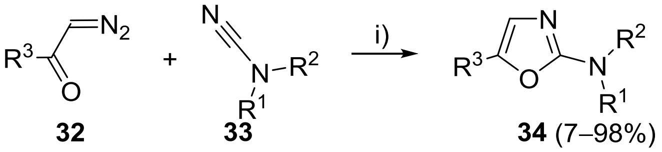


R^1 = Ph, 4-ClC_6H_4, Bn, pyridin-2-yl, MeCH=CH, Me, EtO_2CCH_2

i) **30** (1.3 or 2.0 eq), **2** (1.0 eq), $Rh_2(OAc)_4$ (1 mol%), $CHCl_3$, reflux, 5 or 6 h.

Scheme 9. Rh(II)-catalysed synthesis of oxazoles **31**

Ibata further extended this work using cyanamides **33** as substrates to furnish 2-aminooxazoles **34** (Scheme 10).[20] The substrate scope of this reaction was quite broad, however unsubstituted and monoalkyl cyanamides **33** generated the corresponding oxazole in low yield.

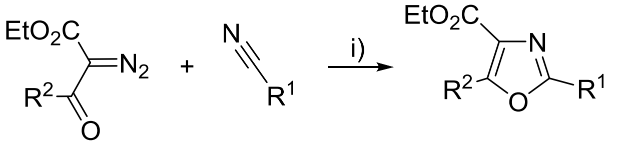


R^1, R^2 = *i*-Pr, H, Me, *t*-Bu, Et, -$(CH_2)_5$-, Ph;
R^3 = 4-$NO_2C_6H_4$, 4-CNC_6H_4, 4-ClC_6H_4, Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, H, Me

i) **32** (1.0 eq), **33** (10 eq or solvent), $Rh_2(OAc)_4$ (5 mol%), CH_2Cl_2, 40 °C or 60 ºC, 3 h.

Scheme 10. Rh(II)-catalysed reaction of diazoacetophenones **32** and cyanamides **33**

More recently Zhu showed fluorination of the 5-substituent was also possible using this diazonium technology (Scheme 11).[21] 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.



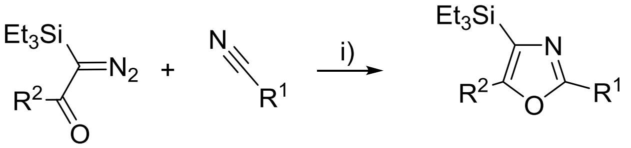
35 **2** **36** (32–95%)

R^1 = C_6H_5, 3-MeC_6H_4, Bn, MeCH=CH, $ClCH_2$;
R^2 = CF_3, ClC_3F_6, C_5F_{11}

i) **35** (1.0 eq), $Rh_2(OAc)_4$ (0.5-2 mol%), **2** (solvent), 80-90 °C, 8 h.

Scheme 11. Rh(II)-catalysed synthesis of oxazoles **36**

Marsden prepared 4-silylated oxazoles **38** by performing a Rh(II)-catalysed reaction of (triethylsilyl)diazoacetates **37** and nitriles **2** (Scheme 12).[22] 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.



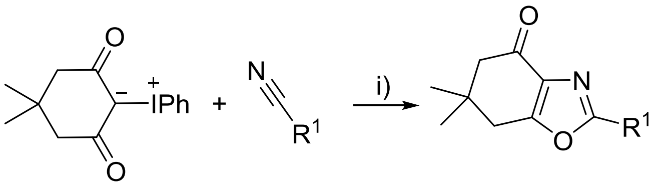
37 **2** **38** (0–81%)

R^1 = Ph, Me, Et, thiophen-2-yl, furan-2-yl, pyridin-2-yl, MeCO, MeO_2C, MeO_2CCH_2, CH_2=CH, MeCH(OH), MeCH(OTBS), Me_2N;
R^2 = EtO, *t*-BuO

i) **37** (1.0 eq), **2** (4.0 eq), $Rh_2(oct)_4$ (1-5 mol%), PhH, 0.5-24 h, reflux.

Scheme 12. Rh(II)-catalysed synthesis of oxazoles **38**

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 Hadjìarapoglou (Scheme 13).[23] Notably, the rhodium catalysed transformation proceeded with higher yields than the analogous Cu(II)-catalysed process.



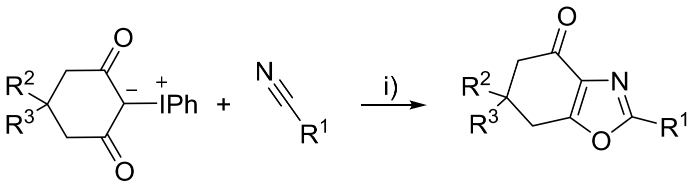
39 **2** **40** (23–68%)

R^1 = Me, $ClCH_2$, $PhCH_2$, Ph, 4-MeC_6H_4

i) **39** (1.0 eq), **2** (solvent) $Rh_2(OAc)_4$ (cat.), reflux or 80-100 °C, 30 min-1 h.

Scheme 13. Rh(II)-catalysed reaction of iodonium ylides **39** and nitriles **2**

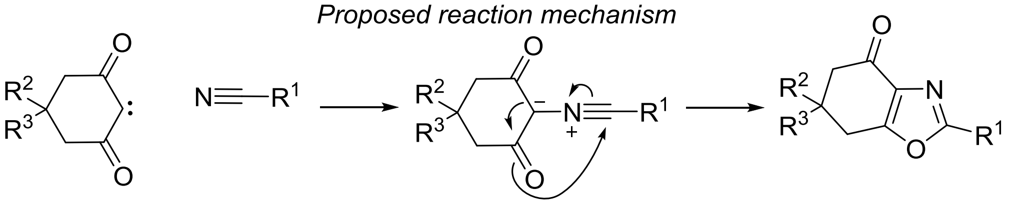
Lee extended the scope of this transformation to the reaction of iodonium ylides **41** and nitriles **2** to generate oxazoles **42** (Scheme 14).[24] The reaction proceeded *via* formation of the carbene **43**, which reacts with **2** to generate a nitrile ylide **44** followed by cyclisation to give **42**. Along with formation of oxazoles, an undesired transformation leading to a dihydrofuran nucleus also takes place.



41 **2** **42** (20–59%)

R^1 = CH_2=CH, CH_2=CMe, MeCH=CH, $MeCH_2CH$=CH;
R^2, R^3 = H, Me, Ph

Proposed reaction mechanism

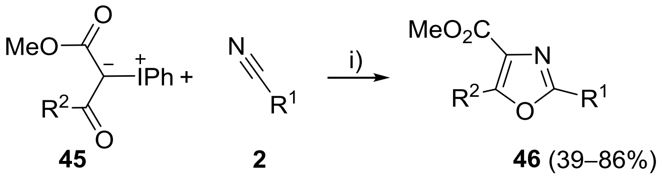


43 **2** **44** **42**

i) **41** (1.0 eq), $Rh_2(OPiv)_4$ (0.5 mol%), **2** (solvent), rt, 12 h.

Scheme 14. Rh(II)-catalysed synthesis of oxazoles **42**

The scope of this approach was extended by Hadjìarapoglou to the synthesis of trisubstituted oxazoles **46** through the reaction of carbomethoxy iodonium ylides **45** and nitriles **2** (Scheme 15).[25] 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 **45** (R^2 = Me), a mixture of oxazoles with a low level of regio control was observed.

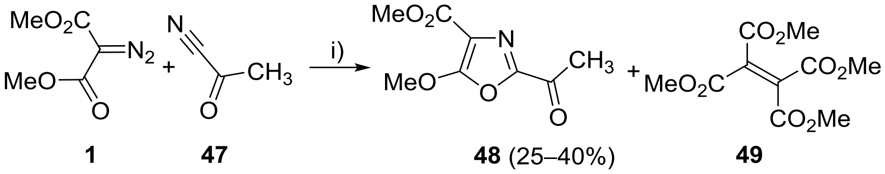


R^1 = Me, $ClCH_2$, $PhCH_2$, Ph;
R^2 = MeO, Me

i) $Rh_2(OAc)_4$ (cat), reflux or 105-125 °C, 1-5 min.

Scheme 15. Rh(II)-catalysed reaction of carbomethoxy iodonium ylides **45** and nitriles **2**

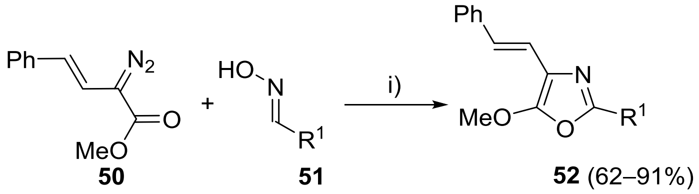
In 2007, Ganem reported that using acyl cyanide **47** as a substrate led to the formation of an inseparable mixture of the oxazole **48** and the diazoester derived dimer **49** (Scheme 16).[26]



i) **1** (1.0-3.0 eq), **47** (1.0 eq), $Rh_2(OAc)_4$ (1-5 mol%), $CHCl_3$, reflux, 8 h.

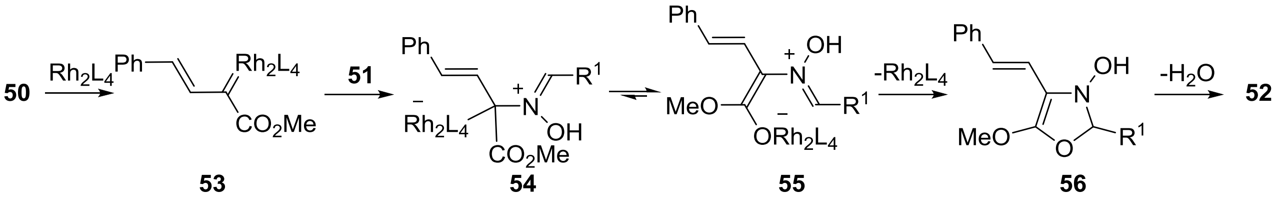
Scheme 16. Rh(II)-catalysed synthesis of oxazole **48**

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.



R^1 = 4-ClC_6H_4, 4-BrC_6H_4, 4-FC_6H_4, Ph, 4-$NO_2C_6H_4$, 4-$MeOC_6H_4$, 4-MeC_6H_4, 3-MeC_6H_4, 2-MeC_6H_4, furan-2-yl, naphthalen-2-yl

Proposed reaction mechanism



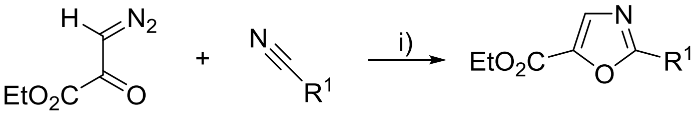
i) **51** (1.0 eq), **50** (1.2 or 1.5 eq), $Rh_2(OAc)_4$ (2 mol%), CH_2Cl_2, rt,1 or 2 h.

Scheme 17. Rh(II)-catalysed synthesis of oxazoles **52**

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.[28] 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 **58** through the Cu(II)-catalysed reaction of ethyl diazopyruvate **57** and nitriles **2** (Scheme 18). This protocol provided moderate yields of the oxazole product **58**.[29]



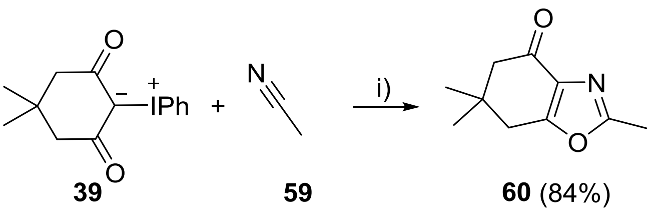
57 **2** **58**

R^1 = Me (35%), Ph (52%)

i) **59** (1.0 eq), **2** (1.8 eq), $Cu(acac)_2$ (0.2 mol%), PhH, reflux, 4 h.

Scheme 18. Cu(II)-catalysed synthesis of oxazole **58**

Iodonium ylides **39** were also shown to be feasible substrates within a Cu(II)-catalysed reaction of acetonitrile **59** *via* a diketocarbene intermediate (Scheme 19).[30] Although the substrate scope was not explored, this protocol shows the potential of Cu(II) as an alternative catalyst in the preparation of oxazoles.

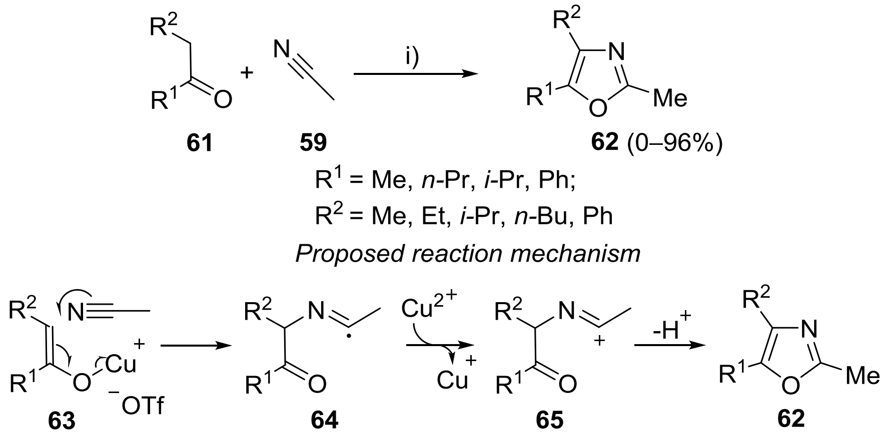


39 **59** **60** (84%)

i) $Cu(acac)_2$ (8 mol%), MeCN (solvent), reflux.

Scheme 19. Cu(II)-catalysed synthesis of oxazoles **60**

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).[31] 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.

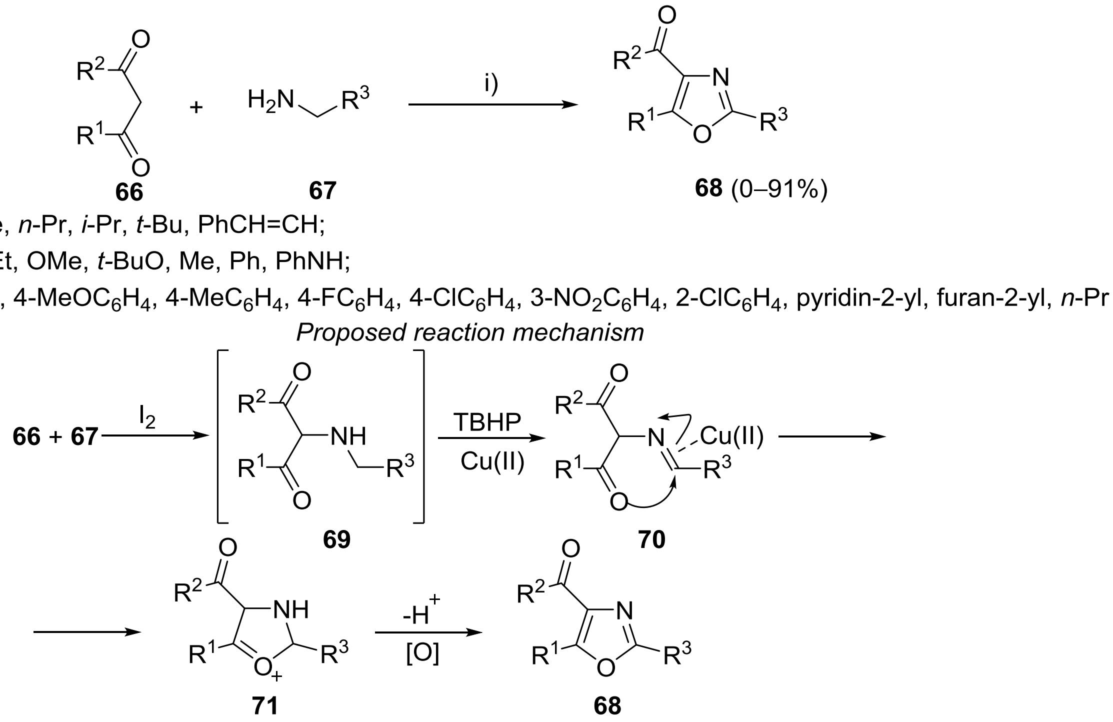


R^1 = Me, *n*-Pr, *i*-Pr, Ph;
R^2 = Me, Et, *i*-Pr, *n*-Bu, Ph

i) Cu(OTf)$_2$ (2.0 eq), *p*-TsOH (cat), MeCN, reflux, 2 h.

Scheme 20. Cu(II)-mediated synthesis of oxazoles **62**

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).[32] The reaction proceeds *via* formation of **69**, which undergoes oxidation to give **70**. Cu(II)-catalysed cyclisation



R^1 = Me, *n*-Pr, *i*-Pr, *t*-Bu, PhCH=CH;
R^2 = OEt, OMe, *t*-BuO, Me, Ph, PhNH;
R^3 = Ph, 4-MeOC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-FC$_6$H$_4$, 4-ClC$_6$H$_4$, 3-NO$_2$C$_6$H$_4$, 2-ClC$_6$H$_4$, pyridin-2-yl, furan-2-yl, *n*-Pr

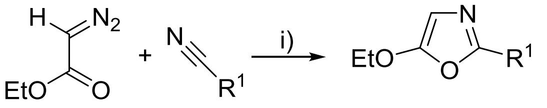
i) **66** (1.0 eq), **67** (2.0 eq), Cu(OAc)$_2$ H$_2$O (10 mol%), TBHP (2.0 eq), I$_2$ (1.2 eq), DMF, rt.

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).[33] 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.[34]



72 **2** **73** (20–30%)

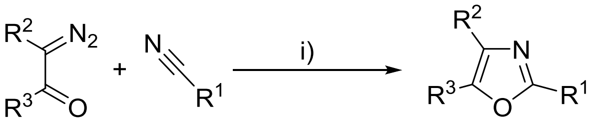
R^1 = Me, Ph, $PhCH_2$, H_2C=CH, H_2C=CMe

i) **74** (1.0 eq), **2** (10.0 eq), $Pd(OAc)_2$ (2 mol%), rt.

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

TUNGSTEN(VI)

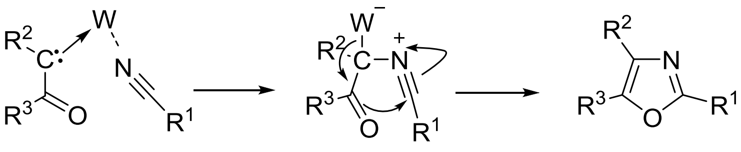
Use of tungsten in the decomposition of diazo compounds was shown to be possible by Kitatani who



74 **2** **75** (20–66%)

R^1 = Ph, Me, Et, CH_2=CH;
R^2 = Ph, H;
R^3 = Ph, MeO

Proposed reaction mechanism



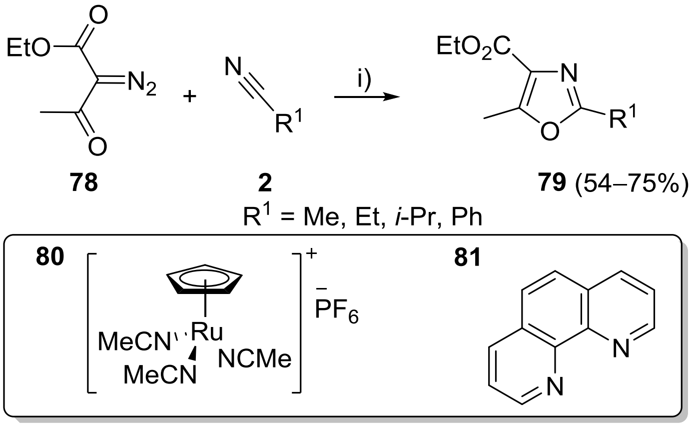
76 **2** **77** **75**

i) **76** (1.0 eq), **2** (solvent), WCl_6 (1.0 eq), rt, 0.25-44 h.

Scheme 23. W(VI)-mediated synthesis of oxazoles **75** described a synthesis of trisubstituted oxazoles **75** (Scheme 23).[35,36] Notably, due to a highly Lewis acidic character and a good affinity for carbenes, WCl_6 proved more effective than copper(II) salts.[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).[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.

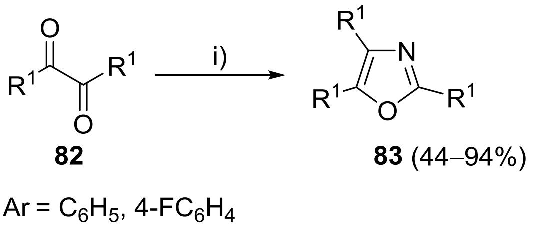


i) **78** (1.0 eq), **81** (2.5 mol%), **80** (2.5 mol%), **2** (solvent), 60 °C, 1 h.

Scheme 24. Ru(II)-catalysed synthesis of oxazoles **79**

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_4OAc (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.

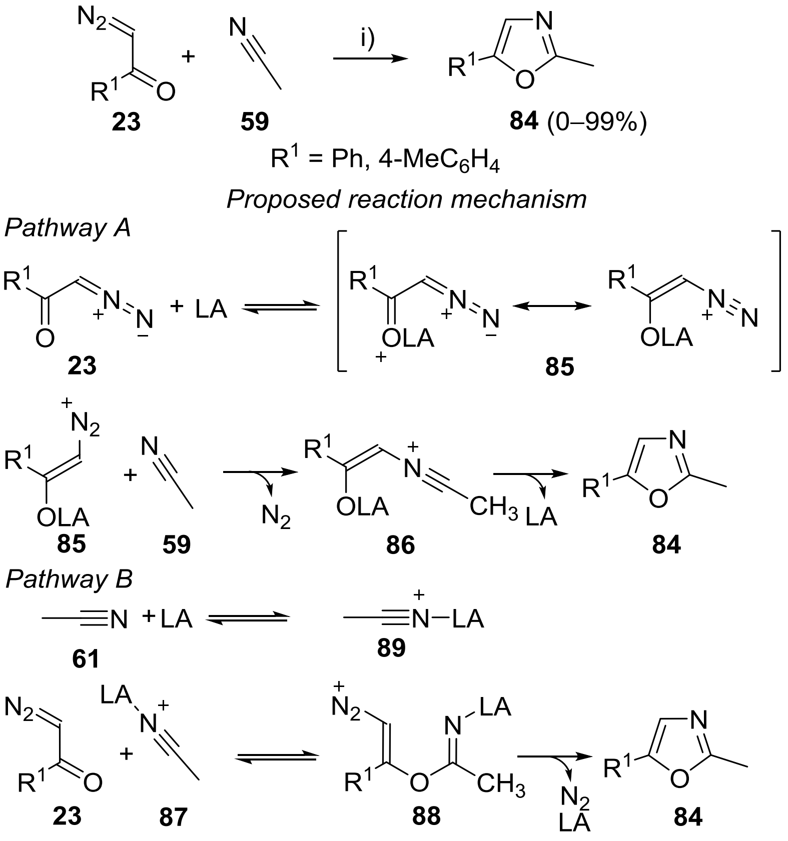


i) **82** (1.0 eq), NH_4OAc (5.0 eq), $SnCl_2 \cdot H_2O$ (5 mol%), EtOH, reflux, 4 h.

Scheme 25. Sn(II)-catalysed synthesis of oxazoles **83**

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.



i) **23** (1.0 eq), LA (0.2-1.4 eq), **59** (solvent), 15 or 25 or 65 °C.

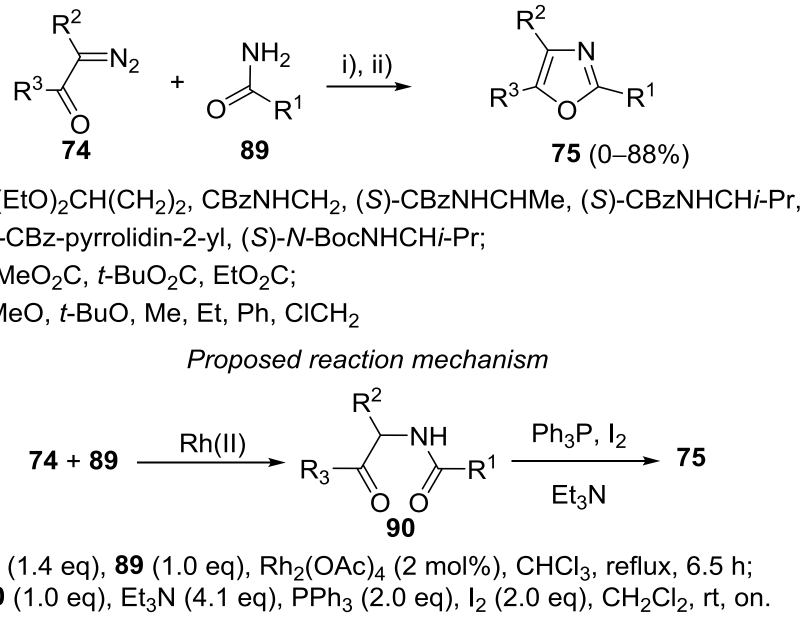
Scheme 26. Lewis acid promoted synthesis of oxazoles **84**

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).[41,42] 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.[43] 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 α-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]

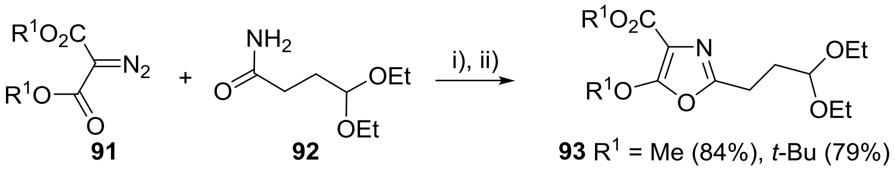


R^1 = $(EtO)_2CH(CH_2)_2$, $CBzNHCH_2$, (*S*)-CBzNHCHMe, (*S*)-CBzNHCH*i*-Pr, (*S*)-*N*-CBz-pyrrolidin-2-yl, (*S*)-*N*-BocNHCH*i*-Pr;
R^2 = MeO_2C, *t*-BuO_2C, EtO_2C;
R^3 =MeO, *t*-BuO, Me, Et, Ph, $ClCH_2$

Proposed reaction mechanism

i) **74** (1.4 eq), **89** (1.0 eq), $Rh_2(OAc)_4$ (2 mol%), $CHCl_3$, reflux, 6.5 h;
ii) **90** (1.0 eq), Et_3N (4.1 eq), PPh_3 (2.0 eq), I_2 (2.0 eq), CH_2Cl_2, rt, on.

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



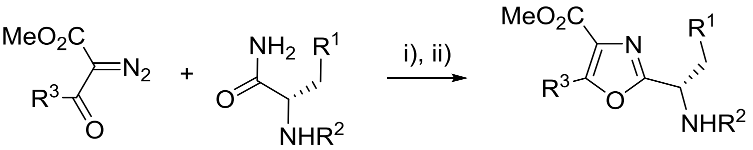
91 **92** **93** R^1 = Me (84%), *t*-Bu (79%)

R^1 = Me, *t*-Bu

i) **91** (1.0 eq), **92** (2.0 eq), $Rh_2(OAc)_4$ (2 mol%), PhMe, reflux, on;
ii) Et_3N (4.1 eq), PPh_3 (2.0 eq), I_2 (2.0 eq), CH_2Cl_2, rt, on.

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).



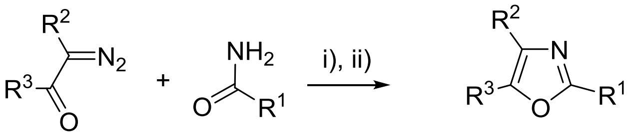
94 **95** **96** (34–84%)

R^1 = Ph, CO_2Bn;
R^2 = $PhCH_2OCO$, *t*-BuOCO;
R^3 = MeO, Me

i) **94** (1.4 eq), **95** (1.0 eq), $Rh_2(OAc)_4$ (2 mol%), $CHCl_3$, reflux, 27 h;
ii) PPh_3 (2.0 eq), I_2 (2.0 eq), Et_3N (4.0 eq), CH_2Cl_2, rt, on.

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).[45] Janda adapted this chemistry for solid-phase synthesis using a polymer-bound α-diazo-β-ketoester.[46]



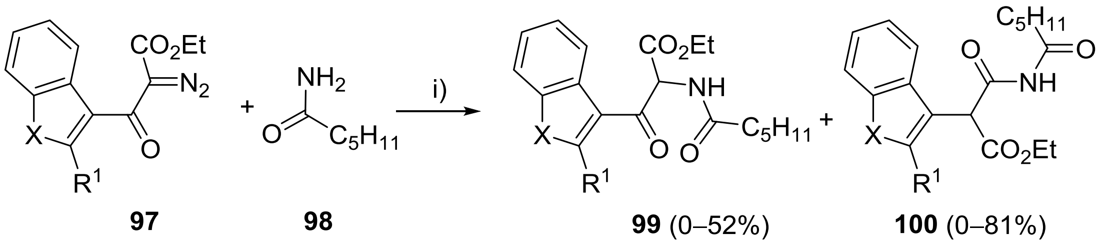
74 **89** **75** (0–80%)

R^1 = H, *n*-pentyl, Ph, 2-BnO-5-$MeOC_6H_3$, thiophen-2-yl, *N*-Boc-piperidin-4-yl, 5-(4-ClC_6H_4)oxazol-4-yl;
R^2 = MeO_2C, Ph, EtO_2C;
R^3 = Me, Ph, 4-ClC_6H_4, 4-$MeO_2CC_6H_4$

i) **74** (1.4 eq), **89** (1.0 eq), $Rh_2(OAc)_4$ (2.5 mol%) or $Rh_2(OOct)_4$ (2.5 mol%), $C_2H_4Cl_2$ or CH_2Cl_2, reflux, 18-20 h;
ii) PPh_3 (2.0 eq), I_2 (2.0 eq), Et_3N (4.1 eq), CH_2Cl_2, rt, 16 h.

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

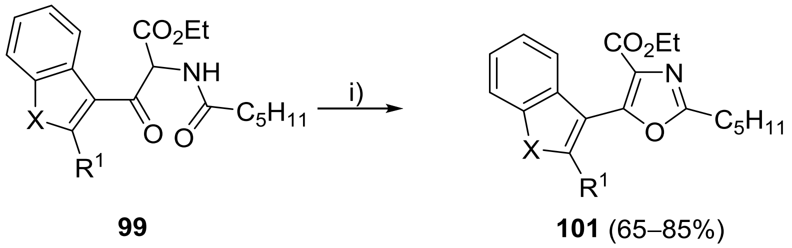
With 3-indolyl α-diazo-β-ketoester **97** substrates a competing N—H insertion and Wolff rearrangement during the Rh(II)-catalysed reaction has been reported (Scheme 31).[47] Ketoamides **99** were subsequently transformed into the corresponding oxazoles **101** upon cyclodehydration (Scheme 32).[47] 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.[47]



X = t-BuO_2CN, $C_6H_5SO_2N$, 2-$NO_2C_6H_4SO_2N$, MeN;
R^1 = H, Cl

i) **97** (1.2-24.0 eq), **98** (1.0 eq), $Rh_2(Oct)_4$ (2-6 mol%), CH_2Cl_2, reflux, 16.5 h.

Scheme 31. Rh(II)-catalysed reaction of 3-indolyl α-diazo-β-ketoester **97** with hexanamide **98**

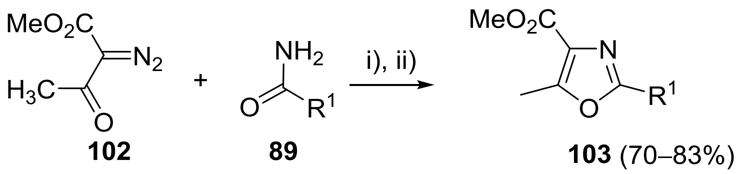


X = t-BuO_2CN, $C_6H_5SO_2N$, 2-$NO_2C_6H_4SO_2N$, MeN;
R^1 = H, Cl

i) **99** (1.0 eq), PPh_3 (2.0 eq), I_2 (2.0 eq), Et_3N (2.1 eq), CH_2Cl_2, rt, 16 h.

Scheme 32. Cyclodehydration of ketoamides **99**

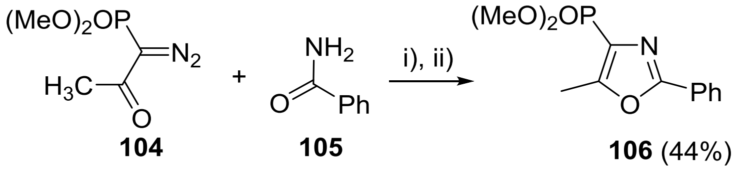
In 2009, Moody described a robust regioselective synthesis of oxazole-4-carboxylates and oxazole-4-phosphonates. For example, Rh(II)-catalysed reaction of *α*-diazo-*β*-keto-carboxylate **102** with carboxamide **89** afforded oxazole-4-carboxylate **103** (Scheme 33) whilst the same transformation applied to *α*-diazo-*β*-keto-phosphonate **104** and benzamide **105** provides oxazole-4-phosphonate **106** (Scheme 34).[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.



R^1 = Ph, 4-$MeOC_6H_4$, 4-BrC_6H_4

i) **102** (1.1 eq), **89** (1.0 eq), $Rh_2(OAc)_4$ (2 mol%), $C_2H_4Cl_2$, reflux, on;
ii) PPh_3 (2.0 eq), I_2 (2.0 eq), Et_3N (4.1 eq), CH_2Cl_2, rt, on.

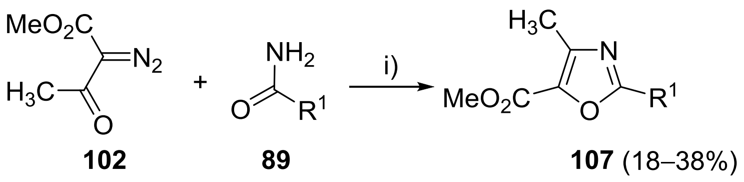
Scheme 33. Rh(II)-catalysed reaction of α-diazo-β-keto-carboxylate **102** with amides **89** followed by cyclodehydration



i) **104** (1.1 eq), **105** (1.0 eq), $Rh_2(OAc)_4$ (2 mol%), CH_2Cl_2, reflux, on;
ii) solid-phase PPh_3 (2.0 eq), I_2 (2.0 eq), Et_3N (4.1 eq), CH_2Cl_2, rt, on.

Scheme 34. Rh(II)-catalysed reaction of α-diazo-β-keto-carboxylate **104** with amides **105** followed by cyclodehydration

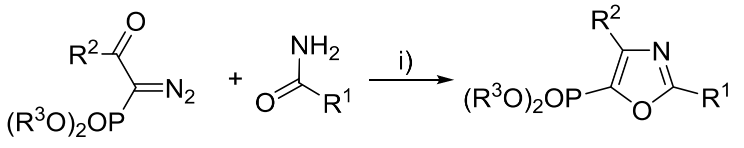
Remarkably, when the above transformation was performed using dirhodium tetrakis(heptafluorobutyramide) as a catalyst, regioisomeric oxazole-5-carboxylates **107** were obtained as the only products (Scheme 35). In the same fashion, oxazole-5-phosphonates **109** (Scheme 36) and oxazole-5-sulfones **111** (Scheme 37) were also prepared.[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.



R^1 = Ph, 4-$MeOC_6H_4$, 4-BrC_6H_4

i) **102** (1.1 eq), **89** (1.0 eq), $Rh_2(NHCOC_3F_7)_4$ (2 mol%), MW irrad, $C_2H_4Cl_2$, 105 °C, 30 min.

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

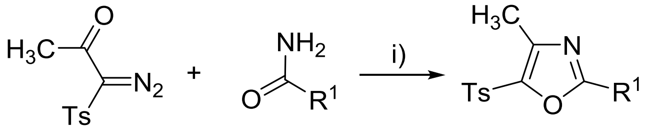


108 **89** **109** (26–73%)

R^1 = Ph, 2-BrC_6H_4, 2-BnOC_6H_4, 4-BrC_6H_4, 4-MeOC_6H_4, 4-$NO_2C_6H_4$, 4-CbzNHC_6H_4, 4-PhC_6H_4, 3,5-$F_2C_6H_3$, thiophen-2-yl, benzothiophen-2-yl, PhCH=CH;
R^2 = Me, Ph;
R^3 = Me, Et

i) **108** (1.1 eq), **89** (1.0 eq), $Rh_2(NHCOC_3F_7)_4$ (2 mol%), PhMe, reflux, 16 h or
108 (1.1 eq), **89** (1.0 eq), $Rh_2(NHCOC_3F_7)_4$ (2 mol%), MW irrad, PhMe, 135 °C, 30 min.

Scheme 36. Rh(II)-catalysed synthesis of oxazole-5-phosphonates **109**



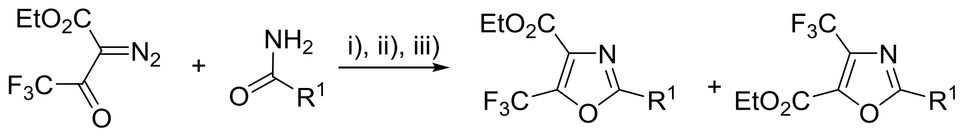
110 **89** **111** (22–81%)

R^1 = Ph, 2-BrC_6H_4, 2-BnOC_6H_4, 4-BrC_6H_4, 4-$NO_2C_6H_4$, 4-CbzNHC_6H_4, 4-PhC_6H_4, thiophen-2-yl, PhCH=CH

i) **110** (1.1 eq), **89** (1.0 eq), $Rh_2(NHCOC_3F_7)_4$ (2 mol%), $C_2H_4Cl_2$, reflux, 16 h or
110 (1.1 eq), **89** (1.0 eq), $Rh_2(NHCOC_3F_7)_4$ (2 mol%), MW irrad, $C_2H_4Cl_2$, 105 °C, 30 min.

Scheme 37. Rh(II)-catalysed synthesis of oxazole-5-sulfones **111**

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).[50] The lack of regioselectivity in formation of 5-trifluoromethyloxazoles **113** is due to a competing O—H insertion process of the carbenoid species generated from **112**, suggesting the trifluoromethyl group influences the electrophilicity of the carbenoid.



112 **89** **113** (13–28%) **114** (30–35%)

R^1 = Ph, 2-BrC_6H_4, 4-MeOC_6H_4, 4-BrC_6H_4

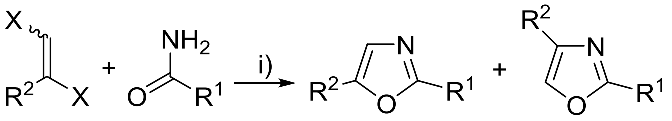
i) **112** (1.1 eq), **89** (1.0 eq), $Rh_2(OAc)_4$ (2 mol%), CH_2Cl_2, MW irrad, 80 °C, 15 min;
ii) $POCl_3$ (2.0 eq), MW irrad, 105 °C, 20 min; iii) Amberlyst 15, MW irrad, 105 °C, 15 min.

Scheme 38. Rh(II)-catalysed synthesis of 5-trifluoromethyloxazoles **113** and 4-trifluoromethyloxazoles **114**

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.



115 **89** **116**

E:*Z* ratio
(100:0 to 0:100)

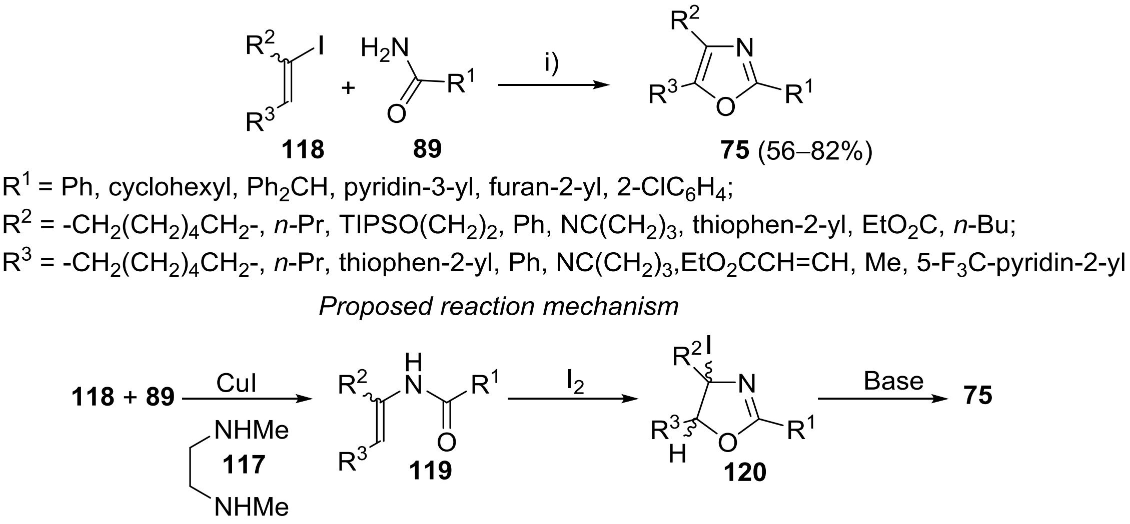
14 : 1
1 : 4
(17–72%)

X = Br, I;
R^1 = Ph, 4-BrC_6H_4, 4-$MeOC_6H_4$, PhCH=CH, H, Me, *n*-Pr, *t*-Bu, CH_2=CH, 4-$H_2NC_6H_4$;
R^2 = Ph, *n*-Hex

i) **115** (1.0 eq), **89** (1.5 eq), K_2CO_3 (3.0 eq), *N*,*N'*-dimethylethylenediamine (20 or 40 mol%), CuI (10 or 20 mol%), PhMe, 110 or 130 °C, 13-62 h.

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.[58] 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,[57] Buchwald applied this strategy[58] 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).[58] 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.



118 **89** **75** (56–82%)

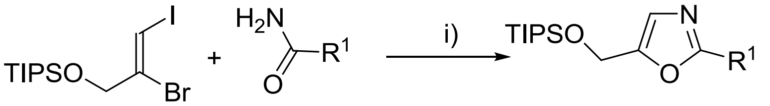
R^1 = Ph, cyclohexyl, Ph_2CH, pyridin-3-yl, furan-2-yl, 2-ClC_6H_4;
R^2 = -$CH_2(CH_2)_4CH_2$-, *n*-Pr, TIPSO$(CH_2)_2$, Ph, $NC(CH_2)_3$, thiophen-2-yl, EtO_2C, *n*-Bu;
R^3 = -$CH_2(CH_2)_4CH_2$-, *n*-Pr, thiophen-2-yl, Ph, $NC(CH_2)_3$,$EtO_2CCH=CH$, Me, 5-F_3C-pyridin-2-yl

Proposed reaction mechanism

118 + **89** **117** **119** **120** **75**

i) **118** (1.0 eq), **89** (1.2 eq), CuI (5 mol%), *N,N'*-dimethylethylenediamine **117** (20 mol%), Cs_2CO_3 (1.5 eq), THF, 80 °C, 3-8 h; ii) I_2 (1.1 eq), K_2CO_3 (2.0 eq), DBU (2.0 eq), rt to 80 °C, 5-10 h.

Scheme 40. Sequential one-pot Cu(I)-catalysed amidation-iodination protocol for the synthesis of oxazoles **75**



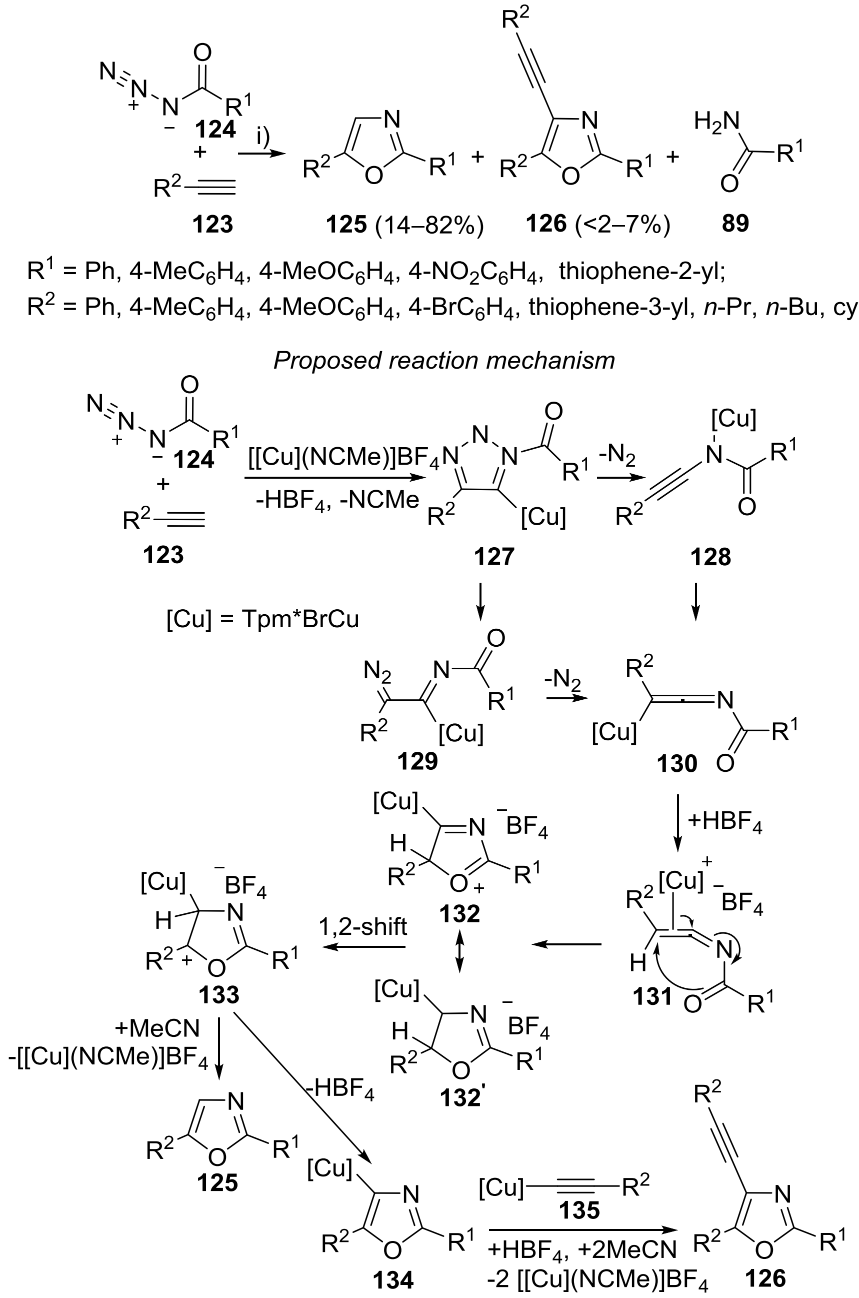
121 **89** **122** (98–99%)

R^1 = Ph, 4-ClC_6H_4, 4-$CF_3C_6H_4$

i) **121** (1.0 eq), **89** (1.2 eq), CuI (5 mol%), *N,N'*-dimethylethylenediamine (20 mol%), Cs_2CO_3 (3.0 eq), THF, 80 °C, 8 h.

Scheme 41. Cu(II)-catalysed synthesis of oxazoles **122**

More recently, Pérez described a catalytic and regioselective synthesis of 2,5-disubstituted oxazoles **125** through the cycloaddition of terminal alkynes **123** and acyl azides **124** using a copper(I) catalyst precursor (Scheme 42).[59] The reaction proceeds *via* the [3+2] cycloaddition of the copper acetylide of **123** with **124** generating a copper triazolyl intermediate **127**. Conversion of **127** to a copper ketenimide **130** proceeds *via* the formation of **128** or **129**. Protonation of **130** promotes cyclisation to **132**/**132'**, followed by a 1,2-hydrogen shift to give **125** and release of the catalyst. Trisubstituted oxazoles **126** can also be generated through the aromatisation of **133** and coupling with a copper acetylide **135**. 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.



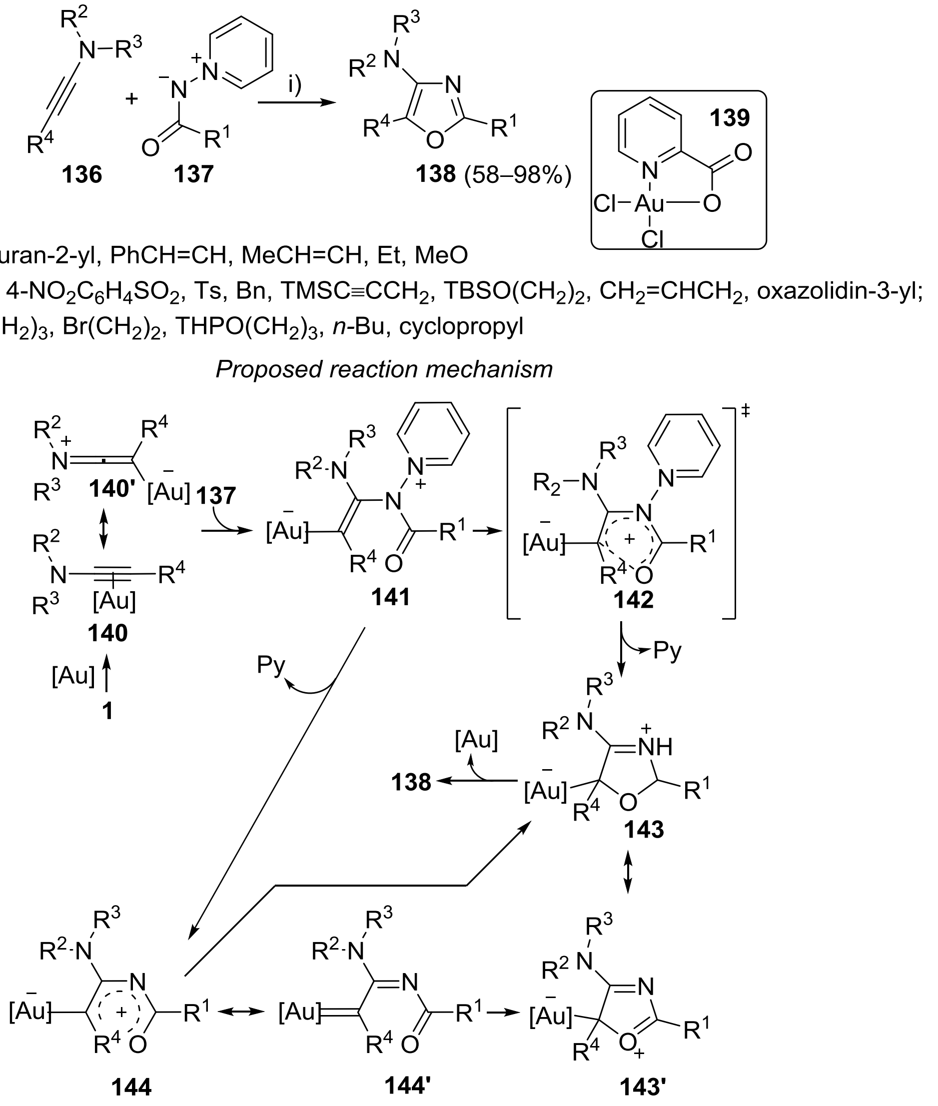
R^1 = Ph, 4-MeC_6H_4, 4-MeOC_6H_4, 4-$NO_2C_6H_4$, thiophene-2-yl;
R^2 = Ph, 4-MeC_6H_4, 4-MeOC_6H_4, 4-BrC_6H_4, thiophene-3-yl, *n*-Pr, *n*-Bu, cyclopropyl

i) **124** (1.0 eq), **123** (1.2 eq), [Tpm*BrCu(NCMe)]BF_4 (5 mol%), $CHCl_3$, 25-60 °C, 12 or 24 h.

Scheme 42. Cu(I)-catalysed cycloaddition of alkynes **123** and acyl azides **124**

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),[60] 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 aminide **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.



R^1 = Ph, 2-BrC$_6$H$_4$, furan-2-yl, PhCH=CH, MeCH=CH, Et, MeO

R^2, R^3 = Ms, Ph, Bn, 4-NO$_2$C$_6$H$_4$SO$_2$, Ts, Bn, TMSC≡CCH$_2$, TBSO(CH$_2$)$_2$, CH$_2$=CHCH$_2$, oxazolidin-3-yl;

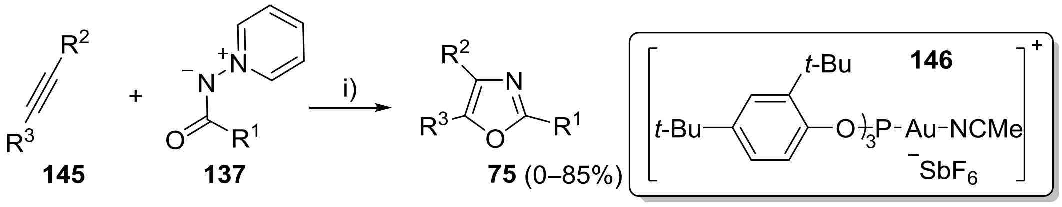
R^4 = Ph, TBDPSO(CH$_2$)$_3$, Br(CH$_2$)$_2$, THPO(CH$_2$)$_3$, *n*-Bu, cyclopropyl

Proposed reaction mechanism

i) **136** (1.0 eq), **137** (1.5 eq), **139** (5 mol%), PhMe, 90 °C, 5 min to 24 h.

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).[61] Remarkably, the reactions proceeded with excellent regioselectivity, due to the π-electron-donating ability of the remote nitrogen in R^2. 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,[60] were generally less effective substrates.

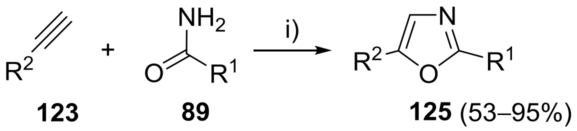


R^1 = Ph, 2-BrC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-FC$_6$H$_4$, furan-2-yl, thiophen-2-yl;
R^2 = indol-3-yl, 1-Me-indol-3-yl, 1-Bn-indol-3-yl,1-allyl-indol-3-yl, 5-Br-1-Me-indol-3-yl, 6-MeO$_2$C-indol-3-yl, 4-Me$_2$NC$_6$H$_4$, 4(morpholin-4-yl)C$_6$H$_4$, 4(pyrrolidin-1-yl)C$_6$H$_4$, 3(pyrrolidin-1-yl)C$_6$H$_4$, 4-MeOC$_6$H$_4$;
R^3 = Ph, thiophen-2-yl, furan-2-yl, 4-MeOC$_6$H$_4$, 4-FC$_6$H$_4$, cyclopropyl, 2-BrC$_6$H$_4$

i) **137** (1.5 eq), **145** (1.0 eq), **146** (5 mol%), m-xylene, 120 °C, 24 or 48 h.

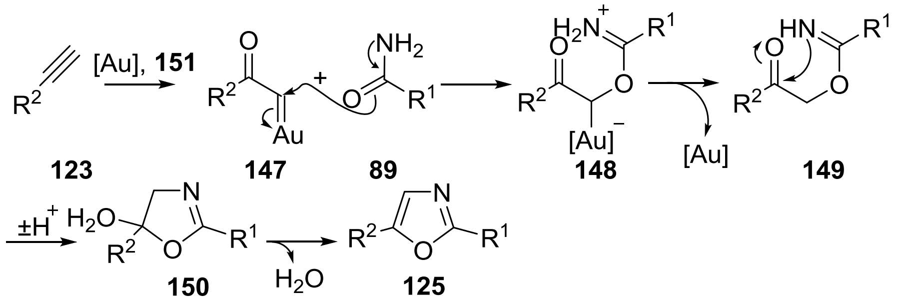
Scheme 44. Au(I)-catalysed synthesis of oxazoles **75**

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).[62] 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.[63] Within this work it was shown that terminal α-oxo gold carbenes (e.g. **147**) could be stabilised with the bidentate ligand Mor-DalPhos[64] 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.



R^1 = 4-MeC$_6$H$_4$, Ph, 4-ClC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-FC$_6$H$_4$, furan-2-yl, thiophen-2-yl, PhCH=CH, MeCH=CH, (Me)$_2$C=CH, 4-MeOC$_6$H$_4$;
R^2 = *n*-decyl, cyclohexyl, cyclopropyl, PhthN(CH$_2$)$_4$, TIPSO(CH$_2$)$_4$, Cl(CH$_2$)$_4$, AcO(CH$_2$)$_4$, Ph(CH$_2$)$_2$, Ph, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$

Proposed reaction mechanism



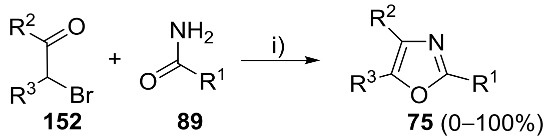
i) **123** (1.5 or 2.0 eq), **89** (1.0 eq), Mor-DalPhosAuCl (5 mol%), NaBArF$_4$ (10 mol%), 8-methylquinoline-*N*-oxide **151** (2.2 or 3.0 eq), chlorobenzene, 60 or 100 °C, 16 h.

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.

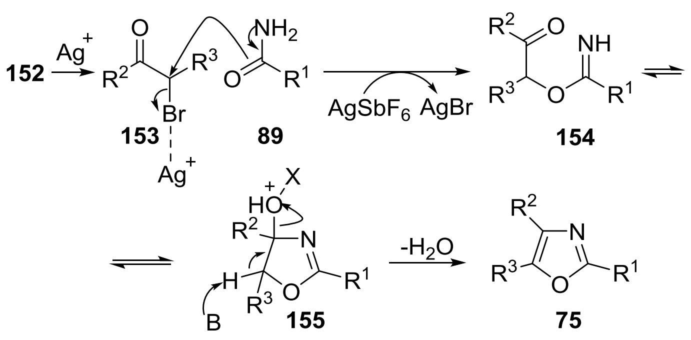
SILVER(I)

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).[65] 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,[66] 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.



R^1 = Ph, 4-BrC$_6$H$_4$, 4-MeOC$_6$H$_4$, 3-MeOC$_6$H$_4$, 4-NO$_2$C$_6$H$_4$, 3-NO$_2$C$_6$H$_4$, thiophen-2-yl, furan-2-yl, pyridin-4-yl, Et, *n*-hexyl, PhCH=CH;
R^2 = Ph, EtO$_2$C, BrCH$_2$CO;
R^3 = H, Me

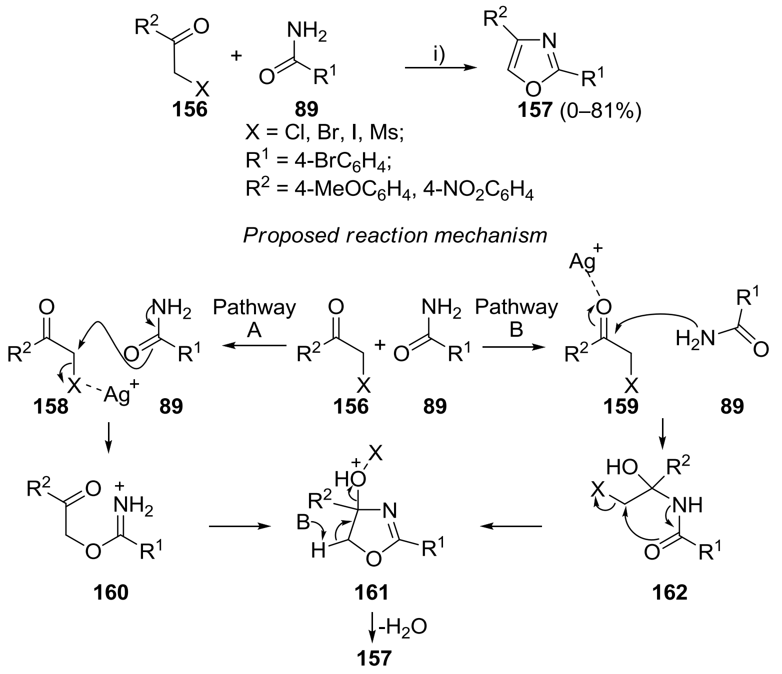
Proposed reaction mechanism



i) **152** (1.0 or 1.8 eq), **89** (1.0 or 2.0 eq), AgSbF$_6$ (1.0 or 2.0 eq), C$_2$H$_4$Cl$_2$, 90 °C, 1 min then MW irrad, 90 °C, 2 or 3 h.

Scheme 46. Ag(I)-mediated synthesis of oxazoles **75**

In a useful study, Moses explored alternative α-haloketone substrates **156** (Scheme 47).[67] 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.

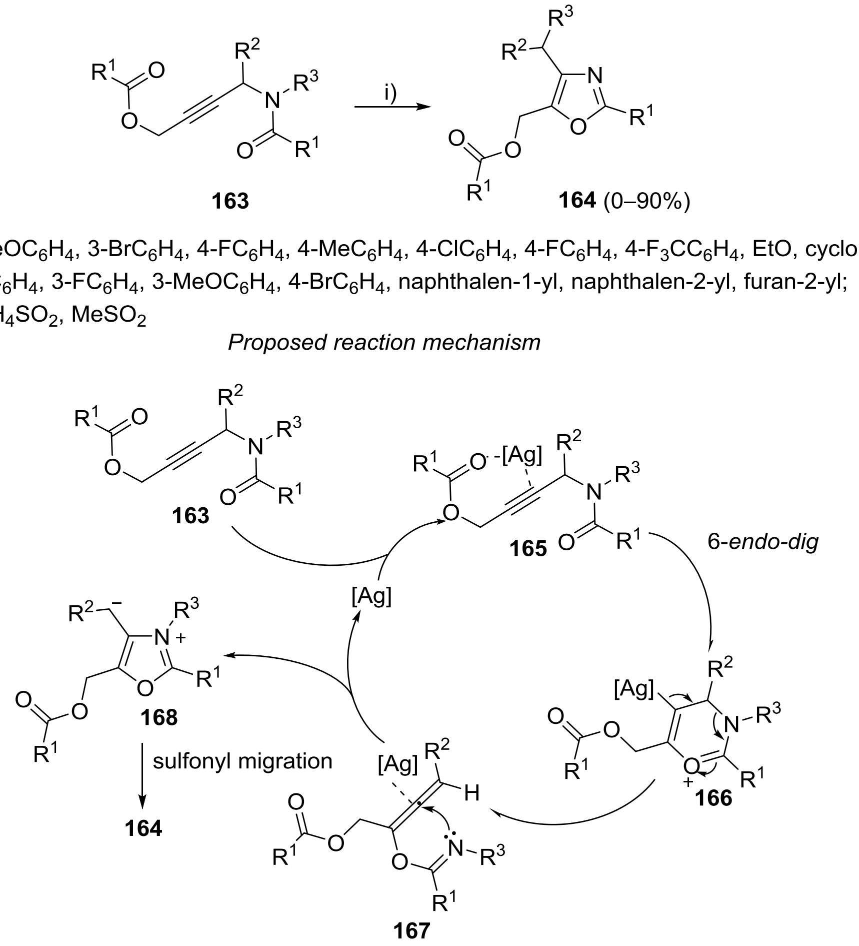


X = Cl, Br, I, Ms;
R^1 = 4-BrC$_6$H$_4$;
R^2 = 4-MeOC$_6$H$_4$, 4-NO$_2$C$_6$H$_4$

Proposed reaction mechanism

i) AgSbF$_6$ (1.0 eq), MW irrad, C$_2$H$_4$Cl$_2$, 90 °C, 2 h.

Scheme 47. Ag(I)-mediated synthesis of oxazoles **157**



R^1 = Ph, 3-MeOC$_6$H$_4$, 3-BrC$_6$H$_4$, 4-FC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-FC$_6$H$_4$, 4-F$_3$CC$_6$H$_4$, EtO, cyclopentyl;
R^2 = Ph, 2-FC$_6$H$_4$, 3-FC$_6$H$_4$, 3-MeOC$_6$H$_4$, 4-BrC$_6$H$_4$, naphthalen-1-yl, naphthalen-2-yl, furan-2-yl;
R^3 = 4-MeC$_6$H$_4$SO$_2$, MeSO$_2$

Proposed reaction mechanism

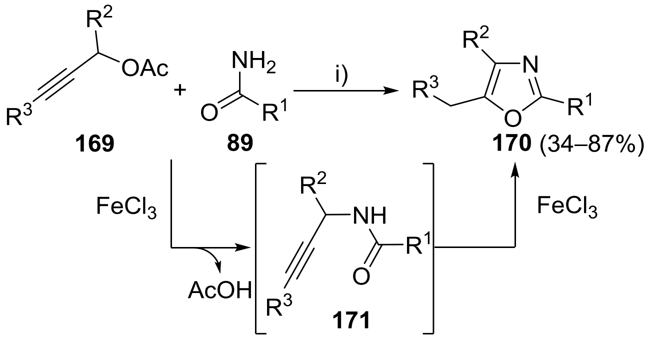
i) AgBF$_4$ (10 mol%), toluene, 80 °C, 10 h.

Scheme 48. Ag(II)-catalysed cyclisation of *N*-sulfonylpropargylamides **163**

The synthesis of trisubstituted oxazoles **164** through the Ag(I)-catalysed cyclisation of *N*-sulfonylpropargylamides **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**.

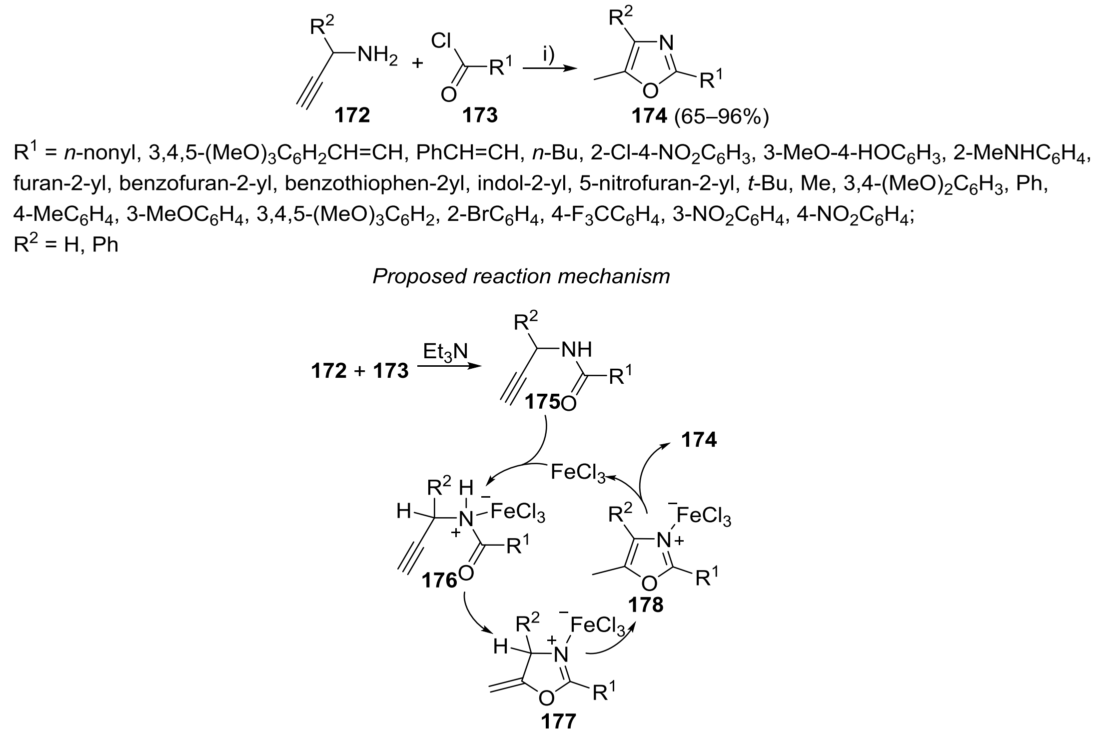


R^1 = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$, 4-ClC_6H_4, Me;
R^2 = Ph, naphthalen-1-yl, 4-$MeOC_6H_4$, 4-BrC_6H_4, 4-$MeO_2CC_6H_4$;
R^3 = TMS, H, *n*-Bu

i) **169** (1.0 eq), **89** (3.0 eq), $FeCl_3$ (15 mol%), silica gel, MW irrad, MeCN, 4-17 min.

Scheme 49. Fe(III)-catalysed synthesis of oxazoles **170**

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.



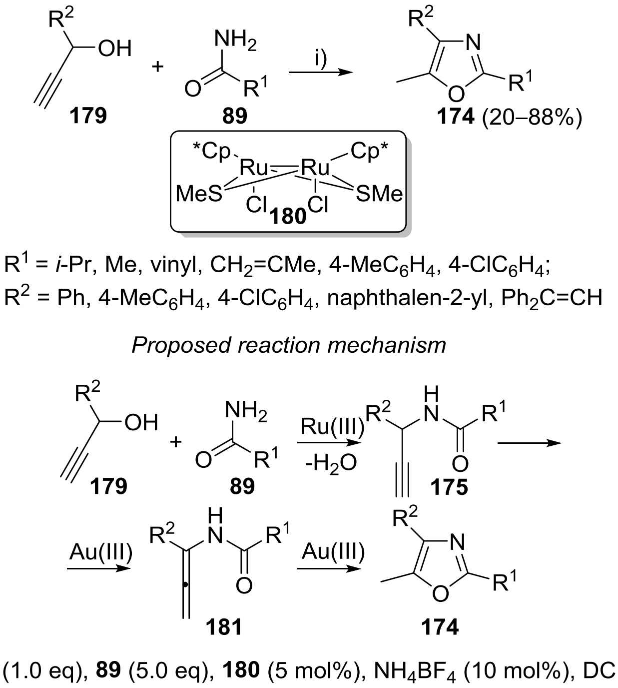
R^1 = *n*-nonyl, 3,4,5-$(MeO)_3C_6H_2CH{=}CH$, $PhCH{=}CH$, *n*-Bu, 2-Cl-4-$NO_2C_6H_3$, 3-MeO-4-HOC_6H_3, 2-$MeNHC_6H_4$, furan-2-yl, benzofuran-2-yl, benzothiophen-2yl, indol-2-yl, 5-nitrofuran-2-yl, *t*-Bu, Me, 3,4-$(MeO)_2C_6H_3$, Ph, 4-MeC_6H_4, 3-$MeOC_6H_4$, 3,4,5-$(MeO)_3C_6H_2$, 2-BrC_6H_4, 4-$F_3CC_6H_4$, 3-$NO_2C_6H_4$, 4-$NO_2C_6H_4$;
R^2 = H, Ph

i) **172** (1.2 eq), **173** (1.0 eq), Et_3N (2.0 eq), CH_2Cl_2, rt, 2-12 h then $FeCl_3$ (30 or 50 mol%), $C_2H_4Cl_2$, 80 °C, 1-12 h.

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

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 = *i*-Pr, Me, vinyl, $CH_2{=}CMe$, 4-MeC_6H_4, 4-ClC_6H_4;
R^2 = Ph, 4-MeC_6H_4, 4-ClC_6H_4, naphthalen-2-yl, $Ph_2C{=}CH$

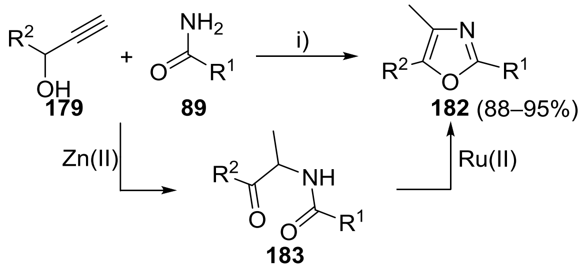
i) **179** (1.0 eq), **89** (5.0 eq), **180** (5 mol%), NH_4BF_4 (10 mol%), DCE, 60 °C, 1 h then $AuCl_3$ (10 mol%), 80 °C, 18 h.

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).[71] 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 oxaxole **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).[72] 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.

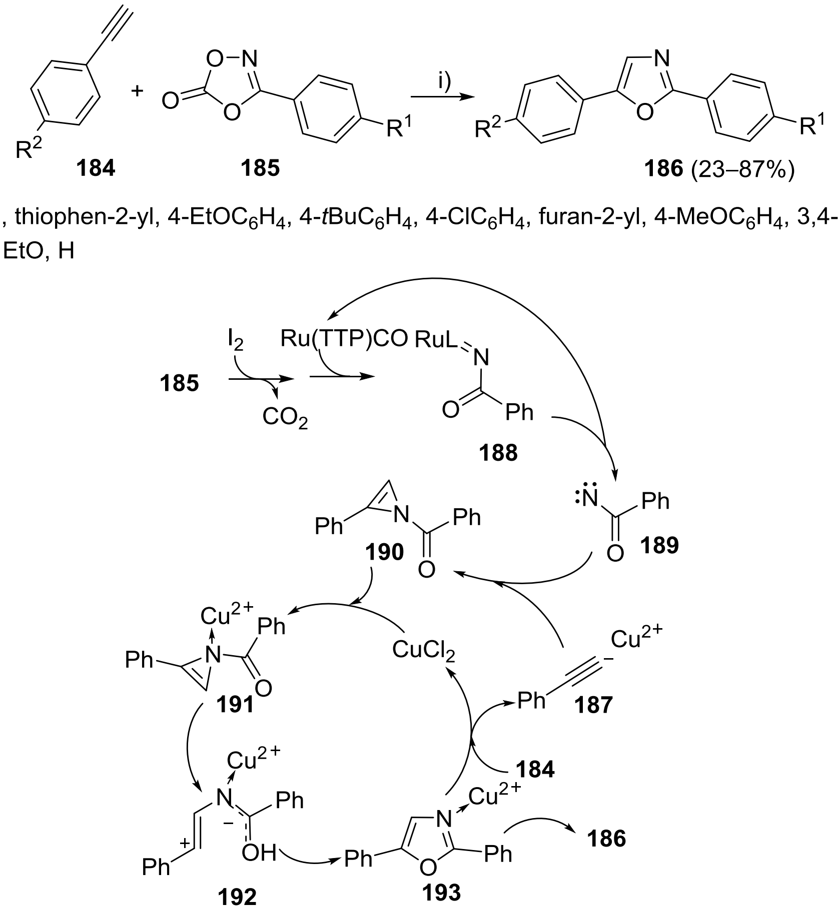


R^1 = Ph, *n*-pentyl, MeC=CH_2;
R^2 = 4-FC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, benzo[*d*][1,3]dioxolyl-5-yl
i) **179** (1.0 eq), **89** (1.2 eq), $Zn(OTf)_2$ (10 mol%), $TpRuPPh_3(MeCN)_2PF_6$ (10 mol%), PhMe, 100 °C, 5 h.

Scheme 52. Zn(II)- and Ru(II)-catalysed reaction of propargylic alcohols **179** with amides **89**

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).[73] 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.



R^1 = H, Me, thiophen-2-yl, 4-$EtOC_6H_4$, 4-*t*BuC_6H_4, 4-ClC_6H_4, furan-2-yl, 4-$MeOC_6H_4$, 3,4-$Me_2OC_6H_3$;
R^2 = MeO, EtO, H

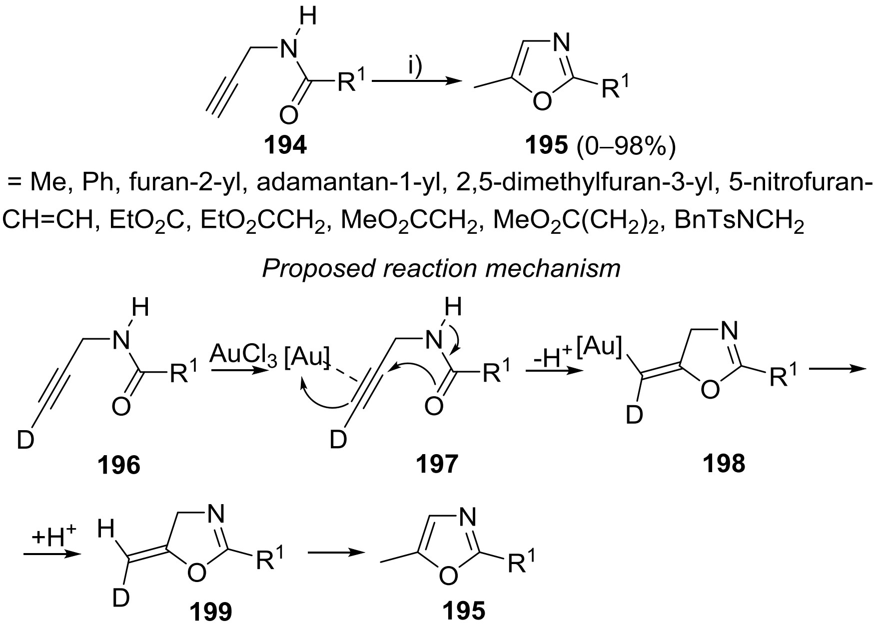
i) **184** (1.0 eq), **185** (4.0 eq), Ru(TTP)CO (10 mol%), $CuCl_2$ (15 mol%), I_2 (30 mol%), PhMe, 50 or 80 °C, 3-4 h.

Scheme 53. Ru(II)- and Cu(II)-catalysed synthesis of oxazoles **186**

O1–C5 BOND DISCONNECTION

GOLD(I), GOLD(III)

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).[74] 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.

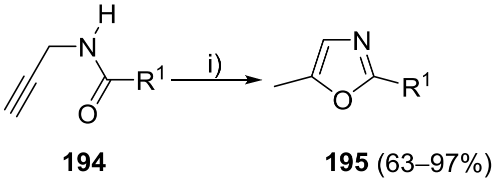


R^1 = Me, Ph, furan-2-yl, adamantan-1-yl, 2,5-dimethylfuran-3-yl, 5-nitrofuran-2-yl, PhCH=CH, EtO_2C, EtO_2CCH_2, MeO_2CCH_2, $MeO_2C(CH_2)_2$, $BnTsNCH_2$

i) $AuCl_3$ (5 mol%, 10 w/w% in CD_3CN), CH_2Cl_2 or CD_3CN, r.t or 45 °C or 50 °C, 2-96 h.

Scheme 54. Au(III)-catalysed cycloisomerisation of *N*-propargylamides **194**

The substrate scope of this approach was subsequently expanded to include aliphatic and aromatic terminal *N*-propargylamides **195** (Scheme 55).[75]

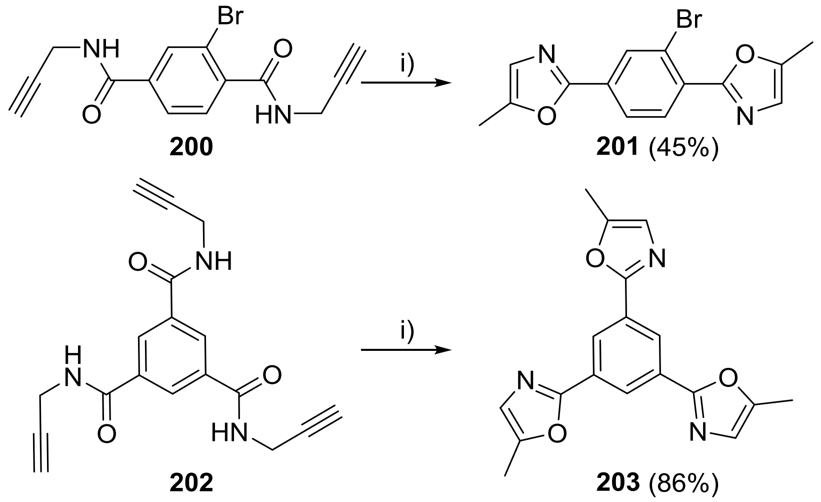


R^1 = *t*-Bu, Bn, thiophen-2-yl, anthracen-9-yl, 1,1'-biphenyl-4-yl

i) $AuCl_3$ (2.5-5 mol%), CH_2Cl_2 or MeCN, rt, 5 min-21 h.

Scheme 55. Au(III)-catalysed cycloisomerisation of *N*-propargylamides **194**

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**.[75] 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.



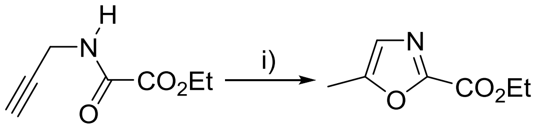
200 **201** (45%)

202 **203** (86%)

i) $AuCl_3$ (2.5-5 mol%), CH_2Cl_2 or MeCN, rt or 50 °C, 5 or 12 h.

Scheme 56. Au(III)-catalysed synthesis of oxazoles **201** and **203**

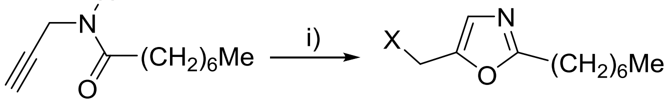
Remarkably, **204**, which failed to provide the corresponding oxazole under Au(III) catalysis,[74] successfully delivered oxazole **205** in good yield using a Au(I) precatalyst (Scheme 57).[75] In the majority of cases under these reaction conditions the proposed intermediate methyleneoxazolines were 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).[75]



204 **205** (81%)

i) $[PPh_3Au]OTs$ (5 mol%), CH_2Cl_2, rt, 48 h.

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

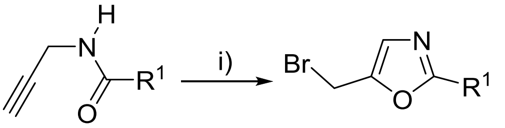


206 **207** (7–29%)
X = Cl, Br

i) NCS or NBS (1.2-5.0 eq), $[Ph_3Au]NTf_2$ (3.0 mol%) or $AuCl_3$ (3.0 mol%), CH_2Cl_2, 20 or 40 ºC, 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-bromomethyloxazoles **208** through a one-pot Au(III)-catalysed cyclisation-bromination of *N*-propargylamides **194** (Scheme 59).[76] 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.[77,78]



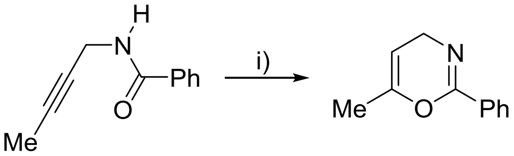
194 **208** (57–88%)

R^1 = Ph, $MeCH_2CHNHBoc$, BnCHNHBoc, *t*-BuCHNHBoc, *N*-Boc-pyrrolidin-2-yl, $NHBoc(CH_2)_3CHNHBoc$, *t*-Bu, Ph, $CH_2=CHCH_2CHMe$

i) $AuCl_3$ (5 mol%), $CHCl_3$, rt then 2,6-lutidine (1.1 eq), Br_2 (1.0 eq), $CHCl_3$, 0 °C to rt.

Scheme 59. One-pot Au(III)-catalysed synthesis of 5-bromomethyloxazoles **208**

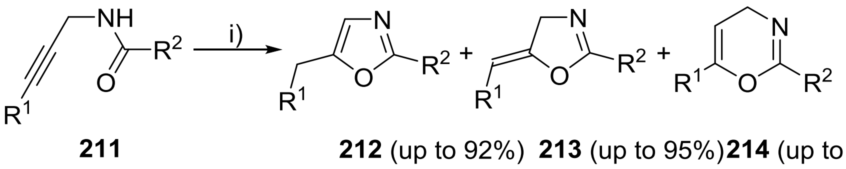
It has also been shown that the Au(I)-catalysed cyclisation of the internal *N*-propargylamide **209** delivered six-membered oxazines **210** *via* a 6-*endo*-*dig* cyclisation pathway (Scheme 60).[79] Under the same reaction conditions, no product was formed using a Au(III) catalyst. The scope of the 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).[80] 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.



209 **210** (20–95%)

i) $[PPh_3Au][NTf_2]$ (5 mol% or 1.0 eq), CH_2Cl_2 or [IPrAu][OTs] (1.0 eq) or Et_3N/PhH or $Et_3N/PhMe$ or Et_3N/THF, rt, up to 6 d.

Scheme 60. Au(I)-catalysed cyclisation of internal *N*-propargylamides **209**



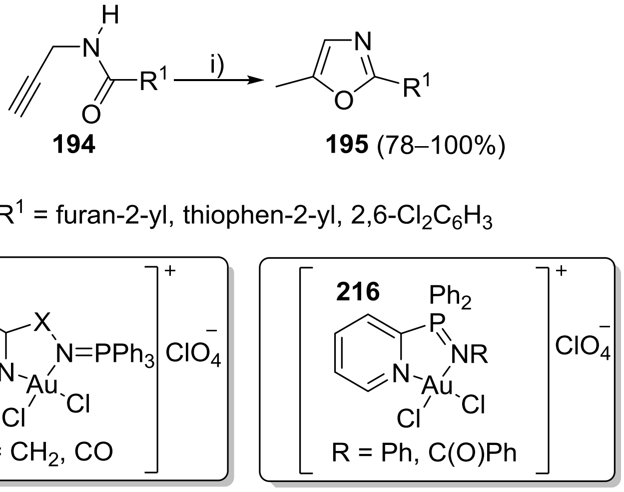
R^1 = Me, Et, *n*-Pr, *n*-Bu, $ClCH_2$, CH_3OCH_2, HC≡C$(CH_2)_3$, HC≡CCH_2OCH_2,HC≡C$(CH_2)_4$, CH_2=CH$(CH_2)_3$, 4-$NO_2C_6H_4$, pyridin-2-yl, naphthalen-1-yl, 4-$MeOC_6H_4$, 4-CNC_6H_4, 4-$CHOC_6H_4$, thiophen-2-yl, 5-formyl-furan-2-yl, Ph;

R^2 = Ph, furan-2-yl, Bn, *t*-Bu, 4-BrC_6H_4, PhCH=CH_2, 2,5-dimethylfuran-3-yl, adamantan-1-yl

i) (IPr)AuCl (5 mol%), AgOTs (5 mol%), THF, rt or 40 °C, 12 h-6 d.

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

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).[81] Yields of oxazoles **195** obtained using the gold iminophosphorane complexes **215** and **216** were comparable to those using $AuCl_3$, albeit with longer reaction times being required.



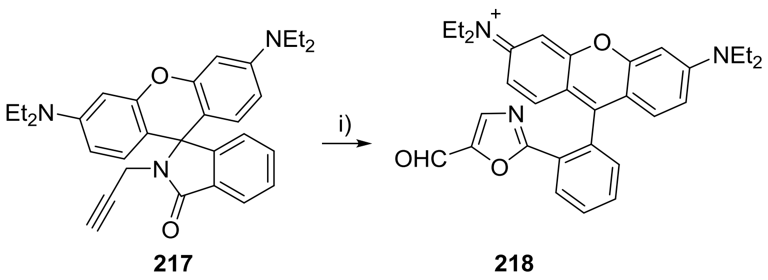
R^1 = furan-2-yl, thiophen-2-yl, 2,6-$Cl_2C_6H_3$

i) $AuCl_3$ (5 mol%) or **215** (5 mol%) or **216** (5 mol%), CH_2Cl_2 , rt, 30-72 h.

Scheme 62. Au(III)-catalysed cycloisomerisation of *N*-propargylamides **194**

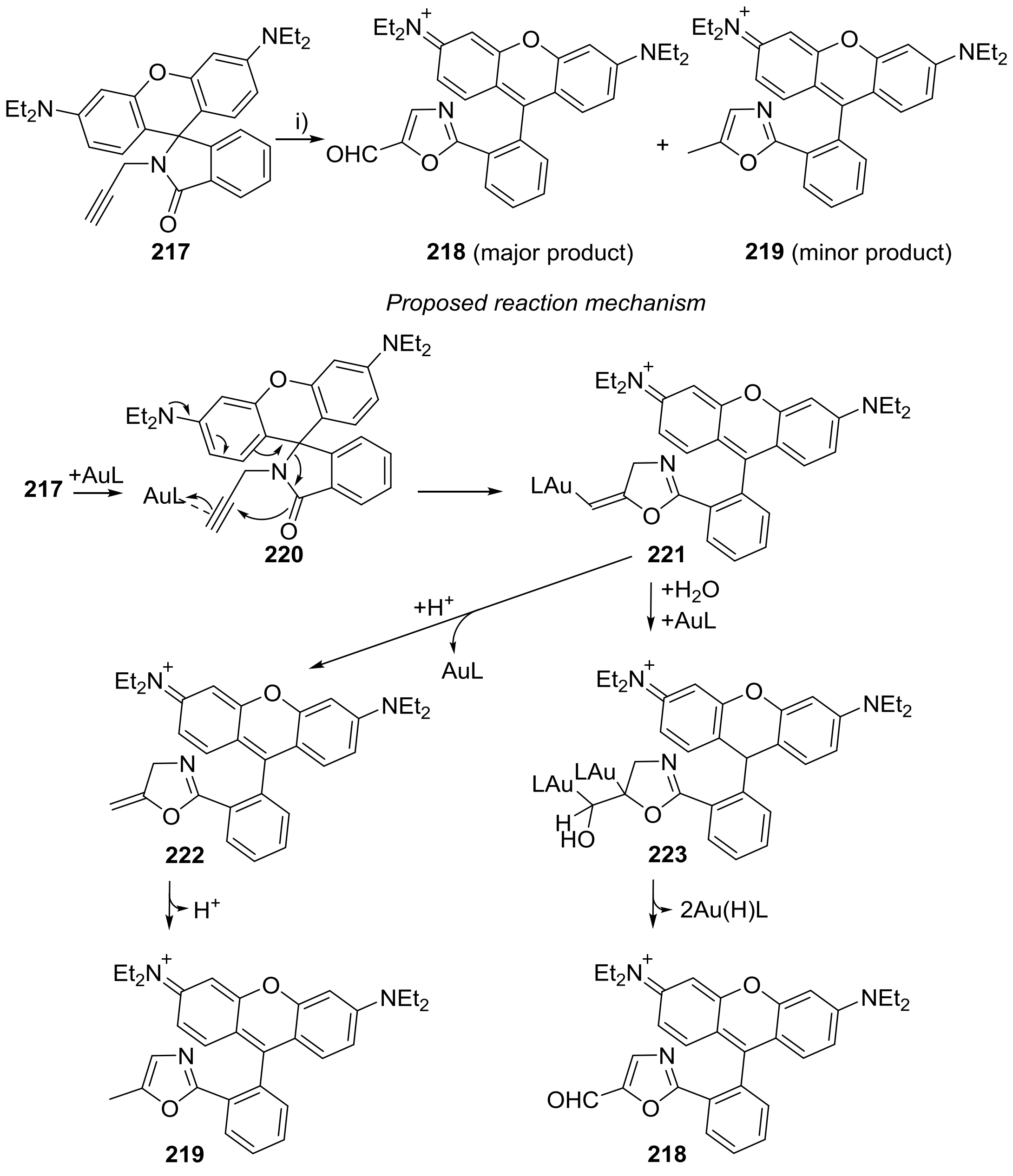
This technology was applied to the preparation of a fluorescent chemical sensor for the detection of Au(III) ions. The protocol is based on the cyclisation of the rhodamine-alkyne derivative **217**, which generates the oxazole **218** in the presence of Au(III) ions (Scheme 63),[82] providing a fluorescent 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).[83] 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.



i) $AuCl_3$, 1:1 EtOH/PBS buffer (pH = 7.4), λ_{ex} = 558 nm.

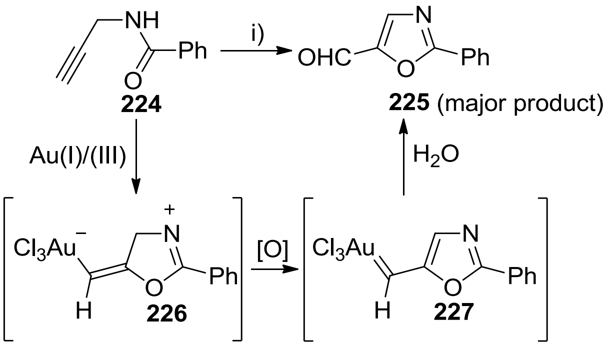
Scheme 63. Au(III)-mediated synthesis of oxazole **218**



i) AuCl or $AuCl_3$, 1:1 MeCN/PBS buffer (pH = 7.2), λ_{ex} = 530 nm.

Scheme 64. Au(I) and Au(III)-mediated synthesis of oxazole2 **218** and **219**

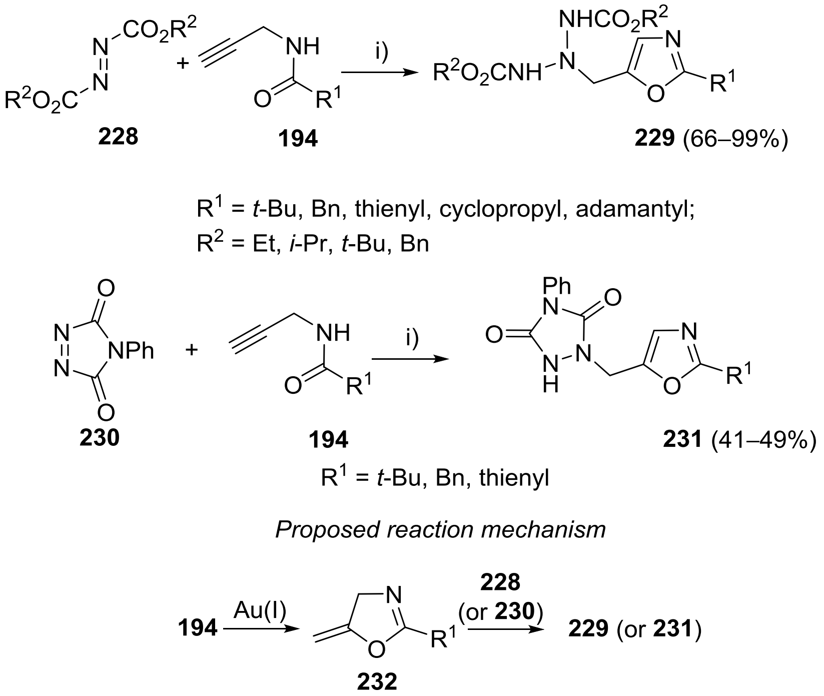
Ahn reported the preparation of 2-phenyloxazole-5-carboxaldehyde **225** through the Au(I)/(III)-mediated cyclisation of *N*-(propargyl)benzamide **224** in aqueous media (Scheme 65).[84] The formyloxazole **225** was only formed as the major product either using a stoichiometric amount of a Au(III) 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.



i) $AuCl_3$ (1.0 eq) or $HAuCl_4$ (1.0 eq) or AuCl (3.5 eq), $MeCN/H_2O$ (1:1 *v/v*), rt, 1 h.

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**



R^1 = *t*-Bu, Bn, thienyl, cyclopropyl, adamantyl;
R^2 = Et, *i*-Pr, *t*-Bu, Bn

R^1 = *t*-Bu, Bn, thienyl

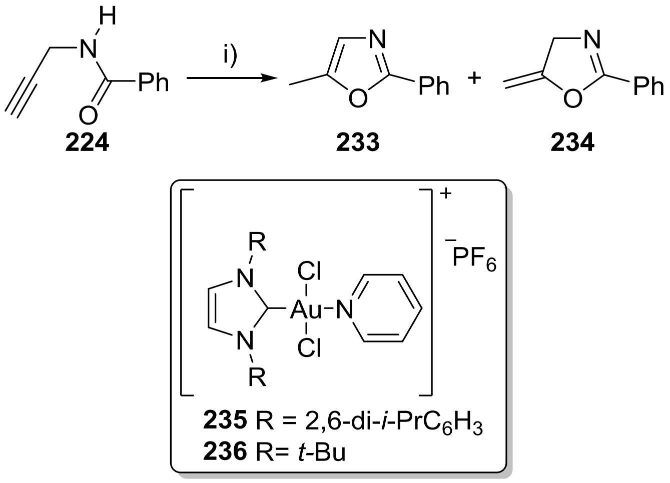
Proposed reaction mechanism

i) **228** or **230** (1.8-1.0 eq), **194** (1.0 eq), $[Ph_3PAuNTf_2]$ (3-7 mol%), $CDCl_2$, rt, 3 h to 11 d.

Scheme 66. Au(I)-catalysed synthesis of oxazoles **229** and **231**

(Scheme 66).[85] 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.[85]

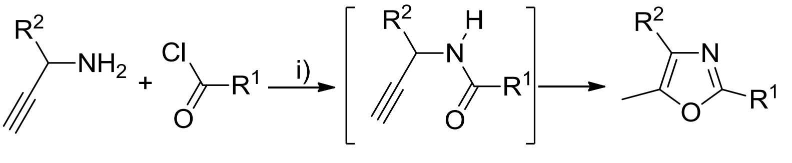
In search for alternative Au(III) catalysts, Blanc and Frémont discovered that the cycloisomerisation of *N*-propargylamide **224** catalysed by *N*-heterocyclic carbene complexes **235** and **236** in the presence of $AgSbF_6$ yielded a mixture of oxazole **233** and oxazoline **234** (Scheme 67).[86]



i) **235** or **236** (5 mol%), $AgSbF_6$ (1.0 eq), CH_2Cl_2, 45 °C, 1.5 or 12 h.

Scheme 67. Au(III)-catalysed cycloisomerisation of *N*-propargylamides **224**

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).[87] The transformation proceeds *via* the reaction of propargyl amines **172** and acid chlorides **173** to give a propargylamide **175**, which



172 **173** **175** **174** (26–95%)

R^1 = *i*-Pr, tetrahydro-2*H*-pyran-4-yl, $PhCH=CH_2$, Ph, pyridin-2-yl, thiazol-4-yl, 1-MeCO-piperidin-4-yl, 2-CF_3-pyridin-5-yl, adamantan-1-yl;
R^2 = Me, EtO_2CCH_2

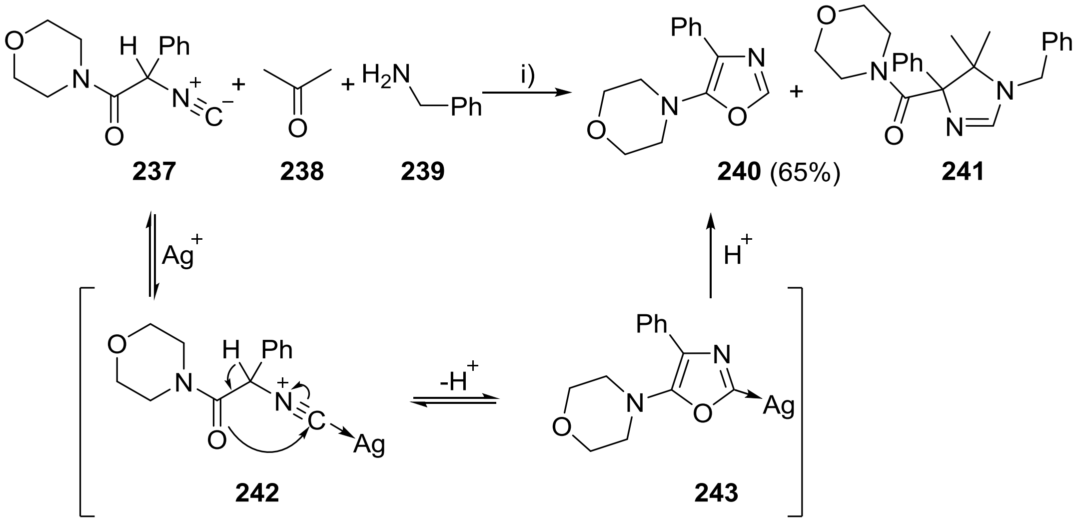
i) **172** (1.5 eq), **173** (1.0 eq), Et_3N (1.5 eq), MeCN, rt, 30 min then $AuCl_3$ (2-30 mol%), 45 °C, 2-6 h.

Scheme 68. Au(III)-catalysed two-step sequential procedure for the synthesis of oxazoles **174** 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)

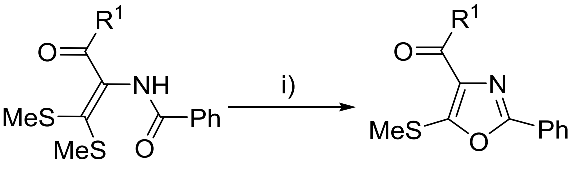
During a study of the multicomponent reaction of α-isocyano amide **237**, acetone **238** and benzylamine **239** leading to 2*H*-2-imidazoline **241** (Scheme 69), Orru discovered conditions where the disubstituted oxazole **240** was obtained as the major product.[88] Oxazole **240** is generated *via* the formation of the activated α-isocyano amide **242** followed by a 5-*endo* cyclisation leading to **243**, which upon proto-demetallation generates oxazole **240**. Selective functionalisation at the C4 and C5 positions is uncommon, therefore this procedure provides access to alternative oxazole substitution patterns.



i) **237** (1.0 eq), **238** (2.0 eq), **239** (1.5 eq), $MgSO_4$ (0.8 eq), AgOAc (2 mol%), MeOH, rt, 21 h.

Scheme 69. Ag(I)-catalysed synthesis of oxazoles **240**

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).[89,90] 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.



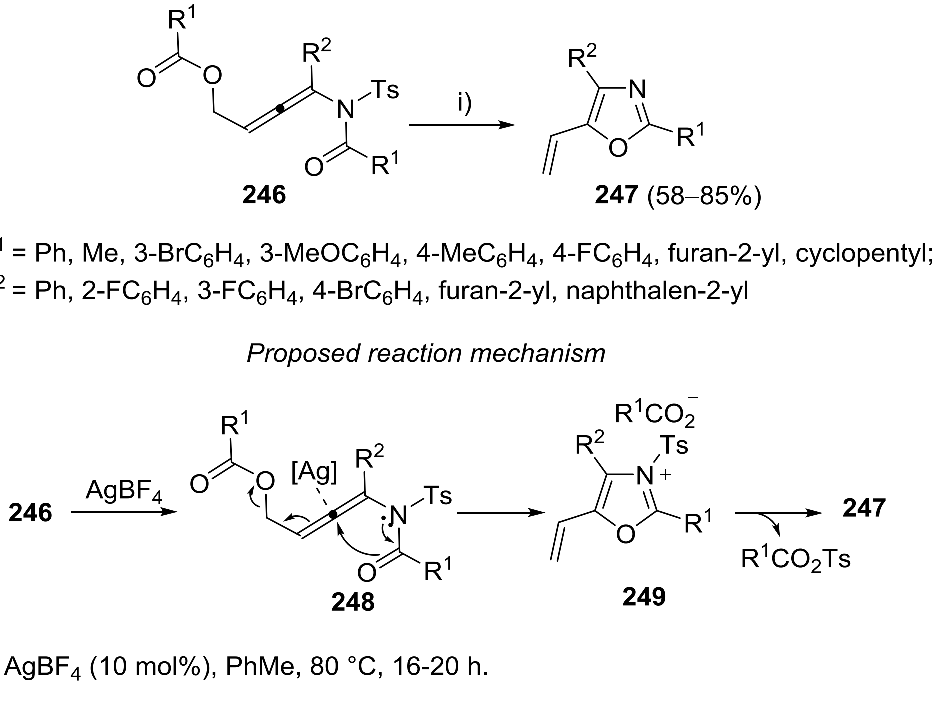
244 **245** (74–98%)

R^1 = EtO, MeO, *t*-BuO, PhO, Et, *n*-Bu, Ph, 4-$MeOC_6H_4$, 2-$NH_2C_6H_4NH$, PhNH, 4-$MeOC_6H_4NH$, 4-FC_6H_4NH, 4-Me-2-BrC_6H_3NH, EtNH indol-3-yl-$(CH_2)_2NH$-, $PhCH_2NMe$, piperidin-1-yl, 4-benzylpiperazin-1-yl, 4-EtO_2C-piperazin-1-yl, $MeSCH_2CH_2(CH)CO_2EtNH$, *i*-Pr-$(CH)CO_2EtNH$, $PhCH_2(CH)CO_2EtNH$

i) **306** (1.0 eq), Ag_2CO_3 (4.0 eq), 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).[68] The reaction proceeds through intramolecular cyclisation of **248** to give



246 **247** (58–85%)

R^1 = Ph, Me, 3-BrC_6H_4, 3-$MeOC_6H_4$, 4-MeC_6H_4, 4-FC_6H_4, furan-2-yl, cyclopentyl;
R^2 = Ph, 2-FC_6H_4, 3-FC_6H_4, 4-BrC_6H_4, furan-2-yl, naphthalen-2-yl

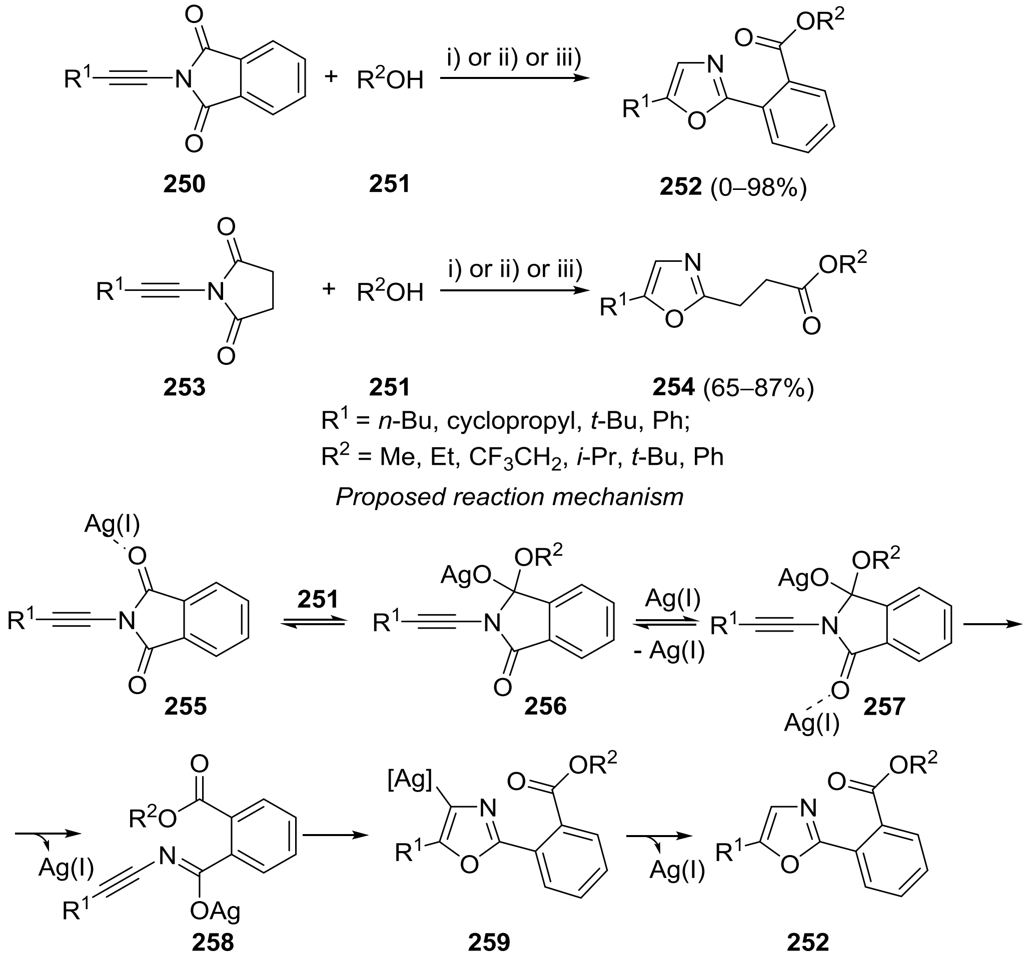
246 → **248** → **249** → **247**

i) $AgBF_4$ (10 mol%), PhMe, 80 °C, 16-20 h.

Scheme 71. Ag(II)-catalysed cyclisation of allenylamides **246**

249, 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).[91] 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.



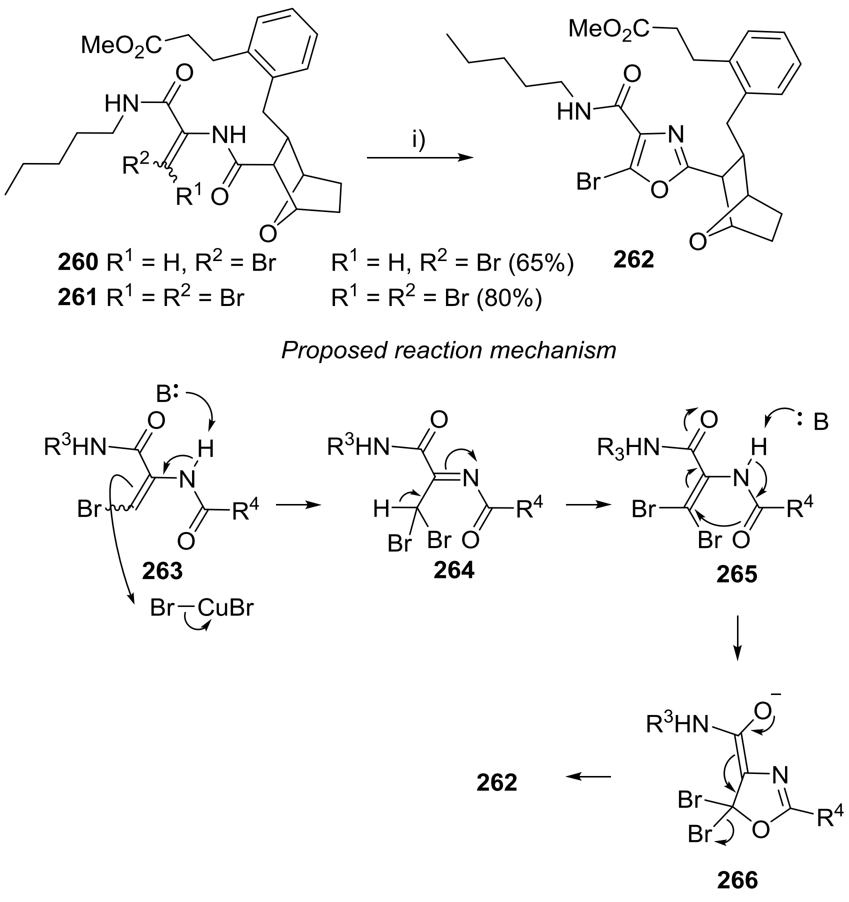
i) **250** or **253** (1.0 eq), **251** (2.5 eq), Ag_2O (30 mol%), CH_2Cl_2, rt, 24 h; ii) **250** or **253** (1.0 eq), **251** (50.0 eq), Ag_2O (30 mol%), CH_2Cl_2, 80 °C, 1-24 h; iii) **250** or **253** (1.0 eq), **251** (solvent), Ag_2O (30 mol%), CH_2Cl_2, 80 °C, 1-24 h.

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)

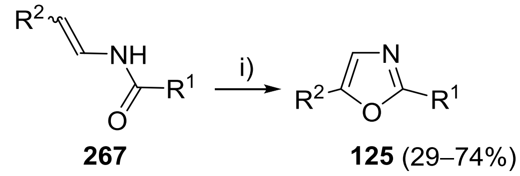
In 1992, Das described a synthesis of trisubstituted oxazole **262** through the Cu(II)-mediated cyclisation of vinyl bromide **260** (and vinyl dibromide **261**) in the presence of a base (Scheme 73).[92] The proposed reaction mechanism involves the formation of a common intermediate followed by cyclisation to generate the oxazole **262** in good yield.



i) $CuBr_2$ (4.0 eq), DBU (8.0 eq), CH_2Cl_2, rt, 24 h.

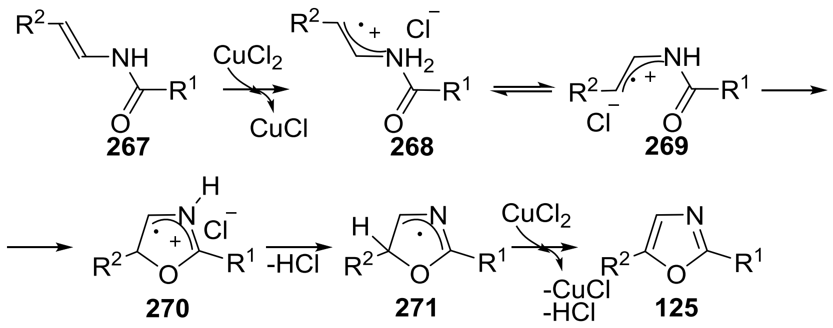
Scheme 73. Cu(II)-mediated synthesis of oxazoles **262**

Stahl described a synthesis of 2,5-disubstituted oxazoles **125** through a Cu(II)-mediated oxidative cyclisation of enamides **267** (Scheme 74).[93] 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.



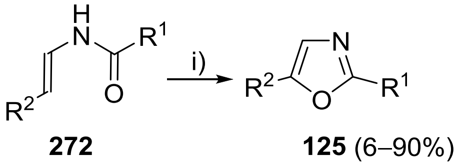
R^1 = Ph, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$, *t*-Bu, PhCH=CH;
R^2 = Ph, 4-$MeOC_6H_4$, 3-4-$(MeO)_2C_6H_3$, 4-ClC_6H_4, 4-MeC_6H_4, 4-*t*-BuC_6H_4, *n*-Bu

Proposed reaction mechanism



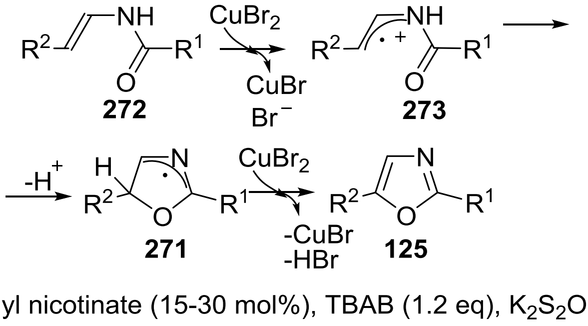
i) $CuCl_2$ (2.0 eq), *N*-methylimidazole (2.0 eq), air, 1,4-dioxane, 140 °C, 20 h.

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



R^1 = Ph, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 4-$F_3CC_6H_4$, 4-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 4-BrC_6H_4, 4-*t*-BuC_6H_4, *t*-Bu, 3,4,5-$(MeO)_3C_6H_2$, cyclohexyl, 1-cyclohexenyl, thiophen-2-yl, thiophen-3-yl, furan-2-yl, 3,4-$(MeO)_2C_6H_3CH$=CH, 2-MeC_6H_4, naphthalen-2-yl, PhCH=CH;
R^2 = Ph, 4-$MeOC_6H_4$, 4-$MeCOC_6H_4$, 4-MeC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-FC_6H_4, 3,4-$F_2C_6H_3$, 2-MeC_6H_4, PhCH=CH, *n*-octyl, thiophen-3-yl , *N*-benzoyl-5-indolyl

Proposed reaction mechanism

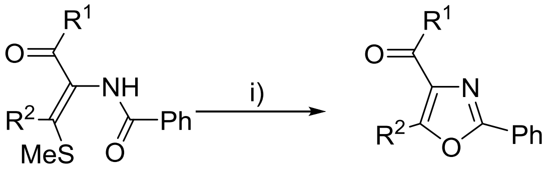


i) $CuBr_2$ (7.5-15 mol%), ethyl nicotinate (15-30 mol%), TBAB (1.2 eq), $K_2S_2O_8$ (1.3 eq), MeCN, rt, 24 h.

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).[94] In a similar manner to the vinylic C—H functionalization developed by Stahl,[93] the reaction involves the single-electron oxidation of **272** by $CuCl_2$, 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).[95] This protocol provides considerable advantages over the previous Ag(I)-mediated cyclisation described above (Scheme 70),[89] including the use of catalytic amounts of copper and the ability to introduce carbon based substituents at the 5-position.



274 **275** (70–92%)

R^1 = 4-$MeOC_6H_4$, *n*-Bu, EtO, C_4H_9O, $PhCH_2O$, *t*-BuO, 3,4-$(MeO)_2C_6H_3CH_2CH_2NH$, indol-3-yl-$(CH_2)_2NH$, morpholin-4-yl, 4-benzylpiperazin-1-yl, 3,4,5-$(MeO)_3C_6H_2NH$, 4-FC_6H_4NH, 4-$CF_3C_6H_4NH$, $Bn(CH)CO_2EtNH$, indol-3-yl-$CH_2(CH)CO_2EtNH$, $HOCH_2(CH)CO_2EtNH$, benzo[*d*][1,3]dioxol-5-yl, thiophen-2-yl;
R^2 = 4-$MeOC_6H_4$, 3,4-$(MeO)_2C_6H_3$, benzo[*d*][1,3]dioxol-5-yl, furan-2-yl, 1-Me-1*H*-indol-3-yl, pyridin-3-yl, Ph, 1-Me-1*H*-pyrrol-2-yl, thiophen-2-yl

i) Cs_2CO_3 (1.0 eq), CuI (10 mol%), 1,10-phenanthroline (20 mol%), DMF, 90 °C , 3-4 h.

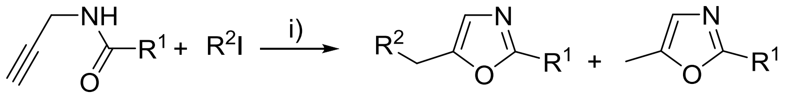
Scheme 76. Cu(I)-catalysed synthesis of oxazoles **275**

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).[96] 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.



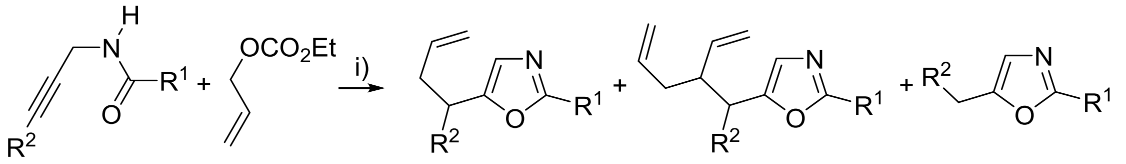
194 **276** **277** (11–83%) **195** (4–49%)

R^1 = Ph, 4-$MeOC_6H_4$, 3-$CF_3C_6H_4$, CF_3, 4-MeC_6H_4;
R^2 = 2-MeC_6H_4, 3-MeC_6H_4, 4-MeC_6H_4, 3,5-$Me_2C_6H_3$, 3-$MeOC_6H_4$, 4-$MeOC_6H_4$, Ph, 4-ClC_6H_4, 3-$CF_3C_6H_4$, 3-FC_6H_4, 4-FC_6H_4, 4-$MeCOC_6H_4$

i) **194** (1.0 eq), **276** (1.2 eq), NaO*t*-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]



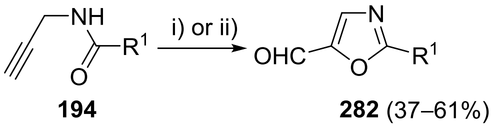
278 **279** **280** (0–70%) **281** (0–80%) **277** (trace–56%)

R^1 = Ph, H, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-ClC_6H_4, 4-$NO_2C_6H_4$, 2-thienyl, 2-furyl, CH=CH_2Ph, CH_2Ch_2Ph;
R^2 = H, Et, *t*-Bu, Ph, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$

i) **278** (1.0 eq), **279** (3.0 or 6.0 eq), $Pd_2(dba)_3$ (2.5 or 5 mol%), IPr·HCl (6 or 12 mol%), Cy_3P (10 or 20 mol%), Cs_2CO_3 (3.0 or 6.0 eq), MeCN, 90 °C, 21 h.

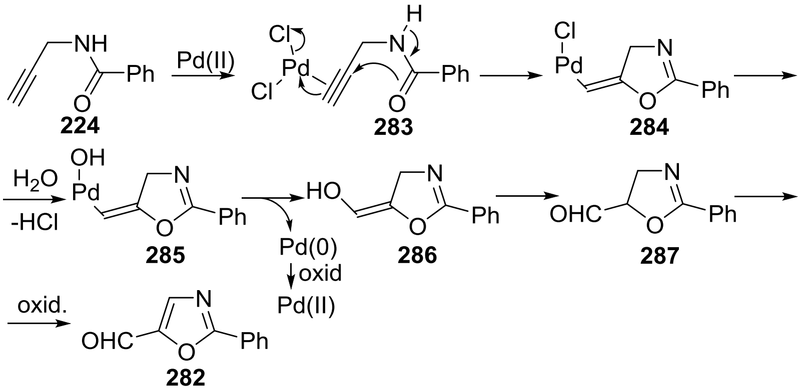
Scheme 78. Pd(0)-catalysed cycloisomerisation-allylation reaction of *N*-propargylamides **278** and allyl ethyl carbonate **279**

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.



R^1 = 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$, Bn, $Ph(CH_2)_2$, *N*-Me-pyrrol-2-yl, pyrrol-2-yl, thiophen-2-yl, furan-2-yl, Me(CH)NHBoc, $(Me)_2CH(CH)NHBoc$

Proposed reaction mechanism



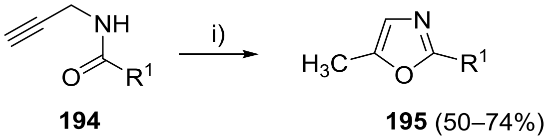
i) **194** (1.0 eq), $PdCl_2(MeCN)_2$ (5 mol%), benzoquinone (1.0 eq), DMF/THF, 60 °C, 3 h;
ii) $PdCl_2(MeCN)_2$ (5 mol%), $CuCl_2$ (10 mol%), DMF, rt, 30 min then **194** (1.0 eq), O_2, DMF, 100 °C, 2 h.

Scheme 79. Pd(II)-catalysed oxidative cyclisation of *N*-propargylamides **194**

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)

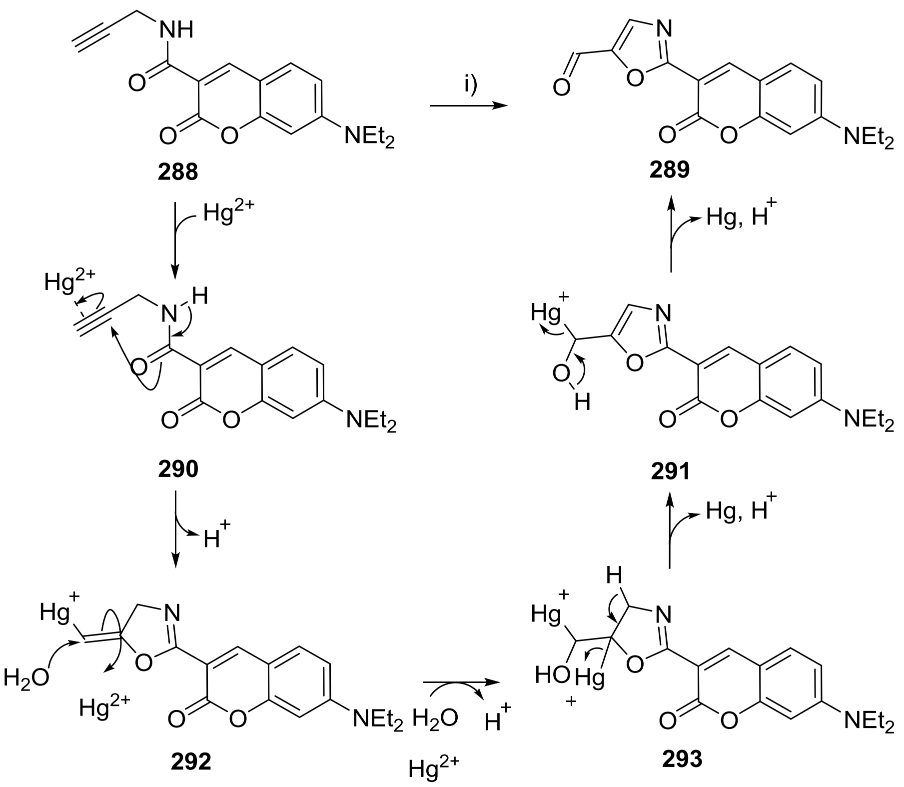
The first example of Hg(II)-mediated cycloisomerisation of *N*-propargylamides **194** to oxazoles was reported by Deryckere in 1973 (Scheme 80).[99] Reaction of **194** with $Hg(OAc)_2$ in the presence of acetic acid provided moderate to good yields of oxazole **195** (50–74%). This protocol has found a number of applications in the synthesis of bioactive oxazole-containing compounds.[100]



R^1 = Ph, 4-$NO_2C_6H_4$, Ph_2CH, pyridin-3-yl
i) $Hg(OAc)_2$ (9.4 eq), $MeCO_2H$ (solvent), 1 h, reflux.

Scheme 80. Hg(II)-mediated cycloisomerisation of *N*-propargylamides **194**

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).[101] 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**.[102]

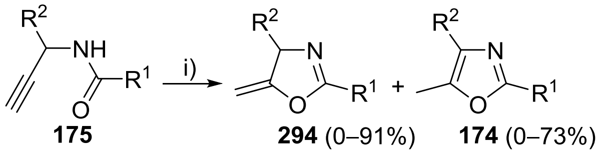


i) Hg(II) ions, EtOH/HEPES, pH = 7.4, λ_{ex} = 438 nm.

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).[103]



R^1 = Ph, Bn, 2-BrC_6H_4, 2-MeOC_6H_4, 4-$NO_2C_6H_4$, *n*-heptyl;
R^2 = H, Me

i) **175** (1.0 eq), $W(CO)_6$ (20 mol%), DABCO (1.0 eq), 350 nm, PhMe, rt, 20 h then $(Me)_3NO$, THF.

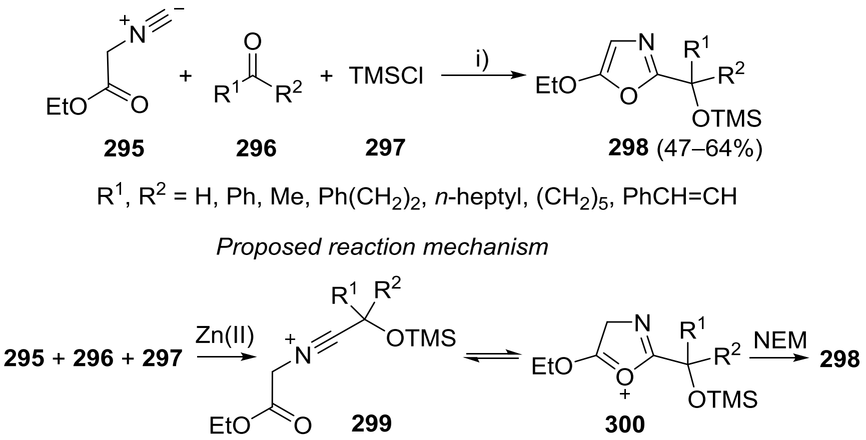
Scheme 82. W(0)-catalysed cyclisation of *N*-propargylamides **175**

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.

O1–C2 BOND DISCONNECTION

ZINC(II)

Ganem reported the synthesis of 2,5-disubstituted oxazoles **298** through the Zn(II)-promoted three-component condensation of ethyl isocyanoacetate **295**, carbonyl compounds **296** and trimethylsilyl chloride **297** in the presence of a base (Scheme 83).[104] 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[105] provides a mild protocol for the synthesis of a range of 2-substituted-5-alkoxyoxazoles in moderate yield.



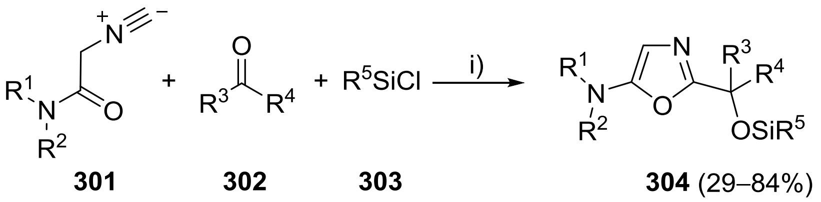
R^1, R^2 = H, Ph, Me, Ph$(CH_2)_2$, *n*-heptyl, $(CH_2)_5$, PhCH=CH

Proposed reaction mechanism

i) **295** (1.2 eq), **296** (1.0 eq), $Zn(OTf)_2$ (0.5 eq), TMSCl (3.0 eq), *N*-ethylmorpholine (3.0 eq), CH_2Cl_2, 0 °C then rt, 24 h.

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

The substrate scope of this transformation was expanded to the condensation of isocyanoacetamides **301** and carbonyl compounds **302** in the presence of silyl chlorides **303** (Scheme 84).[106] A number of

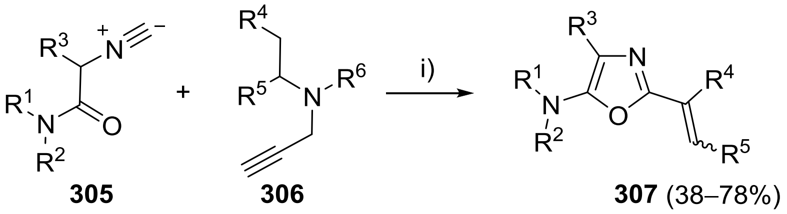


NR^1R^2 = morpholino, NMe_2;
R^3, R^4 = H, Ph, *t*-Bu, $(CH_2)_5$, Ph$(CH_2)_2$, *n*-nonyl;
R^5 = Me_3, Et_3

i) $Zn(OTf)_2$ (0.3 eq), **301** (1.0 eq), **302** (1.3 eq), R^5SiCl (1.6 or 2.0 eq), *N*-ethylmorpholine (2.1 eq), CH_2Cl_2, rt, 12 h.

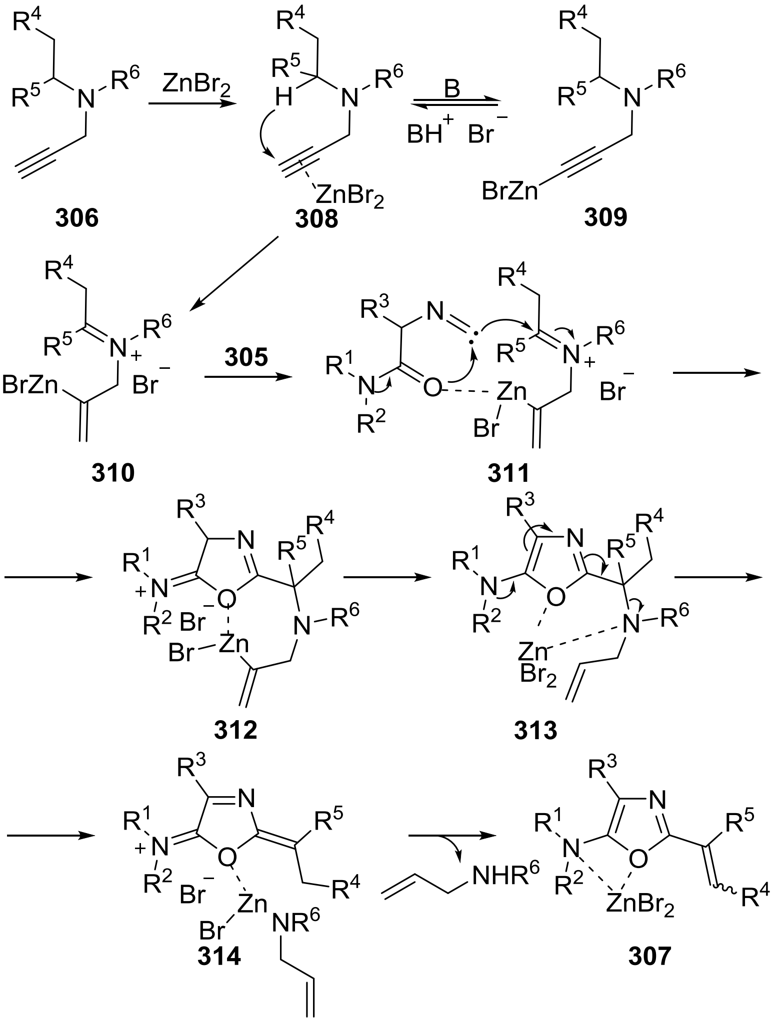
Scheme 84. Zn(II)-promoted synthesis of oxazoles **304**

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 isocyanoacetamides, carbonyl compounds and silyl chlorides.[107]



NR^1R^2 = morpholin-4-yl, pyrrolidin-1-yl;
R^3 = 4-$MeC_6H_4CH_2$, 4-$MeOC_6H_4CH_2$, 4-$FC_6H_4CH_2$, 4-$BrC_6H_4CH_2$, 3-$BrC_6H_4CH_2$, 2-$BrC_6H_4CH_2$, *n*-hexyl, Ph, Bn;
$R^4CH_2CHR^5$ = *i*-Pr, $(MeCH_2)_2CH$, $MeCH_2CHMe$, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.1]heptan-1-yl;
R^6 = *i*-Pr, $(MeCH_2)_2CH$, $MeCH_2CHMe$, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, Me

Proposed reaction mechanism



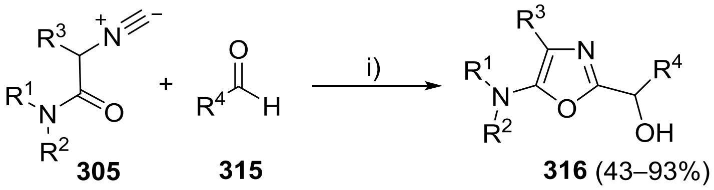
i) **305** (2.0 or 3.0 or 5.0 eq), **306** (1.0 eq), $ZnBr_2$ (1.5 or 5.0 eq), PhMe, 100 °C, 2 h.

Scheme 85. Zn(II)-mediated synthesis of oxazoles **307**

Trisubstituted oxazoles **307** have also been prepared through the Zn(II)-mediated reaction of α-isocyanoacetamidates **305** and propargylamines **306** (Scheme 85).[108] The reaction proceeds *via* the formation of an alkyne-$ZnBr_2$ π-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 isocyanoacetamidates **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-isocyanoacetamides **305** and aldehydes **315** under very mild reaction conditions (Scheme 86).[109] 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.



NR^1R^2 = morpholino, NEt_2;
R^3 = H, Bn;
R^4 = Et, Bn, *i*-Pr, cyclohexyl, *t*-Bu, $BnOCH_2$, CO_2Et, Ph, 2-$MeOC_6H_4$, 3-BrC_6H_4, 4-MeC_6H_4, 4-ClC_6H_4, 4-$NO_2C_6H_4$, *n*-hexyl

i) **305** (1.0 eq), **315 (**1.2 eq), $SnCl_2$ (10 mol%), PhMe, 0 °C.

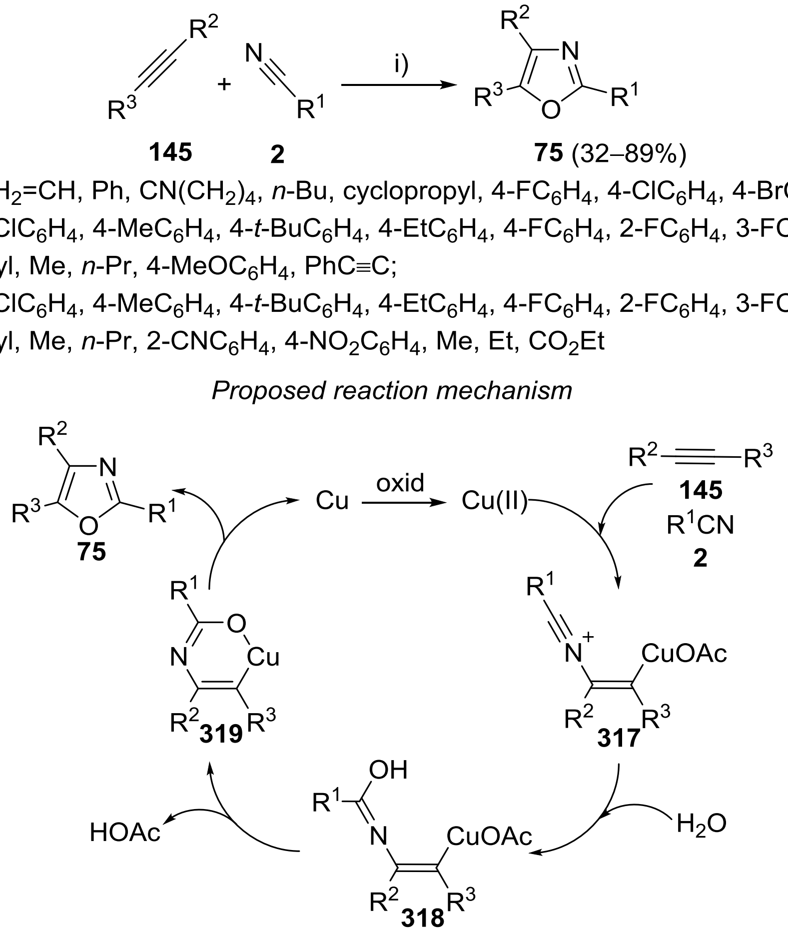
Scheme 86. Sn(II)-catalysed synthesis of oxazoles **316**

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).[110] 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.



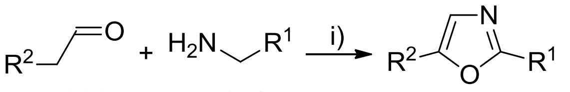
R^1 = Me, CH_2=CH, Ph, $CN(CH_2)_4$, *n*-Bu, cyclopropyl, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-MeC_6H_4;
R^2 = Ph, 4-ClC_6H_4, 4-MeC_6H_4, 4-*t*-BuC_6H_4, 4-EtC_6H_4, 4-FC_6H_4, 2-FC_6H_4, 3-FC_6H_4, naphthalen-1-yl, thiophen-2-yl, Me, *n*-Pr, 4-$MeOC_6H_4$, PhC≡C;
R^3 = Ph, 4-ClC_6H_4, 4-MeC_6H_4, 4-*t*-BuC_6H_4, 4-EtC_6H_4, 4-FC_6H_4, 2-FC_6H_4, 3-FC_6H_4, naphthalen-1-yl, thiophen-2-yl, Me, *n*-Pr, 2-CNC_6H_4, 4-$NO_2C_6H_4$, Me, Et, CO_2Et

Proposed reaction mechanism

i) **2** (2.5 or 3.0 eq), **145** (1.0 eq), $Cu(OAc)_2$ (5 or 10 mol%), $BF_3{\cdot}OEt_2$ (1.0 eq), H_2O (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**

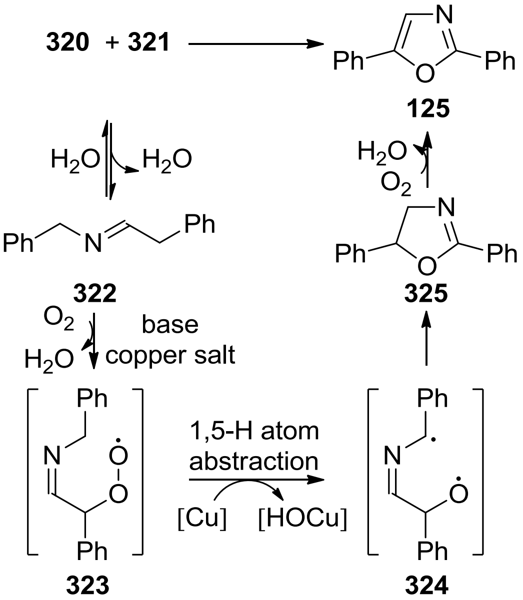
Jiao described a highly efficient synthesis of disubstituted oxazoles **125** through the Cu(II)-mediated aerobic oxidative dehydrogenative annulation of aldehydes **320** and amines **321** (Scheme 88).[111] The proposed mechanism involves the oxidation of an imine **322** to give a radical **323**, 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.



320 **321** **125** (0–89%)

R^1 = 2-MeC_6H_4, 3-MeC_6H_4, 4-MeC_6H_4, 2,4-$Me_2C_6H_3$, 4-$MeOC_6H_4$, 4-$CF_3C_6H_4$, 4-FC_6H_4, 2,5-$F_2C_6H_3$, 4-ClC_6H_4, 3-BrC_6H_4, 4-*t*-BuC_6H_4, naphthalen-1-yl, Bn, 2-$MeC_6H_4CH_2$, 4-$FC_6H_4CH_2$, $PhCHCH_3$, $Ph(CH_2)_2$, $Ph(CH_2)_3$, *n*-Bu, *n*-pentyl, *n*-heptyl, *i*-Bu, Ph;
R^2 = Ph, 2-MeC_6H_4, 3-MeC_6H_4, Me, 4-MeC_6H_4, 4-FC_6H_4, 4-$MeOC_6H_4$, 4-$EtOC_6H_4$

Proposed reaction mechanism

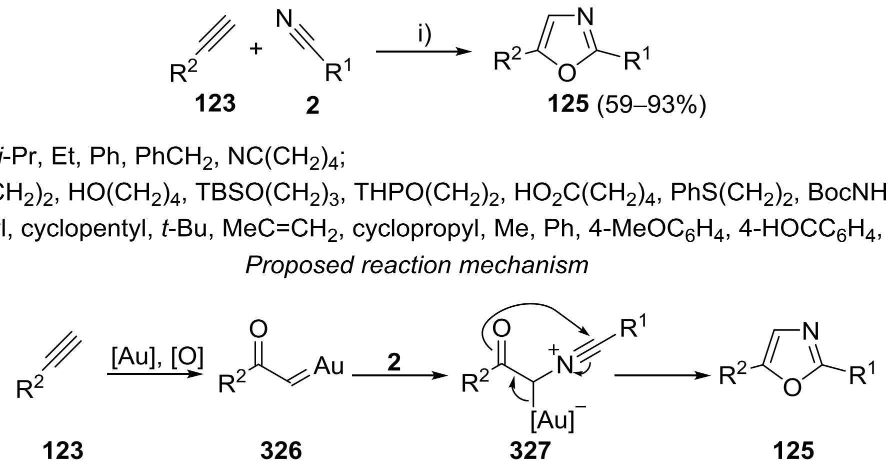


i) **320** (1.0 eq), **321** (1.5), $CuBr_2$ (1.5 eq), pyridine (20 mol%), K_2CO_3 (2.0 eq), PhMe, O_2 (1 atm), 80 °C, 11 or 16 h.

Scheme 88. Cu(II)-catalysed synthesis of oxazoles **125**

GOLD(I)

Au(I)-catalysed [2+2+1] annulation of alkynes **123**, nitriles **2** and an *N*-oxide also leads to the corresponding oxazole (Scheme 89).[112] 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 *α*-diazoketones, generating an *α*-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 $BrettPhosAuNTf_2$ 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.



R^1 = Me, *i*-Pr, Et, Ph, $PhCH_2$, $NC(CH_2)_4$;
R^2 = $Ph(CH_2)_2$, $HO(CH_2)_4$, $TBSO(CH_2)_3$, $THPO(CH_2)_2$, $HO_2C(CH_2)_4$, $PhS(CH_2)_2$, $BocNH(CH_2)_4$, $Cl(CH_2)_4$, cyclohexyl, cyclopentyl, *t*-Bu, $MeC{=}CH_2$, cyclopropyl, Me, Ph, $4\text{-}MeOC_6H_4$, $4\text{-}HOCC_6H_4$, $2\text{-}MeC_6H_4$

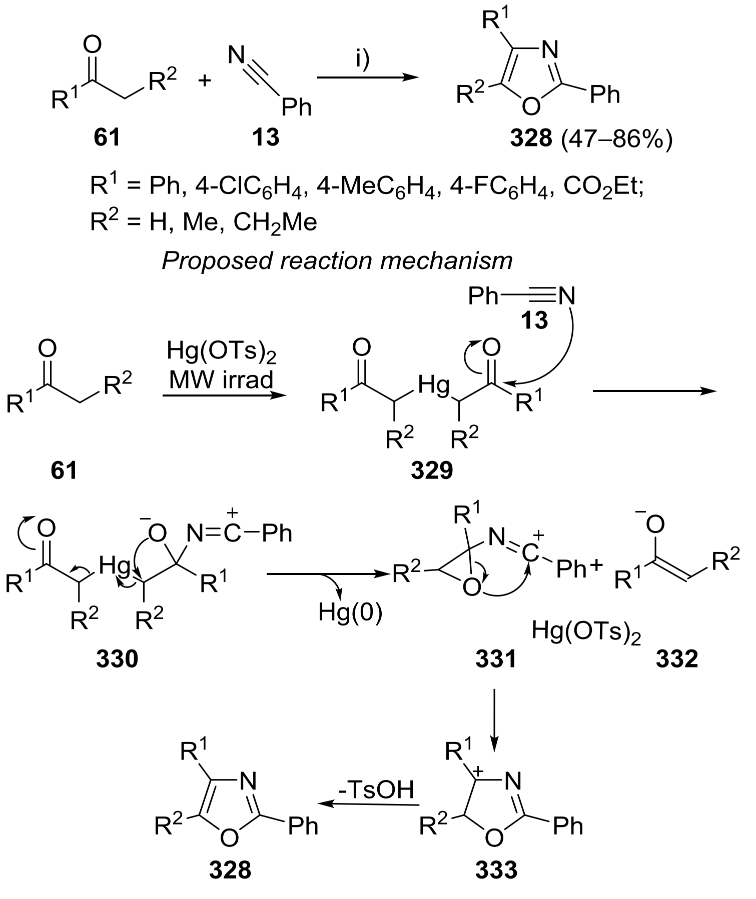
Proposed reaction mechanism

i) **123** (1.0 eq), **2** (solvent), $Ph_3PAuNTf_2$ (5 or 10 mol%), 8-methylquinoline-*N*-oxide (1.3 or 2.6 eq), 60 °C, 3 h or on.

Scheme 89. Au(I)-catalysed [2+2+1] annulation for the synthesis of oxazoles **125**

MERCURY(II)

Lee reported a rapid microwave-assisted synthesis of 2,4- and 2,4,5-substituted oxazoles **328** through the Hg(II)-mediated reaction of aromatic ketones **61** and benzonitrile **13** (Scheme 90).[113] The reaction proceeds



R^1 = Ph, $4\text{-}ClC_6H_4$, $4\text{-}MeC_6H_4$, $4\text{-}FC_6H_4$, CO_2Et;
R^2 = H, Me, CH_2Me

Proposed reaction mechanism

i) **61** (1.0 eq), **13** (5.0 eq), $Hg(OTs)_2$ (1.0 eq), MW irrad, 2-4 min.

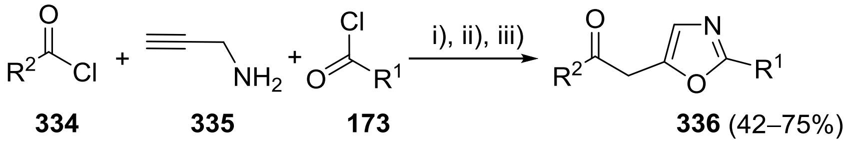
Scheme 90. Hg(II)-mediated synthesis of oxazoles **328** *via* the enolisation of **61** to generate **329**, reaction of **329** with the nitrile to give **333**, which upon aromatisation gives the observed oxazole **328**. Ketones bearing a more acidic methylene group α- to the carbonyl functionality 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

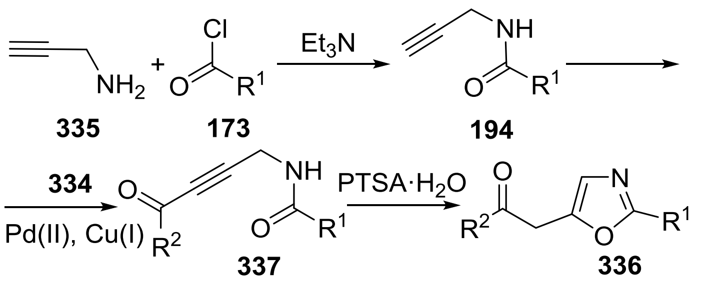
PALLADIUM(II) AND COPPER(I)

An interesting one-pot three-component synthesis of oxazoles **336** using both Cu(I)- and Pd(II)-catalysis was reported by Müller (Scheme 91).[114,115] 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.[114,115]



R^1 = Ph, 4-MeOC$_6$H$_4$, 4-MeC$_6$H$_4$, 2-FC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-NO$_2$C$_6$H$_4$, 2-NO$_2$C$_6$H$_4$, thiophen-2-yl, cyclohexen-1-yl, PhCH=CH$_2$, CH$_2$=CH;
R^2 = Ph, 4-MeC$_6$H$_4$, thiophen-2-yl, PhCH=CH$_2$, 4-MeOC$_6$H$_4$, 4-ClC$_6$H$_4$, 2-BrC$_6$H$_4$, PhCH=CH$_2$

Proposed reaction mechanism

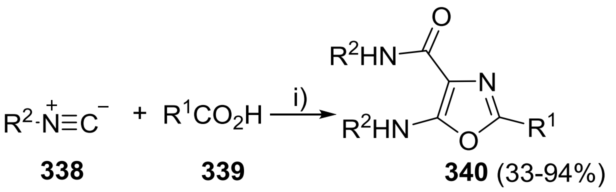


i) **335** (1.0 eq), **173** (1.0 eq), Et$_3$N (1.0 eq), THF, 0 °C then rt, 1 h; ii) **334** (1.0 eq), PdCl$_2$(PPh$_3$)$_2$ (2 mol%), CuI (4 mol%), Et$_3$N (1.0 eq), rt, 1 h; iii) PTSA, H$_2$O (1.0 eq), BuOH, 60 °C, 1 h.

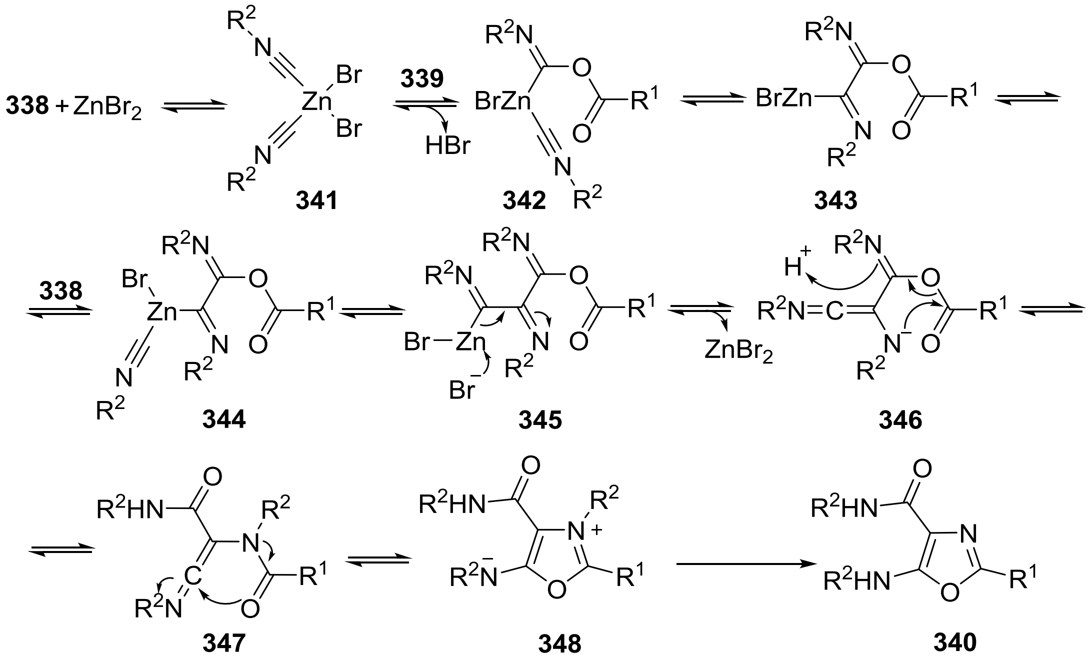
Scheme 91. One-pot three-component synthesis of oxazoles **336**

ZINC(II)

Trisubstituted oxazoles **340** can also be prepared through the Zn(II)-mediated coupling of isonitriles **338** with carboxylic acids **339** (Scheme 92).[116] 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 $ZnBr_2$ is required for this protocol, due to the oxazole's ability to chelate Zn^{2+} 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.



R^1 = Ph, 4-CNC_6H_4, 4-MeO_2C, 4-$NO_2C_6H_4$, 4-$CF_3C_6H_4$, 3-$MeOC_6H_4$, 2-Br-4,5-$(MeO)_2C_6H_2$, indol-2-yl, furan-2-yl, thiophen-2-yl, PhCH=CH, C_6F_5CH=CH, 4-$NO_2C_6H_4CH_2$, 2,2-dimethyl-1,3-dioxolan-4-one-5-yl, 4-MeC_6H_4, *t*-Bu, $Cl(CH_2)_3$;
R^2 = $MeCH_2C(CH_3)_2$, *t*-Bu, $(Me)_3CCH_2C(Me)_2$, adamantan-1-yl, $MeO_2COCH_2C(Me)_2$, benzo[*d*][1,3]dioxol-5-yl



i) **338** (1.7 eq), **339** (1.0 eq), $ZnBr_2$ (1.5 eq), PhMe, 60 or 100 °C, 5 min-2 h.

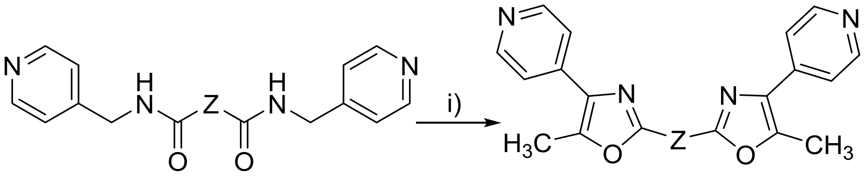
Scheme 92. Zn(II)-mediated synthesis of oxazoles **340**

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.



349 **350** (32–100%)

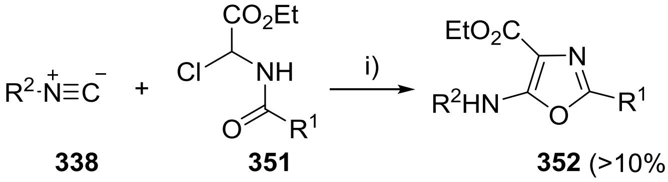
Z = C(Me)$_2$, *p*-biphenyl, *p*-phenyl, CH$_2$CH$_2$

i) SnCl$_4$ (60 mol%, 1 M in CH$_2$Cl$_2$), (MeCO)$_2$O, reflux, 4 h.

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 Me$_2$AlCl proved to be a superior Lewis acid promoter for this transformation, automated parallel reactions were conducted using ZnCl$_2$ due to the convenience of handling this reagent.



338 **351** **352** (>10%)

R^1 = Ph, Me, cyclohexyl, 2-MeC$_6$H$_4$, 2,6-F$_2$C$_6$H$_3$;
R^2 = *t*-Bu, *n*-Bu, cyclohexyl, Bn, 2,6-Me$_2$C$_6$H$_3$

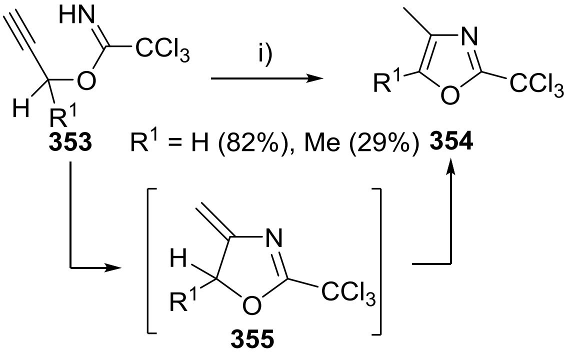
i) Chemspeed Robot, ZnCl$_2$ (1.0-3.0 eq), THF, rt.

Scheme 94. Zn(II)-mediated synthesis of oxazoles **352**

N3–C4 BOND DISCONNECTION

GOLD(III)

The Au(III)-catalysed synthesis of oxazoles **354** through the cycloisomerisation of propargyl trichloroacetimidates **353** was disclosed by Hashmi (Scheme 95).[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^1 = H).



i) $AuCl_3$ (3 mol%, 10 *w/w*% in CD_3CN), $CDCl_3$, rt., 3 d.

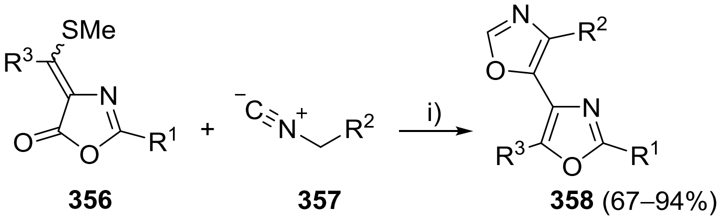
Scheme 95. Au(III)-catalysed cycloisomerisation of propargyl trichloroacetimidates **353**

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

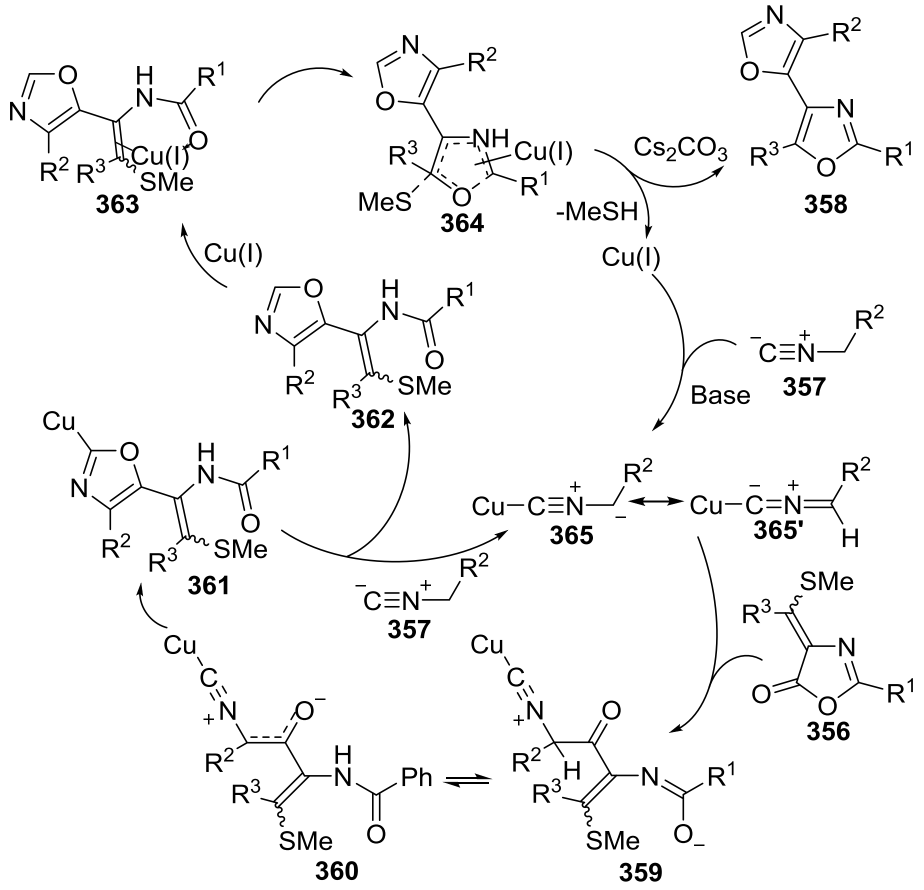
COPPER(I)

Ila reported a novel synthesis of bis-oxazole **358** through the Cu(I)-catalysed reaction of oxazolone **356** and isocyanides **357** (Scheme 96).[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.[89,95]



R^1 = thiophen-2-yl, Ph
R^2 = CO_2Et, pyridin-4-yl, 4-ClC_6H_4, 1-morpholinoformyl, Ts;
R^3 = 4-$MeOC_6H_4$, 3,4-$MeO_2C_6H_3$, thiophen-2-yl, 1-methyl-1*H*-pyrrol-2-yl, 1-methyl-1*H*-indol-3-yl, pyridin-3-yl, benzo[*d*][1,3]dioxol-5-yl

Proposed reaction mechanism



i) CuI (10 mol%), Cs_2CO_3 (1.0 eq), DMF, 90 °C, 4-6 h.

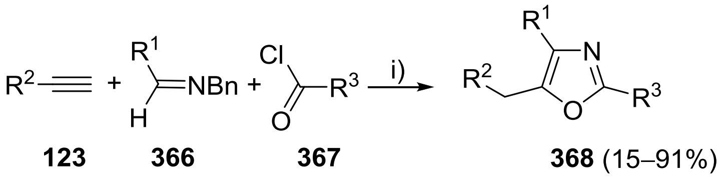
Scheme 96. Cu(I)-catalysed synthesis of oxazoles **358**

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

GOLD(III)

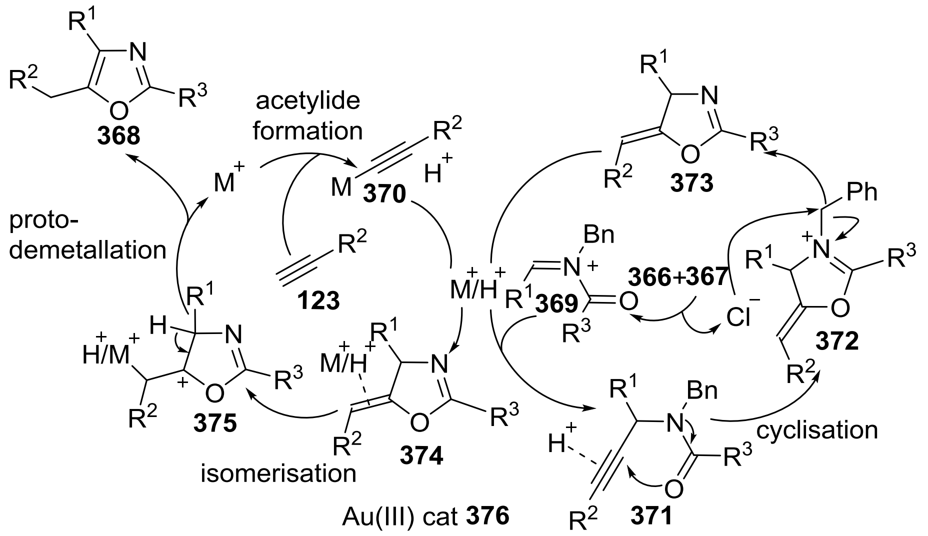
A one-pot three-component Au(III)-catalysed synthesis of trisubstituted oxazoles **368** from *N*-benzylimines **366**, acid chlorides **367** and alkynes **123** was recently described by Strand (Scheme 97).[122] The reaction proceeds *via* coupling of a copper acetylide **370** with an iminium species **369** to give a propargylamide **371**.

Cyclisation of **371** by acid catalysis followed by debenzylation generates **373**. Isomerisation of **373** forms **375**, which upon proto-demetallation furnishes oxazole **368**. 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.[122]



R^1 = adamantan-1-yl, *t*-Bu, $MeO_2CC(Me)_2$, H, Ph, $BnOCH_2C(Me)_2$, $CH_2{=}CHCH_2C(Me)_2$;
R^2 = $4\text{-}FC_6H_4$, *t*-$BuSiMe_2$, $ClCH_2CH_2CH_2$;
R^3 = $4\text{-}FC_6H_4$, thiophen-2-yl, *i*-Bu, $4\text{-}MeOC_6H_4$, *t*-Bu, Ph

Proposed reaction mechanism



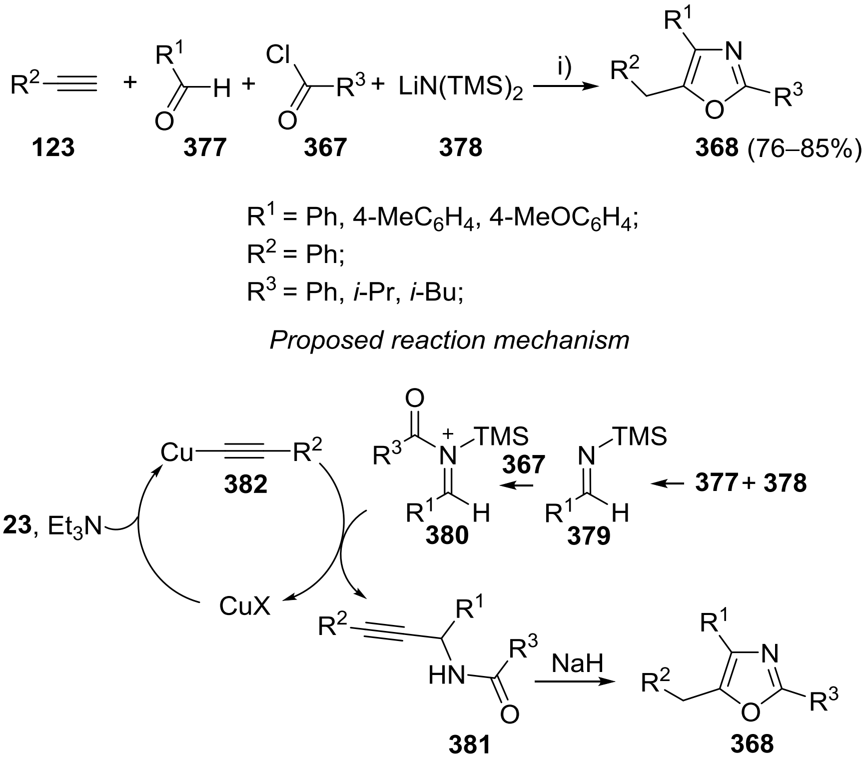
i) **123** (2.0 eq), **366** (1.0 eq), **367** (1.0 eq), Au-(salen) PF_6 **376** (1 or 5 mol%), MW irrad, MeCN, 170 ºC, 15 min.

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

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

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).[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.[123] The protocol allows for the rapid assembly of trisubstituted oxazoles from simple building blocks.



R^1 = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$;
R^2 = Ph;
R^3 = Ph, *i*-Pr, *i*-Bu;

Proposed reaction mechanism

i) $HN(TMS)_2$ (1.1 eq), BuLi (1.1 eq), hexanes, 0 °C, 10 min then **377** (1.0 eq), 1 h, 0 °C then **367** (1.3 eq), rt, 30 min then **123** (1.0 eq), MeCN, CuI (10 mol%), $BF_3{\cdot}Et_2O$ (20 mol%), (i-$Pr)_2NH$ (1.0 eq), 65 °C, 14 h then NaH (0.5 eq), MeCN, rt, 30 min.

Scheme 98. Stepwise one-pot four-component Cu(I)-catalysed synthesis of oxazole **368**

This ambitious process proceeds in remarkably high yields and provides an exceptionally effective way of preparing densely functionalised tri-substituted oxazole products **368**. 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.

ACKNOWLEDGEMENTS

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