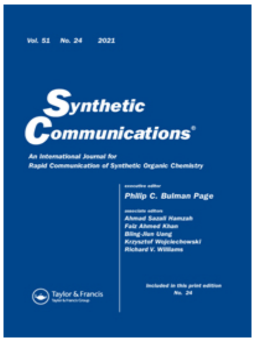


Taylor & Francis
Taylor & Francis Group

Synthetic Communications
An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/lsyc20

A systematic appraisal on catalytic synthesis of 1,3-oxazole derivatives: A mechanistic review on metal dependent synthesis

Suraj R. Shinde, Pankaj Girase, Sanjeev Dhawan, Shaukatali N. Inamdar, Vishal Kumar, Chandrakant Pawar, Mahesh B. Palkar, Mahadev Shinde & Rajshekhar Karpoormath

To cite this article: Suraj R. Shinde, Pankaj Girase, Sanjeev Dhawan, Shaukatali N. Inamdar, Vishal Kumar, Chandrakant Pawar, Mahesh B. Palkar, Mahadev Shinde & Rajshekhar Karpoormath (2022): A systematic appraisal on catalytic synthesis of 1,3-oxazole derivatives: A mechanistic review on metal dependent synthesis, Synthetic Communications, DOI: 10.1080/00397911.2021.1989596

To link to this article: https://doi.org/10.1080/00397911.2021.1989596

SYNTHETIC COMMUNICATIONS®
https://doi.org/10.1080/00397911.2021.1989596

SYNTHETIC COMMUNICATIONS REVIEWS

A systematic appraisal on catalytic synthesis of 1,3-oxazole derivatives: A mechanistic review on metal dependent synthesis

Suraj R. Shinde[a], Pankaj Girase[a], Sanjeev Dhawan[a], Shaukatali N. Inamdar[a], Vishal Kumar[a], Chandrakant Pawar[a], Mahesh B. Palkar[a,b], Mahadev Shinde[a], and Rajshekhar Karpoormath[a]

[a]Department of Pharmaceutical Chemistry, Discipline of Pharmaceutical Sciences, College of Health Sciences, University of KwaZulu-Natal (Westville), Durban, South Africa; [b]K. L. E. Society's College of Pharmacy, J. T. College Campus, Gadag, India

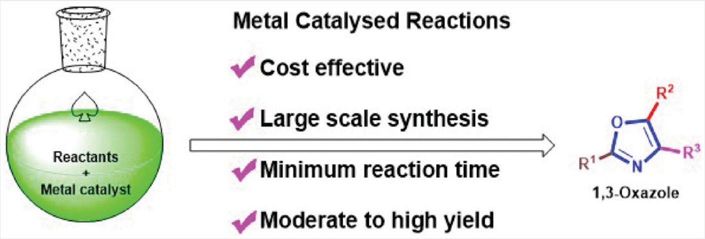
ABSTRACT

1,3-Oxazole, is a distinctive five-membered nitrogen and oxygen containing heterocyclic compound. The versatility of this heterocyclic ring system makes it as an important class of heterocyclic compounds. Consequently, the compounds or derivatives containing 1,3-oxazole scaffold are reported to possess wide variety of applications in medicinal, pharmaceutical, agrochemical, and material sciences. In recent years several potent molecules containing1,3-oxazole as a core sub-unit of the structural frame, have been reported, leading to the significant increase in number of research articles published to explore its broad utility and versatility. Further, it has caught the attention of chemists globally to develop new methodologies for the synthesis of novel promising substituted 1,3-oxazole derivatives as building blocks. However, to date, there is no specific review on 1,3-oxazole and it's derivatives with special emphasis on it's synthetic methodology strategies and applications. We have collected total of 30 research articles published in peer-reviewed international journals in last 4 years with special emphasis on metal dependent synthetic methodology of 1,3-oxazole derivatives. Hence, this review is our sincere effort to comprehensively represent the systematic interpretation of literature describing the metal based catalytic strategies for 1,3-oxazole derivatives. We expect that our review will certainly benefit organic chemists to recognize the challenges in the methods, assist them in the selection of reactants and developing new 1,3-oxazole analogues using various metal catalyst.

ARTICLE HISTORY
Received 13 March 2021

KEYWORDS
Catalysts; derivatives; metal dependent synthesis; 1,3-oxazole

GRAPHICAL ABSTRACT



CONTACT Rajshekhar Karpoormath karpoormath@ukzn.ac.za Department of Pharmaceutical Chemistry, Discipline of Pharmaceutical Sciences, College of Health Sciences, University of KwaZulu-Natal (Westville), Durban, South Africa.

Introduction

A heterocyclic compound or ring structure is a cyclic compound that has atoms of at least two different elements as members of its ring(s). Heterocyclic compounds are pervasive in many areas of life sciences and drug discovery. The history of heterocyclic chemistry became very well-known in the early 1800s followed by the sudden outburst in the invention of heterocyclic compounds rose due to the necessity by the end of World War II.[1] The heterocyclic compounds, in general, exist as a five or six member ring containing hetero atoms such as nitrogen(N), oxygen (O) or sulfur (S). They play a vital role in the biochemical processes in all living cells and occur naturally as well as synthesized by the pharmaceutical companies.[2] Heterocyclic compounds contributes as one of the leading researches in the field of organic chemistry. Majority of the medicinal drugs in the current market contains heterocyclic compounds due to their broad applications.[3] 1,3-Oxazole belongs to one of the simple five member heterocyclic system containing N and O separated by single C (see Fig. 1). The Oxazole derived molecule was first reported by Ladenburg in 1876[4] through the synthesis of 2-methylbenzoxazole which later was classified under the name “Oxazole” by Hantzsch in 1887.[5] Nonetheless, Cornforth and Cornforth in 1947 were the first to synthesize the oxazole molecule.[6] In fact, the oxazole research was progressive only after the Kondrateva’s discovery of oxazole to function as dienes in Diels-Alder reactions.[7] The 1,3-oxazole derivatives acquires a special interest in the oxazole chemistry not until the late 1980s when they were primarily being isolated from naturally occurring marine organisms.[8] They were subjected to extensive biological and synthetic studies due to their wide range of potent biological activities.[8c] Some of the examples of naturally occurring 1,3-oxazole derivatives include Halfordinol, Annuloline, Balsoxin, Texaline, Texamine, Pimprinine, and so on.[9] Both the natural and synthetic 1,3-oxazole derivatives were found to possess a wide range of biological activities such as antipathogenic,[10] anti-inflammatory,[11] anti-microbial,[12] anti-bacterial and anti-tuberculosis properties,[13] anti-mitotic agents with pro-apoptotic activity,[14] anti-depressant,[15]anti-analgestic/anti-thrombotic/anti-cholesteremic activities,[8d] picomolar inhibitory activity against several cell lines,[16] and anti-tumour activities.[8a,17] (refer Fig. 2). Some examples of currently available 1,3-oxazole moiety containing drugs like Aleglitazar,[18] Oxaprozin,[18b,19] Sulfamoxole,[20] Ditazole[18b] are enlisted in Table 1.

The 1,3-oxazole also possesses a wide range of unique applications through its occurrence in naturally available peptides and polymers. The naturally occurring 1,3-oxazole containing peptides are mostly derived from marine source through ribosomal and non-ribosomal pathways.[8] They play a vital role in peptide chain stability thereby

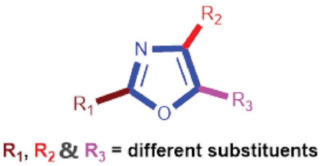


Figure 1. Core structure of 1,3-oxazolescaffold.

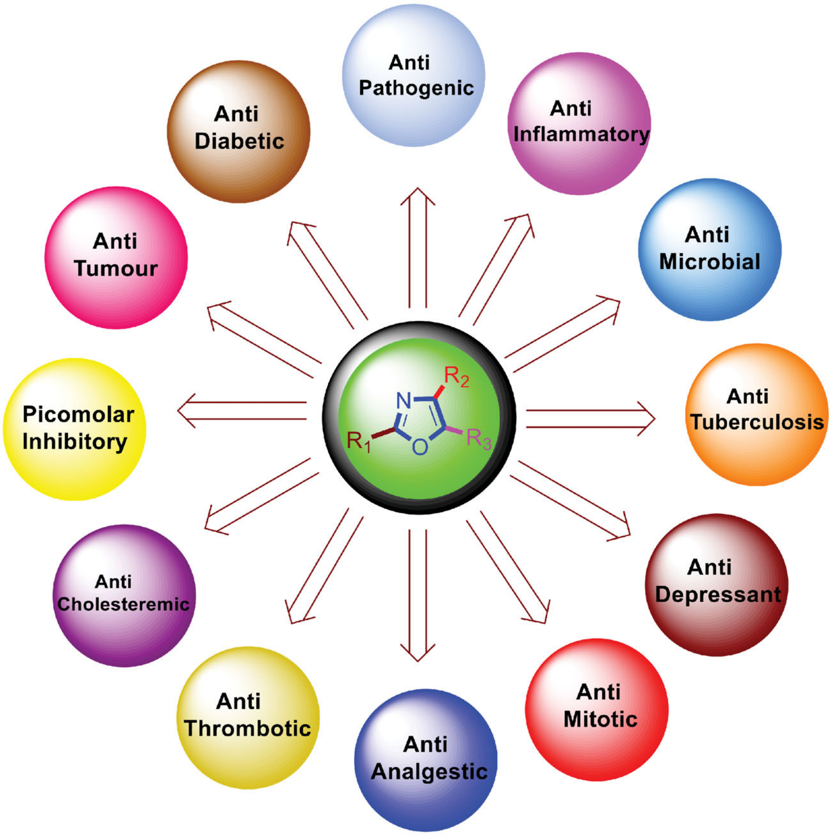


Figure 2. Array of medicinally important biological activities of 1,3-oxazole derivatives.

enabling protein-peptide recognition and DNA/RNA-peptide interactions.[8b] Some examples of naturally occurring oxazole containing cyclic peptides include telomestatin,[21] phorboxazoles,[22] diazonamide,[23] etc. (refer Table 1).

Aromatic and heterocyclic rings in the polymers were initially introduced in 1960s to satisfy the requirements of aerospace industries.[24] It offers a conjugated rigid structure which in turn enhances the thermal stability of the polymers to provide good resistance in harsh environments. The –CF_3 substituted oxazole containing polymers viz. poly(aryl ether oxazole)[25] were also explored to enhance the overall properties of the polymer viz. low dielectric constant, high optical clarity, and low water absorption thereby providing unique applicability to electronic and membrane (gas separation membrane) technologies[26] (refer Table 1).

The significance of oxazole derivatives as a lead structure in various agrochemicals exhibiting herbicidal, fungicidal and insecticidal activities were also reported in crop production chemistry.[27]

This review provides the synthetic overview for the successful metal catalytic synthesis of 1,3-oxazole derivatives. We have also tried to address the reaction pathways for each synthetic strategy and also discussed the synthesis based on the different starting materials to get the desired 1,3-oxazole derivatives in high yield.

Table 1. Important and promising applications of 1,3-oxazole derivatives in peptide, polymer, agrochemical and pharmaceutical industries.

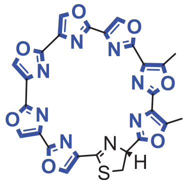
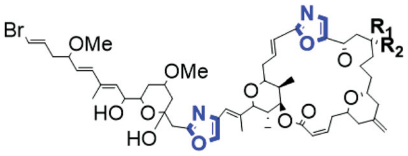
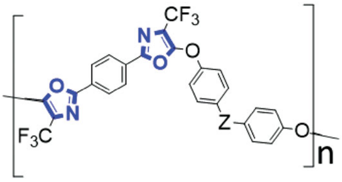
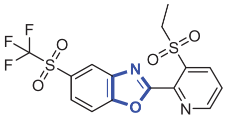
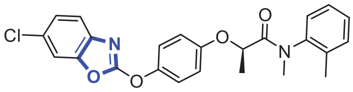
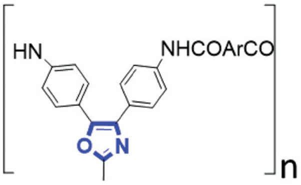
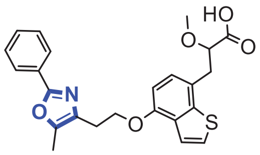
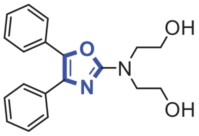
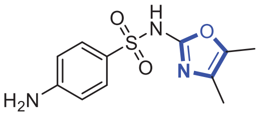
1,3-Oxazole containing molecules	Structure	Uses	Ref.
Telomestatin		Peptides	[21]
Phorboxazoles Phorboxazoles A: R_1-OH, R_2-H Phorboxazoles B: R_1-H, R_2-OH		Peptides	[22]
Poly(ether oxazole)		polymers	[25,26b]
Oxazosulfyl		Insecticides	[27]
Metamifop		Herbicides	[27]
Polyamide		Polymers	[28]
Aleglitazar		Antidiabetic	[18]
Ditazole		Anti-inflammatory	[18b]
Sulfamoxole		Antibacterial	[20]

Table 2. Catalytic (metal dependent) reactions (reported during 2017–2020) with the overall yeilds of 1,3-oxazole.

Sr. no.	Metalbased catalyst used	Reaction pathways	Overall yield	Ref.
1	Copper (II)	• Domino cyclization • Radical coupling • Oxidative cyclization • Intra – molecular cyclization • Inter – molecular cyclization • Oxidative dehydrogenative annulation • Oxidative coupling	9–100%	[29]
2	Palladium	• Oxidative cyclization • Coupling reaction	10–88%	[28,30]
3	Gold	• Oxidative cyclization	2–92%	[31]
4	Ruthenium	• Oxidative cyclization • Coupling cyclization	13–96%	[32]
5	Silver	• Cycloaddition • Oxidative cyclization	33–91%	[20,33]
6	Manganese	• Reductive annulation	42–93%	[34]
7	Zinc	• Oxidative addition cyclization	26–98%	[35]
8	Aluminum	• Oxidative cyclization	41–83%	[36]
9	Iridium	• Oxidative cyclization	50–99%	[37]
10	Scandium	• Oxidative cyclization	17–88%	[38]

Synthesis of 1,3-oxazole derivatives

This portion mainly focuses on the synthesis of 1,3-oxazole derivatives under approaches based on the use of catalyst in the synthetic reactions.

Metal-dependent synthesis of 1,3-oxazole derivatives

This section involves the metal catalyzed synthesis of 1,3-oxazoles molecule which are further sub-categorized by different starting materials that are used. We have also represented the overall yield based on the different reaction conditions performed (Table 2) as well as the details of all the reviewed schemes given preceding to conclusion section (see Table 3).

Acetophenone

Deng et al. in 2019 have reported the synthetic method utilizing copper-mediated coupling cyclization of oxime **1**, aryl-thiol **2**, and trifluoroacetic anhydride **3** into 1,3-oxazole via oxidative annulation reaction.[29c] Here single electron transfer (SET) from Cu(I) to **4a** gave oxime **4b** which on sequential acylation and isomerization led to **4c** which transform into alkyl Cu(III) intermediate **4d** on coordination with Cu(I) and **3b**. The reductive elimination of Cu(I) followed by isomerization produced **4f**. Intermediate **4i** was obtained by Oxidation-radiacal isomerization-cyclization reaction sequence, which on further oxidation delivers final product **4**. The authors enhanced catalyst $Cu(OTf)_2$ that could be able to transform a variety of oximes into structurally varied 1,3-oxazole in good to excellent yield. Thus, developed method was found to be harmonious with substituted thiophenols having a range of electron-donating and withdrawing groups. There action pathway study indicates radical formation involved in the N–O bond breaking and C–N bond forming via one electron transfer (SET) by Cu(I). Further, the intermediate enamine **4f** was produced by exclusion and isomerization of

Table 3. Review of the metal dependent reactions detailing scheme number, catalyst used, yield and year of publication for the synthesis of 1,3-oxazole derivatives.

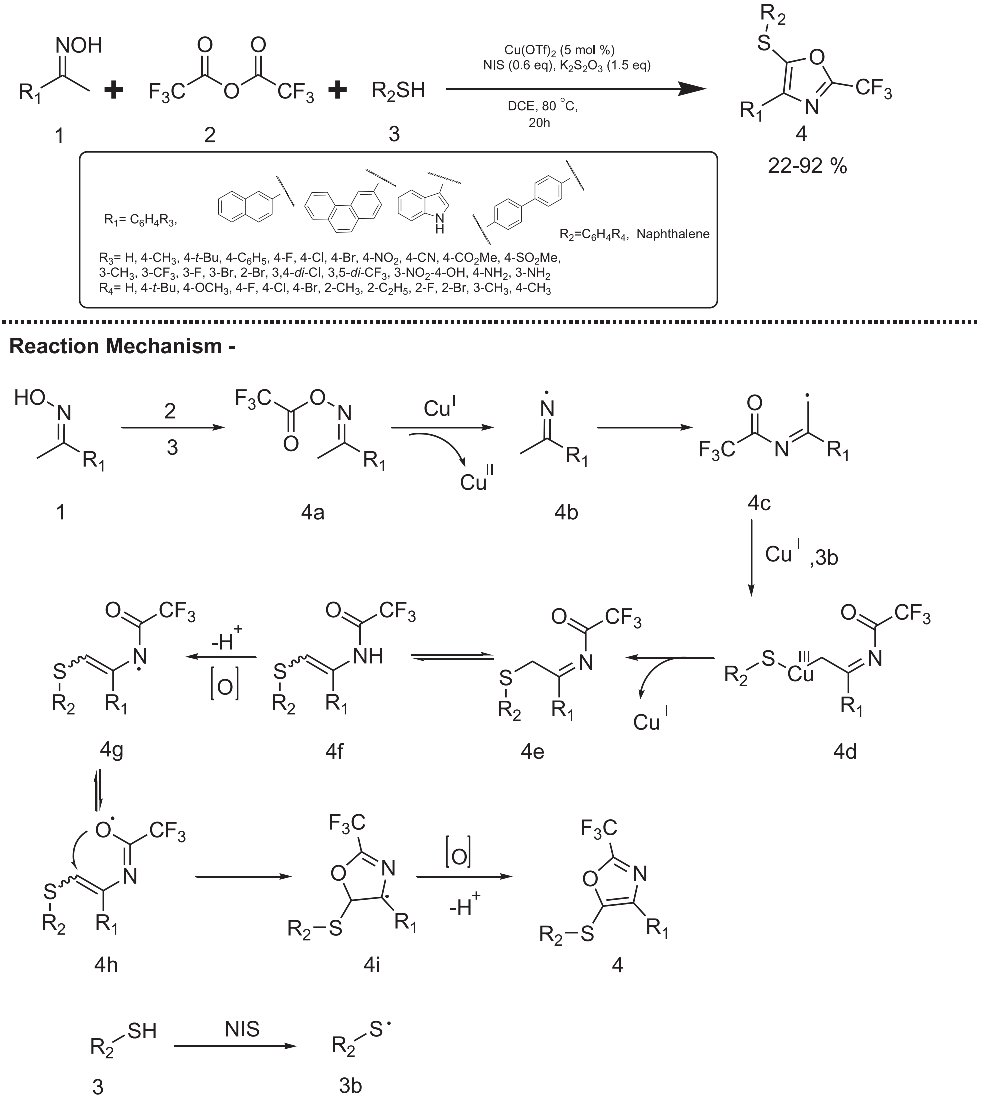
Scheme no.	Catalyst	Yield	Publication year	Ref.
1	$Cu(OTf)_2$	22–92%	2019	Deng et al.[29c]
2	$CuBr_2$	26–75%	2017	Xu et al.[29d]
3	$Mn(OAc)_3.2H_2O$	42–93%	2017	Li et al.[34]
4	$[RuCl_2(p\text{-cymene})]_2$	13–96%	2019	Liu et al.[32]
5	Pd	10–78%	2017	Zhang et al.[28]
6	$(phen)Cu(III)(CF_3)_3$	36–78%	2020	Dong et al.[39]
7	$InCl_3$	15–94%	2020	Nan et al.[40]
8	IPrAuCl	21–76%	2020	Wang et al.[41]
9	Cp_2ZrHCl	26–98%	2017	Zheng et al.[35]
10	$Al(OTf)_3$	41–83%	2018	Hsieh et al.[36]
11	AgOTf	37–91%	2019	Kukushkin et al.[31a]
12	Pd (II)	55–82%	2019	Zhang et al.[30c]
13	$IrCl(CO)(PPh_3)_2$	50–99%	2018	Hu et al.[37]
14	AgMOF	33–83%	2019	Liu et al.[33]
15	CuI	55–95%	2018	Qi et al.[29a]
16	$L10\text{-}Ni(II)\text{-}(OAc)_2.H_2O$	58–96%	2017	Wang et al.[42]
17	$MCM\text{-}41\text{-}PPh_3\text{-}AuNTf_2$	52–92%	2017	Yang et al.[31d]
18	Pd	25–81%	2020	Dai et al.[43]
19	$Pd(OAc)_2$	25–88%	2017	Mali et al.[30a]
20	$Yb(OTf)_3$	38–69%	2017	Sahoo et al.[44]
21	$[Cp^*Co(MeCN)_3(SbF_6)_2]$	29–77%	2018	Yu et al.[45]
22	$Sc(OTf)_3$	17–80%	2018	Niuet al.[38]
23	CuCN	32–75%	2018	Fan et al.[46]
24	Ph_3PAuCl	22–85%	2019	An et al.[31c]
25	$Pd(PPh_3)_2Cl_2$	35–92%	2019	Keivanloo et al.[30b]
26	TMSN3	24–97%	2020	Yoneyama et al.[47]
27	Cu^{2+}	43–100%	2017	Dutta et al.[48]
28	$Cu(OAc)_2$	10–82%	2019	Cai et al.[29g]
29	CuBr	9–80%	2018	Pan et al.[29b]
30	$Cu(OAc)_2$	55–87%	2018	Nagaraju et al.[29e]

intermediate **4d** which gets deprotonate after intra-molecular cyclization to produce the desired1,3-oxazole **4**. The main drawback of this synthetic strategy is that the ortho substituted oximes were relatively not underwent cyclization reaction due to steric hindrance (Scheme 1).[29c]

Xu et al. in 2017 have reported the synthesis of substituted 1,3-oxzoles by reacting acetophenones and coordinated cyanide anions in a copper (II) catalyzed radical coupling reaction.[29d] The authors report that the best results were obtained when the reaction conditions involve copper bromide ($CuBr_2$) as oxidant and $K_3[Fe(III)(CN)_6]$ as a reagent after meticulously analyzing the reaction conditions. The authors also noticed that the substituents on acetophenone were the important factor owing to their electronic properties as different of reactants capably produced the desired final products. The complete mechanistic observations revealed the radical formation involved in the formation of C–O bond via 3-oxo-3-phenylpropanenitrile **7b** intermediate by corresponding acetophenone **5**, which on elimination reaction yields the desired1,3-oxazole (**7**). Nevertheless, this pathway may not work efficiently and the product did not formed in the presence of radical scavengers (Scheme 2).[29d]

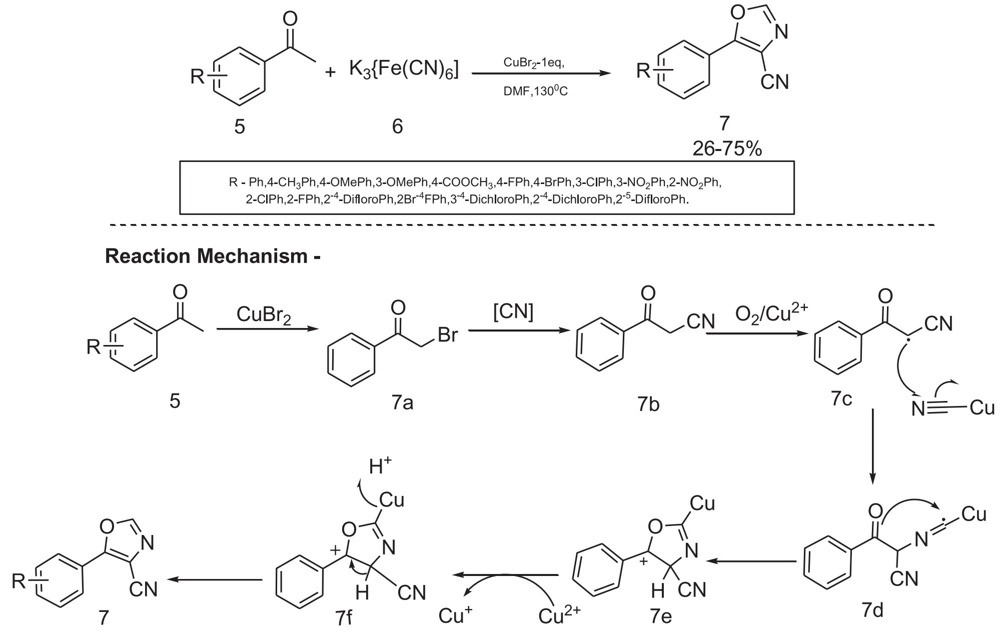
Amide

Li and his coworkers in 2017 reported inexpensive and user-friendly Mn-catalyzed method for the synthesis of 1,3-oxazole using 2-amidodihydrofurans as starting



Scheme 1. copper-mediated coupling synthesis of varied 1,3-oxazole derivatives by acetophenone oxime.[29c]

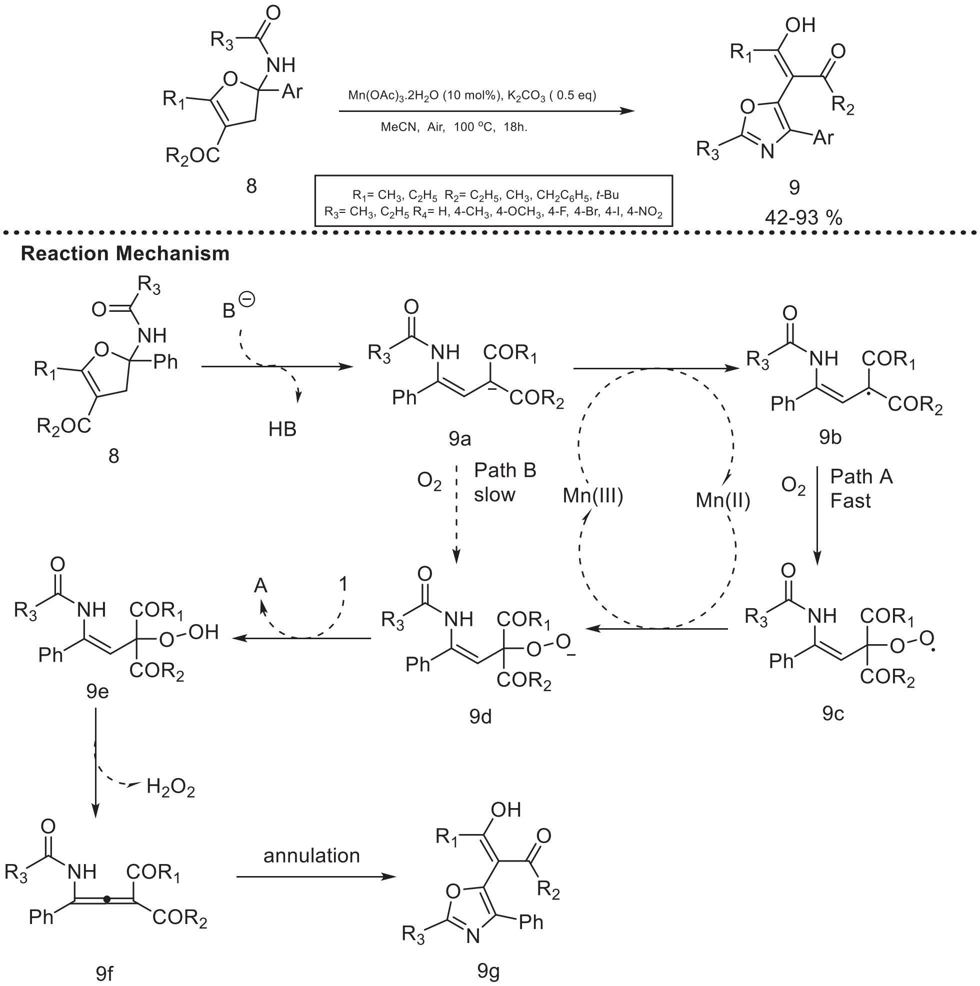
materials.[34] Interestingly it was observed that the reaction of 2-amidodihydrofurans resulted in highest quantity of respective 1,3-oxazoles. The method seems extended to better-yielding aromatic and hetero-aromatic inamides. Suggested pathway involved a γ-dicarbonyl enamide **9a** formed through C–O bond breaking of furan **8** in basic condition, followed by Mn-catalyzed reduction of enamine **9a** converted to peroxy radical **9c** by Mn^{+2} acetate. Single electron transfer from Mn(II) to peroxy radical **9c** gave peroxy anion **9d** followed by protonation deliver intermediate **9e** which was transformed into allene **9f** by elimination of peroxide. Lastly, on the reaction of allene **9f** with peroxide anion **9d** intermediate gave oxazole ring **9g** as final product. However, the synthesis of substituted 1,3-oxazoles without catalyst resulted in 24% yield of the product (Scheme 3).[34]



Scheme 2. copper-mediated synthesis of substituted 1,3-oxazole by acetophenone.[29dx]

The metal-catalyzed intra-molecular C–O cyclization of enamides is an established method for the synthesis of substituted 1,3-oxazole derivatives. It has been demonstrated that through this methodology 2,5-disubstituted and 2,4,5-trisubstituted oxazoles can be synthesized in moderate to excellent yield (Scheme 4). In this work, Liu et al. in 2019 determined that treatment catalytic amount of $[RuCl_2(p\text{-cymene})]_2$ and oxidant $Cu(OAc)_2$. H_2O formed an activated complex with $AgSbF_6$ to mediate this transformation.[32] The researchers performed several reactions for synthesizing various 2,5-disubstituted 1,3-oxazoles and revealed that the substrate with electron donating substituents at *ortho* and *para* position of **11a** furnished higher yields than those electron withdrawing substituents. On the contrary the substrate with electron withdrawing substituents at *meta* position of **11a** furnished better yields than those electron donating substituents. Moreover, researches obtained good to excellent yield of 2,4,5-trisubstituted-1,3-oxazoles from different ester-substituted substrates. In the proposed pathway silver salt activates and generated a cationic ruthenium complex **11c**. The metalation of amide afforded six membered metallacycle **11d** and **11e** and transformed to oxazole **11f** by copper acetate. It has reported that the addition KPF_6, as an additive decreased the catalytic efficacy.[32]

Zhang and his colleagues in 2017developed a novel and convenient method for construction of fully substituted oxazoles *via* Pd-catalyzed oxidative cyclization of *N*-acyl enamides and aryl iodides.[28] It was reported that $Pd(OAc)_2$ and Ag_2CO_3 in TFE (CF_3CH_2OH) furnished the highest yield of the oxazole. The author proposed pathway that involved the initial alkenyl C–H activation by palladium acetate to give intermediate **14a**, that reacted with aryl iodide and give intermediate **14b** *via* oxidative addition reaction. The catalytic pathway is completed by the generation of intermediate **14c** through reductive elimination and oxidized to give corresponding oxazole by silver

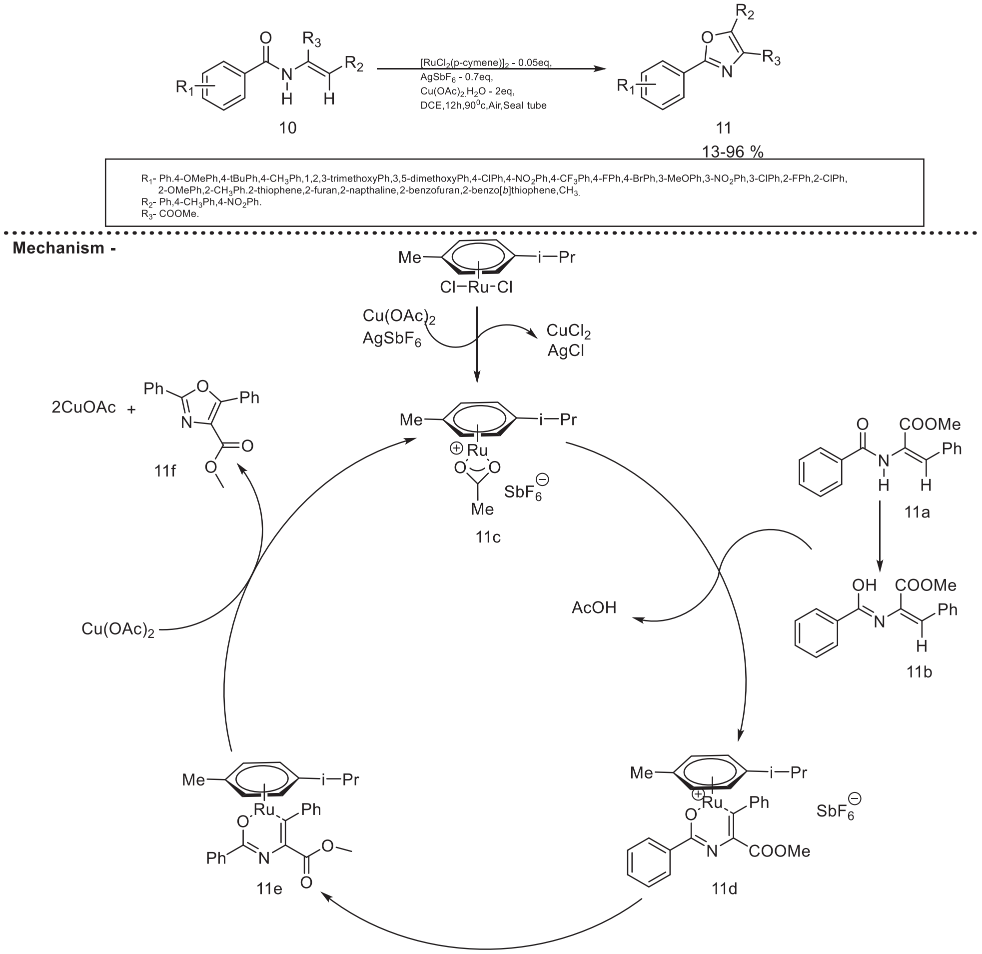


Scheme 3. Manganese catalyzed Synthesis of substituted 1,3-oxazole using amide.[34]

catalyst. The electron donating and electron withdrawing substituents on the aryl iodides were transformed to the corresponding products with good yields. They also observed that this transformation is also sensitive to the steric bulk around the aryl-iodide ring. The enamide derivatives have not showed much effect on reaction and smoothly afforded desired oxazole (Scheme 5).[28]

Dong et al. in 2020 reported copper catalyzed synthesis of 2,2,2-Trifluoroethyl Oxazoles with wide substrate scope, high efficiency and with broad functional group tolerance. A probable mechanism involves the initial radical trifluoromethylation of propargyl amide **16a** to generate vinyl radical intermediate **16b** (Scheme 6). The subsequent cyclization of **16b** produces an iminium type radical intermediate **17a**. The presence of TEMPO promotes the hydrogen atom abstraction from **17a**togive oxazoline **17c**which can isomerize to more stable oxazole **17d** provided that a hydrogen atom exists at the propargyl position.[39]

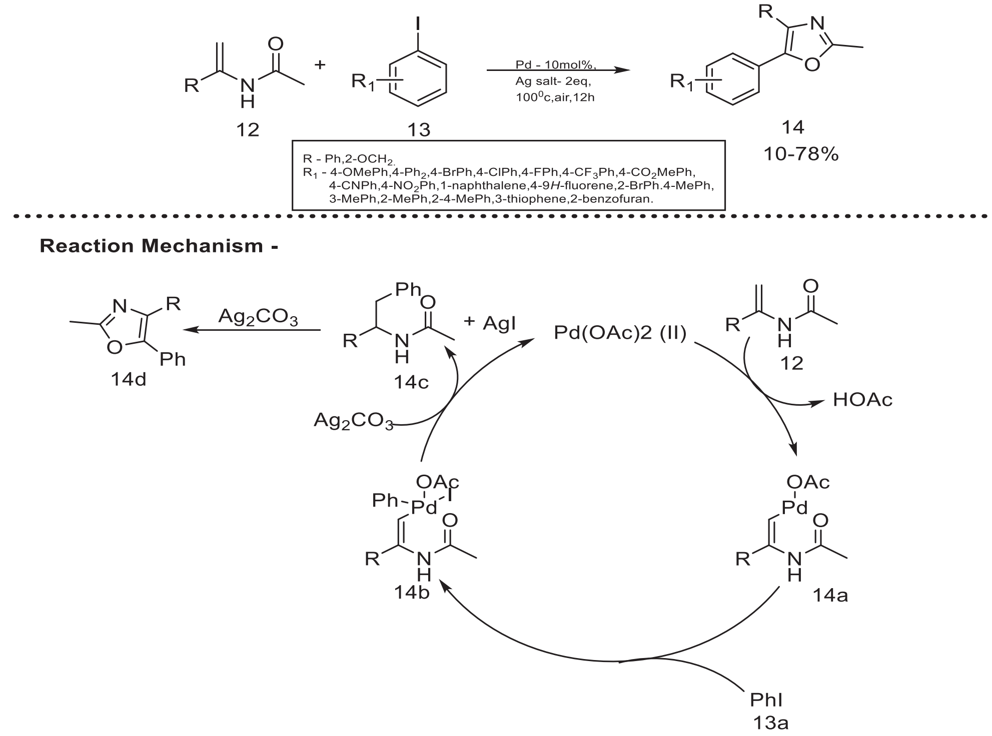
Nan et al. in 2020 reported Indium catalyzed one pot method to construct oxazole derivatives. Firstly, Indium chloride catalyst activated the triple bond of **19a** by forming**19c** via **19b** by the loss of HCl, followed by region specific ring fusion within the



Scheme 4. Ruthenium catalyzed Synthesis of substituted 1,3-oxazole using amide.[32]

molecule **19c** to give the precursor **20a**. In situ, HCl hydrolysis of **20a**, gives oxazoline as an intermediate **M1**. Meanwhile, Indium chloride coordinates with the carbonyl group of p-quinonemethides by forming an electron deficient precursor **20b**, later 1,6-addition of **20b** and **M1** through **20c** produced **20d** by the loss of H^+. In situ produced HCl, hydrolyzes **20d** producing end product **20e** after regenerating the catalyst Indium chloride (Scheme 7).[40]

Wang et al. in 2020 reported the synthesis of poly-substituted oxazole derivative via regio-specific Au-based catalyst to react α-alkynyl amides and alkynoates with nitriles. The protonation of **21** results in the formation of the precursor **21a**. Later, α-oxo Au–carbene intermediate **21b** was formed by the reaction of gold and N–oxide. Then the precursor **21b** is reacting with nitrile to give compound **21c**. The nucleophilicity of amide decreases in the presence of acid in which ketone was reacting with the nitrile results in derivative **22a**. Henceforth, the final compound **22** is formed by losing H^+ (Scheme 8).[41]



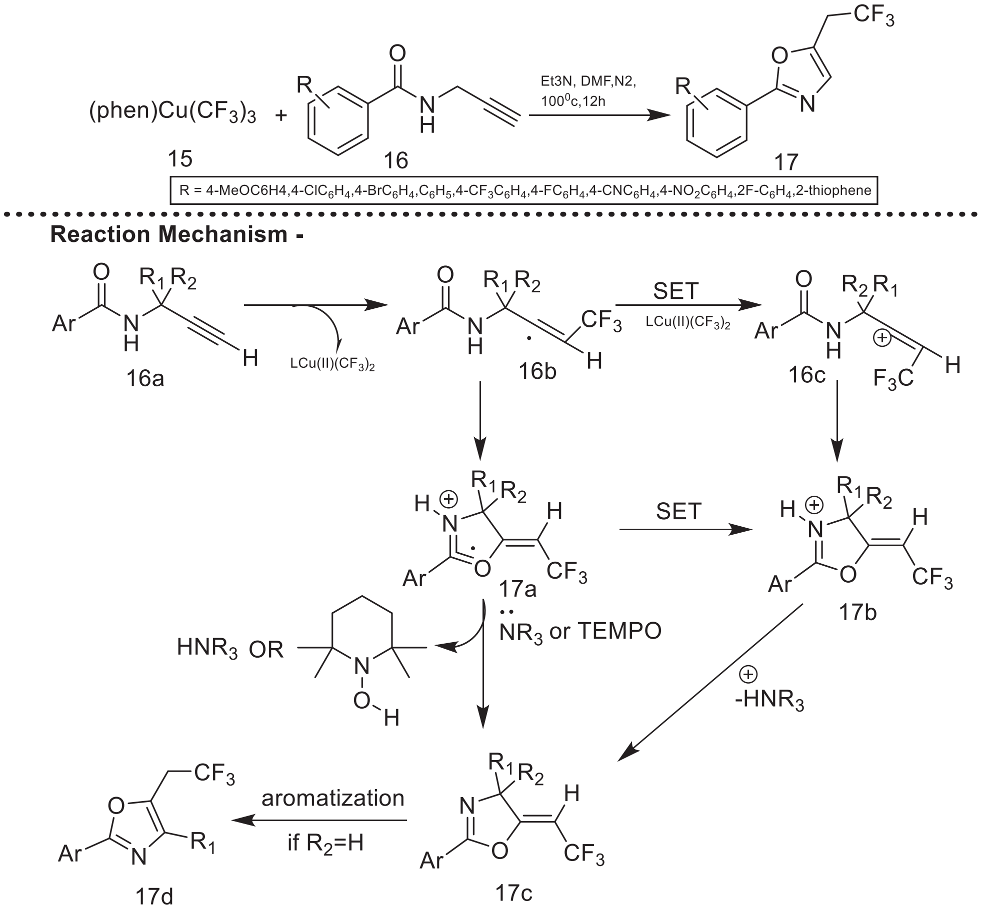
Scheme 5. Palladium catalyzed Synthesis of 1,3-oxazole derivatives using amide.[28]

Isonitrile

Zheng and colleagues in 2017 developed the synthesis of oxazole derivatives by particular reaction of isocyanoacetate and *sec*/*tert*-amides by Schwartz reagent (Cp_2ZrHCl).[35] Zinc chloride and Schwartz reagent with triethylamine (TEA) at RT were necessary for the optimized conditions. High yield with the exception of tert-butyl substituted products, were obtained from tert-amides bearing alkyl groups where lower yields were found due to steric hindrance. While significant yields of benzyl/phenyl-substituted oxazoles were obtained. The proposed pathway suggested the base optimized formation of iminium ion **23b/23z** using Cp_2ZrHCl reduced *tert*/*sec*-amide **23/23x**, converted to oxazole **25a** by reaction of carbanion/enolate **23**. Interestingly, no Lewis acid was required, while triethylamine was crucial for cleaving the amide–Cp_2ZrHCl **23a** (Scheme 9).[35]

Nitrile

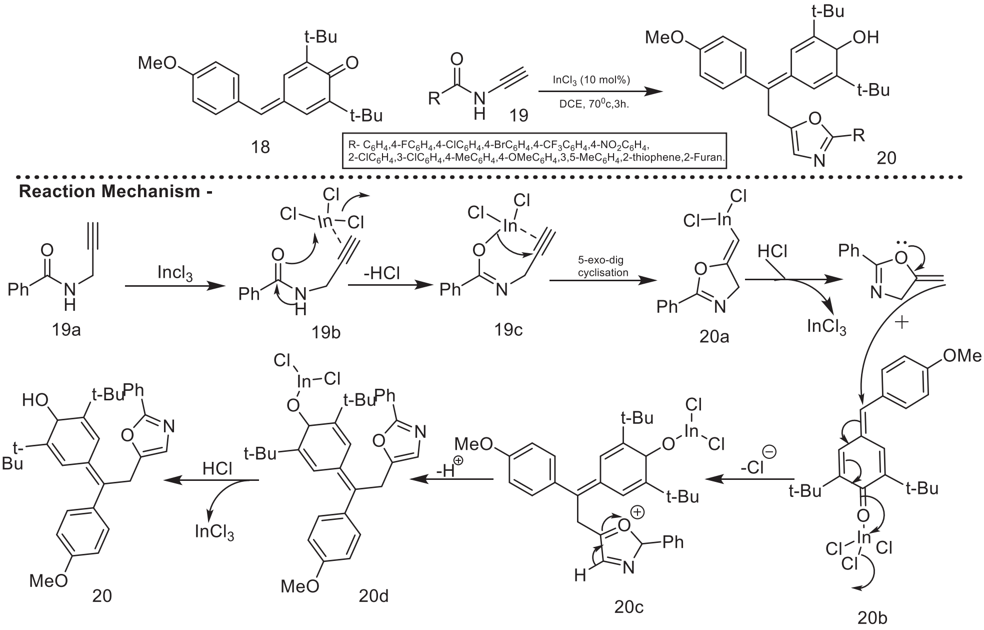
Hsieh *et al*. in 2018 developed a novel single-step tandem [3 + 2] type annulation of 2,2-difluoroethanol with nitriles to optimized 2,4,5-trisubstituted oxazoles using aluminum based reagent under acidic conditions.[36] Oxazole formed when the primary starting material **26** created complex **26a** with Lewis acid that became BF_3–epoxide **26b** and then stable state **26c**. Nucleophilic attack of nitrile **27a** on **26c** subsequently formed **26d**, leading to 1,3-oxazole **28** via the formation of oxazoline **28a** during intramolecular cyclization, followed by optimization by losing HF. Additionally, the formation of carbonyl–BF_3 complex **26y** by 1,2-fluoride shift of **26a**, which reacts with nitrile to allow



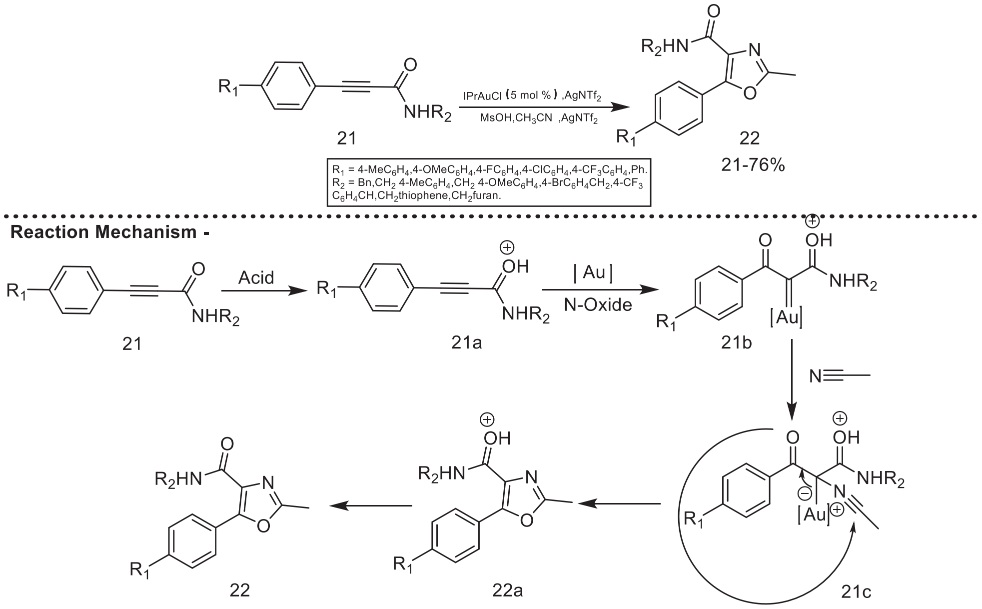
Scheme 6. Copper catalyzed synthesis of 2,2,2-trifluoroethyl oxazoles via alkyne oxytrifluoromethylation.[39]

tandem cyclization reaction leads to oxazole. Many of the types of 2,2-difluoroethanol substitutes, like, CH_3, *n*-Bu, phenyl-ethynyl, 2-furyl and sterically hindered 1-naphthyl at R_1 with phenyl R_2 were tested, and the results indicated that they all produced moderate to good oxazoles. If R_2 is hydrogen, the corresponding oxazoles have formed with various substitution. The researcher further revealed a methodology drawback that nitrogen-based heteroaromatic group at R_1 and saturated alkyl chain was not consistent with acidic conditions (Scheme 10).[36]

Alkynes, esters (or ketones), cyano and pyridine N–oxide as substrates achieved alternative access to 1,3-Oxazoles derivative via gold(I)-catalyzed [2 + 2 + 1] cycloaddition. Kukushkin et al. in 2019 reported that the reaction is progressed by the use of IprAuCl/AgOTf catalyst in acetonitrile at 80 °C produced the desired 1,3-oxazole.[31a] Various nitriles reacted with alkynes produced oxazole to very high yield. The mechanism is based on control experiments indicated the formation of gold carbene intermediate **29c** from nucleophilic oxygenation of intermediate **29a** which reacted with nitrile **29d** converts to cyclised 1,3-oxazole **31** and catalyst was regenerated. The push-pull nitriles gave cyclic product with highest 37% yield (Scheme 11).[31a]

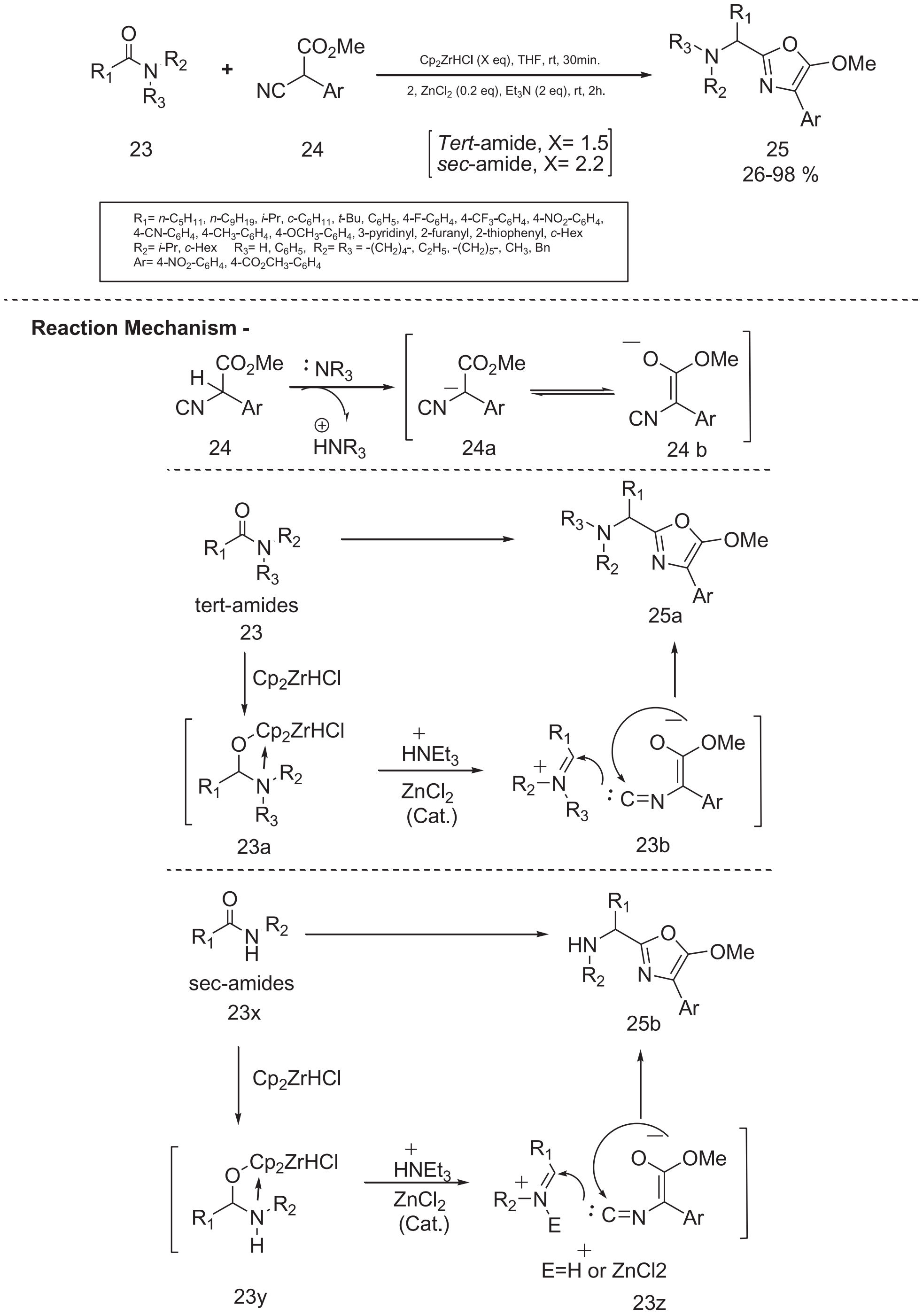


Scheme 7. InCl$_3$-catalyzed 5-exo-dig cyclization of N-propargyl amide construct oxazole derivatives.[40]



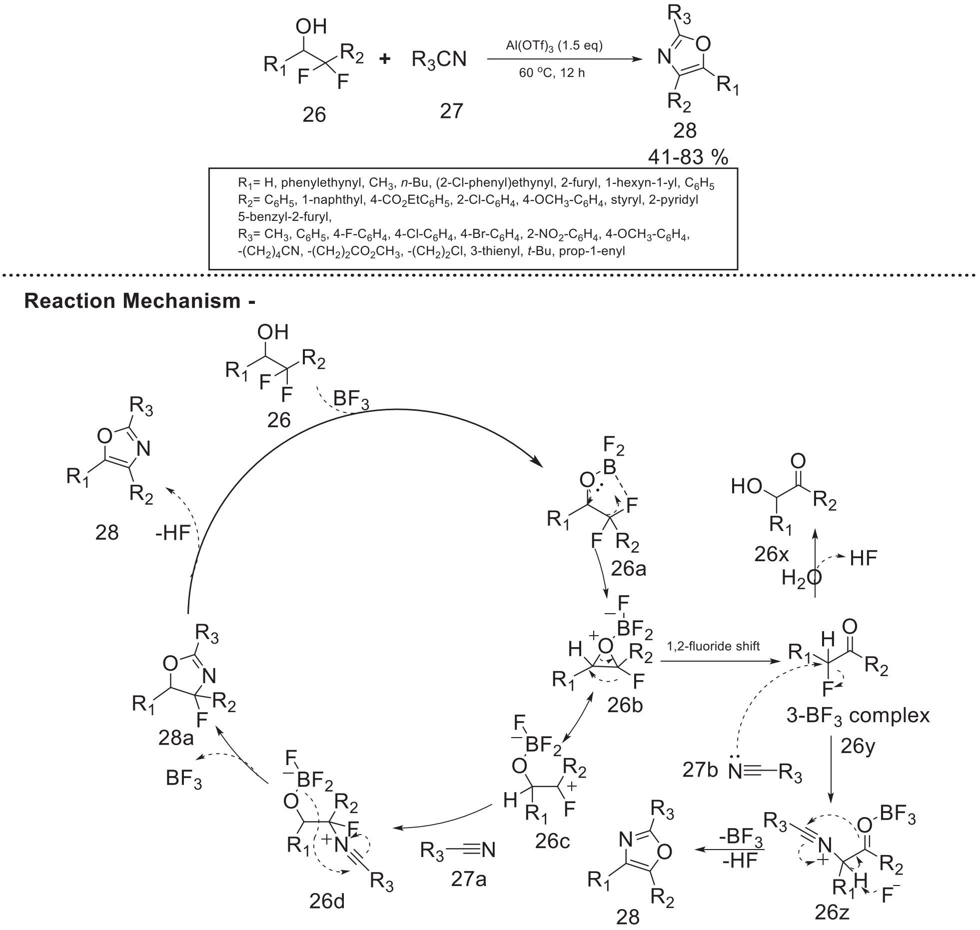
Scheme 8. Gold catalyzed synthesis of polysubstituted oxazoles.

Zhang et al. in 2019 have assembled 2,4,5-trisubstituted oxazoles through intermolecular annulation reaction of O–acyl cyanohydrins with heteroarene by Pd-catalyst.[30c] The formal cyclization proceeds *via* direct addition of electronic-rich C–H of



R_1= n-C_5H_{11}, n-C_9H_{19}, i-Pr, c-C_6H_{11}, t-Bu, C_6H_5, 4-F-C_6H_4, 4-CF_3-C_6H_4, 4-NO_2-C_6H_4, 4-CN-C_6H_4, 4-CH_3-C_6H_4, 4-OCH_3-C_6H_4, 3-pyridinyl, 2-furanyl, 2-thiophenyl, c-Hex
R_2= i-Pr, c-Hex R_3= H, C_6H_5, R_2= R_3 = -$(CH_2)_4$-, C_2H_5, -$(CH_2)_5$-, CH_3, Bn
Ar= 4-NO_2-C_6H_4, 4-CO_2CH_3-C_6H_4

Scheme 9. Zirconium catalyzed synthesis of 5-methoxy-1,3-oxazole using isonitrile.[35]

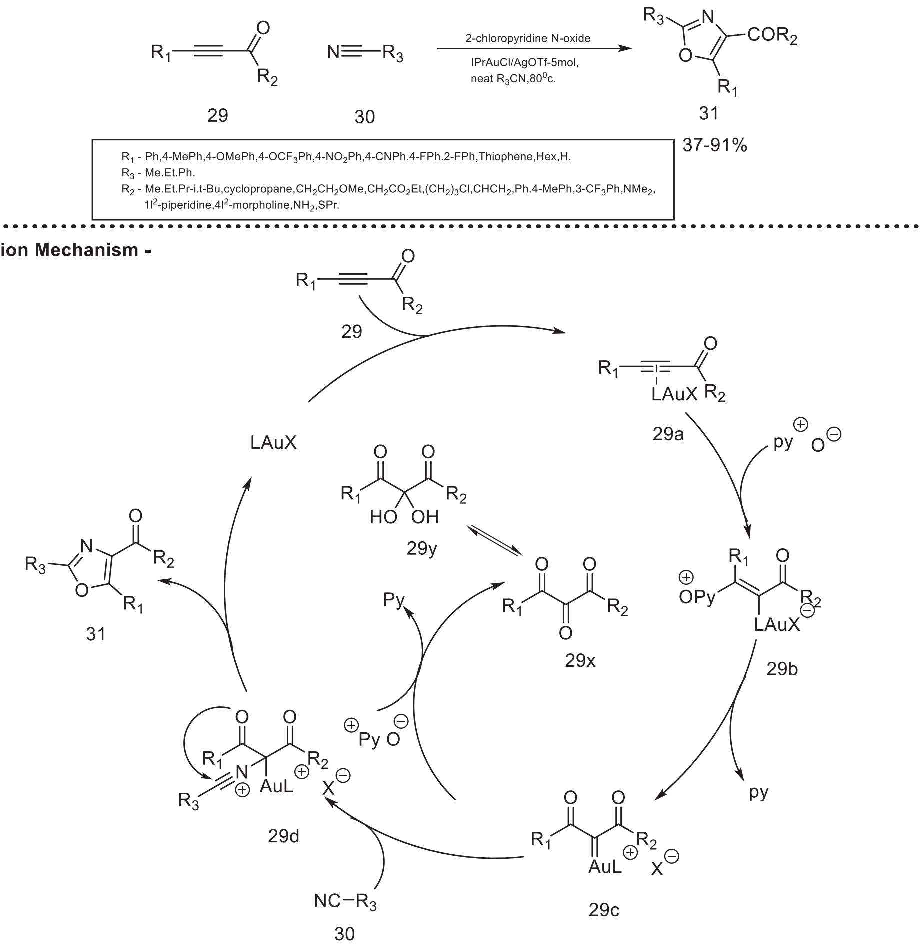


R_1= H, phenylethynyl, CH_3, *n*-Bu, (2-Cl-phenyl)ethynyl, 2-furyl, 1-hexyn-1-yl, C_6H_5
R_2= C_6H_5, 1-naphthyl, 4-$CO_2EtC_6H_5$, 2-Cl-C_6H_4, 4-OCH_3-C_6H_4, styryl, 2-pyridyl
5-benzyl-2-furyl,
R_3= CH_3, C_6H_5, 4-F-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 2-NO_2-C_6H_4, 4-OCH_3-C_6H_4,
-$(CH_2)_4CN$, -$(CH_2)_2CO_2CH_3$, -$(CH_2)_2Cl$, 3-thienyl, *t*-Bu, prop-1-enyl

Scheme 10. Aluminum catalyzed synthesis of2,4,5-trisubstituted oxazoles using nitrile.[36]

heteroarene to nitriles on heating under neutral redox conditions. Both, ligand and palladium Pd (II) catalyst played an important role in this transformation. The reaction plausibly proceeds *via* palladation at a heteroarene [(bpy)Pd(TFA)$_2$] **32x** to give a palladium complex **32a** followed by coordination of cyano group of O-acyl cyanohydrin bearing α-hydrogen **33** and complex **32a** provides intermediate **32b**, which undergoes an addition of a hetero arene group to a cyano group to generate the ketimine Pd(II) complex **32c**. Finally, intramolecular cyclization of ketimine–Pd(II)complex **32c** gives intermediate **34a**, which converted into product by protonolysis, elimination, aromatization and regenerate the Pd(II) species **32x** (Scheme 12). It was important to note that oxazoles with hetero-aromatic substituents could be easily synthesized using standard reaction condition.[30c]

Hu and coworkers in 2018 developed an efficient chemo-selective one-pot approach for the construction of multi-substituted oxazoles.[37] This methodology involved Iridium-catalyzed reductive addition of isocyano-acetates to enamine intermediate of tertiary lactams and tertiary amides to produce 2-(N-heterocycl-2-yl)-5-methoxyoxazoles or amino 5-methoxyoxazoles. Both electron-withdrawing and electron-donating groups

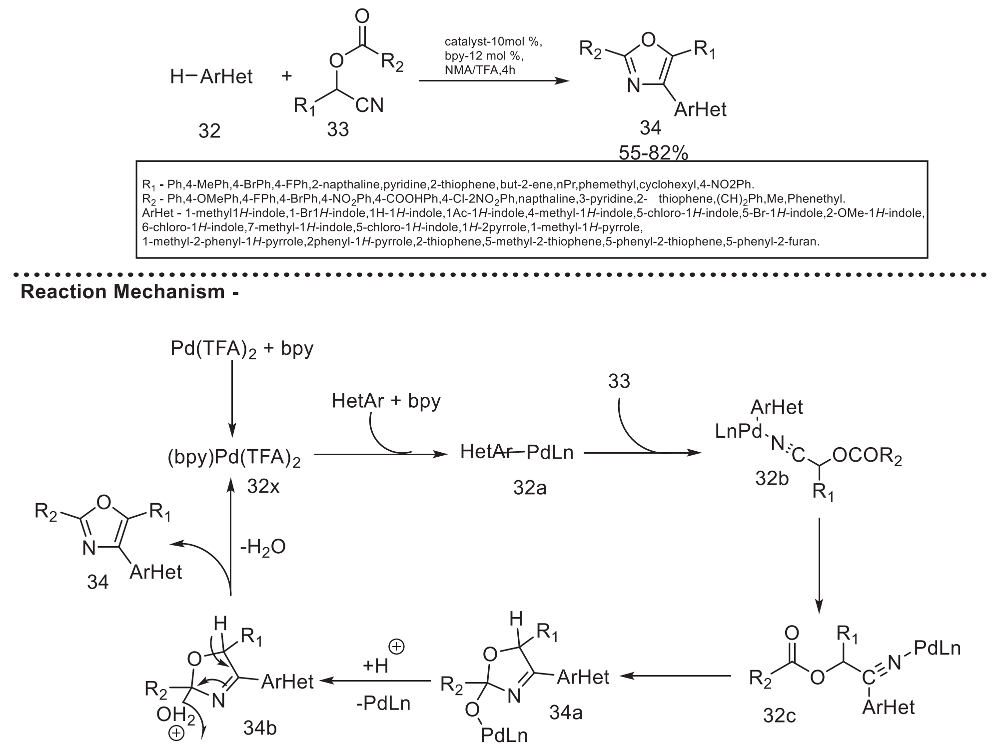


R_1 - Ph,4-MePh,4-OMePh,4-OCF$_3$Ph,4-NO$_2$Ph,4-CNPh.4-FPh.2-FPh,Thiophene,Hex,H.
R_3 - Me.Et.Ph.
R_2 - Me.Et.Pr-i.t-Bu,cyclopropane,CH$_2$CH$_2$OMe,CH$_2$CO$_2$Et,(CH$_2$)$_3$Cl,CHCH$_2$,Ph.4-MePh,3-CF$_3$Ph,NMe$_2$, $1l^2$-piperidine,$4l^2$-morpholine,NH$_2$,SPr.

Scheme 11. Gold catalyzed synthesis of 1,3-oxazoles using nitrile.[31a]

on phenyl ring of isocyano-acetates were well tolerated and afforded the corresponding oxazoles in moderate to excellent yield. The proposed pathway for this reaction, showed in (Scheme 13). The reaction initiated by the base optimized generation of iso-cyanoacetate enolate **36b**, that reacted with the enamine intermediate **36e** of lactam/*tert*-amide and converted to substituted1,3-oxazole **37** *via* nitrilium intermediate. It was noteworthy that the desired oxazole was obtained in excellent yield from *tert*-amides bearing bulky *N,N*-dibenzyl group.[37]

Liu et al. in 2019 established an efficient and precise protocol aimed at regio specific reactions of 2,5-disubstituted oxazoles by [3 + 2] cycloaddition reaction among isocyanides and acyl chlorides using silver-based MOF catalysts. During the optimization, researcher observed that maximum yield of 2,5-disubstituted oxazoles were produced with AgMOFs and dioxane/DMSO as solvent.[33] This observation indicated that the selection of solvent is crucial in achieving desired product. The use of silver acetate was key role in oxazoles annulation reaction with excellent yield. Notably, [3 + 2] cycloaddition had attractive features like substrate selection and tolerance for distinct functional groups. The plausible pathway was hypnotized by control experiment which indicate

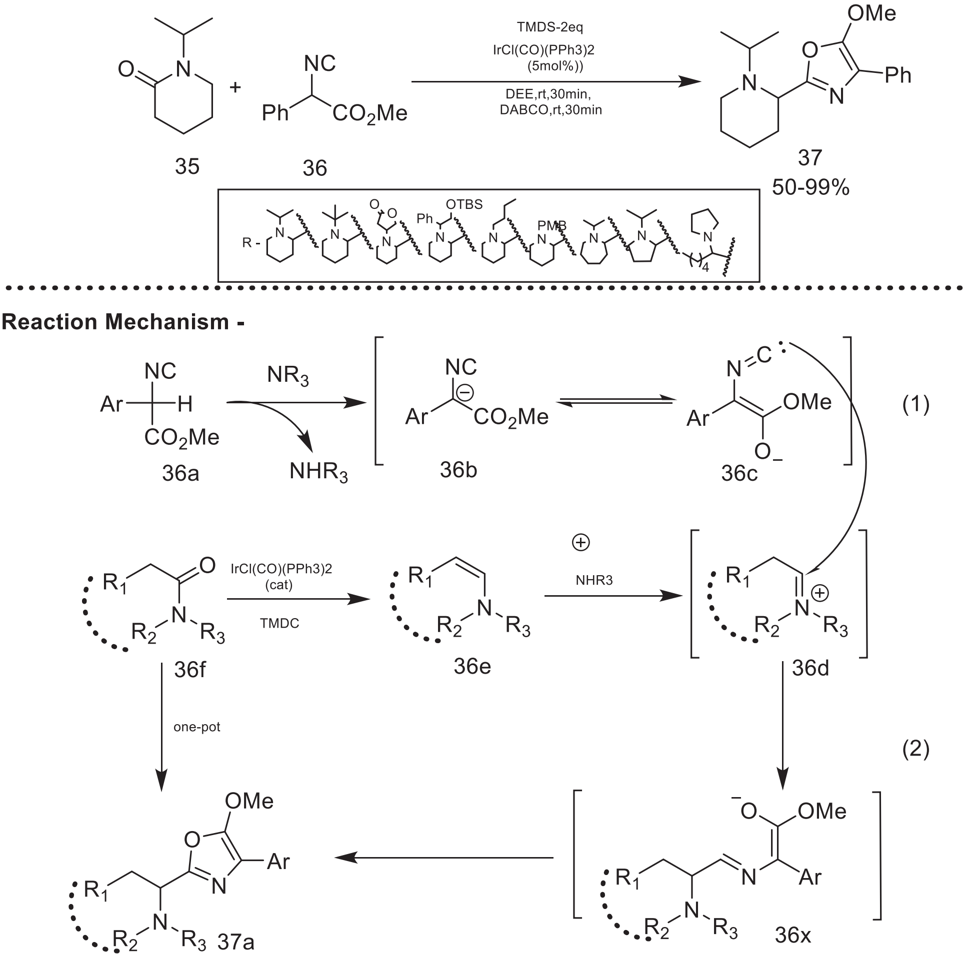


Scheme 12. Palladium catalyzed synthesis of 1,3-oxazoles using nitrile.[30c]

the nitrilium-intermediate **40b** formation with silver. The intra-molecular 1,3–H shift of **40b**, would produce **40c** that transformed to oxazole **40** after intramolecular nucleophilic addition/deprotonation sequence followed in path-A and B (Scheme 14).[33]

The synthesis of a number of highly substituted butenolides and oxazoles has been achieved by Qi and coworker's in 2018 through copper-catalyzed [2 + 3] cyclization reaction between α-hydroxyl ketones and aryl-acetonitriles.[29a] The product was dependent on the structure of the α-hydroxy ketones used. Tertiary α-hydroxy ketones gave 3,4,5,5-tetrasubstituted butenolides as the single products, while secondary α-hydroxy ketones selectively furnished 2,4,5-trisubstituted oxazoles. These reactions were applied to the synthesis of various aryl substituted α-hydroxyl ketones and alkyl aryl substituted nitriles substrates, but reaction could not generate desired product with unsubstituted α-hydroxyl ketone. The proposed pathway involved the formation of oxy anion **41d**, imine intermediate **41c** that undergoes Knoevenagel condensation to give cyclized intermediates **43a**, followed by subsequent dehydration to afford oxazole formation **43b** (Scheme 15).[29a]

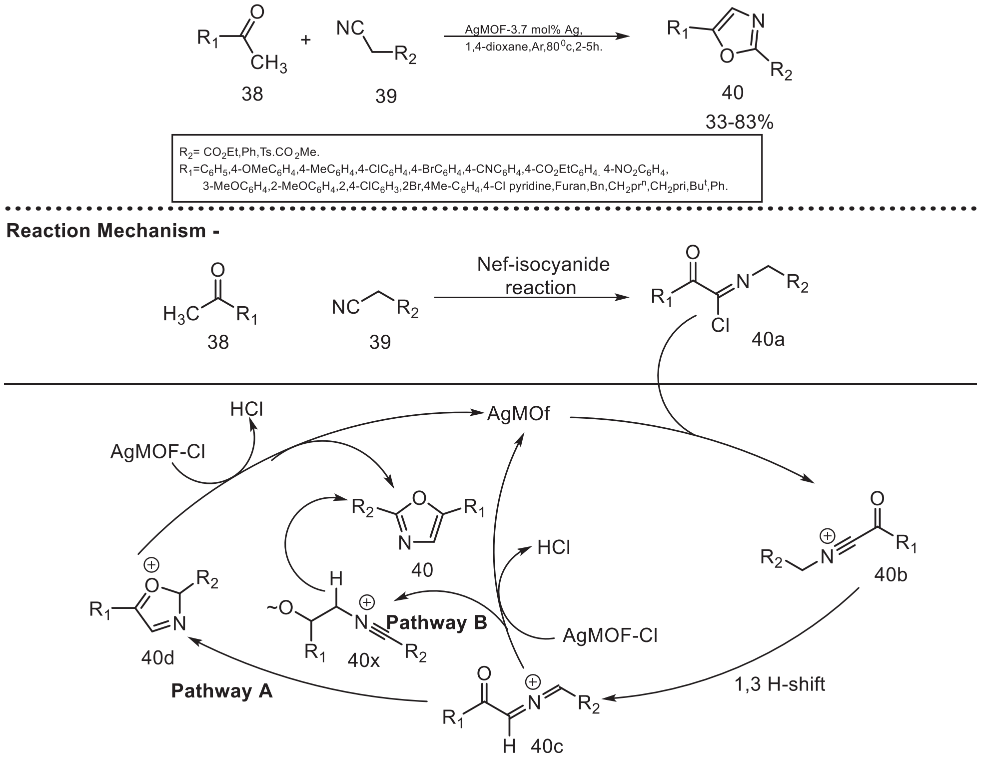
Wang et al. in 2017 developed a straight forward and efficient strategy for the construction of pharmaceutically active oxazole substituted tetrahydroiso-quinolines.[42] In this reported methodology they performed Ugi reaction of C,N–cyclic azo-methine imines **45** and iso-nitriles **44** to yield desired asymmetric product **46** with 96% of enantio-selectivity in presence of Nickel-catalyst and acetonitrile as solvent. The scope of this protocol tolerated a wide range of phenyl-substituted iso-nitriles with both electron-



Scheme 13. Iridium catalyzed synthesis of 1,3-oxazoles using nitrile.[37]

donating and electron-withdrawing groups delivered corresponding oxazole in high yield. The reaction pathway investigation revealed the formation of bidentate coordination of Ni^{II} and iso-nitrile complex **45b**, which is attacked by azo-methine imine to form the oxazole **46a** as final product (Scheme 16). The nickel can be replaced by other metals. Further, It was observed that the *tert*-butyl ester substituted with iso-nitriles has failed to produce corresponding oxazoles with alkyl iso-nitriles.[42]

Yang and coworkers in 2017 successfully implemented heterogeneous gold-catalyzed for the synthesis of 2,5-disubstituted oxazoles *via* [2 + 2 + 1] cyclization of terminal alkynes, nitriles, and oxygen atoms of 8-methylquinoline *N*-oxide.[31d] This method successfully derived a wide range of aromatic, hetero-aromatic and aliphatic 2,5-disubstituted oxazoles with good to excellent yield. Most importantly the MCM-41-immobilized phosphine–gold(I) complex catalyst was easily recovered by filtration and reused around eight time with consistent yield of desired product. The authors observed a constraint in this protocol when they used an electron withdrawing substituted phenyl-acetylenes derivative as the substrate with poor reactivity. The proposed pathway involved the



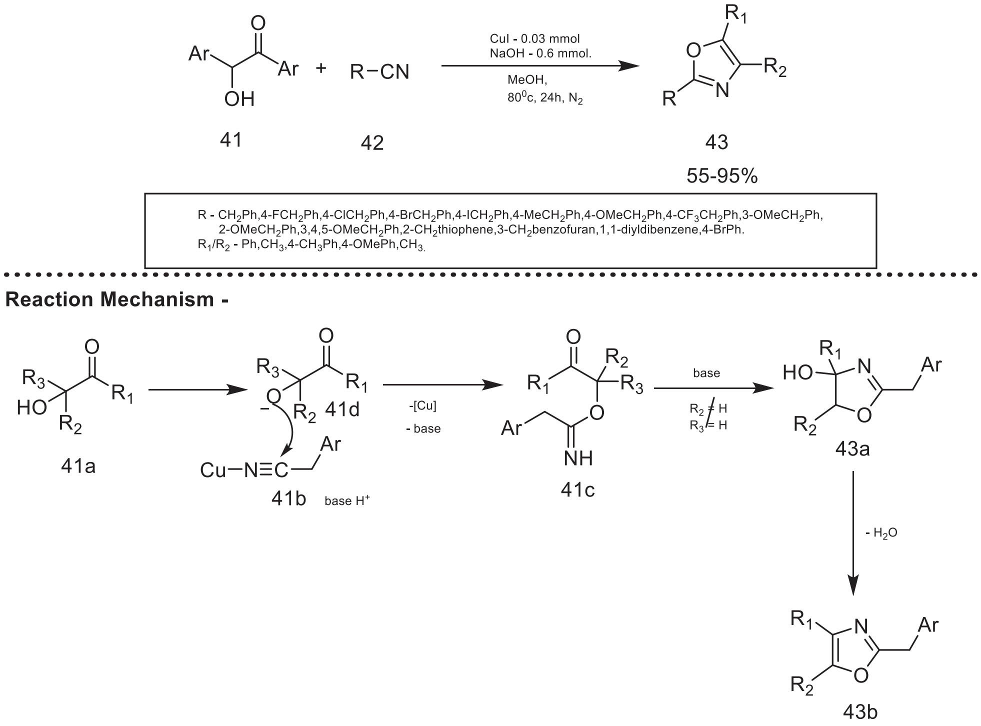
Scheme 14. Silver catalyzed synthesis of 1,3-oxazoles using nitrile.[33]

formation of MCI-41–phosphine–Gold alkyne complex **47x**, followed by oxygen insertion and generation of carbene intermediate **50b** *via* addition–elimination. The nucleophilic attack of nitrile **48** on **50b** affords, intermediate **50c**. The last step involved the regeneration of MCI-41–phosphine–metal complex and intra-molecular cyclization promoted the formation of desired oxazoles, **50** (Scheme 17).[31d]

L. Dai *et al.* in 2020 reported a palladium-catalyzed tandem reaction of cyanomethyl benzoates with arylboronic acids. The mechanism proceeds with the important steps viz **51x** Reaction of palladium catalyst and Ar–boronic acid to give palladium–aryl complex **51y** nitrile and palladium coordinates with each other to give precursor **51b**. **51z** palladation of ester-nitrile forms complex of imine-palladium **51c**. **51w** Precursor **51c** protonates due addition of acid and converts to imine **51d** (compound **51d** tautomerizes to compound **51e** i.e., interconversion of imine to enamine) and palladium catalyst was regenerated. Cyanomethylbenzoates substituted at position-2was the vital step in the formation of oxazoles of interest. Intermediate **53a** specifically converted to 2,4-diaryloxazoles from starting material **51a** (Scheme 18).[43]

Ethyne

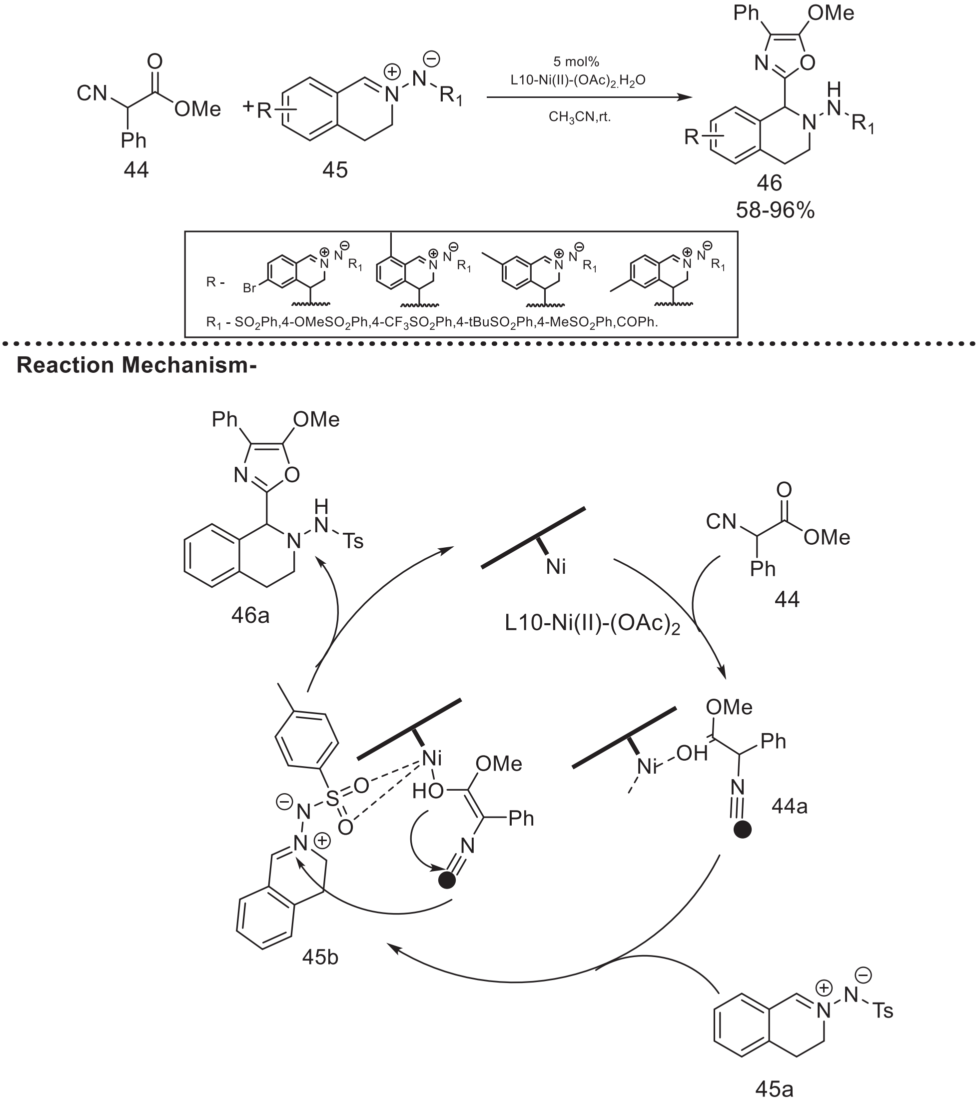
J. Mali and coworkers in 2017 reported the palladium (II) catalyzed cyclization of acid chlorides in the presence of propargyl-amine provides an attractive way for one pot synthesis synthesize of 2-oxazolines and 2-oxazoles.[30a] It has been reported that the use of



Scheme 15. Copper catalyzed synthesis of 1,3-oxazoles using nitrile.[29a]

triethylamine and acetic acid, as an additive was effective in selective oxazole and oxazoline synthesis. In the absence of acid, this reaction delivered oxazole in poor yield that revealed the exclusive oxazole formation required significant amount acidic medium. At the same time authors have shown the importance of reaction timing for the selective synthesis of oxazole. Moreover, the electron donating or electron withdrawing substitutions at *ortho*, *meta* or *para* position on phenyl ring of acid chloride were compatible under optimized condition. The acid chloride with hetero-aromatic ring aliphatic group gives low yield of corresponding oxazole. The plausible reaction pathway involved the activation of alkyne moiety by Pd (II) catalyst, which promoted the intramolecular cyclization and gives cyclised intermediate **56c**. The cyclised intermediate further transformed to oxazoline **56e** and 1,3-oxazole **56** under basic and acidic medium (Scheme 19).[30a]

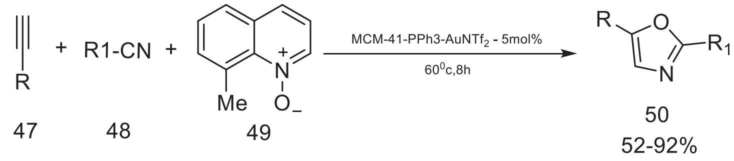
A concise route for region specific synthesis of oxazoles from ynamides using ytterbium-**57x** was developed by Sahoo and coworker in 2017.[44] The carefully optimized reaction conditions revealed that the use of Ph_3PAuCl, $Yb(OTf)_3$, N–iodosuccinamide in **57z** is essential and optimal reaction condition to construct oxazole in best yield. This approach smoothly transferred bulkier group substituted ynamides, naphthyl, phenanthryl and optionally substituted aromatic rings. The author proposed pathway which isillustrated in Scheme 20. The metalo-keteniminium intermediate **57k** is formed from acetonitrile by $Yb(OTf)_{3,}$ Then, a direct attack of ynamide on intermediate **57k** results in **57a**. The Yb–iodo exchange/protodemetalation and hydration sequence of



Scheme 16. Nickelcatalysed synthesis of 1,3-oxazoles using nitrile.[42]

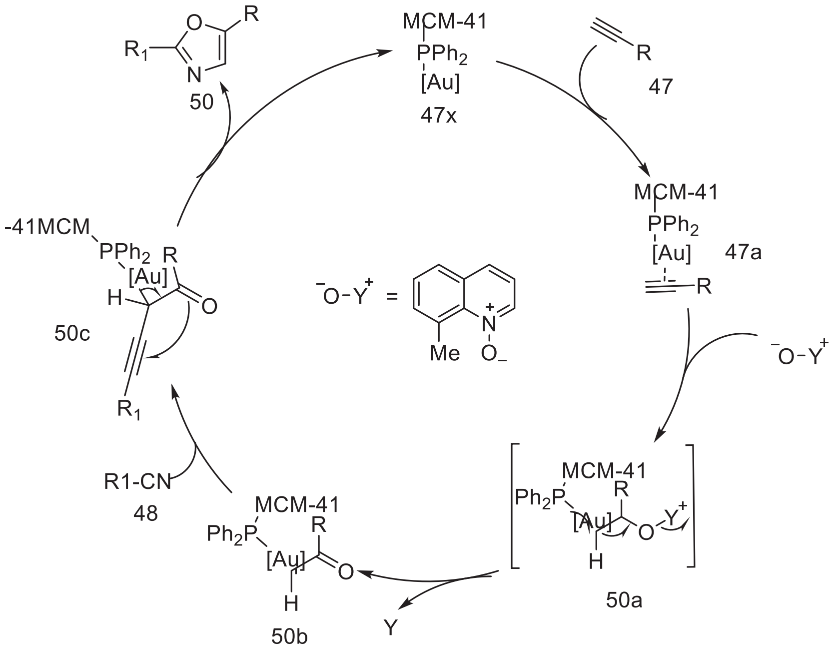
intermediate **57b** afforded *β*-iodo-keteniminium **58a**. Finally, in last step nitrile attack followed by hydration of **58d** gives intermediate **58b** and resulted in the formation of 1,3-oxazole **58** by intra-molecular cyclization and elimination reaction.[44]

X. Yu and coworkers in 2018 developed a novel methodology that involved cobalt(III)-catalyzed cross-coupling of N-pivaloyl-oxyamides and alkynes through [3 + 2] cycloaddition reaction to generate series of 2,5-disubstituted oxazoles.[45] The optimal reaction conditions revealed the desired oxazoles are obtained in higher yields by using combination of [Cp*Co(MeCN)$_3$(SbF$_6$)$_2$] (0.05 equiv.) and alkyne (1.5 equiv.) in DCE as solvent. This method is used to synthesize a wide range of 2,5-disubstituted oxazoles. In the proposed pathway, authors hypothesized the formation of oxazole **61**

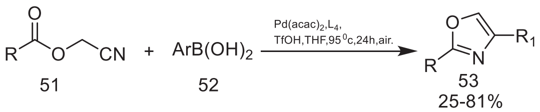


R - Ph,4-MePh,4-BuPh,4-MeOPh,3-MePh,4-ClPh,4-BrPh,3Cl,4MePh,4EtPh-Ph, 2-MePh,2-ClPh,napthalene,4-ethynylbenzene,$(CH_2)_3Me$,$(CH_2)_3Cl$.$(CH_2)_3Ph$, cyclopropane,Cyclohexane,$(CH_2)_4COOH$,$(CH_2)_2THPO$,3-thiophene, (*tert*-butyl)furan.
R_1 - Me,Ph,Propane.CH_2Ph.4-MePh,2-thiophene.

Reaction Mechanism -

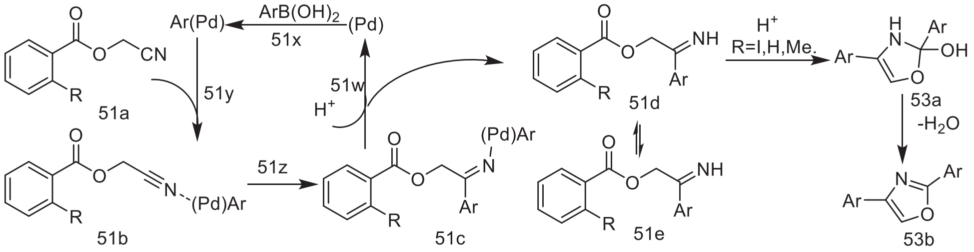


Scheme 17. Phosphine-gold(I) complexcatalysed synthesis of 1,3-oxazoles using nitrile.[31d]

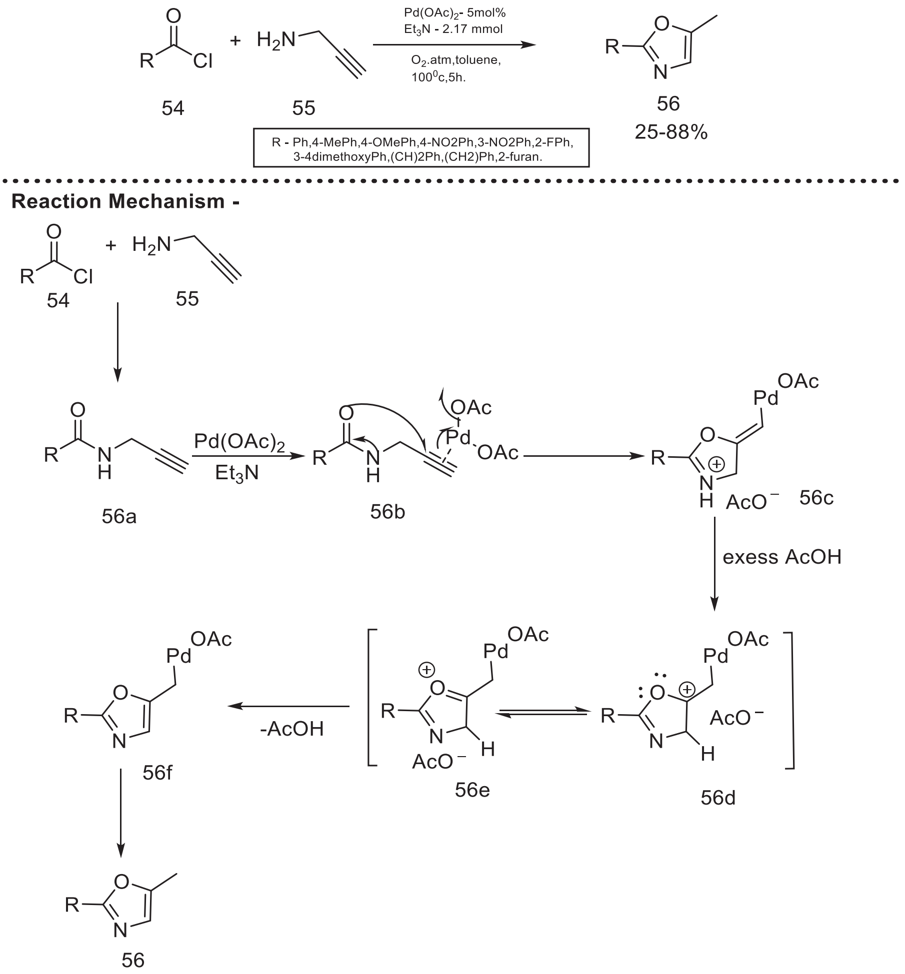


R = C6H5,4-MeC6H4,3-MeC6H4,2-MeC6H4,4-MeOC6H4,2,5-DiClC6H3,4-CF3C6H4,2-thiophene.
R_1= C_6H_5,4-MeC_6H_4,2-MeC_6H_4,2-EtC_6H_4,4-$CF_3C_6H_4$.

Reaction Mechanism -



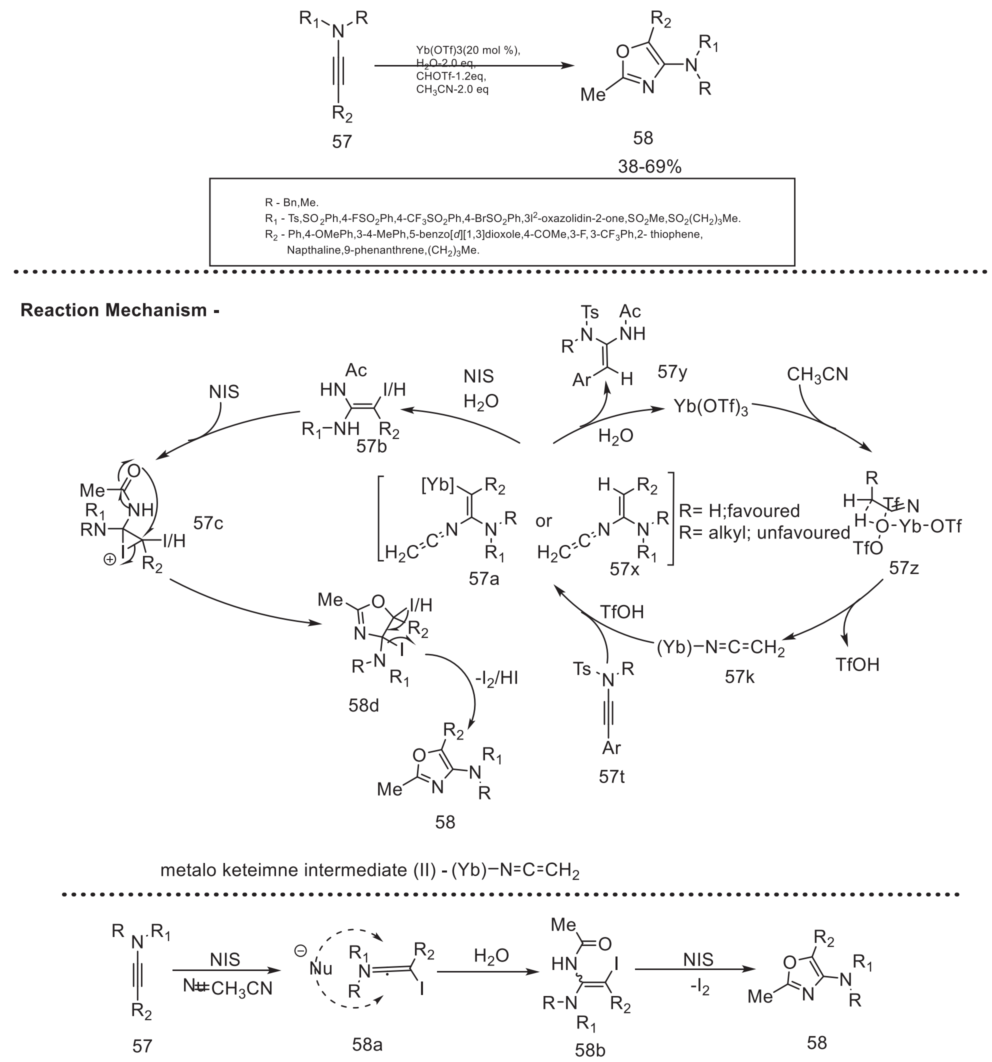
Scheme 18. Palladium catalyzed synthesis of poly-substituted oxazoles.



Scheme 19. Palladium catalyzed synthesis of 1,3-oxazoles using ethyne.[30a]

involved a key Co(III)–alkyne π-complex **61a** as intermediate which further converts to complex **61b** by rigorous C–O and N–O bond formation and cleavage, Finally reductive elimination and C–N bond formation affords cyclized product with Co(III) regeneration. Furthermore, itis concluded that *para* substituted phenyl alkynes are more preferred over *ortho* and *meta* substituents. Alkynes with hetero-aromatic and aliphatic substituents are also found well tolerating the reaction conditions (Scheme 21).[45]

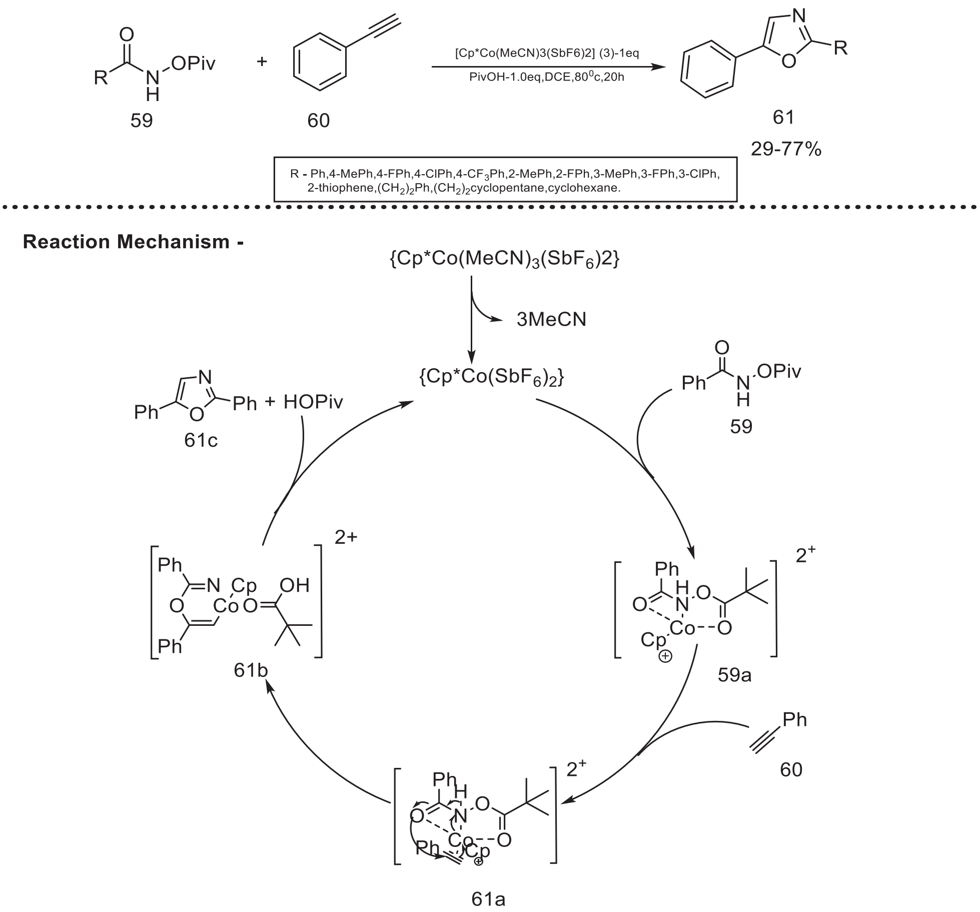
Ben Niu et al. in 2018 utilized Scandium and Rhodium based catalyst for the synthesis of 4-amino-isoquinolin-1(2H)-one and oxazole derivatives through C–H bond functionalization. This reaction occurred by utilizing (pivaloyloxy) benzamide **62** with *N*-methyl-*N*-(phenylethynyl)methane sulfonamide **63** precursor in presence of Lewis acid catalyst $Sc(OTf)_3$.[38] In this methodology the scandium metal played a dual role in promoting C–H activation and optimized cyclization. Besides that, this reaction could be implemented on a variety of *ortho*, *meta* and *para* electron rich or electron deficient substituents on ynamides benzene ring. The overall studies demonstrated that this process can be used to derive verity of fully substituted oxazole with moderate to good



Scheme 20. Ytterbium catalyzed synthesis of 1,3-oxazoles using ethyne.[44]

yield from radially available starting material. Regarding possible pathway illustrated in (Scheme 22), an alkyne C–N bond formation by Sc(lll) species and extrusion of pivalate ion was proposed.[38]

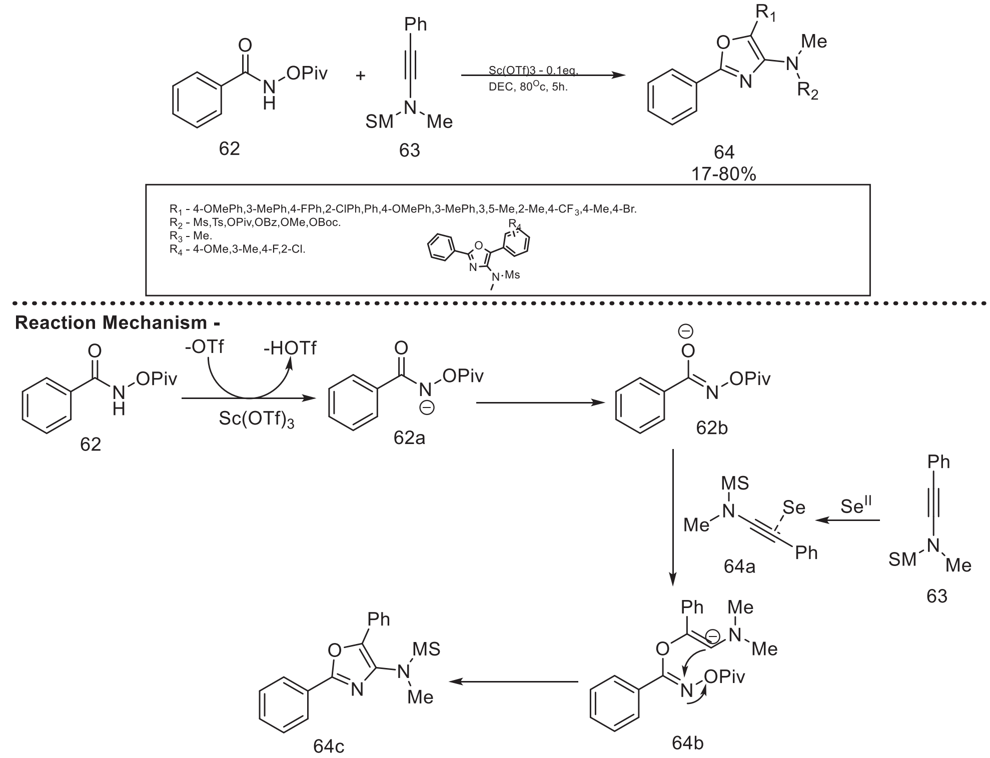
S. Fan and coworkers in 2018 developed a smooth and efficient copper-mediated one-pot synthesis of 2-*o*-cyanoaryl oxazole derivatives though cyclization and coupling of o-bromo *N*-propargyl benzamides with CuCN.[46] The coupling efficacy was enhanced by using L-proline as ligands with 1,10-phen and CuCN in DMAc as optimal solvent for the successful oxazoles synthesis. The CuCN played a dual role as a Lewis acid catalyst and C-nucleophile. The mechanistic pathways revealed the impact of o-bromo *N*-propargyl benzamides substituents on the yield of final oxazole or oxazoline under same optimized conditions. The general pathway can be proposed based on the general aspects know to date: initially addition of copper (I) to the alkyne form copper-



Scheme 21. Cobalt catalyzed synthesis of 1,3-oxazoles using ethyne.[45]

ligand complex, that undergoes subsequent intra-molecular cyclization and proteolysis give oxazoline as intermediate **66b** that subsequently isomerized and give oxazole **66c**. Next, copper cyanide coordinate with oxazole and phenyl ring, the resulted complex transformed to the corresponding oxazole after oxidative addition and reductive elimination step (Scheme 23).[46]

H. An et al. in 2019 reported a facile synthetic method to derive 5-oxazole ketones through intramolecular cyclization of *N*-propargylamide in presence of gold catalyst.[31c] After the course of the preliminary screening, the use of Ph_3PAuCl with oxidant 4-methoxy-TEMPO is established as the best reaction conditions in acetonitrile as solvent. This methodology provides an interesting approach to develop oxazole scaffolds with 5-ketone substitution with an impressive functional group tolerance. Contrary to it alkyl substituted alkynes fails to obtain corresponding cyclized product, which reveals that aryl substituents to alkynes are necessary due to its conjugation. The electron rich substituents at aromatic ring adjacent to the carbonyl part gives better yield compared to the electron deficient substituents. The plausible pathway is presented in (Scheme 24). The gold catalyst initiated the cyclization of propargylated amide and generates a gold-

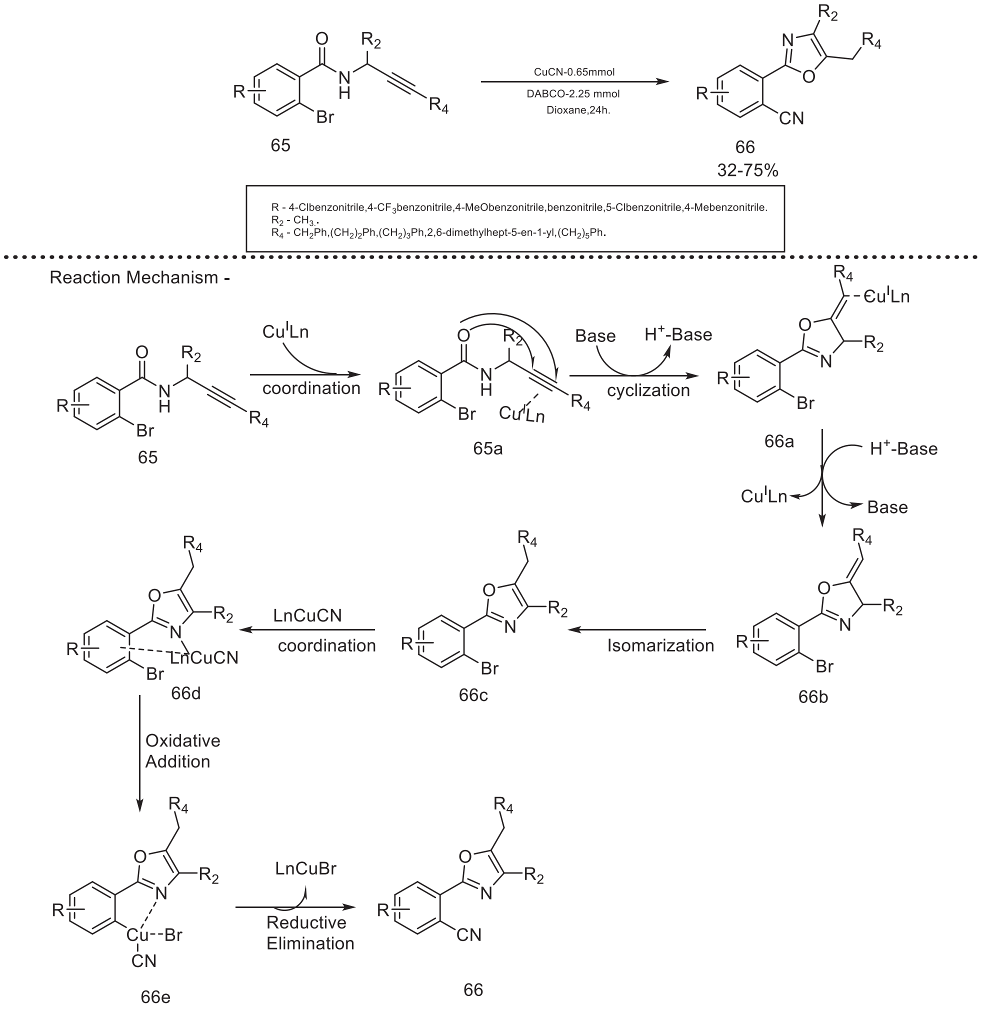


Scheme 22. Scandium and rhodiumcatalysed synthesis of 1,3-oxazoles using ethyne.[38]

vinyl intermediate **68b**. Subsequent attack of *in situ* generated NO on **68b**, generates intermediate **68c** and converted to **68d** by HAT (Hydrogen atom transfer) process. The isomerized form of intermediate **68d** is converted to final desired oxazole by following a sequence of protodeauration and hydrolysis.[31c]

Keivanloo et al. in 2019 established a novel multi-component one pot synthesis of 1,3-oxazole mediated by Pd-catalyst.[30b] They have screened several benzoyl chlorides, propargylamine, and 3-chloro-quinoxaline-2-amines to synthesize corresponding oxazoles in the presence of Et_3N (base) and $Pd(PPh_3)_2Cl_2/CuI$ as catalytic system in acetonitrile. This methodology proceeds through coupling followed by regiospecific cyclization of *N*-propargylamides with 3-chloroquinoxaline-2-amines and the resulted coupling intermediates produced (3-(amino substituted)quinoxalin-2-yl)(2-phenyloxazol-5-yl)methanone. The plausible catalytic pathway involved the Sonogashira coupling by Pd(0)/Cu(l) species to give heteroaryl alkyne intermediate **72b**, which undergoes 5-*exo-dig* cyclization and afforded cyclized intermediate **72d**. Finally, the catalytic cycle completed by the construct oxazole ring **72e** sequencing through isomerization and aromatization (Scheme 25).[30b]

H. Yoneyama et al. in 2020 described synthesis of 2,4-disubstituted oxazoles. In the reaction mechanism TMSN3 and $Bu_2Sn(acac)_2$ **73x** forming anorgano-tin (IV) complex **73 y**, followed by [2 + 3] cyclic addition of acetylene **73** leading to formation of N-[dibutyl(O-acyl)stannyl]triazole **74a**. A stable Bu_2SnO is given out from compound **74a**

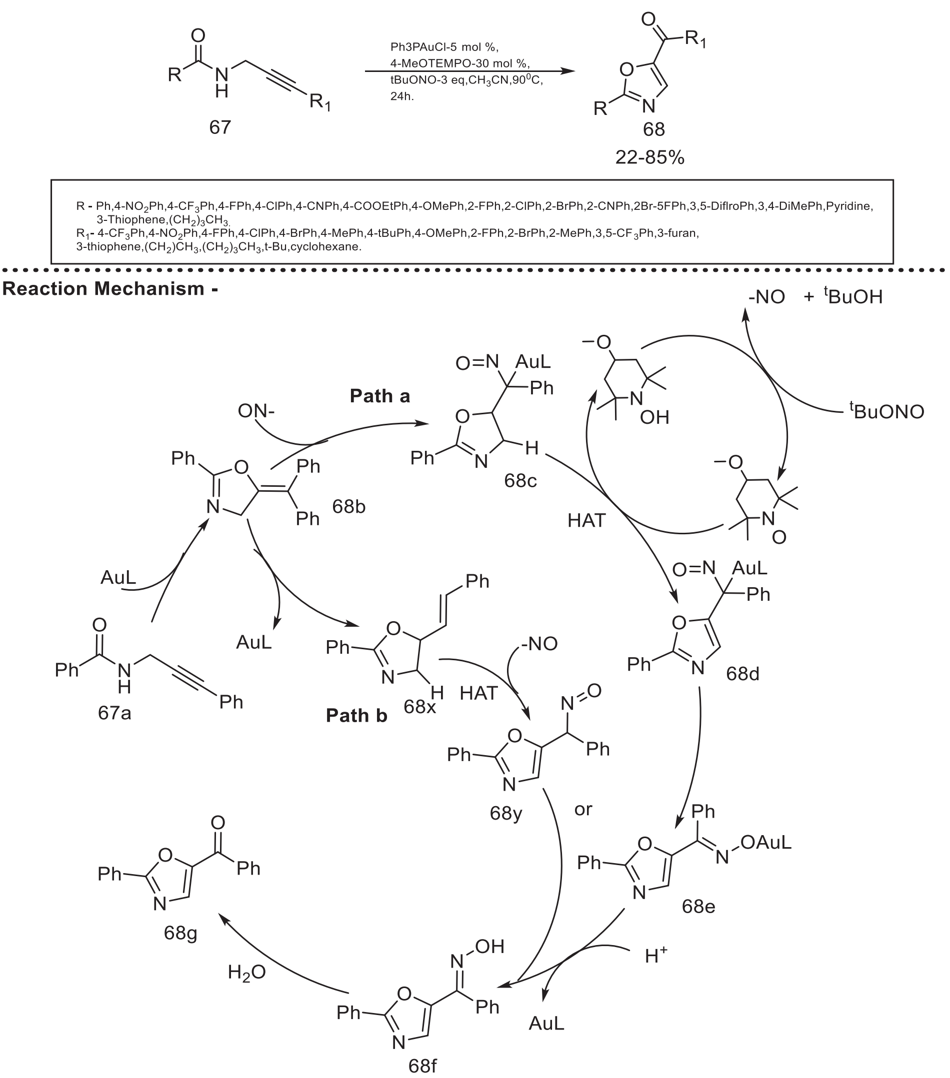


Scheme 23. Coppercatalysed synthesis of1,3-oxazoles using ethyne.[46]

via retro-ene reaction within the molecule to form N-(acyl)triazole **74b**. Removal of N$_2$ from **74c** or **74d** followed by ring formation leads to 2,4-disubstituted oxazole **74** (Scheme 26).[47]

Benzyl amine

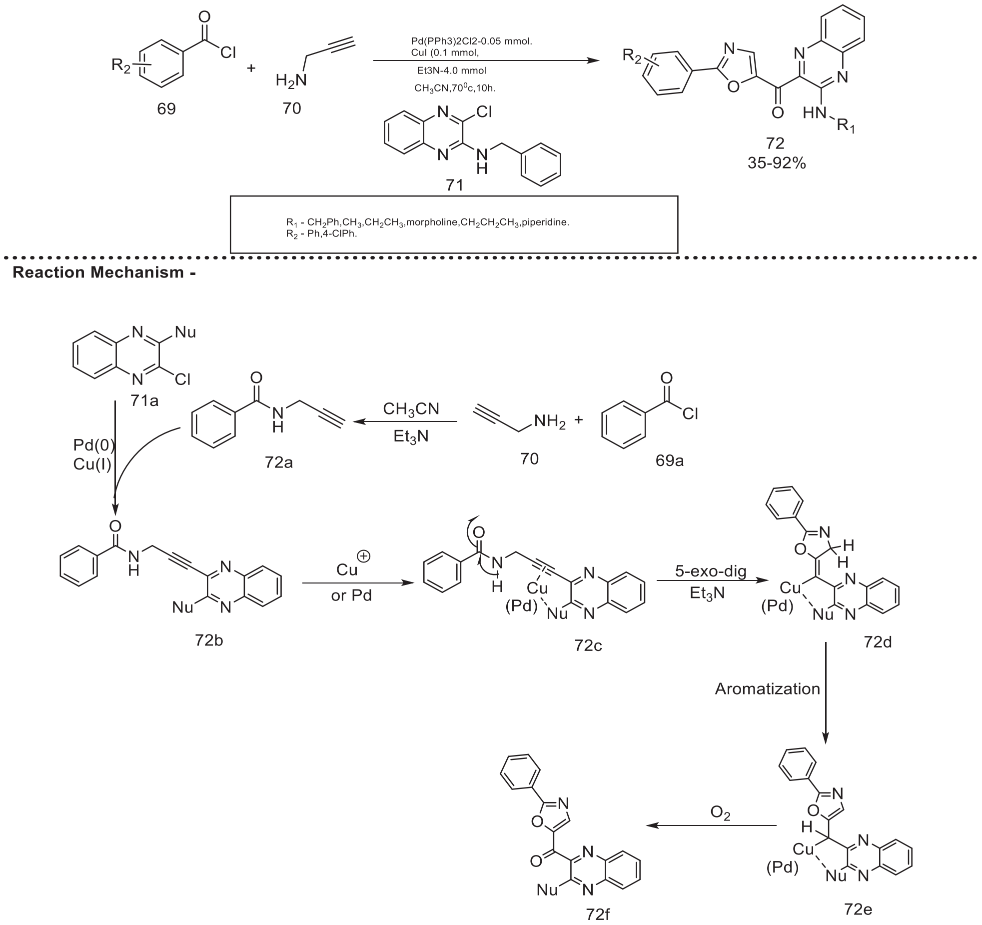
S. Dutta et al. in 2017 reported Cu-catalyzed cyclization of 1,3-dicarbonyls **75** using benzyl amines **76** for the formation of substituted 1,3-oxazole **77** using magnetic silica-based nano-copper catalyst.[48] The nano-copper smoothened the C–C and C–N bond formation in DMF. The substrates transformation is dependent on the solvent polarity. In the mechanism iodine promoted formation of intermediate **75b** from enol isomer **75a**, is observed which further undergo nucleophilic attack by benzyl amine **76** on Cu-coordinated iodo complex which gives **77b**. Finally, intermediate **77b** is converted to the oxazole **77** *via* oxidation, copper-catalyzed cyclization followed by proton



Scheme 24. Gold catalyzed synthesis of 1,3-oxazoles using ethyne.[31c]

abstraction. The time period contributes positively in the reaction conversion, while temperature lowers the rate (Scheme 27).[48]

M. Cai and his group in 2019 established a facile and efficient methodology for the synthesis of fully substituted oxazoles through copper-catalyzed tandem oxidative cyclization of benzyl amines and 1,3-dicarbonyl compounds.[29g] This methodology works well for transformation of varied benzyl amine derivatives and 1,3-dicarbonyl compounds to corresponding fully substituted oxazoles with good to excellent yield. After exploring scope of 1,3-diketones, it is revealed that a *β*-keto ester with different substituents is well tolerated, where in beta-ketoamide affords poor yield of corresponding oxazole. The probable pathway indicates the creation of 2-iodoacetoacetate by the reaction of **79a** with iodine and TBHP and which subsequently undergoes a nucleophilic attack of **78a** results in formation of intermediate **80a**. The oxidized form of A



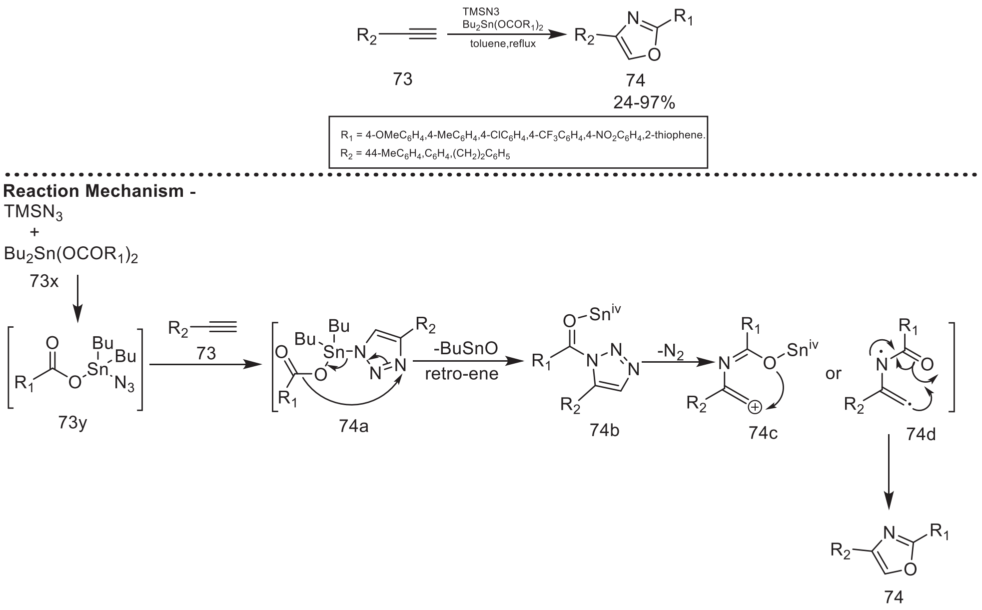
Scheme 25. Palladium and copper based catalysed synthesis of 1,3-oxazoles using ethyne.[30b]

coordinates with copper and generated intermediate **80c** *via* intra molecular cyclization and generate a cyclized intermediate with the expulsion of acetate ion. Final product is proposed to form by protonolysis and oxidation steps respectively (Scheme 28).[29g]

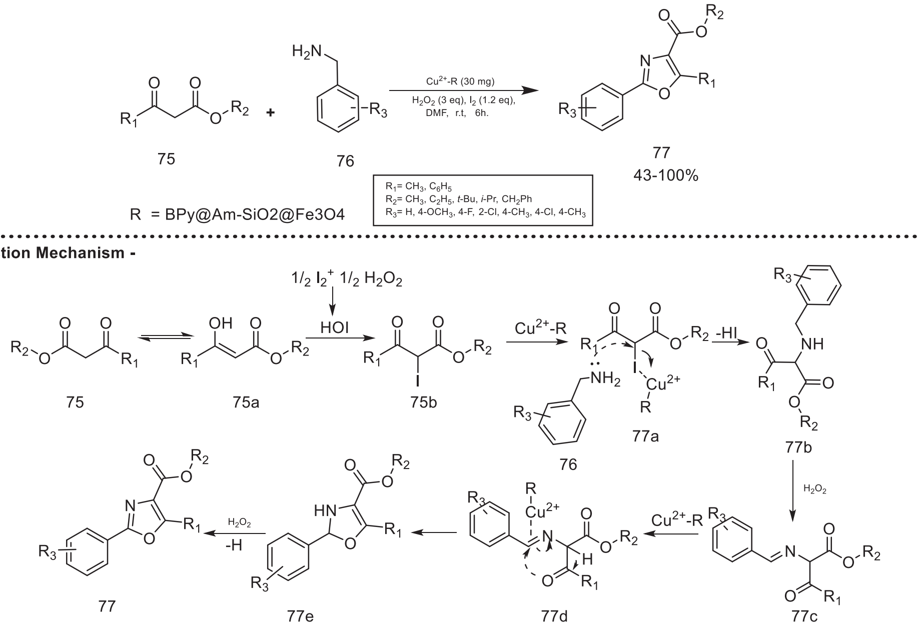
In another approach, J. Pan et al. in 2018 reported the synthesis of oxazole from substrate benzyl amine using Cu-catalyzed annulation between amines **81** and alkynes **82**.[29b] The O_2 activation and C–H bond functionalization are important in converting amines and alkynes to corresponding oxazole **83**. The cyclization required $CuBr_2$ and pyridine in same ratio of toluene and dichloroethane. Variety of benzyl amines and alkynes were applied to form the desired tri-substituted oxazole products with 9–80% yields. The halo substituted benzyl amines and naphthyl-substituted amine gave desired oxazole with medium yields. Phenyl substituted alkynes lowered the rate of the process (Scheme 29).[29b]

N2 containing molecules

A. Nagaraju and coworkers in 2018 reported an efficient route for synthesis of highly substituted 1,3-oxazoles oximes through from cabenoids.[29e] The reaction involved the

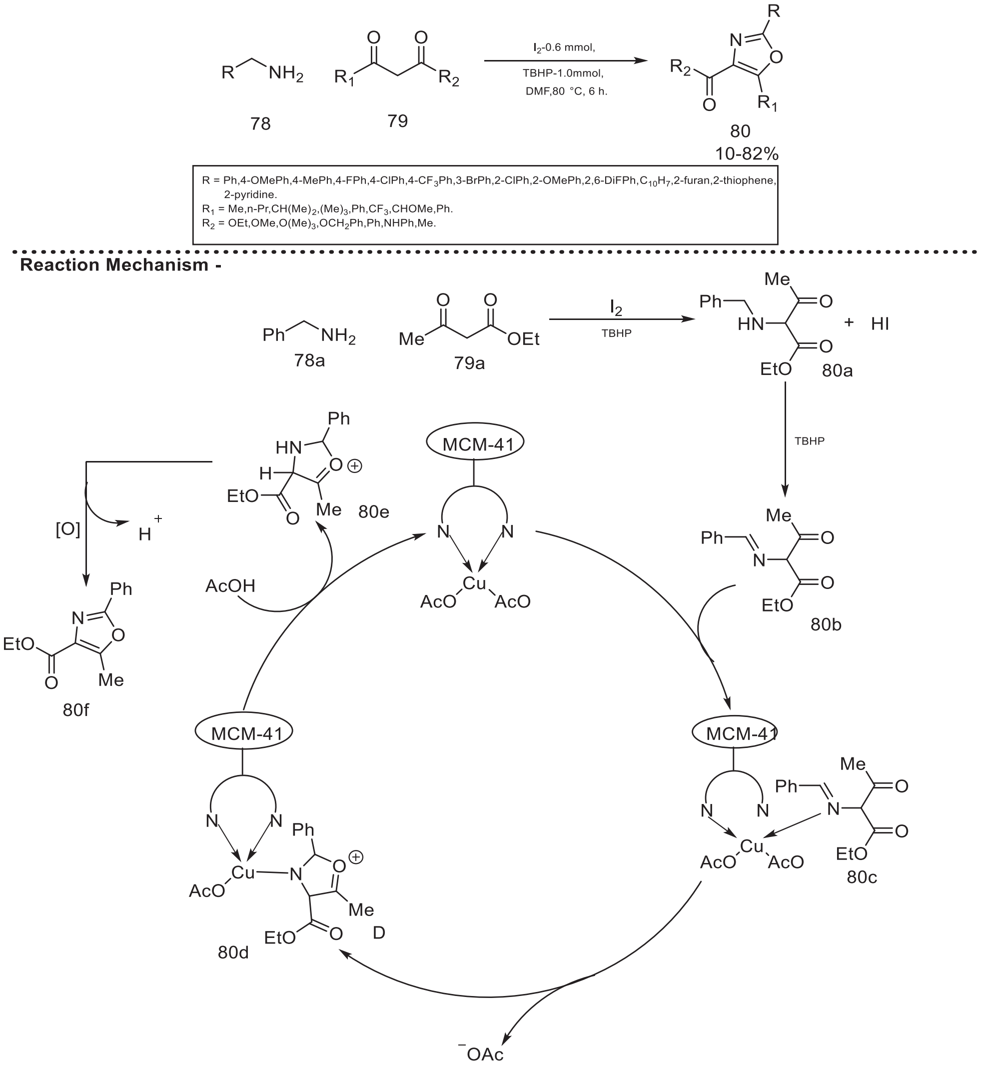


Scheme 26. Synthesis of 2,4-disubstituted oxazole using tin catalyst.



Scheme 27. Copper catalyzed synthesis of 1,3-oxazoles using benzyl amine.[48]

reaction of oximes with EDA in presence of copper-catalyst under mild catalytic condition. Among different used catalyst, $Cu(OAc)_2$ showed higher catalytic activity. This protocol has successfully used for wide range of substituted oximes and ethyl diazoacetate to generate variety of tri-substituted 1,3-oxazoles. The electron rich group



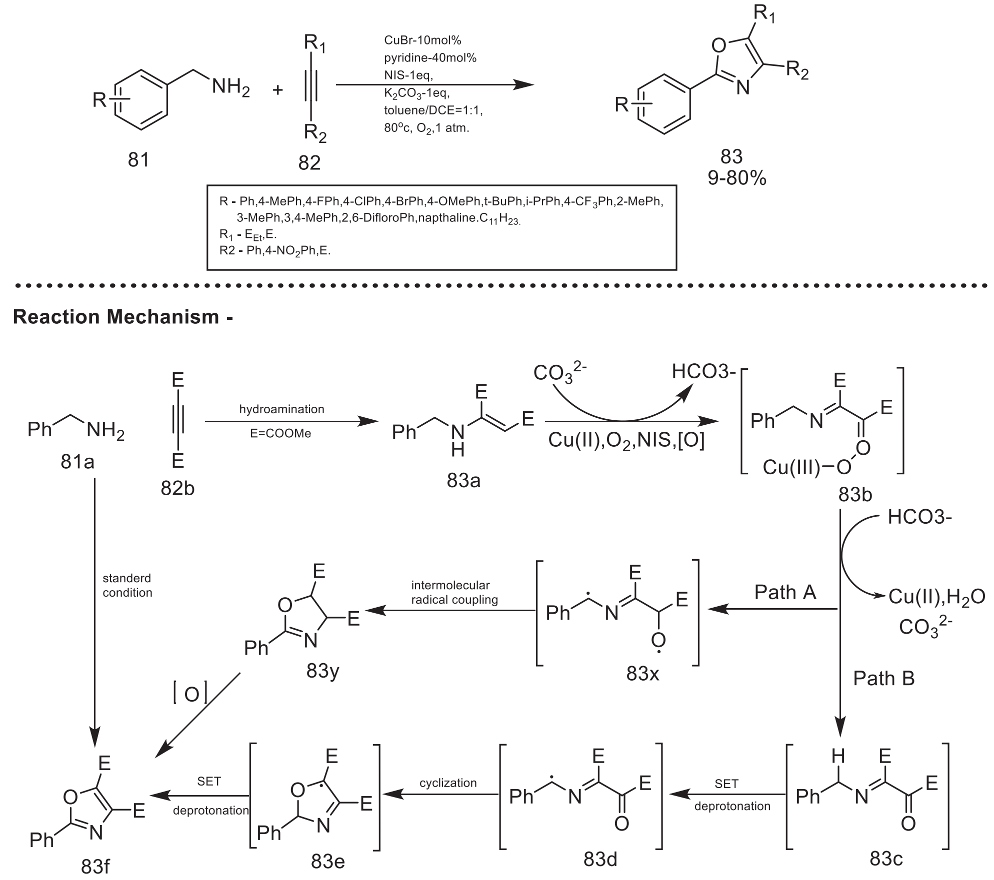
R = Ph,4-OMePh,4-MePh,4-FPh,4-ClPh,4-CF_3Ph,3-BrPh,2-ClPh,2-OMePh,2,6-DiFPh,$C_{10}H_7$,2-furan,2-thiophene, 2-pyridine.
R_1 = Me,n-Pr,$CH(Me)_2$,$(Me)_3$,Ph,CF_3,CHOMe,Ph.
R_2 = OEt,OMe,$O(Me)_3$,OCH_2Ph,Ph,NHPh,Me.

Scheme 28. Copper catalyzed synthesis of 1,3-oxazoles using benzyl amine.[29g]

containing aryl substituent oxime substrate showed better activity that electron deficient group. On other side ester substitution on oxime gives high yield of corresponding oxazole than keto or cyano substitutes. Reaction pathways illustrated below (Scheme 30) revealed the copper catalyzed intramolecular rearrangement of intermediate **86a** followed by elimination of water molecule resulted in oxazole formation.[29e]

Conclusion and remarks

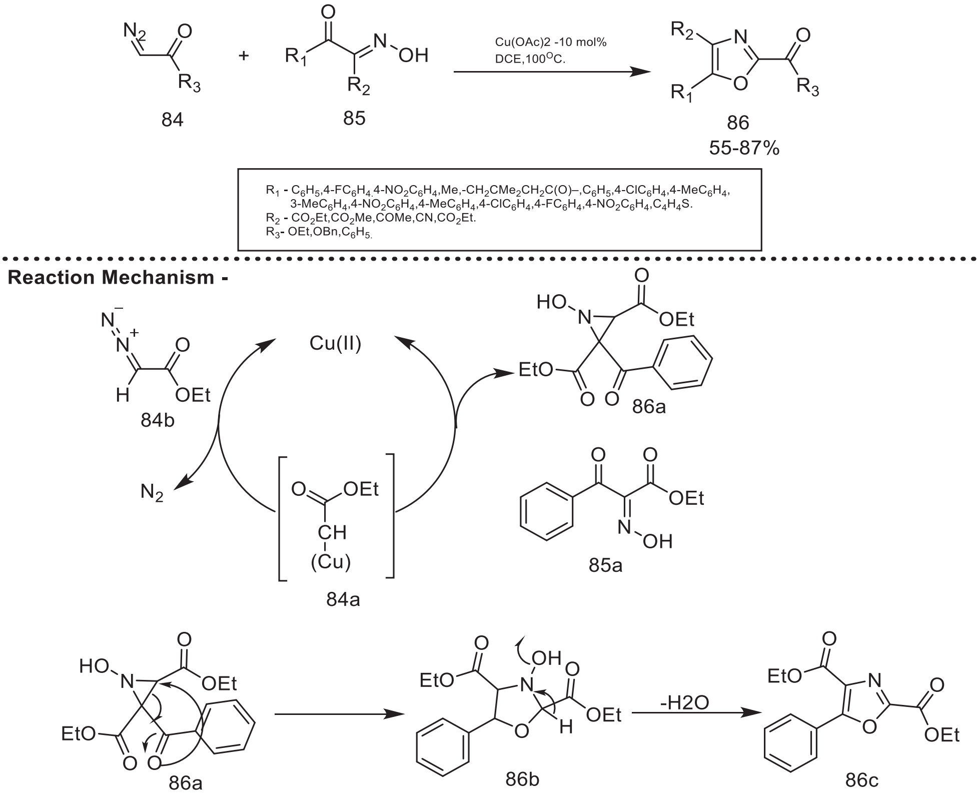
The synthesis of various substituted 1,3-oxazole-based derivatives under metal-dependent reactions is found to be very extensive. This review particularly focused on the recent years (2017–2020) due to the significant progress in the development of



R - Ph,4-MePh,4-FPh,4-ClPh,4-BrPh,4-OMePh,t-BuPh,i-PrPh,4-CF_3Ph,2-MePh, 3-MePh,3,4-MePh,2,6-DifloroPh,napthaline.$C_{11}H_{23}$.
R_1 - E_{Et},E.
R2 - Ph,4-NO_2Ph,E.

Scheme 29. Copper catalyzed synthesis of 1,3-oxazoles using benzyl amine.[29b]

simple yet effective protocols for the synthesis of 1,3-oxazole heterocyclic scaffold. We have also highlighted various protocols that are used and each of their plausible reaction pathways based on the different starting materials used. The use of different starting materials (SM) to develop new protocols does produce a great impact on the application in medicinal chemistry. Here, we noticed that the use of various metals as a catalyst such as nickel, palladium, chromium and copper in one pot synthesis of 1,3-oxazole based derivatives produced excellent yields when used with SM such as nitrile, ethyne and fused oxazoles. In addition, the use of metal nano-catalysts such as copper with starting materials such as benzyl amine and fused oxazole also gave rise to excellent yields of the desired product. In one particular case, the use of manganese attracts high interest due to the less expense of the metal itself as well as the wide use of various aromatic and heteroaromatic substituents in this particular reaction to yield good desired product. Even though there are considerable advancement can be noticed with metal protocols, particular reactivity and selectivity of these metals still needed to be explored for future applications and development in medicinal chemistry.



Scheme 30. Copper catalyzed synthesis of 1,3-oxazoles using N2 containing molecules.[29e]

In conclusion, this review on the synthetic methodology of 1,3-oxazole will assure organic researchers to identify the challenges in the described methods, overcome the drawbacks and improvement in the advancing catalysts and starting materials.

Funding

The authors would like to thank the College of Health Science (CHS), University of KwaZulu-Natal, Durban for the financial support. SRS thanks Nandhini KP for the help. R. Karpoormath is also thankful to National Research Foundation- South Africa (NRF-SA) for funding [Grant No. 103728, 112079 and 129247].

ORCID

Rajshekhar Karpoormath http://orcid.org/0000-0002-1247-5754

References

[1] Purchase, R.; Hanson, J. R. *Sci. Prog.* **2015**, *98*, 219–229. DOI: 10.3184/003685015X14364588807198.

[2] Arora, P.; Arora, V.; Lamba, H. S.; Wadhwa, D. *Int. J Pharm. Sci. Res.* **2012**, *3*, 2947–2954.

[3] Pozharskii, A. F.; Soldatenkov, A. T.; Katritzky, A. R. *Heterocycles in Life and Society: An Introduction to Heterocyclic Chemistry, Biochemistry and Applications*, 2nd ed.; Wiley: Chichester, West Sussex, 2011.

[4] Ladenburg, A. *Ber. Dtsch. Chem. Ges.* **1876**, *9*, 1524–1530. DOI: 10.1002/cber.187600902138.

[5] Hantzsch, A.; Weber, J. H. *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 3118–3132. DOI: 10.1002/cber.188702002200.

[6] (a) Cornforth, J. W.; Cornforth, R. H. *J. Chem. Soc.* **1947**,*24*, 96–102. DOI: 10.1039/jr9470000096. (b) Cornforth, J. W.; Cornforth, R. H. *J. Chem. Soc.* **1949**,*218*, 1028–1030. DOI: 10.1039/jr9490001028.

[7] Kondrat'eva, G. Y. *Russ. Chem. Bull.* **1959**, *8*, 457–462. DOI: 10.1007/BF00917701.

[8] (a) Haustedt, L. O.; Hartung, I. V.; Hoffmann, H. M. R. *Angew. Chem. Int. Ed. Engl.* **2003**, *42*, 2711–2716. DOI: 10.1002/anie.200301643. (b) Mhlongo, J. T.; Brasil, E.; de la Torre, B. G.; Albericio, F. *Mar. Drugs* **2020**, *18*, 203–228. DOI: 10.3390/md18040203. (c) Zheng, X.; Liu, W.; Zhang, D. *Molecules* **2020**, *25*, 1594. DOI: 10.3390/molecules25071594. (d) Turchi, I. J. *Ind. Eng. Chem. Prod. Res. Dev.* **1981**, *20*, 32–76. DOI: 10.1021/i300001a005.

[9] Jacobs, H. M.; Burke, B. A. In *The Alkaloids: Chemistry and Pharmacology*; Brossi, A., Ed.; Academic Press: Orlando, FL, 1989; Vol. 35, pp 259–310.

[10] Swellmeen, L. *Der Pharma Chemica* **2016**, *8*, 269–286.

[11] Kaspady, M.; Venugopala, K.; Raju, K.; Rao, G. *LDDD* **2009**, *6*, 21–28. DOI: 10.2174/157018009787158481.

[12] (a) Phatangare, K.; Borse, B.; Padalkar, V.; Patil, V.; Gupta, V.; Umape, P.; Sekar, N. *J. Chem. Sci.* **2013**, *125*, 141–151. DOI: 10.1007/s12039-012-0324-3. (b) Carmeli, S.; Moore, R. E.; Patterson, G. M. L.; Corbett, T. H.; Valeriote, F. A. *J. Am. Chem. Soc.* **1990**, *112*, 8195–8197. DOI: 10.1021/ja00178a070.

[13] Eswaran, S.; Adhikari, A. V.; Kumar, R. A. *Eur. J. Med. Chem.* **2010**, *45*, 957–966. DOI: 10.1016/j.ejmech.2009.11.036.

[14] Uckun, F. *Curr. Pharm. Des.* **2001**, *7*, 1627–1639. DOI: 10.2174/1381612013397177.

[15] Elmegeed, G. A.; Baiuomy, A. R.; Abdelhalim, M. M.; Hana, H. Y. *Arch. Pharm.* **2010**, *343*, 261–267. DOI: 10.1002/ardp.200900244.

[16] Jin, Z. *Nat. Prod. Rep.* **2011**, *28*, 1143–1191. DOI: 10.1039/c0np00074d.

[17] (a) Kachaeva, M. V.; Hodyna, D. M.; Obernikhina, N. V.; Pilyo, S. G.; Kovalenko, Y. S.; Prokopenko, V. M.; Kachkovsky, O. D.; Brovarets, V. S. *J. Heterocyclic Chem.* **2019**, *56*, 3122–3134. DOI: 10.1002/jhet.3711. (b) Semenyuta, I.; Kovalishyn, V.; Tanchuk, V.; Pilyo, S.; Zyabrev, V.; Blagodatnyy, V.; Trokhimenko, O.; Brovarets, V.; Metelytsia, L. *Comput. Biol. Chem.* **2016**, *65*, 8–15. DOI: 10.1016/j.compbiolchem.2016.09.012. (c) Jin, Z. *Nat. Prod. Rep.* **2009**, *26*, 382–445. DOI: 10.1039/b718045b. (d)Siddiquee, K. A. Z.; Gunning, P. T.; Glenn, M.; Katt, W. P.; Zhang, S.; Schrock, C.; Schroeck, C.; Sebti, S. M.; Jove, R.; Hamilton, A. D.; Turkson, J. *ACS Chem. Biol.* **2007**, *2*, 787–798. DOI: 10.1021/cb7001973. (e) Jin, Z. *Nat. Prod. Rep.* **2005**, *22*, 196–229. DOI: 10.1039/b316104h. (f) Jin, Z. *Nat. Prod. Rep.* **2003**, *20*, 584–605. DOI: 10.1039/b304142p. (g) Roesener, J. A.; Scheuer, P. J. *J. Am. Chem. Soc.* **1986**, *108*, 846–847. DOI: 10.1021/ja00264a052. (h)Takahashi, K.; Kawabata, M.; Uemura, D.; Iwadare, S.; Mitomo, R.; Nakano, F.; Matsuzaki, A. *Tetrahedron Lett.* **1985**, *26*, 1077–1078. DOI: 10.1016/S0040-4039(00)98516-2.

[18] (a) Bénardeau, A.; Benz, J.; Binggeli, A.; Blum, D.; Boehringer, M.; Grether, U.; Hilpert, H.; Kuhn, B.; Märki, H. P.; Meyer, M.; et al. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2468–2473., DOI: 10.1016/j.bmcl.2009.03.036. (b) Kakkar, S.; Kumar, S.; Lim, S. M.; Ramasamy, K.; Mani, V.; Shah, S. A. A.; Narasimhan, B. *Chem. Cent. J.* **2018**, *12*, 130. DOI: 10.1186/s13065-018-0499-x.

[19] Heller, B.; Tarricone, R. *Curr. Med. Res. Opin.* **2004**, *20*, 1279–1290. DOI: 10.1185/030079904125004411.

[20] Velluti, F.; Mosconi, N.; Acevedo, A.; Borthagaray, G.; Castiglioni, J.; Faccio, R.; Back, D. F.; Moyna, G.; Rizzotto, M.; Torre, M. H. *J. Inorg. Biochem.* **2014**, *141*, 58–69. DOI: 10.1016/j.jinorgbio.2014.08.007.

[21] Kim, M. Y.; Vankayalapati, H.; Shin-Ya, K.; Wierzba, K.; Hurley, L. H. *J. Am. Chem. Soc.* **2002**, *124*, 2098–2099. DOI: 10.1021/ja017308q.

[22] Searle, P. A.; Molinski, T. F. *J. Am. Chem. Soc.* **1995**, *117*, 8126–8131. DOI: 10.1021/ja00136a009.

[23] Lindquist, N.; Fenical, W.; Van Duyne, G. D.; Clardy, J. *J. Am. Chem. Soc.* **1991**, *113*, 2303–2304. DOI: 10.1021/ja00006a060.

[24] Mittal, V. *Manufacturing of Nanocomposites with Engineering Plastics*; Woodhead Publishing: Cambridge, UK, 2015; pp 1–13.

[25] Banerji, B.; Adhikary, S.; Majumder, L.; Ghosh, S. *Asian J. Org. Chem.* **2019**, *8*, 514–525. DOI: 10.1002/ajoc.201800742.

[26] (a) Dhara, M. G.; Banerjee, S. *Prog. Polym. Sci.* **2010**, *35*, 1022–1077. DOI: 10.1016/j.progpolymsci.2010.04.003. (b) Maier, G.; Nuyken, O.; Hecht, R. *Makromolekulare Chemie. Macromolecular Symposia* **1993**, *75*, 205–210. DOI: 10.1002/masy.19930750120.

[27] Lamberth, C. *J. Heterocyclic Chem.* **2018**, *55*, 2035–2045. DOI: 10.1002/jhet.3252.

[28] Zhang, W.; Yu, W.; Yan, Q.; Liu, Z.; Zhang, Y. *Org. Chem. Front.* **2017**, *4*, 2428–2432. DOI: 10.1039/C7QO00517B.

[29] (a) Qi, C.; Peng, Y.; Wang, L.; Ren, Y.; Jiang, H. *J. Org. Chem.* **2018**, *83*, 11926–11935. DOI: 10.1021/acs.joc.8b01822. (b) Pan, J.; Li, X.; Qiu, X.; Luo, X.; Jiao, N. *Org. Lett.* **2018**, *20*, 2762–2765. DOI: 10.1021/acs.orglett.8b00992. (c) Xiao, F.; Yuan, S.; Huang, H.; Zhang, F.; Deng, G.-J. *Org. Lett.* **2019**, *21*, 8533–8536. DOI: 10.1021/acs.orglett.9b02934. (d) Xu, C.; Qin, M.; Yi, J.; Wang, Y.; Chen, Y.; Zhang, B.; Zhao, Y.; Gong, P. *RSC Adv.* **2017**, *7*, 24643–24646. DOI: 10.1039/C7RA01983A. (e) Nagaraju, A.; Sandeep, K.; Kumara Swamy, K. C. *Tetrahedron Lett.* **2018**, *59*, 2238–2242. DOI: 10.1016/j.tetlet.2018.05.004. (f) Luo, Z.; Wu, H.; Li, Y.; Chen, Y.; Nie, J.; Lu, S.; Zhu, Y.; Zeng, Z. *Adv. Synth. Catal.* **2019**, *361*, 4117–4125. DOI: 10.1002/adsc.201900485. (g) Wei, L.; You, S.; Tuo, Y.; Cai, M. *Synthesis* **2019**, *51*, 3091–3100. DOI: 10.1055/s-0037-1610710.

[30] (a) Mali, J.; Takale, B.; Telvekar, V. *RSC Adv.* **2017**, *7*, 2231–2235. DOI: 10.1039/C6RA25857C. (b) Keivanloo, A.; Abbaspour, S.; Bakherad, M.; Notash, B. *ChemistrySelect* **2019**, *4*, 1366–1370. DOI: 10.1002/slct.201803653. (c) Zhang, D.; Song, H.; Cheng, N.; Liao, W.-W. *Org. Lett.* **2019**, *21*, 2745–2749. DOI: 10.1021/acs.orglett.9b00700.

[31] (a) Dubovtsev, A. Y.; Dar'in, D. V.; Kukushkin, V. Y. *Adv. Synth. Catal.* **2019**, *361*, 2926–2935. DOI: 10.1002/adsc.201900097. (b) Xu, Y.; Wang, Q.; Wu, Y.; Zeng, Z.; Rudolph, M.; Hashmi, A. S. K. *Adv. Synth. Catal.* **2019**, *361*, 2309–2314. DOI: 10.1002/adsc.201801386. (c) An, H.; Mai, S.; Xuan, Q.; Zhou, Y.; Song, Q. *J. Org. Chem.* **2019**, *84*, 401–408. DOI: 10.1021/acs.joc.8b02334. (d) Yang, W.; Zhang, R.; Yi, F.; Cai, M. *J. Org. Chem.* **2017**, *82*, 5204–5211. DOI: 10.1021/acs.joc.7b00386. (e) Shaikh, A. C.; Ranade, D. S.; Rajamohanan, P. R.; Kulkarni, P. P.; Patil, N. T. *Angew. Chem. Int. Ed. Engl.* **2017**, *56*, 757–761. DOI: 10.1002/anie.201609335.

[32] Liu, J.; Wen, Y.; He, F.; Gao, L.; Gao, L.; Wang, J.; Wang, X.; Zhang, Y.; Hu, L. *Org. Chem. Front.* **2019**, *6*, 846–851. DOI: 10.1039/C8QO01425F.

[33] Liu, J.-Q.; Shen, X.; Shatskiy, A.; Zhou, E.; Kärkäs, M.; Wang, X.-S. *ChemCatChem* **2019**, *11*, 4272–4275. DOI: 10.1002/cctc.201900965.

[34] Li, P.; Zhao, J.; Li, X.; Li, F. *J. Org. Chem.* **2017**, *82*, 4569–4577. DOI: 10.1021/acs.joc.7b00112.

[35] Zheng, J.-F.; Hu, X.-N.; Xu, Z.; Cai, D.-C.; Shen, T.-L.; Huang, P.-Q. *J. Org. Chem.* **2017**, *82*, 9693–9703. DOI: 10.1021/acs.joc.7b01768.

[36] Hsieh, M.-T.; Lee, K.-H.; Kuo, S.-C.; Lin, H.-C. *Adv. Synth. Catal.* **2018**, *360*, 1605–1610. DOI: 10.1002/adsc.201701581.

[37] Hu, X-n.; Shen, T.-L.; Cai, D.-C.; Zheng, J.-F.; Huang, P.-Q. *Org. Chem. Front.* **2018**, *5*, 2051–2056. DOI: 10.1039/C8QO00312B.

[38] Niu, B.; Liu, R.; Wei, Y.; Shi, M. *Org. Chem. Front.* **2018**, *5*, 1466–1470. DOI: 10.1039/C8QO00125A.

[39] Dong, J.-J.; Zhang, S.-L. *Adv. Synth. Catal.* **2020**, *362*, 795–800. DOI: 10.1002/adsc.201901405.

[40] Nan, G.-M.; Li, X.; Yao, T.-Y.; Yan, T.-X.; Wen, L.-R.; Li, M. *Org. Biomol. Chem.* **2020**, *18*, 1780–1784. DOI: 10.1039/c9ob02651g.

[41] Wang, Q.; Hoffmann, S.; Schießl, J.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. *Eur. J. Org. Chem.* **2020**, *2020*, 2384–2388. DOI: 10.1002/ejoc.201900699.

[42] Li, D.; Yang, D.; Wang, L.; Liu, X.; Wang, K.; Wang, J.; Wang, P.; Liu, Y.; Zhu, H.; Wang, R. *Chem. Eur. J.* **2017**, *23*, 6974–6978. DOI: 10.1002/chem.201700970.

[43] Dai, L.; Yu, S.; Xiong, W.; Chen, Z.; Xu, T.; Shao, Y.; Chen, J. *Adv. Synth. Catal.* **2020**, *362*, 1893–1898. DOI: 10.1002/adsc.202000125.

[44] Mallick, R.; Prabagar, B.; Sahoo, A. *J. Org. Chem.* **2017**, *82*, 10583–10594. DOI: 10.1021/acs.joc.7b02124.

[45] Yu, X.; Chen, K.; Wang, Q.; Zhang, W.; Zhu, J. *Chem. Commun. (Camb.)* **2018**, *54*, 1197–1200. DOI: 10.1039/c7cc08611c.

[46] Fan, S.; Tong, T.; Fang, L.; Wu, J.; Li, E.; Kang, H.; Lv, X.; Wang, X. *Tetrahedron Lett.* **2018**, *59*, 1409–1413. DOI: 10.1016/j.tetlet.2018.02.058.

[47] Yoneyama, H.; Oka, N.; Usami, Y.; Harusawa, S. *Tetrahedron Lett.* **2020**, *61*, 151983. DOI: 10.1016/j.tetlet.2020.151983.

[48] Dutta, S.; Sharma, S.; Sharma, A.; Sharma, R. K. *ACS Omega.* **2017**, *2*, 2778–2791. DOI: 10.1021/acsomega.7b00382.