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Copper-catalyzed reductive amination of aromatic and aliphatic ketones with anilines using environmental-friendly molecular hydrogen[†]

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A convenient and practical copper-catalyzed reductive amination was discovered. In the presence of easily available and inexpensive $Cu(OAc)_2$ various ketones react with anilines and molecular hydrogen to give the desired amines in high yields.

Introduction

As one of the most important and effective C-N bond forming processes, reductive amination provides a practical and general access to amines.¹ This sequential condensation of easily available anilines and ketones and subsequent hydrogenation of the in situ formed imine is applied for the synthesis of a variety of industrially important amines as well as building blocks for organic synthesis, biological systems, material science, agrochemicals and pharmaceuticals.^{2,3} Besides silanes,⁴ also formates,⁵ iso-propanol⁶ and Hantzsch esters⁷ are used as hydrogen donors for reductive aminations in organic synthesis. Obviously, a more atom economic and environmental friendly reducing agent constitutes molecular hydrogen,8 whereas water is the only side-product. Typically, precious metal based catalysts, e.g. Rh, Ru, Ir,^{8,9} are applied for the latter transformations. More recently also bio-relevant metals showed worthwhile opportunities.¹⁰ For example, an iron-based catalyst system for the reductive amination of ketones and aldehydes has been developed in our group.¹¹ Based on this experience as well as related zinc-catalyzed hydrogenation reactions,¹² herein we describe a novel and convenient protocol for reductive aminations applying a simple and easily available, inexpensive copper catalyst.^{13,14} To the best of our knowledge, no catalytic approach using copper with molecular hydrogen to perform reductive amination has been reported so far.

Results and discussion

In our initial catalytic investigations we studied the influence of several zinc and copper catalysts on the reaction of acetophenone **1a** and aniline **2a** in the presence of molecular hydrogen

 (80 bar H_2) . It turned out that the addition of 3 Å molecular sieves as a water abstracting agent to the reaction mixture was necessary to shift the condensation equilibrium towards the imine. Consequently, no conversion was observed when performing the reaction without molecular sieves.

As expected no amine is obtained without any catalyst (Table 1, entry 1). As shown in Table 1, all the tested zinc sources (Table 1, entries 2–7) are not active for the reductive amination of ketones, although we recently reported the successful reduction of imines and the reductive hydroamination of alkynes using $Zn(OTf)_2$ as a hydrogenation catalyst.¹²¹ While examining different copper(1) and copper(1) catalysts, it was discovered that the halogenated copper salts CuCl, CuCl₂ and CuBr showed some activity towards the desired reaction (Table 1, entries 9–11). Improved activity was achieved applying Cu(OTf)₂ as a catalyst (Table 1, entry 13). To our delight, in the presence of CuF₂ and Cu(OAc)₂ the desired amine **3a** was obtained in 83 and 72% yield, respectively (Table 1, entries 8 and 14). We assume that copper is needed to activate the *in situ*

Table 1 Reductive amination of acetophenone with aniline: screening
of different zinc and copper catalysts^a

	Ph + 1a	Ph—NH ₂ 2a	10 mol% catalyst, toluene <u>3Å molecular sieves</u> 80 bar H ₂ , 120 °C, 24 h	HN ^{Ph} Ph 3a	
Entry		Catal	yst [mol%]	Yield ^c [%]	
1					
2		ZnF_2		_	
3		ZnCĨ	2	_	
4		1			
5		$Zn(OAc)_2$			
6	$Zn(OTf)_2^2$			9	
7		Zn ₃ (I	$PO_4)_2$	_	
8		CuF ₂		83	
9		CuCl		9	
10		CuCl	2	4	
11		CuBr	•	3	
12		CuI		_	
13		Cu(O	$(Tf)_2$	38	
14		Cu(O	$(Ac)_2$	72	
15^{b}		Cu(O	$(Ac)_2$		

^{*a*} Reaction conditions: 0.5 mmol **1a**, 0.5 mmol **2a**, 0.05 mmol catalyst, 1.5 mL toluene, 80 bar H₂, 120 °C, 24 h. ^{*b*} Addition of 1 equiv. of formic acid. ^{*c*} Determined by GC methods using hexadecane as an internal standard.

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formed imine otherwise $Zn(OAc)_2$ or ZnF_2 would also be active for the reductive amination reaction. In addition, we performed one experiment with additional formic acid to disprove that this acid acts as the active catalyst whereby indeed no amine was formed (Table 1, entry 15). Hence, with these two catalysts further optimizations of various reaction parameters were performed. Besides the investigation of the reaction temperature, the influence of the hydrogen pressure and the catalyst loading were analyzed.

Reducing the catalyst loading to 5 mol% led to a decreased yield of 38% with CuF₂ as the catalyst, while the yield was increased in the presence of Cu(OAc)₂ as catalytic species (Table 2, entry 8). Variation of the hydrogen pressure at 120 °C showed that also 2 mol% of Cu(OAc)₂ catalyzed the reductive amination of **1a** with a high yield of 81% whereas applying CuF₂ the amine **3a** was only formed in low to moderate yields (Table 2, entries 5–8). As shown in Table 2 (entries 3 and 4) already a slight decrease of the temperature led to significantly lower yields between 12 and 36%. Obviously, at least a temperature of 100 °C and a hydrogen pressure of 50 bar is needed to achieve useful yields (>70%) of the amine **3a** with a catalyst loading of 10 mol% (see ESI†). Due to economic aspects, we decided to use 2 mol% Cu(OAc)₂ at 120 °C and 50 bar H₂ for further experiments.

Table 2 Reductive amination of acetophenone with aniline: optimization with $Cu(OAc)_2$ and CuF_2^a

	Ph + Ph 1a	-NH ₂ 3 H 2a	Cu(OAc) ₂ or C 3Å molecular s H ₂ , T, 24 h	uF _{2,} toluene sieves Ph 3a	
Entry	Catalyst loading [mol%]	<i>T</i> [°C]	<i>p</i> [bar]	Yield with Cu(OAc) ₂ ^b [%]	Yield with $\operatorname{CuF_2}^{b}$ [%]
1	5	80	50	21	14
2	5	80	80	22	23
3	5	100	50	31	17
4	5	100	80	36	12
5	2	120	50	81	9
6	5	120	50	82	59
7	10	120	50	72	81
8	5	120	80	83	38
9	10	120	80	72	83

^{*a*} Reaction conditions: 0.5 mmol **1a**, 0.5 mmol **2a**, Cu(OAc)₂ or CuF₂, 1.5 mL toluene, H₂, *T*, 24 h. ^{*b*} Determined by GC methods using hexadecane as an internal standard.

Table 3 Reductive amination of acetophenone with aniline: investigations using $Ni(acac)_2$ as the catalyst^{*a*}

	0 Ph + 1a	Ph—NH ₂ 2a	Ni(acac) _{2,} toluene <u>3Å molecular sieves</u> 50 bar H ₂ , 120 °C, 24 h	HN ^{Ph} Ph 3a
Entry		Yield ^b [%]		
1 2		0.01 2		

^{*a*} Reaction conditions: 0.5 mmol **1a**, 0.5 mmol **2a**, 5×10^{-5} or 0.01 mmol Ni(acac)₂, 1.5 mL toluene, 50 bar H₂, 120 °C, 24 h. ^{*b*} Determined by GC methods using hexadecane as an internal standard.

To ensure that no precious metal impurities are the "real catalysts" for the reduction of the *in situ* formed imine, X-ray fluorescence analysis of the different pre-catalysts has been done. These investigations revealed no detectable amounts of precious metals, *e.g.* Ru, Rh, Ir, Pd and Pt except for Ni. More specifically, in the elemental analysis of the used Cu(OAc)₂ 0.0434% Ni was detected. Thus, we performed two appropriate reactions with 0.01 and 2 mol% of Ni(acac)₂ as the catalyst (Table 3). In both cases acetophenone **1a** did not react with aniline **2a** to give the corresponding amine **3a**.

In order to prove the applicability of the simple copper-based system, seven different anilines 2 were reacted with acetophenone 1a (Table 4, entries 1–7). Both anilines with electrondonating and electron-withdrawing groups were transformed into the desired amines 3b–d in good yields of 87 and 73% (Table 4, entries 2–4).

Furthermore, cyclic and aliphatic amines can be applied in this copper-catalyzed reaction and furnished 3e and 3f in isolated yields up to 77% (Table 4, entries 5 and 6). Applying the aminostilbene 2g, the amine 3g was obtained in which also the C–C double bond was hydrogenated.

Next, a variety of different ketones 1 were converted with aniline **2a** to give the desired amines **3h–n** in up to 86% yields (Table 4, entries 8–14). In order to demonstrate the substrate scope of ketones, functionalized acetophenones with electron-withdrawing and electron-donating groups as well as aliphatic and cyclic ketones were investigated (Table 4, entries 10-14).

Finally, two different aromatic aldehydes **4** were reacted with aniline **2a** under the optimized conditions using a somewhat higher catalyst loading of 5 mol% Cu(OAc)₂ to give the corresponding amines **5a–b** in 88% and 78% yield, respectively (Scheme 1).

In conclusion, we have developed the first copper-catalyzed reductive aminations with molecular hydrogen. Fortunately, the reactions of anilines with aromatic and aliphatic ketones as well as two aldehydes furnished the corresponding amines **3** and **5** in good yields in the presence of a simple copper(II) acetate catalyst. Advantageously, no complicated ligands or additional acid or base is needed.

Experimental section

Unless otherwise stated, all reactions were run under an argon atmosphere with exclusion of moisture from reagents and glassware using standard techniques for manipulating airsensitive compounds. All isolated compounds were characterized by ¹H NMR and ¹³C NMR spectroscopy, high resolution mass spectrometry (HRMS) and HPLC. NMR spectra were recorded on a Bruker AV 300 or AV 400. All chemical shifts (δ) are reported in ppm and coupling constants (*J*) in Hz. All chemical shifts are related to solvent peaks [chloroform: 7.26 (¹H), 77.00 (¹³C)], respectively. All measurements were carried out at room temperature unless otherwise stated. Mass spectra were in general recorded on a Finnigan MAT 95-XP (Thermo Electron) or on a 6210 Time-of-Flight LC/MS (Agilent). Gas chromatography was performed on an HP 6890 with an HP5 column (Agilent).

 Table 4
 Reductive amination of ketones with aniline: substrate scope^a



^{*a*} Reaction conditions: 0.5 mmol **1a**, 0.5 mmol **2a**, 0.01 mmol Cu(OAc)₂, 1.5 mL toluene, 50 bar H₂, 120 °C, 24 h. ^{*b*} 0.025 mmol Cu(OAc)₂. ^{*c*} Isolated yields.



Scheme 1 Reductive amination of benzaldehydes.

Reagents

Unless otherwise stated, commercial reagents were used without purification.

General information

All catalytic hydrogenation experiments using molecular hydrogen were carried out in a Parr Instruments 4560 series autoclave (300 mL) containing an alloy plate with wells for seven 4 mL glass vials.

Reductive amination of ketones using molecular hydrogen

Under an argon atmosphere, a glass vial was charged with $Cu(OAc)_2$ (1.8 mg, 0.01 mmol), ketone 1 (0.5 mmol), amine 2 (0.5 mmol), 3 Å molecular sieves (300 mg) and 1.5 mL toluene. A magnetic stirring bar was added. Afterwards, the vial was capped with a septum equipped with a syringe and set in the alloy plate, which was then placed into the autoclave. Once sealed, the autoclave was purged 3 times with hydrogen, then pressurized to 50 bar and heated at 120 °C for 24 h to give the corresponding secondary amine **3**. After the reaction, the autoclave was purified by column chromatography on silica gel (eluent: heptane–ethyl acetate = 9:1). The isolated compounds were then analyzed by NMR, GCMS and HRMS.

Reductive amination of aldehydes using molecular hydrogen

Under an argon atmosphere, a glass vial was charged with $Cu(OAc)_2$ (1.8 mg, 0.01 mmol), aldehyde 4 (0.5 mmol), aniline 2a (0.5 mmol, 46.6 mg), 3 Å molecular sieves (300 mg) and 1.5 mL toluene. A magnetic stirring bar was added. Afterwards, the vial was capped with a septum equipped with a syringe and set in the alloy plate, which was then placed into the autoclave. Once sealed, the autoclave was purged 3 times with hydrogen, then pressurized to 50 bar and heated at 120 °C for 24 h to give the corresponding secondary amine 5. After the reaction, the autoclave was purfied by column chromatography on silica gel (eluent: heptane–ethyl acetate = 9:1). The isolated compounds were then analyzed by NMR, GCMS and HRMS.

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