Homogeneous Catalysis

Homogeneous Palladium-Catalyzed Transfer Hydrogenolysis of Benzylic Alcohols Using Formic Acid as Reductant

Benjamin Ciszek and Ivana Fleischer*[a]

Abstract: We report the first homogeneous palladium-based transfer hydrogenolysis of benzylic alcohols using an in situ formed palladium-phosphine complex and formic acid as reducing agent. The reaction requires a catalyst loading as low as only 1 mol% of palladium and just a slight excess of reductant to obtain the deoxygenated alkylarenes in good to excellent yields. Besides demonstrating the broad applicability for primary, secondary and tertiary benzylic alcohols, a reaction intermediate could be identified. Additionally, it could be shown that partial oxidation of the applied phosphine ligand was beneficial for the course of the reaction, presumably by stabilizing the active catalyst. Reaction profiles and catalyst poisoning experiments were used to characterize the catalyst, the results of which indicate a homogeneous metal complex as the active species.
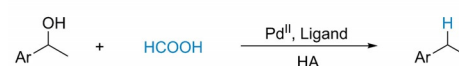
The reduction of C—O to C—H bonds constitutes an essential transformation in organic chemistry, for example, in the deoxygenation of alcohols or carbonyl compounds.[1] The large number of methods reported in the last century account for this, with the most popular one being the Barton–McCombie deoxygenation.[2] A severe drawback of these methods is the need for harsh reaction conditions and high amounts of reducing agents, leading to decreased selectivity and toxic waste. Therefore, catalytic approaches such as hydrogenolysis are of considerable interest. The term hydrogenolysis refers to the cleavage of C—C or C–heteroatom bonds by using hydrogen. Since Padoa and Ponti described the nickel-catalyzed hydrogenolysis of furfuryl alcohol in 1908,[3] numerous protocols for this transformation were developed. More recent works, especially those concerning the transformation of benzylic alcohols and ketones into the corresponding alkylarenes, apply transition-metal catalysts like nickel,[4] cobalt,[4] palladium[5] or ruthenium.[6] Molecular hydrogen is often chosen as reductant because of its low price, the high atom economy of the reduction and for water being the only by-product formed.[7] Nonetheless, hydrogen gas is highly flammable and requires special pressure equipment. For these reasons, so-called transfer hydrogenolysis reactions are applied, using alternative hydride donors like silanes,[5a–d,8] alcohols,[4] cyclohexadiene[9] or formic acid.[10] When applying formic acid as a reducing agent, palladium is most frequently used as the catalyst; however, all reported methods for the deoxygenation of benzylic alcohols with formic acid so far rely on heterogeneous palladium on solid support, requiring high catalyst loadings.[10] Thus, the development of a more selective and active homogeneous catalyst system appears to be highly attractive. Additionally, homogeneous catalysis usually allows for easier catalyst modification and mechanistic investigations.

Intrigued by the lack of a homogeneous palladium-based transfer hydrogenation of benzylic alcohols, we were determined to develop such a method using formic acid as reductant (Scheme 1). Compared to conventionally used hydride

Scheme 1. Heterogeneous versus homogeneous palladium-catalyzed transfer hydrogenolysis.

sources, formic acid bears several advantages concerning its transport and handling and can be easily produced from CO_2 and H_2.[11] Furthermore, it exhibits a higher chemoselectivity than hydrogen gas because overreduction of aromatic systems is prevented.[12] In the transfer hydrogenolysis of alcohols with formic acid, only water and CO_2 are obtained as by-products. Re-using the latter in formic acid synthesis would lead to a highly atom economic and sustainable process.

We chose 1-phenylethanol (**1a**) as a model substrate for the optimization experiments (Scheme 2). Based on our previous studies using Pd-catalysts,[13] the applied catalyst system consisted of a palladium precatalyst, bidentate phosphine ligand **L1** and a Brønsted acid co-catalyst. The initial optimization (for

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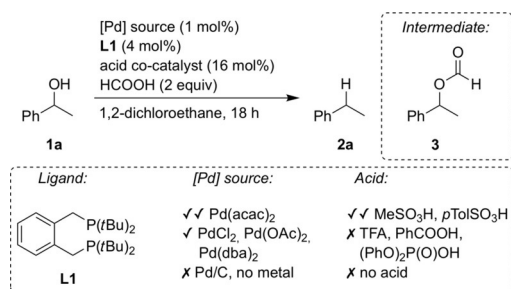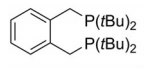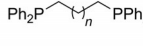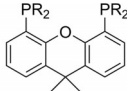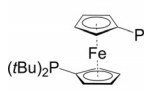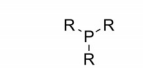
Scheme 2. Optimization of reaction conditions for the palladium-catalyzed transfer hydrogenolysis of 1-phenylethanol.

extended details see the Supporting Information) showed that the use of Pd^{II} as well as soluble Pd^0 precursors in the reaction resulted in excellent to quantitative product yields with Pd(acac)$_2$ being superior. With heterogeneous Pd/C, no significant amount of product was detected. Without any metal, no transfer hydrogenolysis occured at all. The testing of different acid co-catalysts made it apparent that only sulfonic acids like methane- or *para*-toluenesulfonic acid led to high product yields. When weaker Brønsted acids were applied, a possible intermediate of the reaction was identified: Esterification of formic acid with 1-phenylethanol gave 1-phenylethyl formate (**3**); the role of this species will be discussed below. It was found that the transfer hydrogenolysis proceeds smoothly also at lower temperatures, although a prolongation of the reaction time was required in some cases to obtain a good product yield. The reaction was then further optimized in terms of loading of Pd(acac)$_2$, **L1** and methanesulfonic acid as well as the amount of formic acid.

Next, the applied phosphine ligand was varied (Table 1). To our surprise, only one of the tested ligands, namely **L1**, led to a significant amount of product. The use of other bidentate

phosphines either gave no or only minor amounts of product **2 a**. Monodentate phosphines like **L7** or **L8** also showed only marginal activity. Exclusion of any ligand led to a breakdown of the desired reactivity. When searching for reasons for the observed exclusive ligand effect, we came across reports about **L1** forming, under similar conditions, a relatively stable palladium-phosphine-hydride complex that can isomerize C—C double bonds as well as perform the carbonylation of alkenes.[14] We assume this to be an initial hint towards the structure of the catalytically active species in the transfer hydrogenolysis reported in this work.

In the further course of our studies on the homogeneous transfer hydrogenolysis, the use of a new batch (B) of **L1** from a different supplier led to significantly lower product yields for several substrates than the previously used batch (A). ^{31}P-NMR analysis of both samples showed that batch A was delivered already partially oxidized (two signals at $\delta = 62.07$ and 24.15 ppm; integration resulted in a ratio of ligand **L1** to ligand oxide **L1-(O)$_2$** of 3:1, see the Supporting Information for details), whereas batch B contained pure **L1**. To investigate this phenomenon, we conducted a series of transfer hydrogenolysis experiments in which the applied ligand was varied in presence of **L1-(O)$_2$** and the phosphine oxide was varied in presence of **L1** (for details see the Supporting Information). In both series of experiments, Pd^{II} and Pd^0 precursors were used. As expected, none of the other applied phosphine/**L1-(O)$_2$** mixtures yielded significant amounts of product. When applying **L1** with different phosphine oxides, no effect on the reaction outcome was observed with Pd(dba)$_2$ as the palladium precursor, however, starting from Pd(acac)$_2$, product yields differed depending on the introduced phosphine oxide. It was apparent that the presence of a phosphine oxide with certain structural properties was beneficial for the transfer hydrogenation if a Pd^{II} precursor was used, possibly through a stabilizing effect in the formation of the active catalyst.[15]

With the optimized reaction conditions in hand and having gained some insight into the role of the phosphine oxide, a thorough substrate screening was performed (Table 2). The reactivity of various substituted aryl ethanols was investigated, showing a strong influence of the electronic and steric properties of the introduced substituents. Methyl-substituted 1-phe-

Table 1. Ligand effects in the palladium-catalyzed transfer hydrogenolysis of 1-phenylethanol (**1 a**).[a]

[a] General reaction conditions: **1 a** (1.0 mmol), Pd(acac)$_2$ (1 mol %), ligand (4 mol % if not stated otherwise), MeSO$_3$H (16 mol %), formic acid (2.0 mmol) in 1,2-dichloroethane (3 mL), stirred for 18 h at 100 °C in a Schlenk pressure tube. [b] Yields determined using quantitative GC-FID with *n*-pentadecane as internal standard. [c] Amount of applied ligand: 8 mol %.

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Table 2. Substrate scope of the palladium-catalyzed transfer hydrogenolysis of benzylic alcohols.

Pd(acac)₂ (1 mol%)
L1 (4 mol%)
L1-(O)₂ (1.3 mol%)
MeSO₃H (16 mol%)
HCOOH (2 equiv)

1,2-dichloroethane,
100 °C, 18 h

Entry[a]	Product	Ar	R¹	R²	Yield [%][b]
1	**2a**	Ph	Me	H	>99
2	**2b**	4-Me-C₆H₄	Me	H	47
3	**2c**	4-MeO-C₆H₄	Me	H	traces[c]
4	**2d**	4-F-C₆H₄	Me	H	70
5	**2e**	4-Cl-C₆H₄	Me	H	94
6	**2f**	4-Br-C₆H₄	Me	H	62
7	**2g**	4-I-C₆H₄	Me	H	traces[d]
8	**2h**	4-CO₂Me-C₆H₄	Me	H	35[d]
9	**2i**	4-Ph-C₆H₄	Me	H	>99 (96)
10	**2j**	Ph	H	H	98
11	**2k**	4-Me-C₆H₄	H	H	93
12	**2l**	2-MeO-C₆H₄	Me	H	traces[c]
13	**2m**	2-Me-C₆H₄	Me	H	82
14	**2n**	3-MeO-C₆H₄	Me	H	65
15	**2o**	2-naphthyl	Me	H	(94)
16	**2p**	1-naphthyl	Me	H	(95)
17	**2q**	Ph	-(CH₂)₃-	H	>99
18	**2r**	Ph	CH₂C(O)CH₃	H	59
19	**2s**	Ph	Ph	H	87
20	**2t**	Ph	Me	Me	75
21	**2u**	Ph	Ph	Me	66
22	**2v**	Ph	Ph	Ph	(>99)

[a] General reaction conditions: Alcohol (1.0 mmol), Pd(acac)₂ (1.0 mol%), **L1** (4.0 mol%), **L1-(O)₂** (1.3 mol%) (partially oxidized **L1** was applied), MeSO₃H (16 mol%), formic acid (2.0 mmol) in 1,2-dichloroethane (3.0 mL), stirred for 18 h at 100 °C in a Schlenk pressure tube. [b] Yields determined using quantitative GC-FID with n-pentadecane as internal standard. Isolated yields in brackets. [c] Acid-induced dehydrative elimination/dimerization of the aryl ethanol observed. [d] Large amounts of unreacted 1-aryl-ethyl formate were detected after the reaction.

ed substrates were not converted, only the intermediate formates were observed (see the Supporting Information for details). Biphenyl or naphthyl groups in the substrate resulted in excellent isolated product yields (entries 9, 15, 16).

We were delighted to see that primary benzylic alcohols were also transformed to the corresponding toluenes in nearly quantitative yields, excluding a possible elimination-hydrogenation pathway through styrene derivatives (Table 2, entries 10, 11). Diphenylmethanol, which is unable to form an alkene by dehydration, was also transformed in a very good yield of 87% (entry 19). 4-Hydroxy-4-phenylbutan-2-one as a simple aldol product was reduced only at the benzylic hydroxy function in a good yield of 59% (entry 18). Tertiary benzylic alcohols were deoxygenated in good to quantitative yields (entries 20–22). Acetophenone was deoxygenated in only 21% (not shown), demonstrating the clear selectivity of the catalyst for benzylic alcohols over benzylic ketones.

The overall reaction might proceed via different intermediates. The results obtained from the substrate screening indicate that elimination to the corresponding styrene derivative is not required. In several cases, a formate intermediate was obtained as a side product and it was also detected by GC in the transformation of successful substrates. To confirm its formation as reaction intermediate, formate **3** was subjected to the transfer hydrogenolysis conditions (Table 3). Notably, the reaction took place in the absence of formic acid (entry 1). An additional equivalent of HCOOH led to a higher yield (entry 2). Furthermore, we followed the reaction of the acetate analogue **4** as the substrate under standard conditions (entry 3). Here, a transesterification to the formate was observed on GC-FID before any product formation occurred. From these results we concluded that the formate ester is in fact the reaction intermediate.

To establish the homogeneous nature of the catalyst system, a series of experiments was conducted.[16] The reaction was monitored over time by withdrawing samples from the reac-

nylethanols provided the respective products **2b** and **2m** in good to very good yields of 47 and 82% (entries 2, 11). The transformation of para- and ortho-methoxy-substituted 1-phenylethanols led to only traces of the desired products, due to an acid-induced elimination and subsequent dimerization of these electron-rich substrates (entries 3, 12). However, the meta-substituted isomer was deoxygenated in a good yield of 65% (entry 14). 1,2,3,4-Tetrahydro-1-naphthol as a more rigid derivative of the model substrate **1a** was also converted to the corresponding alkane in quantitative yield (entry 17). 1-Phenylethanols decorated with F, Cl and Br were tolerated well in the reaction, no dehalogenation occured despite using Pd as catalyst. The corresponding para-halogenated ethylbenzenes were obtained in good to excellent yields of 62 to 94% (entries 4–6). 1-(para-Iodophenyl)ethanol was deoxygenated only in trace amounts (entry 7); the intermediary formate was observed exclusively. Introduction of an ester group hindered the transfer hydrogenolysis and the corresponding alkane was obtained in 35% yield, accompanied by a large amount of non-reacted formate intermediate (entry 8). Strongly deactivat-

Table 3. Transformation of the possible reaction intermediate and a respective analogue in the transfer hydrogenolysis

Pd(acac)₂ (1 mol%)
L1 (4 mol%)
L1-(O)₂ (1.3 mol%)
MeSO₃H (16 mol%)
HCOOH (x equiv)

1,2-dichloroethane
100 °C , 18 h

3: R = H
4: R = CH₃

Entry[a]	R	formic acid (x equiv)	Yield (2a) [%][b]
1	H	0	65
2	H	1	91
3	CH₃	2	88

[a] General reaction conditions: Ester substrate (1.0 mmol), Pd(acac)₂ (1.0 mol%), **L1** (4.0 mol%), **L1-(O)₂** (1.3 mol%) (partially oxidized **L1** was applied), MeSO₃H (16 mol%), formic acid (0–2.0 mmol) in 1,2-dichloroethane (3.0 mL), stirred for 18 h at 100 °C in a Schlenk pressure tube. [b] Yields determined using quantitative GC-FID with n-pentadecane as internal standard.

tion mixture (for details see the Supporting Information). The obtained reaction profile exhibited an initial linear shape without significant induction period typical for heterogeneous catalysis. Furthermore, qualitative catalyst poisoning experiments were conducted using dibenzo[a,e]cyclo-octatetraene (dct)[17] and mercury[18] (for details see the Supporting Information). Findings from these experiments suggest homogeneous catalyst, since both additives inhibited the reaction.

As Pd nanoparticles (NPs) should be excluded as the active catalyst, commercially available Pd⁰ EnCat® 30NP was tested as the metal source (Table 4). Although under the optimized reac-

Table 4. Nanoparticles as Pd source in the transfer hydrogenolysis.			
Entry[a]	x	y	Yield (2 a) [%][b]
1	4.0	16	35
2	0	16	3
3	8.0	16	61
4	8.0	32	66

Reaction scheme above table:
1a (Ph–CH(OH)–CH₃) → 2a (Ph–CH₂–CH₃)
Conditions: [Pd] NPs (1 mol%), L1 (x mol%), L1-(O)₂ (0.3x mol%), MeSO₃H (y mol%), HCOOH (2 equiv), 1,2-dichloroethane, 100 °C, 18 h

[a] General reaction conditions: 1 a (1.0 mmol), [Pd] NPs (1 mol %), L1 (x mol %), L1-(O)₂ (0.3x mol %) (partially oxidized L1 was applied), acid co-catalyst (y mol %), formic acid (2.0 mmol) in 1,2-dichloroethane (3 mL), stirred for 18 h at 100 °C in a closed schlenk pressure tube. [b] Yields determined using quantitative GC-FID with n-pentadecane as internal standard.

tion conditions a yield of 2 a of 35 % was obtained (entry 1), no product was formed without ligand (entry 2). Interestingly, doubling the amount of L1 led to a higher yield of 61 % (entry 3). From this, we deduce that Pd NPs are not the active catalyst species, but may serve as a reservoir from which the metal can leach into solution to form the active homogeneous catalyst. Such cases of so-called "cocktail catalysis" were already described in the literature.[19]

Based on our findings in the reaction optimization, the transformation of the formate intermediate and the poisoning experiments, we propose the following mechanism for the transfer hydrogenolysis reaction: The formation of the cationic palladium-hydride complex A is initiated either by the acid co-catalyst or formic acid, while the substrate 1 a is transformed into the formate intermediate 3 by esterification (Scheme 3). We do not exclude an equilibrium with styrene for substrates that allow it. The reduction occurs via a six-membered distorted chair-like transition state B in which palladium coordinates the carbonyl group of the formate. The hydride is transferred from the metal center to the substrate, releasing the desired deoxygenated product 2 a and a formate anion, which ligates to the palladium center. Palladium-formato complex C regenerates the active catalyst by release of CO_2, thus closing the catalytic cycle.
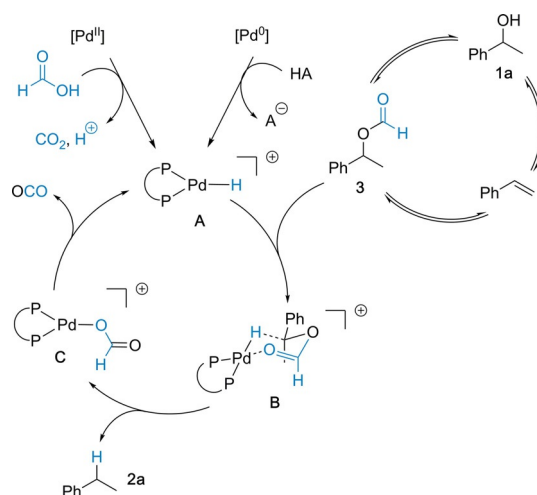
Scheme 3. Proposed reaction mechanism for the palladium-catalyzed transfer hydrogenolysis with formic acid as reductant.

In summary, a new palladium-based homogeneous catalyst for the transfer hydrogenolysis of benzylic alcohols was developed. Formic acid was used as a convenient and potentially sustainable reductant. A series of primary, secondary and tertiary alcohols was successfully converted to the corresponding alkyl arenes. The influence of aryl substituents on the reactivity was evaluated. We found that formic acid not only acts as reductant, but it also activates the substrate through esterification. An essential finding of our investigations was the positive effect of the partially-oxidized ligand on the activity of Pdᴵᴵ catalyst precursors. In addition, the homogeneous nature of the active catalyst was proposed.

Acknowledgements

Conflict of interest

The authors declare no conflict of interest.

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