Supporting information

Catalysis in Flow: Au-Catalysed Alkylation of Amines by Alcohols

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A description of the continuous flow reactor can be found in our earlier paper.[1]

Preparation of catalyst cartridge and calculation of residence time (τ): Using a CatCart Packer[TM], a preweighed catalyst cartridge was packed with ca. 0.6-0.9 g of 1-1.5% Au/TiO$_2$ (provided by World Gold council, Johnson Matthey plc or bought from STREM), sealed on either end with 8 μm filters. The cartridge was then reweighed to determine the precise amount of catalyst loaded. It was then mounted in the X-Cube[TM], where it was filled with toluene. The cartridge was then dismounted and reweighed to furnish the reaction volume (calculated from the weight and density of toluene).

$$\text{residence time } (\tau) = \frac{reaction\ volume\ (mL)}{flow\ rate\ (mL/min)}$$

From this, a residence time of 27 s is calculated at a flow rate of 1.5 mL/min.

Mechanistic studies and kinetic analysis.

The catalysed reaction between aniline **2a** and benzyl alcohol **1a** in toluene by Au/TiO$_2$ (0.9 mol%) was performed at different reaction conditions. Reaction progress was monitored by GC analysis of reaction aliquots, using dodecane as an internal standard. The model for the alkylation reaction was developed using

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[1] Zotova, N.; Hellgardt, K.; Kelsall, G. H.; Hii, K. K. *Green Chem.* **2010**, *12*, 2157-2163.

equations that describe rate of formation of each species observed in the reaction (Scheme 3 in the main text), and simulated using the differential equation solver Berkeley Madonna[TM] program.[2]
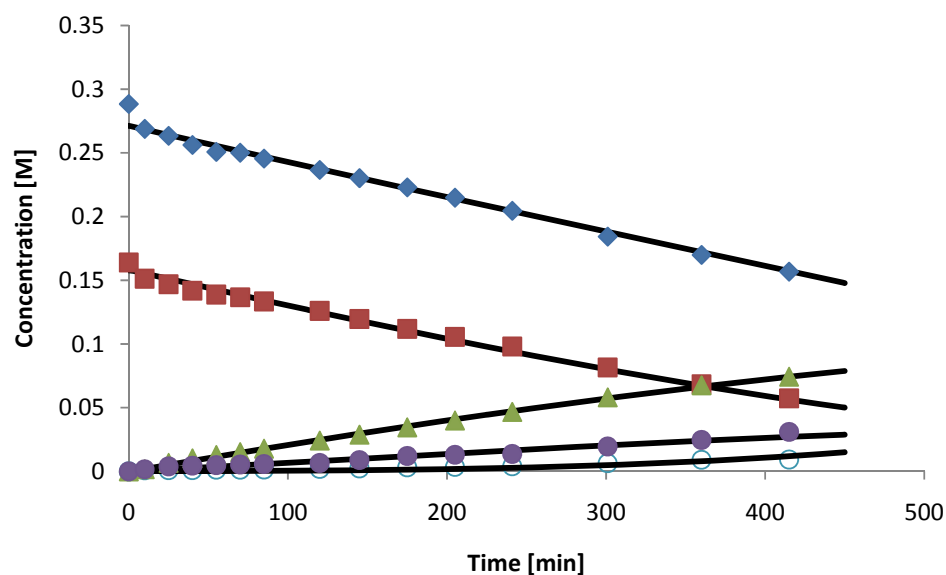

Figure S1. Simulated graphs for reaction performed at 130 °C (Table 1, entry 1). Legend: ♦ = benzyl alcohol **1a**, ■ = aniline **2a**, ▲ = substituted amine **4a**, ● = imine **3a** and ○ = benzaldehyde. Solid black lines = simulated reaction curves.
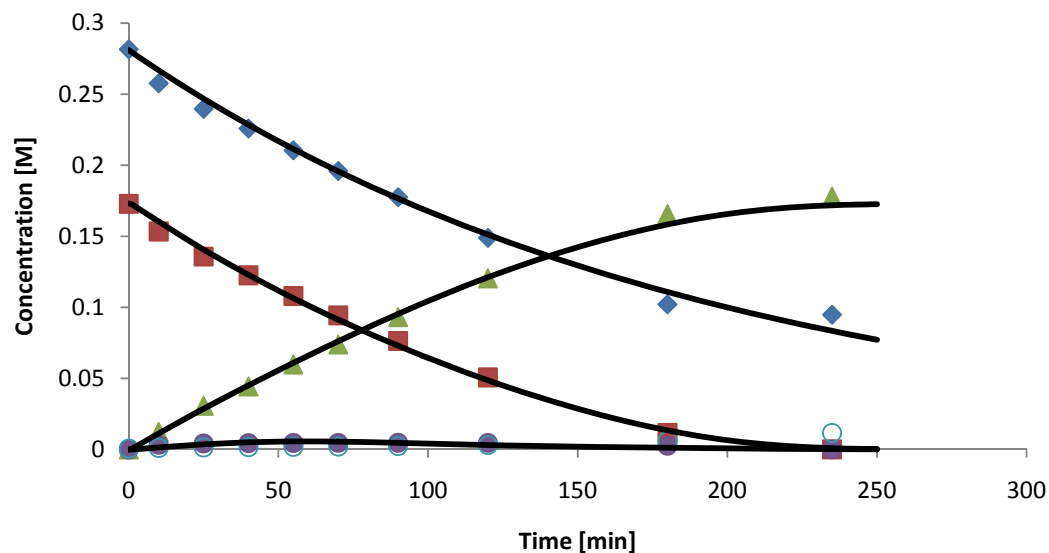

Figure S2. Simulated graphs for reaction performed at 150 °C (Table 1, entry 2). Legend as in Figure 1. Solid black lines = simulated reaction curves.

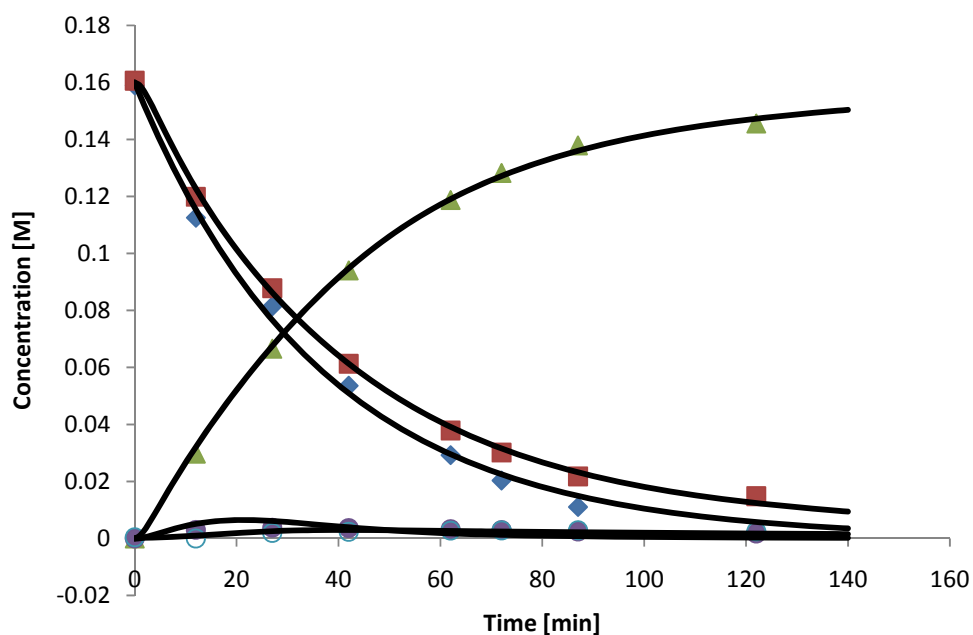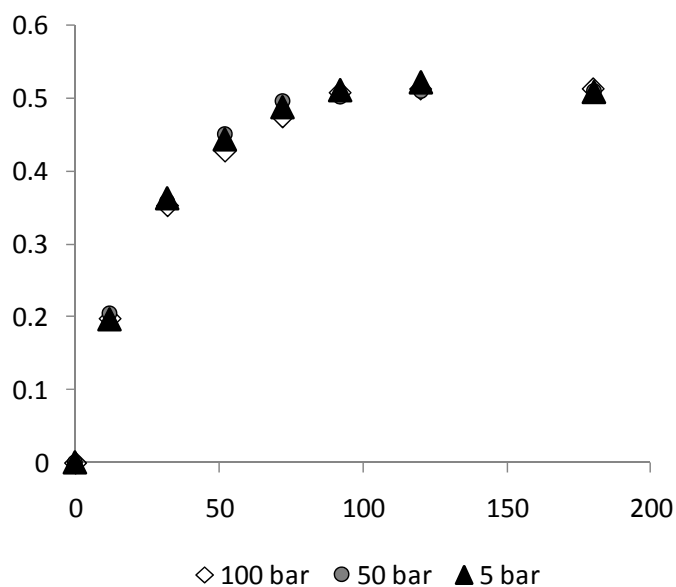
[2] See: http://www.berkeleymadonna.com/

Figure S3. Simulated graphs for reaction performed at 180 °C (Table 1, entry 4). Legend as in Figure 1. Solid black lines = simulated reaction curves.

◇ 100 bar   ● 50 bar   ▲ 5 bar

Figure S4. Temporal conversion profile of alcohol amination catalysed by Au/TiO$_2$. Reaction conditions: **1** (0.5 M), **2** (0.5 M), toluene (10 mL), 0.9 mol% Au/TiO$_2$, 1.5 mL/min flow, 180 °C, at applied pressured of 5, 50 and 100 bar.

The calculated rate constants were presented in Table 4 of the main text. Thermodynamic parameters were extracted from Arrhenius plots, below:
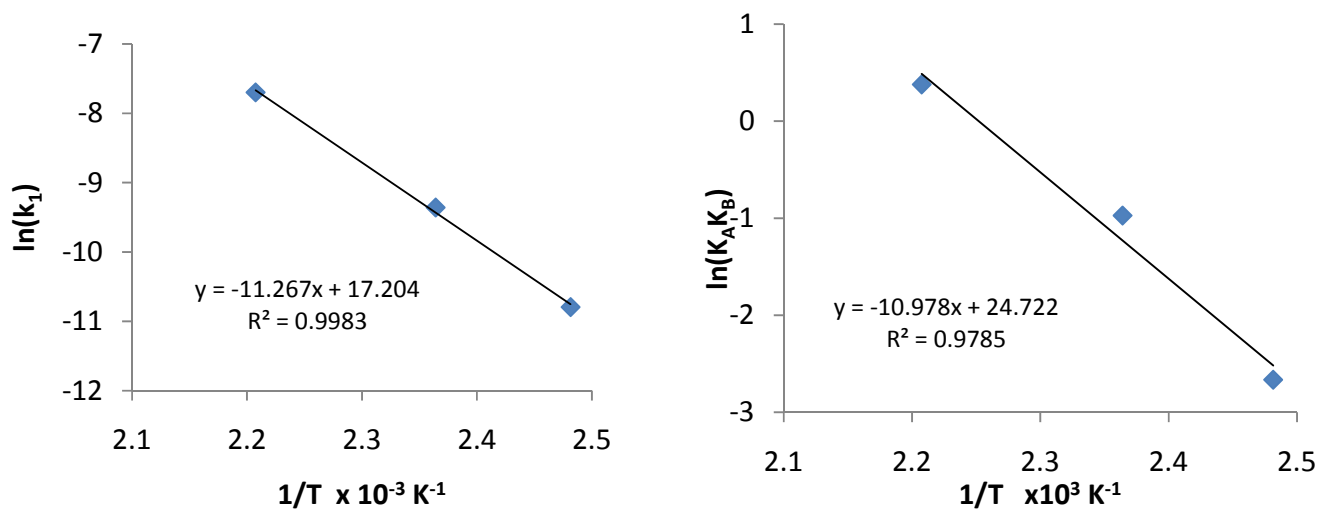

Figure S5. Plots of $\ln(k_1)$ vs $1/T$ (left) and $\ln(K_A K_B)$ *vs* $1/T$ (right).

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¹H NMR spectra.

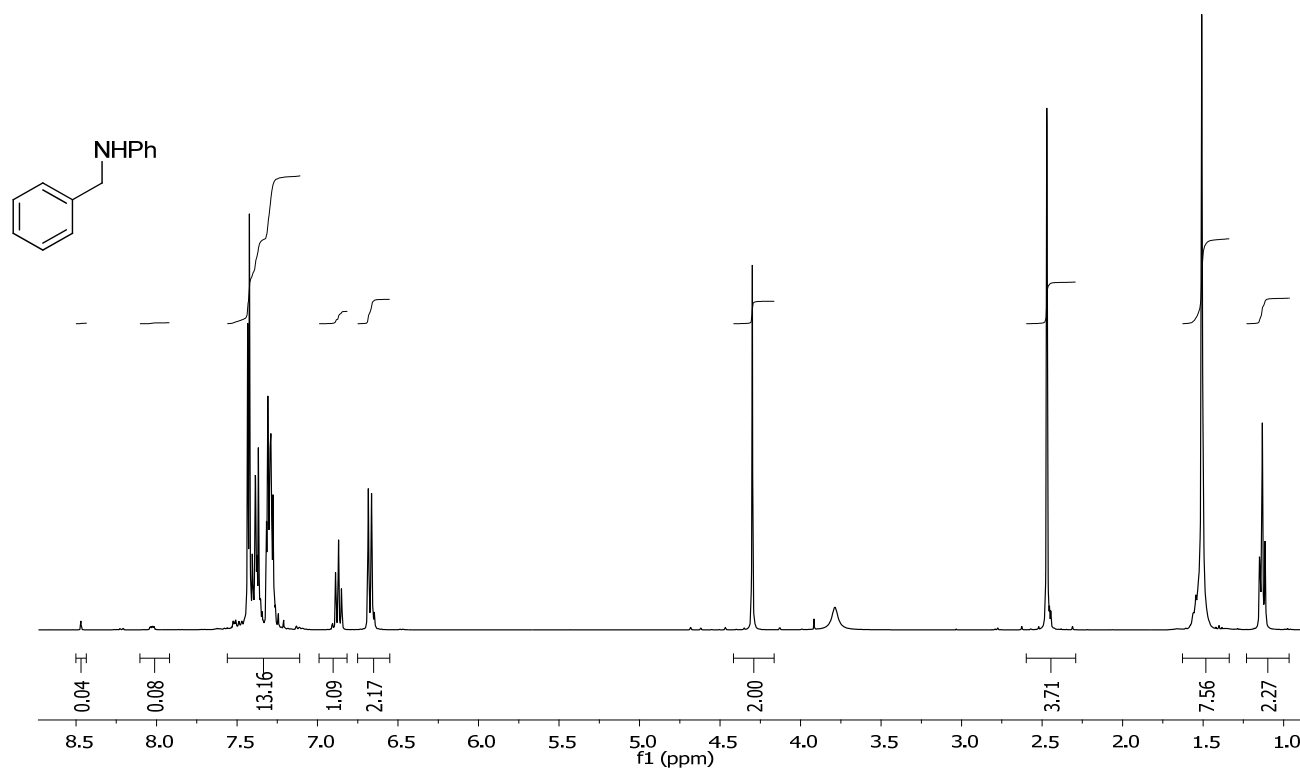¹H-NMR spectra of *crude reaction mixtures* reported in Table 3, obtained directly after solvent evaporation.

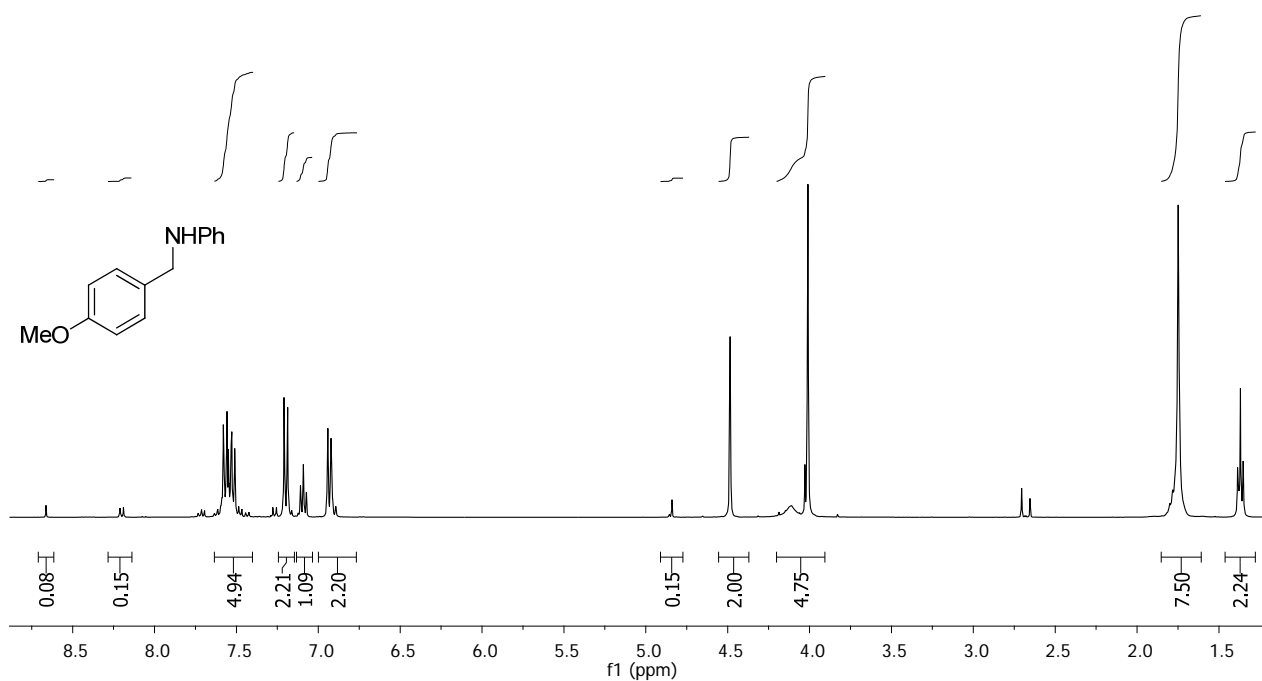**Figure S6.** ¹H NMR spectrum of *N*-phenylbenzylamine (**4a**).[3]

Figure S7. ¹H NMR spectrum of *N*-phenyl(*p*-methoxybenzyl)amine (**4b**).[3]

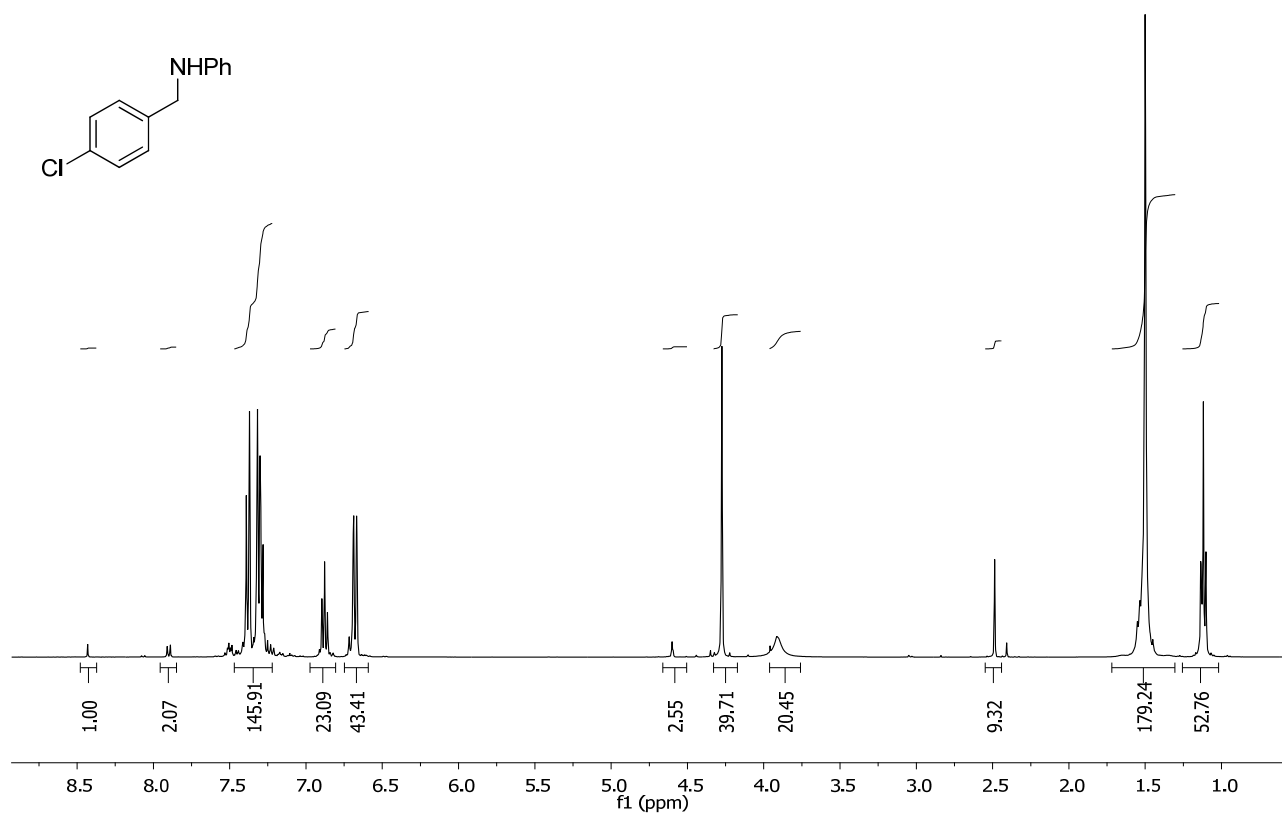[3] Lai, R. Y.; Lee, C.I.; Liu, S. T. *Tetrahedron* **2008**, *64*, 1213-1217.

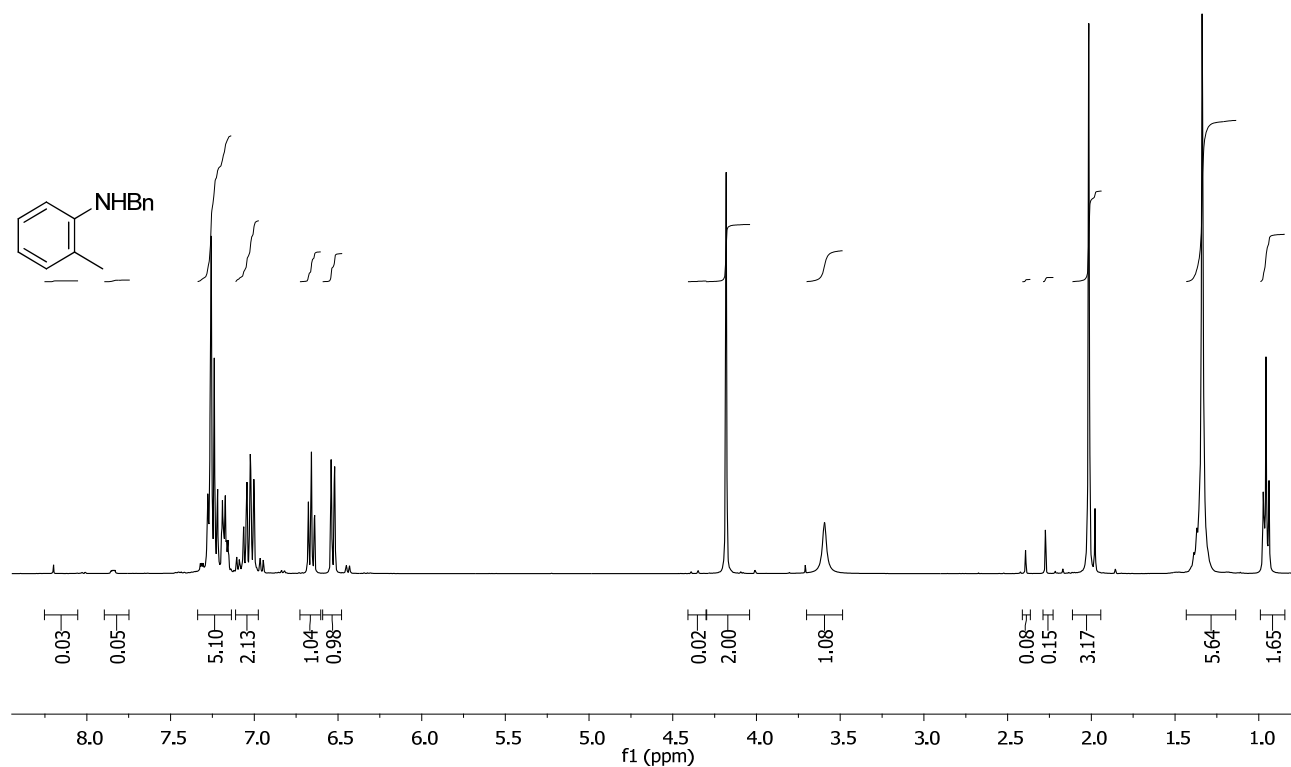**Figure S8.** ^{1}H NMR spectrum of *N*-phenyl(*p*-chlorobenzyl)amine (**4c**).[3]

Figure S9. ^{1}H NMR spectrum of *N*-(*o*-tolyl)benzylamine (**4d**).[3]
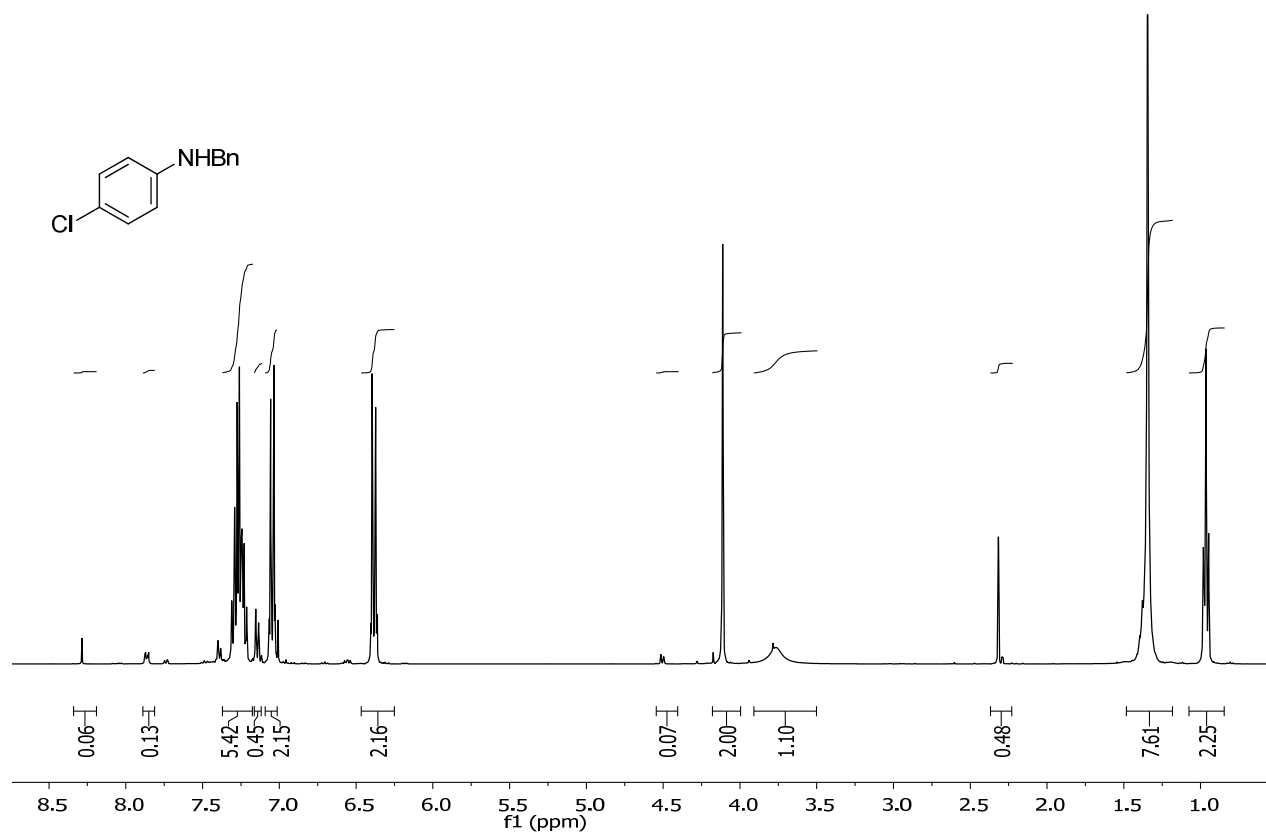
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Figure S10. ^{1}H NMR spectrum of *N*-(*p*-chlorophenyl)benzylamine (**4e**).[3]
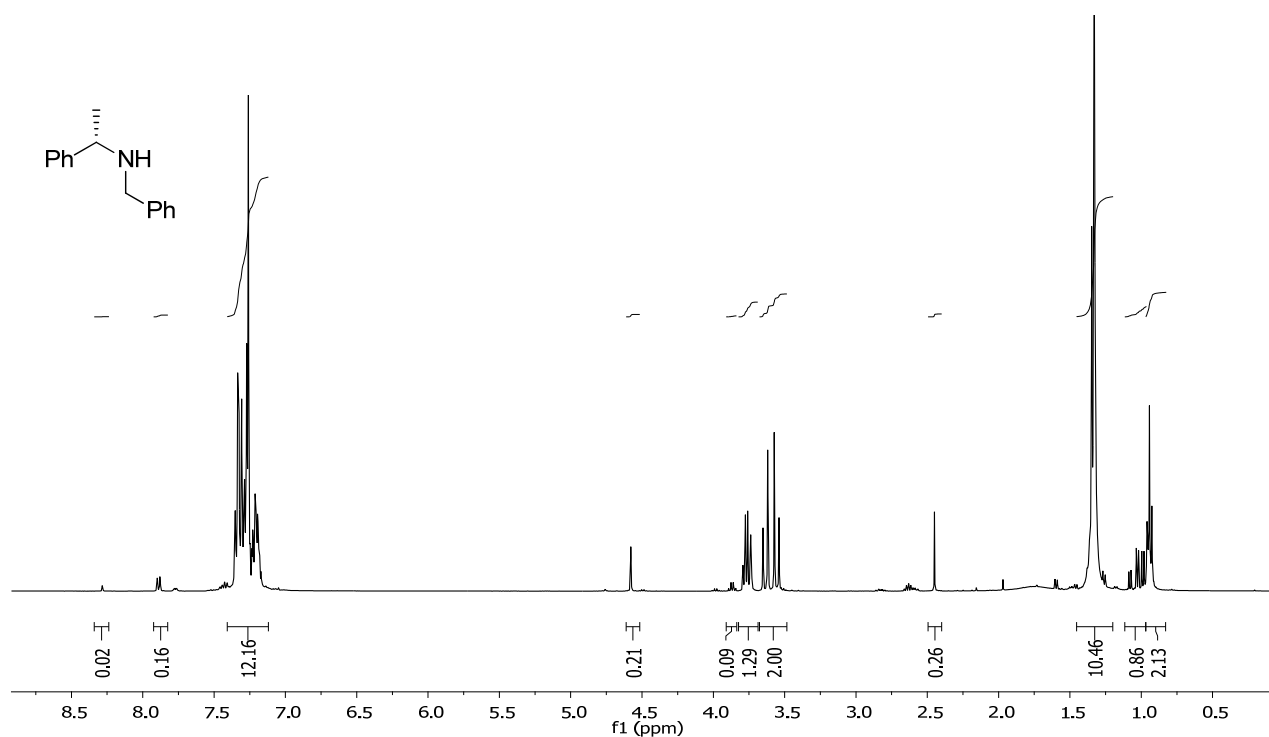

Figure S11. ^{1}H NMR spectrum of (*S*)-*N*-benzyl-α-methylbenzylamine (**4f**).[4]

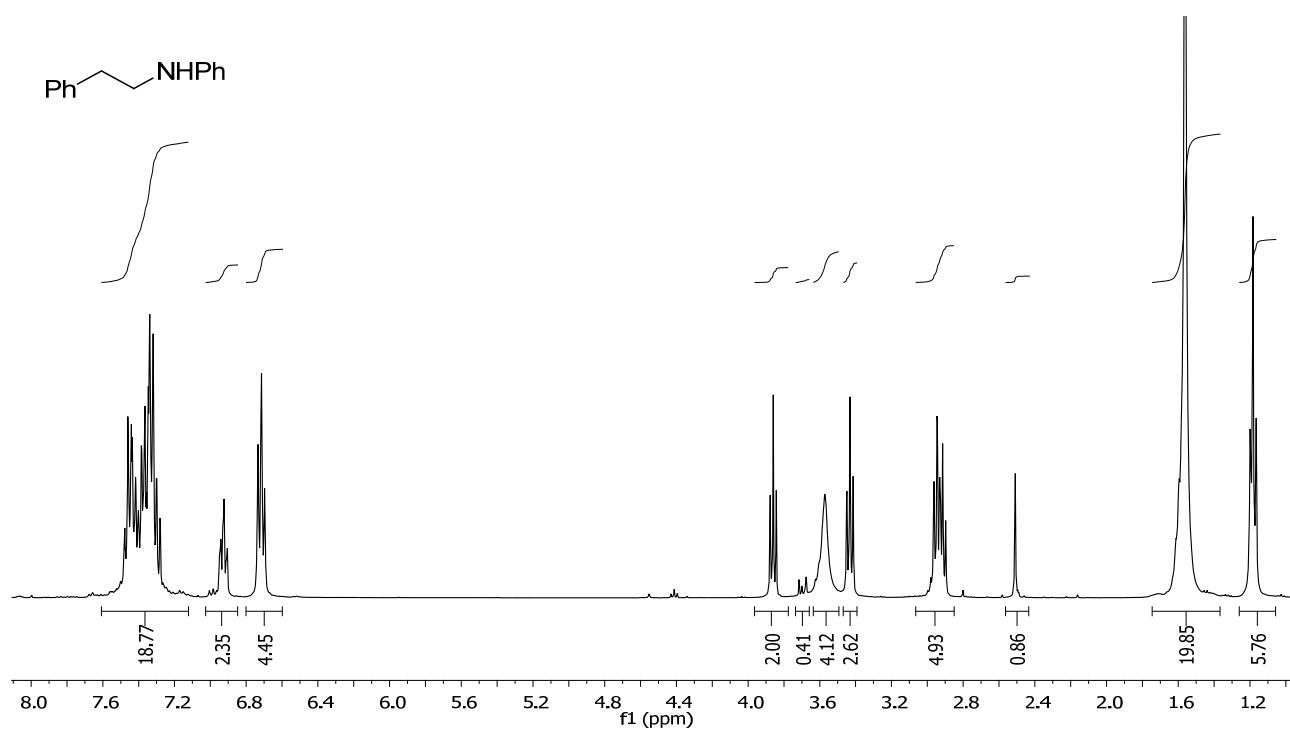[4] Baeza, A.; Pfaltz, A. *Chem.—Eur. J*. **2010**, *16*, 403-6.

Figure S12. ^{1}H NMR spectrum of *N*-phenylphenethylamine (**4g**).[5]
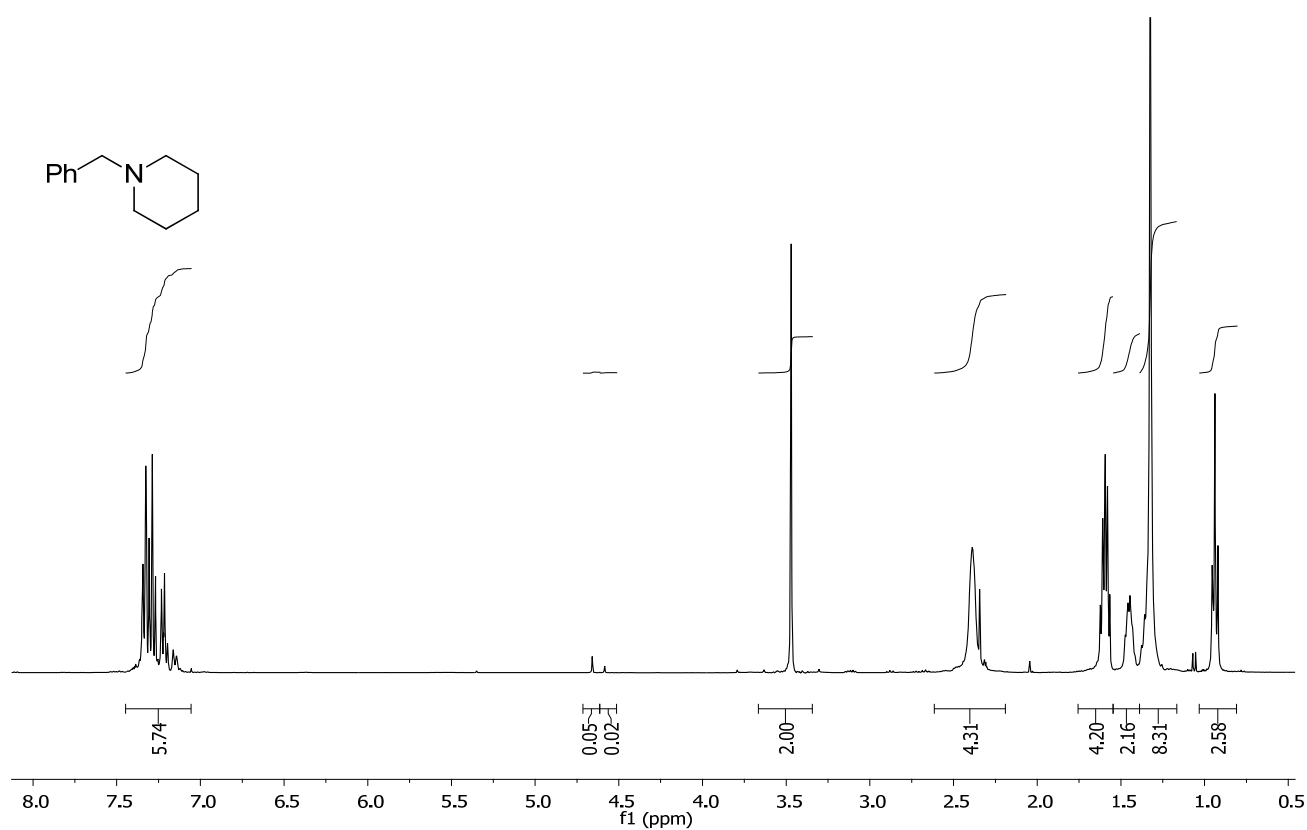

Figure S13. ^{1}H NMR spectrum of *N*-benzylpiperidine (**4h**).[3]

[5] Horrillo-Martinez, P.; Hultzsch, K. C.; Gil, A.; Branchadell, V. *Eur. J. Org. Chem.* **2007**, 3311-3325.
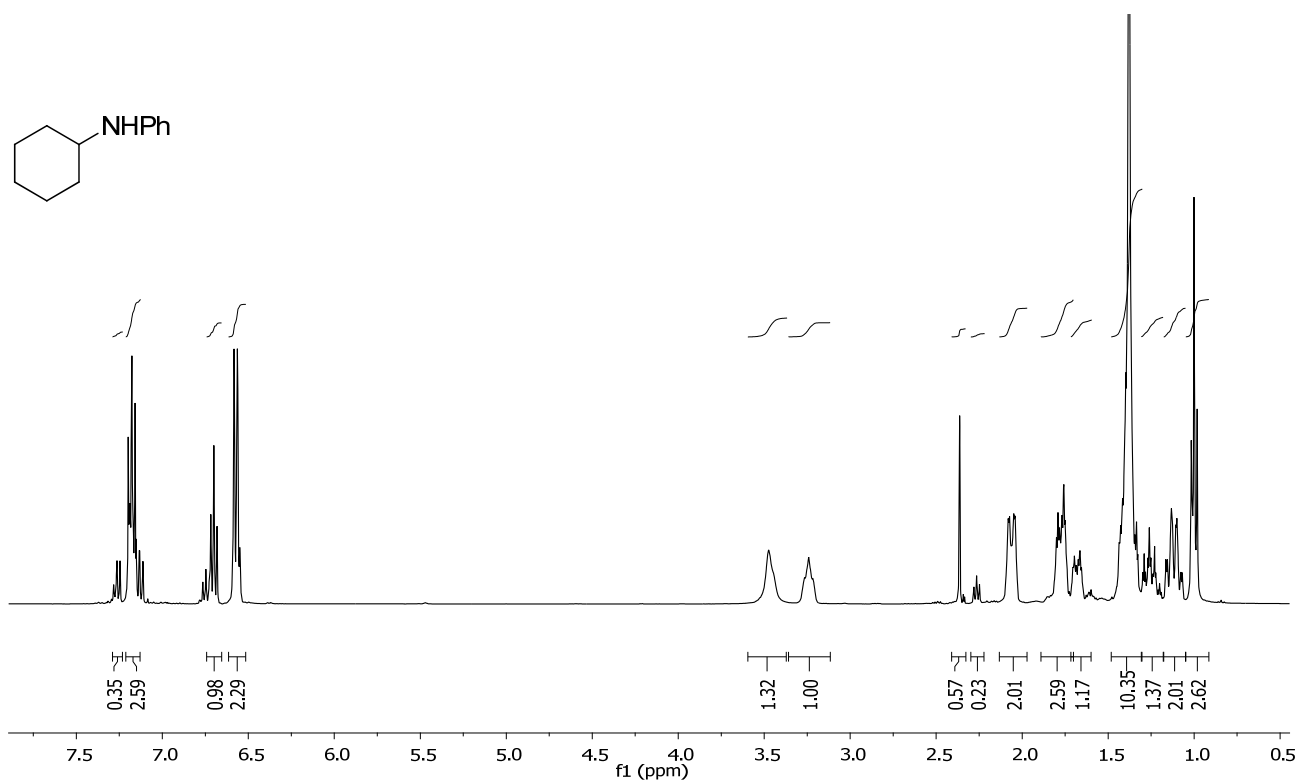
Figure S14. ^{1}H NMR spectrum of cyclohexylphenylamine (**4i**).[6]
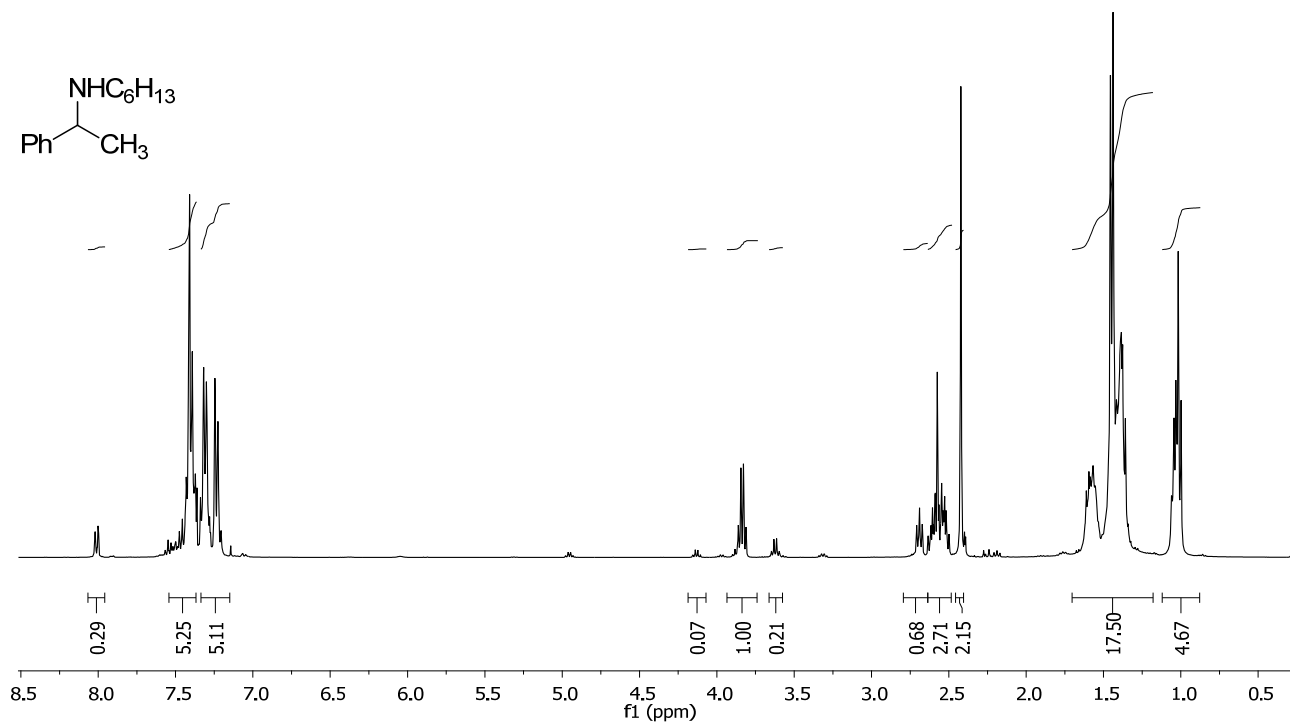

Figure S15. ^{1}H NMR spectrum of *N*-(1-phenylethyl)hexylamine (**4j**).[7]

[6] Yin, P.; Loh, T. P. *Org. Lett.* **2009**, *11*, 3791-3.
[7] Johansson, A.; Abrahamsson, P.; Davidsson, O. *Tetrahedron: Asymmetry* **2003**, *14*, 1261-6.
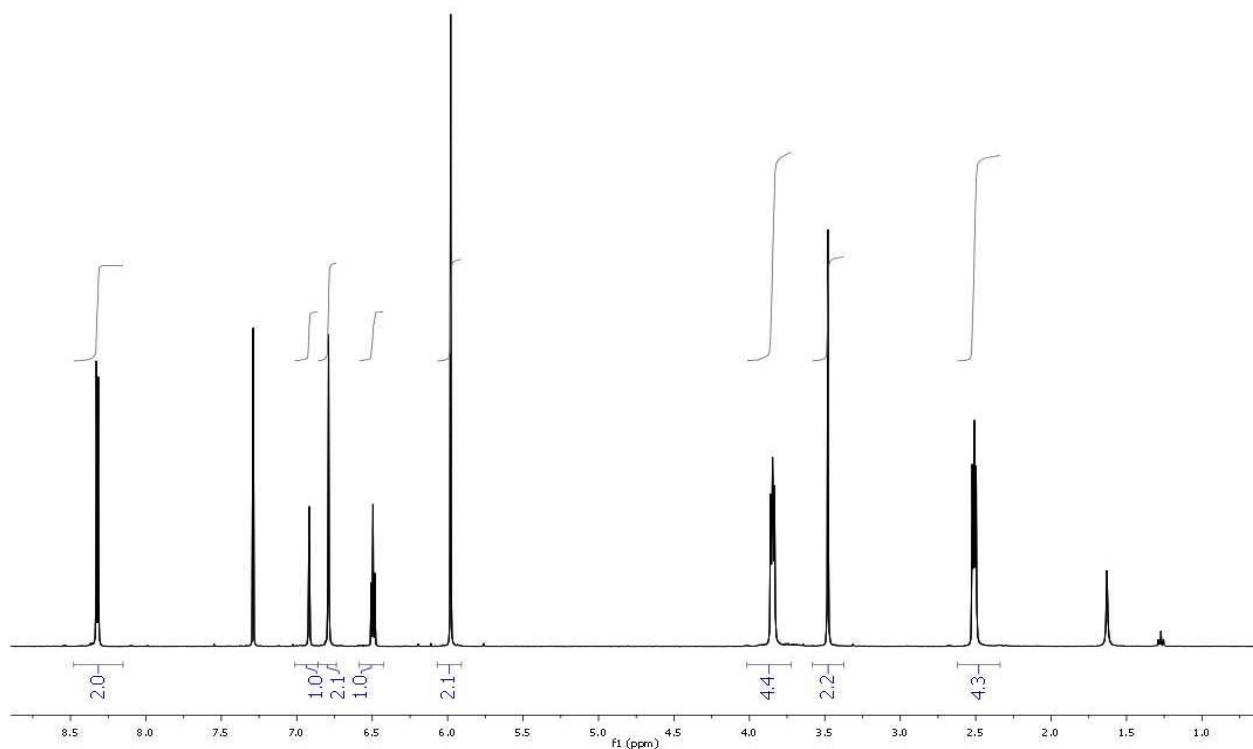
Figure S16. ^{1}H NMR spectrum of Piribedil **4k** (recrystallisedfrom EtOH-H$_2$O).

Investigating leaching of Au/TiO$_2$. Alkylation of amines was performed using standard conditions described in the main text. Upon completion, the solvent was evaporated and residue was re-dissolved in 1 mL of *aqua regia* and diluted to 25 mL. The sample was subjected to ICP analysis. In all cases, %Au was found to be < 0.002 ppm.

Synthesis and characterisation of racemic *N*-benzyl-α-methylbenzylamine (4f). The racemic amine was prepared according to a literature procedure:[8] A mixture of benzaldehyde (0.7893 g, 7.4 mmol), 1-phenyletanamine (0.893 mg, 7.4 mmol) in CH$_3$OH (4 mL) was stirred at room temperature for 2 h. To this NaBH$_4$ (0.21 g, 5.5 mmol) was added in small portions, while maintaining reaction at 20-28°C. The mixture was stirred at room temperature for another 16 h. Then solvent was removed by evaporation under reduced pressure. The residue was slurred with H$_2$O and extracted with CH$_2$Cl$_2$ (3 x 20 mL). The combined organic extract was washed with H$_2$O, dried over MgSO$_4$ and concentrated to give a lightly yellow liquid. The racemic mixture was resolved by chiral HPLC using the following conditions: CHIRALCEL OD-H HPLC column, 9:1 hexane-IPA, 0.5 mL/min, t_R = 8.7 min (*R*-isomer), 9.1 min (*S*-isomer).

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[8] Li, Q.; Chu, D.T.W.; Raye, K.; Claiborne, A.; Seif, L.; Macri, B.; Plattner, J.J. *Tetrahedron Lett.* **1995**, *36*, *8391*.