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FULL PAPER

Heterogeneous catalyzed chemoselective reductive amination of halogenated aromatic aldehydes

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Abstract: The chemoselective conversion of a specific functional group in a multifunctional substrate is of great importance in the chemical industry to obtain cost efficient, sustainable and waste free processes. This work focuses on the chemoselective amination of halogenated aromatic aldehydes with dimethyl amine towards halogenated aromatic amines, a raw material used in the production of f.e. agrochemical active ingredients. It was found that by combining palladium, a metal known for dehalogenation reactions, and copper, known for its direct hydrogenation of aldehydes to alcohols, in one heterogeneous bimetallic catalyst, a synergistic effect is obtained. By depositing copper onto a palladium on carbon catalyst with a Cu/Pd ratio of at least 1:1, the yield could be increased from 66 % (Pd/C) to 98 % (PdCu/C). Moreover, this highly active and stable catalyst also showed suppressed dehalogenation side-reactions in several other chemical conversions such as hydrogenation of nitro functional groups and hydrogenation of aldehydes.

Introduction

The transformation of a specific functional group in a multifunctional substrate is of great importance in the chemical, pharmaceutical and agrochemical industry.[1] Halogen atoms are often used as reactive groups next to other functional groups in precursors and intermediates for active ingredients which can be easily transformed via different (chemical) methods. Chemoselective hydrogenation reactions of various functional groups in the presence of halogens are therefore widely discussed. Several methods are described for enhancing this selectivity in the hydrogenation of aldehydes/ketones,[2] aromatic rings,[3] carboxyl groups,[4] nitrile groups,[5] nitro groups,[6] quinoline components[7] and olefins[8] while concurrent dehalogenation reactions are suppressed. However, limited research was done to develop a chemoselective route for the catalytic (reductive) amination in the presence of a halogen atom, despite the importance of this class of compounds in different applications.[9] Some examples of (reductive) amination reactions of halogenated substrates could be found when the substrate scope of a newly developed catalytic method was broadened,[6a, 6b, 10] but limited research really had the intention to find and optimize an industrially feasible route towards halogenated amines through a (reductive) amination reaction. Hizartzidis et al. utilized flow chemistry in combination with a Pt/C catalyst to increase the chemoselectivity of the reductive amination of halogenated benzaldehydes but low throughputs were achieved.[11] In previously reported research we changed the properties of a palladium on carbon catalyst by calcination in order to decrease the amount of dehalogenation reactions.[12] Although good yields were obtained with this method, diluted conditions were used which limit the industrial feasibility of this route due to increasing solvent recuperation costs. Moreover, besides dehalogenation reactions, several other side reactions can occur such as direct hydrogenation of the aldehyde or substitution of the halogen by the amination agent. These side products also complicate the industrial process and increase purification costs. The research reported in this paper focuses on the modification of the metal catalyst composition as a way to achieve an industrially applicable reductive amination process for halogenated aldehydes.

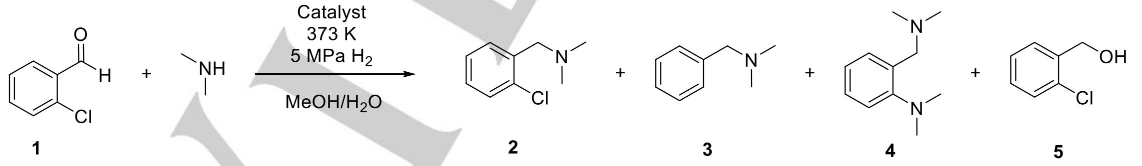
Results and Discussion

In exploratory experiments, we selected the reductive amination of 2-chlorobenzaldehyde (**1**) with dimethyl amine to the corresponding 2-chlorobenzyl N,N-dimethyl amine (**2**) as the model reaction to study the activity and selectivity of different catalysts for the chemoselective reductive amination of halogenated benzaldehydes. Obtaining compound **2** without the C-X bond cleavage (by hydrogenolysis) and direct hydrogenation of the aldehyde is of high importance as both the amine and the halogen functional group are further utilized for f.e. the synthesis of chloromethylphenylglyoxylic esters, an important intermediate for the production of agrochemical active ingredients.[13]

First, a variety of commercially available heterogeneous metal catalysts were screened to investigate their impact on both the dehalogenation reaction (yielding **3**), substitution reaction (yielding **4**) and the direct hydrogenation reaction (yielding **5**). The amine to 2-chlorobenzaldehyde ratio was kept constant (unless mentioned otherwise) and a catalyst amount of 2 wt.% was used regardless of the metal loading. Either methanol or water were used as solvent. It has to be mentioned however that, since water is liberated in the amination reaction, water will influence the equilibrium of the intermediary iminium ion/hemi-aminal formation and thus potentially affect the overall reaction rate. Since the reaction was ran in almost all cases to complete conversion, the effect of water onto the overall reaction rate, could not be assessed. Both the conversion of the aldehyde and the molar yields of the different formed reaction products were calculated based on GC data. The screening results are summarized in Table 1 and Table S1. The data obtained shows some clear trends between the choice of the metal in the catalyst and the yields of the main and side products. Most catalysts (except Raney® Co) show almost complete conversion after 3 hours reaction time. While the catalysts based on palladium (Entry 1 and 2, Table 1) show a lot of dehalogenation activity, both copper catalysts (Entry 9 and 10, Table 1) and platina catalysts (Entry 5 and 6, Table 1) lead to more aldehyde hydrogenation reactions yielding the alcohol **5**. In this series of tested catalysts, only the nickel-based catalysts (Entry 7, Table 1) show a high tendency of both the dehalogenation reaction and the aldehyde hydrogenation reaction towards the alcohol.

Interestingly, it was observed that when a palladium on carbon catalyst was used after a run with a copper sponge catalyst (Entry 11, Table 1), less dehalogenation reaction was observed in comparison with runs with a ‘clean’ palladium catalyst (Entry 1 and 2, Table 1). Postmortem analysis of this catalyst showed besides palladium, also copper onto the activated carbon support. It is believed that Cu(II) salts were left behind onto the reactor surface due to leaching of the sponge copper catalyst. When the palladium on activated carbon was used, these salts adsorbed onto the catalyst surface forming a bimetallic palladium-copper catalyst. When using this bimetallic catalyst which contained both palladium, a metal with a high tendency for dehalogenation reactions and copper, a metal with a high tendency for aldehyde hydrogenation reactions, both side reactions are suppressed simultaneously. This synergistic effect between Pd and Cu is reported earlier in several different type of reactions with halogenated substrates but was unprecedented for reductive amination reactions. Goulas et al. reported Pd-Cu alloy formation in a bimetallic Pd-Cu on hydrotalcite-carbon (HT-C) catalyst which increased the selectivity in oxygenate coupling reactions.[14] Bonarowska showed the effect of copper addition to supported palladium on the catalytic performance on hydroisomerization of n-pentane. Again, Pd-Cu alloy formation was seen as the main reason for the improved selectivity.[15]

Table 1. *Hydrogenation of 2-chlorobenzaldehyde under different conditions*^{a}



Entry	Catalyst	Solvent	t (h)	Conversion (%)	Yield 2 (%)	Yield 3 (%)	Yield 4 (%)	Yield 5 (%)
1a	3 % Pd/C	H_2O	2	>99	64	21	8	<1
1b	3 % Pd/C^b	H_2O	2	>99	70	15	10	<1
2a	0.5 % Pd/C	H_2O	2	>99	62	35	<1	<1
2b	0.5 % Pd/C	MeOH	2	>99	69	28	<1	<1
3	5 % Pd-Pb/CaCO3	H_2O	5	>99	88	<1	3	3
4	5 % Ru/C	H_2O	3	>99	47	1	13	20

5	3 % Pt/C	H_2O	3	>99	72	1	7	10
6	5 % Pt/C	H_2O	3	>99	82	<1	1	8
7a	Raney® Ni	H_2O	3	>99	9	1	1	50
7b	Raney® Ni + borax	H_2O	3	>99	52	7	1	28
7c	Raney® Ni + HAc	H_2O	3	>99	64	13	1	9
8	Raney® Co	H_2O	6	89	10	1	15	23
9	Raney® Cu 2900	H_2O	3	98	80	<1	7	8
10a	Sponge Cu (A3B00)	H_2O	3	>99	86	<1	<1	13
10b	Sponge Cu (A3B00)	MeOH	3	>99	91	<1	<1	7
11a	3 % Pd/C + traces sponge Cu	H_2O	3	>99	92	4	<1	1
11b	3 % Pd/C + traces sponge Cu	MeOH	3	>99	93	3	<1	<1

[a] Reaction conditions: T = 373 K; 5 MPa H_2 pressurized at room temperature; 1.5 h reaction time; 1 g solvent/g o-Cl-BZA; 1.5 eq. dimethyl amine; 2 wt.% catalyst
[b] 3 eq. dimethyl amine

***Table 2**. Effect of the metal ratio and support of Pd-Cu catalysts on the reductive amination of **1** with dimethyl amine*[a,b]

Entry	Catalyst	Pd (%)	Cu (%)	Metal area (m²/g)	Conversion (%)	Yield 2 (%)	Yield 3 (%)	Yield 4 (%)	Yield 5 (%)
1	Pd/C[c]	2.95	n/a	15.0	>99	66	19	8	0.2
2	Pd-Cu_1/C[c]	2.94	1.85	6.8	>99	98	1	0.1	0.2
3	Pd-Cu_2/C[c,e]	2.86	3.55	3.0	>99	98	0.8	0.2	0.4
4a	Pd-$Cu_{4.2}$/C[c,f]	2.63	6.50	4.0	>99	99	0.2	0.3	0.4
4b	Pd-$Cu_{4.2}$/C[d]	0.90	3.80	n.d.	>99	99	<0,1	0.2	0.4
5	Pd-$Cu_{8.4}$/C[c,e]	2.36	11.82	3.3	>99	99	0.4	0.2	0.4
6	Pd-$Cu_{4.2}$/alumina[c]	n.d	n.d.	n.d.	>99	90	6	1	4
7	Pd-$Cu_{4.2}$/silica[c]	n.d	n.d.	n.d.	>99	96	2	0.8	2

[a] Reaction conditions: T = 373 K; 7 MPa H_2 pressurized at room temperature; 1.5 h reaction time; 0.3 g MeOH/g o-Cl-BZA; 1.5 eq. dimethyl amine; 0.5 mg catalyst/g substrate
[b] n.d. = not determined
[c] a Pd loading of 3 wt.% is used
[d] a Pd loading of 1 wt.% is used
[e] average of two experiments
[f] average of four experiments

Encouraged by these results, several different bimetallic palladium/copper catalysts on activated carbon were prepared on purpose using the precipitation method starting from a pre-made palladium on carbon catalyst (unless mentioned otherwise) and copper nitrate. All reactions were performed in MeOH at 100 °C and 7 MPa hydrogen atmosphere. In view of the catalyst application, research was first done on finding the optimum activation procedure for the bimetallic Pd-Cu/C catalysts since Cu(II) species will be present in a freshly synthesized catalyst. The results are given in Table 4S. It was seen that by activating the catalyst in methanol at 180 °C under a 3 MPa hydrogen atmosphere, the highest yield towards the wanted compound **2** was obtained. It is believed that this activation procedure will allow the reduction of all the Cu(II) species into the active Cu(0) species to have a better interaction between the palladium-copper particles and thus minimize dehalogenation reactions. Performing a reductive amination experiment with a non-activated Pd-$Cu_{4.2}$/C catalyst already gives lower amounts of dehalogenation reaction compared to a Pd/C catalyst (Entry 1a, Table 4S versus Entry 1, Table 2). Together with the observation that a second consecutive run with a non-activated Pd-$Cu_{4.2}$/C catalyst results in a lower amount of dehalogenation reaction compared to a first run (Entry 1a and 1b, Table 4S), it is believed that even at the reaction temperature, part of the Cu(II) species can be reduced towards Cu(0) and therefore, already have beneficial effects on suppressing the dehalogenation reactions. Roma et al. have indeed showed that the reduction of Cu(II) species is facilitated in the presence of Pd.[16] The results of the reductive amination reactions with different bimetallic Pd-Cu/C catalysts are given in Table 2 and Table S2. While a monometallic Pd on carbon catalyst resulted in a large amount of dehalogenation reaction (Entry 1, Table 2), switching to a catalyst composed of a 1:1 Pd:Cu molar ratio suppressed the dehalogenation reactions significantly (Entry 2, Table 2). Increasing the Cu amount to an atomic ratio of 4.2 even lowered the dehalogenation reaction down to 0.2 % resulting in a yield of 99 % towards the desired halogenated amine **2**. Although pure Cu catalysts result in significant amounts of direct aldehyde hydrogenation reactions, this was not the case when combined with Pd.

To better understand the effect of the copper addition on the catalytic activity, the morphology of selected Pd-Cu catalysts was investigated by using transmission electron microscopy (TEM) and X-Ray diffraction (XRD). TEM showed that the average particle size of all Pd-Cu/C catalysts are in the range of 3-4 nm with a narrow particle size distribution for Pd-Cu_2/C (Figure S1b), whereas for Pd-$Cu_{4,2}$/C also particles larger than 10 nm were detected (Figure S2b). STEM-EDX analysis of Pd-Cu_2/C confirmed the presence of Pd and Cu with an average Pd:Cu content of 3.07%-3.34% (Figure S1C, spectrum 2) similar to the nominal one of 2,86%-3,55% (Entry 3, Table 2). However large aggregates (Figure S1C, spectrum 3) enriched in Pd were detected. STEM-EDX analysis of Pd-$Cu_{4.2}$/C showed a lower content of Cu compared to the nominal one (calculated Pd-Cu of 3.12%- 5.47%; nominal of Pd-Cu of 2.63%- 6.50%). XRD was also performed on Pd-Cu_2/C and Pd-$Cu_{4.2}$/C to understand the nature of the catalyst. XRD pattern showed the presence of a bimetallic structure (alloy) but also the presence of segregated Pd and Cu species (Figure S3).

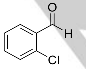
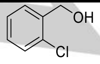
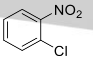
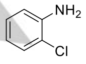
Besides copper, it is known that other metals can also form an alloy when combined with palladium and beneficial effects of this alloying in hydrogenation reactions have been observed for f.e. Pd-Ag,[17] Pd-Au,[17d, 18] Pd-Ru,[6c, 18b, 19] Pd-Zn,[20] Pd-Pb,[21] Pd-Re,[22] etc. In order to investigate the potential of other bimetallic palladium on carbon catalysts in the chemoselective reductive amination of halogenated aldehydes, several different Pd-metal catalysts were prepared and tested in the benchmark reductive amination reaction shown in Table 1. Similar catalyst synthesis procedures and reduction procedures were used as for the Pd-Cu catalysts. The results are given in Table 3 and Table S3. The molar ratio of the second metal is given in the subscript. Although none of the tested bimetallic Pd-metal catalysts gives a selectivity as high compared to the tested Pd-Cu alloys (99 %), there are a few other metal combinations that show a significant increased selectivity towards the reductive amination of 2-chloro-benzaldehyde and a reduced level of dehalogenation reactions in comparison with a monometallic Pd on carbon catalyst while maintaining a proper level of activity. A Pd-Ag alloy with a 1:2 atomic ratio could decrease the dehalogenation reactions below 5 % and increase the yield towards the wanted halogenated amine 2 to 94 % (Table 3, Entry 4). A Pd-Re alloy and a Pd-Mo alloy lead to a yield of 2 of respectively 87 % and 93 % (Table 3, Entry 9 and 11). Although very little dehalogenation activity was also seen for Pd-Rh, Pd-Ru, Pd-Pb and Pd-Sn alloys, the yield towards the aminated halogenated product was also very low. Other, unidentified side-products were formed instead. In this Pd based bimetallic catalyst study, a Pd-Cu alloy with an atomic ratio of 1:4.2 gives the best results, both in terms of selectivity and activity.

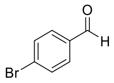
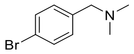
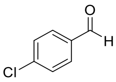
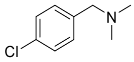
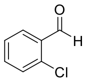
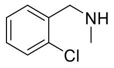
***Table 3**. Effect of a second metal in a bimetallic palladium on carbon catalyst on the reductive amination of **1** with dimethyl amine*[a]

Entry	Catalyst	conversion (%)	Yield 2 (%)	Yield 3 (%)
1	Pd-Fe_2/C	>99	55	35
2	Pd-Ni_2/C	>99	53	37
3	Pd-Co_2/C	>99	53	37
4	Pd-Ag_2/C	98	94	2
5	Pd-Rh_2/C	88	78	2
6	Pd-Ru_2/C	83	23	<1
7	Pd-Pb_2/C	60	27	<1
8	Pd-Sn_2/C	66	13	<1
9	Pd-Re_2/C	95	87	7
10	Pd-Au_2/C	97	82	14
11	Pd-Mo_2/C	97	93	3

[a] Reaction conditions: T = 373 K; 7 MPa H_2 pressurized at room temperature; 0.3 g MeOH/g o-Cl-BZA; 1.5 eq. dimethyl amine; 0.5 mg catalyst/g substrate; 1.5 h reaction time;

***Table 4.** Hydrogenation of alternative substrates with Pd-Cu bimetallic catalyst*[a]

Entry	Substrate	Product	Catalyst	conversion (%)	Yield product (%)	Yield dehalogenated product (%)
1			Pd/C	40	5	21
			Pd-$Cu_{4.2}$/C	37	22	8
2			Pd/C	97	65	33
			Pd-$Cu_{4.2}$/C[b]	11	11	<1
			Pd-$Cu_{4.2}$/C	98	92	7

3			Pd/C Pd-Cu$_{4.2}$/C	>99 >99	<1 81	88 16
4			Pd/C Pd-Cu$_{4.2}$/C	>99 >99	62 96	31 1
5			Pd/C Pd-Cu$_{4.2}$/C	>99 >99	66 95	30 1

[a] Reaction conditions: T = 373 K; 7 MPa H_2 pressurized at room temperature; 0.3 g MeOH/g o-Cl-BZA; 0.5 mg catalyst/g substrate; 1.5 h reaction time;

[b] temp = 50 °C

To show the industrial applicability of the most selective catalyst, the bimetallic Pd-Cu$_{4.2}$/C, the long-term stability was investigated in repeated amination reactions of 2-Cl-benzaldehyde with dimethyl amine. A total of 15 consecutive recycling tests were carried out by reusing the catalyst by filtration without any further intermediate purification or activation. The result of this test, shown in Figure 1, highlights the excellent reusability of this catalytic system. Both selectivity and activity are maintained throughout the consecutive runs. Moreover, Inductively Coupled Plasma (ICP) analysis of the reaction mixtures after each consecutive run revealed no leaching of palladium (< 0.2 ppm) or copper (<0.2 ppm) into the reaction mixture.

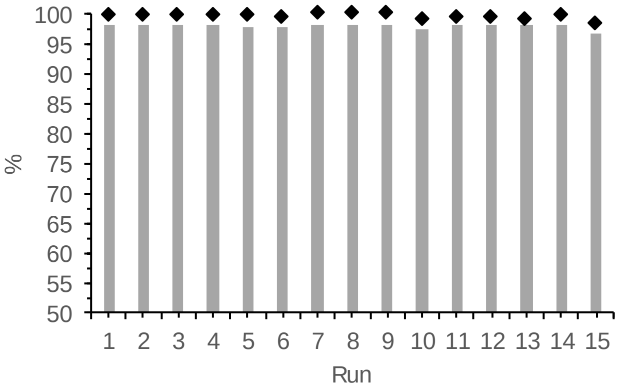


Figure 1. Stability tests using *Pd-Cu$_{4.2}$/C in the amination of 2-Cl-benzaldehyde with DMA*. Conversion: ♦; Yield of **2**: ■

Furthermore, the applicability of the Pd-Cu catalytic system was investigated for other hydrogenation reactions in the presence of a halogen atom such as the hydrogenation of an aldehyde, the hydrogenation of a nitro group and the reductive amination of aldehydes with different amination agents (Table 4). The positive effect of the copper addition to a palladium on carbon catalyst on suppressing the dehalogenation reaction was confirmed in all the cases. Interestingly, with a bromo substituted aldehyde, very prone for dehalogenation, the yield towards the halogenated aminated product could be increased from below 1 % up to 81 % (Table 4, Entry 3) when using a Pd-Cu catalyst instead of a pure Pd catalyst.

Conclusion

In summary, an efficient method was found for the chemoselective reductive amination of halogenated benzaldehyde. By combining palladium, a metal known for dehalogenation reactions and copper, a metal known for the direct reduction of aldehydes, a highly active, selective and stable (15 consecutive runs) catalyst was found for these conversions. The dehalogenation reaction could be suppressed almost completely. Conversions and selectivities as high as 99 % could be obtained in the case of 2-chlorobenzaldehyde and dimethyl amine. Moreover, a clear effect was seen of the Pd:Cu ratio used in the final catalyst on the ratio of the desired reductive amination reaction and the unwanted dehalogenation reaction. When comparing to the other methods used for suppressing the dehalogenation reactions during a reductive amination reactions, the process reported in the current research shows the highest potential for an industrial process due to the high yields and the low amount of solvents needed (in comparison with f.e. the method developed by Villa et al.).[12] Besides reductive amination reactions, it was also shown that this concept can be used for the chemoselective hydrogenation of other substrates such as nitro functional groups or aldehydes in the presence of halogen groups.

Experimental section

Catalyst preparation

The bimetallic Pd/metal on activated carbon catalyst were synthesized starting from a palladium on carbon catalyst (Pd/C), obtained from the company Johnson Matthey. A 10 g L^{-1} aqueous suspension of the Pd/C is stirred continuously while an aqueous mixture of 5 g L^{-1} of the chloride salt of the metal is added slowly to the suspension at ambient temperature. A sodium bicarbonate solution (35 g L^{-1}) is then added dropwise until a pH of 8 is obtained. Hereafter, the catalyst slurry is heated to 70 °C and stirred for 15 minutes. After cooling down, the catalyst slurry is filtered, washed three times with water and dried under vacuum. Prior to the hydrogenation reaction, the catalyst was reduced at 180 °C in MeOH at 3 MPa of hydrogen.

Amination reaction of aldehydes with dimethyl amine/mono methyl amine

In a typical experiment (and unless mentioned otherwise), a 300 mL autoclave (Parr®) was loaded with 90g of an aldehyde obtained from the company Sigma Aldrich, a specific amount of solvent (methanol in most cases) and a certain amount of aminating agent (f.e. dimethyl amine). The reactor was sealed, and the gas phase was flushed three times with nitrogen and then pressurized at 0.5 MPa by the addition of nitrogen gas. The reactor was heated until 80 °C and then continuously stirred for 60 minutes at that temperature. After cooling down, a certain amount of catalyst was added to the autoclave. The autoclave was heated to the reaction temperature and hydrogen was added to the final pressure. After a certain reaction time, the reaction mixture was cooled down and degassed at room temperature. The reductive amination reaction was allowed to proceed for the indicated time at the indicated reaction temperature. Filtration of the reaction mixture was done to separate the liquid reaction mixture from the solid catalyst. Recycling experiments were carried out under the same experimental conditions. After each run, the reaction mixture was removed from the reactor without exposing the catalyst to air and new reagents and solvent were added to the reactor.

Hydrogenation reaction of aldehydes

In a typical experiment (and unless mentioned otherwise), a 300 mL autoclave (Parr®) was loaded with 110g of an aldehyde obtained from the company Sigma Aldrich, a specific amount of solvent (methanol in most cases) and the catalyst. The reactor was sealed, and the gas phase was flushed three times with nitrogen and then pressurized at 0.5 MPa by the addition of hydrogen gas. The autoclave was heated to the reaction temperature and hydrogen was added to the final pressure. After a certain reaction time, the reaction mixture was cooled down and degassed at room temperature. Filtration of the reaction mixture was done to separate the liquid reaction mixture from the solid catalyst.

Hydrogenation of nitro compounds

In a typical experiment (and unless mentioned otherwise), a 50 mL autoclave (Parr®) was loaded with 20g of an nitro compound obtained from the company Sigma Aldrich, a specific amount of solvent (methanol) and the catalyst. The reactor was sealed, and the gas phase was flushed three times with nitrogen and then pressurized at 3 MPa by the addition of hydrogen gas. The autoclave was heated to the reaction temperature and hydrogen was added to the final pressure. After a certain reaction time, the reaction mixture was cooled down and degassed at room temperature. Filtration of the reaction mixture was done to separate the liquid reaction mixture from the solid catalyst.

Purification of compound **2**

After the amination reactions, the reaction mixtures were purified by rectification. The reaction mixture was transferred into a 250 mL Sovirel® reactor equipped with a double jacked heated with thermal oil, a stirrer, a thermocouple and a rectification column containing 20 theoretical plates. A reflux ratio of 4 was used in all cases and distillate samples were taken regularly (every 10 mL).

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Keywords: alloy formation - chemoselectivity - dehalogenation - heterogeneous catalysis - reductive amination

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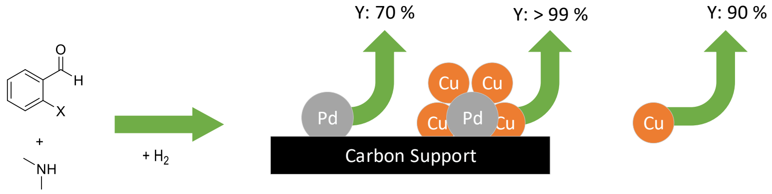

High chemo-selectivity is one of the key parameters for the design of waste free and sustainable chemical processes. This work described the use of a stable bimetallic palladium-copper catalyst for the selective reductive amination of halogenated aromatic aldehydes towards tertiary amines with yields higher than 99 %.