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# Enantiopure $C_1$-Symmetric Bis(imino)pyridine Cobalt Complexes for Asymmetric Alkene Hydrogenation

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Supporting Information

**ABSTRACT:** Enantiopure $C_1$-symmetric bis(imino)-pyridine cobalt chloride, methyl, hydride, and cyclometalated complexes have been synthesized and characterized. These complexes are active as catalysts for the enantioselective hydrogenation of geminal-disubstituted olefins.

Asymmetric hydrogenation of alkenes is one of the most prominent and well-established methods for the synthesis of single-enantiomer products and has found numerous applications in the pharmaceutical, agrochemical, and fine-chemical industries.[1,2] The vast majority of catalysts are based on precious metals, with ruthenium, rhodium, and iridium being the most common.[2,3] Replacing these expensive and toxic elements with more abundant and environmentally compatible first-row transition metals such as iron and cobalt is attractive and an area of catalysis gaining renewed attention.[4,5] While advances in asymmetric iron-catalyzed ketone reduction have been made,[6] examples of enantioselective base-metal-catalyzed alkene hydrogenation are elusive. Ohgo and co-workers[7] have reported the asymmetric hydrogenation of alkenes with low optical yields (7−49%) using dimethylglyoximatocobalt(II) compounds in the presence of quinine. Pfaltz and co-workers[8] reported the hydrogenation of $\alpha,\beta$-unsaturated esters using in situ-generated cobalt semicorrin complexes. While good yields and enantioselectivities (up to 96%) were reported, the use of $NaBH_4$ as stoichiometric reductant is a limitation. Iglesias and co-workers[9] have likewise reported asymmetric hydrogenation with an enantiopure 2-aminocarbonylpyrrolide cobalt(I) complex. Although the activity was modest (~3 $hr^{-1}$), a promising enantioselectivity of 74% was reported for the catalytic hydrogenation of ethyl-$\alpha$-benzoylaminocinnamate.

Aryl-substituted bis(imino)pyridine iron and cobalt compounds have emerged as an effective class of base-metal olefin hydrogenation catalysts. Pioneering studies by Budzelaar and co-workers established the utility of bis(imino)pyridine cobalt dichloride (activated with excess $Al^iBu_3$) and alkyl complexes for the hydrogenation of 1- and 2-alkenes.[10] Spectroscopic and computational studies support the formation of a Co−H bond followed by olefin insertion and turnover-limiting $\sigma$-bond metathesis of the metal alkyl with $H_2$. Our laboratory has reported the high activity[11,12] and functional group tolerance[13] of bis(imino)pyridine iron dinitrogen compounds for the hydrogenation of a range of alkenes. In all cases studied to date, the bis(imino)pyridine ligand and accordingly the corresponding iron or cobalt precursor has been $C_{2v}$-symmetric and hence achiral. Thus, modified ligand architectures are needed to generate single-enantiomer catalysts for asymmetric olefin hydrogenation.

One design, previously described by Bianchini and co-workers,[14] involves the preparation of $C_1$-symmetric bis-(imino)pyridines in which one imine is "anchored" by a large 2,6-diisopropylaryl ring and the other is prepared from a single enantiomer of a chiral alkyl amine (Figure 1). The large aryl substituent prevents the formation of catalytically inactive bis(chelate) metal complexes,[15] while the chiral alkylamines are attractive because of their commercial availability as single enantiomers. Cobalt methyl complexes were initial synthetic targets because of their relative ease of synthesis,[16] diamagnetism, and precedent as precatalysts for alkene hydrogenation.[10]

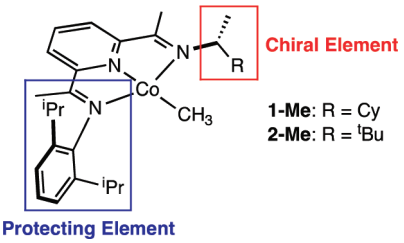
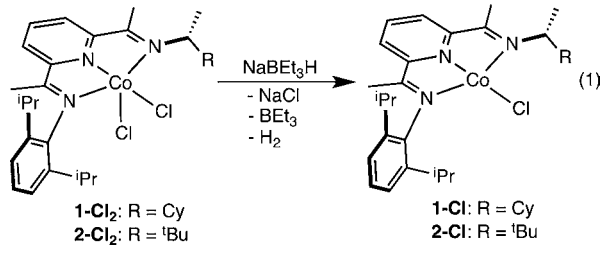



**Figure 1.** Design strategy for enantiopure, $C_1$-symmetric bis(imino)-pyridine cobalt methyl complexes for asymmetric olefin hydrogenation and shorthand designations used in this work.

Treatment of the bis(imino)pyridine cobalt dichloride complexes **1-Cl$_2$** and **2-Cl$_2$** with 1 equiv of $NaBEt_3H$ followed by filtration and recrystallization furnished the corresponding cobalt monochlorides **1-Cl** and **2-Cl** as purple solids (eq 1). In each case, both antipodes were independently synthesized and isolated. In this study, the Cahn−Ingold−Prelog designators refer to the enantiomer of the amine used in the bis(imino)-

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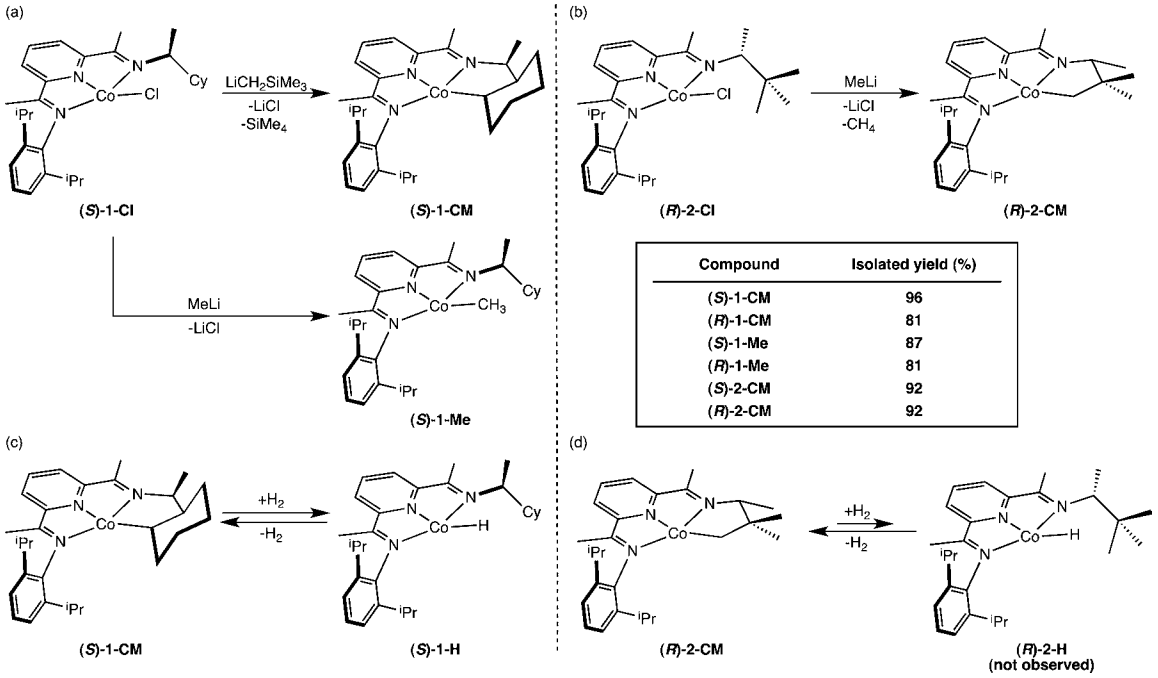
**Scheme 1. Preparation of (a) (*S*)-1-CM and (*S*)-1-Me and (b) (*R*)-2-CM; Hydrogenation of Bis(imino)pyridine Cobalt Complexes (c) (*S*)-1-CM and (d) (*R*)-2-CM**




| Compound | Isolated yield (%) |
|---|---|
| (*S*)-1-CM | 96 |
| (*R*)-1-CM | 81 |
| (*S*)-1-Me | 87 |
| (*R*)-1-Me | 81 |
| (*S*)-2-CM | 92 |
| (*R*)-2-CM | 92 |

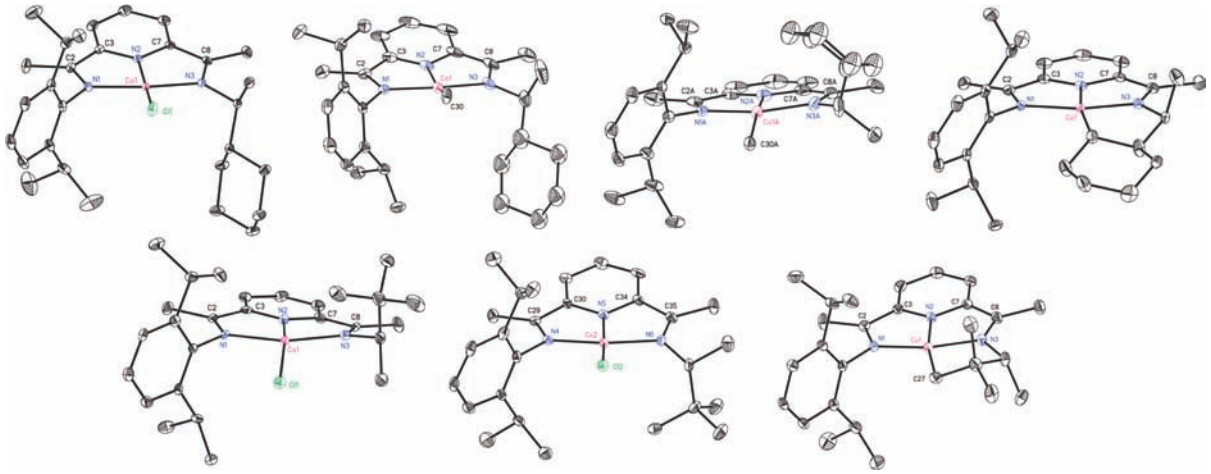


**Figure 2.** Representations of the solid-state structures of compounds reported in this work, shown with 30% probability ellipsoids. First row: (left) (*S*)-**1-Cl**; (middle) two molecules of (*S*)-**1-Me**; (right) (*S*)-**1-CM**. Second row: (left, middle) two molecules of (*R*)-**2-Cl**; (right) (*R*)-**2-CM**. H atoms and solvent molecules have been omitted for clarity. For (*R*)-**2-CM**, only one of three molecules in the asymmetric unit is shown.

pyridine synthesis. Three examples, (*R*)-**1-Cl**, (*S*)-**1-Cl**, and (*R*)-**2-Cl**, were crystallographically characterized; representations of (*S*)-**1-Cl** and (*R*)-**2-Cl** are presented in Figure 2, while (*R*)-**1-Cl** is presented in the Supporting Information.

Consistent with previously reported bis(imino)pyridine halide and alkyl complexes,[17,18] each of the bis(imino)pyridine cobalt chloride complexes is diamagnetic and exhibits $^{1}$H and $^{13}$C NMR spectral properties diagnostic of a thermal population of a triplet excited state (20 °C). The solid-state structures establish distorted four-coordinate compounds in which the chloride ligand is slightly lifted from the idealized cobalt−chelate plane; the magnitude of the "lift" angle is dependent on the orientation of the substituents on the chiral amine. In both enantiomers of **1-Cl**, these are oriented such that the hydrogen atom is directed "back" toward the imine methyl group, placing the alkyl groups above and below the idealized metal−ligand plane. The chloride lift angle is 12.0° in both enantiomers. For (*R*)-**2-Cl**, however, two molecules are present in the asymmetric unit of the solid-state structure (Figure 2). These differ by the orientation of the substituents on the chiral amine: in one case, the hydrogen atom on the chiral carbon is directed toward the imine methyl group (as for **1-Cl**), while the second molecule has that hydrogen atom pointing at the chloride ligand. The lift angle of the chloride ligand varies from 12.5° to 16.0°, the higher lift angle being found when the proton of the chiral carbon points to the imine methyl group. In all cases, the chloride is positioned away from the larger of the alkyl groups (cyclohexyl or *tert*-butyl). The metrical parameters of the chelates signal redox activity[19] and one-electron reduction, confirming that these complexes have a low-spin Co(II) center antiferromagnetically coupled to a bis(imino)pyridine radical anion.[17]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The cobalt methyl complexes (*S*)- and (*R*)-**1-Me** were synthesized by straightforward methylation of the corresponding chloride compounds with MeLi (Scheme 1a). As with **1-Cl**, **2-Cl**, and other reported bis(imino)pyridine cobalt alkyls,[17,18] diamagnetic **1-Me** exhibits $^1$H and $^{13}$C NMR spectral features diagnostic of thermal population of a paramagnetic excited state at 20 °C in benzene-$d_6$. One enantiomer, (*S*)-**1-Me**, was also characterized by X-ray diffraction (Figure 2). The solid-state structure is similar to that of (*R*)-**2-Cl**, where two molecules are present in the asymmetric unit that differ by the orientation of the substituents on the chiral carbon (vide supra). The Co−Me lift angle ranges between 14.6° and 17.3° out of the idealized plane, with the Me directed away from the larger cyclohexyl substituent. The metrical parameters of the bis(imino)pyridine chelate are again consistent with one-electron reduction, establishing a low-spin Co(II) center antiferromagnetically coupled to a radical anion.[17−19]

Replacing MeLi with $LiCH_2SiMe_3$ in the alkylation of (*R*)- or (*S*)-**1-Cl** did not furnish the expected bis(imino)pyridine cobalt alkyl complex but rather resulted in isolation of the cyclometalated compound **1-CM** as a 4:1 mixture of two isomeric products in yields of 96% (*S*) and 81% (*R*) (Scheme 1a). The major products obtained with (*S*)-**1-Cl** and (*R*)-**1-Cl** were characterized by X-ray diffraction; the solid-state structure of the former is presented in Figure 2. Allowing a benzene-$d_6$ solution of **1-Me** to stand at ambient temperature for several days or heating to 80 °C for 5 h resulted in loss of methane and clean formation of the corresponding cyclometalated compound **1-CM** in a 1.7:1 ratio of isomeric products.[20] The identity of the minor product has not been definitively established; treatment of (*S*)-**1-CM** with 2,6-lutidinium deuterochloride regenerated (*S*)-**1-Cl** with the deuterium atom located exclusively within the cyclohexyl ring, but not in the methine position.[22] Both isomers of **1-CM** were converted to **1-H** upon exposure to $H_2$, diminishing the importance of the isomer assignment in the context of catalytic alkene hydrogenation.

Rapid cyclometalation was also observed during the attempted methylation of the enantiomers of the *tert*-butyl-substituted derivative **2-Cl** with MeLi. For both enantiomers, **2-CM** was isolated in 92% yield (Scheme 1b). Diastereotopic doublets were observed at 1.21 and 2.90 ppm in the benzene-$d_6$ $^1$H NMR spectrum for the methylene protons attached to cobalt. These resonances, along with diastereotopic methyl groups centered at 0.62 and 1.36 ppm, are diagnostic of cyclometalation. The *R* enantiomer of **2-CM** was characterized by X-ray diffraction (Figure 2, bottom right).

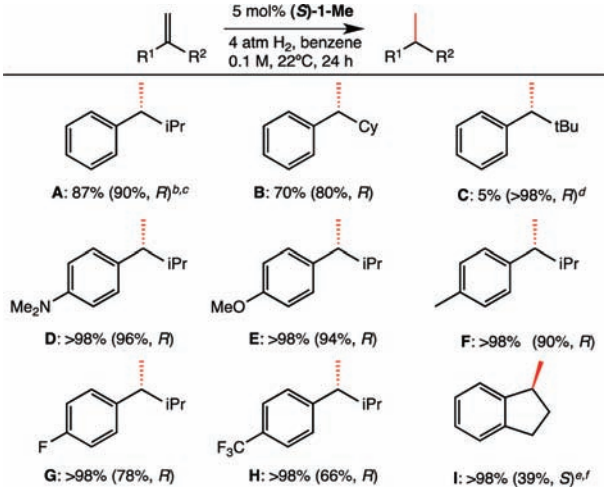
As bis(imino)pyridine cobalt hydrides have been postulated as key intermediates in alkene hydrogenation,[10] the synthesis of enantiopure examples was targeted. Exposure of a benzene-$d_6$ solution of either **1-Me** or **1-CM** to 4 atm $H_2$ resulted in rapid formation of **1-H** (Scheme 1c). The cobalt hydride was characterized by $^1$H NMR spectroscopy and was observable under a dihydrogen atmosphere. Removal of the excess $H_2$ resulted in regeneration of **1-CM**. In contrast, exposure of a benzene-$d_6$ solution of **2-CM** to 4 atm $H_2$ produced no observable change by $^1$H NMR spectroscopy, establishing that this chelate is more stable with respect to hydrogenation (Scheme 1d).

The enantiopurity of both enantiomers of **1-Me** was assessed by the method of Bercaw, where the cobalt alkyl complex was treated with (*S*)-2-methyl-1-butanethiol.[21] The $^1$H and $^{13}$C NMR spectra of the resulting cobalt thiolate complex (*S*,*S*)-**1-SR*** displayed no detectable resonances for (*R*,*S*)-**1-SR***, establishing an optical purity of >98% for (*S*)-**1-Me**.[22]

The enantiopure $C_1$-symmetric bis(imino)pyridine cobalt alkyl and cyclometalated complexes were evaluated as catalysts for the asymmetric hydrogenation of alkenes. A family of substituted styrenes was chosen for the initial screen because of their steric and electronic modularity and relative ease of preparation.[22] We were also interested in the asymmetric hydrogenation of unactivated, unfunctionalized alkenes, as these compounds remain a challenging substrate class for many established precious metal catalysts.[23]

Each catalytic hydrogenation was conducted with 5 mol % (*S*)-**1-Me** and 0.1 M alkene substrate in benzene and 4 atm $H_2$ at 22 °C. As reported in Table 1, (*S*)-**1-Me** is efficient for the hydrogenation of a range of substituted styrene derivatives. Higher activity was observed for less hindered substrates. The $^i$Pr derivative (**A**) reached 90% conversion in 24 h, while the more hindered cyclohexyl- and *tert*-butyl-substituted substrates (**B** and **C**, respectively) reached only 70 and 5%, respectively. Introduction of electron-donating and -withdrawing groups at the 4-position of the styrene had little impact on the activity, as complete conversion (>98%) to the alkane was observed in all cases within 24 h. Attempts to hydrogenate **A** with both enantiomers of **2-CM** produced no conversion; only starting material was observed by GC-FID in both catalytic and stoichiometric experiments. Notably, high enantiomeric excesses (>90% ee) were observed with most of the substrates studied, which to our knowledge represent the highest reported for a base-metal-catalyzed alkene hydrogenation using $H_2$ as the reductant. For the phenylated alkenes, enantiomeric excesses of 80−98% were obtained, with the more sterically crowded olefins producing higher selectivity, albeit with reduced activity. Introduction of electron-donating groups at the 4-position of the aryl ring increased the enantioselectivity of the reaction; values of 96 and 94% ee were measured for the [$NMe_2$]- and [OMe]-derivatives (**D** and **E** respectively). Consistent with this

**Table 1. Enantioselective Hydrogenation of Geminal-Disubstituted Alkenes with (*S*)-1-Me**[a]




[a]Conditions: 0.1 mmol of olefin, 5 μmol of catalyst, 1 mL of benzene. Yields were determined by GC-FID; ee's are shown in parentheses. [b]With (*R*)-**2-Me**: 85% (90% ee; *S* enantiomer). [c]With ($^{iPr}$PDI)Co(Me): 60%. [d]At 45 °C: 12% (0% ee). At 80 °C: 64% (0% ee). [e]Reaction time = 1 h. [f]With (*S*)-**2-CM**: 44% (96% ee; *S* enantiomer) and 56% 3-methyl-1*H*-indene.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trend, reduced ee values of 78 and 66% were determined for the [F]- and [$CF_3$]-derivatives (**G** and **H**, respectively). Optical rotation measurements on **A**, **D**, and **E** prepared from (*S*)-**1-Me** established the preferential formation of the *R* alkane.

The hydrogenation of the less hindered alkene, **I**, was also explored. Such substrates are more challenging for enantioselective hydrogenation because the steric differentiation required for facial discrimination is subtle. Quantitative hydrogenation of **I** with (*S*)-**1-Me** was observed in less than 1 h, but the enantiomeric excess was poor (39%). Performing the hydrogenation at 0 °C did little to improve enantioselectivity (41% ee). Using the more hindered and less active *tert*-butyl-substituted cobalt precatalyst (*S*)-**2-CM** produced 44% yield of the alkane at 22 °C in 24 h. In this case, optical rotation measurements established the preferential formation of the *S* alkane. Isomerization to 3-methyl-1*H*-indene accompanied hydrogenation and accounted for the balance of the material.

Gratifyingly, **I** was obtained in 96% ee, representing, to the best of our knowledge, the highest enantiomeric excess ever observed with any catalyst for this substrate. Improving the conversion by using increased pressures of $H_2$ is currently under study.

In summary, asymmetric hydrogenation of prochiral alkenes has been observed using enantiopure $C_1$-symmetric bis(imino)-pyridine cobalt precatalysts. Importantly, the presence of coordinating functionalities on the olefin is not required for high enantiomeric excess. High activity was related to the suppression of competing cyclometalation, a key feature for future catalyst design.

## ■ ASSOCIATED CONTENT

### Supporting Information

Complete experimental details; the $^1$H NMR spectrum of (*S*)-**1-H**; and crystallographic data for (*R*)-**1-Cl**, (*S*)-**1-Cl**, (*S*)-**1-Me**, (*S*)-**1-CM**, (*R*)-**1-CM**, (*R*)-**2-CM**, and (*R*)-**2-Cl**. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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## ■ REFERENCES

(1) (a) Noyori, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 2008. (b) Knowles, W. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 1999.

(2) (a) Johnson, N. B.; Lennon, I. C.; Moran, P. H.; Ramsden, J. A. *Acc. Chem. Res.* **2007**, *40*, 1291. (b) Schultz, C. S.; Krska, S. W. *Acc. Chem. Res.* **2007**, *40*, 1320. (c) Roseblade, S. J.; Pfaltz, A. *Acc. Chem. Res.* **2007**, *40*, 1402. (d) Minnaard, A. J.; Feringa, B. L.; Lefort, L.; De Vries, J. G. *Acc. Chem. Res.* **2007**, *40*, 1267. (e) Hoge, G. *J. Am. Chem. Soc.* **2003**, *125*, 10219.

(3) Pfaltz, A.; Blankenstein, J.; Hilgraf, R.; Hörmann, E.; McIntyre, S.; Menges, F.; Schönleber, M.; Smidt, S. P.; Wüstenberg, B.; Zimmermann, N. *Adv. Synth. Catal.* **2003**, *345*, 33.

(4) (a) Nakazawa, H.; Itazaki, M. *Top. Organomet. Chem.* **2011**, *33*, 27. (b) Mancheño, O. G. *Angew. Chem., Int. Ed.* **2011**, *50*, 2216 and references therein. (c) Enthaler, S.; Junge, K.; Beller, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3317.

(5) Chirik, P. J.; Wieghardt, K. W. *Science* **2010**, *327*, 794.

(6) (a) Lagaditis, P. O.; Lough, A. J.; Morris, R. H. *J. Am. Chem. Soc.* **2011**, *133*, 9662. (b) Sues, P. E.; Lough, A. J.; Morris, R. H. *Organometallics* **2011**, *30*, 4418. (c) Mikhailine, A.; Lough, A. J.; Morris, R. H. *J. Am. Chem. Soc.* **2009**, *131*, 1394. (d) Mikhailine, A.; Morris, R. H. *Inorg. Chem.* **2010**, *49*, 11039.

(7) Ohgo, Y.; Takeuchi, S.; Natori, Y.; Yoshimura, J. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 2124.

(8) Leutenegger, U.; Madin, A.; Pfaltz, A. *Angew. Chem.* **1989**, *101*, 61.

(9) Corma, A.; Iglesias, M.; del Pino, C.; Sánchez, F. *J. Organomet. Chem.* **1992**, *431*, 233.

(10) Knijnenburg, Q.; Horton, A. D.; van der Heijden, H.; Kooistra, T. M.; Hetterscheid, D. G. H.; Smits, J. M. M.; de Bruin, B.; Budzelaar, P. H. M.; Gal, A. W. *J. Mol. Catal.* **2005**, *232*, 151.

(11) (a) Bart, S. C.; Lobkovsky, E.; Chirik, P. J. *J. Am. Chem. Soc.* **2004**, *126*, 13794. (b) Archer, A. M.; Bouwkamp, M. W.; Cortez, M.-P.; Lobkovsky, E.; Chirik, P. J. *Organometallics* **2006**, *25*, 4269.

(12) Russell, S. K.; Darmon, J. M.; Lobkovsky, E.; Chirik, P. J. *Inorg. Chem.* **2010**, *49*, 2782.

(13) Trovitch, R. J.; Lobkovsky, E.; Bill, E.; Chirik, P. J. *Organometallics* **2008**, *27*, 1470.

(14) Bianchini, C.; Mantovani, G.; Meli, A.; Migliacci, F.; Zanobini, F.; Laschi, F.; Sommazzi, A. *Eur. J. Inorg. Chem.* **2003**, 1620.

(15) (a) Tondreau, A. M.; Darmon, J. M.; Wile, B. M.; Floyd, S. K.; Lobkovsky, E.; Chirik, P. J. *Organometallics* **2009**, *28*, 3928. (b) Wile, B. M.; Trovitch, R. J.; Bart, S. C.; Tondreau, A. M.; Lobkovsky, E.; Milsmann, C.; Bill, E.; Wieghardt, K.; Chirik, P. J. *Inorg. Chem.* **2009**, *48*, 4190.

(16) (a) Kooistra, T. M.; Knijnenburg, Q.; Smits, J. M. M.; Horton, A. D.; Budzelaar, P. H. M.; Gal, A. W. *Angew. Chem., Int. Ed.* **2001**, *40*, 4719. (b) Gibson, V. C.; Humphries, M. J.; Tellmann, D. F.; Wass, A. J. P.; Williams, D. J. *Chem. Commun.* **2001**, 2252.

(17) (a) Knijnenburg, Q.; Hetterscheid, D.; Kooistra, T. M.; Budzelaar, P. H. M. *Eur. J. Inorg. Chem.* **2004**, 1204. (b) Humphries, M. J.; Tellmann, K. P.; Gibson, V. C.; White, A. J. P.; Williams, D. J. *Organometallics* **2005**, *24*, 2039.

(18) Bowman, A. C.; Milsmann, C.; Bill, E.; Lobkovsky, E.; Weyhermüller, T.; Wieghardt, K.; Chirik, P. J. *Inorg. Chem.* **2010**, *49*, 6110.

(19) (a) Bart, S. C.; Chlopek, K.; Bill, E.; Bouwkamp, M. W.; Lobkovsky, E.; Neese, F.; Wieghardt, K.; Chirik, P. J. *J. Am. Chem. Soc.* **2006**, *128*, 13901. (b) Knijnenburg, Q.; Gambarotta, S.; Budzelaar, P. H. M. *Dalton Trans.* **2006**, 5442.

(20) At 45 °C, the conversion of **1-Me** to **1-CM** reached 10% after 24 h.

(21) Baar, C. R.; Levy, C. J.; Min, E. Y. J.; Henling, L. M.; Day, M. W.; Bercaw, J. E. *J. Am. Chem. Soc.* **2004**, *126*, 8216.

(22) See the Supporting Information for details.

(23) Bell, S.; Wuestenberg, B.; Kaiser, S.; Menges, F.; Netscher, T.; Pfaltz, A. *Science* **2006**, *311*, 642.