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Diastereoselective allylation of chiral imines and a stereocontrolled route to 4-hydroxy-*N*-tosylpipecolic acid derivatives

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Abstract—We report an asymmetric route to non-proteogenic amino acids, based on Lewis acid-mediated diastereoselective additions of allyltrimethylsilane to iminoglyoxylic acid derivatives bearing ester or amide chiral auxiliaries. Reactions of allyltrimethylsilane with *N*-tosyl- and *N*-phenyliminoglyoxylates of (*R*)-8-phenylmenthol proceeded with excellent diastereoselectivity (d.e. 98%). In contrast, the reactions of *N*-benzyliminoglyoxylates occurred with low diastereoselectivities and in poor yields. We have applied our methodology to develop a short synthesis of (2*S*,4*R*)-4-hydroxypipecolic acid derivatives. © 2002 Published by Elsevier Science Ltd.

1. Introduction

Chiral non-proteogenic amino acids and their derivatives are important building blocks in organic synthesis.[1] They also play a crucial role as structural features in bioactive natural products and pharmaceutically important compounds. Many enantio- and diastereoselective 1,2-nucleophilic additions of organometallic compounds to imines involving Grignard reagents and organozinc compounds have been exploited.[2] In such reactions, the use of highly nucleophilic organometallic reagents is dictated by the low electrophilicity of the C=N group in comparison to the C=O group. In many cases, the choice of nucleophile is very limited as a result of the possibility of enamine formation and reduction to an amine.

Several methods have been developed to overcome this problem. Activation of the C=N bond by incorporation of electron-withdrawing substituents and coordination of nitrogen with a Lewis acid has been investigated.[3] The use of organometallic nucleophiles of low basicity such as organocerium or organocuprate reagents[4] instead of Grignard and lithium reagents, use of the Barbier procedure,[5] and an allyltin nucleophile[6] have been examined. Introduction of a ligand that would chelate the organometallic nucleophile in an enantioselective fashion (external ligands like oxazolidinones[7] or ephedrines[8]) or a chiral nucleophile (allylboranes[9]) led to improvement in the selectivity and yield.

Another factor complicating additions to the imine functionality is the possibility of geometric isomers around the carbon–nitrogen double bond as each of these isomers may lead to a different stereoisomer of the product.[10]

Hetero-Diels–Alder reactions of *N*-tosyl imines of *N*-glyoxyloyl-(2*R*)-bornano-10,2-sultam with various dienes were recently investigated in our group and showed very good diastereofacial differentiation.[11] In our previous reports on the stereoselectivity of the nucleophilic addition[12] and hetero-Diels–Alder reactions of *N*-glyoxyloyl-(2*R*)-bornano-10,2-sultam[13,14] we described a stereochemical rationalization for the asymmetric induction and the advantages of (2*R*)-bornano-10,2-sultam as a chiral auxiliary. The 10-*N*,*N*-dicyclohexylsulfamoyl-(*R*)-isobornyl glyoxylate was found to be less beneficial (in terms of diastereoselectivity) in the nucleophilic addition of the allyltrimethylsilane to the carbonyl group.[15] Recently, we have also published the preliminary results from our study into the addition of allyltrimethylsilane to the *N*-tosylimine of (*R*)-8-phenylmenthyl glyoxylate.[16]

Thus, we decided to examine the asymmetric 1,2-addition of allyltrimethylsilane to glyoxylimines as a poten-

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tial method for the stereoselective synthesis of α-allyl-amino acids.

2. Results and discussion

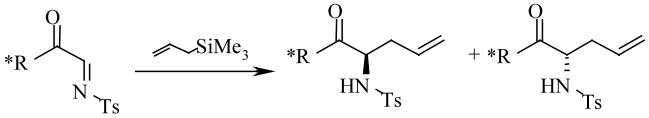
2.1. Preparation of imines

The *N*-tosylimines were obtained from the corresponding derivatives of glyoxylic acid by a method introduced recently by Holmes et al.[17] The reaction of compounds **1a**, **1b**, and **1c** with *p*-toluenesulfonyl isocyanate in refluxing toluene afforded the expected imines **2a**, **2b**, and **2c**, respectively (Scheme 1).

N-Benzyl imines **3a**, **3b** and **3c** were obtained according to the method introduced by Stella[18] using the trifluoroacetic acid-catalyzed reaction of glyoxylates and benzylamine in methylene chloride as a solvent. *N*-Phenylimines **4a**, **4b** and **4c** were obtained by reacting the corresponding glyoxylates with aniline, in the presence of 4 Å molecular sieves as a dehydrating agent.

2.2. Addition of allyltrimethylsilane to imines

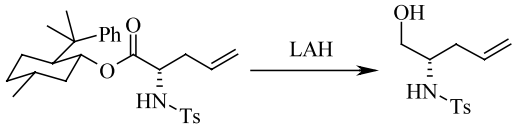
The *N*-tosyl-, *N*-benzyl-, and *N*-phenylimines, obtained according to the above procedures, were used in situ for the nucleophilic addition. We investigated several Lewis acids as imine-activating agents (Table 1, Scheme 2) for additions to *N*-tosylimines. The representative data is presented in Table 1. Stronger, chelating Lewis acids ($ZnBr_2$, $ZnCl_2$, $SnCl_4$, $TiCl_4$) generally gave better yields and selectivities than weaker, non-chelating ones (e.g. $BF_3{\cdot}Et_2O$). Among chiral auxiliaries, the best yield and total diastereoselectivity was obtained for (*R*)-8-phenylmenthyl ester **2b**. Comparable chemical yields, with substantially lower diastereoselectivities, were obtained in the addition of allyltrimethylsilane to the imine of *N*-glyoxyloyl-(2*R*)-bornano-10,2-sultam **2a**. Addition to the *N*-tosylimine of the glyoxylate of 10-*N*,*N*-dicyclohexylsulfamoyl-(*R*)-isobornyl **2c** led to an excess of the (2′*R*)-diastereoisomer with good diastereoselectivity.



2a **5a** **6a**
2b **5b** **6b**
2c **5c** **6c**

Scheme 2.

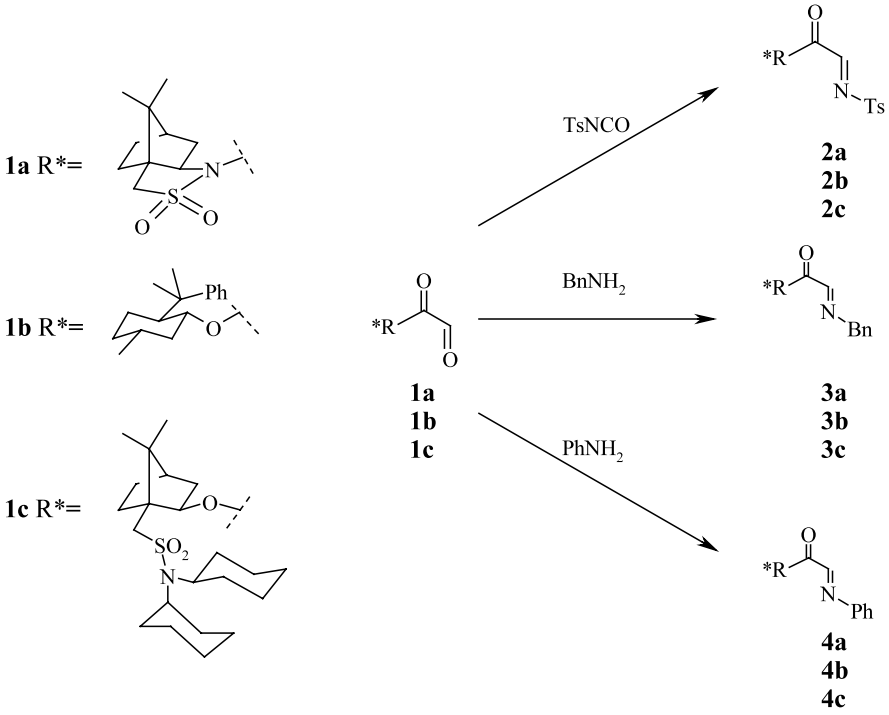
The absolute configurations—(2′*S*) of **6a** and (2′*R*) of **5c**—were determined by X-ray analysis (Figs. 1 and 2, respectively). The relative configuration of adduct **6b** was obtained by converting it into the known compound **7** (Scheme 3).



6b **7**

Scheme 3.

In contrast to *N*-tosylimines, reaction of allyltrimethylsilane with *N*-benzylimines **3a**, **3b** and **3c** gave lower yields and diastereoselectivities (Scheme 4, Table 2).



1a
1b
1c

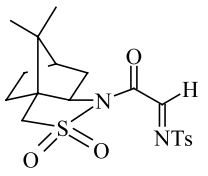
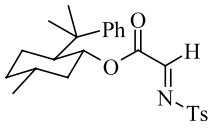
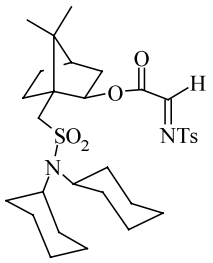
2a
2b
2c

3a
3b
3c

4a
4b
4c

Scheme 1.

Table 1. Results of the addition of allyltrimethylsilane to *N*-tosylimines

Lewis acid	*N*-Tosyl imine								
	 **2a**			 **2b**			 **2c**		
	Yield[a] (%)	D.e. (%)	Abs. conf.	Yield[a] (%)	D.e. (%)	Abs. conf.	Yield[a] (%)	D.e. (%)	Abs. conf.
$BF_3{\cdot}Et_2O$	35	60	*S*	25	8	*S*	0		
$ZnCl_2$	60	80	*S*	60	96	*S*	61	66	*R*
$ZnBr_2$	65	78	*S*	50	96	*S*	60	60	*R*
$TiCl_4$	60	52	*S*	72	96	*S*	56	52	*R*
$SnCl_4$	90	68	*S*	60	96	*S*	0		

[a] Yields calculated for two steps: formation of imine and addition of allyltrimethylsilane.

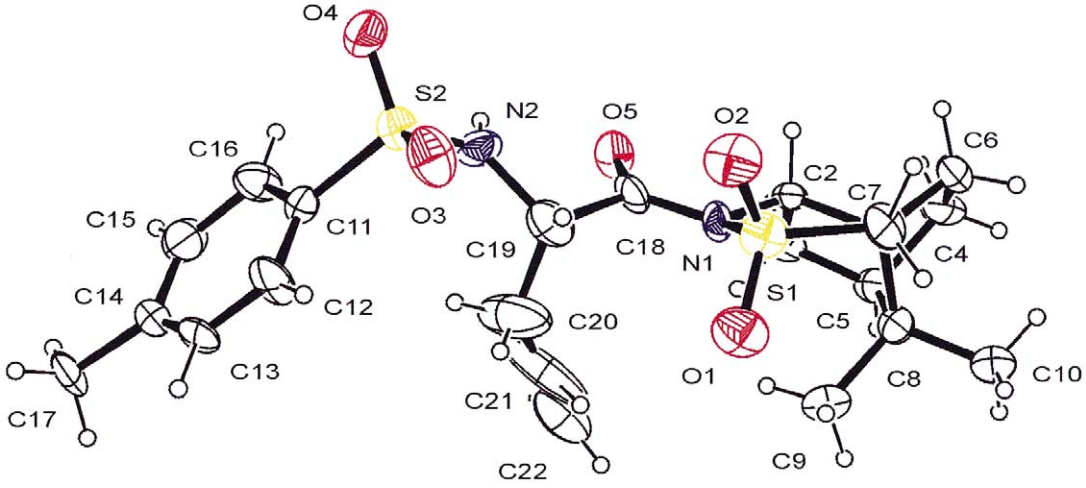
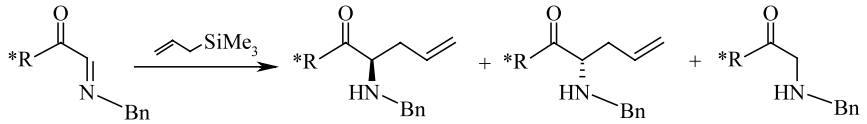


Figure 1. Crystal structure of (*S*)-*N*-tosylallylglycine (2*R*)-bornano-10,2-sultam imide **6a**.

However, compound **3b** (with an (*R*)-8-phenylmenthyl auxiliary), seemed to provide the best diastereoselectivities. No product was observed in the reaction with imine **3a** derived from Oppolzer's chiral auxiliary. In all of these reactions, the main by-product was the amine of the type **A** resulting from reduction of the C=N bond.

The *N*-phenylimines **4a**, **4b**, and **4c** were reacted with allyltrimethylsilane in the presence of $SnCl_4$ giving the allyl-adduct as the major product (Scheme 5, Table 3). We also detected traces of tetrahydroquinoline derivatives of type **B**. Formation of this compound was reported in the reactions of allyltrimethylsilane to diphenylimines in the presence of Lewis acid and 4 Å molecular sieves.[19]



3a **3b** **3c** **8a** **8b** **8c** **9a** **9b** **9c** **A**

Scheme 4.

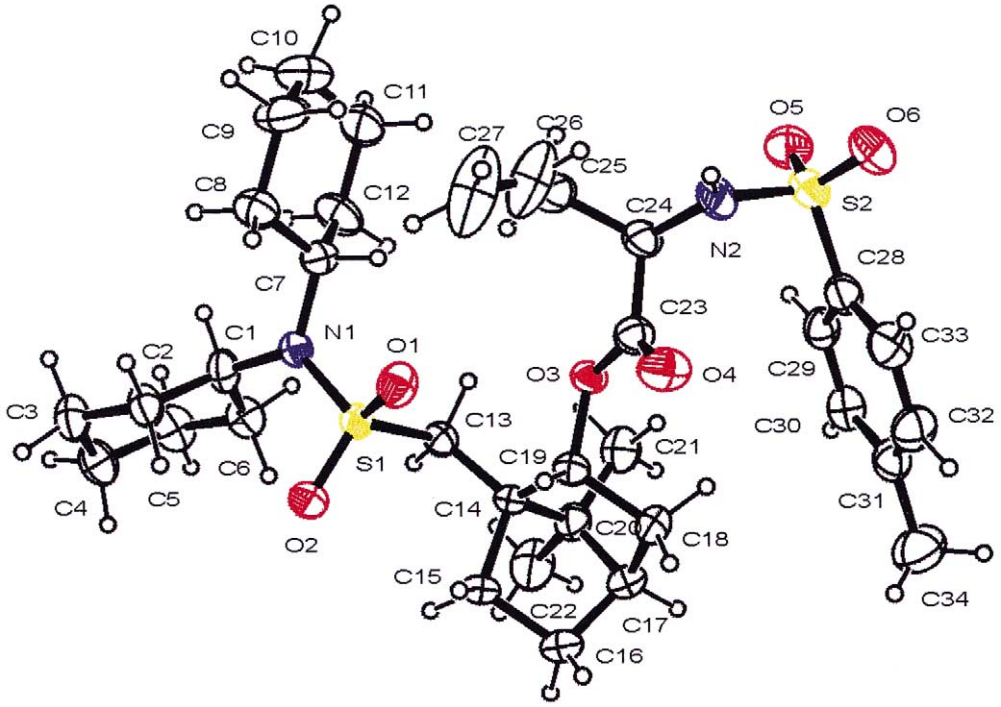


Figure 2. Crystal structure of (*R*)-*N*-tosylallylglycine 10-*N*,*N*-dicyclohexylosulfamoyl-(2*R*)-isobornyl ester **5c**.

Table 2. Results of the addition of allyltrimethylsilane to *N*-benzylimines

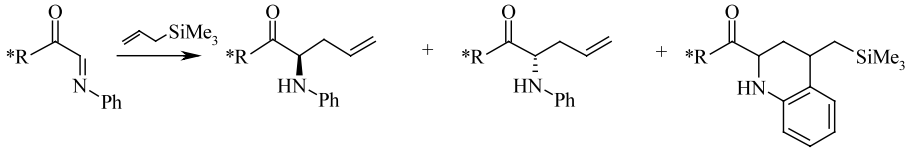
N-Benzylimine	Yield (%)	D.e. (%)
3a	0	–
3b	23	72
3b	20	15

Table 3. Results of the addition of allyltrimethylsilane to *N*-phenylimines

N-Phenylimine	Yield (%)	D.e. (%)
4a	60	62
4b	71	>95
4c	55	10

Several concepts can be considered for the rationalization of diastereoselectivities in the reactions of glyoxylimines with allyltrimethylsilane described in this work. One explanation, concerning reaction with the *N*-tosylimine of *N*-glyoxyloyl-(2*R*)-bornano-10,2-sultam **2a**, is analogous to the proposed rationale for the hetero Diels–Alder reaction that was based on two concepts (Fig. 3): (a) the sterically controlled approach of the thermodynamically more stable SO_2/CO antiperiplanar, CO/CHNTs *s-cis* planar conformer **C**, as proposed by Oppolzer et al.[20] and by Curran et al.[21] for *N*-acryloyl- and *N*-crotonoyl-(2*R*)-bornano-10,2-sultam; and (b) the high reactivity of the less stable SO_2/CO synperiplanar, CO/CHNTs *s-cis* planar conformer **D**, reinforced by the cooperative stereoelectronic effect, as recently formulated by Chapuis et al.[13,14] for *N*-glyoxyloyl-(2*R*)-bornano-10,2-sultam **1a**. The conformational equilibrium may be even more complicated in view of, as recently proposed by Pindur et al.,[22] the reactive SO_2/CO antiperiplanar, CO/CHNTs *s-trans* planar conformation **E**.

Since the sultam ring in *N*-glyoxyloyl-(2*R*)-bornano-10,2-sultam **1a** has a large impact on the conformation in the transition state (due to both electronic and steric effects), we decided to use an auxiliary that lacks the rigidity of sultam **1a** in the stereodifferentiating moiety, the 10-*N*,*N*-dicyclohexylsulfamoyl-(*R*)-isobornyl glyoxylate **1c** (Fig. 4). The electronic interactions between SO_2 and CO that determine the conformation of **2a**



4a **4b** **4c** — **10a** **10b** **10c** — **11a** **11b** **11c** — **B**

Scheme 5.

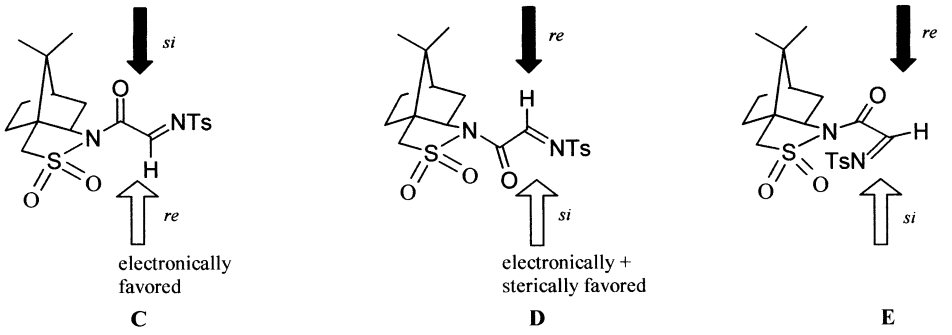


Figure 3.

have no influence on the conformation of **2c**. The reaction center, being subject to less steric restriction, has the *pro*-*R* side of the reacting site less hindered.

Another stereodifferentiating effect has its origin in the π–π stacking effect of the (*R*)-8-phenylmenthyl moiety (Fig. 5). It provides excellent asymmetric induction in the reactions of its various derivatives such as acrylates, acetamidoacrylates, glyoxylates and many others.[23] The excellent stereoselection is believed to benefit from face to face π–π interaction between the aryl moiety and the unsaturated reacting site. We postulate the same model for addition of allyltrimethylsilane to *N*-tosyl-, *N*-benzyl- and *N*-phenylimines of (*R*)-8-phenylmenthyl glyoxylate **1b** to explain the approach from the *pro*-*S* side of the C=N bond, which is the most favorable because the *pro*-*R* side is effectively shielded by the aryl moiety.

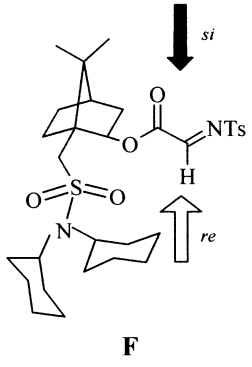


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Figure 4.

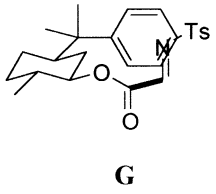

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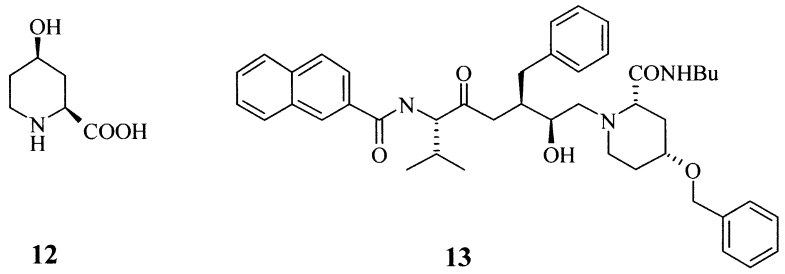
Figure 5.

2.3. Diastereoselective synthesis of (2*S*,4*R*)-4-hydroxypipecolic acid derivatives

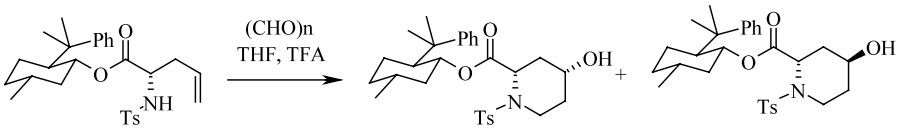
Pipecolic acid derivatives are useful intermediates for the preparation of many biologically important compounds such as immunosuppressants, enzyme inhibitors, cyclopeptide antibiotics,[24] virginiamycin S_2, as well as NMDA antagonists.[25] The naturally occurring (2*S*,4*R*)-4-hydroxypipecolic acid **12** (Fig. 6) was used as a building block in the synthesis of palinavir **13**, a potent HIV protease inhibitor.[26] In the past few years several stereoselective preparations of **12** have been reported.[27]

Having in hand the allylic adduct bearing a chiral auxiliary, we subjected it to cyclization conditions to obtain in one step the corresponding derivative of (2′*S*,4′*R*)-4-hydroxypipecolic acid **14** in 65% yield (Scheme 6). We also obtained its 4′-epimer **15** as the minor diastereoisomer (d.e. ratio 1.7:1). The reaction pathway involves formation of an acyliminium cation, followed by cyclization that produces a carbocation at C-4′. The carbocation transition state affects and eventually lowers the stereoselectivity at the newly formed stereogenic center. The long-distance steric interactions with the chiral auxiliary have no influence on the asymmetric induction.



12 13

Figure 6.



6b **14** **15**

Scheme 6.

The relative configuration of the newly formed stereogenic center was established unambiguously by a series of ^{1}H NMR experiments. The *J*-coupling constants indicate an axial position for H-4′ and, accordingly, the 4′*R*-configuration was assigned.

3. Experimental

Reagent grade solvents (CH_2Cl_2, hexanes, EtOAc, THF) were distilled prior to use. All reported NMR spectra were recorded on a Varian Gemini spectrometer at 200 MHz (^{1}H NMR) and 50 MHz (^{13}C NMR). Chemical shifts are reported as δ values relative to TMS peak defined at $\delta = 0.00$ (^{1}H NMR) or $\delta = 0.0$ (^{13}C NMR). IR spectra were obtained on a Perkin–Elmer 1640 FTIR. Mass spectra were obtained on an AMD-604 Intectra instrument using the EI or LSIMS technique. Chromatography was performed on silica (Kiesel Gel 60, 200–400 mesh). Optical rotations were recorded using a JASCO DIP-360 polarimeter with a thermally jacketed 10 cm cell. All air- or moisture-sensitive reactions were carried out in flame-dried glassware under an atmosphere of argon.

3.1. Preparation of *N*-substituted imines

3.1.1. General procedure for preparation of *N*-tosylimines 2a, 2b, and 2c. To a solution of the corresponding glyoxylic acid derivative (1.5 mmol) in toluene (10 ml) was added tosyl isocyanate (1.5 mmol, 0.23 ml) under argon and the reaction mixture was refluxed for 24 h. The obtained imines were used in situ for allylation reactions.

3.1.2. General procedure for preparation of *N*-benzylimines 3a, 3b, and 3c. To a solution of the corresponding glyoxylic acid derivative (1.5 mmol) in 10 ml of DCM, containing molecular sieves 4 Å, benzylamine was added (3 mmol, 0.33 ml) at 0°C and the reaction mixture was stirred for 0.5 h.

3.1.3. General procedure for preparation of *N*-phenylimines 4a, 4b, and 4c. To a stirred solution of glyoxylic acid derivative (1 mmol), in toluene containing 4 Å molecular sieves, was added aniline (1 mmol, 0.11 ml). The reaction was quenched with 1 M HCl. The reaction mixture was washed with $NaHCO_3$, extracted with DCM, dried over $MgSO_4$, and evaporated. The product was purified by flash chromatography using 10% EtOAc–toluene afforded 80% yield.

3.1.4. General procedure for addition of allyltrimethylsilane to *N*-tosylimines. To a solution of the *N*-tosylimine of 10-*N*,*N*-dicyclohexylosulfamoyl-(*R*)-isobornyl glyoxylate **2c** obtained from 10-*N*,*N*-dicyclohexylosulfamoyl-(2*R*)-isobornyl glyoxylate **1c** (146 mg, 0.32 mmol) in DCM or toluene, $TiCl_4$ (1 M, 5 ml, 0.32 ml, 0.32 mmol) was added at rt (the reactions with other Lewis acids were carried out according to this procedure). After 5 min, $AllSiMe_3$ (0.64 mmol, 0.1 ml) was added dropwise at rt. The reaction was stirred for 12 h and then worked up with $NaHCO_3$, and extracted with DCM. The organic extracts were combined, dried over $MgSO_4$, and evaporated under reduced pressure. The product was purified by flash chromatography using 5% EtOAc–toluene as eluent affording the separate diastereoisomers.

3.1.4.1. (*R*)-*N*-Tosylallylglycine (2*R*)-bornano-10,2-sultam imide, 5a. Mp 154–157°C (hexane–EtOAc); $[\alpha]_D^{20} = -28.2$ (*c* 1, $CHCl_3$); IR (KBr): 3438, 2960, 2921, 1692 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.74–5.53 (m, 1H), 5.39 (d, 1H), 5.14–5.01 (m, 2H), 4.70–4.60 (m, 1H), 3.68–3.62 (m, 1H), 3.44 (qAB, 2H), 2.72–2.47 (m, 1H); ^{13}C NMR (200 MHz, ppm): 170.4, 143.5, 136.4, 131.8, 129.5, 127.6, 119.4, 65.3, 54.4, 52.8, 48.8, 47.7, 44.4, 37.9, 36.3, 32.8, 26.3, 21.5, 20.5, 19.9; EIMS *m*/*e* (%) 489 $(M+Na)^+$ (100), 467 $(M+H)^+$ (5), 260 (22), 224 (50), 105 (40), 91 (12); HR EIMS calcd for $C_{22}H_{30}N_2NaS_2O_5$ (M+Na): 489.1494. Found: 489.1489. Anal. calcd for $C_{22}H_{30}N_2O_5S_2$: C, 56.7; H, 6.4; N, 6.0; S, 13.7. Found: C, 56.5; H, 6.5; N, 5.8; S, 13.5%.

3.1.4.2. (*S*)-*N*-Tosylallylglycine (2*R*)-bornano-10,2-sultam imide, 6a. Mp 120–123°C (hexane–EtOAc); $[\alpha]_D^{20} = -34.6$ (*c* 1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.76–5.55 (m, 1H), 5.46–5.38 (m, 1H), 5.19–5.11 (m, 2H), 4.44 (dt, 1H), 3.89 (t, 1H), 3.53 (qAB, 2H), 2.69–2.54 (m, 1H), 2.40 (m, 3H), 2.36–2.25 (m, 1H), 2.08–1.77 (m, 6H), 1.44–1.22 (m, 2H), 1.04 (s, 3H), 0.95 (s, 3H); ^{13}C NMR (200 MHz, $CDCl_3$): δ 170.2, 143.4, 131.1, 129.6, 127.5, 119.9, 107.0, 65.0, 55.6, 52.8, 48.8, 47.8, 44.5, 38.8, 38.1, 32.8, 26.4, 21.6, 20.7, 19.9.

3.1.4.3. (*S*)-*N*-Tosylallylglycine 8-(*R*)-phenylmenthyl ester, 6b. Oil; $[\alpha]_D^{20} = +20.6$ (*c* 1, $CHCl_3$); IR (KBr): 3282, 2955, 2923, 1726 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.74–7.70 (m, 2H), 7.33–7.11 (m, 7H), 5.6–5.4 (m, 1H), 5.1–4.94 (m, 2H), 4.72 (d, $J = 8.6$, N*H*), 4.55 (dt, $J_1 = 10.8$, $J_2 = 4$, 1H), 3.45–3.35 (m, 1H), 2.42 (s, 3H), 2.42–1.15 (m, 9H), 1.07 (s, 3H), 1.04 (s, 3H), 0.83 (d, $J = 6.4$, 3H); ^{13}C NMR (200 MHz, $CDCl_3$): δ 169.8, 151.9, 143.3, 137.2, 131.6, 128.5, 128.1, 127.2, 125.3, 125.1, 124.9, 119.2, 76.7, 54.8, 40.8, 39.1, 37.3, 34.4, 31.1, 28.9, 26.2, 23.2, 21.6, 21.5; EIMS *m*/*e* (%) 484 $(M+H)^+$ (8), 391 (14), 270 (56), 215 (26), 155 (10), 149 (25), 119 (70), 105 (100), 91 (26); HR EIMS calcd for $C_{28}H_{37}NNaO_4S$ (M+Na): 506.2336. Found: 506.2364. Anal. calcd for $C_{28}H_{37}NO_4S$: C, 69.6; H, 7.7; N, 2.9; S, 6.6. Found: C, 69.2; H, 7.7; N, 2.9; S, 6.6%.

3.1.4.4. (*R*)-*N*-Tosylallylglycine 10-*N*,*N*-dicyclohexylosulfamoyl-(2*R*)-isobornyl ester, 5c. Mp 171–172°C; $[\alpha]_D^{20} = -29.2$ (*c* 1, $CHCl_3$); IR: 3281, 2932, 2855, 1737, 1642, 1598 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.71 (d1/2AB, $J = 8.2$, 2H), 7.26 (d1/2AB, $J = 8.2$, 2H), 5.82–5.58 (m, 1H), 5.38 (d, $J = 9.0$, 1H), 5.22–5.10 (m, 2H), 4.72–4.61 (m, 1H), 3.97–3.82 (m, 1H), 3.36–3.08 (m, 3H), 2.68–2.46 (m, 3H), 2.40 (s, 3H), 1.94–0.96 (m, 27H), 0.86 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (200 MHz, $CDCl_3$): δ 169.3, 143.6, 136.8, 131.4, 129.7, 127.4, 120.2, 80.2, 57.6, 55.2, 54.0, 49.3, 49.2, 44.4, 39.4, 37.4, 33.3, 32.3, 30.9, 27.0, 26.4, 26.3, 25.1, 21.5, 20.4, 20.0; EIMS *m*/*e* (%): 658 M^+ (33), 607 (15), 380 (55), 298 (100), 224 (71), 216 (12), 180 (32); HR EIMS calcd for $C_{34}H_{52}N_2NaO_6S_2$ (M+Na): 671.3154. Found: 671.3154. Anal. calcd for $C_{34}H_{52}N_2O_6S_2$: C, 62.9; H, 8.1; N, 4.3; S, 9.9. Found: C, 62.7; H, 7.9; N, 4.2; S, 10.1%.

3.1.4.5. (*S*)-*N*-Tosylallylglycine 10-*N*,*N*-dicyclohexylosulfamoyl-(2*R*)-isobornyl ester, 6c. Mp 167–168°C; $[\alpha]_D^{20} = -14.0$ (*c* 1, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.72 (d1/2AB, $J = 8.2$, 2H), 7.23 (d1/2AB, $J = 8.2$, 2H), 5.75–5.53 (m, 1H), 5.25 (d, $J = 8.2$, 1H), 5.15–5.00 (m, 2H), 4.83–4.73 (m, 1H), 4.28–4.16 (m, 1H), 3.32–3.20 (m, 3H), 2.65 (d, $J = 13.8$, 1H), 2.40 (s, 3H), 2.25–1.11 (m, 27H), 0.97 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (200 MHz, $CDCl_3$): δ 169.6, 143.4, 137.6, 131.5, 129.8, 126.8, 199.7, 80.6, 57. 697, 55.4, 54.2, 49.6, 49.2, 44.4, 39.4, 37.2, 33.0, 32.7, 30.7, 26.9, 26.5, 26.4, 25.2, 21.6, 20.3, 20.0.

3.1.5. Reduction of (*S*)-*N*-tosylallylglycine 8-(*R*)-phenylmenthyl ester, 6b. To a stirred solution of **6b** (1 mmol, 484 mg) in THF, LAH was added (2 mmol, 76 mg). The reaction was quenched after 12 h with water and 1 M NaOH, then extracted with DCM, dried over $MgSO_4$, and evaporated. The product was purified using flash chromatography 30% EtOAc–toluene as an eluent to afford the product (204 mg) in 80% yield.

3.1.5.1. (*S*)-*N*-Tosylallylglycinol, 7. Mp 40–43°C; $[\alpha]_D^{20} = +17.0$ (*c* 1, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.78–7.74 (m, 2H), 7.34–7.30 (m, 2H), 5.62–5.41 (m, 1H), 5.12–5.04 (m, 2H), 4.74 (d, $J = 7.6$, 1H), 3.69–3.49 (m, 2H), 3.36–3.21 (m, 1H), 2.44 (s, 3H), 2.18 (t, $J = 6.2$, 2H); ^{13}C NMR (200 MHz, $CDCl_3$): δ 143.8, 137.5, 132.4, 129.8, 127.1, 119.7, 53.3, 47.0, 36.5, 21.6; EIMS *m*/*e* (%) 256 $(M+H)^+$ (100), 214 (38), 155 (32), 91 (26); HR EIMS calcd for $C_{12}H_{18}NO_3S$ (M): 256.1007. Found: 256.0997. Anal. calcd for $C_{12}H_{18}NO_3S$: C, 56.5; H, 6.7; N, 5.5; S, 12.6. Found: C, 56.5; H, 6.9; N, 5.3; S, 12.5%.

3.1.6. General procedure for addition of allyltrimethylsilane to *N*-benzylimines. The reaction mixture was cooled to −78°C, and the following reagents were added under an argon atmosphere: trifluoroacetic acid (3 mmol, 0.23 ml), $BF_3{\cdot}Et_2O$ (3 mmol, 0.38 ml) and $AllSiMe_3$ (6 mmol, 1 ml). The reaction mixture was stirred for 12 h at 0°C and quenched with $NaHCO_3$, extracted with DCM, dried over $MgSO_4$, and evaporated. The product was purified by flash chromatography using 5% EtOAc–toluene as eluent, affording the corresponding products.

3.1.6.1. (*RS*)-*N*-Benzylallylglycine 8-(*R*)-phenylmenthyl esters, 8b and 9b. Mixture of diastereoisomers 82:18; IR: 3343, 3061, 3029, 2954, 2924, 1725 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.34–7.01 (m, 5H), 5.73–5.53 (m, 1H), 5.12–4.88 (m, 2H), 4.83 (dt, $J_1 = 4.2$, $J_2 = 10.8$, 1H), 3.68 (qAB, 2H), 2.74–2.68 (m, 1H), 2.24–1.89 (m, 5H), 1.72–1.62 (m, 3H), 1.28 (s, 3H), 1.21 (s, 3H), 1.15–1.00 (m, 2H), 0.87 (d, $J = 6.4$, 3H); ^{13}C NMR (200 MHz, $CDCl_3$): δ 173.7, 151.7, 140.0, 133.8, 128.4, 128.2, 127.9, 127.0, 125.3, 125.1, 117.7, 75.3, 59.4, 51.9, 50.2, 41.6, 39.6, 37.3, 34.6, 31.3, 27.9, 26.6, 25.2, 21.8; EIMS *m*/*e* (%) 419 $(M)^+$ (35), 378 (66), 164 (36), 160 (100), 119 (24), 105 (32), 91 (73); HR EIMS calcd for $C_{28}H_{37}NO_2$ (M): 419.2824. Found: 419.2832. Anal. calcd for $C_{28}H_{37}NO_2$: C, 56.5; H, 6.7; N, 5.5; S, 12.6. Found: C, 56.5; H, 6.9; N, 5.3; S, 12.5%.

3.1.6.2. (*RS*)-*N*-Benzylallylglycine 10-*N*,*N*-dicyclohexylosulfamoyl-(2*R*)-isobornyl esters, 8c and 9c. Mixture of diastereoisomers; ^1H NMR (200 MHz, $CDCl_3$): δ 7.45–7.20 (m, 5H), 5.95–5.72 (m, 1H), 5.23–5.10 (m, 2H), 5.09–5.00 (m, 1H), 3.65–3.98 (m, 2H), 3.65–3.35 (m, 3H), 2.75–2.60 (m, 1H), 2.59–2.48 (m, 1H), 2.22–1.45 (m, 21H), 1.43–1.05 (m, 9H), 1.02–0.97 (m, 2H), 1.02 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (200 MHz, $CDCl_3$): δ 171.6, 141.0, 132.0, 129.6, 128.8, 118.5, 118.2, 113.6, 113.2, 79.5, 61.3, 55.6, 55.4, 53.7, 49.4, 49.2, 49.1, 44.6, 42.9, 39.5, 36.4, 36.3, 33.2, 32.9, 32.6, 32.4, 30.7, 30.4, 26.9, 26.3, 25.1, 20.3, 20.0, 19.9; EIMS *m*/*e* (%) 584 $(M)^+$ (10), 543 (28), 380 (30), 160 (100), 135 (48), 91 (62); HR EIMS calcd for $C_{34}H_{52}N_2O_4S$ (M): 584.3648. Found: 584.3631. Anal. calcd for $C_{34}H_{52}N_2O_4S$: C, 56.5; H, 6.7; N, 5.5; S, 12.6. Found: C, 56.5; H, 6.9; N, 5.3; S, 12.5.

3.1.7. General procedure for addition of allyltrimethylsilane to *N*-phenylimines. To a stirred solution of imine (1 mmol) in toluene, $SnCl_4$ was added (1 M, 1 ml, 1 mmol), followed by $AlSiMe_3$ (2 mmol, 0.32 ml). The reaction was stirred for 3 h, then quenched with $NaHCO_3$, extracted with DCM, dried over $MgSO_4$, and evaporated. The product was purified by flash chromatography using 10% EtOAc–hexane.

3.1.7.1. (*RS*)-*N*-Phenylallylglycine (2*R*)-bornano-10,2-sultam imides, 10a and 11a. Mixture of diastereoisomers 81:19; IR: 2416, 3391, 2986, 2943, 1695, 1605, 1516, 1324 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.18–7.08 (m, 2H), 6.77–6.69 (m, 3H), 5.93–5.83 (m, 0.19H), 5.82–5.72 (m, 0.81H), 5.21–5.14 (m, 2H), 4.84–4.80 (m, 0.81H), 4.79–4.75 (m, 0.19H), 3.93–3.86 (m, 1H), 3.58–3.45 (m, 2H), 2.80–2.72 (m, 1H), 2.64–2.56 (m, 1H), 2.08–1.97 (m, 2H), 1.97–1.81 (m, 4H), 1.44–1.36 (m, 1H), 1.35–1.28 (m, 1H), 1.16 (s, 3×0.81H), 1.09 (s, 3×0.19H), 0.97 (s, 3×0.81H), 0.95 (s, 3×0.19H); ^{13}C NMR (500 MHz, $CDCl_3$): δ 173.4, 172.8, 146.4, 146.3, 133.3, 132.4, 129.3, 129.2, 119.3, 118.9, 118.7, 118.5, 114.4, 114.0, 65.5, 65.1, 56.1, 55.6, 53.5, 53.1, 53.0, 48.8, 48.7, 47.8, 47.8, 44.5, 44.4, 38.3, 38.3, 37.5, 36.3, 32.9, 32.7, 26.4, 26.3, 20.7, 20.5, 19.9, 19.9; EIMS *m*/*e* (%) 488 $(M)^+$ (45), 347 (30), 216 (10), 146 (100), 104 (30), 77 (20); HR EIMS calcd for $C_{21}H_{28}N_2O_3S$ (M): 388.1821.

Found: 388.1825. Anal. calcd for $C_{21}H_{28}N_2O_3S$: C, 65.0; H, 7.2; N, 7.2; S, 8.3. Found: C, 64.8; H, 7.3; N, 7.4; S, 8.1%.

3.1.7.2. (*S*)-*N*-Phenylallylglycine 8-(*R*)-phenylmenthyl ester, 11b. Oil; $[\alpha]_D^{20}=+24.3$ (c 1, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.36–7.15 (m, 5H), 6.80–6.71 (m, 1H), 6.56–6.51 (m, 2H), 5.74–5.54 (m, 1H), 5.10–5.00 (m, 2H), 4.85 (dt, $J_1=4.4$, $J_2=10.8$, 1H), 4.06 (d, $J=7.8$, 1H), 3.42–3.33 (m, 1H), 2.45–2.32 (m, 1H), 2.23–2.10 (m, 2H), 1.91–1.41 (m, 6H), 1.34 (s, 3H), 1.23 (s, 3H), 1.16–1.00 (m, 1H), 0.91 (d, $J=6.2$, 3H); ^{13}C NMR (200 MHz, $CDCl_3$): δ 172.3, 152.2, 146.7, 133.1, 129.3, 128.3, 125.5, 125.3, 118.6, 118.0, 113.7, 75.7, 55.3, 50.3, 41.6, 39.7, 36.4, 34.7, 31.4, 29.3, 26.5, 23.8, 22.0; EIMS m/e (%) 405 $(M)^+$ (14), 364 (41), 215 (31), 146 (99), 119 (52), 105 (100), 91 (20); HR EIMS calcd for $C_{27}H_{35}NO_2$ (M): 405.2668. Found: 405.2675.

3.1.7.3. (*RS*)-*N*-Phenylallylglycine 10-*N*,*N*-dicyclohexylosulfamoyl-(2*R*)-isobornyl esters, 10c and 11c. Mixture of diastereoisomers 55:45; IR: 3393, 3054, 2935, 2856, 1738 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.16–7.00 (m, 2H), 6.73–6.70 (m, 1H), 6.61–6.59 (m, 2H), 5.95–5.70 (m, 1H), 5.21–5.12 (m, 2H), 4.99 (dd, $J_1=1.2$, $J_2=3.2$, 0.55H), 4.93 (dd, $J_1=1.2$, $J_2=3.2$, 0.45H), 4.25 (bs, 1H), 4.11 (bs, 1H), 3.30–3.21 (m, 3H), 2.80–2.50 (m, 3H), 2.04–1.90 (m, 2H), 1.84–1.45 (m, 21H), 1.43–1.05 (m, 9H), 1.02–0.97 (m, 2H), 0.89 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (200 MHz, $CDCl_3$): δ 171.6, 146.3, 132.8, 129.2, 119.2, 118.7, 118.2, 117.0, 113.6, 113.2, 79.6, 57.5, 55.6, 55.5, 53.7, 49.4, 49.2, 49.1, 44.3, 39.9, 39.5, 36.4, 36.3, 33.2, 32.9, 32.6, 32.4, 30.7, 30.4, 26.9, 26.3, 25.1, 20.3, 20.0, 19.8; EIMS m/e (%) 402 $(M+Na)^+$ (5), 380 $(M+H)^+$ (30), 246 (15), 228 (25), 146 (90), 135 (100), 83 (50); HR EIMS calcd for $C_{33}H_{50}N_2NaO_4S$ (M): 593.3389. Found: 593.3360.

3.1.8. Preparation of *N*-tosyl-(2*S*,4*R*)-4-hydroxypipecolic acid (*R*)-8-phenylmenthyl ester, 14. Compound **6b** was dissolved in THF (0.5 ml) and aqueous $(CHO)_n$ (2 ml) was added, followed by TFA (0.1 ml). The mixture was stirred for 48 h and quenched by the addition of $NaHCO_3$. The product was then extracted with DCM, dried over $MgSO_4$, and evaporated to afford pure **14** as an oil; $[\alpha]_D^{20}=-12.8$ (c 1, $CHCl_3$); IR: 3531. 2956, 2926, 1740, 1347, 1159 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 (d, $J=8$, 2H), 7.37–7.32 (m, 2H), 7.32–7.25 (m, 5H), 7.19–7.14 (m, 1H), 4.65 (td, $J_1=4.2$, $J_2=10.8$, 1H), 4.00–3.95 (m, 2H), 3.60–3.54 (m, 1H), 3.45 (td, $J_1=2.9$, $J_2=13.1$, 1H), 2.42 (s, 3H), 2.06 (td, $J_1=2.1$, $J_2=12.2$, 1H), 1.93–1.88 (m, 1H), 1.83–1.76 (m, 1H), 1.70–1.53 (m, 7H), 1.47–1.36 (m, 1H), 1.23 (s, 3H), 1.17 (s, 3H), 0.91–0.83 (m, 2H), 0.82 (d, $J=6.6$, 3H); ^{13}C NMR (200 MHz, $CDCl_3$): δ 169.7, 152.2, 143.0, 137.6, 129.3, 128.2, 127.4, 125.0, 75.7, 63.5, 51.8, 50.4, 41.0, 39.3, 36.7, 34.6, 34.1, 31.5, 31.2, 29.2, 26.3, 23.2, 21.7, 21.6; EIMS m/e (%) 536 $(M+Na)^+$ (40), 254 (28), 176 (100), 105 (60), 91 (39); HR EIMS calcd for $C_{29}H_{39}NNaO_5S$ (M+Na): 536.2447. Found: 536.2434.

3.1.8.1. *N*-Tosyl-(2*S*,4*S*)-4-hydroxypipecolic acid (*R*)-8-phenylmenthyl ester, 15. Oil; $[\alpha]_D^{20}=-9.3$ (c 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72–7.69 (m, 2H), 7.37–7.33 (m, 2H), 7.30–7.25 (m, 4H), 7.21–7.16 (m, 1H), 4.65 (td, $J_1=4.3$, $J_2=10.8$, 1H), 4.16–4.12 (m, 1H), 3.82–3.76 (dquint., 1H), 3.33 (tt, $J_1=4.2$, $J_2=11.4$, 1H), 3.09 (td, $J_1=2.8$, $J_2=13.3$, 1H), 2.45 (s, 3H), 2.09–2.01 (m, 1H), 1.84–1.71 (m, 4H), 1.70–1.63 (m, 1H), 1.61–1.25 (m, 3H), 1.24 (s, 3H), 1.18 (s, 3H), 1.15–1.05 (m, 1H), 0.9–0.86 (m, 2H), 0.84 (d, $J=6.6$, 3H); ^{13}C NMR (200 MHz, $CDCl_3$): δ 168.8, 151.9, 143.2, 137.4, 129.4, 128.2, 127.3, 125.2, 125.1, 75.9, 65.9, 55.1, 50.3, 41.4, 41.0, 39.3, 36.2, 34.5, 34.2, 31.2, 29.1, 26.3, 23.0, 21.7, 21.6.

3.2. X-Ray analyses of 5c and 6a

X-Ray single-crystal diffraction experiments were carried out with an Enraf–Nonius CAD44 diffractometer (CAD4-EXPRESS program[28]) using Cu Kα radiation (1.54178 Å). The program used to solve and refine was SHELX-97.[29]

Compound **6a**: $C_{22}H_{30}N_2O_5S_2$, $M=466.60$, orthorhombic, $a=15.035(3)$, $b=21.214(4)$, $c=7.2830(10)$, space group $P2_12_12_1$, $Z=4$, $D_{calcd}=1.334$ mg/m^{-3}, μ(Cu Kα)$=2.377$ mm^{-1}, 1859 reflections measured, 1659 unique reflections ($R_{int}=0.0555$), which were used in all calculations. Data/restraints/parameters: 1652/0/318. The final $R_1=0.0916$ (all data), $s=-0.02$. Residual electron density: 0.218 and −0.226 e Å^{-3}.

Compound **5c**: $C_{34}H_{51}N_2O_6S_2$, $M=647.89$, orthorhombic, $a=14.444$, $b=15.223$, $c=16.003$, space group $P2_12_12_1$, $Z=4$, $D_{calcd}=1.223$ mg/m^{-3}, μ(Cu Kα)$=1.728$ mm^{-1}, 2653 reflections measured, 2653 unique reflections ($R_{int}=0.0000$), which were used in all calculations. Data/restraints/parameters: 2653/0/398. The final $R_1=0.0525$ (all data), $s=-0.05$. Residual electron density: 0.178 and −0.209 e Å^{-3}.

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre under the deposition numbers CCDC 192272 and 192273 for **5c** and **6a**, respectively.

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