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.

1 Introduction

Natural products have played a vital role in the history and discovery of drugs. 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.

One class of these ‘true alkaloids’ 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. Tropanes were first identified from two plant sources: from the Erythroxylaceae family, to which the coca plant belongs, was isolated the infamous cocaine. 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. 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. Atropine isolated from Atropa belladonna, is a stimulant and pupil dilator, and is a treatment for bradycardia (i.e., slow heart rate) and poisoning. 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. There are more than 20 medicines currently in the market with the tropane framework, 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).
To secure the tropane, or more generally the nortropane (desmethyltropane) nucleus by laboratory synthesis,\textsuperscript{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.\textsuperscript{12} Pyrroles are more aromatic, and the tendency toward aromaticity competes with cycloaddition reactions, which are necessarily dearomatizing.\textsuperscript{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 general 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 cycloadducts 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-oxyallyl cation 2), although related electrophilic species also react (Scheme 1).\textsuperscript{12}

Since pyroles 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.\textsuperscript{14} Via a stepwise mechanism, the 2H-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.\textsuperscript{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.\textsuperscript{12} However, the requirements for reactions with pyroles 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.\textsuperscript{16}
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. 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. In this reaction, catalytically generated metal carbenes first cyclopropanate the diene, and the resultant cis-1,2-divinylcyclopropane then undergoes a Cope rearrangement to provide a cycloheptadiene 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.

The 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 Dienophiles 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. 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 underwent cycloaddition only with N-ethoxycarbonyl-protected pyrrole to provide a moderate yield of cycloadduct (Scheme 3). The same reaction with N-methylypyrrole generated the Friedel–Crafts product in 67% yield.
(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

### 2.2 a,α’-Polyhalo Ketones

Polybromo and polyiodo ketones under reducing conditions generate oxallylic cations that undergo (4+3) cycloadditions.25-28 Different reductants afford oxallylic 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 oxallylic cations, which are comparatively less electrophilic, that underwent (4+3) cycloaddition to any extent.29 Other reductive methods that produce iron or zinc oxallylic 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 oxallyl 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.

Under similar basic and ionizing conditions, chloroureia 19 is dehydrohalogenated to afford a diaza-oxallylic cation 20 that underwent (4+3) cycloadditions with various dienes, including pyrroles, to generate diazacycloadducts 21 and 22 in high yields (Scheme 6).24
For example, Grée and co-workers obtained 30 in only 12% yield following the procedure of Mann and de Almeida Barbosa, but they found that the use of excess 29 improved the yield of 30 to 88%.

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). Pyrroles bearing different electron-withdrawing N-protecting groups have also proceeded to (4+3) cycloadditions under these conditions. Cycloadduct 41 thus obtained is reductively debrominated to afford desired 8-azabicyclo[3.2.1]octenone 42, a valuable meso intermediate for the synthesis of troponoids and other natural products.

Starting from meso 42, Mann and de Almeida Barbosa reported a synthetic route to (±)-scopoline (Scheme 10). The Noyori group converted 42 into (−)-hyoscyamine in 3–4 steps. In 2008, the Perlmutter group enantioselectively desymmetrized 42 in an asymmetric synthesis of the cancer MDR reversal agent, (−)-pervilleine C, and in 2010 Hodgson and co-workers reported a synthesis of (±)-peduncularine from 42.
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 siloxyallylic cations upon acid-induced dehydration (Scheme 11).\textsuperscript{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.\textsuperscript{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 hexafluoropropionate (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.

2.4 Siloxyacrolein

2-Siloxyacrolein under acid activation possesses siloxyallylic cation character, and undergoes (4+3) cycloaddition with electron-deficient N-nosylypyrrole 1f (Scheme 12).\textsuperscript{52} The TIPS-derivative 58a reacted with N-nosylypyrrole 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.

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).\textsuperscript{53} Again, the use of pyrroles with electron-
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 oxallylic 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 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). Epoxidation resulted in a nitrogen-stabilized oxallylic cation 70 that underwent (4+3) cycloaddition with protected pyrrole 1b in moderate yield.

An asymmetric version of this formal (4+3) cycloaddition by a chiral auxiliary approach was developed by Davies and co-workers. 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.

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. While the degree of enantioselectivity depended on the interaction of between the vinyldiazo precursor and the catalysts, the most successful rhodium catalysts were found to be sterically demanding catalysts such as chiral Rh2(PTAD)4 or Rh2(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 [Xc = (S)-pantolactonyl] and a chiral rhodium catalyst [Rh2(S-PTTL)4] to generate cycloadduct 97 in excellent yield and high ee.

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 carried out at 50 °C to prevent the bis-cyclopropanation of the pyrrole and encourage the Cope rearrangement to proceed. 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). 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 azabicycloheptadiene 73. Compound 82 was applied to a racemic synthesis of (±)-scopolamine.

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sterocenters 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)-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 electronic factors. However, (4+3) cycloadditions which can accommodate substituted pyrroles are highly desirable as more complex aza-bridged cycloadducts could be secured.
3.1 α,α’-Polyhalo Ketones

Pyroles 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 pyroles, but under the same conditions, these generally proceeded in lower yields compared with those of the unsubstituted pyroles (cf. Scheme 7). For unsymmetrical 2-substituted pyroles reacting with unsymmetrical oxallyllic cations, the regioselectivity of the cycloaddition varied from 2–4:1. The acetal group was demonstrated to be stable under Et₂Zn reducing conditions, and cycloadducts such as 103 should offer new opportunities and synthetic applications.

(4+3) Cycloadditions of substituted pyroles and 1,1,3,3-tetrabromoacetone were also studied. 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 oxallyllic cation. Whereas both Fe₂(CO)₉ and Et₂Zn mediated the (4+3) cycloaddition of unsubstituted pyroles effectively, only Et₂Zn reduction led to acceptable yields of cycloaddition for 2- and 3-substituted pyroles (Scheme 18). For comparison, the yields for 107 and 114 were only 15% and 13%, respectively, when mediated by Fe₂(CO)₉.

3.2 Siloxyallylic Alcohol Derivatives

Sulfur-stabilized siloxyallylic cations generated from siloxyallylic alcohols underwent (4+3) cycloadditions with unsubstituted pyroles in the presence Tf₂NH in up to 85% yield. Unfortunately, the scope could not be extended to 2-substituted pyroles, which reacted to give a 64% yield of the Friedel–Crafts product. However, 3-substituted pyroles 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.

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. 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).
3.3 Siloxyacrolein

2-Siloxycroleanle 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). 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 regioisomer 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.

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. 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). This cycloadduct contributed the nortropane framework that eventually culminated in the first total synthesis of (±)-isostemofoline.
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. In 2011, Jeffrey and co-workers described aza-oxyallylic cation formation from the dehydrohalogenation of α-halo benzylhydroxylamines. These dienophiles underwent intramolecular 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). 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. Consequently, the stereochemistry of the enantiomerically enriched epoxide directed the cycloaddition to afford cycloadducts with retained ee.

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While (4+3) cycloaddition did not proceed intermolecularly with pyrroles, the intramolecular reaction generated bicyclic alkaloids with embedded nortropane frameworks efficiently (Scheme 25). 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
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.

### 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 nortrpane 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.
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, limited 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 pyroles.

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 pyroles.

For the intramolecular reaction, diastereoselective pyrrole (4+3) cycloadditions with enantiomerically enriched epoxy enolizes as dienophiles, or optically pure pyrrolyl alcohols as dienes hold promise. Additional strategies to construct aza-poly cyclic frameworks by asymmetric (4+3) cycloadditions of pyroles is an area that needs further efforts and research in the future.

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