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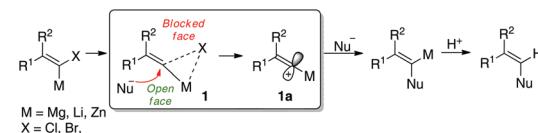
## Introduction

Enediynes are a fascinating class of anti-cancer<sup>1</sup> and antibiotic<sup>2</sup> molecules with a highly unusual chemical structure which has been of interest to synthetic and medicinal chemists for a number of years.<sup>3–5</sup> Their biological mechanism of targeted DNA damage (strand cleavage *via* the Bergman cyclisation)<sup>6</sup> has made the family of natural products to which they belong popular targets for manipulation and functionalisation to improve their drug-like qualities. Many synthetic approaches to enediynes and related compounds however employ toxic and/or expensive protocols based on transition or heavy metals such as tin,<sup>7</sup> copper,<sup>8</sup> palladium,<sup>9</sup> or zinc.<sup>10</sup> Research in our own laboratory has in recent years focused on transition metal free reactions where the benign properties of earth-abundant elements such as lithium,<sup>11</sup> potassium,<sup>12</sup> sodium and sulfur<sup>13</sup> are exploited. In addition, electrophilic vinylidene carbenoids have long been invoked in the preparation of complex molecules and elegant structural work<sup>14a–c</sup> has proposed a structure of an electrophilic, metallated intermediate **1** where the leaving group bridges the carbon atom and the metal and retains the stereochemical information of the starting metallated alkene leading to attack at the opposite face by nucleophiles (outlined in Scheme 1).<sup>14b</sup> In some cases,

## A novel sulfonamide non-classical carbenoid: a mechanistic study for the synthesis of enediynes†

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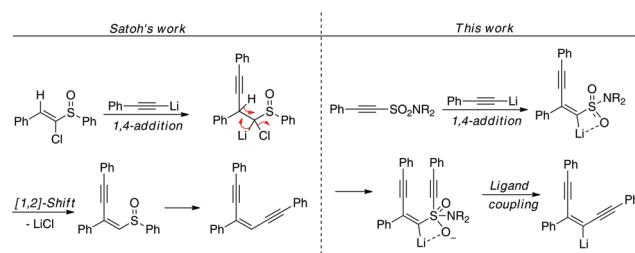
Alkynyl sulfonamides undergo sequential 1,4- then 1,2-addition/rearrangement with lithium acetylides to yield enediynes in the absence of any promoters or catalysts. Mechanistic investigations suggest that the reaction proceeds *via* 1,4-conjugate addition of the nucleophile to the unsaturated system to give a key alkanyl lithium species which is stabilised by an intramolecular coordination effect by a sulfonamide oxygen atom. This species can be considered a vinylidene carbenoid given the carbon atom bears both an anion (as a vinyl lithium) and a leaving group (the sulfonamide). The intramolecular coordination effect serves to stabilise the vinyl lithium but activates the sulfonamide motif towards nucleophilic attack by a second mole of acetylidyde. The resulting species can then undergo rearrangement to yield the enediyne framework in a single operation with concomitant loss of aminosulfinate.



Scheme 1 Classical electrophilic carbenoid model.

full dissociation to give the metallated cationic intermediate **1a** has also been suggested, although the associated model is generally preferred given the preservation of stereochemical information.

We here report a protocol where unsymmetrical enediynes can be prepared *via* simple 1,4-addition of lithium acetylides to alkynyl sulfonamides. At first we considered that the mechanistic pathway would be similar to that described by Satoh, involving a carbenoid intermediate which undergoes a [1,2] shift to yield a diyne product (Scheme 2).<sup>15</sup> However, mechanistic studies have revealed a distinct pathway from



Scheme 2 Comparison of this and previous work.

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other work which allows control of the carbon–carbon bond forming process. In addition, our mechanistic study helps to explain and support other observations in the recent literature.

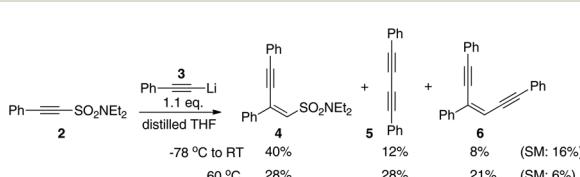
## Results and discussion

In our ongoing investigations into the chemistry of alkynes and organosulfur chemistry, we made the observation that exposure of the unsaturated sulfonamide **2** to a lithium acetylide (*e.g.* **3**) leads to three products; what appears to be the 1,4-addition product **4**, diyne **5** and enediyne **6** (Scheme 3). Furthermore, increasing the temperature of the reaction improves the yield of the diyne and enediyne. Interestingly, both **4** and **6** were isolated as single geometrical isomers. It was also noticed that for enediyne **6**, the incoming nucleophilic alkyne adopts the same configuration as the parent sulfonamide.

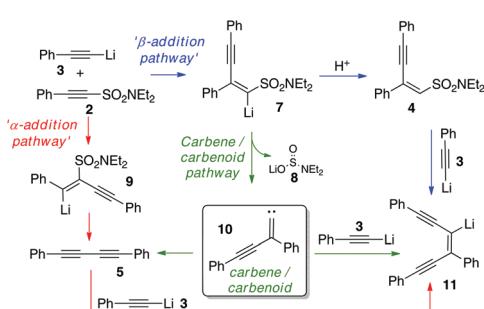
These initial results immediately suggested initial 1,4-addition of the alkyne nucleophile to the conjugated system followed by slower conversion to the products **5** and **6** (*via* carbene/carbenoid pathways with loss of aminosulfinate **8**). At this stage however, we did not know whether **5** and **6** were formed directly from **4** or were the result of other secondary reactions. The various pathways we initially envisaged are outlined in Scheme 4 and we then set out to explore the various possibilities.

We initially wanted to demonstrate that none of the observed products were resulting from nucleophilic addition reactions at sulfur leading to secondary reactions or sulfonyl exchange processes (Scheme 5, which is known for some sulfones<sup>16</sup> but, to our knowledge, have not been described for sulfonamides).

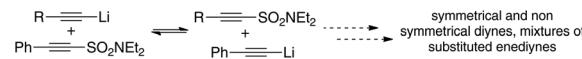
We therefore repeated the reaction with different lithium acetylides. Scheme 6 outlines our results with lithium *m*-meth-



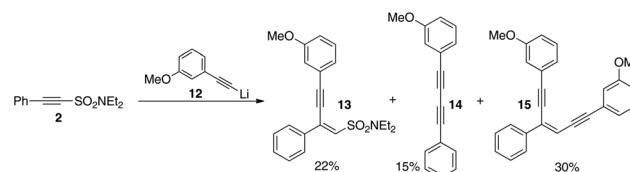
Scheme 3 Initial observations.



Scheme 4 Possible reaction pathways:  $\alpha$ -addition pathway in red,  $\beta$ -addition pathway in blue and the carbenoid pathway in green.



Scheme 5 Potential exchange reactions.



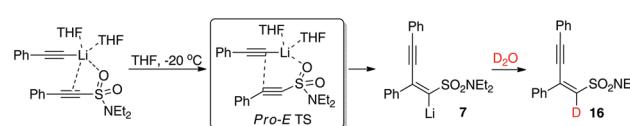
Scheme 6 Non-symmetrical dyynes and enediynes without exchange (both **13** and **15** isolated as pure Z-geometrical isomers).

oxyphenylacetylide with **13**, **14**, and **15** being isolated. No symmetrical dyynes or mixtures of enediynes were observed indicating that sulfonyl exchange is not occurring in this case and gives us confidence that the method will in due course be adaptable to the preparation of various different non-symmetrical analogues.

Satisfied that exchange reactions were not taking place we then proceeded to examine how exactly the various products were formed. Initially we suspected that classical 1,4-addition to the alkynyl sulfonamide led to the intermediate alkenyl-lithium **7** which then was protonated either by adventitious moisture in the reaction mixture or at the work-up stage. The stereochemistry of the addition product (an anti-carbolithiation of the alkynyl sulfonamide) would be expected based on the work of Maddaluno<sup>17</sup> who has studied related systems and noted that carbolithiations of alkynes result in a pro-*E* transition state when the organolithium can coordinate to a substituent on the electrophilic alkyne (Scheme 7). This would explain our observation that only a single geometrical isomer of **4** is formed.

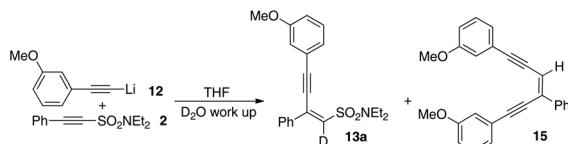
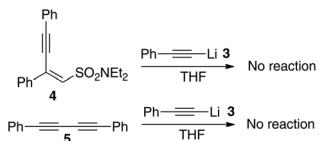
At this stage, we strongly suspected that the enediyne was forming from addition of a second mole of lithium acetylide to **4** or from addition to the diyne **5**. This we tested by isolating both components and exposing them independently to additional lithium acetylide. To our surprise no reaction was observed (Scheme 9). This also suggested to us that a vinylidene carbene might be responsible for the observed reactivity, however all of our attempts to trap such an intermediate (*e.g.* *via* the addition of excess ethyl vinyl ether) failed.

With these preliminary experiments and control reactions in hand we then proceeded to consider the mechanism in more detail. We were first drawn to the incongruous observation outlined in Scheme 8 where work-up of the reaction



Scheme 7 Anti-carbolithiation of **2**.



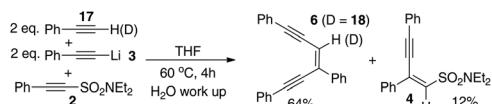
Scheme 8 Deuterium incorporation following *anti*-carbolithiation.

Scheme 9 Ruling out secondary addition reactions.

with  $D_2O$  led to expected isotope incorporation into **13a** but not into enediyne **15**. We reasoned the intermediate 1,4-addition product is relatively stable and exhibits (sluggish) carbénoid behavior at low temperatures only when the reacting partner is highly reactive. The formation of a non-deuterated enediyne was initially more puzzling as *via* our postulated mechanism, this compound would also be expected to be deuterated as the enediyne anion appears to be the end-point for any reaction sequence. As might be expected for the formation of the enediyne, increasing the number of equivalents of the acetylidyne favoured its formation. When four equivalents were employed the yield of the enediyne **6** increases to 53% with an associated drop in the yields of the other two components (16% for **5** and 8% for **4**). Most tellingly however, when a mixture of lithium phenylacetylide (2 eq.) and parent alkyne (2 eq.) were employed, the yield of the enediyne increased dramatically to 64% with only trace amounts of the other components detected (Scheme 10). Crucially, when the deuterated parent alkyne was employed in the same reaction, the deuterium label was identified in the enediyne product **18**.

We therefore reasoned that **7** is moderately stable and can persist in the reaction medium. Its stability is such that it is not protonated by weak proton donors such as phenylacetylene but can survive until the point where the reaction is quenched at the work-up stage. In contrast, the lithiated enediyne is highly reactive and is protonated rapidly even by trace proton sources. The addition of excess phenylacetylene provides a weak proton source that can quench this reactive anion while not interfering with any putative carbénoid or similar precursor.

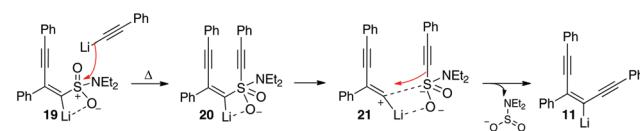
These results prompted us to consider more carefully the precise nature of the reactive intermediate. We first considered that a classic electrophilic carbénoid pathway was operating

Scheme 10 Initial mechanistic studies *via* deuterium incorporation.

(such as that outlined in Scheme 1) where the incoming nucleophile adopts the stereochemistry of the metal in the carbénoid intermediate (Scheme 1). By contrast, in our systems, the nucleophile adopts the opposite stereochemistry (Schemes 3 and 6) suggesting that a pathway distinct from both the classical carbénoid and free carbene mechanisms is in operation.

Given that the reactive intermediate in our reaction appears to exhibit no classical carbene (carbénoid) behavior, and no products of the Fritsch–Weichell–Buttenberg (FWB) rearrangement have been observed in these systems (in this or our related work) we were initially puzzled as to how the mechanistic pathway might be operating. We briefly considered a structure where the sulfonyl group fully dissociates to leave a lithiated vinyl cation (again, invoked in much of the early work on carbénoids, Scheme 1, compound **1a**).<sup>14a–c</sup> Such intermediates however are known to rapidly undergo intramolecular FWB rearrangements even at low temperatures. Similarly, competitive intermolecular addition with the FWB rearrangement was reasoned to be highly unlikely, particularly given the reaction times and elevated temperatures required to maximize the conversion to the enediyne. As such, we have suggested that the sulfonyl group must stay associated with the lithiated alkene prior to the attack of the nucleophile and therefore inhibit the classical carbene/carbénoid behavior that might be expected with superior leaving groups. Since the reaction proceeds with retention of stereochemistry with respect to the sulfonyl group (unusually for sulfonamides) initially attacks the sulfur atom (structures **19** and **20**, Scheme 11). As the temperature increases, weakening of the C–S bond then allows the alkyne nucleophile to be delivered to the cationic carbon atom (structure **21**) and in doing so the stereochemistry of the alkene is preserved. We also considered that a coordination effect by the adjacent lithium atom might assist in promoting the nucleophilic attack at sulfur.

Further support for a process following this route was found when first-principles molecular dynamics simulations were performed. These suggested that the C–S bond in compound **19** was extremely robust, varying from  $1.73 \text{ \AA} \pm 0.12 \text{ \AA}$  over a 5000 fs run at 350 K. It is therefore highly unlikely to spontaneously cleave to yield a metallated cationic intermediate such as **1a**. This data, combined with our other observations would suggest a pathway where the sulfur atom directs the incoming nucleophile to obtain the observed enediyne product is more likely. Such a pathway would also support recent literature observations where phosphonium salts have been employed in a similar fashion; specifically the ‘attack@P’

Scheme 11 Cooperative reactivity *via* nucleophilic attack at sulfur.

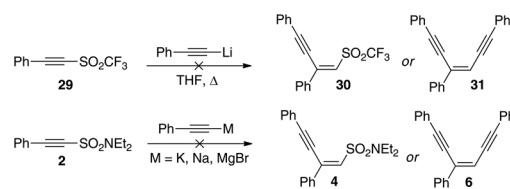
mechanism proposed by Radosevich where an alkynyl phosphonium was employed with a lithium acetylidyne to give enediynes.<sup>18</sup>

In light of the fact that we had established that **4** did not react with lithium acetylides, we realized that our hypothesis could be tested if **4** could be lithiated independently. As such a sample of **4** was independently exposed to one equivalent of lithium tetramethylpiperidine in order to form **7**. This was then exposed to the anion derived from phenylacetylene followed by aqueous work-up. This resulted in the enediyne **6** in moderate yield, the remainder of the mixture being recovered starting material (Scheme 12). In addition to this,  $\beta$ -diphenyldiethylvinyl sulfonamide **23** could also be lithiated with lithium tetramethylpiperidine (LiTMP) and reacts with lithium phenylacetylidyne to give the enyne **24** in good yield (Scheme 13).

Furthermore, we were able to demonstrate the basic character of the intermediate vinyl lithium by preparing the 2-methylphenylacetylinic sulfonamide **25** as depicted in Scheme 14. Exposure of this material to lithium phenylacetylidyne **3** in the same manner as previously would necessarily allow the labile C–H bonds of the benzylic methyl group to come into close contact with the carbenoid centre **26**.

A reactive intermediate exhibiting classical carbene reactivity would be expected to undergo (at least in part) C–H insertion reactions to yield cyclic products. In fact, no cyclic or enediyne products were observed. The major product of the reaction was the monoaddition product which presumably results from initial 1,4-addition (*via* the pro-E TS) to give the vinyl lithium which is then rapidly protonated by the pendant benzylic CH<sub>3</sub> group yielding the benzylic anion **27**. Protonation on work-up then yields the observed product **28**.

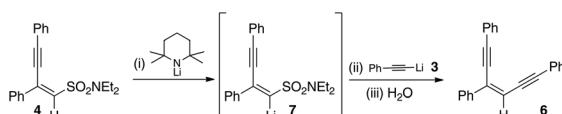
At this juncture, we were curious as to the effect the sulfonamide motif was having on this reaction and whether other sulfonyl acetylenes would participate in similar reactions. We were also interested to see if other metal cations might



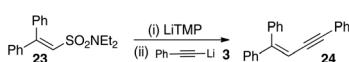
**Scheme 15** Unreactivity of other sulfonyl species and other metal cations.

promote or attenuate the reaction. As the sulfonamide unit is well-known as only weakly activating in 1,4-addition reactions,<sup>19</sup> we reasoned that replacing this unit with the trifluoromethanesulfonyl moiety would result in a more facile reaction. To our surprise, heating the alkynyl trifluoromethylsulfone **29** (as shown in Scheme 15) with lithium phenylacetylidyne resulted in none of compounds **30** or **31** being produced, even with extended reaction times and elevated temperatures. Only the starting compound **29** was recovered. Considering that the triflyl group is one of the most powerfully electron withdrawing group commonly employed in organic synthesis, this was somewhat unexpected. Similarly, generating the magnesium, sodium or potassium salts of the acetylidyne and reacting with **2** also resulted in no reaction occurring with the persistence of starting materials even after several hours at elevated temperatures (60 °C) (Scheme 12).

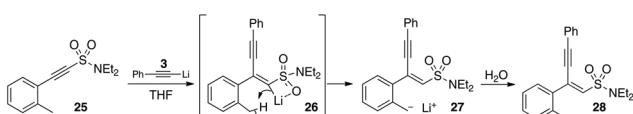
These unexpected results have led us to conclude that a unique combination of the properties of the lithium cation and the sulfonamide motif were allowing this unusual reactivity to occur. We therefore turned to computational methods to assist us in understanding the reactivity of the intermediate vinyl sulfonyl lithium species as the precursor to the carbene. Quantum chemical density functional based approaches suggested that when the cation is lithium there is a strong interaction between the metal ion and the sulfonyl group oxygen(s) with bond lengths of *ca.* 2 Å for both the Li–O and Li–C bonds (Li–C was calculated to have a bond distance of 1.99 Å, Li–O 1.90 Å). We reason that this interaction, facilitated by the small size of the lithium ion and high effective charge density, stabilizes the initial addition product, favouring the equilibrium to a degree that would not be expected simply by considering the relative stability of the alkenyl and acetylinic anions (Scheme 16, Fig. 1). Presumably, the sulfonamide nitrogen atom serves to increase the electron density on the oxygen atoms, strengthening the Li–O interaction compared to other sulfonyl systems. This four-membered coordination complex is strongly reminiscent of the structures proposed by Biellmann,<sup>20</sup> Durst,<sup>21</sup> and Chassaing and Marquet<sup>22</sup> in their studies on



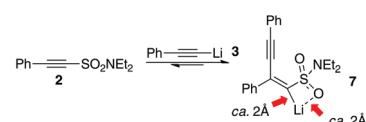
**Scheme 12** Independent lithiation and reaction of **7**.



**Scheme 13** Alternative substrate.

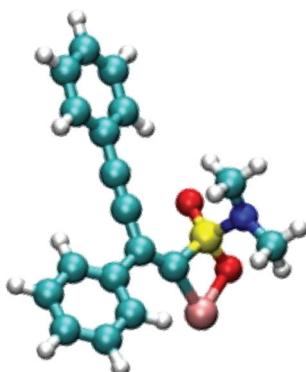


**Scheme 14** Basicity of the carbenoid centre.



**Scheme 16** Proposed stabilised vinyl lithium intermediate indicating the close interaction of carbon, lithium and oxygen atoms.



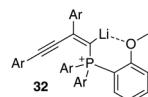


**Fig. 1** Minimum energy configuration of the proposed intermediate (the dimethylamino sulfonamide was used for the MD calculations). Lithium is displayed in pink, oxygen in red, sulfur in yellow, nitrogen in blue, carbon in cyan and hydrogen in white.

lithiated sulfoxides; although their work focused on subsequent reactions with electrophiles. When the alkynyl triflone is employed, the significant electron withdrawing effect of the  $\text{CF}_3$  group appears to lower the electron density on oxygen which is likely to disrupt the Li–O interaction.

The model here exhibits a distinct mode of reactivity when compared to the classical carbenoid systems described by Schleyer and others.<sup>14a–c</sup> The unique cooperativity between the lithium atom and sulfonamide group which essentially results in the displacement of a (relatively poor) leaving group at an  $\text{sp}^2$  centre is brought about by a threefold combination of properties: (i) Li–sulfonamide coordination facilitating the initial 1,4-addition reaction giving a geometrically defined addition product as depicted in Scheme 7 (ii) the formation of a sulfonamide–Li coordination complex, favouring the equilibrium shown in Scheme 16 by stabilising the addition product and (iii) activation of the sulfonyl group to nucleophilic attack by intramolecular coordination in a Lewis-acid manner as outlined in Scheme 11. As an additional note, it has occurred to us that such a coordinating effect may explain why  $\text{PPh}(o\text{-An})_2$  proved to be a superior mediator compared to other phosphines in Radosevich's synthesis<sup>18</sup> of enediynes since an additional coordination effect is available to stabilise the initial 1,4-addition product (32, Fig. 2).

Although focusing on the synthesis of enediynes we were also keen to understand the mechanism by which the minor diyne products were being formed. In addition, having invoked a carbenoid intermediate we were aware that diyne 6 could be formed by intramolecular 1,2-FWB rearrangements and we therefore chose to explore this further.



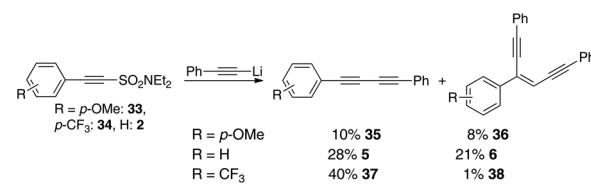
**Fig. 2** Potential stabilising effect of *o*-anisyl group in the synthesis of enediynes.

In considering the likelihood of a 1,2-FWB type rearrangement in these systems we first had to consider the relative migratory aptitude of the aryl group compared to the alkyne. Fortunately, Tykwinski *et al.* have demonstrated that the migratory aptitude of alkynes in FWB rearrangements is poor in coordinating solvents.<sup>23</sup> We therefore concluded that any FWB rearrangement would most likely involve migration of the aryl group and we prepared three substrates to examine any putative rearrangements occurring. By altering the electron demand of the aryl substituent we hoped to gain some insight as to whether a 1,2-rearrangement was competing with enediyne formation. The results are outlined in Scheme 17.

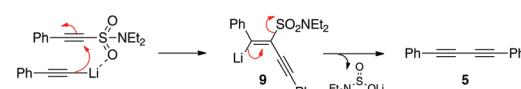
Clearly, increasing the electron withdrawing capability of the aromatic ring on the sulfonamide increases the proportion of diyne formed. This observation is exactly the opposite of what would be expected if a FWB rearrangement were operating. This leads us to conclude that the diyne product is most likely formed by simple 1,3-addition to the unsaturated sulfonamide, again, directed by the strong coordinating effect of the sulfonamide oxygen atoms (Scheme 18).

Such an addition with a strong coordinating effect will almost certainly yield the *trans* lithiated sulfonamide which will rapidly eliminate due to the favourable orbital overlap. This is in sharp contrast to our other work<sup>24</sup> where less coordinating cations lead to *cis* anions where the elimination is much slower and consequently the anion can be trapped prior to elimination. The 1,3-addition–elimination reaction of nucleophiles with alkynyl sulfonyl compounds has been well documented for both carbon nucleophiles (Truce, Ruano)<sup>25,26</sup> and heteroatoms (our previous work)<sup>24</sup> however it is interesting to see that the propensity for this reaction with alkynes is much lower than for other carbon nucleophiles as these have not been reported either by Ruano or Truce's original paper where sulfones have been employed.

As a final note, it is clear that we have only presented diethyl sulfonamides as reactive partners in this study. We have also explored similar reactions with different amino groups attached to sulfur. Although we predicted that increasing the electron withdrawing capacity of the groups attached to nitrogen would facilitate the reaction by improving the



**Scheme 17** Competing reaction investigation.



**Scheme 18** Competing addition–elimination pathway.

group's ability to dissociate, in fact we found very little correlation on the efficiency of the reaction over a wide range of sulfonamides prepared from different amines (morpholine, *N,O*-dimethylhydroxylamine, piperidine). At the present time it is unclear to us why this is the case. Perhaps only a small increase in electron density on the sulfonyl oxygen atoms is required to 'switch on' the observed reactivity which can be provided by many amines, even less nucleophilic variants.

## Conclusions

This preliminary study has uncovered some fascinating aspects of the reactivity of vinyl sulfonamides and how they might be exploited in synthesis. The reactive intermediates in this work present a new class of carbenoid distinct from those described previously with a unique reactivity profile mediated by the pendant sulfonamide motif. Most remarkably, this reactivity manifests itself in a sulfonamide group behaving as a leaving group at an  $sp^2$  centre only when the carbon atom to which it is attached has been deprotonated. Both of these observations are counterintuitive in fundamental organic chemistry. Furthermore, our mechanistic work also helps to support and understand other observations with alternative p-block species that have recently been disclosed in the literature.<sup>14,17</sup> Although our work has focused on simultaneous 1,4-addition of alkynyl nucleophiles to alkynyl sulfonamides, we recognize that the scope for exploiting this new class of tamed carbenoid is vast and research is already underway in our laboratory to optimize its formation and explore its applications.

## Experimental

### General procedure for the treatment of alkynyl sulfonamides with aromatic acetylene to produce vinylsulfonamides, diynes and enediynes

A 100 mL flame-dried flask was charged with a solution of aromatic acetylene (1.1 eq.) in distilled THF (0.01 M) under argon. The solution was cooled to 0 °C and *n*BuLi (2.5 M in hexanes, 1.1 eq.) was added dropwise. The mixture was allowed to warm to RT and stirred for a further 10 min. An additional, 100 mL flame-dried flask was charged with a solution of alkynyl sulfonamide (0.15–0.2 mmol, 1.0 eq.) in distilled THF (0.1 M) under argon. The solution was heated to 60 °C and the previously formed lithiated aromatic acetylene solution was added dropwise (addition rate of 0.0025 mmol min<sup>-1</sup>) with constant stirring. The reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (200 mL), washed with H<sub>2</sub>O (100 mL) then brine (100 mL), dried over MgSO<sub>4</sub> and concentrated *in vacuo* to yield the crude mixture. Separation *via* flash column chromatography (petroleum ether/ethyl acetate) was carried out to yield the purified products.

### (Z)-*N,N*-Diethyl-2,4-diphenylbut-1-en-3-yne-1-sulfonamide (4)

Yellow oil.  $R_f$  = 0.30 (20 : 80 EA : PE); <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$ <sub>H</sub> 7.72 (m, 2 H, ArH), 7.62 (m, 2 H, ArH), 7.44 (m, 3 H,

ArH), 7.39 (m, 3 H, ArH), 6.88 (s, 1 H, C=CH), 3.43 (q,  $J$  = 7.2 Hz, 4 H, NCH<sub>2</sub>), 1.24 (t,  $J$  = 7.6 Hz, 6 H, NCH<sub>2</sub>CH<sub>3</sub>); <sup>13</sup>C-NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$ <sub>C</sub> 136.2 (C<sub>q</sub>), 132.7 (CH), 132.2 (CH), 131.1 (C<sub>q</sub>), 130.3 (CH), 129.7 (CH), 128.9 (CH), 128.6 (CH), 127.2 (CH), 122.3 (C<sub>q</sub>), 103.6 (C<sub>q</sub>), 84.9 (C<sub>q</sub>), 41.9 (CH<sub>2</sub>), 14.5 (CH<sub>3</sub>);  $\nu_{max}/cm^{-1}$  3059, 2973, 2929, 2874, 2252, 2211, 1730, 1680, 1598, 1555, 1489, 1444, 1334, 1266, 1200, 1183, 1145, 1017, 934, 910, 815, 758, 735, 692, 648, 653; LRMS (ESI+) *m/z* (%) 868 (2), 763 (1), 701 (100), 644 (1), 460 (2), 340 (58), 267 (1); HRMS (ESI+) calc'd for C<sub>20</sub>H<sub>22</sub>NO<sub>2</sub>S (M + H)<sup>+</sup> 340.1366, found 340.1370.

### 1,4-Diphenylbuta-1,3-diyne (5)

White solid. M.p. 83–87 °C;  $R_f$  = 0.57 (20 : 80 EA : PE); <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$ <sub>H</sub> 7.54 (d,  $J$  = 7.6 Hz, 4 H, ArH), 7.36 (m, 6 H, ArH); <sup>13</sup>C-NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$ <sub>C</sub> 132.6 (CH), 129.3 (CH), 128.6 (CH), 121.9 (C<sub>q</sub>), 81.6 (C<sub>q</sub>), 74.0 (C<sub>q</sub>);  $\nu_{max}/cm^{-1}$  3047, 2148, 1949, 1879, 1750, 1667, 1591, 1568, 1483, 1438, 1175, 1156, 1066, 1023, 997, 964, 914, 848, 825, 751, 682, 523, 462; LRMS (EI) *m/z* (%) 204 (3), 203 (9), 202 (100), 200 (17), 150 (3), 101 (6); HRMS (EI) calc'd for C<sub>16</sub>H<sub>10</sub> (M<sup>+</sup>) 202.0777, found 202.0780.

### (Z)-Hexa-3-en-1,5-diyne-1,3,6-triyltribenzene (6)

Brown oil.  $R_f$  = 0.56 (20 : 80 EA : PE); <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$ <sub>H</sub> 7.75 (d,  $J$  = 7.5 Hz, 2 H, ArH), 7.61 (m, 2 H, ArH), 7.54 (m, 2 H, ArH), 7.41 (t,  $J$  = 7.5 Hz, 2 H, ArH), 7.36 (m, 7 H, ArH), 6.58 (s, 1 H, C=CH); <sup>13</sup>C-NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$ <sub>C</sub> 136.9 (C<sub>q</sub>), 133.5 (CH), 131.9 (CH), 131.7 (CH), 128.9 (CH), 128.8 (CH), 128.7 (CH), 128.6 (CH), 128.5 (CH), 128.5 (CH), 126.2 (CH), 123.5 (C<sub>q</sub>), 123.2 (C<sub>q</sub>), 113.7 (C<sub>q</sub>), 98.5 (C<sub>q</sub>), 98.4 (C<sub>q</sub>), 89.1 (C<sub>q</sub>), 87.7 (C<sub>q</sub>);  $\nu_{max}/cm^{-1}$  3058, 3031, 2920, 2847, 2198, 2171, 1719, 1676, 1596, 1488, 1443, 1362, 1176, 1069, 914, 843, 756, 690, 529; LRMS (EI) *m/z* (%) 305 (23), 304 (100), 302 (44), 300 (14), 276 (4), 226 (6), 202 (5), 178 (4), 150 (5); HRMS (EI) calc'd for C<sub>24</sub>H<sub>16</sub> (M<sup>+</sup>) 304.1247, found 304.1246.

### (Z)-*N,N*-Diethyl-4-(3-methoxyphenyl)-2-phenylbut-1-en-3-yne-1-sulfonamide (13)

Yellow oil.  $R_f$  = 0.24 (20 : 80 EA : PE); <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$ <sub>H</sub> 7.71 (m, 2 H, ArH), 7.44 (m, 3 H, ArH), 7.29 (t,  $J$  = 7.8 Hz, 1 H, ArH), 7.21 (d,  $J$  = 7.6 Hz, 1 H, ArH), 7.13 (m, 1 H, ArH), 6.96 (m, 1 H, ArH), 6.88 (s, 1 H, C=CH), 3.83 (s, 3 H, CH<sub>3</sub>), 3.42 (q,  $J$  = 7.2 Hz, 4 H, NCH<sub>2</sub>), 1.23 (t,  $J$  = 7.1 Hz, 6 H, NCH<sub>2</sub>CH<sub>3</sub>); <sup>13</sup>C-NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$ <sub>C</sub> 159.5 (C<sub>q</sub>), 136.1 (C<sub>q</sub>), 132.6 (C<sub>q</sub>), 131.2 (CH), 130.3 (CH), 129.7 (CH), 128.9 (CH), 127.2 (CH), 124.7 (CH), 123.2 (C<sub>q</sub>), 116.7 (CH), 116.4 (CH), 103.5 (C<sub>q</sub>), 84.6 (C<sub>q</sub>), 55.5 (CH<sub>3</sub>), 41.9 (CH<sub>2</sub>), 14.5 (CH<sub>3</sub>);  $\nu_{max}/cm^{-1}$  3063, 2928, 2872, 2853, 2204, 1727, 1668, 1596, 1486, 1464, 1429, 1324, 1286, 1262, 1201, 1143, 1040, 1017, 937, 782, 757, 686, 561, 522, 461; LRMS (ESI+) *m/z* (%) 371 (5), 370 (100); HRMS (ESI+) calc'd for (C<sub>21</sub>H<sub>24</sub>NO<sub>3</sub>S) (M + H)<sup>+</sup> 370.1477, found 370.1479.

### 1-Methoxy-3-(phenylbuta-1,3-diy-1-yl)benzene (14)

Yellow oil.  $R_f$  = 0.50 (20 : 80 EA : PE); <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$ <sub>H</sub> 7.53 (dt,  $J$  = 6.5, 1.7 Hz, 2 H, ArH), 7.35 (m, 3 H,



ArH), 7.25 (m, 1 H, ArH), 7.13 (m, 1 H, ArH), 7.05 (s, 1 H, ArH), 6.93 (m, 1 H, ArH), 3.81 (s, 3 H,  $\text{CH}_3$ );  $^{13}\text{C}$ -NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta_c$  159.3 (C<sub>q</sub>), 132.6 (CH), 129.6 (CH), 129.3 (CH), 128.5 (CH), 125.2 (CH), 122.8 (C<sub>q</sub>), 121.8 (C<sub>q</sub>), 117.1 (CH), 116.1 (CH), 83.7 (C<sub>q</sub>), 81.5 (C<sub>q</sub>), 73.9 (C<sub>q</sub>), 73.8 (C<sub>q</sub>), 55.4 (CH<sub>3</sub>);  $\nu_{\text{max}}/\text{cm}^{-1}$  3060, 2998, 2956, 2924, 2851, 2217, 2189, 2145, 1727, 1670, 1592, 1573, 1485, 1463, 1425, 1342, 1315, 1284, 1251, 1168, 1081, 1042, 993, 916, 870, 855, 780, 755, 685, 580, 563, 526, 467; LRMS (CI)  $m/z$  (%) 252 (6), 251 (14), 250 (100), 232 (9); HRMS (CI) calc'd for  $\text{C}_{17}\text{H}_{12}\text{O}$  (M<sup>+</sup>) 232.0883, found 232.0884.

**(Z)-3,3'-(3-Phenylhexa-3-en-1,5-diyne-1,6-diyi)bis(methoxybenzene) (15)**

Yellow oil (4.3 mg).  $R_f$  = 0.34 (20 : 80 EA : PE);  $^1\text{H}$ -NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta_H$  7.74 (d,  $J$  = 7.3 Hz, 2 H, ArH), 7.40 (m, 4 H, ArH), 7.23 (t,  $J$  = 7.8 Hz, 2 H, ArH), 7.14 (m, 2 H, ArH), 7.07 (m, 1 H, ArH), 6.91 (m, 2 H, ArH), 6.57 (s, 1 H, C=CH), 3.79 (s, 3 H, CH<sub>3</sub>), 3.77 (s, 3 H, CH<sub>3</sub>);  $^{13}\text{C}$ -NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta_c$  159.4 (C<sub>q</sub>), 159.4 (C<sub>q</sub>), 138.6 (C<sub>q</sub>), 133.7 (C<sub>q</sub>), 129.6 (CH), 129.5 (CH), 129.0 (CH), 128.7 (CH), 126.2 (CH), 124.4 (C<sub>q</sub>), 124.3 (C<sub>q</sub>), 124.1 (CH), 116.4 (CH), 116.2 (CH), 115.6 (CH), 115.5 (CH), 113.8 (CH), 98.4 (C<sub>q</sub>), 96.4 (C<sub>q</sub>), 95.2 (C<sub>q</sub>), 88.7 (C<sub>q</sub>), 55.4 (CH<sub>3</sub>), 55.3 (CH<sub>3</sub>);  $\nu_{\text{max}}/\text{cm}^{-1}$  3061, 3002, 2958, 2922, 2849, 2835, 2200, 2189, 1724, 1685, 1595, 1575, 1486, 1463, 1450, 1428, 1318, 1285, 1263, 1211, 1175, 1040, 855, 781, 761, 737, 686, 565, 518, 468; LRMS (CI)  $m/z$  (%) 383 (3), 382 (12), 367 (14), 366 (24), 365 (100); HRMS (CI) calc'd for  $\text{C}_{26}\text{H}_{21}\text{O}_2$  (M + H)<sup>+</sup> 365.1536, found 365.1537.

**(E)-N,N-Diethyl-4-phenyl-2-(*o*-tolyl)but-1-en-3-yne-1-sulfonamide (28)**

Colourless oil.  $R_f$  = 0.31 (20 : 80 EA : PE);  $^1\text{H}$ -NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta_H$  7.52 (d,  $J$  = 7.1 Hz, 2 H, ArH), 7.35 (m, 3 H, ArH), 7.30 (m, 1 H, ArH), 7.26 (m, 3 H, ArH), 6.48 (s, 1 H, C=CH), 3.43 (q,  $J$  = 7.2 Hz, 4 H, NCH<sub>2</sub>), 2.49 (s, 3 H, ArCH<sub>3</sub>), 1.26 (t,  $J$  = 7.1 Hz, 6 H, NCH<sub>2</sub>CH<sub>3</sub>);  $^{13}\text{C}$ -NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta_c$  137.6 (C<sub>q</sub>), 135.7 (C<sub>q</sub>), 134.6 (CH), 133.7 (C<sub>q</sub>), 132.2 (CH), 131.0 (CH), 129.6 (CH), 129.2 (CH), 128.6 (CH), 128.5 (CH), 126.4 (CH), 122.4 (C<sub>q</sub>), 104.1 (C<sub>q</sub>), 85.4 (C<sub>q</sub>), 41.9 (CH<sub>2</sub>), 20.3 (CH<sub>3</sub>), 14.6 (CH<sub>3</sub>);  $\nu_{\text{max}}/\text{cm}^{-1}$  3048, 2972, 2933, 2873, 2207, 1598, 1562, 1488, 1456, 1443, 1382, 1352, 1332, 1199, 1142, 1069, 1048, 1015, 994, 932, 879, 826, 755, 724, 688, 569, 555, 529, 507, 462, 429; LRMS (ES<sup>+</sup>)  $m/z$  (%) 408 (3), 378 (3), 377 (12), 376 (45), 356 (9), 355 (27), 354 (100); HRMS (ES<sup>+</sup>) calc'd for  $\text{C}_{21}\text{H}_{24}\text{NO}_2\text{S}$  (M + H)<sup>+</sup> 354.1528, found 354.1507.

**1-Methoxy-4-(phenylbuta-1,3-diyi)benzene (35)**

Colourless oil.  $R_f$  = 0.49 (20 : 80 EA : PE);  $^1\text{H}$ -NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta_H$  7.53 (d,  $J$  = 6.6 Hz, 2 H, ArH), 7.48 (d,  $J$  = 8.6 Hz, 2 H, ArH), 7.35 (m, 3 H, ArH), 6.87 (d,  $J$  = 8.7 Hz, 2 H, ArH), 3.83 (s, 3 H, OCH<sub>3</sub>);  $^{13}\text{C}$ -NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta_c$  160.5 (C<sub>q</sub>), 134.3 (CH), 132.6 (CH), 129.2 (CH), 128.5 (CH), 122.1 (C<sub>q</sub>), 114.3 (CH), 113.8 (C<sub>q</sub>), 81.9 (C<sub>q</sub>), 81.1 (C<sub>q</sub>), 74.3 (C<sub>q</sub>), 72.8 (C<sub>q</sub>), 55.5 (CH<sub>3</sub>);  $\nu_{\text{max}}/\text{cm}^{-1}$  3074, 2953, 2923, 2842, 2541, 2216, 2139, 1887, 1759, 1599, 1566, 1506, 1487, 1457, 1439, 1344,

1290, 1246, 1170, 1106, 1070, 1026, 952, 939, 918, 827, 757, 732, 689, 643, 616, 532, 491, 443; LRMS (CI)  $m/z$  (%) 251 (19), 250 (100), 234 (12), 233 (62); HRMS (CI) calc'd for  $\text{C}_{17}\text{H}_{13}\text{O}$  (M + H)<sup>+</sup> 233.0961, found 233.0960.

**(Z)-(3-(4-Methoxyphenyl)hexa-3-en-1,5-diyne-1,6-diyi)dibenzene (36)**

Brown oil.  $R_f$  = 0.44 (20 : 80 EA : PE);  $^1\text{H}$ -NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta_H$  7.70 (d,  $J$  = 8.6 Hz, 2 H, ArH), 7.61 (m, 2 H, ArH), 7.53 (m, 2 H, ArH), 7.38 (m, 3 H, ArH), 7.34 (m, 3 H, ArH), 6.94 (d,  $J$  = 8.7 Hz, 2 H, ArH), 6.48 (s, 1 H, C=CH), 3.86 (s, 3 H, OCH<sub>3</sub>);  $^{13}\text{C}$ -NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta_c$  160.4 (C<sub>q</sub>), 133.0 (C<sub>q</sub>), 131.9 (CH), 131.7 (CH), 129.5 (C<sub>q</sub>), 128.8 (CH), 128.6 (CH), 128.5 (CH), 128.5 (CH), 127.6 (CH), 123.7 (C<sub>q</sub>), 123.3 (C<sub>q</sub>), 114.1 (CH), 111.7 (CH), 98.2 (C<sub>q</sub>), 97.9 (C<sub>q</sub>), 89.4 (C<sub>q</sub>), 87.8 (C<sub>q</sub>), 55.5 (CH<sub>3</sub>);  $\nu_{\text{max}}/\text{cm}^{-1}$  3052, 2954, 2926, 2836, 2199, 2179, 1880, 1726, 1669, 1603, 1577, 1509, 1487, 1460, 1441, 1362, 1304, 1287, 1250, 1177, 1114, 1068, 1030, 913, 823, 754, 689, 605, 527, 448; LRMS (CI)  $m/z$  (%) 336 (27), 335 (100); HRMS (CI) calc'd for  $\text{C}_{25}\text{H}_{19}\text{O}$  (M + H)<sup>+</sup> 335.1430, found 335.1431.

**1-Phenylbuta-1,3-diyi-4-(trifluoromethyl)benzene (37)**

Colourless oil.  $R_f$  = 0.66 (20 : 80 EA : PE);  $^1\text{H}$ -NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta_H$  7.55 (d,  $J$  = 7.0 Hz, 2 H, ArH), 7.63 (m, 7 H, ArH);  $^{13}\text{C}$ -NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta_c$  132.8 (CH), 132.7 (CH), 130.9 (q,  $J$  = 33.1 Hz, C<sub>q</sub>), 129.7 (CH), 128.6 (CH), 125.8 (C<sub>q</sub>), 125.5 (q,  $J$  = 3.8 Hz, CH), 123.9 (q,  $J$  = 272.6 Hz, C<sub>q</sub>), 121.5 (C<sub>q</sub>), 83.0 (C<sub>q</sub>), 79.9 (C<sub>q</sub>), 76.3 (C<sub>q</sub>), 73.5 (C<sub>q</sub>);  $\nu_{\text{max}}/\text{cm}^{-1}$  2955, 2924, 2853, 2256, 2213, 1916, 1796, 1667, 1612, 1570, 1488, 1462, 1443, 1405, 1317, 1167, 1104, 1064, 1012, 912, 834, 753, 686, 593, 519; LRMS (CI)  $m/z$  (%) 540 (8), 371 (11), 370 (44), 342 (9), 288 (5), 271 (19), 270 (100), 260 (10), 221 (8).

**(Z)-(3-(4-(Trifluoromethyl)phenyl)hexa-3-en-1,5-diyi)dibenzene (38)**

Yellow oil.  $R_f$  = 0.57 (20 : 80 EA : PE);  $^1\text{H}$ -NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta_H$  7.85 (d,  $J$  = 8.2 Hz, 2 H, ArH), 7.67 (d,  $J$  = 8.2 Hz, 2 H, ArH), 7.61 (m, 2 H, ArH), 7.55 (m, 2 H, ArH), 7.40 (m, 3 H, ArH), 7.37 (m, 3 H, ArH), 6.64 (s, 1 H, C=CH);  $^{13}\text{C}$ -NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta_c$  132.1 (C<sub>q</sub>), 131.9 (CH), 131.8 (CH), 131.7 (CH), 130.3 (q,  $J$  = 31.4 Hz, C<sub>q</sub>), 129.1 (CH), 129.0 (CH), 128.6 (CH), 128.6 (CH), 125.7 (q,  $J$  = 3.4 Hz, CH), 125.0 (C<sub>q</sub>), 124.1 (q,  $J$  = 273.6 Hz, C<sub>q</sub>), 123.2 (C<sub>q</sub>), 116.1 (C<sub>q</sub>), 99.9 (C<sub>q</sub>), 99.1 (C<sub>q</sub>), 88.7 (C<sub>q</sub>), 87.0 (C<sub>q</sub>);  $\nu_{\text{max}}/\text{cm}^{-1}$  3079, 3060, 3023, 2954, 2923, 2853, 2183, 1632, 1616, 1597, 1490, 1461, 1443, 1410, 1377, 1324, 1167, 1125, 1069, 1016, 914, 843, 831, 755, 689, 620, 605, 529; LRMS (CI)  $m/z$  (%) 392 (3), 391 (11), 390 (33), 378 (5), 375 (8), 374 (28), 373 (100), 372 (12), 370 (5), 353 (4), 350 (9), 345 (26), 322 (9); HRMS (CI) calc'd for  $\text{C}_{25}\text{H}_{16}\text{F}_3$  (M + H)<sup>+</sup> 373.1199, found 373.1199.

**Conflicts of interest**

There are no conflicts to declare.



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## Notes and references

- 1 A. L. Smith and K. C. Nicolaou, *J. Med. Chem.*, 1996, **39**, 2103–2117.
- 2 M. Gredičak and I. Jerić, *Acta Pharm.*, 2007, **57**, 133–150.
- 3 (a) K. C. Nicolaou, G. Zuccarello, C. Riemer, V. A. Estevez and W. M. Dai, *J. Am. Chem. Soc.*, 1992, **114**, 7360–7371; (b) K. C. Nicolaou and W. M. Dai, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 1387–1416.
- 4 P. A. Magriotis, M. E. Scott and K. D. Kim, *Tetrahedron Lett.*, 1991, **32**, 6085–6088.
- 5 K. C. Nicolaou, Y. Wang, M. Lu, D. Mandal, M. R. Pattanayak, R. Yu, A. A. Shah, J. S. Chen, H. Zhang, J. J. Crawford, L. Pasunoori, Y. B. Poudel, N. S. Chowdari, C. Pan, A. Nazeer, S. Gangwar, G. Vite and E. N. Pitsinos, *J. Am. Chem. Soc.*, 2016, **138**, 8235–8246.
- 6 K. C. Nicolaou, A. L. Smith and E. W. Yue, *Proc. Natl. Acad. Sci. U. S. A.*, 1993, **90**, 5881–5888.
- 7 Z. Wang and K. K. Wan, *J. Org. Chem.*, 1994, **59**, 4738–4742.
- 8 J. H. Ryan and P. J. Stang, *J. Org. Chem.*, 1996, **61**, 6162–6165.
- 9 There are many examples of Pd catalyzed synthetic approaches. For recent examples see: (a) G. W. Kabalka, G. Dong and B. Venkataiah, *Tetrahedron Lett.*, 2005, **46**, 763–765; (b) Y. Liu and H. Gao, *Org. Lett.*, 2006, **8**, 309–311.
- 10 M. J. Dabdoub, V. B. Dabdoub and J. P. Marino, *Tetrahedron Lett.*, 2000, **41**, 437–440.
- 11 J. Cuthbertson and J. D. Wilden, *Tetrahedron*, 2015, **71**, 4385–4392.
- 12 R. M. Chowdhury and J. D. Wilden, *Org. Biomol. Chem.*, 2015, **13**, 5859–5861.
- 13 V. J. Gray, J. Cuthbertson and J. D. Wilden, *Chem. Commun.*, 2014, **79**, 5869–5874.
- 14 (a) A. Maercker, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 1023–1025; (b) P. v. R. Schleyer, T. Clark, A. J. Kos, G. W. Spitznagel, C. Rohde, D. Arad, K. N. Houk and N. G. Rondan, *J. Am. Chem. Soc.*, 1984, **106**, 6467–6475; (c) M. Braun, *Angew. Chem., Int. Ed.*, 1998, **37**, 430–451.
- 15 T. Kimura, Y. Nishimura, N. Ishida, H. Momochi, H. Yamashita and T. Satoh, *Tetrahedron Lett.*, 2013, **54**, 1049–1051.
- 16 T. S. Chou and L. J. Chang, *J. Org. Chem.*, 1985, **50**, 4998–5000.
- 17 C. Freesigné, R. Lhermet, A.-L. Girard, M. Durandetti and J. Maddaluno, *J. Org. Chem.*, 2013, **78**, 9659–9669.
- 18 K. D. Reichl and A. T. Radosevich, *Chem. Commun.*, 2014, **50**, 9302–9305.
- 19 J. J. Reddick, J. Cheng and W. R. Roush, *Org. Lett.*, 2003, **5**, 1967–1970.
- 20 (a) J. F. Biellmann and J. J. Vicens, *Tetrahedron Lett.*, 1974, **15**, 2915–2918; (b) J. F. Biellmann and J. J. Vicens, *Tetrahedron Lett.*, 1978, **19**, 467–470.
- 21 T. Durst and T. Molin, *Tetrahedron Lett.*, 1975, **16**, 63–66.
- 22 G. Chassaing, R. Lett and A. Marquet, *Tetrahedron Lett.*, 1978, **19**, 471–474.
- 23 S. Eisler, N. Chahal, R. McDonald and R. R. Tykwiński, *Chem. – Eur. J.*, 2003, **9**, 2542–2550.
- 24 V. J. Gray, B. Slater and J. D. Wilden, *Chem. – Eur. J.*, 2012, **18**, 15582–15585.
- 25 R. L. Smorada and W. E. Truce, *J. Org. Chem.*, 1979, **44**, 3444–3445.
- 26 (a) J. L. G. Ruano, J. Alemán, L. Marzo, C. Alvarado, M. Tortosa, S. Díaz-Tendero and A. Fraile, *Chem. – Eur. J.*, 2012, **18**, 8414–8422; (b) J. L. G. Ruano, J. Alemán, L. Marzo, C. Alvarado, M. Tortosa, S. Díaz-Tendero and A. Fraile, *Angew. Chem., Int. Ed.*, 2012, **51**, 2712–2716.

