Delivering Enhanced Efficiency in the Synthesis of α-Diazosulfoxides by Exploiting the Process Control Enabled in Flow

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Continuous-flow generation of α-diazosulfoxides results in a two- to three-fold increase in yields and decreased reaction times compared to standard batch synthesis methods. These high yielding reactions are enabled by flowing through a bed of polystyrene-supported base (PS-DBU or PS-NMe_2) with highly controlled residence times. This engineered solution allows the α-diazosulfoxides to be rapidly synthesized while limiting exposure of the products to basic reaction conditions, which have been found to cause rapid decomposition. In addition to improved yields, this work has the added advantage of ease of processing, increased safety profile, and scale-up potential.

Keywords: diazo transfer, sulfoxides, continuous flow, immobilized base, solid-phase synthesis, residence time control

1. Introduction

Utilization of continuous-flow processing for both synthesis and analysis is an area of growing importance in organic chemistry, particularly for the fine chemical and pharmaceutical industries as encapsulated by the many recent reviews published in this area [1–10]. Continuous-flow processing is an attractive option due to the enhanced safety profile, increased mixing, greater temperature control, enhanced efficiency, and easy manipulation for the synthesis of diverse organic compounds. Furthermore, it allows the generation of hazardous or highly reactive compounds which can be utilized in situ, eliminating isolation or stockpiling [8, 11, 12]. Continuous-flow synthesis can also be automated to generate libraries of novel compounds quickly and efficiently, with easy control of reaction conditions and stoichiometric ratios [13]. Recent examples of reactions that have been impactful and are exceptionally well suited to continuous-flow processing are reported in the literature [14, 15]. Notable examples include the report by Zhang et al. from Massachusetts Institute of Technology (MIT) which described a method for on-demand synthesis of four active pharmaceutical ingredients (APIs) from one compact system, allowing for the upstream and downstream processing in one location, in a short amount of time [16]. Another example which highlights the benefits of flow processing is the report by Kobayashi et al., who synthesized drug molecules in an 8-step synthesis without the isolation of intermediates, using only column reactors, packed with heterogeneous catalysts and isolated the target compounds with high enantioselectivity [17]. A recent report by our research group highlights the advantage of flow processing when dealing with hazardous reagents, allowing the generation of tosyl azide in the flow system, followed by in situ diazo transfer and use of a sacrificial quench to neutralize any potential hazard [18].

The diazo transfer reaction is one of the most widely used methods for the generation of α-diazocarbonyl compounds, and efforts are underway to make this process safer and greener so that it is more attractive to industry [11, 12, 19, 20]. Notably, recent work within our group has described a greener diazo transfer methodology in water, with substoichiometric base [19]. Protocols for continuous diazo transfer processes have been recently described by our group and others [18, 21, 22]. The Regitz diazo transfer methodology [23] works consistently well across substrates where the methylene group is doubly activated, namely, β-keto esters, β-keto amides, β-keto sulfones, and phosphonates [20]. However, in contrast, diazo transfer to generate α-diazosulfoxides has proven elusive due to the inherent instability of the α-diazosulfoxide moiety [24]. Careful substrate design by our group led to isolation, for the first time, of stable α-diazosulfoxides, in both racemic and enantiopure form [25]; conformational constraint in lactones and lactams was essential to enable isolation of stable compounds possessing the diazosulfoxide moiety [26, 27]. Based on this work, the instability of simple acyclic α-diazosulfoxides is believed to be due to the overlap of the sulfinyl lone pair with the anti-bonding orbital of the diazo moiety [26]. Constraining the orientation of the sulfoxide and the diazo moiety in cyclic systems provides sufficient stability to isolate and characterize these novel compounds [27].

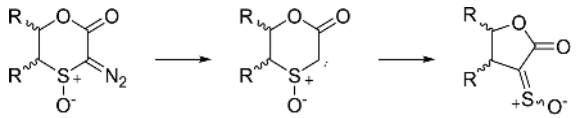
α-Diazosulfoxides, like most other α-diazocarbonyl compounds, are exceptionally reactive compounds under transition metal catalysis, photolysis, thermolysis, and microwave irradiation conditions leading to α-oxo sulfine intermediates in a hetero-Wolff rearrangement (Scheme 1) [28–31]. The utility and synthetic versatility of α-oxo sulfines have been reported and reviewed in the literature [32–36].

While careful design of the cyclic substrates led to successful isolation of α-diazosulfoxides [26, 27], the efficiency of their synthesis was significantly limited by partial decomposition of the labile α-diazosulfoxides within the basic reaction conditions, leading to recovered yields of typically 30% or less. Based on our recent success in effecting diazo transfer to standard precursors in flow systems [18], the potential to control more closely the synthesis and isolation of α-diazosulfoxides by diazo transfer in a continuous-flow system was investigated with the objective of improving product recovery.

2. Results and Discussion

The sulfoxide substrates **1a–d** (Scheme 2) were selected as precursors for this study because they provide a good insight in

Scheme 1. Reactivity of α-diazosulfoxides to form α-oxo sulfines via a hetero-Wolff rearrangement



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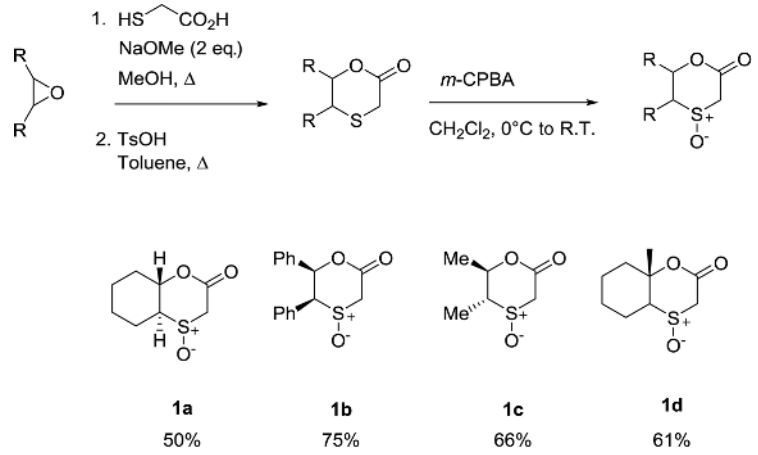
Scheme 2. Synthesis of sulfoxide precursors



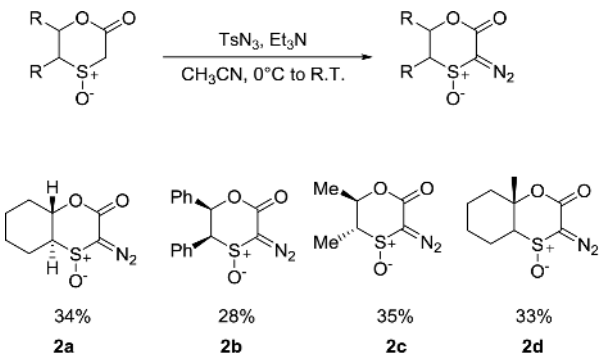
to the robustness of the approach through variation of the steric and conformational properties across the series. The sulfoxides **1a–d** and their corresponding α-diazosulfoxides **2a–d** have been previously reported and characterized (Scheme 2).

Diazo transfer to β-oxosulfoxides under batch conditions is typically conducted overnight to effect reaction completion, providing only moderate yields but with complete consumption of the sulfoxide precursor [27]. The batch procedure consists of 1 eq. of tosyl azide as the diazo transfer reagent, 1 equivalent of triethylamine as base and acetonitrile as solvent. The reaction time in batch is consistently between 16 and 24 h to achieve 100% conversion, with the exception of the *cis*-diphenyl sulfoxide **1b** where the reaction goes to completion in 6 h. To ensure direct comparability of results with the flow chemistry undertaken within this work, the batch synthesis of **2a–d** was repeated using the same batch of sulfoxide precursors **1a–d**, producing yields similar in magnitude to those in our published results as shown in Scheme 3.

Tosyl azide is traditionally used in batch diazo transfer reactions and was initially used in our continuous-flow reactions. However, *p*-dodecylbenzenesulfonyl azide (DBSA) was later used instead of tosyl azide as the diazo transfer reagent for two reasons. Firstly, the relatively low polarity of the dodecylbenzenesulfonyl amide by-product makes chromatographic purification of the α-diazosulfoxides more efficient. The second reason is the additional safety aspect compared to most other diazo transfer reagents. DBSA is an oil at room temperature with an approximate initiation temperature of 151 °C and an impact sensitivity of 150 kg·cm, compared to tosyl azide, which has an impact sensitivity of 50 kg·cm and an initiation temperature of 120 °C [38].

The initial study was an investigation of how the established batch protocol would perform in a continuous-flow reactor (Table 1). The sulfoxide **1a** was selected as the substrate for initial investigation of a flow process. Initial results on transferring the batch reaction conditions directly to continuous flow were not very promising, showing limited success in terms of efficiency of diazo transfer with substantial unreacted sulfoxide recovered, in contrast to the batch reactions. Variation in the equivalents of base, residence time, and temperature (up to 40 °C) did not yield conversion above 40% (Table 1). Conversions were determined by proton nuclear magnetic resonance (^{1}H NMR) spectroscopy of the crude product recovered from the flow reactor; due to the low conversions to product, chromatographic purifications were not conducted for this part of the study.

Scheme 3. Synthesis of α-diazosulfoxides via diazo transfer in batch conditions

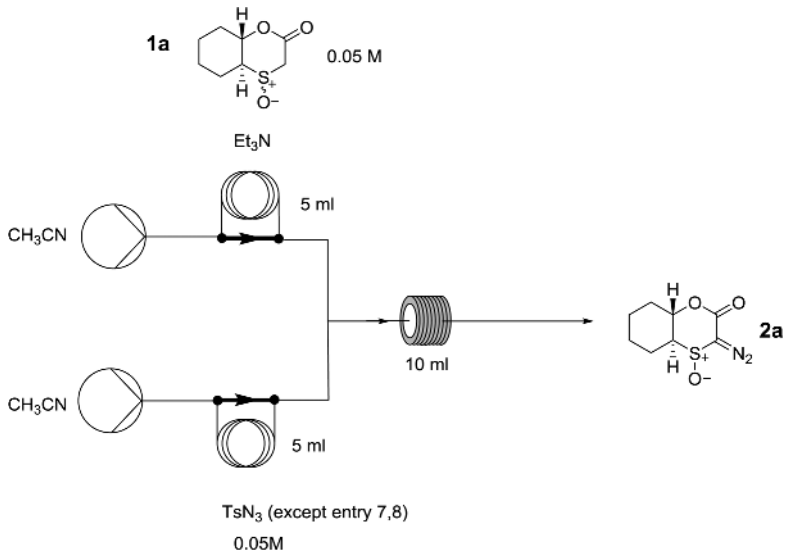


To optimize the diazo transfer reaction under flow conditions, it was decided to subsequently investigate the effect of changing the base. A series of secondary and tertiary amine bases was screened with poor conversion being observed in all cases (Table 2). When DBU was employed (Table 2, entry 5), a significant and rapid red coloration was noted at the "T"-piece where the DBU solution mixes with the sulfoxide and sulfonyl azide solution; this deep color is reminiscent of the final color of the batch process after 16 h (Figure 1), and this coloration was not observed in the other flow reactions (Table 2, entries 1–4). As diazo transfer proceeds under typical batch conditions, the color changes from colorless to yellow and, finally, to red as the reaction progresses over 16 h. We believe that the red color reflects decomposition of the labile α-diazosulfoxide on prolonged exposure to base, as the pure α-diazosulfoxides are yellow crystalline solids. This intense and rapid red coloration observed in the tubing on exposure to DBU in the flow system is indicative of effective diazo transfer with DBU as base, followed by rapid base mediated decomposition on continued exposure to DBU (Table 2, entry 5).

We hypothesized that an effective diazo transfer to these sulfoxide substrates could be realized if a strong base was selected to achieve rapid diazo transfer, while minimizing the associated base-mediated decomposition through reduced reaction times. The close control of the residence time enabled by the use of continuous processing is a parameter which is not accessible in batch conditions and has proven extremely valuable in the literature, resulting in high chemo- and/or stereoselectivity depending on the residence time [39]. To test our hypothesis, we investigated the use of polystyrene-supported DBU (PS-DBU) and other solid-phase bases with the objective of rapid formation of the diazo product but with a very short period of subsequent exposure of this product to the base (Table 3). Controlled exposure of reactions to immobilized reagents is readily facilitated by flowing the reaction through a glass Omnifit® column containing the immobilized reagent [40].

Using polystyrene-supported DBU led to 100% consumption of starting material **1a** producing a crude product (Table 2,

Table 1. Direct transfer of batch conditions to continuous-flow mode



Entry	Residence time (min)	Et_3N (eq.)	Tosyl azide	Temp.	Conversion (%)[a]
1	25	1	1	22	22
2	50	3	1	25	26
3	50	1	1	25	17
4	50	1	1	40	22
5	50	1.9	2	40	38
6	25	1	1	40	26
7	50	1	1 (DBSA)	25	38
8	50	2	1 (DBSA)	40	40

[a] Conversions determined by ^{1}H NMR spectroscopy.

entry 1) which, by ^{1}H NMR spectroscopy, appeared as essentially pure diazosulfoxide **2a** with less evidence of decomposition relative to the product from the homogeneous phase DBU reaction (Table 2, entry 5). Regeneration of polymer-supported DBU has previously been reported using a 1-M solution of DBU in dichloromethane [41]. This method was successfully used in our lab to regenerate the polymer-supported DBU, and this regenerated material was then used in turn, for a second successful diazo transfer reaction with 100% conversion to **2a** achieved. These reactions gave comparable results to the commercially sourced PS-DBU. The use of polystyrene-supported dimethylamine (PS-NMe_2, Amberlyst A21) as a catalyst or reagent in organic synthesis and continuous-flow synthesis is attractive in terms of cost and potential for regeneration [42–44]. Gratifyingly, excellent results were achieved using PS-NMe_2, as base (Table 3 entries 3–4) resulting in complete diazo transfer to **1a** within just 9 min residence time. Accordingly, subsequent studies in expanding the substrate scope focused on the use of PS-NMe_2 (Table 4).

The flow diazo transfer process using PS-NMe_2 and DBSA was applied to the sulfoxide series **1a**–**d** with complete diazo transfer being observed within 9 min in all cases (Table 4). Furthermore, the isolated yields of **2a**–**d** are between 10 and 15%, higher than those observed under standard batch reaction conditions. Notably, sulfoxide **4d** was obtained with a reproducibly high yield of 70% confirming that this process can be improved through use of immobilized base in flow.

The final outcome of the diazo transfer to the sulfoxide series is a combination of the efficiency of diazo transfer and the extent to which the products undergo decomposition under the reaction conditions. Thus, the amount of base and the length of exposure must be finely balanced to effect complete diazo transfer but with minimal exposure of the product to the base. Accordingly, it was decided to direct our optimization towards maximizing the isolated yield, rather than maximum conversion.

Table 5 illustrates the results of a yield optimization study whereby the effect of reducing the equivalents of base and azide, and the residence time were investigated. The reaction residence time was varied by increasing the flow rate for the reactions. Although 100% conversion was achieved using the conditions outlined in Table 3, the highest isolated yields were obtained when 5 eq. of base were used with a median residence

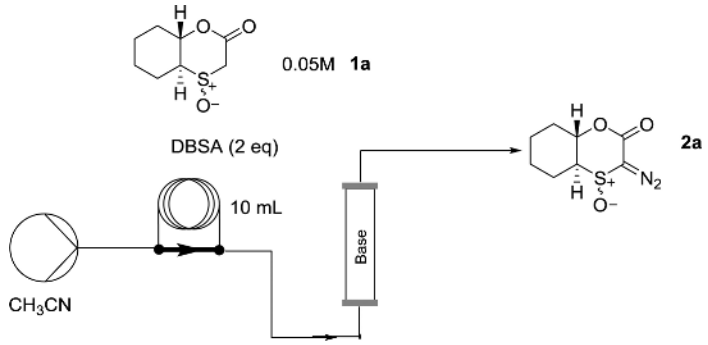
Table 2. Investigation of the use of homogeneous phase bases

Entry	Base (eq.)	Diazo transfer reagent (eq.)	Residence time (min)	Conversion (%)[a]
1	Et_2NH (1.05)	Tosyl azide (1.05)	25	9
2	Et_3N (2)	DBSA (1)	50	40[b]
3	Et_3N (1.9)	Tosyl azide (2)	50	38[b]
4	DIPEA (1.05)	Tosyl azide (1.05)	25	4
5	DBU (1.05)	Tosyl azide (1.05)	25	–[c]

[a] Conversions were determined by ^{1}H NMR spectroscopy. [b] These reactions were carried out at 40 °C. [c] The percentage conversion to α-diazosulfoxide could not be determined due to the decomposition of the product to multiple unidentifiable products.

Figure 1. Comparison of crude reaction mixtures from flow (yellow) and batch (red) reactions

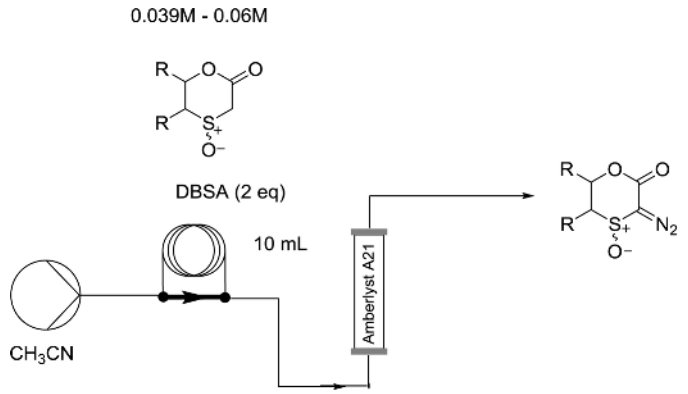
Table 3. Investigation into the use of solid-phase bases

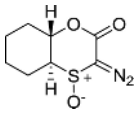
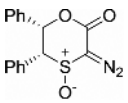
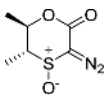
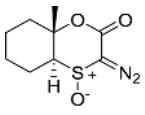


Entry	Base (eq.)	Diazo transfer reagent (eq.)	Residence time (min)	Conversion (%)
1	PS-DBU (5)	Tosyl azide (2)	9	100
2	K_2CO_3 (5)	Tosyl azide (2)	15	3
3	PS-NMe_2 (20)	Tosyl azide (2)	9	100
4	PS-NMe_2 (20)	DBSA (2)	9	100

time of 9 min (Table 5, entry 12). A comparable yield is recorded when a large excess (20 eq.) of base is used with a short residence time of 4.5 min (Table 5, entry 3). The lowest yield was recorded when there was a large excess (20 eq.) of base and a long residence time of 9.5 min (Table 5, entry 1). This supports our hypothesis that significant decomposition of the α-diazosulfoxide occurs under prolonged exposure to basic conditions, either through a large excess of PS-NMe_2 or

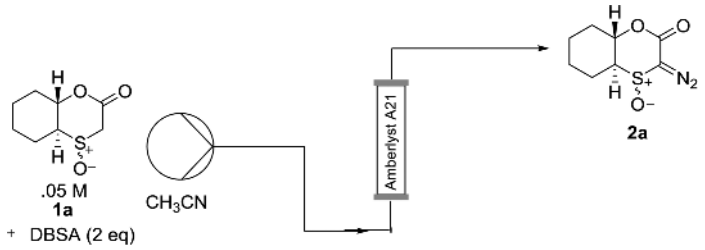
Table 4. Diazo transfer in flow using Amberlyst A21 as base



Entry	Product	Residence time (min)	Conversion (%)	Yield (%)[a]
1	 2a	9	100	49
2	 2b	9	100	30
3	 2c	9	100	47
4	 2d	9	100	70

[a] After column chromatography.

Table 5. Yield optimization by reduction of residence time, and equivalents of base



Entry	Amberlyst A21	Diazo transfer reagent(eq.)	Residence time (min)	Conversion (%)	Yield (%)
1	(20 eq.)	DBSA (2)	9.5	100	47
2	(20 eq.)	DBSA (2)	9	100	49
3	(20 eq.)	DBSA (2)	4.5	100	73
4	(20 eq.)	DBSA (2)	2.25	98	73
5	(7 eq.)	DBSA (2)	4.5	96	68
6	(7 eq.)	TsN_3 (2)	6.5	100	–
7	(7 eq.)	DBSA (1.2)	6.5	73	–
8	(7 eq.)	DBSA (1.2)	9	82	–
9	(7 eq.)	DBSA (1.5)	9	85	54
10	(5 eq.)	DBSA (2)	4.5	77	68
11	(5 eq.)	DBSA (2)	9.5	95	71
12	(5 eq.)	DBSA (2)	9	86	76

extended residence time on the PS-NMe_2. Interestingly, the low yield of 47% (Table 5, entry 1) under the less controlled flow conditions still represents a significant improvement over the standard batch reaction conditions.

These optimized conditions (Table 5, entry 12) from the flow reaction were compared to the standard batch conditions. With 2 eq. of DBSA, 5 eq. of PS-NMe_2, and a reaction time of 16 h, 100% conversion was achieved with an isolated yield of 61% after column chromatography. When the reaction time in batch is reduced to 9 min, as a direct comparison to the flow reaction, a significantly lower conversion of only 39% is achieved (Scheme 4). Interestingly, when the batch comparison was carried out using 20 eq. of the PS-NMe_2 and 9 min reaction time, no α-diazosulfoxide **2a** was recovered.

Using the optimized conditions (Table 5, entry 12) for the α-diazosulfoxide **2a**, a series of α-diazosulfoxides was synthesized (Table 6). A dramatic increase in yield, relative to the batch conditions, was achieved for the series **1a**–**d** using the flow process. Despite working on these compounds for over 16 years, this continuous approach provides access to the lactone based α-diazosulfoxides in synthetically useful quantities for the first time by enabling a level of control over the reaction

Scheme 4. Batch reaction using conditions comparable to the optimized flow process

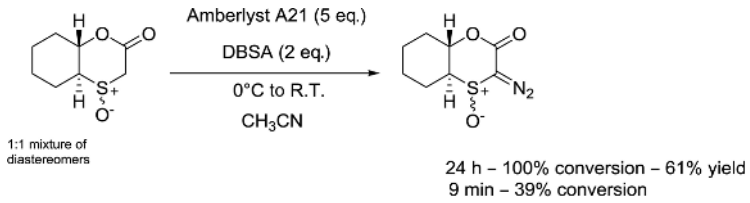
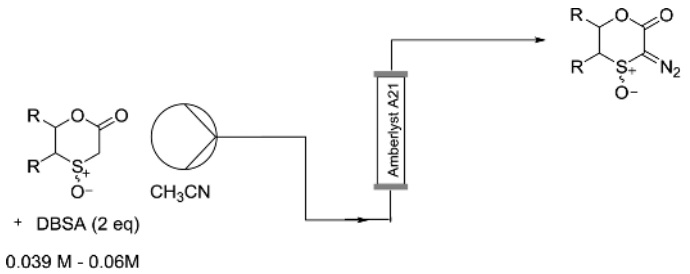
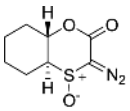
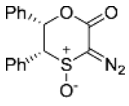
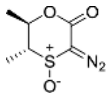
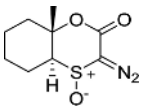


Table 6. Isolated yields of products using the newly established flow procedure



Entry	1	2	3	4
Substrate				
(Flow conversion %) Flow yield (%)	(86) 76	(96) 88	(100) 86	(98) 86
Batch yield (%)	34	28	35	33

residence time, thereby limiting exposure of the product to base, which is not possible under batch conditions.

Substrate **1d** was more soluble in acetonitrile than **1a**–**c**, and consequently, the diazo transfer to **1d** could be conducted at higher concentrations (0.09 M relative to 0.05 M) albeit with a reduction in yield (60% cf. 86%) and partial coloration associated with decomposition, in a manner similar to the batch reactions.

3. Conclusion

In conclusion, by using solid-phase bases and, in particular, PS-NMe_2, in a glass reactor column, we have significantly enhanced the synthesis of α-diazosulfoxides, resulting in a dramatic increase in isolated yields and reduction in reaction times. The new conditions perform consistently well across a range of lactone-derived α-diazosulfoxide substrates with 2- to 3-fold increases in yield over the standard batch conditions. Both PS-NMe_2 and polystyrene-supported DBU are applicable to the reaction. This flow method enables reproducible access to a high yielding synthesis of the α-diazosulfoxides for the first time in over 16 years of research in our team, and also shows greater potential for scale-up. This study highlights the advantages of highly controlled residence times in flow which can enable efficient synthesis of compounds that are sensitive to prolonged exposure to the reaction conditions.

4. Experimental Section

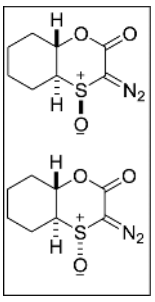
4.1. General. Solvents were distilled prior to use as follows: ethyl acetate was distilled from potassium carbonate, and hexane was distilled prior to use. Organic phases were dried using anhydrous magnesium sulfate. All commercial reagents were used without further purification unless otherwise stated. ^{1}H (300 MHz) and ^{13}C (75.5 MHz) NMR spectra were recorded on a Bruker Avance 300 MHz NMR spectrometer. ^{1}H (400 MHz) and ^{13}C (100.6 MHz) NMR spectra were recorded on a Bruker Avance 400 MHz NMR spectrometer. All spectra were recorded at 300 K in deuterated chloroform ($CDCl_3$) unless otherwise stated, using tetramethylsilane (TMS) as internal standard. Chemical shifts (δ_H and δ_C) are reported in parts per million (ppm) relative to TMS, and coupling constants are expressed in hertz (Hz). Splitting patterns in ^{1}H spectra are designated as s (singlet), d (doublet), dd (doublet of doublets), ddd (doublet of doublet of doublets), t (triplet), q (quartet), and m (multiplet). Infrared spectra were measured using a Perkin Elmer FTIR UATR2 spectrometer. Wet flash column chromatography was carried out using Kieselgel silica gel 60, 0.040–0.063 mm (Merck). Thin-layer chromatography (TLC) was carried out on precoated silica gel plates (Merck 60 PF254). Visualization was achieved by UV (254 nm) light absorption. Low resolution mass spectra (LRMS) were recorded on a Waters Quattro Micro triple quadrupole instrument in electrospray ionization (ESI) mode using 50% acetonitrile–water containing 0.1% formic acid as eluent. High resolution (precise) mass spectra (HRMS) were recorded on a Waters LCT Premier Tof LC–MS instrument in electrospray ionization mode using 50% acetonitrile–water containing 0.1% formic acid as eluent. Samples were prepared for either LRMS or HRMS by employing acetonitrile as solvent. Melting points were obtained using a uni-melt Thomas Hoover Capillary melting point apparatus and are uncorrected.

4.2. Typical Batch Procedure for the Synthesis of α-Diazosulfoxides. Triethylamine (0.29 mL, 1.95 mmol, 1 eq.) was added to a stirring solution of the sulfoxide **1a** (0.39 g, 2.07 mmol) in acetonitrile (20 mL). Tosyl azide (0.40 g, 1.95 mmol) was then added dropwise at 0 °C under nitrogen, and the solution was stirred overnight while slowly returning to room temperature to give a red colored solution. The mixture was concentrated under reduced pressure to give the crude product as an orange oil. Purification by column chromatography provided the pure α-diazosulfoxide **2a**.

4.3. Typical Method for Diazo Transfer in a Continuous-Flow Reactor Using Homogeneous Bases (Tables 1 and 2). Acetonitrile was pumped through the system at a flow rate of 0.1 mL/min for 10 min to purge the system by means of a HPLC pump. The substrate (1 eq.) and triethylamine (1 eq.) were dissolved in acetonitrile (0.05 M). Separately, *p*-tosyl azide (1 eq.) was also dissolved in acetonitrile (0.05 M). The substrate and reagent solutions were injected into flowing streams of acetonitrile (0.1 mL/min each) which were pumped into a T-piece where they met (0.1 mL/min each). The combined stream passed through a 10-mL reactor coil before passing through a back pressure regulator (8 bar). The product was collected and concentrated under reduced pressure without heating.

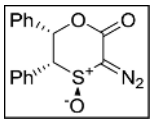
4.4. General Procedure for the Continuous-Flow Synthesis of α-Diazosulfoxides Using Solid-Phase Bases (Tables 3, 4, 5, and 6). Results reported in Tables 3 and 4 were obtained using a Vapourtec R-Series reactor with the sulfoxide and DBSA solutions being injected via a 10-mL sample loop and pumped by HPLC pumps. The results reported in Tables 5 and 6 were obtained using a Vapourtec E-Series flow reactor with peristaltic pumps used to introduce the reagent solutions directly; due to the low solubility of the relatively polar sulfoxide substrates in acetonitrile (0.039–0.06 M), the use of peristaltic pumps proved more effective to ensure a consistent flow rate.

4.5. Typical Procedure for the Synthesis of α-Diazosulfoxides Using Solid-Phase Bases. A packed bed reactor consisting of a fritted low pressure 10 mm ID × 100 mm long Omnifit® glass column was packed with Amberlyst A21 (5 eq.) dispersed among acid washed sand (approx. 4.5 g) and mounted vertically. Acetonitrile was pumped through the column at a flow rate of 5 mL/min for 10 min to prepare the system by means of a peristaltic pump. The sulfoxide (1 eq.) was added to 5 mL of acetonitrile in a 10-mL volumetric flask. Dodecylbenzenesulfonyl azide (2 eq.) was added to the flask, and the solution was made up to the graduation mark with acetonitrile. The solution was pumped through the reactor with a residence time of 9 min at room temperature. The volume of the reactor was established by weighing the packed bed reactor while dry and again following saturation with acetonitrile. The system was fitted with an 8-bar back pressure regulator. The crude solution of product was concentrated under reduced pressure without heating, and conversion was established by ^{1}H NMR spectroscopy. Purification by column chromatography (ethyl acetate–hexane 50:50 — 100% ethyl acetate) gave the pure α-diazosulfoxides in good to excellent yields.

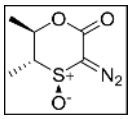


4.5.1. (4R*,4aS*,8aS*)-3-Diazo-hexahydrobenzo[1, 4]oxathiin-2(3H)-one S-oxide and (4R*,4aR*,8aR*)-3-Diazo-hexahydrobenzo[1, 4]oxathiin-2(3H)-one S-oxide — 2a [27]. A 1:0.7 diastereomeric mixture of the sulfoxides **1a** [27] (0.100 g, 0.53 mmol, 1 eq.) and dodecylbenzenesulfonyl azide (0.373 g, 1.062 mmol, 2 eq.) in acetonitrile (10 mL) was pumped through a 10-mm ID packed bed reactor containing Amberlyst A21 0.552g, 2.65 mmol, 5 eq) and acid washed sand

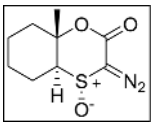
(approx. 4.6g) with a residence time of 9 min. The crude product was a thick yellow oil which showed conversion to be 86% by ^{1}H NMR spectroscopy. Purification by column chromatography (ethyl acetate–hexane 50:50) gave the pure α-diazosulfoxides as a mixture of diastereomers (1:0.7) as a yellow crystalline solid (0.085 g, 76%). (4R*,4aS*,8aS*)-3-Diazo-hexahydrobenzo[1, 4]oxathiin-2(3H)-one S-oxide; δ_H ($CDCl_3$) 1.25–1.82 (4H, m, 4 of H of CH_{2ring}), 1.85–2.02 (2H, m, 2 of H of CH_{2ring}), 2.23–2.36 (1H, m appears as br d, 1 of H of CH_{2ring}), 2.57–2.68 (1H, m appears as br d, 1 of H of CH_{2ring}), 2.95 (1H, ddd appears as dt, *J* 11.0, 11.0, 4.9, C*H*S), 4.04 (1H, ddd appears as dt, *J* 11.0, 11.0, 4.9, C*H*O); (4R*,4aR*,8aR*)-3-Diazo-hexahydrobenzo[1, 4]oxathiin-2(3H)-one S-oxide δ_H (400 MHz, $CDCl_3$) 1.20–1.80 (4H, m, 4 of H of CH_2 ring), 1.85–2.05 (2H, m, 2 of H of CH_2 ring), 2.05–2.27 (1H, m appears as br d, 1 of H of CH_2 ring), 2.30–2.51 (1H, m appears as br d, 1 of H of CH_2 ring), 2.82 (1H, ddd appears as dt, *J* 10.9, 10.9, 4.8, C*H*S), 4.89 (1H, ddd appears as dt, *J* 10.9, 10.9, 4.8, C*H*O). Spectroscopic data is in agreement with those previously published in the literature [27].



4.5.2. (4R*,5S*,6R*)-3-Diazo-5,6-diphenyl-[1, 4]-oxathian-2-one S-oxide — 2b [27]. A 10-mm ID Omnifit® glass column was packed with Amberlyst A21 (0.395 g, 1.9 mmol, 5 eq.) and acid washed sand (approx. 4.6 g). The sulfoxide **1b** [27] (0.100 g, 0.35 mmol, 1 eq.) was added to 5 mL of acetonitrile in a 10-mL volumetric flask. Dodecylbenzenesulfonyl azide (0.270 g, 0.70 mmol, 2 eq.) was added to the flask, and the solution was made up to the graduation mark with acetonitrile. The solution was pumped through the reactor at room temperature with a residence time of 9 min. The crude product was a thick yellow oil which showed conversion by ^{1}H NMR spectroscopy of 96%. Purification by column chromatography (ethyl acetate–hexane 50:50) gave the pure α-diazosulfoxide **2b** as a yellow crystalline solid (0.104 g, 88%); m.p. 125–127 °C (decomp.); ν_{max}/cm^{-1} (neat) 2135 (C=N_2), 1679 (C=O); δ_H (400 MHz) 4.30 (1H, d, *J* 2.0, C*H*S), 6.57 (1H, d, *J* 2.0, C*H*O), 7.14–7.41 (10H, m, aryl rings); δ_C (75.5 MHz) 68.1 (CH, *C*HS), 74.3 (CH, *C*HO), 126.2, 128.7, 128.8, 129.3, 129.7, 129.8 (6× CH, 6 *C*H of aryl rings), 126.8, 135.0 (2×C, *C* of aryl ring). Spectroscopic data is in agreement with those previously published in the literature [27].



4.5.3. (4R*,5R*,6R*)-3-diazo-5,6-dimethyl-[1,4]oxathian-2-one S-oxide — 2c [27]. A 10-mm ID Omnifit® glass column was packed with Amberlyst A21 (0.625 g, 3.00 mmol, 5 eq.) dispersed in acid washed sand (approx. 4.4 g). The sulfoxide **1c** [27] (0.102 g, 0.60 mmol, 1 eq.) was added to 5 mL of acetonitrile in a 10-mL volumetric flask. Dodecylbenzenesulfonyl azide (0.422 g, 1.201 mmol, 2 eq.) was added to the flask, and the solution was made up to the graduation mark with acetonitrile. The solution was pumped through the reactor with a residence time of 9 min and a flow rate of 0.2 mL/min at room temperature. The system was fitted with an 8-bar back pressure regulator, and the resulting clear yellow solution was concentrated under reduced pressure. The crude product was a thick yellow oil which showed complete consumption of the starting sulfoxide by ^{1}H NMR spectroscopy. Purification by column chromatography (ethyl acetate–hexane 50:50) gave the pure α-diazosulfoxide **2c** as a yellow crystalline solid (0.101 g, 86%). δ_H ($CDCl_3$) 1.42 (3H, d, *J* 7.2, CH_3), 1.52 (3H, d, *J* 6.6, CH_3), 2.91 (1H, dq appears as q, *J* 9.8, 7.2, C*H*S), 5.07 (1H, dq, *J* 9.8, 6.5, C*H*O); δ_C ($CDCl_3$) 12.5, 18.8 (2×CH_3), 56.0 (CH, *C*HS), 71.5 (CH, *C*HO), 159.8 (*C* = O). Spectroscopic data is in agreement with those previously published in the literature [27].



4.5.4. (4R*,4aS*,8aS*)-3-Diazo-8a-methyl-hexahydrobenzo [1,4]-oxathiin-2-one S-oxide — 2d [27]. A 10-mm ID Omnifit® glass column was packed with Amberlyst A21 (0.514 g, 5 eq., 2.47 mmol) dispersed in acid washed sand (approx. 4.5 g). The sulfoxide **1d** [27] (0.100 g, 0.49 mmol, 1 eq.) was added to 5 mL of acetonitrile in a 10-mL volumetric flask. Dodecylbenzenesulfonyl azide (0.347 g,0.98 mmol, 2 eq.) was added to the flask, and the solution was made up to the graduation mark with acetonitrile. The solution was pumped through the reactor at room temperature with a residence time of 9 min. The crude product (0.451 g) was a thick yellow oil which showed conversion to be 98% by ^{1}H NMR spectroscopy. Purification by column chromatography (ethyl acetate–hexane 50:50) gave the pure α-diazosulfoxide **2d** as a yellow crystalline solid (0.096 g, 86%). δ_H ($CDCl_3$) 1.30–2.05 (10H, m containing s at 1.42, 7 of H of CH_{2ring} and CH_3), 2.57 (1H, br d, *J* 14.1, 1 of H of CH_{2ring}), 3.02 (1H, dd, *J* 12.7, 4.1, C*H*S); δ_C ($CDCl_3$) 19.6 (*C*H_3), 22.8, 25.3, 25.5, 39.8 (4×*C*H_{2ring}), 68.1 (CH, *C*HS), 81.5 (*C*), 159.7 (*C*=O). Spectroscopic data is in agreement with those previously published in the literature [27].

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Supporting Information

Electronic Supplementary Material (ESM) associated with this article can be found in the online version at doi: 10.1556/1846.2016.00013.

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