Organocatalytic Asymmetric Synthesis of Dihydroisoquinolinones via a One-Pot Aza-Henry–Hemiaminalization–Oxidation Sequence

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Abstract The asymmetric organocatalytic one-pot synthesis of trans-3,4-disubstituted 3,4-dihydroisoquinolin-1(2H)-ones is described. Starting from 2-(nitromethyl)benzaldehydes and various N-protected aldimines, 5 mol% of a quinine-based squaramide organocatalyst was used to synthesize the title compounds as virtually single diastereomers via an aza-Henry–hemiaminalization–oxidation sequence. Moderate to good yields (39–78%) and moderate to very good enantioselectivities (40–95% ee) were reached.

Key words organocatalysis, domino reaction, one-pot reaction, dihydroisoquinolinones, hydrogen bonding

The structural motif of the dihydroisoquinolinones is common in natural products,1 for example in thalflavine (1),2 (+)-pancratistatin (2)3 and (+)-plicamine (3).4 Such compounds exhibit valuable bioactivities, such as cancer cell growth inhibition4c,d and antiviral activity3k for pancratistatin (2), as well as anti-inflammatory and antidepressant activity.1b Other synthetically derived dihydroisoquinolinones are the steroidomimetic drug 4,5 which possesses bioactivity against certain cancer cell lines, and H3 receptor antagonist 5,6 which plays a crucial role for the release of neurotransmitters and in the treatment of neuropathic pain and schizophrenia (Figure 1). Therefore, efforts have been made for the asymmetric construction of these heterocycles.2 Our group has contributed a chiral-auxiliary-based enantioselective procedure utilizing lithiated o-tolualdehydes and aldehyde SAMP or RAMP hydrazones via a 1,2-addition–ring-closure sequence.8

Domino reactions are a versatile tool in organic chemistry nowadays.9 This type of reaction class allows the construction of complex molecules with a highly functionalized framework and multiple adjacent stereocen-
As a one-pot protocol, it lowers cost, reduces the amount of time required and yields more product due to reduced purification steps.

Recently, we reported the enantioselective conjugate addition of 2-(nitromethyl)benzaldehydes 6 to various nitroolefins 7 leading to functionalized 1,2,3,4-tetrahydrodronaphthalen-1-ols 8 via an organocatalytic nitroalkane-Michael-Henry domino reaction (Scheme 1, a). We now report the first organocatalytic asymmetric synthesis of disubstituted 3,4-dihydroisoquinolin-1(2H)-ones 11 by again employing the concept of hydrogen-bonding organocatalysis. In the first step of the protocol, an aza-Henry addition of 6 to aldimines 9 is used, generating two adjacent stereocenters with the same configuration as in the previous work. A subsequent hemiaminalization occurs to generate the envisaged 1,2,3,4-tetrahydroisoquinolin-1-ols 10 (Scheme 1, b).

Attempts to protect the hydroxy function of the relatively sensitive hemiaminals 10 failed; however, an oxidation with pyridinium chlorochromate in the same pot led to the anticipated 3,4-dihydroisoquinolin-1(2H)-ones 11. With this protocol in hand, we were then able to investigate the optimal conditions for this domino transformation.

Firstly, we searched for an appropriate organocatalyst which can coordinate and activate 2-(nitromethyl)benzaldehyde (6a) and the N-tosyl-protected aldimine 9a to merge them to the corresponding 1,2,3,4-tetrahydroisoquinolin-1-ol 10a, followed by the oxidation with pyridinium chlorochromate. This sequence was conducted as a two-step procedure. Almost every organocatalyst we tested furnished the desired dihydroisoquinolinone 11a (Table 1).

A pseudonorephedrine-derived catalyst A was applied to this sequence and the product was obtained in low enantioselectivity (28% ee; Table 1, entry 1). Takemoto’s catalyst B resulted in moderate 36% ee (Table 1, entry 2) and the squaramide derivative C gave a slightly better result with 42% ee (Table 1, entry 3), suggesting that we should stick to the more reactive squaramides. After three days, no product was detected with catalyst D, indicating that a basic amino group is needed for the deprotonation of the nitroalkane (Table 1, entry 4).

The quinine-based squaramide E catalyzed the domino reaction with good enantioselectivity of 65% ee (Table 1, entry 5), whereas the related catalyst F with its pseudo-enantiomeric structure gave only a low ee value (Table 1, entry 6). Next, we evaluated the best solvent and found that in benzene the enantioselectivity was slightly lower than in toluene (63% ee; Table 1, entry 7). The use of m-xylene and mesitylene as further aromatic nonpolar solvents gave lower enantioselectivities (59% and 28% ee) with moderate yields (37% and 43%; Table 1, entries 8 and 9). Acetonitrile and diethyl ether were used as more polar solvents but the previous results could not be matched (11% yield, 3% ee for MeCN and 40% yield, 56% ee for Et2O; Table 1, entries 10 and 11). After four days, n-hexane gave no satisfying result and the product was obtained in 22% yield and 19% ee (Table 1, entry 12). Switching to chlorinated solvents was also not successful, due to low yield and enantioselectivity (Table 1, entries 13–15).

Continuing the optimization of the protocol, we then checked for the best N-protection group for the aldimines (Table 2). The o-nosyl and p-nosyl groups were chosen because of their electron-withdrawing properties, leading to more reactive aldimines (Table 2, entries 1 and 2), but both protecting groups gave lower enantioselectivities (52% and 54% ee). With the benzyloxycarbonyl protecting group the product was obtained as a racemic mixture (Table 2, entry 3). Other attempts with the N-(tert-butoxycarbonyl)imine, the tosyl hydrazone or a benzyl protecting group gave no product at all (Table 2, entries 4–6). With the N-tosyl-protected imine as best substrate we tested for the optimal catalyst loading. Reducing the catalyst amount to 5 mol% or...
Table 1  Catalyst and Solvent Screening for the Aza-Henry–Hemiaminalization–Oxidation Sequence To Form 3,4-Dihydroisoquinolin-1(2H)-one 11a

| Entry | Catalyst | Solvent | Time (d) | Yield (%) | ee (%) |
|-------|----------|---------|----------|-----------|--------|
| 1     | A        | toluene | 3        | n.d.      | 28     |
| 2     | B        | toluene | 3        | n.d.      | 36     |
| 3     | C        | toluene | 3        | n.d.      | 42     |
| 4     | D        | toluene | 3        | 0         | –      |
| 5     | E        | toluene | 4        | n.d.      | 65     |
| 6     | E        | toluene | 3        | n.d.      | 11     |
| 7     | E        | benzene | 3        | n.d.      | 63     |
| 8     | E        | m-xylene| 1        | 37        | 59     |
| 9     | E        | mesitylene | 1    | 43        | 28     |
| 10    | E        | MeCN    | 1        | 11        | 3      |
| 11    | E        | Et2O    | 1        | 40        | 56     |
| 12    | E        | n-hexane| 4        | 22        | 19     |
| 13    | E        | CH2Cl2  | 1        | 18        | 53     |
| 14    | E        | CHCl3   | 1        | 15        | 37     |
| 15    | E        | DCE     | 1        | 13        | 44     |

* All reactions were performed on a 0.2-mmol scale.
* A virtually pure trans-diastereomer was obtained (dr >20:1); yield of isolated product after the two-step sequence.
* Determined by HPLC analysis on a chiral stationary phase.
* n.d. = not determined.
* The opposite enantiomer was obtained in excess.
increasing to 15 mol% gave similar results in yield (39% and 41%) and enantioselectivity (63% and 65% ee; Table 2, entries 7 and 8). Staying with the 5 mol% catalyst loading, we then screened for the best reaction temperature. Decreasing the temperature to 0 °C and –20 °C resulted in better yields and enantioselectivities (Table 2, entries 9 and 10). With the optimized conditions in hand (Table 2, entry 10), we then investigated the scope of this domino sequence.

The reaction of various 2-(nitromethyl)benzaldehydes 6 and N-tosyl-protected aldimines 9 with 5 mol% of the squaramide organocatalyst E was conducted in toluene at –20 °C. To improve the previous protocol, we then oxidized the intermediate hemiaminals directly in the same pot to afford the 3,4-dihydroisoquinolin-1(2H)-ones 11a–l as solids, which can be easily recrystallized from benzene or isopropyl alcohol (Table 3). This one-pot protocol afforded the products in modest to good yields (39–78%) and with moderate to very good enantiomeric excesses (40–95% ee). The model compound was finally obtained in 65% yield and 63% ee, with 95% ee after recrystallization (Table 3, 11a).

Various substituents on the aromatic part of the N-tosyl-protected aldimines 9 were tolerated, as well as on the aromatic core of the benzaldehydes 6. Alkyl or alkoxy substituents on aldimine 9 gave moderate results (Table 3, 11b–d), except for the enantiomeric excess of 11d (94% ee).

In the case of isomers of the naphthyl-substituted aldimines, the 2-naphthyl moiety gave the better results (Table 3, 11e and 11f). Further derivatization of the aldimine 9 with electron-withdrawing groups gave good results in each case (Table 3, 11g–l). The halogenated aromatic core of the benzaldehydes 6 yielded the corresponding products 11j and 11k in the same range as the aldimines with similar substituents on the R2 unit (Table 3, 11h and 11l); only the enantiomeric excess of product 11k was lower. Changing the phenyl group for an indolyl moiety in 9 led to no product. Only the racemic product could be obtained using triethylamine (Table 3, 11l).

The absolute configuration of 3,4-dihydroisoquinolin-1(2H)-one 11a was determined as (3R,4S) by single crystal X-ray structure analysis (Figure 2). The strongly distorted lactam unit results in a dihedral angle of 64°, which explains the coupling constants of ~2 Hz of the vicinal trans-proton NMR signals.

**Table 2** Screening for the Optimized Conditions Including Protection Group, Catalyst Loading and Temperature for the Aza-Henry–Hemiaminalization–Oxidation Sequence

| Entry | PG     | mol% E | Temp (°C) | Time (d) | Yield (%) | ee (%) |
|-------|--------|--------|-----------|----------|-----------|--------|
| 1     | o-nosyl| 10     | r.t.      | 4        | n.d.e     | 52†    |
| 2     | β-nosyl| 10     | r.t.      | 3        | n.d.      | 54†    |
| 3     | Cbz    | 10     | r.t.      | 4        | n.d.      | 0      |
| 4     | Boc    | 10     | r.t.      | 2        | 0         | –      |
| 5     | NHTs   | 10     | r.t.      | 3        | 0         | –      |
| 6     | Bn     | 10     | r.t.      | 2        | 0         | –      |
| 7     | Ts     | 5      | r.t.      | 1        | 39        | 63     |
| 8     | Ts     | 15     | r.t.      | 1        | 41        | 65     |
| 9     | Ts     | 5      | 0         | 3        | 53        | 64     |
| 10    | Ts     | 5      | –20       | 3        | 59        | 65     |

a All reactions were performed on a 0.2-mmol scale.

b A virtually pure trans-diastereomer was obtained (dr >20:1); yield of isolated product after the two-step sequence.

c Determined by HPLC analysis on a chiral stationary phase, unless otherwise indicated.

d n.d. = not determined.

e Determined by SFC analysis on a chiral stationary phase.
The asymmetric synthesis of functionalized 3,4-dihydroisoquinolin-1(2H)-ones 11a–l; General Procedure

Asymmetric Synthesis of 3,4-Dihydroisoquinolin-1(2H)-one Derivatives 11a–l; General Procedure

In a glass vial equipped with a magnetic stirrer bar, a 2-(nitromethyl)benzaldehyde 6 (0.5 mmol, 1.0 equiv) and organocatalyst E (5 mol%) were dissolved in toluene (1 mL). After the mixture was stirred at rt for the appropriate time, PCC (0.75 mmol) was added. This mixture was stirred at rt and monitored by TLC. After completion of the reaction, the solvent was evaporated and the crude mixture was directly purified on silica gel (n-hexane–EtOAc, 5:1 to 2:1) to afford the product 11 as a colorless solid.

(3R,4S)-4-Nitro-3-phenyl-2-tosyl-3,4-dihydroisoquinolin-1(2H)-one (11a)

Synthesized according to the general procedure from 2-(nitromethyl)benzaldehyde (6a; 82 mg, 0.50 mmol) and N-tosylimine 9a (140 mg, 0.54 mmol). The oxidation step was conducted with PCC (160 mg, 0.74 mmol); yield: 136 mg (65%); colorless solid; mp 142 °C (benzene).

Flash column chromatography was performed on SIL G-25 UV254 (particle size 0.040–0.063 mm, Macherey-Nagel). TLC was performed on silica gel 60 F254 plates (Merck, Darmstadt). Visualization of the developed TLC plates was performed with UV radiation (254 nm) or by staining with a KMnO4 solution. Elemental analyses were carried out with a Vario EL elemental analyzer. Melting points were determined with a Büchi Melting Point B-540 apparatus. Optical rotation values were measured on a Perkin-Elmer P241 polarimeter. The ee values were determined by analytical HPLC with a Hewlett-Packard 1100 Series instrument or by analytical SFC with a Thar Waters Method Station 2, using chiral stationary phases. IR spectra were recorded on a Perkin-Elmer FT-IR Spectrum 100 spectrometer. 1H and 13C NMR spectra were measured at ambient temperature with Varian Innova 400 or Varian Innova 600 spectrometers using TMS as internal standard. Mass spectra were recorded on a Finnigan SSQ7000 (EI 70 eV) spectrometer, high-resolution mass spectra on a Finnigan MAT 95 spectrometer and high-resolution ESI mass spectra on a Thermo Fisher Scientific LTQ Orbitrap XL spectrometer.

In conclusion, we have developed the first organocatalytic asymmetric synthesis of functionalized 3,4-dihydroisoquinolin-1(2H)-ones via an aza-Henry/hemiaminalization/oxidation sequence by employing 5 mol% of a quinine-based squaramide organocatalyst. This one-pot protocol utilizes easy accessible 2-(nitromethyl)benzaldehydes and N-tosyl-protected aldimines as substrates to furnish the trans-configured title compounds with two adjacent stereocenters. The substituent pattern could be varied on the aromatic parts (R1, R2) with electron-donating and electron-withdrawing groups, such as alkyl, alkoxy, nitro or halogen atoms. The dihydroisoquinolinones were obtained in modest to good yields (39–78%), as virtually single diastereomers (dr >20:1), and with moderate to very good enantiomeric excesses (40–95% ee).
13C NMR (150 MHz, CDCl3): \( \delta = 21.7 \) (CH3), 61.2 (CHPh), 86.0 (CHNO2), 126.4 (2 × CHAr), 127.6 (C\(_\alpha\)), 128.8 (C\(_\alpha\)), 129.2 (2 × CH\(_\alpha\)), 129.3 (CH\(_\alpha\)), 129.3 (2 × CH\(_\alpha\)), 129.5 (2 × CH\(_\alpha\)), 130.6 (CH\(_\alpha\)), 131.6 (CH\(_\alpha\)), 134.3 (CH\(_\alpha\)), 135.1 (C\(_\alpha\)), 135.2 (C\(_\alpha\)), 145.4 (C\(_\alpha\)), 161.0 (C=O).

IR (film): 2987, 2921, 2311, 2075, 1976, 1690, 1596, 1555, 1453, 1353, 1299, 1246, 1168, 1067, 1014, 908, 846, 806, 727 cm\(^{-1}\).

HRMS: m/z [M + Na\(^+\)] calculated for C\(_{22}\)H\(_{18}\)N\(_2\)O\(_5\)SNa+: 513.1326; found: 513.1326.

(3R,4S)-3-(3,4-Methylenedioxyphenyl)-4-nitro-2-tosyl-3,4-dihydroisoquinolin-1(2H)-one (11d)

Synthesized according to the general procedure from 2-(nitrinemethyl)benzaldehyde (6a: 82 mg, 0.50 mmol) and N-tosylmine 9d (166 mg, 0.55 mmol). The oxidation step was conducted with PCC (156 mg, 0.72 mmol); yield: 92 mg (40%); colorless solid; mp 172 °C (CHCl3); 94% ee; \( R\_d = 0.63 \) (n-hexane–EtOAc, 1:1).

IR (film): 2984, 2906, 2285, 2068, 1982, 1690, 1598, 1556, 1495, 1447, 1354, 1244, 1166, 1029, 914, 810, 722 cm\(^{-1}\).

HRMS: m/z [M + H\(^+\)] calculated for C\(_{24}\)H\(_{21}\)N\(_2\)O\(_5\)S+: 473.1166; found: 473.1163.
IR (film): 3309, 3088, 2920, 2850, 2096, 1736, 1679, 1619, 1593, 1529, 1359, 1303, 1246, 1166, 1115, 1065, 1011, 962, 905, 847, 807, 736, 706 cm⁻¹.

1H NMR (600 MHz, CDCl₃): δ = 2.40 (s, 3 H, CH₃), 5.85 (d, 1H, 1 H, CHNO₂), 6.98 (br s, 1 H, CH₂Ar), 7.17–7.31 (m, 4 H, 4 × CH₂Ar), 7.15–7.19 (m, 2 H, 2 × CH₂Ar), 7.30 (d, 1H, 1H, CH₃), 7.31 (d, 1H, 1H, CH₃), 7.33 (d, 1H, 1H, CH₃), 7.34–7.36 (m, 1 H, CH₂Ar), 7.41 (d, 1H, 1H, CH₂Ar), 7.53 (dd, 1H, J = 1.5 Hz, 1H, CH₂Ar), 7.53 (dd, 1H, J = 1.5 Hz, 1H, CH₂Ar), 7.56 (s, 1 H, CH₁), 7.69–7.71 (m, 1 H, CH₂Ar), 7.77–7.79 (m, 2 H, 2 × CH₂Ar), 7.91 (d, 1H, 1H, CH₂), 7.98 (d, 1H, 1H, CH₂), 8.21 (dd, 1H, J = 2.6 Hz, 2H, 2 × CH₂Ar), 8.67 (t, 1H, 1H, CH₂Ar), 13.60 (s, 3 H, 3 × CH₃).

13C NMR (150 MHz, CDCl₃): δ = 21.7 (CH₃), 61.6 (CH₁), 68.9 (CH₂Ar), 121.3 (CH₃), 126.1 (CH₂Ar), 126.9 (CH₂O), 127.6 (CH₂Ar), 128.2 (CH₂Ar), 128.8 (CH₂O), 129.3 (2 × CH₂Ar), 129.5 (2 × CH₂Ar), 129.4 (CH₂O), 129.6 (2 × CH₂Ar), 130.5 (CH₂Ar), 131.7 (CH₂Ar), 132.5 (CH₂Ar), 133.1 (2 × CH₂Ar), 134.3 (CH₂Ar), 145.5 (CH₂Ar), 161.2 (C=O).

MS (EI, 70 eV): m/z (%) = 472 (M⁺), 464 (100), 462 (5), 392 (23), 244 (25), 235 (15), 211 (22), 65 (18).

HRMS: m/z [M + H⁺] calcd for CₙHₙNₙOₙS₂⁺: 473.1166; found: 473.1161.

IR (film): 2921, 2848, 2105, 1690, 1595, 1553, 1508, 1458, 1422, 1353, 1243, 1166, 1117, 1070, 1013, 975, 907, 810, 711 cm⁻¹.

1H NMR (600 MHz, CDCl₃): δ = 2.42 (s, 3 H, CH₃), 5.74 (d, 1H, 1 H, CHNO₂), 6.92 (d, 1H, 1H, CHNO₂), 7.33 (d, 1H, 1H, CH₂Ar), 7.35–7.38 (m, 1 H, CH₂Ar), 7.51 (d, 1H, 1H, CH₂Ar), 7.58–7.63 (m, 3 H, 3 × CH₂Ar), 7.63–7.66 (m, 1 H, CH₂Ar), 8.05 (d, 1H, 1H, CH₃), 8.31 (d, 1H, 1H, CH₃), 8.31–8.34 (m, 1 H, CH₂Ar), 8.15–8.17 (m, 1 H, CH₂Ar), 8.18–8.21 (m, 1 H, CH₂Ar).

13C NMR (150 MHz, CDCl₃): δ = 21.4 (CH₃), 60.4 (CH₁), 85.3 (CH₂Ar), 121.5 (CH₂Ar), 124.0 (CH₂O), 126.9 (CH₂O), 128.5 (CH₂O), 129.4 (2 × CH₂Ar), 129.6 (3 × CH₂Ar), 130.6 (CH₂Ar), 130.7 (CH₂Ar), 131.2 (CH₂Ar), 132.2 (CH₂Ar), 134.6 (CH₂Ar), 134.7 (CH₂O), 137.7 (CH₂O), 145.9 (CH₂O), 148.7 (CH₂O), 160.6 (C=O).

MS (EI, 70 eV): m/z (%) = 394 (5) [M – NO₂⁺], 376 (16), 330 (100), 239 (9), 212 (17), 183 (25), 155 (13), 91 (19).

HRMS: m/z [M + H⁺] calcd for CₙHₙNₙOₙSF₂⁺: 441.0915; found: 441.0910.

Nal. Calcd for CₙHₙNₙOₙSF₂: C, 59.99; H, 3.89; N, 6.36. Found: C, 59.83; H, 4.11; N, 6.35.

IR (film): 2921, 2848, 2105, 1690, 1595, 1553, 1508, 1458, 1422, 1353, 1243, 1166, 1117, 1070, 1013, 975, 907, 810, 711 cm⁻¹.

1H NMR (600 MHz, CDCl₃): δ = 2.42 (s, 3 H, CH₃), 5.83 (d, 1H, 1 H, CHNO₂), 6.96 (dd, 1H, J = 1.4 Hz, 1 H, CH₂Ar), 7.11 (d, 1H, J = 1.4 Hz, 1 H, CH₂Ar), 7.33–7.37 (m, 2 H, 2 × CH₂Ar), 7.33 (d, 1H, J = 1.4 Hz, 1 H, CH₂Ar), 7.37–7.38 (m, 1 H, CH₂Ar), 7.55–7.60 (m, 2 H, 2 × CH₂Ar), 7.64 (dd, 1H, J = 1.4 Hz, 1 H, CH₂Ar), 7.98 (d, 1H, J = 2.6 Hz, 2 H, 2 × CH₂Ar), 8.18–8.21 (m, 1 H, CH₂Ar).

13C NMR (150 MHz, CDCl₃): δ = 21.5 (CH₃), 60.6 (CH₁), 83.3 (CH₂Ar), 122.1 (CH₂Ar), 127.4 (CH₂O), 128.2 (CH₂Ar), 128.3 (CH₂O), 129.2 (CH₂Ar), 129.3 (2 × CH₂Ar), 129.7 (2 × CH₂Ar), 130.6 (CH₂O), 130.9 (CH₂Ar), 131.7 (CH₂Ar), 133.8 (CH₂O), 133.9 (CH₂O), 134.4 (CH₂O), 135.1 (CH₂O), 145.6 (CH₂O), 161.3 (C=O).

MS (EI, 70 eV): m/z (%) = 456/454 (9/9) [M – NO₂⁺], 438/436 (13/13), 392/390 (99/100), 311 (4), 310 (10), 301/299 (10/10), 155 (22), 91 (24).

HRMS: m/z [M + H⁺] calcd for CₙHₙNₙOₙSF₂⁺: 501.0114; found: 501.0114.
IR (film): 3069, 2985, 2928, 2102, 1731, 1693, 1592, 1558, 1494, 1453, 1360, 1294, 1244, 1167, 1124, 1080, 1047, 911, 846, 810, 761, 731, 698 cm\(^{-1}\).

1\(^H\) NMR (600 MHz, CDCl\(_3\)): \(\delta = 2.41\) (s, 3 H, CH\(_3\)), 5.66 (d, \(J = 2.0\) Hz, 1 H, CHNO\(_2\)), 6.81 (d, \(J = 2.0\) Hz, 1 H, CPHF), 7.18–7.20 (m, 2 H, 2 \(\times\) CHAr), 7.28–7.31 (m, 5 H, 5 \(\times\) CH\(_3\)), 7.48 (d, \(J = 1.8\) Hz, 1 H, CHAr), 7.70 (dd, \(J = 8.5\) Hz, \(J = 1.9\) Hz, 1 H, CHAr), 7.86 (d, \(J = 8.4\) Hz, 2 H, 2 \(\times\) CHAr), 8.03 (d, \(J = 8.5\) Hz, 1 H, CHAr).

13\(^C\) NMR (150 MHz, CDCl\(_3\)): \(\delta = 21.7\) (CH\(_3\)), 61.2 (CHPh), 85.4 (CHNO\(_2\)), 126.3 (2 \(\times\) CHAr), 127.6 (C\(_4\)), 129.1 (C\(_4\)), 129.2 (CHAr), 129.2 (C\(_4\)), 129.3 (2 \(\times\) CHAr), 129.5 (2 \(\times\) CHAr), 130.7 (CHAr), 133.5 (CHAr), 134.7 (C\(_4\)), 134.9 (C\(_4\)), 135.0 (CHAr), 145.6 (C=O), 160.4 (C=O).

HRMS: \([M + H]^+\) calcd for C\(_{22}H_{18}N_2O_5S Br^+: 501.0114; found: 501.0113.

IR (film): 3331, 3076, 2918, 2850, 2694, 2293, 2067, 1941, 1688, 1597, 1555, 1497, 1437, 1355, 1264, 1163, 1085, 1026, 928, 847, 807, 743 cm\(^{-1}\).

1\(^H\) NMR (600 MHz, CDCl\(_3\)): \(\delta = 2.41\) (s, 3 H, CH\(_3\)), 5.70 (d, \(J = 1.9\) Hz, 1 H, CHNO\(_2\)), 6.81 (d, \(J = 1.9\) Hz, 1 H, CPHF), 7.18–7.19 (m, 2 H, 2 \(\times\) CHAr), 7.24–7.27 (m, 1 H, CHAr), 7.28–7.30 (m, 5 H, 5 \(\times\) CH\(_3\)), 7.34 (dd, \(J_{7,16} = 8.4\) Hz, \(J_{9,16} = 4.8\) Hz, 1 H, CHAr), 7.84–7.86 (m, 3 H, 3 \(\times\) CHAr).

13\(^C\) NMR (150 MHz, CDCl\(_3\)): \(\delta = 21.7\) (CH\(_3\)), 61.2 (CHPh), 85.4 (CHNO\(_2\)), 116.3 (d, \(J_{c,f} = 24.3\) Hz, CHAr), 121.6 (d, \(J_{c,f} = 22.5\) Hz, CHAr), 123.6 (d, \(J_{c,f} = 3.8\) Hz, C\(_4\)), 126.3 (2 \(\times\) CHAr), 129.1 (CHAr), 129.3 (2 \(\times\) CHAr), 129.4 (2 \(\times\) CHAr), 131.2 (d, \(J_{c,f} = 7.8\) Hz, C\(_4\)), 129.5 (2 \(\times\) CHAr), 130.7 (CHAr), 131.8 (CHAr), 134.9 (C\(_4\)), 134.9 (C\(_4\)), 135.0 (CHAr), 136.0 (d, \(J_{c,f} = 1.8\) Hz C=O), 163.4 (d, \(J_{c,f} = 253.4\) Hz, C\(_3\)F).

19\(^F\) NMR (565 MHz, CDCl\(_3\)): \(\delta = -105.8\) (d, \(J_{18,19} = 8.0, 8.0\) Hz, \(J_{16,19} = 5.0\) Hz, CHF).

MS (EL, 70 eV): \(m/z\) (\%) = 441 (3) [M + H\(^+\)], 394 (14), 376 (11), 330 (100), 239 (8), 183 (20), 155 (18), 148 (15), 91 (5), 77 (3).

HRMS: \(m/z\) [M + H\(^+\)] calcd for C\(_{22}H_{16}N_2O_5S\(_2\)F: 441.0915; found: 441.0916.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1379398.

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(15) CCDC 1027768 (11a) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.