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Dynamic Covalent Chemistry within Biphenyl Scaffolds: Effects from Endocyclic to Exocyclic Sulfonamides

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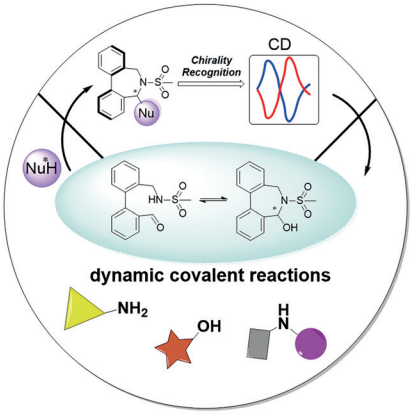

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Abstract There is unabated interest in developing new strategies for the control of atropisomers despite the rich history of atropisomerism. We recently introduced dynamic covalent reactions (DCRs) within biphenyl skeletons for the incorporation and chirality recognition of multiple classes of mononucleophiles. To expand the scope of this strategy, the sulfonamide unit was switched from an endocyclic to an exocyclic position, and the influence of the resulting DCRs on chiral induction was investigated. The intramolecular equilibrium between the open aldehyde and its cyclic hemiaminal favored the ring form, and excellent chirality transfer from the hemiaminal stereocenter to the helical twist of the biphenyl was revealed. The modulation of unique dual reactivity then allowed the realization of DCRs of a diverse set of amines and alcohols. The degree of chirality induction was further explored by employing chiral substrates, affording significant circular dichroism signals.

Key words atropisomerism, biaryls, aldehydes, dynamic covalent chemistry, chirality recognition

The stereoisomerism that governs chirality within a molecule due to nonplanar spatial arrangement of groups about a chiral axis is referred to as axial chirality and it is found in atropisomers, chiral allenes, and spiranes.[1] As the most representative subclass compounds displaying axial chirality, atropisomeric compounds are ubiquitous in natural and synthetic molecules,[2] and they play crucial roles in asymmetric catalysis,[3] drug development,[4] and supramolecular chemistry.[5] As a result, the development of new strategies and methodologies for the control of atropisomerism is an intensive area of research. For biaryls, restriction of the free rotation about the sp^2–sp^2 C–C bond by bulky substituents can permit the creation of atropisomers, which is of significance for the discovery of chiral auxiliaries and ligands.[3a,6] The manipulation of atropisomers provides a means for regulation of chiral molecular assemblies.[7] Moreover, noncovalent interactions such as hydrogen bonding[8] or metal coordination[9] have been used to control atropisomers and the resulting molecular rotors. In addition, the effect arising from bond rotation is closely associated with the function of molecular switches[10] and light-emitting materials.[11]

The field of dynamic covalent chemistry (DCC) has been blossoming over the past decade,[12] as it has found broad utility in the creation of assemblies,[13] modulation of nanomaterials,[14] and the development of sensors and catalysts,[15] as well as in the regulation of physiological functions.[16] The creation and exchange of reversible covalent bonds, in the form of dynamic covalent reactions (DCRs), can readily generate molecular diversity as compared with stepwise covalent synthesis.[12–16] Propelled by its paramount position in enzymatic as well as organic catalysis,[17] the addition of amines to carbonyls to create imines,[18] iminium ions,[19] or hemiaminals/aminals[20] in reversible systems is gaining popularity in DCC research. Despite their availability, DCRs of aldehydes and alcohols suffer from poor thermodynamic stability due to the weak nucleophilicity and coordinating ability of alcohols.[21] The incorporation of readily accessible carbonyl and amino/oxo functions into biaryl skeletons might provide ample opportunities for accessing atropisomers through DCC.

We recently proposed a strategy of bridging together research efforts on DCC and on axial chirality through an intramolecular DCR between aldehyde and sulfonamide units at the 2- and 2′-positions of a biphenyl (**1**; Figure 1a).[22] Diverse intermolecular DCRs of biphenyls **1** with alcohols, thiols, primary amines, and secondary amines were realized based on the dual reactivity; chiroptical sensing of chiral mononucleophiles was also achieved. Building upon these results, we moved the sulfonyl group from an endocyclic position in **1** to an exocyclic position in **2** to fine-tune the structure–reactivity relationship of DCRs and the associated physical organic features [Figure 1(b)]. Although a

similar acidity would be expected for the sulfonamide groups in **1** and **2**, we postulated that the equilibrium between the open aldehyde and its cyclic hemiaminal would be affected by the structural difference between **1** and **2**, which, accordingly, might dictate chirality induction from the hemiaminal stereocenter (labelled * in Figure 1) to the chirality of the biphenyl, as well as in DCRs with other mononucleophiles.

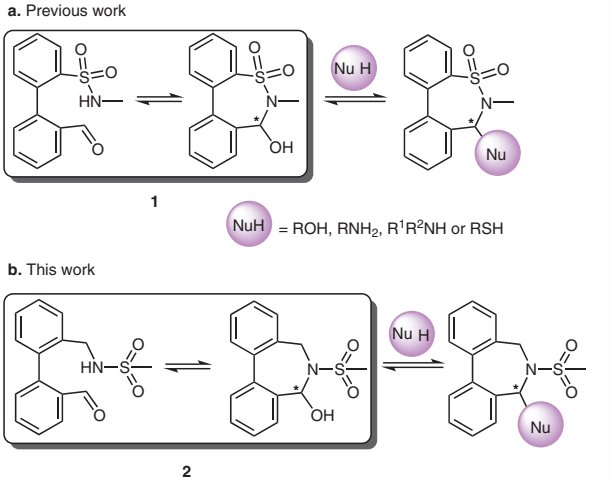

Figure 1 Proposed strategy for DCRs and chirality sensing with open/cyclic atropisomeric biaryls: the sulfonyl group is changed from an endocyclic position in **1** (a) to an exocyclic position in **2** (b).

The biaryl was readily prepared through Suzuki coupling (Scheme S1).[23] Both the aldehyde form **3** and the hemiaminal form **4** were observed in acetonitrile, with the ring form dominant [Figure 2(a)]. The formation of the cyclic hemiaminal (88%) was supported by observation of the methine proton (H_a) and the diastereotopic methylene protons (H_b and H_c) in the ^{1}H NMR spectrum. This is in sharp contrast to the case of **1**, for which the open aldehyde accounts for the majority of the population (66%). We rationalized these findings in terms of the release of steric strain due to the significantly smaller size of CH_2 compared with SO_2, and the resulting structural flexibility. The equilibrium was also explored in $CDCl_3$, and analogous results were obtained (Figure S3). Furthermore, only one set of signals was detected for **4** at room temperature [Figure 2(a)] or below (Figures S6 and S7). These observations were interpreted as resulting from excellent chirality transfer between the hemiaminal stereocenter and the chirality of the biphenyl moiety (dr > 20).

To shed additional light on the chirality-relay process, X-ray quality crystals of **4** were obtained through slow evaporation of a solution of **2** in dichloromethane–hexane [Figure 2(b)].[24] The biphenyl moiety had a torsion angle of 43°, which is comparable to the twist (45°) within the most stable structure of **1**, according to density functional theory

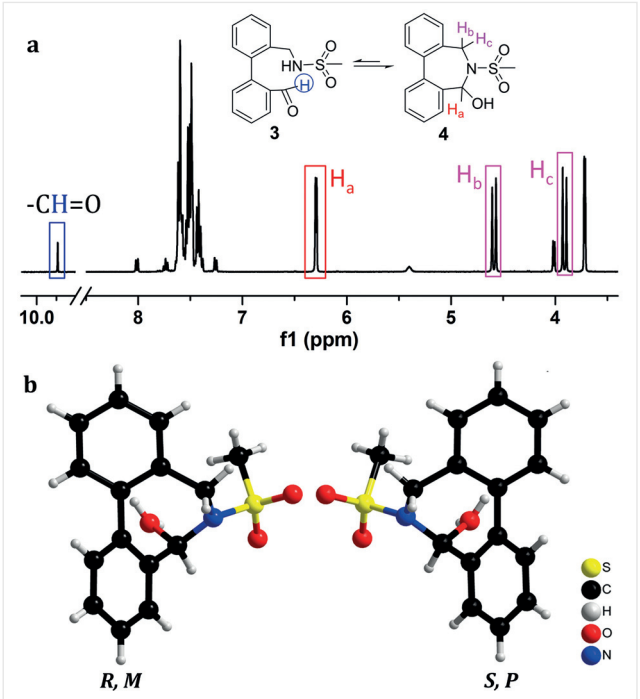

Figure 2 Equilibrium and structural feature of **2**. (a) ^{1}H NMR spectrum of **2** in CD_3CN. (b) Crystal structure of **4** (the enantiomeric structures were chosen from the unit cell of **4**).

calculations. More importantly, to alleviate electronic repulsion between the oxygen lone pairs, the hydroxy group on the hemiaminal carbon is oriented away from the exocyclic sulfonyl oxygen atoms. Moreover, close contacts were detected between the sulfonyl oxygen atoms and the nearby hydrogen atoms, respectively (2.40 and 2.53 Å, Figure S8). Those two intramolecular CH…O hydrogen bonds further rigidify the structure and thereby contribute to the high diastereoselectivity, in addition to the electronic effect described above. On the basis of the crystal structure, an *S*-stereocenter favors a *P*-twist in **4**, whereas an *R*-stereocenter gives an *M*-twist.

With the interconverting open/cyclic atropisomeric system in hand, we examined their DCRs with a series of N- and O-mononucleophiles. We surmised that, as in case of **1**, the reaction of **2** with primary amines might proceed via the open aldehyde **3** [Figure 3(a), Pathway a]. The assembly of **2** with butylamine was therefore examined at r.t. in CD_3CN containing molecular sieves [Figure 3(b)]. The formation of imine **5** was confirmed by the presence in the ^{1}H NMR spectrum of a peak at about δ = 8.02 ppm, corresponding to the imine proton [Figure 3(b)]. Furthermore, a doublet at about δ = 5.50 ppm was observed, indicative of the formation of the cyclic aminal **6**. The existence of **6** was also supported by the presence of two doublets at δ = 3.82 and 4.54 ppm, which were assigned to the diastereotopic methylene protons. The ratio of products **5** and **6** was about 1.0, which is markedly different from that obtained in DCRs

of **1** with primary amines, for which the imine predominates. The difference in the ratio of the imine and its aminal for endocyclic and exocyclic sulfonamides is consistent with the trend of their corresponding parent aldehydes and hemiaminals (Figure 2). An equilibrium between **5** and **6** was also observed for other primary amines (Figures S9–S13).

We next set out to investigate the incorporation of amines that were more sterically hindered. Analogously to the nucleophilic addition of a primary amine to aldehyde **3** to give an imine and its cyclic aminal, with the loss of water as a driving force, the combination of **3** with a secondary amine should lead to an iminium ion **7** and, subsequently, the aminal **8** upon ring closure [Figure 3(a), Pathway a]. Gratifyingly, a high yield (>90%) of the desired product was obtained for the DCR of **2** with piperidine [Figure 3(b)]. Several achiral amines were tested, and **8** was formed diastereoselectively in all cases [see the sharp singlet for the methine proton in Figure 3(b) and Figures S16–S18], thereby emphasizing the generality of our approach.

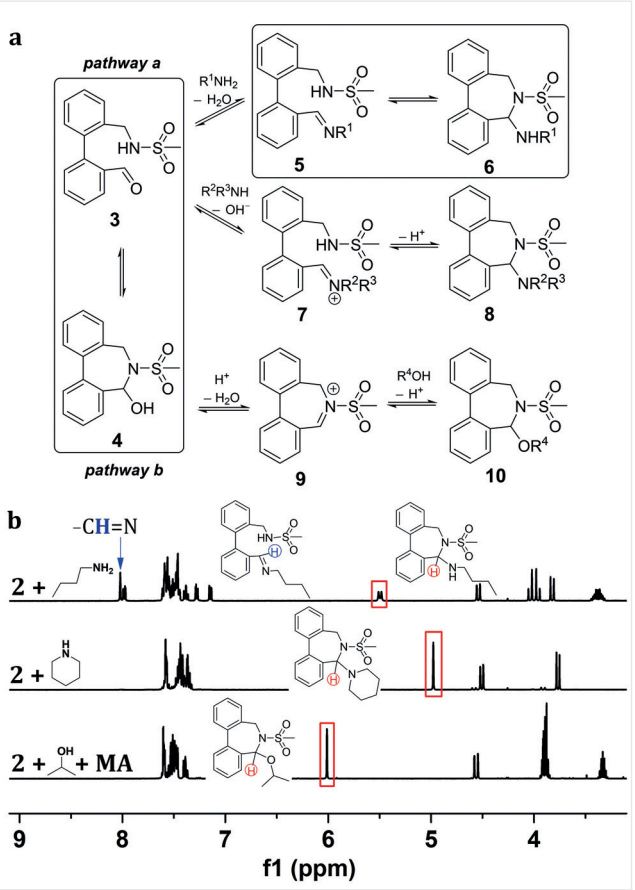

Figure 3 DCRs of **2** (i.e., **3** and **4**) with primary amines, secondary amines, and alcohols. (a) Proposed reaction pathways. (b) ^{1}H NMR spectra of the reaction of **2** with mononucleophiles in CD_3CN.

Encouraged by DCRs of **2** with both primary and secondary amines, we turned our attention to monoalcohols. Unfortunately, no reaction was apparent when **2** was mixed with 3.0 equivalents of propan-2-ol, probably due to the low reactivity of the alcohol group. We postulated that, rather than a direct attack on the carbonyl by an alcohol, a sulfonyliminium ion[25] **9** might be formed from cyclic **4** in the presence of a Brønsted acid [Figure 3(b), Pathway b]. Such a species should be highly electrophilic, and could therefore be captured by an alcohol to afford a hemiaminal ether **10**. In the presence of methanesulfonic acid (MA), the reaction of **2** with propan-2-ol did indeed give hemiaminal ether **10** in a high yield [>90%; Figure 3(b)]. The broad scope of the assembly was confirmed by the successful incorporation of a series of monoalcohols (Figures S23–S29). Again, the formation of dynamic covalent adducts was stereoselective (dr > 20), even with methanol (Figure S23–S25). The nearly perfect chirality induction from the hemiaminal ether stereocenter to the chirality of the biphenyl moiety was verified by X-ray crystallographic analysis of the methanol-derived product **10** (Figures S32–S34).[24] Except for the change from a hydroxy to methoxy group, the structural features of **10** closely resemble those of **4**, and the interplay between the hemiaminal central chirality and the helical twist of the biphenyl was maintained.

Having achieved dynamic covalent bonding of amines and alcohols by using atropisomeric receptors, we probed the reversibility of the process. To this end, a series of in situ component-exchange reactions was performed. For instance, the reaction of **2** with piperidine was initially performed and then *N*-methylpropan-1-amine was added. After equilibrium had been reached, ^{1}H NMR spectroscopy indicated a decrease in the amount of the original assembly, with the emergence of an *N*-methylpropan-1-amine-derived product [Figure 4(A)]. An analogous exchange was also found to occur with primary amines (Figure S35) or alcohols (Figure S37). It is worthwhile mentioning that both imines and their associated aminals participated in the scrambling of primary amines. These results confirm the dynamic nature of our system. Isolated **10**, incorporating methanol, was dissolved in CD_3CN and equilibrated on addition of propan-2-ol and MA. An exchange of alcohols was detected [Figure 4(B)], corroborating the reversibility of this process.

Our next goal was to test the chirality induction with chiral amines or alcohols under thermodynamic control, for the purpose of chirality recognition. Due to the diastereoselective chirality transfer between the hemiaminal stereocenter and the chiral axis of the biphenyl moiety with achiral substrates, we surmised that DCRs of **2** with an enantiomerically pure chiral substrate might give a pair of cyclic diastereomers, taking into consideration the central-to-central asymmetric induction, which would be represented

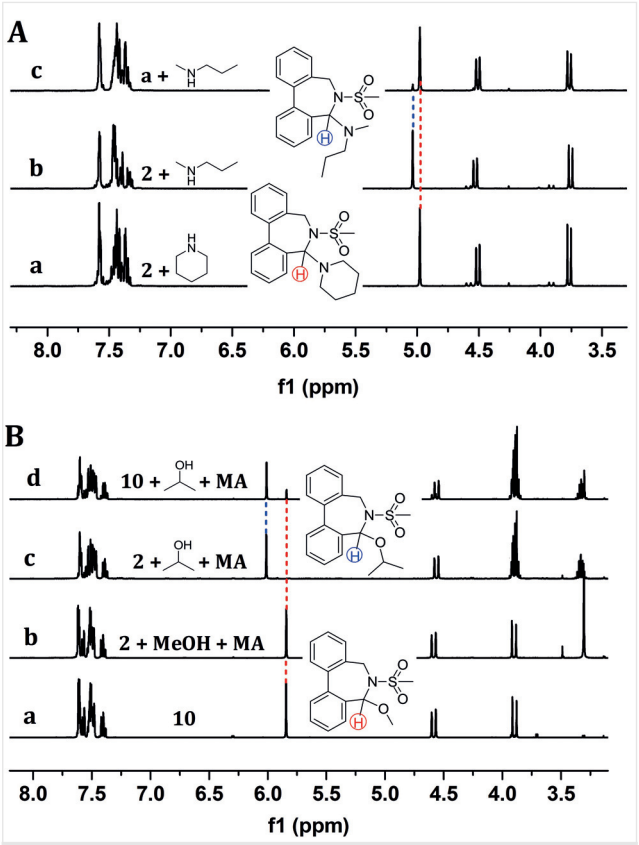

Figure 4 The dynamic nature of the system. A. Component exchange (c) of a piperidine-derived adduct (a) with *N*-methylpropan-1-amine (b). B. Component exchange (d) of the isolated **10** incorporating methanol (a) with propan-2-ol. The in situ reaction of **2** with methanol and propan-2-ol in CD_3CN is shown in (b) and (c), respectively.

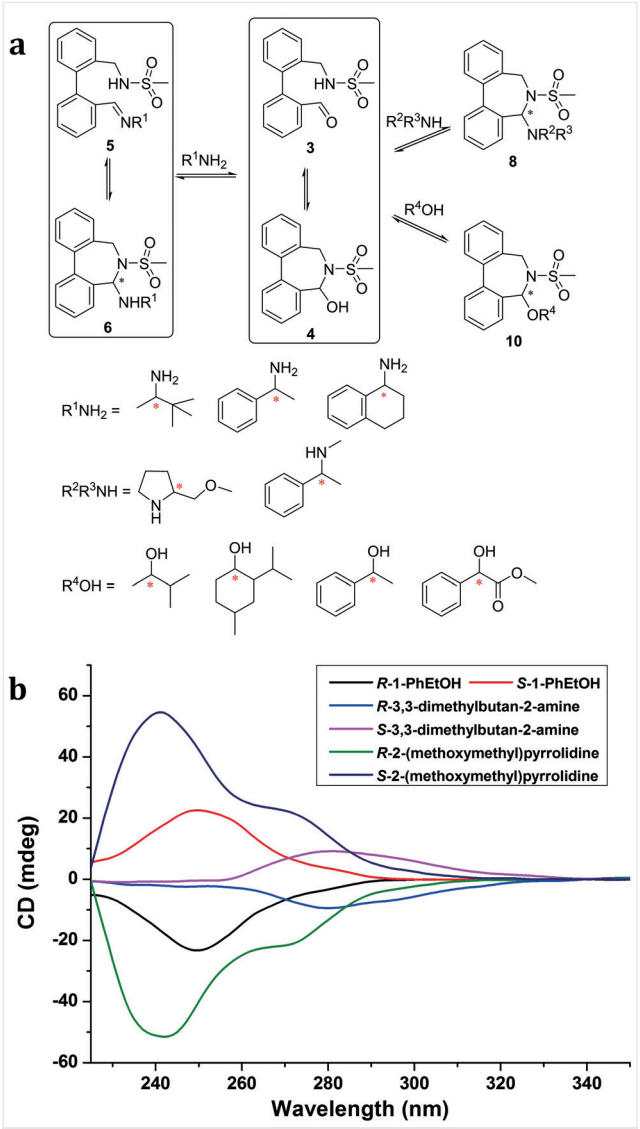

Figure 5 Chirality recognition with **2** (i.e., **3** and **4**). (a) Chirality induction for DCRs of **2** with mononucleophiles; (b) CD spectra of solutions of DCRs of **2** with 1-phenylethanol, 3,3-dimethylbutan-2-amine, and 2-(methoxymethyl)pyrrolidine (0.13 mM).

by the dr value. A suite of chiral amines and alcohols with various substitution patterns were used in DCRs, and modest dr values were obtained (Figures S11–S13, S19–S20, and S26–S29). The degree of diastereoselectivity is controlled by the structure of the chiral substrates and is reflected by the induced helical twist of the biphenyl moiety. We therefore recorded circular dichroism spectra of the adducts (Figure 5).

With the dilute solutions of the assemblies from **2** as presented above, reproducible CD spectra were observed. For example, a strong positive Cotton effect at 242 nm was found for aminal **8** derived from (2*S*)-2-(methoxymethyl)pyrrolidine, which gave a dr value of 3.1. With (1*R*)- or (1*S*)-1-phenylethanol (dr ~1.4), a peak at about 250 nm was found. For 3,3-dimethylbutan-2-amine, a mixture of the imine and aminal (dr ~1.3) gave weaker CD signals at about 280 nm. The absolute magnitude of the CD peaks approximately fell in line with the trend in the dr values. Several chiral alcohols and amines were tested, and CD responses were detected for their corresponding assemblies (Figures S39–S47). Because the reactants (racemic **2** and the chiral substrates) show no interference above 220 nm, any CD signals above this wavelength are indicative of the induced helicity and, in turn, correlate with the chirality of the substrates. As a result, the current platform should be suitable for chiroptical sensing, as previously reported **1**.[22]

In conclusion, we have developed an atropisomeric system for the reversible covalent binding of a series of mononucleophiles. The intramolecular equilibrium between an open aldehyde and its cyclic hemiaminal was investigated in detail, and the structural basis of the diastereoselectivity was elucidated. The regulation of reactivity of those open/ring species then permitted the development of dynamic covalent reactions of a broad range of primary

amines, secondary amines, and alcohols. The dynamic nature of the system was verified through component exchange. Finally, the extent of chirality induction was examined by using chiral substrates, and a significant CD effect was observed. The current exocyclic sulfonamide system complements our recently reported endocyclic platform, and further establishes the value of dynamic covalent interactions for controlling the chirality of atropisomers.

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Supporting Information

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(23) **6-Mesyl-6,7-dihydro-5*H*-dibenzo[*c*,*e*]azepin-5-ol (2)**
Under an argon atmosphere, *N*-(2-bromobenzyl)methanesulfonamide (0.53 g, 2.0 mmol), (2-formylphenyl)boronic acid (0.46 g, 3.0 mmol), and Pd(dppt)Cl_2 (60 mg) were dissolved in 1,4-dioxane (20 mL). A 1 M aq solution of K_3PO_4 (6.0 mL) was added, and the mixture was stirred at 86 °C overnight. The mixture was then cooled to r.t. and brine (15 mL) was added. The mixture was extracted with EtOAc (2 × 30 mL), and the organic layers were combined, washed with water, dried (Na_2SO_4), filtered, concentrated, and purified by column chromatography [silica gel, PE–EtOAc (4:1)] to give a white solid; yield: 0.51 g (88%); mp 92–94 °C. ^{1}H NMR (CD_3CN): δ = 9.72 (s, 1 H, open form), 8.01 (d, *J* = 7.6 Hz, 1 H, open form), 7.73 (t, *J* = 7.6 Hz, 1 H, open form), 7.37–7.63 (m, 61 H, open form 5 H; ring form 56 H), 7.25 (d, *J* = 7.6, 1 H, open form), 6.29 (d, *J* = 4.8 Hz, 7 H, ring form), 5.39 (br s, 1 H, open form), 4.58 (d, *J* = 14.4 Hz, 7 H, ring form), 4.00 (d, *J* = 6.0 Hz, 2 H, open form), 3.90 (d, *J* = 14.4 Hz, 7 H, ring form), 3.71 (d, *J* = 4.8 Hz, 7 H, ring form), 2.98 (s, 21 H, ring form), 2.68 (s, 3 H, open form). ^{13}C NMR (CD_3CN): δ = 191.7, 143.5, 140.8, 139.7, 138.5, 137.6, 136.81, 135.6, 134.9, 134.1, 133.7, 131.1, 130.6, 129.8, 129.5, 129.0, 128.7, 128.7, 128.5, 128.4, 128.2, 128.1, 127.8, 127.7, 127.4, 83.3, 47.5, 44.5, 41.1, 39.1. ESI-HRMS: *m/z* [M + Na]$^+$ calcd for $C_{15}H_{15}NNaO_3S$: 312.0670; found: 312.0667.

(24) CCDC 1840008 and 1840009 contain the supplementary crystallographic data for compounds **4** and **10**, respectively. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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