Influence of catalyst type, solvent, acid and base on the selectivity and rate in the catalytic debenzylation of 4-chloro-N,N-dibenzyl aniline with Pd/C and H2

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Abstract

The influence of catalyst type, solvent, and acid/base modifiers on the catalytic debenzylation of 4-chloro-N,N-dibenzyl aniline with Pd/C and H2 was studied. Under the reaction conditions investigated, the catalyst-type had no significant effect. Solvents: In neutral apolar solvents, the over-all reaction was slow and the main product isolated after 1.9 mol H2-uptake was always 4-chloroaniline. No high intermediary concentration of 4-chloro-N-benzyl aniline (monodebenzylation product) was found. In polar solvents, both debenzylation and dehalogenation were much faster. After 1.9 mol H2-uptake, significant amounts of the dehalogenation product aniline were found. Catalytic amounts of strong acids significantly increased the rate for debenzylation and dehalogenation was suppressed. With equimolar amounts of strong acid, the debenzylation was slower, but high intermediary amounts (> 80%) of the monodebenzylation product could be isolated. A kinetic model to rationalize these effects was developed.

Keywords: Catalytic debenzylation; Pd/C; Chemoselectivity; Kinetic analysis; Influence of reaction parameters

1. Introduction
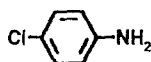
* * * * Should be replaced by Cl-C6H4-NH2. * * * *

N-benzyl groups are important protective groups in organic synthesis [1]. Their removal is in most cases carried out by hydrogenolysis using Pd/C catalysts with H2 as reducing agent. Several problems can be encountered:

- Pd-catalysts are able to hydrogenate many functional groups such as $C = C$, $C \equiv C$, $C \equiv N$, $R-NO_2$, Aryl-Halogen, etc. under mild conditions. Therefore, selective debenzylation is not trivial if such groups are present in the same molecule and should be left untouched [2-4].
- Hydrogenolysis reactions are often slow and require high amounts of catalyst, especially when amines or groups containing sulfur in low oxidation states are present in the same molecule [2-4].

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• Sequential mono-debenzylation of dibenzyl-amines followed by alkylation can be used for the synthesis of amines of the type R–N–R_1R_2 [5]. High selectivity in this reaction sequence is paramount for the success of this strategy.

Even though chemoselectivity and catalyst activity in debenzylation reactions have been the topic of various publications [2–15], there is relatively little known about the selective removal of benzyl groups in molecules containing aromatic halogens [5,6]. Reports of benzylated anilines are scarce and often incomplete [8–10]. The choice of catalyst and solvent as well as the addition of bases or acids were demonstrated to be crucial [2–4,7,15] but never discussed systematically.

4-Chloro-*N,N*-dibenzyl aniline was chosen as a model substrate because with Pd/C and H_2 several interesting parallel reactions are possible. We wanted to investigate (a) the debenzylation of anilines carrying aromatic halogen and (b) the sequential debenzylation of dibenzyl anilines. Our goal was on the one hand to study the effect of reaction parameters (catalyst type, solvent, and acid/base addition) on rate and selectivity for the formation of various intermediates. On the other hand, we were also interested to find conditions, were 4-chloro-*N*-benzyl aniline or 4-chloroaniline could be prepared in high yield with reasonably high rate.

2. Results and discussion

2.1. Reactor and reaction conditions

To keep the experimental setup as simple as possible, all hydrogenations were carried out in glass shakers at ambient temperature (22°C and 25°C) and at low H_2-pressure (1 bar). The concentration of the starting material 4-chloro-*N,N*-dibenzyl aniline was always 5% (w/v), and the catalyst loading was between 0.6% and 6.0% relative to the starting material. The reactions were monitored by measuring the H_2-consumption. In addition, samples were taken during the reaction and analyzed by GLC. The reactions were always stopped after 1.9 mol H_2 had been taken up. Under the reaction conditions studied, 4-chloro-*N*-benzyl aniline, 4-chloroaniline, aniline, *N,N*-dibenzyl aniline and N-benzyl aniline were always the main products. Fig. 1 shows a typical reaction profile (see also Scheme 1).

2.2. Effects of reaction parameters

In the following sections, we will always discuss the maximum concentration of 4-chloro-*N*-benzyl aniline measured during the reaction, the time needed for the uptake of 1.9 mol H_2 and the composition of the reaction mixture after 1.9 mol H_2-uptake. Depending on the reac-
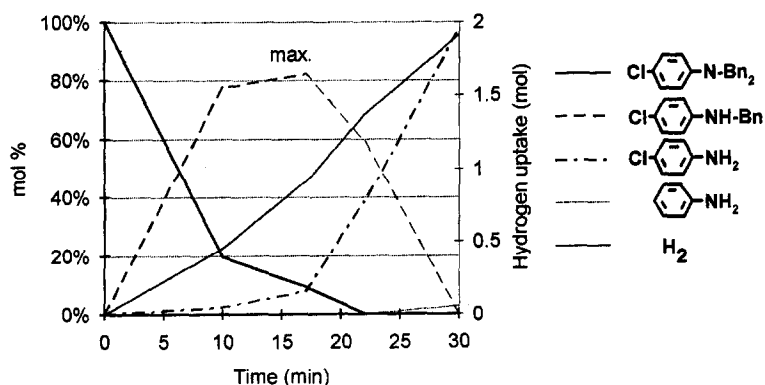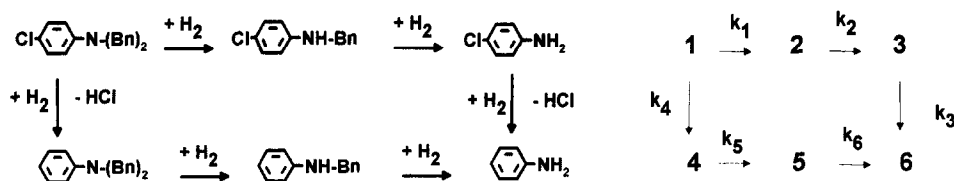

Fig. 1. Typical reaction profile (Exp. 19). Methanol, 1 bar H_2, 0.6% (w/w) 4522 (5% Pd/C), 1 mol/mol H_2SO_4.

Scheme 1. Reaction pathway and scheme used for kinetic analysis.

tion conditions, the above mentioned maximum for 4-chloro-*N*-benzyl aniline was observed between 0.5 and 1.5 mol H_2-uptake. In the experiment shown in Fig. 1, the maximum was observed at about 1 mol H_2.

2.3. Effect of catalyst type

It is well documented that Pd/C catalysts are the most effective ones for debenzylation reactions. However, the catalyst type is known to often have a strong effect on rate and selectivity [11–13]. The following features of Pd/C catalysts are told to be advantageous: Oxidic Pd, eggshell distribution of the Pd on the carrier and high Pd-loading (e.g., Pearlman's catalysts). Accordingly, we chose catalysts where these properties varied using catalysts from several suppliers (see Table 1).

With our substrate and reaction conditions, no significant effect of the catalysts tested was found. The maximum amount of 4-chloro-*N*-benzyl aniline was similar for all catalysts and the product composition after the uptake of 1.9 mol H_2 did not differ much. The reaction rates were also similar for all 5% Pd/C; the Pearl-

man catalyst had the lowest specific activity when corrected for the noble metal content.

Comment: Obviously, neither the relative nor the absolute rates for debenzylation and dehalogenation could be influenced much by the choice of the catalyst. This is in contrast to other debenzylation reactions and shows how much the effect of catalysts can depend on substrate and reaction conditions.

2.4. Effect of solvent

According to the literature, solvents like acetic acid [2–7] or 1,2 dichloro benzene [8] can improve both rate and selectivity of debenzylation reactions, maybe due to the acidic character of the solvent or due to acid formed during dehalogenation. Differences in the solvation (of the transition state or the reaction products), or adsorption of the solvent on catalyst sites could also be responsible for these effects.

Fig. 2 shows the effect of the different solvents on the final product composition and the maximum concentration of 4-chloro-*N*-benzyl aniline. With none of the solvents, a high maximum concentration of this intermediate was ob-

Table 1
Effect of catalyst type. Methanol, 1 bar H_2, 0.6% (w/w) catalysts, no acids or bases

Exp #	Catalyst Type (Pd/C)	Cl-⟨⟩-NH-Bn max.	t (1.9 mol H_2-uptake)	Cl-⟨⟩-N-Bn$_2$ 1.9 mol H_2	Cl-⟨⟩-NH-Bn 1.9 mol H_2	Cl-⟨⟩-NH$_2$ 1.9 mol H_2	⟨⟩-NH$_2$ 1.9 mol H_2
1	4522, 5% Pd (reduced)	34%	72 min	2%	10%	54%	33%
2	E101 N/D 5% Pd (oxidic)	31%	78 min	2%	19%	46%	31%
3	JMC 56 5% Pd (reduced)	30%	99 min	1%	24%	50%	23%
4	Pd(OH)$_2$ 20% Pd (Pearlman)	26%	49 min	1%	18%	42%	36%

served. This means that the rates for the removal of the first and the second benzyl group are always of the same order of magnitude. At the end of the reaction, the amount of aniline (as main dehalogenation product, undesired) was small when using unpolar aprotic solvents, whether halogenated or not. In polar protic solvents however, dehalogenation was much more pronounced.

Fig. 3 shows the correlation of the dielectricity constant [16] of the solvents with
- the average rate for the over-all reaction (both debenzylation and dehalogenation) and
- the percentage of halogenated compounds after 1.9 mol H_2-uptake

In all *unpolar* solvents, the over-all reaction was found to be slow (exception: acetic acid), and little dehalogenation was observed after 1.9 mol H_2-uptake. This correlation between polarity, selectivity and over-all rate was found regardless of whether the solvents were halogenated or not. The reason for the exceptional behavior of acetic acid (fast reaction, little dehalogenation) is probably best explained by the acidic character of this solvent. It is well known that debenzylations are catalyzed by acid
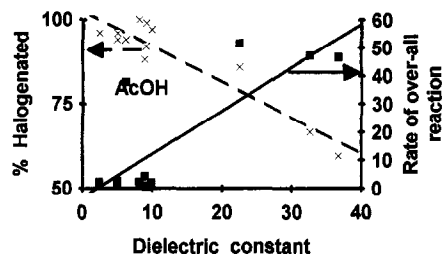
Fig. 3. Correlation of dielectricity constants with % halogenated (x, after 1.9 mol H_2-uptake) and rate of the over-all reaction (■, $1/t$ [uptake of 1.9 mol H_2, minutes]). Same experiments as shown in Fig. 2. Calculation of % halogenated = ([1]+[2]+ [3])/([1]+[2]+[3]+[4]+[5]+[6]), see also Scheme 1.

whereas dehalogenations are not ([2], see also below).

Polar solvents always showed a fast over-all reaction as expected [2]. Since much more dehalogenation was observed than in unpolar solvents, the rate for the hydrogenolysis of C–Cl bond must have increased even more than the rate for debenzylation.

Comment: When this investigation was started, the reason for the high selectivity reported in *o*-dichlorobenzene [8] was attributed to the formation of HCl by dehalogenation of the solvent (see below). This hypothesis has to
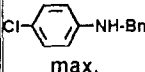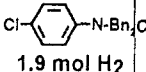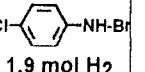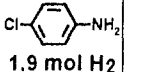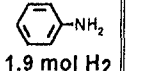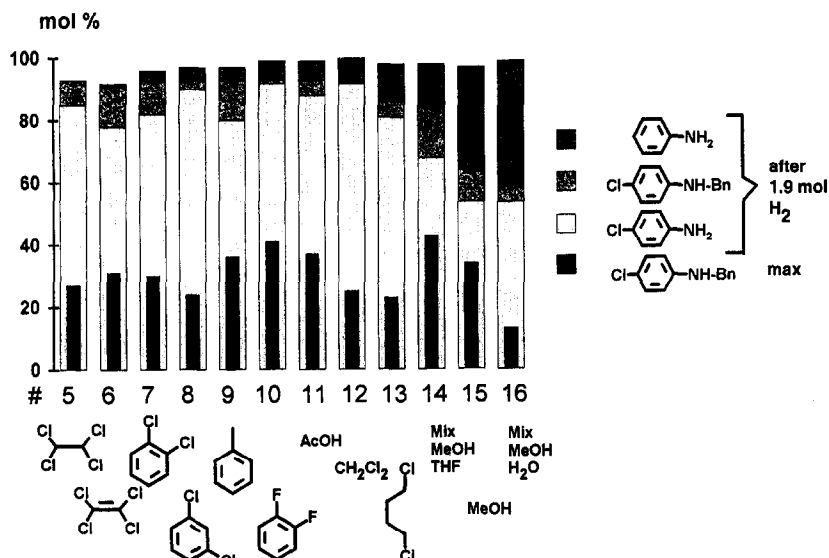
Fig. 2. Maximum concentration of 4-chloro-*N*-benzyl aniline and product composition after 1.9 mol H_2-uptake. 1 bar H_2, 0.6% (w/w) 4522 (5% Pd/C) in all experiments with MeOH or mixtures thereof; 6% (w/w) 4522 for the rest; no acids or bases added.

Table 2
Effect of acid type. Methanol, 1 bar H_2, 0.6% (w/w) 4522 (5% Pd/C), 1 mol/mol acid

Exp. #	Acid	Cl-⟨⟩-NH-Bn max.	t (1.9 mol H_2-uptake)	Cl-⟨⟩-N-Bn₂ 1.9 mol H_2	Cl-⟨⟩-NH-Bn 1.9 mol H_2	Cl-⟨⟩-NH₂ 1.9 mol H_2	⟨⟩-NH₂ 1.9 mol H_2
17	-	34%	72 min	2%	10%	54%	33%
18	HCl	80%	40 min	< 1%	2%	97%	< 1%
19	H_2SO_4	82%	30 min	< 1%	< 1%	98%	2%
20	HNO_3	71%	110 min	< 1%	< 1%	98%	< 1%
21	CH_3COOH	30%	64 min	1%	15%	54%	28%
22	NH_4Cl	28%	53 min	2%	16%	58%	24%

be rejected, however, because in all solvents with low polarity (halogenated or not), little dehalogenation was observed. One possible explanation is, that the transition state for the debenzylation has a lower polarity than the transition state for the dechlorination. This should favor debenzylation over dehalogenation in unpolar solvents. This hypothesis is supported by results of Bodnariuk et al. [18], who propose a highly polar, charged transition state for a dechlorination reaction in the gas-phase. Difference in the solvation of the reaction products HCl and toluene is another explanation for the observed changes in the selectivity: In polar solvents, HCl or protonated products are better solvated than in unpolar solvents, thereby favoring dehalogenation, and vice versa.

2.5. Effect of acid

On the one hand, strong and weak acids are well known as modifiers to increase the rate of debenzylation reactions [2–4,7]. On the other hand Erhardt [5] also reported high selectivity for the mono-debenzylation product when using alkyl-N-(benzyl)$_2$ · HCl as a substrate, but did not discuss why he used the hydrochloride of this dibenzyl amine. Since our substrate 4-chloro-N,N-dibenzyl aniline is ideally suited for the investigation of debenzylation in presence of aromatic halogens and sequential debenzyla-

tions of dibenzyl compounds we tried to tackle the following, hitherto unanswered questions:

* What influence do acid-type and strength have on the rate and selectivity for the formation of the various intermediates?
* What is the dependence on the amount of acid?

2.5.1. Acid-type and acid-strength

Table 2 shows the effect of 1 mol/mol acid on the maximum concentration of 4-chloro-N-benzyl aniline and on the product composition after 1.9 mol H_2-uptake. With strong acids, high intermediate concentrations of the mono-dibenzylation product were observed. With H_2SO_4 (Exp. 19), a maximum of 82% was found. Weak acids in this concentration had no significant effect.

Table 3
Kinetic constants obtained from fitting the measured product concentrations to Eqs. (1)–(4). All experiments were carried out in 60% Methanol/40% THF, 1 bar H_2, 0.6% (w/w) 4522 (5% Pd/C)

Exp. (No.)	Additive	k_1	k_2	k_4	$\Sigma_{res.}$	k_3 [a]
23	0.12 mol/mol NaOH	8	13	1	26.4	25 [a]
24	—	43	30	< 1	1.6	16 [a]
25	0.14 mol/mol HCl	56	49	< 1	9.8	6 [a]
26	0.28 mol/mol HCl	65	50	< 1	5.1	n.d.
27	1.10 mol/mol HCl	39	7	< 1	4.4	n.d.

[a] Independently determined with p-chloroaniline; all values are given as $k * 1000$/min.
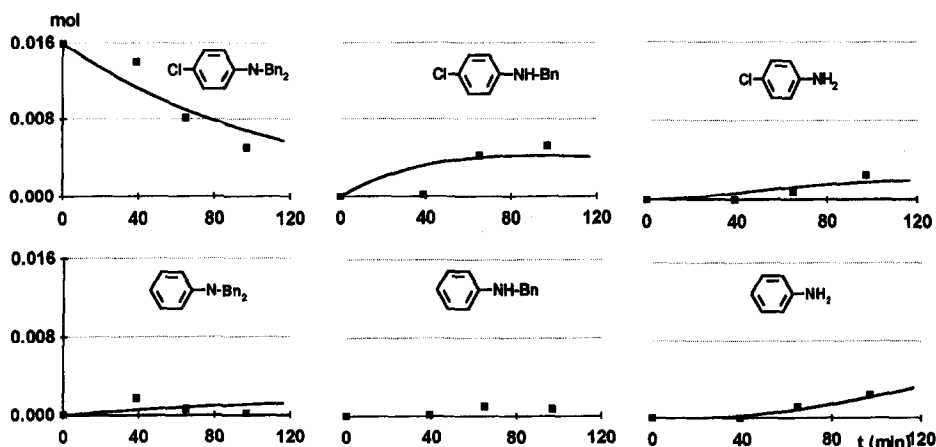
Fig. 4. Measured and calculated concentrations for experiment 23. 60% Methanol/40% THF, 1 bar H_2, 0.6% (w/w) 4522 (5% Pd/C), 0.12 mol/mol NaOH.

With sulfuric and hydrochloric acid, the time needed for the uptake of 1.9 mol H_2 was shorter than for the unmodified system, while with HNO_3 an inhibition was observed. A very high selectivity for 4-chloroaniline (> 97% of the desired product in the reaction mixture) was found when adding strong acids, regardless of the nature of the acid. 1 mol/mol of a weak acid (acetic acid or ammonium chloride) on the other hand had no positive effect on the selectivity.

2.5.2. Concentration-time profiles and kinetic analysis thereof

To get a more detailed insight in the effects of acid and base on the rates and product distribution, various amounts of HCl and NaOH were added as modifiers (Exp. 23–27, Table 3) and the concentration-time profiles were analyzed using the kinetic model shown in Scheme 1. Eqs. (1)–(4) were derived from Scheme 1 in order to calculate the product composition during the reaction. The concentration of **1**, **2**, **3**, **4**,
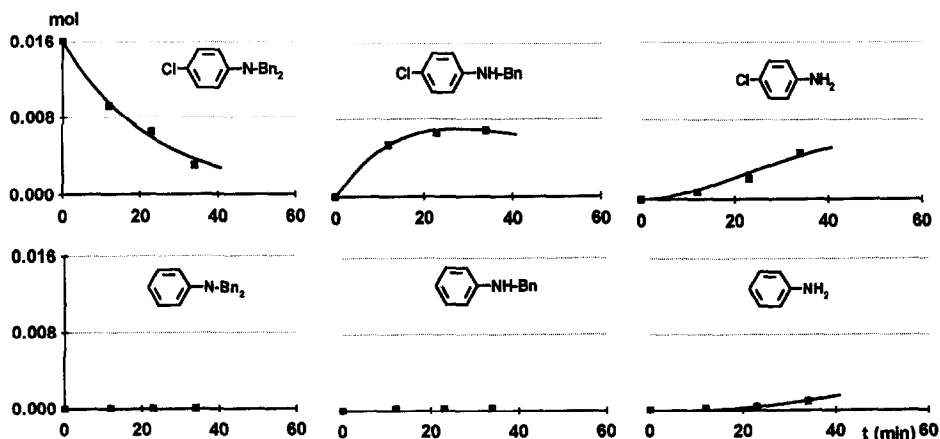

Fig. 5. Measured and calculated concentrations for experiment 24. 60% Methanol/40% THF, 1 bar H_2, 0.6% (w/w) 4522 (5% Pd/C), no acid or base.

and **6** was measured after 0, approximately 0.5, 1.0, and 1.5 mol H_2-uptake and used to determine constants k_1, k_2 and k_4. **5** was never observed in large amounts and there was no evidence that the reaction from **2** to **5** contributed significantly to the over-all reaction.

$$d[\mathbf{1}]/dt = -(k_1 + k_4)*[\mathbf{1}] \tag{1}$$

$$d[\mathbf{2}]/dt = k_1*[\mathbf{1}] - k_2*[\mathbf{2}] \tag{2}$$

$$d[\mathbf{4}]/dt = k_4*[\mathbf{1}] - k_5*[\mathbf{4}] \tag{3}$$

$$d[\mathbf{6}]/dt = k_3*[\mathbf{3}] + k_6*[\mathbf{5}]. \tag{4}$$

Estimated values for k_1, k_2 and k_4 were optimized by minimizing the residuals ($\Sigma_{res.}$) of the measured and calculated concentrations ($\Sigma_{res.}$ = $\Sigma([Calc] - [Obs])^2$, SOLVER routine in Microsoft EXCEL); k_3 was obtained from independent experiments with *p*-chloroaniline.

Figs. 4–6 show the measured and calculated concentrations for experiments 23, 24 and 27. Experiments 25 and 26 had a similar quality of the fit, as can be seen from the residuals. This means that for experiment 23–27 the measured data can be reasonably well be fitted with our simple model. However, because no correction was applied for the acid produced by dehalogenation during the reaction, the constants are not very accurate for experiment 23, where

relatively rapid dehalogenation produces significant amounts of HCl.

Debenzylation: With 0.14 mol/mol OH^- (Exp. 23), the rate constants for the removal of the first and the second benzyl group (k_1 and k_2) were small. Under neutral conditions (Exp. 24), both k_1 and k_2 were much larger and consequently, the time for the uptake of 1 mol H_2 (third data point) decreased from 65 to 23 min. Small amounts of HCl (Exp. 25 and 26) further increased both k_1 and k_2, resulting in fast debenzylation. Because k_1 and k_2 have about the same values in experiments 23–26, the selectivity for formation of 4-chloro-*N*-benzyl aniline did not change and was low. With large amounts of HCl (1.1 mol/mol, Exp. 27), both k_1 and k_2 *decreased*. This means, that both debenzylation reactions were inhibited. Since k_2 dropped much more than k_1 ($k_2/k_1 \sim 1/6$), large amounts of the mono-debenzylated product (maximum 72%) were obtained with 1.1 mol/mol HCl.

Dehalogenation: The rates for the removal of the halogen in 4-chloroaniline and in the starting material, represented by k_3 and k_4 showed just the opposite behavior of k_1 and k_2 (Exp. 23–25). This means that dehalogenation only proceeded fast under basic and neutral conditions, but was very slow in the presence of acid.
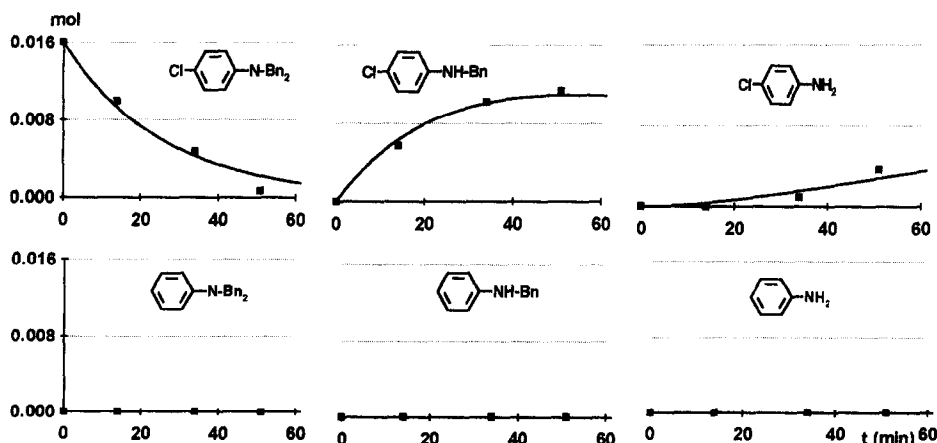

Fig. 6. Measured and calculated concentrations for experiment 27. 60% Methanol 40% THF, 1 bar H_2, 0.6% (w/w) 4522 (5% Pd/C), 1.1 mol/mol HCl.

Comment: With catalytic amounts of HCl as a modifier, 4-chloro-*N,N*-dibenzyl aniline and 4-chloro-*N*-benzyl aniline can be rapidly and selectively debenzylated to 4-chloroaniline with little dehalogenation. Freifelder and Kieboom [2,7] propose that debenzylation occurs as an attack of a Pd-bound 'hydride-ion' on the benzylic carbon. This attack should be facilitated by protonation of the adjacent hetero atom. According to the literature [7], catalytic amounts of a strong acid is sufficient for the rapid deprotection of benzyl ethers and alcohols. This is not the case for amines, however, where 1 equivalent of acid is reported to be necessary. In our case, 4-chloro-*N,N*-dibenzyl aniline is obviously not basic enough to inhibit debenzylation and behaves rather like a benzyl ether.

If 4-chloro-*N*-benzyl aniline is to be obtained as the main product, ≥ 1 mol of acid per mol of substrate must be added, and the reaction has to be stopped after the uptake of 1 mol H_2. High amounts of acid decrease the over-all rate of debenzylation and seem to selectively poison the catalyst. This poisoning is only observed after the substrate is completely protonated and enough 'free' HCl is present. One possible interpretation is that two different types of catalytic centers on the Pd are active in the debenzylation. One of them catalyzes both the removal of the first and the second benzyl group and is deactivated by large amounts of acid. The second one preferentially catalyzes the removal of the first benzyl group and is less sensitive to acid. The situation could be comparable to the Rosenmund-reduction, where so-called regulators (e.g., quinoline–sulfur) are known to make the hydrogenation of the acid chlorides to aldehydes slower but more selective with regard to the formation of the alcohol [2].

3. Experimental

Materials: Ethanol, dichloromethane, ether, methanol, toluene, tetrahydrofurane (THF),

acetic acid, sulfuric acid, 1,4-dichlorobutane, and benzyl chloride were all of puriss. p.a. quality (Fluka). 4-Chloroaniline, tetrachloroethylene and tetrachloroethane were all of p.a. quality and like 1,3-dichlorobenzene (z. synthese, 99%) and 1,2-difluorobenzene (purum, 98%) purchased for Fluka. Hexane, HCl, NH_4Cl, NaCl, $CaCl_2$, $LiOH \cdot H_2O$, NaOH, HNO_3, and aniline were puriss. p.a. (Merck). Dibenzyl aniline (99%) was purchased from TCI (Tokyo Kasei Kogyo) and 1,2-dichlorobenzene (99%) from Siegfried. Monobenzyl aniline (99%) was purchased from Aldrich. The Pd/C catalysts were purchased from Engelhard (4522), Degussa (E 101), JMC (type 58) and Fluka (Pearlman).

4-Chloro-N,N-dibenzyl aniline. 500 ml EtOH, 50 g 4-chloroaniline (MW = 127.58 g, 0.392 mol) and 39.02 g $LiOH \cdot H_2O$ (MW = 41.96 g, 0.93 mol) were placed in a five necked 1.5 l flask with a mechanical stirrer. While heating to reflux under argon, 36 ml benzyl chloride (MW = 126.59 g, d = 1.10 g/ml, 0.312 mol) was added dropwise. A white precipitate formed. After refluxing for 30 min, another 72 ml benzyl chloride (0.624 mol) were added during a 2 h period. After 5.5 h, another 3.9 g $LiOH \cdot H_2O$ (0.093 mol) and 10 ml benzyl chloride (0.087 mol) were added. After refluxing for a total of 23 h, the mixture was cooled with an ice-water bath. The white precipitate was filtered off and washed with 250 ml cold EtOH. The product was dried for 18 h at 90°C (150 Torr). Yield 102.9 g white crystalline powder (MW = 307.82 g, 0.334 mol, 85%). Elemental analysis ($C_{20}H_{18}NCl$). Calc C 78.04, H 5.89, N 4.55 Cl 11.52. Found C 78.03, H 5.86, N 4.49. Mp 104–105°C (Lit. 104.5 [17]), NMR ($CDCl_3$, δ in ppm): 4.60 (s, CH_2, 4H), 6.60 (d, 2H), 7.10 (d, 2H), 7.15–7.40 (m, 10 H). The mono alkylation product was isolated from the filtrate after evaporation of the solvent and chromatography on silica gel as a colorless oil of about 95% purity in 2.5% yield.

Typical debenzylation experiment. A 250 ml glass shaker fitted with a septum for sampling

was charged under argon with 16.0 mmol of the benzyl compound, 95 ml solvent and 5% Pd/C (0.6–6% w/w), suspended in 5 ml solvent. The reaction vessel was evacuated and flushed with H_2. The course of the reaction was followed by monitoring the H_2-consumption. Usually 3–5 samples were taken during the reaction. After the uptake 1.9 mol of H_2, the reaction was stopped. The final solution and all samples were analyzed by GLC analysis.

GLC analysis was carried out on a Varian 3700 machine with a HP3390 A integrator on a 10% OV 101 column (length 2 m, diameter (0.32 cm). Starting T was 100°C, then the oven was heated without delay at a rate of 10°C/min to 220°C and kept for 10 min at 220°C). Response factors of all compounds were determined and used to calculate the product composition.

Acknowledgements

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