Sulfonic Acid Libraries Attained Through Opening of 2-Sulfobenzoic Acid Anhydride

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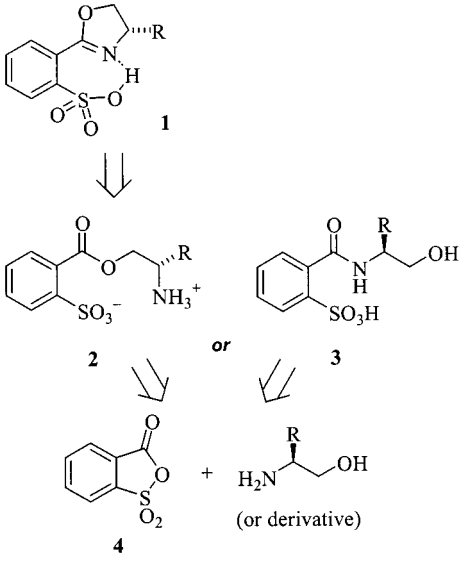
2-Sulfobenzoic acid anhydride opens cleanly with *N*-Boc-protected α-amino alcohols to afford zwitterionic esters 1,2-$C_6H_4(SO_3^-)(CO_2CH_2CHR^1NH_3^+)$ (R^1 = H, alkyl), the species R^1 = *i*Pr is crystallographically characterised. Dehydration of these species affords zwitterionic oxazoline sulfonic acid derivatives 1,2-$C_6H_4(SO_3^-)(C^A{=}NH^+CHR^1CH_2O^A)$ (C^A and O^A are bonded C−O) for R^1 = *i*Pr (X-ray), *i*Bu, *t*Bu, CH_2Ph. Reaction with water regenerates the zwitterionic esters while exposure to $M(OAc)_2$ (M = Cu, Pd) leads to the formation of the crystallographically characterised complexes $M^{II}L_2$ (L = anion of the *i*Pr-oxazolinesulfonic acid). Heating either the zwitterionic esters or oxazolines with R^2NH_2 [R^2 = CH_2Ph, CH_2(1-$C_{10}H_7$), *R*-CH(Me)Ph] leads to S_N2 attack at the oxazoline methylene group leading to the amido sulfonic acids 1,2-$C_6H_4(CONHCHRCH_2NHR^2)(SO_3H)$ based on crystallographic studies on R^1 = *i*Pr, R^2 = CH_2(1-$C_{10}H_7$).

Introduction

One major theme of early 21st century synthesis has become the preparation, through simple chemistry, of compound libraries. Such libraries find application in drug screening, catalysis and materials chemistry.[1] Sulfonic acids, and their derived sulfonamides, are interesting compound classes to target in this arena as both potent pharmaceutical and catalytic ligand lead structures abound.[2,3] We envisaged that the interesting sulfonic acid oxazolines **1** could be attained from either the esters **2** or the amides **3**, and potentially functionalised further to sulfonamides. Either **2** or **3** should be available from suitable "click-reaction"[4] opening of commercial 2-sulfobenzoic acid anhydride (**4**) with amino alcohols or suitable derivatives (Scheme 1). Under appropriate conditions it should be possible to attain a one-step synthesis. While this chemistry is unprecedented there are limited suggestions in patent, and related, literature that the equivalent transformations with diamines have been attained.[5]



Scheme 1. Preparative routes to oxazoline sulfonic acids.

Results and Discussion

Oxazoline Synthesis

Initial investigations were carried out using valinol as a representative α-amino alcohol. Reaction with the anhydride **4** under Dean−Stark conditions in PhCl pleasingly led to direct formation of an oxazoline formulated as tautomer **1a** (R = *i*Pr) in 50−60% recrystallised yield after an overnight reflux. Purification of **1a** is complicated by its polar nature and by the presence of two additional species. Proton NMR and IR spectroscopy confirmed these as residual ester **2a** (ν_{CO} = 1736 cm^{-1}) and amide **3a** (ν_{CO} = 1653 cm^{-1}). The sulfonic acid **1a** could not be chromatographed but crystallised readily from the reaction residue using hot ethanol. Other derivatives of **1** (R = alkyl) were not as crystalline and could not be separated from the ester/

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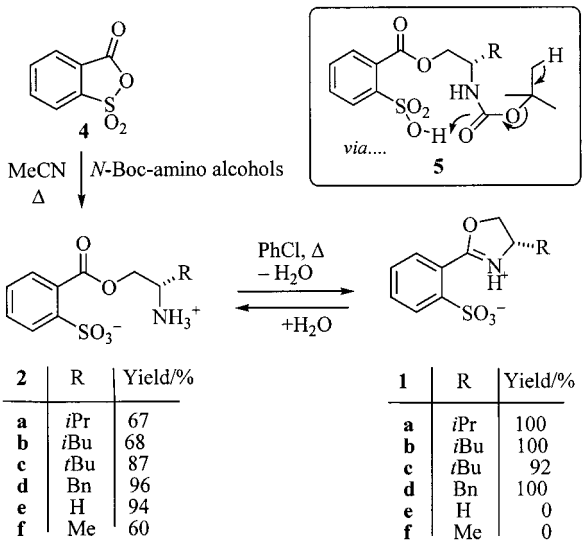
amide mixtures. Even under prolonged heating complete conversion of any amino alcohol and **4** into **1** could not be attained, some **2** and **3** always remained (amoung other products). The origin of this observation was revealed by monitoring the reaction of valinol with **4** by ^{1}H NMR spectroscopy in $CDCl_3$. At room temperature **2a** and **3a** are formed in a 1:1 ratio from **4** and valinol, although the reaction is not clean. We reasoned that the amine function is more nucleophilic and opens **4** quickly, but subsequent deprotonation of the resulting ammonium species by more valinol is rapid leading to an eqimolar mixture of ester **2a** and amide **3a**. Addition of valinol to **4** in the presence of NEt_3 allowed greater formation of **3a** (based on ^{1}H NMR spectra of the crude product) but it's high water solubility, and the presence of $NHEt_3Cl$, prevented its isolation. Importantly, heating the crude amide mixture containing **3a** did not fashion *any* oxazoline indicating that it is the formation of **3** that limits the conversion of **4**. Reaction of *O*-TMS protected valinol with **4** was also attempted to provided a route to **1a** (via **3a**). However, subsequent heating, under Dean–Stark conditions in PhCl, of the *O*-TMS analogue of **3a** also afforded *no* oxazoline **1a**. In contrast, we could readily confirm that the ester **2a** (R = *i*Pr) was cleanly converted to oxazoline **1a** in quantitative yield under identical dehydrating conditions. These observations show that ester **2a** is the key intermediate in the preparation of **1a** and that a general approach to **1** should be attainable by such a route. To overcome the problems associated with co-formation of **3** in the reaction mixtures we utilised *N*-Boc-protected amino alcohols and realised excellent yields of **2** for a range of substituents (Scheme 2). The Boc group ensures clean formation of the desired ester and is subsequently spontaneously deprotected by the unmasked sulfonic acid, presumably via **5**. Because of these features no added acid is required for the transformation. When anhydrous MeCN is used as the solvent at 60 °C, **2** precipitates from the reaction mixture as a white solid, and this has been found to be analytically pure in all the cases we have tried. Reactions carrried out at >5 g gave out large quantities of heat and gas, so precautionary steps should be employed regarding the rate of addition of the *N*-Boc-amino alcohol in such cases. Species **2** are extremely stable and were unchanged after storage for >1 year under standard laboratory conditions.

Dean–Stark dehydration of the esters **2** to **1** proceeds well in PhCl (135 °C, 16 h), except in the cases where R = H, Me, where no product is isolated. This appears to be due solely to the insolubility of **2e–f** in the PhCl but attempts to ovecome this by changing the solvent were not successful. Lack of reactivity is not an issue as **2e–f** take part in other reactions, for example, **2e** reacts with salicylaldehyde to provide the novel ligand **6** [Equation (1)]. The final oxazolines **1** are suseptible to slow hydrolysis on storage under non anhydrous conditions. Heating samples of **1** in water facilitates this degradation. For example, **1a** is completely hydrolysed within 1 h in warm (45–55 °C) D_2O. The formation of **2** by the hydrolysis of **1** is somewhat surprising, as amides are typically produced by acid-catalysed oxazoline

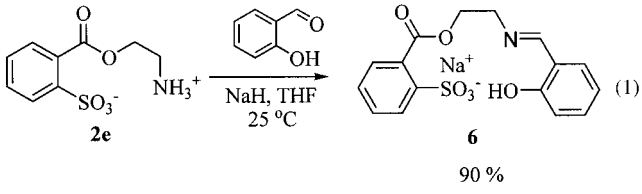


2	R	Yield/%
a	*i*Pr	67
b	*i*Bu	68
c	*t*Bu	87
d	Bn	96
e	H	94
f	Me	60

1	R	Yield/%
a	*i*Pr	100
b	*i*Bu	100
c	*t*Bu	92
d	Bn	100
e	H	0
f	Me	0

Scheme 2. Preparation of esters **2** and oxazolines **1** via *N*-Boc-amino alcohols.

hydrolysis.[6] In our cases the proximity of the sulfonic acid moiety leads to the protonation of the amine functionality, making it a more suitable leaving group than the alcohol-derived substituent. The macroscopic reverse of this chemistry accounts for the formation of **1** from **2**.



Crystallographic Studies

Because of the unusual features observed in the preparation and hydrolysis of the oxazolines **1** we were anxious to confirm our structural assignments crystallographically. Fortunately, both the ester **2a** and its derived oxazoline **1a** could be obtained as single crystals from MeCN and EtOH respectively. Views of **1** and **2a** are presented in Figure 1 and 2, respectively, which also give selected bond angles and distances, including hydrogen bonded H-atoms. The structure of **1a** confirms that the sulfonic acid oxazoline has been isolated in its zwitterionic form consistent with the observed reactivity for its formation and subsequent hydrolysis, although the bond lengths around C(7) suggest some residual double bond character to both the O and N atoms. The acidic H was located from difference Fourier synthesis and then refined as a part of a riding model 0.88 Å from the oxazoline nitrogen, 1.83 Å from the nearest SO_3 oxygen. Relatively few chelating amino sulfonic acids have been subjected to crystallographic studies but these indicate similar zwitterionic structures with N–H distances in the range

0.785−1.015 Å.[7] The O···H distances (2.05−2.511 Å) in these structures are longer than those in **1a**, while the O···H−N angles (100.3−139.4°) are smaller than that of **1a** (153.7°). Overall the placement of the NH proton in **1a** is still, however, consistent with normal hydrogen bonding. In addition to confirming the atom connectivity of ester **2a** is correctly assigned, Figure 2 shows (in contrast to purely intramolecular H-bonding in **1a**), an extensive highly ordered hydrogen bonding network is present in **2**.

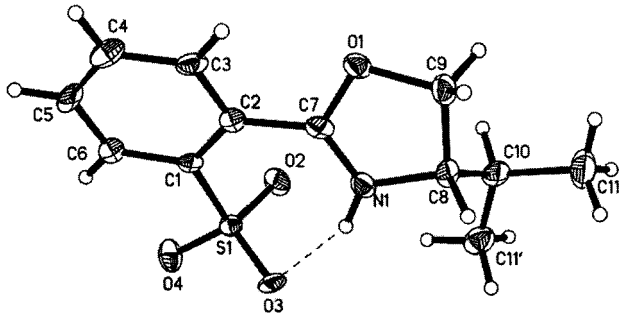


Figure 1. Molecular structure of **1a**. Selected interatomic distances (Å) and angles (°): S(1)−O(1) 1.446(3), S(1)−O(2) 1.449(3), S(1)−O(3) 1.471(3), O(1)−C(7) 1.312(4), O(1)−C(9) 1.478(4), N(1)−C(7) 1.270(5), N(1)−C(8) 1.471(4), N(1)−H(1A)···O(3) 1.83, N(1)···O(3) 2.649(4), N(1)−H(1A)−O(3) 153.7.

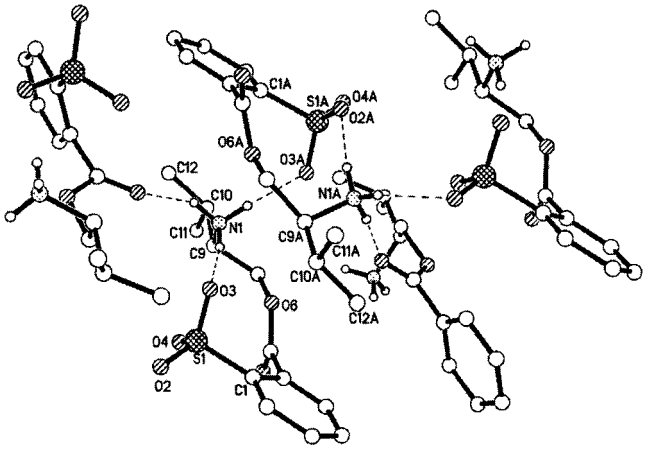
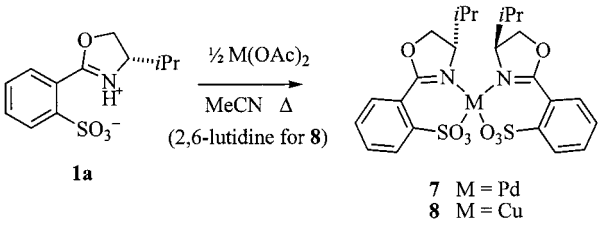


Figure 2. Packing diagram showing five molecules of **2a** showing hydrogen bonding network, the two independent molecules in the structure are labelled. Selected H-bonding distances (Å): N(1)−H(1A)···O(3) 1.93, N(1)···O(3) 2.824(3); N(1)−H(1C)···O(3A) 1.92, N(1)···O(3a) 2.815(3); N(1A)−H(1A1)···O(4) 1.90, N(1A)···O(4A) 2.799(3); N(1)−H(1B)···O(5)(carbonyl) 2.03, N(1)···O(5)^{i} 2.779(3); N(1A)−H(1a1)···O(5A)^{ii} 1.98, N(1a)···O(5A)^{ii} 2.887(3); i = 1 − *x*, *y* − 1/2, −*z*; ii = *x* − 1, *y*, *z*.

One potential use for the oxazoline ligands **1a** is in asymmetric catalysis, therefore we were keen to confirm that this class of ligands can bind metal centres. Acetonitrile solutions of **1a** were reacted with $M(OAc)_2$ (M = Pd, Cu) at 90 °C and in the presence of 2,6-lutidine for copper(II) acetate. On cooling, yellow or dark blue crystals of **7** or **8** respectively formed. Mass spectrometry suggested that metathesis of the acetates had taken place to provide the bis-complex **7** in the case of palladium (Scheme 3). Elemental analysis results indicated identical behaviour for **8**, but in this case no molecular ion could be observed.



Scheme 3. Preparation of metal complexes of **1a**.

X-ray crystallographic analysis confirmed the formation of ML_2 complexes. The molecular structures of **7** and **8** are shown in Figure 3−4, respectively, together with selected bond lengths and angle data. The palladium complex **7** adopts an essencially perfect d^8 square planar configuration and crystallised as an acetonitrile solvate. The Pd−O distances and Pd−O−S are similar to those reported by Tulloch and co-workers for a Pd−OTs complex 2.123 Å and 122.81°, respectively.[8] The two ligands in **7** are inequivalent both in the solid state and in solution. For example, four methyl doublets at δ_H = 1.06, 1.38, 1.39 and 1.62 are observed for the diastereotopic *i*Pr groups. The copper(II) complex adopts a distorted tetrahedral geometry. Again, the coordination of the sulfonic acids mimics those of known copper(II) tosylate species.[9]

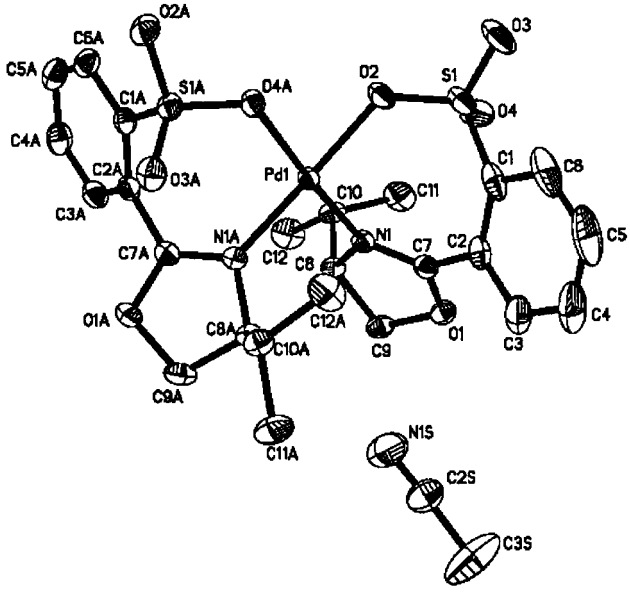


Figure 3. Molecular structure of **7**. Selected interatomic distances (Å) and angles (°): Pd(1)−O(2) 2.016(13), Pd(1)−O(4a) 2.0334(11), Pd(1)−N(1) 1.9952(14), Pd(1)−N(1A) 1.9908(15), O(2)−Pd−O(4A) 83.22(6), O(2)−Pd−N(1) 93.25(6), O(4A)−Pd−N(1A) 94.52(6), N(1)−Pd−N(1A) 89.03(6), O(2)−Pd−N(1) *vs.* O(4A)−Pd−N(1A) interplanar twist angle 1.1 °. An acetonitrile of crystallisation is also shown in the plot.

Reaction of Oxazolines 1 with Primary Amines

Because of the versatility of sulfonamide units we wished to establish a simple derivatisation of the sulfonic acids **1**

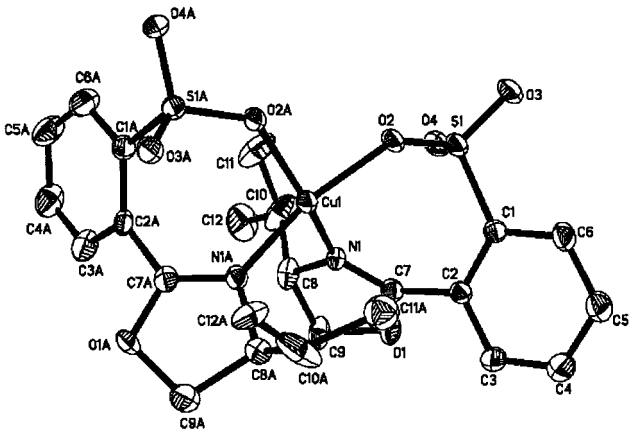
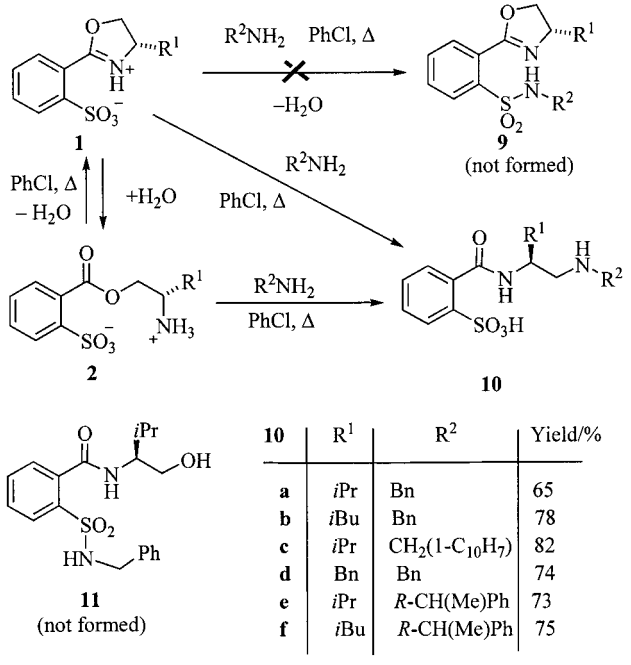


Figure 4. Molecular structure of **8**. Selected interatomic distances (Å) and angles(°) Cu(1)−O(2) 1.940(3), Cu(1)−O(2a) 1.946(3), Cu(1)−N(1) 1.947(4), Cu(1)−N(1A) 1.942(3), O(2)−Cu−O(2A) 86.80(12), O(2)−Cu−N(1) 96.03(13), O(2A)−Cu−N(1A) 94.18(13), N(1)−Cu−N(1A) 92.13(14), O(2)−Cu−N(1) vs. O(2A)−Cu−N(1A) interplanar twist angle 31.4 °.

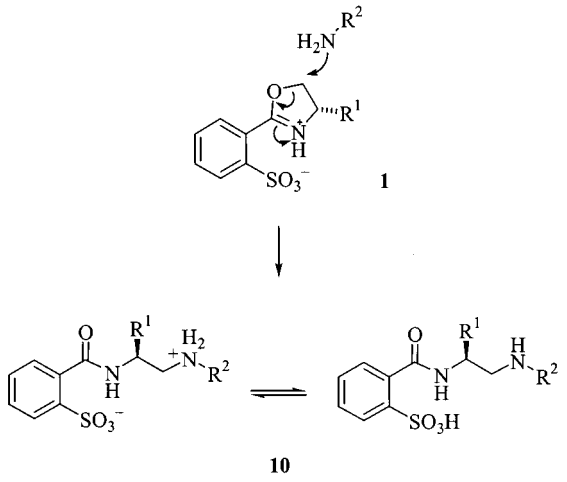
to increase the diversity of our library. Perhaps the most simple method for sulfonamide formation is direct reaction with amines under thermal conditions leading to elimination of water.[10] Reaction of **1a** with $PhCH_2NH_2$ under Dean−Stark conditions (PhCl, 130 °C, 16 h), however, did *not* fashion the expected product **9** (Scheme 4). It was clear that a single new species is formed containing the reaction components and rearrangement chemistry seemed to have occurred.



10	R^1	R^2	Yield/%
a	*i*Pr	Bn	65
b	*i*Bu	Bn	78
c	*i*Pr	$CH_2(1\text{-}C_{10}H_7)$	82
d	Bn	Bn	74
e	*i*Pr	*R*-CH(Me)Ph	73
f	*i*Bu	*R*-CH(Me)Ph	75

Scheme 4. Attempted preparation of sulfonamides via **1** or **2**.

Both combustion analyses and mass spectra of the products indicated empirical formulas with no loss of H_2O. Confusingly, despite their proposed polar constitution these compounds could be isolated by chromatography on silica



Scheme 5. Formation of compounds **10**

gel. Infra-red spectroscopic studies of **10** suggested the presence of an amide group (1650−1620 cm^{-1}) and this is supported by the observation of an amido-like ^{13}C NMR resonance (δ_C = 169.3−172.2) in each case. Proton NMR spectra of **10** clearly indicated the presence of three exchangable *X*-H protons (where *X* = N or O) in each case. Reaction of the esters **2**, under identical conditions also produced **10** (albeit in slightly lower yields of 50−60%). Initial attempts at recrystallisation of **10a** produced only fine needles unsuitable for X-ray analysis. Therefore compound **10a** was subjected to extensive NMR studies in an attempt to define its structure. Exposure of a $CDCl_3$ solution of **10a** to D_2O led to immediate replacement of two broad 1H signals at δ_H = 8.92 and 8.90 (subsequently assigned to the SO_3H and NHR^2 resonances) and commensurate formation of an HOD signal at ca. 4.8 ppm. Further shaking with D_2O led to replacement of a 1H doublet (J = 9.5 Hz) at δ_H = 7.75 (assigned to CONH) over a 10 minute period. The ^1H:^1H COSY spectrum links the latter signal with a broad CH, revealed through the COSY to be itself part of a NHCH(*i*Pr)CH_2OH derived side chain. This led us to speculate initially that **10a** was the hydrolysis product of the desired **9a** (i.e. **11**). The ^1H:^{13}C COSY spectrum of **10a** showed a cross peak from the amido NH to the carbonyl signal at δ_C = 172.2 strongly suggesting that a carbonyl bound amide is formed. However, the proposed structure (**11**) could be discounted as it had already been prepared in complimentary studies by an independent route.[11] Despite our best efforts we could not initially pin down the point of attachment of the R^2NH_2 derived amine unit.[12] Fortunately, we were finally able to crystallise compound **10c** from methanol and confirm the connectivity by an X-ray study (Figure 5).

The slow exchange of the sulfonamide N*H*SO_2 with D_2O and the fact that all examples of **10** may be isolated by chromatography on silica gel suggests strong hydrogen bonding in this class of compound. This is confirmed in the structure of **10c** were the presence of intramolecular H-bonding contacts between the amido NH and the sulfato group and also between the distal amine and the amide car-

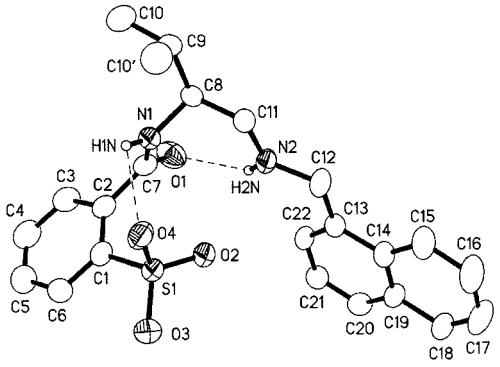


Figure 5. Molecular structure of **10c** showing intramolecular hydrogen bonding. Selected H-bond lengths (Å) and angles (°): N(1)−H(1)N···O(4), H(1)N···O(4) 2.45, N(1)···O(4) 2.965(4), N(2)−H(2)N···O(1), H(2)N···O1 2.34, N(2)···O(1) 3.077(4), N(1)−H(1)N···O(4) 118, N(2)−H(2)N···O(1) 141.

bonyl. Additionally, the unit cell of **10c** contains methanol crystallisation solvent but this could not be modelled in terms of atomic sites. In CD_3OD exchange of all the OH and NH protons in **10** is attained within minutes and spectra run in this solvent are devoid of signals due to these hydrogens. Hydrogen bonding effects also engenders compounds **10** to occlude other polar solvents unless strict anhydrous conditions are attained. For example, **10a**, **d** and **f** readily crystallise as mono or hemi hydrates; a reproducible H_2O signal at 1.9−2.0 ppm integrating to 1 or 2 H can be detected in the ^1H (dried $CDCl_3$) NMR spectra of these compounds in support of the analytical data. The formation of **10** can be most simply rationalised as an S_N2 attack of the amine R^2NH_2 on the methylene of the oxazoline ring; the resulting fragmentation leading directly to the observed products (Scheme 5). Attempted sulfonamide formation from **10** by its exposure to further equivalents of R^2NH_2 (PhCl, 130 °C, 16 h) led only to the recovery of **10**.

Conclusion

The rapid synthesis of oxazolinesulfonic acids **1** has been demonstrated either through esters **2** or directly from 2-sulfobenzoic acid anhydride and *N*-Boc-protected amino alcohols. A useful displacement reaction of **1** or **2** has been discovered allowing simple access into diverse 2-amido-diamine benzenesulfonicacids **10**. The method is eminently suitable for high throughput library synthesis, and investigations into the usefulness and application of such compounds in asymmetric catalysis is currently being undertaken both in our group and in collaboration with others.

Experimental Section

General: Procedures involving moisture sensitive reagents or intermediates were performed under atmospheres of argon or nitrogen using standard Schlenk techniques. Tetrahydrofuran and Et_2O were distilled from sodium benzophenone ketyl. Other solvents were dried appropriately and stored over 4-Å molecular sieves. Light petroleum refers to the fraction boiling in the range 40−60 °C. Infrared spectra were recorded using a Perkin−Elmer 983G (KBr disc), Perkin−Elmer 882 or a Nicolet Avatar 360 FT-IR infrared spectrophotometer. The term "solid state" refers to direct analysis of the oil/solid, using a Nicolet Avatar 360 FT-IR reflecting probe. Proton and ^{13}C NMR spectra were recorded on either JEOL (GX 270) or Bruker (AM400, AV400 and DRX500) spectrometers at ambient temperature unless otherwise noted. Tetramethylsilane was used as an internal standard and *J* values are given in Hz. Mass spectra were obtained on a Micromass 70E (electron-impact ionisation, EI+), Micromass LCT (electrospray ionization, ES+) and VG AutoSpec (fast-atom bomdardment, FAB+) machines. Specific rotations were measured using a Jasco DIP370 Digital polarimeter at ambient conditions and are given in units of $10^{-1}°cm^2g^{-1}$; (*c* in g/100 mL). Boc-amino alcohols were prepared by literature routes.[13] Commercially supplied 2-sulfobenzoic acid anhydride proved unsatisfactory; it was sublimed (170 °C, 0.1 Torr) before use.

Representative Procedure. 2-[(*S*)-4-Isopropyl-4,5-dihydrooxazol-2-yl]benzenesulfonic Acid (1a): Chlorobenzene (15 mL) was added to **2a** (180 mg, 0.63 mmol) and the reaction mixture refluxed with stirring using a Dean−Stark trap (5 mL capacity) for 16 h. Upon completion the reaction was concentrated under vacuum to give **1a** (168 mg; 100%) as a white solid, with no further purification required.[14] M.p. 226−227 °C (EtOH). $[\alpha]_D$ = −44.2 (*c* = 3.89, MeOH). ^1H NMR (400 MHz, CD_3OD): δ = 8.20 (dd, 1 H, *J* = 8.0, 1.0; Ar), 7.98 (dd, 1 H, *J* = 8.0, 1.0; Ar), 7.91 (dt, 1 H, *J* = 8.0, 1.0; Ar), 7.76 (dt, 1 H, *J* = 8.0, 1.0; Ar), 5.26 (apparent t, 1 H, *J* = 9.8), 5.04 (dd, 1 H, *J* = 9.8, 7.4), 4.54 (m, 1 H), 2.17 (m, 1 H, C*H*Me$_2$), 1.17 (d, 3 H, *J* = 6.7; *Me*), 1.11 (d, 3 H, *J* = 6.7; *Me*) ppm, H/D exchange in SO_3H group with D from solvent. ^{13}C NMR (67.8 MHz, CD_3OD): δ = 174.8 (C_{ox}), 146.9, 136.3, 132.2, 131.9, 129.7, 119.2, 77.8, 66.6, 32.9, 18.2 (Me), 18.0 (Me) ppm. IR (solid state): $\tilde{\nu}$ = 1659 s (C=N$_{ox}$), 1501 m, 1456 w, 1340 w, 1254 vs, 1185 vs, 1145 m, 1128 m, 1078 m, 1044 w, 1016 s, 935 m, 800 m, 759 m, 736 s, 691 m cm^{-1}. MS: *m*/*z* (ES+): 846 (M_3H^+(MeCN), 60%), 270 (MH^+, 100). $C_{12}H_{15}NO_4S$ (269.32): calcd. C 53.5, H 5.6, N 5.2; found C 53.6, H 5.6, N 5.1.

Compound **1a** could also be prepared by direct reaction of 2-sulfobenzoic acid anhydride (1.50 g, 8.14 mmol) and L-valinol (0.84 g, 8.14 mmol) in PhCl (50 mL) (Dean−Stark apparatus, reflux 17 h). Evaporation of the PhCl under vacuum followed by recrystallisation of the residue from anhydrous ethanol afforded 1.25−1.32 g (55−60%). This alternative procedure was, however, ineffective for compounds **1b**−**e**.

2-((*S*)-4-Isobutyl-4,5-dihydrooxazol-2-yl)benzenesulfonic Acid (1b): Prepared from **2b** (238 mg, 0.79 mmol), recrystallisation from EtOH gave **1b** (220 mg, 98%) as white crystals. M.p. 201−202 °C (EtOH). $[\alpha]_D$ = −13.8 (*c* = 1.0, EtOH). ^1H NMR (400 MHz, CD_3OD): δ = 8.18 (dd, 1 H, *J* = 8.0, 1.0; Ar), 7.94 (dd, 1 H, *J* = 8.0, 1.0; Ar), 7.88 (dt, 1 H, *J* = 8.0, 1.0; Ar), 7.76 (dt, 1 H, *J* = 8.0, 1.0; Ar), 5.33 (dd, 1 H, *J* = 8.8, 7.8; OC$H_{2\alpha}$), 4.88 (dd, 1 H, *J* = 8.8, 7.0; OC$H_{2\beta}$), 4.86−4.79 (m, 1 H, C*H*N), 1.99 (ddd, 1 H, *J* = 13.5, 7.6, 6.0), 1.88 (m, 1 H, C*H*Me$_2$), 1.75 (ddd, 1 H, *J* = 13.5, 7.9, 6.0), 1.07 (d, 3 H, *J* = 6.5; *Me*), 1.06 (d, 3 H, *J* = 6.5; *Me*) ppm, H/D exchange in SO_3H group with D from solvent. ^{13}C NMR (100 MHz, CD_3OD): δ = 174.8 (C_{ox}), 147.1 (C), 136.2, 132.0, 131.8, 129.7, 119.4 (C), 80.0, 59.7, 43.6, 26.2, 23.0 (Me), 22.1 (Me) ppm. IR (solid state): $\tilde{\nu}$ = 1651 s (C=N$_{ox}$), 1497 w, 1451 w, 1356 w, 1246 vs, 1190 vs, 1172 s, 1133 m, 1078 w, 1018 s, 939 m, 837 w, 792 m, 751 m, 737 s, 697 cm^{-1}. MS: *m*/*z* (ES+): 284 (MH^+,

100%); found (HRMS): MH^+ 284.0982, $C_{13}H_{18}NO_4S$ requires 284.0957.

2-((*S*)-4-*tert*-Butyl-4,5-dihydrooxazol-2-yl)benzenesulfonic Acid (1c): Prepared from **2c** (301 mg, 1.00 mmol), recrystallisation from EtOH gave **1c** (260 mg, 92%) as white crystals. M.p. > 240 °C (dec., EtOH). $[\alpha]_D$ = −23.1 (*c* = 1.0, EtOH). ^{1}H NMR (400 MHz, CD_3OD): δ = 8.24 (dd, 1 H, *J* = 7.7, 1.0; Ar), 8.07 (dd, 1 H, *J* = 7.7, 1.0; Ar), 7.93 (dt, 1 H, *J* = 7.7, 1.0; Ar), 7.78 (dt, 1 H, *J* = 7.7, 1.0; Ar), 5.19 (dd, 1 H, *J* = 10.4, 9.9; OC$H_{2\alpha}$), *overlapped by* 5.15 (dd, 1 H, *J* = 9.9, 7.5; C*H*N), 4.60 (dd, 1 H, *J* = 10.4, 7.5; OC$H_{2\beta}$), 1.14 (s, 9 H, *t*Bu) ppm, H/D exchange in SO_3H group with D from solvent. ^{13}C NMR (100 MHz, CD_3OD): δ = 174.4 (C_{ox}), 147.1 (C), 136.9, 132.9, 132.1, 130.0, 118.8 (C), 76.0, 70.0, 35.1 (Bu), 25.2 (Bu) ppm. IR (solid state): $\tilde{\nu}$ = 1655 s (C=N_{ox}), 1497 m, 1452 w, 1379 w, 1255 vs, 1180 vs, 1131 m, 1082 w, 1017 s, 928 w, 901 w, 749 s, 736 s, 687 cm^{-1}. MS: *m*/*z* (ES+): 284 (MH^+, 100%); found (HRMS): MH^+ 284.0967, $C_{13}H_{18}NO_4S$ requires 284.0957. $C_{13}H_{17}NO_4S$ (283.34): calcd. C 55.1, H 6.05, N 4.9; found C 55.2, H 6.1, N 4.8.

2-((*S*)-4-Benzyl-4,5-dihydrooxazol-2-yl)benzenesulfonic Acid (1d): Prepared from **2d** (0.99 g, 2.96 mmol), recrystallisation from dichloromethane/light petroleum ether gave **1d** (807 mg, 86%) as white crystals. M.p. 190−191 °C (EtOH). $[\alpha]_D$ = −53.2 (*c* = 1.0, EtOH). ^{1}H NMR (400 MHz, CD_3OD): δ = 8.16 (d, 1 H, *J* = 7.8, 1.0; Ar), 7.88 (dt, 1 H, *J* = 7.8, 1.2; Ar), 7.79 (dd, 1 H, *J* = 7.8, 1.0; Ar), 7.71 (dt, 1 H, *J* = 7.8, 1.2; Ar), 7.42−7.34 (m, 5 H, Ar), 5.27 (*apparent* t, 1 H, *J* = 12.1; OC$H_{2\alpha}$), 5.08−5.02 (m, 2 H, OC$H_{2\beta}$ and C*H*N), 3.29 (dd, 1 H, *J* = 13.9, 5.3; C$H_{2\alpha}$Ph), 3.22 (dd, 1 H, *J* = 13.9, 6.8; C$H_{2\beta}$Ph) ppm, H/D exchange in SO_3H group with D from solvent. ^{13}C NMR (100 MHz, CD_3OD): δ = 175.4 (C_{ox}), 146.7 (C), 136.3, 135.9, 131.7, 131.6, 130.7, 130.6, 129.6, 128.6, 119.4 (C), 79.0, 62.2, 40.0 ppm. IR (solid state): $\tilde{\nu}$ = 1653 s (C=N_{ox}), 1574 w, 1499 s, 1454 m, 1345 w, 1255 vs, 1184 vs, 1146 m, 1130 m, 1020 s, 934 m, 786 m, 733 s, 699 s cm^{-1}. MS: *m*/*z* (ES+): 318 (MH^+, 100%); found (HRMS): MH^+ 318.0746, $C_{16}H_{15}NSO_4$ requires 318.0742. $C_{16}H_{17}NO_5S$ (317.36): calcd. C 60.55, H 4.8, N 4.4; found C 60.15, H 4.65, N 4.3.

Representative Procedure. (*S*)-2-Amino-3-methylbutyl 2-Sulfobenzoate (2a): To a stirred solution of 2-sulfobenzoic acid cyclic anhydride **4** (3.73 g, 20.3 mmol) in dry MeCN (40 mL) under inert atmosphere, was added *N*-Boc-L-valinol (4.12 g, 20.3 mmol) as a solution in dry MeCN (10 mL). The reaction mixture was refluxed for 8 h, a white insoluble precipitate being formed during the course of the reaction. The reaction mixture was allowed to cool to room temperature and stirred overnight. The reaction was cooled to 0 °C in the freezer for 12 h, the white insoluble product was filtered off, washed with light petroleum ether then dried under high vacuum to give **2a** (3.91 g, 67%) as a white solid. An additional experiment gave (1.68 g, 87%). M.p. 208−209 °C (EtOH). $[\alpha]_D$ = +36.3 (*c* = 1.0, EtOH). ^{1}H NMR (400 MHz, CD_3OD): δ = 8.05 (dt, 1 H, *J* = 7.5, 1.0), 7.67−7.57 (m, 3 H), 4.80 (dd, 1 H, *J* = 12.1, 3.0; OC$H_{2\alpha}$), 4.28 (dd, 1 H, *J* = 12.1, 9.5; OC$H_{2\beta}$), 3.47 (ddd, 1 H, *J* = 9.5, 7.1, 3.0; C*H*N), 2.08 (d sept, 1 H, *J* = 7.1, 6.9, C*H*Me$_2$), 1.33 (d, 3 H, *J* = 6.9; *Me*), 1.14 (d, 3 H, *J* = 6.9; *Me*) ppm, H/D exchange in OH and NH_2 groups with D from solvent. ^{13}C NMR (100 MHz, CD_3OD): δ = 169.8 (CO), 144.0, 132.1, 132.0, 131.6, 130.0, 129.0, 64.7 (CH_2), 57.1 (CH), 29.6 (CH), 19.1 (CH_3), 18.8 (CH_3) ppm. IR (KBr disc): $\tilde{\nu}$ = 3449 m, 3157 m, 2966 m, 1736 vs (C=O_{ester}), 1618 m, 1519 s, 1300 s, 1243 s, 1226 s, 1198 m, 1179 s, 1122 m, 1082 s, 1017 s, 782 m, 762 m, 740 m, 662 m, 617 s cm^{-1}. MS: *m*/*z* (ES+): 862 (M_3H^+, 100%), 575 (M_2H^+, 50), 288 (MH^+, 10); found (HRMS): MH^+ 288.0923, $C_{12}H_{18}NO_5S$ requires 288.0906. Other compounds were formed in an analogous manner. $C_{12}H_{17}NO_5S$ (287.33): calcd. C 50.2, H 6.0, N 4.9; found C 50.3, H 6.0, N 4.8.

(*S*)-2-Amino-4-methylpentyl 2-Sulfobenzoate (2b): Prepared from *N*-Boc-L-leucinol (500 mg, 2.30 mmol), and **4** (422 mg, 2.30 mmol). Purification by recrystallisation from MeCN gave **2b** (470 mg, 68%) as a white solid. M.p. 231−232 °C (MeCN). $[\alpha]_D$ = +22.2 (*c* = 1.0, EtOH). ^{1}H NMR (400 MHz, CD_3OD): δ = 8.05 (dd, 1 H, *J* = 7.0, 1.0; Ar), 7.67−7.57 (m, 3 H, Ar), 4.74 (dd, 1 H, *J* = 12.2, 3.0; OC$H_{2\alpha}$), 4.19 (dd, 1 H, *J* = 12.2, 9.0; OC$H_{2\beta}$), 3.75 (ddd, 1 H, *J* = 9.0, 7.0, 3.0; C*H*N), 1.81 (sept, 1 H, *J* = 7.0; C*H*Me$_2$), 1.67−1.52 (m, 2 H, CHCH_2*i*Pr), 1.04 (d, 3 H, *J* = 7.0; *Me*), 1.03 (d, 3 H, *J* = 7.0; *Me*) ppm, H/D exchange in OH and NH_2 groups with D from solvent. ^{13}C NMR (100 MHz, CD_3OD): δ = 169.8 (CO), 143.9, 132.2, 132.1, 131.7, 130.0, 129.0, 65.9 (CH_2), 50.1 (CH), 39.2 (CH_2), 25.6 (CH), 22.9 (CH_3), 22.5 (CH_3) ppm. IR (solid state): $\tilde{\nu}$ = 1736 m (C=O_{ester}), 1693 m, 1523 m, 1327 m, 1216 m, 1293 m, 1242 vs, 1228 s, 1188 s, 1175 vs, 1142 s, 1118 w, 1081s, 1017 vs, 754 vs cm^{-1}. MS: *m*/*z* (ES+): 904 (M_3H^+, 100%), 603 (M_2H^+, 30), 302 (MH^+, 30); found (HRMS): MH^+ 302.0994, $C_{13}H_{20}NO_5S$ requires 302.0984. $C_{13}H_{19}NO_5S$ (301.36): calcd. C 51.8, H 6.4, N 4.65; found C 51.5, H 6.4, N 4.3.

(*S*)-2-Amino-3,3-dimethylbutyl 2-Sulfobenzoate (2c): Prepared from *N*-Boc-L-*tert*-leucinol (588 mg, 2.70 mmol), and **4** (496 mg, 2.70 mmol). Purification by recrystallisation from cold MeCN gave **2c** (700 mg, 87%) as a white crystalline solid. M.p. 225−226 °C (MeCN). $[\alpha]_D$ = −25.6 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, CD_3OD): δ = 8.05 (dd, 1 H, *J* = 7.0, 1.0; Ar), 7.65−7.59 (m, 3 H, Ar), 4.89 (dd, 1 H, *J* = 12.0, 3.0; OC$H_{2\alpha}$), 4.26 (dd, 1 H, *J* = 12.0, 10.6; OC$H_{2\beta}$), 3.49 (dd, 1 H, *J* = 10.6, 3.0; C*H*N), 1.14 (s, 9 H, *t*Bu) ppm, H/D exchange in OH and NH_2 groups with D from solvent. ^{13}C NMR (100 MHz, CD_3OD): δ = 169.8 (CO), 144.0, 132.1, 132.0, 131.6, 130.0, 129.0, 64.1 (CH_2), 60.2 (CH), 33.1 (C), 26.6 (CH_3) ppm. IR (solid state): $\tilde{\nu}$ = 2970 w, 1728s (C=O_{ester}), 1633 w, 1528 m, 1303 w, 1280 s, 1245 vs, 1229 s, 1180 vs, 1171 vs, 1147 s, 1118 w, 1109 s, 1082 vs, 1020 vs, 780 m, 758 s, 739 m cm^{-1}. MS: *m*/*z* (ES+): 904 (M_3H^+, 100%), 603 (M_2H^+, 30), 302 (MH^+, 30); found (FAB+, HRMS): MH^+ 302.1081, $C_{13}H_{20}NO_5S$ requires 302.1062. $C_{13}H_{19}NO_5S$ (301.36): calcd. C 51.8, H 6.4, N 4.7; found C 51.6, H 6.4, N 4.7.

(*S*)-2-Amino-3-phenylpropyl 2-Sulfobenzoate (2d): Prepared from *N*-Boc-L-phenylalaninol (2.01 g, 8.0 mmol), and **4** (1.47 g, 8.0 mmol). Purification by recrystallisation from cold MeCN gave **2d** (2.57 g, 96%) as a white powder. Subsequent recrystallisation from EtOH/H_2O gave **2d** (1.69 g, 63%) as off-white crystals. M.p. 174−175 °C (EtOH). $[\alpha]_D$ = +40.0 (*c* = 1.0, EtOH). ^{1}H NMR (400 MHz, CD_3OD): δ = 8.06 (d, 1 H, *J* = 7.5; Ar), 7.66−7.56 (m, 3 H, Ar), 7.40−7.30 (m, 5 H, Ar), 4.63 (dd, 1 H, *J* = 12.1, 2.9; OC$H_{2\alpha}$), 4.22 (dd, 1 H, *J* = 12.1, 7.8; OC$H_{2\beta}$), 3.94−3.88 (m, 1 H, C*H*N), 3.08 (*apparent* dd, 2 H, *J* = 8.5, 4.5; CH_2Ph) ppm, H/D exchange in OH and NH_2 groups with D from solvent. ^{13}C NMR (67.8 MHz, CD_3OD): δ = 169.6 (CO), 143.9, 136.4, 132.0, 131.9, 131.6, 130.3, 130.1, 130.0, 129.0, 128.6, 65.0 (CH_2), 53.0 (CH), 36.3 (CH_2) ppm. IR (solid state): $\tilde{\nu}$ = 3489 w, 3288 w, 1751s (C=O_{ester}), 1618 w, 1524 m, 1291 s, 1255 s, 1239 m, 1217 s, 1190 vs, 1145 m, 1124 s, 1081 s, 1018 s, 981 m, 788 m, 759 s, 788 m, 740 m, 720 w, 706 s cm^{-1}. MS: *m*/*z* (ES+): 671 (M_2H^+, 40%), 336 (MH^+, 100); found (ES+, HRMS): MH^+ 336.0881, $C_{16}H_{18}NO_5S$ requires 336.0906]. $C_{16}H_{17}NO_5S{\cdot}H_2O$ (335.38): calcd. C 54.4, H 5.4, N 4.0; found C 54.0, H 5.3, N 3.8.

2-Aminoethyl 2-Sulfobenzoate (2e): Prepared from *N*-Boc-ethanolamine (4.61 g, 28.6 mmol), and **4** (5.26 g, 28.6 mmol). Precipitated

directly from MeCN to give **2e** (6.60 g, 94%) as a white solid. M.p. > 250 °C (dec., MeCN). IR (solid state): $\tilde{\nu}$ = 3179 w, 1728s (C=O_{ester}), 1485 w, 1455 w, 1372 w, 1292 s, 1256 s, 1218 s, 1184 vs, 1143 s, 1127 s, 1082 s, 1019 s, 985 m, 961 m, 790 m, 759 s, 743 s, 714 m cm^{-1}. MS: *m/z* (ES+): 246 (MH^+, 100%). This compound was too insoluble to give acceptable NMR spectra. $C_9H_{11}NO_5S$ (245.25): calcd. C 44.1, H 4.5, N 5.7; found C 44.0, H 4.6, N 5.5.

(*S*)-2-Aminopropyl 2-Sulfobenzoate (2f): Prepared from *N*-Boc-L-alaninol (1.05 g, 6.0 mmol), purification by recrystallisation from MeCN gave **2f** (930 mg, 60%) as a white solid. M.p. > 250 °C (dec., MeCN). $[\alpha]_D = -22.7$ (c = 0.3, EtOH). ^{1}H NMR (400 MHz, CD_3OD): δ = 8.06 (dd, 1 H, J = 7.0, 1.0; Ar), 7.65−7.59 (m, 3 H, Ar), 4.68 (dd, 1 H, J = 12.0, 3.0; OC$H_{2\alpha}$), 4.20 (dd, 1 H, J = 12.0, 8.8; OC$H_{2\beta}$), 3.79 (ddq, 1 H, J = 8.8, 6.8, 3.0; C*H*N), 1.14 (d, 3 H, J = 6.8; *Me*) ppm, H/D exchange in OH and NH_2 groups with D from solvent. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 170.2 (CO), 140.3, 132.1, 132.0, 130.0, 129.2, 127.8, 66.9 (CH_2), 46.9 (CH), 14.4 (CH_3) ppm. IR (KBr disc): $\tilde{\nu}$ = 1733 s (C=O_{ester}), 1626 w, 1506 w, 1390 w, 1320 m, 1286 m, 1255 s, 1227 vs, 1211 vs, 1197 vs, 1181 vs, 1146 s, 1110 s, 1081 vs, 1024 s, 1014 s, 977 m, 951 w, 843 w, 780 m, 767 s, 739 m cm^{-1}. MS: *m/z* (ES+): 541 (M_2Na^+, 60%), 519 (M_2H^+, 100), 260 (MH^+, 10); found (HRMS): MH^+ 260.0604, $C_{10}H_{14}NO_5S$ requires 260.0593. $C_{10}H_{13}NO_5S$ (259.28): calcd. C 46.3, H 5.05, N 5.4; found C 46.4, H 4.9; N 5.2.

Sodium 2-[(2-{[(1*E*)-(2-Hydroxyphenyl)methylene]amino}ethoxy)-carbonyl]benzenesulfonate (6): To a stirred suspension of NaH (82 mg, 2.04 mmol) in anhydrous THF (5 mL) under an inert atmosphere was added **2e** (500 mg; 2.04 mmol) at room temperature, resulting in immediate H_2 evolution. The reaction was stirred for a further 20 min then salicylaldehyde (0.21 mL, 2.04 mmol) was added in one portion. The reaction mixture turned yellow immediately, and was stirred for 48 h. The reaction was quenched by the addition of MeOH (0.5 mL), and then concentrated under vacuum to give a pale yellow solid. The crude material was taken up in hot EtOAc (10 mL) and hot filtered to give **6** (680 mg, 90%) as a pale yellow solid. M.p. 209 °C (EtOAc). ^{1}H NMR (400 MHz, CD_3OD): δ = 8.59 (s, 1 H, NC*H*), 8.02 (dd, 1 H, J = 6.1, 0.8; Ar), 7.56 (dt, 1 H, J = 6.9, 1.1; Ar), 7.48−7.29 (m, 5 H, Ar), 6.89−6.86 (m, 2 H, Ar), 4.65 (dt, 2 H, J = 5.3, 3.0; CH_2), 4.04 (dt, 2 H, J = 5.9, 1.0; CH_2) ppm, OH proton signal was not observed due to H/D exchange with CD_3OD. ^{13}C NMR (100 MHz, CD_3OD): δ = 170.7 (CO_{ester}), 169.2 (CH_{imine}), 144.1 (C), 133.9, 133.2, 132.8 (C), 131.3, 131.2, 131.1, 129.1, 129.0, 120.0 (C), 119.4, 118.2, 66.1, 57.8 ppm. IR (solid state): $\tilde{\nu}$ = 1739 s (C=O), 1632 s (C=N), 1500 w, 1461 w, 1286 s, 1230 s, 1197 vs, 1137 s, 1119 w, 1085 m, 1026 vs, 922 w, 757 vs, 735 m cm^{-1}. MS: *m/z* (FAB+): 394 (MNa^+, 10%), 372 (MH^+, 25), 329 (15), 307 (30), 289 (15), 176 (30), 154 (100), 137 (65), 107 (20), 91 (15), 77 (15), 57 (20); found (HRMS): MH^+ 372.0508, $C_{16}H_{15}NO_6SNa$ requires 372.0518.

Bis[2-{(4′*S*)-4′,5′-dihydro-4′-isopropyloxazolyl]phenylsulfonato]-palladium(II) (7): Palladium(II) acetate (83.5 mg, 0.37 mmol) and **1a** (100 mg, 0.37 mmol) were refluxed at 90 °C in MeCN (7 mL) with stirring. After 20 min the reaction mixture was allowed to cool to room temperature slowly, followed by cooling to 0 °C for 12 h, The resulting small yellow crystals were filtered to give **7** (150 mg, 100%). M.p. >184 °C (dec., MeCN). ^{1}H NMR (400 MHz, [D$_6$]acetone): δ = 8.29 (dd, 1 H, J = 8.0, 1.0; Ar), 8.13−8.04 (m, 3 H, Ar), 8.00 (dt, 1 H, J = 8.0, 1.0; Ar), 7.93 (dd, 1 H, J = 8.0, 1.0; Ar), 7.88 (dt, 1 H, J = 8.0, 1.0; Ar), 7.81 (dt, 1 H, J = 8.0, 1.0; Ar), 5.08 (*apparent* t, 1 H, J = 9.5 OC$H_{2\alpha}$), 4.97 (dd, 1 H, J = 10.4, 9.1; OC$H_{2\alpha}$), 4.92 (dd, 1 H, J = 9.3, 6.0; OC$H_{2\beta}$), 4.81 (dd, 1 H, J = 9.1, 7.5; OC$H_{2\beta}$), 4.37 (ddd, 1 H, J = 10.4, 7.5, 6.0; C*H*N), 3.98 (ddd, 1 H, J = 9.9, 7.5, 6.0; C*H*N), 2.82 (m, 1 H, C*H*Me$_2$), 2.22 (m, 1 H, C*H*Me$_2$), 1.62 (d, 3 H, J = 7.0; *Me*), 1.42 (d, 3 H, J = 7.0; *Me*), 1.38 (d, 3 H, J = 7.0; *Me*), 1.08 (d, 3 H, J = 7.0; *Me*) ppm. IR (KBr disc): $\tilde{\nu}$ = 3462.6 m, 2964 m, 1624 vs (C=N), 1487 m, 1388 s, 1290 vs, 1250 s, 1168 vs, 1131 s, 1066 m, 1040 w, 1022 w, 974 vs, 771 s, 746 s, 697 m, 668 m, 627 m cm^{-1}. MS: *m/z* (ES^+): 685 (MH^+(MeCN), 100%). $C_{24}H_{28}N_2O_8S_2Pd$·MeCN (684.09): calcd. C 45.7, H 4.6, N 6.1; found C 45.5, H 4.5, N 6.1.

Bis[2-{(4′*S*)-4′,5′-dihydro-4′-isopropyloxazolyl]phenylsulfonato]-copper(II) (8): Copper(II) acetate (20 mg, 0.1 mmol) and **1a** (30 mg, 0.1 mmol) were stirred in dry MeCN (3 mL) followed by the addition of distilled 2,6-lutidine (12.8 μL, 0.1 mmol). The reaction mixture was refluxed at 90 °C for 2 h under an inert atmosphere. The solvent was concentrated in vacuo, taken up into dichloromethane (2 mL) and carefully layered with light petroleum ether (4 mL). Large dark blue crystals formed upon standing for 24 h. The crystals were filtered, dried under high vacuum, to give **8** (46 mg; 80% yield). M.p. > 205 °C (dec., dichloromethane). IR (solid state): $\tilde{\nu}$ = 1634 m (C=N), 1385 m, 1288 s, 1250 m, 1170 vs, 1142 s, 1129 s, 1068 m, 1017 w, 987 s, 929 w, 772 m, 761 m, 746 s, 698 m cm^{-1}. MS: *m/z* (ES+): 884 (L_3Na^+, 40%), 597 (L_2Na^+, 100), 288 (L^+, 70), Cu coordination not observed. $C_{24}H_{28}N_2O_8S_2Cu$ (600.17): calcd. C 48.0, H 4.7, N 4.7; found C 48.4, H 4.9, N 4.4.

Representative Preparation. 2-[(1*S*)-(Benzylaminomethyl)-2-methylpropylcarbamoyl]benzenesulfonic Acid (10a). Method A: To a solution of (*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)benzenesulfonic acid (**1a**) (0.25 g, 0.93 mmol) in chlorobenzene (45 mL) was added benzylamine (0.1 mL, 0.93 mmol). The reaction mixture was refluxed using a Dean−Stark trap (10 mL capacity) at 130 °C for 16 h. The reaction mixture was allowed to cool to room temperature and was concentrated under vacuum to yield a crude off-white solid. Purification by flash chromatography (dichloromethane/MeOH 5%) gave **10a** (217 mg; 65%) as white microcrystalline solid with no further purification required; data as Method B.

Method B: To a solution of **2a** (0.16 g, 0.54 mmol) in chlorobenzene (45 mL) was added benzylamine (59 μL, 0.54 mmol). The reaction mixture was refluxed using a Dean−Stark trap (10 mL capacity) at 130 °C for 16 h. The reaction mixture was allowed to cool to room temperature and was concentrated under reduced pressure to yield an off-white crude solid. Purification by flash chromatography (dichloromethane/MeOH 5%) gave **10a** (99 mg, 50%) as a white solid. R_f = 0.33 (dichloromethane/MeOH 5%). M.p. 156−158 °C (dichloromethane/MeOH). $[\alpha]_D = -32.7$ (c = 0.4, $CHCl_3$). These data were attained under rigorously anhydrous conditions, normally the hemi hydrate was isolated. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.92 (br. signal, 1 H, SO_3H or NH_{amine}), 8.60 (br. signal, 1 H, SO_3H or NH_{amine}), 8.09 (dd, 1 H, J = 6.8, 2.3; Ar), 7.75 (d, 1 H, J = 9.5; CONH), 7.56−7.47 (m, 3 H, Ar), 7.40−7.37 (m, 2 H, Ar), 7.29−7.20 (m, 3 H, Ar), 4.30 (br. signal, 1 H, C*H*NH), 4.17 (*apparent* s, 2 H, CH_2Ph), 3.11 (*apparent* t, 1 H, J = 12.6; CHC$H_{2\alpha}$), 2.98 (dd, 1 H, J = 12.6, 2.5; CHC$H_{2\beta}$), 1.72 (oct, 1 H, J = 6.7; C*H*Me$_2$), 0.83 (d, 3 H, J = 6.7; *Me*), 0.80 (d, 3 H, J = 6.7; *Me*). ^{1}H NMR (400 MHz, CD_3OD): δ = 8.03 (dd, 1 H, J = 7.0, 1.0; Ar), 7.64−7.60 (m, 4 H, Ar), 7.55 (m, 1 H, Ar), 7.47−7.45 (m, 3 H, Ar), 4.34−4.29 (m, 1 H, NHC*H*), 4.33 (d, 2 H, J = 2.0; CH_2Ph), 3.37 (dd, 1 H, J = 11.5, 2.5; CHC$H_{2\alpha}$), 3.21 (dd, 1 H, J = 11.5, 12.5; CHC$H_{2\beta}$), 1.89 (oct, 1 H, J = 7.0: C*H*Me$_2$), 1.03 (d, 3 H, J = 7.0; *Me*), 1.02 (d, 3 H, J = 7.0; *Me*) ppm, OH and NH proton signals not observed due to H/D exchange with CD_3OD. ^{13}C NMR (100 MHz, CD_3OD): δ = 172.2 (CO_{am}), 142.8 (C), 135.7 (C), 132.3 (C), 132.0, 131.5, 131.4, 131.2, 130.7, 130.2, 130.1, 129.6, 128.5,

53.2, 52.8, 51.5, 32.0 (CH), 19.8 (Me), 18.6 (Me) ppm. IR (solid state): $\tilde{\nu}$ = 2966 w, 1653 s (C=O_{am}), 1594 w, 1557 m, 1458 m, 1319 w, 1241 s, 1172 vs, 1140 vs, 1081 s, 1056 w, 1033 m, 1017 vs, 830 w, 753 vs, 741 vs, 729 vs, 699 vs cm^{-1}. MS: *m*/*z* (FAB+): 399 (MNa^+, 15%), 377 (MH^+, 90%), 307 (20), 154 (100), 136 (75), 120 (25), 107 (30), 91 (55), 83 (40), 69 (95), 57 (90); found (HRMS): MH^+ 377.1519, $C_{19}H_{25}N_2O_4S$ requires 377.1535. $C_{19}H_{24}N_2O_4S$ (376.47): calcd. C 60.6, H 6.4, N 7.4; found C 60.2, H 6.4, N 7.1.

2-[(1*S*)-(Benzylaminomethyl)-3-methylbutylcarbamoyl]-benzenesulfonic Acid (10b): Procedure as for **10a**, method A. Purification by flash chromatography (dichloromethane/MeOH 5%) gave **10b** (164 mg, 78%) as a viscous oil (which solidified on prolonged drying) from **1b** (153 mg, 0.54 mmol) and benzylamine (59 μL, 0.54 mmol). R_f = 0.35 (dichloromethane/MeOH 5%). M.p. 267−269 °C (dichloromethane/MeOH 5%). $[\alpha]_D$ = −27.6 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, CD_3OD): δ = 7.96−7.99 (m, 1 H, Ar), 7.53−7.58 (m, 4 H, Ar), 7.39−7.45 (m, 5 H, Ar), 4.55 (m, 1 H, C*H*NH), 4.28 (*apparent* s, 2 H, CH_2Ph), 3.18 (dd, 1 H, *J* = 12.7, 2.9; CHC$H_{2\alpha}$NH), 3.11 (dd, 1 H, *J* = 10.9, 12.7; CHC$H_{2\beta}$NH), 1.70 (m, 1 H, C*H*Me_2), 1.51 (m, 1 H, CHC$H_{2\alpha}$CH), 1.28 (m, 1 H, CHC$H_{2\beta}$CH), 0.98 (d, 3 H, *J* = 6.7; Me), 0.94 (d, 3 H, *J* = 6.7; Me) ppm, OH and NH proton signals not observed due to H/D exchange with CD_3OD. ^{13}C NMR (100 MHz, CD_3OD): δ = 172.2 (CO_{am}), 142.8 (C), 135.8 (C), 132.2 (C), 131.8 (2C), 131.4, 130.9, 130.5 (2C), 130.1, 129.1, 128.5, 53.6, 52.7, 46.2, 41.9, 26.0 (CH), 23.4 (Me), 22.0 (Me) ppm. IR (solid state): $\tilde{\nu}$ = 2957 w, 1662 w, 1631s (C=O_{am}), 1537 m, 1453 m, 1252 s, 1168 s, 1142 s, 1080 m, 1017 s, 747 s, 756 s, 700 s cm^{-1}. MS: *m*/*z* (FAB+): 391 (MH^+, 16%), 176 (29), 155 (25), 154 (86), 136 (70), 97 (40), 69 (76), 57 (100); found (HRMS): MH^+ 391.1704, $C_{20}H_{27}N_2O_4S$ requires 391.1692. $C_{20}H_{26}N_2O_4S$ (390.50): calcd. C 61.5, H 6.7, N 7.2; found C 61.4, H 6.8, N 7.2.

2-(2-Methyl-(1*S*)-{[(naphthalen-2-ylmethyl)amino]methyl}-propylcarbamoyl)benzenesulfonic Acid (10c): Procedure as for **10a**, method A. Purification by flash chromatography (dichloromethane/MeOH 5%) gave **10c** (134 mg, 82%) as a viscous oil from **1a** (102 mg, 0.38 mmol) and 1-naphthylenemethylamine (56 μL, 0.38 mmol). R_f = 0.37 (dichloromethane/MeOH 5%). M.p. 286−288 °C (MeOH). $[\alpha]_D$ = −34.3 (*c* = 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, CD_3OD): δ = 8.26 (dd, 1 H, *J* = 8.5, 1.0; Ar), 8.06−7.98 (m, 3 H, Ar), 7.69 (dd, 1 H, *J* = 7.0, 1.0; Ar), 7.69 (dt, 1 H, *J* = 7.0, 1.0; Ar), 7.63−7.54 (m, 5 H, Ar), 4.89 (s, 2 H, CH_2Ph), 4.39 (m, 1 H, C*H*NH), 3.47 (dd, 1 H, *J* = 13.0, 2.5; CHC$H_{2\alpha}$), 3.32 (dd, 1 H, *J* = 13.0, 11.5; CHC$H_{2\beta}$), 1.90 (oct, 1 H, *J* = 7.0; C*H*Me_2), 1.03 (d, 3 H, *J* = 7.0; Me), 1.01 (d, 3 H, *J* = 7.0; Me) ppm, OH and NH proton signals not observed due to H/D exchange with CD_3OD. ^{13}C NMR (100 MHz, CD_3OD): δ = 172.2 (CO_{am}), 142.7 (C), 135.7 (C), 135.3, 132.8, 132.0, 131.4, 131.1, 130.7, 130.0, 129.6, 128.5, 128.3, 128.1, 127.4, 126.5, 124.1, 54.8, 53.0, 32.0, 19.7 (CH_3), 18.5 (CH_3) ppm. IR (solid state): $\tilde{\nu}$ = 2967 w, 1655 m (C=O_{am}), 1595 m, 1560 m, 1459 m, 1229 m, 1164 s, 1141 m, 1082 m, 1018 s, 802 m, 799 s, 790 s, 774 s, 738 s cm^{-1}. MS: *m*/*z* (FAB+): 427 (MH^+, 5%), 391 (5), 329 9 (7), 307 (40), 289 (15), 176 (10), 154 (100), 137 (65), 120 (10), 107 (20), 91 (12), 77 (15), 57 (20); found (HRMS): MH^+ 427.1719, $C_{23}H_{27}N_2O_4S$ requires 427.1692.

2-[(1*S*)-Benzyl-2-benzylaminoethylcarbamoyl]benzenesulfonic Acid (10d): Procedure as in **10a**, method A. Purification by flash chromatography (dichloromethane/MeOH 5%) gave **10d** (125 mg, 74%) as a white solid from **1d** (127 mg, 0.40 mmol) and benzylamine (59 μL, 0.40 mmol). R_f = 0.3 (dichloromethane/MeOH 5%). M.p. 107−109 °C (MeOH). $[\alpha]_D$ = −44.0 (*c* = 0.35, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.80 (br. d, 2 H, SO_3H and NH), 8.06 (dd, 1 H, *J* = 6.0, 1.0; Ar), 7.65 (d, 1 H, *J* = 9.0; SO_2NH), 7.50 (dt, 1 H, *J* = 1.5, 7.5; Ar) *overlapped by* 7.46 (dt, 1 H, *J* = 1.4, 7.4; Ar), 7.32 (dd, 1 H, *J* = 7.4, 1.4; Ar), 7.26−7.12 (m, 7 H, Ar), 7.04−7.02 (m, 2 H, *J* = 6.0, 1.0; Ar), 4.67 (br. signal, 1 H, CONHC*H*), 4.05 (*apparent* s, 2 H, NHCH_2Ph), 3.07 (br. t, 1H *J* 11.8; CHC$H_{2\alpha}$NH), 2.89 (br. d, 1 H, *J* 11.8; CHC$H_{2\beta}$NH), 2.76 (dd, 1 H, *J* = 13.8, 7.9; CHC$H_{2\alpha}$Ph), 2.70 (dd, 1 H, *J* = 13.8, 7.4; CHC$H_{2\beta}$Ph) ppm. ^{13}C NMR (67.8 MHz, CD_3OD): δ = 171.9 (CO_{am}), 142.8, 138.3, 135.7, 132.2, 131.8, 131.5 (2C), 131.1, 130.6 (2C), 130.3 (2C), 130.1 (2C), 129.7, 129.1, 128.5, 128.0, 52.6 (CH_2), 52.3 (CH_2), 49.6 (CH), 39.2 (CH_2) ppm. The DEPT spectrum confirms the overlap of the CH resonance with the solvent. IR (solid state): $\tilde{\nu}$ = 2359 w, 1651s (C=O_{am}), 1627 m, 1593 w, 1546 s, 1497 w, 1454 m, 1312 w, 1250 vs, 1211 s, 1162 vs, 1138 s, 1081 m, 1018 vs, 869 w, 753 s, 744 vs, 727 m, 699 vs cm^{-1}. MS: *m*/*z* (FAB+): 425 (MH^+, 30%), 307 (25), 289 (15), 154 (100), 136 (75), 107 (25), 91 (30), 77 (25), 69 (25), 57 (35); found (HRMS): MH^+ 425.1544, $C_{23}H_{25}N_2O_4S$ requires 425.1535. $C_{23}H_{24}N_2O_4S{\cdot}1/2H_2O$ (433.52): calcd. C 63.7, H 5.8, N 6.5; found C 63.5, H 5.55, N 6.3.

2-{2-Methyl-(1*S*)-[((1*R*)-phenylethylamino)methyl]propylcarbamoyl}benzenesulfonic Acid (10e): Procedure as in **10a**, method A. Purification by flash chromatography (dichloromethane/MeOH 5%) gave **10e** (156 mg, 73%) from **1a** (148 mg, 0.55 mmol) and (1*R*)-phenylethylamine (71 μL, 0.55 mmol) as a viscous oil. R_f = 0.40 (dichloromethane/MeOH 5%). $[\alpha]_D$ = −42.0 (*c* = 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.18 (br. s, 1 H, SO_3H or NH_{amine}), 8.89 (br. s, 1 H, SO_3H or NH_{amine}), 8.17−8.14 (m, 1 H, Ar), 8.04 (d, 1 H, *J* = 9.0; CONH), 7.72−7.70 (m, 1 H, Ar), 7.75−7.55 (m, 4 H, Ar), 7.44−7.39 (m, 3 H, Ar), 4.62 (br. q, *J* 6.5, 1 H, NHC*H*Ph), 4.43 (br. s, 1 H, NHC*H*i*Pr*), 3.13 (br. t, *J* 12.4, 1 H, CHC$H_{2\alpha}$), 2.86 (br. d, *J* 12.4, 1 H, CHC$H_{2\beta}$), 1.73 (d, 3 H, *J* = 6.8; CH(Ph)*Me*] 1.66 (oct, 1 H, *J* = 6.8; C*H*Me_2), 0.82 (d, 3 H, *J* = 6.8; Me), 0.77 (d, 3 H, *J* = 6.8; Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.5 (CO_{am}), 141.3 (C), 135.6 (C), 133.9 (C), 130.9, 130.4, 129.8, 129.6, 129.5, 127.9, 127.5, 57.8, 50.4, 46.9, 31.0, 20.7, 19.1 (Me), 18.2 (Me) ppm. IR (solid state): $\tilde{\nu}$ = 2969 w, 1652 m (C=O_{am}), 1594 w, 1556 m, 1456 m, 1318 w, 1241 s, 1174 vs, 1140 s, 1080 s, 1016 vs, 782 w, 762 s, 735 s, 702 vs cm^{-1}. MS: *m*/*z* (ES+): 781 (M_2H^+, 100%), 391 (MH^+, 50); found (HRMS): MH^+ 391.1656, $C_{20}H_{27}N_2SO_4$ requires 391.1691.

2-{3-Methyl-(1*S*)-[((1*R*)-1-phenylethylamino)methyl]butylcarbamoyl}benzenesulfonic Acid (10f): Procedure as in **10a**, method A. Purification by flash chromatography (dichloromethane/MeOH 5%) gave **10f** (189 mg, 75%) as a viscous oil from **1b** (0.81 g, 2.85 mmol) and (1*R*)-phenylethylamine (367 μL, 2.85 mmol). R_f = 0.40 (dichloromethane/MeOH 5%). $[\alpha]_D$ = −40.0 (*c* = 0.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.23 (br. s, 1 H, SO_3H or NH_{amine}), 8.91 (br. s, 1 H, SO_3H or NH_{amine}), 8.14 (dd, 1 H, *J* = 7.0, 1.5; Ar), 7.89 (d, 1 H, *J* = 9.0; CONH), 7.67 (dd, 1 H, *J* = 7.0, 1.5; Ar), 7.58−7.53 (m, 4 H, Ar), 7.43−7.41 (m, 3 H, Ar), 4.66 (br. q, *J* 7, 1 H, C*H*(Ph)Me]; *overlapped by* (br. s, 1 H, CONHC*H*), 3.08 (t, 1 H, *J* = 12.0; CHC$H_{2\alpha}$NH), 2.79 (d, 1 H, *J* = 12.0; CHC$H_{2\beta}$NH), 1.75 (d, 3 H, *J* = 7.0; CH(Ph)*Me*]; 1.57−1.48 (m, 1 H, C*H*Me_2), 1.44−1.34 (m, 1 H, CHC$H_{2\alpha}$CH), 1.10 (m, 1 H, CHC$H_{2\beta}$CH), 0.87 (d, 3 H, *J* = 6.9; *Me*), 0.80 (d, 3 H, *J* = 6.9; *Me*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.3 (CO_{am}), 141.3 (C), 135.7 (C), 134.0 (C), 130.8, 130.2, 130.1, 129.6, 129.5, 127.8, 127.5, 58.2, 49.1, 44.0, 41.9, 24.8, 22.7 (CH_3), 22.0 (CH_3), 20.7 (CH_3) ppm. IR (solid state): $\tilde{\nu}$ = 2959 w, 1653 m (CO_{am}), 1595 w, 1548 m, 1457 m, 1387 w, 1305 w, 1235 s, 1174 vs, 1140 s, 1082 s, 1017 vs, 850 w, 758 vs, 743 s, 702 vs, 692 s cm^{-1}. MS: *m*/*z* (FAB+):

427 (MNa^+, 55%), 405 (MH^+, 100), 307 (25), 169 (25), 154 (95), 136 (75), 120 (20), 105 (55), 89 (20), 77 (25), 69 (20), 57 (35), 55 (30); found (HRMS): MH^+ 405.1852, $C_{21}H_{29}N_2O_4S$ requires 405.1848. $C_{21}H_{28}N_2O_4S{\cdot}H_2O$ (422.54): calcd. C 59.7, H 7.2, N 6.6; found C 60.15, H 6.8, N 6.8.

X-ray Crystallographic Studies: Crystals of **1a** and **2a**, were grown from EtOH, those of **7** and **8** from MeCN, that of **10c** from [D_4]MeOH. X-ray diffraction data were collected on SMART[15] area detector diffractometers (APEX and SMART1000), using graphite-monochromated Mo-K_α radiation (λ = 0.71073 Å). SAINT[15] software was used to integrate the data sets and apply the Lorentz and polarisation corrections. An absorption and incident beam decay correction was performed using SADABS for complexes **7** and **8**.[16] No absorption or decay correction was made for species **1a**, **2a** and **10c**. The structures were solved by direct methods using SHELXS-97.[17] The structures were refined on F^2 using full-matrix least-squares (SHELXL-97).[18] Unless otherwise stated, all fully occupied non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were placed in geometrically calculated positions except those of the MeCN molecules in **7** and the NH_3 and methyl hydrogens in compounds **2a** and **1a**, which were all located by difference Fourier synthesis. Geometrically refined hydrogen atoms were refined as part of a riding model, with the hydrogen atoms assigned isotropic displacement parameters 1.2 times the parent atom U_{eq}, except the methyl atoms where it was 1.5 times. Suitable geometric constraints were applied to all disorder models. In both **8** and **10c** a solvent region could not be satisfactorily modelled in terms of atomic sites and the electron density in this region was calculated and accounted for using the SQUEEZE procedure.[19] Neutral atom scattering factors and anomalous dispersion corrections were taken from the *International Tables for Crystallography*.[20] Crystallographic data are summarised in Table 1.

CCDC-246699 to -246703 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44-1223-336-033; E-mail: deposit@ccdc.cam.ac.uk].

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Table 1. Crystal structure data of compounds **1a**, **2a**, **7**, **8**, **10c**

	1a	**2a**	**7**	**8**	**10c**
formula	$C_{12}H_{15}NO_4S$	$C_{12}H_{17}NO_5S$	$C_{26}H_{31}N_3O_8PdS_2$	$C_{26}H_{32}Cl_4CuN_2O_8S_2$	$C_{24}H_{29}N_2O_5S$
M_w	269.31	287.33	684.06	770.00	457.55
crystal system	orthorhombic	monoclinic	monoclinic	hexagonal	orthorhombic
space group	$P2_12_12_1$	$P2_1$	$P2_1$	$P6_1$	$P2_12_12_1$
a (Å)	8.1800(9)	8.7089(12)	8.1006(5)	19.2656(14)	10.520(3)
b (Å)	10.575(1)	12.666(2)	16.6538(10)	−	12.047(4)
c (Å)	14.683(2)	12.559(2)	10.9452(7)	15.1909(16)	20.267(6)
α (°)	90	90	90	90	90
β (°)	90	107.374(2)	104.939(1)	90	90
γ (°)	90	90	90	120	90
V (Å^3)	1270.2(4)	1322.2(6)	1426.79(3)	4882.9(7)	2568(2)
Z	4	4	2	6	4
$\rho_{calcd.}$ [g cm^{-3}]	1.408	1.443	1.592	1.571	1.183
absorption coefficient [mm^{-1}]	0.261	0.26	0.85	1.18	0.16
F(000)	568	608	700	2370	972
crystal size (mm)	0.31×0.20×0.18	0.52×0.24×0.12	0.54×0.32×0.24	0.40×0.12×0.10	0.58×0.30×0.19
Data collection					
T [K]	150(2)	150(2)	150(2)	150(2)	150(2)
$\theta_{min}-\theta_{max}$ (°)	2.4−28.8	2.3 −28.8	1.9 −28.6	2.4 −28.9	2.2−26.4
scan type	ω	ω	ω	ω	ω
h, k, l ranges	−10 to 7, −10 to 14, −19 to 12	−11 to 11, −17 to 14, −7 to 16	−10 to 10, −21 to 22, −14 to 12	−25 to 7, −21 to 22, −20 to 19	−13 to 13, −15 to 14, −25 to 25
total reflections collected	8010	7361	11281	14314	19909
independent reflections	2803 (R_{int} = 0.0635)	5306 (R_{int} = 0.038)	6231 (R_{int} = 0.014)	7458 (R_{int} = 0.052)	5264 (R_{int} = 0.039)
reflections with $I > 2\sigma(I)$	2327	4500	6149	4693	4802
absorption correction	none	none	$T_{min.}$ = 0.653 $T_{max.}$ = 0.801	$T_{min.}$ = 0.716 $T_{max.}$ = 1.000	none
Refinement					
data/restraints/parameters	2803/0/164	5293/1/349	6231/1/363	7458/14/342	5227/0/272
final R indices [$I > 2\sigma(I)$]	R_1 = 0.064, wR_2 = 0.156	R_1 = 0.036, wR_2 = 0.082	R_1 = 0.018, wR_2 = 0.047	R_1 = 0.051 wR_2 = 0.091	R_1 = 0.057 wR_2 = 0.150
final R indices (all data)	R_1 = 0.0751, wR_2 = 0.01624	R_1 = 0.0443, wR_2 = 0.0852	R_1 = 0.0179, wR_2 = 0.0471	R_1 = 0.089 wR_2 = 0.100	R_1 = 0.061 wR_2 = 0.152
goodness-of-fit on F^2	1.01	0.96	1.05	1.02	1.11
absolute structure parameter	0.03(13)	−0.03(7)	0.005(12)	0.020(15)	0.03(11)
final $(\Delta/\sigma)_{max}$	0.001	0.001	0.001	0.001	0.001
largest diff. peak and hole (e·Å^{-3})	0.86 /−0.97	0.33 /−0.43	0.35 /−0.29	0.33/−0.41	0.29/−0.29

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