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Nitrogen ligand influence on the CO-assisted ruthenium-catalyzed reductive amination

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General information

Unless otherwise stated, all reagents were purchased from commercial suppliers and used without further purification. Dichloromethane and MeCN were distilled over calcium hydride.

^{1}H NMR spectra were recorded in $CDCl_3$ on Bruker Avance 300, Bruker Avance 400 and Varian Inova-400 spectrometers. Chemical shifts are reported in parts per million relative to $CHCl_3$ (7.26 ppm). The following abbreviations were used to designate chemical shift multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, dt = doublet of triplets, m = multiplet; coupling constants are given in Hertz (Hz). NMR yields were calculated using DMF as an internal standard.

Analytical gas chromatography (GC) was performed using a Chromatec Crystal 5000.2 gas chromatograph fitted with a flame ionization detector and MS detector. He was used as the carrier gas.

GC settings for the yield determination using FID detector:

Chromatec CR-5MS (30 m, 0.25 mm I.D., 1.0 μm film thickness) capillary columns. The injector temperature was 250 °C, the FID temperature was 250 °C, with a split ratio of 50:1. Column compartment temperature program: 100°C for 2 min, 100→ 80°C at 30 K min^{-1}, 280°C for 3 min. Flow rate 1 ml min^{-1}. Injection volume – 1 μl. Retention time for 4-methoxy-N-(4-methoxybenzyl)aniline is 10.2 min. GC yields were calculated using external calibration.

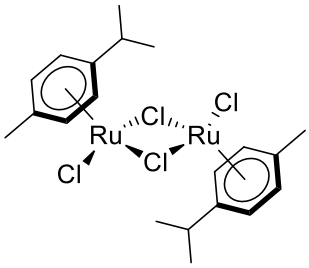
GC settings for the qualitative analysis using MS detector:

Chromatec CR-5MS (30 meters, 0.32 mm I.D., 1.0 μm film thickness) capillary column. The injector temperature was 250 °C, the FID temperature was 250 °C, with a split ratio of 75:1. 60°C for 4 min, 60→250°C at 30 K min^{-1}, 250°C for 12 min. Injection volume – 0.2 μl. Flow rate 1 ml min^{-1}. MSD parameters: ion source temperature 200°C, transfer line temperature 230°C.

Experimental section

Spectroscopic and analytical data for the synthesis of ruthenium complexes

[(*p*-cymene)RuCl$_2$]$_2$



Was prepared according to the literature. A red solid was obtained with 67%. NMR spectra were in agreement with the literature data.[S1]

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.45 (d, J = 5.8 Hz, 2H), 5.31 (d, J = 5.8 Hz, 2H), 2.88 (sept, J = 7.0 Hz, 1H), 2.13 (s, 3H), 1.24 (d, J = 7.0 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 101.2, 96.7, 81.3, 80.5, 30.6, 22.1, 18.9.

General procedure for reductive amination

Caution: carbon monoxide used as a reagent in this protocol is a toxic gas. Corresponding safety precautions should be taken.

A glass vial in a 10 ml stainless steel autoclave was charged with amine (2 equiv.), aldehyde (1 equiv.), acetonitrile (0.28 ml), [(*p*-cymene)RuCl$_2$]$_2$ (0.25 mol%) and additive (0.5 mol%). The autoclave was sealed, flushed three times with 10 bar of CO, and then charged with 50 bar of CO. The reactor was placed into a preheated to 140 °C oil bath. After 22 h of heating, the reactor was cooled to room temperature and depressurized. The reaction mixture was analyzed by NMR and GC.

Caution: carbon monoxide used as a reagent in this protocol is a toxic gas. Corresponding safety precautions should be taken.

GC samples preparation

The model reaction mixture was transferred into a 5 ml vessel, diluted with CH_2Cl_2 to a volume of 5 ml, and mixed thoroughly. Then 200 μl (20 μl for GC-MS analysis) of the solution was transferred into a GC tube and diluted to 1 ml. The yields determined by GC (using external calibration) and NMR (with internal standard) analyses matched within 5%.

GC calibration

The yields of the model reaction were determined using a calibrated GC. Calibration (Figure S1) was performed using CH_2Cl_2 solutions of pure 4-methoxy-*N*-(4-methoxybenzyl)aniline **3a** at three different concentrations, which corresponded to a 19% product yield (0.75 mg ml^{-1}), a 76% yield (3.06 mg ml^{-1}), and a 99% yield (3.96 mg ml^{-1}).

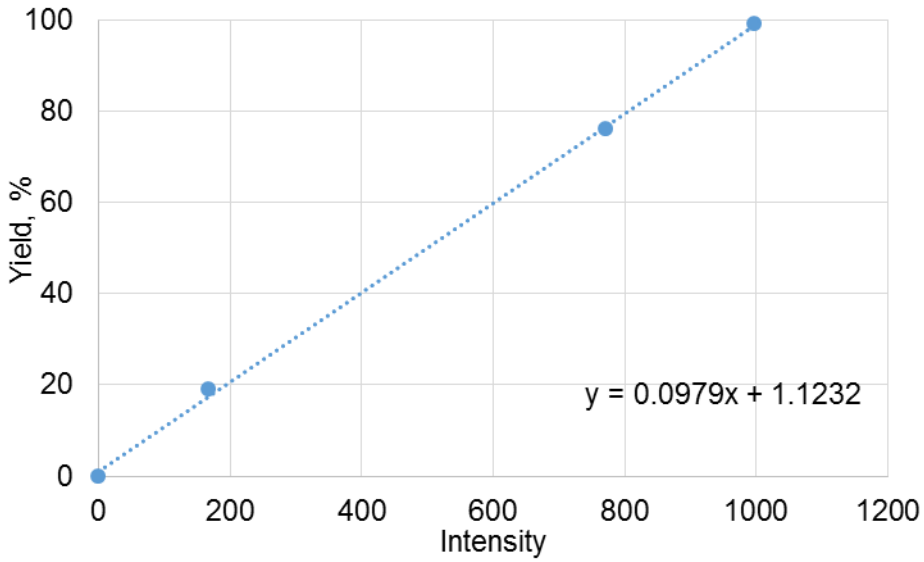
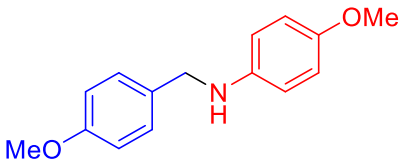


Figure S1 Calibration curve for **3a**.

4-Methoxy-*N*-(4-methoxybenzyl)aniline (3a)



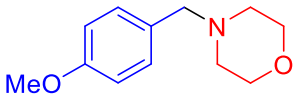
A glass vial in a 10 ml stainless steel autoclave was charged with *p*-anisidine **1a** (80 mg, 0.66 mmol, 2 equiv.), *p*-methoxybenzaldehyde **2** (40 µL, 0.33 mmol, 1 equiv.), [(*p*-cymene)$RuCl_2$]$_2$ (0.5 mg, 0.0016 mmol, 0.25 mol%) as an aliquot in MeCN (83 µl, 6 mg ml^{-1}), and an additive in MeCN (200 µl) were added (the overall volume of MeCN was 283 µl). The autoclave was sealed, flushed three times with 10 bar of CO, and then charged with 50 bar of CO. The reactor was placed into an oil bath preheated to 140°C. After 22 h of heating, the reactor was cooled to room temperature and depressurized. Its content was analyzed using gas chromatography and ^{1}H NMR.

NMR spectrum was in agreement with the literature data.[S1]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 6.73 (d, *J* = 9.1 Hz, 2H), 6.63 (d, *J* = 9.1 Hz, 2H), 4.19 (s, 2H), 3.78 (s, 3H), 3.73 (s, 3H).

The yield of product was determined relatively to δ 4.19 singlet using DMF as internal standard.

4-(4-Methoxybenzyl)morpholine (3b)



A glass vial in a 10 ml stainless steel autoclave was charged with morpholine **1b** (56 µl, 0.66 mmol, 2 equiv.), *p*-methoxybenzaldehyde **2** (40 µl, 0.33 mmol, 1 equiv.), [(*p*-cymene)$RuCl_2$]$_2$ (0.5 mg, 0.0016 mmol, 0.25 mol%) as an aliquot in MeCN (83 µl, 6 mg ml^{-1}), and an additive in

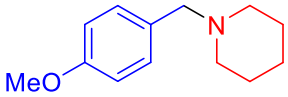
MeCN (200 µl) were added (the overall volume of MeCN was 283 µl). The autoclave was sealed, flushed three times with 10 bar of CO, and then charged with 50 bar of CO. The reactor was placed into an oil bath preheated to 140°C. After 22 h of heating, the reactor was cooled to room temperature and depressurized. Its content was analyzed using gas chromatography and ^{1}H NMR.

NMR spectrum was in agreement with the literature data.[S2]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.3 Hz, 2H), 6.84 (d, *J* = 8.3 Hz, 2H), 3.79 (s, 3H), 3.69 (t, J = 4.7 Hz, 4H), 3.43 (s, 2H), 2.44 – 2.38 (m, 4H).

The yield of product was determined relatively to δ 7.22 doublet using DMF as internal standard.

1-(4-Methoxybenzyl)piperidine (3c)



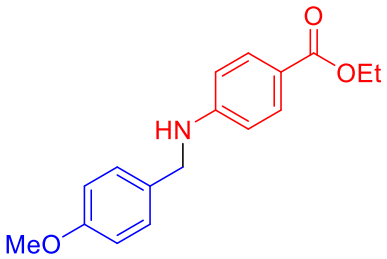
A glass vial in a 10 ml stainless steel autoclave was charged with piperidine **1c** (65 µl, 0.66 mmol, 2 equiv.), *p*-methoxybenzaldehyde **2** (40 µl, 0.33 mmol, 1 equiv.), [(*p*-cymene)$RuCl_2$]$_2$ (0.5 mg, 0.0016 mmol, 0.25 mol%) as an aliquot in MeCN (83 µl, 6 mg ml^{-1}), and an additive in MeCN (200 µl) were added (the overall volume of MeCN was 283 µl). The autoclave was sealed, flushed three times with 10 bar of CO, and then charged with 50 bar of CO. The reactor was placed into an oil bath preheated to 140°C. After 22 h of heating, the reactor was cooled to room temperature and depressurized. Its content was analyzed using gas chromatography and ^{1}H NMR with DMF as an internal standard.

NMR spectrum was in agreement with the literature data.[S2]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.6 Hz, 2H), 3.78 (s, 3H), 3.40 (s, 2H), 2.38 – 2.30 (m, 4H), 1.55 (dt, J = 11.0, 5.4 Hz, 4H), 1.45 – 1.35 (m, 2H).

The yield of product was determined relatively to δ 3.40 singlet using DMF as internal standard.

Ethyl 4-[(4-methoxybenzyl)amino]benzoate (3d)



A glass vial in a 10 ml stainless steel autoclave was charged with ethyl 4-aminobenzoate **1d** (109 mg, 0.66 mmol, 2 equiv.), *p*-methoxybenzaldehyde **2** (40 µl, 0.33 mmol, 1 equiv.), [(*p*-cymene)$RuCl_2$]$_2$ (0.5 mg, 0.0016 mmol, 0.25 mol%) as an aliquot in MeCN (83 µl, 6 mg ml^{-1}), and an additive in MeCN (200 µl) were added (the overall volume of MeCN was 283 µl). The autoclave was sealed, flushed three times with 10 bar of CO, and then charged with 50 bar of CO. The reactor was placed into an oil bath preheated to 140°C. After 22 h of heating, the

reactor was cooled to room temperature and depressurized. Its content was analyzed using gas chromatography and ^{1}H NMR.

NMR spectrum was in agreement with the literature data.[S3]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.8 Hz, 2H), 7.25 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 6.58 (d, *J* = 8.8 Hz, 2H), 4.31 (d, *J* = 6.6 Hz, 2H), 4.30 (q, *J* = 7.2 Hz, 2H), 3.79 (s, 3H), 1.34 (t, *J* = 7.2 Hz, 3H)

The yield of product was determined relatively to δ 6.87 doublet using DMF as internal standard.

References

S1 M. Makarova, O. I. Afanasyev, F. Kliuev, Y. V. Nelyubina, M. Godovikova and D. Chusov, *J. Organomet. Chem.*, 2021, **941**, 121806.

S2 Q. Li, C. W. Liskey and J. F. Hartwig, *J. Am. Chem. Soc.*, 2014, **136**, 8755.

S3 J.-M. Yang, R. Jiang, L. Wu, X.-P. Xu, S.-Y. Wang and S.-J. Ji, *Tetrahedron*, 2013, **69**, 7988.

Additional data for additives influence investigation

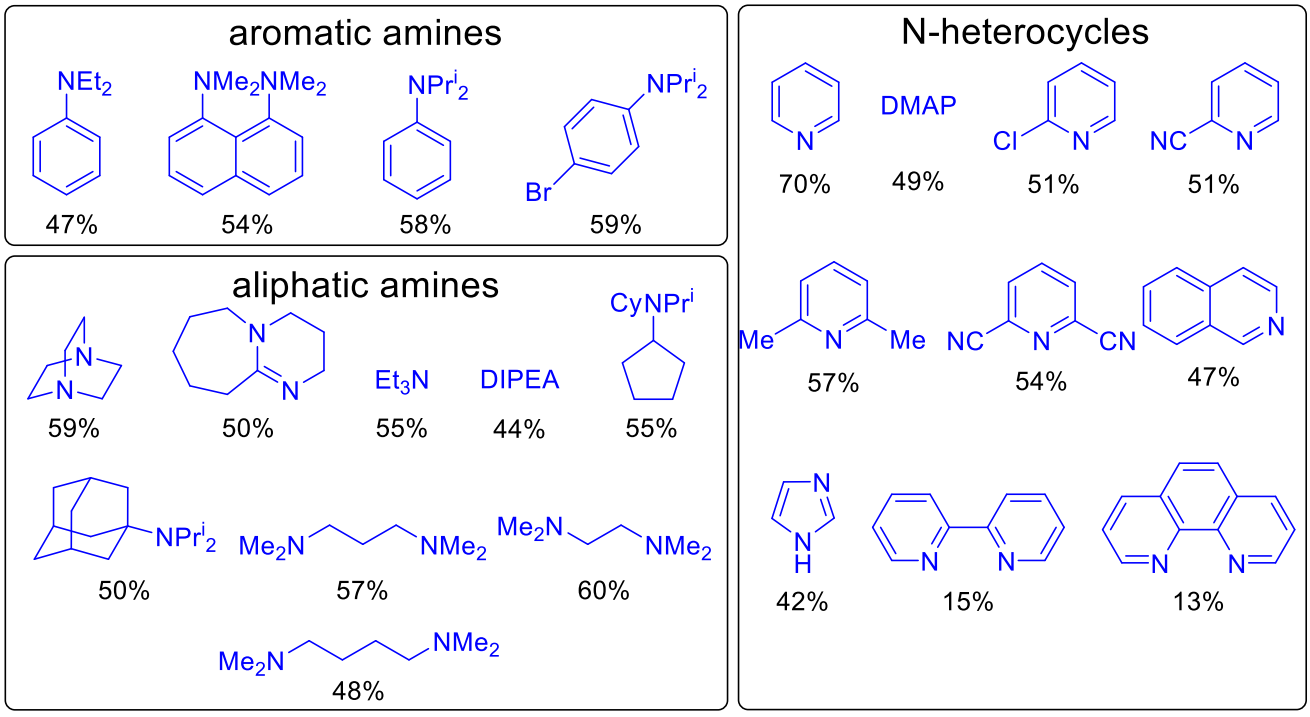


Figure S2. Performance of 0.5 mol% of N-ligands in the model reaction.

$^{1}H,^{13}C$ NMR spectra of [(*p*-cymene)$RuCl_2]_2$

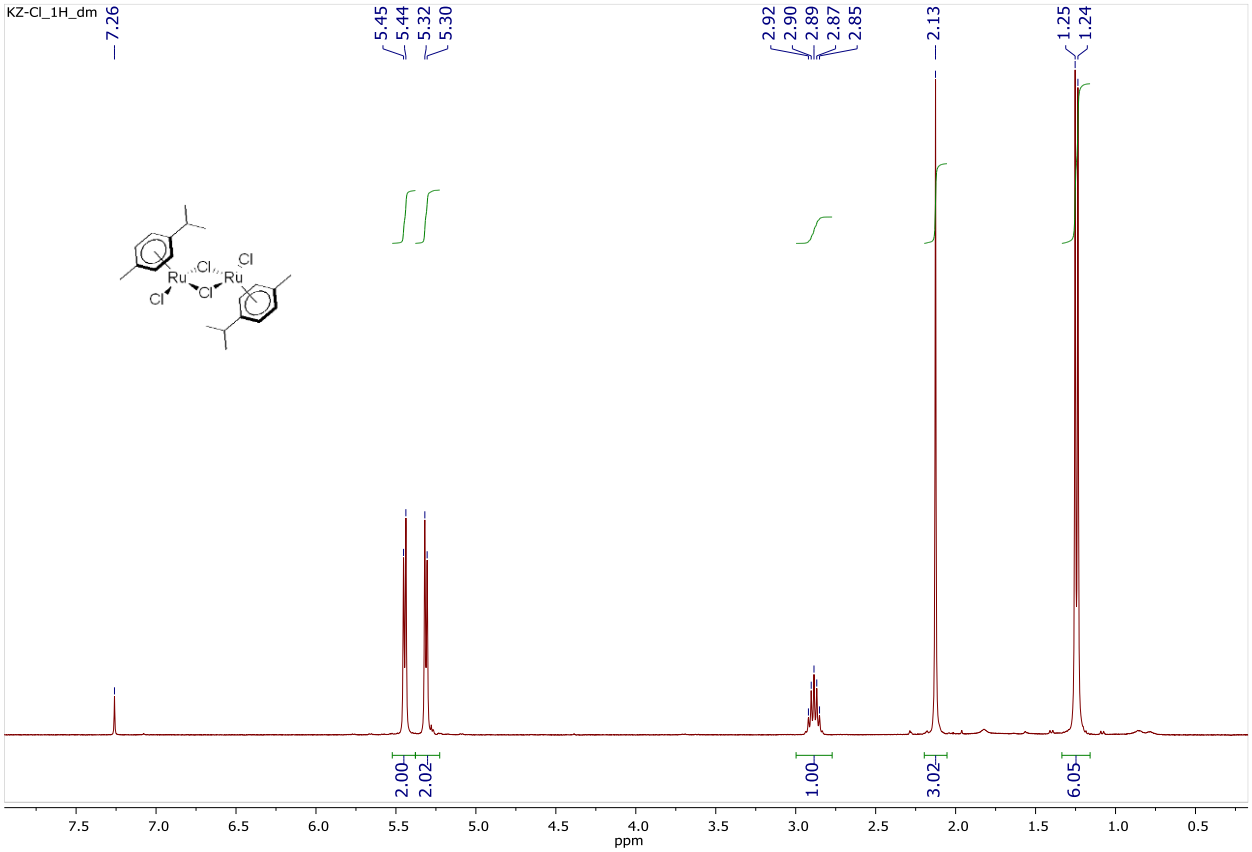


Figure S3. ^{1}H NMR spectrum of [(*p*-cymene)$RuCl_2]_2$.[S1]

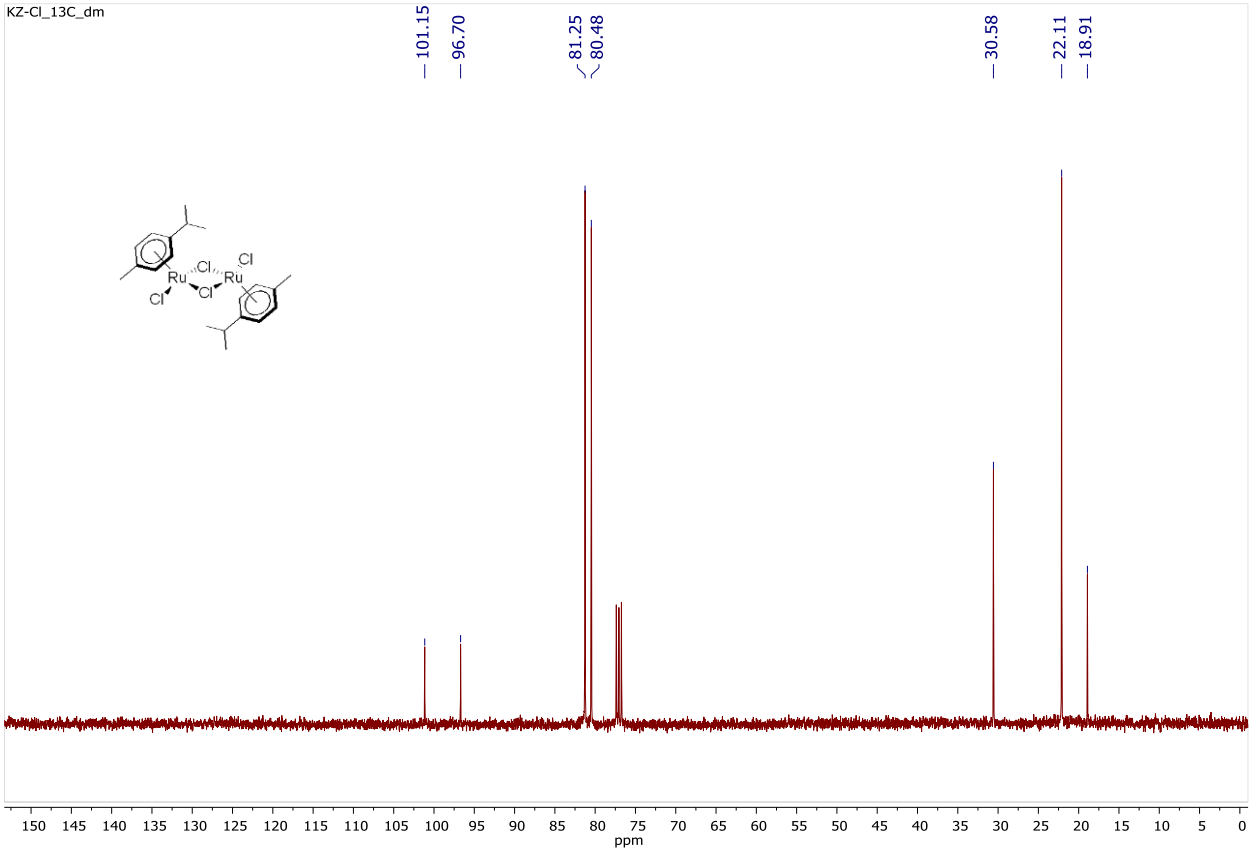


Figure S4. ^{13}C NMR spectrum of [(*p*-cymene)$RuCl_2]_2$.[S1]

Illustrative ^{1}H NMR spectra of compounds 3a-d in reaction mixtures
The signal used for yield determination is highlighted by a green circle.

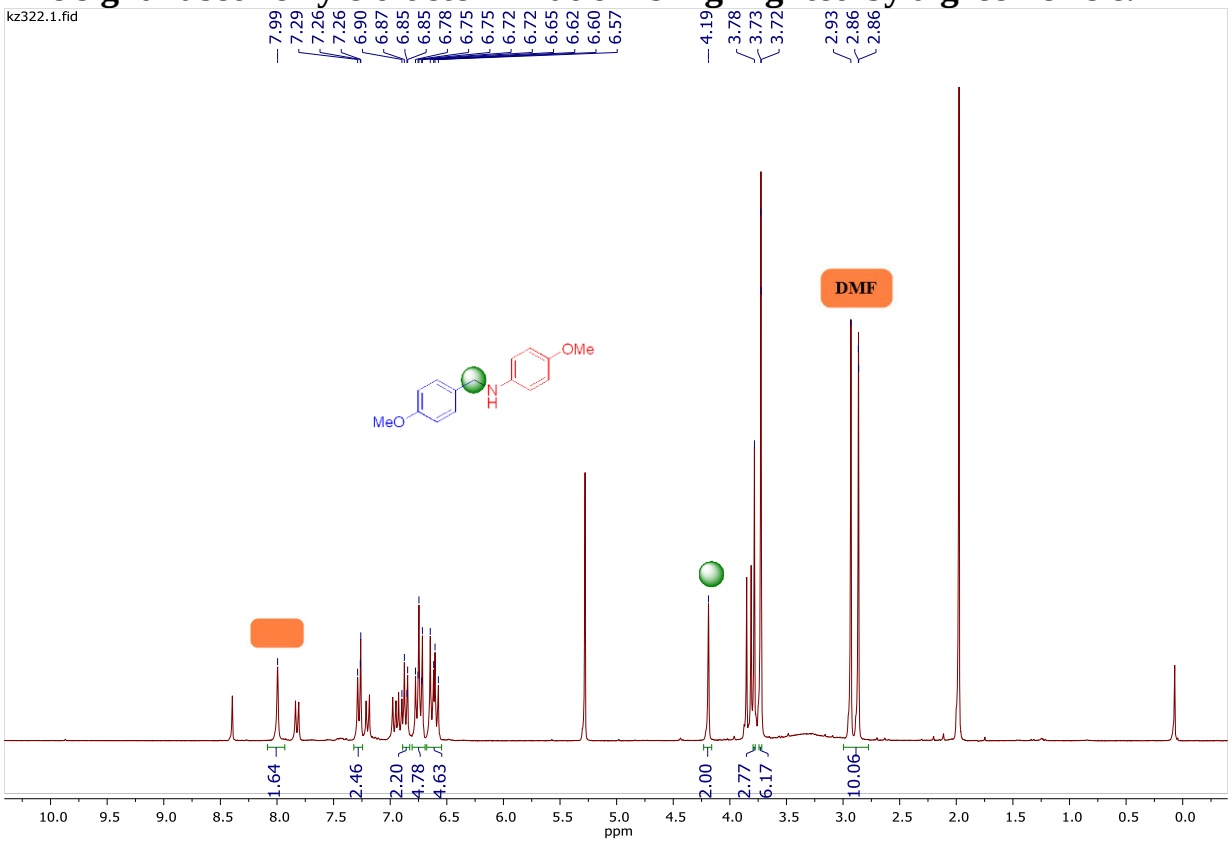


Figure S5. An example spectrum for the reaction mixture with 4-methoxy-*N*-(4-methoxybenzyl)aniline **(3a)**.[S1]

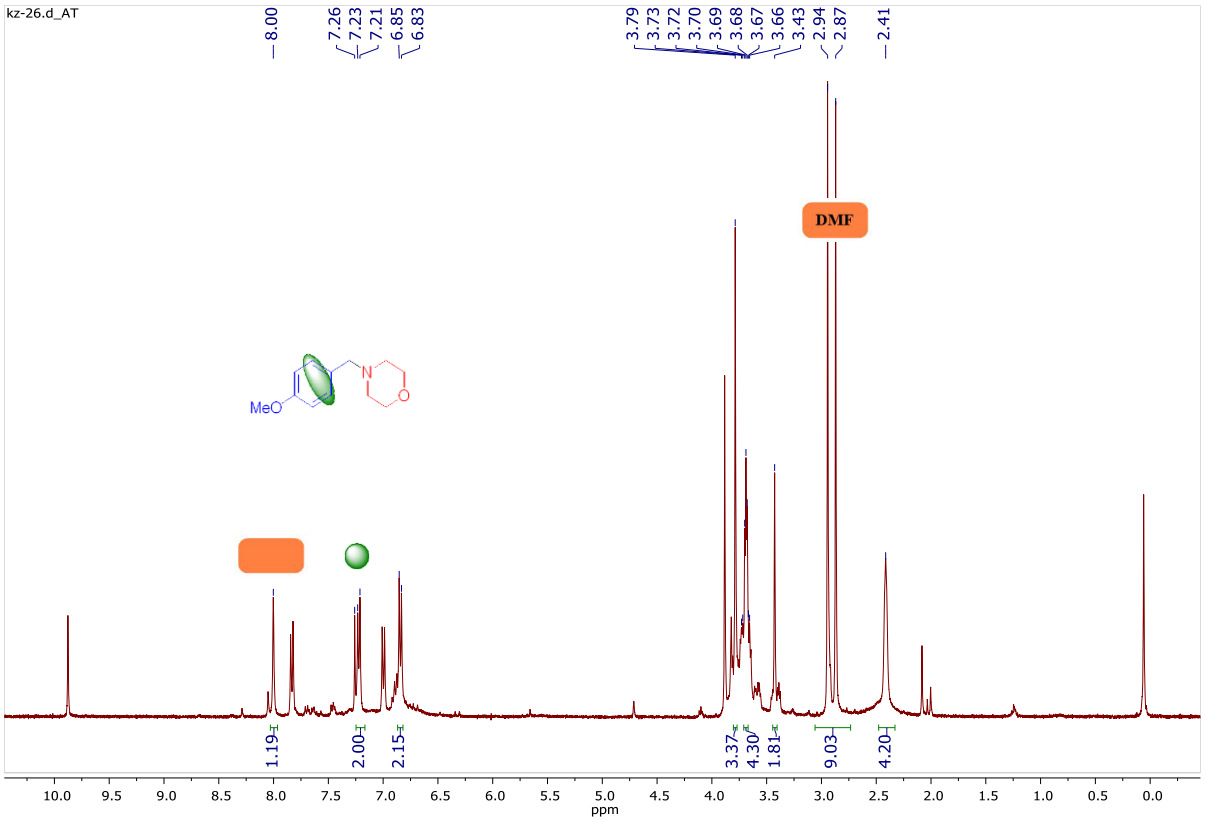


Figure S6. An example spectrum for the reaction mixture with 4-(4-methoxybenzyl)morpholine **(3b)**.[S2]

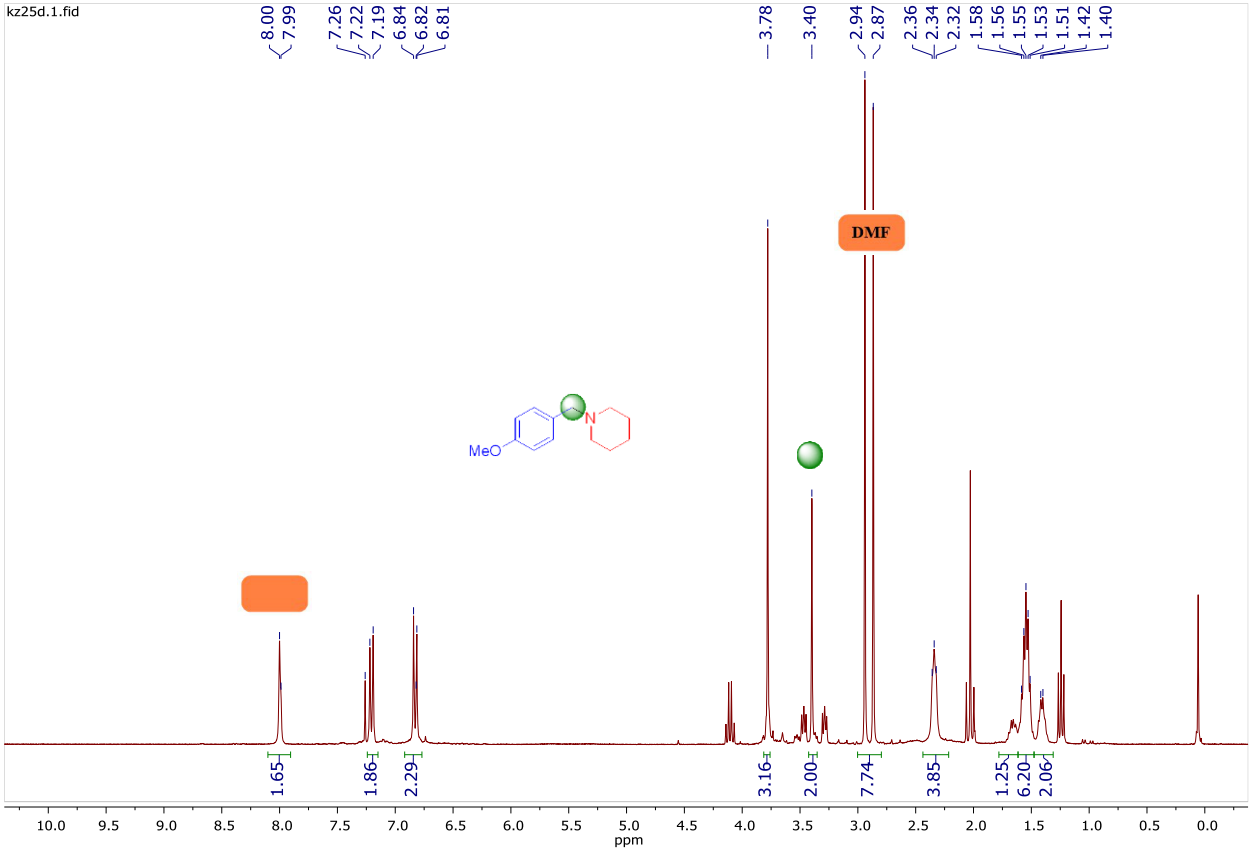


Figure S7. An example spectrum for the reaction mixture with 1-(4-methoxybenzyl)piperidine **(3c)**.[S2]

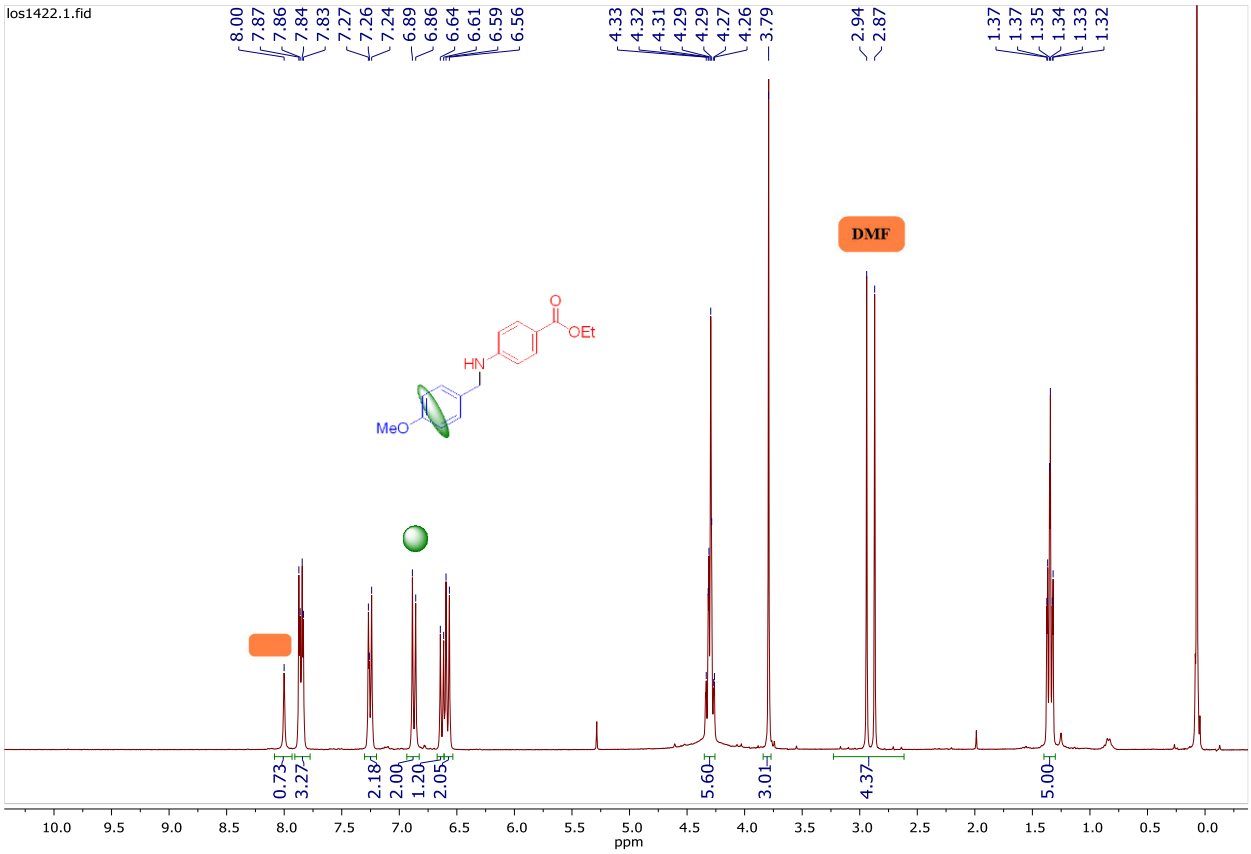


Figure S8. An example spectrum for the reaction mixture with ethyl 4-[(4-methoxybenzyl)amino]benzoate **(3d)**.[S3]