ARTICLE

Synthesis of chiral systems featuring the pyrrole unit: a review

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Synthetic strategies towards pyrroles within chiral frameworks are summarised, focussing on reports published 2010-2023. The synthesis of pyrroles featuring substituents bearing chiral centres are summarised, as are those whereby pyrroles are located within axially chiral systems courtesy of restricted bond rotation.

Introduction

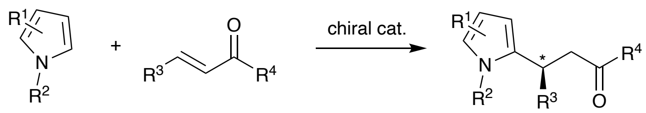
The pyrrole unit is ubiquitous given its role in chlorophyll and heme. Furthermore, many natural products sourced from marine and terrestrial environments feature the pyrrole unit.[1] By following a format similar to that used in our previous review of chiral pyrrolic molecules, published in 2010,[2] we herein summarise subsequent reports regarding the synthesis of chiral pyrroles. We have grouped the various synthetic strategies into six sections, delineated by the position at which chirality is attached and/or by the molecular framework in which the pyrrole unit is embedded: (i) chirality at the α-position; (ii) chirality at the β-position; (iii) chirality at the nitrogen atom; (iv) chirality of pyrroles annulated through the α-position and nitrogen atom; (v) chirality of pyrroles annulated through the α- and β-positions; and (vi) axially chiral pyrroles. Although recent works summarise pyrroles with focus on application or a specific synthetic route,[3–9] we herein review the various approaches leading to chiral systems featuring the pyrrole unit. We apologise to those authors whose work we have not included. Search parameters included structural alignment of the pyrrolic core with words such as chiral, stereoselective, enantioselective, diastereoselective, racemic, asymmetric and axial. In sorting the results and summarising the themes for inclusion herein, we intentionally omitted oligomeric structures and nanomaterials containing pyrroles, and those whereby the molecular structure is not fully characterised.

Chirality at the α-position

The pyrrole heterocycle is considered aromatic and electron-rich courtesy of six π-electrons across the five-atom ring. Sharing a convention used in porphyrin chemistry, the carbon atoms next to the nitrogen atom in pyrrole are often termed the alpha(α)-position, and the adjacent ones are termed the beta(β)-positions. Each of these positions may bear substituents to functionalise (*e.g.*, stabilise) the pyrrole core and/or to decorate the framework. Synthetic strategies towards pyrroles appended with moieties that feature chirality at the α-position are summarised in this section.

Friedel-Crafts with α,β-unsaturated ketones and aldehydes

Several reports focus on stereoselective 1,4-Friedel-Crafts (FC) alkylations at the α-position of pyrroles using α,β-unsaturated aldehydes and ketones bearing various substituents (**Scheme 1**).[10–17] Several of these works also include examples featuring indoles[12,14,16] and dihydroindoles.[16]



*Both enantiomers available in high enantiomeric ratio by varying catalysis conditions

Scheme 1. FC reaction of pyrroles with α,β-unsaturated aldehydes and ketones.

An asymmetric imidazolethione organocatalyst was employed towards the high-yielding synthesis of products featuring various aryl and alkyl R^3-substitutuents (**Scheme 1**). Using pyrrole and *N*-Me pyrrole as starting materials, enantiomeric ratio (er) values up to 98.5:1.5 were obtained.[10] A similar asymmetric imidazolidinone-based catalyst was phosphorylated to enable a group-assisted purification (GAP) handle for the purpose of recycling the catalyst.[11] Indeed, several examples involved *N*-methyl pyrrole and a variety of aryl and alkyl R^3 groups, and the catalyst was recycled and reused three times without significant loss in performance. Similarly, Zn(II)[13,14] complexes of 2,6-bis(5′,5′-diphenyloxazoline)pyridine (PYBOX) chiral ligands catalysed the FC alkylation of pyrroles with substituted-2-enoylpyridine *N*-oxides (R^3 = Ar or alkyl) with er values reaching >99:1. *N*-Substitution of pyrrole with a (1-piperidinyl)carbonyl group resulted in a directed FC alkylation involving crotonates and α,β-unsaturated ketones. Excellent er values were achieved when the reactions were catalysed by Ir(I)[16] complexes of 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP).

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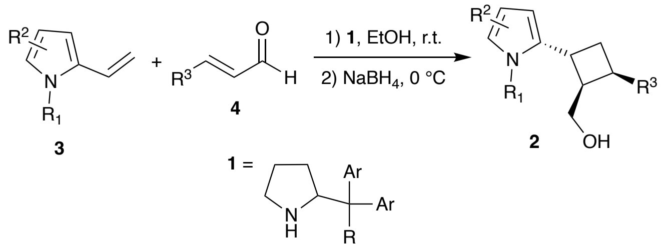
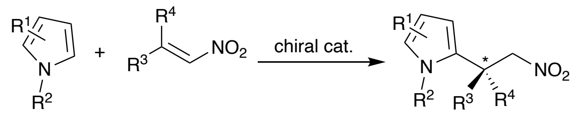
A formal [2+2] cycloaddition sequence was catalysed by a proline-derived organocatalyst **1** (whereby the absolute stereochemistry of the proline was (*S*), and the substituent pattern included Ar = Ph, R = OTMS). The reaction provided pyrroles **2** substituted with cyclobutanes and featuring three contiguous chiral centres.[17] The reaction proceeded *via* a FC alkylation involving 2-vinylpyrroles (**3**) and α,β-unsaturated aldehydes (**4**), followed by reduction (**Scheme 2**). The cyclobutanes were synthesised in good yield and with er values reaching 99:1. The proposed mechanism begins with activation of the enal with the catalyst to form a chiral iminium ion. The 2-vinylpyrrole then adds, *via* the unshielded *Si*-face, to generate a chiral triiminium intermediate that is trapped by an enamine to generate another chiral iminium intermediate that immediately undergoes hydrolysis to release the product from the catalyst.



Scheme 2. Synthesis of cyclobutane derivatives.

Friedel-Crafts with nitroalkenes

The addition of pyrroles to nitroalkenes in the presence of chiral catalysts provides another route to chiral pyrroles (**Scheme 3**).[18–26] For example, a 1,1′-bi-2-naphthol (BINOL)-based chiral phosphoric acid (CPA) was used to provide substituted pyrroles with er values up to 97:3 and yields up to 94% over a wide range of substrates.[19] Interestingly, the proposed mechanism involves hydrogen bonding between the N–H of the pyrrole and the phosphoryl oxygen atom of the catalyst. As such, *N*-substituted pyrroles were not well-tolerated. A subsequent system involving a chiral calcium phosphate provided access to all-carbon quaternary centre-containing products with er values reaching 99:1.[21] Notably, screening of the chiral phosphates of alkali metals and alkaline-earth metals revealed that only those of magnesium and calcium promoted the desired reaction.

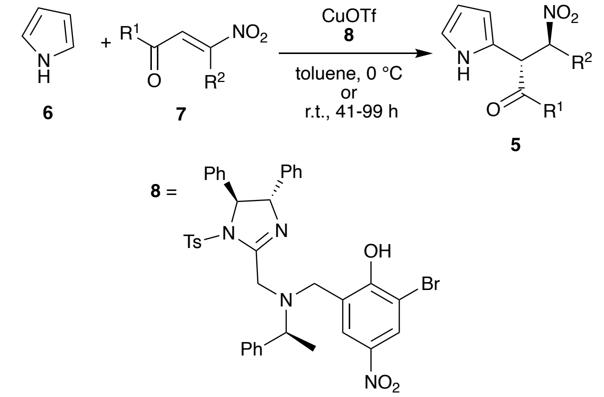


*Both enantiomers synthesised in high er by varying catalysis conditions

Scheme 3. FC reaction of pyrroles with nitroalkenes.

The use of Schiff base chiral ligands and a copper source enabled FC alkylation of pyrroles with nitroalkenes.[22–24] One report describes the evaluation of novel bisphenol A-derived chiral ligands,[23] resulting in er values up to 99.5:0.5 for a range of aryl nitroalkenes and pyrrole. Again, the use of *N*-Me pyrrole did not provide the desired product. Catalyst modification enabled desirable reactivity in aqueous medium with similar selectivity and scope.[24] Another report[22] describes catalysis by a tridentate Schiff base–copper complex, resulting in products with er values up to 99:1 with excellent yields for aryl, heteroaryl and alkyl nitroalkenes.

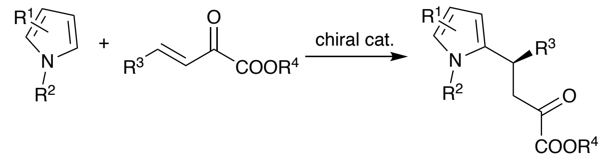
Functionalised products **5** were obtained with er values reaching 96:4, yet with varying diastereoselectivity, when FC addition of pyrrole (**6**) to α-substituted nitroalkenes (**7**) was catalysed by a imidazoline-aminophenol (**8**) and Cu(I) complex (**Scheme 4**).[25]



Scheme 4. FC addition/protonation of pyrroles and α-substituted nitroalkenes.

Friedel-Crafts with ketoesters

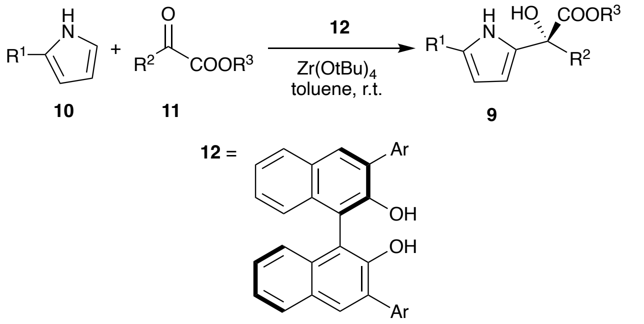
Friedel-Crafts alkylations include the addition of pyrroles to β,γ-unsaturated α-ketoesters (**Scheme 5**).[27–29] One example utilised a dicationic palladium complex with sterically hindered diphosphine ligands to facilitate the asymmetric FC alkylation of *N*-Me pyrrole with β,γ-unsaturated α-ketoesters[27] with excellent yields and er values >99.5:0.5. In another report, it was found that a chiral heteroarylidene-tethered Ph-bis(oxazoline)–Cu(OTf)$_2$ complex effective catalysed the FC alkylation of pyrrole with β,γ-unsaturated α-ketoesters:[28] er values reached 96:4. Later, using a chiral Cu(II)-prolinol derivative complex, the FC alkylation of pyrrole with β,γ-unsaturated α-ketoesters was reported with an er of up to 99:1.[29]



*Both enantiomers synthesised in high er by varying catalysis conditions

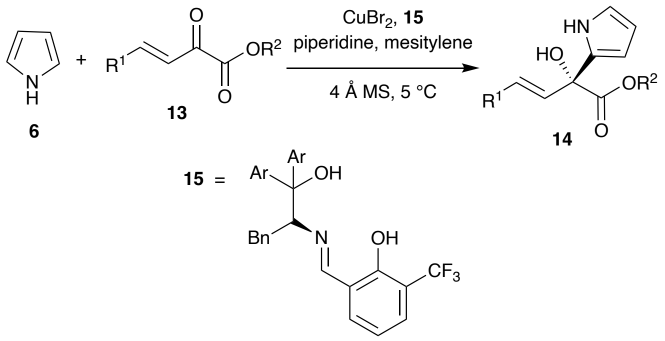
Scheme 5. FC alkylation of pyrroles with unsaturated β,γ-unsaturated α-ketoesters.

A BINOL-derived ligand, in the presence of zirconium *tert*-butoxide, provide an effective catalyst system for the enantioselective synthesis of chiral pyrroles featuring tertiary alcohols (**9**) through the 1,2-addition of pyrroles (**10**) to α-ketoesters **11** (**Scheme 6**).[30] Steric interaction between a naphthyl group on the chiral ligand **12** (Ar = 3,5-(CF$_3$)$_2$C$_6$H$_3$) and the carbonyl group effectively blocks *Si*-face attack by the pyrrole, thus providing er values reaching 96:4.



Scheme 6. Synthesis of tertiary alcohols *via* reaction of pyrroles with α-ketoesters.

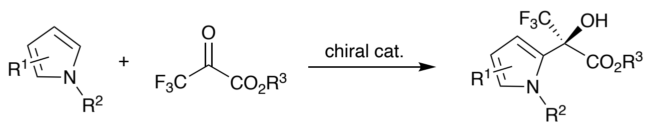
Later, researchers described a chemoselective FC reaction of pyrrole and β,γ-unsaturated α-ketoesters (**13**) to give tertiary alcohols (**14**, **Scheme 7**).[31] In the presence of a catalyst system comprising Schiff-base **15** (Ar = *p*-MeC_6H_4) and Cu, products were formed in excellent yields and with er values up to 95:5. The proposed regioselectivity involves activation of the ketoester through Cu chelation, along with hydrogen bonding of the complexed ligand with the N–H of pyrrole to thus direct enantioselective addition to the adjacent *Re*-face of the β,γ-unsaturated α-ketoester.



Scheme 7. FC 1,2-addition of pyrroles and β,γ-unsaturated α-ketoesters.

Friedel-Crafts reactions with trifluoroacetyl substrates

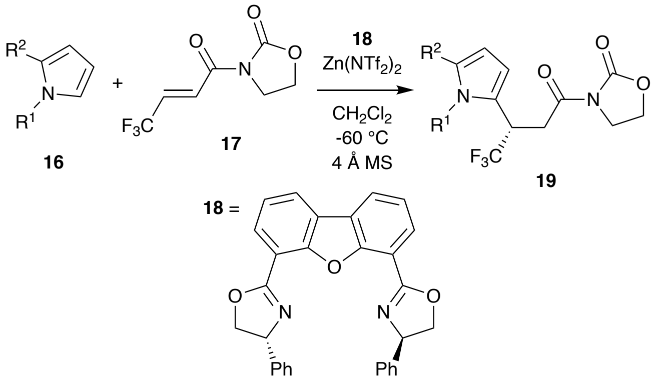
Trifluoroacetyl substrates are used to access CF_3-containing analogues of chiral compounds with the goal of enhancing the pharmacokinetic and pharmacodynamics of drug-like molecules.[32] Various reports focus on the enantioselective 1,2-addition of pyrroles to trifluoropyruvates (**Scheme 8**). One group performed the alkylation of pyrroles through the use of a CPA catalyst,[33] and another utilised a dicationic BINAP-type Pd chiral complex.[34] Yields were generally excellent with er values reaching 99.5:0.5, although the use of *N*-Boc protected pyrroles lacking substitution about the ring was less constructive. In other work, a racemic oxyalkylation involved reaction of pyrroles with various 2-(trifluoroacetyl)-1,3-azoles: regioselectivity and yields of products varied with electronic and steric properties.[35] Related work describes the enantioselective addition of a silyl-protected propargylic boron-containing species to pyrroles bearing trifluoromethyl ketones.[36]



Scheme 8. Synthesis of tertiary alcohols through reaction of pyrroles with trifluoropyruvates.

Friedel-Crafts with acrylates

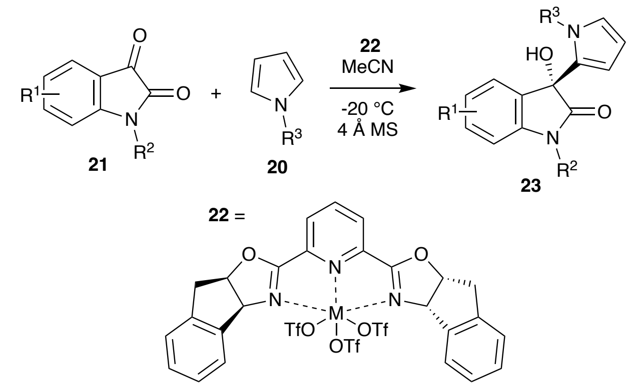
Another class of FC alkylation that has led to the introduction of chiral appendages at the α-position of pyrroles (**16**) involves addition to β-trifluoromethylated acrylates (**17**), promoted by a Zn Lewis acid and the chiral ligand **18** (**Scheme 9**).[37] Products (**19**) were formed in yields up to 99% with er values reaching 99.5:0.5. Follow-up work expanded the scope, alongside a proposal that 1,4-addition of pyrrole to the activated acrylate was followed by enantioselective protonation of the intermediate enolate.[38]



Scheme 9. Alkylation of pyrrole with β-trifluoromethylated acrylates.

Friedel-Crafts with isatins

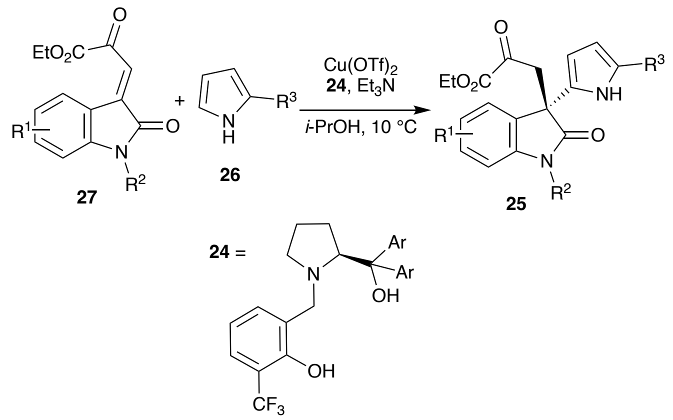
There are a number of reports that focus on the addition of pyrroles to isatins (tribulins, **21**), which is a motif found in natural products and drug candidates.[39–41] For example, the indium$(OTf)_3$-pyBOX catalyst **22** promotes the addition of pyrroles to isatins to afford products **23** with er values reaching 99.5:0.5 (**Scheme 10**).[40] Other work explored an enantioselective FC alkylation of pyrroles with isatins through the use of a tridentate Schiff base/Cu complex.[41] Although the presence of hexafluoroisopropanol, as an additive, was noted as key to the reaction achieving high enantioselectivity, the proposed critical transition state features coordination of the isatin to the asymmetric Cu catalyst, thus inhibiting addition of the pyrrole to the *Re*-face of the isatin.



*Both enantiomers synthesised in high er by varying catalysis conditions

Scheme 10. FC addition of pyrroles to various isatin derivatives.

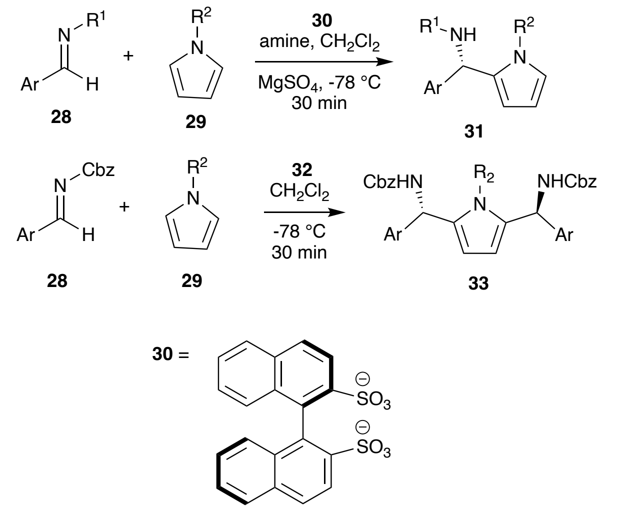
In a subsequent report,[39] the use of a proline-derived chiral ligand (**24**, Ar = *p*-$MeOC_6H_4$) expanded the scope of the methodology to include regioselective and highly stereoselective synthesis of pyrroles **25** bearing substituents featuring quaternary chiral centres from pyrroles (**26**) and isatins (**27**, **Scheme 11**).



Scheme 11. FC addition of pyrroles to various isatin derivatives.

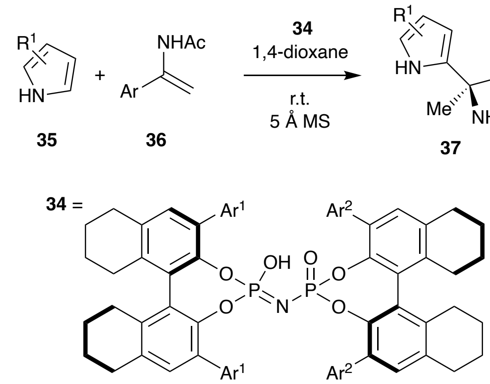
Friedel-Crafts with imines, enamides and sulfimines

There have been some reports of enantioselective FC aminoalkylations of pyrroles and aldimines. One group reported aminoalkylation between Cbz- and Bn-protected aldimines (**28**) and *N*-benzylpyrrole **29** (**Scheme 12**, top).[42] This reaction utilised a chiral BINSA–*N,N*-dimethylbutylamine salt (**30**) acting as a dynamic Brønsted acid–base catalyst system. Products (**31**) were formed in yields of up to 92% with er reaching 99.5:0.5. Subsequent work focused on use of ammonium BINSate catalysts (**32**), *i.e.*, a silica supported heterogeneous system, which proved effective in generating pyrroles **33** *via* the enantioselective FC double aminoalkylation of aldimines with *N*-benzyl pyrrole (**Scheme 12**, bottom).[43]



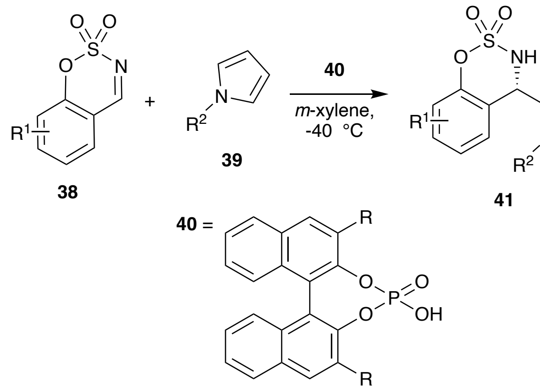
Scheme 12. Aminoalkylation of pyrroles to aldimines.

A chiral BINOL-[H8] imidodiphosphoric acid catalyst (**34**, Ar^1 = 2-naphthyl, Ar^2 = 2-naphthyl) effects the asymmetric addition of pyrroles **35** to enamides **36** and *N*-Ts benzaldimines. Products **37** were formed with er values reaching 99:1 (**Scheme 13**).[44] The use of activated 5 Å molecular sieves was reported to promote reactivity and was found to be essential for optimal er values.



Scheme 13. FC addition of pyrroles to enamines.

The enantioselective CPA-catalysed addition of pyrroles (**9**) to cyclic *N*-sulfimines (**38**) has also been successful, thereby providing access to frameworks of interest as pharmacophores (**Scheme 14**).[45] The use of BINOL-derived CPA catalyst **40** (whereby the catalyst stereochemistry was (*S*), and the substituent constituted an iodo substiuent, *i.e.*, R = I) was compatible with reaction of many cyclic *N*-sulfimines, affording products **41** in yields reaching 92% with er values up to 98.5:1.5.



Scheme 14. Reaction of pyrroles with cyclic *N*-sulfimines.

Work in this vein often targets indoles, yet some substrate scope studies include at least one pyrrolic example such as **42-47** (**Figure 1**).[46–52]

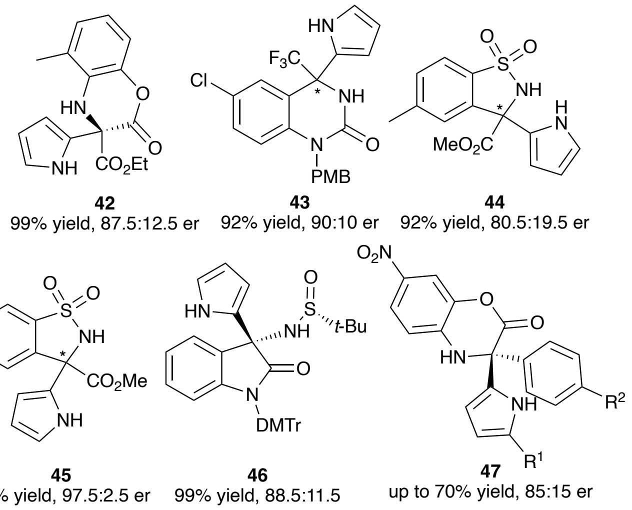
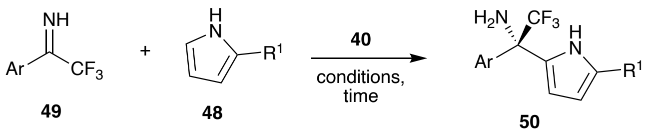


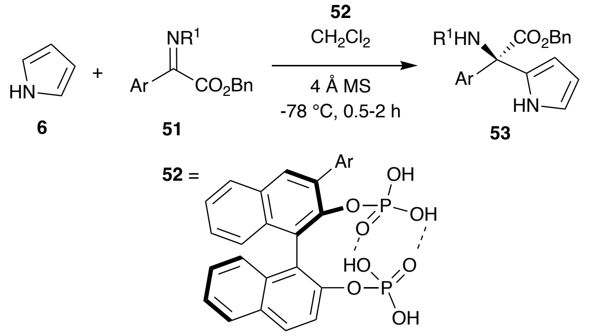
Figure 1. FC alkylation of pyrroles with ketimines and sulfimines.

An enantioselective FC alkylation of pyrroles (**48**) with *N*-unprotected trifluoromethyl ketimines (**49**) involves the use of a BINOL-derived CPA catalyst **40** ((*R*), R = 2,4,6-(iPr)$_3C_6H_2$) (**Scheme 15**).[53] Chiral pyrroles (**50**) were synthesised in excellent yields and with er values up to 98.5:1.5. Curiously, the use of analogous *N*-protected trifluoromethyl ketimines resulted in no reaction – perhaps shedding light on a hydrogen-bonding interaction between the imine and the CPA. In other work,[54] the addition of pyrroles to isatin-derived *N*-Boc ketimines is promoted by CPA catalysis, and again the use of activated molecular sieves is key to excellent enantioselectivity. Another report showcased similar reactivity for alkynyl trifluoromethyl ketimines.[55]



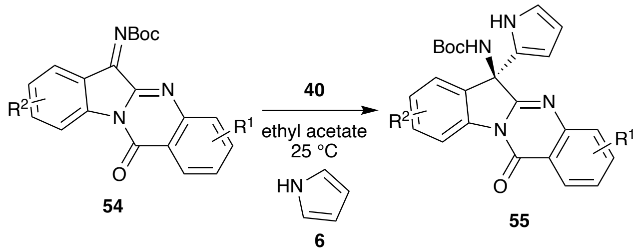
Scheme 15. CPA-promoted reaction of trifluoromethylated imines and pyrroles.

Enantioselective FC alkylation of pyrrole with acyclic α-ketimino esters (**51**) is also catalysed by a BINOL-derived bis(phosphoric acid) catalyst (**52**) to provide pyrroles **53** appended with all-carbon quaternary chiral centres with er values of up to 99:1 (**Scheme 16**).[56] Notably, the absolute configuration of the products for pyrrolic versus indole examples are opposite despite the use of the same catalyst. A preliminary study of mechanistic considerations suggested that the greater π-π stacking interaction of indoles with the catalyst preferentially affords *Si*-face attack.



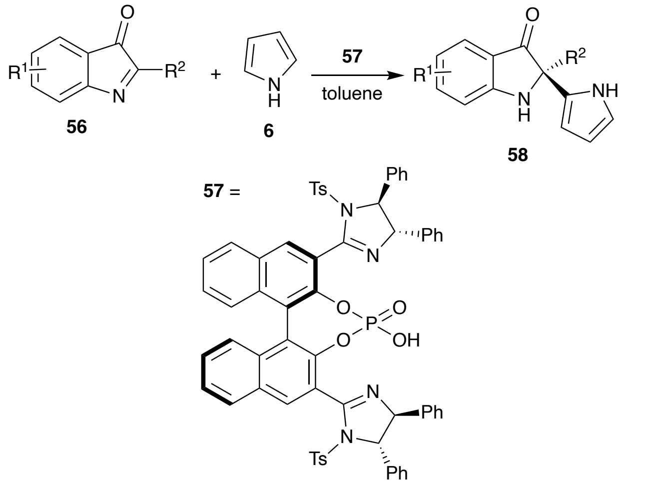
Scheme 16. CPA-promoted FC addition of pyrroles to α-ketimino esters.

Furthermore, the enantioselective aza-FC reaction of ketimines **54** and pyrrole in the presence of a BINOL-derived CPA catalyst (**40**, (*S*), R = 1-pyrenyl) was showcased (**Scheme 17**).[57] The resulting tryptanthrin derivatives (**55**) present interesting drug-like properties. Products were formed in yields up to 99% with er values reaching 99:1.



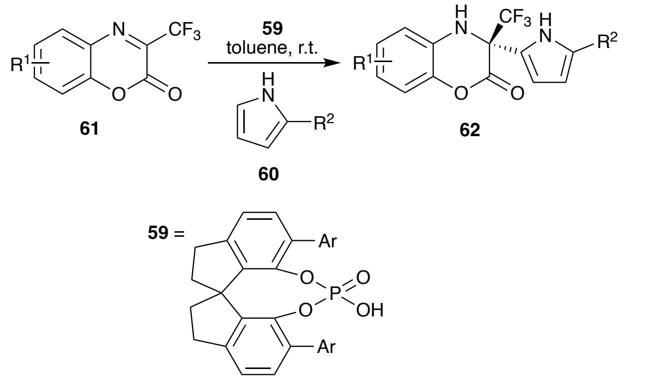
Scheme 17. Enantioselective synthesis of tryptanthrin derivatives.

The addition of pyrrole to cyclic ketimines (**56**), through the use of the BINOL-derived CPA catalyst system **57**, focussed on synthesis of indoline-3-ones (**58**) with an all-carbon atom chiral centre at the pyrrolic α-position (**Scheme 18**).[58] Yields broached 99% with er values reaching 99.5:0.5. This work was expanded to showcase examples of various substitutions on pyrrole, and the key transition state was hypothesised to involve three synergistic hydrogen bond interactions serving to both activate the substrates as well as position them for optimal enantioselectivity. Excellent recovery/reusability of the catalyst was demonstrated.



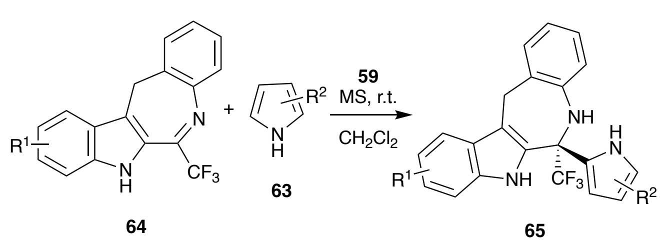
Scheme 18. CPA promoted addition of pyrroles to cyclic ketimines.

A SPINOL-derived CPA catalyst (**59**, (*R*), Ar = 2,4,6-(iPr)$_3$C$_6$H$_2$) was used to perform the enantioselective FC alkylation of pyrroles with trifluoromethyl benzoxazinones (**61**, **Scheme 19**).[59] Brief mechanistic investigations involving experimental and computational work revealed the importance of a triple hydrogen bond arrangement in the transition state. The CF$_3$ moiety was indicated as a hydrogen-bond acceptor to effectively lock the 3-dimensionality of the transition state and hinder *Si*-face addition: products (**62**) were formed in yields up to 96% and up to 98.5:1.5 er values.



Scheme 19. FC reaction of pyrroles with trifluoromethyl benzoxazinones.

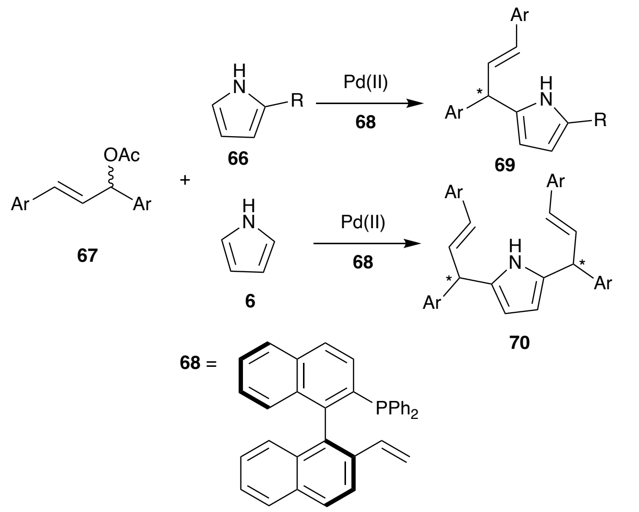
Another report showcases an enantioselective FC reaction of pyrroles with trifluoromethyl dihydrobenzoazepinoindoles (**64**, **Scheme 20**).[60] This reaction was catalysed using a SPINOL-derived CPA (**59**, (*R*), Ar = 2,4,6-(iPr)$_3$C$_6$H$_2$) to afford products (**65**) in yields up to 93% and er values up to 96.5:3.5. Multiple hydrogen bonds in the transition state, and the activating effect of the CF$_3$ group, combine to control the enantioselectivity of facial attack.



Scheme 20. FC alkylation with trifluoromethyl dihydrobenzoazepinoindoles.

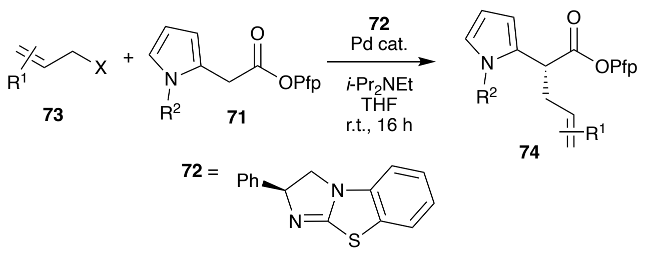
Allylic alkylations

The asymmetric allylic alkylation of pyrroles with 1,3-diaryl-2-propenyl acetates (**67**) proceeds in the presence of the Pd-based chiral alkene-phosphine ligand **68**, with yields of products (**69**) reaching 99% and er values up to 99:1 with reasonable diastereoselectivity for dialkylations (**70**, **Scheme 21**).[61] *N*-Methylated pyrrole was not a suitable substrate for the reaction. Subsequent work explored substate scope tolerance and optimised ligand choice to result in yields of up to 97% and er values reached 98.5:1.5.[62]



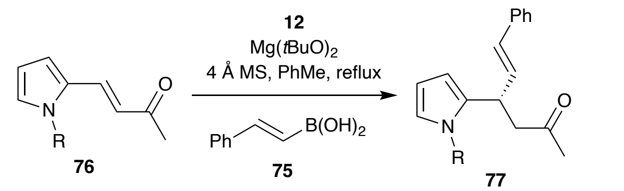
Scheme 21. Allylic alkylation(s) of pyrroles with 1,3-diphenyl-2-propenyl acetate.

An enantioselective allylic alkylation of pyrroles already appended with acetate functionality at the α-position (**71**) proceeds in the presence of a cooperative Lewis base isothiourea (**72**) and palladium catalyst system (**Scheme 22**).[63] Although differing from the reactions discussed above insofar as not relying on the nucleophilicity of the pyrrole for the enantioselective step, reaction with allylic sulfonates, phosphonates and carbonates (**73**) provided the desired compounds **74** in yields of up to 90% with er values reaching 98:2 for various *N*-substituted pyrroles.



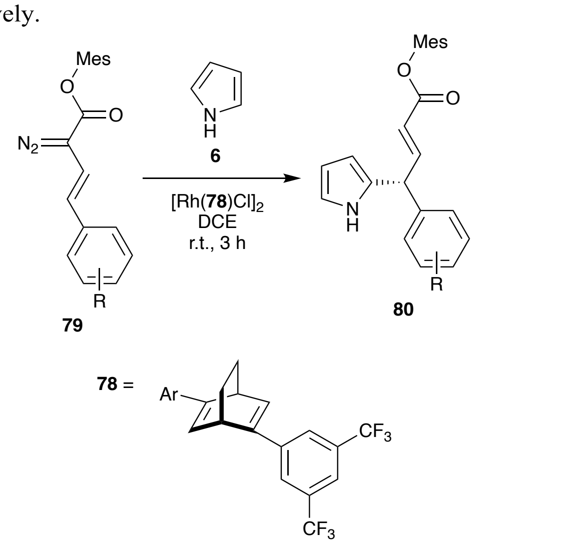
Scheme 22. Enantioselective allylic alkylation of pyrrole acetic acid esters.

The addition of allyl boronic acids to β-pyrrolylenones **76** in the presence of a BINOL catalyst **12** (Ar = (p-CF_3)C_6F_4) and a magnesium-based Lewis acid (**Scheme 23**) provided pyrroles **77** appended with chiral centres: yields reached 90% and er values broached 98.5:1.5.[64]



Scheme 23. Addition of alkenyl, alkynyl, and arylboronate esters to β-arylenones.

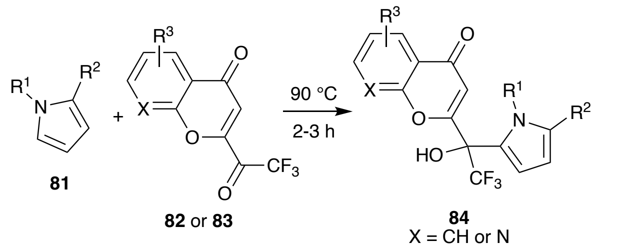
A direct enantioselective C-H functionalisation of pyrrole was explored using a Rh(I) and a chiral carbene **78** (Ar = Ph or 3,5-(CF_3)$_2C_6H_3$) system (**Scheme 24**).[65] Arylvinyldiazoesters (**79**) were reacted with pyrrole to form the desired products (**80**) in yields up to 91% with er and E:Z values of 99.5:0.5 and >99:1, respectively.



Scheme 24. Enantioselective C-H functionalisation of pyrrole with arylvinyldiazoesters.

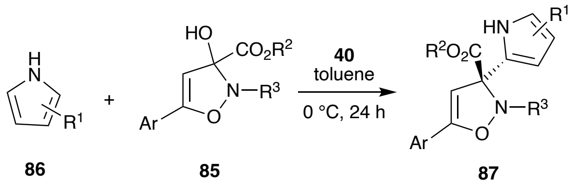
Miscellaneous pyrrole-carbon bond forming reactions

In addition to the alkylations mentioned above, several reports feature reactions using specialised FC acceptors. The uncatalysed 1,2-addition of pyrroles to chromones (**82**, X = CH) or azachromones (**83**, X = N) provides racemic products (**84**), with yields reaching 95% (**Scheme 25**).[66,67]



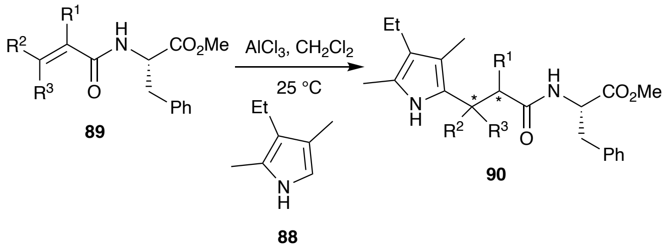
Scheme 25. Racemic synthesis of pyrroles featuring chromones.

The nature of counterions were demonstrated critical through the *in situ* generation of isoxazolium ions in the presence of BINOL-derived CPA catalysts (**40**, (S), R = 2,4,6-(iPr)$_3C_6H_2$) (**Scheme 26**).[68] Asymmetric counteranion-directed FC alkylation involving isoxazoles (**85**) and pyrroles provided products (**87**) in yields up to 99%, with er values reaching 99.5:0.5.



Scheme 26. FC reaction of pyrroles with isoxazolium ions.

Another team used an achiral catalyst system for FC alkylation of 2,4-dimethyl-3-ethylpyrrole (**88**) with chiral acrylamides (**89**) under mild Lewis acidic activated conditions (**Scheme 27**).[69] Although yields for some products (**90**) reached 80%, achieving high diastereoselectivities for the FC alkylations proved challenging. The substrate scope included cyclic chiral acrylamides, including α,β-unsaturated γ-lactams and α,β-unsaturated piperidinones.



Scheme 27. Addition of pyrroles with enantiorich acrylamides.

There are a number of examples[70–76] of FC alkylation reactions, including some that are asymmetric, that mostly focus on the reactivity of indoles yet have substrate scopes that included at least one pyrrolic example, with some featuring intriguing functionalisation patterns as shown in **91-94** (**Figure 2**).

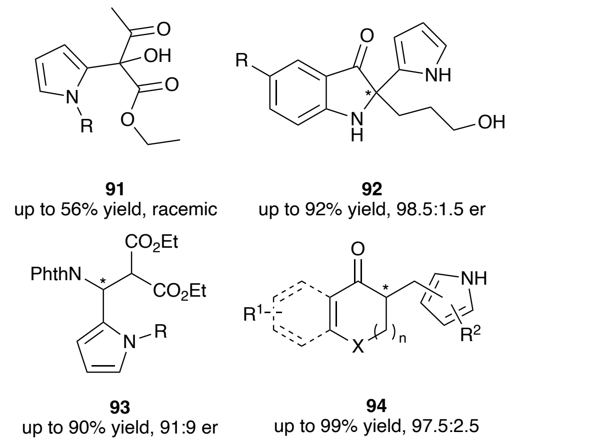
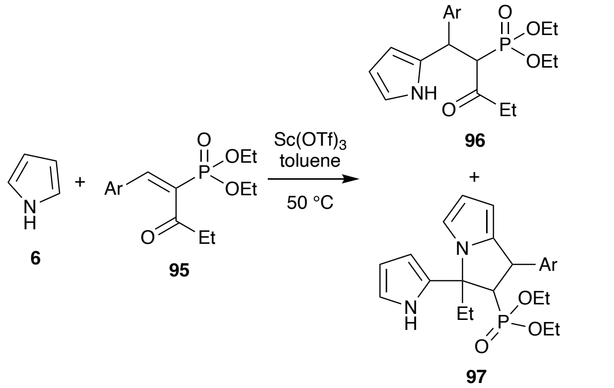


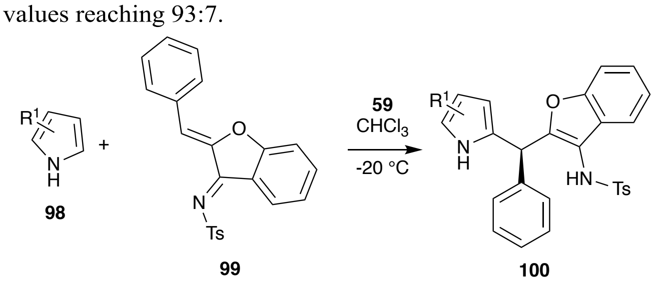
Figure 2. Chiral pyrroles α-functionalised *via* FC reactions.

A racemic 1,4-alkylation/ring annulation reaction sequence between α-phosphoryl-α,β-unsaturated ketones (**95**) and pyrrole proceeds in the presence of scandium triflate (**Scheme 28**).[77] The diastereoselctivities were not explored, and yields reached 73% and 63% for addition (**96**) and cyclisation (**97**), respectively, dependent upon the nature of the aryl substrate within the acceptor.



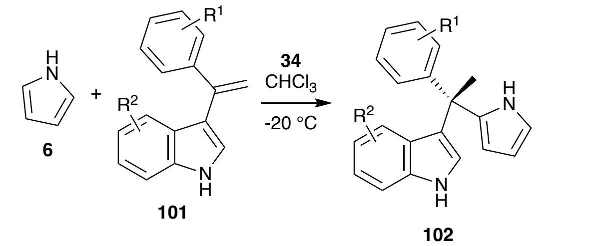
Scheme 28. Alkylation of pyrrole using α-phosphoryl-α,β-unsaturated ketones.

An enantioselective synthesis of heterotriarylmethanes arises through the 1,4-addition of indoles, furans and pyrroles to azadienes (**99**, **Scheme 29**).[78] A chiral SPINOL-derived CPA catalyst (**59**, (*S*), Ar = 9-anthracenyl) was employed to afford functionalised pyrroles (**100**) in yields of up to 95% with er values reaching 93:7.



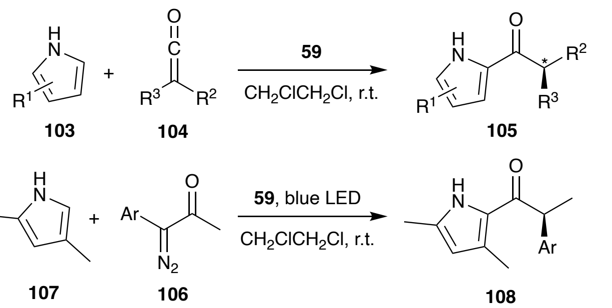
Scheme 29. Enantioselective synthesis of heterotriarylmethanes.

A chiral BINOL-[H8] imidodiphosphoric acid catalyst (**34**, Ar^1 = 3,5-$(CF_3)_2C_6H_3$, Ar^2 = 2-naphthyl) promoted the enantioselective addition of pyrrole to 3-vinylindoles (**101**) affording 1,1,1-triarylethanes (**102**, Scheme 30):[79] yields reached 99%, with er values up to 99:1. The enantioselectivity was proposed to arise as a consequence of the 3,3′-substitution of the catalyst shielding the *Re*-face of a vinylogous iminium intermediate. In related work, a 1,1,1,1-tetraarylmethane featuring pyrrole was showcased *via* 1,8-addition to triaryl methyl alcohols in the presence of a CPA catalyst.[80] Products were afforded in yields up to 99% with er values reaching 98.5:1.5.



Scheme 30. Synthesis of 1,1,1-triarylmethanes.

The enantioselective addition of unsubstituted pyrrole **103** to ketenes (**104**, **Scheme 31**), in the presence of a SPINOL-derived CPA catalyst (**59**, (*R*), Ar = 9-anthracenyl), provided pyrroles (**105**) bearing chirality pendant from the α-position of the heterocycle: yields approached 93% and er values reached 99:1.[81] With asymmetric additions of carbon-based nucleophiles to ketenes being rare, this example is notable. In the same work, α-diazoketones (**106**) were used to generate ketenes *in situ*, *via* Wolff rearrangement, and reacted with 2,4-dimethylpyrrole to afford the corresponding pyrroles (**108**) α-appended with chiral moieties in yields reaching 81% and with er values up to 99.5:0.5.



*Both enantiomers synthesised in high er by varying catalysis conditions

Scheme 31. Addition of pyrroles to ketenes (top) and α-diazoketones (bottom).

In addition to featuring in natural products and serving as key motifs within pharmaceuticals and materials, the complexation properties of pyrrole-containing compounds has garnered much interest. A chiral NNN pincer ligand (**109**) containing a pyrrole framework was synthesised using Paal–Knorr-type cyclisation involving 1,4-diketones (**Figure 3**).[82] Amidation using amino alcohols introduced the two chiral centres, appended to the α-position of the pyrrole. Zn-catalysed cyclisation subsequently delivered the required bis(oxazoline) system with the pyrrole as the central unit. The corresponding Ni(II) catalysts complement the much-studied PmBox catalyst systems.

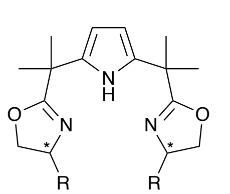


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Figure 3. Chiral pyrrole NNN pincer ligand. R = *(S) i*-Pr, R = *(R)* Ph

Amidation of an α-carboxylated pyrrole and an enantiopure amine was essential to the total synthesis of Nagelamide W (**110**, **Figure 4**).[83] Nagelamide W was isolated in an overall yield of 6% after an 11-step longest linear sequence.

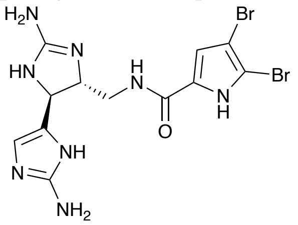

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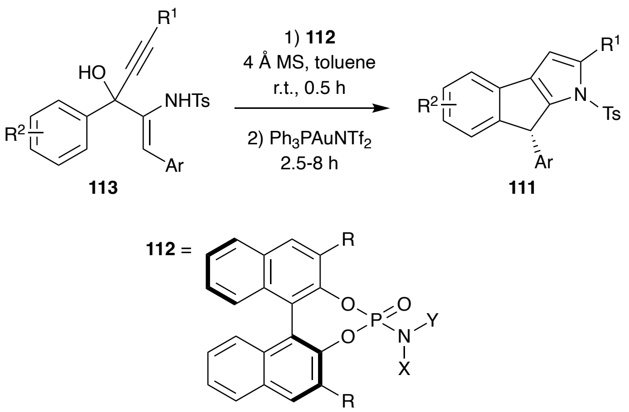
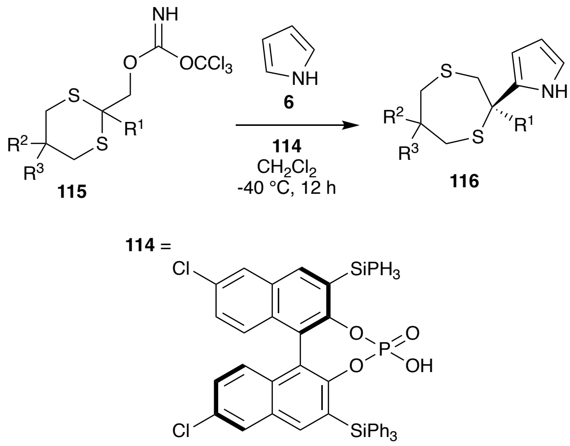
Figure 4. Nagelamide W.

There are a few examples of reactions that generate pyrrole-containing frameworks featuring a chiral centre at the α-position of pyrroles. One such example is the synthesis of 1,8-dihydroindeno[2,1-*b*]pyrroles (**111**) through a chiral BINOL-derived Brønsted acid (**112** , R = (*p*-Ph)C_6H_4, X = H, Y = Tf) and Au(I)catalysed dehydrative Nazarov cyclisation followed by a subsequent hydroamination of *β*-amino-1,4-enyols (**113**, **Scheme 32**).[84] Yields reached 99% with er values up to 99:1.



Scheme 32. Annulated pyrroles with a chiral centre at the α-position.

Other work highlights a (*R*)-BINOL-derived CPA catalyst (**114**) system used towards the enantioselective ring expansion of 1,3-dithianes (**115**) that incorporates a new chiral centre at the α-position of pyrrole or indole (**Scheme 33**).[85] Yields of the corresponding 7-membered ring **116** approached 96% with er values reaching 97:3. The proposed mechanism describes a non-conventional C-H-O hydrogen bond between the conjugate base of the CPA and a cationic intermediate, serving to both bind to the catalyst and effectively lock the stereochemistry such as to maximise regio- and stereoselectivity.



Scheme 33. Enantioselective ring expansion of 1,3-dithianes.

Other reactions that generate pyrroles featuring chirality at the α-position include an asymmetric oxidative coupling with 2-substituted 3-oxindoles (**117**, **Figure 5**,)[86] and a CPA-catalysed stereoselective [3+2] cycloannulation of carbonyl ylides and indolyl-2-methides that were further functionalised with pyrroles (**118**, **Figure 5**,).[87] Enantioselective [4+2] cycloaddition of β,γ-unsaturated α-keto esters and 2-vinylpyrroles, and an intermolecular [2+2] photocyclisation of alkenyl 2-pyrrolyl ketones, also provided pyrroles with high stereopurity.[88,89] Furthermore, a 3-component one-pot synthesis of racemic 3-alkyl/aryl-3-(pyrrole-2-yl/indole-3-yl)-2-phenyl-2,3-dihydro-isoindolinones involves a reusable nanodomain cubic cuprous oxide and proceeds under aqueous conditions (**119**, **Figure 5**,).[90]

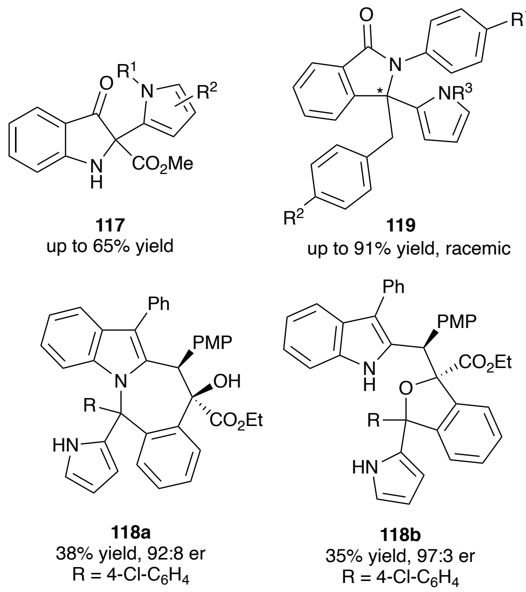
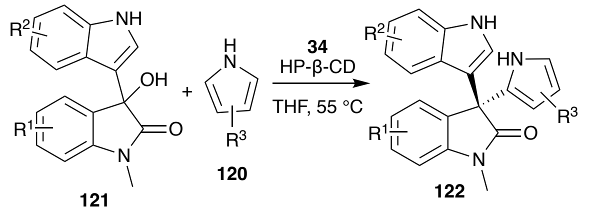


Figure 5. Chiral pyrroles α-functionalised *via* miscellaneous reactions.

The enantioselective reaction of pyrroles and racemic 3-hydroxy-3-indolyloxindoles (**121**) was catalysed by a chiral BINOL-[H8] imidodiphosphoric acid catalyst (**34**, Ar^1 = 1-naphthyl, Ar^2 = 1-naphthyl) alongside use of 2-hydroxypropyl-β-cyclodextrin (HP-β-CD) as an additive (**Scheme 34**).[91] The first step of the proposed mechanistic route involves loss of the hydroxy group from the substrate, *via* formation of a stable chiral ion pair with yields of the prduct (**122**) reaching 99% and er values up to 99:1.



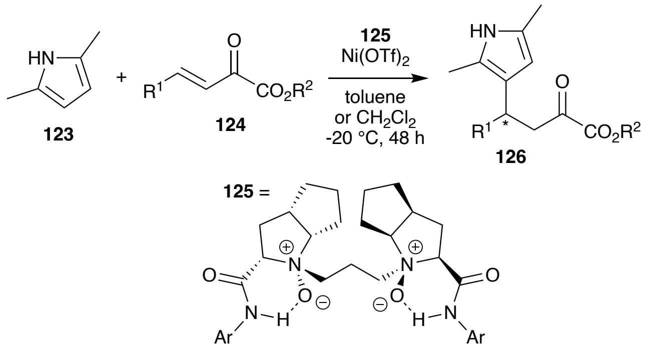
Scheme 34. FC alkylation of pyrroles with 3-hydroxy-3-indolyloxindoles.

Chirality at the β-position

While electrophilic additions to pyrroles are usually regioselective and at the α-position, owing to increased nucleophilicity, there are many examples of stereoselective additions to other sites on pyrroles. In this section, we explore reactions that introduce chiral centres at the β-position of pyrroles, beginning with some examples of FC alkylation reactions.

β-Friedel-Crafts reactions

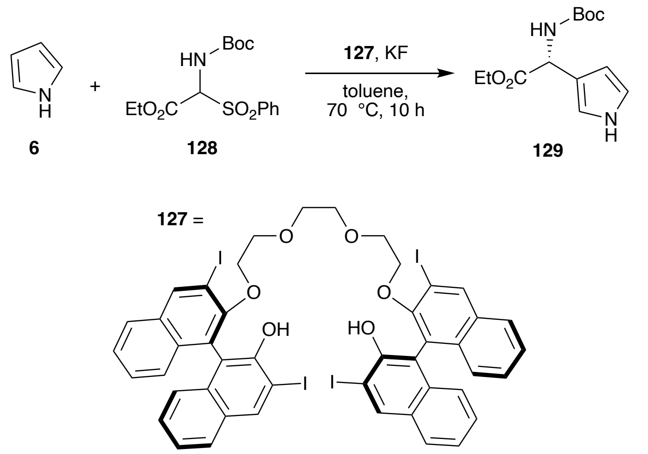
With the two α-positions blocked, 2,5-dimethyl pyrrole was shown to react at a β-position with β,γ-unsaturated α-ketoesters (**124**, **Scheme 35**).[92] The reaction was facilitated by a Ni(II)-complex containing a chiral *N*,*N'*-dioxide ligand (**125**). Products (**126**) were synthesised in yields reaching 95% with er values up to 99.5:0.5. Using calculations and crystallography, the enantioselectivity was rationalised on account of steric effects inhibiting addition to the *Si*-face of the complex.



*Both enantiomers synthesised in high er by varying catalysis conditions

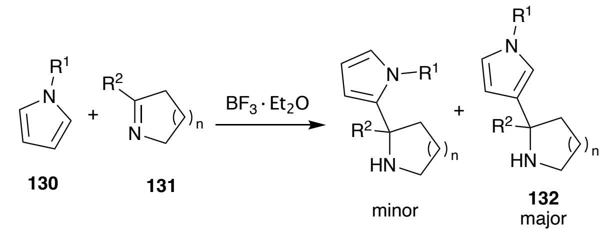
Scheme 35. FC addition of 2,5-dimethyl pyrrole to β,γ-unsaturated α-ketoesters.

In other work, a cooperative catalyst system involving a chiral BINOL-based oligoethylene glycol dimeric cation-binding framework (**127**) and KF, as the base, enabled the enantioselective addition of indoles with α-amidosulfones (**128**) as *in situ* equivalents of sensitive imines.[93] When this work was expanded to include pyrrole (**Scheme 36**), the desired product (**129**) was formed in 74% yield with an er value of 95.5:4.5.



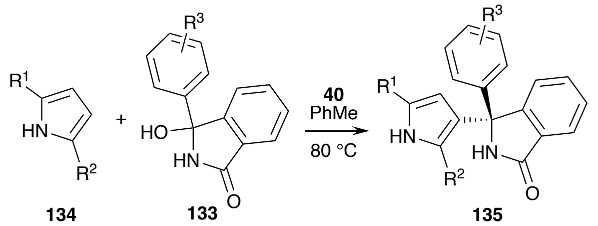
Scheme 36. Addition of pyrroles with α-amidosulfones.

A highly regioselective aminoalkylation of pyrroles with cyclic perfluoroalkylated imines (**131**) is regioselective towards the β-position to provide **132** (**Scheme 37**).[94] This reaction involves the activation of trifluoromethylated imines or pyrrolines with a boron-based Lewis acid, and subsequent addition of *N*-methyl pyrrole to generate the racemic products. Computational analysis attributed the regioselectivity of this reaction to thermodynamically-controlled electrophilic substitution whereby the -CF_3 group critically interacts with the *N*-substituent in order to afford maximum regioselectivity.



Scheme 37. Aminoalkylation of pyrroles with cyclic perfluoroalkylated imines. R^2 = CF_3 or C_2F_5.

Cu(II)-catalysed asymmetric alkylation of isatin derivatives (**133**) with 2,5-dialkyated pyrroles resulted in pyrroles bearing chirality at the β-position.[39] In other work, the use of isoindolinones (**Scheme 38**)[95] and a BINOL-derived CPA catalyst system (**40**, (*R*), R = 2,4,6-(iPr)$_3C_6H_2$) provided **135** in yields up to 96% and er values reaching 98.5:1.5.

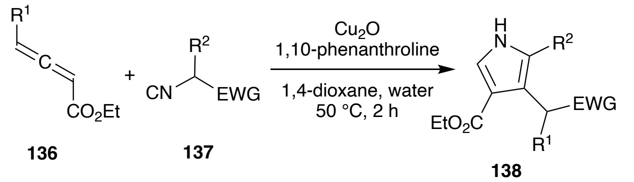


Scheme 38. CPA-catalysed β-FC reaction of isoindolinones and 2,5-dialkyated pyrroles.

Pyrrole forming reactions towards β-position chirality

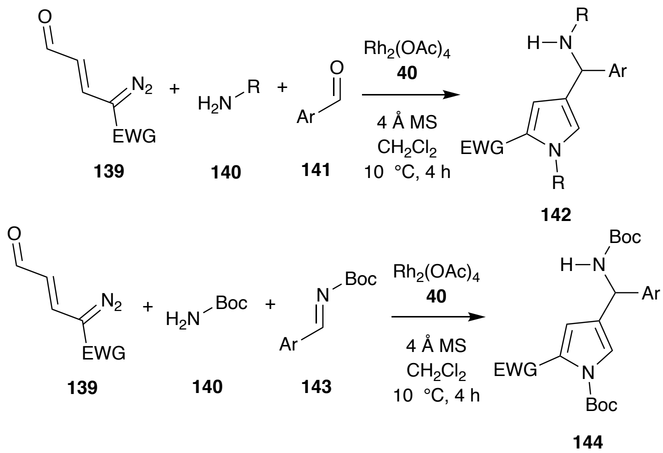
Cyclisation reactions were used to generate pyrrolic frameworks with quaternary centres at the β-position. A Cu-catalysed racemic cyclisation of ethyl allenoates (**136**) and activated isocyanides (**137**, **Scheme 39**)[96] generated yields of **138** reaching

84%. To account for the unexpected position of the electron withdrawing group (EWG) in the product, a skeletal rearrangement was proposed.



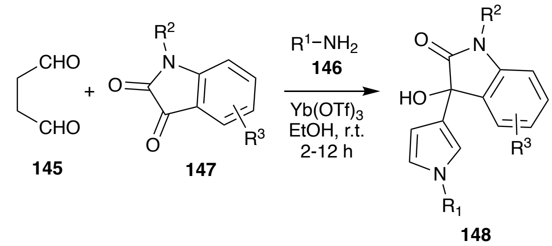
Scheme 39. Cyclisation of ethyl allenoates and activated isocyanides.

A chiral rhodium/CPA system catalyses the multicomponent reaction of enaldiazo compounds (**139**), arylamines (**140**) and aryl aldehydes (**141**, **Scheme 40**), although the use of sterically encumbered anilines results in a decreased yield of pyrrole **142**.[97] This reaction proceeds through an enal carbenoid which contains an ammonium ylide. The proposed sequence involves a Mannich reaction followed by a cyclocondensation cascade. This work was expanded to include *N*-Boc protected aryl imines (**143**). Yields of up to 86% were obtained for the corresponding product **144**, and the use of an axially chiral BINOL-derived CPA (**40**, R = 2,4,6-triisopropylphenyl) provided diastereoselectivity of 92:8 courtesy of the formation of both a chiral centre and axial chirality as a result of a bulky Ar group in products **142** (originating with the reacting aldehyde).



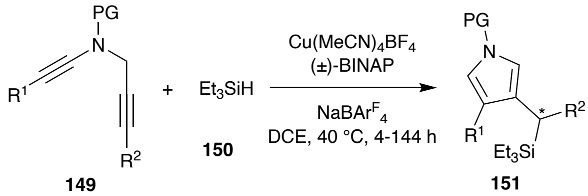
Scheme 40. Multicomponent reaction of enaldiazo compounds, amines, and aryl aldehydes or *N*-Boc aryl imines.

Another strategy to form pyrroles bearing chirality at the β-substituted involves an ytterbium catalyst.[98] This racemic multicomponent reaction, involving an integral Paal-Knorr cyclisation, combines aqueous succinaldehyde (**145**), primary amines (**146**) and isatins (**147**) to result in yields of **148** reaching 91% for an impressive range of examples that include isatins and aryl/alkyl amines (**Scheme 41**). More recently, researchers from the same group reported asymmetric access to β-hydroxyalkylated pyrroles *via* an amine-catalysed aldol/Paal-Knorr reaction sequence.[99] Products were afforded in yields up to 78% with er values >99:1.



Scheme 41. Ytterbium-catalysed synthesis of β-substituted pyrroles.

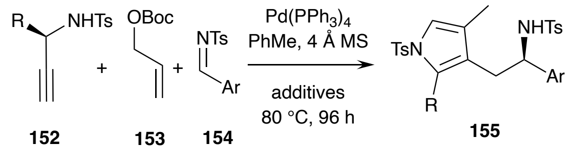
In another cyclisation reaction sequence, a Si-H bond insertion reaction utilised a Cu catalyst.[100] This reaction combined *N*-propargyl ynamides (**149**) and hydrosilanes (**150**), with a vinyl cation serving as a major intermediate (**Scheme 42**). Products (**151**) were formed in yields up to 93% and include one enantioselective example (er 74:26).



*One example of enantioselectivity was reported using a chiral indane-BOX ligand

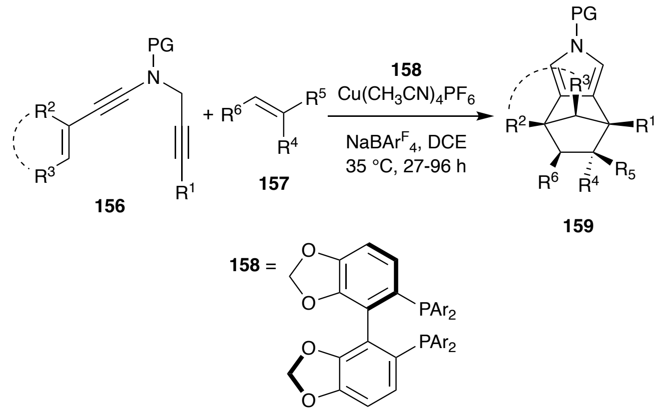
Scheme 42. Reaction of *N*-propargyl ynamides with hydrosilanes.

A three-component reaction uses enantiopure *N*-Ts propargylamines (**152**) with Boc-protected allyl carbonate and aldimines (**154**) in the presence of an acid to generate enantiopure β-alkyated pyrroles (**155**, **Scheme 43**).[101] Through sequential allylic amination, cycloisomerisation, vinylogous addition and aromatisation steps, products were formed in yields up to 80% with er values reaching 98.5:1.5.



Scheme 43. Multicomponent reaction of enantiopure *N*-Ts propargylamines with allyl carbonates and aldimines.

A series of papers discussing Cu-catalysed asymmetric cyclisation reactions included diynes and led to the synthesis of highly functionalised annulated chiral pyrroles with stereochemistry at the β-position. The first report described a [3+2] cycloaddition of alkenyl *N*-propargyl ynamides (**156**) and various styrenes (**157**) in the presence of a chiral Cu and SEGPHOS (**158** , Ar = 3,5-(tBu)$_2$-4-OMeC$_6$H$_2$) catalyst system (**Scheme 44**).[102] This reaction was facilitated *via* a Cu-containing 1,3-dipole intermediate generated through a metal carbene. Yields of the corresponding products **159** reached 90% with excellent diastereoselectivity and er values up to 99.5:0.5. The proposed mechanism suggests that the stereoselectivity arises in the cycloaddition step between the 1,3-copper dipole and the styrene derivative.



Scheme 44. Cu-catalysed reaction of alkenyl diynes with styrenes.

In the subsequent paper, an asymmetric cascade cyclisation/1,2-Stevens rearrangement sequence was described. Use of a chiral copper BOX catalyst system afforded chiral chromeno[3,4-c]pyrroles bearing chirality at the β-position (**160** and **161**, **Figure 6**).[103] The proposed mechanism, suggested to proceed *via* a non-diazo derived carbene that inserts into a Si–O bond, attributes the stereoselectivity to transition state steric repulsion between the protecting groups and the chiral ligand. The final paper in the series documented a Cu-catalysed SEGPHOS-promoted asymmetric cyclisation involving alkenyl diynes (**162**, **Figure 6**,).[104] Further investigations regarding reaction mechanisms led to the proposal that stereoselectivity arises due to steric repulsion between the bulky chiral ligand and the rigid cyclopentene ring that play key roles in the transition state.

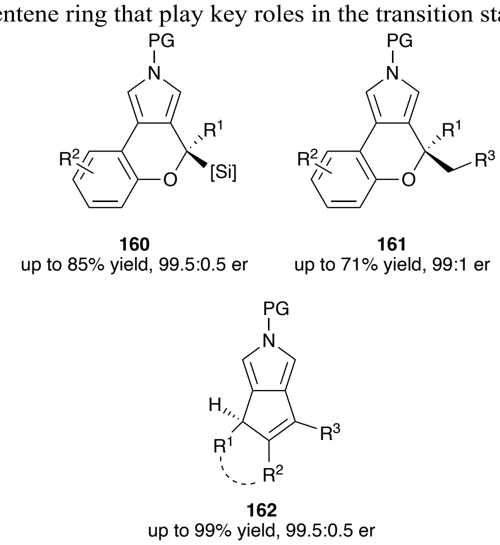
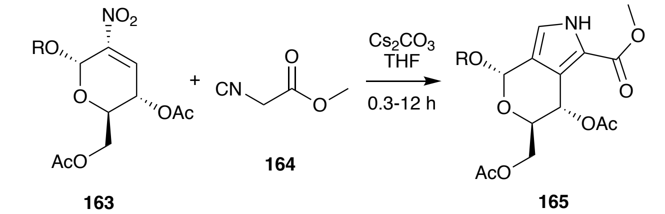


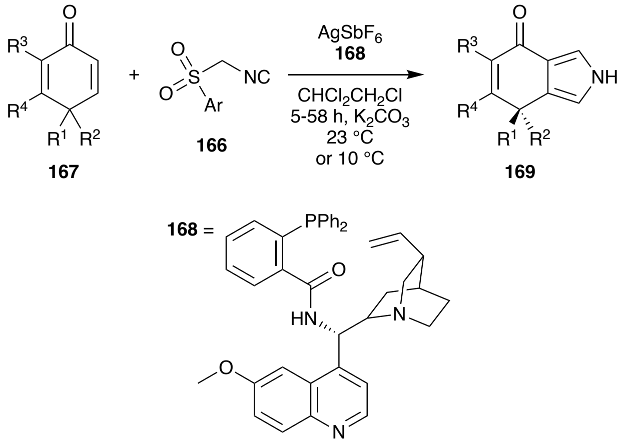
Figure 6. Annulated pyrroles *via* Cu-catalysed asymmetric diiyne cyclisation.

An alternative one-pot stereoselective reaction towards annulated chiral pyrroles uses 2-nitroglycals.[105] This two-step synthetic sequence begins with an *N*-heterocyclic carbene (NHC)-catalysed Ferrier rearrangement, followed by a [3+2] Barton-Zard cyclisation between 2-nitro-2,3-unsaturated glycosides (**163**) and isocyanoacetate (**164**) (**Scheme 45**). The cyclisation step is facilitated by caesium carbonate to afford products **165** in yields up to 99%. The stereochemical integrity of the glycal was transferred to the annulated pyrrolic system with high efficiency.



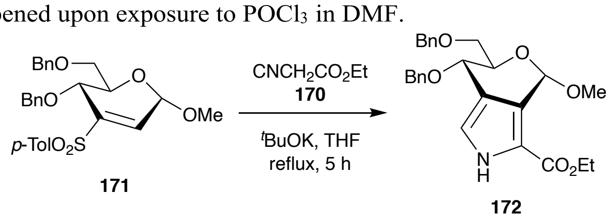
Scheme 45. [3+2] Barton-Zard cyclisation between 2-nitro-2,3-unsaturated glycosides and isocyanoacetate.

A stereoselective Van Leusen pyrrole synthesis results in the desymmetrisation of prochiral cyclohexadiones and the generation of a pyrrole annulated through the two β-positions Yields reached 99%, with a maximum er value of 98:2 (**Scheme 48**).[106] The reaction involved addition of isocyanomethyl sulfone derivatives (**166**) to cyclohexadiones (**167**) in the presence of a silver catalyst and a chiral *Cinchona* alkaloid-based phosphino-carboamide ligand (**168**), and could be extended to effect kinetic resolution of racemic cyclohexadiones to generate pyrroles **169** with er values up to 96:4 and enable recovery of 2-substituted cyclohexadienones in excellent eantiopurity.



Scheme 46. Van Leusen pyrrole synthesis process towards.

A related reaction involved the synthesis of polysubstituted pyrroles featuring carbohydrates at the β-position, generated by reaction of ethylisocyanoacetate (**170**) with vinyl sulfone-modified carbohydrates (*e.g.*, **171**, **Scheme 47**).[107] A wide range of densely functionalised pyrroles (*e.g.*, **172**) were thus prepared in yields up to 92%. The pyranosyl rings were subsequently opened upon exposure to $POCl_3$ in DMF.



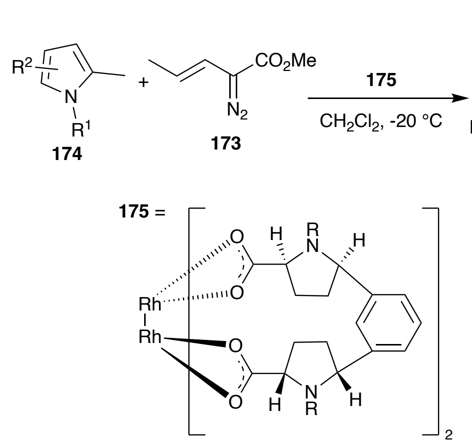
Note: many other derivatives of carbohydrates featuring pyrroles were synthesised

Scheme 47. Chiral pyrroles featuring carbohydrates across the β-positions.

Miscellaneous reactions resulting in chirality at the β-position of pyrroles

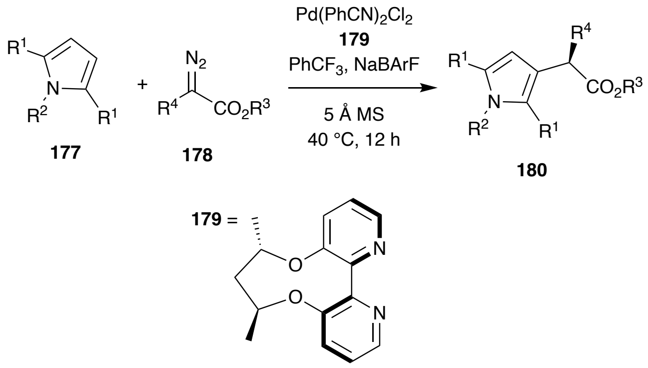
Several other synthetic strategies result in chirality at the β-position of pyrroles yet do not obviously fit within the categories discussed thus far. The asymmetric addition of vinylcarbenoids

(**173**) to pyrroles (and indoles), catalysed by a chiral Rh_2(*S*-biTISP)$_2$ (**175**, R = SO_2-2,4,6-(iPr)$_3C_6H_2$) system (**Scheme 48**), resulted in yields of the desired compounds **176** of up to 72% with er values reaching 95.5:4.5.[108]



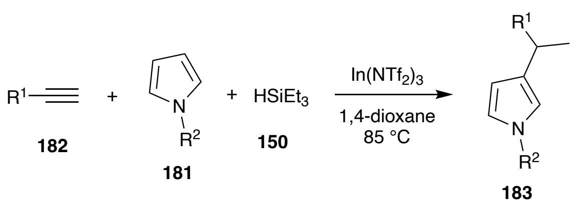
Scheme 48. Addition of pyrroles to vinylcarbenoids.

Similarly, C-H activation of pyrroles by reaction with carbenes, generated from diazoacetates (**178**), was catalysed by a dichlorobis(benzonitrile)palladium catalyst with an axially chiral bipyridine ligand (**179** (
Scheme 49).[109] Products (**180**) were synthesised in yields of up to 93% with er values reaching 95:5.



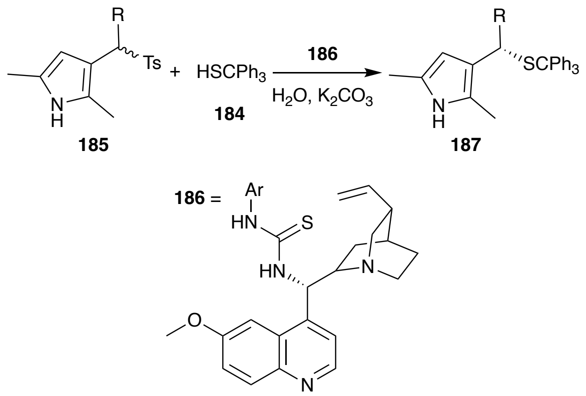
Scheme 49. Reaction of pyrroles with diazoacetates.

The alkylation of pyrroles catalysed by an indium-based system proceeded with very high regioselective at the β-position.[110] This reductive process, involving pyrroles, alkynes (**182**) and triethylsilane, generated racemic pyrroles (**183**) in yields up to 92% (**Scheme 50**). Pyrroles protected with methyl, benzyl, *tert*-butyl and phenyl moieties were utilised, with pyrrole itself (R^2 = H) being unsuccessful.



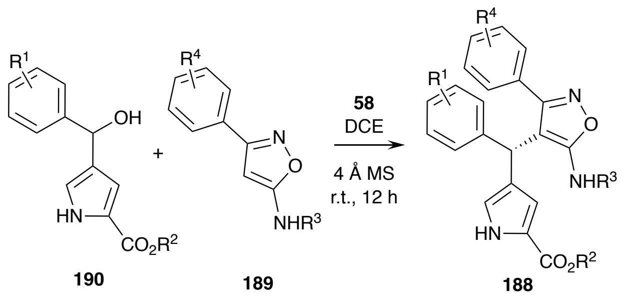
Scheme 50. Reductive addition of pyrroles, alkynes, and hydrosilanes

The asymmetric 1,4-addition of tritylthiol (**184**) to vinylogous imines, generated *in situ*, resulted in thiolation of (arylsulfonyl)pyrroles (**185**). The use of a chiral *Cinchona* alkaloid-based bifunctional organocatalyst (**186**, Ar = 3,5-$(CF_3)_2C_6H_3$), **Scheme 51**)[111] provided the corresponding chiral pyrrole **187** in yields reaching 96% and er values approaching 99:1. The presence of small quantities of water were critical to success.



Scheme 51. Addition of tritylthiol and vinylogous imines generated from 2,5-dimethyl-3-[1-(arylsulfonyl)alkyl]pyrroles.

A SPINOL-derived CPA (**59**, (*S*), Ar = 3,5-(tBu)$_2C_6H_3$) catalysed synthesis of heterotriarylmethanes (**188**) from arylisoxazolamines (**189**) and methidepyrroles (**190**) was reported (**Scheme 52**).[112] These pharmaceutically relevant motifs were isolated in yields up to 97% with er values reaching 96.5:3.5.



Scheme 52. Synthesis of chiral heterotriarylmethanes.

Other examples of reactions at the β-position of pyrroles include a Cu(II)-catalysed C-C and C-N bond-forming reaction. Replacement of the hydroxy substituent of pyrroles prefunctionalised at the β-position results in products bearing (hetero)aromatic substituents at this position (**191** and **192**, **Figure 7**).[113] Furthermore, pyrroles bearing chirality at the β-position were prepared *via* a cascade β-functionalisation/aromatisation reaction of *N*-arylpyrrolidines, followed by *via* double hydride transfer (**193**, **Figure 7**,).[114]

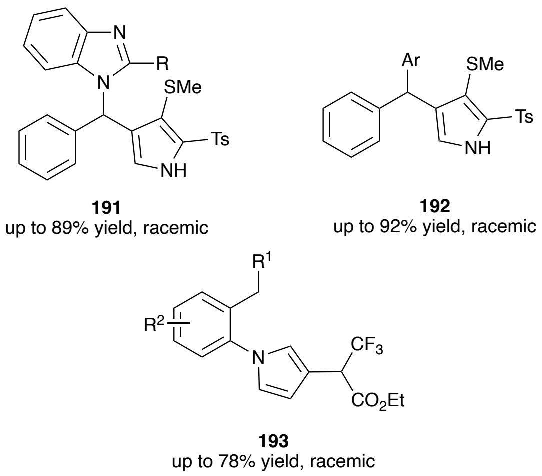


Figure 7. β-Functionalised chiral pyrroles *via* miscellaneous reactions.

Recently, acylation of a heavily functionalised alcohol was used in the final synthetic step towards the total synthesis of (-)-Batrachotoxin (**194**, **Figure 8**).[115] (-)-Batrachotoxin, known as one of the most toxic natural products, was synthesised in 0.71% yield with a longest linear sequence of 22 steps.

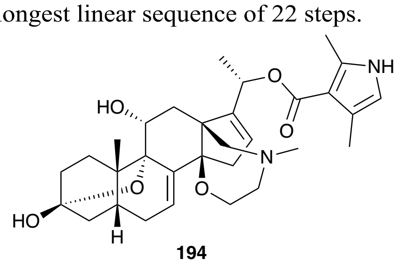


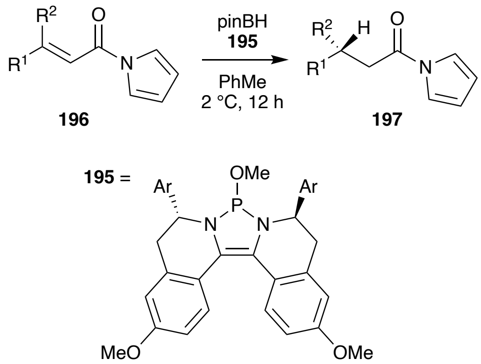
Figure 8. (-)-Batrachotoxin.

Chirality at the nitrogen atom

The chemistry of pyrroles owes much to the characteristics of the nitrogen atom within the heterocyclic ring. Indeed, substitution/functionalisation at this position has provided a rich source of chirality for pyrroles.

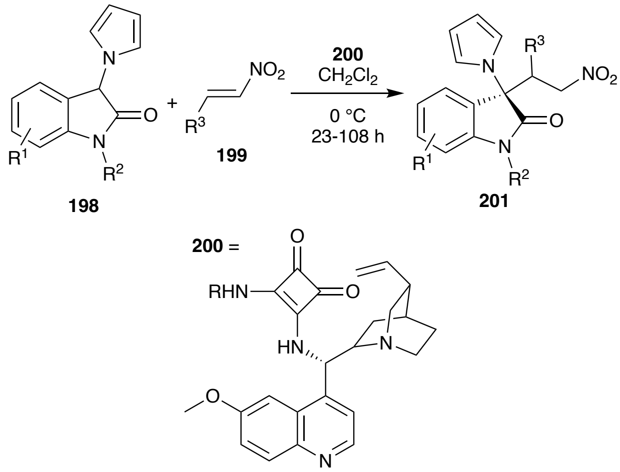
Chirality through reaction of functionality at the N-atom of pyrroles

Reactivity of pre-installed functionality can be used as a strategy for the generation of pyrroles appended with chirality at the nitrogen atom. Utilising a chiral 1,3,2-diazaphospholene (DAP) **195** (Ar = 3,5-$Me_2C_6H_3$) as a catalytic source of hydride, an asymmetric reduction of various alkenes was achieved.[116] This reaction involved the reduction of various α,β-unsaturated acyl pyrroles (**196**) in the presence of the DAP catalyst and pinacolborane (**Scheme 53**). Products (**197**) were formed in yields reaching 99% with er values up to 95.5:4.5.



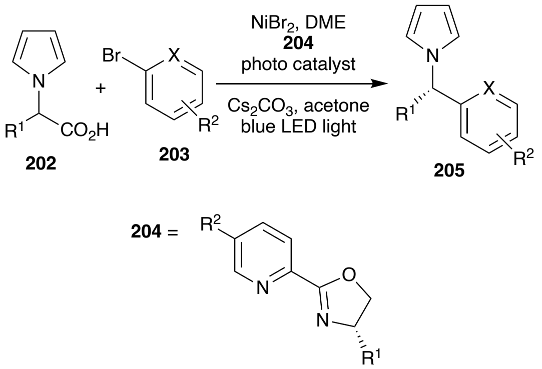
Scheme 53. Reduction of α,β-unsaturated acylpyrroles.

An asymmetric Michael addition of 3-pyrrolyl-oxindoles (**198**) and nitroalkenes (**199**), catalysed by a squaramide *Cinchona* alkaloid catalyst **200** (R = 3,5-$(CF_3)_2C_6H_3$) provides pyrroles *N*-substituted with a moiety containing two chiral centres (**201**, **Scheme 54**).[117] Beginning with racemic 3-pyrrolyl-oxindoles and proceeding with a maximum diastereomeric ratio of 94:6, products were formed in yields up to 98% and er values reaching 99.5:0.5. A similar catalyst system was used to effect asymmetric sulfenylation and selenenylation of racemic 3-pyrrolyl-oxindole, using N-Se/S succinimides as electrophiles, providing 3,3-disubstituted oxindoles. Proceeding through the enol, sulfur- and selenium-based functionality was introduced onto the 3-pyrrolyl-oxindole skeleton with up to 98% yield obtained, and er values reaching >99.5:0.5.[118] Another example used an asymmetric allylic substitution strategy to append vinyl benzoxazinanones and 3-pyrrolic-oxindoles with yields up to 98% and er values reaching 99.5:0.5.[119]



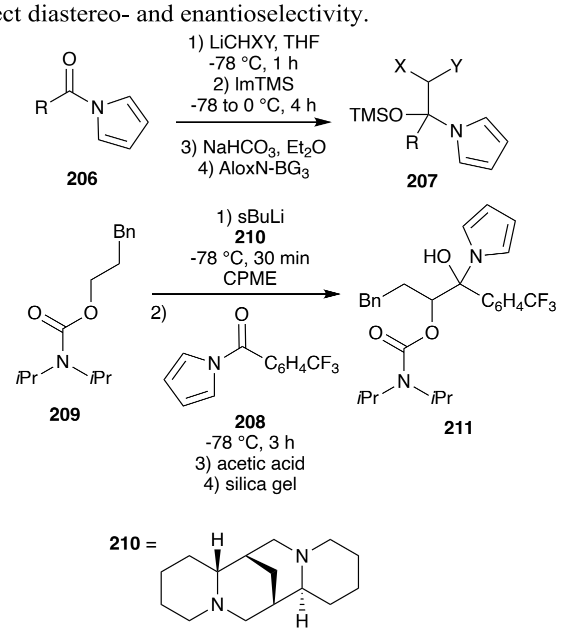
Scheme 54. Asymmetric Michael addition of 3-pyrrolyl-oxindoles and nitroalkenes.

Another example whereby *N*-substituents of pyrroles are stereoselectively functionalised utilised a Ni/photoredox-catalysed decarboxylative aryl coupling approach towards *N*-benzylic heterocycles.[120] This reaction used α-heterocyclic carboxylic acids (**202**) and involved coupling with various aryl bromides **203** (X = CH or N) in the presence of a pyridine oxazoline chiral catalyst (**204**, R^1 = *t*Bu, R^2 = 3-Me), **Scheme 55**). Chiral pyrroles **205** were formed with yields up to 88% and er values reaching 94:6.



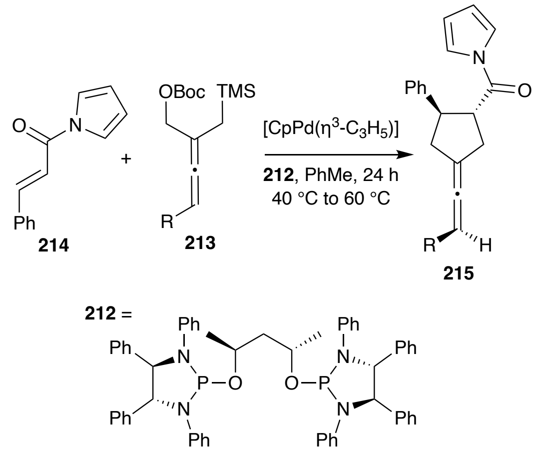
Scheme 55. Ni/photoredox decarboxylative coupling of arylbromides.

Consequent to developing methodology involving trapping the tetrahedral reaction intermediate formed from the addition of halolithium reagents LiCHXY to Weinreb amides, *N*-acyl pyrroles were similarly functionalised. Racemic pyrroles (**207**) bearing chirality at nitrogen were thus prepared, with yields reaching 88% (**Scheme 56**, top).[121] Stereoselective addition to the carbonyl group of the *N*-acyl pyrrole **208** was achieved by applying Hoppe–Beak chemistry to the Weinreb amide **209**, involving the use of (-)-sparteine (**210**) to enantioselectivity generate the corresponding organolithium species (**Scheme 56**; bottom).[122] The product pyrrole (**211**), bearing two chiral centres attached *via* the N-atom, was isolated in 42% yield with almost perfect diastereo- and enantioselectivity.



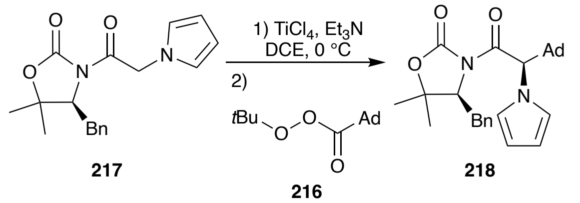
Scheme 56. Stereoselective addition of organolithium reagents to *N*-acylpyrroles.

A [3+2] cycloaddition strategy catalysed by Pd and the bidentate diamidophosphite ligand **212** involved racemic allenes (**213**) and alkenes (**214**) bearing an electron withdrawing substituent. When pyrroles were appended to the alkene, various products (**215**) were generated in yields reaching 88% and er values up to 99:1 (**Scheme 57**).[123] The substituent at nitrogen features stereochemistry in the form of both point chirality and axial chirality. Diastereoselectivity was dependant on substituent patterns for both the allene and the pyrrole-appended alkene, and ranged from modest (2:1) to almost perfect.



Scheme 57. Enantioselective [3+2] cycloaddition of racemic allenes and alkenes.

A highly diastereoselective alkylation of chiral *N*-acyl oxazolidinones with *tert*-butyl peresters proceeds *via* a Ti(IV)-supported enolate.[124] Reaction of a 1-adamantane (Ad) perester (**216**) and a pyrrole *N*-appended with an oxazolidinone (**217**) provided the elaborated pyrrole **218** in 62% yield (**Scheme 58**).



Scheme 58. Synthesis of a pyrrole-containing α-adamantyl alkylated adduct.

The enantioselective synthesis of (-)-Ranirestat (**219**) features an asymmetric allylic alkylation with an allyl *tert*-butyl carbonate and the requisite annulated pyrrole to form the key intermediate and provide the desired enantioselectivity (**Figure 9**).[125]

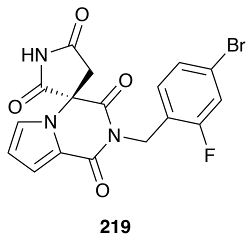
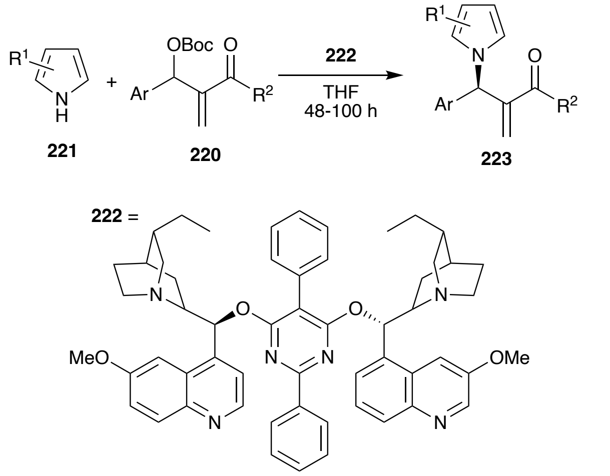


Figure 9. (-)-Ranirestat.

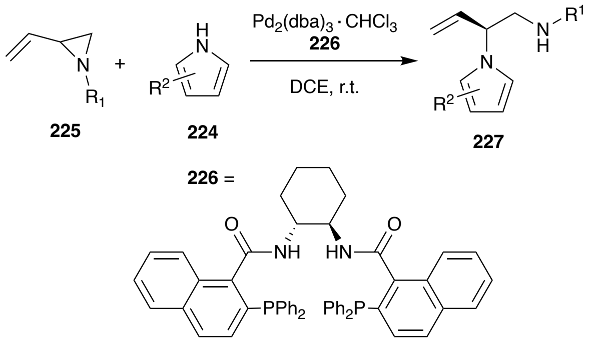
N-Alkylations of pyrroles

Reaction of O-Boc-protected Morita–Baylis–Hillman adducts (**220**) and pyrroles enables asymmetric allylic alkylation (**Scheme 59**),[126,127] facilitated by the chiral *Cinchona* alkaloid catalyst **222** in THF. Products (**223**) were formed in yields of up to 99% with er values reaching 98:2.



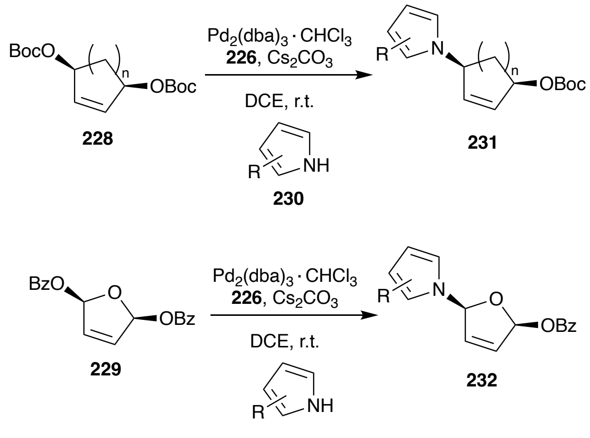
Scheme 59. Asymmetric pyrroles *via* O-Boc Morita–Baylis–Hillman adducts.

Alkylation of pyrroles through nucleophilic opening of aziridines (**225**), catalysed by palladium, generates synthetic intermediates towards various biologically active bromopyrrole alkaloids (**Scheme 60**).[128] This dynamic kinetic asymmetric alkylation was facilitated using the chiral diphenylphosphino benzoic acid (DPPBA) ligand **226**. Pyrroles (**227**) bearing chirality at nitrogen were synthesised in yields up to 99% with er values reaching 98:2.



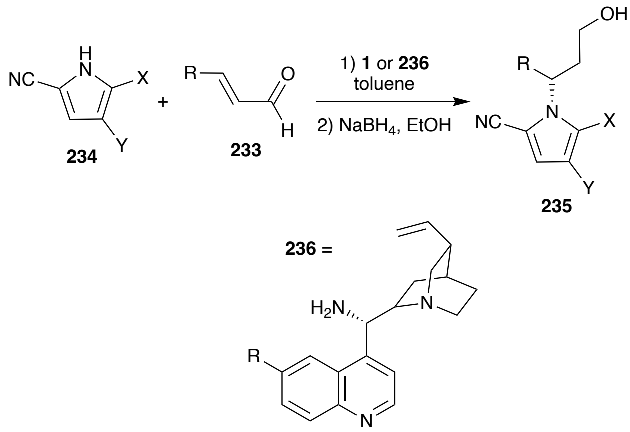
Scheme 60. Reaction of pyrroles with vinyl aziridines.

Use of a similar palladium and DPPBA (**226**) catalyst system was extended to the generation of chiral *N*-substituted pyrroles through asymmetric allylic alkylation using cyclopentene dicarbonates (**228**, **Scheme 61**, top) and dihydrofurans (**229**, **Scheme 61**, bottom) with pyrroles.[129] With perfect regioselectivity and diastereoselectivity reported, desymmetrisation provided products **231** (cyclopentenes) and **232** (dihydrofurans) with yields reaching 96% and er values up to 99.5:0.5. Further functionalisation of the dihydrofuran derivatives led towards a pyrrole-substituted ribonucleoside analogue.



Scheme 61. Reaction of pyrroles with cyclopentene dicarbonates/dihydrofurans.

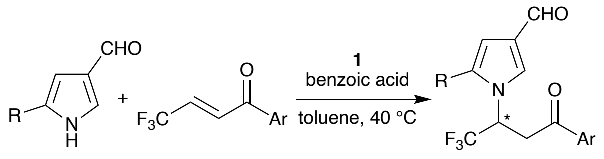
The enantioselective aza-Michael reaction of α,β-unsaturated aldehydes (**233**) and halogenated 2-cyanopyrroles provided synthetic intermediates *en route* to bromopyrrole alkaloids (**Scheme 62**).[130] The reaction used a proline-derived organocatalyst (**1**, (*S*), Ar = Ph, R = OTMS) and provided pyrroles (**235**) bearing chirality at nitrogen in yields up to 78% with er values reaching 97:3. Building on this report, the substrate scope of the enantioselective aza-Michael reaction was explored using a chiral *Cinchona*-based primary amine organocatalyst **236** (R = OMe).[131] Products were formed in yields of up to 72% and er up to 98.5:1.5.



*Catalyst = proline-derived[130] or *Cinchona* alkaloid[131] organocatalyst

Scheme 62. Aza-Michael reaction of pyrroles with α,β-unsaturated aldehydes.

A proline-derived organocatalyst (**1**, (*S*), Ar = Ph, R = $OSiPh_2Me$) was also used for the aza-Michael addition of pyrrole 3-carbaldehydes (**237**) with β-trifluoromethyl enones (**238**) afforidng yields up to 95% (**Scheme 63**).[132] Use of an asymmetric bulky proline-derived catalyst yielded the desired products **239** in 76% yield and er up to 91.5:8.5.

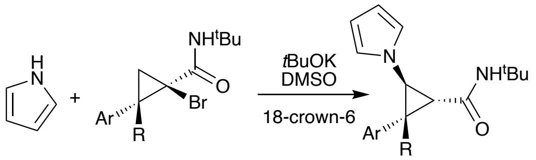


237 238 239

* Asymmetric catalysis conditions were also provided for some examples

Scheme 63. Aza-Michael addition of pyrrole-3-carbaldehydes with enones.

A procedure for S_N2' substitution of bromocyclopropanes was developed for azoles, amines and ethers included pyrrolic examples (**Scheme 64**).[133] A diastereoselective nucleophilic substitution reaction using enantiomerically pure bromocyclopropanes (**240**) and pyrrole provided the corresponding cyclopropylpyrroles (**241**) in yields up to 84% and dr up to 81:1. The mechanism of this reaction features a key cyclopropane intermediate that, following a 1,4-addition/epimerisation pathway, controls the adjacent stereocenters.

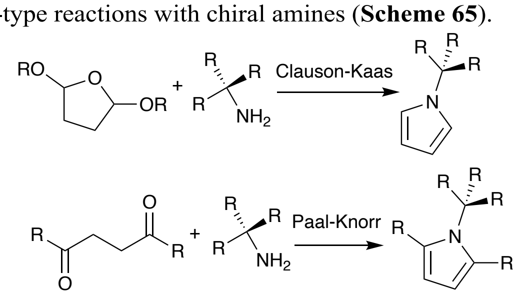


6 240 241

Scheme 64. Nucleophilic substitution of bromocyclopropanes with pyrrole.

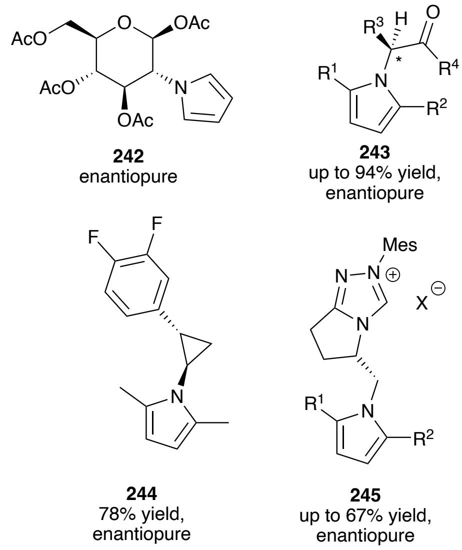
Pyrrole-forming reactions towards chirality at nitrogen

Several reports demonstrate the generation of pyrroles bearing chirality at the nitrogen atom. Various strategies have been used to form the heterocyclic ring, including Clauson-Kaas and Paal-Knorr-type reactions with chiral amines (**Scheme 65**).



Scheme 65. Clauson-Kaas and Paal-Knorr reactions with chiral amines.

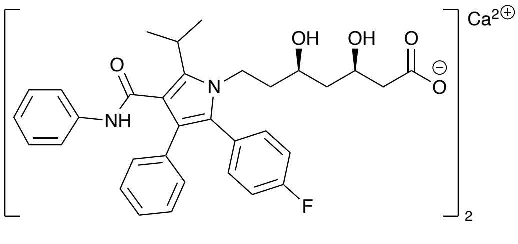
One such example involved use of recyclable ionic liquid catalysts: the one-pot microwave-promoted reaction between 2,5-dimethoxytetrahydrofuran and primary amines yielded pyrroles in yields of up to 91%.[134] When amines bore existing chirality, this was retained in the final products. Other work offered a similar substrate scope, tolerated the inclusion of racemic amines, and involved a procedure that utilised dry grinding and a catalyst system consisting of sulfuric acid immobilised on silica gel.[135] Tetraacetylated D-glucosamine hydrochloride was used as the amine for a Clauson-Kaas reaction to result in a pyrrole *N*-substituted with a high density of chiral centres (**242**, **Figure 10**).[136] Solvent-free[137] and iodide-catalysed[138] conditions enabled Paal-Knorr reactions with retention of stereochemistry for chiral amines (**243**, **Figure 10**), and even for the synthesis of a cyclopropane example (**244**, **Figure 10**). Other work utilised an *N*-mesityl-substituted triazolium salt featuring a pendant amino group that underwent Paal-Knorr reaction to generate pyrroles **245** featuring chirality at the nitrogen atom (**Figure 10**).[139]



* Other enantiomer was synthesised by varying starting chiral amine

Figure 10. *N*-functionalised chiral pyrroles *via* pyrrole forming reactions.

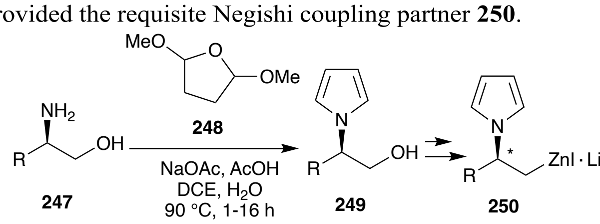
A Paal-Knorr reaction was used for the preparation of Atorvastatin calcium (**246**)—a drug that prevents cardiovascular disease (**Figure 11**).[140] The requisite triaryl 1,4-diketo compound was condensed with the requisite enantiopure amine, in the presence of a weak acid, to provide the target compound in 78% yield.



246

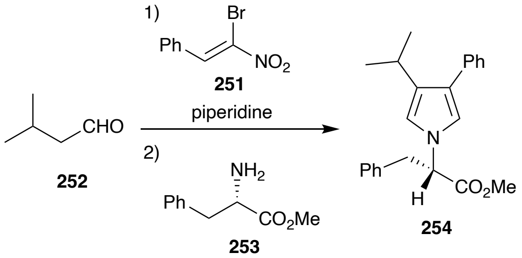
Figure 11. Atorvastatin calcium.

A procedure towards chiral pyrrole-containing nucleophiles for Negishi coupling involves Clauson-Kaas cyclisation.[141] Use of enantiopure β-amino-alcohols (**247**) and 2,5-dimethoxytetrahydrofuran gave pyrroles (**249**) in yields reaching 92%, with retention of chirality (**Scheme 66**). Conversion of the hydroxy substituent to a halide, followed by zinc insertion, provided the requisite Negishi coupling partner **250**.



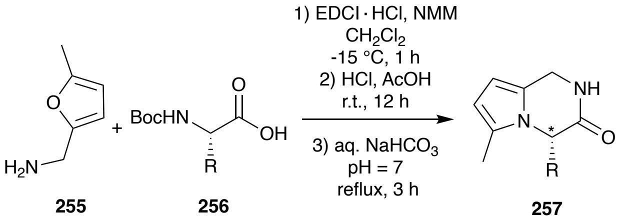
Scheme 66. Synthesis of chiral pyrroles for Negishi coupling.

A one-pot organocatalytic synthesis of 3,4-disubstituted pyrroles involved the reaction of (*Z*)-β,β-bromonitroalkenes (**251**) with primary amines and aldehydes.[142] One reaction used an enantiopure chiral amino acid (**253**) and the final product (**254**) retained stereochemical integrity (98:2 er) with a yield of 72% (**Scheme 67**). The proposed mechanism first involves enamine formation followed by electrophilic attack by the nitroalkene and hydrolysis to release the organocatalyst.



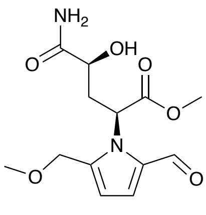
Scheme 67. Reaction of aldehydes, (Z)-β,β-bromo-nitroalkenes and amines.

Another strategy described the synthesis of an annulated pyrrole bearing chirality at the nitrogen atom (**Scheme 68**).[143] This reaction involved a one-pot two-step synthesis between 5-methyl furylamine (**255**) and enantiopure *N*-Boc amino acids (**256**) to generate 4-substituted-6-methyl-1,2-dihydropyrrolo[1,2-*a*]pyrazin-3(4*H*)-ones (**257**). Yields reached 92%, assuming retention of stereochemical integrity from the amine.



Scheme 68. Reaction of 5-methyl furylamine and enantiopure *N*-Boc amino acids.

The total synthesis of Hemerocallisamine I (**258**) employed a modified Maillard reaction between (2*S*,4*S*)-4-hydroxyglutamic acid lactone and a dihydropyranone to form the pyrrolic ring. Deprotection and ring-opening of the lactone led to the desired product (**Figure 12**).[144]



258

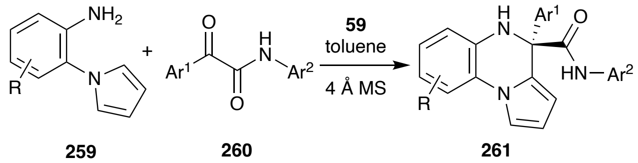
Figure 12. Hemerocallisamine I.

Chirality of pyrroles annulated through the α-position and the nitrogen atom

This section describes reactions of pyrroles with other chemical motifs such as to generate annulated pyrroles.

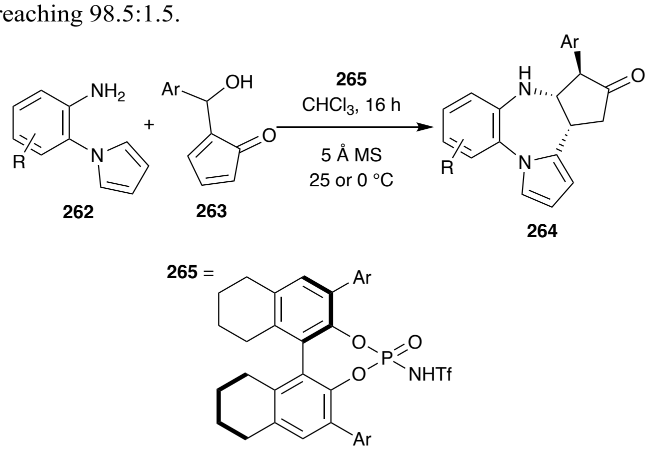
Amides, amines and anilines

Cyclisation and cycloaddition reactions involving amides, amines and anilines have provided rich access to pyrroles bearing chirality. Pyrroles (**259**) *N*-substituted with an aniline unit undergo SPINOL-derived CPA-catalysed (**59**, (*S*), Ar = 9-phenanthyryl) Pictet-Spingler reaction with α-ketoamides (**260**, **Scheme 69**).[145] Products (**261**) were formed in yields reaching 94% with er values up to 99.5:0.5. Investigations into potential reaction mechanisms identified an unexpected CH-N hydrogen bonding interaction between the chiral catalyst and the arene as being largely responsible for the observed stereochemistry.



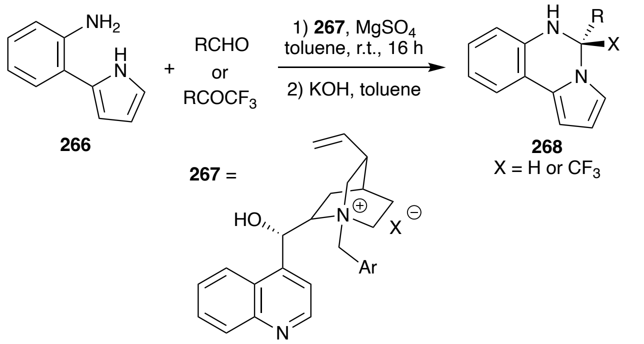
Scheme 69. Pictet-Spingler reaction of 2-(1*H*-pyrrol-1-yl)anilines and ketoamides.

A diastereoselective sequence involving the reaction of *N*-aniline substituted pyrroles (**262**) and enones (**263**) provided seven-membered ring systems (**264**, **Scheme 70**).[146] The reaction was performed in the presence of an (*R*) *N*-triflyl phosphoramide catalyst (**265**, Ar = 2,4,6-(iPr)$_3$C$_6$H$_2$) and involved an aza-Piancatelli rearrangement followed by a FC alkylation cascade. Products were formed in yields up to 98% with er values reaching 98.5:1.5.



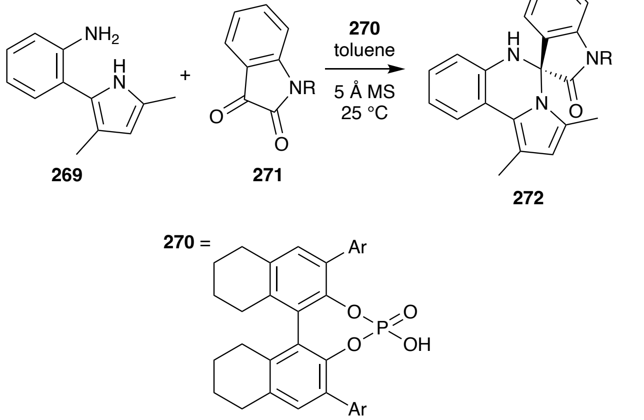
Scheme 70. *N*-triflyl phosphoramide catalysed cascade reaction.

An example using pyrroles (**266**) substituted with anilines at the α-position showcased enantioselective cyclisation involving aldehydes and trifluoromethyl ketones in the presence of a chiral *Cinchona* alkaloid-based phase-transfer catalyst (PTC, **267**, Ar = Ph, X = Cl), **Scheme 71**).[147] The process involved *in situ* imine formation followed by cation-directed cyclisation to provide products **268** in yields of up to 99% with er values reaching 99:1. Complete regioselectivity was reported for reaction at the pyrrolic N-atom.



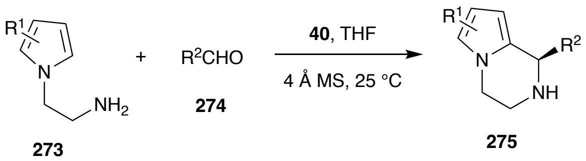
Scheme 71. Cyclisation reaction of pyrroloaniline with aldehydes and ketones.

In another example of pyrroles substituted with anilines at the α-position (**269**) being used to form annulated pyrroles bearing chirality, a BINOL-[H8]-derived CPA-catalysed (**270**, (*R*), Ar = 2,4,6-(iPr)$_3$C$_6$H$_2$) cascade reaction with isatins (**271**) gave spiro chiral aminals (**272**) in yields reaching 91% and er values up to 97:3 (**Scheme 72**).[148]



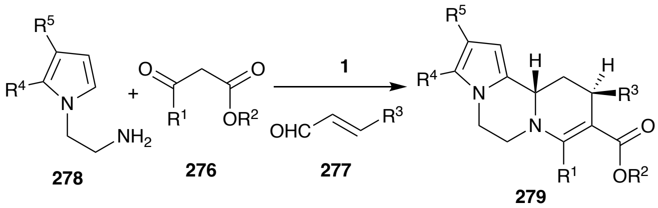
Scheme 72. Stereoselective synthesis of spiro chiral aminals.

An asymmetric condensation of *N*-aminoethylpyrroles **273** and aldehydes in the presence of a BINOL-derived CPA catalyst (**40**, (*R*), R = 2,4,6-(iPr)$_3$C$_6$H$_2$), followed by an intramolecular aza-FC reaction, provided access to chiral 1,2,3,4-tetrahydropyrrolo[1,2-α]pyrazines (**275**, **Scheme 73**).[149] Products were formed in yields up to 95% and er values reaching 97:3.



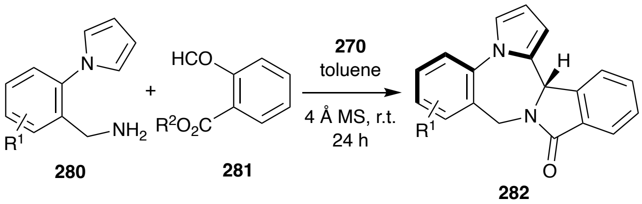
Scheme 73. Imine formation followed by intramolecular aza-FC reaction.

N-Aminoethylpyrroles were also used in a multicomponent reaction sequence to form tricyclic products.[150] This sequence featured iminium activation involving an enantioselective Michael addition followed by a Pictet-Spingler cyclisation (**Scheme 74**). This sequence involved the reaction of β-ketoesters (**276**), acroleins (**277**) and *N*-(2-aminoethyl)pyrroles (**278**) in the presence of a proline-derived organocatalyst (**1**, (*S*), Ar = Ph, R = OTMS). Pyrrolopiperazines (**279**) were synthesised in yields up to 70%. Although the diastereoselectivity was negligible, the enantioselectivity was high and reached 99.5:0.5 er values.

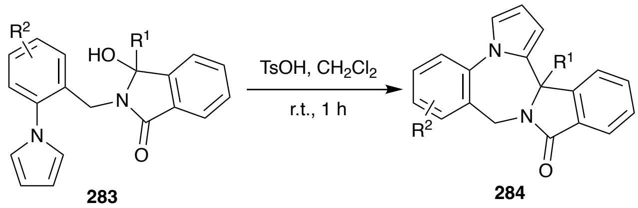


Scheme 74. Enantioselective Michael addition and Pictet-Spingler cyclisation.

Two strategies towards the synthesis of benzo[*f*]pyrrolo[1,2-*a*][1,4]azepines in the presence of CPA catalysts were reported, one involving intramolecular processes and the other featuring only intermolecular interactions.[151] The enantioselective intermolecular sequence involved the addition of [2-(1*H*-pyrrol-1-yl)phenyl]methanamines (**280**) to 2-formylbenzoates (**281**) in the presence of a BINOL-[H8]-derived CPA catalyst (**270**, (*S*), Ar = 1-anthracenyl). The enantioenriched products (**282**) were formed with yields up to 73% and er values reaching 89:11 (**Scheme 75**). The intramolecular reaction provided racemic products and involved a dehydroxylation and ring closing sequence of 3-hydroxy-2-[2-(1*H*-pyrrol-1-yl)benzyl]isoindolin-1-ones (**283**) using TsOH as a catalyst. Products (**284**) were formed as racemic mixtures in yields up to 99% (**Scheme 76**).

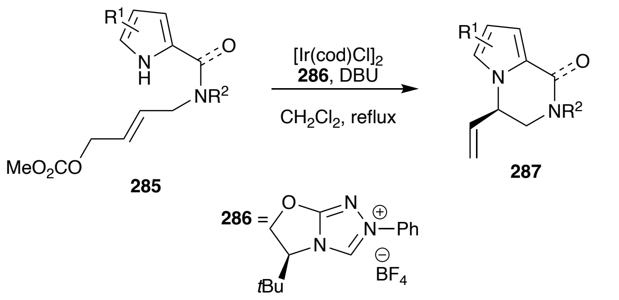


Scheme 75. Intermolecular addition of 2-phenylmethanamines to formylbenzoates.



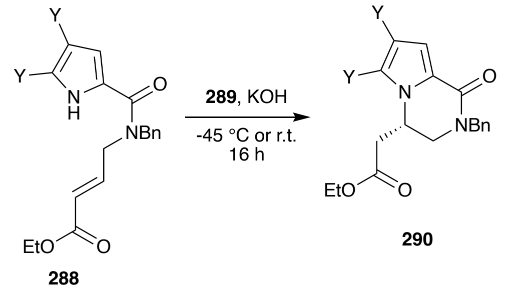
Scheme 76. Intramolecular dehydroxylation/cyclisation sequence.

Pyrroles (**285**) α-appended with amino (or amido) functionality generated annulated products *via* intramolecular allylic amination (**Scheme 77**).[152] The use of an Ir(I) *N*-heterocyclic carbene (NHC) (**286**) complex provided product (**287**) in yields reaching 86% with er values up to 99:1. The allylic amination of pyrrole-tethered allylic carbonates was shown to similarly provide piperazine and piperazinone derivatives.[153] The products, one synthetic step away from analogues of natural products Longamide B and Hanishin, were formed in yields reaching 96% and er up to 99:1.



Scheme 77. Intramolecular allylic amination of pyrroles.

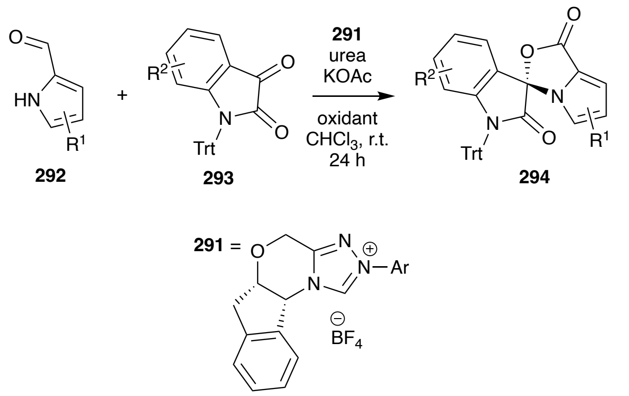
Similarly, an enantioselective intramolecular aza-Michael reaction of pyrroles, through the use of chiral *Cinchona* alkaloid-based PTC (**289**, Ar = 9-anthracenyl or *p*-CF_3-C_6H_4, X = Cl or Br), provided piperazines (**290**) in yields up to 88% with er values reaching 78:22 (**Scheme 78**).[154] The proposed reaction mechanism suggests three key interactions led to the observed stereoselectivity. These include hydrogen bonding interactions between the substrate and the catalyst, conformation and steric effects from the amino-propene unit, and complex π-interaction between pyrrole and the catalyst.



Scheme 78. Asymmetric PTC intramolecular *N*-alkylation.

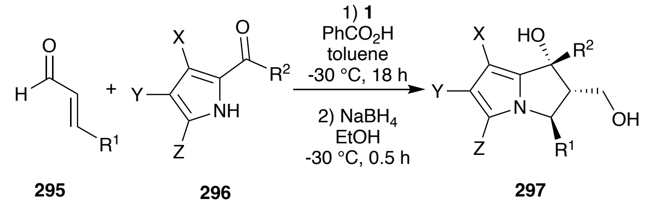
Unsaturated aldehydes

One strategy utilising aldehydes as key reactants involved use of a chiral NHC catalyst (**291**, Ar = C_6F_5) and an aza [3+2] cycloaddition reaction involving formyl indoles or pyrroles, and isatin derivatives (**293**, **Scheme 79**). Under mild basic conditions, and in the presence of an oxidant and a urea additive,[155] products for pyrrolic examples (**294**) were formed in yields reaching 98% with er values up to 99:1.



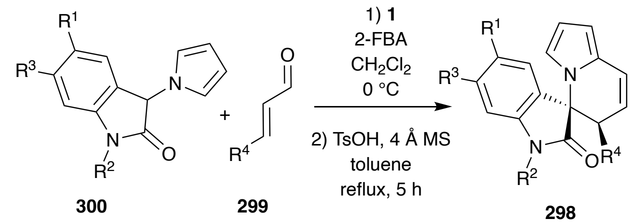
Scheme 79.Aza [3+2] cycloaddition reaction of formyl pyrroles and isatins.

A cascade-type synthesis involving the conjugate addition of α,β-unsaturated aldehydes (**295**) to pyrroles containing electron withdrawing substituents, followed by a subsequent aldol reaction, provided highly functionalised pyrrolizines (**297**) with three consecutive chiral centres (**Scheme 80**).[156] The initial conjugate addition was catalysed using a proline-derived organocatalyst system (**1**, (*S*), Ar = 3,5-$(CF_3)_2C_6H_3$, R = OTMS). The subsequent aldol reaction was facilitated using sodium borohydride in ethanol. Products were formed in yields up to 88%, with excellent diastereoselectivity and with er values reaching 99:1. Building on this work, a chiral diarylprolinol ether-based catalyst was used to effect the formation of chiral pyrrolizine-based triheterocycles through a cascade aza-Michael-aldol reaction of 2-(trifluoroacetyl)pyrroles and α,β-unsaturated aldehydes.[157] Yields reached 77% and er values broached 97.5:2.5. Similarly, another group developed an asymmetric synthesis of 2,3-dihydro-1*H*-pyrrolizines using α,β-unsaturated aldehydes and a pyrrole-based hydrazone in an aminocatalytic cascade reaction.[158] Yields reached 91% and er values exceeded 99:1 *en route* to pharmaceutically relevant scaffolds.



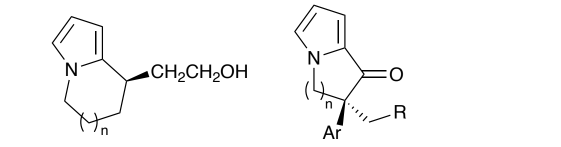
Scheme 80. Functionalised pyrrolizines *via* conjugate addition and aldol reaction.

Annulated pyrroles (**298**) bearing spirocyclic oxindoles were formed *via* an asymmetric cycloaddition involving α,β-unsaturated aldehydes (**299**) and 3-pyrrolyl-oxindoles (**300**, **Scheme 81**).[159] This generally highly diastereoselective Michael/FC cascade sequence, using a chiral proline-derived catalyst **1** ((*S*), Ar = Ph, R = OTMS) and 2-fluorobenzoic acid (2-FBA), followed by dehydration, provided yields up to 93% and er values reaching 98.5:1.5.



Scheme 81. Michael-FC-dehydration cascade towards spirocyclic oxindoles.

Two examples feature intramolecular FC reactions of pyrroles pre-functionalised with α,β-unsaturated aldehydes. One sequence involved the use of a spiropyrrolidine-based organocatalyst and provided various azepine or indolizine frameworks, including those featuring a chiral quaternary centre (**301**, **Figure 13**).[160] Another strategy involved alkene hydroacylation and enantioselective α-(hetero)arylation to access heterocyclic ketones (**302**, **Figure 13**):[161] this reaction was facilitated using a Ni/NHC carbene catalyst system.

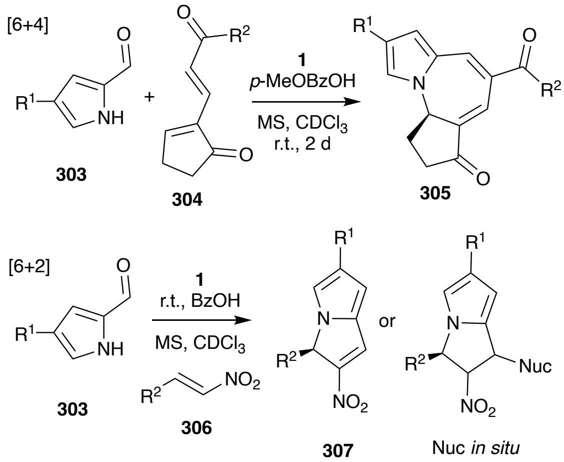


301
n = 1 or 2
up to 90% yield, 99:1 er

302
n = 1 or 2
up to 99% yield, 99.5:0.5 er

Figure 13. Chiral pyrroles annulated through the α-position and nitrogen atom.

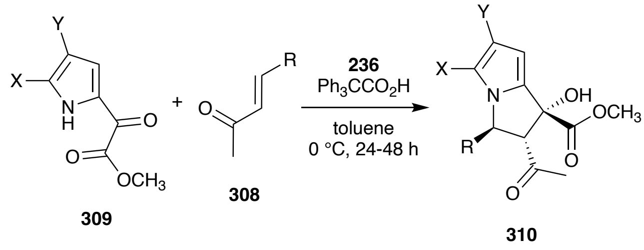
Highly regioselecive and enantioselective [6+4] and [6+2] cycloaddition reactions, through the use of a chiral aminocatalyst that enables formation of azafulvenium intermediates, provided chiral pyrroles annulated through the α- and *N*-positions (**Scheme 82**).[162] The [6+4] cycloaddition reaction involved the reaction of 2-formylpyrroles (**303**) and various electron deficient dienes (**304**) in the presence of a proline-derived organocatalyst (**1**, (*S*), Ar = Ph, R = F), with products (**305**) formed in yields up to 90% and er values reaching 99.5:0.5. The [6+2] cycloaddition reaction involving 2-formylpyrroles and unsaturated nitroalkenes (**306**) in the presence of a proline-derived organocatalyst (**1**, (*R*), Ar = Ph, R = OTBS) provided products (**307**) in yields up to 67% and er values reaching 95.5:4.5. Investigations into the reaction mechanism determined that the observed stereoselectivity was largely due to interactions between the bulky 4π-substrate and the pyrrolidine catalyst. This effect is more prominent in the [6+4] cycloaddition reaction and higher enantioselectivities were generally observed, as compared to the [6+2] reaction.



Scheme 82. Enantioselective [6+4] and [6+2] cycloadditions of pyrroles.

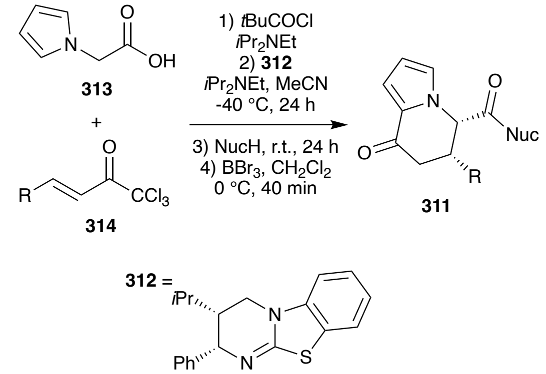
α,β-Unsaturated ketones

An aza-Michael-aldol cascade reaction involving α,β-unsaturated aldehydes (**308**) and 2-trihaloacetylpyrroles (**309**) gave 2-(1*H*-pyrrol-2-yl)-2-oxoacetates (**310**) (**Scheme 83**).[163] The highly diastereoselective cascade process was catalysed by a *Cinchona*-based primary amine organocatalyst (**336**, R = $OCH_2C(CH_3)_3$) to provide yields reaching 92% and er values up to 97.5:2.5.



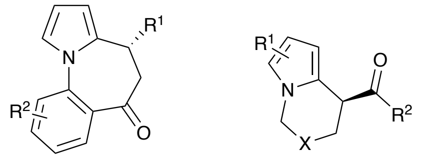
Scheme 83. Aza-Michael-aldol cascade.

A two-step diastereoselective process provided chiral dihydroindolizinones (**311**, **Scheme 84**). The first step used the chiral isothiourea hyperBTM catalyst **312** towards the enantioselective reaction of 2-pyrrolyl acetic acid (**313**) with trichloromethyl enones (**314**) to generate six-membered lactone rings that are nucleophilically opened *in situ*.[164] A subsequent intramolecular FC reaction provided products in yields up to 90% with er values reaching 99:1.



Scheme 84. Enantioselective Michael addition-lactonisation-ring-opening-FC.

Building on the previous report, a one-pot process to highly-functionalised tetrahydroindolizines was developed.[165] Several products were identified, and yields thus varied. The desired products were obtained with diastereoselectivity reaching 95:5, and with er values up to >99:1. Other examples of the synthesis of chiral annulated pyrroles *via* α,β-unsaturated ketones include an asymmetric ring-closing alkylation reaction of pyrroles functionalised with α,β-unsaturated ketones in the presence of a CPA (**315**, **Figure 14**).[166] Another approach utilises a CPA-ruthenium catalyst system to catalyse an olefin metathesis that is followed by intramolecular FC alkylation of *N*-tethered olefin pyrroles and enones (**316**, **Figure 14**).[167]



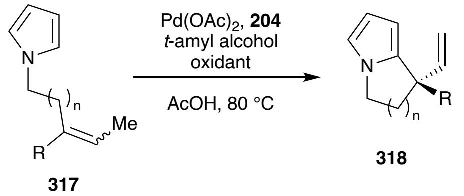
315
up to 99% yield,
96.5:3.5 er

316
X = CH_2 or CH_2O
up to 88% yield, 96.5:3.5 er

Figure 14. Chiral pyrroles annulated through the α- and *N*-positions.

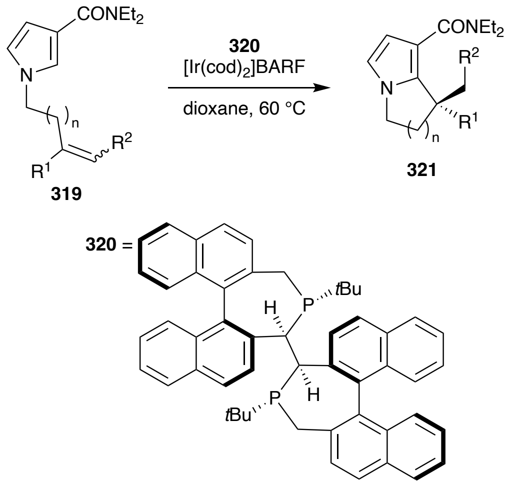
Olefins

Appending alkenyl functionality through the N-atom of pyrroles enables ring closure such as to generate chiral pyrroles annulated through the α- and *N*-positions. A Pd-catalysed oxidative asymmetric Fujiwara-Moritani alkene arylation ring closure reaction of substituted olefin *N*-alkyl pyrroles and indoles in the presence of a nicotine-derived oxazoline ligand (**204**, R^1 = *i*Pr, R^2 = 5-COOMe) provided annulated products (**318**) in yields up to 47% and er values reaching 85:15 (**Scheme 85**).[168]



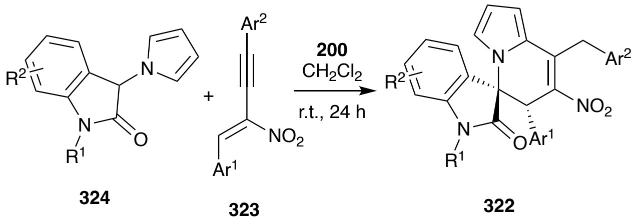
Scheme 85. Fujiwara-Moritani ring closure reaction of substituted *N*-alkyl pyrroles.

Adapting this work through utilisation of a hybrid CpRu/Brønsted acid-catalysed system enabled the dehydrative cyclisation of pyrroles.[169] Products were formed in yields up to 99% and er values reaching 99:1. In a similar vein, an enantioselective intramolecular hydrocarbonation involving alkene-tethered pyrroles (**319**), an Ir(I) catalyst and a chiral (*S*)-binapine ligand (**320**) provided chiral annulated pyrroles (**321**) in yields reaching 99% with excellent er values (**Scheme 86**).[170] The proposed mechanism identified a carbometallation step as critical to the stereoselectivity of the reaction as the transition state leading to the *S* isomer is significantly more stable than that for the *R* enantiomer.



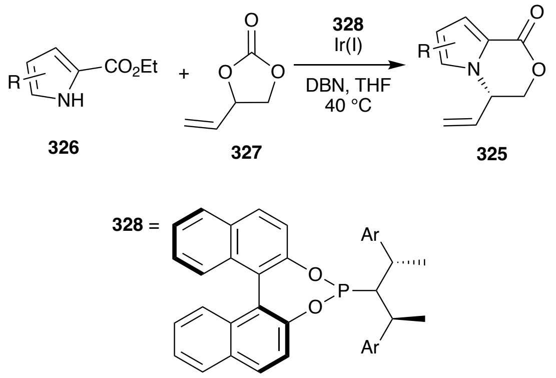
Scheme 86. Intramolecular hydrocarbonation reaction on alkene tethered pyrroles.

Access to annulated pyrroles bearing spirocycles (**322**) was achieved *via* a [3+3] cyclisation process involving a Michael/FC cascade reaction of 1,3-nitroenynes (**323**) and 3-pyrrolyloxindoles (**324**, **Scheme 87**).[171] This process was catalysed using a chiral squaramide *Cinchona* alkaloid catalyst (**200**, R = *i*Pr), and provided yields up to 95% and er values reaching 98.5:1.5



Scheme 87. Michael/FC reaction of 1,3-nitroenynes and 3-pyrrolyloxindoles.

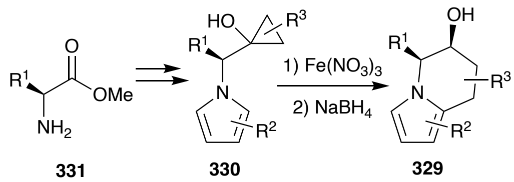
An enantioselective method to afford tricyclic oxazinoindolones (**325**) was extended to 2-carboxylated pyrroles (**Scheme 88**).[172] This method involved an allylation/lactonisation cascade reaction between pyrrolic esters (**326**) and vinyl cyclic carbonates (**327**) in the presence of an Ir(I) catalyst and a chiral phosphoramidite ligand (**328**, Ar = Ph). Various vinyl cyclic carbonates and pyollic esters were used to afford yields up to 80% and er values up to 98:2.



Scheme 88. Asymmetric cascade allylation/lactonisation of pyrollic esters.

Miscellaneous reactions towards chiral pyrroles annulated through the α-position and the nitrogen atom

5,6,7,8-Tetrahydroindolizines are a useful scaffold *via* which to access alkaloids containing pyrrolic and/or pyrrolidinyl moieties.[173] 5,6,7,8-Tetrahydroindolizines (**329**) were synthesised *via* oxidative radical ring opening of the cyclopropanol unit followed by cyclisation to form a 6-membered ring courtesy of attack at the α-position of the pyrrole (**Scheme 89**). 5,6,7,8-Tetrahydroindolizines were afforded in yields up to 90% with dr values >20:1. The requisite pyrrolylcyclopropanols (**330**) were synthesised *via* Clauson-Kass pyrrole synthesis using enantiopure α-ketoamines (**331**) and subsequent Kulinkovich reaction.



Scheme 89. Clauson-Kass pyrrole followed by Kulinkovich reaction to afford pyrrolylcyclopropanols. Radical ring opening of cyclopropanol affords 5,6,7,8-tetrahydroindolizines.

Pyrrole-type *Stemona* alkaloids (**332**, R= O or heterocycle) are annulated *via* the α-position and the nitrogen atom of pyrrole (**Figure 15**).[174] *Stemona* alkaloids have been implicated in a range of biological applications. The key pyrrolic intermediate was formed *via* deoxygenation of a γ-hydroxy pyrrolidone moiety, promoted by Lawesson's reagent.[175]

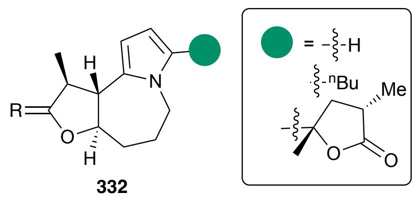
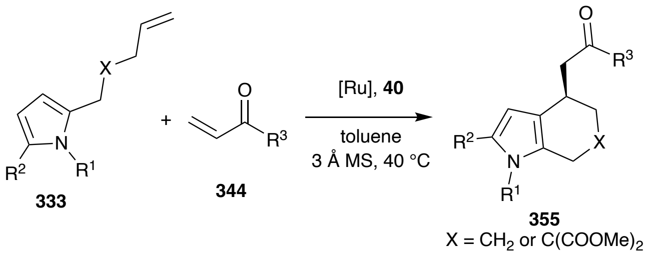


Figure 15. Pyrrole-type *Stemona* alkaloids.

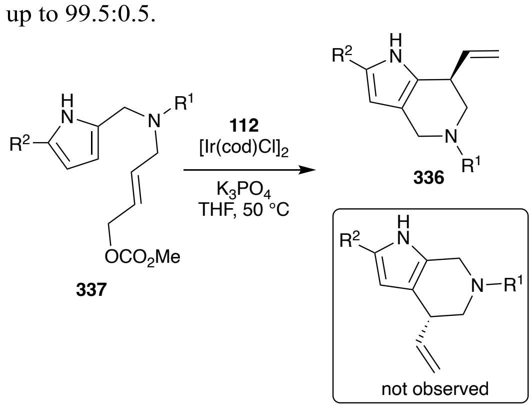
Chirality of pyrroles annulated through the α- and β-positions

A reaction sequence involving olefin metathesis and subsequent intramolecular FC alkylation reactions provides annulated chiral pyrroles. This involved the reaction between pyrroles and α,β-unsaturated ketones (**334**) to provide 4,5,6,7-tetrahydroindoles (**335**) using a BINOL-derived CPA additive (**40**, (*S*), R = 1-naphthyl) and the second generation Hoveyda-Grubbs ruthenium catalyst (**Scheme 90**).[176] After cyclisation, products were formed in yields reaching 93% with er values up to 96.5:3.5.



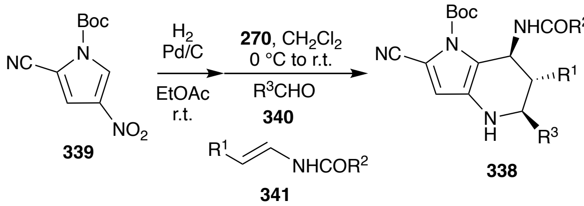
Scheme 90. Olefin metathesis and subsequent intramolecular FC alkylation.

Other work showcased an enantioselective synthesis of polycyclic pyrroles and indoles through an Ir-catalysed intramolecular allylic alkylation reaction in the presence of a chiral ligand (**112**, R = (*p*-Ph)C_6H_4, X = H, Y = Tf) whereby the unanticipated product **336** was formed (**Scheme 91**).[177] An unexpected migration of the methylene group occurred: the original pyrrole (**337**) is α-substituted, yet this substituent appears at the adjacent β-position in the product reaction. Investigations into the reaction mechanism identified a dearomatised spiro intermediate to be responsible for the migration. Products were formed in yields reaching 95% and er values up to 99.5:0.5.



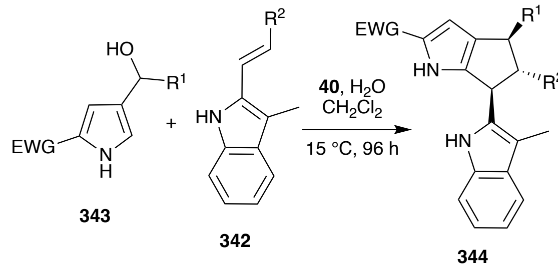
Scheme 91. Ir-catalysed intramolecular allylic alkylation, with migration.

An enantioselective method towards highly functionalised annulated α-β chiral pyrroles (**338**) was developed. A three-component Povarov reaction involving aminopyrroles (**339**), aldehydes (**340**) and enecarbamates (**341**), catalysed by a BINOL-[H8]-derived CPA catalyst (**270**, (*R*), Ar = *p*-ClC_6H_4), provided products in yields reaching 70% with er values approaching 97.5:2.5 (**Scheme 92**).[178]



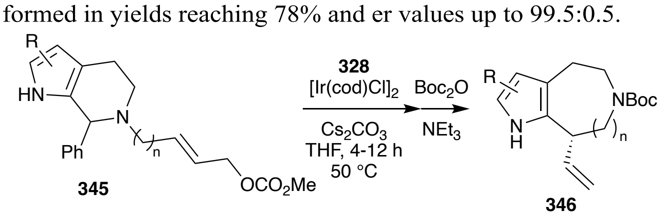
Scheme 92. Three-component Povarov reaction towards annulated chiral pyrroles.

Another annulation employs a [6+2]-cycloaddition between 2-vinylindoles (**342**) and 3-methide-3*H*-pyrroles (**343**) in the presence of a BINOL-derived CPA catalyst (**40**, (*R*), R = 2,3,5,6-Me_4C_6H), **Scheme 93**).[179] The resulting cyclopenta[b]pyrroles (**344**) contain three stereogenic centres and were afforded in yields up to 78% with er and dr values of 98:2 and >20:1, respectively.



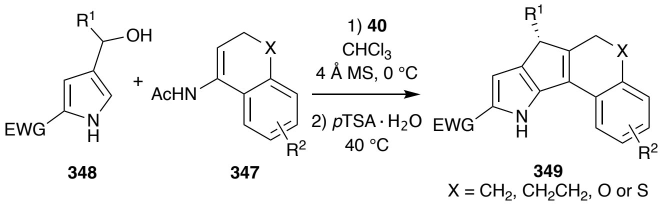
Scheme 93. Synthesis of cyclopenta[b]pyrroles *via* [6+2]-cycloaddition of 3-methide-3*H*-pyrroles with 2-vinylindoles.

Ring expansions of annulated pyrroles (**345**) are accessible *via* an Ir-catalysed sequence involving an allylic dearomatisation, followed by a retro-Mannich and lastly a hydrolysis of the iminium intermediate to form seven- and eight-member ring complexes (**346**, **Scheme 94**).[180] The associated chirality observed in this reaction is due to the chiral phosphoramidite ligand (**328**, Ar = 2-OMeC_6H_4), and was independent of the enantiomeric nature of the starting material. Products were formed in yields reaching 78% and er values up to 99.5:0.5.



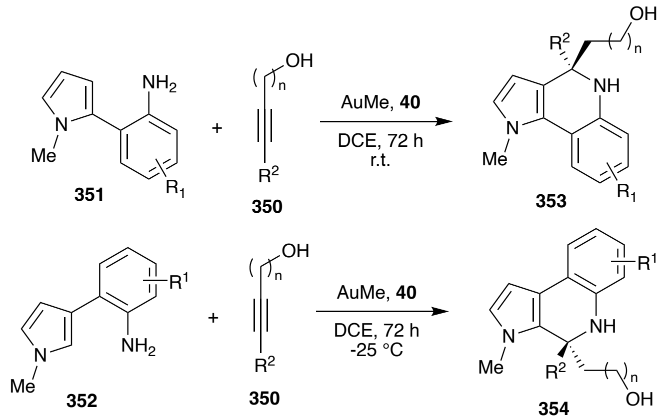
Scheme 94. Ir-catalysed allylic dearomatisation/retro-Mannich/hydrolysis.

The enantioselective addition of cyclic enamides (**347**) and 3-methide-3H-pyrroles (generated *in situ via* dehydration of the corresponding alcohol **348**), followed by cyclisation and elimination, provides chiral pyrroles (**349)** annulated through the α- and β-positions and featuring four rings (**Scheme 95**).[181] Polycyclic products were formed in yields reaching 97% with er values up to 98:2. Investigations into the reaction mechanism determined that double hydrogen bonding between the chiral BINOL-derived CPA catalyst (**4**, ((*R*), R = 2,6-$Et_2C_6H_3$) and both reagents provides a transition state that directs addition to the *Si*-face of the enamide conjugate.



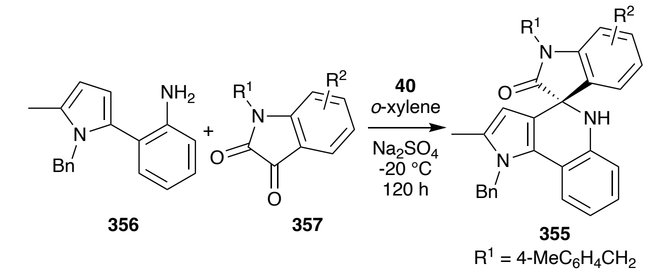
Scheme 95. [3+2] Cycloannulation towards chiral pyrroles.

Similar to the synthesis of pyrroles annulated through the α-position and the N-atom, pyrroles functionalised with anilines can be employed to access pyrroles annulated through the α- and β-positions: protection of the nitrogen atom is often key to achieving the desired regioselective control. A Au(I) and BINOL-derived CPA (**40**, (*S*), R = 2,4,6-(iPr)$_3$C$_6$H$_2$) catalyst system enabled the enantioselective hydroamination and hydroarylation of alkynes featuring a remote hydroxyl group (**350**, **Scheme 96**).[182] Placing aniline on the α- or β-position of pyrrole (**351** and **352**, respectively) results in products annulated and chiral through the α- and β-positions (**353** and **354**, respectively). Similarly, placing the aniline on the N-atom of the pyrrole enables synthesis of chiral pyrroles annulated through the *N*- and α-positions. Products were formed in yields reaching 90% with er values up to 99.5:0.5. The proposed reaction mechanism attributes the stereoselectivity to hydrogen bonding interactions in the transition state involving an imino alcohol complex and the CPA catalyst.



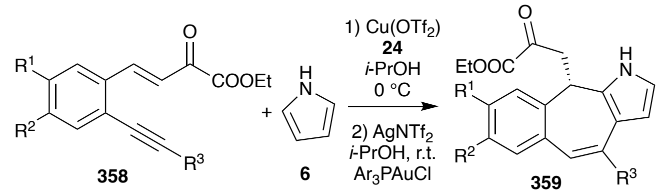
Scheme 96. Enantioselective hydroamination-hydroarylation of alkynes.

Another synthesis of annulated pyrroles functionalised with anilines (**355**) involves a Pictet-Spengler reaction of 2-(1-benzyl-5-methyl-1*H*-pyrrol-2-yl)aniline (**356**) with isatins (**357**) in the presence of a BINOL-derived CPA catalyst (**40**, (*R*), R = 2,4,6-(iPr)$_3$C$_6$H$_2$), **Scheme 97**).[183] Products were formed in yields up to 90% and er up to 94:6.



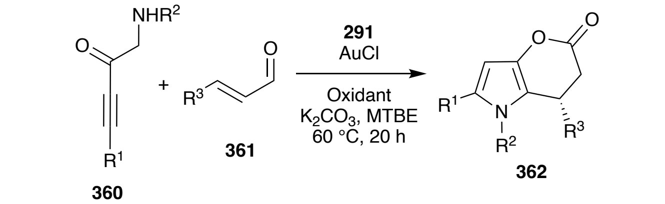
Scheme 97. Reaction of 2-(1-benzyl-5-methyl-1*H*-pyrrol-2-yl)aniline and isatins.

An enantioselective one-pot dual catalytic system involving pyrrole and an alkyne (**358**) was catalysed by a Cu(II) proline ligand (**24**, Ar = Ph) system to afford the requisite FC alkylation product: subsequent cyclisation afforded the desired 7-membered ring **359** in the presence of a Au(III) catalyst and AgNTf$_2$ (**Scheme 98**):[29] products were formed in yields reaching 96% and er values up to 98:2. The FC alkylation was first optimised using β,γ-unsaturated α-ketoesters, thus leading to non-annulated pyrroles featuring chirality at the α-position.



Scheme 98. FC annulation using a one-pot dual catalytic system.

α-Amino-ynones (**360**) and enals (**361**) underwent an enantioselective cascade annulation, catalysed by a Au(I) and NHC (**291**, Ar = Mes) catalyst system, to afford the desired compounds (**362**) in yields up to 84% with er values up to 99.5:0.5 (**Scheme 99**).[184] The proposed mechanism involves a relay system in which Au(I) catalyses reaction of α-amino-ynones and enals.



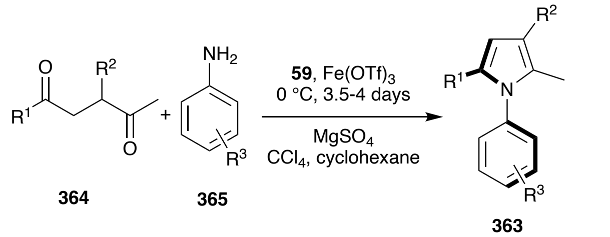
Scheme 99. α,β-Annulated pyrrole synthesis *via* enantioselective Au(I)/NHC relay catalysis.

Axially chiral pyrroles

This review has discussed the generation or incorporation of stereochemistry through point chirality (*i.e.*, stereogenic/chiral centres). Pyrroles may also exhibit stereochemical features by virtue of restricted rotation of substituents (axial chirality.

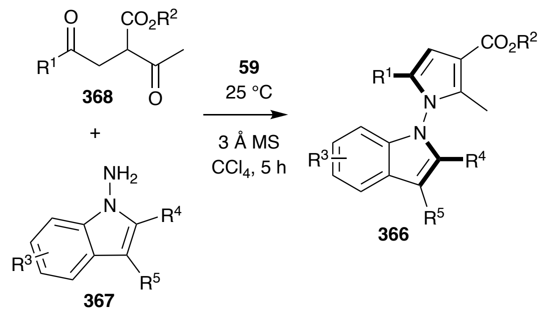
Axial chirality though the nitrogen atom of pyrroles

This section discusses axial chirality of pyrrole-containing compounds beginning with those that are formed using Paal-Knorr pyrrole synthesis. One group synthesised a wide variety of axially chiral arylpyrroles (**363**) through an asymmetric Paal-Knorr reaction of 1,4-diones (**364**) and anilines (**365**).[185] These reactions were catalysed using a Lewis acid, with stereochemical induction provided by a SPINOL-derived CPA catalyst (**59**, (*S*), Ar = 9-anthracenyl). Products were formed in yields of up to 95% with er values reaching 99:1 (**Scheme 100**). The bulky substituted aryl groups at the 1- and 2-positions prevent interconversion of the two axially chiral enantiomers. An intriguing solvent effect is reported whereby the absolute configuration of the final product is reversed upon modification of the reaction solvent.

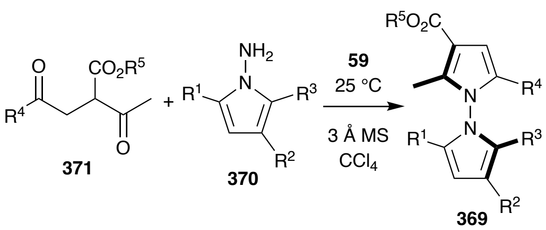


Scheme 100. CPA promoted Paal-Knorr synthesis affording axially chiral pyrroles.

An organocatalytic asymmetric synthesis of axially chiral *N*,*N′*-pyrrolylindoles (**366**) involves the condensation of *N*-aminoindoles (**367**) with 1,4-diketones (**368**), catalysed by a SPINOL-derived CPA system (**59**, (*R*), Ar = 2,4,6-$Me_3C_6H_2$) (**Scheme 101**).[186] Products were formed in yields reaching 98% with er values up to 98:2. This work was also applied to the synthesis of axially chiral *N*,*N′*-bispyrroles (**369**) using *N*-aminopyrroles (**370**) and 1,4-diketones (**371**) (**Scheme 102**): products were formed in yields up to 98% with er values broaching 98.5:1.5. A similar atroposelective strategy towards *N*,*N′*-bispyrroles., published the same year, utilises a double Paal-Knorr reaction.[187] The first step involves the reaction of hydrazines and 1,4-diones to form *N*-amino pyrroles, in the presence of trifluoroacetic acid and magnesium sulfate. The second step condenses another 1,4-dione with the *N*-amino functionalised pyrrole, and is catalysed by a SPINOL-derived CPA (**59**, (*R*), Ar = 2,4,6-(iPr)$_3C_6H_2$) and Fe(III) system. Products were formed in yields reaching 99% and er values up to 99.5:0.5, although yields and stereoselectivity are both reduced when the two transformations are performed one-pot.



Scheme 101. CPA-promoted Paal-Knorr synthesis of chiral *N*,*N′*-pyrrolylindoles.

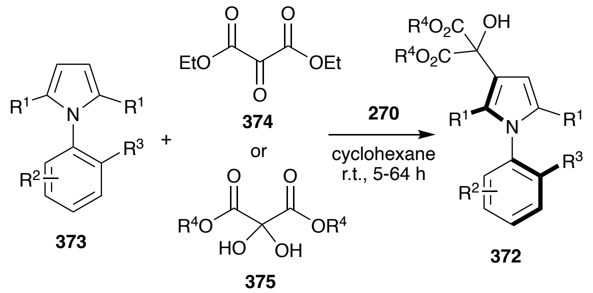


Scheme 102. CPA-promoted Paal-Knorr synthesis of chiral *N*,*N′*-bispyrroles.

Other synthetic approaches to axially chiral *N*-indolylpyrroles include a CPA-catalysed indole-forming reaction between 2,3-diketoesters and pyrrole-bearing 1,3-dione-derived enamines.[188] Products were formed in yields up to 92% with er values reaching 97:3. Similar work was published concurrently and featured a different catalyst system and scope.[189] Another CPA-catalysed reaction provides axially chiral indolylpyrroles via an asymmetric 5-*endo-dig* cyclisation of *o*-alkynylanilines appended with a pyrrole unit.[190] Products are formed in yields up to 99% with er values up to 95:5.

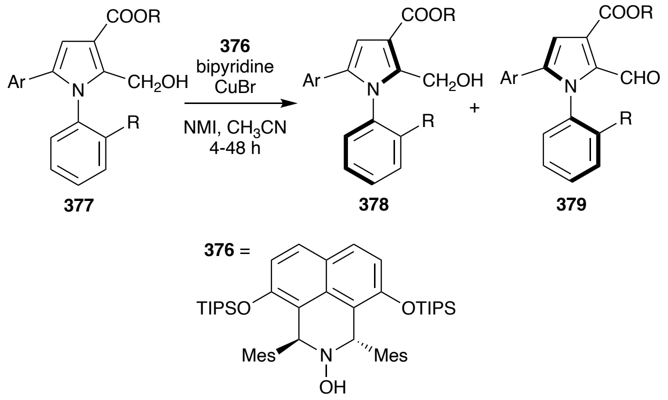
Other synthetic approaches to axially chiral *N*-arylpyrroles include a Au(I)-catalysed cyclisation/dehydration cascade involving intramolecular cyclisation of 1-amino-3-alkyn-2-ols: the enantiopurity of the amino acid derivatives is transferred into axial chirality within *N*-arylated pyrroles in yields up to 98% and er values reaching 99.5:0.5.[191] Furthermore, *N*-benzoylated pyrroles synthesised through the reaction of pyrrole and 2,6-disubstituted benzoyl chlorides were used to study the rates of interconversion of axially chiral stereoisomers.[192]

A variety of desymmetrisation approaches have been used to increase the barrier to aryl-aryl rotation and thus prohibit interconversaion of axially chiral diaryls. Atroposelective desymmetrisation and kinetic resolution was used to provide axially chiral *N*-arylpyrroles (**372**) in yields up to 99% and er values reaching 98.5:1.5 (**Scheme 103**).[193] The desymmetrisation involved β-functionalisation of pyrroles (**373**) *via* a reaction with diethyl ketomalonate (**374**), or mesoxalates (**375**), in the presence of a BINOL-[H8]-derived CPA (**270**, (*S*), Ar = 2,4,6-(iPr)$_3C_6H_2$). The proposed mechanism suggests that hydrogen bonding interactions between the ketomalonate and the CPA catalyst led to the formation of a chiral pocket key to the desymmetrisation. Functionalisation *via* the Friedel-Crafts reaction was also used to desymmetrise prochiral *N*,*N′*-bispyrroles via the use of diethyl ketomalonate and a Cu(II)/chiral BOX catalyst system.[194] Similar alkylation reactions include a rhodium-catalysed C-H insertion reaction that employed diazo substates to achieve desymmetrisation and concurrently increase the barrier to aryl-aryl rotation.[195]



Scheme 103. Atroposelective desymmetrisation of *N*-arylpyrroles.

Another approach involves a Cu(I) and chiral nitroxide (**376**) catalysed oxidative resolution of *N*-arylpyrroles (**377**) (**Scheme 104**).[196,197] Resolution provided one enantiomer of the alcohol **378** with er values reaching 3.5:96.5: the corresponding aldehyde **379** (of opposite axial chirality) was isolated with er values of 76.5:23.5. Given the oxidative nature of the resolution, the nature of the reaction atmosphere affected the outcome.



Scheme 104. Oxidative kinetic resolution of *N*-arylpyrroles.

A diastereo- and atroposelective synthesis of *N*-arylpyrroles utilised a light-induced phosphoric acid catalyst to enable axial C-N aryl-aryl resolution as well as the creation of synchronous quaternary point chirality (**380**, **Figure 16**).[198] Products were afforded in excellent yield, enantiopurity and diastereomeric ratio. Cu(I)-catalysed asymmetric C-H arylation, using a chiral bisphosphine oxide ligand, has also been used to provide axially chiral *N*,*N′*-bispyrroles in excellent yield and enantiopurity (**381**, **Figure 16**).[199] Atroposelective substitution at the α-position of pyrroles, catalysed by a chiral rhodium-based system, has been used to induce axial chirality (**382**, **Figure 16**).[200] Installation of the substituent, achieved through reaction of *N*-arylpyrroles with *N*-acryloyl-1*H*-pyrazole derivatives, is key to increasing the barrier to interconversion of the two atropoisomers: indeed, prior to α-functionalisation, the two axially-related rotamers freely interconverted at room temperature. Employing a similar approach to desymmetrisation, asymmetric C-H activation of aryl groups situated at the N-atom of pyrroles increased the barrier to axial N-C/pyrrole-aryl rotation. C-H activation of the aryl group, utilising L-*tert*-leucine and Pd-electrocatalysis, thus enabled the atroposelective synthesis of axially chiral bi(hetero)aryl complexes (**383, Figure 16**).[201] Another example showcases a similar approach to desymmetrisation and featuring C-H functionalisation at the a-position of the pyrrolic moiety in a pyrrole-indole diaryl system.[202] Similarly, another group performed asymmetric C-H alkylation with acrylates using an Ir-catalysed system to alkylate the indole motif.[203]

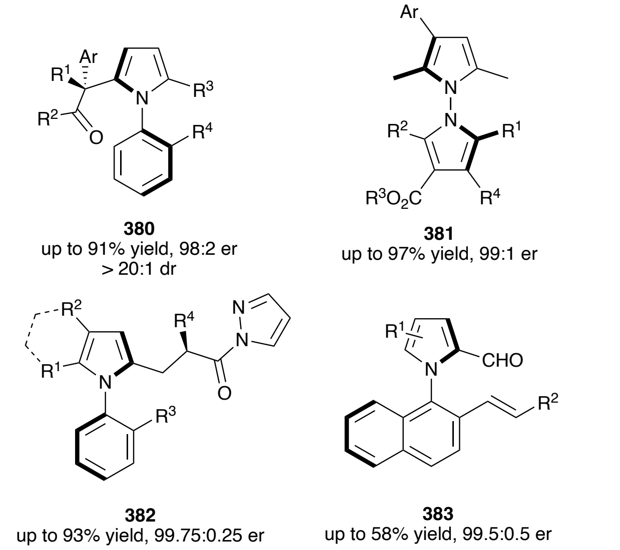
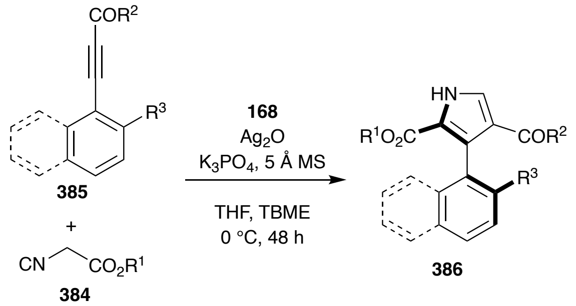


Figure 16. Axially chiral pyrroles *via* desymmetrisation.

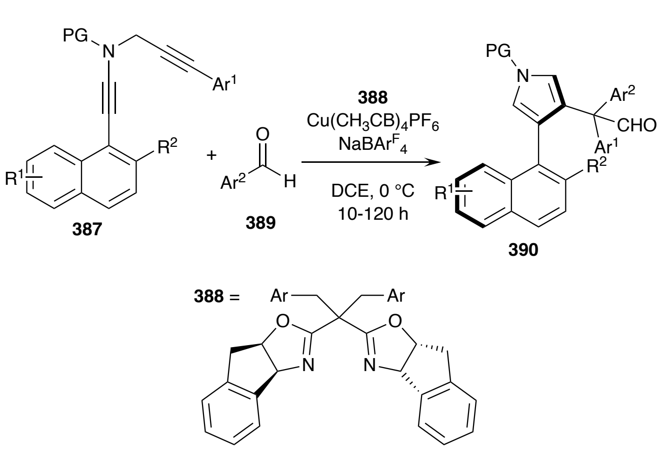
Axial chirality though the α- or β-positions of pyrroles

Axial chirality achieved through connectivity at the α- and β-positions of pyrroles has also been achieved stereoselectively. β-Substitution was achieved *via* heteroannulation involving α-isocyanoacetates and β-aryl-α,β-alkynic ketones (**385**) in the presence of silver oxide and a chiral phosphine ligand derived from a *Cinchona* alkaloid (**168**, **Scheme 105**).[204] Products (**386**) were formed in yields reaching 98% and er values up to 98:2.

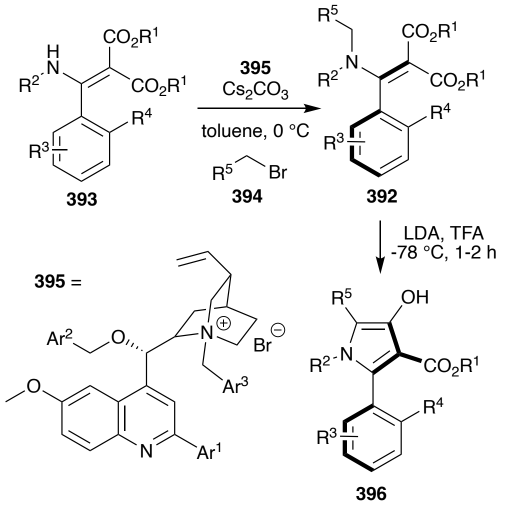


Scheme 105. Asymmetric heteroannulation leading to atropoisomerism.

A Cu-catalysed cyclisation of diynes (**387**) and aldehydes, in the presence of a chiral bisoxazoline ligand (**388**), provides access to axially chiral naphthylpyrroles (**390**) with versatile substitution pattern (**Scheme 106**).[205] In a detailed mechanistic investigation to understand mechanism, regioselectivity and steroselectivity, a 1,3-dioxolane key intermediate was isolated. The desired products were afforded in yields up to 98% with er values up to 99.5:0.5. Another example of diyne cyclisation includes a [4+1] annulation of vinyl cations with 1,2-diketones to form axially chiral arylpyrroles bearing 1,3-dioxole moieties.[206]

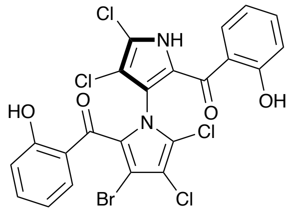


Scheme 106. Asymmetric synthesis of naphthylpyrroles through the β-position of pyrroles.



Scheme 107. Cyclisation of atropisomeric alkenes towards axially chiral pyrroles.

A Barton-Zard approach to axially chiral pyrroles featuring aryl groups at the β-position has also been reported.[207,208] The reaction couples *α*-substituted nitroolefins and α-isocyano substrates, catalysed by a *Cinchona*-derived phosphine ligand in the presence of a Ag-based Lewis acid. Products were formed with yields up to 99% and up to 98:2 er. The utility of pyrrole-based atropisomers featuring suitably-placed phosphino moieties as ligands for asymmetric catalysis was demonstrated for [4+2] cycloaddition. A Paal-Knorr reaction was used to synthesise the racemic bispyrrole core within the first total synthesis of Marinopyrrole B (**391**, **Figure 17**),[209] an antibacterial for methicillin-resistant *Staphylococcus aureus*.

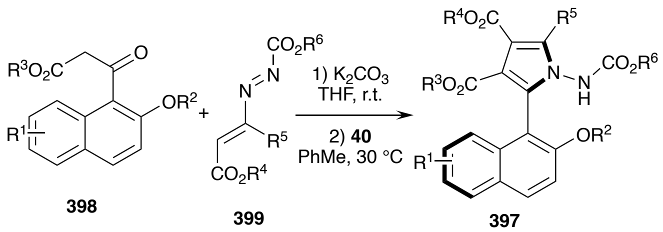


391

Figure 17. Antibacterial (-)-Marinopyrrole B, featuring bipyrrolic axial chirality.

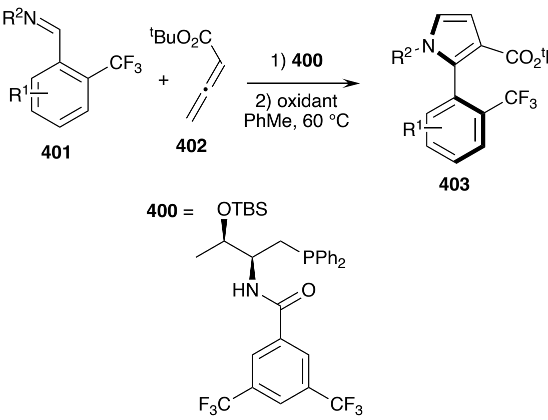
Direct chirality transfer from atropisomeric alkenes has been used to stereoselectively prepare pyrroles with axial chirality by virtue of incorporation of aryl groups at the α-position (**Scheme 107**).[210] The requisite alkenes (**392**) were synthesised through asymmetric organocatalytic *N*-alkylation reactions of enamines (**393**) and allyl bromides (**394**) in the presence of a *Cinchona*-derived organocatalyst (**395**, Ar^1 = 3,5-(tBu)$_2C_6H_3$, Ar^2 = 3,5-(CF_3)$_2C_6H_3$, Ar^3 = 3,4,5-$F_3C_6H_2$). The subsequent cyclisation was facilitated using lithium diisopropylamide to provide pyrroles (**396**) in yields up to 96% and er values reaching 97:3. Another group reported a stereoselective cyclisation reaction that yields a pyrrole boasting both C-C and C-N axial chirality, *i.e.*, through the α-position and through the N-atom.[211]

The synthesis of α-arylpyrrole amino alcohols (**397)** that feature restricted rotation has been explored.[212] An Attanasi reaction between 1,3-dicarbonyl compounds (**398**) and azoalkenes (**399**) in the presence of a BINOL-derived CPA catalyst (**40**, (*R*), R = 10-phen-9-anthracenyl) afforded the desired product in yields up to 89% with er values reaching 99.5:0.5 (**Scheme 108**). Further work involved chiral resolutions with either quinine-catalysed allylation or isothiourea-catalysed acylation.[213]



Scheme 108. Attanasi reaction of 1,3-dicarbonyl compounds and azoalkenes.

Threonine-derived phosphines (**400**) were employed to catalyse an asymmetric [3+2] annulation and oxidative central-to-axial chirality transfer sequence to afford α-arylpyrroles (**Scheme 109**).[214] Aldimines (**401**) were reacted with allenoates (**402**) to afford the enantioenriched diaryls (**403**) in yields up to 75% with er values reaching 97:3.



*Both enantiomers available in high enantiomeric ratio by varying catalysis conditions

Scheme 109. Asymmetric [3+2] annulation of aldimines and allenoates.

Conclusions

Through consideration of the position and source of stereochemical features, pyrroles bearing chirality about the carbon atoms and the N-atom have been reviewed 2010-2023. With recent interest in axial chirality, the pyrrole motif is poised to attract considerable interest given the ability to synthesise analogues with rich, and dense, functionality. This review identifies various strategies by which to stereoselectively produce pyrroles. These include pyrrole-forming reactions, and reactions that utilise the reactivity profiles of pre-formed pyrroles in order to generate chiral centres and/or append functionality such that (stable) atropoisomerism is achieved. In summarising the recent literature it appears that proline-based and CPA-based catalysis are by far the most commonly adopted strategies towards the stereoselective synthesis of pyrroles. Furthermore, emergent curiosity in pyrroles that are (homo)chiral courtesy of atropoisomerism is apparent: reasons for this perhaps lie within a burgeoning interest in active pharmaceutical ingredients offering such stereochemical platforms in a bid for new intellectual property and new, more effective treatment options. As the synthetic chemistry of pyrroles is better understood and harnessed, the stereoselective synthesis of pyrroles bearing point-chirality and facilitating axial chirality will undoubtedly see continued advancement.

Conflicts of interest

There are no conflicts to declare

Acknowledgements

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