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Title: Improving C=N Bond Reductions with (Cyclopentadienone)iron Complexes: Scope and Limitations

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Key Topic: Iron Catalysis

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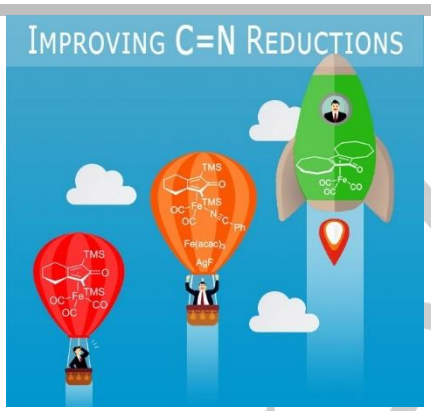
FULL PAPER

The catalytic transfer hydrogenation of imines and the reductive amination of carbonyl compounds have been thoroughly investigated with a cyclooctene-derived (cyclopentadienone)iron pre-catalyst. Additionally, enantioselective ketimine reduction with a chiral (cyclopentadienone)iron complex is reported here for the first time.



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Improving C=N Bond Reductions with (Cyclopentadienone)iron Complexes: Scope and Limitations

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Improving C=N Bond Reductions with (Cyclopentadienone)iron Complexes: Scope and Limitations

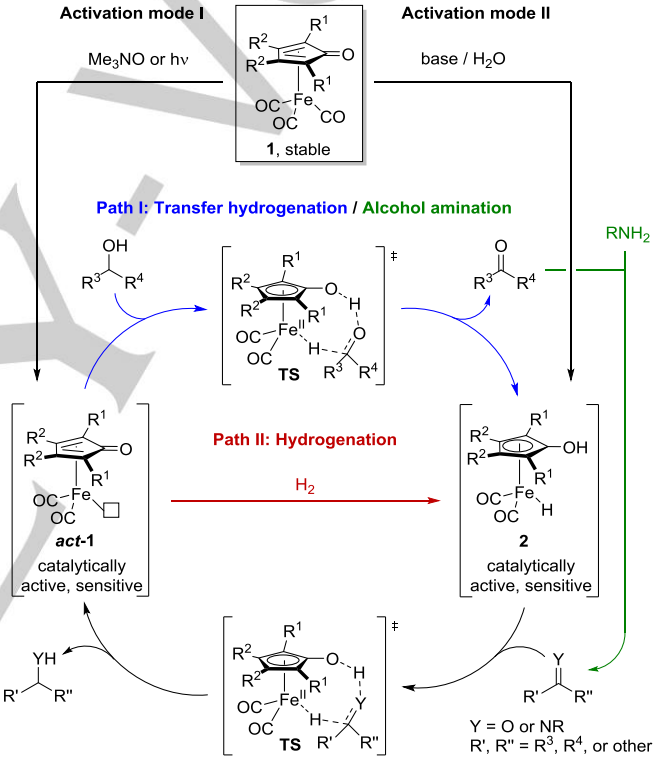
Mattia Cettolin,[a] Xishan Bai,[a] Dennis Lübken,[a] Marco Gatti,[a] Sofia Vailati Facchini,[b] Umberto Piarulli,*[b] Luca Pignataro,*[a] Cesare Gennari*[a]

Abstract: Herein, we broaden the application scope of (cyclopentadienone)iron complexes **1** in C=N bond reduction. The catalytic scope of pre-catalyst **1b**, which is more active than the 'Knölker complex' (**1a**) and other members of its family, has been expanded to the catalytic transfer hydrogenation (CTH) of a wider range of aldimines and ketimines, either pre-isolated or generated in situ. The kinetics of **1b**-promoted CTH of ketimine **S1** were assessed, showing a pseudo-first order profile, with TOF = 6.07 h^{-1} at 50% conversion. Moreover, the chiral complex **1c** and its analog **1d** were employed in the enantioselective reduction of ketimines and reductive amination of ketones, giving fair to good yields and moderate enantioselectivity.

Introduction

In recent years, the catalytic applications of (cyclopentadienone)iron complexes[1] (**1** in Scheme 1) have been increasingly studied. This growing interest is due to several attractive features which distinguish this class of complexes from most other Fe-based homogeneous catalysts:[2] i) they are relatively easy to prepare and do not contain air-sensitive phosphine ligands; ii) they are stable to air, moisture and column chromatography; iii) they can be activated in situ by either de-coordination of a CO ligand[3,4,5,6,7,8a-e,g] (Activation mode I in Scheme 1) or conversion into the corresponding (hydroxycyclopentadienyl)iron complexes **2** (Activation mode II in Scheme 1).[8f,9]

Although it has been recently reported that (cyclopentadienone)iron complexes can also promote C-N and C-O bond-forming reactions,[7] most catalytic applications rely on their ability to reversibly transfer H_2 to polar double bonds, following different pathways (Scheme 1). According to Path I, the activated catalysts ***act*-1** can dehydrogenate alcohols and form the (hydroxycyclopentadienyl)iron complexes **2**, which then transfer H_2 to a polar double bond (transfer hydrogenation). In the presence of an excess of alcohol (typically *i*PrOH) or other reducing agent (e.g. formic acid), this path leads to the reduction of substrate's C=O or C=N bond,[3,4a,9b] whereas Oppenauer-type alcohol oxidation can be achieved in the presence of excess ketone (e.g., acetone).[3b,e,10]



Scheme 1. Catalytic use of complexes **1** in reactions involving hydride transfer.

Moreover, redox-neutral reactions are also possible (Scheme 1, path in green), in which an alcohol substrate – in the presence of an amine – is oxidized and converted into an imine/iminium ion that is then reduced without net hydrogen consumption ('hydrogen borrowing' alcohol amination).[5,6,9a,c] Alternatively, according to Path II (Scheme 1) complex ***act*-1** can directly split molecular hydrogen and form catalyst **2**, which then reduces the substrate (hydrogenation[4b-e,8,9d-g]). In both Path I and II, hydrogen transfer occurs through a pericyclic transition state involving both the iron atom and the 'non-innocent' ligand swinging between the cyclopentadienone (***act*-1**) and the hydroxycyclopentadienyl form (**2**).[9h,i,11]

Among the redox transformations promoted by complexes ***act*-1** and **2**, C=N reduction[12] is one of the most important and probably the one with the largest potential for improvement. Renaud and co-workers pioneered the reductive amination of carbonyl compounds promoted by in situ activated

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(cyclopentadienone)iron complexes under hydrogenation conditions.[8c,d,g] However, this methodology suffers from several limitations such as sub-optimal yields, high catalyst loading and relatively narrow substrate scope, covering mostly aldehydes and only a few ketones.

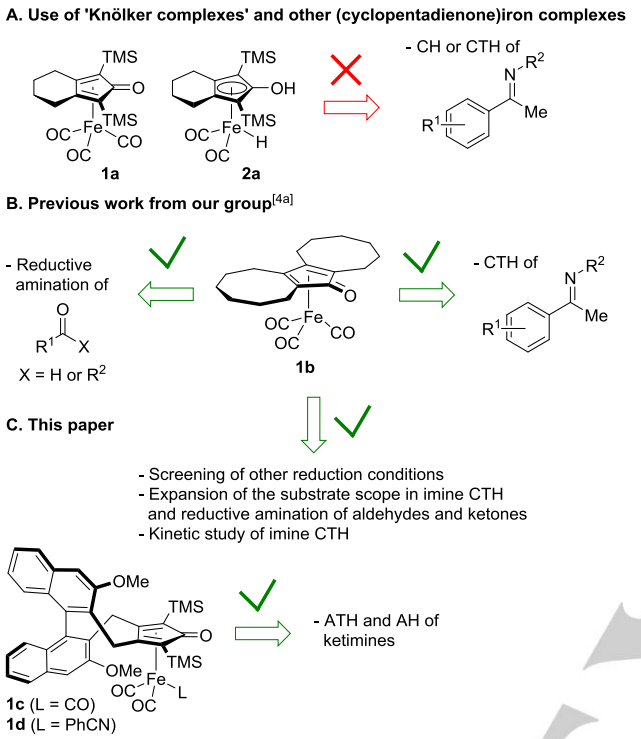


Figure 1. A: Scope limitations of the classical 'Knölker complexes' (**1a** and **2a**) in C=N reduction. B: Studies on pre-catalyst **1b** described previously.[4a] C: Studies on C=N reduction, including the use of chiral complexes **1c-d**, reported in this work. CTH = catalytic transfer hydrogenation; CH = catalytic hydrogenation; ATH = asymmetric transfer hydrogenation; AH = asymmetric hydrogenation.

In general, the ***act*-1**- or **2**-promoted reduction of ketimines (either generated in situ from ketones, or pre-isolated) proved a challenging task, which was achieved by Zhao (in transfer hydrogenation)[9b] and Beller (in highly efficient and enantioselective hydrogenation)[9d-g] employing, respectively, a Lewis acid and a chiral Brønsted acid co-catalyst. Besides intrinsically poor atom economy (two catalysts for a single transformation), the latter approach has the limitation of employing mostly the isolated complexes **2**, which are sensitive to air and light. Last but not least, no chiral type-**1** or type-**2** complex has been yet developed to achieve the enantioselective hydrogenation of ketimines in the absence of chiral co-catalysts.

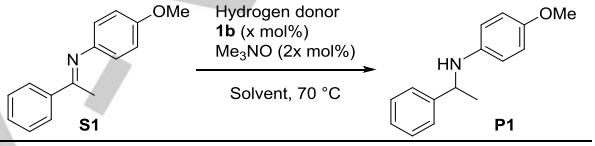
In a recent communication,[4a] we reported our efforts to develop more efficient C=N bond reduction protocols building on the (cyclopentadienone)iron complex **1b** (Figure 1 B), previously synthesized in our labs[4b] and found to be a remarkably more active reduction pre-catalyst than the classical 'Knölker complexes' **1a** and **2a**. Unlike the latter (Figure 1 A),[9g] catalyst **1b** is able, upon activation with Me_3NO, to promote the catalytic transfer hydrogenation (CTH) of acetophenone-derived ketimines (Figure 1 B) and other ketimines/aldimines in good yields using relatively low loading (0.5-2 mol%). Exploiting the high activity of pre-catalyst **1b**, a CTH-based protocol for the reductive amination of aldehydes and ketones was also developed.[4a]

The present paper accounts for our efforts to further implement the potential of (cyclopentadienone)iron complexes in C=N reduction using pre-catalyst **1b**, the chiral complex **1c**[4d,e] and its modified analog **1d** (Figure 1 C).

Results and Discussion

First, pre-catalyst **1b** was tested in the presence of reducing agents different from *i*PrOH. The screening was carried out using the N-arylimine **S1**, which Beller[9g] and Zhao[9b] reported as poorly reactive in catalytic hydrogenation (CH) and in CTH promoted by catalyst **2a** in the absence of co-catalysts.

Table 1. Reduction of (*E*)-*N*-(4-methoxyphenyl)-1-phenylethan-1-imine **S1** promoted by pre-catalyst **1b**.[a]



#	Hydrogen donor	Cat. loading [mol%]	Solvent	Conv. [%][b]
1	*i*PrOH	5	*i*PrOH	72
2	5:2 FA/TEA[c]	5	-	38
3	H_2[d]	5	Toluene	22
4	H_2[d]	5	CH_3OH	60
5	H_2[d]	10	Toluene	98
6	H_2[d]	10	CH_3OH	>99

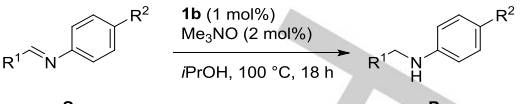
[a] Reaction conditions: T = 70 °C, 18 h. $C_{0,sub.}$ = 0.4 M; [b] Determined by ^{1}H NMR of the crude reaction mixture; [c] FA = formic acid; TEA = trimethylamine; [d] P_{H2} = 20 bar.

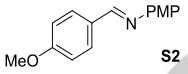
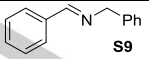
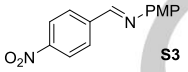
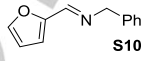
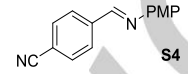
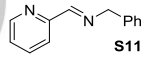
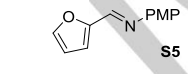
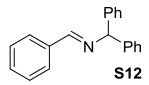
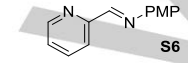
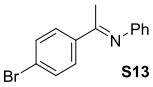
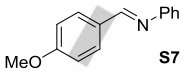
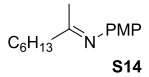
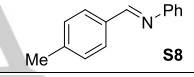
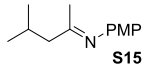
As shown in Table 1, imine **S1** was subjected to different reduction conditions in the presence of in situ activated complex ***act*-1b**. Catalyst activation, which was found critical in order to obtain reproducible results, was performed by adding Me_3NO[8d,10] to a rather concentrated solution of **1b** ($C_{precat.}$ ≥ 0.1 M) and then stirring for 20 min at r.t. before adding the substrate. Replacing *i*PrOH, used in our previously reported CTH methodology,[4a] with the FA/TEA azeotropic mixture (FA = formic acid; TEA = triethylamine) led to a drop of conversion, possibly because of rapid degradation of the active catalyst occurring in the acidic reaction environment (Table 1, entry 2 vs. 1). Also switching from CTH (with *i*PrOH) to CH conditions led to lower conversions (Table 1, entries 3-4 vs. 1), which could be improved only by increasing the catalyst loading to 10 mol% (entries 5-6). These results led us to opt for CTH with *i*PrOH as the optimal reduction method for expanding the application scope of pre-catalyst **1b**.

We thus tested pre-catalyst **1b** with a number of aldimine substrates under the previously established optimal conditions[4a] (*i*PrOH, 100 °C, $C_{0,sub.}$ = 0.25 M, 1 mol% catalyst loading), obtaining the results shown in Table 2. All reactions were carried out on 0.5 mmol scale, and the yield of isolated product was calculated in each case. All the *N*-*p*-methoxyphenyl (PMP)

aldimines (Table 2, entries 1, 3-5) were reduced in nearly quantitative yield with the exception of the 4-nitroaniline-derived imine **S3** (entry 2). Remarkably, imine reduction occurred chemoselectively and the reducible groups of substrates **S3** and **S4** (-NO_2 and -CN, respectively) remained unaffected under the experimental conditions. Notably, also the heterocyclic substrates **S5** and **S6** (Table 2, entries 4-5) reacted smoothly, despite the presence of a heteroatom which could potentially poison the Fe center. We next varied the imine N-substituent, to ascertain its effect on reactivity: as expected, the N-phenyl-protected substrates **S7** and **S8** reacted in high yields (Table 2, entries 6-7). The N-benzylimines **S9**, **S10** and **S11** showed lower reactivity compared to their N-aryl counterparts **S5** and **S6** (Table 2, entries 8-10 vs. 4-5).[13] Substrate **S12**, possessing the easily removable benzhydryl protecting group at nitrogen, gave similar yield to the N-benzyl substituted analog **S9** (Table 2, entry 11 vs. 8). Three ketimine substrates were also tested (Table 2, entries 12-14), as a complement to the screening previously reported by our group.[4a] In these reactions, 2 mol% catalyst loading was used due to the lower reactivity of ketimines compared to aldimines. The acetophenone-derived substrate **S13**, bearing a bromine substituent that allows further functionalization by cross-coupling chemistry, was converted in good yield and without trace of de-bromination byproduct (Table 2, entry 12). Ketimines **S14** and **S15**, deriving from aliphatic ketones, were also included in the screening and underwent CTH in quantitative yield (Table 2, entries 13-14), thus demonstrating that the application scope of **1b** is not restricted to aryl ketones.

Table 2. Extension of scope evaluation in imine CTH promoted by pre-catalyst 1b.[a]



#	Substrate	Yield [%][b]	#	Substrate	Yield [%][b]
1	 **S2**	99	8	 **S9**	66
2	 **S3**	46	9	 **S10**	36[c]
3	 **S4**	99	10	 **S11**	66
4	 **S5**	99	11	 **S12**	67
5	 **S6**	99	12	 **S13**	68[d]
6	 **S7**	99	13	 **S14**	99[d]
7	 **S8**	99	14	 **S15**	99[d]

[a] Reaction conditions: substrate/**1b**/Me_3NO = 100:1:2, $C_{0,sub.}$= 0.25 M (0.5 mmol), T = 100 °C, 18 h, solvent: *i*PrOH. PMP = *p*-methoxyphenyl; [b] Isolated yields; [c] NMR yield; [d] Substrate/**1b**/Me_3NO = 100:2:4.

To get additional information on the catalytic properties of complex **1b** in C=N reduction, we set to study the kinetics of ketimine **S1** CTH (see Scheme Table 1) promoted by this pre-catalyst.

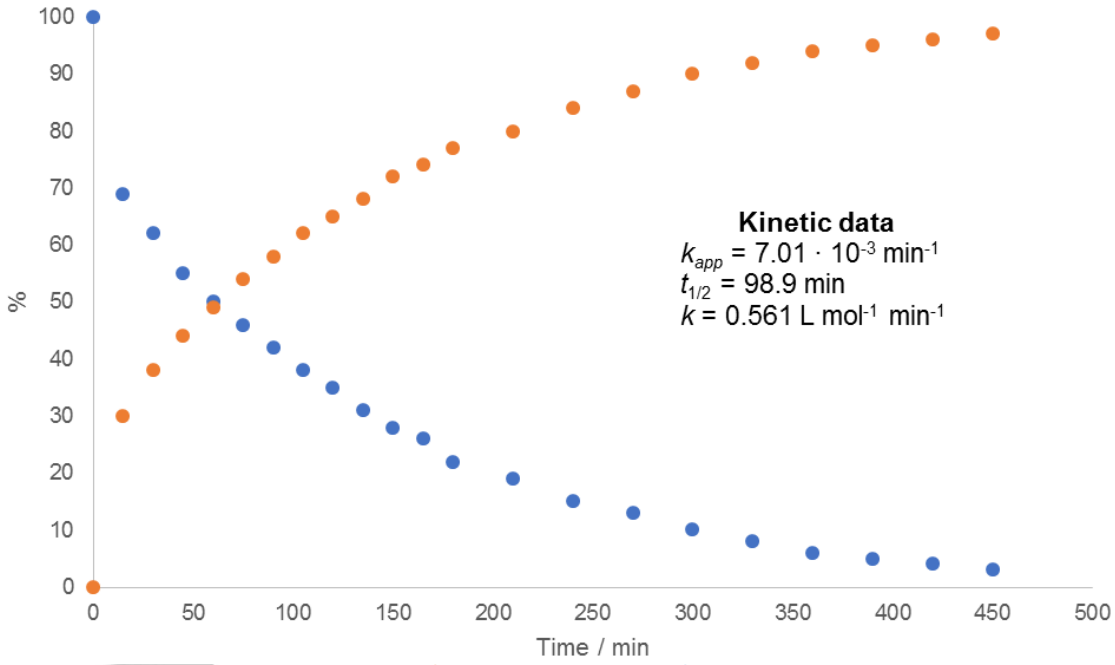
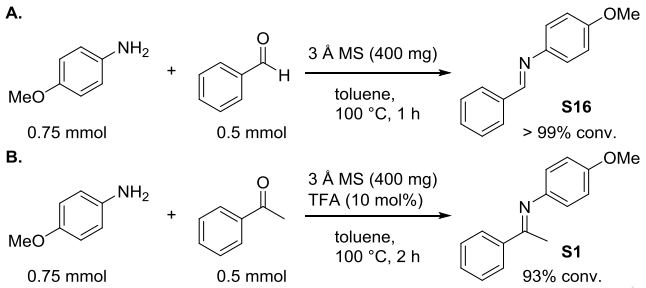


Figure 2. Kinetics of the CTH of **S1** promoted by complex **1b**: ● Conversion to of **P1** (GC); ● Percent of unreacted **S1**. Conditions: **S1**/**1b**/Me_3NO =100:5:10; solvent: *i*PrOH; $C_{0,S1}$ = 0.25 M (0.5 mmol); T = 100 °C; $C_{cat.}$ = 12.5 mM.

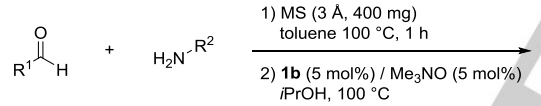
The reaction was run in *i*PrOH at 100 °C in the presence of 5 mol% **1b** and 10 mol% Me_3NO, and conversion was determined by GC analysis of samples taken at regular intervals (every 15 min in the first 3 h and later every 30 min). As can be seen in Figure 2, the reaction showed pseudo-first order dependence on substrate concentration, **S1** having a half-life of 98.9 min under the experimental conditions, corresponding to an average TOF of 6.07 h^{-1} at 50% conversion. A comparison with the classical Knölker complex **1a** is not possible, since very low conversions (2%) were obtained with this complex in the same reaction.[4a]

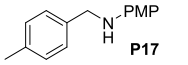
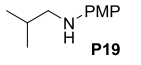
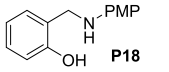
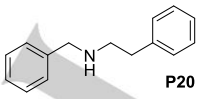
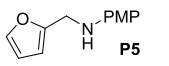
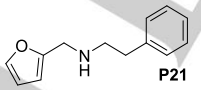
Following the successful use of **1b**-promoted CTH in the reductive amination of aldehydes and ketones,[4a] in this work we devoted additional efforts to study the scope of this attractive methodology. As already reported, effective and reproducible imine formation was found crucial for success of reductive amination, the best conditions[4a] being exemplified in Scheme 2.



Scheme 2. Examples of optimized conditions[4a] for the in situ formation of aldimines (A) and ketimines (B). TFA = trifluoroacetic acid.

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



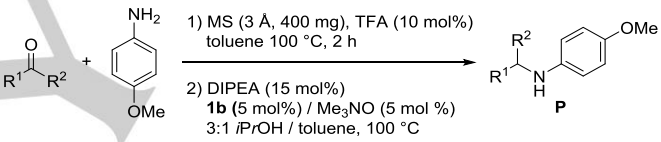
#	Product	Yield [%][c]	#	Product	Yield [%][c]
1	 **P17**	99	4	 **P19**	17[d]
2	 **P18**	44	5	 **P20**	38
3	 **P5**	98	6	 **P21**	67

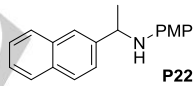
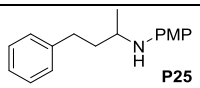
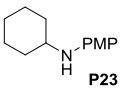
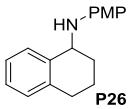
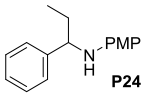
[a] Reaction conditions: aldehyde/amine/**1b**/Me_3NO = 100:150:5:5. Imine formation: toluene, 100 °C, 3 Å MS (400 mg), 1 h. Catalyst activation: *i*PrOH, Me_3NO, r.t., 20 min. CTH: 3:1 *i*PrOH/toluene, $C_{0,sub.}$ in CTH = 0.25 M (0.5 mmol), 100 °C, 18 h; [b] The aldehydes used were distilled over PPh_3 prior to use; [c] Isolated yields; [d] Yield determined by ^1H NMR.

We thus screened a number of new aldehyde (Table 3) and ketone substrates (Table 4) following the optimized reductive amination protocol:[4a] pre-catalyst **1b** was activated with Me_3NO in *i*PrOH, and then added to the imine generated in situ in toluene, so that reduction was carried out in a 3:1 *i*PrOH/toluene mixture. Compared to the CTH of isolated imines, the catalyst loading was slightly increased (to 5 mol%) due to the more challenging nature of reductive amination. The aldehyde substrates were screened in combination with *p*-anisidine and phenethylamine, giving the results shown in Table 3. Both an aromatic and a heteroaromatic substrate (Table 3, entries 1 and 3, respectively) were converted into the corresponding N-PMP amines in excellent yields, whereas the sterically hindered salicylaldehyde formed product **P18** in only 44% yield (entry 2). Isobutyraldehyde showed poor reactivity (Table 3, entry 4), whereas the in situ formed N-alkyl imines proved reactive and formed the corresponding products **P20** and **P21** in fair to good yield (entries 5-6).

Next, the more challenging ketone reductive amination was performed by screening a series of ketones in the presence of *p*-anisidine. In these experiments, *N*,*N*-diisopropylethylamine (DIPEA - 15 mol%) was added to the mixture before the activated catalyst, in order to quench the catalytic amount (10 mol%) of trifluoroacetic acid (TFA) previously added to accelerate imine formation, which would otherwise degrade the catalyst ***act*-1b**.[4a] Delightfully, both aromatic (Table 4, entries 1, 3 and 5) and aliphatic ketones (entries 2, 4) were converted into the corresponding N-PMP-amines in moderate to good yields (ranging from 31% to 68%), including the challenging cyclic substrates (entries 2 and 5).

Table 4. CTH-based reductive amination of ketones promoted by pre-catalyst **1b**.[a,b]



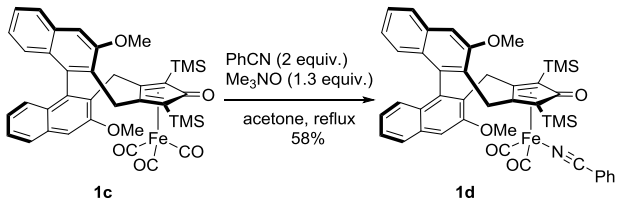
#	Product	Yield [%][c]	#	Product	Yield [%][c]
1	 **P22**	31	4	 **P25**	52
2	 **P23**	41	5	 **P26**	51
3	 **P24**	68			

[a] Reaction conditions: ketone/amine/**1b**/Me_3NO = 100:150:5:5. Imine formation: toluene, 100 °C, 3 Å MS (400 mg), TFA (10 mol%), 2 h. Catalyst activation: *i*PrOH, Me_3NO, r.t., 20 min. CTH: 3:1 *i*PrOH / toluene, $C_{0,sub.}$ in CTH = 0.25 M (0.5 mmol), DIPEA (15 mol%), 100 °C, 18 h; [b] Toluene and DIPEA were freshly distilled over sodium/benzophenone and CaH_2, respectively; [c] Isolated yields.

In 2015, our research group reported a new class of BINOL-derived chiral (cyclopentadienone)iron complexes, and their use in the asymmetric hydrogenation (AH) of ketones.[4d,e] These pre-catalysts proved slightly less active than the 'Knölker complex' **1a** (Figure 1 A) and showed a moderate enantioselectivity (up to 77% *ee* with the best complex **1c**, shown in Figure 1 C).[1a] Building on the experience gained in the transfer hydrogenation of imines with complex **1b**, we decided to test our chiral complexes also in the asymmetric transfer hydrogenation (ATH) of ketimines. Although – as mentioned above – most (cyclopentadienone)iron complexes are not sufficiently active to promote the reduction of ketimines,[9f] Zhao

and co-workers recently reported that the latter substrates can be activated in the presence of a Lewis acid co-catalyst.[9b] However, a preliminary test of pre-catalyst **1c** in the presence of Me_3NO and $Fe(acac)_3$ in the CTH of ketimine **S1** gave no conversion (Table 5, entry 1).

In the attempt to increase the reactivity of the cyclopentadienone iron complex, pre-catalyst **1d** was prepared by dissociation of one CO ligand by Me_3NO and replacement with benzonitrile (Scheme 3). In this case the activated form ***act*-1d** can be obtained by thermal dissociation of the labile nitrile ligand.[14]

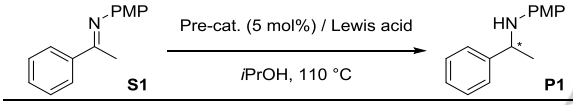


1c **1d**

Scheme 3. Synthesis of the nitrile-substituted chiral complex **1d**.

We tested the catalytic activity of complex **1d** in the CTH of *N*-(4-methoxyphenyl)-1-phenylethan-1-imine **S1** in the presence of several Lewis acids (see Supporting Information and Table 5).

Table 5. Optimization of the imine **S1** ATH promoted by chiral pre-catalysts **1c-d**.[a]



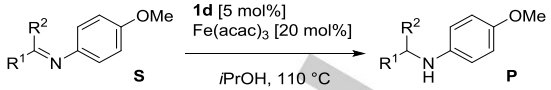
S1 **P1**

#	Pre-cat.	Lewis acid	Amount of Lewis acid [mol%]	Conv. [%][b]
1	**1c**[c]	$Fe(acac)_3$	40	0
2	**1d**	-	-	0
3	**1d**	$Fe(acac)_3$	10	12
4	**1d**	$Fe(acac)_3$	20	44
5	**1d**	$Fe(acac)_3$	40	36
6	**1d**	AgF	40	25

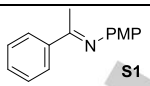
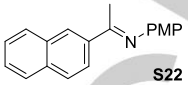
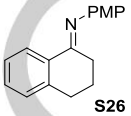
[a] Reaction conditions: **S1**/Pre-cat. = 100:5, solvent: *i*PrOH, T = 110 °C, 48 h, $C_{0,\mathbf{S1}}$ = 0.5 M (1 mmol); [b] Determined by ^{1}H NMR; [c] Complex **1c** pre-activated in the presence of 10 mol% Me_3NO for 20 min at r.t..

As expected, no conversion was obtained without Lewis acid (Table 5, entry 2). On the contrary, appreciable conversions were achieved in the presence of $Fe(acac)_3$ (Table 5, entries 3-5) and AgF (entry 6), 20 mol% of the former giving the best result (entry 4). Under the optimized conditions, three ketimines were screened, giving the results shown in Table 6: substrates **S1** and **S22** were reduced with moderate conversion and poor enantioselectivity (entries 1 and 2), whereas imine **S26** did not react at all (entry 3). The **1d**/$Fe(acac)_3$ catalytic system was also tested under hydrogenation conditions, in order to possibly achieve better conversion than in the ATH protocol. As shown in Table 7, good conversions were indeed obtained for all the three substrates, but unfortunately the level of enantioselectivity remained similar to the one observed in ATH.

Table 6. Ketimine ATH promoted by pre-catalyst **1d**.[a]

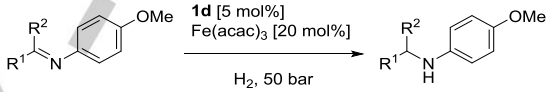


S **P**

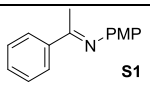
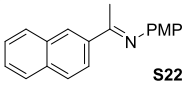
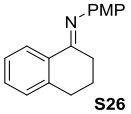
#	Substrate	Conv. [%][b]	*ee* [%]
1	 **S1**	44	33, *R*[c]
2	 **S22**	38	24, *R*[d]
3	 **S26**	0	-

[a] Reaction conditions: imine/**1d**/$Fe(acac)_3$ = 100:5:20; solvent: *i*PrOH, $C_{0,sub.}$ = 0.5 M (1 mmol), T = 110 °C, 48 h; [b] Determined by ^{1}H NMR; [c] Determined by chiral HPLC. Absolute configuration assigned by comparing the order of elution with literature data (see the Supporting Information); [d] Determined by chiral HPLC. Absolute configuration assigned by comparison of the optical rotation sign (see the Supporting Information).

Table 7. Ketimine AH promoted by pre-catalyst **1d**.[a]



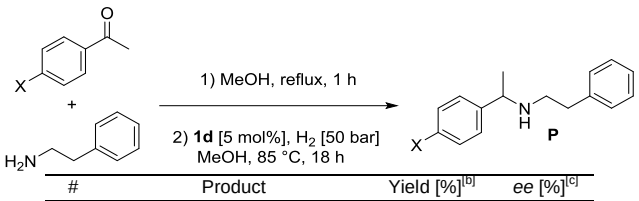
S **P**

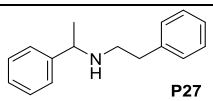
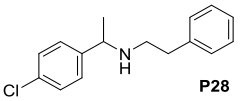
#	Substrate	Conv. [%][b]	*ee* [%]
1	 **S1**	81	33, *R*[c]
2	 **S22**	99	7, *R*[c]
3	 **S26**	74	31, (+)[e]

[a] Reaction conditions: imine/**1d**/$Fe(acac)_3$ = 100:5:20; H_2 (50 bar); solvent: MeOH, $C_{0,sub.}$ = 0.5 M (0.5 mmol), T = 85 °C, 18 h; [b] Determined by ^{1}H NMR; [c] See footnotes [c] and [d] of Table 6; [e] Determined by chiral HPLC: no correlation between sign of optical rotation and absolute configuration has been established so far.

Finally, we tried to establish an enantioselective reductive amination protocol based on complex **1d**. As this pre-catalyst showed higher activity in CH than in CTH (see Table 7 vs. Table 6), we decided to use hydrogenation for the reduction step. Thus, after imine formation (run in MeOH at reflux for 1 h), pre-catalyst **1d** (5 mol% loading) was added and then the mixture was reacted overnight at 85 °C under 50 bar of H_2. As shown in Table 8, the reductive amination of acetophenone and 4-chloroacetophenone proceeded, respectively, in good and fair yield and with a level of enantioselectivity quite modest but slightly higher than the one observed for isolated ketimines **S1** and **S26** (see Table 6 and 7).

Table 8. CH-based reductive amination of ketones promoted by pre-catalyst **1d**.[a]



#	Product	Yield [%][b]	*ee* [%][c]
1	 **P27**	68	42
2	 **P28**	33	47

[a] Reaction conditions: ketone/amine/**1d** = 100:120:5. Imine formation: MeOH, reflux, 1 h. CH: MeOH, $C_{0,sub.}$ in CTH = 0.5 M (0.2 mmol), 85 °C, 18 h; [b] Isolated yields; [c] Determined by chiral HPLC on the amine derivatives (Boc for **P27** and Bz for **P28**).

Conclusions

The work described in this paper complements the results described in a previous communication,[4a] expanding the application scope of (cyclopentadienone)iron complexes in C=N reduction. Owing to the high catalytic activity of our recently reported pre-catalyst **1b** (Figure 1 B),[4a,b] it has been possible to carry out C=N reductions which are usually very sluggish or even impossible using the classical 'Knölker complexes' **1a** and **2a** (Figure 1 A): the application scope of pre-catalyst **1b** has been expanded to reducing agents different from *i*PrOH and to the CTH of numerous additional aldimines and ketimines, both pre-isolated and generated in situ according to a reductive amination protocol. Additionally, the kinetics of CTH promoted by pre-catalyst **1b** have been assessed, showing a pseudo-first order profile.

To further demonstrate the potential of (cyclopentadienone)iron complexes in C=N reduction, we have tested chiral pre-catalyst **1c**[4d,e] and its analog **1d** (Figure 1 B) in the ATH and AH of ketimines and in the reductive amination of ketones. Although rather low *ee* values were obtained, the one described here is the first example of imine enantioselective reduction promoted by a chiral (cyclopentadienone)iron complex, and provides the basis for the future development of more efficient catalysts.

Experimental Section

All reactions were carried out in flame-dried glassware with magnetic stirring under inert atmosphere (nitrogen or argon), unless otherwise stated. Solvents for reactions were distilled over the following drying agents and transferred under nitrogen: CH_2Cl_2 (CaH_2), MeOH (CaH_2), toluene (Na/benzophenone). Dry 2-propanol (over molecular sieves in bottles with crown cap) was purchased from Sigma Aldrich and stored under nitrogen. The reactions were monitored by analytical thin-layer chromatography (TLC) using silica gel 60 F254 pre-coated glass plates (0.25 mm thickness). Visualization was accomplished by irradiation with a UV lamp and/or staining with a potassium permanganate alkaline solution. Flash Column Chromatography was performed using silica gel (60 Å, particle size 40-64 μm) as stationary phase, following the procedure by Still and co-workers.[15] ^{1}H NMR spectra were recorded on a spectrometer operating at 400.13 MHz. Proton chemical shifts are reported in ppm (δ) with the solvent reference relative to tetramethylsilane (TMS) employed as the internal standard ($CDCl_3$, δ = 7.26 ppm; CD_2Cl_2 δ = 5.32 ppm; acetone-d_6, δ = 2.05 ppm; toluene-d_8, δ = 2.08 ppm; CD_3OD, δ = 3.31 ppm). The following abbreviations are used to describe spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad signal, dd = doublet-doublet, ddd = doublet-doublet-doublet, td = triplet-doublet. ^{13}C NMR spectra were recorded either on a 400 MHz spectrometer operating at 100 MHz or on a 600 MHz spectrometer operating at 150 MHz, with complete proton decoupling. Carbon chemical shifts are reported in ppm (δ) relative to TMS with the respective solvent resonance as the internal standard ($CDCl_3$ δ = 77.16 ppm; CD_2Cl_2 δ = 54.00 ppm; acetone-d_6 δ = 29.84 ppm, 206.26 ppm; CD_3OD, δ = 49.00 ppm). The coupling constant values are given in Hz. Infrared spectra were recorded on a standard FT/IR spectrometer. High resolution mass spectra (HRMS) were performed on a Fourier Transform Ion Cyclotron Resonance (FT-ICR) Mass Spectrometer APEX II & Xmass software (Bruker Daltonics) – 4.7 T Magnet (Magnex) equipped with ESI source, available at the UNITECH-COSPECT laboratories, at Università degli Studi di Milano.

Materials: commercially available reagents were used as received. Ketones and aldehydes used in the substrate screening were purchased from commercial suppliers (TCI Chemicals, ACROS, Sigma Aldrich) and distilled over PPh_3 before use. The other commercially available reagents were used as received. 3 Å MS were dried under high vacuum at 200 °C and then stored in an oven at 110 °C.

General Procedure for the CTH of pre-formed imines

Pre-catalyst **1b** (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. After cooling down, the mixture was filtered through a celite pad (rinsing with AcOEt), the volatiles were removed and the product was purified by flash column chromatography (hexane/AcOEt mixtures with 0.5-1% Et_3N).

General Procedure for the reductive amination of aldehydes

3 Å MS (400 mg), aldehyde (0.5 mmol, 1 equiv.) and 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) and stirred for 20 min at r.t.. The activated catalyst solution was dispensed into the vessel containing the imine, followed by dry *i*PrOH (1.25 mL). The reaction vessel was sealed and stirred in a pre-heated oil bath at 100 °C for 18 h. After cooling down, the mixture was filtered through a celite pad (rinsing with AcOEt), the volatiles were removed and the crude was purified by flash column chromatography (hexane/AcOEt mixtures with 0.5-1% Et_3N).

General Procedure for the reductive amination of ketones

3 Å MS (400 mg), ketone (0.5 mmol, 1 equiv.), 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) and stirred for 20 min at r.t.. 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 (1.25 mL). The reaction vessel was sealed and stirred at 100 °C for 18 h. After cooling down, the mixture was filtered through a celite pad (rinsing with AcOEt), the volatiles were removed and the crude was purified by flash column chromatography (hexane/AcOEt mixtures with 0.5-1% Et_3N).

Synthesis of complex 1d

To a stirred solution of **1c** (100 mg, 0.19 mmol, 1.0 equiv.) in dry acetone (11.5 mL) under argon atmosphere, trimethylamine *N*-oxide (16 mg, 0.21 mmol, 1.2 equiv.) and benzonitrile (38 µL, 0.37 mmol, 2.0 equiv.) were added. The reaction was refluxed for 20 hours in a sealed tube. After cooling down the reaction to r.t., the solvent was removed under reduced pressure. Flash chromatography (1:1 hexane/DCM, then 8:2 hexane/AcOEt) afforded the product **1d** as a yellow solid. Yield: 77 mg (58%); m.p. = 184-186 °C; $[\alpha]_D^{20}$ = -13.4 (*c* = 0.13 in DCM); ^{1}H NMR (400 MHz, 9:1 $CDCl_3$ / CD_3OD): δ 7.75 (t, *J* = 8.6 Hz, 2H), 7.66 (d, *J* = 5.8 Hz, 2H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.40 (t, *J* = 7.7 Hz, 2H), 7.32 (dd, *J* = 12, 7.4 Hz, 2H), 7.25 (s, 1H), 7.20 (s, 1H), 7.00 (dd, *J* = 14.7, 7.3 Hz, 2H), 6.82 (dd, *J* = 7.6, 6.4 Hz, 2H), 4.25 (d, *J* = 15.3 Hz, 1H), 3.99 (s, 3H), 3.90 (s, 3H), 3.31 (s, 2H), 2.84 (dd, *J* = 31.3, 15.2 Hz, 2H), 0.31 (s, 9H), 0.22 (s, 9H); ^{13}C NMR (150 MHz, 9:1 $CDCl_3$ / CD_3OD): δ 212.58, 211.82, 178.84, 168.27, 156.30, 155.15, 154.92, 138.15, 137.75, 136.85, 133.80, 133.60, 133.47, 133.27, 132.61, 129.13, 128.24, 127.95, 127.30, 127.15, 126.76, 126.62, 126.17, 126.04, 123.87, 123.61, 111.94, 105.76, 105.32, 105.08, 73.09, 55.25, 55.10, 54.53, 29.82, 25.80, 0.38; FT-IR: *v* = 2954.1, 2922.6, 2898.5, 2851.2, 2299.7, 2058.6, 2003.7, 1947.8, 1677.8, 1618.0, 1593.9, 1446.4, 1422.2, 1407.8, 1328.7, 1238.1, 1195.7, 1109.8, 1018.2, 852.4, 841.8, 745.4, 617.1 cm^{-1}; HRMS (ESI+): m/z 778.21433 $[M + H]^+$ (calcd. for $C_{44}H_{43}FeNO_5Si_2$: 778.21074).

General Procedure for the ATH of ketimines using complexes 1d

A flame dried Schlenk tube containing a stirring bar was charged with imine (0.5 mmol, 1.0 equiv.), $Fe(acac)_3$ (20 mol%), pre-catalyst **1d** (5 mol%) and dry *i*PrOH (1 mL) under argon atmosphere. The reaction mixture was stirred at 110 °C (preheated oil bath) for 48 h. The reaction mixture was cooled down to r.t. and then filtered over deactivated neutral alumina (3% of H_2O) and rinsed with AcOEt. After removing the solvent under reduced pressure, the crude was dissolved in DCM (0.5 mL) and 1 M hydrochloric acid (0.5 mL) was added. The two-phase mixture was stirred for 3 h at r.t. before basifying with 1 M aqueous NaOH. The aqueous layer was extracted with AcOEt (3 × 5 mL) and the combined organic layers dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (hexane/AcOEt mixtures with 0.5-1% Et_3N) afforded the product amine. Ninhydrin staining visualizes the product amine (pale red spot) and *p*-anisidine (dark red spot).

General Procedure for the AH of ketimines using complex 1d

A 10 mL flame-dried autoclave vial containing a stirring bar was charged with imine (0.5 mmol, 1.0 equiv.), $Fe(acac)_3$ (20 mol%), pre-catalyst **1d** (5 mol%) and dry methanol (1 mL) under argon atmosphere. The autoclave was pressurized to 50 bars of hydrogen and stirred at 85 °C for 18 h. The reaction mixture was cooled down to r.t. and then filtered over deactivated neutral alumina (3% of H_2O) and rinsed with AcOEt. After removing the solvent under reduced pressure, the crude was dissolved in DCM (0.5 mL) and hydrochloric acid (1 M, 0.5 mL) was added. The two-phase mixture was stirred for 3 h. at r.t. before basifying with 1 M aqueous NaOH. The aqueous layer was extracted with AcOEt (3 × 5 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (hexane/AcOEt mixtures with 0.5-1% Et_3N) afforded the amine product. Ninhydrin staining allowed to visualize the product amine (pale red spot) and *p*-anisidine (dark red spot).

General Procedure for the enantioselective reductive amination of ketones using complex 1d

A 10 mL flame-dried autoclave vial containing a stirring bar was charged with ketone (0.2 mmol, 1.0 equiv., 0.5 M), phenethylamine (29 mg, 0.24 mmol, 1.2 equiv.) and dry MeOH (0.27 mL) under argon. The reaction mixture was heated to reflux in the sealed autoclave vial for 1 h. A solution of complex **1d** (7.9 mg, 0.01 mmol, 0.05 equiv.) in dry methanol (0.13 mL) was then added to the autoclave vial. The autoclave was pressurized to the final pressure of hydrogen (50 bar) and stirred at 85 °C for 18 h. After cooling down to r.t. and careful venting of remaining hydrogen, the reaction mixture was filtered over deactivated neutral alumina (3% of H_2O) rinsing with AcOEt. After removing the solvent under reduced pressure, the product was purified by flash column chromatography (hexane/AcOEt mixtures with 0.5-1% Et_3N).

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