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Effect of Solvents on the Product Distribution and Reaction Rate of a Buchwald−Hartwig Amination Reaction

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Abstract:

The Buchwald−Hartwig amination reaction between *p*-bromotoluene and piperazine in the presence of the homogeneous catalytic system $Pd(dba)_2$/(±)-BINAP and the base NaO-*t*-Bu was investigated in two different classes of solvents: aprotic, nonpolar and aprotic, polar. The reaction was carried out using microwaves as the heating source, and it was found that the product distribution was strongly dependent on the class of the solvent. Based on the experimental results the selectivity towards the desired monosubstituted aryl piperazine was calculated, and it was found that the most appropriate solvent for the Buchwald−Hartwig amination reaction under the conditions applied was *m*-xylene.

1. Introduction

N-Arylamines are important building blocks in drugs, which affect the central nerve system. In 2001 more than 25 antidepressants and more than 15 antipsychotics that contained *N*-arylated amine blocks were commercially available.[1] *N*-Arylated amines can also be identified in the dye manufacturing industry.[2] Several methods of preparing *N*-arylamines are available in the literature. These methods involve nitration,[3] Ullmann condensation,[4] or a benzyne pathway.[5] These methods have a number of drawbacks related to highly reactive reactants, a large excess of amine,[3] high temperature,[4] and formation of isomeric products.[5] Therefore it was of great interest when the Buchwald−Hartwig amination reaction was presented in 1995.[6,7] This reaction provides the formation of a covalent bond between a carbon atom in an aryl halogen and a nitrogen atom in a primary or secondary amine in the presence of a homogeneous catalytic system and a base. Compared to the other methods the Buchwald−Hartwig amination reaction offers a lower reaction temperature, typically between 80 and 100 °C, a higher selectivity with respect to the *N*-arylated amine, and the reaction does not include highly reactive reactants,[8] which may cause safety problems. Since 1995 the Buchwald−Hartwig amination reaction has formed the basis for a research field with a large number of publications. The articles published have covered many aspects of the reaction including the effect of the catalytic complex,[9,10] the base,[6,11] and the steric properties of the reactants (i.e., the aryl halide and the amine).[12,13] Furthermore, much work has been performed to reveal the chemical reaction mechanism and the kinetics for the reaction.[10,14,15] Conclusions have been summarized in reviews[16,17] illustrating some of the challenges, which may be met in the application of the Buchwald−Hartwig amination reaction. The effect of solvent is, however, a relatively unexplored area. We have been interested in developing a continuous reaction for the monoalkylation of a piperazine and for this reason would like to run the reaction in a solvent that dissolves sodium *tert*-butoxide. From the literature not only is it known that the reaction yields the desired *N*-arylated amine but also both reduction[9] and homo-coupling of the aryl halogen[18] are observed. Furthermore, if the reaction is carried out on amines, which contain more than one nitrogen atom, mul-

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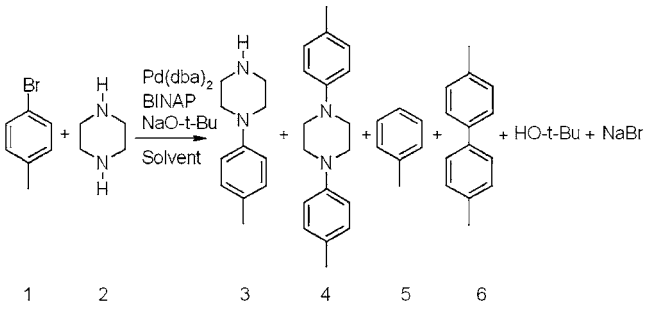
Scheme 1. **Model reaction for formation of substituted piperazines**



tiarylated products are produced. The intention of this work is to highlight the effect of the solvent on the chemical reaction rate and the product distribution.

2. Results and Discussion

2.1. The Reaction. The study is based on the reaction between *p*-bromotoluene (**1**) and piperazine (**2**). The reaction takes place in the presence of a homogeneous catalytic system, which consists of bis(dibenzylideneacetone)palladium(0) ($Pd(dba)_2$) and 2,2′-bis(diphenylphosphino)-1,1′-binaphthalene (BINAP). Sodium *tert*-butoxide (NaO-*t*-Bu) was employed as the base. The overall reaction with the observed products, 1-(4-methylphenyl)piperazine (**3**), 1,4-bis(4-methylphenyl)piperazine (**4**), toluene (**5**), and 1,1′-dimethyl-4,4′-biphenyl (**6**), is shown in Scheme 1.

Furthermore, it is possible that an etherification reaction between **1** and NaO-*t*-Bu takes place under the formation of *tert*-butyl-(4-methylphenyl)-ether.[19,16] However, this component could not be identified under the conditions applied in this work. The reaction in Scheme 1 has previously been studied,[12,9] but none of these studies provide knowledge about the effects of the solvents.

2.2. The Reaction Mechanism. The Buchwald−Hartwig amination reaction proceeds through a catalytic cycle, and it is generally believed that the formation of the *N*-arylated amine involves six different intermediate reaction steps as illustrated in Figure 1.[14,20,21]

In the present work, we have identified two additional side products not accounted for by the above mechanism, namely toluene from the catalyzed reduction of *p*-bromotoluene and 1,1′-dimethyl-4,4′-biphenyl from the homocoupling of *p*-bromotoluene. The literature proposes a mechanism for the reduction of the aryl halide, which involves a β-hydride elimination reaction from the amine,[22,23] which is shown in Figure 1.

The reduction is initiated by a β-hydride elimination from the amine forming a double bond. Subsequently the imine and the reduced aryl halide are released from the catalyst. If

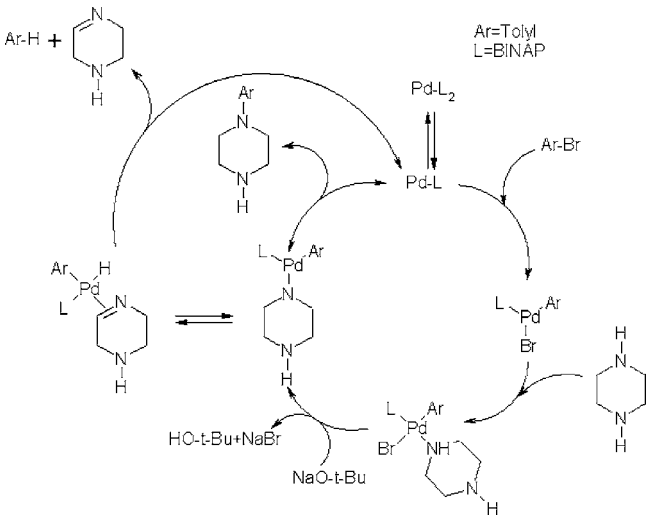


Figure 1. **Reaction mechanism for the formation of *N*-aryl amide and the reduction of the aryl halide.**

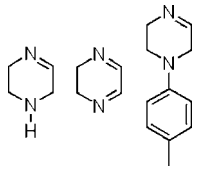


Figure 2. **Possible products from the β-hydride elimination. From left to right: 1,2,3,6-tetrahydro-pyrazine, 2,3-dihydro-pyrazine, 1-*p*-tolyl-1,2,3,6-tetrahydro-pyrazine.**

this mechanism is operating, it is expected that three additional products are formed during the reaction (Figure 2). However, it was not possible to detect these products by LC−MS.

No probable mechanism has been proposed for the homocoupling reaction of *p*-bromotoluene in the presence of NaO-*t*-Bu, but mechanisms where tertiary amines have been used have been presented.[24]

2.3. Reaction Protocol. The classic solvents employed in the Buchwald−Hartwig amination reaction are nonpolar, aprotic solvents such as *m*-xylene and 1,4-dioxane. However, due to the low polarity of these solvents, it is not possible to dissolve the base NaO-*t*-Bu. Consequently it was decided to use a more polar solvent which is able to create a homogeneous system and investigate if there were any effects on the product distribution during the reaction. Initially, we chose NMP since this solvent has successfully been applied in the Heck reaction,[25] which uses the same catalytic system. In the coming part of the article the results for the experiments will be presented. A detailed description of the preparation of the reaction mixtures is given in the Experimental Section. However, it has to be specified that each of the data points presented in Figure 3 to 8 have been obtained for an individual reaction mixture, which subsequently is analyzed by HPLC.

2.4. Aprotic Nonpolar Solvents. To obtain basic knowledge of how the reaction behaves in the classic solvents for

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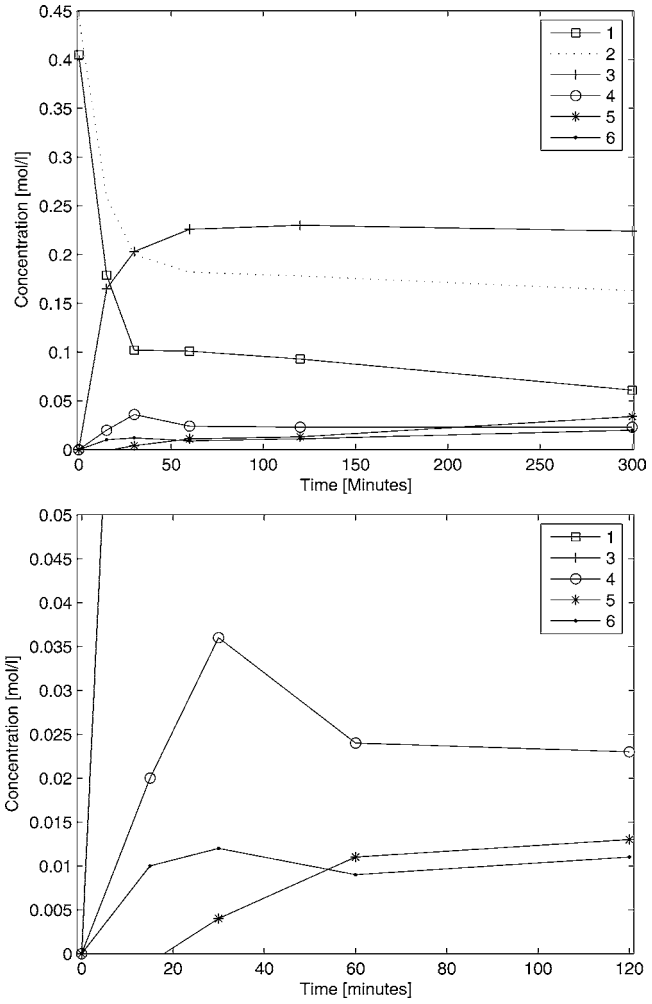

Figure 3. **Concentration versus time for the reaction carried out in *m*-xylene. The lower figure is a magnification of the upper figure.**

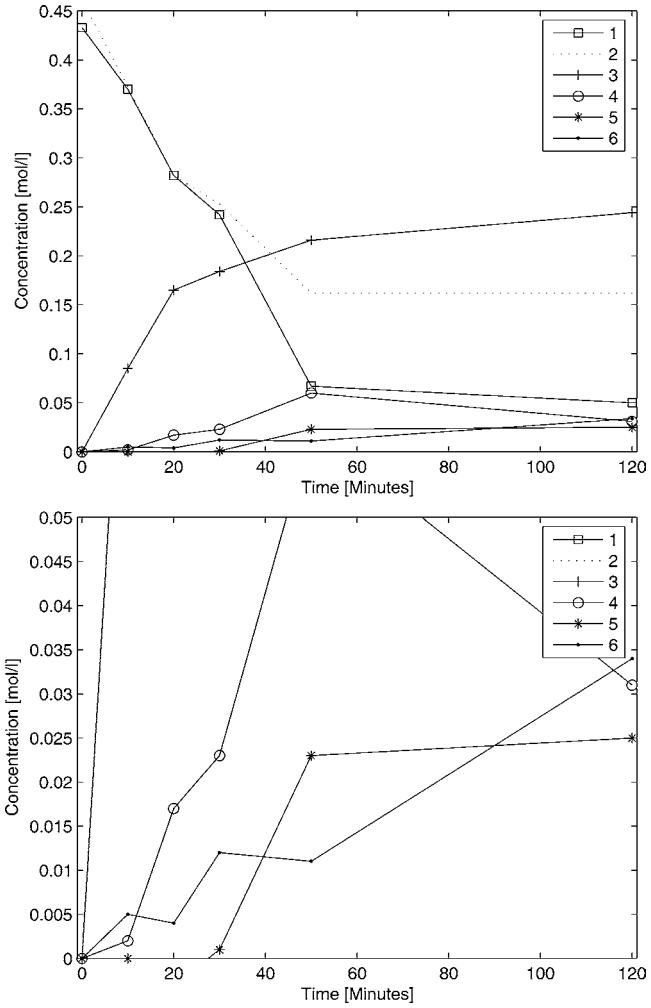

Figure 4. **Concentration versus time for the reaction carried out in 1,4-dioxane. The lower figure is a magnification of the upper figure.**

the Buchwald−Hartwig amination reaction, the reaction is first carried out in *m*-xylene and 1,4-dioxane. These solvents are able to dissolve all the reactants with the exception of NaO-*t*-Bu, resulting in a heterogeneous system. The course of reaction where *m*-xylene was used is shown in Figure 3.

It appears that the reaction proceeds with a high degree of selectivity with respect to the desired product **3**. Small amounts of **4**, **5**, and **6** are produced, but no significant change in selectivity is observed during the reaction. Subsequently the reaction is performed in 1,4-dioxane, and the concentration profiles are shown in Figure 4.

Compared to the results in Figure 3 the same tendencies for the reaction profiles are observed (note the difference in the time scale, which provides higher resolution in the experiment with 1,4-dioxane). However, the production of **4**, **5**, and **6** at endpoint is higher in 1,4-dioxane.

To reveal how the formation of the products depends on the ratio between the reactants an experiment with 1 equiv of **1** and 2.2 equiv of **2** was carried out. The results are displayed in Figure 5.

In Figure 5 it is seen that the conversion of **1** is complete. The production of **5** and **6** was reduced, and the total consumption of **1** for these two products was decreased from 21.4% to 6.9% of the initaial concentration of **1**. The formation of the desired product, **3**, was increased from 56% to 78% based on the initial amount of **1**. Thus aprotic nonpolar solvents provide high selectivity toward the desired *N*-arylated amine. The yield may be further increased by increasing the amount of **2**.

2.5. Aprotic Polar Solvents. After having obtained knowledge about the course of reaction for the Buchwald−Hartwig amination carried out in classic aprotic nonpolar solvents, it was desired to discover what happens if the solvent is changed to an aprotic polar solvent. As previously pointed out these solvents are able to dissolve NaO-*t*-Bu to a higher extent compared to the nonpolar solvents. The concentration profiles for the reaction performed in NMP are shown in Figure 6.

Compared to the reactions described in the previous section it is observed that the reaction profiles have changed. The formation of side product **5** is significant, and it is of the same order as the desired product **3**. In the initial phase of the reaction the formation of **3** is faster than the formation of **5**. However, as the reaction progresses the formation of **5** becomes dominant, and the production of **3** terminates. The termination may be a consequence of the dominant reduction of **1** under the formation of **5**. On the contrary the change

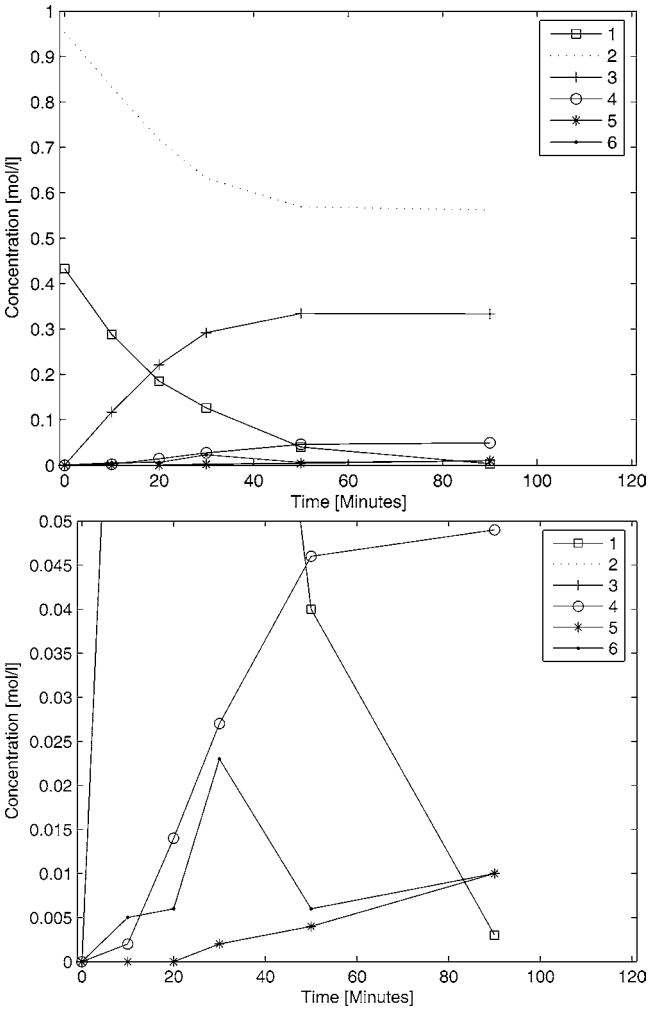

Figure 5. **Concentration versus time for the reaction carried out in 1,4-dioxane with 1.0 equiv of *p*-bromotoluene and 2.2 equiv of piperazine. The lower figure is a magnification of the upper figure.**

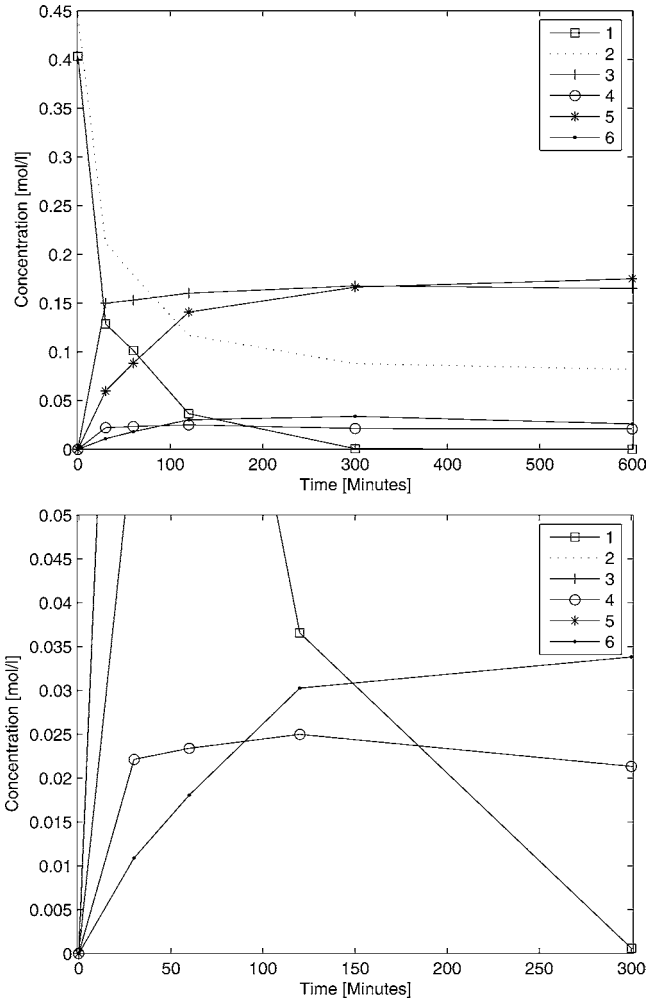

Figure 6. **Concentration versus time for Buchwald−Hartwig amination carried out in NMP. The lower figure is a magnification of the upper figure.**

of solvent does not affect the formation of the side products **4** and **6**.

To clarify this tendency for increased formation of **5**, another aprotic, polar solvent, *N*,*N*-dimethylacetamide (DMAC), was used. The results of this reaction are presented in Figure 7. For reasons unknown the results for **4** and **6** are fluctuating.

From Figure 7 it is observed that the formation of **5** is slower in DMAC compared to NMP. The reaction was also done with 1.0 equiv of **1** and 2.2 equiv of **2**, which is similar to the reaction carried out with 1,4-dioxane. The results are shown in Figure 8. Again it is observed that the formation of the desired product **3** becomes more significant when the ratio of **2** to **1** is increased. However, taking the results obtained for the aprotic polar solvents into consideration, the production of **5** is still significant compared to reactions carried out in *m*-xylene and 1,4-dioxane. For the aprotic polar solvents it is observed that two overall reactions are dominant: formation of the *N*-arylated amine and reduction of the aryl halide.

2.6. Discussion of Key Numbers for the Reaction. A significant difference in the product distribution has been observed dependent on the solvent applied. In Table 1 some of the effects of the solvents have been summarized. In this table the reaction time for the optimal fractional yield with respect to **3**, ϕ_3, has been identified from eq 1.[30] The corresponding conversion of **1**, X_1, and the yield of **3**, X_3, have been calculated according to eqs 2 and 3.

$$\phi_{\mathbf{3},t} = \frac{[\mathbf{3}]_t}{[\mathbf{3}]_t + 2[\mathbf{4}]_t + [\mathbf{5}]_t + 2[\mathbf{6}]_t} \quad (1)$$

$$X_{\mathbf{1},t} = 1 - \frac{[\mathbf{1}]_t}{[\mathbf{1}]_{t=0}} \quad (2)$$

$$X_{\mathbf{3},t} = \frac{[\mathbf{3}]_t}{[\mathbf{1}]_{t=0}} \quad (3)$$

Based on Table 1 it is seen that the solvent that provides the worse fractional yield with respect to **3** is NMP. The

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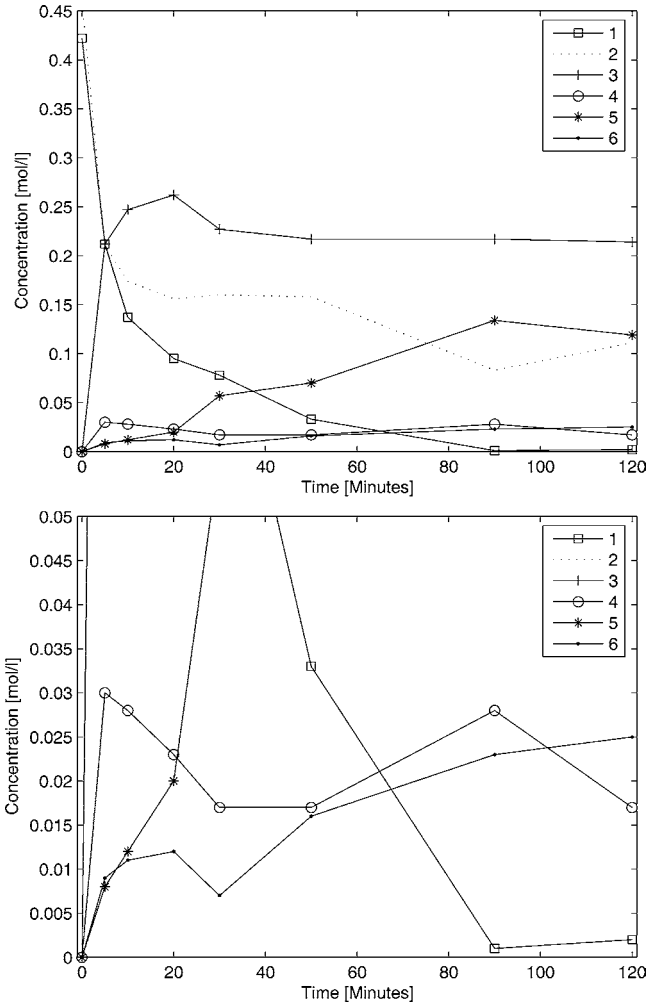

Figure 7. **Concentration versus time for Buchwald−Hartwig amination carried out in DMAC. The lower figure is a magnification of the upper figure.**

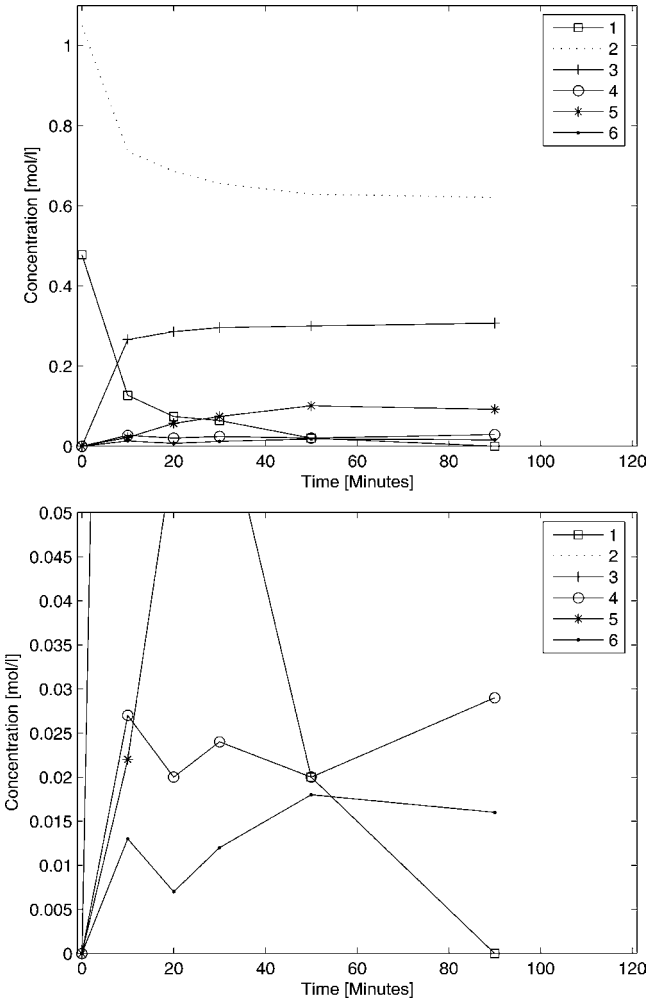

Figure 8. **Concentration versus time for Buchwald−Hartwig amination carried out in DMAC with 1.0 equiv of *p*-bromotoluene and 2.2 equiv of piperazine. The lower figure is a magnification of the upper figure.**

fastest conversion of **1** is in DMAC; after 20 min 79% of the starting material has been converted. Furthermore, the table reveals that the highest fractional yield of **3** is obtained by changing the ratio between the two reactants. The change in the ratio for the reaction performed in 1,4-dioxane does not affect the fractional selectivity significantly, but the yield of **3** is increased from 34% to 69%, and 92% of **1** is converted during the optimal reaction time instead of 42%. For the reaction performed in DMAC with 1.0 equiv of **1** and 2.2 equivalent of **2** the formation of **5** is lowered compared to the results obatined with standard conditions, but no other significant effects have been observed.

Table 1. **Performance for the solvents applied; the number of equivalents refers to piperazine**

solvent	time of reaction [min]	ϕ_3 eq 1	X_1 eq 2	X_3 eq 3
NMP (1.1 equiv)	30	0.54	0.68	0.37
DMAC (1.1 equiv)	20	0.80	0.79	0.58
m-xylene (1.1 equiv)	60	0.75	0.75	0.55
1,4-dioxane (1.1 equiv)	20	0.74	0.42	0.34
DMAC (2.2 equiv)	10	0.72	0.74	0.54
1,4-dioxane (2.2 equiv)	50	0.76	0.92	0.69

2.7. Coupling of the Results to the Reaction Network. Combining the reaction mechanism presented in this article with a chemical reaction network found in the chemical reaction engineering literature,[30] it has been found that the reaction network studied in this article can be divided into two: First, the production of **3** and **4** can be described as two-step irreversible series-parallel reactions according to **1** + **2** → **3** and **1** + **3** → **4**. Second, the production of **5** and **6** can be described by parallel reactions. Taking the two-step irreversible series-parallel reactions into consideration, the theoretical course of reaction will be the following: In the initial phase of the reaction it is expected to observe an increase in the concentration of **3**, whereas the concentrations of the starting materials are decreasing. In most of the experiment 1.0 equiv of **1** and 1.1 equiv of **2** are employed. Therefore as the reaction progresses it is expected that compounds **2** and **3**, which both contain unreacted amine sites, will be competing in the reaction with **1**. However, these characteristics are not observed in the experimental results. From these results it appears that there is a tendency for **2** to be more reactive than **3**, since almost no **4** is formed. The reason for this may be that **3** is more bulky compared to **2**, which means that **2** more easily coordinates to the

palladium complex and by that enters the catalytic cycle.[12]

2.8. Catalytic Deactivation Process. In the study of the reaction it has been observed that the reaction from time to time terminates even though unreacted starting material still is present in the reaction mixture (Figures 3 and 4). This may imply that the catalyst sometimes is deactivated during the course of reaction. A search in the literature for deactivation processes for homogeneous palladium complexes does not reveal any results related to the Buchwald−Hartwig amination reaction. However, deactivation processes for the Heck reaction has been found.[31,32] The catalytic complexes employed in the Heck reaction can also be used in the Buchwald−Hartwig reaction. A number of pathways for the deactivation of the catalyst are presented: Decomposition of reactive metal alkyl with water or oxygen, reactions of the carbon-to-metal bond, and formation of inactive dimers of the catalyst.[31] It will be too speculative to predict which of the mechanisms leads to the termination in our work since a great number of variables affect the reaction. In the experiments where the deactivation is observed the reactions are done in aprotic nonpolar solvents. This suggests that another possibility for the termination of the reaction could be due to the limited solubility of base in the nonpolar solvents.[11]

2.9. Mechanistic Reflections. Taking the reaction mechanisms provided in section 2.2 and the experimental results into consideration some mechanistic reflections may be provided. The reactions performed in NMP and DMAC reveal that in the initial phase of the reaction (approximately the first 20 min) the formation of the desired product **3** is dominant. However, as the reaction progresses the formation of **5** becomes significant. The question is how NMP and DMAC initiates this difference in the product distribution compared to the ones obtained in *m*-xylene and 1,4-dioxane. The obvious difference in the chemical properties between the polar and the nonpolar solvents is the ability for stabilizing the charges on NaO-*t*-Bu. Furthermore, the double bonds or the lone pairs on the amide part in NMP and DMAC may coordinate to the palladium complex. This has the consequence that NaO-*t*-Bu and the palladium complex are more hindered in polar solvents than in apolar solvents. This may have the consequence that the palladium complex, containing the protonated piperazine, in Figure 1, may be in a resting state in the polar solvents, and this may give the palladium complex time to perform the rearrangement that enables the β-hydride elimination. This explanation may be connected to observations made by Beletskaya et al.[26] They found that the reduction of aryl bromides was dominant in reactions where the deprotonation reaction is slow, leaving the palladium complex, containing the protonated piperazine, in the same situation as the above explained. Beletskaya et al. suggested that the slow deprotonation enables the reduction to proceed through amino coordinated complexes according to Figure 9, making the mechanism more complex. However, in this work it has not been possible to reveal the existence of this reaction path.

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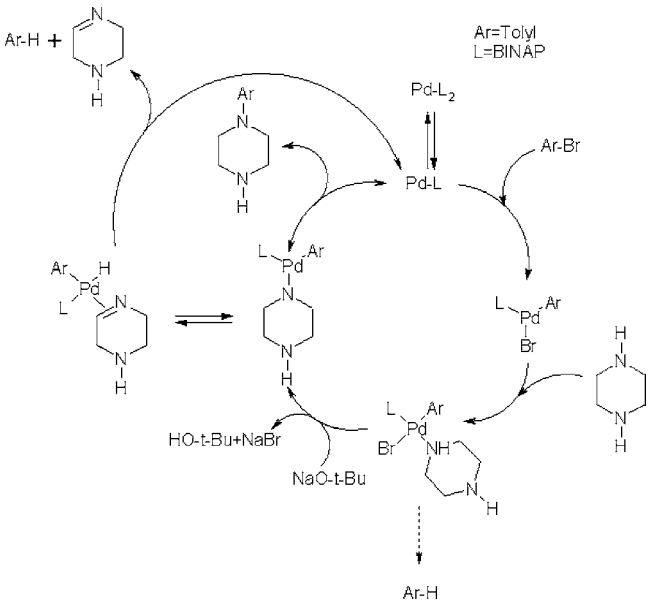

Figure 9. **Possible reaction mechanism for the reduction of the aryl halide.**

3. Conclusion

This study illustrated that the choice of solvent affects the product distribution of the Buchwald−Hartwig amination reaction. The solvent that provided the best selectivity toward the desired product **3** and reduces the production of the side products the most was *m*-xylene. On the contrary it was discovered that both NMP and DMAC initiated the unwanted debromination reaction of *p*-bromotoluene. In connection to the debromination reaction it was also revealed that the formation of the unwanted side products could be suppressed by increasing the ratio between **2** and **1**. Another unexpected observation was that the second amination reaction of **3** was very slow and, thus, only traces of **4** were produced. In connection to the reaction rate it was observed that the fastest conversion of **1** was in DMAC. In relation to the transformation from batch to continuous mode a number of observations lead to the conclusion that this may not be the ideal solution. According to the literature the most efficient way of operating a two-step irreversible series-parallel reaction is in either a batch or a plug flow reactor.[30] Keeping in mind that the formation of **4** (the bisubstituted piperazine) is very slow, meaning that the reaction for practical purposes almost can be neglected and that the reaction in some cases terminates, it may seem irrational to establish a continuous facility.

4. Experimental Section

4.1. Materials. *p*-Bromotoluene was purchased from Merck, and piperazine, from Avocado research chemicals Ltd. 1,4-Dioxane, *m*-xylene, DMAC, NaO-*t*-Bu, $Pd(dba)_2$, and (±)-BINAP were purchased from Aldrich. All the chemicals and solvents, with the exception of piperazine, were used without any prior treatment. Piperazine was crystallized from toluene and subsequently sublimated. This treatment increased the melting point for piperazine from approximately 50 to 108−111 °C. The water content in the solvents applied has not been investigated. However, in a recent publication it has been concluded that water may affect

the reaction rate for the Buchwald−Hartwig reaction. The effect has primarily been related to a better solubility of the base in solvents that contain water,[33] which results in a faster rate of reaction. Reference compounds for analysis calibration of 1-(4-methylphenyl)piperazine was from Fluka; toluene and 1,1′-dimethyl-4,4′-biphenyl were from Aldrich. A reference compound of *tert*-butyl-(4-methylphenyl)-ether was prepared according to a literature procedure.[27] The same applies for 1,4-bis(4-methylphenyl)piperazine, which was also produced according to a literature procedure.[8]

4.2. Preparation of the Reaction Mixtures. The reaction mixtures were prepared as follows: In a flask under nitrogen atmosphere and agitation at room temperature **1**, **2**, $Pd(dba)_2$, BINAP, and NaO-*t*-Bu were dissolved/suspended in the solvent. The solvent was previously purged for 10 min with nitrogen.

The ratio between the reactants in this flask was as follows: 1.00 g (1.0 equiv) of **1**, 0.555 g (1.1 equiv) and 1.11 g (2.2 equiv) of **2**, 0.169 g (0.05 equiv) of $Pd(dba)_2$, 0.274 g (0.075 equiv) of (±)-BINAP, and 0.844 g (1.5 equiv) of NaO-*t*-Bu. The reactants were dissolved/suspended in 12 mL of solvent. The reaction mixture was distributed to a number of process vials. Each of the vials contained approximately 2 mL of the reaction mixture, was equipped with a magnetic stirring bar, and was purged with nitrogen prior to the sealing. Subsequently the reactors were loaded in an autosampler and reacted at 100 °C from 10 to 300 min. Initial investigation of the reaction mixtures left at room temperature for 24 h showed no conversion of the reactants.

4.3. Reproducibility of the Experimental Results. Initially in this study the validity of the method of analysis and the reaction stability were studied. The concentrations of the components in the reactions mixture have all been calculated using Lambert−Beers Law in eq 4.

$$C = \frac{A}{\in \cdot l} \tag{4}$$

Therefore the uncertainties in the final calculation of the concentration are introduced in the determination of the expansion coefficient, $\in \cdot l$, and the absorbance, A, of the reaction mixture. This means that the standard deviation of a composite measurement needs to be found in order to make a conclusion about the reproducibility of the experiments. The standard deviation of a composite measurement is calculated based on the standard deviation on the directly measured values for $\in \cdot l$ and A.[28] The expansion coefficients were determined based on a linear regression. An R^2-value higher than 0.997 was obtained for all the components. Due to the satisfying correlation it was concluded that uncertainties only were introduced to the system from the HPLC analysis.[29] The standard deviation for each of the following components was found using the following method: One mother solution of reaction mixture was prepared. The solution was subsequently equally distributed to four process vials. Each of the vials were reacted for 1 h at 100 °C in NMP. The reaction mixture of each of the vials was analyzed by HPLC twice, and the standard deviation for the concentration determination was calculated. The relative standard deviations for the composite are shown in Table 2.

Table 2. **Relative standard deviation for the detectable compounds**

	component				
	1	3	4	5	6
relative standard deviation [%]	3.2	7.2	33.4	13.5	7.9
average concentration [mol/L]	0.209	0.112	0.00367	0.0382	0.00881

From Table 2 it is observed that the standard deviation differs for the components. The relatively high standard deviation for **4** is due to the low concentration of the compound, which results in ill-defined baseline separation on the HPLC spectrum.

4.4. Quantification of Piperazine. To improve the chemical understanding of the reaction it is desired to obtain the concentration profiles for as many of the reactants and products as possible. The compounds **1**, **3**, **4**, **5**, and **6** are detected by HPLC chromatography; however, piperazine (reactant **2**) does not have any chromophore groups allowing detection by HPLC. It has been attempted to apply gas chromatography followed by flame ionization detection for the concentration determination of piperazine, but it has not been possible to obtain reliable results. Another solution strategy, though somewhat uncertain, has been to base the piperazine determination on the knowledge of the reaction mechanism for the reaction (i.e., a molar balance calculation). According to Scheme 1 component **2** is consumed in the production of **3**, **4**, and **5**. The concentration of **3** and **4** can be correlated directly to the consumption of **2** (Scheme 1). Meanwhile, the correlation between the formation of **5** and the consumption of **2** is more uncertain. According to the mechanism shown in Figure 1 it can be seen that the formation of 1 mol of **5** causes 1 mol of amine to perform a β-hydride elimination reaction. The products from this reaction have been shown in Figure 2. It has not been possible to identify and quantify these products. For simplicity it is assumed that only **2** is oxidized during the β-hydride elimination reaction and that it only performs a single β-hydride elimination. The correctness of this assumption decreases as **2** is converted to **3** during the course of reaction, because **3** may be performing the β-hydride elimination reaction instead of **2**. However, **3** is assumed not to perform any β-hydride elimination reaction. Based on the assumptions stated above the concentration of **2** may be estimated from eq 5.

$$[\mathbf{2}]_t = [\mathbf{2}]_{t=0} - ([\mathbf{3}]_t + [\mathbf{4}]_t + [\mathbf{5}]_t) \tag{5}$$

Equation 5 is used to estimate the concentrations of **2** in the experiments. Note, that eq 5 is valid only if the mechanism of Figure 1 is correct and the above assumptions hold.

4.5. Effect of Stirring. No studies were conducted with the aim of identifying the effect of the stirring velocity in

(33) Dallas, A. S.; Gothelf, K. V. *Journal of Organic Chemistry* **2005**, *70*, 3321−3323.

our work. Mass transfer limitations are only relevant due to a poor solubility of NaO-*t*-Bu. All the other components are completely soluble at the temperature where the reaction is carried out. According to the literature the physical structure of the weak base Cs_2CO_3 can have an impact on the reaction rate,[11] but stronger and more soluble bases such as sodium-*tert*-amylate have been reported not to influence the reaction rate.[14] However, it is beyond the scope of this work to clarify the effect of stirring in the case where NaO-*t*-Bu is applied.

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Supporting Information Available

Additional experimental information. This material is available free of charge via the Internet at http://pubs.acs.org.

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