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Development of New Hydrogenations of Imines and Benign Reductive Hydroaminations: Zinc Triflate as a Catalyst

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The hydrogenation of imines to amines in the presence of catalytic amounts of zinc triflate has been demonstrated for the first time. In addition, an efficient procedure for the reductive hydroamination of alkynes to amines is presented using zinc triflate as a catalyst precursor. In both protocols a variety of different functional groups are tolerated, and the reactions proceed smoothly in high yields.

Introduction

The development of new and improved methods for the synthesis of nitrogen-containing compounds such as imines, enamines, and amines continues to be of significant interest for catalysis research and the chemical industry.[1,2] Amines and their derivatives find wide applications as building blocks in organic synthesis, in biological systems, as ligands for catalysis, and in materials science.[3] As an example of their importance, selected compounds that were among the top 200 pharmaceutical products by worldwide sales in 2009 are shown in Figure 1.[4]

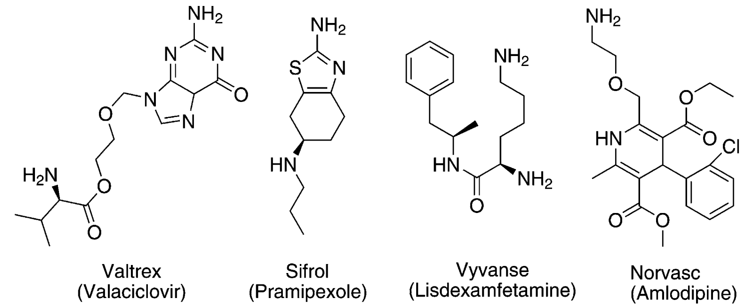

Figure 1. Selection of amines that are among the top 200 pharmaceutical products by worldwide sales in 2009.

Among the various catalytic methods available for the synthesis of amines, catalytic hydrogenation of imines/enamines and the corresponding reductive aminations of carbonyl compounds represent clean and environmentally benign methodologies that are applied in industry for the production of chiral and nonchiral amines.[5,6] As a reducing agent, the use of molecular hydrogen is preferred because of its price and environmental friendliness.[7] To date, hydrogenations have been mainly performed by using expensive precious metal-based catalysts, for example, Ir, Ru, Rh, and Pd complexes.[6d,8–12] Although the advantages are obvious, the reduction of imines with H_2 using nonprecious metal-complexes is considerably less developed.[13] In this respect, our group recently published enantioselective imine hydrogenations using Knölker's iron complex.[14] During these studies, we discovered serendipitously that the hydrogenation of *N*-arylimines to amines also proceeds in the presence of catalytic amounts of zinc(II) triflate ($Zn(OTf)_2$), which we report here for the first time. To expand this reaction, we also investigated the reductive hydroamination reaction of alkynes with amines and hydrogen (Scheme 1).

Catalytic hydroaminations constitute one of the most basic and atom-efficient C–N bond forming processes by the addition of an amine to an unsaturated C–C bond.[15] Starting from commercially available alkynes, in principle the reaction affords the desired amines without any formation of side products. Compared to olefins, alkynes can undergo the reaction more easily because of steric reasons and their weaker π-bonds ($70\ kJ\,mol^{-1}$).[3d] Although two regioisomers, the Markovnikov and anti-Markovnivkov product, might be formed, in general the Markovnikov product is thermodynamically favored in these reactions.[16]

In the past few decades, different catalysts for inter- and intramolecular alkyne hydroaminations have been developed. After the pioneering work of Barluenga et al.[17] using Hg and Tl catalysts, the hydroamination of alkynes is nowadays known to be catalyzed by a variety of early (Ti, Zr, V, Ta)[18] and late transition metal (Ru, Rh, Pd, Pt, Au, Ag),[19] lanthanide (Sm, Lu, Nd),[20] and actinide (U, Th) catalysts.[21] Furthermore, heterogeneous catalysts have been explored, for example, zeolites, ion-exchanged zeolites, and transition metal-exchanged montmorillonites.[22]

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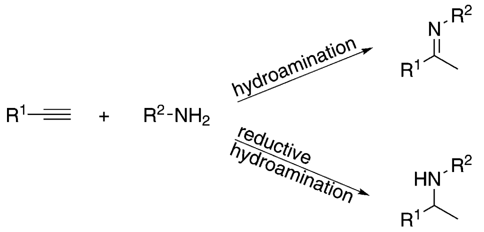


Scheme 1. Hydroamination of alkynes and reductive hydroamination of alkynes.

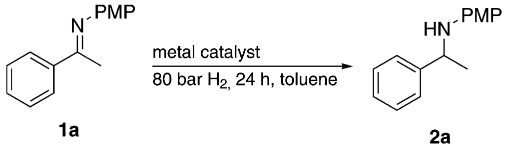
With respect to this work, the use of Zn catalysts by Müller and Blechert[23] as well as by us[15b] for alkyne hydroaminations is of special importance.

Finally, it should be mentioned that Che[24] and Gong[25] have recently independently described the first examples of inter- and intramolecular hydroamination reactions of alkynes using a Au^I catalyst and a Hanztsch ester as the reducing agent. Unfortunately, on applying their protocols, stoichiometric amounts of pyridine are produced as a coproduct, and expensive noble metals in combination with phosphine ligands have to be used.

Results and Discussion

Based on our work with iron catalysts[14] and because of the industrial importance of 1-arylethylamines, we used 4-methoxy-*N*-(1-phenylethylidene)aniline (**1a**) as the starting material in our benchmark reaction (Scheme 2 and Table 1).

Firstly, we investigated the influence of different Lewis acids as catalysts for the hydrogenation of **1a**. As expected, in the absence of a catalyst, no reduction of the imine took place (Table 1, entry 1). The strong Lewis acid $BF_3{\cdot}(C_2H_5)_2O$ activated the imine, but gave no hydrogenation product (Table 1, entry 2). Similarly, a number of Zn, Cu, and Fe salts showed no hydrogenation reactivity (Table 1, entries 3, 4, 6–8). However, to our surprise, the desired amine was formed in 72% yield in the presence of $Zn(OTf)_2$ (Table 1, entry 5). The differences between conversion and product yield resulted from aldol condensation and decomposition of the imine. Entries 9–14 in Table 1 represent the optimization of the $Zn(OTf)_2$-catalyzed hydrogenation. Reducing the H_2 pressure from 80 to 50 bar (1 bar = 10^5 Pa) led to a decreased yield of 42% (Table 1, entry 10). Decreasing the temperature to 65 °C resulted in significantly lower conversion and produced **2a** in only 11% yield (Table 1, entry 9). Conversely, increasing the catalyst loading to 10 mol% (Table 1, entry 11) at 100 °C and 80 bar H_2 gave 95% yield. A similar product yield was obtained at 120 °C and 80 bar H_2 in the presence of 5 mol% $Zn(OTf)_2$ (Table 1, entry 12).



Scheme 2. Hydrogenation of **1a**.

Table 1. Variation of Lewis acids and conditions for imine hydrogenation: benchmark reaction.[a]

Entry	Lewis acid	Amount [mol%]	T [°C]	Conv. [%][b]	Yield [%][b]
1	—	–	100	9	–
2	$BF_3(C_2H_5)_2O$	100	25	41	–
3	$Fe(OTf)_2$	0.01	100	–	–
4	$Cu(OTf)_2$	5	100	87	< 1
5	**$Zn(OTf)_2$**	**5**	**100**	**83**	**72**
6	$Zn(OAc)_2$	5	100	13	–
7	$ZnBr_2$	5	100	19	4
8	$ZnCl_2$	5	100	20	4
9[c]	$Zn(OTf)_2$	5	65	30	11
10[c]	$Zn(OTf)_2$	5	100	57	42
11	$Zn(OTf)_2$	10	100	95	95
12	**$Zn(OTf)_2$**	**5**	**120**	**> 99**	**92**
13	$Zn(OTf)_2$	2	120	74	47
14	$Zn(OTf)_2$	1	120	38	4

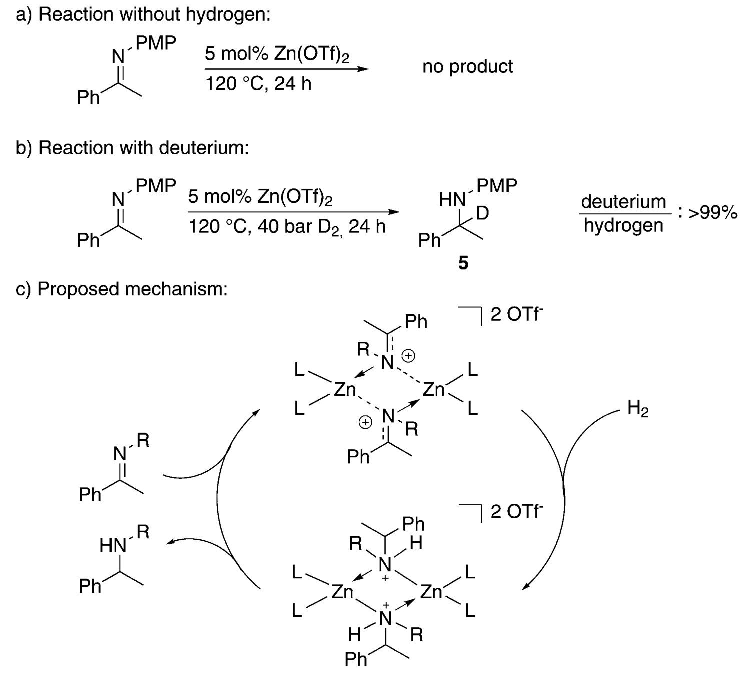
[a] Reaction conditions: **1a** (0.5 mmol), Lewis acid, toluene (0.5 mL), 80 bar H_2, at 100 °C for 24 h. [b] Determined by performing GC analysis using hexadecane as an internal standard. [c] 50 bar H_2.

Clearly, $Zn(OTf)_2$ is a very unusual catalyst for the activation of H_2. Thus, we initially thought that impurities of precious metals might be responsible for the observed activity. However, elemental analysis and inductively coupled plasma spectrometry revealed no detectable amounts of Ru, Rh, Ir, and Pd. Furthermore, various samples of $Zn(OTf)_2$ from different suppliers behave similarly. Finally, $Zn(OTf)_2$ proved to be inactive under the optimized conditions for the hydrogenation of ketones, nitro groups, olefins, and alkynes, which proceeded in the presence of precious metal-based catalysts. To prove the necessity of H_2, we performed one experiment without hydrogen gas. As expected, no amine was obtained. Furthermore, imine **1a** was reacted with D_2 (Scheme 3). Here, NMR spectroscopy clearly showed the formation of **5**. Deuteration was confirmed by using ESI-TOF MS. D/H-exchange at the D–N position was observed, most likely because of the presence of water in the reaction mixture. As expected, both experiments showed that hydrogenation clearly originated from H_2.[26]

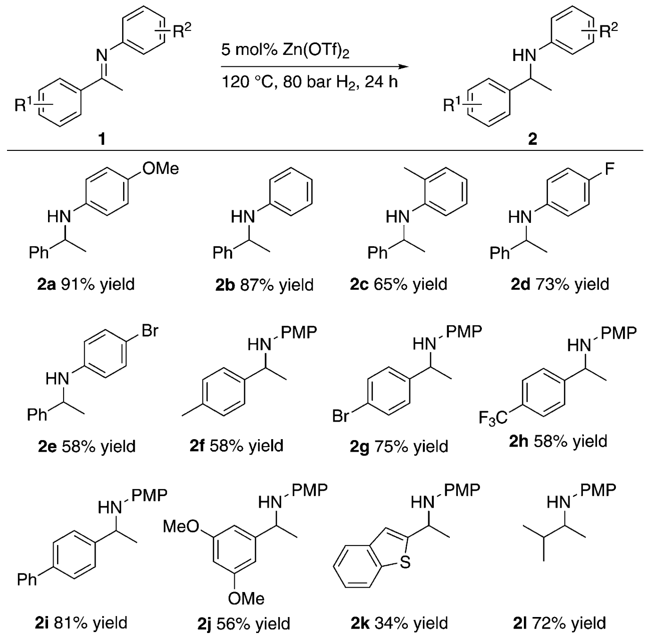
As a preliminary mechanistic proposal, we assume the formation of a Zn-coordinated iminium ion. It is likely that dimeric or higher oligomeric Zn species are formed on which heterolytic hydrogen cleavage could take place.

Next, we studied the scope and limitations of this remarkable catalyst in the hydrogenation of different imines.

As shown in Scheme 4, different *ortho*-, *meta*-, and *para*-substituted electron-withdrawing as well as electron-donating *N*-aromatic imines were hydrogenated to give the corresponding amines in good isolated yields of 58–91%. In addition, mono- and disubstituted *N*-4-methoxyphenylimines with electron-donating and electron-withdrawing groups in *meta*- and *para*-positions were smoothly hydrogenated with isolated yields of 56–81% (Scheme 4, **2f–j**). To our delight, heteroaromatic and aliphatic imines also furnished the desired products **2k** and **2l**



Scheme 3. Mechanistic experiments for the reaction a) without H_2 and b) with D_2. c) Proposed mechanism.



Scheme 4. Zn-catalyzed hydrogenation of imines: substrate scope.

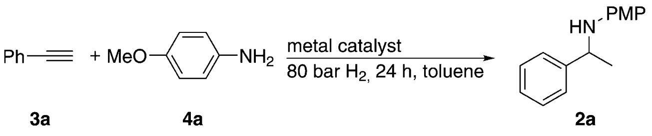
in 34 and 72% yield, respectively (Scheme 4). Unfortunately, *N*-benzylic and *N*-aliphatic imines did not react under these conditions.

After establishing a general procedure for the catalytic hydrogenation of imines, we attempted to use $Zn(OTf)_2$ as a single catalyst for the direct reductive hydroamination of alkynes with primary amines. Advantageously, the isolation of sensitive imines would be avoided here. As a benchmark system, the reaction of phenylacetylene with 4-methoxyaniline was performed in the presence of different Lewis acids (Scheme 5 and Table 2).

Again, $Zn(OTf)_2$ was the only active catalyst and gave a yield of 43% of the desired amine (Table 2, entry 5). The other Lewis acids tested showed low conversions (Table 2, entries 2–3, 6–10), except for $Cu(OTf)_2$ (Table 2, entry 4), which led mainly to aldol condensations.

Then, we focused on the optimization of the reaction conditions. By increasing the catalyst loading to 10 mol%, the yield was raised to 71% (Table 2, entry 11). Applying the alkyne in excess gave the amine in a high yield of 77% in one step (Table 2, entry 12), whereas decreasing the temperature from 120 to 100°C led to a decreased yield of 42% (Table 2, entry 13).

Finally, we used the optimized reaction parameters for other substrates (Scheme 6). As shown in Table 3, the reaction of seven different alkynes and six anilines gave the corresponding amines in moderate to high yields. Alkyl- and alkoxy-substituted as well as halogenated anilines gave the secondary amines in good yields of 79–82% (Table 3, entries 1–4).



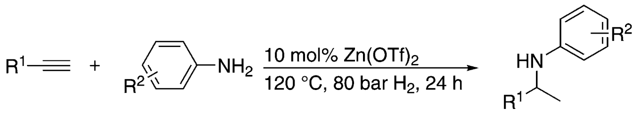
Scheme 5. Reductive hydroamination of phenylacetylene with *p*-methoxyaniline.

Table 2. Variation of catalysts and conditions for the reductive hydroamination.[a]

Entry	Lewis acid	Amount [mol%]	*T* [°C]	Conv. [%][b]	Yield [%][b]
1	–		120	11	–
2	$BF_3(C_2H_5)_2O$	100	25	18	–
3	$Fe(OTf)_2$	0.01	120	15	–
4	$Cu(OTf)_2$	5	120	57	–
5	**$Zn(OTf)_2$**	**5**	**120**	**>99**	**43**
6	$Zn(OAc)_2$	5	120	18	–
7	$ZnBr_2$	5	120	23	–
8	$ZnCl_2$	5	120	26	–
9	ZnF_2	5	120	16	-
10	$Zn_3(PO_4)_2$	5	120	32	-
11	$Zn(OTf)_2$	10	120	>99	71
12[c]	**$Zn(OTf)_2$**	**10**	**120**	**>99**	**77**
13[c]	$Zn(OTf)_2$	10	100	>99	42

[a] Reaction conditions: **3a** (0.65 mmol), **4a** (0.5 mmol), Lewis acid, toluene (0.5 mL), 80 bar H_2, at 120°C for 24 h. [b] Determined by performing GC analysis using hexadecane as an internal standard. [c] **3a** (0.65 mmol).

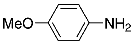
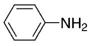
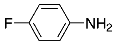
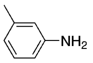
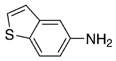
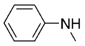
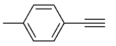
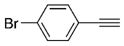
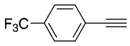
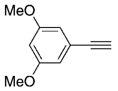
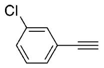
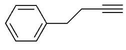
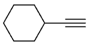
Additionally, the heteroaromatic amine 1-benzothiophen-5-amine (**2o**) reacted smoothly with phenylacetylene in 72%



3 4 2

Scheme 6. $Zn(OTf)_2$-catalyzed reductive hydroamination of arylalkynes: variation of alkynes and anilines.

Table 3. Substrate scope for the zinc-catalyzed reductive hydroamination.[a]

Entry	Alkyne	Amine	Yield [%][b]
1	**3a**		**2a**: 80
2	**3a**		**2b**: 82
3	**3a**		**2d**: 79
4	**3a**		**2m**: 80
5	**3a**		**2o**: 72
6	**3a**		**2p**: 69
7		**4a**	**2f**: 66
8		**4a**	**2g**: 74
9		**4a**	**2h**: 55
10		**4a**	**2j**: 85
11		**4a**	**2q**: 69
12		**4a**	**2r**: 60
13		**4a**	**2s**: 88

[a] Reaction conditions: **3** (0.65 mmol), **4** (0.5 mmol), Lewis acid (0.05 mmol), toluene (0.5 mL), H_2 (80 bar), at 120 °C for 24 h. [b] Isolated yield.

yield. To our surprise, the secondary amine *N*-methylaniline could be applied in the reductive hydroamination reaction with a good yield of 69%, which gave access to the tertiary amine **2p**. Furthermore, mono- and disubstituted terminal arylalkynes bearing electron-withdrawing and electron-donating groups were transformed to the corresponding amines in moderate to good yields of 55–88% (Table 3, entries 7–13). Benzylic and aliphatic primary amines could not be converted with phenylacetylene to the desired amines.

Conclusions

We have developed the first catalytic hydrogenations using $Zn(OTf)_2$ as a catalyst. This rather unusual hydrogenation catalyst enables the specific reduction of *N*-aryl imines with molecular hydrogen to give the desired amines in good yields. Advantageously, no expensive phosphine ligands or precious metals are required in this transformation. Furthermore, we have developed an atom-efficient reductive hydroamination of terminal alkynes with H_2 also using $Zn(OTf)_2$ as a catalyst precursor. Our environmentally friendly, inexpensive, and easy to perform protocols represent an alternative to the more common precious metal-based catalytic hydrogenation of imines.

Experimental Section

Unless otherwise stated, all reactions were performed under an Ar atmosphere with exclusion of moisture from reagents and glassware by using standard techniques for manipulating air-sensitive compounds. All compounds were characterized by using ^1H NMR and ^{13}C NMR spectroscopy, high resolution MS, and FTIR spectroscopy. NMR spectra were recorded by using a Bruker AV 300 or AV 400 spectrometer. All chemical shifts (δ) are reported in ppm and coupling constants (J) in Hz. All chemical shifts are related to solvent peaks [chloroform: $\delta = 7.26$ (^1H) and 77.00 ppm (^{13}C)]. All measurements were performed at room temperature unless otherwise stated. MS were recorded by using a Finnigan MAT 95-XP (Thermo Electron) or a 6210 time-of-flight LC/MS (Agilent) instrument. GC was performed by using a HP 6890 chromatograph with an HP5 column. IR spectra were recorded by using an FTIR Nicolet 6700 (Thermo Electron) instrument.

Unless otherwise stated, commercial reagents were used without purification.

General information

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

Hydrogenation of imines

Under an Ar atmosphere, a glass vial was charged with $Zn(OTf)_2$ (9.1 mg, 0.025 mmol) and **1a** (112.7 mg, 0.5 mmol). Toluene (0.5 mL) and a magnetic stirring bar were 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 three times with H_2, then pressurized to 80 bar (1 bar $= 10^5$ Pa) and heated to 120 °C for 24 h. The autoclave was then cooled to 25 °C, depressurized, and the reaction mixture was purified by performing column chromatography on silica gel (eluent: heptane/ethyl acetate = 9:1) to give **2a** (103.4 mg, 0.46 mmol, 91% isolated yield), which was then analyzed by using NMR, FTIR, and HRMS.

Reductive hydroamination

Under an Ar atmosphere, a glass vial was charged with $Zn(OTf)_2$ (18.2 mg, 0.05 mmol), **3a** (66.4 mg, 0.65 mmol), and **4a** (61.6 mg, 0.5 mmol). Toluene (0.5 mL) and a magnetic stirring bar were added. Afterwards, the vial was capped with a septum equipped with a syringe and was set in the alloy plate, which was then placed into the autoclave. Once sealed, the autoclave was purged three times with H_2, then pressurized to 80 bar and heated to 120 °C for 24 h. The autoclave was then cooled to 25 °C, depressurized, and the reaction mixture was purified by performing column chromatography on silica gel (eluent: heptane/ethyl acetate = 9:1) to give **2a** (90.8 mg, 0.4 mmol, 80% isolated yield), which was then analyzed by using NMR, FTIR, and HRMS.

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Keywords: amines · catalysis · hydroamination · hydrogenation · zinc

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