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Recent approaches in the organocatalytic synthesis of pyrroles

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Organocatalysis has emerged as one of the most important tools for the synthesis of diverse structural scaffolds, and has become one of the most important hot topics of current research. Construction of the pyrrole ring has gained much attention from the last few decades due to its remarkable biological activities, pharmaceutical application, intermediate in the synthesis of many natural products, and material science application. With access to these 5-membered aza heterocycles, organocatalytic approaches have provided a new alternative from the perspective of synthetic efficiency, as well as from the green chemistry point of view, and a vast array of synthetic procedures has been developed. Enlightened by the significance of this growing research area, we aim to describe the recent organocatalytic approaches developed for the construction of pyrroles, and organized them based on substrates employed.

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1. Introduction

Pyrroles are the most well-known five-membered nitrogen-containing heterocyclic aromatic compounds, and are the key structural unit of heme and related porphinoid co-factors,[1] such as heme b, chlorophyll a, vitamin B_{12}, and factor 430. Besides these, the pyrrole ring commonly exists in marine natural products,[2] non-natural products,[3] drug candidates,[4] synthetic intermediates,[5] and optoelectronic materials,[1b] and plays a significant role in the field of medicinal and pharmaceutical chemistry because of their wide-ranging biological activities[6] (Fig. 1). These tremendous biological activities, pharmaceutical applications, use as a synthetic intermediate in many natural products synthesis and material science application have stimulated interest in the synthesis of pyrroles starting from a traditional one, such as the Hantzsch pyrrole synthesis,[7] van Leusen,[8] Knorr,[9] Paal–Knorr pyrrole synthesis[10] to non-classical one,[11] and vast arrays of the synthetic pathway have been developed.

Over the last decade, the use of small organic molecules called organocatalysts in organic transformation has received

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Kartikey Dhar Dwivedi was born in 1992 in Barouhin, a small village in the Rewa District of Madhya Pradesh, India. He obtained his BSc degree from Swami Sharddhanand College (Delhi University), Delhi in 2014, and MSc degree in Chemistry from the Central University of Punjab, Bathinda, India in 2017. Since August 2017, he has been a doctoral fellow (PhD student) in the research group of Dr L. Raju Chowhan at the Central University of Gujarat, Gandhinagar. His research interests include catalysis in organic synthesis, heterogeneous catalysis, and cycloaddition reactions in aqueous medium.

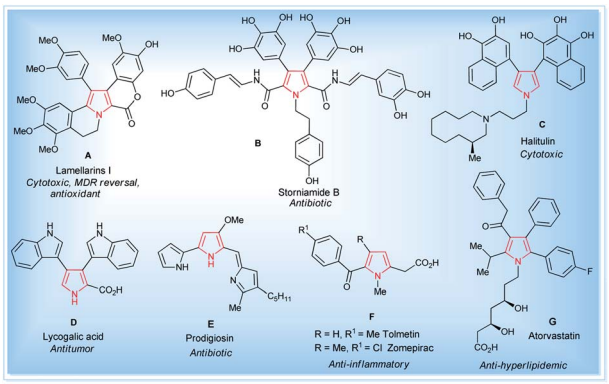


Fig. 1 Some natural (A–E)[1,2] and non-natural compounds (F–G)[3,4] with biological activity containing the pyrrole moiety.

increased attention[12] due to their remarkable properties, including high stability, lower activation energy, high efficiency, transition metal-free nature, reduced toxicity, cost-effectiveness, ready availability and easy recoverability; avoiding expensive catalysts, simple handling in reaction, and the possibility of performing reactions through different activation modes.[13] In addition, the utilization of chiral organic molecules has emerged as a new platform for the synthesis of enantiomerically enriched compounds.[14] Various types of organocatalysts employed for the synthesis of pyrroles are listed in Fig. 2. Encouraged by the growth in the area of organocatalysis in organic transformation and the increased application of the pyrrole heterocycle in many branches of chemistry, an interest was born in our mind to highlight the recent developments for the synthesis of pyrroles by systematically using the different organocatalytic systems in this review. Although several reviews have covered the synthesis of pyrroles based on multicomponent reactions,[15] metal-catalyzed syntheses,[16] and others,[17] the organocatalytic approaches toward its synthesis have not been covered with all details until now. This current review aims to provide access to the works on the synthesis of pyrroles by using various organocatalytic strategies and their development to the present state. On behalf of the appropriate understanding and a convenient presentation, the article is classified according to the nature of the substrates used.

Dr L. Raju Chowhan obtained his BSc degree from Osmania University, Master's degree from Hyderabad Central University, Hyderabad, and PhD from the CSIR-Indian Institute of Chemical Technology, in association with Hyderabad Central University. He joined as an Assistant Professor in the Centre for Applied Chemistry, Central University of Gujarat, Gandhinagar in September 2012. His research interests include the stereoselective synthesis of natural products and the development of novel methodologies for asymmetric synthesis.

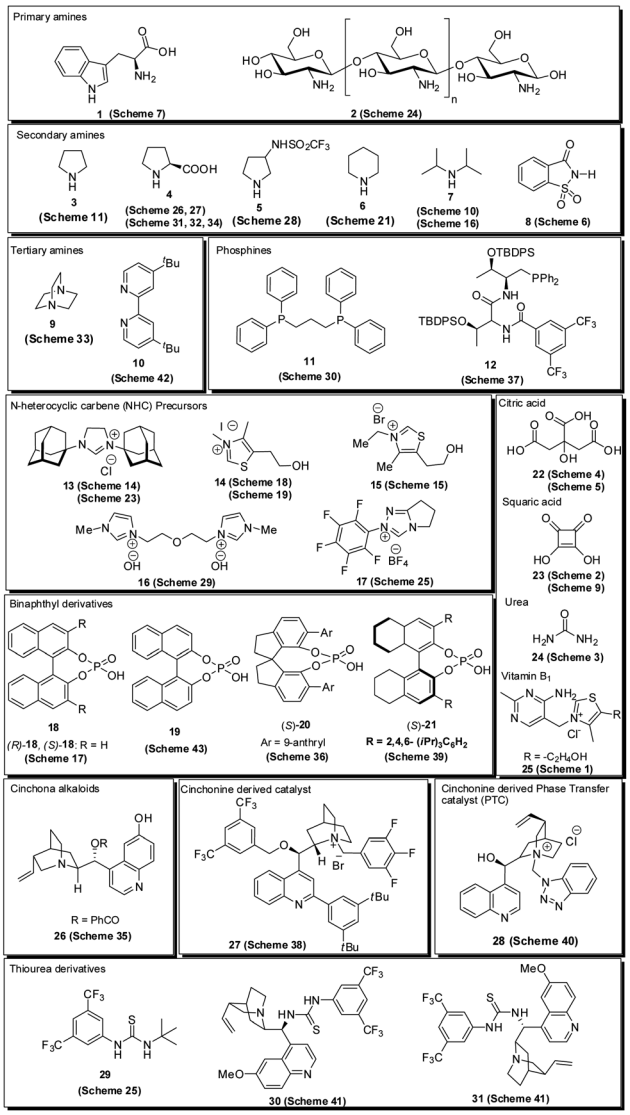
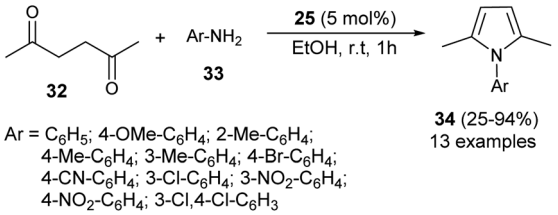


Fig. 2 Organocatalyst used for the synthesis of pyrroles.

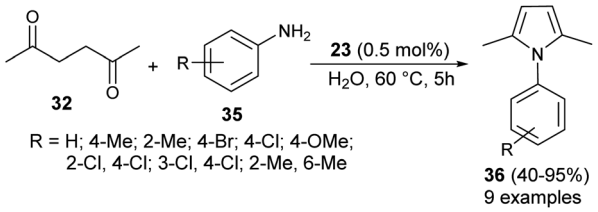
2. Synthesis of pyrroles by two-component cascade reactions

2.1 From dicarbonyl compounds and amines

In 2012, Darabi *et al.* discovered a practical eco-friendly method for the Paal–Knorr pyrrole synthesis based on the metal-free catalyst (Scheme 1).[18] Treatment of hexane-2,5-dione **32** with several substituted aromatic amines **33** in ethanol in the presence of vitamin B_1 (**25**) as an organocatalyst at room temperature for 1 hour gave the corresponding *N*-substituted pyrroles **34** in moderate to excellent yield (25–94%). Aromatic amines possessing different electron-withdrawing and electron-donating substituents at the C-2, C-3, and C-4 position could react with hexane-2,5-dione smoothly to give the desired product in high



Scheme 1 Vitamin B_1-catalyzed synthesis of substituted pyrroles **34**.

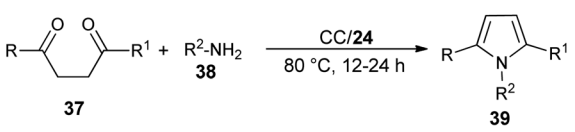


Scheme 2 Squaric acid-catalyzed synthesis of pyrrole derivatives **36**.

yield. However, amines possessing substitution at the C-2 position by the $-NO_2$ group had a detrimental effect on the reactivity, and the desired product was not formed due to the existence of the steric hindrance.

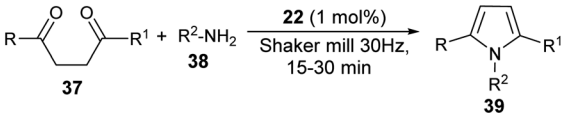
In 2013, Azizi *et al.*[19] reported a novel two-component strategy that affords *N*-substituted pyrroles **36** from the reaction of hexane-2,5-dione **32** with several aromatic amines **35** in water by introducing squaric acid **23** as an organocatalyst at 60 °C for 5 hours in 40–95% yields (Scheme 2). The reaction performed under the ultrasound irradiation condition also afforded the product in good yield. Although the role of squaric acid **23** in this transformation is not clear, it was believed that the Brønsted acidity is the main reason for which the reaction has proceeded.

The combination of urea as an organocatalyst with choline chloride (CC) provided an effective solvent/catalyst system for several organic transformations. In this context, Handy and Lavender in 2013 demonstrated an environmentally friendly protocol for the synthesis of *N*-substituted pyrroles **39** in 56–99% yield *via* the reaction of 1,4-diones **37** with several amines **38** in the presence of choline chloride/urea (**24**) at 80 °C for 12–24 hours (Scheme 3).[20] In this reaction, the use of urea as an organocatalyst activates the carbonyl compound for the Paal–Knorr cycloaddition reaction with amine by forming two H-



R = R^1 = Me, R^2 = Bn, 98%; R = R^1 = Ph, R^2 = Bn, 87%
R = R^1 = Me, R^2 = Hexyl, 99%; R =R^1= Ph, R^2 = Hexyl, 89%
R = R^1 = Me, R^2 = Ph, 78%, R = R^1 = Ph, R^2 = Ph, 82%
R = Me, R^1 =Ph, R^2 = Bn, 94%; R = Me, R^1 = R^2 = Ph, 88%
R = Me, R^1 = Ph, R^2 = Hexyl, 89%

Scheme 3 Synthesis of pyrroles **39** from 1,4-diones and amines.



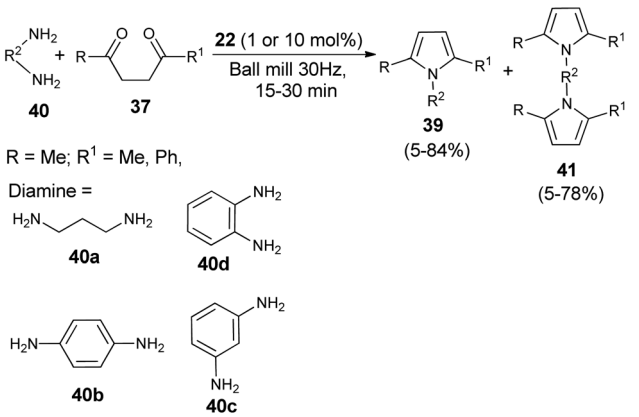
R = R^1 = Me, R^2 = 4-I-C$_6$H$_4$, 74%
R = R^1 = Me, R^2 = C$_6$H$_4$, 66%
R = R^1 = Me, R^2 = C$_2$H$_4$OH, 80%
R = R^1 = Me, R^2 = Benzyl, 71%
R = Me, R^1 = Ph, R^2 = 4-I-Ph, 26%, 52% after 30min
R = Me, R^1 = Ph, R^2 = C$_6$H$_4$, 23%, 49% after 30min
R = Me, R^1 = Ph, R^2 = C$_2$H$_4$OH, 72%

Scheme 4 Mechanochemical method for the synthesis of pyrroles.

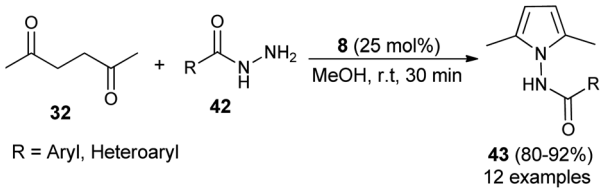
bonds with the carbonyl oxygen. Substitution of different alkyl groups in 1,4-dione **37** and amines **38** leads to a wide-ranging substrate scope with high yields.

A very efficient straightforward method for the synthesis of *N*-substituted pyrroles **39** under solvent-free conditions by using mechanochemical activation and biomass-derived organic acid in a very short reaction time has been developed by Akelis *et al.* (Scheme 4).[21] The synthesis involving the reaction of diketones **37** with various aliphatic and aromatic amines **38** in the presence of citric acid **22** at 30 Hz ball-mill frequency for 15–30 minutes was found to lead to corresponding pyrroles **39** in 23–84% yield. In addition, they further extended the methodology for the desymmetrization of amines or to access bis(pyrroles) **41** by using various aromatic and aliphatic diamines **40** as the reactants under the same reaction condition. The formation of mono-pyrroles **39**, *i.e.*, desymmetrization of amines and bis(-pyrroles) **41** depends on the reactant diketones **37** and diamines **40** (Scheme 5).

In 2015, Bhandari and Gaonkar synthesized a series of *N*-substituted 2,5-dimethylpyrroles **43** through the two-component Paal–Knorr cyclo-condensation reaction of hexane-2,5-dione **32** with several aromatic hydrazides **42** in methanol catalyzed by 25 mol% of saccharin (**8**) at room temperature for 30 minutes (Scheme 6).[22] The methodology offers several significant advantages, including non-toxicity, low cost, ecological safety, easy isolation of the product, and reusability of the catalyst that could be applicable to a wide-ranging substrate scope in good to excellent yield. All heterocyclic, as



Scheme 5 Synthesis of pyrroles by using diamines as the reactants.



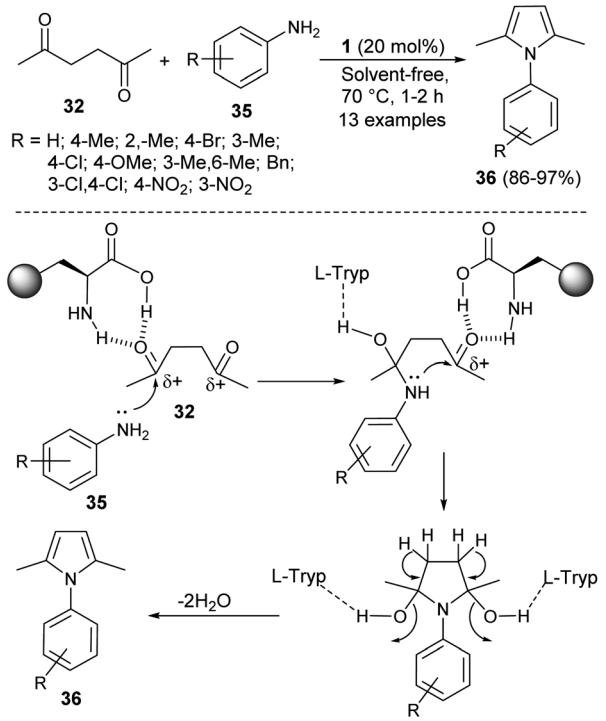
Scheme 6 Saccharin-catalyzed synthesis of pyrroles **43**.

well as aromatic hydrazides, react equally well with hexane-2,5-dione **32** under the standard condition to afford the product **36.**

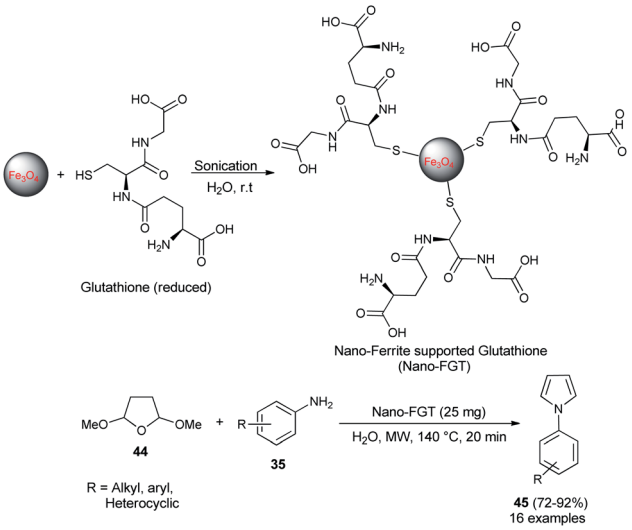
In 2016, Aghapoor *et al.*[23] reported that the treatment of hexane-2,5-dione **32** with several aromatic amines **35** in the presence of the natural primary amino acid L-tryptophan **1** as an organocatalyst at 70 °C under solvent-free condition afforded the corresponding *N*-substituted pyrroles **36** in 86–97% yield in 1–2 hours (Scheme 7). The proposed mechanism for this transformation initiated by the double condensation of hexane-2,5-dione **32** with amines **35** under the presence of catalyst **1.** The catalyst **1** activates the dicarbonyl compound by forming hydrogen bond between the carbonyl oxygen and its amino acid group, and thereby facilitating the nucleophilic attack of N-atom of aromatic amines to the carbonyl carbon. In the final stage, the subsequent removal of water molecules followed by detachment of the catalyst leads to the formation of product **36.**

2.2 From tetrahydro-2,5-dimethoxyfurans and amines

In 2009, Polshettiwar *et al.* reported the synthesis of a novel nanoparticle-supported organocatalyst, namely, Nano-Ferrite supported Glutathione (Nano-FGT) for the synthesis of pyrroles. The catalyst was prepared *via* the immobilization of



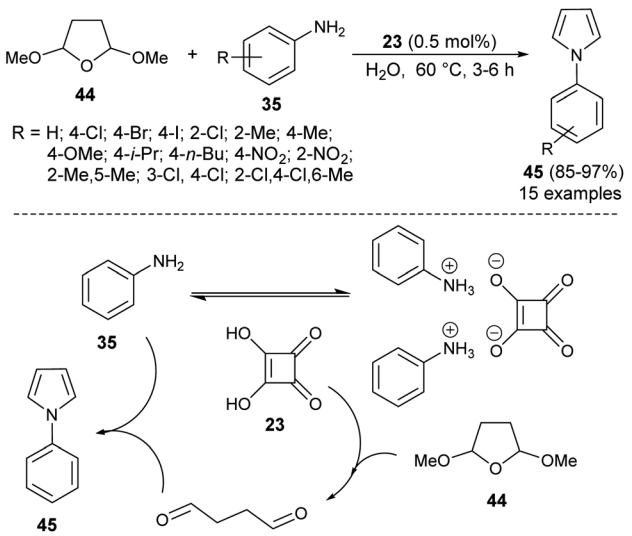
Scheme 7 Synthesis of pyrroles *via* double-condensation reaction.



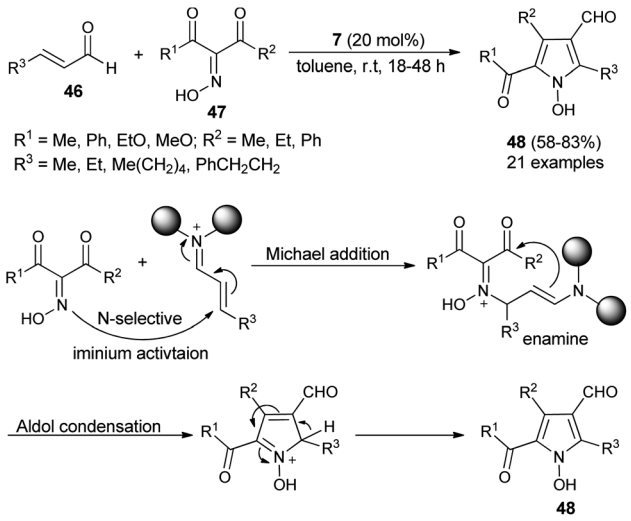
Scheme 8 Nano-FGT catalyzed synthesis of pyrroles **45**.

naturally abundant tripeptide glutathione as an organocatalyst on the nano-ferrite surfaces. The catalytic activity of the prepared nanoparticle-supported organocatalyst was found to be very efficient for the two-component Paal–Knorr condensation reaction of tetrahydro-2,5-dimethoxyfuran **44** with different amines **35** in aqueous medium under microwave irradiation at 140 °C. The corresponding pyrrole **45** was obtained in 72–92% within 20 minutes (Scheme 8).[24] Under the standard reaction condition, as mentioned, various aryl, heteroaryl, and alkyl amines worked well and a total of 16 compounds were synthesized in good to excellent yield.

Another organocatalytic route for the synthesis of *N*-substituted pyrroles **45** in 85–97% yield has been accomplished *via* the treatment of tetrahydro-2,5-dimethoxyfuran **44** with several aryl amines **35** in the presence of **23** as an organocatalyst



Scheme 9 Preparation of *N*-substituted pyrroles **45** from tetrahydro-2,5-dimethoxyfuran and amines.



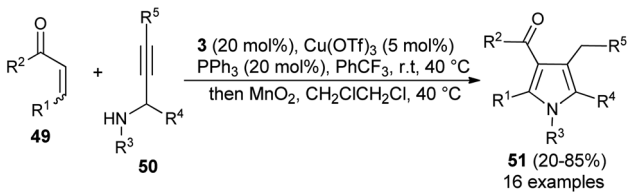
Scheme 10 Synthesis of *N*-hydroxypyrroles **48** *via* Michael addition/aldol condensation reaction.

in the aqueous medium at 60 °C for 3–6 hours (Scheme 9).[19] The suggested way for this transformation starts with the formation of anilinium squarate salt by the reversible acid–base treatment of aniline with squaric acid **23**. The hydrolysis of tetrahydro-2,5-dimethoxyfuran in the presence of a catalytic amount of **23** gave the active 1,4-dicarbonyl compound, which could undergo a cyclo-condensation reaction with aniline to afford the corresponding product **45** (Scheme 9).

2.3 From α,β-unsaturated carbonyl compounds

Due to the attractive advantages, organocatalytic domino reactions have been considered as a powerful tool in organic synthesis from the last decade. In 2009, Tan and his co-workers demonstrated that the one-pot domino reaction of α,β-unsaturated aldehydes **46** and α-carbonyl oximes **47** by using **7** as an organocatalyst in toluene at room temperature for 18–48 hours afforded *N*-hydroxy pyrroles **48** in 58–83% yield (Scheme 10).[25] The reaction has proceeded *via* the domino Michael addition/aldol condensation reaction, and oximes were utilized as *N*-selective nucleophiles for the Michael addition reaction step. The proposed mechanism involves the initial iminium activation of α,β-unsaturated aldehydes by secondary amine catalyst **7** that undergo Michael addition reaction by experiencing a nucleophilic attack from the *N*-selective nucleophile oximes. The subsequent intramolecular aldol condensation reaction and aromatization reaction afforded the final *N*-hydroxypyrroles **48** in good yield.

Similar to the α,β-unsaturated aldehydes, the reactivity of unsaturated ketones was also explored for the synthesis of polysubstituted pyrroles *via* cooperative catalysis. In recent years, cooperative catalysis has drawn much more attention for the production of useful structural units by combining both metal-catalyst and organocatalyst. Treatment of unsaturated ketones **49** with *N*-substituted propargylated amines **50** by using **3** as the organocatalyst in the presence of copper salt at room temperature or 40 °C produces the polysubstituted 3-acyl



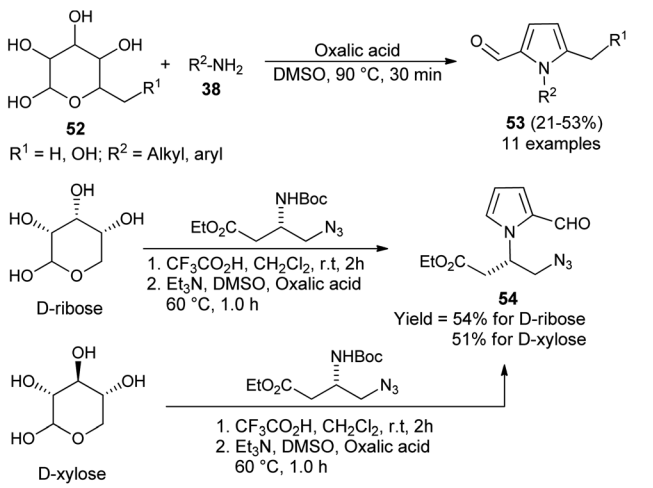
Scheme 11 One-pot synthesis of 3-acyl pyrrole from an unsaturated ketone by cooperative catalysis.

pyrroles **51** in 20–85% yield (Scheme 11).[26] The reaction has proceeded through the iminium activation of unsaturated ketones **49** by **3**, followed by aza-Michael addition with substituted propargylamine that undergoes alkyne carbocyclization reaction, which leads to the formation of corresponding 3-acyl pyrroles **51** after the oxidation reaction.

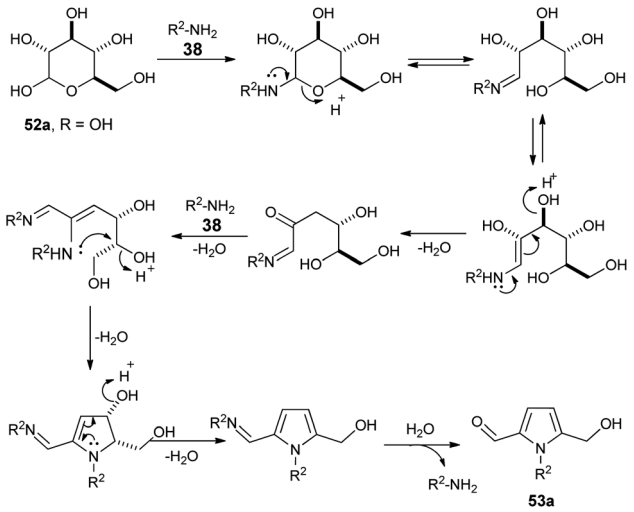
2.4 Other two-component reactions

In 2015, Adhikary *et al.*[27] reported a practical one-pot conversion procedure for the synthesis of *N*-substituted pyrrole-2-carbaldehydes **53** in 21–53% yields *via* the reaction of carbohydrates **52** with primary amines **38** in the presence of oxalic acid in DMSO at 90 °C for 30 minutes (Scheme 12). The reaction of D-ribose with amino-ester, resulting from the *N*-Boc-protected β-amino-ester, led to the formation of *N*-substituted pyrroles **54** in 54% yield. In the case of D-xylose under the same condition, the corresponding product was obtained in 51% yield.

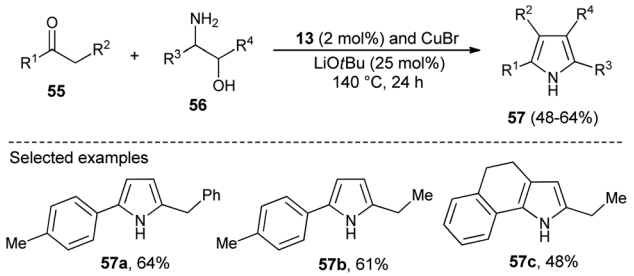
A plausible mechanism for this practical conversion is depicted in Scheme 13. Initially, the *N*-glycosylation of amines **38** from carbohydrates **52a** produces the ring-opened enamine tautomer that facilitates removal of the protonated 3-hydroxyl group to give the imine intermediate. Addition of another amine **38** to the imine intermediates, and then cyclization followed by removal of the protonated 4-hydroxyl group, and further aromatization afforded the corresponding pyrrole **53a**.



Scheme 12 Conversion of carbohydrates into *N*-substituted pyrrole-2-carbaldehydes.



Scheme 13 Plausible mechanism for the conversion of D-glucose **52a** to pyrrole **53a**.



Scheme 14 Cu–NHC catalyzed synthesis of *N*-unsubstituted pyrroles.

N-Heterocyclic carbenes (NHC) as a Lewis base organocatalyst have had a widespread impact on the organic chemistry community due to their several modes of activation. Saturated imidazolium carbene precursors **13**, in combination with CuBr, catalyzed the two-component reaction of ketones **55** and β-amino alcohols **56** in the presence of base LiO*t*Bu at 140 °C for the synthesis of *N*-unsubstituted pyrroles **57** in 48–64% yield after 24 hours (Scheme 14).[28]

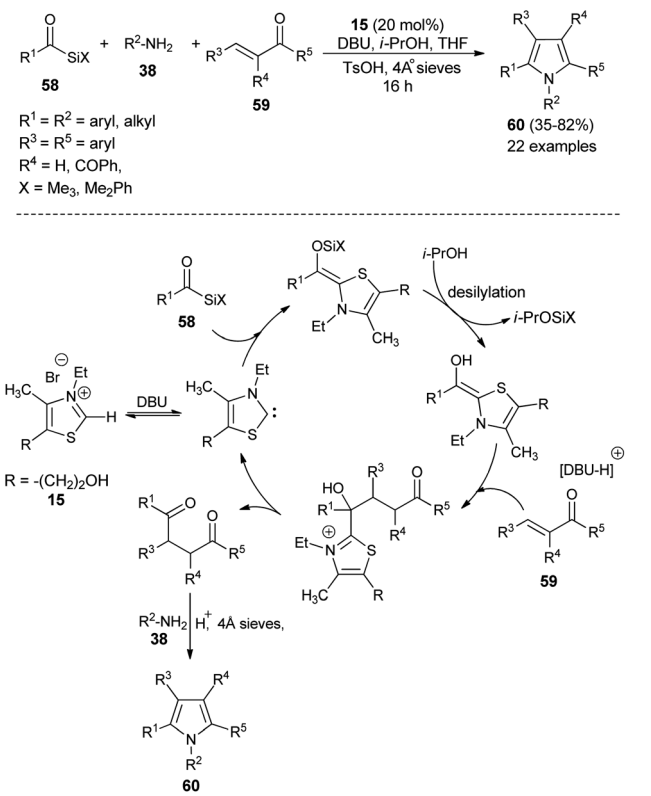
3. Synthesis of pyrroles *via* multicomponent reactions (MCRs)

3.1 From α,β-unsaturated compounds

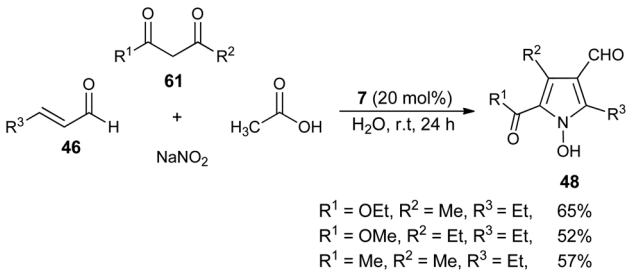
In recent times, multicomponent reactions (MCRs) have increasingly gained favor in organic synthesis due to the formation of diverse molecular structures in a single step with enhanced efficiency, reduced waste, and high atom economy. In this perspective, a one-pot three-component reaction of acylsilanes **58**, α,β-unsaturated carbonyl compounds **59** and amines **38** catalyzed by thiazolium salt **15** in the presence of DBU for the synthesis of highly substituted pyrroles **60** *via* the Sila-Stetter/Paal–Knorr approach was developed by Ashwin and Karl in 2004 (Scheme 15).[29] The reaction proceeded through the combination of thiazolium salt **15** with an amine base DBU that produces the N-heterocyclic carbene/zwitterionic catalyst, which facilitate the preferential acyl anion conjugate addition of acylsilanes **58** to more electrophilic α,β-unsaturated ketones **59**, which leads to the formation of the 1,4-dicarbonyl compound that undergoes the Paal–Knorr condensation reaction upon treatment with amines **38**, acid and dehydrating agent to produce the corresponding pyrroles **60**.

In 2005, a very efficient one-pot four-component reaction of α,β-unsaturated aldehydes **46**, 2,4-diones **61**, acetic acid, and sodium nitrite in the presence of secondary amine 7 in aqueous medium at room temperature was found to provide the green construction of polyfunctionalized *N*-hydroxypyrroles **48** after 24 hours. By using water as a green solvent, the products were isolated in moderate yield ranging from 52–65% (Scheme 16).[25] This protocol displayed various advantages, including mild reaction condition, environmentally friendly nature, simple isolation process, low cost and the catalyst could be easily recovered.

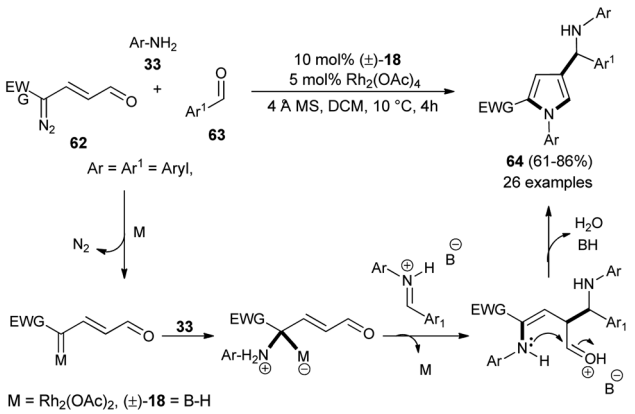
Dawande *et al.* established the direct synthesis of substituted pyrroles **64** with a new stereogenic center in good yield *via* the one-pot three-component reaction of enaldiazo compounds **62**, several substituted aromatic aldehydes **63**, and amines **33** (Ar = Aryl, Boc) by introducing the cooperative catalyst $Rh_2(OAc)_4$ and (±)-BINOL phosphoric acid **18** in DCM at 10 °C for 4 hours (Scheme 17).[30] It is interesting to note that due to the steric hindrance, the amine 2-(trifluoromethyl)-aniline produces the pyrrole in lower yield, whereas the amine 2,4,6-trimethylaniline did not produce the corresponding pyrrole. The methodology



Scheme 15 Synthesis of highly substituted pyrroles 60 *via* Sila-Stetter/Paal–Knorr strategy.



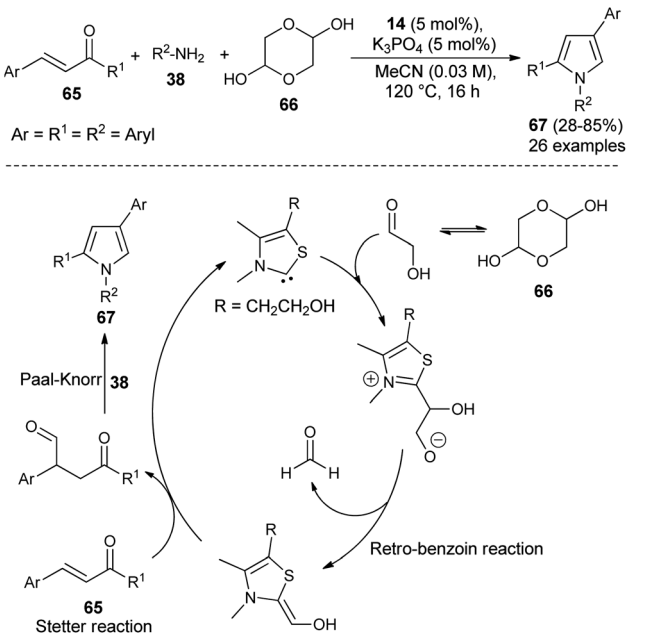
Scheme 16 Four-component synthesis of *N*-hydroxypyrroles **48** in the presence of a secondary amine catalyst.



Scheme 17 Access to pyrroles *via* ammonium ylide/Mannich reaction/cyclization cascade sequence.

was found to be very efficient in the diastereoselective synthesis of the binaphthyl-based chiral pyrrole. The transient protic ammonium ylide generated from the rhodium enalcarbenoid allowing for the vinylogous nucleophilic addition to the iminium species afforded the Mannich product with a new stereogenic center that underwent [4 + 1] cyclo-condensation reaction to give the desired pyrroles **64.**

Recently, it has been shown that the N-heterocyclic carbene catalyzed synthesis of 1,2,4-trisubstituted pyrroles could also be applicable in the synthesis of diverse structural precursors of atorvastatin. The direct one-pot three-component coupling of α,β-unsaturated ketones **65**, glycolaldehyde dimer **66** as a novel C1 building block, and amines **38** using thiazolium salt **14** and K_3PO_4 at 120 °C in MeCN for 16 hours produced the 1,2,4-trisubstituted pyrroles **67** in 28–85% yield (Scheme 18).[31] The mechanism proposed for this reaction sequence involves the addition of thiazol carbene (produces from the reaction of thiazolium salt **14** with K_3PO_4) to the carbonyl carbon of glycolaldehyde, furnishes the anionic intermediate that could undergo retro-benzoin C–C bond cleavage reactions after proton transfer, and thereby the formation of a carbon nucleophile along with formaldehyde. The conjugate addition of a carbon nucleophile with α,β-unsaturated ketones **65** as Michael acceptor *via* Stetter reaction leads to the 1,4-dicarbonyl compound that provides the corresponding pyrroles **67** after subsequent Paal–Knorr cyclo-condensation reaction with the amines **38.**

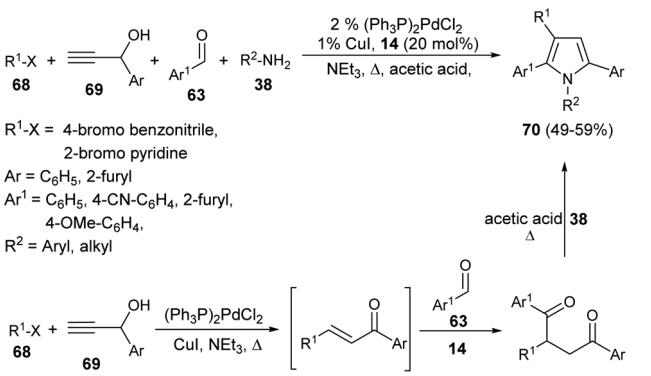


Scheme 18 NHC-catalyzed synthesis of trisubstituted pyrroles **67**.

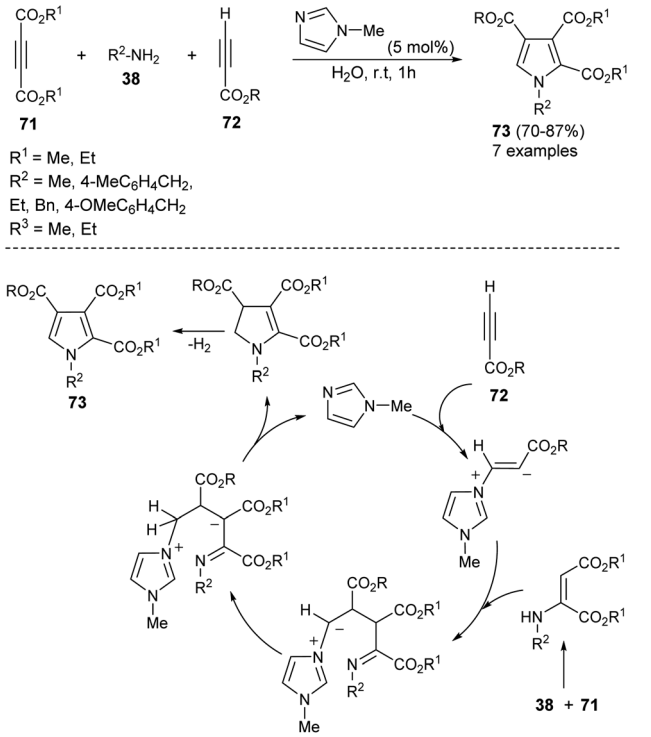
3.2 From alkynes

In 2001, Braun *et al.* successfully synthesized a series of diverse 1,2,3,5-tetrasubstituted pyrroles **70** in 49–59% yield by exploring (hetero)aryl halides **68**, such as 4-bromo benzonitrile or 2-bromo pyridine, terminal propargyl alcohols **69**, aromatic aldehydes **63**, and primary amines **38** as starting materials in the presence of thiazolium salt **14** (Scheme 19).[32] This one-pot four-component method initiated by the coupling-isomerization of aryl halides **68** with propargyl alcohols **69** followed by addition of aldehydes **63** *via* Stetter reaction afforded the 1,4-dicarbonyl compound, and then the subsequent Paal–Knorr reaction with amines **38** furnished the tetrasubstituted pyrroles **70.**

A highly efficient one-pot treatment of primary amines **38** with acetylene dicarboxylates **71** and propiolates **72** in aqueous



Scheme 19 Coupling-isomerization-Stetter–Paal–Knorr strategy for the preparation of tetrasubstituted pyrroles.

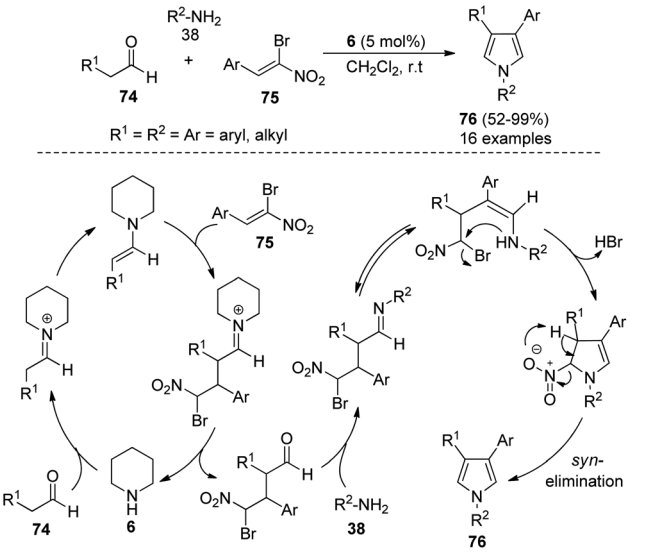


Scheme 20 *N*-Methylimidazole catalyzed three-component synthesis of 2,3,4-trisubstituted pyrroles.

medium by using 5 mol% *N*-methylimidazole as an organocatalyst at room temperature for 1 hour afforded the functionalized pyrroles **73** in 70–87% yield (Scheme 20).[33] The mechanism proposed to explain this reaction begins with the addition of *N*-methylimidazole with propiolates **72**, produces the zwitterionic intermediate, which undergoes addition reaction with an enamine-ester formed *in situ* from **71** and **38**, followed by subsequent proton transfer and intramolecular cyclization to give the dihydropyrrole derivatives with simultaneous regeneration of the catalyst. The final elimination of hydrogen from the dihydropyrrole intermediate yielded the corresponding product **73**.

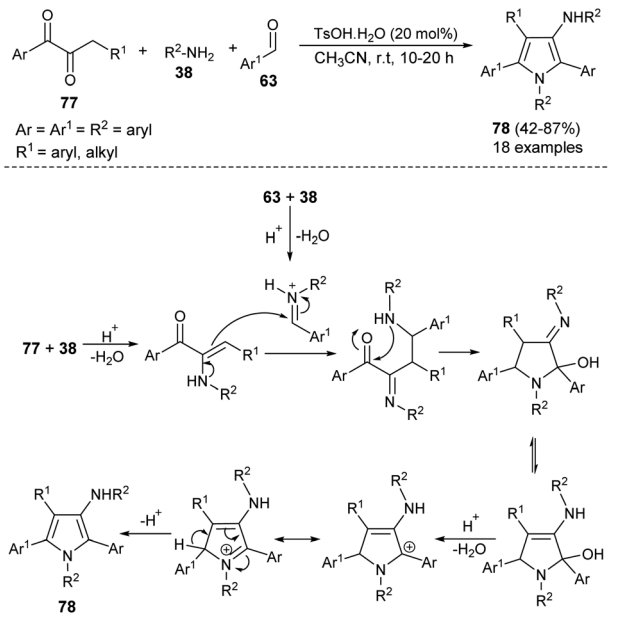
3.3 From carbonyl compounds

In 2012, Martín-Santos *et al.*[34] performed the domino three-component reaction of aldehydes **74**, (*Z*)-β,β-bromonitroalkenes **75**, and amines **38** in the presence of organocatalyst **6** in CH_2Cl_2 at room temperature to form the 3,4-disubstituted pyrroles **76** in good to excellent yield (Scheme 21). The mechanism involved in this reaction starts with the formation of an enamine from the addition of **6** with aldehydes **74** that undergoes Michael addition to (*Z*)-β,β-bromonitroalkenes **75**, and produces the γ-bromo-γ-nitro-aldehyde intermediate after the hydrolysis and regeneration of organocatalyst **6**. The reaction of this intermediate with amines **38**, followed by tautomerization and intramolecular cyclization, and the subsequent *syn*-elimination of the nitro group afforded the final product **76**.

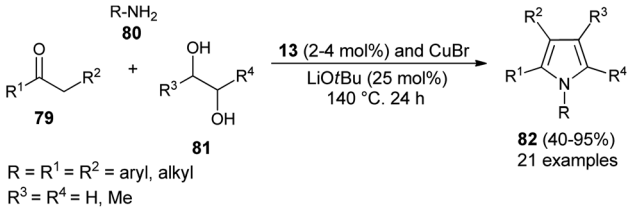


Scheme 21 Synthesis of disubstituted pyrroles by domino MCRs.

The highly efficient one-pot construction of several polysubstituted pyrroles **78** in acceptable to good yield (42–87%) has been obtained *via* the environmentally benign multicomponent reaction of 1,2-diones **77**, aryl amines **38**, and aldehydes **63** in the presence of 4-methylbenzenesulfonic acid monohydrate ($TsOH \cdot H_2O$) as an organocatalyst in acetonitrile at room temperature for 10–20 hours (Scheme 22).[35] The reaction proceeded with the formation of an iminium ion from aryl amines **38** and aldehydes **63** that experiences a nucleophilic attack from the enamine intermediate, generated from aryl amines **38** and 1,2-diones **77**, followed by an intramolecular cyclization and tautomerization to afford the imine form amino alcohol



Scheme 22 Synthesis of polysubstituted pyrroles from 1,2-diones, aldehydes, and aryl amines.



Scheme 23 Synthesis of pyrroles by using the Cu–NHC catalyst system.

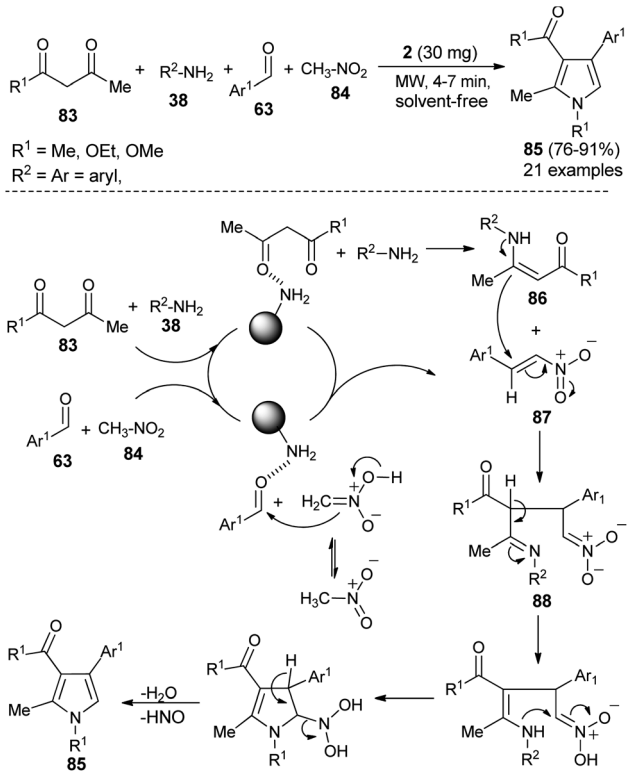
(Scheme 30).[25] The loss of one molecule of water from the imine amino alcohol produces the conjugate iminium ion intermediate that yields the final product **78** *via* deprotonation.

Dang *et al.*[28] noted that the combination of CuBr with carbene precursors benzimidazolium salts **13** lead to the formation of a Cu–NHC complex as an efficient non-noble metal catalyst in the presence of a base, and was found to be a very effective catalyst in the preparation of a variety of 1,2-, 1,2,3-, variety of 1,2-, 1,2,3-, 1,2,3,5- and fully substituted pyrroles (Scheme 23). This Cu–NHC catalyzed one-pot protocol begins with the three-component reaction of different substituted ketones **79**, amines **80**, and diols **81** at 140 °C for 24 hours to produce the corresponding pyrroles **82** in 40–95% yields.

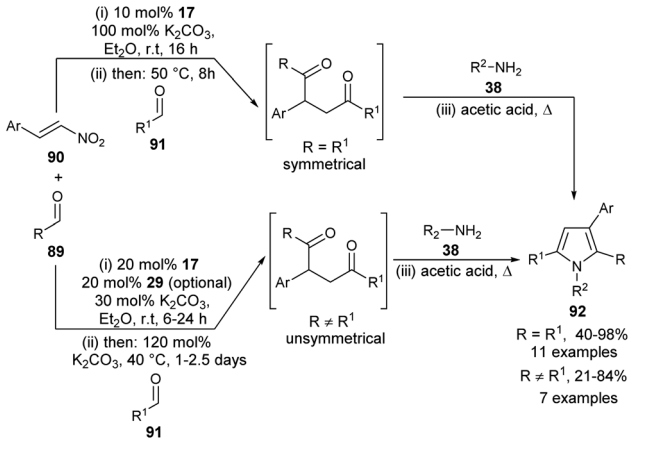
Hassani *et al.* reported an operationally simple and eco-friendly one-pot four-component reaction of 1,3-dicarbonyl compounds **83**, amines **38**, aldehydes **63**, and nitromethane **84** in the presence of chitosan **2** as an organocatalyst under the solvent-free and microwave-irradiation condition to afford the substituted pyrroles **85** in 76–91% yields within 4–7 hours (Scheme 24).[36]

The mechanistic pathway for this solvent-free synthesis involves the initial reaction of dicarbonyl compounds **83** with amines **38** in the presence of **2** to give the enamine intermediates **86**, which react with the nitroalkenes **87** generated from the reaction of aldehydes **63** and nitromethane **84** to afford the imine **88**. In both cases, the carbonyl groups were activated by the catalyst through hydrogen bonding. Through tautomerization and intermolecular cyclization, the imine **88** forms the corresponding pyrroles **85**, after a subsequent loss of a water molecule and nitrosyl hydride.

A highly convergent multi-catalytic multicomponent reaction (MCR) strategy to access very constructive symmetrical and unsymmetrical 2-aryl substituted 1,4-diketone building blocks from readily available aldehydes and nitroalkenes as latent 1,2-dication synthons and their utilization for the one-pot four-step synthesis of polysubstituted pyrroles **92** by using carbene precursor **17** and K_2CO_3 as N-heterocyclic carbene (NHC)-catalyst has been developed (Scheme 25) by Fuchs *et al.*[37] For the synthesis of symmetrical 1,4-diketones, the reaction of aldehydes **89** and nitroalkenes **90** was carried out in the presence of 10 mol% of NHC-precursors **17** and 100 mol% of K_2CO_3 in Et_2O at room temperature for 16 hours, followed by the addition of a second aldehyde **91** at 50 °C for another 8 hours. This 1,4-diketone on treatment with amines **38** in acetic acid under heating condition afforded the corresponding symmetrical pyrroles **92** in 40–98% yield. However, for the synthesis of unsymmetrical 1,4-diketones, the amount of NHC-precursors **17** was increased to 20 mol% and the amount of base was reduced to 30 mol% in the first step, and increased to 120 mol% in the elimination step. Its final addition with amines **38** in heating acetic acid produced the unsymmetrical pyrroles **92** in 21–84% yield. In the case of reactive aldehydes, only NHC was found to be very sufficient to promote the reaction. However, in the case of aldehydes with lower reactivity, an additional thiourea derivative **29** as the H-bonding catalyst is required for the activation of 1,2-bis-electrophilic nitroalkenes.



Scheme 24 Solvent-free microwave-assisted synthesis of pyrroles.

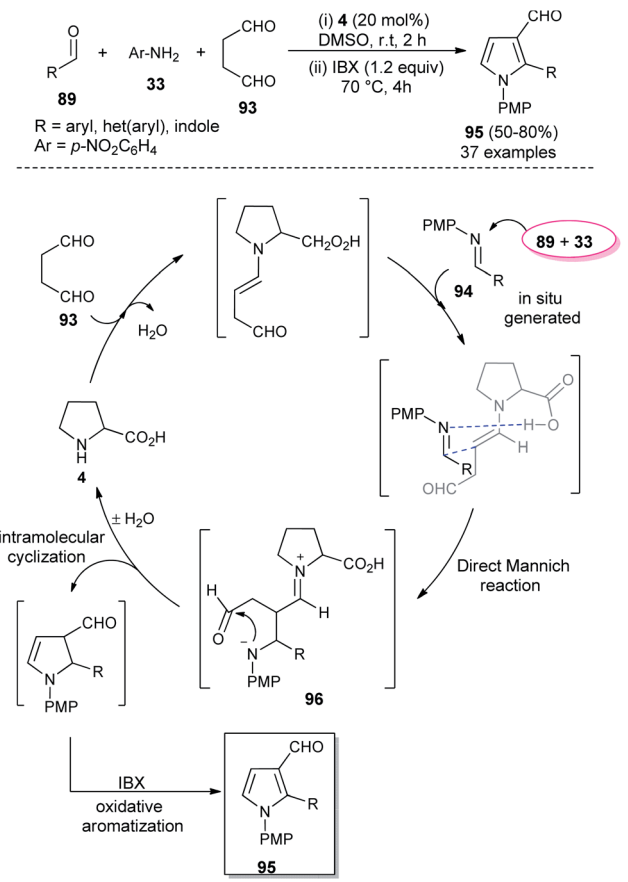


Scheme 25 Synthesis of pyrroles *via* four-step one-pot multicomponent reaction.

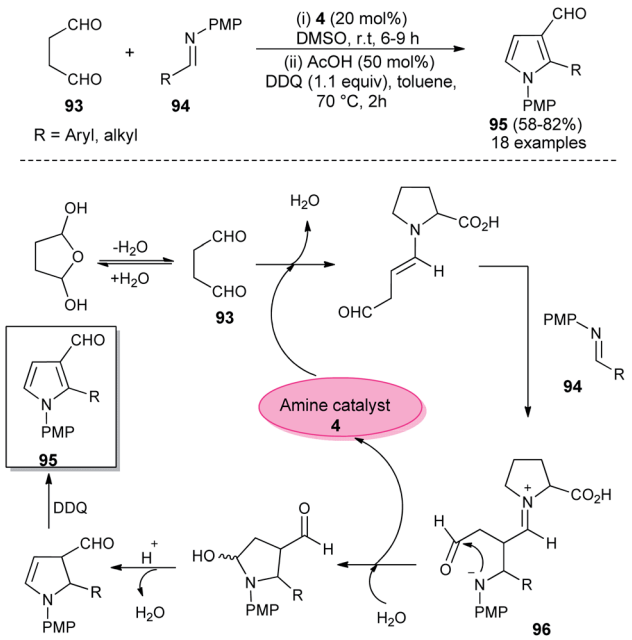
In 2018, Singh *et al.* reported an efficient sequential multi-component strategy toward the synthesis of *N*-aryl pyrrole-3-carbaldehydes **95** *via* the secondary amine **4** catalyzed reaction of aldehydes **89**, arylamines **33**, and succinaldehyde **93** in DMSO by using IBX as the oxidant (Scheme 26).[38] Not only the aryl aldehydes, but also heteroaryl/indole-aldehydes worked well with this methodology, and a total of 37 compounds were synthesized in moderate to good yield. The suggested mechanism for this transformation starts with the *in situ* formation of enamine from the reaction of succinaldehyde **93** and catalyst **4**, which can then react with the *N*-PMP-imines **94** generated *in situ* from aldehydes **89** and amines **33**, *via* a direct Mannich reaction, resulting in the formation of Mannich product **96**. The intermediate **96** then undergoes intramolecular cyclization reaction with subsequent removal of the catalyst, followed by IBX-promoted oxidative aromatization to form the final product **95**.

4. Synthesis of pyrroles *via* multistep reactions

In 2012, Kumar *et al.* developed a robust two-step strategy involving the reaction of succinaldehyde **93** with *N*-PMP aldimines **94** in the presence of organocatalyst **4** in DMSO at room temperature, followed by acid-catalyzed cyclization and



Scheme 26 L-Proline catalyzed synthesis and mechanism of pyrroles *via* sequential multicomponent reaction.

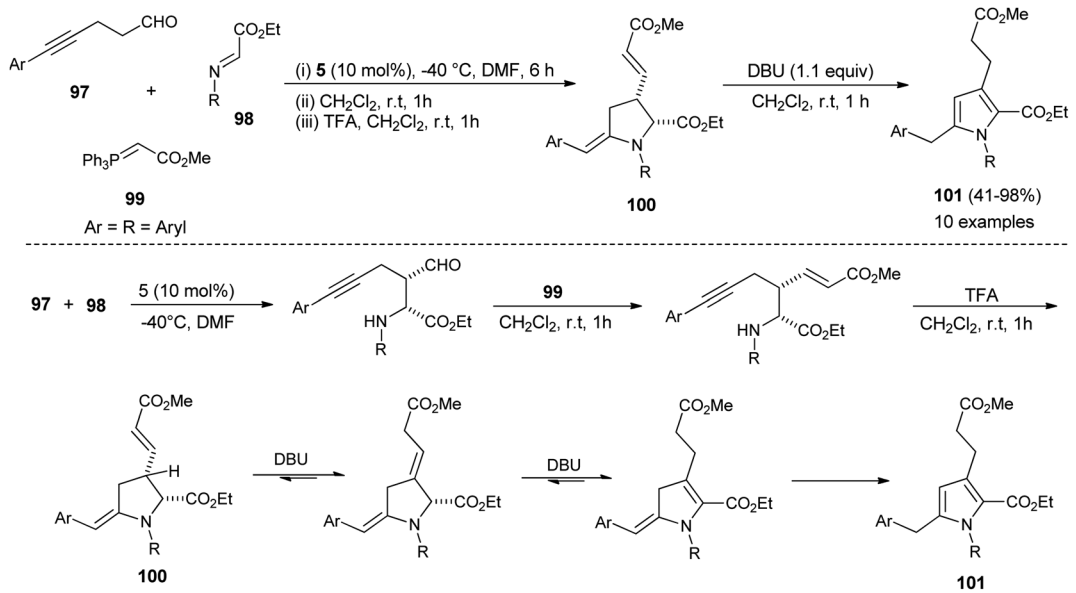


Scheme 27 L-Proline catalyzed synthesis of trisubstituted pyrroles.

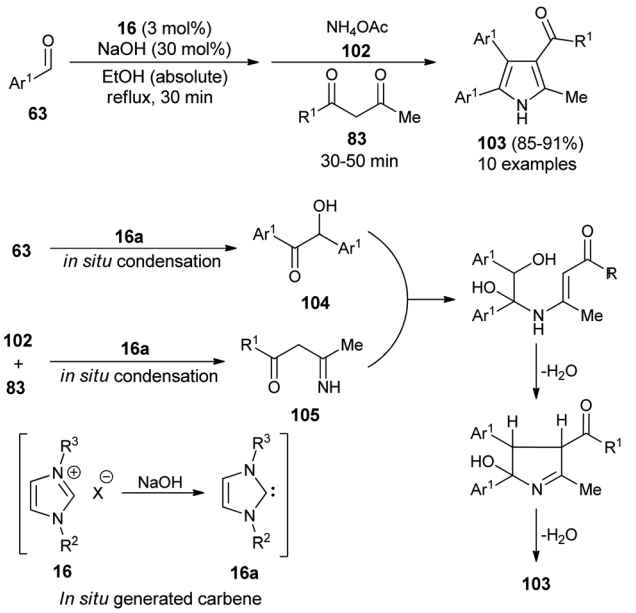
aromatization under the influence of DDQ in toluene at 70 °C for the synthesis of substituted pyrroles **95** in 58–82% yield (Scheme 27).[39] This transformation was completed through the formation of an enamine intermediate **96** from the reaction of succinaldehyde **93** and amine catalyst **4**, which reacts with the *N*-PMP aldimines **94** *via* a direct Mannich reaction, followed by intramolecular cyclization with the simultaneous regeneration of **4**, acid-catalyzed dehydration and final aromatization by DDQ with a subsequent loss of the water molecule to provide the pyrroles **95**.

In 2013, Jean *et al.* reported the regioselective construction of 2-heteroarylmethylene decorated *N*-aryl pyrroles **101** *via* two-step sequence from readily available aldehydes, imines, and phosphonium **99** in the presence of organocatalyst **5** in DMF at −40 °C. The Mannich coupling of aldehydes **97** and imines **98**, followed by Wittig olefination with phosphonium **99** along with proton mediated hydroamination, leads to the rapid access of pyrrolidine **100** (Scheme 28).[40] Isomerization of pyrrolidine **100** by simply using the amine base DBU in CH_2Cl_2 at room temperature afforded the substituted pyrroles **101** in 41–98% yield after 1 hour. The formation of pyrrolidine **100** and subsequent isomerization steps to **101** is shown in Scheme 28. After the formation of pyrrolidine **100**, the deconjugation of the acrylate moiety followed by aromatization in the presence of the DBU base yielded the final product **101**.

In 2016, Niknam *et al.* synthesized a variety of 2,3,4,5-tetra-substituted pyrroles **103** in 85–91% yield through the one-pot multistep reaction of substituted aldehydes **63**, NH_4OAc **102**, and 1,3-dicarbonyl compound **83** by using carbene precursors **16** in the presence of NaOH in absolute ethanol under reflux condition (Scheme 29).[41] The reaction of aldehydes **63** in the presence of N-heterocyclic carbene **16a** (generated *in situ* from **16** and NaOH) produced the corresponding benzoin **104** *via* *in*



Scheme 28 Synthesis of 2-heteroarylmethylene decorated pyrroles.

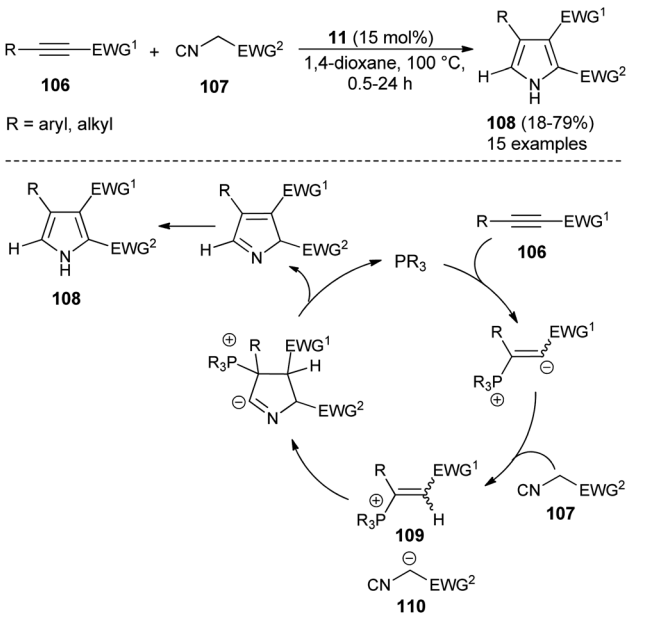


Scheme 29 NHC-catalyzed tandem sequence to access pyrroles **103**.

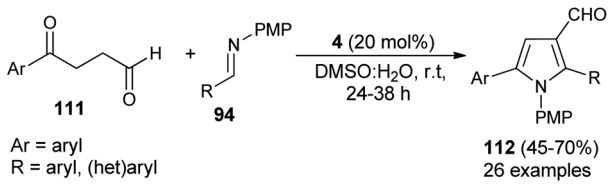
situ condensation reactions after 30 minutes, which reacts with the imine **105** formed *in situ* from the NHC-mediated addition of 1,3-dicarbonyl compound **83** and NH_4OAc **102**. An intramolecular cyclization and aromatization by loss of a water molecule gave the desired product **103**.

5. Synthesis of pyrroles *via* formal [3 + 2] cycloaddition reactions

For the construction of five-membered heterocyclic scaffolds, the [3 + 2] cycloaddition reaction has emerged as one of the most promising approaches, and a vast array of [3 + 2] cycloaddition reactions has been developed for the organocatalytic synthesis of pyrroles. In 2005, Kamijo and co-workers developed an organophosphine **11** catalyzed formal [3 + 2] cycloaddition reaction for the synthesis of 2,3-di-EWG-substituted pyrroles **108** from activated alkynes **106** and isocyanides **107** in dioxane at 100 °C for 0.5–24 hours in 18–79% yield (Scheme 30).[42] The mechanism for this [3 + 2] cycloaddition reaction begins with the 1,4-addition of a nucleophilic catalyst **11** to the activated alkynes **106**. It then produces the zwitterionic intermediate, which after abstraction of acidic proton in the isocyanides **107**, afforded the cationic intermediate **109** and the carbanion **110** that undergoes [3 + 2]



Scheme 30 Synthesis of pyrroles from alkynes and isocyanides *via* [3 + 2] cycloaddition reaction.

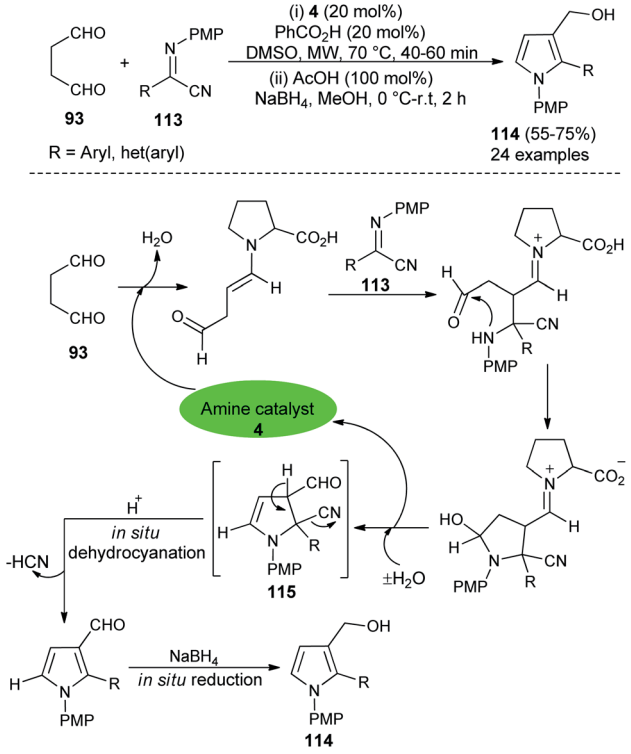


Scheme 31 Secondary amine-catalyzed [3 + 2] annulation to pyrroles.

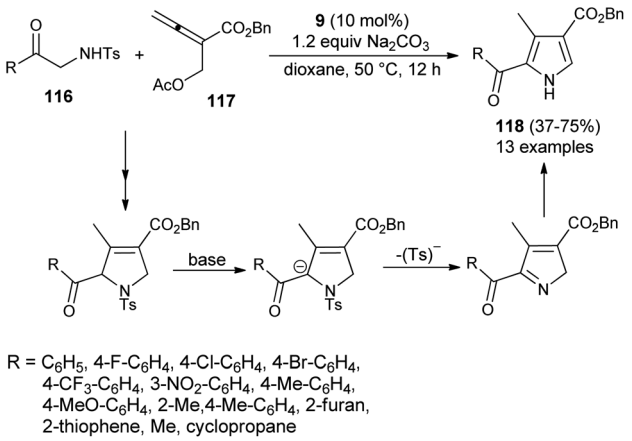
cycloaddition reaction *via* the attack of carbanion **110** to the carbon of cationic intermediate **109** bearing the EWG[1] and thereby facilitates the generation of a new anionic center in the cationic intermediate **109** to attack the isocyanide carbon of **110**, leading to the 5-membered cyclic intermediate. Its intramolecular proton relocation and removal of the catalyst followed by 1,5-hydrogen shift yields the final product **108**.

A straightforward route to access densely substituted 3-formyl pyrroles **112** in 45–70% yield *via* formal [3 + 2] cycloaddition reaction has been demonstrated by Kumar *et al.* in 2014. The protocol is mainly based on the one-pot cascade reaction of substituted 1,4-ketoaldehydes **111** and imines **94** in the presence of the amine catalyst **4** in aqueous DMSO at room temperature in 24–38 hours (Scheme 31).[43] This transformation can be completed *via* the chemoselective Mannich reaction of 1,4-keto aldehydes **111** with imine **94**, followed by intramolecular cyclization and aerobic oxidative aromatization.

In 2016, Mir *et al.*[44] reported a microwave-assisted synthesis of substituted pyrrole-3-methanols **114** in good yield from the one-pot two-step reaction of succinaldehyde **93** and α-



Scheme 32 Microwave-assisted [3 + 2] annulation for the preparation of pyrroles **114**.

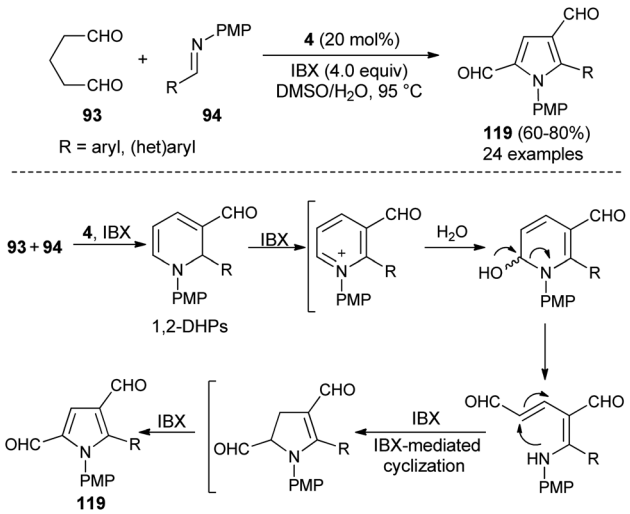


Scheme 33 [3 + 2] Annulation/elimination/isomerization process to access substituted pyrroles **118**.

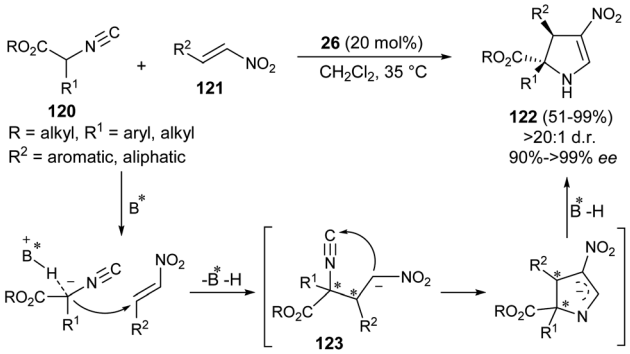
iminonitriles **113** through the amino-catalyzed [3 + 2] annulation (Scheme 32). The reaction was carried out in the presence of the secondary amine **4** in DMSO, along with $PhCO_2H$ as additive under microwave heating at 70 °C for 40–60 minutes, followed by the addition of cold MeOH, AcOH at 0 °C to room temperature, and then the addition of $NaBH_4$ for 2 hours furnished the pyrrole-3-methanols **114** up to 75% yield. The process started with the direct Mannich reaction of an enamine intermediate generated from the reaction of **4** and **93**, with iminonitriles **113**, followed by intramolecular cyclization and then dehydration afforded the enamine intermediate **115**. The simultaneous removal of the catalyst occurred for the next cycle. Its final *in situ* dehydrocyanation and reduction lead to the desired product **114**.

In 2016, Ni *et al.* reported the [3 + 2] cycloaddition reaction to form the trisubstituted pyrroles **118** by the cascade reaction of 2-aminoketone derivatives **116** with allenoate **117** in the presence of tertiary amine **9**, along with Na_2CO_3 in dioxane at 50 °C for 12 hours in 37–75% yield. It is pertinent to note that the 2-tosylamino ketone derivatives **116** were found to be a very efficient 1*N*,2*C*-bis-nucleophile partner for the [3 + 2] annulation with allenoate **117** (Scheme 33).[45] However, the reaction efficiency was found to be somewhat lower due to the lower nucleophilicity of **116**, and results in a moderate yield of the product, as well as incomplete reaction. The overall process involves the amino catalyzed [3 + 2] annulation of allenoate **117** and 2-aminoketone **116** that undergo 1,2-elimination of the Ts^- group in the presence of a base, followed by isomerization route to afford the corresponding pyrroles **118**.

Also, several substituted pyrrole-2,4-dialdehydes **119** were obtained in 60–80% yield through the one-pot reaction of glutaraldehyde **93** and imines **94** using the amine catalyst **4** in aqueous DMSO in the presence of oxidant IBX at 95 °C for 8–9 hours (Scheme 34).[46] This was an unprecedented pseudo-[3 + 2] annulation reaction that proceeded under a metal-free condition, in which not only the substituted and unsubstituted aryl imines, but also heteroaryl imines were well tolerated in the pyrrole synthesis. The mechanism involves the direct Mannich reaction of glutaraldehyde **93** with imines **94**, and then cyclization in presence of organocatalyst **4**, followed by



Scheme 34 Regioselective access to pyrroles *via* pseudo-[3 + 2] annulation reaction.



Scheme 35 Organocatalytic formal [3 + 2] cycloaddition reaction for the asymmetric construction of dihydropyrroles **122**.

regioselective oxidation under the influence of oxidant IBX to produce 1,2-dihydropyridines (DHPs). The oxidation, ring-opening, and IBX-promoted intramolecular cyclization afforded the dihydropyrrole intermediate that undergoes final oxidative aromatization to give the pyrroles **119**.

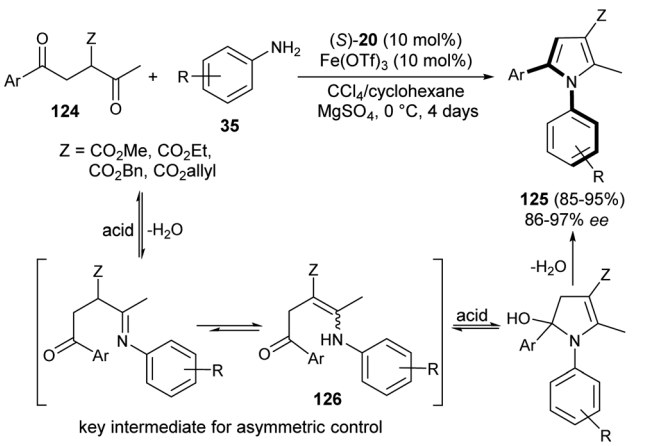
Guo *et al.* developed the first organocatalytic asymmetric construction of optically active 2,3-dihydropyrroles by means of the formal [3 + 2] cycloaddition reaction. Treatment of several isocyanoesters **120** and nitroalkenes **121** in the presence of cinchona alkaloid **26** in CH_2Cl_2 at 35 °C was found to lead to 2,3-dihydropyrroles **122** in 51–99% yield (Scheme 35).[47] Not only the aromatic ring bearing various electron-donating and electron-withdrawing substituents, but also aliphatic nitroalkenes were well tolerated, and resulted in the formation of the products with high diastereoselectivities of up to >20 : 1 with 91 to >99% ee. The process was initiated with the activation of the acidic α-carbon atom of isocyanoesters **120** by the catalyst **26** to undergo enantioselective Michael addition with nitroalkenes **121**, thereby providing the intermediate **123**. The subsequent intramolecular cyclization of **123** followed by protonation afforded the final product **122**.

6. Synthesis of axially chiral pyrroles

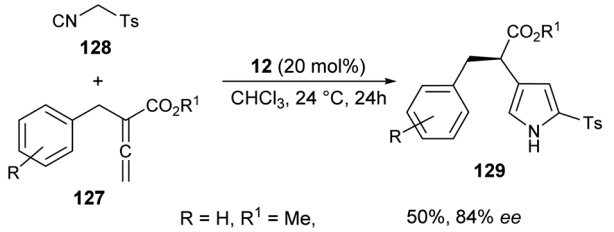
The existence of organocatalysis has led to a chiral revolution in the field of asymmetric synthesis.[48–51] The growth of asymmetric organocatalysis in the synthesis of pyrroles has drawn much more attention due to the inexpensive, metal-free, and non-toxic reaction conditions. In this context, Zhang *et al.* reported a very efficient strategy for the synthesis of axially chiral aryl pyrroles **125** with high enantioselectivity by introducing a chiral phosphoric acid (*S*)-**20** as the organocatalyst and $Fe(OTf)_3$ as the Lewis acid. The combination of two acid systems enhances the enantioselectivity of the corresponding aryl pyrroles **125** (Scheme 36).[52] The reaction of various 1,4-diketones **124** with aromatic amines **35** using the combined acid catalyst system in CCl_4 and cyclohexane at 0 °C afforded the chiral aryl pyrroles **125** in 85–95% yield with 86–97% ee after 4 days. This highly atroposelective transformation of the chiral aryl pyrroles initially involves the formation of the key enamine intermediate **126** from 1,4-diketones **124** and amine **35**, which then undergo acid-catalyzed dehydrative cyclization to produce the desired product **125**.

The chiral phosphine-catalyzed synthesis of enantioenriched 1*H*-pyrroles *via* formal [3 + 2] cycloaddition reaction has been reported by Zhao and co-workers in 2018. Treatment of allenoates **127** and activated isocyanides **128** in the presence of **12** in $CHCl_3$ at 24 °C for 24 hours afforded the enantioenriched pyrroles **129** in 17–50% yield with 81–97% ee (Scheme 37).[53] Several electron-withdrawing and electron-donating substituents on the benzyl ring of allenoate affected the yield and enantioselectivity of the corresponding products. When electron-withdrawing groups were substituted at the *ortho* or 2,6-position, the yield of the product was found to be very low with good enantioselectivity. Whereas, for the electron-donating groups, substitution at the *ortho* position furnished moderate yield with good ee. Also, the electron-donating groups at the *para* position of the benzyl ring were well tolerated by this method.

In 2019, the synthesis of axially chiral 2-aryl pyrroles **132** from enantioenriched atropisomeric alkenes *via* direct chirality



Scheme 36 Atroposelective construction of pyrroles **125** *via* Paal–Knorr reaction strategy.



R = H, R^1 = Me,	50%, 84% *ee*
R = H, R^1 = Et,	34%, 91% *ee*
R = H, R^1 = ^{i}Pr,	20%, 97% *ee*
R = H, R^1 = ^{t}Bu,	17%, 95% *ee*, after 48 h
R^1 = Me, R = 4-Me,	40%, 82% *ee*
R^1 = Me, R = 4-^{i}Pr,	43%, 88% *ee*
R^1 = Me, R = 4-^{t}Bu,	32%, 86% *ee*
R^1 = Me, R = 4-OMe,	30%, 83% *ee*
R^1 = Me, R = 2-Me,	47%, 88% *ee*
R^1 = Me, R = 2-F,	23%, 81% *ee*, after 48 h
R^1 = Me, R = 2,6-F_2,	23%, 88% *ee*

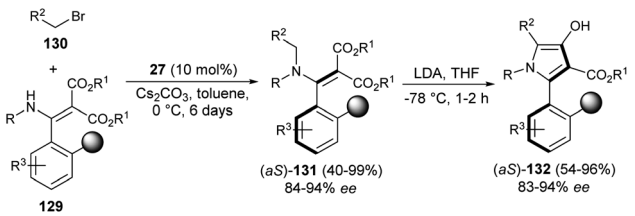
Scheme 37 Enantioselective synthesis of substituted pyrroles **129** *via* [3 + 2] cycloaddition sequence.

transfer strategy was developed by Wang *et al.*[54] The atropisomeric alkenes **131** were produced through the asymmetric reaction of substituted enamines **129** with *N*-alkylating reagents **130** in the presence of the cinchonine-derived organocatalyst **27** and Cs_2CO_3 in toluene at 0 °C for 6 days. Treatment of **131** in the presence of the strong base lithium diisopropylamide (LDA) in THF at −78 °C for 1–2 hours afforded the corresponding axially chiral 2-aryl pyrrole scaffolds **132** in 54–96% yield with 83–94% ee (Scheme 38).

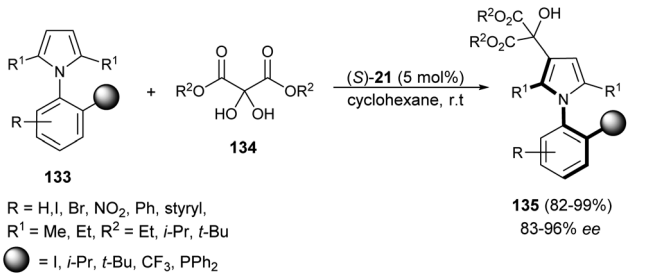
Zhang *et al.*[55] reported an atroposelective synthesis of axially chiral aryl pyrroles **135** from 1*H*-pyrrole **133** and diethyl ketomalonates **134** in the presence of chiral phosphoric acid (*S*)-**21** in cyclohexane at room temperature *via* desymmetrization/kinetic resolution strategy. Products were formed in very high yield (82–99%) with 83–96% ee (Scheme 39).

The reaction of nitroolefin of type **136** with α-isocyanomethyldiphenylphosphine oxide **137** in the presence of the cinchona-derived phase transfer catalyst **28** and CsOH in toluene at −20 °C after 24 hours afforded the corresponding axially chiral pyrrole **138** in 99% yield with high enantioselectivity (Scheme 40).[56] However, when the same reaction was carried out in a Ag_2O/quinine-derived aminophosphine ligand catalytic system, the corresponding product **138** was formed in 75% yield with 21% ee.

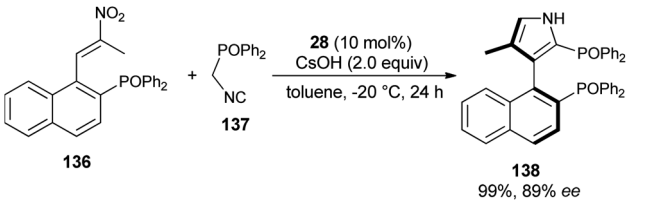
In 2019, Zheng *et al.*[57] also noted that the enantioenriched 3-aryl pyrroles would be obtained from the kinetic resolution



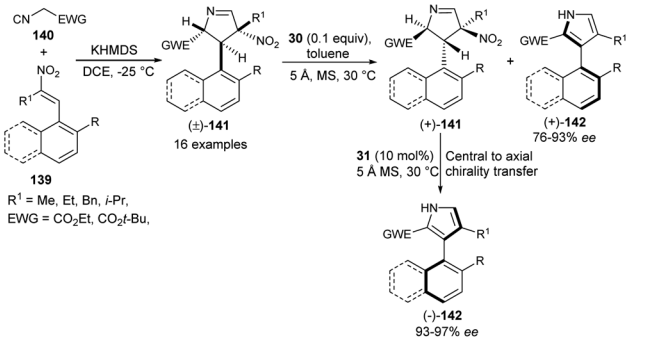
Scheme 38 Synthesis of axially chiral 2-aryl pyrroles *via* chirality transfer approaches.



Scheme 39 Synthesis of axially chiral aryl pyrroles **135** *via* desymmetrization/kinetic resolution strategy.

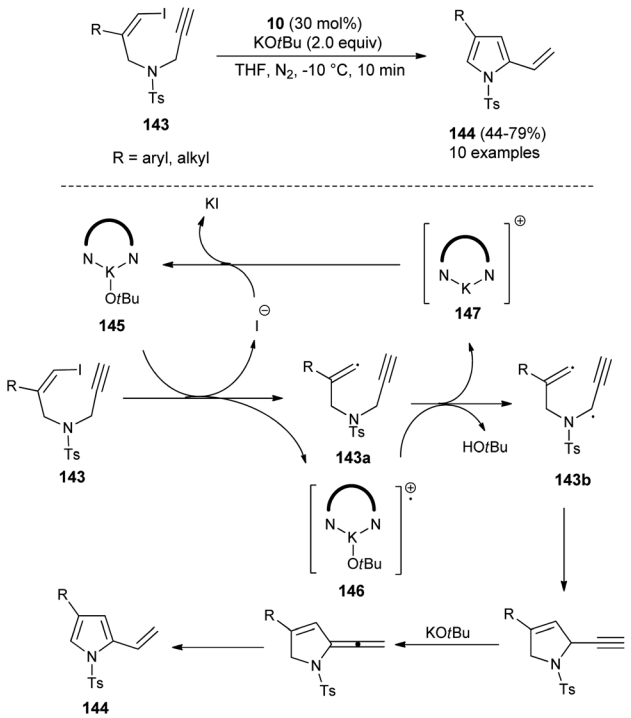


Scheme 40 PTC-catalyzed asymmetric construction of chiral bisphosphine **138** bearing a 3-pyrrole unit.



Scheme 41 Kinetic resolution of **141** *via* enantioselective aromatization sequence to access 3-aryl pyrroles **142**.

of the racemic intermediate of the Barton–Zard reaction *via* the enantioselective aromatization reaction. The process starts with the base potassium hexamethyldisilazide (KHMDS)-catalyzed diastereoselective reaction of nitroolefins **139** with α-isocyano substrates **140** bearing an electron-withdrawing group to produce the Barton–Zard intermediate 3,4-dihydro-2*H*-pyrroles **141** as a racemic product (Scheme 41). This diastereomerically pure (±)-3,4-dihydro-2*H*-pyrroles [(±)-**141**] on treatment with quinine-derived thiourea **30** and 5 Å MS (molecular sieves) in toluene at 30 °C underwent enantioselective aromatization, thereby providing (+)-3-aryl pyrroles [(+)-**142**] in good yield with 76–93% ee, and recovered (+)-3,4-dihydro-2*H*-pyrroles [(+)-**141**] in 50–98% ee. The subsequent aromatization of the resolved (+)-**141** in the presence of another quinidine-derived catalyst **31** in toluene at 30 °C furnishes the (−)-3-aryl pyrroles [(−)-**142**] in 93–100% yield with excellent central-to-axial chirality transfer.

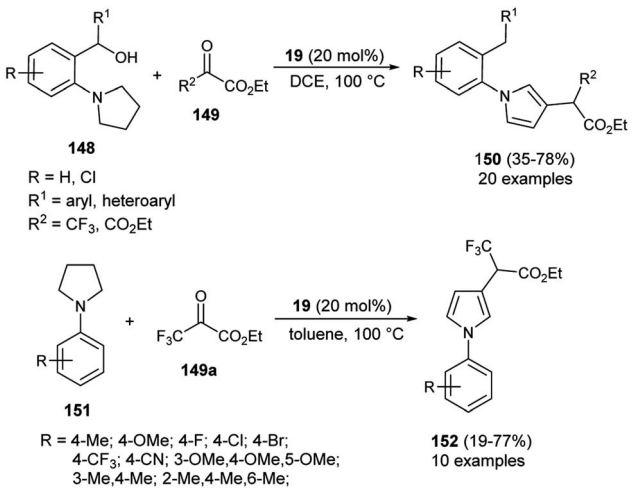


Scheme 42 Organocatalytic cycloisomerization reactions to access substituted pyrroles **144**.

7. Other strategies for the synthesis of pyrroles

In 2019, Meng *et al.*[58] reported that the substrates *Z*-1-iodo-4-*N*-methylbenzenesulfonyl-1,6-enynes **143** bearing vinyl iodide and *N*-propargylamine underwent a cycloisomerization reaction in the presence of organocatalyst **10** and KO*t*Bu in THF at −10 °C, and thereby provided the functionalized pyrroles **144** from non-aromatic to aromatic systems in 44–79% yield within 10 minutes (Scheme 42), although the effect of the organocatalyst in this radical initiation transformation is not clearly described in the report. However, the author suggested a mechanistic pathway for this reaction, which initially involves the homolytic cleavage of the C–I bond of **143** under the influence of complex **145** (**10** and *t*-BuOK), leading to the formation of a vinyl radical **143a** and complex **146** with subsequent removal of the iodide anion. The abstraction of hydrogen by **146** from the propargylic position furnishes the complex **147** that reconverted into the catalyst **145** by treating with iodide. The double radical **143b** undergoes intramolecular cyclization followed by isomerization in the presence of KO*t*Bu and aromatization to yield the corresponding pyrroles **144**.

In 2020, Zhou and his co-workers demonstrated an unprecedented cascade β-functionalization/aromatization reaction of *N*-aryl pyrrolidines for the synthesis of diverse β-substituted aryl pyrroles embedded with trifluoromethyl groups by using 20 mol% of 1,1&-binaphthyl-2,2-diyl hydrogen phosphate **19** as the Brønsted acid catalyst in 1,2-dichloroethane (DCE) as the solvent at 100 °C. The reaction of *N*-aryl pyrrolidines **148** with



Scheme 43 Organocatalytic hydride transfer strategy to access pyrroles **150** & **152**.

ketoesters **149** provided the corresponding β-functionalized pyrroles **150** in 35–78% yields (Scheme 43).[59] This reaction proceeded through the intramolecular [1,5]-hydride transfer (HT) initiated cascade reaction sequence. It is pertinent to note that various halogens present on the aromatic rings and other aromatic rings, such as naphthalene, acenaphthene, biphenyl, furan, and thiophene, were well tolerated with this transformation. They also expanded the methodology for the synthesis of other pyrrole derivatives **152**, and the desired product was obtained in 19–77% yield. To obtained the best yield of the product, the solvent system was replaced by toluene instead of DCE, and the transformation was carried out *via* intermolecular HT-initiated β-C(sp^3)–H functionalization/aromatization sequence.

8. Conclusion

In this review, we have summarized the up-to-date advances on the utilization of organocatalysts for the synthesis of various pyrroles over the last decades. On behalf of the appropriate understanding and a convenient presentation, the article is classified according to the two-component synthesis, multi-component synthesis, multistep synthesis, formal [3 + 2] cycloaddition, synthesis of axially chiral pyrroles, as well as other synthetic strategies. After the renaissance of organocatalysis, the growth in the field of organic synthetic chemistry for the construction of diverse biologically active building blocks in asymmetric, as well as non-asymmetric fashion, has reached an exceptional level in this century. It can be categorized into several activation modes, including amine catalysis, phase-transfer catalysis, hydrogen-bonding catalysis, and others. In sharp contrast devoted towards its development, the synthesis of pyrrole molecules by organocatalytic strategy is limited. However, several metal-free approaches have been discovered, even though they all are not considered organocatalytic routes. Although remarkable results were obtained, the

development of very effective and concise organocatalytic methods for the pyrrole synthesis is still desired. We hope these reviewed methods provide fundamental support to design and develope novel synthetic strategies to access these five-membered *N*-heterocycles that could be of interest in medicinal chemistry, material sciences, as well as many branches of chemistry.

Conflicts of interest

There are no conflicts to declare.

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