REPORT

CATALYSIS

Cobalt-catalyzed asymmetric hydrogenation of enamides enabled by single-electron reduction

Max R. Friedfeld,[1] Hongyu Zhong,[1] Rebecca T. Ruck,[2] Michael Shevlin,[2]* Paul J. Chirik[1]*

Identifying catalyst activation modes that exploit one-electron chemistry and overcome associated deactivation pathways will be transformative for developing first-row transition metal catalysts with performance equal or, ideally, superior to precious metals. Here we describe a zinc-activation method compatible with high-throughput reaction discovery that identified scores of cobalt-phosphine combinations for the asymmetric hydrogenation of functionalized alkenes. An optimized catalyst prepared from (*R*,*R*)-Ph-BPE {Ph-BPE, 1,2-bis[(2*R*,5*R*)-2,5-diphenylphospholano]ethane} and cobalt chloride [$CoCl_2 \cdot 6H_2O$] exhibited high activity and enantioselectivity in protic media and enabled the asymmetric synthesis of the epilepsy medication levetiracetam at 200-gram scale with 0.08 mole % catalyst loading. Stoichiometric studies established that the cobalt (II) catalyst precursor (*R*,*R*)-Ph-BPE$CoCl_2$ underwent ligand displacement by methanol, and zinc promoted facile one-electron reduction to cobalt (I), which more stably bound the phosphine.

Asymmetric catalysis with soluble metal complexes has transformed the preparation of single enantiomers in the pharmaceutical, fragrance, and fine-chemical industries (*1*, *2*). Because different antipodes of chiral molecules often exhibit distinct biological properties, the U.S. Food and Drug Administration has strict requirements for single-enantiomer drugs, and the importance of asymmetric transformations in the pharmaceutical industry will continue to grow. Beginning with Knowles's synthesis of the Parkinson's medication L-dopa by rhodium-catalyzed asymmetric alkene hydrogenation (*3*), catalysis by homogeneous catalysts containing precious metals with tunable ligands has revolutionized the approach to single-enantiomer active pharmaceutical ingredients (APIs).

The widespread application of asymmetric hydrogenation, particularly in the pharmaceutical industry, has motivated efforts to identify catalysts based on earth-abundant first-row transition metals rather than traditionally used precious metals (*4*). In alkene hydrogenation catalysis, rhodium and iridium catalysts operate by predictable, two-electron cycles involving oxidative addition and reductive elimination [for example, M(I)-M(III)]. However, compared to their heavier congeners, first-row transition metals have kinetically and thermodynamically accessible oxidation states separated by one electron, often to the detriment of catalytic chemistry (*5*). Although considerable progress has been made (*6*, *7*), state-of-the-art catalysts with iron, cobalt, and nickel lack many of the favorable properties associated with precious metal catalysts that facilitate scale up. Alkene hydrogenation catalysts with earth-abundant metals are typically air- and moisture-sensitive, requiring rigorously dried solvents; are intolerant of many polar functional groups found in APIs; and have insufficient activity to be applied industrially.

Asymmetric hydrogenation and other enantioselective metal-catalyzed reactions often rely on the successful relay of stereochemical information from a chiral ligand to the substrate (*8*). Therefore, understanding and controlling ligand coordination and dissociation equilibria are key to enabling catalyst stability and communicating stereochemical information. Unlike other tactics for improving catalyst performance, rational control of catalyst activation and deactivation are challenging and often circumvented by increased catalyst loadings (*9*–*11*). With classic transition metal catalysts such as Wilkinson's $(Ph_3P)_3RhCl$ (*12*) and $(Ph_3P)_3RuCl_2$ (*13*) (Ph, phenyl), catalyst activation and, ultimately, performance is limited by phosphine dissociation equilibria and halide coordination (Fig. 1, A and C). These limitations are overcome with weakly coordinating anions and hydrogenation of ancillary diene or triene ligands to create open coordination sites (Fig. 1, B and D), as exemplified by the Schrock-Osborn–type catalysts [(P,P)Rh(diene)][X] (*14*), where X is any noncoordinating anion, and the cationic ruthenium catalyst [(P-P)Ru(H)(triene)][BF_4] (*15*). These design principles have proven useful for fast, reliable catalyst activation and are widely used for new catalyst discovery.

Our laboratory has reported that two-carbon-bridged, C_2-symmetric (bis)phosphines support highly active and enantioselective cobalt catalysts for the asymmetric hydrogenation of simple dehydro-α–amino acid derivatives (*6*). Although these catalysts are state-of-the-art among first-row metals and provide an important demonstration of the promise of earth-abundant metals in asymmetric alkene hydrogenation, major limitations include the use of pyrophoric activators such as $LiCH_2SiMe_3$, extreme air sensitivity of the catalyst, and lack of reactivity among many classes of phosphines, likely owing to catalyst deactivation by irreversible loss of ligand (Fig. 1E). Isolated organometallic compounds such as (*R*,*R*)-QuinoxP*Co$(CH_2SiMe_3)_2$ and (*R*,*R*)-^{i}Pr-DuPhosCo$(CH_2SiMe_3)_2$ (^{i}Pr, isopropyl), albeit more active, require multistep organometallic syntheses and special handling that are likely impractical for industrial application. Here we describe advances in cobalt-catalyzed asymmetric alkene hydrogenation, where mechanistic insights into ligand dissociation equilibria and the unique properties of the first-row transition metals are leveraged to address fundamental limitations of existing catalysts. Two sequential single-electron reductions of substitutionally labile Co(II) complexes result in formation of more robust catalysts in situ. This advance in catalyst activation enabled the discovery of scores of effective metal-ligand combinations for asymmetric hydrogenation, culminating in the use of low catalyst loadings for the practical, pilot-scale synthesis of an API.

The hydrogenation of dehydro-levetiracetam (**1**) was selected for initial catalyst development studies to highlight the challenges associated with API synthesis. The corresponding chiral product, levetiracetam (Keppra), is a widely used medication for epilepsy (*16*). In one patented route (*17*), levetiracetam was prepared by asymmetric hydrogenation using an optimized condition of 0.5 mole % (mol %) of in situ–generated [(*S*,*S*)-Et-DuPhosRh(COD)][OTf] in dichloromethane (Et, ethyl; COD, 1,5-cyclooctadiene; OTf, triflate). The relatively high catalyst loading and use of a noncoordinating, chlorinated solvent reflects the challenges associated with hydrogenation of **1** as a poorly coordinating substrate (*17*) with limited conformational flexibility for achieving two-point binding (*18*).

Initial studies on hydrogenation of **1** relied on high-throughput experimentation to evaluate reaction variables, including solvents, cobalt sources, activators, temperature, and catalyst loadings (tables S1 to S6). A remarkable solvent dependence was identified: Protic solvents such as methanol (MeOH), ethanol, and trifluoroethanol provided the highest yields and enantiomeric excesses (tables S1 to S4). These unexpected results indicated that cobalt hydrides competent for enantioselective alkene hydrogenation could, despite their anticipated hydricity, be formed in protic solvents. The use of alcohol solvents has been prevalent since the discovery of enantioselective

[1]Department of Chemistry, Princeton University, Princeton, NJ 08544, USA. [2]Department of Process Research and Development, Merck Research Laboratories, Rahway, NJ 07065, USA.
*Corresponding author. Email: michael_shevlin@merck.com (M.S.); pchirik@princeton.edu (P.J.C.)

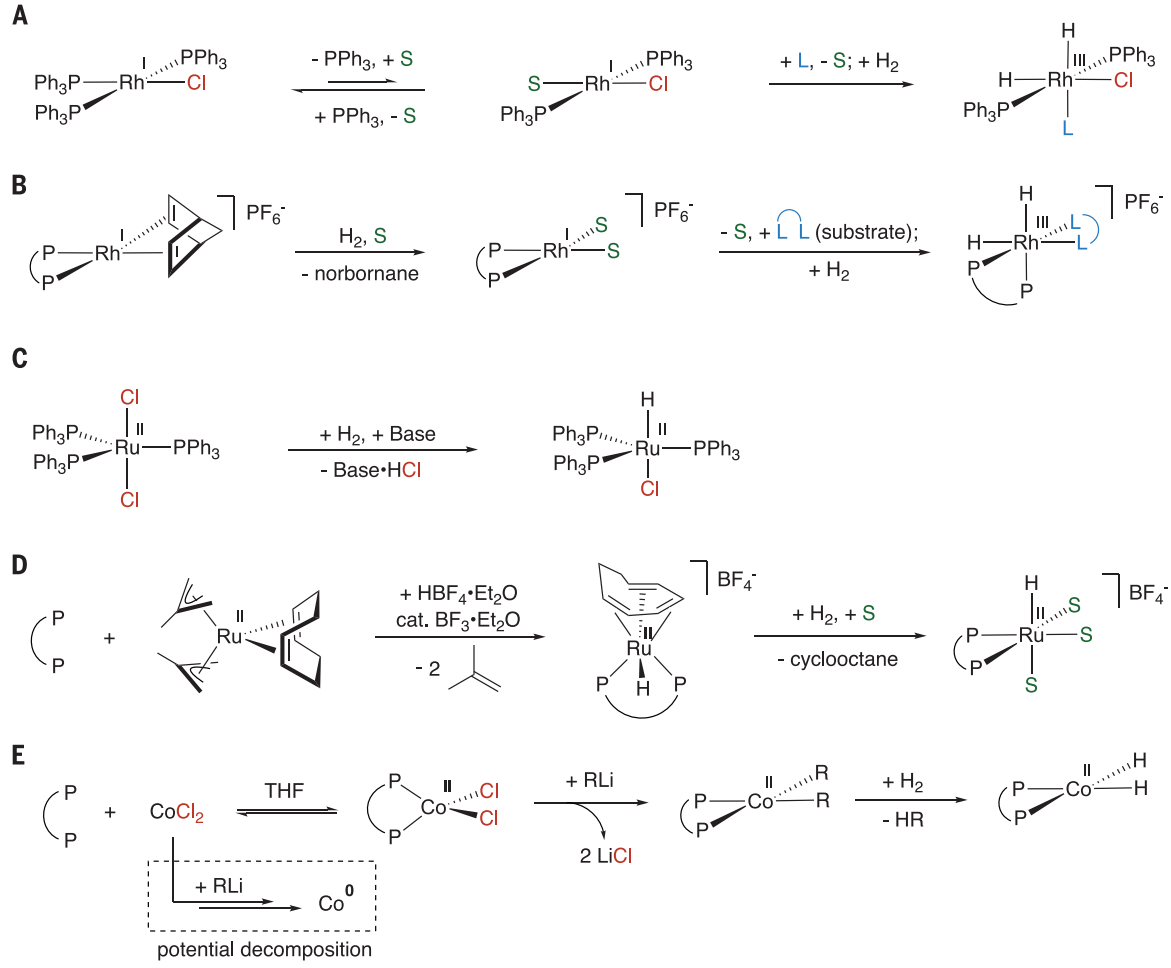


Fig. 1. Catalyst-activation strategies for alkene hydrogenation catalysts. (**A**) Activation of Wilkinson's catalyst $(Ph_3P)_3RhCl$ is limited by unfavorable PPh_3 dissociation equilibrium and strongly coordinating Cl^-. (**B**) Schrock-Osborn–type catalysts are paired with a weakly coordinating anion such as PF_6^- and rely on irreversible hydrogenation of diene ligands to open coordination sites. (**C**) Wilkinson's ruthenium catalyst is activated by base in H_2 to form ruthenium monohydride but suffers from limited coordination sites. (**D**) Cationic ruthenium catalysts are designed to open coordination sites. (**E**) Previous work on cobalt catalysts relied on activation by alkyl lithium reagents and posited formation of cobalt dihydride as an active catalyst. S, solvent molecule; L, neutral ligand; cat., catalyst.

homogeneous hydrogenation with transition metal catalysts (*19*). Catalysts containing Rh(I), Ir(I), and Ru(II) are usually highly active in MeOH, in part, because the solvent can act as a stabilizing ligand occupying open coordination sites on the metal but be readily displaceable by alkene substrates during catalysis (Fig. 1, A, B, and D). Also highly preferred in process scale reactions, MeOH is a green solvent (*20*) with excellent solubility for both H_2 and drug intermediates with polar functional groups.

The proposed mechanism of cobalt-catalyzed hydrogenation of dehydro-α–amino acid derivatives involves formation of a Co(II) dihydride as the active species that promotes alkene insertion (Fig. 1E) (*21*). We wondered whether this potential intermediate could be accessed instead from H_2 oxidative addition to Co(0), a pathway reminiscent of Rh(I) and Ir(I) catalysis. This strategy, in turn, would require a convenient means to reduce cobalt precursors from higher oxidation states.

Mild reducing agents compatible with MeOH, such as readily available and easily handled Zn, Mn, Mg, and Fe powders, were examined for in situ activation of Co(II) phosphine complexes for hydrogenation of **1**. Both high yields and enantiomeric excesses (ee's) of levetiracetam were obtained after optimization with most in situ metallic reductants (table S7), suggesting the generation of reduced Co species in MeOH, which activated H_2 and were effective for the enantioselective reduction of **1**. Filtration of the catalyst suspension to remove excess reductant and the accompanying metal salt had minimal effect on catalyst performance, which simplified the reaction setup. Among the metal powders examined, Zn dust provided the best results, with respect to both product yields and enantioselectivity.

Given the sensitivity of ligand-substrate interactions to subtle structural manipulations, the broad application of earth-abundant transition metal catalysts for asymmetric alkene hydrogenation will depend on the realization of a practical, rapid, and reproducible method for evaluating various metal-ligand combinations for the ever-changing structures of alkenes found in the drug pipeline. Accordingly, the optimized reaction conditions, $CoCl_2$ with Zn dust as an activator in MeOH, were applied to a high-throughput evaluation of an expanded library of 216 chiral bidentate ligands. Zinc activation enabled high activity and enantioselectivity across a broad range of ligands, including bis(phosphine), secondary phosphine oxide–phosphine, phosphine-oxazoline, and phosphine-thioether with varied chelate sizes (Fig. 2C and fig. S13). The number of ligands effective under Zn activation was remarkably higher than the corresponding compatibilities with the previously reported (*6*) organolithium-activation method (Fig. 2A; for Zn activation, only the 192-ligand library results are plotted). The high efficacy of the Zn-activation method was not limited to the asymmetric hydrogenation of **1**. Scores of cobalt-phosphine combinations were identified for the successful asymmetric

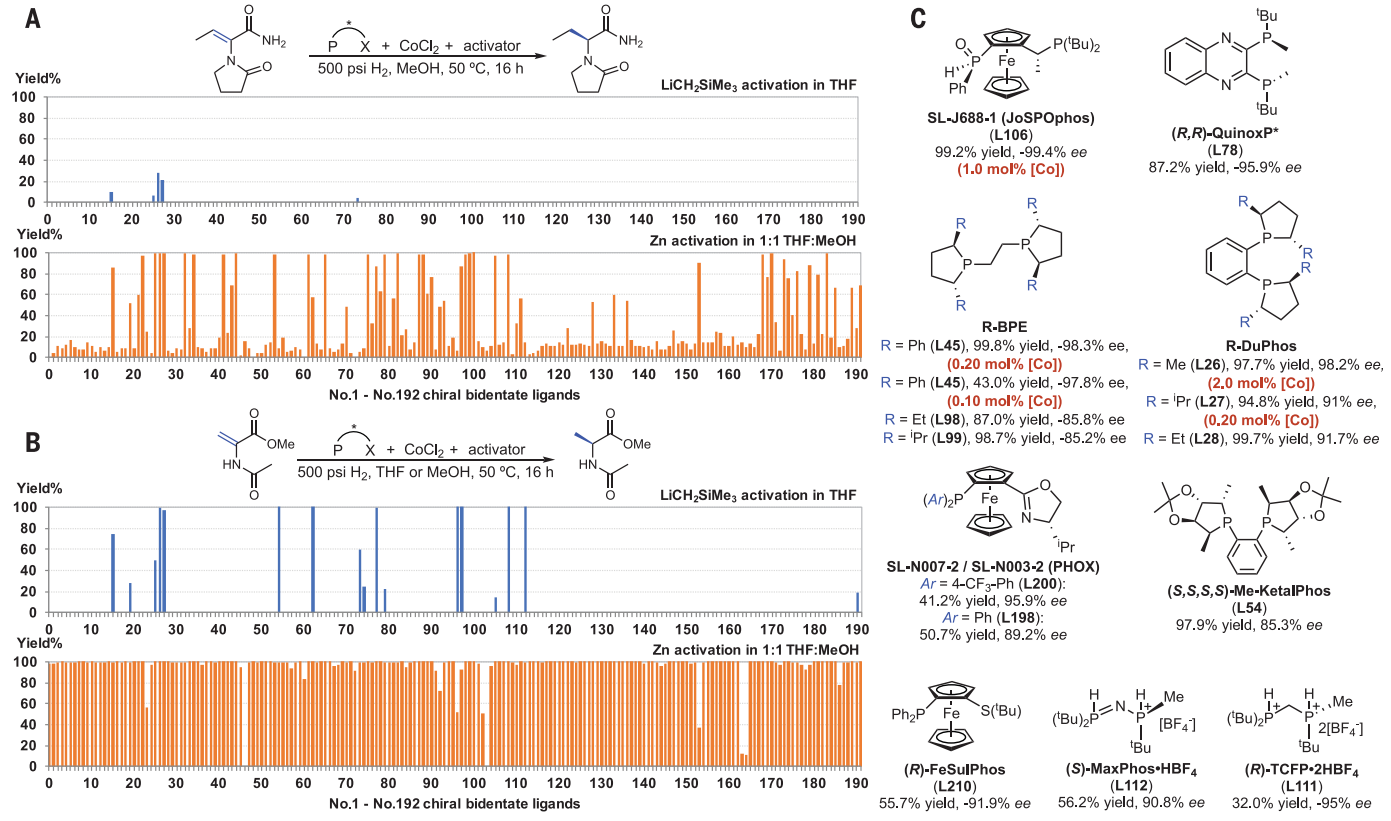
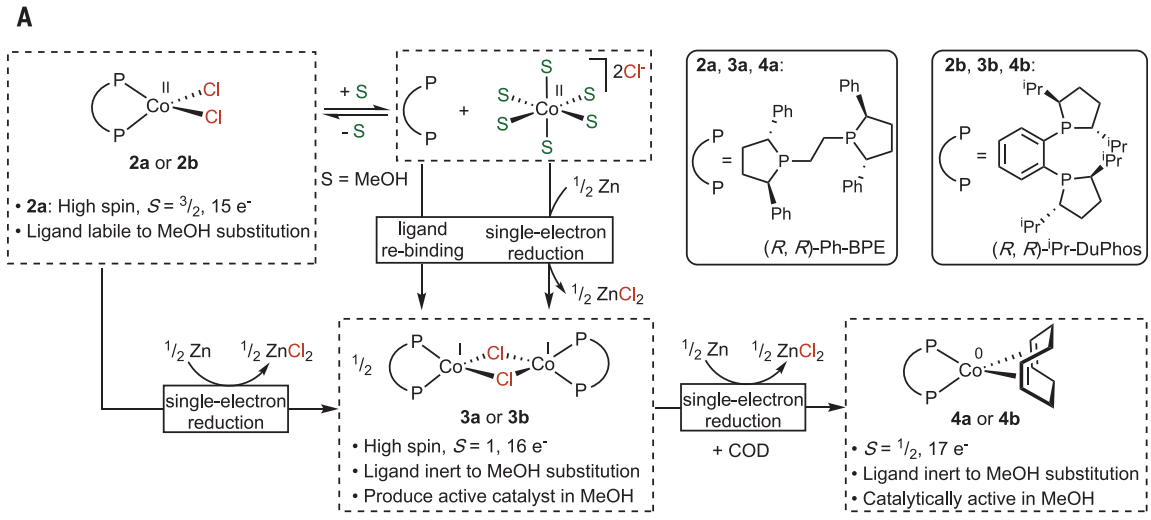


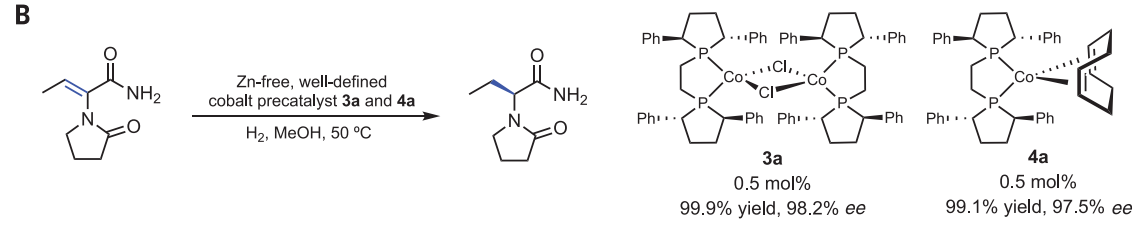
Fig. 2. High-throughput evaluation of chiral phosphine ligands. (**A**) Comparing results of 192 chiral ligands for the asymmetric hydrogenation of dehydro-levetiracetam by using $LiCH_2SiMe_3$ (top, table S9) and Zn (bottom, table S8). (**B**) Ligand compatibility with $LiCH_2SiMe_3$ (top; see also table S19) and Zn (bottom; see also table S20) for hydrogenation of a representative alkene methyl-2-acetamidoacrylate. (**C**) Ligands in the expanded 216-ligand library that give highest enantioselectivity for dehydro-levetiracetam hydrogenation. Catalyst loadings were 10 mol % unless otherwise noted. Positive and negative ee values correspond to (*S*) and (*R*) enantiomers, respectively. Me, methyl; ^{t}Bu, *tert*-buty.

hydrogenation of *N*-(1-phenylvinyl)acetamide, methyl 2-acetamidoacrylate, and methyl (*Z*)-2-acetamido-3-phenylacrylate (figs. S16 to S18 and tables S21 to S24), highlighting the improved versatility over the previously reported $LiCH_2SiMe_3$-activation method (*6*). The hydrogenation of methyl 2-acetamidoacrylate was particularly notable (Fig. 2B), as essentially all phosphines in the library produced quantitative conversion to product. The highly successful Zn-MeOH reduction is likely attributable to enhanced activation and suppressed deactivation of catalyst: Low oxidation-state Co species with open coordination sites are generated owing to the high Cl^- binding affinity of Zn^{2+}, and formation of metallic Co(0) is likely suppressed owing to favorable ligand coordination to reduced Co species. The robustness of the Zn method was also demonstrated by the successful hydrogenation of **1** in the presence of 5 volume % of water in MeOH. Among the many successful ligands identified, (*R*,*R*)-Ph-BPE {Ph-BPE, 1,2-bis[(2*R*,5*R*)-2,5-diphenylphospholano]ethane} and (*R*,*R*)-^{i}Pr-DuPhos were selected for subsequent studies because of their outstanding performance at low (0.20 mol %) catalyst loadings (Fig. 2C and table S17). Although Zn activation of bis(phosphine)-cobalt catalysts has been reported in C–C bond–forming reactions (*22*, *23*), the protocol was not applied to hydrogenation in protic solvents.

Stoichiometric experiments were conducted to determine which oxidation states of Co were formed under catalytic conditions and to understand the origin of the improved catalyst fidelity. Compound (*R*,*R*)-Ph-BPE$CoCl_2$ (**2a**) was isolated after addition of the phosphine to a tetrahydrofuran (THF) solution of $CoCl_2{\cdot}6H_2O$ in 96% yield and crystallographically characterized (fig. S50). A high spin, S = 3/2 ground state for **2a** was determined by electron paramagnetic resonance (EPR) spectroscopy (fig. S9) and solution magnetometry. Surprisingly, dissolution of the dark purple **2a** in MeOH resulted in complete dissociation of the (bis)phosphine from the substitutionally labile Co(II) center to form a proposed solvento complex $[Co(MeOH)_6][Cl]_2$ along with precipitation of free ligand, as judged by ultraviolet-visible spectroscopy and ^{31}P nuclear magnetic resonance spectroscopy (figs. S40 to S44). Phosphine dissociation proved reversible, as removing the MeOH solvent and dissolving the residue in THF reconstituted **2a**. Cobalt dichloride, (*R*,*R*)-^{i}Pr-DuPhos$CoCl_2$ (**2b**), underwent partial ligand dissociation in MeOH (fig. S45). These findings suggest that unfavorable ligand dissociation from Co(II) by MeOH displacement could be a catalyst-deactivation pathway.

Further studies revealed how the Zn-MeOH method overcomes the unfavorable ligand loss for productive catalysis. Under conditions resembling those of the catalytic reaction, an equimolar mixture of (*R*,*R*)-Ph-BPE and $CoCl_2{\cdot}6H_2O$ was stirred with excess Zn in 1:1 THF:MeOH. A chloride-bridged Co(I) dimer $[(R,R)\text{-Ph-BPECo}(\mu\text{-Cl})]_2$ (**3a**) was isolated and crystallographically characterized (fig. S51) as the Zn-reduction product. The analogous ^{i}Pr-DuPhos complex, **3b**, was prepared and characterized (fig. S53) by using the same method. Both Co(I) complexes **3a** and **3b** exhibit S = 1 ground states, as judged by their paramagnetic, EPR-silent nature and solution magnetic moments. Phosphine displacement by MeOH was not observed with **3a** or **3b**, indicating that reduction of Co(II) to Co(I) reduces phosphine lability and enhances inertness to substitution by MeOH. Consistent with these observations, Zn reduction of $[Co(MeOH)_6][Cl]_2$ also yielded **3a** after addition of an equimolar amount of (*R*,*R*)-Ph-BPE. MeOH also facilitated reduction of **2a** by Zn, as the reaction was complete in 15 min at 23°C; an identical procedure in THF required 12 hours. The Zn and MeOH work synergistically to impart catalyst





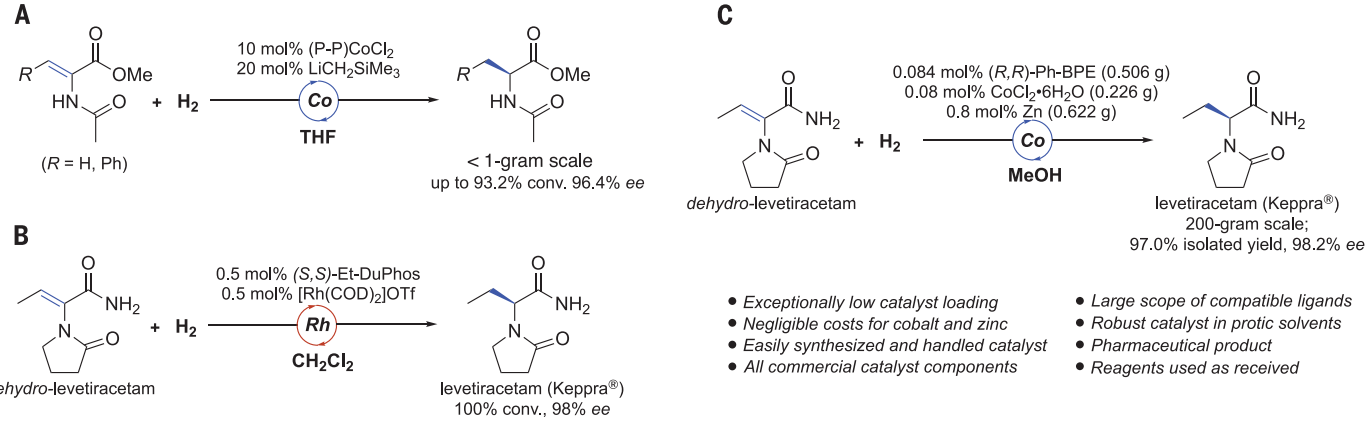


Fig. 3. Cobalt-catalyst activation enabled by single-electron reduction. (**A**) Properties and reactivity of Co(II), Co(I), and Co(0) species; $(P,P)CoCl_2$; $[(P,P)CoCl]_2$; and (P,P)CoCOD under catalytic conditions (Zn-MeOH). (**B**) Single-component, Zn-free Co(I) and Co(0) precatalysts are competent for hydrogenation.

Fig. 4. Applications at large scale. (**A**) Previous work on cobalt-catalyzed asymmetric hydrogenation of dehydro-α–amino acid derivatives. (**B**) Patented route for asymmetric hydrogenation for levetiracetam synthesis by a rhodium catalyst in dichloromethane solvent. (**C**) Industrially relevant cobalt-catalyzed asymmetric hydrogenation for levetiracetam synthesis in MeOH solvent.

fidelity. Phosphine dissociation, a deleterious catalyst-deactivation pathway, is corrected by the fast Zn reduction in MeOH to regenerate and preserve the chiral environment on the metal. Abstraction of chloride by Zn also opens coordination sites on the Co for H_2 activation and alkene coordination.

Cobalt (0) complexes were also prepared by two sequential one-electron reductions upon prolonged treatment with Zn-MeOH in the presence of ancillary ligands (fig. S1). The diene and arene Co(0) derivatives, (*R*,*R*)-Ph-BPECo(COD) (**4a**) and (*R*,*R*)-Ph-BPECo(η^6-C_6H_6) (**5**) were synthesized from Zn reduction of either Co(II) complex **2a** or from Co(I) complex **3a**. Complexes **4a** and **5** were characterized by EPR (figs. S10 and S11), establishing an S = 1/2 ground state, and **5** was also characterized by x-ray diffraction (fig. S52). Compound (*R*,*R*)-^{i}Pr-DuPhosCo(COD) (**4b**) was also prepared from Zn reduction of either **2b** or **3b** and characterized by EPR and x-ray diffraction (figs. S12 and S54). These observations suggest that both Co(I) and Co(0) are accessible via one-electron reductions using the Zn-MeOH protocol.

Alternative routes other than Zn reduction to complexes **3a**, **3b**, **4a**, **4b**, and **5** were also developed (fig. S1). The Co(II) dialkyl complex (*R*,*R*)-Ph-BPECo(CH_2SiMe_3)$_2$ (**6**) was synthesized by reported procedures (*6*), and hydrogenation of an equimolar mixture of **2a** and **6** yielded the monochloride dimer **3a** along with $SiMe_4$. Hydrogenation of **6** in the presence of diene or arene produced the Co(0) complexes **4a** and **5**. The corresponding Co(I) and Co(0) complexes with (*R*,*R*)-^{i}Pr-DuPhos were also prepared from the cobalt dialkyl.

To demonstrate the catalytic performance of the isolated Co(I) and Co(0) sources, reactions with preformed **3a** or **4a** were conducted. Hydrogenation of **1** in the presence of 0.5 mol % of Zn-free **3a** in MeOH with 500 psi (34 atm) of H_2 at 50°C produced levetiracetam in 99.9% yield and 98.2% ee (Fig. 3B), demonstrating that single-component, Zn-free Co(I) complexes are also effective for synthesis of the API. EPR experiments (figs. S47 to S49) support a pathway whereby the substrate **1** induces disproportionation of the Co(I) monochloride **3a** into Co(II)

dichloride **2a** and a Co(0) alkene complex, with the latter undergoing reaction with H_2 to enter the catalytic cycle. A notable pressure dependence was observed with **3a**, as hydrogenation of **1** at 55 psi (3.7 atm) of H_2 resulted in only 38.5% yield after 72 hours, highlighting that H_2 is key to favor equilibria to generate and trap a Co(II) dihydride from **3a** (*21*, *24*). Consistent with this hypothesis, the cobalt diene precursor **4a** was effective at the lower H_2 pressure of 55 psi (3.7 atm) and produced levetiracetam in 99.1% yield and 97.5% ee (Fig. 3B). Hydrogenation of the diene ligand liberated cyclooctane and likely generated the Co(II) dihydride, which, in the absence of chloride, is free from inhibitive binding equilibria. Similar results were obtained with **5**. Deuterium labeling experiments were conducted with the Zn-activated catalyst **3a** and D_2 gas in natural abundance MeOH and furnished 1,2-d_2-levetiracetam (d, deuterium), supporting homolytic H_2 cleavage and formation of cobalt dihydride, distinct from previous systems where heterolytic H_2 cleavage by metal carboxylates and protonation by solvent are the proposed mechanism. (*7*, *25*).

To examine practicality in an industrial setting, the Co catalysts were applied to larger scale hydrogenations. Zinc activation proved optimal and most convenient and was therefore selected for these experiments. Quantities ranging from 1.3 to 20 g of **1** were successfully hydrogenated with 0.06 mol % each of (*R*,*R*)-Ph-BPE and $CoCl_2 \cdot 6H_2O$ in MeOH and 0.6 mol % Zn, producing levetiracetam in up to 100% yield and 97.5% ee in solution. Monitoring H_2 uptake established a highly reactive catalyst in the first few minutes after H_2 was introduced, and the reaction was completed in 4 hours (fig. S15); special care must be taken with higher loadings to avoid heat generation from the exothermic reaction. Immediate introduction of H_2 after catalyst injection results in the best catalyst performance. By using these optimized conditions, a 200-g-scale hydrogenation was carried out with a slightly higher loading of 0.08 mol %, and levetiracetam was obtained in 97% isolated yield and 98.2% ee (Fig. 4C), demonstrating that earth-abundant metals are competent, if not superior to precious metals, for the synthesis of high-value single-enantiomer APIs at an industrial scale in environmentally benign solvent. These findings highlight the benefits of first-row transition metals in catalysis where oxidation states separated by one electron offer distinct strategies for improving catalyst performance and lifetime.

REFERENCES AND NOTES

1. C. S. Shultz, S. W. Krska, *Acc. Chem. Res.* **40**, 1320–1326 (2007).
2. L. A. Saudan, *Acc. Chem. Res.* **40**, 1309–1319 (2007).
3. W. S. Knowles, *Angew. Chem. Int. Ed.* **41**, 1998–2007 (2002).
4. P. J. Chirik, *Acc. Chem. Res.* **48**, 1687–1695 (2015).
5. S. Ge, R. A. Green, J. F. Hartwig, *J. Am. Chem. Soc.* **136**, 1617–1627 (2014).
6. M. R. Friedfeld *et al.*, *Science* **342**, 1076–1080 (2013).
7. M. Shevlin *et al.*, *J. Am. Chem. Soc.* **138**, 3562–3569 (2016).
8. T. P. Yoon, E. N. Jacobsen, *Science* **299**, 1691–1693 (2003).
9. R. H. Crabtree, *Chem. Rev.* **115**, 127–150 (2015).
10. D. Heller, A. H. M. de Vries, in *The Handbook of Homogeneous Hydrogenation*, J. G. de Vries, C. J. Elsevier, Eds. (Wiley-VCH, 2007), pp. 1483–1516.
11. J. M. Hoyt *et al.*, *Organometallics* **33**, 5781–5790 (2014).
12. J. A. Osborn, F. H. Jardine, J. F. Young, G. Wilkinson, *J. Chem. Soc. A* **0**, 1711–1732 (1966).
13. P. S. Hallman, D. Evans, J. A. Osborn, G. Wilkinson, *Chem. Commun. (Camb.)* **0**, 305–306 (1967).
14. R. R. Schrock, J. A. Osborn, *J. Am. Chem. Soc.* **98**, 2134–2143 (1976).
15. D. A. Dobbs *et al.*, *Angew. Chem. Int. Ed.* **39**, 1992–1995 (2000).
16. B. Abou-Khalil, *Neuropsychiatr. Dis. Treat.* **4**, 507–523 (2008).
17. J. Surtees, V. Marmon, E. Differding, V. Zimmerman, PCT international application patent WO 2001064637 A1 (2001).
18. C. R. Landis, J. Halpern, *J. Am. Chem. Soc.* **109**, 1746–1754 (1987).
19. B. D. Vineyard, W. S. Knowles, M. J. Sabacky, G. L. Bachman, D. J. Weinkauff, *J. Am. Chem. Soc.* **99**, 5946–5952 (1977).
20. D. Prat *et al.*, *Org. Process Res. Dev.* **17**, 1517–1525 (2013).
21. X. Ma, M. Lei, *J. Org. Chem.* **82**, 2703–2712 (2017).
22. G. Hilt, *Eur. J. Org. Chem.* **2012**, 4441–4451 (2012).
23. D. K. Kim, J. Riedel, R. S. Kim, V. M. Dong, *J. Am. Chem. Soc.* **139**, 10208–10211 (2017).
24. M. R. Friedfeld, G. W. Margulieux, B. A. Schaefer, P. J. Chirik, *J. Am. Chem. Soc.* **136**, 13178–13181 (2014).
25. T. J. Korstanje, J. I. van der Vlugt, C. J. Elsevier, B. de Bruin, *Science* **350**, 298–302 (2015).

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SUPPLEMENTARY MATERIALS

www.sciencemag.org/content/360/6391/888/suppl/DC1
Materials and Methods
Figs. S1 to S54
Tables S1 to S30
References (*26*–*29*)

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Cobalt-catalyzed asymmetric hydrogenation of enamides enabled by single-electron reduction

Max R. Friedfeld, Hongyu Zhong, Rebecca T. Ruck, Michael Shevlin and Paul J. Chirik

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Reduction can make cobalt act precious

Enzymes rely on abundant metals such as iron and nickel to manipulate hydrogen. Chemists, on the other hand, have largely had to rely on precious metals such as platinum and rhodium for the task. Friedfeld *et al.* now report a simple trick to make cobalt act more like rhodium. Reduction of Co(II) to Co(I) by zinc reinforced binding of phosphine ligands to the metal to facilitate its use in asymmetric hydrogenation of alkenes. The cobalt catalysts tolerated alcohol solvents, unlike their rhodium congeners, and could be applied to a 200-gram-scale reduction at 0.08% loading.

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