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Rhodium(III)-Catalyzed Three-Component 1,2-Diamination of Unactivated Terminal Alkenes

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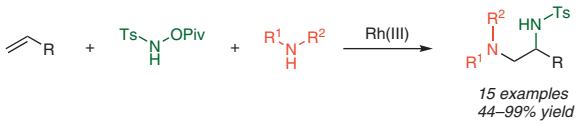

Dedicated to Professor Mark Lautens on the occasion of his 70th birthday

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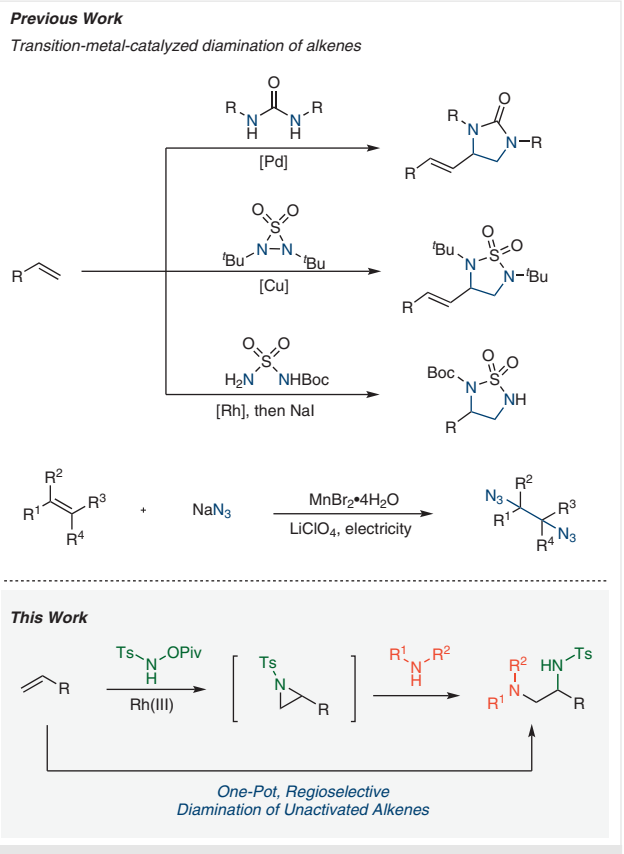
Abstract We report a three-component diamination of simple unactivated alkenes using an electrophilic nitrene source and amine nucleophiles. The reaction provides rapid access to 1,2-vicinal diamines from terminal alkenes through a one-pot protocol. The transformation proceeds smoothly with excellent tolerance for a broad array of primary and secondary amines, affording the desired products in good yield and regioselectivity. The mechanism is proposed to proceed through a Rh(III)-catalyzed aziridination of alkenes with subsequent ring opening by primary or secondary amines.

Key words alkene diamination, rhodium(III) catalysis, one-pot synthesis, nitrene

The 1,2-vicinal diamine is a prevalent structural motif in natural products and pharmaceuticals. Moreover, they are commonly utilized as ligands on various metal complexes to catalyze essential organic transformations.[1] Owing to the high demand, the development of efficient synthetic strategies for the synthesis of 1,2-diamines has been actively pursued. Several notable synthetic approaches exist, including the aza-Henry reaction,[2] a Mannich reaction between α-amino compounds and imines,[3] and the addition of nucleophiles to α-amino imines.[4] Among the potential synthetic precursors for the synthesis of vicinal amines, alkenes are ideal – they are ubiquitous feedstock materials, and contain an unreactive functionality that is well tolerated in other transformations. Thus, the simultaneous addition of two nitrogen functionalities to the alkene double bond is a straightforward and useful way to access 1,2-vicinal diamines (Scheme 1). However, aside from some prominent successes,[5,6] transition-metal-catalyzed 1,2-diamination of alkenes is significantly underdeveloped compared to the much better established dihydroxylation and aminohydroxylation of alkenes. Presumably, this is because 1,2-diamines are generally good ligands and can act as a chelating ligand for the metal complex.



Scheme 1 Transition-metal-catalyzed alkene diamination

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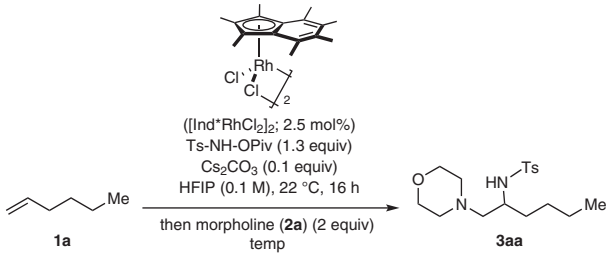
Alternatively, the nucleophilic ring opening of aziridines by amines is an efficient strategy to access diamines from readily available starting materials (Scheme 1).[7] Recently, we reported a Rh(III)-catalyzed formal [4+1] approach to pyrrolidines from simple unactivated terminal alkenes and nitrene sources.[8] Mechanistic investigations led us to propose a Rh-catalyzed intermolecular aziridination with subsequent ring expansion by triflic acid for the synthesis of the five-membered saturated *N*-heterocycle. Motivated by the fact that aziridine formation is highly efficient in this system, we envisioned that this intermediate can be utilized for the one-pot synthesis of vicinal diamines in the presence of exogenous nitrogen nucleophiles. In order to test this idea, we added morpholine (**2a**) as amine nucleophile after the initial aziridination of 1-hexene (**1a**) and 4-methyl-*N*-(pivaloyloxy)benzenesulfonamide (Ts-NH-OPiv) in the presence of a catalytic amount of Cs_2CO_3 (0.1 equiv) and $[Ind^*RhCl_2]_2$ catalyst (2.5 mol%; Ind* = heptamethylindenyl) in HFIP (Table 1).

Table 1 Optimization Table

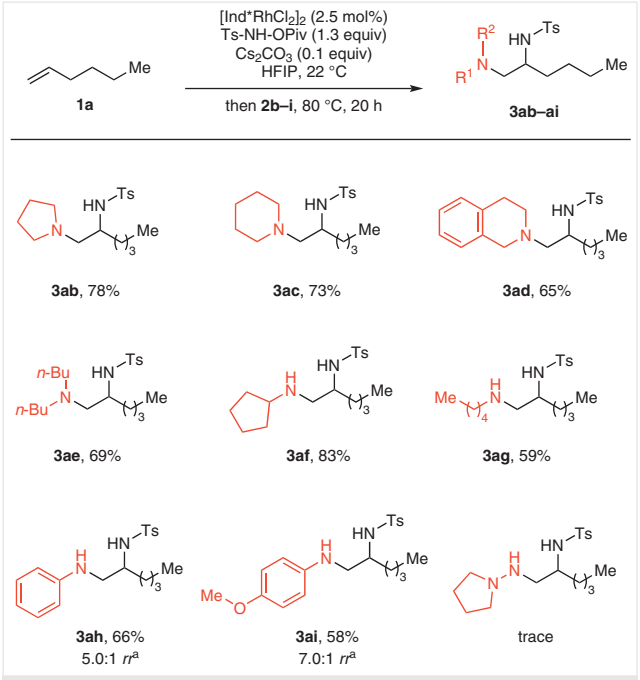


Entry	Concn (M)	Morpholine (equiv)	Temp (°C)	Time (h)	Yield (%)[a]
1	0.1	2	22	8	<5
2	0.1	2	40	8	19
3	0.1	2	80	8	63
4[b]	0.1	2	80	8	28
5	0.1	2	80	20	78
6	0.2	2	80	20	87
7	**0.2**	**3**	**80**	**24**	**99**

[a] Determined by ^{1}H NMR analysis of unpurified reaction mixture.
[b] $AgSbF_6$ (1 equiv) was added.

Preliminary results showed that when morpholine (2 equiv) was added and the reaction mixture was stirred at room temperature or 40 °C, the desired diamination product was formed as a single regioisomer, albeit in low yield (Table 1, entries 1 and 2). Increasing the reaction temperature to 80 °C further improved the reaction yield to 63% (entry 3). Since we observed unreacted aziridine on work-up, a longer reaction time and a higher concentration were applied to complete the reaction, resulting in the yield of **3aa** improving to 87% when the reaction was conducted at 80 °C for 20 hours in 0.2 M of HFIP (entry 6). Lewis acid-promoted aziridine ring opening by amines is well known;[7] however, adding $AgSbF_6$ together with morpholine after aziridination gives a lower yield of **3aa** (entry 4). Finally, a quantitative yield of the desired product was observed at 0.2 M with morpholine (3 equiv; entry 7).

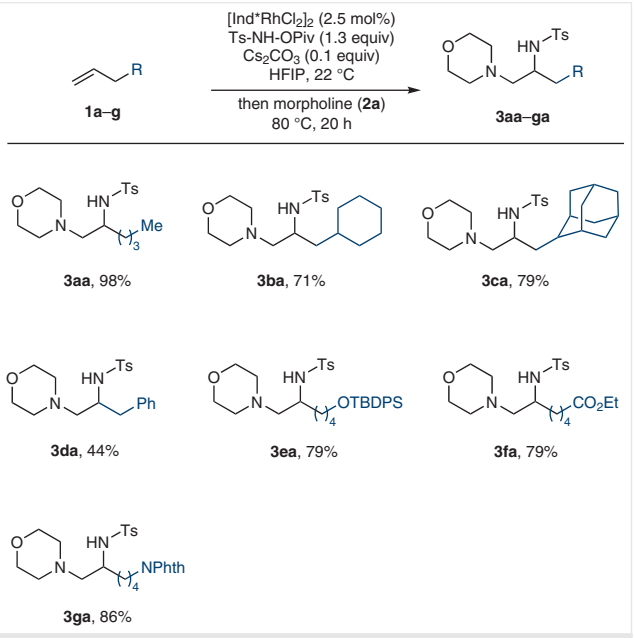
Having optimized the reaction conditions, we next sought to explore the scope of this methodology. First, various commercially available primary and secondary amines **2** were examined using 1-hexene as an alkene coupling partner (Scheme 2). Cyclic secondary amines such as pyrrolidine (**2b**) and piperidine (**2c**) provide diamination products in good yields (**3ab**, **3ac**). Bicyclic 1,2,3,4-tetrahydroisoquinoline (**2d**) also works well as a nucleophile giving 65% of the corresponding 1,2-diamine (**3ad**). The reaction with dibutylamine also delivers the 1,2-vicinal diamine product in good yield (**3ae**). The reaction also proceeds smoothly with primary amines, giving the desired products **3af**–**3ai** in good yield. When aniline (**2h**) and 4-methoxyaniline (**2i**) are used as the nucleophiles, the minor regioisomers are also observed in small amounts (*rr* = regioisomeric ratio). A hydrazine-type nucleophile (1-aminopyrrolidine) was also tested, but only a trace amount of desired product was observed.



Scheme 2 Amine nucleophile substrate scope; [a] Determined by ^{1}H NMR analysis of unpurified reaction mixture

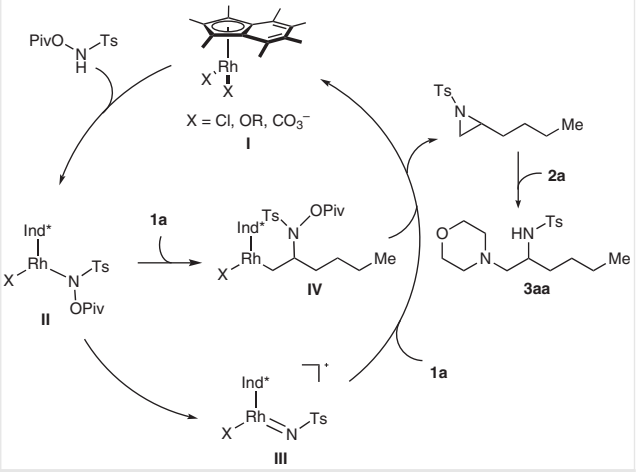
Next, we tested the synthetic utility of this method with a variety of terminal unactivated alkene substrates **1** (Scheme 3). Allylcyclohexane and 2-allyladamantane are successfully converted into the corresponding diamination products in good yield (**3ba**, **3ca**). A variety of functional groups such as phenyl (**3da**), *tert*-butyldiphenylsilyl-pro-

tected alcohol (**3ea**), ethyl ester (**3fa**), and protected amine (**3ga**) are all well tolerated, giving the desired 1,2-diamination products in good yield.



Scheme 3 Terminal alkene substrate scope

On the basis of our previous work[8] and an aziridine ring-opening precedent,[7] we propose the following mechanism for the reaction (Scheme 4). First, the $[Ind^*RhCl_2]_2$ catalyst metalates Ts-NH-OPiv to generate Rh complex **II**, which undergoes Rh–nitrene formation to yield intermediate **III**. Subsequent aziridination with an unactivated alkene coupling partner (**1a**) would give the aziridine intermediate with the regeneration of the active Rh(III) catalyst. Alternatively, the alkene coupling partner (**1a**) could coordinate with Rh complex **II** and undergo alkene migratory insertion



Scheme 4 Proposed mechanism

to form complex **IV**. Subsequent C–N bond formation and N–O bond cleavage would generate the aziridine intermediate. Nucleophilic attack of primary and/or secondary amines to the sterically less hindered terminal carbon of aziridine produces diamination products at elevated temperature.

In summary, we have demonstrated the one-pot synthesis of vicinal diamines from readily available α-olefins through Rh(III)-catalyzed aziridination and subsequent nucleophilic attack by exogenous amines. The reaction exhibits broad functional group tolerance with good yield and regioselectivity.

HFIP, Cs_2CO_3, and **1a**, **1b**, **1d**, **1f**, and **2a–i** were purchased from Sigma Aldrich and used without further purification. Compounds **1c**,[8] **1e**,[9] **1g**,[10] and the $[Ind^*RhCl_2]_2$ catalyst[11] were synthesized following literature procedures. ^1H and ^{13}C NMR spectra were collected at ambient temperature on Bruker 400 MHz and Bruker Avance III 500 MHz spectrometers. Regioisomeric ratios were measured by integration of ^1H NMR spectra of product mixtures prior to purification. Low resolution mass spectra were recorded on a Waters Acquity UPLC-MS or Agilent 5977B GC/MS. Infrared spectra were collected on a Perkin Elmer Spectrum Two FT-IR spectrophotometer. Melting points were measured on a Stanford Research System MPA160 melting point apparatus.

Diamines 3 from Alkenes 1 and Amines 2; General Procedure

A 1 dram vial was charged with $[Ind^*RhCl_2]_2$ (0.0025 mmol, 2.5 mol%), Ts-NH-OPiv (0.13 mmol, 1.3 equiv), alkene **1** (0.1 mmol, 1 equiv), and Cs_2CO_3 (0.01 mmol, 0.1 equiv), which were dissolved in HFIP (0.2 M); the mixture was stirred for 16 h at 22 °C. Then, amine **2** (0.3 mmol, 3 equiv) was added to the vial and the mixture was heated to 80 °C and stirred for an additional 20 h. The mixture was concentrated under reduced pressure and the crude material was purified by flash chromatography, either manually on SiliCycle® SilicaFlash® P60 (230–400 mesh) silica gel or automatically using a Teledyne Isco Lumen CombiFlash with RediSep Rf Disposable Flash columns.

4-Methyl-*N*-(1-morpholinohexan-2-yl)benzenesulfonamide (3aa)

Yield: 20.4 mg, 98%, yellow oil.

R_f = 0.35 (EtOAc/hexane 1:1).

IR ($CDCl_3$): 3272, 2954, 2928, 2858, 1598, 1453, 1329, 1302, 1159, 1115, 1092, 815, 665, 550 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.76 (m, 2 H), 7.29 (m, 2 H), 3.53–3.44 (m, 4 H), 3.13–3.04 (m, 1 H), 2.41 (s, 3 H), 2.24 (d, *J* = 7.4 Hz, 2 H), 2.21–2.12 (m, 1 H), 2.11–2.03 (m, 1 H), 2.07 (dt, *J* = 11.0, 4.3 Hz, 2 H), 1.67 (ddd, *J* = 14.4, 9.6, 4.6 Hz, 1 H), 1.53 (dddd, *J* = 14.0, 11.2, 7.3, 4.1 Hz, 1 H), 1.29–1.18 (m, 3 H), 1.17–1.08 (m, 1 H), 0.84 (t, *J* = 6.9 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 143.5, 137.2, 129.7, 127.4, 66.8, 61.1, 53.3, 50.0, 33.1, 26.9, 22.8, 21.6, 14.1.

LRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{29}N_2O_3S$: 341.2; found: 341.1.

4-Methyl-*N*-[1-(pyrrolidin-1-yl)hexan-2-yl]benzenesulfonamide (3ab)

Yield: 25.2 mg, 78%, pale-yellow oil.

R_f = 0.16 (DCM/MeOH 19:1).

IR ($CDCl_3$): 3287, 2958, 2928, 1382, 1320, 1159, 1093, 909, 731, 660, 549 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 8.2 Hz, 2 H), 7.29 (d, *J* = 8.0 Hz, 2 H), 5.43 (s, 1 H), 3.01 (ddt, *J* = 9.4, 7.3, 4.6 Hz, 1 H), 2.51 (dd, *J* = 12.3, 9.6 Hz, 1 H), 2.41 (s, 3 H), 2.32–2.21 (m, 3 H), 2.16 (td, *J* = 8.2, 4.4 Hz, 2 H), 1.75–1.56 (m, 5 H), 1.51 (dddd, *J* = 14.2, 11.3, 7.2, 4.2 Hz, 1 H), 1.31–1.02 (m, 3 H), 0.83 (t, *J* = 6.9 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 143.3, 137.3, 129.6, 127.4, 58.3, 54.0, 52.3, 33.2, 27.0, 23.7, 22.8, 21.7, 14.1.

LRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{28}N_2O_2S$: 325.2; found: 325.2.

4-Methyl-*N*-[1-(piperidin-1-yl)hexan-2-yl]benzenesulfonamide (3ac)

Yield: 24.8 mg, 73%, yellow oil.

R_f = 0.27 (EtOAc/hexane 1:1).

IR ($CDCl_3$): 2930, 2859, 1709, 1597, 1553, 1455, 1404, 1332, 1160, 1093, 664, 550 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.80–7.71 (m, 2 H), 7.33–7.25 (m, 2 H), 3.07 (ddt, *J* = 10.3, 8.2, 4.2 Hz, 1 H), 2.41 (s, 3 H), 2.28 (dd, *J* = 12.7, 10.3 Hz, 1 H), 2.19 (dd, *J* = 12.6, 4.7 Hz, 1 H), 2.15–2.04 (m, 3 H), 1.70 (ddt, *J* = 10.2, 8.8, 4.1 Hz, 1 H), 1.56–1.46 (m, 1 H), 1.45–1.32 (m, 6 H), 1.32–1.16 (m, 6 H), 1.15–1.05 (m, 1 H), 0.84 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 143.2, 137.3, 129.6, 127.4, 60.9, 54.2, 50.1, 38.7, 33.2, 27.3, 26.9, 25.7, 24.1, 22.8, 21.6, 14.1.

LRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{31}N_2O_2S$: 339.2; found: 339.1.

***N*-[1-(3,4-Dihydroisoquinolin-2(1*H*)-yl)hexan-2-yl]-4-methylbenzenesulfonamide (3ad)**

Yield: 25 mg, 65%, yellow solid; mp 94–98 °C.

R_f = 0.65 (EtOAc/hexane 1:1).

IR ($CDCl_3$): 3276, 2954, 2926, 2867, 1598, 1454, 1328, 1160, 1093, 903, 813, 741, 666, 550 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.73–7.67 (m, 2 H), 7.22–7.17 (m, 2 H), 7.17–7.04 (m, 3 H), 6.78–6.73 (m, 1 H), 3.28 (d, *J* = 14.8 Hz, 1 H), 3.23–3.11 (m, 2 H), 2.85–2.76 (m, 1 H), 2.69 (dt, *J* = 16.4, 5.4 Hz, 1 H), 2.57 (dt, *J* = 11.2, 5.5 Hz, 1 H), 2.50 (ddd, *J* = 15.3, 8.0, 4.3 Hz, 1 H), 2.47–2.41 (m, 2 H), 2.41 (s, 3 H), 1.80–1.71 (m, 1 H), 1.64–1.54 (m, 1 H), 1.35–1.14 (m, 4 H), 0.87 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 143.3, 137.0, 134.0, 129.7, 128.7, 127.3, 126.6, 126.4, 125.7, 60.7, 55.5, 51.1, 50.6, 33.2, 29.1, 27.2, 27.0, 22.9, 21.7, 14.1.

LRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{31}N_2O_2S$: 387.2; found: 387.2.

***N*-[1-(Dibutylamino)hexan-2-yl]-4-methylbenzenesulfonamide (3ae)**

Yield: 26.4 mg, 69%, pale-yellow oil.

R_f = 0.31 (DCM/MeOH 19:1).

IR ($CDCl_3$): 3286, 2976, 2863, 1381, 1349, 1118, 1075, 916, 733, 662, 548 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 8.0 Hz, 2 H), 7.28 (d, *J* = 8.0 Hz, 2 H), 5.39 (s, 1 H), 2.99 (tt, *J* = 9.2, 4.6 Hz, 1 H), 2.40 (s, 3 H), 2.37–2.04 (m, 6 H), 1.68 (dtd, *J* = 12.5, 7.2, 6.4, 3.3 Hz, 1 H), 1.52 (dddd, *J* = 14.0, 11.4, 7.3, 4.1 Hz, 1 H), 1.34–1.18 (m, 6 H), 1.13 (m, 6 H), 0.90–0.80 (m, 9 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 143.3, 137.3, 129.6, 127.5, 57.2, 53.5, 51.1, 32.8, 28.7, 26.9, 22.9, 21.6, 20.7, 14.2, 14.2.

LRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{38}N_2O_2S$: 383.3; found: 383.3.

***N*-[1-(Cyclopentylamino)hexan-2-yl]-4-methylbenzenesulfonamide (3af)**

Yield: 28 mg, 83%, clear brown oil.

R_f = 0.3 (DCM/MeOH 95:5).

IR ($CDCl_3$): 3278, 2953, 2930, 2862, 1598, 1454, 1325, 1157, 1092, 905, 814, 723 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 8.1 Hz, 1 H), 7.28 (d, *J* = 8.1 Hz, 1 H), 3.16 (p, *J* = 6.4 Hz, 1 H), 2.85 (p, *J* = 6.5 Hz, 1 H), 2.49 (s, 1 H), 2.48 (s, 1 H), 2.41 (s, 2 H), 1.76–1.55 (m, 2 H), 1.53–1.33 (m, 2 H), 1.23–1.09 (m, 3 H), 0.79 (t, *J* = 6.9 Hz, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 143.3, 138.0, 129.7, 127.3, 59.6, 53.5, 50.9, 33.3, 33.0, 32.9, 27.7, 24.0, 23.9, 22.6, 21.6, 14.0.

LRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{31}N_2O_2S$: 339.2; found: 339.2.

4-Methyl-*N*-[1-(pentylamino)hexan-2-yl]benzenesulfonamide (3ag)

Yield: 20 mg, 59%, beige solid; mp 59–63 °C.

R_f = 0.2 (DCM/MeOH 95:5).

IR ($CDCl_3$): 3278, 2955, 2926, 2857, 1459, 1326, 1159, 1093, 814, 664 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 8.3 Hz, 2 H), 7.28 (d, *J* = 8.0 Hz, 2 H), 3.20–3.10 (m, 1 H), 2.49–2.45 (m, 2 H), 2.42 (s, 3 H), 2.40–2.26 (m, 2 H), 1.52–1.37 (m, 2 H), 1.36–1.26 (m, 4 H), 1.24–1.12 (m, 6 H), 0.89 (t, *J* = 7.2 Hz, 3 H), 0.81 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 143.3, 138.0, 129.7, 127.3, 53.3, 52.4, 49.8, 33.4, 29.9, 29.5, 27.6, 22.7, 22.6, 21.6, 14.2, 14.0.

LRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{31}N_2O_2S$: 341.2; found: 341.2.

4-Methyl-*N*-[1-(phenylamino)hexan-2-yl]benzenesulfonamide (3ah)

Yield: 23.0 mg, 66%, 5.0:1 *rr*, yellow oil.

R_f = 0.30 (EtOAc/hexane 1:4).

IR ($CDCl_3$): 3400, 3280, 2954, 2930, 2861, 1602, 1508, 1322, 1157, 1091, 749, 665, 550 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ (major isomer) = 7.80–7.76 (m, 2 H), 7.31–7.26 (m, 2 H), 7.18–7.13 (m, 2 H), 6.76–6.69 (m, 1 H), 6.52–6.46 (m, 2 H), 4.84 (d, *J* = 7.9 Hz, 1 H), 3.45–3.36 (m, 1 H), 3.17 (dd, *J* = 12.9, 4.7 Hz, 1 H), 3.06 (dd, *J* = 12.9, 7.3 Hz, 1 H), 2.44 (s, 3 H), 1.55–1.47 (m, 1 H), 1.45–1.38 (m, 1 H), 1.22–1.06 (m, 4 H), 0.79 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ (major isomer) = 147.7, 143.5, 137.6, 129.7, 129.2, 127.2, 117.7, 112.9, 53.5, 48.1, 33.3, 27.6, 22.4, 21.5, 13.8.

LRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{27}N_2O_2S$: 347.2; found: 347.1.

***N*-{1-[(4-Methoxyphenyl)amino]hexan-2-yl}-4-methylbenzenesulfonamide (3ai)**

Yield: 22.0 mg, 58%, 7.0:1 *rr*, yellow oil.

R_f = 0.77 (EtOAc/hexane 1:1).

IR ($CDCl_3$): 3278, 2953 2930, 2860, 1512, 1463, 1322, 1236, 1157, 1091, 1037, 903, 817, 725, 664 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ (major isomer) = 7.76–7.72 (m, 2 H), 7.28–7.24 (m, 2 H), 6.78–6.70 (m, 2 H), 6.46–6.41 (m, 2 H), 4.79 (d, *J* = 7.8 Hz, 1 H), 3.74 (s, 4 H), 3.40–3.32 (m, 1 H), 3.09 (dd, *J* = 12.8, 4.6 Hz, 1 H), 2.97 (dd, *J* = 12.8, 7.2 Hz, 1 H), 2.42 (s, 3 H), 1.53–1.33 (m, 2 H), 1.28–1.20 (m, 1 H), 1.20–1.02 (m, 4 H), 0.77 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ (major isomer) = 152.5, 144.4, 142.0, 137.8, 129.8, 127.3, 114.9, 113.8, 55.9, 52.8, 50.1, 35.1, 27.7, 22.5, 20.2, 12.3.

LRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{29}N_2O_3S$: 377.2; found: 377.2.

N-(1-Cyclohexyl-3-morpholinopropan-2-yl)-4-methylbenzenesulfonamide (3ba)

Yield: 26 mg, 71%, colorless oil.

R_f = 0.30 (EtOAc/hexane 6:4).

IR ($CDCl_3$): 3273, 2921, 2851, 1598, 1448, 1327, 1160, 1117, 1072, 1009, 815 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 8.2 Hz, 2 H), 7.30 (d, *J* = 8.0 Hz, 2 H), 5.21 (bs, 1 H), 3.54–3.45 (m, 4 H), 3.15 (ddt, *J* = 9.9, 8.1, 5.1 Hz, 1 H), 2.42 (s, 3 H), 2.29 (dd, *J* = 12.7, 5.0 Hz, 1 H), 2.22–2.15 (m, 3 H), 2.07 (m, 2 H), 1.76–1.48 (m, 4 H), 1.34–1.07 (m, 5 H), 0.95–0.79 (m, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 143.5, 137.2, 129.7, 127.4, 66.9, 61.9, 53.5, 48.1, 41.7, 34.0, 34.0, 33.1, 29.8, 26.5, 26.2, 21.6.

LRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{33}N_2O_3S$: 381.2; found: 381.2.

N-[(1-Adamantan-2-yl)-3-morpholinopropan-2-yl]-4-methylbenzenesulfonamide (3ca)

Yield: 34 mg, 79%, colorless oil.

R_f = 0.4 (EtOAc/hexane 6:4).

IR ($CDCl_3$): 3270, 2904, 2851, 1452, 1402, 1329, 1160, 1116, 1092, 906, 727 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 8.1 Hz, 2 H), 7.29 (d, *J* = 8.1 Hz, 2 H), 3.51 (t, *J* = 4.7 Hz, 4 H), 3.10 (ddt, *J* = 9.8, 8.2, 5.0 Hz, 1 H), 2.41 (s, 3 H), 2.30 (dd, *J* = 12.7, 5.1 Hz, 1 H), 2.26–2.15 (m, 3 H), 2.10 (dt, *J* = 11.2, 4.6 Hz, 2 H), 2.01 (ddd, *J* = 13.7, 8.3, 4.9 Hz, 1 H), 1.91 (dd, *J* = 12.6, 2.8 Hz, 1 H), 1.79 (tdt, *J* = 14.5, 5.4, 3.0 Hz, 5 H), 1.70 (d, *J* = 3.3 Hz, 2 H), 1.66–1.41 (m, 9 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 143.5, 137.2, 129.7, 127.4, 66.9, 61.8, 53.5, 48.7, 40.4, 39.2, 38.3, 37.1, 32.8, 31.6, 31.6, 31.5, 28.2, 28.0, 21.6.

LRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{37}N_2O_3S$: 433.3; found: 433.3.

4-Methyl-N-(1-morpholino-3-phenylpropan-2-yl)benzenesulfonamide (3da)

Yield: 16.4 mg, 44%, yellow oil.

R_f = 0.36 (EtOAc/hexane 1:1).

IR ($CDCl_3$): 3261, 3060, 3027, 2922, 2854, 2814, 1598, 1453, 1332, 1160, 1115, 1089, 702, 665, 551 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.86–7.74 (m, 2 H), 7.33–7.29 (m, 2 H), 7.28–7.23 (m, 2 H), 7.23–7.18 (m, 1 H), 7.17–7.11 (m, 2 H), 3.51–3.40 (m, 4 H), 3.34–3.24 (m, 1 H), 3.17 (dd, *J* = 13.7, 3.8 Hz, 1 H), 2.79 (dd, *J* = 13.7, 8.1 Hz, 1 H), 2.42 (s, 3 H), 2.24–2.13 (m, 2 H), 2.13–2.02 (m, 2 H), 2.02–1.92 (m, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 143.67, 137.06, 136.76, 129.83, 129.80, 128.53, 127.39, 126.70, 66.80, 60.39, 53.15, 50.95, 39.72, 21.64.

LRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{27}N_2O_3S$: 375.2; found: 375.2.

N-{6-[(*tert*-Butyldiphenylsilyl)oxy]-1-morpholinohexan-2-yl}-4-methylbenzenesulfonamide (3ea)

Yield: 47.1 mg, 79%, colorless oil.

R_f = 0.40 (EtOAc/hexane 2:3).

IR ($CDCl_3$): 3267, 2930, 2857, 1427, 1330, 1160, 1109, 1093, 816, 703, 550, 504 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.81–7.75 (m, 2 H), 7.72–7.64 (m, 4 H), 7.48–7.37 (m, 6 H), 7.33–7.26 (m, 2 H), 5.28 (s, 1 H), 3.70–3.59 (m, 2 H), 3.58–3.47 (m, 4 H), 3.11 (qd, *J* = 7.4, 4.1 Hz, 1 H), 2.42 (s, 3 H), 2.25 (d, *J* = 7.3 Hz, 2 H), 2.22–2.14 (m, 2 H), 2.14–2.05 (m, 2 H), 1.77–1.68 (m, 1 H), 1.60–1.48 (m, 3 H), 1.41–1.27 (m, 2 H), 1.07 (s, 9 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 143.4, 137.0, 135.6, 134.0, 129.6, 127.6, 127.2, 66.7, 63.6, 60.9, 53.2, 49.9, 33.0, 32.5, 26.9, 21.5, 21.0, 19.3.

LRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{33}H_{47}N_2O_4SSi$: 595.3; found: 595.3.

Ethyl6-[(4-Methylphenyl)sulfonamido]-7-morpholinoheptanoate (3fa)

Yield: 32.5 mg, 79%, yellow oil.

R_f = 0.43 (DCM/MeOH 19:1).

IR ($CDCl_3$): 3268, 2930, 2858, 1729, 1329, 1302, 1158, 1116, 1092, 666, 551 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 8.3 Hz, 2 H), 7.30 (d, *J* = 8.0 Hz, 2 H), 4.12 (q, *J* = 7.1 Hz, 2 H), 3.50 (dt, *J* = 12.3, 6.1 Hz, 4 H), 3.09 (qd, *J* = 7.1, 4.6 Hz, 1 H), 2.42 (s, 3 H), 2.29–2.21 (m, 4 H), 2.11 (m, 4 H), 1.74–1.50 (m, 4 H), 1.35 (m, 1 H), 1.25 (t, *J* = 7.1 Hz, 3 H), 1.21 (m, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 173.6, 143.5, 137.0, 129.7, 127.3, 66.7, 60.9, 60.3, 53.3, 49.7, 34.1, 32.9, 24.9, 24.1, 21.6, 14.3.

LRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{32}N_2O_5S$: 413.2; found: 413.2.

N-[6-(1,3-Dioxoisoindolin-2-yl)-1-morpholinohexan-2-yl]-4-methylbenzenesulfonamide (3ga)

Yield: 42.0 mg, 86%, yellow oil.

Rf = 0.25 (EtOAc/hexane 2:1).

IR ($CDCl_3$): 3274, 2938, 2859, 2814, 1708, 1397, 1331, 1159, 1116, 721 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88–7.83 (m, 2 H), 7.79–7.71 (m, 4 H), 7.32–7.27 (m, 2 H), 5.13 (brs, 1 H), 3.70–3.60 (m, 2 H), 3.56–3.46 (m, 4 H), 3.17–3.08 (m, 1 H), 2.42 (s, 3 H), 2.28–2.14 (m, 4 H), 2.14–2.05 (m, 2 H), 1.76–1.67 (m, 1 H), 1.66–1.56 (m, 3 H), 1.40–1.20 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.4, 143.4, 137.1, 133.9, 132.1, 129.6, 127.2, 123.2, 66.7, 61.0, 53.2, 49.7, 37.6, 32.6, 28.5, 21.8, 21.5.

LRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{32}N_3O_5S$: 486.2; found: 486.1.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690756.

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