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Study of the microwave-assisted hydrolysis of nitriles and esters and the implementation of this system in rapid microwave-assisted Pd-catalyzed amination

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ABSTRACT

Microwave-assisted hydrolysis of benzonitriles and methyl benzoates has been studied using a toluene/concd aq KOH two phase system in the presence and absence of phase transfer catalyst. Conditions to allow and avoid smooth hydrolysis could be identified. Based on the latter, the first microwave protocol which allows the rapid Pd-catalyzed amination of aliphatic amines with chlorobenzenes containing sensitive functional groups has been developed.

1. Introduction

Drugs are often synthesized via an amide or carboxylic acid function or possess such a functional group in their final structure. Hydrolysis of a nitrile or an ester function is a commonly used reaction in organic synthesis to obtain carboxylic acids. The reactions can be performed in an acidic or alkaline medium, with the use of enzymes or, in the case of esters, with the aid of metal ions.[1] Nitriles can be hydrolyzed to amides by a whole range of reagents, for example: concentrated H_2SO_4, formic acid and HCl or HBr, acetic acid and BF_3, H_2O_2 and OH^-, sodium percarbonate, dry HCl followed by H_2O.[1] The use of water and certain metal ions or complexes also gives the amide.[1] The described conditions for hydrolysis are in most cases rather harsh. Moreover, long reaction times are often required. To speed up two phase hydrolysis reactions, in which the used ester substrates do not dissolve in the alkaline water phase and therefore are the organic phase, the use of a phase transfer catalyst (PTC) is often applied.[1,2] Another frequently used 'tool' for esters as well as for nitriles in a one phase system is heating the reaction mixture under microwave irradiation, since it is generally known that one of the major advantages of microwave flash heating is the reduction in reaction time. In one reported case, selectivity could even be obtained under microwave irradiation by choosing the appropriate reaction time.[3]

Because of the chemical relevance of hydrolysis reactions, we decided to develop a general microwave-assisted protocol that is simple, easy to use and mild. Short reaction times are desired and one should be able to selectively hydrolyze nitriles to amides or avoid hydrolysis of esters and nitriles by simple tuning of the reaction conditions (e.g., presence or absence of PTC, higher or lower reaction temperature). Avoided hydrolysis is interesting for two phase Pd-catalyzed amination reactions with substrates that contain hydrolysis sensitive nitrile, amide or ester groups. Two phase Pd-catalyzed aminations under classical heating have already been reported by Hartwig and co-workers.[4] We considered a toluene/concentrated aqueous KOH two phase system to be useful for our purpose. KOH is of course a strong nucleophilic base, which principally does not allow to avoid hydrolysis, but we reasoned that when it is used in a very high concentration,[5] the solubility of aq KOH in toluene at a moderate temperature will be avoided or at least seriously diminished. In other words, reaction conditions which potentially avoid hydrolysis but allow Pd-catalyzed aminations should be feasible. To get hydrolysis the concentration of KOH in toluene should be increased. The addition of PTC or simple

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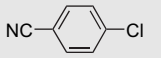
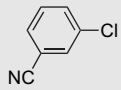
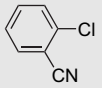
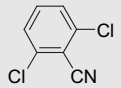
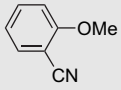
increase of the reaction temperature should fulfill this requirement. Due to their good availability and low cost, and to the fact that they are suitable substrates for Pd-catalyzed amination reactions, chlorobenzonitriles and methyl chlorobenzoate esters are the substrates of choice.

2. Results and discussion

2.1. Microwave-assisted hydrolysis based on a toluene/concentrated aqueous KOH two phase system

The first substrate we examined was 4-chlorobenzonitrile. The reaction conditions used were 1 mmol substrate, 250 μL 21.6 M KOH, 0.5 mL toluene, μW (40 W).[6] In the rest of the article, we will refer to these as standard conditions. The results are summarized in Table 1. In a reaction time of 10 min and at a reaction temperature of 100 °C, no hydrolysis product was found (Table 1, entry 2). When the same experiment was carried out at 150 °C, it had to be stopped after 1 min and 47 s due to a serious increase in pressure (see Section 4.5). 4-Chlorobenzoic acid (72%) and 4-chlorobenzamide (21%) were obtained (Table 1, entry 1). The amount of 4-chlorobenzoic acid can be further increased (80%) (and the amount of 4-chlorobenzamide further reduced (6%)) by using an 80 mL microwave vial in the Discover unit (Table 1, entry 4). In this way, the head to space volume is larger than in a 10 mL vessel allowing a longer reaction time before the reaction needs to be stopped for safety reasons due to the pressure increase by ammonia formation. Clearly, the solubility of concentrated aq KOH in toluene is not high enough to allow hydrolysis of the nitrile at 100 °C but at higher temperature (150 °C) the solubility of aq KOH is sufficient allowing the nitrile to hydrolyze. Since it seems to be possible to selectively avoid or obtain the hydrolysis of a nitrile to a carboxylic acid by altering the temperature, we wondered if it would also be feasible to stop the hydrolysis reaction in the amide stage. To obtain the benzamide and to avoid further hydrolysis, the use of a PTC at lower temperature (100 °C) was examined. Therefore, a hydrolysis experiment was performed by adding 10 mol % of *N*-cetyl-*N*,*N*,*N*-trimethylammonium bromide. Interestingly, an isolated yield of 93% of 4-chlorobenzamide could be obtained together with less than 5% of 4-chlorobenzoic acid (Table 1, entry 3). The PTC brings hydroxide anions to the toluene phase allowing hydrolysis but at 100 °C only the conversion of nitrile to amide is possible.

Table 1
Microwave-assisted hydrolysis experiments of benzonitriles in toluene/aq KOH (21.6 M KOH) at different temperatures[a]

Entry	ArCN	*T* (°C)	Time (min)	PTC added[b]	Recovery ArCN (%)	Amide (%)	Acid (%)
1		150	1.5	No	—	21	72
2		100	10	No	>90[c]	—	—
3		100	10	Yes	—	93	<5
4[d]		150	6	No	—	6	80
5		100	10	No	>90[c]	—	—
6		150	10	No	—	2	96
7		100	10	Yes	—	88	10
8		150	10	No	—	2	97
9		100	10	Yes	43	45	5
10		100	30	Yes	Traces	5	77
11		100	60	Yes	—	—	84
12		100	10	No	>90[c]	—	—
13		150	10	No	—	92[e]	—
14		100	10	No	97[c]	—	—
15		150	120	No	—	62	22
16		100	10	No	>90[c]	—	—
17		150	120	Yes	—	—	82

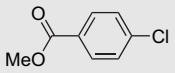
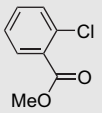
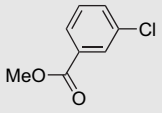
[a] Reactions were conducted under microwave irradiation (power=40 W) on a 1 mmol scale in toluene (0.5 mL) and 250 μL KOH (21.6 M). The indicated isolated yield is the average of two runs.
[b] *N*-Cetyl-*N*,*N*,*N*-trimethylammonium bromide (10 mol %).
[c] No hydrolysis product, or a trace amount that could not be isolated, was observed.
[d] An 80 mL microwave vial was used and the experiment was run on a 5 mmol scale (power=80 W).
[e] 2-Chloro-6-hydroxybenzamide (2%) was formed.

The hydrolysis of some other benzonitriles under microwave irradiation was also tested. 3-Chlorobenzonitrile as substrate showed a similar behaviour as 4-chlorobenzonitrile (Table 1, entries 5–7). 2-Chlorobenzonitrile gave at 150 °C 97% of 2-chlorobenzoic acid, while the use of *N*-cetyl-*N*,*N*,*N*-trimethylammonium bromide at 100 °C in 10 min resulted in a mixture of the corresponding amide and carboxylic acid (Table 1, entries 8 and 9). Increasing the time to 60 min gave 84% of 2-chlorobenzoic acid (Table 1, entry 11). The electron withdrawing *ortho* chlorine atom seems to make the hydrolysis of 2-chlorobenzamide to 2-chlorobenzoic acid easier explaining the formation of carboxylic acid at 100 °C. Nevertheless, for the hydrolysis of 2-chlorobenzonitrile to 2-chlorobenzamide its steric hindrance is the major factor as a slower reaction is observed in comparison with 4-chlorobenzonitrile (Table 1, entries 3 and 9). At 100 °C, without the quaternary ammonium salt, no hydrolysis of 2-chlorobenzonitrile was observed (Table 1, entry 12). Hydrolysis of 2,6-dichlorobenzonitrile under standard conditions at 150 °C for 10 min gave only 2,6-dichlorobenzamide (Table 1, entry 13). This shows that steric hindrance of the two *ortho* chlorine atoms is the determining factor in this case, not allowing the hydrolysis of 2,6-dichlorobenzamide to 2,6-dichlorobenzoic acid. Electron rich *ortho* substituted benzonitriles such as 2-methoxybenzonitrile are also difficult substrates since hydrolysis for 2 h at 150 °C gave a mixture of 62% of 2-methoxybenzamide and 22% of 2-methoxybenzoic acid (Table 1, entry 15). Full conversion to 2-methoxybenzoic acid could be achieved using PTC at high temperature (Table 1, entry 17). This experiment combines the two beneficial effects: better solubility of the base at higher temperature and the transfer of hydroxide anions to the toluene phase. However, 2,6-dichlorobenzonitrile could not be converted to 2,6-dichlorobenzoic acid in a similar experiment because 2,6-dichlorobenzamide was converted to 2-chloro-6-hydroxybenzamide and 2,6-dihydroxybenzamide instead of the aimed 2,6-dichlorobenzoic acid.

Further, the hydrolysis of methyl 4-chloro-, methyl 2-chloro- and methyl 3-chlorobenzoate was examined. Hydrolysis experiments were performed under the developed standard conditions at (a) 100 °C, (b) 150 °C and (c) 100 °C with the addition of 10 mol % PTC. Reaction times and yields are summarized in Table 2. As observed for the chlorobenzonitriles, no hydrolysis occurred at 100 °C in 10 min (Table 2, entries 2, 8 and 11). At 150 °C, as expected, hydrolysis of methyl 4-chloro-, methyl 2-chloro- and methyl 3-chlorobenzoate to their corresponding acids occurred in a reaction time of 10 min (Table 2, entries 1, 7 and 10). When PTC was added, the three esters smoothly hydrolyzed at 100 °C in a reaction time of 10 min (Table 2, entries 3, 9 and 12).

For methyl 4-chlorobenzoate, we also investigated the influence of the type of organic solvent and the concentration of the KOH solution on hydrolysis. When toluene was substituted for dioxane

Table 2
Microwave-assisted hydrolysis experiments of methyl 4-chloro-, methyl 2-chloro- and methyl 3-chlorobenzoate in toluene or dioxane/aq KOH at different temperatures[a]

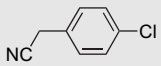
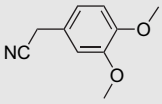
Entry	$ArCO_2Me$	T (°C)	Time (min)	PTC added[b]	[KOH] (M)	Solvent	Recovery $ArCO_2Me$ (%)	Acid (%)
1		150	10	No	21.6	Toluene	—	94
2		100	10	No	21.6	Toluene	>90[c]	—
3		100	10	Yes	21.6	Toluene	—	94
4[d]		100	10	No	21.6	Dioxane	>90	2
5[e]		100	10	No	8	Dioxane	—	74[f]
6[g]		100	10	No	8	Toluene	83	10
7		150	10	No	21.6	Toluene	—	97
8		100	10	No	21.6	Toluene	>90[c]	—
9		100	10	Yes	21.6	Toluene	—	89[f]
10		150	10	No	21.6	Toluene	—	96
11		100	10	No	21.6	Toluene	>93[c]	—
12		100	10	Yes	21.6	Toluene	—	91[f]

[a] Reactions were conducted under microwave irradiation (power=40 W) on a 1 mmol scale in toluene (0.5 mL) and 250 μL KOH (21.6 M). The indicated isolated yield is the average of two runs.
[b] *N*-Cetyl-*N*,*N*,*N*-trimethylammonium bromide (10 mol %) was added.
[c] No hydrolysis product, or a trace amount that could not be isolated, was observed.
[d] Dioxane (0.5 mL) was used.
[e] Dioxane (0.5 mL) and 250 μL 8 M KOH were used.
[f] No $ArCO_2Me$, or a trace amount that could not be isolated, was observed.
[g] 8 M KOH (250 μL) was used.

and with otherwise standard hydrolysis conditions, only traces of the corresponding benzenecarboxylic acid derivatives were formed and more than 90% of the ester could be recovered while a similar experiment with more diluted aqueous KOH (250 μL 8 M KOH, 100 °C, 10 min) yielded 4-chlorobenzoic acid as the sole reaction product with no substrate recovery (Table 2, compare entries 4 and 5). When a hydrolysis experiment was executed in toluene with diluted aqueous KOH (8 M KOH), partial formation of 4-chlorobenzoic acid (10%) was observed (Table 2, entry 6). These results indicate that besides the selection of solvent, also the concentration of base is really essential to allow (or avoid) hydrolysis. Clearly, when the organic solvent is more polar, the solubility of aqueous KOH can only be minimized when concentrated aqueous KOH (21.6 M) is used.

(4-Chlorophenyl)acetonitrile and (3,4-dimethoxyphenyl)acetonitrile were two other substrates which were subsequently subjected to hydrolysis experiments. The challenge for these substrates is that the cyano group is not directly attached to the arene ring, so hydrolysis will be more difficult due to competitive α-deprotonation. Moreover, the hydrolysis products are relevant from a pharmaceutical point of view.[7] (3,4-Dimethoxyphenyl)acetonitrile, for example, can be used for the synthesis of papaverine, an alkaloid from opium, which is used as a vasodilator and antispasmodic.[8] In the papaverine synthesis, (3,4-dimethoxyphenyl)acetonitrile is hydrolyzed to (3,4-dimethoxyphenyl)acetic acid with the aid of H_2SO_4. When the benzylcyanides were subjected to our standard hydrolysis experiment at 100 °C for 10 min, a full recovery of starting material could be achieved (Table 3, entries 3 and 6). Because the nitrile function is not directly attached to the aromatic ring, a reaction temperature of 160 °C was required to obtain the

Table 3
Microwave-assisted hydrolysis experiments of (4-chlorophenyl)acetonitrile and (3,4-dimethoxyphenyl)acetonitrile in toluene/aq KOH (21.6 M) at different temperatures[a]

Entry	Nitrile	T (°C)	Time (min)	Recovery substrate (%)	Amide (%)	Acid (%)
1[b]		160	10	—	32	65
2[b]		160	30	—	—	92
3		100	10	97	—	—
4[b]		160	60	21	24	46
5[b]		160	480	2	6	80
6		100	10	99	—	—

[a] Reactions were conducted under microwave irradiation (power=40 W) on a 1 mmol scale in toluene (0.5 mL) and 250 μL KOH (21.6 M). The indicated isolated yield is the average of two runs.
[b] A set power of 50 W was used.

carboxylic acid derivative of (4-chlorophenyl)acetonitrile. To reach a temperature of 160 °C in a reasonable ramp time, the power was set at 50 W. After 10 min, 32% of 2-(4-chlorophenyl)acetamide and 65% of (4-chlorophenyl)acetic acid were isolated (Table 3, entry 1). A reaction time of 30 min yielded 92% of (4-chlorophenyl)acetic acid (Table 3, entry 2). For the hydrolysis of (3,4-dimethoxyphenyl)acetonitrile at 160 °C and in a reaction time of 60 min, 46% of (3,4-dimethoxyphenyl)acetic acid could be isolated together with 21% of starting material and 24% of the corresponding amide (Table 3, entry 4). A reaction time of 8 h yielded 80% of (3,4-dimethoxyphenyl)acetic acid, 6% of the corresponding amide and still 2% of the starting material (Table 3, entry 5). Interestingly, experiments with the use of PTC at 100 °C did not give the desired amides. Instead, the ApCI-MS spectrum revealed the formation of 3-oxo-2,4-diphenylbutanenitriles (2,4-bis(4-chlorophenyl)-3-oxobutanenitrile and 2,4-bis(3,4-dimethoxyphenyl)-3-oxobutanenitrile). These products are formed via deprotonation of a benzylic proton of the phenylacetonitrile followed by addition to the nitrile function of another substrate molecule and subsequent hydrolysis of the imine.

2.2. Rapid microwave-assisted Pd-catalyzed amination of aryl chlorides containing sensitive functional groups with aliphatic amines based on a toluene/concentrated aqueous KOH two phase system

The palladium-catalyzed amination of aryl halides and sulfonates, pioneered by the research groups of Buchwald and Hartwig, is the most important tool hitherto available to create $C(sp^2)$–N bonds.[9] Recent research has mainly been devoted to the development of new ligands that create more active catalysts for the less reactive aryl chlorides. The interest in aryl chlorides is based on the better availability and lower cost in comparison to the corresponding bromides and iodides. Unfortunately, especially the use of weak inorganic non-nucleophilic bases (K_3PO_4, K_2CO_3, Cs_2CO_3), required for substrates that contain groups sensitive to nucleophilic attack, still requires long reaction times (hours to 1 day) for complete conversion of substrate.[10] To allow fast Buchwald–Hartwig reactions on aryl chlorides, which can be used in library design in pharmaceutical and agrochemical research projects, our laboratory studied the implementation of microwave irradiation. After all, one of the major reported advantages of microwave flash heating is the well known reduction in reaction time.[11] In 2003, we described the first microwave-assisted Pd-catalyzed aminations on aryl chlorides.[12] In 10 min at 150 °C or 200 °C under microwave irradiation,

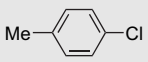
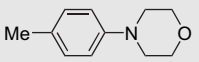
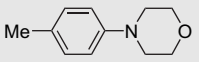
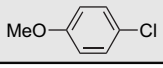
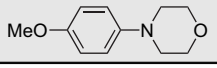
complete conversion of substrates and good yields of arylamines could be obtained with primary and secondary aliphatic amines as well as anilines. The biphenyl based phosphine ligands, 2-(dicyclohexylphosphino)biphenyl (DCPB) and 2-(di-*tert*-butylphosphino)biphenyl (JohnPhos), introduced by Buchwald, proved to be ideal for this purpose and showed a good temperature stability.[13] Remarkably, the protocols developed for aryl chlorides could also be used on aryl bromide substrates without any adaptation. *N*-Heterocyclic carbene based catalysts also proved to be useful for rapid microwave-assisted Buchwald–Hartwig reactions.[14] In all these reports, strong MO*t*-Bu was used as a base. Unfortunately, this base does not allow a large functional group compatibility since the presence of esters, enolizable ketones, nitriles and nitro groups is often incompatible. Although there are some successful examples on the use of weak inorganic bases on aryl bromides in intermolecular microwave-assisted Pd-catalyzed aminations, the applicability seems to be rather limited in amine type since only examples on the use of anilines are described.[15] Interestingly, this limitation to anilines is also true for published examples on pseudohalides such as triflates (for which Cs_2CO_3 was used as inorganic base).[16a] Recently, also nonaflates have been used under microwave irradiation for intermolecular couplings.[16b] In this case, a soluble, non-nucleophilic organic tertiary amine based on an amidine (DBU) or guanidine (MTBD) was selected as base. Although anilines, heteroarylamines, imines and benzamides seem to be viable coupling partners under the developed conditions, no examples on reactions with aliphatic amines were shown. Interestingly, there are only three reports on the use of aryl chlorides in combination with a weak inorganic base in microwave-assisted intermolecular Buchwald–Hartwig reactions.[16c,d,17] In these studies only heteroaryl chlorides or electron-deficient and some electron-neutral aryl chlorides were successfully used. Moreover, the amine coupling partners were very specific as only sulfonamides and sulfoximines were used. Remarkably, all the microwave-assisted protocols which are based on a weak base hitherto published only coupled amines which are relatively acidic (anilines, heteroarylamines, amides, sulfonamides, imines, sulfoximines). The limited scope in terms of the use of the amine type for microwave-assisted Pd-catalyzed aminations on substrates which contain a functional group sensitive to nucleophiles, made us wonder whether our results of Section 2.1 could be implemented for the development of a rapid coupling protocol of aliphatic amines with aryl chlorides while avoiding hydrolysis.

As a test substrate, in order to test the feasibility of our two phase system and to simplify the problem, we selected an electron-neutral chlorobenzene that does not contain a functional group which is sensitive towards nucleophilic attack: 4-chlorotoluene. Morpholine was chosen as the amine since secondary cyclic amines are known to be the easiest coupling partners of the aliphatic amines. Interestingly, under our developed standard conditions at 150 °C and with a loading of 1 mol % $Pd(OAc)_2$/2DCPB, a complete conversion of substrate could be obtained under microwave irradiation in 10 min reaction time. 4-(4-Methylphenyl)morpholine was isolated in 70% yield (Table 4, entry 1). In order to achieve rapid microwave-assisted aminations, it is crucial to take into account the ratio of toluene and concentrated KOH solution. When 1 mL of toluene was used instead of 0.5 mL under otherwise identical conditions, only 9% of 4-(4-methylphenyl)morpholine could be isolated (Table 4, entry 2). This striking difference most probably results from a combination of two effects: (a) reduced concentration of substrate in toluene and (b) diminished contact of the two phases.[18] Our two phase system based on aqueous KOH as a base and microwave irradiation as heating source seems to be superior because when, with the assistance of microwave irradiation, other weak bases were tested for the reaction of 4-chlorotoluene with morpholine, no good results could be obtained. The use of Cs_2CO_3 (2 equiv) in toluene gave a low conversion in a reaction time of 10 min at 150 °C with a 1 mol % loading of $Pd(OAc)_2$/2DCPB. This is a striking difference with our previous study with alcoholate base where the same coupling gave a complete conversion (isolated yield: 83%) in the same reaction time at the same reaction temperature.[12b] Clearly, substitution of NaO*t*-Bu for Cs_2CO_3 is detrimental for the reaction. Unfortunately, the shape of the required 10 mL microwave vials does not allow the use of a larger excess of Cs_2CO_3 in order to test a possible beneficial role of interphase deprotonation as previously described by us for coupling reactions on aryl iodides under classical heating.[19] Therefore, we tried to use a dipolar aprotic solvent (DMF), which gives a higher solubility of the base, but still no good conversion was obtained in 10 min at 150 °C.[20] Doubling the reaction time and/or a further increase of the reaction temperature to 170 °C in DMF did not provide better results. In all cases the isolated yields were less than 30%.

After the successful coupling of an electron-neutral chlorobenzene also electronically rich 4-chloroanisole was tested as substrate. It could be coupled with morpholine under the same reaction conditions of entry 1, but in this case a higher loading of catalyst (5 mol %) was required to get complete conversion in 10 min. The isolated yield (68%) is similar to the one obtained using our MAOS protocol with strong NaO*t*-Bu base (76%) (Table 4, entry 3).[12b]

As our real aim was the use of aryl chlorides which contain functional groups sensitive to nucleophilic attack, we subsequently looked at the amination of 4-chlorobenzonitrile with morpholine. From our hydrolysis experiments, we knew that a reduction of reaction temperature gives a reduced solubility of concentrated aqueous KOH in toluene. In addition, we also proved that it is important to stick to the use of aqueous KOH in the highest concentration to diminish its solubility in toluene at a given temperature. In this way, a reaction temperature could be defined at which

Table 4
Microwave-assisted Buchwald–Hartwig reactions of non-nucleophile sensitive aryl chlorides in a toluene/aq KOH (21.6 M) two phase system[a]

Entry	ArCl	Amine	Catalyst	Pd (mol %)	*T* (°C)	Time (min)	Product	Yield (%)
1			A	1	150	10		70
2[b]			A	1	150	10		9
3[c]			A	5	150	10		68

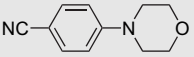
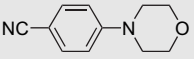
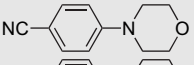
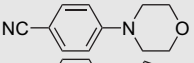
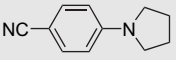
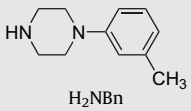
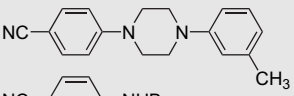
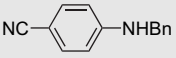
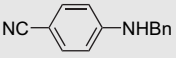
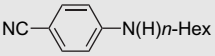
[a] Reactions were conducted under microwave irradiation (power=40 W) on a 1 mmol scale in toluene (0.5 mL). Amine (1.2 equiv) and 250 μL KOH (21.6 M) were used. A=$Pd(OAc)_2$/2DCPB. The indicated isolated yield is the average of two runs.
[b] Toluene (1.0 mL) was used.
[c] A set power of 60 W was used.

no hydrolysis of the nitrile group occurs in a hydrolysis experiment, namely 100 °C. At this temperature, in the case of a Pd-catalyzed amination reaction, a liquid–liquid interphase deprotonation might still allow Pd-catalyzed amination reactions, while hydrolysis sensitive substrates are not attacked. Based on the fact that we previously found solid–liquid interphase deprotonation of Pd(II)–amine complexes is possible, liquid–liquid interphase deprotonation is certainly feasible.[19] Alternatively, a low concentration of concentrated aqueous KOH in toluene does not allow hydrolysis but is still sufficient to allow deprotonation of Pd(II)–amine complex. When the deprotonation step is not rate limiting in the mechanism of the Pd-catalyzed amination reaction, the latter is certainly possible. Of course, a combination of both ways of deprotonation cannot be excluded. Gratifyingly, when 4-chlorobenzonitrile was coupled with morpholine under our developed standard conditions at 100 °C using $Pd(OAc)_2$/2DCPB, no hydrolysis of nitrile was observed and 76% of 4-morpholin-4-ylbenzonitrile could be isolated (Table 5, entry 1).[21] As the reaction temperature is 50 °C lower in comparison to the experiment on 4-chlorotoluene, 5 mol % of catalyst and a reaction time of 30 min was required (see Section 4.5).

We wondered if better results could be obtained using the $Pd[P(t\text{-}Bu)_3]_2$ catalyst described by Hartwig for amination reactions of aryl chlorides in toluene with KOH (solid) in the presence of water using our microwave conditions.[4] For the coupling of morpholine with 4-chlorobenzonitrile a similar yield (74%) was obtained in a reaction time of 30 min at 100 °C, using 5 mol % of $Pd[P(t\text{-}Bu)_3]_2$ (Table 5, entry 2). Importantly, Hartwig reports that the use of PTC is essential for the transport of hydroxide anions to the toluene phase in his protocol. Surprisingly, when we added *N*-cetyl-*N*,*N*,*N*-trimethylammonium bromide (0.5 mol %) for the coupling of 4-chlorobenzonitrile with morpholine in toluene using $Pd(OAc)_2$/2DCPB catalyst in the presence of 21.6 M KOH at 100 °C almost no C–N coupling occurred (Table 5, entry 3). Instead, substrate and 4-chlorobenzamide could be found while the experiment without PTC gave 76% of 4-morpholin-4-ylbenzonitrile.

The fact that we did not need PTC for successful aminations prompted us to see whether it is essential in the oil bath protocol published by Hartwig (1 mol % $Pd[P(t\text{-}Bu_3)_2$, KOH (1.5 equiv), *N*-cetyl-*N*,*N*,*N*-trimethylammonium bromide (0.5 mol %), water (27 μL), toluene (1 mL), 90 °C (oil bath)).[4] Therefore, we randomly repeated some examples under exactly the same reaction conditions as described by his team, only omitting PTC (Fig. 1). Interestingly, for the coupling of 4-chloroacetophenone with morpholine we obtained 86% yield of 1-(4-morpholin-4-ylphenyl)ethanone while Hartwig reports 84% in the presence of *N*-cetyl-*N*,*N*,*N*-trimethylammonium bromide (Fig. 1). Also for the amination of 4-chloroanisole with *N*-methylaniline (82% vs 92%) as well as for the coupling of 4-bromoanisole with morpholine (84% vs 95%) similar yields were obtained, indicating the addition of PTC is not essential in these cases (Fig. 1).[22] Of course, for some examples reported by Hartwig the addition of PTC can have a beneficial effect. After all, for the coupling of 4-chlorotoluene with dibutylamine, which was selected as the test system for the development of the protocol, Hartwig and co-workers clearly showed that the removal of PTC gives a lower conversion in 24 h (23% vs 94%). Unfortunately, we could not reproduce these previously published experiments. Especially in cases with rate determining deprotonations and with less acidic Pd(II)–amine complexes, the addition of PTC might be beneficial in our opinion (as long as it does not destroy the catalyst). However, one needs to be cautious since the higher mentioned experiment with dibutylamine without phase transfer agent was performed at only 70 °C which anyway gives a reduced solubility of aqueous KOH in toluene. In our opinion, one should be very careful not to add PTC in cases where it has no substantial beneficial effect on the Pd-catalyzed amination rate to avoid competitive hydrolysis of sensitive functional groups. This is clearly supported by the previously mentioned hydrolysis experiment of 4-chlorobenzonitrile at 100 °C (μW) in the presence of 10% PTC (Table 1, entry 4), indicating that the PTC brings hydroxide anions in the toluene phase allowing hydrolysis of the nitrile function at 100 °C.

Table 5
Microwave-assisted Buchwald–Hartwig reactions of 4-chlorobenzonitrile in toluene/aq KOH (21.6 M)[a]

Entry	Amine	Catalyst	Pd (mol %)	*T* (°C)	Time (min)	Product	Yield (%)
1		A	5	100	30		76
2		B	5	100	30		74
3[b]		A	5	100	30		Traces
4[c]		A	5	100	30		70
5		A	5	100	30		79
6		A	5	100	30		70
7	H_2NBn	A	5	100	30		65
8		C	5	100	30		79
9	*n*-$HexNH_2$	C	5	100	30		74

[a] Reactions were conducted under microwave irradiation (power=40 W) on a 1 mmol scale in toluene (0.5 mL). Amine (1.2 equiv) and 250 μL KOH (21.6 M) were used. A=$Pd(OAc)_2$/2DCPB, B=$Pd[P(t\text{-}Bu)_3]_2$, C=$Pd(OAc)_2$/2JohnPhos. The indicated isolated yield is the average of two runs.
[b] *N*-Cetyl-*N*,*N*,*N*-trimethylammonium bromide (0.005 equiv) was added.
[c] Scale-up experiment: an 80 mL microwave vial was used and the experiment was run on a 4 mmol scale (power=80 W).

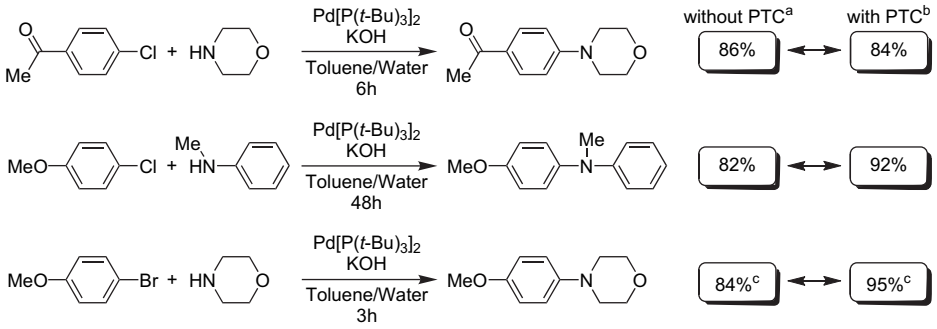


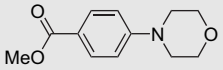
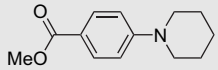
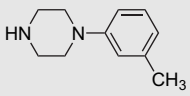
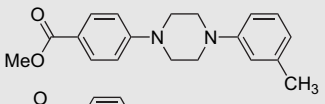
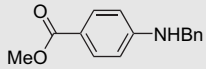
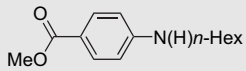
Figure 1. Effect of PTC on Buchwald–Hartwig reactions in toluene/concd aq KOH in an oil bath. [a]Reactions were conducted on a 1 mmol scale in toluene (1 mL) at 90 °C (oil bath). ArX/amine/KOH/H_2O/Pd[P(*t*-Bu)$_3$]$_2$=100/105/150/150/1.0. Isolated yield. [b]*N*-Cetyl-*N*,*N*,*N*-trimethylammonium bromide (0.005 equiv) was added. [c] ArX (1.03 mmol) and 1.03 equiv amine were used.

After the successful implementation of the standard conditions mentioned in Section 2.1 in the Pd-catalyzed amination of 4-chlorobenzonitrile with morpholine, the scalability of the protocol and the coupling of 4-chlorobenzonitrile with other aliphatic amines were screened. When the experiment described in entry 1 of Table 5 was performed on a 4 mmol scale, 70% of 4-morpholin-4-ylbenzonitrile could be isolated, indicating that our microwave-assisted amination protocol is suitable for scale-up reactions. N-Arylation of pyrrolidine gave 79% of 4-pyrrolidin-1-ylbenzonitrile (Table 5, entry 5). 1-(3-Methylphenyl)piperazine, an amine often used in medicinal chemistry, yielded 70% of 4-[4-(3-methylphenyl)piperazin-1-yl]benzonitrile (Table 5, entry 6).[23] Benzylamine yielded 65% of coupled product under these reaction conditions (Table 5, entry 7). As we previously reported for our rapid microwave protocol based on NaO*t*-Bu that primary aliphatic amines gave better results using JohnPhos as ligand, we performed a microwave experiment by substituting DCPB for JohnPhos.[12b] Interestingly, also here a higher yield (79%) could be obtained (Table 5, entry 8). This ligand also allowed the smooth amination of 4-chlorobenzonitrile with hexylamine (74%) (Table 5, entry 9).

Next, we turned our attention to methyl 4-chlorobenzoate, another substrate sensitive towards nucleophilic attack. As no hydrolysis occurred at 100 °C in 10 min (Table 2, entry 2), this temperature was selected for the Pd-catalyzed aminations. As for the aminations on 4-chlorobenzonitrile 30 min proved to be a good reaction time and since an ester function is a very sensitive group, we first tested the influence of time on the hydrolysis at 100 °C. Fortunately, in 30 min no significant formation of 4-chlorobenzoic acid was observed as more than 90% of starting material could be recovered. Pd-catalyzed amination of methyl 4-chlorobenzoate with morpholine using our microwave protocol optimized for 4-chlorobenzonitrile (5 mol% Pd(OAc)$_2$/2DCPB, 0.5 mL toluene, 250 μL 21.6 M KOH, 100 °C, 30 min) gave 58% of methyl 4-morpholin-4-ylbenzoate (Table 6, entry 1). Piperidine, however, gave a lower yield than morpholine (46% of methyl 4-piperidin-1-ylbenzoate) (Table 6, entry 2). Also 1-(3-methylphenyl)piperazine could be coupled in good yield (68%) (Table 6, entry 3). When benzylamine and hexylamine were used as coupling partners, respectively, 74% of methyl 4-(benzylamino)benzoate and 45% of methyl 4-(hexylamino)benzoate were obtained (Table 6, entries 4 and 5). In these last two cases, JohnPhos was chosen as ligand as we found it to give superior results in the corresponding coupling of primary aliphatic amines with 4-chlorobenzonitrile.

The lower yield in the coupling reaction with piperidine is due to hydrolysis of the substrate since approximately 20% of 4-chlorobenzoic acid could also be isolated. Although the substrate itself, in a mixture of toluene and 21.6 M KOH, does not give any hydrolysis at 100 °C (Table 2, entry 2), the used amine clearly determines the amount of hydrolysis product in the Pd-catalyzed amination reaction. This is logical if one takes into account that the amine modifies the polarity of the toluene phase. Consequently, the amine can change the solubility of aqueous KOH in toluene. If there

Table 6
Microwave-assisted Buchwald–Hartwig reactions of methyl 4-chlorobenzoate in toluene/aq KOH (21.6 M)[a]

Entry	Amine	Catalyst	Pd (mol%)	*T* (°C)	Time (min)	Product	Yield (%)
1		A	5	100	30		58
2		A	5	100	30		46[b]
3		A	5	100	30		68
4	H_2NBn	B	5	100	30		74
5	*n*-HexNH_2	B	5	100	30		45[c]

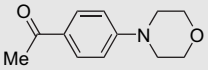
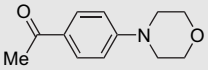
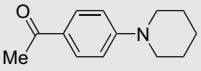
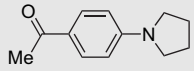
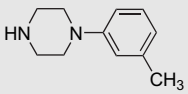
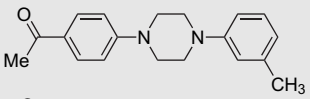
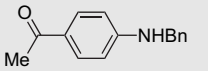
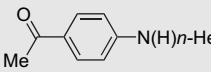
[a] Reactions were conducted under microwave irradiation (power=40 W) on a 1 mmol scale in toluene (0.5 mL). Amine (1.2 equiv) and 250 μL KOH (21.6 M) were used. A=Pd(OAc)$_2$/2DCPB, B=Pd(OAc)$_2$/2JohnPhos. The indicated isolated yield is the average of two runs.
[b] Approximately 20% of 4-chlorobenzoic acid was also formed.
[c] Approximately 40% of 4-(hexylamino)benzoic acid was also formed.

is a substantial increase in polarity, the hydrolysis of substrate becomes an important competing process. Surprisingly, repeating the coupling of methyl 4-chlorobenzoate with aniline reported by Hartwig (1 mol% Pd[P(*t*-Bu$_3$)$_2$], KOH (1.5 equiv), *N*-cetyl-*N*,*N*,*N*-trimethylammonium bromide (0.5 mol%), water (27 μL), toluene (1 mL), 90 °C (oil bath), 1 h) also revealed the formation of 4-chlorobenzoic acid (33%).[4] A control oil bath experiment with methyl 4-chlorobenzoate, omitting catalyst and aniline, gave 70% of 4-chlorobenzoic acid and 25% recovery of substrate in the same reaction time. These experiments clearly indicate that even 0.5 mol% PTC can be sufficient for a substantial competing undesired hydrolysis and the success of the desired process just depends on the Pd-catalyzed amination versus hydrolysis rate. The lower yield in the coupling reaction with hexylamine (Table 6, entry 5) is due to hydrolysis of reaction product since approximately 40% of 4-(hexylamino)benzoic acid could be isolated. An independent hydrolysis experiment on 1 mmol of methyl 4-(hexylamino)benzoate at 100 °C for 30 min revealed that almost complete hydrolysis to the corresponding carboxylic acid occurred, supporting the observation in the Pd-catalyzed amination experiment. This remarkable behaviour prompted us to investigate hydrolysis resistance of some other Buchwald–Hartwig reaction products. Methyl 4-morpholin-4-ylbenzoate at 150 °C under standard hydrolysis conditions for 60 min gave 65% recovery of substrate and the formation of 4-morpholin-4-ylbenzoic acid. For 4-morpholin-4-ylbenzoic acid as well as for 4-(hexylamino)benzoic acid, it is difficult to determine the amount formed as these are zwitterions and therefore very hard to isolate in a quantitative manner. A similar treatment of 4-morpholin-4-ylbenzonitrile resulted in 74% recovery of substrate as well as 19% of 4-morpholin-4-ylbenzamide. These experiments clearly reveal that the reaction products are normally very stable towards hydrolysis since there is a substantial solubility of aq KOH in toluene at 150 °C. The 'protection' of the methoxycarbonyl and cyano groups in the reaction products of the Pd-catalyzed amination reactions can be attributed to the introduced electron releasing amino group. Based on an article of Tomita, the exceptionally smooth hydrolysis of methyl 4-(hexylamino)benzoate might result from an alignment of the apolar hexyl chain into the toluene phase.[24] By this alignment, the polar head of the molecule, the carboxylate group, is pointed to the water phase allowing smooth hydrolysis. Alternatively, but less probable taking into account the structures of the other products in Table 6, methyl 4-(hexylamino)benzoate has a certain solubility in concentrated aqueous KOH.

As a last challenging substrate, we investigated 4-chloroacetophenone. The acetyl group on itself is of course not hydrolysis sensitive, but a competitive α-arylation of the ketone can easily occur. Moreover, it was shown that the product of α,α-diarylation can be hydrolyzed by hydroxide yielding 1,1′-(methylenedi-4,1-phenylene)diethanone and 4-chlorobenzoic acid.[4] When 4-chloroacetophenone was coupled with morpholine using our microwave protocol at 150 °C, 63% of 1-(4-morpholin-4-ylphenyl)ethanone could be obtained in 30 min reaction time (Table 7, entry 1). The ApCI-MS spectrum clearly showed the formation of undesired 1,1′-(methylenedi-4,1-phenylene)diethanone and revealed the presence of another side product that corresponds to 2-(4-acetylphenyl)-1-[morpholin-4-ylphenyl]ethanone. Therefore, the temperature was lowered to 120 °C in a subsequent trial. This proved to be beneficial since 82% of 1-(4-morpholin-4-ylphenyl)ethanone was isolated and the ApCI-MS spectrum did not show the presence of 1,1′-(methylenedi-4,1-phenylene)diethanone, but 2-(4-acetylphenyl)-1-[morpholin-4-ylphenyl]ethanone was still formed at this reaction temperature (Table 7, entry 2). In a similar way, piperidine, pyrrolidine and 1-(3-methylphenyl)piperazine could be introduced in a good yield, respectively, 63%, 73% and 76% (Table 7, entries 3–5). For the reaction of 4-chloroacetophenone with benzylamine JohnPhos was again chosen as ligand. Performing the reaction at 150 °C proved to be no problem in this case since the reaction yielded 71% of 1-[4-(benzylamino)phenyl]ethanone with no indication of 1,1′-(methylenedi-4,1-phenylene)diethanone formation and, as expected, 2-(4-acetylphenyl)-1-[4-(benzylamino)phenyl]ethanone as a side compound (Table 7, entry 6). N-Arylation of hexylamine with 4-chloroacetophenone occurred also smoothly under the same reaction conditions at 120 °C (Table 7, entry 7).

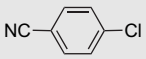
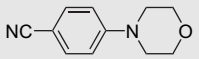
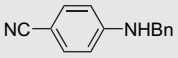
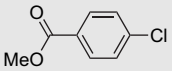
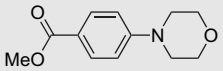
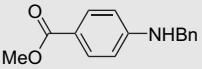
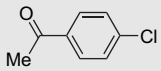
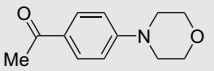
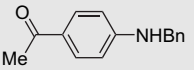
We also investigated the effect of X-Phos ((2-dicyclohexylphosphino)-2′,4′,6′-triisopropylbiphenyl), a new promising ligand

Table 7
Microwave-assisted Buchwald–Hartwig reactions of 4-chloroacetophenone in toluene/aq KOH (21.6 M)[a]

Entry	Amine	Catalyst	Pd (mol%)	*T* (°C)	Time (min)	Product	Yield (%)
1		A	5	150	30		63
2		A	5	120	30		82
3		A	5	120	30		63
4		A	5	120	30		73
5		A	5	120	30		76
6	H_2NBn	B	5	150	30		71
7	*n*-HexNH_2	B	5	120	30		63

[a] Reactions were conducted under microwave irradiation (power=40 W) on a 1 mmol scale in toluene (0.5 mL). Amine (1.2 equiv) and 250 μL KOH (21.6 M) were used. A=Pd(OAc)$_2$/2DCPB, B=Pd(OAc)$_2$/2JohnPhos. The indicated isolated yield is the average of two runs.

Table 8
Microwave-assisted Buchwald–Hartwig reactions of aryl chlorides in toluene/aq KOH (21.6 M) with X-Phos as ligand for the Pd-catalyst[a]

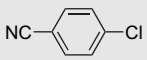
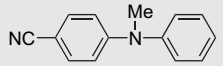
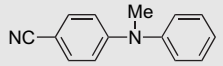
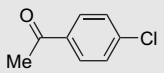
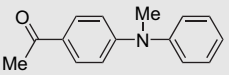
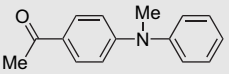
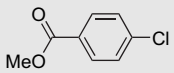
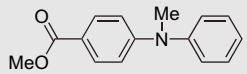
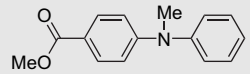
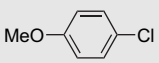
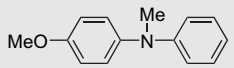
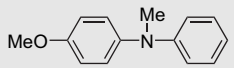
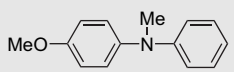
Entry	ArCl	Amine	Pd (mol %)	*T* (°C)	Time (min)	Product	Yield (%)
1			5	100	30		99
2		H_2NBn	5	100	30		50
3			5	100	30		24[b]
4		H_2NBn	5	100	30		54
5			5	120	30		93
6		H_2NBn	5	120	30		66

[a] Reactions were conducted under microwave irradiation (power=40 W) on a 1 mmol scale in toluene (0.5 mL). X-Phos, amine (1.2 equiv) and 250 μL KOH (21.6 M) were used. The indicated isolated yield is the average of two runs.
[b] Approximately 20% ArCl was recovered.

which was introduced by Buchwald in 2003 as a new type of biphenyl based phosphine, on the efficiency of our protocol.[25,26] As can be seen in Table 8, the use of 5 mol % $Pd(OAc)_2$/2X-Phos under otherwise similar conditions rather exceptionally gave a better performance. Usually equal or worse isolated yields were obtained in comparison to DCPB and JohnPhos (compare Table 8 with Tables 5–7).

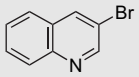
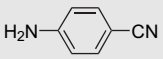
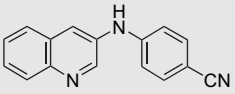
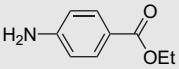
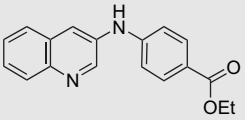
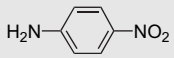
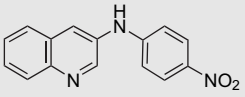
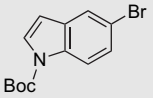
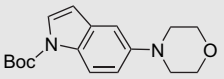
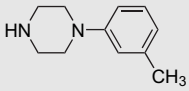
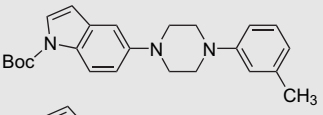
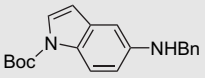
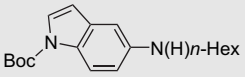
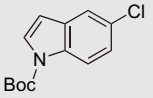
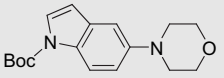
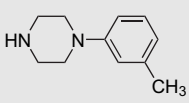
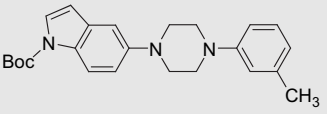
As a penultimate part of this project, we also looked at the coupling of anilines. Although, as mentioned, good microwave-assisted coupling protocols based on weak bases have been reported for this type of amine, we wanted to know whether our conditions (use of our two phase system and microwave irradiation as heating source) are also suitable. *N*-Methylaniline was chosen as model. The amination of 4-chlorobenzonitrile using DCPB gave 53% of 4-[methyl(phenyl)amino]benzonitrile (Table 9, entry 1). The use of X-Phos gave an equal result (Table 9, entry 2). Also for the coupling of *N*-methylaniline with 4-chloroacetophenone a similar yield was

Table 9
Microwave-assisted Buchwald–Hartwig reactions of aryl chlorides with *N*-methylaniline in toluene/aq KOH (21.6 M)[a]

Entry	ArCl	Catalyst	Pd (mol %)	*T* (°C)	Time (min)	Product	Yield (%)
1		A	5	100	30		53
2		B	5	100	30		57
3		A	5	120	30		49
4		B	5	120	30		45
5		A	5	100	30		66
6		B	5	100	30		40
7[b]		A	5	150	30		28
8[b]		B	5	120	30		16
9[b]		C	5	120	30		61

[a] Reactions were conducted under microwave irradiation (power=40 W) on a 1 mmol scale in toluene (0.5 mL). *N*-Methylaniline (1.2 equiv) and 250 μL KOH (21.6 M) were used. A=$Pd(OAc)_2$/2DCPB, B=$Pd(OAc)_2$/2X-Phos, C=$Pd[P(t\text{-}Bu)_3]_2$. The indicated isolated yield is the average of two runs.
[b] Power=60 W.

Table 10
Microwave-assisted Buchwald–Hartwig reactions of 3-bromoquinoline and *tert*-butyl 5-bromo-(and chloro)-1*H*-indole-1-carboxylate in toluene/aq KOH (21.6 M)[a]

Entry	Substrate	Amine	Catalyst	Pd (mol %)	*T* (°C)	Time (min)	Product	Yield (%)
1[b]			A	5	100	30		75
2[b]			A	5	100	30		77
3[b]			A	5	100	30		83
4			A	5	100	30		70
5			A	5	100	30		41
6		H_2NBn	B	5	100	30		29
7		*n*-$HexNH_2$	B	5	100	30		13
8			A	5	100	30		72
9			A	5	100	30		40

[a] Reactions were conducted under microwave irradiation (power=40 W) on a 1 mmol scale in toluene (0.5 mL). Amine (1.2 equiv) and 250 μL KOH (21.6 M) were used. A=$Pd(OAc)_2$/2DCPB, B=$Pd(OAc)_2$/2JohnPhos. The indicated isolated yield is the average of two runs.
[b] Amine (1.05 equiv) was used.

obtained with DCPB and X-Phos (Table 9, entries 3 and 4). Using methyl 4-chlorobenzoate as substrate, DCPB showed to be slightly better than X-Phos (Table 9, entries 5 and 6). Generally, the yields are rather low and it seems that our protocol is not well suited for the introduction of anilines. In fact, also substrates with no hydrolysis sensitive functional groups such as 4-chloroanisole also gave disappointing yields in the reaction with *N*-methylaniline. In this case, $Pd[P(t\text{-}Bu)_3]_2$ gave a more acceptable result as 61% of 4-methoxy-*N*-methyl-*N*-phenylaniline was isolated (Table 9, entries 7–9).

As a last part, we investigated whether our protocol could also successfully be used for amination reactions with heteroaromatic substrates. In these reactions, one of the two coupling partners (the amine or the heteroaromatic substrate) bears a functional group sensitive to nucleophilic attack. 3-Bromoquinoline and *tert*-butyl 5-bromo-(and chloro)-1*H*-indole-1-carboxylate were chosen as model heteroaromatic substrates. Protection of the indole nitrogen is required, since no reaction occurred without N-protection under our microwave reaction conditions. This is probably due to deprotonation of the substrate followed by removal of the corresponding amide from the organic phase to the aqueous phase. The *N*-Boc-protected 5-halo-1*H*-indoles are sensitive substrate towards nucleophilic attack. This was proven by a standard hydrolysis experiment at 150 °C (μW) in a reaction time of 30 min for *tert*-butyl 5-bromo-1*H*-indole-1-carboxylate. The reaction yielded only 10% of *N*-Boc-protected substrate together with 80% of 5-bromo-1*H*-indole.

3-Bromoquinoline was coupled with 4-aminobenzonitrile, ethyl 4-aminobenzoate and 4-nitroaniline under slightly altered standard conditions in, respectively, 75%, 77% and 83% (Table 10, entries 1–3). The use of 1.05 equiv amine instead of 1.2 equiv proved to be better. It is unclear why anilines work so smoothly on this substrate. *tert*-Butyl 5-bromo-1*H*-indole-1-carboxylate and *tert*-butyl 5-chloro-1*H*-indole-1-carboxylate were successfully aminated with morpholine and 1-(3-methylphenyl)piperazine (Table 10, entries 4, 5, 8 and 9). In the coupling reaction of *tert*-butyl 5-bromo-1*H*-indole-1-carboxylate and *tert*-butyl 5-chloro-1*H*-indole-1-carboxylate with 1-(3-methylphenyl)piperazine, respectively, 36% and 34% of starting material could be recovered. Reaction of *tert*-butyl 5-bromo-1*H*-indole-1-carboxylate with benzylamine and hexylamine did not proceed so fast: after 30 min reaction time only 29% and 13% reaction product could, respectively, be isolated together with a recovery of 53% and 74% of starting material (Table 10, entries 6 and 7). Although the coupling yields in these experiments are low (Table 10, entries 5–7), hydrolyzed substrate (5-bromo-1*H*-indole) was never observed. *tert*-Butyl 5-bromo-1*H*-indole-1-carboxylate could be recovered, pointing out that hydrolysis of the

starting material is totally suppressed under these reaction conditions.

3. Conclusions

In this article, we describe an easy, efficient and fast microwave-assisted hydrolysis protocol. Substrates with nitriles and esters as functional groups can be hydrolyzed using a two phase system based on toluene/concd aq KOH. A range of aromatic nitriles can be selectively hydrolyzed to the amide or carboxylic acid stage by, respectively, adding a phase transfer catalyst or by raising the reaction temperature. In the second part of this article, the knowledge of the microwave-assisted hydrolysis protocol allowed the development of a rapid Pd-catalyzed amination protocol of aliphatic amines with aryl chlorides containing functional groups sensitive towards nucleophilic attack. The protocol allows coupling in only 30 min reaction time and the sensitive functional groups remain intact. Interestingly, we found that it is generally not necessary (irrespective from the heating source used) to add a phase transfer catalyst for the deprotonation of the intermediately formed Pd(II)–amine complex. This is in contrast with a previous report of the Hartwig group dealing with oil bath experiments.[4] Based on hydrolysis experiments, we clearly showed that adding phase transfer catalyst makes hydrolysis of the sensitive functional groups possible and the success of the amination reaction upon its addition will therefore be highly dependent on the difference in rate between coupling and hydrolysis (the reaction product is usually not very sensitive towards hydrolysis) and the amount of phase transfer catalyst added. When there is no rate determining Pd(II)–amine deprotonation, the concentration of KOH in the toluene phase is allowed to be very low without affecting the coupling rate. This low concentration is, however, not enough to result in hydrolysis of sensitive functional groups in the reaction times used. Alternatively, the Pd-catalyzed aminations might occur via interphase deprotonation. This reasoning explains the successful implementation of the concentrated aq KOH/toluene two phase system, presented in this article, in microwave-assisted Pd-catalyzed amination reactions.

4. Experimental

4.1. General

All melting points were determined on a Büchi apparatus and are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometer in the solvent indicated with TMS as an internal standard. All coupling constants are given in hertz and chemical shifts are given in parts per million. For mass spectrometric analysis, samples were dissolved in CH_3OH and diluted to a concentration of approximately 10^{-5} mol/L. Injections (10 μL) were directed to the mass spectrometer at a flow rate of 0.7 mL/min (CH_3OH and 0.1% formic acid), using a Kontron HPLC system. Mass spectrometric data were acquired on an AQA Navigator mass spectrometer (ThermoQuest, Finigan) equipped with an ApCI ionization interface. The AQAMax voltage was set to 20 V, the corona voltage to 3.5 kV and the probe temperature to 250 °C. Nitrogen gas was used for nebulation. Mass spectra were acquired by summing the spectra in the elution plug. In positive ion mode, the protonated molecule $[M+H]^+$ is recorded and in negative ion mode the corresponding deprotonated molecule $[M-H]^-$ is recorded.

Microwave heating was carried out with a single-mode Discover (CEM) unit. The temperature was monitored with an infrared sensor. Experiments were performed in sealed reaction vessels with an Al crimp cap with septum.

Toluene (99.85%, water <50 ppm, extra dry over molecular sieve) as well as all substrates and amines were purchased from Acros, except hexylamine, piperidine, 2,6-dichlorobenzonitrile and 2-methoxybenzonitrile, which were obtained from Aldrich. All compounds were used without further purification. 1-(3-Methylphenyl)piperazine was liberated from its hydrochloric acid salt using a 2 M NaOH solution. Boc-protection of 5-bromo-1*H*-indole and 5-chloro-1*H*-indole was performed according to a literature procedure.[27] Concentrated KOH solution (21.6 M) and KOH powder were prepared using KOH flakes (Acros). KOH powder was made with a pestle and mortar and was stored under argon atmosphere. *N*-Cetyl-*N*,*N*,*N*-trimethylammonium bromide was purchased from Merck. $Pd(OAc)_2$ and 2-(dicyclohexylphosphino)biphenyl (DCPB) were purchased from Acros, 2-(di-*tert*-butylphosphino)biphenyl (JohnPhos) and 2-(dicyclohexylphosphino)-2′,4′,6′-triisopropylbiphenyl (X-Phos) from Sigma–Aldrich and $Pd[P(t\text{-}Bu)_3]_2$ from ABCR. For the reactions with $Pd[P(t\text{-}Bu)_3]_2$ as catalyst, an AtmosBag (with zipper lock front entry, two-hand, large, Sigma–Aldrich) was used to work under inert atmosphere. A pre-catalyst stock solution was made for all the catalyst systems and $Pd[P(t\text{-}Bu)_3]_2$ was used as such. Catalyst systems using DCPB or JohnPhos were stirred overnight and X-Phos was stirred for only 10 min (we noticed that the catalyst decomposes in a short time). Pre-catalyst formation and storage was performed under argon atmosphere. Flash column chromatography was performed on Kieselgel 60 (ROCC, 0.040–0.063 mm).

4.2. General procedures

4.2.1. General hydrolysis procedure in toluene/aq KOH (21.6 M) under microwave irradiation (Tables 1–3)

A 10 mL microwave vial was charged with substrate (1.0 mmol) followed by concd aq KOH (21.6 M, 250 μL). The mixture was stirred (a triangular stir bar was used) under nitrogen atmosphere for 1 min. Subsequently, 0.5 mL toluene was added via a syringe and the resulting mixture was stirred and flushed with nitrogen for an additional 2 min. Next, the vial was sealed with an Al crimp cap with a septum and heated at the desired temperature in a CEM Discover microwave apparatus. The set power was 40 W and the total heating time can be found in the tables. After the reaction, the vial was cooled down to room temperature using a propelled air flow, it was opened and poured into a separating funnel. The vial was rinsed alternately with water (100 mL) and CH_2Cl_2 (100 mL). After two more extractions (2×50 mL CH_2Cl_2), the combined organic layers were dried over $MgSO_4$ and subsequently evaporated under reduced pressure, giving the first organic fraction. Then, again 100 mL CH_2Cl_2 was added to the water phase. The latter was acidified with 2 M HCl until pH=7 and extracted. After two more extractions (2×50 mL CH_2Cl_2), the combined organic layers were dried over $MgSO_4$ and subsequently evaporated under reduced pressure, giving the second organic fraction. Finally, 100 mL CH_2Cl_2 was added to the water phase. The water layer was now acidified until pH ~1. After two more extractions (2×50 mL CH_2Cl_2), the combined organic layers were dried over $MgSO_4$ and subsequently evaporated under reduced pressure, giving the third organic fraction. The three organic fractions were characterized via ^{1}H NMR.

When 10 mol% *N*-cetyl-*N*,*N*,*N*-trimethylammonium bromide was added, an additional purification step was often required. To separate the formed amide from the PTC, the first organic fraction was purified by flash column chromatography on silica gel (eluent CH_2Cl_2/MeOH (98/2)). When it was necessary to separate the formed amide from its corresponding carboxylic acid, CH_2Cl_2/7 N NH_3 in MeOH (98/2) was used as eluent system.

4.2.2. General Pd-catalyzed amination procedures

4.2.2.1. Buchwald–Hartwig reactions of aryl halides in toluene/aq KOH (21.6 M) under microwave irradiation, using DCPB, JohnPhos or X-Phos as ligand for the Pd-catalyst (Tables 4–10). A 10 mL microwave vial was charged with aryl halide (1.0 mmol) and amine (1.2 mmol) followed by concd aq KOH (21.6 M, 250 μL). The mixture was stirred (a triangular stir bar was used) under nitrogen atmosphere for 1 min. Subsequently, 0.5 mL of a stock solution of the catalyst in toluene was added via a syringe and the resulting mixture was stirred and flushed with nitrogen for an additional 2 min. Next, the vial was sealed with an Al crimp cap with a septum and heated at the desired temperature in a CEM Discover microwave apparatus. The set power and total heating time can be found in the tables. After the reaction, the vial was cooled down to room temperature using a propelled air flow, it was opened and poured into a separating funnel. The vial was rinsed alternately with water (100 mL) and CH_2Cl_2 (100 mL). In the case of morpholine, pyrrolidine, benzylamine, hexylamine and piperidine the water layer was acidified[†] with 2 M HCl until pH=7 and in the case of *N*-methylaniline, the water layer was acidified until pH ~1.[28] If 1-(3-methylphenyl)piperazine was used, no acidification was performed. After two more extractions (2×50 mL CH_2Cl_2), the combined organic layers were dried over $MgSO_4$ and subsequently evaporated under reduced pressure. Finally, the crude product was purified via column chromatography on silica gel to give the desired arylamines in the yield shown.

4.2.2.2. Microwave amination procedure for the coupling of 4-chlorobenzonitrile with morpholine, using toluene/aq KOH (21.6 M) and Pd[P(t-Bu)$_3$]$_2$ as catalyst (Table 5, entry 2). In an AtmosBag, morpholine (104.5 mg, 1.2 mmol) was added to a suspension of Pd[P(*t*-Bu)$_3$]$_2$ (25.6 mg, 50.0 μmol) and 4-chlorobenzonitrile (137.6 mg, 1.0 mmol) in toluene (0.5 mL) in a microwave vial. A triangular stir bar as well as concd aq KOH (21.6 M, 250 μL) was added. Next, the vial was sealed with an Al crimp cap with a septum, removed from the AtmosBag and heated at the desired temperature in a CEM Discover microwave apparatus. The set power and total heating time can be found in the table. After the reaction vial was cooled down to room temperature using a propelled air flow, it was opened and poured into a separating funnel. The vial was rinsed alternately with water (100 mL) and CH_2Cl_2 (100 mL) and the water layer was acidified with 2 M HCl until pH=7.[28] After two more extractions (2×50 mL CH_2Cl_2), the combined organic layers were dried over $MgSO_4$ and subsequently evaporated under reduced pressure. Finally, the crude product was purified via column chromatography on silica gel to give the desired 4-morpholin-4-ylbenzonitrile.

4.2.2.3. Microwave amination procedure for the coupling of 4-chloroanisole with N-methylaniline, using toluene/aq KOH (21.6 M) and Pd[P(t-Bu)$_3$]$_2$ as catalyst (Table 9, entry 9). In an AtmosBag, 4-chloroanisole (170.6 mg, 1.0 mmol) and *N*-methylaniline (128.6 mg, 1.2 mmol) were added to a suspension of Pd[P(*t*-Bu)$_3$]$_2$ (25.6 mg, 50.0 μmol) in toluene (0.5 mL) in a microwave vial. A triangular stir bar as well as concd aq KOH (21.6 M, 250 μL) was added. Next, the vial was sealed with an Al crimp cap with a septum, removed from the AtmosBag and heated at the desired temperature in a CEM Discover microwave apparatus. The set power and total heating time can be found in the table. After the reaction, the vial was cooled down to room temperature using a propelled air flow, it was opened and poured into a separating funnel. The vial was rinsed alternately with water (100 mL) and CH_2Cl_2 (100 mL), and the water layer was acidified until pH ~1.[28] After two more extractions (2×50 mL CH_2Cl_2), the combined organic layers were dried over $MgSO_4$ and subsequently evaporated under reduced pressure. Finally, the crude product was purified via column chromatography on silica gel to give the desired 4-methoxy-*N*-methyl-*N*-phenylaniline.

4.2.2.4. Buchwald–Hartwig reactions of liquid aryl halides with KOH powder and 27 μL water under conventional heating (Fig. 1).[4] In an AtmosBag, aryl halide (1.0 mmol) and amine (1.05 mmol) were added to a suspension of Pd[P(*t*-Bu)$_3$]$_2$ (5.1 mg, 10.0 μmol) and KOH powder (84.0 mg, 1.5 mmol) in toluene (1.0 mL) in a microwave vial. A stir bar was added, the vial was sealed with an Al crimp cap with a septum and removed from the AtmosBag. Water (27 μL, 1.5 mmol) was added to the mixture by syringe. The reaction mixture was then stirred vigorously at 90 °C. After the reaction, the vial was cooled down to room temperature, it was opened and poured into a separating funnel. The vial was rinsed alternately with water (100 mL) and CH_2Cl_2 (100 mL). In the case of morpholine, the water layer was acidified with 2 M HCl until pH=7 and in the case of *N*-methylaniline, the water layer was acidified until pH ~1.[28] After two more extractions (2×50 mL CH_2Cl_2), the combined organic layers were dried over $MgSO_4$ and subsequently evaporated under reduced pressure. Finally, the crude product was purified via column chromatography on silica gel to give the desired arylamines in the yield shown.

4.3. Characterization data of the hydrolysis products

4.3.1. 4-Chlorobenzamide (Table 1, entry 1)

4-Chlorobenzonitrile (137.6 mg, 1 mmol). Yield 21% (32.6 mg); white powder; mp 177.9–178.6 °C (lit. mp 179–180 °C).[29] The characterization data are identical to those reported in the literature.[30] For comparison, we report here our ^{1}H NMR data: δ_H (DMSO-d_6): 8.02 (br s, 1H), 7.89 (d, *J*=8.6 Hz, 2H), 7.52 (d, *J*=8.6 Hz, 2H), 7.42 (br s, 1H); MS: $[M+H]^+$=156, 158.

4.3.2. 4-Chlorobenzoic acid (Table 1, entry 1)

4-Chlorobenzonitrile (137.6 mg, 1 mmol). Yield 72% (112.7 mg); white powder; mp 238.8–239.8 °C (lit. mp 243 °C).[29] The characterization data are identical to those reported in the literature.[31] For comparison, we report here our ^{1}H NMR data: δ_H (DMSO-d_6): 13.14 (br s, 1H), 7.94 (d, *J*=8.6 Hz, 2H), 7.57 (d, *J*=8.6 Hz, 2H); MS: $[M-H]^-$=155, 157.

4.3.3. 3-Chlorobenzoic acid (Table 1, entry 6)

3-Chlorobenzonitrile (137.6 mg, 1 mmol). Yield 96% (150.0 mg); white powder; mp 154.3–155.3 °C (lit. mp 158 °C).[29] The characterization data are identical to those reported in the literature.[32] For comparison, we report here our ^{1}H NMR data: δ_H (DMSO-d_6): 13.29 (br s, 1H), 7.92–7.88 (m, 2H), 7.70 (ddd, *J*=8.0, 2.2, 1.2 Hz, 1H), 7.55 (dd, *J*=8.1, 8.0 Hz, 1H); MS: $[M-H]^-$=155, 157.

4.3.4. 3-Chlorobenzamide (Table 1, entry 7)

3-Chlorobenzonitrile (137.6 mg, 1 mmol). Yield 88% (136.9 mg); white powder; mp 135.0–137 °C (lit. mp 135.5–137.0 °C).[29] The characterization data are identical to those reported in the literature.[30] For comparison, we report here our ^{1}H NMR data: δ_H (DMSO-d_6): 8.06 (br s, 1H), 7.90 (td, *J*=1.8, 0.3 Hz, 1H), 7.83 (ddd, *J*=7.7, 1.6, 1.1 Hz, 1H), 7.59 (ddd, *J*=8.0, 2.2, 1.1 Hz, 1H), 7.49 (dd, *J*=8.0, 7.7 Hz, 1H), 7.48 (br s, 1H); MS: $[M+H]^+$=156, 158.

4.3.5. 2-Chlorobenzoic acid (Table 1, entry 8)

2-Chlorobenzonitrile (137.6 mg, 1 mmol). Yield 97% (151.7 mg); white powder; mp 140.7–141.1 °C (lit. mp 142 °C).[29] The

[†] When methyl 4-chlorobenzoate, *tert*-butyl 5-bromo-1*H*-indole-1-carboxylate or *tert*-butyl 5-chloro-1*H*-indole-1-carboxylate was used as substrate, no acidification was performed.

characterization data are identical to those reported in the literature.[33] For comparison, we report here our ^{1}H NMR data: δ_H (DMSO-d_6): 13.34 (br s, 1H), 7.80 (ddd, J=7.6, 1.5, 0.6 Hz, 1H), 7.55–7.52 (m, 2H), 7.43 (ddd, J=7.7, 5.4, 3.0 Hz, 1H); MS: $[M-H]^-$=155, 157.

4.3.6. 2-Chlorobenzamide (Table 1, entry 9)

2-Chlorobenzonitrile (137.6 mg, 1 mmol). Yield 45% (70.0 mg); white powder; mp 140.0–141.0 °C (lit. mp 142.4 °C).[29] The characterization data are identical to those reported in the literature.[34] For comparison, we report here our ^{1}H NMR data: δ_H (DMSO-d_6): 7.83 (br s, 1H), 7.54 (br s, 1H), 7.47 (dd, J=8.2, 1.5 Hz, 1H), 7.45–7.34 (m, 3H); MS: $[M+H]^+$=156, 158.

4.3.7. 2,6-Dichlorobenzamide (Table 1, entry 13)

2,6-Dichlorobenzonitrile (172.0 mg, 1 mmol). Yield 92% (174.5 mg); shiny white needles; mp 200.5–201.4 °C (lit. mp 196–201 °C).[35] The characterization data are identical to those reported in the literature.[36] For comparison, we report here our ^{1}H NMR data: δ_H (DMSO-d_6): 8.04 (br s, 1H), 7.77 (br s, 1H), 7.48 (d, J=9.1 Hz, 1H), 7.48 (d, J=7.0 Hz, 1H), 7.40 (dd, J=9.0, 7.0 Hz, 1H); MS: $[M+H]^+$=190, 192, 194.

4.3.8. 2-Methoxybenzamide (Table 1, entry 15)

2-Methoxybenzonitrile (133.2 mg, 1 mmol). Yield 62% (93.6 mg); white powder; mp 127.2–128.0 °C (lit. mp 129 °C).[29] The characterization data are identical to those reported in the literature.[37] For comparison, we report here our ^{1}H NMR data: δ_H (DMSO-d_6): 7.80 (dd, J=7.6, 1.9 Hz, 1H), 7.60 (br s, 1H), 7.47 (ddd, J=8.4, 7.3, 1.9 Hz, 1H), 7.46 (br s, 1H), 7.13 (dd, J=8.5, 0.8 Hz, 1H), 7.02 (td, J=7.5, 1.0 Hz, 1H), 3.89 (s, 3H); MS: $[M+H]^+$=152.

4.3.9. 2-Methoxybenzoic acid (Table 1, entry 15)

2-Methoxybenzonitrile (133.2 mg, 1 mmol). Yield 22% (34.1 mg); white powder; mp 95.2–96.2 °C (lit. mp 101 °C).[29] The characterization data are identical to those reported in the literature.[38] For comparison, we report here our ^{1}H NMR data: δ_H ($CDCl_3$): 10.59 (br s, 1H), 8.20 (dd, J=7.7, 1.8 Hz, 1H), 7.58 (ddd, J=8.4, 7.4, 1.9 Hz, 1H), 7.15 (ddd, J=8.4, 7.4, 1.0 Hz, 1H), 7.07 (dd, J=8.4, 0.9 Hz, 1H), 4.09 (s, 3H); MS: $[M-H]^-$=151.

4.3.10. 2-(4-Chlorophenyl)acetamide (Table 3, entry 1)

(4-Chlorophenyl)acetonitrile (151.6 mg, 1 mmol). Yield 32% (54.3 mg); white to pale beige powder; mp 181.6–182.2 °C (lit. mp 180–182 °C).[39] The characterization data are identical to those reported in the literature.[39] For comparison, we report here our ^{1}H NMR data: δ_H (CD_3COOD): 7.37–7.30 (m, 4H), 3.64 (s, 2H); δ_H (DMSO-d_6): 7.45 (br s, 1H), 7.35 (d, J=8.6 Hz, 2H), 7.27 (d, J=8.5 Hz, 2H), 6.87 (br s, 1H), 3.37 (s, 2H); MS: $[M+H]^+$=170, 172.

4.3.11. (4-Chlorophenyl)acetic acid (Table 3, entry 1)

(4-Chlorophenyl)acetonitrile (151.6 mg, 1 mmol). Yield 65% (110.9 mg); white powder; mp 104.8–105.5 °C (lit. mp 104–106 °C).[40] The characterization data are identical to those reported in the literature.[41] For comparison, we report here our ^{1}H NMR data: δ_H ($CDCl_3$): 9.00 (br s, 1H), 7.30 (d, J=8.5 Hz, 2H), 7.21 (d, J=8.5 Hz, 2H), 3.62 (s, 2H). δ_H (DMSO-d_6): 12.36 (br s, 1H), 7.35 (d, J=8.6 Hz, 2H), 7.28 (d, J=8.5 Hz, 2H), 3.58 (s, 2H); MS: $[M+H]^-$=169, 171.

4.3.12. 2-(3,4-Dimethoxyphenyl)acetamide (Table 3, entry 4)

(3,4-Dimethoxyphenyl)acetonitrile (177.2 mg, 1 mmol). Yield 24% (46.8 mg); white powder; mp 142.2–143.6 °C (lit. mp 146–147 °C).[42] δ_H (DMSO-d_6): 7.32 (br s, 1H), 6.87 (d, J=2.1 Hz, 1H), 6.86 (d, J=8.1 Hz, 1H), 6.78 (br s, 1H), 6.76 (dd, J=8.2, 2.0 Hz, 1H), 3.73 (s, 3H), 3.72 (s, 3H), 3.28 (s, 2H); MS: $[M+H]^+$=196.

4.3.13. (3,4-Dimethoxyphenyl)acetic acid (Table 3, entry 4)

(3,4-Dimethoxyphenyl)acetonitrile (177.2 mg, 1 mmol). Yield 46% (90.3 mg); white/slightly yellow flakes; mp 96.2–97.5 °C (lit. mp 96–99 °C).[35] The characterization data are identical to those reported in the literature.[29] For comparison, we report here our ^{1}H NMR data: δ_H ($CDCl_3$): 7.26 (br s, 1H), 6.84–6.80 (m, 3H), 3.87 (s, 3H), 3.86 (s, 3H), 3.59 (s, 2H); δ_H (DMSO-d_6): 12.18 (br s, 1H), 6.87 (d, J=8.2 Hz, 1H), 6.85 (d, J=2.0 Hz, 1H), 6.76 (dd, J=8.2, 2.1 Hz, 1H), 3.73 (s, 3H), 3.72 (s, 3H), 3.47 (s, 2H); MS: $[M+H]^-$=195.

4.4. Characterization data of the Pd-catalyzed amination products

4.4.1. 4-(4-Methylphenyl)morpholine (Table 4, entry 1)

4-Chlorotoluene (126.6 mg, 1 mmol) and morpholine (104.5 mg, 1.2 mmol). Eluent for column chromatography: heptane/EtOAc (90/10). Yield 70% (124.6 mg); light brown/yellow powder; mp 47.6–48.2 °C (lit. mp 47–48 °C).[10a] The characterization data are identical to those reported in the literature.[4] For comparison, we report here our ^{1}H NMR data: δ_H ($CDCl_3$): 7.09 (d, J=8.2 Hz, 2H), 6.83 (d, J=8.2 Hz, 2H), 3.86 (br t, J=4.8 Hz, 4H), 3.11 (br t, J=4.8 Hz, 4H), 2.28 (s, 3H); MS: $[M+H]^+$=178.

4.4.2. 4-(4-Methoxyphenyl)morpholine (Table 4, entry 3)

4-Chloroanisole (170.6 mg, 1 mmol) and morpholine (104.5 mg, 1.2 mmol). Eluent for column chromatography: first CH_2Cl_2 (100%), then CH_2Cl_2/MeOH (99/1). Yield 68% (131.6 mg); brown solid; mp 68.8–70.0 °C (lit. mp 71 °C).[43] The characterization data are identical to those reported in the literature.[12b] For comparison, we report here our ^{1}H NMR data: δ_H ($CDCl_3$): 6.92–6.82 (m, 4H), 3.86 (br t, J=4.7 Hz, 4H), 3.77 (s, 3H), 3.06 (br t, J=4.7 Hz, 4H); MS: $[M+H]^+$=194.

4.4.3. 4-Morpholin-4-ylbenzonitrile (Table 5, entry 2)

4-Chlorobenzonitrile (137.6 mg, 1 mmol) and morpholine (104.5 mg, 1.2 mmol). Eluent for column chromatography: heptane/EtOAc (70/30). Yield 74% (138.4 mg); white to pale yellow solid; mp 81.5–82.0 °C (lit. mp 85 °C).[10a] The characterization data are identical to those reported in the literature.[44] For comparison, we report here our ^{1}H NMR data: δ_H ($CDCl_3$): 7.52 (d, J=9.0 Hz, 2H), 6.86 (d, J=9.0 Hz, 2H), 3.85 (br t, J=5.0 Hz, 4H), 3.28 (br t, J=5.0 Hz, 4H); MS: $[M+H]^+$=189.

4.4.4. 4-Pyrrolidin-1-ylbenzonitrile (Table 5, entry 5)

4-Chlorobenzonitrile (137.6 mg, 1 mmol) and pyrrolidine (85.3 mg, 1.2 mmol). Eluent for column chromatography: heptane/EtOAc (80/20). Yield 79% (135.3 mg); yellow solid; mp 81.3–82.8 °C (lit. mp 88–90 °C).[45] The characterization data are identical to those reported in the literature.[45] For comparison, we report here our ^{1}H NMR data: δ_H ($CDCl_3$): 7.44 (d, J=9.0 Hz, 2H), 6.50 (d, J=9.0 Hz, 2H), 3.35–3.30 (m, 4H), 2.08–2.00 (m, 4H); MS: $[M+H]^+$=173.

4.4.5. 4-[4-(3-Methylphenyl)piperazin-1-yl]benzonitrile (Table 5, entry 6)

4-Chlorobenzonitrile (137.6 mg, 1 mmol) and 1-(3-methylphenyl)piperazine (194.4 mg, 1.2 mmol). Eluent for column chromatography: heptane/EtOAc (80/20). Yield 70% (386.5 mg); pale yellow powder; mp 132.3 °C. δ_H ($CDCl_3$): 7.51 (d, J=9.1 Hz, 2H), 7.18 (t, J=7.7 Hz, 1H), 6.90 (d, J=9.1 Hz, 2H), 6.80–7.71 (m, 3H), 3.47 (br t, J=5.2 Hz, 4H), 3.32 (br t, J=5.2 Hz, 4H), 2.34 (s, 3H); δ_C ($CDCl_3$): 153.3, 150.9, 139.0, 133.5, 129.1, 121.3, 120.0, 117.2, 114.3, 113.5, 100.6, 49.1, 47.3, 21.8; MS: $[M+H]^+$=278; HRMS (ESI) for $C_{18}H_{20}N_3$ $[M+H]^+$ calcd: 278.1657, found: 278.1657.

4.4.6. 4-(Benzylamino)benzonitrile (Table 5, entry 7)

4-Chlorobenzonitrile (137.6 mg, 1 mmol) and benzylamine (128.6 mg, 1.2 mmol). Eluent for column chromatography: heptane/EtOAc (95/5). Yield 79% (164.9 mg); yellow solid; mp 74.9–75.6 °C (lit. mp 62–66 °C).[46] The characterization data are identical to those reported in the literature.[47] For comparison, we report here our ^{1}H NMR data: δ_H ($CDCl_3$): 7.42 (d, J=8.9 Hz, 2H), 7.37–7.28 (m, 5H), 6.59 (d, J=8.9 Hz, 2H), 4.56 (br s, 1H), 4.37 (s, 2H); MS: $[M+H]^+$=209.

4.4.7. 4-(Hexylamino)benzonitrile (Table 5, entry 9)

4-Chlorobenzonitrile (137.6 mg, 1 mmol) and hexylamine (121.4 mg, 1.2 mmol). Eluent for column chromatography: heptane/EtOAc (90/10). Yield 74% (150.4 mg); pale yellow, low melting solid; mp 31.3–31.7 °C (lit. mp 32–34 °C).[48] The characterization data are identical to those previously reported in the literature.[49] For comparison, we report here our ^{1}H NMR data: δ_H ($CDCl_3$): 7.41 (d, J=8.9 Hz, 2H), 6.51 (d, J=8.9 Hz, 2H), 4.14 (br s, 1H), 3.14 (td, J=7.1, 5.4 Hz, 2H), 1.62 (quintet, J=7.3 Hz, 2H), 1.45–1.28 (m, 6H), 0.90 (t, J=7.1 Hz, 3H); MS: $[M+H]^+$=203.

4.4.8. Methyl 4-morpholin-4-ylbenzoate (Table 6, entry 1)

Methyl 4-chlorobenzoate (170.6 mg, 1 mmol) and morpholine (104.5 mg, 1.2 mmol). Eluent for column chromatography: heptane/EtOAc (99/1). Yield 58% (127.5 mg); shiny white needles; mp 160.8–161.7 °C (lit. mp 162–163 °C).[10a] The characterization data are identical to those reported in the literature.[10a] For comparison, we report here our ^{1}H NMR data: δ_H ($CDCl_3$): 7.96 (d, J=8.8 Hz, 2H), 6.89 (d, J=8.9 Hz, 2H), 3.90 (s, 3H), 3.88 (br t, J=4.9 Hz, 4H), 3.31 (br t, J=4.9 Hz, 4H); MS: $[M+H]^+$=222.

4.4.9. Methyl 4-piperidin-1-ylbenzoate (Table 6, entry 2)

Methyl 4-chlorobenzoate (170.6 mg, 1 mmol) and piperidine (102.1 mg, 1.2 mmol). Eluent for column chromatography: heptane/EtOAc (90/10). Yield 46% (101.4 mg); off-white powder; mp 92.8–94.0 °C (lit. mp 92–95 °C).[49] The characterization data are identical to those reported in the literature.[50] For comparison, we report here our ^{1}H NMR data: δ_H ($CDCl_3$): 7.89 (d, J=9.2 Hz, 2H), 6.85 (d, J=9.1 Hz, 2H), 3.85 (s, 3H), 3.33 (br t, J=5.4 Hz, 4H), 1.70–1.59 (m, 6H); MS: $[M+H]^+$=220.

4.4.10. Methyl 4-[4-(3-methylphenyl)piperazin-1-yl]benzoate (Table 6, entry 3)

Methyl 4-chlorobenzoate (170.6 mg, 1 mmol) and 1-(3-methylphenyl)piperazine (211.5 mg, 1.2 mmol). Eluent for column chromatography: heptane/EtOAc (90/10). Yield 68% (211.3 mg); shiny pale yellow powder; mp 131.6 °C. δ_H ($CDCl_3$): 7.94 (d, J=9.1 Hz, 2H), 7.18 (td, J=7.6, 0.6 Hz, 1H), 6.91 (d, J=9.1 Hz, 2H), 6.80–7.72 (m, 3H), 3.87 (s, 3H), 3.48 (br t, J=5.2 Hz, 4H), 3.33 (br t, J=5.2 Hz, 4H), 2.34 (s, 3H); δ_C ($CDCl_3$): 167.1, 154.1, 151.1, 139.0, 131.3, 129.1, 121.2, 120.1, 117.2, 113.8, 113.5, 51.7, 49.2, 47.7, 21.8; MS: $[M+H]^+$=311; HRMS (ESI) for $C_{19}H_{23}N_2O_2$ $[M+H]^+$ calcd: 311.1760, found: 311.1750.

4.4.11. Methyl 4-(benzylamino)benzoate (Table 6, entry 4)

Methyl 4-chlorobenzoate (170.6 mg, 1 mmol) and benzylamine (128.6 mg, 1.2 mmol). Eluent for column chromatography: heptane/EtOAc (90/10). Yield 74% (178.8 mg); pale yellow flakes; mp 119.4–121.4 °C. The characterization data are identical to those reported in the literature.[51] For comparison, we report here our ^{1}H NMR data: δ_H ($CDCl_3$): 7.86 (d, J=8.9 Hz, 2H), 7.38–7.26 (m, 5H), 6.60 (d, J=8.9 Hz, 2H), 4.49 (br s, 1H), 4.39 (s, 2H), 3.84 (s, 3H); MS: $[M+H]^+$=242.

4.4.12. Methyl 4-(hexylamino)benzoate (Table 6, entry 5)

Methyl 4-chlorobenzoate (170.6 mg, 1 mmol) and hexylamine (121.4 mg, 1.2 mmol). Eluent for column chromatography: heptane/EtOAc (90/10). Yield 45% (105.9 mg); white-pale pink crystals; mp 95.4–96.6 °C (lit. mp 93–94 °C).[52] The characterization data are identical to those reported in the literature.[52] For comparison, we report here our ^{1}H NMR data: δ_H ($CDCl_3$): 7.85 (d, J=8.8 Hz, 2H), 6.53 (d, J=8.9 Hz, 2H), 4.06 (br s, 1H), 3.84 (s, 3H), 3.16 (td, J=7.1, 5.5 Hz, 2H), 1.63 (quintet, J=7.3 Hz, 2H), 1.44–1.29 (m, 6H), 0.90 (t, J=7.1 Hz, 3H); MS: $[M+H]^+$=236.

4.4.13. 1-(4-Morpholin-4-ylphenyl)ethanone (Table 7, entry 1)

4-Chloroacetophenone (170.6 mg, 1 mmol) and morpholine (104.5 mg, 1.2 mmol). Eluent for column chromatography: first heptane/EtOAc (80/20), then heptane/EtOAc (50/50). Yield 63% (129.3 mg); shiny pale yellow powder; mp 93.0–94.4 °C (lit. mp 96–97 °C).[10a] The characterization data are identical to those reported in the literature.[4] For comparison, we report here our ^{1}H NMR data: δ_H ($CDCl_3$): 7.89 (d, J=9.0 Hz, 2H), 6.87 (d, J=9.2 Hz, 2H), 3.86 (br t, J=5.0 Hz, 4H), 3.31 (br t, J=4.9 Hz, 4H), 2.53 (s, 3H); MS: $[M+H]^+$=206.

4.4.14. 1-(4-Piperidin-1-ylphenyl)ethanone (Table 7, entry 3)

4-Chloroacetophenone (170.6 mg, 1 mmol) and piperidine (102.1 mg, 1.2 mmol). Eluent for column chromatography: heptane/EtOAc (90/10). Yield 63% (128.4 mg); shiny white flakes/needles; mp 87.7–88.7 °C (lit. mp 87–88 °C).[49] The characterization data are identical to those reported in the literature.[50] For comparison, we report here our ^{1}H NMR data: δ_H ($CDCl_3$): 7.85 (d, J=9.2 Hz, 2H), 6.85 (d, J=9.1 Hz, 2H), 3.33–3.38 (m, 4H), 2.50 (s, 3H), 1.72–1.61 (m, 6H); MS: $[M+H]^+$=204.

4.4.15. 1-(4-Pyrrolidin-1-ylphenyl)ethanone (Table 7, entry 4)

4-Chloroacetophenone (170.6 mg, 1 mmol) and pyrrolidine (85.3 mg, 1.2 mmol). Eluent for column chromatography: heptane/EtOAc (80/20). Yield 73% (138.4 mg); yellow/orange powder; mp 128.0–128.8 °C (lit. mp 126 °C).[53] The characterization data are identical to those reported in the literature.[54] For comparison, we report here our ^{1}H NMR data: δ_H ($CDCl_3$): 7.86 (d, J=9.0 Hz, 2H), 6.51 (d, J=9.0 Hz, 2H), 3.34–3.39 (m, 4H), 2.50 (s, 3H), 2.00–2.08 (m, 4H); MS: $[M+H]^+$=190.

4.4.16. 1-{4-[4-(3-Methylphenyl)piperazin-1-yl]phenyl}ethanone (Table 7, entry 5)

4-Chloroacetophenone (170.6 mg, 1 mmol) and 1-(3-methylphenyl)piperazine (211.5 mg, 1.2 mmol). Eluent for column chromatography: heptane/EtOAc (90/10). Yield 76% (223.9 mg); yellow powder; mp 106.8 °C. δ_H ($CDCl_3$): 7.90 (d, J=9.1 Hz, 2H), 7.18 (t, J=7.7 Hz, 1H), 6.91 (d, J=9.1 Hz, 2H), 6.80–7.72 (m, 3H), 3.50 (br t, J=5.2 Hz, 4H), 3.32 (br t, J=5.2 Hz, 4H), 2.53 (s, 3H), 2.34 (s, 3H); δ_C ($CDCl_3$): 196.5, 154.1, 151.0, 139.0, 130.4, 129.1, 127.9, 121.2, 117.2, 113.6, 113.5, 49.2, 47.5, 26.1, 21.8; MS: $[M+H]^+$=295; HRMS (ESI) for $C_{19}H_{23}N_2O_1$ $[M+H]^+$ calcd: 295.1810, found: 295.1806.

4.4.17. 1-[4-(Benzylamino)phenyl]ethanone (Table 7, entry 6)

4-Chloroacetophenone (170.6 mg, 1 mmol) and benzylamine (128.6 mg, 1.2 mmol). Eluent for column chromatography: heptane/EtOAc (80/20). Yield 71% (160.0 mg); yellow powder; mp 76.0–78.0 °C (lit. mp 89–91 °C).[45] The characterization data are identical to those reported in the literature.[54] For comparison, we report here our ^{1}H NMR data: δ_H ($CDCl_3$): 7.82 (d, J=8.9 Hz, 2H), 7.39–7.27 (m, 5H), 6.61 (d, J=8.9 Hz, 2H), 4.60 (br s, 1H), 4.41 (s, 2H), 2.49 (s, 3H); MS: $[M+H]^+$=226.

4.4.18. 1-[4-(Hexylamino)phenyl]ethanone (Table 7, entry 7)

4-Chloroacetophenone (170.6 mg, 1 mmol) and hexylamine (121.4 mg, 1.2 mmol). Eluent for column chromatography: heptane/EtOAc (90/10). Yield 63% (139.0 mg); pale yellow powder; mp 73.4–74.0 °C. The characterization data are identical to those

reported in the literature.[55] For comparison, we report here our ^{1}H NMR data: δ_H ($CDCl_3$): 7.82 (d, J=8.9 Hz, 2H), 6.54 (d, J=8.9 Hz, 2H), 4.15 (br s, 1H), 3.17 (td, J=7.1, 5.4 Hz, 2H), 2.49 (s, 3H), 1.63 (quintet, J=7.3 Hz, 2H), 1.44–1.29 (m, 6H), 0.90 (t, J=7.1 Hz, 3H); MS: $[M+H]^+$=220.

4.4.19. 4-[Methyl(phenyl)amino]benzonitrile (Table 9, entry 1)

4-Chlorobenzonitrile (137.6 mg, 1 mmol) and *N*-methylaniline (128.6 mg, 1.2 mmol). Eluent for column chromatography: heptane/EtOAc (70/30). Yield 53% (111.1 mg); yellow viscous oil. The characterization data are identical to those reported in the literature.[56] For comparison, we report here our ^{1}H NMR data: δ_H ($CDCl_3$): 7.45–7.39 (m, 4H), 7.26 (tt, J=7.4, 1.2 Hz, 1H), 7.20 (dd, J=8.5, 1.2 Hz, 2H), 6.72 (d, J=9.2 Hz, 2H), 3.35 (s, 3H); MS: $[M+H]^+$=209.

4.4.20. 1-{4-[Methyl(phenyl)amino]phenyl}ethanone (Table 9, entry 3)

4-Chloroacetophenone (170.6 mg, 1 mmol) and *N*-methylaniline (128.6 mg, 1.2 mmol). Eluent for column chromatography: heptane/EtOAc (80/20). Yield 49% (110.0 mg); yellow flakes; mp 84.8–85.5 °C. The characterization data are identical to those reported in the literature.[57] For comparison, we report here our ^{1}H NMR data: δ_H ($CDCl_3$): 7.82 (d, J=9.2 Hz, 2H), 7.41 (br t, J=7.8 Hz, 2H), 7.26–7.19 (m, 3H), 6.76 (d, J=9.2 Hz, 2H), 3.34 (s, 3H), 2.51 (s, 3H); MS: $[M+H]^+$=226.

4.4.21. Methyl 4-[methyl(phenyl)amino]benzoate (Table 9, entry 5)

Methyl 4-chlorobenzoate (170.6 mg, 1 mmol) and *N*-methylaniline (128.6 mg, 1.2 mmol). Eluent for column chromatography: heptane/EtOAc (95/5). Yield 66% (159.5 mg); pale grey/brown powder; mp 100.8–101.4 °C. The characterization data are identical to those reported in the literature.[10b] For comparison, we report here our ^{1}H NMR data: δ_H ($CDCl_3$): 7.86 (d, J=9.1 Hz, 2H), 7.39 (dd, J=8.7, 7.6 Hz, 2H), 7.23–7.18 (m, 3H), 6.76 (d, J=9.1 Hz, 2H), 3.86 (s, 3H), 3.36 (s, 3H); MS: $[M+H]^+$=242.

4.4.22. 4-Methoxy-N-methyl-N-phenylaniline (Table 9, entry 9)

4-Chloroanisole (170.6 mg, 1 mmol) and *N*-methylaniline (128.6 mg, 1.2 mmol). Eluent for column chromatography: heptane/EtOAc (98/2). Yield 61% (130.1 mg); colourless to pale yellow oil. The characterization data are identical to those reported in the literature.[4] For comparison, we report here our ^{1}H NMR data: δ_H ($CDCl_3$): 7.20 (dd, J=8.8, 7.1 Hz, 2H), 7.09 (d, J=9.1 Hz, 2H), 6.89 (d, J=9.0 Hz, 2H), 6.83–6.76 (m, 3H), 3.81 (s, 3H), 3.25 (s, 3H); MS: $[M+H]^+$=214.

4.4.23. 4-(Quinolin-3-ylamino)benzonitrile (Table 10, entry 1)

3-Bromoquinoline (208.1 mg, 1 mmol) and 4-aminobenzonitrile (124.0 mg, 1.05 mmol). Eluent for column chromatography: CH_2Cl_2/EtOAc (95/5), then CH_2Cl_2/EtOAc (60/40). Yield 75% (183.4 mg); pale yellow powder; mp 197.6–198.4 °C. δ_H ($CDCl_3$): 8.77 (d, J=2.7 Hz, 1H), 8.06 (d, J=8.5 Hz, 1H), 7.90 (d, J=2.6 Hz, 1H), 7.73 (dd, J=8.1, 1.3 Hz, 1H), 7.63 (ddd, J=8.4, 6.9, 1.5 Hz, 1H), 7.56–7.58 (d+ddd, J=8.8, 8.0, 6.8, 1.3 Hz, 3H), 7.09 (d, J=8.8 Hz, 2H), 6.57 (br s, 1H); δ_C ($CDCl_3$): 147.1, 146.3, 145.0, 134.0, 129.2, 128.3, 128.2, 127.6, 126.9, 123.0, 122.8, 119.4, 115.6, 103.1; MS: $[M+H]^+$=246; HRMS (ESI) for $C_{16}H_{12}N_3$ $[M+H]^+$ calcd: 246.1031, found: 246.1030.

4.4.24. Ethyl 4-(quinolin-3-ylamino)benzoate (Table 10, entry 2)

3-Bromoquinoline (208.1 mg, 1 mmol) and ethyl 4-aminobenzoate (173.4 mg, 1.05 mmol). Eluent for column chromatography: CH_2Cl_2/EtOAc (95/5). Yield 77% (224.5 mg); pale yellow flakes; mp 134.3–135.2 °C. δ_H ($CDCl_3$): 8.77 (d, J=2.7 Hz, 1H), 8.03 (br ddd, J=8.4 Hz, 1H), 8.00 (d, J=8.8 Hz, 2H), 7.88 (d, J=2.7 Hz, 1H), 7.71 (br ddd, J=8.1, 1.5, 0.4 Hz, 1H), 7.60 (ddd, J=8.4, 6.9, 1.5 Hz, 1H), 7.52 (ddd, J=8.2, 6.9, 1.3 Hz, 1H), 7.11 (d, J=9.1 Hz, 2H), 6.24 (br s, 1H), 4.37 (q, J=7.1 Hz, 2H), 1.39 (t, J=7.1 Hz, 3H); δ_C ($CDCl_3$): 166.3, 146.9, 146.0, 144.6, 135.0, 131.6, 129.2, 128.5, 127.6, 127.4, 126.8, 122.9, 121.1, 115.4, 60.7, 14.4; MS: $[M+H]^+$=293; HRMS (ESI) for $C_{18}H_{17}N_2O_2$ $[M+H]^+$ calcd: 293.1290, found: 293.1278.

4.4.25. N-(4-Nitrophenyl)quinolin-3-amine (Table 10, entry 3)

3-Bromoquinoline (208.1 mg, 1 mmol) and 1-amino-4-nitrobenzene (145.0 mg, 1.05 mmol). Eluent for column chromatography: CH_2Cl_2/EtOAc (90/10). Yield 83% (220.3 mg); bright orange powder; mp 182.3–182.8 °C. δ_H ($CDCl_3$): 8.81 (d, J=2.7 Hz, 1H), 8.19 (d, J=9.1 Hz, 2H), 8.10 (br ddd, J=8.4, 1.2, 0.6 Hz, 1H), 7.97 (d, J=2.6 Hz, 1H), 7.77 (ddt, J=8.1, 1.5, 0.5 Hz, 1H), 7.67 (ddd, J=8.5, 6.9, 1.5 Hz, 1H), 7.58 (ddd, J=8.1, 6.9, 1.2 Hz, 1H), 7.07 (d, J=9.1 Hz, 2H), 6.48 (br s, 1H); δ_C ($CDCl_3$): 149.3, 146.5, 145.4, 140.9, 133.5, 129.3, 128.6, 128.3, 127.7, 127.0, 126.3, 124.3, 114.4; MS: $[M+H]^+$=266; HRMS (ESI) for $C_{15}H_{12}N_3O_2$ $[M+H]^+$ calcd: 266.0930, found: 266.0936.

4.4.26. tert-Butyl 5-morpholin-4-yl-1H-indole-1-carboxylate (Table 10, entry 4)

tert-Butyl 5-bromo-1*H*-indole-1-carboxylate (296.2 mg, 1 mmol) and morpholine (104.5 mg, 1.2 mmol). Eluent for column chromatography: first heptane/EtOAc (98/2), then heptane/EtOAc (80/20). Yield 70% (211.7 mg); brown/red powder; mp 101.9 °C. δ_H ($CDCl_3$): 8.01 (d, J=9.0 Hz, 1H), 7.54 (d, J=3.6 Hz, 1H), 7.05 (d, J=2.2 Hz, 1H), 7.00 (dd, J=9.0, 2.3 Hz, 1H), 6.48 (dd, J=3.7, 0.6 Hz, 1H), 3.89 (br t, J=4.7 Hz, 4H), 3.15 (br t, J=4.8 Hz, 4H), 1.66 (s, 9H); δ_C ($CDCl_3$): 149.8, 147.8, 131.4, 130.2, 126.3, 115.6, 115.4, 107.5, 107.2, 83.4, 67.1, 51.1, 28.2; MS: $[M+H]^+$=303; HRMS (ESI) for $C_{17}H_{23}N_2O_3$ $[M+H]^+$ calcd: 303.1709, found: 303.1701.

4.4.27. tert-Butyl 5-[4-(3-methylphenyl)piperazin-1-yl]-1H-indole-1-carboxylate (Table 10, entry 5)

tert-Butyl 5-bromo-1*H*-indole-1-carboxylate (296.2 mg, 1 mmol) and 1-(3-methylphenyl)piperazine (211.5 mg, 1.2 mmol). Eluent for column chromatography: heptane/EtOAc (95/5). Yield 41% (160.0 mg); pale yellow powder; mp 132.5 °C. δ_H ($CDCl_3$): 8.02 (d, J=8.9 Hz, 1H), 7.54 (d, J=3.6 Hz, 1H), 7.18 (td, J=7.7, 0.5 Hz, 1H), 7.12 (d, J=2.2 Hz, 1H), 7.06 (dd, J=9.0, 2.4 Hz, 1H), 6.80–6.70 (m, 3H), 6.49 (dd, J=3.7, 0.7 Hz, 1H), 3.37 (br t, J=6.3 Hz, 4H), 3.32 (br t, J=6.3 Hz, 4H), 2.34 (s, 3H), 1.66 (s, 9H); δ_C ($CDCl_3$): 151.4, 149.8, 147.8, 138.9, 131.4, 130.2, 129.0, 126.3, 120.9, 117.2, 116.1, 115.6, 113.5, 108.1, 107.3, 83.4, 51.2, 49.7, 28.2, 21.8; MS: $[M+H]^+$=392; HRMS (ESI) for $C_{24}H_{30}N_3O_2$ $[M+H]^+$ calcd: 392.2338, found: 392.2332.

4.4.28. tert-Butyl 5-(benzylamino)-1H-indole-1-carboxylate (Table 10, entry 6)

tert-Butyl 5-bromo-1*H*-indole-1-carboxylate (296.2 mg, 1 mmol) and benzylamine (128.6 mg, 1.2 mmol). Eluent for column chromatography: first heptane/EtOAc (98/2), then heptane/EtOAc (90/10). Yield 29% (92.5 mg); yellow solid; mp 55.6–56.4 °C. δ_H ($CDCl_3$): 7.90 (d, J=8.3 Hz, 1H), 7.50 (d, J=3.4 Hz, 1H), 7.42–7.38 (m, 2H), 7.37–7.30 (m, 2H), 7.29–7.24 (m, 1H), 6.76 (d, J=2.2 Hz, 1H), 6.69 (dd, J=8.8, 2.4 Hz, 1H), 6.39 (dd, J=3.7, 0.7 Hz, 1H), 4.37 (s, 2H), 3.96 (br s, 1H), 1.65 (s, 9H); δ_C ($CDCl_3$): 149.9, 144.4, 139.8, 131.7, 128.6, 127.6, 127.2, 126.1, 115.8, 112.5, 107.1, 103.0, 83.1, 49.1, 28.3; MS: $[M+H]^+$=323; HRMS (ESI) for $C_{20}H_{23}N_2O_2$ $[M+H]^+$ calcd: 323.1760, found: 323.1765.

4.4.29. tert-Butyl 5-(hexylamino)-1H-indole-1-carboxylate (Table 10, entry 7)

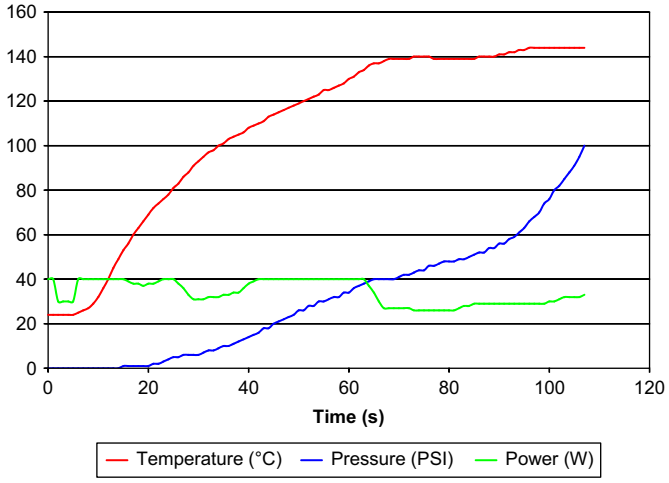
tert-Butyl 5-bromo-1*H*-indole-1-carboxylate (296.2 mg, 1 mmol) and hexylamine (121.4 mg, 1.2 mmol). Eluent for column

chromatography: CH_2Cl_2/heptane (70/30). Yield 13% (41.2 mg); yellow solid; mp 53.6–54.6 °C. δ_H ($CDCl_3$): 7.89 (d, J=7.7 Hz, 1H), 7.48 (d, J=3.3 Hz, 1H), 6.73 (d, J=2.3 Hz, 1H), 6.64 (dd, J=8.8, 2.3 Hz, 1H), 6.41 (d, J=3.4 Hz, 1H), 3.48 (br s, 1H), 3.14 (t, J=7.1 Hz, 2H), 1.68–1.59 (m, 11H), 1.46–1.29 (m, 6H), 0.90 (t, J=6.9 Hz, 3H); δ_C ($CDCl_3$): 149.9, 144.7, 131.7, 128.5, 126.0, 115.7, 112.5, 107.0, 102.8, 83.1, 45.0, 31.7, 29.6, 28.2, 26.9, 22.7, 14.1; MS: $[M+H]^+$=317; HRMS (ESI) for $C_{19}H_{29}N_2O_2$ $[M+H]^+$ calcd: 317.2229, found: 317.2232.

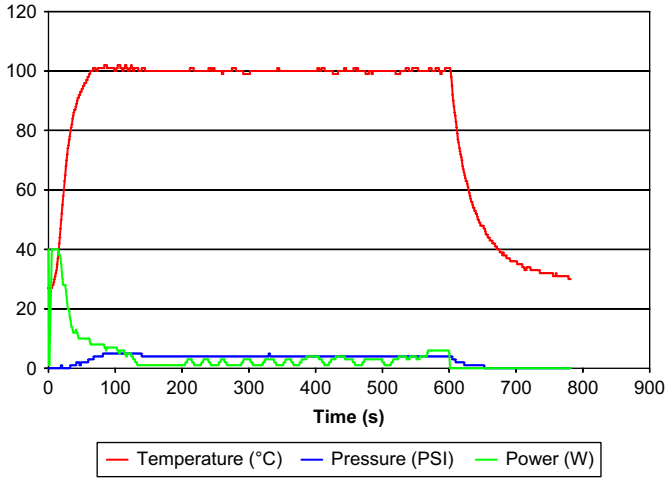
4.5. Additional info

4.5.1. Heating, pressure and power profile for some hydrolysis experiments

Hydrolysis of 4-chlorobenzonitrile at a set temperature of 150 °C (Table 1, entry 1).

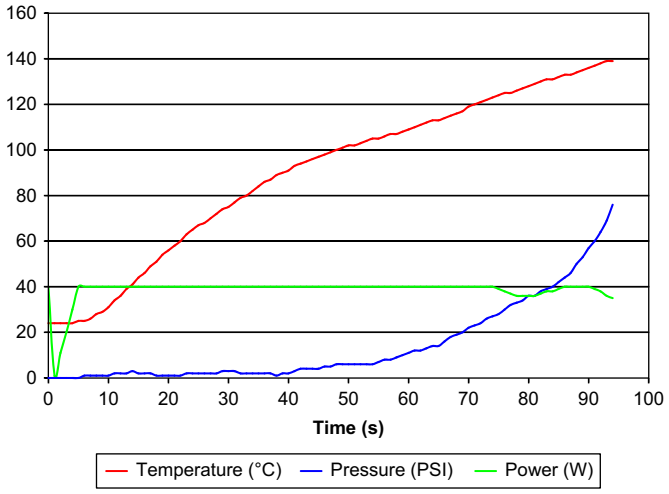


Hydrolysis of 4-chlorobenzonitrile at a set temperature of 100 °C (Table 1, entry 3)

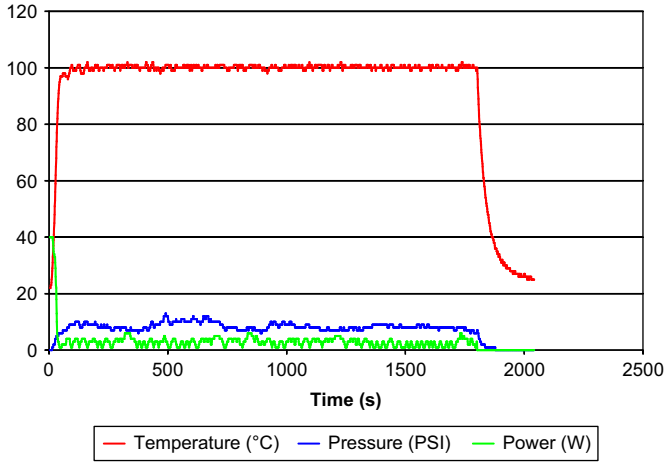


4.5.2. Heating, pressure and power profile for some Buchwald–Hartwig reactions

Buchwald–Hartwig reaction of 4-chlorobenzonitrile with morpholine at a set temperature of 150 °C.



Buchwald–Hartwig reaction of 4-chlorobenzonitrile with morpholine at a set temperature of 100 °C (Table 5, entry 1).



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22. While our work was in progress, Poondra and Turner reported that for intramolecular Buchwald–Hartwig reactions of *N*-alkyl-2-(2-halophenyl)acetamides also no PTC was required. A mixture of toluene and 2 equiv NaOH in water (1:1) was used as the reaction medium at 100 °C (μW). See Poondra, R. R.; Turner, N. J. *Org. Lett.* **2005**, *7*, 863 Also when using solid KOH as base in toluene no PTC seems to be required. This has been shown by Buchwald for one intermolecular Pd-catalyzed amination namely the coupling of 4-chlorotoluene with morpholine. See: Zim, D.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 2413.
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