Supporting Information
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Supporting Information

Nucleophilic Addition to Nitrones Using a Flow Microreactor

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I. General information

NMR spectra were recorded using JEOL JNM-ECZ-400 ($^1$H, 400 MHz, $^{13}$C, 100 MHz), JNM-ECX-400 ($^1$H, 400 MHz, $^{13}$C, 100 MHz), and JNM-ECA-500W spectrometers ($^1$H, 500 MHz, $^{13}$C, 126 MHz). Chemical shifts are reported in ppm using TMS or the residual solvent peak as a reference. Elemental analyses were carried out on a J-Science Lab JM10 micro corder. High-resolution mass spectra were obtained on a Bruker autoflex speed-TK MALDI-TOF mass spectrometer. Stainless steel (SUS316) Helix-shaped micromixer with inner diameter of 200 μm were manufactured by YMC. Teflon (PTFE) microtube reactors with inner diameter of 500 μm was purchased from YMC and GL Sciences. Solutions were fed to the flow microreactor system using syringe pumps, YSP-101, equipped with gastight syringes purchased from Hamilton Co. (2S,4R)-4-(t-Butyldimethylsilyloxy)pyrrolidine-2-carboxylic acid$^1$ and 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline$^2$ were prepared according to the literature procedures. All other reagents were purchased from commercial supplies and used without purification.

II. Preparation of nitrones

II-1. Preparation of N-benzyl-α-phenylnitrone (1a)$^3$

In a 100 mL flask, equipped with a magnetic stirrer bar and a dropping funnel were placed dibenzylamine (4.81 g, 24.4 mmol), Na$_2$WO$_4$•2H$_2$O (0.036 g, 0.109 mmol), and methanol (49 mL). To the stirred solution was added 30% aqueous hydrogen peroxide (7.8 mL, 85 mmol) dropwise with ice bath cooling. After the addition was completed, the reaction mixture was stirred at room temperature for 3 h prior to the addition of water and NaHSO$_3$ with ice bath cooling to decompose excess of hydrogen peroxide. The mixture was extracted with dichloromethane (20 mL × 3), and the combined organic layers were dried over Na$_2$SO$_4$, and the solvent was removed under reduced pressure. The resulting crude product was purified by flash column chromatography on silica gel using hexane–EtOAc (1:1) as eluent to afford nitrone 1a as a white crystal (2.83 g, 55%): $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 5.07 (s, 2H, CH$_2$), 7.35–7.52 (m, 9H, ArH, -CH=N-), 8.19–8.23 (m, 2H, o-ArH, CH=N(O)Bn); HRMS (MALDI-TOF): m/z calcd for C$_{14}$H$_{13}$NO [M + H]$^+$ 212.1075, found 212.1091. The proton is in accordance with that described in the literature.$^3$

II-2. Preparation of 3,4-dihydroisoquinoline N-oxide (1b)$^3$

In a 200 mL flask, equipped with a magnetic stirrer bar and a dropping funnel were placed 1,2,3,4-tetrahydroisoquinoline (3.34 g, 25.1 mmol), Na$_2$WO$_4$•2H$_2$O (0.330 g, 1.00 mmol), and methanol (50 mL). To the stirred solution was added 30% aqueous hydrogen peroxide (7.7 mL, 75 mmol) dropwise with ice bath cooling. After the addition was completed, the reaction mixture was stirred at room temperature for 3 h prior to the addition of water and NaHSO$_3$ with ice bath cooling to decompose excess of hydrogen peroxide. The mixture was extracted with dichloromethane (20
the combined organic layers were dried over Na₂SO₄, and the solvent was removed under reduced pressure. The resulting crude product was purified by flash column chromatography on silica gel using EtOAc as eluent to afford nitrone 1b as a yellow solid (2.65 g, 72%): ¹H NMR (400 MHz, CDCl₃): δ = 3.19 (t, J = 7.8 Hz, 2H, ArCH₂), 4.12 (t, J= 7.8 Hz, 2H, -CH₂N-), 7.11–7.15 (m, 1H, ArH), 7.21–7.31 (m, 3H, ArH), 7.76 (s, 1H, -CH=N-). The proton is in accordance with that described in the literature.³

**II-3. Preparation of (4R)-4-(t-butyldimethylsilyloxy)-1-pyrroline N-oxide (1c)³**

To a solution of (2S,4R)-4-(t-butyldimethylsilyloxy)pyrrolidine-2-carboxylic acid (7.36 g, 30.0 mmol) in CH₂Cl₂ (150 mL) was added a solution of Na₂WO₄•2H₂O (0.980 g, 2.97 mmol) and Et₄NCl (0.498 g, 3.01 mmol) in water (40 mL). To the stirred mixture was added 30% aqueous hydrogen peroxide (7.7 mL, 75.4 mmol) at 0 ºC. Potassium carbonate (4.97 g, 36.0 mmol) was added portionwise at 0 ºC with vigorous stirring and the solution was stirred at room temperature for 12 h. Excess H₂O₂ was decomposed by adding NaHSO₃ with ice bath cooling. The organic layer was separated, and the aqueous layer was extracted with CH₂Cl₂ (60 mL × 3). The combined organic layers were dried over MgSO₄ and evaporated in vacuo. The resulting crude product was purified by flash column chromatography on silica gel using EtOAc–MeOH (86:14) as eluent to afford nitrone (4R)-1c as a white crystal (3.07 g, 48%): ¹H NMR (400 MHz, CDCl₃): δ = 0.08 (s, 6H, Si(CH₃)₂), 0.88 (s, 9H, t-Bu), 2.59–2.67 (m, 1H, NCHCHH), 2.97–3.06 (m, 1H, NCHCHH), 3.78–3.84 (m, 1H, CHN), 4.12 (dddd, 1H, J = 1.5, 3.7, 6.2, 14.4 Hz, CHN), 4.61–4.67 (m, 1H, CHOSi), 6.83–6.86 (m, 1H, NCH). The proton is in accordance with that described in the literature.³

**II-4. Preparation of N-methyl-α-phenylnitrone (1d)⁴**

To a stirred solution of benzylmethylamine (2.42 g, 20.0 mmol) and Na₂WO₄·2H₂O (0.330 g, 1.00 mmol) in MeOH (45 ml) was added 30% aqueous hydrogen peroxide (3.06 g, 27 mmol) dropwise with ice bath cooling. The reaction mixture was stirred at room temperature for 1 h prior to the addition of 1M aqueous solution of NaHSO₃ with ice bath cooling to decompose excess of hydrogen peroxide. The mixture was extracted with dichloromethane (40 mL × 3), and the combined organic layers were dried over Na₂SO₄, and the solvent was removed under reduced pressure. The resulting crude product was purified by flash column chromatography on silica gel using CH₂Cl₂ as eluent to afford nitrone 1d as a slightly yellow solid (1.06 g, 39%): ¹H NMR (400 MHz, CDCl₃) δ = 3.88 (s, 1H, CH₃), 7.35 (s, 1H, NCH), 7.39–7.44 (m, 3H), 8.22 (m, 2H). The proton is in accordance with that described in the literature.⁴
II-5. Preparation of 3,4-dihydro-6,7-dimethoxyisoquinoline N-oxide (1e)\textsuperscript{2,5}

In a 100 mL flask, equipped with a magnetic stirrer bar and a dropping funnel were placed 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (1.93, 10.0 mmol), Na\textsubscript{2}WO\textsubscript{4}•2H\textsubscript{2}O (0.143 g, 0.43 mmol), and methanol (25 mL). To the solution was added 30% aqueous hydrogen peroxide dropwise with ice bath cooling over a period of 30 min. After the addition was completed, the reaction mixture was stirred at room temperature for 3 h prior to the addition of 1M aqueous solution of NaHSO\textsubscript{3} with ice bath cooling to decompose excess of hydrogen peroxide. The mixture was extracted with dichloromethane (10 mL × 3), the combined organic layers were dried over MgSO\textsubscript{4}, and the solvent was removed under reduced pressure. The resulting crude product was purified by flash column chromatography on silica gel using CH\textsubscript{2}Cl\textsubscript{2}–MeOH (49:1) as eluent to afford nitrone 1e as a white solid (1.523 g, 63%): \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta = 3.12\ (t, J = 7.9\ Hz, 2H, CH\textsubscript{2}CH\textsubscript{2}), 3.89\ (s, 3H, OCH\textsubscript{3}), 3.91\ (s, 3H, OCH\textsubscript{3}), 4.08\ (t, J = 8.0\ Hz, 2H, CH\textsubscript{2}N), 6.62, 6.73 ppm, 7.67 ppm (s, 1H, CHN). The proton is in accordance with that described in the literature.\textsuperscript{2}

III. Preparation of 1-(\textit{t}-butyldimethylsiloxy)-1-methoxyethene (B)\textsuperscript{6}

A 1.6 M hexane solution of \textit{n}-butyllithium (22.9 mL, 36.6 mmol) was added dropwise to a stirred solution of diisopropylamine (5.2 mL, 37.1 mmol) in super dehydrated THF (17 mL) at 0 \textdegree C under nitrogen atmosphere, which was stirred for 3 min. To this solution were added methyl acetate (2.7 mL, 30 mmol) and HMPA (3.3 mL, 19.0 mmol) at –78 \textdegree C. After stirring for 30 min at –78 \textdegree C, the reaction mixture was added dropwise to a stirred solution of TBSCl (5.6 g, 36.7 mmol) in \textit{n}-hexane (9 mL). After stirring for 1 h at –78 \textdegree C, the reaction mixture was warmed to 0 \textdegree C and stirred for 1 h. The reaction was quenched by adding saturated aqueous NaHCO\textsubscript{3} solution (10 mL). Hexane (20 mL) was added and the organic layer was washed with water (10 mL × 3). The organic layer was dried over MgSO\textsubscript{4} and the solvent was removed under reduced pressure. The resulting crude product was purified by flash column chromatography on silica gel using CH\textsubscript{2}Cl\textsubscript{2}–MeOH (49:1) as eluent to afford B as a colorless liquid (4.44 g, 79%): bp 110–113 \textdegree C (0.15 mmHg); \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta = 0.17\ (s, 6H, Si(CH\textsubscript{3})\textsubscript{2}), 0.93\ (s, 9H, \textit{t}-Bu), 3.10\ (d, J = 2.8\ Hz, 1H, =CH\textsubscript{2}), 3.23\ (d, J = 2.7\ Hz, 1H, =CH\textsubscript{2}), 3.54\ (s, 3H, OCH\textsubscript{3}). The proton is in accordance with that described in the literature.\textsuperscript{6}

IV. Experimental details of the Figure 2

A dichloromethane (DCM) solution of 1a (0.84 M) and that of benzoyl chloride (0.94 M) were fed to a helix-shaped micromixer by syringe pumps equipped with a gastight syringe through 50 cm length of PTFE microtubes (an inside diameter \(\phi = 500 \mu\text{m}\)) at a defined flow rate (1.000/0.500/0.125/0.063 mL min\textsuperscript{–1}). The resulting mixture was run through a defined length of the microtube (\(\phi = 500 \mu\text{m}, 50/200/500\ cm\)) at 20 \textdegree C before coming out from an outlet. After a steady state was reached, the outflow (0.3 mL) was collected onto water (1 mL), treated with saturated
aqueous NaHCO$_3$ (0.05 mL), and extracted with DCM (0.1 mL × 3). The combined organic layers were concentrated under reduced pressure to give the crude product, which was analyzed by $^1$H NMR spectroscopy to determine the conversion of 1a, estimated from the combined yield of $N,O$-dibenzoyl-$N$-benzylhydroxylamine$^7$ and $O$-benzoyl-$N$-benzylhydroxylamine$^8$, and the yield of 3a.$^9$ The NMR signal patterns of each compound are in accordance with those described in the literatures.$^7$–$^9$

V. Experimental details of the Figure 3

A DCM solution of 1a (0.84 M) and that of benzoyl chloride (0.94 M) were fed to the first micromixer by syringe pumps equipped with a gastight syringe through 50 cm length of PTFE microtubes (φ = 500 μm) at a flow rate 0.063 mL min$^{-1}$. The resulting mixture was delivered to the second micromixer through a 200 cm length of the microtube (φ = 500 μm) at 20 °C, while a DCM solution of A (0.51 M) was equally fed to the same mixer at a flow rate of 0.126 mL min$^{-1}$. The finally resulting mixture was further run through a defined length of microtube (φ = 500 μm, 500 or 1000 cm) at a defined temperature (20 or 30 °C) before coming out from an outlet. After a steady state was reached, the outflow (0.6 mL) was collected onto water (1 mL), treated with saturated aqueous NaHCO$_3$ (0.1 mL), and extracted with DCM (0.2 mL × 3). The combined organic layers were concentrated under reduced pressure to give the crude product, which was analyzed by $^1$H NMR spectroscopy to determine the yields of 2aA (vide infra) and by-products including $N,O$-dibenzoyl-$N$-benzylhydroxylamine$^7$, $O$-benzoyl-$N$-benzylhydroxylamine$^8$, and 3a.$^9$ The NMR signal patterns of each compound are in accordance with those described in the literatures.$^7$–$^9$

VI. Experimental details of the Table 1

VI-1. Synthesis of 2aA (entry 1)

A DCM solution of 1a (1.00 M) and that of benzoyl chloride (1.05 M) were fed to the first micromixer by syringe pumps equipped with a gastight syringe through 50 cm length of PTFE microtubes (φ = 500 μm) at a flow rate of 0.063 mL min$^{-1}$. The resulting mixture was delivered to the second micromixer through a 200 cm length of the microtube (φ = 500 μm) at 20 °C, while a DCM solution of A (0.60 M) was equally fed to the same mixer at a flow rate of 0.126 mL min$^{-1}$. The finally resulting mixture was further run through a 1000 cm of the microtube (φ = 500 μm) at 30 °C before coming out from an outlet. After a steady state was reached, the outflow was collected for 1469 seconds onto water and diluted with ethyl acetate (5 mL) and hexane (2 mL), which was washed successively with saturated NaHCO$_3$ aqueous solution (2 mL × 3) and brine (2 mL × 3), dried over MgSO$_4$, filtered, and concentrated under reduced pressure to give 2aA$^{10}$ as a colorless oil (0.461 g, 84%): $^1$H NMR (400 MHz, CDCl$_3$): δ = 2.60–2.71 (m, 1H, –CH$_2$–Vy), 2.77–2.88 (m, 1H, –CH$_2$–Vy), 3.89 (d, J = 13.6 Hz, 1H, –CH$_2$–Ph), 4.04–4.13 (m, 2H, –CH$_2$–Ar, –CH–), 4.89 (d, J =
10.1 Hz, 1H, -CH\textsuperscript{2}), 4.93 (d, \( J = 17.1 \) Hz, 1H, -CH\textsuperscript{2}), 5.64 (ddt, \( J = 7, 10.1, 17.1 \) Hz, 1H, -CH\textsuperscript{2}), 7.17–7.46 (m, 12H, ArH), 7.53 (t, \( J = 7.3 \) Hz, 1H, p-ArH–CO–); \(^{13}\)C NMR (100 MHz, CDCl\textsubscript{3}): 38.2, 60.3, 71.0, 117.1, 127.6, 128.1, 128.3, 128.5 (overlapping multiple peaks), 129.3, 129.4, 129.5, 133.0, 135.0, 136.4, 138.7, 165.2.

VI-2. Synthesis of 2bA (entry 2)

See note 7 in main text.

VI-3. Synthesis of 2aB (entry 3)

A DCM solution of 1a (1.00 M) and that of benzoyl chloride (1.05 M) were fed to the first micromixer by syringe pumps equipped with a gastight syringe through 50 cm length of PTFE microtubes (\( \phi = 500 \) \( \mu \)m) at a flow rate of 0.063 mL min\(^{-1}\). The resulting mixture was delivered to the second micromixer through a 200 cm length of the microtube (\( \phi = 500 \) \( \mu \)m) at 20 \( ^\circ \)C, while a DCM solution of B (0.60 M) was equally fed to the same mixer at a flow rate of 0.126 mL min\(^{-1}\). The finally resulting mixture was further run through a 1000 cm of the microtube (\( \phi = 500 \) \( \mu \)m) at 30 \( ^\circ \)C before coming out from an outlet. After a steady state was reached, the outflow was collected for 1321 seconds onto water and diluted with ethyl acetate (5 mL) and hexane (2 mL), which was washed successively with saturated NaHCO\textsubscript{3} aqueous solution (2 mL \( \times \) 3) and brine (2 mL \( \times \) 3), dried over MgSO\textsubscript{4}, filtered, and concentrated under reduced pressure. To the resulting residue was added zinc powder (1.15 g, 17.6 mmol) and acetic acid (6.8 mL), which was stirred at 60 \( ^\circ \)C for 1 h. The reaction mixture was filtrated and treated with saturated NaHCO\textsubscript{3} aqueous solution and diluted with Et\textsubscript{2}O. The organic layer was separated, and 2N HCl aqueous solution was added, which was extracted with water (10 mL \( \times \) 3). The combined aqueous layers were extracted with DCM (10 mL \( \times \) 3). Finally, the combined organic layers were dried over MgSO\textsubscript{4}, filtered, and concentrated under reduced pressure to give 2aB as a colorless oil (0.274 g, 73%): \(^1\)H NMR (400 MHz, CDCl\textsubscript{3}): \( \delta = 2.63 \) (dd, \( J = 5.0, 15.6 \) Hz, 1H, CH\textsubscript{2}CO\textsubscript{2}), 2.73 (dd, \( J = 9.2, 15.6 \) Hz, 1H, CH\textsubscript{2}CO\textsubscript{2}), 3.53 (d, \( J = 13.3 \) Hz, 1H, CH\textsubscript{2}Ph), 3.63 (s, 3H, CH\textsubscript{3}), 3.67 (d, \( J = 13.3 \) Hz, 1H, CH\textsubscript{2}Ph), 4.11 (dd, \( J = 5.0, 9.2 \) Hz, 1H, NCH), 7.21–7.38 (m, 10H, ArH). The proton is in accordance with that described in the literature.\textsuperscript{11}

VI-4. Synthesis of 2bB (entry 4)

A DCM solution of 1b (1.00 M) and that of benzyol chloride (1.05 M) were fed to the first micromixer by syringe pumps equipped with a gastight syringe through 50 cm length of PTFE microtubes (\( \phi = 500 \) \( \mu \)m) at a flow rate of 0.063 mL min\(^{-1}\). The resulting mixture was delivered to the second micromixer through a 200 cm length of the microtube (\( \phi = 500 \) \( \mu \)m) at 20 \( ^\circ \)C, while a DCM solution of B (0.60 M) was equally fed to the same mixer at a flow rate of 0.126 mL min\(^{-1}\). The finally resulting mixture was further run through a 1000 cm of the microtube (\( \phi = 500 \) \( \mu \)m) at
30 °C before coming out from an outlet. After a steady state was reached, the outflow was collected for 1299 seconds onto water and diluted with ethyl acetate (5 mL) and hexane (2 mL), which was washed successively with saturated NaHCO$_3$ aqueous solution (2 mL × 3) and brine (2 mL × 3), and dried over MgSO$_4$ and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography on silica gel using a mixture of hexane and ethyl acetate (8:2) as an eluent to afford 2bB as a yellow oil (0.265 g, 60%): $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 2.85 (dd, $J$ = 5.3, 15.6 Hz, 1H, CHHCO$_2$), 2.96 (dd, $J$ = 7.7, 15.6 Hz, 1H, CHHCO$_2$), 3.08 (br t, $J$ = 6.1 Hz, 2H, CH$_2$Ph), 3.49 (dt, $J$ = 6.1, 12.2 Hz, 1H, CHHN), 3.61 (s, 3H, CH$_3$), 3.65 (dt, $J$ = 6.3, 12.3 Hz, 1H, CHHN), 4.98 (dd, $J$ = 5.3, 7.7 Hz, 1H, CHN), 7.12–7.24 (m, 4H, Ph), 7.41 (t, $J$ = 7.7 Hz, 2H, Ph), 7.55 (t, $J$ = 7.4 Hz, 1H, Ph), 7.94 (d, $J$ = 7.7 Hz, 2H, Ph).

VI-5. Synthesis of 2cB (entry 7)

A DCM solution of 1c (1.00 M) and that of benzoyl chloride (1.05 M) were fed to the first micromixer by syringe pumps equipped with a gastight syringe through 50 cm length of PTFE microtubes ($\phi$ = 500 μm) at a flow rate of 1.5 mL min$^{-1}$. The resulting mixture was delivered to the second micromixer through a 5 cm length of the microtube ($\phi$ = 500 μm) at 0 °C, while a DCM solution of B (0.60 M) was equally fed to the same mixer at a flow rate of 3.0 mL min$^{-1}$. The finally resulting mixture was further run through a 200 cm of the microtube ($\phi$ = 500 μm) at 0 °C before coming out from an outlet. After a steady state was reached, the outflow was collected for 68 seconds onto water and diluted with DCM (5 mL), which was washed successively with saturated NaHCO$_3$ aqueous solution (3 mL × 3) and brine (3 mL × 3), dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography on silica gel using a mixture of hexane and ethyl acetate (8:2) as an eluent to afford 2cB as a yellow solid (0.490 g, 74%). The ratio of cis-2cB/trans-2cB was determined by $^1$H NMR analysis to be 77:23. Diastereomerically pure cis-2cB was obtained by recrystallization from hexane in 43% yield: $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 0.06 (s, 6H, SiMe$_2$), 0.88 (s, 9H, t-Bu), 1.70 (ddd, $J$ = 13.5, 9.0, 5.1 Hz, 1H, CHCHHCH), 2.55 (ddd, $J$ = 13.5, 7.6, 7.2 Hz, 1H, CHCHHCH), 2.61 (dd, $J$ = 15.9, 8.4 Hz, 1H, COCH/H), 2.93 (dd, $J$ = 15.9, 5.4 Hz, 1H, COCH/H), 3.28 (dd, $J$ = 12.5, 7.6 Hz, 1H, NCH/H), 3.55 (dd, $J$ = 12.7, 3.2 Hz, 1H, NCH/H), 3.62 (s, 3H, OMe), 3.72 (ddd, $J$ = 9.0, 8.4, 7.2, 5.4 Hz, 1H, NCH), 4.56 (tdd, $J$ = 7.6, 7.6, 5.0, 3.3 Hz, 1H, SiOCH), 7.38–7.47 (m, 2H, m-ArH), 7.53–7.59 (m, 1H, p-ArH), 7.95–8.01 (m, 2H, o-ArH). The proton is in accordance with that described in the literature.$^1$
VI-6. Synthesis of 2cA (entry 9)

A DCM solution of 1c (1.00 M) and that of benzoyl bromide (1.05 M) were fed to the first micromixer by syringe pumps equipped with a gastight syringe through 50 cm length of PTFE microtubes (ϕ = 500 μm) at a flow rate of 1.5 mL min⁻¹. The resulting mixture was delivered to the second micromixer through a 5 cm length of the microtube (ϕ = 500 μm) at 0 °C, while a DCM solution of A (0.60 M) was equally fed to the same mixer at a flow rate of 3.0 mL min⁻¹. The finally resulting mixture was further run through a 1000 cm of the microtube (ϕ = 500 μm) at 0 °C before coming out from an outlet. After a steady state was reached, the outflow (0.4 mL) was collected into MeOH (2 mL), and concentrated under reduce pressure. The yield of 2cA was determined to be 79% by ¹H NMR spectroscopy, which was obtained in a cis/trans ratio of 10:1.

The same reaction was carried out under slightly modified flow conditions (V = 0.5 mL min⁻¹, R2 = 2000 cm), in which the outflow was collected for 270 seconds onto water and diluted with DCM (10 mL), and washed successively with saturated NaHCO₃ aqueous solution (3 mL x 3), brine (3 mL x 3), dried over MgSO₄, filtered, and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography on silica gel using a mixture of hexane and ethyl acetate (98:2) as an eluent to afford 2cA as a colorless oil (0.454 g, 56%, cis/trans = 9:1): ¹H NMR (400 MHz, CDCl₃): δ = 0.05 (s, 3H, SiMe), 0.06 (s, 3H, SiMe), 0.88 (s, 9H, t-Bu), 1.69 (ddd, J = 13.1, 9.1, 5.1 Hz, 1H, OCHCHH), 2.27–2.36 (m, 1H, =CHCHH), 2.39 (ddd, J = 13.1, 7.7, 7.0 Hz, 1H, OCHCHH), 2.56–2.65 (m, 1H, =CHCHH), 3.24–3.38 (m, 2H, NCH and NCH), 3.50 (ddd, J = 12.8, 3.5 Hz, 1H, NCH), 4.55 (ddd, J = 7.7, 7.7, 5.1, 3.5 Hz, 1H, OCH), 5.00–5.05 (m, 1H, =CH), 5.05–5.1 (m, 1H, =CHH), 5.84 (ddd, J = 17.1, 10.1, 7.1 Hz, 1H, =CH), 7.38–7.47 (m, 2H, m-ArH), 7.53–7.59 (m, 1H, p-ArH), 7.92–8.03 (m, 2H, o-ArH), ¹³C NMR (100 MHz, CDCl₃): δ = −4.8, −4.7, 18.1, 25.9, 37.3, 38.8, 65.6, 67.9, 70.1, 117.0, 128.5, 129.4, 133.1, 135.2, 165.2; Anal. Calcd. for C₂₀H₃₁NO₃Si: C 66.44, H 8.64, N 3.87; found: C 66.39, H 8.47, N 3.85. The stereochemistry of 2cA was determined by DPGFSE-NOE experiment shown below.

NOE map for 2cA
VII. Experimental details of the Table 2

VII-1. Synthesis of 2dC (entry 1)

A dichloroethane (DCE) solution of 1d (0.40 M), C (1.20 M), Et₃N (1.60 M), and 1,3,5-trimethoxybenzene (TMB, 70.2 mM, internal standard) and that of trimethylsilyl triflate (1.60 M) were fed to the micromixer by syringe pumps equipped with a gastight syringe through 50 cm
length of the microtubes ($\phi = 500 \mu \text{m}$) at a flow rate of 0.10 mL min$^{-1}$ at 0 °C. The resulting mixture was run through a 1000 cm of the microtube ($\phi = 500 \mu \text{m}$) at 0 °C before coming out from an outlet. After a steady state was reached, the outflow was collected for 1380 seconds onto saturated NaHCO$_3$ aqueous solution (2 mL), which was extracted with DCM (5 mL $\times$ 3). The combined organic layers were dried over MgSO$_4$, filtered, and concentrated under reduced pressure to give the crude product, which was analyzed by $^1$H NMR spectroscopy. The yield of 2dC as a 53:47 mixture of diastereomers was determined to be 79%, which referred to the $^1$H NMR spectral data of a known 2dC analogue having triethylsilyl (TES) group instead of trimethylsilyl (TMS) group: $^1$H NMR (500 MHz, CDCl$_3$): Major diastereomer: $\delta = 0.26$ (s, 9H), 1.07 (d, $J = 7.2$ Hz, 3H, CH$\text{CH}_3$), 2.42 (s, 3H, NCH$\text{3}$), 3.18 (dq, $J = 8.6$, 7.5 Hz, 1H, CHCH$_3$), 3.75 (brs, 1H, PhCH), 7.21–7.24 (m, 2H), 7.32–7.37 (m, 3H); Minor diastereomer: $\delta = 0.29$ (s, 9H), 1.13 (br, 3H, CHCH$_3$), 2.39 (s, 3H, NCH$_3$), 3.34 (br, 1H, CHCH$_3$), 3.54 (br, 1H, PhCH), 7.33–7.43 (m, 5H).

VII-2. Synthesis of 2dD (entry 2)

A DCE solution of 1d (0.40 M), D (1.20 M), Et$_3$N (1.60 M), and 1,3,5-trimethoxybenzene (TMB, 67.8 mM, internal standard) and that of trimethylsilyl triflate (1.60 M) were fed to the micromixer by syringe pumps equipped with a gastight syringe through 50 cm length of the microtubes ($\phi = 500 \mu \text{m}$) at a flow rate of 0.10 mL min$^{-1}$ at 0 °C. The resulting mixture was run through a 1000 cm of the microtube ($\phi = 500 \mu \text{m}$) at 0 °C before coming out from an outlet. After a steady state was reached, the outflow was collected for 1380 seconds onto saturated NaHCO$_3$ aqueous solution (2 mL), which was extracted with DCM (5 mL $\times$ 3). The combined organic layers were dried over MgSO$_4$, filtered, and concentrated under reduced pressure to give the crude product, which was analyzed by $^1$H NMR.
spectroscopy. The yield of \textit{2dD} as a 63:37 mixture of diastereomers was determined to be 100%, which referred to the \textit{\textsuperscript{1}H} NMR spectral data of a known \textit{2dD} analogue having triethylsilyl (TES) group\textsuperscript{12} instead of trimethylsilyl (TMS) group: \textit{\textsuperscript{1}H} NMR (500 MHz, CDCl\textsubscript{3}): Major diastereomer: $\delta$= 0.34 (s, 9H), 2.44 (s, 3H, NCH\textsubscript{3}), 3.54 (br, 1H), 3.74 (s, 3H, OCH\textsubscript{3}), 4.74 (d, $J$ = 3.6 Hz, 1H), 6.72 (d, $J$ = 8.8 Hz, 2H); Minor diastereomer: $\delta$= 0.32 (s, 9H), 2.46 (s, 3H, NCH\textsubscript{3}), 3.75 (s, 3H, OCH\textsubscript{3}), 4.98–4.19 (m, 2H), 6.64 (d, $J$ = 8.6 Hz, 2H); The remaining aromatic protons of both diastereomers appeared at 6.81–7.29 ppm as overlapped peaks that are not assigned.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{spectrum.png}
\caption{\textit{\textsuperscript{1}H} NMR spectrum of \textit{2dD}.}
\end{figure}

\textbf{VII-3. Synthesis of \textit{2dE} (entry 3)}

A DCE solution of \textit{1d} (0.40 M), \textit{E} (1.20 M), E\textsubscript{t}N (1.60 M), and 1,3,5-trimethoxybenzene (TMB, 66.3 mM, internal standard) and that of trimethylsilyl triflate (1.60 M) were fed to the micromixer by syringe pumps equipped with a gastight syringe through 50 cm length of the microtubes ($\phi$ = 500 $\mu$m) at a flow rate of 0.10 mL min\textsuperscript{-1} at 0 °C. The resulting mixture was run through a 1000 cm of the microtube ($\phi$ = 500 $\mu$m) at 0 °C before coming out from an outlet. After a steady state was reached, the outflow was collected for 210 seconds onto saturated NaHCO\textsubscript{3} aqueous solution (2 mL), which was extracted with DCM (5 mL $\times$ 3). The combined organic layers were dried over MgSO\textsubscript{4}, filtered, and concentrated under reduced pressure to give the crude product, which was analyzed by \textit{\textsuperscript{1}H} NMR spectroscopy. The yield of \textit{2dE} as a 72:28 mixture of diastereomers was determined to be 78%, which referred to the \textit{\textsuperscript{1}H} NMR spectral data of a known \textit{2dE} analogue having triethylsilyl (TES) group\textsuperscript{12} instead of trimethylsilyl (TMS) group: \textit{\textsuperscript{1}H} NMR (500 MHz, CDCl\textsubscript{3}): Major diastereomer: $\delta$= 0.46 (s, 9H), 2.50 (s, 3H, NCH\textsubscript{3}), 3.82 (br, 1H), 5.69 (s, 1H); Minor diastereomer: $\delta$= 0.38 (s, 9H), 2.54 (s, 3H, NCH\textsubscript{3}), 4.55 (d, $J$ = 10.0 Hz, 1H), 4.88 (brs, 1H); The remaining aromatic protons of both diastereomers appeared at 6.78–8.29 ppm as overlapped peaks that are not assigned.
VII-4. Synthesis of 2dF (entry 4)

A DCE solution of 1d (0.40 M), F (1.20 M), Et₃N (1.60 M), and 1,3,5-trimethoxybenzene (TMB, 66.0 mM, internal standard) and that of trimethylsilyl triflate (1.60 M) were fed to the micromixer by syringe pumps equipped with a gastight syringe through 50 cm length of the microtubes (ϕ = 500 µm) at a flow rate of 0.10 mL min⁻¹ at 0 °C. The resulting mixture was run through a 1000 cm of the microtube (ϕ = 500 µm) at 0 °C before coming out from an outlet. After a steady state was reached, the outflow was collected for 240 seconds onto saturated NaHCO₃ aqueous solution (2 mL), which was extracted with DCM (5 mL × 3). The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure to give the crude product, which was analyzed by ¹H NMR spectroscopy. The yield of 2dF as a 54:46 mixture of diastereomers was determined to be 67%, which referred to the ¹H NMR spectral data of a known 2dF analogue having triethylsilyl (TES) group¹² instead of trimethylsilyl (TMS) group: ¹H NMR (500 MHz, CDCl₃): Major diastereomer: δ= 0.33 (s, 9H), 2.46 (s, 3H), 5.02 (d, J = 3.9 Hz, 1H); Minor diastereomer: δ= 0.32 (s, 9H), 2.46 (s, 3H), 4.10 (brs, 1H), 4.54 (d, J = 11.1 Hz, 1H); Other protons are not assigned due to peak overlapping.
VII-5. Synthesis of 2eD (entry 5)

A DCE solution of 1e (0.40 M), D (1.20 M), Et$_3$N (1.60 M), and 1,3,5-trimethoxybenzene (TMB, 60.6 mM, internal standard) and that of trimethylsilyl triflate (1.60 M) were fed to the micromixer by syringe pumps equipped with a gastight syringe through 50 cm length of the microtubes ($\phi$ = 500 $\mu$m) at a flow rate of 0.10 mL min$^{-1}$ at 0 °C. The resulting mixture was run through a 1000 cm of the microtube ($\phi$ = 500 $\mu$m) at 0 °C before coming out from an outlet. After a steady state was reached, the outflow was collected for 1400 seconds onto saturated NaHCO$_3$ aqueous solution (2 mL), which was extracted with DCM (5 mL $\times$ 3). The combined organic layers were dried over MgSO$_4$, filtered, and concentrated under reduced pressure to give the resulting crude product that was then dissolved in THF (2 mL). To the solution was added 2M HCl aqueous solution (0.1 mL) and water (2 mL), which was stirred at room temperature for 10 minutes. The mixture was treated with saturated NaHCO$_3$ aqueous solution (4 mL) and extracted with DCM. The combined organic layers were dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography on silica gel using DCM as an eluent to afford 2eD as a beige solid (0.061 g, 74%): $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 2.77 (dt, $J$ = 18.6, 4.6 Hz, 1H, NCH$_2$CHH), 2.98 (ddd, $J$ = 16.0, 8.6, 4.5 Hz, 1H, NCH$_2$CHH), 3.11 (ddd, $J$ = 13.5, 8.8, 4.5 Hz, 1H, NCHHCH$_2$), 3.43-3.51 (m, 1H, NCHHCH$_2$), 3.49 (s, 3H, OCH$_3$), 3.79 (s, 3H, OCH$_3$), 3.81 (s, 3H, OCH$_3$), 4.36 (d, $J$ = 2.9 Hz, 1H, CHCN), 4.86 (d, $J$ = 2.6 Hz, 1H, NCH), 6.00 (s, 1H), 6.59 (s, 1H), 6.92 (d, $J$ = 8.6 Hz, 2H), 7.32 (d, $J$ = 8.8 Hz, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$): 28.0, 41.2, 53.0, 55.5, 55.6, 55.9, 71.5, 109.7, 111.0, 113.7, 114.4, 119.6, 124.1, 125.9, 127.2, 129.6, 146.9, 148.5, 159.5.
VIII. Photos of experimental setup

Photographs of typical experimental setup are shown below.

For Figure 3 and entries 1–5 in Table 1

For entries 7 and 8 in Table 1

for Figure 5c and Table 2
IX. Spectral data

Figure S1. $^1$H NMR spectrum for 1a in CDCl$_3$.

Figure S2. $^1$H NMR spectrum for 1b in CDCl$_3$. 
Figure S3. $^1$H NMR spectrum for 1c in CDCl$_3$.

Figure S4. $^1$H NMR spectrum for 1d in CDCl$_3$. 
Figure S5. $^1$H NMR spectrum for 1e in CDCl$_3$.

Figure S6. $^1$H NMR spectrum for B in CDCl$_3$. 
Figure S7. $^1$H NMR spectrum for 2aA in CDCl$_3$.

Figure S8. $^{13}$C NMR spectrum for 2aA in CDCl$_3$. 
Figure S9. $^1$H NMR spectrum for 2bA in CDCl$_3$.

Figure S10. $^{13}$C NMR spectrum for 2bA in CDCl$_3$. 

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Figure S11. $^1$H NMR spectrum for 2aB in CDCl$_3$.

Figure S12. $^1$H NMR spectrum for 2bB in CDCl$_3$. 
Figure S13. $^1$H NMR spectrum for 2cB in CDCl$_3$.

Figure S14. $^1$H NMR spectrum for 2cA in CDCl$_3$. 
Figure S15. $^1$C NMR spectrum for 2eA in CDCl$_3$.

Figure S16. $^1$H NMR spectrum for 2eD in CDCl$_3$. 
Figure S17. $^{13}$C NMR spectrum for 2eD in CDCl$_3$. 
X. References