Organic & Biomolecular Chemistry

ROYAL SOCIETY OF CHEMISTRY

REVIEW

View Article Online
View Journal | View Issue

Open Access Article. Published on 18 May 2020. Downloaded on 10/24/2025 9:24:05 PM.
This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.

Check for updates

Cite this: *Org. Biomol. Chem.*, 2020, **18**, 3950

Received 17th February 2020,
Accepted 11th May 2020

DOI: 10.1039/d0ob00350f

rsc.li/obc

Recent advances in the synthesis of imidazoles†

Dmitrii A. Shabalin [a] and Jason E. Camp *[b]

The review highlights the recent advances (2018-present) in the regiocontrolled synthesis of substituted imidazoles. These heterocycles are key components to functional molecules that are used in a variety of everyday applications. An emphasis has been placed on the bonds constructed during the formation of the imidazole. The utility of these methodologies based around the functional group compatibility of the process and resultant substitution patterns around the ring are described, including discussion of scope and limitations, reaction mechanisms and future challenges.

Introduction

Imidazoles are an important heterocyclic structural motif in functional molecules and are utilized in a diverse range of applications.[1,2] Despite recent advances, the development of novel methods for the regiocontrolled synthesis of substituted imidazoles is of strategic importance. This is due to the preponderance of applications to which this important heterocycle is being deployed, such as the traditional applications in pharmaceuticals and agrochemicals[3,4] to emerging research into dyes for solar cells and other optical applications,[5–16] functional materials,[17] and catalysis[18] (Fig. 1). It is due to their versatility and utility in a number of these areas that expedient methods for the synthesis of imidazoles are both highly topical and necessary. This review is focused on recent advances in the synthesis of imidazoles and is organized *via* the sorts of bond disconnections that were employed in order to construct the heterocycle. The bonds formed in the reaction are highlighted by being red colored throughout the review and the standard numbering of imidazoles is used in the description of disconnections (Fig. 1).

Synthesis

One-bond formed

There has been limited recent research on the synthesis of imidazoles *via* methods that only form one of the heterocycle's core bonds. Fang *et al.* reported a novel protocol for the cyclization of amido-nitriles **1** to form disubstituted imidazoles **2** (Scheme 1a).[19] The reaction conditions were mild enough for the inclusion of a variety of functional groups including, arylhalides as well as aromatic and saturated heterocycles (Scheme 1b). This reaction is reported to proceed *via* nickel-catalysed addition to nitrile **1**, which followed by proto-demetallation, tautomerization and dehydrative cyclization afforded the desired 2,4-disubstituted *NH*-imidazoles **2** in poor to excellent yield depending on the coupling partners (Scheme 1c).

Two-bonds formed

A two-bond disconnection for the synthesis of imidazoles that has been explored recently is to combine a C^2–N^3 fragment with a N^1–C^4–C^5 unit. For example, Shi *et al.* used this disconnection to form trisubstituted *NH*-imidazoles **8** from the reaction of benzimidates **7** with 2*H*-azirines **6** in the presence of zinc(II) chloride (Scheme 2a).[20] Man *et al.* used a related method for the synthesis of 2-aminoimidazoles **11** (Scheme 2b).[21] Under a variety of condition, vinylazides **9** were converted *in situ* into 2*H*-azirines, which subsequently reacted with cyanamide (**10**) to form the desired 2-aminoimidazoles **11** in moderate to excellent yield. Both of these methods afford *NH*-imidazoles with control of substitution at the 2, 4 and 5 positions. An ester moiety could also be incorporated regioselective at either the C-4 or C-5 positions depending on which protocol was followed (Scheme 2c).

Related work by Tang *et al.* reported the synthesis of 2,4,5-trisubstited *NH*-imidazoles in moderate to good yield (Scheme 3).[22] Thus, reaction of *NBoc*-imidamides **13** with α-azidoenones **12** at 120 °C in acetonitrile gave the desired imidazoles **14** without the need for the addition of a catalyst. The protocol allowed for the inclusion of aromatic and heteroaromatic substituents as well as the ester at the C-5 position. It was proposed that intramolecular cyclization with concomitant loss of nitrogen of azide **12** would afford 2*H*-azirines **15**. Addition of *NBoc*-imidamides **13** to azirines **15** followed by intramolecular cyclization would afford bicyclic intermediate **17**. Ring fragmentation would then lead to the desired imid-

[a]A.E. Favorsky Irkutsk Institute of Chemistry SB RAS, 1 Favorsky St, Irkutsk, 664033, Russian Federation
[b]Department of Chemistry, University of Bath, Claverton Down, Bath, BA2 7AY, UK. E-mail: j.camp@bath.ac.uk

† Electronic supplementary information (ESI) available. See DOI: 10.1039/d0ob00350f

This journal is © The Royal Society of Chemistry 2020

Open Access Article. Published on 18 May 2020. Downloaded on 10/24/2025 9:24:05 PM.
This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.

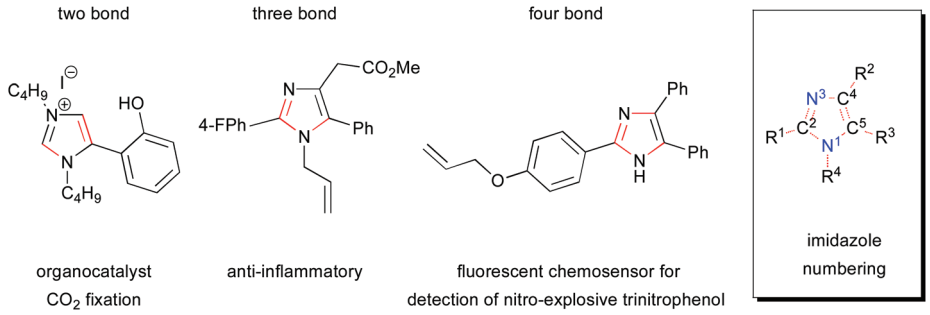
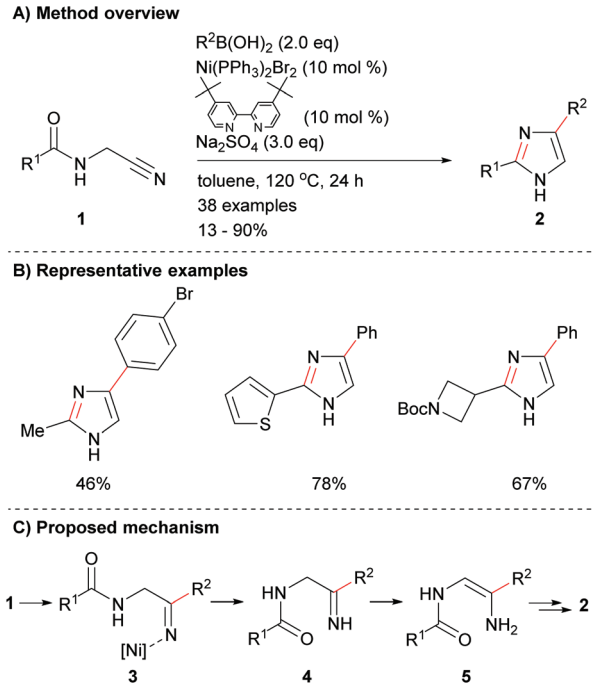
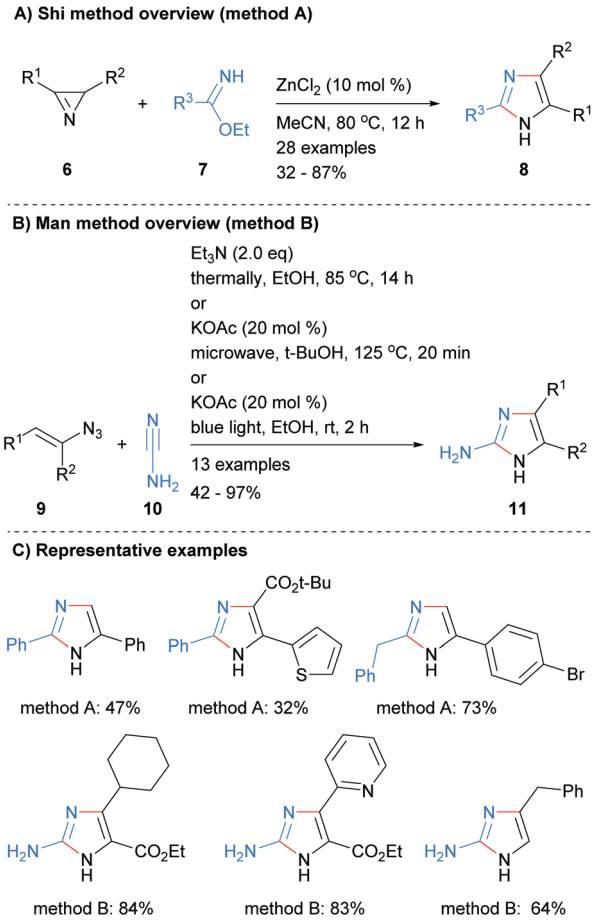


Fig. 1 Examples of two, three and four bond disconnections in the formation of functional imidazole as well as its generic core and substituent labels.



Scheme 1 Nickel-catalysed cyclization of amido-nitriles.



Scheme 2 Metal-catalysed 2*H*-azirines based protocols.

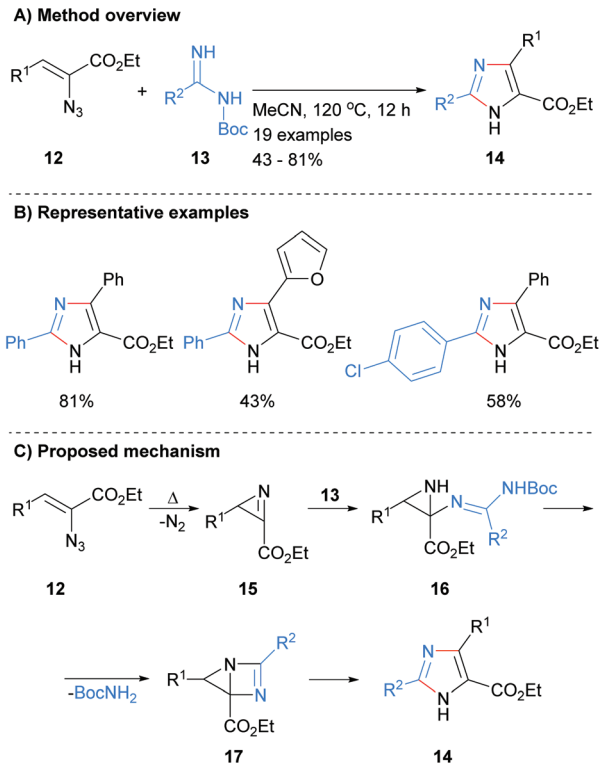
azoles **14**. In contrast to the methods outline in Scheme 2, this protocol require that the starting material contains an ester moiety.

Nitriles have also been used as reagents in metal free reactions for the formation of substituted imidazoles in which two-bonds of the heterocycle are formed. For example Harisha *et al.* recently reported the reaction of α-azidoenones **18** with substituted nitriles to form tri-substituted *NH*-imidazoles **19** (Scheme 4).[23] No significant difference was observed in isolated yield for reactions run under either thermal or microwave conditions. In addition to an arylketone moiety at the C-5 position, the protocol also allowed for the incorporation of vinyl and arylhalide functional groups.

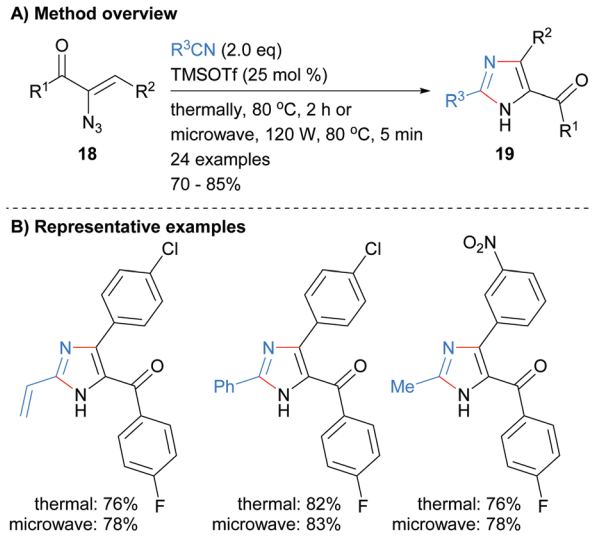
Recently, Yang and co-workers reported the synthesis of protected imidazoles **21** *via* a $BF_3{\cdot}Et_2O$ promoted reaction of triazoles **20** and nitriles (Scheme 5).[24] The products of the reaction are sulphone protected imidazoles that have substitution at the C-2 and C-4 positions. The reaction is proposed to proceed *via* initial ring opening of triazole **20** to form diazoimine **22**. $BF_3{\cdot}Et_2O$ promoted addition of the nitrile affords nitrilium intermediate **24**, which subsequently cyclized to form substituted imidazoles **21** in average to excellent yield.

In related work, Cai and co-workers showed that the addition of the anion derived from methylene isocyanides **26** to ketenimines **25** resulted in the formation of 1,4,5-trisubstitued imidazoles **27** (Scheme 6).[25] Interestingly, this method allows for the

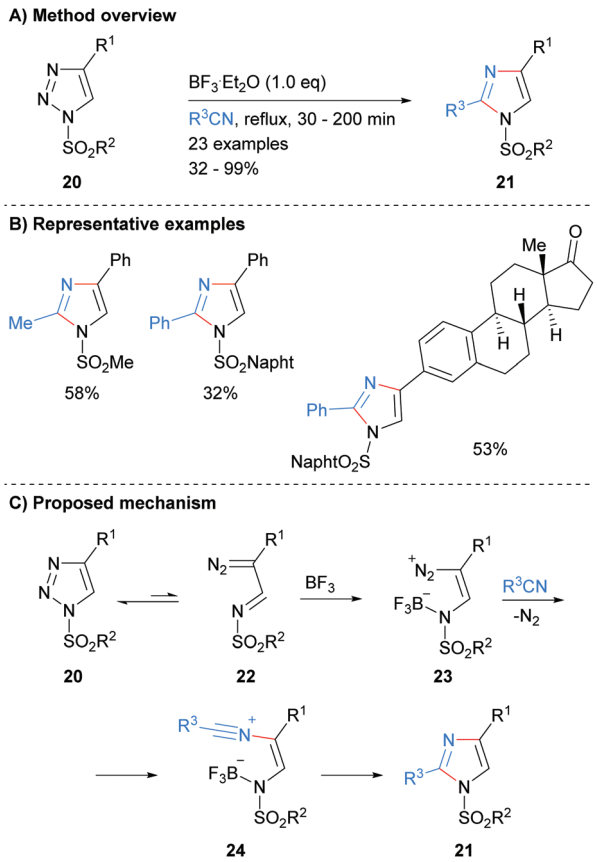
Open Access Article. Published on 18 May 2020. Downloaded on 10/24/2025 9:24:05 PM.
This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.



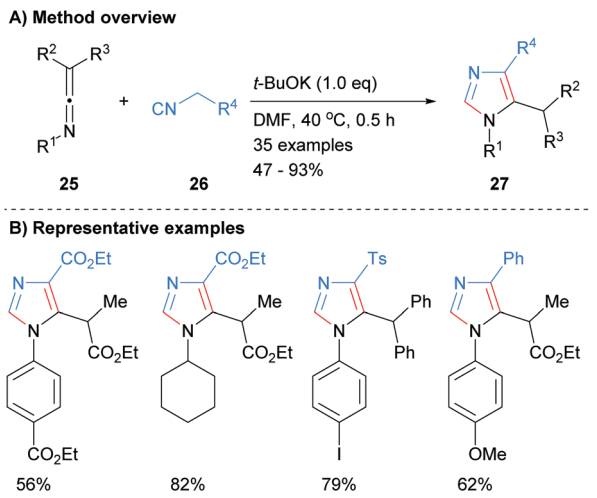
Scheme 3 Metal catalyst free 2*H*-azirines based protocol.



Scheme 4 TMSOTf-Catalysed [3 + 2] cycloaddition protocol.



Scheme 5 $BF_3{\cdot}Et_2O$-Catalysed recyclisation of triazoles.



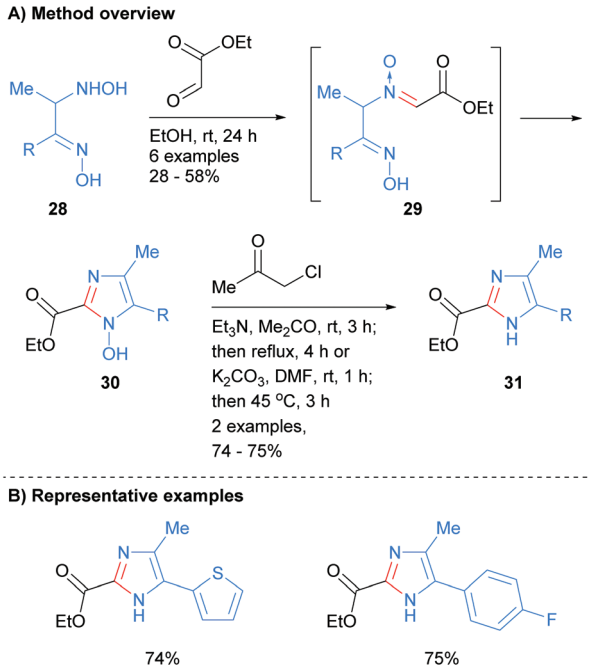
Scheme 6 Base-catalysed [3 + 2] cycloaddition protocol.

synthesis of C-2 unsubstituted imidazoles whilst being functional group tolerant of esters, sulphones and arylhalides.

Recently, Nikolaenkova *et al.* reported the synthesis of 2-carboxylate substituted imidazoles from oxime-hydroxlyamines **28** (Scheme 7).[26] The reaction is reported to proceed *via* initial condensation of hydroxylamine **28** with ethyl glyoxalate to form *N*-oxide **29** *in situ*. Cyclization followed by dehydrative aromatization afforded 1-hydroxyimidazole **30**, which was subsequently reacted with chloro-2-propanone to give *NH*-imidazole **31** in good yield. This method allowed for the synthesis of *NH*-imidazoles with an ester moiety at the C-2 position and was also tolerant of heterocycles and arylhalides.

There has been a significant amount of recent works on the formation of both the N^1–C^5 and N^3–C^4 bonds in a single operation. For example, Strelnikova *et al.* reported the synthesis of

Open Access Article. Published on 18 May 2020. Downloaded on 10/24/2025 9:24:05 PM.
This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.

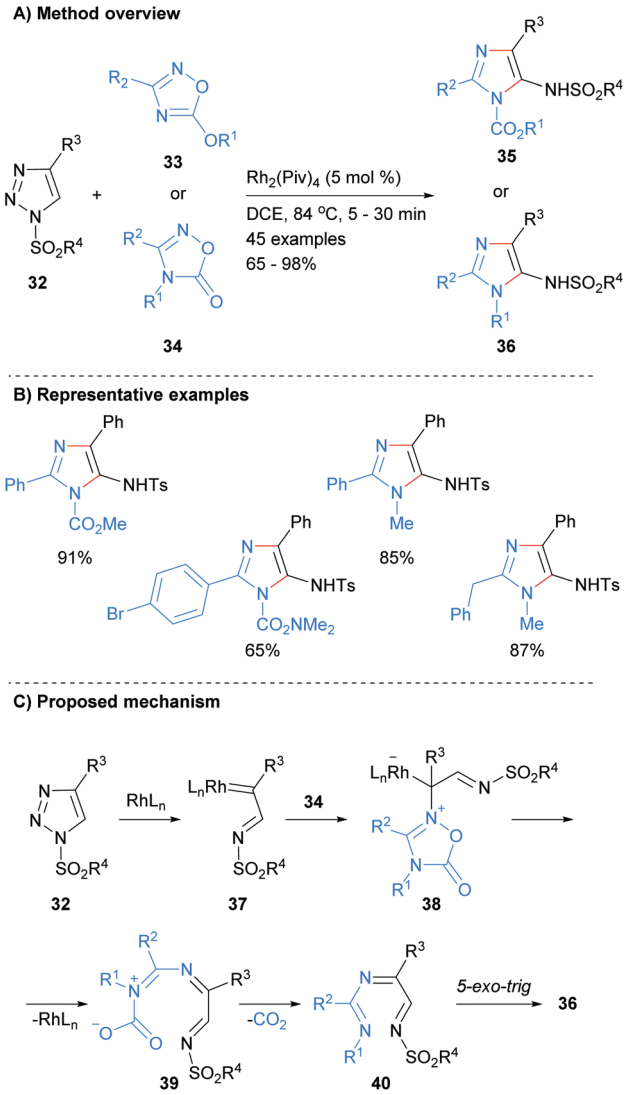


Scheme 7 Condensation of oxime-hydroxlyamine with ethyl glyoxalate.

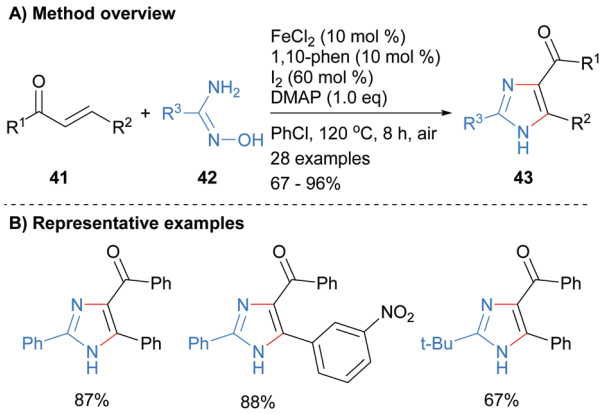
5-sulphonamidoimidazoles **35** or **36** from the reaction of two different heterocyclic starting materials in the presence of a rhodium catalyst (Scheme 8).[27] Thus, reaction of 1,2,4-oxadiazole derivatives **33** and **34** with 1-sulphonyl-1,2,3-triazoles **32** at 84 °C in DCE afforded the desired imidazoles **35** and **36** in good to excellent yield. In addition to a suphonolated amine at the C-5 position, this protocol produced imidazoles substituted at the N-1 position with either an ester or alkyl moieties. The mechanism is proposed to proceed *via* insertion of the rhodium catalyst into triazole **32** to afford carbenoid **37**. Attack of 1,2,4-oxadiazole derivatives **34** onto carbenoid **37** followed by ring-opening, loss of the metal catalyst and carbon dioxide afforded tri-imine **40**. A 5-*exo-trig* cyclization of imine **40** then gave the desired imidazole **36**.

The 1,3-diamine component of an imidazole has also been introduced using either amidoximes or *N*-iminylsulphilimine. For example, Wu and co-workers used an iron catalyst to promote the reaction between amidoximes **42** with enones **41** (Scheme 9).[28] Heating the reagents at 120 °C in the presence of the metal catalyst and iodine afforded imidazole **43** in good to excellent yields. The product *NH*-imidazoles were substituted with a ketone moiety at the C-4 position and the reaction protocol was tolerant to nitroarenes.

In a related protocol, the reaction of *N*-iminylsulphilimine **44** with ynamides **45** was recently reported to afford 4-amino substituted imidazoles **46** in good to excellent yields (Scheme 10).[29] In this gold-catalyzed process the sulphilimines are used as nitrene transfer reagents. The products of the reaction are N-1 phenyl substituted imidazoles that have sulphonolated amines at the C-4 position as well as aryl substitution at the C-2 and C-5 positions.

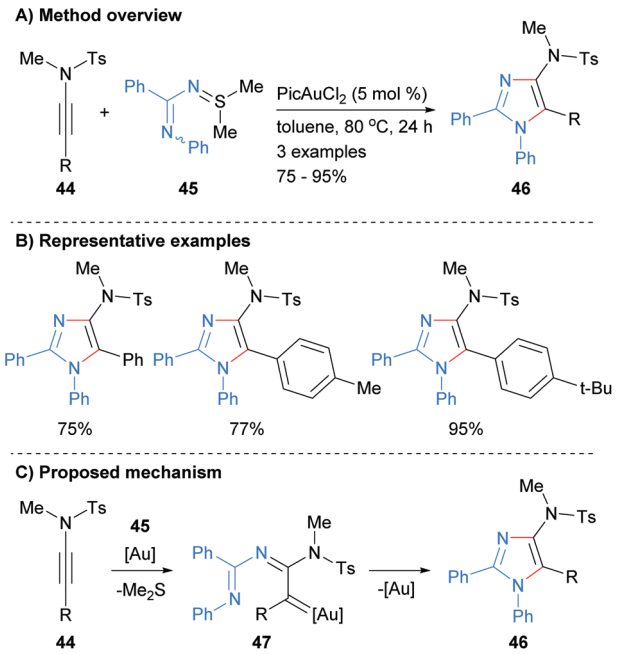


Scheme 8 Rhodium-catalysed transannulation of 1,2,4-oxadiazoles with 1-sulphonyl-1,2,3-triazoles.



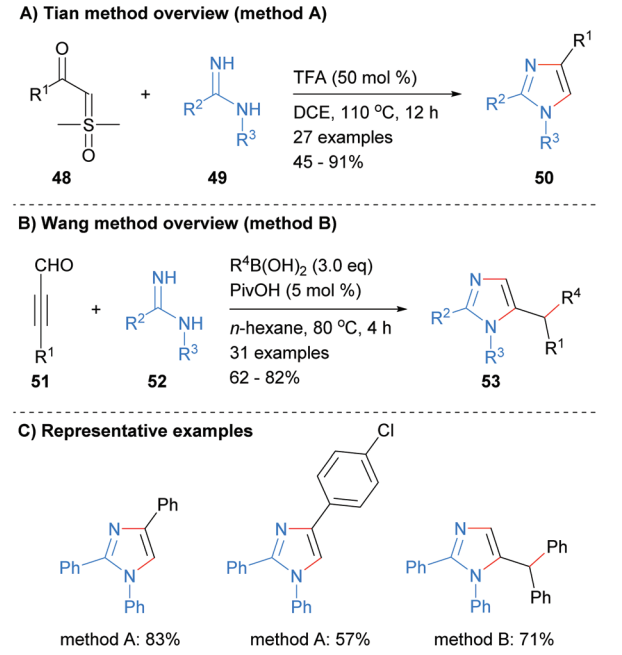
Scheme 9 Iron-catalysed [3 + 2] addition protocol.

Open Access Article. Published on 18 May 2020. Downloaded on 10/24/2025 9:24:05 PM.
This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.

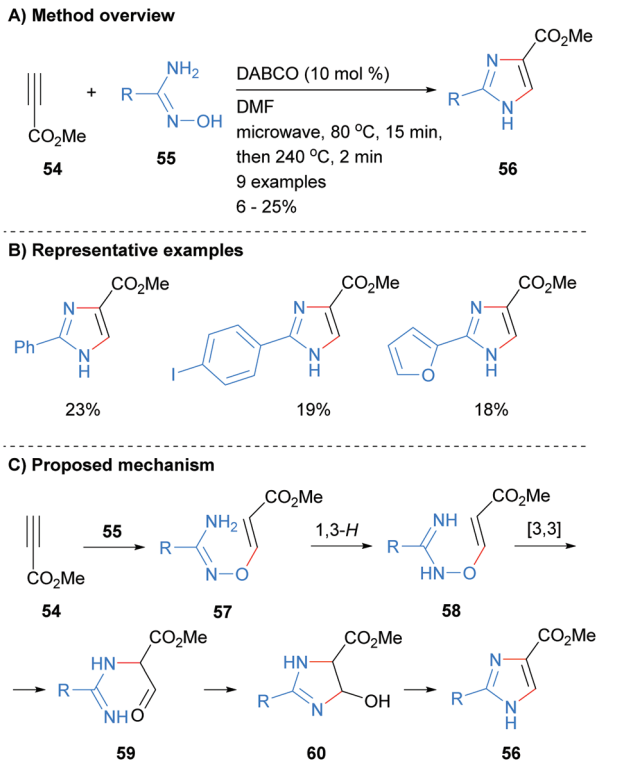


Scheme 10 Gold-catalysed [3 + 2] addition protocol.

Imidamides can also be used as starting materials for the synthesis of imidazoles without the need for a metal catalyst. For example, Tian *et al.* reported the synthesis of substituted imidazole **50** from the reaction of imidamides **49** with sulphoxonium ylides **48** in the presence of trifluoroacetic acid (Scheme 11a).[30] The resultant imidazoles were substituted at the 1, 2 and 4-positions. In contrast, Wang and co-workers reported that the reaction of imidamides **52** with propargyl aldehydes in the presence of a boronic acid afforded 1,2,5-substituted imidazoles in which the boronic acid has transferred its substituent to the C-5′ position (Scheme 11b).[31]

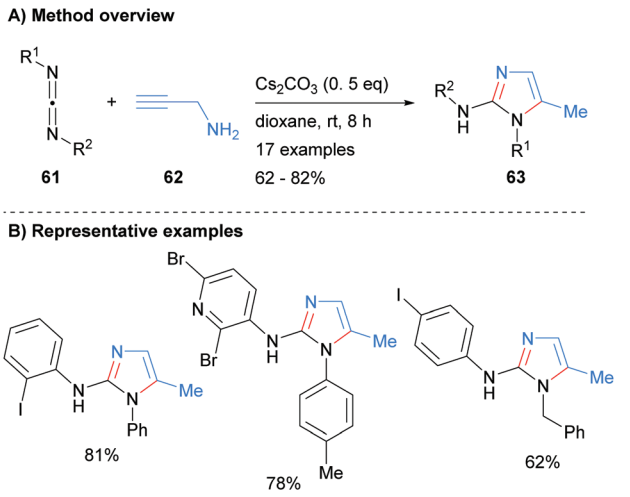


Scheme 11 Acid-catalysed [3 + 2] addition protocols.



Scheme 12 Nucleophilic catalyst-based protocol.

Recently we reported the synthesis of *NH*-imidazoles from the reaction of methyl propiolate (**54**) and substituted amidoximes **55** (Scheme 12).[32] Thus, subjection of activated alkyne **54** with a variety of amidoximes **55** to a two stage microwave protocol in the presence of a catalytic amount of 1,4-diazabicyclo



Scheme 13 Base-catalysed addition of propargylamines to carbodiimides.

This journal is © The Royal Society of Chemistry 2020

Open Access Article. Published on 18 May 2020. Downloaded on 10/24/2025 9:24:05 PM.
This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.

[2.2.2]octane (DABCO) rapidly afford the desired *NH*-imidazoles in moderate yield. The C-4 position was substituted by an ester moiety and the reaction conditions were also tolerant to arylhalides and heterocycles.

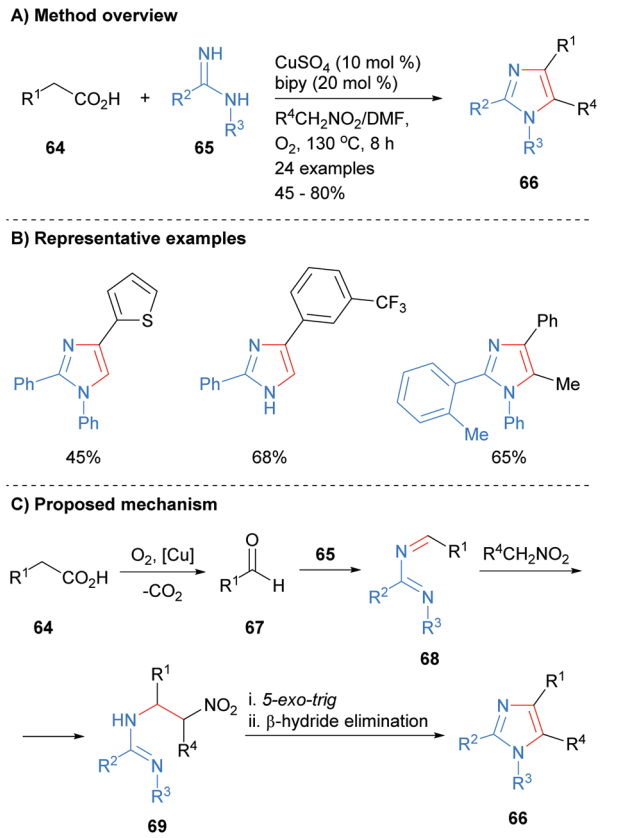
The N^3–C^4–C^5 unit can also be introduced in the form of a carbodiimide. For example, Li *et al.* recently reported the synthesis of 2-aminoimidazoles **63** from the reaction of carbodiimides **61** with propargyl amine (**62**) in moderate to good isolated yield (Scheme 13).[33] The reaction conditions were tolerant of both arylhalides and heteroarylhalides. In addition, the N-1 nitrogen could be substituted by either aryl or benzyl groups depending on the starting material that was employed.

Three-bonds formed

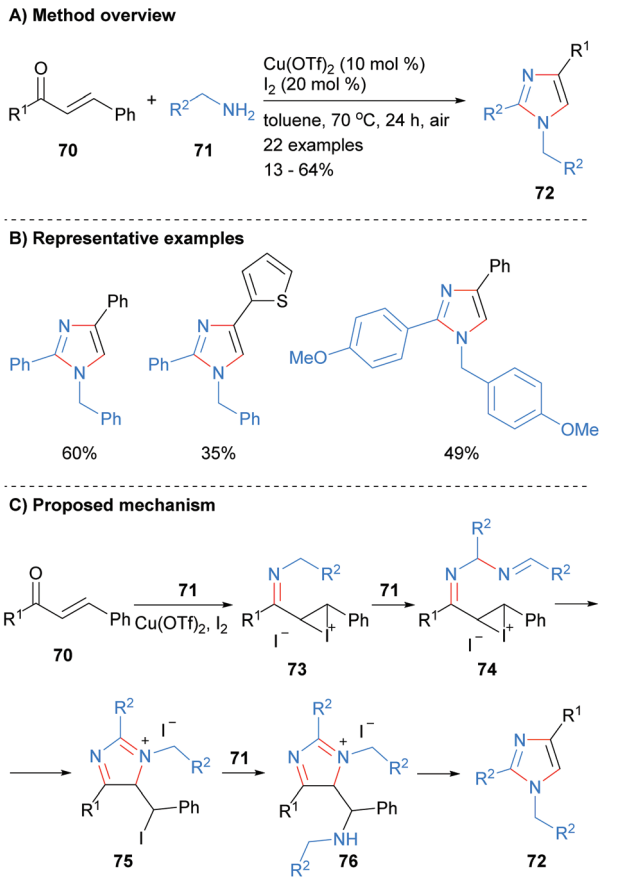
A number of recent methods for the synthesis of imidazoles in which three of the heterocycle bonds are formed have been reported. For example, imidamides **65** were reacted with carboxylic acids **64** in the presence of a copper catalyst to form imidazoles **66** (Scheme 14).[34] In addition to substrate control over the substitution at the N-1 position (H or aryl), the product imidazoles were regioselectively substituted at the C-2 and C-4 positions. In addition, functionality could be introduced at the C-5 position *via* inclusion of a nitroalkane in the reaction mixture. Mechanistically, the reaction is believed to proceed *via* oxidative decarboxylation of carboxylic acid **64** to afford aldehyde **67**. Condensation of imidamide **65** with aldehyde **67** followed by addition of the anion derived from the nitroalkane to the *in situ* formed imine **68** gave substituted imidamide **69**. A 5-*exo-trig* cyclization of imidamide **69** followed by β-hydride elimination afforded imidazole **66**.

The reaction of excess amine with enones has been shown to afford trisubstitued imidazoles. For examples, Salfeena *et al.* recently reported the copper-catalyzed reaction of amines **71** with enones **70** gave imidazoles **72** with substitution at the 1, 2 and 4 positions in poor to moderate yield (Scheme 15).[35] The resultant imidazoles contained a benzyl group at the N-1 position and the reaction conditions were tolerant of aromatic and heteroaromatic functional groups. Mechanistically the reaction was reported to proceed *via* copper promoted imine and iodonium formation on enone **70** to give iodonium **73**. Addition of a second equivalent of amine **71** followed by intramolecular cyclization afforded iminium salt **75**. Finally, addition of a third equivalent of amine **71** to alkyl iodide **75** followed by aromatization *via* fragmentation gave the desired imidazole **72**.

In related work, Geng *et al.* found that ketones **77** and 2-aminobenzylalcohols **78** could be reacted together in the presence of iodine, ferric chloride and toluenesulphonylmethyl isocyanide to afford 1,4-disubstitued imidazoles **79** (Scheme 16).[36] Interestingly, this is one of the few recent examples in which the product imidazole is regioselectively

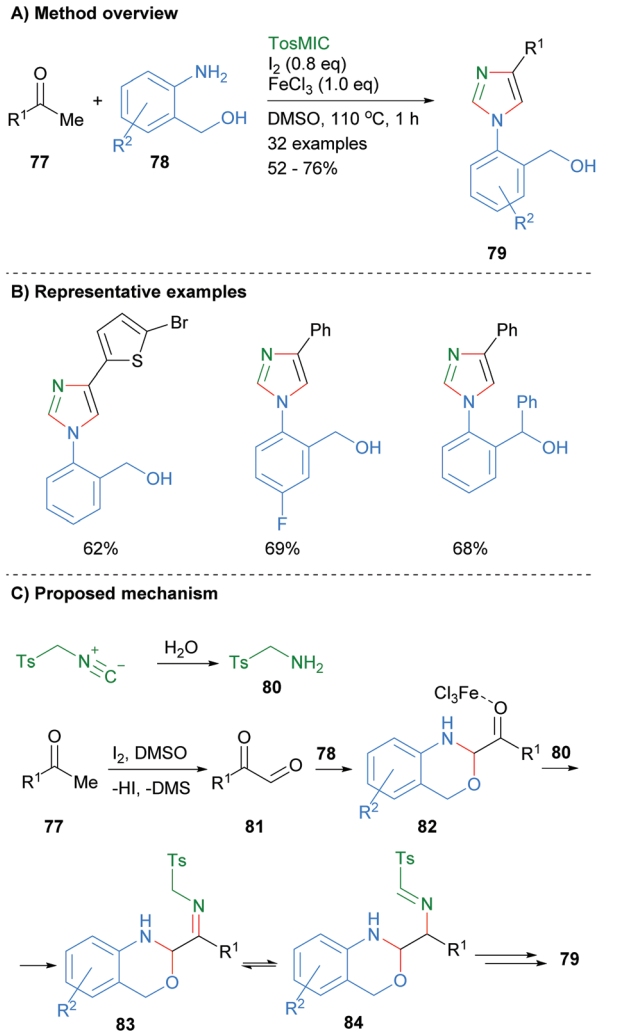


Scheme 14 Copper-catalysed decarboxylative coupling of carboxylic acids, imidamides and nitroalkanes.

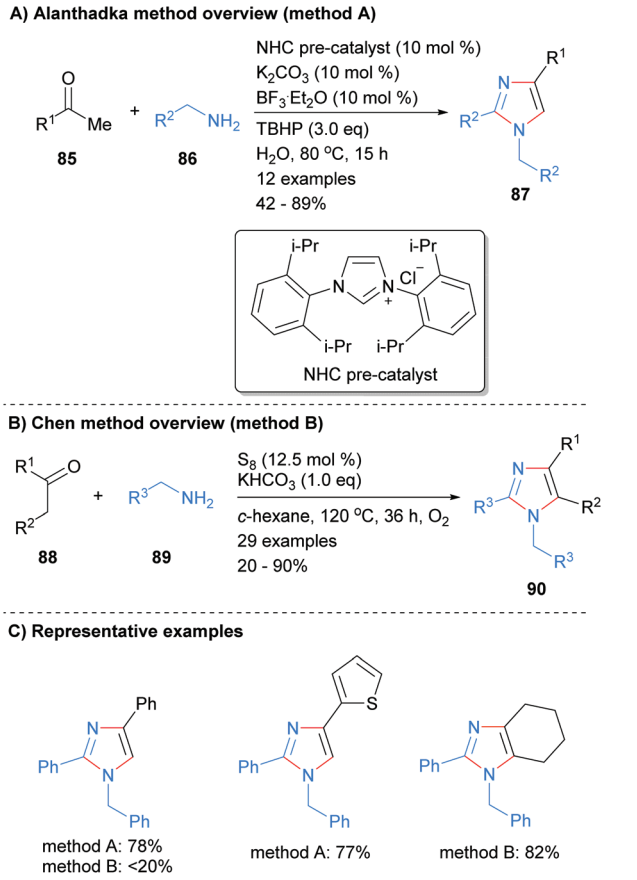


Scheme 15 Copper-catalysed enones C–C bond cleavage protocol.

Open Access Article. Published on 18 May 2020. Downloaded on 10/24/2025 9:24:05 PM.
This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.



Scheme 16 Ferric chloride/iodine-catalysed [2 + 2 + 1] addition protocol.



Scheme 17 Metal catalyst free ketones/benzylamines coupling protocols.

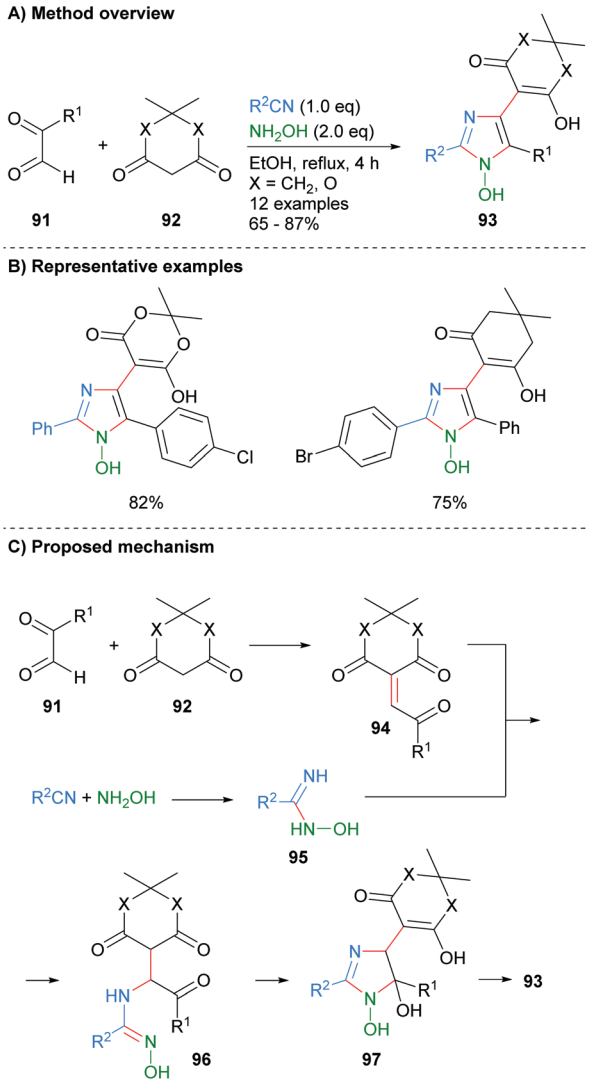
substituted at only the N-1 and C-4 positions with an aromatic group. The reaction is reported to proceed *via* initial oxidation of ketone **77** to keto-aldehyde **81**. Subsequent condensation of aldehyde **81** with 2-aminobenzylalcohol **78** and reaction with the *in situ* formed tosylamine (**80**), afforded imine **83**. Intramolecular cyclization of amine **83** followed by elimination of TsH and aromatization *via* C–O bond cleavage gave 1,4-disubstitued imidazole **79**.

The use of N-heterocyclic carbenes (NHC) as both ligand and organocatalysts have become commonplace in modern organic synthesis since they were characterized by Arduengo *et al.*[37] Alanthadka and co-workers recently built on this extensive research to develop a NHC-catalyzed protocol for the synthesis of 1,2,4-trisubstituted imidazoles **87** from the reaction of acetophenones **85** and benzylic amines **86** (Scheme 17a).[38] The reaction was conducted in the presence of an excess of an oxidant, *tert*-butylhydroperoxide (TBHP), which serves to oxidize an *in situ* formed enamine to an α-aminoaldehyde. Importantly, this process can be run under solvent free conditions. In related work, Chen *et al.* reported the synthesis of tetrasubstituted imidazoles **90** from the reaction of ketones and amines in the presence of elemental sulphur (Scheme 17b).[39] Both methods reported the synthesis of the N-1 benzyl, C-2/C-4 phenyl substituted imidazoles, though the isolated yields were markedly different.

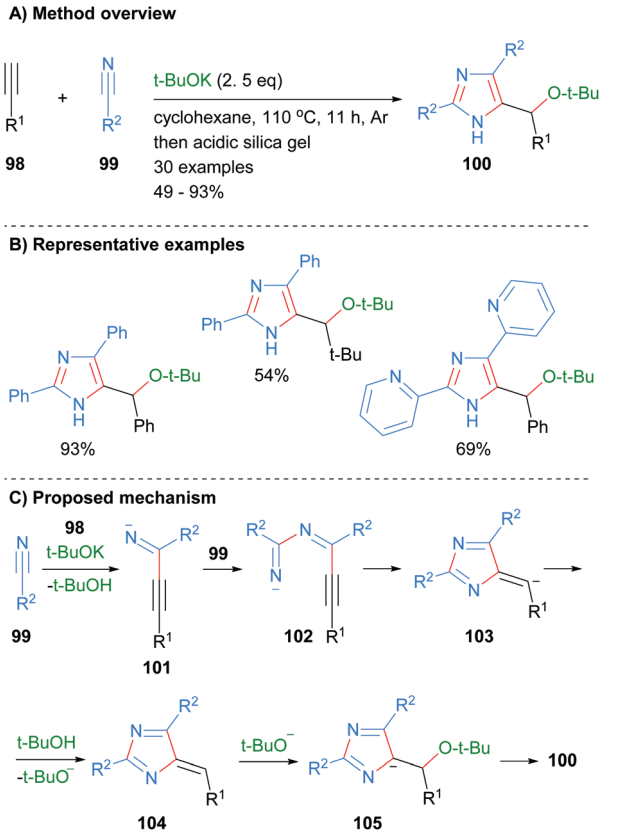
Alizadeh-Bami *et al.* reported a similar disconnection for the synthesis of substituted 1-hydroxyimidazole **93** (Scheme 18).[40] This protocol allowed for the introduction of an additional carbonyl nucleophile, derived from **92**, which resulted in additional substitution at the C-4 position. The product imidazoles were substituted with a hydroxide moiety at the N-1 position (*cf.* Scheme 7 for the conversion of this functional group to an *NH*-imidazole). Mechanistically the reaction is reported to proceed *via* an initial condensation reaction between aldehyde **91** and dicarbonyl **92** to afford enone **94**. Nucleophilic addition of the *in situ* formed *N*-hydroxy-imidamide **95** to enone **94** gave α-aminoketone **96**, which after a cyclodehydration process afforded 1-hydroxyimidazole **93**.

Wang and co-workers also constructed imidazoles **100** using the less common three component disconnection of the heterocycle (Scheme 19).[41] Two equivalents of nitrile **99** were reacted with the acetylide generated *in situ* from alkynes **98** to

Open Access Article. Published on 18 May 2020. Downloaded on 10/24/2025 9:24:05 PM.
This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.



Scheme 18 Metal catalyst free four-component protocol.



Scheme 19 Base-catalysed [2 + 2 + 2] addition protocol.

afford the desired substituted imidazoles in average to excellent yield. The *t*-BuOK acts as both a base and a nucleophile under the reaction conditions. In addition to the alkyl substituent at the C-5 position, reaction protocol afforded *NH*-imidazoles with aryl or heteroaryl substituents. The proposed mechanism for the reaction starts with the reaction of *in situ* formed acetylide of alkyne **98** with first equivalent of nitrile **99** to form imine **101**. Addition of the second equivalent of nitrile **99** to imine **101** followed by 5-*exo-dig* cyclization and protonation gave heterocycle **104**. Addition of *tert*-butoxide to exocyclic methylene **104** followed by aromatization and protonation when purifying on silica afforded imidazoles **100**.

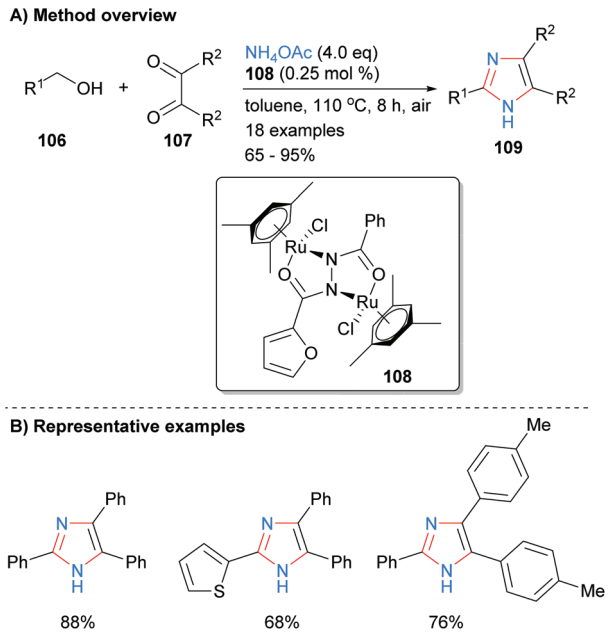
Four-bonds formed

One of the most popular disconnections for the synthesis of imidazoles is the concurrent formation of four bonds of the heterocycles core with both metal-catalyzed and metal-free processes being reported recently. For example, Sundar and Rengan synthesized imidazoles **109** from the three component reaction between benzylic alcohol **106**, 1,2-diketone **107** and excess ammonium acetate (Scheme 20).[42] This borrowing hydrogen process was catalyzed by diruthenium(II) catalyst **108** under aerobic conditions. The method allows for the synthesis of *NH*-imidazoles with regioselective substitution at the C-2, C-4 and C-5 positions and is tolerant of aryl and heteroaryl functional groups.

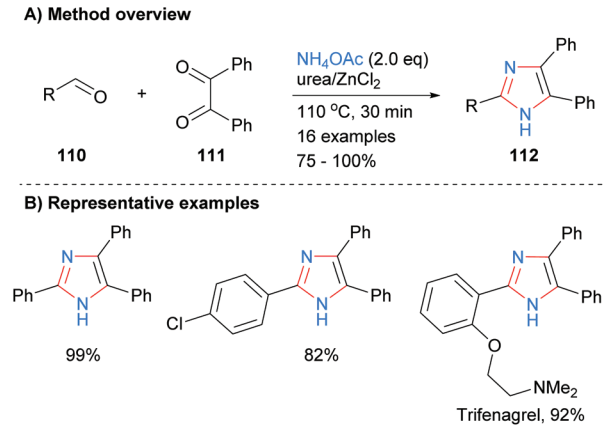
Related work by Higuera *et al.* demonstrated that the use of the deep eutectic solvent (DES) urea/zinc(II) dichloride could catalyze the synthesis of 4,5-diphenyl-2-substituted imidazoles **112** from the reaction of aldehydes **110** with benzyl (**111**) and excess ammonium acetate (Scheme 21).[43] This methodology was applied to the synthesis of the drug trifenagrel, which was isolated in 92% yield. In addition to the arylether and alkylamine functionalities found in trifenagrel, the method also tolerated arylhalides as the aromatic aldehyde partner.

Marzouk *et al.* recently reported the preparation of $ZnFe_2O_4$ nanoparticles as well as their use as catalysts for the synthesis of substituted imidazoles (Scheme 22).[44] Reaction of aldehyde **113** and benzil (**111**) and primary amines in the presence of the heterogenous catalyst afford the desired tetra-substituted imidazoles **116** and **117** in good isolated yields. The authors proposed that the iron acts as a Lewis acid to activate the carbonyl towards nucleophilic addition of amines and imines. Importantly, the catalyst can be easily isolated and reused up

Open Access Article. Published on 18 May 2020. Downloaded on 10/24/2025 9:24:05 PM.
This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.



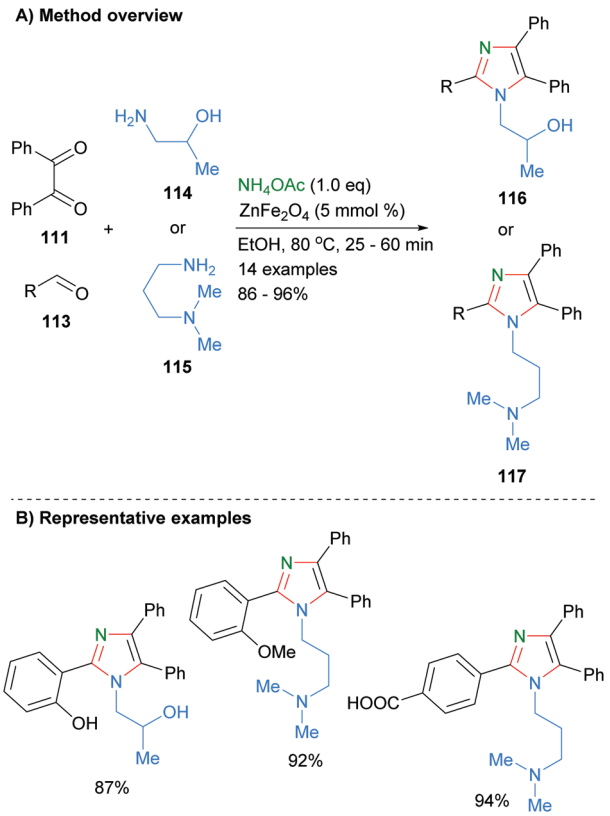
Scheme 20 Ruthenium-catalysed borrowing hydrogen protocol.



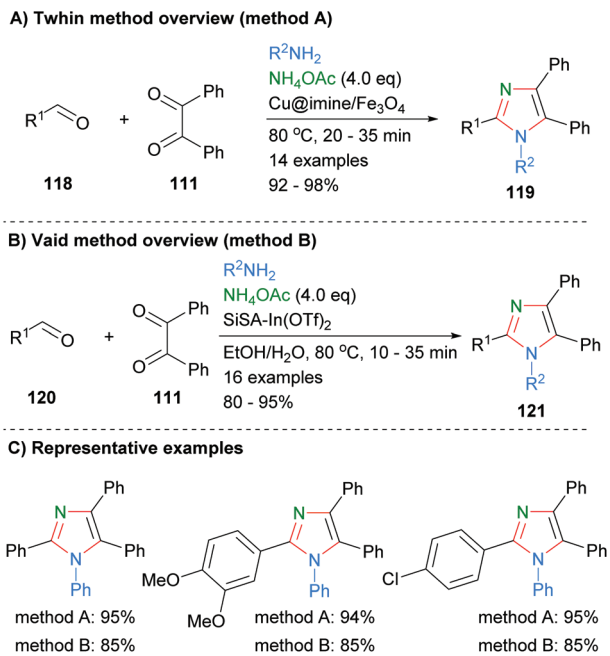
Scheme 21 Urea/zinc(II) dichloride-catalysed aldehyde/diketone/ammonia coupling protocol.

to four times without a significant decrease in product yield. A wide range of functional groups are tolerated under the reaction conditions including phenols, alcohols, carboxylic acids and amines.

Similar approaches were recently reported by Thwin *et al.* who used a copper catalyst to facilitate formation of the imidazoles **119** (Scheme 23a).[45] In addition, a heterogeneous indium catalyst supported on SiSA was used by Vaid and co-workers to promote the formation of imidazoles **121** *via* the same disconnection in good to excellent yields (Scheme 23b).[46] Both of these methods had a similar substrate scope and resulted in the formation of tetrasubstituted imidazoles. On average the use of the cheaper metal, copper, gave approximately a 10% increase in yield when the same substrates were directly compared (Scheme 23c).

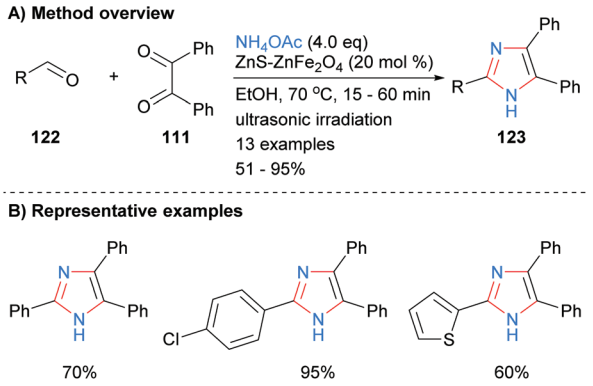


Scheme 22 $ZnFe_2O_4$-catalysed aldehyde/diketone/amine coupling protocol.



Scheme 23 Other examples of aldehyde/diketone/amine coupling protocols.

Open Access Article. Published on 18 May 2020. Downloaded on 10/24/2025 9:24:05 PM.
This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.



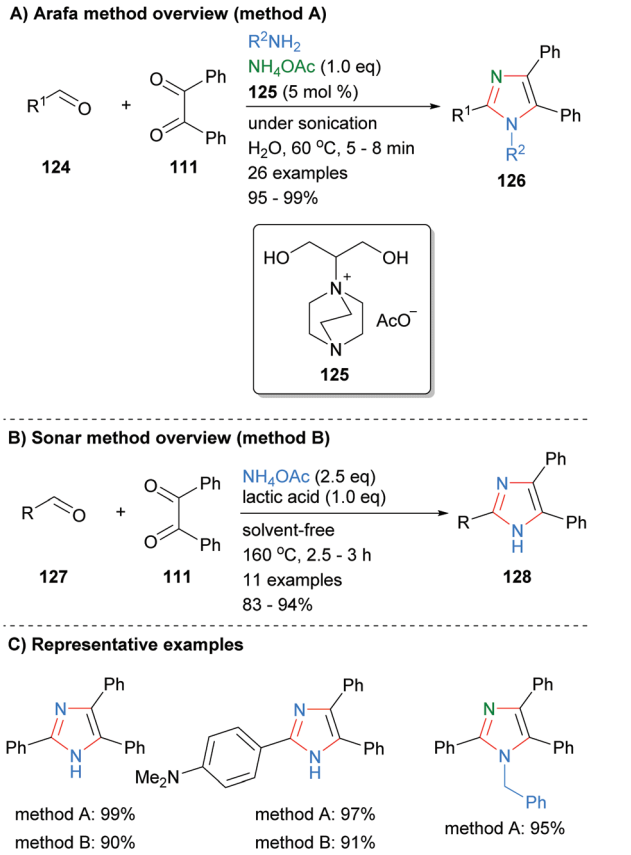
Scheme 24 ZnS-$ZnFe_2O_4$-catalysed aldehyde/diketone/ammonia coupling protocol.

A similar disconnection was undertaken by Varzi and Maleki in which a ZnS-$ZnFe_2O_4$ nanocatalyst was used to synthesize 2,4,5-trisubsttituted-*NH*-imidazoles (Scheme 24).[47] In contrast to the related heterogeneous catalysis methods outlined above (*cf.* Schemes 22 and 23), the resultant imidazoles were unsubstituted at the N-1 position. Aryl and heteroaryl aldehydes were well tolerated under the reaction conditions.

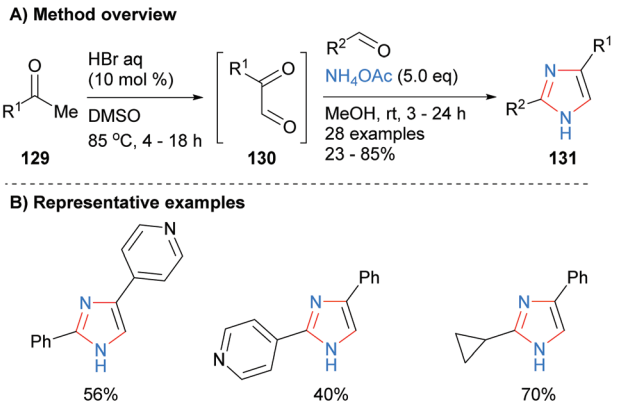
Condensation reactions to form the core four bonds of imidazoles can also be run under a variety of metal-free conditions. For example, Arafa recently reported the synthesis of tri- and tetra-substituted imidazoles **126** over an aqueous 1,4-diazabicyclo[2.2.2]octane (DABCO)[48] based ionic liquid (Scheme 25a).[49] Thus, sonication of aldehyde **124**, 1,2-diketone **111** and an amine donor (ammonium acetate or primary amine) afford the desired imidazoles in excellent yields. The methodology was tolerant of a wide variety of functional groups and the catalyst could be used up to seven times without significant loss of activity. In contrast, Sonar *et al.* used lactic acid to promote the formation of trisubstitued imidazoles from the reaction of aldehydes **127**, benzyl (**111**) and ammonium acetate (Scheme 25b).[50] The high temperature, solvent free conditions afford the desired imidazoles in good to excellent yields. Both of these methods gave the desired imidazoles in good isolated yields, though the high temperatures invoked by Sonar, 160 °C, may limit the ability to incorporate certain functionality.

Toledo and co-workers recently reported that imidazoles **131** could also be synthesized by a metal-free, one-pot process from ketones **129** *via* oxidation and subsequent dehydrative coupling with aldehydes and ammonium acetate (Scheme 26).[51] This method had a reasonable level of functional group tolerance including basic pyridines and cyclopropanes.

Derivatized magnetic nano-catalysts have been used in a wide range of synthetic applications due to the fact that they are easily recoverable.[52] For example, a sulphonated Fe_3O_4@PVA superparamagnetic nano-catalyst was employed by Maleki *et al.* for the synthesis of trisubstitued-*NH*-imidazoles from the condensation reaction of benzyl (**111**), an aldehyde and ammonium acetate (Scheme 27a).[53] The catalyst acts as an



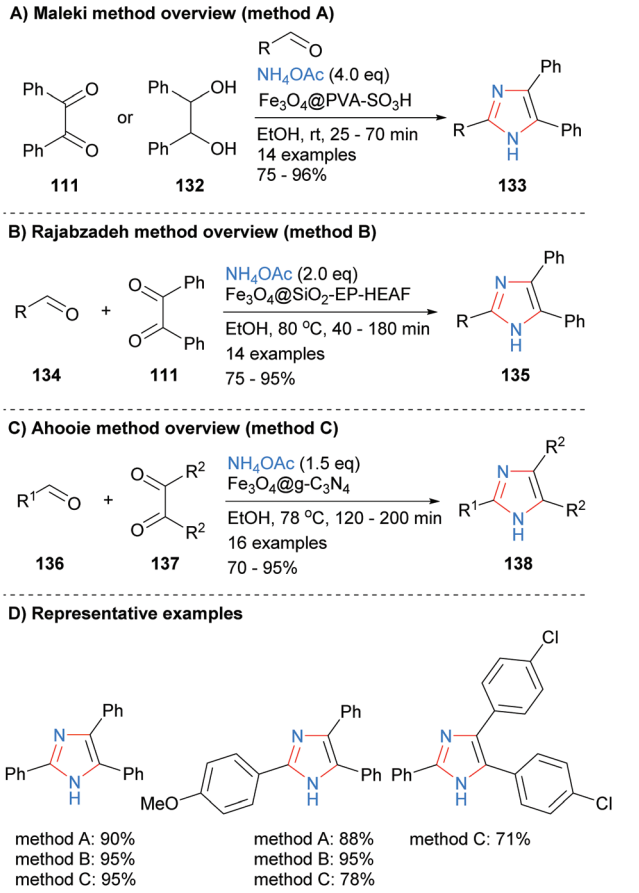
Scheme 25 Metal catalyst free aldehyde/diketone/amine(ammonia) coupling protocols.



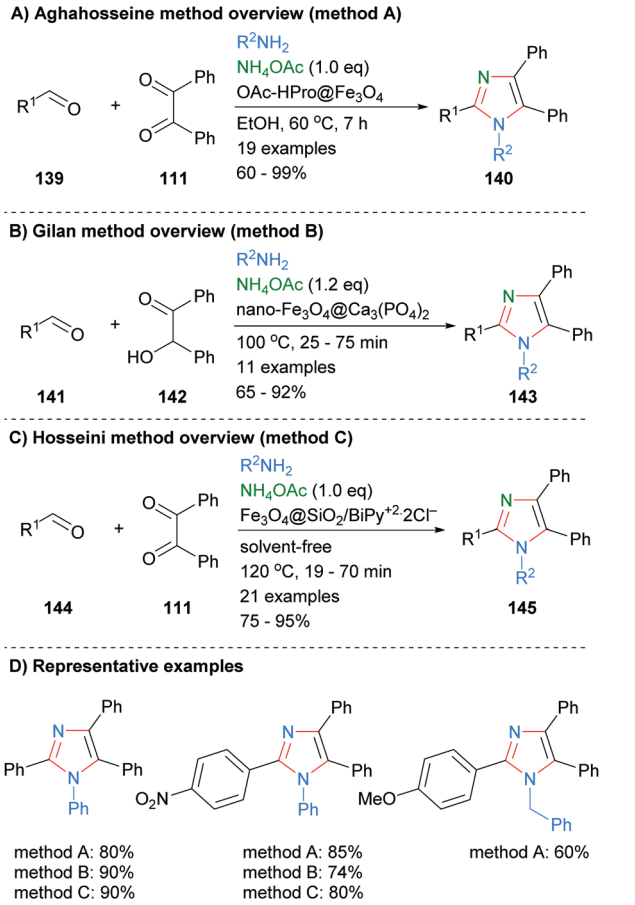
Scheme 26 *In situ* generation of ketoaldehydes *via* acid-catalysed oxidation of ketones.

efficient organic–inorganic Brønsted acid and can be recycled up to ten times without a significant loss of reactivity. In contrast to the work above (*cf.* Scheme 22), the authors propose that the iron core plays no role in the catalytic cycle and that its major role is to provide an easy way to recycle the catalysts *via* its magnetic properties. Similar protocols were developed by both Rajabzadeh *et al.*[54] and Ahooie *et al.*[55] who used Fe_3O_4@SiO_2-EP-HEAF and Fe_3O_4@g-C_3N_4 magnetic nano-

Open Access Article. Published on 18 May 2020. Downloaded on 10/24/2025 9:24:05 PM.
This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.



Scheme 27 Derivatized magnetic nano-catalysts in aldehyde/diketone/ammonia coupling protocols.



Scheme 28 Derivatized magnetic nano-catalysts in aldehyde/diketone/amine coupling protocols.

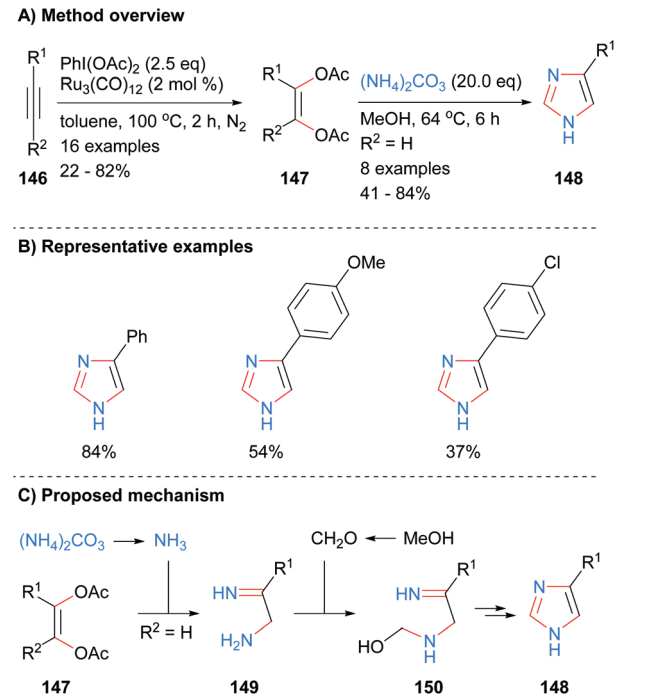
particles, respectively, to catalyse the three-component condensation reaction in ethanol to form 2,4,5-trisubstituted imidazoles (Scheme 27b and c). When the yields of the same product imidazoles were compared it was found that all three methods were relatively high yields, with only method C having one slightly lower for one of the substrates.

Similar condensation protocols for the synthesis of nitrogen substituted imidazoles using magnetic nano-catalysts have also been developed. For example, Aghahosseini *et al.* developed a method using L-proline derived magnetic core nanoparticles as organocatalysts (Scheme 28a).[56] These catalysts were used to form tri- and tetra-substituted imidazoles in moderate to good yield. In a related example, Gilan and co-workers were also able to synthesis 2-substituted imidazoles *via* a three-component condensations approach (Scheme 28b).[57] The reaction was catalyzed by a nano-magnetic catalyst $Fe_3O_4@Ca_3(PO_4)_2$, which was synthesized using eggshell waste. The catalyst gave a good yield of 1,2,4,5-tetra-substitued imidazoles **143** and could be recycled up to four time without significant decrease in isolated product yield. Recently, Hosseini *et al.* also reported that the synthesis of imidazoles **145** could be catalyzed by a supported pyridinium catalyst (Scheme 28c).[58] On average the yields for the synthesis of nitrogen substituted imidazoles using nano-magnetic catalyst were approximately 10% lower than for the *NH*-imidazoles described above (*cf.* Scheme 27).

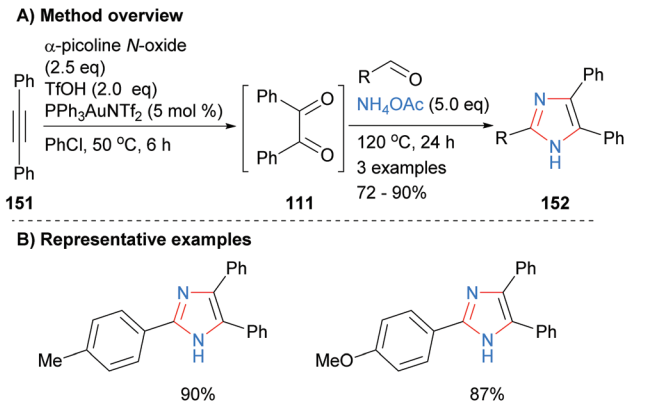
The four core bonds of monosubstitued imidazole **148** were constructed *via* bisfunctionalization of 1,2-disubstituted acetylenes **146** by ruthenium carbonyl to form *cis*-enediol diacetates **147** followed by subsequent reaction with ammonium carbonate (Scheme 29).[59] The difunctionalization protocol obviates the substrate limitations and use of toxic reagents required of previous methodologies. Interestingly, this is one of the few recent examples in the literature in which mono-substituted *NH*-imidazoles were synthesized. Both electron rich and electron deficient aromatics were tolerated under the reaction conditions. Mechanistically, the reaction is proposed to proceed *via in situ* formation of ammonia, which reacts with *cis*-enediol diacetates **147** to give amino imine **149**. Reaction of amine **149** with formaldehyde followed by intramolecular cyclization and aromatization afforded imidazole **148**.

In a related approach Dubovtsev *et al.* also started from a disubstitued acetylene **151**, which when subjected to a one-pot gold-catalyzed oxidation formed benzil (**111**). Subsequent reaction of the *in situ* generated diketone **111** with an aldehyde and ammonium acetate formed 2,4,5-trisubstituted imidazoles (Scheme 30).[60] Both electron neutral and rich arylaldehydes

Open Access Article. Published on 18 May 2020. Downloaded on 10/24/2025 9:24:05 PM.
This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.



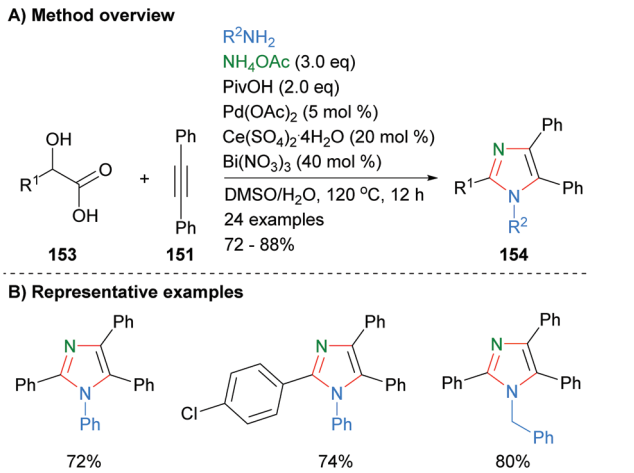
Scheme 29 *In situ* generation of diketone equivalents *via* ruthenium-catalysed oxidation of alkynes.



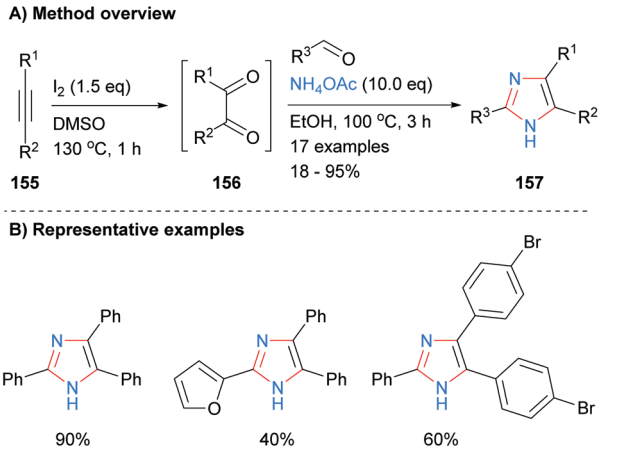
Scheme 30 *In situ* generation of diketone *via* gold-catalysed oxidation of alkynes.

gave the desired *NH*-imidazoles **152** in good isolated yields. Benzil generated in a similar manner was also converted into quinoxaline, 1,2,4-triazines, pyrazines and 1,4-diazepine in one-pot reaction sequences.

Internal alkynes were also employed by Sun *et al.* to from tetrasubstituted imidazoles (Scheme 31).[61] Thus, reaction of diphenylacetylene (**151**) with α-hydroxy carboxylic acids **153** in the presence of excess ammonium acetate and a combination of palladium, cerium and bismuth reagents afforded the desired imidazoles in good yields. In contrast to the methods above (*cf.* Schemes 29 and 30), the method resulted in the formation of tetrasubstitued rather than *NH*-imidazoles. Both phenyl and benzyl functionalities were tolerated at N-1.



Scheme 31 Palladium/cerium/bismuth salts-catalysed condensation of α-hydroxy carboxylic acids with alkynes and amines.



Scheme 32 *In situ* generation of diketone *via* iodine-catalysed oxidation of alkynes.

A one-pot metal and acid free synthesis of 2,4,5-trisubstituted imidazoles was recently reported by Naidoo and Jeena (Scheme 32).[62] Reaction of internal alkynes **155** with iodine in dimethyl sulphoxide (DMSO) afford benzils, which were subsequently reacted with an aldehyde and ammonium acetate *in situ.* Both of the solvents involved, DMSO and ethanol, can be obtained from renewable resources[63] and thus the overall methodology provides a greener alternative to many existing protocols. Both heterocycles and halogenated aromatics were compatible with the reaction conditions.

Outlook and conclusion

This review highlights that there has been a significant amount of recent research (2018-present) on the regioncontrolled synthesis of imidazoles. Table 1 and Table S1† provide an overview of the bond disconnections discussed as well as

Open Access Article. Published on 18 May 2020. Downloaded on 10/24/2025 9:24:05 PM.
This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.

Table 1 Substitution pattern of imidazoles covered in this review[a]

Entry	Bonds	NH	NR	C2	C4	C5	Yield range (%)	Author	Ref.
1	One	✓		✓	✓		13–90	Fang	19
2	Two	✓		✓	✓		6–25	Shabalin	32
3	Two	✓		✓	✓	✓	67–96	Wu	28
4	Two		✓		✓	✓	47–93	Cai	25
5	Two		✓	✓		✓	62–82	Wang	31
6	Two		✓	✓	✓		45–91	Tian	30
7	Two		✓	✓	✓	✓	65–98	Strelnikova	27
8	Three	✓		✓	✓	✓	49–93	Wang	41
9	Three		✓		✓		52–76	Geng	36
10	Three		✓	✓	✓		42–89	Alanthadka	38
11	Three		✓	✓	✓	✓	65–87	Alizadeh-Bami	40
12	Four	✓			✓		41–84	Ruan	59
13	Four	✓		✓	✓		23–85	Toledo	51
14	Four	✓		✓	✓	✓	75–96	Hosseini	58
15	Four		✓	✓	✓	✓	60–99	Aghahosseini	56

[a] Examples we chosen based on the following criteria: (a) number of bonds formed (b) substitution pattern (c) reaction conditions with priority given to methods using lower temperatures and green solvents (d) yield range.

the resultant substitution pattern obtained in the study and can be used as starting point to determine which method(s) would be best suited for a particular application. Due to the importance of this structural motif in existing and emergent technologies, such as pharmaceuticals and agrochemicals as well as dyes for solar cells and other optical applications, functional materials, and catalysis, the development of additional methods is likely to increase. Despite these recent advances, the development of novel methods for the regiocontrolled synthesis of substituted imidazole is of strategic importance. An important consideration in new methods will be to provide regiochemically flexible access to the myriad of imidazole substitution patterns whilst increasing the functional group tolerance of the process. In addition, the ability to rationally and predicatively synthesise imidazoles from renewable starting materials under mild conditions that have a minimal impact on the environment, but which are economically viable will also be key to realise of the applications outlined above. Increased mechanistic understanding as well as reaction design based on the Twelve Principles of Green Chemistry[64] should help deliver clean, concise and high yielding methods for the synthesis of imidazoles. Due to the wide range of potential permutations and the growing importance sustainability, it is clear that there is still significant scope for further discovery.

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 For recent example of natural product synthesis, see: (*a*) M. S. Roy, X. Meg, K. Koda, S. Rasapalli, D. Gout and C. J. Lovely, *Tetrahedron Lett.*, 2019, **60**, 979–982; (*b*) Z. Jin, *Nat. Prod. Rep.*, 2011, **28**, 1143–1191; (*c*) D. P. O'Malley, K. Li, M. Maue, A. L. Zografos and P. S. Baran, *J. Am. Chem. Soc.*, 2007, **129**, 4762–4775.

2 For recent reviews on the synthesis and applications of imidazoles, see: (*a*) N. Kerru, S. V. H. S. Bhaskaruni, L. Gummidi, S. N. Maddila, S. Maddila and S. B. Jonnalagadda, *Synth. Commun.*, 2019, **49**, 2437–2459; (*b*) R. Rossi, G. Angelici, G. Casotti, C. Manzini and M. Lessi, *Adv. Synth. Catal.*, 2019, **361**, 2737–2803; (*c*) M. Hossain and A. K. Nanda, *Sci. J. Chem.*, 2018, **6**, 83–94; (*d*) M. M. Heravi, M. Daraie and V. Zadsirjan, *Mol. Diversity*, 2015, **19**, 577–623; (*e*) K. D. Kreuer, *J. Membr. Sci.*, 2001, **185**, 29–39; (*f*) J. Wang and C. Chen, *Biotechnol. Adv.*, 2009, **27**, 195–226; (*g*) B. H. Lipshultz, *Chem. Rev.*, 1986, **86**, 795–820; (*h*) S. Steenken, *Chem. Rev.*, 1989, **89**, 503–520; (*i*) M. Xue, Y. Yang, Z. Xiadong, Z. Zhang and F. Hunag, *Acc. Chem. Res.*, 2012, **45**, 1294–1308; (*j*) J. Yoon, S. K. Kim, N. J. Singh and K. S. Kim, *Chem. Soc. Rev.*, 2006, **35**, 355–360; (*k*) R. J. Sundberg and R. B. Martin, *Chem. Rev.*, 1974, **74**, 471–517.

3 S. Naureen, F. Chaudhry, M. A. Munawar, M. Ashraf, S. Hamid and M. A. Khan, *Bioorg. Chem.*, 2018, **76**, 365–369.

4 M. V. P. dos Santos Nascimento, A. C. M. Munhoz, B. M. De Campos Facchin, E. Fratoni, T. A. Rossa, M. M. Sá, C. C. Campa, E. Ciraolo, E. Hirsch and E. M. Dalmarco, *Biomed. Pharmacother.*, 2019, **111**, 1399–1407.

5 Z. Mi, Y. Chen, X. Chen, L. Yan, Q. Gu, H. Zhang, C. Chen and Y. Zhang, *Chem. Res. Chin. Univ.*, 2018, **34**, 369–374.

6 M. Mao, X.-L. Zhang and G.-H. Wu, *Int. J. Photoenergy*, 2018, 2061472, DOI: 10.1155/2018/2061472.

7 K. Dhanunjayarao, V. Mukundam, R. V. R. N. Chinta and K. Venkatasubbaiah, *J. Organomet. Chem.*, 2018, **865**, 234–238.

8 S. A. Khan, A. M. Asiri, A.-A. M. Al-Dies, O. I. Osman, M. Asad and M. E. M. Zayed, *J. Photochem. Photobiol., A*, 2018, **364**, 390–399.

 This journal is © The Royal Society of Chemistry 2020

Open Access Article. Published on 18 May 2020. Downloaded on 10/24/2025 9:24:05 PM.
This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.

9 A. A. Bhagwat, K. C. Avhad, D. S. Patil and N. Sekar, *Photochem. Photobiol.*, 2019, **95**, 740–754.
10 A. Hariharan, S. Kumar, M. Alagar, K. Dinakaran and K. Subramanian, *Polym. Bull.*, 2018, **75**, 93–107.
11 Jigyasa and J. K. Rajput, *Sens. Actuators, B*, 2018, **259**, 990–1005.
12 J. Tagare, D. K. Dubey, J.-H. Jou and S. Vaidyanathan, *Dyes Pigm.*, 2019, **160**, 944–956.
13 S. Sambathkumar, S. Priyadharshini, M. Fleisch, D. W. Bahnemann, G. Gnana Kumar, S. Senthilarasu and R. Renganathan, *Mater. Lett.*, 2019, **242**, 28–31.
14 Y. Dong, J. Qian, Y. Liu, N. Zhu, B. Xu, C.-L. Ho, W. Tian and W.-Y. Wong, *New J. Chem.*, 2019, **43**, 1844–1850.
15 H.-L. Ding, L.-D. Chen, N. Wang, K. Li, Y. An and C.-W. Lü, *Talanta*, 2019, **195**, 345–353.
16 J. Jang, Y. Sim, S. Kang, D. Shin, M. Park, K.-Y. Kay and J. Park, *Mol. Cryst. Liq. Cryst.*, 2019, **687**, 14–20.
17 M. Mohagheghnezhad and Z. Rafiee, *Polym. Bull.*, 2019, DOI: 10.1007/s00289-019-02992-9.
18 J. A. Castro-Osma, J. Martínez, F. de la Cruz-Martínez, M. P. Caballero, J. Fernández-Baeza, J. Rodríguez-López, A. Otero, A. Lara-Sánchez and J. Tejeda, *Catal. Sci. Technol.*, 2018, **8**, 1981–1987.
19 S. Fang, H. Yu, X. Yang, J. Li and L. Shao, *Adv. Synth. Catal.*, 2019, **361**, 3312–3317.
20 S. Shi, K. Xu, C. Jiang and Z. Ding, *J. Org. Chem.*, 2018, **83**, 14791–14796.
21 L. Man, R. C. B. Copley and A. L. Handlon, *Org. Biomol. Chem.*, 2019, **17**, 6566–6569.
22 P. Tang, D. Ke, J. Shao, W. Chen and Y. Yu, *Tetrahedron*, 2019, **75**, 4419–4424.
23 M. B. Harisha, P. Dhanalakshmi, R. Suresh, R. R. Kumar, S. Muthusubramanian and N. Bhuvanesh, *ChemistrySelect*, 2019, **4**, 2954–2958.
24 D. Yang, L. Shan, Z.-F. Xu and C.-Y. Li, *Org. Biomol. Chem.*, 2018, **16**, 1461–1464.
25 J. Cai, H. Bai, Y. Wang, X. Xu, H. Xie and J. Liu, *Chem. Commun.*, 2019, **55**, 3821–3824.
26 E. B. Nikolaenkova, A. Ya. Tikhonov and S. Yu. Grishchenko, *Chem. Heterocycl. Compd.*, 2019, **55**, 142–146.
27 J. O. Strelnikova, N. V. Rostovskii, G. L. Starova, A. F. Khlebnikov and M. S. Novikov, *J. Org. Chem.*, 2018, **83**, 11232–11244.
28 P. Wu, X. Zhang and B. Chen, *Tetrahedron Lett.*, 2019, **60**, 1103–1107.
29 X. Tian, L. Song, M. Rudolph, F. Rominger, T. Oeser and A. S. K. Hashmi, *Angew. Chem., Int. Ed.*, 2019, **58**, 3589–3593.
30 Y. Tian, M. Qin, X. Yang, X. Zhang, Y. Liu, X. Guo and B. Chen, *Tetrahedron*, 2019, **75**, 2817–2823.
31 C. Wang, Y. Yu, Z. Su, X. Li and H. Cao, *Org. Lett.*, 2019, **21**, 4420–4423.
32 D. A. Shabalin, J. J. Dunsford, S. Ngwerume, A. R. Saunders, D. M. Gill and J. E. Camp, *Synlett*, 2020, **31**, 797–800.
33 E. Li, Y. Lin, X. Wu, X. Mao, H. Kang, Y. Wen, Y. Bai, X. Wang and X. Lv, *Tetrahedron Lett.*, 2019, **60**, 151122.
34 S. D. Pardeshi, P. A. Sathe, K. S. Vadagaonkar, L. Melone and A. C. Chaskar, *Synthesis*, 2018, **50**, 361–370.
35 C. T. F. Salfeena, R. Jalaja, R. Davis, E. Suresh and S. B. Somappa, *ACS Omega*, 2018, **3**, 8074–8082.
36 X. Geng, C. Wang, C. Huang, Y. Bao, P. Zhao, Y. Zhou, Y.-D. Wu, L. Feng and A.-X. Wu, *Org. Lett.*, 2020, **22**, 140–144.
37 (*a*) A. J. Arduengo III, R. L. Harlow and M. Kline, *J. Am. Chem. Soc.*, 1991, **113**, 361–363; (*b*) D. M. Flanigan, F. Romanov-Michailidis, N. A. White and T. Rovis, *Chem. Rev.*, 2015, **115**, 9307–9387.
38 A. Alanthadka, S. D. Elango, P. Thangavel, N. Subbiah, S. Vellaisamy and U. M. Chockalingam, *Catal. Commun.*, 2019, **125**, 26–31.
39 X. Chen, Z. Wang, H. Huang and G.-J. Deng, *Adv. Synth. Catal.*, 2018, **360**, 4017–4022.
40 F. Alizadeh-Bami, M. Salehzadeh, H. Mehrabi and R. Ranjbar-Karimi, *ARKIVOC*, 2019, (vi), 55–63.
41 Q. Wang, X. Chen, X.-G. Wang, H.-C. Liu and Y.-M. Liang, *Org. Lett.*, 2019, **21**, 9874–9877.
42 S. Sundar and R. Rengan, *Org. Biomol. Chem.*, 2019, **17**, 1402–1409.
43 N. L. Higuera, D. Peña-Solórzano and C. Ochoa-Puentes, *Synlett*, 2019, **30**, 225–229.
44 A. A. Marzouk, A. M. Abu-Dief and A. A. Abdelhamid, *Appl. Organomet. Chem.*, 2018, **32**, e3794.
45 M. Thwin, B. Mahmoudi, O. A. Ivaschuk and Q. A. Yousif, *RSC Adv.*, 2019, **9**, 15966–15975.
46 R. Vaid, M. Gupta, G. Kour and V. K. Gupta, *ChemistrySelect*, 2019, **4**, 9179–9184.
47 Z. Varzi and A. Maleki, *Appl. Organomet. Chem.*, 2019, e5008.
48 For recent examples of nucleophilic catalysis, see: (*a*) J. P. Tellam, G. Kociok-Köhn and D. R. Carbery, *Org. Lett.*, 2008, **10**, 5199–5202; (*b*) G. Sabitha, D. V. Reddy, A. S. Rao and J. S. Yadav, *Tetrahedron Lett.*, 2010, **51**, 4195–4198; (*c*) S. Ngwerume and J. E. Camp, *J. Org. Chem.*, 2010, **75**, 6271–6274; (*d*) W. Chung, P. Lindovská and J. E. Camp, *Tetrahedron Lett.*, 2011, **52**, 6785–6787.
49 W. A. A. Arafa, *RSC Adv.*, 2018, **8**, 16392–16399.
50 J. Sonar, S. Pardeshi, S. Dokhe, R. Pawar, K. Kharat, A. Zine, B. Matsagar, K. Wu and S. Thore, *SN Appl. Sci.*, 2019, **1**, 1045.
51 I. de Toledo, T. A. Grigolo, J. M. Bennett, J. M. Elkins and R. A. Pilli, *J. Org. Chem.*, 2019, **84**, 14187–14201.
52 (*a*) B. Liu and Z. Zhang, *ACS Catal.*, 2016, **6**, 326–338; (*b*) R. G. Chaudhuri and S. Paria, *Chem. Rev.*, 2012, **112**, 2373–2433.
53 A. Maleki, J. Rahimi and K. Valadi, *Nano-Struct. Nano-Objects*, 2019, **18**, 100264.
54 M. Rajabzadeh, H. Eshghi, R. Khalifeh and M. Bakavoli, *Appl. Organomet. Chem.*, 2018, **32**, e4052.
55 T. S. Ahooie, N. Azizi, I. Yavari and M. M. Hashemi, *J. Iran. Chem. Soc.*, 2018, **15**, 855–862.

Open Access Article. Published on 18 May 2020. Downloaded on 10/24/2025 9:24:05 PM.
This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.

56 H. Aghahosseini, A. Ramazani, K. Ślepokura and T. Lis, *J. Colloid Interface Sci.*, 2018, **511**, 222–232.
57 M. M. Gilan, A. Khazaei and N. Sarmasti, *Res. Chem. Intermed.*, 2019, DOI: 10.1007/s11164-018-03724-w.
58 S. Hosseini, A. R. Kiasat and A. Farhadi, *Polycyclic Aromat. Compd.*, 2019, DOI: 10.1080/10406638.2019.1616306.
59 Y. Ruan, Y. Chen, L. Gu, Y. Luo, Z. Yang and L. He, *Synthesis*, 2019, **51**, 3520–3528.
60 A. Yu. Dubovtsev, D. V. Dar'in, M. Krasavin and V. Yu. Kukushkin, *Eur. J. Org. Chem.*, 2019, 1856–1864.
61 W. Sun, M. Zhang, P. Li and Y. Li, *Synthesis*, 2019, **51**, 3221–3230.
62 S. Naidoo and V. Jeena, *Eur. J. Org. Chem.*, 2019, 1107–1113.
63 For recent work on bio-renewable solvents from our group, see: (*a*) T. W. Bousfield, K. P. R. Pearce, S. B. Nyamini, A. Angelis-Dimakis and J. E. Camp, *Green Chem.*, 2019, **21**, 3675–3681; (*b*) J. E. Camp, *ChemSusChem*, 2018, **11**, 3048–3055; (*c*) L. Mistry, K. Mapesa, T. W. Bousfield and J. E. Camp, *Green Chem.*, 2017, **19**, 2123–2128; (*d*) J. E. Camp, S. B. Nyamini and F. J. Scott, *RSC Med. Chem.*, 2020, **11**, 111–117.
64 P. Anastas and N. Eghbali, *Chem. Soc. Rev.*, 2010, **39**, 301–312.

 This journal is © The Royal Society of Chemistry 2020