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Applicability of a Fiber-Supported Catalyst on a Buchwald–Hartwig Amination Reaction

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Abstract:

The applicability of four different heterogeneous palladium catalysts has been evaluated for the Buchwald–Hartwig amination reaction between *p*-bromotoluene and piperazine in the presence of the base NaO-*t*-Bu. The catalyst that provided the highest selectivity toward the desired amination reaction was found to be a polymer-supported palladium dichloride/triphenylphosphine catalyst. Experimental investigations of the catalyst in a reactor setup showed that the undesired reduction reaction of the aryl halide was dominant when the catalyst was reused and washed in solvent prior to reaction and when additional reactants were added to an already reacted reaction mixture. A significant washout of triphenylphosphine and palladium from the catalyst was also identified during the course of reaction and separation.

1. Introduction

Palladium catalysts are widely employed in organic chemical synthesis, and their application covers a large number of different kinds of reactions. These are, for example, coupling reactions such as Heck,[1] Suzuki-Miyaura,[2] Stille,[3] and Buchwald–Hartwig[4] reactions and more traditional reduction and hydrogenation reactions.[5] Homogeneous and heterogeneous catalysts are known; the homogeneous catalyst is kept in solution by organic ligands, and the heterogeneous catalyst is often supported on different kinds of supporting materials such as activated coal, silica, or barium sulfate oxides, which ensure a large surface area of the reactive metal.[5] This means that the nature of the two catalytic systems is different; some of the advantages and drawbacks are listed in Table 1.

Table 1. **Comparison of heterogeneous and homogeneous catalysts**[6]

property	homogeneous catalysis	heterogeneous catalysis
activity (relative to metal content)	high	variable
selectivity	high	variable
reaction conditions	mild	harsh
service life of catalysts	variable	long
sensitivity towards catalyst poisons	low	high
diffusion problems	none	may be important
catalyst recycling	expensive	not necessary
variability of steric and electronic properties of catalysts	possible	not possible

Table 1 shows that the properties of the catalyst are strongly dependent on whether it is homogeneously or heterogeneously distributed within the reaction mixture. One of the major advantages of the heterogeneous catalyst is the convenient separation of the catalyst from the reaction mixture. Apart from ensuring a product that is not contaminated by heavy metals, the separation may also facilitate reuse of the catalyst. This approach is interesting from an industrial point of view, because this gives an opportunity for lowering of the production costs. Therefore it has been of interest to investigate the possibilities for anchoring the homogeneous catalyst on an insoluble polymer support and thereby combining the advantages of both the homogeneous and heterogeneous catalytic system. Normally the immobilization is done by anchoring the catalytically active ligands to a polymer support and subsequently adding the palladium source. Previously these polymer-supported homogeneous catalysts have been applied successfully in different reactions that traditionally take place in the presence of a homogeneous catalyst. Among others these have been the α,α-diarylation reaction,[7] Suzuki coupling reaction,[8] hydroformylation reaction,[9] and amination reaction[10,11] More general introductions to the area of polymer-supported and recyclable

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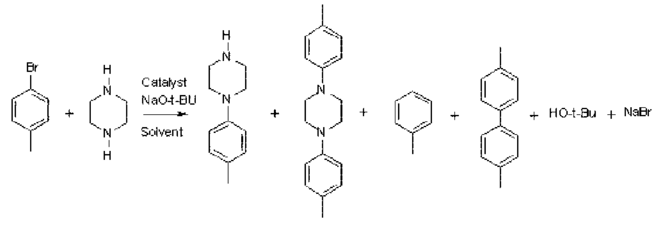
Scheme 1. **Model reaction for formation of N-arylated amines**



1 **2** **3** **4** **5** **6**

catalysts can be found in reviews.[12,13] However, in terms of reuse and separation of the polymer-supported homogeneous catalyst, the results are less prospective. Leaching of metal from the supporting polymer and deactivation of the catalyst upon separation have been reported as unsolved problems.[8,11] The existence of leaching of both active ligands and palladium has the consequence that the polymer-supported catalyst in practice is ending up as a homogeneous catalyst without the advantages of easy separation and reuse. It is essential to solve these problems prior to further implementation of these catalysts. Therefore it is the intention of this article to elaborate on the applicability of a polymer-supported homogeneous catalyst and increase the knowledge of the leaching and deactivation processes. The evaluation of the results may be used to design future production methods to convert homogeneous catalysts into solid-supported catalysts. The investigations will be based on a Buchwald–Hartwig amination reaction, giving both a mono- and a disubstituted piperazine. The analysis will also consider the formation of side products, which are formed outside the catalytic cycle for the amination reaction. Furthermore, the results will be supported by a physical characterization of the catalyst using a scanning electron microscope.

2. Characterization of the Reaction System

2.1. The Reaction. The Buchwald–Hartwig amination reaction has technical challenges that make it relevant as a model reaction: the reaction can be conducted in the presence of a homogeneous palladium catalyst, and it is a reaction that gains more interest in industrial applications.[14] A reason for this is that the product from the reaction, the *N*-aryl amines, are important building blocks in drugs. This is emphasized by the fact that more than 25 antidepressants and more than 15 antipsychotics that contain *N*-arylated amine blocks were commercially available in 2001.[15] Mono- and diarylated piperazines are examples of important compounds in pharmaceutical production. However, the existence of two vacant nitrogen atoms is a major challenge, because most often it is only desired to obtain the monosubstituted piperazine.[16] Typically, the monosubstituted piperazine is obtained by introducing protection groups or by using an excess of piperazine compared to the aryl halide. In the search for alternative production methods of monosubstituted piperazine, we have chosen to base the study on piperazine, thus allowing information on both the mono- and bisubstitution to be obtained. This investigation is based on the reaction between *p*-bromotoluene (**1**) and piperazine (**2**). The reaction proceeds in the presence of a palladium FibreCat system (referred to as the catalyst). Sodium *tert*-butoxide (NaO-*t*-Bu) is employed as the base, and 1,4-dioxane is used as solvent, because it has been concluded in a previous article that this solvent suppressed the formation of undesired side products.[17] 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.

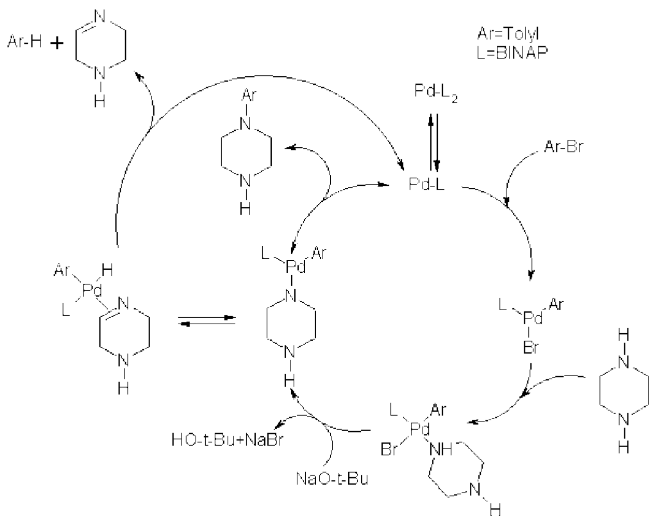


Figure 1. **Reaction mechanism for the formation of *N*-aryl amine and the reduction of the aryl halide.**[17]

2.2. The Reaction Mechanism. Discussions and evaluations of the performance of the FibreCat on the Buchwald–Hartwig amination reaction will be based on the knowledge of the chemical reaction mechanism for the reaction, which is shown in Figure 1. This reaction mechanism has previously been presented and discussed by the authors.[17] This is the generally accepted reaction mechanism for the homogeneously catalyzed reaction,[18–20] and in this work it is assumed that the same mechanism applies in the polymer-supported catalyzed reaction. According to the catalytic cycle in Figure 1, the Buchwald–Hartwig amination reaction proceeds through six different intermediate reaction steps. This reactions mechanism also applies in the formation of 1,4-bis(4-methylphenyl)piperazine.

During the course of reaction, toluene from the catalyzed reduction of *p*-bromotoluene and 1,1′-dimethyl-4,4′-biphenyl from the homocoupling of *p*-bromotoluene are also formed. These products are unwanted side products. The literature proposes a mechanism for the reduction of the aryl halide, which

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Table 2. **Application and chemical composition of the catalysts**[28]

name	primary type of reaction	composition	wt % Pd
FibreCat 1001	bromo and iodo coupling reactions	$Pd(OAc)_2$ on TTP fibers	5.05
FibreCat 1007	chloro coupling reactions		1.77
FibreCat 1026	bromo and iodo coupling reactions	$PdCl_2$ on TTP fibers	4.14
FibreCat 1032	not dedicated to any specific reactants	$Pd(OAc)_2$/TTP on TTP fibers	4.26

involves a β-hydride elimination reaction from the amine,[21,22] this reaction is also shown in Figure 1. The reaction mechanism for the formation of 1,1′-dimethyl-4,4′-biphenyl (i.e., the homocoupling of *p*-bromotoluene) is more unclear. In the literature, coupling of aryl iodide in the presence of a palladium catalyst has been described.[23–25] Furthermore, homocoupling of arylboronic esters and possible reaction mechanism have been discussed in other connections.[26,27] Whether these results can be applied in this article is unknown, but they may be used as an inspiration.

2.3. Review of Prospective Catalysts. The Buchwald–Hartwig amination reaction is normally carried out in the presence of a homogeneous catalyst, which is constituted by palladium coordinated to a phosphine ligand. These characteristics (palladium and phosphine ligand) were formulated as requirements in the survey for the polymer-supported catalytic systems that are to be evaluated in this article. Johnson Matthey has developed four different immobilized catalysts that meet these requirements. The catalyst are listed in Table 2 together with the type of reaction they may facilitate, their chemical composition, and the loading of palladium on a weight basis.[28]

It has not been possible to identify the exact physical structure of the four catalysts. However, in the literature [7,28] it has been reported that the catalyst consists of a polymer backbone to which the catalytically active components are linked; see Figure 2, [7] where **R** represents the places where the active components are bonded.

According to the chemical composition of **R** the catalyst is able to facilitate the type of reactions presented in Table 2. However, a more elaborate discussion about the chemical composition of **R** will be given later. Table 2 indicates that FibreCat 1001 and 1026 are successfully employed in the model reaction presented in Scheme 1. However, experimental investigations of the four different catalysts will form a more elaborate basis for the choice of the most efficient catalyst.

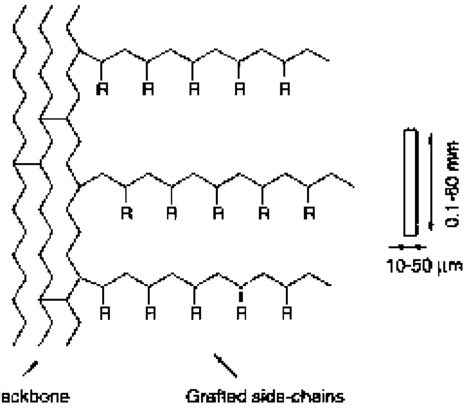

Figure 2. **Structure of a heterogeneous catalyst.**[7]

Table 3. **Experimental protocol**

	experiments
1	screening of catalysts
2	course of reaction
3	reuse of catalyst
4	wash of catalyst in solvent prior to reaction
5	reuse of entire reaction mixture
6	reactivation of catalyst

Table 4. **Results for the screening of catalysts after 3 h of reaction at 90 °C**

catalyst	X_1 (eq 1)	$\varphi_{3,4}$ (eq 2)	φ_5 (eq 3)	Y_3 (eq 4)	Y_4 (eq 5)	Y_5 (eq 6)	Y_6 (eq 7)
FibreCat 1001	0.98	0.11	0.69	0.10	0.01	0.68	0.19
FibreCat 1007	0.47	0.16	0.76	0.07	0	0.36	0.04
FibreCat 1026	0.99	0.81	0.18	0.58	0.23	0.18	0.01
FibreCat 1032	0.96	0.59	0.40	0.48	0.09	0.38	0.01

3. Results and Discussion

3.1. Experimental Protocol. To obtain knowledge of the advantages and limitations of a fiber (or polymer)-supported catalyst, the experimental protocol in Table 3 has been formulated. This protocol will contribute knowledge to the area of heterogeneously catalyzed Buchwald–Hartwig amination reactions. The protocol will reveal the most suitable catalyst for the reaction in Scheme 1, and further investigations of this catalyst will form the basis for preliminary discussions of the prospectives of reusing the catalyst.

The evaluation of the course of the reaction is based on a number of calculations, which can be found in the chemical reaction engineering literature.[29] First it is of interest to determine if the catalytic system is able to convert **1** into products. This is evaluated by eq 1, which gives a number for the fraction of starting material that has been converted. Next it is investigated how the catalytic system is able to perform the desired reaction and suppress unwanted side reactions. Therefore, the fractional yield for the amination reaction has been calculated according to eq 2. Both **3** and **4** are included in eq 2, because it is desired to evaluate the ability of the catalyst to support the amination reaction. In practice this means that it is desired to obtain a value of 1 for $\varphi_{3,4}$; in this case all formed

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products are the mono- and bisubstituted piperanzine (**3** and **4**). The fractional yield of toluene (**5**) is found by eq 3; **5** is the primary side product for the reaction, and therefore it is desired that φ_5 equals 0. It is also of interest to investigate how much of each product that has been formed. This is done by applying eqs 4–7. These equations give the fraction of the maximum theoretical yield of each of the products that have been produced. The subscript *t* in the formulas represents the time of reaction when the numbers have been evaluated.

$$X_{\mathbf{1},t} = 1 - \frac{[\mathbf{1}]_t}{[\mathbf{1}]_{t=0}} \tag{1}$$

$$\varphi_{\mathbf{3,4},t} = \frac{[\mathbf{3}]_t + 2[\mathbf{4}]_t}{[\mathbf{3}]_t + 2[\mathbf{4}]_t + [\mathbf{5}]_t + 2[\mathbf{6}]_t} \tag{2}$$

$$\varphi_{\mathbf{5},t} = \frac{[\mathbf{5}]_t}{[\mathbf{3}]_t + 2[\mathbf{4}]_t + [\mathbf{5}]_t + 2[\mathbf{6}]_t} \tag{3}$$

$$Y_{\mathbf{3},t} = \frac{[\mathbf{3}]_t}{[\mathbf{1}]_{t=0}} \tag{4}$$

$$Y_{\mathbf{4},t} = \frac{2[\mathbf{4}]_t}{[\mathbf{1}]_{t=0}} \tag{5}$$

$$Y_{\mathbf{5},t} = \frac{[\mathbf{5}]_t}{[\mathbf{1}]_{t=0}} \tag{6}$$

$$Y_{\mathbf{6},t} = \frac{2[\mathbf{6}]_t}{[\mathbf{1}]_{t=0}} \tag{7}$$

The reactions presented in the coming part have been performed using the following initial conditions: 1.0 equiv **1**, 2.0 equiv 2, 1.5 equiv NaO-*t*-Bu, and 0.030 molar equiv FibreCat. The solvent applied throughout the article is 1,4-dioxane. The reaction was carried out in a microwave cavity at 90 °C. Data collected for the reactions have been obtained by HPLC. This has allowed the following compounds to be quantified: **1**, **3**, **4**, **5**, and **6**.

3.2. Screening of Different Catalytic Systems. The performance of the four different catalysts is initially evaluated on the model reaction in Scheme 1. It is desired to identify the catalyst that facilitates the amination reaction to the highest extent and suppresses the formation of **5** and **6** the most. The results are displayed in Table 4, and the reaction conditions can be found in the Experimental Section. The first conclusion is that all of the catalysts facilitate conversion of *p*-bromotoluene, **1**. Except FibreCat 1007, all of the catalysts offer nearly full conversion of **1** within the first 3 h of the reaction. The reason for the incomplete conversion may be due to the relative low palladium loading compared to that of the three other catalysts; see Table 2. The relatively low palladium loading of 1007 required that more of the supported catalyst be used, and it was harder to ensure efficient mixing in the thicker slurry.

The next parameter to evaluate is the fractional yield of **3** and **4**, $\varphi_{\mathbf{3,4}}$. This number expresses how well the catalyst supports the desired amination reaction; compare Figure 1. FibreCat 1026 gives a significantly higher $\varphi_{\mathbf{3,4}}$ of 0.81. This catalyst also gives the lowest fractional yield of the undesired side product **5** ($\varphi_{\mathbf{5}} = 0.18$), and only traces of **6** is observed. These observations conclude that the catalyst that has the desired properties is FibreCat 1026.

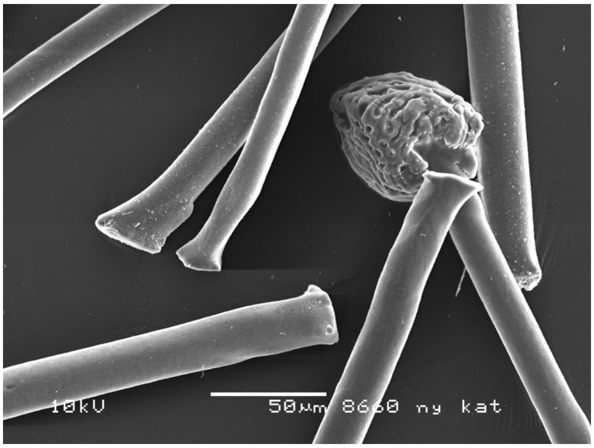

Figure 3. **Structure of unused catalyst.**

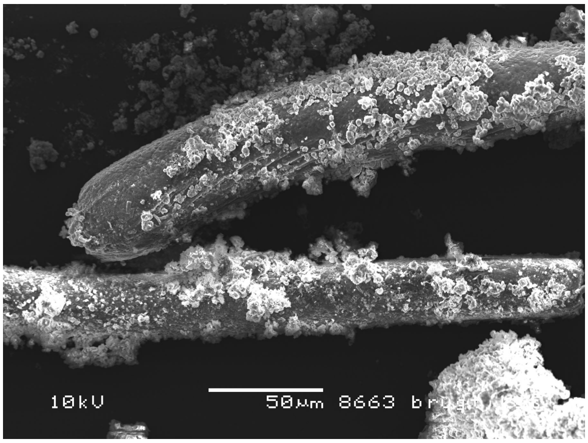

Figure 4. **Structure of used catalyst, which was separated by filtration at room temperature.**

3.3. Characterization of FibreCat 1026. To obtain more information on a macroscopic scale, scanning electron microscope (SEM) pictures were taken of the fresh catalyst, and a representative picture can be seen in Figure 3. This picture shows that the catalyst consists of rods of a length of approximately 200 μm (seen from another not shown SEM picture) and with a diameter of approximately 10–17 μm.

SEM pictures were also taken of the catalyst that has been employed in a reaction in 1,4-dioxane for 3 h at 90 °C, Figure 4.

From the picture it can be seen that the catalyst differs from the one shown in Figure 3. After the reaction the catalyst is covered with a layer of NaBr (confirmed by EDX), which is a side product from the reaction in Scheme 1. Two mechanisms for the precipitation of NaBr on the catalyst may exist: either NaBr precipitates on the catalyst when the reaction mixture is cooled to room temperature, or NaBr precipitates on the catalyst during the course of reaction. In an attempt to reveal which of the two mechanisms is valid, the catalyst was also separated at temperatures close to the reaction temperature, Figure 5.

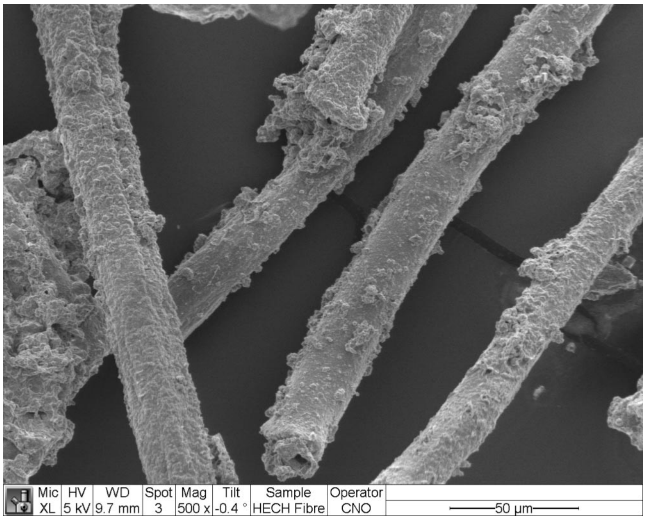

Figure 5. **Structure of used catalyst, which was separated by filtration at 90 °C.**

Comparing Figures 4 and 5, no obvious differences in the precipitation of NaBr are observed. This may indicate that NaBr precipitates during the course of reaction. Finally, the pictures of the used catalyst reveal that the polymer swells during the course of reaction, and the diameter has increased to approximately 25–45 μm.

The BET surface area of fresh catalyst has also been determined, and an average of two measurements gave a surface area of 0.57 ± 0.015 m^2/g. This value is compared to a theoretical calculation of the BET surface area based on eq 8. The dimensions of the rods are obtained from Figure 3. Thus, the dimensions are measured as diameter (average obtained from Figure 3), d_r, 14 μm; length, L, 200 μm; and the density, ρ, is assumed to be 1.0 g/mL.

$$BET = \frac{\text{surface area of rod}}{\text{mass of rod}} = \frac{\pi d_r L + 2\pi d_r^2}{\frac{\pi}{4} d_p^2 L \rho} = \frac{4}{d_r \rho} + \frac{8}{L \rho} \tag{8}$$

By inserting the values into eq 8, the theoretical surface area is estimated to be 0.33 m^2/g. This is close to the measured value of the surface area, and it can be concluded that the support material is nonporous. The slightly higher measured value of the area can be subscribed to irregularities in the surface of the support material.

3.4. Course of Reaction. Besides obtaining understanding of how the catalyst performed during different kinds of treatments, it is also desired to elucidate how the reaction evolves over time. Therefore the concentrations of **1** and the products were investigated over time. These results are presented in Figure 6.

Figure 6 shows that more than 90% of **1** has been converted within the first 10 min of reaction and that nearly all (99%) has been converted after 60 min. Reaction profiles from 60 to 180 min showed that no futher changes in the degree of conversions of all measurable compounds are observed.

In the lower part of Figure 6 it can be seen that the fractional yield $\varphi_{3,4}$ decreases from 0.95 to 0.86 during 1 h of reaction. On the contrary the fractional yield of φ_5 is increasing from 0.05 to approximately 0.13 in the same period. This change in the fractional yield may either be due to different rates of formation for **3**, **4**, and **5** or be due to a change in the reaction mechanism during the course of reaction.

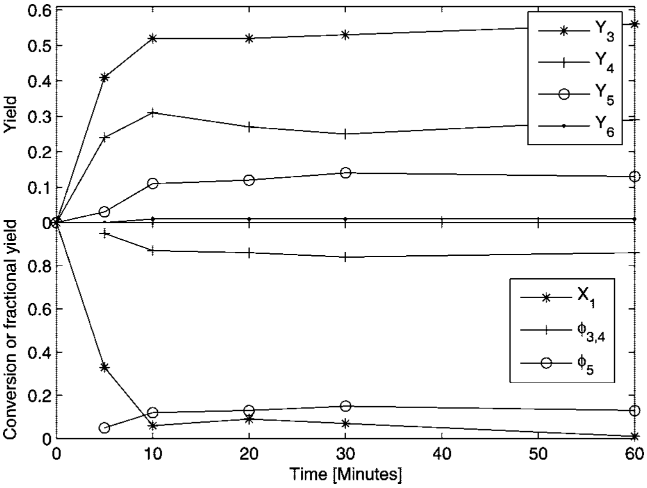

Figure 6. **Course of reaction at 90 °C.**

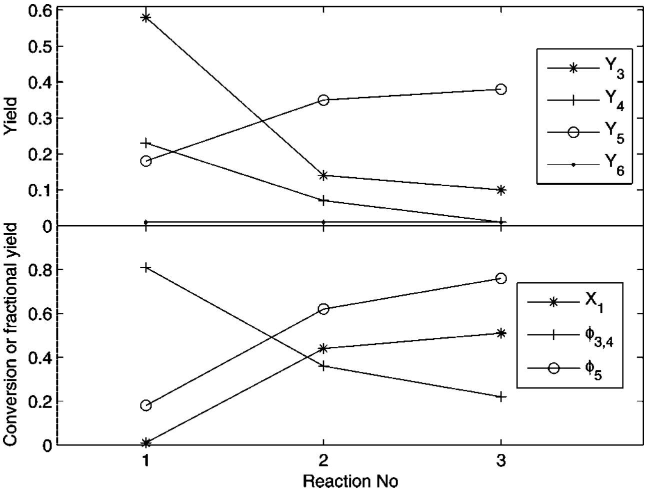

Figure 7. **Performance of a catalyst that is reused two times (3 h at 90 °C).**

3.5. Reaction with Reuse of the Catalyst. One of the possible advantages of applying heterogeneous catalysis is that it may be possible to reuse the catalyst. To investigate the prospective of this approach the following experiment is carried out. A catalyst that has been used once in a reaction is separated from the reaction mixture by filtration and subsequently reemployed in the same reaction. This separation of the catalyst followed by subsequent reaction is repeated twice. The results are presented in Figure 7.

The results in Figure 7 clearly illustrate that the activity of the catalyst decreases significantly; going from nearly full conversion in reaction 1 to about 50% conversion in reactions 2 and 3. More interesting a change in the fractional yield of **3** and **4**, $\varphi_{3,4}$, is observed. This decreases from 0.81 to 0.22 over the three reaction runs, and the fractional yield of the undesired side product **5** increases from 0.18 to 0.76. These observations indicate that the catalyst after the workup supports the reduction reaction rather than the desired amination reaction. It is not known what causes this deactivation process during the reaction

Table 5. **Performance of the FibreCat with and without wash prior to reaction (3 h at 90 °C)**[a]

reaction	X_1 (eq 1)	$\varphi_{3,4}$ (eq 2)	φ_5 (eq 3)	Y_3 (eq 4)	Y_4 (eq 5)	Y_5 (eq 6)	Y_6 (eq 7)
untreated catalyst	0.99	0.81	0.18	0.58	0.23	0.18	0.01
washed catalyst	0.76	0.19	0.73	0.14	0.01	0.56	0.06
dioxane from the wash	0.64	0.95	0.05	0.46	0.15	0.03	0

[a] In a flask 0.073 (0.029 equiv) g of FibreCat 1026 was mixed with 2.0 mL of 1,4-dioxane. The flask was left for 30 min at room temperature with agitation and nitrogen atmosphere. The FibreCat was separated by filtration and introduced to a process vial.

runs, but it may be due to washout of some of the active components from the FibreCat during the filtration of the catalyst, deposition of NaBr on the catalyst, or some unknown deactivation reaction of the catalyst. To clarify if either of the two possibilities exists, two different experiments were carried out and are reported in the following.

3.6. Wash of the Catalyst prior to Reaction. To clarify if the changes in the activity of the catalyst is caused by wash out of active components during the separation of the catalyst, an experiment where the catalyst is washed prior to reaction is carried out. The results are given in Table 5. The first result reported in the table corresponds to the result obtained in Section 3.2; this result is used as a reference in the discussion of the following two results.

The results obtained with the washed catalyst reveal that the catalyst still is able to convert **1** to products. However, compared to the performance of the untreated catalyst the reaction rate has decreased: only 76% of the initial amount of **1** has been converted, in contrast to 99% being converted with the untreated catalyst. A more serious challange observed is the low fractional yield of **3** and **4**, $\varphi_{3,4}$, this has decreased from 0.81 to 0.19. At the same time the fractional yield of **5** has increased significantly from 0.18 to 0.73. These numbers clearly illustrate that the properties of the catalyst applied has changed during the washing process, and by that indicating that active compounds are washed out of the catalyst.

A HPLC analysis of the solvent applied in the wash of the catalyst showed a peak in the chromatogram. It may be possible that the active ligand is released during the wash, thus indicating that the peak originates from triphenylphosphine. Analyzing a reference of pure triphenylphosphine gave a retention time that is equal to the peak observed. After having proved that triphenylphosphine in all probability is released from the catalyst it is decided to perform a reaction where **1**, **2**, and NaO-*t*-Bu are added to the 1,4-dioxane applied in the washing process. The results from this experiment are also presented in Table 5. The results show that the dioxane from the washing process has properties similar to the untreated catalyst. Only 64% of the initial amount of **1** has been converted, but it has been efficiently transformed to **3** and **4** ($\varphi_{3,4} = 0.95$), and only traces of **5** are detected ($\varphi_5 = 0.05$). The dioxane from the wash is able to facilitate the reaction; this indicates that both palladium and triphenylphosphine are released from the FibreCat.

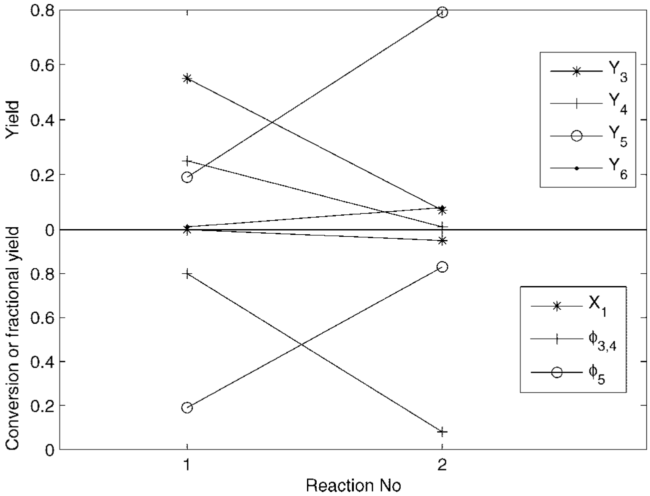

Figure 8. **Results for successive reactions in the same process vial (3 h at 90 °C).**

3.7. Reaction with Reuse of the entire Reaction Mixture. At this point of the work it had been concluded that the catalytically active components are released from the catalyst during reaction and wash, respectively. This means that the catalyst becomes homogeneous and then subsequently is lost when the catalyst is separated. This observation motivates an experiment where the entire reaction mixture is used in successive reactions. The results are given in Figure 8.

From Figure 8 it is clearly seen that the activity of the catalyst does not decrease to the same extent as in the experiments where the catalyst has been separated from the reaction mixture prior to the reuse; compare Figure 7. The activity of the catalyst is still decreasing during the different reactions runs. It is seen that from reaction 1 to reaction 2 the product distribution changes significantly and $\varphi_{3,4}$ decreases from 0.80 to 0.08; on the contrary ϕ_5 increases from 0.19 to 0.83. Thus, the catalyst primarily facilitates the reduction reaction.

3.8. Reactivation of the Catalyst. Previously in section 3.6 it was concluded that both Pd and triphenylphosphine are released from the polymer support during both reaction and simple wash of the catalyst. Therefore, it is of interest to investigate if the washout of the active compounds from the support is reversible, by that meaning that the catalyst can be reactivated. To obtain a deeper understanding of this release mechanism the experiments reported in Table 6 were carried out.

Reaction 1 represents a reaction carried out with fresh catalyst. Reaction 2 is the results obtained when the catalyst from reaction 1 is reused. As reported earlier the activity of the catalyst decreases and the selectivity toward **5** increases when the catalyst is reused. The catalyst employed in reaction 2 is separated, and in an attempt of reactivating the catalyst it is mixed with $PdCl_2$ and TPP. Subsequently, the treated catalyst is employed in reaction 3. From Table 6 it is seen that the activity of the catalyst is not regained upon the treatment. On the contrary it is seen that the fractional yield of **5**, φ_5, increases further. The lack of success for the reactivation may be due to the fact that both $PdCl_2$ and TPP are added in the same operation. $PdCl_2$ may have a higher affinity toward the TPP in the solution than toward the TPP anchored to the polymer

Table 6. **Reactivation experiment (3 h at 90 °C)**

reaction	X_1 (eq 1)	$\varphi_{3,4}$ (eq 2)	φ_5 (eq 3)	Y_3 (eq 4)	Y_4 (eq 5)	Y_5 (eq 6)	Y_6 (eq 7)
1	0.97	0.86	0.10	0.52	0.31	0.09	0.04
2	0.72	0.33	0.60	0.16	0.07	0.44	0.05
3 (addition of $PdCl_2$/TPP)	0.48	0.04	0.75	0.02	0	0.36	0.10
4 (Addition of $PdCl_2$)	0.31	0.06	0.69	0.02	0	0.22	0.08

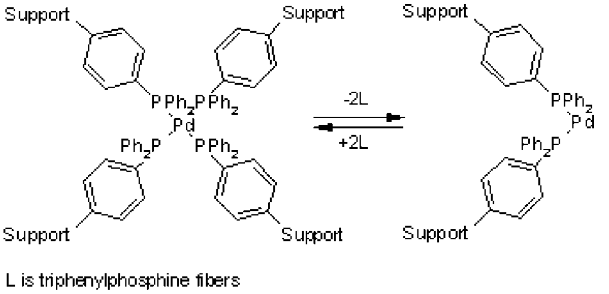

Figure 9. **Dissociation reaction of the palladium complex.**

support, thus inhibiting the reactivation process. Therefore, an experiment where only $PdCl_2$ is added to the used catalyst is conducted (reaction 4). However, from the results it can be concluded that this treatment only leads to a further decrease of the activity.

Taking the reaction mechanism in Figure 1 into consideration, it appears to be challenging to develop a heterogeneous catalyst for this reaction system, which is not leaching palladium. The precondition for the catalyst to be active is the ability for the palladium to dissociate a pair of phosphine ligands; compare Figure 9. Furthermore, it is not known if all TPP is covalently bonded to the polymer support. On the basis of the results reported in this article it does not seem plausible, because it is unlikely that the bond between TPP and the support is broken by a simple wash in 1,4-dioxane at room temperature.

4. Improvements of the Catalyst

On the basis of the experimental results, suggestions for the design of future catalysts can be provided. The results clearly show that the major challenge to solve is the leaching of palladium and the catalytically active ligands. As previously mentioned the leaching seems to be difficult to suppress, because palladium is not covalently bonded to the polymer support; compare Figure 9. A way of improving the ability of the polymer support to withhold the palladium may be to increase the number of polymer-supported TPP per surface unit. Another approach has been to encapsulate both the metal and the active ligand in a polymer.[30] In this method it is the intention that the reactants diffuse into capsules where the reaction takes place and that the products subsequently diffuses out into the reaction mixture. Whether this is a better design for the Buchwald–Hartwig amination reaction is not known. However, the encapsulated homogeneous catalyst has successfully been applied in a flow reactor employed in a Suzuki coupling reaction.[30]

5. Applicability of Microwaves in Chemical Reactions

All reported experiments in the article are conducted using microwaves as heating source. Discussions about a possible change in the reaction behavior due to the use of microwaves are ongoing in the literature.[31,32] In previous articles it has been concluded that no specific microwave effects are observed. Differences in the reaction behavior compared to conventional heating (i.e., oil bath or electrical heating) is caused by the fact that the microwave irradiated system is pressurized. This allows the reaction temperature to be elevated above the boiling point at atmospheric pressure (which is applied in an oil bath), which causes higher reaction rates and increases the solubility of the reactants.[31,32] Since all experiments in this article were carried out below the boiling point of 1,4-dioxane, we have concluded that we have no effect of applying the microwaves. Issues in connection to the scale-up of microwave-assisted reactions are another area of interest from an industrial point of view. Two different approaches have been discussed in the literature: scaled glass vessels up to 100 mL, which are automatically loaded with reaction mixture and subsequently automatically emptied,[33] and microwave cavities equipped with a flow cell.[30] Some of the limiting factors in connection to scaling up of the glass vessels are the limited penetration depth of the microwaves; thus it is difficult to ensure efficient heat transfer in the scaled systems. Regarding the microwave cavity equipped with a flow cell, other parameters such as particles and high viscosity may cause problems. This means that a proper solution varies from reaction to reaction.

6. Conclusion

A study of the prospectives of employing a heterogeneous catalyst in a Buchwald–Hartwig amination reaction has been reported. The catalyst was able to facilitate the desired amination reaction; however, it was also found that the side products toluene and 1,1′-dimethyl-4,4′-biphenyl were produced during the course of reaction. This product distribution is also observed when a homogeneous catalyst is employed. With the aim of reusing the catalyst in subsequent reactions, it was found that the separation of the catalyst from the reaction mixture led to a change in the activity of the catalyst. The recovered catalyst facilitated a slower conversion of *p*-bromotoluene, and the primary product had changed from the amination products to the side product toluene. Further investigations revealed that the changes in the behavior of the catalyst were due to a washout of both palladium and triphenylphosphine from the support material. Attempts to reactivate the catalyst with the addition of additional palladium dichloride and triphenylphosphine indicated that the release mechanism may not be reversible. This addition had the consequence that the fractional yield of

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Table 7. **Course of reaction**

	component				
time of reaction (min)	**1**	**2**	NaO-*t*-Bu	FibreCat 1026	1,4-dioxane
5	0.172 g; 1.0 equiv	0.168 g; 2.0 equiv	0.140 g; 1.5 equiv	0.074 g; 0.029 equiv Pd	2.0 mL
10	0.167 g; 1.0 equiv	0.168 g; 2.0 equiv	0.144 g; 1.5 equiv	0.076 g; 0.030 equiv Pd	2.0 mL
20	0.166 g; 1.0 equiv	0.169 g; 2.0 equiv	0.140 g; 1.5 equiv	0.075 g; 0.029 equiv Pd	2.0 mL
30	0.168 g; 1.0 equiv	0.168 g; 2.0 equiv	0.140 g; 1.5 equiv	0.074 g; 0.029 equiv Pd	2.0 mL
60	0.168 g; 1.0 equiv	0.168 g; 2.0 equiv	0.140 g; 1.5 equiv	0.075 g; 0.029 equiv Pd	2.0 mL

Table 8. **Screening experiments of FibreCats**

		component				
reactor	FibreCat	**1**	**2**	NaO-*t*-Bu	FibreCat	1,4-dioxane
A	1001; 5.05 wt % Pd	0.165 g; 1.0 equiv	0.167 g; 2.0 equiv	0.143 g; 1.5 equiv	0.0613 g; 0.031 equiv Pd	2.0 mL
B	1007; 1.77 wt % Pd	0.165 g; 1.0 equiv	0.167 g; 2.0 equiv	0.144 g; 1.6 equiv	0.175 g; 3.0 equiv Pd	2.0 mL
C	1026; 4.14 wt % Pd	0.164 g; 1.0 equiv	0.166 g; 2.0 equiv	0.143 g; 1.6 equiv	0.076 g; 0.031 equiv Pd	2.0 mL
D	1032; 4.26 wt % Pd	0.168 g; 1.0 equiv	0.171 g; 2.0 equiv	0.147 g; 1.6 equiv	0.073 g; 0.030 equiv Pd	2.0 mL

Table 9. **Reuse of catalyst**

			component		
reaction	**1**	**2**	NaO-*t*-Bu	FibreCat 1026	1,4-dioxane
1	0.164 g; 1.0 equiv	0.166 g; 2.0 equiv	0.143 g; 1.6 equiv	0.076 g; 0.031 equiv Pd	2.0 mL
2	0.168 g; 1.0 equiv	0.166 g; 2.0 equiv	0.140 g; 1.5 equiv		2.0 mL
3	0.165 g; 1.0 equiv	0.169 g; 2.0 equiv	0.142 g; 1.5 equiv		2.0 mL

toluene increased further as the production of 1,1′-dimethyl-4,4′-biphenyl did. These observations lead to the conclusion that, prior to further reuse application of the heterogeneous catalyst, it is necessary to identify parameters that can slow down the release rate of the active components from the polymer support.

7. Experimental Section

7.1. Materials. *p*-Bromotoluene was purchased from Merck; piperazine, toluene, 1,1′-dimethyl-4,4′-biphenyl, and 1,4-dioxane were purchased from Aldrich. All chemicals and solvents were used without any prior treatment. Johnson Matthey Catalyst delivered the four different immobilized catalysts, which have been designed to facilitate cross-coupling reactions. Palladium dichloride and reference compound for the analysis calibration of 1-(4-methylphenyl)piperazine was from Fluka. A reference compound for 1,4-bis(4-methylphenyl)piperazine was produced according to a literature procedure.[16]

7.2. Preparation of the Reaction Mixtures. In the following sections each of the experiments carried out is described. Where nothing else is specified, the reaction was carried out in a microwave cavity under nitrogen atmosphere and agitation (600 rpm) for 3 h at 90 °C.

7.2.1. Course of Reaction. Process vials containing the amounts given in Table 7 were prepared. They reacted under standard conditions for 5, 10, 20, 30, and 60 min. Subsequently, the reaction mixtures were analyzed using HPLC.

7.2.2. Screening of the FibreCats. Four process vials were prepared according to Table 8. The reaction was carried out using standard conditions. After reaction the reaction mixture in the process vials was analyzed by HPLC.

7.2.3. Reaction with Reuse of the Catalyst. In a process vial the compounds listed in reaction 1 in Table 9 were introduced. The reaction was carried out using standard condition. After reaction the reaction mixture was analyzed by HPLC. The catalyst from reaction 1 was collected by filtration, and no further workup of the catalyst was carried out. The catalyst was transfered to a new process vial and compounds according to reaction 2 in Table 9 were introduced. The reaction and analysis were carried out similar to reaction 1. This procedure was also applied in reaction 3.

7.2.4. Wash of the Catalyst Prior to Reaction. In a flask 0.073 (0.029 equiv) g of FibreCat 1026 was mixed with 2.0 mL of 1,4-dioxane. The flask was left for 30 min at room temperature with agitation and nitrogen atmosphere. The FibreCat was separated by filtration and introduced to a process vial, which contained 0.168 g (1.0 equiv) of **1**, 0.168 g (2.0 equiv) of **2**, 0.142 g (1.5 equiv) of NaO-*t*-Bu, and 2.0 mL of 1,4-dioxane. Subsequently, it reacted under standard condition and was finally analyzed by HPLC. The dioxane used in the initial treatment of the catalyst was introduced to a process vial together with 0.164 g (1.0 equiv) of **1**, 0.165 g (2.0 equiv) of **2**, and 0.140 g (1.5 equiv) of NaO-*t*-Bu. This vial reacted under the same conditions as above.

7.2.5. Reuse of the Entire Reaction Mixture. Compounds according to reaction 1 in Table 10 were placed in a process vial. The reaction was carried out using standard condition. After reaction the reaction mixture was analyzed by HPLC. After the analysis new reactants according to reaction 2 in Table 10 were added to the process vial, and it was allowed to react for another 3 h under same conditions as above.

7.2.6. Reactivation of the Catalyst. In a flask 0.073 (0.029 equiv) g of FibreCat 1026 was mixed with 2.0 mL of 1,4-dioxane. The flask was left for 30 min at room temperature with agitation and nitrogen atmosphere. The FibreCat was

Table 10. **Reuse of catalyst**

	component				
reaction	**1**	**2**	NaO-*t*-Bu	FibreCat 1026	1,4-dioxane
1	0.166 g; 1.0 equiv	0.164 g; 2.0 equiv	0.140 g; 1.5 equiv	0.072 g; 0.029 equiv Pd	2.0 mL
2	0.166 g; 1.0 equiv	0.164 g; 2.0 equiv	0.143 g; 1.5 equiv		

separated by filtration and introduced to a process vial, which contained 0.168 g (1.0 equiv) of **1**, 0.168 g (2.0 equiv) of **2**, 0.142 g (1.5 equiv) of NaO-*t*-Bu, and 2.0 mL of 1,4-dioxane. Subsequently, it reacted under standard condition and was finally analyzed by HPLC. The dioxane used in the initial treatment of the catalyst was introduced to a process vial together with 0.164 g (1.0 equiv) of **1**, 0.165 g (2.0 equiv) of **2**, and 0.140 g (1.5 equiv) of NaO-*t*-Bu. This vial reacted under the same conditions as above.

The catalyst from reaction 3 in section 7.2.3 was separated from the reaction mixture by filtration. The catalyst was mixed with 0.007 g $PdCl_2$ (corresponds to the initial amount on a molar basis of Pd in the FibreCat) and 0.007 g triphenylphosphine (corresponds to half the initial amount on a molar basis of Pd in the FibreCat) in 2.0 mL of 1,4-dioxane. The mixture was left for 1 h at room temperature (N_2 atmosphere and agitation). After 1 h the catalyst was collected by filtration and transfered to a process vial together with 0.170 g (1.0 equiv) of **1**, 0.167 g (2.0 equiv) of **2**, 0.140 g (1.5 equiv) of NaO-*t*-Bu, and 2.0 mL of 1,4-dioxane. The reaction was carried out using standard conditions. Finally, the reaction mixture was analyzed by HPLC.

7.3. Reproducibility of the Experimental Results. The quantification of compounds **1**, **3**, **4**, **5**, and **6** was obtained by using HPLC. On the basis of the measured intensities and Lambert–Beers law (eq 9) the concentrations were calculated.

$$C = \frac{A}{\varepsilon \cdot l} \tag{9}$$

From eq 9 it follows that the uncertainties in the calculation of the concentrations, C, are introduced in the determination of the expansion coefficient, $\epsilon \cdot l$, and the absorbance, A, of the reaction mixture. In order to make a conclusion of the reproducibility of the experiments, the standard deviation of a composite measurement needs to be found. The standard deviation of a composite measurement is calculated on the basis of the standard deviation of the direct measured values for $\epsilon \cdot l$ and A.[34] The expansion coefficients were determinedon the basis of a linear regression. A R^2-value higher than 0.995 was obtained for all components. Because of the satisfying correlation it was concluded that uncertainties only were introduced to the system from the HPLC analysis.[35] The standard deviation for each of the following components were found using the following method. Four independent process vials were prepared. Each of the vials reacted for 3 h at 90 °C. For each of the vials two samples were prepared, which subsequently were analyzed twice on the HPLC. The standard deviation for the concentration determination was then calculated, and the relative standard deviations are shown in table 11.

Table 11. **Relative standard deviation for the detectable compounds**

	component				
	1	**3**	**4**	**5**	**6**
relative standard deviation (%)	55.1	4.4	10.4	14.1	41.1
average concentration (mol/L)	0.004	0.2038	0.0454	0.0577	0.002

From Table 11 it is observed that the standard deviation differs for the five components. The high standard deviations for **1** and **6** are due to the low concentration present in the sample (respectively, 0.004 and 0.002 mol/L). In reality the relative standard deviation is expected to be in the same area as for **3**.

7.4. Methods. The reaction mixtures were heated in a 300 W Emrys Optimizer microwave cavity from Personal Chemistry. Emrys Process Vials 2–5 mL were used as reactors. An infrared detector monitored the temperature of the reaction mixture. In all reactions the temperature of the reaction mixture in the microwave cavity did not exceed the boiling point of the solvents at atmospheric pressure.

The experimental results were obtained by HPLC using UV detection at 215 nm. The general procedure for the analysis of the reaction mixtures was as follows. Approximately 0.5 mL of the reaction mixture was transfered to a vial, which was centrifuged for 5 min at 2000 RPM. This treatment ensured an efficient separation of the reaction mixture and the FibreCat. Subsequently, 20 μL of the reaction mixture was transferred from the vial to a sample vial, which contained 1.00 mL of methanol. The HPLC was operated under isocratic conditions, and the mobile phase consisted of methanol and $HCOONH_4/NH_3$ buffer (0.20 M, pH = 9.0, 7:3). The method of analysis applied allowed the following components to be detected and quantified: **1**, **3**, **4**, **5**, and **6**. The quantification of the five components was done by applying the Lambert–Beers law. The extinction coefficient was calculated for each of the five components based on a standard row of four. The components were dissolved in 1,4-dioxane.

The formation of **3** and **4** was confirmed by ^1H and ^{13}C NMR, LC-MS, and HPLC; **5** was confirmed by HPLC; and **6** was confirmed by HPLC and GC-MS. The spectra obtained were compared to the spectra for the reference compounds. Conditions for HPLC: MERCK-HITACHI L-5025 column thermostat, L-4250 UV–vis detector, D-6000 interface, L-6200A intelligent pump, As-2000A autosampler, Colombus column 100 × 4.60 mm, 5μ, C8, 110A. Conditions for NMR: Bruker Avance 500 MHz 2-channel spectrometer. Conditions for LC-MS: API150ex single quadrupole mass spectrometer. Conditions

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for GC-MS: Varian Star 3400 CX, Varian Saturn 2000 equipped with a column from Zebron, ZB-5, 15 m, 0.25 mm, 0.25 μm.

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