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Iron(II)–bis(isonitrile) complexes: novel catalysts in asymmetric transfer hydrogenations of aromatic and heteroaromatic ketones†

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Chiral iron(II)–bis(isonitrile) complexes catalyse the transfer hydrogenation of aromatic ketones with enantioselectivities up to 91% ee, most likely *via* hydride transfer through imine intermediates, generated by *in situ* reduction of the isonitrile ligands, whereas iron acts as a Lewis acid to activate the ketone.

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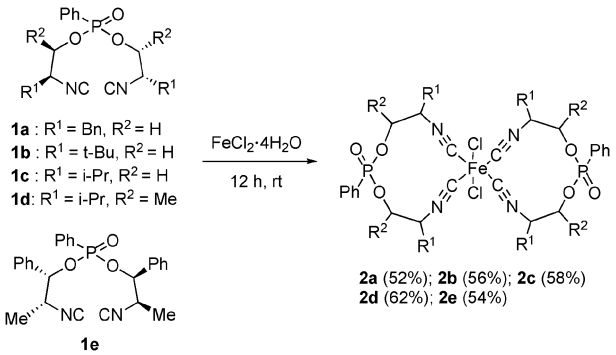
The application of iron, being the most abundant metal on earth, in homogeneous catalysis has recently gained considerable attention,[1,2] promising the substitution of more precious metals such as palladium, rhodium or ruthenium. The latter two transition metals build the edifice for asymmetric transfer hydrogenations of ketones[3,4] as one of the most appealing synthetic routes to chiral alcohols that avoids molecular hydrogen or hydrides as reducing agents. There have been several successful attempts to develop iron catalyst for transfer hydrogenations,[5] which has recently culminated in the spectacular break through by Morris and co-workers who disclosed the first asymmetric version applying iron complexes containing P–N–N–P tetradentate ligands.[6,7]

Based on our interest to utilize chiral oxazolines as synthetic building blocks for chiral ligands,[8] we recently reported the synthesis of a new kind of bis(isonitriles) **1a–c** and their corresponding palladium complexes, which showed good activities in non-stereoselective Wacker oxidations.[9] Herein we report iron complexes of those ligands and demonstrate for the first time the potential of isonitriles as chiral ligands with the asymmetric transfer hydrogenation of aromatic and heteroaromatic ketones.

Bidentate bis(isonitrile) ligands (BINC) **1a–e** could readily be synthesized from amino alcohols in two steps following the protocol developed by us earlier for **1a–c**.[9] The corresponding iron(II) complexes were obtained by treatment of **1a–e** with $FeCl_2{\cdot}4H_2O$ in methanol,[10] which led to the formation of orange coloured $FeCl_2(BINC)_2$ complexes (**2a–e**) in good yields (Scheme 1).

Exchanging the chloride with trichlorostannyl ligands by reacting **2b** with $SnCl_2$ allowed insights into the structure of iron(II)–BINC complexes. X-Ray analysis of the so obtained $Fe(\mathbf{2b})_2(SnCl_3)_2$ revealed that the bidentate isonitrile ligands had coordinated iron(II) in a square planar geometry with the trichlorostannyl ligands taking the axial positions to overall



Scheme 1 Synthesis of iron(II)–bis(isonitrile) complexes **2a–e**.

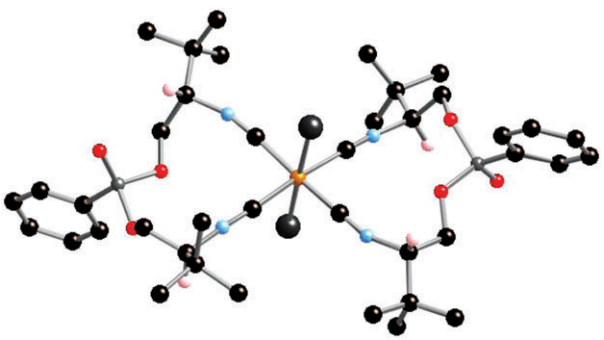


Fig. 1 X-Ray structure of $Fe(\mathbf{2b})_2(SnCl_3)_2$ (Cl atoms on Sn were omitted for clarity).

result in a distorted octahedral complex (Fig. 1). Notably, the iron–isonitrile unit has by and large a linear geometry (169°) with Fe–C and isonitrile C–N bond lengths averaging 1.86 Å and 1.14 Å, respectively, indicating that no or little back bonding from the metal to the ligand takes place.[11]

Complexes **2a–e** were tested as catalysts for transfer hydrogenation of acetophenone using isopropanol as the hydrogen source under basic conditions (Table 1, entries 1–5). Complex **2b** was identified to be an active catalyst at room temperature (entry 2) giving rise to 1-phenylethanol with 90% conversion and 64% ee, demonstrating for the first time the applicability of isonitrile ligands as chiral inductors in asymmetric catalysis. The substitution pattern in the isonitrile ligands appears to play an important role to render **2** an efficient catalyst in transfer hydrogenations. While the isopropyl derivative **2c** still showed appreciable activity and selectivity (Table 1, entry 3), the benzyl complex **2a** and derivatives **2d** and **2e** being substituted at the β-position of the isonitrile were by and large inactive. Since we assume (*vide infra*) that both iron and the isonitrile moiety play an integral role in the hydride transfer to the

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† Electronic supplementary information (ESI) available: Experimental details and spectroscopical data of **2b** and catalytic reactions performed. CCDC 771169. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0cc00508h

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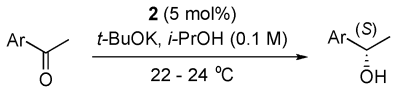
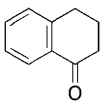
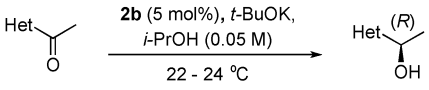
Table 1 Transfer hydrogenation of aromatic ketones with catalysts **2a–2e**

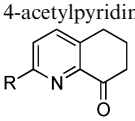
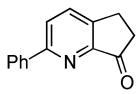
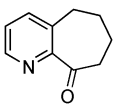


Entry	Ar	Catalyst	Time/h	Conv. %[a]	ee %[b]
1	Ph	**2a**	23	17	n.d.
2	Ph	**2b**	8	90	64
3	Ph	**2c**	8	71	54
4	Ph	**2d**	24	6	10
5	Ph	**2e**	24	24	17
6[c]	*p*-Cl–Ph	**2b**	12	94	60
7[c]	*m*-Cl–Ph	**2b**	1	>99	67
8[c]	*o*-Br–Ph	**2b**	24	60	67
9[c]	*p*-OMe–Ph	**2b**	6	50	58
10[c]	*m*-OMe–Ph	**2b**	1	93	54
11[c]	*o*-OMe–Ph	**2b**	3	56	52
12[c]	Phenylethylketone	**2b**	6	73	64
13	2-Acetonaphthone	**2b**	1	84	64
14[c]		**2b**	3	62	46

[a] Determined by GC using decane internal standard. [b] Determined by HPLC. [c] 0.05 M *i*-PrOH.

Table 2 Transfer hydrogenation of heteroaromatic and pyridyl ketones catalyzed by **2b**



Entry	Ketone		Time/h	Conv. %[a]	ee %[b]
1	2-acetylfuran		3	>99	30
2	2-acetylthiophene		1	70	53 (*S*)
3	3-acetylthiophene		3	36	62
4	2-acetylpyridine		6	85	41
5[c]	3-acetylpyridine		1	95	61
6	4-acetylpyridine		1	99	55 (*S*)
7[d,e]		R = H	24	80	91
8[e]		R = Ph	3	98	72
9[e]		R = Cl	15	93	84
10[e]			6	89	52
11[d]			24	83	83

[a] Determined by GC using decane internal standard. [b] Determined by HPLC. [c] 0.1 M concentration of substrate. [d] 0.2 M concentration of substrate. [e] Isolated yield.

ketone, small conformational changes in the iron–bis(isonitrile) complexes might sufficiently disturb the required arrangement of these two moieties to give catalytic turnover. Control experiments with various nickel or copper salt/**2b** combinations did not give rise to any ketone reduction under the reaction conditions, clearly attributing the asymmetric process described here to iron catalysis.

Catalyst **2b** was subsequently applied to other aromatic methyl ketones, giving rise to the corresponding alcohols with overall similar enantioselectivity ranging from 52 to 67% ee. We noticed, however, considerable rate differences in the reductions: *meta*-substituted aromatic ketones, either with donor (Table 1, entry 10) or acceptor groups (Table 1, entry 7), as well as 2-acetonaphthone (Table 1, entry 13) turned out to be most reactive. Noteworthy in light of pyridine substituted ketones discussed below, constricting the carbonyl group within a six-membered ring (entry 14) did not result in an improvement of enantioselectivity.

Turning to heteroaromatic methylketones (Table 2, entries 1–6), we observed high turn over for the carbonyl reduction, allowing reaction times as little as one hour to achieve complete conversion. Enantioselectivities remained moderate, however, a reversal of the absolute stereochemistry in the products with respect to the aromatic ketones was observed with the exception of 2-acetylthiophene (Table 2, entry 2) and 4-acetylpyridine (Table 2, entry 6).

Using pyridyl ketones in which the carbonyl group was embedded into a cyclic system (entries 7–11) dramatically improved the enantioselectivities, giving rise to the corresponding alcohols in up to 91% ee. It was interesting to note that a substituent in 2-position is detrimental to the enantioselectivity (entries 8–10), which might be an indication that the pyridine nitrogen is in proximity or even interacting with the active centre of the catalyst. The resulting chiral pyridyl alcohols are useful intermediates in the synthesis of ligands for asymmetric catalysis.[12] To the best of our knowledge only kinetic resolutions[13] of racemic pyridyl alcohols were reported by Pfaltz and co-workers but there has been no report on the asymmetric hydrogenation of pyridyl ketones so far.

To gain insight into the mechanism on how the iron–bis(isonitrile) complexes are operating, we carried out some IR experiments (Fig. 2). The spectrum of a solution of iron–bis(isonitrile) complex **2b** in isopropanol (7 mmol l^{-1}) shows a broad absorption of the isonitrile NC group at higher frequency (2177 cm^{-1}, Fig. 2B) than that of the free bis(isonitrile) ligand **1b** (2140 cm^{-1}, Fig. 2A). The high value of $\nu_{(NC)}$ is attributed to the strong σ-bonding interaction between the isonitrile carbon and the charged metal centre. The solution of **2b** in *i*PrOH was then treated with 10 equivalents of *t*-BuOK, resulting in the complete disappearance of the isonitrile band within 10 minutes and the appearance of a new band at 1638 cm^{-1} (Fig. 2C). The latter is assigned to the presence of a C=N double bond, indicating the reduction of isonitrile to the corresponding imine. In contrast, we could find no indication for a Fe–H band, which would have been expected[14] around 1900 cm^{-1}. Moreover, in NMR studies no signals at negative ppm, typical for such species, were observed.

Therefore, we propose that the reaction proceeds by a type of Meerwein–Ponndorf–Verley mechanism as shown in Scheme 2, being different from the reported mechanisms for transfer hydrogenations with ruthenium involving achiral isonitrile ligands.[15] We speculate that the ketone binds *via* its carbonyl group or alternatively through the respective

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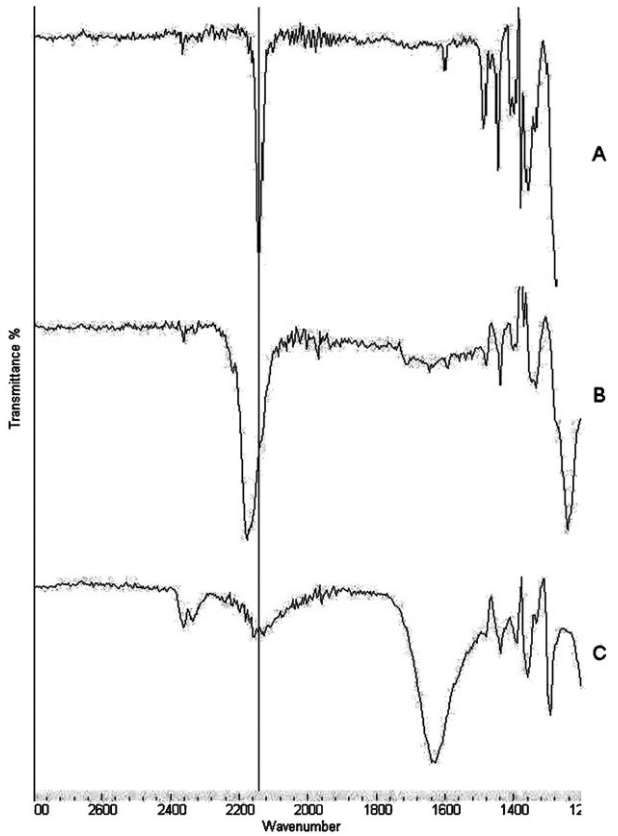
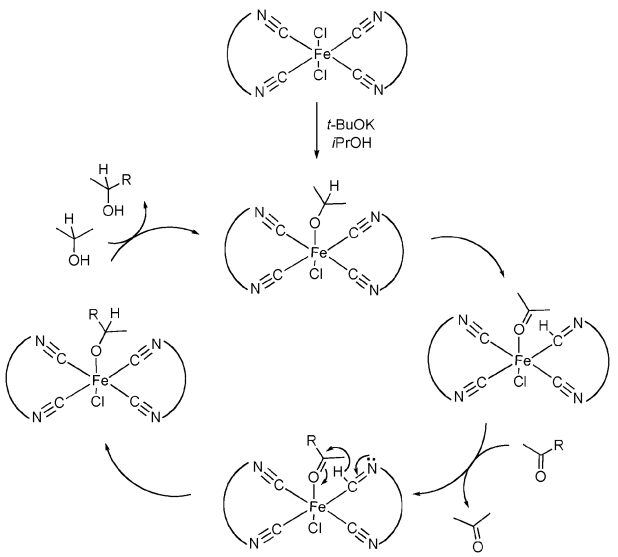


Fig. 2 IR spectra in *i*-PrOH: (A) free ligand **1b**; (B) iron complex **2b**; (C) iron complex **2b** in the presence of 10 equiv. *t*-BuOK.



Scheme 2 Proposed mechanism for iron(II)–bis(isonitrile) catalyzed transfer hydrogenations.

heteroatom in the case of heteroaromatic substrates to the iron centre of the catalyst. Hydride transfer then occurs directly from the reduced isonitrile group acting as the hydrogen donor.

In conclusion, we developed a new type of iron catalyst being effective in asymmetric transfer hydrogenations of ketones. The noteworthy feature of the iron complexes employed in our study are coordinating isonitrile groups that might serve as acceptors for hydrogen that is subsequently delivered to the ketone being activated by the iron centre. In addition, this is the first report that demonstrates the ability of isonitriles to be able to serve as chiral ligands in asymmetric catalyses.

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