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Recent developments in the chemistry of sydnones

Duncan L. Browne, Joseph P.A. Harrity *

Department of Chemistry, University of Sheffield, Sheffield, S3 7HF, UK

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1. Introduction

Since their early discovery by Earl and Mackney in 1935, sydnones have received steady interest over the last century.[1] The pioneering reviews by Ollis and Stewart discuss, in detail, aspects of the reactions, physical properties and structure of sydnones.[2] However, since those reports, sydnones have gained significant interest through the discovery of an array of useful biological properties (e.g., as antibacterial,[3] antineoplastic[4] and *anti*-inflammatory[5] agents), which has driven the development of new functionalisation methods. Similarly, sydnones act as useful and novel precursors for pyrazoles (through cycloaddition with alkynes), which has also served to drive research into their functionalisation and cycloaddition chemistry. This report aims to provide an overview of the recently developed chemistry of sydnones, with particular emphasis on useful reactions for the synthesis of biologically interesting molecules.

2. Properties and synthesis

2.1. Predicted properties of sydnones

Sydnones are the most widely studied members of the group of heterocycles known as mesoionic compounds. In particular, *N*-phenyl

* Corresponding author. Tel.: +44 114 222 9496; fax: +44 114 222 9346.
E-mail address: j.harrity@sheffield.ac.uk (J.P.A. Harrity).

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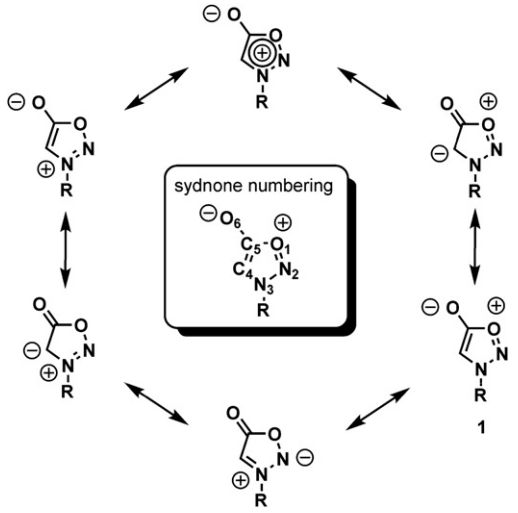
sydnone (**1**; R=Ph) has received the greatest analysis. A non-charged canonical representation of a mesoionic compound cannot be drawn and this issue has attracted much debate in the past with regard to the most appropriate representation of these species. Nonetheless, sydnones are generally represented by a positively charged aromatic ring with an enolate-type exocyclic oxygen (**1**, Scheme 1).



Scheme 1.

An insight into the electronic distribution of sydnones can be gained from molecular orbital calculations (Fig. 1).[6] Depiction **2** shows the calculated bond orders, suggesting an enolate-type bonding mode for the exocyclic oxygen. This observation is backed by the calculated net charges shown in **3**[7] and **4**.[8] Representation **5**, which shows a scaled dipole-moment representation of a sydnone, also ascribes a large negative charge on the exocyclic oxygen atom. However, it appears that the α-carbon (C4) has the bonding characteristics of an enolate carbon, but not the electronic profile that one would expect (compare **2** with **3**, **4** and **5**). This is further complicated by the observation that the C4 proton has a pK_a of ~18–20,[9] which would suggest stabilization of the conjugate base by an adjacent ketone-type moiety. Moreover, the infrared spectra of a range of sydnones from across the literature show an absorbance at approximately 1730 cm^{-1}, also indicative of a carbonyl function.

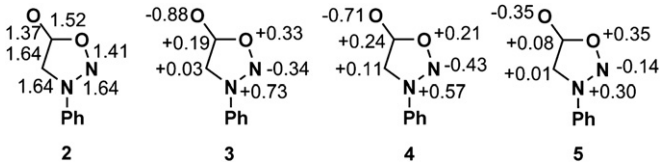


Figure 1.

Interestingly, representations **2**–**5** all suggest that N3 is an iminium-type nitrogen and is therefore acting as an electron-withdrawing substituent on the attached phenyl ring. This suggestion is refuted by the work of Wang and co-workers.[10] They conducted a series of physicochemical calculations, which agreed with the suggestion that the sydnone π-electrons are unequally delocalized. However, they concluded from their studies that N2 and N3 were neutral; C4, O1 and O6 were negatively charged whilst C5 was positively charged. Moreover, they state that there is little π-resonance interaction between the N3 phenyl group and the sydnone ring. Indeed, results from synthetic studies suggest that a combination of these predicted properties are correct and a general reactivity profile of a sydnone can be summarized as depicted in Figure 2.

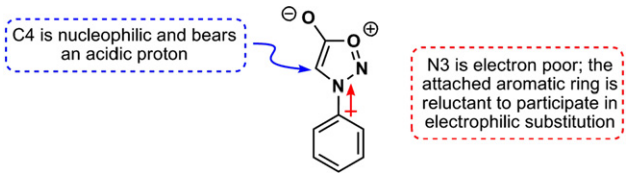
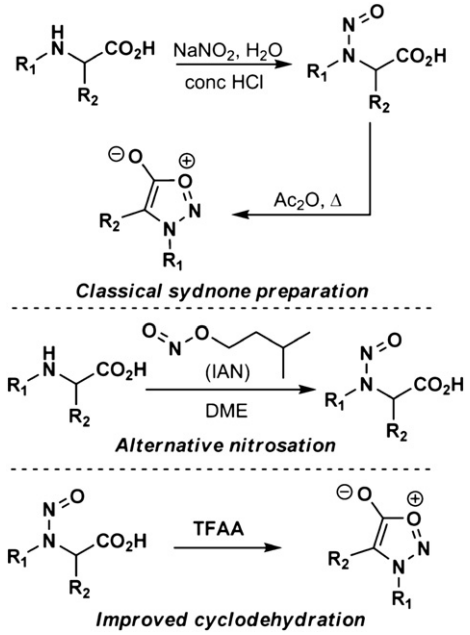


Figure 2.

2.2. Synthesis of sydnones

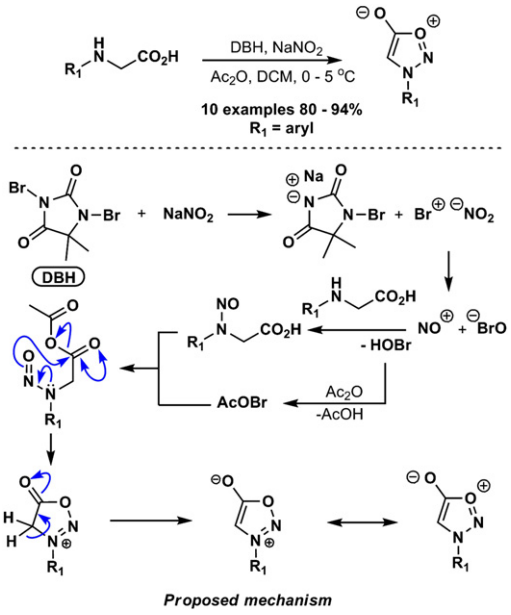
Classically, sydnones are synthesized in just two steps from *N*-substituted amino acids (Scheme 2). *N*-Nitrosation followed by cyclodehydration generally furnishes the mesoionic products in good-to-excellent yields. Whilst this is the most common method, several improvements or alternatives have been introduced. Of particular note, the employment of trifluoroacetic anhydride (TFAA) has superseded the use of acetic anhydride, largely due to an increased rate of cyclisation.[11] Turnbull et al. have described nitrosation using isoamyl nitrite (IAN) for acid-sensitive starting materials (Scheme 2).[12] Thoman and Voaden reported the use of charcoal to improve the purity of the isolated products, which was evidenced by the isolation of a colourless solid (*N*-phenyl sydnone is usually isolated as tan crystals).[13] Notably, the latter report describes the successful synthesis of **1** on a 100 g scale. Interestingly, a proline-derived sydnone (**6**; vide infra) has also been synthesized on a large scale (several kilograms).[14]



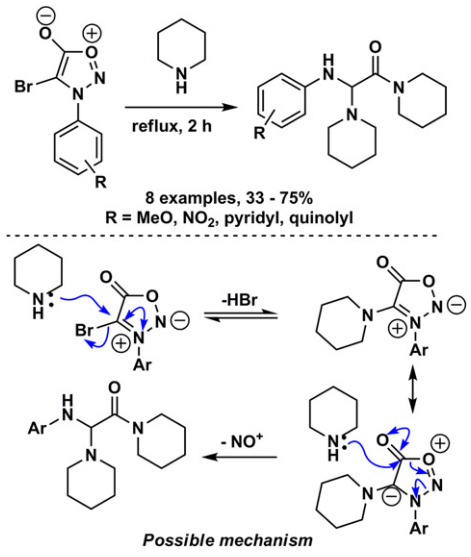
Scheme 2.

Azarifar et al. have reported several one-pot syntheses of sydnones.[15] One approach employs dibromo-dimethylhydantoin (DBH) (Scheme 3). This one-pot procedure avoids isolation of the toxic nitrosamine intermediate and makes use of cheap commercially available materials. Moreover, they report good yields for the formation of a range of sydnones across all methods.

The review by Stewart[2b] lists 117 reported sydnones and also describes several sydnones, which cannot be synthesised. One notable example is the sydnone in which R^1=H. Nitrosation of the required precursor for such a sydnone would result in diazonium salt formation.



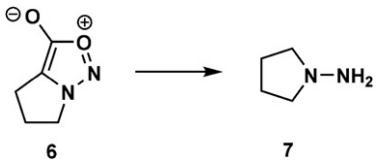
Scheme 3.



Scheme 5.

2.3. Sydnone stability

Many sydnones are isolated as crystalline solids, and are commonly purified by recrystallisation from ethanol. Sydnones can be stored at room temperature, although a few have been known to degrade in the presence of light. Concentrated acids can also cause degradation of sydnones, yielding the hydrazine derivatives with loss of CO_2.[16] In fact, this chemistry has been harnessed to provide a route to monoalkylhydrazines. Heat can also cause degradation of the mesoionic ring system. On progression from a gram to kilogram preparation of **6**, Nikitenko et al. conducted a decomposition analysis, which demonstrated a large exotherm at 180 °C, presumably due to the formation of pyrrolidinehydrazine (**7**) and CO_2 (Scheme 4).[14]



Scheme 4.

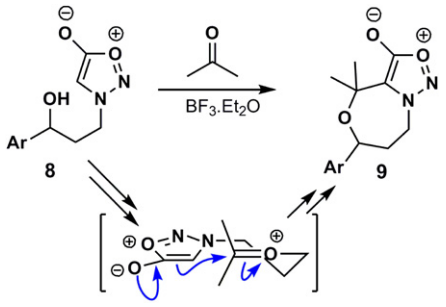
Another interesting mode of sydnone degradation is that discovered by Puranik and Suschitzky.[17] Treatment of a variety of *N*-substituted C4 bromosydnones with piperidine was found to consistently deliver the corresponding glycyl amides in useful yields. A plausible mechanism is shown in Scheme 5.

3. Functionalisation of sydnones at C4 position

As outlined earlier in Figure 2, the C4 position of a sydnone ring is both acidic and nucleophilic. This gives rise to two possible modes of functionalisation: 1) electrophilic aromatic substitution or 2) deprotonation followed by electrophile addition. In general, the sydnone substrates follow the generalised rules for both reactivity modes, although there are also some interesting findings, which highlight the unique character and chemistry of this heterocycle.

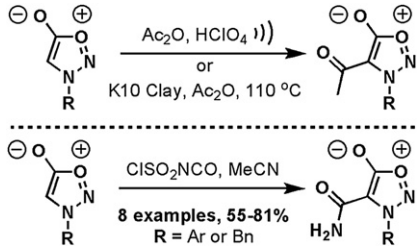
3.1. Electrophilic aromatic substitution reactions

3.1.1. Direct acylation. The classical Friedel–Crafts reaction has remained elusive as a means for the electrophilic acylation of sydnones. Treatment of sydnones with an acid chloride and aluminium chloride fails to return useful levels of the desired products.[18] Presumably, the Lewis acid is sequestered by coordination to the exocyclic oxygen of the sydnone. Zhang and co-workers more recently found that an intramolecular Friedel–Crafts reaction of **8** was possible when employing 3.2 equivalents of $BF_3{\cdot}Et_2O$ and acetone. The reaction is believed to proceed through the highly reactive oxocarbenium intermediate to give **9** (Scheme 6).[19]



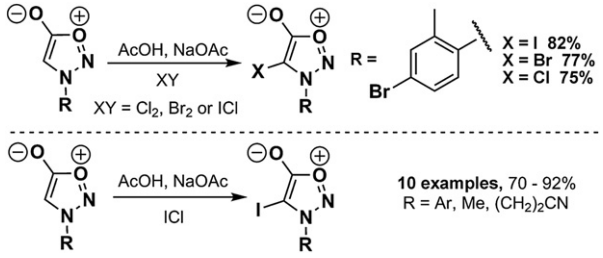
Scheme 6.

Direct acylation has been achieved by sonication with perchloric acid and acetic anhydride, as reported by Tien,[20] and a heterogeneous clay-catalysed protocol developed by Turnbull.[18] Of particular interest is the electrophilic substitution with chlorosulfonyl isocyanate, which has been shown to deliver primary amide-substituted sydnones (Scheme 7).[21]



Scheme 7.

3.1.2. Halogenation. A range of halogenation methods has been developed for the introduction of halogens into the C4 position of a sydnone. To date, chloro, bromo, and iodo analogues have been synthesized, employing a broad spectrum of typical electrophilic halogenating reagents. Dumitrașcu et al. synthesized a range of 4-halo sydnones employing acetic acid, sodium acetate, and the appropriate halogen source (Scheme 8).[22,23] Both *N*-alkyl- and *N*-aryl-substituted sydnones can be transformed by this method in good-to-excellent yields, with esters, nitriles, ethers, carboxylic acids, and halogens being tolerated on the *N*-aryl substituent.



Scheme 8.

Chlorination can also be effected with dichloroiodobenzene and triethylamine, as demonstrated by Turnbull and Ito (Table 1).[24]

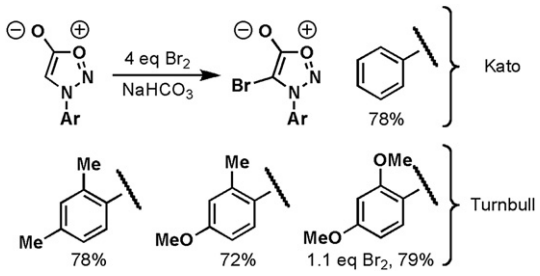
Table 1

R	Yield[a] (%)
Ph	76, 88[b]
Bn	76
2-AcC_6H_4	82
2-MeC_6H_4	59
2-$MeO_2CC_6H_4$	53
4-ClC_6H_4	56
3-$MeOC_6H_4$	79

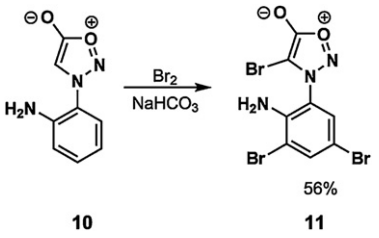
[a] Unoptimised.
[b] At 0 °C.

Bromination has been the most studied sydnone halogenation method.[15a,25–29] Commonly, bromine and sodium bicarbonate are employed and Kato and co-worker exploited these conditions to brominate *N*-phenyl sydnone, furnishing the desired C4 bromo product in 78% yield (Scheme 9).[26] Turnbull et al. built on these findings to systematically assess the issue of a potentially competing *N*-aryl electrophilic bromination. It was demonstrated that the bromination of the sydnone ring is preferred, even in the presence of a dimethoxyphenyl substituent (Scheme 9). In a subsequent paper, the same group assessed bromination of *N*-(2-anilino)sydnone (**10**) and found that bromination of the aryl ring was significantly more competitive than that of the methoxy congeners, giving tribromide **11** (Scheme 10).[30] This result is not that surprising, given the Hammett values of the relevant aryl substituents (*p*-MeO=−0.268, *p*-NH_2=−0.660).[31] Overall, however, these studies do confirm the electron-withdrawing nature of the sydnone nitrogen atom.

N-Halosuccinimides have also been employed for the synthesis of 4-bromo and 4-chloro sydnones.[24]



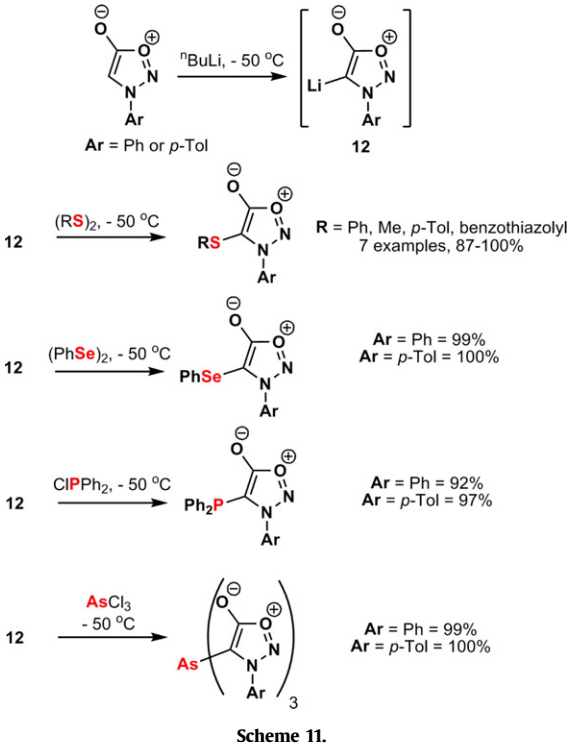
Scheme 9.



Scheme 10.

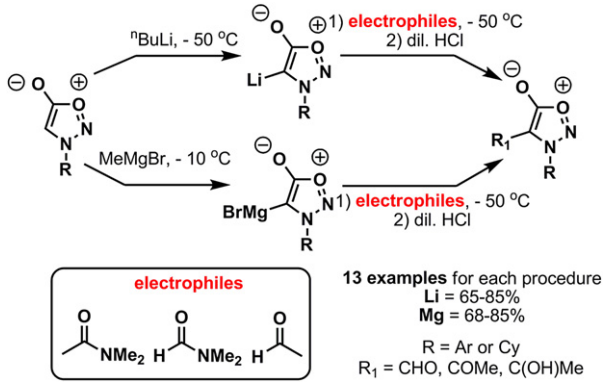
3.2. Lithiation

Lithiation of sydnones provides a convenient means for the introduction of a variety of substituents by two main processes: 1) deprotonation followed by quench with an electrophile or 2) lithiation followed by transmetalation and subsequent chemistries. Lithiation of the sydnone C4 proton is relatively facile and is commonly carried out with *n*-butyllithium. Fuchigami and co-workers reported the synthesis of alkylthio and arylthio sydnones by this method (via the intermediacy of lithiated sydnone **12**).[32] Deprotonation with *n*-butyllithium followed by the addition of a sulphide was found to deliver a selection of thiosydnones. The authors also reported the synthesis of selenide-, phosphide- and arsenide-derived sydnones by an analogous method (Scheme 11). Efforts to

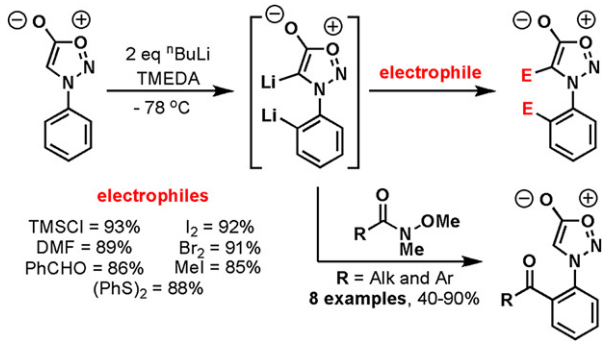


Scheme 11.

make the tin, antimony and tellurium variants were unsuccessful. Tien et al. adopted a similar protocol, but demonstrated the introduction of C4 carboxy groups through the use of some more common electrophiles.[33] In the same paper, they also report the generation of the sydnone anion by treatment with methylmagnesium bromide (Scheme 12). The laboratory of Turnbull has compiled a considerable body of work on the synthesis of fused tricyclic sydnones. Their initial efforts featured a double lithiation of 3-(2-bromophenyl)sydnone and subsequent treatment with an ester, thereby tethering the biaryl rings. The authors subsequently published a protocol for quenching the di-lithiated intermediate with non-tethering electrophiles.[27] In this instance, dilithiation of the non halogenated sydnone could be affected in the presence of TMEDA. Scheme 13 shows that this method not only allows access to the dihalogenated species, but also to diformyl, dithioether, dialkyl, dihydroxyalkyl and disilyl phenyl sydnones (Table 2).[34] Furthermore, treatment of the di-lithiated intermediate with a Weinreb amide species delivered the *ortho* carbonyl compounds in moderate-to-excellent yields.[35]



Scheme 12.



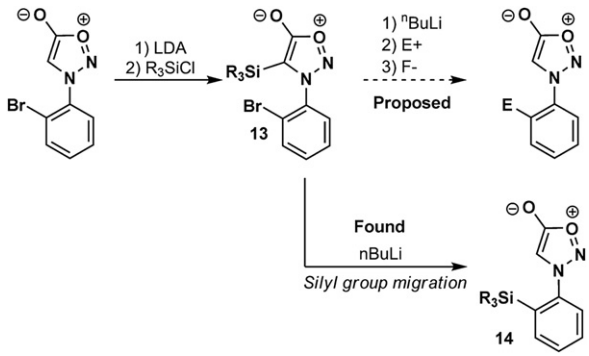
Scheme 13.

Table 2

R^1	R^2	Yield (%)	R^1	R^2	Yield (%)
H	Et	0	^{t}Bu	Me	95
Me	Et	71	Bn	Et	80
Et	Et	76	Ph	Et	86
^{i}Pr	Me	93			

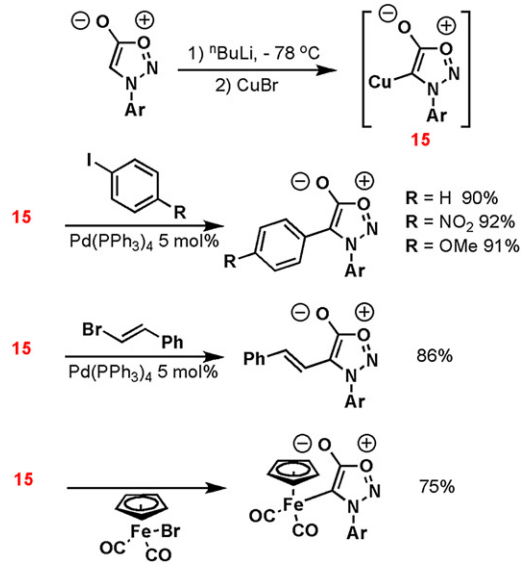
Other efforts to synthesise the *ortho*-silyl sydnones resulted in some interesting findings (Table 3).[36] It was envisaged that deprotonation of an *ortho*-bromo sydnone followed by temporary protection with a silyl group would then allow lithium–halogen exchange and functionalisation of the phenyl ring, ending with removal of the silyl group by a fluoride ion. However, the silyl-protected intermediate **13** underwent silyl migration upon treatment with a second equivalent of BuLi, giving the product **14**. The size of the silyl group was found to have a minimal effect upon the putative intramolecular migration process (Table 3).

Table 3



R_3Si	Yield of **13** (%)	Yield of **14** (%)	2 Step Yield (%)
TMS	85	87	74
TIPS	81	89	72
TBDMS	83	85	71
TBDPS	79	80	63

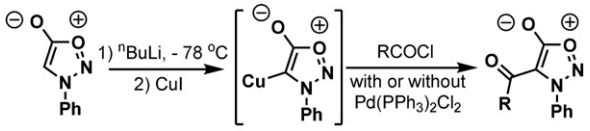
Kalinin and co-worker described the transmetalation of lithiated sydnone to the corresponding organocopper reagents. The intermediate sydnonylcopper **15** was then shown to efficiently undergo palladium-mediated coupling processes with aryl and alkenyl halides in good yields.[37] They also discovered that, on treatment of the 4-copper-3-phenylsydnone with cyclopentadienyl(dicarbonyl)iron bromide, it was possible to obtain the C4 iron sydnone (Scheme 14).



Scheme 14.

This methodology was extended by Turnbull for the acylation and aroylation of the sydnone C4 position. The reaction proceeds via the copper sydnone shown in Table 4, and, curiously some examples work better in the absence of palladium and some in its presence (Table 4). Loadings of the palladium catalyst were not specified.

Table 4



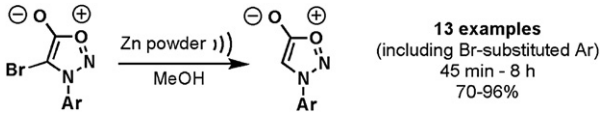
15

Entry	R	Yield with Pd (%)	Yield without Pd (%)
1	Me	97	86
2	Cy	66	64
3	Ph	96	93
4	4-ClC_6H_4	78	82
5	4-MeC_6H_4	89	65
6	4-$MeOC_6H_4$	80	51
7	4-$NO_2C_6H_4$	38	56
8	Bn	63	95

3.3. Modification of C4 halogenated sydnones

Several methods for the removal of a bromine atom from a sydnone have been discovered. Kato and Ohta conducted such studies on the reactivity of C4 bromo-*N*-phenyl sydnone.[26] They found that heating this compound in the presence of magnesium metal, and subsequent quenching with water, returned the unsubstituted parent sydnone, presumably via the Grignard reagent. They also discovered that removal of the bromo substituent could be effected with hydrazine monohydrate, sodium hydrosulfide, sodium sulfide, and sodium thiocresolate. Although no yields were given, the products had identical melting points to an authentic sample of *N*-phenyl sydnone **1**.

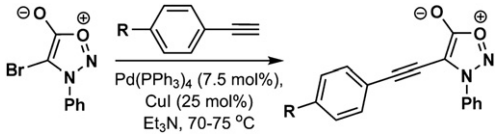
Alternatively, sodium borohydride can be used for the removal of a sydnonyl bromide.[38] Tien developed an ultrasound-accelerated, zinc-mediated method for the removal of bromine from a variety of sydnones (Scheme 15).[20] The overall process of C4 bromination and subsequent removal has been employed as a protecting-group strategy, which allows cleaner reactions at the N3 substituent (vide infra). Aryl halides can be employed in metal-mediated cross-coupling reactions.[39] Palladium-catalysed Sonogashira coupling of bromo sydnones has been reported by Turnbull et al. (Table 5).[40] Interestingly, they found that portionwise addition of both the catalyst and the alkyne was essential for full conversion, an atypical method for this type of reaction.



Scheme 15.

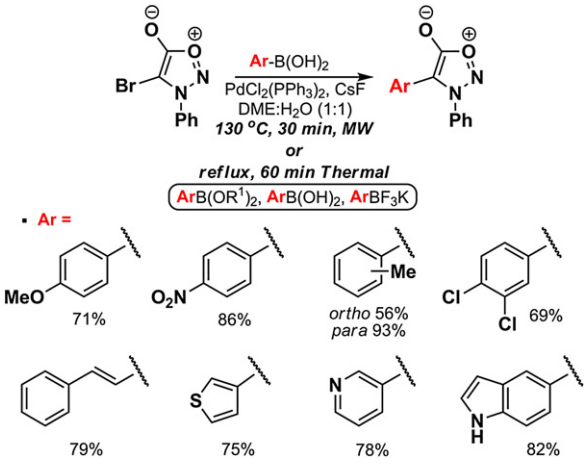
More recently, Browne et al. have investigated the scope of a Suzuki–Miyaura cross-coupling method with C4 bromo-*N*-phenyl sydnone.[41] It was found that a variety of boron-containing substrates could successfully couple under a variety of catalytic conditions. Both traditional and microwave-heating processes delivered the coupled products in good yields, within a simple and practical protocol (Scheme 16). Furthermore, Moran et al. have discovered a direct arylation, alkenylation and alkynylation protocol for the

Table 5

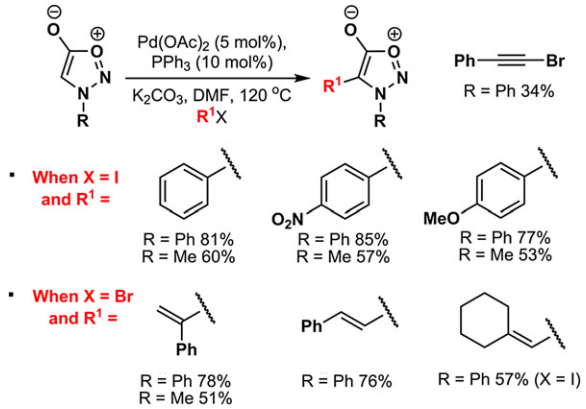


R	Yield (%)	R	Yield (%)
H	79	EtO	92
Me	89	Cl	94
Et	86	NMe_2	82
MeO	89	OTHP	89

synthesis of C4-substituted sydnones.[42] A variety of aromatic iodides and bromides can be coupled in good yield. A selection of bromoalkenes were also successfully appended and one example of a direct alkyne coupling proceeded in moderate yield (Scheme 17).



Scheme 16.

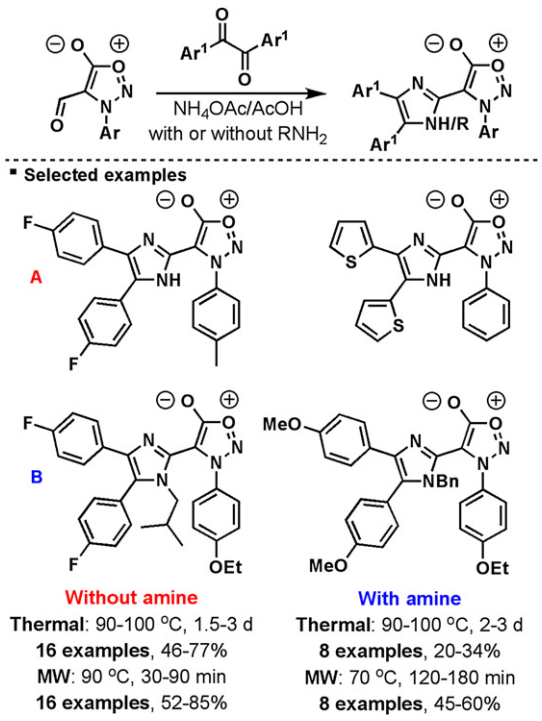


Scheme 17.

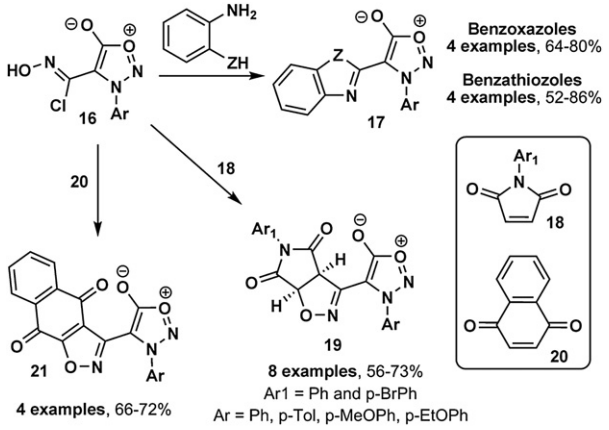
3.4. Modification of C4 carbonyl sydnones

C4 carbonylated sydnones have recently been used by Shih and co-workers for the synthesis of imidazolyl-substituted sydnones.[43] Treatment of 4-formyl sydnones with aromatic glyoxals, in the presence of ammonium acetate and acetic acid, delivers the imidazoles in good yields (Scheme 18). The introduction of a primary amine starting material results in its incorporation into the

imidazole products. The same author has also converted the C4 aldehyde into a chloro oxime (**16**) and studied the reactivity in nitrile oxide cycloadditions and nucleophilic substitution reactions (Scheme 19).[44] The quinone products (**21**) were isolated presumably after the rapid oxidation of the intermediate hydroquinone cycloadducts.

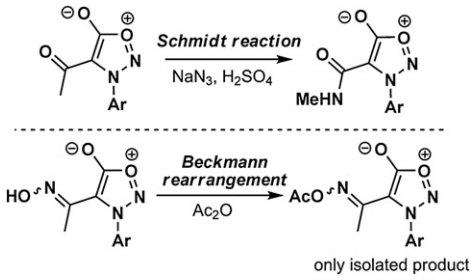


Scheme 18.

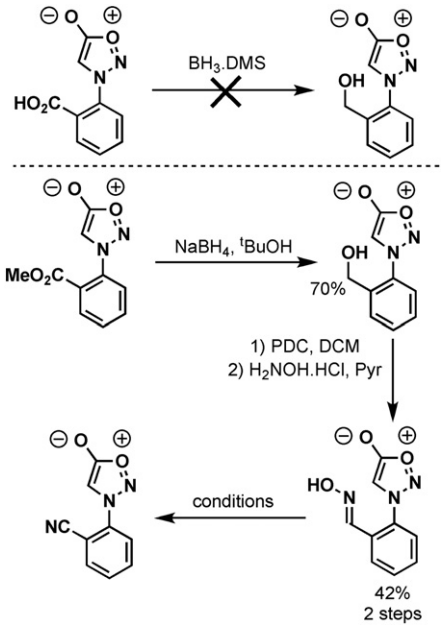


Scheme 19.

Tien has described the application of the Schmidt reaction to C4 acylated sydnones for the synthesis of sydnonyl–methylamides.[45] A range of sydnones were treated with sodium azide and sulfuric acid to give the product deriving from methyl migration (notably, sydnone migration was never observed, Scheme 20). In contrast, attempts to conduct a Beckmann rearrangement on the corresponding ketoximes failed to produce any of the desired amide products. The synthesis and reactivity of an *ortho*-oxime-functionalized *N*-aryl sydnone have been studied by Turnbull.[46] The synthesis of this compound provided some interesting observations. The initial plan commenced with a $BH_3 \cdot DMS$ reduction of the benzoic acid. After a number of efforts were met with the recovery of starting materials (variations included increased temperatures and the use of additives), the authors attributed the problem as arising from the electron-withdrawing nature of the sydnone nitrogen. In this case, the carbonyl was presumed to be relatively electron-deficient and therefore could not trigger the reduction via Lewis-acid coordination. They next turned to nucleophilic hydride reduction of the corresponding methyl ester. On employment of sodium borohydride in *tert*-butyl alcohol, they obtained the desired product in 70% yield, and, presumably, the electron-withdrawing nature of the sydnone ring promoted the reduction of the ester in this case. With this in hand, oxidation with pyridinium dichromate (PDC) and oxime formation with hydroxylamine hydrochloride gave the aldoxime (Scheme 21).

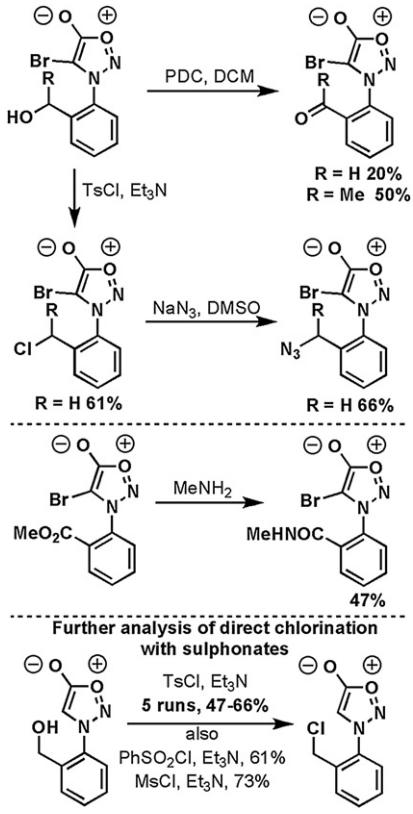


Scheme 20.



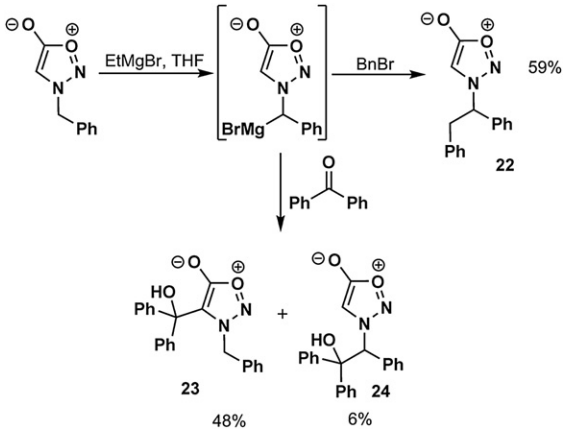
Scheme 21. Conditions: TsCl, Et_3N 56%; MsCl, Et_3N 83%; $BnSO_2Cl$, Et_3N 77%; TfCl, Et_3N 73%; $SOCl_2$, Et_3N 77%, PCl_5, Et_3N 70%; P_4S_{10} 45%.

Both ketoximes and aldoximes were treated with a range of sulphonyl chlorides in the presence of triethylamine. In all cases, the corresponding nitrile products were obtained, presumably via elimination of the *O*-sulfonate oxime intermediate. It is notable that the sydnone ring survives a broad range of dehydration conditions. The same authors then opted to assess the C4 protection with bromine followed by subsequent *N*-phenyl substituent manipulation.[29] Again, some interesting findings were made, which are attributable to the electron-withdrawing nature of the sydnone (Scheme 22). They found that, on attempted tosylation of the primary alcohol, the benzylic chloride product could be obtained.[47] Moreover, and in line with their $NaBH_4$ ester reduction, treatment of the methyl ester with methylamine resulted in amide formation, albeit in moderate yield.



Scheme 22.

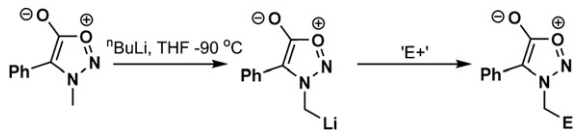
Greco and O'Reilly reported the first deprotonation of a sydnone nitrogen substituent.[48] On treatment of *N*-benzyl sydnone with ethylmagnesium bromide in THF, and subsequent quenching with benzyl bromide, sydnone **22** was isolated in 59% yield. Curiously, quenching the same intermediate with benzophenone resulted in an 8:1 mixture of products **23**:**24**, where the major isomer was that with C4 substitution (**23**, Scheme 23). In a similar fashion, Kalinin et al. found that treatment of *N*-methyl-4-phenylsydnone with butyllithium gives the *N*-lithiomethyl-4-phenylsydnone, which can be quenched with a variety of electrophiles (Table 6).[49] This discovery marks an important method for the rapid elaboration of the sydnone nitrogen substituent.



Scheme 23.

Lastly, in a combination of both sydnone C4 electrophilic aromatic substitution and N3 substituent manipulation, Turnbull and co-workers were able to synthesise a variety of tricyclic sydnones. Treatment of *N*-(2-aminophenyl) sydnone with nitrous acid led to a diazonium intermediate, which underwent intramolecular addition by the sydnone at the C4 position (Scheme 24). Alternatively, synthesis of the azide and conversion into the phosphine imide followed by exposure to an isocyanate or isothiocyanate delivers sydnoquinoxalines in moderate-to-good yields. Both examples serve to highlight the stability of sydnones to a range of relatively harsh reaction conditions and their potential for dual reactivity.[50]

Table 6



'E$^+$'	Yield (%)
AllylBr	67
$ClCO_2Me$	21
TMSCl	36
CO_2	70
p-ClC_6H_4CHO	80
PhC(O)Me	12
PhC(O)Ph	70

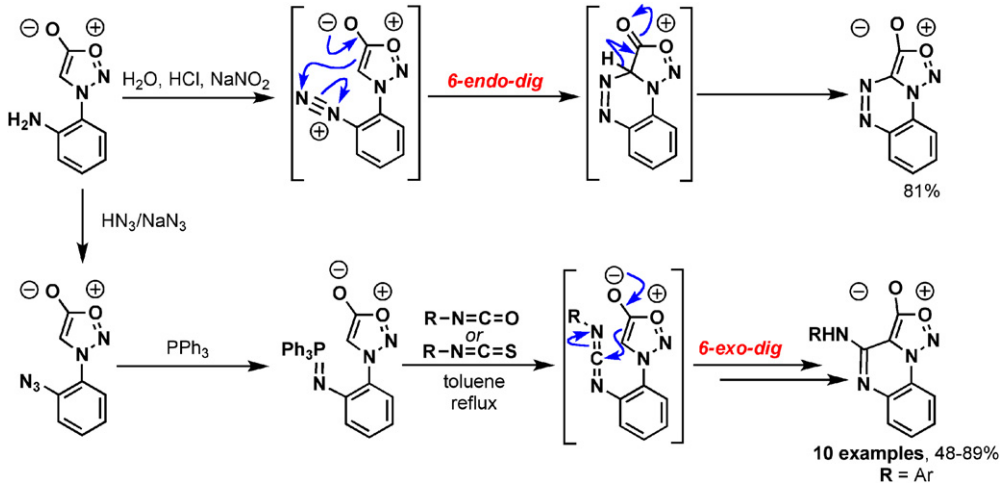
4. Alkyne cycloadditions

Arguably, the most important synthetic application of sydnones is their cycloaddition reaction with alkynes. This process delivers pyrazoles via a [4+2] cycloaddition—retrocycloaddition with the expulsion of carbon dioxide. The reaction was first reported in 1962 by Huisgen,[51] who showed that the cycloaddition was compatible with a range of simple hydrocarbon-substituted alkynes as well as those bearing, alcohol, acetal, acyl, and ester groups. Recent years have seen a growing interest in pyrazole chemistry from both an industrial and academic standpoint (as exemplified in Charts 1 and 2).[52] The interest stems from the recognition of the pyrazole motif as a privileged structure for the discovery of biologically active molecules. Currently, efforts in this area have focused on further defining the reaction scope with respect to more heavily functionalised sydnones and alkynes, with particular emphasis on the impact on reaction regiocontrol.

Cycloaddition reactions of sydnones are most commonly carried out with electron-deficient alkynes. For example, the reactive dienophile, dimethyl acetylenedicarboxylate, reacts readily with C4-substituted sydnones, and this chemistry has been exploited to generate functionalised pyrazole products (Scheme 25).[23,53]

Unsymmetrical alkynyl esters are potentially more synthetically useful, as they provide a simple opportunity for orthogonal functionalisation of the pyrazole products. In addition, these substrates offer a chance to study the regioselectivity of sydnone cycloadditions. Padwa et al. carried out an investigation into the regioselectivity of cycloadditions of methyl propiolate with various C4-substituted sydnones.[54] As outlined in Scheme 26, the reactions were found to proceed in moderate yield and with low levels of regiocontrol. Nonetheless, the 3,5-disubstituted isomer was favoured in all cases. Notably, the *N*-alkyl sydnone substrates were found to be unstable and were therefore generated in situ. Ranganathan extended this chemistry to the proline-derived sydnone **6**. The reaction was found to proceed in high yield, but exhibited essentially no regiocontrol (Scheme 27).[55]

In an effort to address the limitations associated with the poor levels of regiocontrol observed in propiolate cycloadditions, Wong and Yeh undertook a systematic study of the potential for each reaction partner to affect cycloaddition selectivity.[56] Initially, they studied a series of 4-substituted sydnones and found these to provide the corresponding pyrazoles with only very modest selectivity for the 3,5-disubstituted isomer (Table 7).



Scheme 24.

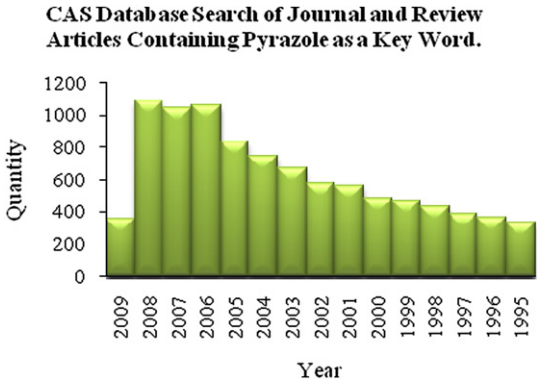


Chart 1.

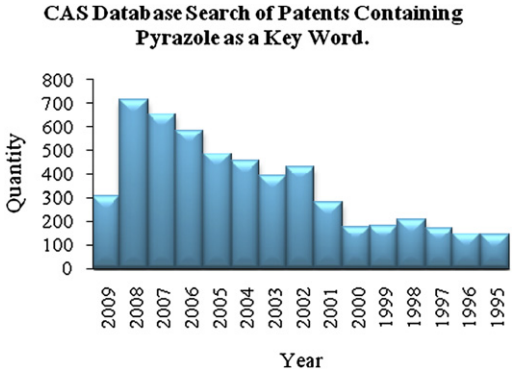
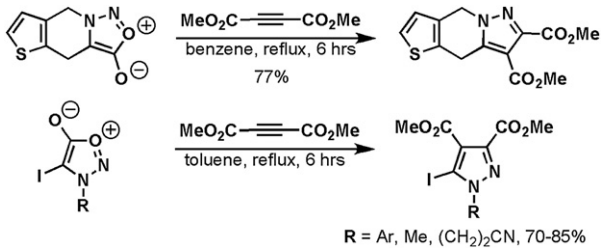
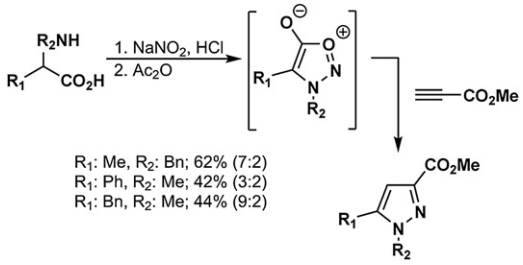


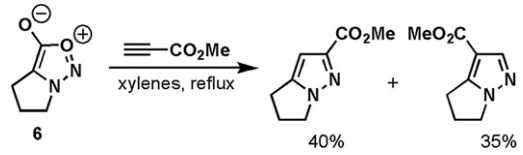
Chart 2.



Scheme 25.

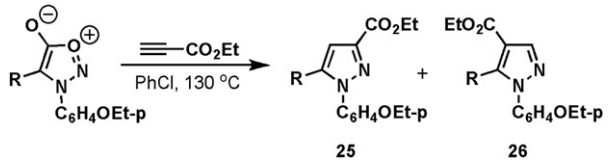


Scheme 26.



Scheme 27.

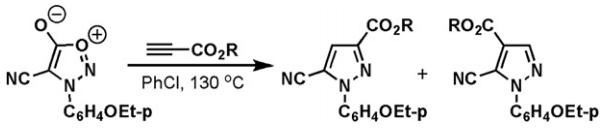
Table 7



R	Yield (**25**:**26**) (%)
H	90 (76:24)
I	81 (56:44)
CN	80 (58:42)
CH_2OH	71 (63:37)
SPh	71 (52:48)

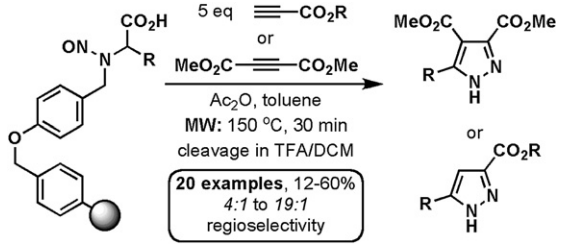
Subsequently, the size of the ester substituent was varied in an effort to improve regiochemical control. As outlined in Table 8, this concept proved to be successful and excellent levels of regiocontrol were observed when diphenylmethyl propiolate was employed. The authors subsequently exploited this chemistry in the synthesis of DHODase inhibitors.[57]

Table 8



R	Yield (**27**:**28**) (%)
Et	80 (58:42)
Bn	76 (57:43)
Bu^t	79 (78:22)
$CHPh_2$	85 (100:0)

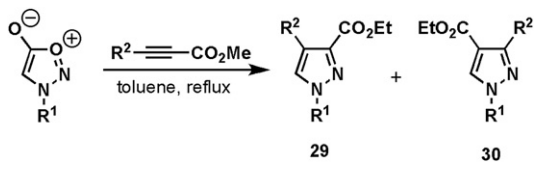
This class of cycloadditions has recently been exploited for the synthesis of *N*-unsubstituted pyrazoles on solid support.[58] Specifically, a series of amino acids were coupled to an Ameba resin and elaborated to the corresponding nitrosamine. A subsequent one-pot cyclodehydration and cycloaddition gave the supported pyrazoles that were released from the resin by TFA-debenzylation (Scheme 28).



Scheme 28.

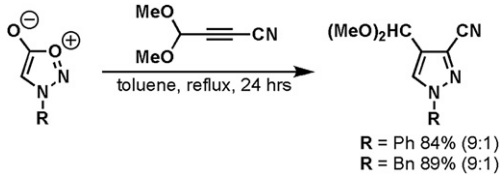
The efficiency and regioselectivity of sydnone cycloadditions with substituted alkynyl esters have been investigated by Fariña and co-workers.[59] Specifically, they noted a dramatic switch in selectivity of cycloaddition of propiolates bearing acetal, aldehyde, and carbinol substituents. Interestingly, alkynes bearing an acetal moiety showed a complementary regiochemical insertion pattern to the corresponding aldehydes (Table 9).

Table 9



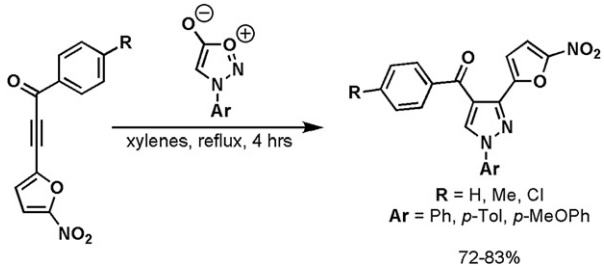
R^1	R^2	Time (h)	Yield (**29**:**30**) (%)
Bn	$CH(OMe)_2$	72	80 (81:19)
Ph	$CH(OMe)_2$	60	84 (79:21)
Bn	CHO	18	90 (28:72)
Ph	CHO	18	93 (34:66)
Bn	CH_2OH	72	75 (50:50)
Ph	CH_2OH	48	79 (40:60)

These authors extended their studies to include acetal-substituted propionitriles[59a] and showed that the selectivities could be enhanced still further (Scheme 29). Notably, an analogous regiochemical insertion pattern to that of the corresponding propiolates was observed.



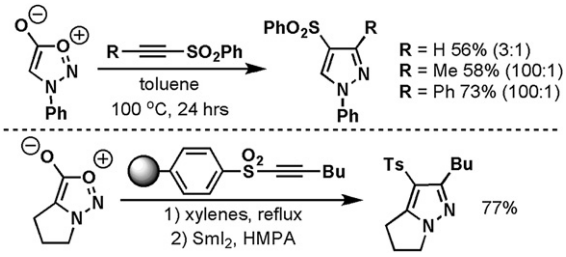
Scheme 29.

An interesting and highly functionalised class of α,β-acetylenic ketones has been employed in sydnone cycloadditions by Hegde et al. and was found to generate the corresponding pyrazoles in excellent yield and as single regioisomers (Scheme 30).[60] The authors also demonstrated that replacing the furan with a 5-nitrothiophene provided similar results. These compounds were further tested for their antibacterial and antifungal activities.[61]



Scheme 30.

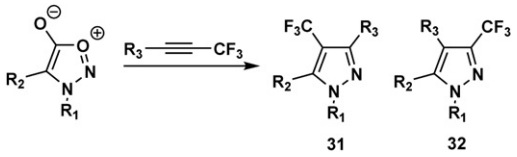
The employment of alkynylsulfones has been documented by Zecchi and co-workers.[62] By analogy to the cycloaddition of propiolates, the terminal alkyne provided the corresponding pyrazole with modest levels of regiocontrol. However, substituted alkynylsulfones have the potential to furnish 1,3,4-trisubstituted pyrazoles in good yield with excellent regioselectivity. This work was recently extended by Back[63] to include solid supported alkynylsulfones that provided the corresponding bicyclic pyrazoles in good yield as single regioisomers after cleavage from a Merrifield resin (Scheme 31).



Scheme 31.

The direct formation of trifluoromethyl-substituted pyrazoles by the cycloaddition of the corresponding alkynes has been reported. In a detailed study of the reaction scope, Meazza showed that alkyne incorporation largely favoured the formation of 4-CF_3 substituted pyrazoles.[64] Interestingly, the introduction of substituents at C4 of the sydnones had a detrimental effect on the reaction regioselectivity (Table 10).

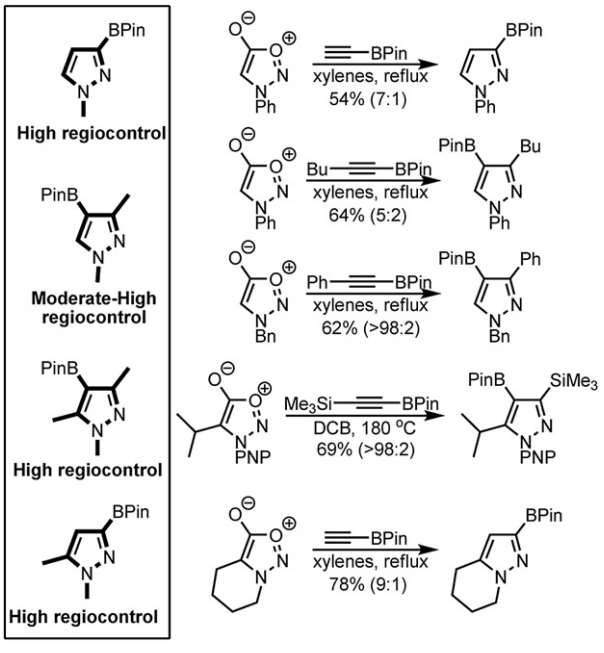
Table 10



R^1	R^2	R^3	Yield (**31**:**32**) (%)
Ph	H	4-$MeOC_6H_4$	56 (93:7)
Ph	H	4-$O_2NC_6H_4$	93 (93:7)
4-$MeOC_6H_4$	H	4-ClC_6H_4	84 (93:7)
Bn	H	4-ClC_6H_4	65 (91:9)
Bu^t	H	4-ClC_6H_4	58 (93:7)
Ph	Me	4-ClC_6H_4	75 (84:16)
Ph	4-ClC_6H_4	4-ClC_6H_4	57 (60:40)
Ph	Br	4-ClC_6H_4	43 (71:29)
Ph	MeS	4-ClC_6H_4	62 (43:57)

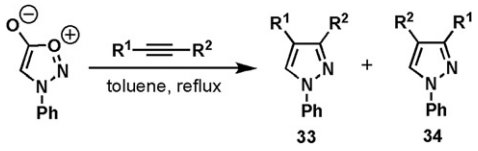
An alternative class of dienophiles studied in sydnone cycloadditions is alkynylboronates. These alkynes have been employed in a range of metal-mediated and thermally promoted cycloaddition reactions toward aromatic and heteroaromatic boronic esters.[65]

In a detailed study carried out in our laboratories, we have found that a broad range of sydnones is compatible with cycloadditions of alkynylboronates, providing a direct method of accessing pyrazoleboronic ester intermediates.[66] Specifically, 4-unsubstituted sydnones underwent highly regioselective cycloaddition with Ph-substituted and terminal alkynylboronates, whereas more modest selectivities were observed using alkynes bearing alkyl or silyl substituents. In contrast, 4-substituted systems showed excellent levels of regiocontrol in all cases examined. A summary of accessible pyrazole scaffolds obtained by this chemistry is provided in Scheme 32. Alkynylstannanes and -silanes have been employed as an alternative to the organoboron reagents and appear to display similarly useful levels of regiocontrol.[67] As outlined in Table 11, a series of terminal silylacetylenes were found to provide the 3-silylpyrazole in high yield and with excellent regiocontrol (entries 1 and 3), although the yield diminished significantly when the bulky Ph_2Bu^tSi group was employed (entry 4). The silyl-substituted stannylacetylene provided the corresponding pyrazole with excellent levels of regiocontrol (entry 2). If it is assumed that the regiochemistry is sterically controlled, then the tributyltin group performs as the smaller moiety, which may reflect the respective bond lengths (C–Sn>C–Si). Finally, the unsymmetrical bis-silylacetylene was poorly selective (entry 5), whereas the electron-deficient alkyne provided the corresponding pyrazoles in excellent yield and with good regioselectivity (entry 6).



Scheme 32.

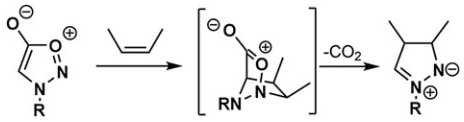
Table 11



Entry	R^1	R^2	Yield (**33**:**34**) (%)
1	H	$SiMe_3$	95 (100:0)
2	Bu_3Sn	$SiMe_3$	80 (100:0)
3	H	$SiMe_2Ph$	75 (100:0)
4	H	$SiPh_2Bu^t$	15 (100:0)
5	$PhMe_2Si$	$SiMe_3$	97 (2:1)
6	COMe	$SiMe_3$	97 (5:1)

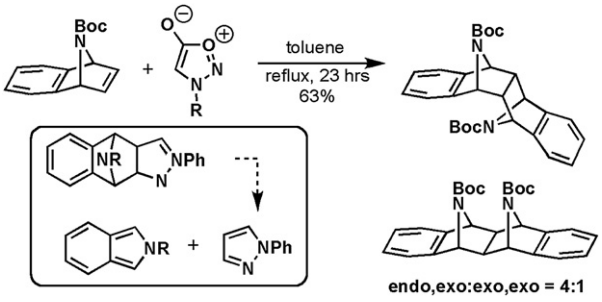
5. Alkene cycloadditions

The dipolar cycloaddition of sydnones to alkenes has been known for over 40 years.[68] Huisgen reported that such cycloadditions could give rise to Δ^2-pyrazolines, and that the addition of an oxidant to this mixture allowed the corresponding pyrazoles to be isolated. Since these early observations, the scope of this potentially synthetically useful cycloaddition has been investigated by a number of researchers. Whilst early studies suggested that alkene cycloadditions proceeded analogously with that of alkynes, they have in fact been found to be rather more complex and a variety of cyclic products have been observed. The general reaction pathway involves a cycloaddition/cycloreversion process with evolution of CO_2. In the case of alkene dienophiles, this gives rise to an azomethine imine and it is the subsequent chemistry of this intermediate that determines the ultimate product distribution (Scheme 33).



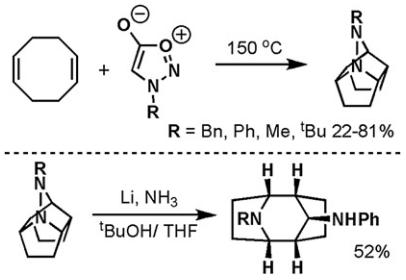
Scheme 33.

Sasaki demonstrated that 7-azanorbornenes could be converted into linear polycycles by sequential cycloaddition reactions with *N*-phenyl sydnone.[69] In this case, the azomethine imine appears to undergo preferential loss of *N*-phenyl pyrazole to furnish an isoindole that in turn undergoes a Diels–Alder reaction with the azanorbornene starting material (Scheme 34).



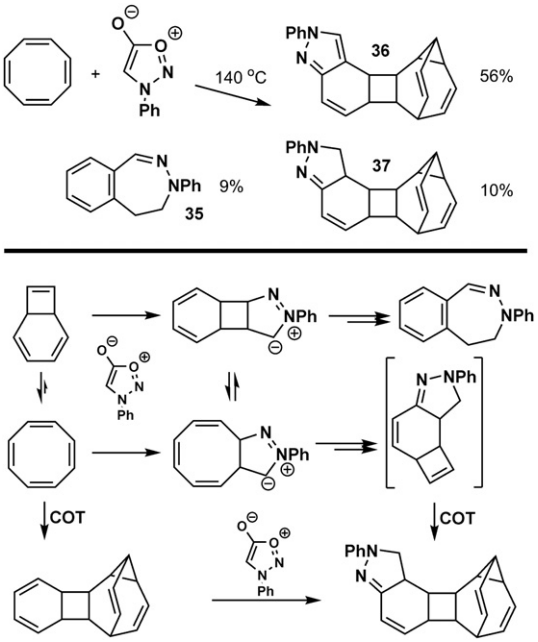
Scheme 34.

An alternative sequence that involves double cycloaddition of sydnones with an alkene was reported by Gribble in 1996.[70] In an extension of Weintraub's observation that sydnones react with 1,5-cyclooctadiene to give caged polycyclic amines (Scheme 35), Gribble also demonstrated that bridged tricycles could be formed after N–N bond reduction.



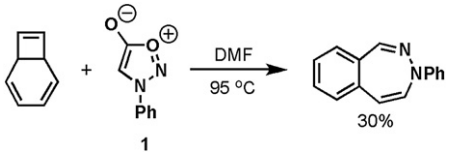
Scheme 35.

Padwa described an unusual cycloaddition reaction of *N*-phenyl sydnone and cyclooctatetraene (COT) to give three structurally interesting products.[71] A number of potential reaction pathways are open to these substrates and these are highlighted in Scheme 36. Specifically, the sydnone could undergo cycloaddition with COT or bicyclooctatriene to generate **35** after ring cleavage and an H-shift. The polycycles **36** and **37** are the result of the cycloaddition of the sydnone with two equivalents of COT. Notably, control experiments suggested that the major product **36** is the result of an oxidation of the initially formed **37**.



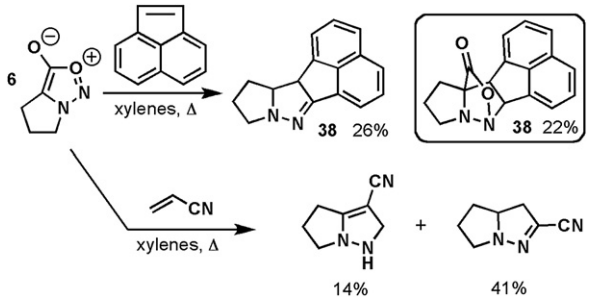
Scheme 36.

In subsequent studies, Kato confirmed the potential of sydnones to react with cyclobutenes to furnish ring-expanded products.[72] Specifically, heating benzocyclobutene with sydnone **1** provided the corresponding benzodiazepine, albeit in low yield (Scheme 37).

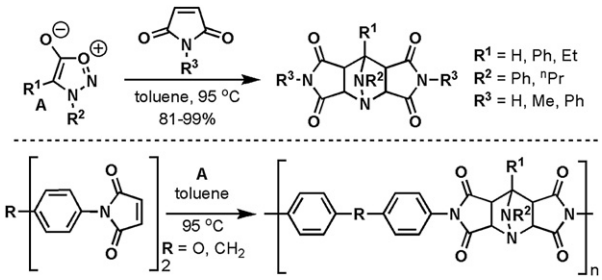


Scheme 37.

During investigations into the cycloaddition of bicyclic sydnone **6**, Ranganathan observed that acenaphthylene generated the expected pyrazoline **38** together with the direct cycloadduct **39** that had failed to undergo CO_2 extrusion (Scheme 38).[55] These studies were extended to include acrylonitrile and provided the corresponding pyrazolines with modest levels of regiocontrol. Maleimide is a common dienophile/dipolarophile used in cycloaddition processes and Sun has explored the employment of this reactive alkene with sydnones. Interestingly, the reaction was found to be highly selective for the formation of bis-imides resulting from a 1:2 cycloaddition of sydnone:maleimide, even when the reaction was conducted in the presence of a large excess of the mesoionic reagent (Scheme 39).[73] In a similar vein to the studies by Sasaki described earlier, a mixture of *endo*/*exo* isomers was obtained. An elegant application of this methodology was subsequently detailed, whereby a bismaleimide was employed within a polymerisation process to generate novel polyimides.[74]

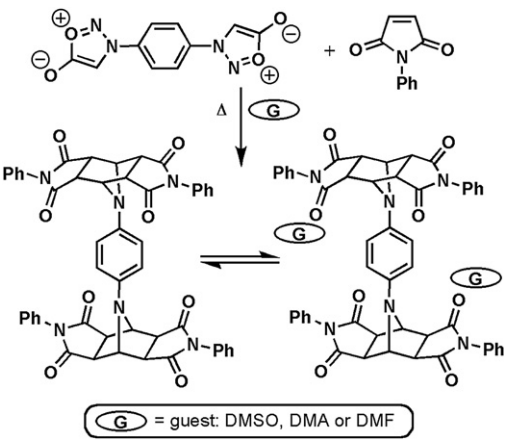


Scheme 38.



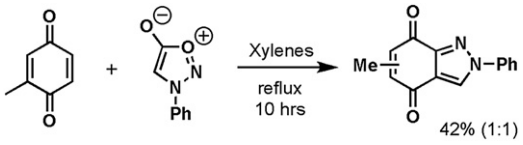
Scheme 39.

The use of a *p*-phenylene-linked bis-sydnone in maleimide cycloadditions has been reported to generate a three-dimensional heterocycle that can form inclusion complexes with DMSO, DMA, and DMF (Scheme 40).[75]



Scheme 40.

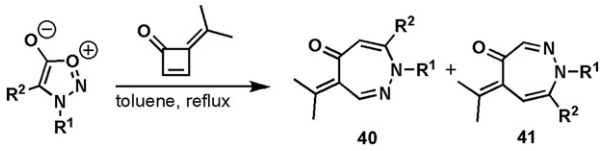
Quinones are an alternative class of activated dienophiles/dipolarophiles and the group of Nan'ya has demonstrated that these can participate in sydnone cycloadditions to produce indazole-4,7-diones.[76] As outlined in Scheme 41, when *p*-toluquinone was employed, the cycloaddition took place exclusively at the less-hindered olefin although the pyrazole was generated as a 1:1 mixture of regioisomers.



Scheme 41.

Martin has shown that diazepinones can be prepared from alkylidenecyclobutenones, presumably via [3+2] cycloaddition followed by in situ ring opening initiated by the azomethine imine intermediate.[77] The authors noted that substitution of the sydnone at C4 provided excellent regiocontrol, but they also observed a surprising dependence on the sydnone *N*-substituent, whereby a Ph group provided consistently high regioselectivities (Table 12).

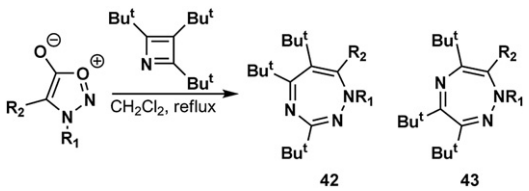
Table 12



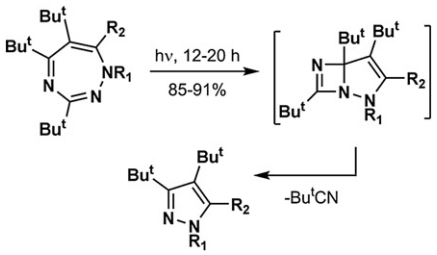
R^1	R^2	Yield (**40**:**41**) (%)
Ph	Me	56 (100:0)
Ph	H	93 (100:0)
Ph	Cl	84 (100:0)
Me	H	65 (4:3)
Bn	H	58 (4:3)
Me	Me	75 (100:0)
$(CH_2)_4$		57 (100:0)
$(CH_2)_3$		43 (100:0)

Kinetically stabilised azetes are an interesting class of anti-aromatic compounds and their participation in cycloaddition reactions with sydnones was reported by Regitz and co-workers in 1997.[78] As outlined in Table 13, this process delivered triazepines with excellent levels of regiocontrol in all but one case. Photolysis of these triazepines provided an effective method for the generation of hindered pyrazoles (Scheme 42).

Table 13



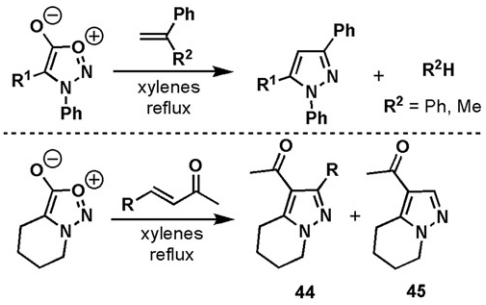
R^1	R^2	Yield (**42**:**43**) (%)
Ph	H	80 (2:3)
Ph	Me	83 (100:0)
o-Tol	H	42 (100:0)
p-Tol	Me	73 (100:0)
Me	H	85 (100:0)



Scheme 42.

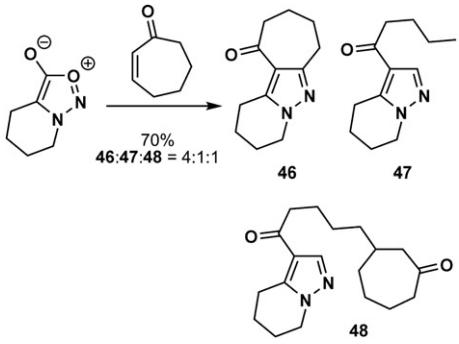
During Huisgen's preliminary investigations of alkene cycloaddition reactions of sydnones, an unexpected aromatisation mode was observed in the reaction of 1,1′-disubstituted alkenes that involved a hydrocarbon elimination reaction.[68] This process was studied and further optimised by Larsen using β-substituted enones.[79] As outlined in Table 14, only alkyl-substituted enones provided the de-alkylated product and this reaction pathway was favoured by more-substituted alkyl groups. Moreover, the authors noted that the proportion of de-alkylated products could be enhanced by slow addition of the enone substrate.

Table 14



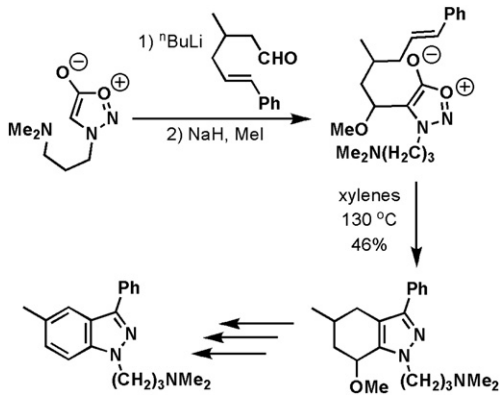
R	Yield **44** (%)	Yield **45** (%)
Me	61	7
Pr^n	20	55
Pr^i	7	72
Bn	12	58
Ph	67	0

Finally, the cycloaddition of cycloheptenone led to a product mixture consisting of the ring-opened product **47** and the conjugate addition adduct **48** (Scheme 43). This product distribution, the dependence on the nature of R with respect to its leaving-group ability and a notable lack of solvent effect led the authors to speculate that the elimination reactions are a radical-based process.



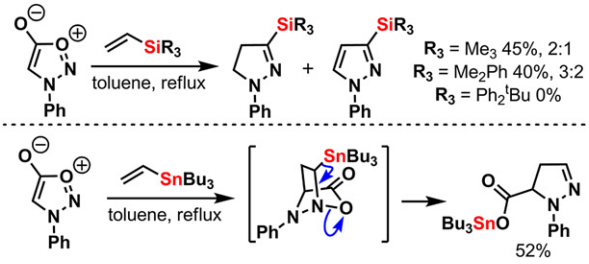
Scheme 43.

Intramolecular reactions provide a powerful strategy for generating products with defined regiochemistry, particularly when the corresponding intermolecular processes are poorly selective. In the context of sydnone cycloadditions, this approach has been employed in the assembly of an antidepressant indazole, FS-32.[80] Lithiation at C4 provided a convenient means to attach the substrate olefin, and the subsequent cycloaddition proceeded in moderate yield and provided the 1*H*-indazole after acid-catalysed condensation and oxidation (Scheme 44).



Scheme 44.

The cycloaddition of sydnones and vinylsilanes and -stannanes has been investigated by Gonzàlez–Nogal and co-workers.[67] Vinylsilanes appear to be relatively unreactive toward cycloaddition and the reaction is sensitive to steric encumberance. Nonetheless, a mixture of pyrazoles and pyrazolines is obtained with excellent regiocontrol (Scheme 45). In contrast, the cycloadduct of the corresponding vinylstannane does not undergo retro-cycloaddition, but instead eliminates the carboxylate to provide a stannyl ester.



Scheme 45.

6. Conclusions and future outlook

In conclusion, sydnones are highly versatile and robust members of the mesoionic class of heteroaromatic compounds. They possess an array of interesting chemical and physicochemical properties, as well as a variety of biological activities. With respect to their functionalisation, modern techniques such as metal catalysed cross-coupling and direct arylation processes have been found to be as directly applicable to these unusual compounds as they are to the more common heteroaromatic substrates. Moreover, some significant advances have been made in the development of sydnone cycloadditions. Whilst alkenes participate in a selection of reaction manifolds, the cycloaddition of alkynes consistently gives pyrazole products. Nonetheless, these all have the potential to furnish some very interesting molecular architectures. Indeed, we speculate that the development of new sydnone functionalisation methods in conjunction with the aforementioned cycloaddition reactions will provide the focus of future research in this area.

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Biographical sketch

Duncan Browne received his MChem. with Study in Industry from the University of Sheffield in 2006. As part of his undergraduate education, he completed a year of industrial experience at GSK in Stevenage in the Metabolic and Viral Diseases CEDD. He completed his Ph.D. degree under the supervision of Prof. Joe Harrity at the University of Sheffield (2006–2009) where he developed an alkynylboronate cycloaddition strategy for the synthesis of pyrazole libraries. Duncan is currently an EPSRC funded Doctoral Prize Fellow at the University of Sheffield and is developing new methods for the synthesis of functional (hetero)aromatic molecules.

Joe Harrity is Professor of Organic Chemistry at the University of Sheffield. He received his B.Sc. degree from the University of Strathclyde in 1991 where he remained to undertake his Ph.D. studies (1991–1994) under the guidance of Prof. W.J. Kerr. He carried out postdoctoral studies in Boston College, USA (1994–1997) with Prof. Amir Hoveyda before returning to take up a lectureship in 1997 at the University of Sheffield. His recent research interests have focused on developing new strategies toward carbon–carbon bond forming processes for which he was awarded the Pfizer Discovery Academic Award in 2004, and the AstraZeneca Award in 2006.