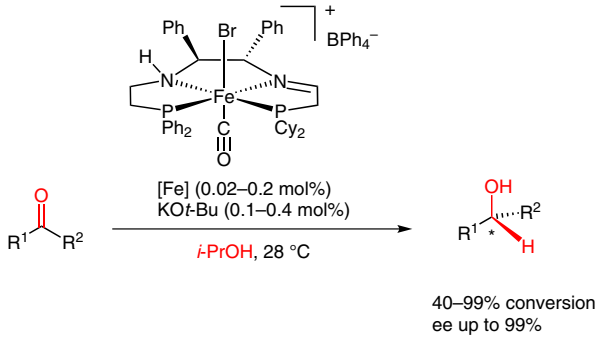
Synthesis S. A. M. Smith, R. H. Morris Paper

An Unsymmetrical Iron Catalyst for the Asymmetric Transfer Hydrogenation of Ketones

Samantha A. M. Smith
Robert H. Morris*

Department of Chemistry, University of Toronto,
80 St. George Street, Toronto, ON, M5S 3H6,
Canada
robert.morris@utoronto.ca

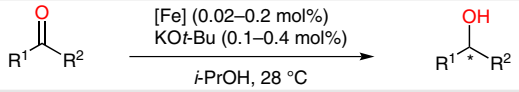


Received: 12.12.2014
Accepted: 14.01.2015
Published online: 20.02.2015
DOI: 10.1055/s-0034-1380147; Art ID: ss-2014-c0753-st

Abstract A new iron(II)(Ph_2P–NH–N–PCy_2) complex with a dicyclohexylphosphino group *trans* to the NH group was found to catalyze the asymmetric transfer hydrogenation of a variety of ketones with high enantioselectivity.

Key words hydrogenation, iron catalysis, chirality, ketones, alcohols

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



Scheme 1 General reaction scheme for the ATH of ketones

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

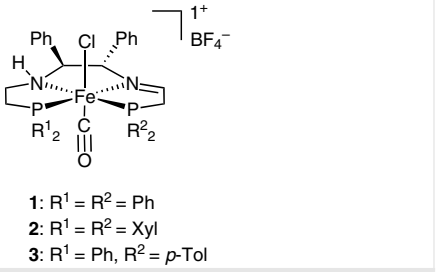
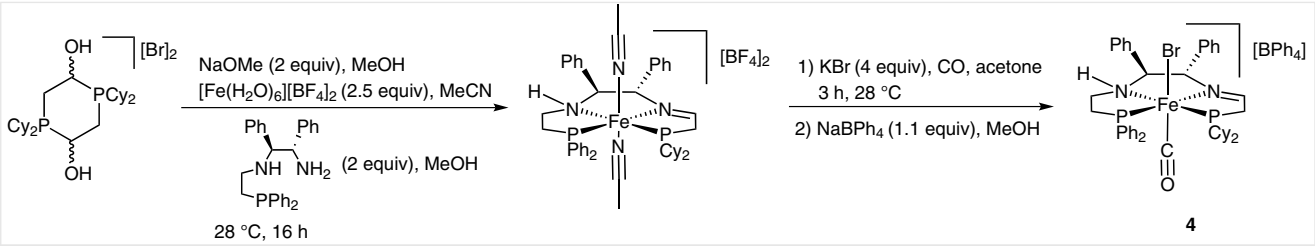


Figure 1 Third generation iron(II) complexes previously reported by our group

For the preparation of the catalyst, the incorporation of an N–H moiety in the tetradentate ligand required an intensive synthetic approach, where first an enantiomerically pure (*S*,*S*)-$R_2PCH_2CH_2NHCH(Ph)CH(Ph)NH_2$ [(*S*,*S*)-P-NH-NH_2] ligand was synthesized and isolated, which then underwent an iron-templated Schiff base condensation with an α-diarylphosphinoacetaldehyde to produce the P–NH–N–P ligand on iron. Complexes **1**–**3** differ only by the aryl phosphine groups, and complex **3** is so far the only example with unsymmetrical phosphine donors. We propose that the use of a more sterically hindered phosphine, such as a dicyclohexylphosphino group on the ligand, may improve



Scheme 2 Synthesis of the new iron(II) Ph_2P–NH–N–PCy_2 complex **4**

the enantioselectivity of this system, and this phosphine can be introduced in the final step of the templated ligand synthesis.

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

The new complex **4** was synthesized using a method similar to that employed for the preparation of **1** and **3** as described briefly above.[3m] Starting with the air- and moisture-stable dicyclohexylphosphonium dimer and the enantiomerically pure (*S*,*S*)-Ph_2P–NH–NH_2 ligand, the Schiff base condensation occurred via a metal-mediated template synthesis as shown in Scheme 2. Substitution of the two acetonitrile moieties with bromide and carbonyl, followed by salt exchange with sodium tetraphenylborate ($NaBPh_4$), afforded complex **4** as a yellow powder in moderate yield (40%) as a mixture of two diastereomers. This complex was characterized by NMR and IR spectroscopy and mass spectrometry. In the $^{31}P\{^1H\}$ NMR spectrum, characteristic doublets at 78.38 ppm and 47.34 ppm, as well as 76.05 ppm and 75.48 ppm corresponded to two structural isomers of the complex, the first being the major isomer (75%:25%). Presumably, one isomer would have its C=O *syn* to the N–H and the other would be *anti*. A carbonyl stretch (ν_{CO}) was found at 1951 cm^{-1}, which is typical for such a complex.

The catalytic activity of complex **4** was tested for the ATH of ketones **K1**–**K16** and one aldehyde, **A1** (Figure 2). For all substrates, the (*R*)-alcohol was produced when using our iron complexes, which have enantiopure (*S*,*S*)-ligands. The results are summarized in Table 1. Overall, complex **4** has a lower activity than **1**, however the enantiomeric excess values of a few substrates have been increased by using the bulky dicyclohexylphosphine. Entries 1–3 (Table 1) show the reduction of acetophenone under different conditions. An enantiomeric excess of 81% was observed when the catalyst/base/substrate (C/B/S) ratio was 1:2:500, but when the catalyst loading was reduced, the enantiomeric excess increased significantly to 93% and 98%, with two and eight equivalents of base, respectively. We found that complex **4** was slightly less active than **1** in the reduction of **K1**, giving a conversion of 11% lower, however the enantiomeric excess was increased significantly by 20%. In our previous work,[3m] we found that complex **2** was more enantioselective for the reduction of acetophenone with a 90% ee, but **4** proved to be superior. Substrates **K2** and **K4** were reduced with very high enantiomeric excess values of 94% and >99%, respectively, however, when a more bulky substrate such as **K3** was tested, no conversion was observed. The effective reduction of **K4** is noteworthy as Noyori-type catalysts do not hydrogenate this substrate.[5] When the substituents on the phenyl ring were varied as for substrates **K5**–**K8**, different effects on the catalysis were observed. Complex **4** gave very high conversions of chloro-substituted ketones **K5** and **K6**, but afforded lower conversions of methyl- and trifluo-

Table 1 Catalytic Results for the ATH of Substrates **K1**–**K16** and **A1** Using Complex **4**[a]

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

[a] Catalyst/base/substrate (C/B/S) ratio = 1:2:500 unless otherwise stated.
[b] Conversion and ee determined by chiral GC.
[c] TON = turnover number.
[d] C/B/S = 1:2:6121.
[e] C/B/S = 1:8:6121.
[f] C/B/S = 1:8:500.

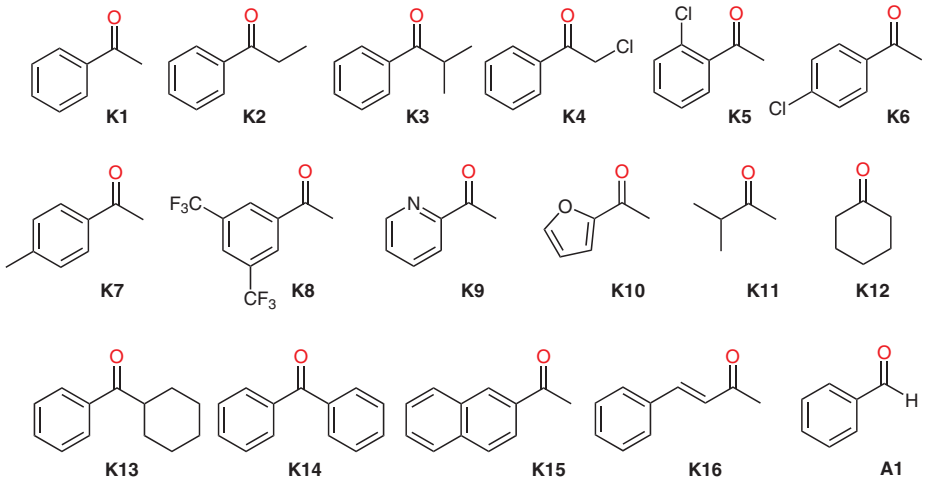
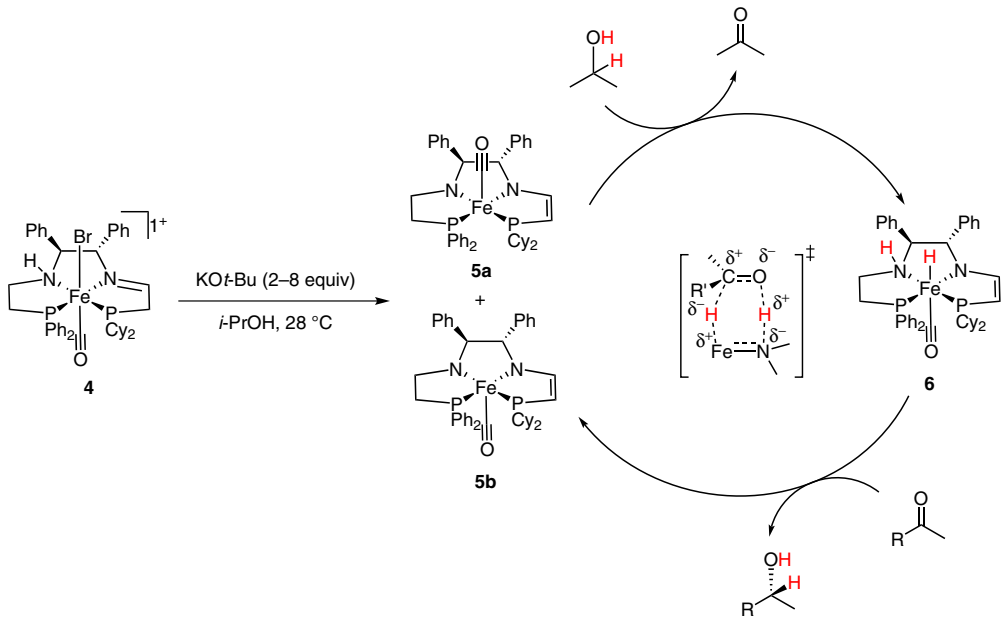


Figure 2 Substrate scope for ATH using complex **4**

romethyl-substituted ketones **K7** and **K8**. The enantiomeric excess values of the more sterically hindered *ortho*- and *meta*-substituted ketones **K5** and **K8** were higher (94% and 95%, respectively) than the *para*-substituted ketones **K6** and **K7**. Complex **4** gave a higher enantiomeric excess (95%) for substrate **K8** than **1** (90%), however, the activity was much lower with only 38% conversion. The resulting alcohol serves as an intermediate in the synthesis of Aprepitant to combat nausea associated with cancer chemotherapy.[6] Complex **4** was found to tolerate an imine functional group with the high conversion of acetylpyridine (**K9**) to (*R*)-α-methyl-2-pyridinemethanol, however, catalysis stopped in the presence of the oxygen-functionalized acetylfuran (**K10**).

Alkyl ketones **K11** and **K12** are deactivated toward reduction by complex **4** with conversions of 44% and 0%, respectively, as is the bulky cyclohexylphenyl ketone **K13**. High conversions of benzophenone (**K14**) and 1-(naphthalen-2-yl)ethanone (**K15**) were observed, with an enantiomeric excess of 80%, matching complex **1**, for the production of (*R*)-α-methyl-2-naphthalenemethanol. The ATH of the olefinic aryl ketone **K16** resulted in a non-selective reduction of both the C=O and C=C bonds, with a 40% conver-



Scheme 3 Proposed catalytic cycle for the ATH of ketones

sion to reduced products and only a 5% ee of the olefin (*R*)-alcohol. This is different compared to complex **1**, which reduced only the C=O moiety, albeit with a low yield (55%). Lastly, the hydrogenation of benzaldehyde (**A1**) was very efficient with quantitative conversion in 10 minutes. The products of the reduction of **K5**, **K8**, and **K9** were isolated via extraction from brine with diethyl ether, and filtration through a pad of Celite. The alcohols 1-(2-chlorophenyl)ethanol and 1-(2-pyridyl)ethanol were isolated in 75% and 58% yields and 95% and 34% ee values, respectively, without any starting ketone being present. The reduction of **K8** did not go to completion, however, and the alcohol was distilled with a resulting yield of only 30% and an enantiomeric excess of 94%.

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

In conclusion, a newly developed unsymmetrical tetradentate P–NH–N–P′ ligand has been synthesized on iron. The new precatalyst **4** was tested in the ATH of C=O bonds and gave a turnover number (TON) of up to 4300 and an enantiomeric excess of up to 99%. In comparing the dicyclohexylphosphino-substituted complex **4** with the previously reported diphenylphosphino complex **1** in the ATH of ketones, we found that the enantioselectivity of this system was increased at the expense of catalytic activity. For example, acetophenone, usually a challenging substrate for enantioselective reduction,[1e] was hydrogenated with a resulting enantiomeric excess of 98%. The flexible synthesis of our third generation catalysts offers the possibility of tuning their structure for the optimum reduction of a given substrate. This is currently under investigation.

All manipulations were performed under an inert atmosphere of either N_2 or Ar using Schlenk techniques or a glovebox, unless otherwise stated. Solvents were dried and degassed under standard procedures prior to use. IR spectra were obtained on samples prepared as KBr discs on a Paragon 500 spectrophotometer. NMR spectra were recorded at ambient temperature and pressure using an Agilent DD2 600 MHz spectrometer [^{1}H (600 MHz) and ^{31}P{^{1}H} (242 MHz)]. The ^{31}P NMR spectra were referenced to 85% H_3PO_4 (0 ppm). The electrospray ionization mass spectrometry (ESI–MS) data were collected on an AB/Sciex QStar mass spectrometer with an ESI source.

trans-(*S*,*S*)-[Fe(Br)(CO)($Ph_2PCH_2CH_2NHCHPhCH$-$PhN=CHCH_2PCy_2$)][BPh_4] (4)

In a glovebox, NaOMe (64 mg, 1.176 mmol) was added to a 100 mL Schlenk flask charged with a stir bar and dicyclohexylphosphonium bromide (378 mg, 5.88×10^{-1} mmol), and MeOH (25 mL) was added with stirring. This solution was stirred for no more than 2 min. A solution of $[Fe(H_2O)_6][BF_4]_2$ (496 mg, 1.47 mmol) dissolved in MeCN (20 mL) was added to the Schlenk flask, followed by a solution of (*S*,*S*)-$Ph_2PCH_2CH_2NHCH(Ph)CH(Ph)NH_2$ in MeOH (10 mL). This resulted in a purple solution which was left to stir at r.t. for 16 h, during which time a color change from purple to pink was observed. The solvent was removed in vacuo. KBr (140 mg, 4.70 mmol) was added to the flask which was sealed and removed from the glovebox. The flask was purged and placed under a CO atmosphere using Schlenk techniques. Acetone (20 mL), in a syringe, was removed from the glovebox and injected into the flask with stirring for 1.5 h. The solvent was removed under vacuum and the residual orange solid was redissolved in acetone (20 mL) while under a CO atmosphere. The solution was stirred for 1 h, after which the solvent was removed and the flask transferred into the glovebox, where the remaining steps occurred. The solid residue was dissolved in CH_2Cl_2 (20 mL) and filtered through a pad of Celite, then through a 25 mm Syringe Filter PTFE membrane (pore size 0.45 µm). The clear orange solution was dried in vacuo and then redissolved in a minimum amount of MeOH. This solution was added to a vial charged with a stir bar and $NaBPh_4$ (402 mg, 1.294 mmol) dissolved in a minimum volume of MeOH, from which a yellow solid precipitated. This solid was filtered off, washed with Et_2O (3 × 15 mL) and dried overnight. If the purity by NMR was not sufficient, the solid was redissolved in a minimum volume of CH_2Cl_2 and precipitated out by addition of Et_2O.

Yield: 530 mg (40%); yellow powder.

IR (KBr): 1951 (CO) cm^{-1}.

^{1}H NMR (600 MHz, CD_2Cl_2): δ = 1.19–1.94 [m, 22 H, P(C_6H_{11})$_2$], 2.58 (m, 2 H, CH_2), 2.74 (m, 2 H, CH_2), 4.38 (t, J_{HH} = 11.88 Hz, 2 H, PCH_2), 4.76 [t, J_{HH} = 12.14 Hz, 1 H, N(H)(Ph)], 4.83 [m, 1 H, N(H)(Ph)], 6.83–7.56 (m, 40 H, ArH), 7.79 (m, 1 H, N=CH).

^{31}P{^{1}H} NMR (242 MHz, CD_2Cl_2): δ = 78.38 and 47.34 (d, J_{PP} = 33.5 Hz, isomer 1), (d, J_{PP} = 33.48 Hz), 76.05 and 75.48 (d, J_{PP} = 38.7 Hz, isomer 2).

HRMS (ESI–TOF, CH_2Cl_2): *m*/*z* [M^+] calcd for $C_{43}H_{53}BrFeN_2OP_2$: 809.2084; found: 809.2070.

Asymmetric Transfer Hydrogenation; General Procedure (Table 1, Entries 1 and 4–19)

A 20 mL vial was charged with a stir bar and complex **4** (10 mg, 8.9×10^{-3} mmol). The substrate (4.43 × 10 mmol) was added and the mixture stirred. If the substrate was a liquid, the mixture was stirred until complex **4** had completely dissolved. *i*-PrOH (3.61 g) was added and the solution was stirred for 5 min. A stock solution of *t*-BuOK (20 mg, 0.18 mmol) in *i*-PrOH (0.98 g) was stirred until all the base had dissolved. This stock solution (0.1 g or 0.4 g, 2 and 8 equiv, respectively) was diluted with *i*-PrOH (1.0 g or 0.7 g, respectively) and added to the reaction vial to activate the precatalyst and start catalysis. Samples (0.1 mL) were taken via syringe and injected into Teflon-sealed GC vials prepared with wet, aerated *i*-PrOH to quench catalysis.

Asymmetric Transfer Hydrogenation; General Procedure (Table 1, Entries 2 and 3)

The quantity of the precatalyst was measured via a stock solution method. A concentrated stock solution was made by dissolving complex **4** (22 mg, 1.97×10^{-2} mmol) in cold CH_2Cl_2 (6.08 g). After all the solid had dissolved, the solution was immediately sucked into a syringe. The solution was then divided into equal portions into several 20 mL vials, such that each portion had 0.2 g of the stock solution, and then CH_2Cl_2 was removed in vacuo. These operations led to a precatalyst quantity of 6.48×10^{-4} mmol in each vial. The base was prepared by dissolving *t*-BuOK (10 mg, 0.089 mmol) in *i*-PrOH (1.02 g, 1.30 mL). *i*-PrOH (6.63 g, 8.44 mL), substrate (3.95 mmol) and a clean stir bar were added to the vial that contained the precatalyst and the resulting solution was stirred for 5 min, or until all the precatalyst had dissolved. The base stock solution (0.015 g or 0.06 g, 2 or 8 equiv base) was added to a vial that contained *i*-PrOH (0.546 g or 0.501 g, respectively), and the mixed solution was then added to the catalyst solution to start the catalytic reaction. Samples (0.1 mL) were taken via syringe and injected into Teflon-sealed GC vials prepared with wet, aerated *i*-PrOH to quench catalysis.

Acknowledgment

NSERC is thanked for a Discovery Grant to R.H.M. S.A.M. thanks Digital Specialty Chemicals Ltd. for an OGSST Scholarship.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1380147.

References

(1) (a) Knowles, W. S.; Noyori, R. *Acc. Chem. Res.* **2007**, *40*, 1238. (b) Dupau, P. *Top. Organomet. Chem.* **2012**, *42*, 47. (c) Saudan, L. A. *Acc. Chem. Res.* **2007**, *40*, 1309. (d) Noyori, R. *Adv. Synth. Catal.* **2003**, *345*, 15. (e) Noyori, R.; Ohkuma, T. *Angew. Chem. Int. Ed.* **2001**, *40*, 40.

(2) Morris, R. H. *Chem. Soc. Rev.* **2009**, *38*, 2282.

(3) (a) Chen, J. S.; Chen, L. L.; Xing, Y.; Chen, G.; Shen, W. Y.; Dong, Z. R.; Li, Y. Y.; Gao, J. X. *Acta Chim. Sin.* **2004**, *62*, 1745. (b) Sui-Seng, C.; Freutel, F.; Lough, A. J.; Morris, R. H. *Angew. Chem. Int. Ed.* **2008**, *47*, 940. (c) Mikhailine, A. A.; Lough, A. J.; Morris, R. H. *J. Am. Chem. Soc.* **2009**, *131*, 1394. (d) Meyer, N.; Lough, A. J.; Morris, R. H. *Chem. Eur. J.* **2009**, *15*, 5605. (e) Zhou, S.; Fleischer, S.; Junge, K.; Das, S.; Addis, D.; Beller, M. *Angew. Chem. Int. Ed.* **2010**, *49*, 8121. (f) Lagaditis, P. O.; Lough, A. J.; Morris, R. H. *J. Am. Chem. Soc.* **2011**, *133*, 9662. (g) Sues, P. E.; Lough, A. J.; Morris, R. H. *Organometallics* **2011**, *30*, 4418. (h) Yu, S.; Shen, W.; Li, Y.; Dong, Z.; Xu, Y.; Li, Q.; Zhang, J.; Gao, J. *Adv. Synth. Catal.* **2012**, *354*, 818. (i) Mikhailine, A. A.; Maishan, M. I.; Lough, A. J.; Morris, R. H. *J. Am. Chem. Soc.* **2012**, *134*, 12266. (j) Mikhailine, A. A.; Maishan, M. I.; Morris, R. H. *Org. Lett.* **2012**, *14*, 4638. (k) Prokopchuk, D. E.; Morris, R. H. *Organometallics* **2012**, *31*, 7375. (l) Sonnenberg, J. F.; Coombs, N.; Dube, P. A.; Morris, R. H. *J. Am. Chem. Soc.* **2012**, *134*, 5893. (m) Zuo, W.; Li, Y.; Lough, A. J.; Morris, R. H. *Science* **2013**, *342*, 1080. (n) Sues, P. E.; Demmans, K. Z.; Morris, R. H. *Dalton Trans.* **2014**, *43*, 7650.

(4) (a) Berkessel, A.; Reichau, S.; von der Hoh, A.; Leconte, N.; Neudorfl, J. M. *Organometallics* **2011**, *30*, 3880. (b) Fleischer, S.; Werkmeister, S.; Zhou, S. L.; Junge, K.; Beller, M. *Chem. Eur. J.* **2012**, *18*, 9005. (c) Fleischer, S.; Zhou, S. L.; Werkmeister, S.; Junge, K.; Beller, M. *Chem. Eur. J.* **2013**, *19*, 4997. (d) Li, Y.; Yu, S.; Wu, X.; Xiao, J.; Shen, W.; Dong, Z.; Gao, J. *J. Am. Chem. Soc.* **2014**, *136*, 4031. (e) Lagaditis, P. O.; Sues, P. E.; Sonnenberg, J. F.; Wan, K. Y.; Lough, A. J.; Morris, R. H. *J. Am. Chem. Soc.* **2014**, *136*, 1367. (f) Zuo, W.; Tauer, S.; Prokopchuk, D. E.; Morris, R. H. *Organometallics* **2014**, *33*, 5791.

(5) Xu, Y.; Docherty, G. F.; Woodward, G.; Wills, M. *Tetrahedron: Asymmetry* **2006**, *17*, 2925.

(6) Brands, K. M. J.; Payack, J. F.; Rosen, J. D.; Nelson, T. D.; Candelario, A.; Huffman, M. A.; Zhao, M. M.; Li, J.; Craig, B.; Song, Z. J.; Tschaen, D. M.; Hansen, K.; Devine, P. N.; Pye, P. J.; Rossen, K.; Dormer, P. G.; Reamer, R. A.; Welch, C. J.; Mathre, D. J.; Tsou, N. N.; McNamara, J. M.; Reider, P. J. *J. Am. Chem. Soc.* **2003**, *125*, 2129.