ChemInform Abstract: Selective Ruthenium-Catalyzed Transfer Hydrogenations of Nitriles to Amines with 2-Butanol.

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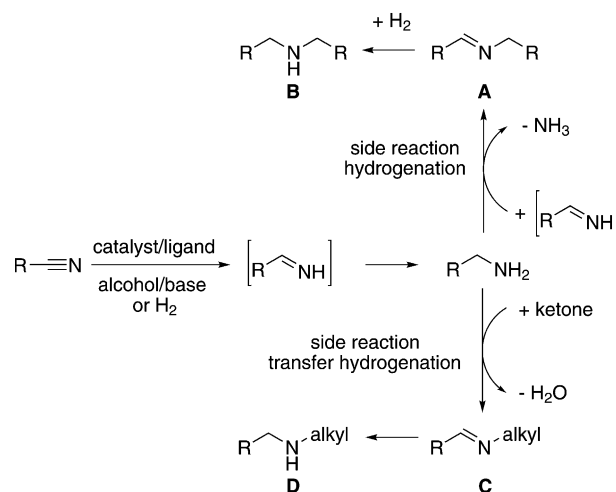# Selective Ruthenium-Catalyzed Transfer Hydrogenations of Nitriles to Amines with 2-Butanol

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Due to their importance in pharmaceuticals, agrochemicals, as organic building blocks, and as intermediates for the materials sciences, as well as in biological processes, amines are of significant interest in academic and industrial research.[1] The most general and often benign processes for the production of amines rely on catalytic reductions. Compared with selective reductions of nitroarenes and aliphatic imines, as well as reductive amination of carbonyl compounds, investigations of the catalytic hydrogenation of aromatic and especially aliphatic nitriles with organometallic complexes are much less common to date.[2–4] Even fewer studies of the related transfer hydrogenation (TH) of nitriles have been reported in recent decades. However, the use of transfer hydrogenation reagents does not require the handling of molecular hydrogen and therefore, advantageously, no high-pressure equipment is needed. Typically, in the more common catalytic transfer hydrogenation of carbonyl compounds, mixtures of formic acid and amines or formate salts, as well as alcohols (typically isopropanol) in combination with a base are used as suitable hydrogen sources.[5]

The first examples of transfer hydrogenation of nitriles were reported by Brown et al.[6] as early as 1982. In this work, ammonium formate was used with a heterogeneous palladium catalyst for the TH of aromatic nitriles. With one notable exception (2,4-dimethylbenzonitrile was converted to 2,4-dimethylbenzylamine) all of the nitriles studied were reductively deaminated to give the corresponding substituted toluenes. More recently, other heterogeneous catalyst systems for this transformation were developed by Gowda et al.[7] in 2002 and most recently by Qian et al. in 2012.[8] With respect to homogeneous catalysts, it is interesting to note that Yamagishi et al.[9] and Albrecht et al.,[10] published ruthenium-based catalyst systems for the hydrogenation of benzonitrile to benzylamine with ammonium formate or isopropanol. Unfortunately, most of the reactions proceeded in only low to moderate yields. In addition, it is noteworthy that in 2011 Williams and co-workers[11] reported the Ru-catalyzed reduction of nitriles with dimethylamino borane as

the reducing agent. Despite these advances, the need for a more general catalytic TH of nitriles remains.

In Scheme 1, the different reaction pathways for the hydrogenation/TH of nitriles are shown. Often, the formation of secondary amines is observed as an unwanted side reaction. Applying alcohols as hydrogen transfer reagents opens the possibility of subsequent reductive amination.

Scheme 1. Reaction pathways for the hydrogenation/TH of nitriles and possible side reactions.
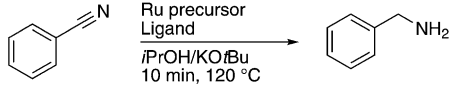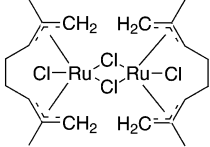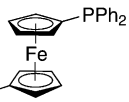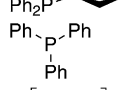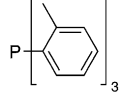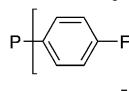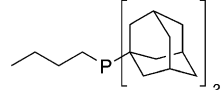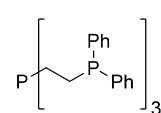
Based on our long-standing interest in transfer hydrogenation[12] and the catalytic reduction of nitriles,[2h,j,l] as well as the general importance of this methodology, we recently set up a project to develop the selective TH of nitriles to form primary amines. Therefore, herein, we present a ruthenium-catalyzed transfer hydrogenation of nitriles to form primary amines with broad substrate scope by applying 2-butanol as a selective reducing agent in the presence of sodium hydroxide.

For our initial studies, we used the benchmark reaction of benzonitrile to benzyl amine to investigate the influence of several catalysts, ligands, and reaction parameters by using isopropanol/KOtBu (Table 1) as the hydrogen transfer agent. We observed neither N-benzylidene-1-phenylmethanamine **A** nor dibenzylamine **B** as side products. Instead, the benzyl amine formed initially reacted further with the resulting ketone (acetone) to form the N-monoalkylated secondary amine **D**.

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Table 1. Variation of catalyst precursors and ligands.[a]

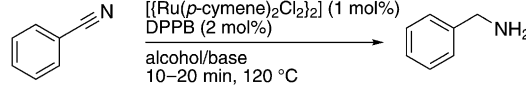| Entry	Ru precursor	Ligand	Yield [%][b]
1	[RuCl$_2$(PPh$_3$)$_3$]	–	68
2	[{Ru(cod)Cl$_2$}$_n$]	–	9
3	[{Ru(benzene)$_2$Cl$_2$}$_2$]	–	5
4	(structure)	–	11
5	[{Ru(p-cymene)$_2$Cl$_2$}$_2$]	Ph$_2$P⁀PPh$_2$	72
6	[{Ru(p-cymene)$_2$Cl$_2$}$_2$]	Ph$_2$P⁀PPh$_2$	59
7	[{Ru(p-cymene)$_2$Cl$_2$}$_2$]	Ph$_2$P⁀PPh$_2$	78
8	[{Ru(p-cymene)$_2$Cl$_2$}$_2$]	Ph$_2$P⁀PPh$_2$	64
9	[{Ru(p-cymene)$_2$Cl$_2$}$_2$]	Ph$_2$P⁀PPh$_2$	<3
10	[{Ru(p-cymene)$_2$Cl$_2$}$_2$]	(ferrocene diphosphine)	76
11	[{Ru(p-cymene)$_2$Cl$_2$}$_2$]	PPh$_3$	74
12	[{Ru(p-cymene)$_2$Cl$_2$}$_2$]	P(o-tolyl)$_3$	6
13	[{Ru(p-cymene)$_2$Cl$_2$}$_2$]	P(C$_6$H$_4$F)$_3$	63
14	[{Ru(p-cymene)$_2$Cl$_2$}$_2$]	(adamantyl phosphine)	44
15	[{Ru(p-cymene)$_2$Cl$_2$}$_2$]	(phosphine)	5

[a] Reaction conditions: benzonitrile (0.5 mmol), Ru precursor (1 mol%), ligand (2 mol%), KOtBu (10 mol%), isopropanol (5 mL), 10 min, 120 °C. [b] Yield determined by GC analysis with hexadecane as the internal standard.

As shown in Table 1, various defined ruthenium precatalysts gave highly active catalyst systems (reaction time: 10 min). For example, the commercially available complex [RuCl$_2$(PPh$_3$)$_3$] led to a good yield (68%) of benzyl amine (Table 1, entry 1). However, in the presence of [{Ru(cod)Cl$_2$}$_n$] (cod = 1,5-cyclooctadiene), [{RuCl$_2$(benzene)$_2$}$_2$] and tetrachlorobis(2,7-dimethyl-2,6-octadienylene)diruthenium, the desired product benzyl amine was obtained in only 5 to 11% yields (Table 1, entries 2–4). In addition, applying [{Ru(p-cymene)$_2$Cl$_2$}$_2$] (**3**) in combination with different ligands furnished the desired product in varying yields between <3 and 78% (Table 1, entries 5–15). Without any ligand present, no conversion of benzonitrile was observed.

Nevertheless, the combination of **3** with different diphosphine ligands, that is, 1,2-bis(diphenylphosphino)ethane (DPPE), 1,3-bis(diphenylphosphino)propane (DPPP), 1,4-bis(diphenylphosphino)butane (DPPB), 1,5-bis(diphenylphosphino)pentane (DPPPE), and 1,1′-bis(diphenylphosphino)ferrocene (DPPF) (Table 1, entries 5–8, 10), displayed high product yields between 64 and 78%. Conspicuously, diphosphine ligands bearing an even number of C atoms between the coordinating phosphorous atoms, except DPPH (DPPH = 1,6-bis(diphenylphosphino)hexane), caused higher yields than chelating ligands bridged with an odd number of C atoms.

Next, with the best catalyst system ([{Ru(p-cymene)$_2$Cl$_2$}$_2$]/ DPPB) in hand, we focused on the role of different bases. As shown in Table 2, there is no clear relationship between
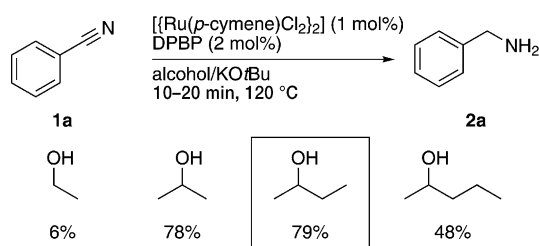
Table 2. Variation of bases.[a]

Entry	Base	Alcohol	t [min]	Yield [%][c]
1	NaOH	iPrOH	10	59
2	KOH	iPrOH	10	–
3	Na$_2$CO$_3$	iPrOH	10	–
4	K$_2$CO$_3$	iPrOH	10	47
5	KOtBu	iPrOH	10	78
6	Cs$_2$CO$_3$	iPrOH	10	64
7[b]	KOtBu	2-BuOH	10	79
8[b]	NaOH	2-BuOH	10	75
9[b]	NaOH	2-BuOH	20	93

[a] Reaction conditions: benzonitrile (0.5 mmol), [{Ru(p-cymene)$_2$Cl$_2$}$_2$] (1 mol%), DPPB (2 mol%), base (10 mol%), isopropanol (5 mL), 120°C. [b] 2-Butanol (5 mL) instead of isopropanol. [c] Yield determined by GC analysis with hexadecane as the internal standard.

base strength and product yield. The reaction did not work in the presence of potassium hydroxide or sodium carbonate (10 mol%; Table 2, entries 2 and 3); however, sodium hydroxide, potassium tert-butoxylate and caesium carbonate resulted in the desired product in good yields between 59 and 78% (Table 2, entries 1, 5, and 6).

To avoid the unwanted N-monoalkylation reaction, alcohols other than isopropanol were tested as transfer hydrogenation reagents (Scheme 2). Gratifyingly, 2-butanol showed nearly the same product yield, without forming any side products. This is probably due to the increased steric bulk, which should suppress the subsequent reductive amination process.

For final optimization of the reaction conditions, a small selection of ligands and bases were tested again with the improved hydrogen-transfer reagent (Table 2). Sodium hydroxide seems to result in nearly the same yield of **2a** as potassium tert-butoxylate, but full conversion appeared to require a longer reaction time (Table 2, entry 8). As a consequence, we doubled the reaction time to 20 min and found an excellent product yield of 93% (Table 2, entry 9).

Scheme 2. Transfer hydrogenation with various alcohols as hydrogen-transfer reagents.

To demonstrate the applicability of the new catalytic method developed herein, the reduction of various *ortho-*, *meta-*, and *para*-substituted aromatic nitriles in the presence of [{Ru(*p*-cymene)Cl$_2$}$_2$] (1 mol %), DPPB (2 mol %), and sodium hydroxide (10 mol %) in 2-butanol (5 mL) was performed. Both electron-donating and electron-withdrawing groups, including disubstituted substrates, gave the corresponding benzyl amines in up to 93 % yields (Table 3, entries 3–7 and 9–11). A more challenging heteroaromatic substrate could be converted into the primary amine in moderate yield (68 %) after 35 min (Table 3, entry 12). The reduction of 1-naphthonitrile gave the respective product with a low yield of 34 % (Table 3, entry 13). Furthermore, applying alkyl nitriles resulted in moderate to good product yields between 42 and 84 % (Table 3, entries 14 and 15).

In summary, we have shown that a commercially available catalyst system consisting of [{Ru(*p*-cymene)Cl$_2$}$_2$]/DPPB allows for rapid transfer hydrogenation of aromatic and aliphatic nitriles. Unwanted reductive amination reactions could be avoided by application of 2-butanol as the hydrogen-transfer reagent. This protocol is the most general transfer hydrogenation methodology demonstrated to date.

Experimental Section

General procedure for the catalytic transfer hydrogenation of nitriles: A vial (12 mL) capped with a septum was charged with [{Ru(*p*-cymene)$_2$Cl$_2$}$_2$] (0.005 mmol) and DPPB (0.01 mmol) under an argon atmosphere. Afterwards, a magnetic stirring bar and dry isopropanol or 2-butanol (5 mL) were added. The solution was stirred for 5 min at room temperature before NaOH (0.05 mmol) was added and the mixture was stirred for another 5 min. Then, the nitrile (0.5 mmol) was added and placed on a preheated alloy plate with wells at 120 °C for 10, 20, or 35 min. After the reaction was finished, hexadecane was added as a standard and the yield was determined by GC.

For isolation as the HCl salt: HCl solution (1 M, 1 mL) was added to the solution. Afterwards, the solvent was removed under vacuum and the HCl salt remained. After washing the salt with ethyl acetate, the product was analyzed by NMR spectroscopy, GCMS, and HRMS.

Acknowledgements

Table 3. Substrate scope.[a]

Entry	Substrate		t [min]	Yield [%][b]
1		**2a**	20	93
2		**2b**	20	65
3		**2c**	20	80
4		**2d**	20	85
5		**2e**	20	73 (70)
6		**2f**	20	83
7		**2g**	20	93 (81)
8		**2h**	20	84
9		**2i**	20	79
10		**2j**	20	82
11		**2k**	20	75 (67)
12		**2l**	35	68
13		**2m**	20	34
14		**2n**	20	84
15		**2o**	20	42

[a] Reaction conditions: benzonitrile (0.5 mmol), [{Ru(*p*-cymene)$_2$Cl$_2$}$_2$] (1 mol %), DPPB (2 mol %), KO*t*Bu (10 mol %), 2-butanol (5 mL), 20 min, 120 °C. [b] Yield determined by GC analysis with hexadecane as the internal standard; yield of the isolated HCl salt in parentheses.

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