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Rapid palladium-catalyzed aminations of aryl chlorides with aliphatic amines under temperature-controlled microwave heating

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Abstract—Rapid Buchwald–Hartwig amination of electron neutral and rich aryl chlorides and bromides have been achieved using temperature-controlled microwave heating. Primary and secondary aliphatic amines can be coupled with these substrates in good yields within a reaction time of only 10 min.

In the last decade, the impact of homogeneous palladium catalysis on the field of organic syntheses has increased exponentially. Within this diverse research area the palladium-catalyzed amination, in the mid nineties independently discovered by Buchwald and Hartwig, has currently established itself as the most powerful method available for the C(sp^2)–N bond formation as it is applicable for both activated and non-activated aryl halogenides.[1] This is exemplified by its use in the synthesis of several natural products such as the alkaloids makaluvamine C,[2] damirones A and B,[2] lavendamycin[3] and isocryptolepine.[4] Besides natural products also drug analogues and drug metabolites have been prepared by a Buchwald–Hartwig reaction. For instance, raloxifene (launched by Eli Lilly to prevent osteoporosis) analogues were synthesized via an alternative route by Schmid and co-workers using 2-bromobenzo-[*b*]thiophenes as the amination substrates.[5] Another example is the synthesis of hydroxyitraconazole, an active metabolite of the antifungal drug itraconazole launched by Janssen Pharmaceutica, in which one of the arylpiperazine moieties is synthesized via a palladium-catalyzed C–N bond formation.[6] Norastemizole, another example of an active metabolite, was smoothly obtained via the selective coupling of 2-chloro-1-(4-fluorobenzyl)benzimidazole with the primary amino group of 4-aminopiperidine.[7] It is a metabolite of the antiallergic drug Astemizole of Janssen Pharmaceutica which has reduced side effects. All these examples clearly indicate the large potential of this C–N bond formation methodology for its use in the preparation of biologically active compounds. However, for incorporation in lead discovery and optimization processes the Buchwald–Hartwig amination reaction still has the major drawback that the reaction times are usually in the order of hours to one day. This might be too long for high-throughput medicinal chemistry programs in which large libraries of compounds have to be made within a short period of time.[8] Moreover, in such programs aryl chlorides, the least reactive substrates of the aryl halogenides, are more preferred compounds than aryl bromides and aryl iodides because of their lower cost and wider availability.[1g] Recently, our laboratory reported a procedure to perform Buchwald–Hartwig aminations of aryl chlorides with anilines within 10 min using temperature-controlled microwave heating.[9,10] The ligand as well as the palladium source reported in this short communication are air stable and commercially available products which are important aspects when aiming for a user-friendly protocol (without the necessity of a glovebox) as required for chemistry in a high-throughput program. As an extension of the published work, we now report the more challenging rapid palladium-catalyzed microwave-assisted amination of aryl chlorides with aliphatic amines.[9,11]

First, we investigated the Buchwald–Hartwig amination of morpholine with chlorobenzene, 4-chlorotoluene and 4-chloroanisole under microwave irradiation since secondary cyclic amines are known to be the easiest coupling partners of the aliphatic amines (Table 1, entries 1–3). We selected the same catalyst, $Pd(OAc)_2$ and 2-(dicyclohexylphosphanyl)biphenyl (DCPB),[12] as we previously found to be optimal for rapid aminations of aryl chlorides with

Keywords: Palladium; Homogeneous catalysis; Buchwald–Hartwig amination; Aryl chlorides; Aryl bromides; Microwave irradiation.
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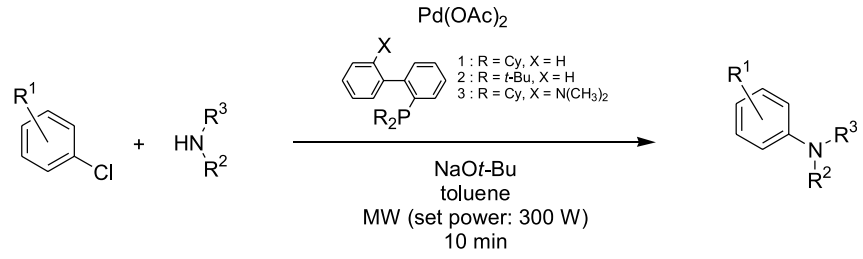
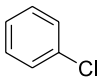
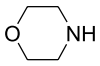
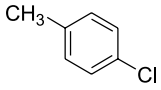
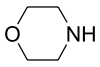
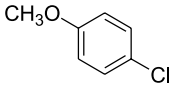
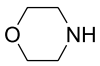
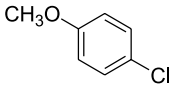
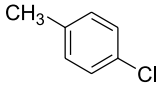
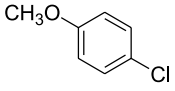
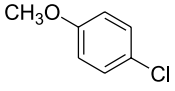
Table 1. Rapid microwave-assisted Buchwald–Hartwig amination of aryl chlorides (CEM Discover apparatus)[22]



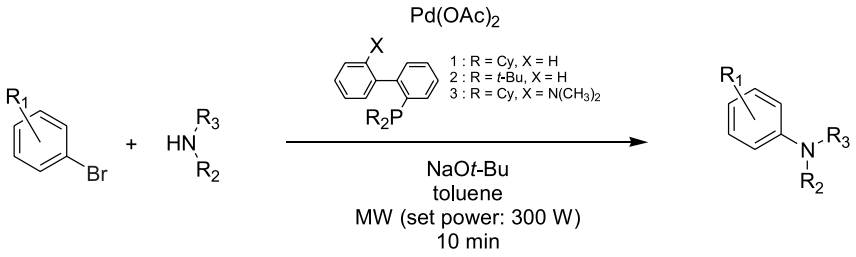
Entry	Aryl Chloride	Amine	Ligand	Pd loading (mol%)	Temp (°C)	Yield[a,b] MW (%)	Yield[a,b] oil bath (%)
1			1	1	150	91	91
2			1	1	150	83	85
3			1	1	150	76	76
4		Bu_2NH	1	1	150	15	
5		Bu_2NH	1	1	200	28	
6		Bu_2NH	1	2	200	35	
7		Bu_2NH	2	1	150	50	47
8		Bu_2NH	3	1	150	54[c]	
9		Bu_2NH	2	2	110	48[d]	43[d]
10		Bu_2NH	2	1	150	70	63
11		$BnNH_2$	2	1	150	81[e]	87[e]
12		$BnNH_2$	2	1	150	85[f]	
13		$BnNH_2$	1	1	150	42[e]	
14		*n*-$HexNH_2$	2	1	150	86[e]	85[e]
15		*n*-$HexNH_2$	2	1	150	87[f]	
16		*n*-$HexNH_2$	1	1	150	20[e]	

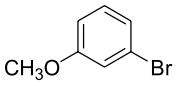
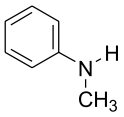
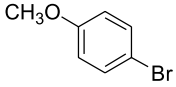
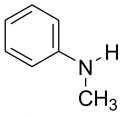
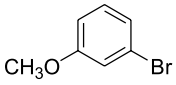
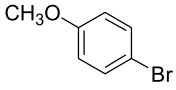
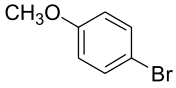
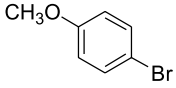
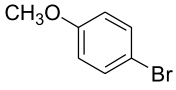
[a] Reaction conditions: $Pd(OAc)_2$ (X mol%), DCPB or DTPB or DCPAB (2 X mol%), aryl chloride (1 mmol), amine (1.2 mmol), NaO*t*-Bu (1.4 mmol), toluene (1 mL).
[b] Yields of isolated products are an average of two runs.
[c] $Pd_2(dba)_3$ was used instead of $Pd(OAc)_2$, a Pd/L ratio of 1.5 was used.
[d] The reaction time was 20 min instead of 10 min.
[e] 1.5 mmol of amine were used instead of 1.2 mmol.
[f] 3 mmol of amine were used instead of 1.2 mmol.

anilines.[9] Interestingly, with a catalyst loading of only 1 mol% and a temperature of 150 °C good results were obtained in a reaction time of only 10 min. The isolated yield decreased as the substrate became more electron rich (Table 1, compare entries 1–3). Nevertheless, even for 4-chloroanisole (Table 1, entry 3), the most electron rich aryl chloride substrate of the three used, 4-(4-methoxyphenyl)morpholine could be obtained in 76% yield.

Next, we tried to couple acyclic secondary and primary amines with aryl chlorides. We selected 4-chloroanisole as our test substrate since electron rich aryl chlorides are more difficult substrates than electron neutral ones.[1g] This can be explained by taking into account that the fundamental processes oxidative addition as well as reductive elimination are disfavoured by decreasing the electrophilicity of the aryl group.[1c,g] In addition, the selectivity of reductive elimination versus β-H elimination from a palladium amide complex is better for electron neutral than for electron rich substrates.[1c] As a test case, we have chosen the coupling of 4-chloroanisole with dibutylamine which is one among the most challenging combinations. Disappointingly, only 15%

Table 2. Rapid microwave-assisted Buchwald–Hartwig amination of aryl bromides (CEM Discover apparatus)[22]



Entry	Aryl bromide	Amine	Ligand	Pd loading (mol%)	Temp (°C)	Yield[a,b] MW (%)	Yield[a,b] oil bath (%)
1			1	1	150	90	91
2			1	1	150	89	87
3			1	1	150	87	88
4			1	1	150	80	83
5		Bu_2NH	1	1	150	49	60
6		Bu_2NH	2	1	150	36	
7		Bu_2NH	3	1	150	54[c]	
8		$BnNH_2$	1	1	150	61[d]	
9		$BnNH_2$	2	1	150	87[d]	93[d]
10		*n*-$HexNH_2$	2	1	150	79[d]	79[d]

[a] Reaction conditions: $Pd(OAc)_2$ (X mol%), DCPB or DTPB or DCPAB (2 X mol%), aryl bromide (1 mmol), amine (1.2 mmol), NaO*t*-Bu (1.4 mmol), toluene (1 mL).
[b] Yields of isolated products are an average of two runs.
[c] $Pd_2(dba)_3$ was used instead of $Pd(OAc)_2$, a Pd/L ratio of 1.5 was used.
[d] 3 mmol of amine were used instead of 1.2 mmol.

of *N*,*N*-dibutyl-4-methoxyaniline and an incomplete reaction was obtained in 10 min under the standard conditions (1 mol% catalyst, 150 °C) (Table 1, entry 4). Neither increasing the temperature to 200 °C (Table 1, entry 5) nor additional increasing of the catalyst loading to 2 mol% (Table 1, entry 6) provided us with acceptable yields and complete conversion of starting material. Finally, we discovered that the use of 2-(di-*t*-butylphosphanyl)biphenyl (DTPB)[12] as the ligand instead of 2-(dicyclohexylphosphanyl)biphenyl (DCPB) gave an acceptable result since a complete conversion of starting material was observed and 50% of *N*,*N*-dibutyl-4-methoxyaniline could be isolated (Table 1, entry 7). An attempt to further increase the yield by performing the reaction at a lower temperature using a double loading of catalyst was unsuccessful (Table 1, entry 9). In this case a reaction time of 20 min was necessary to get a full conversion of starting material. Interestingly, the use 2-dicyclohexylphosphanyl-2′-(*N*,*N*-dimethylamino)biphenyl (DCPAB)[12] another electron rich biphenyl based phosphane, gave a similar result as we obtained with DTPB (Table 1, compare entries 7 and 8). We decided to continue our studies with the latter since DCPAB is substantially more expensive than DTPB.[13] As could be expected the coupling of the less electron rich 4-chlorotoluene with dibutylamine gave a higher yield than 4-chloroanisole (Table 1, compare entries 7 and 10). Under the same conditions as used in entry 7 (1 mol% catalyst, 150 °C, 10 min) we also tried to couple benzylamine and hexylamine with 4-chloroanisole. Since primary aliphatic amines are known to give diarylation, we used a larger excess of amine (1.5 equiv of amine instead of 1.2 equiv) to suppress the formation of undesired diarylated compound. Gratifyingly, *N*-benzyl-4-methoxyaniline and *N*-hexyl-4-methoxyaniline could be obtained in excellent yields (81 and 86%, respectively) (Table 1, entries 11 and 14). The use of 3 equiv of amine did not further significantly increase the yields (Table 1, entries 12 and 15). Reinvestigation of the ligand DCPB for the coupling of 4-chloroanisole with

benzylamine and hexylamine, respectively, showed inferior results in comparison with DTBP as the ligand (entries 13 and 16). Interestingly, a literature search revealed that hitherto for the synthesis of *N*-benzyl-4-methoxyaniline (93%, 1 mol% catalyst, 4 h) and *N*-hexyl-4-methoxyaniline (92%, 2 mol% catalyst, 18 h) from 4-chloroanisole only one palladium-catalyzed amination protocol has been reported using pentaphenylferrocenyl di-*tert*-butylphosphine (PPFDTBP) as the ligand for the catalyst.[14] Although, we obtained somewhat lower yields than Hartwig's group our protocol has the important advantage that high conversion rates are obtained for the synthesis of *N*-benzyl-4-methoxyaniline and *N*-hexyl-4-methoxyaniline. For the former, we observed a moderate speed-up by a factor 24 while the conversion time of the latter increases more than 100 times. Moreover, in this last mentioned case we used only 1 mol% Pd/2 DTPB catalyst while 2 mol% Pd/2 PPFDTBP was used in the literature procedure.

Finally, we investigated if the same protocol developed for aryl chlorides could also be used for aryl bromides.[15,16] This is an important aspect when aiming a generally applicable protocol for incorporation in high-throughput medicinal chemistry programs since aryl bromide substrates are also easily accessible. This would seriously expand the scope of our microwave amination method. Again electron rich substrates (3- and 4-bromoanisole) were selected as test substrates. First, we investigated the amination of 3- and 4-bromoanisole with *N*-methylaniline. Gratifyingly, we found that 90% of 3-methoxy-*N*-methyl-*N*-phenylaniline and 89% of 4-methoxy-*N*-methyl-*N*-phenylaniline were obtained under the standard conditions used for aryl chlorides (1 mol% Pd/2 DCPB, 150 °C, 10 min) (Table 2, entries 1 and 2). Under these conditions also morpholine could be efficiently coupled with 3- and 4-bromoanisole (Table 2, entries 3 and 4). Next, we investigated the amination of 4-bromoanisole with dibutylamine. Interestingly, in this case the DCPB ligand gave a better result than DTPB (Table 2, entries 5 and 6), while the reverse was observed in the related coupling starting from 4-chloroanisole (Table 1, entries 4 and 7). The use of DCPAB as ligand gave a similar yield as obtained with DCPB (Table 2, compare entries 5 and 7). We also tried to couple primary aliphatic amines (benzylamine and hexylamine) with 4-bromoanisole. As mentioned before a larger excess of amine is required for primary amines in order to suppress the formation of undesired diarylated compound. For the coupling of primary aliphatic amines with 4-bromoanisole we immediately used 3 equiv of amine without investigating if a smaller excess would be sufficient. Amination of 4-bromoanisole with benzylamine using DTPB (87%) gave a higher yield than when DCPB (61%) was used (Table 2, entries 9 and 8). Finally, Buchwald–Hartwig amination of 4-bromoanisole with hexylamine, using DTPB as ligand for the catalyst, gave 79% of *N*-hexyl-4-methoxyaniline (Table 2, entry 10).

To investigate a possible existence of non-thermal MW effects,[10h] we executed all the coupling reactions optimized for MW irradiation also in an oil bath at the same temperature as the set temperature of the MW experiments. To allow a reliable comparison the same vessels as used in the MW runs were used. To mimic the flash heating rate of the MW experiments the loaded vessels were immersed in a preheated oil bath. Rapid cooling of the vessels was done in the MW cavity using a propelled air flow. All the oil bath experiments performed, clearly revealed a similar yield as obtained under MW irradiation in the same reaction time (Tables 1 and 2). These results indicate that, for this type of reaction, no specific MW effects have to be taken into account to explain the rapid aminations.[23] The studied MW-assisted reactions are only governed by thermal effects (Arrhenius). Nevertheless, from a practical point of view, the microwave-assisted procedure is still more convenient than classical heating.

In conclusion, we have described general Pd-catalyzed amination conditions for the high-speed coupling of electron rich and neutral aryl chlorides with all types of aliphatic amines under temperature-controlled MW heating at 150 °C with DCPB (secondary cyclic aliphatic amines) or DTBP (acyclic secondary and primary aliphatic amines) as ligand using a low loading of catalyst in only 10 min. Interestingly, the method developed for aryl chlorides can also be applied for the amination of aryl bromides.

1. Experimental

1.1. General

^{1}H NMR spectra were recorded on a Varian Unity 400 spectrometer in the solvent indicated with TMS as the internal standard. All chemical shifts are given in ppm and coupling constants are given in Hz. For column chromatography Kieselgel 60 (ROCC, 0.040–0.063 mm) was used. $Pd(OAc)_2$ (Acros), $Pd_2(dba)_3$ (Acros), DCPB (Strem Chemicals or Acros), DTPB (Strem Chemicals or Acros), DCPAB (Strem Chemicals or Acros), toluene (Acros, extra dry <30 ppm water) as well as all the amines and aryl halides were obtained from commercial sources and used as such.

1.2. General procedure for the rapid palladium-catalyzed amination of aryl halides

A pressure vial of 10 mL was charged with aryl halide (1 mmol), amine (1.2, 1.5 or 3 mmol) and NaO*t*-Bu (0.1345 g, 1.4 mmol) in air. Subsequently the vial was flushed with Ar for 1 min. Then, 1 mL of a stock solution[†] of catalyst was added via a syringe and the resulting mixture

[†] Preparation of the stock solutions of catalyst: the stock solutions of catalyst (Pd/2 L or Pd/1.5 L) were prepared using $Pd(OAc)_2$ or $Pd_2(dba)_3$ as Pd(0) source and DCPB [=2-(dicyclohexylphosphanyl)biphenyl], DTPB [=2-(di-*t*-butylphosphanyl)biphenyl] or DCPAB [=2-dicyclohexylphosphanyl-2′-(*N*,*N*-dimethylamino)biphenyl] as ligand. The stock solutions were stored under an Ar atmosphere. When DTPB was used, the catalyst solution was stirred for 16 h prior to its use.[19]

$Pd(OAc)_2$/DCPB or DTPB. 1 mol% catalyst solution: $Pd(OAc)_2$ (0.0225 g, 0.1 mmol), ligand (0.2 mmol) and toluene (10 mL) were used. 2 mol% catalyst solution: $Pd(OAc)_2$ (0.0449 g, 0.2 mmol), ligand (0.4 mmol) and toluene (10 mL) were used.

$Pd_2(dba)_3$/DCPAB stock solution. 1 mol% catalyst solution: $Pd_2(dba)_3$ (0.0458 g, 0.05 mmol), DCPAB (0.0590 g, 0.15 mmol) and toluene (10 mL) were used.

stirred and flushed with Ar for an additional 2 min. Next, the vial was sealed with an Al crimp cap with septum and heated at the desired temperature (Tables 1 and 2) in a CEM Discover microwave apparatus. The set power for all experiments was 300 W. The total heating time for all reactions was 10 min. After the reaction vial was cooled down to room temperature using a propelled air flow, it was opened and filtered over Celite and rinsed well with 100 mL dichloromethane. The filtrate was subsequently evaporated under reduced pressure and the residue purified by flash column chromatography on silica gel.

The following compounds were prepared in this manner.

1.2.1. 4-Phenylmorpholine (Table 1, entry 1). Eluent for flash column chromatography: CH_2Cl_2. The characterization data obtained for 4-phenylmorpholine are identical to those previously reported in the literature.[20] For comparison, we report here our ^{1}H NMR data: δ_H ($CDCl_3$): 7.28 (dd, J=8.8, 7.3 Hz, 2H), 6.92 (d, J=8.1 Hz, 2H), 6.88 (t, J=7.3 Hz, 1H), 3.86 (br t, J=4.7 Hz, 4H), 3.16 (br t, J=4.7 Hz, 4H).

1.2.2. 4-(4-Methylphenyl)morpholine (Table 1, entry 2). Eluent for flash column chromatography: CH_2Cl_2/heptane (90/10). The characterization data obtained for 4-(4-methylphenyl)morpholine are identical to those previously reported in the literature.[17] For comparison, we report here our ^{1}H NMR data: δ_H ($CDCl_3$): 7.08 (d, J=8.3 Hz, 2H), 6.83 (d, J=8.3 Hz, 2H), 3.85 (br t, J=4.8 Hz, 4H), 3.11 (br t, J=4.8 Hz, 4H), 2.27 (s, 3H).

1.2.3. 4-(4-Methoxyphenyl)morpholine (Table 1, entry 3; Table 2, entry 4). Eluent for flash column chromatography: CH_2Cl_2/heptane (90/10). The characterization data obtained for 4-(4-methoxyphenyl)morpholine are identical to those previously reported in the literature.[17] For comparison, we report here our ^{1}H NMR data: δ_H ($CDCl_3$): 6.91–6.83 (m, 4H), 3.86 (br t, J=4.8 Hz, 4H), 3.77 (s, 3H), 3.05 (br t, J=4.8 Hz, 4H).

1.2.4. *N*,*N*-Dibutyl-4-methoxyaniline (Table 1, entry 7; Table 2, entry 5). Eluent for flash column chromatography: CH_2Cl_2/heptane (90/10). The characterization data obtained for *N*,*N*-dibutyl-4-methoxyaniline are identical to those previously reported in the literature.[14] For comparison, we report here our ^{1}H NMR data: δ_H ($CDCl_3$): 6.80 (d, J=9.0 Hz, 2H), 6.65 (d, J=9.0 Hz, 2H), 3.75 (s, 3H), 3.17 (br t, J=7.5 Hz, 4H), 1.51 (p, J=7.5 Hz, 4H), 1.33 (sx, J=7.4 Hz, 4H), 0.93 (t, J=7.3 Hz, 6H).

1.2.5. *N*,*N*-Dibutyl-4-methylaniline (Table 1, entry 10). Eluent for flash column chromatography: CH_2Cl_2/heptane (1/1). The characterization data obtained for *N*,*N*-dibutyl-4-methylaniline are identical to those previously reported in the literature.[17] For comparison, we report here our ^{1}H NMR data: δ_H ($CDCl_3$): 6.99 (d, J=8.7 Hz, 2H), 6.57 (d, J=8.7 Hz, 2H), 3.22 (br t, J=7.5 Hz, 4H), 2.23 (s, 3H), 1.54 (p, J=7.3 Hz, 4H), 1.33 (sx, J=7.5 Hz, 4H), 0.94 (t, J=7.3 Hz, 6H).

1.2.6. *N*-Benzyl-4-methoxyaniline (Table 1, entry 11; Table 2, entry 9). Eluent for flash column chromatography: CH_2Cl_2/heptane (7/3). The characterization data obtained for *N*-benzyl-4-methoxyaniline are identical to those previously reported in the literature.[14] For comparison, we report here our ^{1}H NMR data: δ_H ($CDCl_3$): 7.38–7.31 (m, 4H), 7.27 (t, J=7.0 Hz, 1H), 6.77 (d, J=9.0 Hz, 2H), 6.61 (d, J=9.0 Hz, 2H), 4.28 (s, 2H), 3.8 (br s, 1H), 3.74 (s, 3H).

1.2.7. *N*-Hexyl-4-methoxyaniline (Table 1, entry 14; Table 2, entry 10). Eluent for flash column chromatography: CH_2Cl_2/heptane (8/2). The characterization data obtained for *N*-hexyl-4-methoxyaniline are identical to those previously reported in the literature.[14] For comparison, we report here our ^{1}H NMR data: δ_H ($CDCl_3$): 6.77 (d, J=9.0 Hz, 2H), 6.56 (d, J=9.0 Hz, 2H), 3.74 (s, 3H), 3.3 (br s, 1H), 3.06 (t, J=7.1 Hz, 2H), 1.59 (p, J=7.4 Hz, 2H), 1.43–1.1.29 (m, 6H), 0,90 (t, J=7.0 Hz, 3H).

1.2.8. 3-Methoxy-*N*-methyl-*N*-phenylaniline (Table 2, entry 1). Eluent for flash column chromatography: CH_2Cl_2/heptane (6/4). The characterization data obtained for 3-methoxy-*N*-methyl-*N*-phenylaniline are identical to those previously reported in the literature.[21] For comparison, we report here our ^{1}H NMR data: δ_H ($CDCl_3$): 7.28 (dd, J=8.4, 7.3 Hz, 2H), 7.15 (t, J=8.1 Hz, 1H), 7.06 (dd, J=8.7, 1.1 Hz, 2H), 6.99 (tt, J=7.3, 1.1 Hz, 1H), 6.58 (ddd, J=8.1, 2.3, 0.8 Hz, 1H), 6.53 (t, J=2.3 Hz, 1H), 6.49 (ddd, J=8.1, 2.3, 0.8 Hz, 1H), 3.75 (s, 3H), 3.30 (s, 3H)

1.2.9. 4-Methoxy-*N*-methyl-*N*-phenylaniline (Table 2, entry 2). Eluent for flash column chromatography: CH_2Cl_2/heptane (1/1). The characterization data obtained for 4-methoxyphenyl-*N*-methyl-*N*-phenylaniline are identical to those previously reported in the literature.[18] For comparison we report here our ^{1}H NMR data: δ_H ($CDCl_3$): 7.19 (dd, J=9.0, 7.2 Hz, 2H), 7.08 (d, J=9.0 Hz, 2H), 6.88 (d, J=9.0 Hz, 2H), 6.79 (d, J=7.2 Hz, 2H), 6.78 (t, J=6.8 Hz, 1H), 3.80 (s, 3H), 3.25 (s, 3H).

1.2.10. 4-(3-Methoxyphenyl)morpholine (Table 2, entry 3). Eluent for flash column chromatography: CH_2Cl_2. The characterization data obtained for 4-(3-methoxyphenyl)-morpholine are identical to those previously reported in the literature.[14] For comparison, we report here our ^{1}H NMR data: δ_H ($CDCl_3$): 7.19 (t, J=8.2 Hz, 1H), 6.53 (br d, J=8 Hz, 1H), 6.46 (br s, 1H), 6.45 (br d, J=8 Hz, 1H), 3.85 (t, J=4.8 Hz, 4H), 3.80 (s, 3H), 3.15 (t, J=4.8 Hz, 4H).

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23. It was not attempted to check whether the studied microwave-assisted aminations were not already finished before 10 minutes. Theoretically, the possibility of a specific microwave effect can therefore not be ruled out. Nevertheless, if there is such a microwave effect, it is surely very small.