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Selective catalytic transfer hydrogenation

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The catalytic transfer hydrogenation of (hetero)aryl nitriles using ammonium formate has been investigated in detail. In the presence of commercially available Pd/C, a straightforward and selective reduction is achieved without any additives under mild conditions.

and Matthias Beller*

Amines are of importance as key intermediates for the synthesis of polymers, dyes, pharmaceuticals, agro- and water-chemicals, solvents as well as numerous fine chemicals.¹ Among the different known routes to form aliphatic or benzylic amines, the catalytic hydrogenation of the corresponding nitriles with molecular hydrogen constitutes one of the established processes.² Here, typically Pd/C,^{3,4} Pd/black⁵ and Ni/RANEY®⁶ are used in liquid-phase hydrogenations.⁷ In addition to these classical heterogeneous catalysts, in recent years homogeneous catalyst systems based on rhenium⁸ or ruthenium⁹ have been developed for this transformation. Unfortunately, for the selective hydrogenation towards primary amines, significant amounts of base are required to prevent the formation of the (unwanted) secondary amines as by-products.^{10,11}

Complementary to catalytic hydrogenations with molecular hydrogen, the use of transfer hydrogenation reagents allows for reductions under ambient conditions without the need for any special high pressure equipment.¹² This is of special interest to organic synthesis as well as fine chemical production in batch processes. In general, different compounds can be utilized as hydrogen donors, including phosphinic acid salts,¹³ isopropanol,¹⁴ hydrazines,¹⁵ formic acid salts¹⁶ and the azeotropic mixture of formic acid-triethylamine.¹⁷ Depending on the catalyst and conditions, functional groups such as ketones,¹⁸ esters,¹⁹ imines²⁰ and nitro groups^{21,22} have been successfully reduced. However, related transfer hydrogenations of nitriles have been much less studied. Notably, it has been pointed out that transfer hydrogenation of the carbon–nitrogen triple bond easily results in the formation of the corresponding methyl group.²³ Although the reduction of benzonitriles has been achieved in the presence of RANEY®/Ni using hydrazine as the transfer reagent,^{24–26} here, limited chemoselectivity was demonstrated and the high toxicity of hydrazine is a significant drawback.^{27–29} Moreover, hydrazine is a highly reactive reducing agent which, in contact with some metals such as copper or iron, can lead to fires and explosions. Using the more favourable ammonium formate as the transfer hydrogenation reagent, only one example is known for the reduction of 2,4-dimethylbenzonitrile to the corresponding benzyl amine.³⁰ Owing to this fact and based on our general interest in reductions of nitriles³¹ and transfer hydrogenations,³² we started to investigate this reaction in more detail.

Initially, we explored the reduction of benzonitrile 1a as a benchmark system in the presence of Pd/C (10% Pd) with three different hydrogen donors: hydrazine hydrate, phosphinic acid and formic acid-triethylamine.† Using H₃PO₂ or hydrazine hydrate in the presence of 1 mol% of Pd/C at 70 °C in THF as the solvent did not show any conversion. However, in the case of HCOOH-NEt₃ some reactivity was observed and small amounts of benzylamine 2a were detected while 3a was formed as the main product (Table 1, entries 1-3). Obviously, the formation of N-formylbenzylamine 3a proceeds via benzylamine as the intermediate which reacts further with formic acid. Such N-formylations have been described under different conditions for the protection of a variety of amines.³³⁻³⁵ Increasing the amount of the catalyst to 5 mol% of Pd/C led to moderate conversion and 46% of the amide 3a was obtained (Table 1, entry 4). Notably, no traces of dibenzylamine were detected. To reduce the amount of formylation, we performed experiments at lower temperature (Table 1, entries 5 and 6). To our delight, benzylamine was formed exclusively in only 40 min at 40 °C or in 1.5 h at room temperature. At room temperature, no formylation of benzylamine was observed even after 24 h. Furthermore, it is known that different combinations of acids and bases

Leibniz-Institute for Catalysis e.V at the University Rostock, Albert-Einstein-Str. 29 a, Germany. E-mail: matthias.beller@catalysis.de; Fax: +49 (381) 1281 51113

Table 1 Benchmark reduction of benzonitrile: optimization^a



Entry	Hydrogen donor	Ratio ^c	$T [^{\circ}C]$	<i>t</i> [h]	Conv. ^d [%]	Yield 2a ^d [%]
1^b	H ₃ PO ₂	_	70	20	n.r.	_
2^b	$N_2H_4 \cdot H_2O$	_	70	20	n.r.	_
3 ^b	HCOOH-NEt ₃	5:2	70	20	14	_
4	HCOOH-NEt ₃	5:2	70	20	46	_
5	HCOOH-NEt ₃	5:2	40	40 min	89	80
6	HCOOH-NEt ₃	5:2	rt	1.5	81	77
7	HCOOH-NEt ₃	3.7:1	40	2	>99	98
8	HCOOH-NEt ₃	7.4:1	40	2	>99	98
9	HCOOH-NEt ₃	11.1:1	40	2	>99	98
10	HCOOH-NEt ₃	14.8:1	40	2	>99	98
11	HCOOH-NEt ₃	18.5:1	40	2	>99	98
12	HCOOH-NEt ₃	37:1	40	2	>99	98
13	НСООН	_	40	2	n.r.	_
14	NEt ₃	_	40	2	n.r.	_

^{*a*} Reaction conditions: benzonitrile (0.38 mmol), Pd/C (5 mol%), THF (1 mL), HCOOH/NEt₃ (1 mL). ^{*b*} 1 mol% Pd/C. ^{*c*} Ratio of HCOOH/NEt₃ is based on molar ratio. ^{*d*} Determined by GC using hexadecane as an internal standard. n.r. = no reaction.

have a significant impact on the activity and selectivity in transfer hydrogenations of ketones.³⁶ Thus, we studied the influence of the NEt₃ concentration. For all HCOOH–NEt₃ combinations, except for the commercially available mixture, complete conversion was achieved (Table 1, entries 7–12). It is worth noting that even a molar ratio of 37:1 (volume ratio of 10/1) for HCOOH–NEt₃ afforded full conversion and 98% yield (Table 1, entry 12), while in the absence of a base, no reaction took place, demonstrating the importance of a small amount of base.

Next, we evaluated the effect of different bases with the same acid/base molar ratios under the previously optimized conditions (Fig. 1).

All tested additives, even the less basic amine, were suitable for the reduction of benzonitrile and gave good to excellent



Furthermore, we tested other commercially available heterogeneous catalysts such as Ru/C, Pt/C or Pd/alumina. Unfortunately, none of them was active in this model reaction (Table 2). On the other hand, Pd/C (10% Pd) from various suppliers (Merck, Sigma Aldrich) formed the desired product in similar yields.

Finally, the reduction of several aromatic nitriles was investigated. As shown in Table 3, 17 (hetero)aromatic nitriles bearing electron-withdrawing as well as electron-donating



Fig. 1 Transfer hydrogenation of benzonitrile: screening of different bases; reaction conditions: benzonitrile (0.38 mmol), Pd/C (5 mol%), THF (1 mL), HCOOH-base (1 mL, 18.5:1). GC yields using hexadecane as an internal standard. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene. Hünig base = N,N-diisopropylethylamine.

Table 2Transfer hydrogenation of benzonitrile: screening of differentheterogeneous catalysts



Entry	Catalyst	<i>T</i> [°C]	<i>t</i> [h]	Yield $2a^b$ [%]
1	Ru/C	25	4	—
2	Ru/C	50	4	—
3	Pt/C	25	4	_
4	Pt/C	50	4	_
5	Pd/alumina	25	18	—
6	Pd/alumina	50	4	10
7	Pd/alumina	80	4	_
8	Pd/C	40	2	98

^a Reaction conditions: benzonitrile (0.38 mmol), THF (1 mL), HCOOH-NEt₃ (1 mL, 18.5:1 molar ratio), catalyst (5 mol%).
 ^b Determined by GC using hexadecane as an internal standard.

Table 3Transfer hydrogenation of (hetero)aromatic nitriles: scopeand limitations a



^{*a*} Reaction conditions: nitrile (0.38 mmol), Pd/C (5 or 10 mol%), THF (1 mL) and HCOOH-NEt₃ (1 mL, 18.5:1) at 40 °C or rt. ^{*b*} Determined by GC using hexadecane as an internal standard. ^{*c*} Ratio of HCOOH/base is based on molar ratio (3.7/1).



Scheme 1 Reduction of cinnamonitrile under standard reaction conditions.

groups were smoothly hydrogenated to the corresponding primary amines under mild conditions (rt-40 °C) using 5 or 10 mol% of Pd/C. Compared to the state-of-the-art system RANEY®/Ni and hydrazinium monoformate,²⁵ benzonitrile was reduced more efficiently giving 98% yield with our catalyst system (Table 3, entry 1). Nitriles with a methoxy group (Table 3, entries 2 and 6) showed high reactivity. The reaction with the methoxy group in the para-position was faster (1 h reaction time) than in the ortho-position (12 h), demonstrating that steric hindrance plays a role in the reduction. In general, no side-products were detected and mostly excellent yields of amines were obtained. In the case of para-phenyl-benzonitrile and 4-cyano-indole (Table 3, entries 8 and 9) the yield did not improve even with prolonged reaction time. Interestingly, high chemoselectivity is achieved for nitriles containing ester and amide functionalities (Table 3, entries 12-14). Heterocycles such as pyridines were also suitable substrates for our reaction, although a molar ratio of 3.7:1 of formic acid-triethylamine had to be used for optimal results (Table 3, entries 15-17). Clearly, the yields were only moderate (Table 3, entries 15 and 16), but such types of substrates are known to be difficult for reduction reactions.

Unfortunately, attempts to hydrogenate aliphatic nitriles under the presented reaction conditions failed. For example, phenylacetonitrile did not show any reaction at all. When cinnamonitrile was used as a substrate, full conversion was achieved but a complex mixture of products was obtained. Among them, 3-phenylpropanenitrile (23%), 3-phenyl-2-en-1-amine (12%), and 3-phenylpropan-1-amine (5%) were identified (Scheme 1). These results suggest that conjugation with the triple bond of the cyano group plays a significant role in the reduction.

Conclusions

A general procedure for the catalytic transfer hydrogenation of aromatic nitriles to the corresponding primary amines is described. Applying commercially available Pd/C (10%) as a heterogeneous catalyst, a variety of different (hetero)aromatic nitriles is reduced smoothly. The procedure is attractive for organic synthesis because the protocol can be easily performed using standard equipment. Advantageously, no additives are needed and the reaction proceeds with good to excellent yields under mild conditions. Related functional groups such as amides and esters were not affected under the optimized conditions allowing the synthesis of interesting bifunctional building blocks.

Notes and references

† General procedure: to a solution of benzonitrile (0.38 mmol) in tetrahydrofuran (1.0 mL), a mixture of formic acid and triethylamine (1.0 mL) was added under an argon atmosphere. After the addition of Pd/C (10%; 5 or 10 mol%) gas evolution is observed and the mixture is stirred for 1 h at the given temperature (rt or 40 °C). Then, the reaction mixture was filtered through a short plug of silica gel and hexadecane was added as an internal standard. The yield was measured by GC (30 m HP Agilent Technologies column, 50–300 °C; benzonitrile: 10.45 min; benzylamine: 10.94 min). The identities of all products, which are known compounds, were proven by GC-MS experiments and comparison with authentic samples.

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