

# Photocatalytic N-Methylation of Amines over Pd/TiO<sub>2</sub> for the Functionalization of Heterocycles and Pharmaceutical Intermediates

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## Supporting Information

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## 1. General Comments

Reactions were conducted using a 300 W Xe lamp (Ushio: BA-x300/ES1 Technology; CERMAX PE300BF) equipped with a UV cold mirror ( $\lambda = 300\text{--}470$  nm) or using 32 W UV-LEDs [two 16W UV-LEDs ( $\lambda_0 = 365$  nm), LN-128UV2-365 (CCS Inc.)]. GC/MS analyses were performed on an Agilent 6850 series network GC system fitted with an Agilent 5975C series Mass Selective Detector (EI) [column: HP-5MS capillary column ( $l = 30$  m,  $d = 0.25$  mm, film thickness =  $0.25$   $\mu\text{m}$ ); chromatographic elution: isothermal at  $50$   $^{\circ}\text{C}$  for 1 min,  $50\text{--}250$   $^{\circ}\text{C}$  at a rate of  $20$   $^{\circ}\text{C}/\text{min}$ , isothermal at  $250$   $^{\circ}\text{C}$  for 4 min,  $250\text{--}300$   $^{\circ}\text{C}$  at a rate of  $20$   $^{\circ}\text{C}/\text{min}$ , isothermal at  $300$   $^{\circ}\text{C}$  for 1 min; carrier gas: He ( $1.5$  mL/min, at 27 psi)]. The amount of  $\text{H}_2$  was determined by Micro-GC (Agilent 490) equipped with a thermal conductivity detector (column: MS5A 10-m BF column; isothermal at  $80$   $^{\circ}\text{C}$ ; carrier gas: Ar). LC/MS analyses were performed on a Thermo Scientific LPG-3400SD (UltiMate 3000) system fitted with a Thermo Scientific Exactive Plus Mass Spectrometer [column: XBridge Peptide BEH C18 column ( $130$   $\text{\AA}$ ,  $3.5$   $\mu\text{m}$ ,  $2.1\text{mm} \times 150$  mm)]. The amount of  $\text{H}_2\text{O}$  was determined using a Karl–Fischer moisture titrator (Kyoto Electronics Manufacturing, MKC-610-DT).  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on a JEOL ECA-500 ( $500$  MHz for  $^1\text{H}$ ,  $125$  MHz for  $^{13}\text{C}$ ) or JEOL ECA-600 ( $600$  MHz for  $^1\text{H}$ ,  $150$  MHz for  $^{13}\text{C}$ ) at  $27$   $^{\circ}\text{C}$ . Chemical shifts are reported as  $\delta$  in ppm and are internally referenced to tetramethylsilane ( $0.0$  ppm for  $^1\text{H}$ ) and  $\text{CDCl}_3$  ( $77.2$  ppm for  $^{13}\text{C}$ ). The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, bs = broad singlet, dd = doublet of doublet, dq = doublet of quartet, and m = multiplet. High-resolution mass spectra (HRMS) were obtained from micrOTOF-QII (ESI, Bruker). Inductively coupled plasma-atomic emission spectrophotometry (ICP-AES) was carried out with Vista Pro (Agilent) using yttrium as an internal standard after digestion of samples ( $10$  mg) with aqua regia ( $2$  mL) for  $12$  h. Transmission electron microscope (TEM) measurements used a FEI Philips Tecnai 20 TEM with samples mounted on a lacey carbon grid. Typical bright-field (BF) imaging was achieved with a  $70$   $\mu\text{m}$  objective aperture, CCD camera and  $200$  KeV source. Scanning TEM (STEM) high-angle annular dark-field (STEM HAADF) imaging and energy dispersive spectroscopy (EDS) analysis was achieved with  $70$   $\mu\text{m}$  C1 and C2 condenser apertures. For powder X-ray diffraction (PXRD), the already fine powder was placed on a zero-background sample holder. PXRD measurements

were achieved using Ni-filtered CuK $\alpha$  radiation from a PAN-analytical X-ray generator operated at 40 kV and 40 mA. The X-ray generator was coupled with a PW3071/60 Bracket goniometer for sample mounting. Step-scan data (step size 0.02° 2 $\theta$ , counting time 3 s/step) were recorded. Acquisition times were 3 hours per sample. NMR, HRMS, and ICP-AES analyses were carried out at the Chemical Instrumental Center, Research Center for Materials Science, Nagoya University. (S)TEM, EDS, and PXRD analyses were carried out at Department of Chemistry, University of Cambridge.

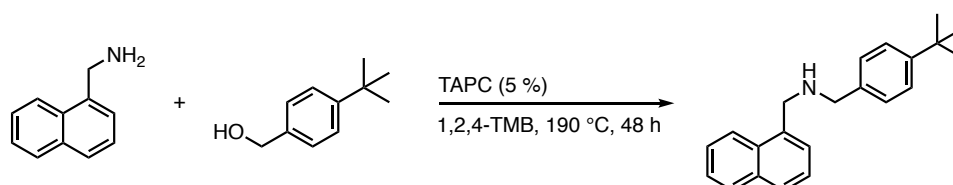
## 2. Materials

1-Naphthalenemethanamine, titanium(IV) oxide (Aeroxide® P25), copper(II) nitrate hemi(pentahydrate), cyclopentyl methyl ether (CPME), 1*H*-indole-5-methanamine (**1c**), 10*H*-phenothiazine-10-ethanamine hydrochloride (1:1) (**1k**), and 1,4,7,10-tetraoxa-15-azacyclopentadecane (**1l**) were purchased from Sigma-Aldrich. 2-(1-Piperazinyl)-3-pyridinecarbonitrile (**1h**) was purchased from Fluorochem. Ammonium formate, chloro[4-(dimethylamino)-*N*-(dimethylamino)phenyl-2-pyridine-carboxamidato]-(pentamethylcyclopentadienyl) iridium(III), anhydrous methanol, hydrochloric acid, sodium carbonate, sodium sulfate, triethylamine, hydrogen tetrachloroaurate(III) tetrahydrate, and hydrogen hexachloroplatinate(IV) hexahydrate were purchased from Kanto Chemicals. 4-*t*-Butylbenzyl alcohol, 1,3,5-triazo-2,4,6-triphosphorine-2,2,4,4,6,6-hexachloride (TAPC), 1,2,4-trimethylbenzene (1,2,4-TMB), acetoacetanilide, 2-(carbobenzoxyamino)-1-ethanol, diphenylacetyl chloride, 3-phenylpropylamine, 3-phenylpropyl bromide, bis(acetonitrile)dichloropalladium(II), sodium borohydride, 2,2-dimethylpropan-1-ol, furfurylamine (**1a**), 1-(3-aminopropyl)-1*H*-imidazole (**1d**), 2-pyridinemethanamine (**1e**), 4-pyridineethanamine (**1f**), *N*-(2-pyridylmethyl)glycine ethyl ester (**1g**), 2-(1-piperazinyl)pyrimidine (**1i**), 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (**1j**), 1,4,8,12-tetraazacyclopentadecane (**1m**), 2-chloro-11-(1-piperazinyl)dibenz[*b,f*][1,4]oxazepine (**1n**), and 1-[2-amino-1-(4-methoxyphenyl)ethyl]cyclohexanol hydrochloride (**1o** •HCl) were purchased from Tokyo Chemical Industry. Acetic acid, sodium acetate, 1-(2-furanylcarbonyl)piperazine (**1b**), colistin sulfate, and *N*-benzylidenebenzylamine were purchased from Wako Chemicals. Methanol-*d*<sub>4</sub> (CD<sub>3</sub>OD, 99.8%) and solvents were purchased from Kanto Chemicals. Ethanol-*d*<sub>6</sub> (CD<sub>3</sub>CD<sub>2</sub>OD, 99%) was

purchased from Cambridge Isotope Laboratories. Silica gel (diameter: 60–210  $\mu\text{m}$ ) was purchased from Kanto Chemical. 50NH<sub>2</sub> silica gel (diameter: 38–63  $\mu\text{m}$ ) was purchased from Wako Chemical.

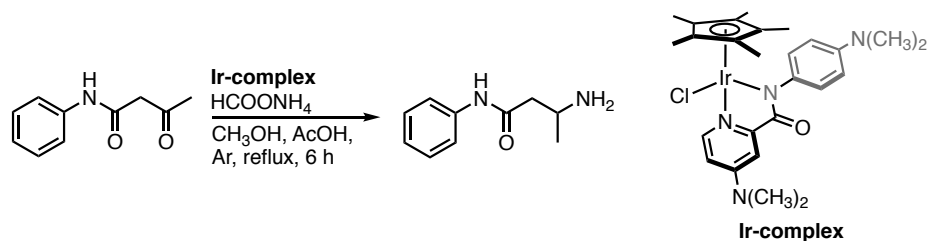
### 3. Substrate Synthesis

#### *N*-[[4-(1,1-Dimethylethyl)phenyl]methyl]-1-naphthalenemethanamine (**1p**)



To a 30-mL heat-dried Young tube equipped with a stirring bar, 1-naphthalenemethanamine (1.57 g, 10.0 mmol), 4-*t*-butylbenzyl alcohol (0.82 g, 5.0 mmol), TAPC (86.9 mg, 0.250 mmol), and 1,2,4-TMB (5 mL) were added under Ar. Then the solution was stirred at 190 °C for 48 h. After the reaction mixture was cooled to 25 °C, TAPC was precipitated by the addition of ethyl acetate (20 mL). After TAPC was filtered, the residue was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate 10:1) to afford **1p** as a yellow oil (0.988 g, 65%). Analytical data for **1p**: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  1.32 (s, 9H), 1.62 (bs, 1H), 3.89 (s, 2H), 4.25 (s, 2H), 7.34 (d,  $J = 8.0$  Hz, 2H), 7.37 (d,  $J = 8.0$  Hz, 2H), 7.42 (dd,  $J = 8.0, 7.5$  Hz, 1H), 7.43–7.52 (m, 3H), 7.76 (d,  $J = 8.0$  Hz, 1H), 7.85 (d,  $J = 8.0$  Hz, 1H), 8.08 (d,  $J = 8.6$  Hz, 1H); <sup>13</sup>C{<sup>1</sup>H} NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  31.5, 34.6, 51.0, 53.5, 123.9, 125.4, 125.5, 125.7, 126.1, 126.2, 127.8, 128.0, 128.8, 132.0, 134.0, 136.1, 137.5, 150.0; HRMS (ESI) calcd for C<sub>22</sub>H<sub>25</sub>NH<sup>+</sup> ( $[M + H]^+$ ) 304.2060, found 304.2063.

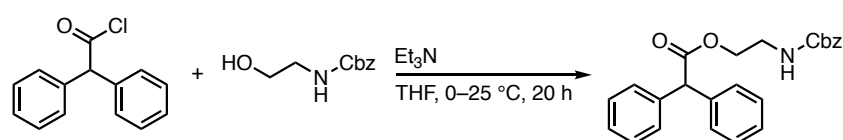
#### 3-Amino-*N*-phenylbutanamide (**1q**)



To a 50-mL Schlenk tube equipped with a stirring bar, acetoacetanilide (0.887 g, 5.01 mmol), ammonium formate (1.58 g, 25.1 mmol), chloro[4-(dimethylamino)-*N*-(dimethylamino)phenyl-2-pyridine-carboxamidato]-(pentamethyl-

cyclopentadienyl)iridium(III) (Ir-complex, 6.5 mg, 10.6  $\mu\text{mol}$ ), acetic acid (0.615 g, 10.2 mmol), and methanol (8 mL) were added. The solution was degassed by three freeze-thaw cycles and heated to reflux for 6 h. After this the reaction mixture was cooled to 25  $^{\circ}\text{C}$ , ammonium formate was precipitated by the addition of ethyl acetate (50 mL). After ammonium formate was filtered, and ethyl acetate was evaporated, the residue was dissolved in 30 mL methanol and 1 mL HCl (35–37%, 12 M aq) was added to the solution. The mixture was stirred at 25  $^{\circ}\text{C}$  for 30 min and methanol was evaporated, then the residue was extracted with H<sub>2</sub>O/ethyl acetate (40 mL/40 mL). The aqueous layer was adjusted to pH 10 using sodium carbonate (s) and was extracted with ethyl acetate (2  $\times$  50 mL). After washing with brine, the organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (methanol) to afford **1q** as a yellow solid (0.460 g, 52%). Analytical data for **1q**: Mp 125.0–126.8  $^{\circ}\text{C}$ ; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  1.22 (d,  $J$  = 6.3 Hz, 3H), 1.75–1.85 (m, 2H), 2.30 (dd,  $J$  = 15.8, 9.0 Hz, 1H), 2.47 (dd,  $J$  = 15.8, 3.5 Hz, 1H), 3.40 (dq,  $J$  = 9.0, 6.3, 3.5 Hz 1H), 7.05–7.09 (m, 1H), 7.30 (t,  $J$  = 7.5 Hz, 2H), 7.52–7.56 (m, 2H), 10.2 (bs, 1H); <sup>13</sup>C{<sup>1</sup>H} NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  25.0, 44.6, 45.2, 119.9, 123.8, 129.0, 138.6, 170.3; HRMS (ESI) calcd for C<sub>10</sub>H<sub>13</sub>N<sub>2</sub>O<sup>-</sup> ([M – H]<sup>-</sup>) 177.1033, found 177.1039.

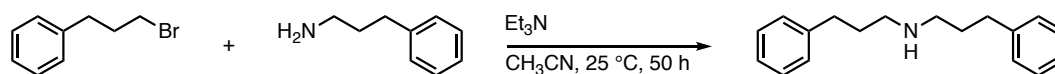
### 2-[[**(Phenylmethoxy)carbonyl**]amino]ethyl-2,2-diphenylacetate (**3r**)



To a 100-mL round-bottom flask equipped with a stirring bar, 2-(carbobenzoxyamino)-1-ethanol (1.97 g, 10.0 mmol), and tetrahydrofuran (10 mL) were added. Then a solution of triethylamine (1.52 g, 15.0 mmol) in tetrahydrofuran (10 mL) was added into the reaction mixture dropwise at 0  $^{\circ}\text{C}$ . Afterwards, a solution of diphenylacetyl chloride (2.54 g, 11.0 mmol) in tetrahydrofuran (15 mL) was added dropwise at 0  $^{\circ}\text{C}$ , before stirring for 20 min. Then the reaction mixture was stirred at 25  $^{\circ}\text{C}$  for 20 h. After the reaction mixture was concentrated under reduced pressure, H<sub>2</sub>O (100 mL) was added and extracted with ethyl acetate (2  $\times$  100 mL). The ethyl acetate extracts were combined, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced

pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate 10:1) to afford **3r** as a colorless oil (3.58 g, 92%). Analytical data for **3r**:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  3.35–3.45 (m, 2H), 4.23 (t,  $J = 4.9$  Hz, 2H), 4.81 (bs, 1H), 5.02 (s, 1H), 5.07 (s, 2H), 7.21–7.39 (m, 15H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  40.2, 57.1, 64.1, 66.9, 127.5, 128.2, 128.3, 128.6, 128.8, 136.5, 138.5, 156.3, 172.5; HRMS (ESI) calcd for  $\text{C}_{24}\text{H}_{23}\text{NO}_4\text{Na}^+$  ( $[\text{M} + \text{Na}]^+$ ) 412.1519, found 412.1505.

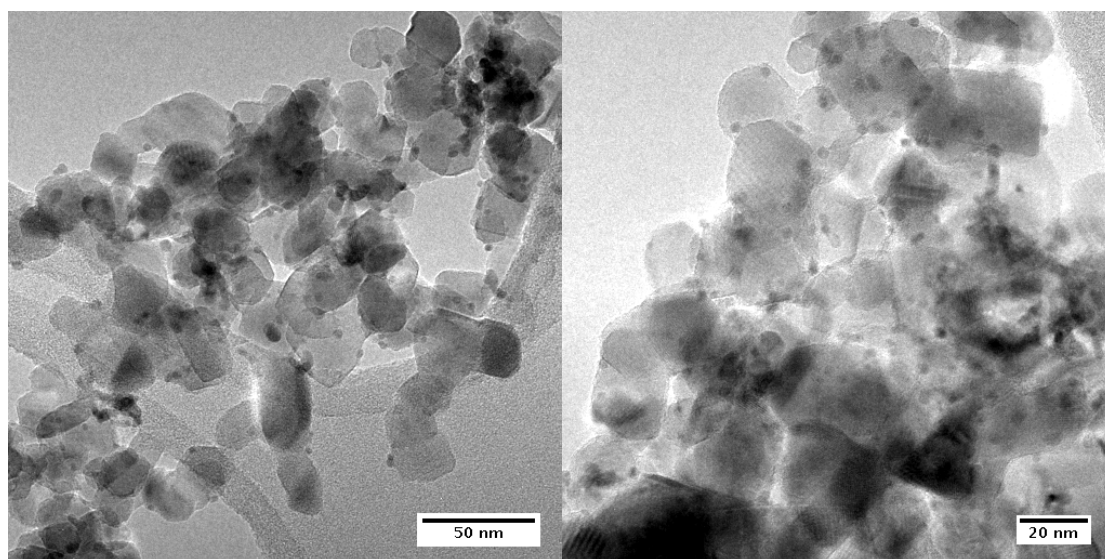
### ***N*-(3-Phenylpropyl)benzenepropanamine (1s)**



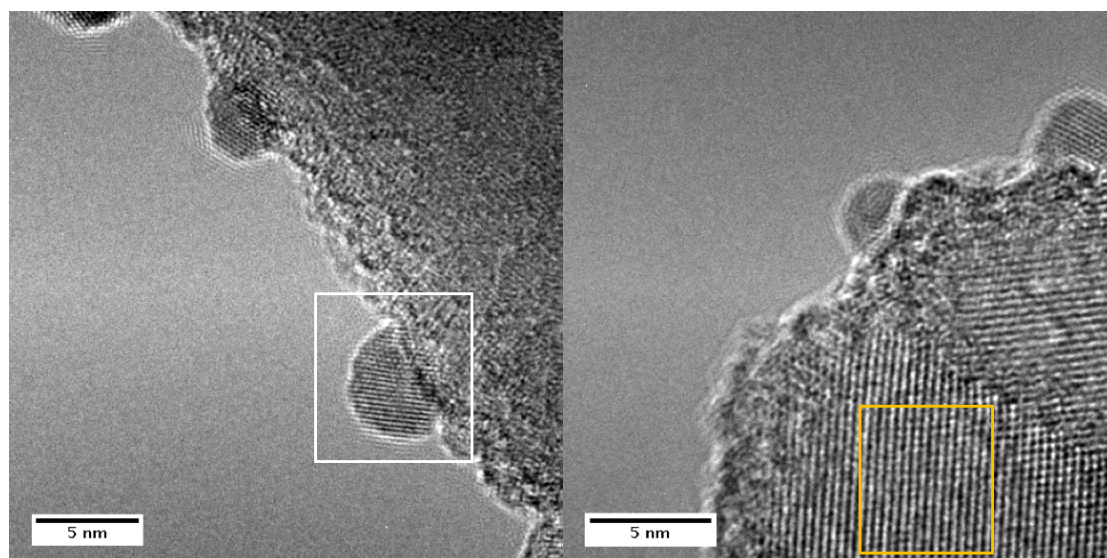
To a 50-mL round-bottom flask equipped with a stirring bar, 3-phenylpropylamine (1.08 g, 7.99 mmol), acetonitrile (10 mL), triethylamine (0.802 g, 7.94 mmol), and 3-phenylpropyl bromide (0.803 g, 4.03 mmol) were added. The reaction mixture was stirred at 25 °C for 50 h (completion of reaction was monitored by TLC). The solution was concentrated under reduced pressure, and white precipitate (triethylamine HBr salt) formed upon addition of ethyl acetate (50 mL). After the triethylamine HBr salt was filtered, the filtrate was concentrated under reduced pressure and purified by silica gel column chromatography (hexane/ethyl acetate 2:1) to afford **1s** as a light-yellow oil (0.410 g, 40%). Analytical data for **1s**:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  1.01 (bs, 1H), 1.80 (tt,  $J = 7.5, 7.4$  Hz, 4H), 2.60–2.66 (m, 8H), 7.16–7.18 (m, 6H), 7.27 (t,  $J = 7.4$  Hz, 4H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  31.9, 33.8, 49.7, 125.9, 128.4, 128.5, 142.3; HRMS (ESI) calcd for  $\text{C}_{18}\text{H}_{23}\text{NH}^+$  ( $[\text{M} + \text{H}]^+$ ) 254.1903, found 254.1890. These data are consistent with the literature values.<sup>1</sup>

<sup>1</sup> Zha, C.; Brown, G. B.; Brouillette, W. J. *Bioorg. Med. Chem.* **2014**, *22*, 95–104.

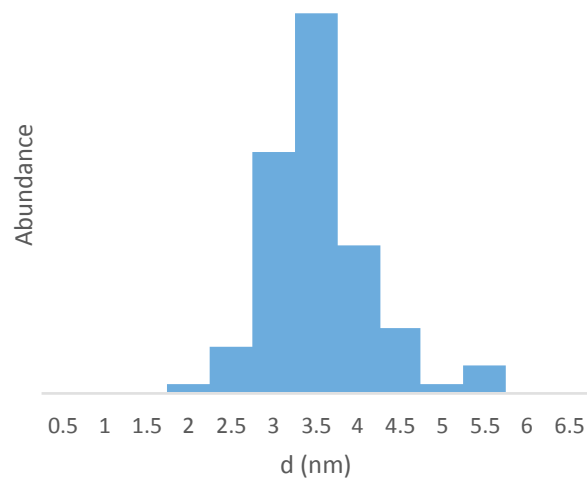
#### 4. Characterization of Pd (5 wt %)/TiO<sub>2</sub>



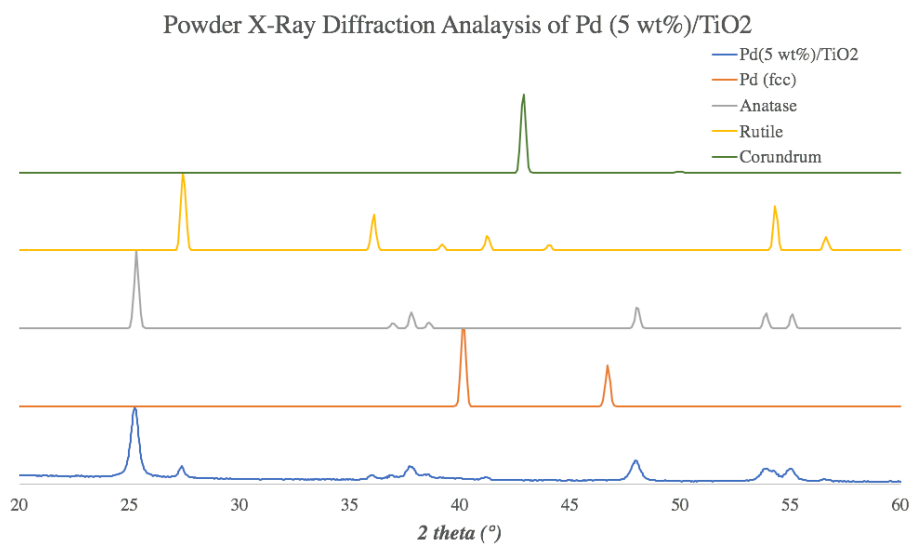
**Figure S1.** Representative BFTEM imaging of Pd (5 wt %)/TiO<sub>2</sub>. Scale bars: 50 nm (left) and 20 nm (right).



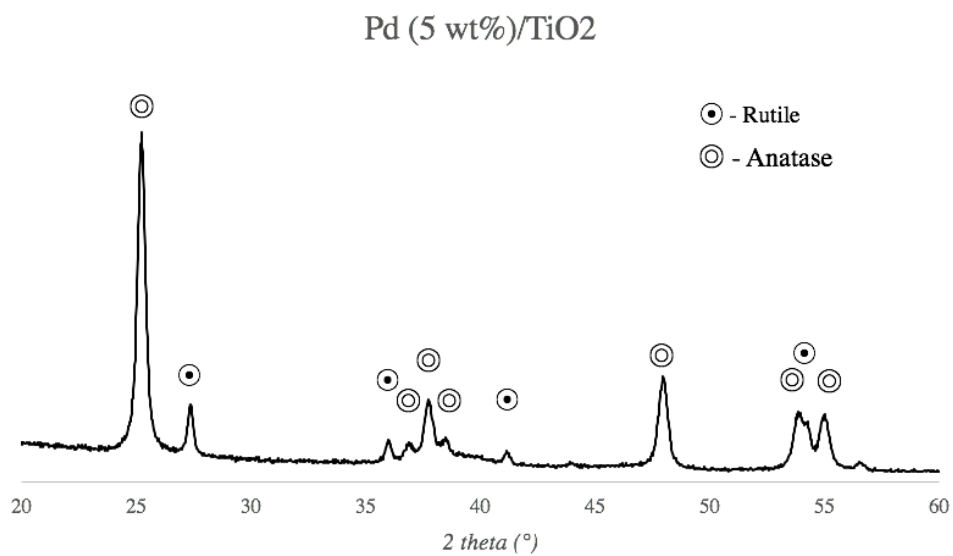
**Figure S2.** Representative high-resolution (HR) BFTEM images of Pd (5 wt %)/TiO<sub>2</sub>. Scale bars: 5 nm. Lattice fringes of particle indicated by a white and orange boxes agree with the [111] reflection of *fcc* Pd (F m -3 m) and [101] reflection of TiO<sub>2</sub> (I 41/a m d S) respectively.



**Figure S3.** Particle size distribution for the Pd NPs in Pd (5 wt %)/TiO<sub>2</sub>. Mean particle size (MPS) =  $3.3 \pm 0.6$  nm.  $N = 100$ .



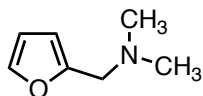
**Figure S4.** Pd (5 wt %)/TiO<sub>2</sub> powder X-ray diffraction pattern compared to the known patterns for Pd and various TiO<sub>2</sub> polymorphs.



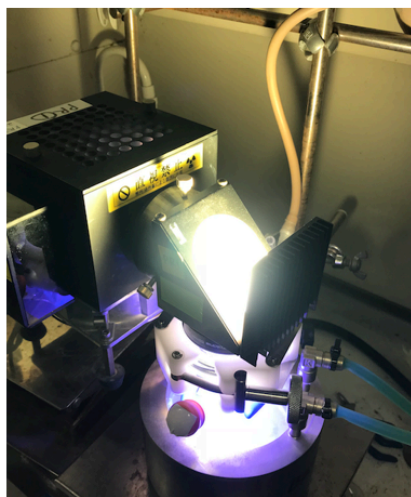
**Figure S5.** Pd (5 wt %)/TiO<sub>2</sub> powder X-ray diffraction pattern with peak assignment.

## 5. Photocatalytic N-Alkylation of Amines

**A representative procedure for N-methylation of **1a** by Pd (5 wt %)/TiO<sub>2</sub> (Table 1, entry 1)**



Pd (5 wt %)/TiO<sub>2</sub> (19.9 mg, 0.9 mol % Pd), anhydrous CH<sub>3</sub>OH (10 mL, 250 mmol), 2,2-dimethylpropan-1-ol (88.2 mg, 1.00 mmol), and furfurylamine (97.3 mg, 1.00 mmol) were added successively to a cylindrical Pyrex glass reaction vessel (diameter: 50 mm, height: 130 mm with a top window made of Pyrex) connected to a rubber balloon. After the resulting mixture was sonicated for 30 sec and deaerated by Ar bubbling *via* cannula for 5 min, the vessel was immersed in a water bath (kept at 25 °C using a cooling circulator), and stirred for 5 h with irradiation [300 W Xe lamp (Ushio: BA-x300/ES1 Technology; CERMAX PE300BF) equipped with a UV cold mirror ( $\lambda = 300\text{--}470$  nm)]. The crude yield was determined by <sup>1</sup>H NMR spectroscopy, monitoring a signal at 2.27 ppm and using 2,2-dimethylpropan-1-ol (0.90 ppm, 9H) as an internal standard.



Irradiation of a reaction vessel



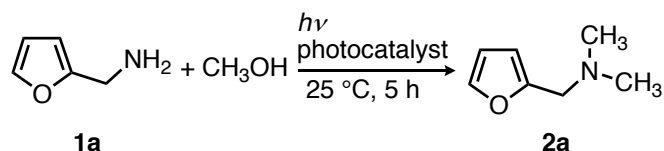
Reaction mixture after centrifugation

### Recycling experiments

As per the representative procedure for N-methylation of **1a** to **2a**, the used photocatalyst was prepared by photoreaction of **1a** with methanol (250 equiv, 10 mL), over Pd (5 wt %)/TiO<sub>2</sub> (20 mg) for 5 h. The reaction mixture was transferred to a 50 mL centrifuge tube and centrifuged (3500 rpm, 10 min). The precipitate was collected

by decantation, washed with methanol (10 mL), and collected by centrifugation and decantation. Drying the precipitate under vacuum (0.01 mm Hg) at rt overnight gave a used photocatalyst. This photocatalyst was used for N-methylation of **1a** to **2a** (2<sup>nd</sup> to 5<sup>th</sup> runs).

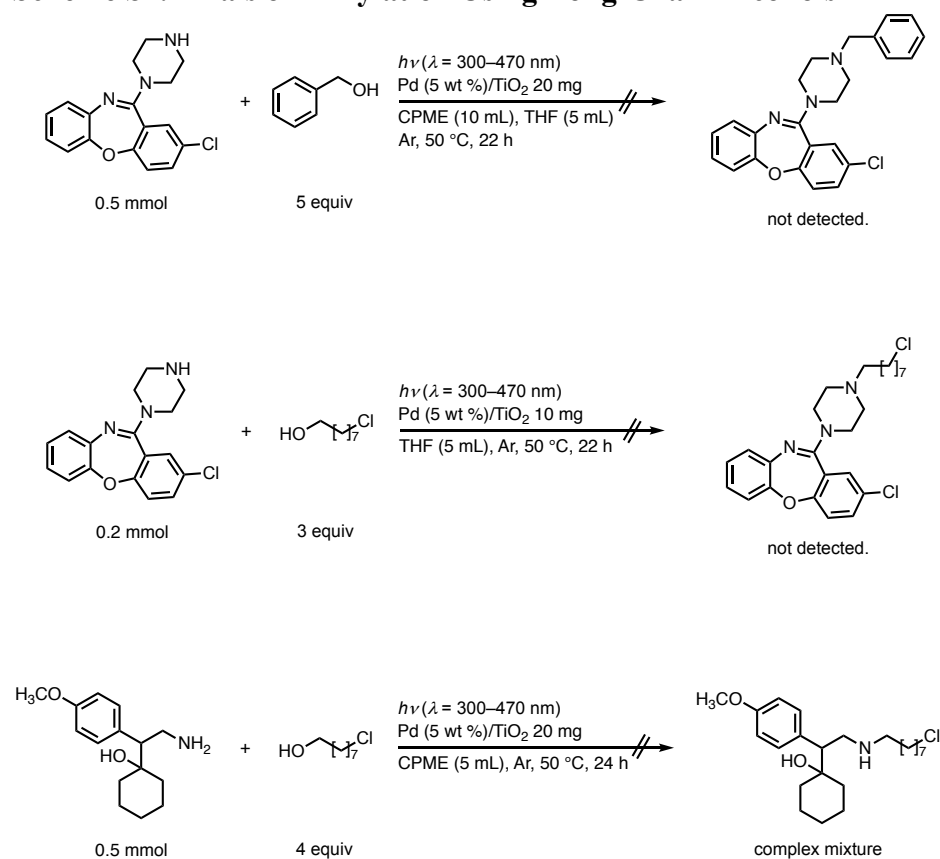
**Table S1. Recycling experiments (Table 1, entries 1, 4–7)**



| run | <b>1a</b> (mmol) | catalyst amount (mg) | methanol (mL) | yield (%) <sup>a</sup> |
|-----|------------------|----------------------|---------------|------------------------|
| 1   | 1.0              | 20.2                 | 10.0          | 96                     |
| 2   | 0.85             | 16.9                 | 8.5           | 94                     |
| 3   | 0.74             | 14.8                 | 7.4           | 90                     |
| 4   | 0.69             | 13.8                 | 6.9           | 89                     |
| 5   | 0.52             | 10.3                 | 5.2           | 89                     |

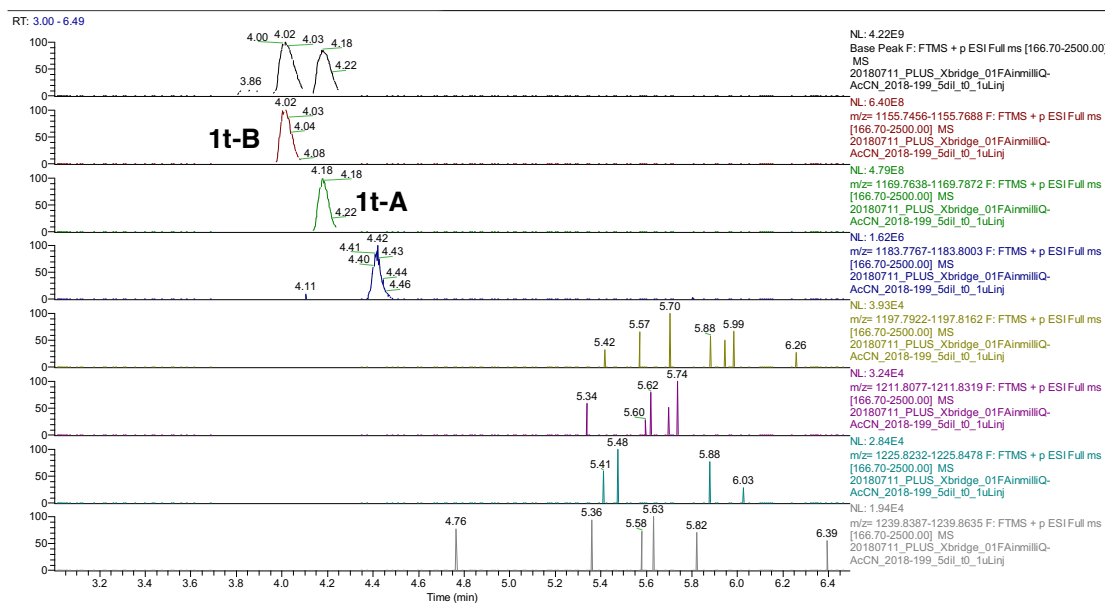
<sup>a</sup><sup>1</sup>H NMR yields using 2,2-dimethylpropan-1-ol as internal standard.

**Scheme S1. Trials on Alkylation Using Long-Chain Alcohols**



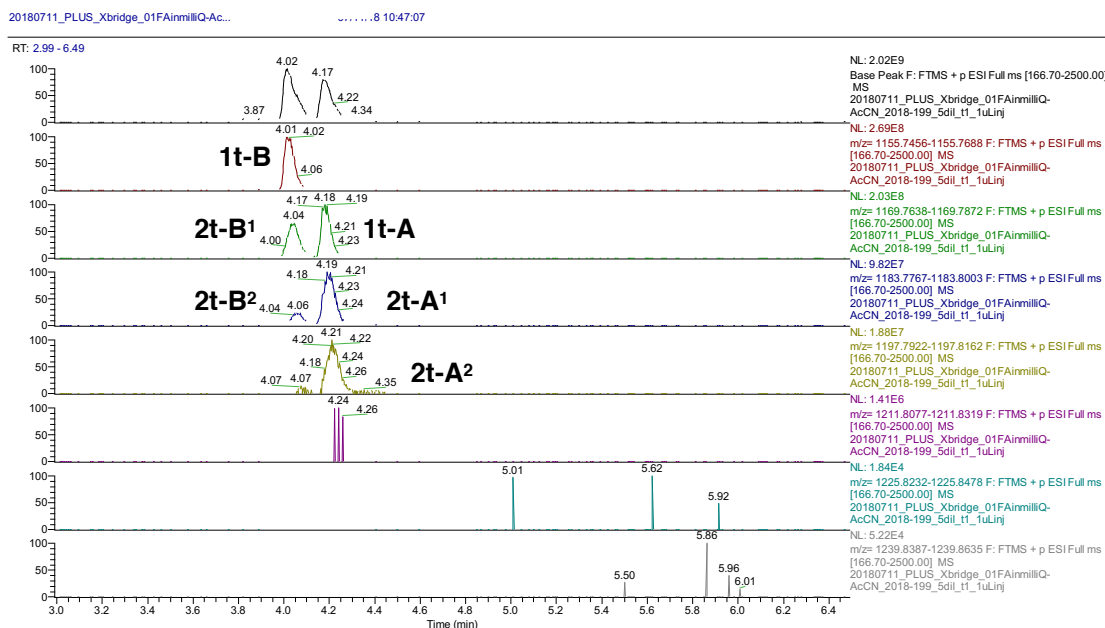
## Photocatalytic N-methylation of colistin by Pd (5 wt %)/TiO<sub>2</sub> (Figure 1)

Pd (5 wt %)/TiO<sub>2</sub> (20.1 mg), sodium carbonate (100 mg), anhydrous CH<sub>3</sub>OH (10 mL), deionized H<sub>2</sub>O (5 mL), and Colistin sulfate (50.2 mg, composed of a mixture of colistin A and B) were added successively to a cylindrical Pyrex glass reaction vessel (diameter: 50 mm, height: 130 mm with a top window made of Pyrex) connected to a rubber balloon. After the resulting mixture was sonicated for 30 sec and deaerated by Ar bubbling *via* cannula for 5 min, the vessel was immersed in a water bath (kept at 25 °C using a cooling circulator), and stirred with irradiation [300 W Xe lamp equipped with a UV cold mirror ( $\lambda = 300\text{--}470$  nm)]. The reaction mixture was analyzed by LC/MS for  $t = 0, 1, 2$  h (Figure S6–S8).



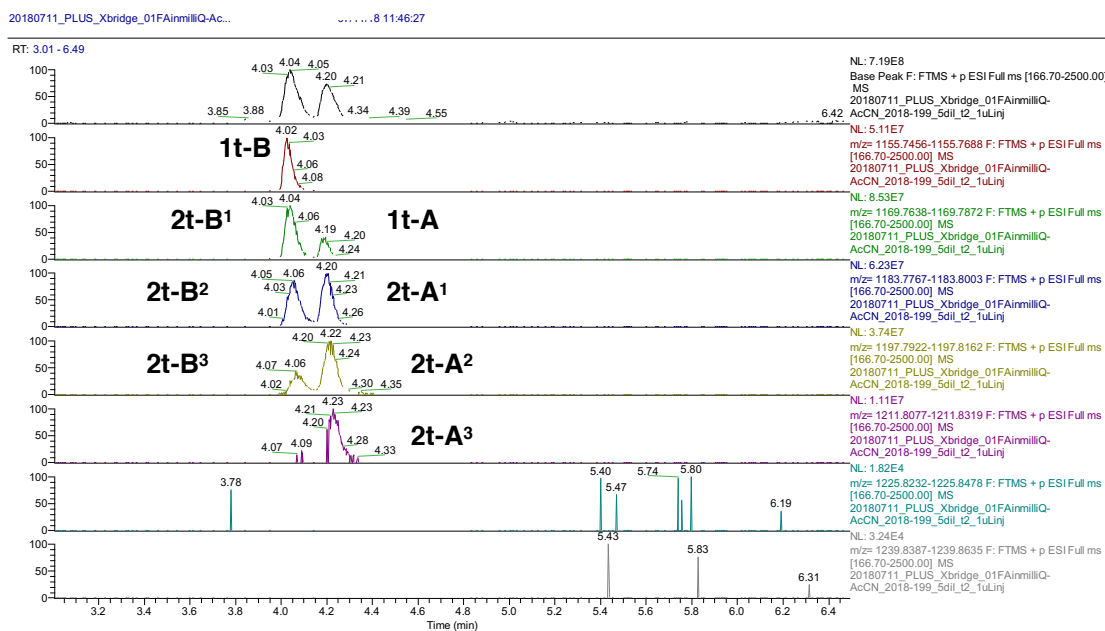
**1t-A** = colistin A ( $[M+H]^+ = 1169.7$ ), **1t-B** = colistin B ( $[M+H]^+ = 1155.7$ )

**Figure S6.** LC/MS analysis at  $t = 0$  h.



**1t-A** = colistin A ([M+H]<sup>+</sup> = 1169.7), **1t-B** = colistin B ([M+H]<sup>+</sup> = 1155.7)  
**2t-A<sup>1</sup>** = mono-*N*-methylcolistin A ([M+H]<sup>+</sup> = 1183.7), **2t-B<sup>1</sup>** = mono-*N*-methylcolistin B ([M+H]<sup>+</sup> = 1169.7)  
**2t-A<sup>2</sup>** = di-*N*-methylcolistin A ([M+H]<sup>+</sup> = 1197.7), **2t-B<sup>2</sup>** = di-*N*-methyl colistin B ([M+H]<sup>+</sup> = 1183.7).

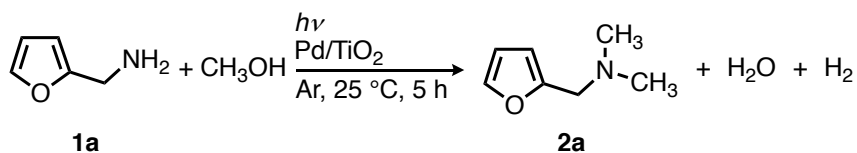
**Figure S7.** LC/MS analysis at  $t = 1$  h.



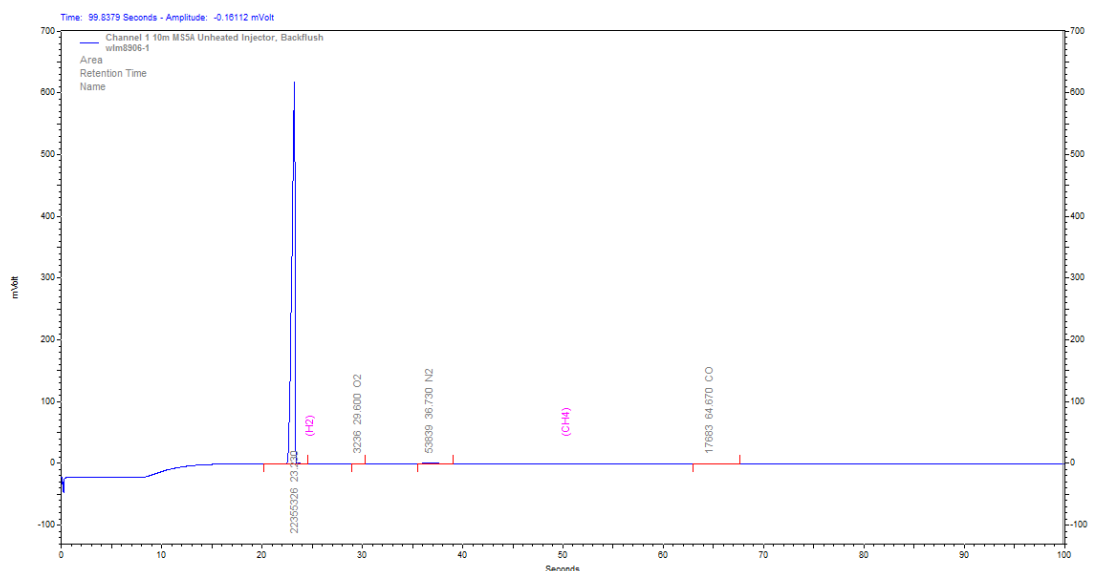
**1t-A** = colistin A ([M+H]<sup>+</sup> = 1169.7), **1t-B** = colistin B ([M+H]<sup>+</sup> = 1155.7)  
**2t-A<sup>1</sup>** = mono-*N*-methylcolistin A ([M+H]<sup>+</sup> = 1183.7), **2t-B<sup>1</sup>** = mono-*N*-methylcolistin B ([M+H]<sup>+</sup> = 1169.7)  
**2t-A<sup>2</sup>** = di-*N*-methylcolistin A ([M+H]<sup>+</sup> = 1197.7), **2t-B<sup>2</sup>** = di-*N*-methyl colistin B ([M+H]<sup>+</sup> = 1183.7)  
**2t-A<sup>3</sup>** = tri-*N*-methyl colistin A ([M+H]<sup>+</sup> = 1211.8), **2t-B<sup>3</sup>** = tri-*N*-methyl colistin A ([M+H]<sup>+</sup> = 1197.7)

**Figure S8.** LC/MS analysis at  $t = 2$  h.

## Quantification of H<sub>2</sub>O and H<sub>2</sub> in N-methylation of **1a** by Pd (5 wt %)/TiO<sub>2</sub>

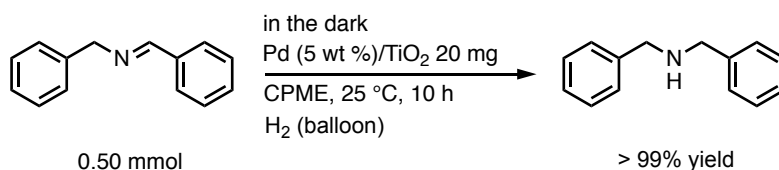


Pd (5 wt %)/TiO<sub>2</sub> (20.0 mg, 0.9 mol % Pd), anhydrous CH<sub>3</sub>OH (10 mL, 250 mmol), 2,2-dimethylpropan-1-ol (88.2 mg, 1.00 mmol), and furfurylamine (97.4 mg, 1.00 mmol) were added successively to a cylindrical Pyrex glass reaction vessel (diameter: 50 mm, height: 130 mm with a top window made of Pyrex). After the resulting mixture was sonicated for 30 sec and deaerated by Ar bubbling *via* cannula for 5 min, the vessel was closed and immersed in a water bath (kept at 25 °C using a cooling circulator), and stirred for 5 h with irradiation [300 W Xe lamp equipped with a UV cold mirror ( $\lambda = 300\text{--}470$  nm)]. 2 mL of the gas phase in the reaction vessel was subjected into Micro-GC via a syringe for quantifying H<sub>2</sub> (18.4 mL, 0.82 mmol, as determined using a calibration line). Generation of H<sub>2</sub>O (75.1 mg, 4.2 mmol) was calculated by analyzing reaction mixture before/after reaction using a Karl–Fischer moisture titrator. <sup>1</sup>H NMR analysis of the crude product indicated the formation of **2a** in 96% yield as determined by monitoring a signal at 2.27 ppm and using 2,2-dimethylpropan-1-ol (0.90 ppm, 9H) as an internal standard.



**Figure S9.** Micro-GC chromatogram of gas phase.

### Hydrogenation of *N*-benzylidenebenzylamine by Pd/TiO<sub>2</sub> under H<sub>2</sub> in the dark



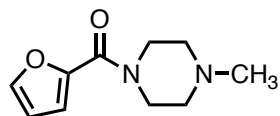
*N*-Benzylidenebenzylamine (97.5 mg, 0.50 mmol), CPME (3.0 mL), and Pd (5 wt %)/TiO<sub>2</sub> (20.2 mg, 1.7 mol % Pd) were added successively to a 40-mL round-bottom centrifugation tube made of Pyrex (IWAKI TE-32) equipped with a stir bar and a septum inlet. After the resulting mixture was sonicated for 20 sec and deaerated by Ar bubbling *via* cannula for 2 min, the tube was covered with Al film and stirred for 10 h at 25 °C under H<sub>2</sub> (balloon, 1 atm). The formation of dibenzylamine (> 99% yield) in the reaction mixture was indicated by GC/MS analysis using *n*-decane as an internal standard.

### Hydrogenation of *N*-benzylidenebenzylamine by Pd/TiO<sub>2</sub> under H<sub>2</sub> with light irradiation

*N*-Benzylidenebenzylamine (97.7 mg, 0.50 mmol), CPME (3.0 mL), and Pd (5 wt %)/TiO<sub>2</sub> (20.2 mg, 1.7 mol % Pd) were added successively to a 40-mL round-bottom centrifugation tube made of Pyrex (IWAKI TE-32) equipped with a stir bar and a septum inlet. After the resulting mixture was sonicated for 20 sec and deaerated by Ar bubbling *via* cannula for 2 min, the tube was stirred for 10 h with light irradiation [32 W UV-LED ( $\lambda_0 = 365$  nm)] at 30 °C under H<sub>2</sub> (balloon, 1 atm). The formation of dibenzylamine (> 99% yield) in the reaction mixture was indicated by GC/MS analysis using *n*-decane as an internal standard.

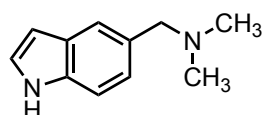
## 6. Characterization of Products

### 1-(2-Furanylcarbonyl)-4-methyl-piperazine (**2b**)



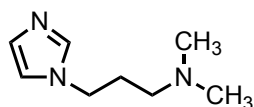
Substrate: 1-(2-furanylcarbonyl)piperazine (180.7 mg, 1.00 mmol);  $t = 10$  h. The product was purified by column chromatography on 50NH<sub>2</sub> silica gel (hexane/ethyl acetate 8:1) to afford **2b** as a light-yellow oil (177.6 mg, 91% yield). Analytical data for **2b**: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  2.33 (s, 3H), 2.46 (t,  $J = 4.9$  Hz, 4H), 3.82 (t,  $J = 4.9$  Hz, 4H), 6.48 (dd,  $J = 3.4, 1.8$  Hz, 1H), 6.99 (d,  $J = 3.4$  Hz, 1H), 7.48 (d,  $J = 1.6$  Hz, 1H); <sup>13</sup>C{<sup>1</sup>H} NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  42.9 (bs), 46.1, 55.2 (bs), 111.3, 116.4, 143.7, 148.0, 159.2; HRMS (ESI) calcd for C<sub>10</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub>Na<sup>+</sup> ([M + Na]<sup>+</sup>) 217.0947, found 217.0947.

### *N,N*-Dimethyl-1*H*-indole-5-methanamine (**2c**)



Substrate: 1*H*-indole-5-methanamine (146.4 mg, 1.00 mmol) ;  $t = 7$  h. The product was purified by column chromatography on 50NH<sub>2</sub> silica gel (hexane/ethyl acetate 10:1) to afford **2c** as a white powder (154.7 mg, 89% yield). Analytical data for **2c**: Mp 130.5–132.3 °C; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>)  $\delta$  2.26 (s, 6H), 3.53 (s, 2H), 6.51 (s, 1H), 7.16–7.18 (m, 2H), 7.32 (d,  $J = 8.2$  Hz, 1H), 7.54 (s, 1H), 8.39 (bs, 1H); <sup>13</sup>C{<sup>1</sup>H} NMR (150 MHz, CDCl<sub>3</sub>)  $\delta$  45.3, 64.9, 102.5, 110.9, 121.3, 123.7, 124.5, 127.8, 130.1, 135.2; HRMS (ESI) calcd for C<sub>11</sub>H<sub>14</sub>N<sub>2</sub>H<sup>+</sup> ([M + H]<sup>+</sup>) 175.1230, found 175.1235.

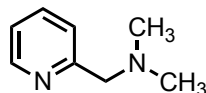
### *N,N*-Dimethyl-1*H*-imidazole-1-propanamine (**2d**)



Substrate: 1-(3-aminopropyl)-1*H*-imidazole (125.4 mg, 1.00 mmol);  $t = 10$  h. After the photocatalyst was removed by filtration, the filtrate was concentrated to give **2d** as a light-yellow oil (148.1 mg, 97% yield). Analytical data for **2d**: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  1.90 (quint,  $J = 6.9$  Hz, 2H), 2.20 (t,  $J = 6.9$  Hz, 2H), 2.20 (s, 6H), 4.01 (t,  $J = 6.9$  Hz, 2H), 6.92 (s, 1H), 7.05 (s, 1H), 7.48 (s, 1H); <sup>13</sup>C{<sup>1</sup>H} NMR (125 MHz,

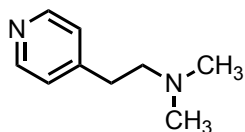
CDCl<sub>3</sub>)  $\delta$  29.0, 44.6, 45.4, 55.8, 119.0, 129.4, 137.4; HRMS (ESI) calcd for C<sub>8</sub>H<sub>15</sub>N<sub>3</sub>Na<sup>+</sup> ([M + Na]<sup>+</sup>) 176.1158, found 176.1172.

#### *N,N*-Dimethyl-2-pyridinemethanamine (**2e**)



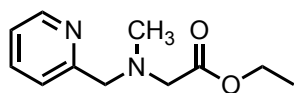
Substrate: 2-pyridinemethanamine (108.4 mg, 1.00 mmol);  $t = 10$  h. The product was purified by column chromatography on silica gel (ethyl acetate) to afford **2e** as a yellow oil (123.5 mg, 91% yield). Analytical data for **2e**: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  2.30 (s, 6H), 3.60 (s, 2H), 7.14–7.19 (m, 1H), 7.39 (d,  $J = 8.1$  Hz, 1H), 7.63–7.68 (m, 1H), 8.54–8.58 (m, 1H); <sup>13</sup>C{<sup>1</sup>H} NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  45.6, 65.8, 122.1, 123.2, 136.5, 149.2, 159.0; HRMS (ESI) calcd for C<sub>8</sub>H<sub>12</sub>N<sub>2</sub>H<sup>+</sup> ([M + H]<sup>+</sup>) 137.1073, found 137.1083. These data are consistent with the literature values.<sup>2</sup>

#### *N,N*-Dimethyl-4-pyridineethanamine (**2f**)



Substrate: 4-pyridineethanamine (122.3 mg, 1.00 mmol);  $t = 9$  h to afford **2f** as a light-yellow oil (139.1 mg, 93% yield). Analytical data for **2f**: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  2.29 (s, 6H), 2.55 (t,  $J = 8.0$  Hz, 2H), 2.77 (t,  $J = 8.0$  Hz, 2H), 7.14 (d,  $J = 4.5$  Hz, 2H), 8.49 (d,  $J = 4.5$  Hz, 2H); <sup>13</sup>C{<sup>1</sup>H} NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  33.6, 45.4, 60.1, 124.1, 149.5, 149.8; HRMS (ESI) calcd for C<sub>9</sub>H<sub>14</sub>N<sub>2</sub>H<sup>+</sup> ([M + H]<sup>+</sup>) 151.1230, found 151.1236. These data are consistent with the literature values.<sup>3</sup>

#### *N*-Methyl-*N*-(2-pyridylmethyl)glycine ethyl ester (**2g**)



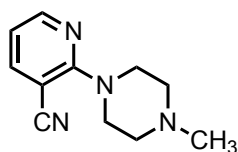
Substrate: *N*-(2-pyridylmethyl)glycine ethyl ester (194.8 mg, 1.00 mmol);  $t = 17$  h. The product was purified by column chromatography on 50NH<sub>2</sub> silica gel (hexane/ethyl acetate 6:1) to afford **2g** as a colorless oil (181.2 mg, 87% yield).

<sup>2</sup>Kim, B-S.; Jiménez, J.; Gao, F.; Walsh, P. J. *Org. Lett.* **2015**, *17*, 5788–5791.

<sup>3</sup>Ghasemi, M. H.; Kowsari, E.; Shafiee, A. *Tetrahedron Lett.* **2016**, *57*, 1150–1153.

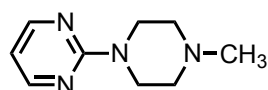
Analytical data for **2g**:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  1.28 (t,  $J = 7.2$  Hz, 3H), 2.44 (s, 3H), 3.36 (s, 2H), 3.86 (s, 2H), 4.19 (q,  $J = 7.2$  Hz, 2H), 7.14–7.21 (m, 1H), 7.48 (d,  $J = 8.0$  Hz, 1H), 7.63–7.70 (m, 1H), 8.55 (d,  $J = 4.0$  Hz, 1H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  14.4, 42.5, 58.2, 60.5, 62.8, 112.2, 123.3, 136.6, 149.3, 158.9, 171.1; HRMS (ESI) calcd for  $\text{C}_{11}\text{H}_{15}\text{N}_2\text{O}_2\text{Na}^+$  ( $[\text{M} + \text{Na}]^+$ ) 231.1104, found 231.1103. These data are consistent with the literature values.<sup>4</sup>

### 2-(4-Methyl-1-piperazinyl)-3-pyridinecarbonitrile (**2h**)



Substrate: 2-(1-piperazinyl)-3-pyridinecarbonitrile (188.4 mg, 1.00 mmol);  $t = 20$  h. The product was purified by column chromatography on 50 $\text{NH}_2$  silica gel (dichloromethane) to afford **2h** as a light-yellow oil (177.5 mg, 88% yield). Analytical data for **2h**:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  2.35 (s, 3H), 2.56 (t,  $J = 4.9$  Hz, 4H), 3.75 (t,  $J = 4.9$  Hz, 4H), 6.75 (dd,  $J = 7.5, 4.6$  Hz, 1H), 7.77 (dd,  $J = 7.7, 2.0$  Hz, 1H), 8.34 (dd,  $J = 4.6, 2.0$  Hz, 1H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  46.1, 48.0, 55.0, 94.9, 114.0, 118.2, 144.0, 151.9, 160.6; HRMS (ESI) calcd for  $\text{C}_{11}\text{H}_{14}\text{N}_4\text{H}^+$  ( $[\text{M} + \text{H}]^+$ ) 203.1291, found 203.1293.

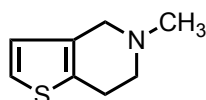
### 2-(4-Methyl-1-piperazinyl)pyrimidine (**2i**)



Substrate: 2-(1-piperazinyl)pyrimidine (164.7 mg, 1.00 mmol);  $t = 11$  h. The product was purified by column chromatography on 50 $\text{NH}_2$  silica gel (hexane/ethyl acetate 8:1) to afford **2i** as a light-yellow oil (162.5 mg, 91% yield). Analytical data for **2i**:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  2.33 (s, 3H), 2.46 (t,  $J = 5.0$  Hz, 4H), 3.84 (t,  $J = 5.0$  Hz, 4H), 6.47 (t,  $J = 4.6$  Hz, 1H), 8.30 (d,  $J = 4.6$  Hz, 2H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  43.6, 46.3, 55.0, 109.9, 157.7, 161.7; HRMS (ESI) calcd for  $\text{C}_9\text{H}_{14}\text{N}_4\text{H}^+$  ( $[\text{M} + \text{H}]^+$ ) 179.1291, found 179.1295.

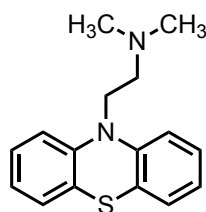
<sup>4</sup>Gavrilova, A. L.; Incarvito, C.; Qin, C. J.; Bosnich, B.; Rheingold, A. L. *Inorg. Chem.* **2001**, *40*, 4101–4108.

### 4,5,6,7-Tetrahydro-5-methylthieno[3,2-c]pyridine (2j)



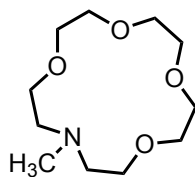
Substrate: using 4,5,6,7-tetrahydrothieno[3,2-c]pyridine (139.6 mg, 1.00 mmol);  $t = 6$  h. After the photocatalyst was removed by filtration, the filtrate was concentrated to give **2j** as a yellow oil (125.6 mg, 82% yield). Analytical data for **2j**:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  2.47 (s, 3H), 2.73 (t,  $J = 5.7$  Hz, 2H), 2.91 (t,  $J = 5.7$  Hz, 2H), 3.50 (s, 2H), 6.71 (d,  $J = 5.2$  Hz, 1H), 7.06 (d,  $J = 5.2$  Hz, 1H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  25.6, 45.7, 52.9, 55.1, 122.7, 125.2, 133.1, 134.0; HRMS (ESI) calcd for  $\text{C}_8\text{H}_{11}\text{NSH}^+$  ( $[\text{M} + \text{H}]^+$ ) 154.0685, found 154.0692.  $^1\text{H}$  NMR data are consistent with the literature values.<sup>5</sup>

### *N,N*-Dimethyl-10*H*-phenothiazine-10-ethanamine (2k)



Substrate: 10*H*-phenothiazine-10-ethanamine, hydrochloride (1:1) (139.4 mg, 0.50 mmol);  $t = 22$  h. The product was purified by column chromatography on silica gel (ethyl acetate) and 50NH<sub>2</sub> silica gel (ethyl acetate) to afford **2k** as a light-yellow oil (85.9 mg, 66% yield). Analytical data for **2k**:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  2.31 (s, 6H), 2.70 (t,  $J = 7.2$  Hz, 2H), 3.99 (t,  $J = 7.2$  Hz, 2H), 6.86–6.94 (m, 4H), 7.09–7.17 (m, 4H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  46.0, 46.6, 56.8, 115.4, 122.6, 124.8, 127.4, 127.5, 145.2; HRMS (ESI) calcd for  $\text{C}_{16}\text{H}_{18}\text{N}_2\text{SH}^+$  ( $[\text{M} + \text{H}]^+$ ) 271.1263, found 271.1271. These data are consistent with the literature values.<sup>6</sup>

### 13-Methyl-1,4,7,10-tetraoxa-13-azacyclopentadecane (2l)

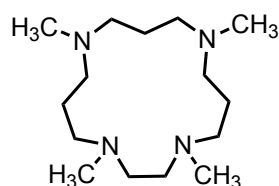


<sup>5</sup>PCT Int. Appl., 2012037411 (A2).

<sup>6</sup>Galons, H.; Miocque, M.; Combet-F, C.; Bensaïd, Y.; Decodts, G. *Chem. Pharm. Bull.* **1985**, *33*, 5108–5109.

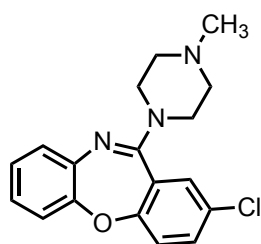
Substrate: 1,4,7,10-tetraoxa-15-azacyclopentadecane (219.6 mg, 1.00 mmol);  $t = 6$  h. After the photocatalyst was removed by filtration, the filtrate was concentrated to give **2l** as a light-yellow oil (222.4 mg, 95% yield). Analytical data for **2l**:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  2.34 (s, 3H), 2.69 (t,  $J = 5.7$  Hz, 4H), 3.64–3.68 (m, 16H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  44.7, 57.0, 69.4, 70.3, 70.5, 70.9; HRMS (ESI) calcd for  $\text{C}_{11}\text{H}_{23}\text{NO}_4\text{H}^+$  ( $[\text{M} + \text{H}]^+$ ) 234.1700, found 234.1707.  $^1\text{H}$  NMR data are consistent with the literature values.<sup>7</sup>

### 1,4,8,12-Tetramethyl-1,4,8,12-tetraazacyclopentadecane (**2m**)



Substrate: 1,4,8,12-tetraazacyclopentadecane (215.1 mg, 1.00 mmol);  $T = 50$  °C,  $t = 26$  h. The product was purified by column chromatography on 50NH<sub>2</sub> silica gel (hexane/ethyl acetate 5:1) to afford **2m** as a colorless oil (171.0 mg, 66% yield). Analytical data for **2m**:  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  1.57–1.64 (m, 6H), 2.21 (s, 6H), 2.24 (s, 6H), 2.38–2.41 (m, 8H), 2.44 (t,  $J = 6.8$  Hz, 4H), 2.46 (s, 4H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  25.2, 25.4, 43.4, 43.9, 54.7, 54.9, 55.0, 55.2; HRMS (ESI) calcd for  $\text{C}_{15}\text{H}_{34}\text{N}_4\text{H}^+$  ( $[\text{M} + \text{H}]^+$ ) 271.2856, found 271.2867.  $^1\text{H}$  NMR data are consistent with the literature values.<sup>8</sup>

### 2-Chloro-11-(4-methyl-1-piperazinyl)dibenz[*b,f*][1,4]oxazepine (**2n**)



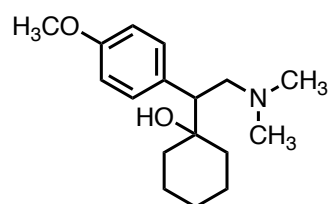
Substrate: 2-chloro-11-(1-piperazinyl)dibenz[*b,f*][1,4]oxazepine (314.1 mg, 1.00 mmol); Pd (5 wt %)/TiO<sub>2</sub> (40 mg, 1.7 mol % Pd);  $T = 50$  °C,  $t = 25$  h. The product was purified by column chromatography on silica gel (hexane/ethyl acetate 4:1 and

<sup>7</sup>Kuo, P-L.; Miki, M.; Ikeda, I.; Okahara, M. *Tetrahedron Lett.* **1978**, *44*, 4273–4276.

<sup>8</sup>Namuswe, F.; Hayashi, T.; Jiang, Y.; Kasper, G. D.; Sarjeant, A. A. N.; Moenne-L., P.; Goldberg, D. P. *J. Am. Chem. Soc.* **2010**, *132*, 157–167.

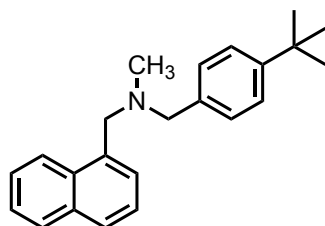
dichloromethane/methanol 30:1) to afford **2n** as a yellow solid (238.2 mg, 73% yield). Analytical data for **2n**: Mp 107.5–110.5 °C; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 2.36 (s, 3H), 2.54 (bs, 4H), 3.55 (bs, 4H), 6.97–7.00 (m, 1H), 7.06–7.10 (m, 2H), 7.12–7.16 (m, 1H), 7.18 (d, *J* = 9.0 Hz, 1H), 7.31 (d, *J* = 2.7 Hz, 1H), 7.38 (dd, *J* = 9.0, 2.7 Hz, 1H); <sup>13</sup>C{<sup>1</sup>H} NMR (150 MHz, CDCl<sub>3</sub>) δ 46.2, 47.4 (bs), 54.9, 120.1, 122.7, 124.6, 125.1, 125.8, 127.1, 129.1, 130.3, 132.5, 140.2, 151.9, 159.0, 159.3; HRMS (ESI) calcd for C<sub>18</sub>H<sub>18</sub>ClN<sub>3</sub>OH<sup>+</sup> ([M + H]<sup>+</sup>) 328.1211, found 328.1211.

### 1-[2-(Dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol (**2o**)



Substrate: 1-[2-amino-1-(4-methoxyphenyl)ethyl]cyclohexanol (prepared by treatment of its hydrochloride salt with sodium carbonate aq. and extraction with ethyl acetate) (1.00 g, 4.02 mmol); *T* = 50 °C, *t* = 48 h. The product was purified by column chromatography on silica gel (hexane/ethyl acetate 1:1) to afford **2o** as a white solid (0.862 g, 77% yield). Analytical data for **2o**: Mp 75.7–77.1 °C; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 0.81–0.99 (m, 2H), 1.24–1.40 (m, 2H), 1.46–1.59 (m, 3H), 1.61–1.79 (m, 3H), 2.29 (dd, *J* = 12.6, 3.5 Hz, 1H), 2.32 (s, 6H), 2.94 (dd, *J* = 12.6, 3.5 Hz, 1H), 3.27 (t, *J* = 12.6 Hz, 1H), 3.79 (s, 3H), 6.81 (d, *J* = 8.6 Hz, 2H), 7.05 (d, *J* = 8.6 Hz, 2H); <sup>13</sup>C{<sup>1</sup>H} NMR (125 MHz, CDCl<sub>3</sub>) δ 21.4, 21.7, 26.1, 31.3, 38.2, 45.6, 51.7, 55.3, 61.3, 74.3, 113.4, 130.2, 132.9, 158.4; HRMS (ESI) calcd for C<sub>17</sub>H<sub>27</sub>NO<sub>2</sub>H<sup>+</sup> ([M + H]<sup>+</sup>) 278.2115, found 278.2117. These data are consistent with the literature values.<sup>9</sup>

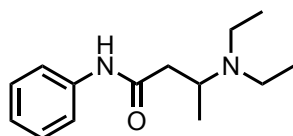
### *N*-[[4-(1,1-Dimethylethyl)phenyl]methyl]-*N*-methyl-1-naphthalenemethanamine (**2p**)



<sup>9</sup>Chavan, S. P.; Khobragade, D. A.; Thakkar, M.; Kalkote, U. R. *Synth. Commun.* **2007**, *37*, 3901–3906.

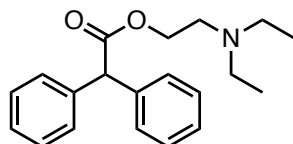
Substrate: *N*-[[4-(1,1-dimethylethyl)phenyl]methyl]-1-naphthalenemethanamine (303.7 mg, 1.00 mmol);  $T = 50\text{ }^{\circ}\text{C}$ ,  $t = 7\text{ h}$ . The product was purified by column chromatography on silica gel (dichloromethane) to afford **2p** as a light-yellow oil (261.6 mg, 82% yield). Analytical data for **2p**:  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  1.30 (s, 9H), 2.20 (s, 3H), 3.57 (s, 2H), 3.92 (s, 2H), 7.26–7.35 (m, 4H), 7.36–7.41 (m, 1H), 7.44–7.49 (m, 3H), 7.75 (d,  $J = 8.6\text{ Hz}$ , 1H), 7.80–7.84 (m, 1H), 8.23 (d,  $J = 8.6\text{ Hz}$ , 1H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  31.6, 34.6, 42.5, 60.6, 62.2, 125.0, 125.2 (3C), 125.6, 125.8, 127.5, 128.0, 128.5, 128.9, 132.7, 134.0, 135.2, 136.4, 150.0; HRMS (ESI) calcd for  $\text{C}_{23}\text{H}_{27}\text{NH}^+$  ( $[\text{M} + \text{H}]^+$ ) 318.2216, found 318.2226. These data are consistent with the literature values.<sup>10</sup>

### 3-(Diethylamino)-*N*-phenylbutanamide (**2q**)



Substrate: 3-amino-*N*-phenylbutanamide (125.3 mg, 0.70 mmol);  $T = 50\text{ }^{\circ}\text{C}$ ,  $t = 10\text{ h}$ . The product was purified by column chromatography on 50 $\text{NH}_2$  silica gel (hexane/ethyl acetate 10:1) to afford **2q** as a light-yellow oil (132.8 mg, 81% yield). Analytical data for **2q**:  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  0.98 (d,  $J = 6.9\text{ Hz}$ , 3H), 1.17 (t,  $J = 7.2\text{ Hz}$ , 6H), 2.22 (dd,  $J = 16.8, 2.9\text{ Hz}$ , 1H), 2.38–2.47 (m, 2H), 2.59 (dd,  $J = 16.8, 12.0\text{ Hz}$ , 1H), 2.75–2.84 (m, 2H), 3.32 (dq,  $J = 16.8, 6.9, 2.9\text{ Hz}$ , 1H), 7.05 (t,  $J = 7.5\text{ Hz}$ , 1H), 7.29 (t,  $J = 7.5\text{ Hz}$ , 2H), 7.55 (d,  $J = 7.5\text{ Hz}$ , 2H), 11.67 (bs, 1H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  13.2, 14.1, 40.1, 42.7, 51.7, 119.4, 123.5, 129.0, 138.9, 170.6; HRMS (ESI) calcd for  $\text{C}_{14}\text{H}_{22}\text{N}_2\text{OH}^+$  ( $[\text{M} + \text{H}]^+$ ) 235.1805, found 235.1810.

### 2-Diethylaminoethyl diphenylacetate (**2r**)

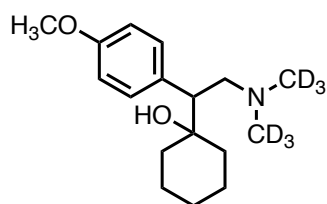


Substrate: 2-[[[(phenylmethoxy)carbonyl]amino]ethyl]-2,2-diphenylacetate (195.0 mg, 0.50 mmol); Pd (5 wt %)/ $\text{TiO}_2$  (40 mg, 3.4 mol % Pd);  $t = 18\text{ h}$ . The product was

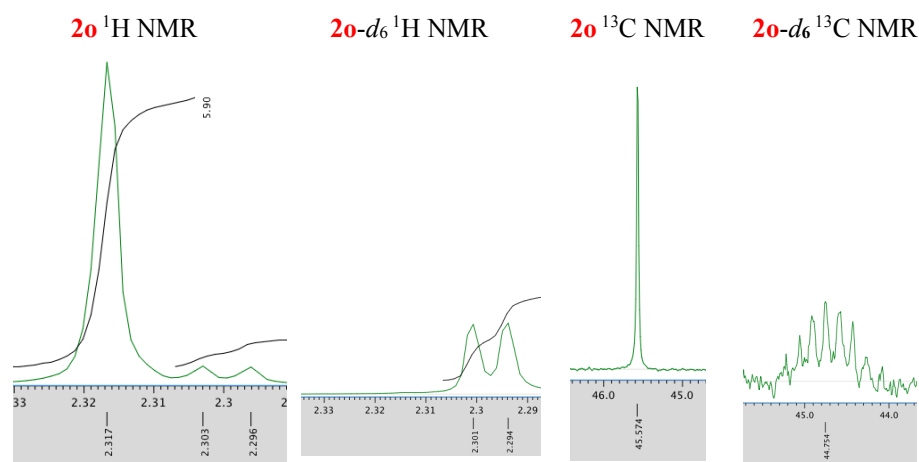
<sup>10</sup>Beydoun, K.; Ghattas, G.; Thenert, K.; Klankermayer, J.; Leitner, W. *Angew. Chem. Int. Ed.* **2014**, *53*, 11010–11014.

purified by column chromatography on 50NH<sub>2</sub> silica gel (hexane/ethyl acetate 3:1) to afford **2r** as a colorless oil (104.1 mg, 67% yield). Analytical data for **2r**: <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 0.96 (t, *J* = 7.2 Hz, 6H), 2.50 (q, *J* = 7.2 Hz, 4H), 2.67 (t, *J* = 6.5 Hz, 2H), 4.22 (t, *J* = 6.5 Hz, 2H), 5.03 (s, 1H), 7.21–7.26 (m, 2H), 7.28–7.34 (m, 8H); <sup>13</sup>C{<sup>1</sup>H} NMR (150 MHz, CDCl<sub>3</sub>) δ 12.0, 47.6, 51.1, 57.2, 63.6, 127.3, 128.7, 138.8, 172.6; HRMS (ESI) calcd for C<sub>20</sub>H<sub>25</sub>NO<sub>2</sub>H<sup>+</sup> ([M + H]<sup>+</sup>) 312.1958, found 312.1962.

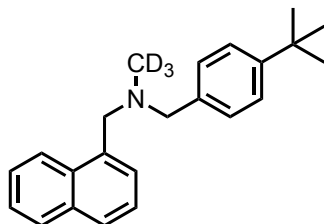
### 1-[2-[Di(methyl-*d*<sub>3</sub>)amino]-1-(4-methoxyphenyl)ethyl]cyclohexanol (**2o-d<sub>6</sub>**)



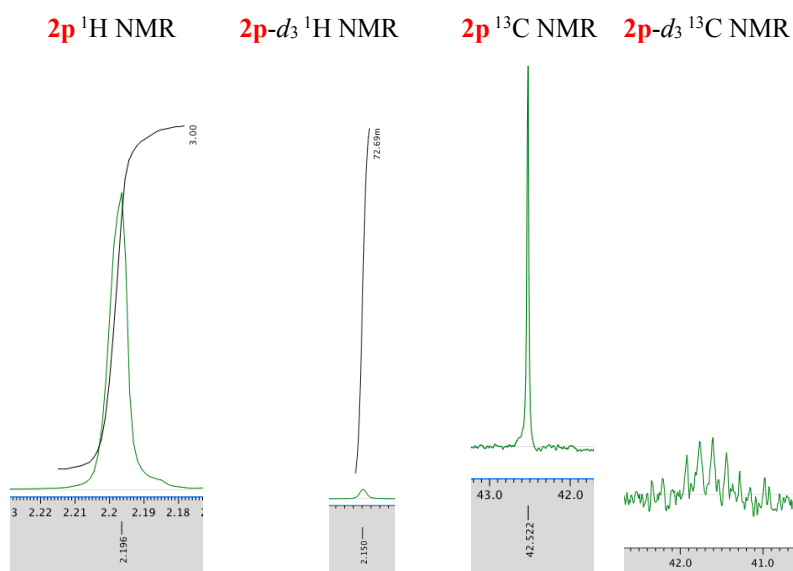
The reaction was carried out in a 25-mL Young tube using 1-[2-amino-1-(4-methoxyphenyl)ethyl]cyclohexanol (50.2 mg, 0.20 mmol), Pd (5 wt %)/TiO<sub>2</sub> (10.2 mg, 2 mol % Pd), and methanol-*d*<sub>4</sub> (2.0 mL) at 50 °C for 12 h. The product was purified by column chromatography on silica gel (ethyl acetate) to afford **2o-d<sub>6</sub>** as a light-yellow oil (52.6 mg, 93% yield, > 95% D). Analytical data for **2o-d<sub>6</sub>**: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 0.81–1.00 (m, 2H), 1.24–1.43 (m, 2H), 1.46–1.60 (m, 3H), 1.61–1.80 (m, 3H), 2.28 (dd, *J* = 12.6, 3.5 Hz, 1H), 2.94 (dd, *J* = 12.0, 3.5 Hz, 1H), 3.27 (t, *J* = 12.6 Hz, 1H), 3.79 (s, 3H), 6.81 (d, *J* = 8.6 Hz, 2H), 7.05 (d, *J* = 8.6 Hz, 2H); <sup>13</sup>C{<sup>1</sup>H} NMR (125 MHz, CDCl<sub>3</sub>) δ 21.4, 21.7, 26.1, 31.3, 38.2, 44.8 (sept, *J*<sub>CD</sub> = 19.7 Hz), 51.7, 55.3, 61.2, 74.3, 113.4, 130.2, 132.9, 158.4; HRMS (ESI) calcd for C<sub>17</sub>H<sub>21</sub>D<sub>6</sub>NO<sub>2</sub>H<sup>+</sup> ([M + H]<sup>+</sup>) 284.2491, found 284.2491.



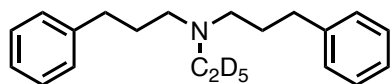
***N*-[[4-(1,1-Dimethylethyl)phenyl]methyl]-*N*-methyl-*d*<sub>3</sub>-1-naphthalenemethanamine (**2p-d<sub>3</sub>**)**



The reaction was carried out in a 25-mL Young tube using *N*-[[4-(1,1-dimethylethyl)phenyl]methyl]-1-naphthalenemethanamine (61.1 mg, 0.20 mmol), Pd (5 wt %)/TiO<sub>2</sub> (9.9 mg, 2 mol % Pd), and methanol-*d*<sub>4</sub> (2.0 mL) at 50 °C for 2 h. The product was purified by column chromatography on silica gel (dichloromethane) to afford **2p-d<sub>3</sub>** as a light-yellow oil (51.2 mg, 80% yield). Analytical data for **2p-d<sub>3</sub>**: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 1.31 (s, 9H), 2.15 (s, 0.07H), 3.57 (s, 2H), 3.92 (s, 2H), 7.26–7.35 (m, 4H), 7.39 (t, *J* = 7.5 Hz, 1H), 7.43–7.50 (m, 3H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.80–7.84 (m, 1H), 8.21–8.25 (m, 1H); <sup>13</sup>C {<sup>1</sup>H} NMR (125 MHz, CDCl<sub>3</sub>) δ 31.5, 34.6, 41.6 (sept, *J*<sub>CD</sub> = 20.0 Hz), 60.5, 62.1, 125.0, 125.2, 125.6, 125.7, 127.5, 128.0, 128.5, 128.9, 132.7, 134.0, 135.2, 136.4, 149.9; HRMS (ESI) calcd for C<sub>23</sub>H<sub>24</sub>D<sub>3</sub>NH<sup>+</sup> ([M + H]<sup>+</sup>) 321.2405, found 321.2408.



### *N*-Ethyl-*d*<sub>5</sub>-*N*-(3-phenylpropyl)benzenepropanamine (**2s-d<sub>5</sub>**)



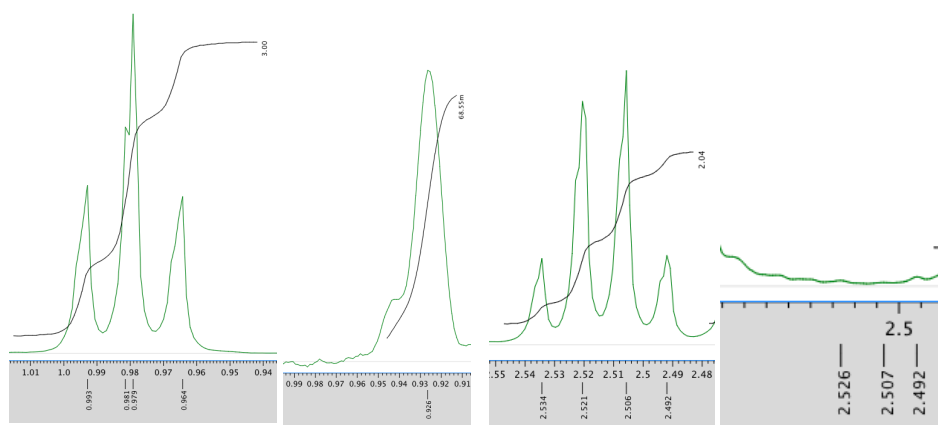
The reaction was carried out in a 25-mL Young tube using *N*-(3-phenylpropyl)benzenepropanamine (51.0 mg, 0.20 mmol), Pd (5 wt %)/TiO<sub>2</sub> (10.0 mg, 2 mol % Pd), and ethanol-*d*<sub>6</sub> (1.0 mL) for 3.5 h. The product was purified by column chromatography on 50NH<sub>2</sub> silica gel (ethyl acetate) to afford **2s-d<sub>5</sub>** as a light-yellow oil (52.8 mg, 92% yield). Analytical data for **2s-d<sub>5</sub>**: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 0.93 (s, 0.07H), 1.75 (dd, *J* = 8.0, 7.0 Hz, 4H), 2.45 (t, *J* = 7.8 Hz, 4H), 2.61 (t, *J* = 8.0 Hz, 4H), 7.13–7.20 (m, 6H), 7.26 (t, *J* = 7.8 Hz, 4H); <sup>13</sup>C{<sup>1</sup>H} NMR (125 MHz, CDCl<sub>3</sub>) δ 11.9, 29.0, 34.0, 47.6, 53.1, 125.8, 128.4, 128.5, 142.6; HRMS (ESI) calcd for C<sub>20</sub>H<sub>22</sub>D<sub>5</sub>NH<sup>+</sup> ([M + H]<sup>+</sup>) 287.2530, found 287.2530.

**2s** <sup>1</sup>H NMR

**2s-d<sub>5</sub>** <sup>1</sup>H NMR

**2s** <sup>1</sup>H NMR

**2s-d<sub>5</sub>** <sup>1</sup>H NMR



**2s** <sup>13</sup>C NMR

**2s-d<sub>5</sub>** <sup>13</sup>C NMR

**2s** <sup>13</sup>C NMR

**2s-d<sub>5</sub>** <sup>13</sup>C NMR

