1-Azadienes in cycloaddition and multicomponent reactions towards N-heterocycles

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1-Azadienes are versatile building blocks for the efficient construction of various N-heterocycles. Depending on the substitution pattern and reaction partner, they may participate in a range of different reactions. An overview of recent methods for the generation of 1-azadienes is presented, as well as their application in cycloaddition, electrocyclization, and multicomponent reactions. Considering the broad range of reactivities and resulting heterocyclic scaffold structures, 1-azadienes are very useful reactive intermediates for the development of modular reaction sequences in diversity-oriented synthesis.

1. Introduction

The number of novel molecular entities brought onto the market as new drugs has decreased steadily over the past decades, while at the same time R&D expenditures increase exponentially. With resistance to drugs currently on the market on the rise, the demand for new active compounds is higher than ever. It is becoming increasingly evident that the nature of the compounds produced by combinatorial chemistry efforts over the past two decades does not fit a rational drug discovery approach. Both structural complexity and chemical diversity are central issues to address in the design and construction of compound collections in order to find and explore potential biological activities.

Natural products display much more scaffold diversity and structural complexity than purely synthetic compounds.[1–5] The diversity of natural compounds, which often contain at least one heterocyclic ring, has been an important inspiration for the development of many drugs.[6] As a result, many medicines are relatively small heterocyclic organic compounds. However, the range of easily accessible and suitably functionalized heterocyclic building blocks for the synthesis of structurally diverse libraries is very limited. As a result, the construction of even a small library of, *e.g.*, 1000 pharmaceutically relevant heterocycle-based compounds is still far from trivial.

To address the issues of complexity and diversity in the synthesis of libraries of biologically active small molecules, diversity-oriented synthesis (DOS)[7] in combination with complexity-generating reactions receives growing attention.[8–14] Again, the scaffold diversity found in natural products is an inspiration for DOS-based library generation.[15–26] Therefore, synthetic methodology for the creation of diverse natural product-like scaffolds based on heterocycles starting from a limited number of inputs is highly desirable. To achieve this, access to densely functionalized intermediates with multiple reactive sites for selective synthetic manipulation can be of key importance.

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2. Properties of 1-azadienes

Many biologically active small molecules contain nitrogen heterocycles because these can present diverse arrays of pharmacophores in a semi-rigid framework of hydrogen bond donors and acceptors. 1-Azadienes are extremely versatile building blocks for the efficient *de novo* construction of such nitrogen heterocycles. They can serve as useful platforms to create structural diversity and complexity in only a few reaction steps. The basis for this versatility lies in the various possible reactivities of 1-azadienes (see Fig. 1). For example, the electron-rich nitrogen atom of the azadiene may react as a nucleophile. On the other hand, the α,β-unsaturated imine may act as an electrophile, in a 1,2-addition or in a Michael-type 1,4-addition. Finally, 1-azadienes can react as heterodienes in cycloaddition reactions. In addition, both the alkene and the imine functionality could, in principle, react as dienophiles, dipolarophiles or carbenophiles, giving rise to the formation of yet different types of N-heterocycles.

Although many possible reactivities of 1-azadienes can be distinguished, they often react with remarkable selectivity in specific cases. The reactivity that a 1-azadiene displays in a given reaction depends both on the reaction partner and on the nature of the substituents. More precisely, the electron density in the 1-azadiene is the important factor. Therefore, we classify 1-azadienes in three categories:

(1) *Electron-deficient 1-azadienes*, bearing electron-withdrawing substituents such as sulfonyl, acyl, or alkoxycarbonyl groups, typically on nitrogen. These tend to react primarily as electrophiles in 1,4-additions, but also react with electron-rich dienophiles in inverse electron-demand hetero-Diels–Alder reactions.

(2) *Electron-rich 1-azadienes*, bearing electron-donating substituents such as alkyl, alkoxy, silyloxy, or dialkylamino groups, typically on nitrogen. These react mostly in hetero-Diels–Alder reactions with electron-poor dienophiles, but they can also react as nitrogen nucleophiles.

(3) *1H-1-Azadienes*, lacking N-substituents, combine all reactivities of 1-azadienes. The type of reaction they participate in depends mostly on reaction partners and reaction conditions. Indeed, 1*H*-1-azadienes can be regarded as the synthetically most versatile type. A limiting factor in the application of 1*H*-1-azadienes is their low stability. In most reactions involving 1*H*-1-azadienes, they are generated *in situ* rather than isolated. This does, however, make them valuable reactive intermediates (see also section 5).

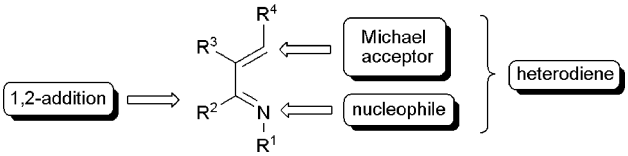


Fig. 1 Different reactivities of 1-azadienes.

It should be noted that no strict rules can be applied to this classification, since 1-azadienes may carry both electron-withdrawing and electron-donating substituents. In most cases, the N-substituent typically has a profound influence on the reactivity. Therefore, we use the nature of the N-substituent as the basis for the above classification.

This *feature article* describes the use of 1-azadienes as reactive intermediates in the synthesis of various types of biologically relevant heterocycles. In some cases, the 1-azadienes are isolated and then used for further reactions. In many cases, however, the 1-azadienes are generated *in situ* and reacted with several types of reactants. First, the synthesis of 1-azadienes will be discussed, followed by their use in the synthesis of various classes of heterocycles. The focus will be on cycloaddition, electrocyclization, and multicomponent reactions.

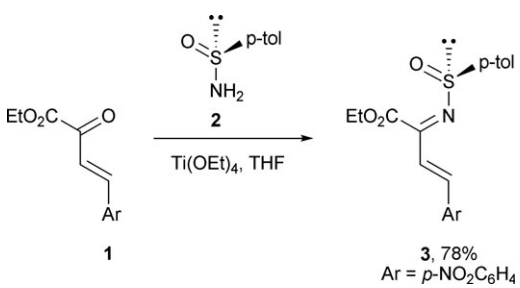
3. Synthesis of 1-azadienes

1-Azadienes can be prepared in a number of ways and some examples in the recent literature are discussed here. We have chosen to present a representative set of reactions rather than a complete overview of all the possible reactions that are used for this purpose.

3.1 Synthesis of electron-deficient 1-azadienes

The most straightforward synthesis of 1-azadienes is the classical condensation reaction between an α,β-unsaturated carbonyl compound and an amine. A recent example by Palacios and co-workers is shown below (Scheme 1).[27] A direct condensation of (*S*)-*p*-toluene-sulfinimide **2** and β,γ-unsaturated α-ketoester **1** yields 1-azadiene **3** in 78% yield.

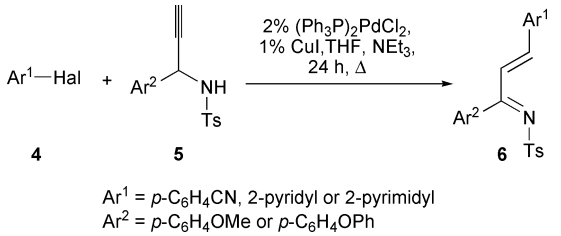
The reaction is performed in the presence of 2 equivalents of titanium tetraethoxide to activate the ketoester. The presence



Scheme 1 Synthesis of chiral sulfinimides.[27]

Romano V. A. Orru

Romano V. A. Orru studied molecular sciences at the Agricultural University in Wageningen, the Netherlands, where he obtained his PhD in 1994. From 1996–2000 he worked in the group of K. Faber at the Technical and Karl-Franszens Universities (Graz, Austria). In early 2000 he was appointed assistant professor and later associate professor at the Vrije Universiteit Amsterdam. Since 2007 he has been a full professor of synthetic and bioorganic chemistry. His current research focuses on the development of novel, diversity oriented, synthetic methodology for the synthesis of pharmaceutically relevant compounds and natural products.



Scheme 2 *In situ* generation of azadienes by rearrangement of Sonogashira products.[28]

of an electron-withdrawing group at the γ-position of the α-ketoester seems to increase the reactivity of the carbonyl group, leading to exclusive formation of the *N*-sulfinylimine. The resulting *N*-sulfinylimines were used in the synthesis of substituted pyridines.[27]

Another method for the *in situ* generation of electron-deficient 1-azadienes was reported by Müller and co-workers (Scheme 2).[28] The 1-azadiene **6** is generated *in situ* from an electron-poor aryl halide **4** and a terminal propargylic *N*-tosylamine **5** *via* a cross-coupling–isomerization sequence. The sequence consists of a Pd^0/Cu^I catalyzed Sonogashira reaction followed by a slow base-catalyzed isomerization.

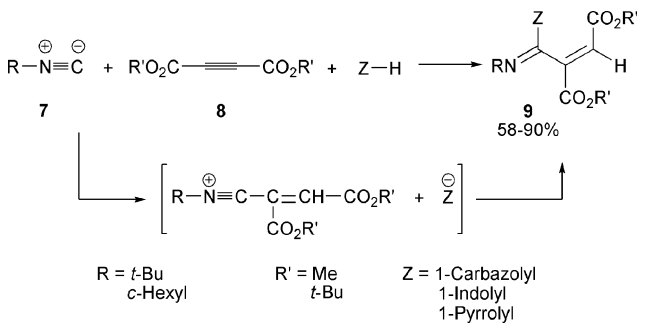
3.2 Synthesis of electron-rich 1-azadienes

The synthesis of *N*-alkyl-1-azadienes has been reported most extensively and some recent examples are presented here.

The use of an isonitrile for the synthesis of 1-azadienes was reported by Yavari *et al.*[29] Addition of an alkyl isonitrile **7** to a dialkyl acetylenedicarboxylate **8** yields an intermediate that can be trapped by fairly strong NH-acids (Z–H) such as carbazole, indole or pyrrole to yield 1-azadienes **9** (Scheme 3).

Using pyrrole as the NH-acid, only 1-azadienes were obtained, but with carbazole or indole highly functionalized ketenimines were formed as side products. The formation of the products results from an initial addition of the alkyl isocyanide to the acetylenic ester, followed by protonation of this adduct by the NH-acid (Z–H). The positively charged adduct can then be attacked at two positions by the nitrogen atom of the anion of the NH-acid. Direct addition leads to 1-azadienes, while conjugate addition leads to ketenimines (Scheme 3).

The group of Palacios contributed considerably with several methods to synthesize N-substituted 1-azadienes. Examples of two different methods are given here. The first example reports the synthesis of α,β-unsaturated γ-imino esters by Wittig or



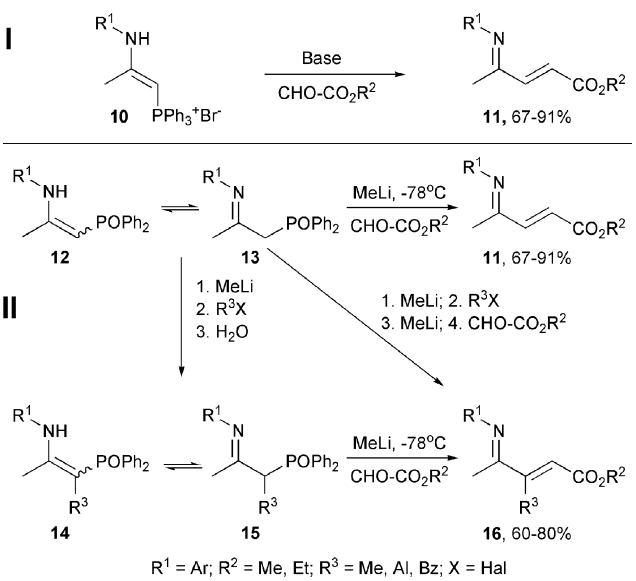
Scheme 3 Synthesis of 1-azadienes by α-addition of NH-acids and alkynes to isocyanides.[29]

Wittig–Horner reaction of alkyl glyoxylates and functionalized phosphonium salts or phosphine oxides, *via* methods **I** and **II**, respectively (Scheme 4).[30]

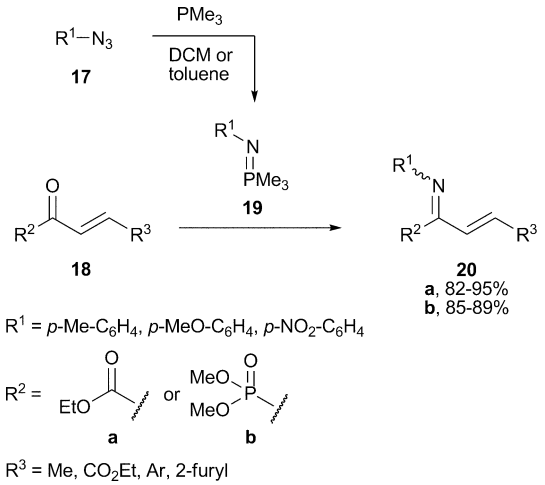
With method **I**, phosphonium salts **10** were deprotonated by a strong base followed by the addition of ethyl glyoxylate (R^2 = Et). After stirring at room temperature for 24 h, aqueous work-up and purification, the corresponding 1-azadienes **11** were obtained in good yields (67–91%). This methodology could also be used for the β-enamino or β-imino phosphine oxides **12** and **13** with MeLi as the base (**II**, Scheme 4). The alkylated phosphine oxides **14** or **15** were used for the generation of 3-substituted 1-azadienes **16**. The alkylated phosphine oxides **14** and **15** were made from **12** and **13** by metallation and subsequent addition of alkyl halides and aqueous work-up. Wittig–Horner olefination of these phosphine oxides **14** and **15** with ethyl glyoxylate leads to the formation of the 1,3-disubstituted-1-azadienes **16**. This process can also be performed in a stepwise fashion from phosphine oxides **12** and **13**. The reaction is compatible with chiral substituents and with functional groups that can later be removed. The 1-azadienes are stable to air and moisture and can be purified, isolated and stored for several hours.

A second example reported by Palacios to arrive at 1-azadienes is the Staudinger reaction of β,γ-unsaturated α-ketoesters **18a** with phosphazenes **19**. The latter were prepared *in situ* by addition of trimethylphosphine to aryl azides **17** (Scheme 5).[31] The α-ketoesters were prepared *via* aldol- or Wittig-type condensation of aldehydes with the corresponding pyruvate-derived reagent.[32]

The 1-azadienes **20a** were obtained as *syn*/*anti* mixtures in yields ranging from 82–95%. The stability of azadienes **20a** towards most common purification techniques like chromatography and distillation was very low, so they were used without purification in further steps. *Via* the same methodology, phosphorylated 1-azadienes **20b** can be made from *P*-trimethyl phosphazenes **19** and β,γ-unsaturated α-ketophosphonates **18b** in a regioselective fashion and in high yields (85–89%,



Scheme 4 Synthesis of 1-azadienes by Wittig-type reactions of imino- and enamino-ylides.[30]

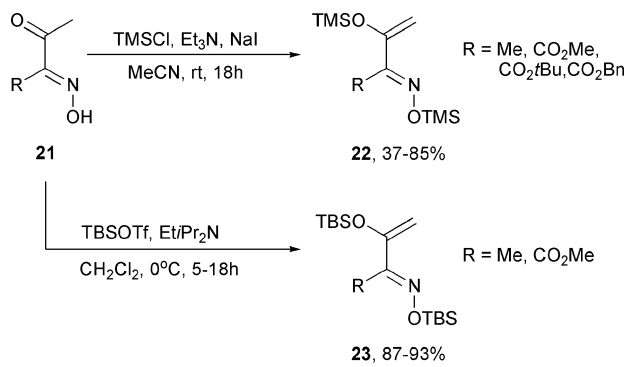


Scheme 5 Synthesis of 1-azadienes derived from α-ketoesters and α-ketophosphonates.[31,33]

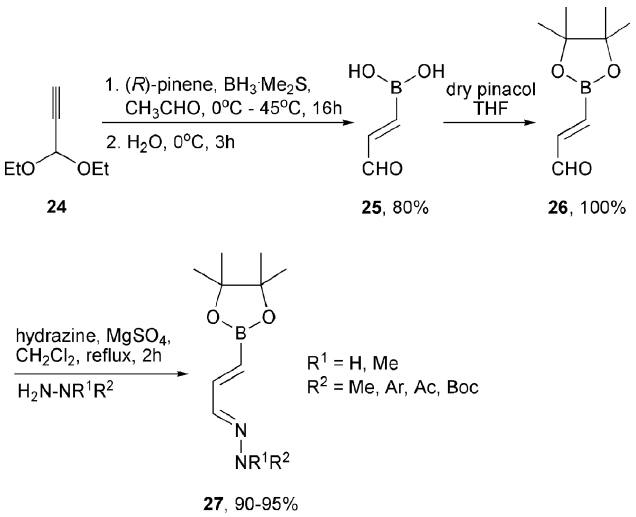
Scheme 5).[33] The 1-azadienes **20b** bearing aromatic, heteroaromatic or alkoxy substituents in the β-position were stable and could be isolated using standard purification techniques; those derived from crotonaldehyde could not be isolated.

The procedures described above all yielded 1-alkyl-1-azadienes. However, 1-azadienes bearing R_2N– or RO–substituents at the 1-position are also relevant. A method reported by Fletcher *et al.* converts α,β-unsaturated oximes **21** to 1,3-bis(silyloxy)-1-azadienes **22** by reaction with trimethylsilyl chloride in the presence of triethylamine and sodium iodide (Scheme 6).[34] The yields of the reaction were quite good (37–85%), but the stability of the 1,3-bis(silyloxy)-1-azadienes proved to be quite low. Therefore, the TMS group was replaced by a TBS group. The corresponding 1,3-bis(silyloxy)-1-azadienes **23** could also be prepared from the α-ketooximes **21**, now by using TBSOTf, in excellent yields (87–93%). This method was also employed to generate analogous 1-(dimethylamino)-1-azadienes from butane-2,3-dione mono-hydrazone in good yields.

Hall and co-workers reported an approach to the synthesis of α,β-unsaturated hydrazones by the three-step sequence depicted in Scheme 7.[35] First, hydroboration of **24** with diisopinocampheylborane, followed by acetaldehyde-promoted oxidative dealkylation and hydrolysis afforded 3-boronoacrolein (**25**) in 80% yield. Then the corresponding boronic ester **26** was



Scheme 6 Synthesis of highly electron-rich 1,3-bis(silyloxy)-1-azadienes.[34]

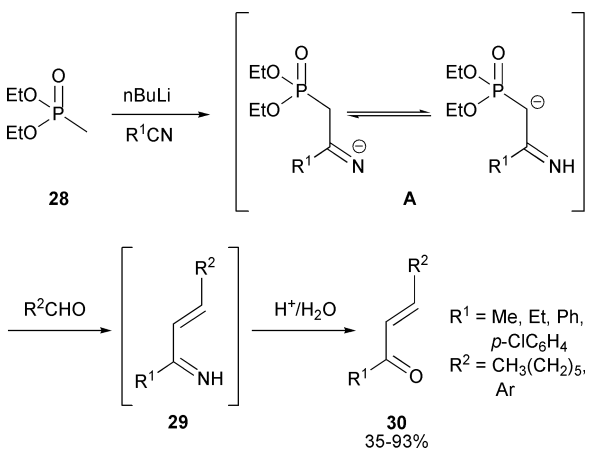


Scheme 7 Three-step synthesis of 1-(dialkylamino)-4-borono-1-azadienes.[35]

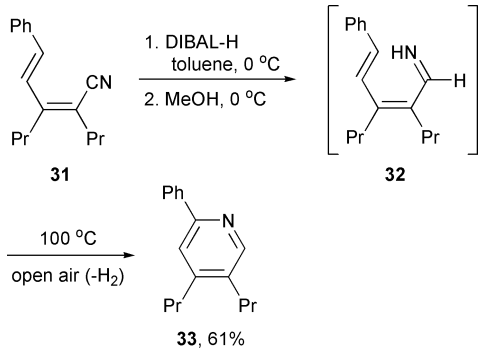
obtained quantitatively *via* a reaction of **25** with pinacol. Finally, the 1-azadienes **27** were formed in 90–95% yield by a condensation reaction with the required hydrazines using anhydrous magnesium sulfate as the drying agent.

3.3 Synthesis of 1*H*-1-azadienes

An efficient way of generating 1*H*-1-azadienes has been reported by our laboratory.[36,37] The method is based on the chemistry reported by Lee and Oh in which a 1-azadiene (**29**) is generated from a phosphonate (**28**), a nitrile and an aldehyde, as an intermediate in the synthesis of α,β-unsaturated ketones **30** (Scheme 8).[38] A nitrile is added to the carbanion of diethyl methylphosphonate **28**, generating the intermediate ketimine anion **A**. This intermediate is then reacted with an aldehyde to give 1*H*-1-azadienes **29**. This method was first used by Lee and Oh[38] and later by Palacios and co-workers[39] to synthesize α,β-unsaturated ketones **30**. The *in situ* generation of 1-azadienes also offers ample possibilities for application in multicomponent reactions, exemplified by various reports from our group[36,37,40,41] and Kiselyov and co-workers[42,43] (see also section 5.2).



Scheme 8 Multicomponent synthesis of 1-azadienes as intermediates in the preparation of α,β-unsaturated ketones.[38]



Scheme 9 Generation of 1-azadienes and 1-azatrienes by DIBAL-H reduction of nitriles.[44]

Another method for generating 1*H*-1-azadienes that involves the use of nitriles is their reduction with diisobutylaluminium hydride (DIBAL-H). Hiyama and co-workers used this method for the generation of 1*H*-1-azatrienes.[44] Thus, reduction of the nitrile **31** with DIBAL-H followed by protonation by MeOH leads to the formation of 1-azatriene **32** (Scheme 9). Such 1*H*-1-azatrienes can then undergo electrocyclization followed by air oxidation at elevated temperature to give pyridines such as **33**.

4. The use of 1-azadienes in the synthesis of N-heterocycles

1-Azadienes have been employed in a range of different reactions to access a wide variety of N-heterocycles, including *e.g.* di- and tetrahydropyridines, pyrimidines, quinolines, thiazines, pyrroles, triazinane diones, and aziridines.

4.1 Cycloaddition reactions

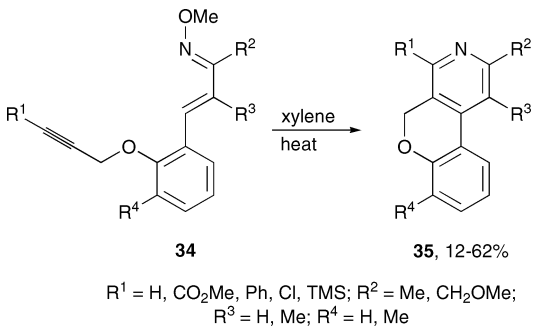
1-Azadienes are frequently applied in [4 + 2] or in [4 + 1] cycloadditions. In these reactions, the 1-azadienes usually serve as the heterodiene partner. However, both the imine and alkene functionality of 1-azadienes can also react as dienophiles, dipolarophiles or carbenophiles in *e.g.* [4 + 2], [2 + 3], or [2 + 1] cycloadditions. Here, we present an overview of the broad range of possible cycloadditions leading to various heterocycles.

4.1.1 [4 + 2] Cycloadditions/hetero-Diels–Alder reactions. Many reports exist on the use of 1-azadienes in hetero-Diels–Alder reactions giving six-membered heterocycles. This topic has been reviewed by Behforouz and Ahmadian in 2000[45] and Mahajan and co-workers in 2002.[46] The former report focuses on the hetero-Diels–Alder reactions of 1-azadienes, while the latter is a review on the synthetic applications of azadienes in general. In this *feature article*, the literature that appeared after these reviews will be discussed. The substitution on the nitrogen atom defines the type of hetero-Diels–Alder that occurs. Electron-rich 1-azadienes typically react in normal electron-demand hetero-Diels–Alder reactions, while electron-deficient 1-azadienes react in inverse electron-demand hetero-Diels–Alder reactions. This section is organized accordingly.

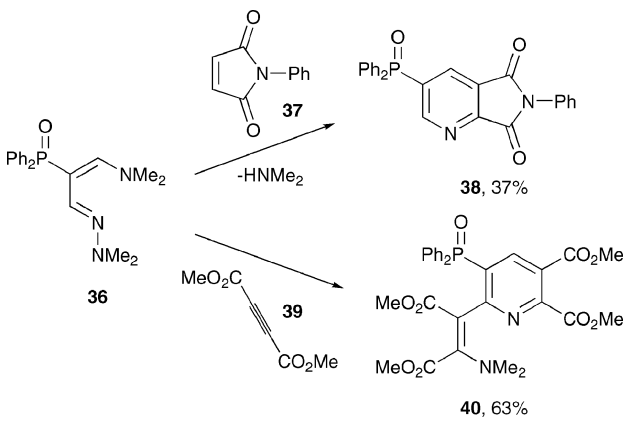
4.1.1.1 Normal electron-demand hetero-Diels–Alder reactions. One of the most recent examples of this type was reported by Moody and co-workers.[47] They use an intramolecular hetero-Diels–Alder reaction of α,β-unsaturated oxime ethers and acetylenic dienophiles in **34** for the synthesis of [*c*]-fused pyridines **35** (Scheme 10).

The α,β-unsaturated oxime ethers **34** (1-azadienes) were synthesized from the corresponding α,β-unsaturated ketones *via* a reaction with methoxylamine hydrochloride and sodium acetate trihydrate. The yields of the pyridines **35** can be reasonable (12–62%); Optimal results were obtained with an electron-deficient acetylene functionality in **34**.

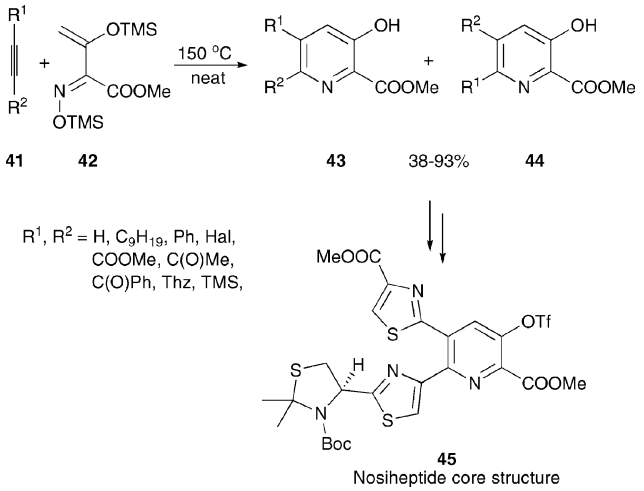
Another reaction generating fused pyridines was reported by Palacios *et al.*[48] Hetero-Diels–Alder reaction of 1-dimethylamino-1-azadiene **36**, containing a phosphine oxide group at C3, with the electron-deficient dienophile *N*-phenylmaleimide **37** gave fused pyridine **38** (Scheme 11). The 1-azadiene **36** can also react with the electron-deficient dimethyl acetylenedicarboxylate **39** yielding the substituted vinyl pyridine **40**. The reaction towards the fused pyridine product **38** was achieved in the absence of solvent at 100 °C. The yield was moderate (37%) and could not be increased by the addition of Lewis acids (BF_3, $AlCl_3$, $Cu(OTf)_2$, $InCl_3$ or $LiClO_4$). The synthesis of the substituted vinyl pyridine **40**, again in the absence of solvent, could be performed at room temperature, furnishing **40** in reasonable yield (63%).



Scheme 10 Intramolecular hetero-Diels–Alder cycloaddition leading to [*c*]-fused pyridines.[47]



Scheme 11 Synthesis of pyridines by hetero-Diels–Alder reactions of electron-rich 1-azadienes.[48]



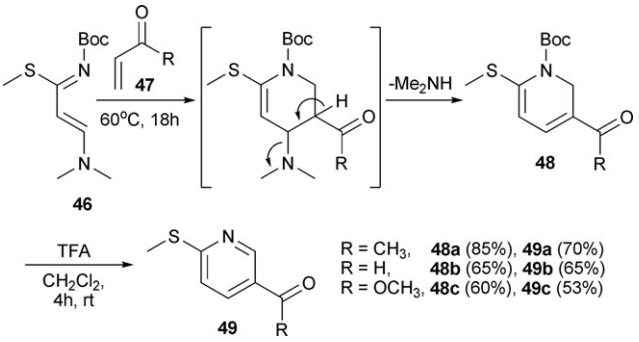
Scheme 12 Hetero-Diels–Alder reactions of electron-rich 1-azadienes with alkynes leading to 3-hydroxypyridine-2-carboxylates.[49]

Arndt and Lu report the synthesis of 3-hydroxypyridines **43** *via* a hetero-Diels–Alder reaction.[49] The products were applied to the synthesis of nosiheptide core structure **45**. The 1-azadiene, a silylated enol oxime **42**, can react with various alkynes **41** (Scheme 12). In the reaction, mixtures of different regioisomers (**43** and **44**) were formed and the overall yield of the reaction varies from reasonable (38%) to good (93%). The choice of the diene and dienophile is flexible as long as electronically activated alkynes are employed, and the diene must not be further deactivated by steric bulk. The regioselectivity can be directed towards the 6-isomer **44** by using monosubstituted alkynyl ketones (R^1 = RC(O)–, R^2 = H). Fletcher *et al*. have used a similar strategy for the synthesis of polysubstituted pyridine derivatives.[34]

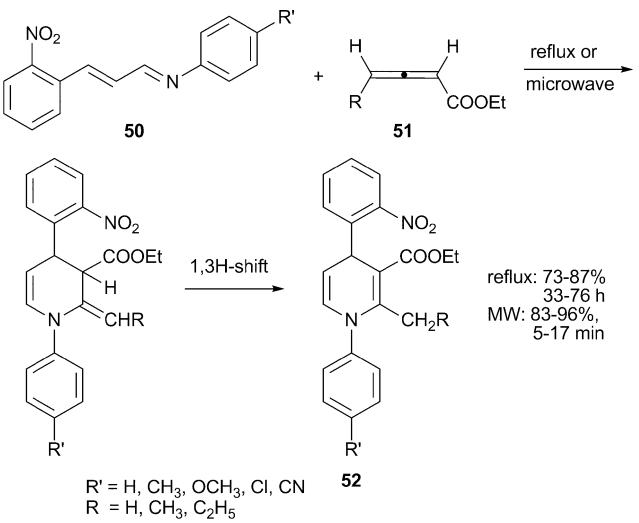
Another method for the synthesis of substituted pyridines has been reported by Deniaud and co-workers, who used the hetero-Diels–Alder reaction of Boc-protected 1-azadiene **46** and acrylic dienophiles **47** (Scheme 13).[50] In this way, they obtained dihydropyridines **48** by a cycloaddition and spontaneous deamination sequence. Aromatization to the pyridines **49** was then achieved by removal of the Boc-group using trifluoroacetic acid followed by spontaneous air oxidation. Three different R groups were used and the yields for both the dihydropyridines **48** (60–85%) and the pyridines **49** (53–70%) are reasonable to good.

Dihydropyridines can also be prepared under microwave conditions. Singh *et al*. reported the thermal and microwave-assisted hetero-Diels–Alder reactions between 1-azadienes **50** and allenic esters **51** for the synthesis of unsymmetrical substituted 1,4-dihydropyridines **52** (Scheme 14).[51] Using microwave irradiation instead of refluxing in dry benzene gave a faster and cleaner reaction, and the products were obtained in higher yields. The yields of **52** under normal reflux conditions vary between 73–87% while with microwave heating **52** could be isolated in 83–96%. Reaction times decreased notably, from 33–76 h under conventional heating conditions to 5–17 min using microwave heating.

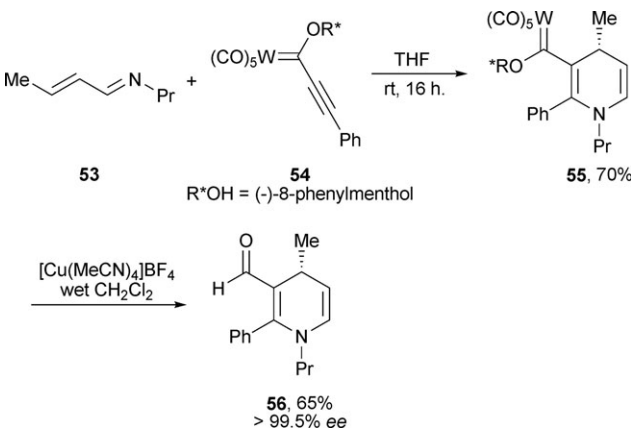
Barluenga and co-workers report an enantioselective synthesis of 1,4-dihydropyridine **56** by reaction of the chiral alkynyl-(alkoxy)carbene complex **54** with 1-azadiene **53** (Scheme 15).[52]



Scheme 13 Synthesis of 2-(methylthio)pyridines by hetero-Diels–Alder reaction of 1-azadienes with α,β-unsaturated carbonyl compounds.[50]

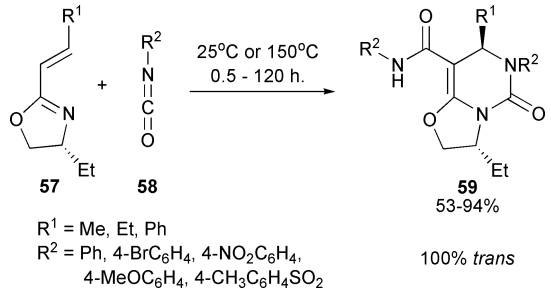


Scheme 14 Synthesis of dihydropyridines by hetero-Diels–Alder reaction of 1-azadienes with allenic esters.[51]



Scheme 15 Enantioselective hetero-Diels–Alder reaction of 1-azadienes and optically pure alkynyl Fischer carbenes leading to dihydropyridines.[52]

The dihydropyridine complex **55** was isolated in 70% yield as a single regio- and diastereoisomer. The complex was demetallated and the chiral auxiliary removed by treatment with [Cu-(MeCN)$_4$]BF$_4$ in wet dichloromethane, giving the corresponding optically pure (ee > 99.5%) aldehyde **56** in 65% yield.

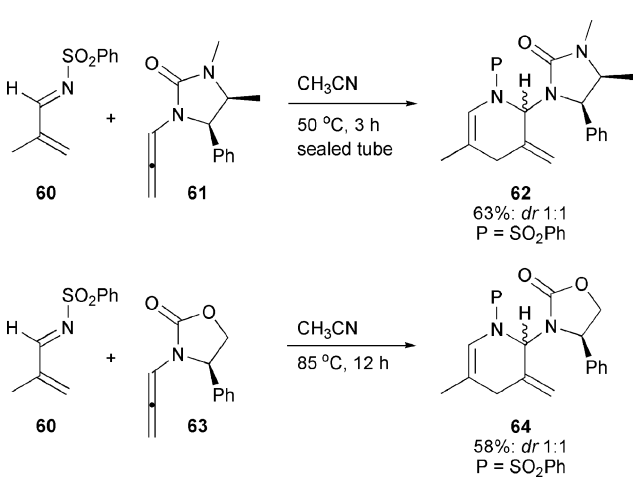


Scheme 16 Hetero-Diels–Alder reaction yielding oxazolo[3,2-*c*]-pyrimidines.[53–55]

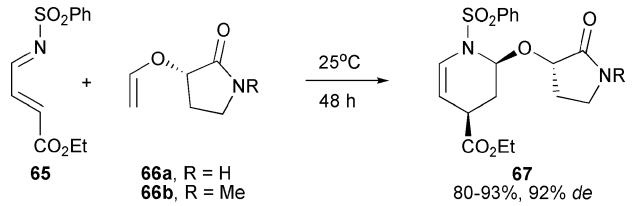
An interesting use of 1-azadienes in natural product synthesis has been reported by Elliott *et al*., who developed a hetero-Diels–Alder reaction for application in their studies towards the total synthesis of batzelladine A.[53–55] They showed that the hetero-Diels–Alder reaction between 2-alkenyl-2-oxazolines **57** (as the 1-azadienes) and isocyanates **58** efficiently (53–94%) gives oxazolo[3,2-*c*]pyrimidines **59** (Scheme 16).

Moreover, the reaction is completely diastereoselective. The *trans* isomers are the only diastereomers obtained. An interesting aspect of these oxazolopyrimidines is that the pure *cis* isomers are obtained upon heating of the pure *trans* isomer above their melting points.

4.1.1.2 Inverse electron-demand hetero-Diels–Alder reactions. *N*-Sulfonyl-1-azadienes are electron-deficient and therefore react as heterodienes in inverse electron-demand hetero-Diels–Alder reactions. A number of reports have appeared on the use of these *N*-sulfonyl substituted 1-azadienes in the synthesis of heterocycles.[56–59] A recent example was reported by Hsung and Berry.[56] The optically pure allenamides **61** and **63** can both react with the *N*-sulfonyl-1-azadiene **60** in a [4 + 2] cycloaddition reaction to give nitrogen heterocycles **62** and **64**, respectively (Scheme 17).[56] These were employed in the synthesis of aza-glycoside related heterocycles. Although the yields of **62** and **64** (63 and 58%, respectively) were good, formation of a 1 : 1 mixture of diastereomers was observed in both cases.



Scheme 17 Inverse electron-demand hetero-Diels–Alder reaction of electron-deficient 1-azadienes with optically pure allenamides.[56]

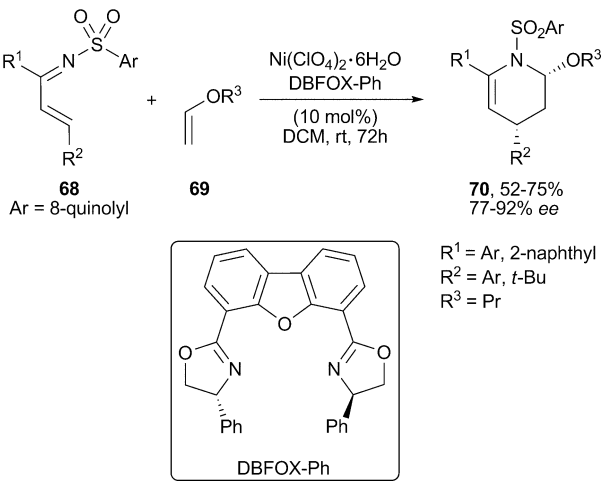


Scheme 18 Auxiliary-assisted asymmetric inverse electron-demand hetero-Diels–Alder reaction.[57]

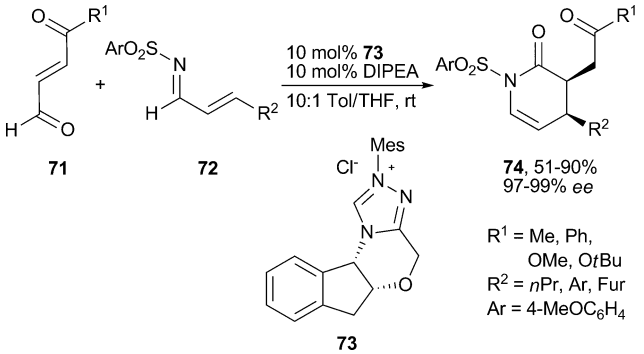
A diastereoselective, auxiliary-assisted, hetero-Diels–Alder reaction reported by Boger and co-workers[57] employs *N*-sulfonyl-1-azadienes **65**. These can react with optically active enol ethers **66** and cycloadducts of type **67** are obtained with high diastereoselectivity (Scheme 18). Three readily available enol ethers bearing chiral auxiliaries were tested along with standard reaction parameters like temperature, solvent, reactant concentration and substitution of the sulfonyl group. The best results were obtained with chiral auxiliaries **66a** and **66b**, which gave high *endo* and facial diastereoselectivity to yield **67** in 80–93% and 92% de.

An enantioselective hetero-Diels–Alder reaction was reported by Carretero *et al*., who reacted *N*-sulfonyl-1-azadienes **68** with vinyl ethers **69** under the influence of a nickel catalyst and the chiral ligand DBFOX-Ph.[58] The reaction affords asymmetric piperidine derivatives **70** (Scheme 19). Carretero showed that combination of a propyl group (R^3) and the 8-quinolyl group (Ar) gave the optimal ee (91%). With this system in hand, the R^1 and R^2 group were varied and the products **70** were isolated in good yields (52–75%), high degrees of *endo* selectivity and with good ee's (77–92%). Aryl substituents of varied electronic and steric nature at the β-position (R^2) are well tolerated and even a *tert*-butyl group was allowed. Variation of R^1 was more limited. *p*-Substituted aryl groups could be used, but with the more sterically demanding 2-naphthyl group, the ee dropped significantly (6%).

Another example that makes use of a chiral catalyst is reported by Bode and co-workers, who use an optically pure *N*-heterocyclic carbene (NHC) to catalyze a hetero-Diels–Alder reaction of **71** and **72** for the synthesis of optically enriched



Scheme 19 Catalytic asymmetric inverse electron-demand hetero-Diels–Alder reaction.[58]



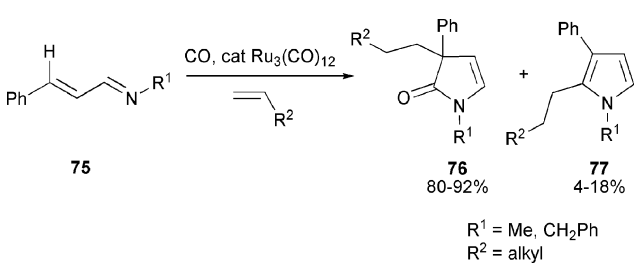
Scheme 20 *N*-Heterocyclic carbene-catalyzed asymmetric inverse electron-demand hetero-Diels–Alder reaction.[59]

dihydropyridones **74** (Scheme 20).[59] Combination of enals **71** and electron-poor 1-azadienes **72** in the presence of the NHC generated *in situ* from **73** efficiently affords the dihydropyridones **74** in yields ranging from 51–90% with ee's of 97–99%. As the NHC catalyst precursor, a chiral triazonium salt with a sterically demanding mesityl group (**73**) was used. Electron-rich and electron-deficient, heterocyclic and aliphatic 1-azadienes **72** are tolerated. Also, a range of different enals **71** could be used. This is the first example of asymmetric organocatalysis in a hetero-Diels–Alder reaction by a metal-free NHC.

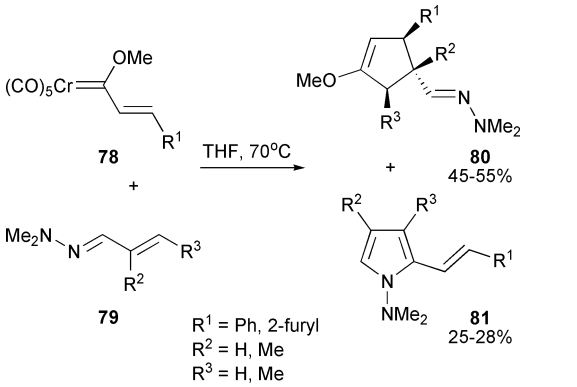
4.1.2 Other cycloaddition reactions. In addition to the various types of hetero-Diels–Alder reactions, 1-azadienes can also be involved in other cycloaddition reactions generating complex and diversely functionalized N-heterocycles.

4.1.2.1 [4 + 1] and [2 + 3] cycloadditions. Imhof and Donnecke reported a reaction between 1-azadiene **75**, CO and various alkenes in the presence of a catalytic amount of $Ru_3(CO)_{12}$ giving 1,3-dihydropyrrolone derivatives **76** (lactams).[60] Usually, small amounts of 2,3-disubstituted pyrroles **77** were observed as side products (Scheme 21). The yield of **76** increased with enhanced basicity of the azadiene nitrogen atom. Therefore, the 1-azadienes **75** with R^1 = Me or Bn performed best in this reaction and the yields of **76** are good to excellent (80–92%). A high *n*/*iso* ratio in **76** is only obtained when α-olefins with long alkyl chains as R^2 are used.

The group of Barluenga reports the use of Fischer carbene complexes **78** and 1-amino-1-azadienes **79** for the synthesis of substituted cyclopentenes **80** (Scheme 22).[61] Pyrroles **81** are formed as side products. The methoxy-cyclopentenes **80** are formed *via* a [2 + 3] cycloaddition generating two or three stereogenic centers (depending on R^1) in a single operation. The pyrroles **81** are formed *via* a [4 + 1] cyclization, a process



Scheme 21 Ru^0-catalyzed alkylative [4 + 1] cycloadditions leading to pyrrolones or pyrroles.[60]

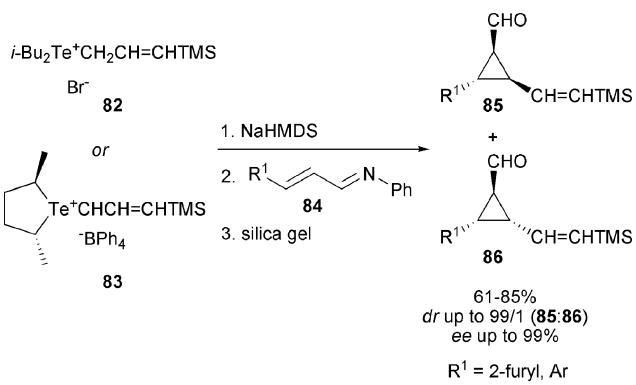


Scheme 22 [2 + 3] *vs.* [4 + 1] cycloaddition of 1-dimethylamino-1-azadienes and alkenyl Fischer carbenes affording cyclopentenes and pyrroles, respectively.[61]

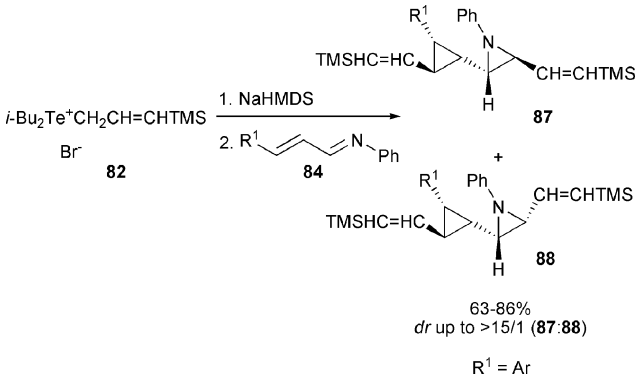
that is rather uncommon for Fischer carbene complexes. Yields of **80** range from 45–55% and of **81** from 25–28%. The methoxycyclopentenes can be converted to the corresponding cyclopentanone hydrazones or cyclopentanone carboxaldehydes by treatment with 0.5 or 3 M aq. HCl, respectively.

The asymmetric version of this reaction involving enantiopure chromium carbene complexes derived from (−)-8-phenylmenthol and (−)-8-(2-naphthyl)menthol has also been studied. This gave, next to the pyrrole side products, diastereomeric mixtures of the expected *trans*,*trans*- and *cis*,*cis*-cyclopentenes.

4.1.2.2 [2 + 1] Cycloadditions. Zheng *et al.* reported the synthesis of vinylcyclopropane-carbaldehydes by reaction of tellurium ylides **82** and 1-azadienes **84** (Scheme 23).[62] Usually, reaction of ylides with 1-azadienes leads to aziridine formation *via* a 1,2-addition.[63] However, after deprotonation of the telluronium salt **82** by NaHMDS, the resulting tellurium ylides undergo a facile [2 + 1] cycloaddition between the C=C π-bond of the azadiene and the carbanion. The corresponding cyclopropane-carbaldehydes **85** and **86** were isolated in good yields (61–85%) and with excellent chemo- and diastereoselectivity.[62] Both electron-withdrawing and electron-donating aryl groups (R^1) are tolerated. An asymmetric version of the reaction employs optically pure telluronium salt **83**. The desired cyclopropanes were isolated in good ee (95–99%).



Scheme 23 [2 + 1] Cycloaddition between 1-azadienes and tellurium ylides leading to cyclopropane-carbaldehydes.[62]



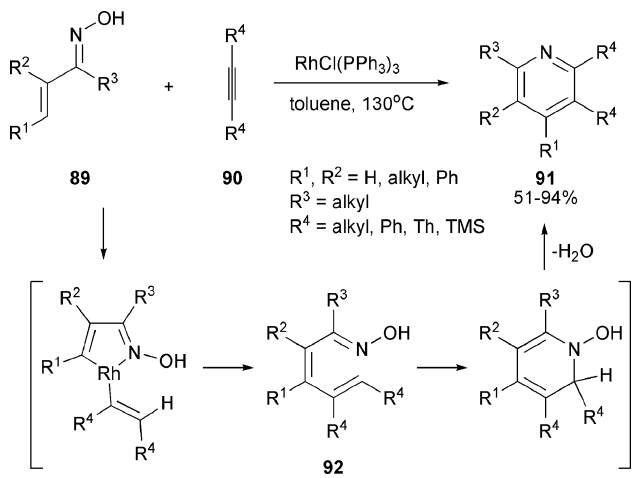
Scheme 24 Formation of cyclopropylaziridines by double [2 + 1] cycloaddition of tellurium ylides to 1-azadienes.[62]

Interestingly, vinylcyclopropylaziridines **87** and **88** are obtained when a 3 : 1 ratio of telluronium salt **82** and 1-azadiene **84** is used (Scheme 24). The products with cumulated three-membered rings could be synthesized with good diastereoselectivity (dr up to 15/1) in reasonable to good yields (63–86%). Again, both electron-withdrawing and electron-donating R^1 groups are tolerated.

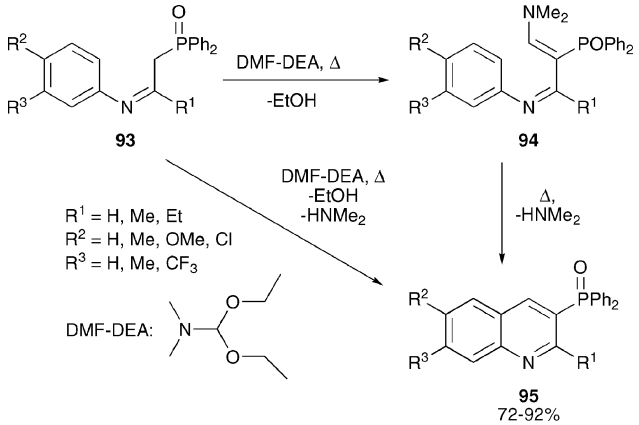
4.2 The use of 1-azadienes in electrocyclization reactions

In addition to the cycloaddition reactions described above, 1-azadienes can be employed in electrocyclization processes as well. For example, Cheng and co-workers reported a Rh^I-catalyzed synthesis of substituted pyridine derivatives **91** from 1-hydroxy-1-azadienes **89** and alkynes **90** (Scheme 25).[64]

First, a rhodium-catalyzed chelation-assisted C–H activation of the 1-azadiene takes place. The formation of the product can be regarded as a β-alkenylation of the 1-azadiene to give a 1-azatriene intermediate (**92**), followed by a 6π-cyclization and dehydration. The product may also be formed *via* a Diels–Alder reaction followed by dehydration. However, performing the reaction without the rhodium catalyst did not give any cycloaddition product. Various substituents are allowed on both the 1-hydroxy-1-azadiene **89** and the acetylene **90**, affording the pyridines **91** in yields between 51–94%.



Scheme 25 Rh^I-Catalyzed β-alkenylation of 1-azadienes followed by electrocyclization–dehydration affording highly substituted pyridines.[64]



Scheme 26 Synthesis of quinolinylphosphine oxides by electrocyclization of *N*-aryl-4-dimethylamino-1-azadienes.[65]

When unsymmetrical internal alkynes are used, mixtures of regioisomers are obtained.

In another electrocyclization, Palacios *et al*. reported the synthesis of quinolinylphosphine oxides **95** from *N*-arylimines **93** (Scheme 26).[65]

The reaction proceeds *via* the intermediate *N*-aryl-1-azadiene **94** that can be isolated. Formation of **94** can be explained by a condensation of the imine starting material with dimethylformamide diethyl acetal (DMF–DEA). The resulting 1-azadiene can then undergo electrocyclization to afford the quinoline **95** by heating to 110 °C in toluene. With this procedure in hand, a small library of quinolinylphosphine oxides **95** was prepared by heating *N*-arylimines with DMF–DEA in refluxing toluene (48 h). The yields are good to excellent (72–92%) and various types of substituents are tolerated. The aromatic ring can bear electron-donating and -withdrawing substituents (R^2 and R^3), while R^1 can be alkyl or H. The quinolinylphosphine oxides **95** can also be made directly from **93** and DMF–DEA without isolation and purification of the intermediate 1-azadiene **94**. Using similar methodology, quinolinyl phosphonates can also be prepared in good yields (68–82%).

5. Multicomponent reactions based on 1-azadienes

As already mentioned in the introduction, DOS-based methods have received considerable attention in the recent literature.[5,7,13,15–18,21–26] The challenge is to address diversity as well as complexity in compound collections in order to probe functional biological activity more efficiently.[20] Synthetic methods that generate multiple molecular scaffolds from the same starting materials or intermediates are considered to be most effective to increase especially structural or skeletal diversity.[9] On the other hand, complexity is most commonly introduced by highly convergent reactions such as the cycloaddition and electrocyclization reactions described in section 4. Also, multicomponent reactions (MCRs) are powerful reactions to generate complex molecules as they combine at least three simple, easily accessible building blocks in a one-pot process.[66–68]

A conceptually novel approach to DOS is the use of **modular reaction sequences** combining MCRs and other complexity-generating reactions. In these sequences, a densely functionalized

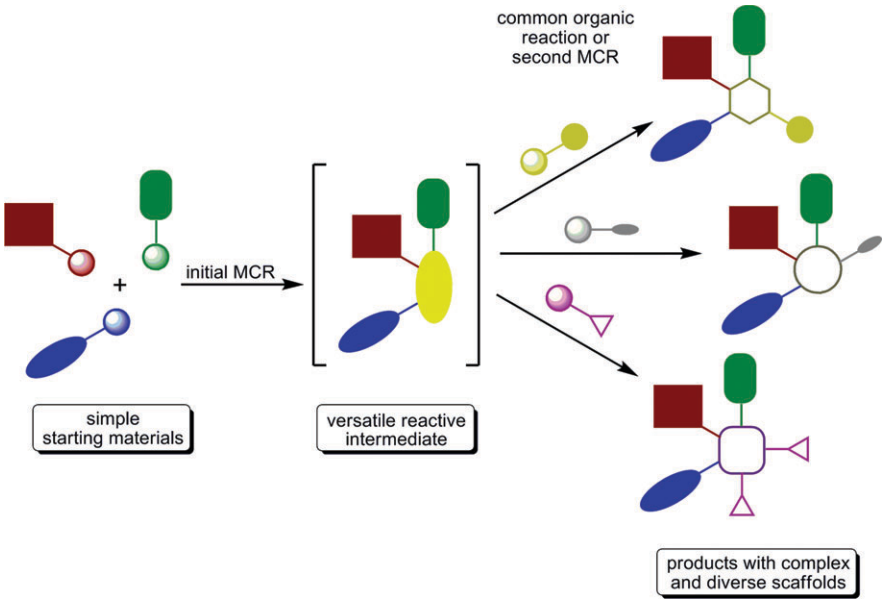


Fig. 2 Modular reaction sequences.

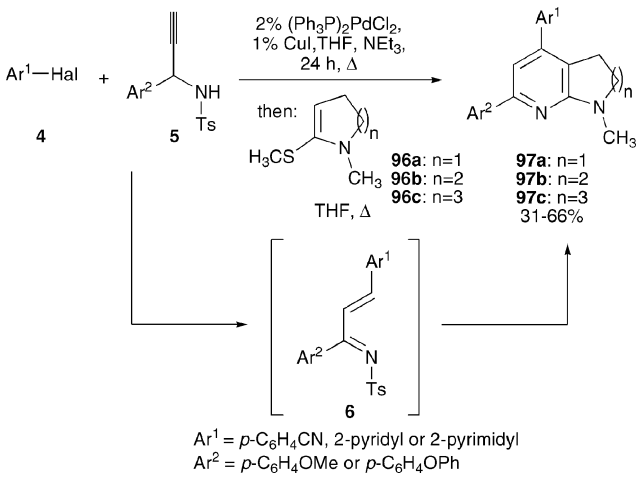
reactive intermediate formed *via* an initial MCR reacts with different additional components yielding a diverse set of complex scaffolds (Fig. 2). In this way, both the diversity and the complexity criteria can be met in the design and construction of compound libraries to identify small molecule modulators of biological systems. 1-Azadienes are such densely functionalized intermediates, which can react as nucleophiles, electrophiles and as dienophiles, dipolarophiles or carbenophiles. Moreover, 1-azadienes can be generated *via* MCR chemistry, as will be discussed in the following sections. Therefore, 1-azadienes are extremely well suited to explore the concept of modular reaction sequences in DOS.

5.1 *N*-Substituted 1-azadienes in MCRs

Müller and co-workers have reported a convenient method for a 1-azadiene-based MCR approach to pyrrolo[2,3-*b*]pyridines **97a**, [1,8]naphthyridines **97b** and pyrido[2,3-*b*]azepines **97c** (Scheme 27).[28] The 1-azadiene **6** is generated *in situ* from an electron-poor aryl halide **4** and a terminal propargyl *N*-tosylamine **5** *via* a coupling–isomerization sequence (see also Scheme 2). After the 1-azadiene formation, the *N*,*S*-ketene acetal **96** is added and an inverse electron-demand hetero-Diels–Alder reaction takes place, followed by aromatization yielding **97** in 31–66% (Scheme 27).

Sridharan *et al.* also reported an *in situ* synthesis of 1-azadienes **100**, by the condensation of α,β-unsaturated aldehydes **98** and aniline derivatives **99**. The azadienes are combined, in the same pot, with β-dicarbonyl compounds **101** yielding 1,4-dihydropyridines **102** (Scheme 28).[69]

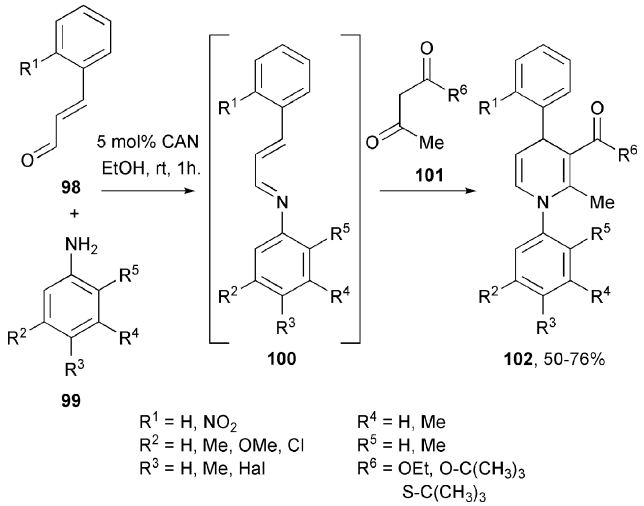
The reaction performs optimally by using 5 mol% ceric ammonium nitrate (CAN) in ethanol at room temperature for 1 h. The optimized reaction conditions were applied to a range of substrates yielding the 1,4-dihydropyridines **102** in reasonable to good yields (50–76%). Several types of electron-releasing and electron-withdrawing groups at all positions of the *N*-aryl group (R^2–R^5) are tolerated, including alkyl,



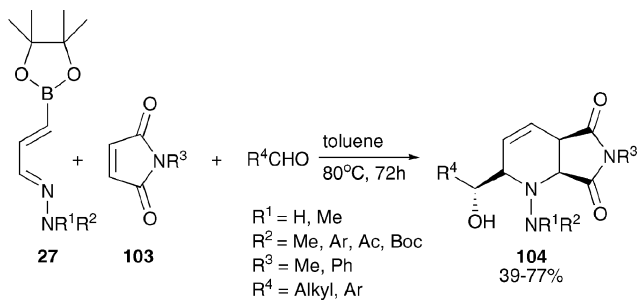
Scheme 27 Multicomponent synthesis of fused pyridines involving 1-azadienes generated *in situ* by isomerization of arylpropargylic sulfonamides.[28]

alkoxy, bromo, chloro and fluoro substituents. The 4-aryl group on the 1-azadiene **100** can also bear substituents (R^1) such as a nitro group, but this can result in a lower yield. For the β-dicarbonyl compound (R^6), ethyl esters (R^6 = OEt) were the standard input. *tert*-Butyl esters can also be employed, but require a longer reaction time (2 h) and gave the corresponding dihydropyridine products in slightly lower yields. *tert*-Butyl β-keto thioesters (R^6 = S*t*Bu) can be efficiently applied in the reaction as well. Limitations of the reaction were found in the use of aliphatic amines or α,β-unsaturated aldehydes other than cinnamaldehyde derivatives, which resulted in complex reaction mixtures containing only small amounts of the desired product.

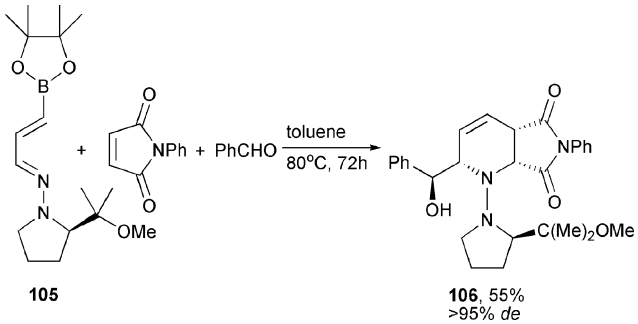
An MCR in which the 1-azadiene is not generated *in situ* has been reported by Hall and co-workers.[35] They report a three-component reaction between 4-borono-hydrazonodienes (1-azadienes) **27**, maleimides **103** and aldehydes for the



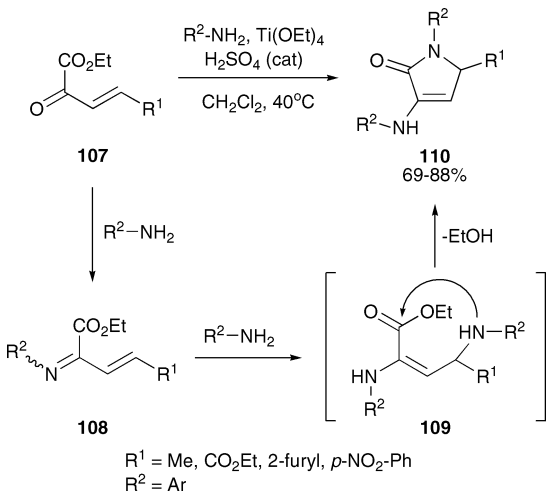
Scheme 28 CAN-catalyzed three-component condensation leading to dihydropyridines.[69]



Scheme 29 Tandem hetero-Diels–Alder–allylboration involving 4-borono-1-azadienes.[35]



Scheme 30 Auxiliary-assisted asymmetric tandem hetero-Diels–Alder–allylboration.[35]



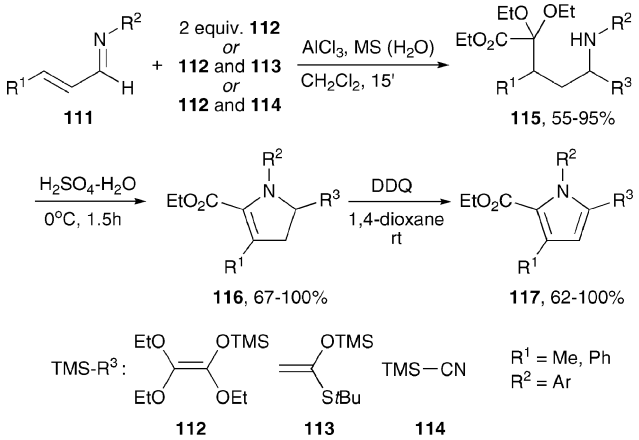
Scheme 31 Three-component condensation reaction towards amino-lactams involving 1-azadienes as intermediates.[32]

synthesis of polysubstituted piperidines **104** *via* a tandem aza-[4 + 2]–allylboration reaction (Scheme 29). The required 4-borono-1-amino-1-azadienes **27** are efficiently synthesized *via* condensation of 3-boronoacrolein pinacol ester with hydrazines (see Scheme 7). Both mono- and disubstituted arylhydrazines can be used and even an acetyl or Boc group can be used as R^2. In the MCR itself, a wide variety of aldehydes (R^4) can be used, including aliphatic aldehydes and electron-rich and electron-poor aromatic aldehydes. The maleimide substituent can also be varied (R^3 = Me, Ph). The yields of the products range from 39–77%. Another interesting feature of this approach is that the absolute stereochemistry can be controlled by using the appropriate chiral auxiliary.[70] Thus, when the L-proline derived 1-azadiene **105** is used, product **106** could be isolated in a remarkable >95% de (Scheme 30).

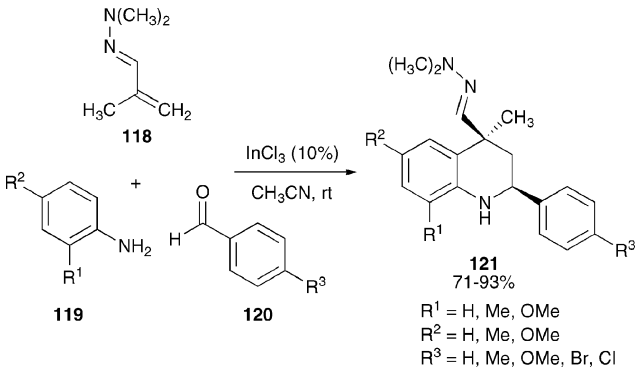
Palacios and co-workers also report a synthesis of lactams **110** that proceeds *via* an intermediate 1-azadiene **108** (Scheme 31).[32] Reaction of this 1-azadiene, which was isolated first, with one equivalent of *p*-toluidine in the presence of $Ti(OEt)_4$ and H_2SO_4 gave the cyclic enamine (lactam) **110**. However, the authors optimized the reaction towards a one-pot procedure. The formation of lactam **110** can be explained by initial condensation of the amine and carbonyl component **107** affording 1-azadiene **108**. Subsequent conjugate addition of a second equivalent of amine yields the linear adduct **109**. This undergoes ring closure with loss of ethanol to give the final product **110**. A small array of lactams was made by reaction of β,γ-unsaturated α-keto esters with two equivalents of an amine in the presence of $Ti(OEt)_4$ and H_2SO_4 in refluxing dichloromethane, yielding only the cyclic products. The yields were moderate to good (69–88%) with R^1 = CO_2R, Me, or 2-furyl. Chiral amines can also be used, yielding a 1 : 1 mixture of diastereomers, which could be separated and isolated to give two optically pure lactams.

A three reaction sequence for the synthesis of pyrroles involving a 1-azadiene-based MCR was reported by Kawai *et al.*[71] (Scheme 32). First, a double nucleophilic addition of an α,α-dialkoxy ketene silyl acetal **112**, ketene silyl thioacetal **113** or trimethylsilyl cyanide **114** to the 1-azadienes **111** was performed, yielding coupling products **115** in reasonable to excellent yields (55–95%). Next, acid-promoted cyclization and subsequent oxidation with DDQ gave the pyrroles **117**. This is actually a two-step process in which first dihydropyrroles **116** are formed in reasonable to excellent yields (67–100%) by treating the coupling products **115** with acid. These dihydropyrroles are then dehydrogenated under the influence of DDQ, yielding, also in reasonable to excellent yields (62–100%), the pyrroles **117**.

Sridharan *et al*. report a three-component reaction between 1-(dimethylamino)-1-azadiene **118**, anilines **119** and aromatic



Scheme 32 Synthesis of highly substituted pyrroles involving a 1-azadiene-based multicomponent reaction.[71]

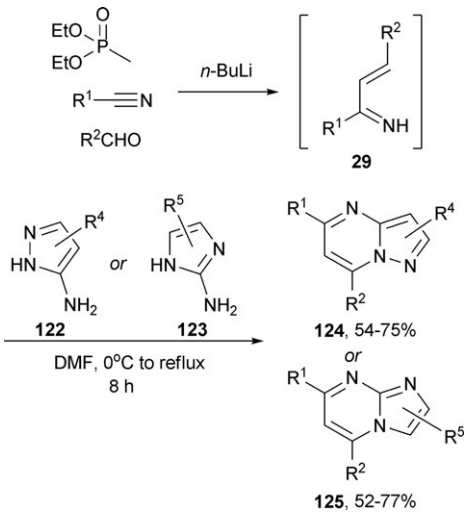


Scheme 33 Synthesis of tetrahydroisoquinolines involving a hetero-Diels–Alder reaction where the 1-azadiene reacts as the dienophile.[72]

aldehydes **120**, yielding tetrahydroquinolines **121** (Scheme 33).[72] In the first step, **119** and **120** react to give a diarylimine. This diarylimine reacts as the diene in a Diels–Alder reaction with the 1-azadiene **118** as the dienophile. The use of 10% indium trichloride in the reaction resulted in the formation of C4 functionalized 1,2,3,4-tetrahydroquinolines **121** in good to excellent yields (71–93%). Both electron-donating and electron-withdrawing substituents R^1–R^3 are tolerated. The reaction proceeds in a diastereoselective fashion to give only the *cis* products **121**. This reaction is the first example of a 1-azadiene reacting as a dienophile in an aza-Diels–Alder reaction.

5.2 1*H*-1-Azadienes in MCRs

The Oh method that was discussed in Scheme 8 for the *in situ* generation of 1*H*-1-azadienes[38] **29** was used by Kiselyov and Smith in an MCR for the synthesis of polysubstituted pyrazolo- and imidazolopyrimidines. The 1-azadiene **29**, generated from diethyl methylphosphonate, a nitrile and an aldehyde, was combined in the same pot with amino heterocycles **122** and **123**, respectively (Scheme 34).[43] The reaction of **29** with 5-aminopyrazoles **122** gives pyrazolo[1,5-*a*]pyrimidines **124**, while the one-pot combination of **29** with imidazoles **123** affords imidazo[1,2-*a*]pyrimidines **125**. Yields were reasonable to good (52–77%) and in both reactions, the

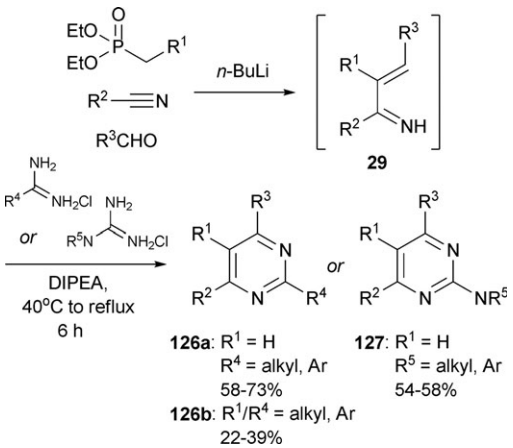


Scheme 34 Multicomponent reaction of *in situ*-generated 1-azadienes with 5-aminopyrazoles and 2-aminoimidazoles to afford pyrazolo- and imidazolopyrimidines, respectively.[43]

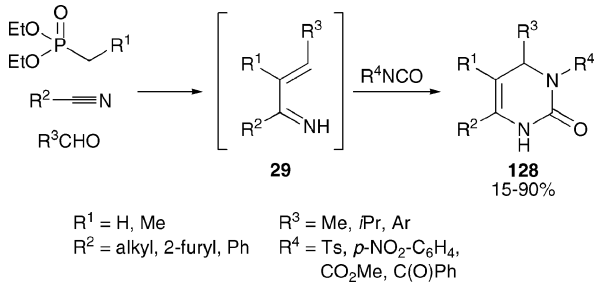
electronic nature of the aryl substituents R^1 and R^2 (donating or withdrawing) did not significantly affect the yield.

In another one-pot procedure also reported by Kiselyov, a similar 1-azadiene is reacted with amidine or guanidine derivatives, yielding polysubstituted pyrimidines **126** or 2-amino pyrimidines **127** (Scheme 35).[42] Different aromatic nitriles (R^2) and aromatic aldehydes (R^3) with electron-donating and electron-withdrawing substituents can be used, as well as various alkyl and aryl groups on the amidine and guanidine derivatives (R^4/R^5). Yields of the products range from reasonable to good, 54–73%. The phosphonate can also be substituted (R^1) to give 5-substituted pyrimidines. However, this is limited to small alkyl groups and the yields drop significantly to 22–39% when the steric bulk is increased from methyl to phenyl or isobutyl.

Our group recently reported a multicomponent reaction between 1*H*-1-azadienes **29** and isocyanates bearing a strong electron-withdrawing group, yielding dihydropyrimidinones **128** (Scheme 36).[36,37] As stated, **29** was generated *in situ* using the modified Oh protocol[38] from diethyl methylphosphonate, a nitrile and an aldehyde.



Scheme 35 Multicomponent reaction of *in situ*-generated 1-azadienes with amidines or guanidines to give highly substituted pyrimidines.[42]

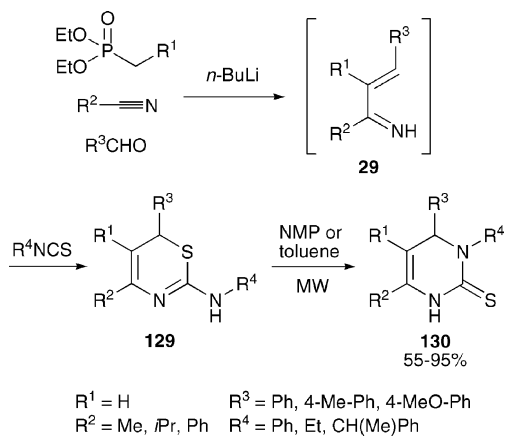


Scheme 36 Multicomponent reaction of *in situ*-generated 1-azadienes with electron-deficient isocyanates to give dihydropyrimidinones.[36,37]

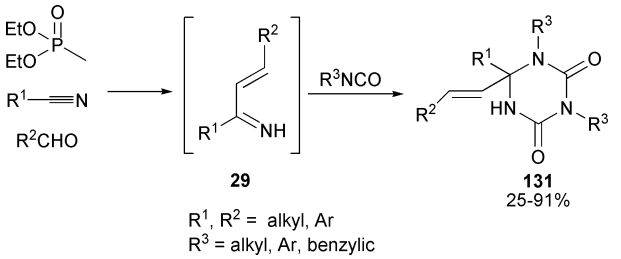
A broad range of different R^2 and R^3 groups can be introduced on the dihydropyrimidinone scaffold with yields of the isolated product ranging from 15–90%. However, variation of R^1 is limited (only H or Me). In the isocyanate input, highly electron-withdrawing R^4 groups are needed. In a modification of this method, isothiocyanates were employed instead of isocyanates.[73] This results in the formation of thiazines **129**, which can be converted into dihydropyrimidinethiones **130** *via* a Dimroth rearrangement.[74] This rearrangement was achieved under microwave irradiation in batch or continuous flow format (Scheme 37). Three different rearrangement protocols were developed that lead to **130** in 55–95% isolated yield. Solvents of choice are either toluene or 1-methyl-2-pyrrolidone (NMP) and reaction temperatures range between 120 °C and 210 °C.

Another very useful variation of these MCRs combines *in situ* generated 1-azadienes **29** with isocyanates bearing less electron-withdrawing (aryl) or even electron-donating (alkyl) substituents.[41] In this case, the initial addition product of the 1*H*-1-azadiene on the isocyanate does not undergo electrocyclization as in the synthesis of dihydropyrimidinones **128**[36,37] or aminothiazines **130**.[73] Instead, the intermediate acts as a nucleophile and reacts with a second equivalent of isocyanate. The second addition product then cyclizes in a 1,2-fashion to afford triazinane diones **131**, a rather unexplored class of N-heterocycles (Scheme 38).

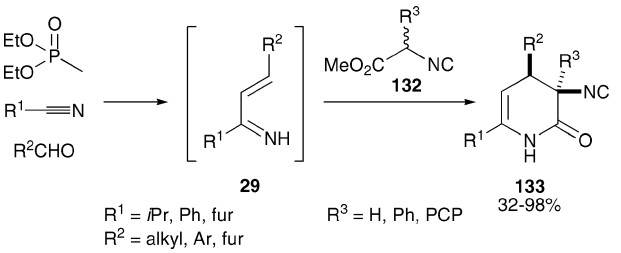
The reaction is quite flexible and isolated yields of the corresponding triazinane diones are moderate to excellent



Scheme 37 Multicomponent reaction of *in situ*-generated 1-azadienes with isothiocyanates leading to aminothiazines and dihydropyrimidinethiones.[73]



Scheme 38 Multicomponent synthesis of triazinane diones.[41]



Scheme 39 Multicomponent reaction of *in situ*-generated 1-azadienes with α-isocyano esters leading to 3-isocyano-3,4-dihydropyridones.[40]

(25–91%). (Hetero)aromatic and aliphatic R^1/R^2 substituents and benzylic and aromatic R^3 substituents could be introduced successfully. As is shown here, isocyanates are versatile reagents in these 1-azadiene-based MCRs for the synthesis of different heterocycles. They are used in other MCRs as well.[75,76]

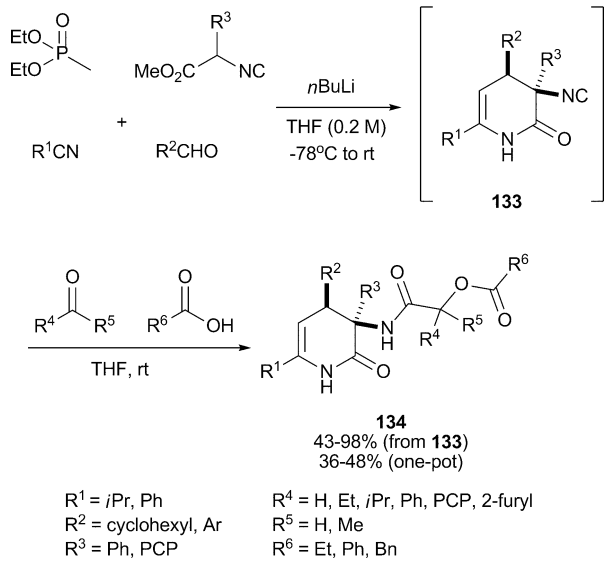
The *in situ*-generated 1*H*-1-azadienes **29** can also react with α-acidic isocyanides **132**, yielding dihydropyridones **133** (Scheme 39).[40] The interesting feature of this reaction is that the isocyanide function stays intact during the reaction, leaving it available in **133** for further differentiation in, for example, additional multicomponent reactions. Furthermore, the products were isolated solely as the 3,4-*cis* diastereomer (*i.e.*, with R^2 and R^3 in *trans* orientation). The choice of the aldehyde (R^2) is crucial for this reaction. Aromatic, heteroaromatic and α,β-unsaturated aldehydes give the expected dihydropyridones, but aliphatic and highly electron-deficient aldehydes do not give the desired product. Different nitriles can also be used. Aromatic, heteroaromatic and aliphatic nitriles give good results, but primary aliphatic nitriles should be avoided. The isocyano ester can also be varied, even towards those lacking additional electron-withdrawing α-substituents. The yields of the reaction are reasonable to excellent (32–98%).

6. A platform for further complexity generation and DOS

The results presented in the previous sections illustrate that 1-azadienes are indeed very versatile building blocks in the synthesis of a wide variety of N-heterocycles. Especially the *in situ* generation of 1*H*-1-azadienes as first reported by Lee and Oh[38] offers a highly versatile platform for the development of 1-azadiene-based MCRs. This is clearly exemplified by contributions from Kiselyov[42,43] and our group.[36,37,40,41,73] The high variability in terms of substitution pattern and resulting

scaffold structures makes it a highly attractive complexity-generating strategy to achieve skeletal diversity in DOS. The strategy can be made even more attractive for DOS by incorporating handles for subsequent additional complexity-generating reactions, such as ring-closing metathesis, cycloadditions or even a second MCR.

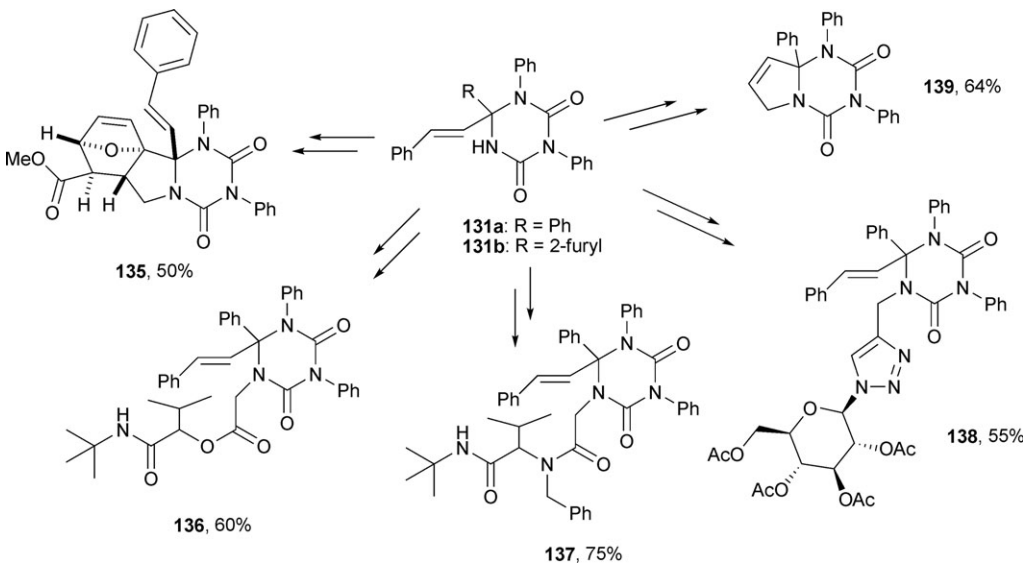
One example of such an approach was recently reported by our laboratory.[77] As shown in Scheme 39, an azadiene-based MCR leading to isocyano-functionalized 3,4-dihydropyridin-2-ones **133** was developed.[40] These products can immediately be used in isocyanide-based multicomponent reactions (I-MCRs). One such reaction is the Passerini reaction and



Scheme 40 One-pot combination of a 1-azadiene-based multicomponent reaction affording isocyano-functionalized dihydropyridones with Passerini reaction: a formal six-component reaction.[77]

combination of the two MCRs would lead to the generation of conformationally constrained depsipeptides **134**.[77] Thus, 3,4-dihydropyridin-2-ones **133** were reacted with a range of commercially available aldehydes and acids under standard Passerini reaction conditions (CH_2Cl_2, rt). The expected depsipeptides **134** were successfully obtained in reasonable to excellent yields (43–98%) as 1 : 1 mixtures of diastereomers (Scheme 40). With these results in hand, we turned to study the combination of both MCRs in one pot, resulting in a six-component reaction. The whole sequence was performed in THF, which is a slight modification of the Passerini-3CR. The one-pot synthesis of depsipeptide **134a** (R^1,R^4 = *i*Pr, R^2 = PMP, R^3 = Ph, R^5 = H, R^6 = Et) was first investigated and this compound could be isolated in 40% yield, the same yield as for the overall yield obtained *via* the two-step procedure (41%). In addition, three other examples of this six-component procedure were performed all with approximately the same yields (36–48%).

Because of the ease of alkylation of the free NH, triazinane diones resulting from a 1-azadiene-based MCR (Scheme 38) can also be used for various types of follow-up chemistry.[78] We selected six different reactions to create a set of highly diverse and complex compounds. For all reactions, a simple alkylation reaction was performed to introduce a handle for further functionalization. Passerini, Ugi, Cu^I-catalyzed [2 + 3] cycloaddition, ring-closing metathesis, and intramolecular Diels–Alder reactions were selected for complexity generation (Scheme 41). The alkylation reactions were easy to perform and typically proceeded in 50–75% yield. Next, the various types of follow-up reactions were performed, yielding the diverse and complex molecules **135–139** shown in Scheme 41. The yields of the reactions were reasonable to good (50–75%), but, more importantly, we have shown that the triazinane scaffold can be a valuable tool for making diverse and complex small molecules.



Scheme 41 Rapid generation of molecular diversity and complexity by combining a multicomponent reaction leading to triazinane diones with additional complexity-generating reactions, including ring-closing metathesis, [2 + 3] cycloaddition, isocyanide-based multicomponent reactions (I-MCRs) and tandem alkylation–intramolecular Diels–Alder cycloaddition.[78]

Conclusions

1-Azadienes are densely functionalized building blocks or intermediates that can react as nucleophiles, electrophiles and as dienophiles, dipolarophiles or carbenophiles. In this *feature article* we discussed various applications of 1-azadienes in cycloaddition, electrocyclization, and multicomponent reactions for the efficient construction of a broad range of N-heterocycles. The use of 1-azadienes to generate complexity and diversity is highlighted. They prove excellent platforms to address skeletal diversity in DOS. Especially in combination with MCR-based strategies, 1-azadienes represent a challenging array of functionalities that can be employed to explore chemical space efficiently and identify small molecular probes for biology.

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