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Cobalt-Catalyzed C–N Bond-Forming Reaction between Chloronitrobenzenes and Secondary Amines

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Cyclic secondary amines react with mono- or dichloronitrobenzene in the presence of a catalytic amount of cobalt(II) chloride. Phosphane ligands are beneficial for the reaction, although the bite-angle effect was not strong. The nitro-substituted tertiary amines formed are important as bioactive compounds and can also be intermediates for the synthesis of substituted anilines. This work represents the first cobalt-catalyzed approach to C–N bond-forming reactions involving aromatic chlorides and cyclic secondary amines. The reaction is *ortho*- and *para*-selective, with *meta*-substituted halides being unreactive in this procedure.

Introduction

Transitional-metal-catalyzed cross-coupling[1] is one of the most valued synthetic methodologies used for carbon–heteroatom bond formation. First reported independently by Buchwald[2] and Hartwig[3] fifteen years ago, with palladium as catalyst, the amination reaction has attracted the interest of many chemists whose efforts at improving the reaction has reached its peak over the past few years. Extensive work has been done to replace palladium[4] with inexpensive and/or nontoxic metals such as nickel,[5] copper,[6] iron,[7] and cobalt.[8] However, some concerns exist over the use of iron as a catalyst in the reaction due to the possible presence of copper impurities in low-purity samples of iron chloride produced by different chemical suppliers.[9] Although recent progresses in cobalt catalysis has been made,[10] only two reports, by Teo et al.[8a] and by Toma et al.,[8b] describe cobalt-catalyzed amination reactions of aryl iodides, bromides, and 2-chloro-substituted aromatic N-heterocycles. The system reported by Teo et al. involves the use of *N*,*N*′-dimethylethylenediamine (DMEDA) as ligand in water, whereby a restricted range of nitrogen nucleophiles can react with aromatic iodides and bromides. The system reported previously by us involves the use of 1,3-bis(diphenylphosphanyl)propane (DPPP) as ligand in *p*-xylene; in this approach, 2-chloro-substituted aromatic N-heterocycles can react with various secondary amines to form tertiary amines. The reaction of halonitrobenzenes with amines at high pressure was reported by Ibata et al.,[11] but the procedure describes the formation of several unwanted products and is, therefore, unselective in many cases. Herein, we report the first cobalt-catalyzed amination of aryl chlorides with cyclic secondary amines. The nitro-substituted tertiary amines formed are important as bioactive compounds[12] and can also be useful intermediates for the synthesis of substituted anilines.[13]

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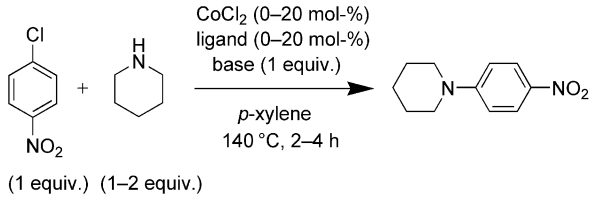
Results and Discussion

The model reaction between 4-chloronitrobenzene and piperidine (Scheme 1) was used for screening bases and ligands to optimize the reaction conditions. The reaction was performed in *p*-xylene at 140 °C for 2–4 h, and the calibrated GC yields of 4-piperidinonitrobenzene are shown in (Table 1).



Scheme 1. Cobalt-catalyzed cross-coupling reaction between 4-chloronitrobenzene and piperidine.

A control reaction conducted in the absence of cobalt catalyst showed 12% product formation (Table 1, Entry 1). When the reaction was performed in the absence of a base, only 3% yield was observed (Table 1, Entry 2). When both cobalt(II) chloride and potassium hydrogen carbonate were used, the yield increased to 24% (Table 1, Entry 3). Other potassium and sodium bases were screened (Table 1, Entries 4–6), but the results did not improve. Increasing the amount of piperidine to 2 equiv. led to an improvement in

Table 1. Optimization of the cobalt-catalyzed cross-coupling reaction.

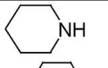
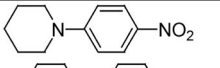
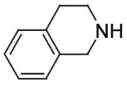
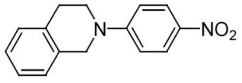
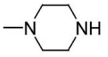
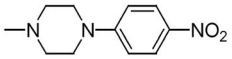
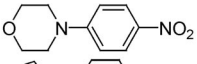
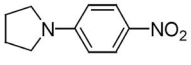
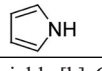
Entry	Base	Amine [equiv.]	Ligand[a] [20 mol-%]	$CoCl_2$ [mol-%]	Time [h]	Yield [%][b]
1	$KHCO_3$	1	none	none	2	12
2	none	1	none	20	2	3
3	$KHCO_3$	1	none	10	2	24
4	$NaHCO_3$	1	none	10	2	17
5	K_2CO_3	1	none	10	2	9
6	K_3PO_4	1	none	10	2	11
7	$KHCO_3$	2	none	10	2	37
8	$KHCO_3$	2	none	20	2	46
9	$KHCO_3$	2	none	20	4	54
10	$KHCO_3$	2	PPh_3	20	4	65
11	$KHCO_3$	2	DPPM	20	4	66
12	$KHCO_3$	2	DPPE	20	4	70
13	$KHCO_3$	2	DPPP	20	4	72
14	$KHCO_3$	2	DPPB	20	4	71

[a] 1,1-Bis(diphenylphosphanyl)methane (DPPM), 1,2-bis(diphenylphosphanyl)ethane (DPPE), 1,3-bis(diphenylphosphanyl)-propane (DPPP), 1,4-bis(diphenylphosphanyl)butane (DPPB). [b] Calibrated GC yield with mesitylene as the internal standard.

the product yield to 37% (Table 1, Entry 7). Increasing the amount of cobalt(II) chloride improved the yield to 46% (Table 1, Entry 8), and when the reaction time was extended to 4 h, the yield further improved to 54% (Table 1, Entry 9). Phosphane ligands also improved the yield (Table 1, Entries 10–14), with DPPP showing the best result (Table 1, Entry 13). The reactivity of several bite-angled phosphane ligands were much more similar in this case than in our previous study on the reaction between 2-chloro-substituted aromatic N-heterocycles and secondary amines.[8b]

Table 2 shows the reactivity of 4-chloronitrobenzene with several amines. In the case of piperidine, the yield was 47% (Table 2, Entry 1), whereas with 1,2,3,4-tetrahydroisoquinoline the yield was 53% (Table 2, Entry 2). For *N*-methylpiperazine and morpholine the yields of the formed products were 54 and 36%, respectively (Table 2, Entries 3 and 4). The most reactive of the amines screened was pyrrolidine,

Table 2. Reactions of 4-chloronitrobenzene with various amines in the presence of cobalt(II) chloride (20 mol-%) and DPPP (20 mol-%), at 140 °C, in *p*-xylene for 4 h.

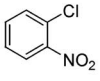
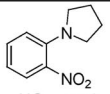
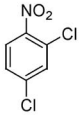
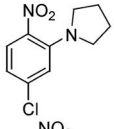
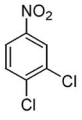
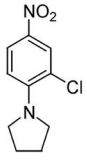
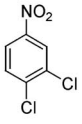
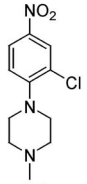
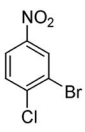
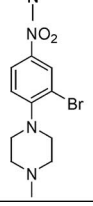
Entry	Amine	Product	Yield[a] [%]
1			47 (72[b])
2			53
3			54
4			36
5			93
6		–	0

[a] Isolated yield. [b] Calibrated GC yield with mesitylene as internal standard.

which gave 93% yield of the expected product (Table 2, Entry 5). In contrast, the five-membered ring amine, pyrrole, showed no reactivity (Table 2, Entry 6).

Table 3 shows the reactivity of various chloronitrobenzenes with amines. 2-Chloronitrobenzene reacted with pyrrolidine to form the expected product in 82% yield (Table 3, Entry 1). 2,4-Dichloronitrobenzene reacted selectively to form the *ortho*-substituted product in 90% yield (Table 3, Entry 2), whereas 3,4-dichlorobenzene reacted selectively to form the *para*-substituted product in 51% yield (Table 3, Entry 3). 3-Chloronitrobenzene was unreactive towards both pyrrolidine and piperidine (Table 3, Entry 4). Because *meta*-substituted chlorides did not react with pyrrolidine, we checked their reactivity towards six-membered ring amines. In the case of *N*-methylpiperazine the yield of the *para*-substituted product was 75% (Table 3, Entry 5). Even when a generally more reactive halide (in the case of corresponding reactions with palladium, copper, nickel, and iron) was present, the *para*-substituted product was obtained in 71% yield (Table 3, Entry 6). Moreover, when the reactivity of *meta*-bromo- and *meta*-iodonitrobenzene were examined, unlike the results obtained by Teo et al.[8a] with cobalt catalysts, no coupling product was obtained. We tried to extend the scope of the reaction to amides and pri-

Table 3. Reactions of various chloronitrobenzenes with amines in the presence of cobalt(II) chloride (20 mol-%) and DPPP (20 mol-%) in *p*-xylene.

Entry	Aryl chloride	Reaction time	Product	Yield[a] [%]
1[b]		1 h		82
2[b]		1 h		90
3[b]		1 h		51
4		4 h	–	0
5		4 h		75
6		4 h		71

[a] Isolated yield. [b] Ligand-free reaction.

mary amines, but were unsuccessful. It is important to note that the presence of a nitro group is critical for this reaction.

Conclusions

We have developed a new methodology for the preparation of nitro-substituted tertiary amines that are useful building blocks for bioactive molecules. Although significant progress has been made over the past few years in cobalt chemistry, the use of chloronitrobenzenes in C–N bond-forming reactions is reported for the first time in this paper. Among the bases screened, potassium hydrogen carbonate gave the best results. The reaction is *ortho*- and *para*-selective, whereas *meta*-substituted halides are unreactive in this procedure. We are examining the mechanism of the present cobalt-catalyzed amination reaction and hope to present a report in the near future.

Experimental Section

General Remarks: All experiments were performed under argon by utilizing Schlenk techniques. Catalysts, ligands, bases, and substrates were purchased from Aldrich, Wako, Kanto, TCI, and Nacalai. *p*-Xylene and amines were distilled before use by common distillation techniques. For GC analysis, a Shimadzu GC-14A instrument was used. For GC-MS analysis, Shimadzu GC-MS-QP5050 and GC-17A instruments were used. A Bruker micrOTOF II device was used for accurate mass determination. A JEOL EX-270 spectrometer was used to record the NMR spectra; $CDCl_3$ was used as solvent, and values are reported in ppm relative to the residual proton signal. Multiplicities are given as follows: s = singlet, d = doublet, t = triplet, dd = doublet of doublets, m = multiplet. Chromatographic separations were performed by using standard column methods with silica (100–200 mesh), alumina gel (200 mesh) and preparative TLC. Elemental analyses were carried out at the Microanalysis Center of Kyoto University.

General Procedure: Table 1. To an oven-dried Schlenk tube that was flushed with argon, *p*-chloronitrobenzene (1.0 mmol), piperidine (1–2 mmol), base (0–1 mmol), cobalt(II) chloride (0–20 mol-%), phosphane ligand (0–20 mol-%), and *p*-xylene (0.5 mL) were consecutively added. The mixture was stirred in an oil bath at 140 °C for 2–4 h. After cooling the Schlenk tube to room temp. and evaporation of the solvent, mesitylene was added as an internal standard and dichloromethane as a solvent before analyzing the mixture by GC.

1-Nitro-4-piperidinobenzene: Table 1, Entry 1. Performed with piperidine (0.099 mL, 1 mmol), *p*-chloronitrobenzene (0.157 g, 1 mmol), potassium hydrogen carbonate (0.100 g, 1 mmol), and *p*-xylene (0.5 mL). Reaction time was 2 h.

1-Nitro-4-piperidinobenzene: Table 1, Entry 2. Performed with piperidine (0.099 mL, 1 mmol), *p*-chloronitrobenzene (0.157 g, 1 mmol), cobalt(II) chloride (0.026 g, 20 mol-%), and *p*-xylene (0.5 mL). Reaction time was 2 h.

1-Nitro-4-piperidinobenzene: Table 1, Entry 3. Performed with piperidine (0.099 mL, 1 mmol), *p*-chloronitrobenzene (0.157 g, 1 mmol), cobalt(II) chloride (0.013 g, 10 mol-%), potassium hydrogen carbonate (0.100 g, 1 mmol), and *p*-xylene (0.5 mL). Reaction time was 2 h.

1-Nitro-4-piperidinobenzene: Table 1, Entry 4. Performed with piperidine (0.099 mL, 1 mmol), *p*-chloronitrobenzene (0.157 g, 1 mmol), cobalt(II) chloride (0.013 g, 10 mol-%), sodium hydrogen carbonate (0.084 g, 1 mmol), and *p*-xylene (0.5 mL). Reaction time was 2 h.

1-Nitro-4-piperidinobenzene: Table 1, Entry 5. Performed with piperidine (0.099 mL, 1 mmol), *p*-chloronitrobenzene (0.157 g, 1 mmol), cobalt(II) chloride (0.013 g, 10 mol-%), potassium carbonate (0.138 g, 1 mmol), and *p*-xylene (0.5 mL). Reaction time was 2 h.

1-Nitro-4-piperidinobenzene: Table 1, Entry 6. Performed with piperidine (0.099 mL, 1 mmol), *p*-chloronitrobenzene (0.157 g, 1 mmol), cobalt(II) chloride (0.013 g, 10 mol-%), potassium phosphate tribasic (0.212 g, 1 mmol), and *p*-xylene (0.5 mL). Reaction time was 2 h.

1-Nitro-4-piperidinobenzene: Table 1, Entry 7. Performed with piperidine (0.198 mL, 2 mmol), *p*-chloronitrobenzene (0.157 g, 1 mmol), cobalt(II) chloride (0.013 g, 10 mol-%), potassium hydrogen carbonate (0.100 g, 1 mmol), and *p*-xylene (0.5 mL). Reaction time was 2 h.

1-Nitro-4-piperidinobenzene: Table 1, Entry 8. Performed with piperidine (0.198 mL, 2 mmol), *p*-chloronitrobenzene (0.157 g, 1 mmol), cobalt(II) chloride (0.026 g, 20 mol-%), potassium hydrogen carbonate (0.100 g, 1 mmol), and *p*-xylene (0.5 mL). Reaction time was 2 h.

1-Nitro-4-piperidinobenzene: Table 1, Entry 9. Performed with piperidine (0.198 mL, 2 mmol), *p*-chloronitrobenzene (0.157 g, 1 mmol), cobalt(II) chloride (0.026 g, 20 mol-%), potassium hydrogen carbonate (0.100 g, 1 mmol), and *p*-xylene (0.5 mL). Reaction time was 4 h.

1-Nitro-4-piperidinobenzene: Table 1, Entry 10. Performed with piperidine (0.198 mL, 2 mmol), *p*-chloronitrobenzene (0.157 g, 1 mmol), cobalt(II) chloride (0.026 g, 20 mol-%), triphenyl phosphane (0.052 g, 20 mol-%), potassium hydrogen carbonate (0.100 g, 1 mmol), and *p*-xylene (0.5 mL). Reaction time was 4 h.

1-Nitro-4-piperidinobenzene: Table 1, Entry 11. Performed with piperidine (0.198 mL, 2 mmol), *p*-chloronitrobenzene (0.157 g, 1 mmol), cobalt(II) chloride (0.026 g, 20 mol-%), 1,3-bis(diphenylphosphanyl)methane (0.077 g, 20 mol-%), potassium hydrogen carbonate (0.100 g, 1 mmol), and *p*-xylene (0.5 mL). Reaction time was 4 h.

1-Nitro-4-piperidinobenzene: Table 1, Entry 12. Performed with piperidine (0.198 mL, 2 mmol), *p*-chloronitrobenzene (0.157 g, 1 mmol), cobalt(II) chloride (0.026 g, 20 mol-%), 1,3-bis(diphenylphosphanyl)ethane (0.080 g, 20 mol-%), potassium hydrogen carbonate (0.100 g, 1 mmol), and *p*-xylene (0.5 mL). Reaction time was 4 h.

1-Nitro-4-piperidinobenzene: Table 1, Entry 13. Performed with piperidine (0.198 mL, 2 mmol), *p*-chloronitrobenzene (0.157 g, 1 mmol), cobalt(II) chloride (0.026 g, 20 mol-%), 1,3-bis(diphenylphosphanyl)propane (0.082 g, 20 mol-%), potassium hydrogen carbonate (0.100 g, 1 mmol), and *p*-xylene (0.5 mL). Reaction time was 4 h.

1-Nitro-4-piperidinobenzene: Table 1, Entry 14. Performed with piperidine (0.198 mL, 2 mmol), *p*-chloronitrobenzene (0.157 g, 1 mmol), cobalt(II) chloride (0.026 g, 20 mol-%), 1,3-bis(diphenylphosphanyl)butane (0.085 g, 20 mol-%), potassium hydrogen carbonate (0.100 g, 1 mmol), and *p*-xylene (0.5 mL). Reaction time was 4 h.

General Procedure: Tables 2 and 3. To an oven-dried Schlenk tube that was flushed with argon, chloronitrobenzene (1.0 mmol), cyclic secondary amine (1–2 mmol), $KHCO_3$ (1 mmol), cobalt(II) chloride (20 mol-%), phosphane ligand (20 mol-%), and *p*-xylene (0.5 mL) were consecutively added. The mixture was stirred in an oil bath at 140 °C for 1–4 h. Isolation was achieved by column chromatography on silica gel, alumina or preparative TLC (hexane/diethyl ether, dichloromethane or acetone). Products were identified by NMR, GC–MS, micrOTOF mass and elemental analyses.

1-Nitro-4-piperidinobenzene: Table 2, Entry 1. Synthesized from 1-chloro-4-nitrobenzene (0.157 g, 1 mmol) and piperidine (0.198 mL, 2 mmol). The product was isolated as a yellow solid (0.097 g, 47%) after silica gel column chromatography (hexane/diethyl ether). ^{1}H NMR (270 MHz, $CDCl_3$, 25 °C): δ = 1.66 (s, 6 H, CH_2), 3.42 (s, 4 H, NCH_2), 6.76 (d, J = 7.2 Hz, 2 H, ArH), 8.06 (d, J = 7.5 Hz, 2 H, ArH) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$, 25 °C): δ = 24.1 (CH_2), 25.1 (CH_2), 48.2 (NCH_2), 112.1 (CH), 126.1 (CH), 137.2 (CNO_2), 154.7 ($CNCH_2$) ppm. GC–MS: *m*/*z* = 205, 176, 165, 159, 150, 131, 120, 103, 91, 77.

1-Nitro-4-[1,2,3,4-tetrahydroisoquinolino]benzene: Table 2, Entry 2. Synthesized from 1-chloro-4-nitrobenzene (0.157 g, 1 mmol) and 1,2,3,4-tetrahydroisoquinoline (0.250 mL, 2 mmol). The product was isolated as a yellow solid (0.134 g, 53%) after silica gel column chromatography (hexane/diethyl ether). ^{1}H NMR (270 MHz, $CDCl_3$, 25 °C): δ = 3.03 (m, 2 H, CH_2), 3.70 (m, 2 H, NCH_2), 4.58 (m, 2 H, NCH_2), 6.82 [d, J = 9.4 Hz, 2 H, ArH (benzene)], 7.26 [m, 4 H, ArH (isoquinoline)], 8.17 [d, J = 9.4 Hz, 2 H, ArH (benzene)] ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$, 25 °C): δ = 28.9 (CH_2), 44.7 (NCH_2), 48.7 (NCH_2), 111.1 (CH), 126.1 (CH), 126.4 (CH), 126.6 (CH), 127.13 (CH), 128.05 (CH), 132.90 (C), 134.95 (C), 137.4 (CNO_2), 153.9 ($CNCH_2$) ppm. GC–MS: *m*/*z* = 254, 253, 207, 165, 127, 115, 104, 91, 78.

1-Methyl-4-(4-nitrophenyl)piperazine: Table 2, Entry 3. Synthesized from 1-chloro-4-nitrobenzene (0.157 g, 1 mmol) and *N*-methylpiperazine (0.222 mL, 2 mmol). The product was isolated as a yellow solid (0.121 g, 54%) after silica gel column chromatography (hexane/diethyl ether/acetone). ^{1}H NMR (270 MHz, $CDCl_3$, 25 °C): δ = 2.35 (s, 3 H, CH_3), 2.55 (t, J = 5.1 Hz, 4 H, CH_2), 3.43 (t, J = 5.1 Hz, 4 H, CH_2), 6.82 (d, J = 9.4 Hz, 2 H, ArH) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$, 25 °C): δ = 45.9 (NCH_3), 46.8 (NCH_2), 54.4 (NCH_2), 112.5 (CH), 125.8 (CH), 138.2 (CNO_2), 154.7 ($CNCH_2$) ppm. GC–MS: *m*/*z* = 221, 179, 161, 150, 120, 104, 87, 70.

1-Morpholino-4-nitrobenzene: Table 2, Entry 4. Synthesized from 1-chloro-4-nitrobenzene (0.157 g, 1 mmol) and morpholine (0.175 mL, 2 mmol). The product was isolated as a yellow solid (0.075 g, 36%) after alumina gel column chromatography (hexane/diethyl ether). ^{1}H NMR (270 MHz, $CDCl_3$, 25 °C): δ = 3.37 (t, J = 4.8 Hz, 4 H, CH_2), 3.87 (t, J = 4.8 Hz, 4 H, CH_2), 6.83 (d, J = 9.1 Hz, 2 H, ArH), 8.13 (d, J = 9.7 Hz, 2 H, ArH) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$, 25 °C): δ = 47.0 (NCH_2), 66.3 (OCH_2), 112.5 (CH), 125.8 (CH), 138.8 (CNO_2), 154.9 ($CNCH_2$) ppm. GC–MS: *m*/*z* = 208, 192, 177, 161, 150, 120, 104, 77.

1-Nitro-4-pyrrolidinobenzene: Table 2, Entry 5. Synthesized from 1-chloro-4-nitrobenzene (0.157 g, 1 mmol) and pyrrolidine (0.164 mL, 2 mmol). The product was isolated as a yellow solid (0.180 g, 93%) after silica gel column chromatography (hexane/dichloromethane). ^{1}H NMR (270 MHz, $CDCl_3$, 25 °C): δ = 1.96 (t, J = 6.4 Hz, 4 H, CH_2), 3.68 (t, J = 6.4 Hz, 4 H, NCH_2), 6.31 (d, J = 9.1 Hz, 2 H, ArH), 7.94 (d, J = 9.1 Hz, 2 H, ArH) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$, 25 °C): δ = 25.1 (CH_2), 47.7 (NCH_2), 110.2 (CH), 126.0 (CH), 136.0 (CNO_2), 151.6 ($CNCH_2$) ppm. GC–MS: *m*/*z* = 192, 191, 176, 162, 145, 136, 117, 106, 90, 77.

1-Nitro-2-pyrrolidinobenzene: Table 3, Entry 1. Synthesized from 1-chloro-2-nitrobenzene (0.157 g, 1 mmol) and pyrrolidine (0.164 mL, 2 mmol). The product was isolated as a yellow oil (0.158 g, 82%) after alumina gel column chromatography (hexane/dichloromethane). ^{1}H NMR (270 MHz, $CDCl_3$, 25 °C): δ = 1.98 (m, 4 H, CH_2), 3.21 (m, 4 H, NCH_2), 6.70 (ddd, J = 7.2, 6.4, 1.0 Hz, 1 H, ArH), 6.90 (d, J = 8.3 Hz, 1 H, ArH), 7.35 (ddd, J = 5.6, 5.1, 1.6 Hz, 1 H, ArH), 7.74 (dd, J = 6.4, 1.6 Hz, 1 H, ArH) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$, 25 °C): δ = 25.6 (CH_2), 50.3 (NCH_2), 115.3 (CH), 115.8 (CH), 126.6 (CH), 132.9 (CH), 137.0 ($CNCH_2$), 142.7 (CNO_2) ppm. GC–MS: *m*/*z* = 192, 175, 157, 145, 117, 104, 91, 77.

4-Chloro-2-pyrrolidino-1-nitrobenzene: Table 3, Entry 2. Synthesized from 2,4-dichloro-1-nitrobenzene (0.192 g, 1 mmol) and pyrrolidine (0.164 mL, 2 mmol). The product was isolated as a yellow solid (0.205 g, 90%) after alumina gel column chromatography (hexane/dichloromethane). ^{1}H NMR (270 MHz, $CDCl_3$, 25 °C): δ = 1.99 (m, 4 H, CH_2), 3.20 (m, 4 H, NCH_2), 6.66 (dd, J = 6.7, 1.89 Hz, 1 H, ArH), 6.89 (d, J = 1.8 Hz, 1 H, ArH), 7.68 (d, J = 8.6 Hz, 1 H, ArH) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$, 25 °C): δ = 25.6 (CH_2), 50.5 (NCH_2), 115.4 (CH), 115.5 (CH), 127.9 (CH), 135.3 (CNO_2), 139.0 (CCl), 143.1 ($CNCH_2$) ppm. GC–MS: *m*/*z* = 226, 209, 180, 178, 153, 138, 111, 89, 75.

2-Chloro-1-pyrrolidino-4-nitrobenzene: Table 3, Entry 3. Synthesized from 1,2-dichloro-4-nitrobenzene (0.192 g, 1 mmol) and pyrrolidine (0.164 mL, 2 mmol). The product was isolated as a yellow solid (0.117 g, 51%) after preparative TLC (hexane/dichloromethane). ^{1}H NMR (270 MHz, $CDCl_3$, 25 °C): δ = 2.00 (s, 4 H, CH_2), 3.65 (s, 4 H, NCH_2), 6.65 (d, J = 9.1 Hz, 1 H, ArH), 7.97 (d, J = 9.1 Hz, 1 H, ArH), 8.17 (s, 1 H, ArH) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$, 25 °C): δ = 25.7 (CH_2), 51.4 (NCH_2), 114.0 (CH), 118.0 (CCl), 123.7 (CH), 128.2 (CH), 137.6 (CNO_2), 150.6 ($CNCH_2$) ppm. GC–MS: *m*/*z* = 225, 191, 179, 170, 154, 145, 117, 102, 89, 75.

1-(2-Chloro-4-nitrophenyl)-4-methylpiperazine: Table 3, Entry 5. Synthesized from 1,2-dichloro-4-nitrobenzene (0.192 g, 1 mmol) and *N*-methylpiperazine (0.222 mL, 2 mmol). The product was isolated as a yellow oil (0.194 g, 75%) after silica gel column chromatography (hexane/dichloromethane/acetone). ^{1}H NMR (270 MHz, $CDCl_3$, 25 °C): δ = 2.32 (s, 3 H, NCH_3), 2.57 (s, 4 H, NCH_2), 3.19 (s, 4 H, NCH_2), 7.01 (d, J = 7.2 Hz, 1 H, ArH), 8.09 (dd, J = 10.0, 2.7 Hz, 1 H, ArH), 8.22 (d, J = 2.7 Hz, 1 H, ArH) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$, 25 °C): δ = 45.9 (NCH_3), 50.3 (NCH_2), 54.6 (NCH_2), 119.2 (CH), 123.2 (CH), 126.4 (CH), 127.2 (CCl), 141.8 (CNO_2), 154.6 ($CNCH_2$) ppm. GC–MS: *m*/*z* = 255, 213, 195, 184, 177, 154, 137, 102, 89, 71.

1-(2-Bromo-4-nitrophenyl)-4-methylpiperazine: Table 3, Entry 6. Synthesized from 2-bromo-1-chloro-4-nitrobenzene (0.236 g, 1 mmol) and *N*-methylpiperazine (0.222 mL, 2 mmol). The product was isolated as a yellow oil (0.213 g, 71%) after silica gel column chromatography (hexane/diethyl ether/acetone). ^{1}H NMR (270 MHz, $CDCl_3$, 25 °C): δ = 2.38 (s, 3 H, NCH_3), 2.63 (s, 4 H, NCH_2), 3.23 (s, 4 H, NCH_2), 7.05 (d, J = 8.9 Hz, 1 H, ArH), 8.14 (dd, J = 6.4, 2.4 Hz, 1 H, ArH), 8.42 (d, J = 2.4 Hz, 1 H, ArH) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$, 25 °C): δ = 45.9 (NCH_3), 50.9 (NCH_2), 54.7 (NCH_2), 117.4 (CBr), 119.6 (CH), 123.8 (CH), 129.7 (CH), 142.3 (CNO_2), 156.2 ($CNCH_2$) ppm. GC–MS: *m*/*z* = 301, 299, 257, 220, 192, 177, 149, 131, 119, 103, 89, 76, 71. MS (micrOTOF): calcd. for $C_{11}H_{14}BrN_3O_2$ 300.0342 and 302.0322; found

300.0326 and 302.0310. $C_{11}H_{14}BrN_3O_2$ (300.15): calcd. C 44.02, H 4.70, N 14.00; found C 43.81, H 4.47, N 13.87.

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