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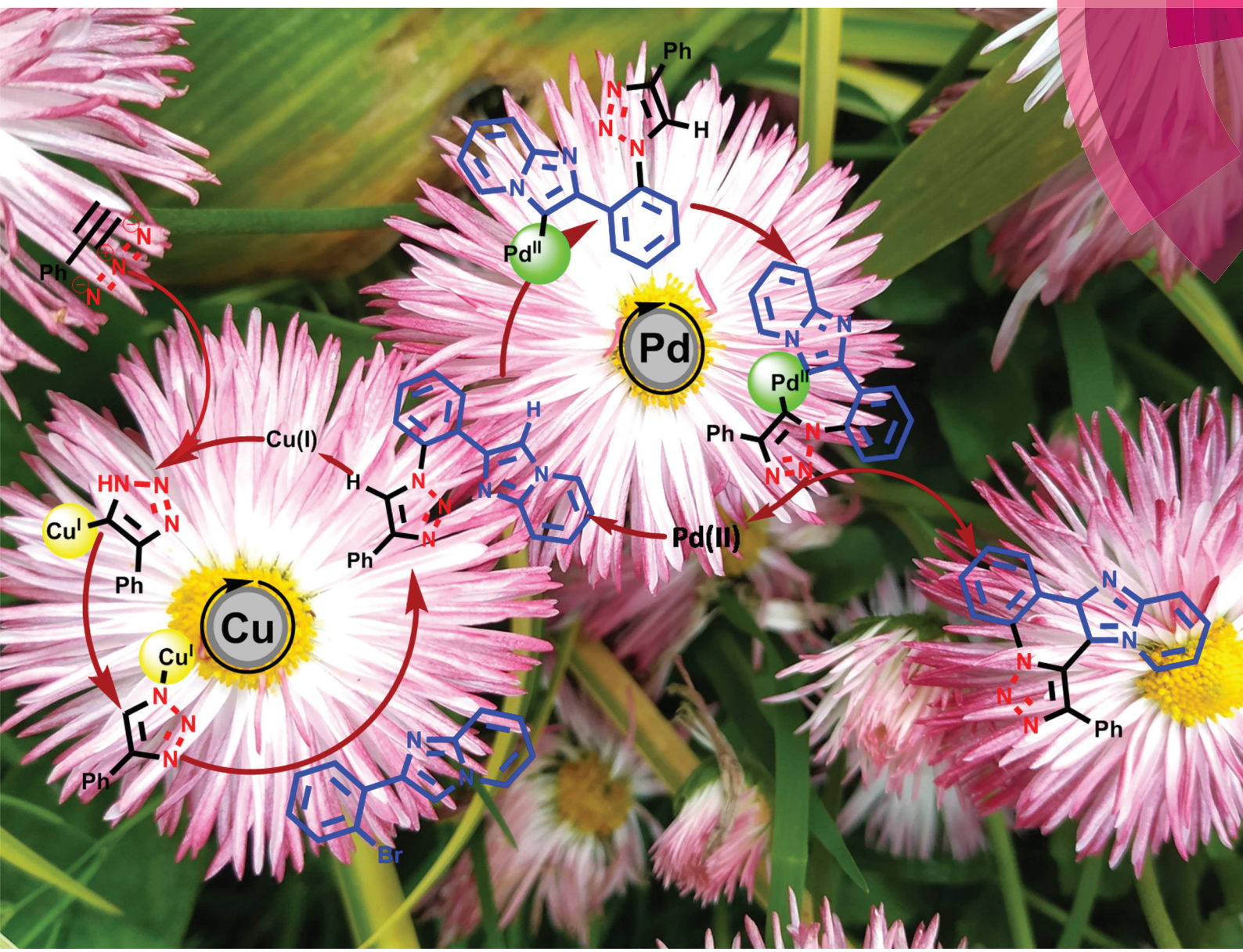

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REVIEW ARTICLE
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REVIEW

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Hetero-bimetallic cooperative catalysis for the synthesis of heteroarenes

Gaurav R. Gupta,[a] Jagrut Shah,[a] Kamlesh S. Vadagaonkar,[a] Aditya G. Lavekar[b] and Anant R. Kapdi *[a]

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Multi-metallic cooperative catalysis has gained a lot of interest in organic synthesis over the past few years exploring various organic transformations. Of all the myriad chemical transformations, multi-metallic cooperative catalysis offers exceptional chemo-, stereo- and regio-selectivities. In recent years, hetero-multi-metallic catalysis has not only been used to synthesise only simpler organic molecules but rather more complex molecules like heteroarenes which include a variety of commercially important molecules. The current review, in this context, emphasises the synthesis of 5- and 6-membered as well as condensed heteroarenes, covering the literature over the last decade. The discussion focusses on the combinations in cooperative catalytic systems in strategies used to achieve selectivity and also highlights the mode of action for the cooperative catalysis leading to the synthesis of a few commercially and biologically relevant heteroarenes. Finally, the review concludes with a brief outlook on the future scope and opportunities in the field of cooperative catalyses and their prospects for providing state-of-the-art solutions for synthetically challenging organic transformations.

1. Introduction

The significance of heterocycles in life and life governing processes has been acknowledged in the literature as an emerging field in the fundamental development of the science of molecules.[1] Today, even a superficial glimpse into the contemporary chemistry as well as biochemistry books discloses the importance of heterocyclic compounds as well as highlights their role in biological processes.[2] In this regard, several well-known heterocycle-based biomolecules including top selling pharmaceuticals and agrochemicals have been listed below (Fig. 1) to highlight the occurrence of heterocycles as important structural motifs in commercially relevant molecules.[3]

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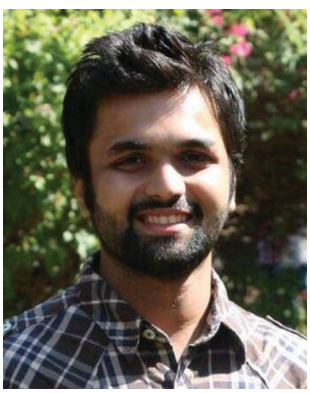
Gaurav R. Gupta

Dr Gaurav R. Gupta, currently a postdoctoral researcher in Dr Anant Kapdi's research group at the Institute of Chemical Technology, Mumbai (India), obtained his PhD degree in Chemistry (2014) from North Maharashtra University, Jalgaon (India) under the guidance of Prof. K. J. Patil. His research mainly focuses on metal mediated synthesis, ionic liquid synthesis, sustainable organic transformations and physico-chemical analysis of the ionic liquids.



Jagrut Shah

Jagrut Shah was born in Mumbai (India) in 1993. He received bachelor's degrees in biotechnology and chemistry in 2014 and 2015, respectively, from Mumbai University.

He then studied organic chemistry and received his master's degree from MSU Baroda in 2017. He joined the research group of Dr Anant Kapdi at ICT Mumbai as a Junior Research Fellow in January 2018 and has been working on multi-metal mediated tandem reactions in nucleoside modification, nanoparticles and colloidal chemistry and photoredox CDC reactions.

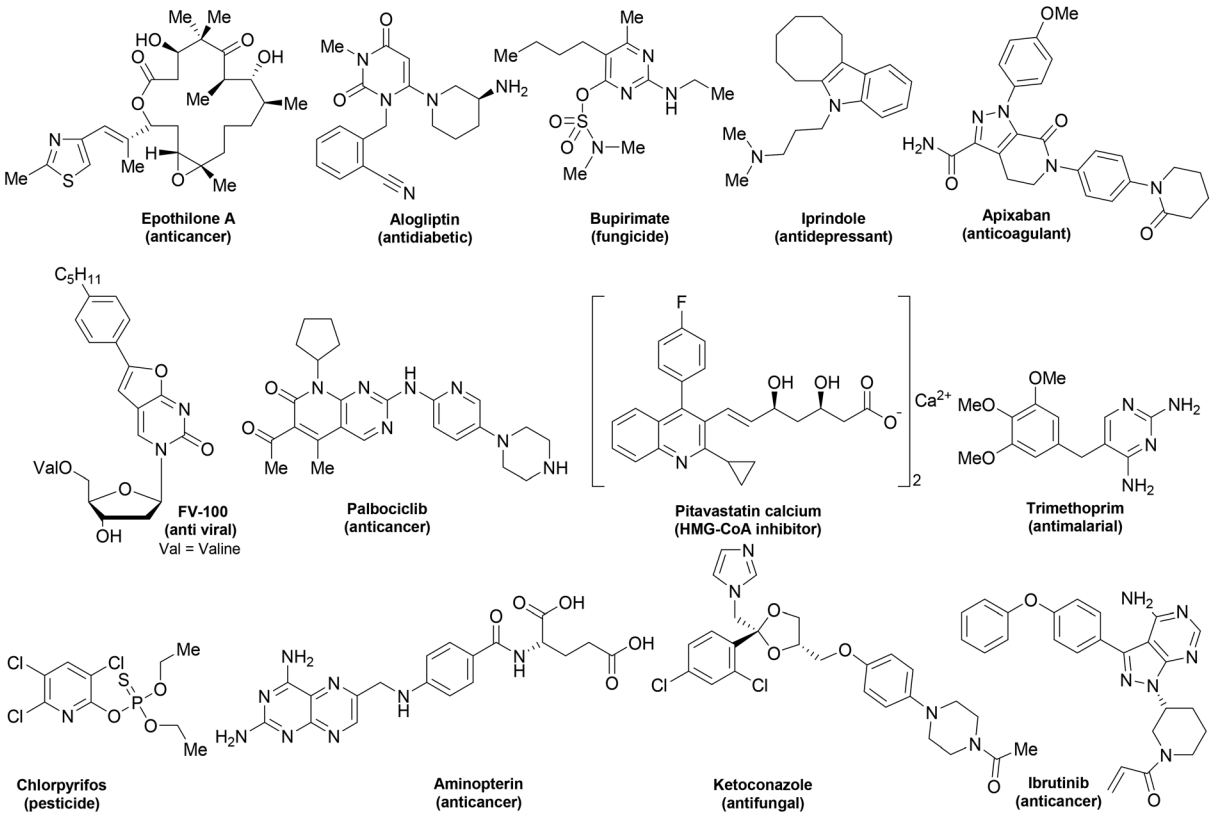


Fig. 1 Heterocyclic structural motifs present in commercially and biologically relevant molecules.

Kamlesh S. Vadagaonkar

Dr Kamlesh S. Vadagaonkar received his master's degree in organic chemistry from the University of Pune in 2006. Subsequently, he worked as a senior research chemist in TCG Life Sciences Pvt. Ltd (formerly Chembiotek Research International Pvt. Ltd), Pune from 2006 to 2010. He completed his PhD degree in February 2018 under the supervision of Prof. Prakash M. Bhate and Dr Atul C. Chaskar at the Institute of Chemical Technology, Mumbai. He has been working as a postdoctoral research associate with Dr Anant R. Kapdi since April 2018. His research focuses on the development of new methodologies for the synthesis of important heterocyclic compounds via *C–H functionalization/activation as well as synthesis of organic materials for optoelectronic applications.*

Aditya G. Lavekar

Dr Aditya G. Lavekar completed his Graduate and Post graduate degree from the Swami Ramanand Teerth Marathwada University, Nanded in 2007 and 2009 respectively. Later he worked as a trainee at the Indian Institute of Chemical Technology, Hyderabad for some brief period. Further he joined as a junior research fellow at the CSIR-Institute of Himalayan Bioresource Technology, Palampur, India and later moved to the CSIR-Central Drug Research Institute, Lucknow, India from where he earned his doctorate in 2018 with affiliation to the Academy of Scientific and Innovative Research, New Delhi under the supervision of Dr Arun K. Sinha. Currently he is working in industry. His research interests are transition-metal-catalyzed one-pot transformations, methodology development for the synthesis of important heterocyclic compounds via *C–H functionalization and medicinal chemistry.*

The enormous efficiency of bimetallic catalysts in natural processes such as the operation of binuclear metalloenzymes, DNA polymerases, phosphatases and ureases in life governing processes has been attributed towards the cooperative effect exerted by two metal centers.[4] Therefore, on the grounds of the principles of dinuclear metallo-enzymes, the utilisation of synergistic cooperation of two metal centers for artificial (homo-bimetallic or hetero-bimetallic) catalysts in order to assess their catalytic potential (simultaneously or consecutively) has been advanced by the scientific community.[5]

Metal-catalysed coupling processes and transition metal-catalysed reactions in particular belong to the most powerful and industrially applied reactions in the chemical and pharmaceutical industries.[6] Furthermore, the ability of transition metal catalysts to perform consonant operations with other catalytic modes in a fully complementary fashion makes them ideal for cooperative transformations. Cooperative catalysis by metal catalysts together with organo-catalysts,[7] photoredox catalysts[8] and within molecular organic frameworks[9] has been well documented throughout the recent decade. The multi-metal catalysis concept consists of two or more metal catalysts involving two independent catalytic cycles performing in concert or in a relay fashion in the same flask. Often the presence of a second transition metal magnifies the impact of synthetic transformation that may not be possible with either of the catalysts alone and may lead to the achievement of many difficult or previously unachievable transformations, which can constitute a revolution in reaction engineering.

The prime objective of this review is therefore to highlight the development in multi-metallic catalytic processes for the sustainable synthesis of heteroaromatic scaffolds by surveying representative examples up to summer 2018. Furthermore, the present review will not only provide a compendium for students and researchers who are dedicated towards the development of organic synthesis, but also stimulate interest in relay/cooperative multi-metallic catalysis as the potential candidate for highly specific syntheses. The review is divided into sections based on the ring size of heteroatoms as well as the number of heteroatoms present in the ring.

Anant R. Kapdi

Dr Anant R. Kapdi studied chemistry at the University of Mumbai (MSc 2002) and York (MSc 2005; Prof. Ian J. S. Fairlamb). He completed his PhD in 2008 under the supervision of Prof. Fairlamb at the University of York, UK before starting postdoctoral work in the research group of Prof. Lutz Ackermann at the Georg-August Universit at Gottingen as an Alexander von Humboldt fellow. After returning to India in 2010, he was successful in securing the prestigious DST Fast Track fellowship and DST Inspire faculty award, C. B. Murarka best Assistant professor award, Fellow of Maharashtra Academy of Sciences and former Associate Editor of RSC Advances. He is currently an UGC-FRP Assistant Professor in the Institute of Chemical Technology, Mumbai. The central theme of his research is related to the application of palladium catalysis for sustainable synthesis of important heterocyclic molecules including pharmaceutical drugs as well as the modification of several bio-active molecules.

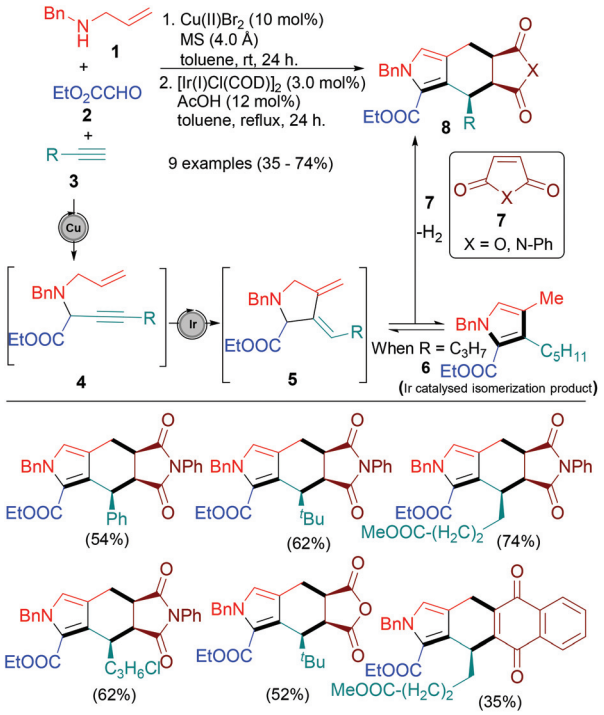
2. Five membered heterocycles

The naturally occurring essential biomolecules are classified as primary and secondary metabolites, and are biosynthesised by plants and animals. The majority of these metabolites are composed of heterocycles, and are considered as fundamental materials associated with life, such as the iron complex heme in blood and the magnesium complex of chlorophyll in plants as is the case with DNA and RNA with paired bases constituting heterocycles (purines and pyrimidines). Amino acids play an important role in numerous biological processes in living beings and are also exploited as suitable building blocks for the biogenesis of a large number of molecules of biological relevance. Out of the 20 essential amino acids, imidazole-cored histidine and pyrrolidine-cored proline bear heterocyclic moieties. State-of-the-art environmentally benign methodologies for the synthesis of heterocycles have always been appreciated from industry as well as academia for their potential impact on living organisms. The following sections explore the development of the catalytic potentials of multi-metallic catalysts for the chemo-, regio-, and stereo-selective syntheses of several new and/or important heterocycles.

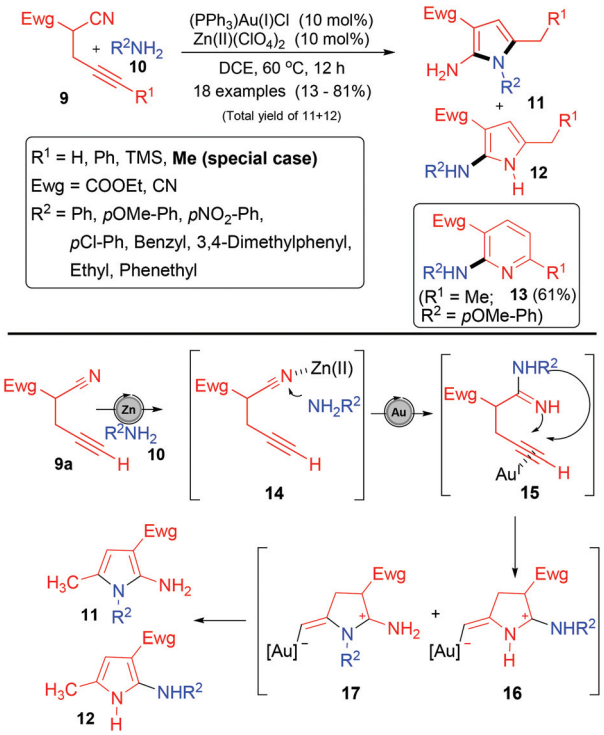
2.1. One heteroatom

Pyrrole motifs are considered as an important class of nitrogen containing heterocycles constituting a main structure as identified in numerous biologically as well as commercially relevant compounds. The pyrrole nucleus is a prolific source of interesting chemical reactions with pyrrole derivatives found in plentiful biologically significant compounds such as chlorophyll, hemoglobin, vitamin B12 and alkaloids, which are actively contributing to the processes of biotransformation of the solar energy, oxygen transport, and other essential life-sustaining transformations.[10] Pyrroles are intensively employed in the synthesis of natural compounds and building blocks for drug design[11] *e.g.* pyrrole containing anti-cancer, anti-biotic CC-1065,[12] or atorvastatin, one of the pyrrole-based best-selling drugs in the history of medicine and pharmaceuticals, is used for lowering the blood cholesterol level, and contains a 2,3-diphenylpyrrole unit.[13]

Even though simple pyrrole analogues continue to be isolated from natural resources, the synthesis of substituted pyrrole precursors still largely depends on the classical Paal–Knorr synthesis. Metal-based catalytic multi-component coupling protocols have recently attracted a lot of attention as a sus-



Scheme 1 Cu-Catalysed multicomponent coupling synthesis of glycinate-tethered 1,6-enynes and Ir-catalysed cyclo-isomerisation affording fused pyrrole-2-carboxylates.



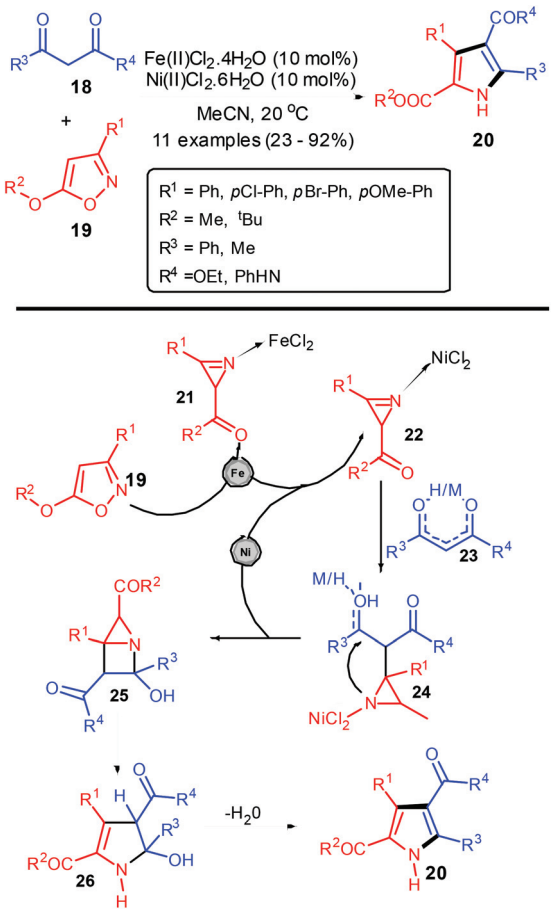
Scheme 2 Au(I)/Zn(II)-Catalysed sequential inter/intramolecular hydroamination reaction of 4-yne-nitriles with amines for the synthesis of 2-aminopyrroles.

tainable and environmentally benign alternative. The convergent synthesis of highly substituted pyrrole analogues along with the principles of green chemistry could also be achieved as a part of this synthetic strategy. In this context, the ability of relay catalysis to commence cyclo-isomerisations has allowed for highly substituted pyrrole frameworks to be furnished under mild reaction conditions.[14] The copper-mediated activation of (C–H) and (N–H) bonds for the synthesis of an exocyclic diene as intermediate **5** was made possible *via* the formation of intermediate **4** by reacting *N*-benzylallylamine **1**, ethyl glyoxalate **2** and terminal alkynes **3** under mild reaction conditions. The dehydrogenative aromatisation of **5** *via* (C–H) activation of 3,4-dehydroproline **7** with Ir species leads to the formation of pyrrole-2-carboxylates **5** in good to moderate yields (Scheme 1). Several examples of the pyrrole-containing tricyclic ring systems were obtained with the developed protocol.

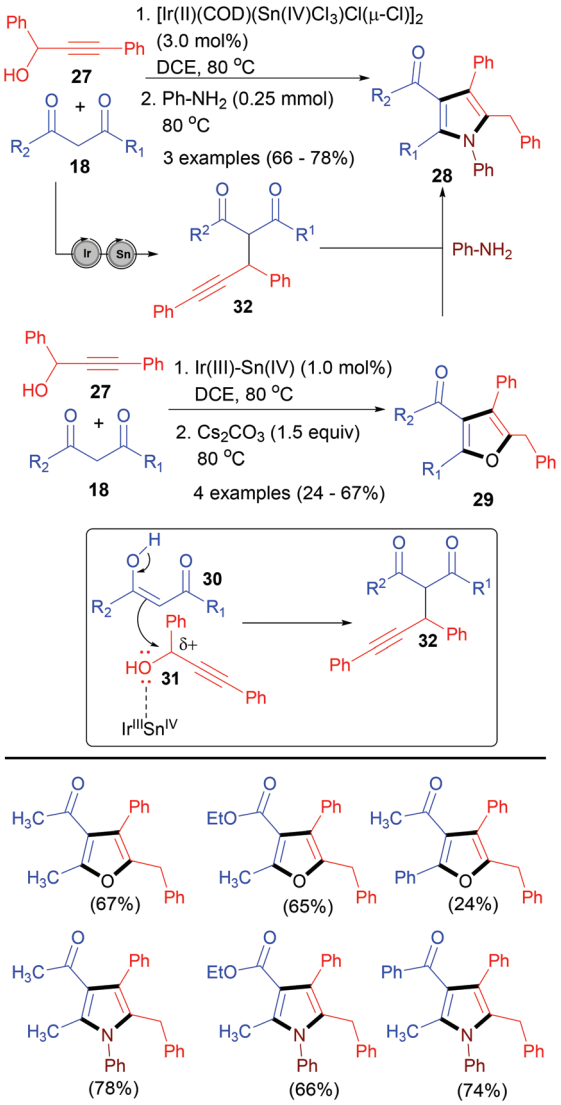
The ability of Zn salts to activate CO and CN functionalities[15] was explored recently towards the one-pot synthesis of derivatives of 2-aminopyrroles **11** and **12** as well as pyridine **13** [16] from yne–nitriles **9** and amines **10** *via* the *exo*-dig cyclisation process in the synergistic presence of gold (Scheme 2). A wide variety of substituted amines **10**, ranging from aliphatic to aromatic (except amines with electron withdrawing groups), were reacted with **9** to afford **11** and **12** in mixtures, with **11** in greater percentage. Furthermore, the scope of the present *exo*-dig cyclisation process was examined for the EWG to be a nitrile group resulting in the same mixtures. However, in the case of methyl substituted internal alkynes, the reaction yielded pyridine **13** as the final product possibly due to *endo*-dig cyclisation.

Recently, Galenko *et al.*[17] investigated the suitability of a Fe/Ni relay catalyst system for the conversion of asymmetric 1,3-diketones **18** and 5-alkoxy- or 5-aminoisoxazoles **10** into the substituted pyrrole framework **20** *via* the formation of aziridines **21** and **22** as intermediates (Scheme 3). Inspired by the experimental results, the authors studied the compatibility of the reaction conditions with different functionalities present in **9** and **10**. The results of the study showed that good to moderate yields of the corresponding products could be achieved using the Fe/Ni relay catalyst system, with regio-selectivity. However, their attempts to synthesise pyrroles failed as lower yields were obtained at high temperature while using $FeCl_2$ as the sole catalyst. This disappointing result, however, highlights the importance of Ni in the Fe/Ni relay catalytic system.

The chemistry of furan was pioneered by Scheele in 1780 when the first furan derivative, furan-2-carboxylic acid or 2-furoic acid, was obtained from the process of dry distillation of mucic acid. Pine wood is the natural source of furan, and furan was also successfully isolated from pine wood in 1870. Currently, tetrahydrofuran as an analogue of furan has found wide use as a solvent for numerous organic transformations. In general, a gas-phase decarbonylation of furan-2-carbaldehyde, dehydration of aldoses or ketoses, Paal–Knorr synthesis, photochemical cyclisation, cyclisation of sulfur and phosphorus ylides, and Feist–Benary synthesis are common practices routinely performed in laboratories for the synthesis of



Scheme 3 Fe/Ni relay catalysis for the conversion of isoxazoles to highly substituted pyrroles.

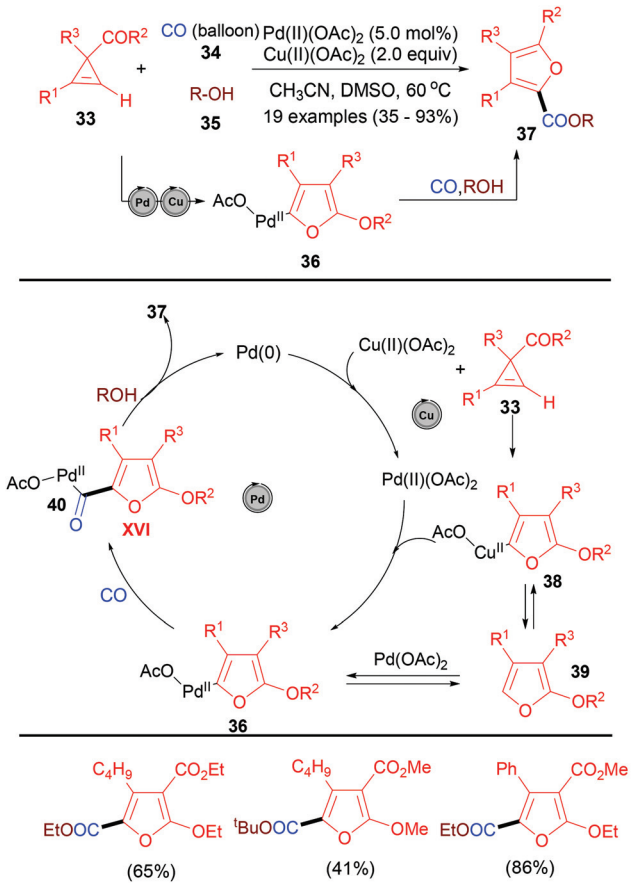


Scheme 4 Synthesis of substituted pyrroles and furans from the derivatives of 1,3-dicarbonyl compounds using Ir/Sn bimetallic catalysts.

furan derivatives on the academic and commercial scale.[18] The synthesis of tetra-substituted furans is still a challenging synthetic quest for synthetic organic chemists.

Recently, the synthesis of polycyclic furan scaffolds *via* cyclisation/cyclo-addition reactions of yne–enones in the presence of a transition-metal catalyst has been reported in the literature.[19] However, the development of an elegant synthetic protocol for the synthesis of tetra-substituted furan compounds with a high order of selectivity, such as chemo- and regio-, from easily accessible starting materials is still missing and is in urgent need of scientific attention. The emergence of cooperative catalysis as a front-runner in the synthesis of substituted pyrroles **28** and furans **29** was described by Chatterjee *et al.*[20] (Scheme 4). The authors explored the catalytic activity of the Ir/Sn bimetallic catalytic system for the propargylation of dicarbonyl compounds **30** with propargyl alcohol **27** to furnish an intermediate **32**. The *exo*-dig cyclo-isomerisation of the resulting intermediate **32** affords pyrroles **28** when treated with amines, while treatment with a base facilitates the formation of substituted furans **29** in moderate to good yields (Scheme 4).

The metal-mediated insertion into carbon monoxide has emerged as an important tool in synthetic organic chemistry with palladium-catalysed carbonylative transformations providing a useful synthetic methodology that has seen tremendous development in recent years with applications ranging from academia to industry.[21] A range of cyclopropenes **33** with diverse electronic properties were allowed to react with carbon monoxide **34** and an alcohol **35** in the presence of Pd/Cu cooperative catalysis conditions furnishing substituted furans **37** (Scheme 5).[22] In addition to this methodology, the synthesis of 2-alkyl-tetrasubstituted furan (35%) and 2,3,5-trisubstituted furan (84%) was also accomplished from the cyclopropene derived from the reaction between ethyl acetoacetate and non-substituted cyclopropane. Interestingly, the commonly used aliphatic alcohols, such as methanol, *n*-butanol, benzyl alcohol and isopropanol, were found to be effective nucleophiles for this transformation. The use of the developed protocol was highlighted by synthesizing substituted furan in measurable yield even with a bulky tertiary butanol. The mechanis-



Scheme 5 Copper–palladium relay strategy for the synthesis of tetra-substituted furans.

tic insights of the present transformation were provided by the authors. Initially, the formation of furan palladium intermediate **36** was carried out by the reaction between cyclopropane **33** and $Cu(OAc)_2$ – **38**, which immediately underwent transmetallation with $Pd(OAc)_2$. The resulting intermediate **36** underwent a series of transformations in a one-pot procedure involving CO insertion, ligand exchange with an alcohol followed by reductive elimination to afford the desired product **37**. Such a procedure accentuated the significance of structure–activity relationships, which play a major role in the development of improved catalyst systems by the combination of different metal precursors.

Subsequently, ground-breaking work from the group of Song and Xu[23a–c] demonstrated that an array of cyclopropenes **41** could be transformed into tetra-substituted furans **43** when treated with acrylates **42** under Pd/Cu relay catalysis. The authors suggested the reaction to commence with the formation of palladium furan-type intermediate **47** and the presence of palladium favouring an intermolecular dehydrogenative Heck reaction between the resulting furan (**46–47**) and an acrylate **42** giving tetra-substituted furans[23a] **43** (Scheme 6) in excellent yields.

Bifurans exhibit an exceptional set of properties similar to that of longer oligofurans and could become a good AIE (aggregation-induced emission) luminogen. The installation of these bifuran units over the organic skeleton could provide an excellent possibility of further developing a rational design of structurally-complex conjugated organic electronic materials. Following the success in using cyclopropenes for the furan synthesis, bifurans were also synthesised under Pd/Cu relay catalytic conditions.[23b]

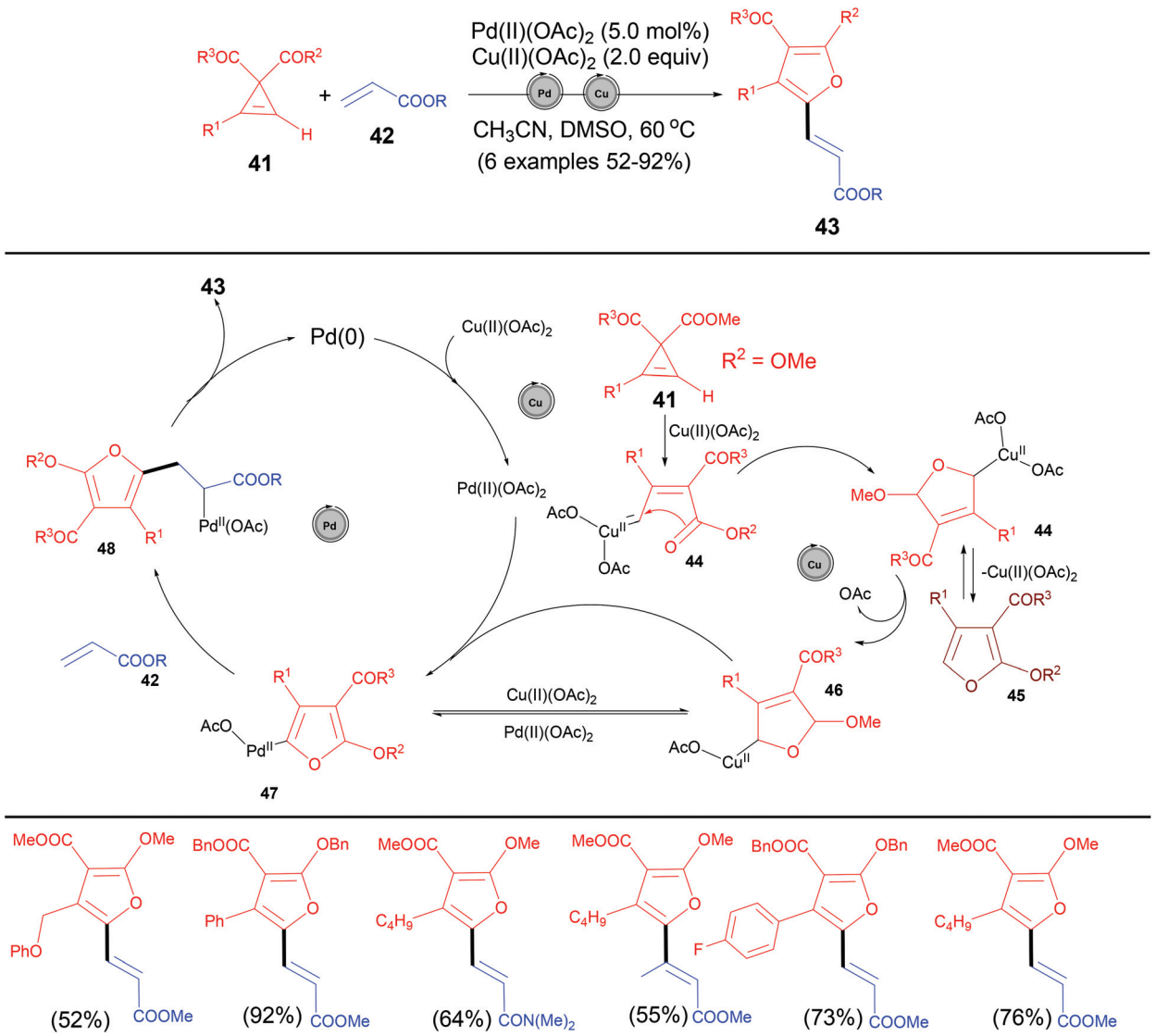
Under the optimised reaction conditions a diverse range of cyclopropenes **49** underwent this transformation to afford the corresponding bifurans **52** in good to excellent yields (Scheme 7).

The Pd/Cu relay catalytic system was also used for the synthesis of *cis*-tetra aryl substituted olefins **57** bearing furan rings, by the reaction between cyclopropenes **54** and alkynes **53** (Scheme 8) proceeding smoothly with high yields of the corresponding products and excellent selectivity highlighting the use of the protocol.[23c] The cooperative effect exerted by the catalyst system was analysed by performing reactions with copper in the absence of palladium as well as with palladium in the absence of copper. The experimental data revealed that the former leads to the formation of tri-substituted furan, while the latter provides no product formation during the course of the reaction.

After the finalisation of the reaction conditions, authors performed a systematic study for the generalisation of the strategy towards the synthesis of tetra-substituted olefins **57** from a wide variety of both aliphatic and aromatic ring substituted cyclopropenes **54**. A variety of symmetric as well as asymmetric disubstituted acetylenes **53** (with both electron rich and withdrawing substituents) as coupling partners were accommodated, thus generating the targeted products in good to moderate yields.

Nucleoside analogues are privileged biological systems known for their spin-active and fluorescent labelling capabilities and their ability to form DNA duplex and triplex structures.

Furo-fused nucleoside analogues have been found to target the Varicella Zoster Virus (VZV) by selectively inhibiting its replication.[24] Based on the pioneering studies by Robins *et al.*[25] the regio-selective synthesis of bicyclic nucleosides predominantly makes use of copper-catalysed 5-*endo*-dig-cyclisation reactions of unprotected 5-alkynyluridines. Pd/Cu-Relay catalysed direct cyclisation of 5-iodo-2′-deoxyuridine **58** could also be accomplished with various alkynes **59** as (Scheme 9) the coupling partner which was first reported by Fresneau *et al.*[26a] To probe the scope of the present strategy, different aromatic alkynes decorated with electron-rich substituents were employed affording the corresponding products **64** in moderate to good yields, while no optimal product formation was observed with electron-withdrawing groups. Subsequently, Kapdi *et al.* also reported a sequential Cu-free Sonogashira reaction followed by Pd/Cu cyclisation for obtaining highly active furo-fused nucleosides including **FV-100, an anti-HSV agent**.[26b] Similarly, cytidine can be used to synthesize the corresponding indoles (with potential biological activities) using the Pd–Au relay system which is yet to be reported.



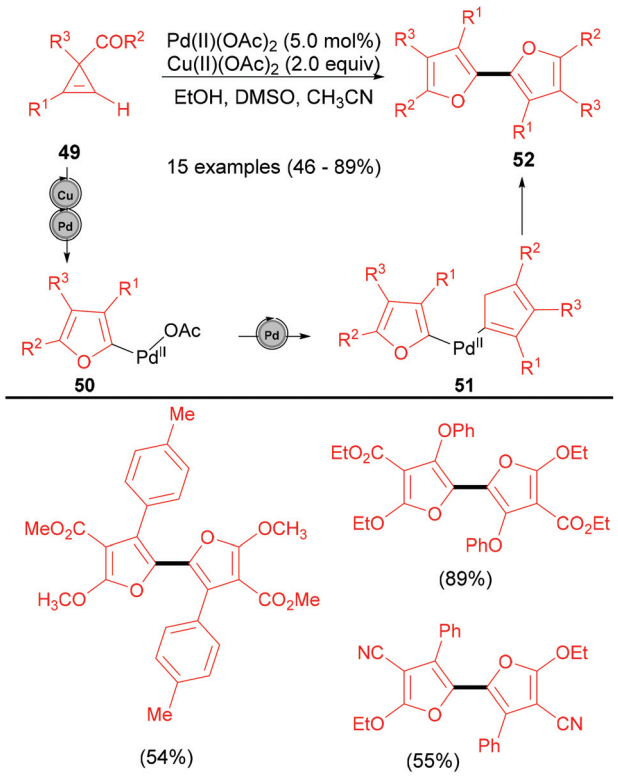
Scheme 6 Pd/Cu relay catalysis in the synthesis of substituted furans *via* the intermolecular dehydrogenative Heck reaction of cyclopropenes.

2.2. Two heteroatoms

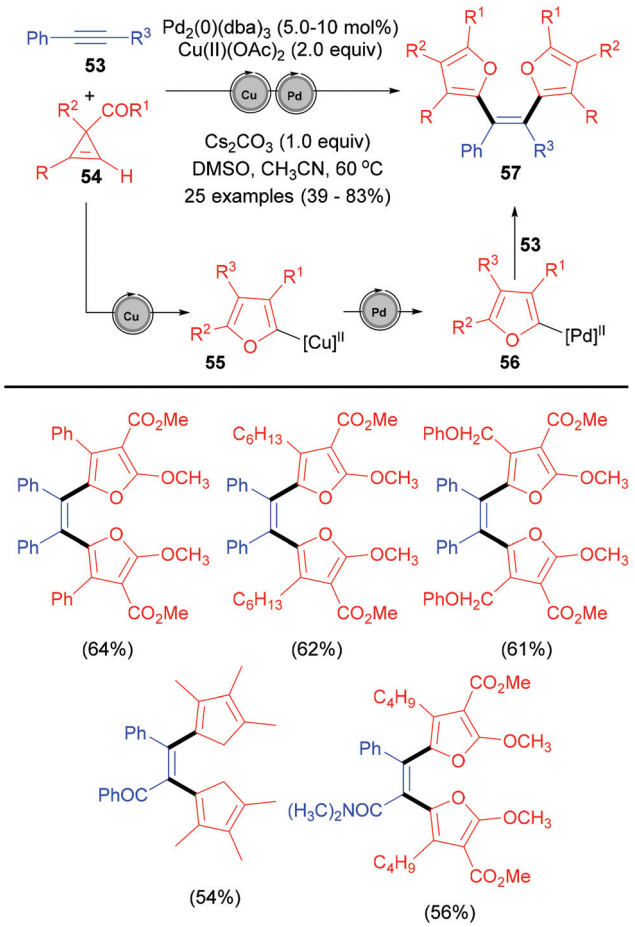
Pyrazoles are structural motifs with only rare occurrence in nature. However, these structural motifs have been extensively explored as pesticides in crop protection and also find applications as analgesic, anti-inflammatory, sedative, and antipyretic drugs and exhibit anti-spasmodic activity. In coordination chemistry, these heterocycles are well-known pluripotent ligands, and are used as optical brighteners and additives in detergents, as UV-stabilisers for polystyrene and as highly selective fluorescence sensors.[27] It is therefore of great interest for synthetic chemists to explore the possibility of developing efficient synthetic procedures to access these privileged scaffolds.

To address this issue, Denißen *et al.*[28] proposed a convenient and highly efficient Pd/Cu relay catalysed microwave-assisted process for the synthesis of biaryl substituted pyrazoles **70** through the formation of an alkyne **69** as an intermediate obtained *via* a sequential Sonogashira alkynylation, followed by a cyclocondensation–Suzuki arylation reaction (Scheme 10). The catalytic system and the optimised reaction conditions appear to be general with regard to the employment of a variety of acyl chlorides **65**, substituted alkynes **66**, substituted hydrazines **67** and boronic acids **68** providing the desired products in acceptable yields with a high order of functional group tolerance. The highlight of the present one-pot sequence strategy was the sequential use of the palladium catalyst without further loading of the catalyst in the tandem Sonogashira alkynylation/Suzuki arylation reaction sequence.

Oxazole is an exceptional five-membered heterocycle found in a wide variety of biologically active natural as well as synthetic organic molecules such as calyculin A, chivosazole A, diazonamide A, disorazole Z, galmic IB-01211, kabiramide C, leiodelide B, leucascandrolide A, mycalolide, neooxazolomycin, neopeltolide, phorboxazole, rhizoxin D, telomestatin, and



Scheme 7 Strategy based on Pd/Cu bimetallic catalysis for the synthesis of bifuran compounds.

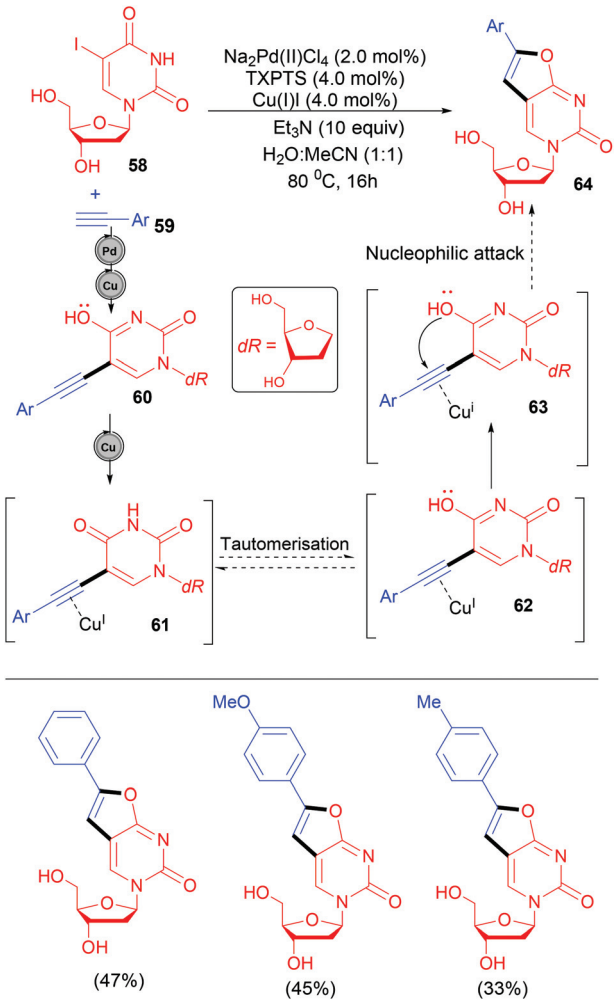


Scheme 8 Pd/Cu bimetallic catalysis in the formation of tetraarylethene.

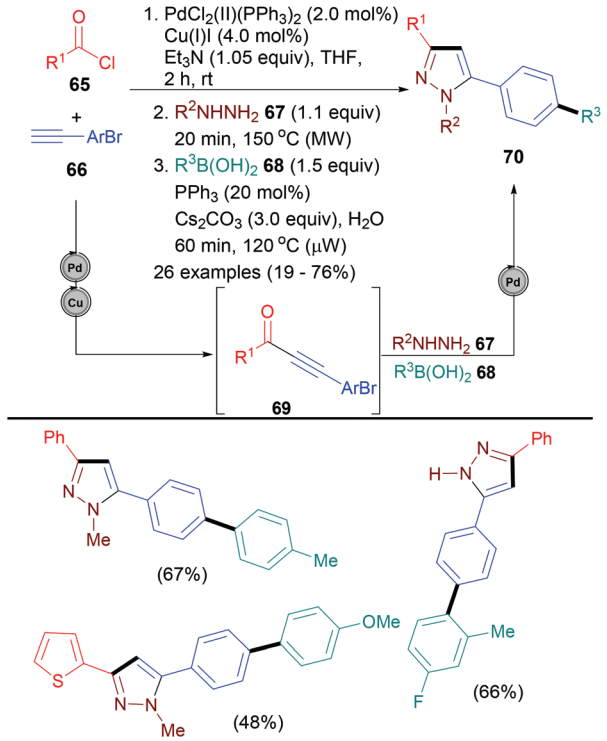
ulapualide A.[29] Their occurrence has fuelled enthusiasm amongst chemists in continuing the search for an innovative, elegant and robust protocol for the synthesis of the oxazole ring structure. In this regard, a synergistic effect of gold and iron catalysts on the conversion of vinyl gold intermediate **73** derived from **71** to substituted oxazole aldehydes **75** was disclosed by Peng *et al.*[30] (Scheme 11). Furthermore, the developed protocol was extended towards the synthesis of indoles and benzofurans from alkynes with both electron-rich and electron-deficient substituents to afford oxazole aldehydes in appreciable yields. The employment of internal alkynes however was found to be unsuitable under these optimised reaction conditions.

The use of multi-metallic cooperative catalyst systems to perform multi-component transformations has provided unique advantages over general synthetic procedures. The extraordinary control over selectivity and functional group tolerance makes this strategy more desirable and accordingly, Wang *et al.* explored such a possibility by reacting aldehydes **76** and *N*-(propargyl)-arylamides **77** under the synergistic effect of Zn/Sc for the preparation of derivatives of oxazole **79**[31] (Scheme 12). The Zn(II)-catalysed cyclo-isomerisation leads to the formation of an intermediate **78**, which on undergoing a Sc(III)-catalysed carbonyl–ene reaction furnishes **79** in good to excellent yields. After finalizing standard reaction conditions, an extensive amount of work was performed with various *o*-, *m*-, and *p*-substituted aromatic aldehydes with electronic properties having no adverse effects on the outcome of the reactions. As an additional finding, the reaction proceeded with a hetero-aromatic propargylic amide with acceptable conversion (43%) into the target molecule, demonstrating the reaction to be not exclusive for carbocyclic propargylic amides only.

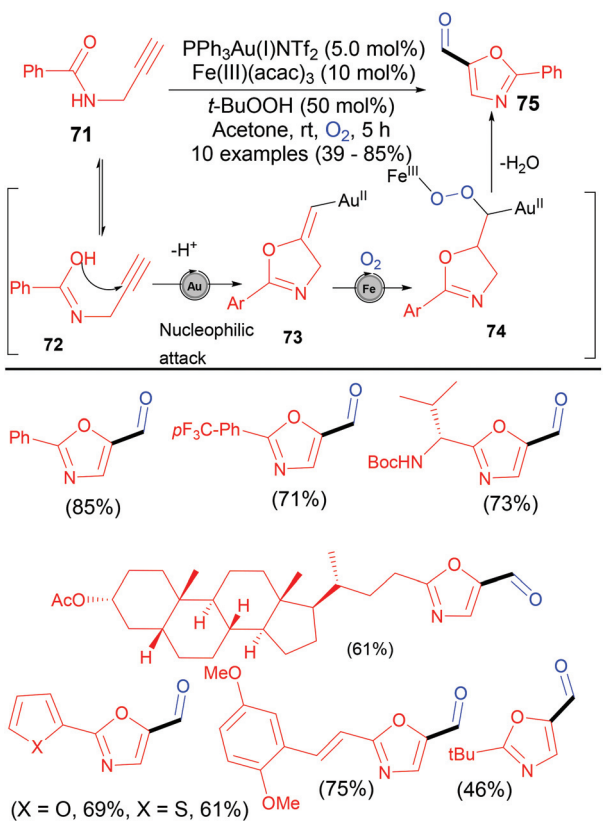
Another noteworthy result by Mai *et al.* discloses the utilisation of gold catalysts in cooperation with Ni and Cu demonstrating the efficient synthesis of oxazole carbonitriles **83** or carboxamides **84** in the presence of a redox-active catalyst, NHPI **81**, *via* the formation of an oxazole–gold complex as an intermediate **83**[32] (Scheme 13). Considering the high value of the functionalised oxazoles, the authors further applied the catalytic system to the Au/NHPI/Ni and Au/NHPI/Cu-catalysed functionalisation of oxazoles from *N*-propargylamide substrates **80** under optimised reaction conditions. Such gold catalysed cyclisation proceeded efficiently to generate the desired products in good yields. The electronic nature of the substituents present was found to have little effect on the transformation. Additionally, the method offers a safe and mild protocol for the conversion of heteroaryl substituted propargylamides as well as 1-adamantyl substituted propargylamides to the corresponding products with an acceptable outcome.



Scheme 9 Pd/Cu-Catalysed cyclisation of 5-iodo-2′-deoxyuridine with various alkynes.



Scheme 10 Regioselective coupling–cyclo-condensation synthesis of 1,3,5-substituted pyrazoles using Pd/Cu bimetallic catalysts.

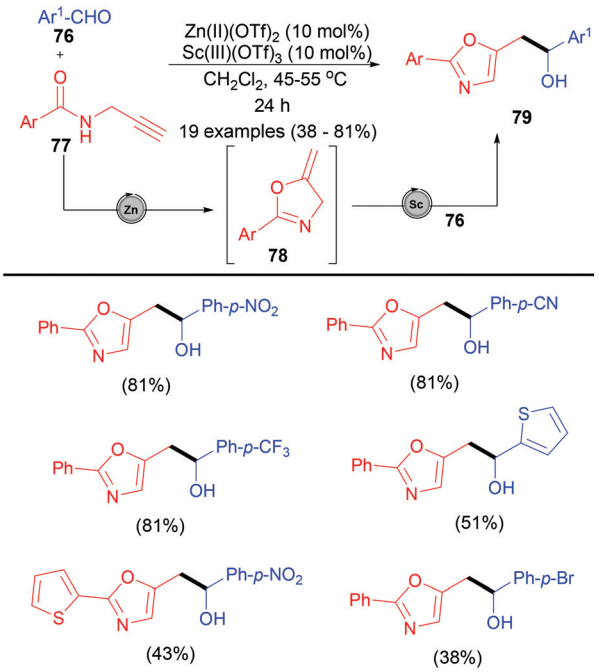


Scheme 11 Synthesis of oxazole aldehydes using Au/Fe bimetallic synergistic catalysts.

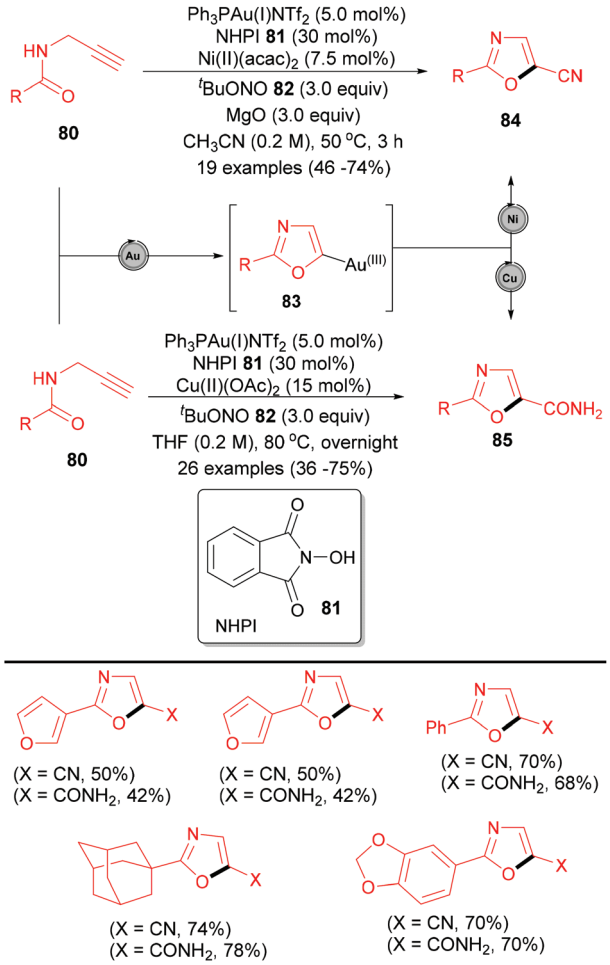
2.3. Three heteroatoms

The fascinating chemistry of 1,2,3-triazoles has attracted a lot of attention from the scientific community.[33] 1,2,3-Triazoles are exploited in quite a large number of applications such as in molten salts, organo-catalysis, and a considerable range of biologically active molecules exhibiting anti-inflammatory, anti-platelet, anti-microbial, anti-tubercular, anti-tumoral, as well as antiviral activities against several neglected diseases.[34] Presently, 1,2,3-triazoles are being investigated intensely with respect to several focal domains of present day science including their exceptional biological relevance and characteristic photo-response. In this context, the advancement of efficient, highly practicable state of the art synthetic approaches for these heterocyclic motifs is highly appreciated.

In 2004, Kamijo *et al.*[35] proposed a very elegant and straightforward synthetic methodology for the regio-controlled formation of 2-allyl-1,2,3-triazole **89** and 1-allyl-1,2,3-triazole **90** ring frameworks from the interaction of alkynes **86**, allyl carbonate **87** and azido trimethylsilane ($TMSN_3$) **88** under the synergistic influence of the Pd/Cu bimetallic catalytic system



Scheme 12 Zn/Sc bimetallic relay catalysis strategy for the construction of an oxazole.



Scheme 13 Au/Ni and Au/Cu-catalysed cyclisations of *N*-propargylamides for the synthesis of functionalised oxazole.

(Scheme 14). Overall, the exploration of the substrate scope demonstrates that this transformation can use a wide range of substituted arylalkynes with a variety of functional groups. The electronic nature of the substituents plays an important role in this transformation and affects the overall yield of the product of the reaction. Notably, electron-withdrawing substituents have much more significant influence in providing regioselectivity for the reaction than their electron-rich counterparts.

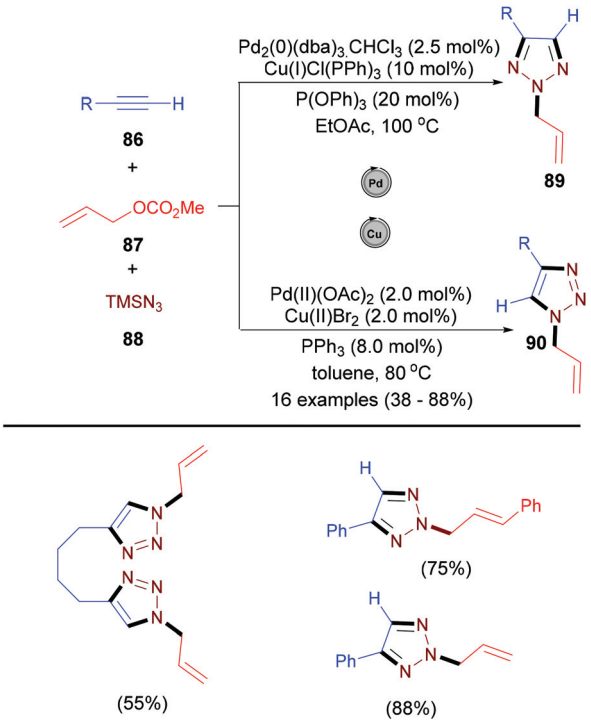
It is pertinent to mention that the use of the Pd/Cu bimetallic catalyst system in the synthesis of triazoles under different conditions has also been studied by various other groups.[36] For example, Wei *et al.*[36a] found that the Cu-catalysed cyclo-addition of alkynes **91** and azides **92** was followed by the coupling transformation with aryl halides **93** under mild reaction conditions affording excellent outcomes of the desired 1,4,5-trisubstituted 1,2,3-triazoles **96** (Scheme 15). A number of cyclo-addition-coupling transformations performed under optimised conditions revealed that the reaction was also tolerant to a wide variety of substituents either electron-withdrawing or electron-donating in nature. In most cases the yield of the isolated product was good. Mechanistically, it was proposed by the authors that the copper-catalysed click reaction between the alkyne and azide proceeds first followed by palladium-catalysed coupling of the aryl halide.

The scope and use of this innovative Pd/Cu chemistry was highlighted by performing the late-stage click reaction in order to obtain biologically relevant natural products derived from oleanolic acid, modification of alkyne sugar and the conversion of amino acid into triazole scaffolds successfully allowing the synthesis of products possessing a high order of selectivity and with high yields of the corresponding compounds.

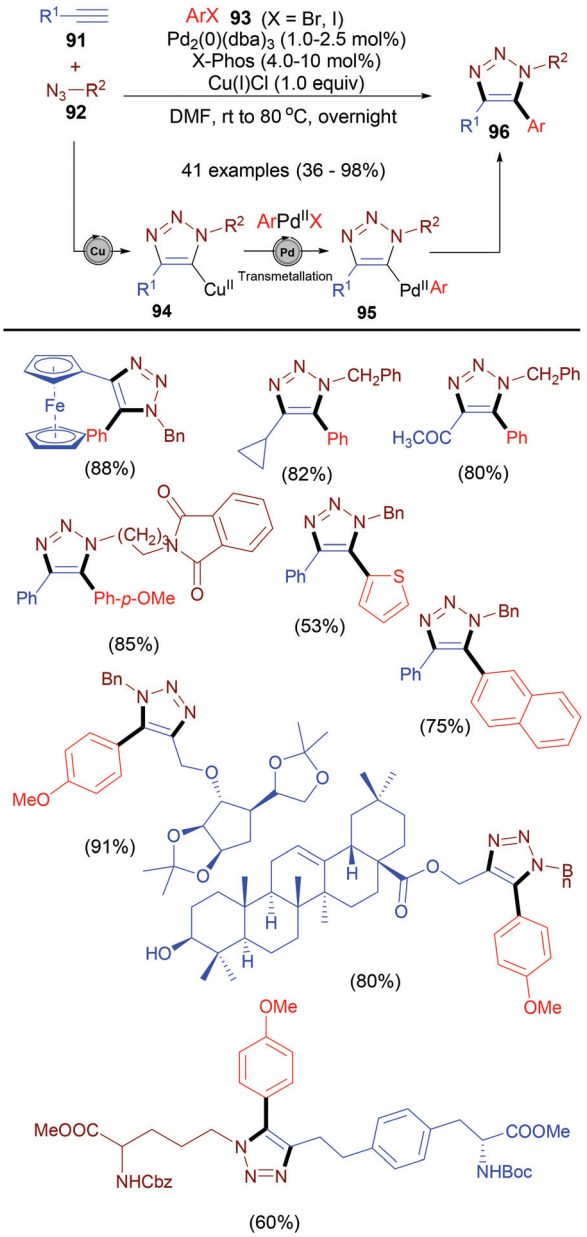
After the successful demonstration of the versatility of cooperative Pd/Cu catalysis, the focus is now shifted towards other cooperative catalytic systems. In this regard, Wang *et al.*[36b] directed their efforts towards the synthesis of 1,2,3-triazole/quinoline-fused-imidazo[1,2-*a*]pyridines **100** from 2-(2-bromophenyl)-imidazo[1,2-*a*]pyridines **97**, alkynes **98**, and sodium azide **99** *via* multicomponent cascade transformation allowing the sequential azide–alkyne cycloaddition, (C–N) coupling, and cross-dehydrogenative (C–C) coupling reactions (Scheme 16). The scope of the reaction was then successfully extended to a variety of alkynes **98** possessing electron-donating or electron-withdrawing groups.

The authors speculated that the electronic nature of the substituents has had no significant effect on the yields of the corresponding products which is evident from the obtained results.

Moreover, 2-ethynylthiophene, aryl-substituted alkynes, dec-1-yne and prop-2-ynylbenzene when employed as substrates were found to be suitable for this cascade transformation.



Scheme 14 Pd/Cu catalysed highly regio-controlled synthesis of allyltriazoles *via* the multi-component coupling reaction sequence.

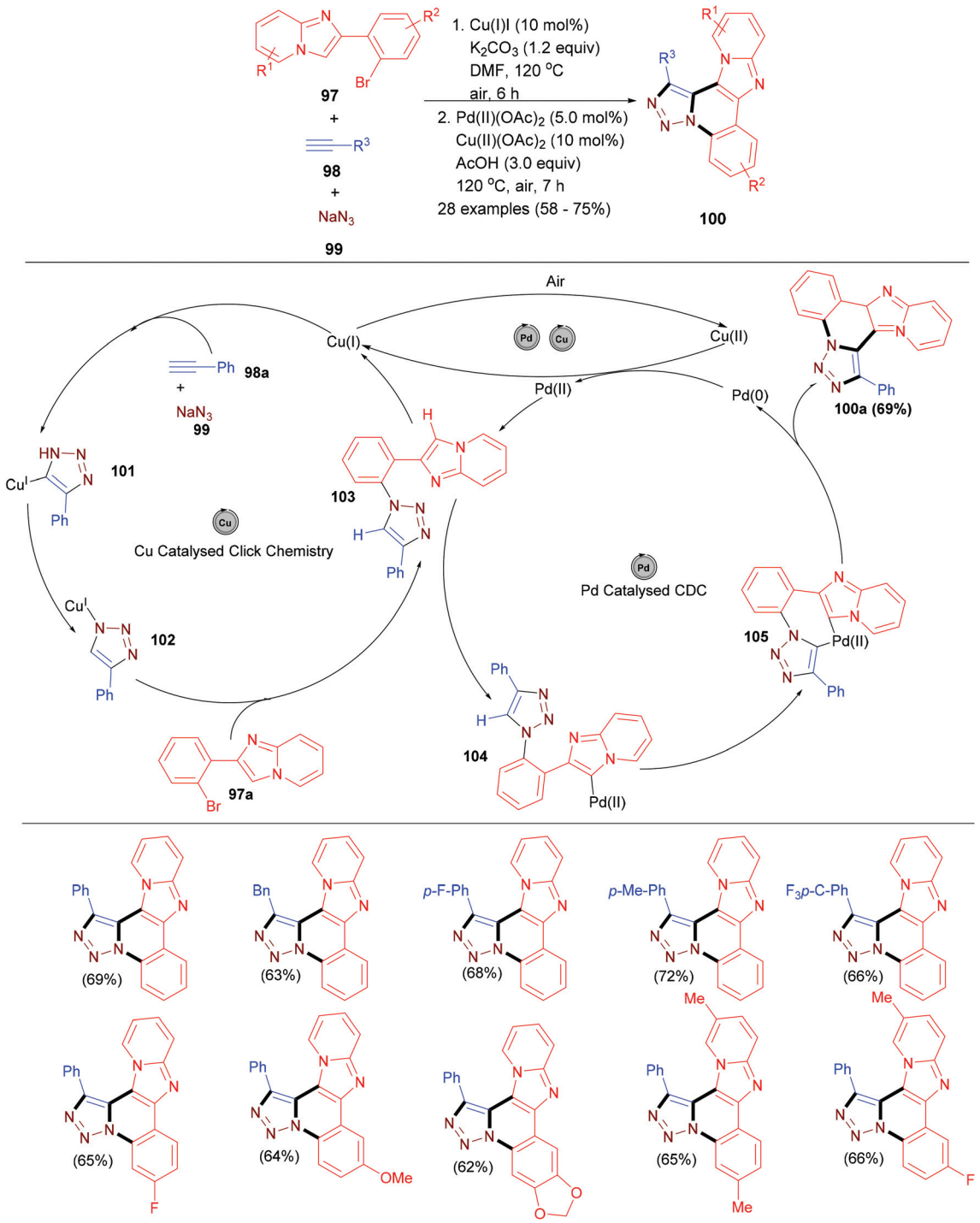


Scheme 15 Cu/Pd-Catalysed multi-component click reaction for the synthesis of 1,2,3-triazoles. Synthetic applications of Cu/Pd-catalysed multi-component click reactions/cross-coupling strategy for the creation of biologically relevant triazole scaffolds.

2.4. Four heteroatoms

The tetrazole scaffold plays a role in the pharmaceutical arena as quite a large number of organic molecules with the tetrazole framework are known to be the bioisosteric replacement for carboxylic acids in drug discovery,[37] most commonly accessed through the Julia-type olefinations.[29] The aminotetrazole structural motif is another synthetically challenging structural motif possessing exceptional biological activities. These are classical examples of nitrogen-enriched aromatic heterocycles, with a broad spectrum of applications in pharmaceuticals, materials science as amide surrogates,[38] antifoggants in photographic materials,[39] plasma-polymer films for biomedical aids,[40] propellants and explosives.[41] Fascinatingly, aminotetrazole scaffolds also exhibit promising anti-HIV and anti-allergic activities.[42] Reports[43] surrounding the synthesis of aminotetrazoles suggest the dearth of protocols that could address the existing synthetic problems such as the employment of toxic reagents, drastic reaction conditions, use of air and moisture sensitive catalysts and limited tolerance towards synthetically useful but labile functional groups. Cooperative catalysis in this regard would provide a useful and attractive alternative to the existing methods.

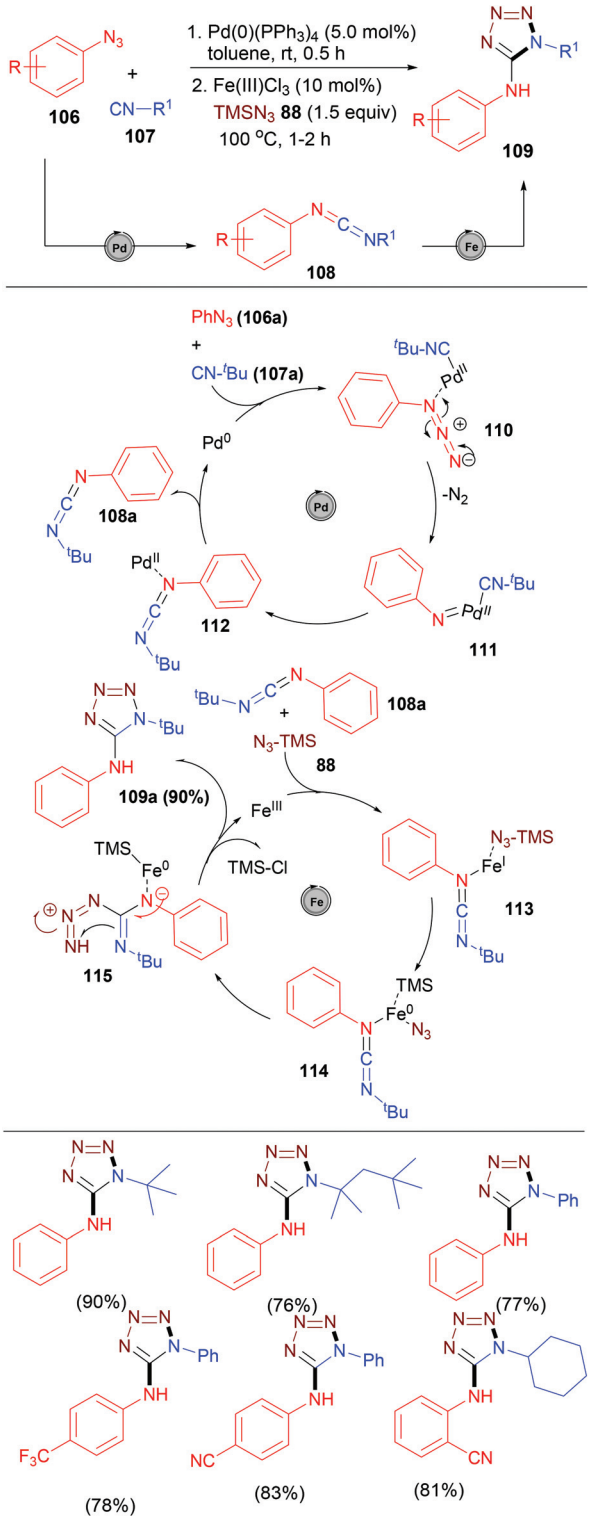
A fascinating example of cooperative catalysis for the synthesis of aminotetrazoles **109** was recently provided by Pathare *et al.* (Scheme 17).[44] This disclosure comes as a part of the investigation carried out towards the development of consecutive Pd(0)-catalysed azide **106** and isocyanide **107** denitrogenative coupling reactions followed by Fe(III)-catalysed cyclo-isomerisation with $TMSN_3$ **88**. These reactions were performed with a wide variety of substituted azides **106** (electron-donating and -withdrawing substituents) and isocyanides **107** (alkyl-, cycloalkyl-, and aryl-substituted) as well as $TMSN_3$ **88** affording the desired products in good to excellent yields. The presence of substituents in the *ortho* (sterically demanding) position was found to have no detrimental effect on the catalytic efficiency of the developed protocol.



Scheme 16 Pd–Cu-Catalyzed synthesis of 1,2,3-triazole/quinoline-fused imidazo[1,2-*a*]pyridines.

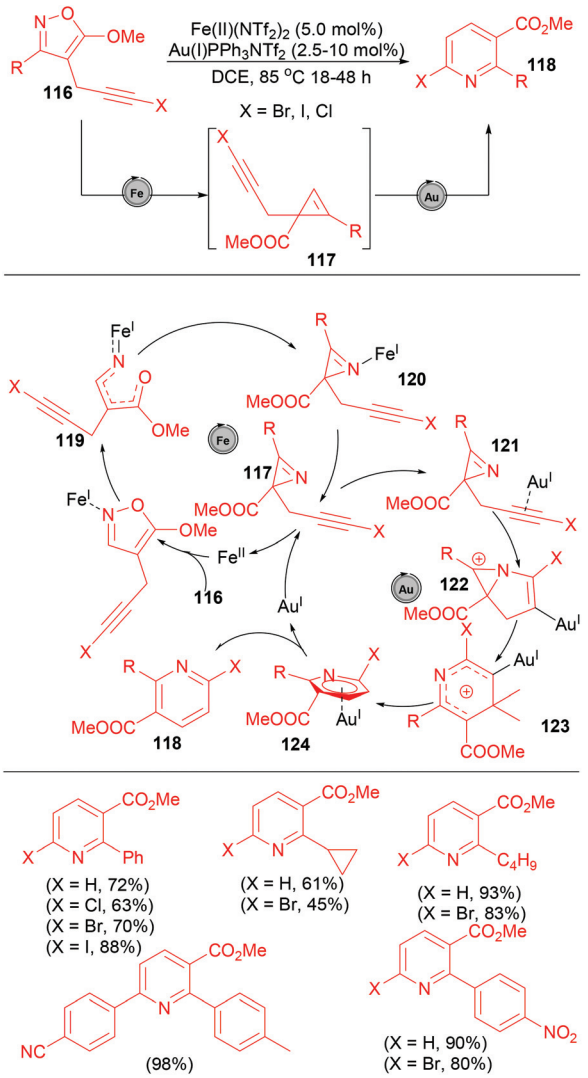
3. Six membered heteroarenes

One of the most important examples of six-membered heteroarenes which has immense applicability is pyridine. Pyridine represents an important class of heterocycles which are prevalent in a number of biologically active natural products, pharmaceuticals, agrochemicals and materials.[45] Based on the significance of pyridine and its derivatives a plethora of synthetic procedures for their synthesis has already been documented in the literature.[46] Cooperative catalysis could provide the necessary sustainable solution for obtaining a variety of substituted pyridines as discussed in this section. While studying the domino isomerisation of 4-propargyl/(3-halopropargyl)-5-methoxyisoxazoles **116** catalysed by Fe/Au,



Scheme 17 One-pot multicomponent Pd/Fe-catalysed synthesis of aminotetrazoles.

Galenko *et al.*[47] observed that the methyl nicotinates/6-halonicotinates **118** were obtained as a result of cycloisomerisation of **116** under the developed experimental conditions (Scheme 18).

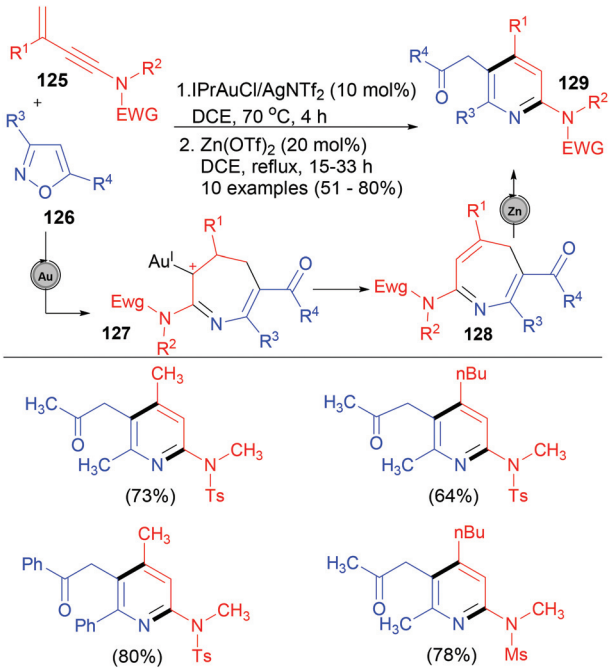


Scheme 18 Conversion of 4-(3-haloprop-2-yn-1-yl)isoxazoles to 2-substituted methyl 6-halonicotinates under Fe(II)/Au(I) relay catalysis.

Isoxazoles that were employed have been recognised as easily available synthetic equivalents for azirines and are formed from **116** *via* the 2-carbonyl-substituted-2*H*-azirine intermediate **117** of **116**. Substituted isoxazoles such as 3-alkyl-substituted, 3-cyclopropyl, 3-bromophenyl, 4-nitrophenyl, cyclopropyl, *tert*-butylsubstituted isoxazoles, 4-(3-(trimethylsilyl)prop-2-yn-1-yl)isoxazoles and terminal halo-substituted isoxazoles were subjected to the developed reaction conditions for the sequential domino isomerisation reaction, providing moderate to excellent yields of the desired products.

With the continued emphasis on cooperative catalysis, cycloisomerisation/annulation strategies were employed by Giri *et al.*[48] for studying Au/Zn catalysed annulation reaction between 3-en-1-ynamides **125** and isoxazoles **126** to afford highly functionalised pyridines **129** (Scheme 19).

The use of Au alone allows the electro-cyclisation of Au-stabilised 3-azaheptatrienyl cations to furnish 4*H*-azepines, while the combined effect of Au(I)/Zn(II) on the same reactants



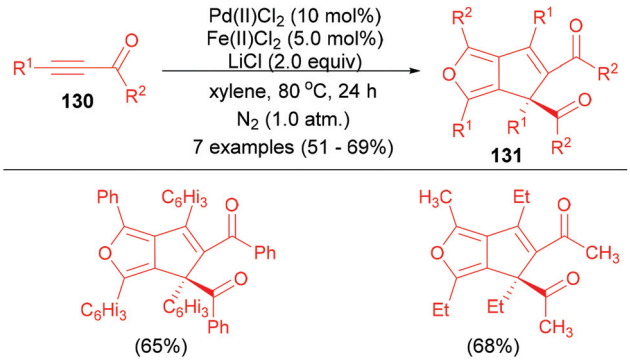
Scheme 19 Au/Ag/Zn multimetallic catalysed [4 + 2]-annulation reaction between 3-en-1-ynamides and isoxazoles.

allows the formation of functionalised pyridines **129**. The Zn catalyst in this regard is useful in converting azepines into the substituted pyridines. The authors also concluded that the yield of the reaction was strictly independent of the electronic as well as steric nature of the substituent present in **125** and **126**.

4. Condensed heteroarenes

Heterocycles play a significant role in life governing processes and have played a major role in the rapid growth of industries in the specific areas of dyes, pharmaceuticals, pesticides, agrochemicals, polymers, *etc*. In this regard, synthetic organic chemists have seized the opportunity to generalise the optimal synthetic strategies to achieve the practical preparation of a variety of heterocyclic compounds. Cyclo-addition reactions involving the concurrent or consecutive formation of two or more bonds in a highly stereo and regio-selective manner could be viewed as an atom-economic and efficient synthetic strategy for obtaining bioactive condensed heterocycles.[46b–d,49] The chemistry of fused heterocycles is one of the most exciting branches of synthetic organic chemistry exhibiting widespread diversity with regard to synthetic procedures, pharmaceutical relevance and industrial significance.[50] Amongst these fused heterocyclic compounds, indoles are widely employed in the field of agriculture (indole-3-acetic acid), drugs (triptans, sertindole, silodosin) and pharmaceuticals (nintedanib, satavaptan).[51]

To access such diverse structural motifs, the development of more advanced synthetic technologies such as cooperative

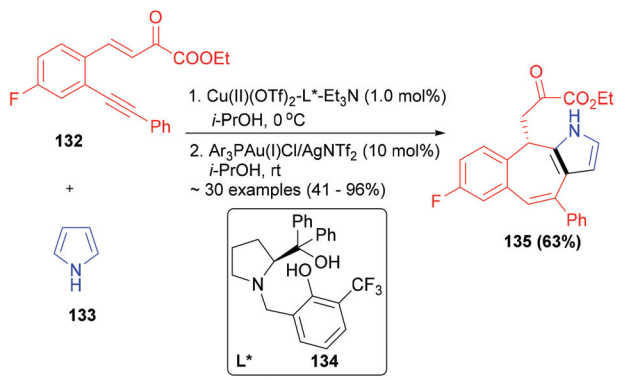


Scheme 20 Pd/Fe-Catalysed cascade cyclisation of 2-yn-1-ones.

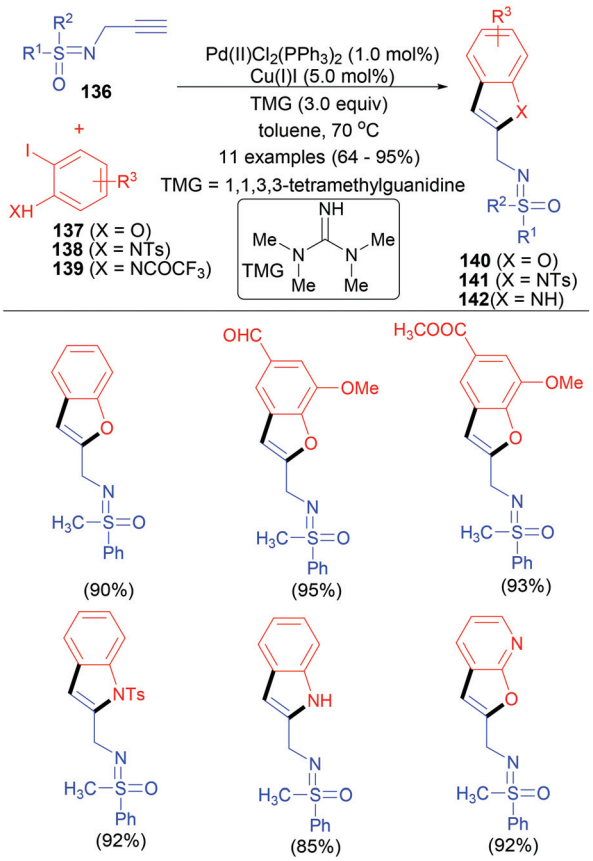
catalysis could hold a lot of promise. To investigate the potential of a multimetallic catalysis strategy for the construction of indoles, Jiang *et al.* combined the catalytic potentials of palladium and iron in a cascade cyclisation procedure involving 2-yn-1-one derivatives **130** affording poly-substituted 4*H*-cyclopenta[*c*]furans **131** in good to excellent yields[52] (Scheme 20). The authors concluded that the electronic nature of the substituents has had negligible effects on the outcome of this Pd/Fe relay catalysed cascade cyclisation process.

One of the commonly used precursors for the synthesis of pyrroles are β,γ-unsaturated α-ketoesters **132** and thus they were employed as starting materials by Hu *et al.* in the Friedel–Crafts alkylation procedure[53] allowing the synthesis of fused pyrrole skeletons **135**. Substituted pyrroles were obtained as a result of the Cu/Au relay catalysed Friedel–Crafts alkylation reaction using **134** as a ligand. Such a synthetic strategy involving multiple C–C bond formations *via* the cooperative action of two metals (Cu and Au) was previously reported for obtaining the pyrrole scaffolds. The present protocol showed excellent functional group compatibility, and several substituted β,γ-unsaturated α-ketoesters were converted into fused pyrrole derivatives in good to excellent yields (Scheme 21).

Following the progress of palladium and copper relay catalysed domino cross-coupling/cyclisation reactions for the syn-



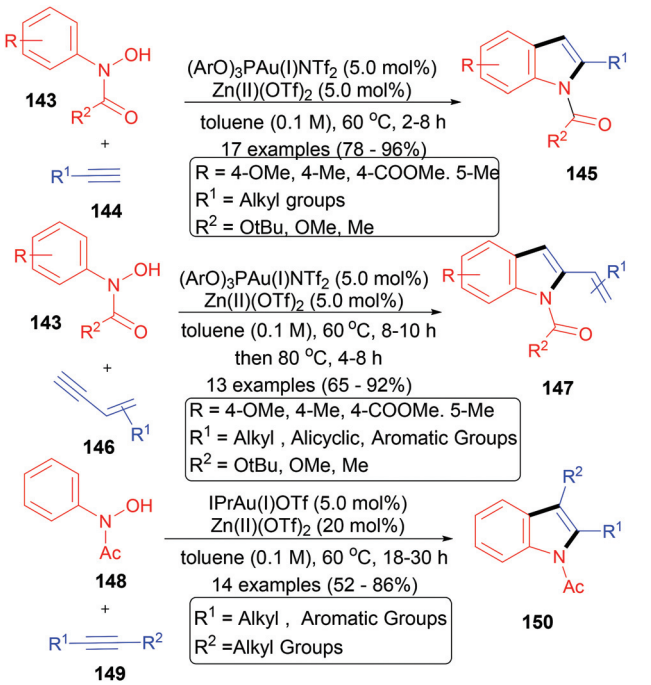
Scheme 21 Synthesis of indoles using Cu/Au bimetallic catalysts.



Scheme 22 Benzo[*b*]furans or indoles synthesised from *N*-propargyl-substituted-sulfoximines.

thesis of benzo[*b*]furans and indoles, Schumacher *et al.*[54] optimised the reaction conditions to accomplish domino cross-coupling/cyclisation reactions of *N*-propargyl substituted sulfoximines **136** with iodoarenes **137–9** for the synthesis of benzo[*b*]furan **140**, indole **142** and *N*-substituted indole **141** (Scheme 22) using Pd/Cu relay catalysis. The presence of electron rich and electron deficient substituents in **136** or **137–9** was found to exert a negligible effect on the catalytic activity, yielding the expected heteroarenes in satisfactory yields. However, a minor drawback in the developed protocol was observed with regard to the presence of a bromine atom in the *para* position of sulfoximine giving poor yields (63%) of the desired product. The scope of the reaction was improved by the incorporation of various functional groups as well as substrates such as 2-iodoarenes, 2-iodo-3-hydroxy pyridine, and *N*-tosyl and *N*-trifluoroacetyl substituted 2-iodoanilides.

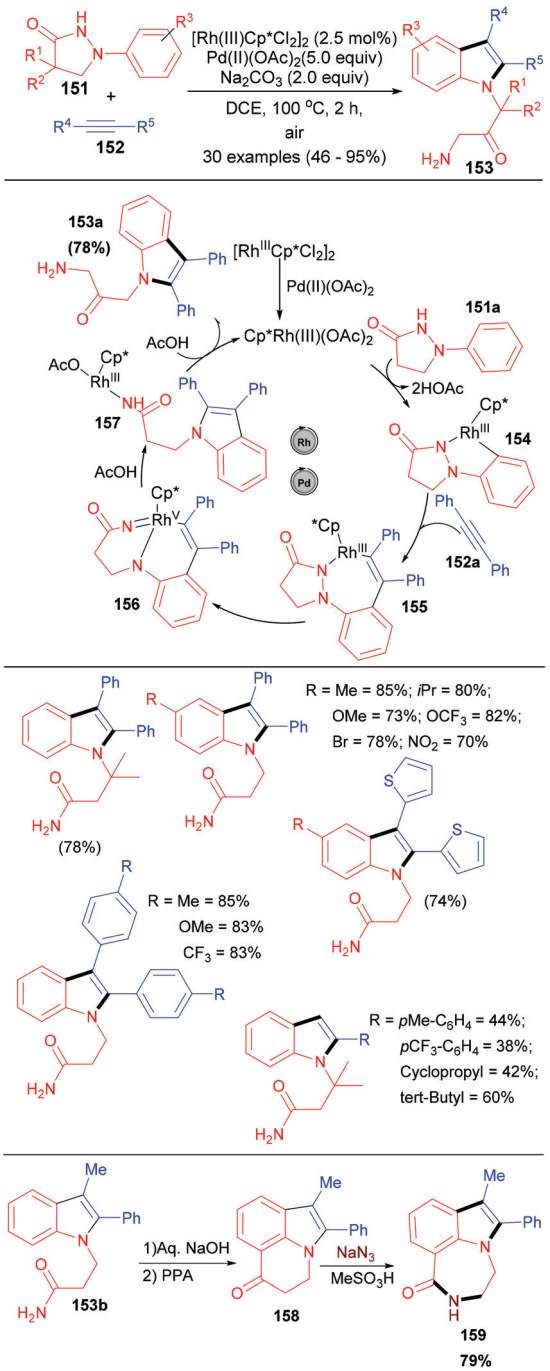
Interestingly, it was found that combining the catalytic efficiency of gold and zinc catalysts for the regio-specific conversion of *N*-aryl-*N*-hydroxy carbamates **143** and **148** with a variety of alkynes **144**, **146**, and **149** allowed the synthesis of *N*-substituted derivatives of 2-alkylindole derivatives **145**, **147**, and **150** respectively (Scheme 23).[55] A wide range of alkynes containing electronically varied alkyl, alkoxy or aryl groups reacted with *N*-aryl-*N*-hydroxy carbamates to afford the regioselective synthesis of the corresponding heteroarenes in good

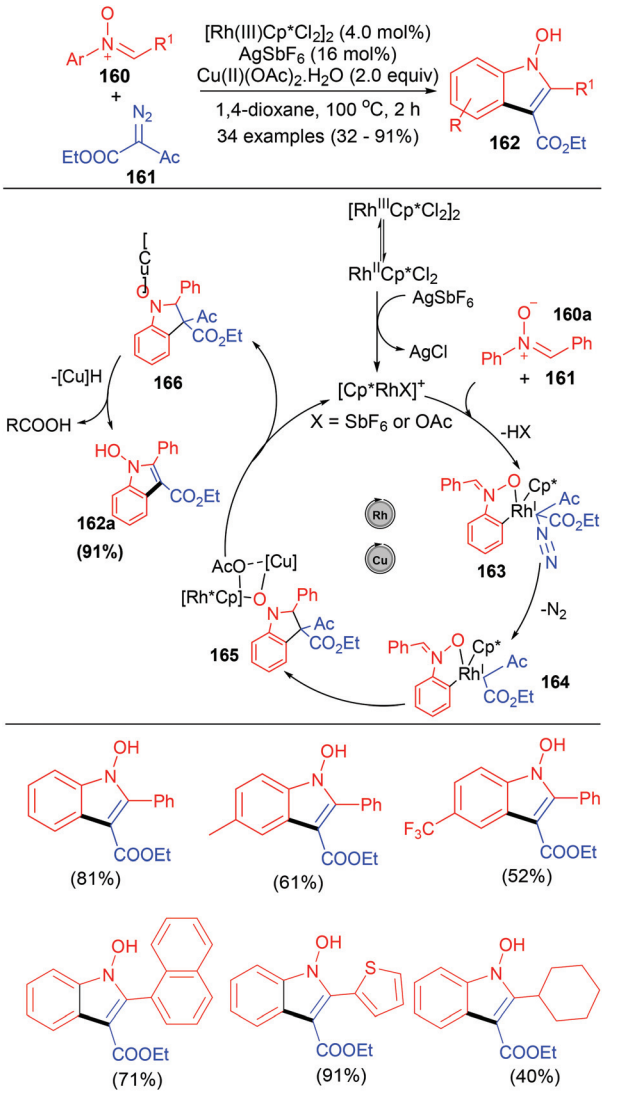


Scheme 23 Highly regio-specific synthesis of the *N*-substituted derivatives of 2-alkylindoles.

to excellent yields. Alkyne counterparts when varied from terminal **144** to internal alkynes **149** provided differently substituted indole products.

Fan *et al.*[56] employed an efficient catalytic system containing rhodium and palladium precursors under cooperative catalytic conditions that allowed the reaction of phenidones **151** and alkynes **152** (including phenylacetylenes and alkylacetylenes) *via* cyclo-isomerisation to afford *N*-substituted indoles **153** in good yields (Scheme 24). In general, **151** with the *ortho*-, *meta*- and *para*-substituted phenyl rings apart from their electronic and steric considerations reacted well with **152** providing the corresponding indole products. A variety of aryl and alkyl-substituted, symmetrical and unsymmetrical alkynes **152** as coupling partners were tested with phenidones **151** with the results suggesting that no significant electronic effects affect the catalytic activity. The versatility and use of the present strategy was showcased by the authors through the synthesis of the potent anticancer poly(ADP-ribose) polymerase-1 (PARP-1) inhibitor **159**. Derivatives of *N*-hydroxyindole are highly privileged biologically active scaffolds from the family of indoles exhibiting a variety of useful biological activities,[57] *viz*. anti-biotic, anti-proliferative and platelet aggregation inhibitory activities.[58] Regardless of their medicinal applications, quite a few number of protocols for the synthesis of these molecules have been documented in the literature.[59] Compared to the commonly investigated protocols, Li *et al.*[60] employed the Rh-catalysed (C–H) bond functionalisation strategy for obtaining derivatives of *N*-hydroxyindole **162** from arylnitrones **160** and α-diazoketoesters or α-diazodiketones **161** (Scheme 25). To improve the potential of the catalytic system,





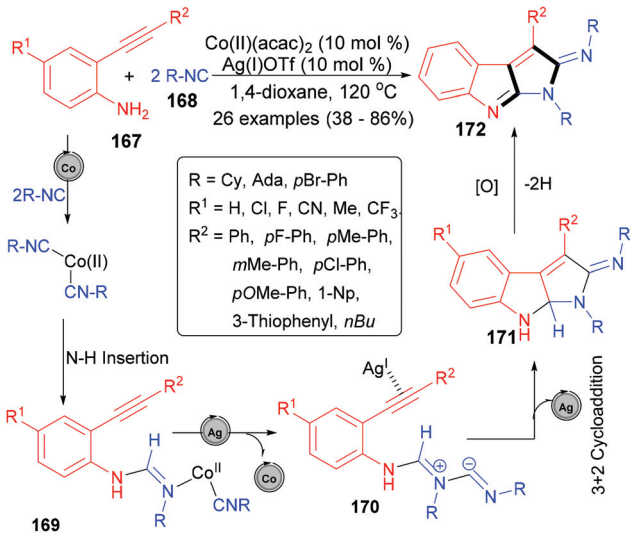
Scheme 24 Rh-Catalysed activation of phenidones for the synthesis of *N*-substituted indoles.

Scheme 25 Rh(III)-Catalysed C–H bond functionalisation for the synthesis of *N*-hydroxyindoles.

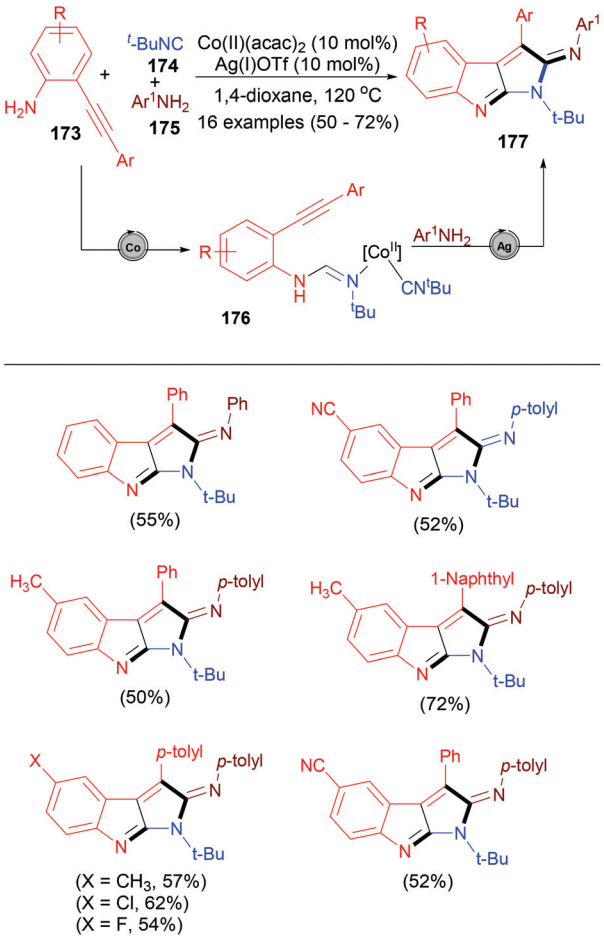
different additives such as PivOH, AcONa, AcOH, and $Cu(OAc)_2$, silver salts such as $AgSbF_6$, AgOTf, $AgNTf_2$ and AgOTs, and solvents such as MeCN, THF, MeOH, DCE and 1,4-dioxane were tested, to obtain respectable yields of the desired products.

Authors probed the versatility of the Rh-catalysed (C–H) bond functionalisation using differently substituted **160** and **161** wherein some notable substrate limitations were encountered. It was observed that when chlorine or trifluoromethyl groups were substituted at the *meta*- or *para*-position with respect to **160** there was significant reduction in reactivity. Under the reaction conditions outlined in Scheme 24, naphthyl or thiophene-substituted **160** were also well tolerated. As a part of the study, authors explored the scope of the electronically as well as geometrically diverse range of **161** reactants to react with **160** under optimised reaction conditions affording a satisfactory conversion of the reactants to the desired products.

Indoles containing natural products are on the summit of biologically relevant compounds because of their uniqueness in structure and structure related interesting bioactivities. A large number of biologically active alkaloids have also been associated with the presence of pyrrolo[2,3-*b*]indole scaffolds[61a,b] such as potent vasodilator – amauromine,[61c] insecticides – okaramine C,[61d] physostigmine,[61e–g] pseudophrynaminol[61h–k] and flustramine C.[61l–n] Cooperative



Scheme 26 Synthesis of Co/Ag bimetallic catalysed pyrrolo[2,3-*b*] indoles *via* insertion of isonitriles into 2-ethynylanilines.



Scheme 27 Co/Ag-Catalysed cascade reaction between 2-ethynylanilines, arylamines and *tert*-butyl isocyanides for the synthesis of arylimi-nated pyrrolo[2,3-*b*]indoles.

hetero-bimetallic catalysis in the form of Co/Ag relay catalysis for the replacement of conventional protocols for the synthesis of highly functionalised pyrrolo[2,3-*b*]indoles is well documented in the literature.[62,63] One such example involving the bicyclic addition of isocyanides **168** with arylethynylanilines **167** for the formation of functionalised pyrrolo[2,3-*b*]indoles **172** was recently introduced by Gao *et al.*[62] (Scheme 26). To gain further insight into the cyclo-addition reaction mechanism, several control experiments were conducted providing evidence that the catalytic cycle proceeded through the cobalt-catalysed formation of intermediate **169**, which subsequently transforms into an intermediate enyne–imine **170** by the synergistic action of cobalt and silver, finally providing **172** *via* silver catalysed [3 + 2] cyclo-addition of **171**. The essential presence of an *ortho*-amine group was advocated to be necessary for better activity.

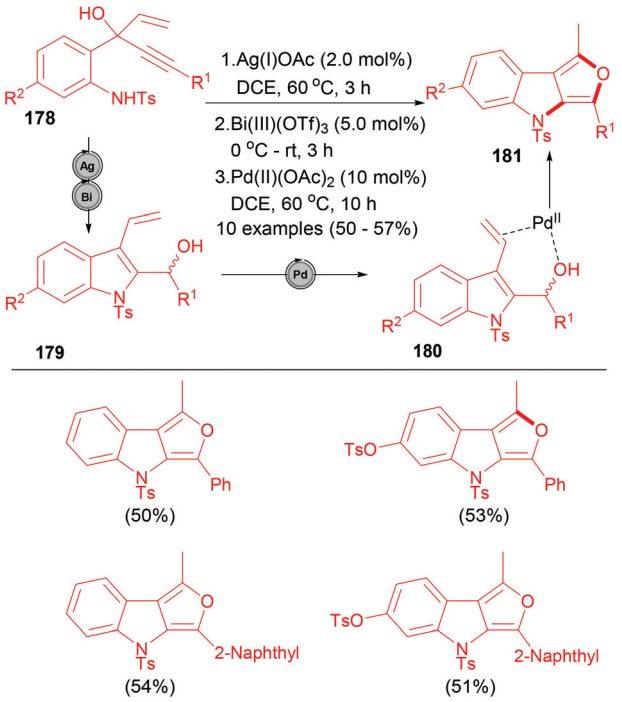
Subsequently, Hao *et al.*[63] disclosed a Co/Ag catalysed convergent, highly stereo-selective synthesis of a wide variety of structurally diverse aryliminated pyrrolo[2,3-*b*]indoles **177** from 2-ethynylanilines **173**, *tert*-butylisocyanide **174**, and arylamines **175** (Scheme 27). Both strategies have dealt with the highly regio-selective synthesis of pyrrolo[2,3-*b*]indole scaffolds showing exceptional tolerance of the electronic nature of the substituents present on the reactants, which were utilised for this transformation.

Multi-catalytic methodologies are in general considered as atom-economical, offering easy separation of the product, as well as possessing excellent functional group tolerance ability; however, the practical advancement of such processes is not always a straightforward task. The feasibility of the reaction parameters and the reagents with the catalytic system and control over selectivity are some of the challenges considered as major hurdles for the implementation of such methods. In this context, an interesting exploration of the catalytic potential of a trimetallic catalyst system based on Ag/Pd/Bi for the synthesis of substituted furo[3,4-*b*]indoles **181** from 3-(2-amino)-4-pentenyn-3-ols **178** was reported by Manisha *et al.*[64] (Scheme 28).

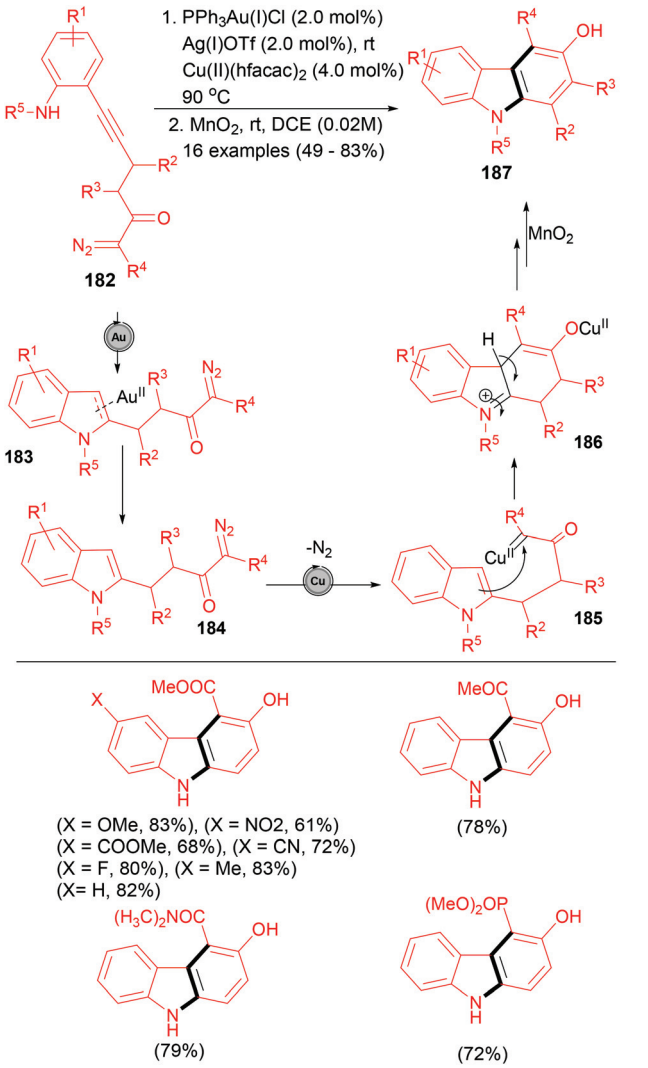
As an indole derivative, carbazoles exhibit a broad spectrum of applications in pharmaceuticals and materials science.[65] The increasing demand for carbazoles and carbazole containing heterocycles due to the biological relevance encourages the scientific community to develop highly efficient and synthetically elegant protocols.

In this regard, Choi *et al.*[66] probed a gold/copper relay sequence involving a cyclo-isomerisation/hydroamination strategy with diazoanilinoalkynes **182** for the synthesis of highly substituted carbazoles **187** (Scheme 29). Differently substituted aryl groups on the diazoanilinoalkyne framework were scrutinised, with the observation that the electronic nature of the substituent has a measurable impact on the outcome of the reaction with the presence of electron-rich substituents affording greater yields as compared to the presence of electron-poor substituents.

Recently, the Rh/Cu-catalysed conversion of 2-arylindoles **188** and a variety of diazo compounds **189** *via* the indole-directed aryl (C–H) bond carbenoid insertion cascade for the



Scheme 28 Divergent relay catalytic approach for the synthesis of substituted furo[3,4-*b*]indoles and cyclopenta[*b*]indoles.



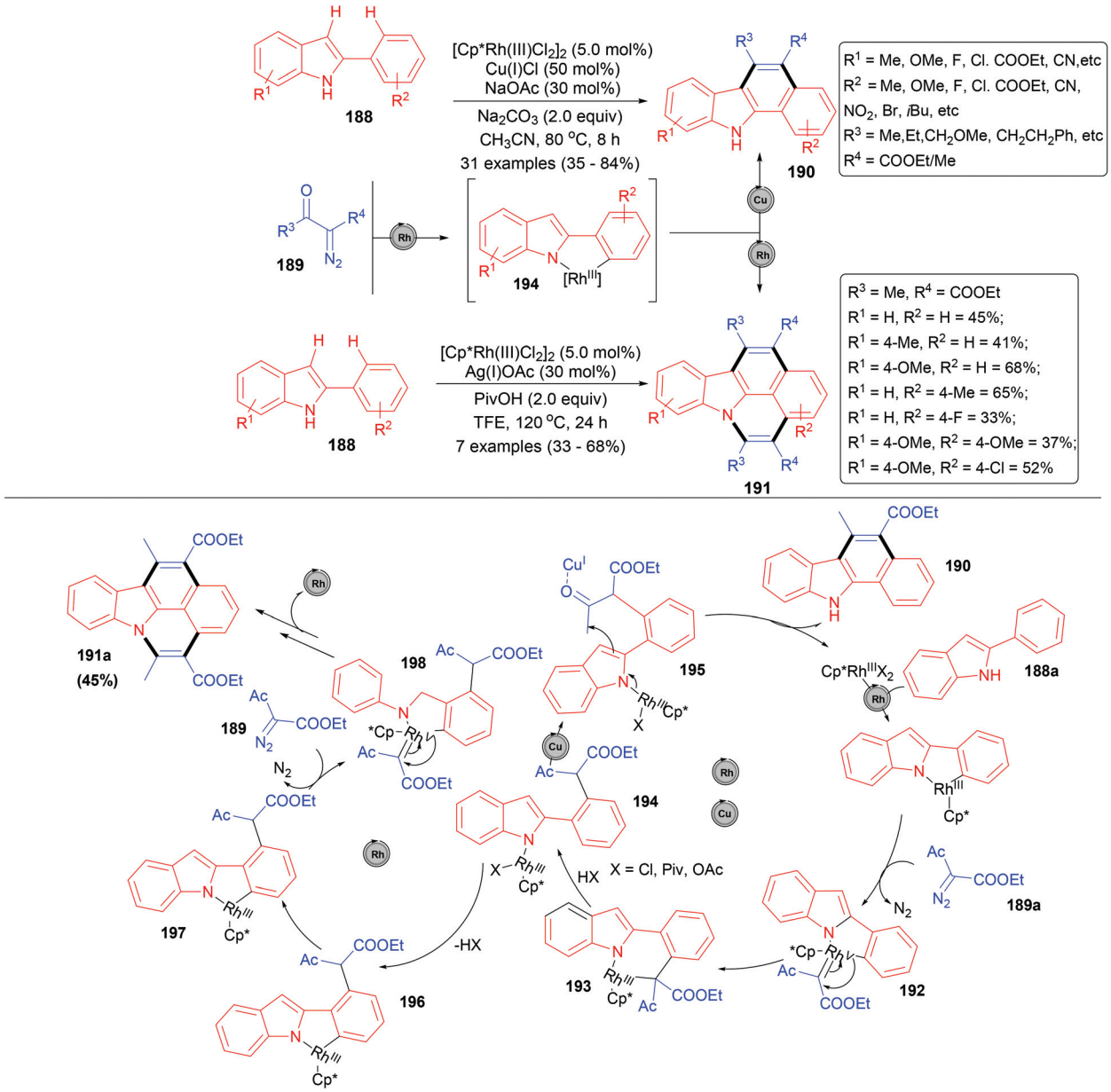
Scheme 29 Au-Catalysed synthesis of carbazoles.

synthesis of 5-ethoxycarbonyl-1,2-benzocarbazoles **190** and 1-indolo[2,1-*a*]isoquinolin-5-yl-ethanones **191** was reported by Zhang *et al.*[67] (Scheme 30). Additionally, the developed protocol was successfully optimised with a diverse range of α-acyldiazo compounds as coupling partners with 2-phenylindole. The developed protocol was able to tolerate substituents such as α-alkylacyl, α-alkoxymethylacyl and α-homoallylic acyl affording **190** in good yields while the presence of linear α-acyl diazoketones resulted in the corresponding product **191** in acceptable to very good yields. However, 11*H*-benzo[*a*]carbazole was furnished as a product when cyclic α-acyl diazoketones were used as the coupling partner. It was also observed that the presence of a substituent on the N-atom of indole restricted the formation of any product. The authors describe the formation of **190** and **191** through the formation of a "rhodacycle" intermediate **194** by the *N*-coordination of 2-phenylindole **188** to the Rh(III) catalyst, and thereafter the synergistic effect of copper afforded the formation of **190**, while, silver (without silver to lesser yields) yielded **191**.

Several natural products such as silicine, ervatamine and actinophyllic acid comprise seven-membered ring skeletons fused with an indole motif and exhibit exceptional biological activities.[68] An important contribution of cooperative catalysis for building these key structural motifs comes in the form of a Ag/Zn relay catalysis protocol involving cyclo-addition/annulation processes providing natural products, silicine and ervatamine as well as indole containing 5,7,6-tricyclic skeletons.[69] A large variety of alkynols (dienophiles) **199** bearing electron-donating and withdrawing substituents were employed as substrates and reacted with dienes **200** under Ag-catalysed hydroamination/[4 + 3] cyclo-addition reactions, thus, affording fused-indole skeletons **206** (Scheme 31). Both diene **203** and dienophiles were accommodated in the presence of electron-donating and electron-withdrawing substituents at different positions, therefore generating the corresponding fused indole framework in acceptable yields. However, in the case of dienes, electron-rich substituents offered better reactivity as compared to electron withdrawing substituents.

The indole moiety diindolylmethane is used in diverse biological applications for its role in antibacterial, anti-fungal, anti-androgenic, anti-cancer, or anti-implantation activities.[70] Likewise, synthetic analogues of diindolylmethane compounds are well-known dyes and used as colorimetric sensors.[71]

A notable advancement in the synthesis of these molecules was achieved by Kayet *et al.*[72] utilising Pd/Ag-relay catalysis in a one-pot Sonogashira-cyclo-isomerisation reaction cascade for the direct step-economical synthesis of diindolylmethanes **211**. This enabled 2-iodoanilines **207**, TMS-acetylene **208** and aldehydes **209** to react under optimised reaction conditions,

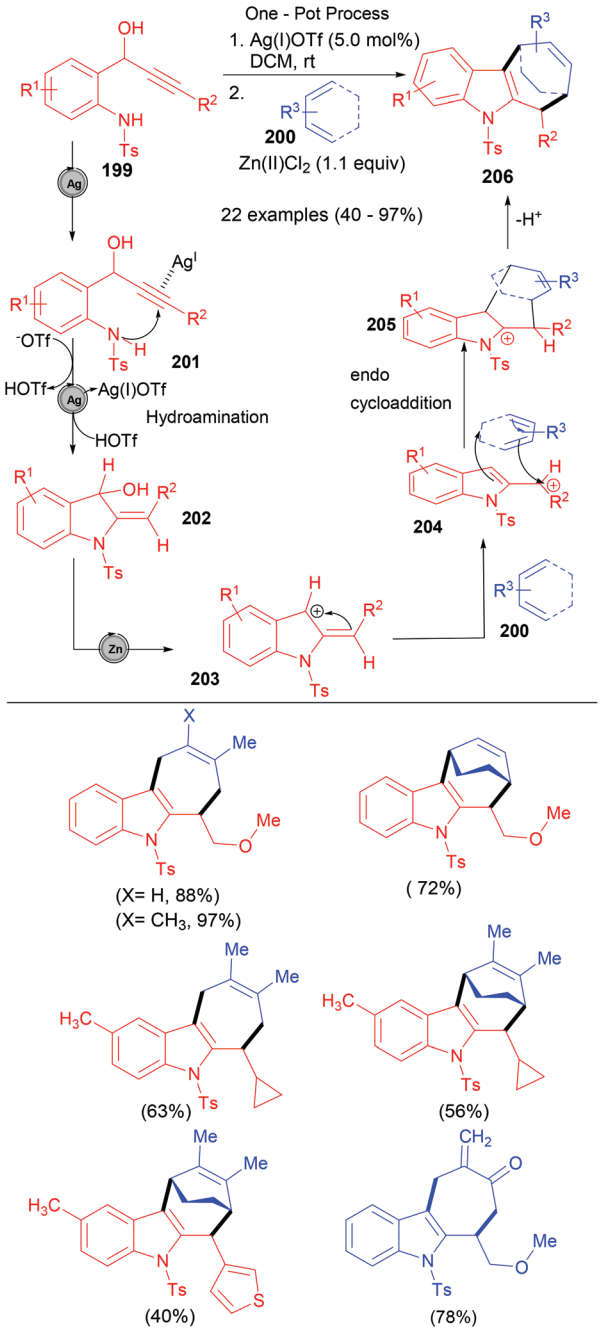


Scheme 30 Rh-Catalysed aryl C–H carbenoid functionalisation in the indole directed cyclisation processes.

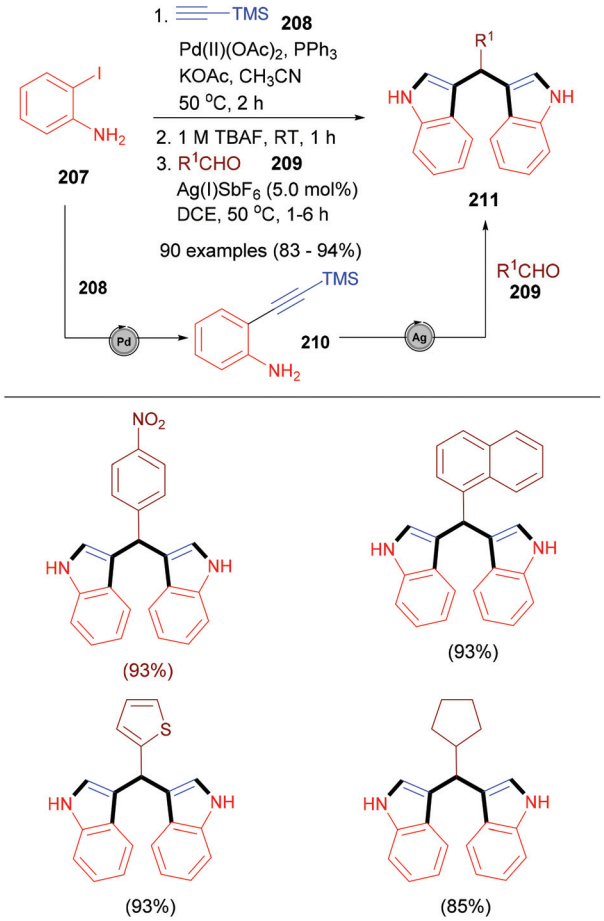
affording 2,2-disubstituted diindolylmethanes **211** (Scheme 32). The results obtained confirm the role of the silver catalyst in the activation of alkynes as well as the carbonyl compounds. It is noteworthy that this procedure was not restricted to the use of aryl or alkyl substituted precursors and alkynes as coupling partners, but also enabled hetero-aromatic substituted iodoanilines and alkynes.

Reddy *et al.*[73] reported a versatile method for the formation of octahydrospiro[pyran-4,4′-pyrido[3,4-*b*]indole] scaffolds **72** based on the employment of a Au/Ag bimetallic catalyst system. The reaction between 3-((3-(2-aminophenyl)prop-2-ynylamino)methyl)but-3-en-1-ol derivatives **212** and aromatic aldehydes **213** reached completion after 2 h at 25 °C affording the corresponding octahydrospiro[pyran-4,4′-pyrido[3,4-*b*]indole]s (**216**) in good yields (Scheme 33). A closer inspection of the substrate scope suggests that electron-rich aldehydes are the most suitable candidates for obtaining maximum yields of the corresponding products compared to electron-deficient aldehydes. Additionally, the incorporation of a heterocyclic aldehyde, namely thiophene-2-carboxaldehyde, was also found to be suitable for this transformation.

1*H*-Indazoles are well-known biologically relevant nitrogen containing heterocycles, providing a broad application window in pharmaceuticals. The incorporation of these motifs over the organic skeletons unveils a wide range of biological functions, such as anti-inflammatory, anti-viral, anti-microbial, and anti-cancer activities.[74] The work reported by Bagle *et al.*[75] impressively shows the potential of the Au/Ag relay catalyst system for



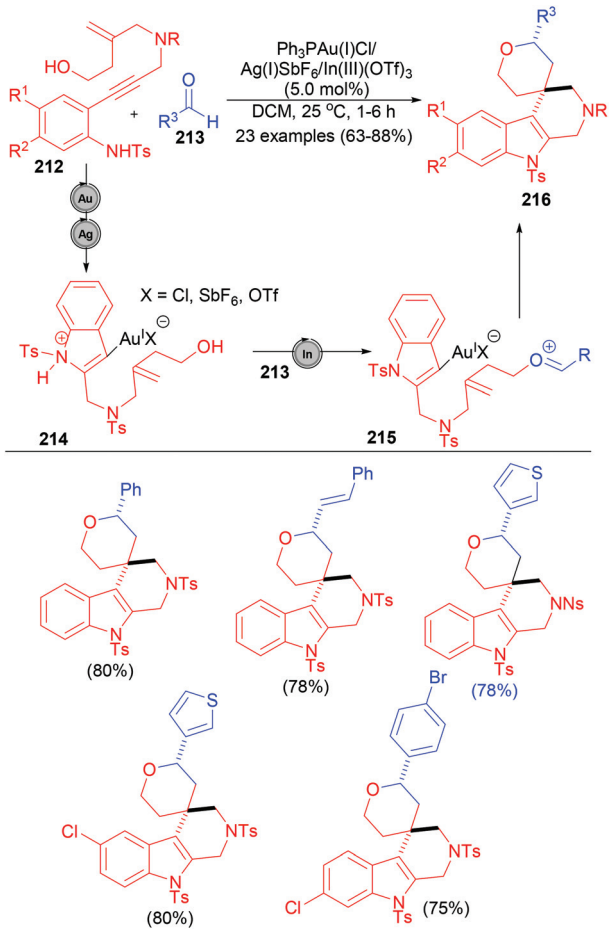
Scheme 31 Ag/Zn relay catalysis in tandem hydroamination/[4 + 3] cyclo-addition processes for the synthesis of seven membered fused indole skeletons.



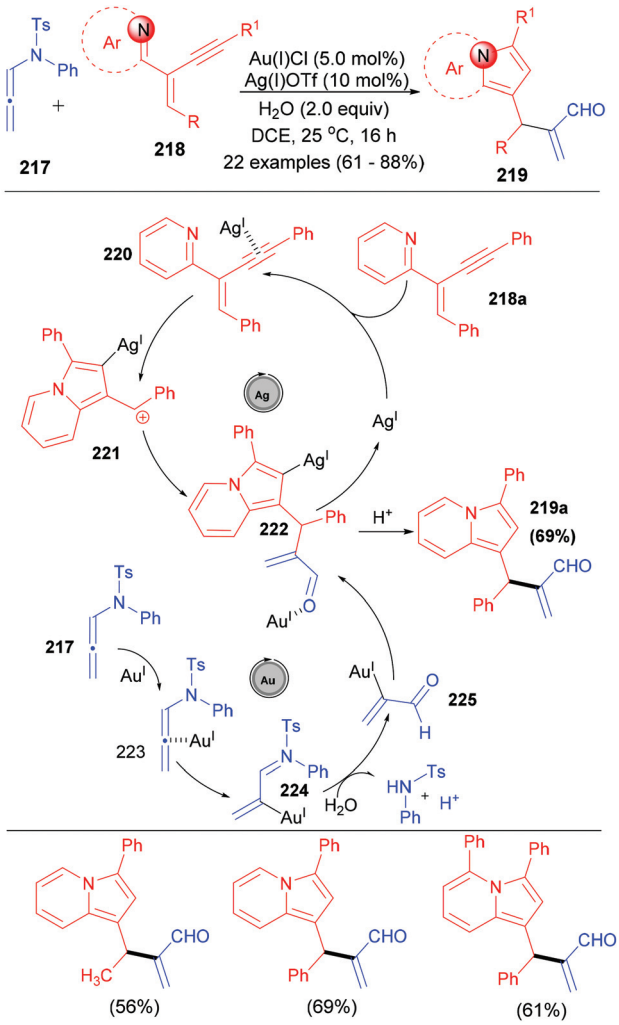
Scheme 32 Synthesis of diindolylmethanes using Pd/Ag bi-metallic catalysts.

the synthesis of indolizines **219.** In comparison to the classical methods of synthesis and metal catalyst protocols, the bi-metallic catalysis offers significant benefits since the overall transformation is step-economical. The authors investigated a platform for the cyclo-addition reaction between α-gold(I) enals (from *N*-allenamides **217**) as nucleophilic enal equivalents and the *in situ* generated silver-bound carbocations (from π-acid-triggered imino-alkyne **218** cyclisation) (Scheme 34). A large number of *N*-allenamides were found to react smoothly with several pyridino-alkynes decorated with electron donating as well as halo groups and afforded the desired products in good to excellent yields. The substituents attached to the alkene part of the pyridino-alkynes bearing both electron-donating and electron-withdrawing groups were well tolerated under the optimised reaction conditions, providing alkyl/aryl substituted indazolines. In addition to that, substituents like Ph and 4-OMe-C_6H_4 decorated on the pyridine ring were also tolerated under optimised reaction conditions.

Recently, an inspiring catalytic protocol involving a Rh catalyst for the synthesis of 1-aryl-indazoles **228** *via* a cooperative rhodium and copper catalysed (C–H) activation and (C–N/N–N) coupling reaction of imidates **226** with nitrosobenzenes **227** as a convenient aminating reagent was demonstrated by Wang *et al.*[76] (Scheme 35). The versatility of the developed strategy was highlighted in terms of step- and atom-economy, and most importantly the formation of H_2O as the sole by-product. The contribution of electronic effects in this reaction was studied by allowing a variety of imidate esters to react with several nitrosobenzenes under optimised reaction conditions. The benzimidates accommodated with both electron-donating and withdrawing groups at *para*- as well as *meta*-positions were found to react smoothly under the optimised reaction con-



Scheme 33 Synthesis of substituted octahydrospiro[pyran-4,4′-pyrido[3,4-*b*]indole] using a Au/Ag/In multi-metallic catalytic system.



Scheme 34 Synthesis of indolizines using Au/Ag bimetallic catalysts.

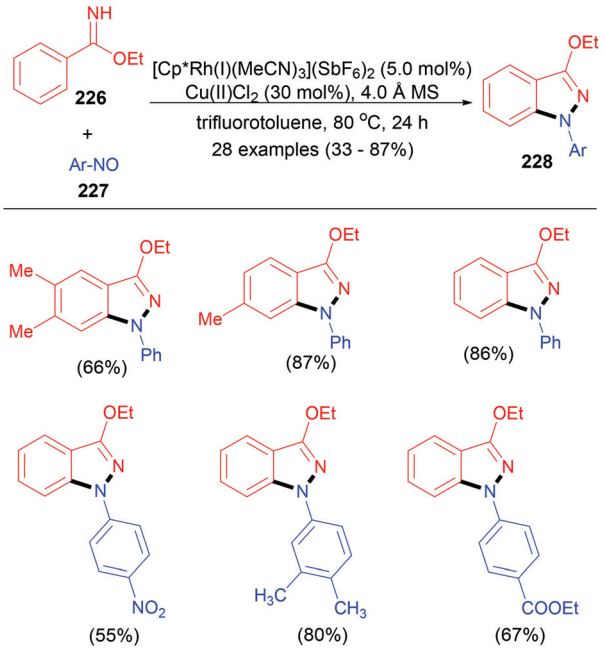
ditions delivering the desired products in moderate to good yields with excellent regio-selectivity.

In addition to the details provided earlier, the authors also examined the synthetic applications of the suggested protocol for the reaction between the synthesised indazole analogue **228a** with 1,4,2-dioxazol-5-one **229** as an amidating reagent, affording the desired product **230** *via* a Rh(III)-catalysed (C–H) activation pathway in acceptable yield (Scheme 36).

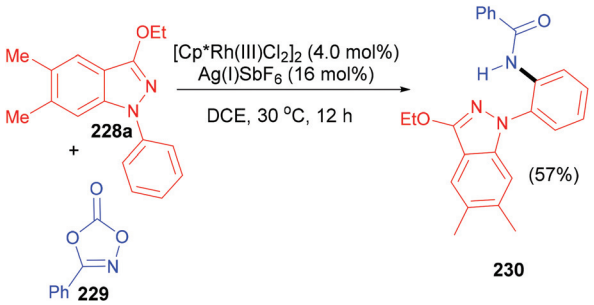
Furthermore, Zhu *et al.*[77] also found that the Pd/Cu relay catalytic system offers a state of the art synthetic strategy for the cross-coupling of 2-alkynyl azobenzenes **231** with terminal alkynes **232** to afford (3-isoindazolyl)allenes **233** in respectable yields. The thermally induced cyclisation of **233** (R^1 = H, R^2 and R^3 = Ph) afforded 5-benzyl-6-phenylindazolo[2,3-*a*]-quinoline **234** in excellent yield (Scheme 37).

Notably, 5-benzyl-6-phenylindazolo[2,3-*a*]-quinolines are highly privileged heterocycles showing interesting biological and optical properties. The reaction proceeds through the formation of a copper–carbene complex of indazole *via* Cu-catalysed cyclo-addition which further takes part in a Pd-catalysed cross-coupling reaction providing indazolo[2,3-*a*]-quinolines.

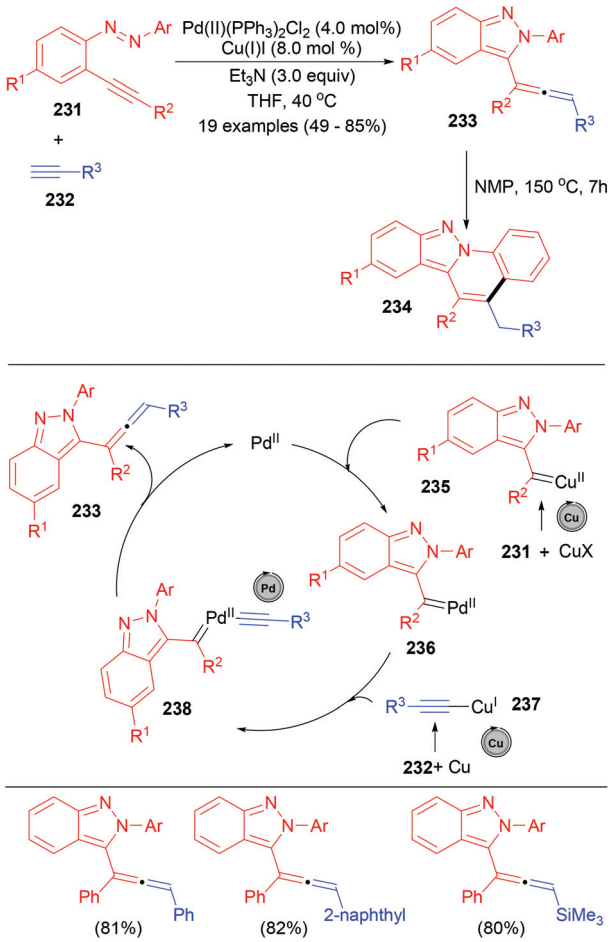
Pyrido[1,2-*a*]benzimidazoles are unique substructures that show exceptional anti-malarial,[78] anti-tumor[79] and anti-viral activities.[80] Extensive efforts have already been dedicated towards the synthesis of biologically important scaffolds of pyrido[1,2-*a*]benzimidazoles.[81] As a part of the scientific endeavor to develop convenient synthetic methods, tolerating a wide range of functional groups, a highly efficient one-pot protocol for the synthesis of these heterocyclic scaffolds is exceedingly desirable. An efficient protocol for an intramolecular electrophilic aromatic substitution reaction for the synthesis of pyrido[1,2-*a*]benzimidazoles **241** from *N*-phenylpyridin-2-amine **237** was introduced by Wang *et al.*[82] in 2010 (Scheme 38). After optimizing the reaction conditions for the synthesis of pyrido[1,2-*a*]benzimidazoles **237**, the authors examined that the contribution of electronic effects in combination with the steric effects exerted by the substituent (R^2) present at *ortho*- or at *para*-positions relative to the aniline nitrogen was found to be well-tolerated. This resulted in good to excellent yields of the desired product **241**. Furthermore, pyridine backbones (R^1) bearing electron-donating as well as electron withdrawing groups were also well tolerated; however, the presence of electron-donating groups provided better reac-



Scheme 35 Rh/Cu cooperative catalysis in the synthesis of 1*H*-indazoles.



Scheme 36 Synthetic exploration of Rh-catalysed C–H bond functionalisation in the synthesis of *N*-(2-(3-ethoxy-5,6-dimethyl 1*H*-indazol-1-yl)phenyl)benzamide.



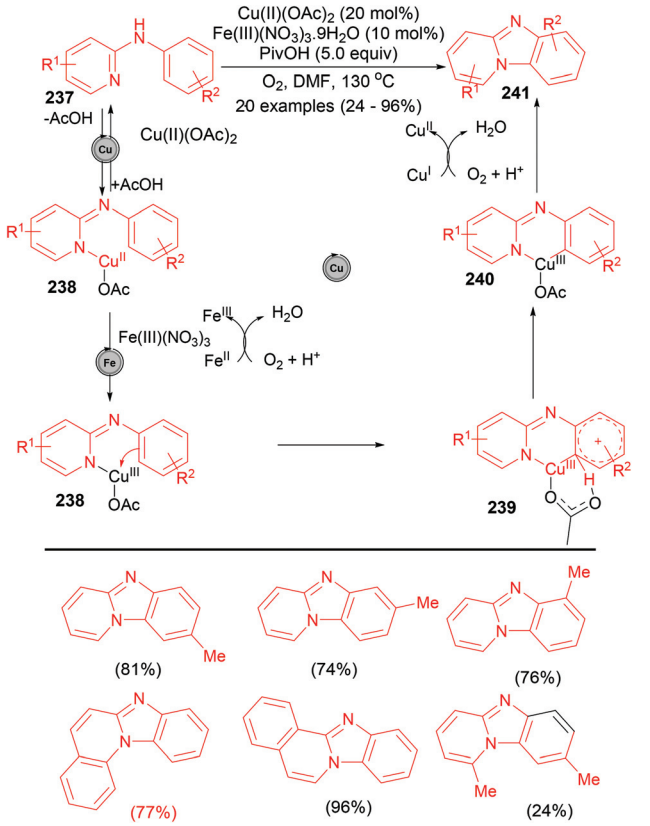
Scheme 37 Pd/Cu catalysed cross-coupling of 1,1-diacyl-1-en-3-ynes with terminal alkynes in the synthesis of indazolo[2,3-*a*]quinolones *via* (3-isoindazolyl)allenes.

tivity as compared to the electron-withdrawing groups, in terms of the outcome of the process. Interestingly, the presence of a methyl group in all positions facilitates the transformation to the product. However, the presence of a methyl group next to the pyridine ring nitrogen exerts a detrimental effect on the overall progress of the reaction which has been attributed to its steric effect, which interferes with the coordination of copper to the pyridine nitrogen.

Benzoxazoles are highly privileged scaffolds commonly present in pharmaceuticals and dyes, and in the synthesis of functional materials.[83] In 2015, Zhu *et al.*[84] reported the Pd/Cu-catalysed method for the preparation of benzoxazoles **246** and **247** from the cyclic diaryliodonium precursor **242** in excellent yields using triphenylphosphine as a ligand and DMF as a solvent (Scheme 39). To elucidate the scope of the present catalytic system, several electronically diverse alkynes **243** and alkenes **244** were properly tolerated as coupling partners furnishing excellent yields of the highly fluorescent benzoxazoles.

Wang *et al.*[85] have recently disclosed an interesting example involving cooperative catalysis using a Rh/Cu relay catalyst system for the reaction between vinylazides **248** with alkynes **152** allowing an easy access to substituted isoquinolines **256**. The authors revealed that their action proceeds with the conversion of vinylazides into azirines *via* thermal cycloisomerisation, which further underwent Rh/Cu-catalysed cycloadditive transformation with alkynes affording isoquinolines as products in excellent yields (Scheme 40).

Strikingly interesting results were documented for alkynes bearing electronically different substituents to react with vinyl azides, which gave the corresponding isoquinolines in good to excellent yields. Moreover, unsymmetrical alkynes such as 1-phenyl-1-propyne, methyl 3-phenylpropiolate and thionylacetylene afforded the corresponding isoquinolines as the sole product. The effect of the electronic nature of the substituent present on the benzene ring of vinyl azides was scrutinised under optimised reaction conditions. The electron withdrawing nature of the substituent was found beneficial for this



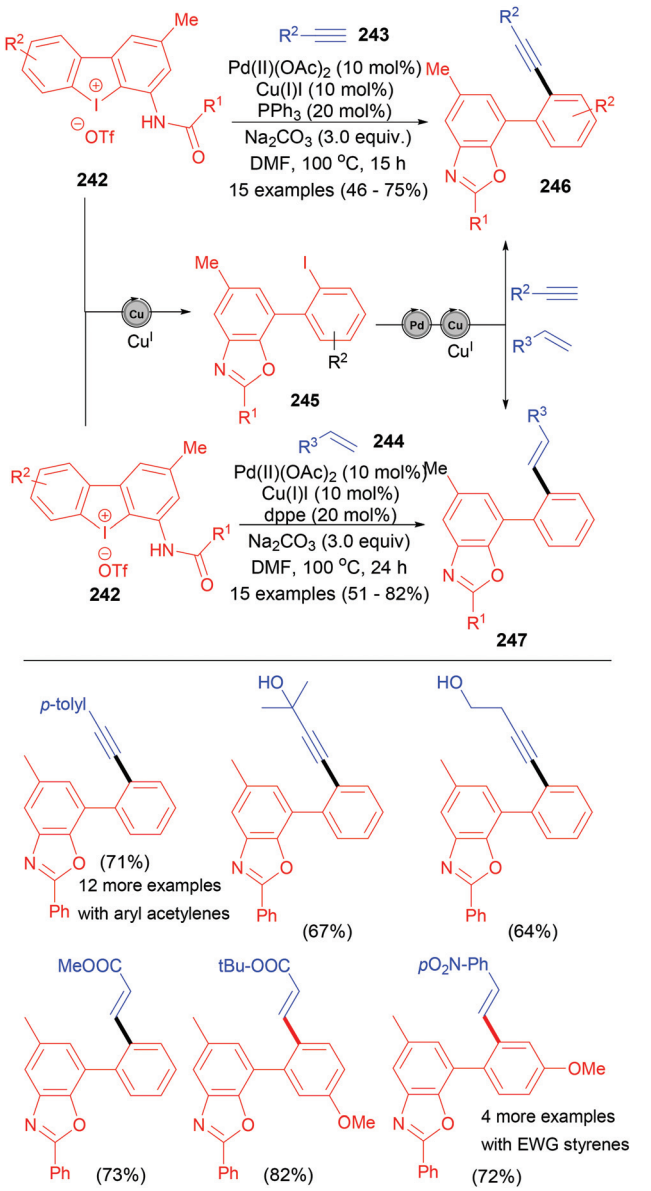
Scheme 38 Synthesis of pyrido[1,2-*a*]benzimidazoles using Cu/Fe bimetallic catalysts.

transformation. Thus, electronically rich substituents present on vinyl azides or sterically demanding vinyl azides such as 1-naphthyl vinyl azide were unsuitable candidates for this reaction. Notably, not only arylvinylazides but also hetero-arylvinylazides were well tolerated under the conditions reported in Scheme 40.

The same group[86] addressed a comparatively mild Rh/Cu cooperative catalysis protocol for the synthesis of isoquinoline derivatives **260** using DMF as a solvent. Authors reported that a wide variety of internal alkynes **152** proved to be well tolerated and to cycloisomerise with differently substituted *O*-acetyloximes of arylketones **257** (Scheme 41) in the presence of the Rh/Cu catalytic relay system. The electronic nature of the substituent present on both the reactants has no significant effect on the regio-selectivity and on the outcome of the final product.

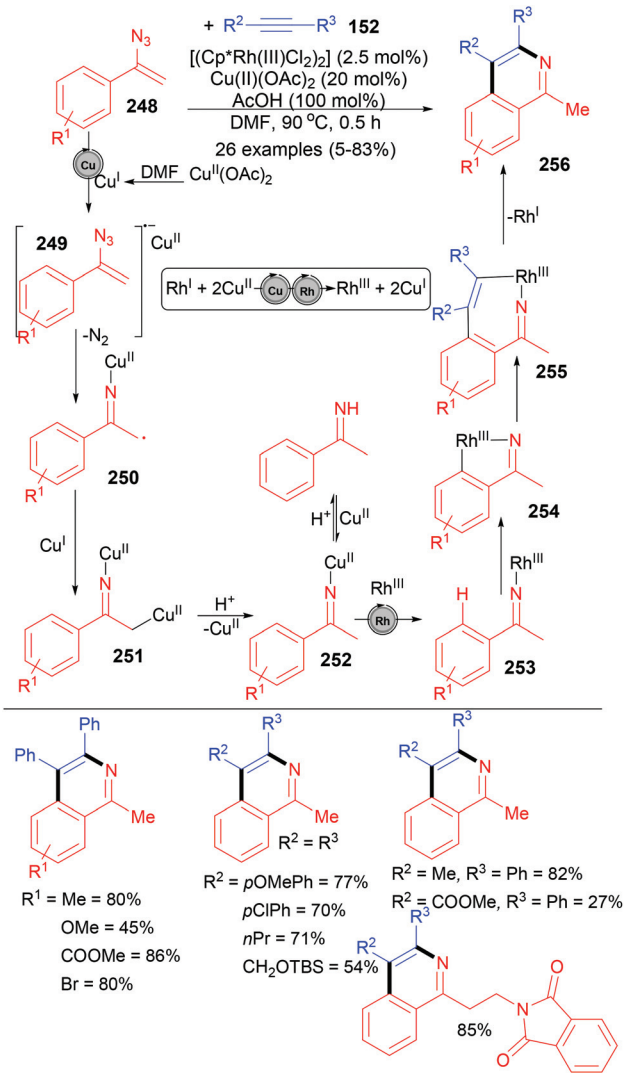
The group also synthesised a 2-heteroatom fused system by utilizing N–Pg indoles, benzofurans, *etc.* as starting acetyl oximes in excellent yields.

A variety of pyrano[4,3,2-*ij*]isoquinoline **263** were also readily prepared from the corresponding benzimidates **261** and α-aroyl sulfur ylides **262** through *ortho*-C–H bond functionalisation under the reaction conditions shown in Scheme 42.[87] The corresponding pyrano[4,3,2-*ij*]isoquinolines were obtained in acceptable to good yields with an outstanding functional group compatibility.

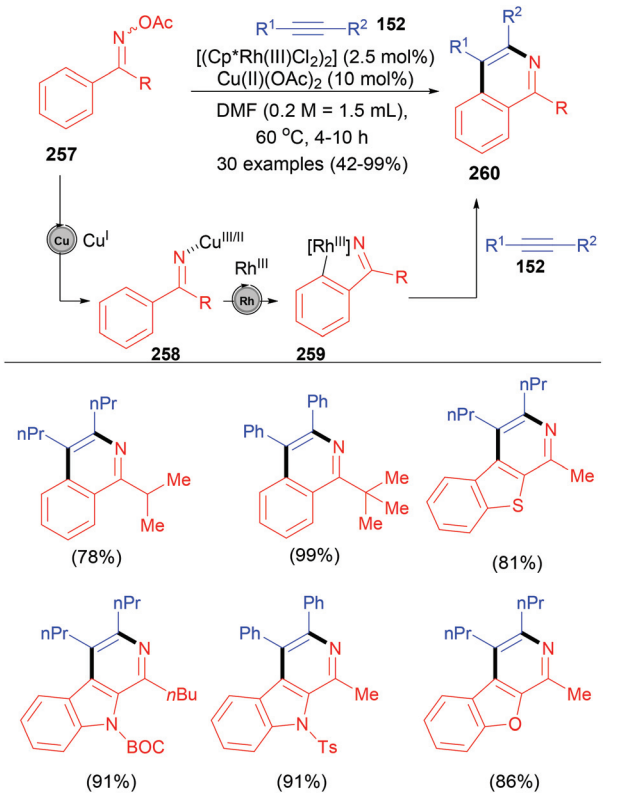


Scheme 39 Pd/Cu relay catalysed regio-selective alkynylation/olefination of cyclic diaryliodonium compounds for the synthesis of benzoxazoles.

H-Pyrazolo[5,1-*a*]isoquinolines have been well recognised for the inhibition of CDC25B, TC-PTP, and PTP1B.[88] In consideration of their biological importance, it is highly desirable that an efficient and robust protocol for the synthesis of *H*-pyrazolo[5,1-*a*]isoquinolines is developed. In this context, Huang *et al.*[89] revealed the Ag/Cu cooperative catalyst system as a very powerful combination for the synthesis of a wide variety of *H*-pyrazolo[5,1-*a*]isoquinolines **273** (Scheme 43). With this aim, Ag catalyses the formation of *N*-iminoisoquinolinium ylides **273** from *N*′-(2-alkynylbenzylidene)hydrazide **270**. Later, bromoalkyne **271** was introduced in the presence of the Ag/Cu relay catalyst to afford a good yield of the desired product under mild reaction conditions using DBU as the base and DCE as the solvent. Overall, the explora-



Scheme 40 Synthesis of isoquinolines using Rh/Cu bimetallic catalysts.



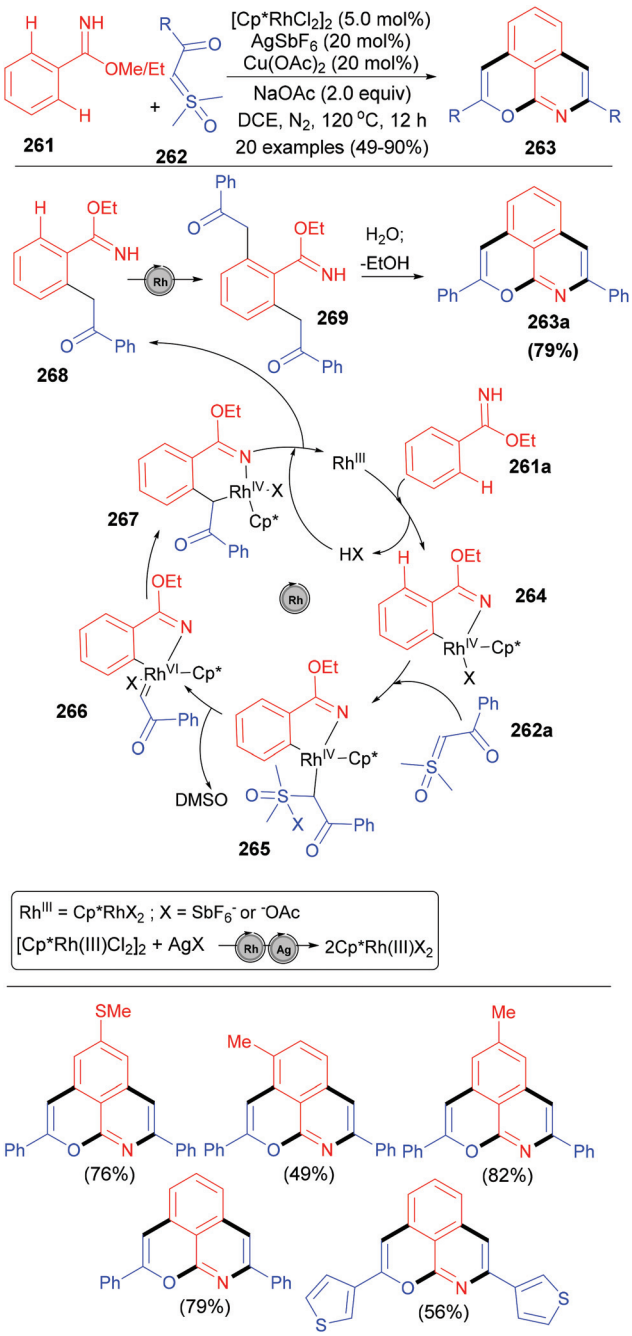
Scheme 41 Rh/Cu relay catalysis for isoquinolines from *O*-acetyl-oximes derived from aryl ketones and internal alkynes.

tion of the substrate scope for the Ag/Cu relay catalytic transformation provides access to a wide range of substituted *N*′-(2-alkynylbenzylidene)-hydrazides and bromoalkynes. Interestingly, the fluoro-substituted *N*′-(2-alkynylbenzylidene) hydrazides were tolerated under optimised reaction conditions which is particularly important because the presence of fluorine as a substituent improves properties such as solubility, bioavailability, metabolic stability *etc*. of the resulting product **273**.

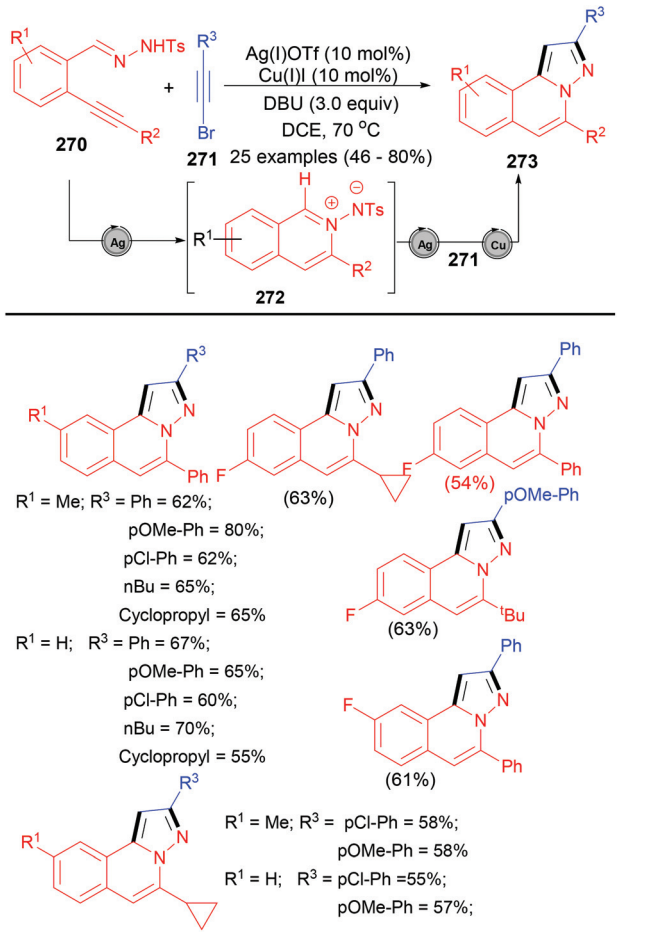
In 2013, Xiao *et al.*[90] investigated the synthesis of *H*-pyrazolo[5,1-*a*]isoquinolines **277** from *N*′-(2-alkynylbenzylidene)hydrazones **274** with alcohols **275**, using Ag/Pd cooperative catalysis under an oxygen atmosphere suggesting the silver (I)-catalysed 6-*endo* cyclisation of *N*′-(2-alkynylbenzylidene) hydrazine (*in situ* generated) **276** *via* insertion. This was followed by a nucleophilic attack of the *in situ* generated enolate to isoquinolinium-2-yl amide **278**, and subsequent intramolecular condensation, and aromatisation affording the H-pyrazolo-[5,1-*a*]isoquinolines (Scheme 44). In addition, the electronic nature of the substituent present on the alkynyl bond of *N*′-(2-alkynylbenzylidene)hydrazine was found to have no significant effect on the outcome of the reaction.

Quinolones are structural motifs performing an important role in the field of medicinal chemistry.[91] The quinoline-based natural products exhibit fascinating biological activities and are extensively employed as anti-malarial, anti-bacterial, anti-fungal, anti-epileptic, anti-inflammatory, analgesic and anti-tumor drugs.[92] Very recently, Shobeiri *et al.*[93] developed a protocol for a series of quinolin-4-yl-methanol derivatives as tubulin inhibitors. The exploration of quinolin-4-yl-propanol derivatives as inhibitors of Factor Xa (FXa)[94] and quinolin-4-yl-ethanol derivatives as inhibitors of PPAR[95] have also been cited in the literature.

Classical methods for the synthesis of quinolines such as Skraup, Doebner–von Miller, Friedlander, Pfitzinger, Conrad–Limpach and Combes synthetic procedures are known to suffer from several synthetic drawbacks.[96] These problems were highlighted in an extensive report by Jiang *et al.*[97] which comprehensively cites the literature regarding the recent development of the synthetic methodology. Various transition metal catalysts had been explored for the synthesis of 2,4-di-substituted-quinoline *via* coupling reactions of alkynes, aldehydes and amines with most of these methods resulting in 2,4-diaryl-quinoline as a product in acceptable yields. Only a few of these protocols were associated with the synthesis of 2-aryl-4-alkylquinoline and they offer limited compatibility



Scheme 42 Multi-metal catalysed *ortho*-C–H bond functionalisation strategy for the synthesis of pyrano[4,3,2-*ij*]isoquinolines.



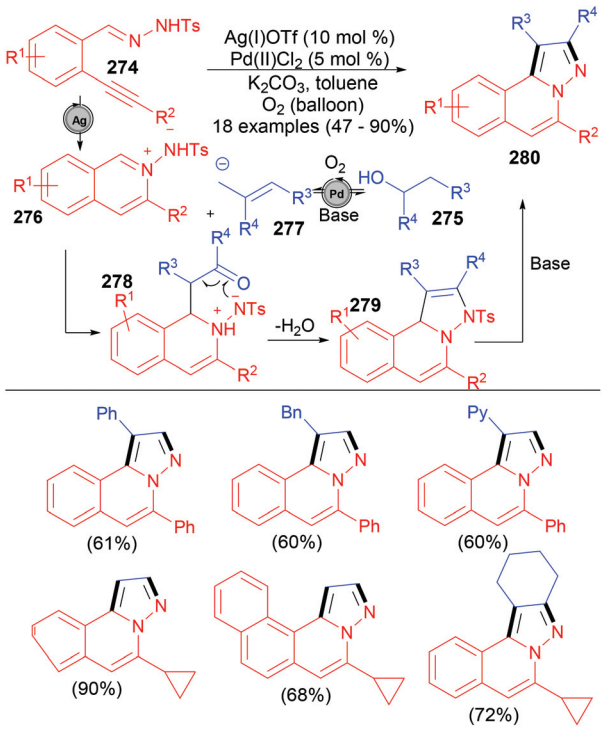
Scheme 43 Silver triflate and palladium acetate catalysed tandem reaction sequence.

with a variety of functional groups. The authors developed a state-of-the-art solution for the construction of 4-hydroxyalkylquinolines **284** in the presence of a Cu/Au cooperative catalyst (Scheme 45) *via* sequential coupling and cyclisation of anilines **281** with aldehyde derivatives **282** and aliphatic alkynes(ols) **283**. Quite a large number of *para*- or *meta*- (F, Cl, NO_2, OMe and CH_3)-substituted aromatic aldehydes and anilines were tolerated. In addition, the electron-rich amines were identified as optimal for producing good to excellent yields of the desired products.

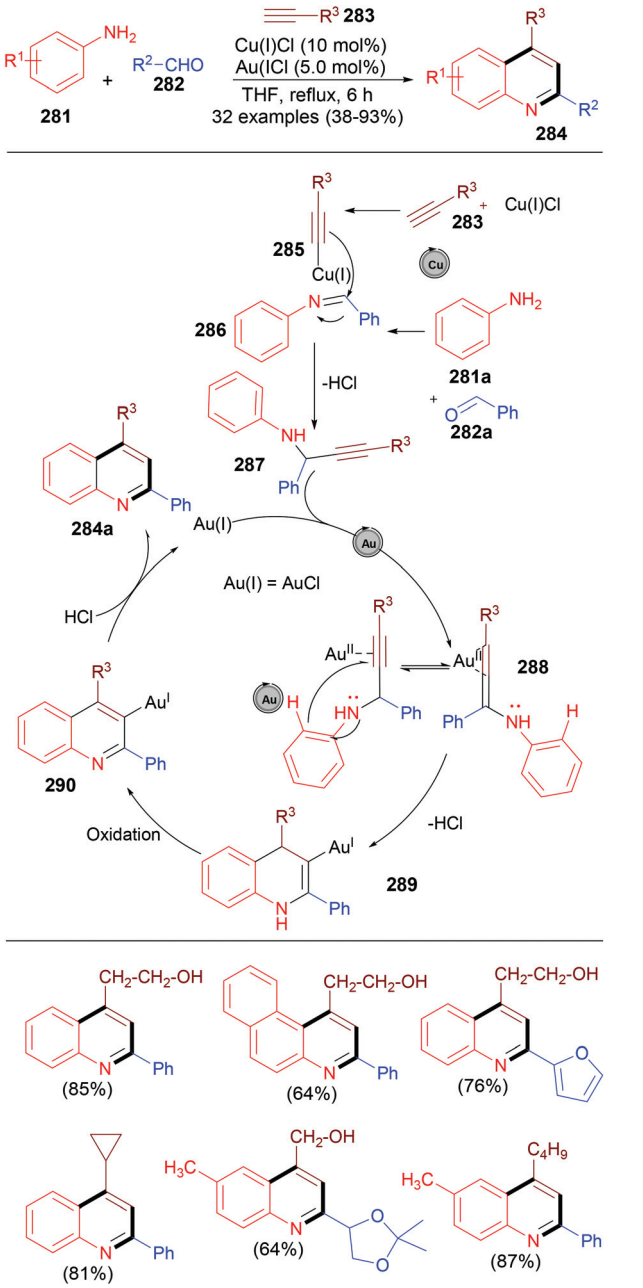
A wide variety of terminal aliphatic alkynes such as but-3-yn-1-ol, pent-4-yn-1-ol, prop-2-yn-1-ol, hex-5-yn-1-ol, pent-4-yn-2-ol and methyl propiolate as well as aryl alkynes (phenyl acetylene) was found to be suitable for this transformation. Furthermore, quite a few aliphatic aldehydes for example formaldehyde, glyceraldehyde or furan-2-carbaldehyde were tested under optimised reaction conditions, providing the corresponding products in good yields.

Luo *et al.*[98] investigated Zr/Cu catalysed sequential Mannich addition reactions and C–C/C–N bond formations in the synthesis of highly substituted quinolones **294** and **295** from arylamines **281**, aldehydes **282** and carbonyl species **292** and **293** respectively, under milder reaction conditions (Scheme 46). An imine intermediate **291** was formed by the reaction between **281** and **282** followed by a synergic catalytic effect exhibited by a zirconocene dichloride and trimellitic acid (**296**) favoring Mannich addition and C–C bond construction reactions, whereas CuO in the presence of an acid catalyses the oxy-dehydrogenation reaction of **291** with **293** and **294**, to afford the corresponding **294** and **295**, respectively.

The method furnishes quinolones in good to excellent yields with an ample substrate scope while employing com-



Scheme 44 Ag/Pd bimetallic catalysis in the synthesis of H-pyrazolo [5,1-*a*]isoquinolines.



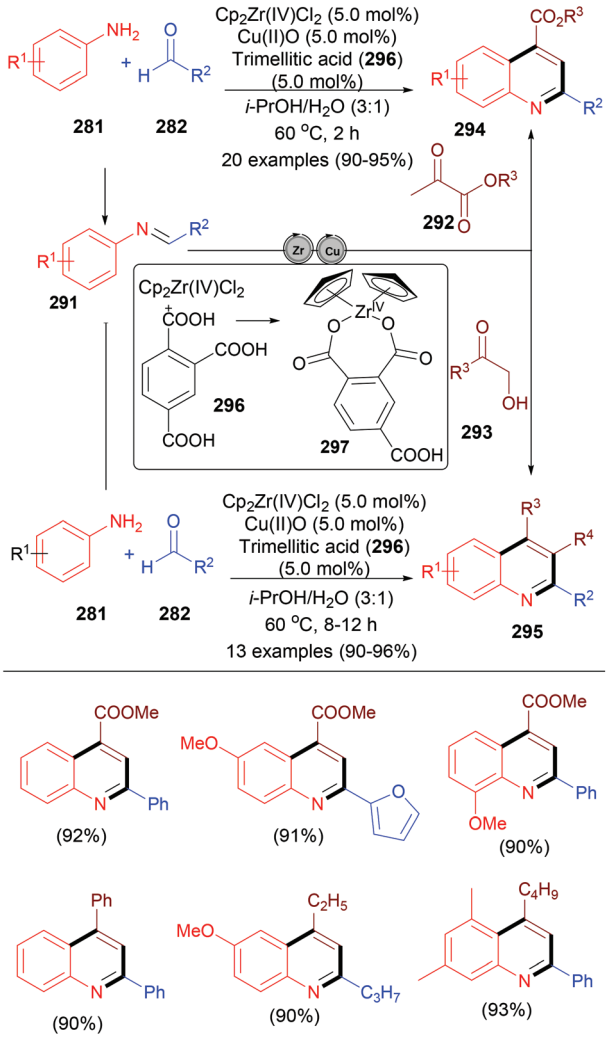
Scheme 45 Cu/Au catalysed synthesis of 4-hydroxyalkyl-quinoline derivatives.

mercially available anilines, aldehydes and aromatic or aliphatic carbonyl compounds.

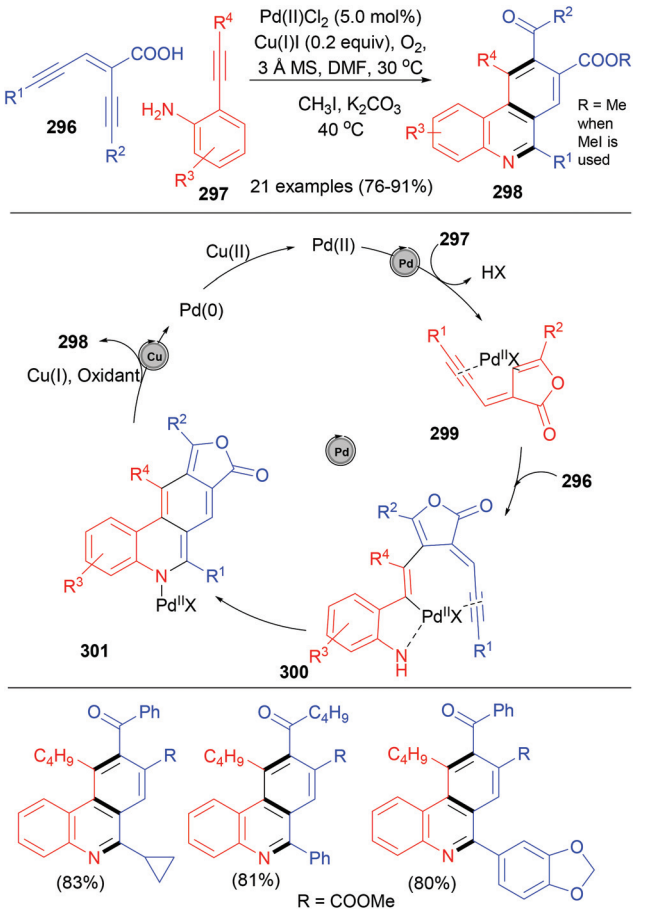
Phenanthridines are important quinolone-based heterocyclic motifs found in numerous natural products, pharmaceutical molecules and other functional materials.[99] In the field of macro and meso-scale organic metal-mediated transformations, palladium can still be considered in its infancy. Liu *et al.*[100] reported an unprecedented synthesis with the Pd/Cu bimetallic-catalysed preparation of 9-acylphenanthridines **298** *via* the insertion of ene–diyne acids **296** with *ortho*-alkynylanilines **297** through sequential tandem crossover-annulation and oxygenation reactions (Scheme 47).

The electronic effect exerted by the substituents present on the aniline part had no significant impact on the outcome of the process. Additionally, substituted acids with a wide variety of electronically diverse substituents were found to be compatible with the optimised reaction conditions, offering good yields of the corresponding products.

Quinazoline and quinazoline-based heterocycles are integral parts of many pharmaceutically important molecules namely erlotinib, gefitinib, prazosin and human adenosine A3 receptor antagonists. Functionalisation of the derivatives of 4-aminoquinazoline is of major synthetic relevance due to the wide range of biologically relevant molecules known.[101] Owing to their exceptional medicinal potential, the synthesis of derivatives of 4-aminoquinazoline has captured much attention in recent years. While the existing synthetic protocols provide efficient access to 4-aminoquinazolines, their utilisation is restricted because vigorous reaction conditions are required and due to the poor selectivity of the reaction. Subsequently, a rapid, highly efficient method for the construction of 4-aminoquinazolines with excellent selectivity and with a broad substrate scope was presented by Jia *et al.*[102] demonstrating the use of Fe/Cu relay catalysis for a one-pot domino reaction consisting of a series of iron and copper mediated transformations such as iron-mediated [3 + 2] cyclo-addition, copper-catalysed S_NAr, reduction, cyclisation, oxidation, and copper-catalysed denitrogenation sequences facilitating an easy access to biologically relevant 2-phenylquinazolin-4-amines **313.** The products were



Scheme 46 Zr/Cu relay catalysis in the synthesis of quinolines involving one-pot sequential Mannich reaction followed by (C–C/C–N) bond formation.

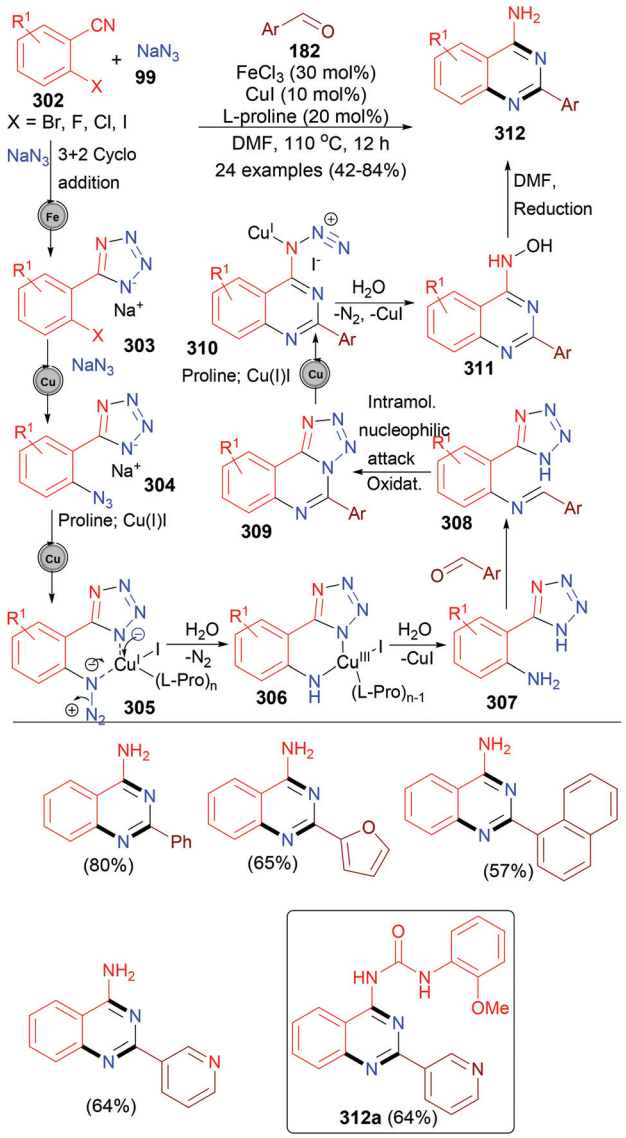


Scheme 47 Pd/Cu relay catalysed tandem annulation/oxygenation protocol for 9-acylphenanthridine.

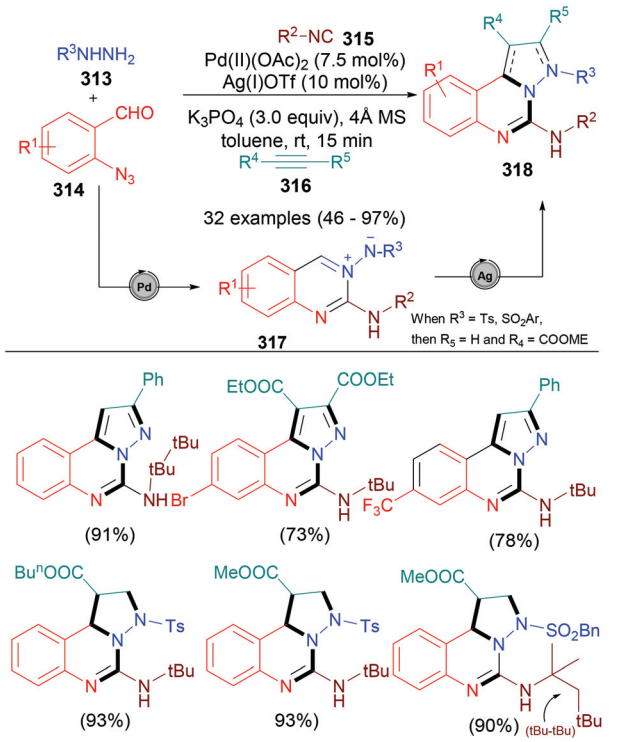
obtained by the reaction between *ortho*-halogenated benzonitriles **302**, sodium azide **99** and aldehydes **182** in moderate to excellent yields under mild experimental conditions *via* the formation of **310** (Scheme 48). The scope and compatibility with different functional groups was studied for the present domino process.

Different aromatic aldehydes with electron-neutral (4-H, 2-Me, 4-Me), electron-donating (4-OMe, 4-OEt, 3,4-$(OMe)_2$) and electron-deficient (3-NO_2) groups and halo substituents were well tolerated under the optimised reaction conditions with highest yields of the desired products. Sterically demanding substrates (1-naphthaldehyde and 2-naphthaldehyde) furnished good yields for the corresponding products while heteroaromatic aldehydes including furan-2-carbaldehyde, thiophene-2-carbaldehyde, and thiophene-3-carbaldehyde were found to be compatible for this domino process. To further expand the choice of substrates for this domino transformation, a variety of *ortho*-halogenated benzonitriles and aryl aldehydes were scrutinised. Phenyl rings of 2-bromobenzonitriles installed with an electron-neutral substituent (4-Me, 5-Me), halogen-substituted 2-bromobenzonitriles (5-F, 5-Cl), *ortho*-halogenated benzonitriles such as 2-fluorobenzonitrile, 2-chlorobenzonitrile and 2-iodobenzonitrile were found to be compatible with the optimised reaction conditions. The developed strategy was further explored towards the synthesis of selective human adenosine A3 receptor antagonist 1-(2-methoxyphenyl)-3-(2-(pyridin-3-yl)quinazolin-4-yl)urea, **312a**, under the optimised set of reaction conditions to afford the product in 64% yield.

Recently, Sawant *et al.*[103] investigated a Pd-catalysed one-pot multi-component synthesis of pyrazolo[1,5-*c*]quinazolines **318** from 2-azidobenzaldehydes **314**, alkynes **316**, sulfonyl hydrazides **313** and isocyanides **315** using toluene as the solvent (Scheme 49). The scope and use of the presented method was highlighted in terms of regio- and stereo-selectivity of the process, with a good tolerance of the electronic nature of the variety of substituents. Additionally, the biological evaluation of the synthesised compounds reveals that some of the pyrazolo[1,5-*c*]quinazolines **318** exhibit potent and selective cytotoxicity against cancer cell lines.



Scheme 48 Fe/Cu relay catalysed domino reaction for the synthesis of quinazolines.



Scheme 49 Pd/Ag relay catalysed one-pot multicomponent synthesis of pyrazolo[1,5-*c*]quinazolines.

5. Miscellaneous heteroarenes

In addition to the synthesis of condensed heteroarene frameworks, several examples of other fused heteroarenes using relay catalysts were reported in the literature, *e.g.* the synthesis of pyrido-fused quinazolinones and phenanthridinones,[104] fluorazones,[105] quinolizinium salts,[106] and quinazoline N-oxides.[107] Rao *et al.*[104] used a bimetallic Pd/Ag catalyst in a direct carbonylation of N-phenylpyridin-2-amines **318** and **319** with DMF as the carbonyl source for the synthesis of pyrido-fused quinazolinones **321** and **322**. The work showed that DMF actually acts as a carbon source, while "*O*" originates from air under the Pd/Ag catalytic conditions (Scheme 50).

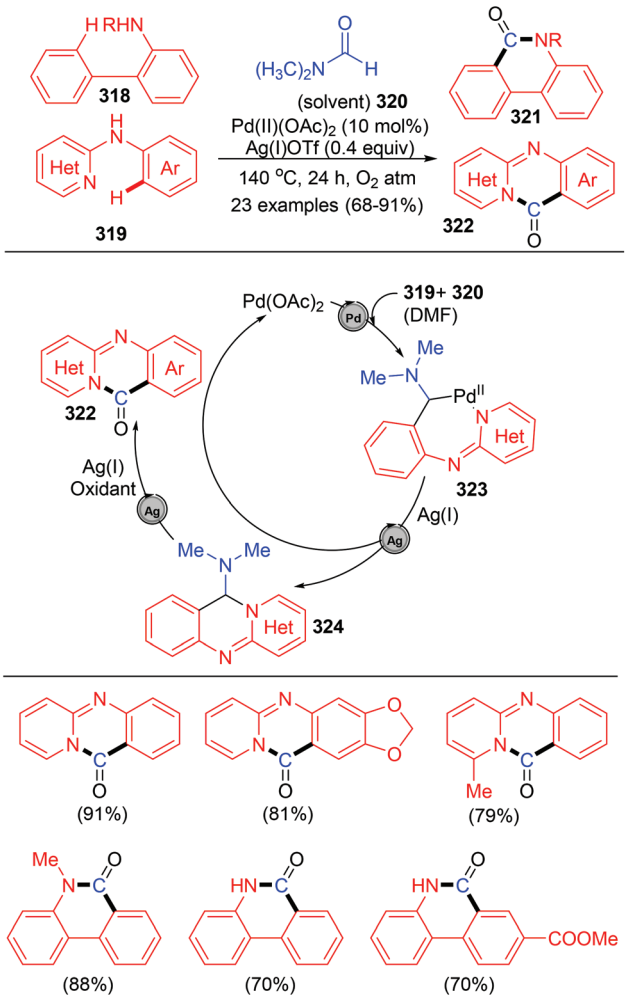
Liao *et al.*[105] used Pd/Cu-relay catalysis for the carbonylative transformation of *N*-aryl pyrroles **325** into biologically important fluorazones **326** under a molecular oxygen atmosphere in toluene/DMSO as the solvent system. The scope and use of the current methodology rests in particular in the good functional group tolerance (Scheme 51).

Initial attempts by the authors suggested that the relay catalytic cascade involving intermolecular cyclo-addition/anion metathesis for obtaining substituted quinolizinium tetrafluoroborate salts **331** from 2-ethylpyridines **329** and alkynes **330** using acetic acid as a solvent could indeed be established under Rh/Cu catalysts in good yields (Scheme 52).[106] The protocol demonstrated excellent compatibility for both substrates. In fact, considerably wide ranges of structurally diverse 2-ethylpyridines **329** and alkynes **330** were well tolerated.

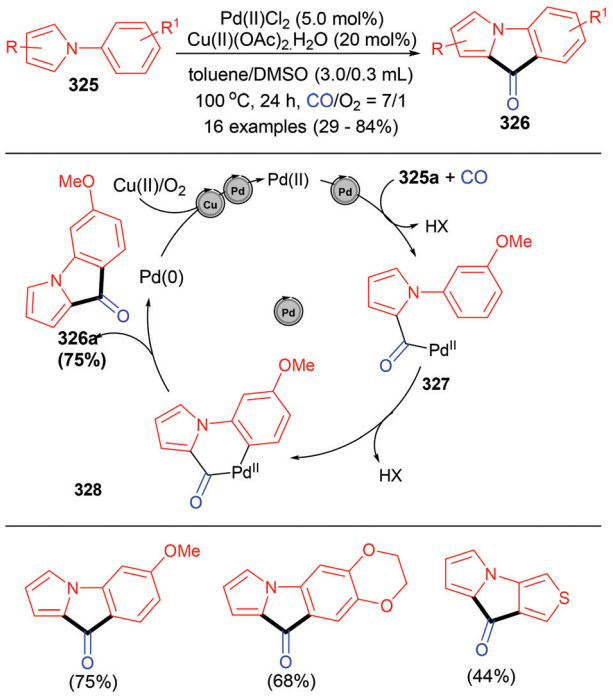
A large number of ketoximes **335** and 1,4,2-dioxazol-5-ones **336** bearing either an electron-donating or electron-withdrawing aryl substituent were applicable to the relay catalytic cascade reaction, leading to the formation of quinazoline *N*-oxides **337** in high yields under mild reaction conditions (Scheme 53).[107]

6. Conclusions

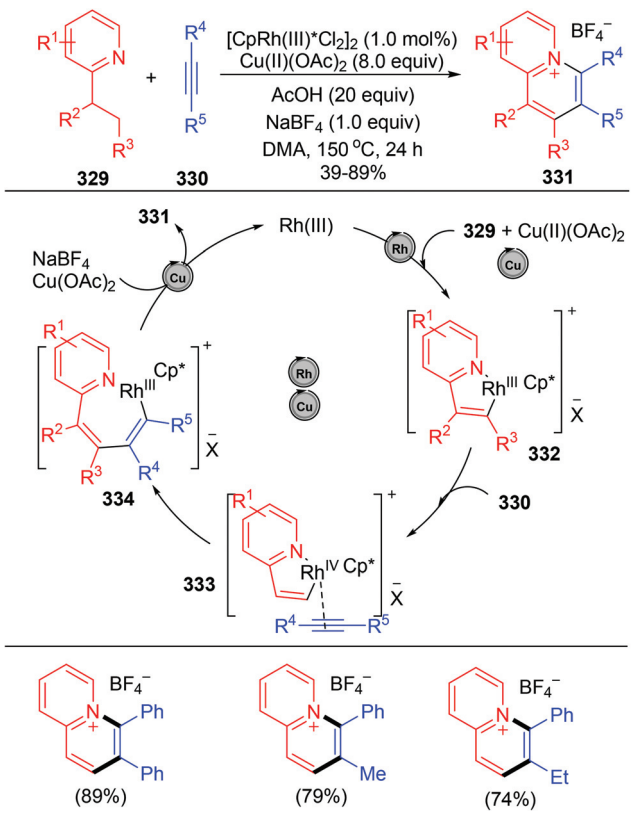
Multimetallic relay catalysis holds exceptional promise and provides researchers with a state-of-the-art solution in synthetic organic chemistry with the possibility of complementing or even replacing the present well-established synthetic protocols. The future of cooperative catalysis looks promising with opportunities in organic transformations (where high selecti-



Scheme 50 Synthesis of pyrido-fused quinazolinones and phenanthridinones using Pd/Ag bimetallic catalysts.

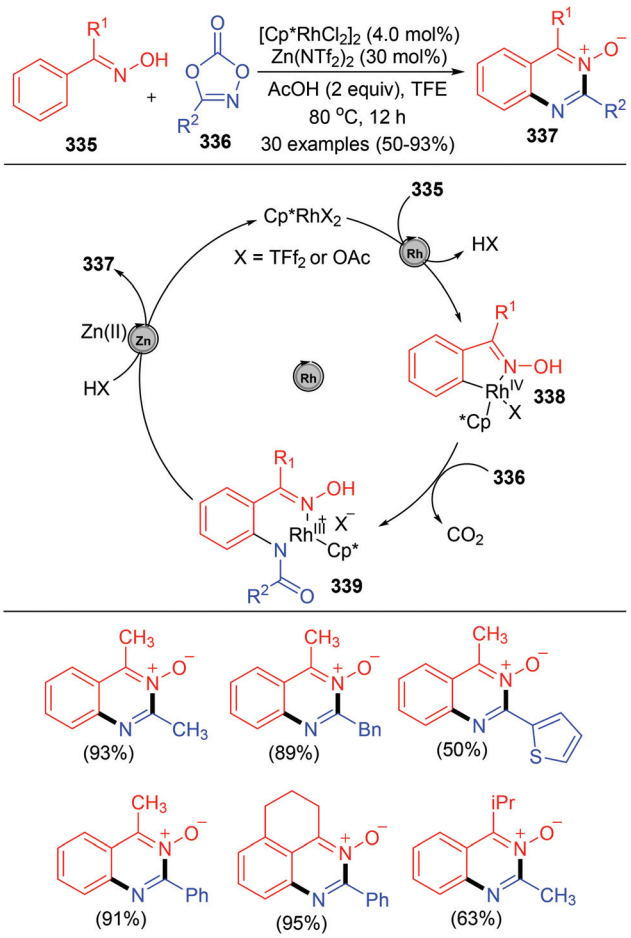


Scheme 51 Synthesis of fluorazones using Pd/Cu catalysts.



Scheme 52 Synthesis of quinolizinium salts using Rh/Cu bimetallic catalysts.

vity is required), for the transformations of highly temperature sensitive reactants into valuable products by utilizing mild conditions, *e.g.* ambient to moderate temperature, and offers good to excellent yields for the tandem as well as domino protocols. Likewise, it is important to develop new protocols where currently shortcomings exist or less research has been done, for *e.g.* newer protocols can be developed for the synthesis of pyrimidine based analogues as currently a few exist. The combination of different transition metals in the presence of additives (if required) such as compounds of the s or p blocks of the periodic table should be a viable approach for highly selective transformations, but a deeper understanding of the mechanistic aspects of these synergistic interactions will also be essential for an even better optimisation of the catalytic performance of the cooperative catalytic system. It is our hope that this review will serve as a guide to the synthetic chemists to modernise the role of cooperative catalytic (either homo-multimetallic or hetero-multimetallic) systems allowing in a single vessel the tandem protocols for the synthesis of biologically relevant highly complex and stereo-chemically challen-



Scheme 53 Synthesis of quinazoline *N*-oxides using Rh/Zn bimetallic catalysts.

ging molecules to occur, which will contribute to the sustainable development of synthetic organic chemistry.

Conflicts of interest

There are no conflicts to declare.

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