



REGULAR ARTICLE

Homogeneous catalyst containing Pd in the reduction of aryl azides to primary amines

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Abstract. Commercially available dichloro[2,2'-bis(diphenylphosphino)-1,1'-binaphthyl]palladium(II) (BINAP.PdCl₂) homogeneous catalyst was used for the reduction of aryl azides to primary amines. The reactions were carried out in water and yields above 95% were obtained in a short time. Sodium borohydride was used as the reducing reagent. A number of aryl azide derivatives have been converted into primary amines, thanks to the hydrogen gas released by sodium borohydride with the help of water and catalyst.

Keywords. Aryl azides; Hydrogenation; Primary amines; BINAP.PdCl₂.

1. Introduction

Primary amines are compounds of industrial importance.^{1,2} Amines, which are indispensable components of organic chemists, are molecules that have proven themselves in many sectors such as medicine, agriculture, paint, etc.³⁻⁶ It is of great importance as both the main substance and the intermediate in synthesis reactions. It is often used as starting material in the synthesis of biologically active derivatives. The primary amines^{7,8} such as deoxyadenosine monophosphate⁹, streptomycin¹⁰ and neamine¹¹ (Figure 1), are valuable organic mediators for the production of many important biological molecules.

Primary amines; It is obtained by easy procedures such as the reduction of nitro^{12,13} and nitrile^{14,15} compounds, as well as by gruelling processes such as Hofmann conversion¹⁶ and reductive amination.¹⁷ It is also possible to synthesize primary amines by reducing aryl azides under suitable conditions.¹⁸ It is possible to find many studies in this field in the literature. The hydrogenation reactions can be carried out in milder conditions if the reaction inputs such as solvent, reducing reactive and catalysts create a synergistic effect. Hydrogen gas is generally used directly in

hydrogenation reactions. However, this procedure is risky and may require higher cost systems.¹⁹⁻²¹ However, in recent years, liquid and solid sources have been used in transfer hydrogenation methods. Cyclohexane, glycerol, ethanol and 2-propanol, which are used as liquid sources, play an active role in both solvent and transfer hydrogenation. However, these liquids are not preferred due to their high heat requirement.²²⁻²⁴ On the contrary, although the use of solid hydrogen sources requires an extra solvent, it is possible to form hydrogen gas at room temperatures. For this reason, solid hydrogen sources such as metal hydride, sodium borohydride, lithium aluminumhydride, ammoniaborane are generally preferred in hydrogenation reactions.^{25,26}

Of course, the catalysts used are also important in the formation of hydrogen gas from these hydrogen sources (Eq. 1).^{27,28} For this purpose, many homogeneous and heterogeneous catalysts are used in the literature. Both types of catalysts have advantages and disadvantages over each other. While homogeneous catalysts are important in terms of solubility and efficiency in the reaction, heterogeneous catalysts are important in terms of removal from the reaction medium.²⁹⁻³¹

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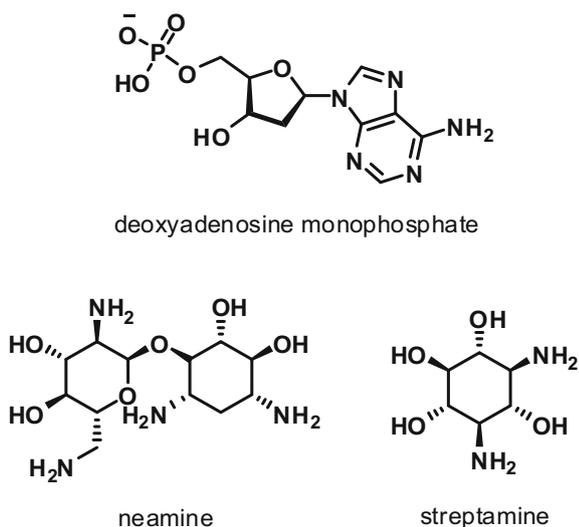


Figure 1. Chemical structure of the primary amines.



Some of the catalysts are commercially available, and most of them are newly introduced to the literature. It is not possible to expect every catalyst used to be effective in the hydrogenation sector. Therefore, choosing the right catalyst is essential.

In this study, a new method was developed for the hydrogenation of aryl azides to primary amines. This developed method was carried out in an environmentally friendly solvent, in water. In addition, sodium borohydride was preferred as solid hydrogen source and commercially available BINAP.PdCl₂ was preferred as catalyst.

2. Experimental

2.1 Materials

The aryl azide compounds, BINAP.PdCl₂ and NaBH₄ used in the study were supplied from Sigma-Aldrich.

2.2 Characterization methods

The NMR spectra were recorded on an AVANCE III 400MHz spectrometer.

2.3 General Procedure for the Synthesis of Primary Amine Compounds

Into a reaction vessel at room temperature were placed the aryl azide derivatives (0.25 mmol), and

BINAP.PdCl₂ (2.0 mg). 1.0 mL of water was added to the reaction vessel. Finally, sodium borohydride was rapidly added to the reaction mixture and the lid of the reaction vessel was tightly closed. The progress of the reaction was monitored by TLC analysis. After the reaction was complete, the solvent was removed by an evaporator. The products were purified by flash column chromatography. The products were identified by ¹H-NMR.

3. Results and Discussion

1-azido-4-methylbenzene was used for optimization reactions. Depending on our previous experience in hydrogenation reactions, sodium borohydride was used 3 equivalents according to the substrate. The amount of catalyst to be used was determined by changing the solvent type to keep the amount of NaBH₄ constant. First of all, toluene, a polar solvent, was used as the solvent. However, no product formation was observed (Table 1, Entry 1). On the other hand, a solvent with high polarity such as dichloromethane was also used. The result is frustration again (Table 1, Entry 4). Both solvents are not suitable solvents for the dehydrogenation of sodium borohydride. As can be seen in Table 1, high yields of reduced products were obtained by using solvents with high polarity such as methanol, ethanol and water (Table 1, Entries 2, 3, 5). The methanol/water mixture also contributes to the production of products with high yields (Table 1, Entry 6). It is preferred that the method developed in the study is only in an aqueous medium (Table 1, Entry 5). The final procedure was created: 0.25 mmol of the 1-azido-4-methylbenzene, 2.0 mg of BINAP.PdCl₂ and 0.75 mmol NaBH₄ gave an adequate performance for the conversion of 1-azido-4-methylbenzene into *p*-toluidine with 1.0 mL of water (Table 1, entry 7).

Table 2 shows that a series of aryl azides were reduced under the effect of homogeneous catalyst. BINAP.PdCl₂ was used as the homogeneous catalyst and NaBH₄ was used as the reducing material. Aryl azides were reduced to primary amines in high yields in water, an environmentally friendly solvent. For example, azidobenzene was converted to aniline oxime with >95% yield within 15 min (Table 2, entry 1). 1-azido-2-bromobenzene and 1-azido-4-bromobenzene were converted to 2-bromoaniline and 4-bromoaniline with >95% yield within 15 min (Table 2, entries 2, 3). 1-azido-3-methylbenzene and 1-azido-4-methylbenzene were converted to *m*-toluidine and *p*-toluidine with high yields (Table 2, entries

Table 1. Optimization of the reaction conditions.^a

Entry	Solvent 1	Solvent 2	Amount of Catalyst (mg)	Time (min)	Yield ^b (%)
1	Toluene	-	4	60	-
2	Methanol	-	4	30	>90
3	Ethanol	-	4	30	>85
4	CH ₂ Cl ₂	-	4	60	-
5	Water	-	4	30	>95
6 ^c	Water	Methanol	4	30	>95
7	Water	-	2	15	>95

^aReaction Conditions: 0.25 mmol of 1-azido-4-methylbenzene, 0.75 mmol NaBH₄, ^bThe yield was determined by the analysis of the ¹H NMR spectra. ^cMethanol/mineral water (1/1 v/v).

Table 2. The reduction of aryl azides in the presence of homogenous catalyst.^a

Entry	R	Time, min	Yield ^b , %	Lit.
1	C ₆ H ₅	15	>95	32
2	2-BrC ₆ H ₄	15	>95	33
3	4-BrC ₆ H ₄	15	>95	33,34
4	3-MeC ₆ H ₄	15	>95	35
5	4-MeC ₆ H ₄	15	>95	35
6	4-MeOC ₆ H ₄	15	>95	34
7	4-NH ₂ C ₆ H ₄	15	>95	34
8	4-IC ₆ H ₄	15	16	35

^aUnless otherwise stated, 0.25 mmol of substrate, 0.75 mmol of NaBH₄, 2.0 mg of BINAP.PdCl₂, 1 mL of water, at room temperature, ^bAll products are known compounds and exhibit satisfactory spectroscopic data.

4, 5). 1-azido-4-methoxybenzene and 4-azidoaniline were converted to 4-methoxyaniline and benzene-1,4-diamine within 15 min (Table 2, entries 6, 7).

1-azido-4-iodobenzene was converted to 4-iodoaniline with a 16% yield within 15 min (Table 2, entry 8). Surprisingly, the reduced product was obtained in a very low yield. It did not change as a result of the prolongation of the reaction time. Because dehalogenation product is observed in the reaction.³⁶ The hydrogenation and dehalogenation reactions are in competition. This risk is always present if the halogen atom attached to the aromatic ring is iodine. The results also support this suspicion. This risk is lower for other halogen atoms, and if the reaction time is prolonged, dehalogenation may be observed first after the reduction reaction.

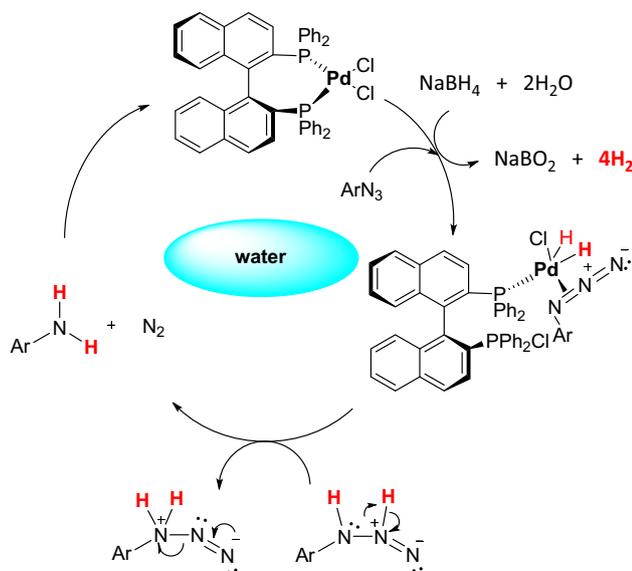
As seen in Table 3, the reduction of azidobenzene to aniline was carried out under the influence of the Pd NPs catalyst. Among the experiments on different solvents in this study, the most interesting one is the reduction in tetrahydrofuran (THF). In addition, the H₂ molecule at 8 atm was used as the hydrogen source. Under these conditions, aniline was synthesized in 16 h at 50 °C with a yield of over 99% (Table 3, entry 1).³² In another study, the aniline compound was obtained in 83% yield under reflux for 8 hours in an environmentally friendly solvent such as water under the influence of ammonium formate (HCOONH₄) and Cu NPs (Table 3, entry 2).³⁴ The reduction of aryl azides to primary amines with high yields at room temperature and in a short time was carried out by our group under the influence of homogeneous and heterogeneous catalyst and sodium borohydride. Of course, catalysts have advantages and disadvantages over each other. While it is seen that the reaction efficiency is higher in the use of homogeneous catalyst, it is possible to practically remove the heterogeneous catalyst from the reaction medium and use it repeatedly (Table 3, entries 3,4).^{33,35} Compared with the present study, the reduction of aryl azides to primary amines was carried out under a homogeneous catalyst only in water and at room temperature (Table 3, entry 5).

In Figure 2, the catalyst is in a plane-square configuration. In the first step, it is thought that 1 mole of phosphorus bonds are separated from the catalyst structure and 1 mole of hydrogen is attached to the structure. 1 mole of hydrogen-bonded to the metal is obtained in the reaction medium by hydrolysis of sodium borohydride. Hydrogen atoms are individually bonded to the metal structure by a covalent bond. The aryl azide compound then coordinates with the metal. The hydrogen atoms in the metal structure are transferred to the aryl azide compound in two stages,

Table 3. The previous studies on the reduction of azidobenzene to aniline.

		Catalyst				
		Ph-N ₃ → Ph-NH ₂				
Entry	Catalyst	Solvent	Hydrogen Source	Time, h	Temperature, °C	Yield ^b , %
1	Pd NPs	THF	H ₂ (8 atm)	16	50	>99
2	Cu NPs	H ₂ O	HCOONH ₄	8	100	83
3	PdAlO(OH) NPs	H ₂ O/CH ₃ OH	NaBH ₄	1/4	25	>99
4	[Ru(p-cymene)Cl ₂] ₂	H ₂ O/CH ₃ OH	NaBH ₄	1/6	25	>95
5 ^a	BINAP.PdCl ₂	H ₂ O	NaBH ₄	1/4	25	>95

^a This Study.

**Figure 2.** Proposed mechanism.

allowing the molecule to be separated from the metal structure. As the molecule separated from the metal turns into the primary amine compound as a result of the arrangement within itself, nitrogen gas is released.³⁵

4. Conclusions

A new method has been developed for the synthesis of primary amines under mild conditions using a series of aryl azide derivatives. Dichloro[2,2'-bis(diphenylphosphino)-1,1'-binaphthyl]palladium(II), a commercially available homogeneous catalyst, was used in this method. Sodium borohydride was used as the hydrogen source. The reaction was carried out in the water and at room temperature, and high yields were obtained. The method has some advantages: i) being practical and environmentally friendly, ii) using water

as a solvent, and iii) obtaining primary amines with high yield in a short time.

Supplementary Information (SI)

¹H-NMR spectra for primary amines. Supplementary information is available at www.ias.ac.in/chemsci.

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Declarations

Conflicts of interest The authors declare no conflict of interest.

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