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Synthesis and Reactivity of α-Diazo-β-keto Sulfonamides

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Abstract:

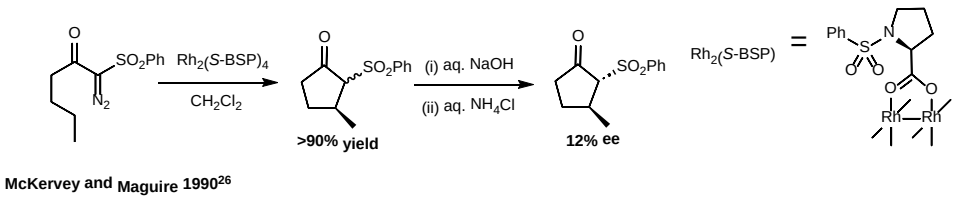
Copper mediated reactions of α-diazo-β-keto sulfonamides **1** leads to a range of products including the alkyne sulfonamides **5**, the enamines **6**, and the α-halosulfonamides **7** and **11** with no evidence for intramolecular C–H insertion in any of the reactions, in contrast to the reactivity of the comparable α-diazo-β-keto sulfones. Use of copper(II) triflate (5 mol%) led to isolation of a series of alkyne sulfonamides **5** (up to 12%) and enamines **6** (up to 64%). Use of copper(II) chloride (5 mol%) formed, in addition, the α-halosulfonamides **7**; use of stoichiometric amounts of copper(II) chloride/bromide enables facile halogenation of the β-keto sulfonamide to form the α-halosulfonamides **7** and **11** (up to 63%).

Introduction:

α-Diazocarbonyl compounds are versatile synthetic intermediates undergoing a wide range of synthetic transformations under transition metal catalysis, photochemical or thermal activation.[1–8] Insertion of the carbenoid derived from α-diazocarbonyl compounds into C–H bonds is a particularly powerful synthetic transformation proceeding under mild conditions utilizing a transition metal catalyst (usually rhodium) at neutral pH. The scope of the C–H insertion reaction has been extensively explored due to its capacity to form new C–C bonds in a highly selective manner and under relatively mild conditions.[2,9–17] While traditionally intermolecular C–H insertion suffered from low selectivities, the Davies group has demonstrated excellent control of this process in recent years using donor acceptor diazo substrates.[12,18–20] The synthetic power of the intramolecular C–H insertion reaction arises from the ability of the carbenoid to select and activate a single C–H bond in a molecule for insertion while not reacting at the adjacent methylene units. For carbocycles, rhodium catalysed

intramolecular C–H insertion displays a strong preference for insertion to form cyclopentanone rings.[21–23] Over the past two decades there has been tremendous progress in stereocontrol in C–H insertion; through the judicious selection of the α-diazocarbonyl compound and transition metal catalyst it allows access to complex enantioenriched products that would have taken several steps or would be difficult to synthesise otherwise.[2,9–17]

Pioneering work in the area of stereoselective C–H insertion reactions was conducted by Taber's group who demonstrated that C–H insertion reactions may occur with high levels of regio- and diastereoselectivities for a series of cyclopentanones in the presence of rhodium(II) carboxylates.[21–25] A key report by McKervey in 1990 described the first asymmetric intramolecular C–H insertion reaction utilizing enantiopure rhodium carboxylates for formation of cyclopentanones in up to 12% ee (Scheme 1).[26] Following these findings, asymmetric C–H insertion reactions have been dominated by the use of rhodium for the last three decades with particular success with both rhodium carboxylates and rhodium carboxamidates.[27–32]



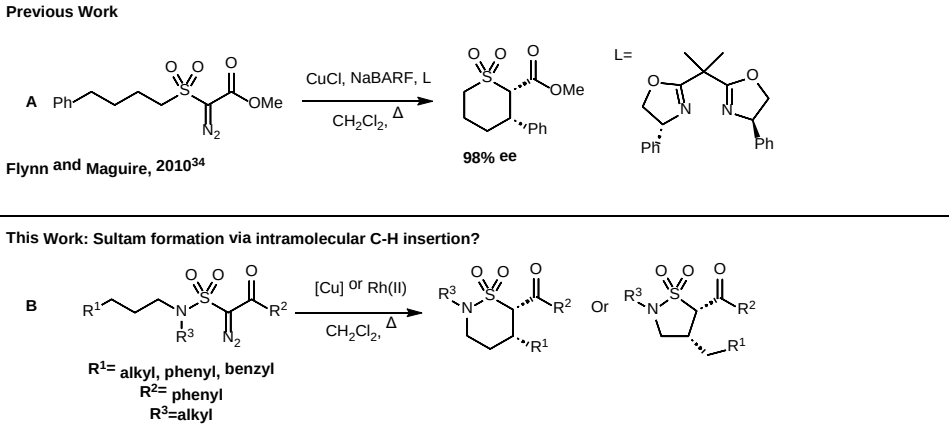
McKervey and Maguire 1990[26]

Scheme 1 Previous Work by McKervey

Despite early limitations in efficiencies and selectivity,[33] in recent years copper has emerged as a powerful alternative to that of rhodium(II) carboxylates especially in C–H insertions with α-diazo-β-keto sulfones. [34–36] The copper catalyst system, comprising of copper-bis(oxazoline) ligand-NaBARF, has been demonstrated by the Maguire group to effect C–H insertion reactions with very high levels of enantiocontrol across a diverse range of α-diazocarbonyl substrates leading to tetrahydrothiopyrans-*S*,*S*-dioxides, sulfolanes, cyclopentanones, β- and γ-lactams (Scheme 2, A).[34–40]

Of particular interest to this study were the reactions conducted in our team by Flynn[34] and later expanded upon by Shiely[36] concerning the copper-bis(oxazoline) catalysed asymmetric transformations of α-diazo-β-keto sulfones to tetrahydrothiopyrans-*S*,*S*-dioxides (up to 98% ee, Scheme 2, A).

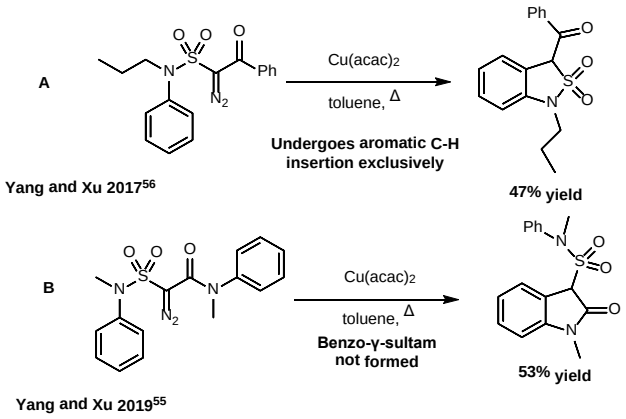
The aim of this study was to investigate firstly, if C–H insertion in α-diazo-β-keto sulfonamides to generate a series of sultams is possible, and, secondly, to explore the enantiocontrol in this insertion process (Scheme 2, B). Doyle has demonstrated highly enantioselective C–H insertion reactions in α-diazoamides leading to lactams through insertion into a C–H bond on the nitrogen substituent.[41–43]



Scheme 2 Previous work within the Maguire group

There are limited reports of α-diazo-β-keto sulfonamides in the literature. Their synthesis has been reported by Regitz[44] and more recently by Krasavin.[45] They have primarily been applied to a number of cycloaddition reactions and O–H insertions,[45–54] however, there are very few reports of their application to C–H insertions, despite a number of attempts principally by Yang and Xu and coworkers.[55–58]

In a recent study, Yang and Xu investigated if aliphatic sp^3 C–H insertions were possible with a range of ester, methyl ketone and benzoyl substituted α-diazo-β-keto sulfonamides with rhodium and copper catalysts, however, 1,4-, 1,5-, or 1,6-C(sp^3)–H insertion was not realised across a wide range of derivatives (Scheme 3, A).[55–57] Instead, only aromatic insertion into the 1,5-C(sp^2)–H bond to form the corresponding benzo-γ-sultam proved possible. Notably, aromatic insertion into an *N*-phenyl substituent on an acetamide is preferred over insertion into *N*-phenyl substituent on a sulfonamide (Scheme 3, B).[55] Mechanistically these reactions were described as electrophilic addition of the carbene to the aromatic ring rather than a concerted C–H insertion. Iwasa's group have described a similar aromatic insertion using an α-diazosulfonamide to form a sultam in a study focused on generation of oxindoles from α-diazoamides under rhodium catalysis.[58]



Scheme 3 Formation of benzo-γ-sultams

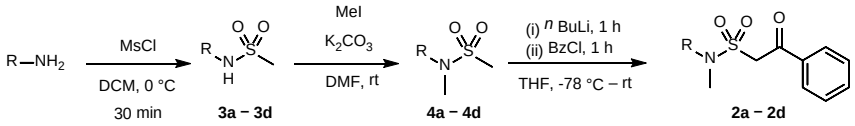
Critically, in Yang and Xu's work, α-diazo-β-keto sulfonamides bearing an aryl ketone with two alkyl substituents on the nitrogen were not investigated. As the α-diazosulfonamides bearing a ketone substituent are different electronically to those bearing an ester substituent, investigation of their reactivity was proposed to establish if intramolecular C–H insertion to form sultams is feasible in the absence of a *N*-aryl group. Herein we report the design and synthesis of a series of α-diazo-β-keto sulfonamides **1a**–**h** and their reactions using both copper and rhodium catalysts. Significantly, there was no evidence for intramolecular C–H insertion to form sultams, in contrast to the reactivity with the analogous α-diazo-β-keto sulfones, and instead alternative reaction pathways were observed as described below.

Discussion:

Two synthetic routes were utilized to access tertiary β-keto sulfonamides **2** bearing a range of *N*-alkyl substituents as summarized in Table 1 and Scheme 4 and 5.[56,59–62] Thus, mesylation of commercially available amines followed by methylation with methyl iodide and subsequent deprotonation using *n* BuLi and benzoylation leads to the β-keto sulfonamides **2a**–**2d** (Route A, Table 1). β-Keto sulfonamides **2e** and **2f** were similarly synthesised without the need for methylation (Route A, Scheme 4). Alternatively, sulfonation of α-bromoacetophenone followed by formation of the sulfonyl chloride and reaction with either dimethylamine or *N*-methylaniline was employed to form β-keto sulfonamides **2g** and **2h** (Route B, Scheme 5).[56] In practice Route A proved more effective in providing the β-keto sulfonamides **2** in pure form for subsequent synthesis. Both synthetic routes afforded multigram quantities of β-keto sulfonamides **2** which were amenable to storage for several months without noticeable degradation. While β-keto sulfonamides **2e, 2g** and **2h** have been previously reported,[56,63,64] the

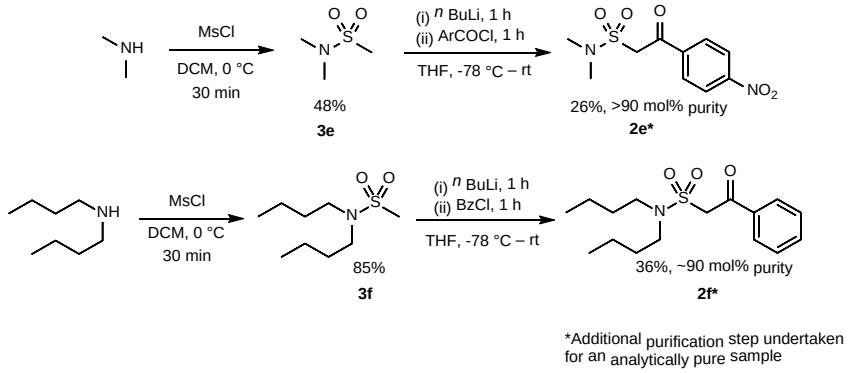
remainder of the series are novel and were fully characterized in this work (see SI for full details).

Table 1: Synthesis of β-keto sulfonamides 2a–2d (Route A)

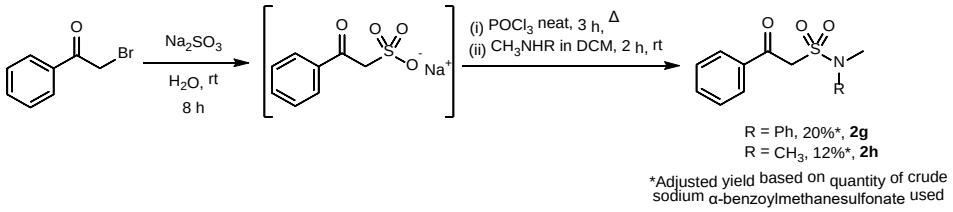


Entry	R	Mesylation	Yield[a]	Methylation	Yield[b]	Benzoylation	Yield[c]
1	$CH_3(CH_2)_3$	**3a**	95%	**4a**	44%	**2a**	85%
2	$Ph(CH_2)_4$	**3b**	89%	**4b**	72%	**2b**	74%[e]
3	$Ph(CH_2)_3$	**3c**	94%	**4c**	65%	**2c**	45%
4	$(CH_3)_2CH(CH_2)_2$	**3d**	72%[d]	**4d**	70%	**2d**	59%

[a]Yield of secondary methane sulfonamide without chromatographic purification
[b]Yield of tertiary methane sulfonamide following chromatographic purification
[c]Yield of β-keto sulfonamide following chromatographic purification
[d]Product was ~87 mol% pure. Additional purification step undertaken for an analytically pure sample.
[e]Product was ~85 mol% pure. Additional purification step undertaken for an analytically pure sample.



Scheme 4: Synthesis of β-keto sulfonamides 2e and 2f (Route A)

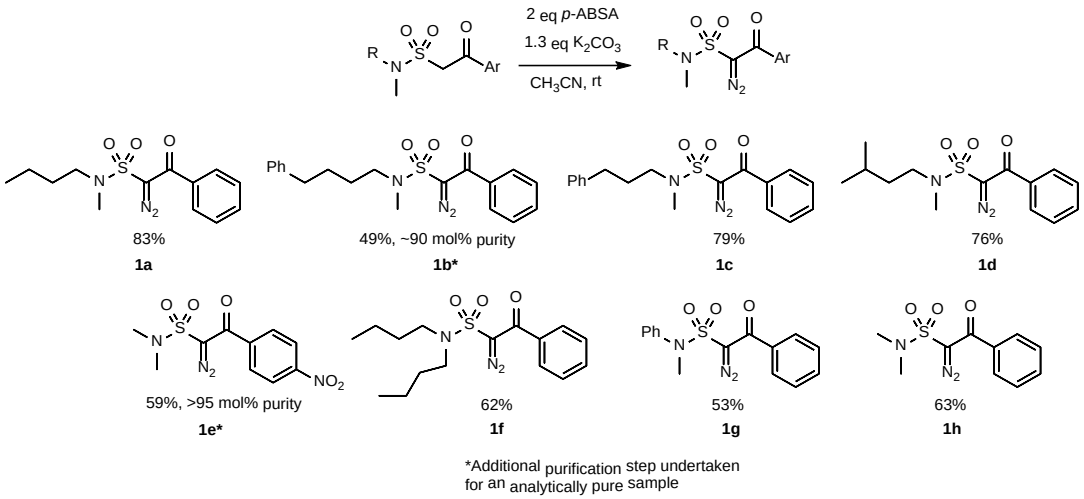


Scheme 5: Synthesis of β-keto sulfonamides 2g and 2h (Route B)

With the series of β-keto sulfonamides in hand, our attention was next directed to the synthesis of the α-diazo-β-keto sulfonamides **1a**–**h** via diazo transfer (Scheme 6).[65] Most reports of diazo transfer to sulfonamides utilise tosyl azide[56,57] or the "SAFE" protocol[45] and to the best of our knowledge the use of *p*-acetamido-benzenesulfonyl azide (*p*-ABSA) has not been reported for this transformation. The use of *p*-ABSA[66] as the diazo transfer reagent was preferable from a

safety perspective[67,68] and also based on previous experience with this reagent within the Maguire group.[9]

Diazo transfer using *p*-ABSA with potassium carbonate in acetonitrile allowed facile access with good yields to eight α-diazo-β-keto sulfonamides **1a**–**h** all of which are novel apart from **1g**. The α-diazo-β-keto sulfonamides **1** were isolated in good yields as either yellow oils (**1b** and **1f**) or yellow solids (**1a, 1c–1e, 1g** and **1h**), were fully characterized during this work and were readily stored in the freezer for extended periods without deterioration.



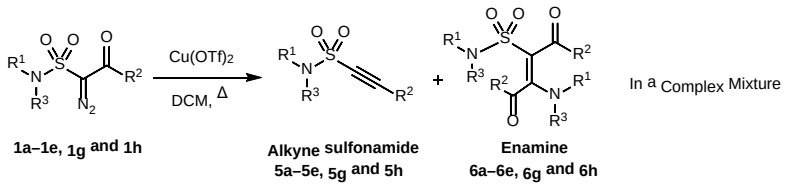
Scheme 6 Synthesis of α-diazo-β-keto sulfonamides 1a–1h

α-Diazo-β-keto sulfonamides **1a**–**1d, 1f** were synthesised in order to investigate if aliphatic C–H insertion occurs in situations where the α-diazo-β-keto sulfonamide bears an aryl ketone and two alkyl substituents on the nitrogen, which had not been previously explored.[55–58] α-Diazo-β-keto sulfonamides **1e, 1g** and **1h** without an extended alkyl chain on the nitrogen which could lead to sultam formation were synthesized for comparison.

The reactivity of the α-diazo-β-keto sulfonamides **1a**–**1h** was explored utilizing a range of metal catalysts including rhodium and copper catalysts. In the presence of $Cu(OTf)_2$ in dichloromethane under reflux, α-diazo-β-keto sulfonamides **1a**–**1e, 1g** and **1h** were completely consumed 4–24 h (typically overnight) yielding complex mixtures from which a series of alkyne sulfonamides **5a**–**5e, 5g** and **5h** and enamines **6a**–**6e, 6g** and **6h** were isolated by chromatography, but critically there was no evidence for sultam formation via intramolecular C–H insertion (Table 2). Examination of the ^{1}H NMR spectra of the crude product mixtures confirmed complete consumption of the α-diazo-β-keto sulfonamides **1a**–**1e, 1g** and **1h** and the major identifiable products in each case were the enamines (~50–70% of the crude mixture) and the alkyne sulfonamides (typically <20% of the crude mixture), in addition to

unidentifiable side products. The alkyne sulfonamides **5** were a minor component of the crude product mixtures and were primarily isolated as oils after chromatography, except for alkyne sulfonamides **5e** and **5g** which were solids, in yields of up to 12%. The more polar enamines **6** were the major component of the crude product mixtures and were isolated in up to 64% yield as yellow oils or solids after chromatography. While the isolated yields of the alkyne sulfonamides remains relatively consistent across the series, isolated yields of the enamines varied somewhat across the series (Table 2), although the ease of chromatographic separation had an impact on the recovered yield with repeated chromatography required to deliver an analytically pure sample for **6e** and **6g**.

Table 2 Reaction of α-diazo-β-keto sulfonamides with $Cu(OTf)_2$



1a–1e, 1g and 1h | **Alkyne sulfonamide 5a–5e, 5g and 5h** | **Enamine 6a–6e, 6g and 6h**

Entry	Diazo	Alkyne	Enamine	Isolated Yield Alkyne Sulfonamide	Isolated Yield Enamine
1	**1a**[a]	**5a**	**6a**	12%	60%
2	**1b**[b]	**5b**	**6b**	2%[c]	40%
3	**1c**[a]	**5c**	**6c**	6%	64%
4	**1d**[a]	**5d**	**6d**	6%	35%
5	**1e**	**5e**	**6e**	5%[c, d]	3%[c, e]
6	**1g**	**5g**	**6g**	6%	33%[c]
7	**1h**	**5h**	**6h**	8%	62%

[a]No reaction for rhodium(II)
[b]Complex mixture obtained in the presence of Rh_2(trifluoroacetate)$_4$
[c]Isolated via repeated column chromatography
[d]By ^{1}H NMR spectroscopy the purity of the compound is ~60 mol%
[e]By ^{1}H NMR spectroscopy the purity of the compound is >85 mol%

The formation of both the alkyne sulfonamides and the enamines from α-diazo-β-keto sulfonamides was completely unprecedented and the reaction pathways are very interesting from a mechanistic and synthetic perspective. While the molecular structure of the enamine **6g** was confirmed by single crystal X-ray crystallography, as the alkyne sulfonamides were primarily oils, structural confirmation was undertaken by comparison with similar compounds reported in the literature.

The enamines **6a**–**6e, 6g** and **6h** are sterically hindered tetrasubstituted alkenes, isolated as E isomers with the two ketones trans to one another as evidenced by the X-ray crystal structure determined for enamine **6g** (Figure 1). Notably, due to the steric demand of the substituents,

there is a significant deviation from planarity across the conjugated system as evidenced by the dihedral angles in the crystal structure. The extended conjugation across the enamine is evidenced by the planarity of enamine nitrogen and bond lengths across the conjugated system. The restricted rotation due to the extended conjugation is evidenced in the ^{1}H NMR spectra of the enamines, most notably through broadened signals seen for the *N*-methyl at δ_C ~42 ppm and the carbonyl *C* δ_C ~192 ppm across the series. The formation of the enamine as the E isomer only presumably reflects that this is the thermodynamically more stable isomer as E/Z isomerism is likely due to conjugation.

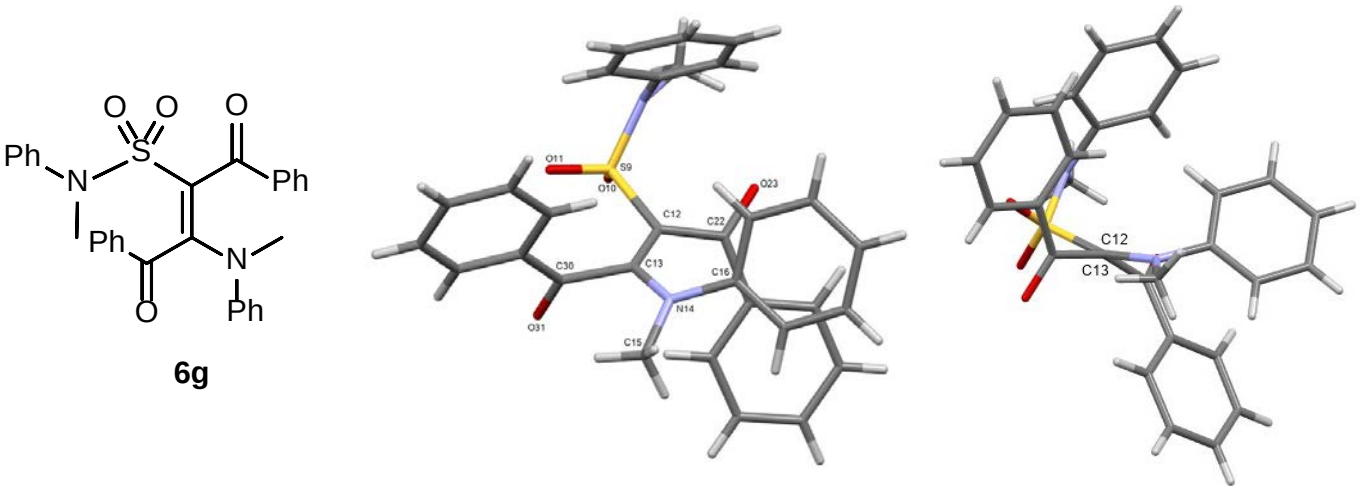
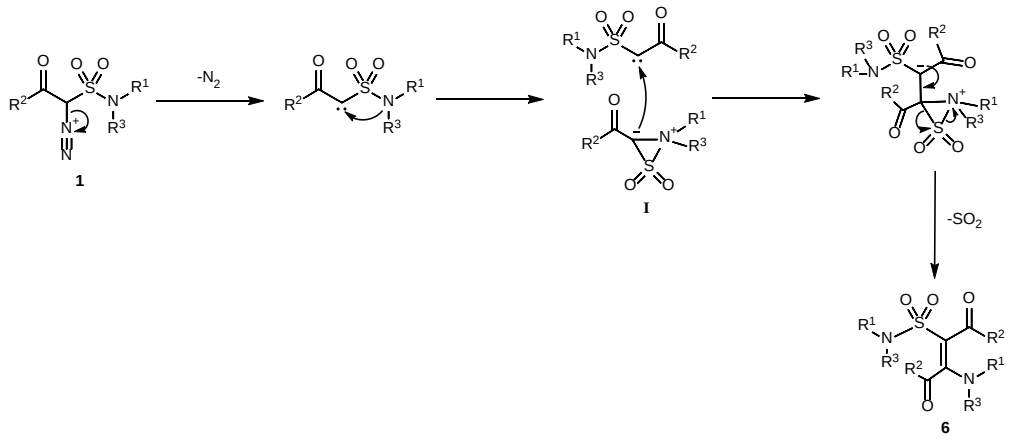


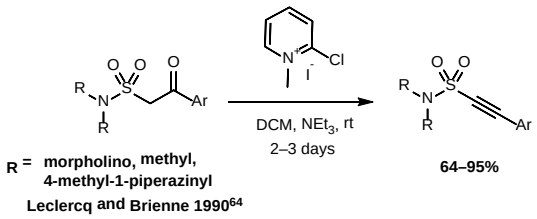
Figure 1 Crystal Structure of Enamine 6g (molecule 1 in the unit cell) X-ray crystal structure of enamine **6g** showing the E configuration of the double bond and the significant deviation from planarity as evidenced by the dihedral angles C22 C12 C13 N14 . . . . 24.2(4), S9 C12 C13 N14 . . . . -159.2(2), C12 C13 C30 O31 . . . . 69.7(4) and C13 C12 C22 O23 . . . . -144.4(3). The bond angles are consistent with trigonal planar conformation at N14 – C13 N14 C16 . . 122.3(3) C13 N14 C15 . . 121.8(3) C16 N14 C15 . . 115.8(3). While there are two molecules in the unit cell they are practically identical within experimental error (see SI).

The transformation of α-diazo-β-keto sulfonamides **1a**–**1e, 1g** and **1h** to these highly strained tetrasubstituted alkenes is notable. The enamine products are clearly formed from two molecules of the α-diazo-β-keto sulfonamide but with loss of one sulfonyl group. A possible reaction mechanism for this transformation is shown in Scheme 7 where involvement of the nitrogen to form an ylide **I** followed by reaction with a second carbene explains the observed outcome, although at this stage there is no direct experimental evidence for this pathway.



Scheme 7 Proposed Mechanism of Enamine Formation

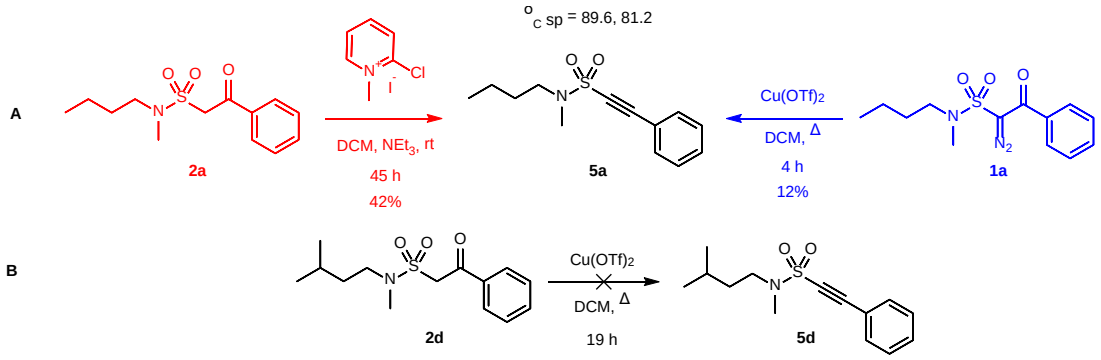
In relation to the alkyne sulfonamides **5a**–**5e, 5g** and **5h**, their structures were proposed initially based on the characteristic sp carbon signals at δ_C ~89 ppm and ~81 ppm and further verified by comparison with literature data of structurally related compounds reported by Leclercq and Brienne.[64] They synthesised a series of arylethynesulfonamides from β-keto sulfonamides via dehydration with 2-chloro-*N*-methylpyridinium iodide (Scheme 8).[64] While they had not reported the reaction of *N*-butyl β-keto sulfonamide **2a** in their study, during this work β-keto sulfonamide **2a** was reacted with 2-chloro-*N*-methylpyridinium iodide yielding alkyne sulfonamide **5a** in 42% yield. Comparison of the ^{1}H and ^{13}C NMR spectra of the alkyne sulfonamide **5a** formed from this reaction with the spectra of the same compound formed by copper(II) triflate mediated reaction of α-diazo-β-keto sulfonamide **1a** confirmed the structural assignment (Scheme 9, A). Furthermore, key spectroscopic features of the alkyne sulfonamides are consistent with data reported by Leclercq and Brienne for example the alkyne stretch in the IR spectra.



Scheme 8 Synthesis of arylethynesulfonamides by Leclercq and Brienne

However, the dehydration reaction proposed by Leclercq and Brienne[64] opens an interesting question into the mechanistic origin of the alkyne sulfonamides. Rather than a direct carbene mediated process with loss of the elements of O and N_2, a possible reaction pathway considered was that the α-diazo-β-keto sulfonamides **1a**–**1e, 1g** and **1h** could be first reduced to the β-keto

sulfonamides **2a**–**2e, 2g** and **2h** followed by dehydration as reported by Leclercq and Brienne. A key experiment was thus performed whereby β-keto sulfonamide **2d** was subjected to our $Cu(OTf)_2$ reaction conditions (Scheme 9, B). Critically, even after prolonged heating at reflux, there was no evidence for the formation of the alkyne sulfonamide **5d** in the NMR spectra of the crude product mixture. This strongly suggests that alkyne sulfonamide **5** formation from reaction of the α-diazo-β-keto sulfonamide **1** proceeds via the carbene rather than via initial reduction to the β-keto sulfonamide **2**. Alkynes are known to form from β-hydroxy-α-diazo compounds,[69–71] via a Grob fragmentation approach[72–75] and from the double elimination of two α-diazo groups.[76,77] However, to the best of our knowledge the formation of an alkyne with loss of O and N_2 across the α-diazocarbonyl compound is a novel transformation. Isolation of the sulfonamide alkynes **5** is more consistent from reactions catalysed with copper triflate than those catalysed with copper chloride, possibly due to the increased Lewis acidity of copper triflate facilitating the elimination process.[78–80]



Scheme 9 Formation of alkyne sulfonamides

Our attention next focused on use of CuCl or $CuCl_2$ as catalyst (Table 3). Akin to our findings with $Cu(OTf)_2$, there was no evidence of sultam formation in the ^1H NMR spectra of the crude product mixtures from **1a**–**1d** and **1f** or in any of the isolated products following column chromatography. Over the course of our investigations with CuCl or $CuCl_2$ (5 mol%), the crude product mixtures were complex containing unreacted α-diazo-β-keto sulfonamide **1a**–**1d**, **1f** and **1g** among other components. However, formation of α-chlorosulfonamides **7a**–**7d**, **7f** and **7g** (~10 mol% with $CuCl_2$ and ~5 mol% with CuCl) was clear by the presence of a characteristic singlet at δ_H ~6.2 ppm in the ^1H NMR spectra of the crude product mixtures. In addition, there was evidence for the presence of minor amounts of β-keto sulfonamides **2a**–**2d**, **2f** and **2g** and, on occasion, the enamines **6a**, **6c**, **6d** and **6g** and the alkyne sulfonamide **5g**. Notably the reactions with CuCl or $CuCl_2$ (5 mol%) are less efficient than those with $Cu(OTf)_2$ in which

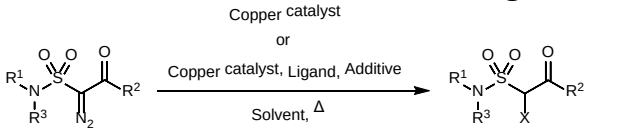
the α-diazo-β-keto sulfonamides **1a**–**1e, 1g** and **1h** are fully consumed over the same reaction time.

In the $CuCl_2$ catalysed reaction of α-diazo-β-keto sulfonamide **1g** the major product isolated was the benzo-γ-sultam **8g** through aromatic 1,5-C(sp^2)–H insertion analogous to the report of Yang and Xu; however, it is interesting that the extent of formation of the α-chlorosulfonamide **7g** (not mentioned in the Yang and Xu work) was not impacted by the alternative reaction pathway (Table 3, entry 15 and Scheme 10).

Based on our earlier success in asymmetric intramolecular C–H insertion in α-diazo-β-keto sulfones using copper-bis(oxazoline) catalysts,[34,36,40] a number of experiments were conducted utilizing the copper-bis(oxazoline) **9** or **10**, NaBARF catalyst system (Table 3, entries 3, 4, 7, 8, 11, 12 and 14). In the event, there was no evidence for C–H insertion, and the extent of formation of the α-chlorosulfonamides **7a**–**7d** was very similar to that seen in reactions catalysed with just $CuCl_2$, however, it was interesting to note that complexity of the ^{1}H NMR spectra of the crude product mixtures was somewhat less in the presence of the (4*S*)-^{t}Bu bis(oxazoline) ligand **10**.

Each of the α-chlorosulfonamides **7a**–**7d**, **7f** and **7g** was isolated as a pure compound and fully characterized albeit in low yields (Table 3, entries 2, 7, 11, 13, 15 and 16). Two possible sources of the chlorine can be envisaged i.e. the copper catalyst or the chlorinated solvent dichloromethane.[81] In this context an interesting trend was seen in the reactions of CuCl or $CuCl_2$ with α-diazo-β-keto sulfonamide **1b**. From the ^{1}H NMR spectra of the crude mixtures it was clear that there was more α-chlorosulfonamide **7b** formed from the reactions involving $CuCl_2$ than from the reactions using CuCl. This was an early indication that the source of the chlorine is more likely to be from the copper catalyst rather than from dichloromethane.

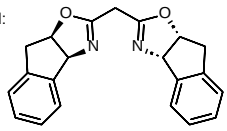
Table 3 Copper chloride and copper bromide mediated reactions of α-diazo-β-keto sulfonamides 1a–1d, 1f and 1g



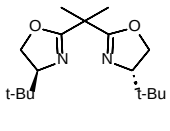
1a–1d, 1f and 1g

X = Cl, 7a–7d, 7f and 7g
X = Br, 11a and 11c

Ligand:



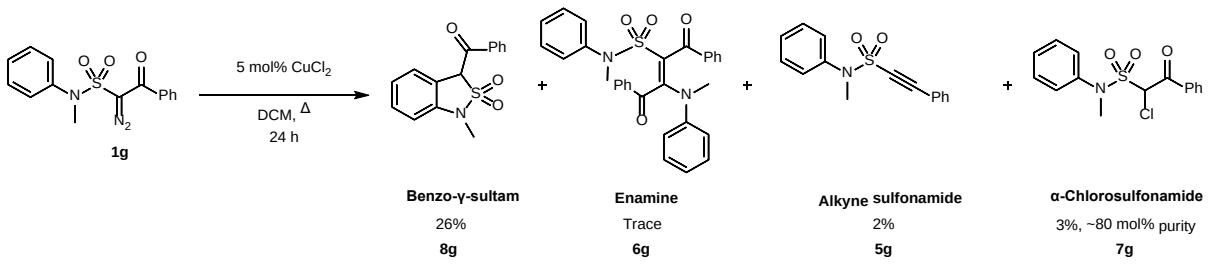
(3*S*,8*R*)-Ind
9



(4*S*)-^{t}Bu
10

Entry	Diazo	Cat	Catalyst loading (mol%)	Ligand, Additive	Solvent	α-halosulfonamide[f]	Yield in crude product (mol%)	Yield (%)
1	**1a**	CuCl	5	–	DCM	**7a**	~6[a]	n.d.
2	**1a**	$CuCl_2$	5	–	DCM	**7a**	~9	2[b]
3	**1a**	$CuCl_2$	5	**9**, NaBARF	DCM	**7a**	~6	n.d.
4	**1a**	$CuCl_2$	5	**10**, NaBARF	DCM	**7a**	~7	n.d.
5	**1b**	CuCl	5	–	DCM	**7b**	~4	n.d.
6	**1b**	$CuCl_2$	5	–	DCM	**7b**	~10	n.d.
7	**1b**	$CuCl_2$	5	**9**, NaBARF	DCM	**7b**	~9	2[b]
8	**1b**	$CuCl_2$	5	**10**, NaBARF	DCM	**7b**	~6	n.d.
9	**1c**	CuCl	5	–	DCM	**7c**	~3	n.d.
10	**1c**	$CuCl_2$	5	–	DCM	**7c**	~8[c]	n.d.
11	**1c**	$CuCl_2$	5	**9**, NaBARF	DCM	**7c**	~5	3[b]
12	**1c**	$CuCl_2$	5	**10**, NaBARF	DCM	**7c**	~12	n.d.
13	**1d**	$CuCl_2$	5	–	DCM	**7d**	~10[e]	2[d]
14	**1d**	$CuCl_2$	5	**9**, NaBARF	DCM	**7d**	~10	n.d.
15	**1g**	$CuCl_2$	5	–	DCM	**7g**	~9[f, g, h]	3[b, i]
16	**1f**	$CuCl_2$	5	–	DCM	**7f**	~10	4[j]
17	**1d**	$CuCl_2$	100	–	DCM	**7d**	~45	45[k]
18	**1d**	$CuCl_2$	100	–	Toluene/ 58 °C	**7d**	~60	63[k]
19	**1d**	$CuCl_2$	5	–	Toluene/ 58 °C	**7d**	~4	4[k]
20	**1a**	$CuBr_2$	100	–	DCM	**11a**	~16	5[k]
21	**1c**	$CuBr_2$	100	–	Toluene/ Δ	**11c**	~23	21[k]

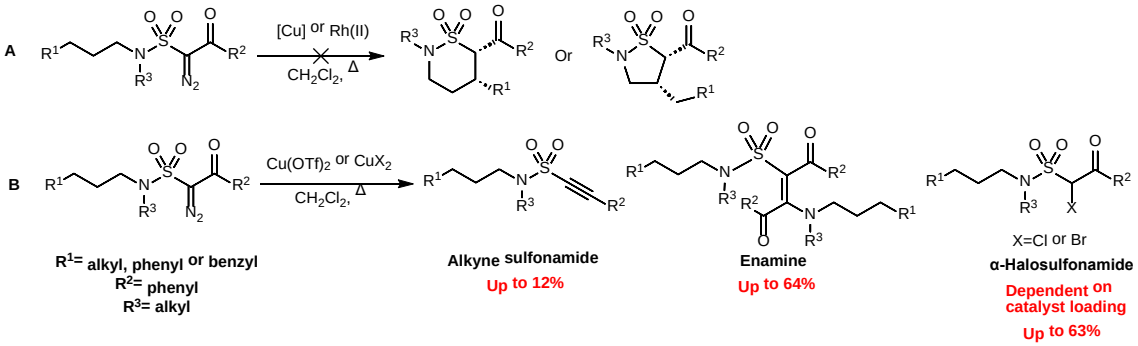
[a]Enamine **6a** also isolated (6%)
[b]Isolated by column chromatography followed by a preparative TLC
[c]Enamine **6c** also isolated (6%, ~85 mol% pure)
[d]Isolated by repeated column chromatography
[e]Enamine **6d** also isolated (20%, ~50 mol% pure)
[f]Benzo-γ-sultam **8g** also isolated (26%)
[g]Enamine present in crude ^{1}H NMR spectrum in trace amounts.
[h]Alkyne **5g** also isolated (2%).
[i]α-Chlorosulfonamide **7g** ~80 mol% purity.
[j]Isolated by column chromatography and a hot hexane recrystallization.
[k]Isolated by column chromatography.
[l]β-Keto sulfonamide **2** detected in ^{1}H NMR spectrum of the crude product mixtures (typically <10 mol%).



Scheme 10 $CuCl_2$ catalysed reaction of α-diazo-β-keto sulfonamide 1g

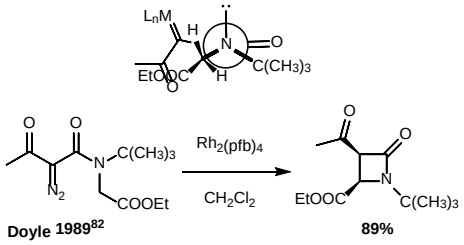
Accordingly, to explore if the CuCl/$CuCl_2$ catalyst is the source of the chlorine, a number of experiments were conducted using stoichiometric amounts of $CuCl_2$ with α-diazo-β-keto sulfonamide **1d** in DCM and toluene as solvent (Table 3, entries 17 and 18). The yield of the α-chlorosulfonamide **7d** was much higher from these reactions (45% and 63% respectively) than from the reactions using just 5 mol% of $CuCl_2$ (<10%, Table 3, entries 13 and 19), strongly indicating that the copper chloride catalyst is indeed the source of the chlorine in the α-chlorosulfonamides **7**, especially as its formation is more efficient in toluene than in DCM. Most of the reactions in toluene were conducted at 58 °C rather than at reflux, apart from Table 3, entry 21, for greater comparability with the reactions in DCM under reflux. As shown in Table 3, entries 20 and 21, formation of the analogous α-bromosulfonamides **11a** and **11c** was possible utilizing $CuBr_2$, albeit at lower yields. Nonetheless, the synthetic versatility in the formation of α-halosulfonamides **7** and **11** from α-diazo-β-keto sulfonamides **1** using an easily handled halide source is notable.

In the event, there was no evidence at any point for intramolecular C–H insertion (Scheme 11, A) in the copper catalysed reactions of the α-diazo-β-keto sulfonamides, and instead a number of novel reactions and mechanistically interesting reaction pathways are observed (Scheme 11, B).



Scheme 11 Unexpected products from copper mediated reactions of α-diazo-β-keto sulfonamides

The absence of any evidence for intramolecular C–H insertion of the α-diazo-β-keto sulfonamides to form sultams is notable considering that the analogous C–H insertion leading to tetrahydrothiopyrans-*S*,*S*-dioxides is a favourable pathway for the α-diazo-β-keto sulfones (Scheme 2, B). Thus, replacing the sulfone linking the carbene to the site of C–H insertion with a sulfonamide linkage diverts the carbene reactivity to other pathways. In contrast, Doyle rationalized β-lactam formation via intramolecular C–H insertion in α-diazoacetoacetamides due to conformational preference where the reacting C–H bond is placed in close proximity to the carbenoid centre (Scheme 12).[82] This difference between the reactivity of α-diazo-β-keto sulfonamides and α-diazoamides is presumably due to the significant structural differences between sulfonamides and amides, such as increased conformational flexibility in the sulfonamides, and while the amide is planar, the sulfonamides are non-planar at sulfur.[83–86]



Scheme 12 C–H insertion in α-diazoacetoacetamides impacted by the conformational preference

In conclusion, copper mediated reactions of α-diazo-β-keto sulfonamides **1** leads to a range of products including the dimeric enamine **6**, the alkyne sulfonamides **5** and the α-halosulfonamides **7** and **11** with no evidence for intramolecular C–H insertion in any of the reactions in contrast to the reactivity of the structurally related α-diazo-β-keto sulfones. While the formation of these products is mechanistically interesting, from a synthetic perspective formation of the strongly sterically congested enamines is potentially useful and equally formation of the α-halosulfonamides **7** and **11** using an easily handled halide source is notable.

Experimental:

Preparation of α-diazo-β-keto sulfonamides (1a–h); General Procedure A

Anhydrous potassium carbonate (1.3 molar eq.) was added to a solution of β-keto sulfonamide **2** (1 molar eq.) in acetonitrile (10 mL per mmol). The mixture was stirred at room temperature and a solution of *p*-ABSA (1 molar eq.) in acetonitrile (5 mL per mmol) was added dropwise over 10 minutes under an atmosphere of nitrogen. The reaction mixture was stirred for 2 h followed by a second addition of *p*-ABSA(1 molar eq.) in acetonitrile (5 mL per mmol) and

was stirred for a further 2 h. A mixture of diethyl ether and hexane (20 mL per mmol of each) was then added to give a 1:1:1 mixture of acetonitrile: diethyl ether: hexane to precipitate the amide salts. The resultant mixture was filtered through a short pad of Celite® and the filtrate concentrated under reduced pressure. The crude α-diazo-β-keto sulfonamide **1** was purified using column chromatography on silica gel.

***N*-Butyl-*N*-methyl-1-diazo-2-oxo-2-phenylethanesulfonamide (1a)**

The title compound was prepared according to general procedure A, from anhydrous potassium carbonate (2.70 g, 19.5 mmol), *N*-butyl-*N*-methyl 2-oxo-2-phenylethanesulfonamide **2a** (4.04 g, 15.0 mmol) and *p*-ABSA (6.20 g, 30.0 mmol) in acetonitrile (300 mL). The crude product was purified by column chromatography on silica gel, employing 10% ethyl acetate in hexane as eluent, to give the pure α-diazo-β-keto sulfonamide **1a**.

Yield: 3.66 g (83%); yellow solid; Mp 45.9–46.6 °C.

IR (ATR): 2118, 1642, 1345, 1145 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.67–7.63 (m, 2H, aromatic *H*), 7.61–7.55 (m, 1H, aromatic *H*), 7.51–7.46 (m, 2H, aromatic *H*), 3.29 (t, *J* = 7.2 Hz, 2H, $CH_3CH_2CH_2CH_2$), 2.97 (s, 3H, NCH_3), 1.64–1.53 (m, 2H, $CH_3CH_2CH_2CH_2$), 1.45–1.31 (m, 2H, $CH_3CH_2CH_2CH_2$), 0.95 (t, *J* = 7.4, 3H, $CH_3CH_2CH_2CH_2$).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 184.2, 136.2, 133.1, 129.1, 127.4, 80.0, 51.0, 35.4, 30.2, 19.8, 13.8.

HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{13}H_{17}N_3O_3SNa$: 318.0883; found: 318.0878.

Anal. Calc for $C_{13}H_{17}N_3O_3S$: C, 52.58; H, 5.80; N, 14.23. Found: C, 52.58; H, 5.82; N, 14.13.

***N*-Methyl-*N*-(4'-phenylbutyl) 1-diazo-2-oxo-2-phenylethanesulfonamide (1b)**

The title compound was prepared according to general procedure A, from anhydrous potassium carbonate (1.98 g, 14.3 mmol), *N*-methyl-*N*-(4'-phenylbutyl) 2-oxo-2-phenylethanesulfonamide **2b** (3.80 g, 11.0 mmol) and *p*-ABSA (5.28 g, 22.0 mmol) in acetonitrile (220 mL). A mixture of diethyl ether and hexane (300 mL: 300 mL) was then added to precipitate the *p*-ABSA sulfonamide salts. Purification by repeated column chromatography (2 columns) on silica gel employing 10% ethyl acetate in hexane as eluent, gave the α-diazosulfonamide **1b** (2.02 g, 49%, ~90 mol% purity) as a yellow oil which was used in the next step without further purification. To obtain an analytically pure sample, a portion (57 mg)

of the crude sample was further purified by column chromatography in 5% ethyl acetate in hexane isolating α-diazo-β-keto sulfonamide **1b** as a yellow oil (37 mg, 65% recovery).

IR (ATR): 2098, 1640, 1347, 1150 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.65–7.54 (m, 3H, aromatic *H*), 7.51–7.44 (m, 2H, aromatic *H*), 7.31–7.23 (m, 2H, aromatic *H*), 7.21–7.14 (m, 3H, aromatic *H*), 3.31 (t, *J* = 7.0, 2H, $PhCH_2CH_2CH_2CH_2$), 2.93 (s, 3H, NCH_3), 2.69–2.62 (m, 2H, $PhCH_2CH_2CH_2CH_2$), *1.76–1.56 (m, 4H, $PhCH_2CH_2CH_2CH_2$).

^{13}C NMR (75.5 MHz $CDCl_3$): δ = 184.1, 142.0, 136.2, 133.1, 129.1, 128.6, 128.5, 127.4, 126.0, 80.0, 51.0, 35.4, 35.3, 28.2, 27.5.

HRMS (ESI+): *m/z* $[M+Na]^+$ calcd for $C_{19}H_{21}N_3O_3SNa$: 394.1196; found 394.1181.

*This signal integrates to 5H due to the presence of water

***N*-Methyl-*N*-(3'-phenylpropyl) 1-diazo-2-oxo-2-phenylethanesulfonamide (1c)**

The title compound was prepared according to general procedure A, from anhydrous potassium carbonate (1.24 g, 9.0 mmol), *N*-methyl-*N*-(3'-phenylpropyl) 2-oxo-2-phenylethanesulfonamide **2c** (2.3 g, 6.9 mmol) and *p*-ABSA (3.32 g, 13.8 mmol) in acetonitrile (140 mL). The crude product was purified by column chromatography on silica gel employing 10% ethyl acetate in hexane as eluent, to give the pure α-diazo-β-keto sulfonamide **1c**.

Yield: 1.95 g (79%); yellow solid; Mp 84–85 °C.

IR (ATR): 2100, 1635, 1347, 1148, 933 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.64–7.61 (m, 2H, aromatic *H*), 7.60–7.55 (m, 1H, aromatic *H*), 7.50–7.45 (m, 2H, aromatic *H*), 7.30–7.25 (m, 2H, aromatic *H*), 7.21–7.17 (m, 3H, aromatic *H*), 3.35 (t, *J* = 7.3 Hz, 2H, $PhCH_2CH_2CH_2$), 2.97 (s, 3H, NCH_3), 2.68 (2H, t, *J* = 7.7 Hz, $PhCH_2CH_2CH_2$), 1.97–1.90 (m, 2H, $PhCH_2CH_2CH_2$);

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 184.1, 141.3, 136.1, 133.1, 129.1, 128.6, 128.5, 127.4, 126.2, 80.0, 50.9, 35.5, 32.8, 29.8.

HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{18}H_{19}N_3O_3SNa$: 380.1039; found: 380.1051.

***N*-Isopentyl-*N*-methyl-1-diazo-2-oxo-2-phenylethanesulfonamide (1d)**

The title compound was prepared according to general procedure A, from anhydrous potassium carbonate (1.80 g, 13.0 mmol), *N*-isopentyl-*N*-methyl 2-oxo-2-phenylethanesulfonamide **2d** (2.83 g, 10.0 mmol) and *p*-ABSA (4.80 g, 20 mmol) in acetonitrile (200 mL). A mixture of diethyl ether and hexane (300 mL: 300 mL), was then added to precipitate the amide salts. The crude product was purified by column chromatography on silica gel employing 7% ethyl acetate in hexane as eluent to give the pure α-diazo-β-keto sulfonamide **1d**.

Yield: 2.35 g (76%); yellow solid; Mp 30–32 °C.

IR (ATR): 2092, 1649, 1351, 1144 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67–7.63 (m, 2H, aromatic *H*), 7.61–7.56 (m, 1H, aromatic *H*), 7.52–7.46 (m, 2H, aromatic *H*), 3.33–3.28 (m, 2H, NCH_2), 2.97 (s, 3H, NCH_3), 1.71–1.59 (m, 1H, $(CH_3)_2CH$), 1.53–1.45 (m, 2H, $(CH_3)_2CHCH_2CH_2$), 0.94 (d, *J* = 6.6, 6H, 2 x CH_3).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 184.2, 136.2, 133.1, 129.1, 127.4, 80.0, 49.6, 36.9, 35.3, 25.6, 22.6.

HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{14}H_{19}N_3O_3SNa$: 332.1039; found: 332.1043.

Anal. Calcd for $C_{14}H_{19}N_3O_3S$: C, 54.35; H, 6.19; N, 13.58. Found: C 54.65; H, 5.99; N, 13.92.

***N, N*-Dimethyl-1-diazo-2-oxo-2-(4'-nitrophenyl)-ethanesulfonamide (1e)**

The title compound was prepared according to general procedure A, from anhydrous potassium carbonate (0.33 g, 2.40 mmol), *N*-*N*-dimethyl 2-oxo-2-(4'-nitrophenyl)-ethanesulfonamide **2e** (0.54 g, 2.00 mmol) and *p*-ABSA (0.96 g, 4.00 mmol) in acetonitrile (40 mL). Purification by column chromatography on silica gel employing 20% ethyl acetate in hexane as eluent gave the α-diazo-β-keto sulfonamide **1e** (0.35 g, 59%, >95 mol% purity) as a pale-yellow solid which was used in the next step without further purification. To obtain an analytically pure sample, a portion (111 mg) was further purified by column chromatography in 20% ethyl acetate in hexane isolating α-diazo-β-keto sulfonamide **1e** (38 mg, 34% recovery) as a pale-yellow solid.

Mp 149–150 °C.

IR (ATR): 2113, 1649, 1508, 1346, 1355, 1147 cm^{-1}.

^{1}H NMR (400 MHz, CD_2Cl_2): δ = 8.36–8.32 (m, 2H, aromatic *H*), 7.85–7.81 (m, 2H, aromatic *H*), 3.00 (s, 6H, 2 x NC*H*$_3$).

^{13}C NMR (100.6 MHz, CD_2Cl_2): δ = 182.3, 150.2, 141.2, 128.6, 124.3, 38.0.

C=N_2 not detected

HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{10}H_{10}N_4O_5SNa$: 321.0264; found: 321.0267.

***N, N*-Dibutyl-1-diazo-2-oxo-2-phenylethanesulfonamide (1f)**

The title compound was prepared according to general procedure A, from anhydrous potassium carbonate (0.54 g, 3.90 mmol), *N*-*N*-dibutyl 2-oxo-2-phenylethanesulfonamide **2f** (0.93 g, 3.00 mmol) and *p*-ABSA (1.44 g, 6.00 mmol) in acetonitrile (60 mL). A mixture of diethyl ether and hexane (70 mL: 70 mL), was then added to precipitate the amide salts. The crude product was purified by column chromatography on silica gel employing 3% ethyl acetate in hexane as eluent to give the pure α-diazo-β-keto sulfonamide **1f**.

Yield: 0.62 g (62%); yellow oil.

IR (ATR): 2095, 1641, 1347, 1146 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.66–7.59 (m, 2H, aromatic *H*), 7.59–7.54 (m, 1H, aromatic *H*), 7.52–7.44 (m, 2H, aromatic *H*), 3.38–3.30 (m, 4H, ($CH_3CH_2CH_2CH_2$)$_2$), 1.66–1.53 (m, 4H, ($CH_3CH_2CH_2CH_2$)$_2$), 1.42–1.28 (m, 4H, ($CH_3CH_2CH_2CH_2$)$_2$), 0.98–0.90 (m, 6H, ($CH_3CH_2CH_2CH_2$)$_2$).

^{13}C (75.5 MHz, $CDCl_3$): δ = 184.1, 136.3, 133.0, 129.1, 127.4, 81.2, 49.2, 31.0, 20.1, 13.8.

HRMS (ESI+): *m/z* $[M+Na]^+$ calcd for $C_{16}H_{23}N_3O_3SNa$: 360.1352; found: 360.1351.

***N*-Methyl-*N*-phenyl-1-diazo-2-oxo-2-phenylethanesulfonamide (1g)**[56]

The title compound was prepared according to general procedure A, from anhydrous potassium carbonate (0.72 g, 5.20 mmol) *N*-methyl-*N*-phenyl 2-oxo-2-phenylethanesulfonamide **2g** (1.16 g, 4.00 mmol) and *p*-ABSA (1.92 g, 8.00 mmol) in acetonitrile (80 mL). The crude product was purified by column chromatography on silica gel employing 10% ethyl acetate in hexane as eluent to give the pure α-diazo-β-keto sulfonamide **1g**.

Yield: 0.67 g (53%); yellow solid; Mp 118–120 °C, lit[56] 124–126 °C.

IR (ATR): 2096, 1646, 1360, 1144 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.60–7.50 (m, 3H, aromatic *H*), 7.49–7.42 (m, 2H, aromatic *H*), 7.41–7.29 (m, 5H, aromatic *H*), 3.58 (s, 3H, NC*H*$_3$).

Spectroscopic characteristics are consistent with previously reported data.[56]

***N, N*-Dimethyl-1-diazo-2-oxo-2-phenylethanesulfonamide (1h)**

The title compound was prepared according to general procedure A, from anhydrous potassium carbonate (0.80 g, 5.80 mmol), *N, N*-dimethyl 2-oxo-2-phenylethanesulfonamide **2h** (1.02 g, 4.46 mmol) and *p*-ABSA (2.14 g, 8.92 mmol) in acetonitrile (91 mL). The crude product was purified by column chromatography on silica gel employing 15% ethyl acetate in hexane as eluent to give the pure α-diazo-β-keto sulfonamide **1h**.

Yield: 0.71 g (63%); yellow solid; Mp 61–62 °C.

IR (ATR): 2098, 1643, 1350, 1150 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.69–7.63 (m, 2H, aromatic *H*), 7.62–7.55 (m, 1H, aromatic *H*), 7.53–7.46 (m, 2H, aromatic *H*), 2.99 (s, 6H, 2 x NC*H*$_3$).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 184.1, 136.1, 133.1, 129.1, 127.5, 79.4, 38.2.

HRMS (ESI+): *m/z* $[M+Na]^+$ calcd for $C_{10}H_{11}N_3O_3SNa$: 276.0413; found: 276.0417.

Synthesis of alkyne sulfonamides (5a–5e, 5g and 5h) and enamines (6a–6e, 6g and 6h); General Procedure B

$Cu(OTf)_2$ (5 mol%) was suspended in doubly distilled DCM (30 mL) and heated while stirring under reflux under N_2. A solution of α-diazo-β-keto sulfonamide **1** (200 mg, 1 eq.) in doubly distilled DCM (20 mL) was added to the stirring solution dropwise over 15 min followed by a rinse with doubly distilled DCM (5 mL). The mixture was heated under reflux while stirring overnight or until reaction completion was indicated by TLC and IR spectroscopy. The reaction mixture was then subsequently cooled and concentrated under reduced pressure to give the crude product. Purification by column chromatography employing ethyl acetate in hexane as eluent gave the alkyne sulfonamides **5** (less polar) and enamine **6** (more polar) products.

***N*-Butyl-*N*-methyl phenylethynesulfonamide (5a)**

(a) *N*-Butyl-*N*-methyl 1-diazo-2-oxo-2-phenylethanesulfonamide **1a** (200 mg, 0.68 mmol), $Cu(OTf)_2$ (12.50 mg, 5 mol%) and DCM (55 mL) were used following general procedure B

for 4 h. The crude mixture was purified by column chromatography employing a gradient eluent of 10% to 30% ethyl acetate in hexane isolating the less polar alkyne sulfonamide **5a**.

Yield: 20 mg (12%); brown oil.

IR (ATR): 2181, 1345, 1148 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.59–7.55 (m, 2H, aromatic *H*), 7.51–7.47 (m, 1H, aromatic *H*), 7.43–7.38 (m, 2H, aromatic *H*), 3.20 (t, *J* = 7.3 Hz, 2H, $CH_3CH_2CH_2CH_2$), 2.91 (s, 3H, NCH_3), 1.68–1.62 (m, 2H, $CH_3CH_2CH_2CH_2$), 1.45–1.37 (m, 2H, $CH_3CH_2CH_2CH_2$), 0.96 (t, *J* = 7.3, 3H, $CH_3CH_2CH_2CH_2$).

^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 132.8, 131.2, 128.9, 118.5, 89.6, 81.2, 50.7, 35.3, 29.4, 19.9, 13.8.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{13}H_{18}NO_2S$: 252.1053; found: 252.1046.

(*E*)-*N*-Butyl-3-(butyl(methyl)amino)-*N*-methyl-1,4-dioxo-1,4-diphenylbut-2-ene-2-sulfonamide (6a)

A second more polar fraction was isolated containing the enamine **6a**.

Yield: 95 mg (60%); yellow oil.

IR (ATR): 1680, 1634, 1315, 1134 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.03–7.95 (m, 4H, aromatic *H*), 7.63–7.42 (m, 6H, aromatic *H*), 3.26–2.50 (br m, 10H, 2 x CH_3NCH_2 including br singlets at 2.79 and 2.62), 1.47–0.92* (m, 8H, 2 x $CH_3CH_2CH_2CH_2$), 0.86–0.67 (m, 6H, 2 x $CH_3CH_2CH_2CH_2$);

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 191.9 br, 191.0, 162.7 br, 140.0, 136.0, 133.9, 132.7, 129.4, 129.1, 128.8, 128.6, 108.1, 55.5, 49.8, 42.3, 34.0, 30.1, 29.8, 19.8, 19.7, 13.8, 13.6.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{26}H_{35}N_2O_4S$: 471.2312; found: 471.2298.

*This signal integrates for 9H due to the presence of water

(b) A mixture of *N*-butyl-*N*-methyl 2-oxo-2-phenylethanesulfonamide **2a** (150 mg, 0.56 mmol) and 2-chloro-*N*-methylpyridinium iodide (171 mg, 0.67 mmol) in DCM (1.1 mL) was stirred and cooled in an ice bath. This was followed by the addition of triethylamine (1.1 mL, 7.97 mmol). The mixture was stirred at room temperature for 45 h and the reaction progress was monitored by TLC. The reaction was quenched with aqueous NaOH (1M, 8 mL) and was then

extracted with DCM (10 mL). The organic phase was then washed with aqueous NaOH (1M, 10 mL), aqueous HCl (1M, 10 mL) and then H_2O (10 mL). The solution was dried and then run through a short plug of Al_2O_3 (neutral) using DCM as the eluent. The mixture was concentrated to give the pure alkyne sulfonamide **5a**.

Yield: 59 mg, (42%); white solid which melted at room temperature.

The spectroscopic features were identical to those described above for *N*-butyl-*N*-methyl phenylethynesulfonamide **5a**.

***N*-Methyl-*N*-(4'-phenylbutyl) phenylethynesulfonamide (5b)**

N-methyl-*N*-(4'-phenylbutyl) 1-diazo-2-oxo-2-phenylethanesulfonamide **1b** (200 mg, 0.54 mmol), $Cu(OTf)_2$ (9.95 mg, 5 mol%) and DCM (55 mL) were used following general procedure B overnight. The crude mixture was purified by column chromatography employing 20% ethyl acetate in hexane as eluent. The less polar alkyne sulfonamide **5b** was isolated as a brown oil (27 mg, ~40 mol%). Further purification by column chromatography in 5% ethyl acetate in hexane gave an analytically pure sample of alkyne sulfonamide **5b**.

Yield: 4 mg (2%); yellow oil.

IR (ATR): 2179, 1353, 1158 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.56–7.53 (m, 2H, aromatic *H*), 7.51–7.47 (m, 1H, aromatic *H*), 7.42–7.38 (m, 2H, aromatic *H*), 7.30–7.25* (m, 2H, aromatic *H*), 7.20–7.16 (m, 3H, aromatic *H*), 3.22 (t, *J* = 6.7 Hz, 2H, $PhCH_2CH_2CH_2CH_2$), 2.88 (s, 3H, NCH_3), 2.67 (t, *J* = 7.1 Hz, 2H, $PhCH_2CH_2CH_2CH_2$), 1.75–1.65 (m, 4H, $PhCH_2CH_2CH_2CH_2$).

^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 142.0, 132.9, 131.3, 128.9, 128.57, 128.52, 126.0, 118.5, 89.7, 81.2, 50.7, 35.42, 35.28, 28.3, 26.8.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{19}H_{22}NO_2S$: 328.1366; found: 328.1367.

*This signal overlaps with $CHCl_3$ and as a result integrates to 6H.

(*E*)-*N*-Methyl-3-(methyl(4'-phenylbutyl)amino)-1,4-dioxo-1,4-diphenyl-*N*-(4'-phenylbutyl)but-2-ene-2-sulfonamide (6b)

A second more polar fraction was isolated containing the enamine **6b**.

Yield: 67.0 mg (40%); yellow oil.

IR (ATR): 1680, 1632, 1315, 1137 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.01–7.93 (m, 4H, aromatic *H*), 7.60–7.56 (m, 1H, aromatic *H*), 7.53–7.47 (m, 3H, aromatic *H*), 7.44–7.40 (m, 2H, aromatic H), 7.27–7.02* (m, 10H, aromatic *H*), 3.30–2.38** (m, 14H, 2 x Ph$CH_2CH_2CH_2CH_2NCH_3$ including singlet at 2.60 and triplets at 2.51, *J* = 7.8 Hz and 2.43, *J* = 7.6 Hz), 1.56–1.16*** (m, 8H, 2 x Ph$CH_2CH_2CH_2CH_2$).

^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 190.9, 142.4, 141.5, 135.9, 133.9, 132.9, 129.4, 129.2, 128.7, 128.6, 128.5, 128.4, 128.3, 126.1, 125.7, 108.2, 55.6, 49.9, 42.3, 35.4, 35.2, 34.1, 28.2, 28.1, 27.5, 27.2.

Four carbons not detected (1 x *C*=O, 1 x aromatic *C*, 1 x aromatic *C*H and 1 x *C*=C).

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{38}H_{43}N_2O_4S$: 623.2938; found: 623.2936.

*This signal integrates for 11H due to the presence of $CHCl_3$.

**This signal integrates for 15H due to width of the peak.

***This signal integrates for 9H due to the presence of water.

_N_-Methyl-_N_-(3'-phenylpropyl) phenylethynesulfonamide (5c)

N-(3'-Phenylpropyl) 1-diazo-2-oxo-2-phenylethanesulfonamide **1c** (200 mg, 0.56 mmol), $Cu(OTf)_2$ (10.3 mg, 5 mol%) and DCM (55 mL) were used following general procedure B for 24 h. Upon reaction completion after 24 h, the crude mixture was purified by column chromatography employing a gradient eluent of 10% to 20% ethyl acetate in hexane isolating the less polar sulfonamide alkyne sulfonamide **5c**.

Yield: 11 mg (6%); brown oil.

IR (ATR): 2180, 1353, 1158 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.56–7.53 (m, 2H, aromatic *H*); 7.51–7.46 (m, 1H, aromatic *H*), 7.42–7.38 (m, 2H, aromatic *H*), 7.32–7.28 (m, 2H, aromatic *H*), 7.22–7.19 (m, 3H, aromatic *H*), 3.24 (t, *J* = 7.4, 2H, Ph$CH_2CH_2CH_2$), 2.92 (3H, s, NCH_3), 2.71 (t, *J* = 7.4, 2H, Ph$CH_2CH_2CH_2$), 2.03–1.97 (m, 2H, Ph$CH_2CH_2CH_2$).

^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 141.2, 132.9, 131.3, 128.9, 128.6, 128.5, 126.3, 118.4, 89.8, 81.1, 50.6, 35.5, 32.9, 29.1.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{18}H_{20}NO_2S$: 314.1209; found: 314.1211.

(*E*)-*N*-Methyl-3-(methyl (3'-phenylpropyl)amino)-1,4-dioxo-1,4-diphenyl-*N*-(3'-phenylpropyl)but-2-ene-2-sulfonamide (6c)

A second more polar fraction was isolated containing the enamine **6c**.

Yield: 106 mg (64%); yellow oil.

IR (ATR): 1680, 1632, 1315, 1138 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.05–7.89 (m, 4H, aromatic *H*), 7.64–7.39 (m, 6H, aromatic *H*), 7.28–7.03 (m, 8H, aromatic *H*), 7.00–6.92 (m, 2H, aromatic *H*), 3.28–2.57 (m, 10H, 2 x C*H*$_2$NC*H*$_3$ including singlets at 2.77 and 2.63), 2.54–2.42 (m, 2H, one of PhC*H*$_2$CH$_2$CH$_2$), 2.41–2.27 (m, 2H, one of PhC*H*$_2$CH$_2$CH$_2$), 1.92–1.41* (m, 4H, 2 x PhCH$_2$C*H*$_2$CH$_2$).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 191.8 br, 191.0, 162.1 br, 141.9, 140.3, 139.8, 136.0, 134.0, 132.9, 129.5, 129.1, 128.8, 128.7, 128.6, 128.42, 128.38, 128.2, 126.3, 125.8, 108.2, 55.2, 50.0, 42.3, 34.1, 32.9, 32.6, 29.8, 29.2.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{36}H_{39}N_2O_4S$: 595.2625; found: 592.2620.

*This signal integrates for 5H due to the presence of water.

***N*-Isopentyl-*N*-methyl phenylethynesulfonamide (5d)**

N-Isopentyl-*N*-methyl-1-diazo-2-oxo-2-phenylethanesulfonamide **1d** (200 mg, 0.646 mmol), $Cu(OTf)_2$ (11.9 mg, 5 mol %) and DCM (55 mL) were used following general procedure B for 19 h. The crude mixture was purified by column chromatography employing a gradient eluent of 10% to 20% ethyl acetate in hexane isolating the sulfonamide alkyne **5d**.

Yield: 10 mg (6%); brown oil.

IR (ATR): 2179, 1344, 1153 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.58–7.56 (m, 2H, aromatic *H*), 7.51–7.47 (m, 1H, aromatic *H*), 7.42–7.39 (m, 2H, aromatic *H*), 3.24–3.20 (m, 2H, NC*H*$_2$), 2.91 (s, 3H, NC*H*$_3$), 1.72–1.65 (m, 1H, (CH$_3$)$_2$C*H*), 1.58–1.53 (m, 2H, (CH$_3$)$_2$CHC*H*$_2$CH$_2$), 0.95 (d, *J* = 6.5 Hz, 6H, 2 x C*H*$_3$).

^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 132.8, 131.2, 128.9, 118.5, 89.7, 81.2, 49.4, 36.1, 35.2, 25.7, 22.5.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{14}H_{20}NO_2S$: 266.1209; found: 266.1213.

(*E*)-*N*-Isopentyl-3-(isopentyl(methyl)amino)-*N*-methyl-1,4-dioxo-1,4-diphenylbut-2-ene-2-sulfonamide (6d)

A second more polar fraction was isolated containing the enamine **6d**.

Yield: 57 mg (35%); yellow oil.

IR (ATR): 1680, 1633, 1315, 1135 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.06–7.93 (m, 4H, aromatic *H*), 7.64–7.42 (m, 6H, aromatic *H*), 3.26–2.54* (m, 10H, 2 x C*H*$_2$NC*H*$_3$ including singlets at 2.78 and 2.62), 1.55–1.16 (m, 6H, 2 x (CH$_3$)$_2$C*H*C*H*$_2$CH$_2$), 0.80 (d, *J* = 6.5 Hz, 6H, 2 x C*H*$_3$), 0.74–0.62 (br m, 6H, 2 x C*H*$_3$).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 192.0, 191.0, 140.1, 136.1, 133.9, 132.7, 129.4, 129.1, 128.8, 128.6, 108.1, 54.3, 48.5, 42.3, 36.8, 36.4, 34.0, 25.8, 25.6, 22.5, 22.2.

One carbon not detected

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{28}H_{39}N_2O_4S$: 499.2625; found: 499.2621.

*This signal integrates for 11H due to the width of the signal.

***N, N*-Dimethyl 4'-nitrophenylethynesulfonamide (5e)**[64]

N, *N*-Dimethyl-1-diazo-2-oxo-2-(4'-nitrophenyl)-ethanesulfonamide **1e** (200 mg, 0.67 mmol), $Cu(OTf)_2$ (12.4 mg, 5 mol %) and DCM (55 mL) were used following general procedure B for 20 h. The crude mixture was purified by column chromatography employing 35% ethyl acetate in hexane as eluent isolating the crude sulfonamide alkyne **5e** as a yellow oil (218 mg, ~33 mol% purity). Further purification by column chromatography employing 20% ethyl acetate in hexane isolated alkyne sulfonamide **5e**.

Yield: 9 mg (5%, ~60 mol% purity); yellow oily solid.

IR (ATR): 2181, 1345, 1148 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.31–8.27 (m, 2H, aromatic *H*), 7.80–7.74 (m, 2H, aromatic *H*), 2.94 (s, 6H, NC*H*$_3$).

^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 149.0, 133.9, 125.0, 124.1, 86.9, 83.6, 38.4.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{10}H_{11}N_2O_4S$: 255.0434; found: 255.0430.

(*E*)-3-(Dimethylamino)-*N*,*N*-dimethyl-1,4-bis(4-nitrophenyl)-1,4-dioxobut-2-ene-2-sulfonamide (6e)

A second more polar fraction was isolated containing the more polar enamine **6e** as a yellow oil (32 mg, ~80 mol%). Further purification by column chromatography, employing a gradient eluent of 50% ethyl acetate in hexane to 100% ethyl acetate, isolated enamine **6e**.

Yield: 5 mg (3%, >85 mol% purity); yellow solid; Mp 198–200 °C.

IR (ATR): 1682, 1626, 1524, 1347 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.44–8.37 (m, 2H, aromatic *H*), 8.35–8.27 (m, 2H, aromatic *H*), 8.18–8.11 (m, 2H, aromatic *H*), 8.08–7.95 (br m, 2H, aromatic *H*), 2.95 (br s, 6H, 2 x NCH_3), 2.50 (br s, 6H, 2 x NCH_3).

^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 189.6, 188.2, 150.9, 149.8, 144.7, 139.8, 129.7, 129.5, 124.7, 123.7, 107.8, 44.6, 36.7.

One carbon not detected.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{20}H_{21}N_4O_8S$: 477.1075; found: 477.1078.

***N*-Methyl-*N*-phenyl phenylethynesulfonamide (5g)**

N-Methyl-*N*-phenyl-1-diazo-2-oxo-2-phenylethanesulfonamide **1g** (200 mg, 0.63 mmol), $Cu(OTf)_2$ (11.7 mg, 5 mol %) and DCM (55 mL) were used following general procedure B for 4.5 h. The crude mixture was purified by column chromatography, employing a gradient eluent of 10% to 100% ethyl acetate in hexane, isolating the less polar sulfonamide alkyne **5g**.

Yield: 10 mg (6%); yellow solid; Mp 87–89 °C.

IR (ATR): 2181, 1356, 1147 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.57–7.53 (m, 2H, aromatic *H*), 7.52–7.48 (m, 1H, aromatic *H*), 7.47–7.39 (m, 6H, aromatic *H*), 7.38–7.33 (m, 1H, aromatic *H*), 3.40 (s, 3H, NCH_3).

^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 141.1, 132.9, 131.4, 129.4, 128.9, 128.4, 126.7, 118.3, 90.8, 81.0, 39.0.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{15}H_{14}NO_2S$: 272.0740; found: 272.0749.

(*E*)-*N*-Methyl-3-(methyl(phenyl)amino)-1,4-dioxo-*N*,1,4-triphenylbut-2-ene-2-sulfonamide (6g)

A second more polar fraction was isolated containing the more polar enamine **6g** as a yellow solid (81 mg, ~83 mol%). Enamine **6g** was then further purified by column chromatography in 20% ethyl acetate in hexane.

Yield: 54 mg (33%); yellow solid; Mp 168–170 °C.

IR (ATR): 1673, 1625, 1312, 1139 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.82–7.70 (m, 2H, aromatic *H*), 7.55–7.44 (m, 6H, aromatic *H*), 7.43–7.25 (m, 7H, aromatic *H*), 7.04–6.95 (m, 3H, aromatic *H*), 6.48–6.38 (br m, 2H, aromatic *H*), 3.44 (s, 3H, one of NCH_3), 2.88 (s, 3H, one of NCH_3).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 191.7, 190.9, 160.4, 144.9, 141.5, 139.4, 135.5, 133.5, 133.2, 129.2, 129.1, 129.0, 128.8, 128.6, 127.8, 127.1, 126.2, 125.1, 111.7, 43.2, 40.2.

One carbon not detected.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{30}H_{27}N_2O_4S$: 511.1686; found: 511.1692.

Orange needle crystals of **6g** were recrystallized from acetone. The crystal analysed by single crystal x-ray diffraction was orthorhombic, $C_{30}H_{26}N_2O_4S$, MW = 510.59, space group $P2_12_12_1$, Z = 8, a = 8.52150(10) Å, b = 20.2175(3) Å, c = 30.0136(5) Å, V = 5170.85(13) $Å^3$, D_c = 1.312 g cm^{-3}, μ = 1.430 mm^{-1}, T = 296 K, R_{int} = 0.0419, R_1 = 0.0370 [$I > 2\sigma(I)$], wR_2 = 0.0936 and S = 1.032. CCDC number = 2356988.

***N, N*-Dimethyl phenylethynesulfonamide (5h)**[87,88]

N, *N*-Dimethyl-1-diazo-2-oxo-2-phenylethanesulfonamide **1h** (200 mg, 0.79 mmol), $Cu(OTf)_2$ (14.5 mg, 5 mol %) and DCM (55 mL) were used following general procedure B for 4.5 h. The crude mixture was purified by column chromatography, employing a gradient eluent of 10% to 100% ethyl acetate in hexane, isolating the alkyne sulfonamide **5h**.

Yield: 14 mg, (8%); yellow oil; Lit[87] Mp 94 °C.

IR (ATR): 2179, 1357, 1162 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.61–7.57 (m, 2H, aromatic *H*), 7.52–7.48 (m, 1H, aromatic *H*), 7.44–7.39 (m, 2H, aromatic *H*), 2.91 (s, 6H, 2 x NCH_3).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 133.0, 131.4, 128.9, 118.3, 90.6, 79.3, 38.5.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{10}H_{12}NO_2S$: 210.0583; found: 210.0579.

(*E*)-3-(Dimethylamino)-*N*, *N*-dimethyl-1,4-dioxo-1,4-diphenylbut-2-ene-2-sulfonamide (6h)

A second more polar fraction was isolated containing the enamine **6h**.

Yield: 95 mg (62%); yellow solid; Mp 159–161 °C.

IR (ATR): 1678, 1627, 1314, 1133 cm^{-1}.

^1H NMR (300 MHz): δ = 8.03–7.93 (m, 4H, aromatic *H*), 7.65–7.42 (m, 6H, aromatic *H*), 2.83–2.55 (m, 12H, 2 x $N(CH_3)_2$ including br singlets at 2.72 and 2.64).

^{13}C NMR (75.5 MHz): δ = 192.0, 190.7, 163.1, 139.9, 135.6, 134.1, 132.8, 129.2, 129.1, 128.70, 128.66, 107.5, 43.6, 37.2.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{20}H_{23}N_2O_4S$: 387.1373; found: 387.1357.

Attempted reaction of β-keto sulfonamide 2d with copper(II) triflate

$Cu(OTf)_2$ (13.0 mg, 5 mol%) was suspended in doubly distilled DCM (30 mL) and heated while stirring under reflux under N_2. A solution of *N*-isopentyl-*N*-methyl 2-oxo-2-phenylethanesulfonamide **2d** (200 mg, 0.71 mmol) in doubly distilled DCM (20 mL) was added to the stirring solution dropwise over 15 min followed by a rinse with doubly distilled DCM (5 mL). The mixture was heated under reflux while stirring for 19 h. The reaction mixture was then subsequently cooled and concentrated under reduced pressure to give the crude product. No evidence for the formation of alkyne sulfonamide **6d** was found.

Synthesis of α-chlorosulfonamides (7a, 7d, 7f, 7g) with $CuCl_2$; General Procedure C

$CuCl_2$ (5 mol%) was suspended in doubly distilled DCM (30 mL) and heated while stirring under reflux under N_2. A solution of α-diazo-β-keto sulfonamide **1** (200 mg, 1 eq.) in doubly distilled DCM (20 mL) was added to the stirring solution dropwise over 15 min followed by a rinse with doubly distilled DCM (5 mL). The mixture was stirred under reflux overnight and the reaction progress was monitored by IR and TLC. The reaction mixture was then subsequently cooled and concentrated under reduced pressure to give the crude product. Purification by column chromatography and then followed in some instances by preparative TLC gave the α-chlorosulfonamides **7a, 7d, 7f** and **7g**.

Synthesis of α-chlorosulfonamides (7b, 7c) with $CuCl_2$, NaBARF and bis(oxazoline) ligand (3*S*, 8*R*)-Ind; General Procedure D

$CuCl_2$ (5 mol%), bis(oxazoline) ligand (3*S*, 8*R*)-Ind **9** (6 mol%) and NaBARF (6 mol%) were suspended in doubly distilled DCM (30 mL) and heated while stirring under reflux for 2 h under N_2. A solution of α-diazo-β-keto sulfonamide **1** (200 mg) in doubly distilled DCM (20 mL) was added to the stirring solution dropwise over 15 min followed by a rinse with doubly distilled DCM (5 mL). The mixture was stirred under reflux overnight and the reaction progress was monitored by IR and TLC. The reaction was then subsequently cooled and concentrated under reduced pressure to give the crude product. Purification by column chromatography and then preparative TLC gave the α-chlorosulfonamide products **7b** and **7c**.

***N*-Butyl-1-chloro-*N*-methyl 2-oxo-2-phenylethanesulfonamide (7a)**

N-Butyl-*N*-methyl 1-diazo-2-oxo-2-phenylethanesulfonamide **1a** (200 mg, 0.68 mmol), $CuCl_2$ (4.65 mg, 5 mol%) and DCM (55 mL) were used following general procedure C. The crude mixture was purified by column chromatography employing a gradient eluent of 10 to 20% ethyl acetate in hexane as eluent, isolating α-chlorosulfonamide **7a** as a yellow oil (21 mg, ~50 mol% purity). Further purification by preparative TLC in 10% ethyl acetate in hexane isolated analytically pure α-chlorosulfonamide **7a**.

Yield: 5 mg (2%); yellow oil.

IR (ATR): 1694, 1347, 1149 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.07–8.04 (m, 2H, aromatic *H*), 7.68–7.64 (m, 1H, aromatic *H*), 7.55–7.51 (m, 2H, aromatic *H*), 6.24 (s, 1H, C*H*Cl), 3.42–3.30 (br m, 2H, $CH_3CH_2CH_2CH_2$), 3.02 (s, 3H, NCH_3), 1.62–1.55* (m, 2H, $CH_3CH_2CH_2CH_2$), 1.37–1.29 (m, 2H, $CH_3CH_2CH_2CH_2$), 0.93 (t, *J* = 7.4 Hz, 3H, $CH_3CH_2CH_2CH_2$).

^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 187.5, 134.8, 134.6, 129.8, 129.1, 70.7, 51.9, 36.2, 30.2, 19.7, 13.8.

HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{13}H_{18}{}^{35}ClNO_3SNa$: 326.0588; found: 326.0587.

*This signal integrates to 4H due to the presence of water

1-Chloro-*N*-methyl-*N*-(4'-phenylbutyl) 2-oxo-2-phenylethanesulfonamide (7b)

N-Methyl-*N*-(4'-phenylbutyl) 1-diazo-2-oxo-2-phenylethanesulfonamide **1b** (200 mg, 0.54 mmol), $CuCl_2$ (3.70 mg, 5 mol%), (3*S*, 8*R*)-Ind **9** (10.9 mg, 6 mol%), NaBARF (29.2 mg, 6 mol%) and DCM (55 mL) were used following general procedure D. Upon stirring the reaction mixture under reflux overnight, the crude α-chlorosulfonamide **7b** was isolated by repeated column chromatography (2 columns) each employing a gradient eluent of 5% to 10% ethyl acetate in hexane as eluent, as a yellow oil (15 mg, ~59 mol% purity). Further purification by preparative TLC in 50% DCM in hexane gave an analytically pure sample of α-chlorosulfonamide **7b**.

Yield: 4 mg (2%); yellow oil.

IR (ATR): 1694, 1347, 1152 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.07–8.03 (m, 2H, aromatic *H*), 7.68–7.64 (m, 1H, aromatic *H*), 7.55–7.51 (m, 2H, aromatic *H*), 7.29–7.24* (m, 2H, aromatic *H*), 7.20–7.15 (m, 3H, aromatic H), 6.23 (s, 1H, C*H*Cl), 3.48–3.29 (br m, 2H, $PhCH_2CH_2CH_2CH_2$), 2.98 (s, 3H, NCH_3), 2.65–2.60 (m, 2H, $PhCH_2CH_2CH_2CH_2$), 1.67–1.60** (m, 4H, $PhCH_2CH_2CH_2CH_2$).

^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 187.3, 141.9, 134.7, 134.4, 129.6, 129.0, 128.41, 128.35, 125.9, 70.5, 51.7, 36.0, 35.3, 27.9, 27.3.

HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{19}H_{22}{}^{35}ClNO_3SNa$: 402.0901; found: 402.0895.

*This signal integrates to 3H as it overlaps with the chloroform signal.

**Water seen δ_H 1.58.

1-Chloro-*N*-methyl-*N*-(3'-phenylpropyl) 2-oxo-2-phenylethanesulfonamide (7c)

N-(3'-Phenylpropyl) 1-diazo-2-oxo-2-phenylethanesulfonamide **1c** (200 mg, 0.56 mmol), $CuCl_2$ (3.9 mg, 5 mol%), (3*S*, 8*R*)-Ind **9** (11.3 mg, 6 mol%), NaBARF (30.4 mg, 6 mol%) and DCM (55 mL) were used following general procedure D. Upon stirring the reaction mixture under reflux for 24 h, the crude α-chlorosulfonamide **7c** was isolated by column chromatography, employing a gradient eluent of 5% to 20% ethyl acetate in hexane, as a yellow oil (65 mg, ~29 mol%). To obtain an analytically pure sample, a portion (20 mg) of this sample was further purified by preparative TLC in 50% DCM in hexane isolating α-chlorosulfonamide **7c**.

Yield: 7 mg (3%); yellow oil.

IR (ATR): 1694, 1348, 1153, 967 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.06–8.02 (m, 2H, aromatic *H*), 7.69–7.64 (m, 1H, aromatic *H*), 7.55–7.51 (m, 2H, aromatic *H*), 7.31–7.25* (m, 2H, aromatic *H*), 7.22–7.16 (m, 3H, aromatic *H*), 6.24 (s, 1H, C*H*Cl), 3.48–3.36 (br m, 2H, $PhCH_2CH_2CH_2$), 3.03 (s, 3H, NCH_3), 2.66–2.60 (m, 2H, $PhCH_2CH_2CH_2$), 1.98–1.90 (m, 2H, $PhCH_2CH_2CH_2$).

^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 187.3, 141.0, 134.7, 134.4, 129.6, 129.0, 128.5, 128.3, 126.1, 70.5, 51.6, 36.2, 32.6, 29.6.

HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{18}H_{20}{}^{35}ClNO_3SNa$: 388.0745; found: 388.0742.

*This signal integrates to 4H as it overlaps with the chloroform signal.

1-Chloro-*N*-isopentyl-*N*-methyl 2-oxo-2-phenylethanesulfonamide (7d)

N-Isopentyl-*N*-methyl-1-diazo-2-oxo-2-phenylethanesulfonamide **1d** (200 mg, 0.65 mmol), $CuCl_2$ (4.4 mg, 5 mol%) and doubly distilled DCM (55 mL) were used following general procedure C. Upon stirring the reaction mixture for 24 h under reflux, the crude α-chlorosulfonamide **7d** was isolated by column chromatography, employing a gradient eluent of 7% to 10% ethyl acetate in hexane as eluent, as a yellow oil (16 mg, ~63 mol% purity). In addition, the more polar enamine **6d** was isolated from this column in a 20% yield (~50 mol% purity). The less polar fraction was further purified by column chromatography in 7% ethyl acetate in hexane isolating α-chlorosulfonamide **7d**.

Yield: 5 mg (2%); yellow oil.

IR (ATR): 1694, 1348, 1150, 961 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.08–8.04 (m, 2H, aromatic *H*), 7.69–7.64 (m, 1H, aromatic *H*), 7.55–7.51 (m, 2H, aromatic *H*), 6.24 (s, 1H, C*H*Cl), 3.43–3.29 (br m, 2H, CH_2N), 3.01 (s, 3H, NCH_3), 1.68–1.56* (m, 1H, $(CH_3)_2CH$), 1.53–1.46 (m, 2H, $(CH_3)_2CHCH_2CH_2$), 0.91 (d, *J* = 6.6 Hz, 6H, 2 x CH_3).

^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 187.5, 134.8, 134.6, 129.8, 128.1, 70.7, 50.6, 37.0, 36.2, 25.6, 22.56, 22.53.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{14}H_{21}{}^{35}ClNO_3S$: 318.0952; found: 318.0927.

*This signal integrates for 4H due to the presence of water.

Investigation of the synthesis of 1-chloro-*N*-isopentyl-*N*-methyl 2-oxo-2-phenylethanesulfonamide (7d) with variation of catalyst loading and solvent

$CuCl_2$ (86.9 mg, 0.65 mmol, 1 molar eq.) was suspended in doubly distilled DCM (30 mL) and heated while stirring under reflux under an atmosphere of N_2. A solution of *N*-isopentyl-*N*-methyl-1-diazo-2-oxo-2-phenylethanesulfonamide **1d** (200 mg, 0.65 mmol) in doubly distilled DCM (20 mL) was added to the stirring solution dropwise over 15 min followed by a rinse with doubly distilled DCM (5 mL). The mixture was then stirred under reflux for 24 h and the reaction progress was monitored by IR and by TLC. The reaction was then subsequently cooled and concentrated under reduced pressure. The α-chlorosulfonamide **7d** was isolated by column chromatography, employing a gradient eluent of 5% to 10% ethyl acetate in hexane as eluent, as a yellow oil (85 mg, 45%).

α-Chlorosulfonamide **7d** 117 mg (63%); yellow oil was isolated from 1 molar equivalent of $CuCl_2$ in toluene following the procedure above but using distilled toluene (55 mL in total) in place of DCM and stirring for 20 h at 58 °C. Full consumption of the α-diazo-β-keto sulfonamide **1d** was evident in the crude product mixture.

α-Chlorosulfonamide **7d** 8 mg (4%); yellow oil was isolated from 5 mol% $CuCl_2$ (4.4 mg, 0.033 mmol) in toluene following the procedure above but using distilled toluene (55 mL in total) in place of DCM and stirring for 4.5 h at 58 °C.

***N, N*-Dibutyl-1-chloro 2-oxo-2-phenylethanesulfonamide (7f)**

N, *N*-Dibutyl 2-oxo-2-phenylethanesulfonamide **1f** (200 mg, 0.59 mmol), $CuCl_2$ (4.1 mg, 5 mol %) and DCM (55 mL) were used following general procedure C. Upon stirring the reaction mixture for 24 h under reflux, the crude α-chlorosulfonamide **7f** was isolated by column chromatography, employing a gradient eluent of 10% to 20% ethyl acetate in hexane, as a yellow oil (22 mg, ~63 mol% purity). The sample was further purified by crystallisation in hot hexane isolating α-chlorosulfonamide **7f**.

Yield: 8 mg (4%); pale yellow solid; Mp 49–51 °C.

IR (ATR): 1695, 1347, 1148 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.09–8.03 (m, 2H, aromatic *H*), 7.68–7.62 (m, 1H, aromatic *H*), 7.55–7.50 (m, 2H, aromatic *H*), 6.16 (s, 1H, C*H*Cl), 3.41–3.23 (m, 4H, $(CH_3CH_2CH_2CH_2)_2$), 1.71–1.56* (m, 4H, $(CH_3CH_2CH_2CH_2)_2$), 1.40–1.27 (m, 4H, $(CH_3CH_2CH_2CH_2)_2$), 0.93 (t, *J* = 7.6, 6H, $(CH_3CH_2CH_2CH_2)_2$).

^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 187.3, 134.74, 134.59, 129.8, 129.0, 70.9, 49.2, 31.1, 20.0, 13.9.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{16}H_{25}{}^{35}ClNO_3S$: 346.1238; found: 346.1240.

*This signal integrates to 5H due to the presence of water.

1-Chloro-*N*-methyl-*N*-phenyl 2-oxo-2-phenylethanesulfonamide (7g)

N-Methyl-*N*-phenyl-1-diazo-2-oxo-2-phenylethanesulfonamide **1g** (200 mg, 0.63 mmol), $CuCl_2$ (4.4 mg, 5 mol %) and DCM (55 mL) were used following general procedure C. Upon stirring the reaction mixture for 24 h, the crude α-chlorosulfonamide **7g** was isolated by column chromatography, employing a gradient eluent of 10% to 20% ethyl acetate in hexane as eluent, as a green oil (22 mg, ~20 mol% purity). The sample was further purified by preparative TLC in 7–10% ethyl acetate in hexane isolating α-chlorosulfonamide **7g**. In addition, the alkyne sulfonamide **5g** was isolated in a 2% yield.

Yield: 6 mg (3%, ~80 mol% purity); yellow oil.

IR (ATR): 1694, 1358, 1147 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.94–7.91 (m, 2H, aromatic *H*), 7.63–7.57* (1H, m, aromatic *H*), 7.55–7.52 (m, 2H, aromatic *H*), 7.49–7.36** (m, 5H, aromatic *H*), 6.17 (s, 1H, C*H*Cl), 3.52 (s, 3H, NCH_3).

^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 186.4, 140.4, 134.8, 134.3, 129.9, 129.7, 128.9, 128.5, 127.7, 69.7, 42.0.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{15}H_{14}{}^{35}ClNO_3SNa$: 346.0275; found: 346.0281.

*****This signal integrates to 1.6H due to the presence of impurities.

**This signal integrates to 7H due to the presence of solvent or impurities.

(1-Methyl-2,2-dioxido-1,3-dihydrobenzo[c]isothiazol-3-yl)phenylmethanone (8g)[56]

A second more polar fraction was isolated containing the more polar benzo-γ-sultam **8g** as a yellow solid (76 mg, ~46 mol% purity). Benzo-γ-sultam **8g** was then further purified by column chromatography employing 15% ethyl acetate in hexane.

Yield: 48 mg (26%); yellow solid; Mp 109–111 °C, lit[56] 112–113 °C.

IR (ATR): 1683, 1315, 1174 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.18–8.09 (m, 2H, aromatic *H*), 7.74–7.65 (m, 1H, aromatic *H*), 7.63–7.53 (m, 2H, aromatic *H*), 7.45–7.36 (m, 1H, aromatic *H*), 7.21–7.15 (m, 1H, aromatic *H*), 7.13–7.03 (m, 1H, aromatic *H*), 6.86–6.76 (m, 1H, aromatic *H*), 6.08 (s, 1H, C*H*COPh), 3.18 (s, 3H, NCH_3).

Spectroscopic characteristics were consistent with previously reported data.[56]

Examination of the ^{1}H NMR spectrum of the crude product mixture indicated that the ratio of the α-chlorosulfonamide **7g** to the benzo-γ-sultam **8g** was approximately 1:3 and these compounds accounted for approximately 10% and 30% of the crude product mixture respectively.

1-Bromo-*N*-butyl-*N*-methyl 2-oxo-2-phenylethanesulfonamide (11a)

$CuBr_2$ (151 mg, 0.68 mmol, 1 molar eq.) was suspended in doubly distilled DCM (30 mL) and heated while stirring under reflux under an atmosphere of N_2. A solution of *N*-butyl-*N*-methyl 1-diazo-2-oxo-2-phenylethanesulfonamide **1a** (200 mg, 0.68 mmol) in doubly distilled DCM (20 mL) was added to the stirring solution in one portion followed by a rinse with doubly distilled DCM (5 mL). The mixture was then stirred under reflux for 16 h and the reaction progress was monitored by IR and by TLC. The reaction was then subsequently cooled, filtered to remove unreacted $CuBr_2$ and concentrated under reduced pressure. Purification by column chromatography, employing a gradient eluent of 10% to 20% ethyl acetate in hexane, isolated the α-bromosulfonamide **11a**.

Yield: 12 mg (5%); yellow oil.

IR (ATR): 1690, 1345, 1149 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.06–8.02 (m, 2H, aromatic *H*), 7.68–7.63 (m, 1H, aromatic *H*), 7.55–7.50 (m, 2H, aromatic *H*), 6.25 (s, 1H, C*H*Br), 3.48–3.28 (br m, 2H, $CH_3CH_2CH_2CH_2$), 3.03 (s, 3H, NCH_3), 1.64–1.55* (m, 2H, $CH_3CH_2CH_2CH_2CH_2$), 1.38–1.30* (m, 2H, $CH_3CH_2CH_2CH_2CH_2$), 0.93 (t, *J* = 7.4 Hz, 3H, $CH_3CH_2CH_2CH_2$).

^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 187.7, 134.8, 134.3, 129.7, 129.1, 58.3, 52.1, 36.3, 30.2, 19.7, 13.8.

HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{13}H_{18}{}^{79}BrNO_3SNa$: 370.0083; found: 370.0088.

*****This signal integrates to 3H due to the presence of water.

******This signal integrates to 3H due to the presence of solvent or impurities.

1-Bromo-*N*-methyl-*N*-(3'-phenylpropyl) 2-oxo-2-phenylethanesulfonamide (11c)

$CuBr_2$ (125 mg, 0.56 mmol, 1 molar eq.) was suspended in distilled toluene (30 mL) and heated while stirring under reflux under an atmosphere of N_2. A solution of *N*-methyl-*N*-(3'-phenylpropyl) 1-diazo-2-oxo-2-phenylethanesulfonamide **1c** (200 mg, 0.56 mmol) in distilled toluene (20 mL) was added to the refluxing mixture in one portion followed by a rinse with distilled toluene (5 mL). The mixture was then stirred under reflux for 2.5 h and the reaction progress was monitored by IR and by TLC and showed complete disappearance of **1c**. The reaction was then subsequently cooled, filtered to remove unreacted $CuBr_2$ and concentrated under reduced pressure. Purification by column chromatography, employing a gradient eluent of 10% to 15% ethyl acetate in hexane, isolated α-bromosulfonamide **11c**.

Yield: 48 mg (21%); yellow oil.

ν_{max} (ATR)/cm^{-1} 1689, 1345, 1152, 966.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.04–8.00 (m, 2H, aromatic *H*), 7.68–7.64 (m, 1H, aromatic *H*), 7.55–7.50 (m, 2H, aromatic *H*), 7.30–7.26* (m, 2H, aromatic *H*), 7.22–7.16 (m, 3H, aromatic *H*), 6.25 (s, 1H, C*H*Br), 3.51–3.36 (br m, 2H, $PhCH_2CH_2CH_2$), 3.04 (s, 3H, NCH_3), 2.67–2.61 (m, 2H, $PhCH_2CH_2CH_2$), 1.99–1.91 (m, 2H, $PhCH_2CH_2CH_2$).

^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 187.7, 141.2, 134.8, 134.3, 129.7, 129.2, 128.6, 128.4, 126.2, 58.3, 51.9, 36.4, 32.7, 29.8.

HRMS (ESI): *m/z* $[M]^+$ calcd for $C_{18}H_{20}{}^{79}BrNO_3S$: 410.0420; found: 410.0419.

*This signal integrates to 4H due to the presence of chloroform.

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SI:

The SI includes details of preparation and characterization of methane sulfonamides (**3a**–**3f**, **4a**–**4d**) and β-keto sulfonamides (**2a**–**2h**), and ^{1}H and ^{13}C NMR spectra of α-diazo-β-keto sulfonamides (**1a**–**1h**), alkyne sulfonamides (**5a**–**5e**, **5g** and **5h**), enamines (**6a**–**6e**, **6g** and **6h**) and α-halosulfonamides (**7a**–**7d**, **7f**, **7g**, **11a** and **11c**).

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