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Recent Advancements in Pyrrole Synthesis

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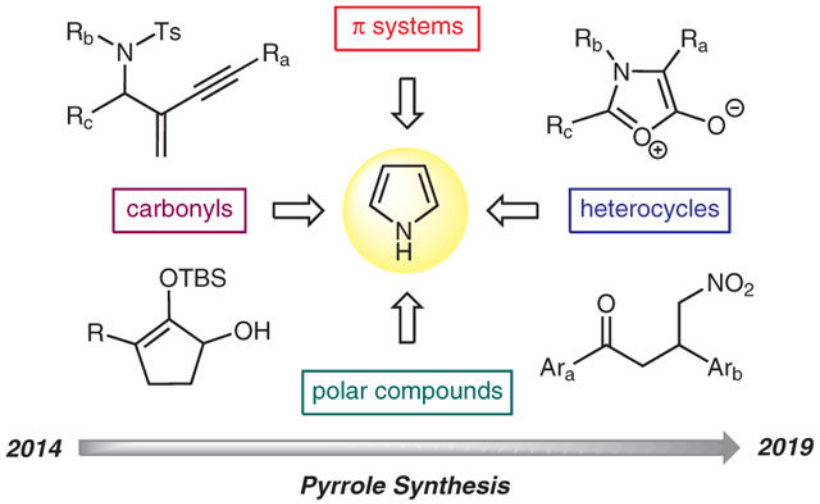
Abstract

This review article features selected examples on the synthesis of functionalized pyrroles that were reported between 2014 and 2019. Pyrrole is an important nitrogen-containing aromatic heterocycle that can be found in numerous compounds of biological and material significance. Given its vast importance, pyrrole continues to be an attractive target for the development of new synthetic reactions. The contents of this article are organized by the starting materials, which can be broadly classified into four different types: substrates bearing **π**-systems, substrates bearing carbonyl and other polar groups, and substrates bearing heterocyclic motifs. Brief discussions on plausible reaction mechanisms for most transformations are also presented.

Graphical Abstract



Keywords

pyrroles; heterocycles; carbonyls; annulation; aromatic

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1 Introduction

Pyrrole is a 5-membered aromatic nitrogen-heterocycle that is ubiquitous in compounds of biological and material significance (Figure 1). For instance, pyrrole is the key structural component in chlorophylls and hemes; both of which are molecules that play a crucial role for the existence of life. Bioactive pharmaceutical compounds and natural products often feature this cyclic motif as their pharmacophore.[1,2] Pyrrole can be also found in diverse forms of organic dyes and materials, such as BODIPY, conjugated polymers, optoelectronics, as well as semiconductors.[3–6] First detected as a component of a coal tar in 1834,[7] some of the pioneering examples on pyrrole synthesis were reported by Knorr, Hantzsch, and Paal at the end of the 19th century.[8–10] Despite its prevalence in synthetic chemistries for over 100 years, pyrrole remains an important synthetic target in modern organic chemistry. Interestingly, between 2000 and 2020 over a dozen review articles have been published to summarize the various advancements that have been made to assemble this highly important molecular structure.[11–24]

In this article, we wish to provide a brief survey on selected pyrrole syntheses that were published between 2014–2019. Upon examining literature precedents within this time span, we discerned that the various starting materials used in these new chemistries can be grouped broadly into four different types: substrates bearing π-systems, substrates bearing carbonyl and other polar groups, and substrates bearing heterocyclic motifs (Figure 2). Guided by this classification, we organized the transformations to highlight each type of the starting materials. Most examples will be accompanied by brief discussions on plausible reaction mechanisms. To further aid content arrangement, we also set criteria that the indicated type of starting materials will either form a part of pyrrole ring or contain key functional groups that directly participate in the pyrrole formation. For example, enones are both discussed in Sections 2.1 (Alkenes) and 3.2 (Ketones). The difference is that in Section 2.1, only the alkene portion of enone forms the pyrrole; whereas in Section 3.2, the entire α,β-unsaturation in the enone participates in pyrrole annulation and becomes a part of the ring. Given the broad extent of this subject matter, it is very difficult to dedicate an exclusive section for functional groups that routinely serve as reaction partners in pyrrole synthesis, such as amines, β-enaminones, and azirines. In fact, these compounds will appear in various sections throughout this manuscript.

2 From π-Systems

New chemistries that strategically exploit the reactivity of π-systems as useful starting materials in pyrrole synthesis remain well precedented in the literature. As exemplified in this section, these π-systems include various forms of alkenes, dienes, allenes, and alkynes.

2.1 Alkenes

Substituted alkenes, including those of α,β-unsaturated and allylic systems, are readily employed as starting materials to access pyrrole scaffolds.[25,26] For instance, Xu and Zhang reported a silver acetate catalyzed tandem reaction of *p*-toluenesulfonylmethyl isocyanide (TosMIC) with 2-methyleneindene-1,3-diones **1** in the presence of K_2CO_3 to access fused pyrrole compounds **2** (Scheme 1).[27] The proposed mechanism is via conjugate addition of

TosMIC anion **3** to the alkene moiety, leading a 5-membered cyclization to imidoyl intermediate **4**. The ensuing cyclization followed by ring opening of the resulting cyclopropanolate **5** and aromatization through elimination of the tosyl group then yielded the pyrrole ring.

Maurya conveyed the preparation of 2,3-fused pyrroles **6** via the reaction of α-azidoenones with naphthols and related compounds in the presence of catalytic $Ru(bpy)_3(PF_6)_2$ under blue LED light irradiation (Scheme 1).[28] The proposed reaction mechanism commences with photosensitized decomposition of the α-azidoenone to yield reactive 2*H*-azirine intermediate **7**, which is trapped by the enolic reaction partner. Tautomerization of the resulting intermediate **8** enables conjugate aziridine opening, which then allows dehydrative cyclization to produce the pyrrole core.

In another example, Zhang and Chan reported an operationally simple and convenient synthesis of vinyl-substituted pyrroles **10** involving annulation between allylic-propargylic diols **9** and arenesulfonamides in the presence of $Yb(OTf)_3$ (Scheme 1).[29] The reaction mechanism is proposed through ionization of the starting material with Yb(III) catalyst to form resonance stabilized carbocation **11**. The ensuing capture by the sulfonamide at the less hindered carbon then provides intermediate **12**. A second alcohol activation and intramolecular amino cyclization facilitate by the Yb catalyst leads to the vinyl-substituted pyrrole product.

2.2 1,6-Dienes

The use of 1,6-dienes in pyrrole synthesis has been reported, in which the pyrrole core can be constructed via a ring-closing metathesis methodology. Scheme 2 depicts two examples. Lamaty demonstrated a strategy using nitro-Grela as the ruthenium ring-closing metathesis catalyst to form substituted pyrrolines **14** from β-amino esters **13**.[30] The ensuing deprotection-aromatization step with NaO*t*-Bu furnished 2-aryl-1*H*-pyrrole-3-carboxylates **15**. The second example by Wu and Li reported the preparation of *N*-sulfonyl-and *N*-acylpyrroles **17** and **18**.[31] Starting with diallylamines **16**, the one-pot protocol involved Grubbs II catalyzed ring-closing metathesis, followed by in situ oxidation of the emerging pyrroline intermediates with a suitable Cu(II) catalyst and O_2 as an oxidant.

2.3 Allenes

Functionalized pyrroles can be assembled from allenes upon treatment with either amines, enaminones, or aziridines (Scheme 3). For instance, Santeusanio reported the synthesis of pentasubstituted hydroxypyrroles **21** by combining 1,2-diaza-1,3-dienes **19**, primary amines, and 2,3-allenoates **20**.[32] The reaction mechanism is proposed through a conjugate addition of amine to the α-carbon of **19**, followed by nucleophilic addition to allenoate **20** to produce intermediate **22**. Subsequent intramolecular cyclization then affords the hydroxypyrrole product **21**.

Luo and Deng developed a novel approach to prepare pyrroles **25** using enamines **23** and allenoates **24** in the presence of I_2 catalyst and TBHP (Scheme 3).[33] This reaction is

proposed to occur via a Michael addition between the two starting materials, followed by I_2-catalyzed annulation of the resulting anionic intermediate **26** in the presence of TBHP.

Another utility of allenes in pyrrole synthesis was described by Pinho e Melo,[34] who treated (1*H*-tetrazol-5-yl)-allenes **27** and aziridines **28** under microwave irradiation at 150 °C in toluene to form tetrasubstituted pyrroles **29** (Scheme 3). Mechanistically this reaction is proposed to involve formal [3+2] cycloaddition via intermediate **30**; subsequent tautomerism and retro-aldol-type fragmentation results in the pyrrole formation.

Tong reported an amine-catalyzed synthesis of pyrroles **33** from β′-acetoxy allenoates **31** and 2-(tosylamino)carbonyl compounds **32** (Scheme 3).[35] In this chemistry, the 1,4-addition of DABCO to allenoate, accompanied by elimination of acetate, produces putative intermediate **34**. Deprotonation by Na_2CO_3 then triggers a sequence of [3+2] annulation, followed by 1,2-elimination of the tosyl group and isomerization to generate trisubstituted pyrrole **33**.

2.4 Alkynes

A wide collection of reactions have been reported between 2014–2019 that showcase the use of triple bonds as starting materials for pyrroles synthesis.[36–41] A number of transition metal catalysts, such as Au, Pd, Cu, Rh, and Ru, have been reported to catalyze reactions between substituted alkynes and amines, enaminones, or oxime to generate pyrroles. In addition, a few reagent-driven syntheses have also been reported.

2.4.1 Gold Catalysis—Chen and Zhu developed a synthetic approach toward substituted pyrroles **37** and formylpyrroles **36** from enyne sulfonamides **35** using a dual IPrAuCl/$AgNTf_2$ catalytic system; formylpyrroles **36** were isolated when the reaction was performed in the presence of DDQ (Scheme 4).[42] The proposed mechanism commences with gold-catalyzed intramolecular cyclization of enyne sulfonamide, followed by 1,3-Ts shift to form 3-methylene-2,3-dihydropyrrole **38**. The ensuing aromatization via 1,3-H shift then afforded pyrrole **37**. Interestingly, the introduction of DDQ readily interrupted aromatization of **38**, leading to oxidation and thus formation of azafulvenium **39**. Nucleophilic addition of MeOH or AcOH, followed by further oxidation and hydrolysis then led to the observed formylpyrrole **36**.

Liu and Li reported the gold-catalyzed hydroamination of electron-deficient alkynes with α-amino ketones using gold catalyst **42** (Scheme 4).[43] In this reaction, the conjugate addition adduct **40** is believed to undergo cyclization-condensation, thereby producing the resulting pyrroles **41**. The addition of MgO to the reaction mixture facilitated the removal of water byproduct and drove the equilibrium forward. Another example of gold-catalyzed pyrrole synthesis was demonstrated by You and Song (Scheme 5), in which the reaction between β-enaminones **43** and terminal alkynes **44** in the presence of $[(bpy)AuCl_2]Cl$, $PhI(OAc)_2$, and KOAc readily accessed 3-alkynylpyrroles **45**.[44] Mechanistic investigations suggest this reaction involves the generation of gold(III) intermediate **47** that subsequently undergoes reductive coupling to yield 2-alkynyl-β-enamino ester **48**. The ensuing pyrrole cyclization,

transmetalation with gold(III) acetylide **46**, and reductive elimination of the resulting intermediate **49** then furnishes the 3-alkynylpyrrole motif.

2.4.2 Palladium Catalysis—An efficient three-component reaction of alkyne esters, amines, and alkenes to form 2,3,4-trisubstituted pyrroles **50** in the presence of Pd(II) catalyst and $K_2S_2O_8$ was conveyed by Zhang and Yi (Scheme 6).[45] The reaction mechanism is proposed to involve regioselective alkene migratory insertion of Pd(II)-activated alkene at the β-position of enamine **51**, which is generated in situ by the reaction of the alkyne ester and amine, to produce intermediate **52**. Facilitated by sulfate radical anion, a sequence of hydrogen abstraction to radical intermediate **53**, followed by, in succession, intramolecular radical addition-cyclization and protonolysis then generates dihydropyrrole and HPdOAc. Oxidation by $K_2S_2O_8$ then affords pyrrole **50** while regenerating the active Pd(II) catalyst via a reductive elimination-oxidation sequence.

Shi reported an efficient $Pd(TFA)_2$-catalyzed reaction for the synthesis of *N*-OR substituted pyrroles **55** from 1-(alk-1-ynyl)cyclopropyloxime derivatives **54** in the presence of different nucleophiles (Scheme 6).[46] This chemistry is believed to occur via activation of the alkyne moiety by Pd(II) to promote intramolecular nucleophilic cyclization to generate *N*-oxyiminium ion **56**. Intermolecular nucleophile-promoted fragmentation of the cyclopropane moiety, followed by protonation of the [Pd]-pyrrole species **57**, then affords the final product.

Werz demonstrated the use of $PdCl_2(PhCN)_2$ catalyst in the synthesis of substituted pyrroles **59** from internal alkynes **58** (Scheme 7).[47] The mechanism of this reaction commences with oxidative addition of the aryl bromide moiety into the Pd(0) source, leading to a *syn*-migratory insertion into the alkyne C≡C bond to form Pd-vinyl species **60**. This is followed by alkene isomerization to **62** via *syn-anti* transition state **61** and coordination of the amine to the palladium resulting in reductive elimination of intermediate **63**. The resulting enamine **64** subsequently undergoes ring-opening isomerization to yield the corresponding 3-aryl-substituted pyrrole.

2.4.3 Catalysis by Other Transition Metals—Apart from the use of gold and palladium, there are several other metal-catalyzed reactions with alkynes to synthesize various functionalized pyrroles (Scheme 8). For instance, Yin reported the preparation of polysubstituted 2-chloropyrroles **66** from *N*-furfuryl-β-enaminones, available from starting furfurylamines **65** and alkyne esters, in the presence of catalytic $CuCl_2$.[48] Mechanistic studies suggest formation of radical cation **67** through single electron transfer (SET) promoted by the copper(II) catalyst, en route to formation of carbocation **68** via chlorination. The ensuing intramolecular capture by the pendant enamine moiety generates iminium ion **69**. A series of deprotonations leads to aromatization and dechlorination to afford pyrrole **70**, which forms radical cation **71** in the presence of $CuCl_2$ and undergoes chlorination to carbocation **72**; loss of a proton then furnishes the 2-chloropyrrole adduct. It is proposed that O_2 serves as a terminal oxidant in the acidic reaction medium, which regenerates $CuCl_2$ from CuCl.

Liu described the use of $[Rh(NBD)_2]BF_4$ catalyst in the reaction of alkynes with 2-vinylaziridines **73** to produce functionalized pyrroles **74** (Scheme 8).[49] In this reaction, the proposed mechanism commences with a rhodium-promoted oxidative ring opening of the aziridine, leading to coordination with the alkyne to give intermediate **75**, which then undergoes migratory insertion followed by reductive elimination to form dihydropyrrole **76**. DABCO then mediates isomerization-aromatization of **76** via a series of proton transfers.

Wan and Wang reported the ruthenium-catalyzed synthesis of polysubstituted pyrroles **78** via intermolecular [3+2] cycloaddition between activated alkynes with 2*H*-azirines **77**.[50] The reaction is proposed to proceed through azirine oxidative ring opening and alkyne insertion by the ruthenium catalyst. The resulting intermediate **79** undergoes reductive elimination and aromatization to provide thermodynamically stable pyrrole ring while regenerating the catalyst.

2.4.4 Reagent-Driven Synthesis—Approaches by which the synthesis of pyrroles from alkynes proceeds in the presence of stoichiometric reagents are shown in Scheme 9. For example, Čikotienė described the reaction of 1-(alk-1-ynyl)cyclopropyl imines **80** with various compounds containing polarized covalent bonds (EX) to produce pyrroles **81**.[51] The mechanism of this reaction is proposed though activation of alkyne with EX, resulting in the fragmentation of the cyclopropyl ring and 5-membered pyrrole cyclization by the imine moiety.

Rao reported an iodine-mediated synthesis of 2,3,5-trisubstituted pyrroles **83** using arylacetylenes and β-enaminones **82** in the presence of K_2CO_3 and DMSO (Scheme 9).[52] The reaction mechanism begins with the α-iodination of the alkyne, followed by Kornblum oxidation to yield dicarbonyl intermediate **84**. The ensuing condensation with β-enaminone, followed by intramolecular cyclization and dehydration then forms the pyrrole ring.

2.5 Propargylic Groups

There are numerous examples on the use of propargylic starting materials, such as propargylic amines, carbonates, and alcohols, in pyrrole synthesis.[53,54] Scheme 10 depicts representative examples. Sakai reported a [4+1] annulation of propargylamines with either ethyl glyoxalate or phenylglyoxal in the presence of $CuCl_2$ and piperidine to yield 1,2,5-trisubstituted pyrroles **86**.[55] This reaction is proposed to proceed via iminium intermediate **87** resulting from the condensation of glyoxylate ester (or phenylglyoxal) and piperidine. The ensuing sequence of nucleophilic addition by the propargylamine **85**, alkyne activation by $CuCl_2$ to induce 5-endo-*dig* cyclization, and protonation generates intermediate **88**, which undergoes aromatization with loss of piperidine to produce the pyrrole core.

Zhu developed a multicomponent reaction between propargyl carbonates, alcohols, and isocyanides in the presence of $Pd(OAc)_2$ catalyst and a stoichiometric amount of *tert*-butylamine for the synthesis of 2-aminopyrroles **90** (Scheme 10).[56] The proposed mechanism involves the intermediacy of (σ-allenyl)palladium(II) species **91**, which is generated upon decarboxylation of propargylic carbonate **89** promoted by in situ generated Pd(0) isocyanide complex. (σ-Allenyl)palladium(II) species **91** undergoes migratory

insertion of isocyanide to give intermediate **92**, and this undergoes nucleophilic addition of a second isocyanide resulting in nitrilium ion **93**. Subsequent β-hydride elimination from nitrilium ion **93** and a further nucleophilic addition of isocyanide gives nitrilium intermediate **94** which then reacts with carbamate anion **95** to afford advanced intermediate **96**. Carbamate anion **95** is produced upon the liberation of CO_2 during decarboxylation of **89**, which is immediately trapped by *t*-BuNH_2. Intermediate **96** undergoes 1,4-addition of alcohol, followed by cyclization of the resulting enamine onto the ketenimine to form the pyrrole ring. Cleavage of the carbamate group then furnishes the final product **90**.

An example of the use of propargylic alcohols was reported by Nandi who demonstrated an efficient synthesis of highly substituted pyrroles in the presence of $InCl_3$ catalyst and α-oxoketene *N,S*-acetals **97** (Scheme 10).[57] This reaction is believed to begin with ionization of the propargylic alcohol by $InCl_3$, leading to nucleophilic substitution by α-oxoketene *N,S*-acetals **97** to form intermediate **99**. The ensuing alkyne activation by $InCl_3$ results in intramolecular 5-membered cyclization, en route to the pyrrole product **98** upon proton transfer.

2.6 Homopropargylic Amines

Homopropargylic amines served as an effective substrates for the synthesis of pyrroles.[58] As exemplified in Scheme 11, Li and Liu reported the preparation of tetrasubstituted pyrroles **100** via the reaction of homopropargylic amines and aryl iodides in the presence of catalytic $Pd(PPh_3)_2Cl_2$, CuI, and excess diisopropylamine.[59] This multistep cascade reaction is presumed to involve a sequence of Sonogashira coupling, intramolecular hydroamination, and reductive elimination. The final oxidation of the 2-pyrroline intermediate **101** with DDQ then yields the final pyrrole product **100**.

3 From Carbonyl Compounds

Carbonyl compounds have been traditionally employed as convenient substrates for pyrrole synthesis. This trend has continued and evidenced by the substantial number of methodologies in the period 2014–2019 that have been developed using these starting materials. The use of nitriles and isonitriles have also been reported.

3.1 Aldehydes

As depicted in Scheme 12, Wen and Wan developed a metal-free cascade reaction of phenylacetaldehydes and anilines, which provided a facile access to 1,3,4-trisubstituted pyrroles upon treatment with the *tert*-butyl hydroperoxide (TBHP).[60] This reaction is proposed to proceed via oxidation of imine **103** to radical intermediate **104**, which then dimerizes to **105**. A series of tautomerization, intramolecular cyclization, and elimination of one aniline molecule then produces triaryl-substituted pyrroles **102**.

Gu and Li described two approaches to the synthesis of pyrroles from aldehydes (Scheme 12). The first method involved treatment of enolizable aldehydes with primary aliphatic amines and catalytic iodine, which served as Lewis acid and mild oxidant.[61] The proposed mechanism commences with the Mannich-aldol condensation between the aldehydes and

amines, which is then followed by iodination to intermediate **107**, thereby enabling intramolecular cyclization to pyrrole **106**. In the second method, enolizable α,β-unsaturated aldehydes and aromatic amines were subjected to catalytic iodine to afford *N*-arylpyrroles **108**. Interestingly, the addition of TBHP to this iodine-mediated reaction led to C-2 iodized pyrroles **109**. A similar reaction mechanism, involving intramolecular cyclization by the imine moiety in iodized intermediate **110**, is proposed. However, the presence of oxidant TBHP readily regenerates molecular iodine from the iodide ion, enabling electrophilic aromatic substitution of the forming pyrroles **108** to furnish 2-iodopyrroles **109**.

The emergence of visible-light photoredox catalysis has facilitated the development of new synthetic methods to access functionalized pyrroles from aldehydes. For instance, Bandini and Protti reported condensation of aryl azides and aldehydes promoted by Ru(II) catalysis and blue LED light for the regioselective preparation of 1,3,4-trisubstituted pyrroles **112** (Scheme 12).[62] In this reaction, aryl azides served both as a source of nitrogen atom for the pyrrole core as well as a formal stoichiometric oxidant. The proposed mechanism begins by the generation of photoexcited $[Ru^{2+}]^*$ complex, which undergoes oxidative quenching by aryl azide to produce anilino radical cation **113** upon protonation of the emerging nitrogen radical intermediate. The transient Ru^{3+} then oxidizes the aldehyde **111** through SET, followed by deprotonation, to generate α-carbonyl radical **114**. The ensuing coupling with another molecule of aldehyde leads to α-hydroxy radical **115**, which is oxidized to 1,4-dialdehyde **116** by anilino radical cation **113**. Finally, Paal–Knorr condensation between both in situ generated aniline and 1,4-dialdehyde then furnishes pyrrole **112** as the major isomer.

3.2 Ketones

Examples of pyrrole synthesis from simple ketones are showcased in Scheme 13. Using aryl methyl ketones and anilines, Zhang reported a one-pot iodine-mediated cascade condensation-cyclization reaction to prepare 1,2,4-triarylpyrroles **117**.[63] The mechanism is proposed to involve α-iodination of ketimine intermediate **118**, allowing for nucleophilic substitution by another molecule of ketimine resulting in iminium ion **119**. Following proton transfer to form enamine **120**, intramolecular Mannich-type condensation then takes place to yield cyclic intermediate **121**. Aromatization upon extrusion of an aniline moiety gives the pyrrole product **117**.

Trofimov showed that ketones could be converted into pyrroles **123** in a one-pot procedure upon treatment with hydroxylamine hydrochloride and KOH, followed by addition of 1,2-dichloroethane (Scheme 13).[64] It is proposed that ketoxime **122** is the putative intermediate in this reaction, which undergoes nucleophilic substitution with 1,2-dichloroethane to form *O*-(2-chloroethyl) ketoxime **124**. The ensuing elimination of chloride to *N*-vinylketoxime **125** then enables 3,3-sigmatropic rearrangement to iminoaldehyde **126**; intramolecular condensation then produces the pyrrole core.

Owing to presence of pyrrole and imidazole units in various medicinally important molecules, Khlebnikov developed a new strategy to synthesize 1-alkyl-3-(1*H*-pyrrol-3-yl)-1*H*-imidazol-3-ium bromides starting from 1-alkyl-3-phenacyl-1*H*-imidazolium

bromides **127** and azirine **128** (Scheme 13).[65] The mechanism of this reaction is proposed to commence with formation of intermediate **130** through addition of the enolate of **127** to azirine. Upon proton transfer, the ensuing ionization of zwitterion intermediate **131** then promotes ring fragmentation, thus allowing 5-membered cyclization and dehydration to furnish the pyrrole product **129**.

Khlebnikov also described another interesting strategy where 1,2,4-tricarbonyl compounds **132** act as Michael acceptors in the presence of 2*H*-azirines **135** and $Cu(OAc)_2$ catalyst en route to the preparation of pyrrole isomers **133** and **134** (Scheme 14).[66] The proposed reaction mechanism commences with a conjugate addition of azirine-metal complex to the tricarbonyl compound. The ensuing intramolecular cyclization of intermediate **136** at two possible carbonyl positions is then followed by azirine fragmentation and aromatization. The resulting two isomeric pyrrole adducts **133** and **134** are easily separable by chromatography.

Chen reported an $FeCl_3$-mediated synthesis of pyrroles from 3-methylenehexane-2,5-dione **137** and primary amines (Scheme 14).[67] This reaction is proposed to proceed via the intermediacy of 2,3-dihydropyrrole intermediate **139**, which is generated by reaction of 3-methylenehexane-2,5-dione and primary amine, followed by intramolecular aza-Michael addition of the resulting enamine. Subsequent oxidative aromatization of this intermediate **139** by Fe^{3+} and O_2 affords pyrrole **138**.

3.2.1 α-Hydroxy and α-Halo Ketones—Functionalized ketones at the α-carbon have been shown to be a convenient starting point for pyrrole synthesis.[68,69] For example, Lei and Lui reported an acid-promoted cross-dehydrative aromatization reaction between α-hydroxyaryl ketones **140** and aryl ketones **141** in the presence of ammonium acetate to access unsymmetrical tetraaryl-substituted pyrroles (Scheme 15).[70] This reaction is proposed to involve in situ generation of α-amino ketone **143** upon a sequence of imine formation and tautomerization between the α-hydroxy ketone and ammonium acetate. The ensuing condensation of α-amino ketone **143** with aryl ketone **141**, followed by tautomerization to enamine intermediate **144** sets the stage for intramolecular cyclization and aromatization to yield the tetraarylpyrroles **142**.

Another example was demonstrated by Kartika, who synthesized pyrrole-derived compounds by subjecting α-hydroxy silyl enol ethers **145** to silylenolates **146**, and then primary amines, in the presence of a Brønsted acid catalyst (Scheme 15).[71] In this reaction, ionization of α-hydroxy silyl enol ether forms unsymmetrical silyloxyallyl cation **148**, which is captured in a regioselective manner by silylenolate **146**. The resulting γ-keto silyl enol ether **149** then undergoes protodesilylation under the Brønsted acidic conditions to unmask the 1,4-diketone moiety **150**, thus enabling Paal–Knorr condensation with various primary amines to install pyrrole structure **147**.

Apart from α-hydroxy ketones, the use of α-halo ketones for pyrrole synthesis has also been documented in the literature (Scheme 16). For instance, Wu reported a photoinduced Hantzsch-type reaction between α-bromo ketones and enaminones to synthesize polysubstituted pyrroles in the presence of catalytic $Ir(ppy)_3$ and triethylamine.[72] The mechanism is proposed through photoexcitation of $Ir(ppy)_3$, which generates alkyl radical

intermediates **154** from α-bromo ketone **151** via SET. The subsequent coupling of **154** with enaminones **152** leads to amino radical **155**, which is oxidized by $Ir(ppy)_3^+$ species to ketimine **156**. The following intramolecular condensation and dehydration assisted by Et_3N generates the pyrrole adduct **153**.

3.2.2 Enones—Enones are used as versatile precursors to pyrrole synthesis due to their facile reactivity as Michael acceptors.[73] As shown in Scheme 17, Opatz showcased cyclocondensation of enones with aminoacetonitriles to form 3,4-dihydro-2*H*-pyrrole-2-carbonitriles **157**.[74] Using one-pot protocols, these synthetic intermediates could be converted into either 2,4-disubstituted pyrroles **158** through microwave-mediated dehydrocyanation or to 3,5-disubstituted pyrrole-2-carbonitriles **159** upon oxidation with DDQ. The key mechanistic step in this reaction is believed to involve a 6π-electrocyclic ring closure of pentadienyl anion **160**, generated upon condensation of the starting enone and aminoacetonitrile, followed by a loss of a proton.

3.3 Cyanides and Isocyanides

Diederich reported the reaction of nitrile-containing buta-1,3-dienes **161** with amines under microwave conditions toward the synthesis of 2-aminopyrroles **162** (Scheme 18).[75] This reaction is proposed to proceed via nucleophilic addition of amine to the nitrile moiety, followed by intramolecular cyclization of the resulting amidine intermediate **163**; subsequent tautomerization then constructed the pyrrole product **162**.

Rao has shown that aliphatic, aromatic, and benzylic nitriles could be converted into 2,3,5-trisubstituted pyrrole diesters **164** via a zinc-mediated pseudo four-component reaction catalyzed by TMSCl (Scheme 18).[76] The reaction proceeds by the addition of the zinc enolate of ethyl bromoacetate **165** to the nitrile to form enamino ester **166**. Then, *C*-alkylation with another molecule of ethyl bromoacetate produces diester **167**, which undergoes Perkin ester condensation with another molecule of zinc enolate **165** to form key intermediate **168**; subsequent dehydrative cyclization results in trisubstituted pyrroles **164**.

Examples on the use of isonitriles in pyrrole synthesis are depicted in Scheme 19. Jiang and Wu developed a palladium-catalyzed three-component reaction using aryl halides, isocyanides, and *N*-tosylhydrazones **169** to assemble substituted 3-aminopyrroles.[77] The key mechanistic steps in this reaction begin with oxidative addition of Pd(0) to aryl halides, followed by double isocyanide insertion to form iminopalladium **171**. This species is then trapped by in situ generated diazo compound **172**, formed as a result of decomposition of *N*-tosylhydrazones **169**, to yield palladium-carbene complex **173**. Migratory insertion, followed by β-hydride elimination, leads to intermediate **174** which undergoes intramolecular cyclization to yield 3-aminopyr-roles **170**.

Darehkordi reported a one-pot multicomponent reaction toward pyrrole synthesis using isocyanides, dialkyl acetylenedicarboxylates, and *N*-aryl-2,2,2-trifluoroacetimidoyl chlorides **175** (Scheme 19).[78] In this example, addition of isocyanide to the acetylenedicarboxylate produces zwitterionic intermediate **177**, which then adds to the imidoyl carbon of **175**. The resulting tetrahedral intermediate **178** proceeds through

intramolecular 5-membered cyclization and aromatization to furnish trifluoromethylated 2-amino-pyrrole **176**.

Bi and Fu investigated the silver-catalyzed formal [3+2]-dipolar cycloaddition reactions between β-enaminones **179** and isocyanoacetates for the facile formation of functionalized pyrroles **180** (Scheme 19).[79] The mechanism of this reaction involves [3+2] cycloaddition of the imine tautomer of β-enaminone **181** with α-metalated isocyanide **182** to form imidazoline intermediate **183**. The enhanced acidity of the proton due to adjacent the electron-withdrawing group in **183** then allows a retro-hetero-Michael addition leading to ring fragmentation of the imidazoline moiety and recyclization to form the pyrrole products **180** via intermediate **184**.

3.4 Formamides

Wang demonstrated $Cu(OTf)_2$-catalyzed multicomponent reactions of *N,N*-disubstituted formamides **185**, TMSCN, and aromatic alkenes or alkynes that led to the synthesis of polysubstituted pyrrole-2-carbonitriles **186** (Scheme 20).[80] The mechanism commences with the generation of an α-aminonitrile via dicyanation of formamide in the presence of the Cu(II) catalyst. Subsequent release of HCN then yields azomethine ylide intermediate **187**, which proceeds to regioselective [3+2] cycloaddition with the dipolarophiles, i.e. alkene or alkyne, to afford intermediate **188**. Finally, oxidative dehydroaromatization with DDQ gives the pyrrole structure **186**.

3.5 β-Enamines

β-Enamines can be effectively employed in intramolecular cyclization upon self-dimerization to generate pyrroles (Scheme 21). For instance, a simple route to polycarbonyl pyrroles **190** via $K_2S_2O_8$ promoted oxidative cyclization of enamine **189** was disclosed by Guan and Gao.[81] In this chemistry, a radical mechanism is proposed. Initial oxidation of enamine **189** by $K_2S_2O_8$ produces amino radical cation **191**, which dimerizes with a second molecule of **189** to form intermediate **192** that undergoes a sequence of intramolecular C–N bond formation, oxidation, and aromatization upon extrusion of ammonia to yield the pyrrole adduct.

Youn demonstrated CuCl-catalyzed oxidative annulation reactions using enamine **193** in the presence of di-*tert*-butyl peroxide (Scheme 21).[82] Mechanistic investigations suggest the possible formation of radical intermediate **195** via SET, leading to self-dimerization. A second oxidation then occurs to generate diketimine intermediate **196**, which undergoes cyclization to generate pyrrole **194**.

3.6 Dicarbonyl Compounds

Various motifs of dicarbonyl compounds have been extensively utilized toward pyrrole synthesis.[83–93] As discussed in this section, this class of starting materials have enabled the development of a broad array of new synthetic reactions.

3.6.1 1,2-Dicarbonyls—The use of 1,2-dicarbonyl compounds toward pyrrole synthesis has been largely confined to arylgloxals (Scheme 22).[94–96] Chen developed a one-pot

procedure involving the Blaise reaction between nitriles and α-bromo esters in the presence of zinc, followed by addition of arylglyoxal monohydrates **197**.[97] This reaction proceeds through formation of β-enaminone **199**, which subsequently undergoes nucleophilic addition with the arylglyoxal **197**; intramolecular cyclization and dehydration of the resulting intermediate **200** gives the pyrrole **198**

Another example of the use of arylglyoxal is the multicomponent tether catalysis that was reported by Yan.[98–101] The protocol in this chemistry involved a simple mixing of ethyl 2-(2-pyridyl)acetates **201**, arylglyoxal monohydrates **202**, and heterocyclic ketene aminals (HKA) **203** in ethanol at reflux. The mechanism is proposed via pyridinium addition intermediate **205**, leading to tethered catalysis intramolecular cyclization to furnish 1,4-keto ester **206**. Intra-molecular cyclization-tautomerization to cyclic intermediate **207** and nucleophilic 1,2-addition by HKA **203** gives advanced intermediate **208**, which undergoes decarboxylative intramolecular cyclization and dehydration to produce 2-amino-4-(2-pyridylmethyl)pyrrole **204**.

Zhong and Chen reported a DABCO-promoted three-component domino reaction using arylglyoxal monohydrates, enamino esters **209**, and 1,3-dicarbonyl compounds to give highly functionalized NH-pyrrole adducts **210** (Scheme 23).[102] This reaction commences with the Knoevenagel-type condensation between arylglyoxal and the 1,3-dicarbonyl compound in the presence of catalytic DABCO, thereby producing α,β-unsaturated intermediate **211**, which serves as a Michael acceptor to electron-rich β-enaminone **209**; cyclization then generates pyrrole **210**.

Doyle developed a unique three-component cascade synthesis of pyrroles **213** by subjecting tricarbonyl compounds **212** to ketones and primary amines (Scheme 23).[103] This reaction proceeds through a sequence of enamine addition to the most electrophilic central carbonyl carbon of **212**, followed by cyclization of the resulting aldol intermediate **214**. Aromatization via dehydration and proton transfer then produce 5-vinylpyrrole product **213**.

3.6.2 1,3-Dicarbonyls—The utility of 1,3-dicarbonyl compounds in pyrrole synthesis is showcased in Scheme 24. For instance, Li and Xu reported the reaction between 1,3-diketones **216** and 1-sulfonyl-1,2,3-triazoles **215** catalyzed by $Rh_2(Piv)_4$ to give 2-carbonylpyrroles **217**.[104] In this chemistry, the Dimroth-type equilibrium of the 1-sulfonyl-1,2,3-triazole to an α-diazo imine enables the generation of α-imino rhodium carbene **218**, which is then captured by the enol ether tautomer of the 1,3-diketone **216**. The resulting zwitterionic intermediate **219** then proceeds through addition-elimination sequences to produce **221**, which undergoes an intramolecular aldol reaction and aromatization to give *N*-sulfonylpyrrole **217**.

Mehrabi described the synthesis of pentasubstituted pyrroles in a one-pot, two-step protocol using alkyl acetoacetates, dialkyl acetylenedicarboxylates, and amines in the presence of K_2CO_3.[105] This reaction begins with Michael addition of alkyl acetoacetate to dialkyl acetylenedicarboxylate giving 4-hydroxypenta-1,3-diene-1,2,3-tricarboxylate **223**. The ensuing condensation with primary amine, followed by cyclization and oxidation by air then yields pyrrole **222**.

3.6.3 1,4-Dicarbonyls—The condensation of primary amines with 1,4-dicarbonyl compounds, the Paal–Knorr reaction, is one of the most well-known approaches to synthesize various *N*-substituted pyrroles.[106] Since 2014, there have been several new advances in this methodology (Scheme 25), particularly those focusing on green chemistry through the use of environmentally benign catalysts, such as $MgI_2 \cdot OEt_2$ by Zhang,[107] citric acid by Rousseau,[108] and saccharin by Gaonkar.[109] As reported by Giray, an uncatalyzed Paal–Knorr reaction could be also performed in boiling water.[110] Rajeshkumar reported the preparation of 4-(arylthio)pyrroles **225** via treatment of 1,4-enediones **224** with arenethiols and ammonium formate.[111] The mechanism is proposed to involve Michael addition of arenethiol to 1,4-enedione **224**, followed by Paal–Knorr condensation with in situ generated ammonia to form imino-carbonyl intermediate **226**, which undergoes intramolecular cyclization and aromatization to generate 4-(arylthio)pyrroles **225**.

The Clauson-Kaas reaction is another well-established methodology to synthesize pyrrole from primary amines and a 1,4-dicarbonyl surrogate in the form of 2,5-dimethoxytetrahydrofuran (DMTHF).[112] Recent advancements in this reaction include a report by Chaudhari, who explored alkaline-earth metal salts, like $Ca(NO_3)_2 \cdot 4H_2O$, as mild Lewis acid catalysts (Scheme 26).[113] A unique variation to the Clauson-Kass reaction was reported by Gu,[114] who treated 2-alkoxy-2,3-dihydrofurans **228** with 2-methylindoles and $FeCl_3$, followed by addition of $Al(OTf)_3$ and arylamine, to produce 2-(3-indolyl)pyrroles **229**. Both Lewis acids were employed in catalytic amounts. This one-pot, two-step protocol is proposed to proceed via addition of two molecules of indole upon Lewis acid promoted ring fragmentation of dihydrofuran **228** to give intermediate **230**. Extrusion of 2-methylindole from **230** gives **231**, which undergoes conjugate addition of amine forming intermediate **232**; dehydrative cyclization and oxidation forms pyrrole **229**.

4 From Polar Compounds

Pyrrole synthesis can be also approached from substrates bearing polar functional groups.[115] As discussed in this section, recent reports have demonstrated the effective use of aminols, diols, and organonitro compounds to construct a broad array of substituted pyrroles.

4.1 Aminols

The conversion of aminols into pyrroles via acceptorless dehydrogenative coupling methodology is shown in Scheme 27. In this example, Shimizu reported the synthesis of 2,5-disubstituted pyrroles **235** from 1,2-amino alcohols **233** and secondary alcohols **234** in the presence of heterogeneous carbon-supported platinum as catalyst and a stoichiometric amount of KO*t*-Bu.[116] Mechanistically, the reaction commences with Pt-catalyzed dehydrogenation of the secondary alcohol to give ketone **236**, which condenses with the 1,2-amino alcohol **234** to form imine **237**. A second Pt-catalyzed dehydrogenation sequence allows the formation of imine aldehyde **238**, which undergoes base-catalyzed dehydrative cyclization to furnish substituted pyrrole **235**.

4.2 Diols

Banerjee developed a nickel-catalyzed methodology that featured cyclization of butyne-1,4-diols **239** and butene-1,4-diols **241** with various amines to afford *N*-substituted pyrroles **240** and **242**, respectively (Scheme 28).[117] In these reactions, it was hypothesized that the nickel catalyst dehydrogenates the alcohol moieties sequentially to allow condensation with the amine, followed by isomerization, cyclization, and dehydration via an acceptorless dehydrogenative coupling pathway. The method serves as an excellent route for the preparation of various *N*-substituted pyrroles owing to its tolerance to free alcohols, pyridines, benzylic moieties, halides, alkoxy, alkyl, and oxygen heterocycles.

4.3 Organonitro Compounds

The use of β-nitroalkenes in pyrrole synthesis is showcased in Scheme 29.[118,119] For instance, Pal and Rao reported an ultrasound-mediated four-component reaction for the preparation of substituted pyrroles using β-keto esters, benzylamines, aromatic aldehydes, and nitromethane in the presence of Amberlyst-15.[120] The mechanism of this reaction is proposed through acid-catalyzed formation of enamine ester **244** from β-keto ester and benzylamine. This intermediate serves as a Michael donor to nitroalkene acceptor **245**, which is formed concurrently from aldehyde and nitromethane under the acidic reaction conditions. The resulting addition product **246** proceeds through intramolecular cyclization and aromatization to yield tetrasubstituted pyrrole **243**.

A closely related reaction was disclosed by Kang and Atar by a multicomponent reaction involving a mixture of nitroalkenes **247**, primary amines, and dialkyl acetylenedicarboxylates using imidazolium-based ionic liquid BAIL **248** (Scheme 29).[121] The mechanism proposed involves a BAIL-promoted conjugate addition of the amine to the alkyne resulting in enamine **250**. Subsequent reaction of this intermediate with nitroalkene generates **251**, which then undergoes a similar cyclization pathway to give pyrrole **249**.

Lykakis and Kostakis reported a facile copper(II)-catalyzed reaction between aldehydes, amines, and β-nitroalkenes **252** to yield polysubstituted pyrroles **253** (Scheme 29).[122] In this chemistry, the pyrrole framework is proposed to be formed via a radical mechanism involving allylic nitrogen radical intermediate **254**, which subsequently adds to nitroalkene **252** at the β-carbon. The resulting aldimine species **255** then undergoes deprotonation, 1,2-migration, cyclization, and aromatization to afford pyrrole **253**.

Another example of the use of β-nitroalkenes in pyrrole synthesis was reported by Khan.[123] In this work, the reaction of aziridines and β-bromo-β-nitrostyrenes **256** under thermal conditions readily furnished 1,2,4-trisubstituted pyrroles **257** in a regioselective manner (Scheme 29). The proposed mechanism involves the in situ formation of unsymmetrical azomethine ylide **258** as a result of aziridine ring fragmentation upon heating. The ensuing [3+2] cycloaddition with β-bromo-β-nitrostyrene **256** leads to 5-membered intermediate **259**, which produces pyrrole **257** upon successive elimination of HBr and HNO_2.

Other types of nitro-containing compounds that have been employed as substrates for pyrrole synthesis are depicted in Scheme 30. For instance, Yu and Zhang reported a catalyst-

free, three-component, one-pot reaction between α-nitroepoxides **260**, primary amines, and dialkyl acetylenedicarboxylates to afford pentasubstituted pyrroles **261**.[124] The mechanism for this transformation commences with the formation of α-amino ketone **262**, which is generated upon nucleophilic ring opening of the α-nitroepoxide by the primary amine, accompanied by the loss of HNO_2. Intermolecular conjugate addition of the amino group in **262** to dialkyl acetylenedicarboxylate leads to a sequence of cyclization and condensation to afford the pyrrole adduct.

Adib disclosed an interesting reaction between 1,3-diaryl-4-nitrobutan-1-one **263** and ammonium acetate in the presence of sulfur and morpholine to give 2,4-diarylpyrroles **264** (Scheme 30).[125] The reaction is believed to proceed via the in situ generation of polysulfide morpholinium ion pair **265**, which promotes the conversion of 1,3-diaryl-4-nitrobutan-1-one into oxime **266**. Condensation of **266** with ammonium acetate gives enamine **267**, which undergoes intramolecular cyclization and aromatization with the loss of hydroxylamine to generate pyrrole **264**.

5 From Heterocycles

Literature survey on pyrrole synthesis between 2014 and 2019 also revealed interesting strategies in which different classes of heterocycles have been effectively employed as starting materials.[126–135] Some examples discussed in this section include münchnones, isoxazoles, carbohydrates, hydroxyprolines, and pyrrolines. It is interesting to note that these heterocyclic motifs readily produce pyrroles that are densely substituted.

5.1 Münchnones

Oxazolium-5-olate systems, commonly referred to as münchnones, are mesoionic compounds that possess excellent reactivity in cycloaddition reactions with dipolarophiles. In fact, the 1,3-dipolar cycloaddition reaction of münchnones has been demonstrated to be one of the most useful approaches to access various substituted pyrroles.[136] As shown in Scheme 31, Harrity reported the regioselective synthesis of pyrroles using münchnones and substituted enamines.[137] In this chemistry, the 1,3-dipolar cycloaddition of the münchnones **268** and substituted enamines forms 5-membered intermediate **271** upon extrusion of CO_2. Subsequent aromatization via elimination of the amino group then generates the pyrrole structures either **269** or **270**.

Methodologies that exploited the in situ generation of münchnones towards synthesis of pyrroles have been also reported. For instance, Gribble demonstrated the preparation of münchnones **274** via treatment of *N*-acylamino acid **272** with *N*,*N*-diisopropylcarbodiimide (DIPC). The ensuing 1,3-dipolar cycloaddition with β-nitroalkene then occurred to yield tetrasubstituted pyrrole **273** upon loss of CO_2 and HNO_2 (Scheme 31).[138] The in situ generation of münchnones could be also catalyzed by transition metals. Arndtsen developed a multicomponent reaction using aryl iodides, imines, and CO in the presence of $Pd(P\textit{t}\text{-}Bu_3)_2$, Bu_4NCl, and DIPEA to produce transient münchnones **277** (Scheme 31).[139,140] This intermediate was then captured by electron-deficient alkynes or alkenes to afford diverse families of highly substituted pyrroles **276** via [3+2] cycloaddition in one synthetic operation.

5.2 Isoxazoles

The utility of isoxazoles as a valuable precursor for the preparation of pyrroles is showcased in Scheme 32. For instance, Kapur reported that exposure of 4-vinylisoxazoles **278** to catalytic $RuCl_3 \cdot xH_2O$ and stoichiometric $Cu(OAc)_2$ furnished trisubstituted pyrroles **279**.[141] The proposed mechanistic pathway involves activation of the isoxazole nitrogen by the Ru catalyst, enabling ring fragmentation to produce ruthenium-carbene intermediate **280**; subsequent 1,5-cyclization then generates the pyrrole ring **279**. The role of $Cu(OAc)_2$ in this transformation is not clearly understood. An analogous transformation was also reported by Khlebnikov, in which $FeCl_2 \cdot 4H_2O$ catalyst was employed to rearrange 4-vinylisoxazoles **281** to 3-carbonylpyrroles **282** via a putative iron-carbene pathway (Scheme 32).[142]

Tang and He reported [3+2] cycloaddition of isoxazoles **284** with *N*-sulfonyl-1,2,3-triazoles **283** in the presence of $Rh_2(esp)_2$ catalyst toward the preparation of 3-aminopyrroles **285** (Scheme 32).[143] This reaction is proposed to commence with the decomposition of triazole **283** to Rh(II)-azavinylcarbene **286**, which is then captured by the isoxazole to yield an isoxazolium ylide intermediate. The ensuing ring-opening to azatriene, recyclization, and aromatization via proton transfer leads to the observed 3-aminopyrrole product **285**.

Another example was reported by Cui, who described the synthesis of pyrroles from isoxazoles **287** and internal ynamides **288** using the $Ph_3PAuCl/AgNTf_2$ catalytic system (Scheme 32).[144] In this chemistry, activation of the internal ynamide with the Au(I) catalyst enables nucleophilic addition of the isoxazole to produce intermediate **290**. N–O Bond cleavage and isomerization then leads to acyclic carbenoid intermediate **291**, which undergoes intramolecular cyclization to afford pyrrole **289** while regenerating the Au(I) catalyst.

5.3 Carbohydrates

Sugars have been shown to serve as viable substrates for pyrrole synthesis.[145] As exemplified in Scheme 33, Koo subjected D-glucose and L-rhamnose to various primary amines in presence of oxalic acid and DMSO.[146] This unique transformation begins with *N*-glycosylation of the amine, followed by tautomerization to enamine **293**; dehydration, tautomerization, and a second imine formation gives intermediate **294**, which undergoes a cyclization and dehydration sequence to furnish pyrrole-2-carbaldehyde **292**.

5.4 *trans*-4-Hydroxy-l-prolines

The use of *trans*-4-hydroxy-l-prolines for the preparation of pyrroles is showcased in Scheme 34. For instance, Roy developed a green synthesis of 3-(pyrrol-1-yl)indolin-2-ones **297** in water.[147] In this chemistry, the surfactant additive, i.e. cetyltrimethylammonium bromide (CTAB), formed an aqueous micellar medium, in which isatin **295** and *trans*-4-hydroxy-l-proline **296** form iminium **298**. This species then undergoes decarboxylation, followed by dehydrative aromatization to form pyrrole **297**.

Another example was reported by Song who demonstrated a simple catalyst-free approach to *N*-(2-hydroxyethyl)pyrroles via a [3+2]-cycloaddition reaction between electron-deficient aldehydes and *trans*-4-hydroxyprolines **300** (Scheme 34).[148] The mechanism proceeds via

condensation between the aldehyde and proline to generate oxazolidin-5-one **302**, which undergoes decarboxylation to azomethine ylide **303** upon heating. A second molecule of aldehyde captures the ylide **303** via intermolecular [3+2] cycloaddition to produce intermediate **304**; dehydrative ring opening and aromatization then produce *N*-(2-hydroxyethyl)pyrroles **301**.

5.5 Pyrrolines

Sun and Xu has developed an interesting synthesis of pyrroles by exploiting the inherent reducing power of 3-pyrrolines (Scheme 35).[149,150] For instance, treatment of 2-(3-pyrrolin-1-yl)benzaldehydes **305** with $Sc(OTf)_3$ promoted an intramolecular redox reaction to generate iminium ion intermediate **307** via 1,5-hydride transfer; subsequent isomerization gave the pyrrole **306**. Interestingly, the intramolecular redox reaction of 2-(3-pyrrolin-1-yl)benzaldehydes could be also performed in the presence amines and $ZnCl_2$ to afford the amino pyrrole variant **309**. In this example, the 1,5-hydride migration occurred upon the generation of iminium ion intermediate **310**.

6 Summary

This review article summarizes selected examples on pyrrole synthesis that have been developed between 2014 and 2019. Since its discovery, pyrrole has become one of the most important and fascinating aromatic heterocycles. Owing to its vast range of significance and applications in different areas of science, pyrrole will remain an important target in organic synthesis. The interesting structural features within pyrrole, including the challenges in introducing substituents regioselectively at various positions around the ring, will continue to provide inspiration for the discovery of new synthetic technologies as well as chemical reactivities.

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Biographies

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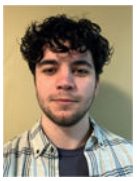
Satish Philkhana is a postdoctoral researcher in the Kartika group at LSU. He earned his Masters degree in organic chemistry from the University of Pune, India and later joined Dr. D. S. Reddy's group at CSIR-National Chemical Laboratory-Pune, India to pursue his doctoral studies on the synthesis of bioactive natural products and their analogues. Upon graduation, he joined Prof. Jennifer Golden's group at University of Wisconsin, Madison as a postdoctoral researcher where he worked on the development of new annulation strategies to access quinolinone-type scaffolds. Currently at LSU, he is exploring new stereoselective methods to generate ketones with bis-quaternary stereocenters at the α,α′-positions.

Fatimat Badmus is a 4th year graduate student in the Department of Chemistry at LSU under the supervision of Prof. Rendy Kartika. Fatimat was born in Osun, Nigeria. She earned her B.Sc. degree in chemistry from Obafemi Awolowo University in 2014 and commenced her graduate studies at LSU in 2017. At LSU, Fatimat is working on the development of new organic synthetic reactions that produce biologically significant heterocyclic scaffolds as well as complex structural motifs.



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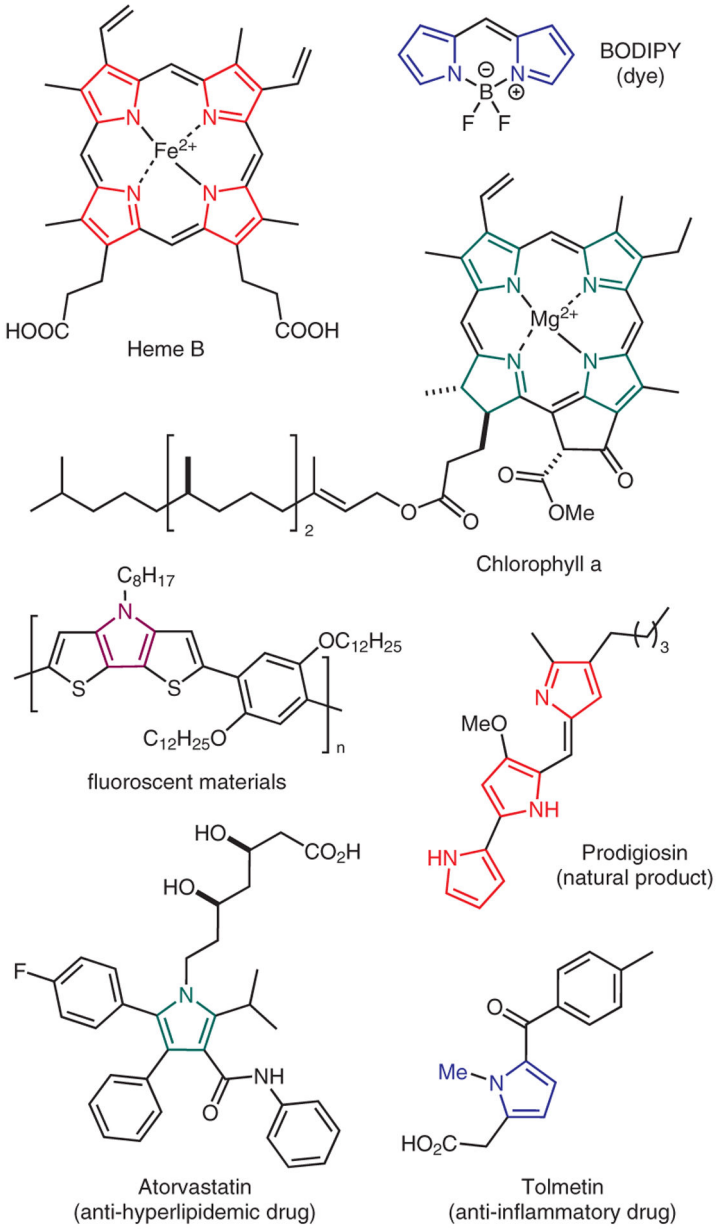


Figure 1.
Importance of pyrrole

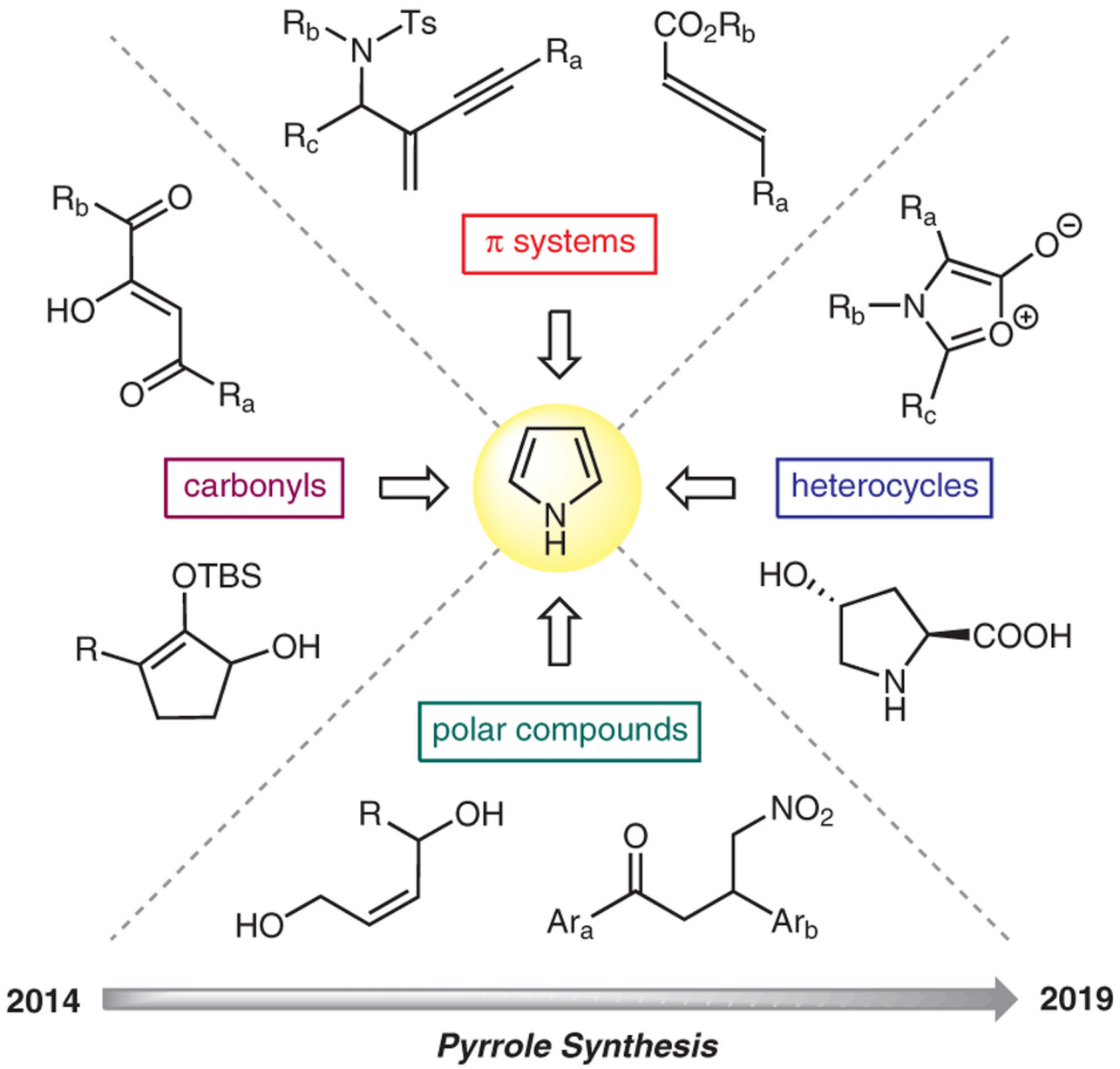
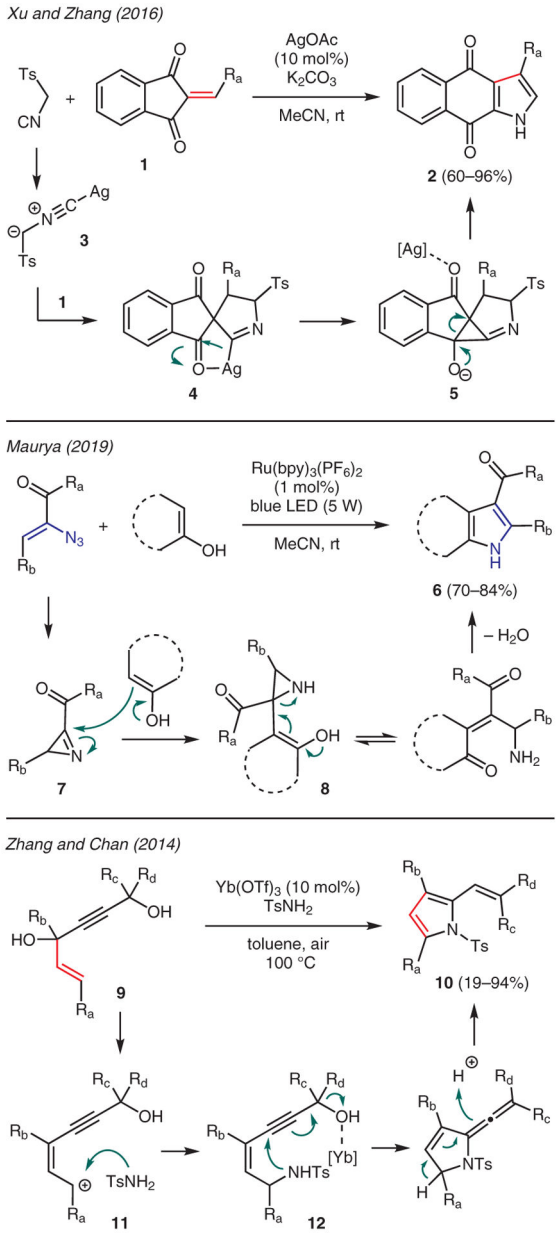
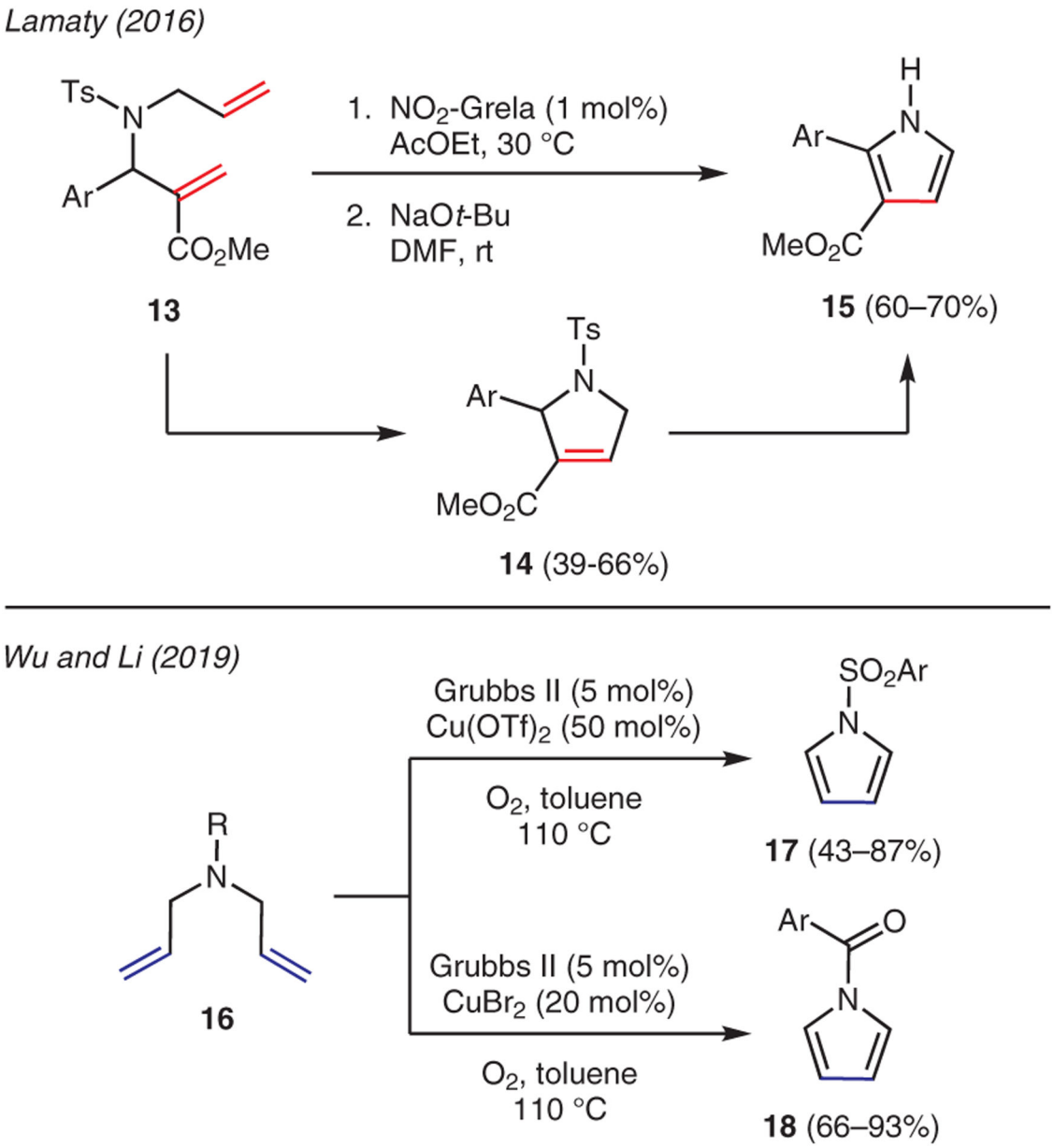


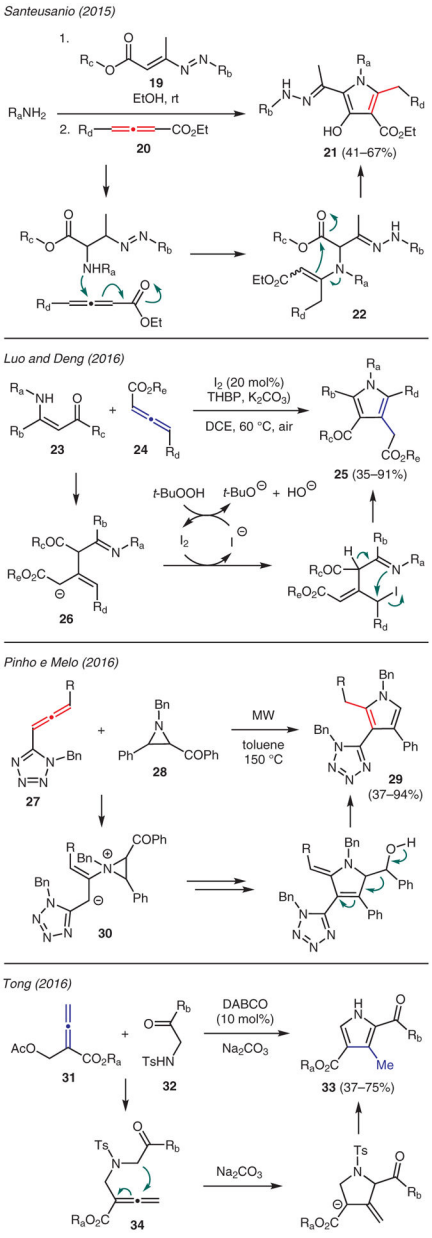
Figure 2.
Pyrrole synthesis classification



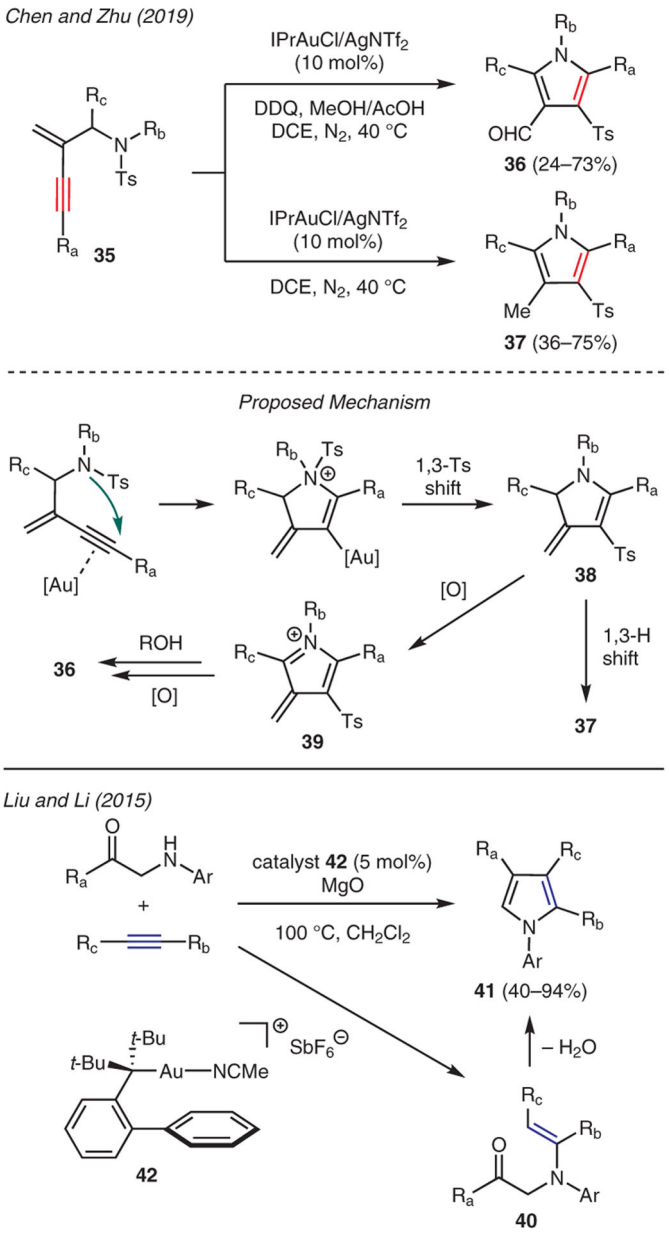
Scheme 1.
From alkenes



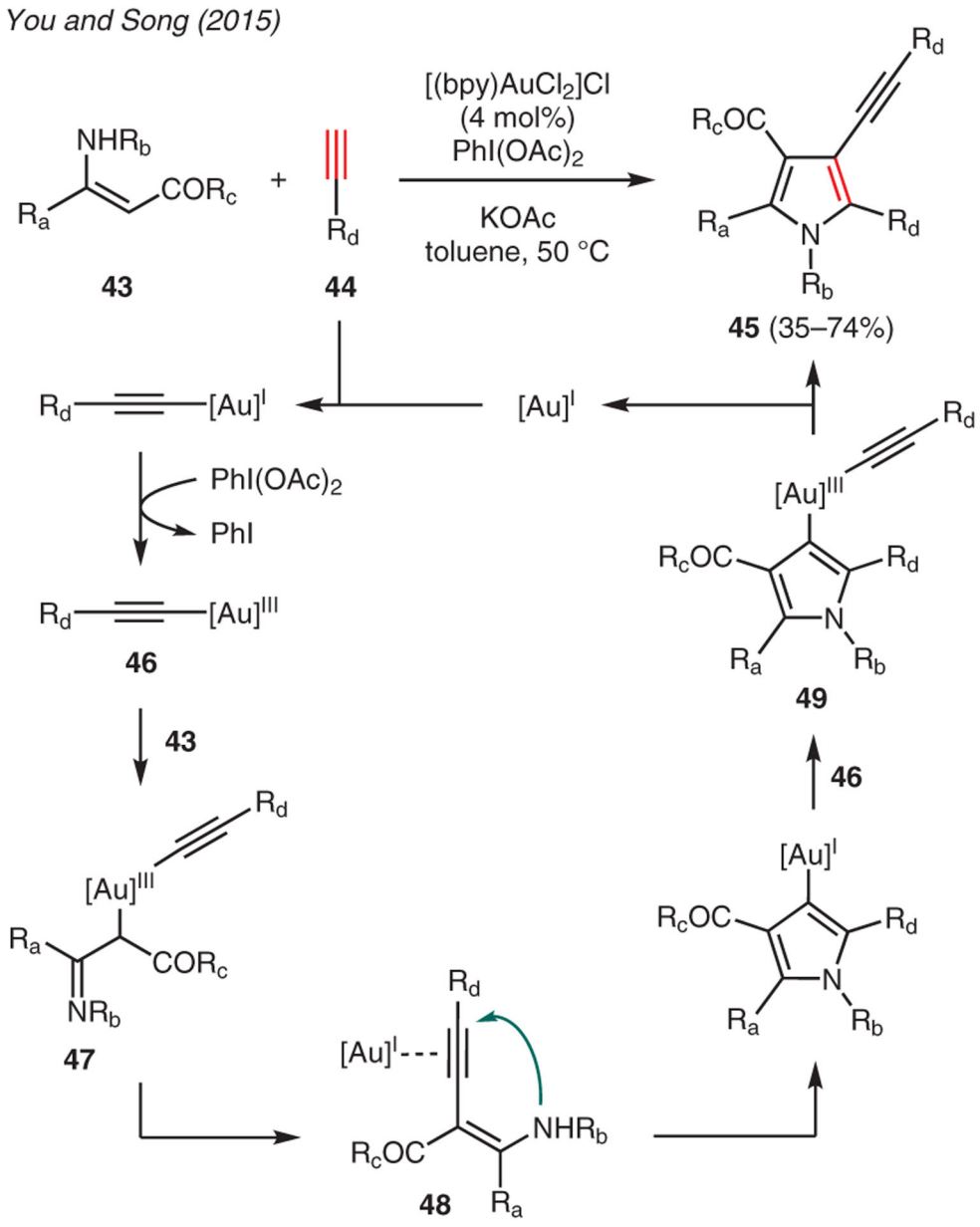
Scheme 2.
From 1,6-dienes



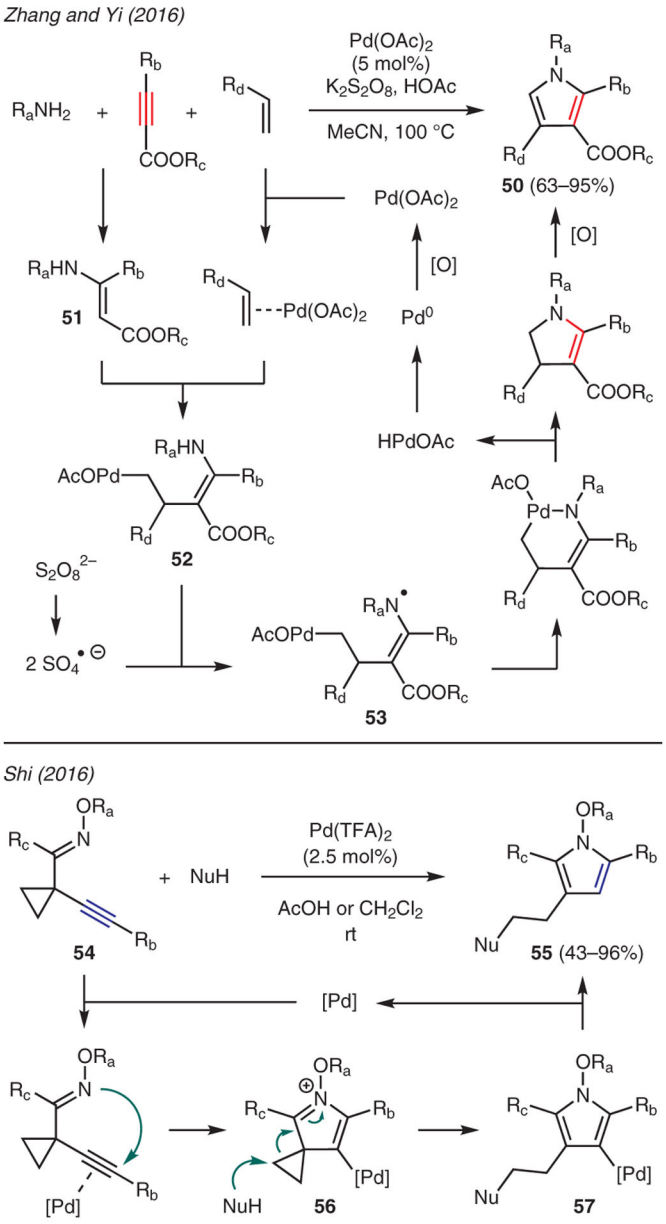
Scheme 3.
From allenes



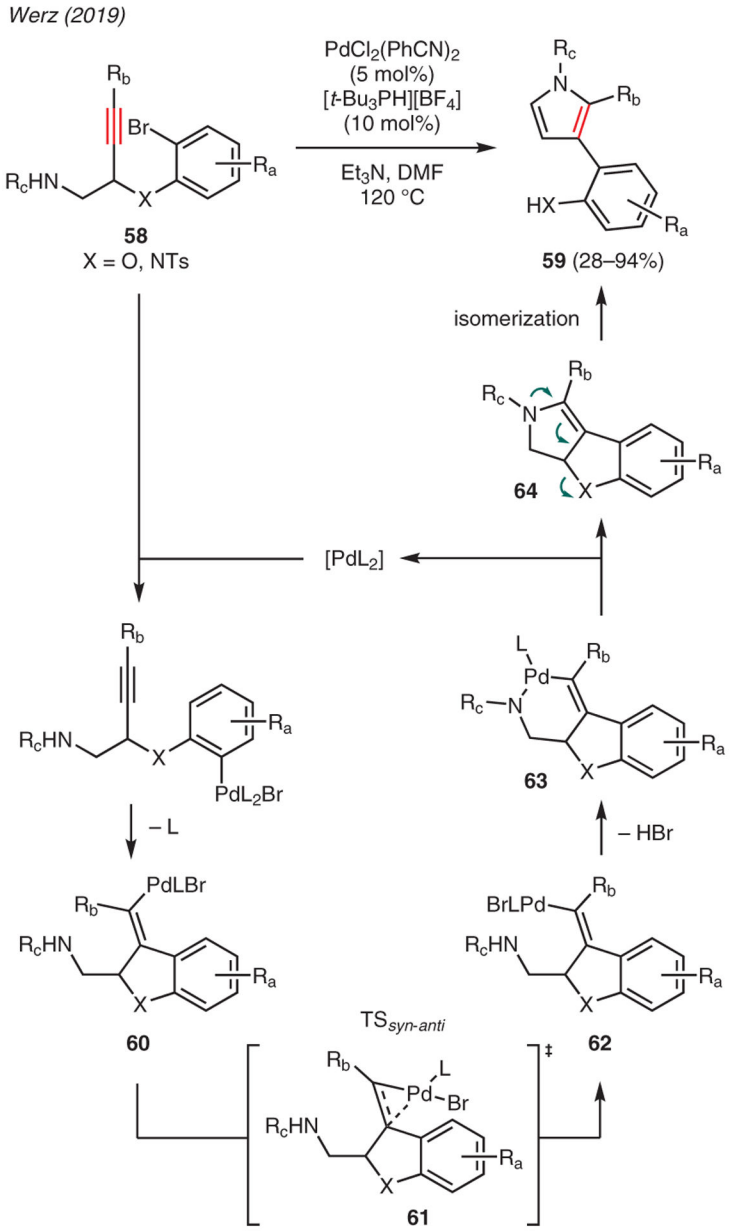
Scheme 4.
From alkynes: gold catalysis



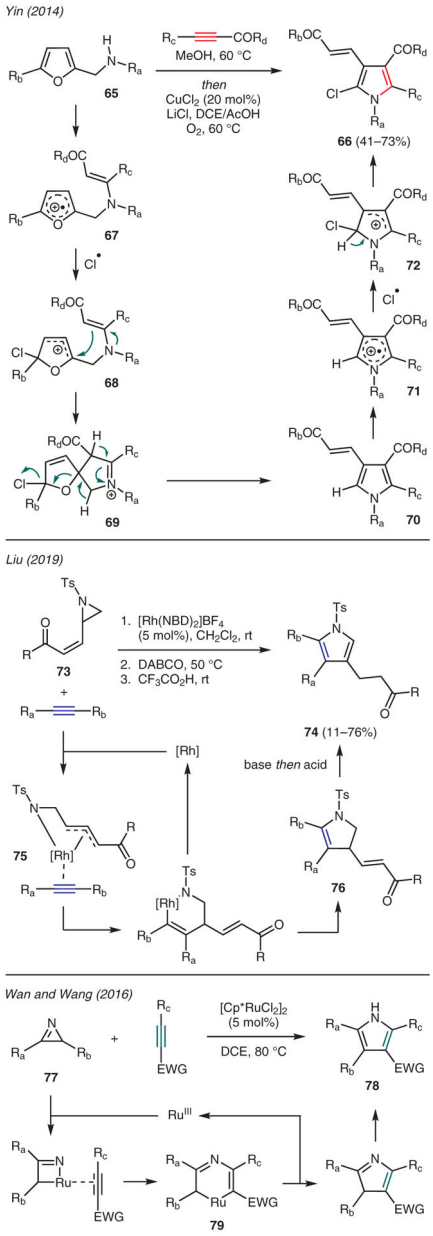
Scheme 5.
From alkynes: gold catalysis



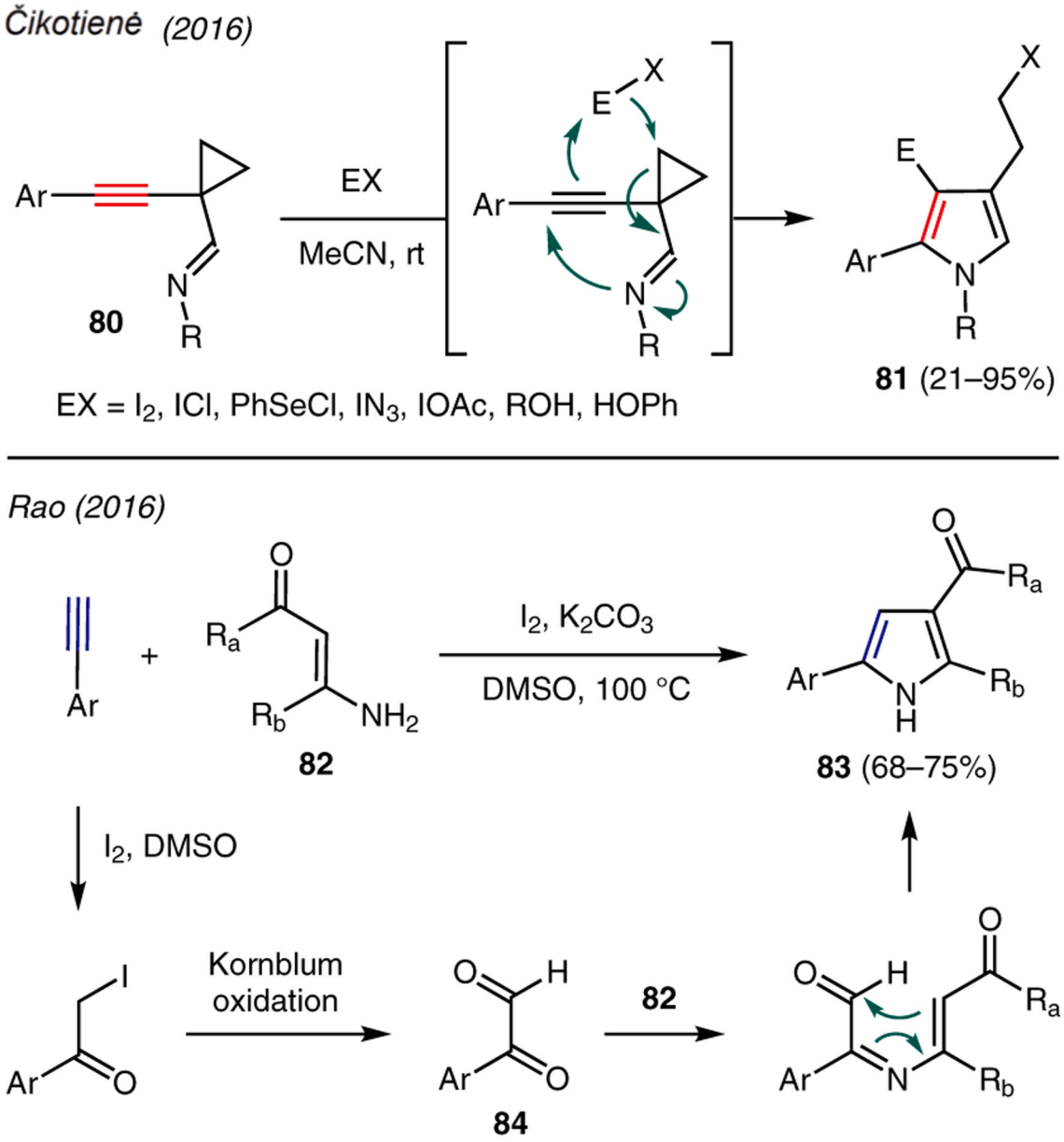
Scheme 6.
From alkynes: palladium catalysis



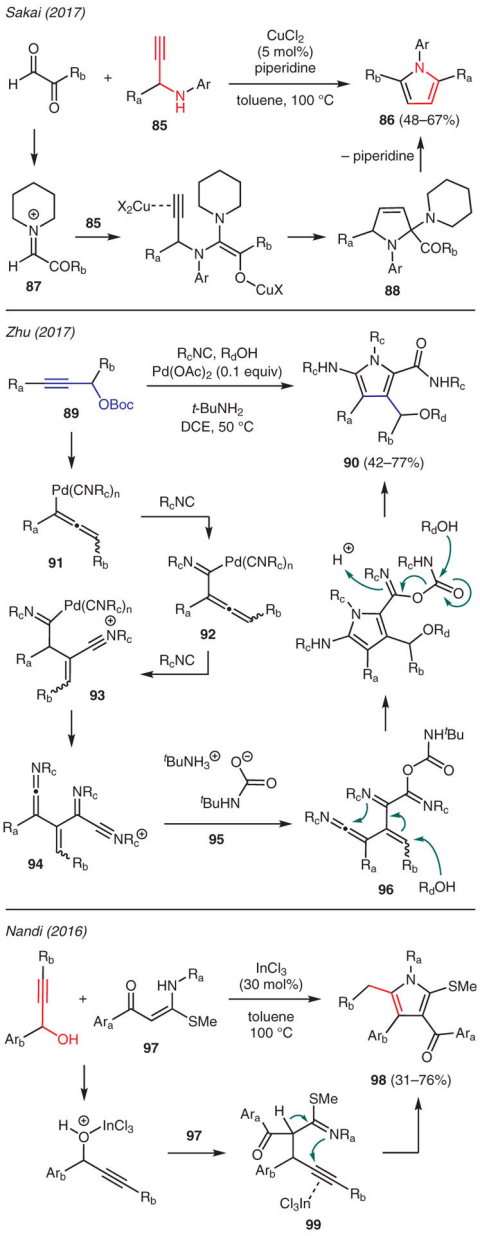
Scheme 7.
From alkynes: palladium catalysis



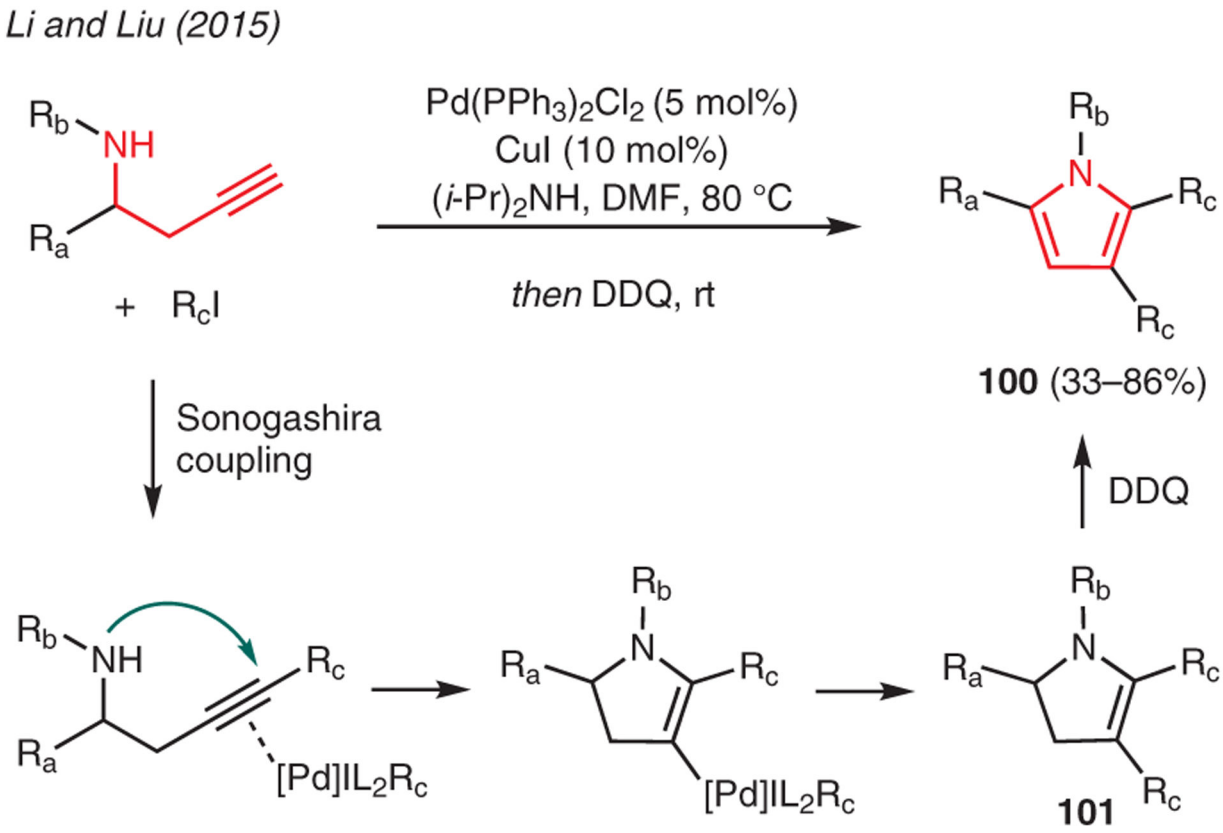
Scheme 8.
From alkynes: transition-metal catalysis



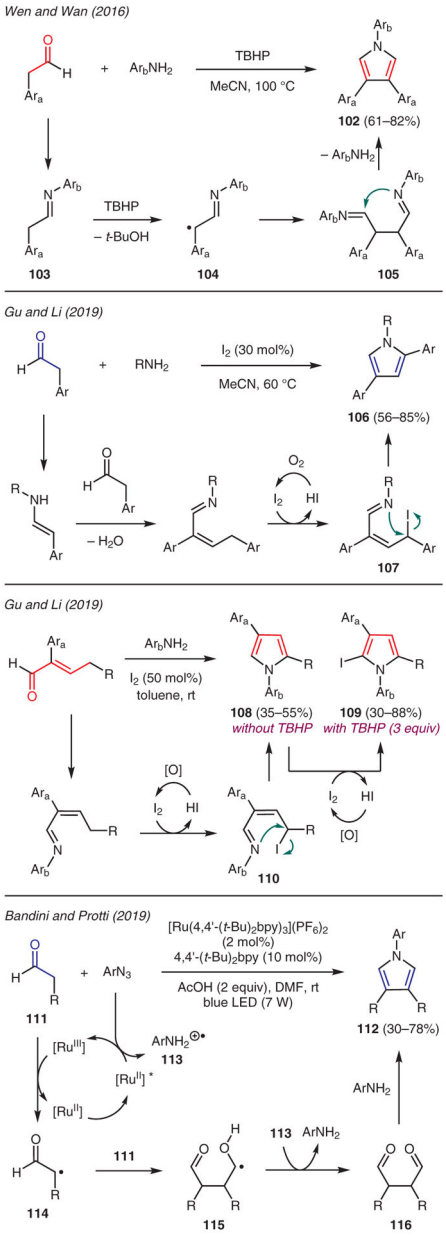
Scheme 9.
From alkynes: reagent-driven



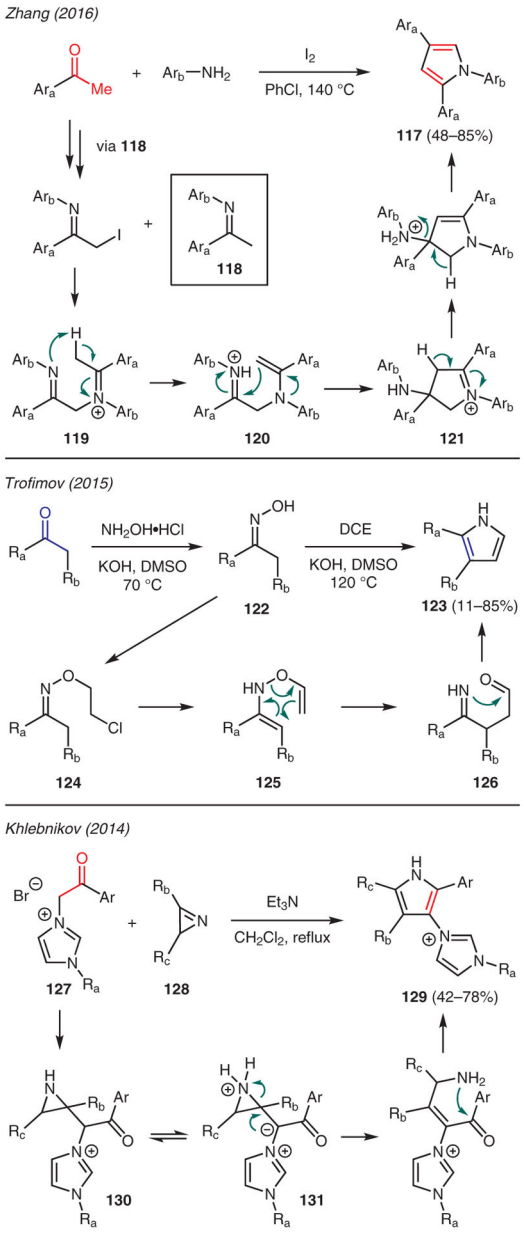
Scheme 10.
From propargylic systems



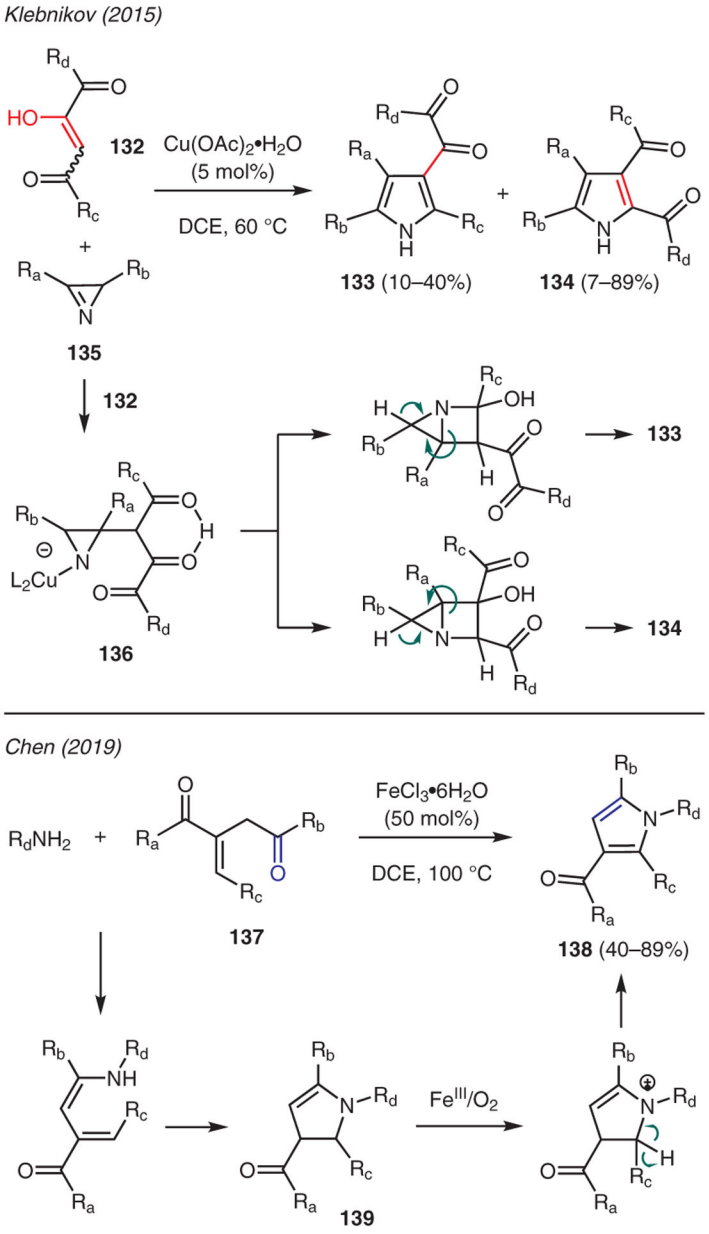
Scheme 11.
From homopropargylic amines



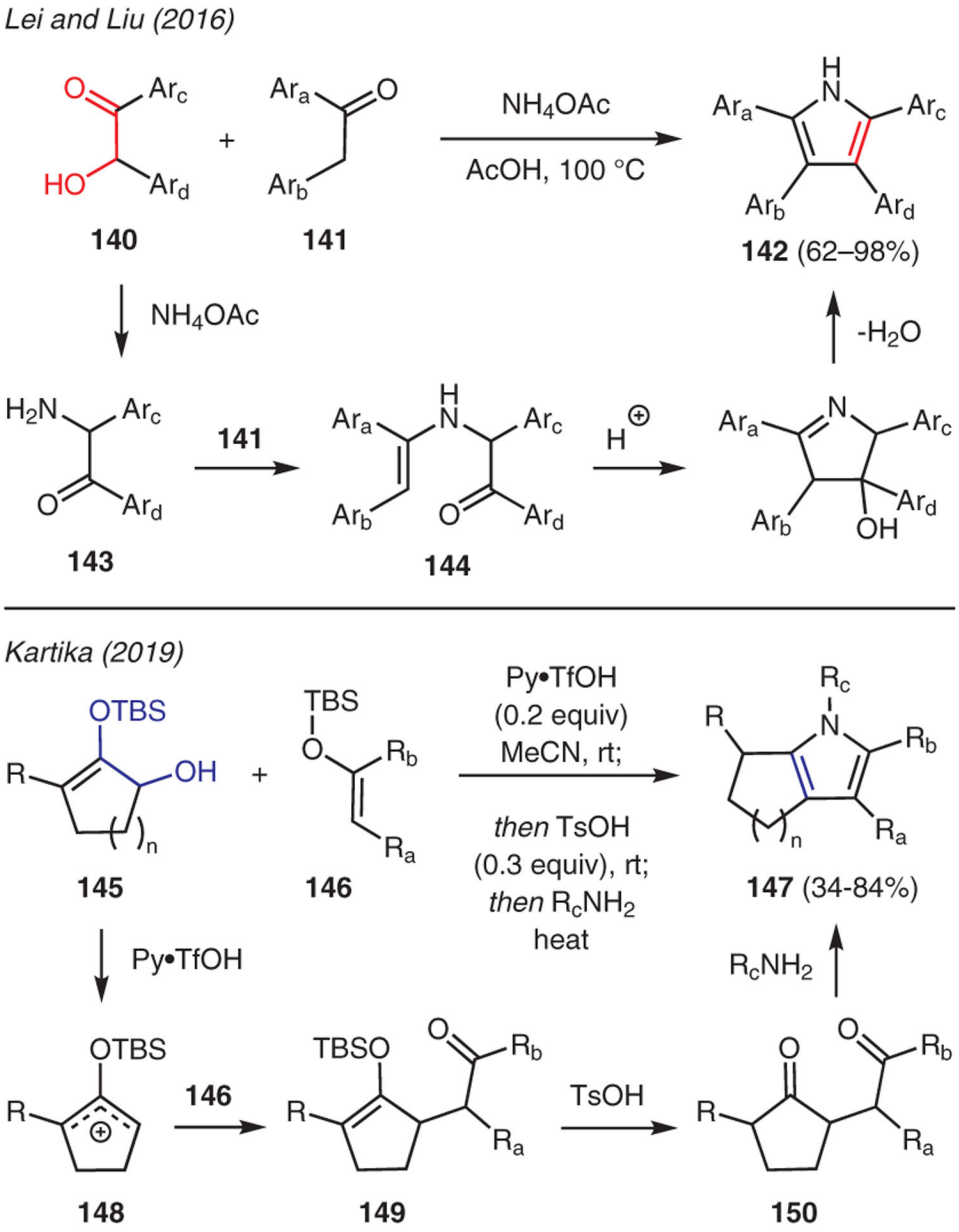
Scheme 12.
From aldehydes



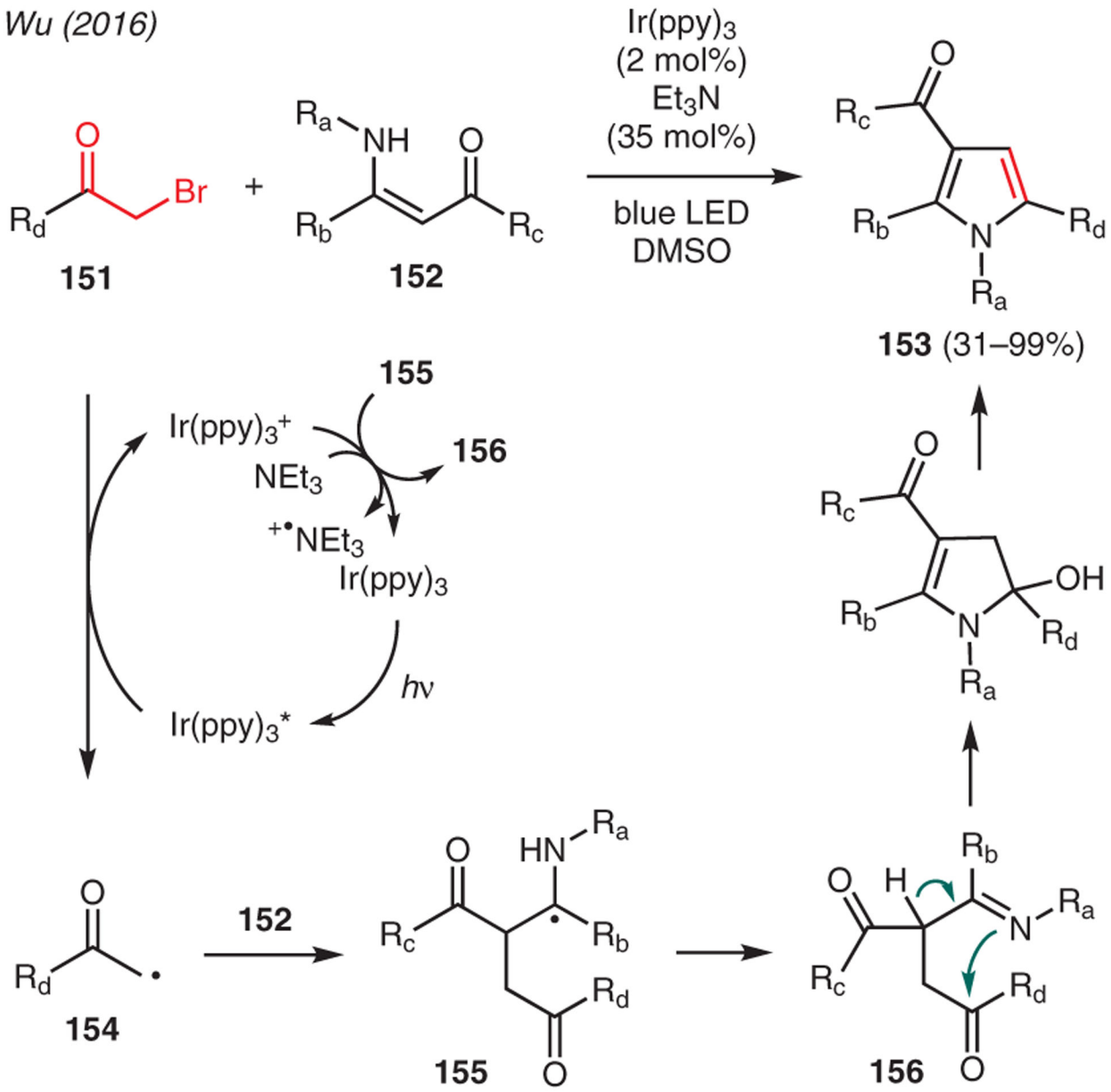
Scheme 13.
From ketones



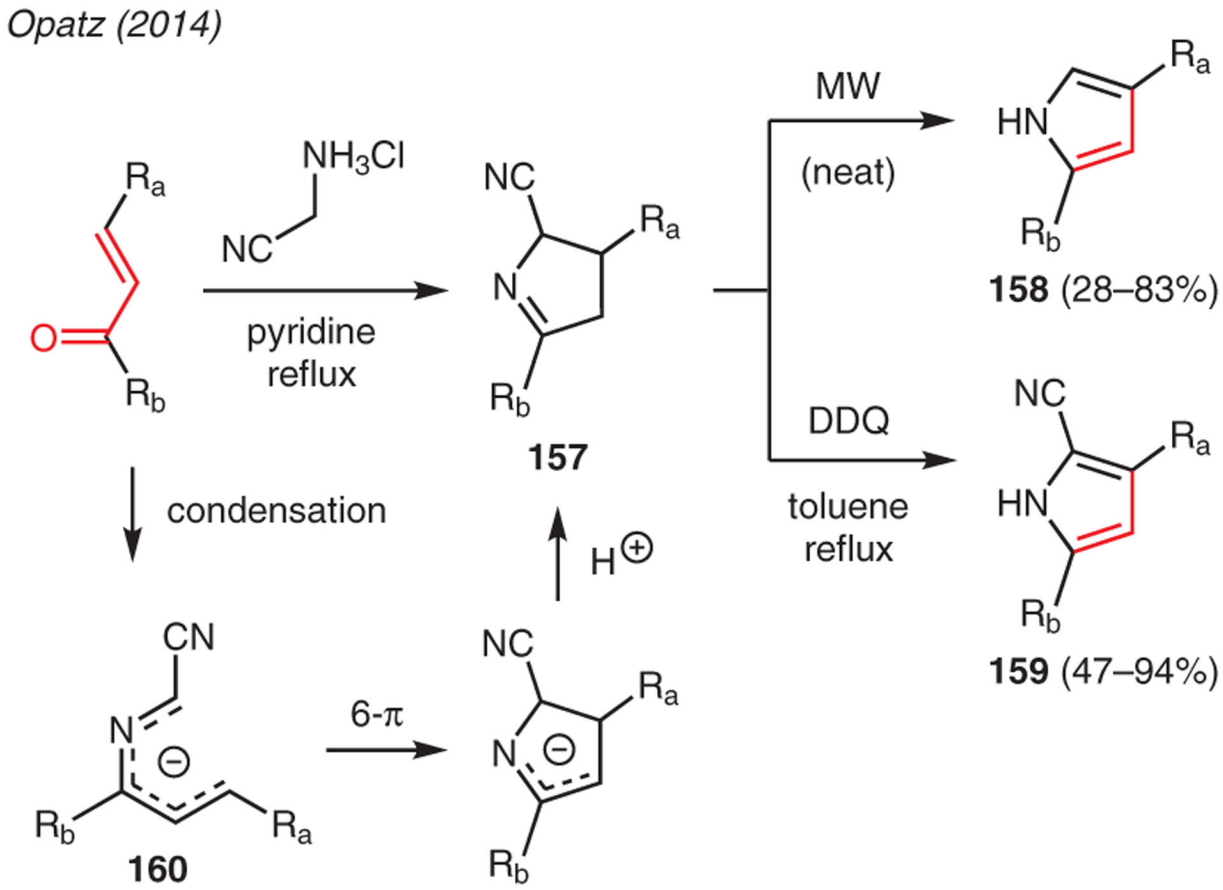
Scheme 14.
From ketones



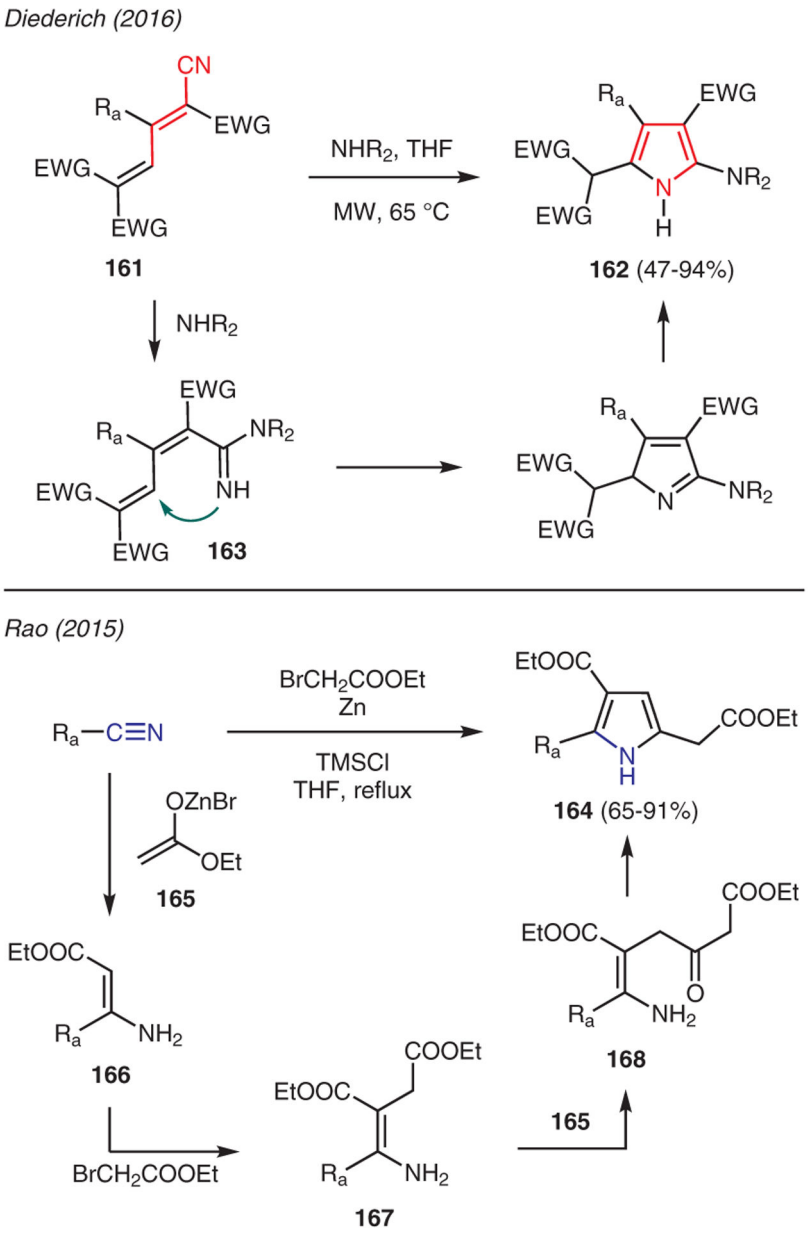
Scheme 15.
From α-hydroxy ketones



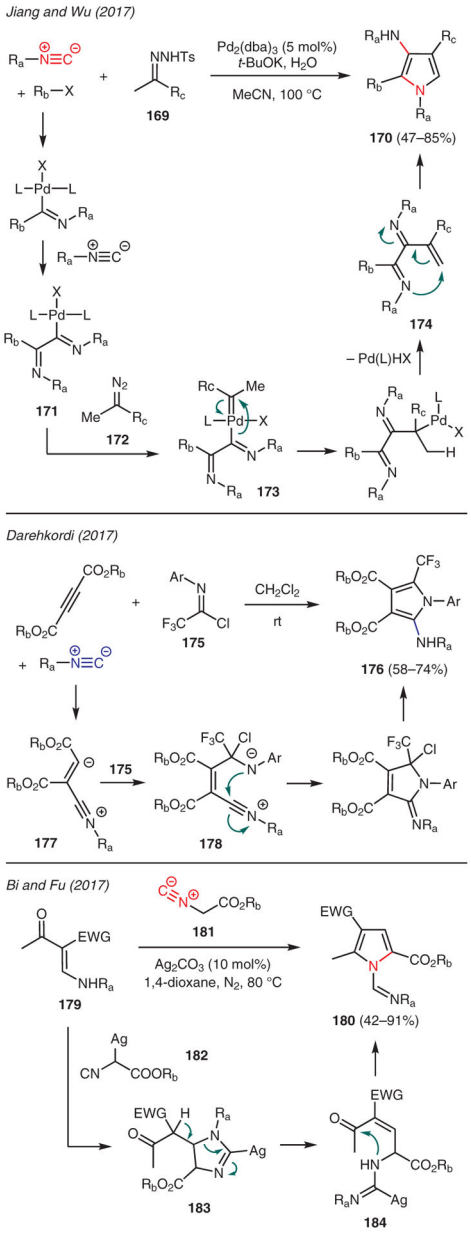
Scheme 16.
From α-bromo ketones



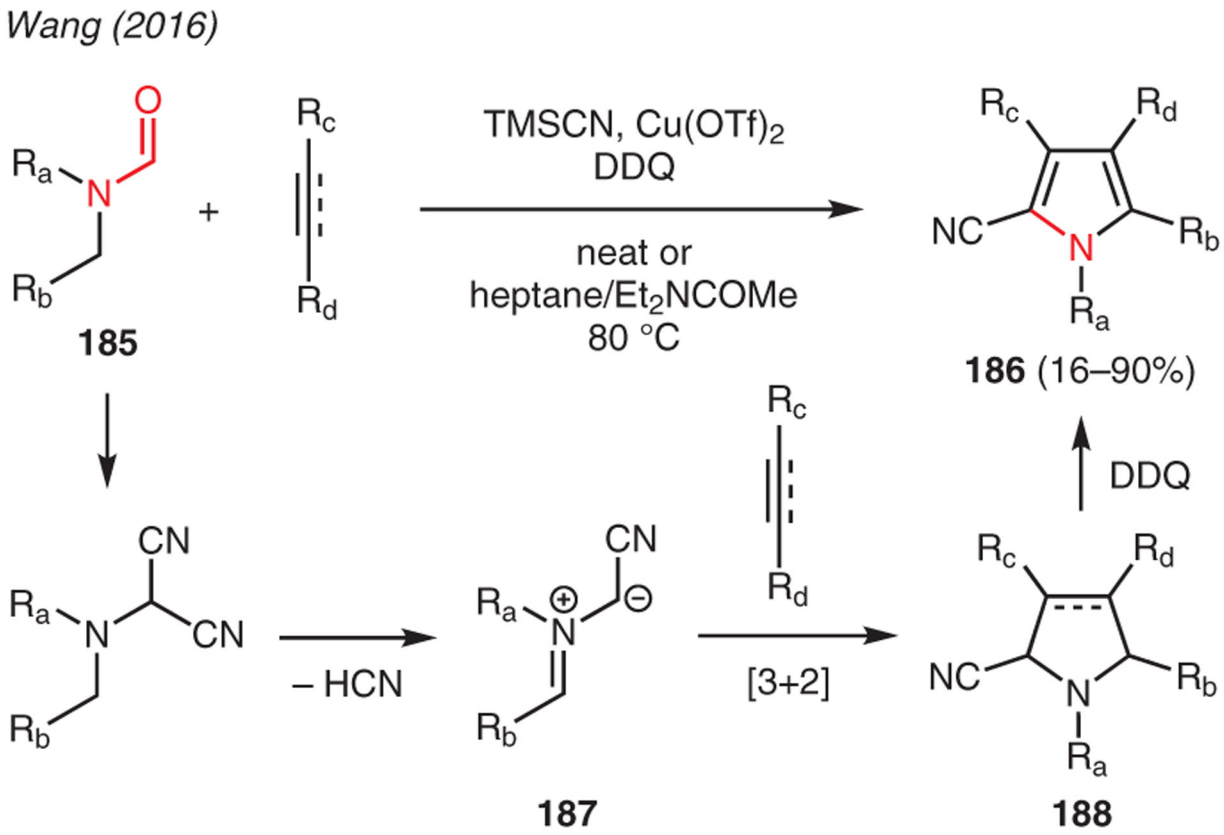
Scheme 17.
From enones



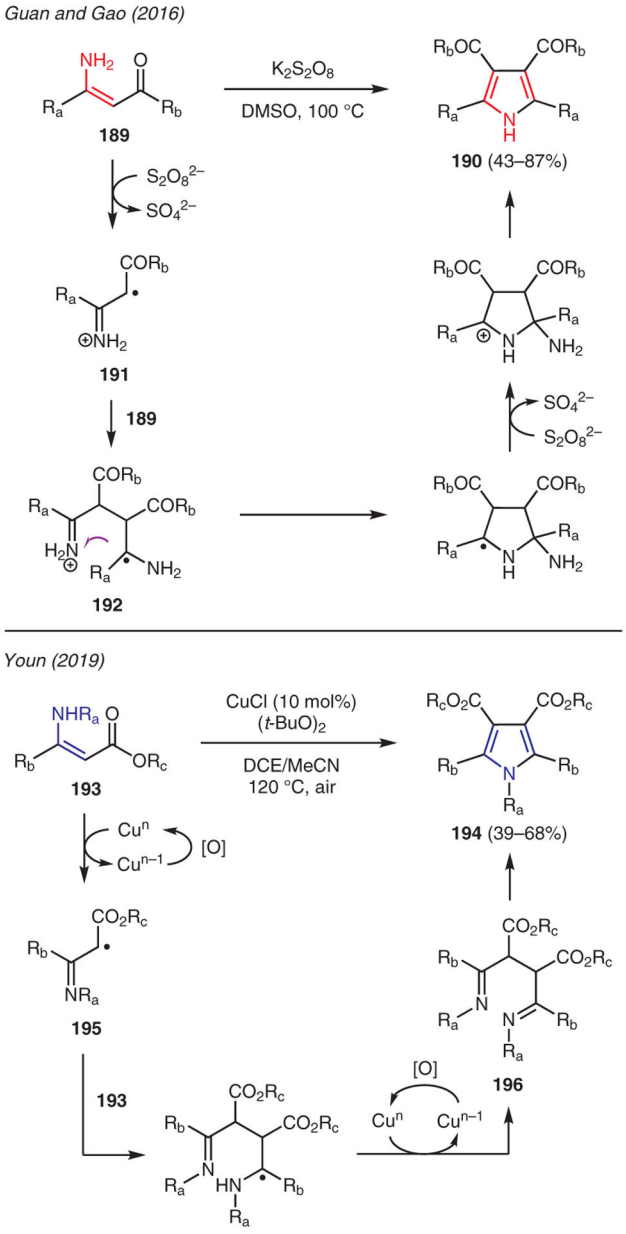
Scheme 18.
From cyanides



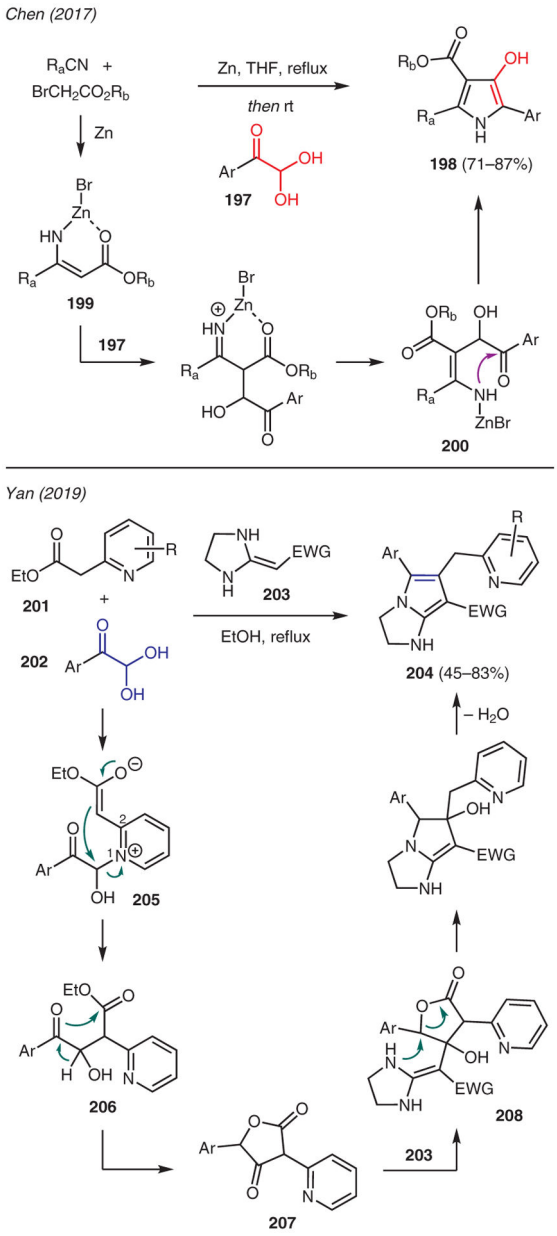
Scheme 19.
From isocyanides



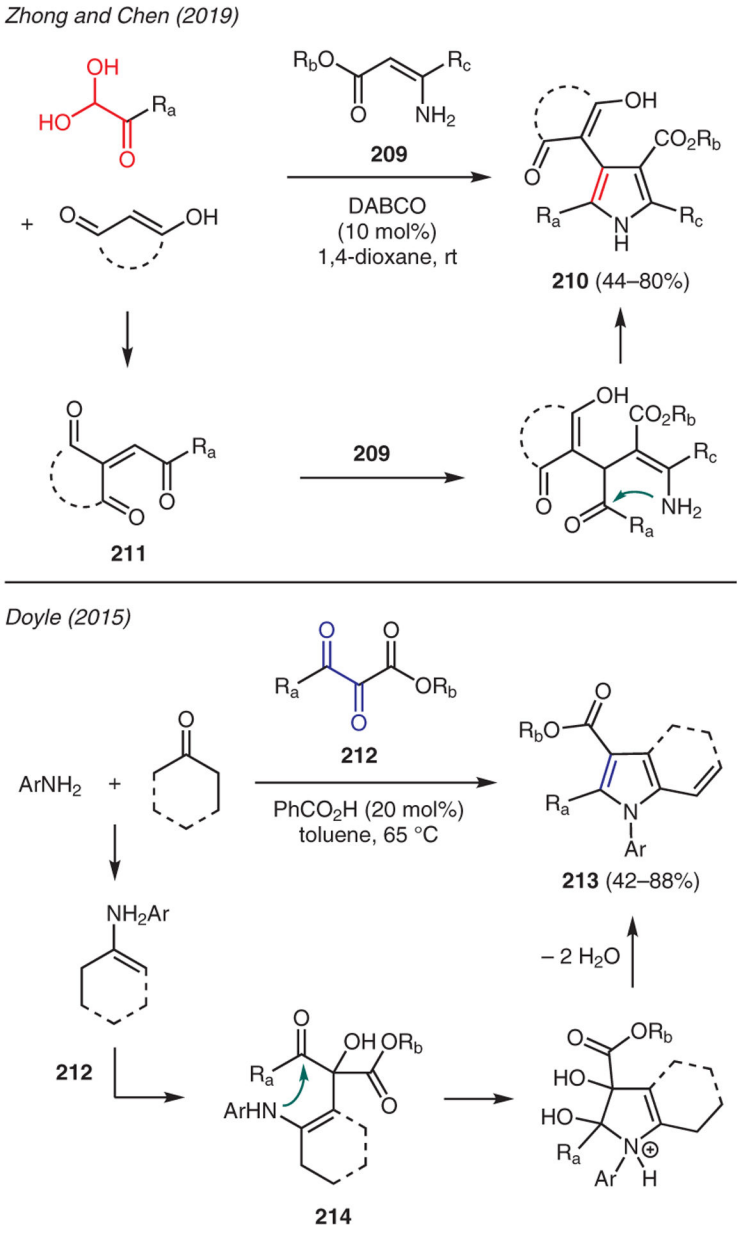
Scheme 20.
From formamides



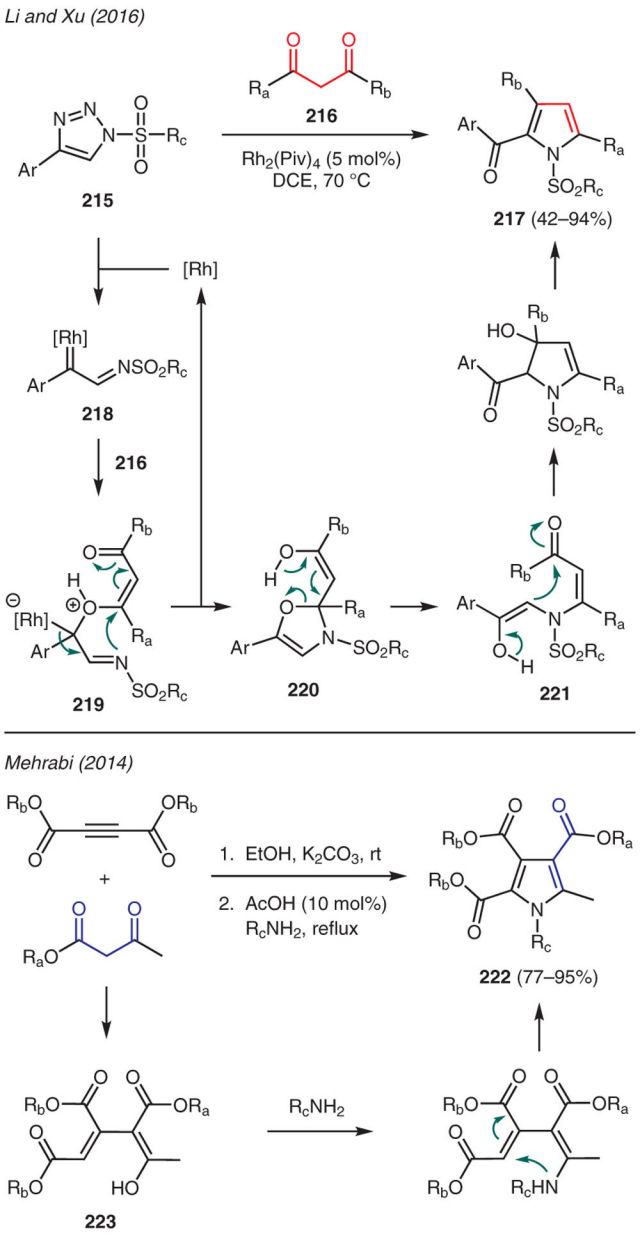
Scheme 21.
From β-enamines



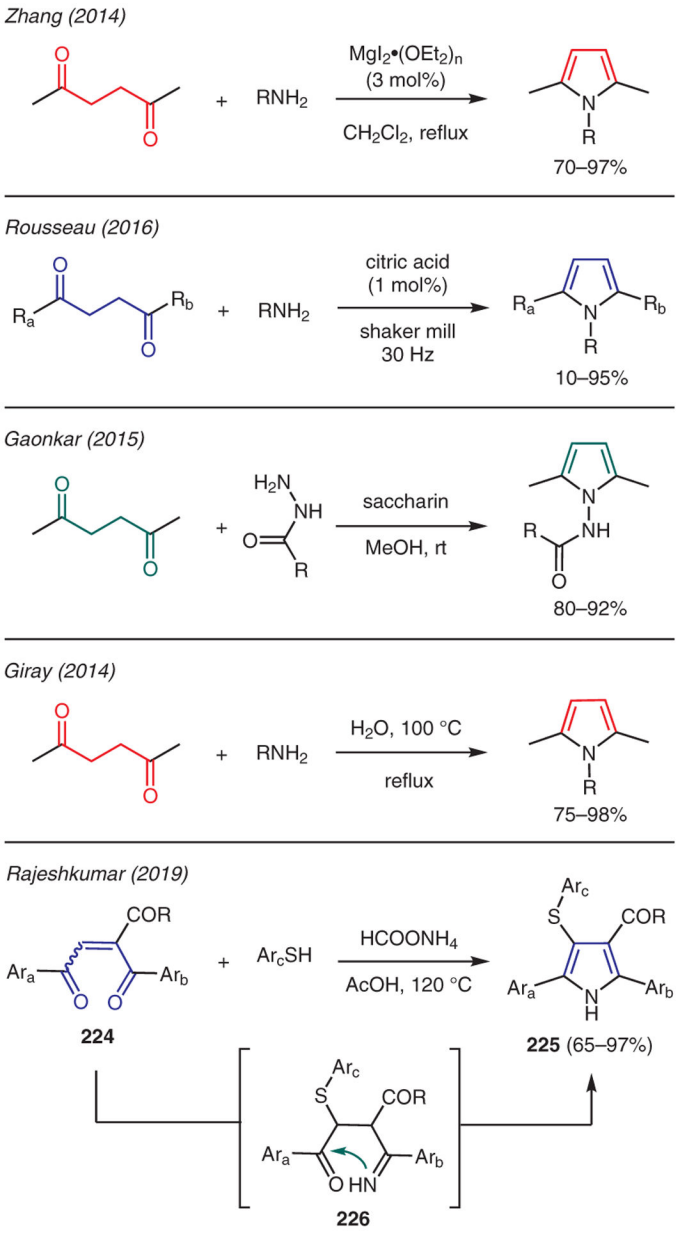
Scheme 22.
From 1,2-dicarbonyls



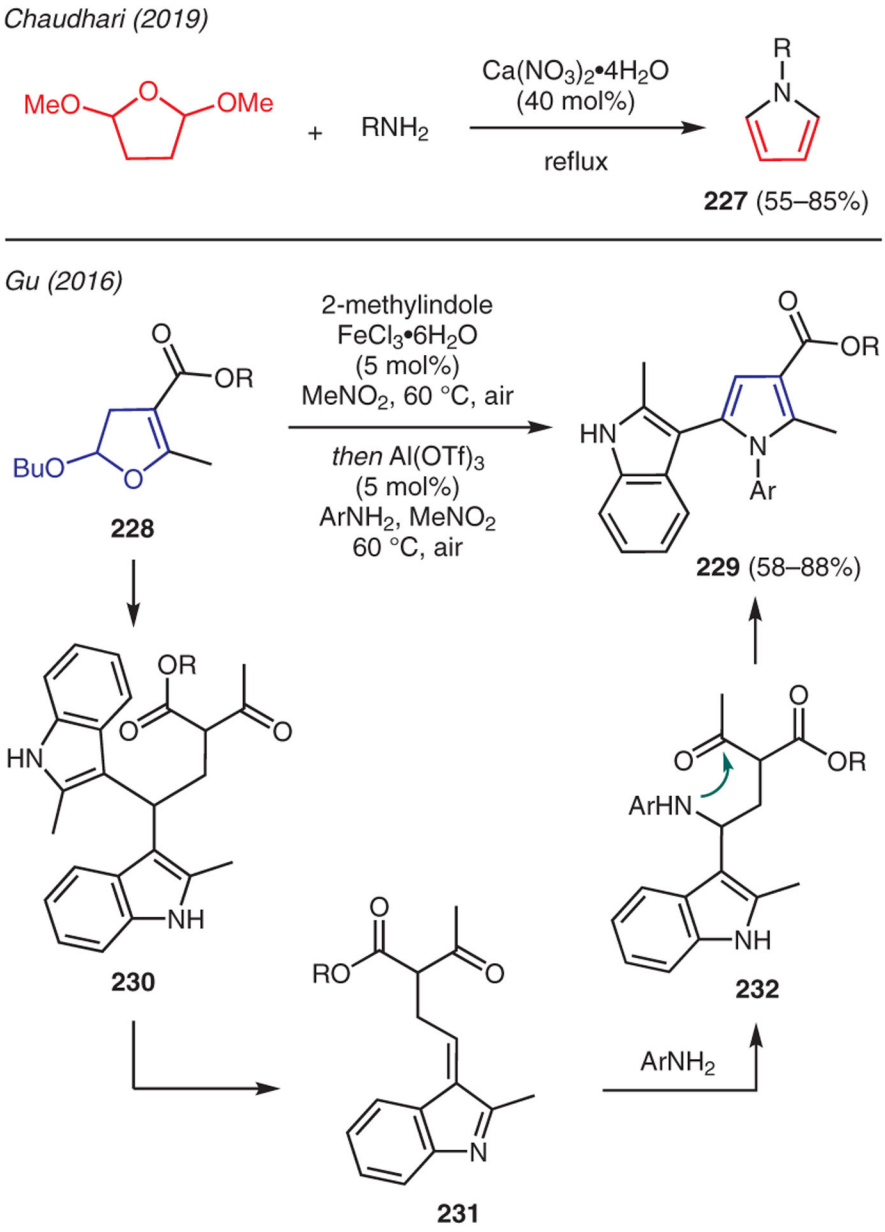
Scheme 23.
From 1,2-dicarbonyls



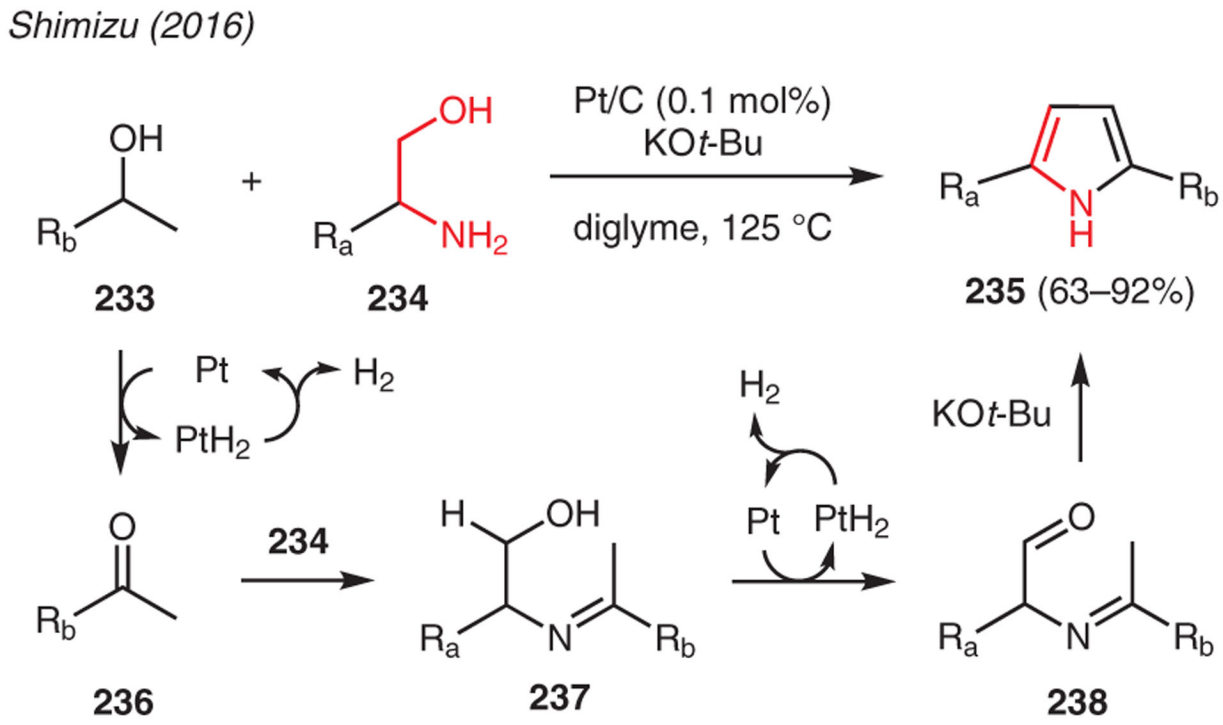
Scheme 24.
From 1,3-dicarbonyls



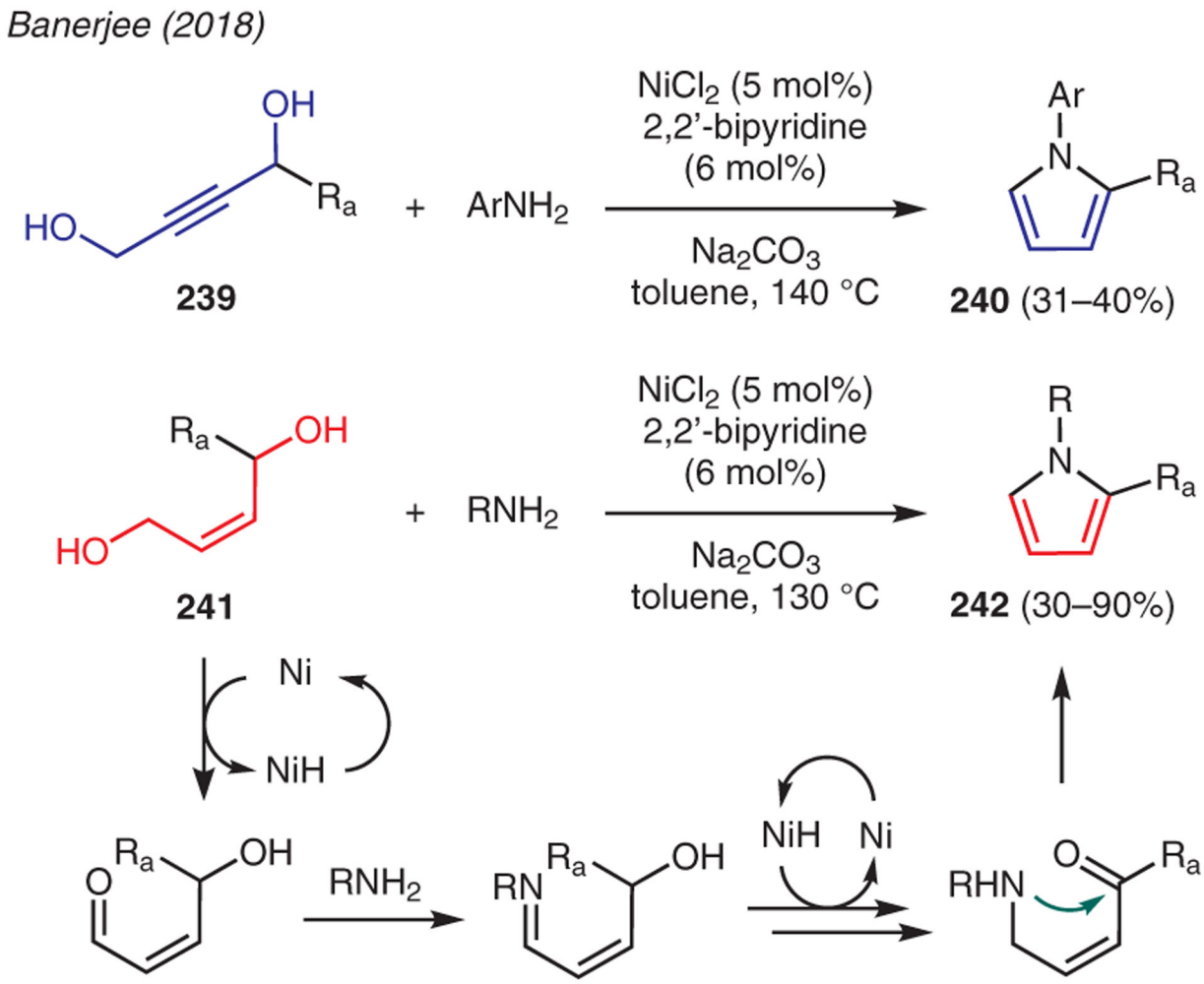
Scheme 25.
From 1,4-dicarbonyls



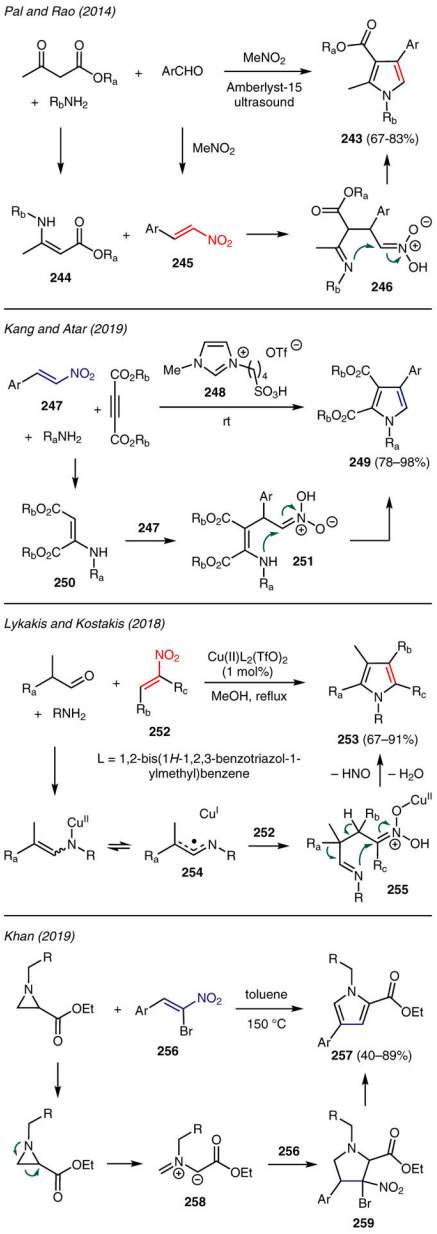
Scheme 26.
From masked 1,4-dicarbonyls



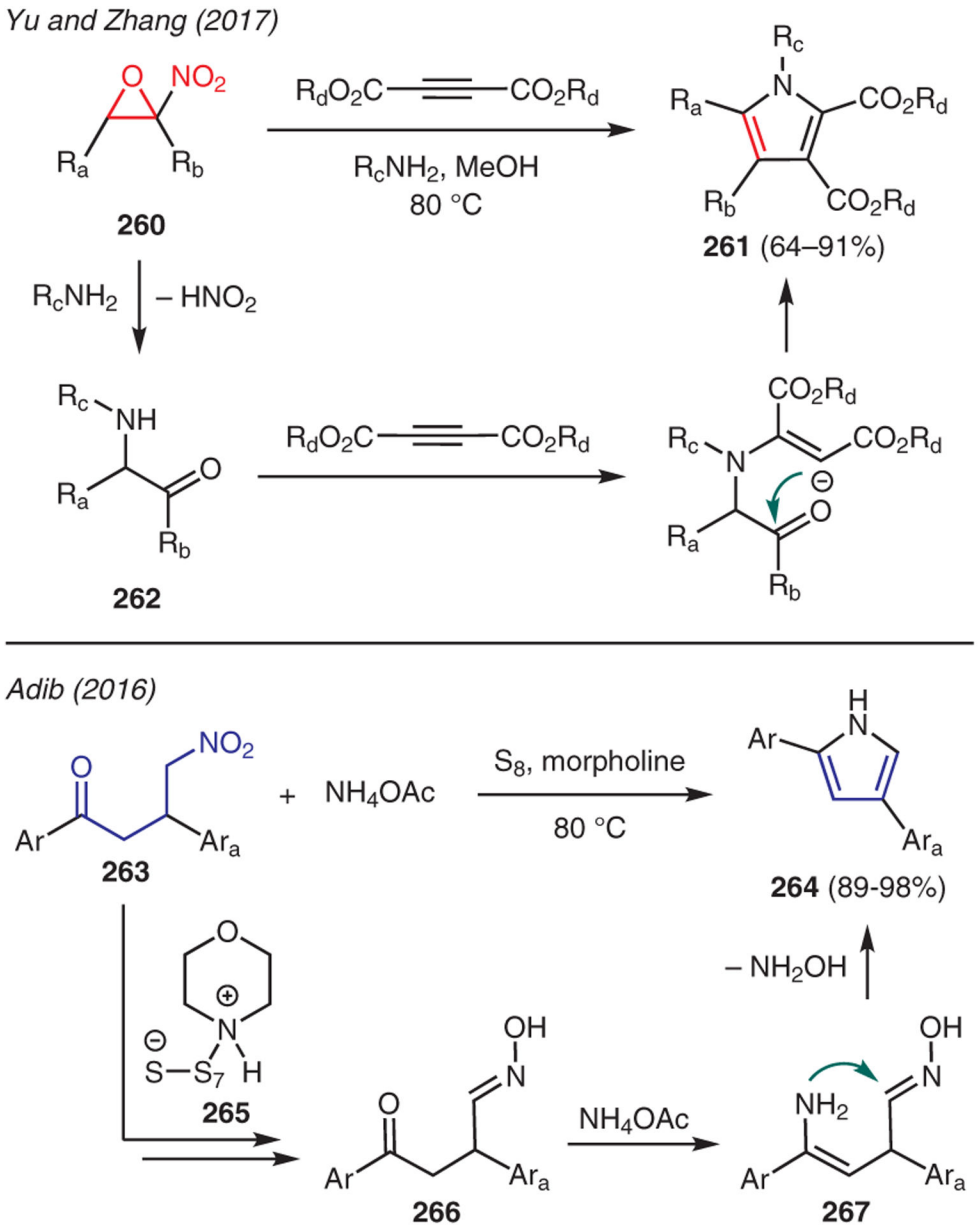
Scheme 27.
From aminols



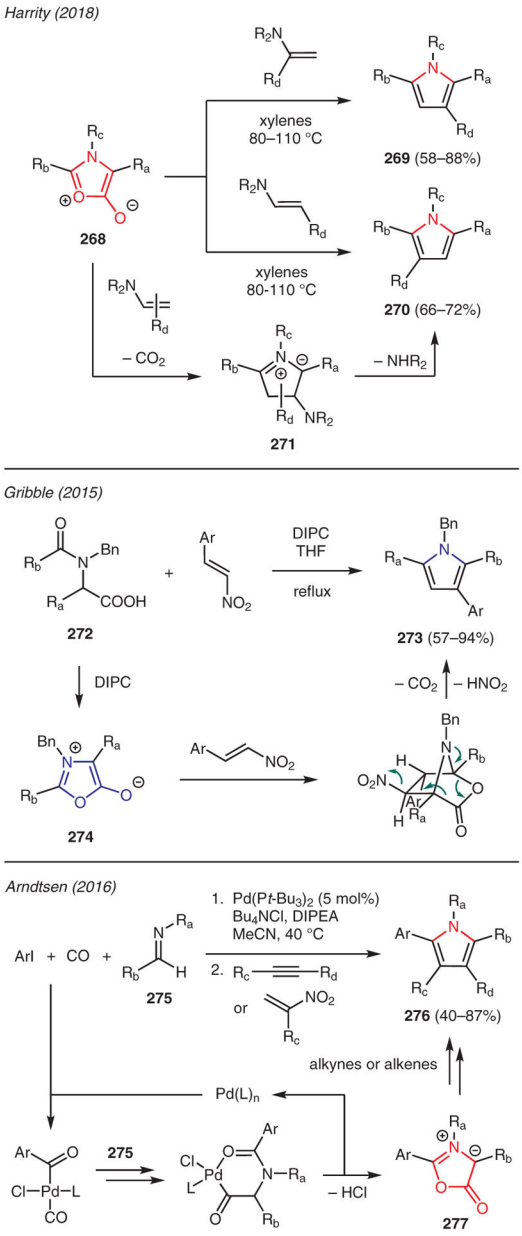
Scheme 28.
From diols



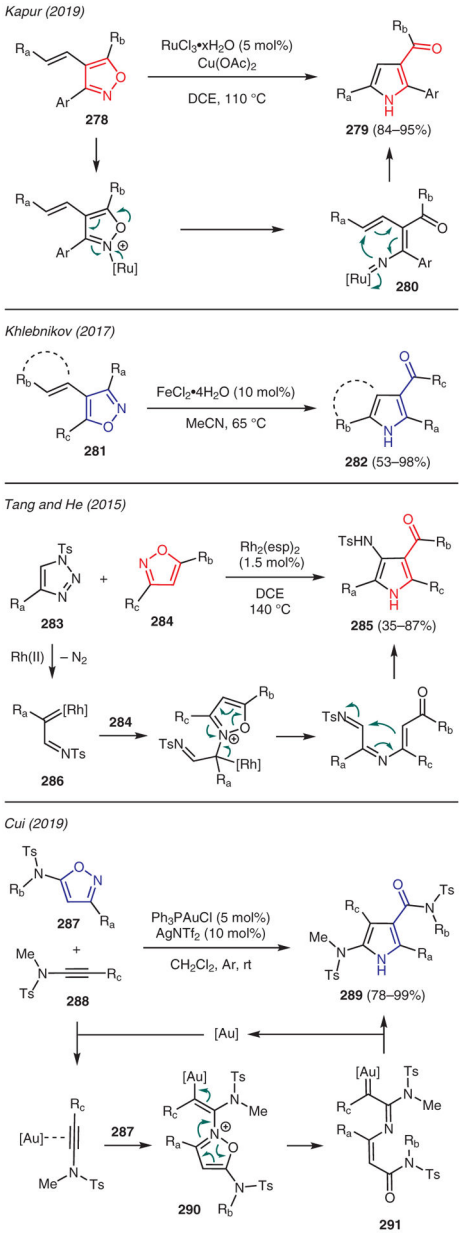
Scheme 29.
From β-nitroalkenes



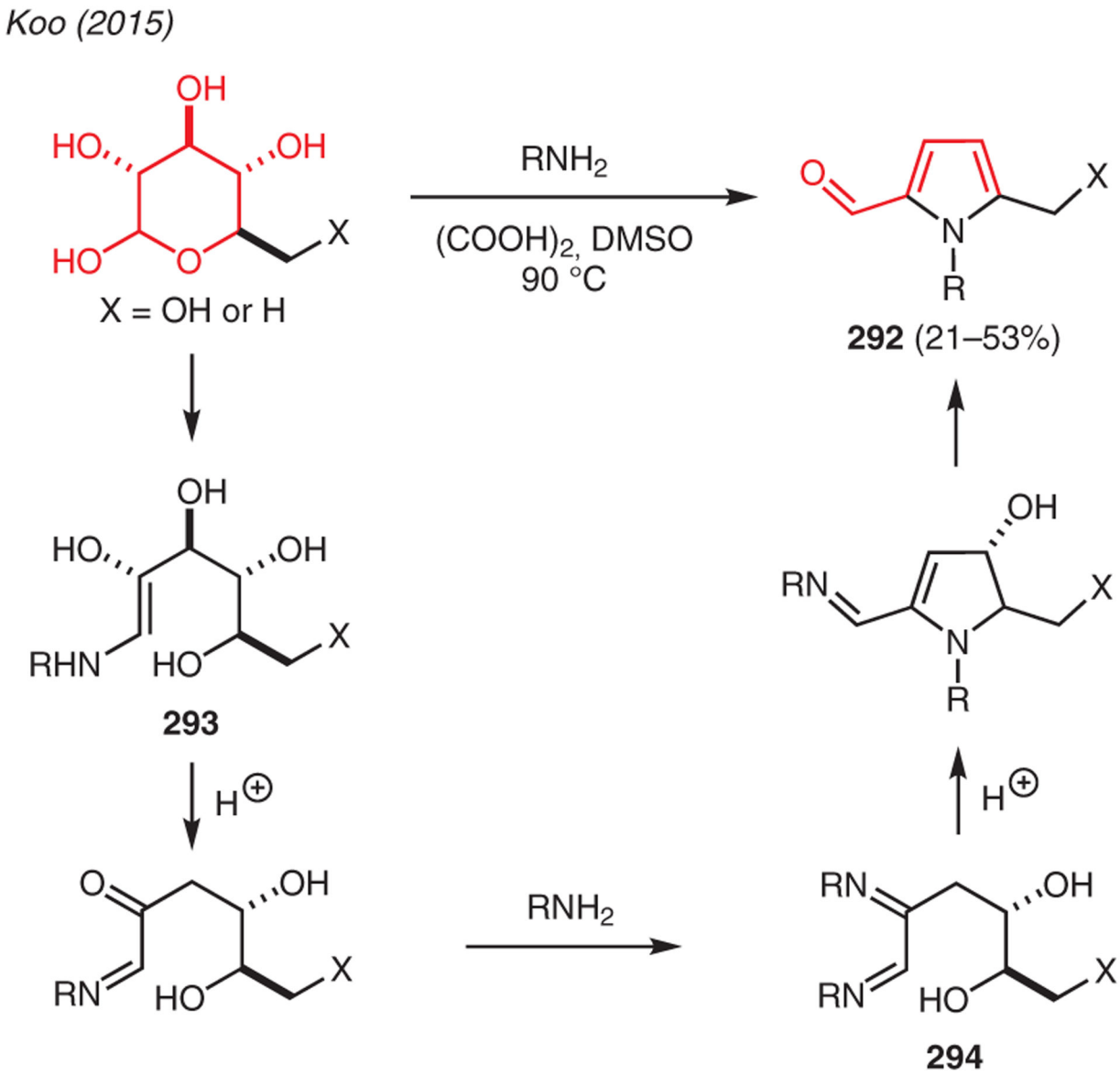
Scheme 30.
From nitro compounds



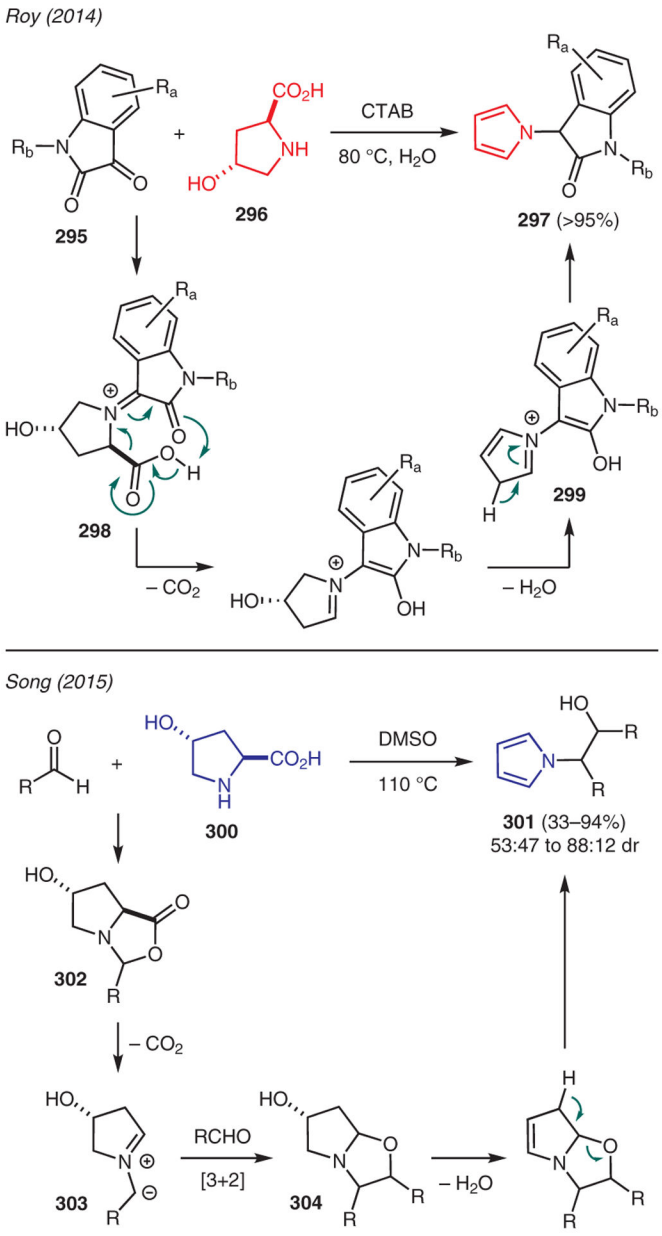
Scheme 31.
From münchnones



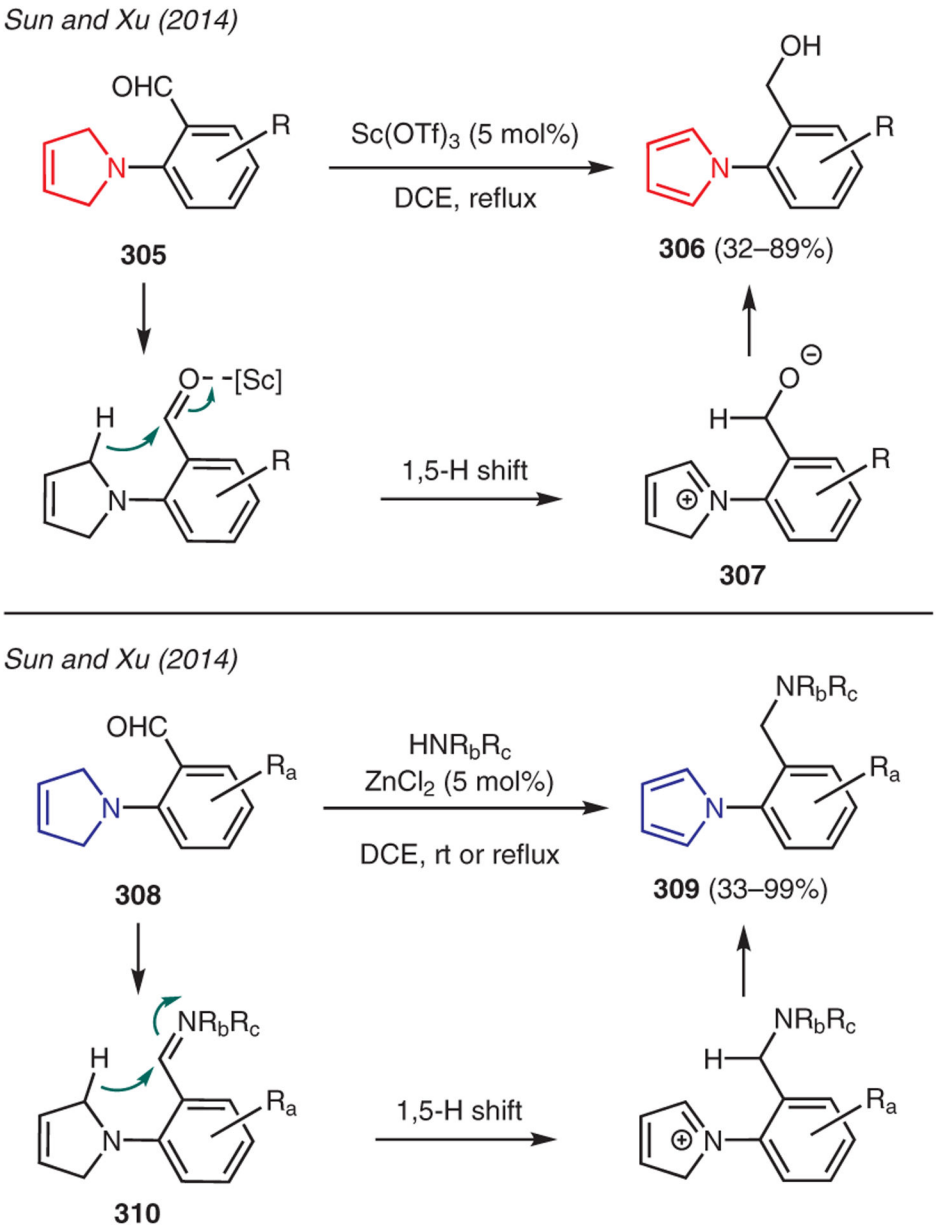
Scheme 32.
From isoxazoles



Scheme 33.
From carbohydrates



Scheme 34.
From *trans*-4-hydroxy-L-prolines



Scheme 35.
From 3-pyrrolines