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Title: Effective iron catalysts for the asymmetric reduction of ketones and imines

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One Sentence Summary: New synthetic methods furnish a variety of very active iron-based catalysts for the production of useful enantiomeric forms of alcohols and amines.

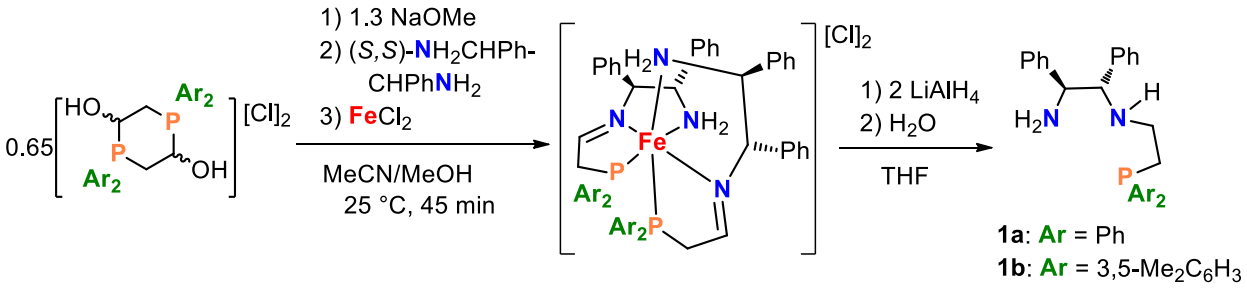
Abstract: We describe the discovery of selective and unusually active iron-based homogenous catalysts. This enables the production of enantio-enriched alcohols and amines used in the pharmaceutical and fine chemical industry without the need of expensive conventional platinum metal complexes. A new method to make enantiopure ligands is introduced that takes advantage of the iron(II) ion as a template. These new ligands permit the efficient, multi-component synthesis of a wide range of highly active iron catalysts with varied structural features. The catalytic mechanism is elucidated by detecting hydride intermediate in an extremely efficient transfer of a hydride plus a proton to ketone substrates.

Main text: Metal-based homogenous catalysts are often used in the synthesis of enantiomerically pure organic molecules such as alcohols, amines and amino acids for use in the pharmaceutical and fine chemical industries (*1*). The metals are usually rare and expensive platinum group metals such as ruthenium and rhodium(*2-4*). Iron is an element essential to life and in high abundance in contrast to platinum group metals and thus its use is preferable for economic and health reasons. Recent research has shown that suitable ligands can be discovered that activate iron-based molecules so that their catalytic performance rivals or surpasses that of industrial catalysts (*5-7*). We describe here an exceptionally efficient class of catalysts for the preparation of enantioenriched alcohols and imines.

Our previous synthetic and mechanistic studies of iron-based transfer hydrogenation catalysts pointed to a promising catalyst structure with a tetradentate P-NH-N-P ligand containing two phosphine donor ends flanking one amine donor and one anionic nitrogen donor (*8, 9*). Active catalysts with this ligand were suspected to be formed by the reduction of one of the imine groups in our previous generation of catalyst precursor (*S,S,*)-[Fe(CO)(Br)(PAr_2CH_2CH=NCHPhCHPhCH=NCH_2PAr_2)]BPh_4 which reduced acetophenone at turnover frequencies up to 15 s^{-1} at 30 °C; until the present work this was an unrivaled rate for this reaction (*8*). The key to the synthesis of the unsymmetrical ligand P-NH-N-P was first the selective synthesis of new enantiopure tridentate ligands P-NH-NH_2 (**1a, 1b**) by an iron(II)-assisted method (Fig. 1). The starting compounds are air- and water- stable dimeric phosphonium compounds that are readily prepared with a variety of substituents at phosphorus (in green in Fig. 1); in the present case these are phenyl and *meta*-xylyl. The latter group is often effective at increasing the selectivity of catalysts (*2, 10*). These phosphonium dimers release reactive phosphine-aldehyde species when they are treated with base (NaOMe) and undergo Schiff-base condensation with an enantiopure diamine at iron(II) to form complexes with two tridentate ligands with phosphine and imine and amine nitrogen donors high yield (*11*). In this work we use the enantiopure diamine (S,S)-$NH_2CHPhCHPhNH_2$ (dpen). These iron complexes are treated with lithium aluminum hydride to reduce the imine linkages and then hydrolyzed to release the new enantiopure compounds **1a** and **1b** in high yield. This method is superior to other

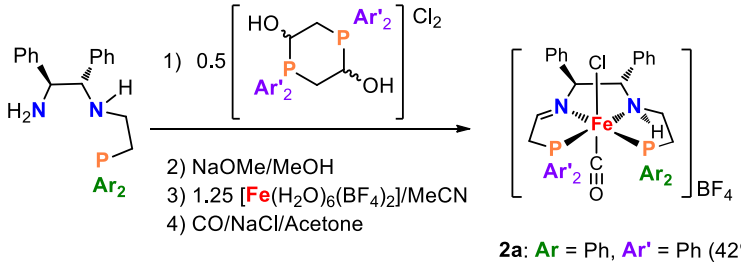
reductive amination methods that would either require an excess of the expensive diamine or would result in a mixture of amine products. The ligands are produced in approx. 90% purity and used directly in the next step.

Fig. 1 The iron(II)-assisted synthesis of enantiopure phosphinodiamine ligands

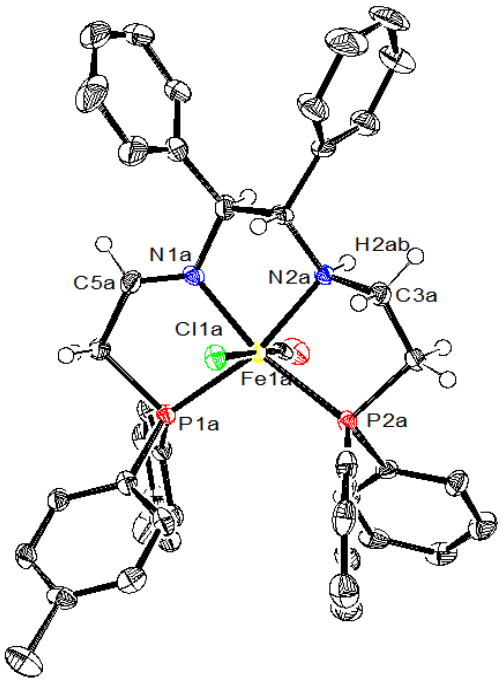


These ligands enable the direct synthesis of a wide range of catalyst precursors as exemplified by the three compounds **2a-2c** produced in the reaction shown in Fig. 2. The iron(II) acts as a template to produce one isomer in the multi-component reaction. In the first step a phosphine-aldehyde component with phenyl, *para*-tolyl or xylyl substituents at phosphorus condenses with a P-NH-NH_2 ligand (**1a or 1b)** at iron in the presence of acetonitrile to produce an intermediate iron complex. The latter is then reacted with one atmosphere of carbon monoxide and sodium chloride in acetone to give the new iron complexes **2a-2c** in acceptable overall yield (40-60%). Remarkably only one diastereomer is formed as indicated by the $^{31}P\{^{1}H\}$ NMR spectra; e.g. complex **2a** when dissolved in CD_2Cl_2 produces two doublet resonances at 58.0 and 62.6 ppm with $^{2}J_{PP}$ = 40 Hz. An X-ray diffraction study of a single crystal of **2b** revealed the expected structure with chloride *trans* to carbonyl in an octahedral complex of Fe(II). The presence of the amine and imine groups is confirmed by the shorter N-C bond length for the latter group: N(2A)-C(3A) (1.486(7) Å) and N(1A)-C(5A) (1.256(7) Å). It is noteworthy that the amino proton and the chloro ligand are located on opposite sides of the coordination plane defined by the Fe, N and P atoms.

Fig. 2. The iron(II)-templated synthesis of enantiopure catalyst precursors and the molecular structure of the cation of complex **2b** as determined by single crystal X-ray diffraction (some hydrogens have been removed for clarity).



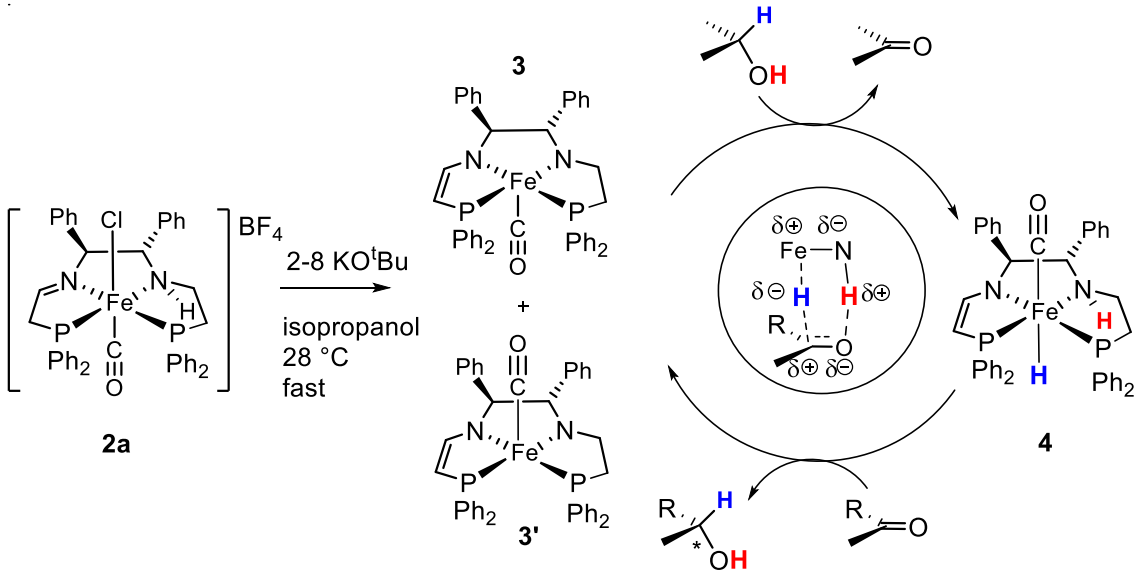
2a: Ar = Ph, Ar' = Ph (42% yield)
2b: Ar = Ph, Ar' = *p*-MeC_6H_4 (41%)
2c: Ar, Ar' = 3,5-$Me_2C_6H_3$ (30%)



When these complexes are treated with at least two equivalents of the base (potassium tertiary butoxide) very reactive, oxygen sensitive catalysts are released for the hydrogenation of ketones by transferring hydrogen from the solvent isopropanol (Fig. 3). There are two features that distinguish these catalysts from the ones that we have reported earlier. First there is no induction period observable, and second, the rate of conversion at 28 °C is unprecedented (*7, 10, 12, 13*). Turnover frequencies (TOF) of greater than 200 s^{-1} (720,000 h^{-1}) at 50% conversion are observed for some substrates (see Table 1) with complete conversion (up to 6100 turn over numbers, TON) attained in seconds. To the best of our knowledge these are the most active transfer hydrogenation systems at this temperature, regardless of the metal used in the catalyst. This activity rivals that of enzymes such as liver alcohol dehydrogenase which transfers a hydride from a zinc ethoxide active site to a pyridinium substrate (*14*) and a synthetic iron-based hydrogenase where a proton and hydride combine to produce dihydrogen (*15*).

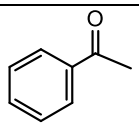
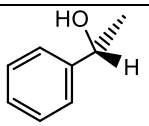
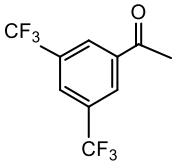
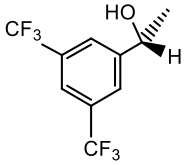
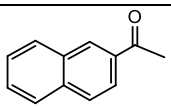
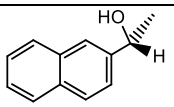
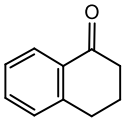
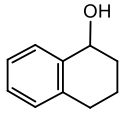
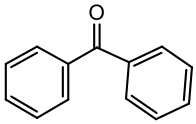
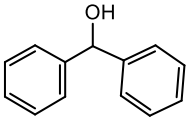
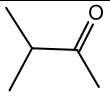
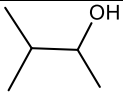
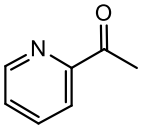
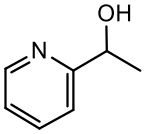
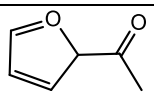
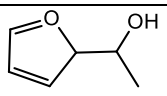
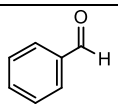
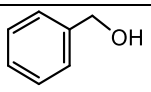
Fig. 3. Very efficient catalytic species, the amido/eneamido complex **3** and its isomer **3'** and the amine-eneamido-hydride complex **4**, for the asymmetric transfer hydrogenation of ketones and imines are

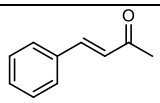
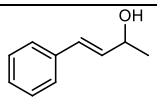
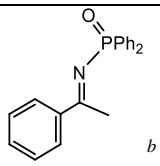
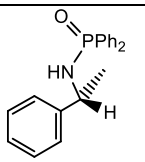
generated when complexes **2a-c** are treated with base in isopropanol solvent. The catalysts **3** and **4,** generated from **2a**, have been identified by NMR and a previous theoretical (DFT) study (*9*).



Entries 1-4 in Table 1 provide a comparison of the utility of the precursors **2a-c** in the hydrogenation of acetophenone. Under standard conditions (acetophenone: KO^{t}Bu: **2** = 6100:8:1), complex **2b** with *para*-tolyl groups provides the highest TOF while complex **2c** with xylyl groups on the phosphorus atoms provides the highest enantiomeric excess (ee) of the (*R*)-1-phenylethanol. The use of **2a** or **2b** results in an erosion of ee over time while that of **2c** has the advantage of no erosion of ee. The racemization of product alcohol by the **2b** system can be minimized by using a less active system containing less base in the ratio of concentrations 6100:2:1 (entry 3 with a TOF of 12 s^{-1}). The reduction of 3,5-bistrifluoromethylacetophenone proceeded with unprecedented activity and enantioselectivity (90% ee for **2a** and 98 ee for **2c).** The high activity, yield and enantioselectivity are very interesting as the (*R*) alcohol product of this reaction serves as an intermediate for the synthesis of an efficient neurokinin 1 (NK_1) antagonist for use as an aprepitant to combat nausea associated with cancer chemotherapy (*16*).

Table 1. Transfer hydrogenation of ketones and imines catalyzed by complexes **2a-c**.[a]

Substrate	Product	Catalyst	Time (s)/ conv. (%)/TON (at equil.)	TOF (s^{-1}) at 50% conv.	ee (%) (*R)* at 10 s/ at equil.
		**2a**	180/82/5000	119	88/78
		2b	180/83/5100	152	86/70
		2b[b]	1000/83/5100	12	86/80
		2c	180/82/5000	70	92/90
		**2a**	180/99/6060	147	91/90
		2c[c]	10/100/2000	200	98
		**2a**	180/84/5140	158	92/91
		**2a**	3600/73/4470	4	34/33
		**2a**	600/88/5400	78	-
		**2a**	3600/67/4100	3	57/54
		**2a**	360/98/6000	222	25/24
		**2a**	360/84/5140	61	51/31
		**2a**	25/99/6060	242	-

		**2a**	240/55/3370	14	40/40
		**2a**[d]	10/100/100	10	>99/>99

[a]General conditions: [Cat] = 6.73×10^{-5} M, [KO^{t}Bu] = 5.45×10^{-4} M, [substrate] = 0.412 M, [^{i}PrOH] = 12.4 M, 28°C. [b] [Cat, **2a**] = 6.73×10^{-5} M, [KO^{t}Bu] = 1.35×10^{-4} M , [substrate] = 0.412 M, [^{i}PrOH] = 12.4 M, 28°C. [c] ketone/Cat = 2000/1 to prevent poisoning by the acidic alcohol; [d] [Cat, **2a**] = 5.89×10^{-4} M, [KO^{t}Bu] = 4.71×10^{-3} M , [imine] = 5.89×10^{-2} M, [^{i}PrOH] = 12.4 M, 28°C

Complex **2a** allowed the efficient reduction of a broad range of other ketones, with good to high enantioselectivities (Table 1). The reduction of 2-acetonaphthone with **2a** led to 84 % conversion and 91 % ee within 3 min. 3,4-dihydronaphthalen-1-one is converted to the corresponding alcohol less efficiently than acetophenone with a relatively low but constant enantioselectivity. When benzophenone was used as the substrate, the corresponding alcohol was obtained in 88% yield within 10 minutes. In addition to the aryl ketone substrates, our iron catalyst was also very reactive in the asymmetric reduction of alkyl ketonic substrates. The reduction of the alkyl ketone substrate is much less favorable than aryl ketone analogues both kinetically and thermodynamically. When the reduction of 3-methyl-2-butaneone was carried out in the presence of **2a** and base, the ee value reached 54% with 67% maximal conversion after 1h. Of further interest is the tolerance of a variety of functional groups; for example 2-acetylpyridine was efficiently reduced to the corresponding alcohol (*R*) in 98% conversion within 6 min. However, the enantioselectivity for this substrate is relatively low. 2-acetyl furan can also be quickly reduced, albeit with a relatively low selectivity. It is noteworthy that benzaldehyde was near quantitatively converted with 6100 TON within 25 seconds with a TOF 260 s^{-1} at 40% conversion. The reaction rate stayed almost constant from the beginning of the reaction until all the substrate was converted. Reduction of *trans*-4-phenyl-3-buten-2-one initially yields the unsaturated alcohol with relatively low enantioselectivity (40% ee), using 4 minutes to reach equilibrium at a turnover number of 3300. The reduction of the C=C double bond on the initially formed unsaturated alcohol occurs later on to eventually afford the saturated alcohol. The chemoselectivity for the polar C=O versus the non-polar C=C double bonds is consistent with an outer sphere proton plus hydride transfer as shown in Fig. 3. Complex **2a** also catalyzes the transfer hydrogenation of the activated imine N-(diphenylphosphinoyl)-acetophenimine in greater than 99% ee and at rates greater than 100 times faster than previously reported iron catalysts (*17, 18*).

The proposed highly reactive catalysts **3/3'** and **4** shown in Fig. 3 were characterized for the first time by NMR and IR spectroscopy. The spectra are quite consistent with the structures predicted recently using DFT calculations where **3** was described as square pyramidal at iron(II) with a carbonyl in the apical position, and the tetradentate ligand unsymmetrical with neutral phosphorus donors, anionic nitrogen donors and different groups, one saturated $–CH_2CH_2-$ and one unsaturated –CH=CH-, linking the phosphorus with the nitrogen on each side (*9*). Complexes **3/3'** were generated as a mixture by reacting complex **2a** with 2 equiv of KO^{t}Bu in THF at room temperature, evaporating the solvent and extracting the product with C_6D_6 for NMR analysis. The $^{31}P\{^1H\}$ NMR spectrum provides evidence for two

diastereomers with the major one displaying two doublets at 75.8 and 85.3 ppm with a ^2J(P,P) coupling constant of 28 Hz and the minor one giving a very similar pattern of doublets at 77.8 and 83.4 ppm with ^2J(P,P) 31 Hz. The ^{1}H and ^{13}C NMR spectra allowed complete assignment of the hydrogen and carbon nuclei in the major diastereomer, all consistent with either of the structures **3/3'** shown in Fig. 3 as described in the supporting material. The other isomer has the carbonyl on the opposite apex of the square pyramid as shown.

The mixed isomers of **3** were highly active for the asymmetric transfer hydrogenation of acetophenone to 1-phenylethanol (*R*) in isopropanol without the addition of base. Approximately 60% of the substrate was reduced at room temperature within 10 min with an 82 % ee. No induction period was observed and the reaction profile is similar to that obtained when only 2 equiv. of base were used with complex **2a** (entry 3 of Table 1). These observations are consistent with our previous hypothesis that the neutral amido-(ene-amido) complex **3** is the real catalyst for the transfer hydrogenation of ketone substrates using bis(imine) iron(II) carbonyl complex as the catalyst precursor in basic isopropanol (*8*).

The reaction of a mixture of **3** and **3'** with isopropanol in the absence of substrate led, within one minute, to an equilibrium mixture of **3** and the hydride complex **4** (Fig. 3). Complex **4** displays a characteristic ^{1}H NMR resonance for the FeH at -2.25 ppm (dd, $^2J_{HP}$ = 70.0 and 70.8 Hz). A second hydride grows in more slowly in the absence of substrate with a resonance at -9.23 ppm (dd, $^2J_{HP}$ = 78.6 and 79.8 Hz). The ratio between the two hydride diastereomers is greater than 5:1 with the -2.25 ppm predominating. Both of the two hydride species were characterized by NMR spectroscopy including ^{1}H, ^{31}P{1H} ^{1}H-^{1}H COSY, HSQC, NOESY in C_6D_6 as described in the supporting material. The major isomer has the structure shown in Fig. 3.

The addition of acetophenone to the C_6D_6 solution of the hydride mixture immediately led to the disappearance of the hydride signals and the corresponding phosphorus resonances and the generation of free 1-phenylethanol. This is fully consistent with the mechanism shown in Fig. 3. The mixture of **3** and **4** can be generated in isopropanol by reaction of **2a** with base before the addition of substrate but this mixture must be used for catalysis with 2 min to obtain the same activity and enantioselectivity as the standard method. The stereochemical configuration of the final alcoholic product is predicted and observed to be *R* on the basis of a hydride transfer from **4** to the ketone hydrogen-bonded to the N-H with the larger group of the ketone (e.g. R is aryl or naphthyl in Fig. 3) thrown to the less bulky diamine side of the catalyst.

As in Noyori-type catalysts (*19*), the addition of excess base, at least up to 8 equivalents relative to catalyst, causes an increase in turn over frequency (compare entries 2 and 3 of Table 1). Our group had proposed that this increases the effective pH of the alcohol which protects the basic amide and hydride reactants (*12*). It might also serve to catalyze the substitution of unreactive octahedral amine complexes (*20*) by amine deprotonation (*21*).

The catalyst systems described here represent versatile, well understood and extremely active asymmetric reduction catalysts based on non precious metals. The new ligands permit the efficient, multi-component synthesis of a very wide range of highly active iron catalysts with varied structural features. In principle, the mirror image catalysts to make the (*R*) form of the alcohols or amines can also be made in the same way using the commercially available diamine (*R,R*)-dpen. Such a diversity of catalysts will be needed to

allow the discovery of the correct structure for the selective reduction of the desired substrate to ensure the highest selectivity.

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Supplementary Materials
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Supplementary Materials for

Effective Iron Catalysts for the Asymmetric Reduction of Ketones and Imines

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General Considerations. All procedures and manipulations involving air-sensitive materials were performed under an argon or nitrogen atmosphere using Schlenk techniques or a glove-box with N_2 or Argon. Solvents were degassed and dried using standard procedures prior to all manipulations and reactions. The starting phosphonium dimmers were prepared as described in our previous publications.[1] Acetophenone and liquid ketone substrates were distilled under argon and stored under molecular sieves in a glovebox prior reduction reaction, while the solid substrates were purified by sublimation. Deuterated solvents were purchased from Cambridge Isotope Laboratories, INC and distilled and dried over activated molecular sieves. All of the other reagents used in the procedures were purchased from commercial sources and utilized without further purification. NMR spectra were recorded at ambient temperature and pressure using Varian Gemini 600 MHz, 400 MHz and 300 MHz spectrometers [^{1}H (600 MHz, 400 MHz and 300 MHz), ^{13}C{^{1}H} (150 MHz, 100 MHz and 75 MHz) and ^{31}P{^{1}H} (242 MHz, 161 MHz and 121 MHz)]. The ^{31}P NMR spectra were referenced to 85% H_3PO_4 (0 ppm). Elemental analyses were performed using a Perkin-Elmer 2400 CHN elemental analyzer at the Department of Chemistry at the University of Toronto. The electrospray ionization mass spectrometry (ESI-MS) data were collected on an AB/Sciex QStar mass spectrometer with an ESI source. Single-crystal X-ray diffraction data were collected using a Nonius Kappa-CCD diffractometer with Mo Kα radiation (λ = 0.71073 Å). The structures were solved and refined using SHELXTL V6.1.

Synthesis of (*S,S*)-PAr$_2$CH$_2$CH$_2$NHCHPhCHPhNH$_2$ (PAr$_2$-N(H)-N(H$_2$)) (Ar = Ph, 1a; Ar = 3,5-Me$_2$C$_6$H$_3$, 1b). Synthesis of 1a. In an argon glovebox, $FeCl_2$ (60 mg, 0.471 mmol) was dissolved in MeOH (5 mL) with stirring for about 5 min. (S, S)-1,2-diphenylethylenediamine (dpen) (100 mg, 0.471 mmol) was dissolved in MeCN (5 mL) in another 20 mL vial. The diphenylphosphino-acetaldehyde hydrochloride dimer (162 mg, 0.306 mmol) was dissolved in MeOH (5 mL), and this solution was added to a suspension of NaOMe (33 mg, 0.612 mmol) in MeOH (3 mL) in a 20 mL flask charged with a stirring bar, and the mixture was stirred for 2 min. The dpen and $FeCl_2$ solution were added to the above colorless solution in sequence and the color of the solution instantaneously became purple. The reaction was monitored by ^{31}P {^{1}H} NMR using D_2O insert to make sure the side product resonating at δ 73.2 ppm does not appear. This side product was probably the bis(imine) P-N-N-P bis(acetonitrile) iron (II) complex according to our previous experience in synthesizing the bis(imine) iron complexes.[1] The optimal reaction time is 45 min. The solvent was evaporated from the resulting purple solution to give a dark red powder. Then $LiAlH_4$ (72 mg, 1.88 mmol) was added followed by 20 mL THF. The resulting black suspension was stirred at room temperature for 20 min in glovebox. The flask was then taken out of the glovebox and the reaction was quenched with 1 mL of degassed H_2O to give a yellow suspension, which was stirred at room temperature for 10 min. THF and the H_2O were removed under vacuum to give a gray solid, to which, in air, was added 50 mL of H_2O and the mixture was stirred for 5 min. The organic product was extracted with dichloromethane (3 × 50 mL). The dichloromethane solution was filtered through a pad of Celite. The solvent of the filtrate was removed under vacuum to obtain a white oily product. The white oily product was used for the synthesis of iron complexes without further purification. The P-N(H)-N(H_2) ligand is slightly air sensitive and ^{31}P {^{1}H} NMR analysis indicates that about 3% of the product was oxidized during the workup. However, it is sensitive to acid, base, aluminum oxide and silica gel and as a result, further purifications were not carried out. ^{1}H NMR spectroscopy indicated that the purity was about 90% with some dpen and a small portion (less than 5%) of unknown impurities. ^{31}P{^{1}H} NMR showed a major singlet around -20.9 ppm for the major product, a small singlet at around

30 ppm for the oxidized product (around 3%) and 2~3 unknown impurities of negligible quantity. Yield: 0.150 g, 75%. ^{1}H NMR (400 MHz, CD_2Cl_2) δ: 1.68 (brs, N*H* and NH_2), 2.21 (m, 2H, CH_2), 2.53 (m, 2H, CH_2), 3.68 (d, 1H, $^{3}J_{HH}$ = 7.4 Hz, NC*H*(Ph)), 3.91 (d, 1H, $^{3}J_{HH}$ = 7.4 Hz, NC*H* (Ph)), 7.14 (m, 10H, Ar*H*), 7.31(m, 10H, Ar*H*). ^{13}C{^{1}H} NMR (100 MHz; CD_2Cl_2) δ: 29.1 (d, J_{CP} = 12.4 Hz, NH*C*H$_2$), 44.3 (d, J_{CP} = 19.2 Hz, P*C*H$_2$), 61.9 (s, *C*H(Ph)), 69.5 (s, *C*H(Ph)), 126.8 (d, $^{3}J_{CP}$ = 6.9 Hz, Ar*C*(*m*)), 127.1 (s, Ar*C*), 127.9 (s, Ar*C*), 130.0 (d, $^{4}J_{CP}$ = 2.6 Hz, Ar*C*(*p*)), 128.4 (d, $^{3}J_{CP}$ = 6.4 Hz, Ar*C*(*m*)), 128.5 (d, $^{3}J_{CP}$ = 7.2 Hz, Ar*C*(*m*)), 132.5 (d, J_{CP} = 18.7 Hz, Ar*C*(*o*)), 132.7 (d, J_{CP} = 18.9 Hz, Ar*C*(*o*)), 138.9 (d, J_{CP} = 22.7 Hz, Ar*C*), 139.0 (d, J_{CP} = 22.5 Hz, Ar*C*), 141.7 (s, Ar*C*), 144.1 (s, Ar*C*). ^{31}P{^{1}H} NMR (161 MHz; CD_2Cl_2) δ: -20.9. HRMS (ESI-TOF, CH_2Cl_2) *m/z* calculated for [($C_{28}H_{29}N_2P$)+H]$^{+}$: 425.2147, found: 425.2150. FT-IR (KBr, cm^{-1}): 508m, 697s, 741s, 803m, 1027s, 1069m, 1097s, 1119m, 1179s, 1258s, 1306w, 1359m, 1376w, 1434s, 1453s, 1481s, 1493s, 1586m, 1601m, 1814w, 1887w, 1955w, 2832w, 2906w, 2969s, 3028s, 3057s, 3302s, 3351s.

Synthesis of 1b. Using the same procedure for **1a**, **1b** was synthesized in a 60 % yield. ^{1}H NMR (400 MHz, CD_2Cl_2) δ: 1.72 (brs, N*H* and NH_2), 2.22 (CH_2, overlapping with the signals of methyl groups, determined by ^{1}H-^{13}C HSQC), 2.26 (s, 6H, CH_3), 2.27 (s, 6H, CH_3), 2.56 (m, 2H, CH_2), 3.68 (d, 1H, $^{3}J_{HH}$ = 7.4 Hz, NC*H*(Ph)), 3.91 (d, 1H, $^{3}J_{HH}$ = 7.4 Hz, NC*H* (Ph)), 6.97 (m, 2H, Ar*H*), 7.04 (m, 3H, Ar*H*), 7.17 (m, 8H, Ar*H*), 7.31 (m, 3H, Ar*H*). ^{13}C{^{1}H} NMR (100 MHz; CD_2Cl_2) δ: 21.0 (s, *C*H$_3$), 29.7 (d, J_{CP} = 11.8 Hz, NH*C*H$_2$), 44.6 (d, J_{CP} = 20.0 Hz, P*C*H$_2$), 61.9 (s, *C*H(Ph)), 69.5 (s, *C*H(Ph)), 126.7 (m, Ar*C*), 127.8~128.0 (m, Ar*C*), 130.0~130.5 (m, Ar*C*), 137.7~137.8 (m, Ar*C*), 138.5~138.7 (Ar*C*(*o*)), 141.8 (s, Ar*C*), 144.1 (s, Ar*C*). ^{31}P{^{1}H} NMR (161 MHz; CD_2Cl_2) δ: -21.5. HRMS (ESI-TOF, CH_2Cl_2) *m/z* calculated for [($C_{32}H_{37}N_2P$)+H]$^{+}$: 481.2773, found: 481.2766. FT-IR (KBr, cm^{-1}): 562w, 697s, 763m, 802s, 844m, 1027s, 1094s, 1261s, 1413m, 1455m, 1492m, 1583s, 1599s, 2852s, 2912s, 2963s, 3026s, 3306m, 3374m.

Synthesis of *trans*-(*S,S*)-[Fe(CO)(Cl)(PPh$_2$CH$_2$CH=NCHPhCHPhNHCH$_2$CH$_2$PPh$_2$)]BF$_4$ (2a). In an argon glovebox, a solution of the diphenylphosphino-acetaldehyde hydrochloride dimer (94 mg, 0.177 mmol) in MeOH (5 mL) were added into a suspension of NaOMe (19 mg, 0.353 mmol) in MeOH (2 mL) in a 20 mL vial charged with a stirring bar. The solution was stirred at room temperature for 2 min. Then a solution of **1a** (150 mg, 0.353 mmol) in MeOH (3 mL) and a solution of [Fe(H_2O)$_6$][BF_4]$_2$ (149 mg, 0.442 mmol, 1.25 equivalents relative to **1**) in MeCN (5 mL) were added. The purple reaction mixture was stirred for 3 h at room temperature. The solvent was removed from the reaction mixture to give a deep purple solid. This was mixed with sodium chloride (41 mg, 0.707 mmol, 2 equivalents relative to **1**) and redissolved in acetone (25 mL) and placed under an atmosphere of carbon monoxide (1.1 atm) and stirred for 1.5 h at room temperature to give an orange solution with a white precipitate. Acetone was removed under vacuum and an addition portion of acetone (25 mL) was added to the obtained yellow solid. The solution was stirred under an atmosphere of carbon monoxide (1.1 atm) for 1 h. Acetone was removed under vacuum to afford a yellow solid. The product was extracted with dichloromethane (5 mL) and the solution was filtered with syringe filter PTFE membrane (pore size 0.45 μm), followed by filtraion through a pad of Celite. The solvent dichloromethane was removed under vacuum to obtain a brown solid to which MeOH (2 mL) was added. The resultant red brown solution was stirred at room

temperature 30 min to cause the precipitation of a yellow crystalline product, which was washed with MeOH (1 mL) and dried under reduced pressure. Yield: 125 mg, 42.1%. ^{1}H NMR (400 MHz, CD_2Cl_2) δ: 2.87 (m, 1H, NHCH_2), 2.99 (m, 2H, PCH_2), 3.47 (m, 1H, NHCH_2), 3.99 (m, 2H, PCH_2), 5.27 (m, 1H, C*H*(Ph)), 5.33 (m, 1H, C*H*(Ph)), 7.17~7.47 (m, 30H, Ar*H*), 7.84 (m, 1H, C*H*=N). ^{13}C NMR (100 MHz, CD_2Cl_2) δ: 35.5 (d, J_{CP} = 26.3 Hz, P*C*H$_2$), 45.6 (s, NH*C*H$_2$), 46.8 (d, J_{CP} = 28.6 Hz, P*C*H$_2$), 70.5 (s, *C*H(Ph)), 80.8 (s, *C*H(Ph)), 128.0 (d, J_{CP} = 9.8 Hz, Ar*C*), 128.2 (d, J_{CP} = 10.0 Hz, Ar*C*), 128.8~129.1 (m, Ar*C*), 129.4 (s, Ar*C*), 130.0~130.2 (m, Ar*C*), 130.5 (s, Ar*C*), 131.0 (s, Ar*C*), 131.1 (d, J_{CP} = 4.8 Hz, Ar*C*), 132.3~132.4 (m, Ar*C*), 132.9 (d, J_{CP} = 8.2 Hz, Ar*C*), 134.1 (d, J_{CP} = 8.1 Hz, Ar*C*), 134.3~134.5 (m, Ar*C*), 173.1 (s, *C*H=N), 212.7 (m, *C*O). ^{31}P{^{1}H} NMR (161 MHz; CD_2Cl_2) δ: 58.0, 62.6, J_{PP} = 40.2 Hz. HRMS (ESI-TOF, CH_2Cl_2) *m/z* calculated for $[C_{43}H_{40}ClFeN_2OP_2]^+$: 753.1654, found: 753.1640. FT-IR (KBr, cm^{-1}): 1976 (ν_{CO}). Anal. Calcd for $C_{43}H_{40}BClF_4FeN_2OP_2$: C, 61.42; H, 4.79; N, 3.33. Found: C, 61.50; H, 4.75; N, 3.25.

Synthesis of *trans*-(*S,S*)-[Fe(CO)(Cl)(P(*p*-MeC$_6$H$_4$)$_2$CH$_2$CH=NCHPhCHPhNHCH$_2$CH$_2$PPh$_2$)]BF$_4$ (2b). Using the same procedure of **2a**, **2b** was synthesized in a 40.5 % yield. Crystals of complex **2b** suitable for X-ray diffraction studies were grown from slow diffusion of methanol to **2b** solution in CH_2Cl_2**.** ^{1}H NMR (400 MHz, CD_2Cl_2) δ: 2.36 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 2.82 (m, 1H, NHCH_2), 2.97 (m, 2H, PCH_2), 3.42 (m, 1H, NHCH_2), 3.94 (m, 2H, PCH_2), 5.14 (m, 1H, C*H*(Ph)), 5.33 (m, 1H, C*H*(Ph)), 6.96~7.48 (m, 28H, Ar*H*), 7.75 (m, 1H, C*H*=N). ^{13}C NMR (100 MHz, CD_2Cl_2) δ: 21.2 (s, *C*H$_3$), 34.6 (d, J_{CP} = 23.7 Hz, P*C*H$_2$), 45.3 (s, NH*C*H$_2$), 46.6 (d, J_{CP} = 26.5 Hz, P*C*H$_2$), 70.5 (s, *C*H(Ph)), 80.3 (s, *C*H(Ph)), 127.9 (d, J_{CP} = 9.8 Hz, Ar*C*), 128.7~129.0 (m, Ar*C*), 129.5 (d, J_{CP} = 10.0 Hz, Ar*C*), 130.5 (s, Ar*C*), 130.9 (s, Ar*C*), 132.0 (d, J_{CP} = 9.8 Hz, Ar*C*), 132.8 (d, J_{CP} = 9.8 Hz, Ar*C*), 134.1 (d, J_{CP} = 8.4 Hz, Ar*C*), 134.2~134.4 (m, Ar*C*), 141.8 (m, Ar*C*), 172.8 (s, *C*H=N), 212.9 (m, *C*O). ^{31}P{^{1}H} NMR (161 MHz; CD_2Cl_2) δ: 58.1, 61.4, J_{PP} = 40.6 Hz. HRMS (ESI-TOF, CH_2Cl_2) *m/z* calculated for $[C_{45}H_{44}ClFeN_2OP_2]^+$: 781.1967, found: 781.1961. FT-IR (KBr, cm^{-1}): 1978 (ν_{CO}). Anal. Calcd for $C_{45}H_{44}BClF_4FeN_2OP_2$: C, 62.20; H, 5.10; N, 3.22. Found: C, 62.15; H, 5.05; N, 3.24.

Synthesis of *trans*-(*S,S*)-[Fe(CO)(Cl)(P(3,5-Me$_2$C$_6$H$_3$)$_2$CH$_2$CH=NCHPhCHPhNHCH$_2$CH$_2$P(3,5-Me$_2$CH$_3$C$_6$H$_5$)$_2$)]BF$_4$ (2c). Using the same procedure of **2a**, **2c** was synthesized in a 30 % yield. ^{1}H NMR (400 MHz, CD_2Cl_2) δ: 2.10~2.33 (m, 24H, CH_3), 2.88 (m, 1H, NHCH_2), 2.98 (m, 2H, PCH_2), 3.61 (m, 1H, NHCH_2), 3.99 (m, 2H, PCH_2), 5.17 (m, 1H, C*H*(Ph)), 5.31 (m, 1H, C*H*(Ph)), 6.00 (m, 2H, Ar*H*), 6.74 (m, 2H, Ar*H*), 6.94 (m, 4H, Ar*H*), 7.05 (m, 2H, Ar*H*), 7.08 (m, 2H, Ar*H*), 7.20 (m, 4H, Ar*H*), 7.30 (m, 6H, Ar*H*), 7.88 (m, 1H, C*H*=N). ^{13}C NMR (100 MHz, CD_2Cl_2) δ: 21.1 (s, *C*H$_3$), 21.2 (s, *C*H$_3$), 35.8 (d, J_{CP} = 26.4 Hz, P*C*H$_2$), 45.4 (s, NH*C*H$_2$), 47.2 (d, J_{CP} = 28.6 Hz, P*C*H$_2$), 70.0 (s, *C*H(Ph)), 83.2 (s, *C*H(Ph)), 129.0 (m, Ar*C*), 129.3 (s, Ar*C*), 129.6 (m, Ar*C*), 130.7 (m, Ar*C*), 131.7~131.9 (m, Ar*C*), 132.2 (s, Ar*C*), 132.7~132.8 (m, Ar*C*), 134.7 (m, Ar*C*), 137.6~137.7 (m, Ar*C*), 138.4~138.5 (m, Ar*C*), 140.0 (m, Ar*C*), 171.2 (s, *C*H=N), 212.6 (m, *C*O). HRMS (ESI-TOF) *m/z* calculated for $[C_{51}H_{56}ClFeN_2OP_2]^+$: 865.2906, found: 865.2890. ^{31}P{^{1}H} NMR (161 MHz; CD_2Cl_2) δ: 55.1, 60.5, J_{PP} = 38.7 Hz. FT-IR (KBr, cm^{-1}): 1980 (ν_{CO}).

Synthesis of Fe(CO)(PPh_2CH=$CHNCHPhCHPhNCH_2CH_2PPh_2$) (3/3'). A vial was charged with **2a** (50 mg, 0.06 mmol), KO^{t}Bu (13 mg, 0.12 mmol) and THF (15 mL) was added. The reaction mixture was allowed to stir at room temperature for 30 min to yield a dark blue solution. The solvent was removed under vacuum and the product was extracted with C_6D_6 for NMR analysis. **3**: ^{1}H NMR (400 MHz, C_6D_6) δ: 2.03 (m, 1H, PCH_2), 2.19 (m, 1H, PCH_2), 2.36 (m, 2H, NCH_2), 3.89 (dd, J_{HP} = 3.7 Hz, J_{HH} = 3.7 Hz, 1H, PC*H*), 4.22 (m, 1H, C*H*(Ph)), 4.70 (m, 1H, C*H*(Ph)), 6.67 (m, 2H, Ar*H*), 6.82 (m, 1H, Ar*H*), 6.90 (m, 4H, Ar*H*), 6.96 (m, 8H, Ar*H*), 7.18 (m, 2H, Ar*H*), 7.34 (m, 5H, Ar*H*), 7.48 (m, 2H, Ar*H*), 7.75 (ddd, J_{HH} = 3.7 Hz, $^3J_{HP}$ = 39.9 Hz, $^4J_{HP}$ = 3.1 Hz, NC*H*), 7.85 (m, 1H, Ar*H*), other peaks overlap with the solvent peak. ^{13}C NMR (100 MHz, C_6D_6) δ: 36.4 (d, J_{CP} = 25.0 Hz, P*C*H$_2$), 56.2 (d, J_{CP} = 9.3 Hz, N*C*H$_2$), 70.9 (d, J_{CP} = 55.4 Hz, P*C*H), 79.3 (s, *C*H(Ph)), 89.8 (s, *C*H(Ph)), 126.4 (s, Ar*C*), 126.9~127.0 (m, Ar*C*), 128.1 (s, Ar*C*), 128.5 (d, J_{CP} = 2.2 Hz, Ar*C*), 128.7 (s, Ar*C*), 129.1 (d, J_{CP} = 1.8 Hz, Ar*C*), 129.6 (d, J_{CP} = 1.8 Hz, Ar*C*), 132.0 (d, J_{CP} = 3.7 Hz, Ar*C*), 132.1 (d, J_{CP} = 4.9 Hz, Ar*C*), 132.5 (d, J_{CP} = 9.6 Hz, Ar*C*), 134.7 (d, J_{CP} = 34.4 Hz, Ar*C*), 135.0 (d, J_{CP} = 39.8 Hz, Ar*C*), 137.7 (s, Ar*C*), 138.3 (s, Ar*C*), 147.6 (s, Ar*C*), 167.2 (d, J_{CP} = 19.4 Hz, N*C*H), 224.0 (m, *C*O), other peaks overlap with the solvent peak. ^{31}P{^{1}H} NMR (161 MHz; C_6D_6) δ: 75.8, 85.3, J_{PP} = 27.9 Hz. FT-IR (KBr, cm^{-1}): 1524 ($\nu_{NCH=CHP}$), 1901 (ν_{CO}). **3'**: 2.33 (m, 1H, NCH_2), 2.45 (m, 2H, PCH_2), 2.59 (m, 1H, NCH_2), 3.96 (dd, J_{HP} = 4.0 Hz, J_{HH} = 3.4 Hz, 1H, PC*H*), 4.44 (m, 1H, C*H*(Ph)), 5.25 (m, 1H, C*H*(Ph)), 7.62 (ddd, $^3J_{HP}$ = 39.6 Hz, NC*H*, determined by ^{1}H-^{1}H COSY), other peaks overlap with those of the major isomer. ^{13}C NMR (100 MHz, C_6D_6) δ: 36.8 (d, J_{CP} = 22.8 Hz, P*C*H$_2$), 55.1 (d, J_{CP} = 9.7 Hz, N*C*H$_2$), 73.9 (dd, J_{CP} = 54.2 Hz, J_{CP} = 4.9 Hz, P*C*H), 81.3 (s, *C*H(Ph)), 90.6 (s, *C*H(Ph)), 164.7 (d, J_{CP} = 18.6 Hz, N*C*H), other peaks overlap with those of the major isomer. ^{31}P{^{1}H} NMR (161 MHz; C_6D_6) δ: 77.8, 83.4, J_{PP} = 31.1 Hz. FT-IR (KBr, cm^{-1}): 1930 (ν_{CO}). The ratio between the two isomers varies with time with the initially major one being converted to the other isomer. The ^{1}H and ^{31}P{^{1}H} NMR spectra of **3/3'** exhibiting the two isomers at different reaction time are shown in Figure S1 and FT-IR spectrum of **3/3'** is shown in Figure S2.

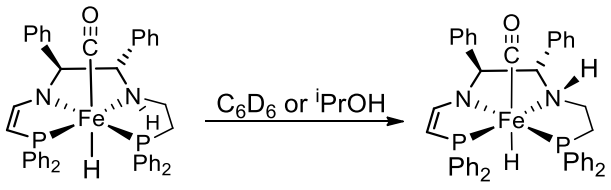
Synthesis of the major isomer of *trans*-(*S,S*)-[Fe(CO)(H)(PPh_2CH=$CHNCHPhCHPhNHCH_2CH_2PPh_2$] (4). A vial was charged with **2a** (20 mg, 0.024 mmol), KO^{t}Bu (11 mg, 0.098 mmol) and THF (5 mL) was added. Note that more than 2 equivalents of base are required; otherwise a side reaction occurs producing an unknown inactive product together with small portions of other hydride complexes. The reaction mixture was allowed to stir at room temperature for 30 min to yield a dark blue solution. The solvent was removed under vacuum to afford a dark powder. Isopropanol (1.5 mL) was added to the powder and the resultant solution was stirred vigorously at room temperature for 1 min. The color of the solution changes immediately from dark red to slightly red. The isopropanol was immediately removed under vacuum using the small port of the glovebox. The obtained red powder was dried under vacuum overnight, and later extracted with C_6D_6 for NMR analysis. The IR sample was prepared inside the glovebox using KBr. ^{1}H NMR analysis revealed a mixture containing **3** and two new hydride signals resonating at -2.25 and -9.23 ppm. Initially the hydride resonance at -2.25 ppm is the major isomer, but the signals slowly disappear and the second hydride signal increases accordingly and finally only the second hydride complex was visible. The resonances of **3** did not change with time in C_6D_6. FT-IR spectrum of this product mixture (Figure S3) also indicates the presence of **3** at 1901 cm^{-1} and new absorption peak at 1872 cm^{-1}. The peak at 1930 cm^{-1} found in Figure S2 disappears. ^{1}H NMR (600 MHz, C_6D_6) δ: -2.25 (dd, $^2J_{HP}$ = 71 and 62 Hz), 1.44 (m, NHCH_2, determined by NOESY and ^{1}H-^{1}H COSY), 2.01 (NHCH_2, overlap with other peaks and indirectly

determined by ^{1}H-^{1}H COSY and NOESY), 2.33 (m, PC*H*$_2$, determined by NOESY and ^{1}H-^{1}H COSY), 2.44 (m, PC*H*$_2$, determined by NOESY and ^{1}H-^{1}H COSY), 3.80 (dd, J_{HH} = 10.8 Hz, J_{HH} = 11.4 Hz, 1H, C*H*(Ph)NH), 4.00 (m, 1H, N*H*, determined by ^{1}H-^{1}H COSY, this signal couples to C*H*(Ph)NH at 3.80 ppm and NHC*H*$_2$ at 2.01 ppm), 4.35 (dd, J_{HP} = 2.2 Hz, J_{HH} = 4.4 Hz, 1H, PC*H*), 4.52 (d, J_{HH} = 10.8 Hz, C*H*(Ph)NCH), 7.66 (m, NC*H*, indirectly determined by ^{1}H-^{1}H COSY, this signal couples to that of the PC*H* at 4.35 ppm). ^{31}P{^{1}H} NMR (242 MHz; C_6D_6) δ: 70.4, 84.9, J_{PP} = 33.2 Hz. FT-IR (KBr, cm^{-1}): 1523 ($\nu_{NCH=CHP}$), 1872 (ν_{CO}), 3500 (ν_{NH}).

Figure S4 shows the ^{1}H NMR of **4** where the hydride signal at -2.25 ppm predominates. In the hydride region, a major doublet of doublet at -2.25 ppm was visible while a small doublet of doublet at -9.23 ppm was also seen. The region for the ligand backbone shows two major components: the major isomer of **4** and **3**. Figure S5 shows the presence of both hydride isomers together with **3** when the initially major hydride complex is converting to the other hydride isomer. Figure S6 shows the second hydride isomer of **4** as the major hydride isomer, together with the presence of **3**. The NOESY spectrum corresponding to the ^{1}H NMR spectrum in Figure S5 is shown in Figure S7. The NOESY spectrum looks messy because it contains all of the NOESY correlations that occur in the three compounds. However, careful analysis of the NOESY spectrum together with ^{1}H NMR and ^{1}H-^{1}H COSY spectra led to clear assignment of the structure of the major isomer of **4**. In Figure S7, the crossing points belonging to the first hydride isomer of **4** were marked with Arabic numerals. The corresponding NOESY correlations were drawn in Figure S8 with red arrows together with the Arabic numerals.

NOESY experiment shows a clear correlation between the signal at δ -2.25 ppm for the hydride and at δ 4.00 ppm for the N-H proton ("1" in Figure S8). Another clear interaction between N-H and the C*H*(Ph) that is close to the ene-amido group indicates that in this hydride complex both the hydride and the amine N-H groups are definitely located in the down side of the coordination plane defined by the iron, nitrogen and phosphine atoms while the CO ligand should then lie above such plane ("2" in Figure S8). In addition, one of the C-H proton of the phenyl substituent of the C*H*(Ph) group that is adjacent to the amino group gives NOE correlations to both the N-H proton and the above mentioned C*H*(Ph) group ("3" in Figure S8). This observation further confirms the "down" nature of the N-H group. The plane defined by the P(Ph$_2$)-Fe-N(H)-C(*H*$_2$) atoms is slightly tilted upward relative to the five-member coordination plane to allow for the down orientation of the N-H group. Such bending results in a clear NOESY connectivity involving protons at C*H*(Ph) (3.80 ppm) and one proton at the C*H*$_2$ group (2.01 ppm) ("4" in Figure S8).

Synthesis of the second isomer of 4.



(i) obtained from the first isomer in C_6D_6: the above C_6D_6 solution of the first hydride was kept at room temperature for 3 h and the solution was measured again. The isomerization occurs faster if there is some

isopropanol left inside the product mixture when the isopropanol solvent was not completely dried. (ii) obtained from **3** in isopropanol: A vial was charged with **2a** (20 mg, 0.024 mmol), KO^{t}Bu (11 mg, 0.098 mmol) and THF (5 mL) was added. The reaction mixture was allowed to stir at room temperature for 30 min to yield a dark blue solution. The solvent was removed under vacuum to afford a dark powder. Isopropanol (1.5 mL) was added to the powder and the resultant solution was stirred vigorously at room temperature for 5 min. The isopropanol was immediately removed under vacuum using the small port of the glovebox. The obtained product was extracted with C_6D_6 for NMR analysis. ^{1}H NMR (600 MHz, C_6D_6) δ: -9.23 (dd, $^2J_{HP}$ = 78.6 and 79.8 Hz), 2.18 and 2.24 (NHCH_2, determine by ^{1}H-^{1}H COSY, NOESY and ^{1}H-^{13}C HSQC), 2.55 and 2.70 (m, PCH_2, determine by ^{1}H-^{1}H COSY, NOESY and ^{1}H-^{13}C HSQC), 2.73 (dd, J_{HH} = 10.8 Hz, J_{HH} = 11.2 Hz, 1H, C*H*(Ph)NH), 4.37 (d, J_{HH} = 11.2 Hz, C*H*(Ph)NCH), 4.46 (dd, J_{HP} = 1.2 Hz, J_{HH} = 4.8 Hz, 1H, PC*H*), 4.81 (m, 1H, N*H*, determined by ^{1}H-^{1}H COSY, this signal couples to C*H*(Ph)NH at 2.73 ppm and NHCH_2 at 2.18 ppm, also confirmed by ^{1}H-^{13}C HSQC), 7.70 (NC*H*, indirectly determined by ^{1}H-^{1}H COSY, this signal couples to that of the PC*H* at 4.46 ppm). ^{13}C NMR (150 MHz, C_6D_6), all the chemical shifts were determined by ^{1}H-^{13}C HSQC, δ: 30.0 (NH*C*H$_2$), 44.6 (P*C*H$_2$), 73.4 (NH*C*H(Ph)), 76.7 (N*C*H(Ph)), 84.2 (P*C*H), 163.0 (N*C*H). ^{31}P{^{1}H} NMR (242 MHz; C_6D_6) δ: 71.4, 75.7, J_{PP} = 27.5 Hz. The structure of this hydride isomer was also determined by NOESY analysis. Unlike in the first hydride, a strong NOE correlation between the N-H group (4.81 ppm) and the adjacent C*H*(Ph) proton (2.73 ppm) was observed, indicating the migration of the amine proton from the down side to the upper side of the coordination plane. The weak NOE contact involving the hydride resonating at δ -9.23 ppm and the other C*H*(Ph) proton (4.37 ppm) indicates that the hydride still lies below the coordination plane.

General Procedure for the Reduction of Acetophenone and Other Ketone Substrates Using Iron-based Precatalysts 2a-2c. For comparison with our 2nd generation of iron catalysts, the reaction conditions for the asymmetric transfer hydrogenation of acetophenone and other ketone substrates catalyzed by **2a-2c** were kept the same as our previous standard conditions.[2] The final concentrations of the reagents were adjusted to be as follows [acetophenone] = 0.412 M, [**2a**], [**2b**] and [**2c**] = 6.73×10^{-5} M, [KO^{t}Bu] = 5.45×10^{-4} M and [^{i}PrOH] = 12.4 M. The quantity of the precatalyst for each single catalytic reaction was measured *via* a stock solution method. A concentrated stock solution was made by dissolving complex **2a** (17 mg, 0.0197 mmol), **2b** (17 mg, 0.0197 mmol) or **2c** (19 mg, 0.0197 mmol) in 6.08 g cold dichloromethane. After all the solids were dissolved, the solution was immediately sucked into a syringe. The solution was then divided into several equal portions in several vials such that each portion has 0.2 g of the stock solution, and then dichloromethane was evaporated to obtain a yellow solid. These operations led to a precatalyst quantity of 6.48×10^{-7} mol in each vial. The base was prepared by dissolving KO^{t}Bu (10 mg, 0.089 mmol) in ^{i}PrOH (1.02 g, 1.30 mL). These solutions were used only after all the solids were completely dissolved and for less than two days. ^{i}PrOH (6.63 g, 8.44 mL), the ketone substrate (3.95×10^{-3} mol) and a clean stirring bar were added to the vial that contains the precatalyst and the solution was stirred for several minutes until all the precatalysts were dissolved. 0.06 g of the base stock solution (5.24×10^{-6} mol of base, 8 equivalent of base) was added into a vial that contains 0.501 g of ^{i}PrOH and the mixed solution was then added into the above solution to initiate the catalytic reaction. The samples were taken by injecting small portions of the reaction mixture into septa-sealed GC vials containing aerated ^{i}PrOH for efficient quenching of the reaction. Samples were analyzed using a Perkin-Elmer Autosystem XL chromatograph with a chiral column (CP chirasil-Dex CB 25 m × 2.5 mm).

Hydrogen gas was used as a mobile phase at a column pressure of 5 psi. The injector temperature was 250 °C, and the FID temperature was 275 °C. The amount of 1-phenethanol in the sample was determined relative to the amount of the acetophenone. The retention times of acetophenone, 1-phenethanol (*R*), and 1-phenethanol (*S*) were found to be 4.83, 8.09, and 8.43 min, respectively, if the temperature of the oven was kept at 130 °C. If 2 equiv. of base were used, the mass of the base stock solution was increased to 4.08 g, while other parameters were kept the same. The retention times of other ketone substrates and the reduced products are shown in Table S1 and Scheme S1. A typical reaction profile in terms of formation of 1-phenylethanol with time and the change of ee of 1-phenylethanol with time are shown in Figure S9. The reaction profile and the change of ee with time using 2 equiv. of base are shown in Figure S10.

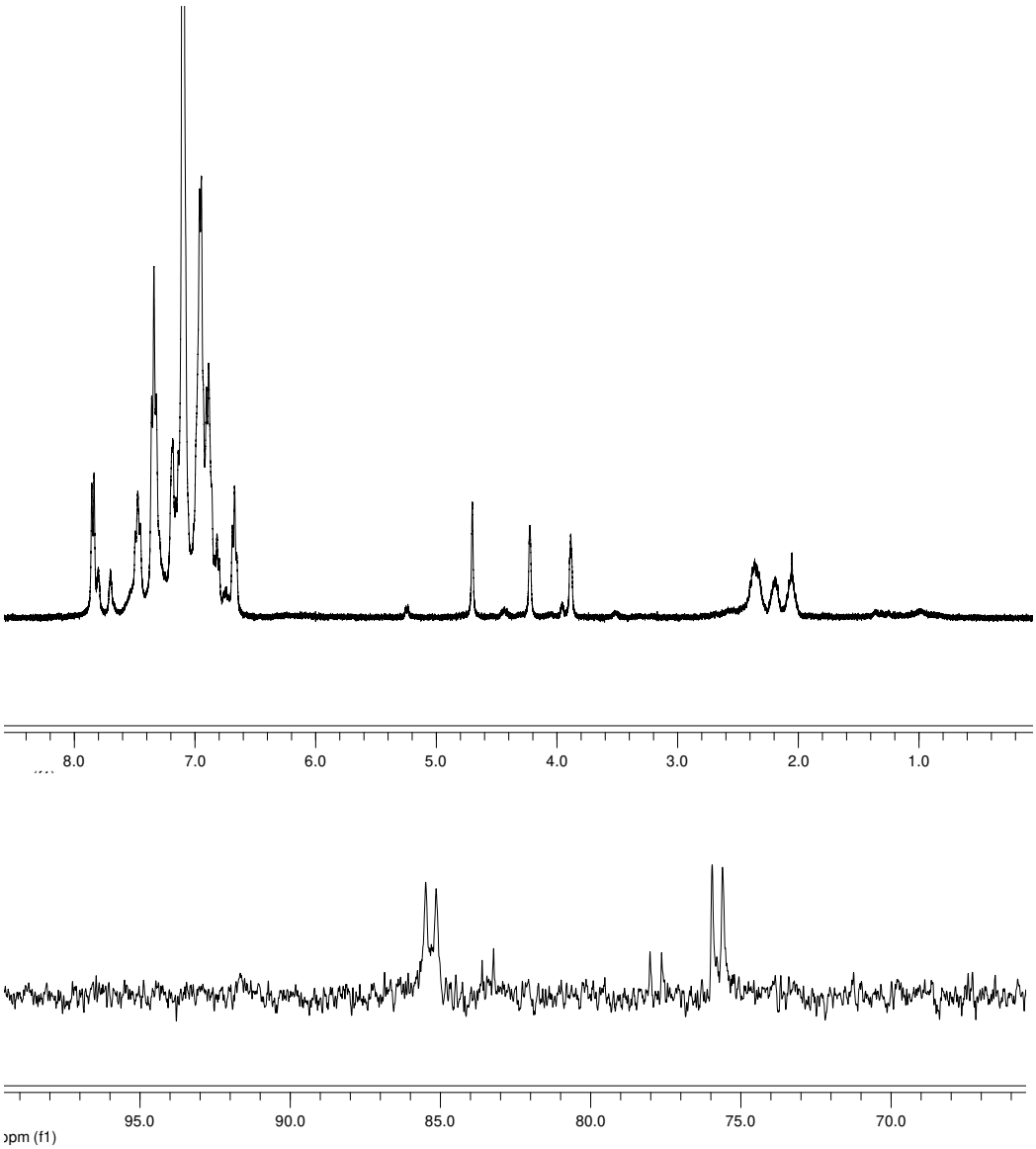
The Procedure for the Reduction of N-(diphenylphosphinoyl)-acetophenimine by Precatalysts 2a. For comparison with our 2nd generation of iron catalysts, the reaction conditions for the asymmetric transfer hydrogenation of N-(diphenylphosphinoyl)-acetophenimine catalyzed by **2a** were kept the same as our previous standard conditions.[3] The final concentrations of the reagents were adjusted to be as follows [**2a**] = 5.89×10^{-4} M, [KO^{t}Bu] = 4.71×10^{-3} M, [imine] = 5.89×10^{-2} M and [^{i}PrOH] = 12.4 M. The procedure for the catalysis was same as that of ketone reduction. The formation of the amine product was monitored by ^{31}P {^{1}H} NMR using D_2O as insert and the more accurate determination of conversion and enantiomeric excess was made by chiral HPLC (WATERS Binary HPLC Pump 1525 coupled with WATERS UV/Vis. Detector 2489) with a chiral column (CHIRALCEL OD-H column; Particle size 5 μm; Dimensions 4.6 mm × 250 mm); the data was analyzed using Waters Empower Pro. The analysis condition: 2-propanol:hexanes = 10:90, flow rate = 0.5 mL/min, $\lambda_{detector}$ = 254 nm. Retention time: product major isomer (*R*) = 14.2 min, product minor isomer = 18.4 min, starting material = 16.6 min.

The Asymmetric Transfer Hydrogenation of Acetophenone Catalyzed by 3/3' in the Absence of Base. A vial was charged with **2a** (50 mg, 0.06 mmol), KO^{t}Bu (13 mg, 0.12 mmol) and THF (18.35 g, 20.60 mL) was added. The reaction mixture was allowed to stir at room temperature for 30 min to yield a dark blue solution. 0.2 g solution was transferred into another clean vial and the solvent of this second solution was removed under vacuum to obtain a black powder. An acetophenone (0.48 g, 3.95×10^{-3} mol) solution in ^{i}PrOH (7.191 g, 9.15 mL) was added into the above black powder to initiate the catalytic reaction. The reaction profile and the change of ee with time are shown in Figure S11.

The Asymmetric Transfer Hydrogenation of Acetophenone Catalyzed by 2a *via* Initial Pretreating 2a with Base Followed by Addition of Acetophenone. To a stirred solution of **2a** (6.48×10^{-7} mol, prepared by stock solution method) in ^{i}PrOH (6.13 g, 7.80 mL) was added a base solution (1.30×10^{-6} mol, 2 equivalent, prepared by stock solution method) in ^{i}PrOH (0.561g). The mixture was stirred for 2 min followed by addition of an acetophenone (0.48 g, 3.95×10^{-3} mol) solution in ^{i}PrOH (0.50 g) to initiate the catalysis. The experimental results indicated that, within experimental error, exactly same catalytic activity and enantioselectivity were observed by this procedure and by the above standard procedure. This non-changing catalytic performance indicates that the catalytically reactive species that was generated by activating the precatalyst with base can survive in isopropanol within 2 min in the absence of ketone substrate without any deactivation or side reactions. This means that the above isolated and characterized

reactive intermediate (**4**) that was generated by reacting complex **2a** with base in isopropanol at room temperature within 1min are the real intermediates that work in the catalysis.

(a)



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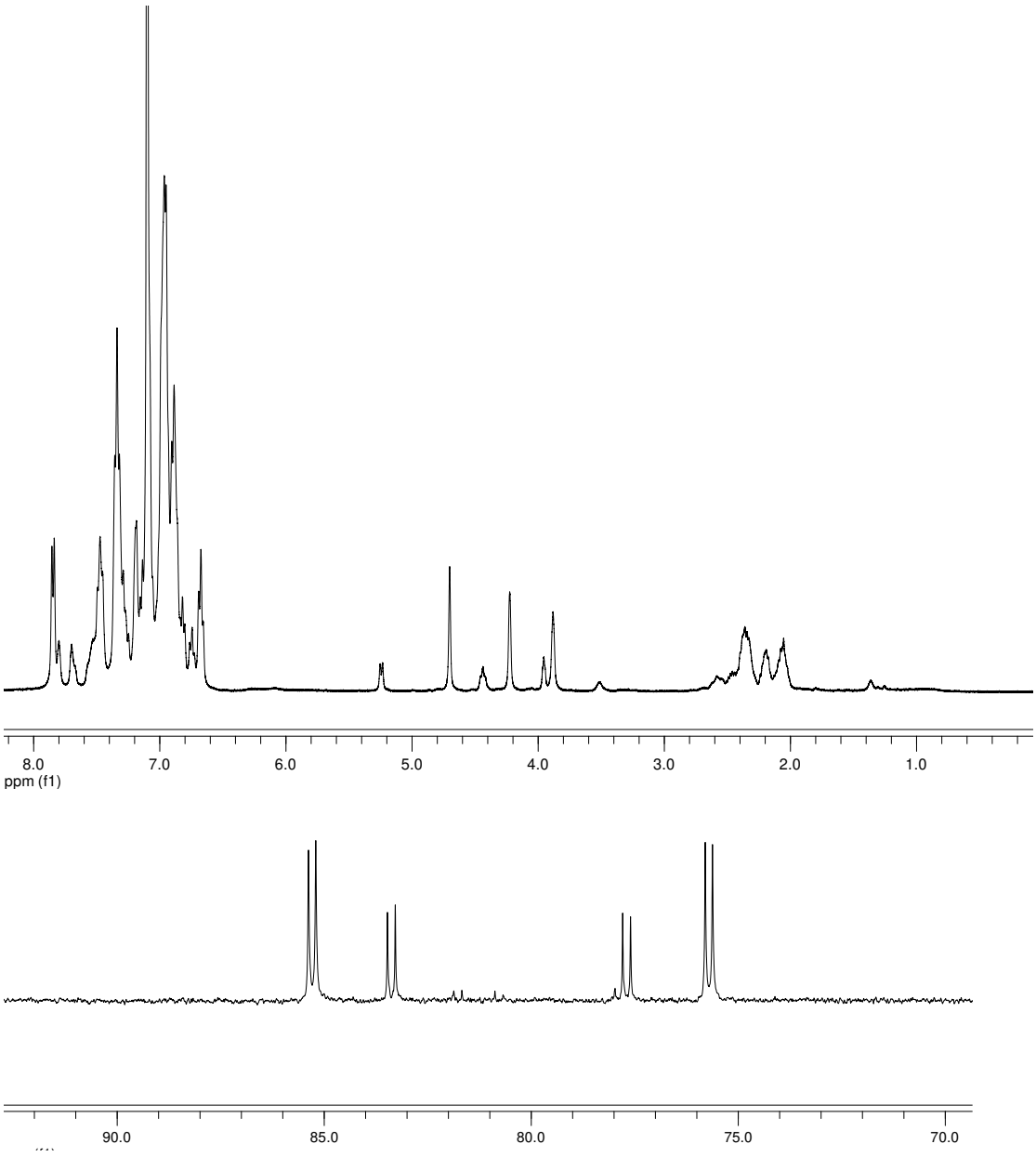

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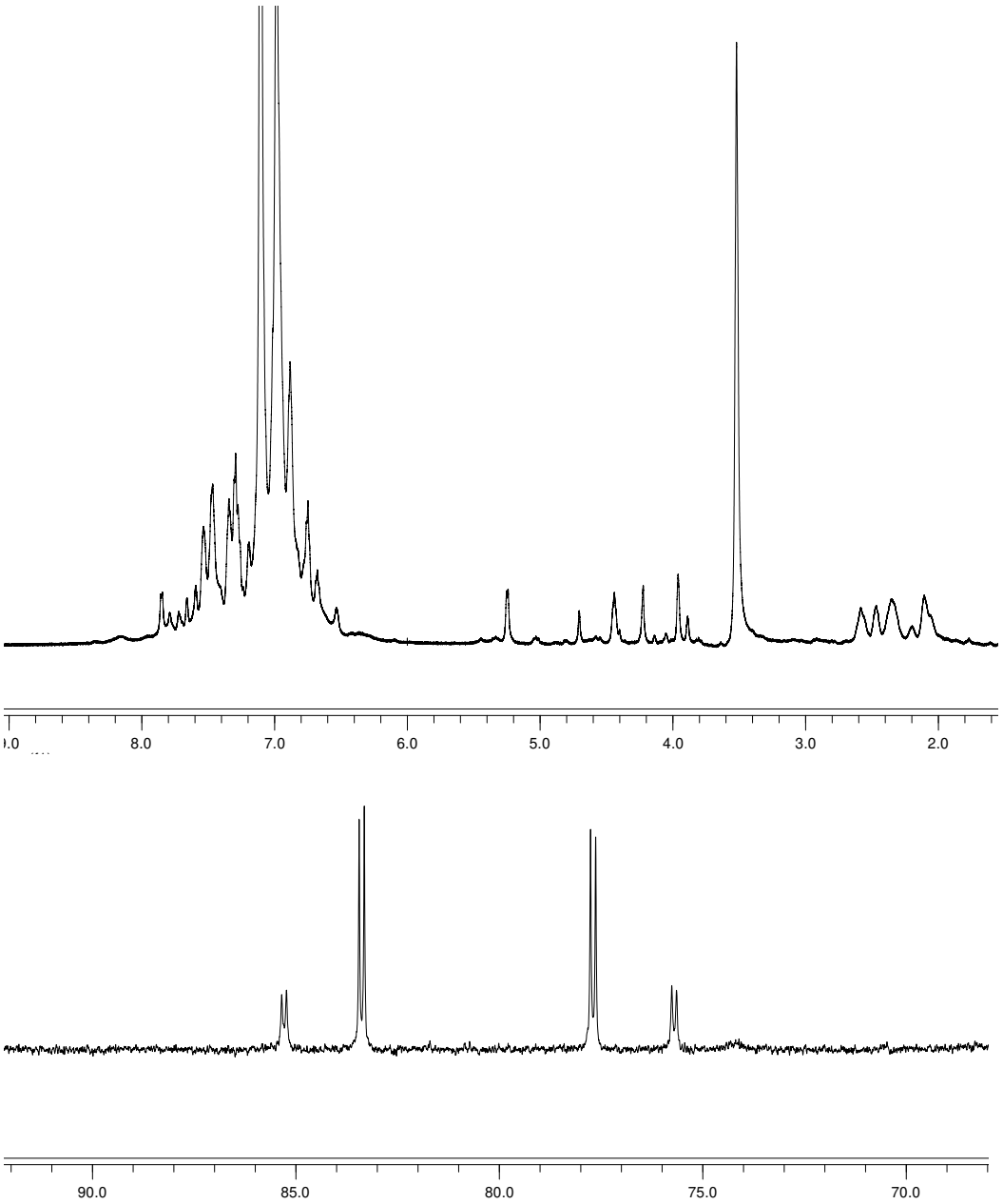

Figure S1. The ^{1}H and ^{31}P $\{^{1}H\}$ NMR spectra of **3/3'.** (a) at 30 min of reaction time; (b) at 60 min of reaction time; (c) at 2 h of reaction time. The peaks at δ 3.57 and 1.40 ppm in ^{1}H NMR are the signals of incompletely removed THF.

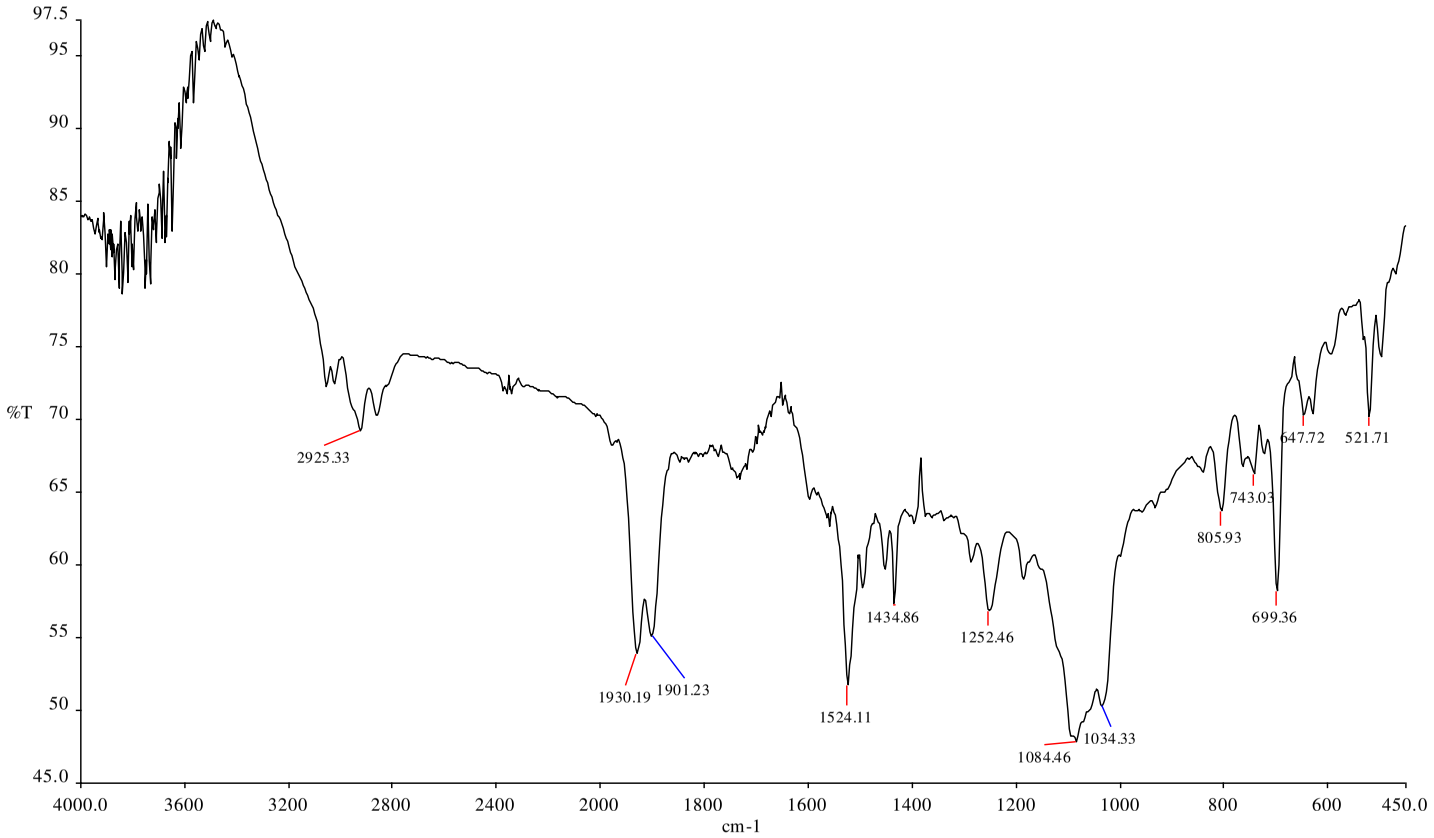
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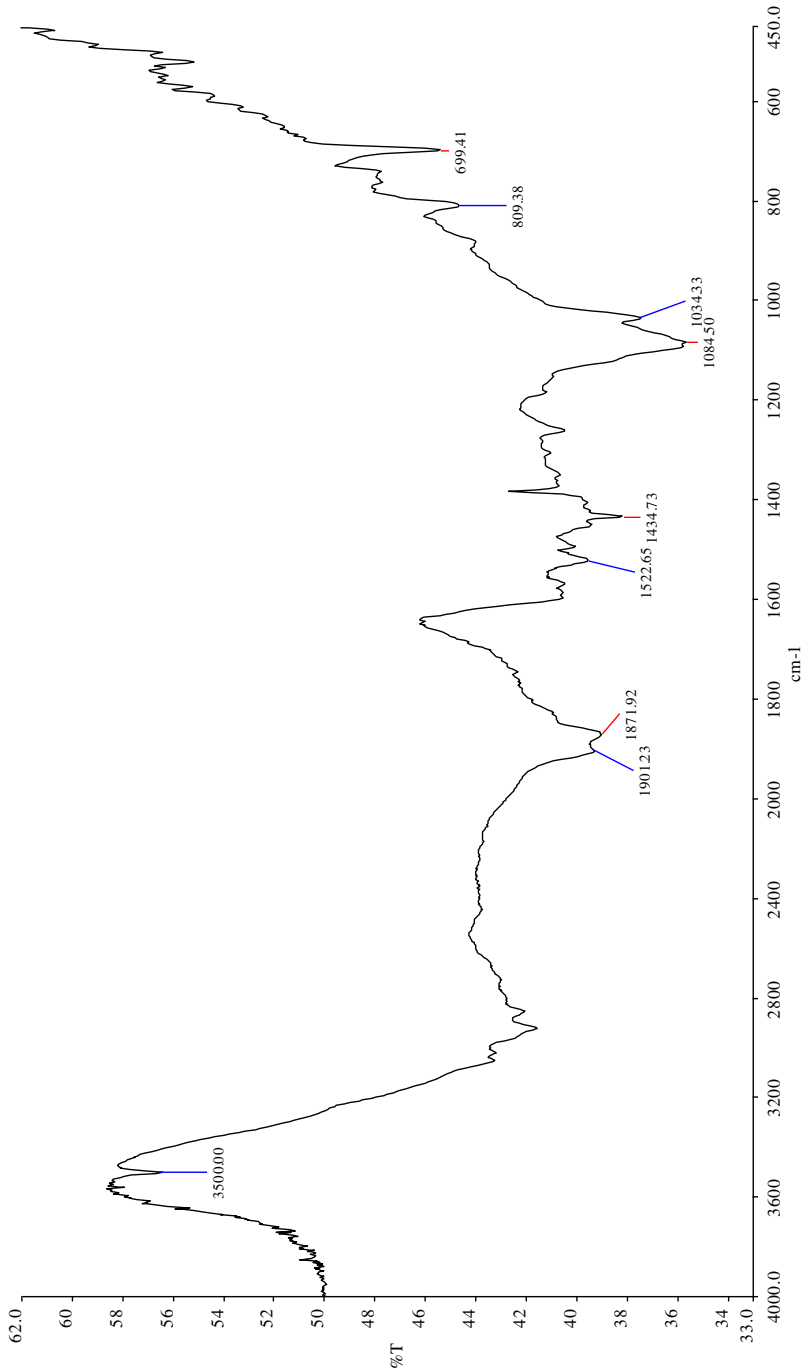
Figure S2. The FT-IR spectrum of **3/3'.** The peak at 1901 cm^{-1} was assigned to **3** and the other peak at 1930 cm^{-1} was supposed to be **3'**, based on the observation that when reacting with isopropanol **3'** disappears to form **4** and **3** is left.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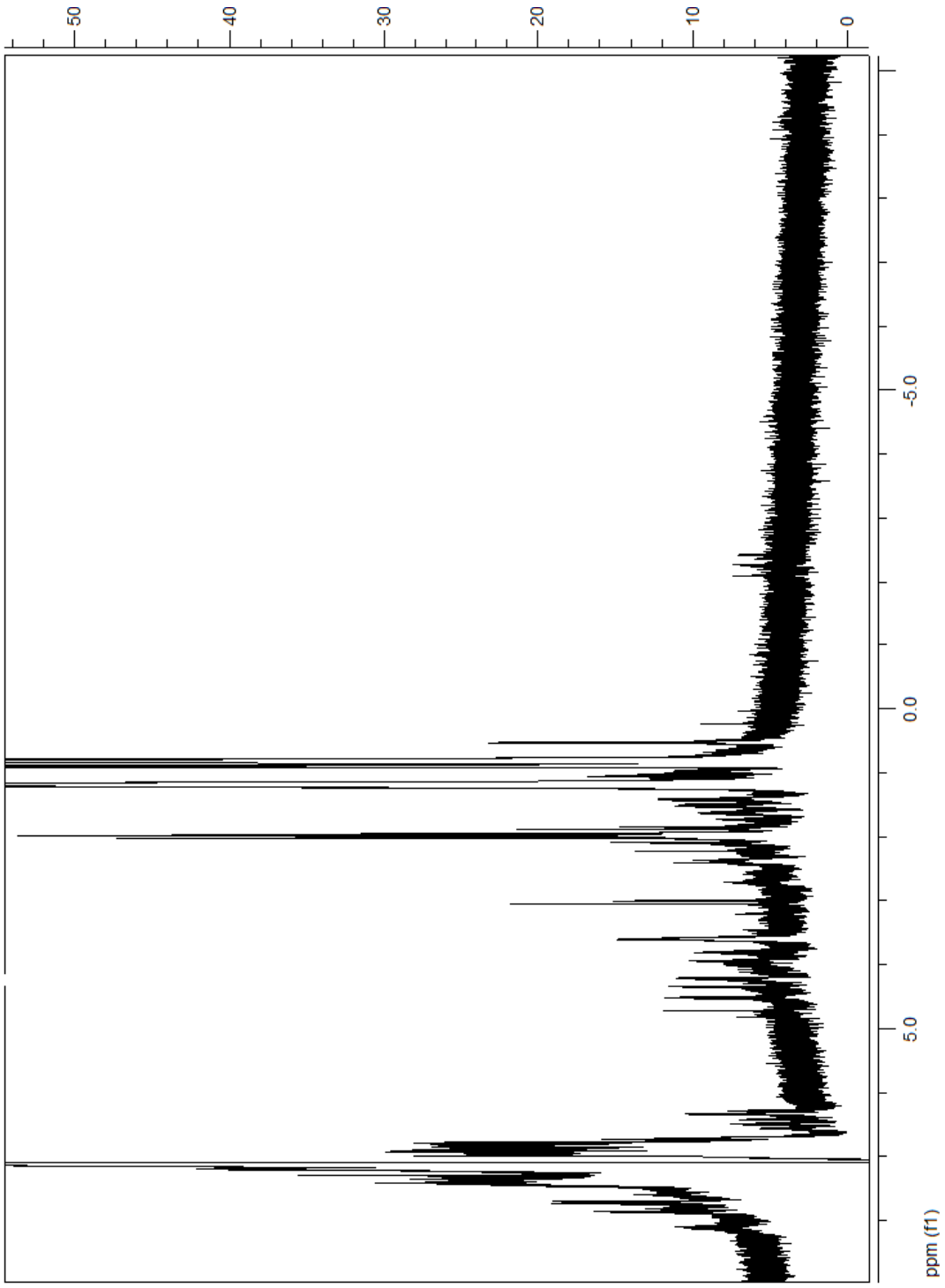
809.38
699.41

Figure S3. The FT-IR spectrum of the equilibrium mixture of the reaction between **3/3'** and isopropanol. The peak at 1901 cm^{-1} was from **3** and the new absorption at 1872 cm^{-1} was supposed to be from the hydride complexes.



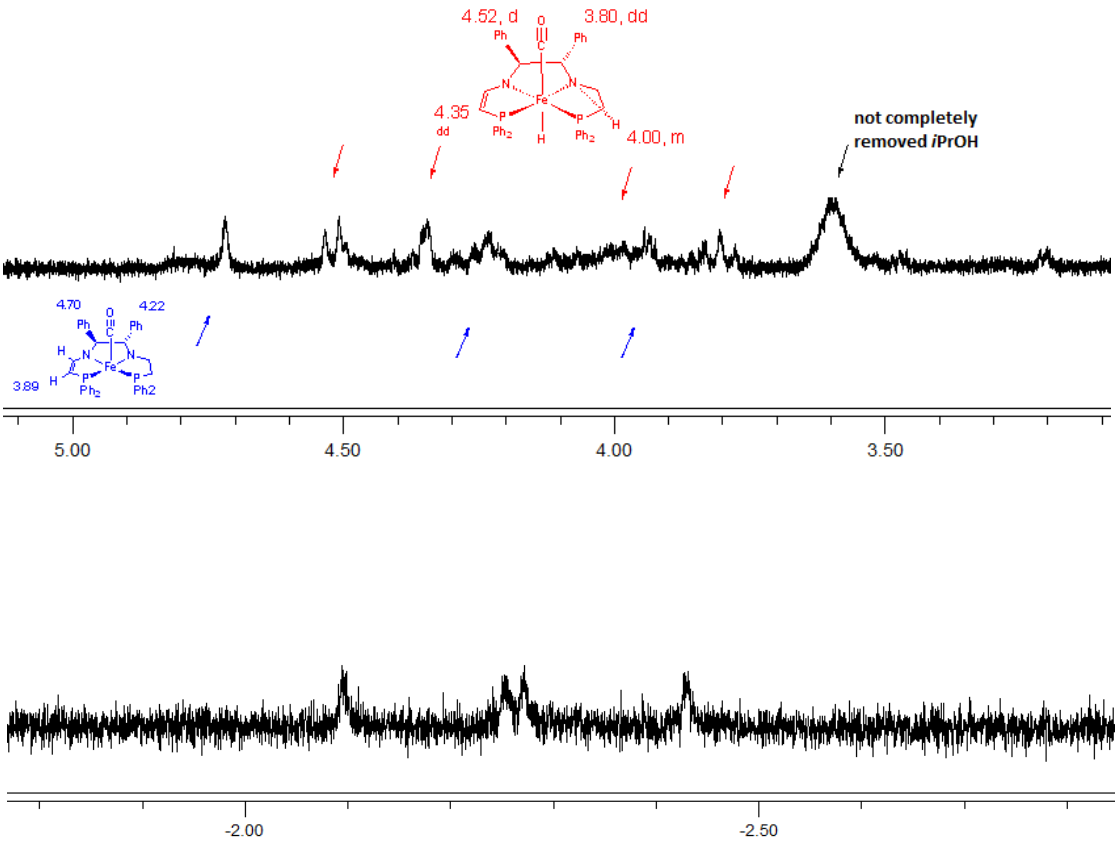
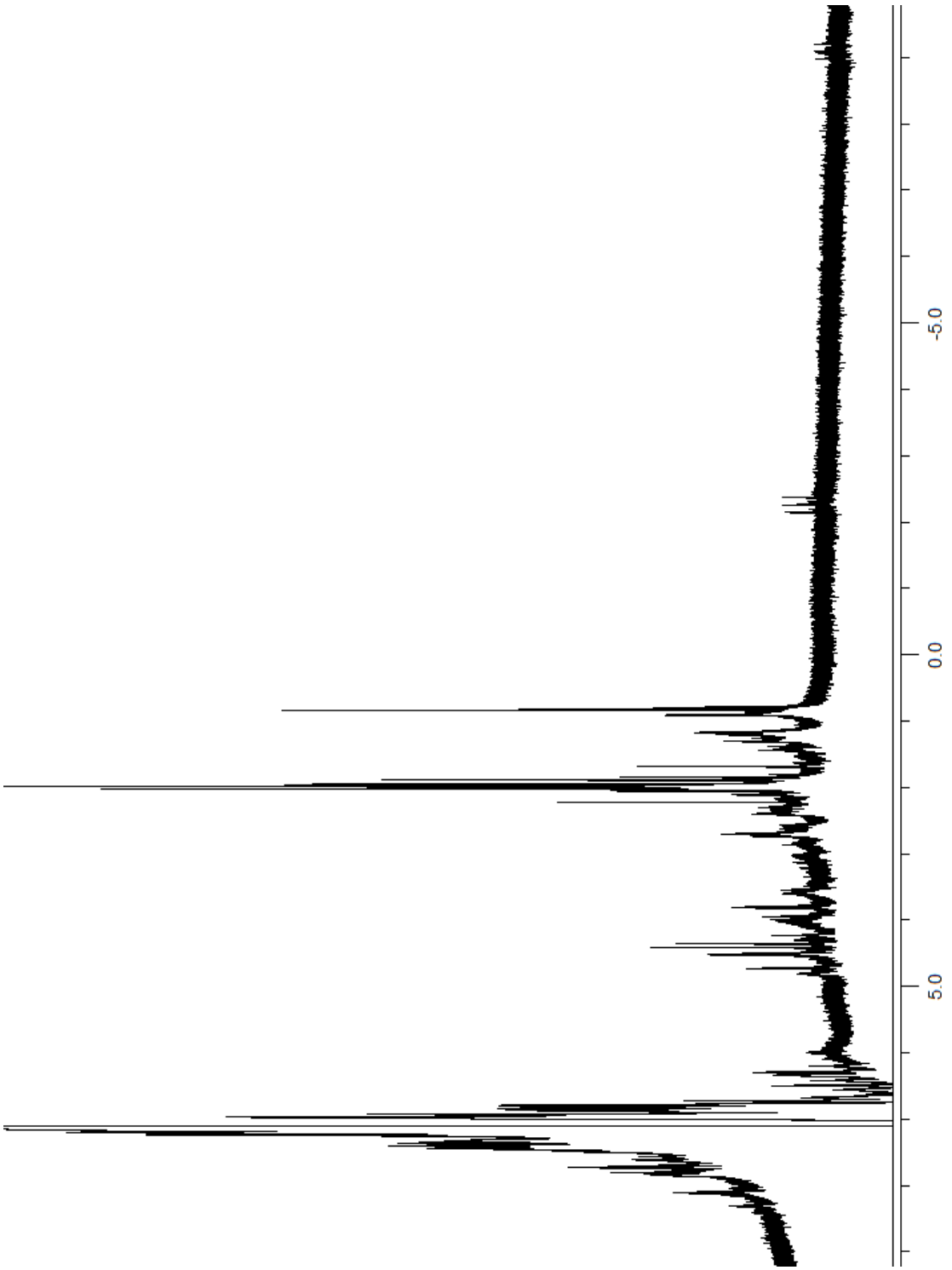


Figure S4. The ^{1}H NMR spectrum of the mixture of **3** and the first hydride of **4**: top, the full spectrum; middle, the ligand backbone region; bottom, the hydride region.


-5.0
0.0
5.0

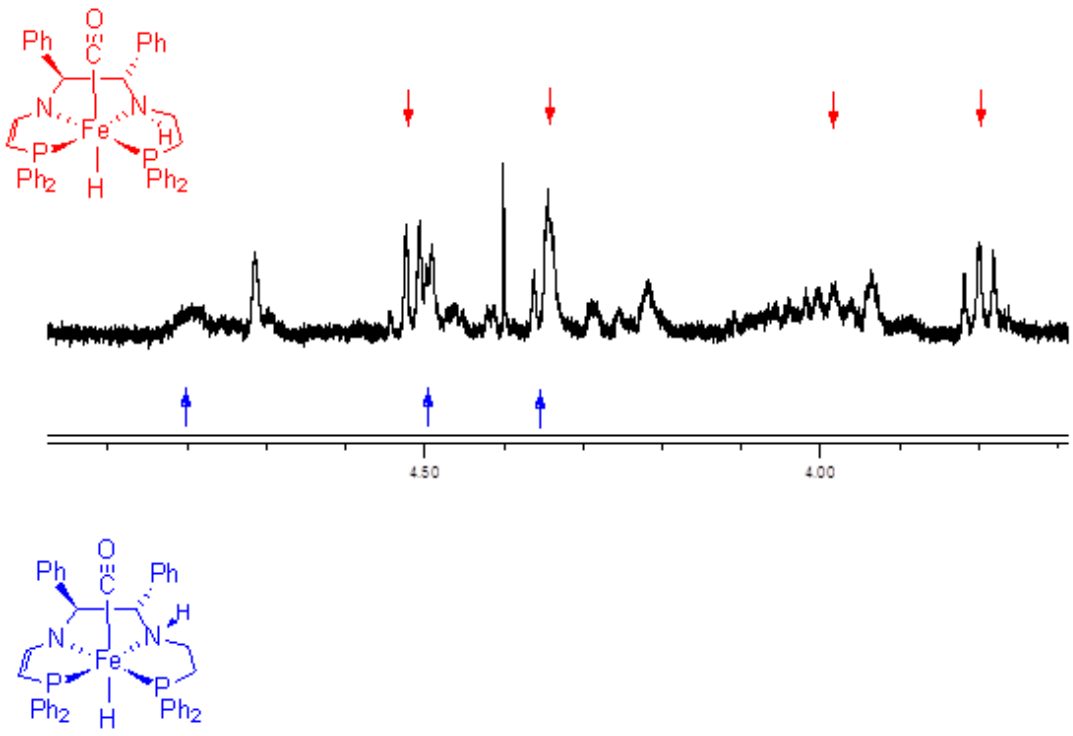


Figure S5. The ^{1}H NMR spectrum of the mixture of **3** and the two hydride complexes of **4** where the first hydride complex is still the major isomer. The three big peaks at δ 4.72, 4.22 and 3.90 ppm are from **3**.

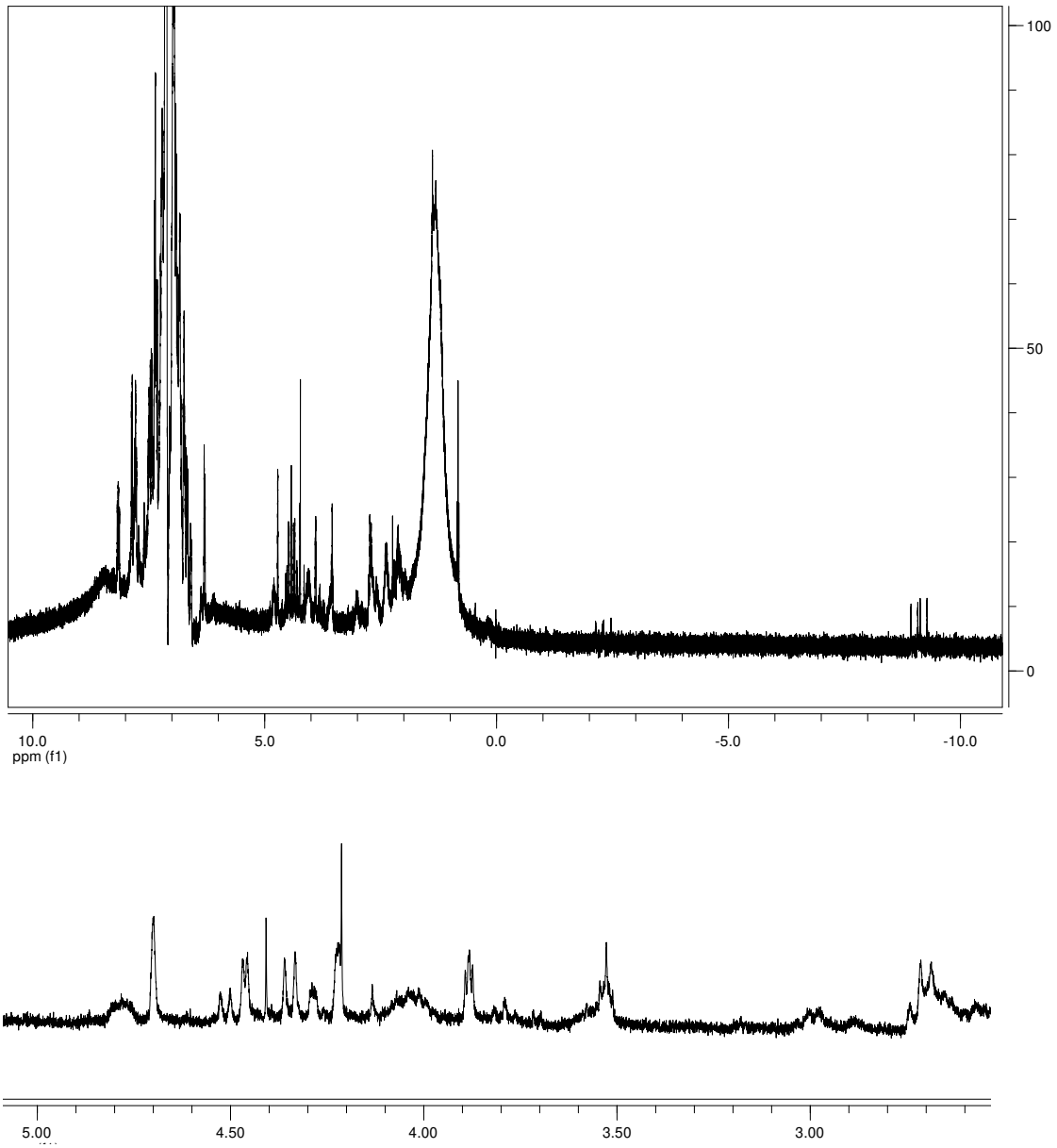


Figure S6. The ^{1}H NMR spectrum of the mixture of **3** and the two hydride complexes of **4** where the second hydride complex is the major isomer. The three big peaks at δ 4.72, 4.22 and 3.90 ppm are from **3**.

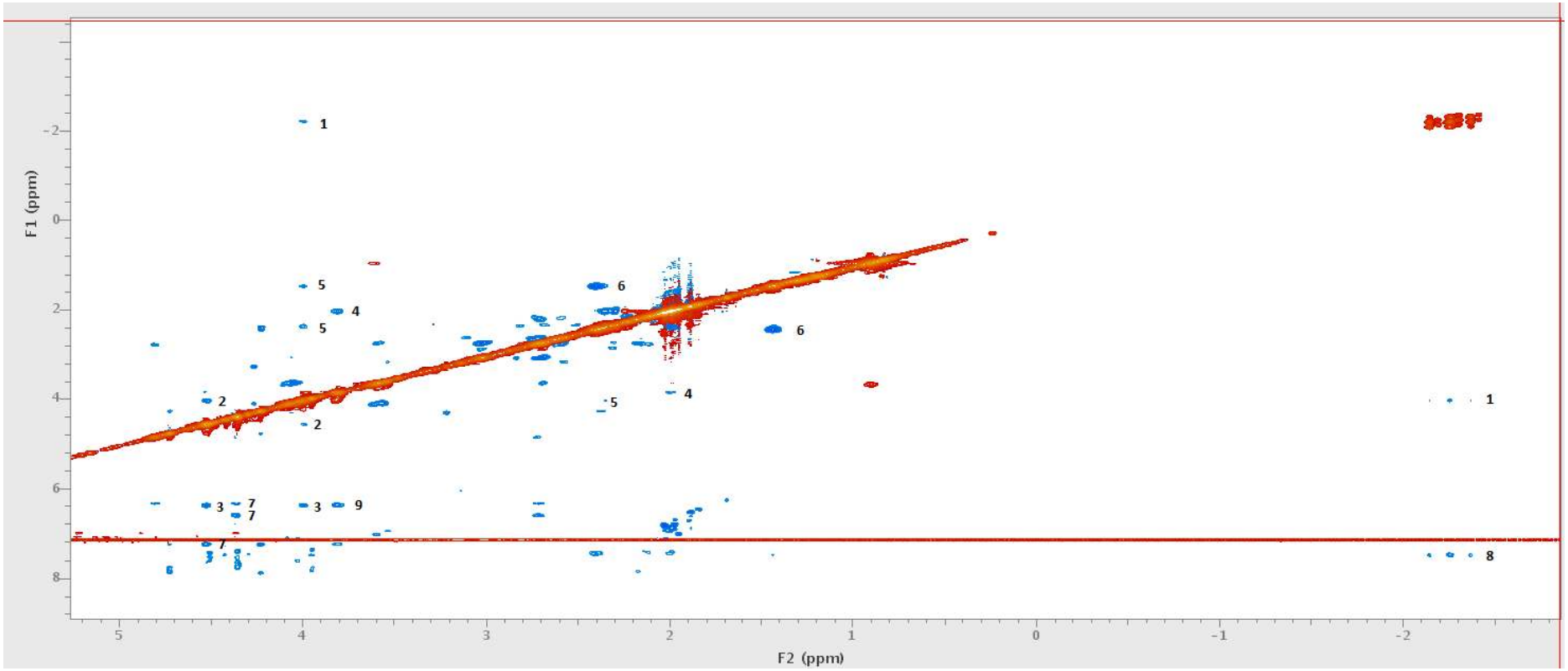

F1 (ppm)
F2 (ppm)
-2
0
2
4
6
8
5
4
3
2
1
0
-1
-2
1
5
4
5
6
6
2
2
5
4
1
3
7
3
9
7
7
8

Figure S7. The NOESY spectrum of the equilibrium mixture containing **3** and the two hydride products with the first hydride complex predominating. Besides those shown in Figure S8, there are also NOE corrections between the H at 4.35 ppm and two phenyl C-H protons resonating at 6.30 and 6.58 ppm (7). Another NOE interaction between the hydride and a nearby phenyl C-H proton was also observed (8).

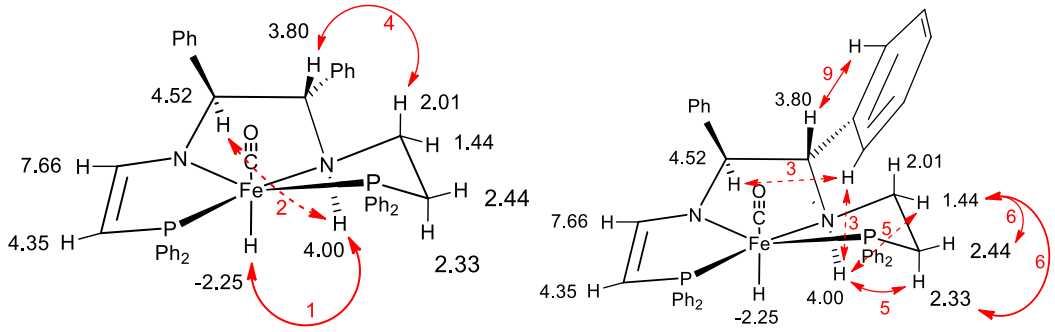


Figure S8. The NOESY correlations found in the first isomer of **4.**

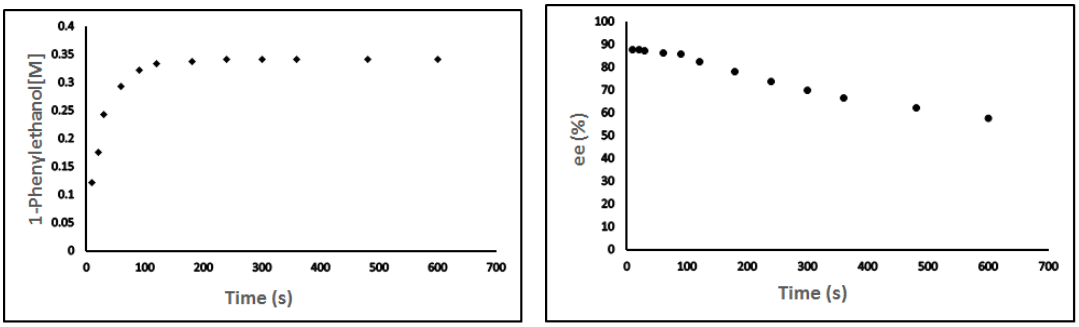


Figure S9. Reaction profiles (left) and ee (right) of catalytic reduction of acetophenone using complexes **2a**. Reaction conditions: [**2a**] = 6.73 × 10^{-5} M, [KO^{t}Bu] = 5.45 × 10^{-4} M, [substrate] = 0.412 M, [^{i}PrOH] = 12.4 M, 28°C.

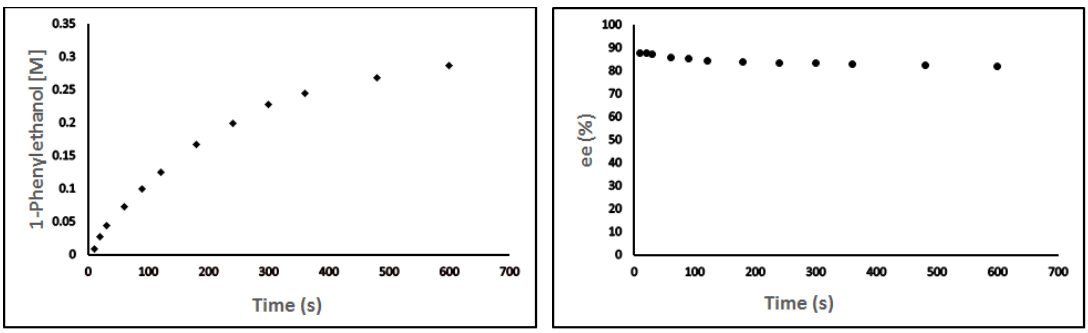


Figure S10. Reaction profiles (left) and ee (right) of catalytic reduction of acetophenone using complexes **2b** with 2 equiv. of base. Reaction conditions: [**2b**] = 6.73×10^{-5} M, [KO^{t}Bu] = 1.35×10^{-4} M , [substrate] = 0.412 M, [^{i}PrOH] = 12.4 M, 28°C.

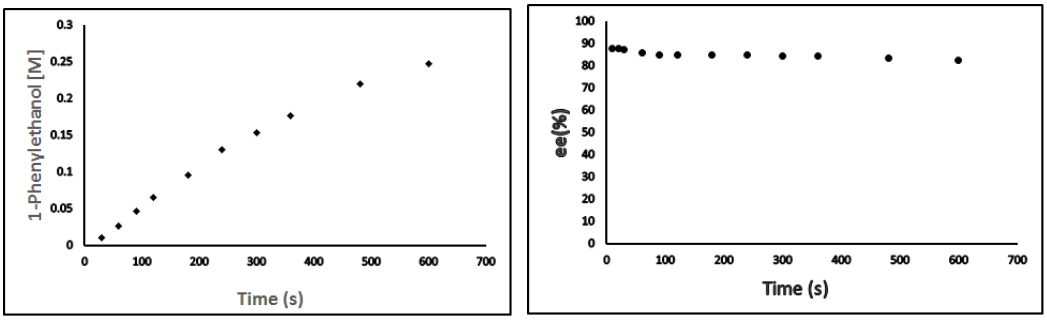


Figure S11. Reaction profiles (left) and ee (right) of catalytic reduction of acetophenone using complexes **3/3'** in the absence of base. Reaction conditions: [**3/3'**] = 6.73×10^{-5} M, [substrate] = 0.412 M, [^{i}PrOH] = 12.4 M, 28°C.

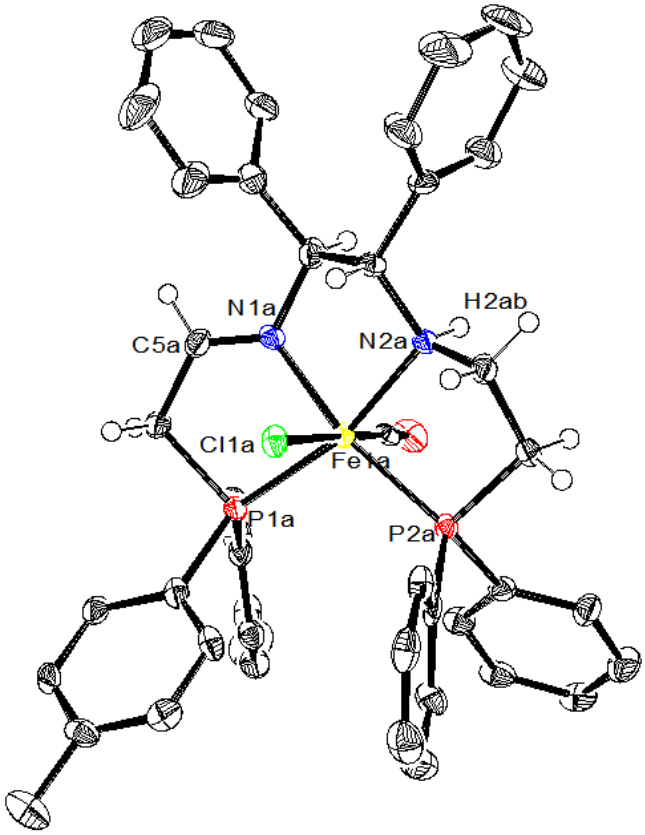
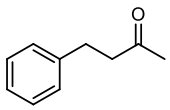
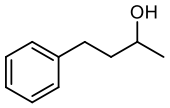
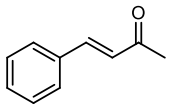
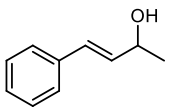


Figure S12. Solid-state molecular structure for **2b** with thermal ellipsoids at 50% probability level. The hydrogens, a BF_4 cation and two methanol molecules were omitted for clarity.

structure				
retention time (min)	12.44	20.51	23.82	30.58

Scheme S1. The retention times of *trans*-4-phenyl-3-buten-2-one and the corresponding alcohol products. The oven temperature was 125 ºC.

Table S1. The oven temperature and retention times of ketone substrates and alcohol products

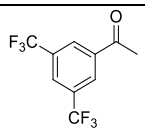
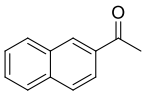
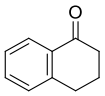
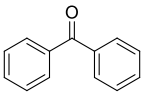
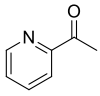
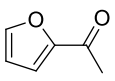
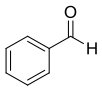
Substrate	Oven temp (ºC)	Retention time of the substrate (min)	Retention time t_R (min)	Retention time t_S (min)
	140	3.77	14.04	13.01
	150	23.1	38.3	40.1
	170	9.23	14.07	13.75
	180	7.94		12.50
	60	3.80	10.37	9.80
	110	6.58	14.69	14.64
	90	6.90	15.41	15.88
	130	3.53		7.31

Table S2. Crystal data and structure refinement for **2b**.

Compound reference	**2b**
Chemical formula	$C_{45}H_{44}ClFeN_2OP_2 \bullet BF_4 \bullet 2(CH_4O)$
Formula Mass	932.96
Crystal system	Triclinic
a/Å	10.7528(7)
b/Å	13.3474(8)
c/Å	16.498(1)
α/°	102.722(2)
β/°	90.685(1)
γ/°	93.474(2)
Unit cell volume/ Å^3	2304.7(2)
Temperature/K	147(2)
Space group	*P*1
No. of formula units per unit cell, *Z*	2
No. of reflections measured	48676
No. of independent reflections	14941
R_{int}	0.0410
Final R_1 values ($I > 2\sigma(I)$)	0.0584
Final $wR(F^2)$ values ($I > 2\sigma(I)$)	0.1280
Final R_1 values (all data)	0.0836
Final $wR(F^2)$ values (all data)	0.1396

References:

1. A. A. Mikhailine, E. Kim, C. Dingels, A. J. Lough, R. H. Morris, Template Syntheses of Iron(II) Complexes Containing Chiral P-N-N-P and P-N-N Ligands. *Inorg. Chem.* **47**, 6587 (2008). doi: 10.1021/ic800884c
2. A. A. Mikhailine, M. I. Maishan, A. J. Lough, R. H. Morris, The Mechanism of Efficient Asymmetric Transfer Hydrogenation of Acetophenone Using an Iron(II) Complex Containing an (S,S)-$Ph_2PCH_2CH{=}NCHPhCHPhN{=}CHCH_2PPh_2$ Ligand: Partial Ligand Reduction Is the Key. *J. Am. Chem. Soc*. **134**, 12266 (2012). doi: 10.1021/ja304814s
3. A. A. Mikhailine, M. I. Maishan, R. H. Morris, Asymmetric Transfer Hydrogenation of Ketimines Using Well-Defined Iron(II)-Based Precatalysts Containing a PNNP Ligand. *Org. Lett.* **14**, 4638 (2012). doi: 10.1021/ol302079q