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ONE-POT SYSTEM FOR REDUCTION OF EPOXIDES USING NaBH₄, PdCl₂ CATALYST, AND MOIST ALUMINA

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Reduction of epoxides with sodium borohydride, a catalytic amount of palladium(II) chloride, and chromatographic neutral alumina preloaded with a small amount of water (moist alumina) in hexane gave alcohols in good to excellent yields and good selectivity of the desired products under mild conditions. The reaction system was operationally simple and environmentally friendly. The alumina can be recovered simply and reused a number of times without any treatment and with good activity.

Keywords: Epoxide; moist alumina; palladium chloride; reduction; sodium borohydride

Epoxides are widely employed as fragrance chemicals and are used in perfumes and deodorants.^[1] Epoxides can be reduced either to alcohols by ring-opening via hydrogenolysis (Fig. 1, path A) or to alkenes by deoxygenation (Path B). Path A enjoys an important position in organic synthesis, and therefore this process has been the subject of extensive research.^[2] It is well known that asymmetrical epoxides afford mixtures of isomeric alcohols, the product ratios of which are strongly dependent on the reducing agents employed. For example, a combination of a hydride reagent (e.g., NaBH₄ or LiAlH₄) and a Lewis acid such as AlCl₃,^[3] zinc borohydride supported on silica gel^[4] and AlPO₄,^[5] and aluminumoxyhydride^[6] produces the least substituted alcohols; however, a disadvantage of these reaction methods is the poor selectivity to the desired product. A mixture of primary and secondary alcohols and other by-products are obtained, requiring with subsequent purification to give the desired product in poor yields.

We have found that our system [sodium borohydride (NaBH₄)/moist alumina in hexane] is excellent for the good selective reduction of aliphatic and aromatic carbonyl compounds to corresponding alcohols in excellent yields.^[7]

Recently, this reaction system was used to develop a new one-pot reduction, which has been applied to the synthesis of chiral alcohols, β -azidoalcohols, allylic alcohols, 1,2-diols, and chiral lactones.^[8]

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Figure 1. Epoxides reduction process (Path A: ring-opening via hydrogenolysis produce alcohols, Path B: deoxygenation produce alkene).

This reaction system was able to utilize the reduction of only various carbonyl compounds, so we developed a new system for the reduction of alkenes that required slightly modified reaction conditions compared with carbonyl compound reduction conditions to produce hydrogenation products in the presence of catalytic amounts of metal salts.^[9]

In the course of our recent investigation into the synthetic utility of $NaBH_4$ under solid–solution biphasic conditions, we found that epoxides were reduced to alcohols by simply adding a catalytic amount of palladium(II) chloride (PdCl₂) to a heterogeneous mixture of $NaBH_4$ and moist alumina (vide infra) in hexane. We now report the reaction of epoxides with the $NaBH_4/metal$ catalyst/moist alumina system because it gives a new, simple reduction of epoxides under mild conditions.

The reaction of styrene oxide (1a) with NaBH₄ and moist alumina in the presence of a variety of metal chlorides gave 2-phenylethanol (2a), along with styrene (4a) and ethylbenzene (5a) in varying amounts (Fig. 2, Table 1). It should be noted that no 1-phenylethanol (3a) was formed in any case, suggesting that regioselective ring opening occurred leading to the primary alcohol 2a. Of the metal salts examined (NiCl₂, CoCl₂, PdCl₂, BiCl₃, CuCl₂, CrCl₂, and ZnCl₂), PdCl₂ may be the catalyst of choice for the present reaction in terms of the conversion of 1a and the yield of 2a. In addition, it is frequently observed that the efficiency of the solid–solution biphasic reactions is dependent on the solid supports employed.^[10] Therefore, another comparative study was performed using various solid supports. Reduction activity and selectivity of products using zeolites, which have a larger surface area and a microporous structure; clays, which have a layered structure; montmorillonite K-10, which has strong acidity; and hydrotalcite, which has strong basicity, are remarkably less than those of neutral alumina. Neutral alumina was superior to the others as a support.

Reduction of typical aryl, aliphatic, and alicyclic epoxides was carried out with the NaBH₄/PdCl₂ catalyst/moist alumina system in hexane (Fig. 3). Table 2



Figure 2. Styrene oxidation reduction.

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	Metal salt	GC yield (%)						
Entry		$1a^b$	2a	3a	4a	5a		
1	NiCl ₂ · 6H ₂ O	38	54	0	trace	6		
2	CoCl ₂ · 6H ₂ O	80	11	0	9	trace		
3	PdCl ₂	0	69	0	0	24		
4	BiCl ₃	63	11	0	8	1		
5	$CuCl_2 \cdot 2H_2O$	56	14	0	27	3		
6	CrCl ₂	85	2	0	0	0		
7	ZnCl ₂	87	2	0	0	0		
8	_	>99	0	0	0	0		

Table 1. Effect of metal salts on the reduction of styrene oxide^a

^{*a*}At 40 °C for 3 h; **1a** (1 mmol), NaBH₄ (2 mmol), moist alumina (H₂O content, 19 wt.%, 2 g), metal salt (0.1 mmol), and hexane (10 ml) were used.

^bRecovered substrate in mol%.

summarizes the optimized yields of alcohols, in which only alcoholic products (2 and 3) are presented, because alkenes were (if any) formed in negligible or only minor amounts. Aryl epoxides (entries 1–7) underwent smooth reduction to give exclusively the alcohols 2. Reductive dechlorination accompanied the reaction of *p*-chlorostyrene oxide (1e), giving 2-phenylethanol in 20% yield. Chloro-substituted aromatic and aliphatic compounds converted to dechlorination compounds using the palladium-supported catalyst; therefore cleavage of the C-Cl bond also occurred in this reaction system.^[11]

In the case of *p*-nitrostyrene oxide (**1f**), the nitro-moiety was susceptible to the reduction and afforded 2-(4-aminophenyl)ethanol and 4-aminophenylethane in 54% and 5%, respectively. Aliphatic (entries 8–10) and alicyclic (entries 11 and 12) epoxides were less reactive toward the present reducing system than the aromatic



Figure 3. Epoxides reduction and structure of epoxides.

							Alcohol ^d		
Entry	Epoxide	NaBH ₄ (mmol)	$Al_2O_3^{\ b}(g)$	PdCl ₂ (mmol)	Temp. (°C)	Time (h)	1^c	2	3
1^e	1a	0.5	0.5	0.1	30	1	0	84	0
2	1b	0.5	0.5	0.1	30	1	0	93	0
3	1c	2.0	2.0	0.2	60	3	0	33	65
4	1d	0.5	0.5	0.1	30	1	0	>99	0
5	1e	1.0	1.5	0.1	30	1	0	70 ^f	0
6	1f	2.0	2.0	0.2	60	3	0	54 ^g	0
7	1g	0.5	0.5	0.1	30	2	0	84	0
8	1h	4.0	4.0	0.4	60	6	91	2	2
9	1i	4.0	3.0	0.3	60	4	25	3	75
10	1j	5.0	4.0	0.4	60	3	25	53	13
11	1k	4.0	3.0	0.3	60	4	89	8	
12	11	4.0	4.0	0.3	60	4	90	4	

Table 2. Reduction of epoxides^a

^aEpoxide (1 mmol) and hexane (10 ml) were used.

^bMoist alumina (H₂O content, 19 wt.%) was used.

^cIsolated yield (mol%).

^dRecovered epoxide in mol%.

^eEthylbenzene (14%) was formed.

^f2-Phenylethanol (20%) was formed.

^g2-(4-Amino-phenyl)ethanol; 4-aminophenylethane (5%) was also formed (see text).

epoxides, and appreciable amounts of the starting materials were recovered. The observed high reactivity of the aromatic substrates as well as the exclusive formation of the alcohols **2** could be responsible for the stability of the intermediate benzylic cations, because in the case of asymmetrical epoxides it is generally accepted that reducing agents preferentially attack carbons, generating more stabilized cations en route to the major products.^[12] However, allylbenzene oxide (**1c**) and 1-decene oxide (**1i**) gave the secondary alcohols **3c** and **3i**, respectively, in preference to the corresponding primary alcohols **2**. These results cannot reasonably be explained only by the relative stabilities of the intermediate carbocations.^[13] Alternative factors such as geometry of the substrates and/or intermediates (i.e., restriction or steric control) on the alumina surface may play a role in determining the observed product distributions. In the absence of moist alumina, no appreciable conversion of **1a**, for example, was observed; therefore, the present reaction certainly took place on the alumina surface. Thus, further studies of the detailed mechanism is currently under way in our laboratory.

The alumina can be recovered by simple filtration (see the Experimental section) and reused a few times with good activity and without any treatment. The alumina might be reused a number of times based on the yield and selectivity of the desired product.

In summary, the reduction of various epoxides with the $NaBH_4/PdCl_2$ catalyst/ moist alumina system in hexane gave the least substituted alcohols in good to excellent yields under mild conditions. This system requires no preparation of the reducing agents, which introduces an additional stage. We are now looking for an alternative synthetic target using the $NaBH_4$ -based heterogeneous system.

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EXPERIMENTAL

A typical experiment was carried out as follows: deionized water (0.095 g) was added to chromatographic neutral alumina (ICN Biomedical, Alumina N, Super I; 0.41 g) in several portions, followed by vigorous shaking of the mixture on every addition for a few minutes until a free-flowing powder was obtained, to afford moist alumina (H₂O content, 19 wt.%), which was immediately used for the reduction. Styrene oxide **1a** (0.12 g, 1 mmol), hexane (10 mL), PdCl₂ (Wako; 0.017 g, 0.1 mmol), freshly prepared moist alumina (0.50 g), and NaBH₄ (Wako; 0.019 g, 0.5 mmol) were placed into a 30-mL round-bottom flask, and the resultant heterogeneous mixture was magnetically stirred at 30 °C. After 1 h, the reaction mixture was filtered, and the filter cake was washed thoroughly with portions of dry ether (in total, ca. 60 mL). The yield of **2a** was determined by gas chromatography (GC) using anisole as an internal standard. The alcohols listed in Table 2 were isolated.

Alcohols thus obtained were identified spectroscopically (¹H NMR, IR, GC-MS) via comparisons with the authentic samples.

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