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Hetero-Diels–Alder reactions of (isobenzo)furans

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Hetero-Diels–Alder reactions of furans and isobenzofurans provide convergent redox-neutral access to hetero-oxanorbornene derivatives. These versatile intermediates serve as precursors to a variety of heterocycles, polymers, and complex natural products. Herein we comprehensively review this area of research and speculate on what developments are required to advance the field.

1. Introduction

Furans enjoy a rich and storied history within the context of the Diels–Alder (DA) reaction. Notable examples include Stork's 1951 total synthesis of cantharidin,¹ generally acknowledged as the first planned stereospecific synthesis,² and Dewar's fundamental mechanistic studies concerning the asynchronicity of DA cycloadditions.³ Today, furyl [4 + 2] cycloadditions regularly feature within the synthesis of natural products and polymers, while the reversibility of these processes lends itself to bioconjugation, drug delivery, and responsive material settings.^{4,5} Notably, the majority of these applications utilize *carbo*-dienophiles. In contrast, *hetero*-DA reactions of (isobenzo)furans remain comparatively exploratory in nature.^{6,7} In an effort to highlight this area of research, while also delineating what we believe to be some of the key unmet challenges, herein we provide the first comprehensive review of furan and isobenzofuran hetero-DA reactions and their applications. Our only exception pertains to the employment of singlet oxygen (¹O₂) as a dienophile, where instead we limit discussion to strategic considerations in natural product synthesis. This review is primarily organized according to the class of hetero-dienophile, as per the categorization and sequencing provided in Scheme 1. Reactions that proceed *via* a stepwise (formal) hetero-DA reaction are not discussed, although in cases where the mechanism is ambiguous or debated, we err on the side of caution, and such examples are included.

2. Diels–Alder reactivity of (isobenzo)furans

Furans are widely described as poor DA dienes.^{5,8} This can largely be attributed to furan aromaticity, often resulting in a

significant diene–dienophile HOMO–LUMO gap. This is further compounded by the generation of ring-strain within their oxanorbornene DA adducts.⁹ The combination of these two effects can manifest in facile retro-DA processes, which while desirable in some contexts is typically unwelcome. In contrast, isobenzofurans tend to be highly reactive as DA dienes while also benefiting from aromatic stabilization of their [4 + 2] cycloadducts, thus reducing the favorability of retro-DA processes.^{10,11} However, isobenzofurans themselves tend to exhibit poor stability profiles,^{11,12} with one notable exception: 1,3-diphenylisobenzofuran. This commercially available crystalline solid, which has been employed extensively within the context of this review, is kinetically stable while also highly reactive in DA settings. Although this makes it an excellent tool in demonstrating DA reactivity, its diphenyl substituents limit applicability in target-oriented settings.

3. C=N bonds as dienophiles

Acyclic dienophiles

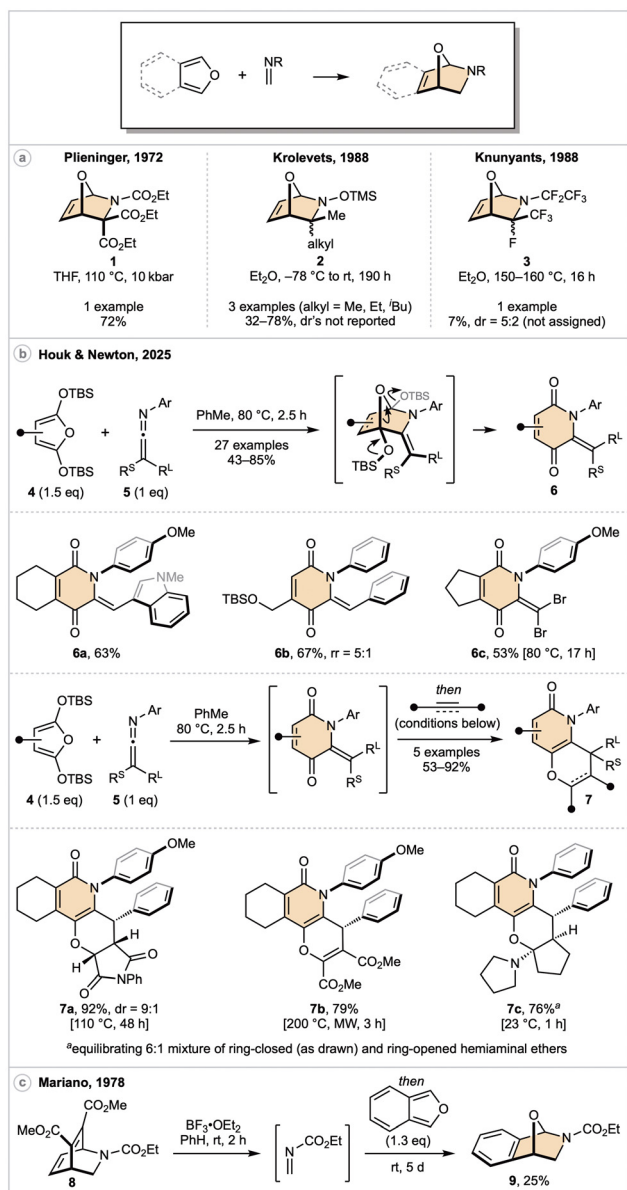
Prior to 2025, only five examples of a furan engaging in an aza-DA reaction with an acyclic CN double bond had been reported, each within a wider study introducing a new class of aza-dienophile (Scheme 2a). The earliest example, from 1972, described the reactions of a highly activated triester imine with a small collection of dienes.¹³ While the cycloaddition with furan proceeded in good yield to generate cycloadduct **1**, high-temperature and high-pressure were both necessary for



Scheme 1 Scope and structure of this review.

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Scheme 2 Acyclic C=N bonds as dienophiles.

reactivity. Several years later, Krolevets reported that *O*-silylated oximes underwent [4 + 2] cycloadditions with either furan or cyclopentadiene, the former generating aza-heterocycles of general structure 2.¹⁴ However, there may be grounds to question the accuracy of this report: only physical properties (*e.g.*, boiling point, density) and in one case an infrared spectrum were reported for each of the cycloadducts. Perhaps more telling, *O*-silylated oximes have never again been employed as a dienophile in an aza-DA reaction. In 1988, Knunyants and coworkers explored the DA chemistry of various perfluorinated dienophiles.¹⁵ Within this study, the authors demonstrated that compound 3 could be accessed from the corresponding imine upon prolonged heating at 160 °C, however the yield was very low.

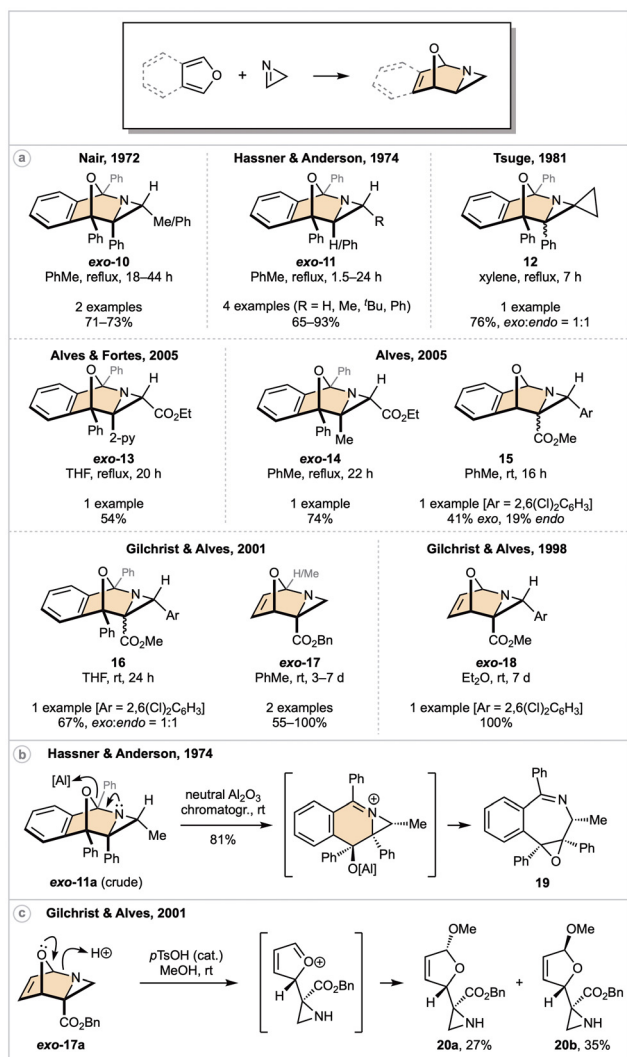
More recently, the authors of this review and their colleagues demonstrated that *N*-aryl ketenimines are highly reactive aza-dienophiles (Scheme 2b).¹⁶ Drawing upon mechanistic studies concerning the reactivity of ketenes as oxa-dienophiles,¹⁷ we hypothesized that ketenimine cycloadducts should be less prone to [3,3]-sigmatropic rearrangement processes that befall their oxa-analogues. Indeed, warming a mixture of our recently reported¹⁸ family of 2,5-bis(*tert*-butyldimethylsilyloxy)furans 4 with ketenimines 5 yielded metastable cycloadducts, typically with excellent regio- and diastereo-control. Fragmentation of the bridging ether occurred upon prolonged heating, providing oxygenated pyridone derivatives 6 in up to 85% yield. A wide reaction scope was demonstrated, including heteroaromatic substituted ketenimines (6a), unsymmetrically functionalized furans (6b), and fully substituted ketenimines (6c). Moreover, this DA/ring-opening process could be telescoped with an oxa-DA reaction to generate fused pyridone/pyran systems 7 in one-pot through the combination of three discrete molecules. With respect to oxa-DA scope, electron-poor olefins (7a), electron-poor alkynes (7b), and electron-rich enamines (7c), were all competent dienophiles. Finally, benchmarking studies were employed to demonstrate *N*-aryl ketenimines are significantly more reactive than related imines, an effect that was computationally ascribed to lower levels of diene distortion during ketenimine cycloaddition.

Given the highly forcing conditions required for the synthesis of 1 and 3, it is surprising that only a single example employing an isobenzofuran has been reported (Scheme 2c).¹⁹ While exploring the DA reactivity of various pyridine derivatives, Mariano observed that treatment of cycloadduct 8 with catalytic BF₃·OEt₂ promoted a retro-DA process at ambient temperature to generate an electron-poor formalimine. The authors successfully trapped this intermediate with isobenzofuran, generating cycloadduct 9 in 25% yield.

Cyclic dienophiles: three-membered rings

The majority of reactions employing azirines as aza-dienophiles have utilized 1,3-diphenylisobenzofuran as coupling partner (Scheme 3a).^{20–22} With this highly reactive diene, electron-withdrawing groups on the azirine are not critical for reactivity. Rather, ring strain is sufficiently activating, provided the cycloaddition is run at elevated temperature (10–14). With the exception of spirocycle 12, each of these cycloadducts was isolated as a single diastereoisomer arising from cycloaddition through the *exo*-mode (defined with respect to the acyclic imine substituent) and on the less-sterically encumbered π -diastereoface of the azirine. In contrast, electron-poor azirines react with isobenzofurans at ambient temperature, albeit with poor diastereoselectivity. For example, cycloadduct 15 was isolated as a 2:1 mixture of *exo*- and *endo*-diastereomers.²² The authors note this reaction was highly reversible: repeating the procedure in refluxing THF exclusively yielded *exo*-15, while an NMR sample of *endo*-15 was observed to slowly convert into its *exo*-analog. A similar interconversion was also observed for 16. It is unclear if *exo*-10, *exo*-11, *exo*-13, and *exo*-





Scheme 3 Cyclic C=N bonds as dienophiles: three-membered rings.

14 also represent a thermodynamic sink or if facile reversibility is limited to electron-poor azirines.

Introduction of a conjugated ester on the azirine motif enables DA reactions with less reactive furan derivatives, as demonstrated by Gilchrist and Alves during their diastereoselective preparation of **exo-17** and **exo-18**.^{23,24} The same authors reported additional (isobenzofuran)/azirine DA reactions, although instability of the presumed cycloadducts prevented their complete characterization.

Many (if not all) of the cycloadducts in Scheme 3 exhibit a poor stability profile as a result (at least in part) of their hemiaminal functionality. For example, Hassner and Anderson observed that subjecting crude **exo-11a** to chromatography with neutral alumina resulted in a ring expansion process, initiated by C–O bond cleavage, ultimately generating epoxide **19** in 81% yield (Scheme 3b).²¹ Notably, the regioselectivity of this type of process was reversed when **exo-17a** was treated with a Brønsted acid (Scheme 2c).²⁴ In this case, C–N bond

cleavage followed by unselective trapping of the oxocarbenium with methanol delivered **20a** and **20b**.

Cyclic dienophiles: four-membered rings

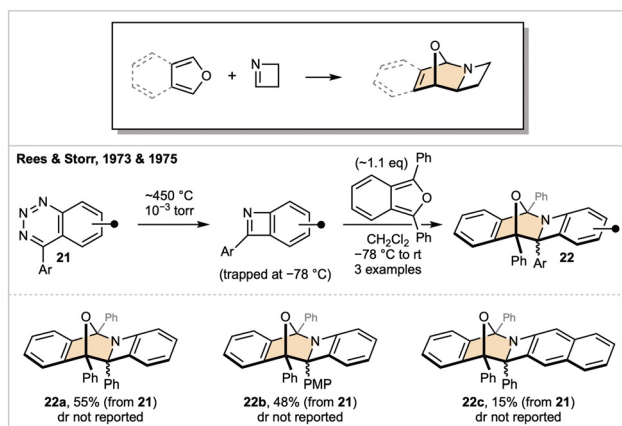
Four-membered aza-dienophiles remain relatively unexplored (Scheme 4). In seminal studies, Rees and Storr achieved the first ever synthesis of an aza-cyclobutadiene derivative *via* flash vacuum pyrolysis of 1,2,3-benzotriazines **21**.²⁵ Depending on the precise substitution pattern, these formally anti-aromatic compounds dimerize at temperatures as low as –40 °C. Despite this, the authors successfully demonstrated aza-cyclobutadienes can be trapped in DA reactions upon low-temperature addition of 1,3-diphenylisobenzofuran to deliver cycloadducts **22**. While the overall yields of this process range from modest to poor, it is not clear if dienophile generation and/or cycloaddition is low yielding, nor is it clear if less reactive furan derivatives can outcompete dienophile dimerization.

Cyclic dienophiles: five-membered rings

The Gaviña laboratory introduced a suite of five-membered aza-dienophiles, several of which were trapped in DA reactions with polymer-bound furoate **23** (Scheme 5).²⁶ A representative example, utilizing ketal **24** as masked dienophile, proceeded *via* acid-promoted deprotection in refluxing dioxane. An aza-DA reaction to generate **25** was followed by basic hydrolysis to yield heteroaromatic **26** in 23% yield over the two steps. Hydrolysis products **27–30** were also accessed *via* the same general approach.

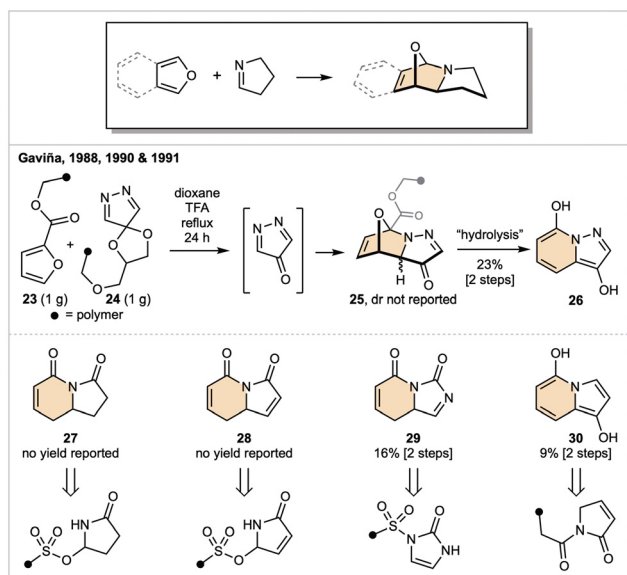
4. C≡N bonds as dienophiles

A DA reaction of an (isobenzofuran) across a CN triple bond has yet to be unequivocally demonstrated. In general, nitriles are rarely used as dienophiles.⁷ Of the few reported examples, most require a highly reactive diene in conjunction with an electron-poor nitrile (*e.g.*, tosyl cyanide).²⁷ In the specific context of isobenzofurans, mechanistic studies from the Rickborn laboratory demonstrate their benzonitrile (formal)



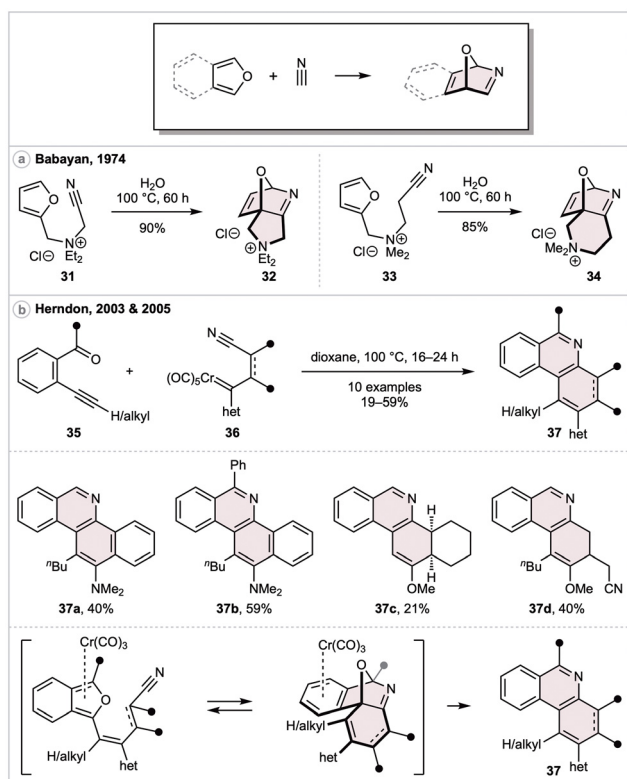
Scheme 4 Cyclic C=N bonds as dienophiles: four-membered rings.





Scheme 5 Cyclic C=N bonds as dienophiles: five-membered rings.

DA adducts undergo cycloreversion upon heating at 40 °C.²⁸ As a consequence, Rickborn brings into question⁷ the accuracy of Babayan's 1974 report detailing the intramolecular DA reactivity of furyl-tethered nitriles (Scheme 6a).²⁹ Here, the authors report a high-yielding cycloaddition occurs upon heating ammonium salts **31** or **33** under aqueous conditions.



Scheme 6 C≡N bonds as dienophiles.

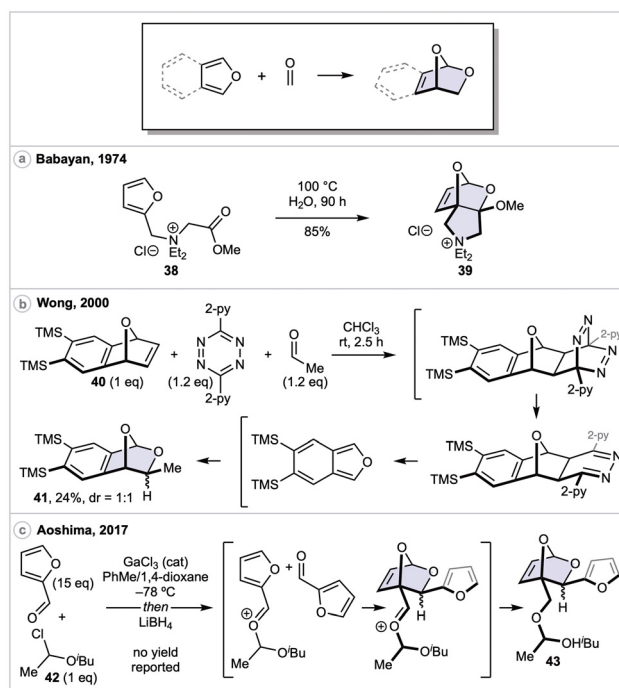
Cycloadducts **32** and **34** were only characterized using infrared spectroscopy and combustion analysis.

A more recent report also describes a potential intramolecular DA reaction with a nitrile as dienophile, although here the ambiguity lies with respect to the precise mechanism.³⁰ The overall transformation involves heating 2-alkynyl-benzoyl derivatives **35** with β-cyanocarbene complexes **36**, providing access to hetero-functionalized phenanthridines in moderate to low yields (*e.g.*, **37a–d**). The authors propose multiple mechanistic possibilities, including chromium η⁵-complexed isobenzofuran derivatives acting as dienes in a reversible cycloaddition, followed by a deoxygenation/aromatization process.

5. C=O bonds as dienophiles

Furyl oxa-DA reactions are remarkably rare. The earliest example, from Babayan's aforementioned 1974 report, detailed an intramolecular oxa-DA of methyl ester **38**—however the resulting cycloadduct **39** was only characterized using infrared spectroscopy and elemental analysis (Scheme 7a).²⁹

In 2000, Wong *et al.* introduced 5,6-bis(trimethylsilyl)isobenzofuran as a new highly reactive DA diene (Scheme 7b).³¹ Proof of principle applications primarily focused on the synthesis of linear polyaromatic compounds using carbodienophiles (*e.g.*, arynes and *para*-quinones), although a single oxa-DA reaction was also reported. Diene synthesis was achieved *via* extension of Warren's approach to isobenzofuran:³² mixing furyl-DA adduct **40**, 3,6-bis(2-pyridyl)-1,2,4,5-tetrazine,



Scheme 7 C=O bonds as dienophiles.



and acetaldehyde at ambient temperature resulted in an inverse electron-demand DA/double retro-DA sequence to furnish the desired silylated isobenzofuran. This was proceeded by an *in situ* oxa-DA reaction with acetaldehyde to yield acetal **41** in 24% yield as a 1:1 mixture of diastereoisomers. Within the same study several carbo-DA examples proceeded in excellent yield, suggesting the oxa-DA reaction is the low yielding step in this transformation.

The most recent report, from Aoshima and coworkers, utilized a Lewis acid-catalyzed cationic furyl oxa-DA reaction for the copolymerization of furfural and 2-acetoxyethyl vinyl ether.³³ A model study designed to probe the mechanism is presented in Scheme 7c, maintaining furfural as diene but introducing ether **42** as a replacement for the vinyl ether propagating species. The authors propose the reaction proceeds *via* GaCl₃-catalyzed formation of a cationic alkylated furfural derivative, which undergoes an oxa-DA reaction across the carbonyl of furfural followed by a LiBH₄ quench to generate **43**.

6. C=Si bonds as dienophiles

In the late 1970's, the Brook laboratory demonstrated C=Si bonds can engage as dienophiles in [4 + 2] reactions with simple 1,3-butadienes,³⁴ later demonstrating such processes do not appear to proceed *via* a radical pathway.³⁵ With respect to (isobenzofuran)s as dienes, only three reactions have been disclosed, all within a single report from Auner and co-worker (Scheme 8).³⁶ In this study, an electron-poor dienophile was generated at low temperature *via* a stepwise S_N2'-type reaction of trichlorovinylsilane and *tert*-butyllithium. The transient silolefin intermediate was then treated with an excess of 2-methylfuran, affording silabicyclic **44** as a single regioisomer in 70% yield, but with minimal diastereocontrol. The authors successfully reacted the same dienophile with furan and 2,5-dimethylfuran, although yields suffered in both cases. At ambient temperature these cycloadducts were observed to slowly revert to a mixture of their respective furan precursors and [2 + 2] dimers of the dienophile. Whether this proceeds

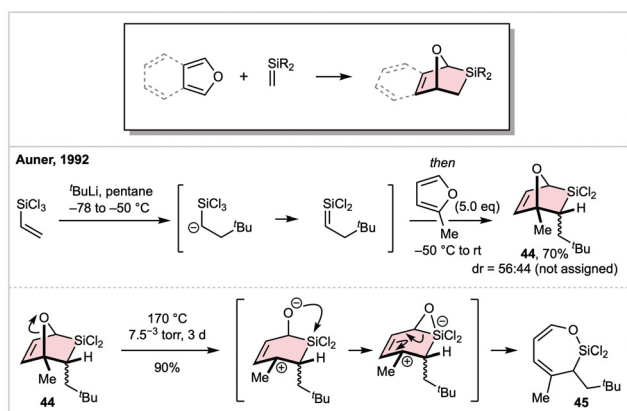
via a retro-DA process remains unclear as attempts at generating crossed [2 + 2] adducts were unsuccessful. Unexpectedly, heating the same furyl cycloadducts for several days under vacuum at 170 °C resulted in a high yielding rearrangement to a dihydro-1,2-oxasilepine (shown for the conversion of **44** to **45**). The authors propose this reaction proceeds *via* cleavage of the oxa-bridge to generate a stabilized allylic carbocation that also benefits from the β-silicon effect, followed by an anionic Brook-type rearrangement to furnish the ring-expanded product.

7. C=P bonds as dienophiles

It wasn't until the late 1970s that synthetic routes to isolable phosphalkenes and phosphalkynes bearing localized C=P and C≡P bonds were reported,³⁷ paving the way for their application in DA settings. Examples employing phosphalkenes as dienophiles began to appear in the early 1980s,³⁸ followed shortly thereafter by the analogous reactions of phosphalkynes.³⁹ The earliest report of a phosphalkene engaging in a DA reaction with an (isobenzofuran) was reported in 1985 by Grobe and coworker (Scheme 9a).⁴⁰ In this example, 2-methylfuran was heated at 70 °C in the presence of stannyl phosphane **46**. Thermolysis of the latter species generated a reactive perfluorinated phosphalkene that underwent an unselective DA reaction to generate isomers **47a-d** in a combined yield of 93%. This reaction is highly reversible and heating the cycloadducts at 70 °C in the presence of 2,3-dimethyl-1,3-butadiene yields the corresponding cross-DA adducts alongside 2-methylfuran. In a series of follow up studies, the Grobe laboratory trapped the same perfluorinated dienophile with furan⁴⁰ and also introduced a related perfluorinated phosphalkene was trapped with 2-methylfuran.⁴⁰

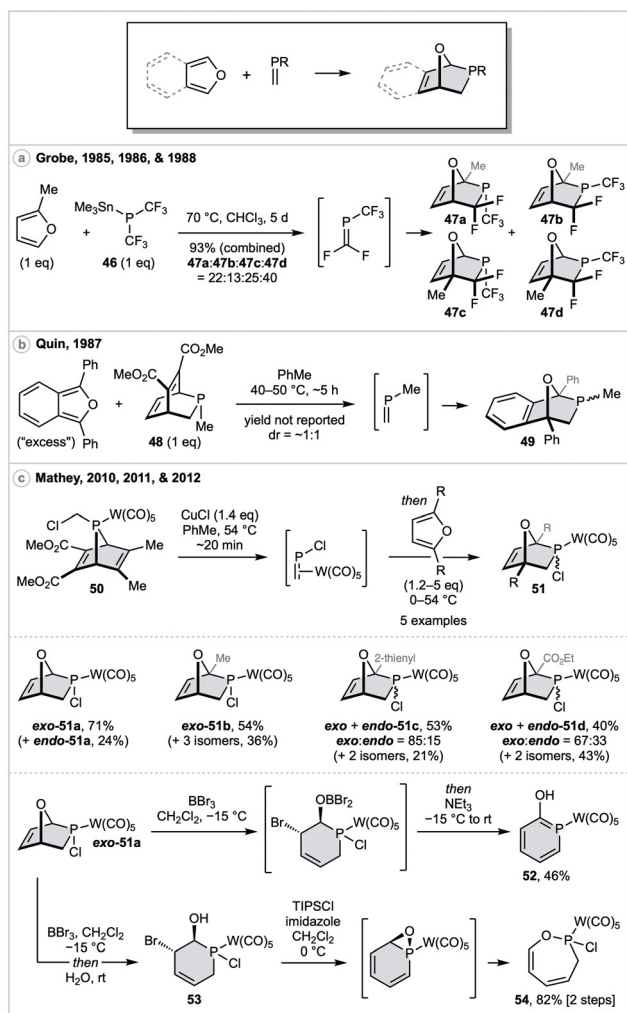
In 1987, Quin *et al.* expanded the scope of phosphalkene dienophiles to include non-perfluorinated derivatives (Scheme 9b).⁴¹ Mild heating of phosphine **48** invoked a retro-DA process to generate 2-phosphapropene (and dimethyl phthalate as byproduct). In the absence of a trapping reagent, 2-phosphapropene decomposed *via* an unspecified intermolecular process. However, conducting the same reaction with an excess of 1,3-diphenylisobenzofuran yielded DA cycloadducts **49** as a 1:1 mixture of diastereomers. The instability of **49**, and the analogous cycloadduct derived from furan as diene, precluded full characterization, and only ³¹P NMR data was acquired.

Over a series of papers, the first disclosed in 1985, Mathey and coworkers demonstrated that 1-chlorophosphathene can be stabilized through π-complexation with a tungsten carbonyl complex.^{42,43} While not stable enough to be isolated in pure form, *in situ* characterization was feasible, and solutions could be heated to 65 °C without decomposition. Several years later, the same group described reactions of this dienophile with (isobenzofuran)s as a convergent means to prepare phosphorus heterocycles (Scheme 9c).⁴⁴ From a mechanistic perspective, the authors propose that heating phosphine **50** gener-



Scheme 8 C=Si bonds as dienophiles.





Scheme 9 C=P bonds as dienophiles.

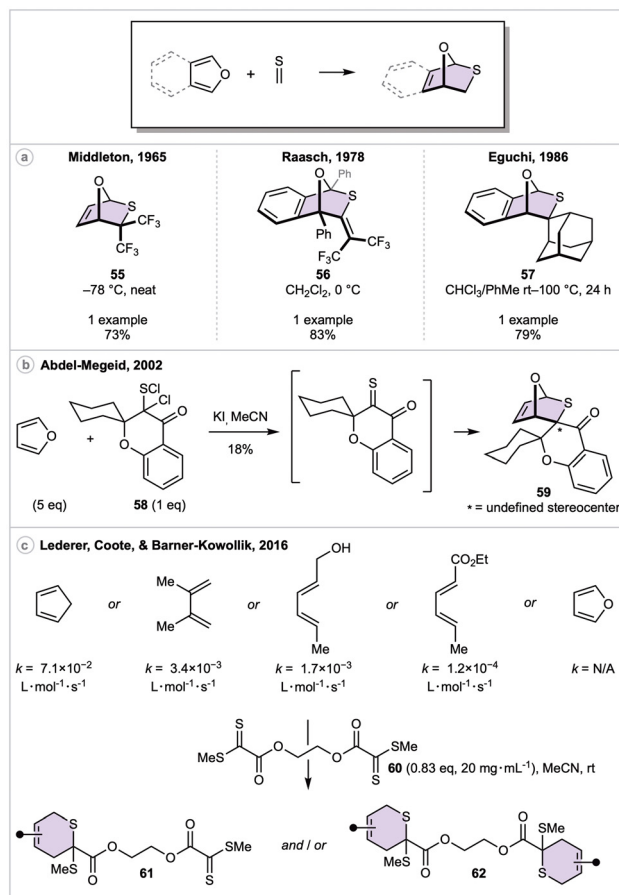
ates a tungsten-bound phosphinidene complex that undergoes a rapid CuCl-promoted rearrangement to generate the active dienophile.⁴³ This intermediate was successfully trapped with a variety of simple furans, and representative cycloadducts include **51a–d**. In each case, a mixture of isomers was obtained, favoring the regioisomer depicted (when relevant) and preferentially reacting *via* the *exo*-mode with respect to the bulky tungsten substituent. Cycloadduct derivatization by either aromatization or ring-expansion was demonstrated. In the case of **exo-51a**, treatment with stoichiometric boron tri-bromide followed by triethylamine yielded tungsten-complexed 2-hydroxyl phosphinene **52** in 46% yield. The reaction appears to proceed *via* an S_N2' -type process to generate a boron-bound alkoxide, followed by a series of elimination events. Alternatively, if the alkoxide was quenched with water then bromohydrin **53** was isolated. A ring-expansion process, reminiscent of the work described by Auner in 1992 (Scheme 8), was achieved by the addition of TIPSCl and imidazole, ultimately leading to oxaphosphepine derivative **54** in 82% yield over the two steps. The Mathey laboratory has

also demonstrated analogous DA/aromatization reactivity with 1,3-diphenylisobenzofuran for the synthesis of a phosphaphthalene.⁴⁵

8. C=S bonds as dienophiles

In 1961, Middleton and coworkers synthesized a small library of perfluorinated thiocarbonyls *via* the reaction of bis(perfluoroalkyl)mercury salts with boiling sulfur.⁴⁶ While the most reactive derivative, hexafluorothioacetone, is not sensitive toward water or oxygen, it dimerizes upon standing within several hours.⁴⁷ Despite this, the authors went on to highlight its exceptional dienophilicity (“reacts instantaneously with butadiene at -78°C to give a quantitative yield of the cyclic adduct”). Four years later, Middleton explored the DA reactivity of these perfluorinated thiocarbonyls in more detail, including the reaction of furan and hexafluorothioacetone for the synthesis of **55** (Scheme 10a). The authors noted this cycloadduct polymerizes on the order of hours when held neat at ambient temperature.⁴⁸

In 1978, Raasch prepared the thioketene derivative of hexafluorothioacetone [*i.e.*, bis(trifluoromethyl)thioketene], observing that it can be stored at ambient temperature for months



Scheme 10 C=S bonds as dienophiles.



with minimal dimerization. A slight excess of this thioketene was mixed with 1,3-diphenylisobenzofuran at 0 °C, resulting in the formation of cycloadduct **56** in 83% yield. The DA reaction appears highly (if not completely) chemoselective for the C=S over C=C bond. Cycloadduct **56** was described as unstable to heat, decomposing by means of a retro-DA reaction. Eight years later, Eguchi *et al.* explored the DA reactivity of adamantanthione, a bench stable thioketone derivative.⁴⁹ Its reaction with isobenzofuran proceeded in 24 hours at 100 °C to afford spirocycle **57** in 79% yield. Attempts to employ either furan or 1,3-diphenylisobenzofuran as dienes were unsuccessful, only yielding unreacted dienophile.

More recently, Abdel-Megeid and coworkers reported a thio-DA reaction of furan and an α -oxo thioketone (Scheme 10b).⁵⁰ Only two dienophiles were reported, including one derived from cyclohexyl-substituted sulfonyl chloride **58**. In this example, addition of potassium iodide generated the reactive α -oxo thioketone, leading to spirocycle **59** in 18% yield, alongside 33% of a dienophile [4 + 2] dimer.

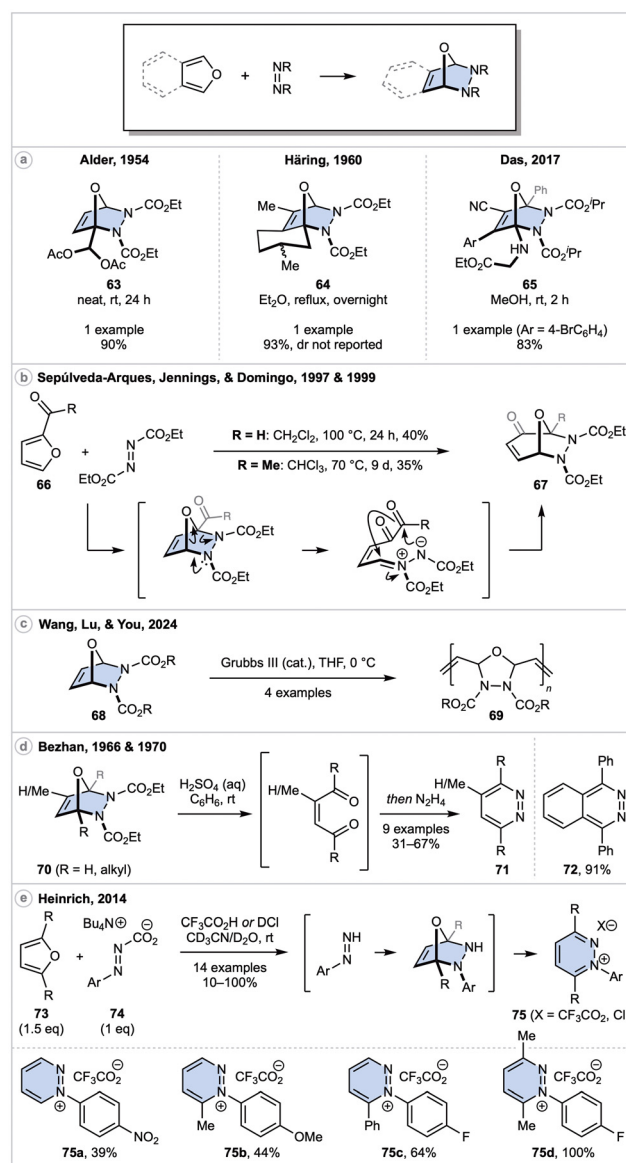
The low reactivity of furans with C=S dienophiles was well demonstrated within a study concerning the development of thermoreversible ligation systems (Scheme 10c).⁵¹ A small library of dienes were successfully reacted across the C=S bond of symmetric thio-dienophile **60**, and their respective rate constants are provided. Notably, ethyl sorbate, an acyclic electronically deactivated diene, proved to be competent in this reaction. However, no cycloaddition was observed with furan, and *ab initio* calculations indicate the equilibrium strongly favors the reactants in this case.

9 N=N bonds as dienophiles

Acyclic dienophiles

The first furyl azo-DA reaction employed diethyl azodicarboxylate as dienophile for the synthesis of cycloadduct **63** (Scheme 11a).⁵² Over the next sixty years, several closely related reports describing the reaction of furans with acyclic dialkyl azodicarboxylates have been disclosed.^{53–56,57,58–61} While most examples employ minimally functionalized furans, a small number of more complex cycloadducts have also been accessed (*e.g.*, **64** and **65**).⁵⁶ Typically, DA reactions of this nature tend to be high-yielding processes that proceed under mild conditions (*e.g.*, ambient or slightly elevated temperatures).

Despite their ease of preparation, few furyl azo-DA cycloadducts have been applied in further settings, perhaps in part due to their modest stability profiles.⁵⁸ Indeed, failed attempts to use them as antitumor agents,⁵⁹ or as precursors to insecticides,⁵⁴ oxadiazoles,⁵⁸ pyridazines,⁵³ or in ring-rearrangement metathesis⁶⁰ have all been reported. Nevertheless, several research groups have productively channeled aza-cycloadduct reactivity/instability (Scheme 11b–e). For example, Sepúlveda-Arques and coworkers observed that heating furans **66** with diethyl azodicarboxylate unexpectedly yielded ring-expanded products **67** (Scheme 11b).⁶² Mechanistic studies suggest a



Scheme 11 Acyclic N=N bonds as dienophiles.

three-step process beginning with an azo-DA reaction, followed by a strain-release promoted ring-opening before re-closure *via* the pendant aldehyde/ketone with concurrent formation of the bridging ether.

A proof-of-principle study introducing degradable polymers derived from furyl azo-DA adducts was reported in 2024 (Scheme 11c).⁶¹ Density functional theory calculations indicated cycloadducts **68**, which were prepared neat on up to 100 g scale, exhibit greater ring-strain (22.8 kcal mol^{−1}) than established degradable ring-opening metathesis polymerization monomers, prompting the authors to explore their suitability in living polymerization reactions. Treatment with Grubbs third generation catalyst provided efficient access to homopolymers **69**, as well as various copolymers upon the inclusion of strained alkene comonomers (not shown). Finally,



controlled polymer degradation, including biodegradation, was effectively demonstrated.

Two conceptually related but mechanistically distinct approaches to pyridazines (or their salts) from furyl azo-DA adducts have been reported (Scheme 11d and e). Not deterred by earlier unsuccessful efforts to access pyridazines *via* hydrolysis of furyl azo-DA cycloadducts,⁵³ Bezhan and coworkers recognized that, while hydrolysis cleaves both CN bonds, this does not represent a dead end. Thus, cycloadducts **70** were treated with sulfuric acid to generate the corresponding 1,4-dicarbonyls, which, following addition of hydrazine, led to pyridazines **71** in up to 67% yield (Scheme 11d).⁵⁷ In addition, one example employing 1,3-diphenylisobenzofuran as diene was reported, leading to derived phthalazine **72** in 91% yield. Strategically speaking, here the azo-dienophile ultimately serves as oxidant through conversion of furans into their corresponding dicarbonyl over the two-step cycloaddition/hydrolysis sequence.

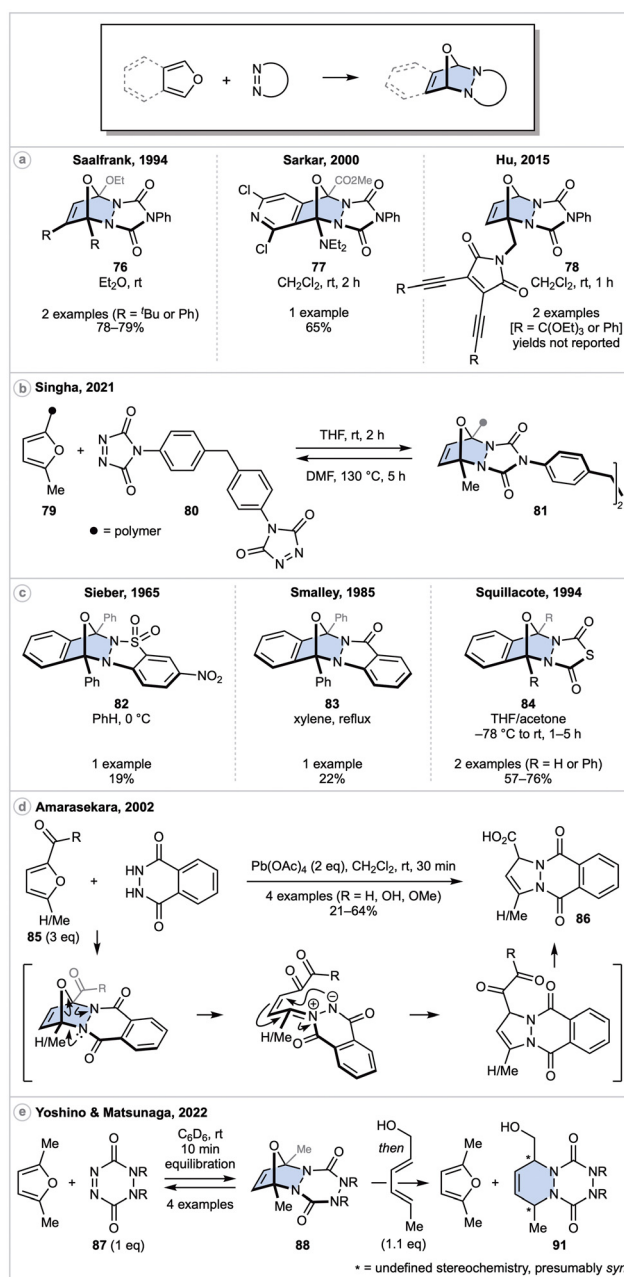
In 2014, Heinrich demonstrated that mixing furans **73** and carboxylate salts **74** in the presence of a strong acid promoted decarboxylation to aryldiazenes (Scheme 11e).⁶³ These unusual dienophiles were initially trapped as their furyl cycloadducts, followed by spontaneous aromatization to yield pyridazinium salts **75**. In general, yields improved as electron-donating substituents were introduced onto the furan backbone (**75a-d**). Several mechanistic experiments were used to discount an alternate furan oxidation/hydrazine recombination mechanism (analogous to that depicted in Scheme 11). A follow-up study from the same group demonstrated aryldiazenes could also be prepared *via* aryl hydrazine oxidation, followed again by trapping in [4 + 2] cycloadditions with furans.⁶⁴

Cyclic dienophiles

Phenyl-1,2,4-triazoline-3,5-dione (PTAD) is a highly reactive cyclic azo-dienophile that has been applied within a wide variety of DA reactions, often to demonstrate DA competency rather than looking toward specific applications.⁶⁵ With respect to (isobenzofuran)s as dienes,^{66–69} representative PTAD cycloadducts include ethoxy derivatives **76**,⁶⁷ dichloropyridine **77**,⁶⁸ and diones **78**⁶⁹ (Scheme 12a).

The reversibility of such DA reactions was leveraged by Singha and coworkers for the preparation of self-healing polymers (Scheme 12b).⁷⁰ Inspired by related approaches using furfuryl/maleimide DA reactions,⁷¹ the Singha laboratory demonstrated that polymer-bound furans **79** undergo a double DA reaction with bis-PTAD derivative **80** upon mixing at ambient temperature, generating crosslinked polymers of general structure **81**. Differential scanning calorimetry and solubility studies were employed to establish the DA reaction is reversible upon heating in DMF at 130 °C, endowing the crosslinked polymers with >80% healing efficiency.

Moving away from PTAD and its derivatives, a small number of studies concerned with the development of new electron-deficient azo-compounds have leveraged isobenzofuran DA reactions to indirectly confirm their generation and/or probe their reactivity (Scheme 12c and d).^{72–74} With this



Scheme 12 Cyclic N=N bonds as dienophiles.

goal in mind and building upon related exploratory work,⁷² the Amarasekara laboratory reported the synthesis and DA reactivity of 1,4-phthalazinedione (Scheme 12d).⁷⁴ Upon mixing furans **85** with phthalhydrazide in the presence of two equivalents of lead tetraacetate, ring-contracted cycloadducts **86** were isolated in up to 64% yield. The authors proposed the reaction proceeded *via* oxidation of phthalhydrazide to 1,4-phthalazinedione, which was immediately trapped in an azo-DA reaction. A ring-opening/ring-closing sequence resembling Sepúlveda-Arques' aforementioned ring-expansion methodology (Scheme 11b) was followed by an oxidative carbonyl-cleave event to generate the final products.



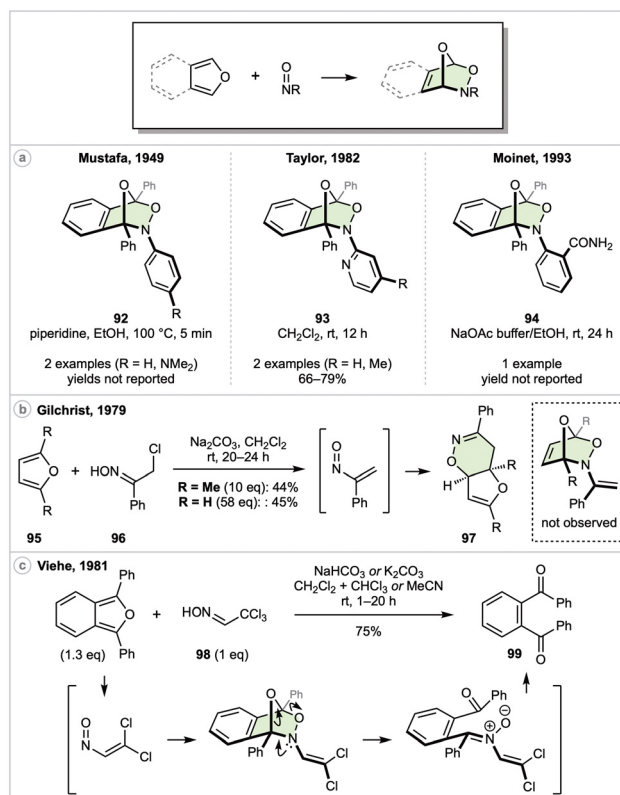
A recent application that takes advantage of facile retro-furyl azo-DA processes was reported by Yoshino and Matsunaga (Scheme 12e).⁷⁵ In the interests of developing new dynamic covalent bonding systems, the authors introduced a small family of *para*-urazine-derived azo-dienophiles. Dienophile design was guided by the hypothesis that attenuation of PTAD dienophilicity may result in a more facile retro-DA process. Proof of principle studies involved mixing 2,5-dimethylfuran with symmetric dienophiles of general structure **87**, all of which reached thermodynamic equilibrium with cycloadducts **88** within *ca.* 10 minutes at ambient temperature. Following addition of sorbic alcohol as a more reactive diene, the majority of the azo-dienophile ultimately funneled to cycloadducts **91** within 90 minutes *via* a retro-DA/cross DA sequence. The authors explored various dienophile substituent effects, confirming the superiority of this new system relative to PTAD, before successfully applying it in a mild and reversible sol-gel transition.

10. N=O bonds as dienophiles

In 1947, during attempts at a cheletropic cycloaddition, Wichterle unknowingly achieved what appears to be the first documented nitroso-DA reaction by mixing of 1,3-butadiene with nitrosobenzene.⁷⁶ This cycloadduct was correctly assigned the following year,⁷⁷ and shortly thereafter Mustafa *et al.* disclosed the first nitroso-DA reaction employing an (isobenzofuran as diene (Scheme 13a).⁷⁸ In this report, 1,3-diphenylisobenzofuran was reacted with either nitrosobenzene or its *para*-dimethylamino derivative to generate (the correctly assigned) cycloadducts **92** in undisclosed yields. Some years later, Taylor introduced two pyridyl derivatives for the synthesis of **93**,⁷⁹ and Moinet in 1993 described an electrochemical synthesis of 2-nitrosobenzamide, which was also trapped with 1,3-diphenylisobenzofuran to generate **94**.⁸⁰

In 1979, Gilchrist and coworker explored the reactions of α -nitrostyrene with various DA dienes (Scheme 13b).⁸¹ In all cases the nitroso component behaved as hetero-diene rather than hetero-dienophile. With respect to furans, mixing **95** with oxime **96** in the presence of a weak base led to DA adducts **97** irrespective of substitution at the 2- and 5-positions of furan. The authors note that **97** may alternatively form *via* a [4 + 2] cycloaddition across the α -nitrostyrene C=C bond, followed by a [3,3]-sigmatropic rearrangement.

In 1981, Viehe and coworkers also explored the reactions of alkenyl nitroso compounds with a variety of dienes, observing that *peri*- and chemo-selectivity (*i.e.*, reacting as a hetero-diene *versus* hetero-dienophile *versus* carbo-dienophile) was associated with degree of alkene substitution.⁸² In the case of 1,3-diphenylisobenzofuran and nitroso precursor **98**, 1,2-dibenzoylbenzene (**99**) was isolated in 75% yield, with the same reaction outcome also observed with 2,5-dimethyl furan (Scheme 13c). Although a precise mechanism was not proposed, presumably the reaction proceeds *via* elimination of HCl to generate a dichloroalkene that is trapped in a nitroso-



Scheme 13 N=O bonds as dienophiles.

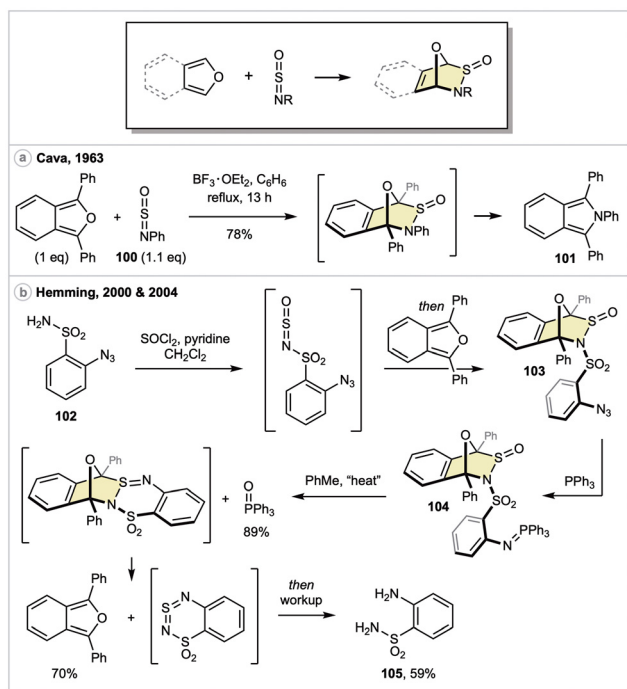
DA reaction. C–O bond cleavage to the corresponding nitrone, followed by hydrolysis, would then yield the observed product. Overall, and in analogy to the aforementioned work of Bezhan (Scheme 11), here the hetero-dienophile ultimately serves as an oxidant.

11. N=S bonds as dienophiles

While a number of DA reactions involving 1,3-butadiene derivatives across N=S bonds have been reported, including sulfur diimides (RN=S=NR)⁸³ and thionitroso compounds (RN=S),⁸⁴ sulfinylamines (RN=S=O) remain the most commonly explored.⁸⁵ With respect to (isobenzofuran as dienes, only two reactions have been described, although perhaps this will change given a renewed interest in this functionality.⁸⁶ The first example, reported by Cava and coworker in 1963, described a Lewis acid-promoted DA reaction between 1,3-diphenylisobenzofuran and *N*-sulfinylaniline (**100**), leading to isoindole **101** in 78% yield (Scheme 14a).⁸⁷ While no mechanistic experiments were conducted, the authors proposed the reaction proceeds first *via* a DA reaction across the N=S bond of the sulfinylamine, followed by rearrangement to a cyclic sultam. A well-precedented extrusion of sulfur dioxide would then deliver the final product.⁸⁸

In 2000, Hemming and coworkers reported the synthesis of a sulfinylamine derivative bearing a pendant azide, followed





Scheme 14 N=S Bonds as dienophiles.

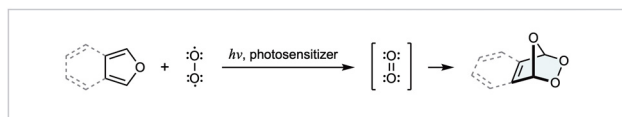
by *in situ* trapping with 1,3-butadienes.⁸⁹ These DA adducts were then applied in a five-step sequence incorporating an aza-Wittig reaction for the synthesis of various benzothiadiazepines. Four years later, the chemistry of an isobenzofuran DA adduct was described, although no details regarding its preparation were provided.⁹⁰ Drawing analogy to their first study, its synthesis presumably proceeds *via* treatment of azide **102** with thionyl chloride followed by addition of 1,3-diphenylisobenzofuran to generate cycloadduct **103** (Scheme 14b). A Staudinger reaction with triphenylphosphine would then yield iminophosphorane **104**. The authors reported that heating this compound in anhydrous toluene yielded triphenylphosphine oxide (89%), 1,3-diphenylisobenzofuran (70%), and aniline **105** (59%). Based on a brief mechanistic study, the authors propose this reaction proceeds *via* an intramolecular aza-Wittig, followed by retro-DA reaction to generate a cyclic sulfur diimide, which finally hydrolyzes upon purification.

12. O=O bonds as dienophiles

O=O synthesis and general reactivity

Cycloadditions of (isobenzofuran)s and $^1\text{O}_2$ have been widely studied and are the subject of several excellent reviews.^{91–93} To distinguish our treatment, we have elected to focus exclusively on applications in complex natural product synthesis, organized primarily by strategic considerations.

$^1\text{O}_2$ is the lowest energy excited state of molecular oxygen and can be photochemically generated upon UV irradiation of ground state triplet oxygen in the presence of a suitable photosensitizer, such as rose bengal (RB), methylene blue (MB), or

Scheme 15 O=O as dienophile: generation of $^1\text{O}_2$.

tetraphenylporphyrin (TPP) (Scheme 15).⁹³ Operationally, this process is usually achieved at low temperatures and in the same flask as the reactant(s), although flow techniques have enabled alternate setups in recent years. Despite being a strong oxidant, $^1\text{O}_2$ exhibits a great degree of chemoselectivity, typically leaving many oxidatively sensitive functional groups untouched (*e.g.*, alcohols, carbonyls). With respect to pericyclic reactivity, $^1\text{O}_2$ most commonly reacts *via* either: (i) a [4 + 2] cycloaddition with a 1,3-butadiene to generate an *endo*-peroxide, (ii) a Schenk-Ene reaction with an olefin bearing an allylic hydrogen, or (iii) *via* a [2 + 2] cycloaddition with an electron-rich olefin, and many of the factors that govern chemo- and *peri*-selectivity have been elucidated.⁹² It is worth highlighting early that Nature often takes advantage of $^1\text{O}_2$ [4 + 2] cycloadditions,⁹³ and as will become apparent, many syntheses discussed herein mirror current understanding of biosynthetic pathways (be it intentionally or otherwise).

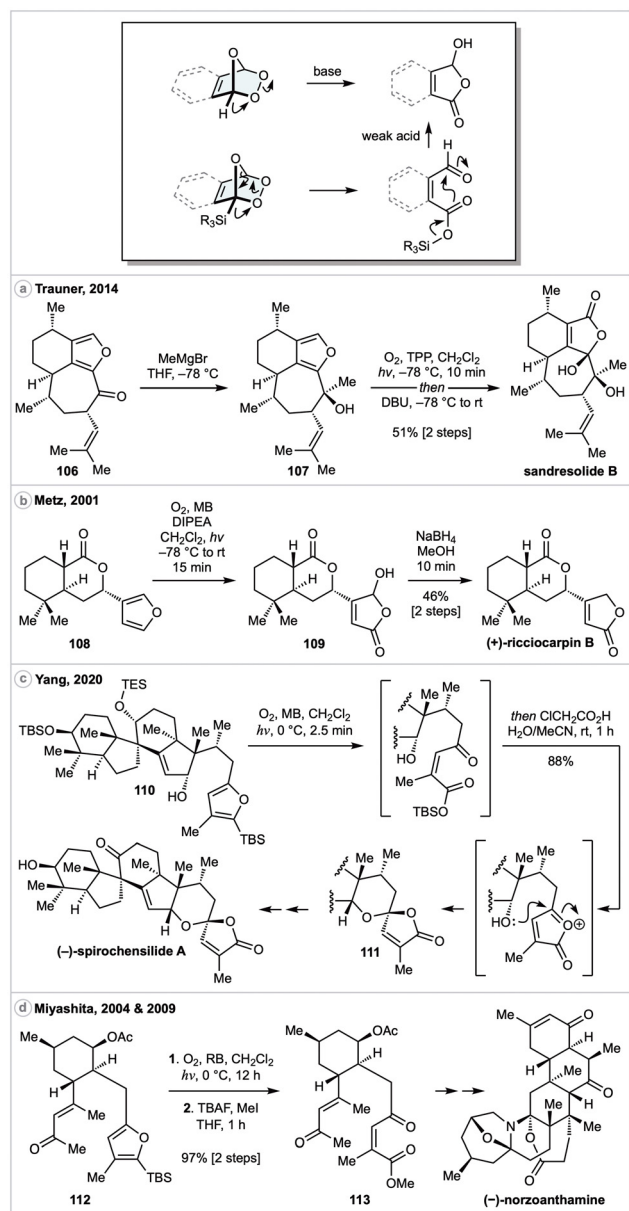
Synthesis of γ -hydroxybutenolides

The late-stage conversion of furans into γ -hydroxybutenolides *via* the intermediacy of $^1\text{O}_2$ cycloadducts is a popular strategy in natural product synthesis (Scheme 16, boxed). One of the most common tactics involves employment of a base to effect a Kornblum–DeLaMare rearrangement, as well demonstrated within Trauner's enantioselective total synthesis of sandresolide B (Scheme 16a).⁹⁴ Diastereoselective addition of methylmagnesium bromide to ketone **106** yielded unstable alcohol **107**, which was subjected crude to a one-pot diastereoselective $^1\text{O}_2$ cycloaddition/Kornblum–DeLaMare rearrangement to provide the natural product in 51% yield from **106**.

γ -Hydroxybutenolides can be readily reduced to butenolides, another motif commonly found in natural products. For example, in 2001 Metz described the conversion of furan **108** into γ -hydroxybutenolide **109**, achieved using MB as photosensitizer in conjunction with a sterically encumbered base to engender chemoselective deprotonation (Scheme 16b).⁹⁵ Reduction with sodium borohydride yielded (+)-ricciocarpin B in 46% yield over two steps.

In 1985, Katsumura, Isoe, and coworkers demonstrated 2-trimethylsilyl substituted furans react faster with $^1\text{O}_2$ relative to their non-silylated congeners.⁹⁶ Moreover, conducting the cycloaddition in methanol resulted in spontaneous and regiospecific conversion into the γ -hydroxybutenolide motif (Scheme 16, boxed). Mechanistically it has been proposed this transformation proceeds *via* a concerted 1,2-silyl migration/O–O cleavage event followed by a desilylative ring-closure upon addition of a weak acid.⁹⁷ Strategically this tactic serves as a useful alternative to Kornblum–DeLaMare-based approaches



Scheme 16 O=O as dienophile: synthesis of γ -hydroxybutenolides.

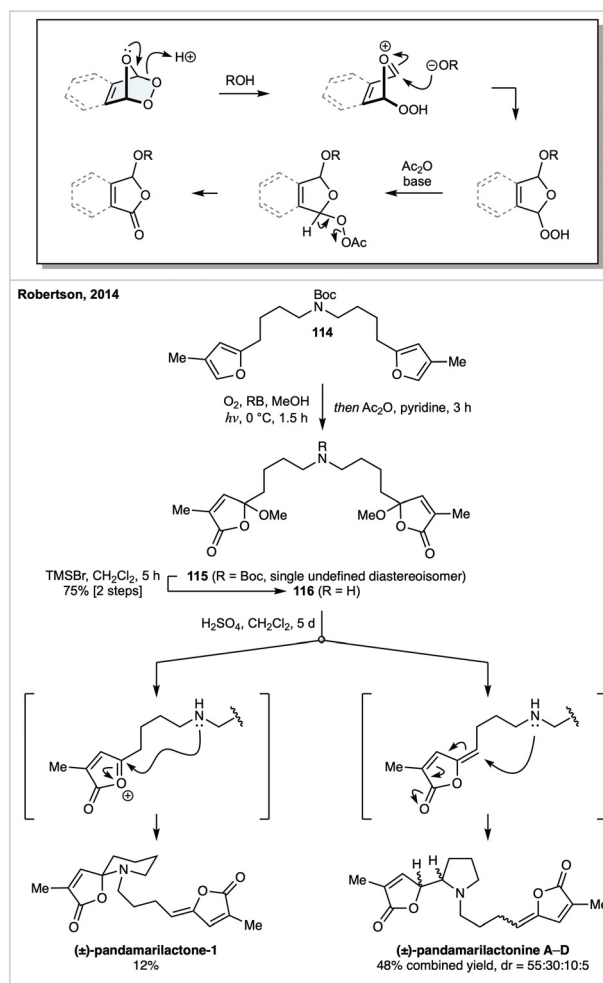
that fail to yield the desired γ -hydroxybutenolide regioisomer,⁹⁶ or if base-sensitive substrates are being considered. In addition, silyl incorporation has been observed to increase cycloaddition yields.⁹⁸ An elegant application of this chemistry was described within Yang and co-workers' synthesis of (-)-spirochensilide A (Scheme 16).⁹⁹ Treatment of furan **110** with $^1\text{O}_2$ was followed by addition of chloroacetic acid, leading to spirocycle **111** in 88% yield. Presumably, the reaction proceeds *via* an γ -hydroxybutenolide intermediate (not shown) that, upon elimination of water, undergoes a diastereoselective 6-*exo*-trig spirocyclization.

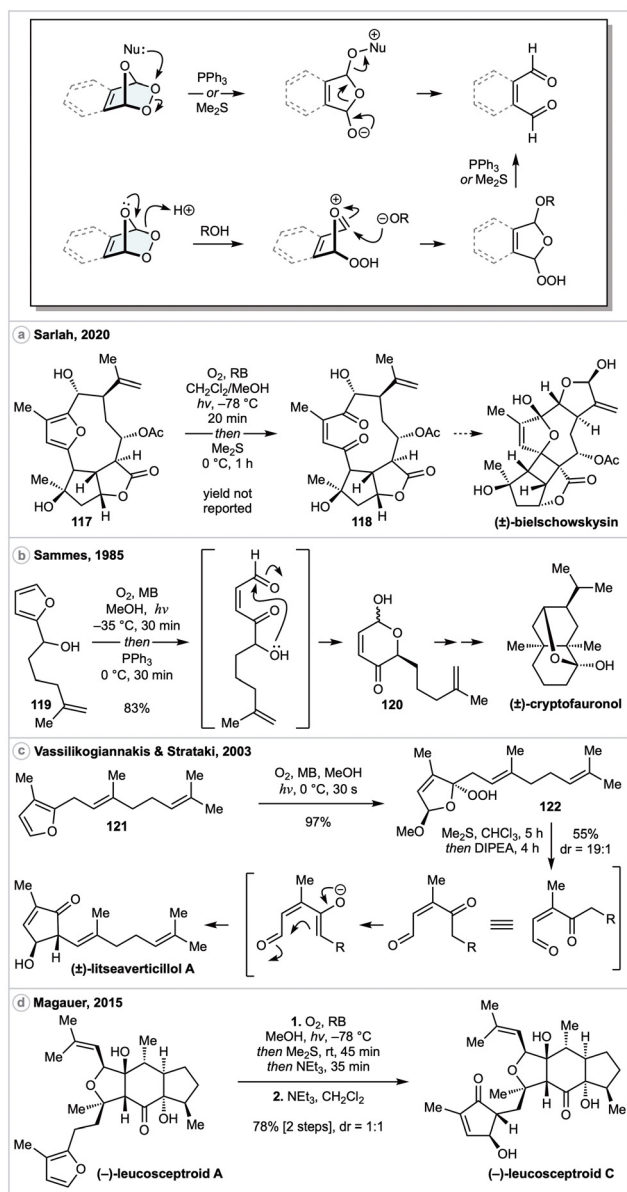
Alternative functionalization of the silylated, ring-opened intermediate is also feasible, as illustrated within Miyashita's synthesis of the complex natural product (-)-norzoanthamine

(Scheme 16d).¹⁰⁰ In this case, furan **112** was converted into the corresponding *Z*-configured unsaturated silyl ester upon reaction with $^1\text{O}_2$. The crude product was then alkylated *via* treatment with tetra-*n*-butylammonium fluoride and methyl iodide, generating doubly activated carbo-dienophile **113** for a subsequent intramolecular DA reaction *en route* to the natural product.

Synthesis of γ -alkoxybutenolides

Alcoholic solvents (typically methanol), will add to furan-derived endoperoxides at temperatures approaching 0°C , resulting in formation of a hydroperoxide (Scheme 17, boxed). Treatment with an acylating reagent then promotes a Kornblum–DeLaMare rearrangement for the synthesis of γ -alkoxybutenolides. The regioselectivity of alcohol addition is typically governed by stabilization of the incipient positive charge (*i.e.*, addition to the more substituted position),¹⁰¹ although the opposite regioselectivity has also been observed (*e.g.*, Scheme 18c). An elegant two-directional synthesis proceeding through γ -alkoxybutenolide intermediates was disclosed by Robertson *et al.* in 2014 (Scheme 17).¹⁰² Tethered bis-furan **114** was subjected to a double $^1\text{O}_2$ cycloaddition.

Scheme 17 O=O as dienophile: synthesis of γ -alkoxybutenolides.



Scheme 18 $\text{O}=\text{O}$ as dienophile: synthesis of α,β -unsaturated 1,4-dicarbonyls.

Employing methanol as solvent led to a bis-hydroperoxide intermediate, which following *in situ* acetylation/elimination yielded bis-methoxybutenolide **115** as a single (undefined) diastereoisomer. Removal of the Boc group was achieved with bromotrimethylsilane, providing secondary amine **116** in 75% yield over two steps. The synthesis was completed *via* a presumably biomimetic sequence of reactions. Mixing **116** in a biphasic mixture of sulfuric acid and dichloromethane promoted methoxide ionization, which was followed by a 6-*exo*-trig cyclization of the pendant amine to generate pandamarilcaone-1 in 12% yield. Competitive deprotonation of the same ionized intermediate, followed by a 5-*exo*-trig aza-Michael cyclization, generated pandamarilactonine A-D in a combined yield of 48%.

Synthesis of α,β -unsaturated 1,4-dicarbonyls

α,β -Unsaturated 1,4-dicarbonyls at the dialdehyde oxidation level can be accessed directly from furyl $^1\text{O}_2$ cycloadducts *via* reduction with triphenylphosphine or dimethyl sulfide (Scheme 18, boxed). For example, in efforts toward $(\pm)$ -bielschowskysin, the Sarlah group demonstrated that macrocyclic furan **117** could be converted into the corresponding α,β -unsaturated diketone **118** under standard conditions (Scheme 18a). However, this intermediate was found to be sensitive toward *E/Z* isomerization, alongside other undetermined decomposition pathways, ultimately thwarting downstream attempts at a late-stage Norrish–Yang cyclization.

In situ trapping of the reduction products has been leveraged in a variety of contexts. One such example in the context of natural product total synthesis was disclosed by Sammes and coworker in 1985 (Scheme 18b).¹⁰³ Attempts at an Achmatowicz reaction for the conversion of furan **119** into pyran **120** under standard conditions (*e.g.*, bromine and methanol or *meta*-chloroperoxybenzoic) proceeded with undesired oxidation of the 1,1-disubstituted olefin. Transitioning to a $^1\text{O}_2$ cycloaddition/reduction sequence proved highly chemoselective and was accompanied by a 6-*exo*-trig cyclization of the pendant alcohol to generate **120** in 83% yield. Several steps were then necessary to access $(\pm)$ -cryptofauranol.

α,β -Unsaturated 1,4-dicarbonyls can also be accessed *via* reduction of the hydroperoxide intermediates introduced in Scheme 17 by treatment with either triphenylphosphine or dimethyl sulfide (Scheme 18, boxed). As demonstrated within Vassilikogiannakis and Strataki's synthesis of $(\pm)$ -litseaverticillol A, reacting furan **121** with $^1\text{O}_2$ in the presence of MeOH led directly to hydroperoxide **122** in near quantitative yield (Scheme 18c).¹⁰⁴ Addition of dimethyl sulfide prompted reductive cleavage to generate an α,β -unsaturated 1,4-dicarbonyl, which following addition of Hünig's base underwent an intramolecular aldol reaction to generate the natural product in 55% yield and with 19:1 diastereoselectivity. This overall transformation has since been applied to a handful of natural products, including Magauer's conversion of $(-)$ -leucosceptroid A to C (Scheme 18d).¹⁰⁵

13. Conclusion and future outlook

Several trends have become apparent throughout the preparation of this review. First and foremost, many (if not all) furyl hetero-DA cycloadducts exhibit poor stability profiles. This is to be expected given at least one sensitive oxygen–carbon–heteroatom bond is generated upon cycloaddition (*e.g.*, ketal or hemiaminal functionality). This is further exacerbated if a weak heteroatom–heteroatom bond is also formed (*e.g.*, nitroso- and azo-dienophiles) or if significant ring strain is generated (*e.g.*, see the discussion surrounding Scheme 11c). These structural features can culminate in facile heteroatom bond cleavage events or mild retro-DA processes, ultimately complicating potential applications. However, if chemoselective cycloadduct functionalization can be achieved,



hetero-DA reactions of (isobenzofuran)s can become very empowering, as has been well demonstrated within the context of $^1\text{O}_2$ as dienophile. Unfortunately, the rest of the field lags significantly behind. Perhaps most telling, with the exception of $^1\text{O}_2$ as dienophile, a furyl hetero-DA reaction has never been successfully applied in the synthesis of a natural product. That being said, a small number of isolated applications concerning the synthesis of various heterocycle families are highly encouraging (e.g., oxygenated pyridones in Scheme 2b, oxaphosphepines in Scheme 9c, pyridazinium salts in Scheme 11e, and biodegradable polymers in Scheme 11c).

Shifting focus from cycloadduct stability to hetero-DA reactivity, many of the dienophile classes discussed herein appear to be only reactive with isobenzofurans. A general tactic for addressing low DA reactivity (or engendering stereo- or regioselectivity) involves the addition of a Lewis- or Brønsted-acid. While such additives are present in a small number of the hetero-DA reactions reviewed (e.g. Schemes 7c, 9c and 14a), it is not clear if they play a role in the cycloaddition itself. Rather, they appear to primarily (or perhaps exclusively) facilitate diene/dienophile generation or post-cycloaddition reactivity. Moreover, given Lewis- or Brønsted-acids can readily decompose hetero-oxanorbornene cycloadducts (e.g., Scheme 3b and c) and likely many of the dienes and dienophiles discussed throughout, it is perhaps not surprising a catalytic enantioselective (isobenzofuran) hetero-DA reaction has yet to be reported. Attempts to move away from frontier molecular orbital control in (isobenzofuran) hetero-DA reactions is also underdeveloped. While introduction of dienophile strain (e.g., arynes, cyclopropenes) is a well-established tactic for achieving DA reactivity with less reactive dienes, methods to employ hetero-derivatives lag significantly behind their carbo-analogs. Thus, with the exception of ketenimines (Scheme 2b), azirines (Scheme 3), and benzannulated azetes (Scheme 4), strain-promoted reactivity is exceptionally rare. Alternatively, enhancing furan reactivity through introduction of a cleavable functionality may also represent a viable approach.

Given the inherent challenges identified, we firmly believe that (isobenzofuran) hetero-DA reactions provide an excellent testing ground for the development of new, highly reactive hetero-dienophiles. We hope this review serves to inspire future practitioners to tackle challenges in this area, ultimately enabling the convergent synthesis of heteroatom-rich motifs.

Data availability

No primary research results, software or code have been included and no new data were generated or analyzed as part of this review.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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