

1,3-Dipolar cycloaddition reactions of azomethine ylides with aromatic dipolarophiles

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Abstract

The 1,3-dipolar cycloadditions of azomethine ylides to aromatic dipolarophiles are reviewed and discussed. The reaction proceeds with stabilized and non-stabilized azomethine ylides, although most studies have been with non-stabilized systems. While simple benzene derivatives do not readily undergo such 1,3-dipolar cycloaddition reactions, the dipolarophilic character of benzene emerges when the benzenoid nucleus is embedded within a polycyclic aromatic hydrocarbon, tethered with the azomethine ylide (an intramolecular process) or substituted with highly electron withdrawing nitro groups. Heteroaromatic systems display similar tendencies towards such cycloaddition processes. The review closes with a consideration of the mechanism of the reactions.

Keywords: Dearomatization, 1,3-dipolar cycloaddition, azomethine ylide, aromatic dipolarophiles, intramolecular cycloaddition, nitrobenzenes

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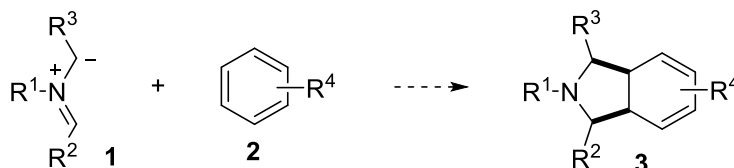
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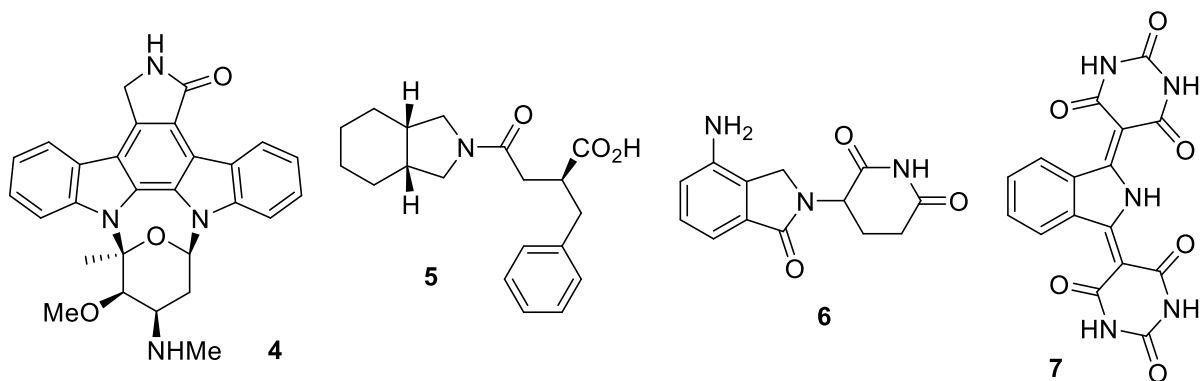
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1. Introduction

A large and structurally diverse range of aromatic compounds are available for use as starting materials in organic synthesis and ultimately find use in numerous fine chemical, pharmaceutical and agrochemical products. As a result, much endeavor has been targeted at methods for functionalization of aromatic compounds. These methods include processes resulting in aromatic carbon-hydrogen functionalization,¹⁻⁵ and processes resulting in loss of the aromatic system, i.e. 'dearomatization' processes.^{6,7} Well-studied examples of dearomatization processes include Birch reduction,⁸⁻¹¹ enzymatic cis-dihydroxylation,¹²⁻¹⁴ oxidative dearomatization of phenols,¹⁵⁻²¹ enzymatic benzene reductions,²² transition-metal complexing dearomatizations,²³⁻²⁵ nucleophilic dearomatization processes²⁶⁻³¹ and catalytic hydrogenation.³²⁻³⁵ An alternative dearomatization process would involve a [4+2] or [3+2] cycloaddition reaction of a diene or 1,3-dipole with an aromatic carbon-carbon double bond.³⁶⁻⁴⁰ A manifestation of this concept is the 1,3-dipolar cycloaddition reaction of an azomethine ylide **1** with a benzenoid aromatic system **2** that would give an isoindole derivative **3** (Scheme 1). Azomethine ylides, which contain four electrons distributed over the π orbitals of a C-N-C group, are examples of bent allyl anion-type 1,3-dipoles.⁴¹ The ylides can be classified as non-stabilized (where R¹, R² and R³ = H or alkyl) or stabilized either by electron-withdrawing/electron-donating groups at the appropriate termini of the ylide or by *N*-metalation.⁴¹ Azomethine ylides are mostly generated in situ due to their high reactivity and/or transient existence; however, in some cases, stabilized azomethine ylides have been isolated.⁴²⁻⁴⁴ The isoindole framework is found within a large range of natural products and frequently features in bioactive natural products, synthetic agrochemicals, pharmaceuticals and dyes.⁴⁵⁻⁴⁷ Although simple and elegant in concept, azomethine ylide 1,3-dipolar cycloaddition dearomatization processes have received only sporadic attention until recently.



Scheme 1

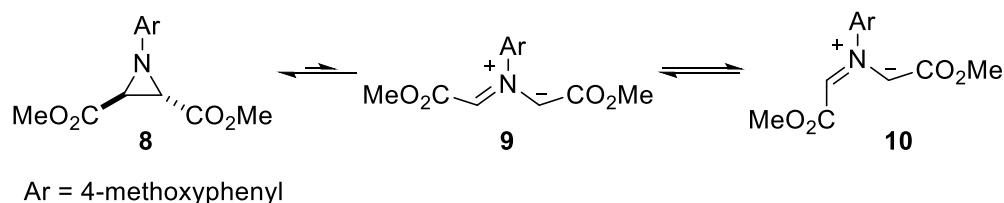


Examples of isoindole-containing natural products, pharmaceuticals and dyes: (+)-staurosporine **4** (indolocarbazole alkaloid),⁴⁵ mitiglinide **5** (type 2 diabetes),⁴⁶ lenalidomide **6** (anticancer, multiple myeloma),⁴⁷ and Pigment Yellow 139 **7** (dye).⁴⁵

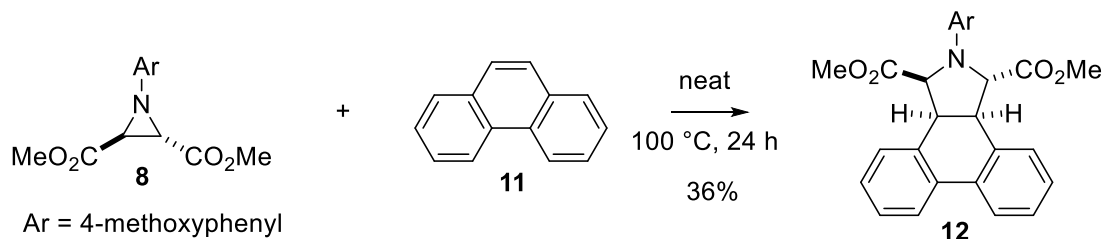
Here is presented a comprehensive review of the literature associated with the 1,3-dipolar cycloaddition reactions of azomethine ylides with benzo- and heteroaromatic systems until the end of 2013. While outside the scope of this review, it is noted that the cycloaddition of azomethine ylides to C₆₀, graphite and related materials is considered an excellent way to functionalize these materials.⁴⁸⁻⁵²

2. 1,3-Dipolar Cycloaddition Reactions of a Stabilized Azomethine Ylide with Polycyclic Aromatic Dipolarophiles

In 1971, Huisgen and Scheer reported the reactions of polycyclic aromatic compounds with a stabilized azomethine ylide, revealing for the first time that, “Only few 1,3-dipoles equal ozone in its ability to attack the aromatic bond. The azomethine ylide (**10**) is one of them”.⁵³ The azomethine ylide **10** was generated by thermal electrocyclic ring-opening of aziridine **8** which gives *exo-exo* azomethine ylide **9** which then isomerises to the more reactive *endo-exo* dipole **10** (Scheme 2). The heating of aziridine **8** with an excess of phenanthrene **11** at 100 °C for 24 h afforded a single cycloadduct **12** isolated in 36% yield (Scheme 3). The stereochemistry of product **12** was taken as evidence that azomethine ylide **10** was the reactive species.

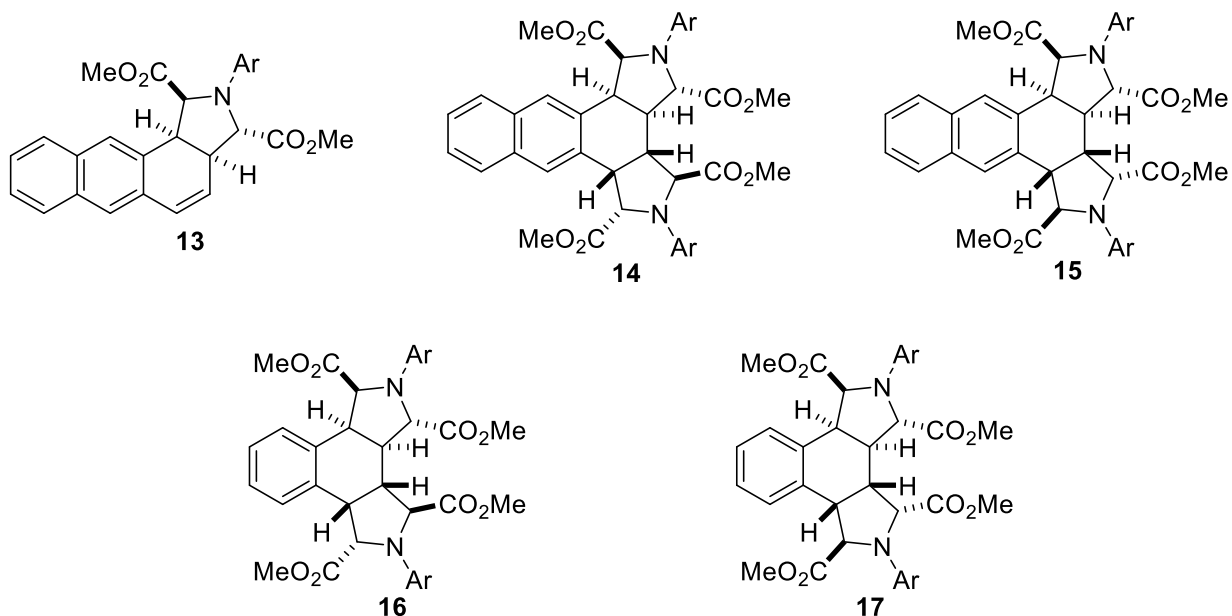


Scheme 2



Scheme 3

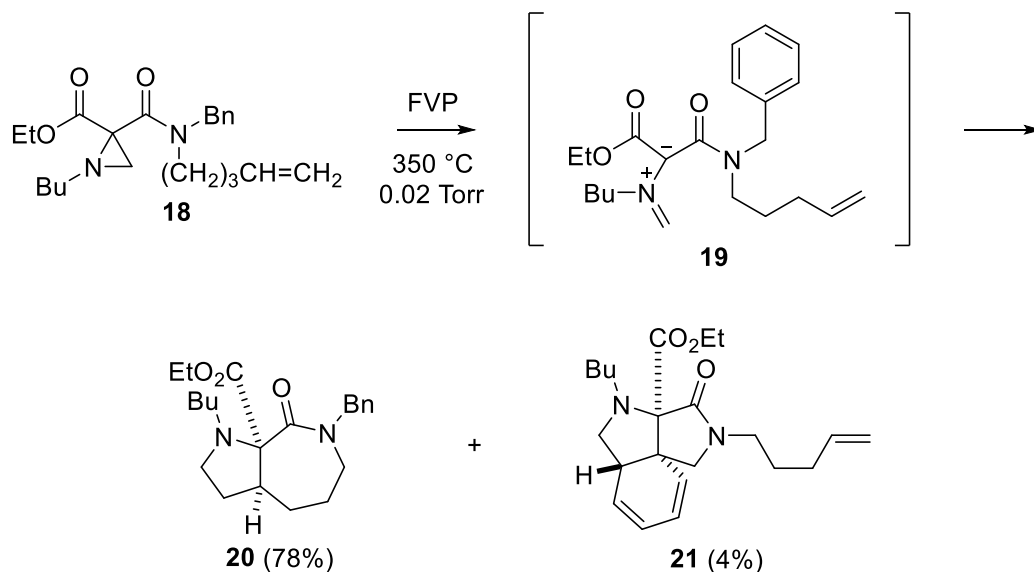
The cycloaddition reactions of linear polycyclic aromatic systems were also explored.⁵³ The reaction of aziridine **8** with excess anthracene in refluxing chlorobenzene for 24 h, led to a *mono* adduct **13**, isolated in 8% yield, and two *bis* adducts, assigned **14** and **15**, isolated in 22% and 40% yield, respectively. While various isomers were considered, the two isomeric *anti bis* adduct structures **14** and **15** (*endo/exo* isomers) were preferred based on spectroscopic analysis, with compound **14** exhibiting spectra consistent with a two-fold axis of symmetry whereas **15** exhibited spectra consistent with a lack of such symmetry elements. The formation of *bis* adducts **14** and **15** was rationalized by the *mono* adduct **13** having a styrene-like olefin whose dipolarophilic character far exceeds that of the aromatic bonds of the starting material, anthracene. Therefore, most of *mono* adduct **13** took up an extra molecule of the azomethine ylide **10** to produce the *bis* adducts, despite there being an excess of anthracene. For the reaction of aziridine **8** with naphthalene at 120 °C for 24 h, only the two *anti bis* adducts **16** and **17** were isolated, in 38% yield. The structures were assigned similarly to the *bis* adducts from anthracene, with **16** exhibiting a symmetry element.



Ar = 4-methoxyphenyl

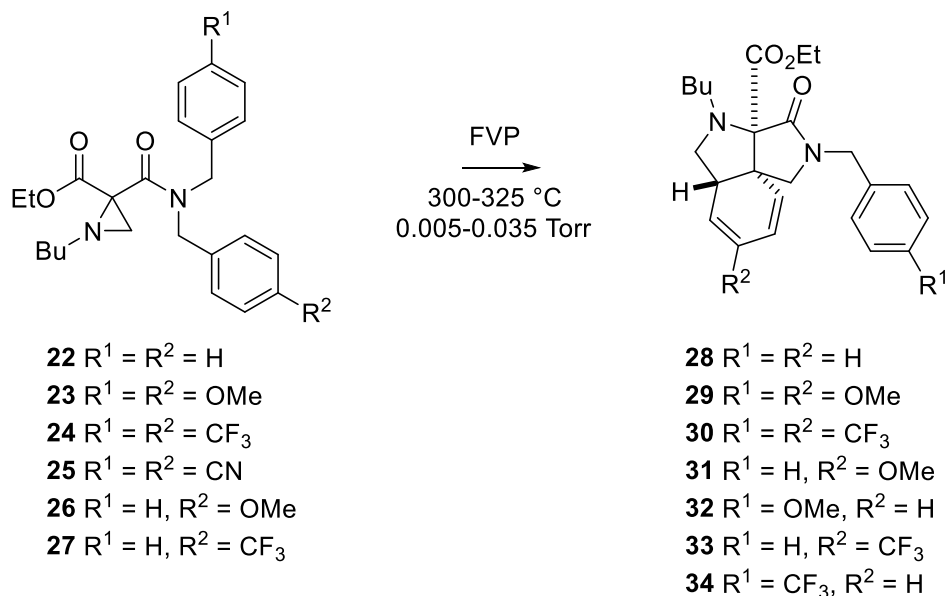
3. Intramolecular Reactions of Stabilized Azomethine Ylides with Aromatic and Heteroaromatic Dipolarophiles

In 1992 Heathcock, *et al.* reported a surprising side reaction involving 1,3-dipolar cycloaddition of a doubly-stabilized azomethine ylide to an unactivated aromatic dipolarophile, whilst studying intramolecular cycloadditions of azomethine ylides tethered with unactivated olefinic dipolarophiles.⁵⁴ Thus, thermolysis of aziridine **18** under flash vacuum pyrolysis conditions provided the expected lactam **20** as a single diastereoisomer in 78% yield along with 4% of a minor side-product **21** (Scheme 4). It was proposed that the reaction proceeded via electrocyclic ring-opening of the aziridine **18** to afford doubly stabilized azomethine ylide **19** which added as expected to the pendant olefin to produce bicyclic lactam **20** or to the pendant phenyl group to product tricyclic lactam **21**.



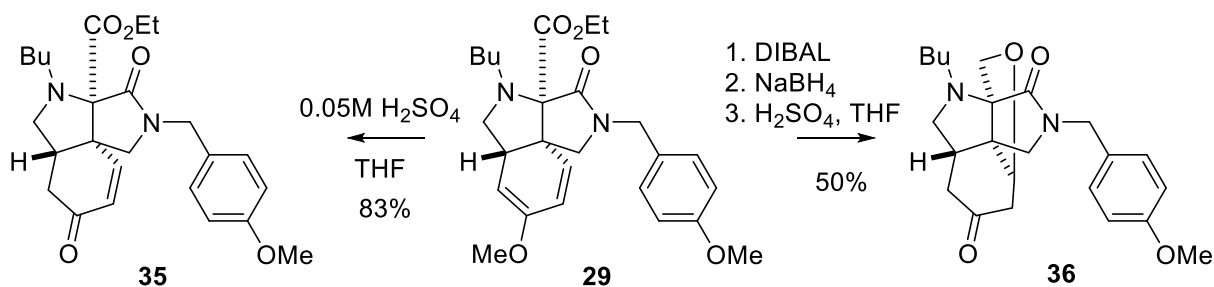
Scheme 4

Heathcock *et al.* recognized the potential utility of this side reaction as it generated a highly functionalized tricyclic compound containing three contiguous stereo-centres (two of which are quaternary) in a stereo-controlled manner.⁵⁴ They sought to increase the yield of the addition to the phenyl group by eliminating the possibility of alkene cycloaddition and prepared a series of analogous dibenzylamides **22** – **27** for pyrolysis studies (Scheme 5). Flash vacuum pyrolysis of each of the symmetrical dibenzylamides **22** – **24** afforded the respective tricyclic product in moderate to good yields (**28**: 67%, **29**: 47% and **30**: 68%). These experiments demonstrated that the intramolecular cycloaddition could proceed with unsubstituted phenyl groups and with phenyl groups substituted with electron-donating or electron-withdrawing groups. Pyrolysis of the *bis*(4-cyanobenzyl)amide **25** resulted in decomposition with none of the expected product obtained, pointing to a potential limitation of this methodology.



Scheme 5

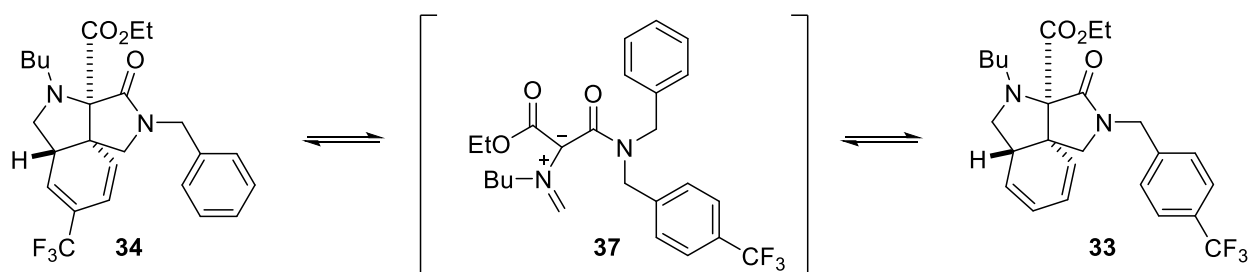
The lower yield of dimethoxy analogue **29** was rationalized in terms of hydrolytic instability of the enol ether moiety and this was confirmed by a deliberate acid catalyzed hydrolysis of enol **29** affording enone **35** in 83% yield (Scheme 6). The stereochemistry of cycloadduct **29** was proven by reduction of the ester to an alcohol, enol hydrolysis and concomitant conjugate addition which gave tetracycle **36** in overall 50% yield (Scheme 6). Such a conjugate addition process could only be achieved with the depicted ring-fusion stereochemistry.



Scheme 6

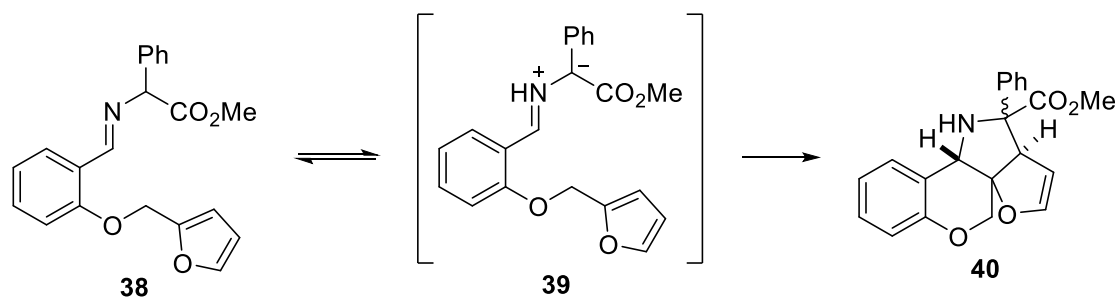
The pyrolysis of the unsymmetrically substituted dibenzylamides provided insight into the reversibility of the cycloaddition process under flash vacuum pyrolysis conditions (Scheme 7).⁵⁴ Pyrolysis of the methoxy analogue **26** afforded a 42% yield of a mixture of cycloadducts **31** and **32** in approximately a 1:1 ratio. Pyrolysis of trifluoromethyl analogue **27** afforded a 71% yield of the cycloadducts **33** and **34** in a ca. 70:30 ratio. These products were separated and then independently subjected to the pyrolytic conditions, which resulted in the same 70:30 ratio of **33**

and **34**. These results demonstrate that the cycloadducts **33** and **34** isomerise via cycloreversion to the azomethine ylide **37** under the flash vacuum pyrolysis conditions (Scheme 7).



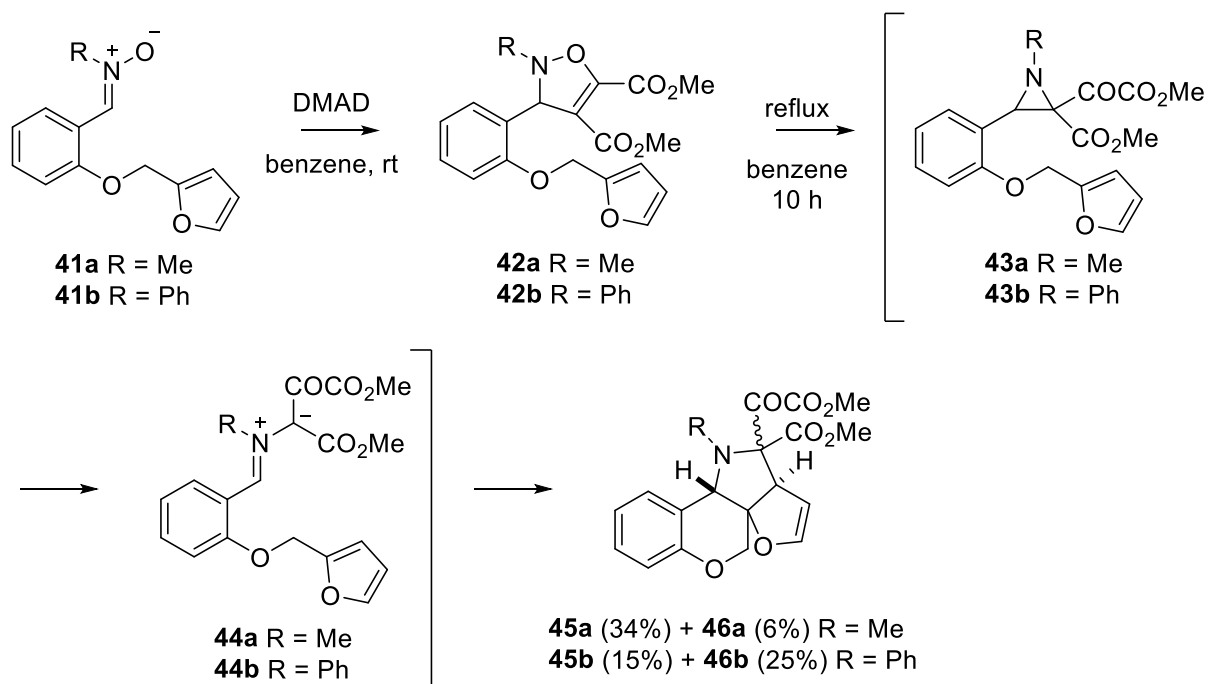
Scheme 7

While the work of Heathcock and coworkers was the first example of an addition of an azomethine ylide to an isolated benzene ring, intramolecular additions of azomethine ylides to a heteroaromatic system, i.e. furan, had been previously reported by Tsuge and coworkers.^{55,56} It is well known that imines of α -amino acid esters readily tautomerize to give azomethine ylides.⁵⁷⁻⁶⁰ The imine **38** was used as a precursor of azomethine ylide **39**.⁵⁵ When a solution of **38** in xylene was refluxed for 30 h, a complex mixture resulted and the intramolecular cycloadduct **40** was obtained in low yield (Scheme 8).



Scheme 8

Tsuge and coworkers obtained improved yields of intramolecular cycloadducts using a different mechanism for generating the azomethine ylide.⁵⁶ 4-Isoxazolines are generally unstable and thermally rearrange to acylaziridines.⁶¹ The thermal or photochemical cleavage of aziridines is a well known source of azomethine ylides that undergo 1,3-dipolar cycloaddition reactions.⁶²⁻⁶⁴ Tsuge and coworkers found that 4-isoxazolines can be used as precursors of azomethine ylides in 1,3-dipolar cycloaddition reactions and exemplified this via intramolecular addition to a pendant furan ring.⁵⁶ The reaction of *N*-methylnitron **41a** with dimethyl acetylenedicarboxylate (DMAD) in benzene resulted in the 4-isoxazoline **42a**, isolated in quantitative yield. (Scheme 9)



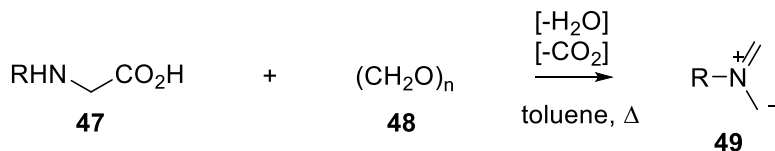
Scheme 9

Heating of **42a** in refluxing benzene for 10 h produced, via ring-contraction to aziridine **43a** then electrocyclic ring-opening to azomethine ylide **44a**, followed by 1,3-dipolar cycloaddition, to give a mixture of stereoisomers **45a** and **46a**, in 34 and 6% yield, respectively. Similarly, heating of the *N*-phenylnitrone **41b** with DMAD in refluxing benzene gave the stereoisomers **45b** and **46b** in 15 and 25% yield, respectively (Scheme 9).

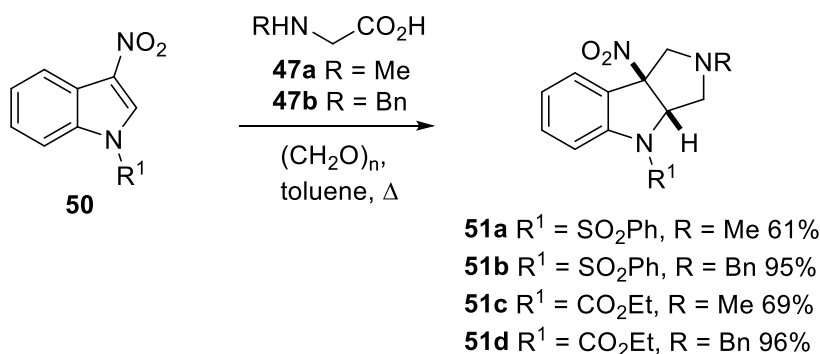
4. Reactions of Non-stabilized Azomethine Ylides with Nitro-substituted Heteroaromatic Dipolarophiles

In 2007, Gribble and coworkers showed that non-stabilized azomethine ylides **49**, generated by decarboxylative condensation of amino acids **47** and formaldehyde **48** (Scheme 10),⁶⁵⁻⁶⁷ reacted with the indole π -bond of 3- and 2-nitroindoles.⁶⁸ For example, reaction of 3-nitroindoles **50** with sarcosine **47a** or *N*-benzylglycine **47b**, and formaldehyde afforded moderate to high yields of the respective cycloadducts **51** (Scheme 11). No such reaction was observed between the azomethine ylide from sarcosine and paraformaldehyde with 1-(phenylsulfonyl)indole, 3-cyano-1-(phenylsulfonyl)indole or 1-benzyl-3-nitroindole. This indicated that the presence of the electron withdrawing nitro group and an electron withdrawing protecting group on the indole nitrogen increased the dipolarophilic reactivity of the indole toward the azomethine ylide. Furthermore, the reaction of **50** ($R^1 = \text{SO}_2\text{Ph}$) with glycine and paraformaldehyde did not furnish a cycloadduct, indicating that azomethine ylides generated from secondary amino acid derivatives

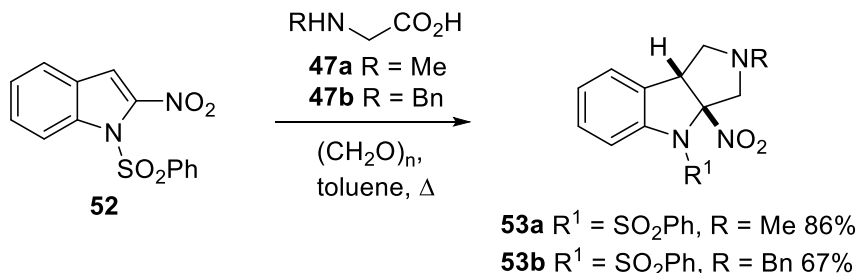
are more effective 1,3-dipoles in this case. The analogous 2-nitroindoles also underwent the cycloaddition reaction. For instance, 1-phenylsulfonyl-2-nitroindole **52** reacted with amino acid derivatives **47a** and **47b** and paraformaldehyde to give the cycloadducts **53a** and **53b** respectively (Scheme 12).



Scheme 10

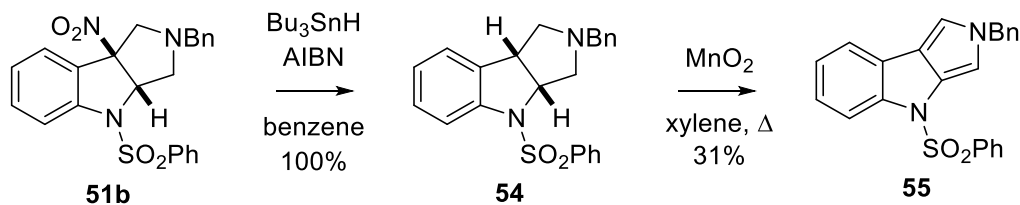


Scheme 11



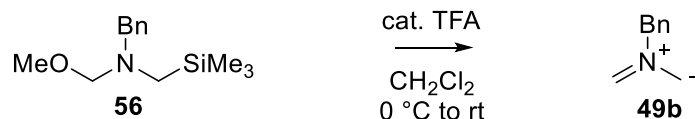
Scheme 12

The potential synthetic versatility of the products was demonstrated by treatment of the cycloadduct **51b** with Bu_3SnH which gave the tetrahydropyrrolo[3,4-*b*]indole **54** in excellent yield followed by oxidation with MnO_2 which provided pyrrolo[3,4-*b*]indole **55** in modest yield (Scheme 13).

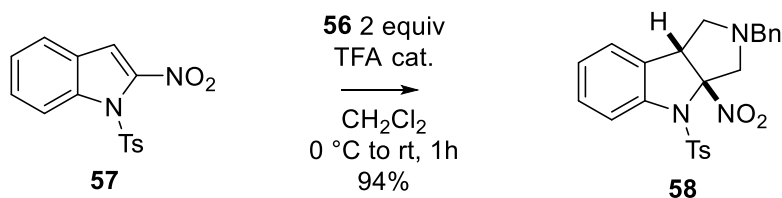


Scheme 13

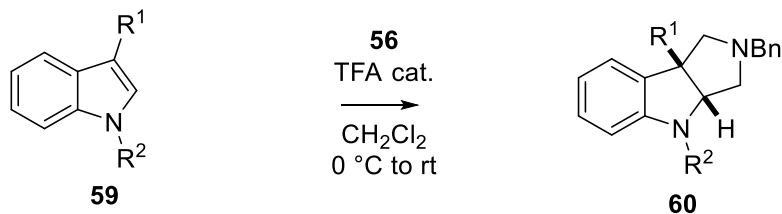
More recently, it has been established that a non-stabilized azomethine ylide formed under mild conditions reacts with nitro-substituted heteroaromatic derivatives.^{69,70} Thus, *N*-benzylazomethine ylide **49b** can be formed *in situ* from reaction of *N*-methoxymethyl-(*N*-trimethylsilylmethyl)benzylamine **56** and a catalytic amount of trifluoroacetic acid at 0 °C to room temperature (Scheme 14).⁷¹⁻⁷³ Consistent with the earlier work of Gribble,⁶⁸ 2-nitro-1-tosylindole **57** underwent efficient cycloaddition reaction to afford the tricyclic product **58** in excellent yield (Scheme 15).⁷⁰ Additionally a series of 3-substituted indoles **59** underwent cycloaddition reactions with the azomethine ylide under these conditions (Scheme 16, Table 1).⁷⁰ Notably, two electron-withdrawing groups are required, one on the indole nitrogen and one at indole position 3, for the cycloaddition process to occur under these conditions. Carbonyl groups are also sufficiently electron-withdrawing to facilitate the desired cycloaddition process (Table 1, entries 5-9). Low isolated yields were obtained for some examples, however, it was reported that the low yields were due to the instability of the product during isolation rather than inefficient cycloaddition reactions.



Scheme 14



Scheme 15

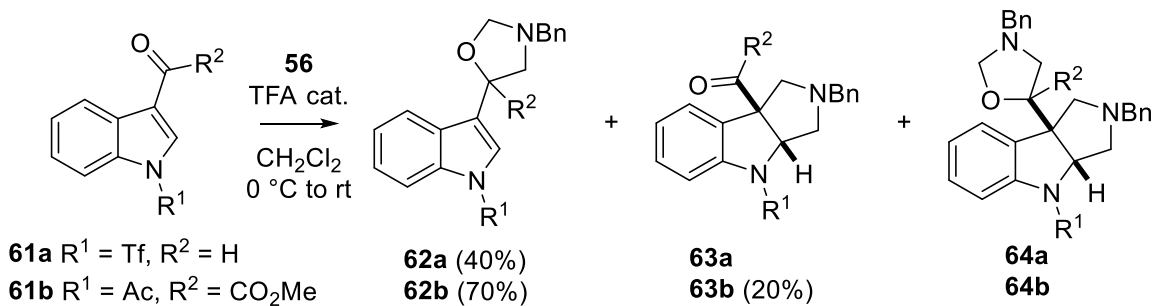


Scheme 16

Table 1. Reactions of 3-substituted indoles **59** with azomethine ylide **49b** to afford pyrroloindoles **60**

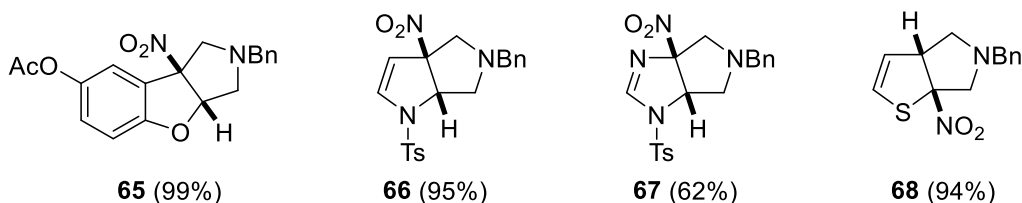
Entry	59/60	R ¹	R ²	Equiv. 56	Duration (h)	Yield 60 (%)
1	a	NO ₂	Ts	2	1	94
2	b	NO ₂	Boc	2	6.5	85
3	c	NO ₂	Ac	1.2	2	86
4	d	NO ₂	Tf	1.2	2	14
5	e	CO ₂ Me	Ts	1.2	6	21
6	f	CO ₂ Me	Boc	1.2	6	25
7	g	CO ₂ Me	Ac	1.2	6	64
8	h	CO ₂ Me	Tf	1.2	6	76
9	i	COMe	Tf	1.2	2	75

Whilst 3-acetylindole derivative **59i** underwent exclusive dearomatizing cycloaddition, alternative cycloaddition pathways were apparent for other 3-carbonyl substituted indoles (Scheme 17).⁷⁰ For *N*-triflylindole-3-carboxaldehyde **61a**, three products, two *mono* adducts and a *bis* adduct, formed in a 6:2:2 ratio. The major product was isoxazolidine **62a** resulting from cycloaddition to the aldehyde moiety, the other products weren't separated, but were assigned as indole C2-C3 cycloadduct **63a** and the product from addition to both the aldehyde and C2-C3 moieties **64a**. For *N*-acetyl-C3-ketocarboxylic acid ester **61b**, isoxazolidine **62b** was obtained in 70% yield, along with **63b** (20%) and minor amounts of *bis* adduct **64b** (not isolated).

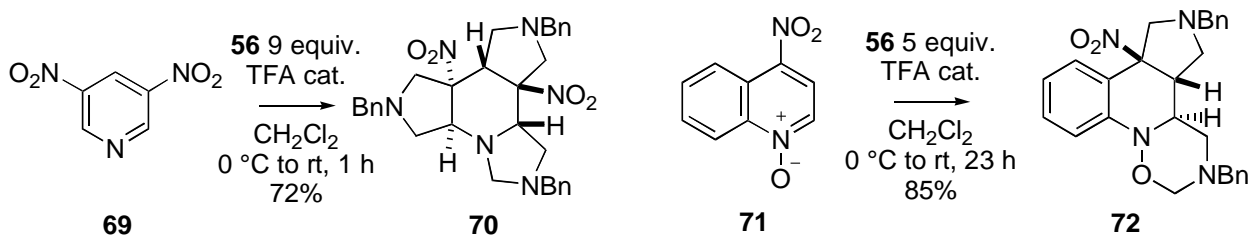


Scheme 17

Additionally, nitro-substituted benzofurans and five-membered heteroaromatic systems also readily undergo cycloaddition reactions with azomethine ylide **49b** generated from precursor **56**. Thus, 5-acetoxy-3-nitrobenzofuran, 3-nitro-1-tosylpyrrole, 4-nitro-1-tosylimidazole and 2-nitrothiophene yield the respective cycloadducts **65** (99% yield obtained using 2 equiv. reagent **56** and a reaction time of 1 h), **66** (95% yield with 3 equiv. **56** for 21 h), **67** (62% yield with 2 equiv. **56** for 2 h) and **68** (94% with 4 equiv. **56** for 22 h).^{69,70}



Cycloaddition reactions of nitropyridines were also explored.^{69,70} While nitropyridine and nitropyridine-*N*-oxide failed to react with azomethine ylide **49b**, 3,5-dinitropyridine **69** underwent rapid reaction to give a *tris* cycloadduct **70**, whose stereochemistry was established as *syn-anti* by 2D NOESY experiments (Scheme 18).⁷⁰ Also, in a further interesting example, 4-nitroquinoline-*N*-oxide **71** underwent regioselective two fold cycloaddition reactions to both the C3-C4 double bond and the nitrene 1,3-dipole to give exclusively the *anti bis* adduct **72**, with the structure and stereochemistry proven by X-ray crystallographic analysis (Scheme 18).^{69,70}

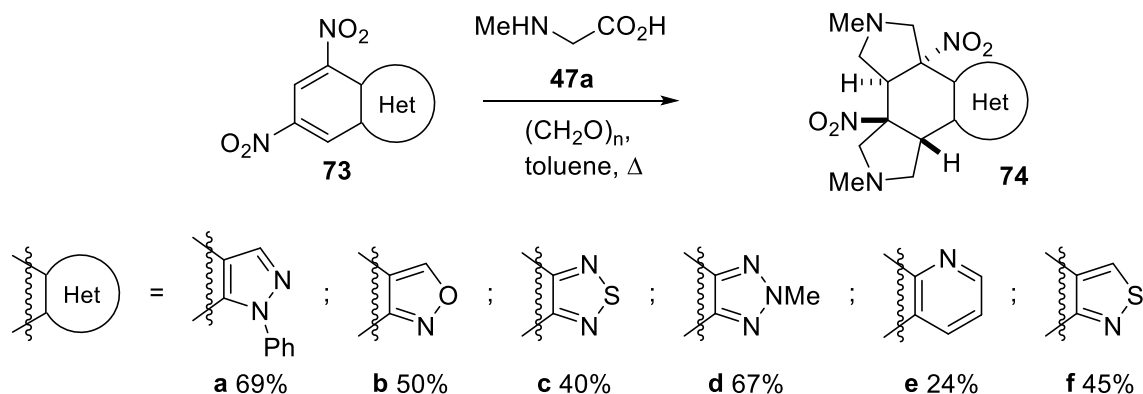


Scheme 18

5. Reactions of Non-stabilized Azomethine Ylides with Nitro-substituted Benzenoid Aromatic Dipolarophiles

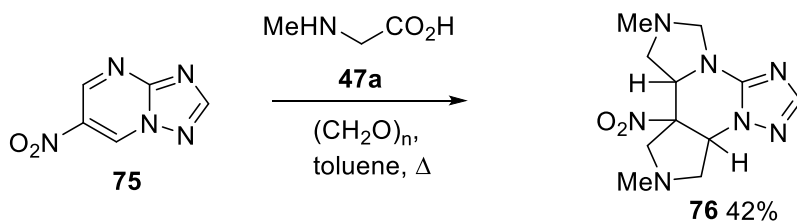
Recently it was found that heterocycle-fused dinitrobenzenes **73** readily undergo 1,3-dipolar cycloaddition reactions with azomethine ylide **49a**, formed by decarboxylative condensation of sarcosine **47a** and paraformaldehyde (Scheme 10), to form novel tetracyclic ring systems **74** (Scheme 19).⁷⁴⁻⁷⁶ Dinitro-indazole **73a**, -benzoxazole **73b**, -benzothiadiazole **73c**, -benzotriazole **73d**, -quinoline **73e** and -benzothiazole **73f** all undergo twofold cycloaddition reactions to afford the respective tetracyclic heterosystems **74a-f**, in low to moderate yields. The reactions are reported to be diastereoselective with only a single isomer isolated and the crystal structures of representative examples showing that the products are the *anti bis* adducts, i.e.,

resulting from cycloaddition of two ylide equivalents to the opposing faces of the dinitrobenzo ring system.



Scheme 19

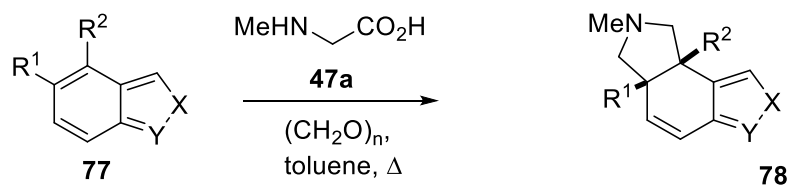
Furthermore, the twofold cycloaddition reaction was possible even in the presence of one nitro group, as illustrated by the reaction of the nitrotriazolo[1,5-*a*]pyrimidine **75** which afforded tetracycle **76**, although in this case the stereochemistry was not established (Scheme 20). Interestingly, this is also an example of reaction of the azomethine ylide with a heteroaromatic C=N bond.



Scheme 20

Certain heterocycle-fused nitrobenzenes undergo selective *mono* additions of azomethine ylide **49a**, formed *in situ* from sarcosine **47a** and paraformaldehyde (Scheme 10).⁷⁷ Thus, benzo-fused heterocycles **77** react to form the tricyclic products **78** without sign of second addition of the azomethine ylide or rearomatization (Scheme 21, Table 2). With introduction of an electron-withdrawing group such as a sulfone at position 4 in **79**, cycloaddition does occur, however, across the nitro-substituted C6-C7 double bond. In this case, the rearomatized products **81** were isolated, presumably by loss of nitrous acid from the initial cycloadducts **80** (Scheme 22, Table 3). It was shown that 6-nitroindazoles substituted with hydrogen or electron-releasing substituents (e.g., OPh, SPh, OMe) at the 4-position do not undergo such cycloaddition reactions,

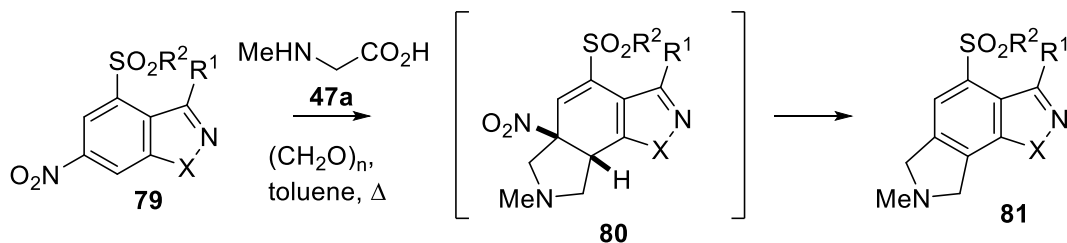
except for a special case where the electron-releasing group is part of a *peri* annelated ring system **82** (Scheme 23).



Scheme 21

Table 2. Reactions of bicyclic heteroaromatics **77** with azomethine ylide **49a**

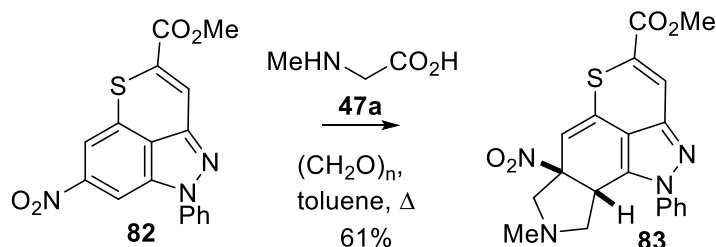
Entry	R ¹	R ²	X	Y	Isolated Yield 78 (%)
1	H	NO ₂	O	N	75
2	H	NO ₂	S	N	42
3	NO ₂	H	O	CH	40
4	NO ₂	H	O	N	98
5	NO ₂	H	S	N	64



Scheme 22

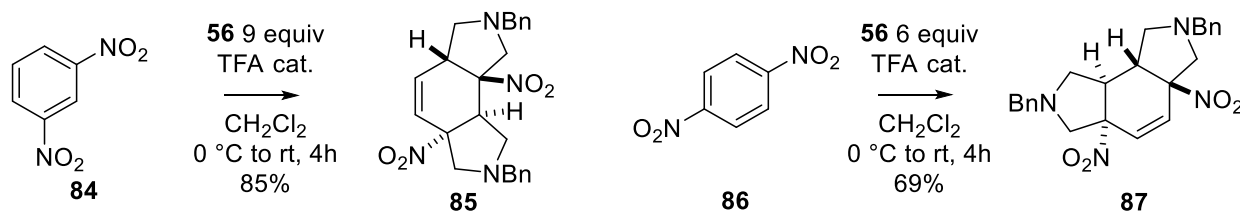
Table 3. Reactions of sulfonyl-substituted heterocycle-fused nitrobenzenes **79** with azomethine ylide **49a**.

Entry	X	R ¹	R ²	Isolated yield 81 (%)
1	NPh	H	Ph	30
2	NPh	H	Bn	32
3	NPh	CO ₂ Et	Bn	54
4	NPh	CONHC ₆ H ₄ -4-OMe	Bn	61
5	O	1,3-dioxan-2-yl	Bn	30
6	O	1,3-dioxan-2-yl	Ph	39
7	O	1,3-dioxan-2-yl	c-C ₆ H ₁₁	64
8	O	1,3-dioxan-2-yl	(CH ₂) ₂ CO ₂ Me	40

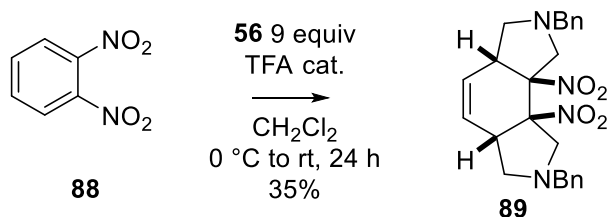


Scheme 23

The ability of azomethine ylide **49b**, formed from reagent **56** (Scheme 14), to undergo cycloaddition reactions with isolated nitrobenzene systems was more recently revealed.^{69,70} While nitrobenzene itself does not react to an observable extent with the ylide **49b**, even with a large excess of the reagent **56**, dinitrobenzenes such as 1,3-dinitrobenzene **84** and 1,4-dinitrobenzene **86** give *bis* adducts **85** and **87** in 85% and 69% yield, respectively (Scheme 24). No evidence for *mono* adducts were observed in these reactions, indicating that the *mono* adduct must be much more reactive towards azomethine ylide **49b** than the starting material. NOESY experiments were used to determine the stereochemistry of *bis* adduct **85**, namely that the pyrrolidine rings are both *cis* fused to the central cyclohexene ring and are in an *anti* relationship relative to one another. The stereochemistry of **87** was also assigned as *anti*. In the case of 1,2-dinitrobenzene **88**, a *bis* adduct was also obtained, albeit in modest yield, however, the stereochemistry was shown by X-ray crystallographic analysis to be the *cis-syn-cis* adduct **89** (Scheme 25). The different reaction rate and stereochemical outcome for 1,2-dinitrobenzene was attributed to a combination of stereoelectronic effects in the starting material and presumed intermediate mono adduct.⁷⁰

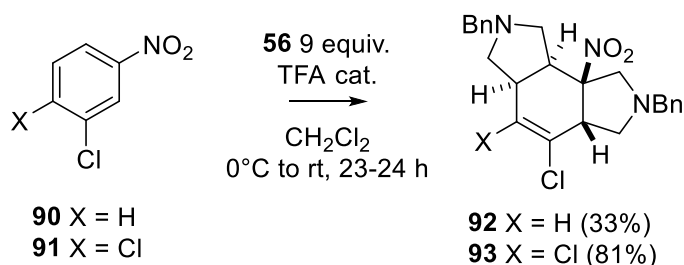


Scheme 24



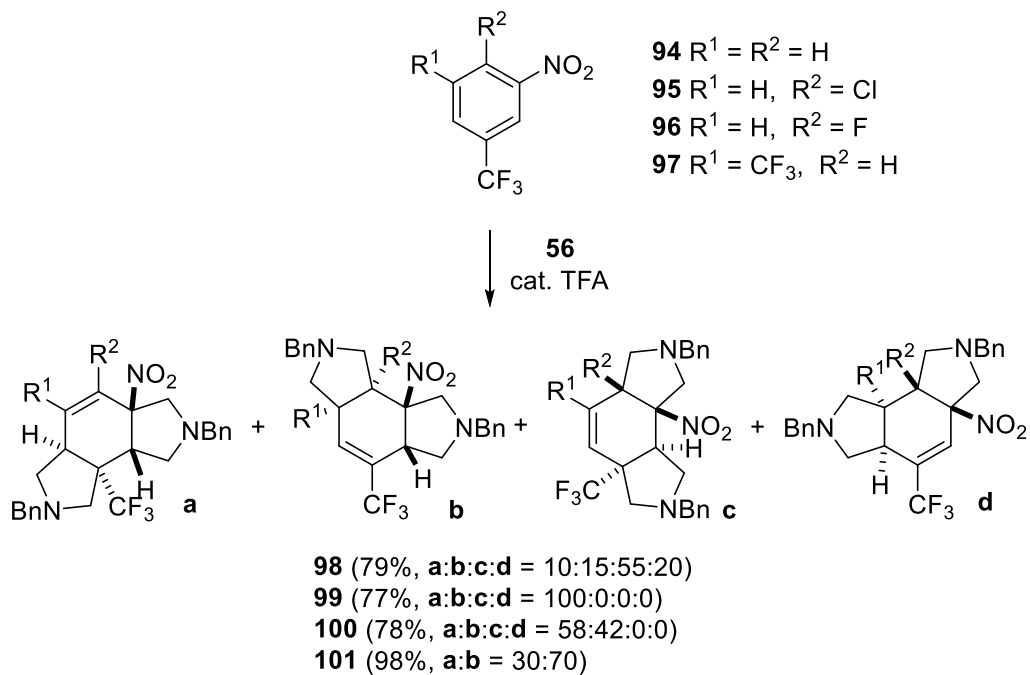
Scheme 25

The *bis* cycloaddition reaction works in a similar manner for nitrobenzenes substituted with electron-withdrawing groups, with a range of regioselectivities being observed depending on the nature of the electron withdrawing group.^{69,70} Whilst theoretically there are four potential *anti bis* adducts that could arise from 3-chloronitrobenzene **90** and 3,4-dichloronitrobenzene **91**, only single regioisomeric *bis* adducts, **92** and **93** were obtained, respectively (Scheme 26). In contrast, the reactions of the corresponding 3-trifluoromethyl-1-nitrobenzene derivatives **94** to **97** delivered a range of products depending on the analogue (Scheme 27). Thus, reaction of 3-trifluoromethyl-1-nitrobenzene **94** with ylide **49b** formed from nine equivalents of reagent **56** over a 24 h period led to a mixture of all four possible *anti* regioisomers **98a-d**, produced in good yield, although only the major regioisomer **98c** was isolated in pure form. For the substrate 2-chloro-5-trifluoromethylnitrobenzene **95**, only one regioisomer **99a** was isolated, a result which was thought to be due to the relative unreactivity of the vinyl chloride moiety towards the azomethine ylide. The related 2-fluoro analogue **96** afforded a *ca.* 1:1 mixture of two regioisomers **100a** and **100b**, indicating similar reactivity of the vinyl fluoride and the vinyl trifluoromethide moieties within the presumed *mono* adduct. As might now be expected, the symmetrical starting material 3,5-bis(trifluoromethyl)nitrobenzene **97** delivered a mixture of the two possible *anti* regioisomers **101a** and **101b**.

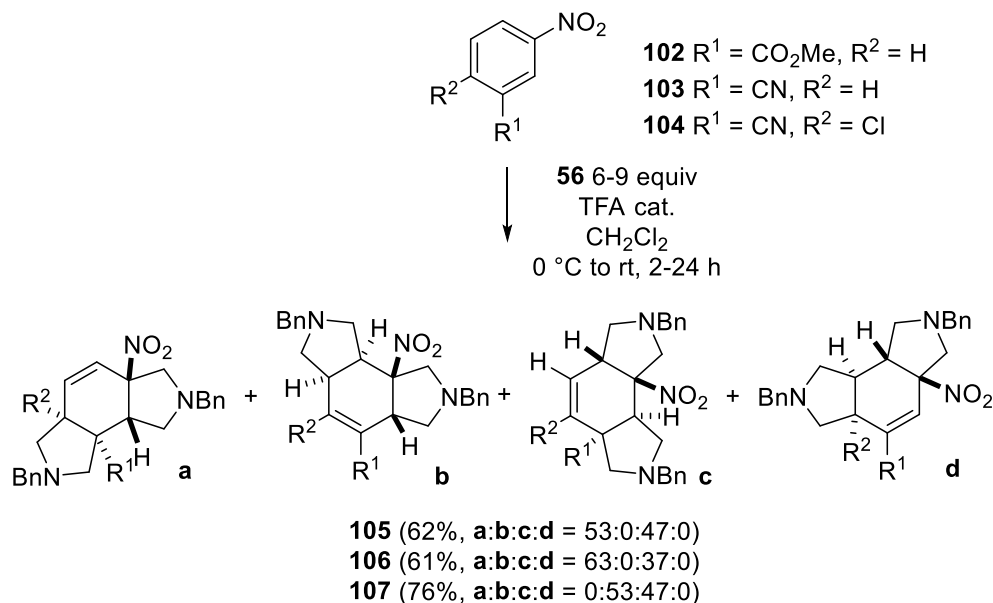


Scheme 26

In the case of nitrobenzenes, substituted with mesomeric electron-withdrawing groups, again mixtures of *anti bis* adducts were obtained (Scheme 28).^{69,70} In the case of methyl 3-nitrobenzoate **102**, a *ca.* 1:1 ratio of two regioisomeric *anti bis* cycloadducts **105a** and **105c** were obtained in a combined yield of 62%. The regio- and stereochemistry of **105a** and **105c** were determined using a range of 2D NMR experiments. Similar results were obtained for the 3-cyano-1-nitrobenzene **103**, whereby *bis* adducts **106a** and **106c** were isolated. Further incorporation of a chloro substituent *para* to the nitro group, as in **104**, also led to two regioisomeric *bis* adducts, however, it was shown that different regioisomers **107b** and **107c** were produced in this case. The lack of reactivity of the vinyl chloride moiety is again apparent, apparently influencing the direction of the second addition of azomethine ylide.



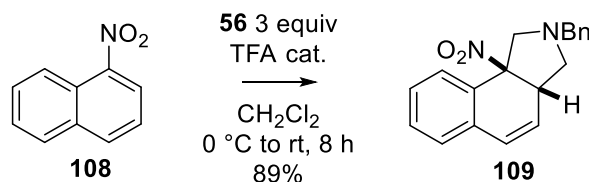
Scheme 27



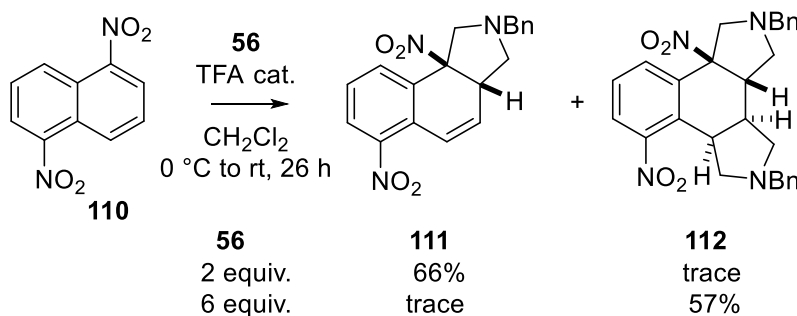
Scheme 28

Nitronaphthalenes were shown to react efficiently with ylide **49b** under these conditions.^{69,70} 1-Nitronaphthalene **108** reacted regioselectively with ylide **49b** to afford a *mono* adduct **109**, demonstrating the greater reactivity of 1-nitronaphthalene over nitrobenzene (Scheme 29). 1,5-

Dinitronaphthalene **110**, with an additional nitro group, led to faster reactions with the ylide **49b**. When just two equivalents of the ylide precursor **56** were used, the *mono* adduct **111** was obtained together with traces amount of *bis* adduct **112**. On the other hand, when 6 equivalents of the ylide precursor **56** were used together with longer reaction times, the *bis* adduct **112** was obtained as the major product (Scheme 30).

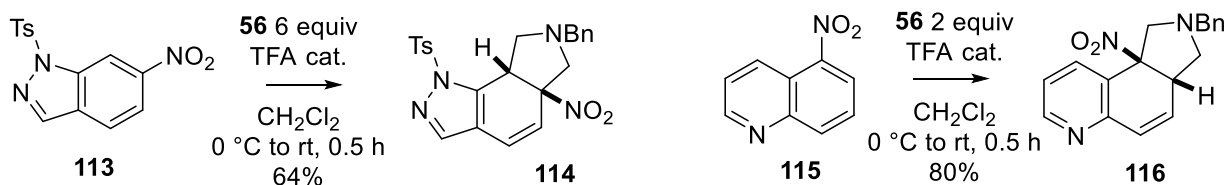


Scheme 29

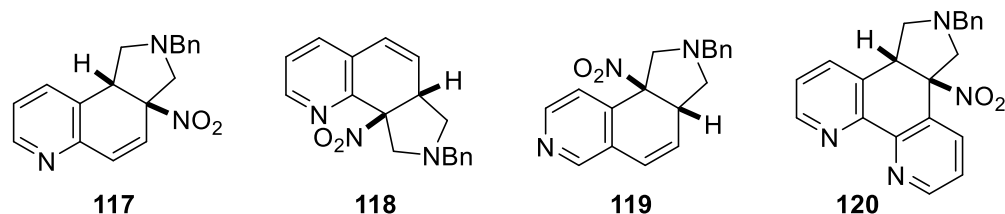


Scheme 30

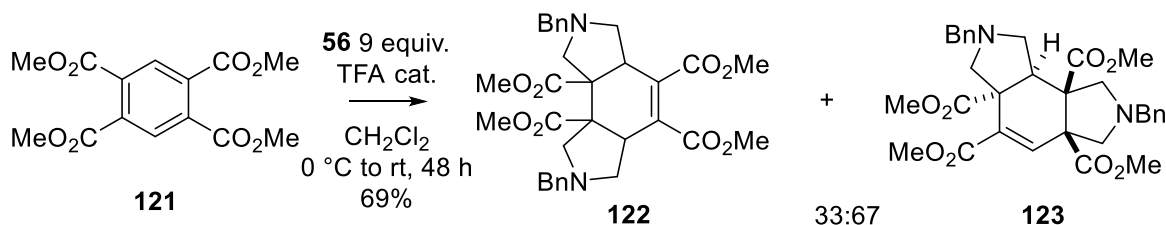
Interestingly, heterocycle-fused nitrobenzenes, 6-nitroindazole **113** and 5-nitroquinoline **115**, underwent selective cycloaddition reactions on the nitrated aromatic ring system to afford single *mono* adducts **114** (64%) and **116** (80%), respectively (Scheme 31).^{69,70} Although not directly comparable, these results are consistent with the observations of cycloaddition on pyrazole-fused dinitrobenzene derivative **73a** and pyridine-fused dinitrobenzene **73e**, discussed earlier (Scheme 19).⁷⁴⁻⁷⁶ Similarly, 6- and 8-nitroquinoline, 6-nitroisoquinoline and 5-nitro-1,10-phenanthroline all undergo selective single cycloaddition on the nitro-substituted ring to give the respective mono cycloadducts **117**, **118**, **119** and **120**.



Scheme 31



Finally and promisingly, it was shown that groups other than the nitro group can facilitate cycloaddition of azomethine ylide **49b** to benzenoid aromatic systems. Thus, the tetramethyl ester of benzene-tetracarboxylic acid **121** underwent cycloaddition reactions to afford a *ca.* 1:2 mixture of *bis* adducts **122** and **123** (Scheme 32).⁷⁰ [Note: Ref. 70, Table 3 Entry 5 indicates that the product depicted here as structure **122** is the minor product from the reaction, whereas the text indicates that it is the major product] Although the stereochemistry of *bis* adduct **123** was determined to be *anti* by 2D NMR experiments, the stereochemistry of symmetrical *bis* adduct **122** was not determined.



Scheme 32

6. Mechanism

The mechanism of the cycloadditions was considered theoretically.⁷⁰ DFT calculations on model compounds indicate that a concerted mechanism features a low activation barrier compared with an alternative cycloaddition process involving a nitrobenzene radical anion and an azomethine ylide radical cation.

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Author's Biography



John H. (Jack) Ryan studied chemistry at The University of Melbourne, gaining a BSc Hons (1st Class) in 1989 and a PhD on cyclopropane chemistry in 1994, supervised by Martin Banwell. He undertook postdoctoral appointments researching iodonium chemistry with Peter Stang (University of Utah), and supramolecular chemistry with George Meehan and Len Lindoy (James Cook University). He gained academic experience lecturing at the University of Tasmania and industry experience as a process research and development chemist at the Institute of Drug Technology Australia. He was appointed to CSIRO as a Research Scientist in 2001 and was promoted to Senior Principal Research Scientist level in 2013. His research interests involve a combination of fundamental (reactive intermediates, reaction mechanisms, heterocyclic chemistry) and applied chemistry (medicinal chemistry, peptide mimetics, fragment-based drug discovery, chemical process development and scale-up and flow chemistry) spanning the fields of human health, natural insecticides, photoprotection and chemical manufacture.