ORGANOMETALLICS

Article

Cite This: *Organometallics* XXXX, XXX, XXX–XXX

pubs.acs.org/Organometallics

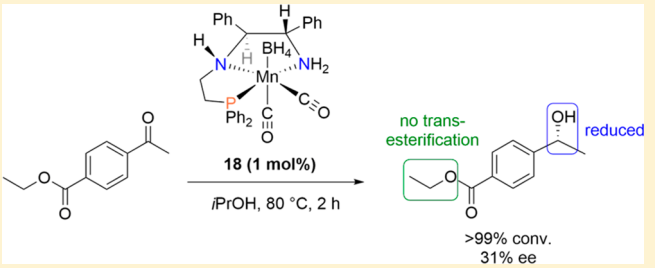
Asymmetric Transfer Hydrogenation of Ketones with Well-Defined Manganese(I) PNN and PNNP Complexes

Karl Z. Demmans, Maxwell E. Olson, and Robert H. Morris*

Department of Chemistry, University of Toronto, 80 Saint George Street, Toronto, Ontario M5S 3H6, Canada

Supporting Information

ABSTRACT: Three new manganese complexes *trans*-[Mn(P−NH−NH−P)(CO)$_2$][Br], (**14**) P−NH−NH−P = (*S*,*S*)-PPh$_2$CH$_2$CH$_2$NH−CHPhCHPhNHCH$_2$CH$_2$PPh$_2$), *fac*-[Mn(P′−NH−NH$_2$)(CO)$_3$][Br], (**15**) P′−NH−NH$_2$ = (*S*,*S*)-PPh$_2$(C$_6$H$_4$)NHCHPhCHPhNH$_2$, and *syn-mer*-Mn(P−NH−NH$_2$)(CO)$_2$Br, (**16**) P−NH−NH$_2$ = (*S*,*S*)-PPh$_2$CH$_2$CH$_2$NHCHPhCHPhNH$_2$ were synthesized and tested for the asymmetric transfer hydrogenation (ATH) of acetophenone in 2-PrOH. The ligands have stereogenic centers derived from the starting diamine, (*S*,*S*)-DPEN. Complex **16** was shown by NOE NMR experiments to have Mn−Br *syn* to the N−H of the secondary amine. Only the precatalyst **16**, upon reaction with potassium *tert*-butoxide (KO^{t}Bu) in 2-PrOH, generated an active system at 80 °C for the ATH of acetophenone to 1-phenylethanol in an enantiomeric excess (ee) of 42% and thus was selected for further investigation into the mechanism of transfer hydrogenation. The corresponding amido complex Mn(P−N−NH$_2$)(CO)$_2$ (**17**), a borohydride complex *syn-mer*-Mn(P−NH−NH$_2$)(CO)$_2$(BH$_4$) (**18**), and an ethoxide complex *anti-mer*-Mn(P−NH−NH$_2$)(CO)$_2$(OEt) (**19′**) were independently synthesized and tested in the ATH of acetophenone. The amido complex **17** and the borohydride complex **18** displayed similar activity to **16** activated in basic 2-PrOH, but the *anti* NH OEt complex **19′** was completely inactive. This result suggested that the NH effect, as described by Noyori, was required to obtain catalytic activity. The *syn* NH BH$_4$ manganese complex is one of the most active manganese ATH catalysts to date and can hydrogenate a variety of aromatic ketones, including base-sensitive substrates such as *p*-acetylbenzoate ethyl ester.



INTRODUCTION

Finding catalysts for the asymmetric hydrogenation of ketones, imines, and alkenes is a valuable pursuit as the enantiomerically pure products are of utmost importance to the fragrance, flavor, and pharmaceutical industries.[1−6] These products can be synthesized via asymmetric direct hydrogenation (ADH) under hydrogen gas, and ATH using ethanol or 2-PrOH as sacrificial alcohols. Other synthetic routes include ammonia-borane, sodium formate in water, or azeotropic mixtures of formic acid and triethylamine.[6−9] Ruthenium, rhodium, and iridium remain the most studied transition metals for the ATH of ketones, but there has been a recent push to use well-defined catalysts based on first-row transition metals..[10−28] To date, there are a rapidly growing number of well-defined iron ATH catalysts but only a few examples based on other first-row transition metals such as nickel,[23] cobalt,[29] or manganese.[30,31]

Notable among well-defined manganese hydrogenation catalysts are Beller's recently reported achiral Mn(P−N−P)(CO)$_2$Br and [Mn(P−N−P)(CO)$_3$][Br] (**1**, Figure 1) precatalysts for the direct hydrogenation (DH) of nitriles, ketones, esters, and aldehydes,[32,33] as well as a one example for the ADH of ketones with a [Mn(P*−N−P*)(CO)$_3$][Br] precatalyst containing stereogenic phospholane rings on the phosphorus donors (**2**, Figure 1).[34] Beller's achiral precatalysts also functioned in the transfer hydrogenation (TH) of ketones at 70 °C in 2-PrOH, producing a racemic mixture of alcohols in 24 h.[35] For the DH of esters, Pidko and co-workers synthesized achiral Mn(P−N)(CO)$_3$Br and [Mn(P−N)$_2$(CO)$_2$][Br] precatalysts, while Milstein and co-workers made achiral Mn(P−N−N)(CO)$_2$Br precatalysts containing a methylene-pyridine moiety to take advantage of their well-known dearomatization-rearomatization mechanism (**3** and **4** Figure 1).[36] Clarke and co-workers reported a chiral [Mn(P−NH−N)(CO)$_3$][Br] precatalyst with a ferrocenyl backbone of the P−NH−N ligand for the ADH of ketones (**5**, Figure 1).[37] For the TH of ketones, Sortais synthesized Mn(N−Y)-(CO)$_3$Br (where Y = N, O) precatalysts (**6a**,**b**, Figure 1).[30] Sortais probed the ATH of ketones by stirring bromopentacarbonylmanganese with a variety of chiral diamines in a 1:1 ratio to produce the active species in situ. While the exact structures of the precatalysts were not known, this study demonstrated that manganese catalysts with bidentate chiral diamines yield an ee of the product alcohols of up to 64%.[38] The most active and enantioselective manganese ATH catalyst to date was synthesized by Zirakzadeh and co-workers (characterized as diastereomeric hydrides species **7** and **7′**, Figure 1).[31] These hydride species required basic conditions to

Received: August 29, 2018

DOI: 10.1021/acs.organomet.8b00625
Organometallics XXXX, XXX, XXX–XXX

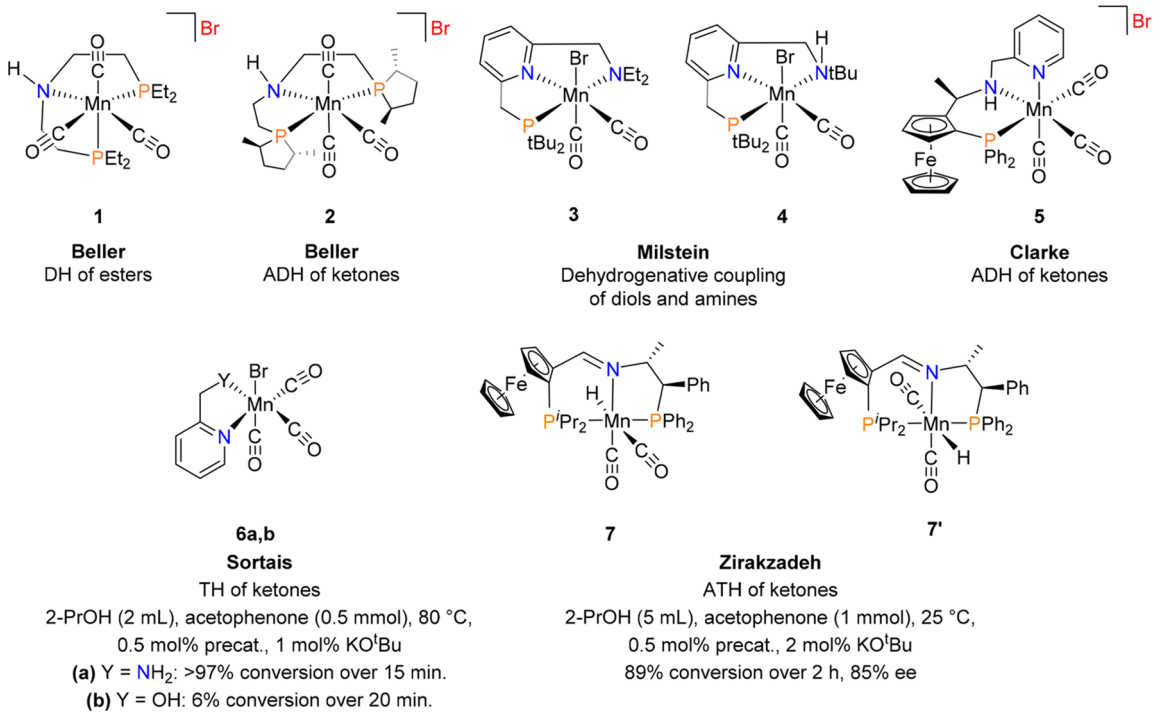


Figure 1. Well-defined manganese precatalysts.

achieve catalytic turnover. In optimized conditions with 0.5 mol % of precatalyst, alcohols with an ee of up to 85% could be obtained at room temperature in only 2 h.[31]

Reported herein are the syntheses, characterizations, and catalytic activities in the ATH of ketones for three new manganese catalysts based on previously reported tetradentate P−NH−NH−P and tridentate P′−NH−NH$_2$, P−NH−NH$_2$ ligands **8**−**10** (see Figure 2) derived from (*S*,*S*)-DPEN.[11,12,14]

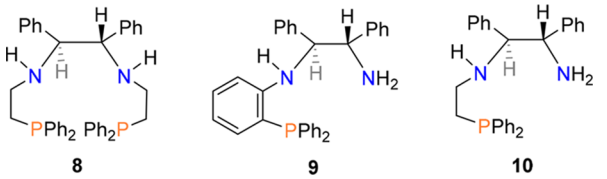


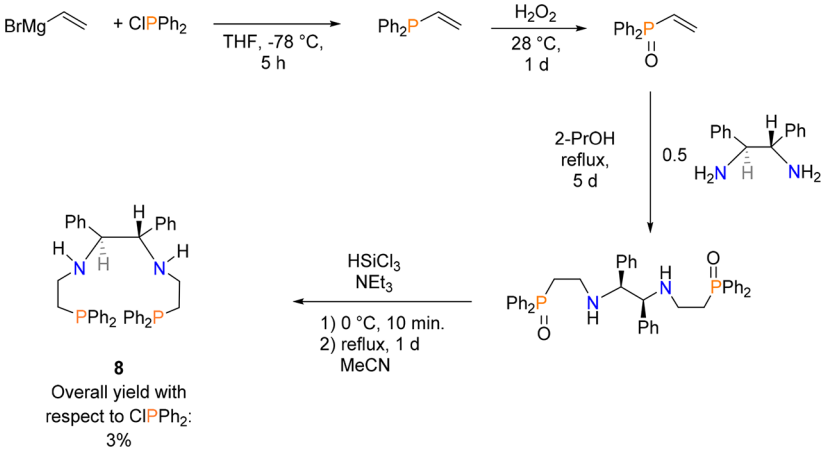
Figure 2. P−NH−NH−P, P′−NH−NH$_2$, and P−NH−NH$_2$ ligands.

RESULTS AND DISCUSSION

Improved Synthesis of the P−NH−NH−P Ligand. The previously reported synthesis of the P−NH−NH−P ligand **8** required four steps over 7 days, including a protection of the phosphine by oxidation and subsequent deprotection with trichlorosilane in basic conditions resulting in a very poor yield of **8** (Scheme 1).[11]

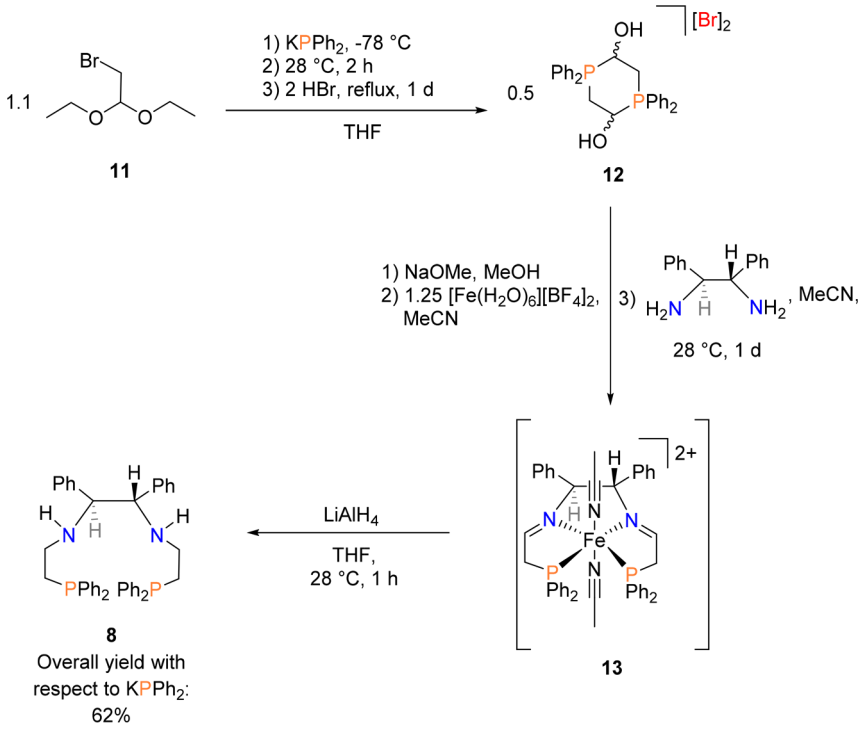
The new synthetic protocol was adapted from the synthesis of the P−NH−NH$_2$ ligand (**10**, Figure 2).[12] The air- and moisture-stable phosphonium dimer **12** (Scheme 2) was synthesized from the acetal **11** according to the literature.[17] All of the subsequent steps were then performed in a single-pot. The dimer **12** was deprotonated in basic methanol to release a diphenylphosphinoacetaldehyde, which undergoes an iron-templated condensation reaction with (*S*,*S*)-DPEN to produce the $[Fe(P-N-N-P)(MeCN)_2]^{2+}$ intermediate **13**, as previously reported.[17] Upon addition of lithium aluminum

Scheme 1. Previous Synthesis of the P−NH−NH−P Ligand 8

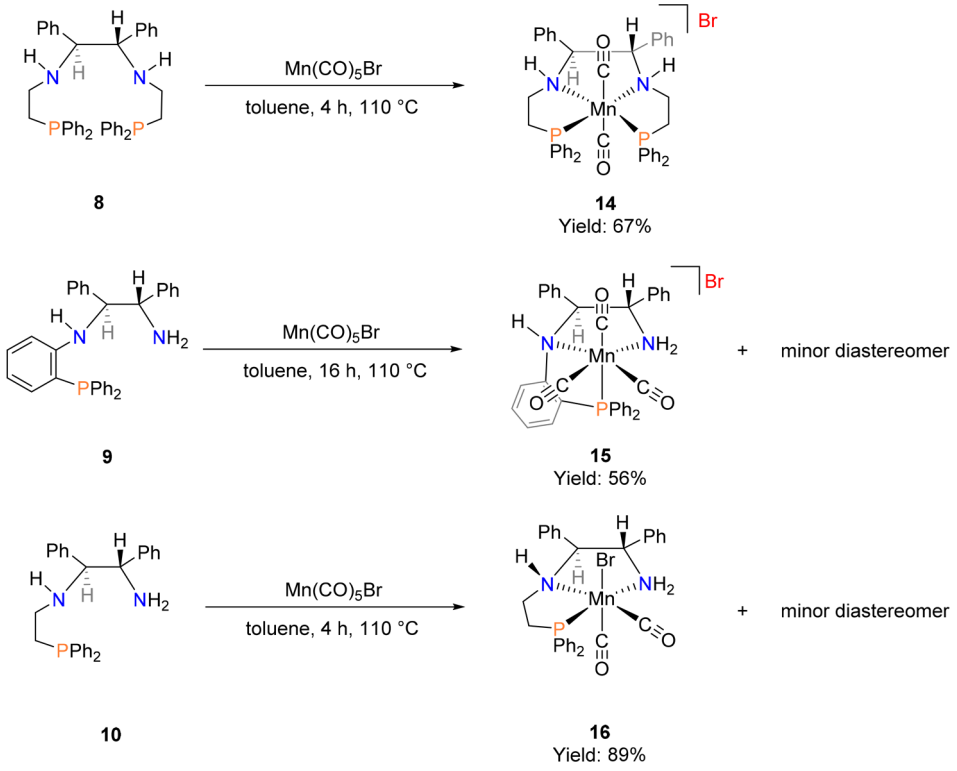


DOI: 10.1021/acs.organomet.8b00625
Organometallics XXXX, XXX, XXX−XXX

Scheme 2. New Synthetic Protocol for the Synthesis of the P−NH−NH−P Ligand 8



Scheme 3. Synthesis of New Manganese Complexes 14−16 with Ligands 8−10



hydride ($LiAlH_4$), the iron(II) was reduced to iron(0), and the imines of the P−N−N−P ligand were reduced to release the P−NH−NH−P ligand **8**. The extraction in the workup may be performed open to air and, if completed in less than 2 h, gives **8** with no observable oxidation of the 2-(diphenylphosphinyl)-ethyl group as confirmed in the $^{31}P\{^{1}H\}$ NMR spectrum. For long-term storage, however, the ligand must be placed under an inert atmosphere.

This alternative synthetic protocol reduced the total amount of time to synthesize the product by 5 days, replaced the energy-intensive hydroamination step with a simple condensation reaction performed at 28 °C (Scheme 2), and afforded the ligand **8** in moderate yield.

DOI: 10.1021/acs.organomet.8b00625
Organometallics XXXX, XXX, XXX−XXX

Table 1. IR Data for the Manganese Complexes 14−16 and Comparison with those of Reported Compounds

manganese complex[a]	CO stretches (cm^{-1})	reference
trans-[Mn(P−NH−NH−P)$(CO)_2$][Br], **14**	1930, 1854	this work
fac-[Mn(P′−NH−NH_2)$(CO)_3$][Br], **15**	2032, 1955, 1914	this work
fac-[Mn(P−N−P)$(CO)_3$][Br], **1**	2007, 1933, 1891	33
mer-[Mn(P*−N−P*)$(CO)_3$][Br], **2**	2009, 1908, 1821	34
fac-[Mn(P−N)$(CO)_3$][Br], **6b**	2029, 1936, 1911	30
fac-[Mn(P−N−N)$(CO)_3$][Br], **5**	1921, 1842	37
mer-Mn(P−NH−NH_2)$(CO)_2$Br, **16**	1915, 1828	this work
mer-Mn(P−N−N)$(CO)_2$Br, **3**	1916, 1829	40
mer-Mn(P−N−N)$(CO)_2$Br, **4**	1909, 1828	39

[a] *P** indicates stereogenic phospholane rings on the phosphorus donors.

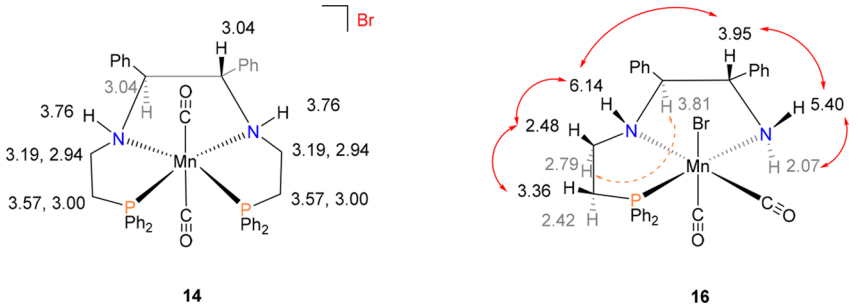


Figure 3. ^{1}H NMR resonances for **14** and **16** in DMSO-d_6. Selected 2D NOESY correlations are shown with arrows.

Synthesis of Manganese Complexes. Treatment of $Mn(CO)_5Br$ with each ligand **8−10** in toluene at 110 °C afforded the corresponding manganese complexes **14−16** in moderate to high yields as shown in Scheme 3.

Over the course of the reaction in toluene, complexes **14** and **15** precipitated out of solution to yield the manganese(I) di- or tricarbonyl bromide salt, respectively. These complexes are greater than 92% pure based on elemental analysis done three times but could not be crystallized to complete purity. Complex **14** has C_2 symmetry, making the two diphenylphosphino donors spectroscopically equivalent and producing a singlet in the $^{31}P\{^1H\}$ NMR spectrum. This symmetry, as indicated also by the ^{1}H NMR data, suggested that a *trans*-carbonyl complex was isolated, and indeed the infrared (IR) spectrum displays the asymmetric and symmetric stretches of the carbonyl ligands at 1930 and 1854 cm^{-1}, respectively. The IR spectrum of complex **15** displayed three stretches for the carbonyl ligands at 2032, 1955, and 1914 cm^{-1}, which suggested the isolation of the *fac*-isomer as the IR data matched closely to those of the precatalyst *fac*-[Mn(P′−N−P)$(CO)_3$][Br] that was crystallographically characterized by Beller and co-workers (**1**, Figure 1).[33−35] Our precatalysts *cis*-*β*-[Fe(P′−NH−NH−P)(CO)(Br)][BPh_4] (P′−NH−NH−P = **9** with an 2-(diphenylphosphinyl)ethyl arm) also preferentially bend at this aniline nitrogen.[14] Reaction of ligand **10** with $Mn(CO)_5Br$ initially formed a precipitate, but after stirring the solution for 4 h at 110 °C, it redissolved. The complex Mn(P−NH−NH_2)$(CO)_2$Br (**16**) was isolated after removal of the toluene in vacuo and washing with pentane and drying as an analytically pure mixture of diastereomers as indicated by the $^{31}P\{^1H\}$ and ^{1}H NMR spectra and elemental analysis. The *mer*-(P−NH−NH_2)-*cis*-dicarbonyl structure of the diastereomers was suggested on comparison with the IR spectrum known *mer*-Mn(P−N−N)$(CO)_2$Br complexes (Table 1).[31,39,40]

The 2D NMR spectra for the manganese complexes **14** and **16** were used to assign each proton, excluding aromatic protons (Figure 3), as outlined in the Supporting Information. The isomer of **16** shown in Scheme 3 is calculated by use of density functional theory (DFT) to be 1.4 kcal/mol more stable than the one with Mn−Br *anti* to NH of the secondary amine (labeled **16′** in the Supporting Information). The NMR spectra for manganese complex **15** indicated the presence of a minor diastereomer. Upon heating to 65 °C the ^{31}P NMR signal of the minor diastereomer disappears, concomitantly with the emergence of a new set of ^{1}H NMR signals (see the Supporting Information). This suggested the formation of a manganese complex bearing an uncoordinated phosphine donor which may broaden the ^{1}H NMR spectrum. A rapid acid−base equilibrium between the highly acidic protonated amino donor bearing a bromo counteranion **15** and the deprotonated manganese complex with hydrogen bromide may also lead to the broadening of the ^{1}H NMR spectrum in this case.

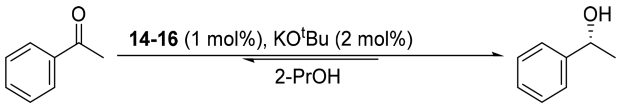
Activity in the ATH of Acetophenone. Manganese complexes **14−16** were tested in the ATH of acetophenone under optimized conditions to compare their catalytic activity. The results are shown in Table 2.

The catalytic activity of these manganese complexes activated in basic 2-PrOH was sluggish at 28 °C, prompting an increase in the temperature of the reaction vessels to 80 °C. *Fac*-[Mn(P′−NH−NH_2)$(CO)_3$][Br] **15** did not catalyze the ATH of acetophenone under these forcing conditions. *trans*-[Mn(P−NH−NH−P)$(CO)_2$][Br] **14** produced 1-phenylethanol in a 3% yield, while *mer*-Mn(P−NH−NH_2)$(CO)_2$Br **16** displayed high activity in basic 2-PrOH with a poor ee of 37%. Precatalyst **16** contains a bromo ligand which can be labilized upon addition of base to produce an amido manganese complex and potassium bromide, while the manganese salt complexes **14** and **15** do not contain a halide to allow for the facile formation of an open site on the manganese center

Activation Studies of Manganese Precatalyst. Further reactions were performed with **16** to detect possible catalytic

DOI: 10.1021/acs.organomet.8b00625
Organometallics XXXX, XXX, XXX−XXX

Table 2. Catalyst Screen for Activity in the ATH of Acetophenone at 28 and 80 °C[a]

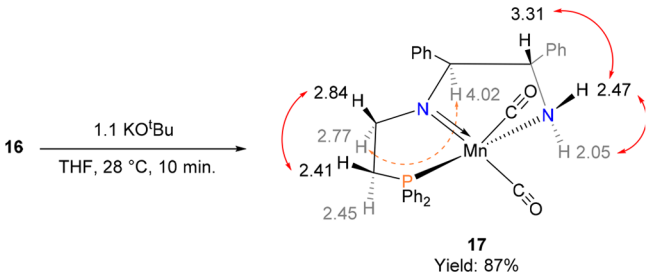


complex	temperature (°C)	conversion (%)	ee (%, (*R*)-alcohol)
none	28	0	-
	80	0	-
14	28	0	-
	80	3	68
15	28	0	-
	80	0	-
16	28	56	40
	80	>99	37

[a]Reactions performed under argon at 28 °C for 24 h or 80 °C for 1 h. Acetophenone:KO^{t}Bu:manganese complex ratio was 100:1:1. Volume of 2-PrOH = 8 mL. [acetophenone] = 0.312 M; [KO^{t}Bu] = 6.25×10^{-4} M; [Mn complex] = 3.13×10^{-4} M; [2-PrOH] = 13.1 M. (*R*)-1-Phenylethanol was the major product. Conversions and ee were determined using a gas chromatograph containing a chiral column. Di-*tert*-butylbenzene was used as an internal standard.

intermediates and synthesize a borohydride complex which enters the catalytic cycle without the addition of KO^{t}Bu. The first step in the activation of **16** was the deprotonation of an amine to form a manganese amido complex as shown in Scheme 4.

Scheme 4. Synthesis of the 5-Coordinate Mn(P−N−NH$_2$)(CO)$_2$ Complex 17. Assignment of ^{1}H NMR (C_6D_6) Resonances Made Using 2D NOESY Correlations (Arrows)

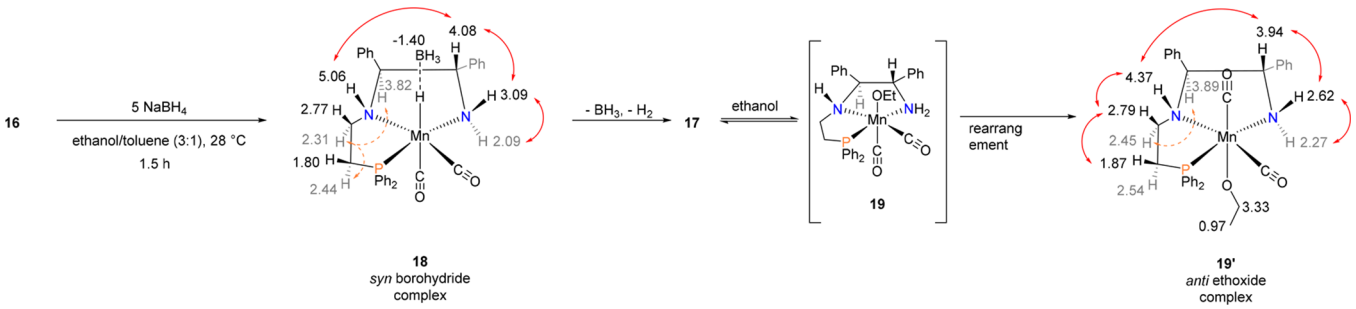


Upon addition of KO^{t}Bu to a bright yellow solution of **16** in THF, there was an immediate color change to deep red, which is characteristic of 5-coordinate manganese amido complexes.[41] The isolated red solid was very oxygen sensitive and characterized only by IR and NMR spectroscopy. The formation of this amido complex by deprotonation of the secondary amine of **16**, rather than the primary amine, was established by analysis of the ^{1}H NMR resonances (Scheme 4), which were assigned by using 2D ^{1}H−^{1}H COSY, 2D ^{1}H−^{1}H NOESY, and ^{1}H−^{13}C HSQC NMR experiments. The IR spectrum of **17** displayed two carbonyl stretches at 1890 and 1808 cm^{-1}, which are comparable to those of Mn(P−N−P)(CO)$_2$ and Mn(P−N−N)(CO)$_2$ complexes found in the literature.[41,42,40]

Several attempts were made to isolate a hydride species by mimicking catalytic conditions without the addition of the substrate. Three hydride species in minute amounts were observed by ^{1}H NMR spectroscopy at −4.12 (d, $^2J_{PH}$ = 72 Hz), − 4.63 (d, $^2J_{PH}$ = 36 Hz), and −4.73 (d, $^2J_{PH}$ = 38 Hz), but the structures of these hydride species could not be discerned because of their low concentration in solution. The attempted direct synthesis of a hydride species via a reaction of **16** with sodium triethylborohydride at −78 °C in toluene initially formed a bright yellow solution, but upon warming to 28 °C the solution immediately turned red. Removal of the solvent in vacuo indicated the presence of the amido complex **17** as confirmed in the ^{31}P{^{1}H} NMR spectrum. It is proposed that the hydride was formed, but preferentially releases hydrogen gas at 28 °C to form the more stable amido complex. Changing to a less reactive hydride source, sodium borohydride, and stirring the solution for 1.5 h produced the manganese borohydride complex containing the Mn−BH$_4$ *syn* to the NH of the secondary amine (**18** in Scheme 5). The yellow powder of **18** was very sensitive to oxygen and was characterized solely by NMR and IR spectroscopy. The *syn* isomer is calculated by use of density functional theory to be 3.8 kcal/mol more stable than the one with Mn−BH$_4$ *anti* to NH of the secondary amine (labeled **18′** in the Supporting Information). If the reaction was stirred for 16 h, then the isolated product was a manganese ethoxide complex containing the Mn−OEt *anti* to the NH of the secondary amine (**19′** in Scheme 5, wherein the apostrophe denotes the *anti* conformation). The yellow powder of **19′** was also very sensitive to the air and was characterized solely by NMR and IR spectroscopy.

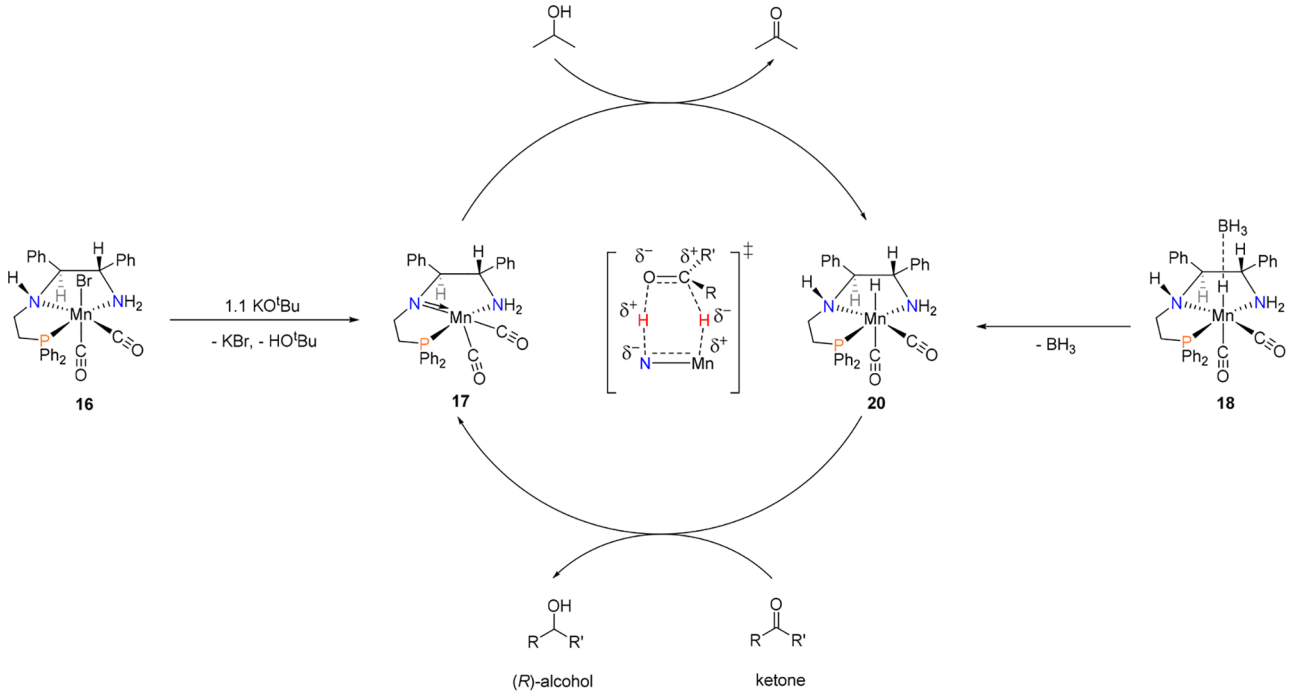
An ethoxide complex is proposed to form by the loss of BH$_3$ and H$_2$ from **18** to produce the amido complex **17**, which then heterolytically cleaves the H−O bond of ethanol to form **19** with a Mn−OEt group *syn* to the NH of the secondary amine. This complex rearranges to the *anti* isomer **19′**, which is calculated by use of density functional theory to be 4.0 kcal/mol more stable than **19** (see Supporting Information). The ^{1}H NMR resonances of **18** and **19′** could be assigned through

Scheme 5. Synthesis of the *Syn* Manganese Borohydride Isomer and the *Anti* Manganese Ethoxide Isomer; Assignment of the ^{1}H NMR (Toluene-d_8) Resonances and 2D NOESY Correlations (Arrows)



DOI: 10.1021/acs.organomet.8b00625
Organometallics XXXX, XXX, XXX−XXX

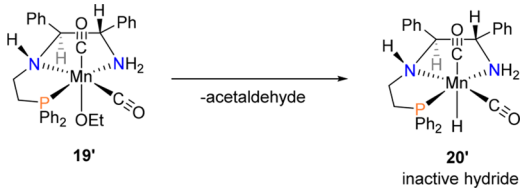
Scheme 6. Proposed Catalytic Cycle for the ATH of Ketones with 16, 17, and 18



analysis of the 2D NMR spectra as outlined in Scheme 5. The $^{31}P\{^1H\}$ NMR spectrum and CO stretches in the IR spectrum of **19′** are similar to the manganese bromide complex **16**, while the CO stretches in the IR spectrum of **18** at 1920 and 1836 cm^{-1} were comparable with those of a *mer*-Mn(P−NH−P)$(CO)_2(BH_4)$ complex bearing *cis*-carbonyl ligands which was characterized by X-ray crystallography by Gauvin et al.[41]

Proposed Catalytic Cycle. The borohydride complex **18** and ethoxide complex **19′** were independently tested in the ATH of acetophenone at 80 °C without the addition of KO^{t}Bu and only **18** produced 1-phenylethanol. The proposed catalytic cycles are presented in Scheme 6 and Scheme 7, respectively.

Scheme 7. Proposed Formation of an Inactive Hydride Species 20′ from 19′



The manganese precatalyst **16** reacts with KO^{t}Bu to produce an amido manganese complex **17**, potassium bromide, and *tert*-butanol. In an outer-sphere, six-membered transition state, a proton and hydride are transferred from 2-PrOH to the amido complex to produce the uncharacterized *syn* NH hydride complex **20**, which may benefit from the NH Effect.[43] The active hydride may also be accessed by stirring a solution of the borohydride complex **18** or amido complex **17** in 2-PrOH without the need for KO^{t}Bu. In this manner, ketones bearing base-sensitive functional groups could also be asymmetrically reduced (*p*-acetylbenzoate ethyl ester, Figure 4). In the subsequent step, the manganese hydride species **20** transfers a hydride and proton in either a concerted or stepwise outer-sphere mechanism to the ketone substrate to release the (*R*)-enantiomerically enriched alcohol product and regenerate the amido complex **17**.

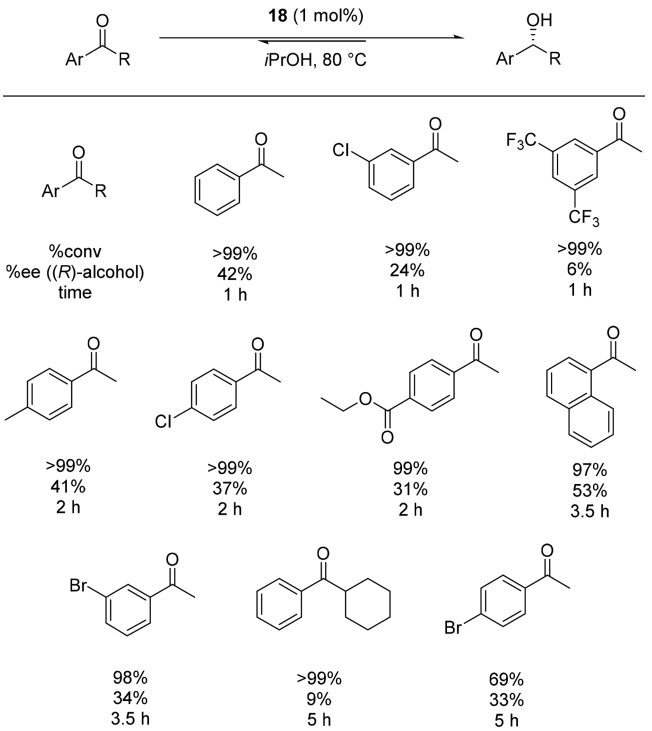


Figure 4. ATH of various ketones with precatalyst **18**. Reactions performed under argon at 80 °C. Ketone:**18** ratio was 100:1. Volume of 2-PrOH = 8 mL. [ketone] = 0.312 M; [**18**] = 3.13×10^{-4} M; [2-PrOH] = 13.1 M. (*R*)-Alcohol was the major species in all cases. Conversions and ee were determined using a gas chromatograph containing a chiral column. Di-*tert*-butylbenzene was used as an internal standard.

DOI: 10.1021/acs.organomet.8b00625
Organometallics XXXX, XXX, XXX−XXX

Garcia et al. studied the use of several alcohols as sacrificial reductants in the transfer hydrogenation of acetophenone with a nickel catalyst prepared in situ.[44] Using ethanol, they observed the initial production of acetaldehyde which reacts with ethanol to produce ethyl acetate. In a similar manner, the ethoxide complex **19′** is postulated to release acetaldehyde to produce an *anti* Mn−H and NH hydride species **20′** (Scheme 7), which is proposed to be unreactive with respect to the hydride transfer to the ketone due to the lack of carbonyl activation by an NH group.

Substrate Scope. With the manganese borohydride complex **18**, the ATH of various ketones was performed in heated 2-PrOH without the addition of KO^{t}Bu. The optimized catalysis results are shown in Figure 4.

The reduction of acetophenone was rapid at 80 °C, only requiring 1 h to produce 1-phenylethanol with a poor ee of 42% (*R*). The addition of electron -donating groups in the para position to the acetyl group on the benzene ring placed electron density near the ketone carbonyl, thus decreasing the electrophilicity of the acetyl carbon and decreasing the rate of catalysis. In contrast, addition of electron-withdrawing groups in the meta position of the benzene ring to the acetyl group, enhanced catalytic activity by increasing the electrophilicity of the acetyl carbon. This was observed in both cases for the bromo- and chloro-substituted acetophenone derivatives. Increasing the bulk of the R group of the acetophenone derivative led to lower rates of catalysis (Figure 4), as observed with the lower activity of the catalyst in the reduction of cyclohexylphenylketone or the bromo-substituted acetophenone in contrast to the chloro-substituted acetophenone. The catalyst was also efficient for the hydrogenation of base-sensitive substrate *p*-acetylbenzoate ethyl ester,[45] producing the ethyl ester alcohol without observation of the trans-esterification product (see SI).

CONCLUSIONS

New manganese complexes **14**−**16** were synthesized and tested in the ATH of acetophenone. Only the *mer*-Mn(P−NH−NH_2)$(CO)_2$Br complex **16** displayed moderate activity at 80 °C and was therefore selected to further investigate the mechanism of transfer hydrogenation. The active hydride species could not be isolated, but the 5-coordinate amido complex Mn(P−N−NH_2)$(CO)_2$ **17** and the borohydride complex *syn-mer*-Mn(P−NH−NH_2)$(CO)_2(BH_4)$ **18** were isolated and demonstrated to be active in the ATH of acetophenone without the addition of KO^{t}Bu for the first time with manganese. An ethoxide isomer *anti-mer*-Mn(P−NH−NH_2)$(CO)_2$(OEt) **19′** was independently synthesized and found to be inactive for ATH of acetophenone. The proposed catalytic cycle for **18** and **19′** relies on the production of a *syn* Mn−H and NH manganese hydride species for the catalysis to proceed. The borohydride complex **18** is one of the most active manganese ATH catalysts to date and can catalyze the hydrogenation of a variety of ketone substrates including the base-sensitive substrate *p*-acetylbenzoate ethyl ester. Compared to Sortais and co-worker's manganese ATH catalysts prepared in situ, the catalyst presented herein displayed similar activity and enantioselectivity.[38] The manganese catalyst prepared by Zirakzadeh remained the most active and enantioselective manganese ATH in the literature to date, with an impressive rate of catalysis at 25 °C and an unmatched enantioselectivity.[31]

EXPERIMENTAL SECTION

General Experimental Considerations. All manipulations were performed under an inert atmosphere of argon using Schlenk or standard glovebox techniques, unless otherwise stated. Solvents and liquid substrates were dried and degassed via distillation prior to use. All solid substrates were heated to 80 °C under vacuum to remove any traces of water before being stored in the glovebox. The P−NH−NH_2 ligand **10**[12] and the orthophenylene P′−NH−NH_2 ligand **9**[14] were synthesized according to literature. NMR spectra were recorded at ambient temperature and pressure using an Agilent 600 MHz, and 500 MHz spectrometer as well as Bruker Avance-III 400 MHz autosampler. The conversions and ee, using di-*tert*-butylbenzene as an internal standard, for each reaction were obtained on a PerkinElmer Clarus 400 Chromatograph equipped with a chiral column (CP chirasil-Dex CB 25 m x 2.5 mm), using hydrogen gas as the mobile phase. The IR spectra were recorded on a Bruker Alpha with an ATR-platinum diamond attachment. All experiments were repeated three times for accuracy.

*Alternative Synthesis of the P−NH−NH−P Ligand (**8**).* This procedure was adapted from the synthesis of (*1S*,*2S*)-N^1-(2-(diphenylphosphinyl)ethyl)-1,2-diphenylethane-1,2-diamine (P−NH−NH_2 ligand, **10**).[12]

In separate vials, the diphenylphosphonium dimer (291 mg, 0.471 mmol, 1 equiv) and sodium methoxide (51 mg, 0.942 mmol, 2 equiv) were dissolved in methanol (8 mL), iron(II) tetrafluoroborate hexahydrate (239 mg, 0.707 mmol, 1.5 equiv) was dissolved in methanol (4 mL), and DPEN (100 mg, 0.471 mmol, 1 equiv) was dissolved in MeCN (4 mL). All solutions were stirred for 2 min and then combined in a 100 mL Schlenk flask to produce a purple solution. After the solutions were stirred for 16 h, they became red, indicating the formation of $[Fe(P{-}N{-}N{-}P)(MeCN)_2][BF_4]_2$ (P−N−N−P = $Ph_2PCH_2CHNCH(Ph)CH(Ph)NCHCH_2PPh_2$).[17] The solvent was removed in vacuo to leave a red residue. $LiAlH_4$ (89 mg, 2.36 mmol, 5 equiv) was added as a powder, and then the mixture was dissolved in THF (20 mL) and allowed to stir for 1 h until the solution turned gray and gas evolution ceased. The Schlenk flask was brought from the glovebox to the Schlenk line and placed under a continuous flow of argon. It was placed in an ice bath, and the excess $LiAlH_4$ was quenched by injecting water (deionized, not degassed) via a syringe dropwise to the solution. After 2 mL of water was added in this manner, the solution was dried in vacuo to leave a gray residue. The following extraction can be performed in air in under 2 h to ensure that the phosphine does not become oxidized. DCM (not dry or degassed, 50 mL) and water (not degassed, 50 mL) was added to the Schlenk flask in order to dissolve the residue. A DCM/water extraction was performed in a 250 mL separatory funnel, extracting the water layer with DCM (50 mL × 2). All of the DCM fractions were combined, dried with magnesium sulfate, filtered through Celite, and then dried in vacuo to isolate the PNNP ligand as a brown oil in a 95% purity as indicated by the singlet in the $^{31}P\{^1H\}$ NMR spectrum at −20.3 ppm. Yield: 185 mg (62%). Full characterization for **8** can be found in the literature.[11]

*Synthesis of trans-[Mn(P−NH−NH−P)$(CO)_2$][Br] (**14**).* The chiral P−NH−NH−P ligand (1*S*,2*S*)-N^1,N^2-bis(2-(diphenylphosphinyl)-ethyl)-1,2-diphenylethane-1,2-diamine **8** (185 mg, 0.290 mmol, 1 equiv) was dissolved in toluene (5 mL) and placed into a 50 mL Schlenk flask. In a separate vial, bromopentacarbonylmanganese(I) (80 mg, 0.290 mmol, 1 equiv) was dissolved in toluene (8 mL) and then added to the Schlenk flask. This was brought out of the glovebox, placed on the Schlenk line, and then heated at 110 °C under Ar. After 4 h, the reaction was removed from the oil bath and allowed to cool to 28 °C. The solution was freeze−pump−thawed two times, then brought back into the glovebox. The solution was filtered to collect the precipitate. The precipitate was washed with toluene (2 mL × 2), dried in vacuo for 10 min, placed in a vial, and then stirred in diethyl ether (15 mL) for 16 h. The solid was collected via filtration, stirred in diethyl ether (5 mL × 2) for 16 h, and then dried in vacuo to isolate the product as a yellow powder. Several attempts were made to crystallize the product to no avail. Yield: 160 mg (67%). ^{1}H NMR

DOI: 10.1021/acs.organomet.8b00625
Organometallics XXXX, XXX, XXX−XXX

spectrum (600 MHz, DMSO-d_6) δ 8.13−6.18 (30H, aromatic protons), 3.76 (br, 2H, N**H**), 3.57 (br, 2H, $PPh_2C\mathbf{H}_2$), 3.19 (br, 2H, $NHC\mathbf{H}_2$), 3.04 (br, 2H, C**H**Ph), 3.00 (br, 2H, $PPh_2C\mathbf{H}_2$), 2.94 (br, 2H, $NHC\mathbf{H}_2$). $^{31}P\{^1H\}$ NMR spectrum (243 MHz, DMSO-d_6) δ 80.8 (s). The 2D $^1H-^{13}C$ HSQC spectrum (500 MHz, DMSO-d_6) showing correlations for the two C**H**Ph protons at (3.04, 67.57), the four protons of the $NHC\mathbf{H}_2$ at (3.19, 49.67) and (2.94, 49.69), and the four protons of the $C\mathbf{H}_2PPh_2$ at (3.57, 22.93) and (3.00, 22.82). IR ATR (CO ligand): 1930 and 1854 cm^{-1}. ESI+ high-resolution mass spec $[M - Br]^+$: calcd, 747.2102; found, 747.2099.

*Synthesis of fac-[Mn(P′−NH−NH$_2$)(CO)$_3$][Br] (**15**).* The chiral P′-NH-NH_2 ligand (*1S,2S*)-N^1-(2-(diphenylphosphinyl)phenyl)-1,2-diphenylethane-1,2-diamine **9** (58 mg, 0.123 mmol, 1 equiv) was dissolved in toluene (5 mL) and placed into a 50 mL Schlenk flask. In a separate vial, bromopentacarbonylmanganese(I) (34 mg, 0.123 mmol, 1 equiv) was dissolved in toluene (8 mL) and then added to the Schlenk flask. This was brought out of the glovebox, placed on the Schlenk line, and heated at 110 °C under Ar. After 16 h, the reaction was removed from the oil bath and allowed to cool to 28 °C. The solution was freeze−pump−thawed two times, then brought back into the glovebox. The workup was the same as that of **14** to produce a yellow powder. Several attempts were made to crystallize the product to no avail. Yield: 48 mg (56%). ^1H NMR spectrum (600 MHz, DMSO-d_6) δ 7.81−6.83 (20H, aromatics from CHPh and PPh_2), 6.81−6.17 (4H, aromatics from orthophenylene), 6.03−5.57 (br, 2H), 4.77 (br, 1H), 4.49 (br, 1 H), 4.15 (br, 1H) .Because of the fluctional behavior of the complex, all of the peaks were broad. $^{31}P\{^1H\}$ NMR spectrum (243 MHz, DMSO-d_6) δ 63.9 (s). IR ATR (CO ligand): 2032, 1955, and 1914 cm^{-1}. ESI+ high-resolution mass spectrometry $[M - Br]^+$: calcd, 611.1296; found, 611.1299.

*Synthesis of syn NH Br mer-Mn(P−NH−NH$_2$)(CO)$_2$(Br) (**16**).* The chiral PNN ligand (*S,S*)-$Ph_2PCH_2CH_2NHCHPh-CHPhNH_2$ **10** (620.5 mg, 1.461 mmol, 1 equiv) was dissolved in toluene (15 mL) and placed into a 100 mL Schlenk flask. In a separate vial, bromopentacarbonylmanganese(I) (401.8 mg, 1.461 mmol, 1 equiv) was dissolved in toluene (20 mL) and then added to the Schlenk flask. This was brought out of the glovebox, placed on the Schlenk line and heated at 110 °C under Ar. After 4 h, the reaction was removed from the oil bath and allowed to cool to 28 °C. The solution was freeze−pump−thawed two time and then brought back into the glovebox. The solution was filtered to remove any salt impurities, and then the filtrate was removed in vacuo to yield a bright yellow residue. The residue was stirred in diethyl ether (20 mL) for 16 h, filtered, then dried in vacuo to isolate the product as a yellow powder. Several attempts were made to crystallize the product to no avail. Yield: 800 mg (89%). ^1H NMR spectrum (600 MHz, DMSO-d_6) δ 7.80−7.00 (br, 40H, aromatic protons), 6.14 (t, 1H, $PPh_2CH_2CH_2N\mathbf{H}$, $^3J_{HH}$ = 12 Hz), 5.40 (m, 1H, $N\mathbf{H}_2CHPh$), 3.95 (m, 1H, $NH_2C\mathbf{H}Ph$), 3.81 (pseudo t, 1H, $NH_2CHPhC\mathbf{H}Ph$, $^3J_{HH}$ = 12 Hz), 3.36 (m, 1H, $PPh_2C\mathbf{H}_2$), 2.79 (m, 1H, $NHC\mathbf{H}_2$), 2.48 (m, 1H, $NHC\mathbf{H}_2$, buried under the DMSO-d_6 signal), 2.42 (m, 1H, $PPh_2C\mathbf{H}_2$, buried under the DMSO-d_6 signal), 2.07 (pseudo t, 1H, $N\mathbf{H}_2CHPh$, $^3J_{HH}$ = 12 Hz). $^{31}P\{^1H\}$ NMR spectrum (243 MHz, DMSO-d_6) δ 83.1 (s). 2D $^1H-^{13}C$ HSQC spectrum (500 MHz, DMSO-d_6) displays the two C**H**Ph at (3.95, 66.88) and (3.81, 66.97), the two protons of the CH_2 adjacent to the amino donor at (2.79, 45.28) and (2.48, 44.99), the two protons of the CH_2 adjacent to the diphenylphosphino donor at (3.36, 29.10) and (2.42, 29.23). There is no cross peak for the three amino protons at 6.14, 5.40, and 2.07 ppm in the HSQC. IR ATR (CO ligand): 1915 and 1828 cm^{-1} and a slight impurity at 2023 cm^{-1} which suggests a side-product. ESI+ high-resolution mass spectrometry $[M - Br]^+$: calcd, 535.1347; found, 535.13. Elemental Analysis [M] Calcd: C, 58.55%; H, 4.75%; N, 4.55%. Found: C, 58.24%; H, 5.12%; N, 4.54%.

*Synthesis of Mn(P−N−NH$_2$)(CO)$_2$ (**17**).* Mn(P−NH−NH_2)(Br)-$(CO)_2$ **16** (425 mg. 0.69 mmol, 1 equiv) was weighed out in a vial and dissolved in THF (8 mL). In a separate vial, KO^{t}Bu (85.2 mg, 0.76 mmol, 1.1 equiv) was weighed out and dissolved in THF (2 mL). The KO^{t}Bu solution was added dropwise to the vial containing **16** to form a dark red solution. The solution was stirred for 1 h, and then the solvent was removed in vacuo. The residue was redissolved in benzene (3 mL), filtered through Celite to remove any solid impurities, and then the filtrate was removed in vacuo. The dark red residue was stirred in pentanes for 16 h. The solid was filtered out and dried under vacuum to isolate the product as a dark red powder. Several attempts were made to crystallize the product to no avail. Yield: 320 mg (87%). ^1H NMR spectrum (600 MHz, C_6D_6) δ 7.71 (dt, $^3J_{HH}$ = 24, 8 Hz, 4H, aromatic protons), 7.30−6.85 (m, overlaps with benzene solvent peak, aromatic protons), 6.58 (d, $^3J_{HH}$ = 7 Hz, 2H, aromatic protons), 4.02 (d, $^3J_{HH}$ = 7 Hz, 1H, $H_2NCHPhC\mathbf{H}PhN$), 3.31 (m, 1H, $H_2NC\mathbf{H}Ph$), 2.84 (m, 1H, $NC\mathbf{H}_2$), 2.77 (m, 1H, $NC\mathbf{H}_2$), 2.47 (m, 1H, $N\mathbf{H}_2CHPh$), 2.45 (dt, $^2J_{HH}$ = 13 Hz, $^3J_{HH}$ = 7 Hz, 1H, $C\mathbf{H}_2PPh_2$), 2.41 (m, 1H, $C\mathbf{H}_2PPh_2$), 2.05 (m, 1H, $N\mathbf{H}_2CHPh$). $^{31}P\{^1H\}$ NMR spectrum (243 MHz, C_6D_6) δ 102.8 (s). The 2D $^1H-^{13}C$ HSQC spectrum (500 MHz, C_6D_6) displays the two C**H**Ph protons at (4.02, 79.76) and (3.31, 69.32), the two protons of the CH_2 adjacent to the amino donor are found at (2.84, 54.03) and (2.77, 54.03), and the two protons of the CH_2 adjacent to the diphenylphosphino donor at (2.47, 35.22) and (2.41, 35.20). There is no cross peak for the amino group proton at 2.05 ppm, while no conclusion can be drawn for the amino proton at 2.45 ppm since it is shrouded by the CH_2 proton at 2.47 ppm. IR ATR (CO ligand): 1890 and 1808 cm^{-1}. DART Mass Spec $[M]^+$: calcd, 534.1269; found, 534.2. High-resolution mass spectroscopy and elemental analysis could not be performed as the product degrades quickly upon exposure to air.

*Synthesis of syn NH BH_4 Isomer mer-Mn(P−NH−NH$_2$)(CO)$_2$(BH$_4$) (**18**).* Mn(P−NH−NH_2)(Br)$(CO)_2$ **16** (50 mg, 0.081 mmol, 1 equiv) was weighed out in a vial, then dissolved in ethanol (4 mL) with toluene (1.3 mL). Sodium borohydride (15 mg, 0.405 mmol, 5 equiv) was added portion-wise. The solution was stirred for 1.5 h, then filtered through Celite to remove any solid impurities. The filtrate was removed in vacuo to yield a yellow-orange powder. The residue was redissolved in THF (5 mL) and filtered to remove excess $NaBH_4$. The filtrate was concentrated to approximately 1 mL, then pentanes was added dropwise to cause precipitation of the product. The product was isolated via filtration, washed with pentanes (2 mL × 3), then dried in vacuo to obtain a yellow powder. Yield: 38 mg (85%). ^1H NMR spectrum (600 MHz, toluene-d_8) δ 7.95 (t, 2H, aromatic protons, $^3J_{HH}$ = 9 Hz), 7.31 (t, 2H, aromatic protons, $^3J_{HH}$ = 9 Hz), 7.22−6.74 (24H, aromatic protons), 6.66 (d, 2H, aromatic protons, $^3J_{HH}$ = 5 Hz), 5.06 (t, 1H, $N\mathbf{H}CH_2$, $^3J_{HH}$ = 12 Hz), 4.08 (t, 1H, $NH_2C\mathbf{H}Ph$, $^3J_{HH}$ = 10 Hz), 3.82 (pseudo t, 1H, $NH_2CHPhC\mathbf{H}Ph$, $^3J_{HH}$ = 12 Hz), 3.09 (pseudo t, 1H, $N\mathbf{H}_2CHPh$, $^2J_{HH}$ = 10 Hz), 2.77 (m, 1H, $NHC\mathbf{H}_2$), 2.44 (t, 1H, $PPh_2C\mathbf{H}_2$, $^3J_{HH}$ = 15 Hz), 2.31 (m, 1H, $NHC\mathbf{H}_2$), 2.09 (m, 1H, $N\mathbf{H}_2CHPh$, buried under toluene signal), 1.80 (m, 1H, $PPh_2C\mathbf{H}_2$), −1.21 to −1.60 (br, $B\mathbf{H}_4$). $^{31}P\{^1H\}$ NMR spectrum (243 MHz, toluene-d_8) δ 89.2 (s). ^{11}B NMR spectrum (192 MHz, toluene-d_8) δ −23.9 (br). 2D $^1H-^{13}C$ HSQC spectrum displays the two CHPh at (4.08, 65.01) and (3.82, 74.24), the two protons of the CH_2 adjacent to the secondary amino donor at (2.77, 50.39) and (2.31, 49.58), the two protons of the CH_2 adjacent to the diphenylphosphino donor at (2.44, 31.67) and (1.80, 31.64). There is no cross peak for the three amino protons at 6.14, 5.40, and 2.07 ppm in the HSQC spectrum. IR ATR (CO ligand): 1920 and 1836 cm^{-1}. High-resolution mass spectroscopy and elemental analysis could not be performed as the product degrades quickly upon exposure to air.

*Synthesis of anti NH OEt Isomer mer-Mn(P−NH−NH$_2$)(CO)$_2$(OEt) (**19′**).* Mn(P−NH−NH_2)(Br)$(CO)_2$ **16** was reacted with $NaBH_4$ as above, but stirred for 16 h. The workup was the same as for **18** to obtain a yellow powder. Yield: 34 mg (75%). ^1H NMR spectrum (600 MHz, toluene-d_8) δ 8.03 (t, 2H, aromatic protons, $^3J_{HH}$ = 9 Hz), 7.37 (t, 2H, aromatic protons, $^3J_{HH}$ = 9 Hz), 7.22−6.74 (24H, aromatic protons), 6.60 (m, 2H, aromatic protons), 4.37 (t, 1H, $N\mathbf{H}CH_2$, $^3J_{HH}$ = 12 Hz), 3.94 (t, 1H, $NH_2C\mathbf{H}Ph$, $^3J_{HH}$ = 10 Hz), 3.89 (pseudo t, 1H, $NH_2CHPhC\mathbf{H}Ph$, $^3J_{HH}$ = 12 Hz), 3.33 (br, 2H, $OC\mathbf{H}_2CH_3$), 2.79 (m, 1H, $NHC\mathbf{H}_2$), 2.62 (pseudo t, 1H, $N\mathbf{H}_2CHPh$, $^2J_{HH}$ = 10 Hz), 2.54 (t, 1H, $PPh_2C\mathbf{H}_2$, $^3J_{HH}$ = 14 Hz), 2.45 (m, 1H, $NHC\mathbf{H}_2$), 2.27 (m, 1H, $N\mathbf{H}_2CHPh$, buried under toluene signal), 1.87 (m, 1H,

DOI: 10.1021/acs.organomet.8b00625
Organometallics XXXX, XXX, XXX−XXX

PPh_2CH_2), 0.97 (br, 3H, OCH_2CH_3), − 1.41 (br, 3H, BH_3). $^{31}P\{^1H\}$ NMR spectrum (243 MHz, toluene-d_8) δ 84.1 (s). 2D $^1H-^{13}C$ HSQC spectrum displays the two CHPh at (3.94, 64.30) and (3.86, 73.36), the two protons of the CH_2 adjacent to the secondary amino donor at (2.80, 49.30) and (2.44, 49.15), the two protons of the CH_2 adjacent to the diphenylphosphino donor at (2.54, 30.58) and the proton at 1.86 was not found in the 2D $^1H-^{13}C$ HSQC spectrum. There is no cross peak for the three amino protons at 4.36, 2.63, and 2.27 ppm in the HSQC spectrum. IR ATR (CO ligand): 1916 and 1830 cm^{-1}. High-resolution mass spectroscopy and elemental analysis could not be performed as the product degrades quickly upon exposure to air.

Testing the Activity of the Compounds 14, 15, and 16 for the ATH of Acetophenone (Table 2). By the Schlenk line, an oil bath was kept at 28 °C or heated to 80 °C. Concurrently, in the glovebox, Stock Solution 1 (SS1) containing a manganese precatalyst **14**, **15**, or **16** (0.025 mmol) was prepared with DCM (1 mL) and quickly placed into a 1 mL syringe. A 10 mL Schlenk flask was charged with 0.1 mL of SS1 and a magnetic stir bar. The solvent was removed in vacuo to obtain 0.0025 mmol of manganese precatalyst in the Schlenk flask. A syringe was filled with 2-PrOH (7 mL) and the needle was stabbed into a rubber stopper. A second syringe was filled with the acetophenone (0.25 mmol), diluted with 2-PrOH (0.5 mL), and the needle was stabbed into the rubber stopper. A third syringe was filled with KO^{t}Bu (0.56 mg, 0.005 mmol) dissolved in 2-PrOH (0.5 mL). Once the temperature of the oil bath was stable, the Schlenk flask was brought out of the glovebox and attached to the Schlenk line under Ar. The three syringes were taken out of the glovebox, the 2-PrOH was injected into the Schlenk flask, and then the Schlenk flask was lowered into the oil bath. After the mixture was stirred for 1 min, the KO^{t}Bu was injected into the Schlenk flask, then immediately ketone substrate was injected into the Schlenk flask, and the stop watch was started. At this stage, the concentrations were calculated to be [acetophenone] = 0.312 M; [Mn complex] = 3.13×10^{-4} M; [KO^{t}Bu] = 6.25×10^{-4} M [2-PrOH] = 13.1 M. After the allotted reaction time, the reaction was removed from heat and opened to air. A 0.1 mL aliquot was taken and added to a GC vial containing di-*tert*-butylbenzene (0.019 mg, 0.1 mmol) in THF (0.9 mL).

General Procedure for the ATH of Ketones Using the Optimized Conditions with No KO^{t}Bu Added (Figure 4). By the Schlenk line, an oil bath was heated to 80 °C. Concurrently, in the glovebox, Stock Solution 1 (SS1) containing manganese complexes **17**, **18**, or **19′** (0.025 mmol) was prepared with benzene (1 mL) and quickly placed into a 1 mL syringe. A 10 mL Schlenk flask was charged with 0.1 mL of SS1 and a magnetic stir bar. The solvent was removed in vacuo to obtain 0.0025 mmol of manganese precatalyst in the Schlenk flask. A syringe was filled with 2-PrOH (7.5 mL), and the needle was stabbed into a rubber stopper. A second syringe was filled with the ketone substrate (0.25 mmol), diluted with 2-PrOH (0.5 mL), and the needle was stabbed into the rubber stopper. Once the temperature of the oil bath was stable, the Schlenk flask was brought out of the glovebox and attached to the Schlenk line under argon. The two syringes were taken out of the glovebox, the 2-PrOH was injected into the Schlenk flask, and then the Schlenk flask was lowered into the oil bath. After the mixture was stirred for 1 min, the ketone substrate was injected into the Schlenk flask, and the stop watch was started. At this stage, the concentrations were calculated to be [acetophenone] = 0.312 M; [Mn complex] = 3.13×10^{-4} M; [2-PrOH] = 13.1 M. After the allotted reaction time, the reaction was removed from heat and opened to air. A 0.1 mL sample was taken and added to a GC vial containing di-*tert*-butylbenzene (0.019 mg, 0.1 mmol) in THF (0.9 mL).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organomet.8b00625.

Extended experimental section; summary of $^{31}P\{^1H\}$ NMR spectra and IR spectra; NMR spectra of newly synthesized compounds and activated complexes; gas chromatograph readouts for the product alcohols, including an NMR spectrum of the base-sensitive *p*-acetylbenzoate ethyl ester for confirmation of the product alcohol; and DFT calculations for the structures of the bromide manganese, borohydride manganese, as well as the ethoxide manganese structures (PDF).

xyz coordinate file of the calculated structures (XYZ).

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: rmorris@chem.utoronto.ca.

ORCID

Robert H. Morris: 0000-0002-7574-9388

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

R.H.M. thanks NSERC for a Discovery Grant. NSERC is thanked for a PGS D awarded to K.Z.D. The authors wish to acknowledge the Canadian Foundation for Innovation, project number 19119, and the Ontario Research Fund for funding of the Centre for Spectroscopic Investigation of Complex Organic Molecules and Polymers and Compute Canada and Sharcnet for a resource allocation grant.

■ REFERENCES

(1) Dupau, P. Ruthenium-catalyzed Selective Hydrogenation for Flavor and Fragrance Applications. *Top. Organomet. Chem.* **2011**, *42*, 47−64.

(2) De Vita, D.; Pandolfi, F.; Cirilli, R.; Scipione, L.; Di Santo, R.; Friggeri, L.; Mori, M.; Fiorucci, D.; Maccari, G.; Arul Christopher, R. S.; Zamperini, C.; Pau, V.; De Logu, A.; Tortorella, S.; Botta, M. Discovery of in Vitro Antitubercular Agents Through in Silico Ligand-based Approaches. *Eur. J. Med. Chem.* **2016**, *121*, 169−180.

(3) Hameed, P. S.; Chinnapattu, M.; Shanbag, G.; Manjrekar, P.; Koushik, K.; Raichurkar, A.; Patil, V.; Jatheendranath, S.; Rudrapatna, S. S.; Barde, S. P.; Rautela, N.; Awasthy, D.; Morayya, S.; Narayan, C.; Kavanagh, S.; Saralaya, R.; Bharath, S.; Viswanath, P.; Mukherjee, K.; Bandodkar, B.; Srivastava, A.; Panduga, V.; Reddy, J.; Prabhakar, K. R.; Sinha, A.; Jimenez-Diaz, M. B.; Martinez, M. S.; Angulo-Barturen, I.; Ferrer, S.; Sanz, L. M.; Gamo, F. J.; Duffy, S.; Avery, V. M.; Magistrado, P. A.; Lukens, A. K.; Wirth, D. F.; Waterson, D.; Balasubramanian, V.; Iyer, P. S.; Narayanan, S.; Hosagrahara, V.; Sambandamurthy, V. K.; Ramachandran, S. Aminoazabenzimidazoles, a Novel Class of Orally Active Antimalarial Agents. *J. Med. Chem.* **2014**, *57*, 5702−5713.

(4) Smith, C. J.; Ali, A.; Hammond, M. L.; Li, H.; Lu, Z.; Napolitano, J.; Taylor, G. E.; Thompson, C. F.; Anderson, M. S.; Chen, Y.; Eveland, S. S.; Guo, Q.; Hyland, S. A.; Milot, D. P.; Sparrow, C. P.; Wright, S. D.; Cumiskey, A.-M.; Latham, M.; Peterson, L. B.; Rosa, R.; Pivnichny, J. V.; Tong, X.; Xu, S. S.; Sinclair, P. J. Biphenyl-Substituted Oxazolidinones as Cholesteryl Ester Transfer Protein Inhibitors: Modifications of the Oxazolidinone Ring Leading to the Discovery of Anacetrapib. *J. Med. Chem.* **2011**, *54*, 4880−4895.

(5) Bhandari, K.; Srivastava, S.; Shanker, G.; Nath, C. Substituted Propanolamines and Alkylamines Derived from Fluoxetine as Potent Appetite Suppressants. *Bioorg. Med. Chem.* **2005**, *13*, 1739−1747.

(6) Kraft, S.; Ryan, K.; Kargbo, R. B. Recent Advances in Asymmetric Hydrogenation of Tetrasubstituted Olefins. *J. Am. Chem. Soc.* **2017**, *139*, 11630−11641.

DOI: 10.1021/acs.organomet.8b00625
Organometallics XXXX, XXX, XXX−XXX

(7) Wills, M. Imino Transfer Hydrogenation Reductions. *Top. Curr. Chem.* **2016**, *374*, 1−36.
(8) Stefane, B.; Pozgan, F. Metal-catalysed Transfer Hydrogenation of Ketones. *Top. Curr. Chem.* **2016**, *374*, 1−67.
(9) Margarita, C.; Andersson, P. G. Evolution and Prospects of the Asymmetric Hydrogenation of Unfunctionalized Olefins. *J. Am. Chem. Soc.* **2017**, *139*, 1346−1356.
(10) Foubelo, F.; Najera, C.; Yus, M. Catalytic Asymmetric Transfer Hydrogenation of Ketones: Recent Advances. *Tetrahedron: Asymmetry* **2015**, *26*, 769−790.
(11) Mikhailine, A. A.; Maishan, M. I.; Lough, A. J.; Morris, R. H. The Mechanism of Efficient Asymmetric Transfer Hydrogenation of Acetophenone Using an Iron(II) Complex Containing an (S,S)-$Ph_2PCH_2CH{=}NCHPhCHPhN{=}CHCH_2PPh_2$ Ligand: Partial Ligand Reduction Is the Key. *J. Am. Chem. Soc.* **2012**, *134*, 12266−12280.
(12) Zuo, W.; Lough, A. J.; Li, Y. F.; Morris, R. H. Amine(imine)-diphosphine Iron Catalysts for Asymmetric Transfer Hydrogenation of Ketones and Imines. *Science* **2013**, *342*, 1080−1083.
(13) Demmans, K. Z.; Ko, O. W. K.; Morris, R. H. Aqueous Biphasic Iron-catalyzed Asymmetric Transfer Hydrogenation of Aromatic Ketones. *RSC Adv.* **2016**, *6*, 88580−88587.
(14) Demmans, K. Z.; Seo, C. S. G.; Lough, A. J.; Morris, R. H. From Imine to Amine: An Unexpected Left Turn. Cis-β iron(II) PNNP′ Precatalysts for the Asymmetric Transfer Hydrogenation of Acetophenone. *Chem. Sci.* **2017**, *8*, 6531−6541.
(15) Bigler, R.; Huber, R.; Stockli, M.; Mezzetti, A. Iron(II)/$(NH)_2P_2$ Macrocycles: Modular, Highly Enantioselective Transfer Hydrogenation Catalysts. *ACS Catal.* **2016**, *6*, 6455−6464.
(16) Bigler, R.; Huber, R.; Mezzetti, A. Iron Chemistry Made Easy: Chiral N_2P_2 Ligands for Asymmetric Catalysis. *Synlett* **2016**, *27*, 831−847.
(17) Mikhailine, A. A.; Kim, E.; Dingels, C.; Lough, A. J.; Morris, R. H. Template Syntheses of Iron(II) Complexes Containing Chiral P-N-N-P and P-N-N Ligands. *Inorg. Chem.* **2008**, *47*, 6587−6589.
(18) Smith, S. A. M.; Morris, R. H. An Unsymmetrical Iron Catalyst for the Asymmetric Transfer Hydrogenation of Ketones. *Synthesis* **2015**, *47*, 1775−1779.
(19) Sues, P. E.; Lough, A. J.; Morris, R. H. Stereoelectronic Factors in Iron Catalysis: Synthesis and Characterization of Aryl-substituted Iron(II) Carbonyl P-N-N-P Complexes and Their Use in the Asymmetric Transfer Hydrogenation of Ketones. *Organometallics* **2011**, *30*, 4418−4431.
(20) Smith, S. A. M.; Prokopchuk, D. E.; Morris, R. H. Asymmetric Transfer Hydrogenation of Ketones Using New Iron(II) (P-NH-N-P′) Catalysts: Changing the Steric and Electronic Properties at Phosphorus P′. *Isr. J. Chem.* **2017**, *57*, 1204−1215.
(21) De Luca, L.; Mezzetti, A. Base-Free Asymmetric Transfer Hydrogenation of 1,2-Di- and Monoketones Catalyzed by a $(NH)_2P_2$-Macrocyclic Iron(II) Hydride. *Angew. Chem., Int. Ed.* **2017**, *56*, 11949−11953.
(22) Mezzetti, A. Iron Complexes with Chiral N/P Macrocycles as Catalysts for Asymmetric Transfer Hydrogenation. *Isr. J. Chem.* **2017**, *57*, 1090−1105.
(23) Magubane, M. N.; Alam, M. G.; Ojwach, S. O.; Munro, O. Q. Orientation Towards Asymmetric Transfer Hydrogenation of Ketones Catalyzed by (Pyrazolyl)ethyl)pyridine Fe(II) and Ni(II) Complexes. *J. Mol. Struct.* **2017**, *1135*, 197−201.
(24) Bigler, R.; Mezzetti, A. Highly Enantioselective Transfer Hydrogenation of Polar Double Bonds by Macrocyclic Iron(II)/$(NH)_2P_2$ Catalysts. *Org. Process Res. Dev.* **2016**, *20*, 253−261.
(25) Sues, P. E.; Demmans, K. Z.; Morris, R. H. Rational Development of Iron Catalysts for Asymmetric Transfer Hydrogenation. *Dalton Trans.* **2014**, *43*, 7650−7667.
(26) Mikhailine, A. A.; Maishan, M. I.; Morris, R. H. Asymmetric Transfer Hydrogenation of Ketimines Using Well-defined Iron(II)-based Precatalysts Containing a PNNP Ligand. *Org. Lett.* **2012**, *14*, 4638−4641.
(27) Naik, A.; Maji, T.; Reiser, O. Iron(II)-bis(isonitrile) Complexes: Novel Catalysts in Asymmetric Transfer Hydrogenations of Aromatic and Heteroaromatic Ketones. *Chem. Commun.* **2010**, *46*, 4475−4477.
(28) Mikhailine, A.; Lough, A. J.; Morris, R. H. Efficient Asymmetric Transfer Hydrogenation of Ketones Catalyzed by an Iron Complex Containing a P-N-N-P Tetradentate Ligand Formed by Template Synthesis. *J. Am. Chem. Soc.* **2009**, *131*, 1394−1395.
(29) Ter Halle, R.; Breheret, A.; Schulz, E.; Pinel, C.; Lemaire, M. Chiral Nitrogen-metal Complexes for the Asymmetric Reduction of Ketones. *Tetrahedron: Asymmetry* **1997**, *8*, 2101−2108.
(30) Bruneau-Voisine, A.; Wang, D.; Dorcet, V.; Roisnel, T.; Darcel, C.; Sortais, J.-B. Transfer Hydrogenation of Carbonyl Derivatives Catalyzed by an Inexpensive Phosphine-Free Manganese Precatalyst. *Org. Lett.* **2017**, *19*, 3656−3659.
(31) Zirakzadeh, A.; de Aguiar, S. R. M. M.; Stoeger, B.; Widhalm, M.; Kirchner, K. Enantioselective Transfer Hydrogenation of Ketones Catalyzed by a Manganese Complex Containing an Unsymmetrical Chiral PNP′ Tridentate Ligand. *ChemCatChem* **2017**, *9*, 1744−1748.
(32) Elangovan, S.; Topf, C.; Fischer, S.; Jiao, H.; Spannenberg, A.; Baumann, W.; Ludwig, R.; Junge, K.; Beller, M. Selective Catalytic Hydrogenations of Nitriles, Ketones, and Aldehydes by Well-defined Manganese Pincer Complexes. *J. Am. Chem. Soc.* **2016**, *138*, 8809−8814.
(33) Elangovan, S.; Garbe, M.; Jiao, H.; Spannenberg, A.; Junge, K.; Beller, M. Hydrogenation of Esters to Alcohols Catalyzed by Defined Manganese Pincer Complexes. *Angew. Chem., Int. Ed.* **2016**, *55*, 15364−15368.
(34) Garbe, M.; Junge, K.; Walker, S.; Wei, Z.; Jiao, H.; Spannenberg, A.; Bachmann, S.; Scalone, M.; Beller, M. Manganese-(I)-catalyzed Enantioselective Hydrogenation of Ketones Using a Defined Chiral PNP Pincer Ligand. *Angew. Chem., Int. Ed.* **2017**, *56*, 11237−11241.
(35) Perez, M.; Elangovan, S.; Spannenberg, A.; Junge, K.; Beller, M. Molecularly Defined Manganese Pincer Complexes for Selective Transfer Hydrogenation of Ketones. *ChemSusChem* **2017**, *10*, 83−86.
(36) van Putten, R.; Uslamin, E. A.; Garbe, M.; Liu, C.; Gonzalez-de-Castro, A.; Lutz, M.; Junge, K.; Hensen, E. J. M.; Beller, M.; Lefort, L.; Pidko, E. A. Non-pincer-type Manganese Complexes as Efficient Catalysts for the Hydrogenation of Esters. *Angew. Chem., Int. Ed.* **2017**, *56*, 7531−7534.
(37) Widegren, M. B.; Harkness, G. J.; Slawin, A. M. Z.; Cordes, D. B.; Clarke, M. L. A Highly Active Manganese Catalyst for Enantioselective Ketone and Ester Hydrogenation. *Angew. Chem., Int. Ed.* **2017**, *56*, 5825−5828.
(38) Wang, D.; Bruneau-Voisine, A.; Sortais, J.-B. Practical (Asymmetric) Transfer Hydrogenation of Ketones Catalyzed by Manganese with (Chiral) Diamines Ligands. *Catal. Commun.* **2018**, *105*, 31−36.
(39) Espinosa-Jalapa, N. A.; Nerush, A.; Shimon, L. J. W.; Leitus, G.; Avram, L.; Ben-David, Y.; Milstein, D. Manganese-catalyzed Hydrogenation of Esters to Alcohols. *Chem. - Eur. J.* **2017**, *23*, 5934−5938.
(40) Espinosa-Jalapa, N. A.; Kumar, A.; Leitus, G.; Diskin-Posner, Y.; Milstein, D. Synthesis of Cyclic Imides by Acceptorless Dehydrogenative Coupling of Diols and Amines Catalyzed by a Manganese Pincer Complex. *J. Am. Chem. Soc.* **2017**, *139*, 11722−11725.
(41) Nguyen, D. H.; Trivelli, X.; Capet, F.; Paul, J.-F.; Dumeignil, F.; Gauvin, R. M. Manganese Pincer Complexes for the Base-free, Acceptorless Dehydrogenative Coupling of Alcohols to Esters: Development, Scope, and Understanding. *ACS Catal.* **2017**, *7*, 2022−2032.
(42) Mukherjee, A.; Nerush, A.; Leitus, G.; Shimon, L. J. W.; Ben David, Y.; Espinosa Jalapa, N. A.; Milstein, D. Manganese-catalyzed Environmentally Benign Dehydrogenative Coupling of Alcohols and Amines to Form Aldimines and H_2: A Catalytic and Mechanistic Study. *J. Am. Chem. Soc.* **2016**, *138*, 4298−4301.
(43) Haack, K.-J.; Hashiguchi, S.; Fujii, A.; Ikariya, T.; Noyori, R. The Catalyst Precursor, Catalyst and Intermediate in the RuII-

DOI: 10.1021/acs.organomet.8b00625
Organometallics XXXX, XXX, XXX−XXX

promoted Asymmetric Hydrogen Transfer Between Alcohols and Ketones. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 285−288.
(44) Castellanos-Blanco, N.; Arevalo, A.; Garcia, J. J. Nickel-catalyzed Transfer Hydrogenation of Ketones Using Ethanol as a Solvent and a Hydrogen Donor. *Dalton Trans.* **2016**, *45*, 13604−13614.
(45) Guo, R.; Chen, X.; Elpelt, C.; Song, D.; Morris, R. H. Applications of Ruthenium Hydride Borohydride Complexes Containing Phosphinite and Diamine Ligands to Asymmetric Catalytic Reactions. *Org. Lett.* **2005**, *7*, 1757−1759.

DOI: 10.1021/acs.organomet.8b00625
Organometallics XXXX, XXX, XXX−XXX