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Taming Silylium Ions for Synthesis: N-Heterocycle Synthesis via Stereoselective C–C Bond Formation

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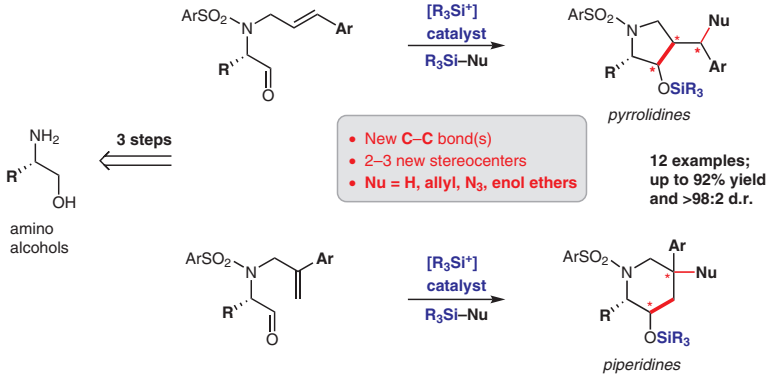

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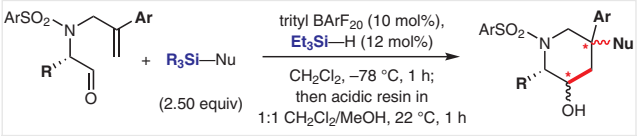
Abstract Silylium ions (formally $[R_3Si]^+$) have long been the subject of investigations and significant debate in both theoretical and experimental chemistry, but few catalytic, synthetic applications have been reported due to the exceptionally high reactivity and Lewis acidity of these elusive species. Results to be discussed include the application of easily accessible silylium ion catalysts to the stereoselective synthesis of various N-heterocyclic pyrrolidine and piperidine scaffolds. The tested substrates are derived from the chiral pool and can be obtained in three high-yielding steps from amino alcohols; subsequent stereoselective silylium ion catalyzed Prins cyclization and trapping with R_3Si–Nu nucleophiles (e.g., Nu = H, allyl, azide, and enol ethers) results in novel nitrogen-containing polycyclic scaffolds with potential medicinal chemistry applications.

Key words silylium ion, silylium catalysis, Lewis acid, Prins cyclization, Hosomi–Sakurai allylation, Si–X reagent, N-heterocycle, polycyclic scaffold

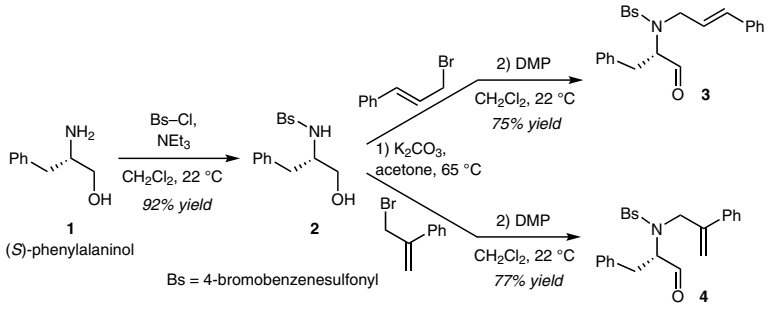
The development of catalytic, synthetic applications of silylium ions has been frustrated by the technicality that, except for in the most extreme cases,[1] they do not exist.[2] Despite their apparent structural similarity to carbenium ions and their reduced Pauling electronegativity (1.8 vs. 2.5), silylium ions are highly Lewis acidic.[3] Their increased size and longer bond lengths reduce the efficiency of stabilizing π-conjugative and hyperconjugative effects, endowing them with a high affinity for both σ- and π-Lewis bases, including solvent molecules and counteranions. Therefore, as silylium ionicity falls on a continuum, the most 'free' examples so far reported are paired with either $[B(C_6F_5)_4]^-$ (i.e., $BArF_{20}$) or $[HCB_{11}R_5X_6]^-$ (halogenated carboranes) as weakly coordinating anions (WCAs) in aromatic or halocarbon solvents.[4] In particular, the reactive $[R_3Si]^+$ equivalent is readily accessible as the solvent-stabilized Lewis pair $[R_3Si(solvent)][B(C_6F_5)_4]$ via simple Bartlett–Condon–Schneider hydride abstraction from R_3Si–H by the commercially available salt $[Ph_3C][B(C_6F_5)_4]$ (abbreviated herein as trityl $BArF_{20}$).[5]

To date, catalytic applications of silylium ions in synthesis include alkene hydrosilylation,[6] carbonyl reduction,[7] imine reduction,[8] C–F bond activation (hydrodefluorination),[9] and C–C bond formation (namely Diels–Alder reactions).[10] Other synthetic examples of note, albeit not technically catalytic or self-regenerative in silylium, include applications in C–C[11] and Si–C[12] bond formation ((sila)-Friedel–Crafts reactions). Few examples exist in which silylium ions are employed to catalyze the construction of substantial molecular complexity; herein we report the application of easily accessible silylium ion catalysts to the stereoselective synthesis of various N-heterocyclic pyrrolidine and piperidine scaffolds from acyclic substrates.

Representative conditions for the silylium ion catalyzed Prins cyclization are given below in Scheme 1; attempts to further optimize the reaction with respect to trialkylhydrosilane, solvent, concentration, and catalyst loading were unfruitful. Using 10 mol% of the in situ generated silylium ion equivalent $[Et_3Si][B(C_6F_5)_4]$ in CH_2Cl_2 at –78 °C, an appropriately substituted aldehyde rapidly cyclizes and the resulting carbocation is trapped by a silyl-protected nucleophile (R_3Si–Nu) to form a substituted piperidine derivative, following subsequent acid-catalyzed removal of the silyl residue.



Scheme 1 Representative reaction conditions



Scheme 2 Representative substrate syntheses

Aldehyde substrates can be obtained in three high-yielding linear steps starting from the corresponding amino alcohols. Representative syntheses of (*S*)-phenylalaninol derivatives **3** and **4** are illustrated in Scheme 2. First, (*S*)-phenylalaninol (**1**) was sulfonylated with 4-bromobenzenesulfonyl chloride (Bs, brosyl) in the presence of triethylamine to afford the Bs-amino alcohol **2** in 92% yield.[13] Bs-amino alcohol **2** was then alkylated with either cinnamyl bromide or 2-phenylallyl bromide in the presence of potassium carbonate to yield the corresponding N-alkylated Bs-amino alcohols (not shown; see Supporting Information). These were then oxidized with Dess–Martin periodinane (DMP) to yield, respectively, the cinnamyl-amino aldehyde **3** in 75% yield (2 steps) and the 2-phenylallyl-amino aldehyde **4** in 77% yield (2 steps).

The trapping nucleophile (R_3Si–Nu) scope of the silylium-catalyzed Prins cyclization was investigated; the best examples are listed in Table 1.[14] Reaction of cinnamyl-amino aldehyde **3** with Et_3Si–H resulted in the formation of pyrrolidine **5** in 77% yield as a mixture of three diastereomers in 76:13:11 d.r. (Table 1, entry 1). The reaction of 2-phenylallyl-amino aldehyde **4** with Et_3Si–H resulted in piperidine **6** in 92% yield and 60:21:19 d.r. (Table 1, entry 2).

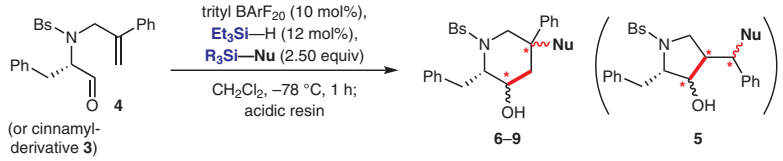
Reaction of **4** with allyltrimethylsilane led to an 84% yield of piperidine **7**, which contains an all-carbon quaternary center (66:34 d.r., Table 1, entry 3); from a mechanistic perspective, this transformation could be considered a vinylogous analogue of the named Hosomi–Sakurai allylation.[15] When trimethylsilyl azide (Me_3Si–N_3) was employed as the trapping nucleophile, alkyl azide **8** was obtained in 78% yield and 79:21 d.r. (Table 1, entry 4). When chlorotrimethylsilane (Me_3Si–Cl) was employed as the trapping nucleophile, no chloride-trapped product was observed (<5%; **9**, Table 1, entry 5); Me_3Si–Cl is apparently insufficiently nucleophilic under these conditions, even upon warming to room temperature.[16] Fortuitously, the $TiCl_4$-promoted classic Prins cyclization (see Supporting Information for details) is complementary in that it produces the chloride-trapped piperidine **9** in 99% isolated yield and 85:9:6 d.r. favoring the vicinal *cis* diastereomer ($^3J_{CH–CH}$ = 5.9 Hz).

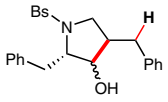
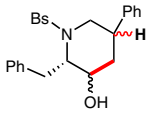
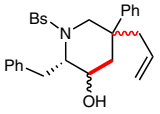
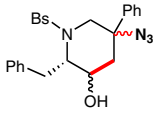
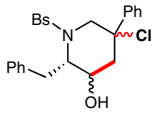
With silyl enol ether trapping nucleophiles, various novel hetero(poly)cyclic piperidines **13–19** are accessible in fair to good yields and as single diastereomers (Table 2). These novel bridged tricyclic piperidine scaffolds contain two stereocenters, one of which is an all-carbon quaternary center. The initial intramolecular Prins cyclization and intermolecular carbocation trapping create the two new C–C bonds (red) in intermediate **I**; subsequent treatment of **I** with Brønsted acid (e.g., Dowex resin 50W-X8) catalyzes annulation (blue bond) and elimination to diastereomerically pure (>98:2 d.r.) tricyclic product. It is noteworthy that the annulation selects for a single diastereomer of trapped product; the yields likely reflect this.[17]

Entry 1 (Table 2) documents the effects of changing the ring size of the silyl enol ether; cyclopentanone-derived **13** is obtained in only trace amounts (^{13}C NMR and HRMS; see Supporting Information), presumably due to ring strain, while cyclohexanone and cycloheptanone derivatives **14** and **15** are obtained in 64% and 22% yields, respectively. Alaninol derivative **16** was obtained in 38% yield (Table 2, entry 2) and the more hindered valinol derivative was not obtainable under any conditions (not shown; see **S17** in the Supporting Information). The presence of a conjugated aryl group on the silyl enol ether is also not well tolerated; see α-tetralone-derivative **17** (11% yield, Table 2, entry 3).[18] Aryl iodide **11**, showcasing aryl substitution on the 2-phenylpropene fragment, undergoes cyclization and annulation to **18** in 24% yield (Table 2, entry 4); such products could potentially be employed in cross-coupling reactions for further synthetic elaboration. Methyl-substituted **19**, derived from the corresponding 2-methylpropenyl-substituted starting material **12**, was obtained in 22% yield (Table 2, entry 5).

In light of the knowledge that deprotection of simple aryl sulfonamides (e.g., tosyl (Ts), brosyl (Bs)) often requires aggressive reagents,[19] we endeavored to demonstrate removal under mild conditions. The 2-naphthalene sulfonamide protected **20** was synthesized for this purpose (55%, see Supporting Information), and employing a modification of a previously reported reductive protocol[20] provided free amine **21** (91% yield, Scheme 3, a). It is also notable that the

Table 1 Scope of Trapping Nucleophiles ($R_3Si–Nu$)[a,b]



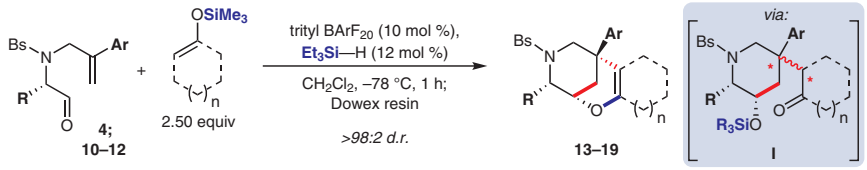
Entry	R_3Si—Nu	Product	Yield (%, NMR)[c]	d.r.[d]
1	Et_3Si—H	 **5**	77	76:13:11
2[e]	Et_3Si—H	 **6**	92	60:21:19
3[f–h]	Me_3Si 	 **7**	84	66:34
4[h,i]	Me_3Si—N_3	 **8**	78	79:21
5[j]	Me_3Si—Cl	 **9**	(<5)	n.d.[b]

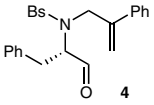
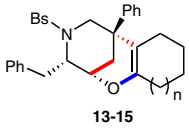
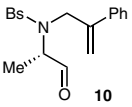
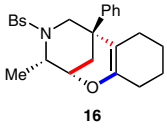
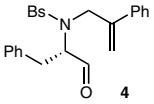
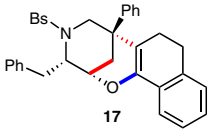
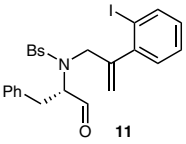
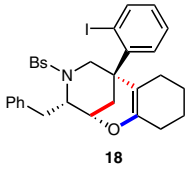
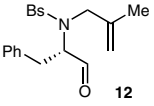
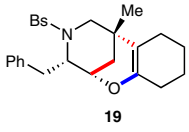
[a] Reactions were run in duplicate on a 0.05–0.1 mmol scale.
[b] Bs = 4-bromo-benzenesulfonyl; n.d. = not determined.
[c] Dimethylformamide (DMF) used as ^{1}H NMR internal standard.
[d] d.r. after purification.
[e] 1.20 equiv Et_3Si–H provided **6** in 69% NMR yield and 51:29:20 d.r.
[f] The reaction was warmed from –78 °C to –30 °C overnight.
[g] 1.10 equiv Me_3Si–allyl provided **7** in 57% NMR yield and 58:42 d.r.
[h] The relative configurations of **7** and **8** were assigned in analogy to the X-ray crystal structure of **20** (vide infra).
[i] 1.10 equiv R_3Si–N_3; 2.50 equiv provided **8** in 85% yield and 62:38 d.r.
[j] The reaction was slowly warmed from –78 to 22 °C over 8 h.

more potent Na-naphthalenide reductant was able to effect the Bs deprotection of **14** (93% yield, see Supporting Information). X-ray analysis of **20** (Scheme 3, b) confirmed the relative stereochemistry of the C–O bond and amino R group to be *cis* (axial-equatorial), respectively, consistent with $^3J_{CH–CH}$ = 3 Hz.[21]

Based on the similarity in reactivity and observed vicinal *cis*-diastereoselectivity in the products resulting from both our putative silylium ion manifold and classical $TiCl_4$-promoted Prins cyclization conditions (vide supra), we suggest the mechanism in Scheme 4 (a): The strongly Lewis acidic silylium ion catalyst $[R_3Si][B(C_6F_5)_4]$ activates the aldehyde to nucleophilic attack by the appended alkene via chairlike transition states **TS** and **TS′**;[22] experimentation has shown **TS′** to be favored to arrive at the *cis*-diastereomer **II′**. The ensuing trap of **II** and **II′** by R_3Si–Nu regenerates the $[R_3Si][B(C_6F_5)_4]$ catalyst.[23] The multiple observed diastereomers can be explained by invoking high facial discrimination in **II** via a 1,3-diaxial interaction, whereas **II′** contains almost no inherent facial bias.

Table 2 Silyl Enol Ethers as Trapping Nucleophiles[a,b]

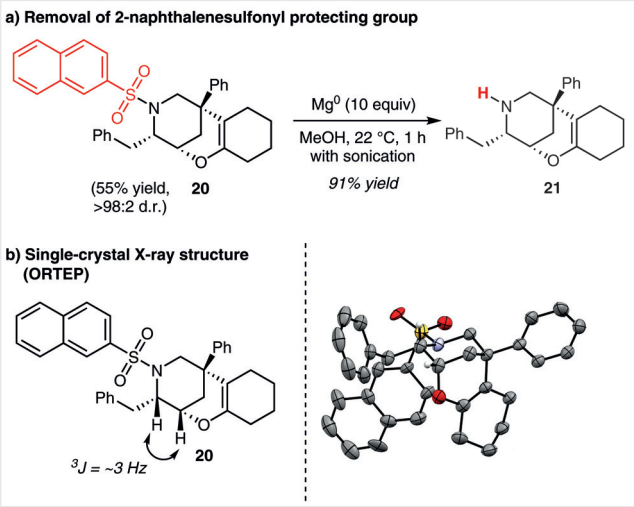


Entry	Substrate	Product	Yield (%, NMR)[c]
1	 **4**	 **13-15**	n = 0: **13**; (trace) n = 1: **14**; 64[d] n = 2: **15**; 22
2	 **10**	 **16**	38
3	 **4**	 **17**	11 (17)
4[e]	 **11**	 **18**	24
5[e]	 **12**	 **19**	22

[a] Reactions were run in duplicate on a 0.05–0.1 mmol scale.
[b] Bs = 4-bromo-benzenesulfonyl.
[c] Dimethylformamide (DMF) used as ^{1}H NMR internal standard.
[d] Compound **14** was obtained in 52% yield using 1.10 equiv of silyl enol ether.
[e] The reaction was warmed from –78 to –30 °C overnight, which increased yield and reproducibility.

Corroboration of our proposed mechanism was obtained by running the Prins cyclization in the absence of suitable trapping nucleophiles; upon warming to room temperature, elimination (an effective carbonyl-ene reaction) occurs to yield *cis*- and *trans*-tetrahydropyridine diastereomers **22** and **23**, respectively (58% yield, 83:17 d.r., Scheme 4, b).[24] Intriguingly, application of the neutral Lewis acid $B(C_6F_5)_3$ at room temperature provides *trans*-**23** in 99% yield.[25] We attribute this reversal of diastereoselectivity to the larger steric environment (and lower reactivity) of $B(C_6F_5)_3$ only allowing for activation of the aldehyde in an exclusively *trans*-diaxial conformation (**TS**).

In summary, we have developed a straightforward synthetic protocol that utilizes readily accessible, in situ generated silylium ions to stereoselectively catalyze the conversion of acyclic amino alcohol derived substrates into stereodefined N-heterocyclic pyrrolidine and piperidine derivatives.[26] This represents an early and nascent example of how silylium ions can be harnessed in complexity-generating organic transformations. We hope that their high reactivity can be further modulated to better control and increase their selectivity. Investigations into the applications of silylium catalysis to organic synthesis are ongoing in our laboratory.



Scheme 3 Deprotection (a) and X-ray structure (b) of piperidine **20**

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1590967.

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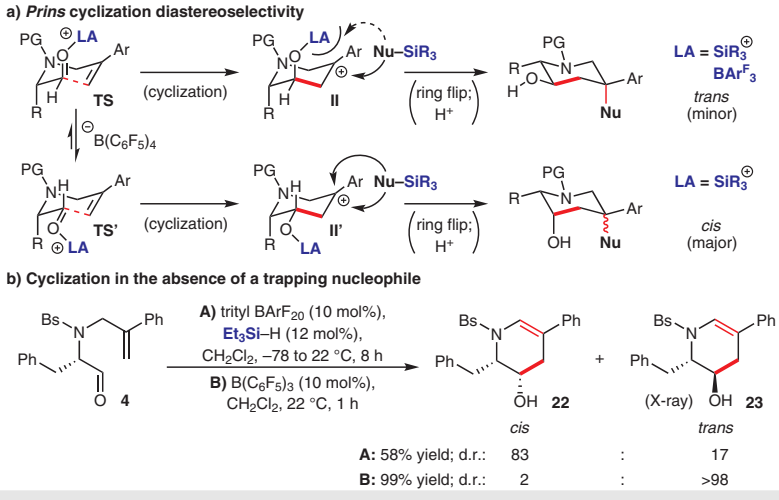

Scheme 4 Proposed mechanism of the silylium-catalyzed Prins cyclization

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(13) The choice of arylsulfonyl protecting group was based on yield and general ease of substrate synthesis. Other N-protecting groups (e.g., Boc, Ac, Bz, TFA, and *p*-Ns) were found to be difficult to install in satisfactory yields and so were not investigated for compatibility in the Prins cyclization.

(14) Other R_3Si–Nu sources, including TMS–I, TMS–CN, and TMS–OAc, provided complex mixtures of products by ^1H NMR and ^{13}C NMR analyses.

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(16) The substrate is consumed; in the absence of a suitable trapping nucleophile, catalytic $[Et_3Si][B(C_6F_5)_4]$ leads to a 54% NMR yield of eliminated products **22** and **23** in 78:22 *cis*/*trans* d.r.

(17) Analysis of crude pre- and post-annulation ^{13}C NMR suggests the reason for exclusively high d.r. but low yield is most likely due to double diastereo-differentiation during annulation of intermediate **I**; diastereomers with a *trans*-configuration of the C–O and C–Nu bonds decompose and/or are easily separated away from the *cis*-bridged products. We have not attempted to isolate or characterize the intermediate ketone diastereomers **I**.

(18) Reaction with the corresponding acyclic acetophenone-derived silyl enol ether yielded only trace cyclized product (see Supporting Information).

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(21) CCDC 1548662 contains the supplementary crystallographic data for this structure. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.

(22) DFT calculations (ωB97X-D//6-311+G**//CPCM:CH_2Cl_2) on 2-methyl-1-(phenylsulfonyl)piperidine show the lowest energy axial conformer to be 3.3 kcal/mol more stable than the lowest energy equatorial conformer. We speculate that this is paralleled in **TS** and **TS'**.

(23) Interestingly, 10 mol% $HBArF_{24}$ ($[H(OEt_2)_2][B(C_6H_3(CF_3)_2)_4]$, Brookhart's acid) as catalyst provided hydride-trapped **6** in an inferior 47% NMR yield but 45:36:19 d.r. favoring the same diastereomers as those resulting from the putative silylium ion catalysis (cf. Table 1, entry 2; see Supporting Information). This suggests that the reaction can be catalyzed by Brønsted acid and that co-catalysis could be operative via adventitious water. See: Schmidt, R. K.; Muether, K.; Mueck-Lichtenfeld, C.; Grimme, S.; Oestreich, M. *J. Am. Chem. Soc.* **2012**, *134*, 4421.

(24) The relative stereochemistry of *cis*- and *trans*-tetrahydropyridine products was determined via X-ray crystallography and comparison of ^1H NMR and ^{13}C NMR data (see **S19** in the Supporting Information).

(25) (a) Attempts to intercept the carbocation with R_3Si–Nu using BCF have been unsuccessful; Et_3Si–H hydrosilylates the aldehyde in 32% NMR yield, along with 44% of **23**, and 7% and 12%, respectively, of minor isomers B and C of **6**. (b) Aldehyde hydrosilylation has been well documented, see: Oestreich, M.; Hermeke, J.; Mohr, J. *Chem. Soc. Rev.* **2015**, *44*, 2202.

(26) **Representative Procedure for the Synthesis of Piperidine 20**
In a dry, N_2-filled glove box, aldehyde **S16** (0.150 mmol, 68.3 mg, 1.00 equiv) and trityl $BArF_{20}$ (0.0150 mmol, 13.8 mg, 0.10 equiv) were weighed into a screw-cap 1 dram vial equipped with a stir bar and sealed with a septum cap. In a separate vial, Et_3SiH (0.0180 mmol, 2.9 µL, 0.12 equiv) and cyclohexanone-derived silyl enol ether (0.375 mmol, 72 µL, 2.50 equiv) were dissolved in 3.00 mL of CH_2Cl_2 and the vial sealed with a septum cap. Both vials were removed from the glove box, and the vial containing the aldehyde and trityl $BArF_{20}$ was cooled to –78 °C in an acetone/$CO_{(s)}$ bath. The room-temperature solution in CH_2Cl_2 was syringed dropwise and slowly down the side of the vial into the vigorously stirring solution over 5–10 min. The reaction was stirred for an additional 2 h at –78 °C, quenched with 50 µL Et_3N, and warmed to r.t. The solution was repeatedly washed with CH_2Cl_2 (3×; to remove excess base) and dried in vacuo. The resulting residue was taken up in 2 mL of 1:1 CH_2Cl_2/MeOH, approximately 10–20 beads of Dowex resin (50W-X8) were added, and the reaction was stirred at 22 °C for 3 h. The mixture was then filtered through a cotton/sand plug, rinsed with 1 mL CH_2Cl_2 (2×), and concentrated in vacuo. The crude residue was purified by silica gel chromatography (R_f = 0.5, *n*-pentane/EtOAc = 5:1), providing heterocycle **20** as a crystalline white solid in 55% yield (44.3 mg). ^1H NMR (600 MHz, $CDCl_3$): δ = 8.50 (d, 1 H *J* = 1.9 Hz), 8.01 (d, 1 H, *J* = 8.7 Hz), 7.99 (d, 1 H, *J* = 8.2 Hz), 7.95 (d, 1 H, *J* = 8.0 Hz), 7.90 (dd, 1 H, *J* = 8.7, 1.9 Hz), 7.67 (ddd, 1 H, *J* = 8.2, 6.9, 1.4 Hz), 7.63 (ddd, 1 H, *J* = 8.2, 6.8, 1.4 Hz), 7.37 (t, 2 H, *J* = 7.7 Hz), 7.29 (dd, 2 H, *J* = 8.2, 1.3 Hz), 7.27–7.22 (m, 3 H), 7.18 (d, 1 H, *J* = 7.4 Hz), 7.16 (dd, 2 H, *J* = 7.1, 1.6 Hz), 4.69 (dd, 1 H, *J* = 11.4, 2.7 Hz), 3.89 (dt, 1 H, *J* = 4.0, 1.9 Hz), 3.57 (dd, 1 H, *J* = 12.7, 3.5 Hz), 3.40 (d, 1 H, *J* = 11.5 Hz), 3.30 (ddd, 1 H, *J* = 11.6, 3.6, 1.8 Hz), 2.85 (t, 1 H, *J* = 12.8, 11.6 Hz), 2.39–2.32 (m, 2 H), 2.24–2.19 (m, 1 H), 1.94–1.90 (m, 1 H), 1.72–1.53 (m, 6 H). ^{13}C NMR (151 MHz, $CDCl_3$): δ = 150.1, 143.5, 139.6, 138.2, 134.8, 132.4, 129.8, 129.4, 129.3, 128.9, 128.6, 128.6, 128.1, 127.8, 127.7, 126.7, 126.6, 126.4, 122.5, 106.3, 67.4, 65.5, 54.1, 39.1, 39.0, 35.8, 27.8, 24.8, 23.4, 23.1. HRMS (ESI$^+$): *m/z* calcd for $C_{34}H_{34}NO_3S^+$ $[M + H]^+$: 536.2260; found: 536.2259. $[\alpha]_D^{26}$ +11.7 (*c* 1.70, CH_2Cl_2, l = 100 mm).