Pyrroles as Dienes in (4+3) Cycloadditions
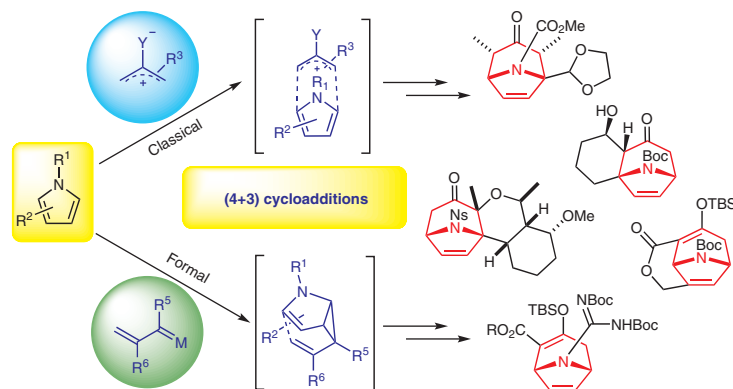
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Abstract This short review summarizes the examples to date of successful (4+3) cycloadditions, including formal (4+3) cycloadditions, where pyrrole derivatives reacted as the diene component, to provide aza-bridged bicyclic and polycyclic adducts.
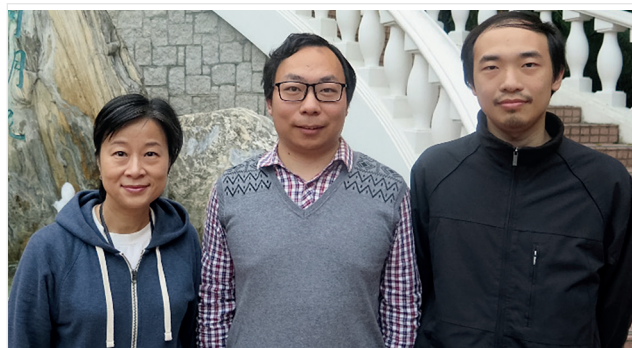
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Pauline Chiu studied at the University of Toronto, Canada. She obtained her M.Sc. degree working on silene chemistry with the late Professor Adrian G. Brook, and her Ph.D. on reactions of oxabicyclic compounds with Professor Mark Lautens. Subsequent to her postdoctoral studies on the total synthesis of gelsemine with Professor Samuel J. Danishefsky at Columbia University, she started her independent career at the Department of Chemistry at The University of Hong Kong, where she has been Full Professor since 2011. Efforts in the Chiu group are directed to research on novel synthetic reactions, and total synthesis of natural products. Her co-authors on this paper are Fan Hu and Jerome P. L. Ng, first- and final-year graduate students in the Chiu group.

1   Introduction

Natural products have played a vital role in the history and discovery of drugs.[1] Alkaloids that can be obtained by isolation using acid-base extractions are among the earliest classes of compounds to be studied and identified from natural sources.[2]
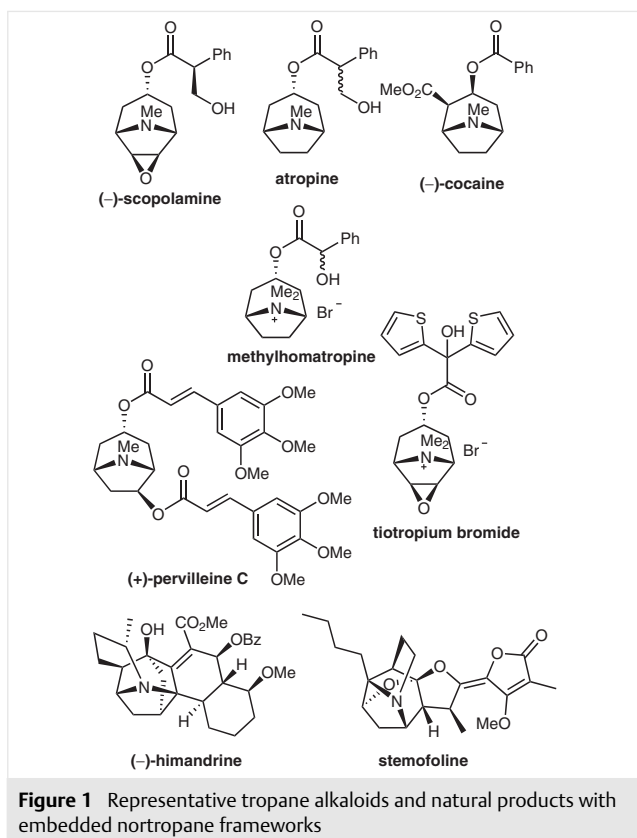
One class of these 'true alkaloids'[2] are the tropanes, characterized by *N*-methyl-8-azabicyclo[3.2.1]octane frameworks (Figure 1), which are among the world's oldest plant medicines.[3] The tropanes were first identified from two plant sources; from the Erythroxylaceae family, to which the coca plant belongs, was isolated the infamous cocaine.[4] The pervilleines are toxic alkaloids isolated from the extracts of the roots of *Erythroxylum pervillei* that shows multidrug resistance reversal ability against MDR cancer cell lines.[5] From the Solanaceae family was isolated many bioactive alkaloids that are powerful anticholinergics. Scopolamine (Figure 1), also known as hyoscine, was isolated from *Hyoscyamus niger* and is a sedative and treats nausea and vomiting.[6] Atropine isolated from *Atropa belladonna*, is a stimulant and pupil dilator, and is a treatment for bradycardia (i.e., slow heart rate) and poisoning.[7] Both of these are on the WHO's Model List of Essential Medicines.

Homatropine methylbromide, and tiotropium bromide are synthetic drugs modelled on the atropine skeleton (Figure 1). The latter was marketed as Spiriva by Boehringer Ingelheim for the management of chronic obstructive pulmonary disease.[8] There are more than 20 medicines currently in the market with the tropane framework,[9] and therefore it is a highly desirable scaffold from a pharmacological perspective. Tropane alkaloids frameworks are also embedded in various natural products, such as himandrine and stemofoline (Figure 1).[10]

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Figure 1 Representative tropane alkaloids and natural products with embedded nortropane frameworks

To secure the tropane, or more generally the nortropane (desmethyltropane) nucleus by laboratory synthesis,[11] a retrosynthetic analysis would suggest a (4+3) cycloaddition with a pyrrole as the diene component, as a convergent and step-economical assembly of the 8-azabicyclo[3.2.1]octane framework. Moreover, stereochemically defined, amine-substituted arrays can also be generated from the cleavage of 8-azabicyclo[3.2.1]octene products of pyrrole (4+3) cycloadditions, to exploit the anticipated stereoselectivity generally available from cycloaddition reactions.

However, effective (4+3) cycloadditions of pyrrole derivatives are considerably more challenging to accomplish, and there are far fewer examples in the literature compared to the analogous reactions of furans.[12] Pyrroles are more aromatic, and the tendency toward aromaticity competes with cycloaddition reactions, which are necessarily dearomatizing.[13] Moreover, pyrroles are rather reactive towards acids, electrophiles, oxidants, and polymerization, which consume the pyrroles from the intended cycloadditions. Finally, the pyrrole cycloadducts themselves are also comparatively less stable and tend to degrade to rearomatized pyrroles as decomposition products.

Yet, due to the high value of the tropane skeleton, studies on the (4+3) cycloaddition of pyrroles with various three-atom dienophiles have continued. Despite the gener-

al incompetence of pyrroles as dienes, there are successful reports in the literature. This short review aims to summarize the range of aza-bridged bicyclic or tricyclic cyclo-adducts that have been obtained from engaging pyrrole derivatives as dienes successfully for (4+3) cycloadditions, through various strategies. Efforts and strategies to render these (4+3) cycloadditions enantioselective in order to procure enantiomerically enriched nortropane frameworks are also highlighted.

1.1 Classical (4+3) Cycloadditions of Allylic Cations and Related Electrophiles

Classical (4+3) cycloadditions generally involve the reaction of a diene **1** with an allylic cation (typically 2-oxy-allylic cation **2**), although related electrophilic species also react (Scheme 1).[12]

**Scheme 1** Allylic cations in classical (4+3) cycloadditions of pyrroles
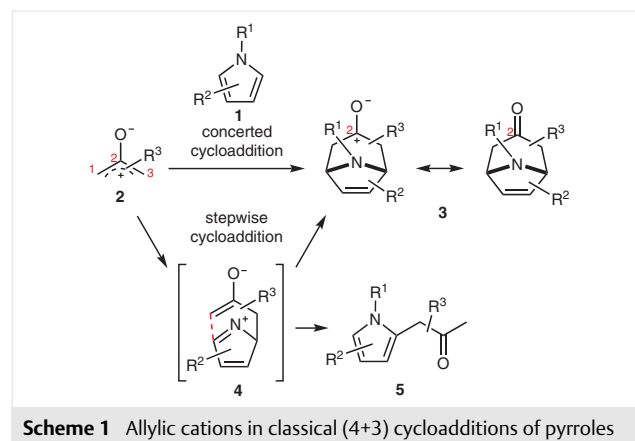
Since pyrroles are more electron-rich compared with furans, they have a characteristically high reactivity for electrophiles. The reactions tend to proceed as substitution reactions rather than additions, to restore aromaticity. When the bond formations are concerted, cycloadditions are more favored.[14] Via a stepwise mechanism, the 2*H*-pyrrolium cationic intermediate **4** stabilized by the nitrogen atom is formed, and its aromatization is a major side reaction that produces a Friedel–Crafts substitution product **5** rather than cycloadduct **3**.[15]

Allylic cations, oxyallyl cations, and their related electrophilic derivatives are reactive intermediates that have been generated in situ from a variety of precursors, and many react promiscuously with furans as dienes.[12] However, the requirements for reactions with pyrroles are more austere, and the properties of these dienophiles need to be tuned and matched to undergo (4+3) cycloaddition successfully with pyrrole derivatives. The pyrrole electron density can also be tuned and decreased by using N-protecting groups that are more electron-withdrawing.[16]

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As in typical (4+3) cycloadditions, pyrrole cycloadditions proceed via *endo*- and *exo*-transition states resulting in diastereomeric cycloadducts. Stepwise cycloadditions could generate additional diastereomers, as would the subsequent epimerizations of certain cycloadducts. Cycloadditions of unsymmetrical dienes and dienophiles would encounter issues of regioselectivity. These selectivities could vary depending on the exact reaction conditions.[17] This summary will have remarks on some of these, but due to the brevity of this review, the emphasis will be on reactivity issues, and readers are directed to the primary literature to seek out the details of each reaction of interest.

1.2 Formal (4+3) Cycloadditions via Domino Cyclopropanation/Cope Rearrangement Reactions

A very versatile method with wide scope for accomplishing an overall, formal (4+3) cycloaddition is via a domino cyclopropanation/Cope rearrangement involving a vinyl carbene, the most selective and commonly used being a metal carbene, as the dienophile.[18] In this reaction, catalytically generated metal carbenes **6** first cyclopropanate the diene **1**, and the resultant *cis*-1,2-divinylcyclopropane **7** then undergoes a Cope rearrangement to provide a cycloheptadiene **8** via a boat transition state (Scheme 2). This is a powerful synthetic strategy because of its possibility for enantioselection through using chiral auxiliaries or chiral catalysis, and its applicability to a wide range of dienes, including pyrroles. This reaction was developed largely due to the efforts of the Davies group and constitutes one of the most successful methods to access nortropane frameworks.
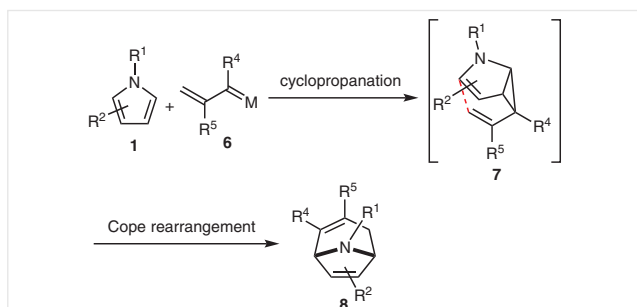
**Scheme 2** Formal (4+3) cycloadditions of pyrroles via cyclopropanation/Cope rearrangement

This reaction is favored by employing donor-acceptor carbenes generated from rhodium catalysts with comparatively electron-rich ligands. It is also favored by nonpolar reaction media and higher reaction temperatures that prevent bis-cyclopropanation of the pyrrole, to promote the Cope rearrangement instead to complete the cascade reaction.

2 Unsubstituted Pyrroles as Dienes in (4+3) Cycloadditions

2.1 α-Halo Ketones and α-Haloureas

Monohalogenated ketones engaged in the first reported (4+3) cycloaddition with furan in 1962.[19] α-Halogenated ketones generate oxyallylic cations for cycloaddition under basic and/or ionizing conditions, via deprotonation and enolate formation, then dehalogenation. Alternatively, enolate-type species like enamines have also been employed as intermediates.

There have only been a few examples of pyrrole derivatives that engaged in (4+3) cycloaddition with α-halo ketones. Mann's early studies showed that α-bromo ketone **9** underwent cycloaddition only with *N*-ethoxycarbonyl-protected pyrrole to provide a moderate yield of cycloadduct **10a** (Scheme 3).[20a] The same reaction with *N*-methylpyrrole generated the Friedel–Crafts product in 67% yield.
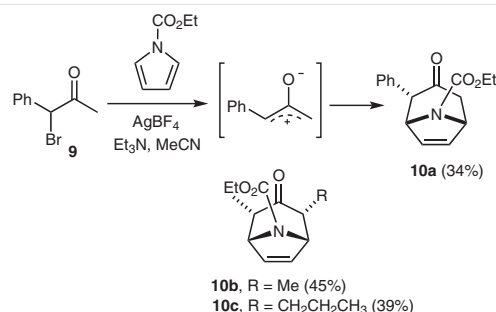
Scheme 3 (4+3) Cycloaddition of pyrrole with the oxyallyl cation derived from 1-bromo-1-phenylpropan-2-one[20a]

In 2006, MaGee and co-workers demonstrated a similar reaction involving bromo ketone **11** bearing a chiral oxazolidone auxiliary that underwent (4+3) cycloaddition with *N*-methoxycarbonyl-protected pyrrole **1a** (R¹ = CO₂Me) via a chiral oxyallylic cation.[20b] The yield was moderate, but the diastereoselectivity was high (Equation 1).
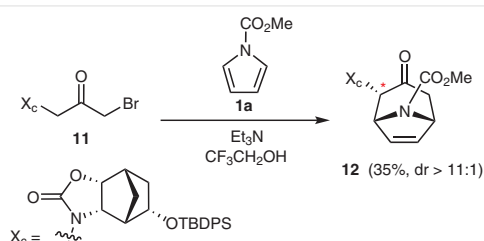
Equation 1 (4+3) Cycloaddition of methyl 1*H*-pyrrole-1-carboxylate and a chiral oxyallyl cation derivative[20b]

The Cha group studied the (4+3) cycloaddition of a cyclic, allylic cation with *N*-Boc-protected pyrrole **1b**.[21] The reaction of 2-chlorocyclohexanone under basic conditions

(Et₃N/CF₃CH₂OH) with **1b** resulted in low cycloaddition yields. However, pre-forming the corresponding enamine **13a**, and dehalogenating with silver tetrafluoroborate in the presence of **1b** generated aza-bridged tricyclic adduct **14a** in 52% yield as a single diastereomer (Scheme 4). Carpenter and co-workers reported another example of this reaction between enamine **13b** and N-tosylated pyrrole **1c**. The cycloadduct **14b** thus obtained was converted into **15**, a recyclable amine capable of mediating the photochemical reduction of CO₂.[22]
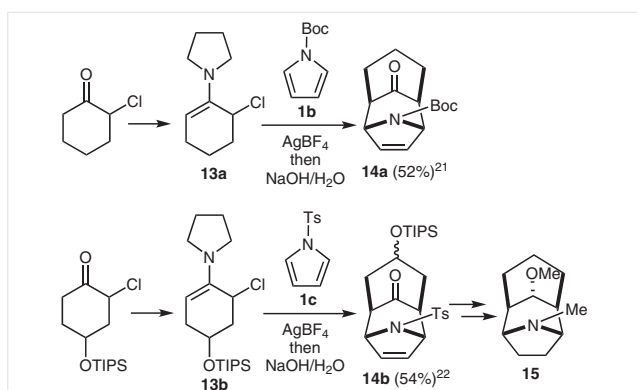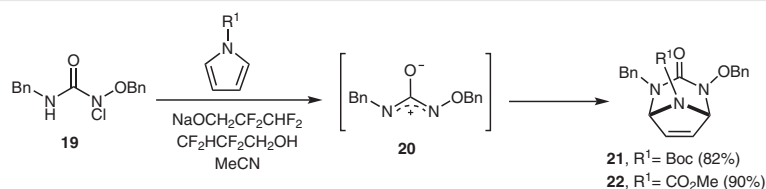

Scheme 4 (4+3) Cycloadditions of pyrroles and cyclic oxyallyl cations[21,22]

Kende and Huang generated chiral imine **16** from optically pure (–)-phenethylamine and 3-chloro-3-methyl-butan-2-one; the chiral imine **16** underwent asymmetric (4+3) cycloadditions with N-Cbz-protected pyrrole **1d** via chiral 2-aminoallyl cation **17** (Scheme 5).[23] After hydrolysis, 8-azabicyclo[3.2.1]octanone derivative **18** was obtained with 41% ee, but in a low yield. This reaction was sensitive to the electronic properties of the pyrrole, and attempts to engage N-methylpyrrole **1e** resulted only in Friedel–Crafts products in 50–70% yields.
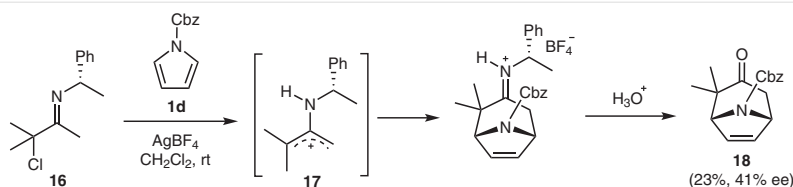
Under similar basic and ionizing conditions, chlorourea **19** is dehydrohalogenated to afford a diaza-oxyallic cation **20** that underwent (4+3) cycloadditions with various dienes, including pyrroles, to generate diazacycloadducts **21** and **22** in high yields (Scheme 6).[24]

2.2 α,α′-Polyhalo Ketones

Polybromo and polyiodo ketones under reducing conditions generate oxyallylic cations that undergo (4+3) cycloadditions.[25–28] Different reductants afford oxyallylic cations with different counterions, which influence the electronic properties of the resultant cations and their subsequent cycloadditions. This is a consequential issue for pyrrole cycloadditions where the success is quite dependent on electronic factors.

For electron-rich pyrroles such as N-methylpyrrole **1e** (Scheme 7), only the reduction of α,α′-dibromo ketones with NaI/Cu resulted in sodium oxyallylic cations, which are comparatively less electrophilic, that underwent (4+3) cycloaddition to any extent.[29] Other reductive methods that produce iron or zinc oxyallylic cations reacted with **1e** to give only Friedel–Crafts products.[30–32]

Pyrroles bearing electron-withdrawing R¹ groups on nitrogen are less nucleophilic, and (4+3) cycloadditions can proceed with more electrophilic oxyallyl cations generated under a wider range of reducing conditions, including Fe₂(CO)₉,[25,33,34] Zn/Cu,[17,27,28,36] Zn/B(OEt)₃,[37,38] and Et₂Zn.[39,40] The resulting cycloadducts having electron-withdrawing groups on the aza-bridge are also more stable under acidic conditions.[35]

Scheme 8 shows the results of cycloadditions with pyrroles bearing electron-deficient R¹ groups.[27,28,33,34,36,39,41,42] The ranges in yields shown are due to different results obtained by different reducing methods. In some cases, the yields varied even by using the same reductive methods, because the reaction conditions were further optimized.

Scheme 5 (4+3) Cycloadditions of N-Cbz-pyrrole and a chiral α-choro imine[23]

Scheme 6 (4+3) Cycloadditions of pyrroles with a diaza-oxyallylic cation[24]

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For example, Grée and co-workers obtained **30** in only 12% yield following the procedure of Mann and de Almeida Barbosa,[39] but they found that the use of excess **29** improved the yield of **30** to 88%.[41]

As the unsubstituted oxyallyl cation without any alkyl groups is too unstable to form, 1,1,3,3-tetrabromoacetone is used as a surrogate to generate the brominated oxyallyl cation **40** for (4+3) cycloadditions (Scheme 9).[35,36] Pyrroles bearing different electron-withdrawing N-protecting groups have also proceeded to (4+3) cycloadditions under these conditions. Cycloadduct **41** thus obtained is reduc-

tively debrominated to afford desired 8-azabicyclo[3.2.1]octenone **42**, a valuable *meso* intermediate for the synthesis of tropinoids and other natural products.[35,36,39,43–50]

Starting from *meso* **42**, Mann and de Almeida Barbosa reported a synthetic route to (±)-scopoline (Scheme 10).[39] The Noyori group converted **42** into (−)-hyoscyamine in 3–4 steps.[35] In 2008, the Perlmutter group enantioselectively desymmetrized **42** in an asymmetric synthesis of the cancer MDR reversal agent, (+)-pervilleine C,[45] and in 2010 Hodgson and co-workers reported a synthesis of (±)-peduncularine from **42**.[43]
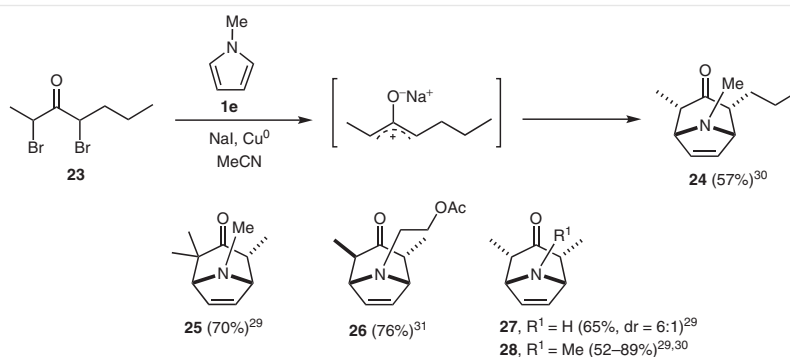
Scheme 7 (4+3) Cycloadditions of *N*-(electron-rich group)-substituted pyrroles[29–31]
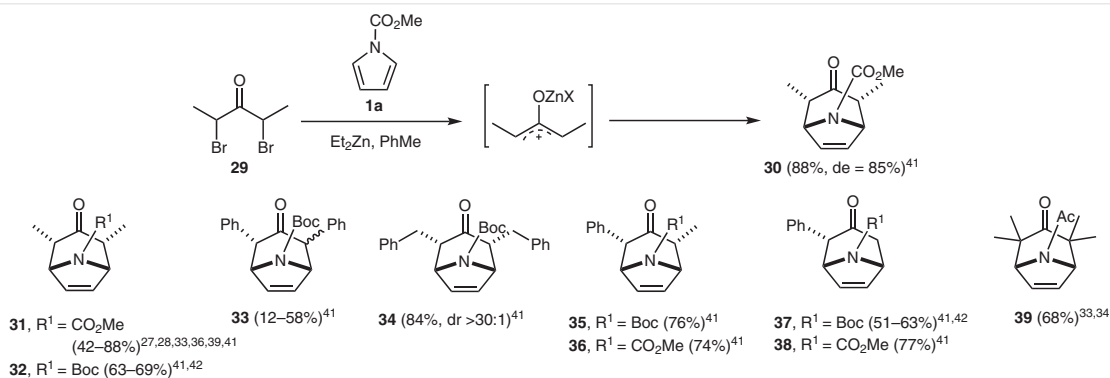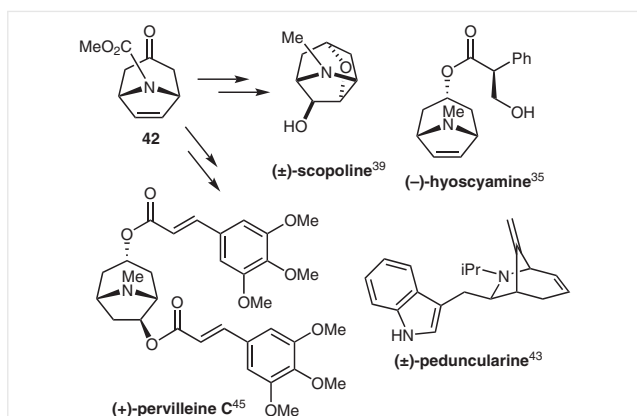

Scheme 8 (4+3) Cycloadditions of *N*-(electron-deficient group)-substituted pyrroles[27,28,33,34,36,39,41,42]
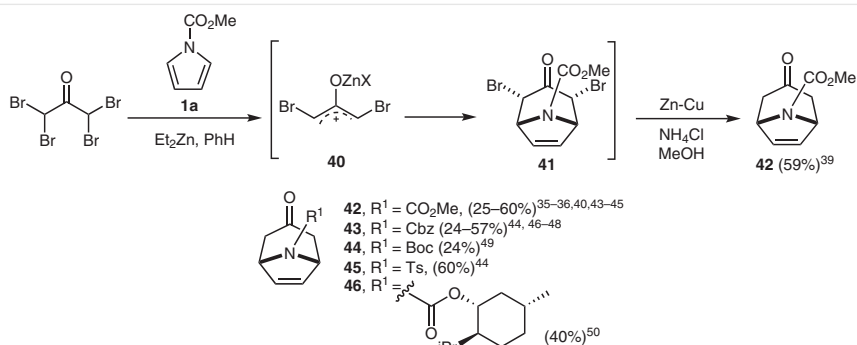
Scheme 9 (4+3) Cycloadditions of pyrroles with 1,1,3,3-tetrabromoacetone[35,36,39,43–50]

**Scheme 10** Natural products from a nortropinone precursor[35,39,43,45]

2.3   Siloxyallylic Alcohol Derivatives

Namba, Tanino and co-workers designed sulfur- and oxygen-substituted siloxyallylic alcohol derivatives **47a** and **47b**, respectively, to generate heteroatom-stabilized siloxy-allylic cations upon acid-induced dehydration (Scheme 11).[51,52] N-Acetyl-, N-benzyl-, and N-Cbz-protected, and un-protected pyrroles all failed to undergo cycloaddition; only N-sulfonylated pyrroles reacted, of which the most electron-deficient nosyl-protected **1f** reacted with the highest cycloaddition yields. These results suggested that electron-withdrawing effect of the pyrrole protecting group, rather than its steric bulkiness, exerted a greater impact to facilitate the (4+3) cycloaddition.

Siloxyallylic alcohol **55a** also underwent a similar (4+3) cycloaddition, showing that sufficient alkyl substitution also stabilized the siloxyallylic cation and promoted its formation.[51] The reaction in dichloromethane proceeded in 54% yield, but increased to generate a 67% yield of the *gem*-dimethylated **57** in the ionizing solvent hexafluoroisopropanol (HFIP) (Equation 2). However, the monomethylated alcohol **55b** failed to undergo cycloaddition under any conditions. These results indicated that a *gem*-dimethyl group is approximately as effective as a thiomethyl group in stabilizing the 2-siloxyallylic cation **56** for reaction with pyrroles, whereas a single methyl group is not sufficient.
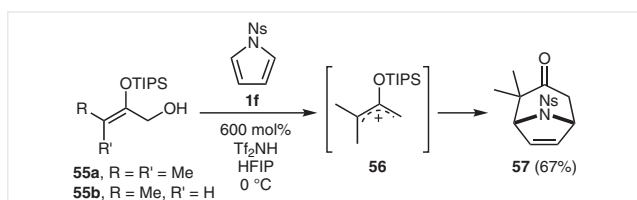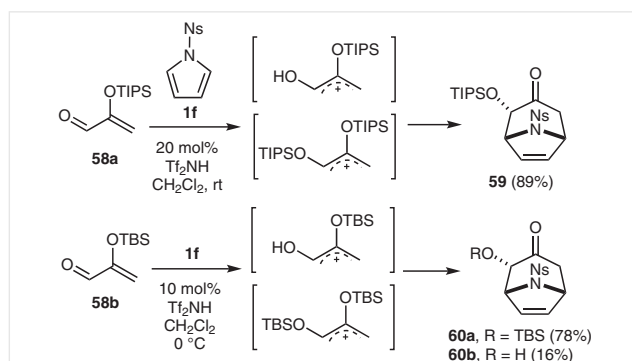

Equation 2 (4+3) Cycloaddition of N-nosylpyrrole with a siloxyallylic alcohol[51]
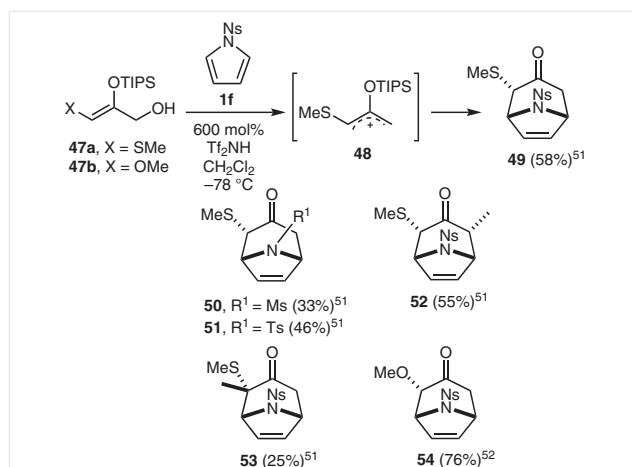
Scheme 11 (4+3) Cycloadditions of pyrroles with heteroatom-stabilized siloxyallylic alcohols[51,52]

2.4   Siloxyacrolein

2-Siloxyacrolein under acid activation possesses siloxy-allylic cation character, and undergoes (4+3) cycloaddition with electron-deficient N-nosylpyrrole **1f** (Scheme 12).[52] The TIPS-derivative **58a** reacted with N-nosylpyrrole **1f** to afford cycloadduct **59** in excellent yield under protic acid catalysis at room temperature. The more reactive TBS-siloxyacrolein **58b** reacted at lower temperature with **1f** with a cycloaddition yield of 94%, consisting of silylated **60a** and desilylated cycloadduct **60b**.

Scheme 12 (4+3) Cycloadditions of N-nosylpyrrole and activated siloxyacroleins[52]

2.5   Allenamides via Epoxidation

The epoxidation of chiral allenamides, and ring opening to generate iminium-stabilized oxyallylic cations for (4+3) cycloaddition has been explored by Hsung and co-workers for the asymmetric synthesis of azabicyclic adducts (Scheme 13).[53] Again, the use of pyrroles with electron-

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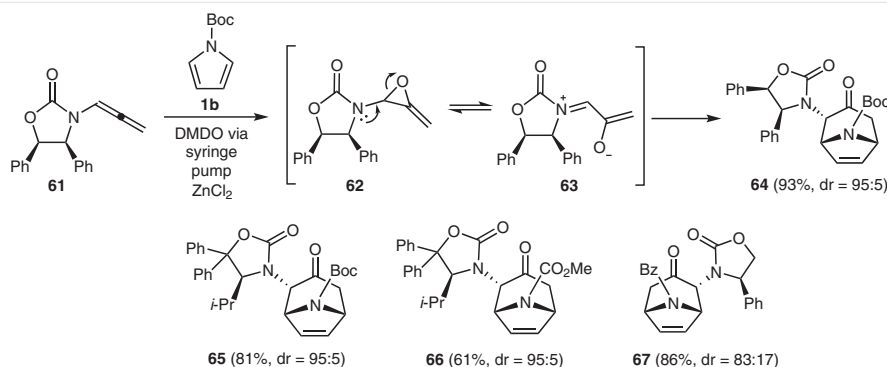
**Scheme 13** (4+3) Cycloadditions of pyrroles with iminium-stabilized oxyallyl cations derived from epoxidation of chiral allenamides[53]

withdrawing *N*-protecting groups, such as **1b**, was key to a successful cycloaddition, in this case to prevent competitive oxidation of the pyrrole, which was still problematic unless the dimethyldioxirane (DMDO) was added via a syringe pump. The oxyallylic cations thus formed were overall relatively neutral and underwent concerted (4+3) cycloadditions that were *endo* diastereoselective. A range of chiral auxiliaries on the allenamide were examined. It was found that, while many auxiliaries promoted highly diastereoselective furan (4+3) cycloadditions, only allenamide **61** and that bearing Seebach's auxiliary reacted to afford cycloadducts **64**, **65**, and **66** in high diastereoselectivities when a pyrrole was the diene.

Hsung and co-workers also investigated the reaction for allenamide **68** derived from an arylamine (Equation 3).[54] Epoxidation resulted in a nitrogen-stabilized oxyallylic cation **70** that underwent (4+3) cycloaddition with protected pyrrole **1b** in moderate yield.
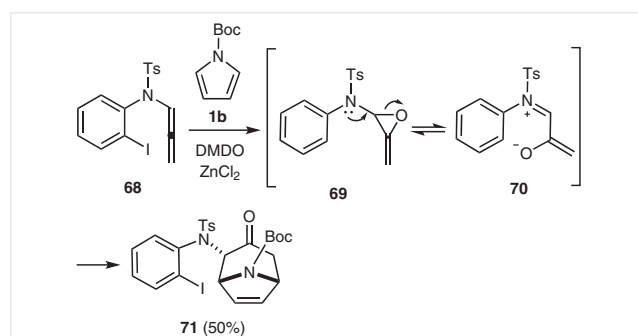
Equation 3 (4+3) Cycloaddition of *N*-Boc-pyrrole with an oxyallyl cation derived from the epoxidation of an allenamide[54]

2.6 Vinylcarbenes as Dienophiles

Davies and co-workers reported the formal (4+3) cycloaddition of pyrroles to afford nortropanes, through a rhodium vinylcarbene cyclopropanation/Cope rearrangement cascade reaction. The cyclopropanation did not require high temperatures, but nevertheless the reaction was car-

ried out at 50 °C to prevent the bis-cyclopropanation of the pyrrole and encourage the Cope rearrangement to proceed.[55–57] Both diazo esters and diazo ketones reacted effectively in this formal cycloaddition.

Davies and other groups studied the scope of this reaction for pyrroles (Scheme 14).[56–60] Cyclopropanation still failed for electron-rich *N*-methylpyrrole **1e**, but for pyrroles bearing electron-withdrawing protecting groups, such as *N*-(methoxycarbonyl)pyrrole **1a**, rhodium(II) acetate catalyzed decomposition of vinyldiazoester **72** induced the domino reaction and directly provided azabicyclohepta-diene **73**. Compound **82** was applied to a racemic synthesis of (±)-scopolamine.[58]

An asymmetric version of this formal (4+3) cycloaddition by a chiral auxiliary approach was developed by Davies and co-workers.[55] Vinyldiazoesters derived from hydroxy esters (*R*)-pantolactone or ethyl (*S*)-lactate as auxiliaries underwent moderately diastereoselective cycloadditions to provide optically enriched azabicyclic products (Scheme 15). Compound **87a** was used in an asymmetric synthesis of (−)-anhydroecgonine methyl ester and (−)-ferruginine.[55]

A catalytic asymmetric formal (4+3) cycloaddition initiated by an asymmetric pyrrole cyclopropanation was also realized by Davies and co-workers using chiral rhodium catalysts.[61] While the degree of enantioselectivity depended on the interaction of between the vinyldiazo precursors and the catalysts, the most successful rhodium catalysts were found to be sterically demanding catalysts such as chiral Rh$_2$(PTAD)$_4$ or Rh$_2$(PTTL)$_4$ bearing adamantyl (Ad) and *tert*-butyl groups respectively, which were found to facilitate high enantiomeric excesses in the cycloadducts (Scheme 16).

In the landmark total synthesis of the pyrrolidine alkaloid, (+)-batzelladine B, Herzon and co-workers exploited the matched effects of the chiral auxiliary [X$_c$ = (*S*)-panto-lactonyl] and a chiral rhodium catalyst [Rh$_2$(*S*-PTTL)$_4$] to generate cycloadduct **97** in excellent yield and high ee.[62] The formal cycloaddition was employed as an efficient strategy to set up, in correct absolute configuration, two
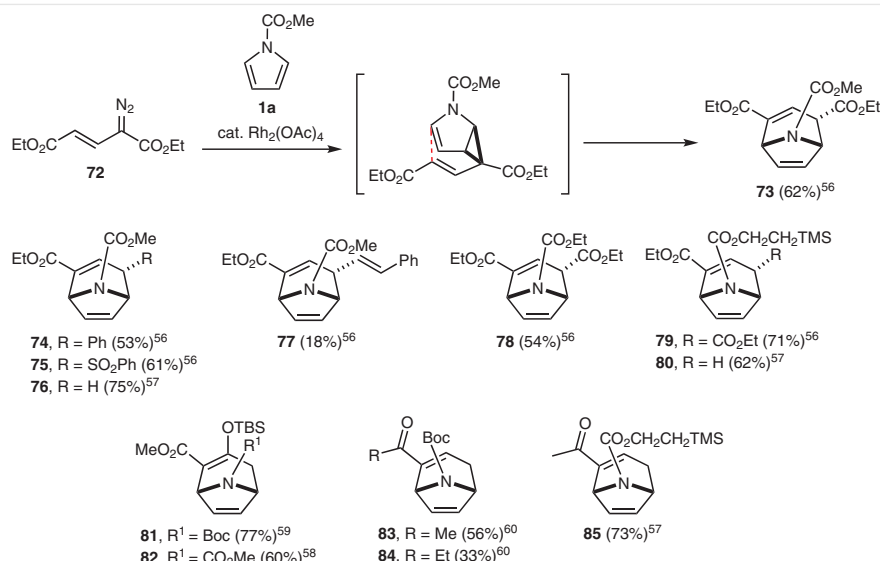
Scheme 14 Formal (4+3) cycloaddition of pyrroles by a domino cyclopropanation/Cope rearrangement reaction[56–60]
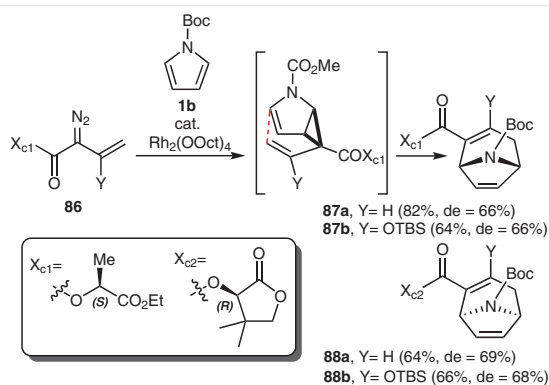
Scheme 15 Asymmetric formal (4+3) cycloadditions of pyrroles by a chiral auxiliary approach[55]

stereocenters of the pyrrolidine moiety, which was revealed by cleaving the three carbon bridge of **97**. Cycloadduct *ent-***96** obtained from catalysis by $Rh_2(R\text{-PTTL})_4$ was similarly used in the follow-up total syntheses of (−)-dehydrobatzelladine C, and (+)-batzelladine K.[63]

3   C-Substituted Pyrroles as Dienes in (4+3) Cycloadditions

Pyrrole derivatives having C2 to C5 substituents can be considerably more challenging dienes for effective cycloadditions than the unsubstituted pyrroles. Firstly, the substituents inevitably increase the steric demands of the cycloaddition transition state. Moreover, substituents also impact on the electron density of the pyrrole, wherein pyrrole (4+3) cycloadditions are particularly sensitive to elec-
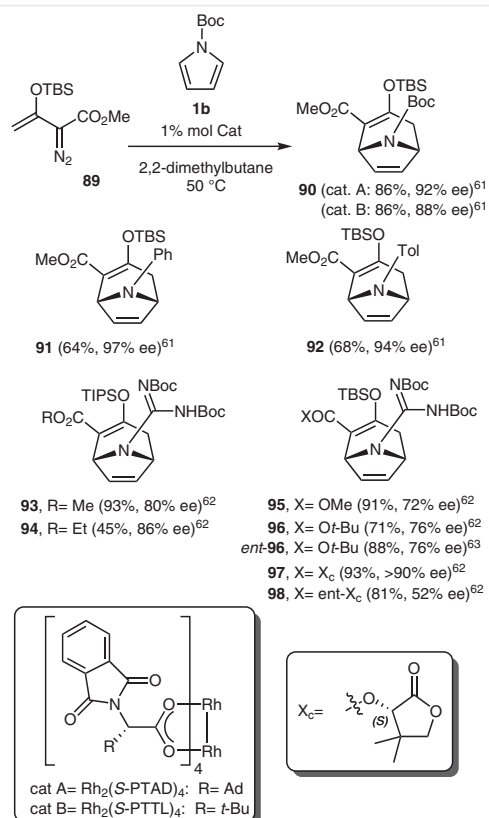
Scheme 16 Formal (4+3) cycloadditions of pyrroles mediated by chiral rhodium catalysts[61–63]

tronic factors. However, (4+3) cycloadditions which can accommodate substituted pyrroles are highly desirable as more complex aza-bridged cycloadducts could be secured.

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3.1 α,α′-Polyhalo Ketones

Pyrroles with substituents on the ring were examined for their (4+3) cycloadditions with α,α′-dibromo ketones (Scheme 17). There are fewer reports of cycloadditions with substituted pyrroles, but under the same conditions, these generally proceeded in lower yields compared with those of the unsubstituted pyrroles (cf. Scheme 7).[29] For unsymmetrical 2-substituted pyrroles reacting with unsymmetrical oxyallylic cations, the regioselectivity of the cycloaddition varied from 2–4:1. The acetal group was demonstrated to be stable under Et$_2$Zn reducing conditions, and cycloadducts such as **103** should offer new opportunities and synthetic applications.[41]
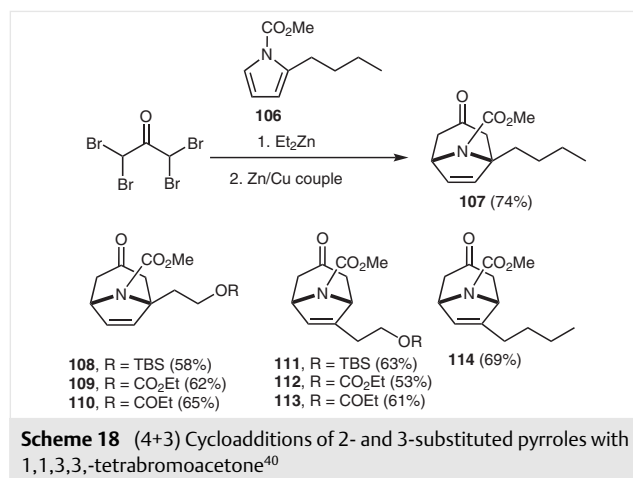
(4+3) Cycloadditions of substituted pyrroles and 1,1,3,3-tetrabromoacetone were also studied.[40] The changes in the electronics of the pyrrole derivatives due to the substituents necessitated more specific reducing conditions and electrophilic requirements of the resultant metal oxyallylic cation. Whereas both Fe$_2$(CO)$_9$ and Et$_2$Zn mediated the (4+3) cycloaddition of unsubstituted pyrroles effectively, only Et$_2$Zn reduction led to acceptable yields of cycloaddition for 2- and 3-substituted pyrroles (Scheme 18).[40] For comparison, the yields for **107** and **114** were only 15% and 13%, respectively, when mediated by Fe$_2$(CO)$_9$.
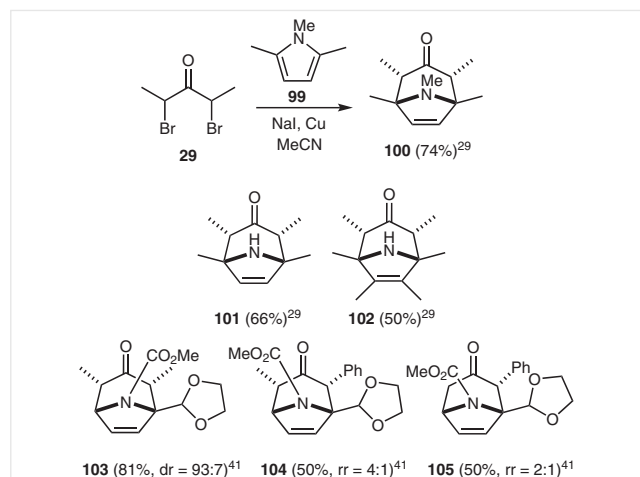
Scheme 17 (4+3) Cycloadditions of substituted pyrroles with α,α′-dibromo ketones[29,41]

3.2 Siloxyallylic Alcohol Derivatives

Sulfur-stabilized siloxyallylic cations generated from siloxyallylic alcohols underwent (4+3) cycloadditions with unsubstituted pyrroles in the presence Tf$_2$NH in up to 85%

Scheme 18 (4+3) Cycloadditions of 2- and 3-substituted pyrroles with 1,1,3,3,-tetrabromoacetone[40]

yield.[51] Unfortunately, the scope could not be extended to 2-substituted pyrroles, which reacted to give a 64% yield of the Friedel–Crafts product. However, 3-substituted pyrroles underwent cycloaddition effectively (Scheme 19), including a 3-bromopyrrole, with the lower yield attributed to the instability of cycloadduct **118** bearing the vinyl bromide functional group.
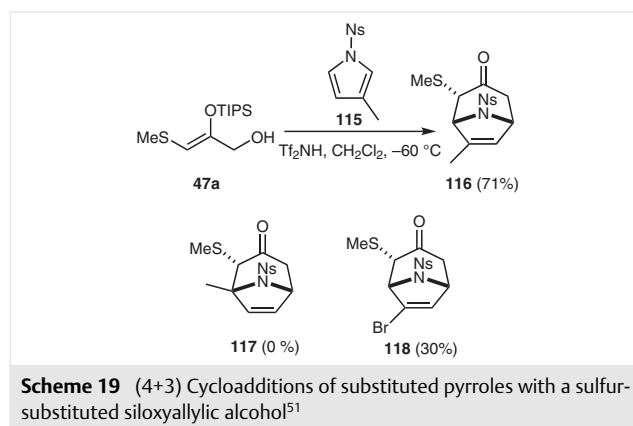
Scheme 19 (4+3) Cycloadditions of substituted pyrroles with a sulfur-substituted siloxyallylic alcohol[51]

In contrast, the geminally dialkyl-substituted siloxyallylic cation derived from alcohol **55a** underwent cycloaddition successfully with 2-methylpyrrole **119** as a single regioisomer, albeit in a moderate yield.[51] However, cycloaddition with 3-methylpyrrole **115** was not regioselective, in contrast with the exclusive regioselectivity observed in the cycloaddition that afforded cycloadduct **116** (Scheme 20).
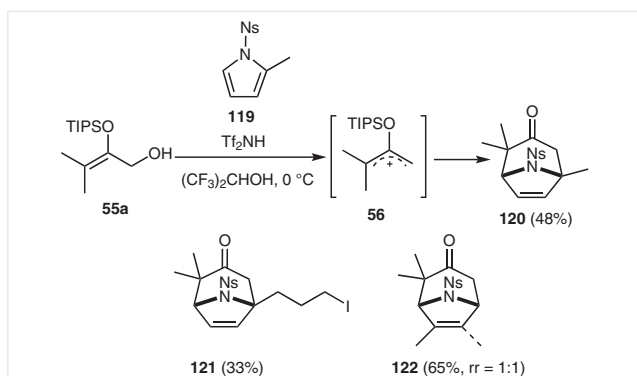
Scheme 20 (4+3) Cycloadditions of 2- and 3-substituted pyrroles with dimethyl-substituted siloxyallylic cation[51]

3.3 Siloxyacrolein

2-Siloxyacrolein can be activated by a catalytic amount of either $Cu(OTf)_2$ or $Sc(OTf)_3$ to undergo (4+3) cycloadditions with various 2-substituted pyrroles (Scheme 21).[52] The regioselectivity is typically high and indicative of a stepwise cycloaddition mechanism initiated by bond formation at the less-substituted carbons on both the pyrrole and the activated acrolein, as a concerted cycloaddition would probably favor the minor re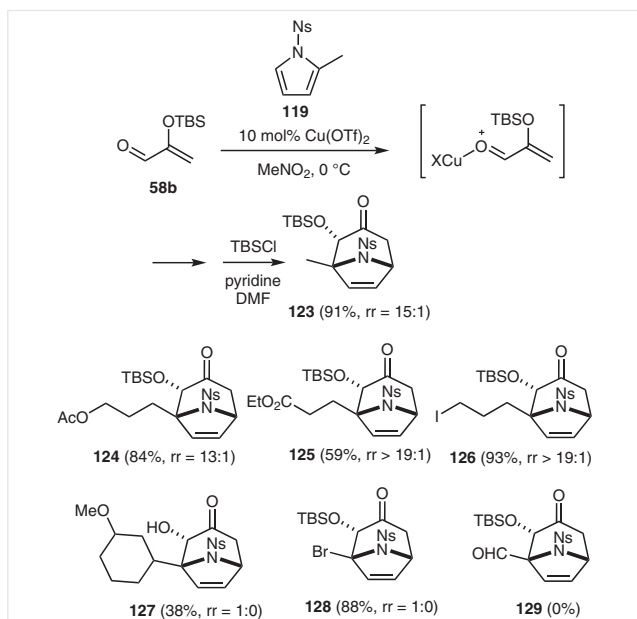gioisomer to avoid steric clash between the two incoming substituents. Interestingly, a 2-bromopyrrole also underwent cycloaddition effectively to yield **128** as the sole regioisomer. However the 2-formylpyrrole derivative did not undergo cycloaddition, probably due to it being too electron-deficient.

Scheme 21 (4+3) Cycloadditions of 2-substituted pyrroles and 2-siloxyacrolein[52]

3.4 Vinylcarbenes as Dienophiles

The formal (4+3) cycloaddition through cyclopropanation/Cope rearrangement as developed by Davies and co-workers has been tremendously successful as applied to pyrroles as dienes.[61] For 2-substituted pyrroles as dienes, the scope remains broad, and the regioselectivities are high, inferring that the cyclopropanation of the unsymmetrically substituted pyrroles was regioselective. Kende and co-workers engaged 2,3-disubstituted pyrrole **130** in a formal (4+3) cycloaddition to secure aza-bridged cycloadduct **131** in excellent yield and as the only regioisomer (Equation 4).[64] This cycloadduct contributed the nortropane framework that eventually culminated in the first total synthesis of (±)-isostemofoline.
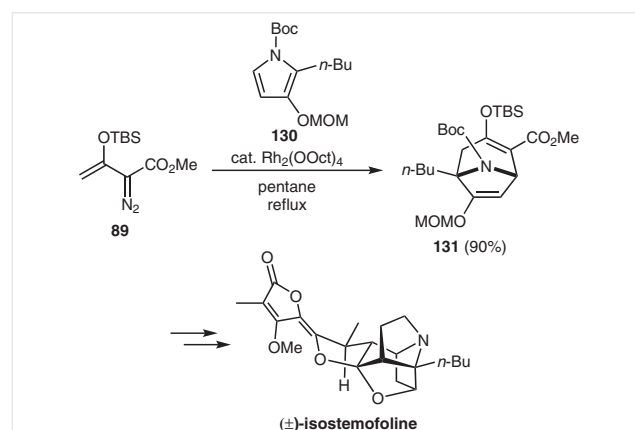
Equation 4 (4+3) Cycloaddition of a 2,3-disubstituted pyrrole leading to a total synthesis of (±)-isostemofoline[64]

Davies and co-workers further demonstrated that the formal (4+3) cycloadditions of 2-, 2,3-, and 2,5-substituted pyrroles provided azabicyclic adducts regioselectively and with excellent enantioselectivities by using chiral rhodium catalyst $Rh_2(PTAD)_4$ (Scheme 22).[61] Quite remarkable is that even a diene as electron-poor as a pyrrole-2-carboxylate also reacted smoothly under these conditions, to provide cycloadduct **136**. Clearly, the rhodium-catalyzed cyclopropanation is more lenient on the electron density requirement of the pyrrole as compared to the classical (4+3) cycloaddition, and this has greatly increased the scope and applications of the intermolecular formal (4+3) cycloaddition. This asymmetric reaction was also applied to pyrrole **130** to provide tropinoid **137** with good ee, intercepting the route of Kende and co-workers to constitute an asymmetric synthesis of isostemofoline.[61]

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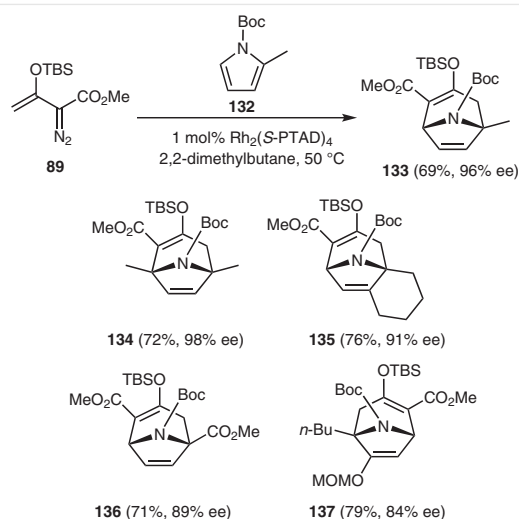
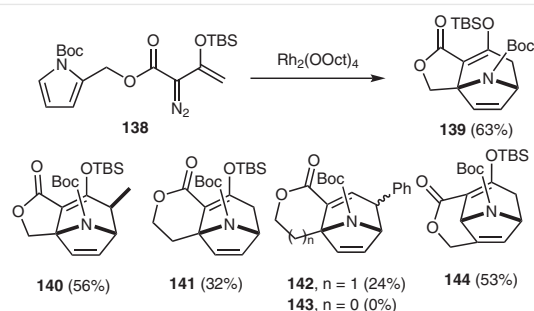**Scheme 22** Asymmetric formal (4+3) cycloadditions of substituted pyrroles[61]

133 (69%, 96% ee)
134 (72%, 98% ee)
135 (76%, 91% ee)
136 (71%, 89% ee)
137 (79%, 84% ee)
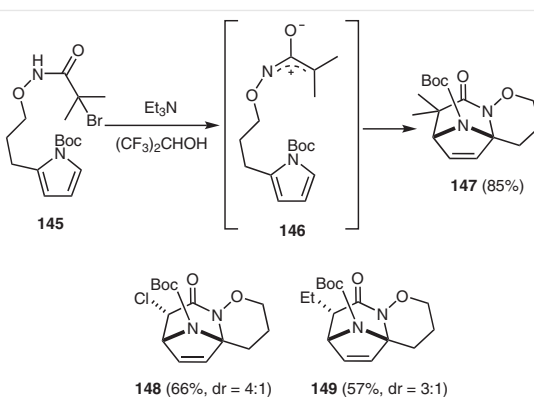
4 Intramolecular Pyrrole (4+3) Cycloadditions

The intramolecular (4+3) cycloaddition of pyrroles is an ideal strategy to construct tropane-embedded frameworks efficiently. However, there have been only a few reports of intramolecular pyrrole cycloadditions in the literature. Synthetic efforts in this area may be deterred possibly due to the challenges presented by pyrrole (4+3) cycloadditions, and the need to prepare more complex substrates that tether the dienophile precursor to the pyrrole, which necessitates additional synthetic work. As intramolecular cycloaddition substrates are by nature substituted pyrroles, the tethers would exert both steric and electronic effects. In this connection, studies that have been done have uncovered some surprising results.

The formal (4+3) cycloaddition of pyrroles tethered to a diazo ester was examined by Davies and co-workers.[65,66] Based on the highly versatile and successful intermolecular reactions, the intramolecular version could be expected to be possibly even more efficient, but this was not the case (Scheme 23).[65,66] Some diazoesters formed carbenes that then reacted to generate little or none of the expected (4+3) cycloadduct. It was postulated that the tether disfavored cyclopropanation and prevented the usual formal (4+3) cycloaddition pathway, giving way to the formation of zwitterions instead. However, donor-acceptor carbenes still reacted effectively to afford (4+3) cycloadducts via zwitterionic intermediates, to afford **139** as a major product, and quite remarkably, even the anti-Bredt tricyclic adduct **144**.

Scheme 23 Intramolecular formal (4+3) cycloadditions of pyrroles[66]

139 (63%)
140 (56%)
141 (32%)
142, n = 1 (24%)
143, n = 0 (0%)
144 (53%)

In 2011, Jeffrey and co-workers described aza-oxyallylic cation formation from the dehydrohalogenation of α-halobenzylhydroxylamines.[67] These dienophiles underwent intermolecular cycloadditions with furans, but this report did not examine the corresponding reaction with pyrroles. In 2013, Jeffrey and co-workers reported an intramolecular version of this cycloaddition that proceeded with a N-substituted pyrrole tethered by the aminoxy bond (Scheme 24).[68]

Scheme 24 Intramolecular aza-(4+3) cycloaddition of tethered pyrroles[68]

145
146
147 (85%)
148 (66%, dr = 4:1)
149 (57%, dr = 3:1)

Chiu and co-workers reported that epoxy enolsilanes activated by silyl triflates engaged in (4+3) cycloadditions with dienes, and computations suggested that the activated epoxide, rather than the typical oxyallylic cation, was the dienophile.[69] Consequently, the stereochemistry of the enantiomerically enriched epoxide directed the cycloaddition to afford cycloadducts with retained ee.

While (4+3) cycloaddition did not proceed intermolecularly with pyrroles, the intramolecular reaction generated bicyclic alkaloids with embedded nortropane frameworks efficiently (Scheme 25).[70] Interestingly, pyrroles bearing a wide range of N-protecting groups, from very electron-donating to highly electron-withdrawing, all underwent effective and diastereoselective cycloadditions. This reaction reliably provided optically enriched aza-polycyclic products from enantiomerically pure epoxy enolsilanes and

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is superior to a chiral auxiliary approach since the functional groups in the cycloadducts can be readily manipulated or incorporated into syntheses. For example, cycloadduct (–)-**160** thus obtained was converted into the pentacyclic substructure of the Type II galbulimima alkaloids.

Namba and co-workers described a clever and concise assembly of an intramolecular (4+3) cycloaddition precursor and its cycloaddition in one-pot cascade that provided a wide variety of polycyclic tropinones (Scheme 26).[71] Acidic conditions promoted both the in situ intermolecular condensation of a pyrrole derivative bearing a nucleophilic residue with a 2-siloxyacrolein, and its subsequent siloxyallylic cation formation and intramolecular (4+3) cycloaddition, to generate azatricyclic adducts.

Both pyrrolyl alcohols and thiols were effective nucleophiles for the condensation, but pyrrolyl amines failed to react. The ensuing intramolecular (4+3) cycloaddition was remarkably efficient, able to form five-, six-, seven-, and even eight-membered intervening rings. Employing structurally diverse pyrrolyl alcohols produced tricyclic and tetracyclic adducts in high yields and as single diastereomers. The cycloaddition was diastereoselective and the use of an optically enriched pyrrolyl alcohol of 85% ee also generated cycloadduct **169** with retained ee and without racemization under the acidic reaction conditions. The nosyl protecting group of the pyrroles appeared to play a vital role, as all other N-protecting groups failed to facilitate this intramolecular (4+3) cycloaddition. Interestingly, allylic alcohols, such as **163**, were also accommodated, resulting in an excellent yield of cycloadduct **164** bearing a dihydropyran moiety.

Scheme 25 Intramolecular (4+3) cycloaddition of pyrroles and tethered epoxy enolsilanes[70]
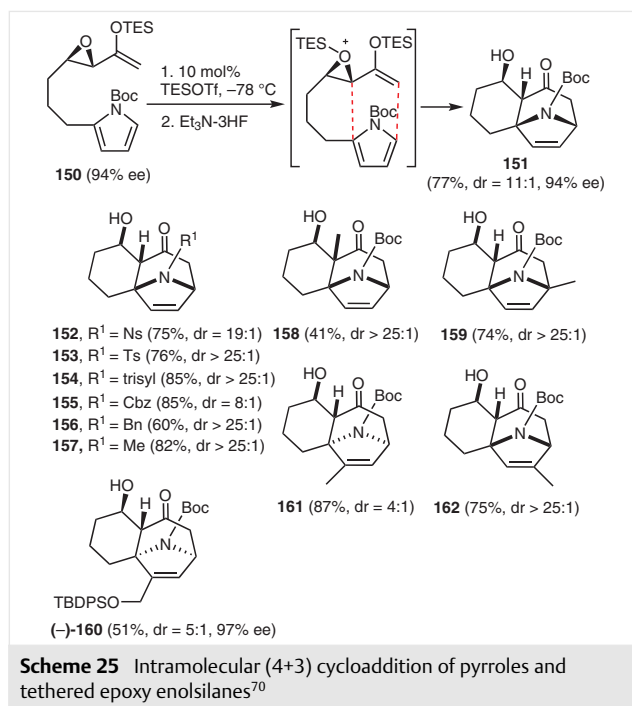
5   Conclusions

This review has summarized all examples reported to date of pyrrole derivatives that reacted as dienes in classical and formal (4+3) cycloadditions to afford nortropane frameworks to show what has been possible for this challenging, but desirable, reaction. The (4+3) cycloadducts have already been applied in a number of natural product synthesis efforts, particularly those of the tropane family.

Scheme 26 Condensation and intramolecular (4+3) cycloaddition cascade reactions of *N*-nosylpyrrole derivatives[71]
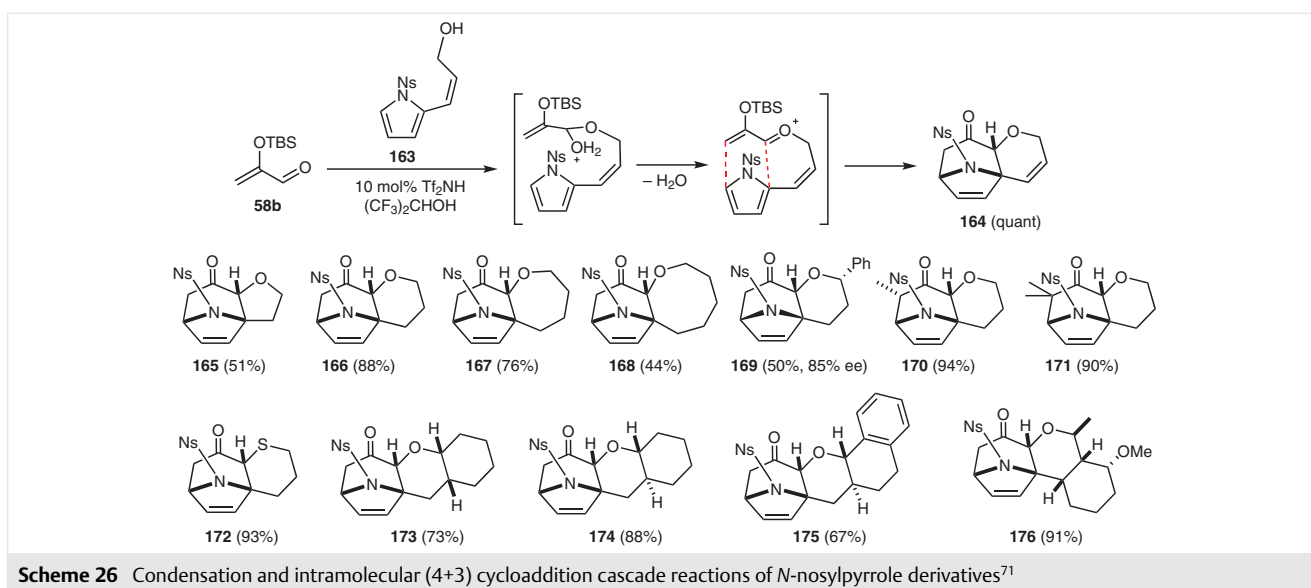
The examples show that the pyrrole (4+3) cycloaddition posed reactivity problems. Friedel–Crafts products are often the side products arising from either a stepwise cycloaddition terminated by deprotonation, or the decomposition of the cycloadduct particularly under acidic conditions. The high aromaticity of the pyrrole and also its reactivity as a nucleophile and proneness to oxidation further complicate the design of successful (4+3) cycloadditions. The substituents on the nitrogen and carbon atoms of the pyrrole that impacted the cycloaddition sterically and electronically, limit scope of the reaction.

However, those pyrrole (4+3) cycloadditions that proceeded were generally diastereoselective, and regioselectivity has been observed in many cases of unsymmetrical dienophiles undergoing cycloaddition with unsymmetrically substituted pyrroles.

Optically pure nortropane derivatives still remain challenging to secure. Some strategies to overcome this limitation include the subsequent enantioselective desymmetrization of *meso* aza-bridged cycloadducts. There are only a limited number of (4+3) cycloaddition strategies to directly generate these compounds with high enantioselectivity, which will allow them to be applied to the asymmetric syntheses of alkaloids or drugs. The method that offers the most elegant solution and wide versatility is the chiral rhodium-catalyzed formal (4+3) cycloaddition of pyrroles. For the intramolecular reaction, diastereoselective pyrrole (4+3) cycloadditions with enantiomerically enriched epoxy enolsilanes as dienophiles, or optically pure pyrrolyl alcohols as dienes hold promise. Additional strategies to construct aza-polycyclic frameworks by asymmetric (4+3) cycloadditions of pyrroles is an area that needs further efforts and research in the future.

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