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Kinetically Controlled Simplification of a [10×10] Dynamic Imine Library

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General Methods and Materials

Reagents and solvents were purchased from commercial suppliers and used without further purification, except PhMe and hexane, which were dried over molecular sieves. Three-necked round bottom flask (50 mL) was used in the slow oxidation. A round bottom flask (50 mL) and a Dean-Stark trap were used as the standard part of the reaction apparatus for the re-equilibration of the leftover imines. Column chromatography[1] and slow distillation[2] were performed in the same way as the reported procedures.

NMR spectra were collected on JEOL ECX-400, ECA-500, and ECA-600 NMR spectrometers, with working frequencies of 400, 500, and 600 MHz, successively, for ^{1}H nuclei. Chemical shifts are reported in ppm units relative to the residual signal of the solvent ($CDCl_3$: 7.26 ppm, DMSO-d_6: 2.49 ppm). ^{13}C NMR spectra were recorded with simultaneous decoupling of ^{1}H nuclei. 1,3,5-Trimethoxybenzene (Alfa Aesar, 99%) was used as the internal standard for the quantification of ^{1}H NMR spectra. The melting points were measured on a Barnstead International Mel-TEMP® apparatus, and are uncorrected. The mass spectra were obtained via LCQ Deca XP Plus from Thermo Finnigan (ESI-MS) or Micromass Autospec Ultima (CI-MS). IR spectra were collected on Thermo Scientific™ Nicolet™ iS™10 FT-IR. For GC-FID analysis, Agilent 7820E spectrometer with a Zebron ZB-5MS capillary column (0.25 mm × 0.25 μm × 25 m) was utilized under the following conditions: (*a*) initial temperature: 50 °C for 1 min; (*b*) first heating ramp of 30 °C/min to 80 °C, which temperature was held for 1 min; (*c*) second heating ramp of 45 °C/min to 260 °C; (*d*) third heating ramp of 2 °C/min to 300 °C, which temperature was held for 2 min. Imines **B2**, **B3**, **C2**, **C3**, and **D4** quantification measurements were based on the integration of their peaks in GC-FID chromatogram and corrected by the corresponding response factors toward the internal standard, biphenyl.

All of the imines have been characterized and reported in the literature, except **J4** and **H4** (for the latter, no NMR data were reported in the literature). Syntheses and NMR data for **J4** and **H4** are provided in the following section.

Experiments are presented in the order following the discussion of the manuscript.
Compound numbers are identical to those in the main text of the manuscript.

Syntheses of Imines

4-*n*-Octyloxy-*N*-[(4-nitrophenyl)methylene]benzeneamine (**H4**)

Equimolar amounts of 4-nitrobenzaldehyde (84 mg, 0.56 mmol) and 4-*n*-octyloxyaniline (122 mg, 0.56 mmol) were added into a 50 mL round bottom flask, along with PhMe (25 mL). The solution was heated at reflux for 12 h with a Dean-Stark trap. After that time, PhMe was evaporated in vacuo, and the resulting solid was recrystallized with PhMe/hexane, to give the title compound as a yellow solid in 72% yield (143 mg).

H4: ^{1}H NMR ($CDCl_3$, 500 MHz): 8.58 (s, 1H), 8.33–8.31 (d, 2H), 8.07–8.05 (d, 2H), 7.32–7.29 (m, 2H), 7.36–7.39 (m, 2H), 6.97–6.93 (m, 2H), 3.99 (t, 2H), 1.83–1.77 (m, 2H), 1.50–1.44 (m, 2H), 1.39–1.23 (m, 8H), 0.90–0.88 (m, 3H) ppm. ^{13}C NMR ($CDCl_3$ 125 MHz): 160.0, 154.6, 149.0, 143.4, 142.1, 129.1, 124.1, 122.7, 115.2, 68.4, 31.9, 29.5, 29.4, 26.2, 22.8, 14.2 ppm. Melting point: 60–61 °C. IR (neat): 2939 2918, 2853, 1596, 1575, 1516, 1505, 1339, 830 cm^{-1}. LRMS (ESI, positive): Calcd ($[M+H]^+$), 355.20; Found, 355.26.

4-*n*-Octyloxy-*N*-[(2,4-dinitrophenyl)methylene]benzeneamine (**J4**)

Equimolar amounts of 2,4-dinitrobenzaldehyde (108 mg, 0.56 mmol) and 4-*n*-octyloxyaniline (122 mg, 0.56 mmol) were added into a 50 mL round bottom flask, along with PhMe (25 mL). The solution was heated at reflux for 12 h with a Dean-Stark trap. After that time, PhMe was evaporated in vacuo, and the resulting solid was washed with hexane, to give the title compound as a yellow solid in 54% yield (120 mg).

J4: ^{1}H NMR ($CDCl_3$, 500 MHz): 9.03 (s, 1H), 8.90 (d, 1H), 8.62 (d, 1H), 8.52 (dd, 1H), 7.39–7.36 (m, 2H), 6.98–6.95 (m, 2H), 4.00 (t, 2H), 1.84–1.78 (m, 2H), 1.50–1.44 (m, 2H), 1.39–1.23 (m, 8H), 0.91–0.88 (m, 3H) ppm. ^{13}C NMR ($CDCl_3$ 125 MHz): 159.9, 149.8, 149.0, 148.2, 142.6, 136.4, 131.2, 127.4, 123.5, 120.5, 155.3, 68.5, 31.9, 29.5, 29.4, 29.3, 26.1, 22.8, 14.2 ppm. Melting point: 69–70 °C. IR (FTIR, neat): 2923, 2856, 1648, 1598, 1573, 1523, 1341, 981, 833 cm^{-1}. HRMS (CI, negative): Calcd, 399.1794; Found, 399.1787.

Iterative Self-Sorting of the [10×10] Imine Library

Self-Sorting #1: Slow Oxidation

Equimolar amounts of 2,4-dimethoxybenzaldehyde (92 mg, 0.56 mmol), benzaldehyde (56 μL, 0.56 mmol), 4-*n*-octyloxybenzaldehyde (134 μL, 0.56 mmol), 4-chlorobenzaldehyde (78 mg, 0.56 mmol), 4-bromobenzaldehyde (102 mg, 0.56 mmol), *o*-tolualdehyde (65 μL, 0.56 mmol), *p*-tolualdehyde (64 μL, 0.56 mmol), 2,4-dinitrobenzalehyde (108 mg, 0.56 mmol), 2-nitrobenzaldehyde (84 mg, 0.56 mmol), 1,2-phenylenediamine (60 mg, 0.56 mmol), aniline (50 μL, 0.56 mmol), 4-*n*-octyloxyaniline (122 mg, 0.56 mmol), *o*-anisidine (63 μL, 0.56 mmol), 4-chloroaniline (70 mg, 0.56 mmol), 4-bromoaniline (94 mg, 0.56 mmol), *p*-anisidine (68 mg, 0.56 mmol), *p*-toluidine (58 mg, 0.56 mmol), 2,4-dimethoxyaniline (86 mg, 0.56 mmol), and 4-aminobenzonitrile (66 mg, 0.56 mmol) were added into a 50 mL three-necked round bottom flask, along with PhMe (25 mL). The mixture was heated at 65 °C for 12 h, followed by slow addition of a solution of I_2 (149 mg, 0.59 mmol) in PhMe (12 mL) at a rate of 1 mL h^{-1}. After the completion of addition, the reaction was kept at 65 °C for 1 h. The brown suspension was cooled down to room temperature, and filtered through a silica gel plug. Silica gel was washed with PhMe (70 mL), followed by hexane/acetone (250 mL, v/v = 3:2). The final product was eluted out with acetone (300 mL), followed by the recrystallization with PhMe/acetone. Product was obtained as a brown powder in 74 % yield (105 mg).

A1$_{\mathbf{ox}}$: ^{1}H NMR (DMSO-d_6, 500 MHz): 8.44 (s, 1H), 7.81–7.80 (d, $^3J_{H-H}$=8.0 Hz, 2H), 7.30–7.28 (d, $^3J_{H-H}$=7.5 Hz, 2H), 7.22–7.15 (m, 4H), 2.43 (s, 3H), 2.39 (s, 3H) ppm. Spectral data agree with the previous literature report.[3]

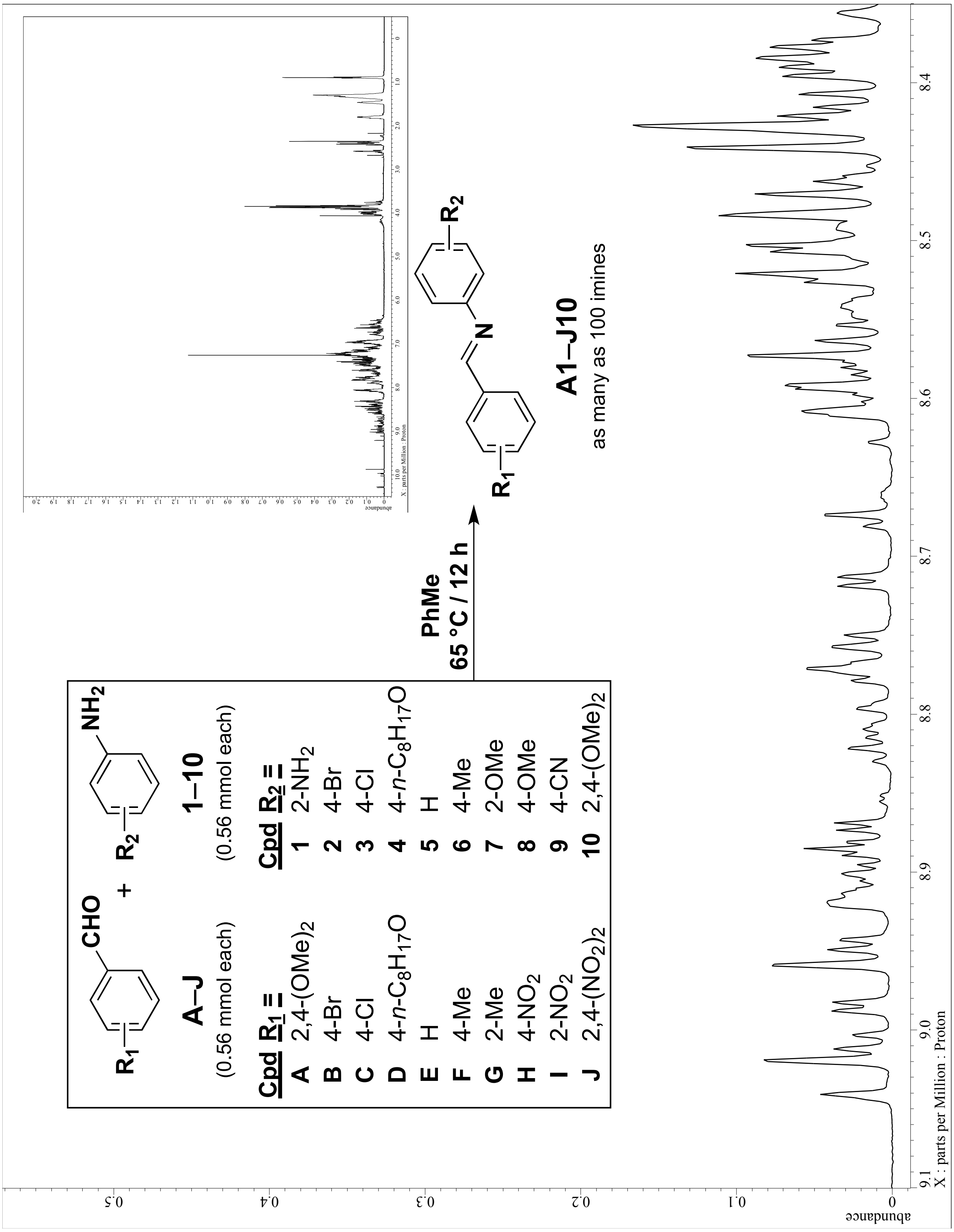

Figure S1. ^{1}H NMR spectrum of the initial [10 × 10] imine library.

Self-Sorting #2: Adsorption-Driven Self-Sorting of [9×9] Imine Library Using Silica Gel-Based Column Chromatography

The filtrate obtained after the first self-sorting step was evaporated in vacuo, and was then added into a 50 mL round bottom flask equipped with a Dean-Stark trap. The mixture was then heated at reflux in PhMe (25 mL) for 12 h. After evaporation of PhMe under vacuum, 2.2 g of oven-dried silica gel was added and mixed with the dried filtrate. This mixture was put on the column pre-loaded with an ~20 cm-high layer of oven-dried silica gel. The column was wrapped with a heating tape and heated to around 50 °C. The elution—first, with a 10:1 hexane/PhMe (v/v, 220 mL) mixture, and then with an 8:1 hexane/PhMe (v/v, 360 mL) mixture—afforded the major sub-library after the evaporation of solvent in vacuo. The yields were calculated using 1,3,5-trimethoxybenzene as the internal standard (268 mg crude, 20.1 mg internal standard).

B2: ^{1}H NMR ($CDCl_3$, 600 MHz): 8.37 (s, 1H), 7.76–7.75 (d, 2H), 7.62–7.61 (d, 2H), 7.51–7.50 (d, 2H), 7.10–7.07 (m, 2H) ppm. **B3**: ^{1}H NMR ($CDCl_3$, 600 MHz): 8.37 (s, 1H), 7.76–7.75 (d, 2H), 7.51–7.50 (d, 2H), 7.36–7.35 (d, 2H), 7.16–7.14 (m, 2H) ppm. **C2**: ^{1}H NMR ($CDCl_3$, 600 MHz): 8.38 (s, 1H), 7.84–7.82 (d, 2H), 7.51–7.50 (d, 2H), 7.46–7.44 (d, 2H), 7.10–7.07 (m, 2H) ppm. **C3**: ^{1}H NMR ($CDCl_3$, 600 MHz): 8.39 (s, 1H), 7.84–7.82 (d, 2H), 7.46–7.44 (d, 2H), 7.36–7.35 (d, 2H), 7.16–7.14 (m, 2H) ppm. Spectral data agree with the previous literature reports.[4]

Calculation of the Yields based on the Integration of ^{1}H NMR Spectra

We assumed that **B2**:**B3**:**C2**:**C3** = 1:1:1:1 (each imine has 28 mmol). Internal standard 1,3,5-trimethoxybenzene (20.1 mg, 0.12 mmol) was added into 268 mg of the crude imine mixture obtained after the first elution. From the integration of the ^{1}H NMR spectrum (Figure S1), the number of moles of **B2** was calculated to be 0.120 mmol × 1.11 = 0.13 mmol. Thus, the yield of **B2** is 0.13 mmol ÷ 0.28 mmol = 46%. Analogous calculations have been performed for all other imines of interest.

Yield of **B3**: 0.12 × 1.34 = 0.16 mmol →→ 0.16 mmol ÷ 0.28 mmol = 57%.

Yield of **C2**: 0.12 × 1.14 = 0.14 mmol →→ 0.14 mmol ÷ 0.28 mmol = 50%.

Yield of **C3**: 0.12 × 1.39 = 0.17 mmol →→ 0.17 mmol ÷ 0.28 mmol = 59%

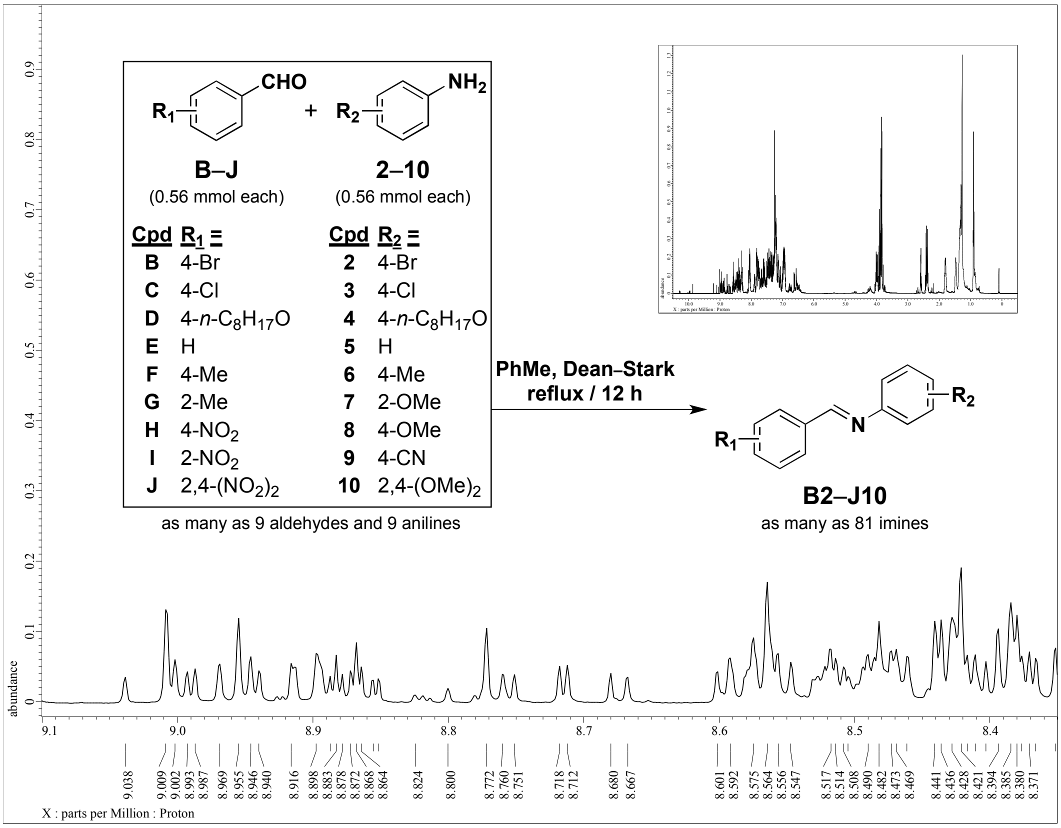

Figure S2. ^{1}H NMR spectrum of the imine library prior to Self-Sorting #2.

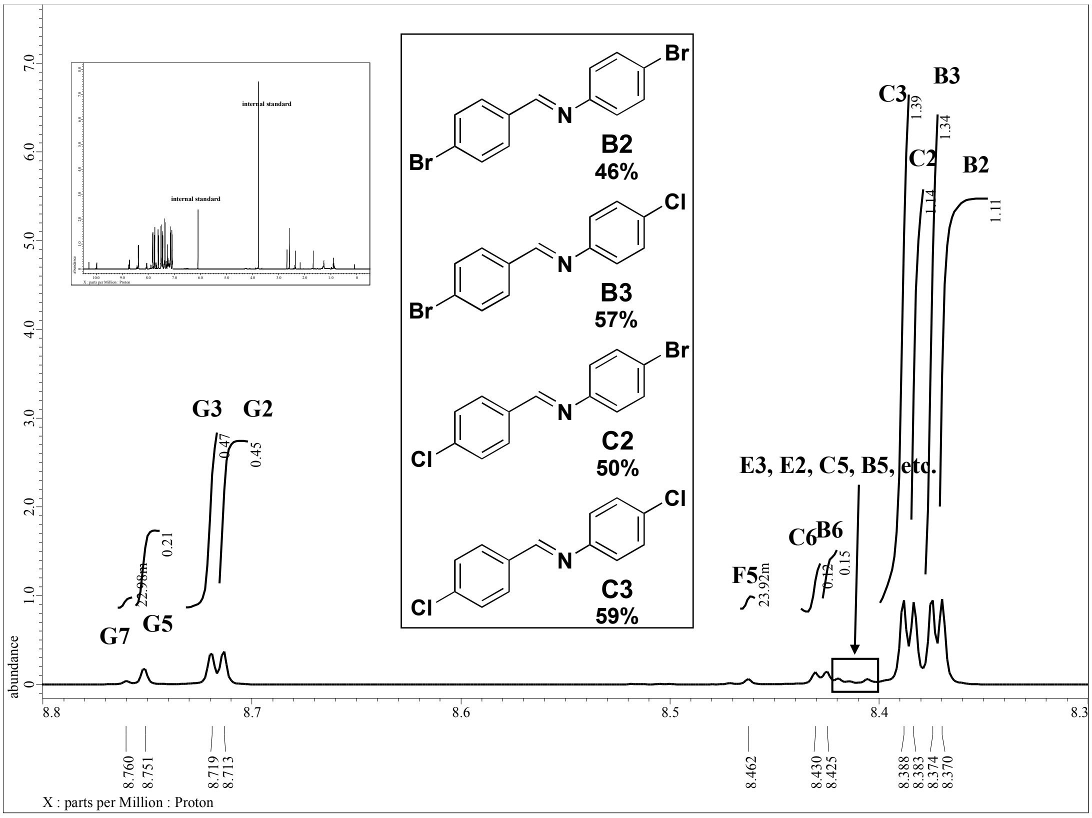

Figure S3. ^{1}H NMR spectrum of the first eluted fraction during Self-Sorting #2.

Self-Sorting #3: Distillation-Driven Self-Sorting of the [7 × 7] Imine Library

The residue of the second section in the column was eluted with EtOAc (400 mL), followed by the evaporation of EtOAc in vacuo. The dried residue was added into a 50 mL round bottom flask equipped with a Dean-Stark trap. The mixture was heated to reflux in PhMe (25 mL) for 12 h. After the evaporation of PhMe under vacuum, the residue was transferred to 25 mL round bottom flask and then equipped with a short distillation condenser. The mixture was distilled under vacuum (0.15 mmHg). The distillation program was as follows: 60 °C for 5 d, 80 °C for 3 d, 100 °C for 2 d, and 120 °C for 2 d. The distillation resulted in a crude dark brown distillation residue (200 mg), which was identified as 4-*n*-octyloxy-*N*-[(4-*n*-octyloxyphenyl)methylene]benzeneamine **D4** (0.34 mmol, 74% purity, 61% yield). Minor imines observed in the distillation residue were 4-*n*-octyloxy-*N*-[(2,4-dinitrophenyl)methylene]benzeneamine (**J4**, 0.13 mmol, 23% yield, 26% purity) and 4-*n*-octyloxy-*N*-[(2,4-dinitrophenyl)methylene]benzeneamine (**H4**, 0.008 mmol).

D4: ^{1}H NMR ($CDCl_3$, 500 MHz): 8.39 (s, 1H), 7.82–7.80 (d, 2H), 7.20–7.18 (d, 2H), 6.97–6.95 (d, 2H), 6.92–6.90 (m, 2H), 4.03–4.00 (t, 2H), 3.98–3.95 (t, 2H), 1.83–1.76 (m, 4H), 1.50–1.43 (m, 4H), 1.37–1.24 (m, 16H), 0.90–0.88 (t, 6H) ppm. **J4**: ^{1}H NMR ($CDCl_3$, 500 MHz): 9.03 (s, 1H), 8.90 (d, 1H), 8.62 (d, 1H), 8.52 (dd, 1H), 7.36–7.39 (m, 2H), 6.95–6.98 (m, 2H), 4.00 (t, 2H), 1.78–1.84 (m, 2H), 1.44–1.50 (m, 2H), 1.23–1.39 (m, 8H), 0.88–0.91 (m, 3H) ppm. Spectral data agree with the previous literature report.[5]

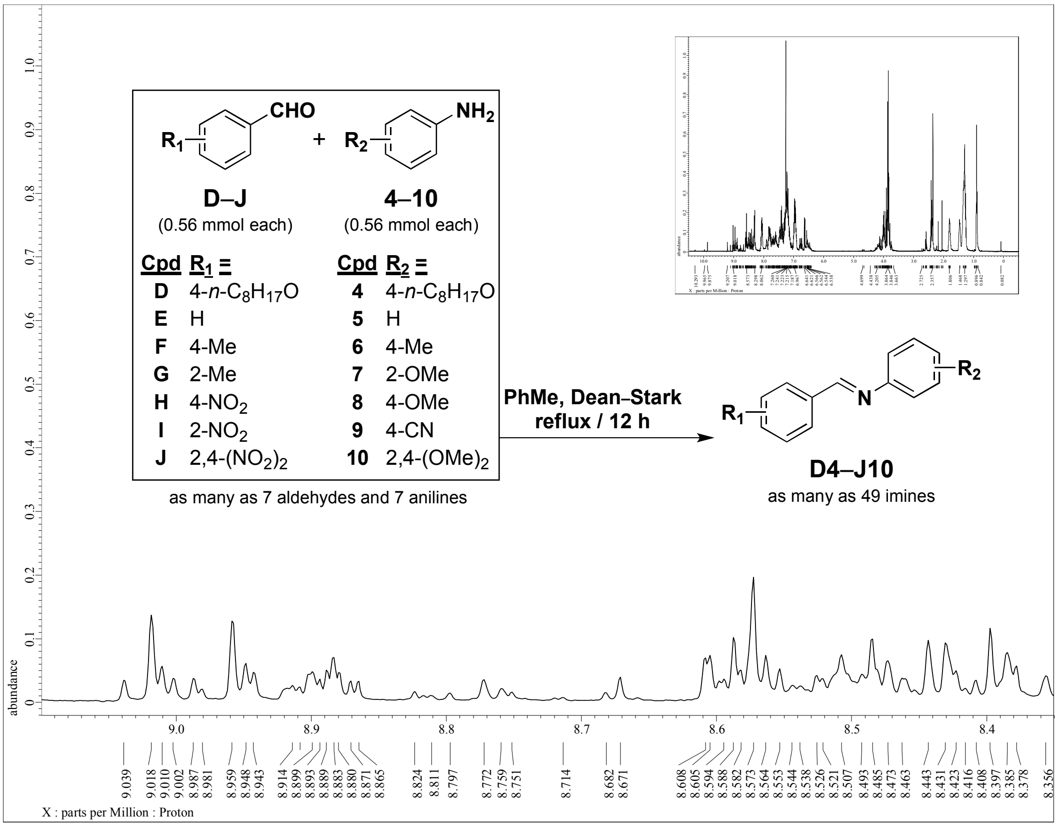

Figure S4. ^{1}H NMR spectrum of the imine mixture prior to distillation in Self-Sorting #3.

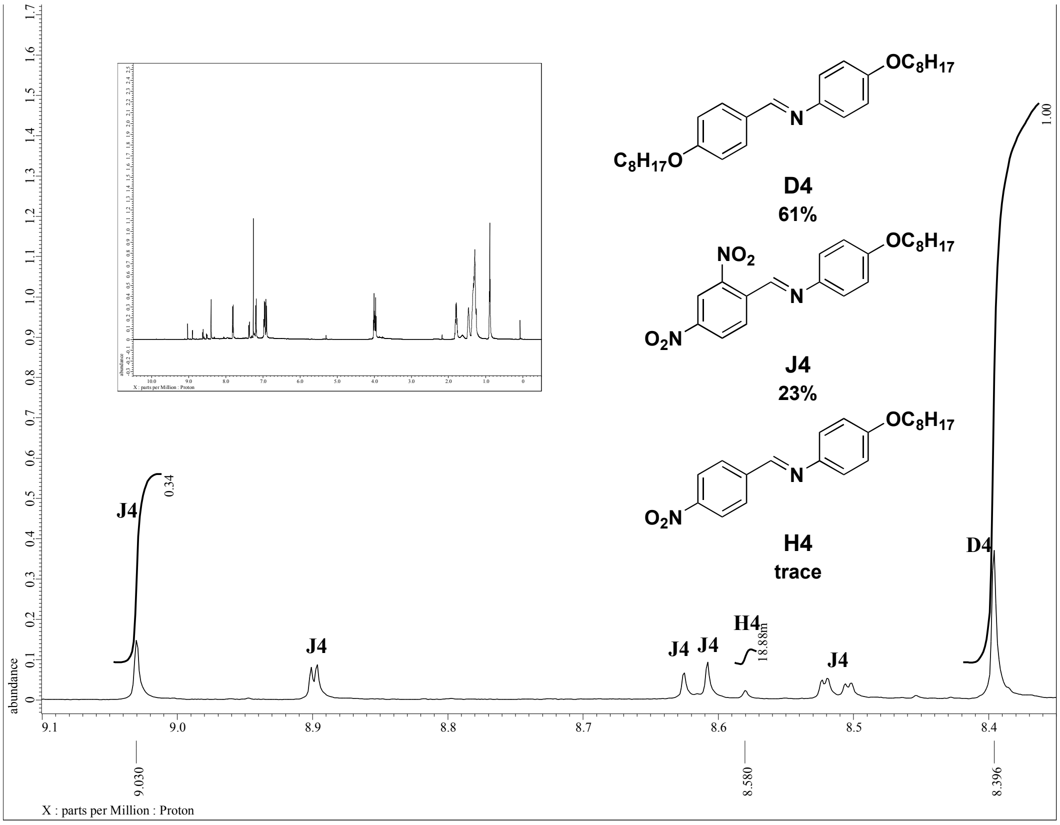

Figure S5. ^{1}H NMR spectrum of the distillation residue, containing imines **D4**, **J4**, and **H4**.

References

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