DOI: 10.1002/adsc.201701316

Efficient Synthesis of Amines by Iron-Catalyzed C=N Transfer Hydrogenation and C=O Reductive Amination

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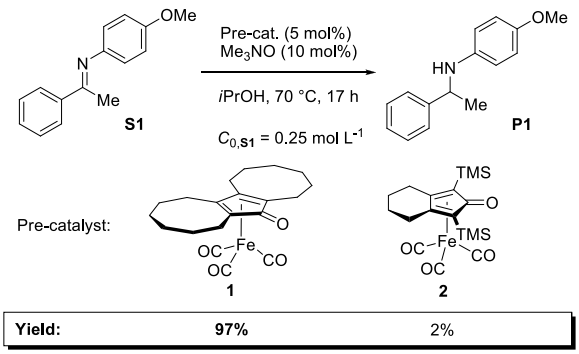
Received: October 12, 2017; Revised: December 2, 2017; Published online: January 12, 2018

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201701316.

Abstract. Here we report the catalytic transfer hydrogenation (CTH) of non-activated imines promoted by a Fe-catalyst in the absence of Lewis acid co-catalysts. Use of the (cyclopentadienone)iron complex **1**, which is much more active than the classical 'Knölker complex' **2**, allowed to reduce a number of N-aryl and N-alkyl imines in very good yields using *i*PrOH as hydrogen source. The reaction proceeds with relatively low catalyst loading (0.5-2 mol%) and, remarkably, its scope includes also ketimines, whose reduction with a Fe-complex as the only catalyst has little precedents. Based on this methodology, we developed a one-pot CTH protocol for the reductive amination of aldehydes/ketones, which provides access to secondary amines in high yield without the need to isolate imine intermediates.

Keywords: hydrogenation; iron; amination; homogeneous catalysis; imines

Amines are a very common and important class of organic compounds, broadly used for the synthesis of bioactive compounds, dyes, fibers and materials.[1] The main methodologies for their preparation involve a reduction as the key step, with imines (either pre-isolated or formed in situ), iminium ions, nitriles, amides, nitro groups, azides as typical substrates.[2] On the lab scale, this transformation is often performed using boron- and aluminum-derived hydrides (e.g., $NaBH_4$, $NaBH_3CN$, $LiAlH_4$), metal salts (e.g., $SnCl_2$) or phosphorus compounds (e.g., PPh_3) as stoichiometric reductants. However, the use of these reducing agents involves formation of a stoichiometric amount of salts or other by-products, with associated environmental costs. For this reason, catalytic hydrogenation (CH)[3] and catalytic transfer hydrogenation (CTH)[4] can be considered much more attractive from an industrial point of view. These methodologies employ cheap reducing agents and present less problems of waste disposal: CH is perfectly atom-economic (H_2 is fully incorporated into the product), whereas in CTH the hydrogen donor (*i*PrOH or Et_3N/HCOOH) acts as both solvent and reductant, forming easy-to-separate by-products such as acetone or CO_2. A number of successful methodologies for amine synthesis relying on the CH of imines,[5] nitriles,[6] amides,[7] azides[8] and nitro groups,[9] or on the CTH of imines/iminium ions[10,11] have been reported. In most of them noble metals (such as Ru, Ir, Rh, Pt) are employed, but in recent years cost and toxicity issues have stimulated the investigation of alternative approaches, such as metal-free methodologies[12] and base metal catalysis.[13] Within the latter area, iron appeared particularly attractive due to its abundancy, low cost and relatively scarce toxicity.[14] Several Fe-catalysts for the hydrogenation of imines/iminium ions,[15,16] nitriles,[17] amides[18] and nitro groups[16] to amines have been developed. On the contrary, quite surprisingly, the number of iron catalysts reported for the CTH of imines is very limited.[19,20] (Cyclopentadienone)iron complexes were used to achieve the direct amination of alcohols with a 'hydrogen borrowing' strategy,[21,22] that is mechanistically related to CTH.[23]

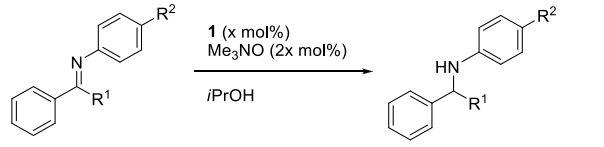


Scheme 1. Preliminary tests of pre-catalysts **1** and **2** in the CTH of a ketimine.

In recent years, our research group has been active in the field of C=O reductions, mainly using (cyclopentadienone)iron complexes.[24,25] Building on this expertise, we report here our efforts to develop an efficient Fe-catalytic methodology for the transfer hydrogenation of non-activated N-aryl and N-alkyl imines. In a preliminary experiment, we tested complex **1**, recently developed in our group,[24a] and the classical 'Knölker complex' **2**[26] in the CTH of *N*-(1-phenylethylidene)-*p*-anisidine **S1** (Scheme 1).

Pre-catalytic complexes **1** and **2** were activated by de-complexation of one CO ligand in the presence of Me_3NO.[15b,e,g,h,21a,d,24] This activation step was found to be delicate and crucial to achieve reproducibility. Under optimized conditions, the pre-catalyst was dissolved in *i*PrOH ($C_{precat.}$ = 0.1 M or higher) and reacted with Me_3NO for 20 min at r.t., before adding the substrate and heating. The catalyst derived from **1** proved substantially more active than the one derived from **2** (97% vs. 2% yield, Scheme 1). This difference in activity is dramatic and more pronounced than that observed in the CH and CTH of ketones.[24a]

Table 1. Imine CTH promoted by pre-catalyst **1**: optimization of the reaction conditions.[a]



S1: R^1 = Me, R^2 = OMe
S2: R^1 = H, R^2 = H
P1: R^1 = Me, R^2 = OMe
P2: R^1 = H, R^2 = H

#	Sub.	Cat. loading [mol%]	$C_{0,sub.}$ [M]	Conv. [%][b]
1	**S1**	5	0.40	72
2	**S1**	5	0.25	97
3	**S1**	5	0.13	89
4	**S1**	2	0.40	71
5	**S1**	2	0.25	>99
6	**S1**	1	0.25	8
7	**S1**	1	0.25	88[c]
8	**S1**	0.5	0.25	4
9	**S1**	0.5	0.25	16[c]
10	**S1**	0.1	0.25	0[c]
11	**S2**	5	0.40	>99
12	**S2**	5	0.25	>99
13	**S2**	5	0.13	>99
14	**S2**	2	0.40	90
15	**S2**	2	0.25	>99
16	**S2**	1	0.25	74
17	**S2**	1	0.25	>99[c]
18	**S2**	0.5	0.25	28
19	**S2**	0.5	0.25	>99[c]
20	**S2**	0.1	0.25	17[c]

[a] Reaction conditions: **1**/Me_3NO = 1:2, T = 70 °C, 18 h, solvent: *i*PrOH.
[b] Determined by ^{1}H-NMR of the crude reaction mixture.
[c] Reaction run at 100 °C.

Moreover, these results confirm what reported by Zhao and co-workers for their pre-catalyst (precursor of the same catalytic species as pre-catalyst **2**), which is able to promote ketimine CTH only in the presence of a substantial amount of Lewis acid.[19a,20]

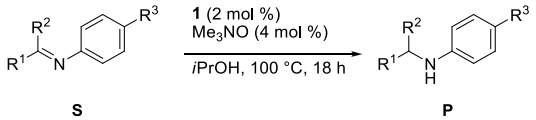
Encouraged by the promising result obtained with pre-catalyst **1**, we set to optimize the reaction conditions using two different model substrates, i.e. ketimine **S1** and aldimine **S2**. Catalyst loading, concentration and temperature were varied as shown in Table 1.

Conversions were determined by ^{1}H NMR analysis of the crude reaction mixtures, as only reduction product and/or staring material signals were visible in the spectra. With ketoimine **S1**, the initial substrate concentration ($C_{0,sub.}$) has a remarkable influence on the conversion, and 0.25 M was found to be the optimal value (Table 1, entry 2 vs. entries 1 and 3). Lowering the catalyst loading to 2 mol% did not impact on conversion (Table 1, entries 4-5), whereas at 1 mol% and at 0.5 mol% the reaction was sluggish (Table 1, entries 6 and 8). Increasing the temperature (100 °C; Table 1, entries 7, 9, 10) restored high conversion when 1 mol% of catalyst loading was used (Table 1, entry 7), while proved ineffective with lower loadings (Table 1, entries 9, 10). As expected, aldimine **S2** was found to be more reactive than ketimine **S1**, giving full conversion with 5 mol% catalyst loading, irrespective of $C_{0,sub.}$ (Table 1, entries 11-13). Experiments run at 2 mol% confirmed that 0.25 M is the optimal $C_{0,sub.}$ value (Table 1, entries 14 vs. 15). Further lowering the catalyst loading down to 0.5% led to a less pronounced decrease of the rate than in the case of **S1** (Table 1, entries 16 and 18 vs. 6 and 8), and full conversion was restored by running the reaction at 100 °C (entries 17 and 19, TON up to 200). At 0.1 mol% catalyst loading, the conversion dropped to 17% (Table 1, entry 20).

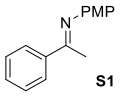
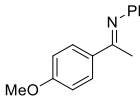
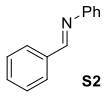
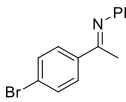
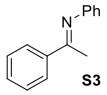
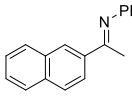
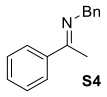
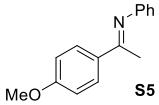
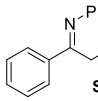
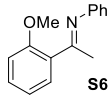
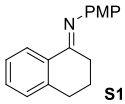
On the basis of the above-discussed optimization, we selected $C_{0,sub.}$ = 0.25 M, 2 mol% loading of **1**, and T = 100 °C as conditions for investigating the substrate scope. The screening was carried out on preparative scale (2 mmol), and isolated yields were assessed for each product (Table 2). Delightfully, excellent yields (83% to quantitative) were obtained with all substrates, with the single exception of the α-tetralone-derived ketimine **S12** (Table 2, entry 12), which was only partially reduced (57% yield). Particularly remarkable are the results obtained with the sterically encumbered imines such as **S6** (Table 2, entry 6), **S9** (entry 9), **S10** (entry 10) and **S11** (entry 11).

As a further challenge, we investigated a reductive amination methodology involving the synthesis of the imine and its catalytic transfer hydrogenation (CTH) in one pot. This kind of protocol, pioneered by Renaud and co-workers in the case of imine catalytic hydrogenation (CH),[15b,e,h] would make imine isolation and purification unnecessary, and thus extend the substrate scope to imines that cannot be readily isolated (e.g., those derived from aliphatic carbonyl compounds).

Table 2. Substrate scope evaluation in the CTH promoted by pre-catalyst **1**.[a]



S P

#	Substrate	Yield [%][b]	#	Substrate	Yield [%][b]
1	 **S1**	99	7	 **S7**	98
2	 **S2**	99[c]	8	 **S8**	99
3	 **S3**	99	9	 **S9**	99
4	 **S4**	99	10	 **S10**	83
5	 **S5**	99	11	 **S11**	99
6	 **S6**	95	12	 **S12**	57

PMP = *p*-methoxyphenyl.

[a] Reaction conditions: substrate/**1**/Me_3NO = 100:2:4, $C_{0,sub.}$= 0.25 M (0.5 mmol), T = 100 °C, 18 h, solvent: *i*PrOH.

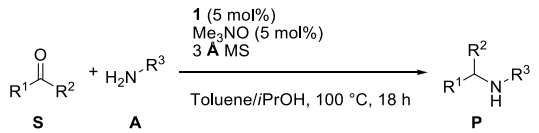
[b] Isolated yields.

[c] 1 mol% catalyst loading, substrate/**1**/Me_3NO = 100:1:2.

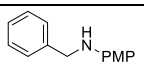
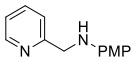
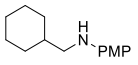
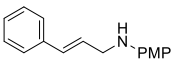
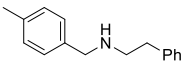
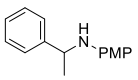
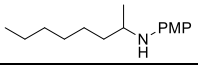
Preliminary tests revealed that successful imine formation is crucial for the reductive amination outcome. Indeed, whenever the conversion to imine was lower than 90% the CTH gave complex mixtures. Thus, we first optimized the imine synthesis step[27] (see the Supporting Information). We then carried out CTH tests by adding the pre-activated catalyst and *i*PrOH to the crude imine solution in toluene.

Good to excellent yields were obtained with both aldehyde and ketone substrates (Table 3). Aromatic and heteroaromatic aldehydes showed the best reactivity (Table 3, entries 1-2), but also products **P15** and **P16** – deriving, respectively, from an aliphatic and an α,β-unsaturated aldehyde – were isolated in good yields (entries 3-4). The reaction worked well also when an aliphatic amine (2-phenylethan-1-amine) was employed instead of 4-methoxyaniline (Table 3, entry 5). While ketones were found less reactive than aldehydes, both the aromatic (Table 3, entry 6) and the aliphatic substrate (entry 7) gave synthetically useful yields.

Table 3. CTH-based reductive amination of aldehydes and ketones promoted by pre-catalyst **1**.[a]



S A P

#	Product		Yield [%][b]
1		**P13**	>99
2		**P14**	93
3		**P15**	74
4		**P16**	75
5		**P17**	90
6		**P1**	80[c]
7		**P18**	60[c]

[a] Reaction conditions: **S**/amine/**1**/Me_3NO = 100:150:5:5; $C_{0,sub.}$= 0.25 M (0.5 mmol). Imine formation and catalyst activation were performed in different pots.

[b] Isolated yields.

[c] Imine formation was performed in the presence of TFA (10 mol%), which was then quenched with DIPEA (15 mol%) before adding the activated catalyst.

In conclusion, we have reported the first catalytic transfer hydrogenation (CTH) of non-activated N-aryl and N-alkyl imines promoted by a Fe-complex in the absence of Lewis acid co-catalysts. Thanks to pre-catalyst **1**[24a] – displaying much higher activity than the classical 'Knölker complex' **2** – it was possible to reduce a number of imines with a cheap reductant (*i*PrOH) using a relatively low catalyst loading (0.5-2 mol%). Remarkably, very good yields were obtained also with non-activated ketimines, whose reduction with a Fe-complex as the only catalyst has little precedents.[15a,b,e,h] Based on this CTH methodology, a reductive amination protocol was also developed, which leads to the one-pot formation of secondary amines in high yield, starting from an aldehyde/ketone and a primary amine.

Experimental Section

General information

All reactions were performed under argon atmosphere in pressure-proof Schlenk vessels fitted with a screw cap.

General Procedure for the CTH of pre-formed imines

Pre-catalyst **1** (3.8 mg, 0.010 mmol, 0.02 equiv.) and Me_3NO (1.6 mg, 0.020 mmol, 0.04 equiv.) were dissolved in dry *i*PrOH (0.1 mL) and the resulting solution, which gradually turned from yellow to dark red, was stirred for 20 minutes at r.t.. The imine substrate (0.5 mmol, 1 equiv.) was added, followed by dry *i*PrOH (1.9 mL). The reaction vessel was sealed and stirred in a pre-heated oil bath at

100 °C for 18 h. The volatiles were removed and the crude was purified by flash column chromatography using a hexane/AcOEt mixture.

General Procedure for the reductive amination of aldimines

3 Å MS (400 mg), the aldehyde (0.5 mmol, 1 equiv.) and the amine (0.75 mmol, 1.5 equiv.) were dissolved in dry toluene (0.5 mL) and the mixture was stirred for 1 h at 100 °C. Meanwhile, in another vessel, pre-catalyst **1** (9.6 mg, 0.025 mmol, 0.05 equiv.) and Me_3NO (1.9 mg, 0.025 mmol, 0.05 equiv.) were dissolved in dry *i*PrOH (0.25 mL). The activated catalyst solution was dispensed into the vessel containing the imine, followed by dry *i*PrOH (1.2 mL). The reaction vessel was sealed and stirred in a pre-heated oil bath at 100 °C for 18 h. The volatiles were removed and the crude was purified by flash column chromatography using a hexane/AcOEt mixture.

General Procedure for the reductive amination of ketimines

3 Å MS (400 mg), the ketone (0.5 mmol, 1 equiv.), the amine (0.75 mmol, 1.5 equiv.) and TFA (4 μL, 0.05 mmol, 0.1 equiv., dispensed as a stock solution in toluene) were dissolved in dry toluene (final total volume: 0.5 mL) and stirred for 2 h at 100 °C. Meanwhile, in another vessel, pre-catalyst **1** (9.6 mg, 0.025 mmol, 0.05 equiv.) and Me_3NO (1.9 mg, 0.025 mmol, 0.05 equiv.) were dissolved in dry *i*PrOH (0.25 mL). Freshly distilled DIPEA (13 μL, 0.075 mmol, 0.15 equiv.) and then the activated catalyst solution were dispensed into the vessel containing the imine, followed by dry *i*PrOH (1.2 mL). The reaction vessel was sealed and stirred at 100 °C for 18 h. The volatiles were removed and the crude was purified by flash column chromatography using hexane/AcOEt mixture.

Acknowledgements

L. P. thanks the Dipartimento di Chimica, Università degli Studi di Milano, for financial support (Piano di Sostegno alla Ricerca 2015-2017 – Action B). We thank Prof. Albrecht Berkessel for inspiring discussions.

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