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β-Amino Phosphine Mn Catalysts for 1,4-Transfer Hydrogenation of Chalcones and Allylic Alcohol Isomerization

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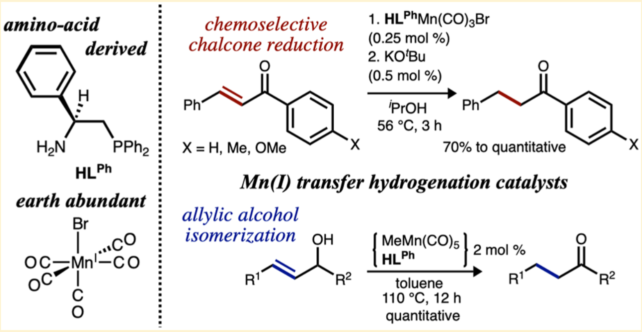
Supporting Information

ABSTRACT: Mn complexes with amino acid derived PN ligands were used in the catalytic transfer hydrogenation (TH) of ketone and chalcone substrates in 2-propanol with mild heating. Moreover, chalcones are reduced selectively to the saturated ketone at short times and can be fully converted to the alcohol when reactions are prolonged. The mechanism of chalcone reduction was briefly considered. Allylic alcohols are not reactive in 2-propanol, but quantitative isomerization occurs in toluene. Thus, we suspect that the allylic alcohols are dehydrogenated and the resulting ketone is formed through a direct 1,4-hydrogenation of the chalcone. Finally, several other related ligands that have been used in Mn-based TH reactions were explored to test the viability of ligand design in favoring chemoselectivity. The β-amino phosphine ligands proved most effective in this regard.



Transfer hydrogenation and dehydrogenation (TH and TdH) are incredibly important transformations in organic synthesis, and the field has been described as experiencing a "golden age".[1] Despite the large number of metal ions that have been found to carry out TH, the first manganese(I)-TH catalysts were only discovered recently.[2−5] Some of these examples use phosphine-free ligands,[3,5] and asymmetric catalysis has been achieved in some instances.[4]

The ever-expanding versatility and unique properties of Mn(I)-based catalysts are nicely demonstrated by the fact that Mn(I) catalysts are supported with bidentate ligands more effectively in comparison to iron and ruthenium.[6] For instance, Pidko[7] recently disclosed the use of β-amino glycine derived phosphine ligands in hydrogenation reactions, and others[3] have used bidentate nitrogen-only chelating ligands in TH reactions. While it is commendable that many Mn(I)-catalyzed TH studies can use cheap, phosphine-free ligands, the exclusion of strong-field supporting ligands destabilizes the low-spin d^6 configuration, resulting in facile electron transfer decompositions to unreactive Mn(II) species. Notably, Pidko has recently addressed this challenge by using a bidentate amino-NHC ligand to prepare catalysts capable of high turnover numbers (TON = 17300).[5]

Herein, we continue the development of ligands for Mn(I) TH catalysts and find that β-amino phosphines are excellent supports for TH and TdH Mn(I) catalysts. A primary motivation for us was that β-amino phosphines can be derived from cheap amino acid feedstocks. In addition, the relatively low price of $HPPh_2$ in comparison to other phosphine precursors enables production on large scales. In this report, we demonstrate that Mn(I) complexes bearing the β-amino phosphine derived from phenylglycine are efficient catalysts for ketone TH, 1,4-chalcone reductions, and allylic alcohol isomerization. The Mn(I) catalysts exhibit exceptional functional group tolerance and rapidly achieve high conversions under mild conditions.

For this work, we prepared PN ligands derived from the amino acids glycine, phenylglycine, and phenylalanine. The general procedure is one adapted from a variety of literature sources. This entails a simple reduction of the amino acid to the alcohol[8] and subsequent cyclization to the oxazolidinone,[9] the latter of which is converted into the free ligand $\mathbf{HL^R}$ (R = H, Ph, Bz) by addition of triflic acid and diphenylphosphine (Scheme 1).[10] The glycine- and phenylalanine-derived ligands are liquids, whereas the phenylglycine-derived PN ligand $\mathbf{HL^{Ph}}$ is a white solid and is easy to work with. Hence, the phenylglycine-derived PN ligand $\mathbf{HL^{Ph}}$ was used for the reactions below.

Coordination to Mn(I) was accomplished by treatment of the free ligand $\mathbf{HL^{Ph}}$ with $Mn(CO)_5Br$ in toluene and heating to 100 °C for 10−12 h in a sealed Schlenk bomb. The material can be recovered by removal of solvent and recrystallized from THF and petroleum ether to afford the crystalline precatalyst $\mathbf{HL^{Ph}}Mn(CO)_3Br$ in good yields (>80% crystalline, Figure 1). The ^{31}P NMR spectrum of crystalline $\mathbf{HL^{Ph}}Mn(CO)_3Br$ in CD_2Cl_2 contains a single peak ($^{31}P\{^1H\}$ NMR 53 ppm). Treatment of the crystalline precatalyst $\mathbf{HL^{Ph}}Mn(CO)_3Br$ with

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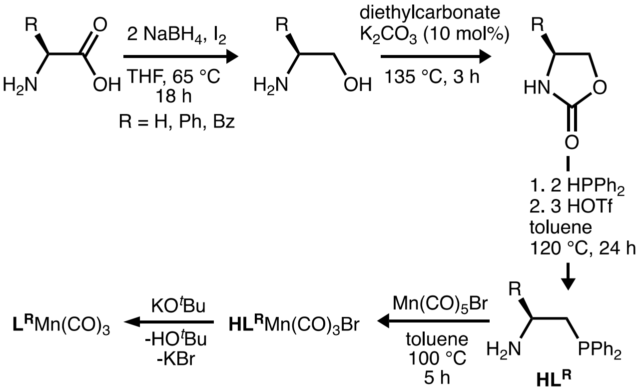
Scheme 1. General Ligand and Catalyst Synthesis



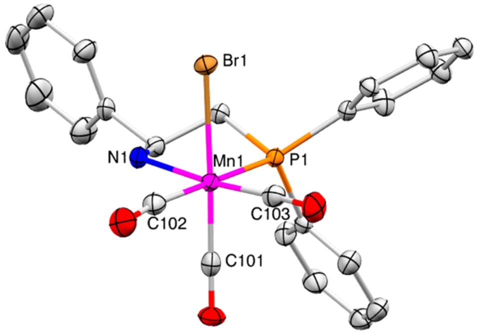


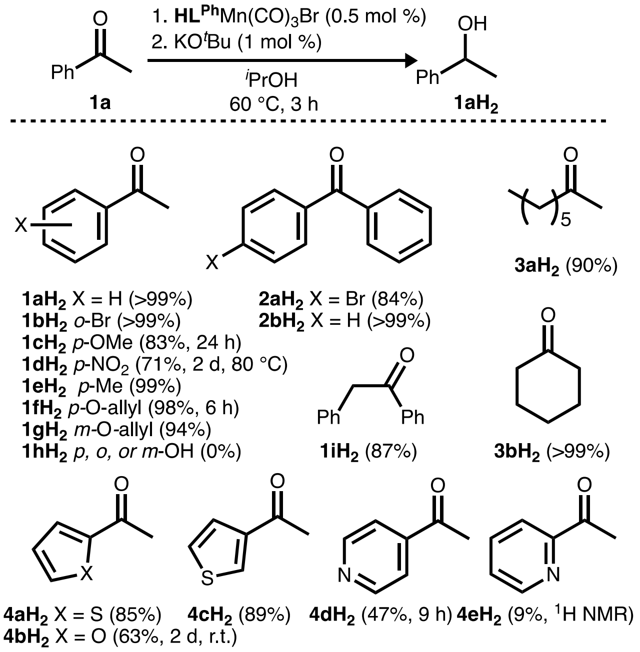
Figure 1. Molecular structure of one of the independent molecules in the unit cell for $HL^{Ph}Mn(CO)_3Br$, both of which have the same configuration. H atoms are not shown and ellipsoids are shown at 50% probability. Selected distances: Mn1−N1 2.100(5) Å; Mn1−P1(1) 2.319(1) Å; Mn1−Br1 2.563(1) Å; Mn1−C101 1.794(5) Å; Mn1−C102 1.821(5) Å; Mn1−C103 1.801(6) Å.

2 equiv of KO^{t}Bu in toluene affords a red species tentatively assigned as the $L^{Ph}Mn(CO)_3$ 16e$^-$ catalyst ($^{31}P\{^1H\}$ NMR 74 ppm) on the basis of its color, facial tricarbonyl motif (Figure S6), and reactivity that is discussed later.

The TH of acetophenone (**1a**) in 2-propanol was found to effectively reach quantitative completion in 3 h at 60 °C with 0.5 mol % catalyst loading and 1 mol % base (Scheme 2, stoichiometry relative to ketone). The conditions optimized for acetophenone were similar for the precatalysts prepared from $\mathbf{HL^{Ph}}$ (>99% $\mathbf{1aH_2}$), $\mathbf{HL^{H}}$ (83% $\mathbf{1aH_2}$), and $\mathbf{HL^{Bz}}$ (>99% $\mathbf{1aH_2}$).[11] A series of control experiments were performed for the acetophenone reduction. For instance, $Mn(CO)_5Br$ is not a catalyst, nor does it convert substrate in the presence of any of the amino alcohol ligand precursors (Scheme 1). Additionally, no catalytic activity was observed when base was excluded for trials with $\mathbf{HL^{Ph}}Mn(CO)_3Br$.

These conditions tolerated a variety of para- and ortho-substituted acetophenones (**1a**−**g**), with the exception of phenolic acetophenones, which were unreactive. *p*-Nitroacetophenone (**1d**) required refluxing for 3 days to achieve an isolated 71% yield. Benzophenones (**2a**,**b**) and aliphatic ketones (**3a**,**b**) were also hydrogenated effectively. 2-Acetylfuran (**4a**) and 2-acetylthiophene (**4b**) were hydrogenated in 63% and 85% isolated yields, respectively. 3-Acetylthiophene (**4c**), which does not form a chelating alcohol, was converted in 89% yield. *p*-Acetylpyridine (**4d**) was hydrogenated in 47% isolated yield after 9 h, but *o*-acetylpyridine (**4e**) was not hydrogenated to an appreciable extent (9% conversion by ^{1}H NMR); presumably the hydrogenated 2-acetylpyridine poisons the catalyst through a bidentate coordination. Transfer dehydrogenation of the parent 1-phenylethanol ($\mathbf{1aH_2}$) in refluxing acetone (56 °C) for 3 h resulted in only 67% conversion to acetophenone, suggesting that TH is favored over TdH under the conditions studied.

Scheme 2. Transfer Hydrogenation Functional Group Tolerance (Isolated Yields)



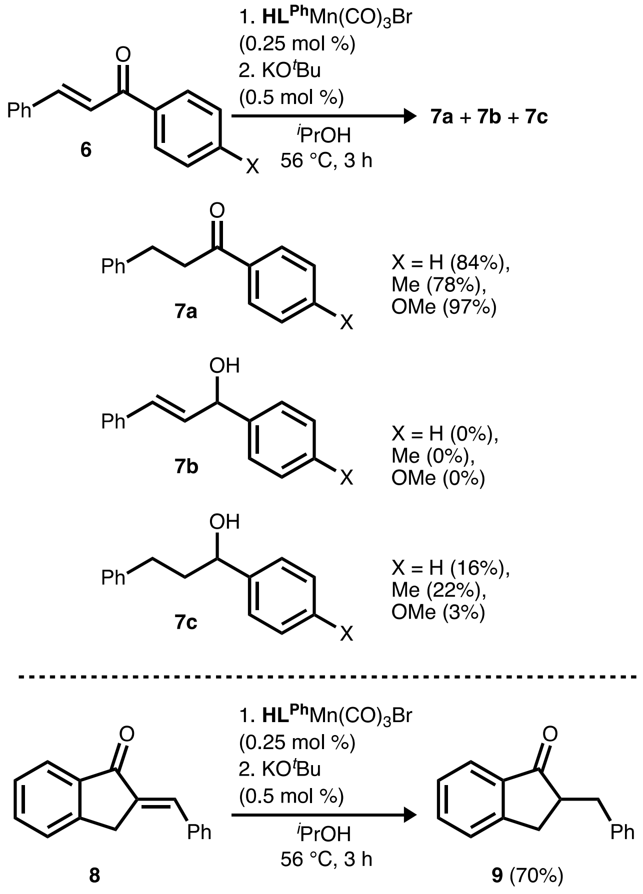
Interestingly, the PN-Mn(I) complexes are chemoselective 1,4-TH catalysts for chalcones to the saturated ketones. Although many conditions are available for 1,4-reductions of chalcones,[12] this report does not require a stoichiometric electron transfer reagent and is the first Mn-catalyzed example. Moreover, the reaction conditions here are mild and the product isolation is simple. For instance, *trans*-chalcone (**6**) can be converted to 1,3-diphenyl-1-propanone (**7a**) at 56 °C in 3 h using 0.25 mol % catalyst loading and 0.5 mol % base (Scheme 3). Complete conversion to the saturated alcohol 1,3-diphenyl-1-propanol (**7c**) can be accomplished through overnight heating under the parent conditions with a higher catalyst loading (0.5 mol %), indicating that the observed chemoselectivity is likely a condition-dependent phenomenon. The benzylidene indanone **8** was also hydrogenated to the ketone **9** under the conditions listed above for the chalcone.

We did not observe the allylic alcohol **7b** in TH reactions with chalcone **6** under the conditions studied, indicating that reduction may occur via a 1,4-hydride addition rather than 1,2-reduction followed by isomerization (Scheme 4). We tested this hypothesis by subjecting 1,3-diphenylprop-2-enol (**7b**) to the parent conditions in 2-propanol and found no reaction; only unreacted **7b** was recovered.

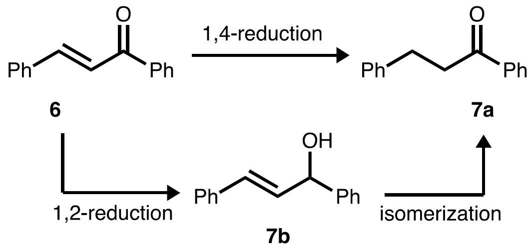
However, **7b** isomerizes to **7a** in toluene in the presence of precatalyst $\mathbf{HL^{Ph}}Mn(CO)_3Br$ and base. Analogous selectivity to the saturated ketone was recently reported by Renaud and co-workers using an iron catalyst.[13]

Isomerization of **7b** into **7a** represents a rare example of a Mn-catalyzed allylic alcohol isomerization reaction.[14] Typically, isomerization of allylic alcohols requires a precious-metal

Scheme 3. 1,4-Transfer Hydrogenation of Chalcones

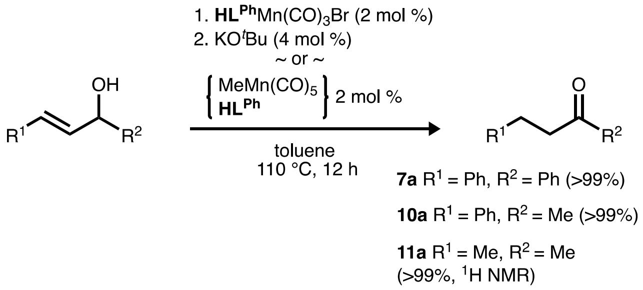


Scheme 4. Possible Mechanisms for Chalcone Reduction



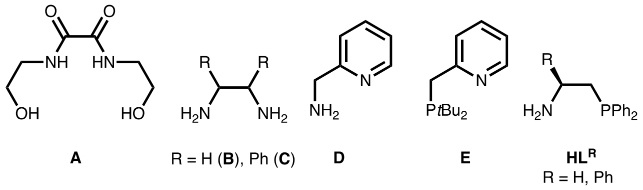
catalyst.[15] Nickel, molybdenum, iron, and cobalt have been utilized,[15a,16] and only one manganese catalyst has been reported.[14] The allylic alcohol isomerization capability of the $\mathbf{HL^{Ph}}$Mn(CO)$_3$Br and base system in toluene was tested for the three different allyl alcohols **7b**, **10b**, and **11b** and gave quantitative conversion (Scheme 5).

Scheme 5. Allylic Alcohol Isomerization Studies



We additionally compared various ligands in the chalcone reduction to see if the phenomenon was general or specific to the PN ligand $\mathbf{HL^{Ph}}$ (Table 1). The oxamide ligand **A** did not afford any significant reaction (<6% alcohol,[17] no saturated ketone) with the remaining **6** untouched. 1,2-Diaminoethane and its 1,2-diphenyl-substituted analogue (ligands **B** and **C**, respectively)[4c] furnished almost no conversion of **6**. Sortais' 2-aminomethylpyridine (ligand **D**) precatalyst complex **D**Mn(CO)$_3$Br was prepared and used under conditions identical with those in Scheme 3.[3a] In this case, the allyl alcohol **7b** was obtained in 27% yield, again with the remainder of starting material unreacted. We additionally tested a new PN-Mn complex with ligand **E** (**E**Mn(CO)$_3$Br, Figure 2) and found no conversion of **6**. In comparison to the parent ligands $\mathbf{HL^{H}}$ and $\mathbf{HL^{Ph}}$, these other catalysts are not chemoselective for the saturated ketone and this highlights the viability of ligand

Table 1. Effect of Ligand in Chalcone (6) Reduction[a]



	yield[b] (%)			
ligand	6	7a	7b	7c
none[c]	100	0	0	0
$\mathbf{HL^{Ph}}$	0	84	0	16
$\mathbf{HL^{H}}$	0	76	0	24
A[d]	94	0	6	0
B[e]	91	0	9	0
C[e]	>99	0	<1	0
D[f]	73	0	27	0
E[g]	100	0	0	0

[a]Conditions as in Scheme 3 for substrate **6**. [b]Yields determined by ^{1}H NMR after solvent removal in vacuo. [c]none = Mn(CO)$_5$Br with no ligand. [d]Catalyst was prepared according to ref 17. [e]Catalyst was prepared according to ref 4c. [f]Catalyst was prepared according to ref 3a. [g]This work; see the Supporting Information.

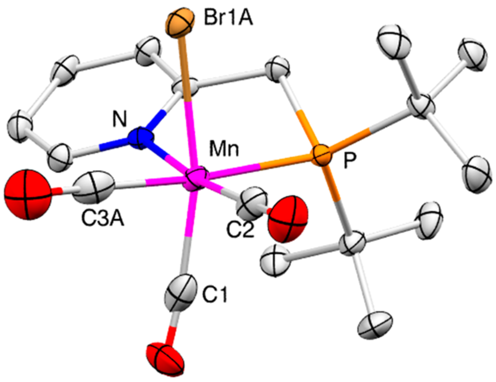


Figure 2. Molecular structure of one of the molecules in the unit cell obtained for **E**Mn(CO)$_3$Br with ellipsoids shown at 50% probability. H atoms are not shown for clarity. See the Supporting Information for a discussion describing the disorder of C3 and Br1. Selected bond lengths: Mn–Br1A 2.543(2) Å; Mn–N 2.088(3) Å; Mn–P 2.355(1) Å; Mn–C1 1.836(6) Å; Mn–C2 1.792(5) Å; Mn–C3A 1.79(1) Å.

design in Mn-based systems that are rapidly emerging in recent years.

An earlier report showed the potential of using methylmanganese pentacarbonyl (**MeMn**), foregoing the need to use a base.[18] A heated mixture of $\mathbf{HL^{Ph}}$ + **MeMn** in toluene forms the same species (^{31}P {^{1}H} NMR 74 ppm; among other species) as when $\mathbf{HL^{Ph}}Mn(CO)_3Br$ and 2 equiv of base are reacted in toluene (Figure S6). When the $\mathbf{HL^{Ph}}$ + **MeMn** toluene mixture with $^{31}P\{^{1}H\}$ NMR 74 ppm was added to a solution of **1a** in 2-propanol and heated, $\mathbf{1aH_2}$ was isolated in 58% yield. Furthermore, a 2 mol % $\mathbf{HL^{Ph}}$ + **MeMn** mixture prepared in the presence of **7b** quantitatively isomerized the substrate to **7a** (Scheme 5).

In conclusion, we have demonstrated that *β*-amino phosphine-supported Mn(I)-carbonyl complexes are excellent catalysts for TH of ketones with good functional group tolerance under mild conditions. Chalcones are selectively reduced to the ketones in short time intervals, and this appears to be a unique property of the catalysts derived from *β*-amino phosphine ligands. Additionally, the isomerization of allylic alcohols by the same catalysts was demonstrated and is related to the selectivity of the chalcone reduction. Importantly, these reactions highlight that Mn(I) is a versatile ion to perform reactions where the ligand controls chemoselectivity. Given its abundance and low toxicity in comparison to most other metal ions, the area of Mn(I) in catalysis is expected to see growth in unique substrate and chemoselective transformations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available online. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organomet.9b00692.

General considerations, ligand synthesis and characterization, complex synthesis and characterization, and substrate scope (PDF)

Accession Codes

CCDC 1959707−1959708 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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