

Supporting Information

Cu(II)-Mediated N-H and N-alkyl Aryl Amination and Olefin Aziridination

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General Methods and Materials

Proton and carbon nuclear magnetic resonance (^1H and ^{13}C NMR) spectra were obtained on a Varian 400 spectrometer at 400 MHz and 101 MHz, respectively, or on a Varian 500 at 500 MHz and 126 MHz, respectively, in CDCl_3 , unless otherwise stated. The ^1H NMR chemical shifts were measured relative to CDCl_3 as the internal reference (CDCl_3 : $\delta = 7.26$ ppm), unless otherwise stated. The ^{13}C NMR chemical shifts were given using CDCl_3 as the internal reference (CDCl_3 : $\delta = 77.00$ ppm). ^1H NMR data are reported as: chemical shift (ppm), multiplicity (s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, app q = apparent quartet, qn = quintet, m = multiplet), and coupling constant (Hz). High resolution mass spectra (HRMS) were obtained using a TripleTOF[®]6600 Quadrupole mass spectrometer. Melting points were measured using an OptiMelt from Stanford Research Systems and are uncorrected. Analytical thin layer chromatography (TLC) used EMD Chemicals TLC silica gel 60 F254 plates (0.040-0.063 mm) with visualization by UV light and/or KMnO_4 , phosphomolybdic acid (PMA) and/or ninhydrin solution(s) followed by heating. Chromatographic purifications utilized preparative thin layer chromatography (PTLC) or flash chromatography using pre-packed SiO_2 columns on a medium pressure automated chromatograph. Unless otherwise noted, yields refer to isolated, purified material with spectral data consistent with assigned structures or, if known, data were in agreement with literature values. All reactions were conducted under an argon atmosphere in oven-dried glassware with magnetic stirring, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification. Reaction solvents were purified via passage through activated, neutral alumina columns and stored under argon. $\text{CsOH} \cdot \text{H}_2\text{O}$, pyridine, $\text{Cu}(\text{OTf})_2$ were purchased from Sigma Aldrich, CuCl_2 was purchased from Strem Chemicals, and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) was purchased from Oakwood Chemicals and used without purification.

Preparation of Aminating Agents

i. Hydroxylamine-O-sulfonic acid: Hydroxylamine-O-sulfonic acid (HOSA) was purchased from Sigma Aldrich (97%) and used without purification.

ii. N-Cyclohexylhydroxylamine-O-sulfonic acid: By modification of literature procedure,¹ *N*-cyclohexylhydroxylamine hydrochloride (500 mg, 3.297 mmol) was dried under high vacuum for 1 h, cooled to rt, then dissolved in dry, degassed DCM (15 mL) under an argon atmosphere. The reaction mixture was cooled to -78°C , then ClSO_3H (328 μL , 4.945 mmol) in 41 μL aliquots was added every 15 minutes over 2 h. After 15 min, the reaction mixture was warmed to room temperature over 30 min. Dry, degassed Et_2O (10 mL) was added slowly, and the resultant solid was collected via filtration under an argon atmosphere. The collected solid was washed with Et_2O (3×5 mL) to obtain a fluffy white solid (480 mg, 74%), m.p. $141\text{--}142^\circ\text{C}$ (dec) that was stored under argon at -20°C . ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 3.30–3.22 (m, 1H), 2.04–1.91 (m, 2H),

1.81–1.68 (m, 2H), 1.64–1.53 (m, 1H), 1.39–1.17 (m, 4H), 1.14–0.99 (m, 1H); ^{13}C NMR (101 MHz, DMSO- d_6) δ 59.55, 26.83, 25.16, 24.01. HRMS (ESI $^+$) Calcd. for $\text{C}_6\text{H}_{12}\text{NO}_4\text{S}$ [$\text{M}-\text{H}$] $^-$ 194.0487, Found 194.0506.

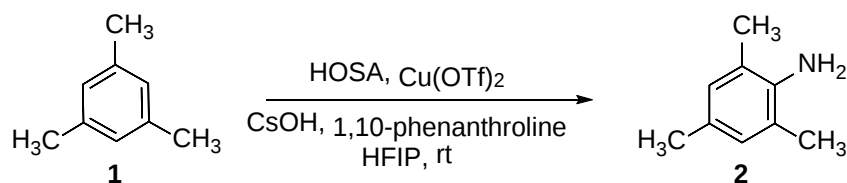
ii. ***O*-Mesitylenesulfonyl-*N*-*tert*-butoxycarbonyl-*N*-methylhydroxylamine:** *O*-Mesitylenesulfonyl-*N*-*tert*-butoxycarbonyl-*N*-methylhydroxylamine (Mes-*O*-NHMe) was prepared according to procedure described by Tamura² and stored under argon at -20 °C.

General Procedure for Arene C-H Amination

A mixture of $\text{Cu}(\text{OTf})_2$ (10 mol%) and 1,10-phenanthroline (10 mol%) in 1,1,1,3,3,3-hexafluoroisopropanol (2-3 mL) was stirred at rt. After 30 min, the greenish solution was cooled to 0 °C and arene (0.4-0.5 mmol), HOSA or other aminating reagent (1.5 equiv) and $\text{CsOH}\cdot\text{H}_2\text{O}$ (1.5 equiv) were added sequentially. After complete consumption of the arene (1-12 h, monitored by TLC), the reaction mixture was diluted with CH_2Cl_2 (10 mL), washed with saturated aqueous Na_2CO_3 (10 mL), brine (10 mL), dried over anhydrous Na_2SO_4 , and concentrated in *vacuo*. The crude residue was purified on a commercial pre-packed SiO_2 column using a medium pressure, automated chromatograph equipped with a UV detector and eluted with EtOAc/hexanes to furnish aminated arene in the indicated yield. Variations in reaction conditions are noted in the table legend for select substrates.

Arene Amination Experimental and Analytical Data

Table 1: Entry 3

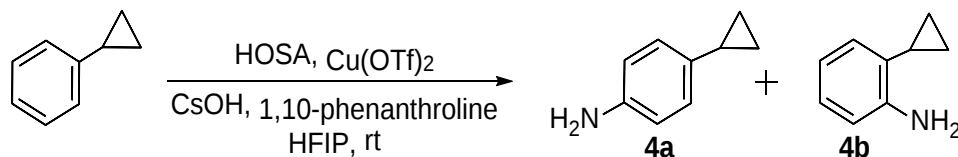


Following the general arene amination procedure, mesitylene (**1**), (50 mg, 0.416 mmol), $\text{Cu}(\text{OTf})_2$ (14.8 mg, 0.041 mmol), $\text{CsOH}\cdot\text{H}_2\text{O}$ (104 mg, 0.624 mmol), 1,10-phenanthroline (7.3 mg, 0.041 mmol) and HOSA (70 mg, 0.624 mmol) were stirred at rt in HFIP (2 mL) for 6 h. Chromatographic purification of the crude product afforded 2,4,6-trimethylaniline (**2**) (42 mg, 75%) as an oil whose spectral data were in agreement with literature values.³ TLC: $R_f \approx 0.4$ (10% EtOAc/hexanes).

5 mmol Scale: A mixture of $\text{Cu}(\text{OTf})_2$ (180 mg, 0.5 mmol) and 1,10-phenanthroline (90 mg, 0.5 mmol) in 1,1,1,3,3,3-hexafluoroisopropanol (24 mL) was stirred at rt. After 30 min, the greenish solution was cooled to 0 °C and mesitylene (600 mg, 5.0 mmol), HOSA (847 mg, 7.5 mmol) and $\text{CsOH}\cdot\text{H}_2\text{O}$ (1.26 g, 7.5 mmol) were added sequentially. After complete consumption of the mesitylene (4 h, monitored by TLC), the reaction mixture was diluted with CH_2Cl_2 (30 mL) and saturated aqueous Na_2CO_3 (40 mL). The resultant two layers were separated and the aqueous layer was further extracted with CH_2Cl_2 (3 $\times$ 30 mL). The combined organic extracts were dried over Na_2SO_4 , filtered and concentrated in *vacuo*. The crude residue was purified on a commercial pre-

packed SiO₂ column using a medium pressure, automated chromatograph equipped with a UV detector and eluted with EtOAc/hexanes to furnish the 2,4,6-trimethylaniline (**2**) (479 mg, 71%) as an oil whose spectral data were in agreement with literature values.³ TLC: R_f ≈ 0.4 (10% EtOAc/hexanes).

Table 2: 4a/b

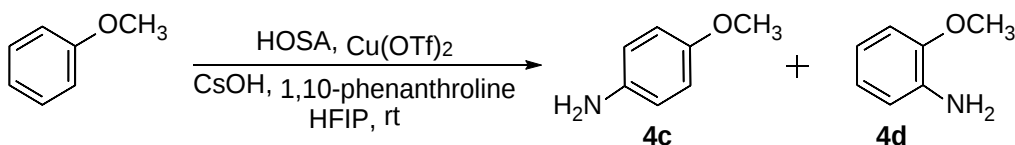


Following the general amination procedure, cyclopropyl benzene (50 mg, 0.424 mmol), Cu(OTf)₂ (15.3 mg, 0.042 mmol), CsOH·H₂O (106 mg, 0.635 mmol), 1,10-phenanthroline (7.6 mg, 0.042 mmol), and HOSA (72 mg, 0.635 mmol) were stirred at rt in HFIP (2 mL) for 6 h. Chromatographic purification of the crude product afforded **4a** (27 mg) and **4b** (9 mg) (36 mg total, 65% combined yield) as oils whose spectral data were in agreement with literature values.

4-Cyclopropylaniline (**4a**)⁴: TLC: R_f ≈ 0.4 (20% EtOAc/hexanes).

2-Cyclopropylaniline (**4b**)⁵: TLC: R_f ≈ 0.6 (20% EtOAc/hexanes).

Table 2: 4c/d

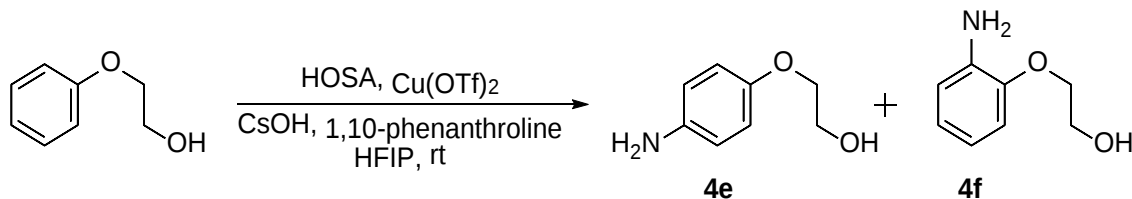


Following the general arene amination procedure, anisole (50 mg, 0.463 mmol), Cu(OTf)₂ (16.7 mg, 0.046 mmol), CsOH·H₂O (116 mg, 0.694 mmol), 1,10-phenanthroline (8.3 mg, 0.046 mmol), and HOSA (78 mg, 0.693 mmol) were stirred at rt in HFIP (2 mL) for 6 h. Chromatographic purification of the crude product afforded **4c** (13 mg) and **4d** (23 mg) (36 mg total, 63% combined yield) as oils whose spectral data were in agreement with literature values.

4-Methoxyaniline (**4c**)⁶: TLC: R_f ≈ 0.4 (30% EtOAc/hexanes).

2-Methoxyaniline (**4d**)⁶: TLC: R_f ≈ 0.6 (30% EtOAc/hexanes).

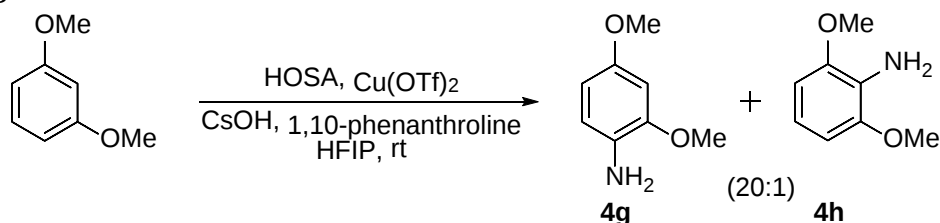
Table 2: 4e/f



Following the general amination procedure, 2-phenoxyethan-1-ol (50 mg, 0.362 mmol), Cu(OTf)₂ (13 mg, 0.036 mmol), CsOH·H₂O (91 mg, 0.543 mmol), 1,10-phenanthroline (6.5 mg, 0.036

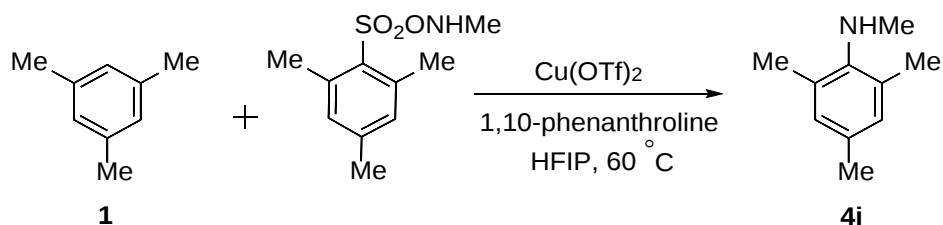
mmol), and HOSA (61 mg, 0.543 mmol) were stirred at rt in HFIP (2 mL) for 12 h. Chromatographic purification of the crude product afforded **4e** (11 mg) and **4f** (27 mg) (38 mg total, 69% combined yield) as solids, whose spectral data were in agreement with literature values. 2-(4-Aminophenoxy)ethan-1-ol (**4e**)⁷: m.p. 72-73 °C. TLC: $R_f \approx 0.4$ (90% EtOAc/hexanes). 2-(2-Aminophenoxy)ethan-1-ol (**4f**)⁸: m.p. 91-92 °C. TLC: $R_f \approx 0.4$ (90% EtOAc/hexanes).

Table 2: 4g/h



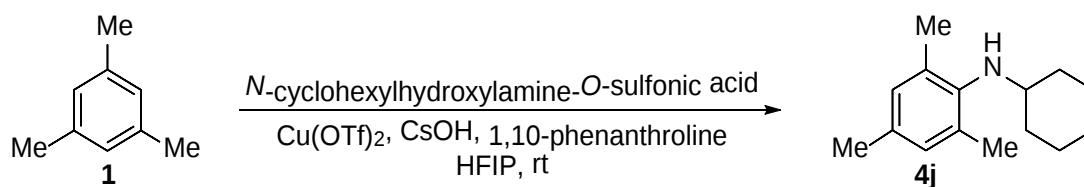
Following the general amination procedure, 1,3-dimethoxybenzene (50 mg, 0.362 mmol), Cu(OTf)₂ (12.9 mg, 0.036 mmol), CsOH·H₂O (91 mg, 0.543 mmol), 1,10-phenanthroline (6.4 mg, 0.036 mmol) and HOSA (61 mg, 0.543 mmol) were stirred at rt in HFIP (1.5 mL) for 1 h. Chromatographic purification of the crude product afforded **4g** (35 mg) and **4h** (2 mg) (37 mg total, 68% combined yield) as solids, whose spectral data were in agreement with literature values. 2,4-Dimethoxyaniline (**4g**)⁹: m.p. 34-35 °C. TLC: $R_f \approx 0.6$ (20% EtOAc/hexanes). 2,6-Dimethoxyaniline (**4h**)¹⁰: m.p. 64-65 °C. TLC: $R_f \approx 0.4$ (20% EtOAc/hexanes).

Table 2: 4i



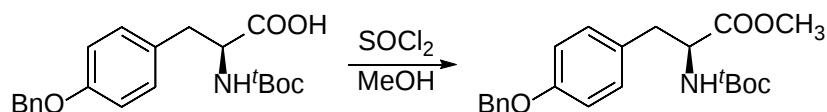
To a stirring, rt solution of Cu(OTf)₂ (14.8 mg, 0.041 mmol) in HFIP (2 mL) was added 1,10-phenanthroline (7.3 mg, 0.041 mmol). After 30 minutes, the greenish solution was cooled to 0 °C and mesitylene (**1**) (50 mg, 0.416 mmol), *O*-mesitylenesulfonyl-*N*-*tert*-butoxycarbonyl-*N*-methylhydroxylamine (Mes-*O*-NHMe) (133 mg, 0.625 mmol) were added. After stirring for 12 h at 60 °C, the reaction mixture was cooled to rt, then diluted with CH₂Cl₂ (5 mL) and washed with saturated aq. Na₂CO₃ (2 mL), brine (2 mL), dried over Na₂SO₄, and concentrated in *vacuo*. The crude residue was purified using a commercial pre-packed SiO₂ column on a medium pressure, automated chromatograph using 8% EtOAc/hexanes to give *N*,2,4,6-tetramethylaniline **4i** (44 mg, 71%) as an oil whose spectral data were in agreement with literature values.³

Table 2: 4j

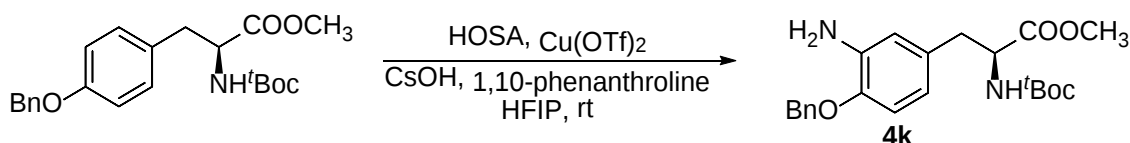


Following the general amination procedure, mesitylene (**1**) (50 mg, 0.417 mmol), Cu(OTf)₂ (14.8 mg, 0.042 mmol), CsOH·H₂O (105 mg, 0.625 mmol), 1,10-phenanthroline (7.5 mg, 0.042 mmol), and *N*-cyclohexylhydroxylamine-*O*-sulfonic acid (124 mg, 0.625 mmol) were stirred at rt in HFIP (2 mL) for 9 h. Chromatographic purification of the crude product afforded **4j** (67 mg, 74%) as an oil whose spectral data were in agreement with literature values.¹¹ TLC: R_f ≈ 0.3 (10% EtOAc/hexanes).

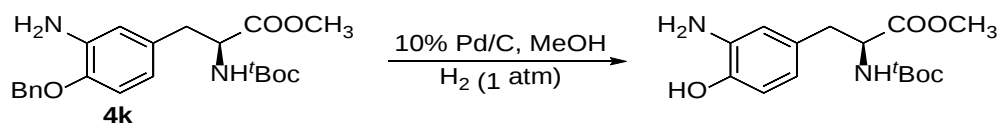
Table 2: 4k



Thionyl chloride (10 μ L) was added dropwise to a stirring, 0 °C solution of *t*-Boc-*O*-benzyl-L-tyrosine (200 mg, 0.538 mmol) in methanol (10 mL). The solution was warmed to rt and stirred for 2 h. The reaction mixture was concentrated in *vacuo* and the residue was purified using a commercial pre-packed SiO₂ column on a medium pressure, automated chromatograph using 20% EtOAc/hexanes to give methyl (S)-3-(4-(benzyloxy)phenyl)-2-((*tert*-butoxycarbonyl)amino)propanoate (185 mg, 89%) as a white solid, m.p. 53-54 °C, whose spectral data were in agreement with literature values.¹² TLC: R_f ≈ 0.5 (30% EtOAc/hexanes).

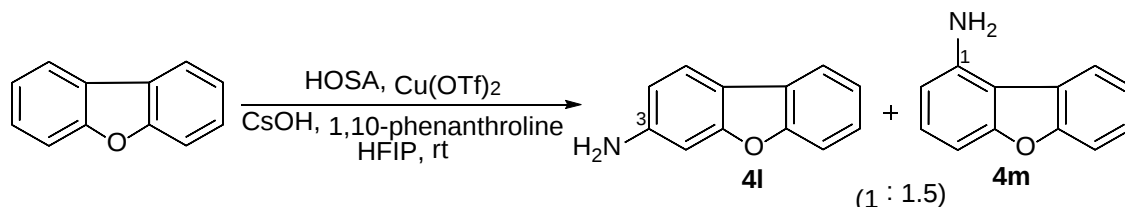


Following the general amination procedure, methyl (S)-3-(4-(benzyloxy)phenyl)-2-((*tert*-butoxycarbonyl)amino)propanoate (50 mg, 0.129 mmol), Cu(OTf)₂ (4.7 mg, 0.013 mmol), CsOH·H₂O (33 mg, 0.195 mmol), 1,10-phenanthroline (2.3 mg, 0.013 mmol), and HOSA (22 mg, 0.194 mmol) were stirred at rt in HFIP (1 mL) for 8 h. Chromatographic purification of the crude product afforded **4k** (33 mg, 64%) as an oil. TLC: R_f ≈ 0.4 (50% EtOAc/hexanes). ¹H NMR (400 MHz, CDCl₃) δ 7.51–7.27 (m, 5H), 6.76 (d, *J* = 8.1 Hz, 1H), 6.51 (s, 1H), 6.44 (d, *J* = 8.4 Hz, 1H), 5.05 (s, 2H), 5.00–4.91 (m, 1H), 4.56–4.47 (m, 1H), 3.71 (s, 3H), 2.99–2.89 (m, 2H), 1.42 (s, 9H); ¹³C NMR (101 MHz, CDCl₃) δ 172.57, 155.21, 145.59, 137.04, 136.37, 130.39, 128.54, 127.99, 127.54, 119.03, 115.96, 111.97, 79.88, 70.42, 54.46, 52.15, 37.59, 28.29. HRMS (ESI⁺) Calcd. for [C₂₂H₂₉N₂O₅+H]⁺ 401.2076, Found 401.2066.



10% Pd/C (5 mg) was carefully added to a solution of (S)-methyl 3-(3-amino-4-(benzyloxy)phenyl)-2-((*tert*-butoxycarbonyl)amino)propanoate (**4k**, 33 mg, 0.083 mmol) in EtOAc (3 mL) and the resulting suspension was stirred at rt under a hydrogen atmosphere (1 atm). After 24 h, the reaction mixture was filtered through a Celite™ pad, the filter cake was washed with EtOAc (5 mL), and the combined filtrates were concentrated in *vacuo*. The residue was purified using a commercial pre-packed SiO₂ column on a medium pressure, automated chromatograph using 30% EtOAc/hexanes to give (S)-methyl 3-(3-amino-4-hydroxyphenyl)-2-((*tert*-butoxycarbonyl)amino)propanoate as a viscous oil (21 mg, 85%) whose spectral data were in agreement with literature values.¹³ TLC: $R_f \approx 0.3$ (60% EtOAc/hexanes).

Table 2: 4l/m

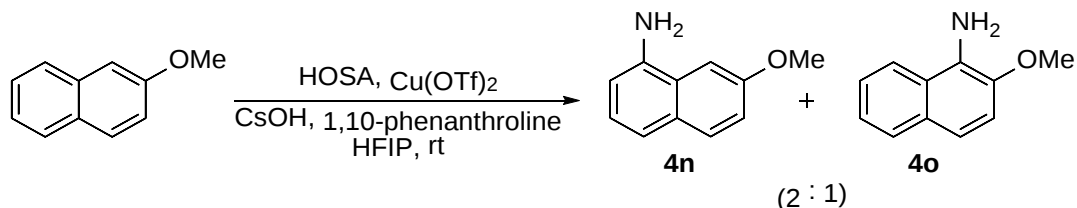


Following the general amination procedure, dibenzo[*b,d*]furan (100 mg, 0.592 mmol), Cu(OTf)₂ (21 mg, 0.059 mmol), CsOH·H₂O (150 mg, 0.893 mmol), 1,10-phenanthroline (10.7 mg, 0.059 mmol) and HOSA (101 mg, 0.893 mmol) were stirred at rt in HFIP (3 mL) for 6 h. Chromatographic purification of the crude product afforded **4l** (32 mg) as oil and **4m** (46 mg) as oil (78 mg total, 73% combined yield) whose spectral data were in agreement with literature values.

Dibenzo[*b,d*]furan-3-amine (**4l**)¹⁴: TLC: $R_f \approx 0.5$ (40% EtOAc/hexanes).

Dibenzo[*b,d*]furan-1-amine (**4m**)¹⁴: TLC: $R_f \approx 0.6$ (40% EtOAc/hexanes).

Table 2: 4n/o



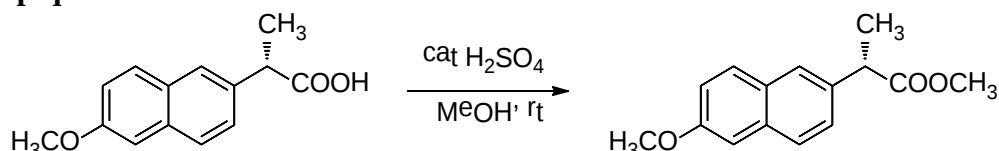
Following the general amination procedure, 2-methoxynaphthalene (50 mg, 0.316 mmol), Cu(OTf)₂ (11.1 mg, 0.031 mmol), CsOH·H₂O (79 mg, 0.474 mmol), 1,10-phenanthroline (5.5 mg, 0.031 mmol) and HOSA (53 mg, 0.474 mmol) were stirred at rt in HFIP (2 mL) for 6 h. Chromatographic purification of the crude product afforded **4n** (24 mg) as a solid and **4o** (11 mg) as an amorphous

solid (35 mg total, 65% combined yield) whose spectral data were in agreement with literature values.

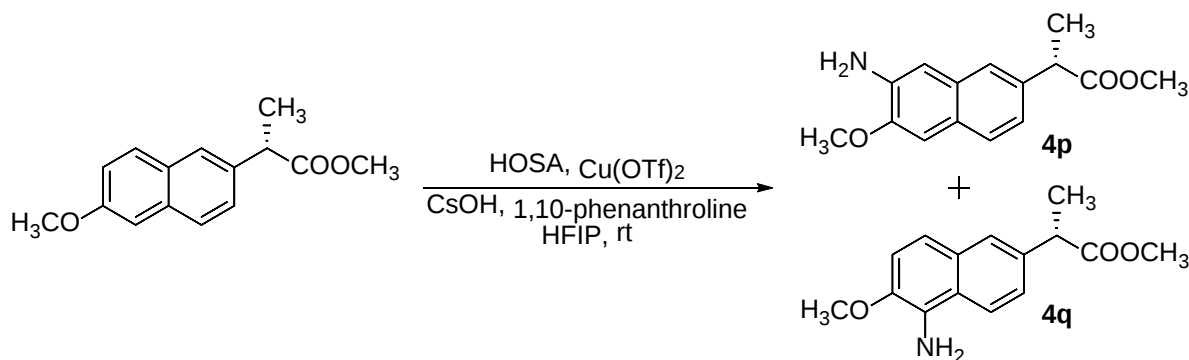
7-Methoxynaphthalene (**4n**)¹⁵: m.p. 134-135 °C. TLC: $R_f \approx 0.6$ (20% EtOAc/hexanes).

2-Methoxynaphthalene (**4o**)¹⁶: TLC: $R_f \approx 0.4$ (20% EtOAc/hexanes).

Table 2: 4p/q



To a solution of (S)-2-(6-methoxynaphthalen-2-yl)propanoic acid (naproxen, 0.5 g, 2.17 mmol) in methanol (15 mL) was added conc. H_2SO_4 (0.1 mL). After stirring 12h, the reaction mixture was diluted with CH_2Cl_2 (20 mL), washed successively with saturated aq. Na_2CO_3 (2 mL), brine (10 mL), dried over anhydrous Na_2SO_4 , and concentrated in *vacuo*. The crude residue was purified with a commercial pre-packed SiO_2 column on a medium pressure, automated chromatograph equipped with a UV detector using EtOAc/hexanes as eluent to furnish methyl (S)-2-(6-methoxynaphthalen-2-yl)propanoate (0.49 g, 88%) as a solid, m.p. 91-92 °C, whose spectral data were in agreement with literature values.⁶ TLC: $R_f \approx 0.5$ (30% EtOAc/hexanes).



Following the general amination procedure, methyl (S)-2-(6-methoxynaphthalen-2-yl) propanoate (50 mg, 0.205 mmol), $Cu(OTf)_2$ (7.3 mg, 0.021 mmol), $CsOH \cdot H_2O$ (52 mg, 0.307 mmol), 1,10-phenanthroline (3.6 mg, 0.021 mmol), and HOSA (34 mg, 0.307 mmol) were stirred at rt in HFIP (1 mL) for 90 minutes. Chromatographic purification of the crude product afforded **4p** (27 mg) and **4q** (14 mg) (41 mg total, 77% combined yield) as solids whose spectral data were in agreement with literature values.

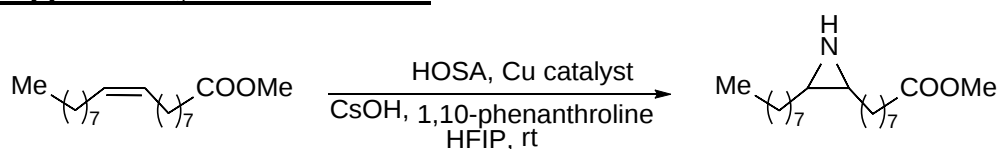
Methyl (S)-2-(7-amino-6-methoxynaphthalen-2-yl)propanoate (**4p**)⁶: m.p. 72-73 °C. TLC: $R_f \approx 0.4$ (40% EtOAc/hexanes).

Methyl (S)-2-(5-amino-6-methoxynaphthalen-2-yl)propanoate (**4q**)⁶: m.p. 96-97 °C. TLC: $R_f \approx 0.5$ (40% EtOAc/hexanes).

General Procedure for N-H/N-Alkyl Aziridination

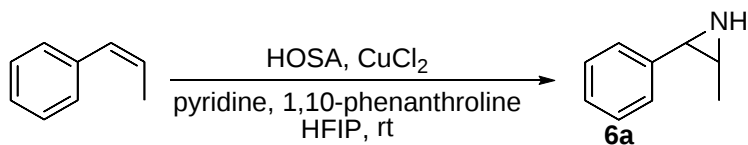
A mixture of CuCl₂ (10 mol%) and 1,10-phenanthroline (10 mol%) in 1,1,1,3,3,3-hexafluoroisopropanol (1-2 mL) was stirred at rt. After 30 min, the greenish solution was cooled to 0 °C and olefin (0.4-0.5 mmol), HOSA or other aminating reagent (1.5 equiv), and CsOH·H₂O (1.5 equiv) or pyridine (1.5 equiv) were added sequentially. After complete consumption of the olefin (1-40 h, monitored by TLC), the reaction mixture was diluted with CH₂Cl₂ (2 mL), washed with saturated aq. Na₂CO₃ (2 mL), brine (2 mL), dried over anhydrous Na₂SO₄, and concentrated in vacuo. The crude residue was purified on a commercial pre-packed SiO₂ column using a medium pressure, automated chromatograph equipped with a UV detector and eluted with EtOAc/hexanes or MeOH/CH₂Cl₂ to furnish aziridine in the indicated yield. Variations in reaction conditions are noted in the Table legend for select substrates.

Screen: Copper Catalyzed Aziridination



Entry	Catalyst	Time (h)	Yield (%)
1	Cu(OTf) ₂	24	50
2	CuCl₂	21	90
3	Cu(II)acetylacetonate	23	10
4	Cu(I)Cl	23	15
5	CuBr ₂	23	50
6	Cu(OAc) ₂	23	70
7	CuTC	23	5

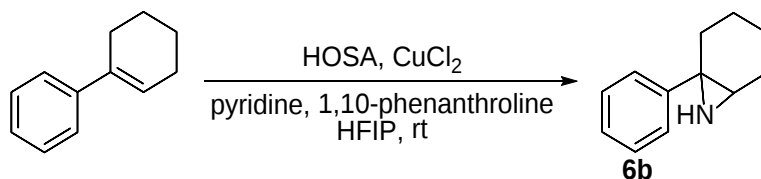
Table 3: 6a



Following the general aziridination procedure, (*Z*)-β-methylstyrene (50 mg, 0.423 mmol), CuCl₂ (5.6 mg, 0.042 mmol), pyridine (51 μL, 0.634 mmol), 1,10-phenanthroline (7.6 mg, 0.042 mmol), and HOSA (72 mg, 0.634 mmol) were stirred at rt in HFIP (2 mL) for 12 h. Chromatographic

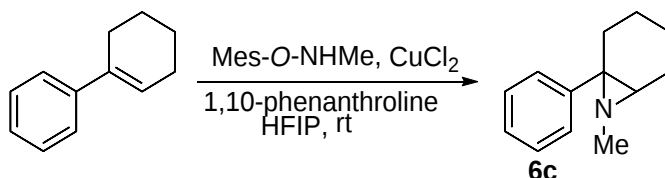
purification of the crude product afforded **6a** (41 mg, 74%) as an oil whose spectral data were in agreement with literature values.¹⁷ TLC: $R_f \approx 0.4$ (5% MeOH/CH₂Cl₂).

Table 3: 6b



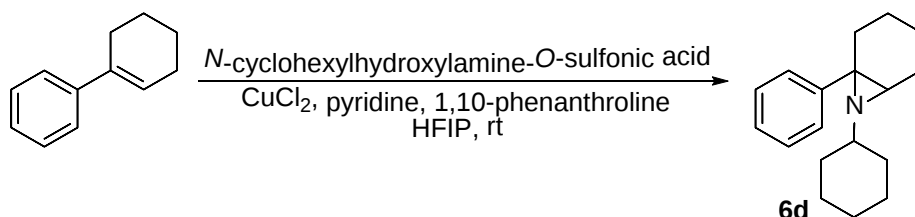
Following the general aziridination procedure, 2,3,4,5-tetrahydro-1,1'-biphenyl (50 mg, 0.316 mmol), CuCl₂ (4.2 mg, 0.032 mmol), pyridine (38 μ L, 0.474 mmol), 1,10-phenanthroline (5.7 mg, 0.032 mmol), and HOSA (53 mg, 0.474 mmol) were stirred at rt in HFIP (2 mL) for 1 h. Chromatographic purification of the crude product afforded **6b** (39 mg, 72%) as oil. TLC: $R_f \approx 0.4$ (5% MeOH/CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) δ 7.38–7.28 (m, 4H), 7.25–7.18 (m, 1H), 2.40–2.31 (m, 1H), 2.20–2.10 (m, 1H), 2.09–1.98 (m, 2H), 1.92–1.79 (m, 1H), 1.56–1.43 (m, 3H), 1.36–1.25 (m, 1H), 1.22–1.07 (m, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 128.35, 126.64, 126.22, 41.29, 38.13, 30.71, 24.62, 20.58, 20.40. HRMS (ESI⁺) Calcd. for [C₁₂H₁₅N+H]⁺ 174.1280, Found 174.1277.

Table 3: 6c



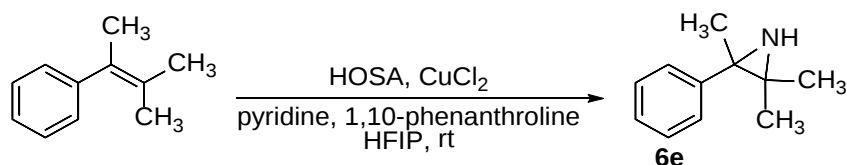
A mixture of CuCl₂ (4.2 mg, 0.032 mmol) and 1,10-phenanthroline (5.7 mg, 0.032 mmol) in 1,1,1,3,3,3-hexafluoroisopropanol (2 mL) was stirred at rt. After 30 min, the greenish solution was cooled to 0 °C and 2,3,4,5-tetrahydro-1,1'-biphenyl (50 mg, 0.316 mmol), Mes-O-NHMe (108 mg, 0.474 mmol) were added and stirred for 3 h at rt. The reaction mixture was then diluted with CH₂Cl₂ (5 mL), washed with saturated aq. Na₂CO₃ (2 mL), brine (2 mL), dried over Na₂SO₄, and concentrated in *vacuo*. The crude residue was purified using a commercial pre-packed SiO₂ column on a medium pressure, automated chromatograph using 4% MeOH/CH₂Cl₂ to obtain *N*-methylaziridine **6c** (50 mg, 84%) as a light yellow oil. TLC: $R_f \approx 0.3$ (5% MeOH/CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) δ 7.44–7.13 (m, 5H), 2.20–2.27 (m, 1H), 1.97 (s, 3H), 1.95–1.84 (m, 3H), 1.76–1.67 (m, 1H), 1.54–1.41 (m, 2H), 1.34–1.16 (m, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 141.02, 129.34, 128.09, 127.02, 47.44, 44.31, 41.98, 33.23, 24.52, 20.81, 20.72. HRMS (ESI⁺) Calcd. for [C₁₃H₁₇N+H]⁺ 188.1436, Found 188.1433.

Table 3: 6d



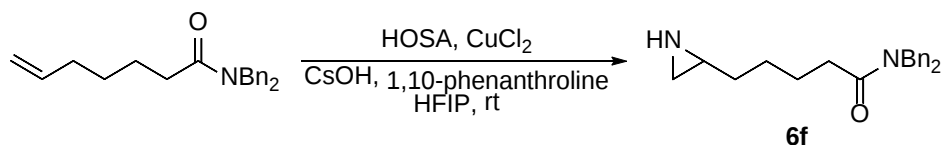
Following the general aziridination procedure, 2,3,4,5-tetrahydro-1,1'-biphenyl (50 mg, 0.316 mmol), CuCl₂ (4.2 mg, 0.032 mmol), pyridine (38 μ L, 0.474 mmol), 1,10-phenanthroline (5.7 mg, 0.032 mmol), and *N*-cyclohexylhydroxylamine-*O*-sulfonic acid (94 mg, 0.474 mmol) were stirred at rt in HFIP (2 mL) for 2 h. Chromatographic purification of the crude product afforded **6d** (62 mg, 78%) as an oil. TLC: $R_f \approx 0.3$ (5% MeOH/CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) δ 7.42–7.18 (m, 5H), 2.42–2.29 (m, 1H), 2.22–2.14 (m, 1H), 2.01–1.90 (m, 1H), 1.88–1.75 (m, 2H), 1.73–1.39 (m, 7H), 1.39–0.94 (m, 7H), 0.82–0.67 (m, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 141.08, 129.51, 127.66, 126.84, 60.45, 47.51, 39.42, 33.55, 32.86, 32.53, 26.02, 25.34, 24.86, 24.32, 20.88, 20.73. HRMS (ESI⁺) Calcd. for [C₁₈H₂₅N+H]⁺ 256.2065, Found 256.2059.

Table 3: 6e

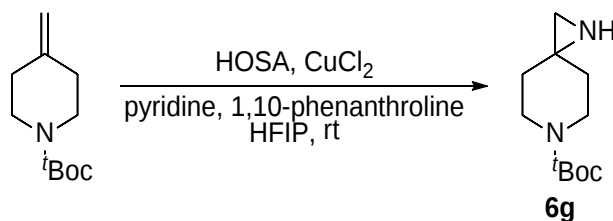


Following the general aziridination procedure, trimethylstyrene (50 mg, 0.342 mmol), CuCl₂ (4.6 mg, 0.034 mmol), pyridine (41 μ L, 0.514 mmol), 1,10-phenanthroline (6.2 mg, 0.034 mmol), and HOSA (58 mg, 0.514 mmol) were stirred at rt in HFIP (2 mL) for 4 h. Chromatographic purification of the crude product afforded **6e** (33 mg, 60%) as an oil whose spectral data were in agreement with literature values.¹⁷ TLC: $R_f \approx 0.5$ (10% MeOH/CH₂Cl₂).

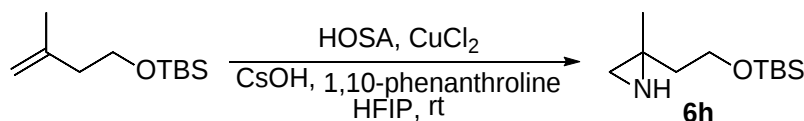
Table 3: 6f



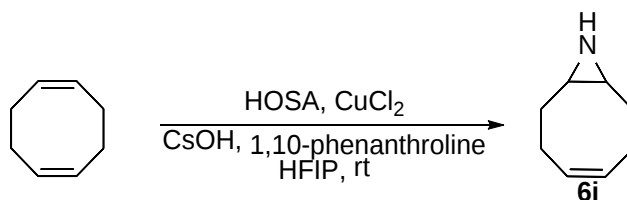
Following the general aziridination procedure, *N,N*-dibenzylhept-6-enamide¹⁸ (50 mg, 0.162 mmol), CuCl₂ (2.1 mg, 0.016 mmol), CsOH·H₂O (40 mg, 0.244 mmol), 1,10-phenanthroline (2.8 mg, 0.016 mmol) and HOSA (27 mg, 0.244 mmol) were stirred at rt in HFIP (1 mL) for 24 h. Chromatographic purification of the crude product afforded **6f** (41 mg, 80%) as an oil, TLC: $R_f \approx 0.4$ (10% MeOH/CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 7.41–7.23 (m, 6H), 7.21–7.12 (m, 4H), 4.59 (s, 2H), 4.43 (s, 2H), 2.42 (t, $J = 7.5$ Hz, 2H), 1.93–1.90 (m, 1H), 1.83–1.67 (m, 3H), 1.56–1.32 (m, 4H), 1.30 (d, $J = 3.5$ Hz, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 173.54, 137.56, 136.65, 129.03, 128.66, 128.34, 127.67, 127.45, 126.40, 49.97, 48.23, 34.22, 33.24, 33.16, 30.20, 27.44, 25.23, 25.20. HRMS (ESI⁺) Calcd. for [C₂₁H₂₆N₂O+H]⁺ 323.2137, Found 323.2117.

Table 3: 6g

Following the general aziridination procedure, *tert*-butyl 4-methylenepiperidine-1-carboxylate (50 mg, 0.254 mmol), CuCl₂ (3.4 mg, 0.025 mmol), pyridine (31 μ L, 0.381 mmol), 1,10-phenanthroline (4.5 mg, 0.025 mmol), and HOSA (43 mg, 0.381 mmol) were stirred at rt in HFIP (1.5 mL) for 24 h. Chromatographic purification of the crude product afforded **6g** (36 mg, 66%) as an oil whose spectral data were in agreement with literature values.¹⁹ TLC: $R_f \approx 0.5$ (10% MeOH/CH₂Cl₂).

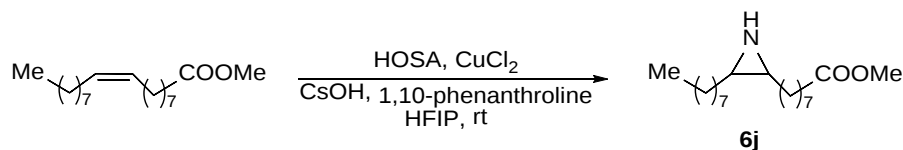
Table 3: 6h

Following the general amination procedure, *tert*-butyldimethyl(3-methylbut-3-en-1-yloxy)silane (50 mg, 0.250 mmol), CuCl₂ (3.3 mg, 0.025 mmol), CsOH·H₂O (63 mg, 0.375 mmol), 1,10-phenanthroline (4.5 mg, 0.025 mmol) and HOSA (42 mg, 0.375 mmol) were stirred at rt in HFIP (1.2 mL) for 24 h. Chromatographic purification of the crude product afforded **6h** (32 mg, 61% yield) as an oil whose spectral data were in agreement with literature values.¹⁹ TLC: $R_f \approx 0.5$ (5% MeOH/CH₂Cl₂).

Table 3: 6i

Following the general aziridination procedure, (1Z,5Z)-cycloocta-1,5-diene (50 mg, 0.462 mmol), CuCl₂ (6.2 mg, 0.046 mmol), CsOH·H₂O (116 mg, 0.693 mmol), 1,10-phenanthroline (8.3 mg, 0.046 mmol), and HOSA (78 mg, 0.693 mmol) were stirred at rt in HFIP (2 mL) for 12 h. Chromatographic purification of the crude product afforded **6i** (44 mg, 77%) as an oil whose spectral data were in agreement with literature values.¹⁹ TLC: $R_f \approx 0.5$ (10% MeOH/CH₂Cl₂).

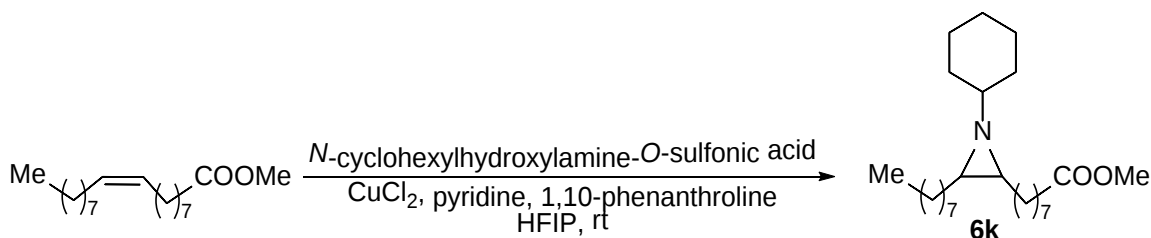
Table 3: 6j



Following the general aziridination procedure, methyl oleate (50 mg, 0.169 mmol), CuCl₂ (2.2 mg, 0.016 mmol), CsOH·H₂O (42 mg, 0.254 mmol), 1,10-phenanthroline (3.1 mg, 0.016 mmol), and HOSA (29 mg, 0.253 mmol) were stirred at rt in HFIP (2 mL) for 21 h. Chromatographic purification of the crude product afforded **6j** (47 mg, 90%) as an oil whose spectral data were in agreement with literature values.¹⁷ TLC: R_f ≈ 0.6 (10% MeOH/CH₂Cl₂).

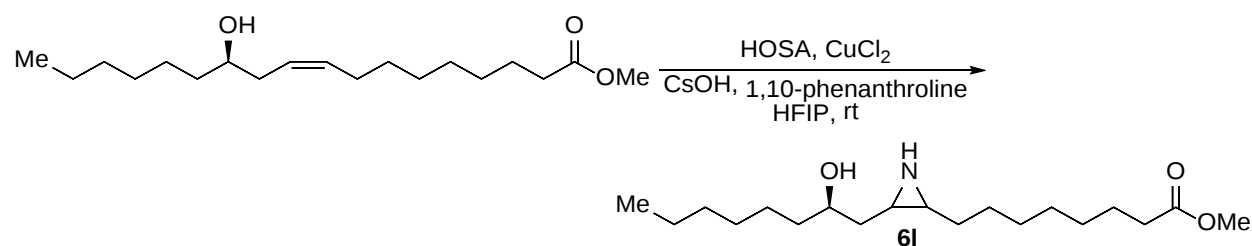
5 mmol Scale: A mixture of CuCl₂ (68 mg, 0.5 mmol) and 1,10-phenanthroline (91 mg, 0.5 mmol) in 1,1,1,3,3,3-hexafluoroisopropanol (24 mL) was stirred at rt. After 30 min, the greenish solution was cooled to 0 °C and methyl oleate (1.5 g, 5.0 mmol), HOSA (858 mg, 7.6 mmol) and CsOH·H₂O (1.27 g, 7.6 mmol) were added sequentially. After complete consumption of the methyl oleate (22 h, monitored by TLC), the reaction mixture was diluted with CH₂Cl₂ (30 mL) and saturated aqueous Na₂CO₃ (40 mL). The resultant two layers were separated and the aqueous layer was further extracted with CH₂Cl₂ (3 × 30 mL). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated in *vacuo*. The crude residue was purified on a commercial pre-packed SiO₂ column using a medium pressure, automated chromatograph equipped with a UV detector and eluted with EtOAc/hexanes to furnish the aziridine compound (**6j**) (1.28 g, 82%) as an oil whose spectral data were in agreement with literature values.¹⁷ TLC: R_f ≈ 0.6 (10% MeOH/CH₂Cl₂).

Table 3: 6k



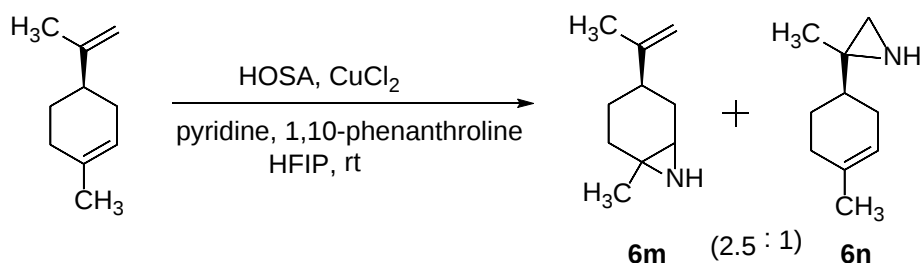
Following the general aziridination procedure, methyl oleate (50 mg, 0.169 mmol), CuCl₂ (2.2 mg, 0.016 mmol), pyridine (20 μL, 0.254 mmol), 1,10-phenanthroline (3.1 mg, 0.016 mmol), and *N*-cyclohexylhydroxylamine-*O*-sulfonic acid (50 mg, 0.254 mmol) were stirred at rt in HFIP (2 mL) for 23 h. Chromatographic purification of the crude product afforded **6k** (44 mg, 74%) as an oil. TLC: R_f ≈ 0.6 (10% MeOH/CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) δ 3.65 (s, 3H), 2.28 (t, *J* = 7.6 Hz, 2H), 1.82–1.68 (m, 4H), 1.64–1.55 (m, 3H), 1.51–1.19 (m, 28H), 1.16–1.00 (m, 4H), 0.89–0.82 (m, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 174.27, 69.16, 51.40, 43.14, 43.08, 34.06, 32.75, 31.85, 29.71, 29.59, 29.50, 29.27, 29.22, 29.08, 28.50, 28.46, 28.20, 28.13, 26.04, 25.13, 24.91, 22.65, 14.09. HRMS (ESI⁺) Calcd. for [C₂₅H₄₇NO₂+H]⁺ 394.3679, Found 394.3701.

Table 3: 6l

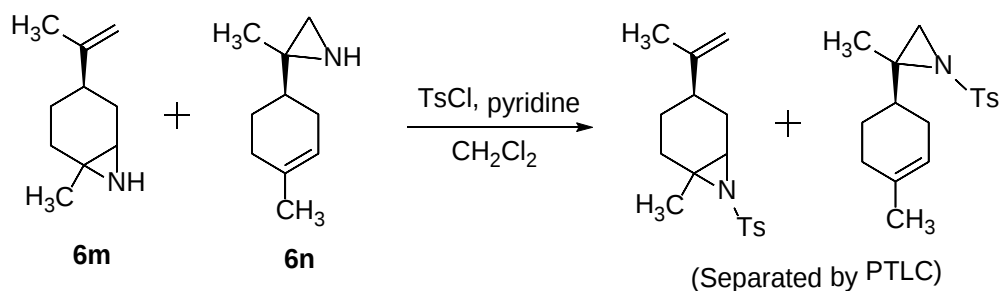


Following the general aziridination procedure, methyl ricinoleate (50 mg, 0.160 mmol), CuCl₂ (2.1 mg, 0.016 mmol), CsOH·H₂O (40 mg, 0.240 mmol), 1,10-phenanthroline (2.8 mg, 0.016 mmol) and HOSA (27 mg, 0.240 mmol) were stirred at rt in HFIP (1 mL) for 24 h. Chromatographic purification of the crude product afforded **6l** (39 mg, 75% combined yield) as a 1:1 mixture of diastereomers whose spectral data were in agreement with literature values.¹⁷ TLC: R_f ≈ 0.5 (10% MeOH/CH₂Cl₂).

Table 3: 6m/n



Following the general aziridination procedure, (*R*)-(+)-limonene (50 mg, 0.367 mmol), CuCl₂ (4.9 mg, 0.037 mmol), pyridine (38 μL, 0.477 mmol), 1,10-phenanthroline (6.5 mg, 0.036 mmol), and HOSA (54 mg, 0.477 mmol) were stirred at rt in HFIP (2 mL) for 8 h. Chromatographic purification of the crude product afforded a 2.5 : 1 mixture of **6m** and **6n** (42 mg, 76% combined yield), each as 1:1 diastereomers and as viscous oils, whose spectral data were in agreement with literature values.¹⁷ TLC: R_f ≈ 0.5 (10% MeOH/CH₂Cl₂). These aziridines were converted to the *N*-tosylation for additional characterization.

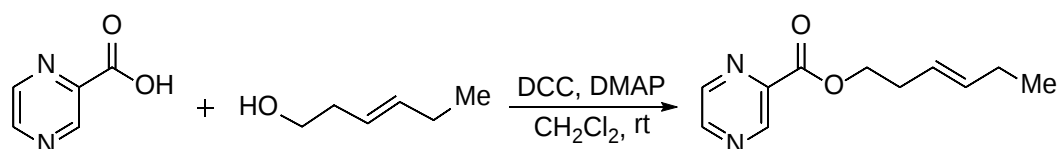


p-Toluenesulfonyl chloride (58 mg, 0.309 mmol) and pyridine (31 μL, 0.387 mmol) were added sequentially to a stirring, 0 °C solution of the above mixture of aziridines (40 mg, 0.258 mmol) in dry CH₂Cl₂ (5 mL). After 18 h, all volatiles were evaporated and the crude product was purified by preparative TLC (2% EtOAc/toluene, 3 elutions) to obtain (4*R*)-1-methyl-4-(prop-1-en-2-yl)-7-tosyl-7-azabicyclo[4.1.0]heptane (55 mg), whose spectral data were in agreement with literature

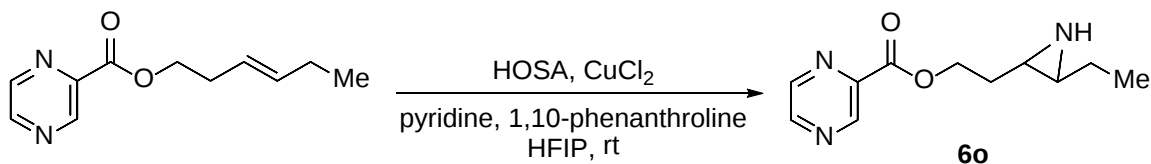
values,²⁰ and (*R*)-2-methyl-2-((*R*)-4-methylcyclohex-3-en-1-yl)-1-tosylaziridine (22 mg, total 95% combined yield) as viscous oils. TLC: $R_f \approx 0.5$ (4% EtOAc/toluene).

(*R*)-2-methyl-2-((*R*)-4-methylcyclohex-3-en-1-yl)-1-tosylaziridin: ^1H NMR (400 MHz, CDCl_3) δ 7.82 (d, $J = 8.1$ Hz, 2H), 7.30 (d, $J = 8.2$ Hz, 2H), 5.35 (dd, $J = 5.9, 3.2$ Hz, 1H), 2.60 (s, 1H), 2.43 (s, 3H), 2.24 (s, 1H), 2.05–1.75 (m, 5H), 1.68–1.59 (m, 6H), 1.48–1.33 (m, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ 143.65, 143.63, 138.09, 134.13, 133.63, 129.41, 129.39, 127.32, 119.95, 119.54, 53.74, 53.49, 41.51, 41.49, 40.71, 40.46, 30.38, 30.13, 27.34, 27.20, 25.18, 25.05, 23.39, 23.34, 21.58, 15.15, 14.98. HRMS (ESI^+) Calcd. for $[\text{C}_{17}\text{H}_{23}\text{NO}_2\text{S}+\text{H}]^+$ 306.1522, Found 306.1521.

Table 3: 6o



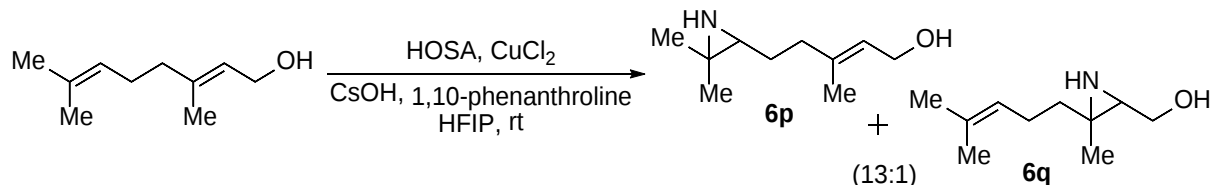
To a solution of pyrazine-2-carboxylic acid (500 mg, 4.032 mmol), DMAP (49.1 mg, 0.403 mmol) and (*E*)-hex-3-en-1-ol (403 mg, 4.032 mmol) at 0 °C in DCM (5 mL) was added DCC (996 mg, 4.838 mmol). The reaction was warmed to rt. After stirring overnight, the reaction mixture was washed with water (2×10 mL) and extracted with DCM (3×10 mL). The combined organic extracts were dried over Na_2SO_4 , filtered and concentrated in *vacuo*. The residue was purified using a commercial pre-packed SiO_2 column on a medium pressure, automated chromatograph using 30% EtOAc/hexanes to give (*E*)-hex-3-en-1-yl pyrazine-2-carboxylate as a viscous oil (700 mg, 84%). TLC: $R_f \approx 0.4$ (50% EtOAc/hexanes); ^1H NMR (400 MHz, CDCl_3) δ 9.23 (s, 1H), 8.73–8.62 (m, 2H), 5.62–5.49 (m, 1H), 5.42–5.31 (m, 1H), 4.38 (t, $J = 7.0$ Hz, 2H), 2.45 (q, $J = 6.9$ Hz, 2H), 1.94 (p, $J = 7.2$ Hz, 2H), 0.88 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 163.93, 147.69, 146.37, 144.57, 143.67, 135.85, 123.50, 77.48, 77.37, 77.16, 76.84, 65.97, 32.04, 25.73, 13.79. HRMS (ESI^+) Calcd. for $[\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}_2+\text{H}]^+$ 207.1128, Found 207.1128.



Following the general aziridination, the above (*E*)-hex-3-en-1-yl pyrazine-2-carboxylate (50 mg, 0.242 mmol), CuCl_2 (3.2 mg, 0.024 mmol), pyridine (29.3 μL , 0.363 mmol), 1,10-phenanthroline (4.3 mg, 0.024 mmol), and HOSA (41 mg, 0.363 mmol) were stirred at rt in HFIP (1.2 mL). After 24 h, chromatographic purification of the crude product afforded **6o** (37 mg, 71% yield) as an oil. TLC: $R_f \approx 0.4$ (10% MeOH/ CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3) δ 9.31 (d, $J = 1.2$ Hz, 1H), 8.75 (dd, $J = 13.1, 1.9$ Hz, 2H), 4.57 (t, $J = 6.2$ Hz, 2H), 2.04–1.91 (m, 1H), 1.90–1.76 (m, 2H), 1.75–1.68 (m, 1H), 1.49–1.35 (m, 2H), 0.97 (t, $J = 7.4$ Hz, 3H), 0.92–0.80 (br s, 1H); ^{13}C NMR (101

MHz, CDCl₃) δ 164.02, 147.80, 146.39, 144.60, 143.54, 77.48, 77.16, 76.84, 64.86, 39.24, 34.26, 33.36, 27.43, 11.75. HRMS (ESI⁺) Calcd. for [C₁₁H₁₅N₃O₃+H]⁺ 222.1247, Found 222.1237.

Table 3: 6p/q

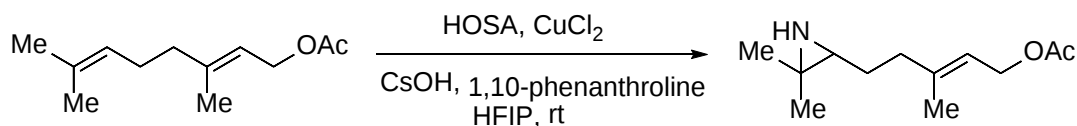


Following the general aziridination procedure, geraniol (50 mg, 0.324 mmol), CuCl₂ (4.3 mg, 0.032 mmol), CsOH·H₂O (81 mg, 0.487 mmol), 1,10-phenanthroline (5.7 mg, 0.032 mmol) and HOSA (55 mg, 0.487 mmol) were stirred at rt in HFIP (1.5 mL) for 14 h. Chromatographic purification of the crude product afforded a 13:1 mixture of **6p** (38 mg) and **6q** (3 mg) (41 mg total, 76% combined yield) as oils whose spectral data were in agreement with literature values.¹⁷

5-(3,3-Dimethylaziridin-2-yl)-3-methylpent-2(*E*)-en-1-ol (**6p**): TLC $R_f \approx 0.3$ (20% MeOH/CH₂Cl₂).

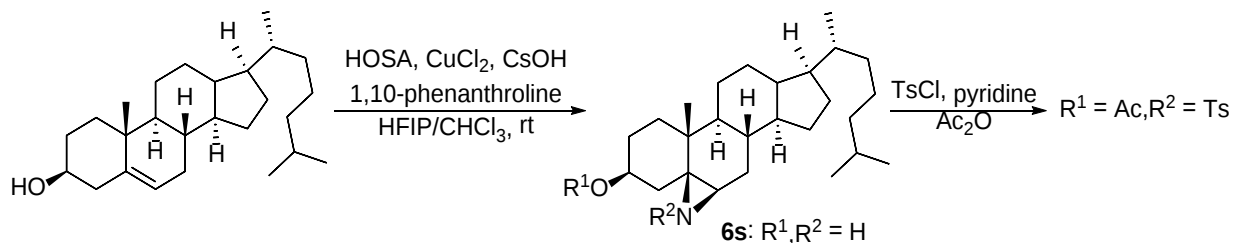
3-Methyl-3-(4-methylpent-3-en-1-yl)aziridin-2 (*E*)-ylmethanol (**6q**): TLC: $R_f \approx 0.4$ (20% MeOH/CH₂Cl₂).

Table 3: 6r



Following the general aziridination procedure, geranyl acetate (50 mg, 0.255 mmol), CuCl₂ (3.4 mg, 0.025 mmol), CsOH·H₂O (64 mg, 0.382 mmol), 1,10-phenanthroline (4.5 mg, 0.025 mmol) and HOSA (43 mg, 0.382 mmol) were stirred at rt in HFIP (1.2 mL) for 14 h. Chromatographic purification of the crude product afforded **6r** (37 mg, 71% yield) as an oil whose spectral data were in agreement with literature values.¹⁷ TLC: $R_f \approx 0.6$ (10% MeOH/CH₂Cl₂).

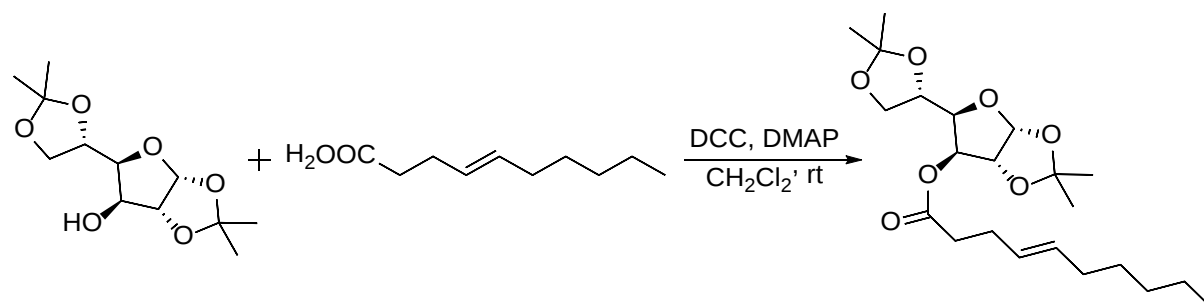
Table 3: 6s



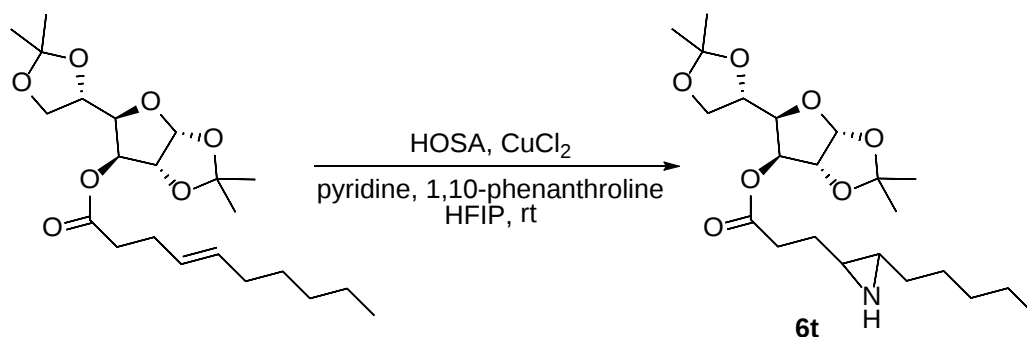
Following the general aziridination procedure, cholesterol (50 mg, 0.129 mmol), CuCl₂ (1.7 mg, 0.013 mmol), CsOH·H₂O (33 mg, 0.194 mmol), 1,10-phenanthroline (2.3 mg, 0.013 mmol), and HOSA (22 mg, 0.194 mmol) were stirred at rt in HFIP/CHCl₃ (2 mL, 1:1) for 40 h. For identification, crude **6s** (41 mg, 0.102 mmol) was *O*-acetylated and *N*-tosylated following literature

procedure.²¹ The residue was purified using a commercial pre-packed SiO₂ column on a medium pressure, automated chromatograph using 10% EtOAc/hexanes as eluent to furnish the title compound as a white solid (56 mg, 73%) whose spectral data were in agreement with literature values,¹⁷ TLC: R_f ≈ 0.6 (20% EtOAc/hexanes).

Table 3: 6t



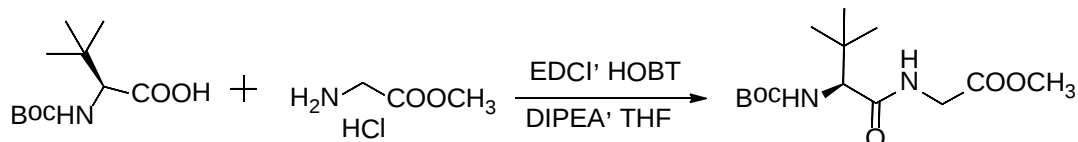
DCC (257 mg, 1.25 mmol) was added to a 0 °C solution of (*E*)-dec-4-enoic acid (163 mg, 0.962 mmol), DMAP (11.7 mg, 0.096 mmol) and diacetone D-glucose (250 mg, 0.962 mmol) in CH₂Cl₂ (10 mL). After stirring at rt overnight, the reaction mixture was washed with water (2 × 10 mL) and the aqueous washed were back extracted with CH₂Cl₂ (3 × 10 mL). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated in *vacuo*. The residue was purified using a commercial pre-packed SiO₂ column on a medium pressure, automated chromatograph using 15% EtOAc/hexanes to give (*E*)-(3*aR*,5*R*,6*S*,6*aR*)-5-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-6-yl dec-4-enoate as a viscous oil (240 mg, 61%). TLC: R_f ≈ 0.5 (20% EtOAc/hexanes). ¹H NMR (400 MHz, CDCl₃) δ 5.82 (d, *J* = 3.6 Hz, 1H), 5.50–5.29 (m, 2H), 5.21 (d, *J* = 2.2 Hz, 1H), 4.43 (d, *J* = 3.7 Hz, 1H), 4.18 (t, *J* = 3.8 Hz, 2H), 4.07–3.95 (m, 2H), 2.41–2.34 (m, 2H), 2.32–2.25 (m, 2H), 1.97–1.89 (m, 2H), 1.48 (s, 3H), 1.37 (s, 3H), 1.31–1.17 (m, 12H), 0.84 (t, *J* = 6.8 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 171.66, 132.08, 127.39, 112.14, 109.19, 104.94, 83.26, 79.68, 75.86, 72.33, 67.11, 34.23, 32.39, 31.27, 29.03, 27.77, 26.74, 26.63, 26.09, 25.17, 22.41, 13.96. HRMS (ESI⁺) Calcd. for [C₂₂H₃₇O₇+H]⁺ 413.2539, Found 413.2533.



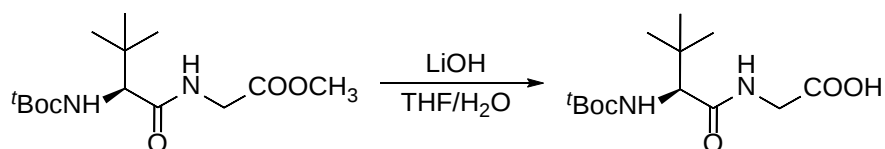
Following the general aziridination procedure, the above (*E*)-(3*aR*,5*R*,6*S*,6*aR*)-5-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-6-yl dec-4-enoate (50 mg, 0.121 mmol), CuCl₂ (1.6 mg, 0.012 mmol), pyridine (19 μL, 0.243 mmol), 1,10-phenanthroline (2.2 mg, 0.012 mmol), and HOSA (18 mg, 0.158 mmol) were stirred at rt in HFIP (1 mL) for 10 h. Chromatographic purification of the crude product afforded **6t** (40 mg, 77%) as

an oil. TLC: $R_f \approx 0.5$ (10% MeOH/ CH_2Cl_2). ^1H NMR (400 MHz, CDCl_3) δ 5.85 (dt, $J = 3.6, 1.7$ Hz, 1H), 5.24 (t, $J = 1.8$ Hz, 1H), 4.51–4.45 (m, 1H), 4.22–4.16 (m, 2H), 4.10–3.98 (m, 2H), 2.48 (t, $J = 6.9$ Hz, 2H), 1.87–1.76 (m, 1H), 1.72–1.56 (m, 3H), 1.50 (s, 3H), 1.46–1.35 (m, 7H), 1.32–1.23 (m, 12H), 0.88 (t, $J = 6.2$ Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 171.85, 171.77, 112.25, 112.23, 109.32, 109.30, 105.01, 83.28, 79.74, 79.72, 76.06, 72.38, 72.34, 67.26, 67.24, 37.95, 37.88, 36.51, 36.41, 34.35, 34.26, 32.19, 31.59, 31.57, 29.07, 27.32, 27.31, 26.84, 26.69, 26.16, 25.28, 25.26, 22.58, 14.00. HRMS (ESI^+) Calcd. for $[\text{C}_{22}\text{H}_{37}\text{NO}_7+\text{H}]^+$ 428.2642, Found 428.2648.

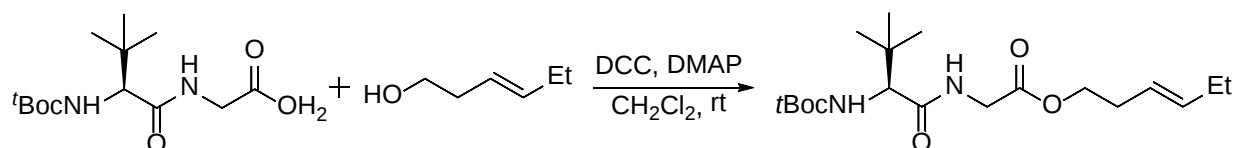
Table 3: 6u



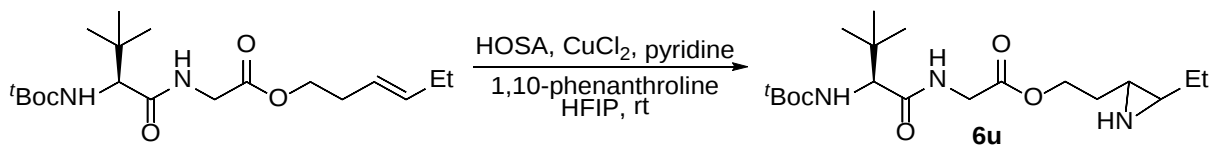
A mixture of *tert*-Boc-*L*-*tert*-leucine (500 mg, 2.161 mmol), glycine methyl ester hydrochloride (298 mg, 2.378 mmol), EDCI (455 mg, 2.378 mmol), HOBT (321 mg, 2.378 mmol), and DIPEA (1.13 mL, 6.485 mmol) in CH_2Cl_2 (15 mL) was stirred at 0 °C for 1 h, then warmed to room temperature for overnight. Water (15 mL) was added and the two layers were separated. The resulting aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were dried over Na_2SO_4 , filtered and concentrated in *vacuo*. The residue was purified using a commercial, pre-packed SiO_2 column on a medium pressure, automated chromatograph using 30% EtOAc/hexanes to give methyl(S)-(2-((*tert*-butoxycarbonyl)amino)-3,3-dimethylbutanoyl)glycinate as a viscous oil (580 mg, 89%) whose spectral data were in agreement with literature values.²² TLC: $R_f \approx 0.4$ (50% EtOAc/hexanes).



LiOH (65 mg, 2.732 mmol) was added portionwise to a 0 °C solution of the above methyl (S)-(2-((*tert*-butoxycarbonyl)amino)-3,3-dimethylbutanoyl)glycinate (550 mg, 1.821 mmol) in THF/ H_2O (1:2, 15 mL). After 3 h, the reaction mixture was acidified with 10% aqueous HCl and extracted with EtOAc (3×15 mL). The combined organic extracts were dried over Na_2SO_4 , filtered and concentrated in *vacuo*. The residue was purified using a commercial pre-packed SiO_2 column on a medium pressure, automated chromatograph using 80% EtOAc/hexanes to give (S)-(2-((*tert*-butoxycarbonyl)amino)-3,3-dimethylbutanoyl)glycine as a viscous oil (490 mg, 94%). TLC: $R_f \approx 0.4$ (100% EtOAc). ^1H NMR (400 MHz, CDCl_3) δ 7.07 (s, 1H), 5.53 (d, $J = 9.2$ Hz, 1H), 4.37 (d, $J = 9.8$ Hz, 1H), 4.15–3.96 (m, 2H), 1.41 (s, 9H), 0.99 (s, 9H); ^{13}C NMR (101 MHz, CDCl_3) δ 171.82, 171.11, 156.54, 80.68, 61.33, 41.35, 34.75, 28.29, 26.34. HRMS (ESI^+) Calcd. for $[\text{C}_{13}\text{H}_{24}\text{N}_2\text{O}_5+\text{H}]^+$ 289.1767, Found 289.1758.

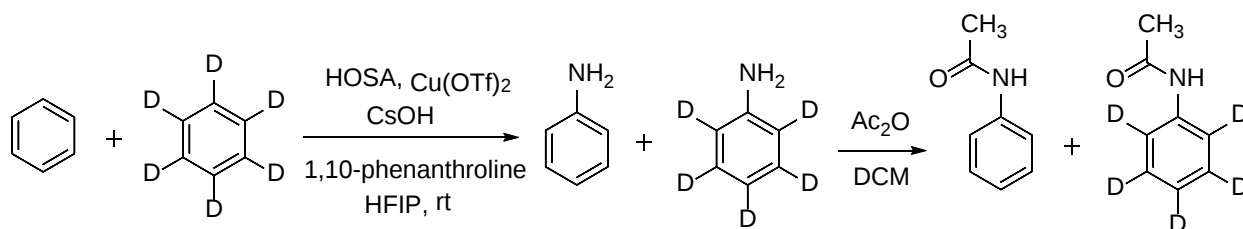


DCC (232 mg, 1.129 mmol) was added to a 0 °C solution of (*E*)-hex-3-en-1-ol (109 μ L, 0.955 mmol), DMAP (10 mg, 0.087 mmol) and (*S*)-(2-((*tert*-butoxycarbonyl)amino)-3,3-dimethylbutanoyl)glycine (250 mg, 0.868 mmol) in CH_2Cl_2 (10 mL). After stirring at rt overnight, the mixture was washed with water (2×10 mL) and the aqueous extracts back extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were dried over Na_2SO_4 , filtered, and concentrated in *vacuo*. The residue was purified using a commercial pre-packed SiO_2 column on a medium pressure, automated chromatograph using 20% EtOAc/hexanes to give (*E*)-hex-3-en-1-yl (*S*)-(2-((*tert*-butoxycarbonyl)amino)-3,3-dimethylbutanoyl)glycinate as a viscous oil (310 mg, 96%). TLC: $R_f \approx 0.4$ (50% EtOAc/hexanes). ^1H NMR (400 MHz, CDCl_3) δ 7.08–6.95 (m, 1H), 5.57–5.45 (m, 1H), 5.38 (d, $J = 9.5$ Hz, 1H), 5.33–5.22 (m, 1H), 4.20–4.11 (m, 1H), 4.07 (t, $J = 7.0$ Hz, 2H), 3.97 (d, $J = 9.5$ Hz, 1H), 3.84–3.71 (m, 1H), 2.32–2.19 (m, 2H), 2.01–1.87 (m, 2H), 1.36 (s, 9H), 0.98 (s, 8H), 0.91 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 171.22, 169.54, 155.74, 135.22, 123.44, 79.43, 64.89, 61.90, 40.99, 34.50, 31.66, 28.19, 26.39, 25.46, 13.56. HRMS (ESI⁺) Calcd. for $[\text{C}_{19}\text{H}_{34}\text{N}_2\text{O}_5 + \text{H}]^+$ 371.2539, Found 371.2540.



Following the general aziridination procedure, the above (*S,E*)-non-3-en-1-yl 2-(2-((*tert*-butoxycarbonyl)amino)-3,3-dimethylbutanamido)acetate (50 mg, 0.135 mmol), CuCl_2 (1.8 mg, 0.013 mmol), pyridine (16 μ L, 0.203 mmol), 1,10-phenanthroline (2.4 mg, 0.013 mmol), and HOSA (23 mg, 0.203 mmol) were stirred at rt in HFIP (1.5 mL) for 21 h. Chromatographic purification of the crude product afforded **6u** (44 mg, 86%) as an oil. TLC: $R_f \approx 0.5$ (10% MeOH/ CH_2Cl_2). ^1H NMR (400 MHz, CDCl_3) δ 6.90 (s, 1H), 5.34 (d, $J = 8.6$ Hz, 1H), 4.22 (t, $J = 5.8$ Hz, 2H), 4.18–4.08 (m, 1H), 3.93 (d, $J = 9.5$ Hz, 1H), 3.89–3.78 (m, 1H), 1.80–1.55 (m, 4H), 1.49–1.27 (m, 12H), 0.99–0.92 (m, 13H); ^{13}C NMR (101 MHz, CDCl_3) δ 171.19, 169.53, 155.70, 79.50, 63.75, 63.73, 61.98, 41.06, 38.97, 34.51, 34.07, 32.97, 28.22, 27.18, 26.43, 11.54. HRMS (ESI⁺) Calcd. for $[\text{C}_{19}\text{H}_{35}\text{N}_3\text{O}_5 + \text{H}]^+$ 386.2655, Found 386.2648.

KIE: Competitive Intermolecular Amination between Benzene and Benzene-*d*₆ (Scheme 1)



Following the general amination procedure, benzene (500 mg, 6.40 mmol), benzene-*d*₆ (538 mg, 6.40 mmol), Cu(OTf)₂ (23 mg, 0.064 mmol), CsOH·H₂O (107 mg, 0.640 mmol), 1,10-phenanthroline (11.5 mg, 0.064 mmol), and HOSA (72 mg, 0.640 mmol) were stirred at rt in HFIP (2 mL). After 9 h, the reaction mixture was diluted with CH₂Cl₂ (10 mL), washed with saturated aqueous Na₂CO₃ (10 mL), brine (10 mL), dried over anhydrous Na₂SO₄, and concentrated in *vacuo*. To the crude mixture dissolved in dichloromethane (3 mL), was added Ac₂O (0.6 mL, 6.40 mmol) and the mixture was stirred overnight until full conversion was obtained as verified by TLC. The reaction mixture was then diluted with saturated aqueous NaHCO₃ (5 mL) and extracted with dichloromethane (3 × 5 mL). The combined organic layers were dried over anhydrous Na₂SO₄, and concentrated in *vacuo*. The crude residue was purified on a commercial pre-packed SiO₂ column using a medium pressure, automated chromatograph equipped with a UV detector and eluted with 30% EtOAc/hexanes to furnish desired products as a mixture of *N*-phenylacetamide/*N*-phenylacetamide-*d*₆ = 1.0/1.0. The ratio of the two products was determined by integration of the ¹H NMR spectrum, i.e., integration of the aromatic signals (m signals at 7.55–7.45 ppm, 7.35–7.24 ppm, 7.16–7.05 ppm) and compared with the integrated signal of –NHCOCH₃ (s signal at 2.16 ppm). Spectral data were in agreement with literature values.¹⁴ ¹H NMR (400 MHz, CDCl₃) δ 7.64 (br s, 2H), 7.55–7.45 (m, 2H), 7.35–7.24 (m, 2H), 7.16–7.05 (m, 1H), 2.16 (s, 6H); ¹³C NMR (101 MHz, CDCl₃) δ 168.54, 137.88, 128.91, 124.24, 119.92, 24.51.

References

1. A. E. Strom, J. F. Hartwig, *J. Org. Chem.* **2013**, 78, 8909–8914.
2. Y. Tamura, H. Ikeda, I. Morita, H. Tsubouchi, M. Ikeda, *Chem. Pharm. Bull.* **1982**, 30, 1221–1224.
3. M. P. Paudyal, A. M. Adebesein, S. R. Burt, D. H. Ess, Z. Ma, L. Kurti, J. R. Falck, *Science* **2014**, 343, 61–65.
4. S. S. Mochalov, R. A. Gazzaeva, A. Z. Kadzhaeva, A. N. Fedotov, E. V. Trofimova, *Chem. Heterocycl. Compd.* **2012**, 47, 1415–1429.
5. A. Nuria, F. J. Carles, T. Emma, C. G. Elena, S. S. Jordi, PCT Int. Appl., 2013149997, 10 Oct **2013**.
6. J. Liu, K. Wu, T. Shen, Y. Liang, M. Zou, Y. Zhu, X. Li, L. Xinyao, N. Jiao, *Chem. Eur. J.* **2017**, 23, 563–567.
7. L. Ding, M. Xu, J. Wang, Y. Liao, J. Qiu, *Polymer* **2014**, 55, 1681–1687.
8. L. Fumagalli, C. Bolchi, S. Colleoni, M. Gobbi, B. Moroni, M. Pallavicini, A. Pedretti, L.

- Villa, G. Vistolia, E. Valotia, *Bioorg. Med. Chem.* **2005**, *13*, 2547–2559.
9. A. Maiti, P. V. N. Reddy, M. Sturdy, L. Marler, S. D. Pegan, A. D. Mesecar, J. M. Pezzuto, M. Cushman, *J. Med. Chem.* **2009**, *52*, 7, 1873–1884.
10. N. Ohtsuka, M. Okuno, Y. Hoshino, K. Honda, *Org. Biomol. Chem.* **2016**, *14*, 9046–9054.
11. L. Yan, X. X. Liu, Y. Fu, *RSC Adv.* **2016**, *6*, 109702–109705.
12. R. Gealageas, A. Devineau, P. P. L. So, C. M. J. Kim, J. Surendradoss, C. Buchwalder, M. Heller, V. Goebeler, E. M. Dullaghan, D. S. Grierson, E. E. Putnins, *J. Med. Chem.* **2018**, *61*, 7043–7064.
13. H. Ylikangas, K. Malmioja, L. Peura, M. Gynther, E. O. Nwachukwu, J. Leppänen, K. Laine, J. Rautio, M. L. Kakkonen, K. M. Huttunen, A. Poso, *Chem. Med. Chem.* **2014**, *9*, 2699–2707.
14. L. Legnani, G. P. Cerai, B. Morandi, *ACS Catal.* **2016**, *6*, 8162–8165.
15. R. E. Mewshaw, R. J. Edsall, C. Yang, E. S. Manas, Z. B. Xu, R. A. Henderson, J. C. Keith, H. A. Harris, *J. Med. Chem.* **2005**, *48*, 3953–3979.
16. S. Messaoudi, J-D. Brion, and M. Alamia, *Adv. Synth. Catal.* **2010**, *352*, 1677–1687.
17. J. L. Jat, M. P. Paudyal, H. Gao, Q. L. Xu, M. Yousufuddin, D. Devarajan, D. H. Ess, L. Kurti, J. R. Falck, *Science* **2014**, *343*, 61–65.
18. B. Lu, J. R. Falck, *J. Org. Chem.* **2010**, *75*, 1701–1705.
19. Z. Ma, Z. Zhou, L. Kurti, *Angew. Chem. Int. Ed.* **2017**, *56*, 9886–9890.
20. P. Roszkowski, J. K. Maurin, Z. Czarnocki, *Tetrahedron: Asymmetry* **2012**, *23*, 1106–1110.
21. D. H. R. Barton, R. S. H. Motherwell, W. B. Motherwell, *J. Chem. Soc. Perkin Trans.* **1983**, 445–451.
22. P. Grosche, F. Sirockin, A. M. Sweeney, P. Ramage, P. Erbel, S. Melkko, A. Bernardi, N. Hughes, D. Ellis, K. D. Combrink, N. Jarousse, E. Altmann, *Bioorg. Med. Chem. Lett.* **2015**, *25*, 438–443.

¹H and ¹³C NMR Spectra

