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Microwave-Promoted Selective Mono-N-Alkylation of Anilines with Tertiary Amines by Heterogeneous Catalysis

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Alkyl anilines are valuable intermediates broadly used in the chemical industry for the manufacture of pharmaceuticals, dyestuffs, synthetic rubbers, herbicides, insecticides and agrochemicals.^[1] Traditional routes for their preparation require N-alkylation of anilines with alkyl halides^[2] in the presence of a base, palladium/copper-catalysed amination^[3] of aryl halides or the more popular reductive amination of carbonyl compounds.^[4] Few of these procedures are truly catalytic. On the other hand, many proceed under harsh reaction conditions, use hazardous reagents and produce large amounts of byproducts.

Recently, Beller et al.^[5a-c] and Williams et al.^[6] independently described *trans* alkylation between amines under homogeneous Ru or Ir catalysis in the presence of different and sometimes complex ligands.^[7] This quite unusual reaction, although prefigured by Murahashi et al.^[8a] in the 1980s, is highly relevant because it opens new possibilities for the selective functionalisation of amines by other simple amines (Scheme 1). Herein, we report a microwave-promoted, selective monoalkylation of aromatic amines with secondary and tertiary aliphatic amines as alkylating agents, cata-



Williams's procedure: 1 mol% Silvo catalyst, *ten*-amyraiconol, 150 °C, 24 Williams's procedure: 1 mol% [{IrCpl₂}], xylene, 155 °C, 10 h

Scheme 1. Homogeneous *trans* amination of substituted anilines with aliphatic amines.

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lysed by Pd/C, to provide the corresponding *N*-alkylaryl amines.

The approach, based on an easily recyclable, heterogeneous catalyst,^[9] shows several fundamental improvements with respect to the previously reported processes: 1) Pd/C is inexpensive and readily available; 2) the catalyst can be recovered by simple filtration; 3) an extremely low contamination of the product by residual Pd is expected and 4) degassing of the solvent is not necessary.^[10] Furthermore Pd/C does not require additional ligands that could become potential contaminants or produce unwanted side products.

In this context, microwave heating^[11] is an attractive tool that has recently been used in organic synthesis to make palladium-catalysed reactions^[12] more economic and soft.

As a starting point of our investigations, we explored the amination reaction of aniline with three structurally different alkyl amines that could act as good alkylating agents: *n*-propylamine, di-*n*-propylamine and tri-*n*-propylamine (Table 1, entries 1–3). The reactions were performed by treating aniline with an excess of alkylamine in the presence of Pd/C (10%) in dry toluene under various conditions. The results are summarized in Table 1.

We observed good alkyl transfer with secondary amines (Table 1, entry 2) and an almost quantitative conversion with tertiary amines (Table 1, entry 3), whereas with primary amines (Table 1, entry 1) the reaction did not proceed and only starting materials were recovered. Particularly noteworthy is the alkyl transfer of tertiary amines.

The secondary amine product was exclusively observed at the end of the reaction without any contamination of *N*,*N*dialkylated aniline or other products coming from scrambling of the groups around the nitrogen. The best ratio of reactants is 1.5 equiv of tertiary amine to 1 equiv of aniline in the presence of 1.5 mol% of Pd/C (10%). Upon increasing the trialkylamine/aniline ratio, only a statistical rise of the internal pressure was observed, without any enhancement in the reaction yields (Table 1, entry 4).^[13]

Regarding the influence of the temperature, the best yield of *N*-propylaniline (92%, Table 1, entry 3) was obtained at $175 \,^{\circ}$ C, whereas at higher temperatures no appreciable in-

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Table 1. Arylation of aliphatic amines: optimisation of the reaction conditions.



Entry ^[a]	\mathbf{R}, \mathbf{R}^1	Solvent	T [°C]	Yield ^[b] [%]
1	$R, R^1 = H$	toluene	175	_
2	$R = Pr, R^1 = H$	toluene	175	56
3	$\mathbf{R}, \mathbf{R}^1 = \mathbf{Pr}$	toluene	175	92
4	$\mathbf{R}, \mathbf{R}^1 = \mathbf{Pr}$	toluene	175	94 ^[c]
5	$\mathbf{R}, \mathbf{R}^1 = \mathbf{Pr}$	toluene	210	93
6	$\mathbf{R}, \mathbf{R}^1 = \mathbf{Pr}$	toluene	155	77
7	$\mathbf{R}, \mathbf{R}^1 = \mathbf{Pr}$	THF	175	82
8	$\mathbf{R}, \mathbf{R}^1 = \mathbf{Pr}$	tBuOH	175	71
9	$\mathbf{R}, \mathbf{R}^1 = \mathbf{Pr}$	neat	175	-
10	$\mathbf{R}, \mathbf{R}^1 = \mathbf{Pr}$	toluene	175	41 ^[d]
11	$\mathbf{R}, \mathbf{R}^1 = \mathbf{Pr}$	toluene	175	49 ^[e]

[a] Reaction conditions: aniline (2.0 mmol), alkyl amine (3.0 mmol), 10% Pd/C (1.5 mol%), solvent (2.5 mL), 1.5 h. [b] Yield of isolated product after column chromatography is based on the amount of starting aniline. [c] Reaction performed by using a 1/3 molar ratio of aniline/tri-*n*-propylamine. [d] Reaction carried out by using palladium black instead of Pd/C. [e] Reaction performed in a preheated oil bath at 175 °C, isolated yield after 2 h.

crease in yield was observed (93%; Table 1, entry 5). On the contrary, working at temperatures below 160°C, reduces the reactivity and conversion (77%; Table 1, entry 6). The aniline alkylation reaction proceeds to completion much more rapidly in non-polar than in polar solvents, and the best conversions were observed in dry toluene (Table 1, compare entries 4, 7 and 8).

Safety issues were encountered under solvent-free conditions (Table 1, entry 9). A quick pressure rise was detected due to extreme microwave absorption with the risk of explosion ("thermal runaway").^[14] The use of palladium black as a catalyst was significantly less effective than palladium on charcoal (Table 1, entry 10).^[15]

To compare microwave irradiation with conventional oilbath heating, the reaction was reproduced at the same temperature in a preheated oil bath. After 2 h, the conversion was low (49%, Table 1, entry 11) and the process went to completion only after 12 h.

To make the protocol highly valuable for economic and environmental concerns, the possibility of recycling the catalyst was also investigated. The reusability of the Pd/C catalyst was tested for the coupling of aniline with tri-*n*-propylamine in toluene at 175 °C. The catalyst was recovered and reused in up to five consecutive cycles^[16] (Table 2), without showing any loss of efficiency.^[17] To ascertain the heterogeneity of the catalyst, further leaching studies were carried out.^[18] Both "Sheldon's hot-filtration test"^[19] and atomic absorption spectroscopy analysis (ICP-MS)^[20] of the filtrate showed only negligible amounts^[21] of leached Pd in the reaction medium, suggesting that the described process is heterogeneously catalysed.^[22] Table 2. Reaction of aniline with tri-*n*-propylamine using recovered Pd/C.

Cycles ^[a]	Yield [%] ^[b]
1	92
2	90
3	89
4	90
5	92

[a] Reaction conditions: aniline (2 mmol), tri-*N*-propylamine (3 mmol), 10% Pd/C (1.5 mol%), toluene (2.5 mL), 175 °C, 1.5 h. [b] Yield of isolated product after column chromatography is based on the amount of starting aniline.

Once the reaction conditions were optimised, the process was extended to other commercially available tertiary amines (Table 3). The reaction was concluded to be useful for general applications and to proceed essentially to completion.

Table 3. Selective monoalkylation of aromatic amines catalysed by Pd/C.

	$\begin{array}{c} R' \\ NH_2 \end{array} + \begin{array}{c} R \\ N \\ R \end{array}$	Pd/C, Toluene, 175 °C, 1.5 h MW	N R
		-NHR ₂	
Entry ^[a]	R	\mathbf{R}^1	Yield [%] ^[b]
1	Pr	Н	92
2	Bu	Н	93
3	hexyl	Н	95
4	$Bn^{[c]}$	Н	41
5	Pr	4-Me	94
6	octyl	4-Me	96
7	Pr	3-Me	91
8	Pr	2-Me	92
9	hexyl	2-Me	94
10	Et	4-OMe	93
11	hexyl	2-OMe	95
12	Pr	2-tBu	66
13	Pr	4-F	40
14	Pr	2-F	31
15	Pr	3-CF ₃	57
16	Et	$4-NO_2$	_
17	Et	4-CN	-

[a] Reaction conditions: aniline (2 mmol), tri-alkylamine (3 mmol), 10% Pd/C (1.5 mol%), toluene (2.5 mL), 175 °C, 1.5 h. [b] Yield of isolated product after column chromatography is based on aniline residue. [c] Bn = benzyl.

Among the trialkylamines used as alkylating agents, tribenzylamine was the least reactive one (Table 3, entry 4). The coupling with aniline was also found to be incomplete after a much longer reaction time. Although *N*-benzylaniline was recovered in a poor yield (41%), the reaction was still highly selective towards monoalkylation.

To investigate the scope and limitations of this procedure, a wide range of structurally different anilines and symmetric tertiary amines were tested. These results are summarized in Table 3. The substitution pattern of the aromatic ring influences the nucleophilicity of the amino group and as a consequence also the yields. We observed that mono-N-alkylation

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of activated and electron-rich aniline derivatives, such as o/m/p-toluidine and o/p-anisidine, proceeded smoothly and selectively to give the corresponding mono-N-alkylated aniline derivatives in nearly quantitative yields (Table 3, entries 5–11).

Even the amination of aniline with a sterically hindered substituent at the *ortho* position was found to be effective, although a lower yield (66%; Table 3, entry 12) was observed. The alkyl transfer reactions with o/p-halogenated anilines were more problematic and gave only low yields (Table 3, entries 13 and 14). The reaction of 3-trifluoro-methylaniline with trihexylamine (Table 3, entry 15) yielded the alkylated aniline in a moderate yield (57%).

The amine coupling of 4-nitroaniline and 4-aminobenzonitrile (Table 3, entries 16 and 17) with different trialkylamines showed no reaction even at higher temperatures or increasing reaction times.

Finally, we explored the coupling of aniline with a set of unsymmetrical tertiary amines; the results are summarized in Table 4. In general, the reaction of *trans* alkylation gives rise to a mixture of two *N*-alkylanilines (**1** and **2**, Table 4), in

Table 4. N-Alkylation of aniline with unsymmetrical tertiary amines.

$\mathbb{NH}_{2} \stackrel{R}{\underset{NH_{2}}{\overset{R}{\overset{N}}}} \mathbb{R}^{R}$		Pd/C, Toluene, 175 °C, 1.5 h ────► MW		$\bigcup_{\substack{N, R \\ H}} + \bigcup_{\substack{N, R^1 \\ 2 \\ H}} + \frac{1}{2} + $	
Entry ^[a]	R	\mathbf{R}^1	1 [%]	2 [%]	Yield [%] ^[b]
1	Bu	Me	75	25	76
2	Me	Bu	45	55	71
3	Bu	Et	77	23	78
4	Et	Bu	42	58	73
5	iPr	Me	_	100	59
6	Me	<i>i</i> Pr	100	-	70

[a] Reaction conditions: aniline (2 mmol), tri-*n*-propylamine (3 mmol), 10% Pd/C (1.5 mol%), toluene (2.5 mL), 175 °C, 1.5 h. [b] Yield of isolated product after column chromatography is based on aniline residue.

which the major component is the *N*-alkylaniline with the longest linear carbon chain bonded to the nitrogen atom. For example, in the case of the reaction of aniline with *N*,*N*-dimethylbutylamine (Table 4, entry 1) or *N*,*N*-dibutylmethylamine (Table 4, entry 2), both the butyl and methyl groups were transferred even if *N*-butylaniline was always obtained as the major product. When *N*,*N*-dimethylisopropylamine or *N*,*N*-diisopropylmethylamine were used (Table 4, entries 5 and 6) only methyl-group transfer occurred.

With regard to the mechanism of this reaction, we propose that the alkylation of aniline proceeds through a hydrogen-borrowing pathway, as previously postulated by the groups of Murahashi, Beller and Williams (Scheme 2).^[5,6,8] Palladium is inserted into the carbon–hydrogen bond close to the nitrogen of the alkylamine **3**, promoting β -hydride elimination, to give the highly reactive intermediate imminium ion **4**.

Nucleophilic attack by the incoming aniline on the iminium ion 4 forms an unstable aminoaminal 5 with subsequent



Scheme 2. Presumed mechanism for the arylation of tertiary amines.

elimination of the secondary amine 6. In the last step, the starting Pd/C catalyst is regenerated and gives the desired secondary aniline product 8.

In conclusion, we have developed a palladium-catalysed N-alkylation of anilines with tertiary amines that occurs under transfer-hydrogenation conditions. The reactions proceed smoothly and efficiently to give the corresponding *N*-alkylanilines in good to excellent yields.

Experimental Section

N-Propylaniline (Table 3, entry 1): 10% Pd/C (0.032 g, 0.03 mmol, 1.5 mol $\%\,$ relative to aniline), freshly distilled aniline (0.186 g, 182.5 $\mu L,$ 2.0 mmol), freshly distilled tri-n-propylamine (0.430 g, 571 µL, 3 mmol) and dry toluene (2.5 mL) was added to an argon-filled 10 mL pressure-resistant vial equipped with rubber septum and an aluminium cap. The mixture was put in the microwave apparatus (CEM Discover, 2.45 GHz,) and irradiated at 175°C with stirring. After 1.5 h the reaction vessel was cooled to room temperature and the palladium catalyst was filtered off. The solvent was removed in vacuo and the crude product was easily purified by column chromatography with hexane/ethyl acetate (95/5) to afford N-propylaniline as a pale yellow liquid (0.250 g, 1.84 mmol, 92%). The analytical values agree well with the literature. ¹H NMR (300 MHz, CDCl₃): $\delta = 7.23 - 7.16$ (m, 2H), 6.74-6.68 (m, 1H), 6.64-6.61 (m, 2H), 3.64 (brs, 1H), 3.10 (t, J=7.2 Hz, 2H), 1.67 (sextuplet, J=7.5 Hz, 2H), 1.02 ppm (t, J = 7.5 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): $\delta = 148.7$, 129.4, 117.3, 112.9, 46.0, 23.0, 11.9 ppm; HRMS: *m/z* calcd for [C₉H₁₃NH]⁺: 136.1126; found: 136.1118.

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- [15] Although palladium black has been widely used as a heterogeneous catalyst in the N-alkylation of amines by amines, in our case the yields were generally low or modest and required a very high percentage of the heterogeneous catalyst. Moreover, the yields depend on the supplier of the palladium black and are difficult to reproduce.
- [16] After the first run, the catalyst was separated by simple vacuum filtration, washed twice with dry toluene and dry THF and dried at 50 °C under vacuum for 4 h. The same procedure was repeated, as for the initial run, for all further cycles.
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- [19] After 45 min, the reaction was stopped and the filtrate, obtained after the removal of the solid catalyst, was irradiated at 175 °C for another 45 min. After separation of the heterogeneous catalyst no conversion was observed in the filtrate.
- [20] The filtrate obtained after hot filtration of the reaction mixture was evaporated under reduced pressure. A mixture of concentrated H_2SO_4 (3 mL) and fuming HNO₃ (2 mL) was added to the residue. This mixture was heated in a fume hood until the nitric fumes disappeared. After cooling to 100 °C, fuming HNO₃ (2 mL) was added, the mixture was heated until evaporation of HNO₃ and this process was repeated three times. Most of the H_2SO_4 was then boiled off and after cooling, a solution of concentrated HCl (2 mL) and concentrated HNO₃ (2 mL) was added and heated until to complete evaporation. The residue was then dissolved in H_2O (24 mL) and the amount of Pd present in this solution was then determined by ICP-MS; see reference [18d].
- [21] Less than 1 ppm leached Pd existed in the filtrate after catalyst removal.
- [22] In a subsequent study, the same model reaction was performed using several soluble palladium catalysts (both Pd with a high oxidation state (Pd^{II}) and Pd with a low oxidation degree (Pd⁰)) instead of heterogeneous Pd/C under standard condition. No reaction with [Pd(PPh₃)₄], [PdCl₂(PPh₃)₂] or di- μ -chlorobis{5-chloro-2-[(4-chlorophenyl)(hydroxyimino- κ N)methyl]phenyl- κ C}palladium dimer was observed and low conversion (23%) with Pd(OAc)₂. All these results, taken as a whole, support the hypothesis that the palladium on charcoal (in this process) is a heterogeneous catalyst.

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