Amine(imine)diphosphine Iron Catalysts for Asymmetric Transfer Hydrogenation of Ketones and Imines

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8. H. U. Blaser, H.-J. Federsel, Eds., *Asymmetric Catalysis on Industrial Scale: Challenges, Approaches and Solutions* (Wiley-VCH, Weinheim, Germany, ed. 2, 2010).
9. C. S. Shultz, S. W. Krska, *Acc. Chem. Res.* **40**, 1320–1326 (2007).
10. N. B. Johnson, I. C. Lennon, P. H. Moran, J. A. Ramsden, *Acc. Chem. Res.* **40**, 1291–1299 (2007).
11. A. M. Rouhi, *Chem. Eng. News* **82**, 47 (2004).
12. J. A. DiMasi, C. Paquette, *Pharmacoeconomics* **22**, (Suppl 2), 1–14 (2004).
13. A. M. Thayer, *Chem. Eng. News* **85**, 11 (2007).
14. W. S. Knowles, M. J. Sabacky, *J. Chem. Soc. Chem. Commun.* 1445 (1968).
15. L. Horner, H. Siegel, H. Büthe, *Angew. Chem. Int. Ed. Engl.* **7**, 942 (1968).
16. R. R. Schrock, J. A. Osborn, *J. Am. Chem. Soc.* **93**, 2397 (1971).
17. J. Halpern, *Science* **217**, 401–407 (1982).
18. M. T. Ashby, J. Halpern, *J. Am. Chem. Soc.* **113**, 589–594 (1991).
19. S. Bell *et al*., *Science* **311**, 642–644 (2006).
20. J. Mazuela, P. O. Norrby, P. G. Andersson, O. Pàmies, M. Diéguez, *J. Am. Chem. Soc.* **133**, 13634–13645 (2011).
21. M. C. Perry *et al*., *J. Am. Chem. Soc.* **125**, 113–123 (2003).
22. B. Plietker, Ed., *Iron Catalysis in Organic Chemistry: Reactions and Applications* (Wiley-VCH, Weinheim, Germany, 2008).
23. U. Leutenegger, A. Madin, A. Pfaltz, *Angew. Chem. Int. Ed. Engl.* **28**, 60–61 (1989).
24. L. O. Nindakova, F. M. Lebed, Z. Y. Zamazei, B. A. Shainyan, *Russ. J. Org. Chem.* **43**, 1322–1329 (2007).
25. L. O. Nindakova, B. A. Shainyan, *Russ. Chem. Bull. Int. Ed.* **54**, 348–353 (2005).
26. Y. Ogho, S. Takeuchi, Y. Natori, J. Yoshimura, *Bull. Chem. Soc. Jpn.* **54**, 2124 (1981).
27. A. Corma, M. Iglesias, C. del Pino, F. Sánchez, *J. Organomet. Chem.* **431**, 233–246 (1992).
28. Q. Knijnenburg *et al*., *J. Mol. Catal. A.* **232**, 151–159 (2005).
29. G. Zhang, B. L. Scott, S. K. Hanson, *Angew. Chem. Int. Ed.* **51**, 12102–12106 (2012).
30. G. Zhang, K. V. Vasudevan, B. L. Scott, S. K. Hanson, *J. Am. Chem. Soc.* **135**, 8668–8681 (2013).
31. S. Monfette, Z. R. Turner, S. P. Semproni, P. J. Chirik, *J. Am. Chem. Soc.* **134**, 4561–4564 (2012).
32. D. Zhu, F. F. B. J. Janssen, P. H. M. Budzelaar, *Organometallics* **29**, 1897–1908 (2010).
33. M. J. Burk, J. E. Feaster, W. A. Nugent, R. L. Harlow, *J. Am. Chem. Soc.* **115**, 10125–10138 (1993).
34. S. J. Roseblade, A. Pfaltz, *Acc. Chem. Res.* **40**, 1402–1411 (2007).
35. P. G. Cozzi, N. Zimmermann, R. Hilgraf, S. Schaffner, A. Pfaltz, *Adv. Synth. Catal.* **343**, 450–454 (2001).
36. X. Cui, K. Burgess, *Chem. Rev.* **105**, 3272–3296 (2005).
37. T. L. Church, P. G. Andersson, *Coord. Chem. Rev.* **252**, 513–531 (2008).
38. The last number in the name indicates the enantiomer of the ligand. SL-A109-1 corresponds to the (*R*) enantiomer, whereas SL-A109-2 is the (*S*) antipode.
39. S. Gischig, T. M. Schmid, G.Consiglio, http://webcsd.ccdc.cam.ac.uk/display_csd_search_results.php?xml_temp_file=/temp/text_numeric_query_04163190013723027145 1cbad7a67a84.xml&identifier=NALPIA.
40. Similarly, performing the hydrogenation of *trans*-methylstilbene with 5 mol % each of SL-A109-2 and $(py)_2Co(CH_2SiMe_3)_2$ without removal of the volatiles, and hence in the presence of two equivalents of pyridine, lowered the conversion and enantioselectivity to 50 and 51%, respectively, indicating that incomplete removal of the volatile byproducts in catalyst generation could also be deleterious to overall performance.

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Supplementary Materials

www.sciencemag.org/content/342/6162/1076/suppl/DC1
Materials and Methods
Figs. S1 to S27
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Amine(imine)diphosphine Iron Catalysts for Asymmetric Transfer Hydrogenation of Ketones and Imines

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A rational approach is needed to design hydrogenation catalysts that make use of Earth-abundant elements to replace the rare elements such as ruthenium, rhodium, and palladium that are traditionally used. Here, we validate a prior mechanistic hypothesis that partially saturated amine(imine)diphosphine ligands (P-NH-N-P) activate iron to catalyze the asymmetric reduction of the polar bonds of ketones and imines to valuable enantiopure alcohols and amines, with isopropanol as the hydrogen donor, at turnover frequencies as high as 200 per second at 28°C. We present a direct synthetic approach to enantiopure ligands of this type that takes advantage of the iron(II) ion as a template. The catalytic mechanism is elucidated by the spectroscopic detection of iron hydride and amide intermediates.

Metal-based homogeneous catalysts are used in the pharmaceutical, fragrance, flavoring, and fine chemicals industries for the synthesis of enantiomerically pure organic molecules such as alcohols, amines, and amino acids (*1*). Rare and expensive late transition metals such as ruthenium and rhodium have typically been used in this context (*2*–*4*). Iron is an element essential to life and is abundant in mineral ores, in contrast to these precious metals, and thus its use is preferable for economic and health reasons. Recent research has shown that suitably designed ligands can activate iron complexes so that their catalytic turnover frequency 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 amines.

Our previous synthetic and mechanistic studies of the iron(II)-based transfer hydrogenation precatalyst (*S*,*S*)-[$Fe(CO)(Br)(PAr_2CH_2CH{=}NCHPhCHPhN{=}CHCH_2PAr_2)$]$BPh_4$ **C** (Fig. 1) suggested that one imine linkage of the bis(imine)diphosphine ligand (P-N-N-P) of **C** was reduced by hydride addition from isopropoxide in a slow activation step (Fig. 1, reaction 3) to produce complexes within the catalytic cycle. These were postulated to be iron amide and iron hydride complexes on the basis of computational chemistry and the trapping of these reactive intermediates by use of hydrogen chloride in ether to give complex **F** (reaction 6). Preliminary results showed that complex **F** with an amine(imine)diphosphine ligand (P-NH-N-P) was a more active catalyst precursor than **C** (*8*, *9*). This system reduced acetophenone at turnover frequencies up to 15 s^{-1} at 30°C; until the present work, this was an unrivaled rate for the transfer hydrogenation of ketones under these conditions (*8*). On this basis, we hypothesized that the direct synthesis of complexes such as **F** containing an unsymmetrical P-NH-N-P ligand would lead to more active catalysts.

A key step toward this goal was the selective synthesis of enantiopure tridentate ligands P-NH-NH_2 (**1a** and **1b**) by an iron(II)-assisted method (Fig. 2, reactions 7 and 8). The starting compounds are air- and water-stable dimeric phosphonium salts **A** that are readily prepared with a variety of substituents at phosphorus (in green in Fig. 2); in the present case, these are phenyl and *meta*-xylyl. The latter group is often effective at increasing the selectivity of catalysts (*2*, *9*). These phosphonium dimers release reactive α-phosphinoacetaldehyde 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 incorporating phosphine, imine, and amine donors (*10*). The optimum reaction conditions include the use of the enantiopure diamine (*S*,*S*)-$NH_2CHPhCHPhNH_2$ [(*S*,*S*)-dpen] and a slight excess of the phosphonium dimer, 0.65 equiv.

These iron complexes are treated with lithium aluminum hydride to reduce the imine linkages and then hydrolyzed to release the enantiopure compounds **1a** and **1b** in high yields. This method is superior to other reductive amination methods that either would require an excess of the expensive diamine or would result in a mixture of amine products. The ligands are produced in ~90% purity and are used directly in the next step.

These ligands enable the direct synthesis (via Fig. 2, reaction 9) of a range of catalyst precursors

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as exemplified by the three compounds **2a** to **2c**. Reaction 9 is analogous to reaction 2 of Fig. 1 where the iron(II) acts as a template to produce one isomer from the multicomponent reaction. Here, the α-phosphinoacetaldehyde released from compound **A** (with phenyl, *para*-tolyl, or xylyl substituents at phosphorus) condenses with the P-NH-NH_2 ligand **1a** or **1b** [rather than the (*S*,*S*)-dpen used previously] at iron(II), thereby leading to an iron complex with the desired partially saturated P-NH-N-P framework. The latter is then treated with 1 atm of carbon monoxide and sodium chloride in acetone to give the new iron complexes **2a** to **2c** in acceptable overall yields (30 to 42%). Remarkably, only one diastereomer is formed, as indicated by the $^{31}P\{^1H\}$ nuclear magnetic resonance (NMR) spectra; for example, complex **2a** when dissolved in CD_2Cl_2 produces two doublet resonances at 58.0 and 62.6 ppm with $^2J_{PP}$ = 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 Å, N(1A)-C(5A) = 1.256 Å (these distances have estimated standard deviations of 0.007 Å). The amino proton and the chloro ligand are located on opposite sides of the coordination plane defined by the Fe, N, and P atoms.

When these complexes are treated with at least 2 equiv of potassium tertiary butoxide (KO^tBu) base, very reactive, oxygen-sensitive catalysts are released for the hydrogenation of ketones by the transferring of hydrogen from the solvent isopropanol (Fig. 3). Two features distinguish these catalysts from the ones that we have reported earlier (*7*, *9*, *11*, *12*): (i) No induction period is observable, and (ii) the rate of conversion at 28°C is substantially higher. Turnover frequencies (TOF) of >200 s^{-1} (720,000 $hour^{-1}$) at 50% conversion are observed for some substrates (see Table 1), with complete conversion [turnover number (TON) up to 6100] attained in seconds. This exceeds the TOF observed for fast transfer hydrogenation catalysts based on ruthenium and osmium (*R*,*S*)-Josiphos complexes that in basic isopropanol reduce acetophenone to (*R*)-1-phenylethanol in 89 to 92% enantiomeric excess (ee) with TOF up to 89 s^{-1} at 60°C (*13*). The ruthenium complex $RuCl_2$(*R*-tol-binap)[(*R*,*R*)-dpen] [tol-binap is 2,2′-bis(di-4-tolylphosphino)-1,1′-binaphthyl] in basic isopropanol catalyzes the pressure hydrogenation (at 45 atm, 30°C) of acetophenone to (*S*)-1-phenylethanol at 80% ee and at a TOF of 63 s^{-1}, whereas a ruthenium(II) complex with a P-NH-NH-P ligands catalyzes the same reaction with a TOF of 92 s^{-1} but at 60°C and with low ee (*14*). The activity of the iron complexes rivals that of enzymes such as liver alcohol dehydrogenase, which transfers a hydride from a zinc ethoxide active site to a pyridinium substrate (*15*), or a synthetic iron-based hydrogenase where dihydrogen is oxidized to protons and electrons (*16*).

A comparison of the utility of the precursors **2a** to **2c** in the hydrogenation of acetophenone (Table 1, top left) under standard conditions (acetophenone:KO^tBu:**2** ratio = 6100:8:1) demonstrates that complex **2b** with *para*-tolyl groups provides the highest TOF; complex **2c** with xylyl groups on the phosphorus atoms provides the highest ee values of the (*R*)-1-phenylethanol. The use of **2a** or **2b** results in an erosion of ee over time; **2c** has the advantage of minimal 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 (third entry of Table 1 with a TOF of 12 s^{-1}). The reduction of 3,5-bistrifluoromethylacetophenone in 90% ee for **2a** and 98% ee for **2c** is particularly noteworthy, 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 (*17*).

Complex **2a** was an effective precatalyst for the efficient reduction of a broad range of aryl ketones (Table 1). It was also active toward alkyl ketones, which are kinetically and thermodynamically less prone to react. Pyridine and furan heterocycles were tolerated, albeit with a drop in enantioselectivity. The reduction of *trans*-4-phenyl-3-buten-2-one initially yields the unsaturated alcohol with relatively low enantioselectivity (40% ee). The reduction of the C=C double bond on the initially formed unsaturated alcohol occurs later, eventually affording the saturated alcohol. The chemoselectivity for the polar C=O versus the nonpolar 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 imines activated with the *N*-(diphenylphosphinoyl) group in >99% ee and at rates greater than 100 times those of previously reported iron catalysts (*18*, *19*).

The proposed highly reactive catalysts **3**, **3′**, and **4** (Fig. 3) were characterized by NMR and infrared spectroscopy. The spectra are quite consistent with the structures predicted recently using density functional theory (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 (*20*). Complexes **3** and **3′** were generated as a mixture by reacting complex **2a** with 2 equiv of KO^tBu in

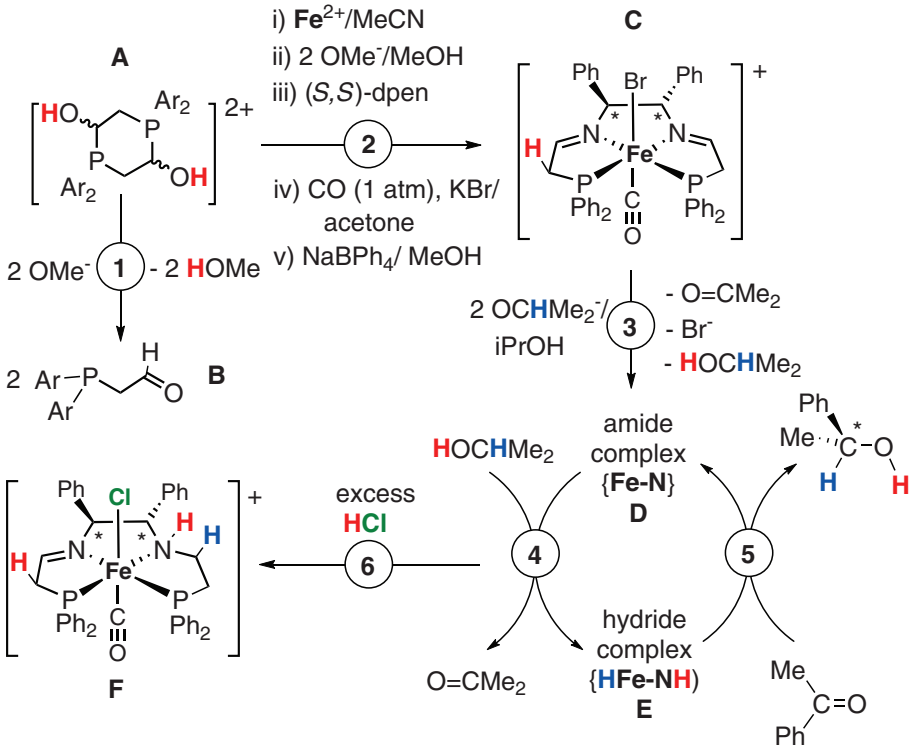


Fig. 1. Reactions established by previous iron catalyst research. (**1**) Reaction of the phosphonium salt **A** with base produces α-phosphinoacetaldehyde **B**. (**2**) Reaction of 2 equiv of **B** (Ar = Ph) with 1 equiv of the diamine (*S*,*S*)-NH_2CHPhCHPhNH_2 [(*S*,*S*)-dpen] at Fe(II) followed by treatment with CO and KBr in acetone and then treatment with $NaBPh_4$ in MeOH precipitates the bis(imine)diphosphine iron(II) complex **C** as the BPh_4^- salt. (**3**) Reaction of isopropoxide with this precatalyst **C** in isopropanol causes its slow activation, a process that is proposed to involve the deprotonation of one side of the ligand and addition of hydride to the imine on the other side, producing an amide species **D**. (**4** and **5**) These reactions constitute the catalytic cycle where the transfer of hydrogen from isopropanol solvent to acetophenone, giving (*R*)-1-phenylethanol is catalyzed by a postulated iron amide **D** and hydride **E**. (**6**) Reaction of the active species **D** and **E** with HCl in ether gives the chloride salt **F** with the amine(imine)diphosphine ligand reduced on the right side as drawn. Here, the active protonic hydrogens are colored red and hydridic hydrogens blue. Ar, aryl; Ph, phenyl; Me, methyl; iPrOH, isopropanol.

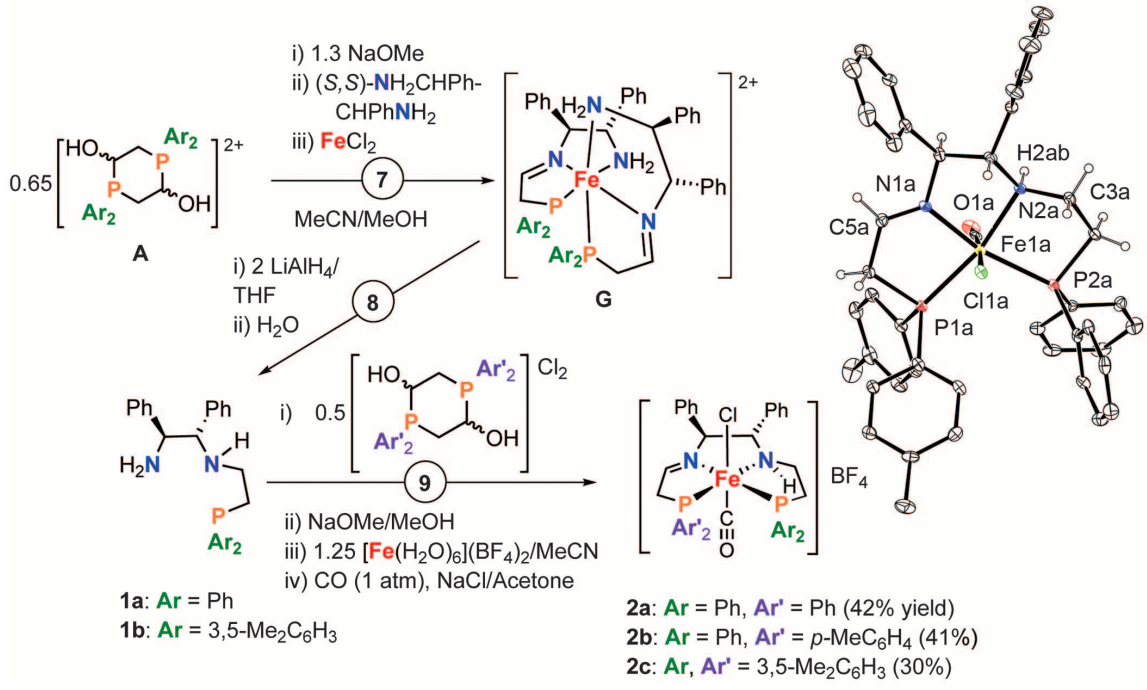


Fig. 2. Iron(II)-assisted synthesis of enantiopure phosphinediamine ligands 1a and 1b (reactions 7 and 8) and iron (II)-templated synthesis of enantiopure catalyst precursors 2a to 2c (reaction 9). The molecular structure of the cation of complex **2b** (right) was determined by single-crystal x-ray diffraction. The thermal ellipsoids are plotted at 50% probability; some hydrogens are removed for clarity.

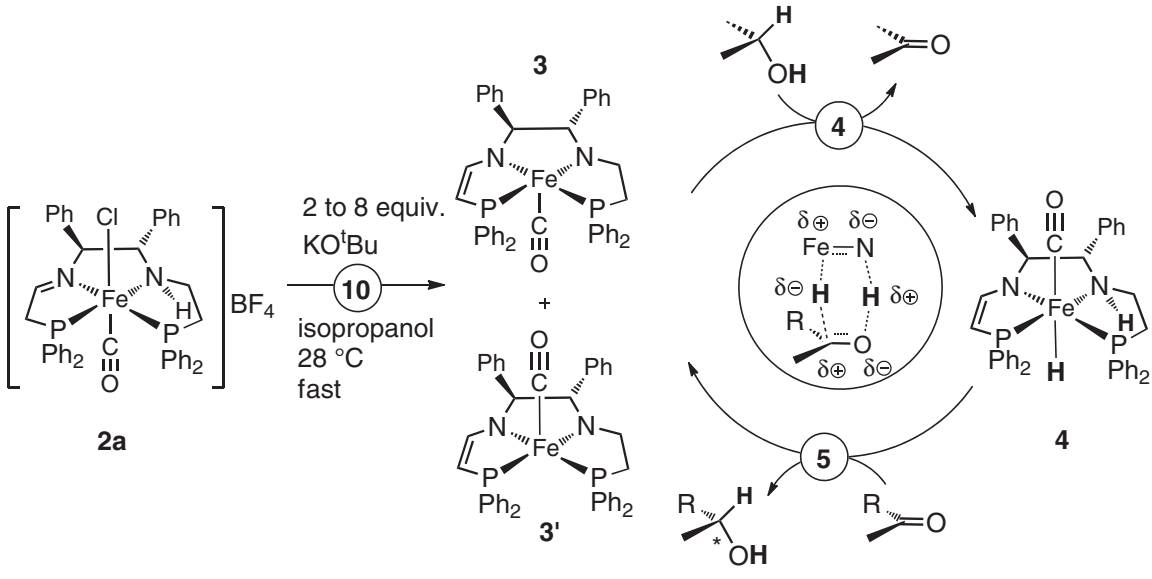


Fig. 3. Proposed mechanism. The amido-eneamido complex **3** and its isomer **3′** and the amine-eneamido-hydride complex **4**, corresponding to catalysts **D** and **E** of Fig. 1, are generated when complexes **2a** to **2c** are treated with base in isopropanol solvent. The structures of catalysts **3** and **4** were proposed in a previous theoretical (DFT) study (*20*) and are verified in the current work by NMR.

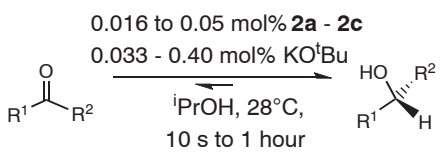
tetrahydrofuran (THF) at room temperature, evaporating the solvent, and extracting the product with C_6D_6 for NMR analysis. The $^{31}P\{^1H\}$ NMR spectrum provides evidence for two diastereomers: (i) a major one displaying two doublets at 75.8 and 85.3 ppm with a ^2J(P,P) coupling constant of 28 Hz and (ii) a minor one with a similar pattern of doublets at 77.8 and 83.4 ppm with ^2J(P,P) of 31 Hz. The ^1H 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** or **3′** shown in Fig. 3 (see supplementary materials). The other isomer is likely to have the carbonyl on the opposite apex of the square pyramid, as shown.

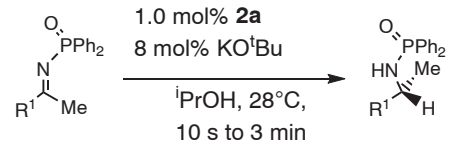
The mixed isomers of **3** were highly active for the asymmetric transfer hydrogenation of acetophenone to 1-phenylethanol (*R*) in isopropanol without the addition of base. About 60% of the substrate was reduced at room temperature within 10 min with 82% ee. No induction period was observed, and the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

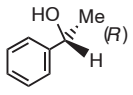
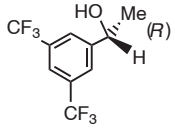
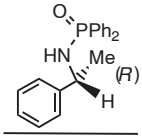
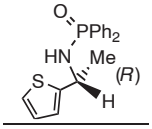
The reaction of a mixture of **3** and **3′** with isopropanol in the absence of substrate led, within 1 min, to a mixture of **3** and the hydride complex **4** (Fig. 3). Complex **4** displayed a characteristic ^1H NMR resonance for the FeH at –2.25 ppm (dd, $^2J_{HP}$ = 70.0 and 70.8 Hz). A second hydride grew 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 signal predominating. Both of the two hydride species were characterized by NMR spectroscopy, including ^1H, $^{31}P\{^1H\}$ ^1H-^1H correlation spectroscopy, heteronuclear single-quantum coherence, and nuclear Overhauser effect spectroscopy, in C_6D_6 (see supplementary material). The major isomer has the structure shown in Fig. 3.

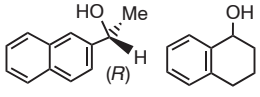
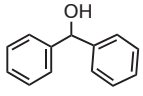
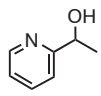
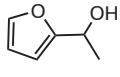
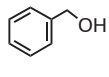
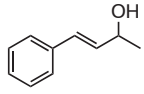
The addition of acetophenone to the C_6D_6 solution of the hydride mixture immediately led to the disappearance of the hydride signals and the corresponding phosphorus resonances and the generation of free 1-phenylethanol. This is fully consistent

Table 1. Transfer hydrogenation of ketones and imines catalyzed by complexes 2a to 2c. General conditions for ketones: [Cat] = 6.73×10^{-5} M, [KO^{t}Bu] = 5.45×10^{-4} M, [ketone] = 0.412 M, [^{i}PrOH] = 12.4 M, 28°C; for imines: [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. The absolute configurations were obtained by gas chromatography or high-performance liquid chromatography by comparison to known standards.





Comparison of catalysts						Amine products using **2a**		
	2a	**2b**	**2b***	**2c**	**2a**	**2c**†	**2a**	**2a**
Time to equil.:	180 s	180 s	1000 s	180 s	180 s	10 s	20 s	180 s
Yield:	82%	83%	83%	82%	99%	100%	100%	100%
TON at equil.:	5000	5100	5100	5000	6060	2000	100	100
TOF at 50% conv.:	119 s^{-1}	152 s^{-1}	12 s^{-1}	70 s^{-1}	147 s^{-1}	200 s^{-1}	10 s^{-1}	5 s^{-1}
ee at 10 s:	88%	86%	86%	92%	91%	98%	>99%	>99%
ee at equil.:	78%	70%	80%	90%	90%	98%	>99%	>99%

Alcohol products using **2a**								
Time to equil.:	180 s	1 h	10 min	1 h	6 min	6 min	25 s	4 min
Yield:	84%	73%	88%	67%	98%	84%	99%	55%
TON at equil.:	5140	4470	5400	4100	6000	5140	6060	3370
TOF at 50% conv.:	158 s^{-1}	4 s^{-1}	38 s^{-1}	3 s^{-1}	100 s^{-1}	61 s^{-1}	242 s^{-1}	14 s^{-1}
ee at 10 s:	92%	34%	-	57%	25%	51%	-	40%
ee at equil.:	83%	33%	-	54%	24%	31%	-	40%

*[Cat, **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. †Ketone: Cat ratio = 2000:1 to prevent poisoning by the acidic alcohol product.

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 within 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) directed to the less bulky diamine side of the catalyst.

As in Noyori-type catalysts (*21*), the addition of excess base, at least up to 8 equiv relative to the catalyst, causes an increase in turnover frequency, as shown in Table 1 for catalyst **2b** where a TOF of 152 s^{-1} is obtained with 8 equiv of base, versus 12 s^{-1} with 2 equiv. Our group had proposed that this excess of base protects the basic amide and hydride reactants by reducing the hydrogen ion concentration in the alcohol medium (*22*). It might also serve to catalyze the substitution of unreactive octahedral amine complexes (*23*) by amine deprotonation (*24*).

The catalyst systems described here represent versatile, well-understood, extremely active asymmetric reduction catalysts based on a nonprecious metal. The new ligands permit efficient multicomponent synthesis of a very wide range of highly active iron catalysts with varied structural features. In principle, the mirror image catalysts can also be made in the same way using the commercially available diamine (*R*,*R*)-dpen, and these can be used to make the (*S*) forms of the alcohols or amines.

References and Notes

1. W. S. Knowles, R. Noyori, *Acc. Chem. Res.* **40**, 1238–1239 (2007).
2. R. Noyori, T. Ohkuma, *Angew. Chem. Int. Ed. Engl.* **40**, 40–73 (2001).
3. S. Bell *et al.*, *Science* **311**, 642–644 (2006).
4. W. A. Nugent, T. V. RajanBabu, M. J. Burk, *Science* **259**, 479–483 (1993).
5. A. M. Tondreau *et al.*, *Science* **335**, 567–570 (2012).
6. K. Junge, K. Schröder, M. Beller, *Chem. Commun.* **47**, 4849–4859 (2011).
7. R. H. Morris, *Chem. Soc. Rev.* **38**, 2282–2291 (2009).
8. A. A. Mikhailine, M. I. Maishan, A. J. Lough, R. H. Morris, *J. Am. Chem. Soc.* **134**, 12266–12280 (2012).
9. P. E. Sues, A. J. Lough, R. H. Morris, *Organometallics* **30**, 4418–4431 (2011).
10. A. A. Mikhailine, E. Kim, C. Dingels, A. J. Lough, R. H. Morris, *Inorg. Chem.* **47**, 6587–6589 (2008).
11. A. A. Mikhailine, R. H. Morris, *Inorg. Chem.* **49**, 11039–11044 (2010).
12. P. O. Lagaditis, A. J. Lough, R. H. Morris, *J. Am. Chem. Soc.* **133**, 9662–9665 (2011).
13. W. Baratta *et al.*, *Organometallics* **29**, 3563–3570 (2010).
14. V. Rautenstrauch, X. Hoang-Cong, R. Churlaud, K. Abdur-Rashid, R. H. Morris, *Chem. Eur. J.* **9**, 4954–4967 (2003).
15. A. Kohen, R. Cannio, S. Bartolucci, J. P. Klinman, *Nature* **399**, 496–499 (1999).
16. T. Liu, D. L. Dubois, R. M. Bullock, *Nat. Chem.* **5**, 228–233 (2013).
17. K. M. J. Brands *et al.*, *J. Am. Chem. Soc.* **125**, 2129–2135 (2003).
18. A. A. Mikhailine, M. I. Maishan, R. H. Morris, *Org. Lett.* **14**, 4638–4641 (2012).
19. S. Zhou *et al.*, *Angew. Chem. Int. Ed.* **49**, 8121–8125 (2010).
20. D. E. Prokopchuk, R. H. Morris, *Organometallics* **31**, 7375–7385 (2012).
21. C. A. Sandoval, T. Ohkuma, K. Muñiz, R. Noyori, *J. Am. Chem. Soc.* **125**, 13490–13503 (2003).
22. K. Abdur-Rashid *et al.*, *J. Am. Chem. Soc.* **124**, 15104–15118 (2002).
23. F. Basolo, R. G. Pearson, *Mechanisms of Inorganic Reactions* (Wiley, New York, 1967).
24. J. M. John, S. Takebayashi, N. Dabral, M. Miskolzie, S. H. Bergens, *J. Am. Chem. Soc.* **135**, 8578–8584 (2013).

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Supplementary Materials

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Materials and Methods
Figs. S1 to S32
Table S1

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