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Unsymmetrical Iron Catalyst for the Asymmetric Transfer Hydrogenation of Ketones.

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Abstract: A new iron(II)(Ph₂P-NH-N-PCy₂) complex with a dicyclohexylphosphino group *trans* to the NH group has been found to catalyze the asymmetric transfer hydrogenation of a variety of ketones with high enantioselectivity.

Key words: hydrogenation, iron catalysis, chirality, ketone alcohol

The reduction of ketones to enantiopure alcohols is a very important transformation in organic synthesis as it provides valuable building blocks for the flavor, fragrance, fine chemical, and pharmaceutical industries.¹ Precious metals with expensive chiral ligands are generally required for the catalytic hydrogenation of ketones, but these metals are costly and potentially toxic.² Thus, there is a current research effort to find highly efficient and enantioselective catalysts based on earth abundant metals for more economical and safer processes without sacrificing activity and selectivity. Recently, iron has received a large amount of attention as a viable catalyst for both asymmetric transfer hydrogenation (ATH)³ and direct hydrogenation (DH)⁴ of polar double bonds. ATH takes place in the presence of a sacrificial reductant as the H⁺/H⁻ source, as shown in **Scheme 1** with isopropanol as the reductant. This transformation will be the focus of this communication.

Scheme 1: General reaction scheme for the ATH of ketones

Three iron(II) complexes (**1-3** in **Figure 1**) of our iron catalysts for ATH have been synthesized and reported recently.^{3m, 4f} Complex **1** was found to be highly active in the ATH of ketones with enzyme-like activity. Turnover frequencies (TOF) up to 200 s⁻¹ and enantiomeric excess (ee) up to 90% was observed for the reduction of 3,4-bis(trifluoromethyl)acetophenone (**K8**). Although complex **1** has unprecedented activity, there is room for improvement with respect to enantioselectivity. Complex **2** has lower activity but provides higher ee (up to 98%) for certain substrates. In some cases there is racemization of the product near the end of the reaction. Complex **3** has higher activity but lower enantioselectivity.

In the preparation of the catalyst, the incorporation of an N-H moiety in the tetradentate ligand required an intensive synthetic approach where first an enantiomerically pure (*S,S*)-R₂PCH₂CH₂NHCH(Ph)CH(Ph)NH₂ ((*S,S*)-P-NH-NH₂) ligand was synthesized and isolated, then it underwent an iron-templated Schiff-base condensation with an α -diarylphosphinoacetaldehyde to produce the P-NH-N-P ligand on iron. Complexes **1-3** differ only by the aryl phosphine groups, and complex **3** is so far the only one with unsymmetrical phosphine donors. We propose that the use of a more sterically hindered phosphine such as a dicyclohexylphosphino group on the ligand may improve the enantioselectivity of this system, and this phosphine can be introduced in the final step of the templated ligand synthesis.

Figure 1: Third generation iron(II) complexes previously reported by our group

The present study describes the catalytic reduction of ketones using a new unsymmetrically substituted catalyst **4** which provides alcohols in excellent enantiomeric enrichment without racemization.

The new complex **4** was synthesized using a similar method to that of **1** and **3** as described briefly above.^{3m} Starting with the air- and moisture-stable dicyclohexylphosphonium dimer and the enantiomerically pure (*S,S*)-Ph₂P-NH-NH₂ ligand, the Schiff-base condensation occurred *via* a metal-mediated template synthesis as shown in **Scheme 2**. Substitution of the two MeCN with bromide and carbonyl, followed by salt exchange with NaBPh₄, afforded complex **4** in moderate yield (40%) as a mixture of two diastereomers. It has been characterized by NMR, ESI-MS, and IR. In the ³¹P{¹H} NMR spectrum, characteristic doublets at 78.38 ppm and 47.34 ppm, as well as 76.05 ppm and 75.48 ppm correspond to two structural isomers of the complex, the first being the major isomer (75%/25%). Presumably, one isomer would have its C=O *syn* to the N-H and the other *anti*. A carbonyl stretch (ν_{CO}) was found at 1951 cm⁻¹, which is typical for such a complex.

Scheme 2: Synthesis of the new iron(II) Ph₂P-NH-N-PCy₂ complex

The catalytic activity of complex **4** was tested for the ATH of ketones **K1-K16** and one aldehyde **A1**, shown in **Figure 2**. For all substrates, the (*R*)-alcohol was produced when using our iron complexes which have enantiopure (*S,S*)-ligands. The results are summarized in **Table 1**. Overall, complex **4** has a lower activity than **1**, however the ee of a few substrates have been increased by using the bulky dicyclohexylphosphine. Entries 1-3 show the reduction of acetophenone under different conditions. An ee of 81% was observed when the C/B/S ratio was 1/2/500, but when the catalyst loading was reduced, the ee increased significantly to 93% and 98% with 2 and 8 equivalents of base, respectively. We found that **4** was slightly less active than **1** in the reduction of **K1**, giving a conversion of 11% lower; however the ee was significantly increased by 20%. In our previous work^{3m} we found that complex **2** was more enantioselective for the reduction of acetophenone with a 90% ee, but **4** surpasses. Substrates **K2** and **K4** were reduced with very high ee of 94% and >99%, respectively; however when a more bulky substrate, such as **K3** was tested, no conversion was observed. The effective reduction of **K4** is noteworthy as Noyori-type catalysts do not hydrogenate it.⁵ When the substituents on the phenyl ring were varied as for substrates **K5-K8**, different effects on catalysis were observed. Complex **4** gave very high conversions of chloro-substituted ketones **K5** and **K6**, but there were lower conversions of methyl- and CF₃-substituted ketones **K7** and **K8**. The ee of the more sterically hindered ortho- and meta-substituted **K5** and **K8** were higher (94% and 95%, respectively) than the para-substituted ketones **K6** and **K7**. Complex **4** gave a higher ee (95%) for substrate **K8** than **1** (90%), however the activity was much lower with only 38% conversion. The resulting alcohol serves as an intermediate in the synthesis of Aprepitant to combat nausea associated with cancer

chemotherapy.⁶ Complex **4** was found to be imine-functional group tolerant with the high conversion of acetylpyridine (**K9**) to (*R*)- α -methyl-2-pyridinemethanol, however catalysis stopped in the presence of the oxygen-functionalized acetylfuran (**K10**).

Figure 2: Substrate scope for ATH using complex **4**

Alkylketones **K11** and **K12** are deactivated to reduction by complex **4** with conversions of 44% and 0%, respectively, as is the bulky cyclohexylphenyl ketone **K13**. High conversions of benzophenone **K14** and acetylnaphthone (**K15**) were observed, with an ee of 80%, matching complex **1**, for the production of (*R*)- α -methyl-2-naphthalenemethanol. The ATH of the olefinic aryl ketone **K16** resulted in a non-selective reduction of both the C=O and C=C bonds with a 40% conversion to reduced products and only a 5% ee of olefin (*R*)-alcohol. This is different than complex **1** which reduced only the C=O moiety, however with a low yield (55%). Lastly, the hydrogenation of benzaldehyde **A17** was very efficient with quantitative conversion in 10 minutes. The products of the reduction of **K5**, **K8**, and **K9** were isolated *via* extraction from brine with ether, as well as filtration through a pad of celite. The alcohols 1-(2-chlorophenyl)ethanol and 1-(2-pyridyl)ethanol were isolated without any starting ketone present at 75% and 58% yield, and with 95 and 34% ee, respectively. The reduction of **K8** did not go to completion,

however, and the alcohol was distilled with a resulting yield of only 30% in 94% ee.

The proposed mechanism of the catalytic reaction is shown in **Scheme 3** and is assumed to follow the one that has previously been reported.^{3m} The precatalyst **4** is activated with 2-8 equivalents of base to form the neutral iron ene-amido species **5a** and **5b**. It has been found that the proton and hydride of the active catalyst must be on the same side of the ligand plane, and the orientations of the amide and vacant site of **5a** do not allow the initial H⁺/H⁻ transfer to occur in the correct way. However, complex **5b** can dehydrogenate *i*PrOH to give the hydride complex **6**. The ketone interacts preferentially in the *re* configuration with **5b** in a 6-membered transition state. The H⁺/H⁻ transfer then occurs to release the product alcohol and the neutral species **5b**, thus closing the catalytic cycle.

Scheme 3: Proposed catalytic cycle for the ATH of ketones

In conclusion, a newly developed unsymmetrical tetradentate P-NH-N-P' ligand has been synthesized on iron. The new precatalyst **4** was tested in the ATH of C=O bonds and gave a TON up to 4300 and ee up to 99%. In comparing the dicyclohexylphosphino-substituted complex **4** with the previously reported diphenylphosphino complex **1** in the ATH of ketones, we find that the enantioselectivity of this system is increased at the expense of catalytic activity. For example, acetophenone, usually a challenging substrate for enantioselective reduction,^{1c} was hydrogenated with a resulting ee of 98%. The flexible synthesis of

Table 1: Catalytic results for the ATH of substrates shown in **Figure 2** using complex **4**^a

Entry	Substrate	Conversion ^b (%)	Time (min)	ee ^b (%)	TON ^c
1	K1	83	20	81	415
2 ^d	K1	36	50	93	3550
3 ^e	K1	71	120	98	4346
4	K2	80	60	94	401
5	K3	0	120	-	0
6	K4	98	2	>99	~500
7	K5	>99	10	94	~500
8	K6	92	10	52	463
9	K7	60	20	65	300
10	K8	38	40	95	190
11	K9	>99	20	34	~500
12	K10	0	120	-	0
13 ^f	K11	44	50	43	221
14	K12	0	120	-	0
15	K13	0	120	-	0
16	K14	92	30	-	462
17	K15	88	20	80	440
18	K16	40	20	5	200
19 ^f	A1	>99	10	-	~500

^a catalyst/base/substrate (C/B/S) ratio = 1/2/500 unless otherwise stated.^b %conversion and %ee determined by chiral GC^c turnover number^d C/B/S = 1/2/6121^e C/B/S = 1/8/6121^f C/B/S = 1/8/500

our third generation catalysts offers the possibility of tuning their structure for the optimum reduction of a given substrate. This is currently under investigation

Experimental Section

All manipulations were done under inert atmosphere of either nitrogen or argon using

Schlenk techniques or a glovebox, unless otherwise stated. Solvents were dried and degassed under standard procedures prior to use. IR spectra were recorded with samples in KBr disks on a Paragon 500 spectrometer. NMR spectra were recorded at ambient temperature and pressure using Agilent DD2 600 MHz spectrometer [¹H (600 MHz) and ³¹P{¹H} (242 MHz)]. The ³¹P NMR spectra were referenced to 85% H₃PO₄ (0 ppm). The electrospray

ionization mass spectrometry (ESI-MS) data were collected on an AB/Sciex QStar mass spectrometer with an ESI source.

Synthesis of trans-(S,S)-[Fe(Br)(CO)(PPh₂CH₂CH₂NHCHPhCHPhN=C HCH₂PCy₂)] [BPh₄] (4): In the glovebox, sodium methoxide (64 mg, 1.176 mmol) was added to a 100 mL Schlenk flask charged with a stir bar and dicyclohexyl phosphonium bromide (378 mg, 5.88x10⁻¹ mmol) and 25 mL methanol was added with stirring. This solution was stirred for no more than 2 minutes. A solution of dissolved [Fe(H₂O)₆][BF₄]₂ (496 mg, 1.47 mmol) in 20 mL acetonitrile was added to the Schlenk flask, followed by a solution of (S,S)-PPh₂CH₂CH₂NHCH(Ph)CH(Ph)NH₂ in 10 mL methanol. This resulted in a purple solution. This was left to stir at room temperature for 16 h, after which a colour change from purple to pink was observed. The solvent was removed *in vacuo*. KBr (140 mg, 4.70 mmol) was added to the flask which was sealed and removed from the glovebox. The flask was purged and placed under CO atmosphere using Schlenk techniques. 20 mL acetone in a syringe was removed from the glovebox and injected into the flask with stirring for 1.5 hours. The solvent was removed under vacuum and the residual orange solid was redissolved in 20 mL acetone while under CO atmosphere. This was stirred for 1 hour, after which the solvent was removed and the flask brought into the glovebox, where the remaining steps occurred. The solid residue was dissolved in 20 mL dichloromethane and filtered through a pad of celite, then through a 25 mm Syringe Filter PTFE membrane (pore size 0.45 µm). The clear orange solution was dried *in vacuo*, then redissolved in minimal methanol. This solution was added to a vial charged with a stir bar and NaBPh₄ (402 mg, 1.294 mmol) dissolved in minimal methanol, from which a yellow solid precipitated. This solid was filtered off and washed with diethyl ether (3x15 mL) and dried overnight. If the purity by NMR was not sufficient, the solid was redissolved in minimal dichloromethane and precipitated out by addition of diethyl ether. Yield: 530 mg (40%)

FT-IR (KBr, cm⁻¹): 1951 (ν_{CO})

HRMS (ESI-TOF, CH₂Cl₂) m/z calculated for [C₄₃H₅₃BrFeN₂OP₂]⁺: 809.2084, found: 809.2070

¹H NMR (600 MHz; CD₂Cl₂) δ: 1.19-1.94 (m, 22H, P(C₆H₁₁)₂), 2.58 (m, 2H, CH₂), 2.74 (m, 2H, CH₂), 4.38 (t, 2H, PCH₂, J_{HH} = 11.88 Hz), 4.76 (t, 1H,

N(H)(Ph), J_{HH} = 12.14 Hz), 4.83 (m, 1H, N(H)(Ph)), 6.83-7.56 (m, 40H, ArH), 7.79 (m, 1H, N=CH)

³¹P {¹H} NMR (242 MHz; CD₂Cl₂) δ: 78.38 and 47.34 (d, J_{PP} = 33.5 Hz, isomer 1); (d, J_{PP} = 33.48 Hz), 76.05 and 75.48 (d, J_{PP} = 38.7 Hz, isomer 2).

General procedure for ATH: Table 1 entries 1, and 4-19: A 20 mL vial was charged with a stir bar and complex 4 (10 mg, 8.9x10⁻³ mmol). The substrate (4.43x10 mmol) was added and the mixture was stirred. If the substrate is a liquid, the mixture was stirred until complex 4 was completely dissolved. 3.61 g iPrOH was added and the solution was stirred for 5 minutes. A stock solution of KOtBu (20 mg, 0.18 mmol) in 0.98 g iPrOH was stirred until all the base was dissolved. 0.1 g or 0.4 g stock solution (2 and 8 eq., respectively) was diluted by 1.0 g or 0.7 g iPrOH, respectively and added to the 20-mL vial to activate the precatalyst and start catalysis. 0.1 mL samples were taken *via* syringe and injected into teflon-sealed GC vials prepared with wet, aerated iPrOH to quench catalysis.

General procedure for ATH: Table 1 entries 2-3: The quantity of the precatalyst was measured via a stock solution method. A concentrated stock solution was made by dissolving complex 4 (22 mg, 1.97x10⁻² mmol) in 6.08 g cold dichloromethane. After all the solid was dissolved, the solution was immediately sucked into a syringe. The solution was then divided into equal portions into several 20 mL vials such that each portion has 0.2 g of the stock solution, and then dichloromethane was removed *in vacuo*. These operations led to a precatalyst quantity of 6.48x10⁻⁴ mmol in each vial. The base was prepared by dissolving KOtBu (10 mg, 0.089 mmol) in iPrOH (1.02 g, 1.30 mL). iPrOH (6.63 g, 8.44 mL), substrate (3.95 mmol) and a clean stirring bar were added to the vial that contains the precatalyst and the solution was stirred for 5 minutes, or until all the precatalyst was dissolved. 0.015 g or 0.06 g of the base stock solution (2 or 8 eq. base) was added into a vial that contains 0.546 g or 0.501 g of iPrOH, respectively, and the mixed solution was then added into the catalyst solution to start the catalytic reaction. 0.1 mL samples were taken *via* syringe and injected into teflon-sealed GC vials prepared with wet, aerated iPrOH to quench catalysis.

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Asymmetric Transfer Hydrogenation Iron Catalyst

Supporting Information for
Unsymmetrical Iron Catalyst for the Asymmetric Transfer Hydrogenation of Ketones.

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Figure S1 The ^1H NMR (600 MHz, CD_2Cl_2) and $^{31}\text{P}\{^1\text{H}\}$ NMR (242 MHz, CD_2Cl_2) spectra of **4**.

Figure S2 The FT-IR spectrum (KBr pellet) of **4**. The peak at 1951 cm^{-1} was assigned to the CO stretch.

Figure S3 Entry 3 reaction profile and ee of the catalytic reduction of acetophenone.

Figure S4.1 Reaction for entry 1, Table 1

GC analysis conditions: Oven temperature 130 °C

Retention time: (*R*)-isomer = 6.693; (*S*)-isomer = 7.193; starting material = 4.093.

Figure S4.2

10 min

Figure S5.1 Reaction for entry 2, Table 1

GC analysis conditions: Oven temperature 130 °C

Retention time: (*R*)-isomer = 6.758; (*S*)-isomer = 7.239; starting material = 4.072.

Figure S5.2

50 min

Figure S6.1 Reaction for entry 3, Table 1

GC analysis conditions: Oven temperature 130 °C

Retention time: (*R*)-isomer = 6.703; (*S*)-isomer = 7.193; starting material = 4.092.

Figure S6.2

120 min

Figure S7.1 Reaction for entry 4, Table 1

GC analysis conditions: Oven temperature 120 °C

Retention time: (*R*)-isomer = 10.966; (*S*)-isomer = 11.992; starting material = 5.349.

Figure S7.2

60 min

Figure S8.1 Reaction for entry 6, Table 1

GC analysis conditions: Oven temperature 120 °C

Retention time: (*R*)-isomer = 14.530; (*S*)-isomer = ; starting material = 3.672.

Figure S8.2

2 min

Figure S9.1 Reaction for entry 7, Table 1

GC analysis conditions: Oven temperature 145 °C

Retention time: (*R*)-isomer = 5.654; (*S*)-isomer = 6.924; starting material = 2.752.

Figure S9.2

10 min

Figure S10.1 Reaction for entry 8, Table 1

GC analysis conditions: Oven temperature 145 °C

Retention time: (*R*)-isomer = 4.737; (*S*)-isomer = 5.213; starting material = 2.588.

Figure S10.2

10 min

Figure S11.1 Reaction for entry 9, Table 1

GC analysis conditions: Oven temperature 130 °C

Retention time: (*R*)-isomer = ; (*S*)-isomer = ; starting material = .

Figure S11.2

20 min

Figure S12.1 Reaction for entry 10, Table 1

GC analysis conditions: Oven temperature 140 °C

Retention time: (*R*)-isomer = 2.735; (*S*)-isomer = 2.606; starting material = 1.399.

Figure S12.2

40 min

Figure S13.1 Reaction for entry 11, Table 1

GC analysis conditions: Oven temperature 100 °C

Retention time: (*R*)-isomer = 13.779; (*S*)-isomer = 14.208; starting material = 5.865.

Figure S13.2

20 min

Figure 13.3

20 mins, after isolation ee was obtainable

Figure S14.1 Reaction for entry 13, Table 1

GC analysis conditions: Oven temperature 60 °C

Retention time: (*R*)-isomer = 9.41; (*S*)-isomer = 9.92; starting material = 3.74.

Figure S14.2

50 min

Figure S15.1 Reaction for entry 16, Table 1

GC analysis conditions: Oven temperature 180 °C

Retention time: product = 5.013; starting material = 3.228.

Figure S15.2

30 min

Figure S16.1 Reaction for entry 17, Table 1

GC analysis conditions: Oven temperature 150 °C

Retention time: (*R*)-isomer = 6.119; (*S*)-isomer = 6.378; starting material = 4.403.

Figure S16.2

20 min

Figure S17.1 Reaction for entry 18, Table 1

GC analysis conditions: Oven temperature 125 °C

Retention time: (*R*)-isomer = 15.743; (*S*)-isomer = 16.157; RED-(*R*)-isomer = 10.677; RED-(*S*)-isomer = 11.051; REDK = 6.416; starting material = 12.175.

Figure S17.2

20 min

Figure S18.1 Reaction for entry 19, Table 1

GC analysis conditions: Oven temperature 160 °C

Retention time: product = 7.04; starting material = 5.28.

Figure S18.2

10 min