Supporting Information

Mechanochemical Nucleophilic Substitution of Alcohols via Isouronium Intermediates

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General information

All reagents were purchased from commercial suppliers (Fluorochem, Sigma-Aldrich and Alfa Aesar) and used without further purification. Inorganic salts (e.g. KF, K2HPO4) were dried prior to use by heating under reduced pressure. Mechanochemical experiments were carried out in a FTS-1000 shaker mill at 30 Hz frequency by using 14 mL ZrO2-coated milling jars with 10 mm ZrO2 milling balls.

Silica gel 40 – 63 μm was used for column chromatography; silica gel 60 F254 plates were used for TLC. Visualization of TLC plates was performed by UV light (254 nm) and phosphomolybdic acid (PMA) stain. 1H NMR (400 MHz), 13C NMR (100.6 MHz) and 31P (162 MHz) spectra were recorded on Bruker Avance III spectrometer. Chemical shifts were referenced to residual protio solvent peaks and solvent resonances (δ 1H 7.26 and δ 13C 77.16 measured in CDCl3; δ 1H 4.79 measured in D2O; δ 1H 3.31 and δ 13C 49.00 measured in CD3OD) as internal standards for 1H NMR and 13C NMR spectra, respectively. All chemical shifts are reported in ppm units. For 31P NMR spectra, 85% aq. H3PO4 was used as an external reference with δ 31P 0.00. FT-IR spectra were recorded on a Bruker Tensor 27 FT spectrometer. HPLC determination of enantiomeric excess was performed with Agilent Technologies 1200 Series chromatograph using Chiralpak AD-H column (250 x 4.6 mm, 5μm) and OJ-H column (250 x 4.6 mm, 5 μm). Specific rotations were measured using an Anton Paar MCP 500 polarimeter. HRMS data was obtained on Agilent Technologies 6540 UHD Accurate-Mass Q-TOF LC/MS system using AJS-ESI method in positive ion detection mode.
1. Optimization Studies

**Attempted single-step protocol:** Alcohol 1 (0.158 mmol), TFFH or TCFH (0.158 mmol, 1.0 equiv), KF or K$_2$HPO$_4$ (0.158–0.474 mmol, 1.0–3.0 equiv.) and morpholine (0.158 mmol, 1.0 equiv.) were placed into a 14 mL ZrO$_2$-coated jar charged with a single 10 mm ZrO$_2$ milling ball. Then LAG additive was added to the jar ($\eta = 0.2 \mu$L·mg$^{-1}$), which was then set to mill at 30 Hz for 60 minutes. The resulting crude reaction mixture was analysed by $^1$H NMR using CDCl$_3$ as a solvent, after separation of insoluble inorganic material.

**Table S1. Conversion of alcohol 1 to amine 2$^{[a]}$**

| Coupling reagent/base | Conversion by $^1$H NMR, % |
|-----------------------|-----------------------------|
| TFFH / K$_2$HPO$_4$   | 6                           |
| TCFH / K$_2$HPO$_4$   | 8                           |
| TFFH / KF             | 8                           |

$^{[a]}$ Characteristic signals of benzylic CH$_2$ protons from starting alcohol 1 ($\delta$ 5.15 ppm) and from the product 2 at ($\delta$ 3.88 ppm) were integrated and recalculated into conversion.

**Competitive reaction:**

The low yield of amine 2 is due faster competitive reaction of morpholine with TFFH and TCFH yielding the corresponding guanidinium salt S1. Characteristic signals of S1 in $^1$H NMR (CDCl$_3$): $\delta$ 3.37–3.24 (m, 4H), 3.84–3.73 (m, 4H), 2.97 (s, 6H), 2.94 (s, 6H). HRMS (AJS-ESI) calc. for C$_9$H$_{20}$N$_3$O$^+$ [M]$^+$ 186.1601, found m/z 186.1602.

**Stepwise protocol:** Alcohol 1 (0.158 mmol, 1 equiv.), coupling reagent (0.158–0.237 mmol, 1.0–1.5 equiv.) and base (0.158–0.474 mmol, 1.0–3.0 equiv.) were placed into a 14 mL ZrO$_2$-coated jar charged with a single 10 mm ZrO$_2$ milling ball. Then LAG additive was added to the jar ($\eta = 0.2 \mu$L·mg$^{-1}$), which was then set to mill at 30 Hz for 60 minutes. The resulting crude reaction mixture was analysed by $^1$H NMR using CDCl$_3$ as a solvent, after separation of
insoluble inorganic material. Then morpholine was added to the resulting mixture (0.158–0.237 mmol, 1.0–1.5 equiv.), and the jar was set to mill at 30 Hz for additional 60 minutes. The resulting crude reaction mixture was analysed by $^1$H NMR using CDCl$_3$ as a solvent, after separation of insoluble inorganic material (Table S2).

Table S2. Optimization studies (extended data set).

| Entry | Coupling agent | Base | LAG (0.2 µL·mg$^{-1}$) | Morpholine | Conv. by $^1$H NMR, % |
|-------|----------------|------|------------------------|-------------|-----------------------|
| **1** |                |      |                        |             |                       |
| **1.1** | TFFH (1.1 equiv.) | KF (2 equiv.) | EtOAc | - | 73% |
| **1.2** | TFFH (1.0 equiv.) | - | EtOAc | - | No reaction |
| **1.3** | TFFH (1.1 equiv.) | K$_2$HPO$_4$ (1.1 equiv.) | EtOAc | - | 70% |
| **1.4** | TFFH (1.1 equiv.) | K$_2$HPO$_4$ (2 equiv.) | EtOAc | - | 77% |
| **1.5** | TFFH (1.1 equiv.) | K$_2$HPO$_4$ (3 equiv.) | EtOAc | - | 74% |
| **1.6** | TFFH (1.5 equiv.) | K$_2$HPO$_4$ (2 equiv.) | EtOAc | - | 88% |
| **1.7** | TFFH (1.1 equiv.) | K$_3$PO$_4$ (2 equiv.) | EtOAc | - | 66% |
| **1.8** | TFFH (1.1 equiv.) | KH$_2$PO$_4$ (1.1 equiv.) | EtOAc | - | 0% |
| **1.9** | COMU (1.1 equiv.) | K$_2$HPO$_4$ (2 equiv.) | EtOAc | - | 65% |
| **1.10** | TFFH (1.1 equiv.) | K$_2$CO$_3$ (2 equiv.) | EtOAc | - | 44% |
| **1.11** | TFFH (1.1 equiv.) | Ca(OH)$_2$ (1.1 equiv.) | EtOAc | - | 19% |
| **1.12** | TFFH (1.1 equiv.) | Cs$_2$CO$_3$ (1.1 equiv.) | EtOAc | - | 52% |
| **1.13** | TFFH (1.1 equiv.) | K$_2$SO$_3$ (1.1 equiv.) | EtOAc | - | 36% |
| **1.14** | TFFH (1.1 equiv.) | NMI (1.1 equiv.) | EtOAc | - | 17% |
| **1.15** | TFFH (1.1 equiv.) | TEA (1.1 equiv.) | EtOAc | - | 46% |
| **1.16** | TFFH (1.1 equiv.) | DBU (1.1 equiv.) | EtOAc | - | 17% |
| **2** |                |      |                        |             |                       |
| **2.1** | TFFH (1.1 equiv.) | K$_2$HPO$_4$ (2 equiv.) | EtOAc | - | 77% |
| **2.2** | TFFH (1.1 equiv.) | K$_2$HPO$_4$ (2 equiv.) | DMF | - | 30% |
| **2.3** | TFFH (1.1 equiv.) | K$_2$HPO$_4$ (2 equiv.) | DMSO | - | 21% |
| **2.4** | TFFH (1.1 equiv.) | K$_2$HPO$_4$ (2 equiv.) | Acetone | - | 65% |
| **2.5** | TFFH (1.1 equiv.) | K$_2$HPO$_4$ (2 equiv.) | DMIS$^b$ | - | 72% |
| **2.6** | TFFH (1.1 equiv.) | K$_2$HPO$_4$ (2 equiv.) | CPME$^b$ | - | 76% |
| **2.7** | TFFH (1.1 equiv.) | K$_2$HPO$_4$ (2 equiv.) | EC$^b$ | - | 76% |
| **2.8** | TFFH (1.1 equiv.) | K$_2$HPO$_4$ (2 equiv.) | DEC$^b$ | - | 60% |
| **2.9** | TFFH (1.1 equiv.) | K$_2$HPO$_4$ (2 equiv.) | ACN | - | 67% |
| **2.10** | TFFH (1.1 equiv.) | K$_2$HPO$_4$ (2 equiv.) | CH$_3$NO$_2$ | - | 65% |
| **2.11** | TFFH (1.1 equiv.) | K$_2$HPO$_4$ (2 equiv.) | $t$-BuOH | - | 62% |
| **2.12** | TFFH (1.1 equiv.) | K$_2$HPO$_4$ (2 equiv.) | CF$_3$CH$_2$OH | - | 7% |
| **2.13** | TFFH (1.1 equiv.) | K$_2$HPO$_4$ (2 equiv.) | HFIP$^b$ | - | 5% |
Preparation of amine 2 in two-step protocol \[^{[c]}\]

| Step | Reagents/Conditions | Solvent | Equiv. | Yield |
|------|---------------------|---------|--------|-------|
| 3.1  | DIC (1.1 equiv.) KF (2 equiv.), CuCl (10 mol%) | EtOAc | 1.3 equiv. | 0% \[^{[d]}\] |
| 3.2  | TFFH (1.5 equiv.) KF (2 equiv.) | EtOAc | 1.5 equiv. | 73% |
| 3.3  | TCFH (1.5 equiv.) K\(_2\)HPO\(_4\) (2 equiv.) | EtOAc | 1.5 equiv. | 8% |
| 3.4  | TFFH (1.5 equiv.) K\(_2\)HPO\(_4\) (2 equiv.) | EtOAc | 1.5 equiv. | 88% |

\[^{[a]}\] Milling time 1 h. Conversion of alcohol 1 into isouronium salt 3, determined by \(^1\)H NMR (characteristic signals of benzylic CH\(_2\) protons from starting alcohol 1 at δ 5.15 ppm and isouronium salt 3 at δ 5.68 ppm were integrated and recalculated into conversion, taking into account also signals of minor reaction by-products at δ 5.95–4.70 ppm). \[^{[b]}\] DMIS – dimethyl isosorbide, CPME – cyclopentyl methyl ether, EC – ethylene carbonate, DEC – diethyl carbonate, HFIP – hexafluoroisopropanol. \[^{[c]}\] Milling time 1 h, followed by addition of morpholine and milling for additional 1 h. Conversion of alcohol 1 into amine 2, determined by \(^1\)H NMR (characteristic signals of benzylic CH\(_2\) protons from starting alcohol 1 at δ 5.15 ppm and amine 2 at δ 3.88 ppm were integrated and recalculated into conversion, taking into account also signals of minor reaction by-products at δ 5.95–4.70 ppm). \[^{[d]}\] O-alkyl isourea derivative S2 was obtained in 75% yield. \[^{[1,2]}\]

**Isouronium salt 3:**

\(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 7.95 (d, \(J = 8.4\) Hz, 1H), 7.90–7.83 (m, 2H), 7.63–7.39 (m, 4H), 5.68 (s, 2H), 3.03 (s, 12H). HRMS (AJS-ESI) calc. for C\(_{16}\)H\(_{21}\)N\(_2\)O\(^+\) [M]\(^+\) 257.1648, found m/z 257.1647.

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**Figure S1.** \(^1\)H NMR (CDCl\(_3\)) spectrum of a crude reaction mixture containing isouronium salt 3 (assignment of signals is shown in color), LAG additive (EtOAc) and tetramethylurea (TMU).
Slight increase of TFFH amount (1.5 equiv.) was needed to attain the best conversion values, probably due to consumption of TFFH reagent in a side reaction leading to generation of pyrophosphate:

Pyrophosphate was detected among the inorganic products by $^{31}$P NMR spectroscopy, as described below:

Alcohol 1 (0.158 mmol), TFFH (0.174 mmol, 1.1 equiv.) and $\text{K}_2\text{HPO}_4$ (0.316 mmol, 2 equiv.) were placed into a 14 mL ZrO$_2$-coated jar charged with a single 10 mm ZrO$_2$ milling ball. Then EA ($\eta = 0.2 \, \mu\text{L} \cdot \text{mg}^{-1}$) as a LAG was added to the jar, which was then set to mill at 30 Hz for 60 minutes. The resulting crude reaction mixture was dissolved in chloroform and filtered. The inorganic residue was then washed with chloroform, dried and analysed by $^{31}$P NMR using D$_2$O/DMSO-$d_6$ (3:1) as solvent. The signals in $^{31}$P NMR spectra of inorganic residue at $\delta$ 0.66 ppm and $-7.89$ ppm correspond to phosphate and assumingly pyrophosphate anions (Figure S2). [3]

![Figure S2. $^{31}$P NMR spectrum of inorganic residue containing phosphate, pyrophosphate and hexafluorophosphate anions.](image-url)
Kinetics studies

Preparation of Isouronium salt 3: Alcohol 1 (0.158 mmol), TFFH (0.237 mmol, 1.5 equiv.) and K$_2$HPO$_4$ (0.316 mmol, 2 equiv.) were placed into a 14 mL ZrO$_2$-coated jar charged with a single 10 mm ZrO$_2$ milling ball. Then ethyl acetate as a LAG additive was added to the jar ($\eta = 0.2$ $\mu$L·mg$^{-1}$), which was then set to mill at 30 Hz for 10, 20, 40 and 60 minutes. The resulting crude reaction mixtures were analysed by $^1$H NMR using CDCl$_3$ as a solvent, after separation of insoluble inorganic material (Table S3, Figure S3).

| Time of reaction, min | Conversion by $^1$H NMR, % |
|----------------------|-----------------------------|
| 10                   | 47                          |
| 20                   | 76                          |
| 40                   | 85                          |
| 60                   | 88                          |

Figure S3. Accumulation of isouronium salt 3 over time.

Transformation of 3 into amine 2: morpholine (0.237 mmol, 1.5 equiv.) was added to the reaction mixture containing isouronium intermediate 3 (generated as described above; 1 h milling time) and the jar was set to mill at 30 Hz for additional 20 and 60 minutes. The resulting crude reaction mixtures was analysed by $^1$H NMR using CDCl$_3$ as a solvent, after separation of insoluble inorganic material (Table S4). No trace of isouronium salt 3 was detected. The conversion of starting alcohol 1 into amine 2 was calculated.
The results show that highly reactive isouronium salt 3 was fully transformed into amine 2 already after 20 min. However, 60 min reaction time was used in the general procedure (see below) to account the differences in nucleophilicity and reactivity of various amines.
2. Reaction in acetonitrile solution

A solution of alcohol 1 (0.158 mmol), TFFH (0.158–0.237 mmol, 1.0–1.5 equiv.) and TEA (0.158–0.316 mmol, 1–2 equiv.) in CD$_3$CN was transferred to a NMR tube. The reaction progress was monitored by $^1$H NMR (Table S5). Addition of morpholine caused fast (within 20 min) transformation of 3 into amine 2.

### Table S5. Reaction in CD$_3$CN solution

| Coupling reagent / Base | Conversion into 3 by $^1$H NMR, % |
|-------------------------|----------------------------------|
|                         | 60 min | 12 hrs  |
| TCFH (1 equiv.) / TEA (1 equiv.) | 3      | 0       |
| TFFH (1 equiv.) / TEA (1 equiv.)  | 52$^{[a]}$ | 25     |
| TFFH (1.5 equiv.) / TEA (2 equiv.) | 37$^{[a]}$ | –       |

$^{[a]}$ Addition of morpholine resulted in fast (within 20 min) and quantitative conversion of 3 into amine 2.
3. General procedure and characterization of products

General procedure. Alcohol (1 equiv.), TFFH (1.5 equiv.) and K₂HPO₄ (2 equiv.) were placed into a 14 mL ZrO₂-coated milling jar charged with a single 10 mm ZrO₂ milling ball. Ethyl acetate (η = 0.2 µL·mg⁻¹) was added and the jar was then set to mill at 30 Hz for 60 minutes. Amine (1.5–3 equiv.) was added to the formed reaction mixture, and the jar was set to mill at 30 Hz for additional 60 minutes. The resulting crude reaction mixture was diluted with ethyl acetate (10–15 mL), filtered, and concentrated under reduced pressure before purification by silica gel chromatography to afford the amine product.

4-(Naphthalen-1-ylmethyl)morpholine (2).

Prepared by following the general procedure from alcohol 1 (0.253 mmol, 40 mg), morpholine (0.379 mmol, 33 µL, 1.5 equiv.), TFFH (0.379 mmol, 100 mg, 1.5 equiv.), K₂HPO₄ (0.506 mmol, 88 mg, 2 equiv.) and ethyl acetate (50 µL). Amine 3 was purified by silica gel chromatography with petroleum ether/acetone (37:3) as eluent and obtained as pale-yellow oil (47 mg, 82%). Rₚ = 0.68 (3:1 petroleum ether/acetone, UV 254 nm). ¹H NMR (CDCl₃, 400 MHz): δ 8.37–8.24 (m, 1H), 7.89–7.80 (m, 1H), 7.80–7.72 (m, 1H), 7.56–7.44 (m, 2H), 7.43–7.34 (m, 2H), 3.89 (s, 2H), 3.68 (m, 4H), 2.49 (m, 4H). ¹³C NMR (CDCl₃, 100.6 MHz): δ 133.99, 133.70, 132.68, 128.53, 128.21, 127.65, 125.89, 125.78, 125.20, 124.92, 67.24, 61.77, 53.93. IR (KBr): ν = 2853, 1508, 1454, 1116, 865 cm⁻¹. HRMS (AJH-ESI) calcd. for C₁₅H₁₈NO⁺ [M+H]⁺ 228.1383, found m/z 228.1382. Spectral data are in agreement with previously reported.[⁴]

4-(Naphthalen-2-ylmethyl)morpholine (4).

Prepared by following the general procedure from alcohol 24 (0.253 mmol, 40 mg), morpholine (0.379 mmol, 33 µL, 1.5 equiv.), TFFH (0.379 mmol, 100 mg, 1.5 equiv.), K₂HPO₄ (0.506 mmol, 88 mg, 2 equiv.) and ethyl acetate (50 µL). Amine 4 was purified by silica gel chromatography with petroleum ether/ethyl acetate (33:7) as eluent and obtained as pale-yellow oil (52 mg, 91%). Rₚ = 0.43 (1:1 petroleum ether/ethyl acetate, UV 254 nm). ¹H NMR (CDCl₃, 400 MHz): δ 7.88–7.79 (m, 3H), 7.76 (s, 1H), 7.56–7.42 (m, 3H), 3.74 (m, 4H), 3.67 (s, 2H), 2.50 (m, 4H). ¹³C NMR (CDCl₃, 100.6 MHz): δ 135.51, 133.41, 132.91, 128.05, 127.85, 127.80, 127.76, 127.49, 126.10, 125.77, 67.14, 63.73, 53.84. IR (KBr): ν = 2808, 1509, 1394, 1116, 791 cm⁻¹. HRMS (AJH-ESI) calcd. for C₁₅H₁₈NO⁺ [M+H]⁺ 228.1383, found m/z 228.1382. Spectral data are in agreement with previously reported.[⁵]

4-(3,5-Dimethoxybenzyl)morpholine (5).

Prepared by following the general procedure from (3,5-dimethoxyphenyl)methanol (0.25 mmol, 42 mg), morpholine (0.375 mmol, 33 µL, 1.5 equiv.), TFFH (0.375 mmol, 99 mg, 1.5 equiv.), K₂HPO₄ (0.5 mmol, 87 mg, 2 equiv.) and ethyl acetate (50 µL). Amine 5 was purified by silica gel chromatography with petroleum ether/acetone (37:3) as eluent and obtained as colorless oil (51 mg, 87%). Rₚ = 0.50 (3:1 petroleum ether/acetone, UV 254 nm). ¹H NMR (CDCl₃, 400 MHz): δ 6.51 (d, J = 2.3 Hz, 2H), 6.36 (t, J = 2.4 Hz, 1H), 3.79 (s, 6H), 3.71 (m, 4H), 3.43
(s, 2H), 2.44 (m, 4H). $^{13}$C NMR (CDCl$_3$, 100.6 MHz): $\delta$ 160.88, 140.52, 107.06, 99.16, 67.17, 63.64, 55.45, 53.77. IR (KBr): $\nu$ = 2956, 1457, 1205, 1154, 1117, 866 cm$^{-1}$. HRMS (AJS-ESI) calcd. for C$_{13}$H$_{20}$NO$_3^+$ [M+H]$^+$ 238.1438, found m/z 238.1440. Spectral data are in agreement with previously reported.$^6$

4-(3,5-Bis(trifluoromethyl)benzyl)morpholine (6).

Prepared by following the general procedure from (3,5-bis(trifluoromethyl)phenyl)methanol (0.25 mmol, 61 mg), morpholine (0.375 mmol, 33 µL, 1.5 equiv.), TFFH (0.375 mmol, 99 mg, 1.5 equiv.), K$_2$HPO$_4$ (0.5 mmol, 87 mg, 2 equiv.) and ethyl acetate (50 µL). Amine 6 was purified by silica gel chromatography with petroleum ether/acetone (19:1) as eluent and obtained as colorless oil (60 mg, 77%). $R_f = 0.62$ (3:1 petroleum ether/acetone, UV 254 nm). $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.81 (s, 2H), 7.77 (s, 1H), 3.73 (m, 4H), 3.60 (m, 2H), 2.46 (m, 4H). $^{13}$C NMR (CDCl$_3$, 100.6 MHz): $\delta$ 141.10, 131.77 (q, $J_{CF} = 272.5$ Hz, CF$_3$), 121.39 (m, $J_{CF} = 3.8$ Hz), 67.02, 62.44, 53.72. IR (KBr): $\nu$ = 2916, 1457, 1205, 1154, 1117 cm$^{-1}$. HRMS (AJS-ESI) calcd. for C$_{13}$H$_{18}$F$_6$NO$_3^+$ [M+H]$^+$ 314.0974, found m/z 314.0975.

Methyl (R)-2-morpholino-2-phenylacetate (7).

Prepared following the general procedure from (S)-mandelic acid methyl ester (0.25 mmol, 41.5 mg), morpholine (0.375 mmol, 33 µL, 1.5 equiv.) TFFH (0.375 mmol, 99 mg, 1.5 equiv.), K$_2$HPO$_4$ (0.5 mmol, 87 mg, 2 equiv.) and ethyl acetate (50 µL). (Racemic 7 was obtained analogously from racemic methyl mandelate.) Amine (R)-7 was purified by silica gel chromatography with petroleum ether/acetone (19:1) as eluent and obtained as pale-yellow oil (49 mg, 84%, 76% ee, lower chromatogram). $R_f = 0.51$ (3:1 petroleum ether/ acetone, UV 254 nm). $[\alpha]_D^{20} = -56.3$ (c 0.23, CHCl$_3$, 76% ee), lit. $[\alpha]_D^{20} = +65.0$ (c 1.1, CHCl$_3$) for (S)-isomer. $^{[7]}$ $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.46–7.39 (m, 2H), 7.37–7.27 (m, 3H), 3.97 (s, 1H), 3.71 (m, 4H), 3.67 (s, 3H), 2.43 (m, 4H). $^{13}$C NMR (CDCl$_3$, 100.6 MHz): $\delta$ 171.77, 135.39, 128.98, 128.75, 128.62, 74.52, 66.89, 52.15, 51.71. IR (KBr): $\nu$ = 2955, 1747, 1451, 1276, 1153, 1118, 878 cm$^{-1}$. HRMS (AJS-ESI) calcd. for C$_{13}$H$_{18}$NO$_3^+$ [M+H]$^+$ 236.1281, found m/z 236.1282. Enantiomeric excess was determined by HPLC [AD-H column (95:5 n-hexane/2-propanol), flow rate 1 mL·min$^{-1}$, detection at 210 nm]: (S)-7 $t_R = 6.3$ min, (R)-7 $t_R = 7.3$ min. Spectral data are in agreement with previously reported.$^{[7]}$

Variation of milling times (see Table S6) showed that optical purity of amine (R)-7 was not affected by duration of the second step (30–120 min, 76–77% ee). But shorter milling time at the 1st step (15 min) resulted in a noticeably higher 85% ee. Thus, partial epimerization

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probably takes place via enolization of the corresponding isouronium intermediate (Figure S4) while S\textsubscript{N}2 reaction with amine is dominant.

| Milling time, min | ee, % |
|-------------------|-------|
| 1\textsuperscript{st} step | 2\textsuperscript{nd} step |
| 60 | 30 | 77 |
| 60 | 60 | 76 |
| 60 | 120 | 76 |
| 15 | 15 | 85 |

Figure S4. Plausible mechanism of racemization.

2-(4-(Morpholinomethyl)phenyl)propan-2-ol (13).

Prepared following the general procedure from 2-(4-(hydroxymethyl)phenyl)propan-2-ol (0.25 mmol, 42 mg), morpholine (0.375 mmol, 33 \( \mu \)L, 1.5 equiv.), TFFH (0.375 mmol, 99 mg, 1.5 equiv.), K\textsubscript{2}HPO\textsubscript{4} (0.5 mmol, 87 mg, 2 equiv.) and ethyl acetate (50 \( \mu \)L). The resulting crude reaction mixture was diluted with water (10 mL) and dichloromethane (5 mL) followed by extraction with dichloromethane (3×5 mL). The organic layers were combined and extracted with 1M HCl (3×5 mL), the pH of the combined acidic layers was adjusted to 9 and aqueous phase was again extracted with dichloromethane (4×5 mL). The organic layers were combined, dried over Na\textsubscript{2}SO\textsubscript{4}, filtered, and concentrated under reduced pressure before purification by silica gel chromatography with dichloromethane/methanol as eluent to give amine 13 as pale-yellow oil (36 mg, 61%). \( R_f = 0.39 \) (10:1 dichloromethane / methanol, UV 254 nm). \( ^1\)H NMR (CDCl\textsubscript{3}, 400 MHz): \( \delta \) 7.48–7.41 (m, 2H), 7.34–7.28 (m, 2H), 3.73 (m, 4H), 3.53 (s, 2H), 2.48 (m, 4H), 1.57 (s, 6H). \( ^{13}\)C NMR (CDCl\textsubscript{3}, 100.6 MHz): \( \delta \) 148.51, 135.32, 129.39, 124.56, 72.49, 66.83, 63.02, 53.53, 31.89. IR (KBr): \( \nu = 3419, 2971, 2809, 1455, 1115, 866 \text{ cm}^{-1} \). HRMS (AJS-ESI) calcd. for C\textsubscript{14}H\textsubscript{22}NO\textsubscript{2}\textsuperscript{+} [M+H]\textsuperscript{+} 236.1645, found m/z 236.1641.
Intermolecular competition experiment.

Primary alcohol 1 (0.25 mmol, 40 mg, 1 equiv.), tertiary alcohol 12 (0.25 mmol, 47 mg, 1 equiv.), TFFH (0.375 mmol, 99 mg, 1.5 equiv.) and K$_2$HPO$_4$ (0.5 mmol, 87 mg, 2 equiv.) were placed into a 14 mL ZrO$_2$-coated jar charged with a single 10 mm ZrO$_2$ milling ball. Then ethyl acetate (55 µL) was added into the jar, which was then set to mill at 30 Hz for 60 min. Then morpholine (0.375 mmol, 33 µL, 1.5 equiv.) was added to the reaction mixture, and the jar was set to mill at 30 Hz for additional 60 minutes. The resulting crude reaction mixture was analyzed by TLC and $^1$H NMR using CDCl$_3$ as a solvent, after separation of insoluble inorganic material. Amine 2 was obtained in 95% yield, tertiary alcohol 12 showed no reaction (Figure S5, C).

No reaction was also observed when tertiary alcohol 12 was submitted to the general reaction protocol, according to TLC and $^1$H NMR analysis (Figure S5, B).

Figure S5. $^1$H NMR (CDCl$_3$) spectra of (A) pure tertiary alcohol 12; (B) recovered alcohol 12 after being submitted to the general reaction protocol; (C) the reaction mixture obtained for intermolecular competition experiment. The mixture contains amine 2, alcohol 12, unreacted morpholine, guanidinium salt S1, EtOAc and TMU (TMU = tetramethylurea); (D) amine 2.
4-(3-phenylprop-2-yn-1-yl)morpholine (14).

Prepared following the general procedure from 3-phenylprop-2-yn-1-ol (0.5 mmol, 61 µL), morpholine (0.75 mmol, 65 µL, 1.5 equiv.), TFFH (0.75 mmol, 198 mg, 1.5 equiv.), K₂HPO₄ (1 mmol, 174 mg, 2 equiv.) and ethyl acetate (75 µL). The resulting reaction mixture was purified by silica gel chromatography with petroleum ether/diethyl ether (1:1) as eluent to give amine 14 as pale-yellow oil (86 mg, 86%). Rᵥ = 0.38 (3:1 diethyl ether/petroleum ether, UV 254 nm). ¹H NMR (CDCl₃, 400 MHz): δ 7.47-7.39 (m, 2H), 7.32-7.27 (m, 3H), 3.77 (m, 4H), 3.51 (s, 2H), 2.64 (m, 4H). ¹³C NMR (CDCl₃, 100.6 MHz): δ 131.85, 128.40, 128.31, 123.12, 85.69, 84.19, 67.05, 52.59, 48.23. IR (KBr): ν = 2855, 1490, 1347, 1116, 757 cm⁻¹. HRMS (AJS-ESI) calcd. for C₁₃H₁₆NO⁺ [M+H]⁺ 202.1226, found m/z 202.1225. Spectral data are in agreement with previously reported.[⁸]

N-Allylindoline (15).

Prepared following the general procedure from allylic alcohol (0.68 mmol, 40 mg), indoline (1.03 mmol, 123 mg, 1.5 equiv.), TFFH (1.03 mmol, 273 mg, 1.5 equiv.), K₂HPO₄ (1.37 mmol, 240 mg, 2 equiv.) and EtOAc (126 µL). Purification was performed by column chromatography on silica gel (5% EtOAc/petroleum ether). Amine product 15 was isolated as yellowish oil (56 mg, 56%). Rᵥ = 0.82 (1:4 EtOAc/petroleum ether, UV 254 nm). ¹H NMR (400 MHz, CDCl₃) δ 7.15–7.05 (m, 2H), 6.70 (td, J = 7.4, 1.0 Hz, 1H), 6.55 (d, J = 7.8 Hz, 1H), 5.95 (ddt, J = 17.2, 10.2, 6.0 Hz, 1H), 5.33 (dq, J = 17.2, 1.6 Hz, 1H), 5.23 (dq, J = 10.2, 1.6 Hz, 1H), 3.74 (dt, J = 6.0, 1.6 Hz, 2H), 3.37 (t, J = 8.3 Hz, 2H), 2.99 (t, J = 8.3 Hz, 2H). ¹³C NMR (100.6 MHz, CDCl₃) δ 152.29, 134.33, 130.34, 127.36, 124.55, 117.80, 117.37, 107.46, 53.33, 52.26, 28.65. IR (KBr): ν = 2920, 1644, 1607, 1488, 1268, 1157, 991 cm⁻¹. HRMS (AJS-ESI) calcd. for C₁₁H₁₄N⁺ [M+H]⁺ 160.1121, found m/z 160.1116. Spectral data are in agreement with previously reported.[⁹]

4-(3-phenylpropyl)morpholine (19).

Prepared following the general procedure from 3-phenylpropan-1-ol (0.5 mmol, 68 µL), morpholine (0.75 mmol, 65 µL, 1.5 equiv.), TFFH (0.75 mmol, 198 mg, 1.5 equiv.), K₂HPO₄ (1 mmol, 174 mg, 2 equiv.) and ethyl acetate (75 µL). The resulting reaction mixture was purified by silica gel chromatography with petroleum ether/diethyl ether (3:5) as eluent to give amine 19 as pale-yellow oil (41 mg, 40%). Rᵥ = 0.34 (3:1 diethyl ether / petroleum ether, UV 254 nm). ¹H NMR (CDCl₃, 400 MHz): δ 7.32–7.24 (m, 2H), 7.22–7.15 (m, 3H), 3.71 (m, 4H), 2.64 (m, 2H), 2.43 (m, 4H), 2.36 (m, 2H), 1.87–1.76 (m, 2H). ¹³C NMR (CDCl₃, 100.6 MHz): δ 142.18, 128.50, 128.43, 125.90, 67.14, 58.49, 53.84, 33.72, 28.38. IR (KBr): ν = 3026, 2943, 2806, 1454, 1118, 748 cm⁻¹. HRMS (AJS-ESI) calcd. for C₁₃H₂₈NO⁺ [M+H]⁺ 206.1539, found m/z 206.1540. Spectral data are in agreement with previously reported.[¹⁰]
Ethyl (R)- and (S)-2-morpholinopropanoates (22).

Ethyl (R)-2-morpholinopropanoate was prepared following the general procedure (reaction time 1 hr for the 1st step and 3 hrs for the 2nd step) from ethyl (S)-2-hydroxypropanoate (0.6 mmol, 69 µL), morpholine (0.9 mmol, 78 µL, 1.5 equiv.), TFFH (0.9 mmol, 238 mg, 1.5 equiv.), K$_2$HPO$_4$ (1.2 mmol, 209 mg, 2 equiv.) and ethyl acetate (90 µL). The resulting reaction mixture was purified by silica gel chromatography with petroleum ether/ethyl acetate (33:7) as eluent to give amine (R)-22 as colourless oil (56 mg, 50%, middle chromatogram, ee > 99%). [α]$^0_{D}$ = +23.2 (c 0.20, CHCl$_3$). (S)-22 was obtained analogously, with the same yield and enantiomeric purity (lower chromatogram, ee > 99%) from (R)-2-hydroxypropanoate. $R_f$ = 0.40 (1:1 petroleum ether/ethyl acetate, PMA). $^1$H NMR (CDCl$_3$, 400 MHz): δ 4.23–4.12 (m, 2H), 3.71 (m, 4H), 3.23 (q, $J$ = 7.0 Hz, 1H), 2.60 (m, 4H), 1.29 (d, $J$ = 7.0 Hz, 3H), 1.28 (t, $J$ = 7.1 Hz, 3H). $^{13}$C NMR (CDCl$_3$, 100.6 MHz) δ 172.94, 67.33, 63.15, 60.58, 50.12, 14.71, 14.52. IR (KBr): ν = 2955, 1735, 1438, 1295, 1166, 1117, 862 cm$^{-1}$. HRMS (AJS-ESI) calcd. for C$_9$H$_{18}$NO$_3^+$ [M+H]$^+$ 188.1281, found m/z 188.1280. Enantiomeric excess (ee > 99% for both enantiomers) was determined by HPLC [OJ-H column (99.5:0.5 n-hexane/2-propanol), flow rate 0.7 mL·min$^{-1}$, detection at 210 nm]: (S)-22 $t_R$ = 13.9 min, (R)-22 $t_R$ = 13.2 min. Spectral data are in agreement with previously reported.$^{[11]}$

Dimethyl 2-morpholinosuccinate (23).

Prepared following the general procedure from dimethyl (S)-2-hydroxysuccinate (0.3 mmol, 48.3 µL), morpholine (0.45 mmol, 39 µL, 1.5 equiv.), TFFH (0.45 mmol, 119 mg, 1.5 equiv.), K$_2$HPO$_4$ (0.6 mmol, 105 mg, 2 equiv.) and ethyl acetate (50 µL). The resulting reaction mixture was purified by silica gel chromatography with petroleum ether/acetonitrile (37:3) as eluent to give amine 23 as white solid (43 mg, 62%; obtained as racemic mixture). $R_f$ = 0.41 (3:1 petroleum ether/acetonitrile, PMA). $^1$H NMR (CDCl$_3$, 400 MHz): δ 3.74 (s, 3H), 3.72–3.69 (m, 1H), 3.68 (s, 3H), 3.67–3.59 (m, 4H), 2.84 (dd, $J$ = 16.0, 8.5 Hz, 1H), 2.74–2.66 (m, 2H), 2.63 (dd, $J$ = 16.0, 6.7 Hz, 1H), 2.54–2.43 (m, 2H). $^{13}$C NMR (CDCl$_3$, 100.6 MHz) δ 171.78, 171.04, 67.48, 63.88, 51.97, 51.70, 50.12 (2C), 34.16. IR (KBr): ν = 2955, 1735, 1438, 1295, 1166, 1117, 862 cm$^{-1}$. HRMS (AJS-ESI) calcd. for C$_{10}$H$_{18}$NO$_3^+$ [M+H]$^+$ 232.1179, found m/z 232.1180. The formation of racemic mixture was confirmed by HPLC [OJ-H column (93:7 n-hexane/2-propanol), flow rate 1 mL·min$^{-1}$, detection at 210 nm]: $t_R$ = 13.48 min, 14.4 min. Spectral data are in agreement with previously reported.$^{[12]}$
Plausible substitution mechanism leading to rac-23 could involve intermediate formation of dimethyl fumarate (detected in the crude reaction mixture, see Figure S6).

**Mechanistic rationale**

![Mechanistic rationale](image)

Figure S6. Plausible substitution mechanism accounting the formation of rac-23 from enantiopure starting material.

4-(Naphthalen-2-ylmethyl)thiomorpholine (25).

Prepared by following the general procedure from 2-naphthalenemethanol (24, 0.25 mmol, 40 mg), thiomorpholine (0.38 mmol, 39 mg, 1.5 equiv.), TFFH (0.38 mmol, 99 mg, 1.5 equiv.), K₂HPO₄ (0.50 mmol, 87 mg, 2.0 equiv.) and EtOAc (50 μL). Purification was performed by column chromatography on silica gel (10% EtOAc/petroleum ether). Amine product 25 was isolated as slightly pink solid (49 mg, 79%). Rᵣ = 0.45 (1:4 EtOAc/petroleum ether, UV 254 nm). ¹H NMR (400 MHz, CDCl₃): δ 7.87–7.79 (m, 3H), 7.74–7.73 (m, 1H), 7.53–7.42 (m, 3H), 3.68 (s, 2H), 2.80–2.73 (m, 4H), 2.73–2.67 (m, 4H). ¹³C NMR (100.6 MHz, CDCl₃) δ 135.80, 133.88, 132.88, 128.02, 127.76, 127.74, 127.69, 127.35, 126.10, 125.73, 63.91, 55.11, 28.13. IR (KBr): ν = 3448, 3054, 2929, 2798, 1597, 1504, 1456, 1359, 1332, 1279, 1102, 1003, 955, 861, 831, 784, 753, 478 cm⁻¹. HRMS (AJS-ESI) calcd. for C₁₅H₁₈NS⁺ [M+H]⁺ 244.1154, found m/z 244.1154.

1-(Naphthalen-2-ylmethyl)piperidine (26).

Prepared following the general procedure from naphthalen-2-ylmethanol (24, 0.25 mmol, 40 mg), piperidine (0.375 mmol, 37 µL, 1.5 equiv.), TFFH (0.375 mmol, 99 mg, 1.5 equiv.), K₂HPO₄ (0.50 mmol, 87 mg, 2 equiv.) and ethyl acetate (50 µL). The resulting reaction mixture was purified by silica gel chromatography with petroleum ether/acetone (19:1) as eluent to give amine 26 as yellowish oil (29 mg, 52%). Rᵣ = 0.58 (3:1 petroleum ether/acetone, UV 254 nm). ¹H NMR (CDCl₃, 400 MHz): δ 7.87–7.78 (m, 3H), 7.77–7.73 (m, 1H), 7.52 (dd, J = 8.4, 1.7 Hz, 1H), 7.50–7.40 (m, 2H), 3.65 (s, 2H), 2.45 (m, 4H), 1.65–1.57 (m, 4H), 1.50–1.40 (m, 2H). ¹³C NMR (CDCl₃, 100.6 MHz): δ 136.29, 133.44, 132.82, 127.83, 127.78, 127.74, 125.97, 125.59, 64.14, 54.72, 26.08, 24.51. IR (KBr): ν = 2934, 2853, 1441, 1153, 1119, 862, 785 cm⁻¹. HRMS (AJS-ESI) calcd. for C₁₆H₂₀N⁺ [M+H]⁺ 226.1590, found m/z 226.1593. Spectral data are in agreement with previously reported. [¹³]
**(R)-Methyl (naphthalen-2-ylmethyl)prolinate (27).**

Prepared by following the general procedure from 2-naphthalenemethanol (24, 0.25 mmol, 40 mg), D-proline methyl ester hydrochloride (0.38 mmol, 62 mg, 1.5 equiv.), TFFH (0.38 mmol, 99 mg, 1.5 equiv.), K$_2$HPO$_4$ (0.50 mmol, 130 mg, 3.0 equiv.) and EtOAc (55 μL). Purification was performed by column chromatography on silica gel (10% EtOAc/petroleum ether). Amine product 27 was isolated as colourless oil (28 mg, 42%). $R_f$ = 0.37 (1:4 EtOAc/petroleum ether, UV 254 nm).

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.86–7.77 (m, 3H), 7.77–7.72 (m, 1H), 7.51 (dd, $J$ = 8.4, 1.7 Hz, 1H), 7.50–7.40 (m, 2H), 4.07 (d, $J$ = 12.8 Hz, 1H), 3.72 (d, $J$ = 12.8 Hz, 1H), 3.62 (s, 3H), 3.31 (dd, $J$ = 8.9, 6.3 Hz, 1H), 3.12–3.04 (m, 1H), 2.49–2.39 (m, 1H), 2.22–2.09 (m, 1H), 2.07–1.85 (m, 2H), 1.88–1.73 (m, 1H).

$^{13}$C NMR (100.6 MHz, CDCl$_3$) δ 174.70, 136.13, 133.42, 132.87, 127.95, 127.87, 127.74, 127.72, 127.67, 126.01, 125.71, 65.60, 59.12, 53.51, 51.85, 29.51, 23.13. IR (KBr): ν = 2950, 1745, 1508, 1435, 1356, 1198 cm$^{-1}$. HRMS (AJS-ESI) calcd. for C$_{17}$H$_{20}$NO$_2$ $^+$ [M+H]$^+$ 270.1489, found m/z 270.1490.

1-(Naphthalen-2-ylmethyl)indoline (28).

Prepared by following the general procedure from 2-naphthalenemethanol (24, 0.25 mmol, 40 mg), indoline (0.38 mmol, 45 mg, 1.5 equiv.), TFFH (0.38 mmol, 99 mg, 1.5 equiv.), K$_2$HPO$_4$ (0.50 mmol, 87 mg, 2 equiv.) and EtOAc (50 μL). Purification was performed by column chromatography on silica gel (10% EtOAc/petroleum ether). Amine product 28 was isolated as solid (56 mg, 86%). $R_f$ = 0.77 (1:4 EtOAc/petroleum ether, UV 254 nm).

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.90–7.78 (m, 4H), 7.60–7.44 (m, 3H), 7.18–7.05 (m, 2H), 6.72 (td, $J$ = 7.4, 1.0 Hz, 1H), 6.59 (d, $J$ = 7.8 Hz, 1H), 4.42 (s, 2H), 3.37 (t, $J$ = 8.3 Hz, 2H), 3.02 (t, $J$ = 8.3 Hz, 2H).

$^{13}$C NMR (100.6 MHz, CDCl$_3$) δ 152.74, 136.25, 133.58, 132.92, 130.21, 128.36, 127.86, 127.82, 127.48, 126.48, 126.34, 126.21, 125.78, 124.67, 117.96, 107.31, 54.18, 53.92, 28.71. IR (KBr): ν = 3042, 2917, 2842, 1604, 1487 cm$^{-1}$. HRMS (AJS-ESI) calcd. for C$_{19}$H$_{18}$N $^+$ [M+H]$^+$ 260.1434, found m/z 260.1432. Spectral data are in agreement with previously reported.

N-(3,5-bis(trifluoromethyl)benzyl)-1-(naphthalen-2-yl)methanamine (30).

Prepared by following the general procedure from 2-naphthalenemethanol (24, 0.25 mmol, 40 mg, 1.0 equiv.), 3,5-bis(trifluoromethyl)benzylamine (0.38 mmol, 91 mg, 1.5 equiv.), TFFH (0.38 mmol, 99 mg, 1.5 equiv.), K$_2$HPO$_4$ (0.50 mmol, 87 mg, 2.0 equiv.) and EtOAc (50 μL). Purification was performed by column chromatography on silica gel (15% EtOAc/petroleum ether). Secondary amine product 30 was isolated as yellowish oil (54 mg, 55%), along with tertiary amine by-product 31 (25 mg, 37%).

$^3$0: $R_f$ = 0.12 (1:4 EtOAc/petroleum ether, UV 254 nm). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.92–7.74 (m, 7H), 7.56–7.43 (m, 3H), 3.99 (s, 2H), 3.95 (s, 2H), 1.77 (s, 1H, NH), $^{13}$C NMR (100.6 MHz, CDCl$_3$) δ 143.21, 137.19, 133.53, 132.92, 131.70 (q, $J_{CF}$ = 33.1 Hz), 128.46, 128.33 (broad), 127.82, 127.81, 126.81, 126.51, 126.31, 125.90, 123.57 (q, $J_{CF}$ = 272.6 Hz, CF$_3$), 121.09 (m, $J_{CF}$ = 4 Hz), 53.54, 52.18. IR (KBr): ν = 1377, 1278, 1173, 1132, 892, 818, 705, 682, 476 cm$^{-1}$. HRMS (AJS-ESI) calcd. for C$_{20}$H$_{16}$F$_6$N $^+$ [M+H]$^+$ 384.1181, found m/z 384.1181.

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**N-(3,5-Bis(trifluoromethyl)benzyl)-1-(naphthalen-2-yl)-N-(naphthalen-2-ylmethyl) methanamine (31).**

By-product was isolated from the previous reaction as colourless oil (25 mg, 37%). Rf = 0.58 (1:4 EtOAc/petroleum ether, UV 254 nm). 

![](image)

\[ \text{1H NMR (400 MHz, CDCl}_3\text{)} \delta 7.93–7.68 (m, 11H), 7.56 (dd, J = 8.4, 1.7 Hz, 2H), 7.53–7.44 (m, 4H), 3.79 (s, 4H), 3.75 (s, 2H). \]

\[ \text{13C NMR (100.6 MHz, CDCl}_3\text{)} \delta 142.67, 136.29, 133.43, 133.02, 131.56 (q, J_{CF} = 33.2 Hz), 128.85 (broad), 128.44, 127.90, 127.85, 127.78, 127.03, 126.30, 125.93, 123.55 (q, J_{CF} = 272.6 Hz, CF}_3\text{), 121.08 (m, J_{CF} = 4 Hz), 58.83, 57.23.} \]

IR (KBr): ν = 3056, 1508, 1355, 1278, 1174, 1133, 817, 682, 476 cm\(^{-1}\). HRMS (AJS-ESI) calcd. for C\(_{31}\)H\(_{24}\)F\(_6\)N\(^+\) [M+H\(^+\)]\(^{1}\) 524.1807, found m/z 524.1803.

**N-Benzyl-1-(naphthalen-2-yl)-N-(naphthalen-2-ylmethyl)methanamine (32).**

Prepared by following the **general procedure** from 2-naphthalenemethanol (24, 0.25 mmol, 40 mg, 1.0 equiv.), benzyl amine (0.125 mmol, 13.5 mg, 0.5 equiv.), TFFH (0.38 mmol, 99 mg, 1.5 equiv.), K\(_2\)HPO\(_4\) (0.50 mmol, 87 mg, 2.0 equiv.) and EtOAc (50 µL). Purification was performed by column chromatography on silica gel (5% EtOAc/petroleum ether). Amine product 32 was isolated as white solid (38 mg, 77%). Rf = 0.35 (1:4 EtOAc/petroleum ether, UV 254 nm). 

\[ \text{1H NMR (400 MHz, CDCl}_3\text{)} \delta 7.88–7.80 (m, 8H), 7.64 (dd, J = 8.4, 1.5 Hz, 2H), 7.52–7.43 (m, 6H), 7.39–7.33 (m, 2H), 7.30–7.23 (m, 1H), 3.78 (s, 4H), 3.67 (s, 2H). \]

\[ \text{13C NMR (100.6 MHz, CDCl}_3\text{)} \delta 139.69, 137.36, 133.48, 132.91, 128.99, 128.40, 128.08, 127.80, 127.78, 127.56, 127.33, 127.06, 126.04, 125.61, 58.30, 58.15. \]

IR (KBr): ν = 3054, 2918, 2804, 1600, 1506, 1449, 1363, 1244, 1123, 949, 902, 857, 817, 742, 698, 477 cm\(^{-1}\). HRMS (AJS-ESI) calcd. for C\(_{29}\)H\(_{26}\)N\(^+\) [M+H\(^+\)]\(^{1}\) 388.2060, found m/z 388.2059. Spectral data are in agreement with previously reported. \(^{15}\)
Formation of ethers from secondary benzylic alcohols.

Secondary benzylic alcohols, such as (S)-α-methyl-2-naphthalenemethanol (8) and diphenylmethanol (9), generated ethers 10 and 11 already during the milling with TFFH and K$_2$HPO$_4$, prior to addition of amine. Stereochemical outcome of the reaction with (S)-8 evidences generation of benzylic cation (Figure S7).

![Mechanistic rationale](image)

**Figure S7.** Formation of ethers from secondary benzylic alcohols.

(Oxybis(methanetriyl))tetrabenzenes 11.

Prepared by milling (1 hour) of alcohol 9 (0.25 mmol, 46.1 mg), TFFH (0.375 mmol, 99 mg), K$_2$HPO$_4$ (0.5 mmol, 87 mg) and ethyl acetate (50 µL) as LAG additive. The resulting reaction mixture was purified by silica gel chromatography with petroleum ether/ethyl acetate (19:1) as eluent to give ether 11 as white solid (13 mg, 30%) and starting alcohol 9 (20 mg). $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.34–7.11 (m, 20H), 5.32 (s, 2H). $^{13}$C NMR (CDCl$_3$, 100.6 MHz): δ 142.35, 128.52, 127.57, 127.40, 80.11. Spectral data are in agreement with previously reported.[16]

2,2'-(oxybis(ethane-1,1-diyl))dinaphthalene 10.

Prepared by milling (1 hour) of (S)-8 (0.25 mmol, 43 mg), TFFH (0.375 mmol, 99 mg), K$_2$HPO$_4$ (0.5 mmol, 87.1 mg) and ethyl acetate (50 µL) as LAG additive. The resulting reaction mixture was purified by silica gel chromatography with petroleum ether/ethyl acetate (19:1) as eluent to give ether 10 as white solid (27.5 mg, 67%). According to HPLC analysis on a chiral stationary phase, a mixture of (S,S)- and meso stereoisomers was obtained (lower chromatogram; ratio (S,S):meso = 42:57; trace amount (~1%) of (R,R)-10 was also detected). HPLC [AD-H column (99:1 n-hexane/2-propanol), flow
rate 1 mL·min⁻¹, detection at 210 nm]: (S,S)-10 \( t_R = 4.8 \text{ min} \), \( meso-10 \) \( t_R = 5.6 \text{ min} \), (R,R)-10 \( t_R = 7.4 \text{ min} \). \([\alpha]_D^{25} = -375 \) (c 0.057, CHCl₃).

\( \text{^1H NMR (CDCl}_3, \text{ 400 MHz, } dr \sim 1:1) \): 7.96–7.72 (m, 14H), 7.68 (s, 2H), 7.57–7.41 (m, 12H), 4.77 (q, \( J = 6.4 \text{ Hz} \), 2H, \( meso \)), 4.48 (q, \( J = 6.5 \text{ Hz} \), 1H, (S,S)-isomer), 1.61 (d, \( J = 6.4 \text{ Hz} \), 6H, \( meso \)-isomer), 1.52 (d, \( J = 6.5 \text{ Hz} \), 6H, (S,S)-isomer). \( \text{^13C NMR (CDCl}_3, \text{ 100.6 MHz) } \delta \): 141.76, 141.62, 133.46, 133.40, 133.22, 133.02, 128.60, 128.22, 128.01, 127.98, 127.89, 127.76, 126.24, 126.06, 125.89, 125.74, 125.40, 125.04, 124.71, 124.46, 74.96, 74.77, 24.74, 23.09. Spectral data are in agreement with previously reported.[17]

Analogously, the same transformation was performed with racemic alcohol 8. HPLC analysis on a chiral stationary phase (upper chromatogram) showed formation of (S,S)-, (R,R)- and \( meso-10 \) stereoisomers (ratio (S,S):\( meso:(R,R) = 23:54:23 \)).

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1 concentration is given for (S,S)-10 stereoisomer
4. Synthesis of APIs

1-Benzyl-4-methylpiperazine hydrochloride (MBZP, 33).

Prepared following the general procedure from benzyl alcohol (1 mmol, 104 μL), 1-methylpiperazine (34, 3 mmol, 333 μL, 3 equiv.; lower amount of amine resulted in enhanced formation of dibenzylic quaternary ammonium salt as by-product), TFFH (1.5 mmol, 396 mg, 1.5 equiv.), K₂HPO₄ (2 mmol, 348 mg, 2 equiv.) and ethyl acetate (150 μL). The resulting reaction mixture was diluted with ethylacetate (3×5 mL), filtered, concentrated under reduced pressure and then diluted with methanol (3×2 mL). The insoluble residue containing quaternary ammonium salt by-product was separated by filtration. The filtrate was concentrated under reduced pressure and treated with dichloromethane (2×2 mL). This caused precipitation of additional portions of the same by-product, which was removed by filtration. The filtrate was concentrated under reduced pressure and dissolved in methanol (3 mL) followed by addition of conc. HCl (220 μL). The precipitate of hydrochloric salt 33 was filtered off and washed with methanol (2×3 mL). Additional portions of 33 were crystallized from the remaining metanolic solution to afford 33 as white crystals (141 mg, 54% yield). ¹H NMR (D₂O, 400 MHz): δ 7.65–7.46 (m, 5H), 4.44 (s, 2H), 3.62 (br. s., 8H), 3.01 (s, 3H). ¹³C NMR (D₂O, 100.6 MHz) δ 131.2, 130.7, 129.5, 127.5, 60.5, 50.2, 48.1, 42.8. IR (KBr): ν = 3423, 2977, 2444, 1428, 1370, 1077, 1023, 756, 705 cm⁻¹. HRMS (AJS-ESI) calcd. for C₁₂H₁₉N₂⁺ [M+H]⁺ 191.1543, found m/z 191.1538.

Synthesis of (4-Benzylpiperazin-1-yl)(pyridin-2-yl)methanone (Piberaline, 35).

Picolinic acid (1 mmol, 123.1 mg), t-butyl piperazine-1-carboxylate (1 mmol, 186 mg, 1 equiv.), COMU (1.1 mmol, 471 mg, 1.1 equiv.) and K₂HPO₄ (3 mmol, 523 mg, 3 equiv.) were placed into a 14 mL ZrO₂-coated jar charged with a single 10 mm ZrO₂ milling ball. Then ethyl acetate (250 μL) was added into the jar, which was then set to mill at 30 Hz for 30 minutes. Aq. NaOH solution (pH 11, 10 mL) was added to the resulting crude reaction mixture, the precipitate was transferred to the glass filter, washed with diluted aq. NaOH (pH 8, 3×5 mL) and dried in air to give amide 37 as white solid (210 mg, 72%). R_f = 0.31 (2:1 ethyl acetate / petroleum ether, PMA). ¹H NMR (CDCl₃, 400 MHz): δ 8.54 (ddd, J = 4.9, 1.8, 1.1 Hz, 1H), 7.77 (td, J = 7.7, 1.8 Hz, 1H), 7.62 (dt, J = 7.7, 1.1 Hz, 1H), 7.31 (ddd, J = 7.7, 4.9, 1.1 Hz, 1H), 3.77–3.69 (m, 2H), 3.58–3.47 (m, 4H), 3.46–3.38 (m, 2H), 1.43 (s, 9H). ¹³C NMR (CDCl₃,
100.6 MHz) δ 167.69, 154.64, 153.74, 148.33, 137.22, 124.74, 124.12, 80.28, 47.07, 43.70 (br., 2C), 42.36, 28.41. IR (KBr): ν = 2973, 1670, 1634, 1567, 1420, 1284, 1171, 1023, 750 cm⁻¹. HRMS (AJ-S-ESI) calcd. for C13H21N3O5Na⁺ [M+Na]⁺ 314.1475, found m/z 314.1469. Spectral data are in agreement with previously reported.[18]

**Piperazin-1-yl(pyridin-2-yl)methanone hydrochloride (38).**

Amide 37 (210 mg, 0.72 mmol) was submitted to gaseous HCl for 5 h. Amide 38 (hydrochloride salt) was obtained as white solid (190 mg, quant. yield). ¹H NMR (D₂O, 400 MHz): δ 8.89–8.81 (m, 1H), 8.50 (td, J = 7.9, 1.6 Hz, 1H), 8.09–7.97 (m, 2H), 4.06 (br. s., 2H), 3.83 (br. s., 2H), 3.46 (br. s., 2H), 3.35 (br. s., 2H). ¹³C NMR (D₂O, 100.6 MHz) δ 164.2, 145.6, 145.1, 144.8, 128.1, 125.4, 44.0, 42.9, 42.6, 39.4. HRMS (AJ-S-ESI) calcd. for C₁₀H₁₄N₃O⁺ [M+H]⁺ 192.1131, found m/z 192.1127.

(4-Benzylpiperazin-1-yl)(pyridin-2-yl)methanone (Piberaline, 35).

Prepared following the general procedure from benzyl alcohol (0.265 mmol, 28 µL), amine 38 (0.265 mmol, 70 mg, 1 equiv.), TFFH (0.398 mmol, 105 mg, 1.5 equiv.), K₃HPO₄ (1.06 mmol, 185 mg, 2 equiv.) and ethyl acetate (60 µL). The resulting crude reaction mixture was diluted with water (10 mL) and dichloromethane (10 mL) followed by extraction with dichloromethane (3×5 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure before purification by silica gel chromatography with petroleum ether/acetone (13:7) as eluent to give amine 35 as pale-yellow oil (50 mg, 67%). Rₚ = 0.42 (10:1 dichloromethane / methanol, UV 254 nm). ¹H NMR (CD₃OD, 400 MHz): δ 8.57 (ddd, J = 4.9, 1.7, 1.0 Hz, 1H), 7.94 (td, J = 7.8, 1.7 Hz, 1H), 7.58 (ddd, J = 7.8, 1.2, 1.0 Hz, 1H), 7.48 (ddd, J = 7.8, 4.9, 1.2 Hz, 1H), 7.36–7.22 (m, 5H), 3.79 (m, 2H), 3.56 (s, 2H), 3.46 (m, 2H), 2.56 (m, 2H), 2.44 (m, 2H). ¹³C NMR (CD₃OD, 100.6 MHz) δ 169.25, 154.87, 149.73, 139.07, 138.43, 130.49, 129.38, 128.47, 126.18, 124.40, 63.64, 54.03, 53.53, 48.16, 43.16. IR (KBr): ν = 2809, 1634, 1423, 1299, 1172, 1024, 998, 744 cm⁻¹. HRMS (AJ-S-ESI) calcd. for C₁₇H₂₀N₃O⁺ [M+H]⁺ 282.1597. Spectral data are in agreement with previously reported.[19]

**t-Butyl 4-(4-((hydroxymethyl)benzoyl)piperazine-1-carboxylate (40).**

![Chemical Structure](image)

4-(Hydroxymethyl)benzoic acid (0.657 mmol, 100 mg), t-butyl piperazine-1-carboxylate (0.986 mmol, 277 mg, 1.5 equiv.), TCFH (0.986 mmol, 184 mg, 1.5 equiv.) and K₂HPO₄ (1.97 mmol, 344 mg, 3 equiv.) were placed into a 14 mL ZrO₂-coated jar charged with a single 10 mm ZrO₂ milling ball. Then CPME (180 µL) was added into the jar, which was then set to mill at 30 Hz for 2 hrs. The resulting reaction mixture was diluted with CPME (5 mL), transferred to the filter and washed with CPME (7×1 mL), the filtrate was concentrated under reduced pressure and then triturated with hexane (20 mL) for 1 hour. The precipitate was then filtered off and dried in air before purification by silica gel chromatography with ethyl acetate (100%) as eluent to give amine 40 as white solid (174 mg, 83%). Rₚ = 0.57 (10:1 ethyl acetate/i-PrOH, UV 254 nm). ¹H NMR (CD₃OD, 400 MHz): δ 7.49–7.44 (m, 2H), 7.44–7.40 (m, 2H), 4.65 (s, 2H), 3.79–3.34 (m, 8H), 1.47 (s, 9H). ¹³C NMR (CD₃OD, 100.6 MHz) δ 172.74, 156.23, 145.36, 135.29, 128.25, 127.96, 81.68, 64.58, 47.72 (br., HSQC, 2C), 44.49 (br., HSQC), 43.28 (br., HSQC), 28.59. IR (KBr): ν = 3360, 2984, 1697, 1619, 1422, 1250,
1175, 1124, 1031, 848 cm\(^{-1}\). HRMS (AJS-ESI) calcd. for C\(_{17}\)H\(_{24}\)N\(_2\)O\(_4\)Na\(^+\) [M+Na\(^+\)] 343.1628, found \(m/z\) 343.1623.

\textit{t-Butyl 4-(4-(morpholinomethyl)benzoyl)piperazine-1-carboxylate (41).}

Prepared following the **general procedure** (milling time 2 hrs for the 1st step and 1 hr for the 2nd step) from alcohol 40 (0.156 mmol, 50 mg), morpholine (0.234 mmol, 20 \(\mu\)L, 1.5 equiv.), TFFH (0.234 mmol, 62 mg, 1.5 equiv.), K\(_2\)HPO\(_4\) (0.312 mmol, 54 mg, 2 equiv.) and ethyl acetate (35 \(\mu\)L). The resulting crude reaction mixture was diluted with water (10 mL) and dichloromethane (10 mL) followed by extraction with dichloromethane (3×5 mL). The combined organic layers were dried over Na\(_2\)SO\(_4\), filtered, and concentrated under reduced pressure. The resulting crude reaction mixture was purified by silica gel chromatography with dichloromethane/methanol (39:1) as eluent, and then with ethyl acetate (100\%) as eluent to give amine 41 as colourless oil (49 mg, 80\%). \(R_f = 0.45\) (10:1 dichloromethane/methanol, UV 254 nm). \(^1\)H NMR (CD\(_3\)OD, 400 MHz): \(\delta\) 7.49–7.44 (m, 2H), 7.44–7.38 (m, 2H), 3.69 (m, 4H), 3.77–3.60 (m, 2H), 3.57 (s, 2H), 3.56–3.33 (m, 6H), 2.47 (m, 4H), 1.47 (s, 9H). \(^13\)C NMR (CD\(_3\)OD, 100.6 MHz) \(\delta\) 172.57, 156.19, 141.02, 135.56, 130.76, 128.23, 81.64, 67.76, 63.78, 54.62, 48.66 (br., HSQC, 2C), 44.45 (br., HSQC), 43.33 (br., HSQC), 28.60. IR (KBr): \(\nu = 2856, 1697, 1636, 1418, 1167, 1117, 866\) cm\(^{-1}\). HRMS (AJS-ESI) calcd. for C\(_{21}\)H\(_{32}\)N\(_3\)O\(_4\) \([M+H]^+\) 390.2387, found \(m/z\) 390.2384. Spectral data are in agreement with previously reported.\(^{[20]}\)
5. Nucleophilic substitution with halogens and oxygen nucleophiles.

2-(Bromomethyl)naphthalene 42.

2-Naphthalenemethanol (0.25 mmol, 40 mg), TFFH (0.275 mmol, 73 mg, 1.1 equiv.) and KF (0.5 mmol, 29 mg, 2 equiv.) were placed into a 14 mL ZrO$_2$-coated jar charged with a single 10 mm ZrO$_2$ milling ball. Then CPME (30 µL) was added into the jar, which was then set to mill at 30 Hz for 60 minutes. After, MgBr$_2$·Et$_2$O (0.25 mmol, 65 mg, 1 equiv.) was added to the reaction mixture, and the jar was set to mill at 30 Hz for additional 60 minutes. The resulting crude reaction mixture was analyzed by $^1$H NMR using CDCl$_3$ as a solvent, after separation of insoluble inorganic material. The analysis revealed 95% conversion of alcohol 24 into bromide 42. The crude reaction mixture was diluted with ethyl acetate (15–20 mL), filtered, concentrated under reduced pressure and purified by silica gel chromatography with petroleum ether/ethyl acetate (19:1) as eluent to give 2-(bromomethyl)naphthalene 42 as white solid (47 mg, 86%). $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.89–7.77 (m, 4H), 7.57–7.44 (m, 3H), 4.68 (s, 2H). $^{13}$C NMR (CDCl$_3$, 100.6 MHz): δ 135.23, 133.31, 133.22, 128.92, 128.11, 128.01, 127.87, 126.91, 126.72, 126.63, 34.21. Spectral data are in agreement with previously reported. [21]

2-(Iodomethyl)naphthalene 43.

2-Naphthalenemethanol (0.25 mmol, 40 mg), TFFH (0.375 mmol, 99 mg, 1.5 equiv.) and K$_2$HPO$_4$ (0.5 mmol, 87 mg, 2 equiv.) were placed into a 14 mL ZrO$_2$-coated jar charged with a single 10 mm ZrO$_2$ milling ball. Then ethyl acetate (50 µL) was added into the jar, which was then set to mill at 30 Hz for 60 minutes. After, KI (0.375 mmol, 62.3 mg, 1.5 equiv.) was added to the reaction mixture and the jar was set to mill at 30 Hz for additional 60 minutes. The resulting crude reaction mixture was analyzed by $^1$H NMR using CDCl$_3$ as a solvent, after separation of insoluble inorganic material. The analysis revealed 96% conversion of alcohol 24 into iodide 43. The crude reaction mixture was diluted with ethyl acetate (15–20 mL), filtered, concentrated under reduced pressure and purified by silica gel chromatography with petroleum ether as eluent to give 2-(iodomethyl)naphthalene 43 as white solid (55 mg, 83%). $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.89–7.73 (m, 4H), 7.53–7.41 (m, 3H), 4.64 (s, 2H). $^{13}$C NMR (CDCl$_3$, 100.6 MHz): δ 136.74, 133.43, 132.95, 128.92, 127.96, 127.89, 127.19, 127.09, 126.63, 126.54, 6.61. Spectral data are in agreement with previously reported. [22]

Nucleophilic substitution of alcohol 1 with CsF.

1-Naphthalenemethanol (0.158 mmol, 25 mg), TFFH (0.174 mmol, 46 mg, 1.1 equiv.) and CsF (0.316 mmol, 48 mg, 2 equiv.) were placed into a 14 mL ZrO$_2$-coated jar charged with a single 10 mm ZrO$_2$ milling ball. Then ethyl acetate (25 µL) was added into the jar, which was then set to mill at 30 Hz for 120 minutes. The resulting crude reaction mixture was analyzed by $^1$H NMR using CDCl$_3$ as a solvent, after separation of insoluble inorganic material. The analysis revealed
40% conversion of alcohol 1 into fluoride 44. Characteristic signal of 44 in $^1$H NMR: $\delta$ 5.85 (d, $J_{HF} = 47.9$ Hz).[23]

**Nucleophilic substitution of alcohol 24 with potassium phenoxide.**

![Diagram](image)

2-Naphthalenemethanol (0.25 mmol, 40 mg), TFFH (0.375 mmol, 99 mg, 1.5 equiv.) and K$_2$HPO$_4$ (0.5 mmol, 87 mg, 2 equiv.) were placed into a 14 mL ZrO$_2$-coated jar charged with a single 10 mm ZrO$_2$ milling ball. Then ethyl acetate (50 µL) was added into the jar, which was then set to mill at 30 Hz for 60 minutes. After, potassium phenoxide (0.375 mmol, 50 mg, 1.5 equiv.) was added to the reaction mixture, and the jar was set to mill at 30 Hz for additional 60 minutes. The resulting crude reaction mixture was analyzed by $^1$H NMR using CDCl$_3$ as a solvent, after separation of insoluble inorganic material. The analysis revealed 46% conversion of alcohol 1 into ether 45. Characteristic signals of benzylic CH$_2$ of 45 in $^1$H and $^{13}$C NMR: $\delta_{H}= 5.23$ ppm, $\delta_{C} = 70.0$ ppm.[24]

**Solvolysis of isouronium salt 3 in methanol.**

![Diagram](image)

1-Naphthalenemethanol (0.316 mmol, 50 mg), TFFH (0.348 mmol, 92 mg, 1.1 equiv.) and KF (0.632 mmol, 37 mg, 2 equiv.) were placed into a 14 mL ZrO$_2$-coated jar charged with with a single 10 mm ZrO$_2$ milling ball. Then ethyl acetate (36 µL) was added into the jar, which was then set to mill at 30 Hz for 60 minutes. The resulting crude reaction mixture was transferred to a vial followed by addition of methanol (2.5 mL) and stirred at room temperature. TLC monitoring revealed full consumption of 3 after 3 hrs. The reaction mixture was diluted with water (5 mL) and extracted with ethyl acetate (3×5 mL). The combined organic layers were dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The resulting crude residue was analyzed by $^1$H NMR, revealing 91% yield of methyl ether 46. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.10 (d, $J = 8.0$ Hz, 1H), 7.87 (d, $J = 7.9$ Hz, 1H), 7.81 (d, $J = 8.0$ Hz, 1H), 7.57–7.40 (m, 4H), 4.91 (s, 2H), 3.46 (s, 3H). $^{13}$C NMR (400 MHz, CDCl$_3$) $\delta$ 133.90, 133.75, 131.88, 128.78, 128.67, 126.62, 126.35, 125.91, 125.31, 124.10, 73.32, 58.29. Spectral data are in agreement with previously reported.[25]
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7. \(^1\text{H}\) and \(^{13}\text{C}\) NMR spectra
$^{13}C$ NMR spectrum of compound 27 in CDCl$_3$.

Key resonances are at:
- 174.70 ppm
- 136.13 ppm
- 133.42 ppm
- 132.87 ppm
- 127.95 ppm
- 127.87 ppm
- 127.74 ppm
- 127.67 ppm
- 126.01 ppm
- 125.71 ppm
- 65.60 ppm
- 59.12 ppm
- 53.51 ppm
- 51.85 ppm
- 29.51 ppm
- 23.13 ppm

Chemical shift range: 0 to 200 ppm.
28
38

\[
\text{\textbf{38}}
\]
(S)-10 (dr ~ 1:1)
